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MURRAY & NADEL'S TEXTBOOK of RESPIRATORY MEDICINE

5th Edition

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Talmadge E. King, Jr
Dean E. Schraufnagel
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Murray and Nadel's

TEXTBOOK OF **RESPIRATORY MEDICINE**

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VOLUME I

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We dedicate this textbook to Dr. Julius H. Comroe, Jr., who was our mentor during the formative years of our professional development. Dr. Comroe was one of the truly great academicians of his generation. He was an investigator of exceptional merit, an educator whose influence was worldwide, and a medical statesman of exemplary integrity and vision. In dedicating this book, we acknowledge especially Dr. Comroe's scholarly contributions and his commitment to the importance of basic science in the solution of clinical problems.

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PREFACE TO THE FIFTH EDITION

As it has been from the beginning, the goal of this textbook is to be a well balanced, authoritative, and fully documented book that integrates the basic scientific principles with the practice of respiratory medicine for clinicians, trainees, students and educators. To accomplish this in a rapidly changing field, we have undertaken significant changes for the fifth edition. Chapters have been created to cover new topics, other chapters have been split into two to cover topics more thoroughly, and still other chapters have been merged to improve presentation of similar material. Key points distilled from each subject are now highlighted at the end of each chapter. Color photographs and illustrations have been incorporated into the chapters wherever possible. The locations of numerous instructional videos, which can be accessed at the textbook's website, are indicated by icons in the printed textbook. An active and regularly updated internet site is an integral part of the textbook, expanding, revising and supporting information from the printed pages.

We are mindful that we are trying to meet the educational needs of an increasingly global and sophisticated readership. There are 26 newly written chapters. These include chapters on genetics, asthma, particle deposition and clearance, innate immunity, lung injury and repair, pulmonary pathology, bronchoscopy (diagnostic and therapeutic), ultrasonography, pulmonary function testing, clinical exercise testing, respiratory impairment and disability, ventilator-associated pneumonia, lymphoma, occupational asthma, bioterrorism, nontuberculous mycobacterial disease, pulmonary vasculitis, sleep disorders, neuromuscular disease, lung transplantation, metastatic lung disease and the biology of non-small cell lung cancer. As for each edition, new authors have been recruited to provide new perspectives and our continuing authors have thoroughly updated their chapters. We are indebted and deeply appreciative of the hard work and dedication of all our authors, nearly half of whom are new to the textbook. Our international contributors, who represent 15 countries, now make up 25% of authors of the fifth edition.

We believe that this textbook remains an important resource for pulmonary physicians. From the time of its first publication in 1988, it retains the spirit of a comprehensive, well-referenced text created by internationally recognized authorities. Each chapter is meant to provide both a comprehensive overview and the authors' expert insights concerning the scientific-clinical foundations of the subject, on which the reader can integrate new knowledge as research progresses.

The online textbook and internet site will enhance the learning experience. Each figure in the printed edition is available from the internet site and can be readily downloaded into teaching presentations. Videos that illustrate procedures and important concepts not appreciated in static images are linked to several of the chapters. Pertinent review questions for each chapter can serve as a self-teaching module. Teaching cases prepared regularly by Dr. Michael Gotway present and explain important radiographic features of pulmonary disease. Literature updates that comment on recent articles should be of interest to the readership and, in addition, at the end of each chapter, links will direct the reader to recent articles and reviews. We aim to keep our online readers engaged and current and to give them reasons to visit the electronic textbook often.

We would like to thank our publisher Elsevier Inc. for their support and suggestions for improvement. We are very pleased with the layout of the book and the improved artwork. The publishing staff and copyeditors deserve special thanks and acknowledgment for their important contributions, particularly Dolores Meloni and Ann Ruzycka Anderson. Copyediting and print layout was skillfully performed by Berta Steiner and her staff at Bermedica Production, Ltd. We greatly appreciate the countless hours of work of authors, publishers, artists and copyeditors to bring this textbook to life. We encourage our readers to contribute also by providing feedback and suggestions for ongoing improvement.

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PREFACE TO THE FIRST EDITION

The rapid growth of knowledge of basic scientific principles and their application to respiratory medicine has resulted in a proliferation of monographs and texts dealing with selected aspects of pulmonary science and clinical medicine, but no single work has provided a comprehensive description of all that is currently known. The *Textbook of Respiratory Medicine* is an attempt to provide a well-balanced, authoritative, and fully documented book that integrates scientific principles with the practice of respiratory medicine. The text is sufficiently detailed and referenced to serve as the definitive source for interested students, house officers, and practitioners, both pulmonary specialists and generalists. It is written by leading experts, to guarantee that the material is authoritative and contemporary.

To deal with such an enormous amount of material, we have divided the book into three major sections. This organization should help guide interested readers from the intricacies of basic science to their application at the bedside. We begin in Part I with Scientific Principles of Respiratory Medicine. As implied, this is where the reader will find detailed information about the anatomy and development of the respiratory tract, respiratory physiology, pharmacology and pathology, and defense mechanisms and immunology. A strong foundation in these basic sciences will make possible a rational and scientific approach to the more specialized clinical material included in the subsequent sections. Part II, Manifestations and Diagnosis of Respiratory Disease, contains four chapters on the cardinal signs and symptoms of respiratory disorders and ten chapters on diagnostic evaluation, ranging from the history and physical examination to the newest and most sophisticated imaging, applied physiologic, and invasive techniques. Discrete clinical disorders are included in Part III, Clinical Respiratory Medicine. There are sections on Infectious Diseases, Obstructive Diseases, Neoplasms, Disorders of the Pulmonary Circulation, Infiltrative and Interstitial Diseases, Environmental and Occupational Disorders, Disorders of the Pleura, Disorders of the Mediastinum, Disorders in the Control of Breathing, Respiratory Manifestations of Extrapulmonary Disorders, and Respiratory Failure. All but one of the sections dealing with a generic clinical problem begin with a chapter entitled "General Principles and Diagnostic Approach." New challenges to adult respiratory medicine have sprung up, and these are reflected in chapters on subjects such as cystic fibrosis (previously a disease only of childhood!), environmental and occupational diseases, disorders of breathing, and respiratory problems associated with unusual atmospheres (high altitude, diving). The book ends with a novel and important section on Prevention and Control.

Putting together a *Textbook* of this scope and magnitude is no easy task and involves making certain decisions that all readers may not agree with. For example, while trying to keep the length of the book as manageable as possible, we decided to permit some overlap of content. Thus, readers will find bronchodilators discussed in the chapter on airway pharmacology and again in the pertinent chapters on obstructive airway diseases. We have also welcomed differences of opinion among authors, provided the issues were clearly stated and the reasons for the author's position documented.

Our struggles were not as arduous as they might have been because we have had considerable help from many sources. First of all was the help from the 95 authors, who worked long and hard on their various contributions. The two editors worked in San Francisco, where they had the benefit of expert secretarial support from Ms. Dorothy Ladd and Mrs. Beth Cost. Special acknowledgment goes to Ms. Aja Lipavsky who, as editorial assistant, handled correspondence, proofing, permissions, and innumerable other details, and prepared the index. At W.B. Saunders in Philadelphia, the book was the brainchild of then-president John Hanley and was published with the guidance of J. Dereck Jeffers, William Lamsback, and the new president Lewis Reines. Production was supervised by Evelyn Weiman.

The long gestation of this book is over, parturition is near, and it will soon begin a life of its own. Like all expectant parents, we are concerned about how our offspring will make its way in the real world. We hope people will like it and find it useful.

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CHAPTER 1

ANATOMY OF THE LUNGS

Kurt H. Albertine, PhD

INTRODUCTION

GROSS AND SUBGROSS ORGANIZATION

AIRWAYS
Cellular Complexity
Bronchial Circulation

PULMONARY CIRCULATION
Pulmonary Vascular Endothelial Cells

TERMINAL RESPIRATORY UNITS
Type II Cell Structure
Type II Cell Functions
Type II Cell Proliferation
Type I Cell Structure
Type I Cell Functions
Type I Cell Proliferation
Relationship between Type II and Type I Cells In Vivo and In Vitro

INNERVATION

AIRSPACE MACROPHAGES, LYMPHATICS, LYMPHOID TISSUE, AND INNATE IMMUNITY

INTRODUCTION

The primary function of the lung is ventilation-perfusion matching such that gas exchange between alveolar air and alveolar capillary blood is efficient (Fig. 1-1). Therefore, this chapter emphasizes the gross, subgross, histologic, and ultrastructural determinants of ventilation-perfusion matching in the normal human lung. Secondary functions of the various cell types in the lung, particularly of alveolar type II and type I epithelial cells and capillary endothelial cells, also are considered.

GROSS AND SUBGROSS ORGANIZATION

The position of the lungs in the chest and in relationship to the heart is shown in Figure 1-2. Figure 1-2A shows a midfrontal section through the thorax of a frozen human cadaver. Figure 1-2B shows a posterior-anterior chest radiograph of a normal human at functional residual capacity (FRC). The two illustrations represent the extremes of the approaches to lung anatomy. The cadaver lung (see Fig. 1-2A) shows the gross anatomic arrangements and relationships. The main distortion is that the lungs are at low volume. The height of the lungs is only about 18 cm, which is well below FRC height (see Fig. 1-2B). The diaphragm is markedly elevated in Figure 1-2A, probably about 5 cm relative to its end-expiratory position in life. Another distortion is the abnormally wide pleural space. But that fixation shrinkage artifact serves as a useful reminder that the lung is not normally attached to the chest wall. In life, the separation between the parietal and the visceral pleuras is only several micrometers.[1,2] The chest radiograph (see Fig. 1-2B) shows that the height of the lung at FRC is approximately 24 cm, with the level of the bifurcation of the pulmonary artery about halfway up the lungs. The diaphragm is lower and flatter than in the cadaver. Conversely, the radiographic detail is only a shadow of dense structures.

In life, the lungs weigh 900 to 1000 g, of which nearly 40% to 50% is blood.[3,4] At end-expiration, the gas volume is about 2.5 L, whereas at maximal inspiration it may be 6 L. Thus, overall lung density varies from 0.30 g/mL at FRC to 0.14 g/mL at total lung capacity (TLC). But the density of the lung is not distributed uniformly, being about 1 g/mL near the hilum and 0.1 g/mL peripherally. If one likens each lung to a half cylinder, more than 50% of all the lung's alveoli are located in the outer 30% of the lung radius (hilum to chest wall). This is why the peripheral portion of the lung appears relatively empty in the chest radiograph (see Fig. 1-2). Variability in density also exists from top to bottom. In Figure 1-2, the blood vessels are more distended in the lower lung fields. The increasing distention of vessels from apex to base also illustrates the increase in vascular distending pressures at the rate of 1 cm H_2O/cm height down the lung.

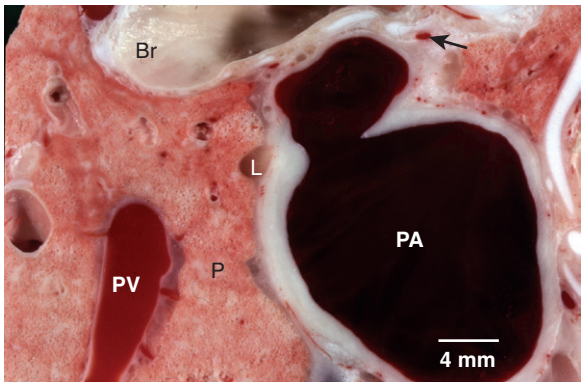

FIGURE 1-1 ■ Frozen block of lung tissue. Air is brought into the lung via the bronchus (Br). Pulmonary arterial (PA) blood is dark purple because it is poorly oxygenated. Gas exchange across the lung's parenchyma (P) results in oxygenated pulmonary venous (PV) blood, which is crimson. Also present in the peribronchovascular connective tissue are bronchial arteries (*arrow*) and lymphatics (L). (Frozen sheep lung, unstained.)

TABLE 1-1. Components of Normal Human Lung

Component	Volume or Mass (mL)	Thickness (μm)	Reference No.
Gas	2400		7
Tissue	900		3, 4
Blood	400		4
Lung	500		8
Support structures	250		5
Alveolar walls	250–300		5, 6
Epithelium	60–80	0.18	5, 6
Endothelium	50–70	0.10	5, 6
Interstitium	100–185	0.22	5, 6
Alveolar macrophages	55		6

The disposition of the various tissues that compose the lung is summarized in Table 1-1. An amazing point is how little tissue is involved in the architecture of the alveolar walls.[5,6] But this is as it should be, because the major physical problem of gas exchange is the slowness of oxygen diffusion through water.[7,8] Thus, the alveolar walls must be extremely thin. In fact, the thickness of the red blood cell forms a substantial portion of the air-blood diffusion pathway. Advantage was taken of this fact to separate the carbon monoxide diffusing capacity measurement into two components: the capillary blood volume and the membrane diffusing capacity.[9] (For a discussion of diffusing capacity, see Chapters 4 and 24.)

The lung has two well-defined interstitial connective tissue compartments arranged in series, as described by Hayek[10] (Fig. 1-3). These are the parenchymal (alveolar wall) interstitium and the loose binding (extra-alveolar) connective tissue (peribronchovascular sheaths, interlobular septa, and visceral pleura). The connective tissue fibrils (collagen, elastin, and reticulin) form a

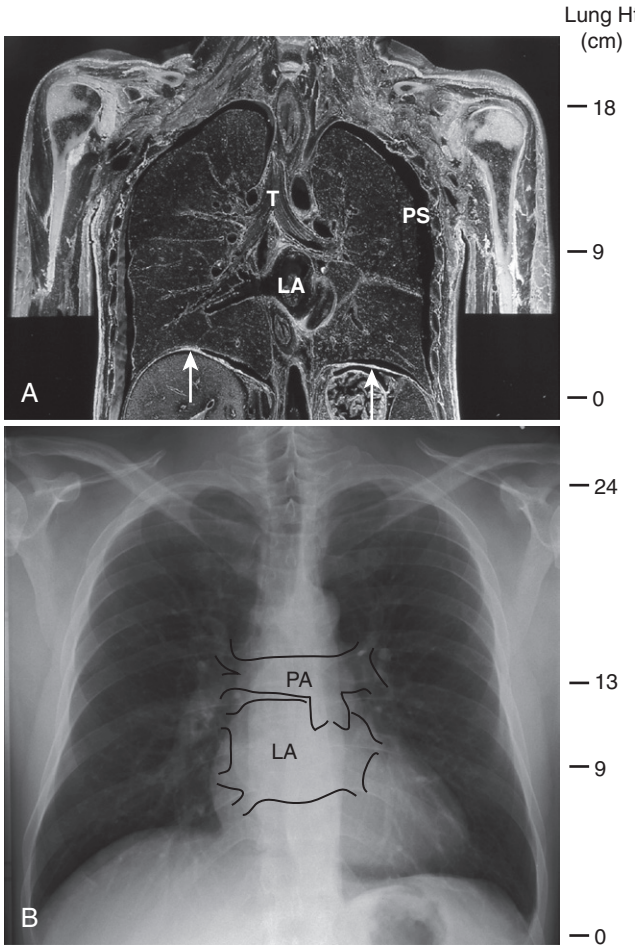

FIGURE 1-2 ■ Comparison views of lung position in the chest and relationship to the heart. **A,** Midfrontal section through the thorax of a frozen cadaver of a 35-year-old human. The cadaver was prepared by routine embalming procedures, stored horizontally for 3 months in 30% alcohol, and frozen in the horizontal position for 1 week at –20°C. Frontal sections were cut with a band saw. Because the cadaver was preserved in the horizontal position, the weight of the abdominal organs compressed the contents of the thoracic cavity. The domes of the diaphragm (*arrows*) are elevated about 5 cm relative to their end-expiratory position in life. Pleural space (PS) width is artifactually enlarged; normally in life, it is several micrometers in width. The trachea (T) is flanked on its left by the aortic arch and on its right by the azygos vein. The left pulmonary artery lies on the superior aspect of the left mainstem bronchus. Pulmonary veins from the right lung enter the left atrium (LA), which is located about 7 cm above the lung's base. These structures at the root of the lungs caused the esophagus to be cut twice as it follows a curved path behind them to reach the stomach. **B**, Chest roentgenogram of a normal human adult taken in the upright position at functional residual capacity. The lung height (cm) was measured from the costodiaphragmatic angle to the tubercle of the 1st rib. The main pulmonary artery (PA) and left atrium (LA) are outlined. The vascular structures, especially the pulmonary veins, are more easily seen near the base of the lung. This is partly because vascular distending pressures are greater near the bottom. The density of the lung is also graded, being higher at the bottom than the top and higher near the hilum than peripherally. (**A,** Reprinted with permission from Koritké JG, Sick H: Atlas of Sectional Human Anatomy. Vol 1: Head, Neck, Thorax. Baltimore: Urban and Schwarzenberg, 1983, p 83.)

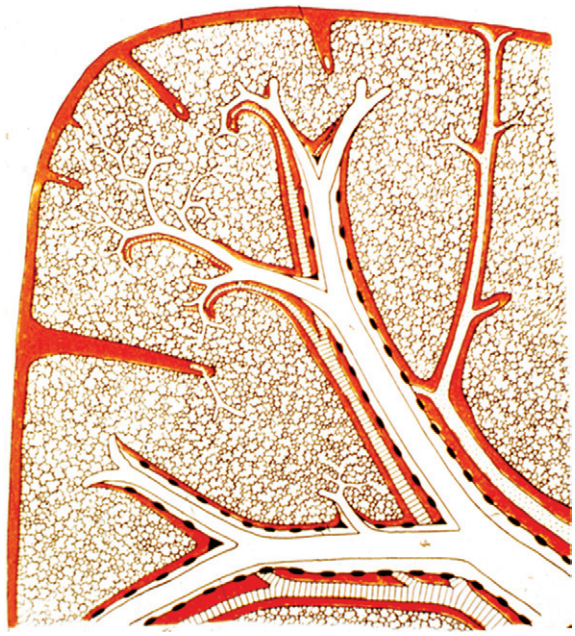

FIGURE 1-3 ■ General plan depicts the interstitial connective tissue compartments of the lung. All of the support structures (airways, blood vessels, interlobular septa, visceral pleura) are subsumed under the loose binding connective tissue. The alveolar walls' interstitium comprises the parenchymal interstitium. This organizational plan of the lung follows the general organization of all organs. (Reproduced with permission from Hayek H: The Human Lung. New York: Hafner, 1960, pp 298–314.)

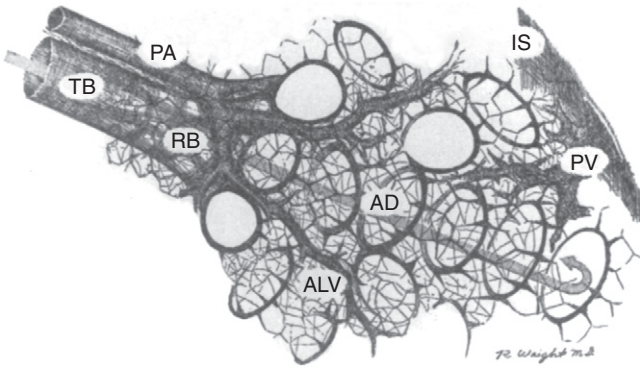

FIGURE 1-4 ■ A drawing of the connective tissue support of the normal human adult lung lobule demonstrates the exchange of fibers composing the "elastic continuum." AD, alveolar duct; ALV, alveolus; IS, interstitial space; PA, pulmonary artery; PV, pulmonary vein; RB, respiratory bronchiole; TB, terminal bronchiole. (Reprinted with permission from Wright RR: Elastic tissue of normal and emphysematous lungs. Am J Pathol 39:355–363, 1961.)

three-dimensional basket-like structure around the alveolar and airways (Fig. 1-4).[11] This basket-like arrangement allows the lung to expand in all directions without developing excessive tissue recoil. Because the connective tissue fibrils in the parenchymal interstitium are extensions of the coarser fibers in the loose-binding connective tissue, stresses imposed at the alveolar wall level during lung inflation are transmitted not only to adjacent alveoli, which abut each other, but also to surrounding

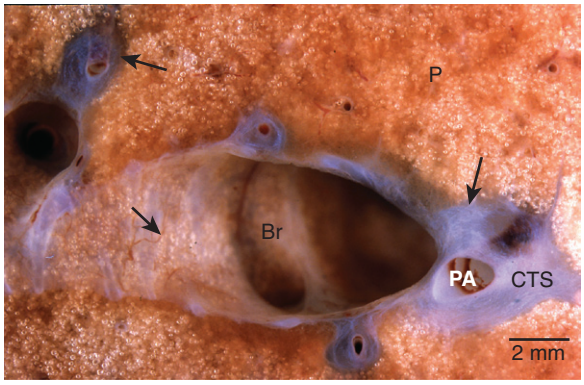

FIGURE 1-5 ■ Interstitial pulmonary edema cuffs (*arrows*) demonstrate the loose-binding (peribronchovascular) connective tissue spaces (CTS) that surround the bronchi (Br), pulmonary arteries (PA), and bronchial blood vessels (*arrowhead*). (Frozen sheep lung, unstained.)

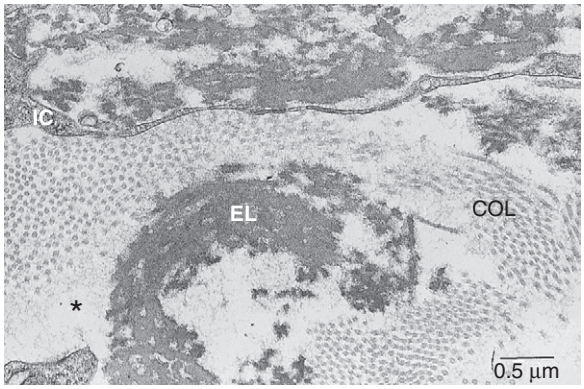

FIGURE 1-6 ■ The connective tissue compartment of the lung contains interstitial cells (IC), fibrils of collagen (COL), and elastin (EL). The bulk of the interstitium, however, is occupied by matrix constituents (*) such as glycosaminoglycans. (Human lung surgical specimen, transmission electron microscopy.)

alveolar ducts and bronchioles, and then to the loose-binding connective tissue supporting the whole lobule, and ultimately to the visceral pleural surface (see Fig. 1-3). These relations become more apparent in certain pathologic conditions. For example, in interstitial emphysema,[12] air enters the loose-binding connective tissue and dissects along the peribronchovascular sheaths to the hilum and along the lobular septa to the visceral pleura. The same separation occurs in pulmonary edema (Fig. 1-5).[13] (Further information about the pathophysiology of acute respiratory distress syndrome is presented in Chapter 90.)

The bulk of the interstitium is not the several varieties of interstitial cells (contractile and noncontractile interstitial cells,[14,15] mast cells, plasma cells, and occasional leukocytes) that reside in the connective tissue spaces of the lung. Nor is the bulk formed by laminin, collagens, elastin and reticulin fibrils, fibronectin, and tenascin (Fig. 1-6). Rather, the bulk of the interstitium is occupied by a matrix of proteoglycans (see Fig. 1-6).[16,17] Proteoglycans constitute a complex group of gigantic polysaccharide molecules (~30 different core proteins, with great diversity of glycosaminoglycan side chains) whose

entanglements impart a gel-like structure to the interstitium. That structural role, although essential, is not the sole role of these important molecules. A growing view is emerging of the lung's extracellular matrix components as regulators of lung physiology, such as determining epithelial cell phenotype; binding of and subsequent signaling by cytokines, chemokines, and growth factors; cell proliferation; migration; differentiation; and apoptosis.[18–25] In disease states, degradation products of extracellular matrix components may activate the Toll-like receptor pathways; thus, the degradation products may serve as endogenous sentinels of tissue damage and initiators of innate immune responses.[20,24–26] (Toll-like receptors are discussed further in the next section.)

AIRWAYS

The airways, forming the connection between the outside world and the terminal respiratory units, are of central importance to our understanding of lung function in health and disease. Intrapulmonary airways are divided into three major groups: bronchi (Fig. 1-7), membranous bronchioles (Fig. 1-8) and respiratory bronchioles/gas exchange ducts (Fig. 1-9). Bronchi, by definition, have cartilage in their wall. Respiratory bronchioles serve a dual function as airways and as part of the alveolar volume (gas exchange).

The anatomic dead space, as measured by the single-breath nitrogen dilution technique, measures principally the volume of the extrapulmonary (upper) airways (see Chapter 43) and the intrapulmonary bronchi.[27] The trachea and bronchi are cartilaginous. The membranous bronchioles (noncartilaginous airways of ~1 mm diameter or less), although exceedingly numerous, are short. They consist of about five branching generations and end at the terminal bronchioles. In contrast to the bronchi, the membranous bronchioles are tightly embedded in the connective tissue framework of the lung and therefore enlarge passively as lung volume increases.[28] Histologically, the bronchioles down to and including the terminal bronchioles ought to contribute about 25% to the anatomic dead space. In life, however, they contribute little because of gas phase diffusion and mechanical mixing in the distal airways resulting from the cardiac impulse. By definition, the respiratory bronchioles and alveolar ducts do not contribute to the anatomic dead space. The volume of the respiratory bronchiole-alveolar duct system is approximately one third of the total alveolar volume, and it is into this space that the fresh air ventilation enters during inspiration.

Most airway resistance resides in the upper airways and bronchi. Normally, smooth muscle tone in the large airways maintains partial constriction. Minimal airway diameter in the human lung, about 0.5 mm, is reached

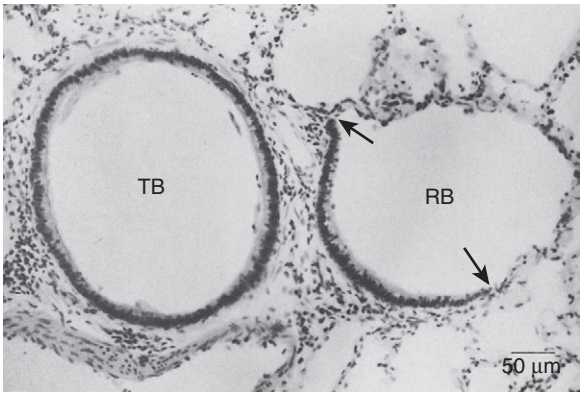

FIGURE 1-8 ■ Cross section of well-distended bronchioles. The wall of the terminal bronchiole (TB) is constructed of ciliated, cuboidal epithelium, thin discontinuous bands of smooth muscle, and submucosal connective tissue. In the respiratory bronchiole (RB), there is an abrupt transition (*arrows*) from cuboidal epithelium to alveolar epithelium. (Human lung surgical specimen, 10-µm-thick paraffin section, light microscopy.)

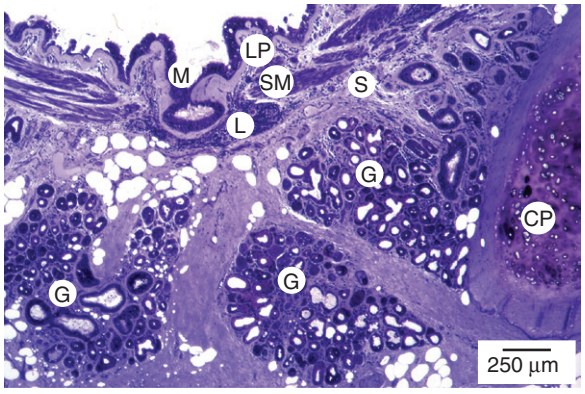

FIGURE 1-7 ■ The bronchial wall is composed of mucosa (M), lamina propria (LP), smooth muscle (SM), and submucosa (S). Seromucous glands (G) are located between the spiral bands of smooth muscle and cartilaginous plates (CP). Diffuse lymphoid tissue (L) has infiltrated the lamina propria and submucosa. (Human lung surgical specimen, right middle lobar bronchus, 2-µm-thick glycol methacrylate section, light microscopy.)

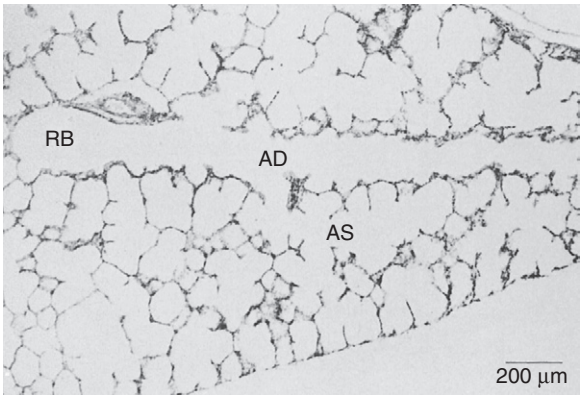

FIGURE 1-9 ■ Longitudinal section of a gas exchange duct shows that its diameter remains relatively constant along the respiratory bronchiole (RB) and alveolar duct (AD). Alveolar sacs (AS) communicate with the gas exchange duct. (Human lung surgical specimen, 10-µm-thick paraffin section, light microscopy.)

at the level of the terminal bronchioles; succeeding generations of exchange ducts (respiratory bronchioles and alveolar ducts) are of constant diameter (see Fig. 1-9).[29,30] The functional significance of centralized resistance is that the terminal respiratory units (the functional alveoli) within a lung subsegment are ventilated chiefly in proportion to their individual distensibilities (compliances) because most of their airway resistance is common. This is demonstrated normally by the finding that regional lung ventilation is dependent upon the initial volumes of the alveoli. Terminal respiratory units toward the top of the lung, which are more expanded at FRC, do not receive as great a share of the inspirate as do the terminal respiratory units near the bottom of the lung.

The balance between anatomic dead space volume, which ought to be as small as possible for efficient alveolar ventilation (dead space–to–tidal volume ratio), and airflow resistance, which means the airway diameter ought to be as large as possible for low work of breathing, requires a compromise. Normally, anatomic dead space is not maximal, nor is resistance minimal.

Cellular Complexity

The cellular complexity of the airways is indicated by the nearly 50 distinct cell types in the lung, at least 12 of which are epithelial cells on the airway surface.[31] Nearly half of the epithelial cells in the normal human airway are ciliated at all airway generations (Fig. 1-10) down to bronchioles (Fig. 1-11).[32] Cilia move the superficial liquid lining layer (see Fig. 1-11) continually toward the pharynx from deep within the lung. As the superficial lining liquid moves centripetally, the summed perimeter of the airways decreases markedly.[5] Mucins float on top of the liquid lining fluid (see Fig. 1-11). When cilia come in contact with mucins, they propel the mucins (together with deposited particulates) mouthward, promoting clearance of the particulates.

The presence of apical junctional complexes between airway epithelial cells (Fig. 1-12) has important functional implications for metabolically regulated secretion and absorption of electrolytes and water from the lining liquid. Apical junctional complexes consist of three elements: *zonula occludens* (tight junction), *zonula adherens*, and *macula adherens* (desmosome).[33] Tight junctions subserve two important functions: restriction of passive diffusion by blocking the lateral intercellular space and polarization of cellular functions (ion and water transport) between the apical and the basolateral membranes.[34] Polarization of chloride and sodium transport allows the airway epithelium to either secrete or absorb ions, followed by water movement.

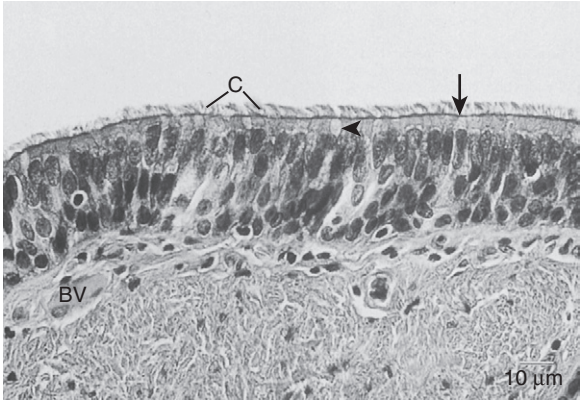

FIGURE 1-10 ■ The bronchial mucosa consists of pseudostratified, columnar epithelium with cilia (C) and goblet cells (*arrowhead*). The cilia, which form a thick carpet, move rhythmically and thereby propel liquid, mucus, cells, and debris centrally toward the pharynx. The dark band immediately beneath the cilia (*arrow*) is produced by the basal bodies. Under the electron microscope, basal bodies are recognized as modified centrioles (see Fig. 1-12). A bronchial blood vessel (BV) is located just beneath the mucosal layer. (Human lung surgical specimen, 10-µm-thick paraffin section, light microscopy.)

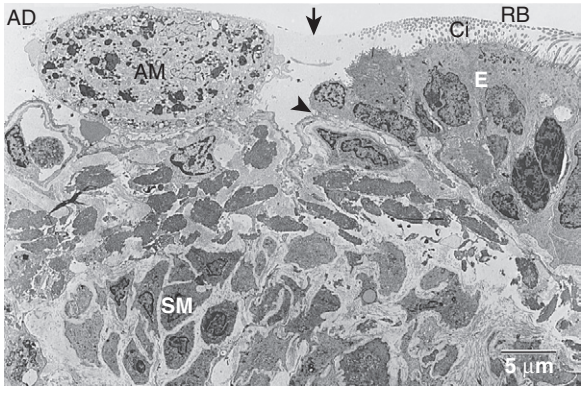

FIGURE 1-11 ■ The respiratory bronchiole (RB)-alveolar duct (AD) junction is demarcated by an abrupt transition (*arrowhead*) from low cuboidal epithelial cells (E) with cilia to squamous epithelial cells. Submerged in the lining liquid (*arrow*) are an alveolar macrophage (AM) and cilia (Ci). Airway smooth muscle cells (SM) extend to this level of the airway tree. (Human lung surgical specimen, transmission electron microscopy).

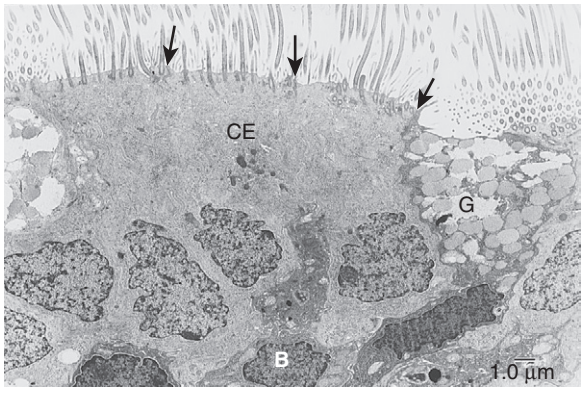

FIGURE 1-12 ■ Cells composing the bronchial epithelium are ciliated epithelial cells (CE), goblet cells (G), and basal cells (B). Goblet cells have abundant mucous granules in the cytoplasm and their apical surface is devoid of cilia. Basal cells, as their name indicates, are located along the abluminal portion of the lining epithelium, adjacent to the basal lamina. The *arrows* at the apical surface of the airway cells indicate the location of junctional complexes between contiguous epithelial cells. (Human lung surgical specimen, transmission electron microscopy.)

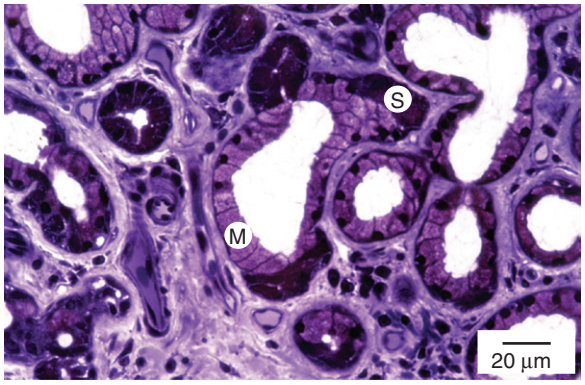

FIGURE 1-13 ■ High-power view shows the submucosal glands illustrated in Figure 1-7. These mixed, compound tubuloacinar glands contain mucus-secreting cells (M) and serous-secreting cells (S). The latter type form crescentic caps, or demilunes, over the ends of the acini. Mucous cells are the predominant glandular cell type.

TABLE 1-2. Airway Epithelial Cell and Glandular Epithelial Cell Products

MUCINS
MUC5AC
MUC5B
MUC7
RECEPTORS
TLRs (such as TLR1, 2, 3, 5, 6)
CHANNELS, TRANSPORTERS
CFTR
Connexins 26, 32, 40, 43
eNOS, iNOS
K^+ channels
Na^+ channels
Cl^- channels
Annexins
Muc 1
CC10 (Clara cells)
GLANDS
Neurotransmitters (e.g., cholinergic, adrenergic, peptidergic)
Inflammatory mediators (e.g., histamine, platelet-activating factor, eicosanoids)

CFTR, cystic fibrosis transmembrane regulator; eNOS, endothelial nitric oxide synthase; iNOS, inducible nitric oxide synthase; TLR, Toll-like receptors.

Trapping of foreign material, such as particulates or bacteria, is accomplished by mucins. Mucins are complex glycoproteins that form gels, exemplified by MUC5A. MUC5A is present in the lung of humans.[35,36] Other mucins (e.g., MUC5B, MUC7)[37,38] become expressed by airway epithelial cells in diseases, such a cystic fibrosis. In that disease, MUC5B is produced by airway epithelial cells.[39] Normally, MUC5B is produced by airway glandular cells[37] but its cell source is expanded in a variety of pulmonary diseases.

Glands are limited to the submucosa of the bronchi. Airway glands secrete water, electrolytes, and mucins into the lumen (Fig. 1-13; see also Fig. 1-7; Table 1-2). Studies of regulation of secretion in vivo and by explant culture systems in vitro have shown that release can be modulated by neurotransmitters, including cholinergic, adrenergic, and peptidergic transmitters,[40,41] and by inflammatory mediators such as histamine,[42] platelet-activating factor,[43] and eicosanoids.[44] Goblet cells, which are mucin-secreting epithelial cells, also are present at most airway levels (see Fig. 1-12). Goblet cells normally decrease in number peripherally and disappear at terminal bronchioles.[10,45] The disappearance of airway glands and goblet cells upstream of ciliated epithelial cells makes sense because that arrangement should minimize backflow of mucus into alveolar ducts and alveoli. Excessive mucin production results in airway obstruction by mucous plugs, especially in small airways. Mucin regulation is discussed in Chapter 11.

Lymphocytes are frequently seen intercalated between airway epithelial cells (Fig. 1-14; see also Fig. 1-10). These cytotoxic T lymphocytes undergo immunoglobulin A (IgA) class antibody responses.[46] T and B lymphocytes also accumulate in the lamina propria beneath the airway epithelium.[47]

Although most of inhaled foreign material and immunologic stimuli are carried up the airways by mucociliary action, some are cleared by the lymphatics (discussed at the end of this chapter). In addition, lymphoid tissue is located in the lungs. Patches are distributed along the tracheobronchial tree (see Fig. 1-7) and, to a lesser extent, along the blood vessels.[48,49] These patches apparently develop in response to antigenic stimulation because they are not present at birth and germ-free animals have little or no pulmonary lymphoid tissue.[48,49] Lymphocytes in these aggregates are principally B cells that express mainly IgA immunoglobulins.[47] The presence of lymphocytes along the airways provides a reminder that the respiratory system is constantly challenged by air-borne immunologic stimuli. The tracheobronchial lymphoid tissue, including bronchus-associated lymphoid tissue (BALT), appears to provide an important locus for both antibody-mediated and cell-mediated immune responses. Epithelial cells that line the airways and compose the airway glands are also important because of their expression of Toll-like receptors (TLRs; see Table 1-2), whose role is identification of pathogen-associated molecular patterns.[50] Activation of TLRs leads to downstream signaling cascades that are involved in mucin production, leukocyte recruitment, antimicrobial peptide production, wound repair, and vascular formation.[51-55]

Some of the other cells associated with the airways are smooth muscle cells, mast cells, basal cells, and Clara cells. Smooth muscle cells form circular bands around the airway epithelium as far peripherally as the respiratory bronchioles (see Fig. 1-7). Tone in the smooth muscle is altered by the autonomic nervous system and by mediators released from mast cells, inflammatory cells, and neuroendocrine cells. During normal breathing, slight tonic contraction of airway smooth

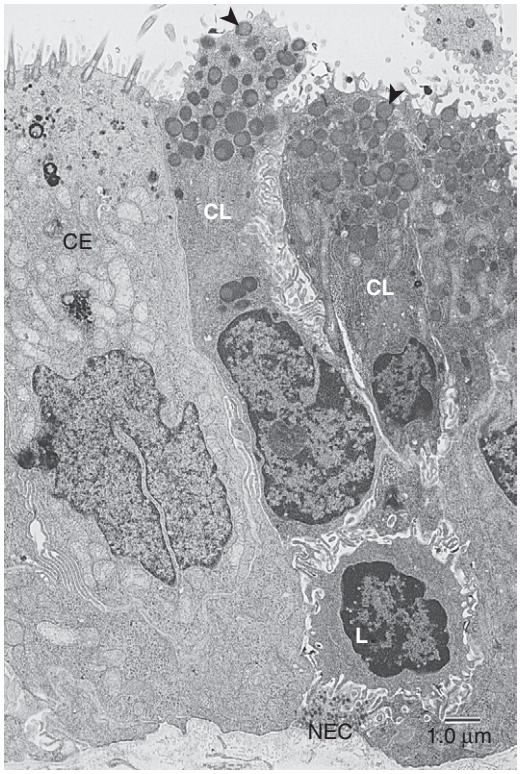

FIGURE 1-14 ■ The terminal airway epithelium consists mainly of ciliated epithelium (CE) and nonciliated, domed Clara cells (CL). Clara cells have the ultrastructural features of secretory cells; namely, they possess basally located rough endoplasmic reticulum, perinuclear Golgi apparatus, apically located smooth endoplasmic reticulum, and prominent membrane-bound granules (*arrowheads*). A lymphocyte (L) is intercalated among the epithelial cells. A small portion of a neuroendocrine cell (NEC) containing characteristic dense-cored vesicles is also visible at the base of the epithelial cells. (Human lung surgical specimen, transmission electron microscopy.)

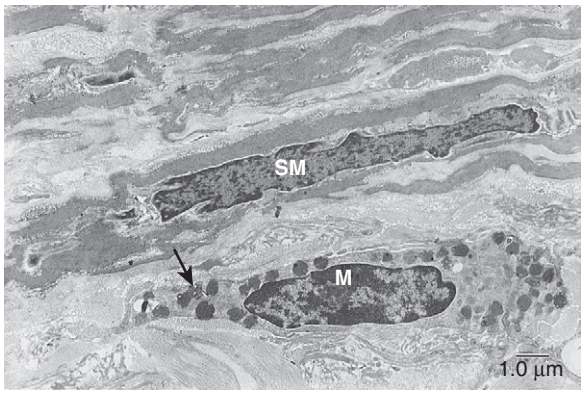

FIGURE 1-15 ■ Mast cell (M) located along an airway. The mast cell is adjacent to the airway smooth muscle cells (SM). Granules in mast cells demonstrate heterogeneous morphology, including whorled and scrolled contents (*arrow*). (Human lung surgical specimen, transmission electron microscopy.)

muscle cells and reflex contraction of the larger airways stiffen them against external compression, as may occur in forced expiration or coughing. The effector of these responses is the parasympathetic limb of the autonomic nervous system (vagus nerves). Excessive vagal stimulation results in severe contraction of airway smooth muscle and increases mucus secretion by submucosal glands, both of which limit airflow through conducting airways by decreasing airway lumen diameter.

Mast cells in the human lung contain membrane-bound secretory granules that are characteristically filled by scrolled, crystalline, or particulate inclusions (Fig. 1-15). These granules contain a host of inflammatory mediators, including histamine, proteoglycans, lysosomal enzymes, and metabolites of arachidonic acid.[56] Not only can these mediators induce bronchoconstriction, they can also stimulate mucous secretion and induce mucosal edema by increasing permeability of bronchial vessels. (For a discussion of specific airway diseases, see Section I, Chapters 38–42 and 44.)

Basal cells are located along the basal lamina of airways (see Fig. 1-12). These small epithelial cells have been classically thought to be precursor cells for other airway epithelial cells.[31,57] However, more recent experiments suggest that columnar secretory cells or Clara cells may also differentiate into ciliated epithelial cells following tissue injury.[58,59]

Clara cells are prominent in the terminal airways. Clara cells, interspersed among the ciliated epithelial cells, are nonciliated and have large apical granules (see Fig. 1-14).[60,61] They have at least four functions in the lung. One function is as progenitor cells for themselves and for ciliated epithelial cells.[62,63] Another function is xenobiotic metabolism that is effected by the cytochrome P-450 mono-oxygenase system.[64–67] A third function is secretion. Clara cells are a source of some of the surfactant apoproteins (SP-A, -B, and -D).[68–70] They also are a source of lipids, proteins (such as Clara cell 10kDa protein), glycoproteins, and modulators of inflammation (such as leukocyte protease inhibitor and trypsin-like protease).[71–73] A fourth function is fluid balance by influencing ion channels.[74,75]

Metabolic substrate is delivered to the trachea (and esophagus), main-stem bronchi and pulmonary vessels into the lung (see Fig. 1-5), as well as to the visceral pleura in humans by the bronchial (systemic) circulation.[45,76,77] Measurements of bronchial blood flow, by microsphere studies in animals, indicate that flow is 0.5% to 1.5% of cardiac output, predominantly to the large airways.[45,76,78–81] The bronchial capillaries form a network in the lamina propria, the submucosa, and external to the cartilage.[82] Venous blood from the trachea and large bronchi enters small bronchial veins, which drain into the azygos or hemiazygos veins. Thus, a substantial part of bronchial blood flow returns to the right side of the heart. Deeper in the lung, however, bronchial blood passes via short anastomotic vessels into the pulmonary venules, thus reaching the left side of the heart to contribute to the venous admixture. (The relationships among the bronchial, pulmonary, and systemic venous circulations are diagrammed in Figure 5-2.)

Bronchial Circulation

The bronchial circulation has enormous growth potential in contrast to the pulmonary circulation, which, after childhood, is unresponsive. In long-standing inflammatory and proliferative diseases, such as bronchiectasis or carcinoma, bronchial blood flow may be greatly increased.[76,83] Scar tissue and tumors larger than 1 mm in diameter receive their blood supply via the bronchial circulation.[84,85] The bronchial circulation is also the primary source of new vessels for repair of tissue after lung injury.

PULMONARY CIRCULATION

In humans, the pulmonary arterial circulation enters each lung at the hilum in a loose connective tissue sheath adjacent to the main bronchus (see Fig. 1-1). The pulmonary artery travels adjacent to and branches with each airway generation down to the level of the respiratory bronchiole (Fig. 1-16). The anatomic arrangements of the pulmonary arteries and the airways are a continual reminder of the relationship between perfusion and ventilation that determines the efficiency of normal lung function. Although the pulmonary veins also lie in loose connective tissue sheaths adjacent to the main-stem bronchus and pulmonary artery at the hilum, once inside the lung, they follow Miller's dictum that the veins will generally be found as far away from the airways as possible.[45] Peripherally, in the respiratory tissue, the pulmonary arteries branch out from the core of the terminal respiratory unit, whereas the veins occupy the surrounding connective tissue envelope (Fig. 1-17). Each small muscular pulmonary artery supplies a specific volume of respiratory tissue, whereas the veins drain portions of several such zones.

Considerable quantitative data about the pulmonary circulation are available for the human lung (Table 1-3).[86–88] Although most of the intrapulmonary blood volume is in the larger vessels down to approximately 500 μm diameter, nearly all of the surface area is in the smaller vessels. For example, the surface area of arterioles 20 to 500 μm diameter exceeds that of the larger vessels by a factor of two, and the maximal capillary surface area is 20 times that of all other vessels.

Because the vertical height of the lung at FRC is about 24 cm (see Fig. 1-2), the pressure within the pulmonary blood vessels varies by approximately 24 cm H_2O over the full height of the lung. Thus, if pulmonary arterial pressure is taken as 20 cm H_2O (15 mm Hg, 1.9 kPA)* at the level of the main pulmonary artery, which is about

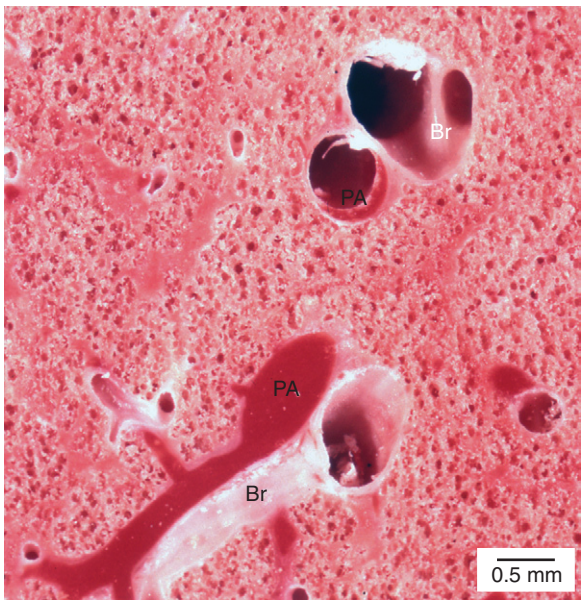

FIGURE 1-16 ■ Divisions of the pulmonary artery (PA) travel beside the bronchi (Br) out to the respiratory bronchioles. Thus, at all airway generations, there is an intimate relationship with the pulmonary arterial system. Note that the loose-binding (peribronchovascular) connective tissue sheaths are not distended, compared with the interstitial edema cuffs in Figure 1-5. (Frozen normal sheep lung, unstained.)

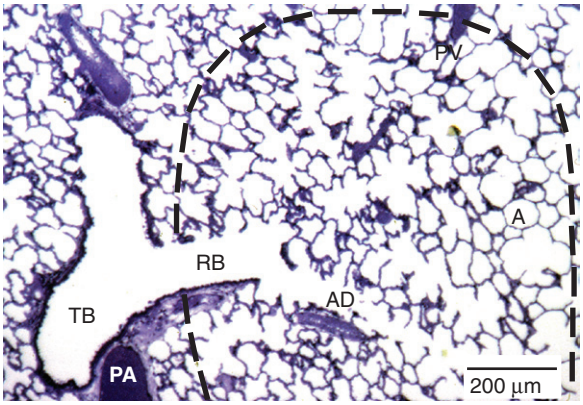

FIGURE 1-17 ■ The terminal respiratory unit (the physiologist's alveolus) consists of the alveoli (A) and alveolar ducts (AD) arising from a respiratory bronchiole (RB). Each unit is roughly spherical, as suggested by the *dashed outline*. Pulmonary venous vessels (PV) are peripherally located. TB identifies a terminal bronchiole. PA identifies a pulmonary artery. (Normal sheep lung, somewhat underinflated, 2-μm-thick glycol methacrylate section, light microscopy.)

TABLE 1-3. Quantitative Data on Intrapulmonary Blood Vessels in Humans

Vessel Class (with diameter)	Volume (mL)	Surface Area (m^2)	Reference No.
Arteries (>500 μm)	68	0.4	59
Arterioles (13–500 μm)	18	1.0	59
Capillaries (10 μm)	60–200	50–70	60
Venules (13–500 μm)	13	1.2	61
Veins (>500 μm)	58	0.1	61

*To convert from kPA to cm H_2O, multiply by 10.3; to mm Hg, multiply by 7.5.

halfway up the height of the lung, pressure in the pulmonary arteries near the top of the lung will be about 12 cm H_2O, whereas pressure in pulmonary arteries near the bottom will be about 36 cm H_2O. Pulmonary venous pressure, which is about 8 cm H_2O at the level of the pulmonary artery in midchest (left atrial pressure), would be −4 cm H_2O near the top of the lung and +20 cm H_2O at the bottom. In the normal lung, the blood volume is greater at the bottom because of increased luminal pressure, which expands those vessels and increases their volume. This effect of distention also decreases the contribution of the blood vessels at the bottom of the lung to total pulmonary vascular resistance.

Postnatally, the normal pulmonary circulation is a low-resistance circuit. The resistance is distributed somewhat differently, however, than in the systemic circulation. Although the pressure drop along the pulmonary capillaries is only a few centimeters of water (similar to the pressure drop in systemic capillaries), the pulmonary arterial and venous resistances are low, so a relatively larger fraction of the total pulmonary vascular resistance (35%–45%) resides in the alveolar capillaries at FRC.[89,90] (For further information about the pathophysiology of pulmonary circulation, see Chapter 4.)

Vasoactivity plays an important part in the local regulation of blood flow in relation to ventilation.[91,92] Because smooth muscle can be found in the pulmonary vessels on both the arterial and the venous side including pre- and postcapillary vessels,[93,94] any segment can contribute to active vasomotion.[95] In pathologic conditions, extension of vascular smooth muscle down to the capillary level may occur.[96,97]

Theoretically, gas exchange may occur through the thin wall of almost any pulmonary vessel. At normal alveolar oxygen tensions, however, little oxygen and carbon dioxide exchange occurs before the true capillaries.[98] Because of their small volume (see Table 1-3), pulmonary arterioles have rapid linear velocity of blood flow. As blood enters the vast alveolar wall capillary network, its velocity slows, averaging about 1000 μm/sec. Flow in the microcirculation is pulsatile because of the low arterial resistance.[99] Pulsations reach the microvascular bed from both the arterial and the venous sides. One sign of severe pulmonary hypertension is the disappearance of capillary pulsations.[100]

The capillary network is long and crosses several alveoli (Figs. 1-18 and 1-19) of the terminal respiratory unit before coalescing into venules. The vast extent of the capillary bed together with the length of the individual paths results in a reasonable transit time for red blood cells, during which gas exchange can occur. The anatomic estimate of approximately 0.5 to 1 second average transit time is essentially the same as that found by the carbon monoxide diffusing capacity method, in which one divides capillary blood volume by cardiac output to obtain mean capillary transit time.[101] In the normal lung, there is sufficient time for equilibrium between the oxygen and the carbon dioxide tensions in the alveoli and the erythrocytes in the pulmonary capillaries. Only under extreme stress (heavy exercise at low inspired oxygen tensions) or in severe restrictive lung disease are red blood cells predicted to pass through the microcirculation too fast too reach diffusion equilibrium.[102]

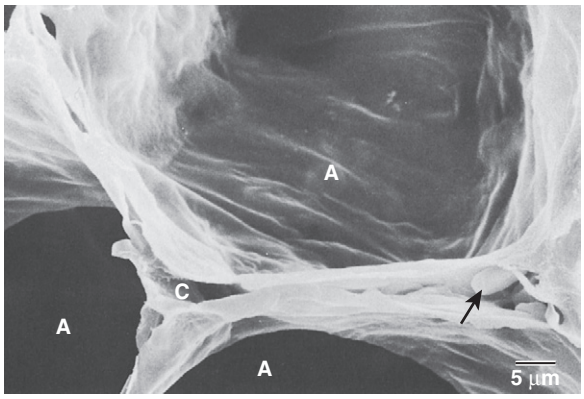

FIGURE 1-18 ■ An alveolar capillary (C) is split longitudinally along its path across three alveoli (A). The alveolar walls are flattened and the wall junctions are sharply curved because the lung is fixed in zone I conditions. Some red blood cells remain in the capillary at an alveolar corner (*arrow*). (Perfusion-fixed normal rat lung, P_{AW} = 30 cm H_2O; P_{PA} = 25 cm H_2O; P_{LA} = 6 cm H_2O; scanning electron microscopy.)

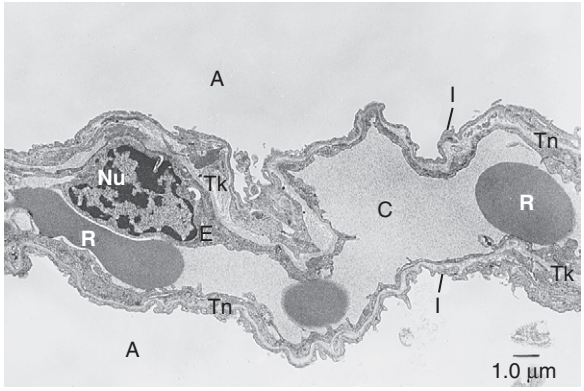

FIGURE 1-19 ■ The thick (Tk) and thin (Tn) sides of an alveolar capillary (C) change as the capillary crosses between alveoli (A). The basal laminae of the capillary endothelium and alveolar epithelium fuse in the thin regions. The nucleus (Nu) of an endothelial cell (E) is visible above a red blood cell (R). I, type I pneumonocyte. (Human lung surgical specimen, transmission electron microscopy.)

Normally, capillary blood volume is equal to or greater than stroke volume. Under normal resting conditions, the volume of blood in the pulmonary capillaries is well below its maximal capacity, however. Recruitment can increase this volume by a factor of about three. Thus, the normal capillary blood volume of 60 to 75 mL is one third of its capacity (200 mL) measured by quantitative histology.[5]

Anatomically, the pulmonary blood vessels can be divided into two groups in a manner similar to the connective tissue compartments. The vessels lying in the loose-binding connective tissue (peribronchovascular sheaths, interlobular septa) are extra-alveolar. Extra-alveolar vessels extend into the terminal respiratory units. Arteries as small as 100 μm in diameter have loose connective tissue sheaths. This is in contrast to the

bronchioles, which are tightly embedded in the lung framework from the membranous bronchioles (1 mm diameter) onward.

The blood vessels within the alveolar walls are embedded in the parenchymal connective tissue and are subject to whatever forces operate at the alveolar level. They are referred to as alveolar vessels in the sense that the effective hydrostatic pressure external to them is alveolar pressure. Not all of the alveolar vessels are capillaries, however. Small arterioles and venules, which bulge into the air spaces, may be affected by changes in alveolar pressure. Likewise, not all of the capillary bed is alveolar under all conditions.[103] The corner capillaries in the alveolar wall junctions are protected from the full effects of alveolar pressure by the curvature and alveolar air-liquid surface tension.[104] This may account for the fact that some blood flow through the lung occurs even under zone 1 condition, in which alveolar pressure exceeds both arterial and venous pressure.[105] One has to go several centimeters up into zone 1 to stop blood flow completely. (For a discussion of distribution of pulmonary blood flow and lung zones, see Chapter 4.)

An important question is whether the normal human lung contains connections between the pulmonary arteries and veins that permit some portion of pulmonary blood flow to bypass the capillary network. Such vessels may occur as congenital or pathologic developments.[106] In the normal lung, however, functioning short circuits probably do not exist. (Pathologic arteriovenous communications are discussed in Chapter 54.)

Pulmonary capillaries are lined by continuous (nonfenestrated) endothelial cells (see Fig. 1-19). These attenuated cells have an individual area of 1000 to 3000 μm^2 and an average volume of 600 μm^3.[107] These large, flat cells cover a surface area of about 130 m^2.[107] Other structural features of pulmonary capillary endothelial cells are the large number of plasmalemmal vesicles and small number of organelles (see Fig. 1-19). Despite having relatively few organelles, pulmonary capillary endothelial cells do have organelles involved in protein synthesis, such as endoplasmic reticulum, ribosomes and Golgi apparatus, and endocytosis (caveoli, multivesicular bodies, and lysosomes).[108] The endocytic apparatus appears to participate in receptor-mediated uptake and transport (transcytosis) of albumin, low density lipoproteins and thyroxin.[109–113] Another route for passage of solutes and water is between adjacent endothelial cells (transcellular transport). However, that passage route is restricted by specialized junctional complexes called tight junctions.[114,115]

Pulmonary Vascular Endothelial Cells

Specialized attributes of the pulmonary circulation's endothelial cells are the remarkable number of metabolic activities (Table 1-4). This is not to say that endothelial cells in other organs do not have similar activities. But the central position of the lung, through which the entire cardiac output passes, places extra responsibility and extra importance upon its endothelial cells.[116–118] For example, angiotensin I, bradykinin, and prostaglandin E_1 are almost completely inactivated in a single passage through the lungs. Pulmonary endothelial cells also express at least two subtypes of endothelin receptors (A and C).[119–121] Their expression coincides with rapid removal of endothelin, suggesting that the lung microcirculation participates in clearance of a potent vasoconstrictor peptide from the blood. Conversely, a potent vasodilator, nitric oxide, is generated locally in the lung, through expression of endothelial nitric oxide synthase.[122–128] A structural indication of a role for endothelial cells in regulation of vascular tone and reactivity is direct contacts between pulmonary endothelial cells in small arteries and veins and the surrounding smooth muscle cells. Such myoendothelial contacts had been described in the lungs of a number of small animals.[129–132] We have seen them in the human lung (Fig. 1-20). Although their functional importance is unknown, they may have some bearing on endothelial-dependent vasoactivity.[133]

In addition to gas exchange, the pulmonary circulation is involved in a number of other functions important to homeostasis. The pulmonary vascular bed serves as a capacitance reservoir between the right and the left sides of the heart. Sufficient blood resides in the pulmonary circulation to buffer changes in right ventricular output for two to three heartbeats. The lung is also a blood filter. The lung is likely to be frequently embolized by material from systemic vascular beds. For example, during intravascular coagulation or in processes involving platelet or neutrophil aggregation, the predominant site of sequestration is the lung. The main anatomic reason for this is that 75% of the total circulating blood

TABLE 1-4. Pulmonary Endothelial Cell Receptors

Albumin
Growth factors (e.g., fetal liver kinase-1, fibroblast growth factors)
Cytokines (e.g., tumor necrosis factor)
Platelet activating factor
Adhesion molecules (e.g., platelet endothelial cell adhesion molecule)
Adenosine
Adenosine triphosphate
β- and α-adrenergic
Endothelin
Dopamine
Muscarinic
Serotonin
Histamine
Angiotensin I and II
Bradykinin
Atrial natriuretic factor
Glucocorticoid
Insulin
Thrombin
Complement components (e.g., C3b, C1q)
Fc fragment

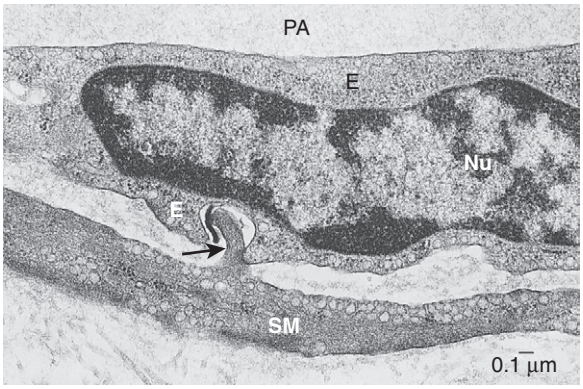

FIGURE 1-20 ■ A myoendothelial cell contact (*arrow*) is made between a pulmonary arteriolar (PA) endothelial cell (E) and a subjacent vascular smooth muscle cell (SM). The distribution and functional significance of such contacts is unknown. One potential role may be to facilitate delivery of endothelium-derived relaxing factor (EDRF) to smooth muscle cells. Nu, nucleus of the endothelial cell. (Human lung surgical specimen, transmission electron microscopy.)

volume is in the venous circuit, and the lung's microvascular bed is the first set of small vessels through which the venous blood flows. Moderate numbers of microemboli generally produce no detectable dysfunction because of the huge array of parallel pathways in the microcirculation. At most, microemboli temporarily block flow to a portion of or to an entire terminal respiratory unit. The fate of such emboli is not clear. Some are phagocytosed and removed into the lung tissue.[134] Some emboli can be degraded to small size, pass through into the systemic circulation, and be removed by the reticuloendothelial system. One example is the macroaggregated serum albumin used in lung-scanning procedures. (Further information about the pathophysiology of thromboembolic disorders is presented in Chapter 51.)

Endothelial cell phenotype in the lung is heterogeneous, with phenotypes that are site-specific. (reviewed by Garlanda and Dejana[135] and Gebb and Stevens[136]). A morphologic example of heterogeneity is the difference in lectin staining in the lung.[137] *Helix pomatia* binds to endothelial cells in pulmonary arteries, whereas *Griffonia simplicifolia* or *Glycine max* binds to endothelial cells in pulmonary microvessels in the rat lung. A functional example is endothelial nitric oxide protein localization, which is more evident in small pulmonary arterial vessels than in capillaries.[122–127] Presumably, the more evident localization reflects the functional role of nitric oxide in regulating pulmonary artery smooth muscle tone. Conversely, capillary endothelial cells appear to have more expression-activated leukocyte adhesion molecule message than arterial endothelial cells.[135,136] Greater expression by capillary endothelial cells may contribute to sequestration of leukocytes in the capillary bed during acute inflammatory reactions. Another endothelial cell function that is site-specific in the lung is Ca^{2+} transients that are induced by pressure elevations as little as 5 cm H_2O. The calcium transients occur in endothelial cells of pulmonary venular capillaries.[138] Moreover, Ca^{2+} oscillations occurred in a subset of endothelial cells. The oscillations are propagated to adjacent endothelial cells. Thus, the subset of Ca^{2+} oscillating cells are referred to as "pacemakers." Those findings indicate the presence of a sensitive endothelial response to pressure challenge in lung venular capillaries. The endothelial response may be relevant in the pathogenesis of pressure-induced lung microvascular injury.

TERMINAL RESPIRATORY UNITS

The "alveolus" of which the physician or pulmonary physiologist speaks is not the alveolus of the anatomist but what we have been referring to as the "terminal respiratory unit." The definition of *terminal respiratory unit* is all alveolar ducts, together with their accompanying alveoli, that stem from the most proximal (first) respiratory bronchiole (see Fig. 1-17). The terminal respiratory unit has both a structural and a functional existence and was first described by Hayek.[10] In the human lung, this unit contains approximately 100 alveolar ducts and 2000 alveoli. At FRC, the unit is approximately 5 mm in diameter, with a volume of 0.02 mL. In normal adult humans, there are about 150,000 such units in both lungs combined.[5] The acinus, an anatomic unit popular among pathologists, contains 10 to 12 terminal respiratory units.[139–141]

The functional definition of the terminal respiratory unit is that gas phase diffusion is so rapid that the partial pressures of oxygen and carbon dioxide are uniform throughout the unit. Diffusion is the name for a thermodynamic process by which molecules express their kinetic energy. Net diffusion occurs when there is a concentration difference of a substance between two volumes. Thus, oxygen in the alveolar duct gas will diffuse into the alveoli, because the incoming air has a higher oxygen concentration than the alveolar gas. Oxygen will also diffuse from the gas adjacent to the alveolar wall through the air-blood barrier into the red blood cells flowing in the capillaries (Fig. 1-21), where oxygen combines with hemoglobin. Carbon dioxide diffuses in the opposite direction. A key point in diffusion is that the process is much faster in the gas phase than in water. Thus, the terminal respiratory unit size is defined in part by the fact that gas molecules can diffuse and equilibrate anywhere within the unit more rapidly than they can diffuse through the membrane into the blood. The main problem is that the solubility of oxygen in water is low relative to its concentration in gas. Carbon dioxide is much more soluble in water, so it diffuses rapidly into the gas phase, even though the driving pressure for carbon dioxide diffusion is only one tenth that for oxygen entering the blood.

Demonstrating that diffusion is limiting in the normal lung is almost impossible, except during heavy exercise while breathing gas containing very low oxygen concentrations.[102] Even at that, it is not so much diffusion that is limiting, but the fact that the transit time of the red blood cells is reduced. Most disorders of alveolar-capillary block are really disorders of capillary blood volume and ventilation-perfusion inequalities.[142]

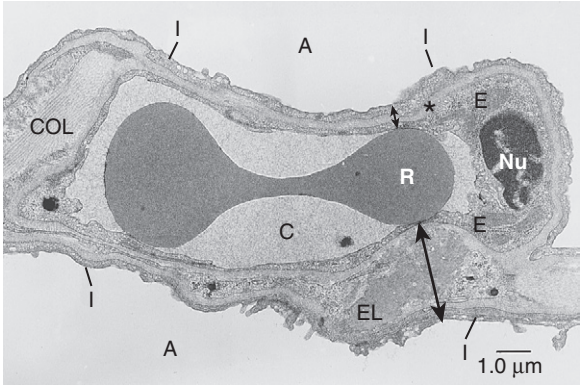

FIGURE 1-21 ■ Cross section of an alveolar wall shows the path for oxygen and carbon dioxide diffusion. The thin side of the alveolar wall barrier (*short double arrow*) consists of type I epithelium (I), interstitium (*) formed by the fused basal laminae of the epithelial and endothelial cells, capillary endothelium (E), plasma in the alveolar capillary (C), and finally, the cytoplasm of the red blood cell (R). The thick side of the gas exchange barrier (*long double arrow*) has an accumulation of elastin (EL), collagen (COL), and matrix that jointly separate the alveolar epithelium from the alveolar capillary endothelium. As long as the red blood cells are flowing, oxygen and carbon dioxide diffusion probably occur across both sides of the air:blood barrier. A, alveolus; Nu, nucleus of the capillary endothelial cell. (Human lung surgical specimen, transmission electron microscopy.)

All portions of the terminal respiratory unit participate in volume changes with breathing.[143,144] Thus, if a unit were to increase its volume from FRC, the alveolar gas that had been in the alveolar duct system would enter the expanding alveoli, together with a small portion of the fresh air. Most of the fresh air would remain in the alveolar duct system. This does not lead to any significant gradient of alveolar oxygen and carbon dioxide partial pressures because diffusion in the gas phase is so rapid that there would be equilibrium within a few milliseconds. But nondiffusible (suspended or particulate matter) would remain away from the alveolar walls and would be expelled in the subsequent expiration.[145] That explains why it is difficult to deposit particulates or aerosols on the alveolar walls and why large inspired volumes and breath-holding are important for obtaining efficient alveolar deposition.

The anatomic alveolus is not spherical. It is a complex geometric structure with flat walls and sharp curvatures at the junctions between adjacent walls (Fig. 1-22A). The most stable configuration is for three alveolar walls to join together, as in foams.[5] The resting volume of an alveolus is reached at minimal volume, which is 10% to 14% of TLC. When alveoli go below their resting volume, they must fold up because their walls have a finite mass

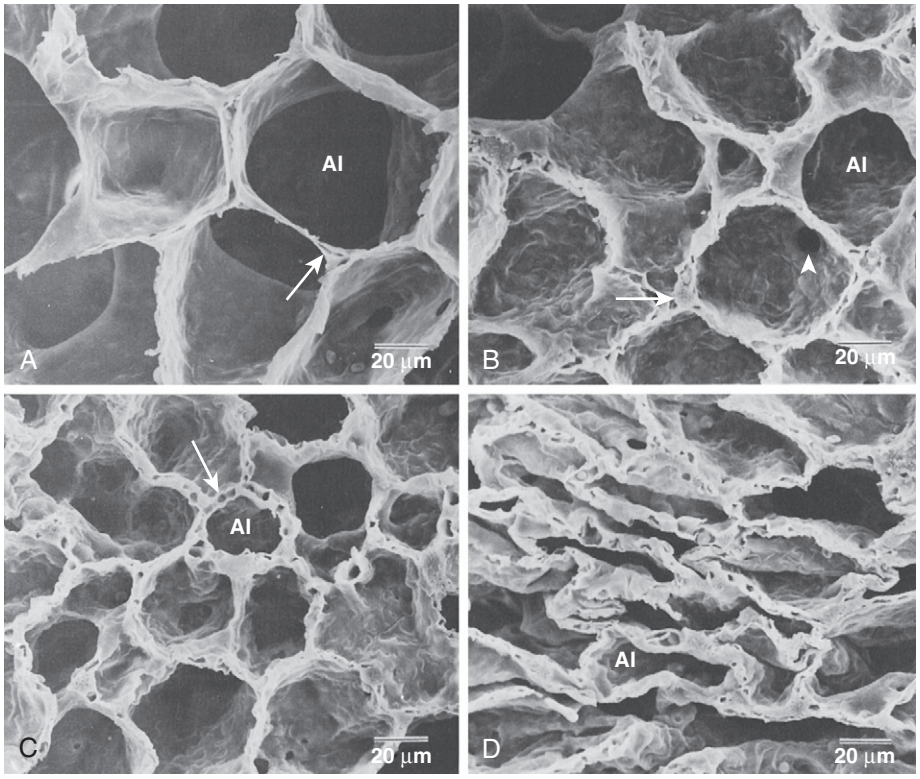

FIGURE 1-22 ■ Alveolar shape changes at representative points along the air deflation pressure-volume curve of the lung. The four micrographs are at the same magnification. The air deflation pressure points are as follows: **A,** 30 cm H_2O (total lung capacity; TLC); **B,** 8 cm H_2O (about 50% TLC); **C,** 4 cm H_2O (near functional residual capacity; FRC); and **D,** 0 cm H_2O (minimal volume). Vascular pressures are constant (P_{PA} = 25 cm H_2O and P_{LA} = 6 cm H_2O). Intrinsic alveolar shape (Al) is maintained from FRC to TLC (**C** through **A**). The alveolar walls are flat, and there is sharp curvature at the junctions between adjacent walls. Note the flat shape of the alveolar capillaries (*arrow*) at TLC (**A,** lung zone 1 conditions) compared with their round shape (*arrow*) at FRC (**C,** lung zone 3 conditions). The alveolar walls are folded and alveolar shape is distorted at minimal lung volume (**D**). The *arrow* in **B** identifies a type II pneumonocyte at an alveolar corner. (Perfusion-fixed normal rat lungs, scanning electron microscopy.)

(see Fig. 1-22D). Most of the work required to inflate the normal lung is expended across the air-liquid interface to overcome surface tension because the liquid-filled lung inflates at low pressure.[146]

The phenomenon of terminal respiratory unit, or alveolar stability, is confused because not only is air-liquid interfacial tension involved, but each flat alveolar wall is part of two alveoli and both must participate in any change. The phenomenon of atelectasis does not usually involve individual alveoli but rather relatively large units.[147]

The alveolar walls are composed predominantly of pulmonary capillaries. In the congested alveolar wall, the blood volume may be more than 75% of the total wall volume. Alveoli near the top of the lung show less filling of the capillaries than those at the bottom.[148,149] This affects regional diffusing capacity, which is dependent on the volume of red cells in the capillaries.

The transition from the cuboidal epithelium of the respiratory bronchiole to alveolar squamous epithelium is abrupt (see Fig. 1-11). Although Macklin[150] speculated that there is something special about the permeability of the bronchiole-alveolar epithelial junctions, no definitive difference has been demonstrated.[151] The controversy continues as to whether this region shows special permeability features.[152–154]

The pleomorphic nature of the alveolar epithelium and the light and electron microscopic structure of its constituent cells have been described many times and are only briefly summarized here. In normal mammals and other air-breathing species, including reptiles and amphibians, the alveolar epithelium is composed of small, cuboidal type II cells and large, flattened type I cells (Fig. 1-23). Type II cells outnumber type I cells (~15% vs. 8%–10% of total peripheral lung cells, respectively) but the type I cell accounts for about 90% to 95% of the alveolar surface area of the peripheral lung.[155] The two cell types have very different functions. In general, type II cells are specialized to be synthetic, secretory, and repair factories, whereas type I cells provide a large, thin cellular barrier specialized for gas exchange. Much more is known about the molecular functions of the type II cell than the type I cell. This is largely due to the availability of methods for isolating rodent and human type II cells in large numbers and high purity, allowing their molecular functions and responses to be studied in vitro.[156,157] Nonetheless, viable type I cells have also been isolated,[158,159] providing an opportunity to characterize their function more thoroughly.

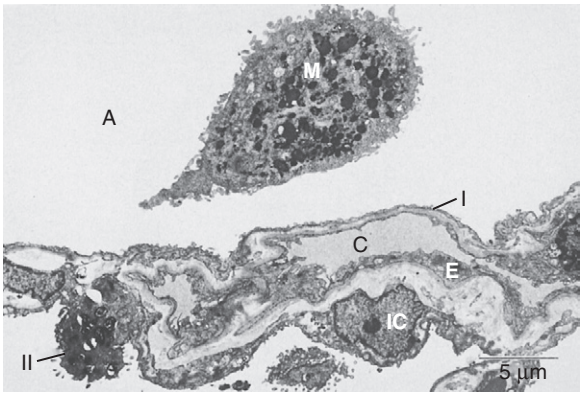

FIGURE 1-23 ■ The cells of the terminal respiratory unit are demonstrated in this micrograph. An alveolar macrophage (M) is located in an alveolus (A). These phagocytic cells are the air space scavengers; they are cleared either up the mucociliary escalator or into the interstitium. These cells can be activated to express and secrete cytokines, which may interact with other cells. Cells of the alveolar wall are the lining type I and II pneumonocytes (I and II, respectively) and the enclosed capillary (C), endothelial cells (E) and interstitial cells (IC). (Human lung surgical specimen, transmission electron microscopy.)

Type II Cell Structure

The typical (e.g., human, rodent) type II cell is a small (300 μm^3), cuboidal cell with short stubby apical microvilli (Fig. 1-24). Under normal conditions, type II cells attach via tight junctions to neighboring type I cells to form a relatively impermeable seal between alveolar air and connective tissue spaces. Although the cells express connexin proteins used to form gap junctions,[160] such junctions have not been consistently observed between type II and type I cells.

The distinguishing feature of a type II cell is its content of intracellular lamellar bodies, membrane-bound inclusions (diameter from <0.1–2.5 µm; mean, ~1 µm) composed of stacked layers of cell membrane–like material (see Fig. 1-24). These granules contain pulmonary surfactant and are composed of phospholipid species similar to those of lavaged surfactant.[161] The granules also contain various proteins, including surfactant proteins (SP) SP-A, SP-B, and SP-C but probably not SP-D, typical lysosomal enzymes, an H^+ transporter, a unique α-glucosidase, and other molecules.[162–164] The limiting membrane of the lamellar body contains an 180-kD ABC-type transporter likely to be involved in lipid transport and membrane movement.[165] Multivesicular bodies, organelles generally involved in endocytosis, are unusually abundant in type II cells, which also express the ABC-transporter membrane protein. Many types of studies indicate that multivesicular bodies are closely related to and participate in formation of lamellar bodies, probably by ferrying phospholipids, proteins, and other materials from synthetic sites within the cell, or after retrieval from alveoli. Kinetic studies suggest, for example, that SP-A in lamellar bodies is derived both directly from the intracellular synthetic pathway and from protein previously secreted by type II cells into alveoli.[166]

Lamellar bodies are secreted by classic mechanisms of calcium-dependent[167] membrane fusion and extrusion of the contents into the alveolar spaces, a process that has frequently been visualized microscopically. Type II cells also internalize and recycle surfactant lipids and proteins, but the cellular pathways are not well characterized in terms of participating organelles, signaling mechanisms, and general molecular regulation. Receptors have been tentatively identified that mediate reentry of surfactant proteins into type II cells, but there is not yet clear agreement about the nature and molecular characteristics of these molecules.

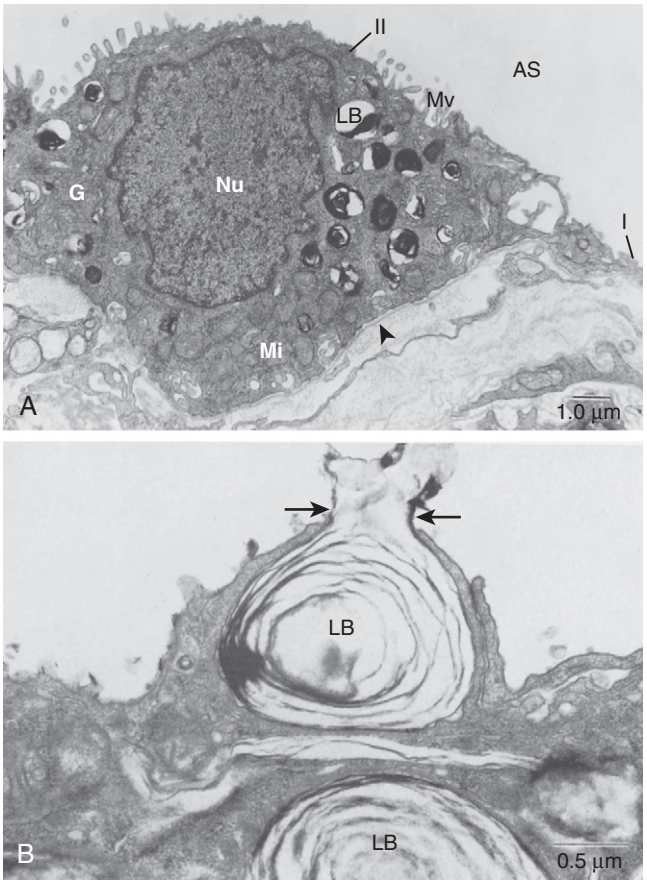

FIGURE 1-24 ■ **A,** Type II (or granular) pneumonocytes (II) are cuboidal epithelial cells that contain characteristic lamellar bodies (LB) in their cytoplasm and have stubby microvilli (Mv) that extend from the apical surface into the alveolar airspace (AS). Other prominent cytoplasmic organelles in type II pneumonocytes are mitochondria (Mi) and Golgi apparatus (G). Adjacent to the type II pneumonocyte is a process of a type I pneumonocyte (I). The abluminal surface of the epithelial cells rests on a continuous basal lamina (*arrowhead*). Nu, nucleus of a type II pneumonocyte. **B,** The apical region of a type II pneumonocyte has two lamellar bodies (LB), one of which has been fixed in the process of secretion by exocytosis (*arrows*). The lamellar osmiophilic bodies are believed to be the source of surface-active material (surfactant). Type II pneumonocytes are usually located in the alveolar corners (see Fig. 1-22B). (Human lung surgical specimen, transmission electron microscopy.)

Type II Cell Functions

The type II cell is the major synthesizing and secreting factory of the alveolar epithelium and implements epithelial repair via its ability to proliferate. The proteins reported to be produced by type II cells in vivo or in vitro are given in Table 1-5, a list that is undoubtedly incomplete. The general types of proteins produced by the type II cell include surfactant-associated proteins that affect surfactant recycling, adsorption of surfactant lipids to an air-liquid interface, and immunomodulatory functions; receptors for several growth factors and secretagogues; growth factors; enzymes; matrix proteins; epithelial mucins; and others. The presence in type II cells of various ion channels and transporters supports earlier evidence that type II cells are actively involved in fluid resorption and transepithelial water fluxes.[168] Type II cells have been reported to express some species of aquaporin (AQP-3, AQP-1),[169,170] water channels that may facilitate transepithelial fluid fluxes.

Some of the aforementioned proteins have been identified only in type II cells maintained in monolayer culture. The molecular behavior of type II cells in culture confounds interpretation of the source of this subgroup of proteins because, when isolated, the cells quickly change from a type II cell phenotype to a type I cell phenotype, as assessed by quantification of the messenger RNAs (mRNAs) of genes specific for either type II or type I cell phenotypes. This change in phenotype is well under way by 24 hours after the cells are isolated and plated and is typified by loss of SP-A, SP-B, and SP-C mRNAs and by induction of type I cell mRNAs, such as T1α, AQP-5, caveolin-1, and carboxypeptidase M.[171–178] Therefore, some of the proteins listed in Table 1-5 may belong in Table 1-6 (type I cell products). Verification of the cellular source of any protein therefore requires direct demonstration of the presence of that protein or its mRNA in cells in the intact lung.

Type II Cell Proliferation

Type II cells can proliferate and generate both new type II and new type I cells. The molecular signals required to initiate type II cell division are beginning to be identified. For example, several growth factors have been shown to trigger type II cell mitosis in vitro and in vivo. These include keratinocyte growth factor (FGF-7) and FGF-1, members of the fibroblast growth factor (FGF) family; hepatocyte growth factor (scatter factor); and heparin-binding epithelial growth factor (HB-EGF).[179–182] Type II cells therefore must express FGF receptors (R), of which there are several variants, as well as c-met, the receptor for hepatocyte growth factor. Activation of another receptor, EGF-R, which is expressed by airway epithelial cells, induces epithelial cell proliferation in sparse cultures; in dense cultures, contact inhibition occurs, cell division ceases, and the cells differentiate into goblet cells.[51] The downstream signaling events by which the ligand-activated receptors stimulate a mitotic event have not been well explored but are presumed to be similar to those in other cell types.

Type I Cell Structure

Scanning electron microscopic studies show that the morphology of a type I cell resembles that of a fried egg with a centrally placed nucleus and extensive, attenuated cytoplasmic processes that form a large surface area for gas exchange (see Fig. 1-22). The cytoplasmic processes of an individual cell may extend into several alveoli. The enormous surface area of these cells presents a logistical problem for transport of new proteins and other substances over long distances and most likely contributes to the vulnerability of the type I cell to injury.

TABLE 1-5. Type II Alveolar Epithelial Cell Products

SURFACTANT-ASSOCIATED PRODUCTS
SP-A
SP-B
SP-C
SP-D

RECEPTORS
EGF-R
ANP-R
Cannabinoid receptor
β-adrenergic-receptor
P2-purinergic receptor
FGF-R
c-met
IL-2-R
Type II MHC
gp 330 (megalin)
HDL receptors
Toll-like receptor 2
RAGE
SP-A, SP-B, SP-C receptors
TGFβ-R
IFN-γ-R
PDGF-R
PTHrP-R
GM-CSF-R

GROWTH FACTORS AND CYTOKINES
IL-8
VEGF
IL-1
Endothelin
CGRP
EGF
PDGF B chain
Monocyte chemotactic polypeptide-1
PTHrP

ENZYMES
Carbonic anhydrase II
Collagenase
Gelatinases A, B
γ-glutamyl transferase
CTP
Na^+/K^+-ATPase
Superoxide dismutase
Cytochrome P-450 enzymes
LAR-PTP
CD 44
Alkaline phosphatase
Lamellar body lysozyme
α-glucosidase
Aminopeptidase N
PKCδ
Plasminogen activator
Tripeptidyl tripeptidase I

MATRIX PROTEINS
Basement membrane components: laminin, fibronectin
Entactin
Tenascin
Type IV collagen

CHANNELS, TRANSPORTERS, OTHERS
CFTR
Connexins 26, 32, 40, 43
Adducin
α1-antitrypsin
Cysteine transporter
eNOS, iNOS
K^+ channels
Na^+ channels
Annexins
Aquaporin-1 (debated)
Aquaporin-3 (human)
Surfactant phospholipids
Leukotriene C4
α_1-acid glycoprotein
5-lipoxygenase activating protein
Muc 1
CC10
Plasminogen activator inhibitor
Tissue factor (procoagulant)
Pneumocin
Lipocortin 1
Maclura pomifera binding proteins
ABC transporter ABCA3
Cl^-/HCO_3^- exchanger AE2

ANP, atrial natriuretic peptide; CC10, clara cell secretory protein: uteroglobulin; CFTR, cystic fibrosis transmembrane regulator; CGRP, calcitonin gene–related peptide; CTP, phosphocholine cytidyltransferase; EGF, epidermal growth fastor; eNOS, endothelial nitric oxide synthase; FGF, fibroblast growth factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; HDL, high-density lipoprotein; IFN-γ, interferon-γ; IL, interleukin; iNOS, inducible nitric oxide synthase; LAR-PTP, leukocyte common antigen–protein tyrosine phosphatase; MHC, major histocompatibility complex; PDGF, platelet-derived growth factor; PKCδ, protein kinase Cδ; -R, receptor; RAGE, receptor for advanced glycation end products; SP, surfactant protein; TGF-β, transforming growth factor-β; VEGF, vascular endothelial growth factor.

Type I cells contain many small, non–clathrin-coated vesicles, or caveolae, open either to the alveolar lumen or interstitium or detached from the surface as small intracytoplasmic vesicles.[183] The number of vesicles appears to be variable, an observation that may have physiologic significance. Immunohistochemistry shows that the vesicles contain caveolin-1 protein.[184] Likewise, biochemical analyses[185] show high concentrations of caveolin protein and mRNA in lung where it is expressed mainly by type I and vascular endothelial cells. Caveolin-1 is scaffolding protein that organizes specialized membrane phospholipids and proteins into vesicles. Caveolin-1 can bind free cholesterol and modulate the efflux of cholesterol from the cell when intracellular concentrations rise,[186] and in other cell systems, its expression is tightly linked to the availability of free cholesterol. Caveolae appear to sequester into the vesicles growth factor receptors, signaling molecules such as G proteins, Ca^{2+} receptors and pumps, and in endothelial cells, endothelial nitric oxide synthase. The general effect of sequestration of receptors and signaling molecules into caveolae is to maintain them in a functionally quiescent state.[187] Little is known about the general role of caveolae in type I cells and, although it has been repeatedly tested, evidence that the vesicles move materials across the cell by transcytosis is scanty.

Type I Cell Functions

Proteins known to be expressed by type I cells are listed in Table 1-6. Most are not expressed by type II cells. Two notable attributes are that many of the proteins are apical membrane proteins and the list is very short. Earlier lectin-binding and histochemical studies showed that the chemical nature of the type I cell apical membrane differs markedly from that of type II cells and this concept is confirmed by the identification of novel type I cell proteins. The general functions of some of these marker proteins are known,[188] although not necessarily in the context of type I cell biology.

The type I cell protein aquaporin-5 (AQP-5) is of particular interest. In vitro studies show that isolated rodent type I cells expressing this water channel have remarkable water permeability, the highest known to date.[159]

TABLE 1-6. Type I Alveolar Epithelial Cell Products

RECEPTORS
RAGE
Purinergic receptor 4 (P2X4)
β_2-Adrenergic receptors
IGFR-2
ENZYMES
CP-M
γ-Glutamyl transferase
Lipid phosphatidic acid phosphatase
Na^+/K^+-ATPase
CHANNELS, TRANSPORTERS, OTHERS
T1α
Caveolin-1
ICAM-1
Aquaporin-5
Aquaporin-4 (human lung)
eNaC
P-glycoprotein
Eotaxin
Plasminogen activator inhibitor 1
$p15^{INK4B}$
VAMP-2
gp 60
Connexins 43,46

CP-M, carboxypeptidase M; eNaC, epithelial sodium channel; gp, glycoprotein; ICAM-1, intracellular adhesion molecule-1; IGFR-2, insulin-like growth factor receptor-2; INK4B, cyclin-dependent kinase 4 inhibitor 2B; RAGE, receptor for advanced glycation end products; VAMP-2, vesicle-associated membrane protein-2.

The cells also express epithelial Na^+ channels and membrane Na^+/K^+-ATPase.[189,190] These observations collectively imply that type I cells may play a major role in pulmonary water fluxes, although this has not yet been directly shown. AQP-5 may not be critical for certain functions related to fluid fluxes because null mutations in the murine AQP-5 gene do not interfere with clearance of edema fluid or fetal lung fluid at birth.[191] In type I cells, ICAM-1, regulated as a differentiation gene rather than by inflammatory mediators, is believed to facilitate alveolar macrophage activation and motility.[192] The physiologic function of type I cell carboxypeptidase M is not known but may be to activate or degrade substrates such as EGF, bradykinin, enkephalins, and other molecules as it does elsewhere.[193] Null mutations in the T1α gene interfere with development of normal alveoli in fetal mice and result in fatal respiratory failure within minutes after birth.[194]

Type I Cell Proliferation

Although it has not been directly tested and proven, type I cells are believed to be incapable of cell division, relying on type II cell progeny for normal turnover and replacement of injured cells.[195]

Relationship between Type II and Type I Cells In Vivo and In Vitro

Early studies demonstrated that, during postinjury repair, postmitotic progeny of type II cells differentiate into type I cells with normal morphology, a process that is also presumed to occur during the normal turnover of type I cells. The in vitro relationships are more complex. When cultured, highly purified type II cells, which are mitotically quiescent, rapidly cease expression of type II cell marker genes, such as SP-A, SP-B, and SP-C, and initiate expression of type I cell genes. If the cells are maintained in the presence of keratinocyte growth factor, in autologous serum, or with a cuboidal shape, type II cell gene expression is maintained and type I cell genes are suppressed. The cells can be manipulated to express either phenotype reversibly. Very little is known about the molecular regulation of either of these two phenotypes (i.e., sets of cell-specific genes) or about the molecular switch or switches that mediate the dramatic changes in expression patterns. Whether reversibility of phenotype (transdifferentiation of type I cells into type II cells) can occur in normal or injured lung in vivo is unknown.

INNERVATION

Innervation of the human lung consists of afferent and efferent pathways.[196–199] The sensory pathways originate in relation to the airway epithelium, submucosa, interalveolar septa, and smooth muscle. Fibers of this pathway include myelinated, slowly adapting stretch receptors (Hering-Breuer reflex) and irritant receptors but most are unmyelinated, slow-conducting C fibers located in the terminal respiratory units, either along the bronchioles or within the alveolar walls (Fig. 1-25). Much speculation has been made about the function of C fibers since Paintal first suggested that they played a role in sensing parenchymal connective tissue distortion, as during pulmonary vascular congestion and interstitial edema.[200–203] The afferent fibers travel in the vagus nerves and terminate in the vagal nuclei in the medulla oblongata.

Determination of the complete distribution of the mucosal sensory nerve endings has been hampered by the lack of dependable morphologic methods for the identification of intraepithelial sensory axons. Ultrastructural techniques have shown that axons, when found, resemble known sensory endings in other organs. The axons are small (<1 μm in diameter), electron-lucent, and contain microtubules and smooth endoplasmic reticulum.[204]

Submucosal sensory nerve endings, in contrast, are more reliably identifiable because the axon can be stained with methylene blue or silver nitrate. Furthermore, studies of axonal transport indicate that the peripheral processes of sensory ganglia project to the submucosa.[205] Ultrastructural observations of these fibers reveal axonal terminals containing numerous membra-

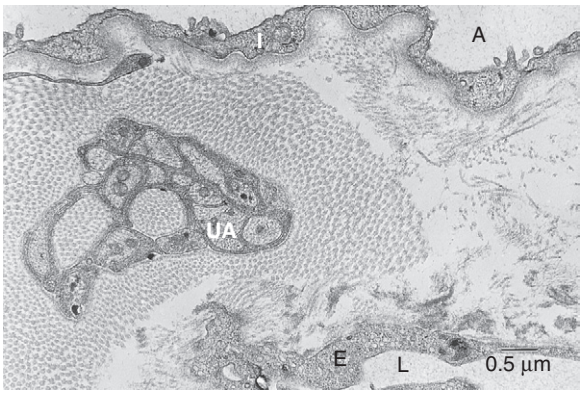

FIGURE 1-25 ■ Unmyelinated axons (UA) known as C-fibers are shown situated in the interstitium of a respiratory bronchiole, between a type I pneumonocyte (I) lining an alveolus (A) and an initial lymphatic (L). Although the presence of small clear vesicles is suggestive of cholinergic (autonomic) axons, unequivocal identification as either motor or sensory fibers is not possible in random thin sections. E, lymphatic endothelial cell. (Human lung surgical specimen, transmission electron microscopy.)

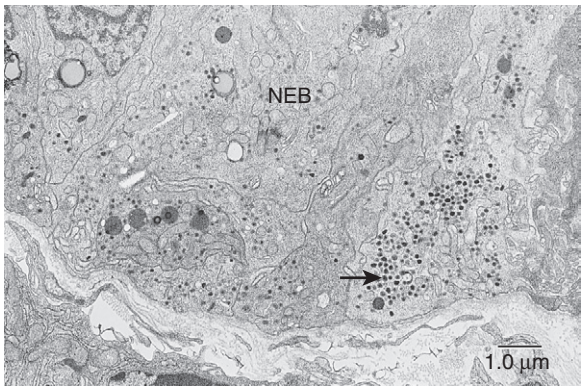

FIGURE 1-26 ■ Neuroepithelial body (NEB) located in a peripheral airway. Neuroepithelial bodies contain aggregates of neuroendocrine cells. A characteristic ultrastructural feature of neuroendocrine cells is the presence of small (0.1-0.3 μm in diameter) dense-cored vesicles in their cytoplasm (*arrow*). Each dense-cored vesicle is bounded by a unit membrane. (Human lung surgical specimen, transmission electron microscopy.)

nous inclusions and mitochondria, which are characteristic of mechanoreceptors.

The motor pathways reach the lung through the sympathetic and parasympathetic nervous systems. Preganglionic contributions to the sympathetic nerves arise from the upper four or five thoracic paravertebral ganglia, whereas the preganglionic parasympathetic nerves originate in the brain-stem motor nuclei associated with the vagus nerves. Postganglionic sympathetic nerve fibers terminate near airways, vascular smooth muscle cells, and submucosal glands. Postganglionic parasympathetic fibers extend from ganglia mainly located external to the smooth muscle and cartilage. Some submucosal ganglia exist, but they are generally smaller and have fewer neurons.

Mucosal motor nerve endings also exist.[206] Characteristic ultrastructural features are axonal profiles containing many small, agranular vesicles and few mitochondria. Unfortunately, the source and function of these axons is unknown. A goblet cell secretomotor role is doubtful because goblet cells in isolated epithelial strips do not secrete glycoproteins when bathed in drugs that mimic neurotransmitters.[207] Alternatively, a likely role may be release of mucus by direct response to mechanical and chemical signals. Another effector role of nerves in the lung is epithelial ion transport, a process that is stimulated by catecholamines,[208] acetylcholine,[209] and neuropeptides.[210] This role is further supported by the presence of α-adrenergic, β-adrenergic, and muscarinic receptors throughout the airway epithelium.[211]

Submucosal tracheal gland efferent nerve endings consist of cholinergic, adrenergic, and peptidergic axonal profiles.[212,213] Discrimination among these axonal types is partially aided by their ultrastructural appearance: cholinergic axons have small, agranular vesicles; adrenergic axons have small, dense-cored vesicles; peptidergic axons have many large, dense-cored vesicles. One must realize, however, that these descriptive definitions are not absolutely reliable.

Cholinergic, adrenergic, and peptidergic nerve endings are present around tracheal glands and do not show patterns of selective innervation density between serous and mucous cells.[211] Serous and mucous granule secretion is stimulated more by muscarinic than by adrenergic agents. Peptidergic agents, such as vasoactive intestinal peptide, have species-specific excitatory or inhibitory effects on glandular secretion.[214,215]

The lung also contains a component of the diffuse neuroendocrine system (APUD [amine uptake and decarboxylation] system).[216,217] This system is composed of single neuroendocrine cells and clusters of such cells, known as neuroepithelial bodies, distributed along the airway epithelium out to the region of alveolar ducts.[218–221] The neuroepithelial bodies are preferentially located at airway bifurcations. Pulmonary neuroendocrine cells are ultrastructurally characterized by dense-cored vesicles in their cytoplasm (Fig. 1-26). The dense-cored vesicles are considered to be the storage sites of amine hormones (serotonin, dopamine, norepinephrine) and peptide hormones (bombesin, calcitonin, leu-enkephalin).[222] Neurons are also associated with the airway epithelial and the neuroendocrine cells; they appear to be the storage sites for vasoactive intestinal peptide[222,223] and substance P.[224,225]

Despite the growing recognition that a diffuse neuroendocrine system is located in the lung, we do not understand its normal functional role, although one postulate is that these cells release hormones that affect smooth muscle. For example, hypercapnia and acute alveolar hypoxia in newborn rabbits cause the airway neuroendocrine cells to degranulate.[226,227] Thus, neuroendocrine cells may act as peripheral chemoreceptors.

AIRSPACE MACROPHAGES, LYMPHATICS, LYMPHOID TISSUE, AND INNATE IMMUNITY

The clearance of particulate matter impinging on the alveolar surfaces is dependent on the slow turnover and movement of the alveolar surface liquid, as well as on the phagocytic function of the macrophages and the clearance function of the pulmonary lymphatics.[228,229] The majority of the macrophages that reach the terminal airways (see Figs. 1-11 and 1-23) are expelled with the surface film as it is pulled up onto the mucociliary escalator. Some macrophages penetrate into the lung interstitium and can be seen as deposits of pigment within interstitial foci. Alveolar macrophages actively express and secrete cytokines, such as tumor necrosis factor-α and transforming growth factor-α.

Lymphatics of the lung have been subdivided into two principal groups based on their location: a superficial plexus and a deep plexus.[10,45,196,230] The superficial plexus is located in the connective tissue of the visceral pleura. This plexus is prominent in the human lung.[10,45,196] Lymphatics of the deep plexus are situated in the peribronchovascular connective tissue sheaths of the lung. Both plexuses are made up of initial and collecting lymphatics, and communications exist between the two plexuses.[10,45,153,196] Lymphatics in the deep plexus are distributed around the airways, extending peripherally to the respiratory bronchioles and next to branches of the pulmonary arteries and veins.[10,45,153,196] Lymphatics are not in the alveolar walls. Lymph is propelled centripetally toward the lung's hilum or pulmonary ligament to reach regional lymph nodes. In the human, pulmonary lymph flows to extrapulmonary lymph nodes located around the primary bronchi and trachea.[10,45,196]

KEY POINTS

- The primary function of the lung is ventilation-perfusion matching such that gas exchange between alveolar air and alveolar capillary blood is efficient.
- The anatomic arrangements of the pulmonary arteries beside the airways are a reminder of the relationship between perfusion and ventilation that determines the efficiency of normal lung function.
- The major physical problem of gas exchange is the slowness of oxygen diffusion through water. Thus, the alveolar walls must be extremely thin. Because of that thinness, the thickness of the red blood cell forms a substantial portion of the air-blood diffusion pathway.
- The airways form the connection between the outside world and the terminal respiratory units so the airways are central importance to our understanding of lung function in health and disease.
- Most airway resistance resides in the upper airways and bronchi.
- The cellular complexity of the airways is indicated by the nearly 50 distinct cell types in the lung, at least 12 of which are epithelial cells on the airway surface.
- Smooth muscle cells form circular bands around the airway epithelium as far peripherally as the respiratory bronchioles. Tone in the smooth muscle is altered by the autonomic nervous system and by mediators released from mast cells, inflammatory cells, and neuroendocrine cells.
- A relatively large fraction of the total pulmonary vascular resistance (35%–45%) resides in the alveolar capillaries at FRC.
- Because smooth muscle can be found in the pulmonary vessels on both the arterial and the venous side down to pre- and postcapillary vessels, any segment can contribute to active vasomotion and therefore pulmonary vascular resistance.
- Normally, capillary blood volume is equal to or greater than stroke volume. Thus, under normal resting conditions, the volume of blood in the pulmonary capillaries is well below its maximal capacity. Recruitment can increase capillary blood volume threefold.
- Specialized attributes of the pulmonary circulation's endothelial cells are the remarkable number of metabolic activities.
- Alveolar type II cells outnumber type I cells (~15% vs. 8%–10% of total peripheral lung cells, respectively) but the type I cell accounts for about 90% to 95% of the alveolar surface area of the peripheral lung.
- The type II cell is the major synthesizing and secreting factory of the alveolar epithelium and implements epithelial repair via its ability to proliferate.

- The type I cell may play a major role in pulmonary water flux, as well as activate or degrade vasoactive substrates.
- Sensory pathways in the lung originate in relation to the airway epithelium, submucosa, interalveolar septa, and smooth muscle.
- Motor pathways reach the lung through the sympathetic and parasympathetic nervous systems.
- The clearance of particulate matter impinging on the alveolar surfaces is dependent on the slow turnover and movement of the alveolar surface liquid, mucins, as well as on the phagocytic function of the macrophages and the clearance function of the pulmonary lymphatics.

References

1. Agostoni E, Miserocchi G, Bonanni MV: Thickness and pressure of the pleural liquid in some mammals. Respir Physiol Neurobiol 6:245–256, 1969.
2. Albertine KH, Wiener-Kronish JP, Bastacky J, Staub NC: No evidence for mesothelial cell contact across the costal pleural space of sheep. J Appl Physiol 70:123–134, 1991.
3. Staub NC: Pulmonary edema. Physiol Rev 54:678–811, 1974.
4. Armstrong JD, Gluck EH, Crapo RO, et al: Lung tissue volume estimated by simultaneous radiographic and helium dilution methods. Thorax 37:676–679, 1982.
5. Weibel ER: Morphometry of the Lung. New York: Academic Press, 1963.
6. Crapo JD: Morphometric characteristics of cells in the alveolar region of mammalian lungs. Am Rev Respir Dis 128:S42–S46, 1983.
7. Glazier JB, Hughes JMB, Maloney JE, West JB: Vertical gradient of alveolar size in lungs of dogs frozen intact. J Appl Physiol 23:694–705, 1967.
8. Comroe JH Jr. Physiology of Respiration (2nd ed). Chicago: Year Book, 1974.
9. Forster RE: Exchange of gases between alveolar air and pulmonary capillary blood: Pulmonary diffusing capacity. Physiol Rev 37:391–452, 1957.
10. Hayek H: The Human Lung. New York: Hafner, 1960.
11. Young CD, Moore GW, Hutchins GM: Connective tissue arrangement in respiratory airways. Anat Rec 198:245–254, 1980.
12. Macklin CC: Transport of air along sheaths of pulmonic blood vessels from alveoli to mediastinum. Arch Intern Med 64:913–926, 1939.
13. Gee MH, Havill AM: The relationship between pulmonary perivascular cuff fluid and lung lymph in dogs with edema. Microvasc Res 19:209–216, 1980.
14. Brody JS, Vaccaro C: Postnatal formation of alveoli: Iinterstitial events and physiologic consequences. Fed Proc 38:215–223, 1979.
15. Kaplan NP, Grant MM, Brody JS: The lipid interstitial cell of the pulmonary alveolus: Age and species differences. Am Rev Respir Dis 132:1307–1312, 1985.
16. Horowitz AL, Crystal RG: Content and synthesis of glycosaminoglycans in the developing lung. J Clin Invest 56:1312–1318, 1975.
17. Ehrich K: Proteoglycan synthesis by rat lung cells cultured *in vitro*. J Biol Chem 256:73–80, 1981.
18. Sannes PL, Khosla J, Peters BP: Biosynthesis of sulfated extracellular matrices by alveolar type II cells increases with time in culture. Am J Physiol 273:L840–L847, 1997.
19. Sannes PL, Khosla J, Li CM, Pagan I: Sulfation of extracellular matrices modifies growth factor effects on type II cells on laminin substrata. Am J Physiol 275:L701–708, 1998.
20. Gallagher JT: Heparan sulfate: Growth control with a restricted sequence menu. J Clin Invest 108:357–361, 2001.
21. Allen BL, Filla MS, Rapraeger AC: Role of heparan sulfate as a tissue-specific regulator of FGF-4 and FGF receptor recognition. J Cell Biol 155:845–858, 2001.
22. Esko JD, Selleck SB: Order out of chaos: Assembly of ligand binding sites in heparan sulfate. Annu Rev Biochem 71:435–471, 2002.
23. Frevert CW, Kinsella MG, Vathanaprida C, et al: Binding of interleukin-8 to heparan sulfate and chondroitin sulfate in lung tissue. Am J Respir Cell Mol Biol 28:464–472, 2003.
24. Smits NC, Robbesom AA, Versteeg EM, et al: Heterogeneity of heparan sulfates in human lung. Am J Respir Cell Mol Biol 30:166–173, 2004.
25. Frevert CW, Sannes PL: Matrix proteoglycans as effector molecules for epithelial cell function. Eur Respir Rev 14:137–144, 2005.
26. Kajikawa O, Frevert CW, Lin SM, et al: Gene expression of Toll-like receptor-2, Toll-like receptor-4, and MD2 is differentially regulated in rabbits with *Escherichia coli* pneumonia. Gene 344:193–202, 2005.
27. Horsfield K, Cumming G: Morphology of the bronchial tree in man. J Appl Physiol 24:373–383, 1968.
28. Klingele TG, Staub NC: Terminal bronchiole diameter changes with volume in isolated, air-filled lobes of cat lung. J Appl Physiol 30:224–227, 1971.
29. Bastacky J, Hayes TL, Schmidt BV: Lung structure as revealed by microdissection. Am Rev Respir Dis 128:S7–S13, 1983.
30. Weibel ER. The Pathway for Oxygen. Structure and Function of the Mammalian Respiratory System. Cambridge: Harvard University Press, 1984.
31. Breeze RG, Wheeldon EB: The cells of the pulmonary airways. Am Rev Respir Dis 116:705–777, 1977.
32. Greenwood MF, Holland P: The mammalian respiratory tract surface. A scanning electron microscopic study. Lab Invest 27:296–304, 1972.
33. Gumbiner B: Structure, biochemistry and assembly of epithelial tight junctions. Am J Physiol 253:C749–C758, 1987.
34. Schneeberger EE, McCarthy KM: Cytochemical localization of Na^+-K^+-ATPase in rat type II pneumocytes. J Appl Physiol 60:1584–1589, 1986.
35. Hovenberg HW, Davies JR, Carlstedt I: Different mucins are produced by the surface epithelium and the submucosa in human trachea: Iidentification of MUC5AC as a major mucin from the goblet cells. Biochem J 318:319–324, 1996.
36. Ordonez CL, Khashayar R, Wong HH, et al: Mild and moderate asthma is associated with airway goblet cell hyperplasia and abnormalities in mucin gene expression. Am J Respir Crit Care Med 163:517–523, 2001.
37. Sharma P, Dudus L, Nielsen PA, et al: MUC5B and MUC7 are differentially expressed in mucous and serous cells of submucosal glands in human bronchial airways. Am J Respir Cell Mol Biol 19:30–37, 1998.
38. Chen Y, Zhao YH, Di YP, Wu R: Characterization of human mucin 5B gene expression in airway epithelium and the genomic clone of the amino-terminal and 5′-flanking region. Am J Respir Cell Mol Biol 25:542–553, 2001.
39. Burgel PR, Montani D, Danel C, et al: A morphometric study of mucins and small airway plugging in cystic fibrosis. Thorax 62:153–161, 2007.
40. Leikauf GD, Ueki IF, Nadel JA: Autonomic regulation of viscoelasticity of cat tracheal gland secretions. J Appl Physiol 56:426–430, 1984.

41. Paul A, Picard J, Mergey M, et al: Glycoconjugates secreted by bovine tracheal cells in culture. Arch Biochem Biophys 260:75–84, 1988.
42. Shelhamer JH, Marom Z, Kaliner M: Immunologic and neuropharmacologic stimulation of mucous glycoprotein release from human airways *in vitro*. J Clin Invest 66:1400–1408, 1980.
43. Adler KB, Schwarz JE, Anderson WH, Welton AF: Platelet activating factor stimulates secretion of mucin by explants of rodent airways in organ culture. Exp Lung Res 13:25–43, 1987.
44. Maron Z, Shelhamer JH, Kaliner M: Effects of arachidonic acid, monohydroxyeicosatetraenoic acid and prostaglandins on the release of mucous glycoproteins from human airways *in vitro*. J Clin Invest 67:1695–1702, 1981.
45. Miller WS. The Lung (2nd ed). Springfield, IL: Charles C. Thomas; 1947.
46. Bienenstock J: The lung as an immunological organ. Am Rev Respir Dis 35:49–62, 1984.
47. McDermott MR, Befus AD, Bienenstock J: The structural basis for immunity in the respiratory tract. Int Rev Exp Pathol 23:47–112, 1982.
48. Bienenstock J, Johnston N, Perey DYE: Bronchial lymphoid tissue. I. Morphologic characteristics. Lab Invest 28:686–692, 1973.
49. Bienenstock J, Johnston N, Perey DYE: Bronchial lymphoid tissue. II. Morphologic characteristics. Lab Invest 28:93–98, 1973.
50. Sha Q, Truong-Tran AQ, Plitt JR, et al: Activation of airway epithelial cells by toll-like receptor agonists. Am J Respir Cell Mol Biol 31:358–364, 2004.
51. Takeyama K, Dabbagh K, Lee HM, et al: Epidermal growth factor system regulates mucin production in airways. Proc Natl Acad Sci U S A 96:3081–3086, 1999.
51a. Burgel P-R, Nadel JA: Epidermal growth factor receptor-mediated immune responses and their roles in airway diseases. Eur Respir J 32:1068–1081, 2008.
52. Tjabringa GS, Aarbiou J, Ninaber DK, et al: The antimicrobial peptide LL-37 activates innate immunity at the airway epithelial surface by transactivation of the epidermal growth factor receptor. J Immunol 171:6690–6696, 2003.
53. Koff JL, Shao MX, Kim S, et al: *Pseudomonas* lipopolysaccharide accelerates wound repair via activation of a novel epithelial cell signaling cascade. J Immunol 177:8693–8700, 2006.
54. Nakanaga T, Nadel JA, Ueki IF, et al: Regulation of interleukin-8 via an airway epithelial signaling cascade. Am J Physiol 292:L1289–L1296, 2007.
55. Koff JL, Shao MX, Ueki IF, Nadel JA: Multiple TLRs activate EGFR via a signaling cascade to produce innate immune responses in airway epithelium. Am J Physiol 294:L1068–L1075, 2008.
56. Peters SP, Schulman ES, Dvorak AM. Mast cells. *In* Massaro D (ed): Lung Biology in Health and Disease. Lung Cell Biology. New York: Marcel Dekker, 1989, pp 345–399.
57. Lane BP, Gordon R: Regeneration of rat tracheal epithelium after mechanical injury. I. The relationship between mitotic activity and cellular differentiation. Proc Soc Exp Biol Med 145:1139–1144, 1974.
58. Keenan KP, Combs JW, McDowell EM: Regeneration of hamster tracheal epithelium after mechanical injury. I. Focal lesions: Quantitative morphologic study of cell proliferation. Virchows Arch B Cell Pathol Incl Mol Pathol 41:193–214, 1982.
59. Hook GR, Bastacky J, Conhaim RL, et al: A new method for pulmonary edema research: Scanning electron microscopy of frozen-hydrated edematous lung. Scanning 9:71–79, 1987.
60. Plopper CG, Hill LH, Mariassy AT: Ultrastructure of the nonciliated bronchiolar epithelial (Clara) cell of mammalian lung. III. A study of man with comparison of 15 mammalian species. Exp Lung Res 1:171–180, 1980.
61. Plopper CG, Hyde DM, Buckpitt AR: Clara cells. *In* Crystal RG, West JB, Barnes PJ, et al (ed): The Lung: Scientific Foundations. New York: Raven Press, 1991, pp 215–228.
62. Plopper CG, Nishio SJ, Alley JL, et al: The role of the nonciliated bronchiolar epithelial (Clara) cell as the progenitor cell during bronchiolar epithelial differentiation in the perinatal rabbit lung. Am J Respir Cell Mol Biol 7:606–613, 1992.
63. Ji CM, Plopper CG, Pinkerton KE: Clara cell heterogeneity in differentiation: Correlation with proliferation, ultrastructural composition, and cell position in the rat bronchiole. Am J Respir Cell Mol Biol 13:144–151, 1995.
64. Boyd MR: Evidence of the Clara cell as a site of cytochrome P450–dependent mixed function oxidase activity in the lung. Nature 269:713–715, 1977.
65. Devereux TR, Domin BA, Philpot RM: Xenobiotic metabolism by isolated pulmonary cells. Pharmacol Ther 41:243–256, 1989.
66. Buckpitt A, Chang AM, Weir A, et al: Relationship of cytochrome P450 activity to Clara cell cytotoxicity. IV. Metabolism of naphthalene and naphthalene oxide in microdissected airways from mice, rats, and hamsters. Mol Pharmacol 47:74–81, 1995.
67. Watt KC, Plopper CG, Weir AJ, et al: Cytochrome P450 2E1 in rat tracheobronchial airways: Response to ozone exposure. Toxicol Appl Pharmacol 149:195–202, 1998.
68. Yoneda K: Ultrastructural localization of phospholipases in the Clara cell of the rat bronchiole. Am J Pathol 93:745–750, 1978.
69. Walker SR, Williams MC, Benson B: Immunocytochemical localization of the major surfactant apoprotein in type II cells, Clara cells, and alveolar macrophages of rat lung. J Histochem Cytochem 34:1137–1148, 1986.
70. Miller YE, Walker SR, Spencer JR, et al: Monoclonal antibodies specific for antigens expressed by rat type II alveolar epithelial and nonciliated bronchiolar cells. Exp Lung Res 15:635–649, 1989.
71. Massaro G: Nonciliated bronchiolar epithelial (Clara) cells. *In* Massaro D (ed):. Lung Biology in Health and Disease. Lung Cell Biology. New York: Marcel Dekker, 1989, pp 81–114.
72. Peão MN, Aguas AP, de Sa CM, Grande NR: Anatomy of Clara cell secretion: Surface changes observed by scanning electron microscopy. J Anat 182:377–388, 1993.
73. Cardoso WV, Stewart LG, Pinkerton KE, et al: Secretory product expression during Clara cell differentiation in the rabbit and rat. Am J Physiol 264:L543–L552, 1993.
74. Van Scott MR, Hester S, Boucher RC: Ion transport by rabbit nonciliated bronchiolar epithelial cells (Clara cells) in culture. Proc Natl Acad Sci U S A 84:5496–5500, 1987.
75. Van Scott MR, Davis CW, Boucher RC: Na^+ and Cl^- transport across rabbit nonciliated bronchiolar epithelial (Clara) cells. Am J Physiol 256:C893–C901, 1989.
76. Cudkowicz L. Bronchial arterial circulation in man. *In* Moser KL (ed): Lung Biology in Health and Disease. Pulmonary Vascular Diseases. New York: Marcel Dekker, 1979, pp 111–232.
77. Albertine KH, Wiener-Kronish JP, Staub NC: Blood supply of the caudal mediastinal lymph node in sheep. Anat Rec 212:129–131, 1985.
78. Anderson WD: Thorax of Sheep and Man. An Anatomy Atlas. Minneapolis: Dillon Press, 1972.
79. Malik AB, Tracy SE: Bronchovascular adjustments after pulmonary embolism. J Appl Physiol 49:476–481, 1980.
80. Magno MG, Fishman AP: Origin, distribution and blood flow of bronchial circulation in anesthetized sheep. J Appl Physiol 53:272–279, 1982.
81. Baile EM, Nelems JM, Schuler M, Pare PD: Measurement of regional bronchial arterial blood flow and bronchovascular resistance in dogs. J Appl Physiol 53:1044–1049, 1982.
82. Pietra GG, Magno M, Johns L, Fishman AP. Bronchial veins and pulmonary edema. *In* Fishman AP, Renkin EM (eds): Pulmonary Edema. Bethesda, Md: Am Physiol Society, 1979. pp 195–200.
83. Charan NB: The bronchial circulatory system: Structure, function and importance. Respir Care 29:1226–1235, 1984.
84. Wright RD: The blood supply of abnormal tissues in the lung. J Pathol Bacteriol 47:489–499, 1938.
85. Cudkowicz L, Armstrong JB: The blood supply of malignant pulmonary neoplasms. Thorax 8:152–156, 1953.
86. Singhal S, Henderson R, Horsfield K, et al: Morphometry of the human pulmonary arterial tree. Circ Res 33:190–197, 1973.
87. Weibel ER: Morphological basis of alveolar-capillary gas exchange. Physiol Rev 53:419–495, 1973.
88. Horsfield K, Gordon WI: Morphometry of pulmonary veins in man. Lung 159:211–218, 1981.
89. Bhattacharya J, Staub NC: Direct measurement of microvascular pressures in the isolated perfused dog lung. Science 210:327–328, 1980.

90. Nagasaka Y, Bhattacharya J, Nanjo S, et al: Micropuncture measurement of lung microvascular pressure profile during hypoxia in cats. Circ Res 54:90–95, 1984.
91. Grover RF, Wagner WW Jr., McMurtry IF, Reeves JT: Pulmonary circulation. *In* Shepherd JT, Abboud FM (eds): Handbook of Physiology: The Cardiovascular System. Baltimore: Williams & Wilkins, 1983, pp 103–136.
92. Dawson CA: Role of pulmonary vasomotion in physiology of the lung. Physiol Rev 4:544–616, 1984.
93. Hislop A, Reid L: Normal structure and dimensions of the pulmonary arteries in the rat. J Anat 175:71–84, 1978.
94. Rhodin JAG: Microscopic anatomy of the pulmonary vascular bed in the cat lung. Microvasc Res 15:169–193, 1978.
95. Rippe B, Parker JC, Townsley MI, et al: Segmental vascular resistances and compliances in the dog lungs. J Appl Physiol 62:1206–1215, 1987.
96. Reid LM: The pulmonary circulation: Remodeling in growth and disease. Am Rev Respir Dis 119:531–554, 1979.
97. Reid L, Meyrick B: Microcirculation: Definition and organization at tissue level. Ann N Y Acad Sci 384:3–20, 1982.
98. Conhaim RL, Staub NC: Reflection spectrophotometric measurement of O_2 uptake in pulmonary arterioles of cats. J Appl Physiol 48:848–856, 1980.
99. Lee GD, DuBois AB: Pulmonary capillary blood flow in man. J Clin Invest 34:1380–1390, 1955.
100. Wasserman K, Butler J, VanKessel A: Factors affecting the pulmonary capillary blood flow pulse in man. J Appl Physiol 21:890–900, 1966.
101. Vreim CM, Staub NC: Indirect and direct pulmonary capillary blood volume in anesthetized open-thorax cats. J Appl Physiol 34:452–459, 1973.
102. Staub NC: Alveolar arterial oxygen tension gradient due to diffusion. J Appl Physiol 18:73–80, 1963.
103. Nicolaysen G, Hauge A: Determinants of transvascular fluid shifts in zone I lungs. J Appl Physiol 48:256–264, 1980.
104. Staub NC: Effects of alveolar surface tension on the pulmonary vascular bed. Jpn Heart J 7:386–399, 1966.
105. Bruderman I, Somers K, Hamilton WK, et al: Effect of surface tension on circulation the excised lungs of dogs. J Appl Physiol 19:707–714, 1964.
106. Wagenvoort CA, Wagenvoort N: Arterial anastomoses, bronchopulmonary arteries and pulmobronchial arteries in perinatal lung. Lab Invest 1:13–24, 1967.
107. Weibel ER. Lung cell biology. *In* Fishman AP (ed): Handbook of Physiology. Baltimore: Williams & Wilkins, 1985, pp 47–91.
108. Simionescu M: Cellular organization of the alveolar-capillary unit: Structural-functional correlations. *In* Said SI (ed):The Pulmonary Circulation and Acute Lung Injury. Mt. Kisco, NY: Futura Publishing, 1991, pp 13–42.
109. Vasile E, Simionescu M, Simionescu N: Visualization of the binding, endocytosis and transcytosis of low density lipoproteins in the arterial endothelium in situ. J Cell Biol 96:1677–1689, 1983.
110. Milici AJ, Watrous NE, Stukenbok H, Palade GE: Transcytosis of albumin in capillary endothelium. J Cell Biol 105:2603–2612, 1987.
111. Heltianu C, Dobrila L, Antohe A, Simionescu M: Evidence for thyroxin transport by the lung and heart capillary endothelium. Microvasc Res 37:188–203, 1989.
112. Villaki S, Johns L, Cirigliano M, Pietra GG: Binding and uptake of native and glycosylated albumin-gold complexes in perfused rat lungs. Microvasc Res 32:190–199, 1986.
113. Nistor A, Simionescu M: Uptake of low density lipoproteins by the hamster lung. Am Rev Respir Dis 134:1266–1272, 1986.
114. Schneeberger EE: Structure of intercellular junctions in different segments of the intrapulmonary vasculature. Ann N Y Acad Sci 384:54–63, 1982.
115. Walker DC, MacKenzie AL, Wiggs BR, et al: Assessment of tight junctions between pulmonary epithelial and endothelial cells. J Appl Physiol 64:2348–2356, 1988.
116. Junod AF: Metabolism, production and release of hormones and mediators in the lung. Am Rev Respir Dis 112:93–108, 1975.
117. Gillis CN, Green NM: Possible clinical implications of metabolism of bloodborne substrates by the human lung. *In* Bakhle YS, Vane JR (eds): Lung Biology in Health and Disease. Metabolic Functions of the Lung. New York: Marcel Dekker, 1977, pp 173–193.
118. Malcorps CM, Dawson CA, Linehan JH, et al: Lung serotonin uptake kinetics from indicator-dilution and constant-infusion methods. J Appl Physiol 57:720–730, 1984.
119. Furuya S, Naruse S, Nakayama T, Nokihara K: Effect and distribution of intravenously inject ^{125}I-endothelin 1 in rat kidney and lung examined by electron microscopic radioautography. Anat Embryol (Berl) 185:87–96, 1992.
120. Lippton HL, Hauth TA, Cohen GA, Hyman AL: Functional evidence for different endothelin receptors in the lung. J Appl Physiol 75:38–48, 1993.
121. Markewitz BA, Kohan DE, Michael JR: Endothelin-1 synthesis, receptors, and signal transduction in alveolar epithelium: Evidence for an autocrine role. Am J Physiol 268:L192–L200, 1995.
122. Abman SH, Chatfield BA, Hall SL, McMurtry IF: Role of endothelium-derived relaxing factor during transition of pulmonary circulation at birth. Am J Physiol 259:H1921–H1927, 1990.
123. Kobzik L, Bredt D, Lowenstein C, et al: Nitric oxide synthase in human and rat lung: Immunocytochemical and histochemical localization. Am J Respir Cell Mol Biol 9:371–377, 1993.
124. North AJ, Star RA, Brannon TS, et al: Nitric oxide synthase type I and type II gene expression are developmentally regulated in rat lung. Am J Physiol 266:L635–L641, 1994.
125. Shaul PW: Nitric oxide in the developing lung. Adv Pediatr 42:367–414, 1995.
126. Sherman TS, Chen Z, Yuhanna IS, et al: Nitric oxide synthase isoform expression in the developing lung epithelium. Am J Physiol 276:L383–L390, 1999.
127. MacRitchie AN, Albertine KH, Sun J, et al: Reduced endothelial nitric oxide synthase in lungs of chronically ventilated preterm lambs. Am J Physiol Lung Cell Mol Physiol 281:L1011–L1020, 2001.
128. Barberà JA, Peinado VI, Santos S, et al: Reduced expression of endothelial nitric oxide synthase in pulmonary arteries of smokers. Am J Respir Crit Care Med 164:709–713, 2001.
129. Rhodin JAG: The ultrastructure of mammalian arterioles and precapillary sphincters. J Ultrastruct Res 18:181–223, 1967.
130. Rhodin JAG: Architecture of the vessel wall. *In* Bohr DF, Somlyo AP, Sparks HV (eds): Handbook of Physiology. Section 2. The Cardiovascular System. Bethesda, Md: Am Physiol Society, 1980, pp 1–31.
131. Komuro T, Desaki J, Uehara Y: Three-dimensional organization of smooth muscle cells in blood vessels of laboratory rodents. Cell Tissue Res 227:429–437, 1982.
132. Vanhoutte PM, Rubanyi GM, Miller VM, Huston DS: Modulation of vascular smooth muscle contraction by the endothelium. Annu Rev Physiol 48:307–320, 1986.
133. Furchgott RF: Role of endothelium in responses of vascular smooth muscle. Circ Res 53:557–573, 1983.
134. Policard A: Modifications pulmonaires consecutives a l'injection d'huile de paraffine dans le peritoine. Bull Hist Appl 19:29–54, 1942.
135. Garlanda C, Dejana E: Heterogeneity of endothelial cells. Specific markers. Arterioscler Thromb Vasc Biol 17:1193–1202, 1997.
136. Gebb S, Stevens T: On lung endothelial cell heterogeneity. Microvasc Res 68:1–12, 2004.
137. King J, Hamil T, Creighton J, et al.: Structural and functional characteristics of lung macro- and microvascular endothelial cell phenotypes. Microvasc Res 67:139–151, 2004.
138. Kuebler WM, Ying X, Bhattacharya J: Pressure-induced endothelial $Ca^{(2+)}$ oscillations in lung capillaries. Am J Physiol 282:L917–L923, 2002.
139. Hansen JE, Ampaya EP, Bryant GH, Navin JJ: Branching pattern of airways and air spaces of a single human terminal bronchiole. J Appl Physiol 38:983–989, 1975.
140. Hansen JE, Ampaya EP: Human air space shapes, sizes, areas, and volumes. J Appl Physiol 38:990–995, 1975.
141. Schreider JP, Raabe OG: Structure of the human respiratory acinus. Am J Anat 162:221–232, 1981.
142. Finley TN, Swenson EW, Comroe JHJ: The cause of arterial hypoxemia at rest in patients with "alveolar-capillary block syndrome." J Clin Invest 41:618–622, 1962.

143. Storey WF, Staub NC: Ventilation of terminal air units. J Appl Physiol 17:391–397, 1962.
144. Klingele TG, Staub NC: Alveolar shape changes with volume in isolated, air-filled lobes of cat lungs. J Appl Physiol 28:411–414, 1970.
145. Altshuler B, Palmes ED, Yarmus L, Nelson N: Intrapulmonary mixing of gases studied with aerosols. J Appl Physiol 14:321–327, 1959.
146. Clements JA: Surface phenomena in relation to pulmonary function. Physiologist 5:11–28, 1962.
147. Fung YC: Stress, deformation, and atelectasis of lung. Circ Res 37:481–496, 1975.
148. Vreim CE, Staub NC: Pulmonary vascular pressures and capillary blood volume changes in anesthetized cats. J Appl Physiol 36:275–279, 1974.
149. Bachofen H, Wangensteen D, Weibel ER: Surfaces and volumes of alveolar tissue under zone II and zone III conditions. J Appl Physiol 53:879–885, 1982.
150. Macklin CC: Pulmonary sumps, dust accumulations, alveolar fluid and lymph vessels. Acta Anat (Basel) 23:1–33, 1954.
151. Policard A, Collet A, Pregerman S: Le passage entre bronchioles et alveoles pulmonaires. Presse Med 68:999–1002, 1960.
152. Tucker AD, Wyatt JH, Undery D: Clearance of inhaled particles from alveoli by normal interstitial drainage pathways. J Appl Physiol 35:719–732, 1973.
153. Leak LV: Pulmonary lymphatics and their role in the removal of interstitial fluids and particulate matter. *In* Brain JD, Proctor DF, Reid LM (eds): Lung Biology in Health and Disease. Respiratory Defense Mechanisms. New York: Marcel Dekker, 1977, pp 31–85.
154. Staub NC: Alveolar flooding and clearance. Am Rev Respir Dis 127:S44–S51, 1983.
155. Crapo JD, Barry BE, Gehr P, et al: Cell number and cell characteristics of the normal human lung. Am Rev Respir Dis 125:332–337, 1982.
156. Mason RJ, Dobbs LG, Greenleaf RD, Williams MC: Alveolar type II cells. Fed Proc 36:2697–2702, 1977.
157. Dobbs LG, Gonzalez R, Williams MC: An improved method for isolating type II cells in high yield and purity. Am Rev Respir Dis 134:141–145, 1986.
158. Weller NK, Karnovsky MJ: Isolation of pulmonary alveolar type I cells from adult rats. Am J Pathol 124:448–456, 1986.
159. Dobbs LG, Gonzalez R, Matthay MA, et al: Highly water permeable type I alveolar epithelial cells confer high water permeability between the airspace and the vasculature in rat lung. Proc Natl Acad Sci U S A 95:2991–2996, 1998.
160. Abraham V, Chou MI, George P, et al: Heterocellular gap junctional communication between alveolar epithelial cells. Am J Physiol 280:L1085–L1093, 2001.
161. Hallman M, Miyai K, Wagner RM: Isolated lamellar bodies from rat lung. Lab Invest 35:79–86, 1976.
162. de Vries ACJ, Schram AW, Tager JM, et al: A specific acid alpha glucosidase in lamellar bodies of human lung. Biochim Biophys Acta 837:230–238, 1985.
163. Wadsworth SJ, Spitzer AR, Chander A: A: Ionic regulation of proton chemical (pH) and electrical gradients in lung lamellar bodies. Am J Physiol 73:L427–L436, 1997.
164. Weaver TE, Na CL, Stahlman MT: Biogenesis of lamellar bodies, lysosome-related organelles involved in storage and secretion of pulmonary surfactant. Semin Cell Dev Biol 13:263–270, 2002.
165. Muguleta S, Gray JM, Notarfrancesco KL, et al: Identification of LBM180, a lamellar body limiting membrane protein of alveolar type II cells, as the ABC transporter protein ABCA3. J Biol Chem 277:22147–22155, 2002.
166. Osanai K, Mason RJ, Voelker DR: Trafficking of newly synthesized surfactant protein A in isolated rat alveolar type II cells. Am J Respir Cell Mol Biol 19:929–935, 1998.
167. Wirtz HR, Dobbs LG: Calcium mobilization and exocytosis after one mechanical stretch of lung epithelial cells. Science 250:1266–1269, 1990.
168. Mason RJ, Williams MC, Widdicombe JH, et al: Transepithelial transport by pulmonary alveolar type II cells in primary culture. Proc Natl Acad Sci U S A 79:6033–6037, 1982.
169. Folkesson HG, Matthay MA, Hasegawa H, et al: Transcellular water transport in lung alveolar epithelium through mercury-sensitive water channels. Proc Natl Acad Sci U S A 91:4970–4974, 1994.
170. Kreda SM, Gynn MC, Fenstermacher DA, et al: Expression and localization of epithelial aquaporins in the adult human lung. Am J Respir Cell Mol Biol 24:224–234, 2001.
171. Whitsett JA, Weaver T, Hill W, et al: Synthesis of surfactant associated glycoprotein A by rat type II cells. Primary translation products and post translational modification. Biochim Biophys Acta 828:162–171, 1985.
172. Dobbs LG, Williams MC, Gonzalez R: Monoclonal antibodies specific to apical surfaces of rat alveolar type I cells bind to surfaces of cultured but not freshly isolated type II cells. Biochim Biophys Acta 970:146–156, 1988.
173. Christensen PJ, Kim S, Simon RH, et al: Differentiation-related expression of ICAM-1 by rat alveolar epithelial cells. Am J Respir Cell Mol Biol 8:9–15, 1993.
174. Danto SI, Shannon JM, Borok Z, et al: Reversible transdifferentiation of alveolar epithelial cells. Am J Respir Cell Mol Biol 12:497–502, 1995.
175. Borok Z, Lubman RL, Danto SI, et al: Keratinocyte growth factor modulates alveolar epithelial cell phenotype in vitro: Expression of aquaporin 5. Am J Respir Cell Mol Biol 18:554–561, 1998.
176. Borok Z, Danto SI, Lubman RL, et al: Modulation of T1alpha expression with alveolar epithelial phenotype *in vitro*. Am J Physiol 19:L155–L164, 1998.
177. Campbell LA, Hollins J, Al-Eid A, et al: Caveolin-1 expression and caveolae biogenesis during cell transdifferentiation in lung alveolar epithelial primary cultures. Biochem Biophys Res Commun 262:744–751, 1999.
178. Forbes B, Wilson CG, Gumbleton M: Temporal dependence of ectopeptidase expression in alveolar epithelial cell culture: Implications for study of peptide absorption. Int J Pharm 180:225–234, 1999.
179. Leslie CC, McCormick-Shannon K, Mason RJ: Heparin-binding growth factors stimulate DNA synthesis in rat alveolar type II cells. Am J Respir Cell Mol Biol 2:99–106, 1990.
180. Panos RJ, Rubin JS, Aaronson SA, Mason RJ: Keratinocyte growth factor and hepatocyte growth factor/scatter factor are heparin-binding growth factors for alveolar type II cells in fibroblast-conditioned medium. J Clin Invest 92:969–977, 1993.
181. Leslie CC, McCormic-Shannon K, Shannon JM, et al: Heparin-binding EGF-like factor is a mitogen for rat alveolar type II cells. Am J Respir Cell Mol Biol 16:379–387, 1997.
182. Morikawa O, Walker TA, Nielsen LD, et al: Effect of adenovector-mediated gene transfer of keratinocyte growth factor on the proliferation of alveolar type II cells *in vitro* and *in vivo*. Am J Respir Cell Mol Biol 23:626–635, 2000.
183. Gil J, Silage DA, McNiff JM: Distribution of vesicles in cells of the air-blood barrier in the rabbit. J Appl Physiol 50:334–340, 1981.
184. Kasper M, Reimann T, Hempel U, et al: Loss of caveolin expression in type I pneumocytes as an indicator of subcellular alterations during lung fibrosis. Histochem Cell Biol 109:41–48, 1998.
185. Fra AAM, Pasqualetto E, Mancini M, Sitia R: Genomic organization and transcriptional analysis of the human genes coding for caveolin-1 and caveolin-2. Gene Expr 243:75–83, 2000.
186. Fielding CJ, Fielding PE: Relationship between cholesterol trafficking and signaling in rafts and caveolae. Biochim Biophys Acta 1610:219–228, 2003.
187. Anderson RGW, Jacobson K: A role for lipid shells in targeting proteins to caveolae, rafts, and other lipid domains. Science 296:1821–1825, 2002.
188. Williams MC: Alveolar type I cells: Molecular phenotype and development. Annu Rev Physiol 65:669–695, 2003.
189. Borok Z, Liebler JM, Lubman RL, et al: Na transport proteins are expressed by rat alveolar epithelial type I cells. Am J Physiol 282:L599–L608, 2002.
190. Johnson MD, Widdicombe JH, Allen L, et al: Alveolar epithelial type I cells contain transport proteins and transport sodium, supporting an active role for type I cells in regulation of lung liquid homeostasis. Proc Natl Acad Sci U S A 99:1966–1971, 2002.
191. Ma T, Fukuda N, Song Y, et alS: Lung fluid transport in aquaporin-5 knockout mice. J Clin Invest 105:93–100, 2000.

192. Paine R, Morris SB, Jin H, et al: ICAM-1 facilitates alveolar macrophage phagocytic activity through effects on migration over the AEC surface. Am J Physiol 283:L180–L187, 2002.
193. Skidgel RA, Erdos EG: Cellular carboxypeptidases. Immunol Rev 161:129–141, 1998.
194. Ramirez MI, Millien G, Hinds A, et al: T1, a lung type I cell differentiation gene, is required for normal lung cell proliferation and alveolus formation at birth. Dev Biol 256:61–72, 2003.
195. Evans MJ, Cabral LJ, Stephens RJ, Freeman G: Transformation of alveolar type II cells to type I cells following exposure to nitrogen dioxide. Exp Mol Pathol 22:145–150, 1975.
196. Nagaishi C: Functional Anatomy and Histology of the Lung. Baltimore: University Park Press, 1972.
197. Richardson JB, Ferguson CC:. Morphology of the airways. *In* Nadel JA (ed): Lung Biology in Health and Disease. Physiology and Pharmacology of the Airways. New York: Marcel Dekker, 1980, pp 1–30.
198. Richardson JB: Recent progress in pulmonary innervation. Am Rev Respir Dis 128:S5–S8, 1983.
199. Spencer H. Pathology of the Lung. Oxford: Pergamon, 1985.
200. Paintal AS: Mechanism of stimulation of type J pulmonary receptors. J Physiol (Lond) 203:511–532, 1969.
201. Meyrick B, Reid L: Nerves in rat intra-acinar alveoli: An electron microscopic study. Respir Physiol 11:367–377, 1971.
202. Fox B, Bull TB, Guz A: Innervation of alveolar walls in the human lung: An electron microscopic study. J Anat 131:683–692, 1980.
203. Coleridge JCG, Coleridge HM: Afferent vagal C fiber innervation of the lungs and airways and its functional significance. Rev Physiol Biochem Pharmacol 99:1–110, 1984.
204. Basbaum CB: Innervation of the airway mucosa and submucosa. Semin Respir Med 5:308–313, 1984.
205. Bower A, Parker S, Maloney V: An autoradiographic study of the afferent innervation of the trachea, syrinx, and extrapulmonary primary bronchus of *Gallus domesticus*. J Anat 12:169–180, 1978.
206. Das RM, Jeffrey PK, Widdicombe JG: The epithelial innervation of the lower respiratory tract of the cat. J Anat 12:123–131, 1978.
207. Sherman JM, Cheng PW, Tandler B, Boat TF: Mucous glycoproteins from cat tracheal goblet cells and mucous glands separated with EDTA. Am Rev Respir Dis 124:476–479, 1981.
208. Al-Bazzaz FJ, Cheng E: Effect of catecholamines on ion transport in dog tracheal epithelium. J Appl Physiol 47:397–403, 1979.
209. Marin MG, Davis B, Nadel JA: Effect of acetylcholine on $C1^-$ and Na^+ fluxes across dog tracheal epithelium *in vitro*. Am J Physiol 231:1546–1549, 1976.
210. Nathanson I, Widdicombe JH, Barnes PJ: Effect of vasoactive intestinal peptide on ion transport across the dog tracheal epithelium. J Appl Physiol 55:1844–1848, 1983.
211. Barnes PJ, Basbaum CB: Mapping of adrenergic receptors in the trachea by autoradiography. Exp Lung Res 5:183–192, 1983.
212. Murlas C, Nadel JA, Basbaum CB: A morphometric analysis of the autonomic innervation of cat tracheal glands. J Auton Nerv Syst 2:23–37, 1980.
213. Dey RD, Shannon WA Jr, Said SI: Localization of VIP-immunoreactive nerves in airways and pulmonary vessels of dogs, cats, and human subjects. Cell Tissue Res 220:231–238, 1981.
214. Coles SJ, Said SI, Reid LM: Inhibition of vasoactive intestinal peptide of glycoconjugate and lysozyme secretion by human airways *in vitro*. Am Rev Respir Dis 124:531–553, 1981.
215. Peatfield AC, Barnes PJ, Bratcher C, et al: Vasoactive intestinal peptide stimulates tracheal submucosal gland secretion in ferret. Am Rev Respir Dis 128:89–93, 1983.
216. Pearse AGE, Takor T: Embryology of the diffuse neuroendocrine system and its relationship to the common peptides. Fed Proc 38:2288–2294, 1979.
217. Keith IM, Will JA: Dynamics of the neuroendocrine cell-regulatory peptide system in the lung. Exp Lung Res 3:387–402, 1982.
218. Richardson JB, Beland J: Non-adrenergic inhibitory nerves in human airways. J Appl Physiol 42:74–771, 1976
219. Will JA, DiAugustine RP: Lung neuroendocrine cells and regulatory peptides: Distribution, functional studies, and implications. A symposium. Exp Lung Res 3:185–418, 1982.
220. Hoyt RF Jr, Feldman H, Sorokin SP: Neuroepithelial bodies (NEB) and solitary endocrine cells in the hamster lung. Exp Lung Res 3:299–311, 1982.
221. Sorokin SP, Hoyt RFJ, Grant MM: Development of neuroepithelial bodies in fetal rabbit lungs. I. Appearance and functional maturation as demonstrated by high resolution light microscopy and formaldehyde-induced fluorescence. Exp Lung Res 3:237–259, 1982.
222. Cutz E: Neuroendocrine cells of the lung. An overview of morphologic characteristics and development. Exp Lung Res 3:185–208, 1982.
223. Lauweryns JM, Godderis P: Neuroepithelial bodies in the human child and adult lung. Am Rev Respir Dis 111:47–49, 1975.
224. Said SI, Mutt V: Long acting vasodilator peptide from lung tissue. Nature 224:699–700, 1969.
225. Wharton J, Polak JM, Bloom SR, et al: Substance P-like immunoreactive nerves in mammalian lung. Invest Cell Pathol 2:3–10, 1979.
226. Moosavi H, Smith P, Health D: The Feyrter cell in hypoxia. Thorax 28:729–741, 1973.
227. Lauweryns JM, Van Lommel AT, Domm RJ: Innervation of rabbit intrapulmonary neuroepithelial bodies. Quantitative and qualitative ultrastructural study after vagotomy. J Neurol Sci 67:81–92, 1985.
228. Hocking WG, Golde DW: The pulmonary-alveolar macrophage. N Engl J Med 301:580–587, 1979.
229. Sorokin SP: Dynamics of lysosomal elements in pulmonary alveolar macrophages: I. The postactivation lysosomal cycle. Anat Rec 20:117–143, 1983.
230. Staub NC, Albertine KH: Biology of lung lymphatics. *In* Johnston M (ed): Experimental Biology of the Lymphatic Circulation. Amsterdam: Elsevier Science, 1985, pp 305–325.

CHAPTER 2

LUNG GROWTH AND DEVELOPMENT

John M. Shannon, PhD • James M. Greenberg, MD

INTRODUCTION

STAGES OF LUNG DEVELOPMENT

TISSUE INTERACTIONS AND LUNG DEVELOPMENT

MOLECULAR REGULATION OF LUNG DEVELOPMENT

Diffusible Mediators of Lung Development

Transcriptional Regulation of Lung Development

Summary

INTRODUCTION

Multicellular life requires the use of O_2 for the generation of high-energy compounds (e.g., adenosine triphosphate [ATP]) to sustain the metabolic activities of complex organisms. Because multicellular organisms depend on O_2, they have evolved systems for its efficient acquisition and distribution. A benchmark in the adaptation of vertebrates living on land was the development of a gas exchange system that provided a sufficient amount of O_2 to meet the metabolic requirements of cellular respiration. As organisms increased in size, the surface area required for adequate gas exchange became significantly larger; for example, the surface area of the adult human lung epithelium has been estimated to be 70 m^2.[1] The problem of generating such a large surface area in a confined space has been solved in the basic structure of the lung, where branched epithelial tubules conduct air to millions of alveoli that lie closely apposed to the lung microvasculature. The epithelium lining the surface of the lung is continuously exposed to biologic and chemical hazards, which has also necessitated the development of an innate defense system in the lung. Early embryologic experiments established that lung morphogenesis is critically dependent on reciprocal interactions between the lung endoderm and its surrounding splanchnic mesoderm, which supplies progenitors of endothelial cells, smooth muscle cells, mesothelial cells, and fibroblasts. As we discuss, these interactions are complex and highly regulated in time and space. Disruptions in the lung developmental program, be it for genetic or epigenetic reasons, can lead to compromised structure and function. A better understanding of the molecular mechanisms controlling lung development will optimize therapeutic strategies to treat the diseased or malformed lung. Several additional recent reviews are also available.[2-5]

STAGES OF LUNG DEVELOPMENT

Lung development has traditionally been divided into five stages that are primarily based on histologic appearance (Fig. 2-1). The basic branching pattern of the pulmonary tree and an associated vascular plexus is established during the **embryonic** and **pseudoglandular** stages. The epithelial branching program, which is under genetic control, is stereotyped and utilizes three geometrically distinct local modes of branching that occur in three different sequences.[6] The **embryonic stage** of human lung development begins with the emergence of the laryngotracheal groove from the floor of the foregut endoderm during the fourth week of gestation. A few days later, the caudal end of the primordium enlarges and bifurcates, giving rise to the left and right bronchial buds. These buds elongate caudally during the fifth week of gestation, when a second round of branching occurs, resulting in three secondary buds in the right lung and two in the left. These buds will become the primary lobes of the left and right lung. A third round of branching gives rise to bronchial tubules that will become the bronchopulmonary segments in the mature lung. Concurrent with these events in the distal region, the cranial portion of the primordium gives rise to the trachea and larynx, which separate from the esophagus by the end of this stage. The lung epithelium at this stage is tall columnar, and shows no morphologic evidence of differentiation (see Fig. 2-1A). At the molecular level, however, some aspects of epithelial differentiation have already begun; for example, the most distal epithelial

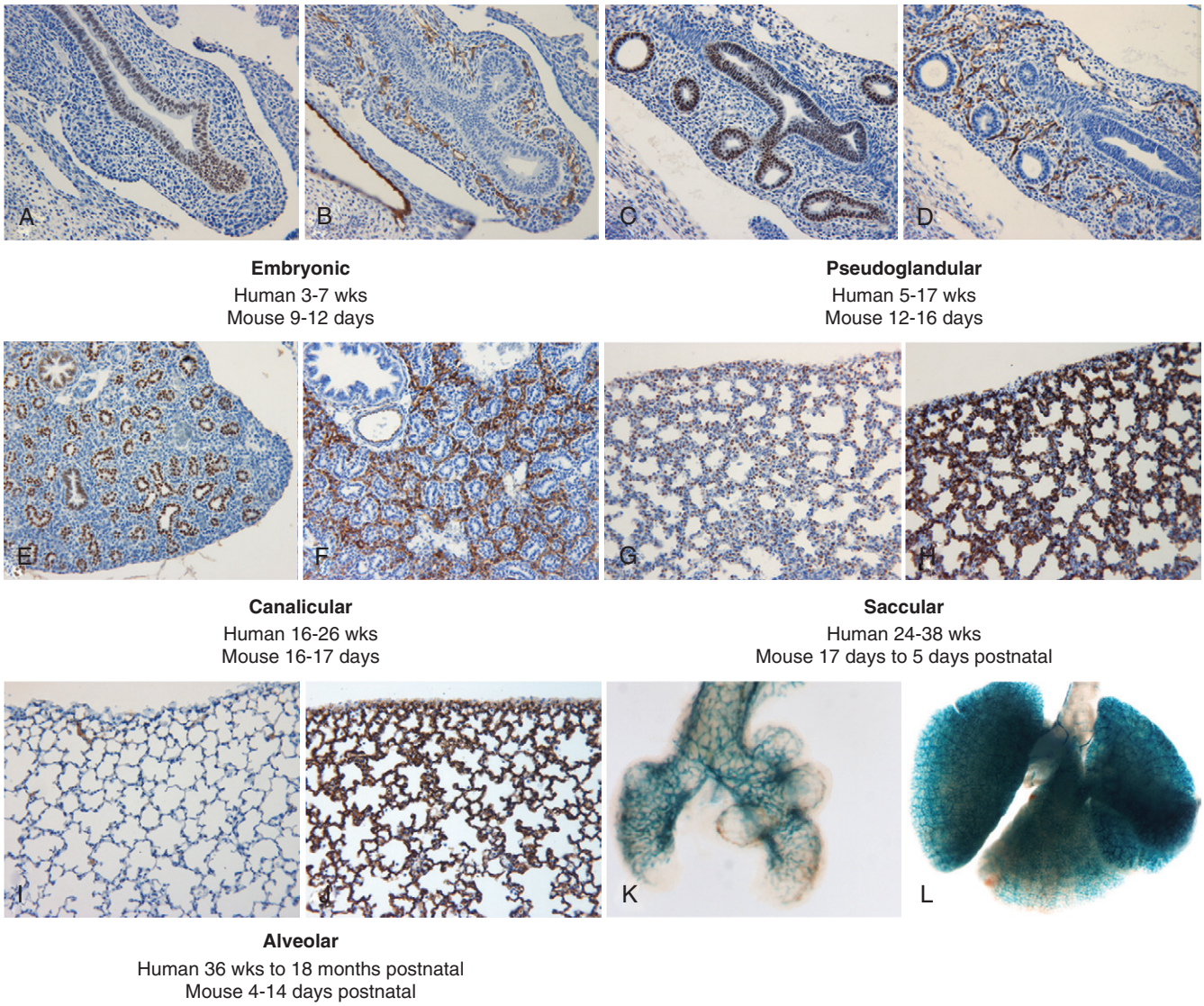

FIGURE 2-1 ■ Morphology of the stages of lung development. Mouse lungs from the indicated developmental stages were stained with antibodies against thyroid transcription factor 1 (TTF-1; **A, C, E, G, I**) to identify respiratory epithelial cells, or with antibodies against CD34 (**B, D, F, H, J**) to identify vascular cells. All images of sectioned lungs are at the same magnification. **K** and **L,** The lungs are from embryonic and saccular stage mice, respectively, in which the Tie2 promoter drives expression of the β-galactosidase transgene to histochemically mark endothelial cells. **A,** During the embryonic stage, the lung epithelium consists of apparently undifferentiated tall columnar cells. **B** and **K,** Vascular precursors are already present and form a plexus surrounding the epithelium. Dichotomous and lateral branching of the epithelium continues in the pseudoglandular stage (**C**) and the vasculature branches in parallel with the developing airways (**D**). Epithelial acini appear during the canalicular stage (**E**), and the vasculature becomes more abundant and closely apposed to the epithelium (**F**). **G,** Type I cell differentiation increases air space size during the saccular stage. **H** and **L,** The vasculature has continued to expand, fully investing the lung parenchyma. Fusion of the epithelial and endothelial basal laminae brings capillaries and type I epithelial cells into close association. **I,** The formation, lengthening, and thinning of secondary septae during the alveolar stage markedly increase the epithelial surface area. **J,** The capillaries, which until now have existed as a double septal network, have fused into one.

cells express mRNA for the lung-specific marker surfactant protein C (*Sftpc*).[7] The lung mesenchyme, which is derived from splanchnic mesoderm, is loosely organized at the beginning of this stage and lacks apparent vascular structures. In situ hybridization studies probing for the vascular endothelial cell growth factor (VEGF) receptor *Flk-1* have demonstrated, however, that vascular precursors are closely apposed to the distal epithelium at the time of bud induction.[8] These cells form a vascular plexus (see Fig. 2-1B and K) by a process termed "vasculogenesis," wherein vessels are formed de novo by the organization of vascular precursors. By the end of embryonic stage, pulmonary arteries and veins connect this plexus to the atria; the pulmonary arteries and veins grow into the lung by angiogenesis, with new branches arising from preexisting vessels.

Dichotomous and lateral branching of the lung epithelium continues during the **pseudoglandular stage**, which lasts from week 5 to week 17 of gestation. This results in the final pattern of the pulmonary tree,

which comprises 22 to 23 generations of bronchial tubules. Terminal bronchioles branch distally to give rise to the acinar tubules and buds that will eventually form pulmonary acini in the adult (see Fig. 2-1C). Morphologic differences in the epithelium are apparent. The proximal epithelium is initially populated by relatively undifferentiated columnar, glycogen-rich cells, but ciliated, nonciliated, goblet, mucous, basal, and neuroendocrine cells are identifiable by the end of this stage. Distal epithelial cells, which are the precursors of alveolar type II cells, are cuboidal-columnar and contain copious amounts of glycogen. Smooth muscle cells differentiate in the mesenchyme and surround the epithelium perpendicular to the long axis of the tubules; this proceeds in a proximal-to-distal manner. The pulmonary vasculature branches in parallel with the airway epithelium (see Fig. 2-1D), and pulmonary lymphatics initiate as buds from the veins.[9]

Patterning of the pulmonary tree is completed at the beginning of the **canalicular stage** (16–26 weeks; see Fig. 2-1E), and the cells constituting the proximal epithelium continue to differentiate as ciliated, nonciliated, and secretory cells. Among the latter are Clara cells, identifiable by the presence of the cell-specific Clara cell secretory protein (CCSP). Acinar tubules and buds, which are lined by cuboidal epithelial cells, expand and differentiate to form pulmonary acini consisting of respiratory bronchioles, alveolar ducts, and alveoli. Nascent type II cells containing increasing amounts of surfactant-associated proteins and phospholipids become prominent in the distal epithelium. Differentiation of squamous type I cells from type II cells begins. A dramatic expansion of the pulmonary capillary bed (vascular canals) in the lung parenchyma gives this stage its name (see Fig. 2-1F). These vessels surround the developing acini and come in direct contact with the epithelium, giving rise to the primordial air-blood barrier.

During the **saccular stage**, which persists from week 24 until term, the terminal acinar tubules in the lung periphery continue to branch and air space size increases. Alveolar type II cells undergo significant maturation, as evidenced by increased synthesis of surfactant proteins (SP-) A, B, C,[10] and D[11] as well as surfactant phospholipids.[12] Glycogen stores, which serve as a substrate for phospholipid synthesis,[13] decrease, while the number of lamellar bodies increases. Squamous type I cells continue to differentiate and constitute an increased proportion of the distal lung surface, thereby increasing the effective area for gas exchange (see Fig. 2-1G). Septal walls consist of a central connective tissue core with a capillary network on each side. Subsequent fusion of the basal laminae of the distal epithelium and endothelium brings capillaries into close association with type I cells, which decreases the diffusion distance between air spaces and capillaries to allow more efficient gas exchange (see Fig. 2-1H and L).

The transition from the canalicular to saccular stage of lung development marks the threshold of viability for preterm infants who have access to neonatal intensive care support.[14,15] Prior to 22 weeks' gestation, there is insufficient available surface area in the distal pulmonary tree to support safe, reliable oxygenation and ventilation, even when surfactant replacement therapy and sophisticated mechanical ventilation techniques are available. Survival at 23 weeks' gestation ranges from 15% to 30%. Mortality decreases with each additional week of gestation; by 25 weeks, survival exceeds 60%, although significant morbidity in the form of bronchopulmonary dysplasia (BPD) and neurodevelopmental compromise persist.[16]

As the threshold of viability is crossed, respiratory distress syndrome (RDS) becomes the primary source of morbidity and mortality for the preterm infant. RDS is a consequence of deficient surfactant production, leading to terminal airway atelectasis and epithelial injury. The subsequent capillary leak produces the hyaline membranes that are classically associated with this disease. Surfactant replacement therapy has dramatically improved RDS survival rates and reduced morbidity. Term infants affected by RDS typically have comorbid conditions such as maternal diabetes, which delay maturation of the surfactant production system.

Genetic mutations leading to SP-B deficiency result in a clinical presentation indistinguishable from the early stages of RDS. Affected infants, however, are typically full term and have only a transient response to surfactant replacement therapy, which leads to early neonatal death or the development of severe neonatal chronic lung disease. The only definitive treatment is lung transplantation. Lethal respiratory failure in a mouse model of SP-B deficiency can be reversed with targeted expression of an SP-B transgene, demonstrating potential for gene therapy.[17] Mutations of SP-C produce a spectrum of pulmonary disorders during infancy including pulmonary interstitial fibrosis.[18] As with SP-B deficiency, surfactant replacement therapy has little or no benefit, with lung transplantation as the only documented potential cure. Other genetic defects of the surfactant production system also lead to fatal surfactant deficiency in the neonate. Infants deficient in ABCA3, which transports surfactant phospholipids to lamellar bodies, have normal SP-B expression and unexplained lethal respiratory failure and death within 1 month of birth.[19]

The final stage of lung development is the **alveolar stage**, which lasts from week 36 of gestation through the first 18 months of postnatal life. As the name implies, the generation of true alveoli from terminal saccules occurs during this stage. Interstitial tissue in primary septae is reduced, while secondary septae markedly lengthen and thin (see Fig. 2-1I). Concomitant with these changes is the fusion of the double septal capillary network into one (see Fig. 2-1J). This remodeling requires an initial burst of interstitial fibroblast proliferation, which subsequently slows down and the cells synthesize increased amounts of collagen and elastin. Septation results in a marked increase in the number of alveoli from approximately 30 million at term to 300 million in the adult. Increased numbers of type II and type I cells accompany alveolar expansion, with type I cells now covering 97% of the alveolar surface area.[20]

BPD, which is typically restricted to infants born prior to 32 weeks' gestation, represents a particularly challenging complication. The condition is only associated

with preterm birth and is defined by a characteristic appearance on chest radiograph and persistent requirement for supplemental oxygen beyond 36 weeks postconception.[21] In the era of surfactant replacement therapy, BPD is distinguished by alveolar simplification due to the apparent arrest of alveolarization that occurs in utero during the third trimester.[22] Compromise of oxygenation and ventilation may worsen as infant somatic growth progresses and attendant metabolic demands outstrip pulmonary function. Respiratory morbidity is not restricted to infants born prior to 32 weeks' gestation. When compared with term infants, so-called late-preterm infants born between 32 and 37 weeks' gestation are more likely to require respiratory support, including positive-pressure ventilation after birth.[23] Given the dramatic increase in alveolar number during the late third trimester, it follows that late preterm infants may have a smaller margin of safety when making the transition to extrauterine life.

TISSUE INTERACTIONS AND LUNG DEVELOPMENT

A basic tenet of lung development is that it requires inductive interactions between the endodermal epithelium and the mesodermal mesenchyme. This is particularly evident in the embryonic and pseudoglandular stages, where it has been conclusively shown that lung epithelium must be associated with lung mesenchyme in order to survive[24] and branch.[25] The factors that drive branching morphogenesis are diffusible, because embryonic lung epithelium branches when separated from lung mesenchyme by a filter that prevents direct cell-cell contact, but allows diffusion of soluble factors.[26] Importantly, these experiments also showed that survival of lung mesenchyme is dependent on the presence of lung epithelium, underscoring that induction is reciprocal. The fate of the entire respiratory endoderm, from the trachea to the bud tips, however, is not fully committed during the embryonic stage. Reciprocal recombination experiments have shown that distal lung mesoderm can reprogram tracheal endoderm to branch and differentiate like lung,[27,28] and that tracheal mesoderm can reprogram lung endoderm to differentiate like trachea.[29,30]

Bronchopulmonary sequestration may represent an intriguing manifestation of aberrant pulmonary endoderm-mesoderm interaction. These masses of abnormal lung tissue, which may be contained within the lung or in an extrapulmonary location such as the abdomen, may be in direct communication with gastrointestinal tract structures suggesting ectopic induction of embryonic foregut. The histopathologic appearance of these lesions includes typical cellular components of pulmonary parenchyma along with inflammatory and fibrotic components (Fig. 2-2C).[31]

Normal lung function requires the precise alignment of the distal epithelium and the vasculature to meet the respiratory requirements of the developing organism. Certain lethal congenital malformations of the lung, such as alveolar capillary dysplasia (ACD), are due to a perturbation in the relationship between vascular and airway development. ACD is characterized by a paucity of alveolar capillaries, thickened pulmonary mesenchyme, and misalignment of the pulmonary veins, which reflect the reciprocal relationship required for airway and vascular development (see Fig. 2-2B). The alveolar simplification of BPD is also accompanied by a relative paucity of alveolar capillaries that is reminiscent of ACD. Evidence that VEGF-A, which is produced by lung epithelial cells, can reverse the alveolar defect further reinforces the concept of interdependent development of vascular and airway structures.[32]

MOLECULAR REGULATION OF LUNG DEVELOPMENT

Elucidation of the factors that regulate lung growth and development has been the focus of an intense research effort. This stems not only from a desire to understand the basis of pulmonary pathologies present at birth but also from the possibility that understanding how the lung develops will provide insight into how the lung repairs itself following injury or disease. Given the morphogenetic precision required to generate a lung that can function effectively in gas exchange, coupled with the fact that the lung contains over 40 differentiated cell types,[1] it is not surprising that the molecular regulation of lung development is proving to be very complex. Identifying the factors involved provides only part of the story. When, where, how much, and for how long these factors are expressed must also be considered. The fact that there is crosstalk between some of the identified pathways significantly increases the level of complexity.

Diffusible Mediators of Lung Development

Fibroblast Growth Factors and Fibroblast Growth Factor Receptors

In both humans and mice, the fibroblast growth factor (FGF) family comprises 22 structurally related molecules[33]; among these, FGF1, 2, 7, 9, 10, and 18 have been localized to the developing lung. FGFs bind and signal through high-affinity, ligand-dependent transmembrane receptors (FGF-Rs) that contain an intracellular tyrosine kinase domain. There are four FGF-Rs, all of which are expressed in the lung. Alternative mRNA splicing results in two isoforms each for FGF-R1, FGF-R2, and FGF-R3 that have distinct ligand specificities.[34] FGF-R activation is modulated by heparin or heparin sulfate.[35]

FGF1 and FGF2 are not critical for lung development, because the single deletion of either gene or the double ablation of both has no effect on lung development. FGF10 is an ideal candidate for mediating tissue interactions in the lung, because it is expressed in the mesenchyme, whereas its primary receptor, FGF-R2b, is expressed by epithelial cells. Ablation of either FGF10[36] or FGF-R2b[37] results in complete pulmonary agenesis caudal to the trachea. The basis for this phenotype

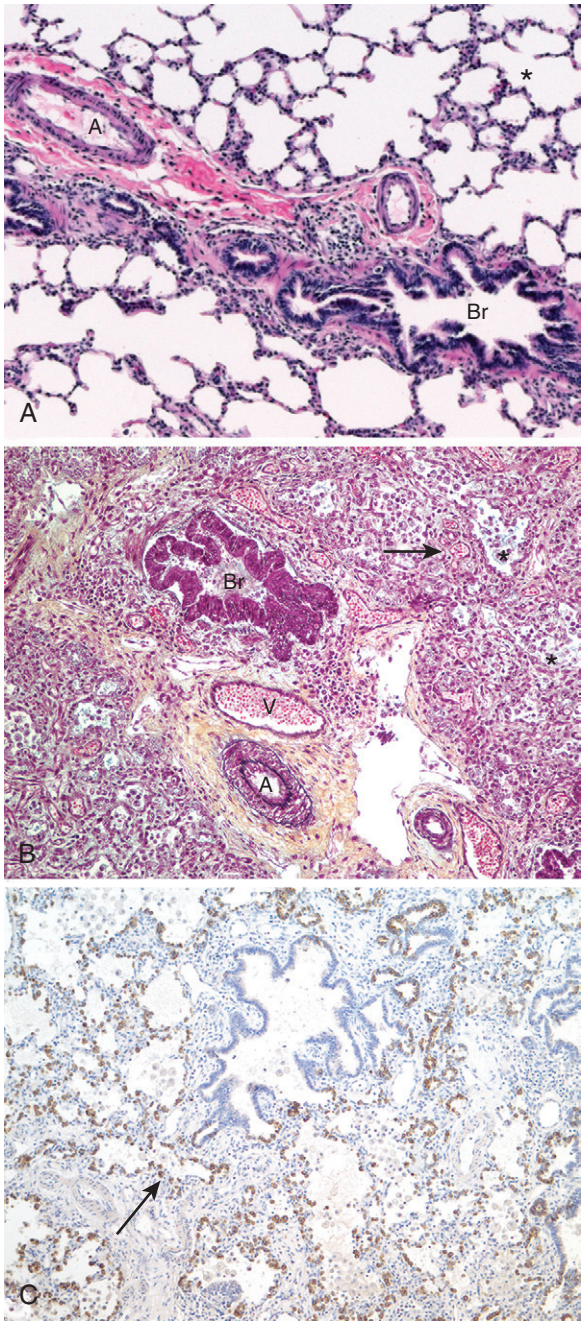

FIGURE 2-2 ■ Histopathologic features of alveolar capillary dysplasia and extralobar pulmonary sequestration. **A,** Section of normal lung stained with hematoxylin and eosin demonstrates a typical bronchovascular bundle incorporating a small bronchus (Br) and artery (A), without an accompanying vein. A typical alveolar network with abundant air spaces (*) is present. **B,** Pentachrome-stained section from a full-term newborn with alveolar capillary dysplasia. There is abundant mesenchyme separating rudimentary, dysplastic terminal airspaces (*). Alveolar capillaries (*arrow*) are sparse in number and distended. There is misalignment of the pulmonary vasculature. A pulmonary artery (A) with prominent muscularis and bronchus (Br) are accompanied by an anomalous pulmonary vein (V). The paucity of alveolar capillary structures accounts for the profound pulmonary hypertension in these patients. Original magnification ×10). **C,** Immunohistochemistry of extralobar pulmonary sequestration demonstrates expression of prosurfactant protein C in epithelium (brown-staining cells). The sequestration has the histologic appearance of primitive lung at the canalicular stage of development with an abundance of mesenchyme separating nascent air space structures (*arrow*). (**A–C,** Micrographs kindly provided by Dr. Susan Wert, Division of Pulmonary Biology, and Dr. Gail Deutsch, Division of Pathology, Cincinnati Children's Hospital Medical Center.)

comes from the ability of FGF10 to induce lung epithelial budding by chemoattraction[38,39]; in the absence of FGF10 primary bud formation cannot occur. Like FGF10, FGF9 acts as a mediator of reciprocal tissue interactions, because it is expressed in the epithelium and mesothelium, whereas its receptor, FGF-R2c, is found in the mesenchyme. FGF9 controls lung mesenchyme size by regulating cell proliferation.[40] The observation that the amount of available mesenchyme appears to control lung branching[24] is consistent with the result that the lungs of FGF9 null mice are severely hypoplastic, with decreased amounts of mesenchyme and reduced FGF10 expression.[41] The observation that FGF18 null mice exhibit reduced alveolar size resulting from reduced cell proliferation during the saccular stage[42] suggests a role for FGF18 in late lung development. FGF7 has been shown to markedly stimulate lung epithelial cell proliferation,[43] and pretreatment with FGF7 protects against lung injury, but by a mechanism more complex than increased cell proliferation.[44] Transgenic overexpression of FGF7 in the developing mouse lung results in lesions resembling cystic adenomatoid malformations[45]; examination of human congenital cystic adenomatoid malformations (CCAM), however, shows that FGF7 expression is actually decreased and FGF10 expression is unchanged.[46] FGF7 is a potent stimulator of surfactant protein gene expression and surfactant phospholipid synthesis in type II cells.[47,48] Although intraperitoneal

injection of neutralizing antibodies against FGF7 inhibits postnatal lung growth and alveolus formation,[49] mice with a targeted deletion of FGF7 have no apparent lung phenotype.[50] FGFs are also required during alveoligenesis, because mice with deletions of both FGF-R3 and FGF-R4 fail to form normal alveoli.[51]

The Sprouty (Spry) proteins, which antagonize FGF-R signaling, modulate the effects of FGFs in the developing lung. Transgenic misexpression of either Spry2[52] or Spry4[53] disrupts branching and causes lung hypoplasia. Although single deletion of either Spry2 or Spry4 has no effect on lung development, mice null for both genes have defects in multiple organs, including the lung.[54]

Retinoic Acid

Retinoic acid (RA), the active derivative of vitamin A, is essential for the normal development of many tissues, including the lung. Maternal vitamin A deficiency results in severe respiratory phenotypes in offspring, including tracheoesophageal fistula, lung hypoplasia, and lung agenesis.[55] RA signals through RAR and RXR nuclear receptors, both of which have α, β, and γ isoforms, and these are expressed in the lung from the outset of development. Mice with double deletions of RARα/RARβ or RARα/RXRβ show the same lung abnormalities as those seen in vitamin A–deficient embryos.[56] The mechanism by which RA controls lung morphogenesis is not fully resolved. Data from cultured early embryonic foreguts suggest that RA controls transforming growth factor-β (TGF-β) activity in the prospective lung field, which in turn controls the expression of FGF10, thereby affecting lung bud induction.[57] RA also influences perinatal alveolus formation in rodents,[58] which has led to its use clinically for the prevention of BPD.[59] The effect, however, is modest: about 15 infants must be treated to prevent 1 case of BPD.[60] The mechanism is not understood in detail, but is likely related to maintenance of alveolarization after preterm delivery, reducing the potential for alveolar simplification. The morphogenetic effects of RA have also led to investigation of its potential efficacy in inducing alveolar regeneration. RA has been shown to prevent and reverse emphysematous changes induced by elastase in rats[61] or by dexamethasone in mice.[62] Although studies of chronic obstructive pulmonary disease (COPD) patients treated with RA have not established a definitive clinical benefit, changes in some parameters of lung function suggest that further study may be warranted.[63]

Sonic Hedgehog

The hedgehog signaling pathway plays a important role in the development of multiple organs.[64] Sonic hedgehog (Shh) is expressed in the developing lung epithelium[65] and its primary receptor, Patched-1 (Ptc), is found in mesenchymal cells,[66] suggesting that Shh is part of a epithelial-mesenchymal inductive loop. Shh is initially expressed throughout the epithelium, but becomes restricted to subsets of cells from day E16.5 onward.[67] Shh null mice form lungs, indicating that Shh is not required for lung bud induction, but these lungs are severely hypoplastic,[68] suggesting that Shh is involved in regulating branching morphogenesis. Shh deletion profoundly affects lung growth and patterning, but the specification of epithelial cell types appears to be unaffected.[69] Because Shh serves as a survival factor for lung mesenchymal cells,[70] the lung hypoplasia seen in Shh null embryos may be due to a decrease in mesenchymal mass. Shh is also a negative regulator of FGF10, which is critical for lung bud induction.[69] Clinical syndromes with respiratory phenotypes that are consistent with disruption of Shh signaling include VACTERL (vertebral abnormalities, anal atresia, cardiac abnormalities, tracheoesophageal fistula and/or esophageal atresia, renal agenesis and dysplasia, and limb defects),[71] and Smith-Lemli-Opitz (SLO).[72] SLO is phenocopied by mutations in Δ-7-dehydrocholesterol reductase (DHCR7), which is involved in cholesterol synthesis[73]; cholesterol modification of Shh is required for effective signaling.[74]

Shh levels are modulated by binding to Ptc.[75] Shh up-regulates Ptc expression, and any Ptc in excess of that involved in signaling binds Shh and sequesters it, creating a negative feedback loop that restricts its spread. Another molecule regulating Shh levels is hedgehog-interacting protein 1 (HHIP1), a membrane-bound protein that binds all mammalian hedgehog proteins and, like Ptc, is up-regulated in response to Shh.[76] Targeted deletion of HHIP1 results in lung hypoplasia[77] that may be due to a loss of FGF10 expression at the prospective sites of bud formation as a result of increased Shh signaling.

Three GLI genes (1, 2, and 3) code for zinc finger transcription factors that are the principal effectors of hedgehog signaling. All three GLI genes are expressed in distinct but overlapping domains in lung mesenchyme, with expression being highest in the distal tips.[78,79] The analysis of compound mutant mice has demonstrated the complexity of how GLI genes affect lung development. Embryos expressing different combinations of GLI genes show a range of lung defects, the most striking of which is the absence of lungs, trachea, and esophagus in $GLI2^{-/-}$, $GLI3^{-/-}$ compound mutants.[80] The presence of a single GLI3 allele ($GLI2^{-/-}$, $GLI3^{+/-}$) is sufficient to allow formation of hypoplastic lungs in which the left and right lungs do not separate, and the embryos have tracheoesophageal fistula. The phenotype seen in GLI2/GLI3 double-null embryos is more severe than that seen in Shh-null animals; this suggests that the GLI genes may lie downstream in signaling pathways other than Shh, or that the other hedgehog proteins (Indian and Desert) may be active in the lung. Mutations in the human GLI3 gene cause Pallister-Hall and Greig syndromes, which affect development of several organ systems, including the lung.[81]

TGF-β Superfamily

The TGF-β superfamily comprises activins, inhibins, the bone morphogenetic proteins (BMPs), mullerian inhibiting substance, and TGF-β1, 2, and 3. TGF-β1 treatment of cultured embryonic lung explants[82] or misexpression

of TGF-β1 targeted to the lung in vivo[83] severely inhibit branching morphogenesis. This is likely due to the ability of TGF-β1 to inhibit FGF10 expression.[57] TGF-β1 signals through a heteromeric complex of type I (TGF-βrI) and type II (TGF-βrII) receptors, and exerts its effects on downstream target genes via the SMAD family of proteins.[84] Inhibition of TGF-βrII in cultured embryonic lungs increases lung branching,[85] as does attenuation of SMAD2/3,[86] underscoring the inhibitory nature of TGF-β1 on lung morphogenesis. TGF-β1–null mice show no apparent lung phenotype, although it should be noted that 50% of these mice die on E10.5, prior to the onset of lung development.[87] Most TGF-β2–null mice die shortly before or during birth with a wide range of developmental defects. The lungs of neonates have dilated conducting airways and collapsed terminal and respiratory bronchioles.[88] Deletion of TGF-β3 results in retarded development and differentiation of the lung epithelium, mesenchyme, and vasculature.[89] The fact that TGF-β3 appears to promote morphogenesis contrasts with the inhibitory function of TGF-β1, suggesting that these ligands affect distinct aspects of lung development.

Of the four BMPs expressed in the developing lung (BMP3, 4, 5, and 7), BMP4 has been the focus of the most studies. BMP4 is expressed in the ventral foregut mesenchyme prior to lung bud induction, and then is expressed in the distal epithelium and proximal mesenchyme after the lung has formed. In the mouse, epithelial expression declines in the distal epithelium prior to birth, but begins in the capillary endothelium. BMP4 expression is upregulated by FGFs in the epithelium and by Shh in the mesenchyme. Although the evidence to date suggests a role for BMP4 in modulating epithelial cell proliferation, determination of whether BMP4 supports or antagonizes proliferation has been controversial. Paradoxically, lung-targeted overexpression of either BMP4[66] or the BMP4 antagonists Noggin[90] or Gremlin[91] have the same effect of reducing cell proliferation and lung size. Specific deletion of BMP4 or BMPR1a from the distal lung epithelium results in reduced proliferation, increased apoptosis, and cystic morphogenesis.[92] These data support a model in which BMP4 produced by the distal epithelium acts in an autocrine manner to promote the proliferation and survival of undifferentiated progenitor cells in the distal lung epithelium.

Wnts and β-catenin

Members of the Wnt family of secreted glycoproteins are critically involved in cell fate determination, proliferation, survival, and motility in organogenesis. Wnt ligands bind their receptors to activate a pathway that ultimately stabilizes β-catenin, which then interacts with nuclear T-cell factor/lymphoid enhancer factor (TCF/LEF) transcription factors to modulate transcription of downstream target genes.[93] Wnts 1, 2a, 2b, 5a, 7b, and 11 are expressed in the lung. Deletion of both Wnt2a and 2b abrogates specification of lung progenitors in the foregut endoderm, resulting in lung agenesis.[93a] Inactivation of Wnt5a results in a foreshortened trachea, overexpanded distal airways, and retarded lung maturation.[94] Mice null for Wnt7b die at birth from respiratory failure; early mesenchymal cell proliferation is reduced, leading to lung hypoplasia, and defects in the smooth muscle layer around major pulmonary vessels results in hemorrhage.[95] Proximal-distal airway patterning and epithelial cell differentiation are disrupted when Wnt signaling is globally inhibited in the developing lung, either by targeted epithelial deletion of β-catenin[96] or by misexpression of the Wnt antagonist Dickkopf 1.[97] Constitutive activation of Wnt signaling in the developing lung epithelium with hyperactive β-catenin results in lungs that lack fully differentiated cell types.[98]

Platelet-Derived Growth Factor

The platelet-derived growth factor (PDGF) family consists of five different disulfide-linked dimers built up of four different polypeptide chains encoded by four different genes. PDGF-A, which homodimerizes with itself or heterodimerizes with PDGF-B, plays an important role in lung development. PDGF-A is expressed in distal lung epithelium, whereas its receptor, PDGFRα, is expressed in nearby mesenchymal cells, indicative of a paracrine signaling loop between the epithelium and the mesenchyme. Deletion of PDGF-A results in arrested alveolus formation and postnatal death.[99] The lungs lack the differentiated alveolar myofibroblasts that produce elastin, which is critical for alveolus formation.

VEGF

VEGF-A, C, and D are all found in the lung. The temporal and spatial expression of VEGF-A during lung development implies a central role in the maturation and organization of the pulmonary vascular network. VEGF-A is expressed in epithelial and mesenchymal compartments during the embryonic and pseudoglandular stages, becoming more restricted to the epithelium as development progresses into the canalicular stage.[8,100] VEGF-A exists as three isoforms (120, 164, and 188) that have distinct functions in vascular development.[101] Genetic studies in mice demonstrate the importance of local tissue concentrations of VEGF-A to effect appropriate vascular development and distal airway structures. Increased expression of VEGF164 in distal epithelium disrupts assembly of the vascular plexus and arrests airway branching without affecting endothelial cell proliferation or survival, indicating that crosstalk between the developing epithelium and vasculature is required for normal morphogenesis.[102] VEGF-A expression is controlled by multiple mediators, such as FGFs and Shh.[103]

Glucocorticoids

Glucocorticoids exert potent effects on a variety of different tissues, with a common theme that they induce the precocious appearance of normal developmental events. The effects of glucocorticoids on lung function have been a topic of intense interest since the observation that dexamethasone accelerates lung maturation in premature lambs.[104] Glucocorticoid receptors are

present on the developing pulmonary epithelium as airway branching progresses during the pseudoglandular stage of lung development. Epithelial expression persists through the saccular and alveolar stages, accompanied by the onset of expression within the mesenchymal compartment.[105] Exogenous glucocorticoids stimulate morphologic maturation and many aspects of surfactant phospholipid biosynthesis.[106] Targeted disruption of the glucocorticoid receptor in mice leads to respiratory distress and early neonatal death[107]; the lungs of these animals are atelectatic with blunted alveolarization. Although the number of type II cells is increased by 30%, the relative expression of SP-A and SP-C is decreased by 50%. The number of type I cells is decreased by 50%, as are the type I cell markers T1α and aquaporin 5, suggesting that glucocorticoids facilitate the differentiation of type II cells into type I cells.[108] Somewhat paradoxically, however, mice null for corticotropin-releasing hormone show deficits in septal thinning, air space formation, and content of SP-A and SP-B, but have no deficit in surfactant phospholipid biosynthesis.[109]

Given the broad distribution of pulmonary glucocorticoid receptors in the developing lung, it is not surprising that the therapeutic effects of glucocorticoid treatment are complex. Clinical experience suggests that glucocorticoids have contrasting biologic effects depending upon whether treatment is directed toward the fetal lung or the preterm neonatal lung. Women in preterm labor are routinely treated with glucocorticoids to reduce the incidence and severity of neonatal RDS.[110] Antenatal steroid treatment accelerates fetal lung maturation by inducing mesenchymal thinning and enhancing pulmonary function, presumably through stimulation of surfactant production. Morphometric studies in sheep suggest that antenatal steroid treatment may also induce some blunting of alveolarization[111]; these effects have been reversed in experimental animals by retinoic acid.[62] Glucocorticoid treatment has also been employed to treat preterm infants experiencing severe BPD. Although early studies and anecdotal reports suggested that steroid treatment could reverse the fibrosis and scarring associated with BPD and significantly improve pulmonary mechanics,[112] subsequent studies demonstrated no clear improvement in long-term pulmonary outcome and increased risk for neurodevelopmental impairment.[113]

Transcriptional Regulation of Lung Development

The diffusible molecules mediating tissue interactions in the developing lung initiate signaling cascades that lead to changes in gene expression. The diversity of cell types found in the lung, which all differentiate under tight spatial and temporal control, makes regulation of gene expression by transcription factors in the developing lung highly complex. Although no lung-specific transcription factors have yet been found, research has identified several transcription factors in addition to those described previously that are crucial to normal lung development.

Thyroid Transcription Factor 1

Thyroid transcription factor 1 (TTF-1; also known as Nkx2.1) is found in the presumptive respiratory region of the foregut endodermal epithelium before lung bud induction. TTF-1 is a homeodomain protein that is found in the forebrain, thyroid, and lung, where it interacts with multiple partners to influence several key aspects of development.[4] Mice null for TTF-1 have a tracheal-esophageal fistula, with main-stem bronchi connecting to hypoplastic, cystic lungs.[114] Whereas differentiation of the most proximal epithelium is somewhat preserved in TTF-1–null lungs, markers of distal epithelial differentiation, including the surfactant proteins, are completely lacking. Similarly, mutation in the human TTF-1 gene leads to thyroid dysfunction and respiratory failure.[115] The control of TTF-1 expression in lung development is not understood.

FOX Family

The FOX family of transcription factors contains more than 50 members, all of which share a winged helix DNA binding domain. FOXA1 and FOXA2 are closely related proteins found in the foregut endoderm and its derivatives. Their spatial and temporal expression patterns are similar in the lung. Mice lacking FOXA2 do not form endoderm and hence cannot form lungs[116]; targeted deletion of FOXA2 in lung epithelial cells, however, demonstrates that it is required for alveolarization and epithelial cell differentiation.[117] Deletion of FOXA1 in mice delays some aspects of sacculation and alveolarization pre- and perinatally, but these differences normalize by 2 weeks of age,[118] suggesting compensation by FOXA2. Deletion of both genes inhibited cell proliferation, branching morphogenesis, and epithelial cell differentiation,[119] indicating that FOXA1/2 play a central role in lung development.

FOXF1 is expressed in lung mesenchyme and controls genes involved in epithelial-mesenchymal interactions, because a haploinsufficiency results in defective branching, lobation, and epithelial differentiation.[120] FOXJ1 controls expression of left-right dynein, which is required for correct anchoring of basal bodies; deletion of FOXJ1 causes situs inversus, the loss of motile cilia in airway epithelial cells, sinusitis, and bronchiectasis.[121] Although these features are associated with Kartagener's syndrome in humans, no mutations in the *FOXJ1* gene have been directly linked to this disorder. FOXM1B is associated with proliferating cells in both the lung epithelium and mesenchyme, but mice null for FOXM1B only show decreased proliferation in the mesenchyme, which is accompanied by severe abnormalities in vascular development.[122] FOXP1 and FOXP2, which are known transcriptional repressors, are expressed in the lung epithelium; both genes are expressed distally, but only FOXP1 is expressed proximally. $FOXP2^{-/-}$ mice show impaired alveolarization, an effect exacerbated in compound mutant $FOXP2^{-/-}$, $FOXP1^{+/-}$ mice, which have hypoplastic lungs and die at birth. The basis for this neonatal lethality is not known, but is associated with decreased levels of N-myc and Hop and increased expres-

sion of T1α, all genes known to be critical regulators of lung development.[123]

GATA-6

GATA-6, a zinc finger transcription factor that is required for visceral endoderm differentiation,[124] is the only GATA family member expressed in the distal epithelium of the developing lung. Mice bearing a dominant-negative GATA-6/Engrailed fusion protein under control of the SP-C promoter show reduced numbers of proximal airway tubules. Lung epithelial cell differentiation is also affected, with these mice completely lacking detectable alveolar type I cells.[125] Loss of GATA-6 in the lung epithelium causes a loss of differentiation and the precocious appearance of bronchoalveolar stem cells that is the result of increased Wnt signaling.[126] GATA-6 regulates expression of Wnt7b, and also interacts with TTF-1 to control expression of SP-A, B, and C.[4]

SOX Family

Members of the SOX family of transcription factors, which contain a high mobility group (HMG) DNA binding domain, function as key regulators of cell fate and differentiation. Of the 20 known SOX proteins, SOX2, 4, 9, 11, and 17 are found in the developing lung. SOX2 is highly expressed in nonbranching epithelium but repressed by FGF10 in epithelial cells that are actively invading the surrounding mesenchyme,[127] suggesting that silencing of SOX2 is required for the epithelium to branch. Overexpression of SOX2 in lung epithelial cells inhibits lung branching by forcing the cells to prematurely commit to a differentiation program, thereby rendering the cells incompetent to respond to branching signals.[128] SOX9 is widely expressed in the embryonic lung epithelium throughout development. Whereas mice with a global deletion of SOX9 have significant skeletal and cartilage malformations, targeted deletion of SOX9 from the respiratory epithelium has no apparent effect.[129] SOX11 is also expressed throughout the developing lung epithelium, and mice null for SOX11 have significant lung hypoplasia.[130] SOX17 expression in the lung is dynamic, being first detected in the mesenchyme during the embryonic stage, then in the conducting airway epithelium during the canalicular stage. Because its misexpression in the distal epithelium disrupts branching and causes the ectopic expression of proximal airway markers, SOX17 is thought to play a key role in specifying differentiation of airway epithelial cells.[131,131a]

Summary

Beginning as a single outpocketing of the foregut, the human lung endoderm develops into an elaborate network of airways connected to alveoli that are intimately apposed to the microvasculature. The number of different cell types in the lung, combined with the morphogenetic specificity required to generate an organ capable of maintaining efficient gas exchange, makes the molecular regulation of lung development very complex. The number of soluble factors known to mediate tissue crosstalk in the developing lung continues to grow, and it is becoming increasingly evident that the importance of these factors is dependent on their temporal and spatial expression. Adding to this complexity is the influence of insoluble extracellular matrix molecules, which we have not discussed here. Not only does matrix provide structural integrity for the developing lung, but it also contributes crucial cell signaling functions and influences the availability of diffusible factors to neighboring cells. The list of transcription factors regulating gene expression relevant to lung growth and differentiation is also extensive. As the sheer number of transcription factors, signaling molecules, growth factors, matrix molecules, and related proteins continues to expand, it becomes possible to construct transcriptional and proteomic networks reflecting the molecular developmental "blueprint" required to make the transition from primitive endoderm to mature lung. Crucial pathways, nodes and intersections will undoubtedly become apparent and should serve as the basis for targeted therapeutic interventions to treat lung injury and disease. Those who treat pulmonary disorders will best serve their patients by understanding the molecular and developmental basis supporting their clinical care.

KEY POINTS

- The lung epithelium begins as two buds from foregut endoderm. Subsequent branching morphogenesis and alveolarization lead to a mature organ containing over 300 million alveoli.
- Development of the pulmonary vasculature mirrors epithelial morphogenesis.
- Lung development requires reciprocal interactions between the epithelium and the mesenchyme derived from splanchnic mesoderm.
- Tissue interactions are mediated by an array of diffusible signaling molecules. Variations in the temporal and spatial expression of these mediators add complexity to these interactions.
- Diverse classes of transcription factors that lie downstream of diffusible mediators further regulate morphogenesis and effect the differentiation of individual cell types.

References

1. Crapo JD, Barry BE, Gehr P, et al. Cell number and cell characteristics of the normal human lung. Am Rev Respir Dis 125:332–337, 1982.
2. Shannon JM, Hyatt BA. Epithelial-mesenchymal interactions in the developing lung. Annu Rev Physiol 66:625–645, 2004.
3. Warburton D, Bellusci S, De Langhe S, et al. Molecular mechanisms of early lung specification and branching morphogenesis. Pediatr Res 57:26R–37R, 2005.
4. Maeda Y, Dave V, Whitsett JA. Transcriptional control of lung morphogenesis. Physiol Rev 87:219–244, 2007.
5. Cardoso WV, Lu J. Regulation of early lung morphogenesis: Questions, facts and controversies. Development 133:1611–1624, 2006.
6. Metzger RJ, Klein OD, Martin GR, Krasnow MA. The branching programme of mouse lung development. Nature 453:745–750, 2008.
7. Kalina M, Mason RJ, Shannon JM. Surfactant protein C is expressed in alveolar type II cells but not in Clara cells of rat lung. Am J Respir Cell Mol Biol 6:595–600, 1992.
8. Gebb SA, Shannon JM. Tissue interactions mediate early events in pulmonary vasculogenesis. Dev Dyn 217:159–169, 2000.
9. Oliver G, Alitalo K. The lymphatic vasculature: Recent progress and paradigms. Annu Rev Cell Dev Biol 21:457–483, 2005.
10. Schellhase DE, Emrie PA, Fisher JH, Shannon JM. Ontogeny of surfactant apoproteins in the rat. Pediatr Res 26:167–174, 1989.
11. Persson A, Chang D, Rust K, et al. Purification and biochemical characterization of CP4 (SP-D), a collagenous surfactant-associated protein. Biochemistry 28:6361–6367, 1989.
12. King RJ, Ruch J, Gikas EG, et al. Appearance of apoproteins of pulmonary surfactant in human amniotic fluid. J Appl Physiol 39:735–741, 1975.
13. Bourbon JR, Rieutort M, Engle MJ, Farrell PM. Utilization of glycogen for phospholipid synthesis in fetal rat lung. Biochim Biophys Acta 712:382–389, 1982.
14. Sauve RS, Robertson C, Etches P, et al. Before viability: A geographically based outcome study of infants weighing 500 grams or less at birth. Pediatrics 101:438–445, 1998.
15. Costeloe K, Hennessy E, Gibson AT, et al. The EPICure study: Outcomes to discharge from hospital for infants born at the threshold of viability. Pediatrics 106:659–671, 2000.
16. Vohr BR, Wright LL, Poole WK, McDonald SA. Neurodevelopmental outcomes of extremely low birth weight infants <32 weeks' gestation between 1993 and 1998. Pediatrics 116:635–643, 2005.
17. Lin S, Na CL, Akinbi HT, et al. Surfactant protein B (SP-B) –/– mice are rescued by restoration of SP-B expression in alveolar type II cells but not Clara cells. J Biol Chem 274:19168–19174, 1999.
18. Cameron HS, Somaschini M, Carrera P, et al. A common mutation in the surfactant protein C gene associated with lung disease. J Pediatr 146:370–375, 2005.
19. Shulenin S, Nogee LM, Annilo T, et al. ABCA3 gene mutations in newborns with fatal surfactant deficiency. N Engl J Med 350:1296–1303, 2004.
20. Stone KC, Mercer RR, Gehr P, et al. Allometric relationships of cell numbers and size in the mammalian lung. Am J Respir Cell Mol Biol 6:225–243, 1992.
21. Jobe AH, Bancalari E. Bronchopulmonary dysplasia. Am J Respir Crit Care Med 163:1723–1729, 2001.
22. Jobe AJ. The new BPD: An arrest of lung development. Pediatr Res 46:641–643, 1999.
23. Wang ML, Dorer DJ, Fleming MP, Catlin EA. Clinical outcomes of near-term infants. Pediatrics 114:372–376, 2004.
24. Masters JRW. Epithelial-mesenchymal interaction during lung development: The effect of mesenchymal mass. Dev Biol 51:98–108, 1976.
25. Rudnick D. Developmental capacities of the chick lung in chorioallantoic grafts. J Exp Zool 66:125–154, 1933.
26. Taderera JT. Control of lung differentiation in vitro. Dev Biol 16:489–512, 1967.
27. Alescio T, Cassini A. Induction in vitro of tracheal buds by pulmonary mesenchyme grafted on tracheal epithelium. J Exp Zool 150:83–94, 1962.
28. Shannon JM. Induction of alveolar type II cell differentiation in fetal tracheal epithelium by grafted distal lung mesenchyme. Dev Biol 166:600–614, 1994.
29. Wessells N. Mammalian lung development: Interactions in formation and morphogenesis of tracheal buds. J Exp Zool 175:455–466, 1970.
30. Shannon JM, Nielsen LD, Gebb SA, Randell SH. Mesenchyme specifies epithelial differentiation in reciprocal recombinants of embryonic lung and trachea. Dev Dyn 212:482–494, 1998.
31. Matsubayashi J, Ishida T, Ozawa T, et al. Subphrenic bronchopulmonary foregut malformation with pulmonary-sequestration-like features. Pathol Int 53:313–316, 2003.
32. Thebaud B, Ladha F, Michelakis ED, et al. Vascular endothelial growth factor gene therapy increases survival, promotes lung angiogenesis, and prevents alveolar damage in hyperoxia-induced lung injury: Evidence that angiogenesis participates in alveolarization. Circulation 112:2477–2486, 2005.
33. Itoh N, Ornitz DM. Functional evolutionary history of the mouse Fgf gene family. Dev Dyn 237:18–27, 2008.
34. Zhang X, Ibrahimi OA, Olsen SK, et al. Receptor specificity of the fibroblast growth factor family. The complete mammalian FGF family. J Biol Chem 281:15694–15700, 2006.
35. Rapraeger AC, Krufka A, Olwin BB. Requirement of heparan sulphate for bFGF-mediated fibroblast growth and myoblast differentiation. Science 252:1705–1708, 1991.
36. Sekine K, Ohuchi H, Fujiwara M, et al. Fgf10 is essential for limb and lung formation. Nat Genet 21:138–141, 1999.
37. De Moerlooze L, Spencer-Dene B, Revest J, et al. An important role for the IIIb isoform of fibroblast growth factor receptor 2 (FGFR2) in mesenchymal-epithelial signalling during mouse organogenesis. Development 127:483–492, 2000.
38. Weaver M, Dunn NR, Hogan BL. Bmp4 and Fgf10 play opposing roles during lung bud morphogenesis. Development 127:2695–2704, 2000.
39. Bellusci S, Grindley J, Emoto H, et al. Fibroblast growth factor 10 (FGF10) and branching morphogenesis in the embryonic mouse lung. Development 124:4867–4878, 1997.
40. White AC, Xu J, Yin Y, et al. FGF9 and SHH signaling coordinate lung growth and development through regulation of distinct mesenchymal domains. Development 133:1507–1517, 2006.
41. Colvin JS, White AC, Pratt SJ, Ornitz DM. Lung hypoplasia and neonatal death in Fgf9-null mice identify this gene as an essential regulator of lung mesenchyme. Development 128:2095–2106, 2001.
42. Usui H, Shibayama M, Ohbayashi N, et al. Fgf18 is required for embryonic lung alveolar development. Biochem Biophys Res Commun 322:887–892, 2004.
43. Ulich TR, Yi ES, Longmuir K, et al. Keratinocyte growth factor is a growth factor for type II pneumocytes in vivo. J Clin Invest 93:1298–1306, 1994.
44. Ray P. Protection of epithelial cells by keratinocyte growth factor signaling. Proc Am Thorac Soc 2:221–225, 2005.
45. Simonet WS, DeRose ML, Bucay N, et al. Pulmonary malformation in transgenic mice expressing human keratinocyte growth factor in the lung. Proc Natl Acad Sci U S A 92:12461–12465, 1995.
46. Jancelewicz T, Nobuhara K, Hawgood S. Laser microdissection allows detection of abnormal gene expression in cystic adenomatoid malformation of the lung. J Pediatr Surg 43:1044–1051, 2008.
47. Shannon JM, Pan T, Nielsen LD, et al. Lung fibroblasts improve differentiation of rat type ii cells in primary culture. Am J Respir Cell Mol Biol 24:235–244, 2001.
48. Mason RJ, Pan T, Edeen KE, et al. Keratinocyte growth factor and the transcription factors C/EBP alpha, C/EBP delta, and SREBP-1c regulate fatty acid synthesis in alveolar type II cells. J Clin Invest 112:244–255, 2003.
49. Padela S, Yi M, Cabacungan J, et al. A critical role for fibroblast growth factor-7 during early alveolar formation in the neonatal rat. Pediatr Res 63:232–238, 2008.
50. Guo L, Degenstein L, Fuchs E. Keratinocyte growth factor is required for hair development but not for wound healing. Genes Dev 10:165–175, 1996.
51. Weinstein M, Xu X, Ohyama K, Deng CX. FGFR-3 and FGFR-4 function cooperatively to direct alveogenesis in the murine lung. Development 125:3615–3623, 1998.

52. Mailleux AA, Tefft D, Ndiaye D, et al. Evidence that SPROUTY2 functions as an inhibitor of mouse embryonic lung growth and morphogenesis. Mech Dev 102:81–94, 2001.
53. Perl AK, Hokuto I, Impagnatiello MA, et al. Temporal effects of Sprouty on lung morphogenesis. Dev Biol 258:154–168, 2003.
54. Taniguchi K, Ayada T, Ichiyama K, et al. Sprouty2 and Sprouty4 are essential for embryonic morphogenesis and regulation of FGF signaling. Biochem Biophys Res Commun 352:896–902, 2007.
55. Wilson JG, Roth CB, Warkany J. An analysis of the syndrome of malformations induced by maternal vitamin A deficiency. Effects of restoration of vitamin A at various times during gestation. Am J Anat 92:189–217, 1953.
56. Mendelsohn C, Lohnes D, Decimo D, et al. Function of the retinoic acid receptors (RARs) during development (II). Multiple abnormalities at various stages of organogenesis in RAR double mutants. Development 120:2749–2771, 1994.
57. Chen F, Desai TJ, Qian J, et al. Inhibition of Tgf beta signaling by endogenous retinoic acid is essential for primary lung bud induction. Development 134:2969–2979, 2007.
58. Massaro GD, Massaro D. Postnatal treatment with retinoic acid increases the number of pulmonary alveoli in rats. Am J Physiol 270:L305–L310, 1996.
59. Darlow BA, Graham PJ. Vitamin A supplementation to prevent mortality and short and long-term morbidity in very low birthweight infants. Cochrane Database Syst Rev 4:CD000501, 2007.
60. Tyson JE, Wright LL, Oh W, et al. Vitamin A supplementation for extremely-low-birth-weight infants. National Institute of Child Health and Human Development Neonatal Research Network. N Engl J Med 340:1962–1968, 1999.
61. Massaro GD, Massaro D. Retinoic acid treatment abrogates elastase-induced pulmonary emphysema in rats. Nat Med 3:675–677, 1997.
62. Stinchcombe SV, Maden M. Retinoic acid induced alveolar regeneration: Critical differences in strain sensitivity. Am J Respir Cell Mol Biol 38:185–191, 2008.
63. Roth MD, Connett JE, D'Armiento JM, et al. Feasibility of retinoids for the treatment of emphysema study. Chest 130:1334–1345, 2006.
64. Jacob L, Lum L. Hedgehog signaling pathway. Sci STKE 2007:cm6, 2007.
65. Urase K, Mukasa T, Igarashi H, et al. Spatial expression of *Sonic Hedgehog* in the lung epithelium during branching morphogenesis. Biochem Biophys Res Commun 225:161–166, 1996.
66. Bellusci S, Furuta Y, Rush MG, et al. Involvement of Sonic hedgehog (*Shh*) in mouse enbryonic lung growth and morphogenesis. Development 124:53–63, 1997.
67. Miller LA, Wert SE, Whitsett JA. Immunolocalization of sonic hedgehog (Shh) in developing mouse lung. J Histochem Cytochem 49:1593–1604, 2001.
68. Litingtung Y, Lei L, Westphal H, Chiang C. Sonic hedgehog is essential to foregut development. Nat Genet 20:58–61, 1998.
69. Pepicelli CV, Lewis PM, McMahon AP. Sonic hedgehog regulates branching morphogenesis in the mammalian lung. Curr Biol 8:1083–1086, 1998.
70. Weaver M, Batts L, Hogan BL. Tissue interactions pattern the mesenchyme of the embryonic mouse lung. Dev Biol 258:169–184, 2003.
71. Kim J, Kim P, Hui CC. The VACTERL association: Lessons from the Sonic hedgehog pathway. Clin Genet 59:306–315, 2001.
72. Oldak M, Grzela T, Lazarczyk M, et al. Clinical aspects of disrupted Hedgehog signaling (review). Int J Mol Med 8:445–452, 2001.
73. Yu H, Wessels A, Chen J, et al. Late gestational lung hypoplasia in a mouse model of the Smith-Lemli-Opitz syndrome. BMC Dev Biol 4:1, 2004.
74. Lewis PM, Dunn MP, McMahon JA, et al. Cholesterol modification of sonic hedgehog is required for long-range signaling activity and effective modulation of signaling by Ptc1. Cell 105:599–612, 2001.
75. Chen Y, Struhl G. Dual roles for patched in sequestering and transducing Hedgehog. Cell 87:553–563, 1996.
76. Chuang PT, McMahon AP. Vertebrate Hedgehog signalling modulated by induction of a Hedgehog-binding protein. Nature 397:617–621, 1999.
77. Chuang PT, Kawcak T, McMahon AP. Feedback control of mammalian Hedgehog signaling by the Hedgehog-binding protein, Hip1, modulates Fgf signaling during branching morphogenesis of the lung. Genes Dev 17:342–347, 2003.
78. Platt KA, Michaud J, Joyner AL. Expression of the mouse Gli and Ptc genes is adjacent to embryonic sources of hedgehog signals suggesting a conservation of pathways between flies and mice. Mech Dev 62:121–135, 1997.
79. Grindley JC, Bellusci S, Perkins D, Hogan BLM. Evidence for the involvement of the *Gli* gene family in embryonic mouse lung development. Dev Biol 188:337–348, 1997.
80. Motoyama J, Liu J, Mo R, et al. Essential function of Gli2 and Gli3 in the formation of lung, trachea and oesophagus [see comments]. Nat Genet 20:54–57, 1998.
81. Craig DW, Itty A, Panganiban C, et al. Identification of somatic chromosomal abnormalities in hypothalamic hamartoma tissue at the GLI3 locus. Am J Hum Genet 82:366–374, 2008.
82. Serra R, Pelton RW, Moses HL. TGFβ1 inhibits branching morphogenesis and N-*myc* expression in lung bud organ cultures. Development 120:2153–2161, 1994.
83. Zhou L, Dey CR, Wert SE, Whitsett JA. Arrested lung morphogenesis in transgenic mice bearing an SP-C—TGF-β1 chimeric gene. Dev Biol 175:227–238, 1996.
84. Schmierer B, Hill CS. TGFbeta-SMAD signal transduction: Molecular specificity and functional flexibility. Nat Rev Mol Cell Biol 8:970–982, 2007.
85. Zhao J, Bu D, Lee M, et al. Abrogation of transforming growth factor-beta type II receptor stimulates embryonic mouse lung branching morphogenesis in culture. Dev Biol 180:242–257, 1996.
86. Zhao J, Lee M, Smith S, Warburton D. Abrogation of Smad3 and Smad2 or of Smad4 gene expression positively regulates murine embryonic lung branching morphogenesis in culture. Dev Biol 194:182–195, 1998.
87. Shull MM, Ormsby I, Kier AB, et al. Targeted disruption of the mouse transforming growth factor-β1 gene results in multifocal inflammatory disease. Nature 359:693–699, 1992.
88. Sanford LP, Ormsby I, Gittenberger-de Groot AC, et al. TGFbeta2 knockout mice have multiple developmental defects that are non-overlapping with other TGFbeta knockout phenotypes. Development 124:2659–2670, 1997.
89. Kaartinen V, Voncken JW, Shuler C, et al. Abnormal lung development and cleft palate in mice lacking TGF-beta 3 indicates defects of epithelial-mesenchymal interaction. Nat Genet 11:415–421, 1995.
90. Weaver M, Yingling JM, Dunn NR, et al. Bmp signaling regulates proximal-distal differentiation of endoderm in mouse lung development. Development 126:4005–4015, 1999.
91. Lu MM, Yang H, Zhang L, et al. The bone morphogenic protein antagonist gremlin regulates proximal-distal patterning of the lung. Dev Dyn 222:667–680, 2001.
92. Eblaghie MC, Reedy M, Oliver T, et al. Evidence that autocrine signaling through Bmpr1a regulates the proliferation, survival and morphogenetic behavior of distal lung epithelial cells. Dev Biol 291:67–82, 2006.
93. Logan CY, Nusse R. The Wnt signaling pathway in development and disease. Annu Rev Cell Dev Biol 20:781–810, 2004.
93a. Goss AM, Tian Y, Tsukiyama T, et al. Wnt2/2b and beta-catenin signaling are necessary and sufficient to specify lung progenitors in the foregut. Dev Cell 17:290–298, 2009.
94. Li C, Hu L, Xiao J, et al. Wnt5a regulates Shh and Fgf10 signaling during lung development. Dev Biol 287:86–97, 2005.
95. Shu W, Jiang YQ, Lu MM, Morrisey EE. Wnt7b regulates mesenchymal proliferation and vascular development in the lung. Development 129:4831–4842, 2002.
96. Mucenski ML, Wert SE, Nation JM, et al. beta-Catenin is required for specification of proximal/distal cell fate during lung morphogenesis. J Biol Chem. 278:40231–40238, 2003.
97. Shu W, Guttentag S, Wang Z, et al. Wnt/beta-catenin signaling acts upstream of N-myc, BMP4, and FGF signaling to regulate proximal-distal patterning in the lung. Dev Biol 283:226–239, 2005.
98. Okubo T, Hogan BL. Hyperactive Wnt signaling changes the developmental potential of embryonic lung endoderm. J Biol 3:11, 2004.

99. Bostrom H, Willetts K, Pekny M, et al. PDGF-A signaling is a critical event in lung alveolar myofibroblast development and alveogenesis. Cell 85:863–873, 1996.
100. Greenberg JM, Thompson FY, Brooks SK, et al. Mesenchymal expression of vascular endothelial growth factors D and A defines vascular patterning in developing lung. Dev Dyn 224:144–153, 2002.
101. Ng YS, Rohan R, Sunday ME, et al. Differential expression of VEGF isoforms in mouse during development and in the adult. Dev Dyn 220:112–121, 2001.
102. Akeson AL, Greenberg JM, Cameron JE, et al. Temporal and spatial regulation of VEGF-A controls vascular patterning in the embryonic lung. Dev Biol 264:443–455, 2003.
103. White AC, Lavine KJ, Ornitz DM. FGF9 and SHH regulate mesenchymal Vegfa expression and development of the pulmonary capillary network. Development 134:3743–3752, 2007.
104. Liggins GC. Premature delivery of foetal lambs infused with glucocorticoids. J Endocrinol 45:515–523, 1969.
105. Rajatapiti P, Keijzer R, Blommaart PE, et al. Spatial and temporal expression of glucocorticoid, retinoid, and thyroid hormone receptors is not altered in lungs of congenital diaphragmatic hernia. Pediatr Res 60:693–698, 2006.
106. Rooney SA. Regulation of surfactant-associated phospholipid synthesis and secretion. *In* Polin RA, Fox WW, Abman SH (eds). Fetal and Neonatal Physiology (Vol 2, 3rd ed.) Philadelphia: WB Saunders, 2004:1041–1054.
107. Cole TJ, Blendy JA, Monaghan AP, et al. Targeted disruption of the glucocorticoid receptor gene blocks adrenergic chromaffin cell development and severely retards lung maturation. Genes Dev 9:1608–1621, 1995.
108. Cole TJ, Solomon NM, Van Driel R, et al. Altered epithelial cell proportions in the fetal lung of glucocorticoid receptor null mice. Am J Respir Cell Mol Biol 30:613–619, 2004.
109. Muglia LJ, Bae DS, Brown TT, et al. Proliferation and differentiation defects during lung development in corticotropin-releasing hormone-deficient mice. Am J Respir Cell Mol Biol 20:181–188, 1999.
110. Roberts D, Dalziel S. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev 3:CD004454, 2006.
111. Willet KE, Jobe AH, Ikegami M, et al. Lung morphometry after repetitive antenatal glucocorticoid treatment in preterm sheep. Am J Respir Crit Care Med 163:1437–1443, 2001.
112. Mammel MC, Green TP, Johnson DE, Thompson TR. Controlled trial of dexamethasone therapy in infants with bronchopulmonary dysplasia. Lancet 1:1356–1358, 1983.
113. Postnatal corticosteroids to treat or prevent chronic lung disease in preterm infants. Pediatrics 109:330–338, 2002.
114. Kimura S, Hara Y, Pineau T, et al. The *T/ebp* null mouse: Thyroid-specific enhancer-binding protein is essential for the organogenesis of the thyroid, lung, ventral forebrain, and pituitary. Genes Dev 10:60–69, 1996.
115. Devriendt K, Vanhole C, Matthijs G, de Zegher F. Deletion of thyroid transcription factor-1 gene in an infant with neonatal thyroid dysfunction and respiratory failure. N Engl J Med 338:1317–1318, 1998.
116. Ang SL, Wierda A, Wong D, et al. The formation and maintenance of the definitive endoderm lineage in the mouse: involvement of HNF3/forkhead proteins. Development 119:1301–1315, 1993.
117. Wan H, Kaestner KH, Ang SL, et al. Foxa2 regulates alveolarization and goblet cell hyperplasia. Development 131:953–964, 2004.
118. Besnard V, Wert SE, Kaestner KH, Whitsett JA. Stage-specific regulation of respiratory epithelial cell differentiation by Foxa1. Am J Physiol Lung Cell Mol Physiol 289:L750–L759, 2005.
119. Wan H, Dingle S, Xu Y, et al. Compensatory roles of Foxa1 and Foxa2 during lung morphogenesis. J Biol Chem 280:13809–13816, 2005.
120. Mahlapuu M, Enerback S, Carlsson P. Haploinsufficiency of the forkhead gene Foxf1, a target for sonic hedgehog signaling, causes lung and foregut malformations. Development 128:2397–2406, 2001.
121. Chen J, Knowles HJ, Hebert JL, Hackett BP. Mutation of the mouse hepatocyte nuclear factor/forkhead homologue 4 gene results in an absence of cilia and random left-right asymmetry. J Clin Invest 102:1077–1082, 1998.
122. Kim IM, Ramakrishna S, Gusarova GA, et al. The forkhead box m1 transcription factor is essential for embryonic development of pulmonary vasculature. J Biol Chem 280:22278–22286, 2005.
123. Shu W, Lu MM, Zhang Y, et al. Foxp2 and Foxp1 cooperatively regulate lung and esophagus development. Development 134:1991–2000, 2007.
124. Morrisey EE, Tang Z, Sigrist K, et al. GATA6 regulates HNF4 and is required for differentiation of visceral endoderm in the mouse embryo. Genes Dev 12:3579–3590, 1998.
125. Yang H, Lu MM, Zhang L, et al. GATA6 regulates differentiation of distal lung epithelium. Development 129:2233–2246, 2002.
126. Zhang Y, Goss AM, Cohen ED, et al. A Gata6-Wnt pathway required for epithelial stem cell development and airway regeneration. Nat Genet 40:862–870, 2008.
127. Que J, Okubo T, Goldenring JR, et al. Multiple dose-dependent roles for Sox2 in the patterning and differentiation of anterior foregut endoderm. Development 134:2521–2531, 2007.
128. Gontan C, de Munck A, Vermeij M, et al. Sox2 is important for two crucial processes in lung development: Branching morphogenesis and epithelial cell differentiation. Dev Biol 317:296–309, 2008.
129. Perl AK, Kist R, Shan Z, et al. Normal lung development and function after Sox9 inactivation in the respiratory epithelium. Genesis 41:23–32, 2005.
130. Sock E, Rettig SD, Enderich J, et al. Gene targeting reveals a widespread role for the high-mobility-group transcription factor Sox11 in tissue remodeling. Mol Cell Biol 24:6635–6644, 2004.
131. Park KS, Wells JM, Zorn AM, et al. Sox17 influences the differentiation of respiratory epithelial cells. Dev Biol 294:192–202, 2006.
131a. Lange AW, Keiser AR, Wells JM, et al. Sox17 promotes cell cycle progression and inhibits TGF-beta/Smad3 signaling to initiate progenitor cell behavior in the respiratory epithelium. PLoS One 4:e5711, 2009.

CHAPTER 3

Mendelian Genetics, Disease Modifying or Associated Genes, and Epigenetics of Lung Disease

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THE PATH FORWARD

INTRODUCTION

There are two fundamental causes of most human diseases, genetic polymorphisms and environmental exposures. The first step in any investigation of the genetic causes of a disease or phenotype is to determine the relative importance of these two causes of the disorder. To begin this process, one must determine the heritability of the disease of interest. *Heritability* is defined as the estimated percentage of phenotypic variation that is due to genetic factors. Often, the first step is to determine if the trait, disease, or phenotype aggregates in families, but this will not prove that the trait of interest is genetic as traits can aggregate in families for purely environmental reasons, such as cigarette smoking, or because the prevalence of the trait is high, such as obesity. So the only direct way to determine whether a disease has a genetic cause is to measure heritability. Heritability can be estimated in twin studies, that is, a greater concordance of the phenotype between identical (monozygotic) twins than fraternal (dizygotic) twins. Such data provide evidence of significant heritability. For lung disorders, heritabilities range from 20% to 90% depending on the type of lung disease, the mode of inheritance, and the degree of environmental influence.

There are two primary types of genetic disorders: monogenic (due to a single gene) or complex (due to multiple genes). Monogenic disorders demonstrate high heritability, segregate in families in a predictable way, and are caused by a single major gene with less obvious environmental influence. The single gene usually has specific variation in the coding region of the gene that leads to an abnormal protein that causes an obvious clinical phenotype. Often the phenotype has multiple components, suggesting multiple effects of the gene. This is called pleotropy or one gene having many effects. There are currently over 10,000 monogenic disorders that have been identified and are characterized in Online Mendelian Inheritance in Man (OMIM) (http://www.ncbi.nlm.nih.gov/sites/entrez?db=omim). Linkage mapping and then positional cloning (described later) have been the primary means of their identification. With the completion of the Human Genome Project,

attention has been turned to trying to identify genes associated with complex genetic disorders initially using similar methods but now primarily with genetic association studies.

In contrast to monogenic disorders, complex genetic disorders are caused by multiple genes and multiple environmental exposures, with each gene having a much smaller effect than that seen in monogenic disorders. Because of the multiple gene-gene and gene-environment interactions, there is no obvious mendelian mode of inheritance for complex traits. The most common hypothesis for the genetic basis of common disease is the common disease/common variant hypothesis. This hypothesis suggests that key genetic determinants of common diseases have a relatively high allele frequency, that is, 5% to 40%, and modest effect sizes. Given the modest effect sizes (odds ratios on the order of 1.1–1.4), large sample sizes are necessary to identify the genetic variants associated with complex traits despite the high allele frequency expected in these disorders.

The dichotomy described previously is now beginning to be broken down as geneticists realize that the clinical phenotype of many monogenic disorders varies as a result of other genes and environmental exposures. As genes for complex traits begin to be identified, their role in monogenic disorders is also being elucidated.

Scope of the Problem

Some complex genetic disorders, such as age-related macular degeneration, are oligogenic, where a small number of genes, 3 to 5, explain the bulk of the clinical phenotype. However, for most complex traits, literally hundreds of genes with small effects are involved in disease causation and thus there are a series of challenges that have faced complex trait geneticists as we enter the genome era of medicine.

Initial problems relating to genotyping reliability and completeness that were present at the time of release of the initial sequence of the genome have been largely resolved, but many problems still remain. Because genetic association studies are the backbone of gene finding in complex traits, issues of sample size and population stratification (confounding by allele frequency differences in cases and controls, discussed later) remain problems for investigators. The ability to determine if genetic effects are real or not requires replication of results in independent populations, a process that is difficult with the presence of phenotypic heterogeneity across populations. With the move to testing of 500,000 to 1 million markers in whole genome association studies, the problem of multiple comparisons is a major issue, and ultimately putting 100 to 500 genes together in networks to model disease occurrence will require formidable bioinformatics capabilities. Finally, the ultimate challenge of finding the actual functional variants in putative disease genes is still a laborious process without a clear-cut methodology for success.

Potential Impact of Human Genetics

Genetics has the potential, because of its hypothesis-free nature, to identify novel mechanisms of disease pathobiology and, hence, to identify novel targets for a therapeutic intervention or disease prevention. In addition, genetics has the potential to predict specific subgroups of patients with different clinical course or response of their disease or differences in treatment. Finally, genetics has the potential to allow for early detection of susceptible individuals at risk of a specific disease phenotype or to allow avoidance of environmental factors that are known to cause the disease or to institute preventive therapy before disease develops. Of all of these applications, the predictive one is likely to be implemented first. But the application of each of these genetic insights is still just beginning to occur and it may take time for genetics to become routinely used at the bedside.

MOLECULAR CHARACTERIZATION OF GENETIC VARIATION

Molecular genetics is elegant in its simplicity. Just four base pairs (two purines [adenine and guanine] bind to two pyrimidines [thymine and cytosine]) code for 20 amino acids that form the molecular building blocks of complex proteins. However, the assemblage of inherited genes (genotypes), control mechanisms, resultant proteins, and posttranslational modifications has the capacity to create a complex panoply of unique biologic, physiologic, or visible traits of an organism (phenotypes). The relationship between these rather simple molecular characteristics and the vast array of complex phenotypes is, in part, explained by a number of seminal discoveries that were made more than 50 years ago.

Gregor Mendel[1] was the first to demonstrate that discrete traits could be inherited as separable factors (genes) in a mathematically predictable manner. Mendel's laws describe the relationship between genotype and phenotype and establish the concept that each gene has alternative forms (alleles). Charles Darwin[2] made the observation that evolution represents a series of environmentally responsive "genomic" upgrades, and Thomas Morgan[3] established the concept of linkage by using *Drosophila* to discover that genes were organized (and inherited) on individual chromosomes, that recombination or exchange of genetic material between maternal and paternal chromosomes occurred during meiosis, and that the frequency of recombination could be used to establish the relative distance between genes. However, it was not until 1944 that Avery, MacLeod, and McCarty while working with *Pneumococcus* discovered that DNA was the essential molecule that transmitted the genetic code.[4] The double-helix structure of DNA was discovered by Watson, Crick, Chargaff, Franklin, and Wilkins in 1953,[5] and over the next 50 years, genetics assumed a central role in understanding the biologic and physiologic differences between and among species and between states of health and states of disease. In

aggregate, these seminal discoveries led to a number of basic principles in molecular genetics that provide the basic mechanisms that link the four base pairs (adenine [A] binding to thymine [T] and guanine [G] binding to cytosine [C]) to health and disease.

Genomic Maps

Over the past several decades, genomic maps have evolved from karyotypes (microscopic visualization of chromosomes during metaphase) to restriction enzyme sites to genetic maps to maps with specific base pair sequence. In fact, to date, there are 15 vertebrates, 8 invertebrates, 7 protozoa, 42 plants, 17 fungi, and hundreds of bacteria and viruses that have been sequenced and are available on the National Center for Biotechnology Information (NCBI) website (www.ncbi.nlm.nih.gov). Not only have these genomic maps been critical to identifying which genes and sequence changes cause disease or enhance the risk of adverse outcomes, these species-specific maps have also led to a very clear understanding of molecular evolution and have provided essential tools to understand aspects of molecular biology. The construction of these genomic maps are based on the observation that the sequence of DNA is different from one organism to the next within the same species, and these allelic/sequence differences have been exploited to develop a number of commonly used DNA markers to create genomic maps (Table 3-1).

Genetic maps are based on the frequency of recombinant events defined as the exchange of genetic material between the maternal and the paternal chromosomes during meiosis. While Mendel's second law states that traits (or genes) are inherited independently, we now know that some genes do not segregate independently because they are on the same chromosome. Humans have 24 linkage groups, corresponding to the 22 autosomes, plus X and Y chromosomes. Genes on the same chromosome that are closer together are more likely to be inherited together (linked) than genes that are farther apart (may demonstrate independent assortment). In general, the greater the distance between genes on the same chromosome, the higher the recombination frequency (Fig. 3-1). Thus, the recombination frequency represents a measure of genetic linkage and is the fundamental event used to create a genetic linkage map. The unit of measurement for genetic linkage maps is the centimorgan (cM), with 1 cM equivalent to a recombination frequency of 1% (one recombinant event/100 meioses). While recombination frequencies vary across the chromosome, in general, at least for the human genome, a recombination frequency of 1% is equivalent to approximately 1 million base pairs. Genetic maps are constructed by identifying the number of recombinant events observed in parental meioses and are dependent on several factors: (1) the meioses observed; (2) the heterozygosity of the marker; (3) the physical distance between markers; and (4) the likelihood of recombination at that site. Genetic maps use a rather indirect method to estimate the order of genes and the relative distance between genes.

Genetic maps are routinely used in family-based linkage studies to identify the general location of genes that influence human traits and conditions. Highly polymorphic markers can be used as tags to identify regions of DNA that are associated with the occurrence of disease in families. These regions of DNA then serve as the targets to comprehensively interrogate the sequence of genes and their regulatory components. However, a

TABLE 3-1. Commonly Used DNA Markers

Restriction fragment length polymorphisms (RFLPs)—Presence or absence of a specific nucleotide sequence that can be cleaved by a restriction enzyme. These bacterial restriction enzymes fragment DNA only at sites that contain specific base pair sequences.

Variable number of tandem repeat polymorphisms (VNTRs)—Noncoding polymorphic base pair repeats in DNA (di-, tri-, and tetranucleotide repeats of CA or GT) that are present throughout the genome. At each site, the number of times a sequence is repeated may vary from one individual to the next.

Microsatellite polymorphism—Variable number of repetitions of a small number of base pairs within a sequence.

Single nucleotide polymorphisms (SNPs)—Individual point substitutions of a single nucleotide that do not change the length of the DNA sequence and occur throughout the genome (every several hundred base pairs).

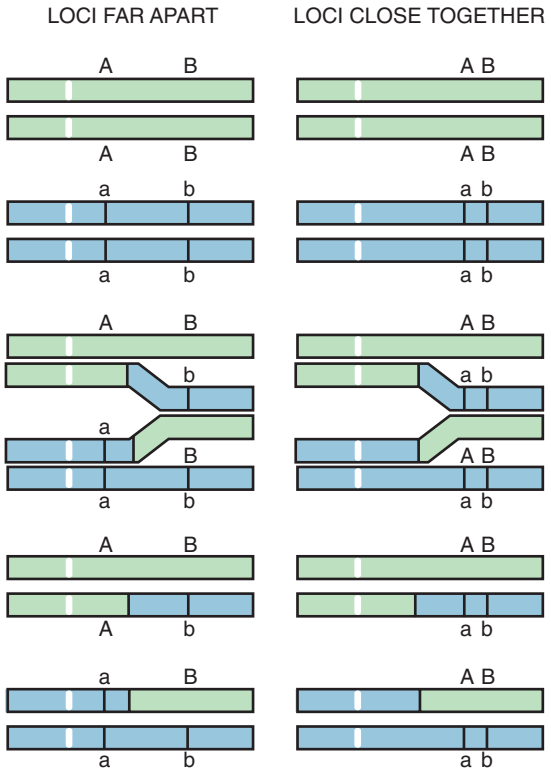

FIGURE 3-1 ■ Crossover between homologous chromosomes in meiosis. On the left is an example in which two loci are far apart on the chromosomes and so remain unlinked. On the right, the loci are relatively close to one another and so after recombination are more likely to remain together.

genetic linkage map should not be confused with a physical map of the genome since it is based on the rate of recombination, not the physical distance, between markers.

In contrast to a genetic map, a physical map describes the physical location of genes and the physical relationship between genes on each chromosome. Although the gene order from a genetic map and a physical map should theoretically be the same, the relative distance between genes may be quite different when comparing a genetic map (based on recombination frequency) with a physical map. The reason for this discrepancy is that some chromosomal regions, referred to as recombination hotspots, have much higher recombination frequencies than other regions. However, genetic maps provide a framework for the construction of physical maps.

While we typically think of physical maps as sequence-based, many years before sequence-based maps became available, investigators relied on lower resolution cytogenetic (chromosomal) and radiation hybrid maps. Cytogenetic maps are based on chromosomal banding patterns and have been used to locate genes in patients with chronic granulomatous disease, Duchenne's muscular dystrophy, and fragile X syndrome. Radiation hybrid maps, like genetic maps, estimate the physical distance between markers, but use breaks in DNA induced by radiation to determine the distance. By changing the dose of radiation, one can produce more (or less) resolved maps. Radiation hybrid maps have been extremely useful in ordering markers in a region when highly polymorphic markers were scarce.

Two major breakthroughs occurred during the early 2000s that has forever changed human genetics—the sequencing of the human genome[6,7] and the International HapMap Project[8] to identify the sequence specific differences and similarities between individuals. With the sequencing of the human genome, investigators for the first time had a detailed road map of the human genome that identified the genes, regulatory units, and noncoding sequence with a very high degree of resolution. Among the 3.2 billion base pairs in the human genome, less than 1% uniquely identifies each human being.[9] Single nucleotide polymorphisms (SNPs) are predicted to occur at least every 300 base pairs. While only 40% of these SNPs will result in amino acid changes, these SNPs provide the genetic diversity that underlies the variable susceptibility to environmental stimuli and the variable risk of disease development and progression.[9] By comparing the genetic sequences of different individuals, the HapMap Project was able to identify chromosomal regions where genetic variants were shared between individuals. While the initial HapMap project focused on four populations from African, Asian, and European ancestry, ongoing work is expanding these maps of shared genetic material.

In aggregate, the human DNA sequence and the shared genetic patterns between individuals have enabled geneticist to define the organization of genetic variants on chromosomes and the common inheritance of genetic variants. These developments have provided the polymorphic markers and the regions that are tagged to these markers that facilitate the identification of regions and genes. Consequently, real progress is now being made in identifying common genetic variations that contribute to complex diseases such as asthma,[10] age-related macular degeneration,[11] type 2 diabetes,[12] and prostate cancer.[13]

Comparative Genomics

Because DNA structure and protein functions are often conserved through evolution, the use of model organisms can enhance the efficiency of gene discovery and can provide insights into biologic responses to endogenous and exogenous forms of stress. Although genes present in humans oftentimes have counterparts in other species, the homology between gene and chromosomal structure across species does not necessarily lead to conserved protein function. However, the conservation of gene sequence and chromosomal structure in different organisms has resulted in accelerated gene discovery, insights into human biology, and a data-driven understanding of evolution. Despite this excitement, the field of comparative genomics is at a very early stage of development[14] and is dependent on evolving databases, like Gene Ontology functional classifications,[15] to facilitate these cross-species comparisons.

Comparative genomics is a powerful approach to search for disease-causing genes. Identifying similar regions of DNA associated with concordant phenotypes in multiple species enhances the confidence that a gene causing that disease resides in that locus. The overlapping DNA for concordant phenotypes between species can be used to substantially narrow the region of interest. Because there are approximately 340 known conserved segments between mice and humans,[16] a mouse region of interest associated with a trait can be used to narrow the human region of interest associated with a disease. In addition, the genomes of model organisms, such as mice, flies, worms, or yeast, can be manipulated through genetic engineering (resulting in deficiency or overexpression of a gene or controlled expression of a human allele) to further understand the function of a specific gene. For example, the discovery of the importance of the Toll-like receptors in innate immunity in mammals occurred as a direct result of the observation that a defective receptor in flies caused them to be much more susceptible to *Aspergillus fumigatus*.[17,18] The importance of this finding is clearly illustrated in the variations in the Toll-like receptors that alter the response to microbial pathogens[19] and modify the risk of developing a variety of diseases that are associated with innate immunity.[20] The ease with which we can observe and apply knowledge across model systems should be exploited so that we can efficiently understand the biologic and clinical importance of key regulatory genes.

Public Databases

If compiled in books, the data produced in defining the human genome would fill 200 volumes, each the size of a 1000-page phone book. Reading it would require 26

TABLE 3-2. Genetic Variation-Focused Databases on the Web

Mutation Databases	
HUGO	www.genomic.unimelb.edu.au/mdi/dblist/dblist.html
OMIM	www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM
SNP Databases	
SNP Consortium	snp.cshl.org
dbSNP	www.ncbi.nlm.nih.gov/SNP/
Genetic Marker Maps	
Genome Database	www.gdb.org
Marshfield Maps	research.marshfieldclinic.org/genetics/Map_Markers/maps
Genome Browsing	
Human Genome Browser	genome.uscs.edu/index.html
Map Viewer	www.ncbi.nlm.nih.gov/mapview/

years working around the clock. While new tools are being developed to analyze, store, and present the data from genome maps and sequences, several databases presently exist that can be accessed through the Internet.

Important lessons can be learned from a detailed consideration of the characteristics of identified mutations in Mendelian diseases using online resources such as OMIM, the Human Gene Mutation Database (HGMD), and LocusLink.[21] For example, the data on the relative frequency of types of mutations underlying disease phenotypes indicate that mendelian disease genes most often have alterations in the normal protein-coding sequence. For general information on accessing sequence information, several available reviews provide details on available databases and searching strategies.[22] Table 3-2 gives the genetic variation–focused databases available on the Web. The NCBI is responsible for the final and reference assembly of the human genome (http://www.ncbi.nlm.nih.gov). Each DNA sequence is annotated with sequence features and other experimental data, including location of SNPs, expressed sequence tags, and clones. Up-to-date genetic sequence information can be obtained from Ensembl (http://www.ensembl.org), the University of California at Santa Cruz Genome Browser, and NCBI's GenBank. NCBI's Map Viewer provides a tool through which genetic maps and sequence data can be visualized and is linked to other tools such as Entrez, the integrated retrieval system providing access to numerous component databases (http://www.ncbi.nlm.nih.gov/Entrez/index.html). The database of Single Nucleotide Polymorphisms (dbSNP) at the NCBI allows the user to search for SNPs within a region of interest (http://www.ncbi.nlm.nih.gov/SNP).

GENETIC EPIDEMIOLOGY

Genetic Markers and Their Inheritance

The human genome is composed of approximately 3 billion base pairs. With the exception of identical twins, each human being has a unique DNA sequence. There are at least 10 million locations in the genome where DNA sequence varies between individuals. These locations are referred to as *polymorphic*, where there are at least two variants (also known as alleles) that occur with greater than 1% frequency. There are two commonly studied polymorphisms in human genetics; short tandem repeat (STR) markers (also known as microsatellites) and single nucleotide polymorphisms (SNPs). In general, STR markers are used for linkage and SNPs are used for genetic association studies, although technically, either marker can be used for both types of investigation.

STR markers are repeats of two, three, or four bases that are reasonably frequent in the genome. They tend to have multiple, common alleles that allow the transmission of specific regions on a chromosome to be followed accurately through a pedigree. They are not usually disease-susceptibility variants themselves, although they may be linked to such a variant.

There are approximately 12 million SNPs in the human genome. These are single base pair changes that result in allelic variation at a locus. So one could be c or g, and hence, all individuals are one or the other allele. These are the most common source of genetic variation used in genetic association studies. In addition to SNPs and STRs, insertions, deletions, and larger structural variations also occur commonly in the human genome.

Disorders that are monogenic typically have SNPs, insertions, or deletions within a single gene that result in a clear phenotype that segregates in families in a recognizable pattern. These patterns are clinically recognizable as definable Mendelian modes of inheritance (e.g., autosomal dominant, autosomal recessive, or x-linked dominant or recessive). Examples of monogenic disorders would be chronic obstructive pulmonary disease (COPD) due to severe alpha$_1$ antitrypsin deficiency, which results from mutations in the SERPIN A1 gene; or cystic fibrosis, which is the most common autosomal recessive disorder in white, which is due to mutations in the cystic fibrosis transmembrane conductance regulator gene (CFTR).

Linkage and Positional Cloning

Linkage analysis is a property of families and encompasses a group of genetic methods to analyze the distribution of DNA markers within families to determine whether there is a relationship between a particular region of the genome and a phenotype of interest. A requirement of linkage is to have family data, either extended pedigrees, trios, or affected sib pairs. The technique uses the concept of linkage disequilibrium or nonrandom assortment of alleles and the tendency of nearby genetic loci to be inherited together. When a mutation occurs on a particular chromosome, initially there is a large shared segment of DNA and hence linkage disequilibrium around it. With each subsequent generation, this region of linkage disequilibrium becomes smaller as a result of meiotic recombination. A basic approach in linkage analysis is to determine if alleles at two independent loci segregate together more often than one would

expect by random assortment or chance. This can be assessed by comparing the frequency of recombinant chromosomes in which a crossing over event has rearranged the parental chromosomes with the frequency of nonrecombinant chromosomes. When the loci are linked, parental chromosomes are more common than recombinant chromosomes. The strength of the linkage, expressed as the recombination fraction, is dependent on the genetic distance between loci. The more tightly linked the two loci are, the less likely it is to find recombinant chromosomes.

Linkage results are usually expressed as a LOD score, which is the result of a statistical test to determine if genetic loci are linked. LOD scores are log of the base 10 of the odds that the loci are linked and depend on study design. Linkage studies are usually based on STR or SNP markers distributed through the genome to search for susceptibility genes located anywhere on the genome. One of the tested markers will be close enough to demonstrate evidence of linkage. Typically, a genome-wide linkage scan requires about 400 STR markers that are equally spaced across the genome. LOD scores of 3 to 3.6 correspond to significant linkage. Linkage analysis was originally developed using a specific genetic model in which the allele frequency penetrance and mode of inheritance are specified. Positional cloning typically begins with genome-wide linkage studies, followed by fine mapping of linked regions with genetic association studies, either case-control or family-based, which are described later. Thus, the technique is ideal for classic Mendelian, monogenic disorders, but is less well adapted for complex traits, where these parameters are often not known. However, nonparametric methods have been widely used in complex traits, and this approach can be combined with genetic association within the linked region to identify disease susceptibility genes, particularly for asthma and Crohn's disease.[23–27]

Genetic Association and Candidate Genes

Zhang and Risch[28] have suggested that association studies can be a very powerful approach for finding genetic determinants of a complex disorder. Currently, genetic association studies are the most commonly used study designs to find disease genes in complex traits. These can be used in conjunction with linkage studies (positional cloning) or de novo with candidate genes or genome-wide association studies (GWAS). There are two basic types of study designs used for genetic association studies. These are the case-control study, and the family-based study.

Case-control studies are the most frequently performed type of genetic association studies because they are the easiest to do. In their simplest form, population-based genetic association studies are similar to epidemiologic case-control studies and involve identifying genetic markers with significant allele-frequency differences between individuals with the phenotype of interest (cases) and a set of unrelated control individuals.[29] A statistical association between genotypes at a marker locus and the phenotype can arise for three reasons: (1) the allele is the actual disease allele, (2) the allele being studied is in linkage disequilibrium with the true disease allele, and (3) a spurious association due to population stratification. Indeed, case-control genetic association studies have already contributed to identifying genes associated with complex disorders, as in the cases of apolipoprotein E-4 with late-onset Alzheimer's disease[30] and factor V gene with venous thrombosis.[31] Thus, performing valid case-control studies remains important in elucidating genetic risk factors for complex traits. Silverman and Palmer[32] have reviewed these factors that may adversely affect the results of any association study in complex diseases. They have recommended five key elements in the performance of valid case-control genetic association studies for complex diseases. These include (1) proper selection of gene polymorphisms, (2) accounting for population stratification, (3) assessment of Hardy-Weinberg equilibrium, (4) replication, and (5) adjustment for multiple comparisons.

Ideally, cases and control study subjects should be drawn from the same base population. Failure to do so will often result in biased selection that can adversely influence the results, often resulting in a spurious association. When subjects with different evolutionary histories and hence different genetic backgrounds are differentially selected to be cases and controls, this can cause spurious results, termed "population stratification." An approach useful in case-control studies to control this problem is to assess for population stratification in case and control groups by genotyping randomly distributed polymorphic markers.[33,34] Failure to demonstrate association to these random markers suggests that significant population stratification is not present, and case-control genetic association studies can likely be performed without significant risk of erroneous results due to population stratification. If population stratification is demonstrated between the case and the control populations, methods to detect significant disease gene associations have been developed based on correction for the degree of stratification.[34,35] A second major problem with case-control studies is that often too small sample size is used, often resulting in spurious association. Because of the small effect size seen in complex trait genetic association, sample size in the thousands is needed with replication to generate unequivocal results.

Family-based genetic association tests (FBAT) are based on the transmission disequilibrium test (TDT), which provides a test of linkage and association without bias from population stratification or admixture.[36,37] Parents and an individual offspring (child or proband) with the disease phenotype are recruited. Only trios with at least one heterozygous parent at the genetic marker of interest are used for testing. The test is predicated on hypothesizing that if a genetic locus is uninvolved in the phenotype of interest, one would expect the parents' allele at that locus to be transmitted equally (i.e., Mendelian, transmitted 50% of the time). However, if the locus is actually associated with disease, there will be over- (or under-) transmission of the allele at that

locus—and its transmission will differ significantly from the expected 50%.

Family-based association studies cost more than case-control studies because one has to recruit and genotype three people instead of two. In addition, not all diseases can utilized the family-based design because often parents have died and hence are not available for study. Despite these disadvantages, there are also powerful reasons to use trios if possible. First, unlike the case-control study, the family-based association study is immune to population stratification because you are using the parental genotype as the control. Second, within each trio, only one person (the subject) must be phenotyped. This is particularly useful when phenotyping is very expensive or invasive. Family-based testing also offers an important method of assessing genotyping quality, because data can be analyzed for mendelian errors.

Linkage disequilibrium with a gene or a region of a chromosome is very helpful in genetic association studies. When two SNPs are on separate chromosomes, they will segregate randomly (i.e., carrying the minor allele at SNP A does not affect your chances of carrying the minor allele at SNP B). If, conversely, the SNPs are in linkage disequilibrium, with little or no recombination between them, the genotype at SNP B can serve as a surrogate for SNP A. Thus, testing of all SNPs in a gene or a region of the genome is unnecessary. One need only select a subset of SNPs that will accurately capture the linkage disequilibrium pattern of the region of interest to be comprehensive. SNP selection in genetic association studies involves two major approaches: GWAS, in which 500,000 to 1 million SNPs are genotyped, or candidate gene studies, in which a single gene is genotyped.

Genome-Wide Association Studies

In GWAS, SNPs are selected to cover as much of the genome as possible. SNPs across all chromosomes and most genes are selected to assess association with a phenotype of interest. There are currently two companies Affymetrix and Illumina that have different SNP selection strategies and different chip chemistry for doing GWAS. Affymetrix has selected 1 million SNPs randomly distributed across the genome whereas Illumina has selected 500,000 haplotype-tagging SNPs, based on the HAPMAP project. Both platforms provide 80% coverage of common variants.

There are three major issues with GWAS as currently conceived. The first issue is cost. One can genotype an individual for about $500/subject with a per SNP cost of less than 1 cent. While this genotyping cost is reasonable, the large sample size required for these studies results in millions of dollars for a single case-control study. The second major issue in these studies is multiple comparisons; if one is doing over 500,000 separate statistical tests, then there needs to be a careful plan to deal with multiple comparisons; this usually involves replication in several other populations. Finally, one needs to be able to manipulate large amounts of data and strong bioinformatics is necessary for both computation and data storage.

Candidate Gene or Region-based Testing

There are three types of candidate gene studies. One can use this approach to follow up a region of linkage to determine which gene or genes in a region are responsible for the linkage signal. One can use this approach to follow up genes or SNPs of interest that are identified by GWAS. Finally, one can use known biology to direct the choice of specific candidate genes of interest for association testing. The number of SNPs studied depends on the number of genes or the region, the size of the genes, and the ultimate purpose of the study. Numbers of SNPs test can vary from simple replication of one or two SNPs previously identified to full sequencing of a region of interest to identify new variation and potentially functional SNPs and then their testing in a population. Cost and available genotyping platforms are all important determinants of SNP selection.

Gene by Environment Interaction

Because both genes and environmental exposures are known to cause complex traits, performing studies to test both factors in one study design is of great value. The study designs outlined previously, family-based or case-control, can be used to test both sets of variables. There are two major issues in these studies, accurate measurement of exposure and statistical power.

Much has been made of the difficulties of accurately measuring the environment as an exposure for genetic association studies. While some environmental factors such as diet are hard to measure accurately and require complex techniques, other exposures such as cigarette smoking can be measured with precision. Accurate measure of exposure will greatly enhance the ability of these studies to provide new insights into disease pathogenesis.

The second major issue in these types of studies is having a large enough sample size to have both exposed and unexposed among the case group to detect an effect. With allele frequencies that can be less than 10%, very large groups of subjects are necessary for these studies. At minimum, 1000 cases and 1000 controls will be needed even for allele frequencies of 30%. Finally, it will be difficult to replicate these types of studies because finding several studies with similar exposures measured in similar ways is often impossible.

EPIGENETICS

Epigenetics is the study of changes in gene transcription that are dependent on the molecules that bind to DNA, rather than the sequence of DNA.[38,39,39a] This includes both heritable changes in gene expression in the progeny of cells or of individuals and stable, long-term alterations in the transcriptional potential of a cell or tissue that are not necessarily heritable. Because epigenetic processes are highly interdependent and regulate gene expression in an age, state, cell-, and tissue-dependent manner,

TABLE 3-3. Known Epigenetic Mechanisms

DNA methylation—The methyl group is transferred from *S*-adenosylmethionine to the C-5 position of cytosine by a cytosine-methyltransferase. Hypermethylation of CpG motifs, particularly at promoter and enhancer sites, silence gene transcription. Alternatively, hypomethylation of these motifs enhances gene transcription.

Noncoding RNAs—Bind to DNA and interfere with transcription and posttranscriptional regulation of gene expression.

Histone modification—Histones, the building blocks of nucleosomes, undergo numerous posttranslational modifications (methylation, acetylation, or phosphorylation with >100 conserved, covalent modifications) that regulate chromatin structure and gene expression.

collectively, these mechanisms constitute a complex system of molecular controls that affects biologic processes and human diseases.

Whereas the fundamental mechanisms of epigenetics continue to evolve, it is recognized that epigenetic regulation of the genome results in a hierarchy of transcriptional switches that facilitate development and differentiation, normal tissue function, and the ability of the host to respond to stress.[38,39] There are three primary mechanisms that are known to govern gene expression (DNA methylation, noncoding RNAs, and histone modification) and may be inherited, independent of the sequence of DNA (Table 3-3). DNA methylation is controlled by cytosine-methyltransferase, which transfers the methyl group from *S*-adenosylmethionine to the C-5 position of cytosine. Hypermethylation of CpG motifs, particularly at promoter and enhancer sites, silences gene transcription. Alternatively, hypomethylation of these motifs enhances gene transcription. Noncoding RNAs bind to DNA and interfere with transcription and posttranscriptional regulation of gene expression. Histones, the building blocks of nucleosomes, undergo numerous posttranslational modifications (methylation, acetylation, or phosphorylation with > 100 conserved, covalent modifications) that affect chromatin structure and alter gene expression. In aggregate, these mechanisms serve to regulate the transcriptional activity of specific genes, at specific stages of development, and in response to specific forms of endogenous and exogenous stress. Importantly, these mechanisms are conserved in eukaryotic organisms, from yeast to humans.

Epigenetic mechanisms can have profound effects on cellular, tissue, and whole organism phenotype. Phenotypes that are known to be affected by epigenetic regulation include fundamental mechanisms such as stem cell differentiation[40] and inactivation of the X chromosome,[41] carcinogenesis[42] and cancer prognosis,[43] and even basic aspects of learning and memory.[44,45] Moreover, genomic imprinting (epigenetic mechanisms that lead to preferential expression of either the maternal or the paternal allele) has been shown to be the cause of rare genetic anomalies such as the Prader-Willi, Angelman's, Beckwith-Wiedemann, and Siover-Russell syndromes.

A convincing demonstration of the profound effect that epigenetic mechanisms can have on in vivo phenotypes is the coat color of the agouti mouse.[46] Transposable elements (retrotransposons and DNA transposons) constitute over 35% of the human genome and are normally silenced (epigenetically) by cytosine methylation within CpG dinucleotides of DNA. The yellow agouti mice harbor a transposable element in the *agouti* gene; expression of this gene results in a yellow mouse, lack of expression due to methylation results in a brown mouse. It has been shown that the concentration of methyl donors in the diet of pregnant agouti mice has transgenerational effects on coat color of the progeny due to altered expression of the *agouti* gene caused by methylation of the *agouti* promoter.[46] Genetically identical pups could be produced that were either preferentially yellow or brown depending on whether the pregnant mice were treated with a low-methylation or a high methylation diet (Fig. 3-2). While the yellow mice express the *agouti* gene, these mice undoubtedly express other genes that enhance their risk for obesity, diabetes, and cancer.

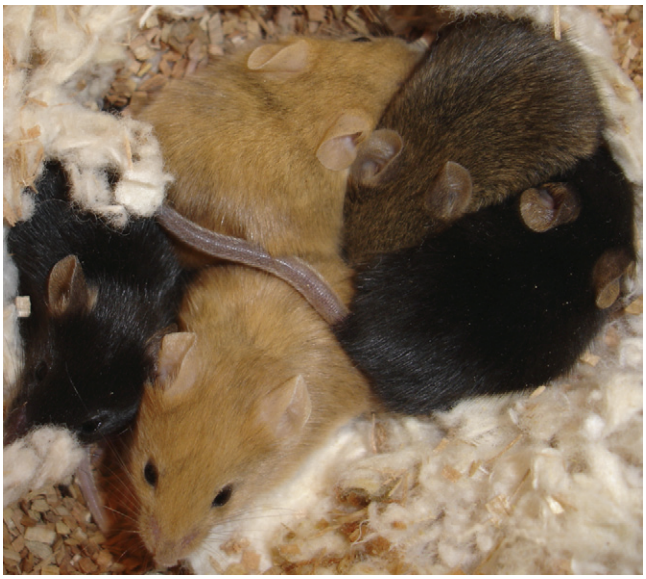

FIGURE 3-2 ■ Genetically identical agouti pups that are either preferentially yellow or brown depending on whether they were gestationally exposed to a low-methylation or a high-methylation diet.

Whereas epigenetic marks can be inherited, these potent regulators of transcription can also be modified throughout development[42] and by the environment.[47] For instance, whereas monozygotic twins are genetically identical, twin pairs often differ in phenotype (anthropomorphic features as well as disease outcomes). Global and locus-specific differences in DNA methylation and histone acetylation patterns indicate that early in life, monozygotic twins are epigenetically identical whereas older twin pairs have divergent epigenetic marks that are associated with differences in gene expression.[42] These findings suggest that various life events can alter epigenetic marks that may account, in part, for these phenotypic differences in twin pairs. Moreover, environmental endocrine disruptors (methoxychlor and vinclozolin)

have been shown to induce transgenerational effects on male fertility that occur as a result of DNA methylation.[47] In aggregate, these findings suggest that the epigenome can be reprogrammed, potentially affecting the risk, etiology, and treatment of various disease states.

The technology to measure epigenetic changes is continuing to evolve, and with the advent of pyrosequencing, it will soon be feasible to detect the epigenetic modifications of the entire genome during states of stress and disease. DNA methylation has been traditionally evaluated using methylation-sensitive restriction enzymes in conjunction with Southern blotting. However, this labor intensive approach has been largely replaced by bisulfite modification of DNA that deaminates unmethylated cytosines to uracils without affecting methylated cytosines. The cloned region of DNA is then amplified by polymerase chain reaction (PCR) and sequenced, with the unmethylated cytosine (that was converted to a uracil) being replaced by a thymine and the methylated cytosine amplifying as a cytosine. Methylation-specific polymerase chain reaction (MSP), a method that uses primers specific for methylated or unmethylated genomic DNA, is higher throughput but is unable to detect the exact pattern of DNA methylation. Thus, more global approaches, such as methylation-specific digital karyotyping,[48] array-based methylation hybridization, or methylated DNA immunoprecipitation coupled with either tiling arrays that include most of the human promoters or pyrosequencing are now being used. Functionally relevant methylation changes can be detected using demethylating agents with expression microarrays. However, the expression changes induced by demethylating agents could be caused by indirect effects of the drug.

High-quality antibodies have been used to detect known modifications in the amino acid residues of histones. While these antibodies can be used for Western blotting, they are more commonly used in a chromatin immunoprecipitation (ChIP) assay to measure the concentration of specific histone modifications at specific loci. ChIP can be used in conjunction with either microarrays (ChIP-chip) or pyrosequencing (ChIP-sequencing) to evaluate global changes in histone modifications. As the cost of sequencing decreases, these assays will become increasingly accessible.

Considering the importance of the environment in the development of lung disease, it is somewhat surprising that more attention has not been devoted to epigenetic mechanisms that lead to acute and chronic forms of lung disease. Epigenetic mechanisms (silencing of tumor suppressor genes) and patterns (hypomethylated DNA) have been associated with a number of tumors. In fact, it has recently been reported that the methylation pattern of six genes is associated with the development of lung cancer.[49] However, research is just beginning to emerge demonstrating the relevance of epigenetic changes and nonmalignant forms of lung disease. In humans, bronchial biopsies and alveolar macrophages have increased histone acetyltransferase (HAT) activity and reduced histone deacetylase (HDAC) activity in some diseases.[50–52] These consequent increases in histone acetylation enhance gene transcription and are thought to be important in the transcriptional regulation of inflammatory mediators in these airway diseases. In fact, steroid-treated asthmatics have reduced HAT and increased HDAC activity, presumably resulting in less airway inflammation.[52] In murine studies, methylation has been shown to alter the expression and activity of lineage-specific transcription factors that affect the maturation of naive T cells.[53–55] These results suggest that a hypomethylated state results in a Th1 phenotype whereas a hypermethylated state results in a Th2 phenotype. Because cigarette smoke, vitamin supplementation, and other environmental exposures can alter the epigenetic marks along the human genome, studying the importance of changes in DNA methylation, expression of noncoding RNAs, and structural changes in amino acid residues of histones should help us to understand the fundamental mechanisms associated with the etiology and progression of several types of lung disease.

Moreover, the epigenome can be modified by a variety of drugs. Compounds that alter DNA methylation and the amino acid residues on histones are most actively being investigated among patients with cancer. Two DNA methylation inhibitors, 5-aza-deoxycytidine and 5-azacytidine, have recently been approved by the U.S. Food and Drug Administration for the treatment of myelodysplastic syndrome, a preleukemic disease. Compounds that inhibit histone deacetylase (HDACi) have proapoptotic and antitumor properties and are undergoing phase I trials. Suberoylanilide hydroxamic acid, an HDACi, has been approved for the treatment of T cell cutaneous lymphoma. Interestingly trichostatin A, another HDACi, has been shown to decrease ovalbumin-induced allergic airway disease in a murine model of asthma.[56] As we begin to understand the role of epigenetic mechanisms in the development to lung disease, it will become much more obvious how we can modify these mechanisms therapeutically to reduce the burden of lung disease among our patients.

APPLICATION TO PULMONARY DISEASES

Asthma

Although there are more than 500 genetic association studies for asthma, most suffer from the methodologic problems discussed previously (Fig. 3-3). Most of the positive findings of these studies have not been adequately replicated. To date, there have been reports of positive associations between variants in over 100 genes and asthma phenotypes. Using the gene as the unit of replication (a liberal criterion), 54 associations have been replicated in at least two populations and 25 associations were "replicated" in at least six populations.[57] Replication is very loosely defined in this review. Space constraints do not allow us to cover all of these 79 genes but we review some genes of particular interest later. Candidate genes for association studies of asthma and/or its intermediate phenotypes have been selected on

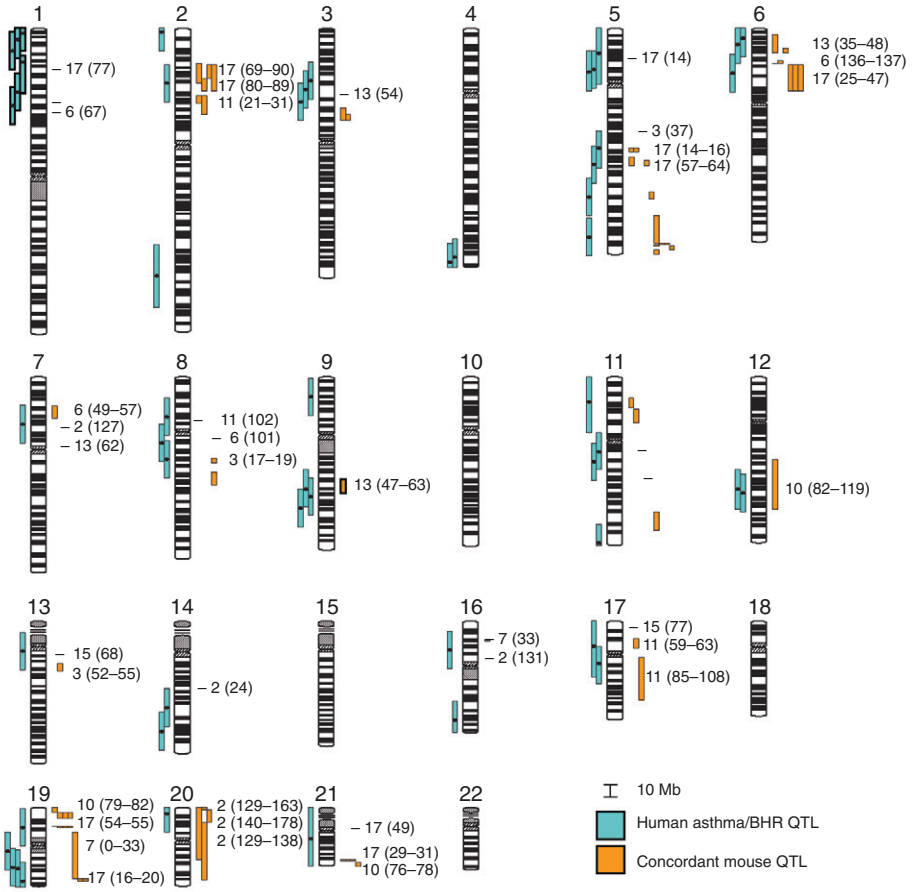

FIGURE 3-3 ■ Chromosome map of human QTLs for asthma and BHR and mouse concordant regions. The 95% confidence intervals (CIs) of human QTL are shown as *blue bars* to the left of their respective chromosome, with the peaks indicated by a *black line*. These data are also given in Table 3-1. Mouse asthma QTLs that are concordant to Human QTL are shown to the right of each chromosome with the mouse chromosome and the position given in parentheses. Chromosomes are drawn to scale, based on the length of each chromosome from the Human Genome Browser (www.ensembl.org/Homo_sapiens). As many of the human studies do not report CIs or names of the markers that flank the intervals, determining accurate CIs is difficult. Here (and in Table 3-1), we generated a conservative CI by including a region of 15 million base pairs both up and downstream of the peak. (From Stylianou IM, Singh J, Schwartz DA, Paigen B: Comparative genomics of asthma. In Postma DS, Weiss ST [eds]: Genetics of Asthma and Chronic Obstructive Pulmonary Disease. London: Taylor & Francis, 2006, pp 159–177, with permission.)

the basis of the results of genome-wide linkage analyses ("positional") and/or their biologic plausibility in asthma pathogenesis ("functional"). With regard to the 25 genes "replicated" in five or more association studies, careful review of these genes finds a substantial number of negative studies for all of them. The number of negative studies is likely biased toward the null because of publication bias.

Five potential asthma susceptibility genes have been identified using a positional cloning approach.[24-27,58] In all but one case,[58] significant linkage between a chromosomal region and asthma phenotypes was found in a genome-wide linkage analysis, and fine-mapping studies of linkage and association were then performed in the linked genomic region. Following fine-mapping studies, an association between variants in a specific gene and asthma phenotypes was identified in at least two populations. Using positional cloning, Laitinen and coworkers[27] identified a novel asthma susceptibility gene (G protein–coupled receptor for asthma susceptibility [*GPR154* also known as *NPSR1*]) on chromosome 7p. These investigators provided adequate functional data on *GPR154* by showing not only that the mouse orthologue of *GPR154* (GPRA) is up-regulated in murine lung after ovalbumin challenge in sensitized mice but also that, in humans, *GPR154* encodes protein isoforms that are produced in distinct patterns by bronchial epithelial cells and smooth muscle cells in asthmatic and healthy individuals. Four additional genes on chromosomes 6p21 (HLA-G),[58] 13q14 (PDH finger protein 11 [PHF11]),[25] 2q14 (dipeptidylpeptidase 10 [DPP10]), and 20p13 (disintegrin and metalloprotease 33 [ADAM 33])[26] have been identified by positional cloning as potential asthma-susceptibility genes. However, there is inadequate functional data for these seven genes, and linkage dysequilibrium (LD) with variants in adjacent genes could also explain the associations between these genes and asthma phenotypes. For example, several groups have tried to replicate the

association between ADAM33 and asthma phenotypes, with mixed results.[59–62] In summary, positional cloning has identified seven potential asthma-susceptibility genes. Results of functional studies and replication studies of these five genes suggest that GPR154 is most likely to influence asthma pathogenesis. None of these genes replicates in all populations, suggesting that there are likely multiple genetic determinants of asthma and none that appears to be universal.

Finally, to date, only one gene, *ORMDL3*, has been identified by GWAS.[10] This association finding has been confirmed by others.[63,64,64a] Most asthma GWAS are underpowered, hence pooling or meta-analysis may be the way forward to identify more genetic determinants.

Asthma genes are being identified at an increasing rapid pace, and it is likely that by 2015, many, if not most, of the genetic determinants of the disorder will be identified. However, it is likely to take a longer time frame to translate this basic research into clinically useful information that will benefit patients.

Chronic Obstructive Lung Disease

COPD is characterized by incompletely reversible airflow obstruction and excess mucous production in the airways. In the United States, COPD affects 16 million individuals, is the fourth leading cause of death, and the only one among the leading causes of death to be increasing in prevalence.[65] The role of genetic predisposition in the pathogenesis of COPD had been overlooked until very recently, and yet there are intriguing features in this disease to strongly suggest gene-environment interactions. First, the Framingham Study demonstrated that longitudinal decline in lung function is inherited with a heritability of approximately 20%, which increases substantially when the subjects were stratified according to smoking status.[66] Environmental exposures such as smoking and pollution have been implicated in the pathogenesis of COPD since the 1960s, yet "only" 10% to 20% of smokers develop COPD symptoms, further indicating that a susceptibility factor may exist in some individuals. Alpha$_1$-antitrypsin is a prototypical susceptibility gene that is associated with increased rates of COPD development in active smokers. Recent studies have also implicated alpha$_1$-antitrypsin in the decline in pulmonary function observed in passive smoke exposure and occupational exposures in susceptible individuals with severely or moderately decreased levels. Furthermore, although, traditionally, emphysema and chronic bronchitis are considered to be clinically distinct chronic obstructive diseases, in practice there is a substantial gray zone between "pure" irreversible airway obstruction (i.e., COPD) and "pure" reversible obstruction (i.e., asthma). Many physicians are therefore now suspecting that asthma and COPD may be sharing common characteristics and genetic background (the so-called Dutch hypothesis). However, genomic research in COPD is still in its early stages, and specific genes have yet to be conclusively identified.[67,67a] Initial linkage studies have singled out regions in chromosomes 2 and 4[68,69] and serpine2[70] that may be linked to COPD susceptibility.

Acute Respiratory Distress Syndrome

Acute lung injury (ALI) leading to acute respiratory distress syndrome (ARDS) is a common complication of systemic inflammation and sepsis, occurring in approximately 50% of such patients. The mortality of ARDS remains high at about 30% to 40%, despite recent advances in mechanical ventilation and patient management. The pathogenesis of ALI/ARDS is thought to derive from the effects of systemic inflammation, cytokine production, and oxidative damage. However, the sporadic (nonfamilial) nature of ARDS hampers genetic analysis of human subjects. Genetic analysis of inbred mouse strains first revealed that ALI susceptibility was strain dependent and, therefore may, in part, be genetically determined.[71] Human studies identified angiotensin-converting enzyme (ACE) as a candidate gene for ARDS susceptibility.[72] Subsequent animal studies verified the role of ACE in ARDS susceptibility and further showed that ACE2, an ACE isoform that metabolizes the ACE product angiotensin II, is protective against ARDS.[73] This was the first set of studies to conclusively show a link and a mechanism for genetic susceptibility and ARDS pathogenesis. A candidate gene approach utilizing preexisting gene expression profiles in animal models as well as human data was used by the Johns Hopkins Translational Respiratory Program.[74] A number of candidate genes, mostly from the inflammation and coagulation pathways, were identified: interleukin (IL) -1β, IL-6, tissue factor, plasminogen activator inhibitor 1, and chemokine receptors were the most abundantly up-regulated proteins. Surfactant protein B (SP-B) polymorphisms have also been associated with increased susceptibility to ARDS.[75] SP-B has not been used therapeutically in adults with ARDS; however, a recent study in infants and children with ARDS showed significant improvement in survival with a surfactant that contained SP-B.[76] It appears that proteins involved in inflammation and coagulation represent promising candidates for susceptibility testing in ALI/ARDS, but results are still quite preliminary.

Lung Cancer

Lung cancer is now the most common cause of cancer-related deaths in the United States, and yet no more than 100 years ago, lung cancer was quite rare. The rise in lung cancer incidence demonstrates the effects of changing environmental exposures on human disease. Inhalation of environmental carcinogens causes the vast majority of lung cancer cases. Cigarette smoke dominates this list. Since at least the 1950s, it has been recognized that cigarette smoking causes most lung cancer cases. However, only a minority of smokers develops lung cancer, again suggesting the role of susceptibility in lung cancer pathogenesis. Unfortunately, cigarette smoke contains more than 4000 chemicals, a fact that makes the search for a single susceptibility factor much more difficult. Investigators have focused on specific classes of tobacco compounds that are known carcinogens, such as the polycyclic aromatic hydrocarbons (PAH). These are nontoxic in themselves but are metabolized

in the body by enzymes such as CYP1A1 into DNA-binding diol-epoxides. Several studies from Japan have shown a significant association of high-activity CYP1A1 variants with the occurrence of lung cancer.[77] Conversely, the main PAH-detoxifying enzymes are the glutathione *S*-transferases GSTM1 and GSTP1. Polymorphisms in these enzymes that lead to reduced activity have also been linked to lung cancer susceptibility.[78] The carcinogenic effect of cigarette smoke is thought to rely upon DNA binding and mutations of tumor suppressor genes, such as P53. PAH and other smoke constituents like acrolein can bind to so-called mutational hotspots of the P53 gene and induced DNA damage.[79] Accordingly, the ability of the organism to correct and repair DNA damage is closely linked to cancer susceptibility.[80,81] For example, a recent analysis of a European cohort of 116 patients with lung cancer showed a significant association between SNPs in the DNA repair enzymes XRCCI and BRCA2 and exposure to urban pollution in the susceptibility to cancer.[82]

Genomic medicine not only is helpful in detecting genes associated with the development of lung cancer but also can be used to guide therapy[83] and to determine the prognosis of the patient.[84,85,85a] Indeed lung cancers can now be categorized based on their gene expression profile.[84–87a] Furthermore, somatic mutations in proto-oncogenes such as K-RAS, BRAF, and epidermal growth factor receptor (EGFR) have been identified that could potentially become targets of cancer drugs. Indeed, one of the most encouraging reports in lung cancer research was the recent finding that certain non–small cell lung cancers harbor mutations in the EGFR. These cell lines become malignant through EGFR-induced apoptosis inhibition, but simultaneously become extremely sensitive to EGFR tyrosine kinase inhibitors like gefitinib or erlotinib. This was an impressive accomplishment of genomic medicine that provided a seamless link between the pathogenesis of lung cancer, the prediction of treatment effect based on genetic cancer characteristics, and the successful application of treatment to patients with lung cancer.[85]

Interstitial Lung Disease

Interstitial lung disease (ILD) is thought to result from the aberrant response of reparatory mechanisms to repetitive environmental lung injury. Several environmental factors like cigarette smoke, wood and metal dust, asbestos, radiation, infections, and drugs have been implicated in the pathogenesis of ILD. Although a clear-cut genetic susceptibility factor to these environmental triggers is still lacking, there is nevertheless intriguing evidence suggesting that genetic susceptibility may play a role in environmental ILD. Genetic diseases such as Hermansky-Pudlak syndrome, Nieman-Pick disease, or dyskeratosis congenita are associated with the occurrence of ILD.[88] Furthermore, mutations in SP-C[89,90] and telomerase genes[91,92] have been found in familial and sporadic cases of ILD. Finally, familial cases of ILD have been described in the absence of a distinct clinical syndrome. Interestingly, cigarette smoke was a major risk factor in familial cases of ILD, suggesting that a host-environment interaction may underlie the genetic susceptibility to familial ILD.[93] Genomic analysis of mouse models of fibrotic lung disease (using bleomycin and radiation as environmental triggers) has identified distinct genetic loci of susceptibility[94] and identified specifically the major histocompatibility complex II antigen H2-Ea as a candidate gene. Genomic methods have been applied to familial ILD, cases as well and a putative candidate gene, ELMOD2, has been suggested.[95] The exact role of this gene in ILD pathogenesis is still speculative. Recently, a large database of over 200 familial ILD patients has been compiled and analyzed in a U.S. multicenter trial.[93] Preliminary linkage analysis of these patients shows regions of particular interest on chromosomes 10, 11, and 12. Further genetic analysis will hopefully identify distinct candidate genes in these regions. Later efforts will attempt to replicate the familial ILD findings in "sporadic" ILD cases. The goal is to identify the genes involved in the pathogenesis and susceptibility of those who develop ILD with the ultimate hope of effective treatment options.

THE PATH FORWARD

Although the Human Genome Project has successfully mapped the human genome and has developed innovative technology for genomic studies, we remain limited in how this information can be used to improve clinical medicine and public health. This limitation arises from the simple fact that genetics is not the sole determinant of health or disease. In fact, although an emerging consensus suggests that many of the complex and prevalent diseases that humans develop occur as a result of multiple biologically unique gene-gene and gene-environment interactions, even this conceptual framework is limited. The development of disease in humans, environmental and otherwise, is simply far more complex. Environmental exposures affect those that are vulnerable temporally (age), spatially (geographically), and by unique circumstance (comorbid disease, nutritional status, economic status, race, and genetics). Even this paradigm fails to address the complex interaction of endogenous and exogenous risks that ultimately interact to cause disease. Moreover, diseases are not usually single entities; rather, most diseases represent several or many specific pathophysiologic processes that can be fully understood only by focusing on the genetic and environmental contributions to etiology and pathogenesis. Environmental health research and genomic research are logical, even necessary, partners. Ultimately, the discoveries that are made in environmental genomics will lead to better diagnosis, treatment, and prevention of these common, complex human diseases.

KEY POINTS

- Heritability is the best way to determine if a disease has a genetic basis.
- Complex genetic disorders account for the majority of lung diseases and are caused by multiple genetic variations and multiple environmental factors.
- Model organisms can enhance the efficiency of gene discovery and can provide insights into biologic responses to endogenous and exogenous forms of stress.
- The human genome is composed of approximately 3 billion base pairs. There are approximately 12 million SNPs in the human genome.
- Linkage analysis is a property of families and encompasses a group of genetic methods to analyze the distribution of DNA markers within families to determine if there is a relationship between a particular region of the genome and a phenotype of interest.
- Genome wide association studies (GWAS) have emerged as the most commonly used study design to find disease genes in complex disorders.
- Epigenetics is the study of changes in gene transcription that are dependent on the molecules that bind to DNA, rather than the sequence of DNA. This includes both heritable changes in gene expression and stable, long-term alterations in the transcriptional potential of a cell or tissue that are not necessarily heritable.
- Asthma is a heritable disorder but the genetics are complex with almost every chromosome demonstrating linkage and over 100 genes found to be associated with the development of asthma.
- The role of genetic predisposition in the pathogenesis of COPD had been overlooked until very recently, and yet there are intriguing features in this disease to strongly suggest gene-environment interactions.
- Because only a minority of smokers develops lung cancer, genetic and epigenetic mechanisms need to be considered.
- ILD is caused by environmental and genetic factors. Mutations in SP-C and the telomerase genes have been shown to enhance the risk of developing this disorder.

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References

1. Mendel G: Gregor Mendel's letters to Carl Nageli, 1866–1873. Genetics 35:1–29, 1950.
2. Darwin C: The Origin of Species. New York: PF Collier and Son, 1909.
3. Morgan TH: Chromosomes and associative inheritance. Science 34:636–638, 1911.
4. Bracco RM, Krauss MR, Roe AS, Macleod CM: Transformation reactions between *Pneumococcus* and three strains of *Streptococci*. J Exp Med 106:247–259, 1957.
5. Watson JD, Crick FH: Molecular structure of nucleic acids: A structure for deoxyribose nucleic acid. Nature 171:737–738, 1953.
6. McPherson JD, Marra M, Hillier L, et al: A physical map of the human genome. Nature 409:934–941, 2001.
7. Venter JC, Adams MD, Myers EW, et al: The sequence of the human genome. Science 291:1304–1351, 2001.
8. The International HapMap Project. Nature 426:789–796, 2003.
9. Kruglyak L, Nickerson DA: Variation is the spice of life. Nat Genet 27:234–236, 2001.
10. Moffatt MF, Kabesch M, Liang L, et al: Genetic variants regulating ORMDL3 expression contribute to the risk of childhood asthma. Nature 448:470–473, 2007.
11. Klein RJ, Zeiss C, Chew EY, et al: Complement factor H polymorphism in age-related macular degeneration. Science 308:385–389, 2005.
12. Grant SF, Thorleifsson G, Reynisdottir I, et al: Variant of transcription factor 7-like 2 (TCF7L2) gene confers risk of type 2 diabetes. Nat Genet 38:320–323, 2006.
13. Amundadottir LT, Sulem P, Gudmundsson J, et al: A common variant associated with prostate cancer in European and African populations. Nat Genet 38:652–658, 2006.
14. Stuart JM, Segal E, Koller D, Kim SK: A gene-coexpression network for global discovery of conserved genetic modules. Science 302:249–255, 2003.
15. Harris MA, Clark J, Ireland A, et al: The Gene Ontology (GO) database and informatics resource. Nucleic Acids Res 32(Database issue):D258–D261, 2004.
16. Pennacchio LA: Insights from human/mouse genome comparisons. Mamm Genome 14:429–436, 2003.
17. Lemaitre B, Nicolas E, Michaut L, et al: The Dorsoventral Regulatory Gene Cassette *spatzle/Toll/cactus* controls the potent antifungal response in drosophila adult. Cell 86:973–983, 1996.
18. Medzhitov R, Preston-Hurlburt P, Janeway CA: A human homologue of the *Drosophila* Toll protein signals activation of adaptive immunity. Nature 388:394–397, 1997.
19. Arbour NC, Lorenz E, Schutte B, et al: TLR4 mutations are associated with endotoxin hyporesponsiveness in humans. Nat Genet 25:187–191, 2000.
20. Cook DN, Pisetsky DS, Schwartz DA: Toll-like receptors in the pathogenesis of human disease. Nat Immunol 5:975–979, 2004.
21. Botstein D, Risch N: Discovering genotypes underlying human phenotypes: Past successes for mendelian disease, future approaches for complex disease. Nat Genet 33(Suppl):228–237, 2003.
22. Hammond MP, Birney E: Genome information resources—Developments at Ensembl. Trends Genet 20:268–272, 2004.
23. Hoffjan S, Nicolae D, Ober C: Association studies for asthma and atopic diseases: A comprehensive review of the literature. Respir Res 4:14, 2003.

24. Allen M, Heinzmann A, Noguchi E, et al: Positional cloning of a novel gene influencing asthma from chromosome 2q14. Nat Genet 35:258–263, 2003.
25. Zhang Y, Leaves NI, Anderson GG, et al: Positional cloning of a quantitative trait locus on chromosome 13q14 that influences immunoglobulin E levels and asthma. Nat Genet 34:181–186, 2003.
26. Van Eerdewegh P, Little RD, Dupuis J, et al: Association of the ADAM33 gene with asthma and bronchial hyperresponsiveness. Nature 418:426–430, 2002.
27. Laitinen T, Polvi A, Rydman P, et al: Characterization of a common susceptibility locus for asthma-related traits. Science 304:300–304, 2004.
28. Zhang H, Risch N: Mapping quantitative-trait loci in humans by use of extreme concordant sib pairs: Selected sampling by parental phenotypes. Am J Hum Genet 59:951–957, 1996.
29. Palmer LJ, Knuiman MW, Divitini ML, et al: Familial aggregation and heritability of adult lung function: Results from the Busselton Health Study. Eur Respir J 17:696–702, 2001.
30. Strittmatter WJ, Saunders AM, Schmechel D, et al: Apolipoprotein E: High-avidity binding to beta-amyloid and increased frequency of type 4 allele in late-onset familial Alzheimer disease. Proc Natl Acad Sci U S A 90:1977–1981, 1993.
31. Ridker PM, Hennekens CH, Lindpainter K, et al: Mutation in the gene encoding for coagulation factor V and the risk of myocardial infarction, stroke, and venous thrombosis in apparently healthy men. N Engl J Med 332:912–917, 1995.
32. Silverman EK, Palmer LJ: Case-control association studies for the genetics of complex respiratory diseases. Am J Respir Cell Mol Biol 22:645–648, 2000.
33. Pritchard JK, Rosenberg NA: Use of unlinked genetic markers to detect population stratification in association studies. Am J Hum Genet 65:220–228, 1999.
34. Devlin B, Roeder K: Genomic control for association studies. Biometrics 55:997–1004, 1999.
35. Reich DE, Cargill M, Bolk S, et al: Linkage disequilibrium in the human genome. Nature 411:199–204, 2001.
36. Spielman RS, McGinnis RE, Ewens WJ: Transmission test for linkage disequilibrium: The insulin gene region and insulin-dependent diabetes mellitus. Am J Hum Genet 52:506–516, 1993.
37. Lange E, Boehnke M: A novel approach for identification of common ancestral haplotypes associated with complex phenotypes. Am J Hum Genet 63(Suppl):A17, 1998.
38. Feinberg AP, Tycko B: The history of cancer epigenetics. Nat Rev Cancer 4:143–153, 2004.
39. Gal-Yam EN, Saito Y, Egger G, Jones PA: Cancer epigenetics: Modifications, screening, and therapy. Annu Rev Med 59:267–280, 2007.
39a. Garzon R, Calin GA, Croce CM: MicroRNAs in cancer. Annu Rev Med 60:167–179, 2009.
40. Bibikova M, Chudin E, Wu B, et al: Human embryonic stem cells have a unique epigenetic signature. Genome Res 16:1075–1083, 2006.
41. Amos-Landgraf JM, Cottle A, Plenge RM, et al: X chromosome-inactivation patterns of 1,005 phenotypically unaffected females. Am J Hum Genet 79:493–499, 2006.
42. Fraga MF, Ballestar E, Paz MF, et al: Epigenetic differences arise during the lifetime of monozygotic twins. Proc Natl Acad Sci U S A 102:10604–10609, 2005.
43. Seligson DB, Horvath S, Shi T, et al: Global histone modification patterns predict risk of prostate cancer recurrence. Nature 435:1262–1266, 2005.
44. Fischer A, Sananbenesi F, Wang X, et al: Recovery of learning and memory is associated with chromatin remodelling. Nature 447:178–182, 2007.
45. Miller CA, Sweatt JD: Covalent modification of DNA regulates memory formation. Neuron 53:857–869, 2007.
46. Waterland RA, Jirtle RL: Transposable elements: Targets for early nutritional effects on epigenetic gene regulation. Mol Cell Biol 23:5293–5300, 2003.
47. Anway MD, Cupp AS, Uzumcu M, Skinner MK: Epigenetic transgenerational actions of endocrine disruptors and male fertility. Science 308:1466–1469, 2005.
48. Hu M, Yao J, Cai L, et al: Distinct epigenetic changes in the stromal cells of breast cancers. Nat Genet 37:899–905, 2005.
49. Belinsky SA, Liechty KC, Gentry FD, et al: Promoter hypermethylation of multiple genes in sputum precedes lung cancer incidence in a high-risk cohort. Cancer Res 66:3338–3344, 2006.
50. Ito K, Ito M, Elliott WM, et al: Decreased histone deacetylase activity in chronic obstructive pulmonary disease. N Engl J Med 352:1967–1976, 2005.
51. Ito K, Caramori G, Lim S, et al. Expression and activity of histone deacetylases in human asthmatic airways. Am J Respir Crit Care Med 166:392–396, 2002.
52. Cosio BG, Mann B, Ito K, et al: Histone acetylase and deacetylase activity in alveolar macrophages and blood mononocytes in asthma. Am J Respir Crit Care Med 170:141–147, 2004.
53. Kim HP, Leonard WJ: CREB/ATF-dependent T cell receptor-induced FoxP3 gene expression: A role for DNA methylation. J Exp Med 204:1543–1551, 2007.
54. Fields PE, Kim ST, Flavell RA: Cutting edge: Changes in histone acetylation at the IL-4 and IFN-gamma loci accompany Th1/Th2 differentiation. J Immunol 169:647–650, 2002.
55. Shin HJ, Park HY, Jeong SJ, et al: STAT4 expression in human T cells is regulated by DNA methylation but not by promoter polymorphism. J Immunol 175:7143–7150, 2005.
56. Choi JH, Oh SW, Kang MS, et al: Trichostatin A attenuates airway inflammation in mouse asthma model. Clin Exp Allergy 35:89–96, 2005.
57. Ober C, Hoffjan S: Asthma genetics 2006: The long and winding road to gene discovery. Genes Immun 7:95–100, 2006.
58. Nicolae D, Cox NJ, Lester LA, et al: Fine mapping and positional candidate studies identify HLA-G as an asthma susceptibility gene on chromosome 6p21. Am J Hum Genet 76:349–357, 2005.
59. Howard TD, Postma DS, Jongepier H, et al: Association of a disintegrin and metalloprotease 33 (ADAM33) gene with asthma in ethnically diverse populations. J Allergy Clin Immunol 112:717–722, 2003.
60. Werner M, Herbon N, Gohlke H, et al. Asthma is associated with single-nucleotide polymorphisms in ADAM33. Clin Exp Allergy 34:26–31, 2004.
61. Lind DL, Choudhry S, Ung N, et al: ADAM33 is not associated with asthma in Puerto Rican or Mexican populations. Am J Respir Crit Care Med 168:1312–1316, 2003.
62. Raby BA, Silverman EK, Kwiatkowski DJ, et al: ADAM33 polymorphisms and phenotype associations in childhood asthma. J Allergy Clin Immunol 113:1071–1078, 2004.
63. Tavendale R, Macgregor DF, Mukhopadhyay S, Palmer CN: A polymorphism controlling ORMDL3 expression is associated with asthma that is poorly controlled by current medications. J Allergy Clin Immunol 121:860–863, 2008.
64. Galanter J, Choudhry S, Eng C, et al: ORMDL3 gene is associated with asthma in three ethnically diverse populations. Am J Respir Crit Care Med 177:1194–1200, 2008.
64a. Vercelli D: Discovering susceptibility genes for asthma and allergy. Nat Rev Immunol 8:169–182, 2008.
65. Mannino DM, Gagnon RC, Petty TL, Lydick E: Obstructive lung disease and low lung function in adults in the United States: Data from the National Health and Nutrition Examination Survey, 1988–1994. Arch Intern Med 160:1683–1689, 2000.
66. Gottlieb DJ, Wilk JB, Harmon M, et al: Heritability of longitudinal change in lung function. The Framingham study. Am J Respir Crit Care Med 164:1655–1659, 2001.
67. Cookson WO: State of the art. Genetics and genomics of chronic obstructive pulmonary disease. Proc Am Thorac Soc 3:473–475, 2006.
67a. Bossé Y: Genetics of chronic obstructive pulmonary disease: a succinct review, future avenues and prospective clinical applications. Pharmacogenomics 10:655–667, 2009.
68. Silverman EK, Palmer LJ, Mosley JD, et al: Genomewide linkage analysis of quantitative spirometric phenotypes in severe early-onset chronic obstructive pulmonary disease. Am J Hum Genet 70:1229–1239, 2002.
69. Wilk JB, DeStefano AL, Arnett DK, et al: A genome-wide scan of pulmonary function measures in the National Heart, Lung, and Blood Institute Family Heart Study. Am J Respir Crit Care Med 167:1528–1533, 2003.

70. Demeo DL, Mariani TJ, Lange C, et al: The SERPINE2 gene is associated with chronic obstructive pulmonary disease. Am J Hum Genet 78:253–264, 2006.
71. Leikauf GD, McDowell SA, Wesselkamper SC, et al: Acute lung injury: Functional genomics and genetic susceptibility. Chest 121(3 Suppl):70S–75S, 2002.
72. Marshall RP, Webb S, Bellingan GJ, et al: Angiotensin converting enzyme insertion/deletion polymorphism is associated with susceptibility and outcome in acute respiratory distress syndrome. Am J Respir Crit Care Med 166:646–650, 2002.
73. Imai Y, Kuba K, Rao S, et al: Angiotensin-converting enzyme 2 protects from severe acute lung failure. Nature 436:112–116, 2005.
74. Grigoryev DN, Finigan JH, Hassoun P, Garcia JG: Science review: Searching for gene candidates in acute lung injury. Crit Care 8:440–447, 2004.
75. Gong MN, Wei Z, Xu LL, et al: Polymorphism in the surfactant protein-B gene, gender, and the risk of direct pulmonary injury and ARDS. Chest 125:203–211, 2004.
76. Willson DF, Thomas NJ, Markovitz BP, et al: Effect of exogenous surfactant (calfactant) in pediatric acute lung injury: A randomized controlled trial. JAMA 293:470–476, 2005.
77. Nakachi K, Imai K, Hayashi S, Kawajiri K: Polymorphisms of the CYP1A1 and glutathione S-transferase genes associated with susceptibility to lung cancer in relation to cigarette dose in a Japanese population. Cancer Res 53:2994–2999, 1993.
78. Ryberg D, Skaug V, Hewer A, et al: Genotypes of glutathione transferase M1 and P1 and their significance for lung DNA adduct levels and cancer risk. Carcinogenesis 18:1285–1289, 1997.
79. Feng Z, Hu W, Hu Y, Tang MS: Acrolein is a major cigarette-related lung cancer agent: Preferential binding at p53 mutational hotspots and inhibition of DNA repair. Proc Natl Acad Sci U S A 103:15404–15409, 2006.
80. Ryk C, Kumar R, Thirumaran RK, Hou SM: Polymorphisms in the DNA repair genes XRCC1, APEX1, XRCC3 and NBS1, and the risk for lung cancer in never- and ever-smokers. Lung Cancer 54:285–292, 2006.
81. Kiyohara C, Takayama K, Nakanishi Y: Association of genetic polymorphisms in the base excision repair pathway with lung cancer risk: A meta-analysis. Lung Cancer 54:267–283, 2006.
82. Manuguerra M, Saletta F, Karagas MR, et al: XRCC3 and XPD/ERCC2 single nucleotide polymorphisms and the risk of cancer: A HuGE review. Am J Epidemiol 164:297–302, 2006.
83. Thomas RK, Weir B, Meyerson M: Genomic approaches to lung cancer. Clin Cancer Res 12(14 Pt 2):4384s–4391s, 2006.
84. Beer DG, Kardia SL, Huang CC, et al: Gene-expression profiles predict survival of patients with lung adenocarcinoma. Nat Med 8:816–824, 2002.
85. Potti A, Mukherjee S, Petersen R, et al: A genomic strategy to refine prognosis in early-stage non-small-cell lung cancer. N Engl J Med 355:570–580, 2006.
85a. Linardou H, Dahabreh IJ, Bafaloukos D, et al: Somatic EGFR mutations and efficacy of tyrosine kinase inhibitors in NSCLC. Nat Rev Clin Oncol 6:352–366, 2009.
86. Bhattacharjee A, Richards WG, Staunton J, et al: Classification of human lung carcinomas by mRNA expression profiling reveals distinct adenocarcinoma subclasses. Proc Natl Acad Sci U S A; 98(24):13790–13795, 2001.
87. Garber ME, Troyanskaya OG, Schluens K, et al: Diversity of gene expression in adenocarcinoma of the lung. Proc Natl Acad Sci U S A 98:13784–13789, 2001.
87a. Schembri F, Sridhar S, Perdomo C, et al: MicroRNAs as modulators of smoking-induced gene expression changes in human airway epithelium. Proc Natl Acad Sci USA 106:2319–2324, 2009.
88. Raghu G, Mageto Y: Genetic predisposition of interstitial lung disease. *In* Schwarz MI, King TE (eds): Interstitial Lung Disease (3rd ed). London: BC Decker, 1998, pp 119–132.
89. Nogee LM, Dunbar AE 3rd, Wert SE, et al: A mutation in the surfactant protein C gene associated with familial interstitial lung disease. N Engl J Med 344:573–579, 2001.
90. Thomas AQ, Lane K, Phillips J 3rd, et al: Heterozygosity for a surfactant protein C gene mutation associated with usual interstitial pneumonitis and cellular nonspecific interstitial pneumonitis in one kindred. Am J Respir Crit Care Med 165:1322–1328, 2002.
91. Armanios MY, Chen JJ, Cogan JD, et al: Telomerase mutations in families with idiopathic pulmonary fibrosis. N Engl J Med 356:1317–1326, 2007.
92. Tsakiri KD, Cronkhite JT, Kuan PJ, et al: Adult-onset pulmonary fibrosis caused by mutations in telomerase. Proc Natl Acad Sci U S A 104:7552–7557, 2007.
93. Steele MP, Speer MC, Loyd JE, et al: Clinical and pathologic features of familial interstitial pneumonia. Am J Respir Crit Care Med 172:1146–1152, 2005.
94. Haston CK, Wang M, Dejournett RE, et al: Bleomycin hydrolase and a genetic locus within the MHC affect risk for pulmonary fibrosis in mice. Hum Mol Genet 11:1855–1863, 2002.
95. Hodgson U, Pulkkinen V, Dixon M, et al: ELMOD2 is a candidate gene for familial idiopathic pulmonary fibrosis. Am J Hum Genet 79:149–154, 2006.

CHAPTER 4

VENTILATION, BLOOD FLOW, AND GAS EXCHANGE

Peter D. Wagner, MD • Frank L. Powell, PhD • John B. West, MD, PhD, DSc

INTRODUCTION

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INTRODUCTION

This first chapter in the section on respiratory physiology is devoted to the primary function of the lung: gas exchange. In addition, the principles of ventilation and blood flow that underlie gas exchange are reviewed. Although the lung has other functions, such as metabolizing some compounds, filtering unwanted materials from the circulation, and acting as a reservoir for blood, gas exchange is its chief function. Respiratory diseases frequently interfere with ventilation, blood flow, and gas exchange and may ultimately lead to respiratory failure and death.

VENTILATION

The anatomy of the airways and the alveolar region of the lung is discussed in Chapter 1. There we saw that the airways consist of a series of branching tubes that become narrower, shorter, and more numerous as they penetrate deeper into the lung. This process continues down to the terminal bronchioles, which are the smallest airways without alveoli. All these bronchi make up the *conducting airways.* Their function is to lead inspired gas to the gas-exchanging regions of the lung. Because the conducting airways contain no alveoli and therefore take no part in gas exchange, they constitute the *anatomic dead space.*

Each terminal bronchiole subtends a respiratory unit, or *acinus.* The terminal bronchioles divide into respiratory bronchioles that have occasional alveoli budding from their walls. Finally, we come to the alveolar ducts, structures that are completely lined with alveoli. This alveolated region of the lung where gas exchange occurs is known as the *respiratory zone.* The region distal to the terminal bronchioles is sometimes referred to as the *transitional and respiratory zone* because the nonalveolated regions of the respiratory bronchioles do not strictly have a respiratory function. The distance from the terminal bronchiole to the most distal alveolus is only about 5 mm, but the respiratory zone makes up most of the lung (its volume being some 2 to 3 L).

From a functional point of view, the morphology of the human airways was greatly clarified by the studies of Weibel.[1] He measured the number, length, width, and branching angles of the airways, and he proposed models that, although they are idealized, make pressure-flow and other analyses much more tractable.

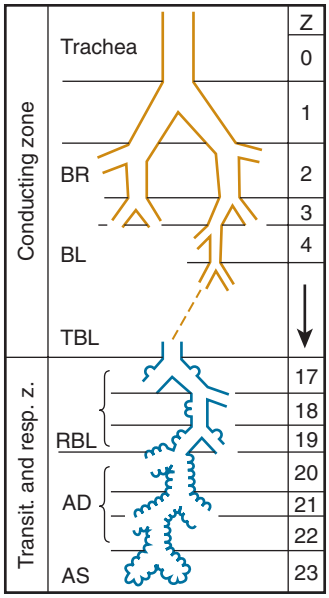

FIGURE 4-1 ■ Idealization of the human airways according to Weibel's model A. AD, alveolar duct; AS, alveolar sac; BL, bronchiole; BR, bronchus; RBL, respiratory bronchiole; TBL, terminal bronchiole; Z, airway generation. Note that the RBL, AD, and AS make up the transitional and respiratory zones. (Redrawn from Weibel ER: Morphometry of the Human Lung. Berlin: Springer-Verlag, 1963.)

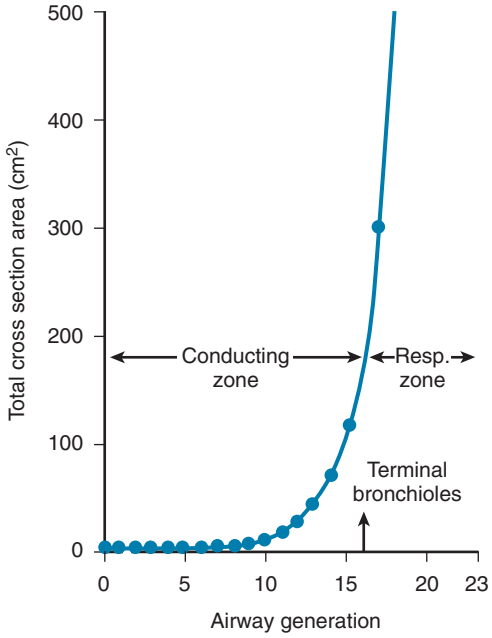

FIGURE 4-2 ■ Diagram showing the extremely rapid increase in total cross-sectional area of the airways in the respiratory (Resp.) zone as predicted from the Weibel model in Figure 4-1. (Redrawn from West JB: Respiratory Physiology—The Essentials [8th ed]. Baltimore: Lippincott Williams & Wilkins, 2008.)

The most commonly used Weibel model is the so-called model A, shown in Figure 4-1. Note that the first 16 generations (Z) make up the conducting airways ending in the terminal bronchioles. The next three generations constitute the respiratory bronchioles, in which the degree of alveolation steadily increases. This is the transitional zone. Finally, there are three generations of alveolar ducts and one generation of alveolar sacs. These last four generations constitute the true respiratory zone.

This idealized, dichotomously branching airway system is clearly an oversimplification. For example, in some regions of the human lung, there are far fewer than 23 generations from the trachea to the alveolar sacs, whereas other regions contain more generations. Some of the inadequacies of the model have been pointed out by Horsfield,[2] who has proposed other models, particularly of the most distal regions of the airways. In some respects, it makes more sense to begin counting at the terminal alveoli and work backward toward the origin. Such a system has been used to classify the tributaries of rivers.

However, the Weibel model has been of great value to respiratory physiology, and an example of its use is shown in Figure 4-2. Here the model clarifies the nature of gas flow in all generations of the airways in the lung. Figure 4-2 shows that, if the total cross-sectional area of the airways of each generation is calculated, there is relatively little change in area until we approach generation 16, that is, the terminal bronchioles. However, near this level, the cross-sectional area increases very rapidly. This has led some physiologists to suggest that the shape of the combined airways is similar to a trumpet or even a thumbtack!

The result of this rapid change in area is that the mode of gas flow changes in the region of the terminal bronchioles. Proximal to this point, flow is convective, or "bulk," that is, the sort of flow that occurs when beer is poured out of a pitcher. However, when the gas reaches the region approximating the level of the terminal bronchioles, its forward velocity decreases dramatically because of the very rapid increase in cross-sectional area. As a consequence, molecular diffusion begins to take over as the dominant mode of gas transport. Indeed, diffusion within the gas phase is the major mechanism of gas flow in the alveoli. Naturally, there is no sharp transition; flow changes gradually from primarily convective to primarily diffusive in the general vicinity of generation 16.

One implication of this change in mode of flow is that many aerosol particles penetrate to the region of the terminal bronchioles by convective flow, but they do not penetrate further because of their large mass and resulting low diffusion rate. Thus, sedimentation of these particles is heavy in the region of the terminal respiratory bronchioles. This is one reason why this region of the lung is particularly vulnerable to the effects of air pollutants.

Another implication of this dichotomously branching airway tree is that the greater the number of branch points, the greater is the potential for nonuniform distribution of airflow among the distal airways and alveoli. Thus, when experimental assessment of nonuniform flow is made, the greater the spatial resolution of the

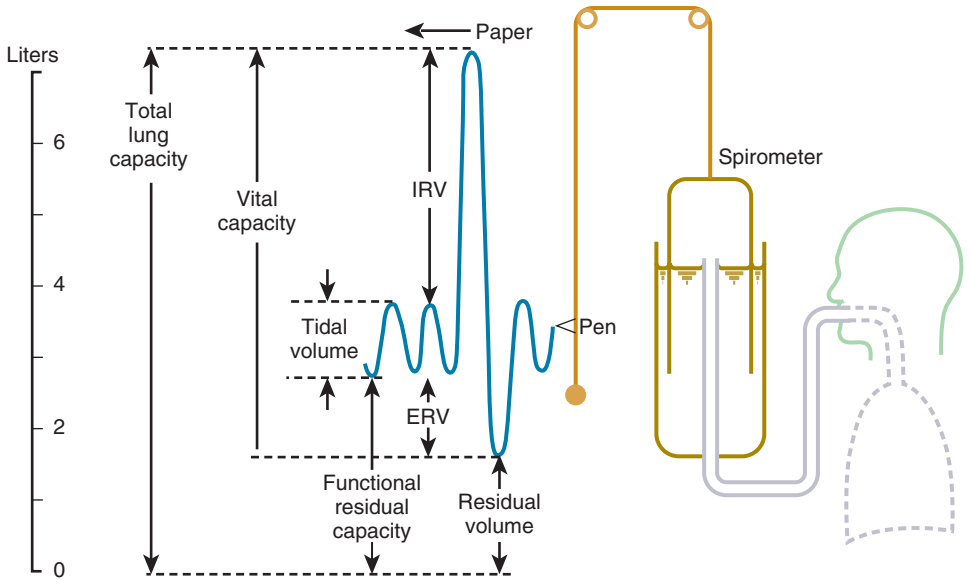

FIGURE 4-3 ■ Major divisions of lung volumes. Values are illustrative only; there is considerable normal variation. ERV, expiratory reserve volume; IRV, inspiratory reserve volume. (Modified from West JB: Respiratory Physiology—The Essentials [8th ed]. Baltimore: Lippincott Williams & Wilkins, 2008.)

method, the greater will be the amount of nonuniformity detected. In addition, repeated, possibly minor, differences in flow distribution at each branch point will give rise to spatial correlation of flow. In other words, neighboring regions will tend to have more similar flows than regions located far apart, other factors being equal.

Lung Volumes

Figure 4-3 shows the major divisions of lung volume. *Total lung capacity* (TLC) is the volume of gas contained in the lungs at maximal inspiration. The *vital capacity* (VC) is the volume of gas that can be exhaled by a maximal expiration from total lung capacity. The volume remaining in the lung after maximal expiration is the *residual volume* (RV). *Tidal volume* (V_T) refers to the normal respiratory volume excursion. The lung volume at the end of a normal expiration is the *functional residual capacity* (FRC). The diagram also indicates the *inspiratory reserve volume* (IRV) and the *expiratory reserve volume* (ERV).

Functional Residual Capacity, Residual Volume, and Total Lung Capacity

These three volumes cannot be measured with a simple spirometer because there is no way of knowing the volume remaining in the lung after a maximal expiration (i.e., the residual volume). However, if the functional residual capacity is measured, the other two volumes can be derived by simple spirometry.

The functional residual capacity can be measured conveniently by helium dilution in a closed circuit. The subject is connected to a spirometer of known volume that contains a known concentration of helium (a very insoluble gas) and then rebreathes until the helium concentration in the spirometer and in the lungs is the same. The exhaled carbon dioxide is absorbed with soda lime, and oxygen is added to maintain a constant total volume. After equilibration, the total amount of helium is assumed to be unchanged because so little of it is removed by the blood because of its very low solubility. The functional residual capacity can then be derived from the following equation:

$$C_1 \times V_1 = C_2 \times (V_1 + V_2) \quad (1)$$

where C_1 and C_2 are the helium concentrations before and after equilibration, V_1 is the volume of the spirometer, and V_2 is the volume of the lung. If the subject is switched into the equipment when at functional residual capacity, V_2 gives that volume.

Another popular way of measuring the functional residual capacity is with a body plethysmograph. This is a large airtight box in which the subject sits. At the end of a normal expiration, a shutter closes the mouthpiece, and the subject is asked to make respiratory efforts. As the subject tries to inhale, the gas in the lungs expands, lung volume increases slightly, and the pressure in the box rises slightly because its gas volume decreases. Boyle's law (pressure times volume is constant at constant temperature) can then be used to calculate the change of volume of the plethysmograph. The equation is $P_1V_1 = P_2(V_1 - \Delta V)$, where P_1 and P_2 are the box pressures before and after the inspiratory effort, V_1 is the preinspiratory box volume, and ΔV is the change in the volume of the box (or lung). If mouth pressure is also measured during the respiratory efforts, Boyle's law can also be applied to the lung and functional residual capacity can be derived. The equation here is $P_3V_2 = P_4(V_2 + \Delta V)$, where P_3 and P_4 are the mouth pressures before and after the inspiratory effort, and V_2 is the functional resid-

ual capacity. Because this is the only unknown (ΔV was measured previously), V_2 can be calculated.

In patients with lung disease, the functional residual capacity measured by helium dilution may be substantially less than that measured by body plethysmography. The reason is that the body plethysmograph measures the total volume of gas in the lung, including any that is trapped behind closed airways, and that therefore does not communicate with the mouth. By contrast, the helium dilution method measures only communicating gas or ventilated lung volume. In young normal subjects these volumes are virtually identical, but they may be considerably different in patients with severe lung disease. Also in these patients, the volume that is obtained for functional residual capacity rises as the time for equilibration is increased because helium continues to penetrate into additional areas of poorly ventilated lung.

Total and Alveolar Ventilation

Total Ventilation

Total ventilation, also called minute ventilation, is the total volume of gas exhaled per minute. It is equal to the tidal volume times the respiratory frequency. The volume of inhaled air is slightly greater than the exhaled volume because more oxygen is inhaled than carbon dioxide is exhaled, but the difference is usually less than 1%.

Alveolar ventilation is the amount of fresh inspired air (non–dead space gas) that enters the alveoli per minute and is therefore available for gas exchange. Strictly, the alveolar ventilation is also measured during expiration, but the inhaled and exhaled volumes are almost the same.

Alveolar Ventilation

Because the tidal volume (V_T) is made up of the dead space volume (V_D) and the volume of gas entering (or coming from) the alveoli (V_A), the alveolar ventilation can be measured from the following equations:

$$V_T = V_D + V_A \tag{2}$$

Multiplying by respiratory frequency gives

$$\dot{V}_E = \dot{V}_D + \dot{V}_A \tag{3}$$

where $\dot{V}_A$ is the alveolar ventilation, and $\dot{V}_E$ and $\dot{V}_D$ are the expired total ventilation and dead space ventilation, respectively.

Therefore,

$$\dot{V}_A = \dot{V}_E - \dot{V}_D \tag{4}$$

A difficulty with this method is that the anatomic dead space is not easy to measure, although a value for it can be assumed with little error. One milliliter per pound of body weight is a common assumption.

Another way of measuring alveolar ventilation in normal subjects is to use the *alveolar ventilation equation,* which expresses mass conservation of carbon dioxide by defining carbon dioxide production $(\dot{V}_{CO_2})$ as the product of alveolar ventilation $(\dot{V}_A)$ and fractional alveolar concentration of carbon dioxide $(F_{A_{CO_2}})$. Because concentration is proportional to partial pressure, the relationship can be written as:

$$\dot{V}_{CO_2} = \dot{V}_A \times F_{A_{CO_2}} = \dot{V}_A \times P_{A_{CO_2}} / K \tag{5}$$

This can then be rearranged as follows:

$$\dot{V}_A = \frac{\dot{V}_{CO_2}}{P_{A_{CO_2}}} \times K \tag{6}$$

where $\dot{V}_{CO_2}$ is the volume of carbon dioxide exhaled per unit time, $P_{A_{CO_2}}$ is the alveolar P_{CO_2}, and K is a constant. In patients with normal lungs, the P_{CO_2} of alveolar gas and that of arterial blood are virtually identical. Therefore, the arterial P_{CO_2} can be used to determine alveolar ventilation from Equation 6. The equation then becomes

$$\dot{V}_A = \frac{\dot{V}_{CO_2}}{Pa_{CO_2}} \times K \tag{7}$$

This procedure is also often used in patients with lung disease, but the value then obtained is the "effective" alveolar ventilation. This is not the same as the alveolar ventilation as defined in Equation 4. Because patients with lung disease must increase their total ventilation to overcome the inefficiency of gas exchange caused by ventilation-perfusion inequality just to keep arterial P_{CO_2} normal, $\dot{V}_A$ from Equation 7 will be less than that from Equation 4.

Anatomic Dead Space

The anatomic dead space is the volume of the conducting airways. The normal value is in the range of 130 to 180 mL and depends on the size and posture of the subject. The value increases slightly with large inspirations because the radial traction exerted on the bronchi by the surrounding lung parenchyma increases their size. Anatomic dead space can be measured by Fowler's method,[3] in which a single breath of oxygen is inhaled and the concentration of nitrogen in the subsequent expiration is analyzed, as shown in Figure 4-4.

Physiologic Dead Space

Unlike anatomic dead space, which is determined by the anatomy of the airways, physiologic dead space is a functional measurement based on the ability of the lungs to eliminate carbon dioxide. It is defined by the Bohr equation:

$$\frac{V_D}{V_T} = \frac{P_{A_{CO_2}} - P_{E_{CO_2}}}{P_{A_{CO_2}}} \tag{8}$$

where A and E refer to alveolar and mixed expired gas, respectively. In subjects with normal lungs, the P_{CO_2} of alveolar gas and that of arterial blood are virtually the same, so that the equation is often written

$$\frac{V_D}{V_T} = \frac{Pa_{CO_2} - P_{E_{CO_2}}}{Pa_{CO_2}} \tag{9}$$

Physiologic dead space is very nearly the same as anatomic dead space when the lung is normal. However, in the presence of ventilation-perfusion inequality (i.e.,

when the ratio of local ventilation to local blood flow is *not* everywhere the same), physiologic dead space is increased, chiefly because of the ventilation going to lung units with abnormally high ventilation-perfusion ratios. Indeed, the physiologic dead space is often reported as one of the indices of the degree of mismatching of ventilation and blood flow within the lung.

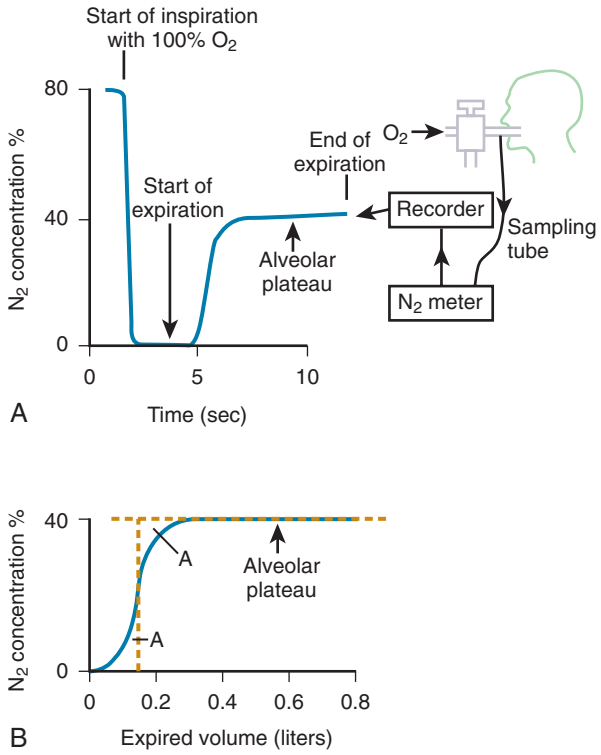

FIGURE 4-4 ■ Fowler's method of measuring the anatomic dead space with a rapid N_2 analyzer. **A** shows that, following a test inspiration of 100% O_2, the N_2 concentration rises during expiration to an almost level "plateau" representing pure alveolar gas. In **B**, N_2 concentration is plotted against expired volume, and the dead space is the volume up to the *vertical dashed line,* which makes the areas **A** and **B** equal. (Redrawn from West JB: Respiratory Physiology—The Essentials [8th ed]. Baltimore: Lippincott Williams & Wilkins, 2008.)

Inequality of Ventilation

Not all the alveoli are equally ventilated, even in the normal lung. There are several reasons for this, related both to gravitational (topographic) and to nongravitational influences on gas distribution.

Topographic Inequality

Regional differences in ventilation can be measured by having the patient inspire a radioactive gas such as xenon (^{133m}Xe). In one technique, the patient inhales a single breath of gas, and its concentration is detected by a radiation camera placed behind the chest. An additional measurement is made after the patient has rebreathed long enough to allow the xenon to equilibrate throughout the different regions of the lungs, thus reflecting regional lung volumes. By comparing the first and the second measurements, the ventilation per unit alveolar volume can be obtained.

Measurements in upright normal subjects show that the ventilation per unit volume of the lung is greatest near the base of the lung and becomes progressively smaller toward the apex. When the subject lies supine, this difference becomes much less, but the ventilation of the lowermost (posterior) lung exceeds that of the uppermost (anterior). In the lateral decubitus position, again, the dependent lung is better ventilated. The above results refer to an inspiration from functional residual capacity.

An explanation of this topographic inequality of ventilation is shown in Figure 4-5A, which depicts conditions at functional residual capacity.[4] Experimental studies show that the intrapleural pressure is less negative at the bottom than at the top of the lung. This pattern can be attributed to the weight of the lung, which requires a larger pressure below the lung than above it to balance the downward-acting weight forces. There are two consequences of this lower expanding pressure on the base of the lung. First, the resting volume of the alveoli is smaller, as shown by the pressure-volume curve. Second, the change in volume for a given change in intrapleural pressure is greater because the alveoli are operating on a steeper part of the pressure-volume curve. Thus, the ventilation (change in volume per unit resting

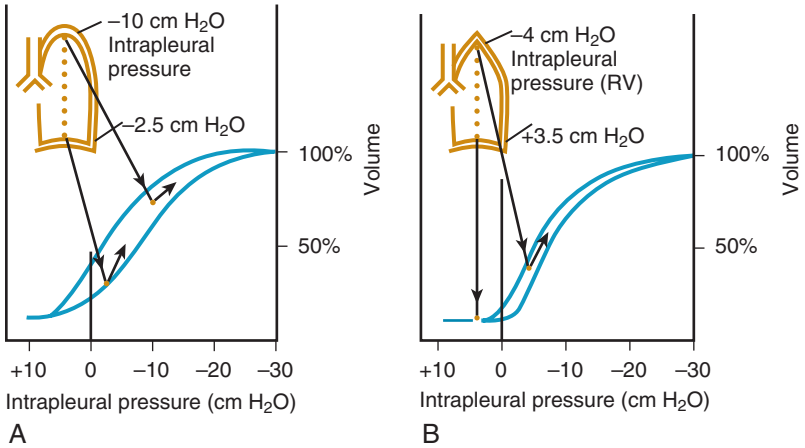

FIGURE 4-5 ■ The topographic inequality of ventilation down the lung. **A,** An inspiration from functional residual capacity. **B,** The situation at very low lung volumes (see text for details). (Redrawn from West JB: Respiratory Physiology—The Essentials [8th ed]. Baltimore: Lippincott Williams & Wilkins, 2008.)

volume) is greater at the base than the apex. However, if a normal subject makes a small inspiration from residual volume (rather than from functional residual capacity), an interesting change in the distribution of ventilation is seen. The major share of the ventilation goes to the apex of the upright lung, whereas the base is very poorly ventilated. Figure 4-5B shows why a different pattern is seen in this case. Now the intrapleural pressures are less negative, and the pressure at the base of the lung actually exceeds atmospheric pressure. For a small fall in intrapleural pressure, no gas will enter the extreme base of the lung, and only the apex will be ventilated. Thus the normal pattern of uneven ventilation is reversed in this early phase of inhalation.

Note that the explanations shown in Figure 4-5 are oversimplifications. They assume that the pressure-volume behavior of a portion of the lung is identical to that of the whole lung. However, this is not strictly true, because the regional distortion is opposed to some extent by the surrounding tissue. A more satisfying explanation is that both the topographic inequality of ventilation and the regional differences of intrapleural pressure are caused by distortion of the lung by its weight.[5] Such an explanation obviates making unwarranted assumptions about the local pressure-volume behavior of distorted lung.

More recently, xenon-enhanced computed tomography has been used to measure regional ventilation by determining the wash-in and washout rates of the radiodense, nonradioactive gas xenon measured in serial computed tomography scans.[6] Other techniques have been developed as well using hyperpolarized helium; they give similar results.[7]

Airway Closure

At residual volume, the compressed region of the lung at the base in Figure 4-5B does not have all its gas squeezed out because small airways, probably in the region of the respiratory bronchioles, close first and trap gas in the distal alveoli. This is known as *airway closure.* It occurs only at lung volumes below functional residual capacity in young normal subjects. However, this volume at which the basal airways close (*closing volume*) increases with age and may encroach on the functional residual capacity in older, apparently normal people. The reason for this increase is that the aging lung loses some of its elastic recoil and the intrapleural pressures therefore become less negative, thus approaching the situation shown in Figure 4-5B. Under these conditions, basal regions of the lung may be only intermittently ventilated, with resulting defective gas exchange. A similar situation frequently develops in patients with chronic obstructive pulmonary disease in whom lung elastic recoil may be reduced.

Nontopographic Inequality

In addition to the topographic inequality of ventilation caused by gravitational factors (see Fig. 4-5), nongravitational mechanisms also exist. This is proved by the fact that astronauts in space show uneven ventilation by both the single-breath and the multibreath nitrogen washout methods.[8,9] These methods are described in Chapter 24. Such findings have been confirmed by studies in which inspired gas is labeled by small particles. Such studies show considerable variability in ventilation at a given horizontal level.

Several factors are responsible for uneven ventilation in the distal, smaller regions of the lung. One of these is the existence of uneven time constants.[10] The time constant of a region of lung is given by the product of its resistance and compliance (analogous to the time constant in electrical circuits, which is the product of electrical resistance and capacitance). Lung units with different time constants inhale and exhale at different flow rates. Depending on the breathing frequency, a unit with a large time constant does not complete its filling before expiration begins and therefore is poorly ventilated. The faster the frequency, the greater the inequality of ventilation. In addition, a unit with a small time constant, which therefore fills rapidly, may receive a higher proportion of gas from the anatomic dead space, which reduces its alveolar ventilation.

Another cause of uneven ventilation in small lung units is the asymmetry of their structure, which can result in a greater penetration of gas by diffusion into the smaller units than into the larger.[11] The resulting somewhat complex behavior is known as diffusion- and convection-dependent inhomogeneity and may play an important role in lung disease.

A further possible reason for uneven ventilation at the level of small lung units is concentration gradients along the small airways. This is known as *series inequality.* Recall that inspired gas reaches approximately the region of the terminal or respiratory bronchioles by convective flow, but gas flow over the rest of the distance to the alveoli is accomplished principally by molecular diffusion within the airways. If there is abnormal dilation of an airway, the diffusion process may not be complete within the breathing cycle, and the distal alveoli will be less well ventilated than the proximal alveoli.

BLOOD FLOW

Blood flow is an equal partner with ventilation in the business of pulmonary gas exchange. This has not always been appreciated, partly because the process of ventilation is more obvious, especially in the dyspneic patient. In addition, the pulmonary circulation is relatively inaccessible, and this has impeded research. Much has been learned about the pulmonary circulation in the past few years, especially its metabolic functions. This topic overlaps with the pharmacology of pulmonary blood vessels, which is covered in Chapter 8. The anatomy of the pulmonary circulation is described in Chapters 1 and 6.

Pressures of the Pulmonary Circulation

The pressures in the pulmonary circulation are very low compared with those in the systemic circulation, and

this feature is responsible for much of its special behavior. The normal pressures in the human pulmonary artery are often given as about 25 mm Hg systolic, 8 mm Hg diastolic, and 15 mm Hg mean. Because the normal mean arterial pressure in the systemic circulation is about 100 mm Hg, the average arterial pressure is six times higher than that in the pulmonary circulation.

Pressure Inside Blood Vessels

Because the pulmonary artery pressure is so low, hydrostatic effects within the pulmonary circulation are very important. The adult upright human lung is some 30 cm high, giving a hydrostatic difference in pressure between the extreme apex and the base of 30 cm blood, which is equivalent to about 23 mm Hg. As a result, there are very substantial differences in pressure within the small pulmonary arteries and the capillaries between the top and bottom of the upright lung. This topic is discussed further in the section on the distribution of pulmonary blood flow.

Various techniques have been used to determine the pattern of pressure drop along the pulmonary blood vessels. These include measurement of the transudation pressure on the pleural surface of isolated lung, measurement of the pressure transient resulting from the injection of a slug of low- or high-viscosity blood into the pulmonary artery,[12] and direct puncture of different-sized vessels along with direct measurement of hydrostatic pressure.[13,14] The direct puncture measurements indicate that much of the normal pressure drop in the pulmonary circulation probably occurs in the pulmonary capillaries, and that the mean capillary pressure is approximately halfway between that in the pulmonary artery and that in the pulmonary vein (Fig. 4-6). It appears that the distribution of the pressure drop is consistent with the main function of the pulmonary circulation, which is to expose as large an area of blood as possible to the alveolar gas, while minimizing the work of the right heart.

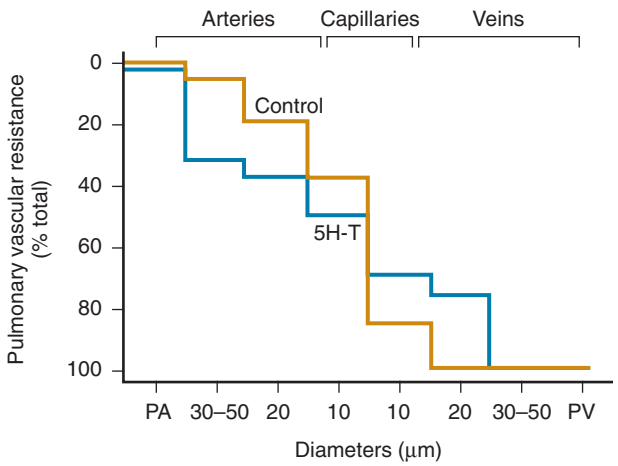

FIGURE 4-6 ■ Pressure drop along the pulmonary circulation as determined by direct puncture of vessels. The effects of 5-HT (5-hydroxytryptamine [serotonin]) are also shown. PA, pulmonary artery; PV, pulmonary vein. (Redrawn from Bhattacharya J, Nanjo S, Staub NC: Factors affecting lung microvascular pressure. Ann N Y Acad Sci 384:107–114, 1982.)

The distribution of pressure along the pulmonary blood vessels probably depends on lung volume. At low states of lung inflation, the resistance of the extra-alveolar vessels (see next section) increases, and more pressure drop occurs across the pulmonary arteries and veins. By contrast, there is evidence that, at very high states of lung inflation, the resistance of the capillary bed is increased, and therefore an additional pressure drop will occur in the capillaries.

The pressures in the pulmonary circulation are highly pulsatile; indeed, if we take the normal systolic and diastolic pressures in the main pulmonary artery as 25 and 8 mm Hg, respectively, this is one of the most pulsatile vascular pressures in the body. There is good evidence that the pulsatility of pressure, and therefore flow, extends to the pulmonary capillaries.[15]

Pressures Outside Blood Vessels

It is now known that some pulmonary blood vessels are exposed to alveolar pressure (or very nearly), whereas others are outside the influence of alveolar pressure but are very sensitive to the state of lung inflation. These two types of vessels are known as alveolar and extra-alveolar, respectively (Fig. 4-7).

The alveolar vessels are largely capillaries that course through the alveolar walls. The pressure to which they are exposed is very nearly alveolar pressure. However, it can be shown that, when the lung is expanded from a very low lung volume, this pressure falls several centimeters below alveolar pressure because of surface tension effects in the alveolar lining layer.[16] By contrast, during deflation from high lung volumes, the pericapillary pressure is very close to alveolar pressure.

The extra-alveolar vessels are not exposed to alveolar pressure. The caliber of these vessels is determined by the radial traction of the surrounding alveolar walls and therefore depends on lung volume. When the lung inflates, the caliber of these vessels increases; when the lung deflates, their caliber decreases because of the elastic tissue in their walls, and also because of a small amount of smooth muscle tone.

The small vessels (of approximately 30-μm diameter) in the corners of the alveolar walls behave in a manner that is intermediate between that of the capillaries and the extra-alveolar vessels. These corner vessels can certainly remain open when the capillaries are closed. Indeed, this is the normal appearance in zone 1 lung[17] (see later section on the distribution of blood flow). However, the shape and attachments of the corner vessels are very different from those of the larger extra-alveolar vessels, and it is unlikely that the pressure outside them varies in the same way as the lung expands.

The extra-alveolar vessels are surrounded by a potential perivascular space (see Fig. 1-5), which has an important role in the transport of extravascular fluid in the lung. The lymph vessels run in this space, although

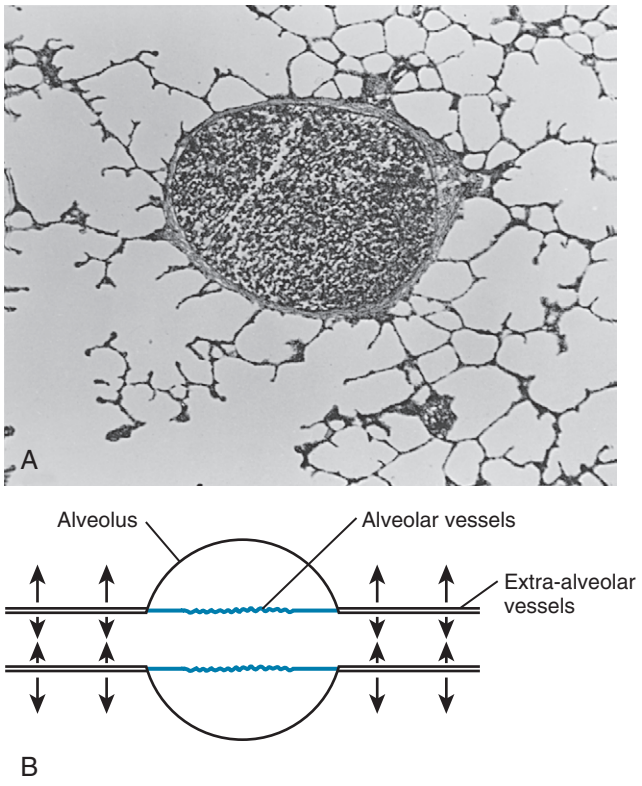

FIGURE 4-7 ■ **A,** Section of lung showing an extra-alveolar vessel (in this case, a small vein) surrounded by alveoli. Note the potential perivascular space. **B,** Diagram of alveolar and extra-alveolar vessels. The former are mainly the capillaries and are exposed to alveolar pressure. The latter have their lumina enlarged by the pull of radial traction (*outward-oriented arrows*) of the surrounding parenchyma. (Modified from West JB: Respiratory Physiology—The Essentials [8th ed]. Baltimore: Williams & Wilkins, 2008.)

lymph can also traverse the space outside lymph vessels. One of the earliest histologic signs of interstitial pulmonary edema is "cuffing" of the perivascular space around the extra-alveolar vessels.[18,19]

A distinction should be drawn between the net pressure (sum of forces per unit area) pulling on the wall of an extra-alveolar vessel on the one hand, and the fluid hydrostatic pressure in the perivascular space on the other. The fluid hydrostatic pressure determines the movement of fluid into this region, and there is evidence that it is very low compared with the hydrostatic pressure in the interstitium of the alveolar wall. As a consequence, fluid that passes from the capillaries into the interstitial space of the alveolar wall eventually finds its way to the perivascular low-pressure region by virtue of the hydrostatic pressure gradient.[20] The pressure responsible for expanding extra-alveolar vessels may not be as low because of points of contact between the two sides of the potential perivascular space.

Pulmonary Vascular Resistance

Pulmonary vascular resistance is given by the following relationship:

$$\frac{\text{Pulmonary arterial pressure} - \text{pulmonary venous pressure}}{\text{Pulmonary blood flow}} \quad (10)$$

Because all three variables are pulsatile as a result of the heartbeat, mean values are generally used.

This definition is similar to that used for electrical resistance, which is the difference of voltage across a resistor divided by the current. However, whereas the resistance of an electrical resistor is independent of the voltage at both ends and the current, this is not the case for pulmonary vascular resistance. For example, an increase in either pulmonary arterial pressure or pulmonary venous pressure generally results in a decrease in pulmonary vascular resistance because capillary pressure rises, resulting in recruitment and distention (see later). Again, if pulmonary blood flow is increased (e.g., by raising pulmonary arterial pressure), pulmonary vascular resistance usually decreases.

It is important to appreciate that a single number for pulmonary vascular resistance is a very incomplete description of the pressure-flow properties of the pulmonary circulation. However, in practice, pulmonary vascular resistance is often a useful measurement because, although the normal value varies considerably, we often need to compare the normal lung with a markedly abnormal one in which the vascular resistance is greatly increased.

In practice, pulmonary venous pressure is difficult to measure, although an estimate can be obtained by wedging a catheter in a small pulmonary artery (the so-called pulmonary artery wedge pressure). Therefore, sometimes the ratio of pulmonary artery pressure to blood flow is reported, and the term *total pulmonary vascular resistance* is used for this.

Pressure-Flow Relations

If pulmonary blood flow is plotted against pulmonary arterial pressure, while pulmonary venous pressure, alveolar pressure, and intrapleural pressure are held constant (thus fixing lung volume), the slope of the line continually increases. This shows that pulmonary vascular resistance decreases as pressure is raised. Such measurements are best made on isolated lung preparations because of the near impossibility of changing one pressure at a time in the intact animal.

Figure 4-8 shows the changes in pulmonary vascular resistance in an isolated lung as *either* pulmonary arterial *or* pulmonary venous pressure is raised, all other pressures being held constant. Note that, as arterial pressure is increased, pulmonary vascular resistance falls. Of course, this is associated with an increase in blood flow. Note also that pulmonary vascular resistance decreases when venous pressure is raised (with pulmonary artery pressure held constant). In this case, pulmonary blood flow will fall.

The decreases in pulmonary vascular resistance shown in Figure 4-8 help to limit the work of the right heart under conditions of high pulmonary blood flow. For example, during exercise, both pulmonary arterial

and venous pressures rise. Although the normal pulmonary vascular resistance is remarkably small (the normal 5-L/min pulmonary blood flow is associated with an arterial-venous pressure difference of only about 10 mm Hg), the resistance falls to even lower values when the pulmonary arterial and venous pressures rise as during exercise.

Two mechanisms are responsible for the fall in pulmonary vascular resistance shown in Figure 4-8. These are *recruitment,* that is, opening up of previously closed blood vessels, and *distention,* that is, increase in caliber of vessels. Figure 4-9A shows experimental data from rapidly frozen dog lung preparations, indicating the importance of recruitment as the pulmonary artery pressure is raised from low values.[21] Note that the number of open capillaries per millimeter of length of alveolar wall increased from about 25 to over 50 as pulmonary artery pressure was raised from zero to less than 15 cm H_2O. Figure 4-9B shows data on the importance of distention of pulmonary capillaries.[17] Note that the mean width of the capillaries increased from about 3.5 to nearly 7 µm as the capillary pressure was increased to approximately 50 cm H_2O. Beyond that, there was very little change.

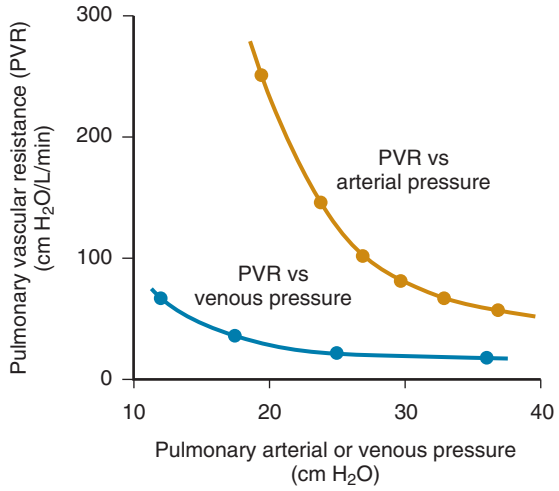

FIGURE 4-8 ■ Fall in pulmonary vascular resistance that occurred as the pulmonary arterial or venous pressure was raised in a canine lung preparation. When one pressure was changed, the other was held constant. (Redrawn from West JB: Respiratory Physiology—The Essentials [8th ed]. Baltimore: Lippincott Williams & Wilkins, 2008.)

The mechanism of recruitment of pulmonary capillaries is not fully understood. It has been suggested that, as the pulmonary arterial pressure is increased, the critical opening pressures of various arterioles are successively overcome. However, it has been shown that the variation in red blood cell concentration within areas supplied by single arterioles accounted completely for the variation between areas supplied by different arterioles.[21] This suggests that recruitment occurs at the capillary rather than the arterial level.

A possible mechanism of recruitment of pulmonary capillaries is based on the stochastic properties of a dense network of numerous interconnected capillary segments.[22] It can be shown in such a model that, if each capillary segment requires a very small critical pressure across it before flow begins, and the network contains a distribution of these critical pressures, recruitment can occur over a large range of arterial pressures. For example, in a network with as many elements as exist in the human pulmonary capillary bed,[1] a critical pressure of the order of only 0.02 cm H_2O for the individual segments could result in recruitment over a range of arterial pressures from 0 to 30 cm H_2O. Such a very small critical pressure could result from the intrinsic flow properties of blood, especially when the diameter of the red cells equals that of the capillary lumen.

The mechanism of distention of pulmonary capillaries is apparently simply the bulging of the capillary wall as

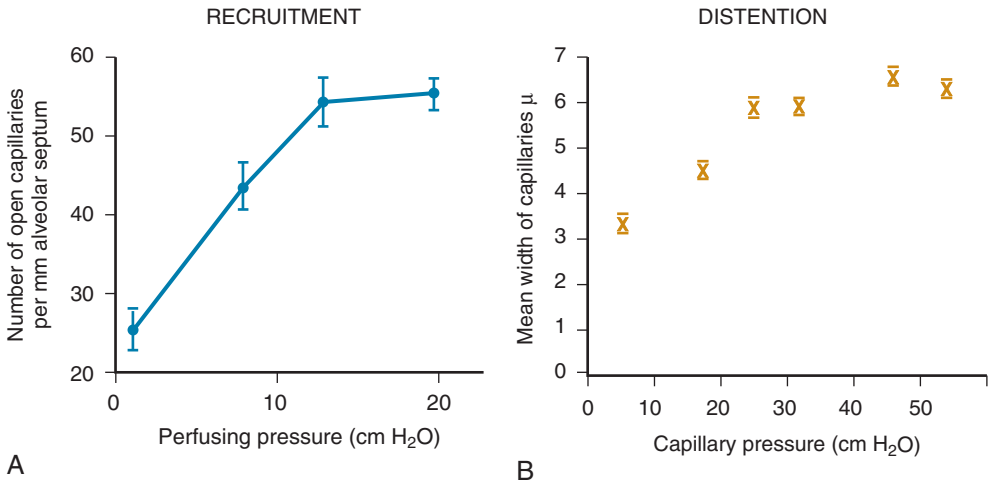

FIGURE 4-9 ■ **A,** Data showing recruitment of pulmonary capillaries as the pulmonary arterial pressure is raised. **B,** Data showing distention of pulmonary capillaries as their pressure is increased. (**A** redrawn from Warrell DA, Evans JW, Clarke RO, et al: Pattern of filling in the pulmonary capillary bed. J Appl Physiol 32:346–356, 1972. **B** redrawn from Glazier JB, Hughes JMB, Maloney JE, West JB: Measurements of capillary dimensions and blood volume in rapidly frozen lungs. J Appl Physiol 26:65–76, 1969.)

the transmural pressure of the capillaries is raised. As Figure 4-9B shows, the mean capillary diameter increases as capillary transmural pressure rises. Probably this behavior is caused by a change in shape of the capillaries rather than actual stretching of the capillary wall. There is evidence that the strength of the wall (at least on the thin side) comes from the type IV collagen in the basement membranes (see later), which has a high tensile strength and Young's modulus (i.e., is very stiff). It is unlikely that it stretches appreciably when the capillary transmural pressure rises to 30 cm H_2O. However, surface tension forces, and also longitudinal tension in the alveolar wall associated with lung inflation, tend to flatten the capillaries at low capillary transmural pressures, and this means that their diameter can increase when capillary pressure rises. Some photomicrographs of pulmonary capillaries with very high intracapillary pressures show remarkable bulging in rapidly frozen lung preparations.[17]

Recruitment and distention also provide mechanisms for increasing both the surface area of the lung microvasculature in contact with alveolar gas and the red cell transit time through the microvasculature, which may facilitate gas exchange.

Effect of Lung Volume

Lung volume has an important influence on pulmonary vascular resistance. Figure 4-10 shows that, as lung volume is increased from very low values, vascular resistance first decreases and then increases. The lung normally operates near the minimal value of vascular resistance, that is, functional residual capacity coincides with a low vascular resistance.

The increase in pulmonary vascular resistance at very low lung volume is caused by the decrease in caliber of the extra-alveolar vessels. Because these vessels are normally held open by the radial traction of the surrounding parenchyma, their caliber is least in the collapsed lung. Under these conditions, the presence of elastic tissue and smooth muscle with tone in the wall of these vessels may result in a measurable critical opening pressure of about 7 cm H_2O.[23] Also, at low lung volumes, vascular resistance is extremely sensitive to vasoconstrictor drugs, such as serotonin, which cause contraction of vascular smooth muscle.[24]

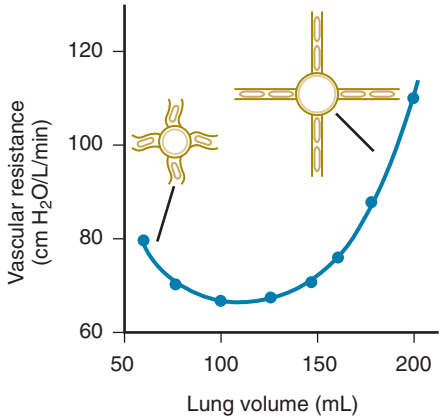

FIGURE 4-10 ■ Effect of changing lung volume on pulmonary vascular resistance. Data were taken from a canine lung preparation. (Redrawn from West JB: Respiratory Physiology—The Essentials [8th ed]. Baltimore: Lippincott Williams & Wilkins, 2008.)

Another factor that may contribute to the high pulmonary vascular resistance at low states of lung inflation is folding and distortion of pulmonary capillaries.[25,26] However, the possible importance of distortion of the pulmonary capillaries as a cause of the increase of vascular resistance at low lung volumes is still uncertain.

At high states of lung inflation, the increase in pulmonary vascular resistance is probably caused by narrowing of the pulmonary capillaries. An analogy is a piece of thin rubber tubing that narrows considerably when it is stretched across its diameter. This distortion increases the resistance to fluid moving through it. Direct measurements on rapidly frozen dog lungs show that the mean width of the capillaries is greatly decreased at high states of lung inflation.[17]

In considering the effects of lung inflation, a distinction should be made between "positive" and "negative" pressure inflation. The results shown in Figure 4-10 were found with negative-pressure inflation, that is, when the lung was expanded by reducing pleural pressure and the relationship between pulmonary arterial and alveolar pressures was held constant. If positive-pressure inflation is used (i.e., alveolar pressure is increased with respect to pulmonary arterial pressure), pulmonary vascular resistance increases even more at high states of lung inflation. The reason is that lung inflation is then associated with a decrease in the transmural pressure of the capillaries, and they are, in effect, squashed by the increased alveolar pressure. This is actually the case in normal subjects, for example, during inhalation to total lung capacity. Although alveolar pressure remains at atmospheric pressure at the end of inspiration (glottis open), pulmonary arterial and venous pressures fall along with intrapleural pressure. Thus, the net result is to decrease the transmural pressure across the pulmonary capillaries, and this is an additional contributing factor in the increase of pulmonary vascular resistance.

Other Factors

Various drugs affect pulmonary vascular resistance. In some instances, the effects depend on the species of animal. However, in general, serotonin, histamine, and norepinephrine cause contraction of pulmonary vascular smooth muscle and increase vascular resistance. These drugs are particularly effective as vasoconstrictors when the lung volume is small and the radial traction of surrounding parenchyma on the extra-alveolar vessels is weak. Drugs that often relax smooth muscle in the pulmonary circulation include acetylcholine and isoproterenol. However, normal pulmonary blood vessels have little resting tone, so the degree of potential relaxation is small.

The autonomic nervous system exercises a weak control on the pulmonary circulation. There is evidence that increased sympathetic tone can cause vasoconstric-

tion and stiffening of the walls of the larger pulmonary arteries. Both α- and β-adrenergic receptors are present.[27] Increased parasympathetic activity has a weak vasodilator action. As already indicated, any changes of vascular smooth muscle tone are much more effective at low states of lung inflation (when the extra-alveolar vessels are narrowed) or in the fetal state (when the amount of smooth muscle present is much greater than in the adult).

Pulmonary edema increases vascular resistance by a mechanism that is poorly understood. It may be that there are different mechanisms, depending on the type and stage of edema. Interstitial pulmonary edema causes marked cuffing of the perivascular spaces of the extra-alveolar vessels. Presumably this increases their vascular resistance,[28] because, as already indicated, these vessels rely on the radial traction of the surrounding parenchyma to hold them expanded. In addition, however, it may be that edema in the interstitium of the alveolar wall encroaches on the pulmonary capillaries to some extent, thus increasing their vascular resistance.[29] Hypoxic pulmonary vasoconstriction is discussed in a later section and in Chapter 6.

Distribution of Pulmonary Blood Flow

Just as for ventilation, blood flow is not partitioned equally to all alveoli, even in the normal lung. Both gravitational (topographic) and nongravitational factors affect the distribution of blood flow.

Normal Distribution

The topographic distribution of pulmonary blood flow can conveniently be measured using radioactive materials. In one technique, ^{133m}Xe is dissolved in saline and injected into a peripheral vein. When the xenon reaches the pulmonary capillaries, it evolves into the alveolar gas. If the subject undertakes a 15-second breath-holding period, the pattern of radioactivity within the lung can be measured using a gamma camera or similar device. This pattern reflects the regional distribution of blood flow. Subsequently, the distribution of alveolar volume is obtained by having the subject rebreathe radioactive xenon until the gas is evenly distributed. By combining the two measurements, the blood flow per unit alveolar volume of the lung can be obtained. The distribution of blood flow can also be measured with radioactive albumin macroaggregates, and with a variety of other radioactive gases, including ^{15}O-labeled carbon dioxide and ^{13}N. More recently, functional magnetic resonance imaging of the lung has been used to assess distribution of pulmonary blood flow.[30] This noninvasive technique does not expose subjects to radioactivity, can therefore be used repetitively, and shows great promise for the future.

In the normal upright human lung, pulmonary blood flow decreases approximately linearly with distance up the lung, reaching very low values at the apex.[31] If the subject lies supine, the rates of apical and basal blood flow become the same, but differences can be detected between the anterior (uppermost) and posterior (lowermost) regions of the lung. During exercise in the upright position, both apical and basal blood flow rates increase and the relative differences down the lung are reduced.

The factors responsible for the uneven topographic distribution of blood flow can be studied conveniently in isolated lung preparations. These studies show that, in the presence of normal vascular pressures, blood flow decreases approximately linearly up the lung[32] as it does in intact humans. However, if the pulmonary arterial pressure is reduced, blood flow rises only to the level at which pulmonary arterial and alveolar pressures are equal; above this point, no flow can be detected. If venous pressure is raised, some measurements show a more uniform distribution of blood flow in the region of the lung below the point at which pulmonary venous is equal to alveolar pressure.

Three-Zone Model for the Distribution of Blood Flow

Figure 4-11 shows a simple model that has proved to be useful in understanding the factors responsible for the topographic inequality of blood flow in the lung.[32] The lung is divided into three zones according to the relative magnitudes of the pulmonary arterial (Pa), alveolar (PA), and venous (Pv) pressures.

Zone 1 is that region of the lung above the level at which pulmonary arterial and alveolar pressures are equal; in other words, alveolar pressure exceeds arterial pressure in this region. Measurements in isolated lungs show that there is no blood flow in zone 1, the explanation being that the collapsible capillaries close because the pressure outside exceeds the pressure inside. Micrographs of rapidly frozen lung from zone 1 show that the

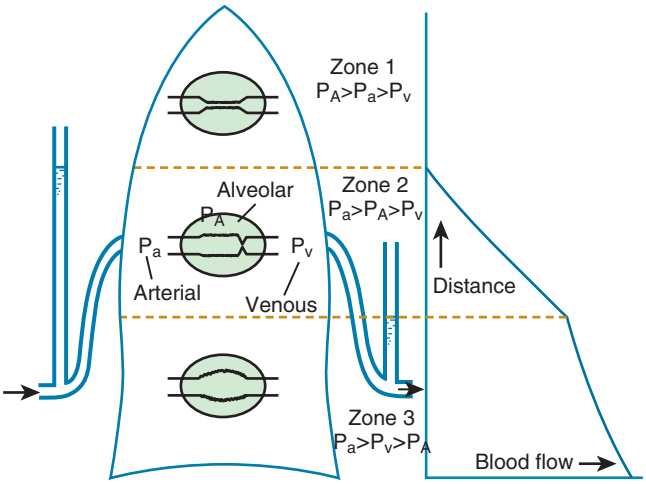

FIGURE 4-11 ■ Three-zone model designed to account for the uneven topographic distribution of blood flow in the lung. P_a, pulmonary arterial pressure; P_A, pulmonary alveolar pressure; P_v, pulmonary venous pressure. (Redrawn from West JB, Dollery CT, Naimark A: Distribution of blood flow in isolated lung: Relation to vascular and alveolar pressures. J Appl Physiol 19:713–724, 1964.)

capillaries have collapsed, although occasionally trapped red blood cells can be seen within them.[17]

The level to which blood rises can be influenced by the surface tension of the alveolar lining layer, as discussed earlier. If measurements are made on a lung immediately after it is inflated from a near-collapsed state, blood flow rises 3 or 4 cm above the level at which pulmonary arterial and alveolar pressures are equal.[16] This can be explained by the reduced surface tension, which lowers the pericapillary hydrostatic pressure.

Zone 2 is that part of the lung in which pulmonary arterial pressure exceeds alveolar pressure, but alveolar pressure exceeds venous pressure. Here the vessels behave as Starling resistors,[33] that is, as collapsible tubes surrounded by a pressure chamber. Under these conditions, flow is determined by the difference between arterial and alveolar pressures, rather than by the expected arterial-venous pressure difference. One way of looking at this is that the thin wall of the vessel offers no resistance to the collapsing pressure, so the pressure inside the tube at the downstream end is equal to chamber pressure. Thus, the pressure difference responsible for flow is perfusion minus chamber pressure.

This behavior has been variously referred to as the waterfall[33] or sluice[34] effect and can be demonstrated in rubber-tube models on the laboratory bench. However, it should be emphasized that the flow properties of capillaries are very different from those of the typical bench-top model. For example, the Reynolds number of the capillaries is very low, with the result that there is no instability as typically occurs in a rubber-tube model, which usually oscillates. Again, the capillaries contain a train of red blood cells that essentially fill the diameter of the small vessels. Thus these vessels cannot collapse in the same way as in a rubber-tube model. Nevertheless, operationally, the lung in zone 2 condition has essentially the same pressure-flow behavior as that of the laboratory Starling resistor.

The increase in blood flow down zone 2 can be explained by the hydrostatic increase in pulmonary arterial pressure down the zone, whereas the alveolar pressure remains constant. Thus the pressure difference determining flow increases linearly with distance.

Zone 3 is that part of the lung in which venous pressure exceeds alveolar pressure. Radioactive gas measurements show that blood flow increases down this zone, although in some preparations at least, the rate of increase is apparently less than in zone 2. Because the pressure difference responsible for flow is arterial minus venous pressure, and because these two pressures increase similarly with distance down the zone, it is not immediately apparent why blood flow increases down this zone. However, the transmural pressure of the capillaries increases, and because the vessels are distensible, their vascular resistance decreases down the zone. This appears to be the major factor responsible for the increase in blood flow down zone 3. Micrographs of rapidly frozen lung confirm the increase in caliber of the capillaries down zone 3.[17] However, it is also possible that there is some recruitment of capillaries that contributes to the increase in blood flow.

The Effect of Lung Volume on the Distribution of Blood Flow—Zone 4

In spite of its simplicity, the three-zone model of Figure 4-11, based on the effects of pulmonary arterial, alveolar, and venous pressures, accounts for many of the distributions seen in the normal lung. However, other factors play a role; one of these is lung volume. For example, under most circumstances, a zone of reduced blood flow, known as zone 4, is seen in the lowermost region of the upright human lung.[35] This zone becomes smaller as lung volume is increased, but careful measurements indicate that a small area of reduced blood flow is present at total lung capacity at the lung base. As lung volume is reduced, this region of reduced blood flow extends further and further up the lung so that, at functional residual capacity, blood flow decreases down the bottom half of the lung. At residual volume, the zone of reduced blood flow extends all the way up the lung, so that blood flow at the apex exceeds that at the base.[35]

These patterns cannot be explained by the interactions of the pulmonary arterial, venous, and alveolar pressures as in Figure 4-11. Instead, we have to take into account the contribution of the extra-alveolar vessels. As pointed out previously (see Fig. 4-10), the caliber of these vessels is determined by the degree of lung inflation; as lung volume is reduced, the vessels narrow. In the upright human lung, the alveoli are less well expanded at the base than at the apex because of distortion of the elastic lung caused by its weight (see Fig. 4-5). As a result, the extra-alveolar vessels are relatively narrow at the base, and their increased contribution to pulmonary vascular resistance results in the presence of a zone of reduced blood flow in that region. As overall lung volume is reduced, the contribution of the extra-alveolar vessels to the distribution of blood flow increases, and zone 4 extends further up the lung. At residual volume, the caliber of the extra-alveolar vessels is so small that they completely dominate the picture and determine the distribution of blood flow.

The role of the extra-alveolar vessels can be exaggerated by injecting vasoconstrictor drugs such as serotonin.[36] Under these conditions, zone 4 extends further up the lung. The opposite effect is seen if a vasodilator drug such as isoproterenol is infused into the pulmonary circulation.

The contribution of the extra-alveolar vessels increases in the presence of interstitial pulmonary edema, because this creates a cuff of fluid around the vessels and thereby narrows them. This is thought to be the cause of the increased pulmonary vascular resistance seen at the base of the human lung in conditions of interstitial pulmonary edema,[28] in which the distribution of blood flow often becomes inverted (e.g., in chronic mitral stenosis).[37] Under these conditions, the blood flow to the apex of the upright lung consistently exceeds the flow to the basal regions. However, the effects of interstitial edema on blood flow distribution are still not fully understood.

Increased Acceleration and Weightlessness. Because the topographic distribution of blood flow in the normal lung can be attributed to gravity, it is not

surprising that, during increased acceleration, the distribution of blood flow becomes more uneven.[38] For example, during exposure to +3*g* acceleration, that is, three times the normal acceleration experienced by someone in the upright posture, the upper half of the lung is completely unperfused. The amount of unperfused lung is approximately proportional to the *g* level.

By contrast, in astronauts during sustained microgravity in space, the distribution of blood flow becomes more uniform.[39] Because it is not possible to use radioactive gases in this environment, the inequality of blood flow has been determined indirectly from the size of the cardiogenic oscillations for P_{CO_2}. Cardiogenic oscillations are fluctuations in the concentrations of gases such as oxygen, carbon dioxide, and nitrogen during a single expiration caused by preferential emptying of different parts of the lung due to the movement of the heart. During hyperventilation, the P_{CO_2} was reduced in the alveolar gas, and during the breath-hold period, it then increased at a rate determined by the blood flow per unit of alveolar volume. It was found that there is a marked reduction in the inequality of blood flow during sustained microgravity compared with that observed in the upright posture before or after the flight. In particular, there is evidence that the topographic differences are essentially abolished. Interestingly, however, some inequality of pulmonary blood flow still remains, indicating that gravity-independent mechanisms are also present.

Nongravitational Factors Influencing the Distribution of Pulmonary Blood Flow. Although gravity is a major factor determining the uneven distribution of blood flow in the upright human lung, it is now clear that nongravitational factors also play an important role. There are several possible mechanisms. One is that there may be regional differences of vascular conductance, with some regions of the pulmonary vasculature having an intrinsically higher vascular resistance than others. This has been shown to be the case in isolated dog lungs,[40] and there is some evidence for higher blood flows in the dorsal-caudal than the ventral regions of the lung in both intact dogs and horses. Another possible factor is a difference in blood flow between the central and peripheral regions of the lung,[41] although this is controversial. Some measurements show differences in blood flow along the acinus, with the more distal regions of the acinus being less well perfused than the proximal regions.[42,43] Finally, as pointed out earlier, because of the complexity of the pulmonary circulation at the alveolar level, including the very large number of capillary segments, it is likely that there is inequality of blood flow at this level. Reference has already been made to the possibility of recruitment of pulmonary capillaries based on the stochastic properties of a dense network of numerous interconnected capillary segments.[22] There is also work suggesting that the distribution of pulmonary blood flow in small vessels may follow a fractal pattern.[44] The term *fractal* describes a branching pattern of both structure (blood vessels) and function (blood flow) that repeats itself with each generation. This means that any subsection of the vascular tree exhibits the same branching pattern as the entire tree. Were a picture of such a subsection to be enlarged, it would overlie and match the pattern of the whole tree. Just as mentioned for ventilation earlier, repeated branching of blood vessels with fractal properties has implications for how blood flow is distributed independently of gravitational influences. The greater the number of branch points, the greater is the likely inequality of perfusion among alveoli. This implies that the finer the spatial resolution of the method used to assess flow distribution, the greater is the likely amount of inequality detected.

Abnormal Patterns of Blood Flow

The normal distribution of pulmonary blood flow is frequently altered by lung and heart disease. Localized lung disease, such as fibrosis and cyst formation, usually causes a local reduction of flow. The same is true of pulmonary embolism, in which the local reduction in blood flow, as determined from a perfusion scan, is usually coupled with normal ventilation, and this pattern provides an important diagnostic clue. Bronchial carcinoma may reduce regional blood flow, and occasionally a small hilar lesion can cause a marked reduction of blood flow to one lung, presumably through compression of the main pulmonary artery. Generalized lung disease, such as chronic obstructive pulmonary disease and bronchial asthma, also frequently causes patchy inequality of blood flow. Sometimes, asthmatic patients whose disease is thought to be fairly well controlled show marked impairment of blood flow in some lung regions.

Heart disease frequently alters the distribution of blood flow, as might be expected from the factors responsible for the normal distribution (see Fig. 4-11). For example, patients with pulmonary hypertension or increased blood flow through left-to-right shunts usually show a more uniform distribution of blood flow.[45] Diseases in which pulmonary artery pressure is reduced, such as tetralogy of Fallot with oligemic lungs, are associated with reduced perfusion of the lung apices. Increased pulmonary venous pressure, as in mitral stenosis, initially causes a more uniform distribution than normal. However, in advanced disease, an inversion of the normal distribution of blood flow is frequently seen, with more perfusion to the upper than to the lower zones. The mechanism for this shift is not fully understood, but, as indicated earlier, perivascular edema causing an increased vascular resistance of the extra-alveolar vessels is thought to be a factor.

Active Control of the Pulmonary Circulation

The distribution of pulmonary blood flow and the pressure-flow relations of the pulmonary circulation are normally dominated by the passive effects of the hydrostatic pressure gradient described earlier. Thus, the roles of gravity, of variation in vascular lengths and diameters, and of recruitment and distention can account for much of the behavior of the normal circulation. The normal

adult pulmonary circulation has little smooth muscle in the walls of the vessels, and active control of vascular tone is weak. However, in conditions in which there is an increase in the amount of smooth muscle (e.g., in the fetal lung), in long-term residence at high altitude, or in prolonged pulmonary hypertension, the tone of the vascular smooth muscle plays a more significant role. *Nevertheless,* some active control of the circulation is seen in the normal lung, as described in the next section.

Hypoxia

One example of active control is hypoxic pulmonary vasoconstriction. This consists of contraction of smooth muscle in the walls of small blood vessels in a region of a lung with alveolar hypoxia. The precise mechanism of this response is still not known, but because it occurs in excised isolated lungs, it clearly does not depend on central nervous system connections. Furthermore, excised segments of pulmonary artery can be shown to constrict if their environment is made hypoxic, so it appears to be a local action of the hypoxia on the artery itself. It is also known that it is the P_{O_2} of the alveolar gas, not of the pulmonary arterial blood, that chiefly determines the response.[46] This can be proved by perfusing a lung with blood containing a high P_{O_2} while keeping the alveolar P_{O_2} low. Under these conditions, the response is well seen.

The stimulus-response curve of hypoxic pulmonary vasoconstriction is very nonlinear (Fig. 4-12). When the alveolar P_{O_2} is altered in the region above 100 mm Hg, little change in vascular resistance is seen. However, when the alveolar P_{O_2} is reduced to approximately 70 mm Hg, obvious vasoconstriction may occur, and at a very low P_{O_2} approaching that of mixed venous blood, the local blood flow may be almost abolished. The data shown in Figure 4-12 are from anesthetized cats.[47] However, there are species differences in the stimulus-response curves. For example, there is an almost linear reduction of blood flow between alveolar P_{O_2} values of 150 and 40 mm Hg in the coatimundi (a small South American mammal).[48] The preparation in which these measurements were made had the additional advantages that the chest was closed and the measurements were made in a very small region of lung. These conditions probably give better information on the role of the phenomenon in the local regulation of blood flow.

The major site of the vasoconstriction is in the small pulmonary arteries.[49] In the normal human lung, the small arteries have a meager amount of smooth muscle, and this tends to be uneven in its distribution. This may explain why in global alveolar hypoxia (e.g., at high altitude) there is evidence that the constriction is uneven. For example, alveolar hypoxia nearly doubles the dispersion of transit times through the pulmonary circulation of a lobe of dog lung,[50] and the distribution of India ink particles injected into the pulmonary circulation during alveolar hypoxia is more uneven than during normoxia.[51] This uneven vasoconstriction probably plays a role in the mechanism of high-altitude pulmonary edema[52] (see later).

The mechanisms of hypoxic pulmonary vasoconstriction are still not fully understood. Studies indicate that voltage-gated potassium channels in the smooth muscle cells are involved, leading to increased intracellular calcium ion concentrations.[53-56]

Endothelium-derived vasoactive substances play a role. Nitric oxide (NO) is an endothelium-derived relaxing factor for blood vessels. It is formed from L-arginine and is a final common pathway for a variety of biologic processes. NO activates soluble guanylate cyclase, which leads to smooth muscle relaxation through the synthesis of cyclic guanosine monophosphate. Inhibitors of NO

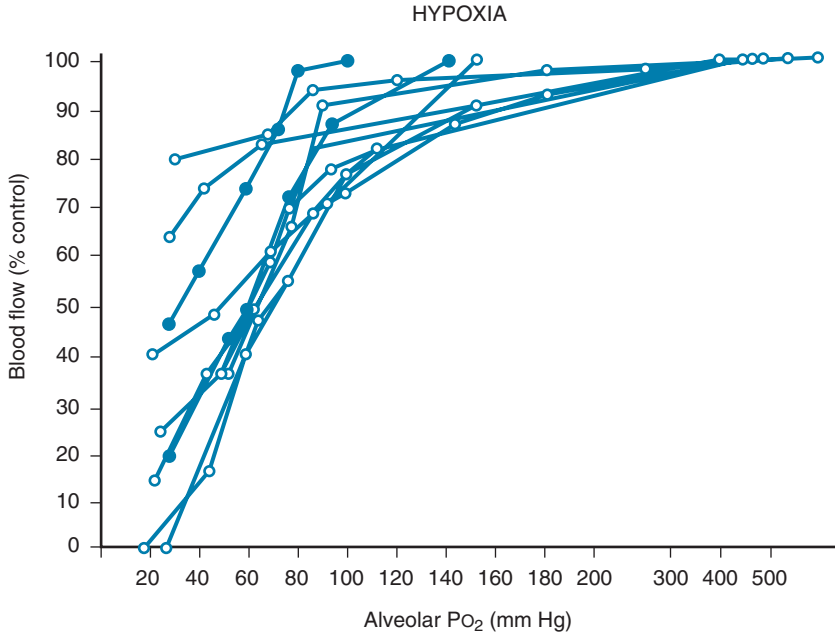

FIGURE 4-12 ■ Stimulus-response curves of hypoxic pulmonary vasoconstriction. The abscissa shows alveolar P_{O_2}. Data are derived from feline lung preparation. (Redrawn from Barer GR, Howard P, Shaw JW: Stimulus-response curves for the pulmonary vascular bed to hypoxia and hypercapnia. J Physiol [Lond] 211:139–155, 1970.)

synthesis augment hypoxic pulmonary vasoconstriction in animal preparations, and inhaled NO reduces hypoxic pulmonary vasoconstriction in humans.[57] The required inhaled concentration of NO is extremely low (about 20 parts per million), and the gas is very toxic at high concentrations.

Pulmonary vascular endothelial cells also release potent vasoconstrictor peptides, known as endothelins.[58] Their role in normal physiology and disease is still being evaluated.

Hypoxic pulmonary vasoconstriction has the effect of directing blood flow away from hypoxic regions of lung. Other things being equal, this reduces the amount of ventilation-perfusion inequality in a diseased lung and limits the depression of the arterial P_{O_2}. An example of this is seen in patients with asthma who are treated with certain bronchodilators. These sometimes cause a reduction in arterial P_{O_2} as a result of an increase in blood flow to poorly ventilated areas.[59,60] Whether this can be explained by the reversal of hypoxic pulmonary vasoconstriction is uncertain, but it seems a possible mechanism in some cases. In patients with severe chronic obstructive pulmonary disease, an elevated pulmonary artery pressure is frequently seen, and often this is exacerbated by a recent bronchial infection. Prolonged nocturnal treatment with oxygen has been shown to reduce the degree of pulmonary hypertension and to improve the prognosis in these patients. The mechanism of improvement is presumably a gradual inhibition by hyperoxia of increased smooth muscle tone originally caused by the hypoxia.

Residence at high altitude results in hypoxic pulmonary vasoconstriction, both in newcomers and in permanent residents. The increase in pulmonary artery pressure is especially marked during exercise. If 100% oxygen is given to normal subjects after they have been exposed to hypoxia for as little as 2 weeks, the pulmonary artery pressure does not immediately return to the normal level.[61] This suggests that some structural change in the pulmonary vessels has already occurred. There is considerable variation in the response of pulmonary artery pressure to alveolar hypoxia, leading some investigators to divide people into "responders" and "nonresponders."

The most important situation in which hypoxic pulmonary vasoconstriction occurs is in the perinatal period. During fetal life, pulmonary vascular resistance is very high, partly because of hypoxic vasoconstriction, and only some 15% of the cardiac output flows through the lungs. The rest bypasses the lungs via the ductus arteriosus. The vasoconstriction is particularly effective because of the abundance of smooth muscle in the pulmonary arteries. At birth, when the first few breaths oxygenate the alveoli, the vascular resistance falls dramatically because of relaxation of vascular smooth muscle, and pulmonary blood flow increases enormously. In this situation, the release of hypoxic vasoconstriction is critical in the transition from placental to air breathing, and it is this situation that is presumably responsible for the evolutionary pressure to maintain the phenomenon, which seems to be weak and variable in adult life.

Other Physiologic Substances

Many peptides and other substances can potentially alter the tone of muscular pulmonary blood vessels, although the roles of these substances under physiologic conditions are still being clarified.[62] They include angiotensin II, bradykinin, vasopressin, atrial natriuretic peptide, endothelin, somatostatin, products of both the cyclooxygenase and lipoxygenase arms of the arachidonic acid cascade, and calcitonin gene–related peptide. Some substances show species differences, and some evoke either vasoconstriction or vasodilation, depending on their concentration. Biogenic amines such as acetylcholine, histamine, serotonin, and norepinephrine also affect pulmonary vascular smooth muscle. Additional information about the pharmacology of the pulmonary blood vessels is provided in Chapter 8.

Damage to Pulmonary Capillaries by High Wall Stresses

It has become clear that the blood-gas barrier has a basic dilemma. On the one hand, the barrier has to be extremely thin to allow efficient gas exchange by passive diffusion (see Chapter 1). On the other hand, the blood-gas barrier must be immensely strong because of the large mechanical stresses that develop in the capillary wall when the pressure in the capillaries rises, or when the wall is stretched by inflating the lung to high volumes. There is evidence that the blood-gas barrier is just strong enough to withstand the highest stresses to which it is normally subjected. Unusually high capillary pressures or lung volumes result in ultrastructural damage or "stress failure" of the capillary wall, leading to a high-permeability type of pulmonary edema, or even pulmonary hemorrhage.

When the capillary transmural pressure is raised in animal preparations, disruption of the capillary endothelium, alveolar epithelium, or sometimes all layers of the capillary wall is seen. In the rabbit lung, the first changes occur at a transmural pressure of about 24 mm Hg, and the frequency of breaks increases as the pressure is raised.[63] Although at first sight these capillary pressures seem to be very high, there is now good evidence that the capillary pressure rises to the mid-30s (mm Hg) in the normal lung during heavy exercise.[64] This is largely secondary to the increase in left ventricular filling pressure, which has not been appreciated until recently.[65]

It can be shown that, at these increased capillary transmural pressures, the "hoop" or circumferential stresses in the capillary wall become extremely high. Indeed, they approach the breaking stress of collagen. The main reason for the very high stresses is the extreme thinness of the wall, which, in the human lung, is less than 0.3 μm in some places. It is now believed that the strength of the blood-gas barrier on the thin side comes from type IV collagen in the basement membranes.

Stress failure is the mechanism of several clinical conditions characterized by high-permeability pulmonary edema or hemorrhage.[66] Neurogenic pulmonary edema

has been shown to be associated with very high capillary pressures, the edema is of the high-permeability type, and ultrastructural damage to the capillaries has been demonstrated, consistent with stress failure. High-altitude pulmonary edema is apparently caused by uneven hypoxic pulmonary vasoconstriction (referred to earlier), which allows some of the capillaries to be exposed to high pressure.[67] Again, the edema is of the high-permeability type, and typical ultrastructural changes in the capillaries have been demonstrated in animal preparations.[68]

A particularly interesting condition is bleeding into the lungs in galloping racehorses. This is very common and is caused by the extremely high pulmonary capillary pressures, which approach 100 mm Hg. Direct evidence of stress failure of pulmonary capillaries has been shown in these animals.[69] In fact, it is probable that elite human athletes develop some ultrastructural changes in their blood-gas barrier during extreme exercise because significantly higher concentrations of red blood cells, total protein, and leukotriene B_4 are seen in their bronchoalveolar lavage fluid than in sedentary controls.[70] This only occurs at extremely high levels of exercise.[71] A similar group of athletes who exercised at submaximal levels for 1 hour showed no changes in the bronchoalveolar lavage fluid.[72]

Overinflation of the lung is known to increase the permeability of pulmonary capillaries, and stress failure is apparently the mechanism because it has been shown that, for the same capillary transmural pressure, the frequency of capillary wall damage is greatly increased at high lung volumes.[73] This is because some of the increased tension in the alveolar wall associated with lung inflation is transmitted to the capillary wall. This may be important in ventilator-induced pulmonary injury. Finally, conditions in which the basement membrane of the capillary wall is damaged are associated with alveolar bleeding because type IV collagen of the basement membranes is responsible for most of the strength of the capillaries. The best example is Goodpasture's syndrome.

Metabolic Functions of the Pulmonary Circulation

Although the primary purpose of the pulmonary circulation is to provide the lung with mixed venous blood so that oxygen can be added and carbon dioxide removed, the pulmonary circulation has other functions, particularly metabolism.

A number of vasoactive substances are metabolized by the lung.[74] Because it is the only organ whose microcirculation receives the whole cardiac output, the lung is uniquely suited to modifying blood-borne substances. Indeed, a substantial fraction of all the vascular endothelial cells in the body is located in the lung.

The only known example of biologic activation by passage through the pulmonary circulation is the conversion of the relatively inactive polypeptide angiotensin I to the potent vasoconstrictor angiotensin II.[75] The latter is up to 50 times more active than its precursor but is unaffected by passage through the lung. The conversion of angiotensin I is catalyzed by an enzyme, angiotensin I–converting enzyme, which is located in small pits (*caveolae intracellulares*) in the surface of the capillary endothelial cells.

A number of vasoactive substances are completely or partially inactivated during passage through the lung. Bradykinin is largely inactivated (up to 80%), and the enzyme responsible is angiotensin I–converting enzyme. The lung is the major site of inactivation of serotonin (5-hydroxytryptamine), not by enzymatic degradation, but by an uptake and storage process. Some of the serotonin may be transferred to platelets in the lung or stored in some other way and released during anaphylaxis. The prostaglandins E_1, E_2, and $F_{2\alpha}$ are also inactivated in the lung, which is a rich source of responsible enzymes. Norepinephrine is also taken up by the lung to some extent (up to 30%). Histamine appears not to be affected by the intact lung.[74]

Some vasoactive materials pass through the lung without significant gain or loss of activity. These include epinephrine, prostaglandins A_1 and A_2, angiotensin II, and vasopressin (also called antidiuretic hormone). Additional information on pulmonary vascular pharmacology can be found in Chapter 8.

Several vasoactive substances are normally synthesized or stored within the lung but may be released into the circulation in pathologic conditions. For example, in anaphylaxis, or during an asthma attack, histamine, bradykinin, prostaglandins, and "slow-reacting substance" are discharged into the circulation. Other conditions in which the lung may release potent chemicals include pulmonary embolism (see Chapter 51) and alveolar hypoxia.

There is also evidence that the lung plays a role in the clotting mechanism of blood under normal and abnormal conditions. For example, in the interstitium, there are large numbers of mast cells containing heparin. In addition, the lung is able to secrete special immunoglobulins, particularly immunoglobulin A, in bronchial mucus, which contribute to its defenses against infection. The synthesis of phospholipids such as dipalmitoylphosphatidylcholine, a component of pulmonary surfactant (see Chapter 9), is an important function of alveolar type II cells that prevents lung collapse. Surfactant turnover is rapid, and if the blood flow to a region of lung is obstructed (e.g., by an embolus), surfactant may become locally depleted with consequent atelectasis. Protein synthesis is also significant because collagen and elastin form the structural framework of the lung. Under abnormal conditions, proteases are apparently liberated from leukocytes or macrophages in the lung, causing breakdown of proteins and, possibly, emphysema (see Chapter 39). Another important activity is carbohydrate metabolism, especially the elaboration of the mucins and proteoglycans of bronchial mucus (see Chapter 11).

In addition to its metabolic functions, the lung has other functions apart from its primary gas-exchanging role. One is to act as a reservoir for blood. As stated previously, the lung has a remarkable ability to reduce

its pulmonary vascular resistance through the mechanisms of recruitment and distention as vascular pressures are raised. The same mechanisms allow the lung to increase its blood volume with relatively small rises in pulmonary arterial or venous pressures. This occurs, for example, when a subject lies down after standing. Blood then drains from the legs into the lung. The weightlessness that occurs when astronauts enter orbit also results in an increased pulmonary blood volume.

Another function of the lung is to filter blood. Small intravascular thrombi are removed from the circulation before they can reach the brain or other vital organs. There is also evidence that many white blood cells are sequestered by the lung, although the significance of this is not clear.

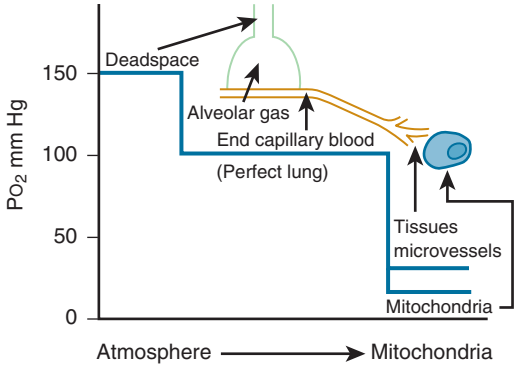

FIGURE 4-13 ■ Scheme of the oxygen partial pressures from air to tissues. This shows a hypothetically perfect situation. (Redrawn from West JB: Ventilation/Blood Flow and Gas Exchange [5th ed]. Oxford: Blackwell Scientific, 1990.)

GAS EXCHANGE

As we have seen, the primary function of the lungs is gas exchange, that is, to allow oxygen to move from the air into the blood, and to allow carbon dioxide to move out. It is now established that movement of gas across the blood-gas interface is by simple passive diffusion; the gases travel from an area of high to an area of low partial pressure. We have also seen that the structure of the lung is well suited to this mechanism of gas exchange. The blood-gas barrier is extremely thin (only 0.3 µm over much of its extent), and its area is between 50 and 100 m^2. Because Fick's law of diffusion states that the amount of gas that moves across a tissue sheet is proportional to the area but inversely proportional to the thickness, the blood-gas barrier is ideal for its gas-exchanging function.

An important concept in any discussion of gas exchange is partial pressure. The partial pressure of a gas is found by multiplying its concentration by the total pressure. For example, dry air has 20.9% oxygen. The P_{O_2} in dry air at sea level, where the barometric pressure is 760 mm Hg, is therefore (20.9/100) × 760 = 159 mm Hg. When air is inhaled into the upper airways, it is warmed and saturated with water vapor. The water vapor pressure at 37° C is 47 mm Hg. Under these conditions, the total dry gas pressure is only 760 − 47 = 713 mm Hg. The P_{O_2} of moist inspired air is therefore (20.9/100) × 713 = 149 mm Hg. In general, the relationship between the partial pressure (P) and fractional concentration (F) of a gas when water vapor is present is given by $P_X = F_X (P_B - P_{H_2O})$, where P_B stands for barometric pressure and X refers to the species of gas.

Figure 4-13 shows an overview of the oxygen cascade from the air that we breathe to the tissues where it is utilized. The solid line marked "perfect" represents an ideal situation that does not actually exist but does make a useful backdrop for purposes of discussion. One of the first surprises is that, by the time the oxygen has reached the alveoli, its partial pressure has fallen from about 150 to about 100 mm Hg. The reason for this apparent extravagance is that the P_{O_2} in the alveolar gas is determined by a balance between two factors. On the one hand, we have the essentially continuous addition of oxygen by the process of alveolar ventilation, and on the other the continuous removal of oxygen by the pulmonary blood flow. The net result is that the alveolar P_{O_2} settles out at about 100 mm Hg.

It might be argued that the process of ventilation is intermittent with each breath and not continuous. By the same token, pulmonary capillary blood flow is known to be pulsatile. However, the volume of gas in the lung at functional residual capacity is sufficiently large to damp out these oscillations, with the result that the alveolar P_{O_2} varies by only about 3 or 4 mm Hg with each breath, and less with each heartbeat. Thus, alveolar ventilation and capillary blood flow can be regarded as continuous processes from the point of view of gas exchange.

In an ideal lung (see Fig. 4-13), the effluent pulmonary venous blood (which becomes the systemic arterial blood) would have the same P_{O_2} as that of the alveolar gas, namely, about 100 mm Hg. This is very nearly the case in the normal lung. However, when the arterial blood reaches the peripheral tissues, a substantial fall in P_{O_2} occurs en route to the mitochondria. The movement of oxygen in the peripheral tissues is essentially by passive diffusion, and the mitochondrial P_{O_2} is certainly considerably lower than that in arterial or mixed venous blood. Indeed, the P_{O_2} in the mitochondria may vary considerably throughout the body, depending on the type of tissue and its oxygen uptake. Nevertheless, it is useful to bear in mind that the mitochondria are the targets for the oxygen transport system and that any fall in the arterial P_{O_2} caused, for example, by inefficient pulmonary gas exchange must be reflected in a reduced tissue P_{O_2}, other factors being equal.

For carbon dioxide, the process is reversed. There is essentially no carbon dioxide in the inspired air, and the alveolar P_{CO_2} is about 40 mm Hg. Under normal conditions, arterial and alveolar P_{CO_2} values are the same, whereas the P_{CO_2} of mixed venous blood is in the range of 45 to 47 mm Hg. The P_{CO_2} of the tissues is probably quite variable, depending, for example, on the state of metabolism. Nevertheless, any inefficiency of the lung for carbon dioxide removal tends to raise the P_{CO_2} of the tissues, other factors being equal.

Causes of Hypoxemia

Hypoxemia refers to a reduction in arterial P_{O_2} to below normal values. There are four major processes that can impair pulmonary gas exchange and cause hypoxemia when breathing room air at sea level: hypoventilation, diffusion limitation, shunt, and ventilation-perfusion inequality. These are now discussed in turn.

Hypoventilation

Hypoventilation is used here to refer to conditions in which alveolar ventilation is abnormally low in relation to oxygen uptake or carbon dioxide output. Alveolar ventilation is the volume of fresh inspired gas going to the alveoli (i.e., non–dead space ventilation), as mentioned earlier. As we shall see, hypoventilation always causes arterial hypoxemia (unless the patient is breathing an enriched oxygen mixture) and a raised arterial P_{CO_2}. It should be noted that other conditions (e.g., ventilation-perfusion inequality) can also result in carbon dioxide retention, and some physicians use the terms *hypoventilation* and *carbon dioxide retention* interchangeably. This confusing practice is not followed here.

We saw in the last section that the P_{O_2} of alveolar gas is determined by a balance between the rate of addition of oxygen by alveolar ventilation and the rate of removal by the pulmonary blood flow to satisfy the oxygen demands of the tissues. Hypoventilation occurs when the alveolar ventilation is reduced and the alveolar P_{O_2} therefore settles out at a lower level than normal. For the same reason, the alveolar P_{CO_2}, and therefore arterial P_{CO_2}, are also raised.

Causes of hypoventilation include depression of the respiratory center by drugs, such as morphine derivatives and barbiturates; diseases of the brain stem, such as encephalitis; abnormalities of the spinal cord conducting pathways, such as high cervical dislocation; anterior horn cell diseases, including poliomyelitis, affecting the phrenic nerves or supplying the intercostal muscles; diseases of nerves to respiratory muscles (e.g., Guillain-Barré syndrome); diseases of the myoneural junction, such as myasthenia gravis; diseases of the respiratory muscles themselves, such as progressive muscular dystrophy; thoracic cage abnormalities (e.g., crushed chest); upper airway obstruction (e.g., thymoma); hypoventilation associated with extreme obesity (pickwickian syndrome); and other miscellaneous causes, such as metabolic alkalosis and idiopathic states. For discussion of hypoventilation, see Chapter 78.

Note that, in all these conditions, the lungs are normal. Thus, this group can be clearly distinguished from those diseases in which the carbon dioxide retention is associated with chronic lung disease. In the latter conditions, the lungs are abnormal, and a major factor in the raised P_{CO_2} is the ventilation-perfusion inequality that causes gross inefficiency of pulmonary gas exchange.

The rise in alveolar P_{CO_2} as a result of hypoventilation can be calculated using the *alveolar ventilation equation* (see earlier section on "Alveolar Ventilation" for derivation):

$$\dot{V}_A = \frac{\dot{V}_{CO_2}}{P_{A_{CO_2}}} \times K \tag{6}$$

where K is a constant. This can be rearranged as follows:

$$P_{A_{CO_2}} = \frac{\dot{V}_{CO_2}}{\dot{V}_A} \times K \tag{11}$$

Because in normal lungs the alveolar ($P_{A_{CO_2}}$) and arterial (Pa_{CO_2}) P_{CO_2} are almost identical, we can write:

$$Pa_{CO_2} = \frac{\dot{V}_{CO_2}}{\dot{V}_A} \times K \tag{12}$$

This very important equation indicates that the level of P_{CO_2} in alveolar gas or arterial blood is inversely related to the alveolar ventilation. For example, if the alveolar ventilation is halved, the P_{CO_2} doubles. Note, however, that this is true only after a steady state has been reestablished and the carbon dioxide production rate is the same as before. In practice, if the alveolar ventilation of a patient is suddenly decreased (e.g., by changing the setting on a ventilator), the P_{CO_2} rises over a period of 10 to 20 minutes. The rise is rapid at first and then is more gradual as the body stores of CO_2 are gradually filled.[76]

The same principles as used for carbon dioxide can be applied to oxygen to understand the effect of hypoventilation on alveolar (and thus arterial) P_{O_2}. The corresponding mass conservation equation for oxygen is as follows:

$$\dot{V}_{O_2} = \dot{V}_I \times F_{I_{O_2}} - \dot{V}_A \times F_{A_{O_2}} \tag{13}$$

Here, $\dot{V}_I$ is inspired *alveolar* ventilation (sometimes written as $\dot{V}_{IA}$), while $\dot{V}_A$ is expired alveolar ventilation. Equation 13 expresses oxygen uptake as the difference between the amount of oxygen inhaled per minute (volume of inspired gas $[\dot{V}_I] \times$ fractional concentration of oxygen $[F_{I_{O_2}}]$) and that exhaled per minute (volume of alveolar ventilation $[\dot{V}_A] \times$ fractional concentration of oxygen in alveolar gas $[F_{A_{O_2}}]$). Normally, because a little more oxygen is taken up per minute than is carbon dioxide exhaled, $\dot{V}_I$ exceeds $\dot{V}_A$. However, this difference is usually no more than 1% of the ventilation, and clinically it can most often be ignored. If this is done, $\dot{V}_I$ may then be replaced by $\dot{V}_A$, and Equation 13 simplifies to

$$\dot{V}_{O_2} = \dot{V}_A \times (F_{I_{O_2}} - F_{A_{O_2}}) \; or$$
$$\dot{V}_{O_2} = \dot{V}_A \times \frac{(P_{I_{O_2}} - P_{A_{O_2}})}{K} \tag{14}$$

where $P_{I_{O_2}}$ is the partial pressure of oxygen in the inspired gas. Thus, as ventilation falls, $P_{A_{O_2}}$ must fall as well to maintain the rate of O_2 uptake necessary for metabolic function. Equations 11 (reexpressed as $\dot{V}_{CO_2} = \dot{V}_A \times P_{A_{CO_2}}/K$) and 14 can be usefully combined. If Equation 11 is divided by Equation 14, we get

$$\frac{\dot{V}_{CO_2}}{\dot{V}_{O_2}} = R = \frac{P_{A_{CO_2}}}{(P_{I_{O_2}} - P_{A_{O_2}})} \tag{15}$$

Here, R is the respiratory exchange ratio (volume of carbon dioxide exhaled/oxygen taken up in the same time). Both K and $\dot{V}_A$ cancel out when the division is performed. Rearranging this equation yields

$$P_{A_{O_2}} = P_{I_{O_2}} - \frac{P_{A_{CO_2}}}{R} \quad (16)$$

This is called the alveolar gas equation, and it uniquely relates alveolar P_{O_2} to P_{CO_2} for given values of inspired P_{O_2} and R. It is the basis of calculations of the alveolar-to-arterial P_{O_2} difference, a commonly used index of inefficiency of pulmonary gas exchange. Because we assumed that $\dot{V}_I = \dot{V}_A$ in deriving this equation, it is an approximation. It is possible to rigorously account for the difference between $\dot{V}_I$ and $\dot{V}_A$, and when this is done, the alveolar gas equation contains an additional term:

$$P_{A_{O_2}} = P_{I_{O_2}} - \frac{P_{A_{CO_2}}}{R} + \left[P_{A_{CO_2}} \times F_{I_{O_2}} \times \frac{(1-R)}{R} \right] \quad (17)$$

The term in brackets is the correction factor for the difference between inspired and expired volumes. It is generally small during air breathing (1 to 3 mm Hg) and can be ignored in most clinical settings.

As an example of the use of this equation, suppose that a patient with normal lungs takes an overdose of a barbiturate drug that depresses alveolar ventilation. The patient's alveolar P_{CO_2} might rise from 40 to 60 mm Hg (the actual value is determined by the alveolar ventilation equation). If the patient's respiratory exchange ratio is 1, the small correction factor disappears, and the alveolar P_{O_2} is given by

$$\begin{aligned} P_{A_{O_2}} &= P_{I_{O_2}} - \frac{P_{A_{CO_2}}}{R} \\ &= 149 - 60 \\ &= 89 \text{ mm Hg} \end{aligned}$$

Note that the alveolar P_{O_2} falls by 20 mm Hg; this is the same amount by which the P_{CO_2} rises. On the other hand, if R = 0.8, which is a more typical resting value, and we ignore the small correction factor in Equation 17, then

$$\begin{aligned} P_{A_{O_2}} &= 149 - 60/0.8 \\ &= 74 \text{ mm Hg} \end{aligned}$$

Note that in this case the P_{O_2} falls more than the P_{CO_2} rises.

Both examples emphasize that, in practical terms, the hypoxemia is generally of minor importance compared with the carbon dioxide retention and consequent respiratory acidosis. This is further illustrated in Figure 4-14, which shows calculated changes in gas exchange as a result of hypoventilation. Note that severe hypoventilation sufficient to double the P_{CO_2} from 40 to 80 mm Hg decreases the alveolar P_{O_2} from only, say, 100 to 50 or 60 mm Hg. Although the arterial P_{O_2} is likely to be a few millimeters of mercury lower than the alveolar value, the arterial oxygen saturation is approximately 80%. However, there is substantial respiratory acidosis with an arterial pH of about 7.2. This fact emphasizes again that the hypoxemia is usually not as important as the carbon dioxide retention and respiratory acidosis in pure hypoventilation.

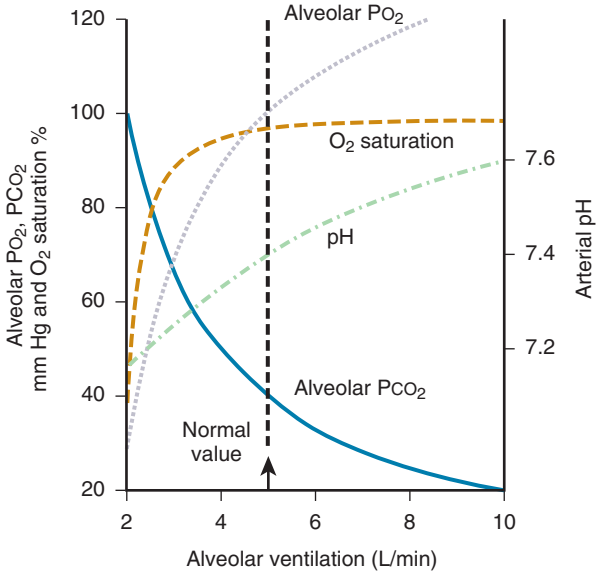

FIGURE 4-14 ■ Gas exchange during hypoventilation. Note the relatively large rise in P_{CO_2} and consequent fall in pH compared with the modest fall in arterial oxygen saturation. (Redrawn from West JB: Pulmonary Pathophysiology—The Essentials [7th ed]. Baltimore, Lippincott Williams & Wilkins, 2007.)

A feature of alveolar hypoventilation is that, although the arterial P_{CO_2} is always raised, the arterial P_{O_2} may be returned to normal very easily by giving supplementary oxygen. Suppose that the patient with barbiturate intoxication just discussed is given 30% oxygen to breathe. If we assume that the ventilation remains unchanged, it can be shown (from Equation 17) that the alveolar P_{O_2} rises from 74 to about 139 mm Hg. Thus, a relatively small increase in inspired P_{O_2} is very effective in eliminating the arterial hypoxemia of hypoventilation.

Diffusion Limitation

It is now generally believed that oxygen, carbon dioxide, and indeed all gases cross the blood-gas barrier by simple passive diffusion. Fick's law of diffusion states that the rate of transfer of a gas through a sheet of tissue is proportional to the tissue area (A) and the difference in partial pressure ($P_1 - P_2$) between the two sides, and is inversely proportional to the thickness (T):

$$\dot{V}gas = \frac{A}{T} \times D \times (P_1 - P_2) \quad (18)$$

As we have seen already, the area of the blood-gas barrier in the lung is enormous (50 to 100 m^2), and the thickness is less than 0.3 μm in some places, so the dimensions of the barrier are ideal for diffusion.

The rate of diffusion is also proportional to a constant, D, which depends on the properties of the tissue and the particular gas. The constant is proportional to the solubility (Sol) of the gas, and inversely proportional to the square root of the molecular weight (MW):

$$D \propto \frac{Sol}{\sqrt{MW}} \quad (19)$$

This means that, per mm Hg difference between capillary and alveolar partial pressures, carbon dioxide diffuses about 20 times more rapidly than oxygen through tissue sheets, because carbon dioxide has a much higher solubility (24:1 at 37° C), but the square roots of the molecular weights are not very different (1.17:1). Note that this calculation applies only to tissue sheets and not to the uptake of oxygen or output of carbon dioxide by the lung, wherein chemical reaction rates also play a role (see later discussion).

Oxygen Uptake along the Pulmonary Capillary

Figure 4-15 shows calculated changes in the P_{O_2} of the blood along the pulmonary capillary as oxygen is taken up under normal conditions. The calculation is based on Fick's law of diffusion (see Equation 18). One of the several assumptions is that the diffusion characteristics of the blood-gas barrier are uniform along the length of the capillary. The calculation is complicated by the fact that the change in the P_{O_2} of the capillary blood depends on the oxygen dissociation curve. This is not only nonlinear but is also influenced by the simultaneous elimination of carbon dioxide. The calculation is often known as the Bohr integration because it was first carried out in a simplified form by Christian Bohr.[77] Modern computations take into account reaction times of oxygen with hemoglobin and also reaction rates associated with carbon dioxide elimination (see later discussion). Such complicated calculations have only become feasible with the advent of the digital computer.[78]

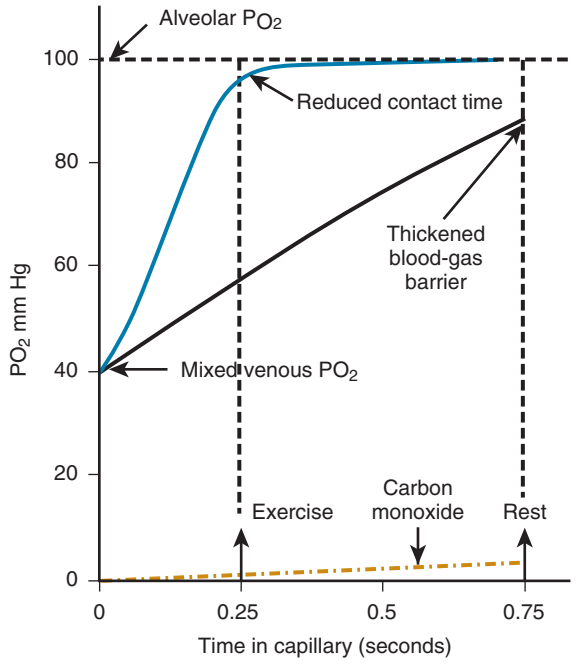

FIGURE 4-15 ■ Typical time courses for the change in P_{O_2} in the pulmonary capillary when diffusion is normal, when the contact time is reduced, and when the blood-gas barrier is abnormally thick. The time course for carbon monoxide uptake is also shown. (Redrawn from West JB: Pulmonary Pathophysiology—The Essentials [7th ed]. Baltimore: Lippincott Williams & Wilkins, 2007.)

Figure 4-15 shows that the time spent by the blood in the pulmonary capillary under normal resting conditions is about 0.75 second. This number is obtained by dividing the volume of blood in the pulmonary capillaries (about 75 mL) by the cardiac output (about 6 L/min).[79] The figure shows that the P_{O_2} of pulmonary capillary blood very nearly reaches that of alveolar gas after approximately a third of the available time in the capillary. This means that there is normally ample time for essentially complete oxygenation of the blood or, as it is sometimes said, the normal lung has substantial diffusion "reserves."

If the blood-gas barrier is thickened, the rate of transfer of oxygen across the barrier is reduced in accordance with Fick's law, and the rate of rise of P_{O_2} is slower, as shown in Figure 4-15. Under these circumstances, a P_{O_2} difference between alveolar gas and end-capillary blood may develop. This means that there is some diffusion limitation of oxygen transfer. It is important to appreciate that under most conditions oxygen transfer is perfusion limited, and only under unusual conditions such as severe interstitial lung disease is there some diffusion limitation.

It can be shown[80] that whether gas transfer is perfusion or diffusion limited depends on the ratio of D, the diffusive conductance of the blood-gas barrier, to the product of the slope of the oxygen-hemoglobin dissociation curve (commonly referred to as beta [β]) and the total pulmonary blood flow rate $(\dot{Q})$: $D/(\dot{Q}\beta)$.

It is clear that, for a gas such as oxygen, the slope of the blood dissociation curve is not a constant but depends on the P_{O_2} and also to a lesser extent on factors that shift the dissociation curve, such as pH, P_{CO_2}, temperature, and red cell 2,3-diphosphoglycerate concentration. Under hypoxic conditions, when the lung is operating on the lower, straighter part of the oxygen dissociation curve, the slope is sometimes assumed to be linear to simplify the analysis. Figure 4-16 shows the extent to which perfusion and diffusion limit the transfer of gas under various conditions.[80] Although the figure is based on a number of simplifying assumptions, it is conceptually valuable.

Note that the physiologically inert gases nitrogen and sulfur hexafluoride (*right-hand end of* Fig. 4-16) are completely perfusion limited in their transfer. (*Physiologically inert* means that, being carried in blood only in physical solution, their blood concentration is directly proportional to partial pressure; that is, they obey Henry's law of solubility.) The same perfusion limitation applies to oxygen in hyperoxia because, high on the dissociation curve, the value of β is very low so that $(D/\dot{Q}\beta)$ is very high and diffusion limitation is not seen. However, oxygen transfer under conditions of hypoxia can be partly diffusion limited because the lung is working low on the dissociation curve, where the slope (β) is much higher than normal. This is particularly the case for oxygen transfer during hypoxic exercise. Indeed,

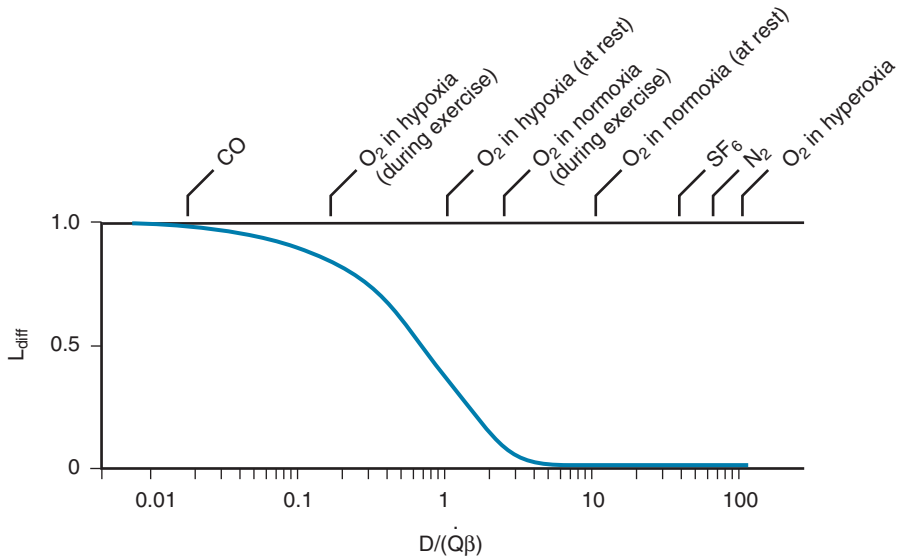

FIGURE 4-16 ■ Diffusion-limited transfer of various gases in the lung. Diffusion limitation (L_{diff}) is on a scale of 0 (no limitation) to 1 (complete limitation). See text for details. (Redrawn from Scheid P, Piiper J: Diffusion. *In* Crystal RG, West JB, Barnes PJ, Weibel ER [eds]: The Lung: Scientific Foundations [2nd ed]. New York: Raven Press, 1997.)

the most marked diffusion limitation that ever occurs in the normal lung is during maximal exercise at extreme high altitude in well-acclimatized subjects.[81,82] On the summit of Mount Everest, there is apparently diffusion limitation even at rest.

Figure 4-16 also shows that the transfer of carbon monoxide by the lung is markedly diffusion limited. This follows from the very steep slope of the dissociation curve of carbon monoxide with blood (that is, β is very large). Another way of looking at this is to say that the avidity of hemoglobin for carbon monoxide is so high that the partial pressure in the blood hardly rises along the pulmonary capillary (see Fig. 4-15). Under these conditions, it is intuitively clear that the amount of carbon monoxide that is taken up depends almost entirely on the diffusion properties of the blood-gas barrier.

Reaction Rates with Hemoglobin

When oxygen (or carbon monoxide) is added to blood, its combination with hemoglobin is quite fast, being close to completion in 0.2 second. Such reaction rates can be measured using special equipment in which reduced hemoglobin and dissolved oxygen are rapidly mixed and the rate of formation of oxyhemoglobin is measured photometrically. Although oxygenation occurs rapidly within the pulmonary capillary, even this rapid reaction significantly delays the loading of oxygen by the red cell.

The transfer of oxygen from the alveolar gas to its combination with hemoglobin in the red cell can therefore be regarded as occurring in two stages: (1) diffusion of oxygen through the blood-gas barrier, including the plasma and red cell interior; and (2) reaction of the oxygen with hemoglobin (Fig. 4-17A). Although at first sight these two processes are very different, it is possible to treat them mathematically in a similar way and to regard each as contributing its own "resistance" to the transfer of oxygen. Such an analysis was carried out by Roughton and Forster,[83] who showed that the following relationship exists:

$$\frac{1}{D_L} = \frac{1}{D_M} + \frac{1}{(\theta \times V_C)} \qquad (20)$$

where D_L refers to the diffusing capacity of the lung, D_M is the diffusing capacity of the membrane (which includes the plasma and red cell interior), θ is the rate of reaction of oxygen (or carbon monoxide) with hemoglobin (expressed per milliliter of blood), and V_C is the volume of blood in the pulmonary capillaries.

In the normal lung, the resistances offered by the membrane and blood reaction components are approximately equal. This means that, if the capillary blood volume is reduced by disease, the measured diffusing capacity of the lung is lowered. In fact, the equation can be used to separate the two components. To do this, the diffusing capacity is measured at both high and normal alveolar P_{O_2} values. Increasing the alveolar P_{O_2} reduces the value of θ for carbon monoxide because the carbon monoxide has to compete with a high pressure of oxygen for the hemoglobin. If the resulting measurements of $1/D_L$ are plotted against 1/θ, as shown in Figure 4-17B, the slope of the line is $1/V_C$, whereas the intercept on the vertical axis is $1/D_M$.

Diffusing Capacity

Carbon monoxide is usually the gas of choice for measuring the diffusion properties of the lung because, as Figure 4-16 shows, its transfer is almost entirely diffusion limited. It is true that part of the limitation has to do with the rate of reaction of carbon monoxide with hemoglobin (see Fig. 4-17A), but this is conveniently included in the measurement of diffusion properties. Although it

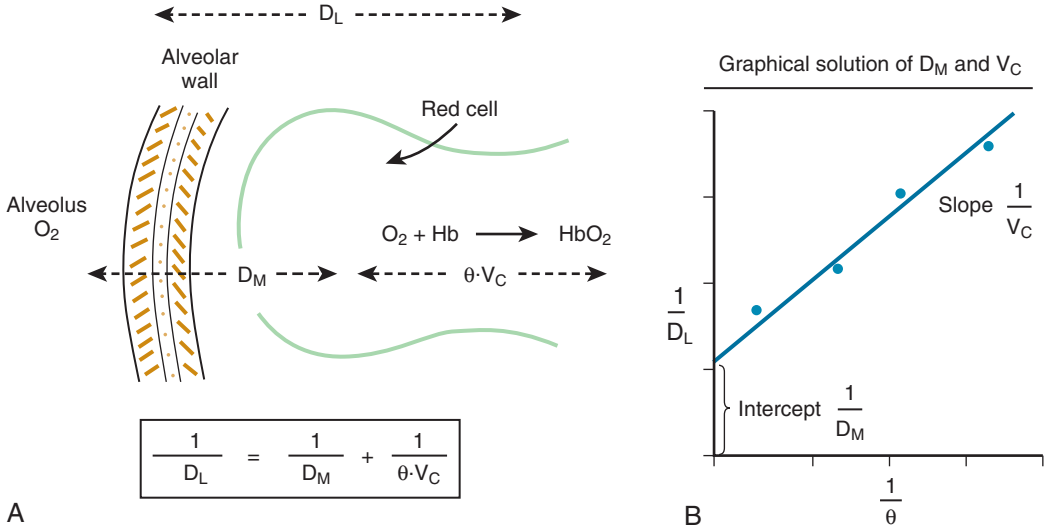

FIGURE 4-17 ■ **A,** The two components of the measured diffusing capacity (D_L) of the lung: that due to the diffusion process itself (D_M) and that attributable to the time taken for oxygen (or carbon monoxide) to react with hemoglobin (Hb) ($\theta \cdot V_C$). **B,** $1/D_L$ plotted against $1/\theta$ can be used to derive D_M and V_C.

could be argued that we are really more interested in oxygen and the effects of any diffusion limitation on this gas, oxygen uptake is typically perfusion limited under normoxic conditions (see Fig. 4-16) and partly perfusion and diffusion limited under hypoxic conditions. For this reason, measurements using oxygen are often difficult to interpret, although techniques utilizing isotopes of oxygen have been proposed.[80] However, for the measurement of diffusion properties in the pulmonary function laboratory, carbon monoxide is the best gas.

As indicated earlier, Fick's law states that the amount of gas transferred across a tissue sheet is proportional to the area, a diffusion constant, and the difference in partial pressure, and is inversely proportional to the thickness:

$$\dot{V}gas = \frac{A}{T} \times D \times (P_1 - P_2) \qquad (18)$$

The actual lung is so complex that it is not possible to determine the area and the thickness of the blood-gas barrier during life. Instead, the equation is written to combine the factors A, T, and D into one constant, D_L, as follows:

$$\dot{V}gas = D_L \times (P_1 - P_2) \qquad (21)$$

where D_L is called the diffusing capacity of the lung, and consequently includes the area, thickness, and diffusion properties of the tissue sheet, as well as the properties of the diffusing gas. Thus, the diffusing capacity for carbon monoxide is given by:

$$D_L = \frac{\dot{V}_{CO}}{(P_1 - P_2)} \qquad (22)$$

where P_1 and P_2 are the partial pressures of carbon monoxide in alveolar gas and capillary blood, respectively. Because the partial pressure of carbon monoxide in capillary blood is so small (see Fig. 4-15), it can generally be neglected. In this case, the equation becomes:

$$D_L = \frac{\dot{V}_{CO}}{P_{A_{CO}}} \qquad (23)$$

or, in words, the diffusing capacity of the lung for carbon monoxide is the volume of carbon monoxide transferred in milliliters per minute per millimeter of mercury of alveolar partial pressure of CO.

Some people, for example, cigarette smokers, have sufficient carboxyhemoglobin in their blood that the partial pressure of carbon monoxide in the pulmonary capillaries cannot be neglected. In this case, an estimate of the partial pressure of carbon monoxide in pulmonary capillary blood can be made using a rebreathing technique, and Equation 22 is then used to determine diffusing capacity.

Measurement. Several techniques are available for measuring the diffusing capacity of the lung for carbon monoxide. In the *single-breath method,* a single inspiration of a dilute mixture (about 0.3%) of carbon monoxide is made, and the rate of disappearance of carbon monoxide from the alveolar gas during a 10-second breath-hold is calculated. This is usually done by measuring the inspired and expired concentrations of carbon monoxide with an infrared analyzer. Alternatively, a respiratory mass spectrometer can be used if ^{18}O-labeled carbon monoxide is employed. At the end of the breath-holding period, a post–dead space sample of alveolar gas is obtained by discarding the first 750 mL of the expiration. The alveolar concentration of carbon monoxide is not constant during the breath-holding period, but allowance can be made, assuming that the disappearance of carbon monoxide follows an exponential law. Helium is also added to the inspired gas to give a measurement of lung volume by dilution. The appropriate equation is:

$$D_L = \frac{\dot{V}_A \times K}{t} \log_e \left[\frac{F_{I_{CO}} \times F_{A_{He}}}{F_{I_{He}} \times F_{A_{CO_2}}} \right] \quad (24)$$

where $\dot{V}_A$ is the alveolar volume in liters, t is breath-holding time in seconds, K is a constant, and the fractional concentrations of carbon monoxide and helium in inspired and expired gas are as indicated. Further details of this method, which requires considerable care for accurate results, can be found in more specialized texts.[84]

The diffusing capacity can also be measured using the *steady-state method.* The subject breathes a low concentration of carbon monoxide (about 0.1%) for 0.5 minute or so, until a steady state of gas exchange has been reached. The constant rate of disappearance of carbon monoxide from alveolar gas is then measured for a further short period, along with the alveolar concentration. This technique is better suited to measurements during exercise in which breath-holding becomes a problem. The normal value of the diffusing capacity for carbon monoxide depends on age, sex, and height (as is the case for most pulmonary function tests), and appropriate regression equations are available.[84]

Interpretation. As Figure 4-17A indicates, the uptake of carbon monoxide is determined by the diffusion properties of the blood-gas barrier (including plasma and red cell interior) and the rate of combination of carbon monoxide with blood. The *diffusion properties* of the alveolar membrane depend on its thickness and area. Thus, the diffusing capacity is reduced by diseases in which the thickness is increased, including diffuse interstitial pulmonary fibrosis, asbestosis, and sarcoidosis. It is also reduced when the area is decreased, for example, by pneumonectomy. The fall in diffusing capacity that occurs in emphysema may be caused by the loss of alveolar walls and capillaries, but unevenness of ventilation and diffusion may also play a role (see later discussion).

The *rate of combination* of carbon monoxide with blood is reduced whenever the number of red cells in the capillaries is reduced. This occurs in anemia and also in diseases that reduce the capillary blood volume, such as pulmonary embolism.

Figure 4-17B shows how it is possible to separate the membrane and blood components of the diffusing capacity by making measurements at high and normal values of alveolar P_{O_2}. However, this is only possible in subjects with nearly normal lungs. In many patients in whom the measured diffusing capacity is low, the interpretation is uncertain. The reason for this is the unevenness of ventilation and diffusion properties throughout the diseased lung. Such lungs tend to empty unevenly, with the result that the post–dead space sample of expired gas that is analyzed for carbon monoxide is not representative of the whole lung. Partly as a consequence of this, different methods of measuring diffusing capacity in patients with diseased lungs frequently give very different results. For this reason, the diffusing capacity is sometimes referred to as the *transfer factor* (especially in Europe) to emphasize that it is more a measure of the lung's overall ability to transfer gas into the blood than a specific test of diffusion characteristics. Nevertheless, the test gives considerable information in the nearly normal lung, and even in patients with severe disease, the results are empirically useful for assessing the severity and type of lung disease in the pulmonary function laboratory. (For a discussion of clinical tests, see Chapter 24.)

Shunt

Shunt refers to the entry of blood into the systemic arterial system without going through ventilated areas of lung. Even the normal cardiopulmonary system shows some depression of the arterial P_{O_2} as a result of this factor. For example, in the normal lung, some of the bronchial artery blood is collected by the pulmonary veins after it has perfused the bronchi. Because the oxygen concentration of this blood has been reduced, its addition to the normal end-capillary blood results in a reduction of arterial P_{O_2}. Another source is a small amount of coronary venous blood that drains directly into the cavity of the left ventricle through the thebesian veins. Of course, most of the coronary venous blood ends up in the coronary sinus, and only a minute fraction reaches the left ventricle directly. Such shunts depress arterial P_{O_2} only by about 1 to 2 mm Hg.

In patients with congenital heart disease, there may be a direct addition of venous blood to arterial blood across a defect between the right and left sides of the heart. Generally, this is associated with some increase in pressure on the right side; otherwise, the shunt is only from left to right. In lung disease, there may be gas-exchanging units that are completely unventilated because of airway obstruction, atelectasis, or alveolar filling with fluid or cells. The blood draining from these constitutes a shunt. It could be argued that such units are simply at the extreme end of the spectrum of ventilation-perfusion inequality (see next section), but the gas-exchange properties of unventilated units are so different (e.g., during oxygen breathing) that it is convenient to separate them.

When the shunt is caused by the addition of mixed venous blood (pulmonary arterial) to blood draining from the capillaries (pulmonary venous), it is possible to calculate the amount of shunt flow. This is done using a mixing equation. The total amount of oxygen delivered into the systemic circulation per minute is the total blood flow $(\dot{Q}_T)$ multiplied by the oxygen concentration in the systemic arterial blood (Ca_{O_2}), or $\dot{Q}_T \times Ca_{O_2}$. This must equal the sum of the amounts of oxygen in the shunted blood $(\dot{Q}_S \times C\bar{v}_{O_2})$ and the nonshunted or end-capillary blood $(\dot{Q}_T - \dot{Q}_S) \times Cc'_{O_2}$. Thus

$$\dot{Q}_T \times Ca_{O_2} = (\dot{Q}_S \times C\bar{v}_{O_2}) + (\dot{Q}_T - \dot{Q}_S) \times Cc'_{O_2} \quad (25)$$

Rearranging, this gives

$$\frac{\dot{Q}_S}{\dot{Q}_T} = \frac{(Cc'_{O_2} - Ca_{O_2})}{(Cc'_{O_2} - C\bar{v}_{O_2})} \quad (26)$$

The oxygen concentration of end-capillary blood is usually calculated from the alveolar P_{O_2} and the hemoglobin concentration, assuming 100% oxyhemoglobin saturation.

When the shunt is caused by blood that does not have the same oxygen concentration as mixed venous blood (e.g., bronchial venous blood), it is generally not possible to calculate its true magnitude. However, it is often useful to calculate an "as if" shunt, that is, what the shunt *would* be if the observed depression of arterial oxygen concentration were caused by the addition of mixed venous blood. An analogous procedure is frequently used to quantitate the degree of hypoxemia caused by ventilation-perfusion inequality, although it is clearly recognized in this case that there may be relatively little or even no blood flow to completely unventilated lung units.

An important diagnostic feature of a shunt is that the arterial P_{O_2} does not rise to the normal level (which in theory should be about 670 mm Hg) when the patient is given 100% oxygen to breathe. The reason for this is that the shunted blood that bypasses ventilated alveoli is never exposed to the higher alveolar P_{O_2}. Its addition to end-capillary blood, therefore, continues to depress the arterial P_{O_2}. Nevertheless, some elevation of the arterial P_{O_2} occurs because of the oxygen added to the capillary blood of the ventilated lung. Most of this added oxygen is in the dissolved form rather than attached to hemoglobin because the blood that is perfusing ventilated alveoli is normally nearly fully saturated.

The administration of 100% oxygen to a patient with a shunt is a very sensitive method of detecting small amounts of shunting. This is because when the arterial P_{O_2} is very high, a very small reduction of arterial oxygen concentration caused by the addition of the shunted blood causes a relatively large fall in P_{O_2}. This is directly attributable to the almost flat slope of the oxygen dissociation curve in this region.

A patient with a shunt usually does not have an increased P_{CO_2} in the arterial blood in spite of the fact that the shunted blood is rich in carbon dioxide. The reason is that the chemoreceptors sense any elevation of arterial P_{CO_2} and respond by increasing the ventilation. As a consequence, the P_{CO_2} of the unshunted blood is reduced by the hyperventilation until the arterial P_{CO_2} is back to normal. Indeed, in some patients with large shunts caused, for example, by cyanotic congenital heart disease, the arterial P_{CO_2} is low because the arterial hypoxemia increases the respiratory drive.

Ventilation-Perfusion Relationships

It has been known for many years that mismatching of ventilation and blood flow is the most common cause of hypoxemia in lung disease. More recently, the role of uneven ventilation and blood flow as a cause of carbon dioxide retention has also been appreciated. Early intimations of the importance of the subject go back to Krogh and Lindhard[85] and Haldane.[86] However, a very rapid advance in our understanding occurred in the late 1940s when Fenn and colleagues[87] and Riley and Cournand[88] introduced graphic analysis of gas exchange. This was an important advance because the interrelationships of ventilation, blood flow, and gas exchange depend on the oxygen and carbon dioxide dissociation curves that are not only nonlinear but interdependent, and direct solutions to the gas exchange equations that relate the ventilation-perfusion ratio to gas exchange (see below, Equations 28 and 29) are not possible.

A more recent phase began with the introduction of digital computer procedures to describe the oxygen and carbon dioxide dissociation curves.[89,90] These new procedures enabled investigators to answer questions about gas exchange that had been impossibly difficult prior to that time. The behavior of distributions of ventilation-perfusion ratios was analyzed,[91] and Wagner and his colleagues[92] introduced the multiple inert gas elimination technique, which allowed, for the first time, information about the dispersion, number of modes, and shape of the distributions of ventilation, of perfusion, and of their ratio to be obtained.

Gas Exchange in a Single Lung Unit

The P_{O_2}, P_{CO_2}, and P_{N_2} in any gas-exchanging unit of the lung are uniquely determined by three major factors: (1) the ventilation-perfusion ratio, (2) the composition of the inspired gas and the composition of the mixed venous blood, and (3) the slopes and positions of the relevant blood-gas dissociation curves.

Formally, the key role of the ventilation-perfusion ratio can be derived as follows. The amount of carbon dioxide exhaled into the air from alveolar gas per minute is given by a rearrangement of Equation 5:

$$\dot{V}_{CO_2} = \dot{V}_A \times P_{A_{CO_2}} / K \tag{5}$$

where $\dot{V}_{CO_2}$ is the carbon dioxide output, $\dot{V}_A$ is the alveolar ventilation, K is a constant, and there is no carbon dioxide in the inspired gas.

The amount of carbon dioxide lost into alveolar gas from capillary blood per minute is given by

$$\dot{V}_{CO_2} = \dot{Q}(C\bar{v}_{CO_2} - Cc'_{CO_2}) \tag{27}$$

where $\dot{Q}$ is blood flow, and $C\bar{v}_{CO_2}$ and Cc'_{CO_2} are the concentrations of carbon dioxide in mixed venous and end-capillary blood, respectively. Now, in a steady state, the amount of carbon dioxide lost from the alveoli and from the capillary blood must be the same. Therefore

$$\dot{V}_A \times P_{A_{CO_2}} \times K = \dot{Q}(C\bar{v}_{CO_2} - Cc'_{O_2}) \; or$$
$$\frac{\dot{V}_A}{\dot{Q}} = \frac{(C\bar{v}_{CO_2} - Cc'_{O_2})}{P_{A_{CO_2}}} \times K \tag{28}$$

Thus, the alveolar P_{CO_2} and the corresponding end-capillary CO_2 concentration (assuming end-capillary and alveolar P_{CO_2} are identical) are determined by (1) the ventilation-perfusion ratio, (2) the mixed venous CO_2 concentration, and (3) the carbon dioxide dissociation curve relating P_{CO_2} to carbon dioxide concentration.

Although this equation looks simple, its appearance is deceptive, because when the ventilation-perfusion ratio increases (for example), the alveolar P_{O_2} rises. This means that the oxygen saturation of the blood increases and therefore that the relationship between P_{CO_2} and carbon dioxide concentration is altered. Thus, the alveolar P_{O_2} is an implicit variable in the equation. In addition,

the relationship between P_{CO_2} and carbon dioxide concentration is nonlinear. This is the reason that it was only possible to solve the equation graphically until the introduction of numerical analysis by computer.

Just as, in the context of the alveolar ventilation equation (see "Hypoventilation" earlier), both oxygen and carbon dioxide exchange were able to be expressed in equations of similar form, it is possible to write an equation similar to Equation 28 for oxygen exchange based on the same principles as applied for carbon dioxide. Again, the approximation is made that inspired alveolar ventilation ($\dot{V}_I$) = expired alveolar ventilation ($\dot{V}_A$) to keep the equation simple, but as for the alveolar gas equation, the fact that $\dot{V}_I$ and $\dot{V}_A$ are generally not quite the same can formally be taken into account. Using this approximation, the equation for oxygen is

$$\frac{\dot{V}_A}{\dot{Q}} = K \times \frac{(Cc'_{O_2} - C\bar{v}_{O_2})}{(P_{I_{O_2}} - P_{A_{O_2}})} \qquad (29)$$

Just as for carbon dioxide, the alveolar and end-capillary P_{O_2} values are taken to be identical, implying diffusion equilibrium across the blood-gas barrier. It is seen that the determinants of alveolar P_{O_2} are threefold, as for carbon dioxide: (1) the ventilation-perfusion ratio, (2) inspired and mixed venous oxygen levels, and (3) the relationship between P_{O_2} and oxygen concentration (i.e., the oxygen dissociation curve).

Graphic analysis of these relationships is assisted by the use of the oxygen–carbon dioxide diagram, in which P_{O_2} is on the horizontal axis and P_{CO_2} on the vertical axis. This diagram has been used to solve many problems related to ventilation-perfusion relationships.[93] A simple introduction to the diagram is given elsewhere.[94] It shows the solutions to Equations 28 and 29 for each value of the ventilation-perfusion ratio from zero to infinity.

Figure 4-18 is an example of the use of the oxygen–carbon dioxide diagram to show how the P_{O_2} and P_{CO_2} of a lung unit alter as the ventilation-perfusion ratio is either decreased below or increased above the normal value. Note that for a given composition of inspired gas (I) and mixed venous blood ($\bar{v}$), the possible combinations of P_{O_2} and P_{CO_2} are constrained to a single line known as the ventilation-perfusion ratio line. Each point on that line uniquely corresponds to a value of the ventilation-perfusion ratio. Note also that, at the extremes of the spectrum of ventilation-perfusion ratios, the P_{O_2} and P_{CO_2} of end-capillary blood are those of mixed venous blood when the ventilation-perfusion ratio is zero, and the P_{O_2} and P_{CO_2} of alveolar gas are the same as those of inspired gas for a ventilation-perfusion ratio of infinity. In this diagram and in the rest of this section, we assume that there is complete diffusion equilibration between the P_{O_2} and P_{CO_2} of alveolar gas and end-capillary blood. This is a reasonable assumption unless there is marked thickening of the blood-gas barrier or one is considering a subject exercising in hypoxia.

Figure 4-19 shows the P_{O_2}, P_{CO_2}, and oxygen concentration of end-capillary blood of a lung unit as its ventilation-perfusion ratio is increased from extremely low to extremely high values. The lung is assumed to be breathing air, the P_{O_2} and P_{CO_2} of mixed venous blood are normal (40 and 45 mm Hg, respectively), and the hemoglobin concentration is 14.8 g/100 mL. The normal value of the ventilation-perfusion ratio is in the range of 0.8 to 1. Note that as the ratio is altered either above or below that value, the P_{O_2} changes rapidly. By contrast, the oxygen concentration increases little as the ventilation-perfusion ratio is raised above the normal value because the hemoglobin is already almost fully saturated. The P_{CO_2} falls considerably as the ventilation-perfusion ratio is raised, but rises relatively little at lower ventilation-perfusion ratio values. The quantitative information in this figure is consistent with the graphic analysis of Figure 4-18.

Pattern in the Normal Lung

Both ventilation and perfusion vary throughout the lung. It is thus instructive to look at the topographic inequality

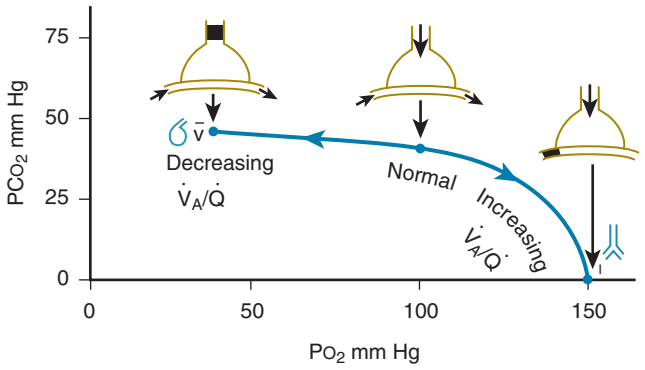

FIGURE 4-18 ■ Oxygen–carbon dioxide diagram shows how the P_{O_2} and P_{CO_2} of a lung unit alter as the ventilation-perfusion ratio ($\dot{V}_A/\dot{Q}$) is changed. I, inspired gas; $\bar{v}$, mixed venous blood. (Redrawn from West JB: Respiratory Physiology—The Essentials [8th ed]. Baltimore: Lippincott Williams & Wilkins, 2008.)

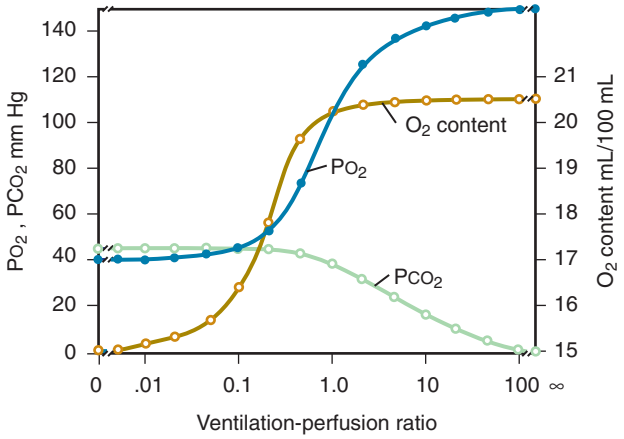

FIGURE 4-19 ■ Changes in P_{O_2}, P_{CO_2}, and end-capillary oxygen content in a lung unit are shown as its ventilation-perfusion ratio is altered. See text for assumptions. (Redrawn from West JB: State of the art: Ventilation-perfusion relationships. Am Rev Respir Dis 116:919–943, 1977.)

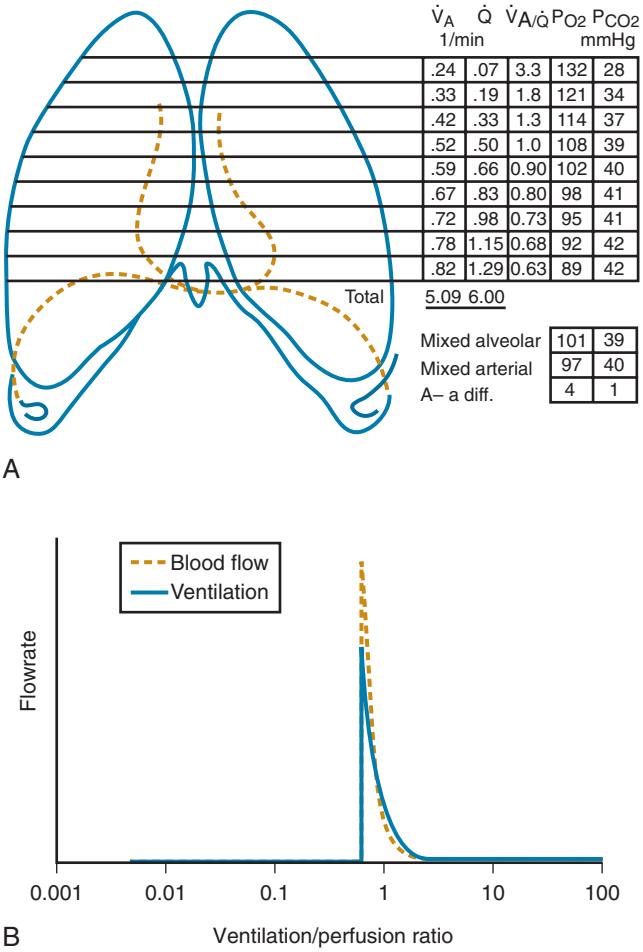

FIGURE 4-20 ■ **A,** Regional differences of gas exchange down the upright normal lung. The lung is divided into nine imaginary slices. $\dot{Q}$, blood flow; $\dot{V}_A$, gas flow. **B,** Topographic distribution of blood flow and ventilation taken from **A** are reexpressed as plots of blood flow and ventilation against ventilation-perfusion ratio. This transformation quantifies the distribution of ventilation-perfusion ratios. (**A** Redrawn from West JB: Respiratory Physiology—The Essentials [8th ed]. Baltimore: Lippincott Williams & Wilkins, 2008.)

of gas exchange that occurs in the normal upright lung as a result of ventilation-perfusion inequality. We saw previously that both ventilation and blood flow per unit volume decrease from the bottom to the top of the upright lung. However, the changes for blood flow are more marked than those for ventilation. As a consequence, the ventilation-perfusion ratio increases from low values at the base to high values at the apex of the normal upright lung (Fig. 4-20A).

Because the ventilation-perfusion ratio determines the gas exchange in any region (Equations 28 and 29), the corresponding pattern of variation in P_{O_2} and P_{CO_2} in the lung can be calculated. Normal composition of mixed venous blood is here assumed. Note that the P_{O_2} increases by some 40 mm Hg from base to apex, whereas the P_{CO_2} falls by about 14 mm Hg. The pH is high at the apex because the P_{CO_2} there is low (the base excess is the same throughout the lung). Very little of the total oxygen uptake occurs at the apex, principally because the blood flow there is very low.

Figure 4-20A also helps to explain why ventilation-perfusion inequality interferes with overall gas exchange. Note that the base of the lung has most of the blood flow, but the P_{O_2} and oxygen concentration of the end-capillary blood are lowest there. As a result, the effluent pulmonary venous blood (which becomes the systemic arterial blood) is loaded with moderately oxygenated blood from the base. The net result is a depression of the arterial P_{O_2} below that which would occur if ventilation and blood flow were uniformly distributed.

The same argument applies to carbon dioxide. In this case, the P_{CO_2} and carbon dioxide concentrations of the end-capillary blood are highest at the base, where the blood flow is greatest. As a result, the P_{CO_2} of arterial blood is elevated above that which would occur if there were no ventilation-perfusion inequality. In other words, a lung with mismatched ventilation and blood flow is inefficient at exchanging gas, be this oxygen or carbon dioxide. In fact, the inefficiency applies to any gas that is being transferred by the lung. The extent of the impairment of gas exchange caused by any given amount of ventilation-perfusion inequality depends on the solubility, or slope of the blood dissociation curve, of the gas. For example, in a lognormal distribution of ventilation-perfusion ratios, gases with medium solubility experience the greatest interference with pulmonary transfer.[95] In the normal lung, despite the degree of inequality due to gravity shown in Figure 4-20A, the overall effect on gas exchange is very small, reducing arterial P_{O_2} by only about 4 mm Hg (compared to that in a homogeneous lung).

The data in Figure 4-20A, showing values for ventilation, blood flow, and ventilation–blood flow ratio at all nine levels from apex to base, can usefully be considered as a frequency distribution of ventilation-perfusion ratios. This is accomplished by separately plotting ventilation and blood flow in each of the nine regions on the ordinate against the corresponding ventilation-perfusion ratio of each region. This is shown in Figure 4-20B. Such a distribution depicts succinctly the range of ventilation-perfusion ratios in the lung as a whole, and also shows the relative amounts of ventilation and blood flow associated with each. This narrow distribution should be compared to distributions in disease, which are discussed later in this chapter.

Traditional Assessment of Ventilation-Perfusion Inequality

A central question that has engaged the attention of physiologists and physicians for many years has been how best to assess the amount of ventilation-perfusion inequality. Ideally, we would like to know the actual distribution of ventilation-perfusion ratios (see next section), but the procedure required for this is too complicated for many clinical situations. Traditionally, we rely on measurements of P_{O_2} and P_{CO_2} in arterial blood and expired gas.

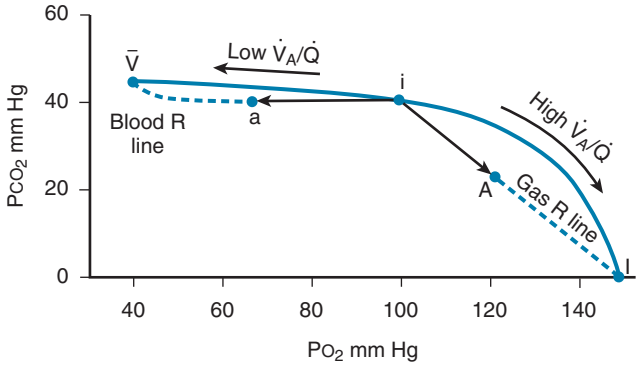

FIGURE 4-21 ■ Oxygen–carbon dioxide diagram showing the points for ideal gas (i), arterial blood (a), and alveolar gas (A). See text for details. $\dot{Q}$, blood flow; R lines, respiratory exchange ratio; $\dot{V}_A$, ventilation. (Redrawn from West JB: Respiratory Physiology—The Essentials [8th ed]. Baltimore: Lippincott Williams & Wilkins, 2008.)

The *arterial* P_{O_2} certainly gives some information about the degree of ventilation-perfusion inequality. In general, the lower the P_{O_2}, the more marked is the mismatching of ventilation and blood flow. The chief merit of this measurement is its simplicity, but a disadvantage is that its value is so sensitive to the overall ventilation and pulmonary blood flow.

We can quickly dismiss the *arterial* P_{CO_2}. This is so sensitive to the level of ventilation that it gives little information about the extent of the ventilation-perfusion inequality, though it should be added that the most common cause of an increased P_{CO_2} in chronic lung disease is mismatching of ventilation and blood flow.

Because of these limitations, the *alveolar-arterial* P_{O_2} difference is frequently measured and is more informative than the arterial P_{O_2} alone because it is less sensitive to the level of overall ventilation. To understand the significance of this measurement, we need to look in more detail at how gas exchange is altered by the imposition of ventilation-perfusion inequality.

Figure 4-21 shows an oxygen–carbon dioxide diagram with the same ventilation-perfusion line as that in Figure 4-18. Suppose initially that this lung has no ventilation-perfusion inequality. The P_{O_2} and P_{CO_2} of the alveolar gas and arterial blood would then be represented by point i, known as the ideal point. This is at the intersection of the gas and blood respiratory exchange ratio (R) lines; these are the lines that indicate the possible compositions of alveolar gas and arterial blood that are consistent with the overall respiratory exchange ratio (carbon dioxide output/oxygen uptake) of the whole lung. In other words, a lung in which R = 0.8 would have to have its mixed alveolar gas point (A) located somewhere on the line joining points i and I. A similar statement can be made for the arterial gas point (a).

What happens to the composition of mixed alveolar gas and arterial blood as ventilation-perfusion inequality is imposed on the lung? The answer is that both points diverge away from the ideal point (i), along the appropriate gas and blood R lines. The more extreme the degree of ventilation-perfusion inequality, the further the divergence. Moreover, the type of ventilation-perfusion inequality determines how much each point will move. For example, a distribution containing a large amount of ventilation to units with high ventilation-perfusion ratio especially moves point A down and to the right away from point i. By the same token, a distribution containing large amounts of blood flow to units with low ventilation-perfusion ratios predominantly moves point a leftward along the blood R line.

It is clear that the horizontal distance between points A and a (i.e., the mixed alveolar-arterial P_{O_2} difference) would be a useful measure of the degree of ventilation-perfusion inequality. Unfortunately, this index is impossible to obtain in most patients because A denotes the composition of *mixed* expired gas, excluding the anatomic dead space gas. In most diseased lungs, the alveoli empty sequentially, with poorly ventilated alveoli emptying last, so that a post–dead space sample is not representative of all mixed expired alveolar gas. In a few patients who have essentially uniform ventilation but uneven blood flow, this index can be used, and it is occasionally reported in patients with pulmonary embolism. In this instance, the P_{O_2} of end-tidal gas is taken to represent mixed expired alveolar gas.

Because the mixed expired alveolar P_{O_2} is usually impossible to obtain, a more useful index is the P_{O_2} difference between ideal alveolar gas and arterial blood, that is, the horizontal distance between points i and a. The ideal alveolar P_{O_2} is calculated from the alveolar gas equation:

$$P_{A_{O_2}} = P_{I_{O_2}} - \frac{P_{A_{CO_2}}}{R} + \left[P_{A_{CO_2}} \times F_{I_{O_2}} \times \frac{(1-R)}{R} \right] \qquad (17)$$

To use this equation, we assume that the P_{CO_2} of ideal alveolar gas is the same as the P_{CO_2} of arterial blood. The rationale for this is that the line along which point a moves (in Fig. 4-21) is so nearly horizontal that the value is close enough for clinical purposes. It is important to note that this ideal alveolar-arterial P_{O_2} difference is caused by units situated on the ventilation-perfusion ratio line between points i and $\bar{v}$, that is, units with abnormally low ventilation-perfusion ratios. This means that a diseased lung may have substantial ventilation-perfusion inequality but a nearly normal ideal alveolar-arterial P_{O_2} difference if most of the inequality is caused by units with abnormally high ventilation-perfusion ratios.

Physiologic shunt is another useful index of ventilation-perfusion inequality. It measures that movement of the arterial point away from the ideal point along the blood R line (see Fig. 4-21). It is therefore caused by blood flow to lung units with abnormally low ventilation-perfusion ratios. To calculate physiologic shunt, we pretend that all of the leftward movement of the arterial point a is caused by the addition of mixed venous blood $\bar{v}$ to ideal blood i. This is not so unreasonable as it might at first seem because units with very low ventilation-perfusion ratios put out blood that has essentially the same composition as that of mixed venous blood (see Figs. 4-18 and 4-19). The shunt equation is used in the following form:

$$\frac{\dot{Q}_{PS}}{\dot{Q}_T} = \frac{(Ci_{O_2} - Ca_{O_2})}{(Ci_{O_2} - C\bar{v}_{O_2})} \quad (30)$$

where $\dot{Q}_{PS}$ refers to physiologic shunt, $\dot{Q}_T$ refers to total blood flow through the lung, and Ci_{O_2}, Ca_{O_2}, and $C\bar{v}_{O_2}$, refer, respectively, to the oxygen concentrations of ideal, arterial, and mixed venous blood. The oxygen concentration of ideal blood is calculated from the ideal P_{O_2} and the oxygen dissociation curve. The normal value for *physiologic shunt* is less than 0.05.

The last traditional index to be discussed is *physiologic dead space* (also known as wasted ventilation). Whereas physiologic shunt reflects the amount of blood flow going to lung units with abnormally low ventilation-perfusion ratios, physiologic dead space is a measure of the amount of ventilation going to units with abnormally high ventilation-perfusion ratios. Thus the two indices provide measurements of both ends of the spectrum of ventilation-perfusion ratios.

To calculate physiologic dead space, we pretend that all the movement of the alveolar point A away from the ideal point i (see Fig. 4-21) is caused by the addition of inspired gas I to ideal gas. Again, this is not so unreasonable as it may first appear, because units with very high ventilation-perfusion ratios behave very much like point I (see Fig. 4-21). Because, as indicated earlier, it is usually impossible to obtain a pure sample of mixed expired gas, we generally collect mixed expired gas and measure its composition, E. The mixed expired gas contains a component from anatomic dead space, which therefore moves its composition further toward point I. The Bohr equation (Equation 9) is then used in the form

$$\frac{V_{D_{phys}}}{V_T} = \frac{(Pa_{CO_2} - P_{E_{CO_2}})}{Pa_{CO_2}} \quad (31)$$

where $V_{D_{phys}}$ is physiologic dead space, V_T is tidal volume, and $P_{E_{CO_2}}$ is mixed expired P_{CO_2}, and again we exploit the fact that the P_{CO_2} of ideal gas and that of arterial blood are virtually the same. The physiologic dead space/tidal volume ratio is sensitive to tidal volume because of the large contribution of anatomic dead space. The normal value for physiologic dead space is less than 0.3. (For applications of these principles in pulmonary function testing, see Chapter 24.)

Distributions of Ventilation-Perfusion Ratios

The analysis of ventilation-perfusion inequality briefly described in the last section is sometimes known as the *three-compartment model* because the lung is conceptually divided into an unventilated compartment (shunt), an unperfused compartment (dead space), and a compartment that is normally ventilated and perfused (ideal). This way of looking at the diseased lung, which was introduced by Riley and Cournand,[88] has proved to be of great clinical usefulness in assessing the effects of mismatching of ventilation and blood flow.

However, it was recognized many years ago that real lungs must contain some sort of distribution of ventilation-perfusion ratios and that a three-compartment model is therefore very remote from reality. The great difficulty of dealing with distributions of ventilation-perfusion ratios made progress very slow, although many clinical physiologists saw the measurement of distributions as an important goal.

The breakthrough came with the application of computer methods for analyzing the behavior of distributions, a very complex area because of the nonlinear and interdependent oxygen and carbon dioxide dissociation curves. With computer analysis, it was possible to make considerable advances in the understanding of the behavior of distributions of ventilation-perfusion ratios.[91] A key advance was the introduction of the multiple inert gas elimination technique, which allowed patterns of distributions to be recovered in patients with lung disease.[92]

Multiple Inert Gas Elimination Technique. The principles governing inert gas elimination by the lung are identical to those of O_2 and CO_2, and are dictated by equations corresponding to Equations 28 and 29. When an inert gas dissolved in saline is steadily infused into the peripheral venous circulation, it arrives at the lungs, and some of the gas will be exhaled. The proportion of gas that is eliminated by ventilation from the blood of a given lung unit depends only on the blood-gas partition coefficient of the gas (λ) and the ventilation-perfusion ratio $(\dot{V}_A/\dot{Q})$.[96,97] The relationship is given by the following equation:

$$\frac{Pc'}{P\bar{v}} = \frac{\lambda}{(\lambda + \dot{V}_A/\dot{Q})} \quad (32)$$

where Pc' and $P\bar{v}$ are the partial pressures of the gas in end-capillary blood and mixed venous blood, respectively. Equation 32 looks different from Equations 28 and 29 only because inert gases obey Henry's law, allowing concentration to be simply replaced by the product of solubility and partial pressure. This in turn permits the rearrangement of terms ending up with Equation 32. The ratio of end-capillary to mixed venous partial pressure is known as the *retention.* This equation is derived from exactly the same considerations of mass balance as applied to carbon dioxide in Equation 5.

In practice, a mixture of six gases (typically, sulfur hexafluoride, ethane, cyclopropane, isoflurane, ether, and acetone) is dissolved in saline and infused into a peripheral arm vein at the rate of about 3 mL/min until a steady state of gas exchange is achieved (about 10 to 20 minutes). Samples of mixed expired gas and arterial blood are then taken, and the gas concentrations in each are determined by gas chromatography. At the same time, cardiac output is obtained (e.g., by indicator dilution, echocardiography, or other method), and total ventilation is also measured. From these data, mixed venous concentrations of each inert gas can be calculated and retention determined. In patients who already have an indwelling pulmonary arterial catheter, a sample of mixed venous blood could be taken instead to directly measure mixed venous inert gas levels.

A graph is then constructed, as shown in Figure 4-22. The upper panel shows the data points of inert *gas retention* (arterial partial pressure divided by mixed venous partial pressure), which are joined for clarity by the broken line. Below this are the data points for *excretion*

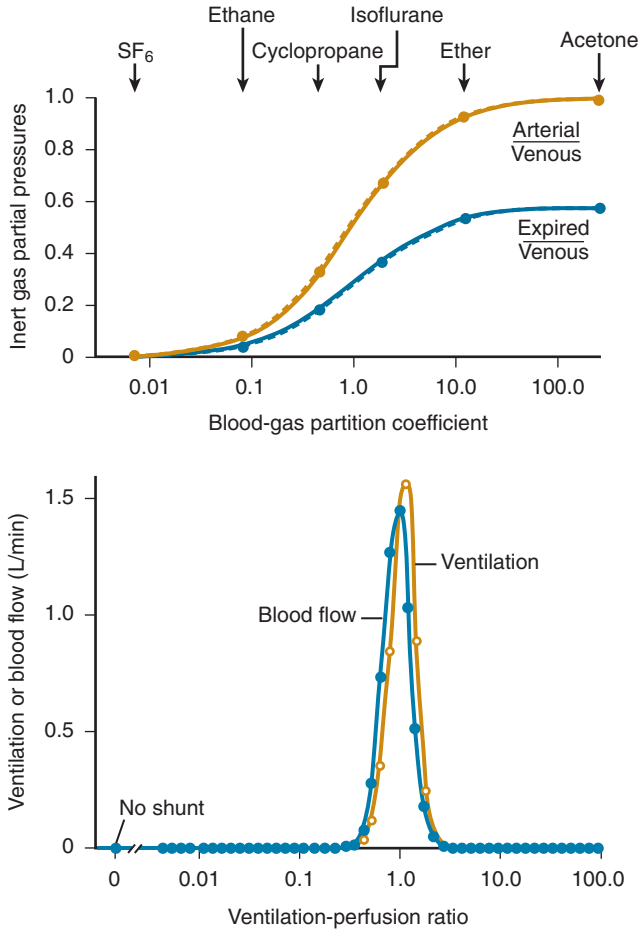

FIGURE 4-22 ■ Use of the multiple inert gas elimination technique to determine the distribution of ventilation-perfusion ratios in a 22-year-old normal subject. *Upper panel,* Data points for inert gas retention (*upper curve*) and excretion (*lower curve*). *Broken lines* join the points. The two *solid lines* show the values of retention and excretion for a lung with no ventilation-perfusion inequality. *Lower panel,* The recovered distribution of ventilation-perfusion ratios. SF_6, sulfur hexafluoride. (Redrawn from Wagner PD, Laravuso RB, Uhl RR, West JB: Continuous distributions of ventilation-perfusion ratios in normal subjects breathing air and 100% O2. J Clin Invest 54:53–68, 1974.)

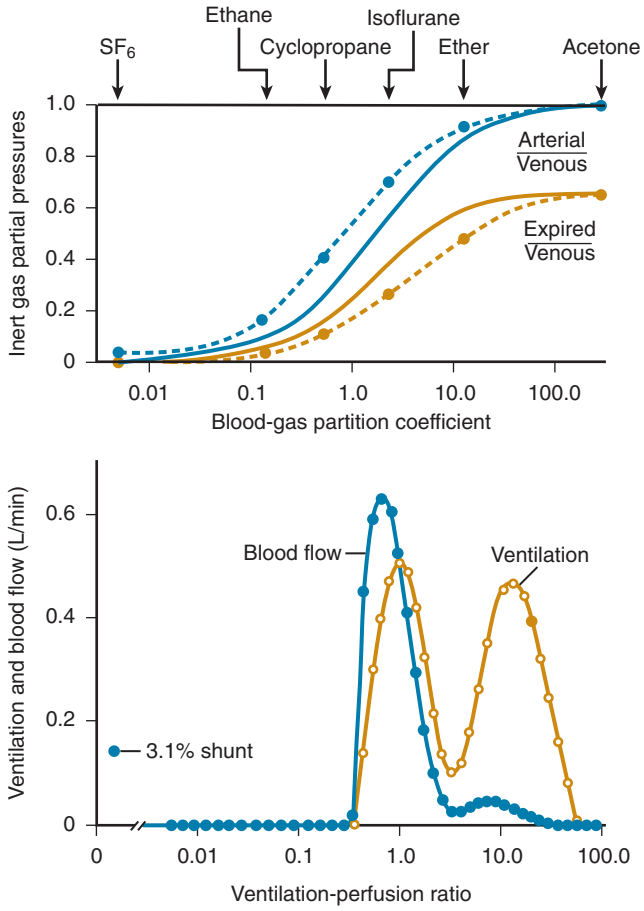

FIGURE 4-23 ■ Distribution of ventilation-perfusion ratios in a 60-year-old patient with chronic obstructive lung disease, predominantly emphysema. *Upper panel,* The retention and excretion solubility curves. *Lower panel,* The recovered distribution of ventilation-perfusion ratios. SF_6, sulfur hexafluoride. (Redrawn from Wagner PD, Dantzker DR, Dueck R, et al: Ventilation-perfusion inequality in chronic obstructive pulmonary disease. J Clin Invest 59:203–216, 1977.)

(mixed expired partial pressure divided by mixed venous partial pressure). Both are plotted against the partition coefficient. Again, the points are joined by a broken line. For comparison, the two solid lines show the values of retention and excretion for a lung with no ventilation-perfusion inequality but with the same overall ventilation and blood flow. The broken and solid lines are very close together in Figure 4-22, and the differences are more easily seen in Figure 4-23, where the lung is diseased.

These plots, called the retention-solubility and excretion-solubility curves, contain information about the distribution of ventilation-perfusion ratios in the lung. For example, if a lung contains units that are perfused but not ventilated (shunt), these particularly increase the retention of the least soluble gas, sulfur hexafluoride. Conversely, if the distribution contains large amounts of ventilation to lung units with very high ventilation-perfusion ratios, the excretion of the high-solubility gases is chiefly affected. The relationship between the distribution of ventilation-perfusion ratios and the retention-solubility and excretion-solubility curves can be expressed formally by a set of simultaneous linear equations.[98] These equations, one for each inert gas, simply reflect the principles of mass conservation and relate the ventilation-perfusion distribution (i.e., the paired set of gas-exchange unit blood flows and ventilations) to a measured set of inert gas retention and excretion values. The distribution of ventilation-perfusion ratios that is consistent with the pattern of inert gas retention and excretion is then determined using computer programs that solve these simultaneous equations.

The potential and limitations of this transformation have been explored in great detail.[98] The recovered distribution is not unique, but in most cases the range of possible distributions compatible with the data is small. No more than three modes of a distribution can be recovered, and only smooth distributions can be obtained. In

spite of these limitations, however, the technique gives much more information about patterns of distribution of ventilation-perfusion ratios in patients with lung disease than has previously been available.

Distribution in Normal Subjects. Figure 4-22 shows retention and excretion-solubility curves and the derived distribution of ventilation-perfusion ratios from a 22-year-old normal volunteer.[99] First, note that the retentions and excretions as indicated by the data points and broken lines in the upper panel are almost superimposed on the solid lines for a homogeneous lung. The recovered distribution (lower panel) is consistent with these data and shows that the plots of both ventilation and blood flow are narrow, spanning only one decade of ventilation-perfusion ratios (i.e., from a ventilation-perfusion ratio of about 0.3 to one 10 times higher, of about 3). In particular, there was essentially no ventilation or blood flow outside this range on the ventilation-perfusion ratio scale. Note also that there was no shunt, that is, blood flow to unventilated alveoli.

The absence of shunt was a consistent finding in all the normal subjects studied and was initially surprising. It should be pointed out that, first, this technique is very sensitive, in that a shunt of only 0.5% of the cardiac output approximately doubles the arterial concentration of sulfur hexafluoride. Apparently, young normal subjects are able to ventilate essentially all of their alveoli. Second, bronchial and thebesian shunts are not detected by the method.

In older normal subjects, increased dispersion of the distribution is found. This is consistent with the gradual fall in arterial P_{O_2} known to occur with aging.

Distributions in Lung Disease. Figure 4-23 shows a typical distribution of ventilation-perfusion ratios from a patient with chronic obstructive lung disease. The distribution is typical of the pattern seen in patients believed to have, predominantly, emphysema.[100] The upper panel shows that the measured retentions and excretions (dots, dashed lines) deviated greatly from those expected in a homogeneous lung with the same total ventilation and blood flow (solid lines). Consistent with this, the lower panel shows a broad bimodal distribution, with large amounts of ventilation to lung units with extremely high ventilation-perfusion ratios (alveolar dead space). Note the small shunt of 3.1%. The mild hypoxemia in this patient (arterial P_{O_2} of 63 mm Hg) is explained mostly by the slight displacement of the main mode of blood flow to the left of normal. Presumably the high ventilation-perfusion ratio mode reflects ventilation to lung units in which many capillaries have been destroyed by the emphysematous process, reducing their perfusion. Patients with acute pulmonary embolism often show a ventilation-perfusion ratio pattern similar to that in Figure 4-23. This is well explained by continuing ventilation in poorly perfused embolized regions. Sometimes, shunts are seen as well, possibly from scattered atelectasis, possibly from edema, and possibly from right-to-left shunting through a patent foramen ovale when right atrial pressure is elevated.

Patients with chronic obstructive lung disease whose predominant lesion is severe bronchitis generally show a different pattern. The main abnormality in the distribution is a large amount of blood flow going to lung units with very low ventilation-perfusion ratios, between 0.005 and 0.1. This explains the more severe hypoxemia in this type of patient, and is consistent with the large physiologic shunt that is usually found. Presumably, the low ventilation-perfusion ratios in some lung units are the result of partially blocked airways due to retained secretions and airway disease that reduces airway diameter. However, it is interesting that these patients generally do not show much shunting (blood flow to unventilated alveoli), and a possible explanation is collateral ventilation. It should be emphasized that the distributions found in severe chronic bronchitis show considerable variability.

A particularly interesting pattern of ventilation-perfusion ratios has been seen in some patients with asthma, even in remission.[101] Figure 4-24A shows an obvious bimodal appearance, with some 25% of the total blood flow going to lung units with ventilation-perfusion ratios in the region of 0.1. However, there was no blood flow to unventilated units. When this patient was given a β-adrenergic bronchodilator by aerosol, the distribution changed, as shown in Figure 4-24B. There was a marked increase in the amount of blood flow to low ventilation-perfusion ratio units, and this was associated with a corresponding decrease in arterial P_{O_2} from 81 to 70 mm Hg. However, the pattern was short lived; 5 minutes later, the distribution had returned to the pattern shown in Figure 4-24A, and the P_{O_2} was back to the prebronchodilator level. The bronchodilator effects of the drug on the airflow had a much longer duration.

Such a fall in arterial P_{O_2} is often seen in asthmatics after bronchodilator therapy even with improved airflow.[59,60] The reason for the redistribution of blood flow is probably that the blood vessels supplying the hypoxic low ventilation-perfusion ratio units dilate preferentially in response to the β-adrenergic agonists. Modern bronchodilators cause less hypoxemia than shown in Figure 4-24, and also less deterioration in the ventilation-perfusion ratio distribution.

It was surprising that this almost asymptomatic patient had as much ventilation-perfusion ratio inequality as shown in Figure 4-24. The extent of the abnormality of the distribution suggests that there were many more abnormalities in the lung, including obstruction of small airways, than were indicated by the patient's symptoms. One lung model consistent with the observed data is that about half of the small airways were totally occluded by mucous plugs (for a discussion of mucus hypersecretion, see Chapter 11) and/or airway wall edema, and that the ventilation of the lung subtended by them occurred through collateral channels. However, it should be emphasized that not all well-managed asthmatics show such abnormal distributions of ventilation-perfusion ratios. In some, the distribution is unimodal with little or no increase in dispersion. Importantly, the extent of ventilation-perfusion ratio inequality cannot be predicted from the impairment in spirometry. Patients with acute respiratory distress syndrome commonly show a full

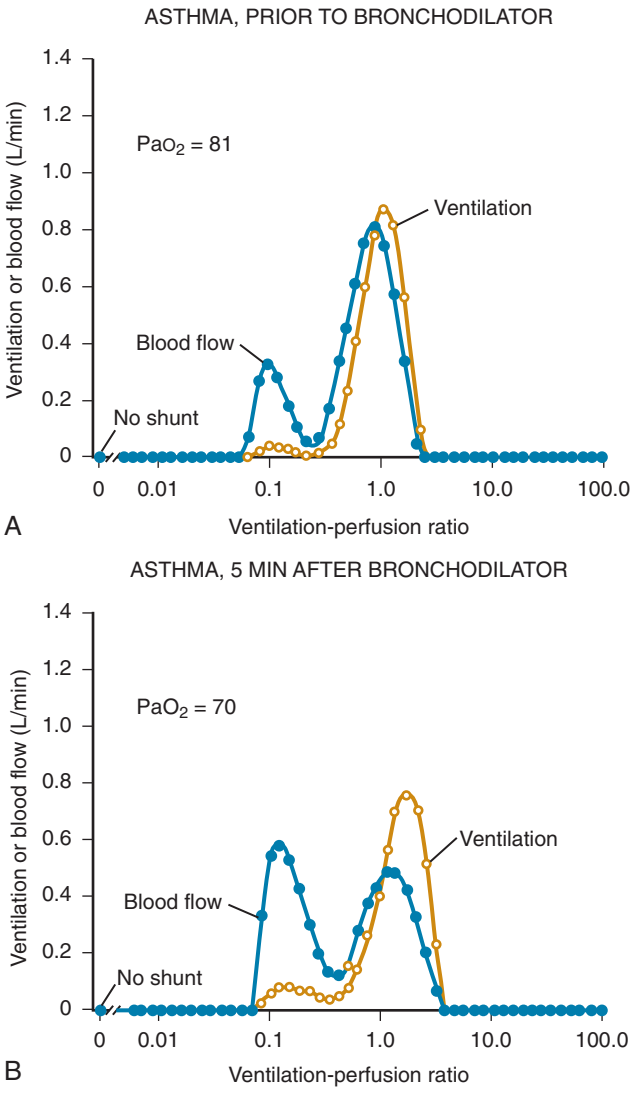

FIGURE 4-24 ■ Distribution of ventilation-perfusion ratios in a patient (DM) with asthma before **(A)** and after **(B)** the administration of isoproterenol by aerosol. (Redrawn from Wagner PD, Dantzker D, Iacovoni VE, et al: Ventilation-perfusion inequality in asymptomatic asthma. Am Rev Respir Dis 118:511–524, 1978.)

spectrum of ventilation-perfusion ratio abnormalities: especially shunt, but also low ventilation-perfusion ratio regions, areas of normal ventilation-perfusion ratio, high ventilation-perfusion ratio regions, and increased ventilation of unperfused lung.

Ventilation-Perfusion Inequality and Carbon Dioxide Retention

It is important to appreciate that ventilation-perfusion inequality interferes with the uptake and elimination of all gases by the lung (oxygen, carbon dioxide, carbon monoxide, and anesthetic gases). In other words, mismatching of ventilation and blood flow reduces the overall gas-exchange efficiency of the lung. There has been considerable confusion in this area, particularly about the role of ventilation-perfusion inequality in carbon dioxide retention.

Imagine a lung that is uniformly ventilated and perfused and that is transferring normal amounts of oxygen and carbon dioxide. Suppose that the matching of ventilation and blood flow is suddenly disturbed while everything else remains unchanged. What happens to gas exchange? It can be shown that the effect of this "pure" ventilation-perfusion inequality (i.e., with all other factors held constant) is to reduce both the oxygen uptake and carbon dioxide output of the lung.[91] The lung becomes less efficient as a gas exchanger for both gases, and therefore, mismatching of ventilation and blood flow must cause hypoxemia and hypercapnia (carbon dioxide retention), other things being equal.

In practice, however, patients with ventilation-perfusion inequality often have a normal arterial P_{CO_2}. The reason for this is that, whenever the chemoreceptors sense a rising P_{CO_2}, there is an increase in ventilatory drive. The consequent increase in ventilation to the alveoli usually effectively returns the arterial P_{CO_2} to normal. However, such patients can only maintain a normal P_{CO_2} at the expense of this increased ventilation to their alveoli. The ventilation in excess of what they would normally require is sometimes referred to as *wasted ventilation* and is necessary because the lung units with abnormally high ventilation-perfusion ratios contribute little to eliminating carbon dioxide. Such units are part of the alveolar (physiologic) dead space.

Patients with ventilation-perfusion ratio inequality that causes carbon dioxide retention are sometimes said to be "hypoventilating," but in fact they may actually be breathing more than normal. "Hypoventilation" in this setting is used by people who define the adequacy or inadequacy of alveolar ventilation by whether it maintains a normal arterial P_{CO_2}. Thus, hypoventilation in this context really simply means an increased arterial P_{CO_2}. "Alveolar ventilation" in this context does not refer to all the gas entering the lung alveoli but is related to "ideal alveolar" gas and excludes alveolar dead space gas. In this chapter, the term *alveolar* has been used to refer to all the gas in the lung, excluding the conducting airways that contain anatomic dead space. True hypoventilation was discussed in an earlier section when the relationship between alveolar ventilation and P_{CO_2} was examined.

Historically, it is easy to see how the term *hypoventilation* came to be applied so indiscriminately. When in the late 1950s it became possible to measure the P_{CO_2} of the arterial blood in the clinical setting, carbon dioxide retention was found to be a common and serious complication of chronic lung disease that could always be abolished by artificially increasing the ventilation. Thus, it was natural to say that these patients had an abnormally low ventilation, and the term *hypoventilation* had the advantage of keeping an important therapeutic option in the forefront.

However, far from having a reduced ventilation, most of these patients are moving far more air into their alveoli than normal subjects. Indeed, all patients with chronic lung disease and ventilation-perfusion inequality who have a *normal* arterial P_{CO_2} *must* have *increased* the ventilation to their alveoli, and this applies to most patients with carbon dioxide retention as well.

Although patients with mismatched ventilation and blood flow can usually maintain a normal arterial P_{CO_2} by increasing the ventilation to the alveoli, this is much less effective at increasing the arterial P_{O_2}. The reason for the different behavior of the two gases lies in the different shapes of the carbon dioxide and oxygen dissociation curves. The carbon dioxide dissociation curve is almost straight in the physiologic range, with the result that an increase in ventilation raises the carbon dioxide output of lung units with both high and low ventilation-perfusion ratios. By contrast, the nonlinearity of the oxygen dissociation curve means that only units with moderately low ventilation-perfusion ratios benefit appreciably from the increased ventilation. Those units that are very high on the flat portion of the dissociation curve (high ventilation-perfusion ratio) increase the oxygen concentration of their effluent blood very little. Furthermore, those units that have a very low ventilation-perfusion ratio continue to put out blood having an oxygen concentration close to that of mixed venous blood. The net result is that the mixed arterial P_{O_2} rises only modestly, and some hypoxemia always remains.

In summary, carbon dioxide retention can result from two clearly distinct mechanisms: pure hypoventilation, and ventilation-perfusion inequality. The latter is a common cause in clinical practice.

Effect of Changes in Cardiac Output on Gas Exchange in the Presence of Ventilation-Perfusion Inequality

In a lung with no ventilation-perfusion inequality, the cardiac output has no effect on arterial P_{O_2} or P_{CO_2}. This follows from Equations 5 and 14, which do not contain cardiac output. By contrast, these equations show that the level of total ventilation is very important.

However, in a lung with ventilation-perfusion inequality, cardiac output can have a major effect on arterial P_{O_2}, and this is important in some clinical settings. A reduction in cardiac output reduces the P_{O_2} of mixed venous blood, which in turn exaggerates the hypoxemia. This sometimes occurs in patients with myocardial infarction, in whom the reduction in arterial P_{O_2} seems to be out of proportion to the degree of ventilation-perfusion inequality because of the reduced cardiac output. The opposite is sometimes seen in patients with bronchial asthma, who may have unusually high cardiac outputs, especially when treated with some β-agonist drugs. The result is that the arterial P_{O_2} is higher than would be expected from the degree of ventilation-perfusion inequality. This important effect of cardiac output on gas exchange is often overlooked in the clinical setting.

Blood-Gas Transport

Oxygen

Oxygen is carried in the blood in two forms. A small amount is dissolved, but by far the most important component is in combination with hemoglobin.

Dissolved oxygen plays a small role in oxygen transport because its solubility is so low (0.003 mL O_2/100 mL blood/mm Hg). Thus, normal arterial blood with a P_{O_2} of about 100 mm Hg contains only 0.3 mL of dissolved oxygen per 100 mL, whereas about 20 mL is combined with hemoglobin.

Dissolved oxygen can become important under some conditions. The most common is when a patient is given 100% oxygen to breathe. This typically raises the alveolar P_{O_2} to over 600 mm Hg, with the result that, if the lungs are normal, the dissolved oxygen may increase from 0.3 to approximately 2 mL/100 mL blood. This dissolved oxygen then becomes a significant proportion of the normal arterial-venous oxygen concentration difference of about 5 mL O_2/100 mL blood.

Hemoglobin consists of heme, an iron-porphyrin compound, and a protein (globin) that has four polypeptide chains. There are two types of chains, alpha and beta, and differences in their amino acid sequences give rise to different types of human hemoglobin. The newborn infant has predominantly hemoglobin F (fetal), and this is gradually replaced over the first year or so of postnatal life. Hemoglobin S (sickle) has valine instead of glutamic acid in the beta chains. As a consequence, the affinity of hemoglobin for oxygen is reduced, and, in addition, the deoxygenated form tends to crystallize within the red cell. This causes the cell shape to change from biconcave to sickle, and the result is an increased fragility and likelihood of thrombus formation. Many abnormal hemoglobins with altered oxygen affinities have been described.

Methemoglobin is formed when the ferrous ion of normal hemoglobin A is oxidized to the ferric form. This can occur as a result of various drugs and chemicals, including nitrites, sulfonamides, and acetanilid. In one form of hereditary methemoglobinemia, there is a deficiency of the enzyme cytochrome b_5 reductase within the red cell. Methemoglobin is not useful for carrying oxygen, and, in addition, it increases the oxygen affinity of the remaining hemoglobin, thus impairing the unloading of oxygen to the tissues.

Blood is able to transport large amounts of oxygen because that molecule forms an easily reversible combination with hemoglobin (Hb) to give oxyhemoglobin (HbO_2):

$$O_2 + Hb \rightleftharpoons HbO_2 \tag{33}$$

The relationship between the partial pressure of oxygen and the number of binding sites of the hemoglobin that have oxygen attached is known as the *oxygen dissociation curve* (Fig. 4-25). Each gram of pure hemoglobin can combine with 1.39 mL of oxygen, and in normal blood with 15 g Hb/100 mL, the *oxygen capacity* (when all the binding sites are full) is 1.39 × 15, or about

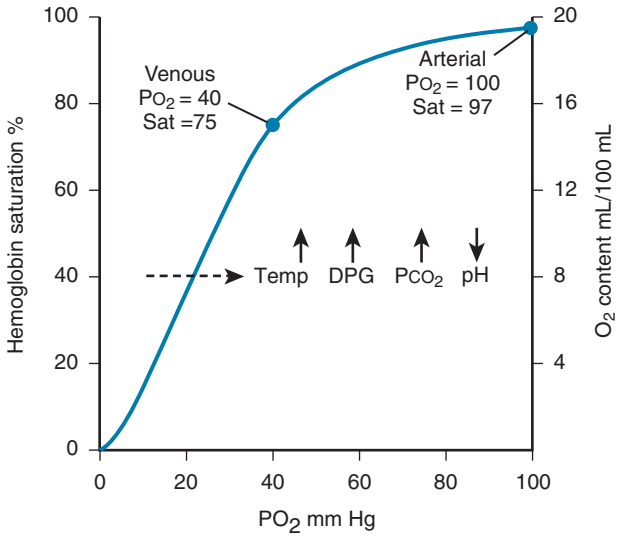

FIGURE 4-25 ■ Oxygen dissociation curve showing typical values for arterial and mixed venous blood. The curve is shifted to the right by increases of temperature, P_{CO_2}, 2,3-diphosphoglycerate (DPG), and H^+ concentration. Sat, saturation. (Redrawn from West JB: Respiratory Physiology—The Essentials [8th ed]. Baltimore: Lippincott Williams & Wilkins, 2008.)

20.8 mL O_2/100 mL of blood. The total *oxygen concentration* of a sample of blood, which includes the oxygen combined with hemoglobin and the dissolved oxygen, is given by

$$O_2 \text{ concentration} = (1.39 \times Hb) \times \frac{\% \text{ saturation}}{100} + (0.003 \times P_{O_2}) \quad (34)$$

where Hb is the hemoglobin concentration.

The characteristic shape of the oxygen dissociation curve has several advantages. The fact that the upper portion is almost flat means that a fall of 20 to 30 mm Hg in arterial P_{O_2} in a healthy subject with an initially normal value (e.g., about 100 mm Hg) causes only a minor reduction in arterial oxygen concentration. However, this also means that noninvasive monitoring of oxygen saturation by pulse oximetry will often fail to indicate substantial falls in arterial P_{O_2}. Another consequence of the flat upper part of the curve is that the diffusive loading of oxygen in the pulmonary capillary is hastened. This results from the large partial pressure difference between alveolar gas and capillary blood that continues to exist even when most of the oxygen has been loaded. The steep lower part of the oxygen dissociation curve means that considerable amounts of oxygen can be unloaded to the peripheral tissues with only a relatively small drop in capillary P_{O_2}. This maintains a large partial pressure difference between the blood and the tissues, which assists in the diffusion process.

Cyanosis refers to the blue color of skin and mucous membranes when the hemoglobin is desaturated. It is not a reliable sign of hypoxemia; if hypoxemia is suspected, the arterial P_{O_2} should be measured. Cyanosis depends on the amount of reduced hemoglobin present and therefore is often marked in patients with polycythemia but is difficult to detect in the presence of anemia. Various factors affect the position of the oxygen dissociation curve (see Fig. 4-25). It is shifted to the right by an increase of temperature, hydrogen ion concentration, P_{CO_2}, and concentration of 2,3-diphosphoglycerate in the red cell. A rightward shift indicates that the affinity of oxygen for hemoglobin is reduced. Most of the effect of the increased P_{CO_2} in reducing the oxygen affinity is due to the increased H^+ concentration. This is called the *Bohr effect,* and one consequence is that, as peripheral blood loads carbon dioxide, the unloading of oxygen is assisted.

2,3-Diphosphoglycerate is an end product of red cell metabolism.[102,103] Conditions in which its concentration is changed include chronic hypoxia, which tends to increase the concentration. The concentration falls in stored blood. A useful measure of the position of the dissociation curve is the P_{O_2} for 50% oxygen saturation; this is known as the P_{50}. The normal value for human blood is about 27 mm Hg.

Small amounts of carbon monoxide in the blood increase the affinity of the remaining oxygen for hemoglobin and therefore cause a leftward shift of the dissociation curve. As a result, the unloading of oxygen in the peripheral tissue is hampered. In addition, of course, the oxygen concentration of the blood is reduced because some of the hemoglobin is bound to carbon monoxide.

Carbon Dioxide

Carbon dioxide is transported in the blood in three forms: dissolved (about 5% of the total), as bicarbonate (about 90%), and in combination with proteins as carbamino compounds (about 5%). Dissolved carbon dioxide obeys Henry's law, and because carbon dioxide is some 24 times more soluble than oxygen in blood, dissolved carbon dioxide plays a much more significant role in its carriage compared to oxygen. For example, about 10% of the carbon dioxide that evolves into the alveolar gas from the mixed venous blood comes from the dissolved form.

Bicarbonate is formed in blood by the following hydration reaction:

$$CO_2 + H_2O \overset{CA}{\rightleftharpoons} H_2CO_3 \rightleftharpoons H^+ + HCO_3^- \quad (35)$$

The hydration of carbon dioxide to carbonic acid (and vice versa) is catalyzed by the enzyme carbonic anhydrase (CA), which is present in high concentrations in the red cells but is absent from the plasma (some carbonic anhydrase is apparently located on the surface of the endothelial cells of the pulmonary capillaries). Because the majority of the carbonic anhydrase is in the red cell, most of the hydration of carbon dioxide occurs there, and bicarbonate ion moves out of the red cell to be replaced by chloride ions to maintain electrical neutrality (chloride shift). Some of the hydrogen ions formed in the red cell are bound to hemoglobin, and because reduced hemoglobin is a better proton acceptor

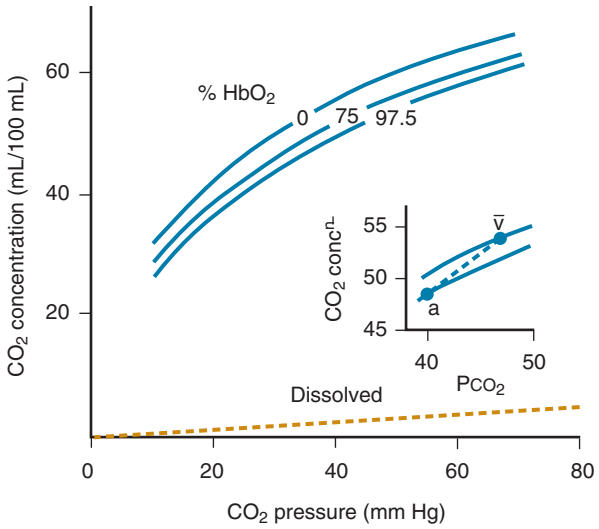

FIGURE 4-26 ■ Carbon dioxide dissociation curves for blood of different oxygen saturations (HbO_2). *Inset,* The "physiologic curve" between arterial (a) and mixed venous ($\bar{v}$) blood. (Redrawn from West JB: Respiratory Physiology—The Essentials [8th ed]. Baltimore: Lippincott Williams & Wilkins, 2008.)

than the oxygenated form, deoxygenated blood can carry more carbon dioxide for a given P_{CO_2} than oxygenated blood can (Fig. 4-26). This is known as the *Haldane effect.*

Carbamino compounds are formed when carbon dioxide combines with the terminal amine groups of blood proteins. The most important protein is the globin of hemoglobin. Reduced hemoglobin can bind more carbon dioxide than oxygenated hemoglobin, so the unloading of oxygen in peripheral capillaries facilitates the loading of carbon dioxide, whereas oxygenation has the opposite effect.

The carbon dioxide dissociation curve, that is, the relationship between P_{CO_2} and total carbon dioxide concentration, is shown in Figure 4-26. Note that the curve is much more linear in its working range than the oxygen dissociation curve (see Fig. 4-25) and also that, as we have seen, the lower the saturation of hemoglobin with oxygen, the larger the carbon dioxide concentration for a given P_{CO_2}.

The transport of carbon dioxide by the blood plays an important role in the acid-base status of the body. This topic is discussed at length in Chapter 7.

KEY POINTS

- The magnitudes of ventilation and perfusion, as well as their distribution, are key factors determining pulmonary gas exchange.
- Distribution of ventilation is predominantly affected by gravity in the normal lung, but intrinsic lung structure also plays a role.
- Distribution of perfusion is likewise mainly determined by gravity but intrinsic lung structure is also important.
- Distribution of ventilation-perfusion $(\dot{V}_A/\dot{Q})$ ratios is accordingly also nonuniform, the $\dot{V}_A/\dot{Q}$ ratio being generally higher in nondependent lung regions and lower in dependent lung regions.
- Regional alveolar P_{O_2} and P_{CO_2} are determined principally by the $\dot{V}_A/\dot{Q}$ ratio of each region. Secondary factors are the P_{O_2} and P_{CO_2} of inspired gas and mixed venous blood, and also the O_2 and CO_2 dissociation curves.
- Diffusion limitation is determined by the value of $D/\dot{Q}\beta$—the ratio of diffusing capacity (D) to the product of β (slope of the oxygen-hemoglobin dissociation curve) and $\dot{Q}$ (pulmonary blood flow). Its role in contributing to hypoxemia in lung disease is minor compared with $\dot{V}_A/\dot{Q}$ inequality.
- There are four causes of hypoxemia: hypoventilation, alveolar-capillary diffusion limitation, shunt, and $\dot{V}_A/\dot{Q}$.
- There are two principal causes of hypercapnia: hypoventilation and $\dot{V}_A/\dot{Q}$ inequality.
- $\dot{V}_A/\dot{Q}$ inequality is the most important cause of gas-exchange abnormalities in most lung diseases.

References

1. Weibel ER: Morphometry of the Human Lung. Berlin: Springer-Verlag, 1963.
2. Horsfield K: Pulmonary airways and blood vessels considered as confluent trees. *In* Crystal RG, West JB, Barnes PJ, Weibel ER (eds): The Lung: Scientific Foundations (2nd ed). New York: Raven Press, 1997, pp 1073–1079.
3. Fowler WS: Lung function studies. II. The respiratory dead space. Am J Physiol 154:405–416, 1948.
4. Milic-Emili J, Henderson JAM, Dolovich MB, et al: Regional distribution of inspired gas in the lungs. J Appl Physiol 21:749–759, 1966.
5. West JB: Distortion of the lung within the chest. Fed Proc 38:11–16, 1979.
6. Marcucci C, Nyhan D, Simon BA: Distribution of pulmonary ventilation using Xe-enhanced computed tomography in prone and supine dogs. J Appl Physiol 90:421–430, 2001.
7. Altes TA, Rehm PK, Harrell FEA: Ventilation imaging of the lung: comparison of hyperpolarized helium-3 MR imaging with Xe-133 scintigraphy. Acad Radiol 11:729–734, 2004.

8. Guy HJ, Prisk GK, Elliott AR, et al: Inhomogeneity of pulmonary ventilation during sustained microgravity as determined by single-breath washouts. J Appl Physiol 76:1719–1729, 1994.
9. Prisk GK, Guy HJ, Elliott AR, et al: Ventilatory inhomogeneity determined from multiple-breath washouts during sustained microgravity on Spacelab ShS-1. J Appl Physiol 78:597–607, 1995.
10. Otis AB, McKerrow CB, Bartlett RA, et al: Mechanical factors in distribution of pulmonary ventilation. J Appl Physiol 8:427–443, 1956.
11. Paiva M: Uneven ventilation. *In* Crystal RG, West JB, Barnes PJ, Weibel ER (eds): The Lung: Scientific Foundations (2nd ed). New York: Raven Press, 1997, pp 1403–1413.
12. Brody JS, Stemmler EJ, Dubois AB: Longitudinal distribution of vascular resistance in the pulmonary arteries, capillaries and veins. J Clin Invest 47:783–799, 1968.
13. Bhattacharya J, Nanjo S, Staub NC: Micropuncture measurement of lung microvascular pressure during 5-HT infusion. J Appl Physiol 52:633–637, 1982.
14. Bhattacharya J, Nanjo S, Staub NC: Factors affecting lung microvascular pressure. Ann N Y Acad Sci 384:107–114, 1982.
15. Lee GD, Dubois AB: Pulmonary capillary blood flow in man. J Clin Invest 34:1380–1390, 1955.
16. Pain MCF, West JB: Effect of the volume history of the isolated lung on distribution of blood flow. J Appl Physiol 21:1545–1550, 1966.
17. Glazier JB, Hughes JMB, Maloney JE, West JB: Measurements of capillary dimensions and blood volume in rapidly frozen lungs. J Appl Physiol 26:65–76, 1969.
18. Drinker CK: Pulmonary Edema and Inflammation. Cambridge, MA: Harvard University Press, 1945.
19. Staub NC: Pulmonary edema. Physiol Rev 54:678–811, 1974.
20. Taylor AE, Adkins WK, Khimenko PL, et al: Fluid balance. *In* Crystal RG, West JB, Barnes PJ, Weibel ER (eds): The Lung: Scientific Foundations (2nd ed). New York: Raven Press, 1997, pp 1549–1566.
21. Warrell DA, Evans JW, Clarke RO, et al: Pattern of filling in the pulmonary capillary bed. J Appl Physiol 32:346–356, 1972.
22. West JB, Schneider AM, Mitchell MM: Recruitment in networks of pulmonary capillaries. J Appl Physiol 39:976–984, 1975.
23. West JB, Dollery CT: Distribution of blood flow and the pressure-flow relations of the whole lung. J Appl Physiol 20:175–183, 1965.
24. Rudolph AM, Auld PAM: Physical factors affecting normal and serotonin-constricted pulmonary vessels. Am J Physiol 198:863–872, 1960.
25. Kapanci Y, Assimacopoulos A, Irle C, et al: "Contractile interstitial cells" in pulmonary alveolar septa: A possible regulator of ventilation/perfusion ratio? J Cell Biol 60:375–392, 1974.
26. Mazzone RW: Influence of vascular and transpulmonary pressures on the functional morphology of the pulmonary microcirculation. Microvasc Res 20:295–306, 1980.
27. Lock JE, Olley PM, Coceani F: Direct pulmonary vascular responses to prostaglandins in the conscious newborn lamb. Am J Physiol 238:H631–H638, 1980.
28. West JB, Dollery CT, Heard BE: Increased pulmonary vascular resistance in the dependent zone of the isolated dog lung caused by perivascular edema. Circ Res 17:191–206, 1965.
29. Muir AL, Hogg JC, Naimark A, et al: Effect of alveolar liquid on distribution of blood flow in dog lungs. J Appl Physiol 39:885–890, 1975.
30. Mai VM, Berr SS: MR perfusion imaging of pulmonary parenchyma using pulsed arterial spin labeling techniques: FAIRER and FAIR. J Magn Reson Imaging 9:483–487, 1999.
31. West JB, Dollery CT: Distribution of blood flow and ventilation/perfusion ratio in the lung, measured with radioactive CO_2. J Appl Physiol 15:405–410, 1960.
32. West JB, Dollery CT: Distribution of blood flow in isolated lung: relation to vascular and alveolar pressures. J Appl Physiol 19:713–724, 1964.
33. Permutt S, Bromberger-Barnea B, Bane HN: Alveolar pressure, pulmonary venous pressure and the vascular waterfall. Med Thorac 19:239–260, 1962.
34. Banister J, Torrance RW: The effects of the tracheal pressure upon flow: Pressure relations in the vascular bed of isolated lungs. Q J Exp Physiol 45:352–367, 2003.
35. Hughes JMB, Glazier JB, Maloney JE, West JB: Effect of lung volume on the distribution of pulmonary blood flow in man. Respir Physiol 4:58–72, 1968.
36. Hughes JMB, Glazier JB, Maloney JE, West JB: Effect of extra-alveolar vessels on distribution of blood flow in the dog lung. J Appl Physiol 25:701–712, 1968.
37. Dollery CT, West JB: Regional uptake of radioactive oxygen, carbon monoxide and carbon dioxide in the lungs of patients with mitral stenosis. Circ Res 8:765–771, 1960.
38. Glaister DH: Effect of acceleration. *In* West JB (ed): Regional Differences in the Lung. New York: Academic Press, 1977, pp 323–379.
39. Prisk GK, Guy HJB, Elliott AR, West JB: Inhomogeneity of pulmonary perfusion during sustained microgravity on SLS-1. J Appl Physiol 76:1730–1738, 1994.
40. Beck KC, Rehder K: Differences in regional vascular conductances in isolated dog lungs. J Appl Physiol 61:530–538, 1986.
41. Hakim TS, Lisbona R, Dean GW: Gravity-independent inequality in pulmonary blood flow in humans. J Appl Physiol 63:1114–1121, 1987.
42. Wagner PD, McRae J, Read J: Stratified distribution of blood flow in secondary lobule of the rat lung. J Appl Physiol 22:1115–1123, 1967.
43. Ewan PW, Jones HA, Nosil J, et al: Uneven perfusion and ventilation within lung regions studied with nitrogen-13. Respir Physiol 34:45–59, 1978.
44. Glenny RW, Robertson HT: Fractal modeling of pulmonary blood flow heterogeneity. J Appl Physiol 70:1024–1030, 1991.
45. Dollery CT, West JB, Wilken DEL, et al: Regional pulmonary blood flow in patients with circulatory shunts. Br Heart J 23:225–235, 1961.
46. Duke HN: Site of action of anoxia on the pulmonary blood vessels of the cat. J Physiol (Lond) 125:373–382, 1954.
47. Barer GR, Howard P, Shaw JW: Stimulus-response curves for the pulmonary vascular bed to hypoxia and hypercapnia. J Physiol (Lond) 211:139–155, 1970.
48. Grant BJB, Davies EE, Jones HA, Hughes JMB: Local regulation of pulmonary blood flow and ventilation/perfusion ratios in the coati mundi. J Appl Physiol 40:216–228, 1976.
49. Kato M, Staub NC: Response of small pulmonary arteries to unilobar hypoxia and hypercapnia. Circ Res 14:426–440, 1966.
50. Dawson CA, Bronikowski TA, Linehan JH, Hakim TS: Influence of pulmonary vasoconstriction on lung water and perfusion heterogeneity. J Appl Physiol 54:654–660, 1983.
51. Lehr AE, Tuller MA, Fisher LE, et al: Induced changes in the pattern of pulmonary blood flow in rabbit. Circ Res 13:119–131, 1963.
52. Hultgren HN: High altitude pulmonary edema. *In* Staub NC (ed): Lung Water and Solute Exchange (Vol 7). New York: Marcel Dekker, 1978, pp 437–469.
53. Post JM, Hume JR, Archer SL, Weir EK: Direct role for potassium channel inhibition in hypoxic pulmonary vasoconstriction. Am J Physiol Cell Physiol 262:C882–C890, 1992.
54. Yuan XJ, Goldman WF, Tod ML, et al: Hypoxia reduces potassium currents in cultured rat pulmonary but not mesenteric arterial myocytes. Am J Physiol 264:L116–L123, 1993.
55. Sweeney M, Yuan XJ: Hypoxic pulmonary vasoconstriction: Role of voltage-gated potassium channels. Respir Res 1:40–48, 2000.
56. Mandegar M, Remillard CV, Yuan XJ: Ion channels in pulmonary arterial hypertension. Prog Cardiovasc Dis 45:81–114, 2002.
57. Frostell C, Fratacci M-D, Wain JC, et al: Inhaled nitric oxide: A selective pulmonary vasodilator reversing hypoxic pulmonary vasoconstriction. Circulation 83:2038–2047, 1991.
58. Miyauchi T, Masaki T: Pathophysiology of endothelin in the cardiovascular system. Annu Rev Physiol 61:391–415, 1999.
59. Tai E, Read J: Response of blood gas tension to aminophylline and isoprenaline in patients with asthma. Thorax 22:543–549, 1967.
60. Knudson RJ, Constantine HP: An effect of isoproterenol on ventilation/perfusion in asthmatic versus normal subjects. J Appl Physiol 22:402–406, 1967.
61. Groves BM, Reeves JT, Sutton JR, et al: Operation Everest II: elevated high-altitude pulmonary resistance unresponsive to oxygen. J Appl Physiol 63:521–530, 1987.

62. Rodman DM, Voelkel NF: Regulation of vascular tone. *In* Crystal RA, West JB, Barnes PJ, Weibel ER (eds): The Lung: Scientific Foundations (2nd ed), New York: Raven Press, 1997, pp 1473–1492.
63. Tsukimoto K, Mathieu-Costello O, Prediletto R, et al: Ultrastructural appearances of pulmonary capillaries at high transmural pressures. J Appl Physiol 71:573–582, 1991.
64. West JB, Mathieu-Costello O: Structure, strength, failure and remodeling of pulmonary capillaries. Annu Rev Physiol 61:543–572, 1999.
65. West JB: Left ventricular filling pressures during exercise: A cardiological blind spot? Chest 113:1695–1697, 1998.
66. West JB, Mathieu-Costello O: Stress failure of pulmonary capillaries. *In* Crystal RG, West JB, Barnes PJ, Weibel E (eds): The Lung: Scientific Foundations (2nd ed). New York: Raven Press, 1997, pp 1493–1501.
67. West JB, Mathieu-Costello O: High altitude pulmonary edema is caused by stress failure of pulmonary capillaries. Int J Sports Med 13:S54–S58, 1992.
68. West JB, Colice GL, Lee YJ, et al: Pathogenesis of high-altitude pulmonary oedema: direct evidence of stress failure of pulmonary capillaries [see comments]. Eur Respir J 8:523–529, 1995.
69. West JB, Mathieu-Costello O, Jones JH, et al: Stress failure of pulmonary capillaries in racehorses with exercise-induced pulmonary hemorrhage. J Appl Physiol 75:1097–1109, 1993.
70. Hopkins SR, Schoene RB, Henderson WR, et al: Intense exercise impairs the integrity of the pulmonary blood-gas barrier in elite athletes. Am J Respir Crit Care Med 155:1090–1094, 1997.
71. West JB: Vulnerability of pulmonary capillaries during exercise. Exerc Sports Sci Rev 32:24–30, 2004.
72. Hopkins SR, Schoene RB, Henderson WR, et al: Sustained submaximal exercise does not alter the integrity of the lung blood-gas barrier. J Appl Physiol 84:1185–1189, 1998.
73. Fu Z, Costello ML, Tsukimoto K, et al: High lung volume increases stress failure in pulmonary capillaries. J Appl Physiol 73:123–133, 1992.
74. Silverman ES, Gerritsen ME, Collins T: Metabolic functions of the pulmonary endothelium. *In* Crystal RG, West JB, Barnes PJ, Weibel E (eds): The Lung: Scientific Foundations (2nd ed). New York: Raven Press, 1997, pp 629–651.
75. Marshall RP: The pulmonary renin-angiotensin system. Curr Pharm Design 9:715–722, 2003.
76. Farhi LE, Rahn H: Gas stores of the body and the unsteady state. J Appl Physiol 7:472–484, 1955.
77. Bohr C: Uber die spezitische tatigkeit der lungen bei der respiratorischen gasaufnahme und ihr verhalten zu der durch die alveolarwand stattfindenden gasdiffusion. Scand Arch Physiol 22:221–280, 1909.
78. Wagner PD, West JB: Effects of diffusion impairment on O_2 and CO_2 time courses in pulmonary capillaries. J Appl Physiol 33:62–71, 1972.
79. Roughton FJW: The average time spent by the blood in the human lung capillary and its relation to the rates of CO uptake and elimination in man. Am J Physiol 45:621–633, 1945.
80. Scheid P, Piiper J: Diffusion. *In* Crystal RG, West JB, Barnes PJ, Weibel E (eds): The Lung: Scientific Foundations (2nd ed). New York: Raven Press, 1997, pp 1681–1691.
81. West JB, Lahiri S, Gill MB, et al: Arterial oxygen saturation during exercise at high altitude. J Appl Physiol 17:617–621, 1962.
82. Wagner PD, Sutton JR, Reeves JT, et al: Operation Everest II: pulmonary gas exchange during a simulated ascent of Mt. Everest. J Appl Physiol 63:2348–2359, 1987.
83. Roughton FJW, Forster RE: Relative importance of diffusion and chemical reaction rates determining rate of exchange of gases in the human lung with special reference to true diffusing capacity of pulmonary membrane and volume of blood in the lung capillaries. J Appl Physiol 11:290–302, 1957.
84. Cotes JE: Lung Function: Assessment and Application in Medicine. Oxford, UK: Blackwell Scientific Publications, 1965, p 232.
85. Krogh A, Lindhard J: The volume of the dead space in breathing and the mixing of gases in the lungs in man. J Physiol (Lond) 51:59–90, 1917.
86. Haldane JS: Respiration. New Haven, CT: Yale University Press, 1922.
87. Fenn WO, Rahn H, Otis AB: A theoretical study of composition of alveolar air at altitude. Am J Physiol 146:637–653, 1946.
88. Riley RL, Cournand A: "Ideal" alveolar air and the analysis of ventilation/perfusion relationships in the lung. J Appl Physiol 1:825–847, 1949.
89. Kelman GR: Calculation of certain indices of cardio-pulmonary function using a digital computer. Respir Physiol 1:335–343, 1966.
90. Olszowka AJ, Farhi LE: A system of digital computer subroutines for blood gas calculations. Respir Physiol 4:270–280, 1968.
91. West JB: Ventilation/perfusion inequality and overall gas exchange in computer models of the lung. Respir Physiol 7:88–110, 1969.
92. Wagner PD, Saltzman HA, West JB: Measurement of continuous distributions of ventilation-perfusion ratios: Theory. J Appl Physiol 36:588–599, 1974.
93. Rahn H, Fenn WO: A Graphical Analysis of the Respiratory Gas Exchange. Washington, DC: American Physiological Society, 1955.
94. West JB: Ventilation/Blood Flow and Gas Exchange (5th ed). Oxford and Philadelphia: Blackwell Scientific Publications and Lippincott, 1990, pp 1–120.
95. West JB: Effect of slope and shape of dissociation curve on pulmonary gas exchange. Respir Physiol 8:66–85, 1969.
96. Kety SS: The theory and applications of the exchange of inert gas at the lungs and tissues. Pharmacol Rev 3:1–41, 1951.
97. Farhi LE: Elimination of inert gas by the lungs. Respir Physiol 3:1–11, 1967.
98. Evans JW, Wagner PD: Limits on VA/Q distributions from analysis of experimental inert gas elimination. J Appl Physiol 42:889–898, 1977.
99. Wagner PD, Laravuso RB, Uhl RR, West JB: Continuous distributions of ventilation-perfusion ratios in normal subjects breathing air and 100% O_2. J Clin Invest 54:54–68, 1974.
100. Wagner PD, Dantzker DR, Dueck R, et al: Ventilation-perfusion inequality in chronic obstructive pulmonary disease. J Clin Invest 59:203–216, 1977.
101. Wagner PD, Dantzker DR, Iacovoni VE, et al: Ventilation-perfusion inequality in asymptomatic asthma. Am Rev Respir Dis 118:511–524, 1978.
102. Benesch R, Benesch RE: Intracellular organic phosphates as regulators of oxygen release by hemoglobin. Nature 221:618–622, 1969.
103. Chanutin A, Curnish RR: Effect of organic and inorganic phosphates on the oxygen equilibrium of human erythrocytes. Arch Biochem 121:96–102, 1967.

CHAPTER 5

RESPIRATORY SYSTEM MECHANICS AND ENERGETICS

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INTRODUCTION

TERMINOLOGY
Flow
Volume
Pressure
Compliance and Resistance
Time Constants

RESPIRATORY MECHANICS IN STATIC CONDITIONS
Elastic Recoil of the Lungs
Elastic Recoil of the Chest Wall
Integration of Lung and Chest Wall Mechanics
Clinical Applications

THE RESPIRATORY SYSTEM IN DYNAMIC CONDITIONS
Resistive Work Due to Gas Flow through Airways
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Auto-PEEP during Positive-Pressure Ventilation of COPD

ENERGETICS AND WORK OF BREATHING
Measuring Work of Breathing Done by a Positive-Pressure Ventilator in a Paralyzed Patient
Measuring Work of Breathing in a Spontaneously Breathing Patient
Oxygen Cost of Breathing

INTRODUCTION

Respiration, defined as the transport of oxygen from air to tissues and the transport of carbon dioxide from tissues to the air, is essential for survival. One major component of the process of respiration is *ventilation*, which involves the movement of oxygen from the ambient air to the alveoli and of carbon dioxide in the other direction. An understanding of respiratory system mechanics and energetics is essential in understanding normal ventilation and its disruption in disease.

This chapter reviews basic terminology, respiratory mechanics under static conditions, mechanics under dynamic conditions, and energetics, including measurements of the work of breathing. The chapter also highlights how physiologic principles can be applied to specific clinical problems.

TERMINOLOGY

Flow

Flow is defined as the volume of gas passing a fixed point per unit time. Flow is distinctly different from *gas velocity*, which is the distance moved by a gas molecule per unit time. At a constant flow, gas velocity will be greater in narrower tubes (Fig. 5-1). Flow is usually measured with a pneumotachograph, which consists of a tube with a known fixed resistance. Flow can be calculated by measuring the pressure drop across the resistor.

Volume

Volume is defined by the space occupied by a gas. The number of molecules of a gas contained in a fixed volume

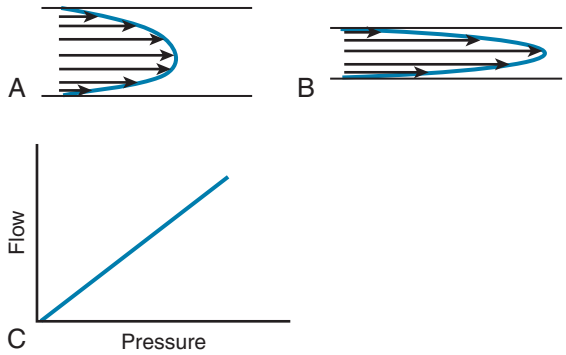

FIGURE 5-1 ■ Laminar flow through a tube. **A,** Schematic depiction of the spatial and velocity profiles of gas molecules within a laminar flow system. The velocity of the gas molecules is proportional to the length of *arrows*. For laminar flow, velocity is greatest in the center of the tube and least close to the edge. **B,** When tube diameter is reduced, the same gas flow rate will result in increased velocity of the individual gas molecules. **C,** During laminar flow, there is a linear relationship between pressure and flow.

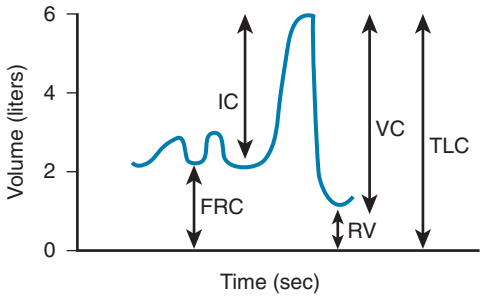

FIGURE 5-2 ■ Subdivisions of lung volume. Volume-time tracing of a subject taking two normal tidal breaths, inhaling to total lung capacity (TLC), and exhaling to residual volume (RV). Vital capacity (VC) and inspiratory capacity (IC) may be measured with a spirometer. The measurement of functional residual capacity (FRC), RV, and TLC requires a determination of intrathoracic gas volume by helium dilution, nitrogen washout, or plethysmography.

is influenced by temperature and pressure. For an ideal gas, the relationship between lung volume, pressure, temperature, and the number of molecules of gas is described by the combined gas law:

$$PV = nRT$$

where P is the absolute pressure of the gas, V is the volume, n is the number of moles of gas, R is the universal gas constant (8.3145 J/(mol K)), and T is the temperature in degrees Kelvin.

This equation summarizes earlier gas laws, including Boyle's law (PV = constant), Charles' law (V/T = constant), Gay-Lussac law (P/T = constant), and Avogadro's law (n/V = constant). The volume of a gas should thus increase as the number of molecules of gas increases, the temperature increases, or the applied pressure decreases. Although this equation theoretically applies only to an ideal or perfect gas, it is an adequate approximation for clinical purposes.

Lung volumes can be measured by a variety of techniques. The volume of gas entering and leaving the lung can be determined by a spirometer that measures volume displacement or by integrating flow over time using a pneumotachograph (flowmeter). Total gas volume in the lung can be measured using helium dilution or body plethysmography, and each of these techniques has advantages and disadvantages.[1] For the single-breath helium dilution technique, subjects inhale a fixed concentration of helium in a known volume; helium's low blood solubility allows it to be used as a tracer. The helium mixes with and is diluted by the gas already in the lung; the subject then exhales and the concentration of helium in the expired air is measured. The ratio of exhaled concentration to inhaled concentration allows calculation of the lung volume. The multiple-breath equilibrium technique is more reliable, although the concept is the same. With the multiple-breath technique, the patient breathes into a reservoir with a known helium concentration until the exhaled helium concentration reaches equilibrium. In general, helium dilution measurements tend to underestimate total lung volume, especially in patients with substantial airway obstruction who may have gas trapped in lung units that do not mix with inspired gas.

For the body plethysmography technique, subjects are completely enclosed in a gas-tight container. Lung volume can be calculated by comparing changes in alveolar pressure (measured at the mouth while the patient pants against an occluded mouthpiece) with changes in pressure in the container.[2] Body plethysmography may overestimate lung volumes, because it will include measurement of abdominal gas if that gas is compressed and decompressed during the panting maneuver.

Although not commonly used in clinical practice, lung volumes may also be measured using three-dimensional reconstructions of radiographic studies (chest roentgenography, computed tomography, or magnetic resonance imaging).[3–6] Changes in lung volumes can also be estimated using measurements of thoracic cage displacement with magnetometers or inductance plethysmography.[7,8]

The subdivisions of lung volumes are shown in Figure 5-2. Some of these subdivisions can be measured by spirometry alone (vital capacity, tidal volume), whereas others require use of helium dilution or plethysmography. *Total lung capacity* (TLC) is the lung volume at the end of a maximal inspiration. *Residual volume* (RV) is the volume at the end of a maximal expiratory effort. *Functional residual capacity* (FRC) refers to the volume in the lung at the end of a normal tidal exhalation, where there is relaxation of both inspiratory and expiratory muscles.

Pressure

The pressure of a gas is generated from the momentum of molecules colliding against a surface and is expressed as the force per unit area. Pressure, as opposed to force,

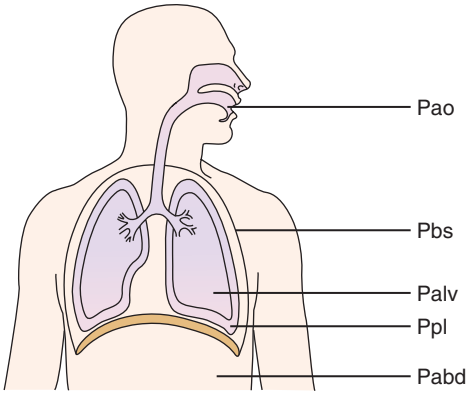

FIGURE 5-3 ■ Respiratory system pressures. Pao, pressure at airway opening; Pbs, pressure at body surface; Palv, pressure in alveolus; Ppl, pressure in pleural space; Pabd, pressure in abdomen. Transpulmonary pressure: Pao – Ppl; translung pressure: Palv – Ppl; transchest wall pressure: Ppl – Pbs; transrespiratory system pressure: Pao – Pbs; transdiaphragmatic pressure: Ppl – Pabd. Under static conditions, when the subject is not on assisted ventilation, Pao is equal to 0 (atmospheric pressure). However, Pao may be positive when the patient is receiving positive-pressure mechanical ventilation. Pbs is equivalent to atmospheric pressure unless the subject is in a negative pressure device such as an iron lung.

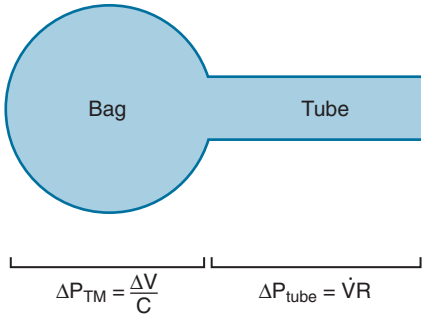

FIGURE 5-4 ■ Bag-and-tube analogy of the respiratory system, where ΔPtm = change in transmural pressure (inside – outside) of bag; ΔV = change in volume; C = compliance; $\dot{V}$ = flow; R = resistance; and ΔPtube = pressure difference from one end of the tube to the other.

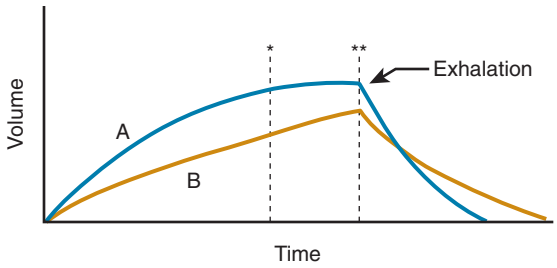

FIGURE 5-5 ■ Time constants. Shown are two units, one with a very short time constant, A, and one with a long time constant, B. Each is inflated under a constant pressure until point (**) and then exhalation is passive. At point **, unit A is completely filled, but unit B is not. Of note, decreasing inspiration time to point * will worsen heterogeneity in ventilation, when time constants are uneven.

is the same in all directions. Respiratory system pressures are usually reported relative to atmospheric pressure.

The pressures relevant to the respiratory system are shown in Figure 5-3. Pleural pressure can be measured directly, with a probe inserted directly into the pleural space. Esophageal pressure is usually used as a surrogate for pleural pressure because it is easier to measure using an air-filled balloon inserted into the esophagus.[9] The best place is in the middle third of the esophagus, approximately 35 to 45 cm from the nares.[10,11] Balloons placed in the proximal third can be affected by movement of the neck, and balloons placed in the distal third can record falsely high readings owing to compression by the heart. Absolute values of pressure may be difficult to interpret in the supine position owing to the weight of the mediastinum.

Compliance and Resistance

The respiratory system can be thought of as a combination of bags and tubes (Fig. 5-4). In its most simplistic form, the respiratory system can be compared with a single tube (representing the airways) attached to a single bag (representing the lung and chest wall).

As the pressure across the wall of a bag increases (called transmural pressure, or pressure inside minus pressure outside), the volume inside the bag increases until an equilibrium is reached (see Fig. 5-4). The ratio between the change in volume and the change in transmural pressure is the compliance of the bag. A large compliance indicates that volume changes markedly for every change in pressure. The inverse of compliance is elastance, with a greater value indicating a stiffer system.

In a tube, flow is proportional to the pressure difference between the two ends and inversely proportional to the resistance (flow = pressure difference/resistance) (see Fig. 5-4). Resistance, however, has a nonlinear relationship to diameter; reducing the diameter by half results in a 16-fold increase in resistance!

Time Constants

When a pressure is applied to a lung unit (Fig. 5-5), the time required to fill the unit is dependent on its compliance and resistance. That is, it will take longer to fill if resistance is high because the flow will be reduced. Similarly, it will take longer to fill the unit if compliance is high because it will require more volume. The product of the resistance and compliance (RC) of a lung unit is the time constant and represents the time required for the lung unit to fill to 63% of the final volume if a constant pressure is applied. Areas of the lung with small time constants (i.e., low resistance and/or low compliance) will fill more rapidly than areas with larger time constants.

The effect of variations in time constants of lung units is shown in Figure 5-5. This concept has clinical implications when there are heterogeneous time constants

between parallel lung units, as in patients with chronic airflow obstruction. As long as respiratory frequency is slow, all units will fill to their static equilibrium. However, if respiratory rate increases so that the inspiratory time becomes less than the time constant of some units, these units will receive less ventilation and contribute to ventilation-perfusion ($\dot{V}/\dot{Q}$) mismatch.

RESPIRATORY MECHANICS IN STATIC CONDITIONS

We first consider the lung during static conditions, during which measurements are made while the respiratory system is maintained at a fixed volume with no gas flow. Even under static or no-flow conditions, pressure gradients are still required to distend the respiratory system (analogous to the bag described previously). The energy used to distend the respiratory system (elastic work) during inhalation is stored as potential energy. Because of this stored energy, normal exhalation does not require work and is a passive process. This contrasts with resistive work (discussed later in this chapter), which cannot be stored as potential energy and is dissipated as heat.

The elastic work done against the respiratory system has both lung and chest wall components.

Elastic Recoil of the Lungs

If removed from the body, an isolated lung will deflate to a minimal volume containing only trapped gas, due to its elastic recoil. Because airways close before complete alveolar emptying, application of a negative pressure to the airway opening will not remove the trapped gas. Complete emptying of the trapped gas can be accomplished by exposing the isolated lung to a vacuum. The relationship between lung volume and transpulmonary pressure during inflation is shown in Figure 5-6. Lung compliance is fairly high at moderate lung volumes, but then decreases markedly near TLC. At this volume, very large increases in transmural pressure result in small changes in volume.

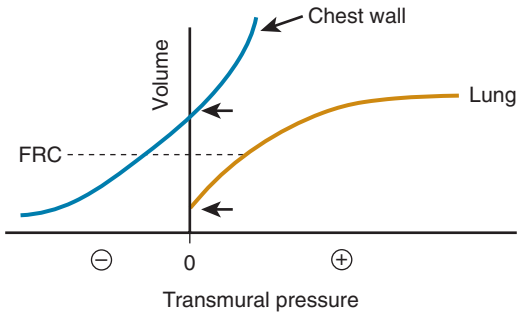

FIGURE 5-6 ■ Volume-pressure curves of lung and chest wall. The relationship between transmural (inside–outside) pressure of lung and relaxed chest wall volume are shown. At FRC, outward chest wall recoil is balanced by inward lung recoil. At FRC, transmural pressure for the lung = Pao – Ppl; because Ppl is negative, this yields a positive value. For the chest wall, transmural pressure = Ppl – Pbs, which yields a negative value. The static equilibrium of the chest wall is above FRC whereas that for the lung is below FRC (*arrows*).

Two major factors are responsible for the elastic recoil of the lung: (1) lung connective tissue and (2) surface tension related to the air-liquid interface of the alveolar surface.

Lung Connective Tissue

A network of connective tissue fibers provides the framework for the alveoli and structural integrity for the lung. The fibers are composed mostly of collagen and elastin. These fibers have different mechanical properties, which help to explain the shape of the pressure-volume curve of the lung.

Collagen fibers exhibit high tensile strength but are relatively noncompliant—they can be extended by only 2% of their length.[12] This contrasts with elastin, which has a lower tensile strength and is more compliant; elastin fibers can be stretched by as much as 130% of their length. Experiments using selective destruction of fibers by collagenase or elastase show that elastin fibers are the major contributors to the pressure-volume relationships at low lung volumes, whereas collagen is more important at higher volumes approaching TLC.[13,14] At low lung volumes, elastin fibers bear much of the stress and collagen fibers are curled and unstressed. As lung volume increases, collagen fibers uncurl and straighten and have a major stiffening effect on the lung. In other words, the major role of collagen is to limit overdistention of the lung, and the major role of elastin is to facilitate inflation while providing lung stability to maintain the configuration of internal structures.

Destruction of lung connective tissue, for instance from smoking-induced emphysema, can substantially increase lung compliance.[15] Contraction of smooth muscle in the airways and alveolar ducts may also affect elastic recoil, because contraction of smooth muscle reduces volume by exerting traction on the lung (similar to a drawstring).[16] The clinical importance of this effect in humans is unclear. Although contraction of airway smooth muscle in the peripheral lung units (small airways and alveolar ducts) changes lung compliance in several different animal species, there is little effect of contraction of lung smooth muscle on the shape of the pressure-volume curve in humans.[17-19]

Alveolar Surface Forces and Surfactant

When a lung is completely filled with water, compliance is much greater than when it is filled with air.[20] This suggests that the majority of lung elastic recoil is due to surface tension at the air-liquid interface lining the alveoli, rather than the recoil from elastin and collagen connective tissue fibers.

Because of intermolecular forces of attraction between molecules of liquids, the surface of an air-liquid interface is under tension (Fig. 5-7). That is, a molecule in the interior of a liquid is subjected to an equal force

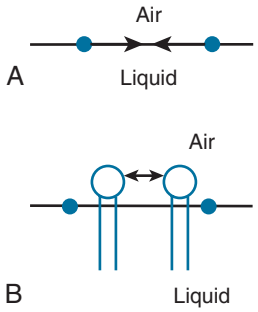

FIGURE 5-7 ■ Surface tension and surfactant. **A,** There is a force of attraction between water molecules at the surface (surface tension). **B,** Addition of surfactant reduces surface tension because charged molecules repel each other.

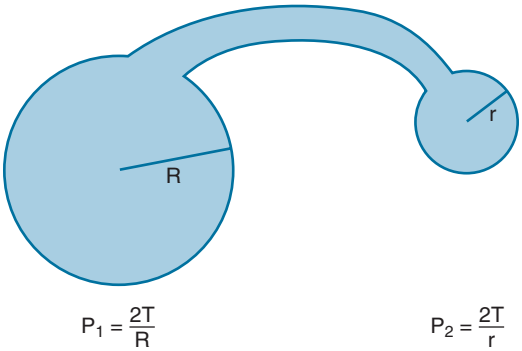

FIGURE 5-8 ■ Laplace's law. Consider two gas-filled fluid bubbles with equal surface tension (T) but differing radii, connected by a tube. Because of the smaller radius of curvature, P2 > P1, leading to gas flow from the smaller to the larger bubble.

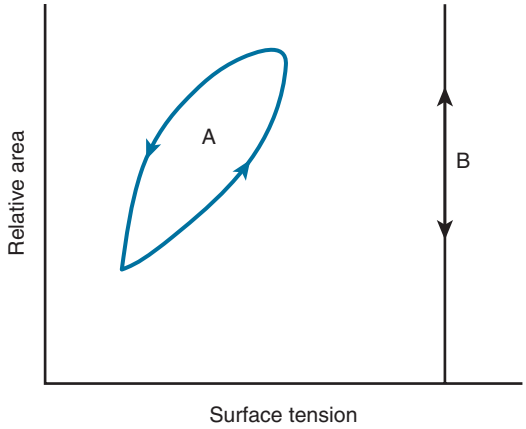

FIGURE 5-9 ■ Area–surface tension relationship. The surface area–tension relationship for lung washings containing surfactant is shown in the loop, A (with the *upward arrow* indicating inspiration and the *downward arrow* exhalation). As the area increases, surface tension increases. Also, the upward expansion and downward contraction demonstrate hysteresis of the area-tension relationship. This contrasts with the surface tension of water without surfactant, B, in which tension is greater but remains constant.

in all directions by other liquid molecules. However, the molecules at the surface are pulled toward each other and by molecules below the surface, and these forces (surface tension) cause a tendency for the surface to collapse.

Because of surface tension, a positive pressure must be present to prevent the collapse of a gas-filled bubble of liquid. The pressure of gas within a bubble is related to the surface tension (T) and the radius of curvature of the bubble (r) by the law of Laplace (P = 2T/r) (Fig. 5-8). The surface of the alveolus with an air-liquid interface can be likened to a bubble with a radius of approximately 0.1 mm at FRC. If the surface tension were similar to that of water (72 mN/m), the lungs would be very noncompliant and ventilation with transpulmonary pressures in the physiologic range (3-5 cm H_2O) would be impossible. Furthermore, the high surface tension would lead to alveolar instability and cause alveolar collapse. That is, smaller alveoli with smaller radii of curvature would, by the nature of the Laplace law, have higher alveolar pressures than larger alveoli with greater radii of curvature. Because gas travels from an area of higher pressure to one of lower pressure, smaller alveoli would tend to empty into larger alveoli, eventually resulting in one large air-filled alveolus with all other alveolar units collapsed.

A number of factors contribute to alveolar stability in normal lungs. First, the connective tissue scaffolding limits overdistention of alveoli. Second, alveoli are interconnected (alveolar interdependence) by common walls and structures. Therefore, if one alveolus began to collapse, it would stretch adjacent alveolar walls, creating a tethering effect on the collapsing unit. Third, surfactant has an important stabilizing effect.

Surfactant is a surface-active material secreted by type II alveolar epithelial cells.[21] Surfactant is composed predominantly of phospholipids such as phophatidyl choline, although other lipids, carbohydrates, and proteins are also present.[22] The phospholipids tend to aggregate at the air-liquid interface, with the hydrophobic ends (fatty acids) of the phospholipids projecting into the gas phase and the hydrophilic ends projecting into the alveolar-lining fluid. Because the hydrophilic ends are charged, the surfactant molecules tend to repel each other, thus reducing surface tension (see Fig. 5-7). Surfactant alters surface tension of alveolar-lining fluid, but does so in relation to the surface area (Fig. 5-9). That is, as surface area expands (e.g., during inhalation), surface tension increases, presumably because surfactant molecules are farther apart and exert less effect. Thus, in smaller alveoli (that have reduced surface area compared with larger alveoli), there is a greater reduction in surface tension, reducing gas pressure in these alveoli relative to larger alveoli. This stabilizes alveoli by helping to equalize pressures in alveoli of varying sizes (see Fig. 5-8).

In addition to surfactant lipids, there are four surfactant proteins (SP-A to -D). SP-B and SP-C are hydrophobic membrane proteins that enhance the spreading of surfactant over the alveolar surface and help to stabilize the lipid layer. SP-A and SP-D are involved in the innate immune response by binding to, and facilitating the phagocytosis of, bacteria and viruses.[23] Congenital deficiency of SP-B leads to progressive respiratory failure and

death in the first months of life.[24] Partial deficiency of SP-B has been associated with chronic interstitial lung disease in children,[25] whereas SP-C deficiency is associated with severe familial interstitial lung disease.[26]

Hysteresis and Stress Adaptation

When normal lungs are inflated and deflated slowly, the pressure-volume curves are not identical. During inflation of the lung, the pressure required at any given lung volume is greater than that during deflation (Fig. 5-10). The difference between the inflation and the deflation curves is due to hysteresis and stress adaptation.

Hysteresis refers to changes in mechanics measurements due to the volume-history of the lung and is caused by several factors. First, the effect of surfactant on surface tension is dependent on volume history (see Fig. 5-9). Surfactant has less effect on reducing surface tension during inspiration than during expiration. This is due to movement of surfactant molecules from below the surface of the fluid to the liquid surface during inhalation. Second, much higher pressures are required to open collapsed alveoli than are required to keep them open. In disease states characterized by collapse of alveoli (e.g., adult respiratory distress syndrome [ARDS]), significant hysteresis of the pressure volume curves can be seen[27] (see Fig. 5-10). This has clinical significance in patients with ARDS because higher inflation pressures are required to ventilate the lungs.

In contrast, *stress adaptation* refers to the time dependence of mechanics measurements. When lung tissue is stretched to a particular length, the tension required to maintain the length gradually diminishes due to time-dependent properties of surfactant and deformation of viscoelastic tissues of the lung. Therefore, after a sustained lung inflation, the pressure required to keep the lung at that volume will decrease.

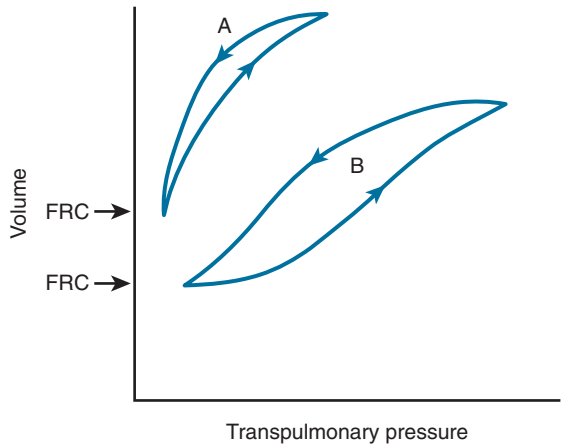

FIGURE 5-10 ■ Hysteresis in a normal lung and an acutely injured lung. In acute respiratory distress syndrome (ARDS), B, the lung is stiffer than the normal lung, A, and greater inflation pressure is required at any given lung volume. Furthermore, the degree of hystereis is much greater in ARDS lungs, with a greater separation of the volume-pressure curves on inspiration (*upward arrow*) and exhalation (*downward arrow*).

Recruitment Maneuvers in Acute Respiratory Distress Syndrome

ARDS is a disease characterized by surfactant dysfunction. The dysfunction of surfactant increases surface tension at the air-liquid interface of the alveoli, leading to collapse, intrapulmonary shunting, and hypoxemia.[28] Owing to alveolar collapse, hysteresis may be especially marked in patients with ARDS (see Fig. 5-10). The hysteresis and lung collapse necessitate high inflation pressures to ventilate the lungs, increasing work of breathing and potentially leading to barotrauma; low tidal volumes are used in ARDS to mitigate further lung injury.[29]

Because of this difference between opening and closing pressures, "recruitment maneuvers" have been used in ventilated patients with ARDS who remain hypoxemic despite moderate levels of externally applied positive end-expiratory pressure (PEEP).[30–32] A recruitment maneuver consists of a sustained inflation at a constant high pressure, which opens collapsed alveoli. Because closing pressures are much less than opening pressures, the alveoli stay open (at least temporarily) after the sustained inflation is ended, as long as the lung is not allowed to return to a very low volume (Fig. 5-11).

Elastic Recoil of the Chest Wall

The chest wall is made up of the rib cage laterally, the sternum anteriorly, the vertebral column posteriorly, and the diaphragm caudally. Movement of the chest wall by the muscles of ventilation generates pressure gradients between the alveoli and the surrounding air, enabling gas to be moved in and out of the lungs.

Respiratory Muscles

The diaphragm consists of two separate muscles joined by a central tendon. The crural diaphragm arises from the first three lumbar vertebrae and the medial and lateral arcuate ligaments. The costal diaphragm arises from the inner surfaces and upper margins of the lower six ribs and sternum. Both costal and crural fibers insert onto the central tendon. The phrenic nerve innervates the diaphragm, with costal fibers innervated from the 3rd and 4th cervical spinal segments, and crural fibers from the 4th and 5th segments. In normal subjects, the lower part of the rib cage encloses the upper part of the abdomen at FRC. In this area, the diaphragm is pushed against the lower rib cage (zone of apposition) with fibers arranged in a cranial-caudal direction (Fig. 5-12). Contraction of the diaphragm leads to a piston-like up-and-down motion of the diaphragm. Furthermore, diaphragm contraction leads to an increase in abdominal pressure, which pushes the rib cage upward and outward.[33,34]

In patients with substantial hyperinflation (e.g., emphysema), the position of the diaphragm is lower, with loss of the zone of apposition.[35] When the zone of apposition is lost, contraction of the diaphragm is less mechanically advantageous and can result in paradoxical inward movement of the lower rib cage during inhalation (Hoover's sign) and less piston-like motion of the

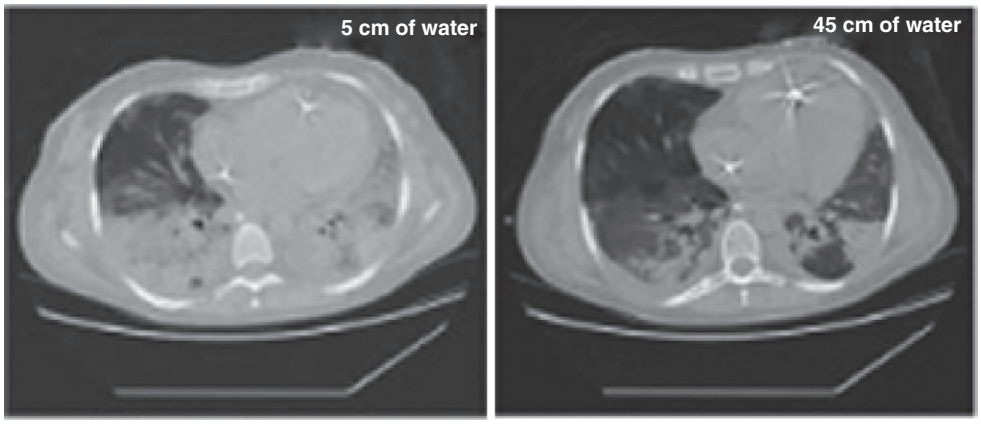

FIGURE 5-11 ■ Recruitment in ARDS. A slice of a computed tomography (CT) scan of the lung in a patient with ARDS at 5 cm H_2O airway pressure (*left*) and at 45 cm H_2O pressure (*right*) demonstrating lung recruitment with higher airway pressures. (From Gattinoni L, Caironi P, Cressoni M, et al: Lung recruitment in patients with the acute respiratory distress syndrome. N Engl J Med 354:1775–1786, 2006, with permission.)

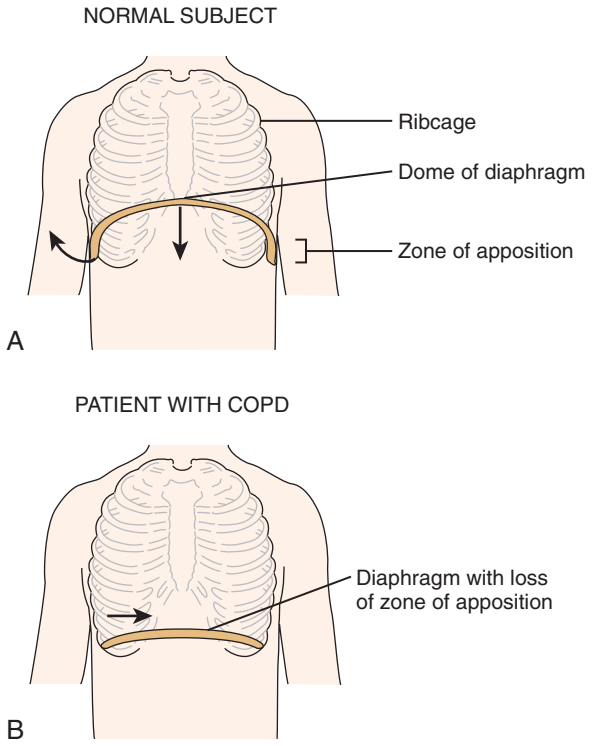

FIGURE 5-12 ■ Normal subject and patient with chronic obstructive pulmonary disease (COPD). **A,** In a normal subject, the lower part of the diaphragm lies next to the lower ribcage (zone of apposition). As indicated by the *arrows*, contraction of the diaphragm will pull the dome downward and push the lower rib cage upward and outward (due to increased abdominal pressure). **B,** In a patient with COPD and hyperinflation, there is loss of the zone of apposition. As indicated by the *arrow*, contraction of the diaphragm may lead to inward movement of the lower rib cage.

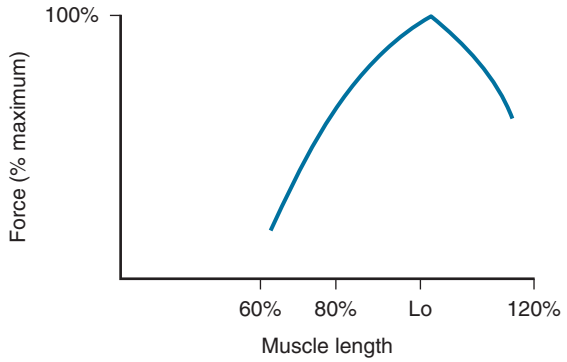

FIGURE 5-13 ■ Force-length characteristics of skeletal muscle. Skeletal muscle displays a characteristic force-length curve with a reduction in force generating capacity at lengths below or above optimal length (Lo).

diaphragm dome.[36] Furthermore, the length of the diaphragm is shortened, which creates a further mechanical disadvantage because the ability of the muscle to generate force is attenuated at shorter lengths (Fig. 5-13). However, in animals and humans, compensatory shortening of the diaphragm through loss of sarcomeres has been shown to mitigate these effects and help to improve the length-tension characteristics of the diaphragm.[37,38] The improved symptoms experienced by patients with COPD following lung volume reduction surgery may be related to increased length of the zone of apposition and improved mechanical function of the diaphragm.[39]

During inhalation, the rib cage moves laterally and anteriorly. The lateral movement and elevation of the ribs is akin to a "bucket-handle" motion, and the anterior motion of the sternum is akin to a "pump-handle" motion (Fig. 5-14). The muscles of the rib cage include the internal intercostal muscles, the external intercostal muscles, and the parasternal muscles. Internal intercostal muscles are used mainly for exhalation, while external muscles are used for inhalation.[40] The parasternal muscles are located next to the sternum; although they are part of the internal intercostal muscle layer, their major function is to raise the sternum during inhalation.[41]

Other muscles used in inhalation include the scalene muscles, which help to elevate the rib cage and prevent paradoxical inward movement of the upper rib cage with diaphragm displacement.[42] Under conditions of ventilatory stress, other muscles not normally used

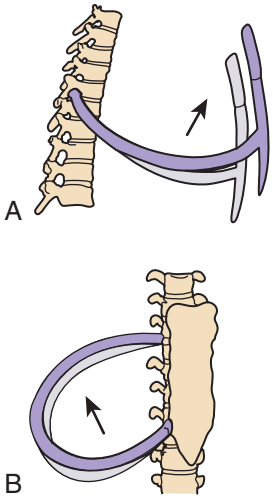

FIGURE 5-14 ■ Movement of rib cage during inspiration. Diagram indicating pump handle (**A**) and bucket-handle (**B**) rotations of the ribs. In both panels, the sternum and rib are shown before (*gray*) and after (*purple*) rib cage expansion. (From De Troyer A, Loring SH: Actions of the respiratory muscles. In Roussos C [ed]: The Thorax [Part A]. New York: Marcel Dekker, 1995, pp 535–563.)

for respiration can be recruited. These include the sternocleidomastoid, pectoralis, trapezius, and muscles of the vertebral column. Contraction of the muscles in the abdominal wall can be used to aid exhalation.

Fatigue of Respiratory Muscles

Skeletal muscle fatigue refers to a reduction in the force-generating capacity of the muscles after excessive activity that is recoverable by rest. This should be differentiated from *respiratory muscle injury*, in which there is also loss of force-generating capacity. Injured muscles do not recover quickly with rest, but may experience slow recovery of function due to regeneration.[43]

Fatigue occurs when the rate of work required by the muscles exceeds the rate of energy supply. Usually, there is substantial reserve of the respiratory muscles such that fatigue does not occur. However, under conditions of excessive elastic or resistive load (either experimentally induced or due to disease states) and/or inadequate energy supply (e.g., during hypoxemia or cardiogenic shock), fatigue occurs and impairs respiratory muscle performance.[44,45] Recovery from fatigue usually requires more than 24 hours of rest.[46]

One measure of workload of the diaphragm is the pressure-time index. This is the product of the percentage of maximal pressure (i.e., transdiaphragmatic pressure/maximal transdiaphragmatic pressure) exerted by the muscle multiplied by the percentage of time spent during inspiration (inspiratory time/total time). In normal subjects, a value greater than 0.15 to 0.18, if sustained, will lead to fatigue and loss of force-generating capacity of the diaphragm.[47]

Central respiratory fatigue occurs when there is a reduction in central motor output to the muscles. Central fatigue can be identified when direct electrical stimulation of respiratory muscles increases muscle force generation as compared with a maximal voluntary effort.[48] This may represent an attempt to prevent damage to the muscles under conditions of inadequate energy supply. Central fatigue should be differentiated from peripheral fatigue, which represents failure at or past the level of the neuromuscular junction. With peripheral fatigue, a reduction in force generation occurs despite a constant electrical stimulation. Peripheral fatigue may occur because of transmission failure at the neuromuscular junction, reduced adenosine triphosphate (ATP), reduced calcium availability from the sarcoplasmic reticulum, or reduced calcium sensitivity of the myofilaments (caused by acidosis or increased inorganic phosphate).[49]

Respiratory Muscle Atrophy during Positive-Pressure Mechanical Ventilation

Although excessive loading of the respiratory muscles can lead to fatigue and a reduction in force generation, excessive unloading of the muscle may lead to muscle atrophy. Mechanical ventilation in paralyzed rats and baboons leads to diaphragmatic atrophy.[50,51] Furthermore, human studies in organ donors have shown significant diaphragm atrophy after 18 to 69 hours of diaphragmatic inactivity.[52] However, the clinical significance of disuse atrophy in ventilated patients is still unclear. Patients who are not paralyzed may still have substantial activation of respiratory muscles while receiving mechanical ventilation,[53,54] and this degree of stimulation may be adequate to prevent atrophy.[55–57] Furthermore, other potential causes of muscle weakness or injury in the intensive care unit include electrolyte disturbances, malnutrition, medications and toxins (e.g., alcohol, corticosteroids, aminoglycosides), sepsis-related cytokines, and inflammatory disorders (e.g., polymyositis), so that attributing muscle weakness to atrophy of muscle fibers in the clinical setting is difficult.

Chest Wall Compliance

The compliance of the chest wall can be determined by measuring changes in the transmural pressure across the thorax (pleural pressure minus body surface pressure) relative to change in volume. The volume-pressure curve of the relaxed chest wall is shown in Figure 5-6. In contrast to the lung, the resting volume of the relaxed chest wall is approximately 1 L above FRC. The difference between the resting volume of the lung and chest wall can be appreciated in patients with a pneuomothorax, in which the chest wall recoils outward and the lung recoils inward. When the chest wall is distended above this resting volume, the relaxed chest wall recoils inward, while it recoils outward at volumes below this. The compliance of the normal chest wall is approximately 200 mL/cm H_2O, but it becomes progressively stiffer at lower lung volumes and it is this stiffness in normal young subjects that predominantly determines RV.[58]

Factors such as ossification of costal cartilage, arthritis of costovertebral joints, skin eschars from burns, obesity, and abdominal distention may reduce chest wall compli-

ance. Chest wall compliance increases in the sitting position compared with the supine position, but the overall effect is usually modest.[59]

Integration of Lung and Chest Wall Mechanics

The chest wall and lung are juxtaposed, and in the absence of pleural disease (such as pneumothorax or pleural fibrosis), changes in chest wall volume are essentially identical to changes in lung volume (Fig. 5-15). Furthermore, the chest wall and lung are linked by the pleural pressure, with the transmural pressure (inside minus outside pressure) of the chest wall equal to

Pleural pressure – Body surface pressure

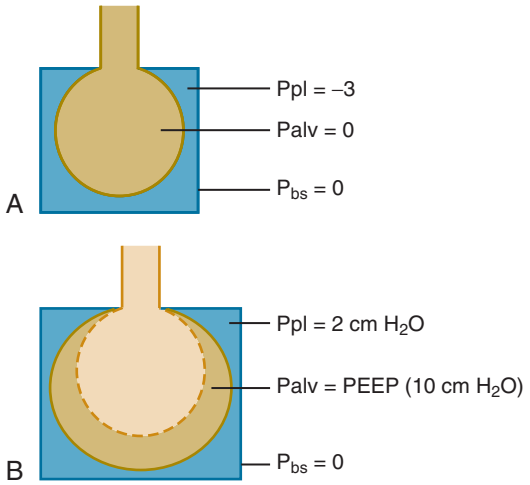

FIGURE 5-15 ■ Changes in pleural pressure with applied positive end-expiratory pressure (PEEP). **A,** Consider a lung at end-exhalation with no PEEP. **B,** With the application of PEEP, there is an increase in the volume of the respiratory system (lung and chest wall) and an increase in pleural pressure (Ppl). The magnitude of the increase in Ppl is dependent on the relative compliances of the lung and chest wall. Change in lung volume is the same as change in chest wall volume:

$$\Delta\text{Lung volume } (V_L) = \Delta\text{Chest wall volume } (V_{CW}).$$

Because compliance (C) = $\Delta V/\Delta$transmural pressure (ΔP):

$$C_L * \Delta P_L = C_{CW} * \Delta P_{CW}$$

Because $\Delta P_{CW} = \Delta Ppl$ and $\Delta P_L = PEEP - \Delta Ppl$:

$$C_L * (PEEP - \Delta Ppl) = C_{CW} * \Delta Ppl$$

Rearranging:

$$\Delta Ppl = PEEP * (C_L/(C_L + C_{CW}))$$

In other words, the percentage of PEEP transmitted to the pleural space is a function of the ratio of chest wall to lung compliance. If lung compliance (C_L) is low and chest wall compliance is high, very little of the PEEP will be transmitted to the pleural space and vice versa. In this example, the chest wall and lung compliances are equal and thus the increase in pleural pressure is equal to ½ (5 cm H_2O pressure) of the applied PEEP (10 H_2O pressure). Pleural pressure will increase from –3 cm to +2 cm H_2O pressure.

and that of the lung equal to

Alveolar pressure – Pleural pressure

An integration of lung and chest wall mechanics can be graphically represented by plotting the pleural pressure against the relaxed volumes of the lung and chest wall (Campbell diagram) (Fig. 5-16). These plots help to explain the determinants of the commonly measured static lung volumes.

At FRC (relaxation volume), the outward recoil pressure of the chest wall is balanced by the inward recoil of the lung. The pleural pressure at which this occurs is negative (approximately –3 to –4 cm H_2O) in normal subjects. Changes in the compliance of the lung or chest wall may change the relaxation volume (see Fig. 5-16). Increases in lung compliance (e.g., due to emphysema) will tend to shift the pressure-volume curve of the lung upward and to the left. If chest wall compliance remains constant, FRC will increase. In contrast, if lung compliance is reduced (e.g., due to pulmonary fibrosis), there will be shifting of the pressure-volume curve of the lung to the right, leading to a reduction in FRC. Similarly, changes in chest wall compliance can lead to increases or decreases in FRC.

FRC is believed to represent the balance of forces in a relaxed state of no muscle activation. However, FRC may not be completely passively determined. There appears to be a reduction in FRC with paralysis compared with the relaxed state, suggesting that inspiratory muscle tone of the rib cage muscles may contribute to FRC.[60]

With activation of inspiratory and expiratory muscles, the configuration of the chest wall changes. This is dem-

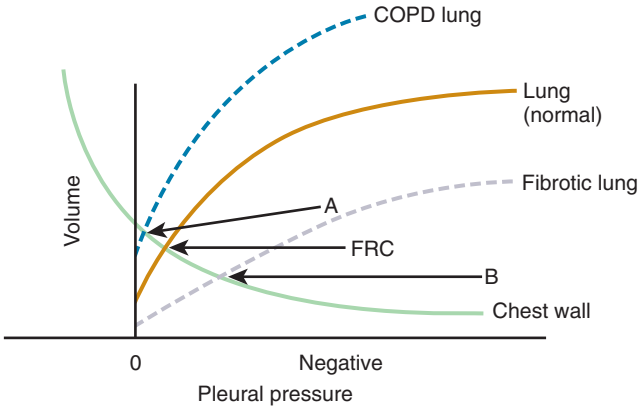

FIGURE 5-16 ■ Integration of lung and chest wall mechanics. Changes in lung and relaxed chest wall volumes as a function of pleural pressure (Campbell diagram). This is basically the same plot as in Figures 5-5 and 5-6 except that the x axis is simply Ppl rather than transmural pressure for the lung and chest wall. The point at which the two curves meet is the functional residual capacity (FRC) (lung recoil balanced by chest wall recoil). If lung compliance is increased (e.g., in COPD), the point at which the two curves meet (FRC) is greater (point A). In contrast, if lung compliance is reduced (e.g., in pulmonary fibrosis), the point at which the two curves meet is less (point B).

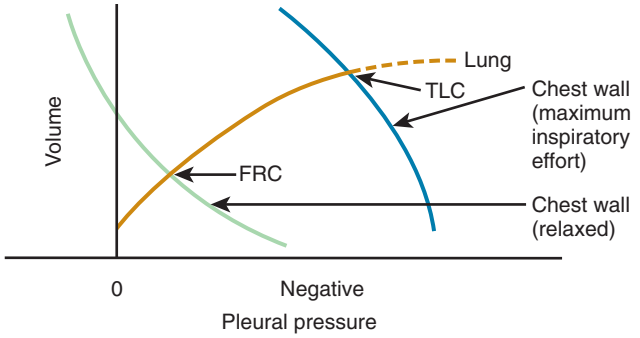

FIGURE 5-17 ■ Maximal inspiratory effort (Campbell diagram). With maximal inspiratory effort, the volume-pressure curve of the chest wall moves to the right. The point at which there is intersection of this curve and the lung volume-pressure curve is the total lung capacity (TLC).

onstrated in Figure 5-17. Activation of inspiratory muscles effectively shifts the pressure-volume curve of the chest wall, so that at any given pleural pressure, volume of the chest wall is increased relative to the relaxed state. The horizontal difference between the relaxed curve and the curve with inspiratory muscle activation represents the net pressure generated by the inspiratory muscles.

TLC is determined by the balance between inward lung recoil plus the inward chest wall recoil and the strength of the inspiratory muscles. However, in normal subjects, TLC is predominantly determined by the markedly increased stiffness of the lung at high lung volume, rather than the recoil of the chest wall or respiratory muscle strength.[61] In support of this concept, inspiratory muscle training in normal subjects increases strength substantially (55% increase in maximal inspiratory pressure) but results in a very modest change in TLC and VC (about 4%).[62] The situation in patients with neuromuscular disease is very different; in such individuals, reduced TLC is largely due to respiratory muscle weakness and can be improved to some extent by inspiratory muscle training.[63]

Activation of expiratory muscles shifts the volume-pressure curve of the chest wall in the other direction, and the degree of shift is a measure of the net pressure exerted by the expiratory muscles. In young subjects, RV is determined by the balance of static forces among the outward recoil of the chest wall, inward lung recoil (small component), and expiratory muscle strength.[61]

In older subjects or patients with obstructive lung disease, RV is not determined by this balance of forces, but is rather determined by airway closure. In such individuals, airway closure and trapping of gas occur during exhalation before a static balance is achieved.[61]

Calculation of Total Respiratory System Compliance from Lung and Chest Wall Compliance

The chest wall and lung act as capacitors in series, analogous to electrical capacitors. The relationship between total respiratory system compliance and lung–chest wall compliance is indicated by the following formula:

$$1/\text{Total compliance} = 1/\text{Lung compliance} + 1/\text{Chest wall compliance}$$

Alternatively, since elastance = 1/compliance,

$$\text{Total elastance} = \text{Elastance of lung} + \text{Elastance of chest wall}$$

As an example, in a supine paralyzed subject, lung compliance is approximately 150 mL/cm H_2O pressure and chest wall compliance is approximately 200 mL/cm H_2O pressure[64]; the calculated compliance of the respiratory system would thus be approximately:

$$1/(1/200 + 1/150) = 85.7 \text{ mL/cm } H_2O$$

Clinical Applications

The Impact of Positive End-Expiratory Pressure on Pleural Pressure

In patients receiving positive-pressure mechanical ventilation, pressure is usually applied at the end of exhalation to prevent alveolar collapse.[65] Some—but not all—of this PEEP is transmitted from the alveolar space to the pleural space (see Fig. 5-15). This is important because pericardial pressure will increase to a similar extent as pleural pressure. Increases in pericardial pressure reduce venous return and can lead to reduced cardiac output and hypotension.[66] Furthermore, PEEP will increase central venous pressure and pulmonary artery occlusion pressure to a magnitude similar to the increase in pleural pressure. If this is not taken into account, errors may be made when using these pressures to assess volume status.

The proportion of PEEP transmitted to the pleural space is dependent on the relationship between the compliances of the chest wall and the lung (see Fig. 5-15). When the compliances of the lung and chest wall are equal, 50% of the PEEP is transmitted to the pleural space. However, if lung compliance is much less than chest wall compliance (e.g., in a thin patient with severe ARDS), the pleural pressure will change minimally with PEEP. In contrast, if lung compliance is much greater than chest wall compliance (e.g., in a patient with emphysema and kyphoscoliosis), a much greater proportion of PEEP will be transmitted to the pleural space.

Plateau Pressures in Patients Receiving Positive-Pressure Mechanical Ventilation

In patients receiving positive-pressure mechanical ventilation, the plateau pressure is the distending pressure of the respiratory system at end inspiration when there is no flow. When possible, plateau pressures are limited to a maximum of 30 to 35 cm H_2O, because higher pressures can damage the lung through overdistention. This recommendation is based in part on animal studies that show that pressures below this range seem to protect the lungs from injury.[67] There is also a physiologic basis for this practice, because at TLC in a normal subject, the distending pressure across the lung (alveolar − pleural

pressure) is approximately 35 cm H_2O.[68] Therefore, limiting the plateau pressure to less than 35 cm H_2O should limit lung expansion to below TLC, and not overdistend the lung. Although controversial, some investigators have argued that in patients who have substantial heterogeneity of lung compliance (such as patients with ARDS), even plateau pressures below 30 to 35 cm H_2O might be harmful[69] because heterogeneity leads to opening of some alveoli while adjacent ones may remain closed, causing substantial shear stress even at modest airway pressures.[70]

A related issue is the clinical significance of the plateau pressure in patients with a stiff chest wall. The plateau pressure is usually used as a surrogate marker of transpulmonary pressure (pressure used to distend the lung), when it is actually a measure of transrespiratory system pressure. When lung compliance is much less than chest wall compliance, this is a reasonable assumption, because during mechanical ventilation, pleural pressure will not be substantially greater than body surface pressure. However, in conditions in which the chest wall is stiff (e.g., obesity, post–abdominal surgery) the plateau pressure may substantially overestimate the distending pressure of the lung, because pleural pressure may be much greater than body surface pressure. Under these conditions, tolerance of higher plateau pressure should be considered if there are problems with oxygenation. Indeed, some investigators have suggested that measurement of pleural pressure (with an esophageal balloon) could be useful in titrating mechanical ventilation in ARDS.[71]

THE RESPIRATORY SYSTEM IN DYNAMIC CONDITIONS

The work to distend the chest wall and lung during inhalation is stored as potential energy (elastic work). Work also must be done to overcome the inertia of the gas (which is negligible when breathing air at normal breathing frequency and atmospheric pressures) and nonelastic resistance (resistive work), which cannot be stored, but is dissipated as heat. Resistive work has two components that must be considered.

Resistive Work Due to Gas Flow through Airways

When gas flows through an airway, frictional and viscous forces cause energy loss and a pressure drop along the airway. The extent of this pressure drop is dependent on the resistance to gas flow, physical properties of the gas (e.g., density and viscosity), and the nature of flow (laminar versus turbulent).

Laminar versus Turbulent Flow

The least frictional drop occurs with pure laminar flow, in which gas molecules travel in a straight line. The velocity profile of the gas is parabolic, with the molecules closer to the wall traveling slower than molecules in the center of the airway (Fig. 5-18). When gas flow is laminar, the flow is proportional to the pressure gradient along the airway and inversely proportional to resistance.

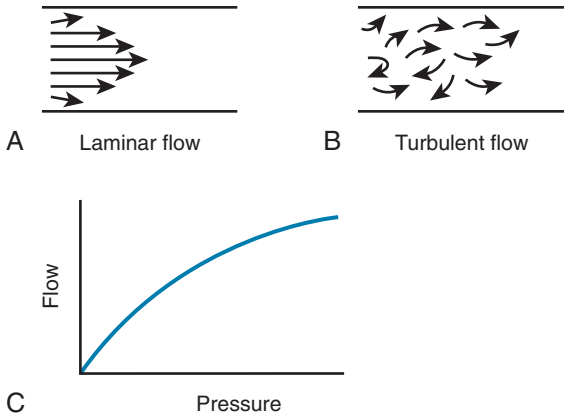

FIGURE 5-18 ■ Laminar versus turbulent flow. Schematic depiction of the spatial and velocity profiles of gas molecules within a laminar (**A**) and a turbulent (**B**) flow regime. The velocity of the gas molecules is proportional to the length of *arrows*. During turbulent flow, there is chaotic molecular movement between lamina that results in ever greater pressure being required to achieve incremental flow. **C,** Note the alinear pressure-flow relationship with turbulent flow.

$$\text{Flow} = \Delta P / R$$

For a straight airway under conditions of laminar flow, resistance of the tube is related to viscosity, length, and radius of the tube by the Poiseuille equation:

$$\text{Resistance} = 8 * \text{length} * \text{viscosity} / (\pi * \text{radius}^4)$$

Because of this relationship, flow through a tube is dramatically affected by even small changes in tube diameter, because resistance increases as the fourth power of the radius (i.e., reducing the radius by half causes a 16-fold increase in resistance).

When flow is turbulent, the orderly pattern of gas molecule movement is replaced with a haphazard pattern (see Fig. 5-18). Turbulent flow results in much greater pressure losses due to friction, with the pressure drop along the airway proportional to the square of flow (as opposed to a linear relationship in the case of laminar flow)[72]:

$$\Delta P = \text{constant} * \text{flow}^2$$

Because resistance is defined as the pressure gradient divided by the flow rate, the "resistance" for turbulent flow is not constant, but increases in proportion to flow.

In contrast to laminar flow, turbulent flow is inversely proportional to gas density, but is not affected by viscosity. The driving pressure required is proportional to the fifth power of the radius of the airway.

Reynold's Number

Reynold's number is a dimensionless coefficient that predicts whether flow through an unbranched airway will

be predominantly laminar, turbulent, or mixed. The equation is as follows:

$$Re = pdV/u$$

where p is the gas density, d is the diameter of the airway, V is the mean gas velocity, and u is the viscosity. In general, a value of Re of less than 2000 is associated with laminar flow, whereas a value greater than 4000 is associated with predominantly turbulent flow.[73] Intermediate values are associated with mixed flow patterns. Decreased airway radius or gas viscosity and increased gas density or gas velocity predispose to turbulent flow.

The cross-sectional diameter of the central airways (e.g., trachea) is much greater than the smaller peripheral airways (e.g., bronchioles). However, the entire cross-sectional area of the peripheral airways is much greater than that of the central airways. Therefore, as gas moves from the peripheral to the central airways during exhalation, the gas velocity increases as the airway diameter increases. This results in predominantly turbulent flow in the larger central airways (except at very low flow rates) and predominantly laminar flow in the periphery.

Clinical Effects of Heliox

Heliox is a mixture of oxygen and helium. Heliox has a density less than air and a viscosity greater than air. For instance, a mixture of 20% oxygen and 80% helium has a density of 0.33 relative to air and a viscosity of 1.08 relative to air.[73] Because gas density influences the resistance during turbulent flow, this gas mixture can be especially beneficial in patients who have upper airway narrowing (e.g., partial tracheal obstruction).[74] Substituting heliox for air or oxygen reduces gas density, lowering Reynold's number, and helps to convert turbulent to laminar flow. This reduces the pressure required to move gas through the airways and diminishes the work of breathing, unloading the respiratory muscles.

Heliox may be useful in patients with asthma or COPD, although this is controversial.[75,76,76a] The reason for a beneficial effect is unclear, because flow in the smaller bronchioles, which contribute most of the increased airways resistance in asthma, should be laminar rather than turbulent. Alternatively, the effectiveness of heliox in asthma might be related to narrowing of large central airways from secretions and conversion of flow from turbulent to laminar in larger airways.

Flow Limitation

In a normal subject, increasing expiratory effort will increase air flow until a threshold is reached. Once this effort threshold is exceeded, expiratory flow will not increase with a further increase in effort, resulting in flow limitation as opposed to pressure limitation[77] (Fig. 5-19). In contrast, patients with very poor effort or marked expiratory muscle weakness may be unable to generate high expiratory pressures, resulting in pressure limitation before flow limitation occurs. If flow were not relatively effort independent, measures such as forced expiratory volume in 1 second (FEV_1) would have little utility in monitoring patients.

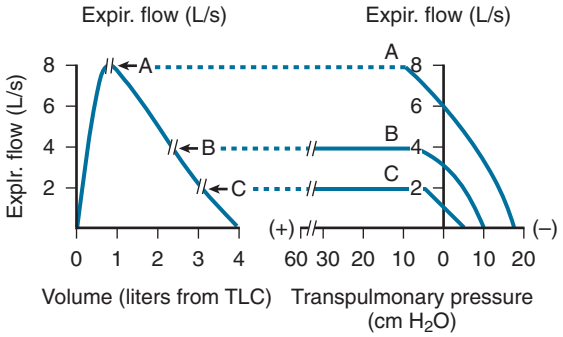

FIGURE 5-19 ■ Expiratory flow limitation. *Left,* The expiratory flow volume curve for a normal subject. Maximal flow rates are plotted against their corresponding volumes at A, B, and C and define the maximal expiratory flow-volume curve. *Right,* Three isovolume pressure-flow curves for the same subject. Once a threshold transpulmonary pressure is achieved, no increase in flow is seen. (From Hyatt RE: Forced expiration. *In* Macklem PT, Mead J [eds]: Handbook of Physiology. Section 3. The Respiratory System. Vol III: Mechanics of Breathing [part 1]. Bethesda, MD: American Physiological Society, 1986, pp 295–314.)

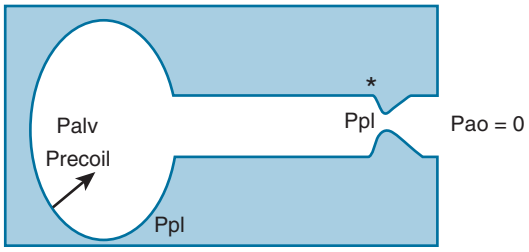

FIGURE 5-20 ■ Equal pressure point theory. At the equal pressure point (EPP; *), pressure inside the tube is equal to the pressure outside the tube (pleural pressure) due to pressure drop related to flow resistive losses from alveolus to *. Downstream (mouthward) from the EPP, the airway is compressed. Once an EPP develops, increasing expiratory effort, although increasing the alveolar pressure, simply increases the downstream compression and causes no increase in flow.

The concept of expiratory flow limitation is important, and the reason that flow is limited is because of the properties of the airways. For simplicity, the airways are often likened to a rigid tube, but in reality, the airways are partially collapsible. During inhalation, pleural pressure is negative, and the intrathoracic airways tend to be pulled open. During active exhalation, pleural pressure becomes positive, increasing pressure around the intrathoracic airways and predisposing to their collapse.

Several theories have been developed to explain the limitation of flow at less than maximal effort.

Equal Pressure Point Theory (Fig. 5-20). Consider the respiratory system depicted as a bag (lung) inside a box (chest wall) connected by a tube that extends through the box (intrathoracic airway). The pressure inside of the lung is equal to the pleural pressure (created by expiratory muscle activation) plus the recoil pressure of the lung. As air travels down the airway, pressure in

the airway will decrease, predominantly due to frictional losses. A point is eventually reached where the pleural pressure in the box is equivalent to the pressure inside the tube, termed the equal pressure point (EPP).[78,79] Downstream (mouthward) of this EPP, the pressure outside the airway exceeds the pressure within the airway, and the airway tends to collapse. Further increases in effort increase pleural pressure, but this simply causes greater narrowing of the airway downstream of the EPP, so that flow remains constant. Under these conditions, the airway acts as a Starling resistor; flow is now not proportional to the difference between alveolar and mouth pressure, but rather is proportional to the difference between alveolar pressure and pressure at the EPP. In this case, the pressures downstream from the EPP have no effect on expiratory flow.

This concept can be mathematically expressed as follows:

Because:

$$\text{Alveolar pressure} = \text{Pleural pressure} + \text{Elastic recoil pressure of the lung}$$

and

$$\text{Pressure at EPP} = \text{Pleural pressure}$$

and

$$\text{Driving pressure for flow} = \text{Alveolar pressure} - \text{Pressure at EPP}$$

therefore

$$\begin{aligned}\text{Driving pressure} &= (\text{Pleural pressure} \\ &\quad + \text{Lung recoil pressure}) \\ &\quad - \text{Pleural pressure} \\ &= \text{Lung recoil pressure}\end{aligned}$$

Therefore, further increases in effort will increase alveolar and EPP pressure equally, resulting in no difference in driving pressure and airflow.

The Bernoulli Effect and Wave Speed Theory. The Bernoulli effect provides an alternative explanation for flow limitation.[80] As gas flows through a tube, the lateral pressure exerted by the gas is less than the pressure driving flow by an amount proportional to the velocity of the gas. If the tube is collapsible, as gas velocity increases, there is a tendency for the tube to collapse, leading to a reduction in airflow.

The wave speed theory is yet another explanation for expiratory flow limitation.[81] When fluid is pushed through a collapsible tube, a pressure wave is propagated along the wall of the tube. The speed of this pressure wave is dependent on the characteristics of the tube and the density of the gas rather than the driving pressure. The velocity of the gas in the tube cannot exceed the velocity of the pressure wave, and thus the velocity of this wave represents a "speed limit" for the gas in the tube.

Interestingly, the maximal flow of gas derived using the Bernoulli effect and wave speed theory are identical, as shown by the following formula:

$$\text{Maximal flow} = A * \sqrt{((A * / \text{gas density}) * dP/dA)}$$

where A represents the cross-sectional area of the airway wall and dP/dA represents the slope of the relationship between changes in transmural pressure of the tube and changes in tube area. Therefore, maximal flow should increase if the tube area increases, gas density decreases, or tube stiffness increases.

The EPP mechanism might be more important at lower lung volumes and flows, while the Bernouilli and wave speed effects might predominate at higher volumes and flows.[82]

Other Resistive Work

Besides of the elastic work done by the respiratory muscles on the lung and chest wall, an additional component of work is expended to overcome what is sometimes called "tissue resistance." This is energy required to distort the lung and chest wall during inhalation and is dissipated as heat.

The breakdown of the various components of the total resistive work is shown Table 5-1.

Auto-PEEP during Positive-Pressure Ventilation of COPD

An appreciation of the dynamics of the respiratory system aids in understanding clinical scenarios, such as patients with COPD who are treated with positive-pressure ventilation for respiratory failure.[83] Because lung resistance and compliance are increased in these patients, their lungs contain individual lung units with long time constants, and there may be insufficient time for the lungs to completely empty at the end of exhalation. Heterogeneity of time constants will result in heterogeneity of emptying times. If insufficient time is allowed for complete emptying of lung units, the result will be a positive mean alveolar pressure in the alveolus at the end of exhalation. This has been termed "auto-PEEP" or "intrinsic PEEP."

PEEPs have a number of adverse consequences. First, the positive pressure at end-exhalation increases intratho-

TABLE 5-1. Components of Respiratory System Resistance

	Mouth/Pharynx	Large Airways	Small Airways	Lung Tissue	Chest Wall	Total
Resistance (cm H_2O L/s)	0.5	0.5	0.2	0.2	1.2	2.6
% of resistance	19	19	8	8	46	100

Adapted from O'Donnell DE, Laveneziana P: Dyspnea and activity limitation in COPD: Mechanical factors. COPD 4:225–236, 2007.

racic pressure and can reduce venous return, causing hypotension.[66] Second, the high end-expiratory alveolar pressure acts as an inspiratory threshold load. That is, in order to generate a negative pressure that is great enough to trigger the ventilator and initiate inspiratory flow, the inspiratory respiratory muscles must exert adequate pressure to counteract the auto-PEEP pressure and reduce alveolar pressure to a subatmospheric value.[84] Third, high auto-PEEP may lead to inspiratory efforts that are ineffective in triggering the ventilator if the respiratory muscles cannot reduce alveolar pressure to less than the applied PEEP[85] (Fig. 5-21). This may lead to patient ventilator dyssnchrony and discomfort. Fourth, auto-PEEP and the consequent hyperinflation of the lung at end-exhalation place the inspiratory muscles at a mechanical disadvantage,[36] which can lead to failure of weaning from mechanical ventilation.

Auto-PEEP is treated by increasing the applied PEEP from the ventilator, which may improve patient-ventilator synchrony.[86] Increasing applied PEEP will not reduce expiratory flow if the applied PEEP is less than the level of auto-PEEP, because these patients are usually flow- rather than pressure-limited. However, increasing the applied PEEP will decrease inspiratory muscle work and facilitate ventilator triggering.

The end-expiratory occlusion method is commonly used to measure auto-PEEP (Fig. 5-22) (static auto-PEEP). The expiratory line in the ventilator is occluded at the end of an exhalation.[87] If auto-PEEP is present, airway pressure will increase until a plateau is reached (usually 4-5 seconds). This value represents an "average" measure of auto-PEEP after redistribution of volume from some alveoli to others depending on regional compliance (pendelluft). Pendelluft is the transient movement of gas from one lung unit to another.

Alternatively, auto-PEEP may be measured under dynamic conditions (dynamic auto-PEEP) when the patient is spontaneously breathing.[87] This can be done by inserting an esophageal balloon to measure pleural pressure and measuring the reduction in pleural pressure necessary to initiate inspiratory flow. Dynamic auto-PEEP is usually less than that measured under static conditions, because it reflects the region of the lung with the least amount of auto-PEEP, as opposed to the average amount of auto-PEEP.

Auto-PEEP is not limited to mechanical ventilation. Spontaneously breathing patients who have COPD can develop positive end-expiratory alveolar pressure, especially when they increase their inspiratory rate during exertion, a phenomenon that has been termed "dynamic hyperinflation." This increases work of breathing (see later) and contributes to exercise limitation in these patients.

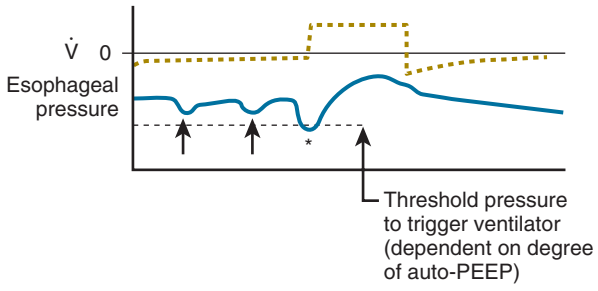

FIGURE 5-21 ■ Failure to trigger the ventilator in a COPD patient. Graph of flow (V̇) and esophageal pressure over time in a patient with COPD and auto-PEEP receiving positive-pressure mechanical ventilation. The patient has made two attempts (↑) at triggering inspiration but could not, due to the positive end-expiratory alveolar pressure. When pleural pressure is sufficiently negative to exceed the ventilator's threshold (*dotted line*), this triggers the ventilator (*) and a breath is provided. Note the failure of expiratory flow to reach 0 prior to a triggered breath.

Measurement of Static Compliance and Resistance during Mechanical Ventilation

In the intensive care unit, measurement of respiratory system compliance and resistance can be helpful in assessing the timing for weaning from mechanical ventilation or determining the reasons for failure of a spontaneous breathing trial. Normal respiratory system compliance in a supine subject is approximately 100 cm H_2O/mL. A markedly decreased compliance should prompt a search for causes of reduced lung (e.g., edema) and/or chest wall compliance (abdominal distention) that might be potentially reversible. Similarly, a markedly increased resistance should prompt a search for reversible causes, including bronchospasm, or partial endotracheal tube obstruction from kinking or secretions.

Calculation of compliance and resistance should be performed with a square wave flow pattern after an inspiratory pause. Patients need to be relaxed or paralyzed to obtain accurate measurements. If respiratory efforts are present, airway pressures may not reflect transmural pressures across the respiratory system, but rather may reflect pleural pressures.

Consider a paralyzed sedated patient treated with positive-pressure mechanical ventilation in the assist-control mode. The changes in flow, volume, and pressure over time are shown in Figure 5-23. Assume a constant inspiratory flow rate (1 L/sec) and a tidal volume of 500 mL (0.5 sec inspiratory time). Because flow is constant, volume increases linearly over time. Peak pressure is 40 cm H_2O, plateau pressure is 35 cm H_2O, and PEEP is set at 5 cm H_2O.

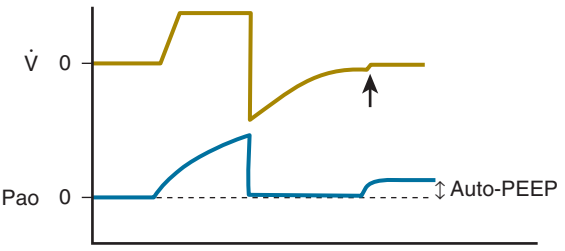

FIGURE 5-22 ■ Measurement of auto-PEEP while on a ventilator. Flow (V̇) and airway pressure (Pao) over time. *Arrow* represents the point at which the expiratory line is occluded, leading to an increase in measured pressure that represents the degree of auto-PEEP.

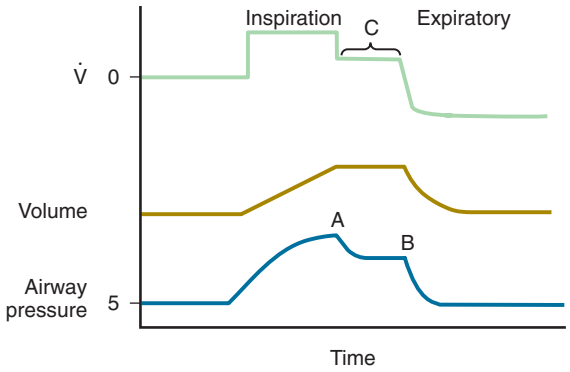

FIGURE 5-23 ■ Ventilator mechanics. **A,** Peak pressure (40 cm H_2O). **B,** Plateau pressure (35 cm H_2O). **C,** Inspiratory pause.

Using the bag and tube analogy of the respiratory system (see Fig. 5-4), the components of pressure required are as follows:

$$\begin{aligned}\text{Total pressure} = {} & \text{Pressure to distend respiratory system} \\ & + \text{Pressure to maintain gas flow} \\ & + \text{Inertial pressure losses}\end{aligned}$$

Because the inertial component can be ignored at the respiratory rates commonly used:

$$\begin{aligned}\text{Total pressure} = {} & \text{Pressure to distend respiratory system} \\ & + \text{Pressure to maintain gas flow} \\ = {} & \Delta\text{Volume}/\text{compliance} + \text{Flow} * \text{resistance}\end{aligned}$$

The difference between plateau pressure (measured during an inspiratory hold) and PEEP represents the pressure required to distend the respiratory system at 0 flow.

Therefore,

$$\begin{aligned}\text{Plateau pressure} - \text{PEEP} = {} & \Delta\text{Volume}/\text{compliance} \\ & + \text{Flow} * \text{resistance}\end{aligned}$$

Because flow = 0, rearranging the equation yields:

$$\text{Compliance} = \Delta\text{Volume}/(\text{Plateau pressure} - \text{PEEP}) \quad (1)$$

The difference between peak pressure (A) and plateau pressure (B) represents the pressure required to overcome resistance of the respiratory system (this predominantly represents flow resistance, but also includes contributions from tissue resistance, stress relaxation, and pendelluft) and the pressure required to distend the respiratory system.

Therefore,

$$\begin{aligned}\text{Peak pressure} - \text{PEEP} = {} & \Delta\text{Volume}/\text{compliance} \\ & + \text{Flow} * \text{resistance}\end{aligned} \quad (2)$$

Rearranging Equations 1 and 2:

$$\text{Peak pressure} - \text{Plateau pressure} = \text{Flow} * \text{resistance}$$

Because flow is known:

$$\text{Resistance} = (\text{Peak pressure} - \text{Plateau pressure})/\text{Flow}$$

Going back to our patient:

$$\text{Compliance} = 500\ \text{mL}/(30\ \text{cm}\ H_2O) = 16.7\ \text{mL/cm}\ H_2O$$
$$\text{Resistance} = 40 - 35\ \text{cm}\ H_2O/1\ \text{L/s} = 5\ \text{cm}\ H_2O/\text{L/s}$$

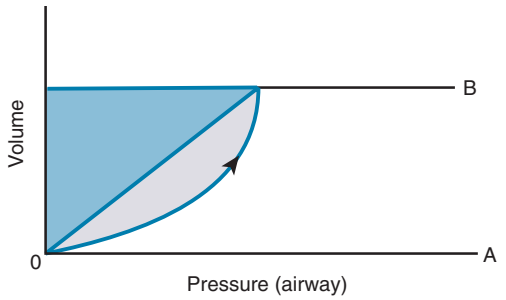

FIGURE 5-24 ■ Work of breathing during mechanical ventilation. Consider a paralyzed patient receiving one tidal breath while on positive-pressure mechanical ventilation (point A to point B). The *diagonal blue line* represents the volume-pressure curve of the static respiratory system; the *shaded dark blue area* to the left of this line thus represents the elastic work done during the inflation. This work can be stored as potential energy and can be used during exhalation. The *gray shaded area* to the right of the line represents the resistive work done.

In other words, the patient's compliance is severely reduced, suggesting an extremely stiff respiratory system. However, the resistance is relatively low.

ENERGETICS AND WORK OF BREATHING

When a force is applied to an object over a distance, energy is required; the work done is equal to:

$$\text{Work} = \text{force} * \text{distance}$$

Similarly, because pressure is force over an area and volume is an area multiplied by a distance, work in a fluid system may be defined as the integral of applied pressure over a change in volume:

$$\text{Work} = \int \text{PdV}$$

During inspiration, work must be performed to distend the respiratory system (elastic work) which is stored as potential energy. Also, nonelastic work must be done to generate flow through the airways (to overcome resistance to gas flow), to deform the lung and chest wall (to overcome tissue resistance), and to accelerate gas (to generate the inertial component). This work cannot be stored as potential energy and is dissipated as heat. The inertial component is minimal and is usually ignored in measuring total work.

Measuring Work of Breathing Done by a Positive-Pressure Ventilator in a Paralyzed Patient

Consider a paralyzed patient receiving positive-pressure mechanical ventilation, such that the entire work of breathing is performed by the ventilator (Fig. 5-24). On a volume-pressure plot, pressure applied to the airway will track to the right of the static volume-pressure curve of the respiratory system, because additional pressure is

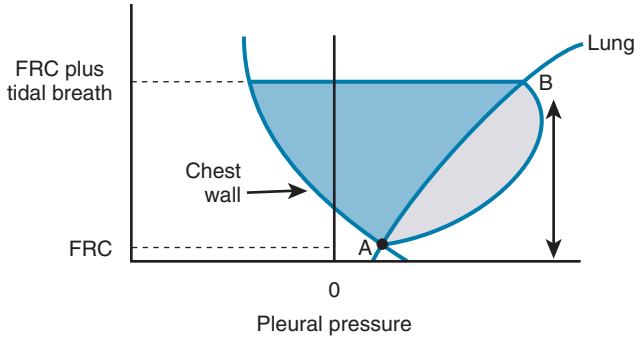

FIGURE 5-25 ■ Work of breathing during spontaneous breathing (Campbell diagram). A portion (from FRC to FRC plus tidal volume) of the volume-pleural pressure (VP) curves of the lung and relaxed chest wall are shown. Consider a patient taking a spontaneous breath from FRC (point A) with a volume equal to the height of the *double-headed arrow* (point B). In order to overcome elastic forces of the lung and chest wall, the inspiratory muscles must exert a force equal to the horizontal distance between the chest wall and lung VP curves. Thus, the entire elastic work done will be equal to the *blue shaded area*. Furthermore, resistive work must also be done, necessitating the inspiratory muscles to generate an even greater negative pleural pressure. This is indicated by the *gray shaded area*. The total work done will be the sum of both areas.

required to overcome resistive forces. The *blue shaded area* represents the elastic work done by the ventilator during one inhalation, while the *gray shaded area* represents the resistive work that was expended to generate flow and overcome tissue resistance. With exhalation, the stored elastic energy can be used to deflate the lungs, so that exhalation is normally a passive process. Increases in resistance or decreases in compliance can markedly increase the work of breathing.

Measuring Work of Breathing in a Spontaneously Breathing Patient

In a spontaneously breathing patient, work is performed by the inspiratory muscles rather than a ventilator. Graphing the pressure-volume characteristics of the lung and chest wall against pleural pressure is useful in illustrating the work performed by the inspiratory muscles (Fig. 5-25). During inspiration, pleural pressure decreases to expand the lungs (see Fig. 5-25A and B). The distance between the two curves at any given lung volume represents the pressure the inspiratory muscles must exert to overcome elastic forces of the lung and chest wall. The *blue shaded area* thus represents the elastic work of breathing against the lung and chest wall. To overcome the resistive forces, additional pressure and work are required, as indicated by the *gray shaded area*.

Under normal conditions, exhalation is passive, because the stored potential energy from elastic work is more than sufficient to overcome resistive work. However, in the presence of severe airflow obstruction (e.g., an asthma attack), resistive work may exceed this stored energy, requiring active generation of force by expiratory muscles and additional work for exhalation.

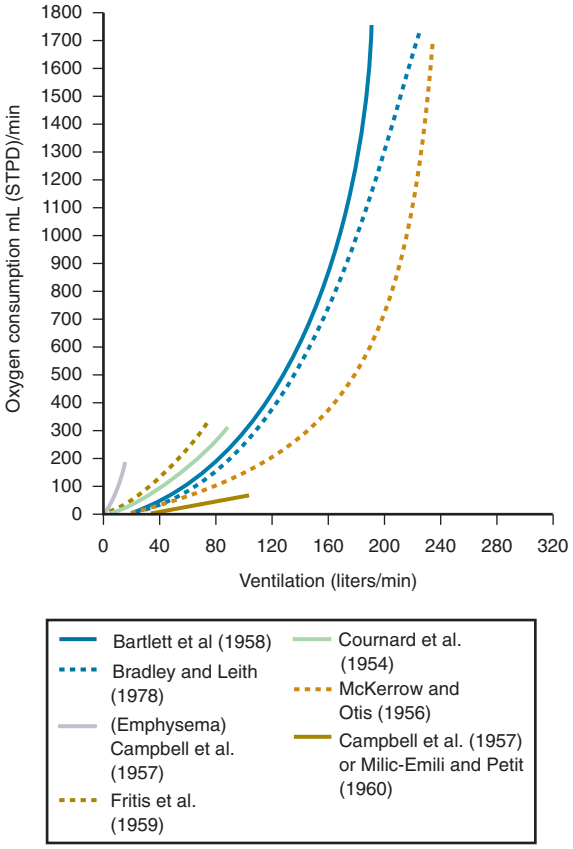

FIGURE 5-26 ■ Oxygen cost of breathing. Oxygen cost of breathing at varying levels of ventilation. Note the variability among studies and the steeper slope in patients with emphysema. (From Roussos C, Zakynthinos S: Respiratory muscle energetics. In Roussos C [ed]: The Thorax [Part A]. New York: Marcel Dekker, 1995, pp 681–749.)

Oxygen Cost of Breathing

The oxygen cost of breathing (V_{O_2} resp) is an indicator of the total amount of energy required by the respiratory muscles for ventilation. At rest, the oxygen cost of breathing is low, 0.25 to 0.5 mL/L of ventilation, or 1% to 2% of total body oxygen consumption. However, at maximal exercise in normal subjects, the oxygen cost of breathing represents approximately 10% to 15% of total oxygen consumption.[88] The oxygen cost of breathing can increase markedly as minute ventilation increases (Fig. 5-26).

Patients with COPD have an increased oxygen cost of breathing as a function of ventilation (see Fig. 5-26). This may be related to a combination of increased work of breathing and decreased efficiency due to dynamic hyperinflation. Dynamic hyperinflation is an increase in end-expiratory lung volume that occurs when patients with airflow obstruction develop auto-PEEP due to the long time constants for gas distribution in the lungs and increased respiratory rate.[89]

In addition, tonic inspiratory muscle activity at end-expiration contributes to dynamic hyperinflation. Although this dynamic increase in lung volume can have a beneficial effect by dilating intraparenchymal airways

to decrease the resistive work, the end-expiratory alveolar pressure acts as an inspiratory threshold load, which increases the work of breathing. Furthermore, the mechanical efficiency of the inspiratory muscles is compromised by hyperinflation because the zone of diaphragmatic apposition is reduced and the inspiratory muscles are shorter than the optimal length for force generation. The efficiency of breathing (defined as the ratio between the rate of mechanical work accomplished and the rate of energy consumed) may be further diminished if postural or other stabilizing muscles (trunk, neck, shoulder) need to be recruited.

KEY POINTS

- An understanding of the mechanical properties of the lung and chest wall under static and dynamic conditions is important for appreciating the determinants of lung volumes and expiratory flows under normal and pathological conditions.
- Under conditions of laminar flow, flow is directly proportional to the pressure difference along the path of flow. Under conditions of turbulent flow, flow is directly proportional to the square root of the pressure difference.
- The majority of the elastic recoil of the lung is due to surface forces generated by fluid lining the alveoli.
- The unique properties of surfactant help to stabilize alveoli at low lung volumes and prevent their collapse.
- At FRC (relaxation volume), the outward recoil pressure of the chest wall is balanced by the inward recoil of the lung. TLC is determined by the balance between the maximal inspiratory pressure generated by the respiratory muscles and the opposing pressure generated by the inward recoil of the lungs and chest wall. In young subjects, RV is determined by the balance of pressure generated by the expiratory muscles and the opposing pressures generated by the outward recoil of the chest wall and inward of the lungs (normally a small component). In older subjects or patients with obstructive lung disease, RV is not determined by this balance of forces, but is rather determined by airway closure.
- In patients with airflow obstruction who are treated with positive-pressure ventilation, dynamic hyperinflation (auto-PEEP) can lead to hemodynamic compromise, increased work of breathing, an inspiratory threshold load, mechanical inefficiency of the diaphragm, and patient-ventilator asynchrony.

References

1. Kendrick AH: Comparison of methods of measuring static lung volumes. Monaldi Arch Chest Dis 51:431–439, 1996.
2. Paré PD, Wiggs BJ, Coppin CA: Errors in the measurement of total lung capacity in chronic obstructive lung disease. Thorax 38:468–471, 1983.
3. Blackie SP, Al-Majed S, Staples CA, et al: Changes in total lung capacity during acute spontaneous asthma. Am Rev Respir Dis 142:79–83, 1990.
4. Cooper ML, Friedman PJ, Peters RM, Brimm JE: Accuracy of radiographic lung volume using new equations derived from computed tomography. Crit Care Med 14:177–181, 1986.
5. Clarenbach CF, Senn O, Brack T, et al: Monitoring of ventilation during exercise by a portable respiratory inductive plethysmograph. Chest 128:1282–1290, 2005.
6. Kauczor HU, Heussel CP, Fischer B, et al: Assessment of lung volumes using helical CT at inspiration and expiration: Comparison with pulmonary function tests. AJR Am J Roentgenol 171:1091–1095, 1998.
7. Clarenbach CF, Senn O, Brack T, et al: Monitoring of ventilation during exercise by a portable respiratory inductive plethysmograph. Chest 128:1282–1290, 2005.
8. Banzett RB, Mahan ST, Garner DM, et al: A simple and reliable method to calibrate respiratory magnetometers and Respitrace. J Appl Physiol 79:2169–2176, 1995.
9. Baydur A, Behrakis PK, Zin WA, et al: A simple method for assessing the validity of the esophageal balloon technique. Am Rev Respir Dis 126:788–791, 1982.
10. Zin WA, Milic-Emili J: Esophageal Pressure Measurement. *In* Hamid Q, Shannon J, Martin J (eds): Physiologic Basis of Respiratory Disease. Hamilton, Ontario: BC Decker, 2005, pp 639–647.
11. Paré PD, Harvey K, Mildenberger M, Brooks LA: Effects of balloon volume and position on the pressure volume curve of the lung. Clin Invest Med 6:143–146, 1983.
12. Stromberg DD, Wiederhielm CA: Viscoelastic description of a collagenous tissue in simple elongation. J Appl Physiol 26:857–862, 1969.
13. Snider GL, Sherter CB, Koo KW, et al: Respiratory mechanics in hamsters following treatment with endotracrael elastase or collagenase. J Appl Physiol 42:206–215, 1977.
14. Stamenović D: Micromechanical foundations of pulmonary elasticity. Physiol Rev 70:1117–1134, 1990.
15. Hogg JC: Pathophysiology of airflow limitation in chronic obstructive pulmonary disease. Lancet 364:709–721, 2004.
16. Loring SH, Drazen JM, Smith JC, Hoppin FG Jr: Vagal stimulation and aerosol histamine increase hysteresis of lung recoil. J Appl Physiol 51:477–484, 1981.
17. Colebatch HJ, Engel LA: Constriction of the lung by histamine before and after adrenalectomy in cats. J Appl Physiol 37:798–805, 1974.

18. Nadel JA, Colebatch JH, Olsen CR: Location and mechanism of airway constriction after barium sulfate microembolism. J Appl Physiol 19:387–394, 1964.
19. Ploy-Song-Sand Y, Corbin RP, Engel LA: Effects of intravenous histamine on lung mechanics in man after beta-blockade. Appl Physiol 44:690–695, 1978.
20. Hoppin FG Jr, Stothert JC Jr, Greaves IA, et al: Lung recoil: Elastic and rheologic properties. *In* Macklem P, Mead J (eds): Handbook of Physiology. Section 3. The Respiratory System. Vol III: Mechanics of Breathing (Part 1). Bethesda, MD: American Physiological Society, 1986, pp 195–216.
21. Whitsett JA, Weaver TE: Hydrophobic surfactant proteins in lung function and disease. N Engl J Med 347:2141–2148, 2002.
22. Frerking I, Gunther A, Seeger W, Pison U: Pulmonary surfactant: Functions, abnormalities, and therapeutic options. Intensive Care Med 27:1699–1717, 2001.
23. Haagsman HP, Hogenkamp A, van Eijk M, Veldhuizen EJ: Surfactant collectins and innate immunity. Neonatology 93:288–294, 2008.
24. Nogee LM, Wert SE, Proffit SA, et al: Allelic heterogeneity in hereditary surfactant protein B (SP-B) deficiency. Am J Respir Crit Care Med 161:973–981, 2000.
25. Ballard PL, Nogee LM, Beers MF, et al: Partial deficiency of surfactant protein B in an infant with chronic lung disease. Pediatrics 96:1046–1052, 1995.
26. Nogee LM, Dunbar AE III, Wert SE, et al: A mutation in the surfactant protein C gene associated with familial interstitial lung disease. N Engl J Med 344:573–579, 2001.
27. Hickling KG: The pressure-volume curve is greatly modified by recruitment. A mathematical model of ARDS lungs. Am J Respir Crit Care Med 158:194–202, 1998.
28. Kollef MH, Schuster DP: The acute respiratory distress syndrome. N Engl J Med 332:27–37, 1995.
29. Malhotra A: Low-tidal-volume ventilation in the acute respiratory distress syndrome. N Engl J Med 357:1113–1120, 2007.
30. Valente Barbas CS: Lung recruitment maneuvers in acute respiratory distress syndrome and facilitating resolution. Crit Care Med 31(4 Suppl):S265–S271, 2003.
31. Brower RG, Morris A, MacIntyre N, et al: Effects of recruitment maneuvers in patients with acute lung injury and acute respiratory distress syndrome ventilated with high positive end-expiratory pressure. ARDS Clinical Trials Network, National Heart, Lung, and Blood Institute, National Institutes of Health. Crit Care Med 31:2592–2597, 2003.
32. Hodgson C, Keating JL, Holland AE, et al: Recruitment manoeuvres for adults with acute lung injury receiving mechanical ventilation. Cochrane Database Syst Rev 2009;(2):CD006667.
33. Gauthier AP, Verbanck S, Estenne M, et al: Three-dimensional reconstruction of the in vivo human diaphragm shape at different lung volumes. J Appl Physiol 76:495–506, 1994.
34. Cohn D, Benditt JO, Eveloff S, McCool FD: Diaphragm thickening during inspiration. J Appl Physiol 83:291–296, 1997.
35. Decramer M: Hyperinflation and respiratory muscle interaction. Eur Respir J 10:934–941, 1997.
36. Garcia-Pachon E: Paradoxical movement of the lateral rib margin (Hoover sign) for detecting obstructive airway disease. Chest 122:651–655, 2002.
37. Walsh JM, Webber CL Jr, Fahey PJ, Sharp JT: Structural change of the thorax in chronic obstructive pulmonary disease. J Appl Physiol 72:1270–1278, 1992.
38. Farkas GA, Roussos C: Adaptability of the hamster diaphragm to exercise and/or emphysema. J Appl Physiol 53:1263–1272, 1982.
39. Gorman RB, McKenzie DK, Butler JE, et al: Diaphragm length and neural drive after lung volume reduction surgery. Am J Respir Crit Care Med 172:1259–1266, 2005.
40. De Troyer A, Kirkwood PA, Wilson TA: Respiratory action of the intercostal muscles. Physiol Rev 85:717–756, 2005.
41. De Troyer A, Estenne M: Coordination between rib cage muscles and diaphragm during quiet breathing in humans. J Appl Physiol 57:899–906, 1984.
42. Saboisky JP, Gorman RB, De Troyer A, et al: Differential activation among five human inspiratory motoneuron pools during tidal breathing. J Appl Physiol 102:772–780, 2007.
43. Wang X, Jiang T, Reid D, Road J: Ventilatory muscle injury. *In* Hamid Q, Shannon J, Martin J (eds): Physiologic Basis of Respiratory Disease. Hamilton, Ontario: BC Decker, 2005, pp 639–647.
44. Aubier M, Trippenbach T, Roussos C: Respiratory muscle fatigue during cardiogenic shock. J Appl Physiol 51:499–508, 1981.
45. Vassilakopoulos T, Zakynthinos S, Roussos CH: Respiratory muscles and weaning failure. Eur Respir J 9:2383–2400, 1996.
46. Laghi F, D'Alfonso N, Tobin MJ: Pattern of recovery from diaphragmatic fatigue over 24 hours. J Appl Physiol 79:539–546, 1995.
47. Bellemare F, Grassino A: Evaluation of human diaphragm fatigue. J Appl Physiol 53:1196–1206, 1982.
48. Bellemare F, Bigland-Ritchie B: Central components of diaphragmatic fatigue assessed by phrenic nerve stimulation. J Appl Physiol 62:1307–1316, 1987.
49. Zakynthinos A, Roussos C: Respiratory muscle fatigue. *In* Hamid Q, Shannon J, Martin J (eds): Physiologic Basis of Respiratory Disease. Hamilton, Ontario: BC Decker, 2005, pp 289-307.
50. Shanely RA, Zergeroglu MA, Lennon SL, et al: Mechanical ventilation-induced diaphragmatic atrophy is associated with oxidative injury and increased proteolytic activity. Am J Respir Crit Care Med 166:1369–1374, 2002.
51. Anzueto A, Peters JI, Tobin MJ, et al: Effects of prolonged controlled mechanical ventilation on diaphragmatic function in healthy adult baboons. Crit Care Med 25:1187–1190, 1997.
52. Levine S, Nguyen T, Taylor N, et al: Rapid disuse atrophy of diaphragm fibers in mechanically ventilated humans. N Engl J Med 358:1327–1335, 2008.
53. Marini JJ, Rodriguez RM, Lamb V: The inspiratory workload of patient-initiated mechanical ventilation. Am Rev Respir Dis 134: 902–909, 1986.
54. Marini JJ, Capps JS, Culver BH: The inspiratory work of breathing during assisted mechanical ventilation. Chest 87:612–618, 1985.
55. Gayan-Ramirez G, Testelmans D, Maes K, et al: Intermittent spontaneous breathing protects the rat diaphragm from mechanical ventilation effects. Crit Care Med 33:2852–2853, 2005.
56. Leung P, Jubran A, Tobin MJ: Comparison of assisted ventilator modes on triggering, patient effort, and dyspnea. Am J Respir Crit Care Med 155:1940–1948, 1997.
57. Ayas NT, McCool FD, Gore R, et al: Prevention of human diaphragm atrophy with short periods of electrical stimulation. Am J Respir Crit Care Med 159:2018–2020, 1999.
58. Leith DE, Mead J: Mechanisms determining residual volume of the lungs in normal subjects. J Appl Physiol 23:221–227, 1967.
59. Barnas GM, Green MD, Mackenzie CF, et al: Effect of posture on lung and regional chest wall mechanics. Anesthesiology 78:251–259, 1993.
60. Wahba RW: Perioperative functional residual capacity. Can J Anaesth 38:938–939, 1991.
61. Leith DE, Brown R: Human lung volumes and the mechanisms that set them. Eur Respir J 13:468–472, 1999.
62. Leith DE, Bradley M: Ventilatory muscle strength and endurance training. J Appl Physiol 41:508–516, 1976.
63. Rutchik A, Weissman AR, Almenoff PL, et al: Resistive inspiratory muscle training in subjects with chronic cervical spinal cord injury. Arch Phys Med Rehabil 79:293–297, 1998.
64. Lumb AB (ed): Elastic forces and lung volumes. *In* Nunn's Applied Respiratory Physiology (6th ed). Italy: Elsevier, 2005, pp 25–38.
65. Brower RG, Lanken PN, MacIntyre N, et al: Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. National Heart, Lung, and Blood Institute ARDS Clinical Trials Network. N Engl J Med 351:327–336, 2004.
66. Luecke T, Pelosi P: Clinical review: Positive end-expiratory pressure and cardiac output. Crit Care 9:607–621, 2005.
67. Parker JC, Hernandez LA, Longenecker GL, et al: Lung edema caused by high peak inspiratory pressures in dogs: Role of increased microvascular filtration pressure and permeability. Am Rev Respir Dis 142:321–328, 1990.
68. Rahn H, Otis AB, Chadwick LE, Fenn WO: The pressure-volume diagram of the thorax and lung. Am J Physiol;146:161–178, 1946.
69. Hager DN, Krishnan JA, Hayden DL, et al: Tidal volume reduction in patients with acute lung injury when plateau pressures are not high. Am J Respir Crit Care Med 172:1241–1245, 2005.
70. Mead J, Takishima T, Leith D: Stress distribution in lungs: A model of pulmonary elasticity. J Appl Physiol 28:596–608, 1970.
71. Talmor D, Sarge T, Malhotra A, et al: Mechanical ventilation guided by esophageal pressure in acute lung injury. N Engl J Med 359:2095–2104, 2008.

72. Lumb AB (ed): Respiratory system resistance. *In* Nunn's Applied Respiratory Physiology (6th ed). Italy: Elsevier, 2005, pp 39–54.
73. Lumb AB (ed): Elastic forces and lung volumes. *In* Nunn's Applied Respiratory Physiology (6th ed). Italy: Elsevier, 2005, pp 25–38.
74. Curtis JL, Mahlmeister M, Fink JB, et al: Helium-oxygen gas therapy. Use and availability for the emergency treatment of inoperable airway obstruction. Chest 90:455–457, 1986.
75. Colebourn CL, Barber V, Young JD: Use of helium-oxygen mixture in adult patients presenting with exacerbations of asthma and chronic obstructive pulmonary disease: A systematic review. Anaesthesia 62:34–42, 2007.
76. Rodrigo GJ, Rodrigo C, Pollack CV, Rowe B: Use of helium-oxygen mixtures in the treatment of acute asthma: A systematic review. Chest 123:891–896, 2003.
76a. Maggiore SM, Richard JC, Abroug F, et al: A multicenter, randomized trial of noninvasive ventilation with helium-oxygen mixture in exacerbations of chronic obstructive lung disease. Crit Care Med 38:145–151, 2010.
77. Hyatt RE: Expiratory flow limitation. J Appl Physiol 55(1 Pt 1):1–7, 1983.
78. Wilson T, Rodarte J, Butler J: Wave-speed and viscous flow limitation. *In* Macklem P, Mead J (eds): Handbook of Physiology. Section 3: The Respiratory System. Bethesda, MD: American Physiological Society, 1986, pp 55–61.
79. Mead J, Turner JM, Macklem PT, Little JB: Significance of the relationship between lung recoil and maximum expiratory flow. J Appl Physiol 22:95–108, 1967.
80. Pedley T, Drazen J: Aerodynamic theory. *In* Macklem P, Mead J (eds): Handbook of Physiology. Section 3: The Respiratory System. Bethesda, MD: American Physiological Society; 1986, pp 41–54.
81. Dawson SV, Elliott EA: Wave-speed limitation on expiratory flow—A unifying concept. J Appl Physiol 43:498–515, 1977.
82. Bates JH: Physics of expiratory flow limitation. In Hamid Q, Shannon J, Martin J (eds): Physiologic Basis of Respiratory Disease. Hamilton, Ontario: BC Decker, 2005, pp 55–60.
83. Ward NS, Dushay KM: Clinical concise review: Mechanical ventilation of patients with chronic obstructive pulmonary disease. Crit Care Med 36:1614–1619, 2008
84. MacIntyre NR, Cheng KC, McConnell R: Applied PEEP during pressure support reduces the inspiratory threshold load of intrinsic PEEP. Chest 111:188–193, 1997.
85. Thille AW, Rodriguez P, Cabello B, et al: Patient-ventilator asynchrony during assisted mechanical ventilation. Intensive Care Med 32:1515–1522, 2006. Epub 2006;August 1.
86. Petrof BJ, Legaré M, Goldberg P, et al: Continuous positive airway pressure reduces work of breathing and dyspnea during weaning from mechanical ventilation in severe chronic obstructive pulmonary disease. Am Rev Respir Dis 141:281–289, 1990.
87. Maltais F, Reissmann H, Navalesi P, et al: Comparison of static and dynamic measurements of intrinsic PEEP in mechanically ventilated patients. Am J Respir Crit Care Med 150(5 Pt 1):1318–1324, 1994.
88. Aaron EA, Seow KC, Johnson BD, Dempsey JA: Oxygen cost of exercise hyperpnea: Implications for performance. J Appl Physiol 72:1818–1825, 1992.
89. O'Donnell DE, Laveneziana P: Dyspnea and activity limitation in COPD: Mechanical factors. COPD 4:225–236, 2007.

CHAPTER 6

Pulmonary Circulation and Regulation of Fluid Balance

Jeffrey R. Jacobson, MD • Joe G. N. Garcia, MD

INTRODUCTION

PULMONARY HEMODYNAMICS
Pulmonary Vascular Pressures
Pulmonary Vascular Resistance
Pulmonary Vascular Compliance
Pulmonary Perfusion
Mechanical Stress and Strain
Pulmonary Vascular Response to Hypoxia
Neural Regulation of Pulmonary Vascular Resistance
Humoral Regulation of Pulmonary Vascular Resistance

LUNG FLUID AND SOLUTE EXCHANGE
Pathogenesis of Pulmonary Edema
Transcapillary Exchange
Sites of Fluid and Solute Exchange
Pulmonary Lymphatic Vessels
Lung Interstitium
Transvascular Transport of Plasma Molecules
Capillary Endothelial Permeability
Strategies to Reverse Permeability and Restore Barrier Integrity

PULMONARY VASCULAR GENOMICS

INTRODUCTION

The pulmonary circulation, which is interposed between the right and left ventricles, has the following functions: (1) to deliver the entire cardiac output under low pressure from the right ventricle to the pulmonary microvessels and, in that process, to exchange carbon dioxide for oxygen across the alveolar-capillary membrane; (2) to act as a source of production, release, and processing of humoral mediators; and (3) to serve as a barrier to the exchange of fluid and solutes and thus maintain lung fluid balance. The morphology of the pulmonary circulation is ideally adapted for these functions. Nearly the entire cardiac output is brought into contact with alveolar gas at the 1- to 2-μm-thick alveolar-capillary membrane for about 0.75 to 1 second. This juxtaposition of capillaries with alveoli provides the vast surface area needed for effective gas exchange: well over 100 m^2 (more than one half the area of a singles tennis court). The structural arrangement is such that the distance through which oxygen and carbon dioxide must diffuse between gas and blood is about one tenth of the distance of diffusion in peripheral tissues. (Additional information about the anatomy of the pulmonary circulation is found in Chapter 1, and about the physiologic factors that govern the distribution of blood flow and ventilation in Chapter 4.)

As indicated, the pulmonary circulation has important functions in addition to its role in gas exchange. The microvessels exchange solutes and water, and the mechanisms regulating the balance of fluid and solutes in extravascular spaces of the lung are critical in the understanding of the pathophysiology of pulmonary edema (see later in this chapter and in Chapter 55). The pulmonary vascular endothelium, the monolayer of cells that line all vessels, is a multidimensional tissue whose specialized functions include direct lung vascular barrier regulation, participation in inflammatory responses, and the processing of mediators before they are delivered to the systemic circulation.

PULMONARY HEMODYNAMICS

Thorough, in-depth reviews of hemodynamic aspects of the pulmonary circulation have been written by Fishman,[1] Dawson,[2] Hughes and Morrell,[3] and Gao and Raj.[4] The effect of gravity on the distribution of blood flow in the lungs and the influence this has on gas exchange is fully discussed in Chapter 4 of this book.

Pulmonary Vascular Pressures

Pressure and flow are highly pulsatile throughout the pulmonary circulation. The pressure pulsatility decreases across the pulmonary circuit, but the pulsatile nature of the flow persists on the venous side.[1] Pulmonary arterial pressure (P_{PA}) is normally approximately 25/9 mm Hg and is roughly one fifth the value of systemic arterial pressure. Because P_{PA} is low, hydrostatic pressure differences due to gravity result in substantial differences in vascular pressure from the top to the bottom of the lung. If the pulmonary artery is considered to be a column of blood approximately 25 cm high, P_{PA} will be 25 cm H_2O (or 18 mm Hg) higher at the bottom of the lung than at the top. This pressure difference results in a nonuniform distribution of blood flow, as discussed subsequently in the section on "Distribution of Pulmonary Blood Flow."

P_{PA} is measured by inserting a cardiac catheter or a balloon-tipped flotation catheter into the pulmonary artery.[2] Inflating the balloon leads to advancement ("floating") of the catheter (Fig. 6-1) until it "wedges" and occludes a peripheral pulmonary artery. With the balloon inflated, the pressure measured in the tip of the catheter is called the *pulmonary artery wedge pressure* (P_{PW}).[5] This procedure effectively extends the static fluid within the catheter lumen into the vascular bed, and the measured pressure is thus at the site where this extended column next joins a vessel in which blood is flowing. The wedge pressure (normally 5 to 10 mm Hg) is an estimate of the vascular pressure at the point of confluence of pulmonary veins and hence reflects left atrial pressure (P_{LA}).

Changes in pressure distal to the confluence of the pulmonary veins, such as that induced by constriction of the pulmonary venules, can alter the relationship between P_{LA} and P_{PW}. Also, the precise location of the tip of the catheter in the lung influences the measurement of P_{PW} (Fig. 6-2). Zone 1 is the region of the lung defined by West (see Fig. 4-11) in which alveolar pressure (Palv) > P_{PA} > pulmonary venous pressure (P_{PV}), and therefore there is minimal blood flow through the alveolar vessels. Zone 2 is where P_{PA} > Palv > P_{PV}, and therefore flow increases linearly descending into the lung. Positioning the catheter in the upper lung (in zone 1 or 2) results in a P_{PW} different from P_{LA} because higher alveolar pressures occlude the fluid column. Under these conditions, P_{PW} provides an incorrect measurement of pulmonary vascular outflow pressure. A catheter wedged in zone 3, where P_{PA} > P_{PV} > Palv, provides an accurate measurement of P_{LA}.

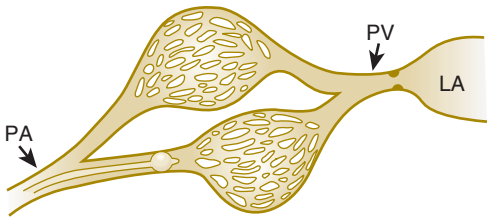

FIGURE 6-1 ■ Method of determining pulmonary wedge pressure. By placing a catheter through the right heart and pulmonary artery (PA) and occluding a small pulmonary artery with a balloon (*circle*), the static fluid column within the catheter is functionally extended from the catheter tip through the capillaries and into pulmonary veins (PV). The pressure measured is at the confluence of veins, where flow is again present. Because the pressure drop from a large vein to the left atrium (LA) is small, wedge pressure is a reflection of left atrial pressure except when (1) there is a change in downstream resistance, indicated by constriction (*solid semicircles*) proximal to the LA or (2) the catheter is in an artery perfusing a capillary bed where alveolar pressure exceeds PV pressure (i.e., zone 1 or 2). In the latter case, when the balloon is inflated, pressure within the capillary bed falls toward PV pressure, capillaries are compressed, and the fluid column interrupted, and wedge pressure will no longer reflect left atrial pressure (see Fig. 6-2).

Pulmonary Vascular Resistance

Pulonary vascular resistance (PVR) is calculated by the following equation:

$$PVR = \frac{\overline{P_{PA}} - \overline{P_{LA}}}{\dot{Q}_T} \quad (1)$$

where $\dot{Q}_T$ is pulmonary blood flow, $\overline{P_{PA}}$ is mean pulmonary artery (inflow) pressure, and $\overline{P_{LA}}$ mean left atrial (outflow) pressure, which is often estimated by mean P_{PW} ($\overline{P_{PW}}$) PVR is expressed in units of mm Hg/L/min, or in dynes/sec/cm^5 (to convert units to dynes/sec/cm^5, PVR in mm Hg/L/min is multiplied by 1332). The normal

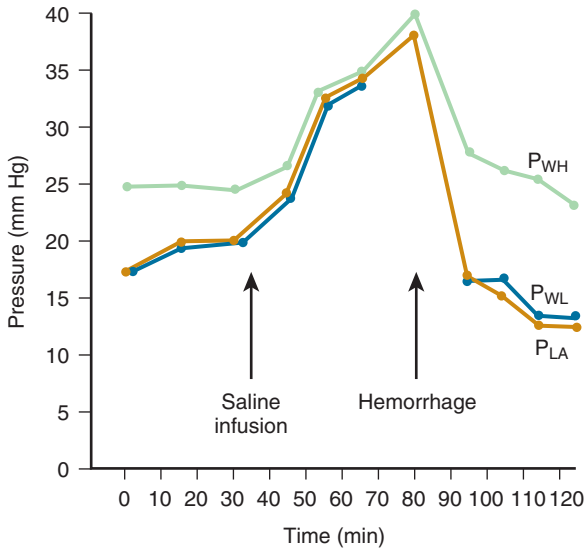

FIGURE 6-2 ■ Illustration of the influence of catheter position on wedge pressure measurement. When the catheter is wedged in a low position (i.e., zone 3), wedge pressure (P_{WL}) reflects left atrial pressure (P_{LA}). When the catheter is wedged in a high position (P_{WH}), however, the pressure does not reflect left atrial pressure, because when the catheter is wedged, pulmonary capillary pressure falls toward pulmonary venous pressure, which is less than alveolar pressure (i.e., zone 2), and the capillary bed is compressed. With a saline infusion, pulmonary venous pressure rises, capillaries open (i.e., zone 3), and P_{WH} is equal to P_{LA}. Hemorrhage again lowers pulmonary venous pressure, and again P_{WH} is greater than P_{LA}. (Redrawn from Todd TR, Baile EM, Hogg JC: Pulmonary arterial wedge pressure in hemorrhagic shock. Am Rev Respir Dis 118:613–616, 1978.)

PVR value is about 0.1 mm Hg/L/min, or 100 dynes/sec/cm^5. This value is approximately one tenth the value of systemic vascular resistance.

The use of Equation 1 (from Ohm's law) is complicated by the fact that resistance is not independent of PPA or PLA. As an example, if both PPA and PLA were elevated to such a degree that the pressure difference remained unchanged, PVR would nevertheless decrease because of distention of vessels by higher intravascular pressures. Thus, inferences regarding resistance changes in the vasculature require consideration of multiple mechanical factors that affect vascular resistance, including not only vascular pressures but also lung volume and inflation pressure. PVR is a function of lung volume because inflation distends some vessels and compresses others, as described later in the discussion of alveolar and extra-alveolar vessels.

PVR can also be potentially modeled by Poiseuille's equation, which describes for laminar flow the relationship of resistance (R) of a tube to the tube's physical characteristics and viscosity of perfusing fluid:

$$R = \frac{8}{\pi} \cdot \frac{l}{r^4} \cdot \eta \qquad (2)$$

where l is the length of the tube, r is the radius of the tube, and η is the viscosity of the perfusion fluid. It is evident from this equation that the critical determinant of PVR is the tube's radius, because resistance is proportional to l/r^4. Although this suggests that a 50% decrease in the tube radius, which might be encountered with constriction of a vessel, increases resistance 16-fold, this derived relationship may be excessively robust.

Ohm's law and the Poiseuille equation, although useful in describing the resistance properties of pulmonary vessels, have limitations that must be considered when changes in the calculated PVR value are interpreted. Blood flow is pulsatile, blood vessels are complex distensible branching tubes (not rigid cylinders), and blood-formed elements in the plasma constitute a nonhomogeneous fluid. These characteristics are not accounted for in either equation. Nevertheless, the ratio of pulmonary perfusion pressure to blood flow under strictly controlled conditions is a useful measure of pulmonary vasomotor tone. Its usefulness depends on knowledge of levels of intravascular pressure, pulmonary blood volume, and lung volume.

Vascular Resistance Profile

The vascular resistance profile in the pulmonary circuit has been estimated by the use of micropipettes to measure the pressure drop across the pulmonary circulation.[6] In zone 3 conditions, where vascular resistance is not influenced by alveolar pressure, most of the resistance lies in pulmonary microvessels with nearly half of the total in alveolar capillaries (Fig. 6-3). These results indicate that the diameters of small pulmonary arteries and capillaries account for the greater part of pressure drop across the pulmonary vascular bed. This finding is in striking contrast to the systemic circulation, in which the greatest pressure drop occurs in arterioles.

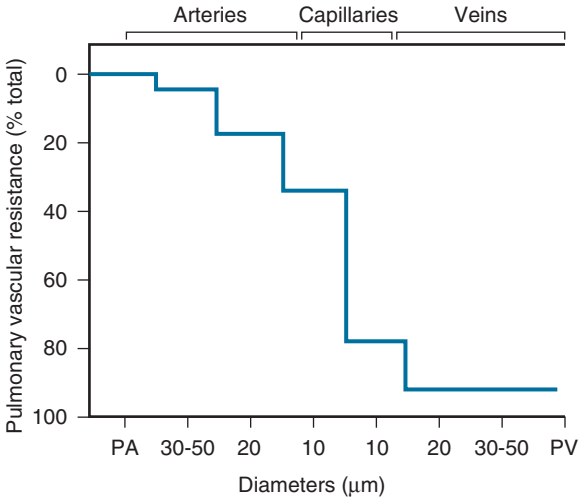

FIGURE 6-3 ■ Distribution of vascular resistance as determined by micropuncture measurement of pressures. Unlike the situation in the systemic circulation, most of the vascular resistance in the pulmonary circuit is in the capillaries. Measurements were made in subpleural vessels of isolated dog lung under zone 3 conditions. (Redrawn from Bhattacharya J, Staub NC: Direct measurement of microvascular pressures in isolated perfused dog lung. Science 210:327–328, 1980.)

Other investigators have used indirect approaches to measure the distribution of vascular resistance, such as observing vascular pressures after rapid vascular occlusion or injection with a low-viscosity bolus.[1] These techniques localize vascular resistance sites in relation to sites of vascular volume or compliance. Vascular occlusion experiments have localized nearly half of the vascular resistance within a central compartment that also includes 75% of the vascular compliance.[7] Because these compartments are defined functionally rather than anatomically, the central compartment may include small arteries and veins in addition to capillaries. Models of this type are particularly useful in identifying sites of vascular action of neural humoral mediators. Hypoxia primarily constricts arteries, as does sympathetic stimulation and serotonin, whereas histamine primarily constricts veins, and catecholamines increase both arterial and venous resistance.[2]

Functional Description of Pulmonary Vessels

The diameter of any vessel is determined by the transmural pressure difference, defined as the pressure difference acting across the vessel wall; that is, intraluminal (or intravascular) pressure (Piv) minus perivascular (or interstitial hydrostatic) pressure (Pi). The transmural pressure difference (Piv – Pi) is important in determining the diameter of pulmonary vessels because of the distensible nature of the pulmonary vascular bed. An increase in intraluminal pressure (e.g., secondary to increased left atrial pressure) increases transmural pressure and thus dilates pulmonary vessels. A decrease in perivascular pressure also dilates pulmonary vessels.

The intrapulmonary vascular tree is subdivided into three major types of vessels that are defined by the

pressures around the vessel: *extra-alveolar, alveolar,* and *corner vessels.*[1] The definitions of these three types of vessels are based on functional rather than anatomic descriptions, but in general, extra-alveolar vessels are considered to be pre- and postcapillary vessels in series with alveolar vessels, which are the capillaries.

Extra-Alveolar Vessels. Extra-alveolar vessels are defined as the intrapulmonary vessels affected by intrapleural pressure and *not* by alveolar pressure changes. The extra-alveolar vessels in the lung parenchyma are surrounded by collagen fibers, lymphatic vessels, and loose areolar tissue and include arteries, veins, venules, and arterioles. These vessels are affected by changes in pleural pressure and the closely related interstitial fluid pressure. Both pressures are the result of lung inflation and the recoil force generated by elastin in lung tissue. The pressure in the perivascular interstitial space surrounding the large pulmonary arteries or veins is somewhat more negative than the pleural pressure and becomes more so when the lung is inflated.[8] Changes in pleural or interstitial pressure have marked effects on the vascular caliber of extra-alveolar vessels. A decrease in the pleural pressure such as that occurring at high lung volumes passively dilates these vessels, whereas an increase in pleural pressure, such as that occurring at low lung volumes compresses the vessels.

Alveolar Vessels. These vessels are the capillaries within the interalveolar septa, which are surrounded by alveoli and are subjected to alveolar pressure and *not* to pleural pressure: thus, an increase in alveolar pressure compresses these vessels. The perivascular tissue of the septa consists of the extracellular matrix, whose constituents include fibronectin, laminin, heparan sulfate, and collagen fibrils. As the lung expands, the alveolar wall, which is pleated at functional residual capacity, unfolds,[9] and connective tissue elements in the wall change their conformation. Because of the surface tension of the layer of surfactant at the air-liquid interface, the actual pericapillary pressure is normally slightly less than the alveolar pressure,[10] but is always higher than the pressure around extra-alveolar vessels.[1]

Corner Vessels. These vessels are capillaries embedded in the thick alveolar-capillary septum between three alveoli or within pleats in alveolar walls.[9] Corner vessels are distinguishable from capillaries in the thin septum (the alveolar vessels), and hence are not subject only to changes in alveolar pressure. Alveolar vessels are compressed by increases in the alveolar pressure, whereas the corner vessels remain patent.[11] Corner vessels bypass the alveoli, and allow septal tissue to remain perfused in the presence of increases in alveolar pressure.

Mechanical Effects on Pulmonary Vascular Resistance

Transmural Pressure. The importance of transmural pressure is highlighted by the experiments described in Figures 6-4 and 6-5. At a controlled P_{LA} (see Fig. 6-4), increases in P_{PA} cause a decrease in PVR, but the effect is progressively less as P_{LA} is raised.[12] This indicates that the vessels are nearly maximally dilated at high levels of

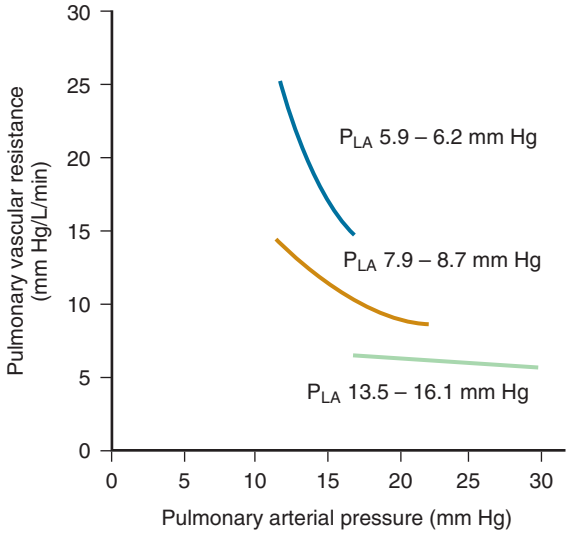

FIGURE 6-4 ■ Pulmonary vascular resistance depends on pulmonary arterial pressure. As pulmonary arterial pressure increases as a result of increasing flow, vessels are distended and resistance falls. This effect is diminished at higher left atrial pressures (P_{LA}) because the vascular bed is near maximal distention. (Data from Borst HG, McGregor M, Whittenberger JL, Berglund E: Influence of pulmonary arterial and left atrial pressures on pulmonary vascular resistance. Circ Res 4:393–399, 1956.)

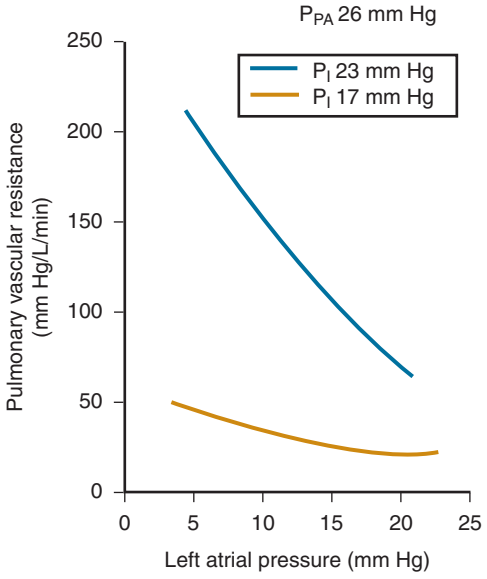

FIGURE 6-5 ■ Increases in left atrial pressure decrease pulmonary vascular resistance. In an isolated lung lobe, pulmonary artery pressure was held constant (P_{PA} = 26 mm Hg), the alveolar pressure was increased to either 23 or 17 mm Hg, pleural pressure was zero, and left atrial pressure varied. Pulmonary vascular resistance drops as left atrial pressure increases because the higher transmural pressure dilates vessels. The curves are for two different levels of lung inflation pressure. At higher inflation pressures (P_I) and lung volumes, vascular resistance is increased at all levels of left atrial pressure because alveolar vessels are stretched and compressed (see Fig. 6-6). (Data from Roos A, Thomas LJ Jr, Nagel EL, Prommas DC: Pulmonary vascular resistance as determined by lung inflation and vascular pressures. J Appl Physiol 16:77–84, 1961.)

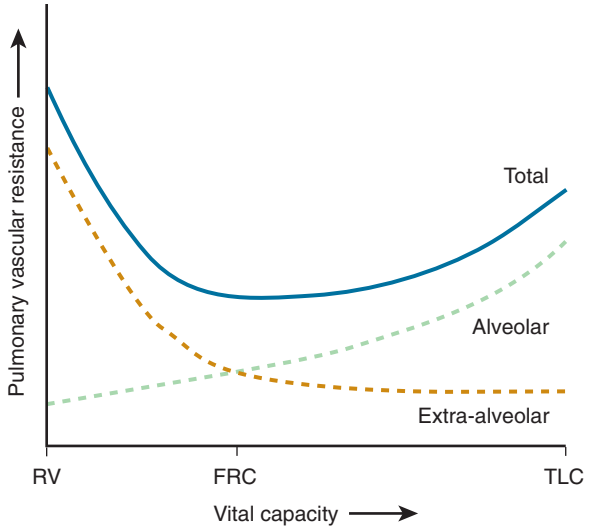

FIGURE 6-6 ■ Pulmonary vascular resistance increases as lung volume is decreased from functional residual capacity (FRC) to residual volume (RV) because of the influence of rising intrapleural pressure on extra-alveolar vessels. Resistance also increases with lung inflation from FRC to total lung capacity (TLC) because of stretched and flattened alveolar vessels. (Redrawn from Murray JF: The Normal Lung [2nd ed]. Philadelphia: WB Saunders, 1986.)

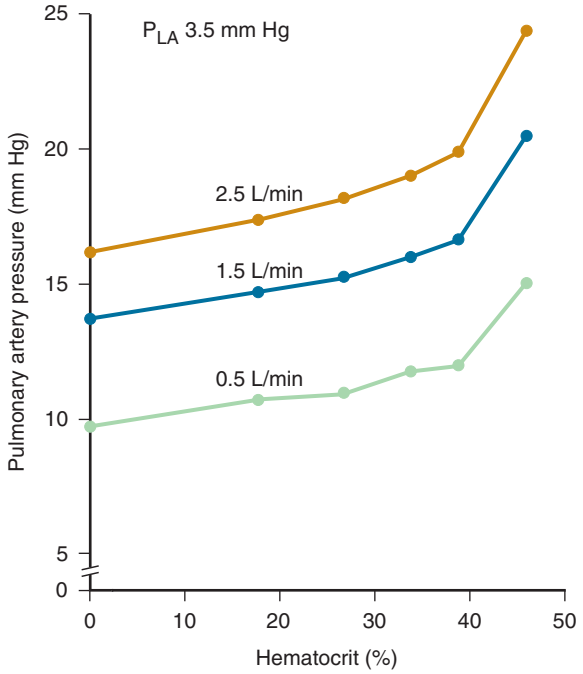

FIGURE 6-7 ■ Effect of hematocrit on pulmonary artery pressure at three levels of blood flow (0.5, 1.5, and 2.5 L/min are depicted). Left atrial pressure (P_{LA}) was held constant at 3.5 mm Hg. As hematocrit is increased at constant levels of pulmonary flow, pulmonary artery pressure increases, reflecting the higher vascular resistance caused by increased blood viscosity. (Redrawn from Murray JF, Karp RB, Nadel JA: Viscosity effects on pressure-flow relations and vascular resistance in dogs' lungs. J Appl Physiol 27:336–341, 1969.)

P_{LA} and that, once this occurs, additional increases in transmural pressure brought on by elevating P_{PA} do not produce further marked decreases in PVR. A similar phenomenon is demonstrated in Figure 6-5, where P_{LA} is increased at two different levels of transpulmonary pressure (23 and 17 mm Hg) while P_{PA} is held constant throughout. As P_{LA} is increased, PVR decreases because transmural pressure increases and vessels are progressively distended.[13] At a constant P_{PA} and P_{LA}, PVR is increased at the higher level of transpulmonary pressure because alveolar vessels are compressed by high alveolar pressures.

Lung Volume. A change in lung volume has opposite effects on the caliber of alveolar and extra-alveolar vessels, as shown in Figure 6-6. During lung inflation from residual volume to total lung capacity, resistance of alveolar vessels progressively increases, whereas resistance of extra-alveolar vessels progressively decreases. Alveolar vessels are compressed and elongated as lung volume increases. In contrast, interstitial pressure surrounding extra-alveolar vessels decreases, and the increased transmural pressure causes a decrease in resistance of these vessels. Corner vessels are also subjected to this same interstitial pressure and thus show a decreased resistance with lung inflation. Because the resistances of alveolar and extra-alveolar vessels are in series, the resistances add and the change in PVR forms a "U"-shaped curve, with the nadir of the curve operating at approximately functional residual capacity, the usual end-expiratory lung volume.

Viscosity. The viscosity term (η) of Poiseuille's formula (Equation 2) predicts that an increase in blood viscosity produces a proportional increase in PVR. The primary factor determining viscosity of the blood is the hematocrit.[14] Viscosity is also a function of the deformability of red blood cells in pulmonary microvessels and the viscosity of plasma. Figure 6-7 shows the effects of changes in the hematocrit on pulmonary arterial pressure at three levels of blood flow. After each level of blood flow, it is evident that blood hematocrit values over 40% cause increases in P_{PA} and PVR.

Pulmonary Vascular Compliance

Pulmonary Vascular Pressure-Volume Curve

The pulmonary vasculature is a highly compliant circuit, and pulmonary blood volume normally constitutes about 10% of total blood volume. The distribution of blood volume among the arterial, capillary, and venous volumes, however, varies among species, and depends on techniques of measurement and whether the arteries, capillaries, and veins are defined functionally or anatomically. Human capillary blood volume has been functionally estimated[15] to be approximately 75 mL, or about 10% to 20% of total pulmonary blood volume, but estimates in animals have generally shown a higher proportion of pulmonary blood volume within the capillaries[2]; for example, by morphologic methods, between 60 and 200 mL, or one third of total pulmonary blood volume, has been localized in capillaries.[16]

The pressure-volume curve of the pulmonary vasculature is linear at low levels of pulmonary perfusion pressure, with small changes in volume resulting in small changes in pressure, but becomes nonlinear at higher pressures, at which small changes in volume cause large pressure changes. Pulmonary vascular compliance is defined as $\Delta V/\Delta P$, where ΔV is the change in pulmonary vascular volume and ΔP is the change in transmural pressure. Microvessels are usually identified as the primary site of vascular compliance,[17] although others have postulated that larger pulmonary vessels may contribute to the compliance.

Changes in Vascular Compliance

Pulmonary vascular compliance is regulated by alterations in sympathetic nerve activity; compliance decreases with sympathetic activation.[18] The pulmonary circulation serves as a vascular reservoir that responds to sympathetic stimulation by increasing left atrial filling pressure and increasing cardiac output. Pulmonary vascular compliance can also be influenced by changes in lung volume secondary to alterations in intrapleural pressure. Because a substantial fraction of blood volume is localized in large pulmonary arteries and veins, which are largely extra-alveolar vessels, lung inflation increases transmural pressure, passively enlarges these vessels, and thereby increases blood volume within the pulmonary circuit. Reduction in lung volume has the opposite effect of reducing pulmonary blood volume within the pulmonary circuit.

Pulmonary Perfusion

Distention and Recruitment

Pulmonary microvessels can be recruited (i.e., new vessels are "brought into play" in the microcirculation) or already-perfused vessels can be distended (i.e., vessels dilate as a result of increased transmural pressure). The question of which process occurs in response to increasing the pulmonary capillary pressure—or more importantly, which is the dominant process under a particular circumstance—is unresolved. (See also Fig. 4-9 and related discussion.) There are regional differences in the relative importance of recruitment and distention of pulmonary vessels. Alveolar vessels in the upper lung regions (zone 1) are more likely to be recruited when transmural pressure rises, because vessels are normally collapsed in this region; both recruitment and distention occur in zone 2 conditions because of the uneven perfusion in this region; and distention is likely to predominate in zone 3 vessels when transmural pressure rises, because this lung region is more uniformly perfused than other regions.

Distribution of Pulmonary Blood Flow

Because of gravity and the prevailing low pulmonary artery perfusion pressure, the regional distribution of blood flow within the lung varies considerably. The factors that govern intrapulmonary blood flow were largely defined during the 1960s in a series of elegant experiments by West and coworkers, which are described in detail in Chapter 4. The model that unites all these factors (see Fig. 4-11) subdivides the lung into three perfusion zones depending on the relationships among mean P_{PA}, mean P_{PV}, and P_{alv}.

Zone 1 is the region of the lung in which $P_{alv} > P_{PA} > P_{PV}$ and, in theory, there is no blood flow because alveolar vessels are collapsed; in reality, however, blood flow persists to some extent because pericapillary pressure in zone 1 is slightly lower than P_{alv}; because corner vessels are not subject to changes in P_{alv}; and because of the pulsatile nature of pulmonary capillary pressure, with intermittent bursts of flow occurring during systole.

Zone 2 is the region of the lung in which $P_{PA} > P_{alv} > P_{PV}$. Accordingly, blood flow begins just below the level of lung where $P_{PA} = P_{alv}$ and progressively increases, moving linearly downward from there; pulmonary perfusion in zone 2 is determined by the $P_{PA} - P_{alv}$ difference, rather than the conventional arterial minus *venous* pressure difference.

Zone 3 is the more dependent region of the lung in which $P_{PA} > P_{PV} > P_{alv}$. As conditions move downward, even though P_{PA} and P_{PV} increase by the same amount, perfusion increases within the zone because the increasing intravascular pressures progressively dilate vessels, which lowers regional vascular resistance and causes blood flow to steadily increase. The preponderance of blood flow in zone 3 in comparison with the other zones favors gas exchange because other factors (also described in Chapter 4) cause ventilation to be preferentially distributed to this region.

To describe conditions in the most dependent portion of the lung, zone 4 was added to account for the factors that decrease regional perfusion from the peak observed in zone 3. Blood flow in zone 4 is not determined by the relationships among P_{PA}, P_{PV}, and P_{alv}, but by lung volume and other local conditions at the base of the lung that affect the caliber of blood vessels, which are fully described in Chapter 4.

Because of the prevailing intravascular pressures, there is no zone 1 in the lung of healthy humans under ordinary conditions, even when upright (see Fig. 56-2). Most of the normal lung functions in zone 3 conditions, and only the uppermost region is in zone 2. However, a decrease in intravascular pressures, as in hemorrhagic shock, or an increase in intra-alveolar pressure, as with mechanical ventilation—especially with positive end-expiratory pressure—expands zone 2 and possibly creates zone 1. Variations to the zone-gravity model have been proposed by Hlastala and Glenny[19]; they continue to emphasize the role of gravity in determining blood flow distribution, but their conceptual framework incorporates additional concepts of fractal vascular trees and perfusion heterogeneity, and suggests that the structure of the pulmonary vascular system is an additional critical factor in determining regional blood flow.

Mechanical Stress and Strain

The pulsatile nature of blood pressure and flow exposes blood vessels to constant hemodynamic forces in the form of cyclic stretch and shear stress. The endothelium converts these mechanical stimuli to intracellular signals that affect cellular functions, including proliferation, migration, remodeling, apoptosis, and permeability, as well as gene expression. The cytoskeleton is the key structural framework for the endothelial cells to transmit mechanical forces between its luminal, abluminal, and junctional surfaces to its interior, including the cytoplasm, nucleus, and focal adhesion sites. Changes in mechanical stress activate multiple sensing mechanisms and signaling networks in endothelial cells, resulting in physiologic and pathologic functional responses.

Shear Stress

The flow of blood parallel to the vessel surface produces fluid shear stress from the friction of blood against the vessel wall. Endothelial cells are the primary vascular cells exposed to shear stress from laminar blood flow. The response of endothelial cells to physiologic levels of shear stress serves a number of regulatory functions, including vascular remodeling via the production of growth-promoting and growth-inhibiting substances; the modulation of hemostasis and thrombosis through the secretion of procoagulant, anticoagulant, and fibrinolytic agents; inflammation through the expression of chemotactic and adhesion molecules on membrane surfaces; and vascular smooth muscle cell contraction through the release of vasodilators and vasoconstrictors.[20] Endothelial cell perfusion at the physiologic shear rate of 10 dynes/cm^2 has been associated with barrier enhancement (see later discussion and Fig. 6-15), suggesting that shear stress is important in normal barrier maintainance.[21] Furthermore, disruption or unsteady blood flow at atherosclerosis-prone regions of blood vessels can impair these functions, leading to proatherogenic and/or prothrombotic states. Endothelial cells use multiple sensors for shear stress, including membrane receptors such as integrins, vascular endothelial growth factor receptor-2, ion channels, and platelet endothelial cell adhesion molecule-1.[22] These sensors can interact with each other and transactivate multiple signaling pathways,[23] including p38 and p42/44 mitogen-activated protein kinase, tyrosine kinase, and focal adhesion kinase, leading to differential gene expression,[20] as well as rapid actin cytoskeletal rearrangement as evidenced by flow-directed reorientation of the endothelium.[24]

Shear stress also serves a protective role by reducing endothelial cell turnover through inhibition of cell proliferation and suppression of apoptosis via activation of both p53 and the PI3K-Akt survival pathway, and nitric oxide production. The variability of vessel properties along with the pulsatile nature of blood flow results in temporal and spatial variations of shear stress on the vessel wall. In the straight part of the vessel, blood flows undisturbed with a mean shear rate of 10 to 70 dynes/cm^2. However, blood flow patterns in the bends and bifurcations are disturbed with eddies in which peak shear rates can exceed 100 dynes/cm^2. Thus, the nature of blood flow has varying effects on the endothelium depending on the microenvironment of the vasculature.[25]

Cyclic Stretch

Another important mechanical force generated in the lung circulation either by circulating blood, which results in the rhythmic, pulsatile distention of the arterial wall, or by tidal breathing, is cyclic stretch (CS). Blood pressure is the major determinant of vessel stretch, although arterial wall distention normally does not exceed 10% to 12% stretch.[26–28] Similar to shear stress, cyclic stretch induces reorientation of the endothelium, but transverse to the direction of strain.[26,29] Cultured endothelial cells stretched at 5% CS for 2 hours activate Rac signaling[30] and induce redistribution of actin[26] and cortactin[30] (an actin-binding protein) toward the cell periphery. Furthermore, in comparison to static conditions, physiologic stretch induces desensitization to edemagenic agents, as evidenced by the reduction of thrombin-induced paracellular gap formation.[26,30] In contrast, excessive distention of 18% CS induces Rho activation and increased sensitivity to edemagenic agonists.[26,29]

Long-term cyclic stretch increases the content of signaling and contractile proteins, including Rho GTPase, myosin light chains, myosin light chain kinase, ZIP kinase, PAR1, caldesmon, and hsp27, suggesting regulation at both the translational and posttranslational levels.[26,31] Chronic increased blood pressure activates vascular cell proliferation, collagen, and fibronectin synthesis, which results in thickening of the vascular wall leading to hypertension-induced vascular remodeling. Clinically, acute lung overdistention caused by mechanical ventilation at high tidal volumes can also induce remodeling of extracellular matrix constituents such as collagen, elastin, proteoglycans, glycosaminoglycans, and matrix metalloproteinases.[32] This reorganization, in part, influences cellular responses to mechanical stress via increased inflammatory cytokine production, macrophage activation, acute inflammation, and barrier dysfunction resulting in pulmonary edema. Reduction in tidal volume causes less extracellular matrix disorganization[32] and has improved patient mortality from ventilator-induced lung injury.[33]

Pulmonary Vascular Response to Hypoxia

Response Elements

Alveolar hypoxia, an alveolar P_{O_2} of less than 70 mm Hg, typically elicits pulmonary vasoconstriction. In general, experiments with isolated lungs, perfused in either the forward or reverse direction and ventilated with a variety of gas mixtures, have shown that the most important stimulus for vasoconstriction is alveolar hypoxia, as opposed to the P_{O_2} of pulmonary arterial blood.[2] The basis of increased resistance is constriction of small precapillary vessels.[34] Although smaller arteries constrict,

larger arteries dilate in response to elevated pressures,[34,35] and pulmonary veins do not constrict.[35] The vasoconstrictor response to hypoxia is unique to lungs in that local exposure of systemic vessels to hypoxia results in vasodilation. Hypoxic pulmonary vasoconstriction serves a regulatory function in matching perfusion to ventilation by redirecting perfusion away from poorly oxygenated (i.e., hypoxic) regions of the lung. Alveolar hypoxia in a lung segment causes significant diversion of blood flow to the normoxic lung.

Neurohumoral signals generated during hypoxia have been invoked to explain the response, but the basis of the constriction still remains unknown (recently reviewed by Stenmark and colleagues[36]). A major limitation in understanding the mechanisms has been the inability to obtain smooth muscle cells of microvessels of pulmonary arteries, the primary sites of contraction during hypoxia, which retain their contractile phenotype. Because the hypoxic pulmonary vasoconstrictor response occurs in isolated-perfused lungs and in isolated small (<300 μm) pulmonary arteries,[37] it is unlikely that it is directly the result of nerve stimulation. However, local activation of peptidergic nerves and axon reflexes cannot be discounted. Studies over the years have failed to identify blood-borne or released mediators to account for the hypoxic vasoconstriction response. Mediators such as catecholamines, histamine, serotonin, angiotensin II, thromboxane, leukotrienes C_4 and D_4, endothelin, and platelet-activating factor do not appear to be primarily responsible for hypoxic vasoconstriction,[2] although they can modulate the magnitude of the hypoxic response by influencing the basal pulmonary vasomotor tone. There exists the possibility that there may be a complex interplay between these mediators or that an unidentified chemical mediator is responsible. Several candidates have been now identified by genomic strategies.[38]

Chronic exposure to hypoxia increases the muscular content of small arteries, which are normally devoid of smooth muscle. People native to high altitude in the Andes have been shown to have increased muscularization of arteries as small as 20 μm,[39] which suggests differential responsiveness to growth factors such as platelet-derived growth factor that induce vascular smooth muscle cell proliferation. Not all high-altitude natives have shown this increase in muscularization, nor do all animals that live at high altitudes, which indicates a differential response to growth factors or differences in their release, neither of which is dependent simply on long-term residence at high altitude. Both cellular influences, which involve vascular smooth muscle cells, endothelial cells, and fibroblasts, and molecular mechanisms, such as release of vascular endothelial growth factor, are responsible for the pulmonary vascular remodeling seen during hypoxia.[40]

The increase in PVR induced by hypoxia is augmented by increases in plasma hydrogen ion concentration and in partial pressure of carbon dioxide, but only as it affects pH.[41] Intracellular mechanisms activated by hypoxia may also be activated by intracellular hydrogen ion concentration. The increased hydrogen ion concentration in pulmonary vascular smooth muscle cells resulting from hypoxia or elevated carbon dioxide is an important intracellular signal mediating the interaction between actin and myosin filaments and thus vascular tone.

Cyclooxygenase inhibitors (e.g., indomethacin) augment the hypoxic pulmonary vasoconstrictor response. Inhibition of the cyclooxygenase cascade, which prevents prostacyclin generation, is a likely basis of indomethacin-induced augmentation of vasoconstriction. An increase in left atrial pressure and in blood volume can prevent the hypoxia-induced pulmonary vasoconstriction, which indicates that transmural pressure changes influence the response.

A significant factor with the potential of influencing the hypoxic pulmonary vasoconstrictor response is nitric oxide (NO). Vasodilation of pulmonary artery rings in response to acetylcholine was found to depend on an intact endothelium that releases NO.[42] Antagonists of endothelium-dependent relaxation potentiated the hypoxic pulmonary vasoconstriction.[43] Pulmonary vascular endothelial cells activated by hypoxia may not release NO to the same extent as systemic vessels; thus, absence of the moderating influence of NO could lead to hypoxia-induced pulmonary vasoconstriction. Therefore, the magnitude of hypoxic pulmonary vasoconstriction is related to the concomitant generation of NO.

There are other endothelium-derived relaxing factors (besides NO), because not all endothelium-dependent vascular smooth muscle relaxation can be fully prevented by inhibitors of the L-arginine–NO generating pathway. Endothelium-derived hyperpolarizing factor (EDHF) is the likely mediator of endothelium-derived relaxation that cannot be attributed to NO.[44] EDHF mediates its vasodilator effect by causing the Ca^{2+}-dependent K^+ channels to open, leading to hyperpolarization.[45] However, the role of EDHF in the control of basal pulmonary vasomotor vasoconstriction in general and in hypoxic pulmonary vasoconstriction in particular is not yet known.

A constricting factor, the peptide endothelin, is released by both systemic and pulmonary endothelial cells by hypoxia.[46] Because removal of the endothelium from isolated pulmonary artery strips abolishes hypoxia-induced vasoconstriction,[46] this peptide may be involved in hypoxic pulmonary vasoconstriction. However, these experiments were made with arteries larger than those generally considered to be responsible for hypoxic pulmonary vasoconstriction.

Because the search for a chemical mediator has been unsuccessful, investigators have proposed mechanisms whereby hypoxia has a direct effect on vascular smooth muscle cells. This has led to the redox theory, which postulates that the proximal mitochondria electron transport chain serves as an oxygen-sensing unit that decreases production of reactive oxygen species in response to hypoxia, resulting in a decrease in superoxide or H_2O_2, thereby inhibiting the K^+ channel that elicits membrane depolarization.[47] This in turn leads to opening of a Ca^{2+} channel and influx of Ca^{2+}-mediating contraction of pulmonary arterial smooth muscle.[47] Because metabolic inhibitors enhance hypoxic vasoconstriction,

hypoxia-induced decrease in oxidative phosphorylation has also been suggested as a possible mechanism.[48] Evidence of energy failure has not been found except at such low oxygen levels that vessels actually dilate rather than constrict.[49] However, it is likely that changes in oxidative phosphorylation may be a sensing and signal transduction mechanism that activates the inhibition of K^+ channels.[48]

Vasoconstriction is likely mediated by an increase in intracellular calcium ion concentration ($[Ca^{2+}]_i$) in smooth muscle cells, the "Ca^{2+} hypothesis."[50] The increased $[Ca^{2+}]_i$ combines with the Ca^{2+}-binding protein calmodulin to activate the enzyme myosin light chain kinase (MLCK), resulting in the phosphorylation of myosin and contraction. Ca^{2+} channel blockers inhibited and Ca^{2+} channel agonists enhanced the hypoxia-induced constriction of pulmonary vessels.[51] At the same time, hypoxia augments RhoA- and Rho kinase–mediated Ca^{2+} sensitization, resulting in increased RhoA and Rho kinase activity with consequent dephosphorylation of myosin light chain phosphatase and further increased myosin light chain phosphorylation effecting contraction.[52] The importance of Rho kinase signaling in this context is suggested by the attenuation of hypoxia-induced pulmonary vasoconstriction in mice treated with a Rho kinase inhibitor.[53] Ca^{2+} influx may occur in response to membrane depolarization induced by hypoxia,[54] with resulting increased Ca^{2+} permeability, release of intracellular stores of Ca^{2+}, or both. It is not clear how hypoxia causes depolarization of pulmonary vascular smooth muscle membrane or whether this leads to the influx of Ca^{2+} via voltage-gated channels responsible for activating pulmonary vascular smooth muscle contractility.

Neural Regulation of Pulmonary Vascular Resistance

Adrenergic and cholinergic efferent nerves are present in pulmonary arteries and veins in all mammals in which innervation has been examined. However, there is considerable variation in the distribution and amount of innervation. Innervation of the pulmonary vasculature is typically less than that of the systemic arterial vessels. The concentration of fibers is greatest in large vessels and at branch points and decreases in smaller vessels.[55] α-Adrenergic receptors predominate in the pulmonary vascular bed, particularly in the fetal circulation, where there is high basal vasomotor tone and greater reactivity to α-adrenergic stimulation. Stimulation of α-adrenergic receptors mediates the constriction of pulmonary vessels, whereas β-adrenergic receptors mediate dilation. Stimulation of the sympathetic nerve efferents characteristically produces pulmonary vasoconstriction and decreased distensibility of pulmonary vessels.[56] α-Adrenergic mechanisms probably contribute little to normal adult pulmonary vasomotor tone. Blockade of the α-adrenergic receptors with receptor antagonists modifies neither baseline pulmonary vasomotor tone nor the response to hypoxia. Because pulmonary vessels are normally in a dilated state, β-adrenergic responses are not evident. However, β-adrenergic blockade enhances the vasoconstrictor response to catecholamines, which stimulate both α- and β-receptors, and increases in tone augment responses to β-adrenergic agents.[57]

There is limited understanding of the functional significance of sympathetic and parasympathetic innervation of pulmonary vessels. It is unclear why the pulmonary vascular bed is so richly innervated and yet stimulation of these nerves produces relatively small changes in vasomotor tone in the adult lung. One possibility is that neural mechanisms balance the distribution of vascular resistance and compliance in the pulmonary vascular bed and thereby finely regulate regional and total pulmonary perfusion.[1] It is also possible that vasodilator influences (i.e., NO, EDHF, and prostacyclin [PGI_2]) normally predominate and thus mask the constrictor effect of sympathetic stimulation.

Humoral Regulation of Pulmonary Vascular Resistance

Numerous pulmonary vasoconstrictor mediators, as reviewed by Barnes and Liu,[58] have been identified. These include norepinephrine (a stimulator of α-adrenergic receptors), angiotensin II, histamine, endothelin, serotonin, thromboxane, leukotrienes C_4 and D_4, and platelet-activating factor.[1] These mediators bind to their receptors on pulmonary vascular smooth muscle cells and induce pulmonary vascular smooth muscle contraction by activation of second messenger pathways. As in the peripheral circulation, changes in pulmonary vasomotor tone induced by these constrictors are regulated by NO.[59]

Various pulmonary vasodilator substances have also been identified. These include acetylcholine, which mediates its effects in part by NO release; bradykinin, which has heterogeneous responses with direct as well as NO-dependent actions; PGI_2; and prostaglandin E_1.[59,60] It is important to note that the magnitude of the effects of both pulmonary vasoconstrictors and vasodilators is dependent on the species and initial baseline pulmonary vasomotor tone. The latter is particularly important because pulmonary vasoconstrictors such as platelet-activating factor induce constriction in the pulmonary vascular bed when it has low basal tone, whereas they are potent dilators during elevated pulmonary vascular tone.[60] The basis for this divergent effect is unclear but may reflect differential activation of second messenger pathways in pulmonary vascular smooth muscle cells in the basal state in comparison with conditions of increased tone.

In addition to angiotensin II, however, the role of the renin-angiotensin system in pulmonary vascular regulation is now well recognized. Angiotensin II, a key component of the renin-angiotensin system, is generated primarily by angiotensin-converting enzyme (ACE) from angiotensin I, and its effects are mediated through angiotensin type I (AT-1) and type II (AT-2) receptors, both of which are expressed in the normal lung.[61] The pulmonary endothelium represents a major site of ACE

expression and angiotensin II production.[62] Notably, ACE2 is a homologue of ACE expressed in the lung that inactivates angiotensin II, leading to the downstream generation of angiotensin-(1-7), which acts through AT-2 receptors to induce vasodilation, serving as a counterbalance to the vasoconstrictive effects of angiotensin II through AT-1 receptors. Although components of the renin-angiotensin system have been implicated in a variety of lung diseases, including pulmonary hypertension and fibrotic lung diseases, the system has been most strongly linked to the pathophysiology of pulmonary vascular leak syndromes. For example, ACE2 serves as the receptor for the coronavirus responsible for severe acute respiratory syndrome (SARS), first identified in 2003.[63] The significant mortality rate from SARS—greater than 50% in patients older than 65—is largely attributable to the subsequent development of acute respiratory distress syndrome (ARDS), which is characterized by profound lung vascular leak.[64] ACE and AT-2 have been found to serve a protective role in ARDS, whereas ACE2, angiotensin II, and AT-1 appear to mediate lung edema and injury associated with ARDS.[65]

LUNG FLUID AND SOLUTE EXCHANGE

Pulmonary edema is defined as the accumulation of water in the lungs' extravascular spaces. It occurs in a sequential process, first developing in the hilar region of the lungs followed by fluid filling of the interstitial compartment. Finally, fluid enters the alveoli in an all-or-nothing manner.[66] When associated with alveolar flooding, pulmonary edema becomes a cataclysmic event that results in impaired gas exchange and arterial hypoxemia. The healthy lung consists of about 80% water, as measured gravimetrically. The characteristics of fluid exchange between the vascular space and interstitium of lungs have been reviewed by Taylor and Parker[67] and Staub,[66] and factors regulating pulmonary vascular endothelial permeability have been reviewed by Dudek and Garcia[68] and more recently by Mehta and Malik.[69]

Pathogenesis of Pulmonary Edema

Sites of Fluid Accumulation

In addition to the longitudinal gradient in the interstitial fluid pressure from the alveolar septum to the lung hilum (as discussed in a later section and illustrated in Fig. 6-13), there are vertical pressure gradients within the pulmonary circulation. The vertical gradients are the result of differences in hydrostatic pressure in pulmonary microvessels at different lung heights, vertical pleural fluid pressure, and regional lung volume. A greater capillary hydrostatic pressure in the dependent lung regions favors edema formation in these regions. Although it is predicted from this that there should be greater lung water content in the dependent lungs, no such vertical gradient has been found by either measurement of extravascular lung water content or morphometric determinations of the interstitial space.[70,71] Because the gradient of alveolar-septal fluid pressure to small vessel adventitial pressure is greater in the lung apex than in the lung base, there is likely to be greater accumulation of fluid in the extravascular space of the upper lung than in the dependent lung, even though the fluid filtration rate is greater in the dependent lung region.[67]

Fluid that cannot be cleared by the lymphatic channels accumulates in the connective tissue surrounding smaller vessels and bronchioles.[72] The fluid migrates down the interstitial fluid pressure gradient to interstitial spaces around larger vessels and airways. If lymphatics in the connective tissue sheaths are unable to remove the excess fluid, undrained fluid becomes compartmentalized and forms perivascular cuffs.[73] After an increase in the interstitial fluid volume from 35% to 50%, individual alveoli begin to flood in an all-or-nothing manner.[72] Initially, the distribution of alveolar flooding is patchy, but this is followed by rapid flooding.

The exact route by which fluid moves into the alveoli is not known. Fluid movement may involve bulk flow through large epithelial pores or channels or may be the result of increased transport through intercellular pathways in respiratory epithelium of terminal bronchioles,[72] with the possibility of epithelial detachment from the underlying matrix resulting in movement of fluid directly into the alveoli.[74]

Mechanisms of Pulmonary Edema

Increased Pulmonary Capillary Pressure. The relationship between left atrial pressure and the rate of formation of pulmonary edema is shown in Figure 6-8. For

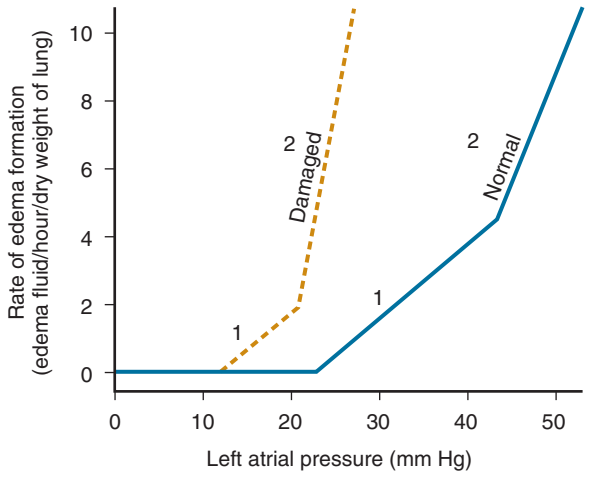

FIGURE 6-8 ■ Graph showing the rate of edema formation as a function of left atrial pressure. In the normal lung (*solid line*), edema does not form until left atrial pressure exceeds 20 to 25 mm Hg. Above this pressure, edema forms slowly at first (1), and then more rapidly (2) at higher pressures. If the endothelium is damaged (*dashed line*) or if plasma colloid osmotic pressure is reduced, then edema begins to form at lower left atrial pressures. (Redrawn from Guyton AC, Lindsay AW: Effect of elevated left atrial pressure and decreased plasma protein concentration in the development of pulmonary edema. Circ Res 7:649–653, 1959.)

left atrial pressures up to 20 to 25 mm Hg, water content does not increase in the normal lung.[75] The water content begins to increase only when the pulmonary capillary pressure reaches a critical value. Fluid accumulation in the lung is minimized by "safety factors" that are activated below this critical capillary pressure.[67] The pulmonary extravascular water content increases progressively as a result of the inability of these safety factors to reduce fluid filtration rate after capillary hydrostatic pressure increases above the critical value. The primary safety factors (discussed later) are the increase in lymph flow, decrease in interstitial colloid osmotic pressure, increase in interstitial hydrostatic pressure, and decrease in albumin exclusion volume. These changes serve to minimize the increase in the extravascular lung water content when left atrial pressure is increased.

Decreased Plasma Oncotic Pressure. A decrease in the plasma protein concentration, such as in hypoalbuminemia, reduces the intravascular absorptive pressure and thus increases the net transcapillary filtration pressure. In this case, the critical capillary pressure at which lungs begin to gain water decreases in direct proportion to the reduction in plasma oncotic pressure (see Fig. 6-8).[67]

Increased Lung Vascular Permeability. Two general pathways allow movement and flow of fluid, macromolecules, and leukocytes into the interstitium and subsequently into the alveolar air spaces to produce clinically significant pulmonary edema during inflammatory lung processes. The transcellular pathway utilizes a tyrosine kinase–dependent, gp60-mediated transcytotic albumin route whose regulation and function are unclear, but that may serve to uncouple protein and fluid permeability.[76] However, there is general consensus that the primary mode of fluid and transendothelial leukocyte trafficking occurs by the paracellular pathway,[68] as shown by electron microscopy studies that demonstrate the formation of paracellular gaps at sites of active inflammation within the vasculature.[77]

The mechanisms mediating alterations in pulmonary vascular endothelial permeability occurring as a result of a variety of mechanical stress factors, inflammatory mediators, and activated neutrophil products (such as reactive oxygen species, proteases, and cationic peptides) have been discussed earlier. The critical functional definition of increased lung vascular permeability is the extravasation of protein-rich fluid into the interstitial space and ultimately into the alveolar space,[72] resulting in fulminant pulmonary edema. In high-permeability pulmonary edema, the alveolar fluid protein concentration approximates the plasma protein concentration, whereas in hydrostatic edema (i.e., edema resulting from increase in the pulmonary capillary hydrostatic pressure), the ratio of alveolar fluid to plasma protein concentration is usually less than 0.6.[67] The increase in lung vascular permeability shifts the relationship between left atrial pressure and pulmonary extravascular water content to the left (see Fig. 6-8).

Lymphatic Insufficiency. The lymphatic vessels are capable of removing excess extravascular fluid because of their effectiveness as pumps. Lymphatic propulsion is determined by the intrinsic contractility of lymphatic vessels, by inspiration and expiration, and by lymphatic valves, which account for the unidirectional lymph flow.[72] Lymphatics, however, have a limited capacity to increase lymph flow, as shown in Figure 6-9. Beyond their critical capacity, the lymph flow does not increase in direct proportion to the increase in interstitial fluid volume and may actually decrease because of compression of the lymphatic channels.[78] The extent to which lymphatic insufficiency serves as an important mechanism of fluid accumulation in the lung is not clear. Some studies have indicated that surgical removal of the lymphatics predisposes the lung to edema, although the increase in water content is usually transient.[79]

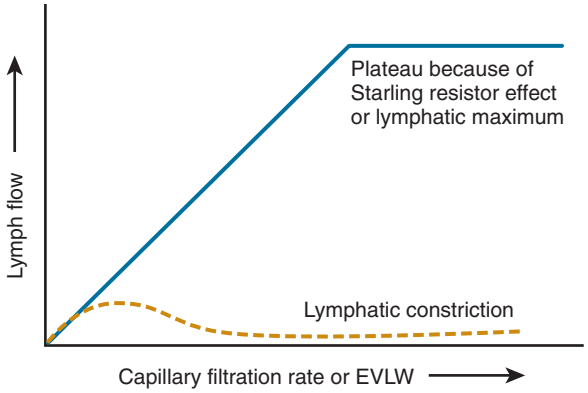

FIGURE 6-9 ■ Graph showing the relationship between capillary filtration rate and lymph flow in the normal lung (*solid line*) and with increased lymphatic resistance (*dashed line*). In a normal lung, the lymph flow plateau is reached because of pressure effects of the increase in interstitial fluid volume (Starling resistor effect), as well as attainment of maximum lymph flow, whereas with lymphatic constriction or obstruction the capillary fluid filtration rate continues, but without a concomitant increase in lymph flow. (Redrawn from Malik AB: Mechanisms of neurogenic pulmonary edema. Circ Res 57:1–20, 1985.)

Safety Factors in Lung Fluid Homeostasis. The safety factors that were mentioned in the discussion of increased pulmonary capillary pressure become operative when fluid begins to accumulate in the interstitial space. A decrease in the exclusion volume for albumin (or an increase in its actual volume of distribution) merits particular attention because it is important in decreasing the interstitial protein concentration and thereby decreasing interstitial colloid osmotic pressure. Albumin is normally excluded from approximately 40% of the pulmonary interstitial space by the matrix proteins collagen, hyaluronic acid, and laminin.[67] An increase in the interstitial fluid volume disrupts the structure of interstitial matrix proteins and decreases the albumin exclusion volume (Fig. 6-10A); this, in turn, increases the volume available for albumin equilibration, which allows albumin protein concentration to decrease. Therefore, the increase in the albumin distribution volume amplifies the decrease in interstitial colloid osmotic pressure, which would not drop to the same extent without the concomitant decrease in the exclusion volume. Figure 6-10B indicates the effect of albumin exclusion on the colloid

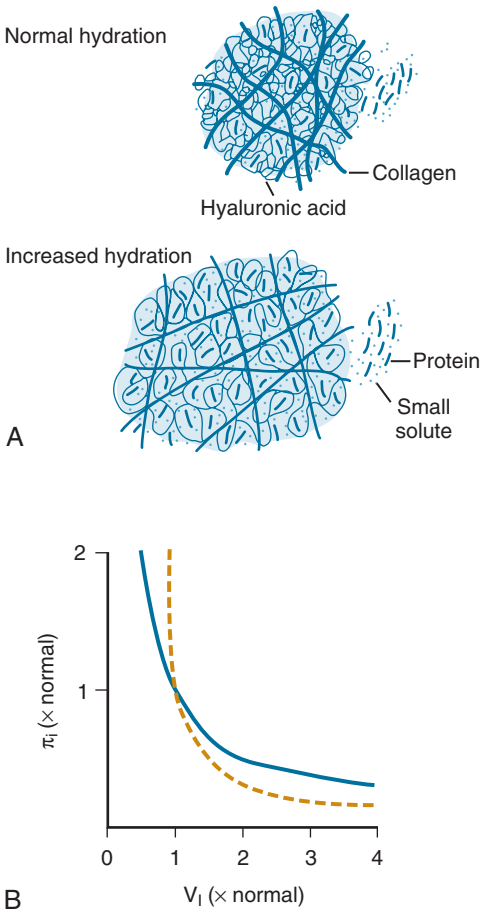

FIGURE 6-10 ■ **A,** Schematic diagram showing the pulmonary interstitial matrix. Normally, protein is excluded from 40% of the interstitial space. When interstitial water content increases, the matrix is disrupted and the exclusion volume decreases, making more of the matrix accessible to proteins. The increased distribution volume helps to maintain a lower concentration of protein and decreased colloid osmotic pressure than would otherwise occur. (Redrawn from Parker JC, Falgout HJ, Parker RE, et al: The effect of fluid volume loading on exclusion of interstitial albumin and lymph flow in the dog lung. Circ Res 45:440–450, 1979.) **B,** With an increase in interstitial volume (V_I), the colloid osmotic pressure (π_i) of extravascular proteins decreases. The *solid line* represents the decrease in π_i occurring by dilution of a fixed interstitial space when V_I increases. The *dashed line* is the decrease in π_i that occurs when exclusion volume is initially present and is decreased with increasing V_I. (Redrawn from Taylor AE, Parker JC, Kvietys PR, Perry M: Pulmonary interstitium in capillary exchange. Ann N Y Acad Sci 384:148–168, 1982.)

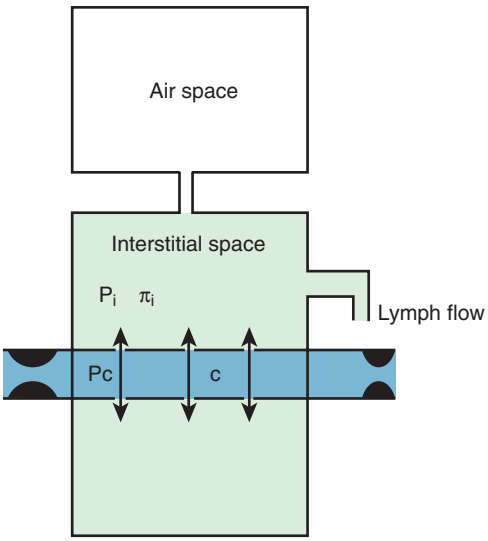

FIGURE 6-11 ■ Schematic representation of the pulmonary capillary tissue–lymphatic system. Starling's forces are capillary hydrostatic pressure (Pc), plasma colloid osmotic pressure (πc), interstitial hydrostatic pressure (P_i), and colloid osmotic pressure of tissue fluid (π_i). The alveolar epithelial junctions are tight compared with the interendothelial junctions in lung and thereby restrict solute transport into the air spaces. The *background shading* represent plasma proteins in plasma, tissue fluid, and lymph. The lymph flow represents the overflow in the system, that is, the difference between the amount of fluid filtered and the amount reabsorbed. A major determinant of Pc is the precapillary-to-postcapillary resistance ratio as regulated by the smooth muscle tone of the arteries and veins, represented by the narrowings in the precapillary and postcapillary vessels. (Redrawn from Malik AB: Mechanisms of neurogenic pulmonary edema. Circ Res 57:1–20, 1985.)

osmotic pressure when the interstitial fluid volume is increased. For the same increase in the interstitial fluid volume, the interstitial oncotic pressure is lower when albumin exclusion is decreased, indicating the critical role of this safety factor.[67] In addition, the role of the bronchial circulation in lung fluid balance edema generation and/or clearance has received attention by virtue of its ability to modulate lymph clearance under basal conditions and after lung injury.[34,80]

Transcapillary Exchange

Fluid Flux Equation

The Starling equation describes filtration of fluid across the capillary wall. The equation states:

$$Jv = LpS[(Pc - Pi) - \sigma d(\pi c - \pi i)] \quad (3)$$

where Jv is the net transcapillary filtration rate (in cm^3/sec), Lp is the hydraulic conductivity of the membrane, S is the surface area, Pc is the pulmonary capillary hydrostatic pressure, Pi is the interstitial hydrostatic pressure, πc is the capillary plasma colloid osmotic (or oncotic) pressure, and πi is the interstitial fluid colloid osmotic (oncotic) pressure. The term σd is the osmotic reflection coefficient of the vessel wall; σd = 0 if the membrane is freely permeable to the molecules crossing the membrane, and σd = 1 if the membrane "rejects" the molecule, thus being impermeable. Because albumin is the dominant plasma protein in terms of concentration, we consider here primarily the σd of albumin. LpS has been defined as the capillary filtration coefficient (Kf,c).

According to convention, Pc acts outward (i.e., from the vessel to the extravascular space) and Pi acts inward, whereas πc acts inward and πi acts outward (Fig. 6-11). The direction and magnitude of movement of water

across the vessel wall are determined by the sum of hydrostatic and colloid osmotic pressure differences across the wall. Pc + πi constitutes the driving force for filtration, and πc + Pi is the driving force for absorption. The ability of these pressures, called the *Starling forces,* to determine filtration and absorption is dependent on the semipermeable nature of the endothelial barrier—that is, the ability of the endothelial barrier to restrict the free flux of plasma proteins. Therefore, plasma and interstitial colloid osmotic pressures are a direct function of plasma and interstitial protein concentrations, respectively.

Because Pc decreases along the alveolar capillary, filtration is more likely to occur at the arterial end of the pulmonary capillary, and absorption at the venous end. However, this is an idealized situation, because some vessels only filter fluid and other vessels only absorb it. Regional pulmonary capillary pressures determine whether vessels filter or absorb fluid. Dilation of a small pulmonary artery increases Pc, and this increases net transcapillary filtration rate, whereas a constricted pulmonary artery reduces Pc, and this increases net absorption rate. Only about 2% to 5% of the plasma perfusing the pulmonary circulation is filtered, and of this, 80% to 90% is absorbed back into capillaries and venules. The residual fluid in the extravascular space ultimately enters the lymphatic circulation, through which it is returned to the circulation.[67]

In the healthy human lung, the Starling forces have defined average values. Pc at mid-lung level is 10 mm Hg, Pi is −3 mm Hg, πc is 25 mm Hg, and πi is 19 mm Hg.[67] The most accurate of these pressures is πc, which is a direct function of plasma protein concentration and thus can be easily determined by an osmometer. The other values are determined indirectly and hence represent best estimates.

The summation of Starling's forces in the lung indicates that there is a net outward filtration pressure. Assuming that σd = 1 and, according to the values just given, the net filtration pressure is 7 mm Hg. This indicates that filtration across pulmonary vessels is greater than absorption. It must be noted that Pc and Pi in the lungs vary according to the height in the lung. When upright, both pressures are greater in the dependent regions of the lung than in the lung apex.

The slightly negative Pi value within alveolar septae results from the retractile force of the layer of surfactant at the air-liquid interface; the more negative Pi values toward the hilum are generated by the elastic wall tension of vessels and radial traction exerted by the alveolar attachment sites during lung inflation.[67] Increasing lung volume decreases Pi at both sites, whereas a reduction in lung volume increases Pi.

The total osmotic pressure of plasma is approximately 6000 mm Hg, whereas the colloid osmotic (or oncotic) pressure is only 25 mm Hg. The oncotic pressure plays a critical role in fluid exchange across the vessel wall because the barrier is semipermeable to plasma proteins. In contrast, electrolytes (which are responsible for most of the osmotic pressure of 6000 mm Hg) rapidly equilibrate on both sides of the vessel wall.

The transcapillary oncotic pressure gradient (Δπ = πc − πi) is determined by the albumin concentration gradient:

$$\Delta\pi = \sigma d RT(Civ - Ci) \quad (4)$$

where R is the gas constant, T is the absolute temperature, σd is the albumin osmotic reflection coefficient, and Civ and Ci are the intravascular and interstitial albumin concentrations, respectively. The equation indicates that Δπ varies in proportion to the transcapillary albumin concentration difference (Civ − Ci), which implies that, as a result of increased permeability and the beginning of albumin leakage from the vessel, a decrease in (Civ − Ci) causes a decrease in Δπ. It is also important to note from this equation that the effective Δπ is determined by σd, which is dependent on the permeability characteristic of the vessel (see subsequent explanation).

To determine LpS or Kf,c experimentally, a known change is made in either the hydrostatic or osmotic gradient, and the change in Jv is measured.[67] Quantitative inferences regarding hydraulic conductivity can then be made. Such inferences must be made carefully, however, because changes in surface area secondary to recruitment of pulmonary capillaries will also change Kf,c.

The reflection coefficient (σd) defines the permeability of the transported molecule across the capillary. The reflection coefficient is a critical constant in determining the effective Δπ value. The reflection coefficient for albumin, which does not pass freely across the pulmonary endothelial barrier, is 0.8.[67] Albumin σd decreases when endothelial albumin permeability is increased. A decrease in σd results in a decrease in Δπ, which then becomes less of an absorptive force offsetting the hydrostatic force favoring filtration.

Solute Flux Equation

The movement of solutes across the porous endothelial barrier (Js) is often defined by the linear equation of Kedem and Katchalsky[81]:

$$Js = Jv(1 - \sigma f)Cm + PS(\Delta C) \quad (5)$$

where Cm is the mean concentration of the solute within the endothelial pores (or interendothelial junctional clefts), σf is the solvent drag reflection coefficient,[82] PS is the permeability surface area product, and ΔC is solute concentration difference across the endothelial monolayer. The first term, Jv(1 − σf)Cm, represents the convective transport of solute or ultrafiltration. The second term, PS(ΔC), represents the diffusive transport of solute. Cm is the mean concentration of solute in the membrane and is therefore between the concentration on the blood side and the lower concentration on the interstitial side. It can be taken as the average only at very low levels of Jv and approaches blood concentration at high Jv.[82] Under ideal conditions, σd = σf, but ideal conditions often do not apply. Because of this and because Cm is usually unknown, Equation 5 is useful only under relatively limited experimental conditions.[67] Specialized equations that consider multiple pores and the effects of

protein and barrier charge as well as effect of Jv and protein concentrations within the pore are beyond the scope of this text.

Diffusion

Diffusion is a key factor in the delivery of gases and solutes across vessel walls. Diffusion is described by the following equation:

$$J = DA\left(\frac{dc}{dx}\right) \quad (6)$$

where J is flux or amount of substance transferred per unit time, D is diffusibility of the membrane for a particular molecule, A is the diffusional pathway cross-sectional area, and dc/dx is the concentration gradient of the solute across the membrane. The component of solute flux that is due to diffusion can also be written as J = PS(Civ − Ci), where P is capillary permeability of the substance, S is the capillary surface area, Civ is the intravascular concentration of substance within the capillary, and Ci is concentration of substance in the interstitial liquid.

Diffusion of solutes varies according to characteristics of the solute. Diffusion of lipid-insoluble macromolecules such as proteins is restricted to pores (or interendothelial junctions). Only approximately 0.02% of the capillary surface area constitutes the so-called pores.[83] Diffusion of these molecules becomes restricted at molecular weights above 60 kD because the size of the molecule is greater than that of the junctional pores. The permeability of these molecules is also influenced by their electrostatic charge in relation to the negative charge on endothelial cell membrane as well as charge interactions between molecules.[84] In addition to paracellular transport through junctions, transport of macromolecules such as albumin also occurs by means of vesicles involving a transcytotic mechanism.[85] There is evidence that transcytosis of albumin across the endothelial barrier (which does not fit the standard model described by the solute flux equation) is governed by a 60-kD albumin "docking" molecule or receptor that activates the signaling machinery responsible for formation of vesicles and their transport to the basolateral membrane.[85]

Sites of Fluid and Solute Exchange

Capillary Endothelium

It is important to note that most of the fluid and solute exchange occurs at the level of the pulmonary microvascular endothelium, which is of the continuous nonfenestrated type, because this layer has the largest surface area available for both diffusion and filtration. Several pathways are available for transport of solutes and water: vesicles, interendothelial junctions, and transendothelial channels. Low-molecular-weight lipid-soluble substances and water can diffuse directly through endothelial cells (transcellular pathway) as well as between cells (paracellular pathway). Lipid-soluble (lipophilic) molecules such as carbon dioxide and oxygen diffuse rapidly across the entire capillary endothelial surface area. Water also freely crosses the entire surface area of the membrane by means of aquaporin water channels.[86] Macromolecules and low-molecular-weight water-soluble molecules are transported via interendothelial junctions as well as the transcellular route. The molecular basis of the endothelial transport pathways is summarized in Figure 6-12, which demonstrates the interactions at the level of the intercellular junctions, the extracellular matrix, and a specific vesicular pathway.[85,87–92]

Because lymph provides an estimate of interstitial fluid concentrations of various solutes, the lymph-to-plasma concentration ratio (CL/CP) of solutes and the radius of these solutes can be measured to provide an approximation of the sieving characteristic of pulmonary microvessel endothelial cells.[82] The plasma concentration of these solutes remains constant, but there is a decrease in the lymph concentration with an increase in the solute radius. This finding emphasizes the size-selective nature of the pulmonary microvascular endothelial barrier.[82]

Another important characteristic of the pulmonary capillary wall barrier is the extracellular matrix, which consists of a complex array of molecules: laminin, type I and type IV collagen, proteoglycans, fibronectin, and vitronectin.[67] The three-dimensional arrangement of matrix proteins provides a restrictive barrier to the transport of molecules, and the matrix can sieve molecules of different molecular weights.[93] Therefore, both endothelium and extracellular matrix are barriers to solute transport. Increases in vascular permeability may be the result of alterations in one or both of these barriers.

Alveolar Epithelium

Alveolar epithelial type I and type II cells lining the terminal alveoli serve as a barrier to movement of water and solutes into the alveolar space. The calculated interepithelial junctional radius is only approximately 2 Å, much smaller than the junctional radius of the pulmonary endothelial cells, and differs considerably from that in the pulmonary artery.[94] Most lipid-insoluble molecules do not cross the epithelial barrier. Water and ions can penetrate this barrier only to a limited degree, whereas low-molecular-weight lipid-soluble substances such as oxygen and carbon dioxide are freely permeable.

Alveolar-Capillary Septum

The alveolar-capillary barriers have both thin and thick portions, as described previously. The thick septum is defined by its greater interstitial space, which is filled with connective tissue fibers, type I and type IV collagen, laminin, fibronectin, vitronectin, and proteoglycans. Fluid and solute exchange occurs primarily in the thick septum because it is the more compliant portion of the barrier. Gas exchange occurs through the thin portion of the septum, which is a relatively noncompliant space because endothelial and epithelial cells are virtually adherent to each other.[67]

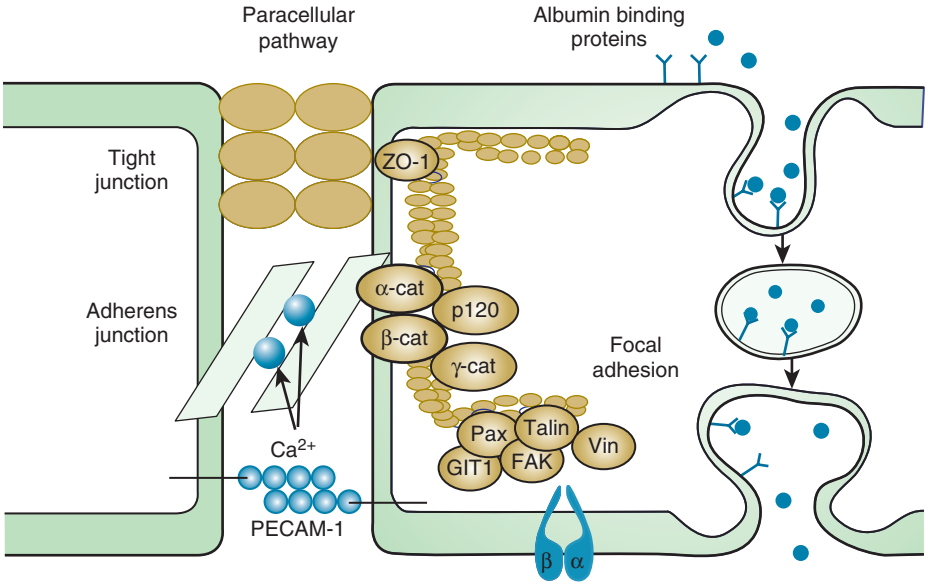

FIGURE 6-12 ■ Schematic representation of molecular pathways of transendothelial transport. In a **paracellular pathway** of diffuse transport at intercellular junctions, there is polar organization of tight and adherens junctions of endothelial cells and interactions of linking proteins that form junctions. Solutes of less than 7.5-nm radius (e.g., albumin is 3.6 nm) can diffuse through junctions. Cell-cell connections include tight junctions composed of transmembrane-occluding proteins linked to the actin cytoskeleton by the zona occludens family (ZO-1); adherens junctions mediated by Ca^{2+}-dependent association of cadherin proteins in turn linked to the α-, β-, and γ-catenin (cat) complex; and platelet-endothelial cell adhesion molecule-1 (PECAM-1)–associated junctions. Cell-matrix tethering is maintained by focal adhesion plaques composed of α- and β-integrin transmembrane proteins linked to the actin cytoskeleton by a complex of proteins, including talin, paxillin (Pax), vinculin (Vin), and focal adhesion kinase (FAK). Fibronectin and vitronectin are in the subendothelial matrix compartment and are bound by integrin receptors that span plasma membrane. Endothelial cells maintain tight connections with each other and the underlying matrix to tilt the balance toward increased barrier integrity. In a **transcellular pathway** of vesicular (nondiffusive) transport, vesicular transport of albumin occurs by either solid- or fluid-phase pathways. The endothelial cell surface expresses albumin-binding proteins (Y) that bind albumin (*solid circles*). Formation of vesicles contain albumin bound to albumin-binding proteins and those free in cytosol. The vesicle membrane fuses with the abluminal cell membrane, and albumin bound to binding protein and free albumin are extruded to the abluminal side. (For references, see text.)

Pulmonary Lymphatic Vessels

The lung has an extensive network of lymphatic channels that are involved in the drainage of fluid and solutes and trafficking of lymphocytes and other blood-formed elements. The terminal lymphatics are found in loose areolar tissue surrounding pulmonary vessels and, to some extent, in the thick interstitial septum. There are two primary interstitial compartments, the extra-alveolar and alveolar, and lymphatics are largely confined to the extra-alveolar interstitium. Fluid is believed to leak from capillaries in the alveolar walls and move toward the spaces surrounding airways, where it enters the distal ends of lymphatics.[66] The fluid in the alveolar walls is presumably propelled by the prevailing pressure gradient toward the extra-alveolar space.[8] The pulmonary lymph flow increases in response to increased interstitial fluid volume (see Fig. 6-9), reflecting the ability of pulmonary lymphatics to drain the lung interstitial compartment. However, the relationship between interstitial fluid volume and lymph flow is not linear. Beyond a critical fluid volume, pulmonary lymph flow can no longer increase in proportion to the increase in fluid volume. This "lymphatic failure" may be related to impaired pumping or propulsive force of lymphatics, constriction of terminal lymphatics by extravascular fluid compression, and compartmentalization of fluid in the alveoli in such a way that it is inaccessible to the lymphatic system. Whatever the mechanism of "lymphatic failure," the relative inability to adequately drain the interstitium is a primary cause of edema formation.[66]

Lung Interstitium

Interstitial Pressures

An interstitial liquid pressure gradient has been measured from the alveolar wall to the lung hilum.[8] As indicated in Figure 6-13, interstitial pressure decreases from the alveoli to hilar interstitial space. This decrease in pressure is the basis for interstitial drainage of the liquid filtered across the microvessels. The filtered fluid moves along the interstitial fluid pressure gradient into the connective tissue surrounding the pulmonary artery, airways, and veins.[66] The lymphatic vessels of the perivascular space then effectively drain this excess fluid. When fluid filtration exceeds the pumping capacity of the lymphatic system, fluid first accumulates in the hilar regions and in sheaths around the large pulmonary vessels, where pressure is lowest and interstitial compliance is highest. This

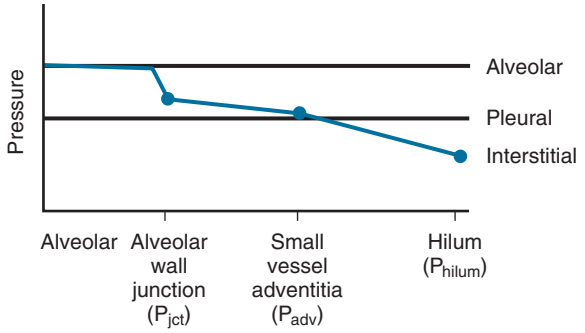

FIGURE 6-13 ■ Pressure gradient in the interstitium of the lung. Fluid from alveolar vessels in the thick septa moves down the pressure gradient to alveolar wall junctions (P_{ict}), to the adventitia surrounding small vessels (P_{adv}), and to the hilum (P_{hilum}). Experiments were done in isolated dog lung with an alveolar pressure of 5 cm H_2O and a pleural pressure of 0 cm H_2O, and pressures were measured at the hilum, in small vessel adventitia, and at the alveolar wall junction. (Redrawn from Staub NC: Pathophysiology of pulmonary edema. *In* Staub NC, Taylor AE [eds]: Edema. New York: Raven, 1984, pp 719–746.)

accounts for the "cuffs" of fluid that are typically observed around vessels in edematous lungs and that are often visible near the hila in chest radiographs.

Interstitial Compliance

The compliance of interstitial tissue is a nonlinear function and has two phases[95]: a low compliance at low interstitial fluid volumes and high compliance during the interstitial edema or alveolar flooding phase. At low levels of tissue hydration, tissue pressure changes markedly in response to a small change in tissue volume, indicative of low tissue compliance. Tissue expands with increased levels of hydration, and compliance increases dramatically. The increase in compliance occurs as the tissue fluid pressure approaches alveolar pressure. At an interstitial fluid pressure of greater than zero (i.e., values greater than the alveolar pressure), the tissue fluid accumulates with only a small change in the interstitial pressure. The high-compliance portion of the curve may represent the transition from interstitial edema to alveolar edema[67]; that is, the pressure inflection point may be the maximum interstitial volume before alveolar flooding occurs. This inflection point occurs at a lung weight gain of 35% to 50% and an interstitial pressure of 2 to 3 cm H_2O.[1] The abrupt increase in compliance attenuates further increases in interstitial hydrostatic pressure, which might forestall edema formation.

The lung is unique in that there are regional differences in compliance of the lung interstitium. The interstitial spaces surrounding large vessels or bronchi have higher compliance than interstitium in the septal region.[95] Once the perivascular spaces surrounding extra-alveolar vessels and bronchi are filled with fluid, the interstitial pressures equilibrate throughout the interstitial space. The continuing high level of fluid filtration then increases interstitial pressure to a critical level, and the epithelial barrier is breached (potentially facilitated by injury to the alveolar epithelium), resulting in rapid flooding of alveoli.[67]

TABLE 6-1. Factors Governing the Transport of Plasma Molecules Across Vascular Endothelium

PLASMA, HEMODYNAMIC, AND MECHANICAL FORCES
Hydrostatic pressure gradient
Oncotic pressure gradient
Shear stress
Cyclic stretch
PROPERTIES OF THE PERMEANT MOLECULES
Molecular size
Molecular shape
Molecular charge
Molecular chemistry (binding of molecules to cell surface receptors)
Generation of transendothelial gradients by the concentration of the permeating molecule
PROPERTIES OF ENDOTHELIAL CELLS AND MATRIX
Endothelial cell surface charge
Structure of the endothelial cell surface
Location in vasculature (site specificity)
Composition, charge, and density of the extracellular matrix

Transvascular Transport of Plasma Molecules

A list of the factors governing the transport of plasma proteins across the vascular endothelial monolayer is presented in Table 6-1. As is evident from this list, these factors can be subdivided into plasma and hemodynamic forces, properties of the permeant molecules, and properties of the lung endothelium and the underlying extracellular matrix.

Capillary Endothelial Permeability

Pore Theory

The pore theory describes the transport of lipid-insoluble molecules according to their size through cylindric or long, slit-shaped water-filled channels between endothelial cells, although it does not distinguish the type of paracellular pathway by which these molecules are transported (these pathways are listed in Table 6-2). Pore theory is based on the premise that selected areas form a system of "pores" whose combined total area represents less than 0.02% of the total endothelial surface area.[83] The size selectivity of the endothelial monolayer for plasma proteins is determined by the ratio of molecular radius to pore radius.[96] In most analyses, the heterogeneous pore radii in vascular endothelial cells range from 5 to 280 Å. The ratio of small to large pores is estimated to range from 30,000 : 1 for dextran transport[97] to 438 : 1 for lymph protein fluxes.[82] Albumin

TABLE 6-2. Routes of Endothelial Transport of Lipid-Insoluble Molecules

Transcellular (Cell Membrane)

Consists of three barriers in series (plasma membrane, cytoplasm, plasma membrane).

Vesicles

Involves equilibration of luminal and abluminal fluids.

Transport may be dependent on concentration gradient and rate of vesicular turnover.

Small and Large "Pores"

Continuous route exists from the luminal to the abluminal sides.

Flux of water and solutes across these pathways can be diffusive and convective.

Diffusive and convective transport may be coupled.

Molecular sieving (i.e., restriction of solute permeation as molecular size approaches the pore dimension) is a characteristic of pore pathways.

Fused Plasmalemmal Channels

Created by transient fusion of two or more vesicles.

Exhibit the same characteristics as junctional large pores.

TABLE 6-3. Physical Characteristics of Tracer Molecules Used to Determine Selectivity of the Pulmonary Vascular Endothelial Barrier

Molecule	Molecule Weight (kD)	Stokes-Einstein Radius (Å)	D_{37}*
Mannitol	0.182	4.4	0.9
Sucrose	0.342	5.2	0.721
Inulin	5.5	11–15	0.296
Cytochrome *c*	12	16.5	0.13†
α-Thrombin	36.6	28	0.08‡
Ovalbumin	43	27/6	0.11
Albumin (BSA)	69	36.1	0.093
Plasminogen	82	45.1	0.043
Fibrinogen	340	106	0.033

*Diffusion coefficient in water at 37° C = $D_{37} \times 10^{-5}$.
†Free diffusion coefficient in water at 20° C.
‡Free diffusion coefficient in water at 27° C.
BSA, bovine serum albumin.

molecules have a Stokes-Einstein radius of 36 Å, and therefore are transported through both large and small pores.

The pathways of fluid and solute exchange across the continuous pulmonary vascular endothelial cell monolayer are shown in Figure 6-12. Lymph has long been used to make inferences about the pore sizes of the endothelial barrier in many studies involving assessment of lung vascular permeability,[66] although several caveats exist. One caveat is that that lymph solutes become concentrated during their passage through the lymphatic circulation,[82,98] indicating that lymph may not necessarily reflect the interstitial fluid or events occurring at the endothelial barrier. Despite these caveats, much valuable information has been obtained from these studies on the mechanism of increased vascular permeability in the intact pulmonary microcirculation.[82]

In an attempt to validate the pore theory, selectivity of the pulmonary vascular endothelial cell barrier (i.e., the monolayer without its constituent extracellular matrix components) for different-sized molecules (varying from 0.18 to 340 kD and listed in Table 6-3) was determined with the use of cultured endothelial monolayers.[99] Predictably, the permeability of the endothelial monolayer to tracer molecules decreased with increasing molecular weight. The transendothelial flux of protein fractions in a 20% fetal calf serum solution confirmed the selective nature of the cultured endothelium in contrast to lack of selectivity of gelatin-coated microporous filters without the endothelial monolayer. When modeled according to the pore theory, these data better represent a two-pore model; the calculated pore radii were 65 Å and 304 Å for small- and large-pore pathways, respectively, and the ratio of small pores to large pores was 160:1.[99] Neutral dextrans with molecular weights of 6 to 500 kD also diffused across the endothelium in a similar manner. Thus, the endothelial barrier discriminates between solutes according to their molecular size, and size selectivity is consistent with a diffusional pathway through pores of heterogeneous radii. Two critical shortcomings of the pore theory, however, are that it does not account for either molecule-pore interactions that result from frictional and electrostatic effects within these hypothetical pores[95] or the vesicular transport of these molecules.[92]

Mechanisms of Increased Endothelial Permeability

In the following sections, some of the important mechanisms contributing to the increase in pulmonary vascular permeability are discussed. Specific mechanisms are covered in greater detail in reviews by Dudek and Garcia[68] and by Minshall et al.[85]

Characteristics of Increased Vascular Endothelial Permeability. A variety of bioactive agonists, cytokines, growth factors, and mechanical forces alter pulmonary vascular barrier properties and serve to increase vascular permeability.[6,68,100,101] The serine protease thrombin represents an ideal model for the examination of agonist-mediated lung endothelial activation and barrier dysfunction (Fig. 6-14). Thrombin evokes numerous endothelial cell responses that regulate hemostasis, thrombosis, and vessel wall pathophysiology and is recognized as an important mediator in the pathogenesis of acute lung injury[68] (discussed in detail in Chapter 55). Thrombin increases endothelial leakiness to macromolecules by ligating its specific cell membrane receptor, resulting in cell activation.[102,103] Direct activation by thrombin is dependent upon its ability to proteolytically cleave the extracellular NH_2-terminal domain of the PAR-1 receptor, a member of the family of proteinase-activated receptors (PARs).[102,103] The cleaved NH_2-terminus, acting as a tethered ligand, is then able to

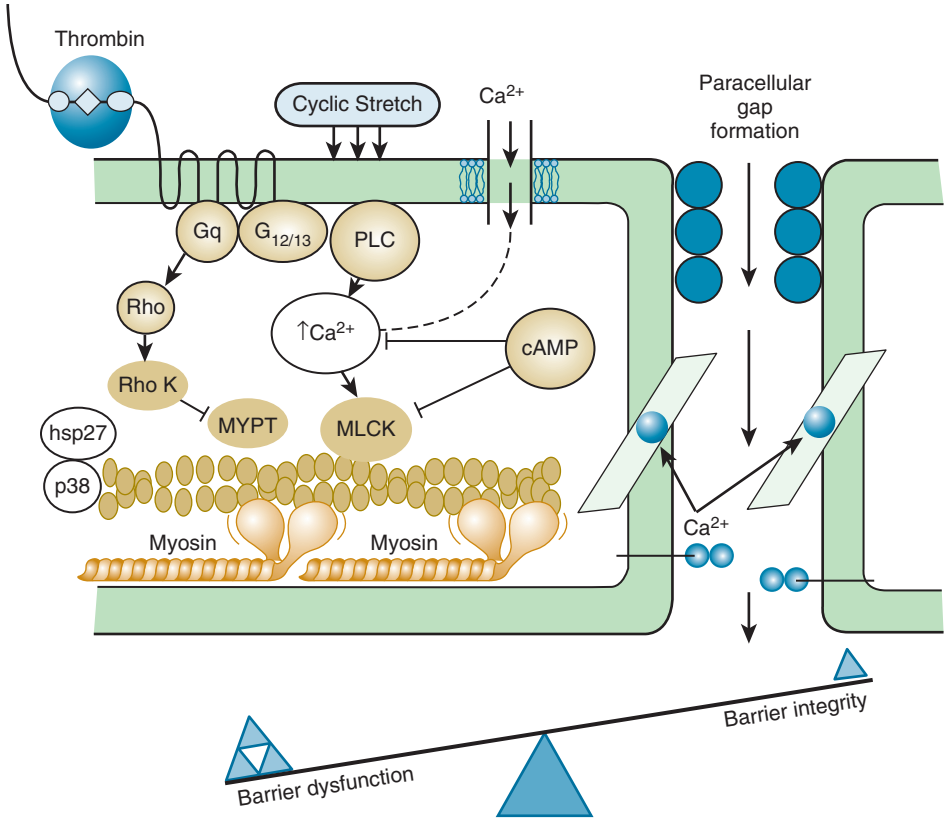

FIGURE 6-14 ■ Schematic depicting disruption in endothelial cell (EC) barrier homeostasis by thrombin. In this working model of barrier regulation, under basal conditions, a balance exists between actomyosin contractile and cellular adhesive forces. When contractile forces predominate, as depicted in the thrombin-stimulated model, ECs pull apart to form paracellular gaps, favoring barrier disruption. Thrombin cleavage of the PAR-1 receptor on the surface of EC activates both heterotrimeric G proteins (G_q, $G_{12/13}$) and small GTPases such as Rho. Activated Rho (Rho GTP) induces Rho kinase (Rho K), which via phosphorylation of the phosphatase regulatory subunit inhibits the myosin light chain phosphatase (MYPT). Rho kinase and myosin light chain kinase (MLCK) activation occurs via independent pathways. Increased cytosolic Ca^{2+} (via inositol triphosphate [IP_3] production) activates the Ca^{2+}/calmodulin-dependent MLCK, with conformational changes allowing the enzyme to access the preferred substrate (myosin light chain [MLC]). Rho kinase and MLCK activation both culminate in increased MLC phosphorylation, which in turn enables actomyosin contraction resulting in increased stress fiber formation, cellular contraction, paracellular gap formation, and ultimately barrier dysfunction. Increases in cyclic AMP (cAMP) influence both Ca^{2+} mobilization and MLCK activity. Also depicted are other representative regulatory proteins whose activity either increases or decreases EC tension. Inhibition of heat shock protein 27 (hsp27) activity, by p38 mitogen-activated protein kinase (MAPK)–catalyzed phosphorylation, also induces actin stress fiber formation, and the actin capping/severing protein gelsolin is likewise involved in stress fiber–dependent contraction.

activate the receptor and initiate a number of downstream effects, including the activation of phospholipases A_2, C, and D; increase in cytosolic Ca^{2+}; and release of von Willebrand factor, endothelin, NO, and PGI_2.[103–105] Thrombin binding alone without receptor cleavage is insufficient to elicit the complex signaling cascade that results in increased endothelial permeability.[104,106] The effect of thrombin on endothelial permeability is rapid (within 2 minutes) and reversible[101] and, like histamine, is critically dependent on G protein–transduced signals.[30,68] These intracellular signals result in increases in cytosolic calcium, activation of the contractile apparatus, and characteristic alterations in the cytoskeletal elements, a feature of other inflammatory mediators as well.[26,68,100,107]

Intracellular Ca^{2+} Shifts. The increase in vascular endothelial permeability is signaled in many edemagenic models by a rise in $[Ca^{2+}]_i$.[100,108] The thrombin-induced increase in pulmonary vascular permeability is partially inhibited by decreasing the availability of cytosolic Ca^{2+}.[103,109,110] The direct application of Ca^{2+} ionophore (to increase intracellular Ca^{2+}) also increased transendothelial albumin permeability,[110,111] decreased transendothelial electrical resistances, and increased hydraulic conductivity of intact microvessels.[111] Increased $[Ca^{2+}]_i$ may operate by signaling cytoskeletal rearrangement via actin polymerization/depolymerization that requires interactions of F-actin with actin-binding proteins.[68,112,113] This is now well appreciated to occur via activation of Ca^{2+}-dependent kinase systems (MLCK, Ca^{2+}/calmodulin-dependent kinase II, protein kinase C [PKC], etc.),[112–114] and phosphorylation of cytoskeletal proteins involved in endothelial barrier regulation, such as vimentin,[112,115] caldesmon,[115] β-catenin,[116] vinculin,[117] α-actinin,[118] myosin light chain (MLC),[109] filamin,[113] cortactin,[119] VASP,[120] and microtubule-associated proteins.[121]

Thrombin and other permeability-increasing agents such as histamine cause a rapid initial rise in cytosolic [Ca^{2+}] in pulmonary artery endothelial cells, followed by a second phase of slow decay.[103,122,123] The initial Ca^{2+} rise in endothelial cells is caused by mobilization from intracellular stores in response to increased inositol polyphosphate generation (particularly inositol 1,4,5-triphosphate) derived from phospholipase C–activated hydrolysis of phosphoinositides.[110,122] The second phase is caused by Ca^{2+} influx through store-operated channels[123] and, although not as well understood, this is the critical Ca^{2+} signal responsible for the increase in permeability.[124] Inhibition of the lipoxygenase pathway of arachidonate metabolism abolished this long-lived Ca^{2+} rise and changes in F-actin cytoskeletal reorganization,[125] which suggests that lipoxygenase products open Ca^{2+} channels and prolong the rise in $[Ca^{2+}]_i$, which in turn provides the signal for cytoskeletal reorganization. Lipoxygenase products, namely monohydroxyeicosatetraenoic acids (HETEs), directly increase lung vascular permeability by opening Ca^{2+} channels as described. HETEs thus generated may be messengers responsible for this second critical phase of the Ca^{2+} increase.[126]

Protein Kinase C Activation and Other Barrier-Regulatory Signals. Despite the clear contribution of MLCK/Rho kinase–driven increases in MLC phosphorylation to tension development and increased vascular permeability, alternate pathways that do not require an increase in MLC phosphorylation are also involved in barrier regulation. PKC is a family of serine/threonine kinases comprising at least 12 isotypes, with the conventional and novel isoforms of this kinase family requiring a rise in cytosolic Ca^{2+} for activation (see Siflinger-Birnboim and Johnson[127]). PKC-mediated pathways exert a prominent effect on barrier regulation in a time- and species-specific manner likely reflecting differences in PKC isotype-specific expression in different species[101,109,115]; PKC activation is also an important signal transduction pathway by which extracellular mediators, including thrombin, increase transendothelial albumin flux, and thus may be causally linked to phosphorylation of cytoskeletal proteins such as caldesmon, an actin-, myosin-, and calmodulin-binding protein present in actomyosin cross-bridges and stress fibers.[115] Finally, p60src kinase and p38 mitogen-activated protein (MAP) kinase activation also has been linked to endothelial stress fiber formation and contractile regulation, endothelial cell migration, and cytokine-induced permeability.[107,119,128] The mechanism through which p38 MAP kinases exert these effects is unclear but may involve the actin binding proteins caldesmon and hsp27, known p38 MAP kinase targets whose actin polymerization regulatory activity is influenced by phosphorylation.[109]

Basement Membrane and Matrix Components. Cell-matrix adhesions are essential for barrier maintenance and restoration and exist in dynamic equilibrium with endothelial contractile forces.[129] An organized basement membrane and extracellular matrix surrounding the endothelium may control transendothelial solute flux, and this may be dependent on particular extracellular matrix constituents (e.g., certain matrix proteins are known to restrict albumin transport because of the negative charge of their glycosaminoglycan constituents).[82] In vivo studies indicate that the interstitial matrix is capable of 14-fold reduction in diffusive transport of albumin.[130] Application of extracellular matrix consisting primarily of type I collagen to microporous filters produced a 10-fold reduction in the transport of albumin. Albumin restriction was not increased by coating the filters with fibronectin, which indicates that only certain matrix components impose a restrictive barrier.[131]

Endothelial focal adhesions are composed of extracellular matrix proteins (collagen, fibronectin, laminin, vitronectin, proteoglycans), transmembrane integrin receptors, and cytoplasmic focal adhesion plaques (containing α-actinin, vinculin, paxillin, and talin), which combine to provide additional adhesive forces in barrier regulation and form a critical bridge for bidirectional signal transduction between the actin cytoskeleton and the cell-matrix interface[29,132] (see Fig. 6-12). The core matrix proteins, because of their position and points of contact with endothelial cells, may determine cell-substratum adhesion and thereby determine vascular permeability in normal conditions and in response to inflammatory mediators such as tumor necrosis factor.[133] Extracellular stimuli can be transmitted to the cytoskeleton through focal adhesion rearrangement linked to integrin ligation, and antibodies to β_1-integrin alter endothelial attachment, cell spreading, and permeability.[134] Integrin binding to the extracellular matrix induces the attachment of integrins to intracellular actin fibers, a process that stimulates tyrosine phosphorylation of multiple focal adhesion proteins as well as tyrosine phosphorylation–dependent Ca^{2+} influx.[135] The extracellular matrix can also be remodeled by endothelial cell–released proteases, causing endothelial cells layered on this matrix to become more permeable.[133]

Endothelial Water Permeability and Albumin Transcytosis. The pulmonary vascular endothelium provides the primary resistance to the transvascular flow of water,[82] although the relative distribution of transcapillary water flow through the paracellular and transcellular pathways remains controversial.[77,136] Albumin is a major determinant of endothelial water permeability because albumin's interaction with the vessel wall regulates the vessel wall hydraulic conductivity.[137] This observation forms the cornerstone of the "fiber matrix" hypothesis, which specifies that interactions between albumin and the glycocalyx component of the endothelium and hyaluronic acid and sulfated proteoglycans regulate water flow across the endothelial barrier.[138]

Hydraulic conductivity has been measured in endothelial cells grown on matrix-covered porous filters.[139] Hydraulic conductivity across filters alone was 100-fold less than hydraulic conductivity across the pulmonary artery endothelial monolayer. These values are 10- to 100-fold greater than those reported for intact vessel walls,[137] which reflects the lack of a series resistance to albumin movement in the absence of basement membrane and adjacent interstitial components.[130] Exposure of monolayers to albumin (0.5 to 2.5 mg/mL) decreased the hydraulic conductivity in a concentration-dependent

manner. Physicochemical interaction of albumin with endothelial cells may be responsible for this effect because the response did not occur when albumin was replaced with a 70-kD dextran molecule.[139] From work with frog mesenteric vessels, it has been suggested that interactions of albumin with the capillary endothelium occurred by association of arginine residues on the albumin molecule with negative charge on the endothelium.[137] This interaction has been confirmed in mammalian pulmonary vascular endothelial cells in which the arginyl residues of albumin are required for the response; this raises the possibility that a charge interaction of albumin with the endothelial cell is mediated via the arginyl residues.[139]

The transport of albumin from the abluminal to the luminal side of the endothelial monolayer presents an intriguing potential for an active mechanism of albumin transport, which may regulate the plasma albumin concentration.[140] Studies indicate that transendothelial flux of proteins such as insulin, transferrin, and albumin involves recognition by receptors located on the luminal side of the endothelial cell.[92,141,142] Receptor-mediated transcytosis of solutes is an important mechanism of transport across the pulmonary microvascular endothelial barrier. Albumin binds to the endothelial cell surface protein glycoprotein 60 (gp60) or albondin on the luminal side of the endothelium.[92,141,142] Once bound, albumin activates signaling via the tyrosine kinase pathway, thereby activating the formation of vesicles,[76] and albumin crosses the endothelial cell by shuttling from the luminal to the abluminal sides of the cell.[92,141,142]

Several "albumin receptors," such as gp60[143] and the smaller 18-kD and 31-kD cell surface proteins (specific for denatured albumin),[91,144] have been described. Albumin binding to endothelial cells and its potential role in transendothelial flux of albumin was explored with bovine pulmonary artery endothelial cell monolayers.[145] In the presence of unlabeled albumin (0 to 60 mg/mL), binding of tracer ^{125}I-labeled albumin to endothelial monolayers was saturated at 5 mg/mL unlabeled albumin, which indicates that unlabeled albumin competed with labeled albumin for sites on the endothelial surface. Binding of ^{125}I-labeled albumin to endothelial monolayers was reduced at 4°C, which indicates that albumin binding was reversible. Binding of ^{125}I-labeled albumin was independent of the concentration of other unlabeled proteins. The apparent equilibrium binding affinity constant (K_d) for albumin binding is 7.2×10^{-5} mol, with a maximum number of 4.2×10^{7} binding sites per cell. Albumin binds with a higher affinity in pulmonary microvessel endothelial cells, which is consistent with a greater number of vesicles present in these cells.[92]

The lectin *Ricinus communis* agglutinin (RCA) binds to gp60 in rat epididymal fat pad endothelial cells.[143] RCA also precipitates gp60 on plasmalemmal membrane, which indicates that gp60 is present in these cells.[145] Addition of RCA to the endothelial monolayer reduced ^{125}I-labeled albumin permeability by 40%, which was similar to the decrease in albumin permeability observed with excess unlabeled albumin, although several other lectins that did not bind to gp60 had no effect. These findings demonstrate a role for albumin binding to endothelial cell membrane gp60 in the transendothelial flux of albumin. Although the proportion of albumin transport in macrovascular endothelium dependent on binding of albumin is 40%, there are relatively few vesicles in macrovascular endothelium in comparison with microvessel endothelial cells. It is conceivable that pulmonary microvessel cells have a greater proportion of albumin transport dependent on gp60 because these cells have far more vesicles. Another study has employed antibody directed against gp60 to cross-link, and thereby to activate, the receptor.[76] This was shown to increase preferentially the transcellular permeability of albumin, which indicates the importance of gp60 in regulating lung fluid balance. Whether gp60 activation plays an active role in mediating increased lung vascular permeability in disease states is unknown; however, receptor-linked transport of albumin may be important in the transport of lipids such as albumin-linked long-chain free fatty acids and hormones.[146] The up-regulation of gp60 may be a factor in inflammatory responses characterized by increased pulmonary vascular endothelial permeability to albumin.

Strategies to Reverse Permeability and Restore Barrier Integrity

Despite significant progress in understanding the molecular and cellular events regulating increased permeability, mechanisms of vascular barrier restoration are less well understood, and a wide range of potential therapeutic agents for modulating barrier function in a clinically advantageous way are under investigation. Historically, however, increasing the level of cyclic nucleotides has represented the sole strategy for retarding the edema phase observed in inflammatory lung syndromes. Increases in intracellular cyclic AMP (cAMP) concentrations decrease pulmonary vascular endothelial permeability and inhibit the permeability-increasing effects of thrombin and histamine in association with inhibition of F-actin reorganization.[147–149] The reduction in paracellular permeability involves activation of cAMP-dependent protein kinases that phosphorylate proteins such as MLCK,[114] thereby reducing its capacity to phosphorylate MLCs, as well as regulating phosphatases that dephosphorylate proteins such as MLCs (see Fig. 6-12), which serves to reduce stress fiber formation.[147,149–151] Increases in cellular cAMP also prevent the increase in $[Ca^{2+}]_i$ and isotype-specific PKC activation, downstream signals regulating permeability.[149]

Recently, additional agonists have been identified that augment lung endothelial barrier function, and either attenuate or prevent agonist-mediated barrier dysfunction.[152–156] Given that alteration in endothelial permeability is a key event in angiogenesis, it is not surprising that angiogenic growth factors such as hepatocyte growth factor,[153] angiopoietin,[154] and sphingosine 1-phosphate (S1P)[152] are now recognized to have significant barrier-enhancing properties. For example, S1P, a sphingolipid metabolite generated by numerous cell types, including

endothelium and platelets, is a potent endothelial cell chemotactic and angiogenic factor, which effects robust and sustained endothelial barrier enhancement.[152] Ligation of endothelial differentiation gene-1 (EDG1) receptor by S1P results in strong barrier enhancement in vitro[152,157] and in vivo.[158,159] S1P significantly attenuates thrombin-induced barrier disruption,[152] while rapidly restoring barrier integrity in the isolated perfused murine lung.[159] A single intravenous dose of S1P, given 1 hour after intratracheal endotoxin administration, produced highly significant reductions in multiple indices of inflammatory lung injury, including vascular leak, as demonstrated in both murine[158,159] and canine[159] models of acute lung injury (ALI). This profound barrier enhancement is mediated by G protein–dependent signaling cascades, leading to cytoskeletal rearrangement with increased peripheral actin resulting in increased endothelial junctional integrity (Fig. 6-15).[152,160]

Other barrier-promoting agonists that have been identified include the S1P analogue FTY720, statins, activated protein C, adenosine triphosphate (ATP), high-molecular-weight hyaluronan, methylnaltrexone, and oxidized phospholipids (for review, see Wolfson et al[161]). FTY720, an unphosphorylated S1P analogue, is a derivative of the natural immunosuppressant myriocin that has been recently described to cause peripheral lymphopenia by inhibiting cellular egress from lymphoid tissues.[162] FTY720 induces delayed endothelial barrier enhancement through a G_i-coupled receptor, which acts through a unknown mechanism that is EDG1 independent and distinct from the pathways described for S1P.[163] Nevertheless, intraperitoneal FTY720 protected against intratracheal lipopolysaccharide (LPS) in a murine model of ALI.[159] Simvastatin, a hydroxymethylglutaryl coenzyme A reductase inhibitor that lowers serum cholesterol levels, has been demonstrated to improve endothelial barrier function through activation of a Rac1-dependent cytoskeleton mechanism that is independent of its cholesterol-lowering effects.[164] Similarly, activated protein C, an anticoagulant, confers a barrier-protective actin configuration and enhances the vascular barrier in vitro and in vivo.[165] Through a mechanism that does not involve adenosine receptors, ATP induces barrier enhancement via phospholipase C- and Rac1-dependent cytoskeleton reorganization.[166,167] In addition, injection of nonhydrolyzable ATP in mice confers protection from endotoxin-induced lung injuries.[168] High-molecular-weight hyaluronan associates with CD44 receptors, which transactivate EDG1 to induce Akt1- and Rac1-dependent pathways.[169] Methylnaltrexone is a peripherally restricted mu opioid receptor antagonist that protects against the edemagenic morphine agonist DAMGO as well as thrombin

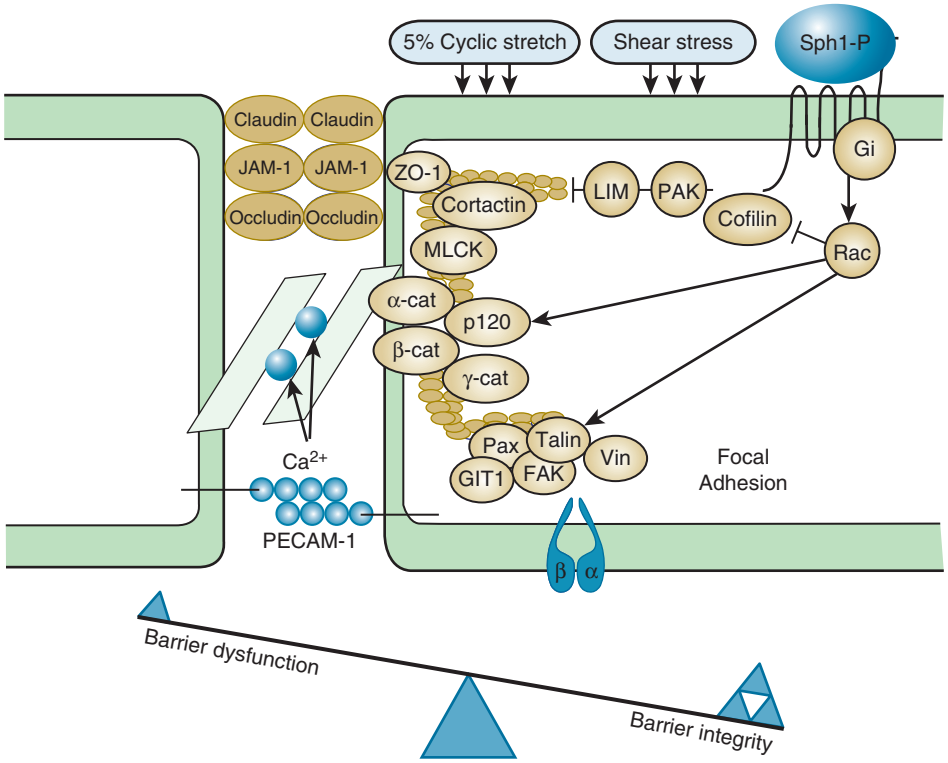

FIGURE 6-15 ■ Schematic depicting enhanced endothelial cell barrier function by sphingosine 1-phosphate (Sph1-P), a platelet-derived lipid growth factor, which activates specific G protein–coupled EDG (endothelial differentiation gene) receptors, leading to profound cytoskeletal rearrangement and increased barrier function in vitro and in vivo. Ligation of EDG results in activation of the small GTPase Rac, a signaling cascade that results in cytoskeletal rearrangement and increased cortical actin with increased linkage to the adherens junction and focal adhesions. Rac activation initiates intracellular events dependent on specific protein kinase C (PKC) isotypes, p21-associated kinase (PAK), LIM kinase, the actin-severing protein cofilin, and MLCK, which all contribute to increased cell-cell and cell-matrix tethering. Abbreviations as in Figures 6-12 and 6-14. (For references see text.)

and LPS challenge via inhibition of EDG3 activation.[170] Lastly, oxidized phospholipids confer barrier enhancement by inducing a unique zip-like configuration of peripheral actin through activation of Rac1- and Cdc42-dependent pathways.[171] Furthermore, treatment with OxPAPC at the onset of high-tidal-volume mechanical ventilation was protective in a murine model of ventilator-induced lung injury.[172]

The identification of novel biologically compatible agents that can preserve or restore vascular integrity offers promise for the future management of pulmonary edema associated with increased vascular leak in the critically ill. Notably, nearly each of these agents has been successfully evaluated in preclinical models of ALI and one agent, FTY720, is in Phase III trials, while three other agents—statins, activated protein C, and methylnaltrexone—are currently approved by the Food and Drug Administration for other medical conditions. Thus, the prospects for the rapid translation of these lung vascular barrier-protective strategies to clinical practice are high.

PULMONARY VASCULAR GENOMICS

Understanding the genetic basis of pulmonary vascular disease has the potential to offer invaluable insights into the functional significance and role of individual genes in the normal physiology as well as pathobiology of the pulmonary circulation. Several complex lung diseases are characterized by a component of vascular dysfunction, including asthma, chronic obstructive pulmonary disease, and pulmonary hypertension; however, ALI, including its most severe form ARDS, represents lung pathologies that are primarily defined by derangements in vascular function. Accordingly, a growing literature on the genetic basis for ALI is of great interest. Candidate gene-based association studies have become the preferred type of analysis, relying on the identification of common variants, usually single nucleotide polymorphisms (SNPs), between unrelated controls and cases. Since ALI is a clinical syndrome that occurs in patients with complex phenotypes, genomic studies are difficult to design and must be carefully interpreted. Nonetheless, several promising candidate genes have now emerged; for example, an intronic Alu insertion/deletion (I/D) polymorphism of ACE has been shown to correspond to variance in plasma ACE activity, with greater enzymatic activity associated with the D allele.[173] Subsequently, the homozygous ACE deletion (DD) has been implicated in the development and prognosis of ARDS in a European population.[174] Separately, pre–B-cell colony-enhancing factor (PBEF), previously a largely unknown cytokine, was identified as a novel biomarker in cell and animal models relevant to the pathobiology of ALI as well as in bronchoalveolar lavage fluid samples from patients with ALI.[175] PBEF was also found to induce increased endothelial permeability,[176] and an association study identified a specific SNP in the PBEF gene corresponding to a transcription factor binding site, the -1543C/-1001G haplotype, that conferred increased susceptibility to ALI as well as ALI mortality.[175] Several other genes, including those for MLCK,[177] interleukin-6,[178] interleukin-10,[179] macrophage migration inhibitory factor,[180,181] vascular endothelial growth factor,[182] and the growth arrest and DNA damage-inducible gene GADD45α,[183] have also demonstrated some degree of association with ALI and are plausibly related to its pathobiology, making them intriguing targets for further investigation.

Appendix can be found on Expert Consult

KEY POINTS

- The pulmonary circulation serves both respiratory and nonrespiratory functions.
- The low-pressure, low-vascular-resistance characteristics of the pulmonary circulation differ substantially from the systemic circulation, as do the responses to hypoxia.
- Hypoxic pulmonary vasoconstriction serves to improve gas exchange by redirecting perfusion away from poorly ventilated (i.e., hypoxic) regions of the lung; despite extensive study, the mechanism(s) underlying this important reponse remain unknown.
- The pulmonary microvessels serve as primary sites for fluid and solute exchange, chiefly in the thick portion of the alveolar walls, which depends on the balance of forces that govern fluid filtration. Fluid is continuously being filtered in healthy human lungs and removed through pulmonary lymphatics.
- A variety of pathophysiologic events and mediators can perturb this balance and culminate in either hydrostatic or high-permeability pulmonary edema.
- Increases in vessel wall permeability characterize acute lung injury and other inflammatory lung disorders. A variety of pathogenic mechanisms are involved in the development of leaky pulmonary vessels that are intimately linked to the endothelial cytoskeleton, through paracellular and transcytotic pathways. The end result of lung vascular injury is an accumulation of protein-rich fluid in the extravascular spaces.

References

1. Fishman AP: Pulmonary circulation. *In* Fisher AB (ed): Handbook of Physiology, Section 3: The Respiratory System, Vol I: Circulation and Nonrespiratory Function. Bethesda, MD: American Physiological Society, 1985, pp 93–165.
2. Dawson CA: Role of pulmonary vasomotion in physiology of the lung. Physiol Rev 64:544–616, 1984.
3. Hughes JMB, Morrell NW: Pulmonary Circulation. London: Imperial College Press, 2001, p 356.
4. Gao Y, Raj JU: Role of veins in regulation of pulmonary circulation. Am J Physiol Lung Cell Mol Physiol 288:L213–L226, 2005.
5. Swan HJ, Ganz W, Forrester J, et al: Catheterization of the heart in man with use of a flow-directed balloon-tipped catheter. N Engl J Med 283:447–451, 1970.
6. Bhattacharya J, Nanjo S, Staub NC: Micropuncture measurement of lung microvascular pressure during 5-HT infusion. J Appl Physiol 52:634–637, 1982.
7. Linehan JH, Dawson CA, Rickaby DA: Distribution of vascular resistance and compliance in a dog lung lobe. J Appl Physiol 53:158–168, 1982.
8. Lai-Fook SJ: Perivascular interstitial fluid pressure measured by micropipettes in isolated dog lung. J Appl Physiol 52:9–15, 1982.
9. Gil J: Alveolar wall relations. Ann N Y Acad Sci 384:31–43, 1982.
10. Gil J: Influence of surface faces on pulmonary circulation. *In* Fishman AP, Renkin EM (eds): Pulmonary Edema. Bethesda, MD: American Physiological Society, 1979, pp 53–64.
11. Lamm WJ, Kirk KR, Hanson WL, et al: Flow through zone 1 lungs utilizes alveolar corner vessels. J Appl Physiol 70:1518–1523, 1991.
12. Borst HG, McGregor M, Whittenberger JL, et al: Influence of pulmonary arterial and left atrial pressures on pulmonary vascular resistance. Circ Res 4:393–399, 1956.
13. Roos A, Thomas LJ Jr, Nagel EL, et al: Pulmonary vascular resistance as determined by lung inflation and vascular pressures. J Appl Physiol 16:77–84, 1961.
14. Murray JF, Karp RB, Nadel JA: Viscosity effects on pressure-flow relations and vascular resistance in dogs' lungs. J Appl Physiol 27:336–341, 1969.
15. Roughton FJ, Forster RE: Relative importance of diffusion and chemical reaction rates in determining rate of exchange of gases in the human lung, with special reference to true diffusing capacity of pulmonary membrane and volume of blood in the lung capillaries. J Appl Physiol 11:290–302, 1957.
16. Weibel ER: Design and structure of the human lung. *In* Fishman AP (ed): Pulmonary Diseases and Disorders. New York: McGraw-Hill, 1980, pp 224–271.
17. Dawson CA, Linehan JH, Rickaby DA: Pulmonary microcirculatory hemodynamics. Ann N Y Acad Sci 384:90–106, 1982.
18. Pace JB: Sympathetic control of pulmonary vascular impedance in anesthetized dogs. Circ Res 29:555–568, 1971.
19. Hlastala MP, Glenny RW: Vascular structure determines pulmonary blood flow distribution. News Physiol Sci 14:182–186, 1999.
20. Li YS, Haga JH, Chien S: Molecular basis of the effects of shear stress on vascular endothelial cells. J Biomech 38:1949–1971, 2005.
21. Birukov KG, Birukova AA, Dudek SM, et al: Shear stress-mediated cytoskeletal remodeling and cortactin translocation in pulmonary endothelial cells. Am J Respir Cell Mol Biol 26:453–464, 2002.
22. Chen KD, Li YS, Kim M, et al: Mechanotransduction in response to shear stress: Roles of receptor tyrosine kinases, integrins, and Shc. J Biol Chem 274:18393–18400, 1999.
23. Lehoux S, Castier Y, Tedgui A: Molecular mechanisms of the vascular responses to haemodynamic forces. J Intern Med 259:381–392, 2006.
24. Malek AM, Izumo S: Mechanism of endothelial cell shape change and cytoskeletal remodeling in response to fluid shear stress. J Cell Sci 109(Pt 4):713–726, 1996.
25. Nerem RM, Alexander RW, Chappell DC, et al: The study of the influence of flow on vascular endothelial biology. Am J Med Sci 316:169–175, 1998.
26. Birukov KG, Jacobson JR, Flores AA, et al: Magnitude-dependent regulation of pulmonary endothelial cell barrier function by cyclic stretch. Am J Physiol Lung Cell Mol Physiol 285:L785–L797, 2003.
27. Birukov KG: Small GTPases in mechanosensitive regulation of endothelial barrier. Microvasc Res 77:46–52, 2009.
28. Reinhart-King CA, Fujiwara K, Berk BC: Physiologic stress-mediated signaling in the endothelium. Methods Enzymol 443: 25–44, 2008.
29. Birukova AA, Chatchavalvanich S, Rios A, et al: Differential regulation of pulmonary endothelial monolayer integrity by varying degrees of cyclic stretch. Am J Pathol 168:1749–1761, 2006.
30. Birukova AA, Smurova K, Birukov KG, et al: Role of Rho GTPases in thrombin-induced lung vascular endothelial cells barrier dysfunction. Microvasc Res 67:64–77, 2004.
31. Birukova AA, Rios A, Birukov KG: Long-term cyclic stretch controls pulmonary endothelial permeability at translational and post-translational levels. Exp Cell Res 314:3466–3477, 2008.
32. Pelosi P, Rocco PR: Effects of mechanical ventilation on the extracellular matrix. Intensive Care Med 34:631–639, 2008.
33. Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 342:1301–1308, 2000.
34. Wagner WW Jr, Latham LP, Capen RL: Capillary recruitment during airway hypoxia: Role of pulmonary artery pressure. J Appl Physiol 47:383–387, 1979.
35. Kato M, Staub NC: Response of small pulmonary arteries to unilobar hypoxia and hypercapnia. Circ Res 19:426–440, 1966.
36. Stenmark KR, Fagan KA, Frid MG: Hypoxia-induced pulmonary vascular remodeling: Cellular and molecular mechanisms. Circ Res 99:675–691, 2006.
37. Madden JA, Dawson CA, Harder DR: Hypoxia-induced activation in small isolated pulmonary arteries from the cat. J Appl Physiol 59:113–118, 1985.
38. Teng X, Li D, Champion HC, et al: FIZZ1/RELMalpha, a novel hypoxia-induced mitogenic factor in lung with vasoconstrictive and angiogenic properties. Circ Res 92:1065–1067, 2003.
39. Arias-Stella J, Saldana M: The terminal portion of the pulmonary arterial tree in people native to high altitudes. Circulation 28: 915–925, 1963.
40. Stenmark KR, Mecham RP: Cellular and molecular mechanisms of pulmonary vascular remodeling. Annu Rev Physiol 59:89–144, 1997.
41. Loeppky JA, Scotto P, Riedel CE, et al: Effects of acid-base status on acute hypoxic pulmonary vasoconstriction and gas exchange. J Appl Physiol 72:1787–1797, 1992.
42. Palmer RM, Ferrige AG, Moncada S: Nitric oxide release accounts for the biological activity of endothelium-derived relaxing factor. Nature 327:524–526, 1987.
43. Brashers VL, Peach MJ, Rose CE Jr: Augmentation of hypoxic pulmonary vasoconstriction in the isolated perfused rat lung by in vitro antagonists of endothelium-dependent relaxation. J Clin Invest 82:1495–1502, 1988.
44. Nagao T, Vanhoutte PM: Endothelium-derived hyperpolarizing factor and endothelium-dependent relaxations. Am J Respir Cell Mol Biol 8:1–6, 1993.
45. Edwards G, Dora KA, Gardener MJ, et al: K^+ is an endothelium-derived hyperpolarizing factor in rat arteries. Nature 396:269–272, 1998.
46. Holden WE, McCall E: Hypoxia-induced contractions of porcine pulmonary artery strips depend on intact endothelium. Exp Lung Res 7:101–112, 1984.
47. Michelakis ED, Hampl V, Nsair A, et al: Diversity in mitochondrial function explains differences in vascular oxygen sensing. Circ Res 90:1307–1315, 2002.
48. Kozlowski RZ: Ion channels, oxygen sensation and signal transduction in pulmonary arterial smooth muscle. Cardiovasc Res 30:318–325, 1995.
49. Buescher PC, Pearse DB, Pillai RP, et al: Energy state and vasomotor tone in hypoxic pig lungs. J Appl Physiol 70:1874–1881, 1991.
50. Archer S, Michelakis E: The mechanism(s) of hypoxic pulmonary vasoconstriction: potassium channels, redox O_2 sensors, and controversies. News Physiol Sci 17:131–137, 2002.

51. Tolins M, Weir EK, Chesler E, et al: Pulmonary vascular tone is increased by a voltage-dependent calcium channel potentiator. J Appl Physiol 60:942–948, 1986.
52. Jernigan NL, Walker BR, Resta TC: Chronic hypoxia augments protein kinase G-mediated Ca^{2+} desensitization in pulmonary vascular smooth muscle through inhibition of RhoA/Rho kinase signaling. Am J Physiol Lung Cell Mol Physiol 287:L1220–L1229, 2004.
53. Fagan KA, Oka M, Bauer NR, et al: Attenuation of acute hypoxic pulmonary vasoconstriction and hypoxic pulmonary hypertension in mice by inhibition of Rho-kinase. Am J Physiol Lung Cell Mol Physiol 287:L656–L664, 2004.
54. Fagan KA: Selected Contribution: Pulmonary hypertension in mice following intermittent hypoxia. J Appl Physiol 90:2502–2507, 2001.
55. Daly ID, Hebb CO: Pulmonary and Bronchial Vascular Systems: Their Reactions Under Controlled Conditions of Ventilation and Circulation. London: Arnold, 1966.
56. Ingram RH Jr, Szidon JP, Fishman AP: Response of the main pulmonary artery of dogs to neuronally released versus blood-borne norepinephrine. Circ Res 26:249–262, 1970.
57. Hyman AL, Kadowitz PJ: Enhancement of alpha- and beta-adrenoceptor responses by elevations in vascular tone in pulmonary circulation. Am J Physiol 250(6 Pt 2):H1109–H1116, 1986.
58. Barnes PJ, Liu SF: Regulation of pulmonary vascular tone. Pharmacol Rev 47:87–131, 1995.
59. Vanhoutte PM, Rubanyi GM, Miller VM, et al: Modulation of vascular smooth muscle contraction by the endothelium. Annu Rev Physiol 48:307–320, 1986.
60. Malik AB, Johnson A: Role of humoral mediators in the pulmonary vascular response. *In* Weir EK, Reeves JT (eds): Lung Biology in Health and Disease. Vol 38: Pulmonary Vascular Physiology and Pathophysiology. New York: Marcel Dekker, 1989, pp 445–468.
61. Bullock GR, Steyaert I, Bilbe G, et al: Distribution of type-1 and type-2 angiotensin receptors in the normal human lung and in lungs from patients with chronic obstructive pulmonary disease. Histochem Cell Biol 115:117–124, 2001.
62. Studdy PR, Lapworth R, Bird R: Angiotensin-converting enzyme and its clinical significance—a review. J Clin Pathol 36:938–947, 1983.
63. Li W, Moore MJ, Vasilieva N, et al: Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. Nature 426:450–454, 2003.
64. Peiris JS, Yuen KY, Osterhaus AD, et al: The severe acute respiratory syndrome. N Engl J Med 349:2431–2441, 2003.
65. Imai Y, Kuba K, Rao S, et al: Angiotensin-converting enzyme 2 protects from severe acute lung failure. Nature 436:112–116, 2005.
66. Staub NC: Pulmonary edema. Physiol Rev 54:678–811, 1974.
67. Taylor AE, Parker JC: Pulmonary interstitial spaces and lymphatics. *In* Fishman AP, Fisher AB (eds): Handbook of Physiology. Section 3: The Respiratory System. Vol I: Circulation and Nonrespiratory Function. Bethesda, MD: American Physiological Society, 1985, pp 167–230.
68. Dudek SM, Garcia JG: Cytoskeletal regulation of pulmonary vascular permeability. J Appl Physiol 91:1487–1500, 2001.
69. Mehta D, Malik AB: Signaling mechanisms regulating endothelial permeability. Physiol Rev 86:279–367, 2006.
70. Baile EM, Pare PD, Dahlby RW, et al: Regional distribution of extravascular water and hematocrit in the lung. J Appl Physiol 46:937–942, 1979.
71. Snashall PD, Keyes SJ, Morgan B, et al: Regional extravascular and interstitial lung water in normal dogs. J Appl Physiol 49:547–551, 1980.
72. Staub NC: Pathophysiology of pulmonary edema. *In* Staub NC, Taylor AE (eds): Edema. New York: Raven, 1984, pp 719–746.
73. Gee MH, Williams DO: Effect of lung inflation on perivascular cuff fluid volume in isolated dog lung lobes. Microvasc Res 17:192–201, 1979.
74. Bachofen M, Bachofen H, Weibel ER: Lung edema in the adult respiratory distress syndrome. *In* Fishman AP, Renkin EM (eds): Pulmonary Edema. Bethesda, MD: American Physiological Society, 1979, pp 241–252.
75. Guyton AC, Lindsey AW: Effect of elevated left atrial pressure and decreased plasma protein concentration on the development of pulmonary edema. Circ Res 7:649–657, 1959.
76. Minshall RD, Tiruppathi C, Vogel SM, et al: Endothelial cell-surface gp60 activates vesicle formation and trafficking via G_i-coupled Src kinase signaling pathway. J Cell Biol 150:1057–1070, 2000.
77. Hirata A, Baluk P, Fujiwara T, et al: Location of focal silver staining at endothelial gaps in inflamed venules examined by scanning electron microscopy. Am J Physiol 269(3 Pt 1):L403–L418, 1995.
78. Malik AB: Mechanisms of neurogenic pulmonary edema. Circ Res 57:1–18, 1985.
79. Magno M, Szidon JP: Hemodynamic pulmonary edema in dogs with acute and chronic lymphatic ligation. Am J Physiol 231:1777–1782, 1976.
80. Wagner EM, Blosser S, Mitzner W: Bronchial vascular contribution to lung lymph flow. J Appl Physiol 85:2190–2195, 1998.
81. Kedem O, Katchalsky A: Thermodynamic analysis of the permeability of biological membranes to non-electrolytes. Biochim Biophys Acta 27:229–246, 1958.
82. Taylor AE, Granger DN: Exchange of macromolecules across the microcirculation. *In* Renkin EM, Michel CC (eds): Handbook of Physiology. Section 2: The Cardiovascular System. Vol IV: Microcirculation. Bethesda, MD: American Physiological Society, 1984, pp 467–520.
83. Simionescu M, Simionescu N: Ultrastructure of the microvascular wall: Functional correlations. *In* Renkin EM, Michel CC (eds): Handbook of Physiology. Section 2: The Cardiovascular System. Vol IV: Microcirculation. Bethesda, MD: American Physiological Society, 1984, pp 41–101.
84. Taylor AE, Granger DN: Equivalent pore modeling: vesicles and channels. Fed Proc 42:2440–2445, 1983.
85. Minshall RD, Tiruppathi C, Vogel SM, et al: Vesicle formation and trafficking in endothelial cells and regulation of endothelial barrier function. Histochem Cell Biol 117:105–112, 2002.
86. Kozono D, Yasui M, King LS, et al: Aquaporin water channels: Atomic structure molecular dynamics meet clinical medicine. J Clin Invest 109:1395–1399, 2002.
87. Siflinger-Birnboim A, Cooper JA, del Vecchio PJ, et al: Selectivity of the endothelial monolayer: Effects of increased permeability. Microvasc Res 36:216–227, 1988.
88. Simionescu N, Simionescu M, Palade GE: Structural basis of permeability in sequential segments of the microvasculature of the diaphragm. II. Pathways followed by microperoxidase across the endothelium. Microvasc Res 15:17–36, 1978.
89. Luna EJ, Hitt AL: Cytoskeleton–plasma membrane interactions. Science 258:955–964, 1992.
90. Takeichi M: Cadherins: A molecular family important in selective cell-cell adhesion. Annu Rev Biochem 59:237–252, 1990.
91. Ghinea N, Eskenasy M, Simionescu M, et al: Endothelial albumin binding proteins are membrane-associated components exposed on the cell surface. J Biol Chem 264:4755–4758, 1989.
92. Schnitzer JE, Carley WW, Palade GE: Specific albumin binding to microvascular endothelium in culture. Am J Physiol 254(3 Pt 2):H425–H437, 1988.
93. Granger HJ, Shepherd AP: Dynamics and control of the microcirculation. Adv Biomed Eng 7:1–63, 1979.
94. Taylor AE, Gaar KA Jr: Estimation of equivalent pore radii of pulmonary capillary and alveolar membranes. Am J Physiol 218:1133–1140, 1970.
95. Lai-Fook SJ, Toporoff B: Pressure-volume behavior of perivascular interstitium measured in isolated dog lung. J Appl Physiol 48:939–946, 1980.
96. Renkin EM: Capillary transport of macromolecules: Pores and other endothelial pathways. J Appl Physiol 58:315–325, 1985.
97. Grotte G: Passage of dextran molecules across the blood-lymph barrier. Acta Chir Scand Suppl 211:1–84, 1956.
98. Taylor A, Townsley MI, Korthuis RJ: Macromolecule transport across the pulmonary microvessel walls. Exp Lung Res 8:97–123, 1985.
99. Siflinger-Birnboim A, Del Vecchio PJ, Cooper JA, et al: Molecular sieving characteristics of the cultured endothelial monolayer. J Cell Physiol 132:111–117, 1987.

100. Moore TM, Chetham PM, Kelly JJ, et al: Signal transduction and regulation of lung endothelial cell permeability: Interaction between calcium and cAMP. Am J Physiol 275(2 Pt 1):L203–L222, 1998.
101. Garcia JG, Siflinger-Birnboim A, Bizios R, et al: Thrombin-induced increase in albumin permeability across the endothelium. J Cell Physiol 128:96–104, 1986.
102. Lollar P, Owen WG: Clearance of thrombin from circulation in rabbits by high-affinity binding sites on endothelium: Possible role in the inactivation of thrombin by antithrombin III. J Clin Invest 66:1222–1230, 1980.
103. Garcia JG, Patterson C, Bahler C, et al: Thrombin receptor activating peptides induce Ca^{2+} mobilization, barrier dysfunction, prostaglandin synthesis, and platelet-derived growth factor mRNA expression in cultured endothelium. J Cell Physiol 156:541–549, 1993.
104. Vogel SM, Gao X, Mehta D, et al: Abrogation of thrombin-induced increase in pulmonary microvascular permeability in PAR-1 knockout mice. Physiol Genomics 4:137–145, 2000.
105. Garcia JG, Fenton JW 2nd, Natarajan V: Thrombin stimulation of human endothelial cell phospholipase D activity: Regulation by phospholipase C, protein kinase C, and cyclic adenosine 3′5′-monophosphate. Blood 79:2056–2067, 1992.
106. Aschner JL, Lennon JM, Fenton JW 2nd, et al: Enzymatic activity is necessary for thrombin-mediated increase in endothelial permeability. Am J Physiol 259(4 Pt 1):L270–L275, 1990.
107. Garcia JG, Schaphorst KL, Verin AD, et al: Diperoxovanadate alters endothelial cell focal contacts and barrier function: Role of tyrosine phosphorylation. J Appl Physiol 89:2333–2343, 2000.
108. Stevens T, Garcia JG, Shasby DM, et al: Mechanisms regulating endothelial cell barrier function. Am J Physiol Lung Cell Mol Physiol 279:L419–L422, 2000.
109. Garcia JG, Davis HW, Patterson CE: Regulation of endothelial cell gap formation and barrier dysfunction: Role of myosin light chain phosphorylation. J Cell Physiol 163:510–522, 1995.
110. Lum H, Aschner JL, Phillips PG, et al: Time course of thrombin-induced increase in endothelial permeability: Relationship to Ca^{2+}_i and inositol polyphosphates. Am J Physiol 263(2 Pt 1):L219–L225, 1992.
111. Garcia JG, Schaphorst KL, Shi S, et al: Mechanisms of ionomycin-induced endothelial cell barrier dysfunction. Am J Physiol 273(1 Pt 1):L172–L184, 1997.
112. Borbiev T, Verin AD, Birukova A, et al: Role of CaM kinase II and ERK activation in thrombin-induced endothelial cell barrier dysfunction. Am J Physiol Lung Cell Mol Physiol 285:L43–L54, 2003.
113. Borbiev T, Verin AD, Shi S, et al: Regulation of endothelial cell barrier function by calcium/calmodulin-dependent protein kinase II. Am J Physiol Lung Cell Mol Physiol 280:L983–L990, 2001.
114. Garcia JG, Lazar V, Gilbert-McClain LI, et al: Myosin light chain kinase in endothelium: Molecular cloning and regulation. Am J Respir Cell Mol Biol 16:489–494, 1997.
115. Stasek JE Jr, Garcia JG: The role of protein kinase C in alpha-thrombin-mediated endothelial cell activation. Semin Thromb Hemost 18:117–125, 1992.
116. Dudek SM, Jacobson JR, Chiang ET, et al: Pulmonary endothelial cell barrier enhancement by sphingosine 1-phosphate: Roles for cortactin and myosin light chain kinase. J Biol Chem 279:24692–24700, 2004.
117. Schaphorst KL, Pavalko FM, Patterson CE, et al: Thrombin-mediated focal adhesion plaque reorganization in endothelium: Role of protein phosphorylation. Am J Respir Cell Mol Biol 17:443–455, 1997.
118. Edlund M, Lotano MA, Otey CA: Dynamics of alpha-actinin in focal adhesions and stress fibers visualized with alpha-actinin-green fluorescent protein. Cell Motil Cytoskeleton 48:190–200, 2001.
119. Garcia JG, Verin AD, Schaphorst K, et al: Regulation of endothelial cell myosin light chain kinase by Rho, cortactin, and p60(src). Am J Physiol 276(6 Pt 1):L989–L998, 1999.
120. Huttelmaier S, Harbeck B, Steffens O, et al: Characterization of the actin binding properties of the vasodilator-stimulated phosphoprotein VASP. FEBS Lett 451:68–74, 1999.
121. Birukova AA, Smurova K, Birukov KG, et al: Microtubule disassembly induces cytoskeletal remodeling and lung vascular barrier dysfunction: Role of Rho-dependent mechanisms. J Cell Physiol 201:55–70, 2004.
122. Jaffe EA, Grulich J, Weksler BB, et al: Correlation between thrombin-induced prostacyclin production and inositol trisphosphate and cytosolic free calcium levels in cultured human endothelial cells. J Biol Chem 262:8557–8565, 1987.
123. Ryan US, Avdonin PV, Posin EY, et al: Influence of vasoactive agents on cytoplasmic free calcium in vascular endothelial cells. J Appl Physiol 65:2221–2227, 1988.
124. Chetham PM, Babal P, Bridges JP, et al: Segmental regulation of pulmonary vascular permeability by store-operated Ca^{2+} entry. Am J Physiol 276(1 Pt 1):L41–L50, 1999.
125. Goligorsky MS, Menton DN, Laszlo A, et al: Nature of thrombin-induced sustained increase in cytosolic calcium concentration in cultured endothelial cells. J Biol Chem 264:16771–16775, 1989.
126. Burhop KE, Selig WM, Malik AB: Monohydroxyeicosatetraenoic acids (5-HETE and 15-HETE) induce pulmonary vasoconstriction and edema. Circ Res 62:687–698, 1988.
127. Siflinger-Birnboim A, Johnson A: Protein kinase C modulates pulmonary endothelial permeability: A paradigm for acute lung injury. Am J Physiol Lung Cell Mol Physiol 284:L435–L451, 2003.
128. Bogatcheva NV, Garcia JG, Verin AD: Role of tyrosine kinase signaling in endothelial cell barrier regulation. Vascul Pharmacol 39(4–5):201–212, 2002.
129. Jockusch BM, Bubeck P, Giehl K, et al: The molecular architecture of focal adhesions. Annu Rev Cell Dev Biol 11:379–416, 1995.
130. Fox JR, Wayland H: Interstitial diffusion of macromolecules in the rat mesentery. Microvasc Res 18:255–276, 1979.
131. Lum H, Malik AB: Regulation of vascular endothelial barrier function. Am J Physiol 267(3 Pt 1):L223–L241, 1994.
132. Schoenwaelder SM, Burridge K: Bidirectional signaling between the cytoskeleton and integrins. Curr Opin Cell Biol 11:274–286, 1999.
133. Partridge CA, Horvath CJ, Del Vecchio PJ, et al: Influence of extracellular matrix in tumor necrosis factor-induced increase in endothelial permeability. Am J Physiol 263(6 Pt 1):L627–L633, 1992.
134. Lampugnani MG, Resnati M, Dejana E, et al: The role of integrins in the maintenance of endothelial monolayer integrity. J Cell Biol 112:479–490, 1991.
135. Bhattacharya S, Ying X, Fu C, et al: $alpha_v beta_3$ integrin induces tyrosine phosphorylation-dependent Ca^{2+} influx in pulmonary endothelial cells. Circ Res 86:456–462, 2000.
136. Michel CC: The fluid movement through capillary walls. *In* Renkin EM, Michel CC (eds): Handbook of Physiology. Section 2: The Cardiovascular System. Vol IV: Microcirculation. Bethesda, MD: American Physiological Society, 1984, pp 142–156.
137. Michel CC, Phillips ME, Turner MR: The effects of native and modified bovine serum albumin on the permeability of frog mesenteric capillaries. J Physiol 360:333–346, 1985.
138. Curry FE, Michel CC: A fiber matrix model of capillary permeability. Microvasc Res 20:96–99, 1980.
139. Powers MR, Blumenstock FA, Cooper JA, et al: Role of albumin arginyl sites in albumin-induced reduction of endothelial hydraulic conductivity. J Cell Physiol 141:558–564, 1989.
140. Schnitzer JE, Oh P: Albondin-mediated capillary permeability to albumin: Differential role of receptors in endothelial transcytosis and endocytosis of native and modified albumins. J Biol Chem 269:6072–6082, 1994.
141. Ghitescu L, Fixman A, Simionescu M, et al: Specific binding sites for albumin restricted to plasmalemmal vesicles of continuous capillary endothelium: receptor-mediated transcytosis. J Cell Biol 102:1304–1311, 1986.
142. Michel CC: The transport of albumin: A critique of the vesicular system in transendothelial transport. Am Rev Respir Dis 146(5 Pt 2):S32–S36, 1992.
143. Schnitzer JE, Carley WW, Palade GE: Albumin interacts specifically with a 60-kDa microvascular endothelial glycoprotein. Proc Natl Acad Sci U S A 85:6773–6777, 1988.
144. Ghinea N, Fixman A, Alexandru D, et al: Identification of albumin-binding proteins in capillary endothelial cells. J Cell Biol 107:231–239, 1988.

145. Siflinger-Birnboim A, Schnitzer J, Lum H, et al: Lectin binding to gp60 decreases specific albumin binding and transport in pulmonary artery endothelial monolayers. J Cell Physiol 149:575–584, 1991.
146. Peters TJ: Serum albumin. *In* Putman FW (ed): The Plasma Proteins: Structure, Function, and Genetic Control, 2nd ed. New York: Academic Press, 1975, pp 133–181.
147. Patterson CE, Lum H, Schaphorst KL, et al: Regulation of endothelial barrier function by the cAMP-dependent protein kinase. Endothelium 7:287–308, 2000.
148. Stelzner TJ, Weil JV, O'Brien RF: Role of cyclic adenosine monophosphate in the induction of endothelial barrier properties. J Cell Physiol 139:157–166, 1989.
149. Stevens T, Creighton J, Thompson WJ: Control of cAMP in lung endothelial cell phenotypes: Implications for control of barrier function. Am J Physiol 277(1 Pt 1):L119–L126, 1999.
150. Liu F, Verin AD, Borbiev T, et al: Role of cAMP-dependent protein kinase A activity in endothelial cell cytoskeleton rearrangement. Am J Physiol Lung Cell Mol Physiol 280:L1309–L1317, 2001.
151. Patterson CE, Davis HW, Schaphorst KL, et al: Mechanisms of cholera toxin prevention of thrombin- and PMA-induced endothelial cell barrier dysfunction. Microvasc Res 48:212–235, 1994.
152. Garcia JG, Liu F, Verin AD, et al: Sphingosine 1-phosphate promotes endothelial cell barrier integrity by Edg-dependent cytoskeletal rearrangement. J Clin Invest 108:689–701, 2001.
153. Liu F, Schaphorst KL, Verin AD, et al: Hepatocyte growth factor enhances endothelial cell barrier function and cortical cytoskeletal rearrangement: Potential role of glycogen synthase kinase-3beta. FASEB J 16:950–962, 2002.
154. Thurston G, Rudge JS, Ioffe E, et al: Angiopoietin-1 protects the adult vasculature against plasma leakage. Nat Med 6:460–463, 2000.
155. Birukov KG, Leitinger N, Bochkov VN, et al: Signal transduction pathways activated in human pulmonary endothelial cells by OxPAPC, a bioactive component of oxidized lipoproteins. Microvasc Res 67:18–28, 2004.
156. Jacobson JR, Dudek SM, Birukov KG, et al: Cytoskeletal activation and altered gene expression in endothelial barrier regulation by simvastatin. Am J Respir Cell Mol Biol 30:662–670, 2004.
157. Schaphorst KL, Chiang E, Jacobs KN, et al: Role of sphingosine-1 phosphate in the enhancement of endothelial barrier integrity by platelet-released products. Am J Physiol Lung Cell Mol Physiol 285:L258–L267, 2003.
158. McVerry BJ, Peng X, Hassoun PM, et al: Sphingosine 1-phosphate reduces vascular leak in murine and canine models of acute lung injury. Am J Respir Crit Care Med 170:987–993, 2004.
159. Peng X, Hassoun PM, Sammani S, et al: Protective effects of sphingosine 1-phosphate in murine endotoxin-induced inflammatory lung injury. Am J Respir Crit Care Med 169:1245–1251, 2004.
160. Shikata Y, Birukov KG, Garcia JG: S1P induces FA remodeling in human pulmonary endothelial cells: Role of Rac, GIT1, FAK, and paxillin. J Appl Physiol 94:1193–1203, 2003.
161. Wolfson RK, Lang GD, Jacobson JR, et al: Therapeutic strategies to limit lung endothelial cell permeability. In Rounds S, Voelkel N (eds): The Pulmonary Endothelium: Function in Health and Disease. Hoboken, NJ: John Wiley & Sons, Ltd, 2009, pp 337–354.
162. Matloubian M, Lo CG, Cinamon G, et al: Lymphocyte egress from thymus and peripheral lymphoid organs is dependent on S1P receptor 1. Nature 427:355–360, 2004.
163. Dudek SM, Camp SM, Chiang ET, et al: Pulmonary endothelial cell barrier enhancement by FTY720 does not require the S1P1 receptor. Cell Signal 19:1754–1764, 2007.
164. Chen W, Pendyala S, Natarajan V, et al: Endothelial cell barrier protection by simvastatin: GTPase regulation and NADPH oxidase inhibition. Am J Physiol Lung Cell Mol Physiol 295:L575–L583, 2008.
165. Finigan JH, Dudek SM, Singleton PA, et al: Activated protein C mediates novel lung endothelial barrier enhancement: Role of sphingosine 1-phosphate receptor transactivation. J Biol Chem 280:17286–17293, 2005.
166. Jacobson JR, Dudek SM, Singleton PA, et al: Endothelial cell barrier enhancement by ATP is mediated by the small GTPase Rac and cortactin. Am J Physiol Lung Cell Mol Physiol 291:L289–L295, 2006.
167. Kolosova IA, Mirzapoiazova T, Adyshev D, et al: Signaling pathways involved in adenosine triphosphate-induced endothelial cell barrier enhancement. Circ Res 97:115–124, 2005.
168. Kolosova IA, Mirzapoiazova T, Moreno-Vinasco L, et al: Protective effect of purinergic agonist ATPgammaS against acute lung injury. Am J Physiol Lung Cell Mol Physiol 294:L319–L324, 2008.
169. Singleton PA, Dudek SM, Ma SF, et al: Transactivation of sphingosine 1-phosphate receptors is essential for vascular barrier regulation: Novel role for hyaluronan and CD44 receptor family. J Biol Chem 281:34381–34393, 2006.
170. Singleton PA, Moreno-Vinasco L, Sammani S, et al: Attenuation of vascular permeability by methylnaltrexone: Role of mOP-R and S1P3 transactivation. Am J Respir Cell Mol Biol 37:222–231, 2007.
171. Birukov KG, Bochkov VN, Birukova AA, et al: Epoxycyclopentenone-containing oxidized phospholipids restore endothelial barrier function via Cdc42 and Rac. Circ Res 95:892–901, 2004.
172. Nonas S, Birukova AA, Fu P, et al: Oxidized phospholipids reduce ventilator-induced vascular leak and inflammation in vivo. Crit Care 12:R27, 2008.
173. Rigat B, Hubert C, Alhenc-Gelas F, et al: An insertion/deletion polymorphism in the angiotensin I-converting enzyme gene accounting for half the variance of serum enzyme levels. J Clin Invest 86:1343–1346, 1990.
174. Marshall RP, Webb S, Bellingan GJ, et al: Angiotensin converting enzyme insertion/deletion polymorphism is associated with susceptibility and outcome in acute respiratory distress syndrome. Am J Respir Crit Care Med 166:646–650, 2002.
175. Ye SQ, Simon BA, Maloney JP, et al: Pre-B-cell colony-enhancing factor as a potential novel biomarker in acute lung injury. Am J Respir Crit Care Med 171:361–370, 2005.
176. Ye SQ, Zhang LQ, Adyshev D, et al: Pre-B-cell-colony-enhancing factor is critically involved in thrombin-induced lung endothelial cell barrier dysregulation. Microvasc Res 70:142–151, 2005.
177. Gao L, Grant A, Halder I, et al: Novel polymorphisms in the myosin light chain kinase gene confer risk for acute lung injury. Am J Respir Cell Mol Biol 34:487–495, 2006.
178. Sutherland AM, Walley KR, Manocha S, et al: The association of interleukin 6 haplotype clades with mortality in critically ill adults. Arch Intern Med 165:75–82, 2005.
179. Gong MN, Thompson BT, Williams PL, et al: Interleukin-10 polymorphism in position -1082 and acute respiratory distress syndrome. Eur Respir J 27:674–681, 2006.
180. Gao L, Flores C, Fan-Ma S, et al: Macrophage migration inhibitory factor in acute lung injury: Expression, biomarker, and associations. Transl Res 150:18–29, 2007.
181. Damico RL, Chesley A, Johnston L, et al: Macrophage migration inhibitory factor governs endothelial cell sensitivity to LPS-induced apoptosis. Am J Respir Cell Mol Biol 39:77–85, 2008.
182. Medford AR, Keen LJ, Bidwell JL, et al: Vascular endothelial growth factor gene polymorphism and acute respiratory distress syndrome. Thorax 60:244–248, 2005.
183. Meyer NJ, Huang Y, Sammai S, et al: Gadd45α is a novel acute lung injury candidate gene which influences ventilator-induced lung injury: role of Akt signaling. FASEB J 23:1325–1337, 2009.

CHAPTER 6
APPENDIX

ENDOTHELIAL CELL FUNCTION

The main function of the pulmonary circulation is to deliver the entire output of the right ventricle as a thin film of blood within alveolar capillaries to facilitate the uptake of oxygen and the elimination of carbon dioxide. As described in Chapter 6, the structure of blood vessels and the physiologic principles that regulate blood flow in the lungs are admirably suited to this purpose, and one of the accompaniments of this rich perfusion is the constant extravasation and subsequent removal of fluid and solutes from the lung parenchyma. These fundamental operating factors have recently been enriched by new knowledge concerning the molecular mechanisms that underlie the regulation of endothelial cell permeability and that govern the formation, maturation, and death of endothelial cells, topics that are discussed in this appendix.

EFFECTS OF CELLULAR AND MOLECULAR CHARGE

The permeability of pulmonary microvessels to fluid and solutes depends in part on the properties of the endothelium and the underlying extracellular matrix. The intact endothelial cell membrane is nonthrombogenic, due in part to the release and effect of prostacyclin (prostaglandin I_2) and to the negative cell membrane charge of circulating blood and endothelial cells.[1,2] The endothelial cell surface has a complex molecular composition consisting of sialyl residues that are responsible for its negative charge.[3] Collectively known as the glycocalyx, the glycoproteins and glycolipids in this meshwork combine to form an endothelial cell surface layer of anionic polymers that is variable across the vasculature. The plasmalemmal membrane, vesicles, and paracellular channel structures contain microdomains of anionic sites consisting of distributions of glycosaminoglycans, sialoconjugates, and monosaccharide residues.[3–5] The selective permeability of the endothelial barrier to plasma proteins such as albumin is related in part to the anionic charge of the albumin molecule as well as the surface charge on the endothelial cell. For example, flux of albumin across glomerular capillaries is critically dependent on the negative charge of the capillary endothelial cells and the extracellular matrix proteins constituting the basement membrane.[6] Disruption of cell surface negative charge sites results in "leakage" of albumin across the capillary-matrix complex.[6]

The endothelial cell membrane surface charge influences the transport of albumin, which has an isoelectric point of 4.1.[3] The distribution of charge sites provides a means of preferentially gating albumin across the endothelial monolayer. Neutralization of negative charges on pulmonary vascular endothelial cells with cationic ferritin increases the flux of ^{125}I-labeled albumin, indicating that cell surface negative charge contributed significantly to albumin transport. Another charge-related effect is the result of negative charge distribution of interstitial macromolecules (heparan sulfate, chondroitin sulfate, and other complex proteoglycans), which potentially leads to repulsion of albumin and its increased transport through specific domains of the matrix.[7–9]

Because of its intrinsic negative charge, albumin permeability is greater than would have been predicted from its molecular size. For example, dextran sulfate (negatively charged dextran, whose molecular weight of 500 kD is much greater than that of albumin) was found to be threefold more permeable than neutral dextran of the same molecular weight. Data on sheep lung lymph also indicated that plasma-to-lymph transport of negative dextrans across the pulmonary vascular endothelial barrier is greater than transport of neutral dextrans.[9] Thus, the negatively charged molecules are transported preferentially across the endothelial barrier because of charge-related gating phenomena, despite the net negative charge of endothelial cell membranes.[9]

REGIONAL DIFFERENCES IN ENDOTHELIAL PERMEABILITY

Endothelial cells from different sites in the vasculature have many common features, but specific properties of the cells distinguish large vessel endothelial cells from those of small vessels within an organ and distinguish among those from different organs (e.g., between the blood-brain barrier and pulmonary vascular endothelial cells).[4,10,11] The albumin permeability value in cultured pulmonary microvessel endothelial cells is approximately one half to one fifth of the value of similarly

cultured cells from the main-stem pulmonary artery,[12] a feature also noted in vivo.[13] Interestingly, cells from microvessels are significantly more restrictive to sucrose and inulin than cells from large vessels, which indicates that transport occurring via paracellular pathways is reduced to a greater degree. The greater restriction to sucrose and inulin in comparison with albumin indicates that other routes of albumin transport (i.e., vesicles) are involved in albumin flux across pulmonary microvessel endothelial cells. The greater complexity of the intercellular junctions could account for the significantly lower inulin and sucrose permeabilities observed in pulmonary microvessel endothelial cells. Finally, microvascular cells proliferate at a higher level than macrovascular cells and retain phenotypically distinct calcium and cyclic nucleotide signaling responses as well as oxidant-mediated signaling transduction.[11]

Studies of endothelial cells from different sites in the vasculature have identified organ-specific antigens on capillary endothelial cells that may be responsible for the different degrees of permeability of regional vascular beds.[11,13,14] There are phenotypic differences in the lectin binding domains of different pulmonary vascular endothelial cells.[12] Lectins (*Ricinus communis* agglutinin and peanut agglutinin) bind to pulmonary microvessel endothelial glycoproteins (galactose-containing glycoproteins with molecular weights of 160 to 220, 60, and 30 to 40 kD). Differences in cell surface glycoproteins of endothelial cells in vascular beds that are related to the permeability characteristics of these vascular endothelial cells in situ have also been described.[15,16]

CYTOSKELETAL ALTERATIONS

Majno and Palade[17] first observed that lung endothelial cells exhibit a rounded morphology, producing paracellular gaps during inflammatory edema. This profound conformational change in the endothelial cell architecture was similarly observed after thrombin or histamine challenge,[18–21] and disruption in the integrity of the endothelial cell monolayer is now recognized as a cardinal feature of inflammation. The dramatic cell shape change, which results in paracellular gap formation, implicates the direct involvement of endothelial structural components comprising cytoskeletal proteins: microfilaments, microtubules, and intermediate filaments.[22] A useful paradigm to understand the basis for cytoskeletal influences on barrier regulation is via their effects on the balance of competing contractile forces, which generate centripetal tension, and adhesive cell-cell and cell-matrix tethering forces, which promote monolayer integrity.[22] This equilibrium is intimately influenced by the dynamic microfilamentous actin-based endothelial cytoskeleton via a variety of actin-binding proteins (capping, nucleating, and severing proteins), which are critical participants in cytoskeletal rearrangement and tensile force generation as well as in the regulation of endothelial junctional stability.[22] G-actin is a globular monomer that assembles reversibly to form polymerized actin fibers (or F-actin), conferring strength to structural elements regulating cell shape, particularly when accompanied by phosphorylated myosin.[22] F-actin filaments within peripherally distributed cortical bands are essential for maintenance of endothelial integrity and basal barrier function. Edemagenic agents, such as thrombin, initiate cytoskeletal rearrangement characterized by the loss of peripheral actin filaments with a concomitant increase in organized F-actin cables that span the cell as "stress fibers."[18] The formation of cytoplasmic stress fibers, critical to cellular contraction and increased intracellular tension, occurs via the coordinate activation of the small GTPase Rho and Ca^{2+}/calmodulin-dependent myosin light chain linase (MLCK), which together increase the level of phosphorylated myosin light chains (MLCs) in a spatially distinct manner (Fig. 6A-1).[23–27] The resultant increases in actin stress fiber formation and actomyosin cellular contraction disrupt the barrier-regulatory balance with tethering forces and destabilize cytoskeletal-junctional linkages, culminating in increased vascular permeability (see Fig. 6A-1). Consistent with this model, thrombin-induced endothelial cell permeability and formation of intercellular gaps is associated with disruption in the integrity of paracellular adherens junctions and reorganization of focal adhesion plaques.[24,28–31] Direct inhibition of either MLCK or Rho kinase as well as Ca^{2+}/calmodulin antagonism attenuates thrombin-induced MLC phosphorylation, gap formation, and barrier dysfunction,[25–27] as well as the increased vascular permeability observed in many,[21,24,32,33] but not all,[34–36] models of lung edema. The role of these gaps in increasing paracellular permeability has also been determined by osmotically shrinking endothelial cells with addition of hypertonic solution to the cell-bathing medium.[37] This resulted in formation of intercellular gaps and increased paracellular permeability, effects that were reversed by rehydrating the cells.[37]

The role of microtubule proteins in barrier regulation is becoming increasingly appreciated,[38,39] whereas the function of intermediate filaments in endothelial cell barrier regulation is much less defined.[22] Microtubules are polymers of α- and β-tubulin that form a lattice network of rigid hollow rods spanning the cell in a polarized fashion from the nucleus to the periphery while undergoing frequent assembly and disassembly.[40,41] Microtubules and actin filaments exhibit complex but intimate functional interactions during dynamic cellular processes.[39–42] Microtubule disruption with agents such as nocodazole or vinblastine induces rapid assembly of actin filaments and focal adhesions,[39,42] isometric cellular contraction[39] that correlates with the level of MLC phosphorylation, increased permeability across endothelial cell monolayers,[39,42] and increased transendothelial leukocyte migration,[42] events that can be reversed or attenuated by microtubule stabilization with paclitaxel. The mechanisms involved in these effects are poorly understood; however, microfilament-microtubule crosstalk represents an intriguing area of endothelial cell barrier regulation.

Besides activation of the contractile apparatus by receptor-mediated pathways, mechanical signals are also transduced to the endothelial cell cytoskeleton.[43,44]

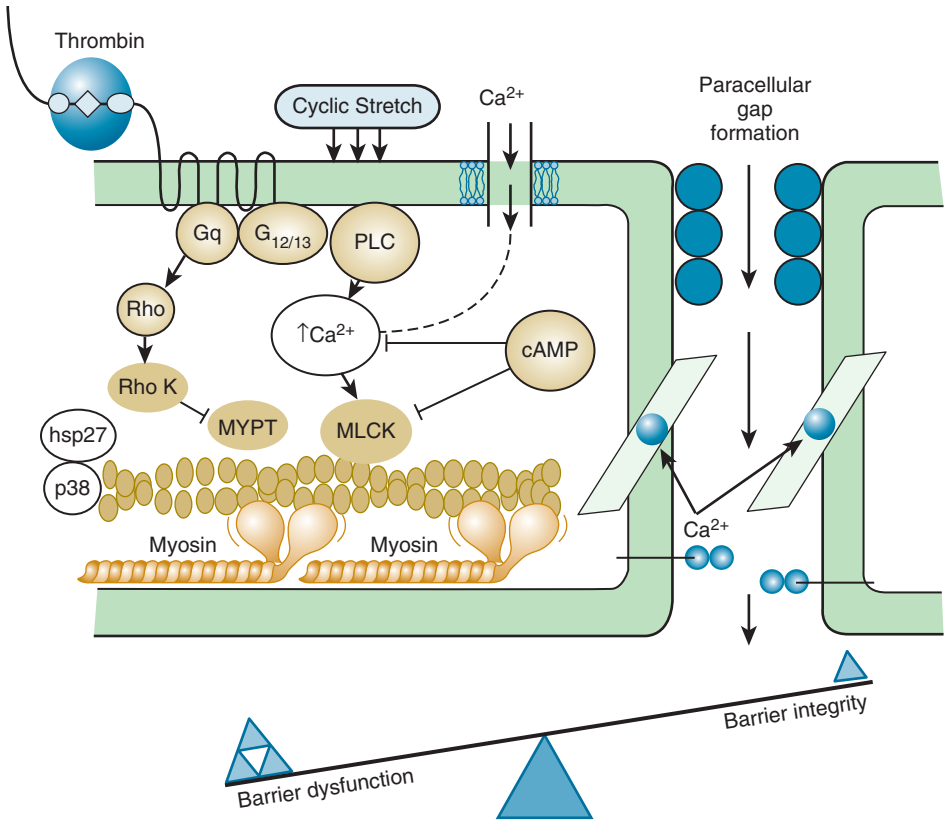

FIGURE 6A-1 ■ Schematic depicting disruption in endothelial cell (EC) barrier homeostasis by thrombin. In this working model of barrier regulation, under basal conditions, a balance exists between actomyosin contractile and cellular adhesive forces. When contractile forces predominate, as depicted in the thrombin-stimulated model, ECs pull apart to form paracellular gaps, favoring barrier disruption. Thrombin cleavage of the PAR-1 receptor on the surface of EC activates both heterotrimeric G proteins (G_q, $G_{12/13}$) and small GTPases such as Rho. Activated Rho (Rho-GTP) induces Rho kinase (Rho K), which via phosphorylation of the phosphatase regulatory subunit inhibits the myosin light chain phosphatase (MYPT). Rho kinase and myosin light chain kinase (MLCK) activation occurs via independent pathways. Increased cytosolic Ca^{2+} (via inositol triphosphate [IP_3] production) activates the Ca^{2+}/calmodulin-dependent MLCK, with conformational changes allowing the enzyme to access the preferred substrate (myosin light chain [MLC]). Rho kinase and MLCK activation both culminate in increased MLC phosphorylation, which in turn enables actomyosin contraction resulting in increased stress fiber formation, cellular contraction, paracellular gap formation, and ultimately barrier dysfunction. Increases in cyclic AMP influence both Ca^{2+} mobilization and MLCK activity. Also depicted are other representative regulatory proteins whose activity either increases or decreases EC tension. Inhibition of heat shock protein 27 (hsp27) activity, by p38 mitogen-activated protein kinase (MAPK)–catalyzed phosphorylation, also induces actin stress fiber formation, and the actin capping/severing protein gelsolin is likewise involved in stress fiber–dependent contraction.

Although the mechanism for this signal transduction is not well understood, the complex array of proteins that constitutes the lung endothelial glycocalyx may be involved. Nuclear magnetic resonance techniques have demonstrated that cell surface proteoglycans behave as viscoelastic anionic polymers, undergoing shear-dependent conformational changes that may function as blood flow sensors to transduce signals into endothelial cells.[45] Components of the glycocalyx, such as heparan sulfate proteoglycans and sialoproteins, modulate cell-cell and cell-matrix adhesions via effects on the cytoskeleton and alter endothelial barrier properties.[46–48] Syndecan is a heparan sulfate proteoglycan known to influence cytoskeletal organization, cell-cell adhesion, and motility,[47] and mediates cationic peptide–induced signaling that leads to endothelial cytoskeletal rearrangement and barrier dysfunction.[46] Cationic peptide–mediated barrier dysfunction is associated with syndecan-1 and syndecan-4 clustering and actin stress fiber formation, whereas removal of cell surface heparan sulfated proteoglycans attenuates these responses.[46] Thus, the glycocalyx in general, and heparan sulfate proteoglycans in particular, may represent not only sensors for mechanical stress and cytoskeletal rearrangement, but endothelial-surface binding domains for inflammatory cationic peptides as well. This provides potential mechanistic insight for the recent observation that neutrophil-derived cationic peptides are responsible for the increase in vascular permeability produced during endothelial cell interaction with activated neutrophils.[49,50]

ANGIOGENESIS

New blood vessel formation, or angiogenesis, is a complex process involving endothelial cell activation,

migration, maturation, and remodeling. These events may occur in a variety of contexts including during normal development and growth, in response to wound healing, or as part of the pathogenesis of a number of cancers and autoimmune diseases.[51] In the embryo, endothelial cells differentiate from angioblasts[52] and then give rise to the early vascular plexus and primitive blood vessels, a process referred to as vasculogenesis.[53] Angiogenesis is then defined by the generation of new capillaries by endothelial cells either by sprouting or by splitting from preexisting vessels. Sprouting angiogenesis involves endothelial detachment from the basement membrane, migration, and subsequent proliferation, tube formation, and, finally, functional maturation of the new vessel. Angiogenesis characterized by the splitting of existing vessels involves endothelial proliferation within the vessel of origin followed by the generation of a separate lumen and a capillary pillar that then splits from the original vessel and matures into a new vessel.[54] While the mode of angiogenesis may vary according to the organ involved or the initiating angiogenic signals, non-sprouting is the primary process in lung vascular development.[55]

A number of angiogenic factors are now recognized as capable of activating endothelial cells, including extracellular matrix proteins and their integrin receptors,[56] one of the most important of which is vascular endothelial growth factor (VEGF). This is evidenced by its key role in vasculogenesis: mice lacking the VEGF receptor, Flt-1, fail to develop fully functional blood vessels.[57] In addition, VEGF has been found to mediate angiogenesis in malignant gliomas[58] and in a number of other tumors.[59] These findings have led to the inhibition of VEGF as a promising therapeutic strategy in the management of patients with advanced malignancies.[60] In patients with lung disease, pulmonary hypertension is a devastating condition that is characterized by aberrant angiogenesis. Evidence suggests that VEGF signaling modulates disease progression,[61] and therapies that affect VEGF signaling have shown promise in a rat model of pulmonary hypertension.[62]

APOPTOSIS AND ENDOTHELIAL CELL DYSFUNCTION

Endothelial cells have relatively low turnover rates due in part to the protective effects of physiologic mechanical forces, including shear stress and cyclic stretch. However, due to the positioning of the endothelium at the surface of blood and tissue, endothelial cells are constantly exposed to multiple biochemical and biophysical stresses, such as endotoxins, tumor necrosis factor-α (TNF-α), and oxidative stress. One potential consequence of excessive stress is apoptosis, or programmed cell death. Apoptotic cells undergo a well-ordered morphologic and molecular pattern of death, including cytoskeletal rearrangement, membrane blebbing, nuclear condensation, DNA fragmentation, and cell shrinkage (see reviews by Lu et al.[63] and Pober and Min[64]). Frequently, apoptotic cells do not elicit an inflammatory response and are phagocytosed by neighboring cells.[65] In contrast, cells undergoing necrosis demonstrate cellular and nuclear swelling, often accompanied by inflammation in damaged tissues.[66] Thus, endothelial cells may undergo apoptosis or necrosis, depending on the stimulus. Upon death and detachment of cells from vessel walls, if the subendothelial basement membrane damage is limited to a small fraction of the endothelial cell lining, viable neighboring cells can spread quickly and cover the damaged space to attenuate procoagulant effects. However, more severe damage is likely to lead to extensive loss of endothelial cells, after which platelets will be exposed to the damaged basement membrane and induce thrombosis.[67]

There are two fundamental signaling pathways by which apoptosis is mediated, the extrinsic and intrinsic pathways. The extrinsic pathway is initiated by external death ligands, whereas the intrinsic pathway is triggered by internal apoptotic signals and involves mitochondria. These pathways merge and share mechanisms utilizing the aspartate-specific cysteinyl proteases (caspase) cascades.[63] The best-characterized extrinsic pathways are the binding of Fas ligand (FasL) to Fas receptors[68] and TNF-α to TNF receptor 1,[69] which trigger adapter proteins to be recruited to activate the initiator caspase of the caspase cascade. Fas/FasL-mediated lung apoptosis has been implicated in acute lung injury and acute respiratory distress syndrome (ARDS). Furthermore, Fas/FasL-mediated apoptosis induces the release of cytokines, leading to the progression from ARDS to pulmonary fibrosis, in which excess collagen deposition causes the destruction of normal lung architecture.[70] In contrast, the intrinsic pathway may be initiated upon exposure to stresses, such as cytotoxic drugs, oxidants, radiation, and growth factor deprivation, which results in mitochondrial release of several apoptogenic proteins into the cytosol, such as cytochrome *c* that readily binds to Apaf-1 to activate caspase-9. A common mediator of endothelial cell injury is neutrophil-generated reactive oxygen species (ROS), a by-product of the partial reduction of molecular oxygen. The most potent pathway for generating ROS is catalyzed by the enzyme phagocyte oxidase, which is expressed by neutrophils and macrophages, although vascular cells express the homologous nonphagocyte oxidase. ROS may react directly with cellular macromolecules or combine with nitric oxide to form even more reactive peroxynitrite. These oxidative stresses can cause barrier dysfunction and may antagonize TNF responses.[71] There are a variety of stimuli, either extrinsic or intrinsic, that may cause apoptosis in lung endothelial cells. Understanding the mechanisms by which these stimuli induce apoptosis and dysfunction may ultimately point toward novel therapeutic strategies for diseases involving the pulmonary vasculature.

References

1. Skutelsky E, Danon D: Redistribution of surface anionic sites on the luminal front of blood vessel endothelium after interaction with polycationic ligand. J Cell Biol 71:232–241, 1976.

2. Pelikan P, Gimbrone MA Jr, Cotran RS: Distribution and movement of anionic cell surface sites in cultured human vascular endothelial cells. Atherosclerosis 32:69–80, 1979.
3. Simionescu N, Simionescu M, Palade GE: Differentiated microdomains on the luminal surface of the capillary endothelium. I. Preferential distribution of anionic sites. J Cell Biol 90:605–613, 1981.
4. Simionescu M, Simionescu N: Ultrastructure of the microvascular wall: Functional correlations. *In* Renkin EM, Michel CC (eds): Handbook of Physiology. Section 2: The Cardiovascular System. Vol IV: Microcirculation. Bethesda, MD: American Physiological Society, 1984, pp 41–101.
5. Ghinea N, Simionescu N: Anionized and cationized hemeundecapeptides as probes for cell surface charge and permeability studies: Differentiated labeling of endothelial plasmalemmal vesicles. J Cell Biol 100:606–612, 1985.
6. Michel CC: The fluid movement through capillary walls. *In* Renkin EM, Michel CC (eds): Handbook of Physiology. Section 2: The Cardiovascular System. Vol IV: Microcirculation. Bethesda, MD: American Physiological Society, 1984, pp 142–156.
7. Taylor A, Townsley MI, Korthuis RJ: Macromolecule transport across the pulmonary microvessel walls. Exp Lung Res 8:97–123, 1985.
8. Perry MA, Benoit JN, Kvietys PR, et al: Restricted transport of cationic macromolecules across intestinal capillaries. Am J Physiol 245:G568–G572, 1983.
9. Lanken PN, Hansen-Flaschen JH, Sampson PM, et al: Passage of uncharged dextrans from blood to lung lymph in awake sheep. J Appl Physiol 59:580–591, 1985.
10. Stevens T: Molecular and cellular determinants of lung endothelial cell heterogeneity. Chest 128(6 Suppl):558S–564S, 2005.
11. Gebb S, Stevens T: On lung endothelial cell heterogeneity. Microvasc Res 68:1–12, 2004.
12. Del Vecchio PJ, Siflinger-Birnboim A, Shepard JM, et al: Endothelial monolayer permeability to macromolecules. Fed Proc 46:2511–2515, 1987.
13. Parker JC, Yoshikawa S: Vascular segmental permeabilities at high peak inflation pressure in isolated rat lungs. Am J Physiol Lung Cell Mol Physiol 283:L1203–L1209, 2002.
14. Auerbach R, Alby L, Morrissey LW, et al: Expression of organ-specific antigens on capillary endothelial cells. Microvasc Res 29:401–411, 1985.
15. Belloni PN, Nicolson GL: Differential expression of cell surface glycoproteins on various organ-derived microvascular endothelia and endothelial cell cultures. J Cell Physiol 136:398–410, 1988.
16. Schnitzer JE, Oh P: Albondin-mediated capillary permeability to albumin: Differential role of receptors in endothelial transcytosis and endocytosis of native and modified albumins. J Biol Chem 269:6072–6082, 1994.
17. Majno G, Palade GE: Studies on inflammation. 1. The effect of histamine and serotonin on vascular permeability: An electron microscopic study. J Biophys Biochem Cytol 11:571–605, 1961.
18. Garcia JG, Siflinger-Birnboim A, Bizios R, et al: Thrombin-induced increase in albumin permeability across the endothelium. J Cell Physiol 128:96–104, 1986.
19. Phillips PG, Lum H, Malik AB, et al: Phallacidin prevents thrombin-induced increases in endothelial permeability to albumin. Am J Physiol 257(3 Pt 1):C562–C567, 1989.
20. Shasby DM, Shasby SS, Sullivan JM, et al: Role of endothelial cell cytoskeleton in control of endothelial permeability. Circ Res 51:657–661, 1982.
21. Stevens T, Garcia JG, Shasby DM, et al: Mechanisms regulating endothelial cell barrier function. Am J Physiol Lung Cell Mol Physiol 279:L419–L422, 2000.
22. Dudek SM, Garcia JG: Cytoskeletal regulation of pulmonary vascular permeability. J Appl Physiol 91:1487–1500, 2001.
23. Birukova AA, Smurova K, Birukov KG, et al: Role of Rho GTPases in thrombin-induced lung vascular endothelial cells barrier dysfunction. Microvasc Res 67:64–77, 2004.
24. Garcia JG, Schaphorst KL, Verin AD, et al: Diperoxovanadate alters endothelial cell focal contacts and barrier function: Role of tyrosine phosphorylation. J Appl Physiol 89:2333–2343, 2000.
25. Carbajal JM, Gratrix ML, Yu CH, et al: ROCK mediates thrombin's endothelial barrier dysfunction. Am J Physiol Cell Physiol 279:C195–C204, 2000.
26. Garcia JG, Davis HW, Patterson CE: Regulation of endothelial cell gap formation and barrier dysfunction: Role of myosin light chain phosphorylation. J Cell Physiol 163:510–522, 1995.
27. Verin AD, Patterson CE, Day MA, et al: Regulation of endothelial cell gap formation and barrier function by myosin-associated phosphatase activities. Am J Physiol 269(1 Pt 1):L99–L108, 1995.
28. Corada M, Mariotti M, Thurston G, et al: Vascular endothelial-cadherin is an important determinant of microvascular integrity in vivo. Proc Natl Acad Sci U S A 96:9815–9820, 1999.
29. Dejana E: Endothelial adherens junctions: Implications in the control of vascular permeability and angiogenesis. J Clin Invest 100(11 Suppl):S7–S10, 1997.
30. Dudek SM, Jacobson JR, Chiang ET, et al: Pulmonary endothelial cell barrier enhancement by sphingosine 1-phosphate: Roles for cortactin and myosin light chain kinase. J Biol Chem 279:24692–24700, 2004.
31. Schaphorst KL, Pavalko FM, Patterson CE, et al: Thrombin-mediated focal adhesion plaque reorganization in endothelium: Role of protein phosphorylation. Am J Respir Cell Mol Biol 17:443–455, 1997.
32. Garcia JG, Verin AD, Herenyiova M, et al: Adherent neutrophils activate endothelial myosin light chain kinase: Role in transendothelial migration. J Appl Physiol 84:1817–1821, 1998.
33. Parker JC: Inhibitors of myosin light chain kinase and phosphodiesterase reduce ventilator-induced lung injury. J Appl Physiol 89:2241–2248, 2000.
34. Petrache I, Verin AD, Crow MT, et al: Differential effect of MLC kinase in TNF-alpha-induced endothelial cell apoptosis and barrier dysfunction. Am J Physiol Lung Cell Mol Physiol 280:L1168–L1178, 2001.
35. Garcia JG, Schaphorst KL, Shi S, et al: Mechanisms of ionomycin-induced endothelial cell barrier dysfunction. Am J Physiol 273(Pt 1):L172–L184, 1997.
36. Garcia JG, Wang P, Schaphorst KL, et al: Critical involvement of p38 MAP kinase in pertussis toxin-induced cytoskeletal reorganization and lung permeability. FASEB J 16:1064–1076, 2002.
37. Shepard JM, Goderie SK, Brzyski N, et al: Effects of alterations in endothelial cell volume on transendothelial albumin permeability. J Cell Physiol 133:389–394, 1987.
38. Birukov KG, Leitinger N, Bochkov VN, et al: Signal transduction pathways activated in human pulmonary endothelial cells by OxPAPC, a bioactive component of oxidized lipoproteins. Microvasc Res 67:18–28, 2004.
39. Petrache I, Birukova A, Ramirez SI, et al: The role of the microtubules in tumor necrosis factor-alpha-induced endothelial cell permeability. Am J Respir Cell Mol Biol 28:574–581, 2003.
40. Goode BL, Drubin DG, Barnes G: Functional cooperation between the microtubule and actin cytoskeletons. Curr Opin Cell Biol 12:63–71, 2000.
41. Klymkowsky MW: Weaving a tangled web: The interconnected cytoskeleton. Nat Cell Biol 1:E121–E123, 1999.
42. Birukova AA, Smurova K, Birukov KG, et al: Microtubule disassembly induces cytoskeletal remodeling and lung vascular barrier dysfunction: Role of Rho-dependent mechanisms. J Cell Physiol 201:55–70, 2004.
43. Birukov KG, Birukova AA, Dudek SM, et al: Shear stress-mediated cytoskeletal remodeling and cortactin translocation in pulmonary endothelial cells. Am J Respir Cell Mol Biol 26:453–464, 2002.
44. Birukov KG, Jacobson JR, Flores AA, et al: Magnitude-dependent regulation of pulmonary endothelial cell barrier function by cyclic stretch. Am J Physiol Lung Cell Mol Physiol 285:L785–L797, 2003.
45. Siegel G, Walter A, Kauschmann A, et al: Anionic biopolymers as blood flow sensors. Biosens Bioelectron 11:281–294, 1996.
46. Dull RO, Dinavahi R, Schwartz L, et al: Lung endothelial heparan sulfates mediate cationic peptide-induced barrier dysfunction: A new role for the glycocalyx. Am J Physiol Lung Cell Mol Physiol 285:L986–L995, 2003.
47. Echtermeyer F, Baciu PC, Saoncella S, et al: Syndecan-4 core protein is sufficient for the assembly of focal adhesions and actin stress fibers. J Cell Sci 112(Pt 20):3433–3441, 1999.
48. Takeda T, Go WY, Orlando RA, et al: Expression of podocalyxin inhibits cell-cell adhesion and modifies junctional properties in Madin-Darby canine kidney cells. Mol Biol Cell 11:3219–3232, 2000.

49. Dull RO, Garcia JG: Leukocyte-induced microvascular permeability: How contractile tweaks lead to leaks. Circ Res 90:1143–1144, 2002.
50. Gautam N, Olofsson AM, Herwald H, et al: Heparin-binding protein (HBP/CAP37): A missing link in neutrophil-evoked alteration of vascular permeability. Nat Med 7:1123–1127, 2001.
51. Folkman J: Angiogenesis in cancer, vascular, rheumatoid and other disease. Nat Med 1:27–31, 1995.
52. Asahara T, Isner JM: Endothelial progenitor cells for vascular regeneration. J Hematother Stem Cell Res 11:171–178, 2002.
53. Risau W, Flamme I: Vasculogenesis. Annu Rev Cell Dev Biol 11:73–91, 1995.
54. Patan S, Haenni B, Burri PH: Implementation of intussusceptive microvascular growth in the chicken chorioallantoic membrane (CAM): 1. Pillar formation by folding of the capillary wall. Microvasc Res 51:80–98, 1996.
55. Pardanaud L, Yassine F, Dieterlen-Lievre F: Relationship between vasculogenesis, angiogenesis and haemopoiesis during avian ontogeny. Development 105:473–485, 1989.
56. Hynes RO: A reevaluation of integrins as regulators of angiogenesis. Nat Med 8:918–921, 2002.
57. Fong GH, Rossant J, Gertsenstein M, et al: Role of the Flt-1 receptor tyrosine kinase in regulating the assembly of vascular endothelium. Nature 376(6535):66–70, 1995.
58. Plate KH, Breier G, Weich HA, et al: Vascular endothelial growth factor is a potential tumour angiogenesis factor in human gliomas in vivo. Nature 359(6398):845–848, 1992.
59. Millauer B, Longhi MP, Plate KH, et al: Dominant-negative inhibition of Flk-1 suppresses the growth of many tumor types in vivo. Cancer Res 56:1615–1620, 1996.
60. Ellis LM, Hicklin DJ: VEGF-targeted therapy: Mechanisms of antitumour activity. Nat Rev Cancer 8:579–591, 2008.
61. Voelkel NF, Cool C, Taraceviene-Stewart L, et al: Janus face of vascular endothelial growth factor: The obligatory survival factor for lung vascular endothelium controls precapillary artery remodeling in severe pulmonary hypertension. Crit Care Med 30(Suppl):S251–S256, 2002.
62. Moreno-Vinasco L, Gomberg-Maitland M, Maitland ML, et al: Genomic assessment of a multikinase inhibitor, sorafenib, in a rodent model of pulmonary hypertension. Physiol Genomics 33:278–291, 2008.
63. Lu Q, Harrington EO, Rounds S: Apoptosis and lung injury. Keio J Med 54:184–189, 2005.
64. Pober JS, Min W: Endothelial cell dysfunction, injury and death. Handb Exp Pharmacol (176 Pt 2):135–156, 2006.
65. Saraste A, Pulkki K: Morphologic and biochemical hallmarks of apoptosis. Cardiovasc Res 45:528–537, 2000.
66. Majno G, Joris I: Apoptosis, oncosis, and necrosis: An overview of cell death. Am J Pathol 146:3–15, 1995.
67. Walker LN, Ramsay MM, Bowyer DE: Endothelial healing following defined injury to rabbit aorta: Depth of injury and mode of repair. Atherosclerosis 47:123–130, 1983.
68. DosReis GA, Borges VM: Role of Fas-ligand induced apoptosis in pulmonary inflammation and injury. Curr Drug Targets Inflamm Allergy 2:161–167, 2003.
69. Wallach D, Varfolomeev EE, Malinin NL, et al: Tumor necrosis factor receptor and Fas signaling mechanisms. Annu Rev Immunol 17:331–367, 1999.
70. Chapman HA: A Fas pathway to pulmonary fibrosis. J Clin Invest 104:1–2, 1999.
71. Bradley JR, Johnson DR, Pober JS: Endothelial activation by hydrogen peroxide: Selective increases of intercellular adhesion molecule-1 and major histocompatibility complex class I. Am J Pathol 142:1598–1609, 1993.

CHAPTER 7

ACID-BASE BALANCE

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INTRODUCTION AND PHYSIOLOGY

Although the mammalian respiratory system is designed primarily for gas exchange, it also contributes to acid-base regulation in combination with the kidneys. Increased metabolism results in the production of large amounts of carbon dioxide (CO_2) and fixed acids. CO_2 concentration can be adjusted rapidly and precisely by the respiratory center in defense of arterial and body pH. Conversely, alterations in the pressure of carbon dioxide (P_{CO_2}) due to changes in alveolar ventilation can be the primary cause of abnormalities in pH. The ability of the kidneys to rapidly dispose of nonvolatile acids (or bases as appropriate) is somewhat slower than the respiratory system, but nonetheless critical. Only a brief review of acid-base chemistry can be provided here; the reader is referred elsewhere for more comprehensive review.[1]

Choice of Respiratory and Metabolic Parameters

By the early 20th century, the importance of reactions of CO_2 and bicarbonate ion (HCO_3^-) with H^+ and OH^- in acid-base balance was established:

$$CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^- \quad (1)$$

$$CO_2 + OH^- \leftrightarrow HCO_3^- \quad (2)$$

Reaction 2 provides the dominant pathway to HCO_3^- from CO_2,[2] but rates of formation of either H_2CO_3 (carbonic acid) in Reaction 1, or HCO_3^- directly in Reaction 2 are relatively slow. Rates of each are normally accelerated by carbonic anhydrase, present in erythrocytes, vascular endothelium, alveolar epithelium, and in most cells, including the kidney.[2-4] Under physiologic conditions, $[H_2CO_3]$ is small compared with $[CO_2]$ and the relative amounts of HCO_3^- and CO_2 can be calculated from the Henderson-Hasselbalch equation:

$$pH = pK_a + \log\left[HCO_3^-\right]/\alpha\, P_{CO_2} \quad (3)$$

where pH indicates the negative logarithm of the H^+ concentration, and the constant pK_a (= 6.1 at 37°C) designates the negative logarithm of the apparent dissociation constant of CO_2 through the equilibria with carbonic acid and its dissociation products in Reaction 1. It is the pH at which the concentrations of HCO_3^- and dissolved CO_2 are equal. In Equation 3, dissolved CO_2 has been replaced by $\alpha\, P_{CO_2}$, where α is the solubility coefficient and is equal to 0.03 $mmol \cdot L^{-1} \cdot mm\ Hg^{-1}$ at 37°C. These values remain relatively constant with clinical

changes in pH and ionic strength,[5] however, they are significantly influenced by temperature (see later discussion on hypo- and hyperthermia). For convenience, taking the appropriate values for α and pK_a and the antilog of the expression yields

$$H^+ = 24\ P_{CO_2}/HCO_3^- \quad (4)$$

with P_{CO_2} and HCO_3^- in their usual units (mm Hg and mmol/L, respectively), H^+ concentration is obtained in nanomoles per liter, which can be readily converted to pH (pH of 7.4 corresponds to a H^+ concentration of 40 nmol/L). Better understanding of the properties of this buffer system is obtained by examining the plasma values of each component. Ordinarily, buffering in both directions is most efficient when the pK_a is close to the prevailing pH. At a normal plasma pH of 7.4, there is 20 times more HCO_3^- than dissolved CO_2. The large difference between the pK_a and normal pH values in the case of the HCO_3^-/CO_2 buffer system might seem a disadvantage; however, protection is afforded against increased nonvolatile acid generation, which represents the more frequently encountered physiologic disturbance.[6] Higher HCO_3^- concentrations permit greater buffering of significant quantities of acid, and the CO_2 produced can be rapidly eliminated by increasing ventilation.

Measurements of P_{CO_2} and pH are readily made in arterial blood, but the pH detected is that in plasma rather than that in the red blood cells; plasma pH is about 0.2 units greater than erythrocyte pH. The intracellular acid-base status of the body compartments is seldom measured, and the plasma pH is often assumed to be representative of the body as a whole and its changes reflecting qualitatively what is happening in cells. This simplification is frequently inappropriate. For example, intracellular pH may be acidotic in patients with hypokalemia, but who have an alkaline plasma. It is therefore more exact to refer to deviations of plasma pH as *acidemia* and *alkalemia* rather than as acidosis and alkalosis. The latter terms refer to processes and do not designate the actual pH or compartments.

Plasma HCO_3^- is routinely calculated from measured arterial P_{CO_2} and pH using Equation 2. Alternatively, HCO_3^- can be estimated from the total CO_2 that can be released from plasma with a strong acid (the *CO_2 content*). CO_2 content is usually measured with electrolyte concentrations in venous blood and will be about 5% higher than arterial HCO_3^- because it also includes H_2CO_3, dissolved CO_2, carbonate, and CO_2 bound to amino acids (carbamates). Venous CO_2 content is generally about 2 to 4 mEq/L higher than the arterial plasma HCO_3^-. If the difference in these values is significantly greater than 4 mEq/L, then a clerical error may have occurred, the arterial and venous samples were not taken concurrently, the cardiac output is low, or the metabolic rate is high with exertion. The pH and P_{CO_2} of blood are particularly likely to change if blood samples are exposed to air, if they are not kept cool, or if analysis is delayed. Exposure to air decreases P_{CO_2}, raises pH, and more gradually decreases CO_2 content. Nonetheless differences in CO_2 content of arterial and venous plasma are usually quite small, and venous samples can be used to provide reasonable estimates of the arterial HCO_3^- and directional changes.

The Henderson-Hasselbalch equation indicates that pH can be calculated from two variables: P_{CO_2} and HCO_3^-. P_{CO_2} can be interpreted as a "ventilatory" parameter that reflects the adequacy of ventilation relative to the rate of CO_2 production. If arterial P_{CO_2} exceeds the normal range (35–45 mm Hg), then the patient is hypoventilating, and conversely, if the P_{CO_2} is lower, the patient is hyperventilating. These terms should be distinguished from hyperpnea and hypopnea, which refer to the total ventilation, and from tachypnea and bradypnea, which indicate respiratory rate. Rather than total ventilation, the key parameter that determines P_{CO_2} at any rate of CO_2 production is alveolar ventilation, because ventilation of dead space does not lead to the loss of CO_2. The effect of changing the V_D/V_T ratio of dead space (V_D) to tidal volume (V_T) is shown in Figure 7-1, where CO_2 production is assumed to be 200 mL/min.

The utility of P_{CO_2} as a ventilatory parameter is readily illustrated by a few brief examples. A heavily exercising person who has a normal P_{CO_2} is neither hyperventilating nor hypoventilating, despite the obvious hyperpnea and tachypnea. A person may demonstrate hypoventilation (high P_{CO_2}) from either a fall in alveolar ventilation at a constant metabolic rate or a rise in the rate of CO_2 production without a proportionate increase in alveolar ventilation. Patients with severe lung disease hypoventilate despite both hyperpnea and tachypnea at rest, because they are ventilating a large dead space. An increase in CO_2 production may be caused by an increased

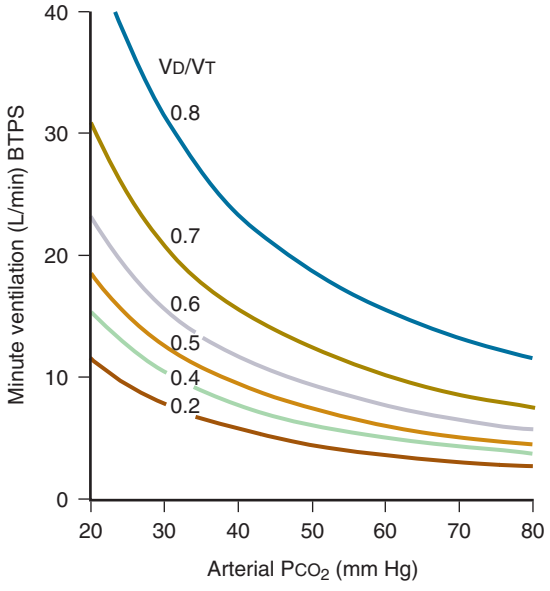

FIGURE 7-1 ■ The relationships among minute volume of ventilation (V_E), arterial P_{CO_2}, and the ratio of dead space to tidal volume (V_D/V_T) in a patient producing 200 ml of CO_2 each minute. BTPS, volume corrected for body conditions (body temperature, ambient pressure, and saturation with water vapor).

metabolic rate (e.g., exercise or fever) or, occasionally, by an acute release of CO_2 from HCO_3^- stores due to a severe, acute metabolic acidosis, such as occurs during and after cardiopulmonary arrest or a grand mal seizure, when large amounts of lactic acid are produced and HCO_3^- is converted to CO_2. Regardless of the cause of ventilation failing to keep pace with CO_2 production, the concomitant increase in arterial P_{CO_2} is classified as hypoventilation. Conversely, hyperventilation with a fall in P_{CO_2} is frequently seen as a respiratory compensation for metabolic acidosis, hypoxia, anxiety or other conditions that stimulate ventilation.

In contrast to P_{CO_2}, interpretation of changes in the HCO_3^- in Equation 3 is not as simple or straightforward and has remained more problematic. Because CO_2 is the only volatile acid in significant amounts in the blood and is directly regulated, it is accurately defined as a "ventilatory" or "respiratory" parameter. It would be ideal if HCO_3^-, as an easily measured base, could be considered a "nonrespiratory" or "metabolic" parameter in the same manner as CO_2 is considered respiratory. An ideal "metabolic" parameter should be uninfluenced by changes in P_{CO_2} and should represent the predominant base. However, as shown in Figure 7-2, HCO_3^- may vary significantly with P_{CO_2} in some solutions. If CO_2 is bubbled through a saline solution containing HCO_3^- ("unbuffered" solution), the bicarbonate remains relatively constant over a broad range of P_{CO_2}. A different circumstance is observed in isolated samples of whole blood in vitro: HCO_3^- concentrations rise appreciably as P_{CO_2} increases.

The difference in the responses of biologic fluids to CO_2 exposure is determined by differences in the buffering systems in these compartments. As indicated in Figure 7-2, the production of HCO_3^- from CO_2 in blood is increased when H^+ becomes associated with other buffer anions, which include hemoglobin, proteins, and inorganic phosphates. Red cell hemoglobin is particularly important and effective in buffering H^+ for three reasons. First, the hemoglobin concentration is extremely high within red blood cells. Second, there is an abundance of titratable imidazole groups on the hemoglobin molecule, whose pK_a is very close to the pH within the cells and thus able to titrate large amounts of H^+. Third, the buffering capacity of hemoglobin is very enhanced by its oxylabile character (the Haldane effect) so that at low PO_2 values, such as those encountered in systemic capillaries and venous blood, its affinity for H^+ is increased, allowing more CO_2 conversion to HCO_3^-. The opposite occurs in the lungs as the blood is oxygenated in the pulmonary capillaries.

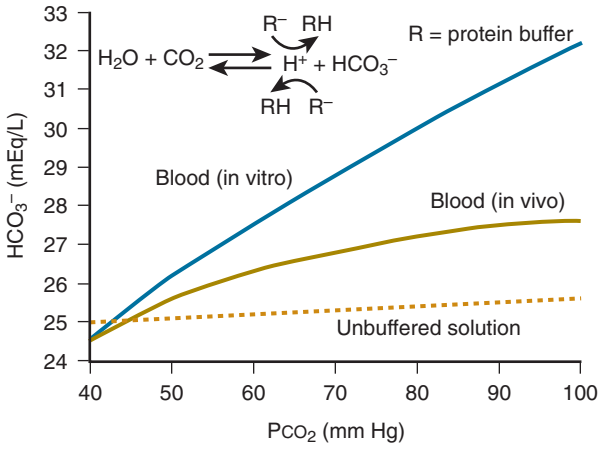

FIGURE 7-2 ■ The relation between P_{CO_2} and HCO_3^- in samples of isotonic saline with 25 mEq/L $NaHCO_3$ (unbuffered solution), in samples of whole blood (in vitro), and in samples of arterial blood drawn from patients 20 minutes after exposure to elevations of P_{CO_2} (in vivo).

Recognition that HCO_3^- concentration is not independent of P_{CO_2} in either plasma or blood (and is not strictly "nonrespiratory") and that other nonbicarbonate buffer pairs participate in H^+ buffering led to the development of alternative approaches yielding more reliable and quantitative measures to compensate for buffering related specifically to blood buffers. Among many schemes devised for this purpose, mention should be made of the HCO_3^--pH graphs of Davenport[7] and the concepts of buffer base and base excess of Sigaard-Anderson.[8] Each of these can predict accurately in vitro changes in blood after addition of acid or base or exposure to high or low P_{CO_2}, but have proved less reliable when patients are exposed to metabolic and respiratory challenges. The actual response of HCO_3^- to an acute change in P_{CO_2} was determined empirically in normal subjects and it was found that, when P_{CO_2} increased to 78 mm Hg, arterial plasma HCO_3^- increased only 3 mEq/L.[9] The range of HCO_3^- that would be expected in 95% of samples obtained in a normal population after acute increases in P_{CO_2} is indicated in Figure 7-3A. However, there is a tendency for HCO_3^- to fall somewhat more when animals are hyperventilated, as noted in Figure 7-3B,[10] due to a slight increase in lactate, which in turn may be due to an alkalosis-mediated increase the activity of the enzyme phosphofructokinase (see later discussion).[11] The relatively small changes in HCO_3^- that occur in response to acute changes in P_{CO_2}[1] are responsible for the popularity of HCO_3^- as a useful though by no means ideal "seat-of-the-pants" metabolic parameter among clinicians and the gradual decline in the use of the buffer base system for diagnostic purposes. This has been furthered by a growing appreciation that rigorous quantitation of acid-base deficits or excess with the intent of rapid chemical correction by either changes in ventilation or provision of fixed acids or bases, although appealing theoretically, have not proved useful or defensible (see discussion on treatment of metabolic acidosis). Regardless of which metabolic parameter is used, it must ultimately be validated with empirical observations made in subjects who are intentionally hyperventilated or hypoventilated (see Fig. 7-3).

The Strong Ion Approach

The traditional Henderson-Hasselbalch/van Slyke acid-base approach for analyzing acid-base problems has been challenged by an alternative paradigm, the "strong ion approach," applied to physiologic fluids.[12,13] The

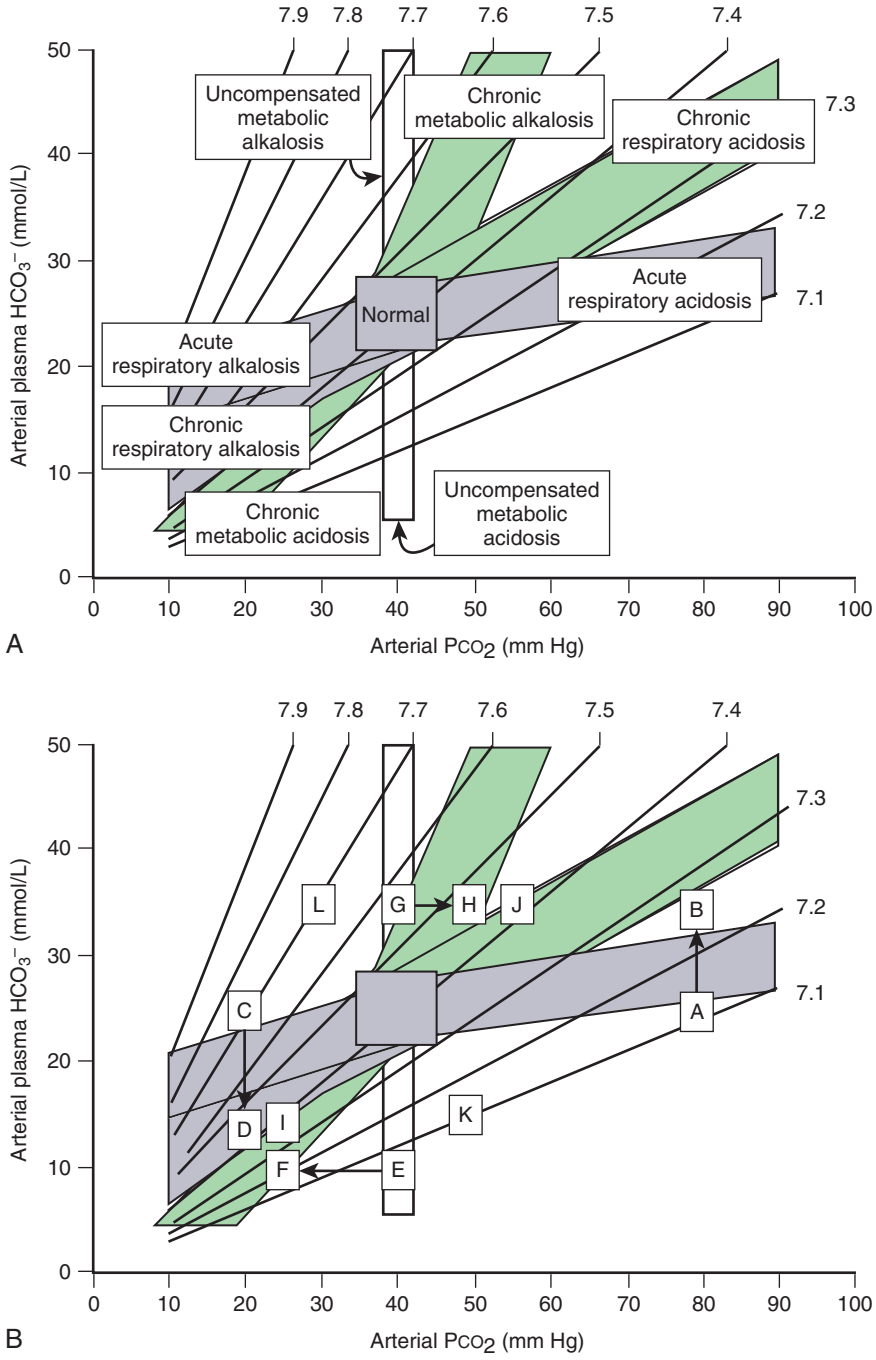

FIGURE 7-3 ■ The relation between HCO_3^- and P_{CO_2} in a variety of clinical disorders. For discussion, see text. **A,** The 95% confidence levels for acute and chronic respiratory and metabolic abnormalities.[11,85] **B,** The interpretation of examples in Table 7-1 is based on the assumption that P_{CO_2} is a purely respiratory parameter and HCO_3^- is a purely metabolic parameter.

"metabolic" parameter was divided into two components. A distinction was made between "strong" acids and bases, which are completely dissociated, and weak buffer molecules, which are partially dissociated, at physiologic pH. "Strong" ions include the electrolytes and many organic and inorganic ions such as lactate, acetoacetate, and sulfate, with pK_a values such that within clinically relevant pH ranges, they are fully dissociated. The weak buffers consist primarily of serum proteins and phosphate, with pK_a values less than one unit from physiologic pH. There are several advantages to this conceptual approach. The value of pH is calculated on the basis of three simple assumptions: (1) the total concentrations of each of the ions and acid-base pairs is known and remains unchanged, (2) the solution remains electroneutral, and (3) the dissociation constants of each of the buffers are known. Both the pH and the bicarbonate are dependent variables, which can be calculated from the concentrations of the strong and weak electrolytes and the P_{CO_2}. The strong ion differ-

ence (SID) is calculated by subtracting the strong anions from the strong cations. An increase in chloride relative to sodium results in a decrease in SID and acidification of the plasma. This explains why saline infusion results in acidosis. The strong ion approach also provides a more exact estimate of H^+ concentrations than the Henderson-Hasselbalch equation because the dissociation constant of water is also considered, but this is a relatively small correction.[14]

The relatively complex nature of the equations and increased parameters incorporated in the strong ion approach limit its clinical application and adoption. Solution of these equations requires knowledge of numerous electrolytes and protein and phosphate concentrations, which may not always be available simultaneously with arterial blood gases. In clinical circumstances, whatever extra precision the strong ion approach may theoretically provide over more conventional analyses, measurement errors of all the input parameters and the need to assume a single effective pK_a value for the many proteins in blood and tissue will reduce any putative superiority of this approach. P_{CO_2} and pH are directly measured and the bicarbonate either calculated from these parameters or estimated from the total CO_2 content, and they need not be calculated from the balance of electrolytes and weak buffers, many of which are unknown. Although the distinction between strong and weak acids and bases is readily made in plasma, it is less precise in other biologic fluids such as urine and gastrointestinal secretions. For these reasons, we have therefore chosen to retain the older approach.

Nomenclature of Acid-Base Disorders

In using CO_2 and HCO_3^- to estimate the respiratory and metabolic factors determining pH, the nomenclature of the acid-base disorders becomes quite simple with an additional assumption that compensation for a primary deviation is never complete. If arterial pH is low, the primary disorder must be an acidosis, and if high, a primary alkalosis is present. A secondary or compensatory change in either the respiratory or the metabolic parameter restores pH toward normal, but this effect should remain incomplete. On the basis of this approach, abnormal combinations of pH, P_{CO_2}, and HCO_3^- can be designated in terms of a primary disorder and any compensation that might be present.

Examples of virtually every combination of such changes are provided in Table 7-1 and illustrated in Figure 7-3. Figure 7-3A indicates the ranges in which HCO_3^- and P_{CO_2} changes have been observed in normal persons subjected to acute or chronic respiratory or metabolic changes. Figures 7-3A and B are based on the simple assumption that HCO_3^- changes reflect metabolic events, whereas changes in P_{CO_2} reflect respiratory events (as indicated in Table 7-1). Some comments concerning the reliability of this preliminary analysis are provided in Table 7-1 and are discussed later in the chapter. Horizontal deviations on these coordinates indicate respiratory changes, whereas vertical deviations designate metabolic changes. Four primary disorders (A, C, E, and G) and four compensatory responses (B, D, F, and H) are shown in Figure 7-3. Each of the latter responses returns the pH toward 7.4, but never fully, and the pH remains abnormal in the same direction as the primary change. Note that if respiratory and metabolic parameters change proportionately, pH remains unchanged (I and J). In this circumstance, the disorder is considered a "mixed" combination of primary disorders. Another "mixed" disorder arises when both parameters are altered in a fashion that changes the pH in the same direction (K and L) and neither change can be considered as compensatory. A third type of "mixed" disorder must be entertained if a patient simply fails to "compensate" in the expected manner for a primary disorder after sufficient time has elapsed.

Because the three variables must be related by Equation 2, not all combinations of pH, P_{CO_2}, and HCO_3^- are possible. One combination (M), which is chemically impossible and cannot be plotted, must represent a laboratory error or timing differences at which various parameters were obtained, is indicated in Table 7-1. "Triple disorders" may also be encountered involving a mixture of two independent processes that induce a metabolic alkalosis and a metabolic acidosis (detected by an increase in the anion gap), plus either a respiratory alkalosis or a respiratory acidosis. Measurement of specific organic acids in plasma may permit identification of even more complex disorders.

Several caveats should be heeded regarding both this and other systems that classify acid-base disorders strictly on the basis of pH, P_{CO_2}, and a metabolic parameter. Distinction between primary and compensatory disorders is based simply on which alteration was proportionately greater at the time the blood was drawn rather than on the sequence of events involved. For example, it is common for patients with chronic obstructive pulmonary disease (COPD) to be admitted to the hospital with compensated respiratory acidosis. With therapy, the P_{CO_2} may decrease, leaving what might otherwise in the absence of the clinical history be taken as "a primary metabolic alkalosis with secondary respiratory compensation." Winters[15] suggested that a distinction be made between the "physiologic" language commonly used by the physician and the "laboratory" terminology that is strictly based on blood parameters.

Laboratory definitions of primary and secondary or compensatory alterations of acid-base disorders assume that one is greater than the other and that there has been sufficient time for compensatory processes to reach their full quantitative expression. As discussed later, complete respiratory compensations occur within hours, but full renal compensation takes several days. Thus, in any rapidly evolving and changing disease scenarios, clinicians should not always assume that lack of an expected compensations dictates consideration of a second or third primary disorder. Under some circumstances, however, compensation (correction to normal pH) may be complete in the apparent absence of what could be identified as a second primary disorder. For example, full compensation is observed among COPD patients who are chronically hypercapnic, whose lung function can

TABLE 7-1. Laboratory Classification of Acid-Base Disorders

Location in Figure 7-3	Metabolic Parameter HCO_3^- (mEq/L)	pH	Respiratory Parameter P_{CO_2} (mm Hg)	Preliminary Interpretation	Comments Based on Bands (Fig. 7-3)
Normal range	23–27	7.38–7.42	38–42		
A	25	7.12	80	Respiratory acidosis	A small increase in (uncompensated) HCO_3^- usually occurs with acute respiratory acidosis
B	35	7.25	80	Respiratory acidosis (compensated)	Compensation has not reached expected confidence levels
C	25	7.71	20	Respiratory alkalosis (uncompensated)	A decrease in HCO_3^- would be expected; acute respiratory alkalosis
D	15	7.50	20	Respiratory alkalosis (compensated)	Compensation exceeded expected range
E	10	7.03	40	Metabolic acidosis (uncompensated)	A completely uncompensated metabolic acidosis should be very transient if the ventilator response is normal
F	10	7.23	25	Metabolic acidosis (compensated)	Compensation is nearly maximal
G	35	7.56	40	Metabolic alkalosis (uncompensated)	
H	35	7.46	50	Metabolic alkalosis (compensated)	Compensation is in expected range
I	16	7.40	25	Metabolic acidosis and respiratory alkalosis	Mixed disorder
J	35	7.40	56	Metabolic alkalosis and respiratory acidosis	Mixed disorder
K	15	7.10	50	Metabolic acidosis and respiratory acidosis	Mixed disorder
L	35	7.67	30	Metabolic alkalosis and respiratory alkalosis	Mixed disorder
M	15	7.30	60	Laboratory error	

Interpretation based on assumption that P_{CO_2} and HCO_3^- are respiratory and metabolic parameters.

improve over the course of the day with clearance of secretions. With better ventilation and $\dot{V}_A/\dot{Q}$ matching, arterial P_{CO_2} falls and pH increases to normal or even higher than normal levels before the kidneys can quantitatively respond (see discussion on compensations later). Full compensation is also characteristic of the chronic hyperventilation observed at high altitude.

If HCO_3^- were a strictly metabolic ("nonrespiratory") variable, then changes in P_{CO_2} would result in movement along a line perpendicular to the HCO_3^- axis (e.g., A and C in Fig. 7-3B). The actual response of HCO_3^- to acute and chronic changes can be indicated by the 95% confidence bands shown in Figure 7-3. Note that both A and C deviate from the expected responses to acute changes in P_{CO_2} (see comments in Table 7-1). Because P_{CO_2} is assumed to be a reliable index variable of ventilation, E and G represent metabolic changes without respiratory compensation.

Compensations

Respiratory Acidosis

Although the acute increase in HCO_3^- is relatively modest after onset of hypercapnia, HCO_3^- continues to rise if hypercapnia persists and reaches a peak value after about 5 days. This is related primarily to an increase in the exchange of H^+ for Na^+ in the proximal tubule and increased HCO_3^- reabsorption (see later discussion). Increases in plasma HCO_3^- require an initial net loss of H^+, which is made possible by the loss of increased quantities of NH_4^+ in the urine. Once plasma HCO_3^- has reached a new steady state, H^+ secretion need only be sufficient to reabsorb HCO_3^- from the tubular fluid, and NH_4^+ and H^+ excretion usually return to normal. In contrast, excretion of both net NH_4^+ and net H^+ remains elevated in chronic metabolic acidosis, because the daily load of nonvolatile acids must be excreted, over and above the acid excretion needed for reabsorption of HCO_3^-. Differences in NH_4^+ and net H^+ excretion in chronic respiratory and metabolic acidosis may be related to the fact that proximal tubular fluid contains high concentrations of HCO_3^- in chronic respiratory acidosis but low concentrations in chronic metabolic acidosis. Increased HCO_3^- flux into the proximal tubular cells in chronic respiratory acidosis keeps intracellular pH relatively alkaline compared with the situation observed in chronic metabolic acidosis. Intracellular acidosis stimulates secretion of NH_4^+ in chronic metabolic acidosis.[16]

TABLE 7-2. Rules of Chronic Compensation

Primary Disorder	Secondary Compensation	EXAMPLES	
		Primary Change	Compensation
↑ P_{CO_2}	↑ HCO_3^-: 4 mEq/L for each 10-mm Hg increase in P_{CO_2} (±3 mEq/L)	P_{CO_2}: 40 → 80	HCO_3^-: 24 → 40 pH: 7.1 → 7.32
↓ P_{CO_2}	↓ HCO_3^-: 2.5 mEq/L for each 10-mm Hg decrease in P_{CO_2} (±3 mEq/L)*	P_{CO_2}: 40 → 20	HCO_3^-: 24 → 19 pH: 7.70 → 7.60
↓ HCO_3^-	↓ P_{CO_2}: 1–1.5 mm Hg for each mEq/L decrease in HCO_3^-	HCO_3^-: 24 → 9	P_{CO_2}: 40 → 25 pH: 7.00 → 7.20
↑ HCO_3^-	↑ P_{CO_2}: 0.5–1.0 mm Hg for each mEq/L increase in HCO_3^-	HCO_3^-: 24 → 4	P_{CO_2}: 40 → 50 pH: 7.56 → 7.46

*HCO_3^- seldom falls below 18 mEq/L in acute and 16 mEq/L in chronic respiratory alkalosis.

Respiratory Alkalosis

Hypocapnia results in a decrease in renal acid excretion and a fall in HCO_3^- that becomes fully evident within 2 to 3 days. As indicated in Table 7-2, HCO_3^- decreases by 2.5 mEq/L for each decrease of 10 mm Hg in P_{CO_2}[17] and does not generally fall much below 16 mEq/L in respiratory alkalosis unless there is an independent metabolic acidosis present. In contrast, an increase of about 4 mmol of HCO_3^- may be expected when P_{CO_2} is increased in steps of 10 mm Hg. Confidence bands for chronic compensation are indicated in Figure 7-3A.

Metabolic Acidosis

Respiratory compensation for metabolic disorders is quite fast (within minutes) and reaches maximal values within 24 hours. A decrease in P_{CO_2} of 1 to 1.5 mm Hg should be observed for each milliequivalent decrease of HCO_3^- in metabolic acidosis.[18] A simple rule for deciding whether the fall in P_{CO_2} is appropriate for the degree of metabolic acidosis is that the P_{CO_2} should be equal to the last two digits of the pH. For example, compensation is adequate if the P_{CO_2} decreases to 28 when the pH is 7.28. Alternatively, the P_{CO_2} can be predicted by adding 15 to the observed HCO_3^- (down to a value of 12). Although reduction in P_{CO_2} plays an important role in correcting any metabolic acidosis, evidence suggests that it may in some respects be counterproductive because it inhibits renal acid excretion.

Metabolic Alkalosis

Compensation for metabolic alkalosis results in a decrease of ventilation and a rise of P_{CO_2} by about 0.6 to 0.7 mm Hg for each milliequivalent increase in HCO_3^-, but it seldom results in a P_{CO_2} much greater than 55 mm Hg[19] because the accompanying hypoxemia from hypoventilation generates an opposing ventilatory stimulus. Furthermore, compensatory increases in P_{CO_2} may be more pronounced in patients with metabolic alkalosis who have not lost K^+. Losses of K^+ are associated with an intracellular rise in H^+, including the neurons of the respiratory center.[20] A variety of other factors have been reported that can increase P_{CO_2} values in patients with metabolic alkalosis.[21] Respiratory compensation for metabolic alkalosis, like that for metabolic acidosis, can have a counterproductive effect on renal H^+ transport: increases in P_{CO_2} associated with metabolic alkalosis decrease intracellular pH in the kidney, thereby promoting acid secretion and further increasing serum HCO_3^- levels.[22]

Role of the Kidney in Acid-Base Balance

Response to Acidosis and Excretion of Acid

Daily about 1 mEq/kg of "fixed" acids (i.e., acids other than H_2CO_3) are produced in metabolism with a typical protein diet. These nonvolatile acids cannot be excreted by the lungs and must be lost by other routes, or buffered, to avoid progressive retention. Both sulfate and phosphate are produced, and these may be accompanied by a variety of organic acids, some of which escape metabolism and contribute to the daily acid load. Successful elimination by the kidneys depends on both tubular H^+ transport and the presence of urinary buffers. In absence of buffers, less than 0.1 mEq of acid/L would be excreted even at the lowest urinary pH (4.5) generated by the kidneys.

Three kinds of buffers are found in urine: bicarbonate, ammonium, and titratable acids. Daily there is filtration of 3600 mEq of HCO_3^- with trivial losses in the urine. Most of the filtered HCO_3^- is reclaimed by an exchange of intracellular H^+ for Na^+ (through a Na^+-H^+ antiporter, "NHE_3") rather than direct HCO_3^- reabsorption, although the latter process may be stimulated in acidotic states. Intracellular H^+ is derived from carbonic anhydrase–mediated hydration of CO_2 to H_2CO_3 and the dissociation of H_2CO_3 to H^+ and HCO_3^-. H^+ entering the proximal tubule combines with HCO_3^- and rapidly regenerates CO_2 and H_2O, accelerated by the presence of carbonic anhydrase (type IV) on the luminal surface of the proximal tubule cells. The HCO_3^- formed within proximal tubule cells moves across the basolateral membranes in exchange for Cl^- ($Na^+/HCO_3^-/CO_3^{2-}$ symporter).

Removal of HCO_3^- from proximal tubular fluid is essential, and failure to do so inevitably leads to hyperchloremic acidosis. However, HCO_3^- reabsorption does not result in acid excretion in the urine and therefore cannot contribute to fixed acid excretion. Unlike HCO_3^-, titratable acids and ammonium do reach the urine, and H^+ is carried into the urine by these buffers. The principal titratable anion is $H_2PO_4^-$, but during ketoacidosis, β-hydroxybutyric acetate also can act as an effective buffer. NH_4^+ is produced from glutamine by the proximal tubular cells and can be stimulated by chronic acidosis. NH_4^+ is secreted into the proximal tubule; some of this ion is reabsorbed in the thick ascending limb of the tubule, and a fraction is converted into NH_3. This increases medullary concentration of NH_3, which diffuses into the collecting ducts. Because the collecting duct fluid tends to be very acid, NH_3 becomes "trapped" as NH_4^+. Details regarding renal metabolism and excretion of NH_3 and NH_4^+ can be found elsewhere.[23]

Movement of H^+ into the proximal nephron differs in a number of important respects from transport in the distal nephron. Because the proximal tubule is responsible for absorbing most of the filtered HCO_3^-, considerably more H^+ transport occurs at this location than distally (~3600 mEq, as described earlier, vs. 50–100 mEq of fixed acids). However, the ability of the proximal tubule to concentrate H^+ is limited, and the fluid leaving the proximal tubule has a pH of about 6.8. Although the more distal portions of the tubule secrete less total H^+ than the proximal tubules, they increase H^+ concentration by almost 1000-fold compared with plasma, producing a urinary pH as low as 4.5. This permits net renal excretion of the acids normally generated by metabolism. Distal tubular acid secretion is mediated by H^+-ATPase and K^+/H^+-ATPase on the luminal surface of the intercalated cells of the collecting tubules and by transporters on inner medullary cells. This process is accelerated by electrogenic Na^+ reabsorption by adjacent principal cells, a process that makes the electrical potential of the tubular lumen more negative and thereby enhances secretion of H^+.

Because CO_2 readily diffuses across cell membranes, the P_{CO_2} and pH of the renal tubular cells are affected promptly by changes in arterial P_{CO_2}. These changes initiate changes in renal H^+ excretion, with an increase during hypercapnia and decrease by hypocapnia.

Response to Alkalosis

Alkalosis can be initiated by losses of acid in the gastric fluid or urine, a shift of hydrogen ions into the cells (frequently associated with hypokalemia), excessive alkali administration, or decreases in the extracellular volume (e.g., following diuretics). Under normal circumstances, an abrupt increase in plasma HCO_3^- above the normal threshold of 25 mEq/L initiates a prompt compensating renal loss of HCO_3^-, by both decreased proximal reabsorption and increased distal secretion.[24,25] Understanding the pathogenesis of metabolic alkalosis must explain not only how it is initially generated but also the manner in which it is maintained.

The second or "maintenance" phase of metabolic alkalosis can be attributed to several mechanisms that reduce HCO_3^- losses by the kidneys: (1) Decreases in renal perfusion due to extracellular contraction result in increases in the renin-angiotensin-aldosterone system, which increases reabsorption of Na^+ especially by the principal cells of the collecting duct. This is associated with increased hydrogen ion secretion via the apical proton pump H^+-ATPase in the adjacent A-type intercalated cells. (2) Reduced concentrations of Cl^- reaching the macula densa in the late thick ascending limb and early distal tubule also stimulate the renin-angiotensin-aldosterone system. Furthermore, reductions in Cl^- reaching the collecting duct reduce exchange of HCO_3^- for Cl^- through the apical chloride/bicarbonate exchanger in the B-type intercalated cells. (3) Hypokalemia stimulates secretion of H^+ ion by H^+/K^+-ATPase in the collecting duct. It also increases NH_4^+ secretion with generation of alpha ketoglutamine, which is metabolized to HCO_3^-. Hypokalemia causes an intracellular acidosis and a reduction in glomerular filtration rates which also reduce HCO_3^- losses in the urine.[26] During the maintenance phase, the urine becomes relatively acidotic, a phenomenon that actually worsens or at least maintains the alkalosis that was originally generated by vomiting. This is sometimes referred to as *paradoxical aciduria* or *alkalosis of contraction*. In effect, acid-base balance is sacrificed to conserve Na^+ and defend extracellular fluid (ECF) volume. Increased distal nephron Na^+ delivery and increased Na^+ reabsorption drives K^+ secretion. More K^+ is lost from the kidneys than the gastric losses with vomiting. In effect, even the intracellular electrolyte status is imperiled to maintain ECF volume. Cl^- in the glomerular filtrate is largely reabsorbed during the maintenance stage, and little appears in the urine.[27]

Intracellular Acid-Base Physiology

Intracellular buffers are an important early defense against acid-base perturbations. Metabolic acidosis induced by HCl infusions is rapidly buffered by plasma HCO_3^- and other buffers, but acid diffuses into the interstitial space over a period of 15 minutes and into cells over 2 to 4 hours to be buffered. Ultimately, approximately 40% of the infused acid is buffered extracellularly, primarily by HCO_3^-, and the remainder cellularly and by bone buffers. In contrast, almost all respiratory acidosis buffering is intracellular or with bone, because HCO_3^- cannot directly neutralize carbonic acid. However, the fall in pH that is associated with a rise in P_{CO_2} can be moderated by electroneutral exchange of red cell HCO_3^- for Cl^- and by increases in plasma HCO_3^- mediated by the movement of H^+ from the ECF into cells in exchange for Na^+ and K^+. Buffering of respiratory acidosis by these means is relatively modest (~1 mmol/L for each 10 mm Hg in P_{CO_2}). More substantial buffering requires renal secretion of H^+, which increases plasma HCO_3^- concentrations by 4 mmol/L for each 10-mm Hg increase in P_{CO_2}.

Temperature is an important physiologic variable, and its effects on acid-base status are relevant to intracellular

as well as extracellular buffers. Reeves and Rahn[28] proposed that metabolic and respiratory mechanisms function to preserve the ionic charge on proteins, including enzymes and chemoreceptors involved in pH regulation, rather than maintain a constant intracellular and extracellular pH. Because enzyme function is influenced by ionic charge, maintenance of a constant charge is presumably homeostatically advantageous. Only imidazole groups of histidine and, to a lesser extent, the α-NH_3^+–terminal amino groups of peptides are present in significant concentrations and change their extent of dissociation appreciably in physiologic pH ranges. The pH of the intact organism is then regulated in a manner that keeps the dissociation of the imidazole groups constant at various temperatures. When sealed samples of blood are cooled to 15°C, the CO_2 content of the blood must remain constant, but the pH increases to 8.0 and the P_{CO_2} falls to 12 mm Hg. Despite these dramatic changes in pH and P_{CO_2}, the fraction of the imidazole groups that are dissociated remains virtually unchanged. This phenomenon can be attributed to the fact that changes in temperature have a similar effect on the dissociation constants of water and imidazole. Independence of protein charge from temperature changes was presumably important in our poikilothermic ancestors. It also facilitates clinical interpretation of acid-base balance in hypothermia and hyperthermia, because acid-base parameters measured at 37°C can provide a reasonable index of the acid-base status of the patient, regardless of whether the patient's temperature is normal, elevated, or depressed. Temperature corrections, however, are needed for P_{CO_2} and P_{O_2} in order to accurately assess lung gas exchange efficiency by the alveolar gas equation.

The relatively hidden environment of the intracellular fluid has begun to be probed since the late 1980s by a combination of microelectrodes and imaging methods utilizing fluorescent dyes and magnetic resonance spectroscopy. What has emerged is a process of transmembrane acid-base exchanges with the ECF that, combined with chemical buffering, accomplish very impressive intracellular pH regulation in the face of acidotic and alkalotic challenges, particularly in critical organs such as the heart and brain.[29] To defend against intracellular acidosis, cells activate both membrane H^+ translocating ATPases and Na^+/H^+ antiporters to export H^+. Both processes are energy-requiring; the first uses adenosine triphosphate (ATP) directly and the second utilizes the inward electrochemical gradient for sodium flux established by continued Na^+K^+-ATPase pumping that maintains a lower intracellular Na^+ concentration. Less has been studied on the mechanisms of defense against intracellular alkalosis, but evidence points to the activation of both neutral and electrogenic transporters that export HCO_3^- in exchange for chloride (anion exchangers similar to AE-1 in red cells responsible for Cl^-/HCO_3^- exchange) or couple HCO_3^- export to other cations like sodium ($Na^+/HCO_3^-/CO_3^{2-}$ symporter).

METABOLIC ACIDOSIS

Anion Gap Concept

The most useful classification of metabolic acidosis is based on the concept of the anion gap, whose calculation is made by subtracting the sum of plasma concentrations of Cl^- and HCO_3^- from that of Na^+ (Fig. 7-4). This difference provides an index of the relative concentrations of plasma anions other than Cl^- and HCO_3^-. Normally, the anion gap is between 8 and 16 mEq/L, although somewhat lower values (5–11 mEq/L) have been observed when newer techniques for measuring ion activities rather than total concentrations are used.[30,31] Among other anions present in plasma are albumin (with multiple anionic groups at physiologic pH that normally constitute about half of the gap), lactate, pyruvate,

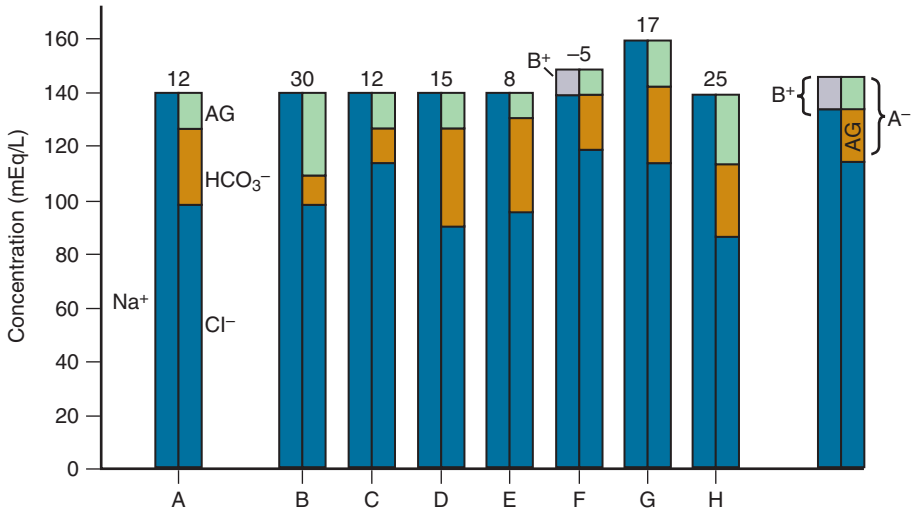

FIGURE 7-4 ■ Anion gap (AG) profiles are shown for eight different conditions (see text). The value of the AG is shown above each bar. **A,** normal; **B,** anion gap acidosis; **C,** hyperchloremic acidosis; **D,** primary metabolic alkalosis; **E,** secondary metabolic alkalosis; **F,** excess cations (B^+) other than Na^+; **G,** hypernatremia; **H,** excess anion gap in absence of acidosis. The bar outside the graph demonstrates the relation between excess cations (B^+), excess anions (A^-), and the anion gap (AG).

sulfate, and phosphate. Elevations of the anion gap usually indicate accumulation of some acid other than HCl in the plasma and are generally accompanied by a similar decrease in HCO_3^- ("anion gap acidosis") (B in Fig. 7-4). Alternatively, reduction in [HCO_3^-] may be caused by an increase in [Cl^-] without an increase in the anion gap ("hyperchloremic acidosis") (C in Fig. 7-4).

Examples of both anion gap and hyperchloremic metabolic acidosis are discussed later, along with a third and less common form, "dilutional acidosis." However, some general comments concerning the anion gap concept are warranted. First, although addition of acids other than H_2CO_3 and HCl to plasma tends to increase the anion gap, this effect is somewhat less than might be expected, because H^+ tends to combine with negative groups on the albumin molecules, thereby reducing the contribution of this protein to the anion gap. Alkalosis tends to increase the number of anionic groups on albumin, thereby increasing the anion gap. Recognition of this phenomenon may be helpful when the CO_2 content of the blood is available but the arterial pH and P_{CO_2} are not. For example, if an elevated HCO_3^- is related to a primary metabolic alkalosis, then the anion gap tends to be greater than when it is secondary to a compensatory respiratory acidosis (compare D and E in Fig. 7-4). Second, because approximately half of the anion gap is normally related to negative charges on albumin, hypoalbuminemia decreases the anion gap by about 2.5 mEq/L for each decrease in albumin concentration of 1 g/dL.[32] Third, electroneutrality requires that the sum of known cations (Na^+) and unknown cations (B^+) must equal the sum of known anions ($Cl^- + HCO_3^-$) and unknown anions (A^-)[1]:

$$Na^+ + B^+ = (Cl^- + HCO_3^-) + A^- \quad (5)$$

Consequently, the anion gap must equal the difference between the unknown anions and cations (see Fig. 7-4):

$$\text{Anion gap} = Na^+ - (Cl^- + HCO_3^-) = A^- - B^+ \quad (6)$$

A low anion gap may therefore reflect an increase in cations other than Na^+ (e.g., calcium [Ca^{2+}], magnesium [Mg^{2+}], lithium [Li^+], and abnormal cationic proteins in multiple myeloma) (see F in Fig. 7-4). As illustrated in Figure 7-4, the "anion gap" is actually less than the concentration of unknown anions, by a value equal to the concentration of unknown cations. Fourth, losses of water during dehydration increase the levels of all solute concentrations, including those that compose the anion gap (see G in Fig. 7-4). Retention of water has the opposite effect. Fifth, administration of large quantities of sodium salts of anionic antibiotics (e.g., penicillin and related drugs) or other anions (e.g., lactate, citrate, acetate) can also increase the anionic gap without acidosis (see H in Fig. 7-4). If anions of this type have not been administered and the patient is not dehydrated, then an increased anion gap suggests an underlying metabolic acidosis, even if the pH is normal or high (H in Fig. 7-4).

Finally, because much of the H^+ produced in the body is buffered by non-HCO_3^- buffers within cells, the decrease in HCO_3^- tends to be less than the increase in the anion gap when metabolic acidosis is present. For example, the increase in the anion gap averages about 60% more than the decrease of HCO_3^- in lactic acidosis. Because ketones are more readily lost in the urine than lactate, the increase in the anion gap is generally similar to the decrease in HCO_3^- in conditions that result in ketoacidosis[33] (see later discussion). Conversely, if the decrease in HCO_3^- exceeds the increase in the anion gap, it is likely that at least part of the acidosis is caused by a non–anion gap acidosis.

Causes

Lactic Acidosis

Approximately 1400 mEq of lactate are normally produced each day,[34] but production can increase by an order of magnitude in heavy exercise. At rest, production is balanced by consumption and precisely regulated so that serum levels are kept at about 1 mEq/L. Most lactate is produced by the skeletal muscles, but with various stresses such as ischemia, profound hypoxemia, sepsis, and high sympathetic tone, other tissues may also generate lactate. In resting healthy individuals, the liver and, to a lesser extent, the kidneys are responsible for most of its consumption,[34] with oxidation in red skeletal muscle accounting for the remainder. During physical exertion, although lactate is the main gluconeogenic precursor in liver and kidneys, oxidation in working muscle accounts for 70% to 80% of lactate disposal. Newer work and analysis of glycolytic intermediary metabolism suggest we may have to reconsider our classic thinking about what we have long termed "lactic acidosis." From a strict biochemical standpoint, it is lactate and not lactic acid that is generated at the terminal point in glycolysis when pyruvate is reduced to lactate by lactate dehydrogenase (LDH), a step that consumes rather than produces a proton (Fig. 7-5).

$$\text{Pyruvate} + \text{NADH} + H^+ \leftrightarrow \text{Lactate} + NAD^+$$

In terms of proton production, stiochiometric analysis of the glycolytic pathway shows the pathway to be proton neutral. Thus, the acidosis that develops when lactate rises with exercise and possibly with other conditions associated with lactate accumulation and acidosis may be misleading.[35] It has been suggested, in fact, that if there were no lactate formation, the degree of acidosis arising in these circumstances would even be greater. The hydrogen ion that is formed in states of "lactic acidosis" arises from ATP whose hydrolysis generates a hydrogen ion.

$$ATP + H_2O \leftrightarrow ADP + PO_4^- + H^+$$

Under conditions where adenosine diphosphate (ADP) is not rephosphorylated, H^+ will accumulate. This occurs with true O_2 deficiency in ischemic (severe hypoperfusion) or very hypoxemic states when O_2 delivery cannot be maintained to support aerobic metabolism. Although the production of excessive quantities of lactate is thought to be linked in some way to tissue hypoxia in many clinical conditions associated with lactic

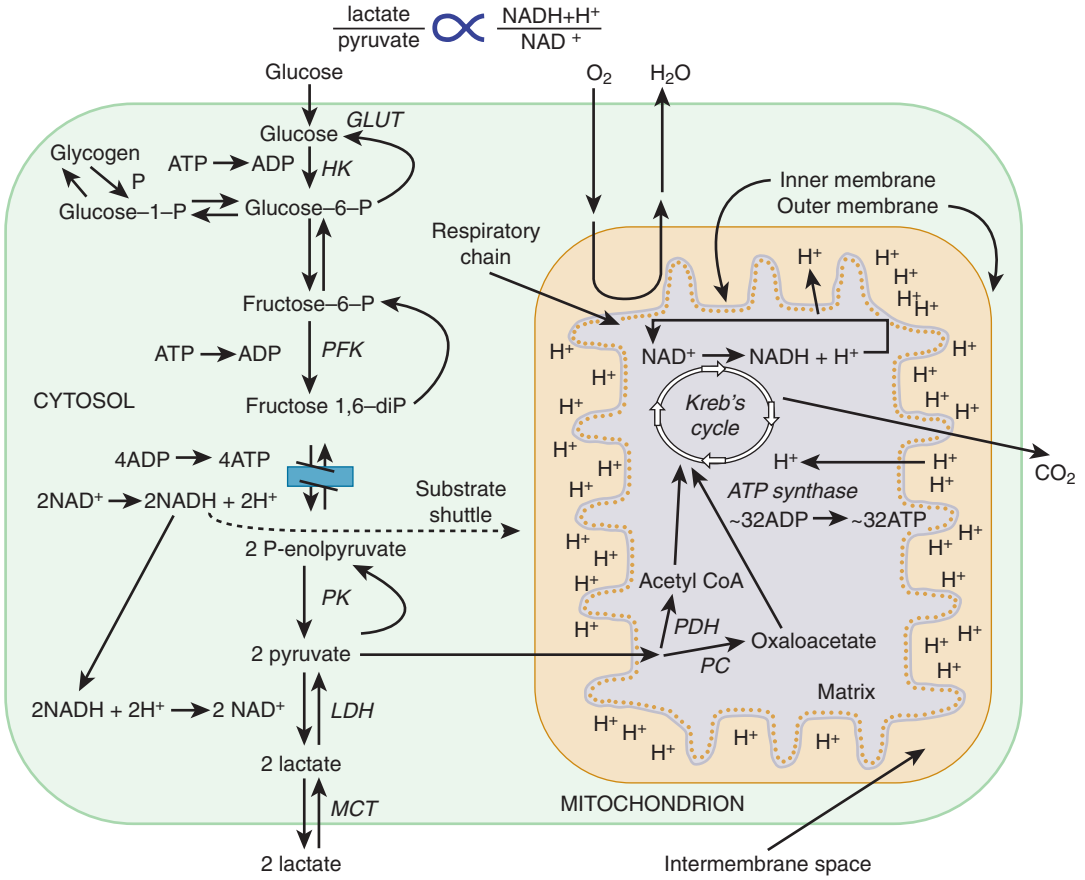

FIGURE 7-5 ■ The metabolic events responsible for the development of lactic acidosis during hypoxia are indicated schematically. Both enhancements and reduction of metabolic reactions that produce lactic acid are shown (see text). Factors affecting the balance between lactate and pyruvate are indicated in the equation at the top of the figure. ADP, adenosine diphosphate; ATP, adenosine triphosphate; CoA, coenzyme; k, constant; LDH, lactate dehydrogenase; NAD^+, nicotinamide adenine dinucleotide (oxidized); NADH, nicotinamide adenine dinucleotide (reduced); P, phosphate; PC, pyruvate carboxylase; PDH, pyruvate dehydrogenase; PFK, phosphofructokinase; PK, pyruvate kinase. Stoichiometry is not shown for most of the reactions within the mitochondrion (other than ADP and ATP).

acidosis, the evidence of tissue hypoxia is largely negative when sought for in maximally exercising muscle[36] or in sepsis,[37] though it would be difficult to detect small local regions of tissue hypoxia. The benign, or rather efficacious, nature of lactate has been demonstrated in "lactate clamp" studies,[38] in which lactate concentration is raised to 4 mM by infusion of a sodium lactate/lactic acid mixture along with glucose and lactate tracers. Under these conditions, lactate is the preferred fuel and because its disposal via gluconeogenesis or oxidation involves proton removal, lactate infusions have a mild alkalinizing effect. Nevertheless, the increase in lactate and production of acid during heavy exercise is presumably attributable to an increase in the fraction of glucose diverted to glycolytic rather than mitochondrial metabolism.

As indicated in Figure 7-5, glucose is normally metabolized to pyruvate, which is in equilibrium with lactate, at a ratio of 1:10 at rest and rising to 1:100 with exercise. Metabolism of lactate can occur only if it is converted back to pyruvate either in the cytosol or in the mitochondria (see discussion later). Pyruvate can be transported into the mitochondria in either of two ways. In gluconeogenic organs, CO_2 can be added to pyruvate by the enzyme pyruvate carboxylase to form oxaloacetate, which can then be converted to phosphoenol pyruvate and converted to glucose-6-phosphate (G-6-P) and glucose. Alternatively, pyruvate can be oxidized to acetyl coenzyme A (CoA) by pyruvate dehydrogenase (PDH). Acetyl CoA then combines with oxaloacetate and is metabolized to form both ATP and nicotinamide adenine dinucleotide (NAD^+). In absence of oxygen, reduced NADH cannot be oxidized to NAD^+, and ATP production by the cytochrome system is blocked. Because the carboxylase reaction requires ATP and the dehydrogenase reaction requires NAD^+, pyruvate can no longer enter the mitochondria, and concentrations of both cytosolic pyruvate and lactate increase. Increased cytosolic NADH results in a disproportionate lactate increase. In addition, accumulation of cytosolic ADP, adenosine monophosphate (AMP), and phosphates activates phosphofructokinase and pyruvate kinase. This in turn increases metabolism of glycogen and glucose, which are effectively converted to lactate, a sequence of events referred to as the *Pasteur effect*. In effect, hypoxia promotes lactic acidosis both by increasing lactate production and by reducing its metabolism (see Fig. 7-5).

Anaerobic production of ATP is much less efficient than aerobic production. For each millimole of glucose

converted to 2 mmol of pyruvate, a net of 2 mmol of ATP is produced. In the absence of oxidative metabolism, NADH and H^+ accumulate, encouraging lactate formation. If, in contrast, pyruvate is metabolized aerobically, an additional 36 mmol of ATP is produced by way of the Krebs cycle. Note that the protons and electrons can be "shuttled" across the mitochondrial membranes in a manner that tends to equalize the redox potentials of the mitochondria and cytoplasm.

As mentioned previously, in many supposedly hypoxic tissue states, such as heavy exercise, seizures, and sepsis, O_2 delivery is not always insufficient and other causes for increased lactate formation and acidosis must be considered. One important cause is heightened sympathetic activation and catecholamine stimulation of glycolysis in excess of mitochondrial capacity for pyruvate uptake and metabolism arising from stimulated membrane ATP utilization by Na^+/K^+-ATPase and accumulation of ADP, H^+, and phosphate.[37] It has been suggested that lactate itself can enter the mitochondria in what has been termed the *intracellular lactate shuttle* under conditions in which pyruvate entry for reasons not entirely known may be insufficient by the classic entry pathways.[38,39] Mitochondrial lactate entry is facilitated by a monocarboxylic transporter-LDH complex localized on the inner mitochondrial membrane where pyruvate can be regenerated for utilization in the Krebs cycle. Other reasons given for increased cytosolic lactate production include regeneration of NAD^+ to maintain high rates of glycolysis and to provide necessary redox equivalents to support high glycolytic and electron transport chain function.[40]

The diagnosis of lactic acidosis is based on the presence of an acidosis and a lactate concentration significantly greater than the normal concentration of 1 mEq/L (usually >5 mEq/L). Regardless of the actual role of lactate generation in acidification, use of the term "lactic acidosis" is justified by the presence of both acidosis and increased lactate contractions in this condition. Arterial lactate samples are usually collected because unless a mixed venous sample is obtained, peripheral venous samples reflect blood lactate concentrations leaving only a portion of the body and may therefore be unrepresentative of the whole body. Under normal circumstances, lactate concentrations exceed those of pyruvate by a factor of 10. Significant increases in this ratio suggest true tissue hypoxia, states of high adrenergic tone, or nonhypoxic abnormalities in intermediary metabolism.

Considering the marked arterial hypoxemia in some patients with severe respiratory insufficiency or cyanotic heart diseases, it may seem paradoxical that lactic acidemia is not observed more frequently. Lactic acidosis is much more likely to appear when tissue perfusion is impaired than when arterial P_{O_2} is moderately reduced. Several compensations for chronic arterial hypoxemia help minimize tissue hypoxia: cardiac output and hematocrit rise, and hemoglobin O_2 affinity falls if pH declines in those with CO_2 retention, because of increased 2,3-diphosphoglycerate concentrations.

Skeletal muscle represents the principal site of lactate turnover. During moderate exercise, blood lactate levels normally remain unchanged despite elevated production. In a progressive (ramp) test, when work rates increase above what is referred to as the *anaerobic threshold*, lactate concentrations increase because the rate of rise in lactate production exceeds its rate of disposal. Although it was formerly thought at this level of exercise O_2 consumption exceeds O_2 delivery to the muscle cell mitochondria, this now seems somewhat less likely and it may be linked to rising catecholamine-stimulated nonhypoxic glycolysis.[40] During vigorous exercise, lactate levels may transiently increase to 20 mEq/L or greater. Excessive production of lactate by skeletal muscles can also be observed during grand mal seizures and may accompany severe shivering in the hypothermic patient (Table 7-3).

Cohen and Woods[41] divided the causes of lactic acidosis into two types: type A, in which tissue hypoxia is evident, and type B, in which the tissue P_{O_2} appears to be normal. Type A disorders include all forms of shock, adult respiratory distress syndrome, acute hypoxemia, and a variety of conditions that impair oxygen delivery, such as carbon monoxide poisoning and severe anemia. As explained above, the actual role of tissue hypoxia in Type A disorders remains controversial. Type B disorders, which are not usually associated with tissue hypoxia, include common illnesses that may be associated with lactic acid accumulation; a variety of drugs and poisons that can induce lactic acidosis (associated with

TABLE 7-3. Causes of Anion Gap Acidosis

KETOACIDOSIS
Diabetes mellitus
Starvation
Ethanol
Inheritable errors of metabolism
LACTIC ACIDOSIS
Type A: Tissue Hypoxia
Poor tissue perfusion: shock due to hypovolemia, sepsis, cardiogenic, idiopathic
Severe hypoxemia: pulmonary disorders (e.g., asthma, excessive inhaled β_2-adrenergic agents), acute respiratory distress syndrome, carbon monoxide poisoning
Exercise above anaerobic threshold, seizures, shivering
Rhabdomyolysis
Severe anemia, carbon monoxide
Type B: Altered Lactate Metabolism without Hypoxia
Liver disease, renal failure, diabetes mellitus, malignancies (especially hematopoietic)
Drugs: biguanides, ethanol, methanol, salicylates, ethylene glycol, isoniazid toxicity, zidovudine (AZT), metformin, chemotherapy, nitroprusside, propofol
Rhabdomyolysis
Hereditary: glucose-6-phosphatase deficiency, fructose-1,6-phosphatase deficiency
D-Lactic acidosis
UREMIA
MISCELLANEOUS TOXIC ANIONS
Ethylene glycol (glyceraldehyde, oxalate, hippurate)
Methanol (formaldehyde, formate)
Paraldehyde (acetoacetate)
Salicylates
Aminocaproic acid

myoglobinemia recently following propofol administration[42]), and congenital metabolic enzyme deficiencies. In diabetic patients, low insulin levels reduce the metabolism of pyruvate by PDH, resulting in an increased lactate concentration. Evidence has also been reported that accumulation of ketones in the plasma may inhibit the monocarboxylic acid pump that is responsible for hepatic uptake of lactate.[43] In some patients with diabetic ketoacidosis (DKA), elevated lactate may be caused by ECF volume depletion due to osmotic diuresis induced by hyperglycemia. Malignancies, particularly lymphoproliferative and myeloproliferative disorders, may result in overproduction of lactic acid. Renal or hepatic failure may also lead to lactic acidosis.

Although L-lactate is usually the cause of lactic acidosis, D-lactate accumulation due to intestinal bacterial metabolism has been documented in patients with short bowel syndrome, bowel ischemia, or obstruction; it can be detected only if an appropriate bacterial enzyme is used in the lactic acid assay.[44] D-Lactic acidosis can also be expected with use of Ringer's lactate solution, which contains a racemic mixture of lactic acid stereoisomers. However, much of the D-lactate is lost in the urine because, unlike L-lactate, it is not reabsorbed by the renal tubules, and some of the D-lactate is metabolized in mammals.[45] The anion gap therefore may be relatively normal. Furthermore, although neurologic changes have been described in patients with D-lactic acidosis, there is reason to believe that these may be caused by other metabolites absorbed from the gastrointestinal tract rather than by the D-lactate itself.[45] D-Lactic acidosis may be treated by avoiding foods that contain lactobacillus (e.g., yogurt and sauerkraut), by decreasing dietary carbohydrates, and by administration of oral antibiotics.

Diabetic Ketoacidosis

Accumulation of acetoacetate, β-hydroxybutyrate, and acetone ("ketone bodies") is referred to as *ketoacidosis*. This disorder appears to require both increased mobilization of free fatty acids from lipid stores and their excessive conversion within hepatocytes to ketone bodies (Fig. 7-6). Triglycerides within fat are normally broken down by lipase into free fatty acids and glycerol. The activity of lipase is enhanced by low concentrations of insulin and increased concentrations of glucagon, catecholamines, and growth hormone. Free fatty acids released from adipocytes are taken up by the liver and linked to CoA to form acyl CoA. Acyl CoA is either transformed by esterification to triglycerides and lipoproteins or transferred into the mitochondria as a complex with carnitine and then metabolized to CO_2 and water in the Krebs cycle or converted to ketone bodies. The fraction of acyl CoA that is transferred into the mitochondrial matrix is increased by raised glucagon concentrations. This transport is mediated by the enzyme acylcarnitine transferase I (ACT I), which in turn is inhibited by the amount of malonyl CoA present. Normal inhibition of ACT I by malonyl CoA is indicated by the *curved arrow* in Figure 7-6. The concentration of malonyl CoA falls when glucagon is increased or insulin deficiency is present, and transport of the acyl fragment into the mitochondrial matrix is consequently increased. Increased

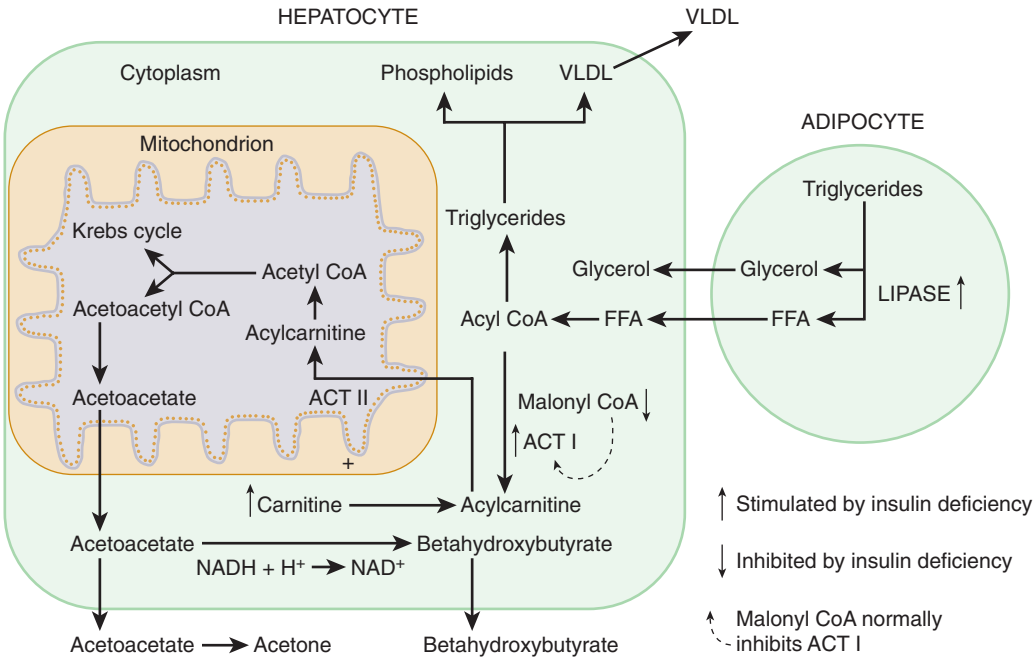

FIGURE 7-6 ■ Factors encouraging ketoacidosis. Some reactions are stimulated by insulin deficiency (*broad arrow up*), whereas others (*broad arrow down*) are inhibited by insulin deficiency and increased glucagon. The *open curved arrow* indicates that acylcarnitine transferase (ACT) I is normally inhibited by malonyl coenzyme A (CoA). FFA, free fatty acid; NAD^+, nicotinamide adenine dinucleotide (oxidized); NADH, nicotinamide adenine dinucleotide (reduced); VLDL, very-low-density lipoprotein.

glucagon also increases the amount of carnitine present, further accelerating movement of acyl CoA into the mitochondria. The acyl CoA complex entering the mitochondria is degraded successively to form acetyl CoA, which under normal circumstances is incorporated into the Krebs cycle and oxidatively metabolized to CO_2. In DKA, the quantities of acetyl CoA produced exceed the capacity of handling by the Krebs cycle and are converted to ketone bodies. Ketoacids are normally taken up and metabolized to CO_2 and water by muscle and kidney rather than by the liver, but this process may be reduced in DKA.[45]

An equilibrium normally exists between β-hydroxybutyrate, acetoacetate, and acetone. There is usually two to three times as much β-hydroxybutyrate as acetoacetate, but this ratio may be significantly increased if tissue P_{O_2} is reduced. Because standard tests for ketones measure acetone (which is not an acid) and acetoacetate but do not detect β-hydroxybutyrate (which is not a ketone), hypoxia may lead to an underestimate of the severity of "ketoacidosis." In normal subjects, the ratio of β-hydroxybutyrate to acetoacetate is 2 : 1. With DKA, this ratio increases to 2.5 : 1 to 3 : 1, and with poor tissue perfusion and associated lactic acidosis, it can exceed 8 : 1.[46] As insulin sensitivity and volume status improve with therapy, conversion of β-hydroxybutyrate to acetoacetate may increase the amount of ketone bodies detected, which may be misinterpreted as worsening of the ketoacidosis.[47]

Starvation often leads to ketoacidosis within 1 or 2 days, particularly after exercise,[48] but HCO_3^- levels seldom decline below 18 mEq/L. Starvation ketoacidosis is also attributed to decreased insulin concentrations, but these do not fall to levels as low as those encountered in DKA, and there is evidence that ketosis stimulates insulin secretion with normal pancreatic function. Alcoholics who binge and then abruptly stop drinking and eating may develop severe ketoacidosis,[49] which may be underestimated because of a disproportionate rise in β-hydroxybutyrate. They usually become dehydrated from vomiting prior to hospital admission and they may develop severe acidosis, frequently with concomitant lactic acidosis. Glucose concentrations are frequently low, and glucose (given with thiamine to avoid acute beriberi) stimulates insulin secretion and corrects the ketoacidosis. Insulin must generally be avoided in these patients. Supplementation with K^+, PO_4^{3-}, and Mg^{2+} is frequently required. Several congenital errors of metabolism that result in ketoacidosis have also been described. Ingestion of a high-fat diet, paraldehyde, or isopropyl alcohol may also result in a positive test for ketones.

Uremic Acidosis

Renal insufficiency does not usually produce an anion gap acidosis until the glomerular filtration rate falls below 20 mL/min and blood urea nitrogen and creatinine increase to more than 40 mg/dL (14.3 mmol/L) and 4 mg/dL (354 μmol/L), respectively. However, there is some variation in the filtration threshold at which anion gap acidosis occurs because of differences in diet and sites of renal damage.[46] The loss of nephrons is accompanied by a decrease in the ability to excrete both NH_4^+ and anions. Numerous anions normally kept low by normal renal clearance contribute to the anion gap, including sulfate, phosphate, and lactate. With acute renal failure, HCO_3^- concentrations characteristically decline by 1 to 2 mEq/day, but more rapid decreases occur in the presence of hypercatabolism. Hemodialysis becomes necessary when HCO_3^- level falls to less than 10 mEq/L. Milder forms of renal insufficiency may be accompanied by hyperchloremic acidosis (see later discussion).

Toxic Forms of Anion Gap Acidosis

As noted in Table 7-3, numerous substances can be converted to hydrogen ions and anions by metabolism, resulting in an anion gap acidosis. Central nervous system (CNS) stimulation by large ingestions of aspirin initially can cause hyperventilation in adults, but is soon followed by an anion gap metabolic acidosis. Salicylates are themselves anions, but most of the acidosis observed after an overdose is related to formation of organic acids, particularly lactic acid and ketones.[50] With very high aspirin concentrations, red cell HCO_3^-/Cl^- exchange is impaired and this may lead to tissue CO_2 retention, which may not be apparent in arterial blood owing to the previously mentioned ventilatory stimulation. The initial respiratory alkalosis contributes to lactate production. $NaHCO_3$ administration promotes both redistribution of salicylates from tissues to blood and urinary excretion by ionic trapping, but severe alkalosis and K^+ losses must be avoided; hemodialysis may be helpful. Glucose infusions are used to increase the cerebrospinal fluid (CSF) concentration of glucose, which is frequently decreased.[51]

Volatile alcohol ingestions are frequent causes of metabolic acidosis, most commonly methanol, isopropanol, or ethylene glycol. Methanol, which is converted to formic acid, and ethylene glycol, which is converted to oxalic acid and other toxic anions, are both metabolized by alcohol dehydrogenase and cause acidosis directly through their metabolites. Although isopropyl alcohol ingestion leads to CNS depression and urinary ketones (acetone), it is not metabolized to an organic acid, and acidosis is seen only if vascular collapse and lactic academia occur. Ethanol (to a serum concentration of 100–150 mg/L), or preferably fomepizole, should be used to inhibit the formation of toxic metabolites from methanol and ethylene glycol, and hemodialysis may be used to clear these metabolites.

Alcohols and ethylene glycol should be suspected if serum osmolality by freezing point depression exceeds by more than 20 mmol/L that calculated from laboratory values of Na^+, glucose, and urea by the following equation:

$$\text{Serum osmolality} = 2 \times [Na^+] + \text{BUN}/2.8 + \text{glucose}/18 \quad (7)$$

where sodium is in mEq/L and blood urea nitrogen (BUN) and glucose are in milligrams per deciliter. Vapor pressure measurements of osmolality do not detect the presence of volatile alcohols. The "osmolar gap" may

also be increased in "pseudohyponatremia" (due to the presence of excess lipid or protein in the plasma) and after administration of mannitol or radiopaque dyes, and these factors also need to be assessed.

Hyperchloremic Acidosis

Metabolic acidosis in the absence of an elevated anion gap is usually associated with hyperchloremia. Hyperchloremic acidosis may be observed in a variety of renal and gastrointestinal disorders, the latter being more common.

Renal Tubular Acidosis

Metabolic acidosis arises from a variety of renal tubular disorders. Disorders of renal tubular function that result in hyperchloremic acidosis can be divided into four categories that can be differentiated by their clinical and laboratory characteristics.[52] Particular defects in various membrane transport proteins that account precisely for certain inherited forms of renal tubular acidosis (RTA) have been identified,[53–56] but the classic definitions still remain the most useful clinically, and these are outlined here.

Type 1 Renal Tubular Acidosis. Type 1, or "classic," RTA involves defects in distal tubular acid secretion. Only distal nephrons can produce an acidic urine, so that with injury or dysfunction, it is impossible for urine pH to be lowered below 5.3, regardless of how acidotic the patient. Serum HCO_3^- can be below 10 mEq/L. Urinary HCO_3^- excretion is usually low, because most HCO_3^- reabsorption occurs proximally. HCO_3^- infusion therefore can be used to prove that the defect is distal (type 1 RTA) rather than proximal (type 2 RTA): the fraction of filtered HCO_3^- lost in urine remains low in type 1 but is high in type 2 RTA. Another defect observed with type 1 RTA is an inability to generate high P_{CO_2} in the urine after infusion of HCO_3^-. Normal subjects produce urine with P_{CO_2} values that exceed those in the plasma by more than 30 to 100 mm Hg. This phenomenon is related to distal tubular H^+ transport to form H_2CO_3. The subsequent generation CO_2 from HCO_3^- in the distal nephron is relatively slow because there is little carbonic anhydrase on the luminal surface. Dissipation of the CO_2 from urine beyond the collecting ducts is inefficient because of the small surface-to-volume ratio of the lower urinary tract. Because patients are unable to secrete H^+ ions in the distal tubules, their urinary P_{CO_2} remains less than 40 mm Hg.

As indicated in Table 7-4, many disorders are associated with distal RTA. It can be caused by a wide variety of mutations, most of which affect carbonic anhydrase II, anion exchanger, or the proton pump (H^+-ATPase) in intercalated cells of the renal cortical collecting duct.[57] Chronic acidosis leads to osteopenia with Ca^{2+}, Mg^{2+}, and PO_4^{2-} loss in the urine. Precipitation of Ca^{2+} and PO_4^{2-} is normally inhibited by tubular secretion of citrate. As citrate secretion tends to be reduced, this and an alkaline urine with calciuria and hypocitraturia appears to be responsible for nephrolithiasis and nephrocalcinosis that characterize distal RTA.[58] K^+ losses tend to be increased because of increased exchange of K^+ for Na^+ in the distal tubule. Concentration defects are common.

In absence of therapy, acidosis progresses relentlessly in distal RTA because fixed acids cannot be excreted

TABLE 7-4. Causes of Hyperchloremic Acidosis

RENAL TUBULAR ACIDOSIS

Type 1 (Distal, Classic), Hypokalemic

- Congenital defects without systemic disease (anion exchanger, AE1 deficient) or with systemic disease (e.g., Ehlers-Danlos, sickle cell anemia)
- Hyperglobulinemia (e.g., systemic lupus erythematosus, idiopathic pulmonary fibrosis, Sjögren's syndrome, thyroiditis, chronic active hepatitis, biliary cirrhosis, vasculitis)
- Drug toxicity (e.g., amphotericin B, toluene, analgesics, lithium)
- Nephrocalcinosis (e.g., primary hyperparathyroidism, vitamin D intoxication, hyperoxaluria, Fabry's disease, Wilson's disease)
- Tubular and interstitial renal disease (e.g., pyelonephritis and obstructive renal disease, renal transplant rejection)

Type 2 (Proximal), Hypokalemic

- Congenital disorders: isolated or associated with mental retardation, ocular abnormalities
- Selective (acetazolamide, sulfonamides) or associated with loss of glucose, phosphate, amino acids, low-molecular-weight proteins, lysozyme, light chains, uric acid
- Genetic (e.g., cystinosis, Wilson's disease)
- Dysproteinemias (e.g., multiple myeloma, monoclonal gammopathy)
- Drug or chemical toxicity (e.g., outdated tetracycline, heavy metals, ifosfamide)
- Secondary hyperparathyroidism with hypocalcemia (e.g., vitamin D deficiency or resistance)
- Renal interstitial disease (e.g., medullary cystic disease, Sjögren's syndrome, renal transplant)

Type 3

- Type I and II, carbonic anhydrase II deficiency

Type 4, Hyperkalemic

- Mineralocorticoid deficiency: Addison's disease, tuberculosis, metastatic carcinoma, autoimmune, adrenal hemorrhage, acquired immunodeficiency syndrome (AIDS), critically ill patients, drugs (ketoconazole, phenytoin, rifampin)
- Hyporeninemic states: diabetes mellitus, nephritis, lupus, AIDS
- Mineralocorticoid resistance: pseudohypoaldosteronism (congenital, spironolactone)
- Medications: potassium-sparing diuretics (amiloride, triamterene), angiotensin-converting enzyme inhibitors, trimethoprim, pentamidine, nonsteroidal anti-inflammatory drugs, cyclosporine A, β-adrenergic inhibitors, α-adrenergic agonists, heparin, digitalis overdose, lithium, insulin antagonists (diazoxide, somatostatin), succinylcholine

NONRENAL HYPERCHLOREMIC ACIDOSIS

- Diarrhea
- Pancreatic drainage
- Ureterosigmoidostomy
- Cholestyramine (diarrhea), NH_4Cl and hyperalimentation with amino acid infusions, $CaCl_2$
- Toluene exposure (hippurate production)
- Loss of ketones that could have been converted to bicarbonate

at their rate of production. Hypokalemia may be particularly severe with consequent muscle weakness or even paralysis. Treatment with 1 mEq/kg $NaHCO_3$ daily (roughly the rate of bodily fixed acid generation) is usually sufficient in adults; more is required in children. Bone demineralization is reduced by this therapy, and K^+ losses are minimized.

Type 2 Renal Tubular Acidosis. In type 2 or proximal RTA, HCO_3^- reabsorption is impaired because of a defect in the proximal ion exchange of H^+ for Na^+, which is mediated by an apical membrane Na^+/H^+ antiporter. Normally, HCO_3^- is completely removed from glomerular filtrate until serum HCO_3^- concentrations exceed 22 to 24 mEq/L, and maximal reabsorption rates are not observed until concentrations are about 28 mEq/L. In proximal RTA, maximal reabsorption values may top out at a serum concentration of about 18 mEq/L. The distal tubules cannot absorb more than 15% to 20% of the filtered load of HCO_3^-, so HCO_3^- is lost in the urine, causing the urine pH to rise even when the patient is acidotic. When serum HCO_3^- is normalized to 25 mmol/L by HCO_3^- infusion, more than 10% of the filtered HCO_3^- is lost in the urine in type 2 RTA, compared with less than 5% in normal subjects and those with type 1 RTA. If serum HCO_3^- level falls below the HCO_3^- recovery threshold, then urinary HCO_3^- loss ceases, urine pH falls, and the acidosis does not progress. A typical patient will have a stable serum HCO_3^- value in the range of 12 to 20 mEq/L. It is common to find that patients with proximal RTA do maximally acidify their urine, but only in the presence of a significant metabolic acidosis. In some patients, it may be necessary to decrease serum HCO_3^- to less than their usual level with NH_4Cl administration before maximal urine acidification is observed.

Proximal RTA may be an isolated tubular lesion, but it is more frequently associated with other proximal tubular defects that lead to loss of glucose, phosphate, amino acids, and low-molecular-weight proteins (Fanconi's syndrome). Nephrolithiasis and nephrocalcinosis are not characteristic, but patients are susceptible to osteomalacia and rickets if the acidification defect is associated with calcium and phosphate loss. They require much more $NaHCO_3$ (10–15 mEq/kg/day) to correct their acidosis than do patients with distal RTA. Sodium citrate is better tolerated than $NaHCO_3$, and thiazides can decrease administered alkali needs. Large amounts of $NaHCO_3$ exacerbates losses of K^+, and supplements and/or potassium-sparing diuretics are commonly required. Serum phosphate may be reduced if there is a defect in is reabsorption, and alkaline phosphatase may be increased. Some illnesses associated with proximal RTA are indicated in Table 7-4.

Type 3 Renal Tubular Acidosis. A true type 3 RTA includes features of both proximal and distal forms, but it does not have great clinical significance. The largest patient group in this category, rarely seen nowadays, was infants or young children with hereditary distal RTA that manifested some proximal bicarbonate loss transiently. A similar combination of defects is also observed in a small number of patients with an inherited form of carbonic anhydrase II deficiency.[59]

Type 4 Renal Tubular Acidosis. Type 4 RTA is caused by either decreased aldosterone production or tubular hyporesponsiveness to the hormone. Because aldosterone stimulates distal secretion of H^+ and K^+, deficiency results in hyperchloremic hyperkalemic acidosis, whereas other forms of RTA are usually associated with hypokalemia. Hyperkalemia suppresses proximal NH_3 production. Consequently, even though urine pH may be low, the amount of acid lost may be insufficient to avoid acidosis. A wide variety of disorders lead to low aldosterone production (see Table 7-4), but decreased renin secretion in older patients with diabetic renal disease is common. Decreased aldosterone production occurs in critically ill patients with sepsis and cardiogenic shock. Potassium-sparing diuretics, angiotensin-converting enzyme inhibitors, intravenous solutions, and heparin (which can inhibit aldosterone secretion) may also cause hyperkalemia and type 4 RTA. Hyperkalemia is associated with a high incidence of arrhythmias (25%), hypertension, and weakness.

Most K^+ found in the urine is secreted into the cortical collecting duct, and detection of decreased secretion is facilitated by calculating the transtubular potassium gradient (TTKG):

$$\text{TTKG} = \left\{[K^+]_{\text{urine}} / [K^+]_{\text{plasma}}\right\} \Big/ \left\{[\text{Osm}]_{\text{urine}} / [\text{Osm}]_{\text{plasma}}\right\} \qquad (8)$$

where [Osm] designates osmolality. This ratio corrects the urine–to–plasma potassium ratio for urine concentration, which occurs more distally in the nephron. The TTKG should be greater than 8 in patients with hyperkalemia and should increase after administration of mineralocorticoids in patients with aldosterone deficiency. Failure of TTKG to increase after mineralocorticoids suggests loss of tubular sensitivity.

Acidosis of Progressive Renal Failure

Hyperchoremic RTA without hyerkalemia is characteristic of many renal diseases associated with loss of renal tissue and a decrease in the glomerular filtration rate. Retention of acid in these patients is attributable to a decrease in the ability of the kidneys to excrete NH_4^+. Although the decline in serum bicarbonate is relatively modest, it is generally recommended that serum HCO_3^- concentrations should be maintained above 22 mEq/L with modest $NaHCO_3$ supplementation to minimize bone reabsorption, insulin resistance, and protein catabolism.[60]

Gastrointestinal Causes of Hyperchloremic Acidosis

Diarrhea is a more common cause of hyperchloremic acidosis than are renal tubular disorders. Cl^- is selectively absorbed by the bowel in exchange for HCO_3^-, more so in the colon than proximally. Normally, stool fluid volume and Cl^- losses are modest, but significant HCO_3^- loss can occur in diarrhea. Lactic acid and other organic acids are produced by bowel microorganisms, and these reduce the actual HCO_3^- stool concentrations.[61] However, these organic anions are not readily absorbed from the

colon with fast transit, and the net result is that HCO_3^- is lost from the body, whereas serum Cl^- is increased without a rise in the anion gap. Absorption of NH_4^+ generated by gut bacteria contributes to the acidosis. Passage of urine into the bowel after ureterosigmoidostomy or ureteroileostomy can produce hyperchloremic acidosis.

Each liter of diarrheal fluid can result in the loss of 200 mEq of HCO_3^-. Pancreatic and biliary fluid contain 50 to 100 mEq of HCO_3^-/L, and severe hyperchloremic acidosis occurs after losses of these fluids. Cholestyramine contains an anion-exchange resin that can generate hyperchloremic acidosis by releasing Cl^- in exchange for HCO_3^-. K^+ losses in diarrheal stool (30–60 mEq K^+/L) in exchange for Na^+ can be severe. Furthermore, extracellular volume depletion promotes aldosterone secretion, which in turn enhances urinary K^+ loss. Chronic acidosis increases renal NH_4^+ secretion, distinguishing it from RTA, which can be detected by measuring the urine net charge (see later).

Miscellaneous Causes of Hyperchloremic Acidosis

Respiratory alkalosis is normally compensated by a decrease in proximal HCO_3^- reabsorption. Correction of respiratory alkalosis may transiently produce a hyperchloremic acidosis, as can some hyperalimentation fluids, NH_4Cl, or $CaCl_2$. Toluene, inhaled by glue sniffers, is converted to benzoic acid and hippurate, which are rapidly renally excreted with cations, resulting in hyperchloremic acidosis. Some intravenous solutions of synthetic amino acids that may be titrated with excess HCl (hydrochloric acid) and saline infusions lower HCO_3^- and increase Cl^- concentrations (see later discussion).

Urine Net Charge and Osmolar Gap

Measurement of the urine net charge (UNC), or urine anion gap, can be used to help distinguish between hyperchloremic acidosis due to diarrhea or to RTA. Unlike serum, the urine seldom contains significant HCO_3^- in acidotic patients, but K^+ and NH_4^+ concentrations can be considerable. The UNC is calculated from the following equation:

$$UNC = Na^+ + K^+ - Cl^- \quad (9)$$

If urinary NH_4^+ is high, then urinary Cl^- concentration will exceed that of Na^+ plus K^+, and the UNC will be negative by 20 to 50 mEq/L. UNC provides an estimate of urine NH_4^+ and is negative with hyperchloremic acidosis caused by diarrhea because renal NH_4^+ production is increased in response to the metabolic acidosis. In contrast, UNC is more positive in patients with RTA, with impaired production and/or excretion of NH_4^+. The presence of ketones and other anions can also cause UNC to be negative, and direct NH_4^+ measurements provide a more reliable index of renal tubular acid metabolism.[62] NH_4^+ concentrations have also been estimated by calculating the urine osmolar gap, which represents the difference between observed and calculated urine osmolarity.

Dilutional Acidosis

A modest acidemia is observed when water dilutes blood after being pulled from cells by increased extracellular solute concentrations such as glucose.[63] It is generally attributed to the fact that plasma HCO_3^- falls to a greater degree than does P_{CO_2}, which is regulated by the brain.[64] Saline infusions may have a similar effect; however, the dilution that occurs with inappropriate antidiuretic hormone secretion is not usually accompanied by acidosis.[65]

Clinical Manifestations

Perhaps the most obvious sign of metabolic acidosis is the respiratory response, which consists of slow but deep breathing known as Kussmaul's respiration. It is particularly effective because the dead-space contribution to ventilation is minimized. Patients with metabolic acidosis are often asymptomatic and their hyperventilation may not be clinically obvious. With more severe acidosis, dyspnea may be troubling and patients complain of headache, nausea, and vomiting. This may be followed by confusion, stupor, and even coma, which are particularly likely to be present in respiratory acidosis. Acidosis may reduce the myocardial catecholamine responsiveness and induce arteriolar vasodilation, but these effects are largely blunted by increased catecholamine and cortisol secretion.[66] Venoconstriction is characteristic of acidosis[67] and may shift blood into the central volume and trigger pulmonary edema.[68] Arrhythmias, including ventricular fibrillation, can be fatal.

Hyperkalemia (despite total body K^+ depletion) is sometimes observed with metabolic acidosis. It is often associated with DKA, but this is related in large part to the plasma hyperosmolarity that causes water and K^+, the main intracellular cation, to exit cells. Infusions of organic acids are much less likely to cause hyperkalemia than are infusions of inorganic acids,[69] and the conventional wisdom that serum K^+ increases in a predictable fashion with metabolic acidosis[70] has not proved to be very useful. Nor is hyperkalemia found in most patients with types 1, 2, or 3 RTA or with diarrhea because of the simultaneous losses of both HCO_3^- and K^+ that occur with these disorders.

Chronic retention of more than 10 mEq H^+/day may be tolerated over a period of years in patients with chronic renal disease because of buffering by bone alkaline constituents (calcium, phosphate, and carbonate).[71] When acid production exceeds the release of bone buffers, a fall in HCO_3^- is inevitable. Recent evidence suggests that the acid load of the typical protein-rich Western diet may not be fully excreted by the kidneys and the very slight failure to eliminate the entirety must be handled by bone buffering. Over many decades of life, this cumulative bone buffering may help to explain the high incidence of osteopenia and osteoporosis in the elderly.

Therapy

Treatment of metabolic acidosis should focus primarily on correcting the metabolic disorder responsible for its emergence and the hemodynamic, oxygenation, and electrolyte derangements that ensue, rather than the academia itself. For example, insulin and volume replacement are the mainstays of diabetic therapy, dialysis for uremic acidosis, and reversal of shock, local ischemia, and hypoxemia for lactic acidosis. If another illness is responsible for lactic acidosis (see Table 7-3), then appropriate therapy must be selected.[1]

$NaHCO_3$ administration or other alkaline agents for metabolic acidosis is clearly indicated in patients with chronic metabolic acidosis, such as those with significant hyperchloremic acidosis (e.g., RTA) to prevent bone and muscle catabolism, relieve exertional dyspnea, and promote growth in children. In acute severe metabolic acidosis (especially the endogenous anion gap acidoses), it is becoming clear that HCO_3^- administration is not always helpful or effective. However, alkalinizing agents are still indicated for associated severe hyperkalemia or to enhance excretion of acid metabolites of certain toxins.[72] In severe DKA despite arterial pHs as low as 6.8, bicarbonate administration does not alter rates of glucose correction or ketoacid clearance when compared with equivalent sodium administration given as NaCl. Equivalent evidence in sespis, severe hypoxemia, and cardiogenic shock (again in randomized saline-controlled studies described previously for DKA) found no obvious benefits and often slightly worse parameters in the bicarbonate-treated patients (for review of these studies, see reference 72). A number of possible negative consequences of attempted alkalinization in these conditions have been articulated. These include a shift of the oxygen-hemoglobin dissociation curve to the left that may impair O_2 delivery in already hypoxic tissues, greater lactic acid production[73] or suppression of hepatic lactate clearance with an increase in pH, and nonmetabolic generation of CO_2 from HCO_3^- with paradoxical intracellular acidosis.[74] Increases in P_{CO_2} associated with $NaHCO_3$ may not be observed in the arterial blood even though mixed venous P_{CO_2} is significantly increased.[75] Excessively rapid infusions of $NaHCO_3$ may result in a paradoxical diminution of CSF and brain interstial pH if they reduce the drive to breathe.[76] Equilibration of HCO_3^- with the CSF is much slower than the corresponding equilibration of CO_2, and the rise in P_{CO_2} caused by hypoventilation tends to make the CSF more acid before the HCO_3^- can diffuse into this compartment. Because the usual alkaline solutions administered are extremely hypertonic, there may be an abrupt fall in serum K^+ as potassium is returned to the cellular compartment. $NaHCO_3$ infusions should be kept as low as possible (usually < 200 mmol) to avoid volume overload, which may alternatively be minimized by hemodialysis against a $NaHCO_3$ solution. As the underlying disorders improve, both ketone bodies and lactate may be metabolized to HCO_3^-, resulting in the development of post-therapeutic alkalosis. Although it is often claimed that when the pH is much lower than 7.2, $NaHCO_3$ infusions may prove to be lifesaving by enhancing cardiac contractility and response to pressors, the supporting data are rather unconvincing. As mentioned previously in studies comparing equivalent NaCl and $NaHCO_3^-$, any brief benefits noted with bicarbonate in blood pressure may simply be the result of volume expansion by any sodium-containing fluid. Regardless of the cause of acidemia, if base administration is considered necessary, $NaHCO_3$ is preferable to lactate solutions, because lactate is completely ionized at any pH still compatible with life and it does not provide buffering until it is converted to HCO_3^- by normal hepatic function.

As a first estimate of the amount required to raise serum HCO_3^- by a given number of milliequivalents per liter, it is common practice to assume that HCO_3^- enters a space 40% or 50% of the total body weight. Not infrequently, much more is required to repair the deficit. However, no attempt should be made to increase the pH to more than 7.2 with such infusions, and it is prudent to raise the HCO_3^- concentration no more than halfway toward normal during the first day. Determinations of arterial blood P_{O_2}, P_{CO_2}, HCO_3^-, and pH must be repeated at frequent intervals to monitor the response to therapy.

However, given the failure of controlled trials to show any benefit with bicarbonate administration in the most severe endogenous anion gap metabolic acidoses and the negative observations alluded to earlier, it may be better, although difficult, to refrain from using alkalinizing fluids at all in these circumstances. In fact, animal organ and cellular studies reveal the surprising and counterintuitive findings that recovery from ischemia or O_2 deprivation is clearly enhanced when the perfusing media is acidic and recovery is worse under alkalotic conditions, a phenomenon termed *the pH paradox*.[72] Many explanations have been offered, the most intriguing being that acidosis may blunt the activity of many enzymes and proteins responsible for much of the associated excessively activated oxidative and proinflammatory pathways in hypoxic and septic injuries that may perpetuate ongoing injury. Another potential argument against aggressive attempts to reduce lactic acidosis, independent of treating the initial cause(s) is the failure of dichloroacetate, a compound that stimulates PDH activity and pyruvate entry into the mitochondria, to alter outcomes in patients with severe lactic acidosis.[77] By limiting lactate formation, the drug may deny cells a preferred fuel under stress as proposed by Brooks and colleagues.[39]

METABOLIC ALKALOSIS

For both diagnostic and therapeutic reasons, it is helpful to divide the causes of metabolic alkalosis into those associated with a decrease in the extracellular volume (chloride responsive) and those associated with a normal or increased extracellular volume (chloride resistant) (Table 7-5).

TABLE 7-5. Causes of Metabolic Alkalosis

Loss of H^+ from the body

CHLORIDE-RESPONSIVE WITH URINE Cl^- < 20 mEq/L

Gastrointestinal losses of chloride: stomach (vomiting, aspiration, villous adenomas, congenital chloride-wasting diarrhea)

Renal losses of chloride: loop and thiazide diuretics, posthypercapnic

Sweat losses of chloride: cystic fibrosis

Hyperventilation in chronic respiratory acidosis

CHLORIDE-RESISTANT WITH URINE Cl^- > 20 mEq/L AND HYPERTENSION

Hyperaldosteronism (primary or secondary), Cushing syndrome, cortisol 11-beta-ketoreductase deficiency, licorice, etc.

Liddle's syndrome: increased epithelial sodium channel (ENaC) in collecting duct.

CHLORIDE-RESISTANT WITH URINE Cl^- > 20 mEq/L, HYPOTENSION OR NORMOTENSION

Bartter's syndrome: impaired reabsorption of sodium ions and chloride ions in the thick ascending loop of Henle (variants)

Gitelman's syndrome: impaired thiazide-sensitive sodium/chloride transporter (NCCT) in the distal convoluted tubule occurs

EXCESSIVE INTAKE OF HCO_3^-

Milk-alkali syndrome

Administration of poorly absorbed anions (e.g., penicillin)

Bicarbonate dialysis in end-stage renal disease

Recovery from ketoacidosis or lactic acidosis after bicarbonate administration

Massive blood transfusions (citrate)

EXTRACELLULAR FLUID VOLUME CONTRACTION

Causes

Chloride Responsive Alkalosis

Gastrointestinal Losses. As indicated previously, gastrointestinal tract acid losses generate an alkalosis that is initially associated with increased renal Na^+ excretion. ECF volume depletion causes the glomerular filtration rate to fall and is associated with increased aldosterone secretion. Each of these effects enhances HCO_3^- reabsorption, and alkalosis persists even after all initiating factors (e.g., protracted vomiting and continuous nasogastric suction) have abated. In these patients, Cl^- is avidly reabsorbed from the tubules and urine concentrations remain lower than 10 mEq/L. Correction of the metabolic alkalosis depends on replacement of Cl^- losses, principally given as saline. Although diarrhea usually generates a hyperchloremic acidosis (see earlier discussion), alkalosis may rarely be seen with Cl^--HCO_3^- exchange across the ileal mucosa[78] due to villous adenomas of the colon.

Renal Losses. Diuretics are the most common cause for excessive renal losses of ECF. When Na^+ delivery of to the distal nephron persists despite extracellular volume depletion (e.g., after diuretic therapy), H^+ secretion by this segment is enhanced. In these conditions, Cl^- concentrations in the urine may be appreciable. Both loop diuretics (furosemide, bumetanide, ethacrynic acid) and thiazides can promote H^+ and K^+ secretion from the more distal segments of the nephron. This frequently results in severe hypokalemic alkalosis.

Losses in Sweat. Metabolic alkalosis has also been reported in patients with cystic fibrosis, who tend to lose proportionately more Cl^- than HCO_3^- in their sweat.

Alkalosis is not infrequently observed in mechanically ventilated patients treated for chronic hypercapnia. Care must be taken to avoid abrupt increases in ventilation, which may result in life-threatening metabolic alkalosis. The arterial pH and plasma levels of HCO_3^- of these persons may remain high and inhibit spontaneous ventilation unless Cl^- losses are restored, generally in the form of KCl. Acetazolamide may also be helpful because it inhibits renal tubular HCO_3^- reabsorption, but its use requires careful monitoring in those not mechanically ventilated with limited lung function (forced expiratory volume in 1 second [FEV_1] < 1 L) and avoided in those with renal or hepatic insufficiency.

Administration of sodium salts of penicillin or other anions that cannot be reabsorbed by the renal tubules may stimulate acid and K^+ losses in patients who are volume depleted.

Chloride-Resistant Alkalosis

Metabolic alkalosis may also be associated with either normal or increased ECF volume, particularly in the presence of excessive aldosterone secretion. Mineralocorticoids act to increase both H^+ and K^+ secretion and Na^+ retention by the distal nephron. This results in a hypokalemic alkalosis that is associated with a modest ECF volume expansion. Na^+ and Cl^- retention appears to be limited by ECF expansion, and output and intake of Na^+ become equal. Unlike situations in which the ECF is decreased, Cl^- is lost in the urine with metabolic alkalosis that is caused by excessive mineralocorticoid secretion (urine Cl^- > 20 mEq/L). Maintenance of the metabolic alkalosis is a result of persistent excess mineralocorticoid secretion as well as hypokalemia.

Any alteration in the renin-angiotensin-aldosterone axis that promotes aldosterone secretion also causes this form of metabolic alkalosis (see Table 7-5) by its stimulatory effects on two different populations of cells in the distal nephron.[79] Distal tubular exchange of K^+ for Na^+ appears to be confined to principal cells, located in the cortical collecting duct. Because more Cl^- ions than cations are left behind, a negative lumen potential is established that facilitates H^+ secretion by the more distally positioned alpha intercalated cells. Patients with edema due to liver disease, nephrotic syndrome, or congestive heart failure may secrete excessive aldosterone because their effective arterial blood volume is reduced, even though their total ECF volume is increased. The development of hypokalemic alkalosis is particularly likely to occur when they receive diuretics.

The pathogenesis of several forms of congenital hypokalemic, hypochloremic metabolic alkalosis with hyperaldosteronism (Bartter's syndrome and Gitelman's syndrome) has been traced to a variety of abnormalities in renal tubular transporters.[80]

Excessive Intake of HCO_3^-

Although the kidneys normally can excrete large quantities of HCO_3^-, metabolic alkalosis may occasionally be generated by excessive intake of HCO_3^- or other anions that are metabolized to HCO_3^-, especially in patients with renal insufficiency. For example, metabolic alkalosis may be observed in patients who ingest extremely large amounts of HCO_3^- and milk (milk-alkali syndrome), after fasting (due to conversion of ketones to HCO_3^-),[81] and after transfusions of large amounts of blood (conversion of citrate to HCO_3^-).[82] In the absence of volume depletion or renal disease, alkalosis due to increased HCO_3^- intake rapidly resolves once intake is restricted.

Extracellular Fluid Contraction

Water loss from plasma may induce a modest alkalemia that is sometimes referred to as a "contraction" alkalosis and is related to the relatively greater increase of HCO_3^-, compared with P_{CO_2}. It would probably be more appropriate to designate this as a *concentration alkalosis* to distinguish it from the alkalosis of contraction that is caused by ECF fluid depletion, which promotes renal acid excretion and alkalemia (see earlier discussion).[65,83]

Clinical Manifestations

Metabolic alkalosis is frequently overlooked and often remains untreated even after discovery. Nevertheless, it may be associated with significant mortality.[84,85] Alkalosis tends to increase the affinity of hemoglobin for oxygen, thereby reducing oxygen delivery to the tissues. It also decreases ventilation by suppressing the carotid body and may constrict the peripheral vasculature, further limiting oxygen supply to tissues.

Neuromuscular hyperirritability may be observed in alkalosis and has been attributed in part to increased calcium binding to albumin. Twitching and tetany may be preceded by Chvostek's and Trousseau's signs, and seizures can ensue. Metabolic alkalosis is usually associated with hypokalemia, which may be responsible for both supraventricular and ventricular arrhythmias.[85] Alkalosis promotes intracellular movement of K^+ and may also cause an increase in the anion gap because of removal of H^+ from albumin and increased generation of lactate.

Therapy

Treatment of metabolic alkalosis depends on the status of the ECF volume. Patients with ECF volume loss can be distinguished from those with excess volume on the basis of urine Cl^-, which is usually lower than 10 mEq/L in the former and higher than 20 mEq/L in the latter setting. For patients who have sustained severe volume losses, fluids that contain Na^+, Cl^-, K^+, and Mg^{2+} are frequently indicated.

Fluid administration to edematous patients with alkalosis is usually inappropriate. Spironolactone is useful in the presence of excessive mineralocorticoid secretion. The carbonic anhydrase inhibitor acetazolamide may be helpful and in patients with posthypercapnic alkalosis, although it may increase loss of K^+. Although NH_4Cl and arginine hydrochloride may be used to treat alkalosis, their use must be avoided in patients with severe liver disease (as for acetazolamide) because they may precipitate hepatic coma by decreasing urea synthesis and/or elevating NH_3 concentrations. These agents may also induce hyperkalemia and increase urea levels in patients with azotemia. Infusions of HCl (at a concentration of 100–200 mEq/L) may be safer in patients with liver and kidney disease, but these infusions require central access confirmed radiologically by location of the catheter tip in the superior vena cava to minimize the likelihood of tissue necrosis and hemolysis caused by the acid infusion. Alternatively, intubation and intentional hypoventilation to increase the P_{CO_2}, thereby reducing arterial pH, may be employed. Severe metabolic alkalosis can also be treated by hemodialysis. Histamine H_2 receptor antagonists or gastric proton pump (H^+/K^+-ATPase) inhibitors are useful in patients receiving nasogastric suction.

RESPIRATORY ACIDOSIS

General Considerations

Respiratory acidosis is a frequently frustrating problem for patients with respiratory insufficiency. P_{CO_2} is normally kept within narrow limits by the respiratory center within the CNS. Chemoreceptors that respond to changes in P_{CO_2} are present in the medulla, close to the floor of the fourth ventricle, and in the carotid bodies. Both sites are stimulated by pH changes associated with alterations in P_{CO_2}. Normally, arterial P_{CO_2} is controlled primarily by the central chemoreceptors. However, they may be suppressed by chronic hypoxia and hypercapnia; mostly in patients with severe COPD. When this occurs, ventilation is maintained by the carotid bodies responding to alterations in P_{O_2} and pH. If P_{O_2} is raised excessively, carotid body output may be suppressed, leading to progressive hypercapnia and narcosis. Acute increases in P_{CO_2} are buffered by non-HCO_3^- buffers to form HCO_3^-, but HCO_3^- concentrations seldom exceed 30 mEq/L during the first 24 hours of hypercapnia. Increases in P_{CO_2} result in an intracellular acidosis within the renal tubular cells that favors acid excretion, and over the next few days, acid excretion is accelerated by a rise in NH_4^+ formation.

Causes

Any process interfering with ventilation can lead to respiratory acidosis (Table 7-6; see also Chapter 73). COPD is the most frequent cause of this problem, related primarily to mechanical conditions that decrease alveolar ventilation. Interstitial lung disease is less likely to increase P_{CO_2} values unless it is severe. Extensive infiltrative processes (including pneumonias and all forms of pulmonary edema) and large pleural effusions can

TABLE 7-6. Causes of Respiratory Acidosis

CENTRAL NERVOUS SYSTEM DEPRESSION
Drugs: opiates, sedatives, anesthetics
Oxygen therapy in chronic obstructive pulmonary disease
Obesity-hypoventilation syndrome
Central nervous system disorders
NEUROMUSCULAR DISORDERS
Neurologic: multiple sclerosis, poliomyelitis, phrenic nerve injuries, high cord lesions, Guillain-Barré syndrome, botulism, tetanus
End plate: myasthenia gravis, succinylcholine chloride, curare, aminoglycosides, organophosphorus
Muscle: hypokalemia, hypophosphatemia, muscular dystrophy
AIRWAY OBSTRUCTION
Chronic obstructive pulmonary disease
Acute aspiration, laryngospasm
CHEST WALL RESTRICTION
Pleural: effusions, empyema, pneumothorax, fibrothorax
Chest wall: kyphoscoliosis, scleroderma, ankylosing spondylitis, extreme obesity
SEVERE PULMONARY RESTRICTIVE DISORDERS
Pulmonary fibrosis
Parenchymal infiltration: pneumonia, edema
ABNORMALITIES IN BLOOD CO_2 TRANSPORT
Decreased perfusion: heart failure, cardiac arrest with cardiopulmonary resuscitation, extensive pulmonary embolism
Severe anemia
Carbonic anhydrase inhibition—high-dose acetazolamide
Red cell anion exchange: high-dose loop diuretics, salicylates, nonsteroidal anti-inflammatory drugs

decrease alveolar ventilation. With significant acute pulmonary artery embolic obstruction, wasted ventilation may increase suddenly and explain sudden increases in ventilation or hypercapnia if ventilation cannot be increased. In such situations, dead-space ventilation may be measured directly by sampling both arterial blood and mixed expired gases. A paralyzed diaphragm or extensive rib fractures that lead to a unilateral flail chest can produce a paradoxical mode of ventilation. When inhalation occurs in the unaffected lung, air is forced out of the contralateral lung and some of this exhaled air is inhaled by the normal lung; the opposite sequence of events occurs when the unaffected lung exhales. This pattern of ventilation is referred to as "pendelluft" or "pendulum breathing"; it can result in rebreathing with respiratory acidosis.

Hypoventilation is the most serious complication of a wide variety of neuromuscular disorders (see Table 7-6). The central respiratory centers may be depressed acutely or chronically by narcotics or by any process that injures the brain stem, including chronic hypoxemia and hypercapnia. A complex disturbance of the respiratory center may be encountered in patients with the obesity-hypoventilation syndrome. Apneic episodes during sleep are common in these persons and are related to airway obstruction or to a central failure to initiate ventilation, or both.

Rarely, if cardiac output is low, if anemia is severe, and/or if certain drugs that interfere with the normal high efficiency of red cell CO_2 transport and exchange are used (see Table 7-6), CO_2 retention in the tissues may develop and yet not be reflected in the arterial P_{CO_2}.[86] In fact, as CO_2 rises in the vicinity of the central chemoreceptors, ventilation may be stimulated sufficiently to cause a paradoxical arterial hypocapnia that can be mistakenly taken as evidence of a primary respiratory alkalosis. If some measure of P_{CO_2} is taken in the venous circulation (mixed venous P_{CO_2}), one will find an elevated P_{CO_2} and lower pH, revealing the true state of CO_2 homeostasis.[87]

Clinical Manifestations

If hypoventilation is caused by neuromuscular or mechanical problems, the patient will be dyspneic and tachypneic. In contrast, if the respiratory center is impaired, ventilation may be reduced without any sense of dyspnea.

The physiologic and clinical consequences of respiratory acidosis tend to be more serious in acute than in chronic states. Elevations in P_{CO_2} cause systemic vasodilation that is particularly evident in the cerebral circulation. Cerebral blood flow and intracerebral pressures increase and may lead to a picture of pseudotumor cerebri with papilledema, retinal venous distention, and retinal hemorrhages. The patient may complain of dyspnea and manifest myoclonic jerks, asterixis, tremor, restlessness, and confusion. Coma may be observed at P_{CO_2} values of 70 to 100 mm Hg when hypercapnia onset is abrupt. Significantly higher levels may be well tolerated in patients with chronic respiratory acidosis, who have much higher HCO_3^- concentrations from renal compensation. Peripheral vasodilation and increased cardiac output promote warm, flushed skin and a bounding pulse. Arrhythmias are observed occasionally. Mild increases in serum phosphate and K^+ and decreases in lactate and pyruvate have been described in acute respiratory acidosis, and a modest increase in serum Na^+ may occur in both acute and chronic hypercapnia.[88]

Therapy

Treatment of respiratory acidosis depends on the restoration of adequate ventilation. In COPD, attention must be focused on bronchodilation, adequate oxygen supplementation, and relief of anxiety and other reasons for increased metabolic rate. Indiscriminate and uncontrolled administration of high concentrations of oxygen should be avoided. The phenomenon of oxygen-induced hypercapnia in these patients is usually observed in the emergency room and intensive care unit when they present severely hypoxemic, already hypercapnic, and tired. Sudden correction of arterial hypoxemia causes further hypercapnia by a combination of three mechanisms: (1) by depression of formerly high hypoxia-driven peripheral chemoreceptor drive causing more

hypoventilation, (2) relief of hypoxic pulmonary vasoconstriction in poorly ventilated lung regions that further reduce the ability of these units to eliminate CO_2 as local perfusion increases without concomitant increase in local ventilation, and (3) significant correction of hypoxemia causes hemoglobin to be better saturated so that previously buffered protons on deoxyhemoglobin are released with subsequent generation of new CO_2 from HCO_3^- stores (Haldane effect). Low-flow oxygen generally suffices to increase P_{O_2} to satisfactory levels (~60 mm Hg and arterial oxygen saturation [Sa_{O_2}] ~ 90%); greater elevations are neither needed nor advisable. If the use of a ventilator becomes necessary, care must be taken that P_{CO_2} is not decreased by more than 10 mm Hg each hour to avoid life-threatening metabolic alkalosis.

Central respiratory depression may be relieved by naloxone if opiates are responsible. Aminophylline acts as a respiratory center stimulant, but blood levels must be monitored carefully. Correction of pH with HCO_3^- is generally contraindicated in patients with respiratory acidosis, because it decreases the respiratory chemoreceptor drive.[89] However, infusions of $NaHCO_3$ are used to moderate acidosis in patients being mechanically ventilated who are intentionally hypoventilated to minimize lung injury ("permissive hypercapnia"), although this remains controversial[90] because of the possible moderating influences of acidosis on inflammatory and oxidative injuries described above with reference to metabolic acidosis.

RESPIRATORY ALKALOSIS

Although respiratory alkalosis is a common disorder and, at times, is a serious prognostic sign, it seldom has a significant impact on the clinical status of patients and generally requires little in the way of specific therapy to reverse hyperventilation directly. In view of the rapidity with which CO_2 equilibrates between extracellular and cellular compartments, this observation is somewhat puzzling. Changes in pH related to hyperventilation are quickly moderated by tissue buffering and, to a lesser extent, by release of lactic acid, as described earlier. However, HCO_3^- concentrations do not usually fall below 18 mEq/L acutely, and even with renal compensation, a HCO_3^- concentration below 16 mEq/L should raise the possibility of an independent metabolic acidosis.

General Considerations

Many manifestations of respiratory alkalosis may be related in part to a fall in free serum Ca^{2+} due to increased binding to serum proteins. Phosphate may also decline slightly and sometimes fall to rather low concentrations in patients who have prolonged severe respiratory alkalosis.[86] It has been suggested that this decline in phosphate is related to activation of glycolysis and phosphorylation of the glucose metabolites thereby produced. Mild hyponatremia and hyperchloremia, as well as hypokalemia,[69] have also been reported in patients with acute respiratory alkalosis. Some of the CNS changes of acute respiratory alkalosis may be caused by hypocapnic cerebral vasoconstriction leading to reduced blood flow and tissue hypoxia. Often, deliberate hyperventilation is used to reduce cerebral blood flow in states of impending brain herniation from high intracranial pressure, but evidence is mounting that it is useful only for a few hours as a temporizing measure to allow more definitive pressure relief by other means.

Causes

It is convenient to divide the causes of respiratory alkalosis into three major categories: hypoxia, pulmonary diseases, and CNS disorders (Table 7-7). Both central (arterial) and peripheral (capillary) hypoxia are causes of hyperventilation. Decreases in arterial P_{O_2} stimulate the carotid bodies directly. In contrast, tissue hypoxia caused by decreased cardiac output, shock, severe anemia, or excessive hemoglobin oxygen affinity results in the production of lactic acid and other stimuli, which are sensed in blood by the carotid chemoreceptors and by other less well defined chemoreception in the affected tissues themselves. Acute ascent to altitudes greater than 8000 feet may lead to acute mountain sickness. Symptoms generally include dyspnea, malaise, headache, insomnia, anorexia, nausea, vomiting, periodic respiration, and tachycardia. These hypoxic manifestations diminish gradually over a few days as acclimatization occurs.

Many pulmonary disorders are associated with hyperventilation. Hypoxia certainly plays a role, but in addition, receptors have been described in lung tissue that are activated by local irritant stimuli and fluid

TABLE 7-7. Causes of Respiratory Alkalosis

CENTRAL NERVOUS SYSTEM DISORDERS
Hyperventilation syndrome, anxiety
Cerebrovascular disease
Meningitis, encephalitis
Septicemia, hypotension
Hepatic failure
Drugs
Salicylates
Nicotine
Xanthines
Progestational hormones
Mechanical ventilators
HYPOXIA
High altitude
Septicemia
Hypotension
Severe anemia
Decreased cardiac output
PULMONARY DISEASE
Interstitial fibrosis
Pneumonia
Pulmonary embolism
Pulmonary edema (some patients)

accumulation[91] and remain so even after hypoxemia has been corrected.

CNS disorders are among the most common causes of respiratory alkalosis. Anxiety can provoke hyperventilation ("hyperventilation syndrome"). Central stimulation of respiration is also common in a wide variety of intracerebral injuries. Many drugs and hormones (notably salicylates, theophylline, and progesterone) stimulate ventilation (see Table 7-7), and hyperventilation may be an early sign of both sepsis due to gram-negative bacteria and hepatic insufficiency due to the accumulation of ammonia and amines that are known to be responsible for respiratory center stimulation.

Clinical Manifestations

Panic, weakness, and a sense of impending doom are common, as are paresthesias and muscle weakness or cramping. As in metabolic alkalosis, Trousseau's and Chvostek's signs can often be elicited and overt tetany or seizures may follow, particularly in patients with previous seizure diatheses. Vision and speech may become impaired and syncope can follow. Transient electrocardiographic changes can resemble those of myocardial ischemia; this finding can be particularly misleading because it is not uncommon for hyperventilating patients to complain of chest discomfort.

Therapy

Reassurance and rebreathing in a small paper bag are frequently all that is needed to control hyperventilation attacks associated with anxiety. In more severe cases, β-adrenergic inhibitors have proved useful, and specific therapy for anxiety may be indicated. Administration of acetazolamide or corticosteroids before ascent to high altitudes may prevent acute mountain sickness in susceptible persons. Ventilation is stimulated by acetazolamide, but the mechanism by which corticosteroids work remains unknown. Correction of respiratory alkalosis in other conditions, such as hepatic coma and pulmonary disorders, depends on treatment of the primary disorder. CO_2 inhalation by patients with hepatic coma has not been helpful.[92]

KEY POINTS

- Current theory and practice justify the use of P_{CO_2} and HCO_3^- as useful "respiratory" and "metabolic" parameters for analyzing changes in acid-base balance when they are critically judged in the context of each patient's history, physical examination, and other imaging and laboratory information.
- The relative magnitude and the direction in which each parameter changes make it possible to classify primary, compensatory, and mixed disorders.
- Alterations in the blood gas values can be misleading, because changes in laboratory variables may be consistent with but cannot prove a specific sequence of clinical events, particularly if the temporal progression of the disease is not well appreciated.
- The "anion gap" approach to analysis of acid-base problems continues to be a useful tool for detecting a variety of problems; both increases and decreases in this parameter can yield important clinical information.
- In terms of therapy, the most effective measures are those that treat the underlying cause, and if one must attempt chemical remediation, it should be done judiciously and be closely monitored.

References

1. Gennari FJ, Androgue HJ, Galla JH, Madias NE (eds): Acid-Base Disorders and Their Treatment. Boca Raton, FL: Taylor and Francis, 2005.
2. Maren TH: Carbonic anhydrase: Chemistry, physiology, and inhibition. Physiol Rev 47:595–781, 1967.
3. Meldrum NV, Roughton FJW: Carbonic anhydrate: Its preparation and properties. J Physiol (Lond) 80:113–142, 1933.
4. Effros RM, Chang RS, Silverman P: Acceleration of plasma bicarbonate conversion to carbon dioxide by pulmonary carbonic anhydrase. Science 199:427–429, 1978.
5. Hood I, Campbell EJ: Sounding boards. Is pK OK? N Engl J Med 306:864–866, 1982.
6. Gamble JL (ed): Chemical Anatomy, Physiology and Pathology of Extracellular Fluid. Cambridge, MA: Harvard University Press, 1954.
7. Davenport HW (ed): The ABC of Acid-Base Chemistry (4th ed). Chicago: University of Chicago Press, 1958.
8. Sigaard-Anderson O (ed): The Acid-Base Status of Blood. Baltimore: Williams & Wilkins, 1964.
9. Brackett NCJ, Cohen JJ, Schwartz WB: Carbon dioxide titration curve of normal man: Effect of increasing degrees of acute hypercapnia on acid-base equilibrium. N Engl J Med 272:6–12, 1965.
10. Arbus GS, Herbert LA, Levesque PR, et al: Characterization and clinical application of the "significance band" for acute respiratory alkalosis. N Engl J Med 280:117–123, 1969.
11. Eichenholz A, Mulhausen RO, Anderson EW, et al: Primary hypocapnia: A cause of metabolic acidosis. J Appl Physiol 17:283–288, 1962.
12. Stewart PA: Modern quantitative acid-base chemistry. Can J Physiol Pharmacol 61:1444–1461, 1983.
13. Constable PD: Hyperchloremic acidosis: The classic example of strong ion acidosis. Anesth Analg 96:919–922, 2003.

14. Atkins P, dePaula J (eds): Chemical equilibrium. *In* Physical Chemistry (7th ed). New York: WH Freeman, 2002, pp 243–344.
15. Winters RW: Terminology of acid-base disorders. Ann Intern Med 63:873–884, 1965.
16. Krapf R, Berry CA, Alpern RJ, et al: Regulation of cell pH by ambient bicarbonate, carbon dioxide tension, and pH in the rabbit proximal convoluted tubule. J Clin Invest 81:381–389, 1988.
17. Gennari FJ, Goldstein MB, Schwartz WB: The nature of the renal adaptation to chronic hypocapnia. J Clin Invest 51:1722–1730, 1972.
18. Albert MS, Dell RB, Winters RW: Quantitative displacement of acid-base equilibrium in metabolic acidosis. Ann Intern Med 66:312–322, 1967.
19. Dubose TDJ: Metabolic alkalosis. Semin Nephrol 1:281–289, 1981.
20. Goldring RM, Casson PJ, Henemann HO, et al: Respiratory adjustment to chronic metabolic alkalosis in man. J Clin Invest 47:188–202, 1968.
21. Tuller MA, Mehdi F: Compensatory hypoventilation and hypercapnia in primary metabolic alkalosis: Report of three cases. Am J Med 50:281–290, 1971.
22. Madias NE, Adrogue HJ, Cohen JJ: Maladaptive renal response to secondary hypercapnia in chronic metabolic alkalosis. Am J Physiol Renal Physiol 238:F283–F289, 1980.
23. DuBose TD Jr, Good DW, Hamm LL, et al: Ammonium transport in the kidney: New physiological concepts and their clinical implications. J Am Soc Nephrol 1:1193–1203, 1991.
24. Bastani B, Purcell H, Hemken P, et al: Expression and distribution of renal vacuolar proton-translocating adenosine triphosphatase in response to chronic acid and alkali loads in the rat. J Clin Invest 88:126–136, 1991.
25. Schuster VL: Cortical collecting duct bicarbonate secretion. Kidney Int Suppl 33:S47–S50, 1991.
26. Berger BE, Cogan MG, Sebastian A: Reduced glomerular filtration and enhanced bicarbonate reabsorption maintain metabolic alkalosis in humans. Kidney Int 26:205–208, 1984.
27. http://www.emedicine.com/med/TOPIC1459.HTM
28. Reeves RB, Rahn H: Patterns in vertebrate acid-base regulation. *In* Wood SC, Lenfant C (eds): Evolution of Respiratory Processes: A Comparative Approach. New York: Marcel Dekker & Brasel, 1979, pp 225–252.
29. Dubyak GR: Ion homeostasis, channels, and transporters: An update on cellular mechanisms. Adv Physiol Educ 28:143–154, 2004.
30. Emmett M, Narins RG: Clinical use of the anion gap. Medicine 56:38–54, 1977.
31. Winter SD, Pearson JR, Gabow PA, et al: The fall of the serum anion gap. Arch Intern Med 150:311–313, 1990.
32. Gabow PA: Disorders associated with an altered anion gap. Kidney Int 27:472–483, 1985.
33. Oh MS, Carroll HJ, Goldstein DA, et al: Hyperchloremic acidosis during the recovery phase of diabetic ketosis. Ann Intern Med 88:925–927, 1978.
34. Connor H, Woods HF: Quantitative aspects of L(+)-lactate metabolism in human beings. *In* Porter R (ed): CIBA Symposium No. 87: Symposium on Metabolic Acidosis (CIBA Foundation). London: Pitman Books, 1982, pp 214–227.
35. Robergs RA, Ghiasvand F, Parker D: Biochemistry of exercise-induced metabolic acidosis. Am J Physiol Regul Integr Comp Physiol 287:R502–R516, 2004.
36. Richardson RS, Noyszewski EA, Leigh JS, Wagner PD. Lactate efflux from exercising human skeletal muscle: Role of intracellular Po_2. J Appl Physiol 85:627–634, 1998.
37. James JH, Luchette FA, McCarter FD, Fischer JE: Lactate is an unreliable indicator of tissue hypoxia in injury and sepsis. Lancet 354:505–508, 2004.
38. Brooks GA: Lactate shuttles in nature. Biochem Soc Trans 32:258–264, 2002.
39. Hashimoto T, Hussein R, Cho H-S, et al: Evidence for the mitochondrial lactate oxidation complex in rat neurons: Demonstration of an essential component of brain lactate shuttles. PLoS One 3:e2915, 2008.
40. Gladden LB: Lactate metabolism: A new paradigm for the third millennium. J Physiol. 558:5–30, 2004.
41. Cohen RD, Woods HF (eds): Clinical and Biochemical Aspects of Lactic Acidosis. Oxford: Blackwell Scientific, 1976.
42. Kam PC, Cardone D: Propofol infusion syndrome. Anaesthesia 62:690–701, 2007 .
43. Metcalfe HK, Monson JP, Welch SG, et al: Inhibition of lactate removal by ketone bodies in rat liver: Evidence for a quantitatively important role of the plasma membrane lactate transporter in lactate metabolism. J Clin Invest 78:743–747, 1986.
44. Oh MS, Uribarri J, Alveranga D, et al: Metabolic utilization and renal handling of D-lactate in men. Metabolism 34:621–625, 1985.
45. Wildenhoff KE: Blood ketone body disappearance rate in diabetics and normals after rapid infusion of dl-3-hydroxybutyrate: Studies before and after diabetic treatment. Acta Med Scand 200:79–86, 1976.
46. Carroll HJ, Oh MS: Disturbances in acid-base balance. *In* Carroll HJ, Oh MS (eds): Water, Electrolyte and Acid-Base Metabolism. Philadelphia: JB Lippincott, 1989, pp 206–286.
47. Narins RG, Jones ER, Strohen MC, et al: Diagnostic strategies in disorders of fluid, electrolyte and acid-base homeostasis. Am J Med 72:496–519, 1982.
48. Grey NJ, Karl I, Kipnis DM: Physiologic mechanisms in the development of starvation ketosis in man. Diabetes 24:10–16, 1975.
49. Fulop M, Hoberman HD: Alcoholic ketosis. Diabetes 24:785–790, 1975.
50. Smith PK, Gleason HL, Stoll CG, et al: Studies on the pharmacology of salicylates. J Pharmacol Exp Ther 87:237–255, 1946.
51. Thurston JH, Pollock PG, Warren SK, et al: Reduced brain glucose with normal plasma glucose in salicylate poisoning. J Clin Invest 49:2139–2145, 1970.
52. Halperin ML, Goldstein MB, Stinebaugh MJ, et al: Renal tubular acidosis. *In* Narins RG, Halperin ML, Carlisle EJF, et al (eds): Maxwell and Kleeman's Clinical Disorders of Fluid and Electrolyte Metabolism. New York: McGraw-Hill, 1996, pp 875–910.
53. Rodriguez SJ: Renal tubular acidosis: The clinical entity. J Am Soc Nephrol 13:2160–2170, 2002.
54. Igarashi T, Sekine T, Inatomi J, et al: Unraveling the molecular pathogenesis of isolated proximal renal tubular acidosis. J Am Soc Nephrol 13:2171–2177, 2002.
55. Karet FE: Inherited distal renal tubular acidosis. J Am Soc Nephrol 13:2178–2184, 2002.
56. Fry AC, Karet FE: Inherited renal acidoses. Physiology (Bethesda) 22:202–211, 2007.
57. Nicoletta JA, Schwartz GJ: Distal renal tubular acidosis. Curr Opin Pediatr 16:194–198, 2004.
58. Simpson DP: Citrate excretion: A window on renal metabolism. Am J Physiol Renal Physiol 244:F223–F234, 1983.
59. Sly WS, Whyte MP, Sundaram V, et al: Carbonic anhydrase II deficiency in 12 families with the autosomal recessive syndrome of osteopetrosis with renal tubular acidosis and cerebral calcification. N Engl J Med 313:139–145, 1985.
60. DuBose TD Jr: Disorders of Acid-Base Balance. *In* Brenner BM (ed): Brenner and Rector's The Kidney (8th ed). Phildelphia: Saunders Elsevier, 2007, pp 505–546.
61. Wrong O, Metcalfe-Gibson A: The electrolyte content of faeces. Proc R Soc Med 58:1007–1009, 1965.
62. Kirschbaum B, Sica D, Anderson FP: Urine electrolytes and the urine anion and osmolar gaps. J Lab Clin Med 133:597–604, 1999.
63. Winter RW, Scaglione PR, Hahas GG, et al: The mechanism of acidosis produced by hyperosmotic infusions. J Clin Invest 43:647–658, 1964.
64. Garella S, Chang BS, Kahn SI: Dilution acidosis and contraction alkalosis: Review of a concept. Kidney Int 8:279–283, 1975.
65. Cohen JJ, Hulter HN, Smithline N, et al: The critical role of the adrenal gland in the renal regulation of acid-base equilibrium during chronic hypotonic expansion: Evidence that chronic hyponatremia is a potent stimulus to aldosterone secretion. J Clin Invest 58:1201–1208, 1976.
66. Mitchell JH, Wildenthal K, Johnson RL Jr: The effects of acid-base disturbances on cardiovascular and pulmonary function. Kidney Int 1:375–389, 1972.
67. Sharpey-Schafer EP, Semple SJ, Halls RW: Venous constriction after exercise: Its relation to acid-base changes in venous blood. Clin Sci 29:397–406, 1965.

68. Harvey RM, Enson Y, Lewis ML, et al: Hemodynamic effects of dehydration and metabolic acidosis in Asiatic cholera. Trans Assoc Am Physicians 79:177–186, 1966.
69. Adrogue HJ, Madias NE: Changes in plasma potassium concentration during acute acid-base disturbances. Am J Med 71:456–467, 1981.
70. Perez GO, Oster JR, Vaamonde CA: Serum potassium concentration in acidemic states. Nephron 27:233–243, 1981.
71. Goodman AD, Lemann J, Lennon EJ, Relman AS: Production excretion and net balance of fixed acid in patients with renal acidosis. J Clin Invest 44:495–506, 1965.
72. Swenson ER: Metabolic acidosis. Respir Care 46:342–353, 2001.
73. Fraley DS, Adler S, Bruns FJ, et al: Stimulation of lactate production by administration of bicarbonate in a patient with a solid neoplasm and lactic acidosis. N Engl J Med 303:1100–1102, 1980.
74. Stacpoole PW: Lactic acidosis: The case against bicarbonate therapy. Ann Intern Med 105:276–279, 1986.
75. Weil MH, Rackow EC, Trevino R, et al: Difference in acid-base state between venous and arterial blood during cardiopulmonary resuscitation. N Engl J Med 315:153–156, 1986.
76. Posner JB, Plum F: Spinal-fluid pH and neurologic symptoms in systemic acidosis. N Engl J Med 277:605–613, 1967.
77. Stacpoole PW, Wright EC, Baumgartner TG, et al: A controlled clinical trial of dichloroacetate for treatment of lactic acidosis in adults. N Engl J Med 327:1564–1569, 1992.
78. Bieberdorf FA, Gorden P, Fordtran JS: Pathogenesis of congenital alkalosis with diarrhea: Implications for the physiology of normal ileal electrolyte absorption and secretion. J Clin Invest 51:1958–1968, 1972.
79. Stone DK, Seldin DW, Kokko JP, et al: Mineralocorticoid modulation of rabbit medullary collecting duct acidification: A sodium-independent effect. J Clin Invest 72:77–83, 1983.
80. Naesens M, Steels P, Verberckmoes R, et al: Bartter's and Gitelman's syndromes: From gene to clinic. Nephron Physiol 96:65–78, 2004.
81. Stinebaugh BJ, Schloeder FX: Glucose-induced alkalosis in fasting subjects: Relationship to renal bicarbonate reabsorption during fasting and refeeding. J Clin Invest 51:1326–1336, 1972.
82. Litwin MS, Smith LL, Moore FD: Metabolic alkalosis following massive transfusion. Surgery 45:805–813, 1959.
83. Di Sant'Agnese PA, Darling C, Perera GA, et al: Sweat electrolyte disturbances associated with childhood pancreatic disease. Am J Med 15:777–784, 1953.
84. Anderson LE, Henrich WL: Alkalemia-associated morbidity and mortality in medical and surgical patients. South Med J 80:729–733, 1987.
85. Sliwinski M, Hoffman M, Biederman A, et al: Association between hypokalaemic alkalosis and development of arrhythmia in early postoperative period. Anaesth Resusc Intensive Ther 2:193–204, 1974.
86. Swenson ER: Tissue and cellular carbon dioxide transport and acid-base balance. *In* Haddad GG, Abman SH, Cherniack V (eds): Basic Mechanisms of Pediatric Respiratory Disease. London: BC Decker, 2002, pp 216–233.
87. Androgue JH, Rashad MN, Gorin AB, et al: Arteriovenous acid-base disparity in circulatory failure: Studies on mechanisms. Am J Physiol 257:F1087–F1093, 1980.
88. Mostellar ME, Tuttle EPJ: The effects of alkalosis on plasma concentrations and urinary excretion of inorganic phosphate in man. J Clin Invest 43:138–149, 1964.
89. Bear R, Goldstein M, Phillipson E, et al: Effect of metabolic alkalosis on respiratory function in patients with chronic obstructive lung disease. Can Med Assoc J 117:900–903, 1977.
90. Laffey JG, O'Croinin D, McLoughlin P, Kavanagh BP: Permissive hypercapnia—Role in protective lung ventilatory strategies. Intensive Care Med 30:347–356, 2004.
91. Paintal AS: Mechanism of stimulation of type J pulmonary receptors. J Physiol (Lond) 203:511–532, 1969.
92. Hoyumpa AM, Schenker S: Bock US Hepatic encephalopathy. *In* Berk JE, Haubrich WS, Kalser MH, et al (eds): Gastroenterology (4th ed). Philadelphia: WB Saunders, 1985, pp 3083–3120.

CHAPTER 8

PHARMACOLOGIC PRINCIPLES

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INTRODUCTION

CELL INTERACTIONS IN THE LUNG
Vascular Endothelium
Airway Epithelium
Inflammatory Cells
Nerves

RECEPTORS
Receptor Classification
G Protein–Coupled Receptors
Receptor Dimerization
G Proteins
Second Messengers
Cytokine Receptors
Enzyme-Linked Receptors
Ion Channel Receptors
Intracellular Receptors
Receptor Subtypes
Receptor Interactions

DRUG-RECEPTOR INTERACTIONS
Radioligand Binding
Agonists and Antagonists

RECEPTOR REGULATION
Desensitization
Steroid Modulation
Receptor Ontogeny
Pulmonary Diseases
Transcriptional Control

ION CHANNELS
Calcium Channels
Potassium Channels
Sodium Channels
Chloride Channels

ENZYMES
Protein Kinases
Protein Phosphatases

PHARMACOKINETICS
Absorption
Distribution
Clearance

ROUTES OF DRUG DELIVERY
Inhaled Route
Oral Route
Parenteral Route

AUTONOMIC PHARMACOLOGY
Overview of Airway Innervation
Afferent Nerves
Cholinergic Nerves
Neurogenic Inflammation
Neurogenic Inflammation in Human Airways
Bronchodilator Nerves
Neural Control in Disease

INFLAMMATORY MEDIATORS
Histamine
Leukotrienes
Prostaglandins
Platelet-Activating Factor
Endothelins
Nitric Oxide
Oxygen-Derived Free Radicals
Adenosine
Bradykinin
Cytokines
Chemokines
Multiple Mediators
Anti-inflammatory Mediators

TRANSCRIPTION FACTORS
Activator Protein-1
Nuclear Factor-κB
JAK-STAT
GATA-3
T-Bet
CREB
Glucocorticoid Receptors
Nuclear Factor of Activated T Cells
Coactivators
Histone Modification

INTRODUCTION

Pulmonary pharmacology is concerned with the action of drugs on target cells of the lung. Learning the mechanisms and action of drugs will improve our understanding of their use in therapy. This should lead to advances in drug development, making treatment more specific and maximizing the beneficial effects of therapy. Drugs may also be used as specific probes to analyze pathophysiologic processes in lung disease. This chapter concerns the general pharmacologic principles of drug action in the lung, with particular emphasis on the application of pharmacology to understanding lung diseases and their therapy.

CELL INTERACTIONS IN THE LUNG

The structure of human lungs is complex, with over 40 different cell types. Each cell type may be subject to different control mechanisms and may be influenced in a variety of ways. Whereas some cells, such as airway smooth muscle, have been extensively investigated, other cells have been less well characterized.

There may be complex interactions between different cells in the lung, and damage to one cell type may lead to abnormal function in a different cell type. These interactions are now beginning to be investigated using systems biology approaches that analyze complex interactive networks using newly developed mathematical modeling approaches.[1] Analysis of cell-to-cell communication may be important in understanding the mode of action of various pharmacologic agents, because drugs usually act on many cell types both directly and indirectly through cell-cell interactions.

Vascular Endothelium

Vascular endothelial cells are activated by many different agonists to release vasodilators, including nitric oxide (NO) and prostacyclin.[2] Thus, acetylcholine (ACh), which relaxes vessels in vitro through the release of NO, induces a constrictor response if endothelial cells are removed mechanically. Endothelial cells play a critical role in regulating both the bronchial and the pulmonary circulations, and NO is the predominant vasodilator in these vessels.[3]

Airway Epithelium

Airway epithelium releases many mediators that may affect airway and vascular smooth muscle in the airway wall and thereby play a critical role in the regulation of airway caliber. Airway epithelial cells release relaxant factors, including NO and prostaglandins, and mechanical removal of airway epithelium causes enhanced contractile and reduced relaxant responses of airway smooth muscle in vitro.[4] The existence of an epithelium-derived relaxant factor (EpDRF) different from NO and prostaglandins has been demonstrated in superfusion experiments, but its identity has never been determined. The effect of epithelial removal is most striking for the effects of peptides, such as tachykinins and bradykinin. This is explained by the release of prostaglandin (PG) E_2 from epithelial cells and by degradation by the enzyme neutral endopeptidase (NEP), which is expressed in high concentration by airway epithelial cells. Epithelial cells also synthesize several other mediators, including peptides such as endothelin-1 (a potent constrictor peptide, chemokines that attract inflammatory cells such as neutrophils and eosinophils), and growth factors that result in structural changes in the airways (e.g., fibrosis, airway smooth muscle hyperplasia). Epithelial cells synthesize several key cytokines, such as thymic stromal lymphopoietin (TSLP), which plays a key role in regulating dendritic cells to orchestrate airway inflammation, interleukin (IL) -33, which orchestrates T lymphocytes and B-cell–activating factor (BAFF), which regulates B lymphocytes, thus playing a critical role in linking innate and acquired (Fig. 8-1) immunity.[5]

Inflammatory Cells

Many stimuli produce effects on airway function by releasing mediators from inflammatory cells in the airways. A good example is allergen, which does not directly constrict airway smooth muscle, but activates airway mast cells to release bronchoconstrictor mediators, such as leukotriene (LT) D_4 and histamine, which then contract airway smooth muscle cells. Another example is adenosine, which releases histamine from mast cells in asthmatic airways. These are examples of *indirect* bronchoconstrictors, in contrast to *direct*

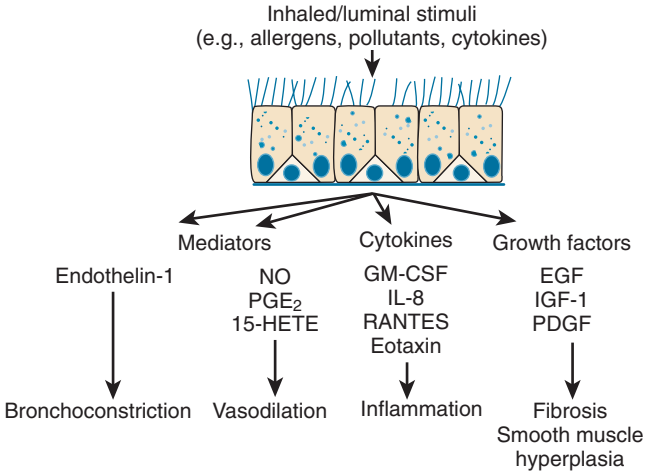

FIGURE 8-1 ■ Epithelial cells as a source of inflammatory mediators. Airway epithelial cells may be activated by stimuli in the airway lumen to produce a wide variety of inflammatory mediators that have effects on airway function. EGF, epidermal growth factor; GM-CSF, granulocyte-macrophage colony stimulating factor; 15-HETE, 15 hydroxyeicosatetraenoic acid; IGF-1, insulin-like growth factor-1; IL-8, interleukin-8; NO, nitric oxide; PDGF, platelet-derived growth factor; PGE_2, prostaglandin E_2; RANTES, release by activated normal T cells expressed and secreted.

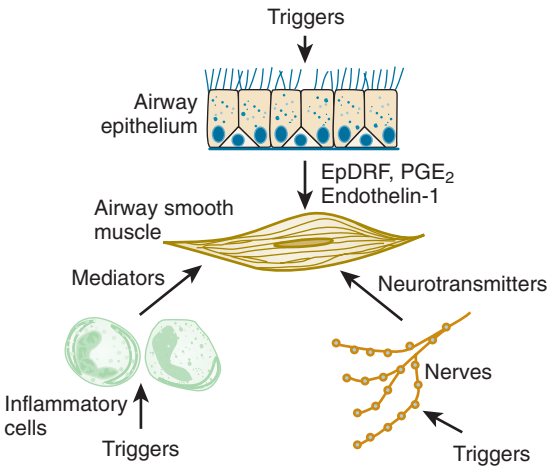

FIGURE 8-2 ■ Cell interaction in the airways. Airway smooth muscle tone may be determined by the direct effect of agonists acting on receptors on airway smooth muscle cells or indirectly via the release of mediators from epithelial cells, inflammatory cells or nerves, which may be triggered by various factors. EpDRF, epithelium-derived relaxing factor; PGE_2, prostaglandin E_2.

bronchoconstrictors, such as histamine, methacholine, and LTD_4, which act directly on airway smooth muscle cells (Fig. 8-2). Other inflammatory cells (e.g., macrophages and eosinophils) may also be involved in indirect bronchial challenges and may be activated by allergens through low affinity immunoglobulin (Ig) E receptors (FcεRII, CD23).

Nerves

Several stimuli may also activate nerves to release bronchoconstrictor neurotransmitters. Thus, irritant gases (e.g., sulfur dioxide) may activate sensory nerves to cause reflex cholinergic bronchoconstriction. Other stimuli (e.g., bradykinin) may activate sensory nerves to release tachykinins.[6] Other mediators may release neurotransmitters from motor nerves via activation of prejunctional receptors. These stimuli that evoke bronchoconstriction via neural mechanisms are also examples of indirect bronchoconstrictors.

RECEPTORS

Nearly all hormones, neurotransmitters, mediators, cytokines, and growth factors produce their effects by interacting with specific protein recognition sites, or receptors, on target cells. Because receptors are specific, they allow a cell to recognize only selected signals from the myriad of molecules that come into contact with the cell. Receptors play an important role in disease, because their function may be altered, resulting in abnormal cellular responsiveness. Many drugs used in the treatment of pulmonary diseases stimulate (agonists) or block (antagonists) specific receptors.

There have been major advances in elucidating the function, regulation, and structure of receptors. This has been made possible by the development of radioligand binding, in which highly potent radiolabeled agonists or antagonists are used to characterize and directly quantify and map receptors. Many different receptors have been cloned, making it possible to deduce their amino acid structure and to determine the critical parts of the receptor protein that are involved in ligand binding and interaction with second messenger systems. Receptor cloning and production of pure receptor proteins has also made it possible to produce specific antibodies for use in immunocytochemical studies. Furthermore, advances in molecular biology have made it possible to study the regulation of receptor genes. Some receptors termed "orphan receptors" have also been cloned, but their endogenous ligands have not yet been identified. This has led to the discovery of new endogenous ligands and identification of novel drug targets. The cloning of the human genome has revealed many orphan receptors. Understanding their functions could lead to novel therapies.

Receptor Classification

Most receptors are proteins located within the cell membrane. They interact with specific ligands outside the cell, leading to a conformational change that results in activation of a second messenger system within the cell and subsequently to a cellular response. Cell surface receptors include (Fig. 8-3):

- Guanine-nucleotide binding protein (G protein)–coupled receptors (GPCRs; e.g., β-adrenergic receptors, chemokine receptors).
- Ion-channel–linked receptors (e.g., nicotinic receptors).
- Enzyme-linked receptors (e.g., platelet-derived growth factor receptors).
- Cytokine and growth factor receptors, which usually have at least two subunits (e.g., IL-5 receptors).
- Intracellular receptors, such as steroid and thyroid receptors, are intracellular and the ligand diffuses into the cell and usually binds to cytosolic receptors, which translocate to the nucleus and interact with recognition binding sites on DNA to regulate the transcription of target genes.

Molecular cloning techniques have made it possible to recognize several receptor families that share a common structure and to trace the evolutionary lineage of receptors within receptor families.

G Protein–Coupled Receptors

Many different receptors interact with G proteins, which act as a coupling mechanism linking receptor activation to second messenger systems. All of these receptors appear to have structural similarities and are members of a large supergene family. More than 1000 GPCRs, making up greater than 1% of the human genome have now been cloned and sequenced.[7,8] Each receptor is a single polypeptide chain, ranging in size from approximately 400 to more than 1000 amino acids with seven hydrophobic sequences that cross the cell membrane.

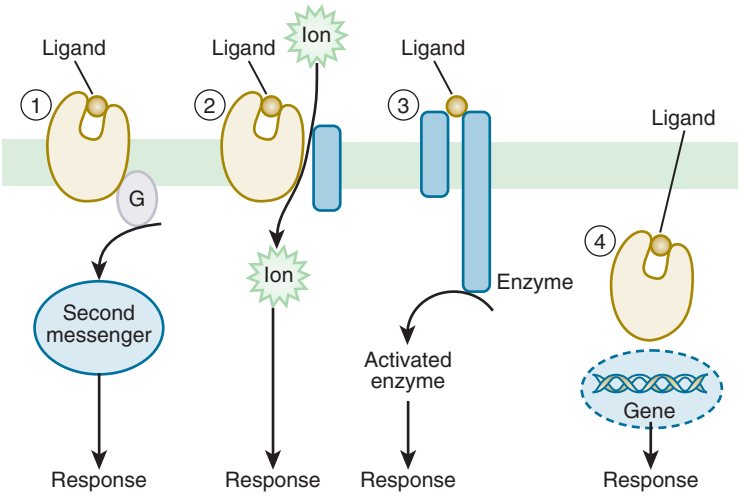

FIGURE 8-3 ■ Several classes of receptor are recognized. (1) G protein–coupled receptors, which activate second messengers to induce a response; (2) receptor-operated ion channels; (3) enzyme-linked receptors; (4) intracellular receptors, which translocate to the nucleus to regulate gene expression.

Many drugs used in the treatment of respiratory diseases work through interaction with GPCRs. In addition, many unknown (orphan) GPCRs have been discovered and are now targets for the development of novel drugs.[9] For example, polymorphisms of the orphan receptor G protein for asthma susceptibility (GPRA) was discovered when polymorphisms of its gene were linked to increased asthma susceptibility and airway hyperresponsiveness.[10] The endogenous agonist of this receptor has now been identified as neuropeptide S, which has been linked to anxiety and arousal, but the function of neuropeptide S in asthma has not yet been defined.[11]

Rhodopsin as a Model Receptor

The first and most carefully characterized GPCR was rhodopsin in light-sensitive rods of the retina, which is coupled to a unique G protein called transducin, and this has served as a useful structural model for other receptors in this group. Analysis of the amino acid sequence of rhodopsin revealed seven hydrophobic (lipophilic) stretches of 20 to 25 amino acids that are linked to hydrophilic regions of variable length. The most likely spatial arrangement of the receptor in the cell surface membrane is for the seven hydrophobic sections (each of which is in the form of an α-helix) to spanning the cell membrane. The intervening hydrophilic sections are exposed alternately intracellularly and extracellularly with the amino (N)-terminal exposed to the outside and the carboxy (C)-terminal within the cytoplasm. The extracellular regions of rhodopsin recognize the specific ligand (retinal) and the intracellular regions interact with transducin. All other GPCRs share this serpentine motif. More recently, the three-dimensional structure of other GPCRs, including the β_2-adrenergic receptor, have been characterized, and these generally conform with the rhodopsin model.[12]

Structure

All GPCRs share the common feature of seven similar hydrophobic transmembrane segments (7TM). There is

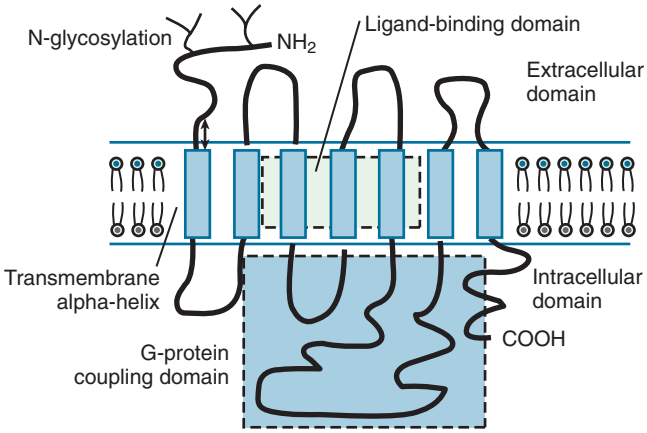

FIGURE 8-4 ■ Structure of a G protein–coupled receptor. The peptide chain is folded seven times across the cell membrane. The hydrophobic segments that cross the cell membrane are in the form of an α-helix. Small ligands interact deep within the cell membrane between the α-helices, whereas peptide ligands interact with the extracellular parts of the receptor. Intracellular loops (especially the third intracellular loop) are important in interaction with the G protein. Most of these receptors are glycosylated at extracellular loops.

also some sequence homology of the intracellular loops (which interact with various species of G proteins) but less similarity in the extracellular domains. For example, there is a 50% homology between rat β_2-adrenergic and muscarinic M_2-receptors. There is also close homology between the same receptor in different species. Thus, there is 95% homology between rat and pig heart M_2-receptors. These similarities demonstrate that G receptor–linked receptors form part of a supergene family that may have a common evolutionary origin.

Members of the G protein receptor supergene family are generally 400 to 500 amino acids in length and the receptor cDNA sequence consists of 2000 to 4000 nucleotide bases (2–4 kb) (Fig. 8-4).[8] The molecular weight of the cloned receptors predicted from the cDNA sequence is 40 to 60 kDa, which is usually less than the molecular mass of the native receptor, when assessed by SDS

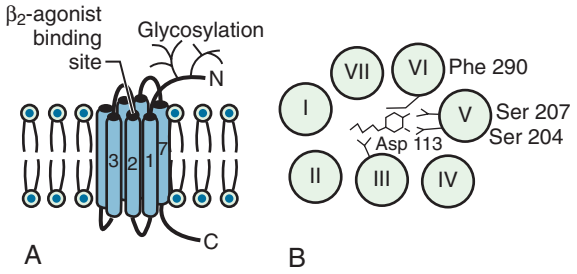

FIGURE 8-5 ■ Ligand-binding domain of the β_2-adrenergic receptor, showing the clustering of the 7 transmembrane domains to form a binding cleft (**A**) and the interaction between the catecholamine and the critical amino acids in the transmembrane domains (**B**). Asp, aspartate; Phe, phenylalanine; Ser, serine.

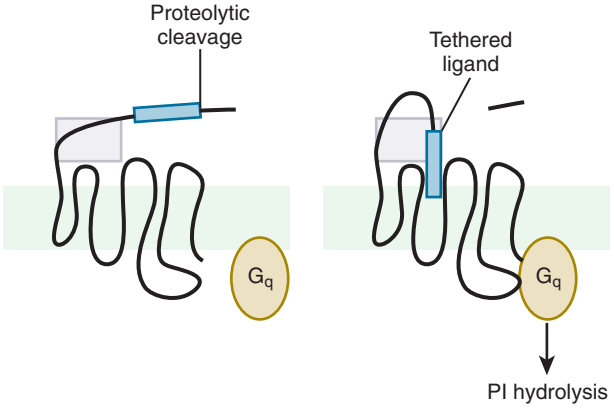

FIGURE 8-6 ■ Proteinase-activated receptors (PARs) are G protein–coupled receptors that are activated by proteinases, such as thrombin (PAR1, 2, 4) and tryptase (PAR2). Cleavage occurs at the N-terminal end of the receptor to reveal a tethered ligand sequence that then inserts into the binding cleft of the receptor, resulting in coupling of a G protein (usually G_q) to effector mechanisms such as phosphoinositide (PI) hydrolysis.

polyacrylamide gel electrophoresis. This discrepancy is explained by *glycosylation* of the native receptor. For example, β_2-receptors contain two sites for glycosylation on asparagine (Asn/N) residues near the N-terminus, and it is estimated that N-glycosylation accounts for 25% to 30% of the molecular mass of the native receptor. Receptor glycosylation does not affect receptor affinity for ligand or coupling to G proteins, but may be important for the trafficking of the receptor through the cell during down-regulation or for keeping the receptor correctly orientated in the lipid bilayer.

Another feature of these receptors is palmitoylation, when cysteine residues covalently bind palmitic acid via a thioester bond, thus anchoring the receptor chain to the cell membrane. This confers three-dimensional stability on the receptor. Disruption of this bond in β-receptors (by mutation of Cys341) alters both binding characteristics and coupling to G proteins and may affect desensitization of the receptor.[13]

Deletion mutagenesis (deleting sections of the peptide sequence) and site-directed mutagenesis (substitution of single amino acids in the polypeptide chain) have established that the ligand-binding domain is well conserved between members of the same family. In the case of β-adrenoceptors, there is good evidence for a ligand-binding cleft between the transmembrane spanning domains within the cell membrane.[14] Critical amino acids for the interaction of endogenous adrenergic agonists (norepinephrine and epinephrine) are asparagine (Asp) in the third transmembrane loop (TM3, Asp113) and serines in TM5 (Ser204, Ser207), which interact with the hydroxy groups on the catechol ring (Fig. 8-5).

The binding site for antagonists differs from those of naturally occurring ligands and for antagonist binding to β-receptors TM7 appears to be critical. Binding of substance P to the NK_1-receptor occurs to extracellular domains of the receptor, whereas antagonist binding of the nonpeptide NK_1-antagonist CP96,345 binds to a transmembrane domain (His197).[15]

One special type of GPCR is the proteinase-activated receptor (PAR), exemplified by receptors for thrombin and tryptase.[16] There are currently four PARs recognized; thrombin activates PAR1, 3, and 4, whereas trypsin, mast cell tryptase, and other serine proteases activate PAR2. Ligands for these receptors are enzymes that cleave a site on the extracellular domain of the receptor, thus revealing an active site that then binds to and activates the remaining receptor protein (Fig. 8-6). PAR may play an important role in lung diseases, leading to a search for specific antagonists.[16]

Receptor Dimerization

It is now recognized that most GPCRs undergo physical association with themselves (homodimerization) but also with other GPCRs (heterodimerization) and that this may profoundly influence receptor function and interaction with signaling pathways, providing a novel mechanism of receptor interactions that may be relevant to pulmonary disease.[17-19] Recognition of GPCR heterodimers might also lead to the development of new drugs that recognize only the heterodimers and therefore have a greater selectivity. For example, heterodimerization between prostaglandin E (PGE_1) receptors and β_2-receptors in airway smooth muscle cells results in uncoupling of β_2-receptors and a diminished bronchodilator response to β_2-agonists (Fig. 8-7).[20] β_2-Receptors are also known to dimerize with β_1-, β_3-, opioid-, and angiotensin (AT_1)-receptors. Heterodimerization of chemokine receptors may be important in determining cell recruitment and may account for why selective antagonist of one receptor may inhibit responses to other chemokines that signal through different receptors.[21] For example, CXCR1/CXCR2 and CCR2/CCR4 heterodimers have been identified and appear to be induced when the chemokine ligands for both receptors are present together.

G Proteins

G proteins link activation of 7TM receptors to enzymes or ion channels that then mediate the characteristic response.[22] All G proteins have GTPase activity and

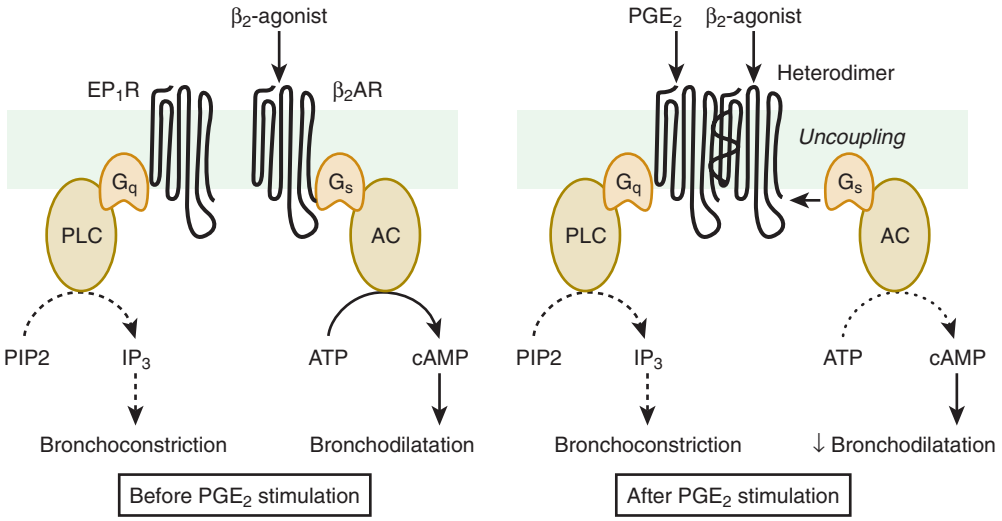

FIGURE 8-7 ■ Heterodimerization of prostaglandin E_1-receptors (EP_1R) and β_2-adrenergic receptors (β_2AR) in airway smooth muscle cells. Under basal conditions (*left panel*), a β_2-agonist activates a stimulatory G protein (G_s) thus stimulating adenylyl cyclase (AC) to increase cyclic 3′,5′-adenosine monophosphate (cAMP) and produce bronchodilatation. Prostaglandin $(PG)E_2$ (*right panel*) promotes the dimerization of EP_1R with β_2AR, uncoupling it from Gs, thus reducing the bronchodilator response to a β_2-agonist. EP_1R signals through a different G protein (Gq)–coupled to phospholipase C (PLC) and the formation of inositol-1,4,5-trisphosphate (IP_3), which releases calcium ions to cause bronchoconstriction, but PGE_2 alone does not activate this pathway sufficiently to induce bronchoconstriction.

catalyze the conversion of guanosine triphosphate (GTP) to guanosine diphosphate (GDP). Several distinct G proteins have now been characterized and cloned. They are made up of three separate units and are termed "heterotrimeric G proteins"; the α-subunit interacts with the receptor, binds GTP, and interacts with the effector enzyme, such as adenylyl cyclase and phospholipase C. The β- and γ-subunits are hydrophobic and are associated as a βγ complex within the cytoplasmic surface of the cell membrane. G proteins are freely diffusible within the cell membrane and the pool of G proteins may interact with several receptors. In the resting state, the G protein exists as a αβγ heterotrimer with GDP occupying the binding site on the α-subunit. When a receptor is occupied by an agonist, a conformational change occurs and the intracellular loops of the receptor protein acquire a high affinity for αβγ, resulting in the dissociation of GDP and its replacement with GTP, which in turn causes α-GTP to dissociate from the βγ-subunits (Fig. 8-8). α-GTP is the active form of the G protein and diffuses to associate with effector molecules, such as enzymes and ion channels. This process is terminated by hydrolysis of GTP to GDP via the GTPase activity of the α-subunit. The resulting α-GDP dissociates from the effector molecule and reassociates with βγ, in readiness for activation again.[23]

In addition to the classical heterotrimeric G proteins with αβγ-subunits, there are several other small G proteins with GTPase activity, such as the Rho, Rab, and Rac subfamilies, that are not activated directly by GPCRs, but play a key role in regulating actin and cytoskeletal organization.[24] Rho activates specific Rho kinases leading to a cascade of interacting signals with in the cell. For example, Rho GTPases are involved in contractile responses in airway smooth muscle and in fibrosis so that

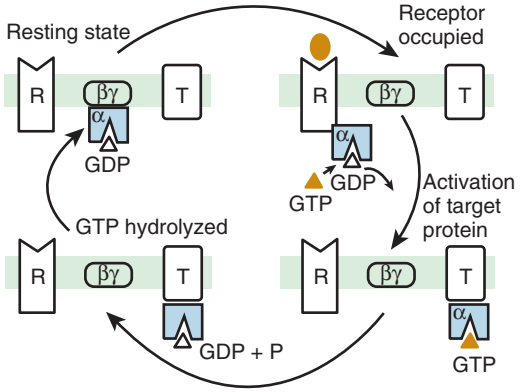

FIGURE 8-8 ■ Transducing function of G proteins is shown. G proteins couple receptor activation to a target membrane protein, such as an enzyme (e.g., adenylyl cyclase) or an ion channel (T). Each G protein is made up of three subunits (α, β, and γ) (not shown). In the inactive state, guanine diphosphate (GDP) binds to the α-subunit, but when a receptor (R) is activated, it interacts with the α-subunit, displacing GDP for guanine triphosphate (GTP), and resulting in the association of the α-subunit with the effector system. GTP is then hydrolyzed by the intrinsic GTPase activity of the α-subunit, resulting in activation of T. This then allows the α-subunit to associate with the βγ-subunits, which remain fixed in the hydrophobic cell membrane. The α-subunit is therefore believed to act as a "shuttle," coupling receptor activation to stimulation of the target protein.

Rho kinase inhibitors might have therapeutic potential in asthma.[25] Rab GTPases are involved in secretion and may therefore play a role in mucus secretion and in mast cell degranulation.[26]

Several receptors, such as β-receptors and vasoactive intestinal polypeptide (VIP)-receptors, stimulate

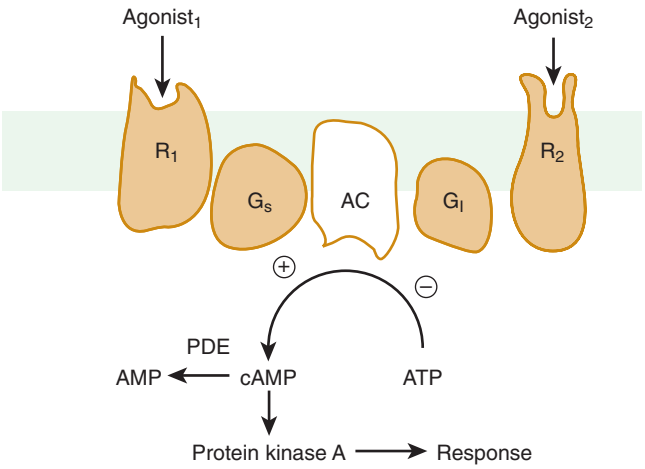

FIGURE 8-9 ■ G proteins and adenylyl cyclase are depicted. Receptors (R_1, R_2) are coupled to G proteins that stimulate (G_s) or inhibit (G_i) adenylyl cyclase (AC), resulting in increased or decreased formation of the second messenger, cyclic adenosine 3′,5′-monophosphate (cAMP) from adenosine triphosphate (ATP). cAMP is degraded to adenosine monophosphate (AMP) via phosphodiesterases (PDE). cAMP activates protein kinase A, which phosphorylates target proteins, leading to a response.

adenylyl cyclase via the stimulatory G protein G_s, whereas activation of other receptors, such as muscarinic M_2-receptors inhibit adenylyl cyclase via G_i (Fig. 8-9).[22] G_s may be stimulated directly by cholera toxin, whereas G_i is inhibited by *Pertussis* toxin, so that these toxins have proved to be useful in elucidating the involvement of a particular G protein in a particular receptor-mediated response. Other G proteins are now recognized. They couple receptors, which activate phosphoinositide hydrolysis (G_0, G_q) and activate particular ion channels in the cell membrane (e.g., G_k, which is coupled to potassium channels). G proteins may play a very important role in the regulation of cell responsiveness, and there is evidence that receptors may become uncoupled from G proteins under certain conditions. For example, in fatal asthma, there is evidence for a reduced responsiveness of airway smooth muscle to β-agonists, yet the number and affinity of β-receptors on airway smooth muscle is not reduced and the response to other smooth muscle relaxants is not impaired, suggesting that the receptors have become *uncoupled* in severe asthma.[27]

Whereas receptors affect the function of G proteins, G proteins also influence the interaction of ligands with their receptors. Thus, when coupled to an inactive G protein, the receptor exists in a state of high affinity for the agonist. Agonist binding releases G_α from contact with the receptor, resulting in a reduction in agonist affinity, referred to as the "guanine-nucleotide shift."

Second Messengers

The ligand that activates a receptor is described as the first messenger and leads, via activation of a G protein, to the typical cellular response via a second messenger, such as a change in intracellular calcium ion (Ca^{2+}) concentration or cyclic 3′,5′-adenosine monophosphate (cAMP) concentration. Whereas the number of surface receptors that may respond on any particular cell is very large, only a very limited number of signal transduction and second messenger systems have been described. Thus, the surface receptors determine cellular responsiveness and sensitivity, rather than the intracellular mechanisms that are activated by the receptor-ligand interaction. Considerable progress has been made in understanding the intracellular mechanisms involved in receptor-mediated effects, through the development of techniques such as intracellular dye indicators that reflect intracellular concentrations of ions (e.g., fura-2, which detects intracellular Ca^{2+} concentrations), via more sensitive biochemical assays and via the development of patch clamping techniques.

Adenylyl Cyclase

Many receptors produce their effects by interaction with the membrane-bound enzyme adenylyl cyclase (AC) to either increase or decrease production of cyclic 3′,5′ adenosine monophosphate (cAMP) (see Fig. 8-9). At least nine closely related forms of AC have now been differentiated, and there is increasing evidence that these isoforms may be differentially regulated.[28] Thus, protein kinase C (PKC) phosphorylates and activates certain isoforms (types 1,2,3), which may be a mechanism for receptor interactions whereas PKC has no effect on other isoforms (4,5,6). The formation of cAMP leads to the characteristic cellular response via the activation of a specific protein kinase, protein kinase A (PKA), by dissociating a regulatory (inhibitory) subunit. PKA then phosphorylates serine and threonine residues on specific proteins, such as regulatory proteins, ion channels, and enzymes within the cell, which lead to the characteristic response. For example, in airway smooth muscle cells, PKA phosphorylates large conductance calcium-activated potassium (K^+) channels, which open, leading to K^+ efflux from the cell, hyperpolarization and relaxation.[29] PKA also phosphorylates and therefore inactivates myosin light chain kinase, resulting in a direct relaxant effect on the contractile machinery.

It is now increasingly recognized that cAMP also activates signaling mechanisms other than PKA, such as ion channels and the ubiquitous guanine nucleotide exchange factors Epac 1 and 2.[30] For example, cAMP-induced inhibition of IL-5 in human T lymphocytes is independent of PKA.[31] Conversely, β_2-agonists inhibit the release of certain cytokines from airway smooth muscle cells via an effect on PKA, because these responses are completely inhibited by transfection with the selective endogenous PKA inhibitor called "PKA inhibitor-α."[32]

Phosphodiesterases

cAMP is hydrolyzed within cells by a family of enzymes termed "phosphodiesterases" (PDEs). At least 12 PDE families have now been distinguished on the basis of substrate specificity, inhibition by selective inhibitors, and by molecular cloning.[33] In airway smooth muscle, PDE3 and PDE4 isoenzymes are involved in

cAMP-mediated relaxation, whereas in inflammatory cells (mast cells, eosinophils, neutrophils, macrophages, T-lymphocytes) and airway epithelium, PDE4 predominates. This has led to the development of several selective PDE4 inhibitors for the treatment of asthma and chronic obstructive pulmonary disease (COPD), although side effects after oral administration are a major problem that has limited development.[34] Each PDE has several isogenes and each subtype of PDE has several splice variants, so multiple forms of PDE exist in the cell. This may allow precise control of intracellular cyclic nucleotide concentrations. For example, there are four distinct PDE4s (PDE4A, PDE4B, PDE4C, and PDE4D), each of which has several splice variants that are differentially expressed and regulated.[35] This may be relevant in drug design. Thus, inhibition of one subtype may mediate the desired effect and another may be responsible for side effects. For example, PDE4B appears to mediate the anti-inflammatory effect of PDE4 inhibitors, whereas PDE4D mediates the nausea and vomiting that are often dose-limiting.[36,37]

Phosphatidylinositol Hydrolysis

Another signaling system involves breakdown of a membrane phospholipid, phosphatidylinositol (PI), which results in increased intracellular Ca^{2+} concentration. Over 100 receptors are coupled via G_q or G_i to the membrane-associated enzyme phosphoinositidase or phospholipase C (PLC), which converts phosphoinositide(4,5)bisphosphate (PIP2) to inositol (1,4,5)trisphosphate (IP_3) and *1,2 sn*-diacylglycerol (DAG) (Fig. 8-10). Four main groups of PLC have now been identified (PLC-β, PLC-γ, PLC-δ, PLC-ε), each of which has subclasses (e.g., PLC-β1, PLC-β2, PLC-β3) based on amino acid structure of different cloned genes.[38] These isoenzymes are differentially coupled to different receptors and are subject to differential regulation.

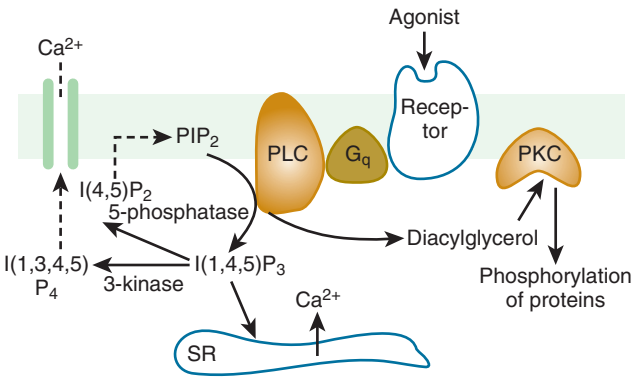

FIGURE 8-10 ■ Phosphoinositide hydrolysis is shown. Occupation of a surface receptor leads to activation of the enzyme phospholipase C (PLC) via a G protein (G_q). PLC converts phosphoinositide 4,5,-bisphosphate (PIP_2) to inositol (1,4,5) trisphosphate and diacylglycerol. $I(1,4,5)P_3$ binds to receptors on sarcoplasmic/endoplasmic reticulum (SR) to release calcium ions (Ca^{2+}), resulting in a rise in intracellular Ca^{2+} concentration and cell activation. $I(1,4,5)P_3$ is dephophorylated to $I(4,5)P_2$, inositol phosphate and inositol, which is then re-incorporated into membrane phophoinositides. In some cells, it is further phosphorylated to $I(1,3,4,5)P_4$, which may be involved with calcium entry and refilling of intracellular stores. Diacylglycerol activates protein kinase C (PKC), which phosphorylates various regulatory proteins in the cell.

IP_3 binds to a specific receptor on endoplasmic/sarcoplasmic reticulum, leading to the release of Ca^{2+} from intracellular stores. Thus, PI hydrolysis links occupation of a surface receptor to intracellular Ca^{2+} release. Most of the mediators that contract airway smooth muscle act on receptors activating PI hydrolysis in airway smooth muscle.[39] IP_3 is broken down into the inactive IP_2 by IP_3 kinase and subsequently to inositol, which is reincorporated into phophoinositides in the cell membrane. IP_3 may also be phosphorylated by IP_3 kinase to IP_4, which may be involved in opening receptor-operated calcium channels and the refilling of intracellular stores. Using the fluorescence indicator dye fura-2, it has been possible to monitor changes in intracellular [Ca^{2+}] in response to receptor-mediated activation. In addition, IP_3 has been introduced into cells in a "caged" inactive form that may then be activated by a flash of light, to allow the kinetics of activation to be investigated. The use of these techniques in single cells has demonstrated that calcium release in response to agonists or IP_3 occurs in a series of oscillations, which is probably mediated via calcium-induced calcium release and the opening of calcium channels on the cell membrane.[40] The frequency of oscillation may be important in the type of cell activation that ensues.

The formation of DAG activates PKC by causing it to translocate to the cell membrane and by dramatically increasing its sensitivity to Ca^{2+}. Activated PKC is then capable of phosphorylating various cell membrane-associated proteins, including some receptors, G proteins, and regulatory proteins. Many isoenzymes of PKC are now recognized, and they play a critical role in the regulation of inflammatory and structural cells of the airways, although the role of individual isoenzymes in regulating cell function is not yet clear, because selective inhibitors have been difficult to find.[41] One isoenzyme may be activated by arachidonic acid, a product of phospholipase A_2 hydrolysis. DAG is also formed by the activation of phospholipase D on phosphatidic acid, representing yet another level of complexity.[42] PKC may be activated directly by tumor-promoting phorbol esters, such as phorbol 12-myristate 13-acetate (PMA), which have therefore been useful in examining the role of PKC. In some species, PMA and other phorbol esters cause prolonged contractile responses in airway smooth muscle, but in other species, bronchodilation is observed. It has been suggested that PKC may be important for the prolonged contractile responses seen in asthmatic airways. Several PKC isoenzymes have been identified in human airway smooth muscle.[43] PKC inhibitors, such as staurosporine (which is not very selective) and Ro 31-8220, have been developed and may be useful in elucidating the role of PKC, but they are nonselective for different isoforms. PKC is involved in activation of inflammatory cells and in particular the release of oxygen-derived free radicals from these cells.[44]

Guanylyl Cyclase

It was previously believed that, while relaxation of smooth muscle is brought about by receptors that activate cAMP, contraction is due to the production of another cyclic nucleotide, cyclic 3′,5′-guanosine monophosphate (cGMP), formed by the activation of guanylyl cyclase.[45] This is now known to be incorrect and the increase in cGMP is secondary to a rise in intracellular Ca^{2+} concentration. Indeed, cGMP causes relaxation of smooth muscle and is the major mechanism of vasodilation after nitrovasodilators (such as sodium nitroprusside) and dilators (such as ACh), which release NO from endothelial cells. cGMP is also involved in the relaxant response of airway smooth muscle to nitrovasodilators and to atrial natriuretic peptide (ANP), which is a potent bronchodilator in vitro.[46] Guanylyl cyclase existing in particulate form binds natriuretic peptides, but also acts in a soluble form that binds NO.[47] cGMP is broken down by PDEs, and in particular the PDE5 isoenzyme.[48] PDE5 inhibitors have potent vasodilator effects on pulmonary vessels and weak bronchodilator effects.

Ion Channel–Coupled Signaling

G proteins may also couple receptors to ion channels, including K^+, Na^+, and Ca^{2+} channels. Thus, certain muscarinic receptors are coupled via G proteins (G_0) to K^+ channels and to Ca^{2+} channels. In airway smooth muscle, β_2-receptors are directly coupled via G_s to the opening of large conductance K^+ (maxi-K) channels, and the same channels are inhibited by M_2-receptors via G_i.[29] These G proteins allow rapid cell activation by GPCR, in contrast to the slower responses mediated by changes in cyclic nucleotides.

Cytokine Receptors

The effects of cytokines are mediated via specific surface receptors, many of which have now been cloned. There is a very complex network of cytokines and chemokines (small chemotactic cytokines) that orchestrate the inflammation in asthma, COPD, and interstitial lung disease. All of their complex effects are mediated by surface receptors.[49]

Chemokine Receptors

Chemokines, such as CXCL8 (IL-8), CCL5 (regulated on activation, normal T cell expressed and secreted [RANTES]), and CCL11 (eotaxin), bind to receptors that are coupled to G proteins. Their receptors have the typical 7TM GPCR structure.[50,51] Many chemokines have overlapping activities and interact with common receptors on target leukocytes. Over 20 chemokine receptors have now been characterized. They appear to be differentially expressed on different inflammatory cells, thus explaining the differential chemotactic effects of these cytokines. For example, eosinophils express CCR3 that is activated by CCL5, CCL13 (MCP-4), CCL11, CCL24 (eotaxin-2), and CCL26 (eotaxin-3), thus accounting for the selective chemotactic effects of these chemokines on eosinophil migration. Because of the 7TM structure of chemokine receptor, small molecule inhibitors are feasible. This has led to the development of several chemokine antagonists for the treatment of asthma and COPD.[52,53]

Most cytokine receptors have a primary structure that is quite different from the 7TM-spanning segments associated with G protein–linked receptors. Many cytokine receptors have at least two subunits that interact to activate signal transduction pathways within the cell.[54] Thus, the receptor for tumor necrosis factor-α (TNF-α) is a 55-kD peptide that has a single transmembrane-spanning helical segment, an extracellular domain that binds TNF-α, and an intracellular domain.[55] The intracellular domain leads to activation of several kinases and ceramide, which subsequently lead to the activation of transcription factors, such as nuclear factor-κB (NF-κB) and activator protein-1 (AP-1). The structure of the receptor is analogous to the nerve growth factor receptor. A second receptor for TNF p75 has also been cloned, but differs markedly in sequence, and may be linked to different intracellular pathways.[55] There are now almost 30 receptors and 20 cytokines in the TNF superfamily, which have complex and interacting signal transduction pathways.[56]

Molecular cloning has now revealed that, although cytokines may be structurally diverse, their receptors may be grouped into various families that share structural homology.[57] One family of receptors includes the receptors for IL-1 and platelet-derived growth factor (PDGF); these receptors belong to the immunoglobulin superfamily, which includes T-cell antigen receptors and certain cell-surface adhesion molecules. Another cytokine receptor superfamily, the hematopoietin receptor superfamily includes receptors for IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, interferons, and granulocyte-macrophage colony stimulating factor (GM-CSF). Prolactin, growth factor, and erythropoietin receptors are also included in this family. The receptor proteins are oriented with an extracellular N-terminal domain and a single hydrophobic transmembrane-spanning segment. There is striking homology in the extracellular ligand-binding domain with four conserved cysteine residues. There is very close homology between the receptors for IL-3, IL-5, and GM-CSF, all of which stimulate growth of eosinophils. Molecular cloning has demonstrated that each of these receptors consists of α and β chains and share a common β chain, which may explain why they have overlapping biologic activities.

The second messenger system used by cytokines is highly complex, involving many interacting pathways that allow for the possibility of signal splitting, so the same activating signal may result in the activation of several parallel pathways. Which signal pathway predominates is determined by other signals impinging on the cell. Most cytokines activate a group of transcription factors and result in prolonged cellular activation and gene transcription, in contrast to the relatively rapid and transient signaling of most GPCRs.

Enzyme-Linked Receptors

Some receptors contain an enzyme domain within their structure, so that when the enzyme is activated by a ligand, the enzyme becomes activated, leading to signal transduction through the formation of a specific substrate within the cell. The best characterized of these enzyme-linked receptors are receptor tyrosine kinases (RTKs), which have intrinsic protein tyrosine kinase activity.

Receptor Tyrosine Kinases

Activation of RTKs results in phosphorylation of tyrosine residues on certain target proteins that are usually associated with cell growth and chronic activation of cells. More than 50 different RTKs belonging to at least 14 distinct families have now been identified.[58] These receptors include the growth factor receptors epithelial growth factor (EGF) receptor, PDGF receptor, vascular-endothelial growth factor (VEGF) receptors, and insulin (Fig. 8-11). Small molecule inhibitors, such as gefitinib and erlotinib, which block EGF receptors, have been developed for treating lung cancer.[59]

All RTKs share a similar general structure, consisting of a large extracellular N-terminal portion, which contains the ligand recognition domain, a single short membrane-spanning region (α-helix), and a cytoplasmic C-terminal portion (~250 amino acids) that contains the tyrosine kinase activity and autophosphorylation sites. The extracellular domain usually contains cysteine-rich regions and/or immunoglobulin-like motifs, with a large number of disulfide bonds forming a highly specific tertiary structure that is needed to establish ligand-binding specificity. All RTKs (with the exception of the insulin receptor family) undergo a transition from a monomeric to a dimeric state (either homodimers or heterodimers) following binding of their specific ligands. Another characteristic of RTKs is that they undergo internalization into two types of intracellular vesicles: pitted vesicles coated with the protein clathrin and smooth vesicles lacking clathrin. There is a spontaneous internalization, but this is rapidly accelerated when the receptor is occupied by a ligand. A proportion of the receptors are degraded, whereas a proportion is recycled to the cell surface.

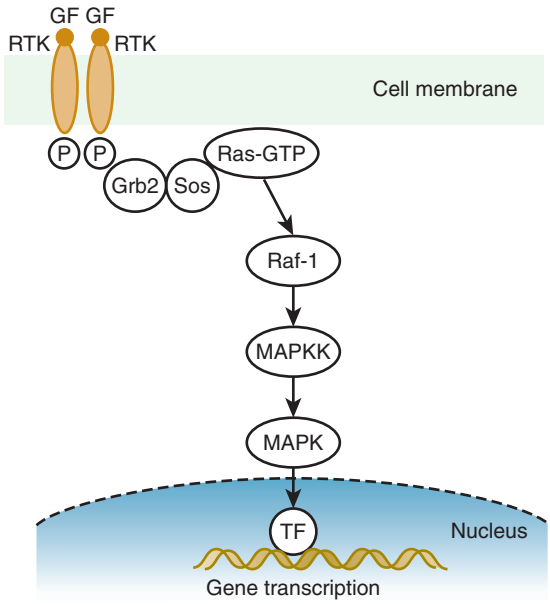

FIGURE 8-11 ■ Activation of receptor tyrosine kinase receptors (RTK) by growth factors (GF) results in a cascade of enzyme activation, involving the adaptor proteins Grb2, Sos, and Ras-GTP, leading to the activation of Raf-1 and mitogen-activated protein kinases (MAPK), which then activate transcription factors (TF) to regulate expression of genes involved in cell proliferation. MAPKK, MAPK kinase.

Signal Transduction

RTKs phosphorylate intracellular molecules containing Src homology 2 and 3 (SH2 and SH3) domains. These SH2 and SH3 domains are short sequences of about 100 and 50 to 60 amino acids, respectively, that function to specify the interaction with a target protein.[60] The SH2 motifs recognize phosphotyrosine residues and are responsible for interactions with autophosphorylated RTKs, whose specificity depends on the amino acid sequences surrounding both the tyrosine autophosphorylation site on the RTK and the substrate's SH2 domain. RTK substrate proteins containing SH2 and SH3 motifs may contain enzymatic activity. The best-characterized RTK enzyme substrates are cytoplasmic protein tyrosine kinases, such as Src, Syk, the $p21^{ras}$-GTPase-activating protein (GAP) and PLC-γ1. Alternatively, the substrate may function as adaptor proteins, composed almost entirely of SH2 and SH3 domains. Examples include Grb2 and the p85 subunit of PI3K.

Most RTKs stimulate the mitogen-activated protein kinase (MAPK) pathways through a complex multistep signaling cascade initiated by translocation of the adaptor protein Grb2 to the cytoplasmic membrane. This results in the activation of Ras proteins, small-molecular-weight GTPases, which in turn activate Raf (a serine/threonine kinase that activates the MAPK pathway[61]). There is increasing evidence that RTKs may interact with several cell-signaling pathways to elicit their effects, and it now seems likely that specific pathways are selected under certain conditions. For example, PDGF, which may exist in the dimeric forms AA, BB or AB, may interact with different receptor dimers (αα, αβ, ββ), resulting in activation of different signal transduction pathways.

MAPK Pathways

RTKs and other extracellular signals activate several MAPK cascades, resulting in a cascade of kinase activation that results in activation of transcription through the transcription factors Jun, Elk-1, and ATF2.[62,63]

Receptor Serine/Threonine Kinases

Similar to RTKs, there are some receptors that are linked to serine/threonine kinase activity. The best known

example is transforming growth factor-β (TGF-β), which exists in three mammalian isoforms encoded by separate genes, all of which may have complex and divergent effects on cell activity.[64] TGF-β receptors signal through regulatory Smad pathways within the cell, including Smad2 and Smad3, together with coactivator Smads, whereas inhibitory Smads, such as Smad6 and Smad7 act as a feedback inhibitory mechanism. Some of the effects of TGF-β are mediated via inhibition of cyclins that regulate the cell cycle, and this may account for the diverse effects of TGF-β depending on the stage of the cycle.[65]

Receptor Protein Tyrosine Phosphatases

Little is known about the third type of enzyme-linked receptors, which have a high level of intrinsic enzyme activity.[66] Occupation by a ligand may turn this enzyme activity off, thus resulting in cell activation. These receptors appear to be important in cell differentiation and include CD45 (also known as "leukocyte common antigen") that is involved in T-lymphocyte signaling.[67]

Ion Channel Receptors

Although several receptors are linked via G proteins to ion channels, such as Ca^{2+} and K^+ channels as discussed previously, other receptors are ion channels themselves. The best-characterized example is the nicotinic acetylcholine receptor (nAChR), which is made up of four subunits that form a cation channel. When activated by Ach, the channel opens to allow the passage of Na^+ ions.[68] This type of receptor, which can respond rapidly because no intracellular mechanisms are involved, is known as a fast receptor and is usually involved in synaptic transmission (Fig. 8-12). nAChRs are involved in ganglionic transmission in parasympathetic ganglia within the airways and are blocked by hexamethonium, which therefore blocks ganglionic transmission and cholinergic reflex bronchoconstriction. nAChRs are widely distributed and α4β2 nAChRs in the brain are responsible for nicotine addiction. Varenicline is a partial antagonist of α4β2 nAChRs acting to block the addictive effects of nicotine and its withdrawal symptoms.[69] Ion channel receptors are oligomeric proteins containing approximately 20 transmembrane segments arranged around a central aqueous channel. Binding of the ligand and channel opening occur very rapidly (within milliseconds). Other examples include glutamate and gamma-aminobutyric acid ($GABA_A$) receptors. This is in contrast to the *slow* receptors, such as GPCRs, which involve a series of catalytic steps.

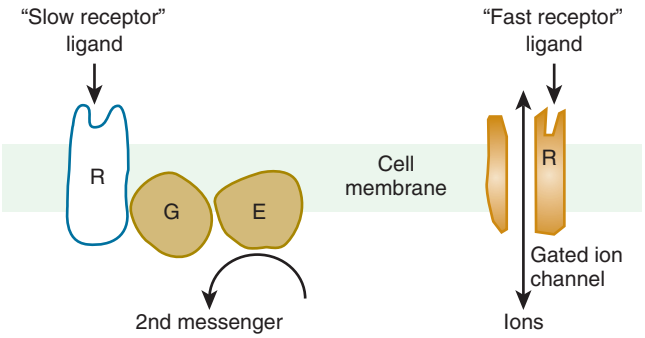

FIGURE 8-12 ■ Fast and slow receptors are depicted. Some receptors are ion channels and consist of several subunits grouped around an aqueous channel through which ions (e.g., Na^+, K^+, Ca^{2+}, Cl^-) enter or leave the cell when agonists bind to one or more of the subunits. Such receptors function very rapidly (in milliseconds) and are involved in neurotransmission (e.g., nicotinic receptors in airway ganglia). Other receptors, which are coupled via G proteins (G), produce their effects more slowly, because a sequence of enzymatic events is necessary before a response occurs. E, enzyme; R, receptor.

Intracellular Receptors

Several ligands cross the cell membrane to interact with intracellular (cytosolic) receptors rather than surface receptors. There is a family of steroid receptors that recognize different endogenous steroids such as glucocorticoids, mineralocorticoids, androgens, and estrogens. Indeed, steroid receptors belong to a supergene family, which also includes thyroid hormone, retinoic acid (vitamin A), and vitamin D receptors.[70] The exploration of cDNA libraries for related sequences has led to the discovery of over 40 "orphan" nuclear receptors, whose ligands are now being identified.[71] One new class of nuclear receptors so identified are the peroxisome proliferator–activated receptors (PPARs), α, γ, and β/δ subtypes have been characterized and selective ligands have now been identified. PPAR may be involved in metabolism and inflammation and may be endogenously activated by lipid mediators.[72] For example, PPAR-γ agonists, such as rosiglitazone, appear to have anti-inflammatory effects on lung inflammation and are also potentially antifibrotic. Thus, they have the potential for treating small airway fibrosis in COPD as well as interstitial lung diseases. Several other orphan receptors, including liver X receptors (LXR), farnesoid X receptors (FXR), pregnane X receptors (PXR), and retinoic acid X receptors (RXR), appear to play roles in the inflammatory processes and may lead to the discovery of novel anti-inflammatory treatments.[73]

Intracellular receptors share a common general structure. There is a central DNA-binding domain, characterized by the presence of 2 "zinc fingers," which are loops stabilized by four cysteine/histidine residues around a zinc ion. These zinc fingers anchor the receptor to the double helix at specific hormone response elements (HREs) in the promoter region of target genes. Ligands bind in the C-terminal domain, which also contains sequences important for binding of associated chaperone proteins (e.g., heat shock proteins) and a nuclear localization signal, involved in transporting the receptor from the cytoplasm into the nucleus. The N-terminal domain is involved in transcriptional regulation and in the interaction with other transcription factors.

Steroid Receptors

Several steroid receptors have now been cloned and their structures have been shown to differ. However,

there is some homology between these receptors: they interact with nuclear DNA, where they act as modulators of the transcription of specific genes. Only a limited number of genes appear to respond directly to steroids. Glucocorticoid receptors (GRs) are normally present in the cytosol in an inactive form bound to two molecules of a 90-kDa heat shock protein (hsp90), which cover the DNA-binding domain. Binding of a steroid to its receptor results in the dissociation of hsp90. The occupied receptor then undergoes a conformational change that allows it to bind to DNA.[74,75]

The DNA-binding domain of steroid receptors is rich in Cys residues. Formation of a complex with zinc is able to fold the peptide chain into a finger-shaped conformation, and the zinc is coordinated by four Cys residues. GRs have two "zinc fingers" which are loops of approximately 15 residues, each of which is held in shape by four cysteine residues surrounding an atom of zinc. Zinc fingers are essential for the interaction with the DNA double helix. Steroid receptors recognize specific DNA sequences—the so-called glucocorticoid response elements (GREs) which have the consensus sequence GGTAnnnTGTTCT. Dimers of GR occupied by steroid bind to the GRE on the DNA double helix and either *increase* (+GRE) or much less commonly *decrease* (–GRE) the rate of transcription by influencing the promoter sequence in the target gene. Indeed, repression of target genes may be the most important aspect of corticosteroid action in inflammatory diseases such as asthma, because corticosteroids may inhibit the transcription of many cytokines that are involved in chronic inflammation. The major mechanism of gene repression is mediated via an interaction between the activated glucocorticoid receptor and transcription factors, such as NF-κB and AP-1 that are activated via inflammatory signals such as cytokines. NF-κB activates inflammatory genes by recruiting coactivator molecules that have histone acetyltransferase activity, leading to acetylation of core histones associated with inflammatory genes, which results in increased gene transcription. Activated GRs inhibit coactivator molecules and also recruit histone deacetylase-2 (HDAC2) which deacetylates the hyperacetylated histones, resulting in switching off of the activated inflammatory genes (Fig. 8-13).[75]

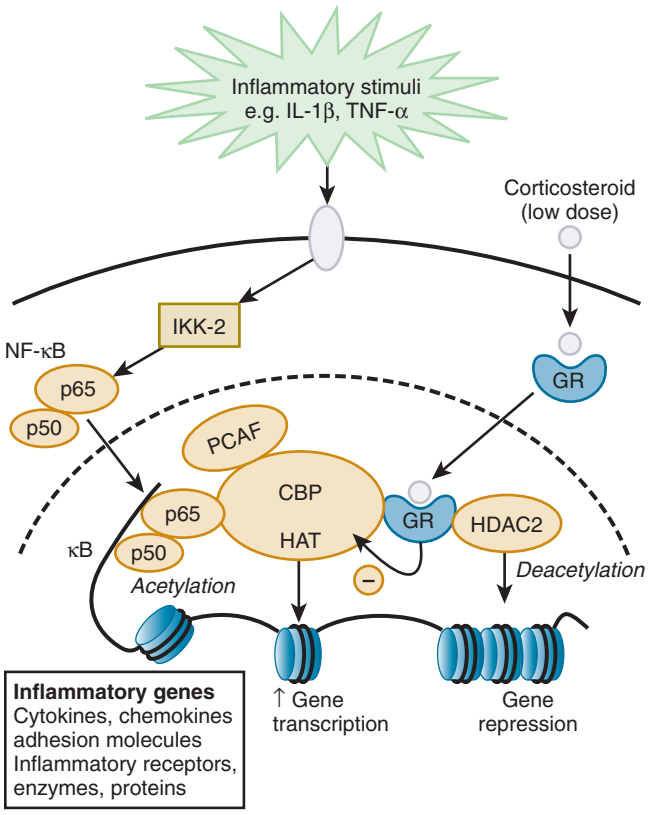

FIGURE 8-13 ■ Corticosteroid suppression of activated inflammatory genes. Inflammatory genes are activated by inflammatory stimuli, such as interleukin-1β (IL-1β) or tumor necrosis factor-α (TNF-α), resulting in activation of IKK2 (inhibitor of I-κB kinase-2), which activates the transcription factor nuclear factor κB (NF-κB). A dimer of p50 and p65 NF-κB proteins translocates to the nucleus and binds to specific κB recognition sites and also to coactivators, such as CREB-binding protein (CBP), which have intrinsic histone acetyltransferase (HAT) activity. This results in acetylation of core histone H4, resulting in increased expression of genes encoding multiple inflammatory proteins. Glucocorticoid receptors (GR), after activation by glucocorticoids, translocate to the nucleus and bind to coactivators to inhibit HAT activity directly and recruit histone deacetylase-2 (HDAC2), which reverses histone acetylation, leading in suppression of these activated inflammatory genes.

Receptor Subtypes

The existence of receptor subtypes is often first indicated by differences in the potency of a series of agonists in different tissues. This could be due to differing proportions of coexistent receptor subtypes, or may indicate the existence of a novel receptor subtype. Molecular biology can resolve these possibilities, because molecular techniques can discriminate between different subtypes of receptor and show that they are encoded by different genes. Thus, the human β_1-receptor is clearly different from the β_2-receptor in its amino acid sequence, with a 54% homology, and the NK_1-receptor, which is selectively activated by substance P, has a 48% homology with the NK_2-receptor, which is activated by the related tachykinin neurokinin A. A third tachykinin receptor, NK_3-receptor, which is selectively activated by neurokinin B has also been cloned. Molecular biology techniques have thus confirmed the evidence for the existence of receptor subtypes obtained by classical pharmacologic techniques, using the rank order of potency of different agonists and antagonists.

Using cross-hybridization in which a known receptor cDNA sequence is hybridized with a genomic library, it has also been possible to detect previously unknown subtypes of a receptor. For example, an atypical β-receptor, which does not clearly fit into the β_1- or β_2-receptor subtypes, has been suspected in adipose tissue and in some smooth muscle preparations. A distinct β_3-receptor has been identified, cloned, sequenced, and expressed.[76] The β_3-receptor is clearly different from either β_1- or β_2- receptors (~50% amino acid sequence homology). β_3-Receptors appear to be important in

regulation of metabolic rate, but they have not been detected in lung homogenates.[77] Without the techniques of molecular biology, this receptor would probably still remain undiscovered. A putative β_4-receptor in cardiac tissue has also been proposed, based on atypical β_1-receptor–mediated responses in cardiac tissue, but this has not been confirmed by cloning.[78]

Molecular biology has been particularly useful in advancing our understanding of muscarinic receptors. Five distinct muscarinic receptors have been cloned from rat and human tissues.[79] The m1-, m2- and m3-receptors correspond to the M_1-, M_2-, and M_3-receptors identified pharmacologically, whereas m4- and m5-receptors are previously unrecognized pharmacologic subtypes that occur predominantly in the brain, and for which no selective drugs have yet been developed. Interestingly, m4-receptors have been demonstrated in rabbit lung using antibodies against the cloned m4-receptor, and their presence has been confirmed by cDNA probes for the m4-receptor. These m4-receptors are localized to vascular smooth muscle and to alveolar walls, but they have not been observed in lungs of other species, including humans.[80] The reason for so many different subtypes of a receptor that recognize a single agonist is still not certain, but it seems likely that they are linked to different intracellular pathways and that the regulation of the intracellular portion of the amino acid sequence may be unique to each receptor subtype. The m1-, m2-, and m5-receptors stimulate PI hydrolysis through a *Pertussis*-insensitive G protein, whereas m2- and m4-receptors inhibit AC via G_i. It is possible that the difference in protein structure may reflect regulation at a transcriptional level from DNA through different promoters, leading to variations in tissue or developmental expression, or to differences at a posttranslational level, allowing regulation by intracellular mechanisms such as phosphorylation at critical sites on intracellular loops.

Receptor Interactions

Activation of one receptor may influence the function of a separate receptor via a number of interacting mechanisms. The opposing effects of receptors that increase and decrease ACe activity via G_s and G_i, respectively, is well described. In airway smooth muscle, M_2-receptors inhibit AC, whereas β_2-receptors stimulate this enzyme. Thus, there are opposing effects. This may explain why it is more difficult for β-agonists to reverse contraction of airway smooth muscle induced by cholinergic agonists compared to histamine. Conversely, β-agonists may also influence the expression of M_2-receptors.[81] Several other interactions between receptors are recognized. Receptors that increase cAMP oppose the effects of receptors that elevate intracellular Ca^{2+} via several mechanisms, including stimulation of Ca^{2+} sequestration and exchange.[82]

PI hydrolysis leads to activation of PKC, which then phosphorylates receptors and G proteins, resulting in uncoupling and impaired receptor function (Fig. 8-14).[83] In airway smooth muscle, this may be an important interaction in inflammation, because inflammatory mediators

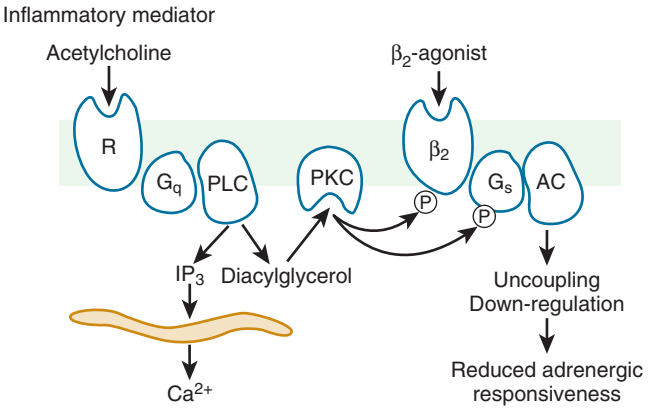

FIGURE 8-14 ■ Receptor interactions. The activation of one surface receptor may affect the function of a different receptor type via interaction of intracellular mechanisms. For example, activation of an inflammatory mediator or muscarinic receptor (R) on airway smooth muscle cells may stimulate phosphoinositide hydrolysis, with activation of protein kinase C (PKC) via diacylglycerol formation. This may result in phosphorylation (P) of other receptors, such as β_2-receptors (β) or a stimulatory G protein (G_s), resulting in down-regulation and uncoupling of β-receptors, with reduced responsiveness to β-agonists. AC, adenylyl cyclase; G_q, receptor-coupled G protein that activates phosphoinositide hydrolysis; IP_3, inositol (1,4,5) trisphosphate; PLC, phospholipase C.

will stimulate PI hydrolysis in airway smooth muscle cells, and will phosphorylate G proteins via activation of PKC, leading to uncoupling of β_2-receptors. This may explain the reduced bronchodilator response to β-agonists in vitro observed in airways taken from patients with fatal asthma attacks. G protein–receptor kinases (GRKs) may be activated by GPCR occupation and then phosphorylate other receptors, leading to altered signaling in heterologous GPCRs.[84] Receptor interactions may also occur through receptor heterodimerization as discussed previously.

An additional type of interaction may operate at the level of gene transcription: Cytokines may activate transcription factors that have an effect on a target gene. Furthermore, steroid receptors may interact with the same gene with an opposing effect. There may also be a direct interaction between transcription factors within the cytoplasm. For example, activated glucocorticoid receptors bind directly to the AP-1 complex and thereby prevent its interaction with the target gene. In human lung, for example, cytokines such as TNF-α and phorbol esters that activate PKC lead to activation of AP-1 and NF-κB binding to DNA; this effect may be blocked by glucocorticoids. cAMP may exert a profound modulatory effect on MAPK signaling pathways and may activate the transcription factor cAMP response element–binding protein (CREB), which itself interacts with GRs and with AP-1.[85]

A good example of receptor interaction is provided by the interaction of β_2-receptors and GR, an effect that is relevant to the treatment of asthma and COPD. Thus, for example, combination inhalers containing a long-acting β_2-agonist and a corticosteroid are now commonly

used as first-line therapy. Corticosteroids increase the expression of β_2-receptors in lungs and thus enhance the effects of β_2-agonists and prevent receptor down-regulation.[86,87] In turn, β_2-agonists increase the action of GR by facilitating nuclear translocation to the cytoplasm and increasing the binding of GR to GRE, thus increasing the effects of corticosteroids.

DRUG-RECEPTOR INTERACTIONS

The binding of a drug to its receptor is a dynamic process and follows the laws of mass action. At equilibrium, there is a balance between the rate of association and the rate of dissociation of a drug. The concentration of drug giving half maximal activation is the EC_{50}, which describes the potency of the drug. The *affinity* of the drug describes the balance between association and dissociation and can be quantified as the dissociation constant K_d, which is the logarithm of the concentration of drug needed to occupy 50% of the receptors. Drugs with a low K_d therefore have a high affinity for their receptor.

Radioligand Binding

Binding between a hormone or drug and its receptor may be studied directly by radioligand binding. A radiolabeled ligand (usually a high-affinity antagonist, such as [^{125}I]iodocyanopindolol for β-receptors) is incubated with a receptor preparation (either a membrane preparation from the tissue of interest or, in the case of some ligands, with intact cells). The binding interaction between ligand and receptor obeys the law of mass action. As the concentration of ligand is increased, the proportion of ligand binding to receptors increases until saturation occurs when all the receptors are occupied. Nonspecific binding to nonreceptor sites is determined by parallel incubations with radioligand in the presence of an excess of unlabeled agonist or antagonist (e.g., 200 μM isoproterenol or 1 μM propranolol for β-receptors). Specific binding (i.e., total nonspecific binding) may be analyzed by a Scatchard plot, which will give a straight line if a single class of binding site is involved, the slope of which is related to binding affinity ($1/K_d$) and the intercept on the x-axis gives the maximum number of binding sites (Bmax)—a measure of receptor density (Fig. 8-15). Radioligand-binding studies can also be used to investigate selectivity of drugs for the receptor using competition between the competitor drug and a fixed concentration of radioligand. Receptors may be characterized in this way, using the rank order of potency of agonists or antagonists.

Binding studies can also be used to determine the distribution of receptors in tissues, using autoradiography. The radioligand is incubated with frozen sections of the tissue of interest using optimal conditions and using an excess of nonradiolabeled competitor to define nonspecific binding, as in membrane-binding studies. The distribution of specific binding is then used to **indicate and map** tissue localization of receptors.

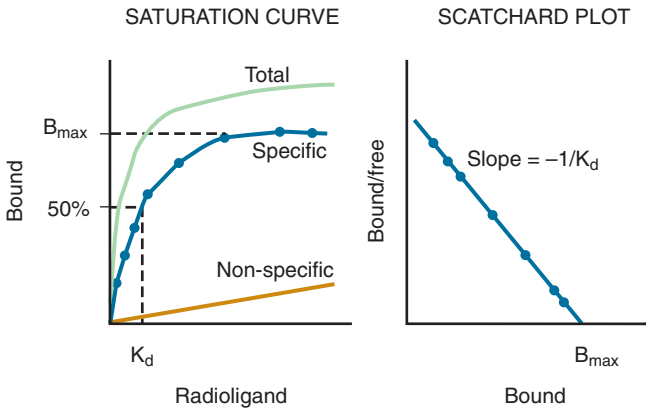

FIGURE 8-15 ■ A Scatchard plot of receptor binding (bound) is shown. With a single receptor population, a plot of bound/free against bound ligand gives a straight line with a slope inversely related to the dissociation constant (K_d) and an intercept equal to the maximal number of binding sites (Bmax).

Agonists and Antagonists

After binding to the receptor, the response is activated via second messenger systems described previously. Different agonists may elicit variable degrees of response, which is described as *efficacy*. A drug that produces less than a maximal response (Emax) is known as a *partial agonist*. In airway smooth muscle, isoproterenol is a full agonist and produces a maximal response, whereas albuterol and salmeterol act as partial agonists, giving less than 50% of the maximal relaxation seen with isoproterenol.

Antagonists have zero efficacy. They block the effects of an agonist by interfering with its binding to the receptor. When antagonists interact with agonists at a common receptor, the antagonism is competitive. This can be demonstrated by a rightward shift in the log concentration-response curve (Fig. 8-16). For true competitive antagonism (e.g., between a β_2-antagonist and a β-agonist in airway smooth muscle), the shift is parallel. The amount of shift observed with each concentration of agonist can be used to calculate the affinity of the antagonist for the particular receptor.

Sometimes, a drug interferes with an agonist effect in a noncompetitive manner by inhibiting any of the steps that lead to the typical agonist effect. This results in a nonparallel shift in the agonist dose-response curve and a reduced maximal response (see Fig. 8-16). Studies with overexpressed GPCRs or mutated receptors have demonstrated that there may be constitutive activation of the receptor in the absence of agonists. Drugs that reduce this constitutive activation by binding to the receptor are known as *inverse agonists*.[88] It is now clear that many drugs that were assumed to be antagonists at GPCRs act as inverse agonists, and this may be explained by stabilization of the inactive state of the receptor.[89] There may be constitutive overactivity of GPCRs in disease, and this could account for phenomena such as bronchoconstriction after β-adrenergic blockers in asthmatics but not in

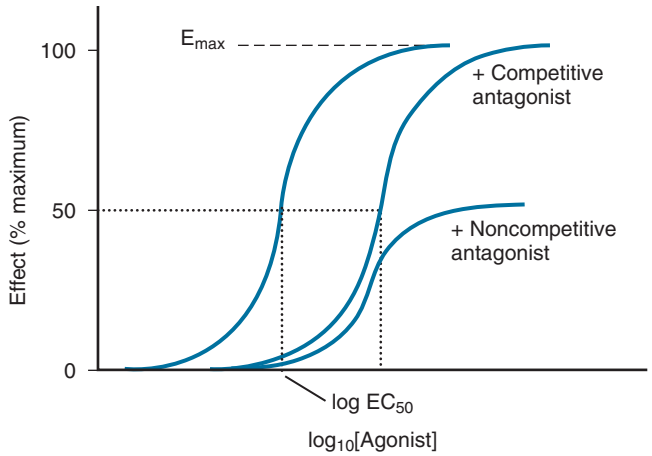

FIGURE 8-16 ■ Dose-response curve to an agonist is affected by the presence of antagonists. A competitive antagonist causes a parallel rightward shift in the dose-response curve, with an increase in the concentration of drug that yields half-maximal activation (EC_{50}) but no change in the maximal response (Emax), whereas a noncompetitive antagonist shifts the dose-response to the right in a nonparallel fashion and also decreases Emax.

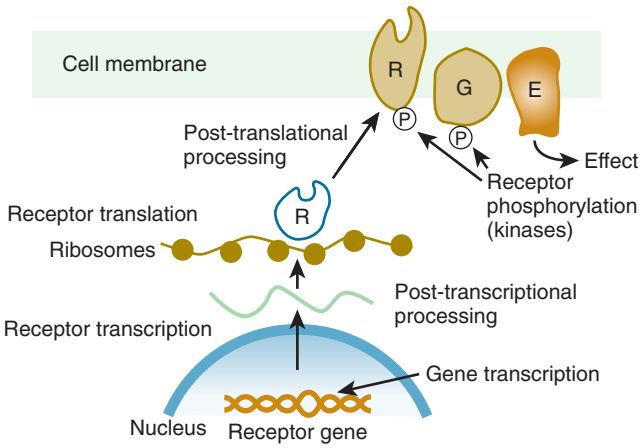

FIGURE 8-17 ■ Regulation of receptor expression. The expression and function of surface receptors can be regulated in several ways, including effects on receptor synthesis (gene transcription, posttranscriptional processing/mRNA stability, protein translation and posttranslational processing). Once the receptor is inserted in the membrane, it can be inactivated and uncoupled by phosphorylation via various kinases. E, effect; G, G protein; P, phosphorylation; R, receptor.

normal individuals, for example, as a result of the inverse agonism of certain β-blockers.[88]

Another type of antagonism relevant to lung diseases is *functional antagonism*, which describes an interaction between two agents that have opposite functional effects on the same cellular response. Thus, β-agonists act as functional antagonists in airway smooth muscle because they counteract the contractile effects of any spasmogen, including histamine, LTD_4, thromboxane, bradykinin, and ACh.

Two drugs may interact to produce effects that are more than additive. When two drugs given together produce a greater effect than the additive effect of the drugs given separately the result is known as *synergy*. *Potentiation* occurs when one drug given alone has no effect, but increases the response to a second drug. *Tolerance* refers to a diminishing response to a drug that is administered repeatedly, whereas *tachyphylaxis* usually describes tolerance of rapid onset. Tolerance may be seen after only one administration of a drug. *Desensitization* is a term that includes rapid and long-term loss of response.

The interaction between a ligand and its receptor has several characteristics. Binding is rapid reversible, and temperature-dependent. There is stereoselectivity with the *levo*-isomer (*R*-isomer) usually binding more effectively than the *dextro*-isomer (*S*-isomer). Many ligands are a mixture of the active *R*-isomer with the inactive *S*-isomer. Thus, the racemic mixture has half of the activity. It is claimed that for some racemates the inactive isomer is actually detrimental. For example, *S*-albuterol (levalbuterol) has been reported to increase airway hyperactivity in animal models, observing that the *R*-albuterol is more effective than *RS*-albuterol.[90] However, no clear advantage of *R*-albuterol over *RS*-albuterol has been demonstrated in clinical studies.[91]

RECEPTOR REGULATION

Receptors are subject to many regulatory factors operating at several sites (Fig. 8-17). Some factors influence the gene transcription of receptors, either increasing or decreasing transcription. Other factors influence the stability of mRNA and thus the amount of receptor protein that is formed. Translation of receptor protein may also be regulated. Once the receptor protein is inserted into the membrane, the receptor may be regulated by phosphorylation as a result of various receptor kinases. Receptor phosphorylation is one of the major means or receptor regulation.[92] Some receptors are also tyrosine-nitrated or ubiquitinated, resulting in abnormal function and increased degradation.

Desensitization

Tachyphylaxis or desensitization occurs with most receptors when exposed to an agonist. This phenomenon has been studied in some detail with β_2-receptors and involves several distinct processes that may operate simultaneously or sequentially.[93]

G Protein–Receptor Kinases

In the short term, desensitization involves *phosphorylation* that uncouples the GPCR from G_s, via the action of enzymes called *G protein receptor kinases*, of which seven are now identified.[94] This has been studied in most detail for β-receptors, which are phosphorylated by GRK2, also known as β-adrenergic receptor kinase (βARK). The site of this phosphorylation appears to be on the Ser/Thr-rich region of the third intracellular loop and the C-terminal tail, because their replacement reduces the rate of desensitization. GRK2 is also involved

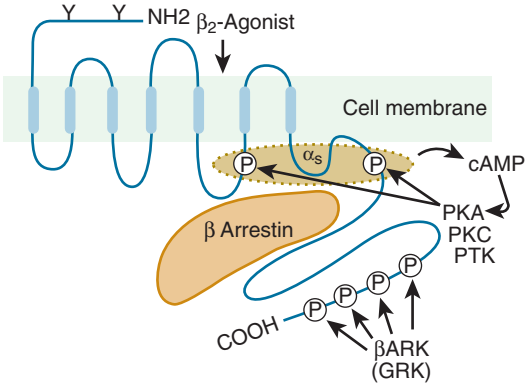

FIGURE 8-18 ■ Mechanisms of short-term desensitization of β_2-adrenergic receptors. The β-receptor is phosphorylated by β-adrenergic receptor kinase (βARK) and other G protein receptor kinases (GRK) on its carboxyl tail (COOH), resulting in increased binding of β-arrestin, which leads to uncoupling of the receptor from the α-subunit of the stimulatory G protein (α_s) and internalization of the receptor. Protein kinase A (PKA), activated by an increase in cyclic 3′,5′ adenosine monophosphate (cAMP), phosphorylates the receptor at other sites on the third intracellular loop or may phosphorylate GRK. Protein kinase C (PKC) and protein tyrosine kinases (PTK) may also phosphorylate the receptor, resulting in uncoupling.

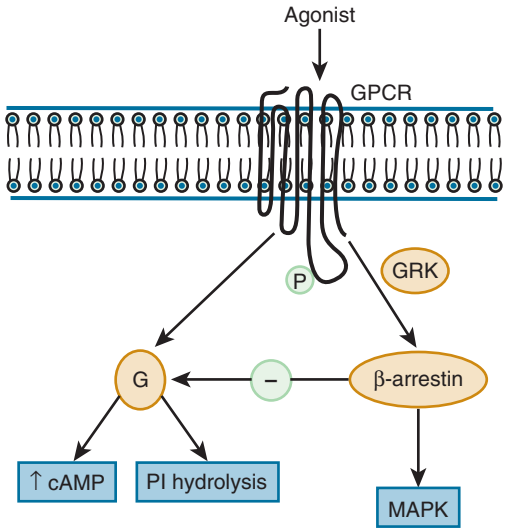

FIGURE 8-19 ■ G protein–coupled receptors signal through G proteins and also via β-arrestins. When the receptor is occupied by its agonist, signal transduction pathways are activated, such as changes in cyclic AMP (cAMP) or increased phosphoinositide (PI) hydrolysis. Agonists also phosphorylate the receptor via G protein receptor kinases (GRK), which recruit β-arrestin that then stimulates other signaling pathways, such as mitogen-activated protein kinases (MAPK) and also inhibits G protein–mediated signal transduction.

in the phosphorylation of several other receptors, including muscarinic and tachykinin receptors. The expression of GRK2 varies among cells. There is low expression of GRK2 in airway smooth muscle cells that show resistance to desensitization, whereas expression of this enzyme is high in mast cells, which are much more easily desensitized.[95] GRK2 expression is increased in lungs after exposure to β_2-agonists, thus contributing to uncoupling of β_2-receptors.[96] Expression is increased by corticosteroids, which reverse uncoupling and restore responsiveness to β_2-agonists.[97] GPCRs are also regulated by other kinases, including PKA and PKC.[92] For β_2-receptors, this appears to be via phosphorylation of GRK2, enhancing its ability to uncouple receptors, rather than direct phosphorylation of β_2-receptors.

Arrestins

Another protein, β-arrestin, is also involved in uncoupling the phosphorylated β-receptor from the G protein and in resensitization of receptors (Fig. 8-18). There are two β-arrestins, and they appear to be universally expressed and involved in the coupling of many GPCRs. β-Arrestins determine whether β_2-receptors are degraded within the cell by endocytosis or are recycled to the cell membrane (Fig. 8-19).[98] In addition to terminating receptor function, β-arrestins also allow receptors to interact with signal transduction pathways (such as MAPK and PI3K) independently and therefore allow the receptor to regulate different responses in the cell. Ligands that preferentially stimulate the interaction between receptor and β-arrestins have now been identified, and these drugs may have a different spectrum of activity from the classical drugs that activate receptor–G protein coupling. Ligands that are biased toward receptor–G protein interaction with less effect on β-arrestins do not desensitize the receptor and thus have greater and more prolonged effects.

Down-Regulation

Longer-term mechanisms of desensitization include down-regulation of surface receptor number, a process that involves internalization (*sequestration*) of the receptor and its subsequent degradation. Down-regulation of β_2-receptors results in a rapid decline in the steady-state level of β_2-receptor mRNA. This suggests that down-regulation is achieved in part either by inhibiting the gene transcription of receptors or by increased posttranscriptional processing of the mRNA in the cell. Using actinomycin D to inhibit transcription, it has been found that β_2-receptor mRNA stability is markedly reduced in these cells after exposure to β-agonists.[99] Furthermore, by isolating nuclei and performing a nuclear run-on transcription assay, it is apparent that β-agonist exposure does not directly alter receptor gene transcription. Longer-term exposure to β-agonists may also result in inhibition of β-receptor gene transcription, mediated via the effects of a CREB. Long-term exposure to β-agonists results in reduced transcription of β_2-receptors in the airways.[100,101]

Steroid Modulation

Certain G protein–linked receptors are also influenced by glucocorticoids. Thus, pulmonary β-receptors are increased in density by pretreatment with glucocorticoids.[102] Corticosteroids increase the steady-state level of

β_2-receptor mRNA in cultured smooth muscle cells, indicating that steroids may increase β-receptor density by increasing the rate of gene transcription. The increase in mRNA occurs rapidly (within 1 hour), preceding the increase in β-receptors, and then declines to a steady-state level about twice normal. The cloned β-receptor gene contains three potential glucocorticoid responsive elements, and incubation of human lung with glucocorticoids results in a doubling of the rate of transcription.[102] By contrast, corticosteroids decrease transcription of tachykinin NK_2 receptors.[103]

Receptor Ontogeny

Another area in which molecular biology of receptors may be relevant is in studying the development of receptors and the factors that determine expression of particular receptor genes during development. In fetal lung, there is a marked increase in the expression of β_2-receptors in the perinatal period, an effect that is critically dependent on glucocorticoids.[104] There may be differential expression of receptor subtypes during development. For example, muscarinic receptor subtypes in the lung show differential changes during the perinatal period.[105] Receptors also play an important role in lung development. For example, receptors for hepatocyte growth factor are expressed in airway epithelium during lung development and appear to be involved in the branching of airways.[106]

Pulmonary Diseases

There are several pulmonary diseases in which altered expression of receptors may be relevant to understanding their pathophysiology. Molecular biology offers a new perspective in investigating these abnormalities of receptor expression by providing insights into whether the abnormality arises through altered transcription of the receptor gene or abnormalities in posttranscriptional or posttranslational processing. There is some evidence that β-adrenoceptor function may be impaired in airway smooth muscle of patients with fatal asthma.[107] However, binding and autoradiographic studies have not demonstrated any reduction in β-receptors in airway smooth muscle, suggesting that the reduced bronchodilator responses to β-agonists may be due to uncoupling of the receptor.[108] Similarly, no differences in muscarinic receptors have been detected in asthmatic lungs using binding approaches.[108]

Relatively few studies have explored whether there are any differences in the expression of mediator receptors in asthmatic airways. There is some evidence for increased expression of platelet-activating factor (PAF)-receptor mRNA in lungs of asthmatic patients, although whether this has functional significance is not known.[109] Bradykinin B_1- and B_2-receptors are up-regulated by inflammatory stimuli such as TNF-α, and this effect appears to be due to prolongation of mRNA half-life.[110] There is also evidence for increased NK_1-receptor expression in the lungs of patients with asthma and COPD.[111,112]

Transcriptional Control

Receptor genes, like other genes, may be regulated by transcription factors, which may be activated within the cell under certain conditions, leading to increased or decreased receptor gene transcription, which may in turn alter the expression of receptors at the cell surface. Little is known about the transcription factors that regulate receptors, but these factors may be relevant to diseases, such as chronic inflammation. The transcription factor AP-1, a Fos-Jun heterodimer, may be activated via PKC. AP-1 has been shown to increase transcription of several genes, including some receptor genes. For example, the gene coding for the NK_1-receptor has an AP-1 site, which leads to increased gene transcription and a GRE site, which conversely results in decreased transcription.[113] Chronic cell stimulation, via activation of PKC, may therefore lead to an increase in NK_1-receptor gene expression, which could lead to increased neurogenic inflammation. An increased NK_1-receptor gene expression is present in asthmatic airways.[111] By contrast, glucocorticoids reduce NK_1-specific mRNA in human lungs, probably via an inhibitory effect of glucocorticoid receptors on AP-1.

ION CHANNELS

Movement of ions across the cell membrane is important in determining the state of cell activation. Ions cross the cell membrane through protein-lined pores called "channels," several of which have now been cloned and characterized electrophysiologically. Most channels are made up of distinct subunits that are grouped together in the cell membrane (e.g., nAChRs as discussed previously). Whether the channel is open or closed depends on different factors for each channel, but may be determined by receptor activation, the polarization of the cell membrane, or the presence of particular ligands that interact directly with the channel.

Calcium Channels

Voltage-Gated Channels

Several types of calcium ion (Ca^{2+}) channels have now been identified and characterized electrophysiologically by molecular cloning and with the use of antagonists and toxins. Voltage-gated channels mediate Ca^{2+} entry into cells in response to membrane depolarization. Electrophysiologic studies reveal different Ca^{2+} currents designated L-, N-, P-, Q-, R-, and T-type. High-voltage-activated Ca^{2+} channels that have been characterized biochemically are complexes of a pore-forming α1-subunit of approximately 190 to 250 kDa, a transmembrane, disulfide-linked complex of α2- and δ-subunits, an intracellular β-subunit, and in some cases, a transmembrane γ-subunit. Ten α1-subunits, four α2δ complexes, four β-subunits, and two γ-subunits are now identified.[114] The Cav1 family of α1-subunits conduct L-type Ca^{2+} currents, which initiate muscle contraction, endocrine secretion,

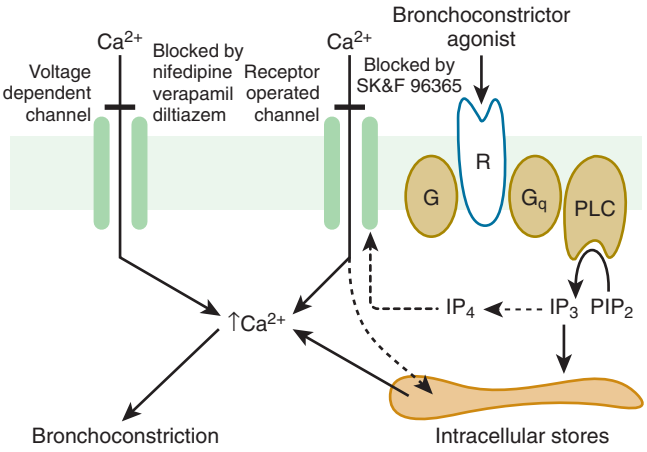

FIGURE 8-20 ■ Calcium ion (Ca^{2+}) channels. There are at least two classes of calcium channels in the cell membrane. One is activated by depolarization (voltage-dependent channels) and the other via receptors (R). Calcium ions (Ca^{2+}) are also released from intracellular stores via phosphoinositide hydrolysis and the action of inositol (1,4,5) trisphosphate (IP_3). G, G protein; IP_4, inositol (1,3,4,5) tetrakis phosphate; PIP_2, phosphoinositide 4,5,-bisphosphate; PLC, phospholipase C.

and gene transcription and are regulated by protein phosphorylation. The Cav2 family of α1-subunits conduct N-type, P/Q-type, and R-type Ca^{2+} currents, which initiate rapid synaptic transmission and are regulated primarily by direct interaction with G proteins and SNARE proteins and secondarily by protein phosphorylation. The Cav3 family of α1-subunits conduct T-type Ca^{2+} currents, which are activated and inactivated more rapidly and at more negative membrane potentials than other Ca^{2+} current types.

L-Type channels (for long-lasting) open in response to depolarization of the cell, resulting in influx of Ca^{2+} to increase intracellular Ca^{2+} concentration (Fig. 8-20); these channels are blocked by dihydropyridines, such as nifedipine, and by verapamil. Voltage-sensitive calcium channels are important in contractile responses of pulmonary vascular smooth muscle, but are less important in the contractile response of airway smooth muscle or in the activation of inflammatory cells. T-Type calcium channels are also opened by depolarization but are insensitive to dihydropyridines. Electrophysiologic studies have revealed the presence of both L- and T-channels in airway smooth muscle, although the L-channels are less sensitive to dihydropyridines than the L-channels in the myocardium.[115] N-Type channels, which are largely restricted to neurons, are also sensitive to depolarization and insensitive to dihydropyridines, but are blocked by ω-conotoxin.

Receptor-Operated Channels

Receptor-operated channels (ROCs) are channels that open in response to activation of certain receptors; these receptors are not well defined but, recently, blockers have been developed. Contraction of airway smooth muscle in response to agonists such as acetylcholine and histamine is independent of external Ca^{2+} and is not associated with ^{45}Ca uptake, suggesting that calcium entry is not important for initiation of contractile responses. Entry of Ca^{2+} via ROCs may be important in refilling intracellular stores. ROCs are members of an increasing group of calcium channels called transient receptor potential (TRP) cation channels, which is a superfamily of at least over 30 channel proteins divided into 6 main groups. TRP channels are involved in regulation of inflammatory cells, structural cells, and sensory nerves and may be important novel targets for drug discovery.[116] For example, TRPV channels on sensory nerves mediate the response to capsaicin and acids. TRPC3 and TRPC6 are expressed in human airway smooth muscle and may correspond to ROCs involved in Ca^{2+} entry.[117]

A rise in intracellular Ca^{2+} concentration is associated with cell activation, but recovery depends on removal of Ca^{2+} by sequestration or by pumping Ca^{2+} out of the cell in exchange for Na^+. In airway smooth muscle, there is a pump that exchanges $3Na^+$ for each Ca^{2+}. It is linked to the activity of Na^+-K^+-ATPase, which maintains the inwardly directed Na^+ gradient by exchanging intracellular Na^+ for extracellular K^+. In airway smooth muscle, there is also an active uptake of Ca^{2+} into intracellular stores that may be stimulated by cAMP.[39]

I_{CRAC}

When Ca^{2+} is released from intracellular stores via the action of IP_3, these stores are refilled by calcium entry via specific channels called CRAC, measured as a current called I_{CRAC} (Ca^{2+} release-activated Ca^{2+} current) that is activated by depletion of intercellular stores (store-operated calcium entry).[118] This is an important mechanism in inflammatory cells, such as mast cells and T lymphocytes. Inhibitors of I_{CRAC} are therefore potential immunomodulators or antiallergy drugs. TRPC1 is thought to function as a component of store-operated calcium channels.[119]

In airway smooth muscle, several types of calcium channels have been identified. These may lead to contraction via different spasmogens. L-Channels respond to depolarization, and ROCs are activated by various spasmogens, but contraction initially is independent of Ca^{2+} entry and due to release of Ca^{2+} from internal stores in response to IP_3. These internal stores are then refilled via store-operated calcium channels. In addition, cyclic adenosine diphosphate (cADP)-ribose also mobilizes calcium from the sarcoplasmic reticulum by acting on ryanodine receptors.[39]

Potassium Channels

Recovery of cells after depolarization depends on the movement of potassium ions (K^+) out of the cell via K^+ channels in the cell membrane. This results in hyperpolarization of the cell with relaxation of smooth muscle and inhibition of cell activity. Conversely, blockade of K^+ channels with drugs such as tetraethylammonium and 4-aminopyridine results in increased excitability or

hyperresponsiveness of cells. More than 50 different K^+ channel genes have been identified in humans, using selective toxins, patch-clamping techniques, and cloning.[120] K^+ channels may be subdivided into four main classes:

1. *Voltage-gated channels*, which open on depolarization of the membrane, which are rectifying channels that return the cell membrane to its previous polarized state. This is a diverse group of channels, some of which are blocked by α-dendrotoxin.
2. *Ca^{2+}-activated channels* open in response to elevation of intracellular Ca^{2+} concentration. Large conductance (maxi-K and big) K^+ channels are found in smooth muscle and neurons and are blocked by the scorpion venoms charybdotoxin and iberiotoxin as well as several small molecules.[121] Small conductance channels, some of which are blocked by apamin are found in neurons.
3. *Receptor-coupled channels* are opened by certain receptors via a G protein, but no specific blockers have been found.
4. *ATP-sensitive channels* are opened by a fall in intracellular ATP concentration. These channels are found in smooth muscle and in the islet cells of the pancreas. They are blocked by sulfonylureas, such as glibenclamide, and are opened by drugs such as cromakalim (BRL 34915), its active enantiomer lemakalim (BRL 38227), RP 53891, and by HOE 245.

K^+ channels play an important role in relaxation of airway smooth muscle.[122,123] β-Agonist-induced bronchodilation is markedly inhibited by charybdotoxin,[124] indicating that opening a maxi-K channel is involved in the relaxant response. K^+ channel openers, such as cromakalim and levcromakalim act on ATP-sensitive K^+ channels and are dilators of animal and human airways.[125] K^+ channel openers therefore have potential as bronchodilators and vasodilators, although when given orally, they may cause cardiovascular side effects due to systemic vasodilation which limit their usefulness in asthma therapy.[122] K^+ channels are also involved in neurotransmitter release. Cromakalim inhibits cholinergic neurotransmission and the release of neuropeptides from sensory nerves in airways.[126] Modulation of neurotransmission is also mediated by opening of maxi-K channels, because charybdotoxin reverses the modulatory effect of many agonists on sensory and cholinergic nerves.[127] K^+ channels are also involved in mucus secretion.[128] K^+ channel openers therefore have several potential applications in the therapy of airway disease.[129]

Sodium Channels

Na^+ channels are involved in depolarization and release of neurotransmitters. Drugs that block Na^+ channels, such as tetrodotoxin and local anesthetics, act as nerve blockers. However, tetrodotoxin has no direct effect on smooth muscle, however. Na^+ channels in airway epithelium (ENaC) play an important role in regulating mucus hydration and mucociliary clearance and play a key role in alveolar fluid absorption. ENaC dysfunction is important in acute respiratory disease syndrome and in cystic fibrosis.[130,131] Each channel is comprised of three subunits designated α, β, and γ, and several new drugs that target these channels are in development for the treatment of lung disease.

Chloride Channels

Although less well characterized than other ion channels, it is increasingly recognized that chloride (Cl^-) channels play an important role in pulmonary physiology and pathology. The cystic fibrosis transmembrane regular (CFTR) that is functionally abnormal in cystic fibrosis plays a critical role in airway hydration and has been extensive investigated. Calcium-activated Cl^- channels (CLCA) play an important role in mucus secretion and are now targeted to treat mucus hypersecretion.[132] Volume- and voltage-dependent Cl^- channels appear to play a role in airway responses to indirect bronchoconstrictors and are blocked by furosemide and cromolyn sodium.[133]

ENZYMES

Many drugs produce their therapeutic effect by inhibition of particular enzymes. Most commonly the drug molecule is a substrate analogue that acts as a *competitive inhibitor*. The interaction between drug and enzyme obeys the law of mass action and may be analyzed in the same way as drug-receptor interactions. An example is L-N^G-nitro arginine, which acts as a competitive inhibitor of NO synthase by substituting for the natural substrate L-arginine. The enzyme blockade may be overcome by increasing the concentration of L-arginine, whereas D-arginine, which is not a substrate for this enzyme has no effect. Many drugs act noncompetitively. An example is aspirin, which noncompetitively blocks cyclooxygenase by acetylating the active (catalytic site) of the enzyme. Another type of interaction involves a false substrate, where the drug undergoes chemical transformation by the enzyme to form a product that subverts the normal metabolic pathway. The best example of this is α-methyldopa which mimics DOPA, causing norepinephrine to be replaced by methylnorepinephrine, which is inactive.

Enzymes are increasingly recognized as playing an important part in the pathophysiology of various diseases and are increasingly a target for drug therapy. Drugs that inhibit 5-lipoxygenase, which generates leukotrienes, such as zileuton, are now used in the treatment of asthma. Drugs that inhibit neutrophil elastase may be useful in the future management of cystic fibrosis and COPD, whereas drugs that inhibit tryptase and chymase from mast cells may be potential treatments in asthma.

Protein Kinases

Signal transduction within cells is regulated by *kinases*, which phosphorylate substrate molecules that are often

themselves kinases, resulting in a cascade of phosphorylation. Over 700 kinases are now recognized in the human genome. Kinase cascades link the activation of surface receptors to functional responses, including secretion, differentiation, and gene expression. For example, multiple kinases are activated when cells are exposed to the proinflammatory cytokines IL-1β and TNF-α.[134,135] MAPK and PI3K cascades are of particular important in inflammatory responses, as well as cell proliferation and survival, as discussed previously. Many novel kinase inhibitors are now in development and are predicted to be the major development in drug therapy in the future.[136]

MAP Kinases

Over 10 MAPK have been identified, and these kinase cascades include a MAPK kinase (MAPKK or MEK) and a MAPKK/MEK kinase (MAPKKK/MEKK) (Fig. 8-21). These signaling pathways serve as a means of connecting cell-surface receptors to specific transcription factors and other regulatory proteins, thus allowing extracellular signals to regulate the expression of specific genes. There is now increasing recognition that there are interactions between the MAPK pathways, resulting in different cellular responses to the same activating stimuli. MAPK may be activated by several types of stress and other extracellular stimuli. Selective inhibitors, such as SB203580, which blocks the p38α pathway, and PD098059, which blocks the extracellular signal-regulated kinase (ERK) pathway have now been developed and this has resulted in a better understanding of these complex signaling pathways. p38α/β MAPK inhibitors are now in clinical development for the treatment of inflammatory diseases, such as COPD and asthma, but they may have to be delivered by inhalation because there is a high risk of systemic side effects.[62,135]

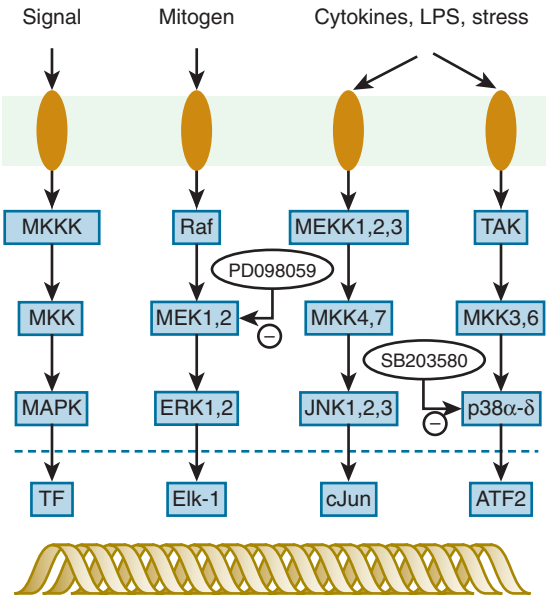

FIGURE 8-21 ■ Mitogen-activated protein kinase pathways. Extracellular signals activate mitogen-activated protein (MAP) kinase kinase kinase (MAPKKK), MAP kinase kinase (MAPKK), MAP kinase (MAPK), and then transcription factors (TF). Three major cascades are now recognized. ATF, activating transcription factor; ERK, extracellular signal-regulated kinase; JNK, Jun N-terminal kinase; LPS, lipopolysaccharide; MEK, MAP/ERK kinase; TAK, transforming growth factor-β-activating kinase.

Phosphoinositide 3-Kinases

PIP2 is converted to PI(1,4,5)trisphosphate (PIP3) by the enzyme phosphoinositide-3-kinase (PI3K), which results in phosphorylation of the downstream kinases Akt (protein kinase B) and mammalian target of rapamycin (mTOR) (Fig. 8-22). This signal transduction pathway is of critical importance in regulation of cell proliferation and inhibition of apoptosis, as well as many other cellular functions such as metabolism, chemotaxis, and cytokine secretion. Several isoforms of PI3 kinase are now recognized, which are differentially regulated and expressed. For example, PI3K-γ is expressed in monocytes and granulocytes and plays a key role in chemotactic responses and inflammatory cytokine release, whereas PI3K-δ is involved in mediating corticosteroid resistance

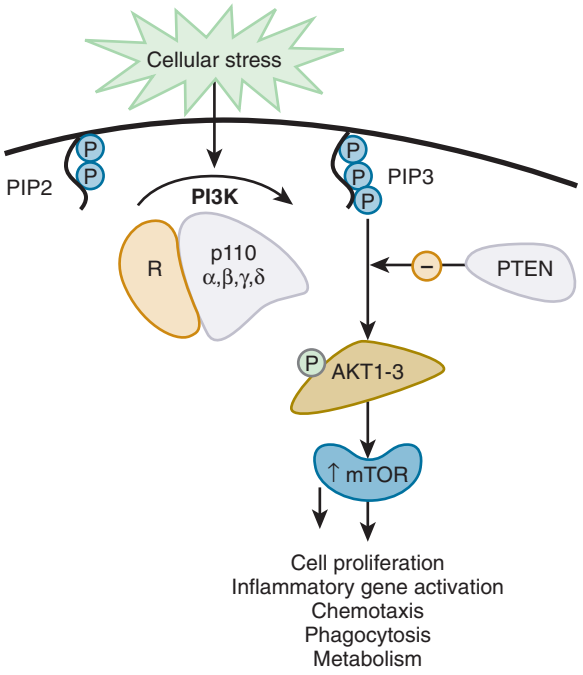

FIGURE 8-22 ■ Phosphoinositide-3-kinase (PI3K) converts phosphoinositide (4,5) diphosphate (PIP2) to phosphoinositide (3,4,5) trisphosphate (PIP3) in response to various cellular stresses, including oxidative stress and inflammatory mediators, acting on receptor tyrosine kinases or G protein–coupled receptors. PI3K consists of a regulatory subunit (R, p85, or p101) and a catalytic domain (p110) of the α-, β-, γ-, or δ-subtype. Activated PI3K then phosphorylates Akt1-3 (protein kinase B), which then phosphorylates mammalian target of rapamycin (mTOR). Further kinase cascades lead to a variety of cellular responses, including proliferation, activation of inflammatory genes, chemotaxis, phagocytosis. and metabolic functions. The activation of PI3K is inhibited by PTEN (phosphatase and tensin homologue deleted on chromosome 10).

induced by oxidative stress.[137] An endogenous inhibitor of the PI3K pathway PTEN (phosphatase and tensin homologue deleted on chromosome 10) is an important feedback mechanism, and this enzyme is often defective and mutated in cancers, including lung cancer.[138] PI3 kinase inhibitors, such as wortmannin and LY294002, have proved to be useful in elucidating the role of PI-3K-Akt signaling pathways, but isoenzyme-selective inhibitors are now in development for the treatment of inflammatory diseases, such as asthma and COPD.

Protein Phosphatases

The effects of kinases are counteracted by phosphatases that dephosphorylate the protein targets of kinase activity. While there are approximately 700 protein kinases, only approximately 200 protein phosphatases have been identified, and these tend to have a broader specificity than kinases. Their regulation is less well understood than that of kinase pathways, and there are few useful inhibitors. Approximately 100 protein tyrosine phosphatases have been identified, and several of these inhibit inositol phosphates. Several MAPK phosphatases have now been identified; the best characterized is MAPK phosphate-1 (MKP-1), which is also known as dual-specificity kinase-1 (it dephosphorylates both threonine and tyrosine residues[63]). MKP-1 inhibits p38, JNK, and ERK MAPK pathways, and its gene is rapidly induced by corticosteroids, contributing to their anti-inflammatory effects.[139] As discussed previously, PTEN appears to be the major phosphatase regulating the PI3K pathways, whereas *Src* homology 2 domain-containing tyrosine phosphatases-1 and -2 (SHP-1, SHP-2) regulate multiple inflammatory, growth factor, and metabolic pathways, including PI3K signaling.

PHARMACOKINETICS

To achieve the intended pharmacologic response, it is necessary to achieve an effective concentration of a drug at its site of action in the lungs. Several steps are involved in determining the concentration of a drug at its site of action. These include *absorption*, *distribution* to various tissues, *metabolism*, and finally *excretion*.

Absorption

Absorption of drugs involves their passage across a cell membrane. For some drugs, this may involve specially mediated transport systems or movement through specific channels, but for most drugs, this involves simple diffusion down a concentration gradient. The rate of transport depends on the lipid solubility of the drug. Most drugs exist in solution as weak acids or weak bases, and there is therefore an equilibrium between the ionized form, which does not readily penetrate lipid membranes, and the nonionized fraction, which is lipophilic and may cross the cell membrane. The equilibrium between ionized and nonionized forms is determined by the *pKa* of the drug, which is defined as the pH at which 50% of the drug is in the ionized state. As an example, cromolyn sodium is a weak acid with a pKa of 2. At physiologic pH, it exists almost entirely in an ionized state and is therefore not absorbed from the gastrointestinal tract, which is why it must be delivered directly to the lungs by inhalation.

Lipid solubility is also important in determining whether absorbed drugs may cross the blood-brain barrier and exert central effects. Highly lipophilic compounds such as ethanol and nicotine readily cross the blood-brain barrier. Atropine also crosses the blood-brain barrier, which results in central nervous system side effects such as hallucinations, but its quaternary derivatives ipratropium bromide and tiotropium bromide are ionized and have low lipid solubility, so they are not able to cross the blood-brain barrier. Therefore, central side effects, such as hallucinations (which limit the use of atropine) are not seen. Similarly, the nonsedative antihistamine cetirizine differs from its parent drug hydroxazine by the presence of a carboxyl group, which makes the drug less lipophilic so central side effects such as sedation are avoided.

Distribution

The concentration of a drug obtained at the site of action is determined by the volume of distribution of the drug, its clearance and the half-life of the drug. The volume of distribution (Vd) describes the body space available to contain the drug. Thus, for parenteral drugs that are extensively bound to plasma proteins the volume of distribution will be largely confined to the vascular space, whereas for drugs that are lipid soluble the volume of distribution (Vd) will be much greater because the drug is taken up into adipose tissues throughout the body. The concentration of a drug in the blood (C) is determined by the equation:

$$C = \text{Drug Dose}/Vd$$

For example, the Vd for theophylline is approximately 35 L in a 70-kg person. An approximate loading dose required to give a plasma concentration of 15 mg/L would therefore be $C \times Vd$ or $15\ \text{mg/L} \times 35\ \text{L} = 525\ \text{mg}$. If Vd is reduced by diseases such as cardiac or renal failure, then a correspondingly lower dose is necessary to give the same plasma concentration and to avoid toxic doses.

Clearance

The clearance of a drug describes its elimination from biologic fluids; the half-life ($t_{1/2}$) is the time required to eliminate 50% of a drug from the body, after absorption and distribution are complete. Although clearance and half-life may readily be established for systemically administered drugs, little is known about the clearance of inhaled drugs because the local concentrations in the lungs are not known.

Systemically administered drugs are biotransformed to an inactive state, which usually involves oxidation, reduction, or hydrolysis, converting the drug to more

polar forms that may be more readily excreted by the kidney. Biotransformation usually takes place in the liver, but for inhaled drugs, biotransformation may also take place in the lungs. Hepatic metabolism of drugs may be increased if metabolizing enzymes are induced by drugs such as phenobarbitone and rifampicin, which increase the activity of cytochrome P-450 (CYP)-related oxidative enzymes. This results in more rapid elimination of theophylline and will require an increased dose of theophylline to maintain therapeutic levels. Decreased clearance is seen with certain drugs, including erythromycin, certain quinolone antibiotics (ciprofloxacin but not ofloxacin), allopurinol, cimetidine (but not ranitidine), serotonin uptake inhibitors (fluvoxamine), and the 5-lipoxygenase inhibitor zileuton, which interfere with CYP-450 (especially CYP 1A2) function.[140]

ROUTES OF DRUG DELIVERY

Drugs may be delivered to the lungs by oral or parenteral routes, but also by inhalation. The choice depends on the drug and on the respiratory disease.

Inhaled Route

Inhalation is the preferred mode of delivery of many drugs with a direct effect on airways, particularly for asthma and for COPD.[141] It is the only route for delivery of some drugs such as cromolyn sodium and anticholinergics and is the preferred route of delivery for β_2-agonists and corticosteroids. Antibiotics may also be delivered by inhalation in patients with chronic respiratory sepsis (e.g., in cystic fibrosis). The major advantage of delivery by inhalation of drugs is the ability to deliver doses that are effective with a much lower risk of side effects. This is particularly important with the use of inhaled corticosteroids, which largely avoids systemic side effects. In addition, drugs such as bronchodilators have a more rapid onset of action than when taken orally, so more rapid control of symptoms is possible.

Particle Size

The size of particles for inhalation is of critical importance in determining the site of deposition in the respiratory tract. The optimum size for particles to settle in the airways is 2 to 5 μm mass median aerodynamic diameter (MMAD). Larger particles settle out in the upper airways and smaller particles may remain suspended and are therefore exhaled. There is increasing interest in delivering drugs to small airways, particularly in COPD and severe asthma.[142] This involves delivering drug particles of approximately 1 μm MMAD, which is now possible using drugs formulated in hydroxyfluoralkane (HFA) propellant.[143]

Pharmacokinetics

Of the total aerosolized drug delivered, only 5% to 10% enters the lower airways with a pressurized metered-dose inhaler (pMDI). The fate of the inhaled drug is poorly understood. Drugs are absorbed from the airway lumen and have direct effects on target cells in the airway. Drugs may also be absorbed into the bronchial circulation and may then be delivered to more peripheral airways via the circulation. Whether drugs are metabolized in the airways is often uncertain, and there is little understanding of the factors that influence local absorption and metabolism of inhaled drugs. Drugs with higher molecular weights tend to be better retained in the airways. Nevertheless, it is known that several drugs have great therapeutic efficacy when given by the inhaled route. The novel inhaled corticosteroid ciclesonide is an inactive prodrug that is activated by esterases in the respiratory tract to the active principle des-ciclesonide.[144] More peripheral distribution of a drug delivered in smaller particles also increases alveolar deposition and thus is likely to increase absorption from the lungs into the general circulation, resulting in more systemic side effects. Thus, although HFA pMDIs deliver more inhaled corticosteroid to smaller airways, there is also increased systemic absorption.

Delivery Devices

Several ways of delivering inhaled drugs are possible[145]:

Metered-Dose Inhalers. Drugs were previously propelled from a canister with a chlorofluorocarbon (freon) propellant, but the propellant has been replaced by HFA, which is "ozone friendly."[146] These devices are convenient, portable, and deliver 100 to 400 doses of drug. They are usually easy to use, although it is necessary to coordinate inhalation with action of the device, so it is important that patients are taught to use these devices correctly.[147]

Spacer Chambers. Large-volume spacer devices between the metered-dose inhaler (MDI) and the patient reduce the velocity of particles entering the upper airways and the size of the particles by allowing evaporation of liquid propellant. This reduces the amount of drug that impinges on the oropharynx and increases the proportion of drug entering the lower airways. The need for careful coordination between activation and inhalation is also avoided, because the pMDI can be activated into the chamber and the aerosol subsequently inhaled from the one-way valve. Perhaps the most useful application of spacer chambers is in the reduction of the oropharyngeal deposition of inhaled corticosteroids and thus the local side effects of these drugs. Large-volume spacers also reduce the systemic side effects of drugs, because less drug is deposited in the oropharynx and therefore swallowed; it is the swallowed fraction of the drug that is absorbed from the gastrointestinal tract that makes the greatest contribution to the systemic fraction. This is of particular importance in the use of certain inhaled steroids, such as beclomethasone dipropionate, which can be absorbed from the gastrointestinal tract. Spacer devices are also useful in delivering inhaled drugs to small children who are not able to use a pMDI. Children as young as 3 years are able to use a spacer device fitted with a face mask.

Dry Powder Inhalers. Drugs may also be delivered as a dry powder using devices that scatter a fine powder dispersed by air turbulence during inhalation. These devices may be preferred by some patients, because careful coordination is not as necessary as with the MDI, but some patients find the dry powder irritating. Several multiple-dose dry powder inhalers (DPIs) are now available, which are more convenient.[148] Some devices deliver doses of pure drug and therefore avoid the problems of additives such as surfactants, which are necessary in pMDIs and which may provoke throat irritation, coughing, and even a fall in lung function–sensitive asthmatic patients. DPIs are also easier to use in children. DPIs have been developed to deliver peptides and proteins such as insulin systemically.

Nebulizers. Two types of nebulizer are available. Jet nebulizers are driven by a stream of gas (air or oxygen), whereas ultrasonic nebulizers utilize a rapidly vibrating piezoelectric crystal and thus do not require a source of compressed gas. The nebulized drug can be inspired during tidal breathing, and it is possible to deliver much higher doses of drug. Nebulizers are therefore useful in treating acute exacerbations of asthma and COPD, for delivering drugs when airway obstruction is extreme (e.g., in severe COPD), for delivering inhaled drugs to infants and small children who cannot use the other inhalation devices, and for delivering drugs such as antibiotics when relatively high doses must be delivered. Small handheld nebulizers are now in development.

Oral Route

Drugs for treatment of pulmonary diseases may also be given orally. The oral dose is much higher than the inhaled dose required to achieve the same effect (by a ratio of more than 20 : 1), so systemic side effects of oral delivery are far more common. When there is a choice of inhaled versus oral route for a drug (e.g., β-agonist or corticosteroid), the inhaled route is always preferable; the oral route should be reserved for the few patients unable to use inhalers (e.g., small children, patients with physical problems such as severe arthritis of the hand). Theophylline is ineffective by the inhaled route and therefore must be given orally. Corticosteroids may have to be given orally for parenchymal lung diseases (e.g., in interstitial lung diseases and emphysema), although it may be possible in the future to deliver such drugs into alveoli using specially designed inhalation devices and aerosols with a small particle size.

Parenteral Route

The intravenous route should be reserved for delivery of drugs in the severely ill patient who is unable to absorb drugs from the gastrointestinal tract. Side effects are generally frequent due to the high plasma concentrations.

AUTONOMIC PHARMACOLOGY

Airway nerves regulate the caliber of the airways and control airway smooth muscle tone, airway blood flow, and mucus secretion.[149] They may also influence the inflammatory process and play an integral role in host defense. Autonomic innervation is relevant to respiratory pharmacology in that many of the drugs used to treat airway diseases have effects on neural control or on autonomic receptors in the respiratory tract.

Overview of Airway Innervation

Neural control of airway function is more complex than previously recognized. Many neurotransmitters are now identified, and these act on a multitude of autonomic receptors. Three types of airway nerve are recognized (Fig. 8-23):

- Parasympathetic nerves that release Ach.
- Sympathetic nerves that release norepinephrine.
- Afferent (sensory nerves) whose primary transmitter may be glutamate.

In addition to these classical transmitters, multiple neuropeptides have now been localized to airway nerves and may have potent effects on airway function.[150] All of these neurotransmitters act on receptors that are expressed on the surface of target cells in the airway. It is increasingly recognized that a single transmitter may act on several subtypes of receptor and may lead to different cellular effects mediated via different second messenger systems.

Several neural mechanisms are involved in the regulation of airway caliber, and abnormalities in neural control may contribute to airway narrowing in disease (Fig. 8-24). Neural mechanisms may be involved in the pathophysiology of airway diseases, such as asthma and COPD, contributing to the symptoms and possibly to the inflammatory response.[6] There is a close interrelationship between inflammation and neural responses in the airways; inflammatory mediators may influence the release of neurotransmitters via activation of sensory

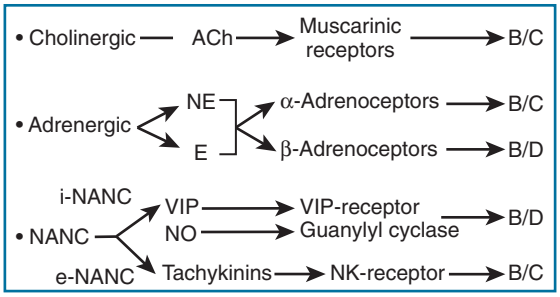

FIGURE 8-23 ■ Mechanisms of autonomic innervation of lungs. Three types of efferent neural mechanism regulate airway smooth muscle tone. Cholinergic nerves cause constriction via release of acetylcholine (ACh), which acts on muscarinic receptors. Adrenergic mechanisms include sympathetic nerves, which release norepinephrine (NE) and circulating epinephrine (E), which act on α- and β-adrenoceptors, resulting in bronchoconstriction (B/C) or bronchodilatation (B/D). Nonadrenergic noncholinergic (NANC) mechanisms include inhibitory NANC (i-NANC) B/D via release of vasoactive intestinal polypeptide (VIP) in some species, and nitric oxide (NO) and excitatory NANC (e-NANC) mechanisms, which lead to bronchoconstriction via release of tachykinins from sensory nerves.

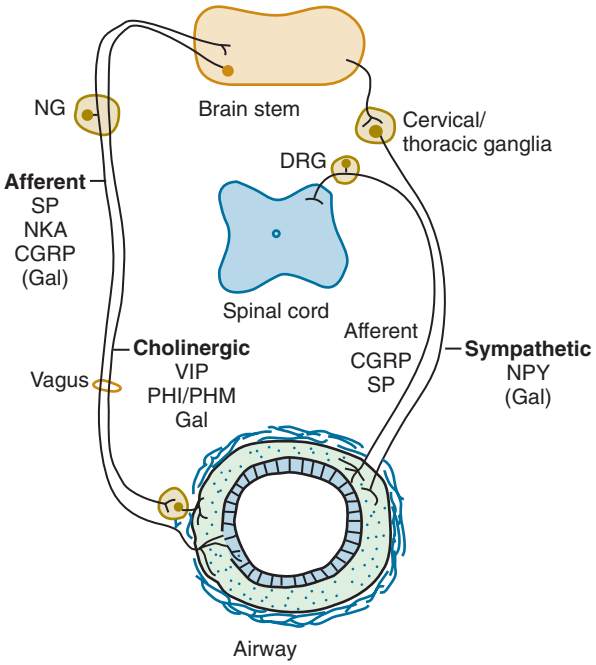

FIGURE 8-24 ■ Neural control of airways. Efferent cholinergic fibers travel in the vagus nerves and synapse in parasympathetic ganglia within the airways. The vagus nerves also transmit sensory information to the central nervous system, the nerve cell bodies of which are localized to the nodose ganglion (NG). Sympathetic nerves to the lungs arise in dorsal root ganglia (T1-7). Various neuropeptides coexist in these classical autonomic nerves. In parasympathetic nerves, vasoactive intestinal polypeptide (VIP), peptide histidine isoleucine/methionine (PHI/PHM), and galanin (Gal) are present. In sympathetic nerves, neuropeptide Y (NPY) and sometimes Gal are present. In afferent nerves (containing C fibers), substance P (SP), neurokinin A (NKA), calcitonin gene-related peptide (CGRP), and sometimes Gal exist. Some afferent fibers whose nerve cell bodies are situated in the upper thoracic dorsal root ganglia (DRG) enter the spinal cord.

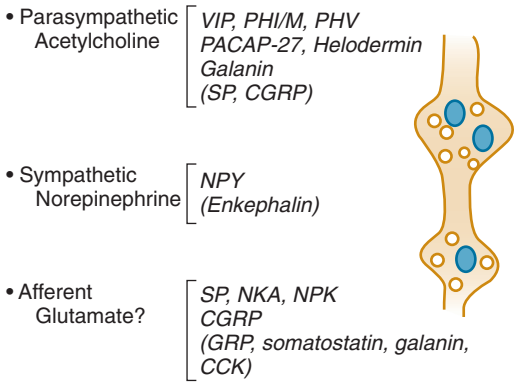

FIGURE 8-25 ■ Cotransmission in airways. Multiple neuropeptides and other transmitters coexist with classical transmitters in airway nerves. Thus, parasympathetic nerves, which contain acetylcholine (ACh), also contain vasoactive intestinal polypeptide (VIP), peptide histidine isoleucine/methionine (PHI/M), histidine isoleucine valine (PHV), helodermin, pituitary adenylate cyclase-activating peptide (PACAP-27), and galanin. Sympathetic nerves, which contain norepinephrine, also contain neuropeptide Y (NPY) and enkephalins. Afferent nerves, in which glutamate may be the primary transmitter, contain substance P (SP), neurokinin A (NKA), neuropeptide K (NPK) and calcitonin gene-related peptide (CGRP).

nerves leading to reflex effects and via stimulation of prejunctional receptors that influence the release of neurotransmitters.[151] In turn, neural mechanisms may influence the nature of the inflammatory response, either reducing inflammation or exaggerating the inflammatory response.

Neural Interactions

Complex interactions between various components of the autonomic nervous system are now recognized. Adrenergic nerves may modulate cholinergic neurotransmission in the airways, and sensory nerves may influence neurotransmission in parasympathetic ganglia and at postganglionic nerves. This means that changes in the function of one neural pathway may have effects on other pathways.

Cotransmission

Although it was once the dogma that each nerve has its own unique transmitter, it is now apparent that almost every nerve contains multiple transmitters. Thus, airway parasympathetic nerves, in which the primary transmitter is ACh, also contain the neuropeptides VIP, peptide histidine isoleucine/methionine (PHI/M), pituitary adenylate cyclase activating peptide (PACAP), helodermin, galanin, and NO (Fig. 8-25). These cotransmitters may have either facilitatory or antagonistic effects on target cells or may influence the release of the primary transmitter via prejunctional receptors. Thus, VIP modulates the release of ACh from airway cholinergic nerves. Sympathetic nerves, which release norepinephrine, may also release neuropeptide Y (NPY) and enkephalins, whereas afferent nerves may contain a variety of peptides including substance P (SP), neurokinin A (NKA), CGRP, galanin, VIP, secretoneurin, and cholecystokinin.

The physiologic role of neurotransmission may be in "fine-tuning" of neural control. Neuropeptides may be preferentially released by high-frequency firing of nerves, and their effects may therefore become manifest only under conditions of excessive nerve stimulation. Neuropeptide neurotransmitters may also act on target cells different from the primary transmitter, resulting in different physiologic effects. Thus, in airways, ACh causes bronchoconstriction, but VIP, which is co-released, may have its major effect on bronchial vessels, thus increasing blood flow to the airways. In chronic inflammation, the role of cotransmitters may be increased by alterations in the expression of their receptors or by increased synthesis of transmitters via increased gene transcription.

Afferent Nerves

The sensory innervation of the respiratory tract is mainly carried in the vagus nerves.[6] The neuronal cell bodies are localized to the nodose and jugular ganglia and input

to the solitary tract nucleus in the brain stem. A few sensory fibers supplying the lower airways enter the spinal cord in the upper thoracic sympathetic trunks, but their contribution to respiratory reflexes is minor and it is uncertain whether they are represented in humans. There is a tonic discharge of sensory nerves that has a regulatory effect on respiratory function and also triggers powerful protective reflex mechanisms in response to inhaled noxious agents, physical stimuli, or certain inflammatory mediators.

The larynx is richly supplied with sensory nerves that are derived from the superior laryngeal nerve. There are numerous sensory arborizations with the appearance of mechanoreceptors. Electrophysiologic studies indicate that many afferents function like rapidly adapting (irritant) receptors in the lower respiratory tract. It is this rich sensory innervation that allows the larynx to function as the first-line defense of the lower airways.

At least three types of afferent fibers have been identified in the lower airways.[152] Most of the information on their function has been obtained from studies in anesthetized animals. It has been difficult to apply electrophysiologic techniques to humans, so it is difficult to know how much of the information obtained in anesthetized animals can be extrapolated to human airways.

Slowly Adapting Receptors

Myelinated fibers associated with smooth muscle of proximal airways are probably slowly adapting (pulmonary stretch) receptors (SAR) that are involved in reflex control of breathing. Activation of SARs reduces efferent vagal discharge and mediates bronchodilation. During tracheal constriction, the activity of SARs may serve to limit the bronchoconstrictor response. SARs may play a role in the cough reflex because when these receptors are destroyed by a high concentration of SO_2, the cough response to mechanical stimulation is lost.

Rapidly Adapting Receptors

Myelinated fibers in the epithelium, particularly at the branching points of proximal airways, show rapid adaptation. Rapidly adapting receptors (RARs) account for 10% to 30% of the myelinated nerve endings in the airways. These endings are sensitive to mechanical stimulation and to mediators such as histamine. The response of RARs to histamine is partly due to mechanical distortion consequent on bronchoconstriction, although if this is prevented by pretreatment with isoproterenol, the RAR response is not abolished, indicating a direct stimulatory effect of histamine. It is likely that mechanical distortion of the airway may amplify irritant receptor discharge.

RARs with widespread arborizations are very numerous in the area of the carina, where they have been termed "cough receptors"; cough can be evoked by even the slightest touch in this region. RARs respond to inhaled cigarette smoke, ozone, serotonin and $PGF_{2\alpha}$, although it is possible that these responses are secondary to the mechanical distortion produced by the bronchoconstrictor response to these irritants. Neurophysiologic studies using an in vitro preparation in guinea pig trachea and bronchi show that a majority of afferent fibers are myelinated and belong to the Aδ-fiber group. Although these fibers are activated by mechanical stimulation and low pH, they are not sensitive to capsaicin, histamine, or bradykinin.

C Fibers

There is a high density of unmyelinated (C) fibers in the airways and they greatly outnumber myelinated fibers. In the bronchi, C fibers account for 80% to 90% of all afferent fibers in cats. C fibers play an important role in the defense of the lower respiratory tract. C fibers contain neuropeptides, including SP, NKA, and CGRP, which confer a motor function on these nerves. Although capsaicin has often been used to classify C fibers, it now appears that some of the C fibers are capsaicin-insensitive.[153] Bronchial C fibers are insensitive to lung inflation and deflation, but they typically respond to chemical stimulation. In vivo studies suggest that bronchial C fibers in dogs respond to the inflammatory mediators histamine, bradykinin, serotonin, and prostaglandins. They are selectively stimulated by capsaicin given either intravenously or by inhalation, which acts via TRPV1 (or vanilloid) receptors[154] and are also stimulated by SO_2 and by cigarette smoke. Because these fibers are relatively unaffected by lung mechanics, it is likely that these agents act directly on the unmyelinated endings in the airway epithelium.

Both RARs and C fibers are sensitive to water and hyperosmotic solutions, with RARs showing a greater sensitivity to hypotonic and C fibers to hypertonic saline. In the in vitro guinea pig trachea preparation, Aδ fibers and C fibers are stimulated by water and by hyperosmolar solutions; a small proportion of Aδ fibers are also stimulated by low chloride solutions, whereas the majority of C fibers are activated. Pulmonary C fibers that are activated via the pulmonary circulation appear to have different properties from bronchial C fibers. Lobeline, which stimulates pulmonary but not bronchial C fibers, causes cough when perfused through the pulmonary circulation, suggesting that pulmonary C fibers may be involved in the cough reflex.

Defense Reflexes

Afferent nerves play a critical role in defense of the airways. There are powerful protective reflexes evoked by stimulation of afferent nerve endings on the surface of the larynx that serve to limit access of noxious agents to the gas-exchanging surface. If this line of defense is breached, there are additional defensive reflexes activated within the lower respiratory tract. These reflexes include changes in the pattern of breathing (rapid shallow breathing or in infants, apnea), constriction of the airways, increased airway secretions, and increased blood flow in the tracheal and bronchial circulations. These responses comprise a coordinated response that limits the access of the noxious agent to the delicate

gas-exchanging surface of the lungs in order to preserve oxygenation.

Cough

Cough is an important defense reflex, which may be triggered from either laryngeal or lower airway afferents.[155] It is characterized by violent expiration, which provides the high shear rate needed to expel foreign particles and mucus from the lower respiratory tract. There is debate about which are the most important afferents for initiation of cough, and this may be dependent on the stimulus. Thus, RARs are activated by mechanical stimuli (e.g., particulate matter), bronchoconstrictors, and hypotonic saline and water, whereas C fibers are more sensitive to hypertonic solutions, bradykinin, and capsaicin. In normal humans, inhaled capsaicin is a potent tussive stimulus, and this is associated with a transient bronchoconstrictor reflex that is abolished by an anticholinergic drug. It is not certain whether this is due to stimulation of C fibers in the larynx, but as these are very sparse, it is likely that bronchial C fibers are also involved. Citric acid is commonly used to stimulate coughing in experimental challenges in human subjects; it is likely that it produces cough by a combination of low pH (which stimulates C fibers) and low chloride (which may stimulate laryngeal and lower airway afferents). Inhaled bradykinin causes coughing and a raw sensation retrosternally, which may be due to stimulation of C fibers in the lower airways. Bradykinin appears to be a relatively pure stimulant of C fibers.[156] PGE_2 and $PGF_{2\alpha}$ are potent tussive agents in humans and also sensitize the cough reflex. This may be relevant to airway defenses. Noxious agents may stimulate the release of prostaglandins (particularly PGE_2) from airway sensory nerves, and this may lead to enhanced sensitivity of the cough reflex and thus a greater likelihood of expelling the noxious agent if it persists. Bronchoconstriction and increased mucus secretion are often caused by the same stimuli that provoke cough, thereby increasing the efficiency of the cough reflex.

Cholinergic Nerves

Cholinergic nerves are the major neural bronchoconstrictor mechanism in human airways, and they are the major determinants of airway caliber.

Cholinergic Control of Airways

Cholinergic nerve fibers arise in the nucleus ambiguous in the brain stem and travel down the vagus nerve and synapse in parasympathetic ganglia, which are located within the airway wall. From these ganglia, short postganglionic fibers travel to airway smooth muscle and to submucosal glands.[157] In animals, electrical stimulation of the vagus nerve causes release of ACh from cholinergic nerve terminals, with activation of muscarinic cholinergic receptors on smooth muscle and gland cells, which results in bronchoconstriction and mucus secretion. Prior administration of a muscarinic receptor antagonist, such as atropine, prevents vagally induced bronchoconstriction. Cholinergic innervation is greatest in large airways and diminishes peripherally, although in humans, muscarinic receptors are localized to airway smooth muscle in all airways. In humans, studies that have tried to distinguish large and small airway effects have shown that cholinergic bronchoconstriction predominantly involves larger airways, whereas β-agonists are equally effective in large and small airways. This relative diminution of cholinergic control in small airways may have important clinical implications; anticholinergic drugs are likely to be less useful than β-agonists when bronchoconstriction involves small airways. In animals, there is a certain degree of resting bronchomotor tone caused by tonic parasympathetic activity. This tone can be reversed by atropine, and enhanced by administration of an inhibitor of acetylcholinesterase (which normally rapidly inactivates ACh released from nerve terminals). Normal human subjects also have resting cholinergic bronchomotor tone; atropine causes bronchodilation.

Extraneuronal ACh

ACh may be synthesized by several types of cells other than neurones, such as airway epithelial cells, and this may contribute to cholinergic tone in the airways, especially in small airways where cholinergic innervation is sparse.[158]

Muscarinic Receptors

Four subtypes of muscarinic receptor have now been identified by binding studies and pharmacologically in lungs.[159] The muscarinic receptors, which mediate bronchoconstriction in human and animal airways, belong to the M_3-receptor subtype, whereas mucus secretion appears to be mediated by M_1- and M_3-receptors. Muscarinic receptor stimulation results in vasodilation via activation of M_3-receptors on endothelial cells, which release NO. M_1-Receptors are also localized to parasympathetic ganglia, where they facilitate the neurotransmission mediated via nicotinic receptors (Fig. 8-26).

Inhibitory muscarinic receptors (autoreceptors) have been demonstrated on cholinergic nerves of airways in animals in vivo and in human bronchi in vitro.[159] These prejunctional receptors inhibit ACh release and may serve to limit vagal bronchoconstriction. Autoreceptors in human airways belong to the M_2-receptor subtype, whereas those on airway smooth muscle and glands belong to the M_3-receptor subtype. Drugs such as atropine and ipratropium bromide, which block both prejunctional M_2-receptors and postjunctional M_3-receptors on smooth muscle with equal efficacy therefore increase ACh release, which may then overcome the postjunctional blockade. This means that such drugs will not be as effective against vagal bronchoconstriction as against cholinergic agonists, and it may be necessary to reevaluate the contribution of cholinergic nerves when drugs that are selective for the M_3-receptors are in clinical use. The presence of muscarinic autoreceptors has been demonstrated in human subjects in vivo. A cholinergic

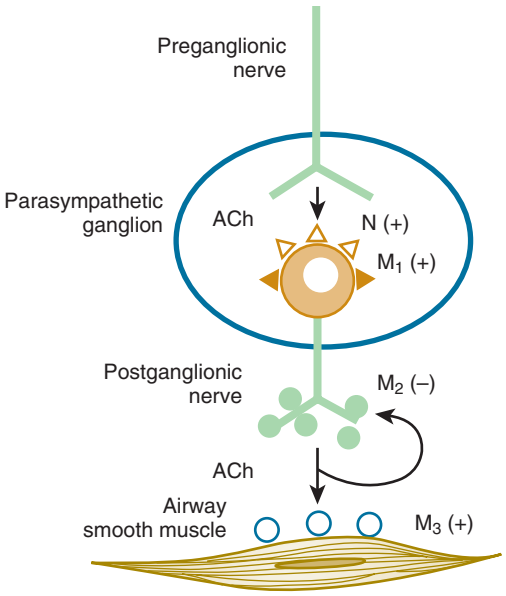

FIGURE 8-26 ■ Cholinergic neural pathways and muscarinic receptor subtypes. Preganglionic cholinergic fibers travel down the vagus nerve to relay in parasympathetic ganglia localized within the airways. Neurotransmission through ganglia is mediated via release of acetylcholine (ACh) from preganglionic terminals acting on nicotinic receptors (N) on ganglionic neurones. M_1-receptors on the same cells appear to facilitate ganglionic transmission. The postganglionic nerve terminal also releases ACh, which acts on M_3-receptors on target cells to cause contraction of airway smooth muscle and mucus secretion. M_2-receptors on preganglionic nerves act as feedback inhibitory receptors to inhibit ACh release from the nerve terminal. *Arrow,* neurotransmission.

agonist, pilocarpine, which selectively activates M_2-receptors, inhibits cholinergic reflex bronchoconstriction induced by sulfur dioxide in normal subjects, but such an inhibitory mechanism does not appear to operate in asthmatic subjects, suggesting that there may be dysfunction of these autoreceptors. Such a defect in muscarinic autoreceptors may then result in exaggerated cholinergic reflexes in asthma, because the normal feedback inhibition of ACh release may be lost. This might also explain the sometimes catastrophic bronchoconstriction that occurs with β-blockers in asthma that, at least in mild asthmatics, appears to be mediated by cholinergic pathways. Antagonism of inhibitory β-receptors on cholinergic nerves would result in increased release of ACh, which could not be switched off in the asthmatic patient. This explains why anticholinergics block β-blocker–induced asthma. The mechanisms that lead to dysfunction of prejunctional M_2-receptors in asthmatic airways are not certain, but it is possible that M_2-receptors may be more susceptible to damage by oxidants or other products of the inflammatory response in the airways. Experimental studies have demonstrated that influenza virus infection and eosinophils in guinea pigs may result in a selective loss of M_2-receptors compared with M_3-receptors, resulting in a loss of autoreceptor function and enhanced cholinergic bronchoconstriction.[160] Muscarinic receptors are also expressed on inflammatory cells. Thus, neuronal and extraneuronal ACh may have proinflammatory effects.[158]

Cholinergic Reflexes

A wide variety of stimuli are able to elicit reflex cholinergic bronchoconstriction through activation of sensory receptors in the larynx or lower airways. Activation of cholinergic reflexes may result in bronchoconstriction and an increase in airway mucus secretion through the activation of muscarinic receptors on airway smooth muscle cells and submucosal glands. Cholinergic reflexes may also increase airway blood flow, particularly in proximal airways. Stimulation of the vagus nerves in animals results in vasodilation in proximal airways that is partially reduced by atropine, suggesting a cholinergic component. The residual component is likely to be due to release of neuropeptides (such as VIP and CGRP) and NO. Cigarette smoke inhalation results in an increase in airway blood flow in pigs, through effects of exogenous NO contained in cigarette smoke, but also via release of endogenous NO from airway nerves. Cholinergic reflexes may also increase mucociliary clearance, presumably via an effect of ACh on ciliated epithelial cells.

Several inhaled irritants have been found to activate cholinergic reflexes in human airways, resulting in bronchoconstriction. These include SO_2, metabisulfite, and bradykinin. Both water (fog) and hypertonic saline also produce cough and bronchoconstriction in asthmatic patients, although the role of cholinergic reflexes in the bronchoconstrictor responses has not been fully evaluated. The activation of cholinergic reflexes by airway irritants is clearly part of a defensive reflex; the bronchoconstriction serves to reduce the penetration of the noxious substance and increases the efficiency of the cough mechanism, the increase in mucus secretion and increased mucociliary clearance result in more efficient removal of the irritant, and the increase in airway blood flow may serve to bring in inflammatory cells.

Cholinergic reflexes may also be activated from extrapulmonary afferents, and these reflexes may also contribute to airway defenses. Esophageal reflux may be associated with bronchoconstriction in asthmatic patients. In some patients, this may be due to aspiration of acid into the airways; in other cases, acid reflux into the esophagus activates a reflex cholinergic bronchoconstriction (the "reflux reflex"). Presumably, this reflex evolved to prevent aspiration of stomach contents. There are also reflexes that may be activated by stimulation of sensory receptors in the nose, resulting in bronchoconstriction and laryngeal narrowing. This may serve as an early warning system so noxious agents inhaled through the nose are prevented from being inhaled into the lungs.

Neurogenic Inflammation

Pain, heat, redness, and swelling are the cardinal signs of inflammation. Sensory nerves may be involved in the generation of each of these signs. There is now considerable evidence that sensory nerves participate in

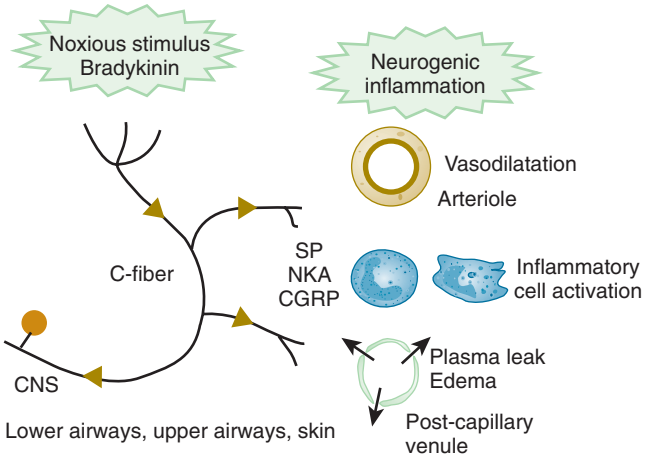

FIGURE 8-27 ■ Neurogenic inflammation in the airways. Activation of sensory nerves by noxious stimuli release neuropeptides such as substance P (SP), neurokinin A (NKA), and calcitonin gene-related peptide (CGRP), which together cause plasma exudation, vasodilatation, and inflammatory cell recruitment and activation. CNS, central nervous system.

inflammatory responses. This "neurogenic inflammation" is due to the antidromic release of neuropeptides from C fibers, via an axon reflex. The phenomenon is well documented in several organs, including skin, eye, gastrointestinal tract, and bladder.[161] There is also increasing evidence that neurogenic inflammation occurs in the respiratory tract.[162] It may contribute to the inflammatory response in asthma and COPD and may have evolved as an airway defense mechanism.

Activation of airway C fibers may release several neuropeptides, including tachykinins (SP, NKA) and CGRP. In some population of C fibers, other neuropeptides such as galanin, VIP, and NPY, are also present.[163] These peptides have potent effects on airway function and may lead to a chronic inflammatory state with narrowing of the airways (Fig. 8-27). This presumably evolved as a mechanism of defense against invading organisms and as a mechanism to repair the airway damaged by noxious agents in the respiratory tract.

Tachykinins

SP and NKA, but not NKB, are localized to sensory nerves in the airways of several species.[164] SP-immunoreactive nerves are abundant in rodent airways, but are sparse in human airways. SP-immunoreactive nerves in the airways are found beneath and within the airway epithelium, around blood vessels, and to a lesser extent, within airway smooth muscle. SP-immunoreactive nerve fibers also innervate parasympathetic ganglia, suggesting a sensory input that may modulate ganglionic transmission and so result in ganglionic reflexes. SP in the airways is localized predominantly to capsaicin-sensitive unmyelinated nerves in the airways, but chronic administration of capsaicin only partially depletes the lungs of tachykinins, indicating the presence of a population of capsaicin-resistant SP-immunoreactive nerves, as in the gastrointestinal tract. Similar capsaicin denervation studies are not possible in human airways, but after extrinsic denervation by heart-lung transplantation, there appears to be a loss of SP-immunoreactive nerves in the submucosa.

Tachykinins have many different effects on the airways, which are mediated via NK_1-receptors (preferentially activated by SP) and via NK_2-receptors (activated by NKA). Tachykinins constrict smooth muscle of human airways in vitro via NK_2-receptors. The contractile response to NKA is significantly greater in smaller human bronchi than in more proximal airways, indicating that tachykinins may have a more important constrictor effect on more peripheral airways, whereas cholinergic constriction tends to be more pronounced in proximal airways. In vivo, SP does not cause bronchoconstriction or cough, whereas NKA causes bronchoconstriction in asthmatic subjects. Mechanical removal of airway epithelium potentiates the bronchoconstrictor response to tachykinins, largely because the ectoenzyme NEP (E.C. 3.4.24.11), which is a key enzyme in the degradation of tachykinins in airways. SP also stimulates mucus secretion from submucosal glands and goblet cells, stimulates plasma extravasation, and increases airway blood flow, effects that are mediated via NK_1-receptors. Tachykinins are metabolized by NEP, and inhibition of NEP by phosphoramidon or thiorphan markedly potentiates bronchoconstriction and mucus secretion in animal and human airways. The activity of NEP in the airways appears to be an important factor in determining the effects of tachykinins; any factors that inhibit the enzyme or its expression may be associated with increased effects of exogenous or endogenously released tachykinins. Several of the stimuli known to induce bronchoconstrictor responses in asthmatic patients have been found to reduce the activity of airway NEP.[165]

Calcitonin Gene–Related Peptide

CGRP is co-stored and colocalized with SP in afferent nerves. CGRP is a potent vasodilator with long-lasting effects.[166] CGRP is an effective dilator of bronchial vessels in vitro and produces a marked, long-lasting increase in airway blood flow in anesthetized animals. Receptor mapping studies have demonstrated that CGRP receptors are localized predominantly to bronchial vessels rather than to smooth muscle or epithelium in human airways. It is likely that CGRP is the predominant mediator of arterial vasodilation and increased blood flow in response to sensory nerve stimulation in the bronchi. CGRP is a bronchoconstrictor, largely due to the release of spasmogens, such as endothelin-1. It also has eosinophil chemotactic activity.

Neurogenic Inflammation in Human Airways

Although there is clear evidence for neurogenic inflammation in rodent airways, it has been difficult to study in human airways.[162] There are few SP-immunoreactive airways in humans, as discussed previously, but there is

an apparent increase in patients with asthma, although this has not been confirmed in other studies. The role of neurogenic inflammation in response to inhaled irritants in normal individuals is likely to be minimal or absent. While capsaicin induces bronchoconstriction and plasma exudation in rodents, inhaled capsaicin causes cough and only a *transient* bronchoconstriction in humans, suggesting that neuropeptide release is unimportant in human airways. Bradykinin is a potent bronchoconstrictor and tussive agent in asthmatic patients, an effect that is reduced by a tachykinin antagonist. Because normal airways fail to constrict in response to bradykinin, although it induces cough, this provides some evidence that neurogenic inflammation may be enhanced in asthma but is not present normally. NEP inhibitors potentiate the bronchoconstrictor response to inhaled NKA in normal and asthmatic subjects, but there is no effect on baseline lung function in asthmatic patients, indicating that there is unlikely to be basal release of tachykinins. It is possible that NEP may become dysfunctional after viral infections or exposure to oxidants and airway irritants such as cigarette smoke, but this has not yet been investigated in humans. Tachykinin antagonists are effective in a variety of animal models of asthma, but there is presently little evidence that they are efficacious in human airway disease.

Neurotrophins

Neurotrophins, such as nerve growth factor (NGF), may be released from inflammatory and structural cells in airways and stimulate the increased synthesis of neuropeptides, such as SP, in airway sensory nerves, as well as sensitizing nerve endings in the airways.[167] NGF is released from human airway epithelial cells after exposure to inflammatory stimuli. Neurotrophins may play an important role in mediating bronchial hyperresponsiveness in asthma and may account for the plasticity of sensory nerves in inflammation, when increased expression of neuropeptides is found in airway sensory nerves.[168]

Bronchodilator Nerves

Neural bronchodilator mechanisms exist in airways, and there are considerable species differences.

Sympathetic Nerves

Sympathetic innervation of human airways is sparse, and there is no functional evidence for innervation of airway smooth muscle, in contrast to the sympathetic neural bronchodilator mechanisms that exist in other species.[169] Sympathetic nerves may regulate bronchial blood flow and to a lesser extent mucus secretion. Sympathetic nerves may also influence airway tone indirectly through a modulatory effect on parasympathetic ganglia; sympathetic nerve profiles have been observed in close proximity to parasympathetic ganglia and to postganglionic cholinergic nerve terminals in human airways.

Circulating Catecholamines

In the absence of sympathetic nerves, circulating epinephrine may play a role in regulating airway tone. β-Adrenergic blockade causes bronchoconstriction in asthmatic patients, but not in normal subjects, suggesting an increased adrenergic drive in asthma. This might be provided by circulating epinephrine in asthma. However, circulating concentrations of epinephrine are normal, even in acute exacerbations of asthma. The mechanism whereby β-blockers cause bronchoconstriction in asthma is still not completely understood, but may be due to blockade of prejunctional β_2-receptors on cholinergic nerves in the airways, resulting in increased ACh release in asthma, in which the normal autoreceptor feedback via prejunctional M_2-receptors may be defective (as discussed previously).

Adrenergic Receptors

β-Adrenoceptors are present in high concentration in lung tissue, and autoradiographic mapping studies show that they are localized to several cell types.[170] Binding studies show that approximately two thirds of pulmonary β-receptors are of the β_2-receptor subtype. These receptors are localized to airway smooth muscle, epithelium, vascular smooth muscle, and submucosal glands, whereas β_1-receptors are localized to submucosal glands. There is a uniform distribution of β-receptors on the alveolar wall, and the ratio of $\beta_1 : \beta_2$ receptors is 2 : 1. The possibility that β-receptors are abnormal in asthma has been investigated extensively. The original suggestion that there is a primary defect in β-receptor function in asthma has not been substantiated, and any defect in β-receptors is likely to be secondary to the disease, perhaps as a result of inflammation or as a consequence of adrenergic therapy.

α-Adrenergic receptors that mediate bronchoconstriction have been demonstrated in airways of several species, and may be demonstrated only under certain experimental conditions. However, there is now considerable doubt about the role of α-receptors in the regulation of tone in human airways, because it has proven difficult to demonstrate their presence functionally or by autoradiography. α-Receptors may play an important role in regulating airway and pulmonary blood flow.

Inhibitory Nonadrenergic Noncholinergic Nerves

There are bronchodilator nerves in human airways that are not blocked by adrenergic blockers and are therefore described as inhibitory nonadrenergic noncholinergic (i-NANC).[171] The neurotransmitter for these nerves in some species, including guinea pigs and cats, is VIP and related peptides. The i-NANC bronchodilator response is blocked by α-chymotrypsin, an enzyme that very efficiently degrades VIP, and by antibodies to VIP. However, although VIP is present in human airways and VIP is a potent bronchodilator of human airways in vitro, there is no evidence that VIP is involved in neurotransmission

of i-NANC responses in human airways. Furthermore, α-chymotrypsin, which completely blocks the response to exogenous VIP, has no effect on neural bronchodilator responses. It is likely that VIP and related peptides may be more important in neural vasodilation responses and may result in increased blood flow to bronchoconstricted airways.

The predominant bronchodilator neurotransmitter of human airways is NO. NO synthase inhibitors, such as N^G-L-arginine methyl ester, virtually abolish the i-NANC response.[172] This effect is more marked in proximal airways, consistent with the demonstration that nitrergic innervation is greatest in proximal airways. NO appears to be a cotransmitter with ACh, and NO acts as a "braking" mechanism for the cholinergic system by acting as a functional antagonist to ACh in airway smooth muscle.[173]

Neural Control in Disease

Autonomic control of airways may be abnormal and contribute to the pathophysiology in several airway diseases.

Asthma

There is compelling evidence that neural mechanisms contribute to the pathophysiology of asthma.[174] It has long been proposed that there is an imbalance in autonomic control in asthma, with a preponderance of bronchoconstrictor mechanisms (muscarinic, α-adrenergic) or a deficit in bronchodilator mechanisms (β-adrenergic). While there is no convincing evidence for a primary defect in autonomic control in asthma, there are several abnormalities that arise as a consequence of the disease. Activation and sensitization of airway sensory nerves may result in the symptoms of cough and chest tightness that are so unpleasant in asthmatic patients. Cholinergic reflex bronchoconstriction may be important, particularly during exacerbations of asthma, when anticholinergic drugs are relatively effective. The defective function of prejunctional M_2-receptors may contribute to exaggerated reflex bronchoconstriction. Furthermore, loss of neuronally produced NO by the action of superoxide anions, generated from inflammatory cells, may leave the cholinergic neural bronchoconstriction unopposed. Whether neurogenic inflammation is present in asthmatic airways is uncertain, but is favored by the possible loss of NEP in asthma, by increased synthesis of SP, and by increased expression of NK_1-receptors. On the other hand, the clinical response to tachykinin antagonists, which are very effective in animal models of asthma, has been disappointing.

COPD

The airways are structurally narrowed in COPD, so even with vagal cholinergic tone, there is a relatively greater effect on caliber than in normal airways, purely for geometric reasons. This may explain why anticholinergics are as or more effective than inhaled β_2-agonists as bronchodilators in these patients. Neural mechanisms may explain the mucus hypersecretion seen in cigarette smokers, and irritants in cigarette smoke may stimulate reflex secretion.

INFLAMMATORY MEDIATORS

Many different mediators have been implicated in pulmonary diseases, and they may have a variety of effects that could account for some of the pathologic features of inflammatory lung diseases.[175,176] Mediators such as histamine, prostaglandins, and leukotrienes contract airway smooth muscle, increase microvascular leakage, increase airway mucus secretion, and attract other inflammatory cells (Fig. 8-28). Each mediator has many effects and many mediators have similar effects, so it is theoretically unlikely that antagonizing a single mediator will have a major impact in complex diseases such as asthma. However, some mediators may play a more prominent role—for example, LTD_4 appears to be dominant bronchoconstrictor mediator in asthma, whereas LTB_4 may play a key role in the neutrophilic inflammation of COPD. Mediator antagonists and synthesis inhibitors have been very useful in elucidating the role of specific mediators in the pathophysiology of asthma and COPD. Inflammation in asthma may be acute and chronic. The chronic inflammation is likely to be mediated by cytokines released within the airway wall, and there is increasing recognition that cytokines play a critical role in orchestrating and perpetuating the chronic inflammation of asthma and COPD.

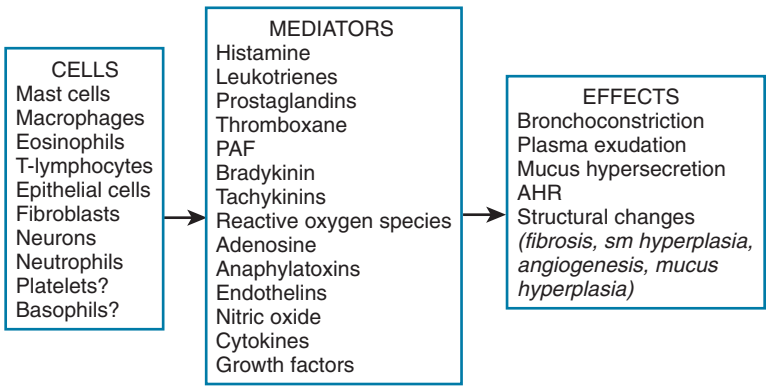

FIGURE 8-28 ■ Inflammatory mediators in asthma. Multiple inflammatory cells release a whole range of inflammatory mediators, which then act on inflammatory receptors on target cells of the airway to produce the typical inflammatory effects. AHR, airway hyperresponsiveness; PAF, platelet-activating factor; sm, smooth muscle.

Histamine

Histamine was the first mediator implicated in the pathophysiology of asthma. It has multiple effects on the airways, which are mediated by four types of histamine receptor. H_1-Receptors mediate bronchoconstriction, activation of sensory reflexes, vasoconstriction, and vasodilation of bronchial vessels and airway microvascular leakage; H_2-receptors mediate mucus secretion and vasodilation (some species); H_3-receptors mediate modulation of cholinergic and sensory nerves, but they may also act as feedback inhibitory receptors to histamine secretion in mast cells; and H_4-receptors are involved in chemotaxis of inflammatory cells.[177] Despite all of these effects, antihistamines have been disappointing in the treatment of asthma.

Leukotrienes

The cysteinyl-leukotrienes LTC_4, LTD_4, and LTE_4 are potent constrictors of human airways and appear to play an important role in the acute inflammatory response in asthma. The development of potent specific leukotriene antagonists has demonstrated that these mediators contribute approximately half of the bronchoconstrictor responses to triggers, such as allergens and exercise. Furthermore, chronic treatment shows a beneficial effect on asthma symptoms and on lung function. There is increasing evidence that LTD_4 may increase eosinophilic inflammation in the airways. LTB_4 is a potent chemotactic agent for neutrophils and is likely to play an important role in neutrophilic inflammatory diseases of the airways, such as COPD and cystic fibrosis.

Prostaglandins

Prostanoids (prostaglandins and thromboxane) are formed from arachidonic acid by the enzyme cyclooxygenase that is widely expressed in the lungs. A constitutive form of the enzyme (COX-1) releases low basal levels of prostaglandins, whereas another form of COX is inducible by endotoxin and by cytokines (COX-2). A new class of prostanoids, the isoprostanes, have been described, which are formed nonenzymatically via oxidation of arachidonic acid, and these mediators are useful markers of oxidative stress in lung diseases.[178] The most prevalent of these, 8-isoprostane (8 epi-$PGF_{2\alpha}$), is a potent constrictor of human airways.

Platelet-Activating Factor

PAF attracted considerable attention because it mimics many of the features of asthma, including smooth muscle hyperresponsiveness. Although PAF appears to be produced by the inflammatory cells involved in asthmatic inflammation and mimics many of the pathophysiologic features of asthma, potent PAF antagonists such as apafant (WEB 2086) and modipafant in chronic asthma have been clinically disappointing.[179] PAF may play a role in acute respiratory distress syndrome (ARDS).

Endothelins

Endothelins are potent peptide mediators that are potent vasoconstrictors and bronchoconstrictors.[180] They also induce airway smooth muscle cell proliferation and fibrosis and may therefore play a role in the chronic inflammation of asthma. There is evidence for increased expression of endothelins in asthma, particularly in airway epithelial cells.

Nitric Oxide

NO is produced in several cells in the airways by NO synthases.[181] An inducible form of the enzyme (iNOS) is expressed in epithelial cells and in inflammatory cells of asthmatic patients and can be induced by cytokines in airway epithelial cells in vitro. This may account for the increased concentration of NO in the exhaled air of asthmatic patients.[182] NO itself is a potent vasodilator and may increase plasma exudation in the airways; it may also amplify the Th2-lymphocyte–mediated response. When NO is produced from iNOS in the presence of oxidative stress, the potent radical peroxynitrite, a molecule that may have several detrimental effects, is produced.

Oxygen-Derived Free Radicals

Many inflammatory cells produce oxygen-derived free radicals such as superoxide anions. Oxidative stress may play an important role in asthma and in COPD.[183] Hydrogen peroxide causes contraction of airway smooth muscle and has been implicated in hyperactive airway smooth muscle in animal models. Oxygen radicals may lead to changes in receptor function, which could influence airway reactivity and may activate NF-κB to increase the expression of multiple inflammatory genes. Oxidative stress may also impair the action of corticosteroids.

Adenosine

Adenosine is released from various cell types under conditions of stress, such as hypoxia. Adenosine has a potent bronchoconstrictor effect in asthmatic patients and releases histamine from "primed" mast cells via an α_{2b}-receptor.[184] Theophylline is an antagonist of adenosine receptors, but it is unlikely that this action accounts for its antiasthma effect, although it may underlie serious side effects such as cardiac arrhythmias and seizures.

Bradykinin

Bradykinin is a potent bronchoconstrictor in asthma and causes contraction of airways largely via indirect means, particularly via activation of sensory nerves.[185] It may be an important mediator of cough in asthma, because it has the capacity to sensitize afferent nerves to various activating stimuli.[156]

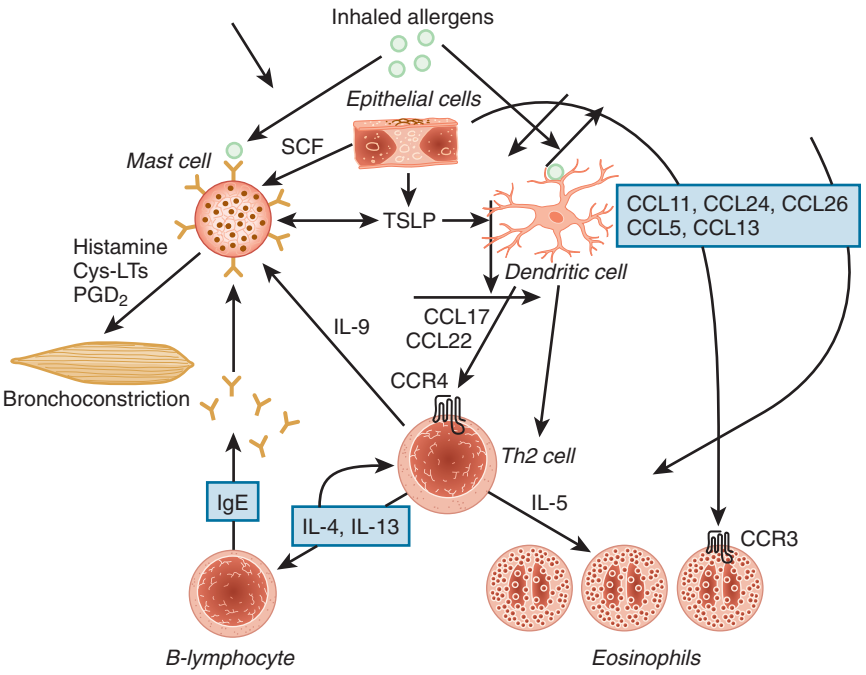

FIGURE 8-29 ■ Cytokines involved in asthma. Epithelial cells play an important role in orchestrating the inflammation of asthma through the release of multiple cytokines, including SCF (stem cell factor, which maintains mast cells in the airways), TSLP (thymus stromal lymphopoietic, which acts on dendritic cells to release the Th2 chemoattractants CCL17 and CCL22 that act on CCR4), and several chemokines that attract eosinophils by activating CCR3. T helper 2 (Th2) cells orchestrate the inflammatory response in asthma through the release of interleukin (IL)-4 and IL-13 (which stimulate B cells to synthesize IgE), IL-5 (which is necessary for eosinophilic inflammation), and IL-9 (which stimulates mast cell proliferation). Mast cells are thus orchestrated by several interacting cytokines and play an important role in asthma through the release of the bronchoconstrictor mediators histamine, cysteinyl-leukotrienes and PGD2.

Cytokines

Cytokines are increasingly recognized to be important in chronic inflammation and play a critical role in orchestrating the type of inflammatory response (Fig. 8-29). Many inflammatory cells (macrophages, mast cells, neutrophils, eosinophils, and lymphocytes) are capable of synthesizing and releasing these proteins, and structural cells such as epithelial cells, endothelial cells, and smooth muscle cells may also release a variety of cytokines and may therefore participate in the chronic inflammatory responses in asthma and COPD.[49] While inflammatory mediators such as histamine and leukotrienes may be important in the acute and subacute inflammatory responses and in exacerbations of asthma, it is likely that cytokines play a dominant role in chronic inflammation. Almost every cell is capable of producing cytokines under certain conditions. Research in this area is hampered by a lack of specific antagonists, although important observations have been made using specific neutralizing antibodies. The cytokines that appear to be of particular importance in asthma include the lymphokines secreted by T-lymphocytes: IL-4 and IL-13 are critical in switching B lymphocytes to produce IgE and for expression of vascular cell adhesion molecule-1 (VCAM-1) in endothelial cells, and IL-5, which is critical in the differentiation, survival, and priming of eosinophils. **TSLP** is produced by epithelial cells in asthma and acts on dendritic cells leading to the recruitment of Th2 cells into the airways. Other cytokines, such as IL-1, IL-6, TNF-α, and GM-CSF, are released from a variety of cells, including macrophages and epithelial cells; they may be important in amplifying inflammatory responses. TNF-α may be an important amplifying mediator in asthma and is produced in increased amounts in airways of patients with severe asthma.

By contrast, other cytokines are inhibitory to the inflammatory process: IL-10 is a potent anti-inflammatory cytokine that appears to be underexpressed in asthma and may be linked to asthma severity. Interferon-γ and IL-12 are inhibitory to Th2 cell expression and have potential as anti-inflammatory therapies.

Chemokines

Chemokines are chemotactic cytokines that orchestrate the trafficking of inflammatory cells to sites of inflammation. They activate GPCRs with the typical 7TM structure, so small molecule inhibitors are feasible candidates for therapies.[50] Most chemokines have four characteristic cysteines, and depending on the motif displayed by the first two cysteines, they have been classified into CXC, CC, C, and CX3C chemokine classes. Key chemokines in asthma include CCL11, which activates CCR3 on eosinophils and mast cells, and in COPD, CXCL1 and CXCL8, which activate CXCR2 on neutrophils and monocytes.

Multiple Mediators

It is clear that no single mediator can be responsible for all the features of asthma, and it is likely that multiple mediators constitute an "inflammatory soup," which may vary from patient to patient, depending on the relative state of activation of the different inflammatory cells and signals. There may be important interactions between the different mediators, and the concept of "priming" may be very important because a combination of mediators may have a much greater effect than each mediator alone. This may be particularly important in the actions of cytokines, which may have no effect in isolation, but may have a very pronounced effect after a cell has been exposed to another cytokine.

Anti-inflammatory Mediators

Although most attention has focused on the proinflammatory effects of mediators, other mediators appear to down-regulate the inflammatory response. IL-10 has potent anti-inflammatory effects and may show reduced secretion in asthma and COPD.[186] Several lipid mediators have anti-inflammatory effects, including lipoxins, protectins, and resolvins.[187]

TRANSCRIPTION FACTORS

In inflammatory lung diseases, there is an increased expression of several proteins involved in the inflammatory cascade. These proteins include cytokines, inflammatory enzymes, receptors for inflammatory mediators, and adhesion molecules. The increased expression of these proinflammatory proteins is usually the result of increased gene transcription. Changes in gene transcription are regulated by transcription factors, which are proteins that bind to DNA. This suggests that transcription factors may play a key role in the pathophysiology of inflammatory lung diseases, because they regulate the increased gene expression that may underlie the chronic inflammatory processes in diseases such as asthma and COPD.[188] Corticosteroids are the most effective therapy in asthma and may reduce inflammation in asthmatic airways largely by inhibiting the transcription factors that regulate abnormal gene expression.[75] Transcription factors bind to regulatory sequences, usually in the 5′ upstream promoter region of target genes, to increase or decrease the rate of gene transcription. This results in increased or decreased protein synthesis and altered cellular function. Transcription factors may be activated via surface receptors through phosphorylation by several kinases, or may be activated by ligands acting on nuclear receptors (such as corticosteroids or vitamin D_3). Transcription factors may therefore convert transient signals at the cell surface into long-term changes in gene transcription, thus acting as "nuclear messengers" (Fig. 8-30).

Several families of transcription factors exist and members of each family may share structural characteristics. These families include helix-turn-helix (e.g., POU), zinc finger (e.g., glucocorticoid receptors), basic protein-leucine zipper (CREB, NF-κB, AP-1), and β-sheet motifs (e.g., HU). Many transcription factors are common to several cell types, whereas others are cell specific and determine the phenotypic characteristics of a cell.

Transcription factors play an important role in the long-term regulation of cell function, growth, and differentiation. Transcription factors may play an important role in chronic diseases such as asthma and COPD. Thus, there is increasing evidence that transcription factors are critical in the expression of cytokine genes and may therefore be involved in inflammatory and immune diseases. Indeed, it is increasingly recognized that some therapies used in the treatment of these diseases, such as corticosteroids and cyclosporin A, may function through interaction with transcription factors. It remains a possibility that abnormal functioning of transcription factors may determine disease severity and responsiveness to treatment. Transcription factors may also interact with each other, resulting in inhibition, or sometimes enhancement, of transcriptional activity.

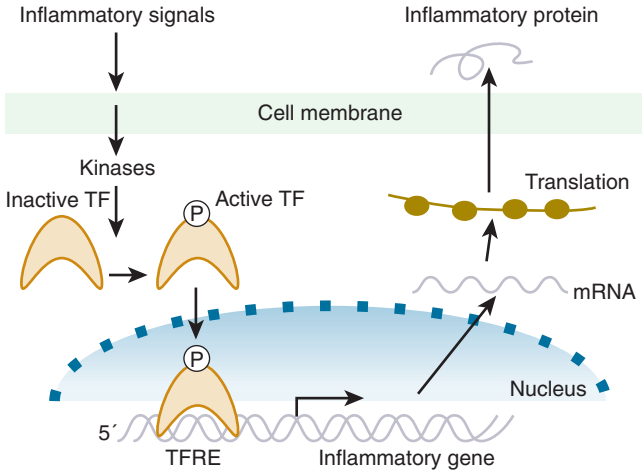

FIGURE 8-30 ■ Transcription factors and inflammation. Extracellular inflammatory stimuli activate transcription factors (TF) via kinases, which then translocate to the nucleus where they bind to transcription factor recognition elements (TFRE) in the promoter region of inflammatory genes, resulting in increased transcription and synthesis of inflammatory proteins. P, phosphorylation.

There is still little information about the regulation of transcription factors in the lungs, particularly in disease. However, molecular methods have been developed for investigation of transcription factor expression and activity. These methods include immunoblotting and immunocytochemistry to detect the transcription factor protein, electrophoretic mobility shift assays to measure transcription factor activation, and DNA footprinting to determine binding to recognition sequences in particular genes. Many transcription factors have now been identified and many are implicated in asthma and COPD. In the future, the genetic control of transcription factor expression may be an increasingly important aspect of research. This may be one of the critical mechanisms regulating expression of disease phenotypes and their responsiveness to therapy.

Activator Protein-1

AP-1 is a heterodimer of Fos and Jun oncoproteins, which is a member of the bZIP transcription family. It was originally described by binding to the TPA (tetradecanoylphorbol-13-acetate) response element (TRE) and responsible for the transcriptional activation of various genes that were activated by phorbol esters (such as tetradecanoyl acetate [TPA], also known as PMA) via activation of PKC.[189] AP-1 is a collection of related transcription factors belonging to the Fos (c-Fos, FosB, Fra1, Fra2) and Jun (c-Jun, JunB, JunD) families, which dimerize in various combinations through a region known as a "leucine zipper." AP-1 may be activated via PKC and by various cytokines, including TNF-α and IL-1β, via

several types of protein tyrosine kinase and mitogen-activated MAPKs. Jun N-terminal kinases (JNK) play a critical role in the regulation of cellular responsiveness to cytokine signals. There is increased expression of c-Fos in asthmatic airways. Certain signals rapidly increase the transcription of the *fos* gene, resulting in increased synthesis of Fos protein. Other signals lead to activation of kinases that phosphorylate c-Jun, resulting in increased activation.

Nuclear Factor-κB

NF-κB also plays an important role in the regulation several inducible inflammatory and immune genes, including iNOS, COX-2, TNF-α, IL-1β, GM-CSF, several chemokines, and adhesion molecules (Fig. 8-31).[190] NF-κB is present in the cytoplasm in an inactive form complexed to an inhibitory protein IκB. Specific kinases phosphorylate IκBe, resulting in its rapid degradation by a protease (proteasome), which reveals nuclear localization signals on NF-κB. NF-κB itself is made up of two subunits, usually a protein of 65 kDa (p65, Rel A), and a protein of 50 kDa (p50), which are members of the Rel family. Free NF-κB localizes to the nucleus, where it binds to a specific κB recognition elements on the promoter region of target genes. NF-κB may be activated by cytokines, such as TNF-α, phorbol esters, certain viruses (including rhinovirus), and oxidants. NF-κB is activated via a specific kinase IκB kinase-2 (IKK2), for which there are now small molecule inhibitors.[191] There is evidence for NF-κB activation in asthma and COPD[192,193] and many of the inflammatory genes activated in these diseases are regulated by NF-κB. Corticosteroids potently inhibit NF-κB–mediated gene transcription.

JAK-STAT

Several cytokines, including interferons and IL-6, activate specific cytosolic tyrosine kinases known as Janus kinases (JAK), of which several types have been recognized (Fig. 8-32).[194] Members of the JAK family include JAK1, JAK2, JAK3, TyK1, and TyK2 and may be differentially activated by different cytokines. Thus, IL-2 activates JAK1 and JAK3; IL-6 activates JAK1, JAK2, and JAK3; whereas IL-5 activates JAK2 only. JAKs then tyrosine phosphorylate a family of transcription factors known as signal transducers and activators of transcription (STATs).

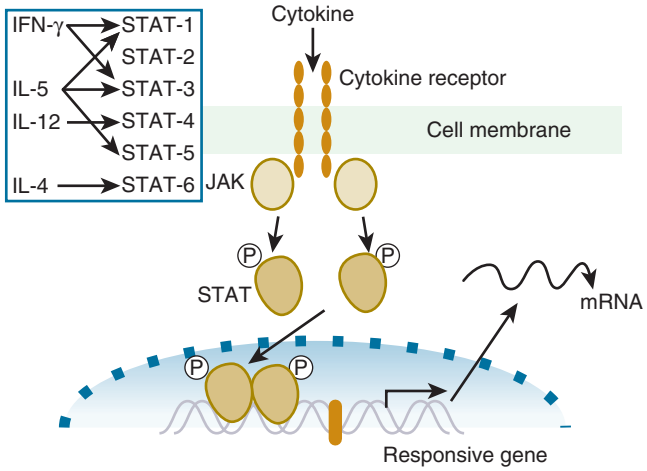

FIGURE 8-32 ■ JAK-STAT pathways. Cytokine binding to its receptor results in activation of Janus kinases (JAK), which phosphorylate (P) intracellular domains of the receptor, resulting in phosphorylation of signal transduction-activated transcription factors (STATs). Activated STATs dimerize and translocate to the nucleus where they bind to recognition elements on certain genes. IFNγ, interferon-γ; IL, interleukin.

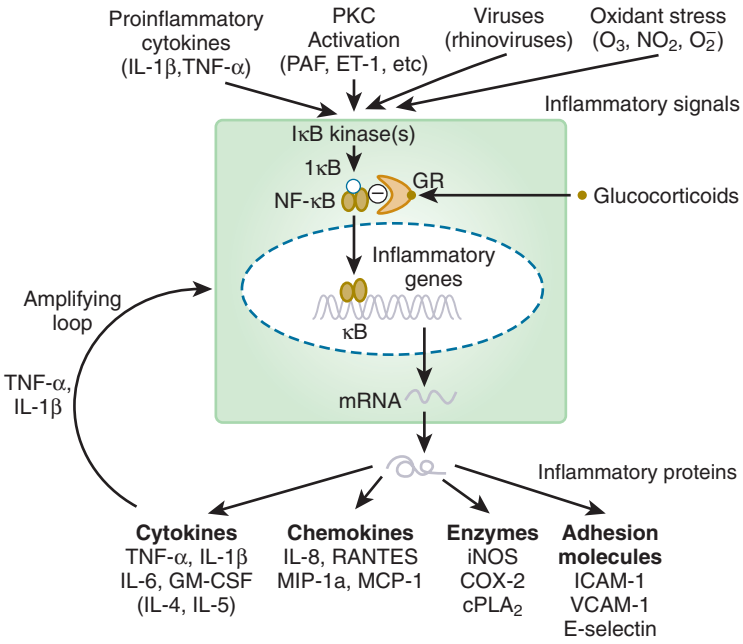

FIGURE 8-31 ■ Nuclear factor-κB (NF-κB) is activated by a variety of inflammatory signals, resulting in the coordinated expression of multiple inflammatory genes, including cytokines, chemokines, enzymes, and adhesion molecules. Activation of NF-κB by inhibitor if NF-κB (IκB) kinases leads to degradation of IκB and translocation of NF-κB to the nucleus where it binds to recognition sites (κB) in the promoter region of many inflammatory genes. The cytokines interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α) both activate and are regulated by NF-κB and may act as an amplifying "feed-forward" loop. The actions of NF-κB are inhibited by glucocorticoids via activation of glucocorticoid receptors (GR). COX2, inducible cyclooxygenase; $cPLA_2$, inducible phospholipase A_2; ET-1, endothelin-1; GM-CSF, granulocyte-macrophage colony-stimulating factor; ICAM, intercellular adhesion molecule; IL, interleukin; iNOS, inducible nitric oxide synthase; MCP, macrophage chemotactic peptide; MIP, macrophage inflammatory protein; NO_2, nitrogen dioxide; O_2^-, superoxide anions; O_3, ozone; PAF, platelet-activating factor; PKC, protein kinase C; VCAM, vascular cell adhesion molecule.

STATs dimerize and then bind to response elements on promoter sequences to regulate the transcription of specific genes. Some STATs appear to be highly specific. Thus, STAT6 is activated only by IL-4 and IL-13, whereas STAT4 is activated only by IL-12.

GATA-3

GATA-3 plays a pivotal role in the differentiation of Th2 cells and the expression of the Th2 cytokine genes IL-4, IL-5, and IL-13.[195] It is mainly expressed in Th2 cells, and inhibition of GATA-3 using antisense oligonucleotides or dominant-negative mutants inhibits Th2 gene expression and eosinophilia in mice after allergen exposure. GATA-3 activation involves phosphorylation by p38 MAPK and its subsequent translocation to the nucleus.[196]

T-Bet

T-Bet plays a critical role in the differentiation of Th1 cells and in the secretion of IFN-γ, which suppresses Th2 cells.[197] There is a reduction in T-bet expression in asthma, which may predispose to increased Th2 cells.[198]

CREB

Increased concentrations of cAMP also result in the activation or inhibition of gene transcription. cAMP activates PKA, which phosphorylates a transcription factor (CREB), which binds to a CRE in the promoter region of certain genes.[199] CREB is a member of large family of CRE-binding proteins, including members of the adenosine triphosphate (ATF) family. CREB itself binds to another protein, CREB-binding protein (CBP), which binds several other transcription factors and acts as a coactivator molecule, which then leads to changes in chromatin structure and increased transcription. CREB appears to be important in the regulation of β_2-adrenoceptor expression; down-regulation of CREB activity may account for the reduced gene expression of β_2-adrenoceptors during chronic desensitization.

Glucocorticoid Receptors

GRs themselves are transcription factors that regulate the transcription of several steroid-responsive target genes. Glucocorticoids bind to GR in the cytoplasm, resulting in rapid nuclear localization of GR. GR binds to positive GREs, resulting in increased gene transcription (as in the case of β_2-receptors) or occasionally to negative GREs (as in the case of osteocalcin and IL-6).[74] As discussed previously, many of the anti-inflammatory effects of steroids may be due to interactions between GR and transcription factors, such as AP-1 and NF-κB, that have been activated by cytokines and that regulate the expression of several inducible genes. Although it was once believed that this was explained by a direct protein-protein interaction between GR and activated transcription factors, it is more likely that this is due to reversing the effects of these transcription factors on chromatic remodeling.[75] A small proportion of asthmatic patients are steroid-resistant and fail to respond to even high doses of oral steroids. This may be due to reduced nuclear localization of GR, to competition from activated transcription factors such as AP-1, or to abnormalities in histone acetylation patterns.[200,201]

Nuclear Factor of Activated T Cells

Nuclear factor of activated T cells (NFAT) is an example of a cell-specific transcription factor; it is largely confined to T lymphocytes. NFAT is of key importance in the regulation of the expression of IL-2 and other T-cell–derived cytokines, such as IL-4 and IL-5. Activation of T cells results in activation of calcineurin, which activates a preformed cytoplasmic NF-AT (NF-ATp). AP-1 forms a transcriptional complex with NF-AT to increase IL-2 gene expression.[202] This may be inhibited by cyclosporin A and tacrolimus (FK 506), which inhibit calcineurin, or by corticosteroids, which inhibit AP-1 directly.

Coactivators

Many transcription factors interact with large coactivator molecules, such as CBP and p300, which bind near the start site of transcription and regulate the activation of RNA polymerase II, which results in transcription of mRNA.[203] These coactivator molecules may therefore integrate the activity of several transcription factors and these may compete for binding on this molecule, resulting in negative interactions (termed "squelching"). CBP and other coactivators have intrinsic histone acetyltransferase (HAT) activity that results in the acetylation of core histones that is essential for opening up the chromatin structure and gene activation (Fig. 8-33).

Histone Modification

DNA is tightly wound around core histones in resting cells, and this configuration of the chromatin structure (DNA and associated proteins in the chromosome) is associated with gene repression or inactivation. Gene activation follows acetylation of these core histones by the HAT activity of coactivators. The consequent change in the charge on histone unwinds DNA, making it available to RNA polymerase and transcription factors, resulting in increased gene expression.[203] Increased expression of inflammatory genes that are activated by NF-κB is associated with acetylation of specific lysine residues of histone-4 (Fig. 8-34).[204] Histone acetylation is reversed by histone deacetylases (HDACs), which act as corepressors.[205] Corticosteroids switch off inflammatory genes activated by NF-κB and AP-1 by recruiting HDAC2 to the actively transcribing gene complex.[75] In asthma, there is an increase in HAT activity and a decrease in HDAC activity in bronchial biopsies.[206] In COPD, there is a marked reduction in HDAC2 activity, which may account for the corticosteroid resistance in this disease.[207] This may be secondary to oxidative stress and the formation of peroxynitrite, which result in activation of PI3K-δ and nitration of tyrosine residues on HDAC2 (Fig. 8-35).[200,208]

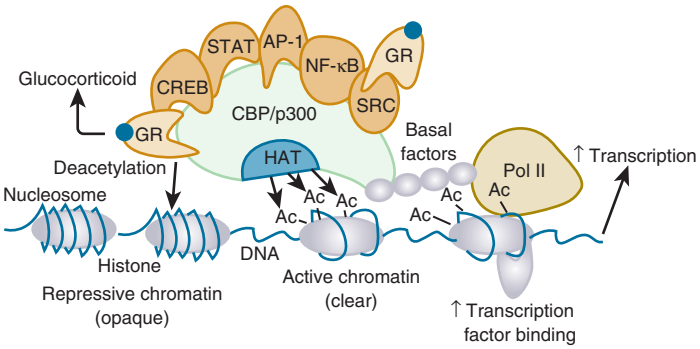

FIGURE 8-33 ■ Coactivator molecules. Multiple transcription factors bind to coactivator molecules, such as CREB-binding protein (CBP) or p300, which have intrinsic histone acetyltransferase (HAT) activity, resulting in acetylation (Ac) of histone proteins around which DNA is wound in the chromosome. This leads to unwinding of DNA, which allows increased access of transcription factors, thus resulting in increased gene transcription. Glucocorticoid receptors (GR), after activation by corticosteroids, bind to a steroid receptor coactivator that is bound to CBP. This results in deacetylation of histone, with increased coiling of DNA around histone, thus preventing transcription factor binding, leading to gene repression. AP-1, activator protein-1; CREB, cyclic adenosine monophosphate response element–binding protein; DNA, deoxyribonucleic acid; NF-κB, nuclear factor κB; Pol II, RNA polymerase II; SRC, steroid receptor coactivator molecule; STAT, signal transduction activated transcription factor.

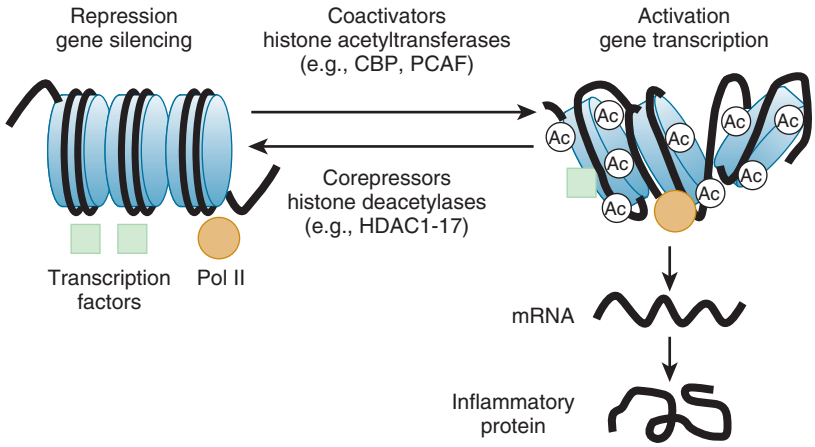

FIGURE 8-34 ■ Gene activation and repression are regulated by acetylation (Ac) of core histones. Histone acetylation is mediated by coactivators, which have intrinsic histone acetyltransferase activity, whereas repression is induced by histone deacetylases (HDACs), which reverse this acetylation. CBP, CREB-binding protein; PCAF, p300/CBP activating factor; Pol II, RNA polymerase II.

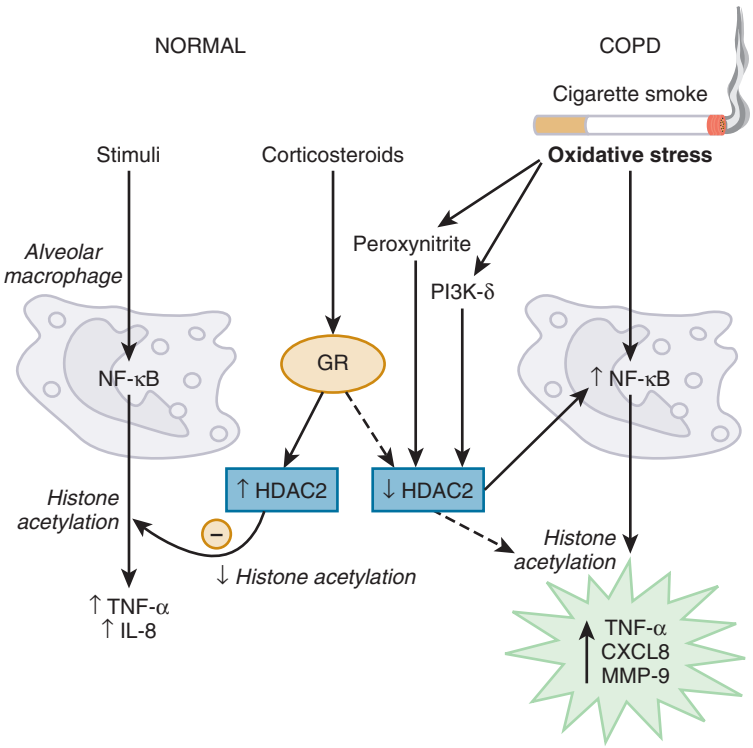

FIGURE 8-35 ■ Proposed mechanism of corticosteroid resistance in chronic obstructive pulmonary disease (COPD) patients. Stimulation of normal alveolar macrophages activates nuclear factor-κB (NF-κB) and other transcription factors to turn on histone acetyltransferase, leading to histone acetylation and subsequently to transcription of genes encoding inflammatory proteins, such as tumor necrosis factor-α (TNF-α) and CXCL8 (IL-8). Corticosteroids reverse this by binding to glucocorticoid receptors (GR) and recruiting histone deacetylase-2 (HDAC2). This reverses the histone acetylation induced by NF-κB and switches off the activated inflammatory genes. In COPD patients, cigarette smoke activates macrophages, as in normal subjects, but oxidative stress, acting through the formation of peroxynitrite and the activation of phosphoinositide-3-kinase-δ (PI3K-δ), impairs the activity of HDAC2. This amplifies the inflammatory response to NF-κB activation, but also reduces the anti-inflammatory effect of corticosteroids because HDAC2 is now unable to reverse histone acetylation.

Histones may also be modified by methylation, phosphorylation, and ubiquitination, resulting in short-term and long-term modification of chromatin structure that has a profound effect on gene expression. These epigenetic changes are increasingly recognized to be important in driving the chronicity of inflammatory diseases, such as asthma and COPD.[209] Methylation of DNA plays an important role in long-term gene suppression and is thought to be of critical importance in lung cancer where tumor suppressor genes are commonly inactivated.[210]

KEY POINTS

- Respiratory pharmacology is concerned with understanding the mechanism of action and use of drugs used to treat respiratory diseases and with the use of pharmacologic methods to elucidate pathophysiologic mechanisms of these diseases.
- Multiple receptors on or inside pulmonary cells respond to multiple external stimuli to mediate their functional effects, and these receptors are important current and future targets for drug therapy.
- The structure, coupling, signaling pathways, and interactions of these receptors provide important insights into the mechanism of action of respiratory drugs and disease mechanisms.
- Multiple interacting signal transduction pathways, including kinases and phosphatases, have now been identified in pulmonary cells.
- Transcription factors play a key role in the regulation of gene expression in pulmonary cells and have provided novel targets for the development of new drugs.
- Pulmonary pharmacology deals with the absorption, metabolism, distribution, and excretion of drugs, and there is particular emphasis in understanding the inhaled route of delivery.

References

1. van Riel NA: Dynamic modelling and analysis of biochemical networks: Mechanism-based models and model-based experiments. Brief Bioinform 7:364–374, 2006.
2. Michiels C: Endothelial cell functions. J Cell Physiol 196:430–443, 2003.
3. Barnes PJ, Liu S-F: Regulation of pulmonary vascular tone. Physiol Rev 47:87–118, 1995.
4. Folkerts G, Nijkamp FP: Airway epithelium: More than just a barrier. Trends Pharmacol Sci 19:334–341, 1998.
5. Schleimer RP, Kato A, Kern R, et al: Epithelium: At the interface of innate and adaptive immune responses. J Allergy Clin Immunol 120:1279–1284, 2007.
6. Undem BJ, Carr MJ: The role of nerves in asthma. Curr Allergy Asthma Rep 2:159–165, 2002.
7. Hermans E: Biochemical and pharmacological control of the multiplicity of coupling at G-protein-coupled receptors. Pharmacol Ther 99:25–44, 2003.
8. Lagerstrom MC, Schioth HB: Structural diversity of G protein-coupled receptors and significance for drug discovery. Nat Rev Drug Discov 7:339–357, 2008.
9. Howard AD, McAllister G, Feighner SD, et al: Orphan G-protein-coupled receptors and natural ligand discovery. Trends Pharmacol Sci 22:132–140, 2001.
10. Laitinen T, Polvi A, Rydman P, et al: Characterization of a common susceptibility locus for asthma-related traits. Science 304:300–304, 2004.
11. Bernier V, Stocco R, Bogusky MJ, et al: Structure-function relationships in the neuropeptide S receptor: Molecular consequences of the asthma-associated mutation N107I. J Biol Chem 281:24704–24712, 2006.
12. Huber T, Menon S, Sakmar TP: Structural basis for ligand binding and specificity in adrenergic receptors: Implications for GPCR-targeted drug discovery. Biochemistry 47:11013–11023, 2008.
13. Inglese J, Freedman NJ, Koch WJ, Lefkowitz RJ: Structure and mechanism of the G protein-coupled receptor kinases. J Biol Chem 268:23735–23738, 1993.
14. Lefkowitz RJ: Seven transmembrane receptors: Something old, something new. Acta Physiol (Oxf) 190:9–19, 2007.
15. Fong TM, Cascieri MA, Yu H, et al: Amino-aromatic interaction between histidine 197 of the neurokinin-1 receptor. Nature 362:350–353, 1993.
16. Kawabata A, Kawao N: Physiology and pathophysiology of proteinase-activated receptors (PARs): PARs in the respiratory system: Cellular signaling and physiological/pathological roles. J Pharmacol Sci 97:20–24, 2005.
17. Prinster SC, Hague C, Hall RA: Heterodimerization of G protein-coupled receptors: Specificity and functional significance. Pharmacol Rev 57:289–298, 2005.
18. Barnes PJ: Receptor heterodimerization: A new level of cross-talk. J Clin Invest 116:1210–1212, 2006.
19. Dalrymple MB, Pfleger KD, Eidne KA: G protein-coupled receptor dimers: Functional consequences, disease states and drug targets. Pharmacol Ther 118:359–371, 2008.
20. McGraw DW, Mihlbachler KA, Schwarb MR, et al: Airway smooth muscle prostaglandin-EP1 receptors directly modulate β_2-adrenergic receptors within a unique heterodimeric complex. J Clin Invest 116:1400–1409, 2006.
21. Wang J, Norcross M: Dimerization of chemokine receptors in living cells: Key to receptor function and novel targets for therapy. Drug Discov Today 13:625–632, 2008.
22. Oldham WM, Hamm HE: Heterotrimeric G protein activation by G-protein-coupled receptors. Nat Rev Mol Cell Biol 9:60–71, 2008.
23. Perez DM, Karnik SS: Multiple signaling states of G-protein-coupled receptors. Pharmacol Rev 57:147–161, 2005.
24. Sah VP, Seasholtz TM, Sagi SA, Brown JH: The role of Rho in G protein-coupled receptor signal transduction. Annu Rev Pharmacol Toxicol 40:459–489, 2000.

25. Schaafsma D, Gosens R, Zaagsma J, et al: Rho kinase inhibitors: A novel therapeutical intervention in asthma? Eur J Pharmacol 585:398–406, 2008.
26. Collins RN: Rab and ARF GTPase regulation of exocytosis. Mol Membr Biol 20:105–115, 2003.
27. Bai TR, Mak JCW, Barnes PJ: A comparison of beta-adrenergic receptors and in vitro relaxant responses to isoproterenol in asthmatic airway smooth muscle. Am J Respir Cell Mol Biol 6:647–651, 1992.
28. Hanoune J, Defer N: Regulation and role of adenylyl cyclase isoforms. Annu Rev Pharmacol Toxicol 41:145–174, 2001.
29. Kume H, Hall IP, Washabau RJ, et al: Adrenergic agonists regulate K_{Ca} channels in airway smooth muscle by cAMP-dependent and -independent mechanisms. J Clin Invest 93:371–379, 1994.
30. Bos JL. Epac proteins: Multi-purpose cAMP targets. Trends Biochem Sci 31:680–686, 2006.
31. Staples KJ, Bergmann M, Barnes PJ, Newton R: Stimulus-specific inhibition of IL-5 by cAMP-elevating agents and IL-10 reveals differential mechanisms of action. Biochem Biophys Res Commun 273:811–815, 2000.
32. Kaur M, Holden NS, Wilson SM, et al: Effect of β2-adrenoceptor agonists and other cAMP-elevating agents on inflammatory gene expression in human airways smooth muscle cells: A role for protein kinase A. Am J Physiol Lung Cell Mol Physiol 295:L505–L514, 2008.
33. Soderling SH, Beavo JA: Regulation of cAMP and cGMP signaling: New phosphodiesterases and new functions. Curr Opin Cell Biol 12:174–179, 2000.
34. Currie GP, Butler CA, Anderson WJ, Skinner C: Phosphodiesterase 4 inhibitors in chronic obstructive pulmonary disease: A new approach to oral treatment. Br J Clin Pharmacol 65:803–810, 2008.
35. Houslay MD: PDE4 cAMP-specific phosphodiesterases. Prog Nucleic Acid Res Mol Biol 69:249–315, 2001.
36. Jin SL, Conti M: Induction of the cyclic nucleotide phosphodiesterase PDE4B is essential for LPS-activated TNF-alpha responses. Proc Natl Acad Sci U S A 99:7628–7633, 2002.
37. Robichaud A, Stamatiou PB, Jin SL, et al: Deletion of phosphodiesterase 4D in mice shortens alpha(2)-adrenoceptor-mediated anesthesia, a behavioral correlate of emesis. J Clin Invest 110:1045–1052, 2002.
38. Rhee SG: Regulation of phosphoinositide-specific phospholipase C. Annu Rev Biochem 70:281–312, 2001.
39. Jude JA, Wylam ME, Walseth TF, Kannan MS: Calcium signaling in airway smooth muscle. Proc Am Thorac Soc 5:15–22, 2008.
40. Tsien RW, Tsien RY: Calcium channels, stores, and oscillations. Annu Rev Cell Biol 6:715–760, 1990.
41. Dempsey EC, Cool CD, Littler CM: Lung disease and PKCs. Pharmacol Res 55:545–559, 2007.
42. Thompson NT, Bonser RW, Garland LG: Receptor-coupled phospholipase D and its inhibition. Trends Pharmacol Sci 12:404–407, 1991.
43. Webb BJL, Lindsay MA, Barnes PJ, Giembycz MA: Protein kinase C isoenzymes in airway smooth muscle. Biochem J 324:167–175, 1997.
44. Evans DJ, Lindsay MA, Webb BL, et al: Expression and activation of protein kinase C-zeta in eosinophils after allergen challenge. Am J Physiol 277:L233–L239, 1999.
45. Lucas KA, Pitari GM, Kazerounian S, et al: Guanylyl cyclases and signaling by cyclic GMP. Pharmacol Rev 52:375–414, 2000.
46. Hamad AM, Clayton A, Islam B, Knox AJ: Guanylyl cyclases, nitric oxide, natriuretic peptides, and airway smooth muscle function. Am J Physiol Lung Cell Mol Physiol 285:L973–L983, 2003.
47. Kuhn M: Structure, regulation, and function of mammalian membrane guanylyl cyclase receptors, with a focus on guanylyl cyclase-A. Circ Res 93:700–709, 2003.
48. Rybalkin SD, Yan C, Bornfeldt KE, Beavo JA: Cyclic GMP phosphodiesterases and regulation of smooth muscle function. Circ Res 93:280–291, 2003.
49. Barnes PJ: The cytokine networks in asthma and chronic obstructive pulmonary disease. J Clin Invest 118:3546–3556, 2008.
50. Jin T, Xu X, Hereld D: Chemotaxis, chemokine receptors and human disease. Cytokine. 44:1–8, 2008.
51. Allen SJ, Crown SE, Handel TM: Chemokine: receptor structure, interactions, and antagonism. Annu Rev Immunol 25:787–820, 2007.
52. Palmqvist C, Wardlaw AJ, Bradding P: Chemokines and their receptors as potential targets for the treatment of asthma. Br J Pharmacol 151:725–736, 2007.
53. Donnelly LE, Barnes PJ: Chemokine receptors as therapeutic targets in chronic obstructive pulmonary disease. Trends Pharmacol Sci 27:546–553, 2006.
54. Grotzinger J. Molecular mechanisms of cytokine receptor activation. Biochim Biophys Acta 1592:215–223, 2002.
55. Sprang SR: The divergent receptors for TNF. Trends Biochem Sci 15:366–368, 1990.
56. Aggarwal BB: Signalling pathways of the TNF superfamily: A double-edged sword. Nat Rev Immunol 3:745–756, 2003.
57. Kishimoto T, Taga T, Akira S: Cytokine signal transduction. Cell 76:253–262, 1994.
58. van der Geer P, Hunter T, Lindberg RA: Receptor protein-tyrosine kinases and their signal transduction pathways. Annu Rev Biol 10:251–337, 1994.
59. Ciardiello F, Tortora G: EGFR antagonists in cancer treatment. N Engl J Med 358:1160–1174, 2008.
60. Pawson T: Regulation and targets of receptor tyrosine kinases. Eur J Cancer 38(Suppl 5):S3–S10, 2002.
61. Burgering BMT, Bos JL: Regulation of Ras-mediated signalling: More than one way to skin a cat. Trends Biochem Sci 20:18–22, 1995.
62. Cuenda A, Rousseau S: p38 MAP-kinases pathway regulation, function and role in human diseases. Biochim Biophys Acta 1773:1358–1375, 2007.
63. Boutros T, Chevet E, Metrakos P: Mitogen-activated protein (MAP) kinase/MAP kinase phosphatase regulation: Roles in cell growth, death, and cancer. Pharmacol Rev 60:261–310, 2008.
64. Shi Y, Massague J: Mechanisms of TGF-beta signaling from cell membrane to the nucleus. Cell 113:685–700, 2003.
65. Clarke DC, Liu X: Decoding the quantitative nature of TGF-beta/Smad signaling. Trends Cell Biol 18:430–442, 2008.
66. Walton KM, Dixon JE: Protein tyrosine phosphatases. Annu Rev Biochem 12:101–120, 1993.
67. Mustelin T, Rahmouni S, Bottini N, Alonso A: Role of protein tyrosine phosphatases in T cell activation. Immunol Rev 191:139–147, 2003.
68. Steinlein OK, Bertrand D: Neuronal nicotinic acetylcholine receptors: From the genetic analysis to neurological diseases. Biochem Pharmacol 76:1175–1183, 2008.
69. Cahill K, Stead LF, Lancaster T: Nicotine receptor partial agonists for smoking cessation. Cochrane Database Syst Rev 1:CD006103, 2007.
70. Evans RM: The steroid and thyroid hormone receptor superfamily. Science 247:889–895, 1988
71. Shi Y: Orphan nuclear receptors in drug discovery. Drug Discov Today 12:440–445, 2007.
72. Straus DS, Glass CK: Anti-inflammatory actions of PPAR ligands: New insights on cellular and molecular mechanisms. Trends Immunol 28:551–558, 2007.
73. Wang K, Wan YJ. Nuclear receptors and inflammatory diseases. Exp Biol Med (Maywood) 233:496–506, 2008.
74. Rhen T, Cidlowski JA: Antiinflammatory action of glucocorticoids—New mechanisms for old drugs. N Engl J Med 353:1711–1723, 2005.
75. Barnes PJ: How corticosteroids control inflammation. Br J Pharmacol 148:245–254, 2006.
76. Emoring LJ, Marullo S, Briend-Sutren M-M, et al: Molecular characterization of the human β_3-adrenergic receptor. Science 245: 1118–1121, 1989.
77. Kriff S, Lonnqvist F, Raimbault S, et al: Tissue distribution of β_3-adrenergic receptor mRNA in man. J Clin Invest 91:344–349, 1993.
78. Kaumann AJ, Preitner F, Sarsero D, et al: (–)-CGP 12177 causes cardiostimulation and binds to cardiac putative beta 4-adrenoceptors in both wild-type and beta 3-adrenoceptor knockout mice. Mol Pharmacol 53:670–675, 1998.
79. Eglen RM, Choppin A, Dillon MP, Hegde S: Muscarinic receptor ligands and their therapeutic potential. Curr Opin Chem.Biol 3:426–432, 1999.

80. Mak JCW, Haddad E-B, Buckley NJ, Barnes PJ: Visualization of muscarinic m_4 mRNA and M_4-receptor subtypes in rabbit lung. Life Sci 53:1501–1508, 1993.
81. Rousell J, Haddad E-B, Webb BIJ, et al: β-Adrenoceptor-mediated down-regulation of M_2-muscarinic receptors: Role of cAMP-dependent protein kinases and protein kinase C. Mol Pharmacol 49:629–635, 1996.
82. Werry TD, Wilkinson GF, Willars GB: Mechanisms of cross-talk between G-protein-coupled receptors resulting in enhanced release of intracellular Ca^{2+}. Biochem J 374:281–296, 2003.
83. Grandordy BM, Mak JCW, Barnes PJ: Modulation of airway smooth muscle β-receptor function by a muscarinic agonist. Life Sci 54:185–191, 1994.
84. Vazquez-Prado J, Casas-Gonzalez P, Garcia-Sainz JA: G protein-coupled receptor cross-talk: Pivotal roles of protein phosphorylation and protein-protein interactions. Cell Signal 15:549–557, 2003.
85. Adcock IM, Stevens DA, Barnes PJ: Interactions between steroids and β_2-agonists. Eur Respir J 9:160–168, 1996.
86. Barnes PJ: Scientific rationale for combination inhalers with a long-acting β2-agonists and corticosteroids. Eur Respir J 19:182–191, 2002.
87. Giembycz MA, Kaur M, Leigh R, Newton R: A Holy Grail of asthma management: Toward understanding how long-acting β_2-adrenoceptor agonists enhance the clinical efficacy of inhaled corticosteroids. Br J Pharmacol 153:1090–1104, 2008.
88. Parra S, Bond RA: Inverse agonism: From curiosity to accepted dogma, but is it clinically relevant? Curr Opin Pharmacol 7:146–150, 2007.
89. Strange PG: Mechanisms of inverse agonism at G-protein-coupled receptors. Trends Pharmacol Sci 23:89–95, 2002.
90. Ameredes BT, Calhoun WJ: (R)-albuterol for asthma: pro [a.k.a. (S)-albuterol for asthma: con]. Am J Respir Crit Care Med 174: 965–969, 2006.
91. Barnes PJ: Treatment with (R)-albuterol has no advantage over racemic albuterol. Am J Respir Crit Care Med 174:969–972, 2006.
92. Tobin AB: G-protein-coupled receptor phosphorylation: Where, when and by whom. Br J Pharmacol 153(Suppl 1):S167–S176, 2008.
93. Kohout TA, Lefkowitz RJ: Regulation of G protein-coupled receptor kinases and arrestins during receptor desensitization. Mol Pharmacol 63:9–18, 2003.
94. Ribas C, Penela P, Murga C, et al: The G protein-coupled receptor kinase (GRK) interactome: Role of GRKs in GPCR regulation and signaling. Biochim Biophys Acta 1768:913–922, 2007.
95. McGraw DW, Liggett SB: Heterogeneity in beta-adrenergic receptor kinase expression in the lung accounts for cell-specific desensitization of the beta2-adrenergic receptor. J Biol Chem 272:7338–7344, 1997.
96. Finney PA, Donnelly LE, Belvisi MG, et al: Chronic systemic administration of salmeterol to rats promotes pulmonary β2-adrenoceptor desensitization and down-regulation of Gsa. Br J Pharmacol 132:1261–1270, 2001.
97. Mak JC, Hisada T, Salmon M, et al: Glucocorticoids reverse IL-1β-induced impairment of β-adrenoceptor-mediated relaxation and up-regulation of G-protein-coupled receptor kinases. Br J Pharmacol 135:987–996, 2002.
98. Violin JD, Lefkowitz RJ: Beta-arrestin-biased ligands at seven-transmembrane receptors. Trends Pharmacol Sci 28:416–422, 2007.
99. Hadcock JR, Wang HY, Malbon CC: Agonist-induced destabilization of β-adrenergic receptor mRNA: Attenuation of glucocorticoid-induced up-regulation of β-adrenergic receptors. J Biol Chem 264:19928–19933, 1989.
100. Nishikawa M, Mak JCW, Shirasaki H, et al: Long term exposure to norepinephrine results in down-regulation and reduced mRNA expression of pulmonary β-adrenergic receptors in guinea pigs. Am J Respir Cell Mol Biol 10:91–99, 1994.
101. Mak JCW, Nishikawa M, Shirasaki H, et al: Protective effects of a glucocorticoid on down-regulation of pulmonary β_2-adrenergic receptors *in vivo*. J Clin Invest 96:99–106, 1995.
102. Mak JCW, Nishikawa M, Barnes PJ: Glucocorticosteroids increase β_2-adrenergic receptor transcription in human lung. Am J Physiol 12:L41–L46, 1995.
103. Katsunuma T, Mak JCW, Barnes PJ: Glucocorticoids reduce tachykinin NK_2-receptor expression in bovine tracheal smooth muscle. Eur J Pharmacol 344:99–107, 1998.
104. Hislop AA, Mak JC, Kelly D, et al: Postnatal changes in β-adrenoceptors in the lung and the effect of hypoxia induced pulmonary hypertension of the newborn. Br J Pharmacol 135: 1415–1424, 2002.
105. Hislop AA, Mak JCW, Reader JA, et al: Muscarinic receptor subtypes in porcine lung during postnatal development. Eur J Pharmacol 359:211–221, 1998.
106. Ohmichi H, Koshimizu U, Matsumoto K, Nakamura T: Hepatocyte growth factor (HGF) acts as a mesenchyme-derived morphogenic factor during fetal lung development. Development 125:1315–1324, 1998.
107. Bai TR: Abnormalities in airway smooth muscle in fatal asthma: A comparison between trachea and bronchus. Am Rev Respir Dis 143:441–443, 1991.
108. Haddad E-B, Mak JCW, Barnes PJ: Expression of β-adrenergic and muscarinic receptors in human lung. Am J Physiol 270:L947–L953, 1996.
109. Shirasaki H, Nishikawa M, Adcock IM, et al: Expression of platelet activating factor receptor mRNA in human and guinea-pig lung. Am J Resp Cell Mol Biol 10:533–537, 1994.
110. Haddad EB, Fox AJ, Rousell J, et al: Post-transcriptional regulation of bradykinin B_1 and B_2 receptor gene expression in human lung fibroblasts by tumor necrosis factor-α: Modulation by dexamethasone. Mol Pharmacol 57:1123–1131, 2000.
111. Adcock IM, Peters M, Gelder C, et al: Increased tachykinin receptor gene expression in asthmatic lung and its modulation by steroids. J Mol Endocrinol 11:1–7, 1993.
112. Bai TR, Zhou D, Weir T, et al: Substance P (NK_1)- and neurokinin A (NK_2)-receptor gene expression in inflammatory airway diseases. Am J Physiol 269:L309–L317, 1995.
113. Ihara H,.Nakanishi S: Selective inhibition of expression of the substance P receptor mRNA in pancreatic acinar AR42J cells by glucocorticoids. J Biol Chem 36:22441–22445, 1990.
114. Catterall WA: Structure and regulation of voltage-gated Ca^{2+} channels. Annu Rev Cell Dev Biol 16:521–555, 2000.
115. Kotlikoff MI: Calcium currents in isolated canine airway smooth muscle cells. Am J Physiol 254:C793–C901, 1988.
116. Li S, Westwick J, Poll C: Transient receptor potential (TRP) channels as potential drug targets in respiratory disease. Cell Calcium 33:551–558, 2003.
117. Corteling RL, Li S, Giddings J, et al: Expression of TRPC6 and related TRP family members in human airway smooth muscle and lung tissue. Am J Respir Cell Mol Biol 30:145–154, 204, 2003.
118. Parekh AB: Store-operated Ca^{2+} entry: Dynamic interplay between endoplasmic reticulum, mitochondria and plasma membrane. J Physiol 547:333–348, 2003.
119. Ambudkar IS, Ong HL, Liu X, et al: TRPC1: the link between functionally distinct store-operated calcium channels. Cell Calcium 42:213–223, 2007.
120. Shieh CC, Coghlan M, Sullivan JP, Gopalakrishnan M: Potassium channels: Molecular defects, diseases, and therapeutic opportunities. Pharmacol Rev 52:557–594, 2000.
121. Nardi A, Olesen SP: BK channel modulators: A comprehensive overview. Curr Med Chem 15:1126–1146, 2008.
122. Black PN, Ghatei MA, Takahashi K: Formation of endothelin by cultured airway epithelial cells. FEBS Lett 255:129–132, 1989.
123. Kotlikoff MI: Potassium currents in canine airway smooth muscle cells. Am J Physiol 259:L384–L395, 1990.
124. Miura M, Belvisi MG, Stretton CD, et al: Role of potassium channels in bronchodilator responses in human airways. Am Rev Respir Dis 146:132–136, 1992.
125. Black JL, Armour CL, Johnson PRA, et al: The action of a potassium channel activator BRL 38227 (lemakalim) on human airway smooth muscle. Am Rev Respir Dis 142:1384–1389, 1990.
126. Ichinose M, Barnes PJ: A potassium channel activator modulates both noncholinergic and cholinergic neurotransmission in guinea pig airways. J Pharmacol Exp Ther 252:1207–1212, 1990.
127. Stretton CD, Miura M, Belvisi MG, Barnes PJ: Calcium-activated potassium channels mediate prejunctional inhibition of peripheral sensory nerves. Proc Natl Acad Sci U S A 89:1325–1329, 1992.

128. Rogers DF, Lei Y, Kuo H-P, et al: A K^+ channel activator, lemakalin, inhibits cigarette smoke-induced plasma exudation and goblet cell secretion in guinea pig trachea. Am Rev Respir Dis 143:A754, 1991.
129. Pelaia G, Gallelli L, Vatrella A, et al: Potential role of potassium channel openers in the treatment of asthma and chronic obstructive pulmonary disease. Life Sci 70:977–990, 2002.
130. Eaton DC, Helms MN, Koval M, et al: The contribution of epithelial sodium channels to alveolar function in health and disease. Annu Rev Physiol 71:403–423, 2009.
131. Donaldson SH, Boucher RC: Sodium channels and cystic fibrosis. Chest 132:1631–1636, 2007.
132. Patel AC, Brett TJ, Holtzman MJ: The role of CLCA proteins in inflammatory airway disease. Annu Rev Physiol 71:425–449, 2009.
133. Norris AA, Alton EW: Chloride transport and the action of sodium cromoglycate and nedocromil sodium in asthma. Clin Exp Allergy 26:250–253, 1996.
134. Saklatvala J, Dean J, Finch A: Protein kinase cascades in intracellular signalling by interleukin-I and tumour necrosis factor. Biochem Soc Symp 64:63–77, 1999.
135. Adcock IM, Chung KF, Caramori G, Ito K: Kinase inhibitors and airway inflammation. Eur J Pharmacol 533:118–132, 2006.
136. Cohen P: Protein kinases—The major drug targets of the twenty-first century? Nat Rev Drug Discov 1:309–315, 2002.
137. Ito K, Caramori G, Adcock IM: Therapeutic potential of phosphatidylinositol 3-kinase inhibitors in inflammatory respiratory disease. J Pharmacol Exp Ther 321:1–8, 2007.
138. Carracedo A, Pandolfi PP: The PTEN-PI3K pathway: Of feedbacks and cross-talks. Oncogene 27:5527–5541, 2008.
139. Clark AR, Martins JR, Tchen CR: Role of dual specificity phosphatases in biological responses to glucocorticoids. J Biol Chem 283:25765–25769, 2008.
140. Pelkonen O, Turpeinen M, Hakkola J, et al: Inhibition and induction of human cytochrome P450 enzymes: Current status. Arch Toxicol 82:667–715, 2008.
141. Newhouse MT, Dolovich MB: Control of asthma by aerosols. N Engl J Med 315:870–874, 1986.
142. Sturton G, Persson C, Barnes PJ: Small airways: An important but neglected target in the treatment of obstructive airway diseases. Trends Phamacol Sci 29:340–345, 2008.
143. Usmani OS, Biddiscombe MF, Barnes PJ: Regional lung deposition and bronchodilator response as a function of β2-agonist particle size. Am J Respir Crit Care Med 172:1497–1504, 2005.
144. Derendorf H: Pharmacokinetic and pharmacodynamic properties of inhaled ciclesonide. J Clin Pharmacol 47:782–789, 2007.
145. Virchow JC, Crompton GK, Dal Negro R, et al: Importance of inhaler devices in the management of airway disease. Respir Med 102:10–19, 2008.
146. McDonald KJ, Martin GP: Transition to CFC-free metered dose inhalers—Into the new millennium. Int J Pharm 201:89–107, 2000.
147. Smaldone GC: Advances in aerosols: Adult respiratory disease. J Aerosol Med 19:36–46, 2006.
148. Chan HK: Dry powder aerosol delivery systems: Current and future research directions. J Aerosol Med 19:21–27, 2006.
149. Barnes PJ (ed): Autonomic Control of the Respiratory System. London: Harwood, 1997.
150. Barnes PJ: Neuropeptides and asthma. Allergy Clin Immunol Int 12:54–60, 2000.
151. Barnes PJ: Modulation of neurotransmission in airways. Physiol Rev 72:699–729, 1992.
152. Taylor-Clark T, Undem BJ: Transduction mechanisms in airway sensory nerves. J Appl Physiol 101:950–959, 2006.
153. Kollarik M, Dinh QT, Fischer A, Undem BJ: Capsaicin-sensitive and -insensitive vagal bronchopulmonary C-fibres in the mouse. J Physiol 551:869–879, 2003.
154. Jia Y, Lee LY: Role of TRPV receptors in respiratory diseases. Biochim Biophys Acta 1772:915–927, 2007.
155. McGarvey LP, Morice AH: Clinical cough and its mechanisms. Respir Physiol Neurobiol 152:363–371, 2006.
156. Fox AJ, Lalloo UG, Belvisi MG, et al: Bradykinin-evoked sensitization of airway sensory nerves: A mechanism for ACE-inhibitor cough. Nat Med 2:814–817, 1996.
157. Canning BJ, Fischer A: Neural regulation of airway smooth muscle tone. Respir Physiol 125:113–127, 2001.
158. Wessler I, Kirkpatrick CJ: Acetylcholine beyond neurons: The non-neuronal cholinergic system in humans. Br J Pharmacol 154:1558–1571, 2008.
159. Barnes PJ: Muscarinic receptor subtyes in airways. Life Sci 52:521–528, 1993.
160. Fryer AD, Adamko DJ, Yost BL, Jacoby DB: Effects of inflammatory cells on neuronal M_2 muscarinic receptor function in the lung. Life Sci 64:449–455, 1999.
161. Maggi CA, Meli A: The sensory efferent function of capsaicin sensitive sensory nerves. Gen Pharmacol 19:1–43, 1988.
162. Barnes PJ: Neurogenic inflammation in the airways. Respir Physiol 125:145–154, 2001.
163. Belvisi MG: Sensory nerves and airway inflammation: Role of A delta and C-fibres. Pulm Pharmacol Ther 16:1–7, 2003.
164. Joos GF, Germonpre PR, Pauwels RA: Role of tachykinins in asthma. Allergy 55:321–337, 2000.
165. Nadel JA: Neutral endopeptidase modulates neurogenic inflammation. Eur Resp J 4:745–754, 1991.
166. Springer J, Geppetti P, Fischer A, Groneberg DA: Calcitonin gene-related peptide as inflammatory mediator. Pulm Pharmacol Ther 16:121–130, 2003.
167. Freund-Michel V, Frossard N: The nerve growth factor and its receptors in airway inflammatory diseases. Pharmacol Ther 117: 52–76, 2008.
168. Myers AC, Kajekar R, Undem BJ: Allergic inflammation-induced neuropeptide production in rapidly adapting afferent nerves in guinea pig airways. Am J Physiol Lung Cell Mol Physiol 282:L775–L781, 2002.
169. Barnes PJ: Neural control of human airways in health and disease. Am Rev Respir Dis 134:1289–1314, 1986.
170. Barnes PJ: Beta-adrenergic receptors and their regulation. Am J Respir Crit Care Med 152:838–860, 1995.
171. Lammers JWJ, Barnes PJ, Chung KF: Non-adrenergic, non-cholinergic airway inhibitory nerves. Eur Respir J 5:239–246, 1992.
172. Belvisi MG, Ward JR, Mitchell JA, Barnes PJ: Nitric oxide as a neurotransmitter in human airways. Arch Int Pharmacodyn Ther 329:111–120, 1995.
173. Ward JK, Belvisi MG, Fox AJ, et al: Modulation of cholinergic neural bronchoconstriction by endogenous nitric oxide and vasoactive intestinal peptide in human airways in vitro. J Clin Invest 92:736–743, 1993.
174. Barnes PJ: Is asthma a nervous disease? Chest 107:119S–125S, 1995.
175. Barnes PJ, Chung KF, Page CP: Inflammatory mediators of asthma: An update. Pharmacol Rev 50:515–596, 1998.
176. Barnes PJ: Mediators of chronic obstructive pulmonary disease. Pharm Rev 56:515–548, 2004.
177. Huang JF, Thurmond RL: The new biology of histamine receptors. Curr Allergy Asthma Rep 8:21–27, 2008.
178. Montuschi P, Barnes PJ, Roberts LJ: Isoprostanes: Markers and mediators of oxidative stress. FASEB J 18:1791–1800, 2004.
179. Kuitert LM, Angus RM, Barnes NC, et al: The effect of a novel potent PAF antagonist, modipafant, in chronic asthma. Am J Respir Crit Care Med 151:1331–1335, 1995.
180. Goldie RG, Henry PJ: Endothelins and asthma. Life Sci 65:1–15, 1999.
181. Ricciardolo FL, Sterk PJ, Gaston B, Folkerts G: Nitric oxide in health and disease of the respiratory system. Physiol Rev 84:731–765, 2004.
182. Kharitonov SA, Barnes PJ: Exhaled biomarkers. Chest 130:1541–1546, 2006.
183. Rahman I, Biswas SK, Kode A: Oxidant and antioxidant balance in the airways and airway diseases. Eur J Pharmacol 533:222–239, 2006.
184. Vass G, Horvath I: Adenosine and adenosine receptors in the pathomechanism and treatment of respiratory diseases. Curr Med Chem 15:917–922, 2008.
185. Barnes PJ: Bradykinin and asthma. Thorax 47:979–983, 1992.
186. Barnes PJ: IL-10: A key regulator of allergic disease. Clin Exp Allergy 31:667–669, 2001.

187. Bonnans C, Levy BD: Lipid mediators as agonists for the resolution of acute lung inflammation and injury. Am J Respir Cell Mol Biol 36:201–205, 2007.
188. Barnes PJ: Transcription factors in airway diseases. Lab Invest 86:867–872, 2006.
189. Shaulian E, Karin M: AP-1 as a regulator of cell life and death. Nat Cell Biol 4:E131–E136, 2002.
190. Barnes PJ, Karin M: Nuclear factor-κB: A pivotal transcription factor in chronic inflammatory diseases. N Engl J Med 336:1066–1071, 1997.
191. Karin M, Ben-Neriah Y. Phosphorylation meets ubiquitination: The control of NF-κB activity. Annu Rev Immunol 18:621–663, 2000.
192. Hart LA, Krishnan VL, Adcock IM, et al: Activation and localization of transcription factor, nuclear factor-κB, in asthma. Am J Respir Crit Care Med 158:1585–1592, 1998.
193. Caramori G, Romagnoli M, Casolari P, et al: Nuclear localisation of p65 in sputum macrophages but not in sputum neutrophils during COPD exacerbations. Thorax 58:348–351, 2003.
194. Aaronson DS, Horvath CM: A road map for those who don't know JAK-STAT. Science 296:1653–1655, 2002.
195. Barnes PJ: Role of GATA-3 in allergic diseases. Curr Mol Med 8:330–834, 2008.
196. Maneechotesuwan K, Xin Y, Ito K, et al: Regulation of Th2 cytokine genes by p38 MAPK-mediated phosphorylation of GATA-3. J Immunol 178:2491–2498, 2007.
197. Agnello D, Lankford CS, Bream J, et al: Cytokines and transcription factors that regulate T helper cell differentiation: New players and new insights. J Clin Immunol 23:147–161, 2003.
198. Finotto S, Neurath MF, Glickman JN, et al: Development of spontaneous airway changes consistent with human asthma in mice lacking T-bet. Science 295:336–338, 2002.
199. Mayr B, Montminy M: Transcriptional regulation by the phosphorylation-dependent factor CREB. Nat Rev Mol Cell Biol 2:599–609, 2001.
200. Adcock IM, Barnes PJ: Molecular mechanisms of corticosteroid resistance. Chest 134:394–401, 2008.
201. Barnes PJ, Adcock IM: Glucocorticoid resistance: A major barrier to the treatment of inflammatory diseases. Lancet 373:1905–1917, 2009.
202. Macian F: NFAT proteins: Key regulators of T-cell development and function. Nat Rev Immunol 5:472–484, 2005.
203. Barnes PJ, Adcock IM, Ito K: Histone acetylation and deacetylation: Importance in inflammatory lung diseases. Eur Respir J 25:552–563, 2005.
204. Ito K, Barnes PJ, Adcock IM: Glucocorticoid receptor recruitment of histone deacetylase 2 inhibits IL-1b-induced histone H4 acetylation on lysines 8 and 12. Mol Cell Biol 20:6891–6903, 2000.
205. Thiagalingam S, Cheng KH, Lee HJ, et al: Histone deacetylases: Unique players in shaping the epigenetic histone code. Ann N Y Acad Sci 983:84–100, 2003.
206. Ito K, Caramori G, Lim S, et al: Expression and activity of histone deacetylases (HDACs) in human asthmatic airways. Am J Respir Crit Care Med 166:392–396, 2002.
207. Barnes PJ: Reduced histone deacetylase in COPD: Clinical implications. Chest 129:151–155, 2006.
208. Barnes PJ: Role of HDAC2 in the pathophysiology of COPD. Ann Rev Physiol 71:451–464, 2009.
209. Adcock IM, Ford P, Barnes PJ, Ito K: Epigenetics and airways disease. Respir Res 7:21, 2006.
210. Bowman RV, Yang IA, Semmler AB, Fong KM: Epigenetics of lung cancer. Respirology 11:355–365, 2006.

CHAPTER 9
PULMONARY SURFACTANT

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INTRODUCTION

Pulmonary surface-active material (surfactant) allows one to breathe effortlessly. Without surfactant, the work of breathing increases markedly and respiratory distress develops rapidly. In the absence of surfactant, the work of breathing may increase from less than 2% to more than 10% of total oxygen consumption. Surfactant provides the low surface tension at the air-liquid interface that is necessary to prevent atelectasis, alveolar flooding, and severe hypoxia. A complex but highly regulated process has evolved for the synthesis, secretion, and reutilization of surface-active material. Metabolism of surfactant includes synthesis, intracellular transport, packaging of phospholipids and proteins into lamellar bodies, exocytosis, absorption to the air-liquid interface, physical separation of the surfactant components during compression at the air-liquid interface, clearance or uptake of extracellular surfactant by type II cells, intracellular processing of recycled surfactant components from alveolar fluid, and finally, secretion of recycled material. Theoretically, any of these steps could be altered in disease and lead to gas-exchange abnormalities.

The most important step in this dynamic process is the rapid adsorption of phospholipids into the air-liquid interface, and this adsorption requires the surfactant-associated proteins, especially B (SP-B). Surfactant proteins are critical for the intracellular and extracellular macromolecular organization of the phospholipids. With each breath and respiratory cycle, there is a significant swing in surface tension that squeezes some constituents from the monolayer at low lung volumes (i.e., high surface pressure) and allows others to adsorb to the air-liquid interface at high lung volumes (i.e., low surface pressure). Humans breathe about 12 times a minute, which allows a few seconds for adsorption. However, smaller species such as mice breathe about 350 times a minute and require extremely rapid rates of adsorption. Because of the duration of the respiratory cycle, it is possible that the regulation of adsorption and the role of specific surfactant components could be different in large and small animals. In addition to its well-recognized property of providing alveolar stability, surfactant is also important for maintaining the patency of small airways and preventing alveolar flooding. The critical component of surfactant that provides the low surface tension

is dipalmitoylphosphatidylcholine (DPPC). This is an unusual species of phosphatidylcholine in that both of the fatty acids at the sn-1 and sn-2 positions are saturated. DPPC molecules can pack closely together and allow the surface monolayer to withstand the high film pressures required to produce a low surface tension at low lung volumes. This chapter reviews the physiologic function of surfactant, its important components, its metabolism, its alterations in disease, and its use in replacement therapy in the treatment of hypoxic respiratory failure (newborn respiratory distress syndrome [NRDS] and acute respiratory distress syndrome [ARDS]). Additional discussion of ARDS can be found in Chapters 90 and 91. Finally, we also discuss SP-A and SP-D as important components of innate immunity and host defense.[1]

PHYSIOLOGIC FUNCTIONS OF PULMONARY SURFACTANT

The discovery of pulmonary surfactant came from direct physiologic observation and an understanding of the Laplace relationship for calculating surface tension. In 1929, von Neergaard[2] discovered that there was a marked difference in the elastic recoil properties of the lung depending on whether the lung was filled with air or saline. It takes more pressure to inflate the lungs with air than with saline (Fig. 9-1). From these observations, von Neergaard[2] deduced that the surface tension in the lung was extremely low. Clements[3] and Pattle[4] independently demonstrated that extracts of lung-lowered surface tension and the phospholipids of surfactant were responsible for lowering surface tension. Soon after this discovery, Avery and Mead[5] demonstrated that a deficiency in surface-active material caused NRDS. During a cycle of inflation and deflation with air, there is hysteresis such that as the lungs are inflated, a greater pressure is required at any given lung volume than during deflation. During inflation, surfactant must be absorbed into the surface. During deflation, as the surface area decreases, the film pressure rises and the surface tension falls, and the phospholipid molecules already present in the air-liquid interface get packed closely together. High film pressures are generated on exhaling to low lung volumes, and some components of the film such as unsaturated phospholipids and the surfactant proteins are squeezed out of the monolayer. The surface film generated at low lung volumes is thought to be composed of nearly pure (95%) DPPC. Epifluorescence studies with hydrophilic markers have shown that as the film is compressed, there are areas from which aqueous markers are excluded. Fixation of the lung with osmium vapors has shown that some of the alveolar surface is covered with multilayers of phospholipids, which serve as a reservoir of surfactant to enter the film at high lung volumes (low surface pressures). These multilayers are thought to be a ready source of surfactant when the lung expands during inspiration.[5a]

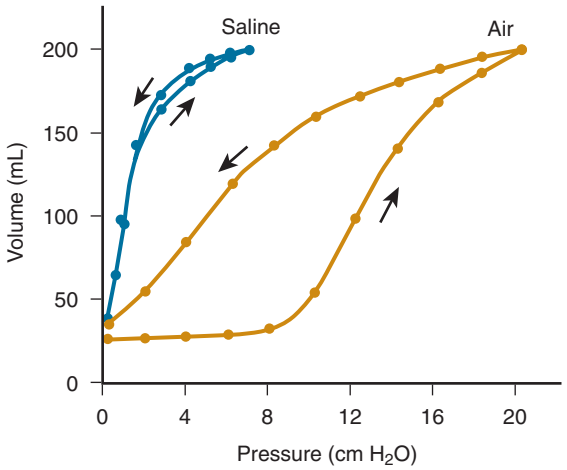

FIGURE 9-1 ■ Air and saline volume-pressure curves. This figure depicts the classic physiologic observation that led to the discovery of surfactant. It takes more pressure to inflate the lung with air than with saline. However, the pressure difference is much less than would be expected if the alveolar lining had the same surface tension as other biologic fluids. The surface tension in the alveoli that is calculated on the basis of the Laplace relationship and known alveolar dimensions is extremely low. The descending limb of the air volume-pressure curve is very reproducible and is used to estimate the surface tension of the lung and static compliance. (Adapted from Radford EP Jr: Recent studies of mechanical properties of mammalian lungs. In Remington JW [ed]: Tissue Elasticity. Washington, DC: American Physiological Society, 1957, pp 177–190.)

There are four surfactant-associated proteins, each of which has different functions. SP-A, SP-B, and SP-C were isolated from preparations of surface-active material obtained by lavage, whereas SP-D was identified in the search for extracellular matrix proteins secreted by type II cells. From in vitro studies on film formation, it became clear that SP-A, SP-B, and SP-C could increase the rate of delivery of phospholipids to the air-liquid interface. DPPC by itself has an extremely low rate of adsorption. SP-A and SP-B were found to be necessary for the formation of tubular myelin (Fig. 9-2).[6] Tubular myelin is a unique extracellular form of surfactant in which an organized lattice of surfactant bilayers is formed; these bilayers appear to have right angles in both transmission electron micrographs and freeze fracture images. Tubular myelin is the physical form of surfactant intermediate between the lamellar body that is secreted and the surface monolayer. Tubular myelin is a major component of large-aggregate surfactant, the form that sediments rapidly on centrifugation and is very surface-active. However, because SP-A–deficient mice lack tubular myelin and have normal respiratory mechanics, the formation of tubular myelin is not absolutely necessary for surfactant function.[7]

The major physiologic functions of surfactant are to lower surface tension and provide alveolar stability, but surfactant has other functions as well. Surfactant prevents alveolar flooding. A high surface tension would tend to draw fluid from the interstitium into the alveolar space. Surfactant is also important for maintaining the patency and stabilization of small airways.[8] Studies in narrow fluid-filled tubes have demonstrated the critical importance of low surface tension and the need for added surfactant to reduce opening pressures. For this reason, surfactant is important in asthma, constrictive

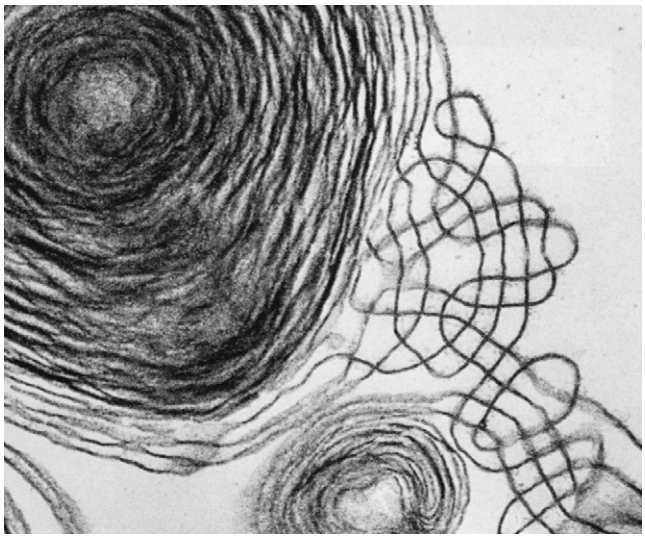

FIGURE 9-2 ■ Tubular myelin. Pulmonary surfactant forms a unique three-dimensional structure composed of phospholipids and the surfactant proteins SP-A, SP-B, and presumably SP-C. Tubular myelin is found only extracellularly and is thought to represent a reservoir of surfactant that can rapidly adsorb to the air-liquid interface. Tubular myelin is isolated as a component of large aggregate surfactant, which is the fraction that sediments readily and is most surface active. (Electron micrograph courtesy of Mary Williams, Boston University.)

bronchiolitis, and other diseases of small airways. Finally, there is also compelling evidence that SP-A and SP-D play important roles in host defense.[9,10]

TABLE 9-1. Composition of Pulmonary Surfactant

Phospholipids: 85%*	**% of Phospholipids**
Phosphatidylcholine	76.3
Dipalmitoylphosphatidylcholine	47.0
Unsaturated phosphatidylcholine	29.3
Phosphatidylglycerol	11.6
Phosphatidylinositol	3.9
Phosphatidylethanolamine	3.3
Sphingomyelin	1.5
Other	3.4
Neutral Lipids: 5%†	
Cholesterol, free fatty acids	
Proteins: 10%‡	
SP-A	
SP-B	
SP-C	
SP-D	
Other	

*The phospholipid composition is constant in most mammalian species. Disaturated phosphatidylcholine represents about two thirds of the total phosphatidylcholine. Dipalmitoylphosphatidylcholine makes up the majority species of the disaturated phosphatidylcholine fraction and is the critical molecule for providing the low surface tension.
†There is about 5% neutral lipid, of which the majority is cholesterol and free fatty acids. There is relatively little triglyceride and cholesterol ester.
‡The composition of the surfactant proteins is not known precisely, but on a mass basis, there appears to be more SP-A than SP-D and more SP-A than SP-B and SP-C.

COMPOSITION

Lipids

The critical components of purified lipids are DPPC, unsaturated phosphatidylcholine, phosphatidylglycerol, and the surfactant proteins (Table 9-1).[11] The quantity of saturated phosphatidylcholine is related to the alveolar surface area in a variety of species, and phosphatidylcholine is the dominant chemical constituent present in the surface film at low surface tension.[12] Phosphatidylglycerol is an anionic phospholipid that is thought to be important in the electrostatic and calcium-dependent interactions with the surfactant proteins. A reduction in the percentage of phosphatidylglycerol is the earliest and most sensitive alteration in the composition of surfactant in lung injury. However, the function of phosphatidylglycerol can be replaced by phosphatidylinositol without detectable physiologic consequences in terms of surfactant function.

Proteins

The surfactant proteins can be divided into two distinct groups: the hydrophilic proteins, SP-A and SP-D, and the hydrophobic proteins, SP-B and SP-C. SP-A and SP-D are collagenous glycoproteins that function as calcium-dependent lectins, and for this reasons, these proteins are referred to as *collectins* (Fig. 9-3).

SP-A and SP-D are important components of innate immunity and are not thought to be critical to surfactant function.[10,13–15] The SP-A–deficient mouse has normal lung function, but increased susceptibility to a variety of infectious agents. As described in more detail later, SP-D binds surfactant phospholipids poorly, is found mainly in the lipid-free supernatant, and should not be considered as an integral surfactant protein for physiologic considerations. Both SP-A and SP-D are very important in host defense and are broad-range pattern recognition molecules. Both of these proteins bind to many of the same microorganisms, help clear microbes from the alveolar compartment, and interact with immune effector cells. SP-C and SP-B are important physiologic components of natural surfactant.[16] These proteins are extremely hydrophobic and are intimately involved in the trafficking of phospholipids, stacking of phospholipids in the lamellar body, and the formation and maintenance of the surface monolayer. SP-B is critical for film formation (adsorption) from vesicular lipids, for formation of tubular myelin (a major reservoir of extracellular surfactant), for removing liquid-phase lipids from the monolayer, and for enriching the monolayer in gel-phase phospholipids (DPPC).[17] These aspects of SP-B function are facilitated by interactions with anionic phospholipids, especially phosphatidylglycerol, and are enhanced by SP-A. SP-C is also involved in film formation and creation of the surface reservoir of surfactant lipids, but its effects are not facilitated by SP-A. The precise

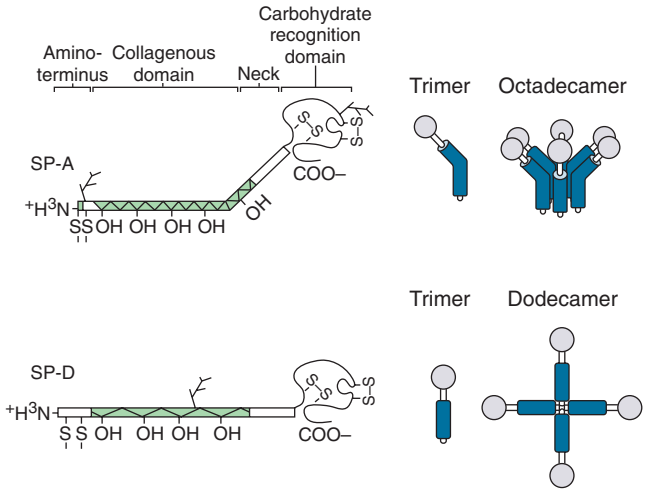

FIGURE 9-3 ■ Structural organization of surfactant proteins A and D (SP-A and SP-D). SP-A and SP-D are collagenous glycoproteins with four important domains. The N-terminal region contains cysteines for intermolecular disulfide bonding to form covalent oligomeric units and has one of the N-linked oligosaccharides in SP-A. The collagen-like domain imparts structural rigidity and elongated molecular structure to both proteins. In SP-A, the collagen region has a kink, which accounts for the bend in the collagen region and the bouquet-like structure of the oligomer. In SP-D, the collagen domain is straight and contains the only N-linked carbohydrate. The neck contributes to the trimeric assembly of polypeptide subunits and spacing for the terminal carbohydrate recognition domain (CRD). The CRD is a globular region of the molecule that plays a major role in the recognition of multiple ligands. In SP-A, the CRD accounts for most of the binding to dipalmitoylphosphatidylcholine vesicles, type II cells, macrophages, and inhaled organisms. The N-linked carbohydrate of SP-A is important for binding to certain microbes, such as influenza virus. In SP-D, the CRD unit is responsible for all the reported interactions with viruses and bacteria. (Adapted from Kuroki Y, Voelker DR: Pulmonary surfactant proteins. J Biol Chem 269:25943–25946, 1994.)

topography of SP-C in the fluid phase of the monolayer and surface-associated bilayers is not known precisely. In mice, a deficiency in SP-B causes a severe respiratory insufficiency and gas-exchange abnormalities, whereas a deficiency in SP-C is not critical for surfactant function. However, SP-C deficiency can lead to chronic inflammatory interstitial lung disease in certain murine strains. SP-B is the one surfactant protein that is critical for surfactant function.

Surfactant Protein A

SP-A was the first surfactant protein identified by its association with surfactant phospholipids. SP-A is a large octadecameric protein with a molecular mass of about 650 kDa.[18] Early studies focused on the role of SP-A in surfactant homeostasis in vitro. The functions of SP-A in vitro include lipid binding and formation of tubular myelin, acceleration of the adsorption of surfactant to the air-liquid interface, and inhibition of surfactant secretion. However, the physiologic importance of these in vitro observations on surfactant regulation has been seriously questioned, because the SP-A–deficient mouse has normal surfactant function.[7,19] Nevertheless, the clearance of surfactant has been reported to be decreased in SP-A–null mice.[20] SP-A binds surfactant phospholipids avidly, especially DPPC, and is critical for the formation of tubular myelin.[6] Over 99% of SP-A in lavage fluid is bound to phospholipid. The current estimate for the concentration of SP-A in rat alveolar lining fluid is 360 μg/mL of total SP-A and 4 to 11 μg/mL of free SP-A.[21] In normal human volunteers, the concentration of total SP-A in alveolar fluid has been calculated to be 180 μg/mL.[22] SP-A may also be important for the function of surfactant during acute lung injury, when a variety of serum factors can inhibit sufactant function, and these effects are partially inhibited by SP-A. However, as demonstrated by the SP-A knockout mouse, SP-A is not essential for normal metabolism and processing of surfactant in vivo.[19]

The major function of SP-A appears to be in innate immunity, in which SP-A binds to a variety of microorganisms, promotes their clearance by phagocytic cells, and directly alters the function of immune effector cells.[9] SP-A like SP-D is a multivalent pattern-recognition molecule and binds to a wide variety of glycoproteins and other ligands. The binding is somewhat promiscuous, has a low affinity, and physiologic effects are likely due to the polyvalent structure of SP-A and the multiple binding sites on cells and organisms. Nevertheless, several putative receptors for SP-A have been identified.[14,23,24] One of the newer functions of SP-A is to serve as a fetal hormone of parturition. Mendelson and colleagues[25] have suggested that the fetal lung secretes SP-A, which activates fetal macrophages that migrate to the uterine wall where they produce IL-1β and initiate labor.

SP-A is localized primarily to the gas-exchange units of the lung and small airways. In rodents, SP-A is found alveolar type II cells and also in nonciliated bronchiolar cells that line the conducting airways. In humans, almost all the SP-A is found in the alveoli, and very little is found in the respiratory epithelium that lines the conducting airways. However, there is SP-A in human tracheal submucosal glands and low-level expression in some nonpulmonary tissues.

Synthesis and Secretion

The gene for SP-A is located on chromosome 10 very near the closely related proteins SP-D and mannose-binding lectin. Humans have two genes for SP-A, which code for proteins with minor amino acid alterations in the collagen domain.[26,26a] Newly synthesized SP-A undergoes a variety of posttranslational modifications that include proteolytic removal of the signal peptide, addition of N-linked carbohydrates, sialylation, acetylation, and sulfation. A number of factors have been reported to increase the synthesis of SP-A, including cyclic adenosine monophosphate (cAMP), keratinocyte growth factor (KGF), and interleukin (IL)-1. Corticosteroids produce a biphasic dose-response with stimulation at low concentrations and inhibition at high concentrations.

Secretion of SP-A from type II cells occurs by two different routes. The dominant route is by direct constitutive secretion independent of lamellar body exocytosis.[27,28] In addition, there is regulated secretion associated with lamellar bodies, in as much as some SP-A is contained within lamellar bodies. Newly synthesized SP-A is secreted directly, and the SP-A found in lamellar bodies is probably derived from recycled SP-A. Most of the intracellular form of SP-A is not heavily glycosylated.

Structure and Function

SP-A is a collagenous glycoprotein with a complex, highly ordered tertiary structure (see Fig. 9-3). The overall organizational structure of SP-A is very similar to serum mannose-binding lectin (MBL) and the complement component C1q. These molecules form a polarized bouquet-like structure composed of 18 monomers that are organized as six trimeric units. The structural domains for several of the properties of SP-A have been determined. As shown in Figure 9-3, the N-terminal cysteines are important in the formation of covalent intermolecular cross-links that stabilize the higher-ordered oligomers. The collagenous region plays a prominent role in the trimerization of monomeric forms of SP-A. The kink in the collagenous portion is due to an additional amino acid that interrupts the gly-X-Y repeats typical of collagen-like domains. The rigid collagenous region provides the overall bouquet-like structure to SP-A. The neck region forms a coiled coil motif and is important for maintaining the structure and stability of the terminal carbohydrate recognition domain (CRD). The C-terminal CRD unit is critical for most SP-A functions and consists of a globular domain that binds carbohydrate and other ligands recognized by SP-A. The structure of the CRD unit is highly conserved in this class of calcium-dependent lectins. The macromolecular structure of SP-A is 20 nm from the N-terminal to the C-terminal CRD unit and across the array of CRD units. Although the carbohydrate moieties of SP-A are not essential for many of its activities, these are the sites for binding to influenza and herpes simplex type 1 virus. The most important details about protein structure come from its crystal structure, which revealed a hydrophobic-binding pocket in the CRD that likely accounts for lipid-binding properties of SP-A.[29]

The relatively normal physiology of mice with genetic deletion of SP-A was unexpected. The observation that surfactant was normal in the SP-A deficient mice was unanticipated in view of the documented effects of SP-A in vitro.[7] However, these SP-A–deficient mice demonstrated the importance of SP-A in host defense for viral and bacterial pathogens. SP-A–deficient mice are more susceptible to infection by group B *Streptococcus*, *Pseudomonas aeruginosa*, *Haemophilus influenza*, respiratory syncytial virus, and *Pneumocystis carinii*.

Binding to Infectious Organisms

SP-A binds to a variety of microorganisms, including viruses, bacteria, mycobacteria, fungi, and *Pneumocystis*.[30] Most of the binding of SP-A to microbial surfaces occurs via the CRD portion of SP-A. These interactions are calcium dependent and inhibited by sugars such as mannose. It has been proposed that SP-A associated with tubular myelin is one of the first barriers for host protection; multivalent SP-A could bind both surfactant lipid in alveolar fluid and inhaled organisms or particles.[31] This might protect the lung from infection and aggregate inhaled particles and microbes to facilitate clearance.

Viruses. SP-A binds influenza, herpes simplex, respiratory syncytial virus, and presumably many more respiratory viruses. SP-A binds influenza and inhibits hemagglutination and infection, although the effect is not as dramatic as with SP-D. SP-A binds to influenza by the terminal sialic acid residues on the N-linked carbohydrate of SP-A. Thus, carbohydrate moieties on both microorganisms and SP-A play a role in the process by which SP-A interacts with pathogens. The SP-A–deficient mouse demonstrates a role for SP-A in respiratory viral infections and its importance in host defense.[32,33]

Bacteria. SP-A binds to both gram-positive and gram-negative bacteria and is thought to be an important component of host defense. SP-A binds to and increases phagocytosis of *Streptococcus pneumoniae,* group A *Streptococcus*, and *Staphylococcus aureus*. SP-A stimulates phagocytosis of opsonized *S. aureus*, but the effect is dependent on the growth conditions of the organism and thereby the chemical composition of their external coat. More recently, SP-A has been reported to bind to peptidoglycan, an important component of the cell wall of gram-positive bacteria. Hence, SP-A may be an important host-defense molecule for gram-positive organisms.

SP-A binds gram-negative bacteria with the rough form of lipopolysaccharide (LPS), aggregates these bacteria, and increases phagocytosis and killing.[34,35] SP-A binds to the smooth variants of *Escherichia coli* poorly. Gram-negative bacteria that colonize the respiratory tract usually display the smooth form of LPS, whereas those that colonize the gastrointestinal tract display rough forms of LPS. SP-A binds the lipid A moiety and not the oligosaccharides of LPS, which is the ligand for SP-D. In addition, isolated SP-A binds to and increases the phagocytosis of *H. influenzae*, *Klebsiella,* and *P. aeruginosa*.[36] In addition, Wu and coworkers[34] demonstrated that SP-A and SP-D could directly kill gram-negative bacteria by increasing their membrane permeability.

Mycobacteria, Fungi, Mycoplasma, and *Pneumocystis.* SP-A enhances the adherence and subsequent phagocytosis of mycobacteria by macrophages. This effect has been attributed to an interaction between the N-linked carbohydrate on SP-A and macrophages and is thought to be due to increased surface expression of the mannose receptor on macrophages.[37] Lipoglycans, especially mannosylated lipoarabinomannan, are important ligands for SP-A on mycobacteria. Weikert and associates[38] reported that SP-A increased the binding and phagocytosis of mycobacteria by rat macrophages and human monocytes and that this interaction occurred through a specific 210-kDa SP-A receptor. In other studies, several different putative SP-A receptors on

macrophages have been described, and these receptors include Toll-like receptor 2 (TLR2), CD14, calreticulin, C1qRp, and signal-inhibitory regulatory protein α (SIRPα) as well as the 210-kDa receptor.[9] The increased phagocytosis of mycobacteria by SP-A may facilitate some killing but also allows mycobacteria to escape to an intracellular replicative environment.

SP-A is also important in host defense against fungal infections, especially *Histoplasma* and *Aspergillus*. Madan and colleagues[39] reported that human SP-A bound to *Aspergillus fumigatus* conidia and enhanced their phagocytosis and killing by human neutrophils and alveolar macrophages. McCormack and coworkers[40] reported that SP-A could directly kill extracellular, but not intracellular, *Histoplasma*. There is no convincing evidence for SP-A in the clearance of fully encapsulated *Cryptococcus neoformans* or *Candida albicans*. SP-A also binds to and inhibits the growth of mycoplasma, although the role of SP-A in clearance and killing of mycoplasma appears to be modest.

SP-A binds to gp120, the major surface glycoprotein of *P. carinii*, but does not clear the infection. Although SP-A binds and stimulates adherence of fully encapsulated *Pneumocystis* to macrophages, SP-A does not enhance phagocytosis by macrophages. Pneumocystis can persist extracellularly in the alveolar space for a long time in the presence of physiologic levels of SP-A.

Interaction with Phagocytic Cells

SP-A has been reported to bind to several receptors on macrophages and to modulate the expression of microcidal factors and TLR2 and 4 and the clearance of apoptotic cells.[9,41,42,42a] The binding of SP-A to alveolar macrophages appears to be specific and not seen with other mononuclear phagocytes as Kupffer cells, resident peritoneal macrophages, or peritoneal macrophages.[43,44] Some have cautioned that the stimulation of inducible nitric oxide synthase (iNOS) and nitric oxide (NO) production in early experiments could be due to endotoxin contamination in the SP-A and SP-D preparations.[45] The studies on direct activation of inflammatory cells is complex and their results depend on the method of SP-A isolation and the state of the inflammatory cells, especially if they have been primed by a cytokine such as interferon gamma. In addition, it is important for in vitro studies to evaluate the effect of SP-A in the presence of surfactant phospholipids to stimulate the in vivo situation, since SP-A may bind surfactant phospholipids with a higher affinity than microbes or inflammatory cells. Many of the effects of isolated SP-A do not occur if the experiments are done in the presence of surfactant phospholipids. Finally, transforming growth factor-β (TGF-β) has also been reported in some preparations of SP-A, which could account for some anti-inflammatory properties.[46]

SP-A appears to suppress the secretion of inflammatory cytokines by macrophages in the normal lung but enhances cytokine production during infection or lung injury. This is sometimes referred to as the inflammatory paradox of SP-A. Gardai and associates[47] formulated an interesting mechanism for these observations. In the normal lung, SP-A interacts with macrophages through its CRD domain and binds to SIRP-α, which in turn suppresses cytokine production. However, during infection, SP-A binds the organism with its CRD domain and interacts with macrophages via its N-terminal domain and the calreticulin/CD91 complex to stimulate the production of inflammatory cytokines. Hence, SP-A can both stimulate and inhibit inflammatory cytokine production in vitro. It is important to recall that in vivo, there is a complex interaction between SP-A, the phospholipids of surfactant, inhaled microbes, and receptors on inflammatory cells. Each has a different binding affinity for SP-A and independent regulation.

SP-A has also been shown to bind to apoptotic cells and to increase their uptake and removal by macrophages.[41] Uptake proceeds through a common receptor complex involving calreticulin and CD91, which is also involved in the uptake of apoptotic cells mediated by C1q or mannose-binding lectin.[41] However, SP-A appears to be less important than SP-D in clearance of apoptotic cells in vivo.

Surfactant Protein B

SP-B is the one surfactant protein that has been demonstrated to be crucial for surfactant function and is thought to be critical in the adsorption and surface spreading of phospholipids.[16,48,49] Mice with homozygous null alleles for SP-B die of respiratory insufficiency shortly after birth, and heterozygotes have impaired surfactant function. SP-B is required for organizing phospholipids in lamellar bodies, for the formation of tubular myelin, and for delivering phospholipids to the alveolar air-liquid interface. SP-B is thought to be important in film formation and in entry of phospholipids into the surface monolayer, when the film is expanded during inspiration. The five amphipathic helices of SP-B are envisioned to lie along the lipid bilayer or surface monolayer.[48] SP-B interacts with phospholipid bilayers by electrostatic interactions between the polar head groups of the phospholipids and its positively charged amino acids and through the nonpolar faces of the amphipathic helices that interact with the phospholipid acyl chains. SP-B is positively charged and has a preference for interacting with negatively charged phospholipids, such as phosphatidylglycerol. This surfactant protein is squeezed out of the monolayer at moderate film pressures (40–45 mN/m) and does not insert directly into the monolayer or lipid bilayers. SP-B can convert lipid vesicles into phospholipid sheets and is likely to be very important in moving lipid into the monolayer with each respiratory cycle.

Mature SP-B is a homodimer composed of two 79–amino acid polypeptide chains linked by disulfide bonds. The monomer has an expected mass of 8.7 kDa and the homodimer, 17.4 kDa. Each monomer has five amphipathic helices that interact with the surface of the monolayer but do not span the monolayer. There are three internal disulfide bridges within the monomer (C8–C17, C11–C71, and C35–C46) and an interchain disulfide at

C48. SP-B is a member of the family of saposin-like proteins that perturb phospholipid bilayers.

As demonstrated in congenital SP-B deficiency in infants and in genetically altered mice, highly structured lamellar bodies do not form in the absence of SP-B.[50,51] In SP-B deficiency, there is also aberrant processing of SP-C that results in the secretion of a partially processed 12-kDa form of SP-C. The SP-B knockout mouse has severe respiratory deficiency at birth, and heterozygotes have impaired surfactant function and susceptibility to lung injury.[50,51] Lamellar body formation may depend on the ability of SP-B to organize and bind with two adjacent lipid bilayers. Secretion of SP-B occurs exclusively as a component of lamellar bodies. In genetically targeted mice with conditional expression of SP-B, reduction of SP-B below 25% of the wild-type level results in respiratory failure.[49] SP-B is found in natural surfactant preparations, although the content may vary from batch to batch and may differ from that found in surfactant isolated from normal animals. SP-B is also found in Clara cells, but the function of SP-B associated with Clara cells is not known.

There is one gene for SP-B that is located on human chromosome 2. The synthesis of SP-B is markedly stimulated by corticosteroids in vitro. This protein undergoes extensive intracellular processing before the mature homodimer is formed. Within the endoplasmic reticulum (ER), the signal peptide is cleaved, and a prepro 42-kd species of SP-B is formed. In multivesicular bodies, general additional proteolytic cleavages occur to remove a 16-kDa amino terminal peptide and a 30-kDa C-terminal peptide. The final processing of SP-B probably occurs within the multivesicular bodies, and the mature homodimer is formed by the time SP-B arrives in the lamellar body.

Surfactant Protein C

SP-C is an extremely hydrophobic protein that is unique to surfactant and alveolar type II cells.[52,53] SP-C is expressed only in the lung and is a highly specific marker for identifying type II cells. However, the precise physiologic function of this protein is not completely understood. The fully processed form of SP-C is a 35–amino acid lipopeptide that has two palmitates attached as thioesters at amino acids C5 and C6. The segment between residues 13 and 28 forms a very hydrophobic α-helix containing aliphatic amino acids, mainly valine. This α-helix is the membrane-spanning portion of SP-C and is extremely stable. In most species, there are two positively charged amino acids, lysine at position 11 and arginine at position 12, which appear to be necessary to move the protein from the ER into the Golgi network, where the palmitoylation occurs. The precise orientation of the palmitates relative to the valine-rich α-helix is not fully resolved, but both regions are probably important for interactions with phospholipid bilayers or monolayers. SP-C can mix with phospholipids and promote spreading and fusion of phospholipids. SP-C inserts into the monolayer and is squeezed out of the surface monolayer only at relatively high film pressures (>55 mN/m). Presumably, SP-C is important in organizing the phospholipids during the respiratory cycle. SP-C is thought to stabilize the surface film and minimize film collapse. Unlike SP-B, SP-C does not appear to interact with SP-A and is not critical for the formation of tubular myelin. SP-C is found in all preparations of natural surfactant, and a recombinant form of SP-C is used in one type of surfactant replacement therapy.

There is one human gene for SP-C that is located on human chromosome 8. Like SP-B, SP-C is synthesized as a larger prepro form of 21 kDa and processed by proteolytic cleavage of both N-terminal and C-terminal fragments. Most of the posttranslational processing occurs before SP-C arrives at the lamellar body. There is apparently some interaction between the processing of SP-B and SP-C, because in hereditary deficiency of SP-B, an aberrantly processed 12-kDa form of pro SP-C accumulates in type II cells and in alveolar fluid. The SP-C promoter has been an important tool for overexpressing a variety of transgenes in type II cells in mice.

The physiologic role of SP-C is still not completely known. In outbred Swiss black mice, SP-C–null mice appear normal until about 6 months of age, at which time they developed chronic pneumonitis and air space enlargement.[54] This demonstrates that SP-C is not absolutely necessary for surfactant function. However, in the 129J strain, mice develop chronic pneumonitis within 3 months.[55] The genetic background and disease-modifying genes are, therefore, likely involved in clinical manifestations of SP-C deficiency and mutations. These observations provide the background for investigating genetic variants in SP-C as a cause of idiopathic interstitial lung diseases, which is discussed later. SP-C mutations produce a misfolded protein that accumulates and causes ER stress in type II cells and chronic interstitial lung disease.

Surfactant Protein D

SP-D is a calcium-dependent lectin and an important component of innate immunity.[9,56–58] Recombinant SP-D has even been proposed as a therapeutic agent in the treatment of pulmonary infections. The gene for SP-D is near the locus of SP-A on human chromosome 10. SP-D is a collagenous glycoprotein with a complex but highly ordered tertiary structure (see Fig. 9-3). Identical monomers of SP-D assemble as trimers and then combine to form the final dodecamer. This produces a large symmetrical cruciform-shaped molecule with a distance of about 100 nm between the terminal CRDs, about five times larger than SP-A. The CRD unit is primarily responsible for binding to surface ligands on microorganisms and provides for the multivalency of the oligomers.

Conceptually, SP-D should be thought of as a protein distinct from the surfactant system. SP-D binds the phospholipids of surface-active material weakly and is mostly soluble in alveolar fluid. However, SP-D does bind two lipids with carbohydrate motifs, phosphatidylinositol and glucosylceramide, but not phosphatidylcholine. The location of SP-D in the lung also suggests that it is not directly involved with the surfactant system. SP-D is

found in ER of type II cells and in the secretory granules of Clara or nonciliated bronchiolar cells but not in lamellar bodies of type II cells or in tubular myelin. Like SP-A, SP-D is highly expressed in conducting airways of rodents but sparsely in the major conducting airways in humans. SP-D is highly expressed in the hyperplastic type II cells present in interstitial lung diseases. SP-D is also present on many other mucosal surfaces.[59]

The phenotype of the SP-D knockout mouse was unexpected from prior in vitro studies. The knockout mouse shows an increase in the extracellular pools of surfactant and an accumulation of large foamy macrophages with excess metalloprotease activity, which results in alveolar wall destruction and subsequent air space enlargement.[60] The implications are that SP-D regulates macrophage function and that an absence of SP-D leads to a reduced clearance of surfactant. SP-D–deficient mice are also susceptible to infection with influenza A virus and *Aspergillus*. In addition, a large number of apoptotic cells are found in the air spaces and lavage fluid of SP-D–null mice, indicating the importance of SP-D in the clearance of apoptotic cells.

Structure and Function

The overall structure of SP-D is similar to that of SP-A, and the primary structure consists of four domains (see Fig. 9-3). The amino terminal segment contains cysteines that form interchain disulfide bonds that cross-link subunits to form covalent oligomeric structures. The adjacent collagen-like region promotes the formation of noncovalent trimers, imparts a rigid longitudinal structure to the molecules, and organizes the spatial distribution of the carboxy terminal CRDs. The coiled-coil motif of the neck forms and contributes to the spacial organization of the CRD domains. The C-terminal CRD domain contains the calcium- and carbohydrate-binding sites. The crystal structure of the CRD and neck region of SP-D has shown a distinct spatial distribution of the three CRDs, has defined the carbohydrate-binding pocket, and has allowed for computer docking studies to demonstrate the importance of specific vinyl hydroxyl groups in sugars for binding to SP-D.[61,62] As in the case of SP-A, the full oligomerization of SP-D appears to play an important role in maintaining biologic potency that may result from specific spatial cross-linking of ligands as well as amplification of relatively weak interactions through multiple binding sites.

Binding to Infectious Organisms

SP-D is an important host-defense molecule and binds a variety of organisms, usually through its CRD domain.[63] In terms of monosaccharide binding, SP-D has a preference for maltose, glucose, and mannose. The binding of SP-D to organisms can be altered by physiologic glucose concentrations, and impaired binding in the presence of glucose may be important in diabetics.[64]

Viruses. SP-D binds influenza A, inhibits hemagglutination, and inhibits infection.[65] It is interesting to note that the annual severity of influenza infections is related to their ability to bind to SP-D[66] and strains with less SP-D binding are more virulent. The binding is related to the N-linked carbohydrate on the influenza viral coat. SP-D has also been shown to bind SARS-CoV spike protein and to inhibit respiratory synctial virus infection. Although studies on the interaction of SP-D with viruses have been reported for only a few viruses, it is likely that SP-D binds to many respiratory viruses. In humans, high concentrations of SP-D would be suspected to be found only in the gas-exchange regions of the lung, whereas in rodents with abundant Clara cells, SP-D is found at high concentrations along conducting airways.

Bacteria. SP-D binds to bacteria and should be considered an important molecule in host defense. SP-D binds both major components of gram-positive cell walls, peptidoglycan and lipoteichoic acid.[57,67] SP-D also binds to LPS and to gram-negative bacteria with the rough form of LPS and aggregates these bacteria. Like SP-A, SP-D binds the smooth variants of *E. coli* poorly. The binding is thought to be due to the interaction of the CRD of SP-D with the core oligosaccharides of LPS moiety of *E. coli*. SP-D binds and increases phagocytosis of nonmucoid *Pseudomonas*, which is a common cause of nosocomial pneumonia.[68] Interestingly, SP-D binds to the unencapsulated forms of *Klebsiella*, whereas SP-A binds to the encapsulated varieties.[69] Hence, SP-A and SP-D can work in partnership in clearance of *Klebsiella*. Although SP-D binds many bacteria, clearance of group B *streptococci* and *H. influenzae* is normal in the SP-D–deficient mice.[70] Presumably, this is due to compensation by SP-A.

Fungi, Mycobacteria, Mycoplasma, and *Pneumocystis.* SP-D is likely important in defense against fungal infections. SP-D binds to *A. fumigatus* conidia and histoplasma and enhances their phagocytosis and killing. SP-D also binds to and agglutinates *Saccharomyces cerevisiae* and the cell wall ligand for binding is beta (1–6) glucan.[71] This binding is inhibited by pustulan, an extremely effective competitive inhibitor of SP-D. SP-D also binds *Alternaria*, a common mold and aeroallergen, and SP-D may be important in clearing a variety of inhaled fungal spores. SP-D agglutinates *Mycobacterium tuberculosis* but inhibits its phagocytosis by human macrophages. Once in macrophages, SP-D promotes phagosome-lysosome fusion and thereby intracellular killing.[72] SP-D also binds *Mycoplasma* and the binding site on *Mycoplasma* appears to be a lipid component of the cell membrane.[73]

The *P. carinii* surface glycoprotein gp120 is a ligand for SP-D, and the binding is calcium dependent and inhibited by glucose and mannose. Although SP-D binds to *P. carinii*, is found in association with the organisms in vivo, and stimulates adherence of the microbe to macrophages, it does not enhance phagocytosis by macrophages. In this case, there is clear association of SP-D with the organism but no evidence of enhanced clearance.

Interactions with Phagocytic Cells

SP-D has been reported to bind to several different receptors on macrophages and to stimulate microbicidal

metabolism, as indicated by the production of reactive oxygen species.[9] Rat SP-D enhances oxygen radical production by alveolar macrophages but not peritoneal macrophages.[74] Surfactant lipids do not alter this effect of SP-D. In general, unlike SP-A, the effects of SP-D are not inhibited by the addition of surfactant phospholipids. However, there remain concerns that in the early studies the stimulation of macrophages by SP-D could be due to endotoxin contamination.[45] Holmskov and coworkers[75] isolated a 340-kDa SP-D-binding protein that is found on the surface of alveolar macrophages and may be a SP-D receptor. Other possible receptors for SP-D include the calreticulin and CD-91 complex, SIRP-α, and CD14.[41,47,76]

SP-D is also involved in the clearance of apoptotic cells, and this has been demonstrated both in vitro and in vivo. The SP-D–deficient mouse has an increased number of apoptotic cells in its lavage fluid and clears instilled apoptotic cells at a reduced rate.[41,70] SP-D binds to apoptotic cells and facilitates their ingestion by macrophages through the calreticulin and CD91 complex.

The interactions of both SP-D and SP-A with organisms and phagocytic cells are complex, and the clear identification of the receptors for these proteins is awaited in order to sort out apparently conflicting observations. The interaction will be affected by the organism, the growth cycle of the organism, the phagocytic cell, and the state of activation of the phagocytic cell as well as the source of SP-A or SP-D and the presence or absence of contaminating endotoxin and TGF-β in the surfactant protein preparation. A clear association of alterations in SP-A and SP-D in host defense in humans has not been reported.

SECRETION AND EXTRACELLULAR PROCESSING OF SURFACTANT

Secretion of the phospholipid components of surfactant has been studied extensively (Fig. 9-4).[77] Turnover studies have demonstrated that the surfactant system is dynamic; 10% to 20% of the surfactant pool is secreted each hour.[78,79] There are several different independent pathways for stimulating secretion that work through different receptors and signaling mechanisms. In vivo secretions are stimulated by hyperventilation or even a single deep breath or sigh. Stretch is an important physiologic stimulation, which signals exocytosis through an elevation of intracellular calcium.[80] In vitro, tetradecanoyl acetate (TPA) and adenosine triphosphate (ATP) greatly stimulate basal secretion. TPA activates protein kinase C directly, and ATP stimulates protein kinase C indirectly via a $P2Y_2$ purinergic receptor and activation of phospholipase C. Agents that stimulate secretion via cAMP-dependent pathways such as β-agonists and cholera toxin stimulate secretion more modestly. Other agents that have been reported to stimulate secretion include calcium ionophores, arachidonate, prostaglandin E_2, vasopressin, endothelin, and serum lipoproteins.

Secretion of surfactant is also under negative control. Inhibitors of secretion in vitro include SP-A and DPPC. In vitro, SP-A inhibits secretion at very low concentrations (~1 μg/mL), and this occurs to a lesser extent in the presence of phospholipid. However, this inhibition of secretion observed in vitro appears not to occur in vivo, because in the SP-A knockout mouse, surfactant secretion and turnover are normal.[19] However, the role of SP-A as a negative regulator of surfactant secretions remains a controversial area. Secretion requires active extrusion of the lamellar body contents, and in vitro SP-A may constrain this final phase of secretion.[81] In vivo secretion is likely highly regulated, and there may be multiple checks and balances such that alteration in one pathway might not alter turnover.

After exocytosis by alveolar type II cells, the secreted lamellar bodies undergo physical rearrangements

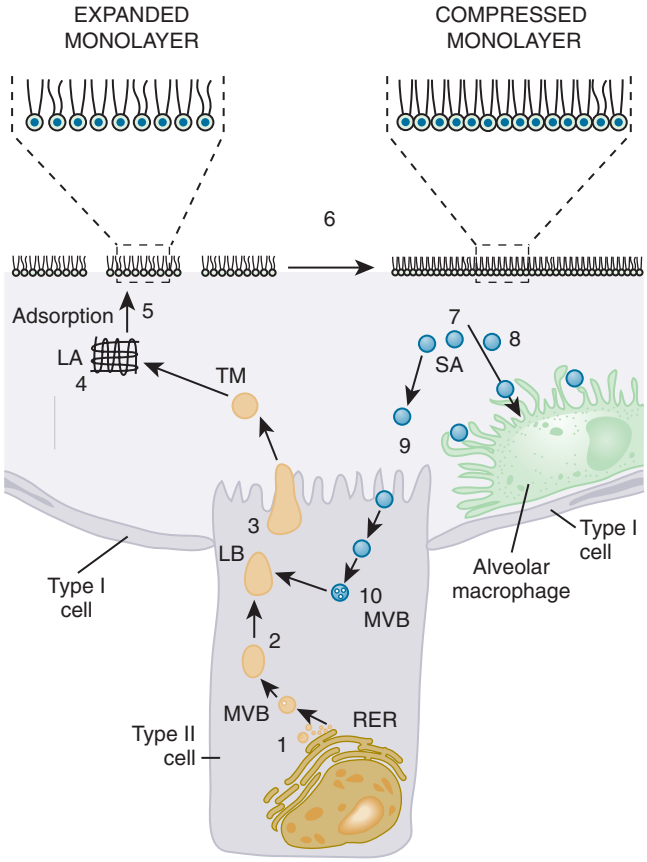

FIGURE 9-4 ■ Metabolic trafficking of surfactant phospholipids. The phospholipids are synthesized in the rough endoplasmic reticulum (RER) and processed in the Golgi network of the alveolar type II cell (*1*). They are transported to the multivesicular bodies (MVB) (*2*), where the first lamellae are formed. These lamellae increase to form lamellar bodies (LB), which are subsequently secreted by exocytosis (*3*). The secreted LB unfolds to form tubular myelin (TM) (*4*) and other large aggregates (LA). These forms adsorb into the expanded surface monolayer (*5*). This is a critical step for producing a low surface tension in the lung. During the respiratory cycle, as the film is compressed during exhalation, the film pressure rises, and a compressed, closely packed monolayer of nearly pure dipalmitoylphosphatidylcholine is formed (*6*). Material is excluded from the monolayer (*7*) and forms small aggregates (SA). Some of these aggregates are ingested by macrophages (*8*), and some are endocytosed by reprocessing by alveolar type II cells (*9* and *10*).

extracellularly (see Fig. 9-2). The initial change is the conversion from the multilamellar state to tubular myelin (see Fig. 9-4). This requires SP-A, SP-B, calcium, and the surfactant phospholipids and can be reproduced in vitro.[6] In lavage samples (LA), surfactant can be isolated by differential centrifugation. These aggregates contain SP-A and SP-B and are composed of tubular myelin, multilamellar structures, and other loose lipid arrays, which are the expected forms of secreted and unraveling lamellar bodies. LA forms adsorb rapidly to the air-liquid interface and can be considered an extracellular reservoir of surfactant. LA can be converted into smaller aggregates (SA), which are much less surface active. These SA are thought to represent surfactant that has left the air-liquid interface and is available to be taken up by type II cells and reprocessed. The conversion of LA to SA is facilitated by an enzyme called convertase that has some of the properties of a carboxylesterase.[82] Although there are at least four routes for the catabolism of surface-active material, the two dominant routes are uptake by type II cells and catabolism by alveolar macrophages.[78] The current estimates are that 25% to 85% of secreted surfactant is recycled by adult type II cells[83,84] and about 15% is catabolized by macrophages. Relatively little pulmonary surfactant goes up the mucociliary escalator, and very little enters the bloodstream or lymphatics. Catabolism of extracellular surface-active material is regulated by granulocyte-macrophage colony-stimulating factor (GM-CSF) and its ability to activate macrophages.[85] Adult idiopathic alveolar proteinosis is caused by an autoantibody to GM-CSF[86,87]; some pediatric forms of alveolar proteinosis are due to mutations in the receptor for GM-CSF.[88,89] The extracellular pool of surfactant, perhaps excess surfactant, appears to be regulated predominantly by alveolar macrophage clearance.

SURFACTANT ABNORMALITIES IN LUNG DISEASE

Primary Surfactant Deficiency of the Newborn

Epidemiology and Clinical Features

The importance of the pulmonary surfactant system in the pathophysiology of the NRDS was first reported by Avery and Mead in the late 1950s.[5] The observation that NRDS was due to a primary surfactant deficiency has been confirmed by the tremendous impact that exogenous surfactant administration has had on infant mortality.

The incidence of NRDS varies with gestational age and birth weight. Approximately 15% of infants born between 34 and 37 weeks of gestational age (<1700 g) develop NRDS, whereas 50% of infants between 30 and 34 weeks of gestational age (<1500 g) and 70% of those born at less than 30 weeks of gestational age (<1250 g) develop this disease. These rates may also be influenced by other factors, including race, gender, socioeconomic status, and maternal health.

Infants with NRDS develop sternal retractions, nasal flaring, tachypnea, and grunting shortly after birth. There is a marked decrease in lung compliance, which is associated with hypoxemia, and diffuse bilateral parenchymal infiltrates. Mechanical ventilatory support usually requires high oxygen concentrations and ventilatory pressures. Even though artificial ventilation and exogenous surfactant have decreased infant mortality, there still exists a major disability rate among the survivors, particularly in the infants of very low birth weight. The most common of these disabilities is bronchopulmonary dysplasia. Accurate fetal lung maturity assessments have led to maternal treatment strategies that have resulted in a decrease in the incidence of NRDS by 10% to 30%. Ultrasonic anthropometric measurements are helpful but do not accurately estimate lung maturity in the third trimester. Amniotic fluid surfactant analysis reliably predicts the risk of NRDS. Pathologic changes typical of NRDS include widespread atelectasis, capillary congestion, microhemorrhage, edema, and hyaline membranes.[5] Mechanical ventilation of these infants has been shown to retard alveolarization and to increase interstitial collagen deposition and bronchial smooth muscle within the lung. As a result, more "protective" ventilatory strategies, including high-frequency oscillation, as well as NO administration, are currently being used.

Treatment

Fujiwara and colleagues[90] reported the first successful use of exogenous surfactant in neonates with NRDS in 1980. Several large clinical trials demonstrated significant improvement in gas exchange, decreased barotrauma, and decreased infant mortality in response to this therapy. Results of these trials have also shown that prophylactic administration of surfactant before the first breath is superior to surfactant given after a period of ventilation. These differences were particularly notable in the infants of very low birth weight (<28 weeks of gestational age). Prophylactic treatment is reserved for infants less than 28 weeks of gestational age. Otherwise, surfactant should be administered once the diagnosis of NRDS is established, usually within 30 minutes after birth. The usual dose of surfactant administered to these infants is approximately 100 mg phospholipid/kg body weight. Although surfactant therapy is very effective for NRDS, approximately 30% of affected infants do not respond to this therapy.

Hereditary Surfactant Protein B Deficiency

Although most cases of NRDS result from immaturity, there are inherited forms specifically due to SP-B deficiency.[91,92] Associated abnormalities include aberrant structured tubular myelin, decreased number of lamellar bodies, and abnormal processing of SP-C. Regardless of gestational age, affected patients develop respiratory distress in the first few days of life that is refractory to all therapy, including surfactant supplementation. Death

eventually ensues in the first few months of life, unless they receive a lung transplant. Although the most common abnormality involves a 1-bp deletion and 3-bp insertion in codon 121 in exon 4, which results in a premature stop codon, other mutations also occur and can lead to respiratory failure. The heterozygotes represent about 1 in 3000 individuals in the general population, would be predicted to have about half the SP-B level, and might be more sensitive to acute respiratory distress syndrome (ARDS). In mice, about 20% of wild-type SP-B is required for normal function. Mice with 50% reduction are more susceptible to acute lung injury. NRDS also results from other deficiencies in surfactant synthesis and assembly. The most common deficiency is the ATP-binding cassette family member A3 (ABCA3), a lamellar body phospholipid transport protein.[93,94]

Hereditary Surfactant Protein C Deficiency and Mutations

Deficiency of SP-C would not be expected to produce acute respiratory failure. In mice, SP-C deficiency causes diffuse nonspecific chronic interstitial pneumonitis over months to years and depends on the genetic strain. A splice site mutation in intron 4 of the SP-C gene produces chronic interstitial lung disease with an autosomal dominant inheritance pattern.[92,95,96] Recently, additional cases of nonspecific interstitial pneumonitis (NSIP) and usual interstitial pneumonitis have been reported with a single gene mutation.[97] This kindred also showed an autosomal dominant inheritance pattern. The hypothesis is that the mutations cause a misfolded SP-C protein, which accumulates and produces ER stress and chronic lung disease.[97a]

Acute Respiratory Distress Syndrome

Early descriptions of ARDS suggested that surfactant abnormalities play an important role in the lung dysfunction observed in these patients. Petty and Ashbaugh[98] recorded abnormal pressure-volume curves in lungs isolated from patients dying of ARDS. Morphologic changes noted in the lung tissue of these patients at autopsy were similar to those of preterm infants suffering from NRDS. The clinical criteria used to diagnose ARDS, including severe hypoxemia, decreased lung compliance, and bilateral infiltrates on chest radiograph, are also similar to those used to diagnose NRDS. As opposed to a primary deficiency of surfactant, however, ARDS is more complex, with many different etiologies and an elaborate inflammatory cascade resulting in lung injury and alveolar edema. The underlying alveolar epithelium is severely damaged in ARDS, whereas the alveolar epithelium is relatively intact at the onset of NRDS.

Surfactant Alterations

Extensive animal studies and several human reports characterizing surfactant alterations in ARDS and acute lung injury have shown a decrease in the percentage of phosphatidylcholine, phosphatidylglycerol, and DPPC and a corresponding increase in phosphatidylinositol, sphingomyelin, and in some cases lysophosphatidylcholine.[99,100] Decreased levels of SP-A and SP-B have also been demonstrated in bronchoalveolar lavage (BAL) samples from patients with ARDS, and surface tension–lowering properties of the isolated surfactant are abnormal.[99] These abnormalities correlated with the severity of ARDS. BAL samples isolated from patients with severe ARDS also show an increase in poorly surface-active small aggregate (SA) and a decrease in large aggregate (LA). In animal models of acute lung injury, there is a severe reduction of surfactant protein gene expression at the onset of respiratory insufficiency.[101]

Mechanisms Leading to Surfactant Dysfunction

With increased alveolar permeability in patients with ARDS, a number of proteins enter the air space and can either alter the structure of surfactant phospholipids and proteins within the bulk phase or directly compete with surfactant molecules for space at the air-liquid interface. Interestingly, this nonstoichiometric inhibition of surfactant by plasma proteins can be overcome in vitro by increasing the concentration of surfactant. This observation provides rationale for administering large doses of exogenous surfactant to patients with ARDS. Other factors inactivating endogenous surfactant include lipid peroxidation of surfactant or perhaps direct oxidation of surfactant, degradation of phosphatidylcholine through phospholipases, and cleavage of surfactant proteins by proteases leaking into the air space. Thrombogenic components leaking into the air space can also coagulate and incorporate surfactant phospholipids into fibrin clots, thereby rendering the surfactant inaccessible to the air-liquid interface. An additional mechanism contributing to surfactant inactivation that has recently been described is an increase in the neutral lipids, primarily cholesterol. Although physiologic levels of cholesterol are essential for organizing the surface film, elevated levels may inhibit surfactant function.[102] Cholesterol is increased in patients with lung injury, and exposure of functional surfactant to this neutral lipid results in a loss of surfactant function.[100] Another mechanism contributing to surfactant dysfunction in ARDS involves the increased conversion of LA into SA. An important factor contributing to this conversion process is the large change in alveolar surface area determined by the size of the tidal volume. Indeed, in vivo studies have shown that increased tidal volumes, but not respiratory rates or positive end-expiratory pressure (PEEP) levels, correlated with an increased conversion of LA into SA,[103] and this was associated with physiologic deterioration. Hence, the deleterious effects of mechanical ventilation on lung function may be mediated, in part, by changes in alveolar surfactant aggregate forms. Minimizing these phasic changes in surface area by means of smaller tidal volumes allows surfactant to be maintained in LA forms and results in improved physiologic outcomes.[103] These findings are supported by clinical trials demonstrating

improved patient outcomes when lower tidal volumes are used in patients with ARDS.[104,105]

Pneumonia

There is increasing evidence that the pulmonary surfactant system plays a role in the pathophysiology of pneumonia. Surfactant or isolated surfactant component enhances macrophage phagocytic activity and migration, suppresses lymphocyte proliferation, decreases mediator release from activated inflammatory cells, and directly enhances both bacterial and viral killing. In addition, pneumonia elicits an inflammatory response that may lead to alveolar edema and an increase in proteins within the air space. These proteins, as well as phospholipases directly secreted from bacteria, may inhibit surfactant function. BAL samples obtained from patients with bacterial pneumonia showed decreased phosphatidylcholine and phosphatidylglycerol levels, as well as decreased SP-A levels.[99]

Experience with administering exogenous surfactant to patients with pneumonia is limited. Animal studies involving mice with viral pneumonitis has shown promising results, and a recent clinical trial in children with respiratory syncytial viral pneumonia demonstrated improved gas exchange, lung mechanics, and length of stay in the intensive care in surfactant-treated patients compared with controls.[106] Further studies are necessary to determine whether there is a role for exogenous surfactant in treatment of severe pneumonia.

Interstitial Lung Diseases

In addition to diseases involving acute alveolar inflammation, surfactant alterations have also been characterized in various interstitial lung diseases. Decreased levels of DPPC and of phosphatidylglycerol and increased levels of phosphatidylinositol have been observed in BAL fluid from patients with idiopathic pulmonary fibrosis (IPF).[107] BAL fluid of patients with IPF reveals reduced levels of SP-A and little change in SP-D.[107–109] The reduction in SP-A in BAL fluid is found in a variety of diffuse interstitial lung diseases. The ratio of SP-A to phospholipid, used to correct for recovery of total surfactant, is reduced in patients with IPF and predicts the subsequent 5-year survival rate among patients with IPF. In addition, Günther and associates[110] demonstrated that surfactant biophysical properties were impaired in IPF.

SP-A and SP-D have also been measured in serum and may serve as biomarkers of lung disease, especially when alveolar epithelial integrity is compromised. Serum concentrations of SP-A and SP-D are increased in patients with alveolar proteinosis, ARDS, and IPF.[108,111,112,112a] Measuring SP-A and SP-D in serum might be useful in the diagnosis of alveolar proteinosis, because the serum levels are quite high, the image on high-resolution computed tomographic scanning is nearly specific, and a biopsy can be avoided. More clinical correlations between serum values of SP-A and SP-D and usual clinical variables are needed to judge their value in the care of patients with interstitial lung disease. A small subset of patients with familial pulmonary fibrosis has been attributed to SP-C mutations. Most of the cases have histopathologic diagnosis of NSIP, but a few have the morphologic features of usual interstitial pneumonia (UIP).[97] Recently, mutations in SP-A2 have been also reported to be associated with interstitial lung disease and lung cancer.[113]

Obstructive Lung Diseases

Surfactant proteins may be synthesized in the peripheral airways and/or transported to the airways via the mucociliary escalator. The role of surfactant as a down-regulator of inflammation and the importance of surfactant in maintaining the openness of conducting airways suggest that surfactant alterations may be important in obstructive lung diseases.[114,115] BAL samples from patients with asthma showed decreased SP-A levels and a normal phospholipid composition.[22] The surface activity of the surfactant was abnormal, which was attributed to the inhibitory effects of proteins recovered in these samples. Studies in animal models of asthma and human studies have shown that pretreatment with exogenous surfactant inhibited subsequent allergic bronchoconstriction.[116,117] Interestingly, mice with an asthmatic response to *A. fumigatus* have been shown to have airway hyperresponsiveness, reduced surface activity in lavage fluid extracts, and reduced SP-B. Instillation of IL-4 reduced SP-B protein levels in lavage.[118] In these murine models of asthma, instillation of SP-D can also mitigate the inflammatory response.[119,120] No surfactant alterations have been demonstrated in patients with chronic bronchitis or emphysema.

Cystic fibrosis is characterized by colonization of both gram-negative and gram-positive bacteria and early airway inflammation. Both SP-A and SP-D are reduced in BAL from patients with cystic fibrosis, and the relative deficiency could contribute to bacteria colonization.[121] Serum SP-D has been reported to be increased in COPD and associated with an increased risk of COPD exacerbations.[121a]

Other Lung Diseases

Alveolar proteinosis is due to decreased clearance of surfactant[121b] (see Chapter 63). Alveolar phospholipids and surfactant proteins SP-A, SP-B, and SP-D are markedly increased in lavage samples from affected patients. SP-A and SP-D are also increased in the sera of these patients.[108,112] Decreased catabolism of surfactant results in an excess accumulation of multilamellated structures within the alveoli. Adult alveolar proteinosis has been shown to be an autoimmune disease produced by an antibody to GM-CSF, which results in decreased macrophage clearance of surfactant.[86,87] Pediatric forms of alveolar proteinosis are due to alterations in GM-CSF signaling, usually due to alterations in the GM-CSF receptor.[88,89] Effective treatment involves removing this material through whole-lung lavage and/or treatment with exogenous GM-CSF.

The ischemia-reperfusion injury associated with lung transplantation results in alterations in pulmonary

surfactant similar to those observed in patients with severe ARDS. Surfactant administered shortly after transplantation and reperfusion results in improved gas exchange in comparison to non–surfactant-treated lungs. Moreover, when surfactant is administered to donor lungs before storage, longer storage times are tolerated (up to 38 hours) with relatively little physiologic dysfunction observed after reperfusion.

Measurement of SP-A and SP-D in pleural fluid might also be useful to distinguish metastatic adenocarcinoma of the lung from other adenocarcinomas or mesothelioma.[122] In addition, surfactant protein gene expression can be used to screen for micrometastases in lymph nodes.[123] In mice with pulmonary adenomas, serum SP-D correlates extremely well with tumor size.[124]

SURFACTANT THERAPY FOR ACUTE RESPIRATORY DISTRESS SYNDROME

Numerous reports have suggested that exogenous surfactant administration may be of benefit in patients with ARDS.[125] To date, a few large multicenter clinical trials have evaluated this therapy and have shown inconsistent and somewhat disappointing results. The protein-free synthetic surfactant colfosceril palmitate (Exosurf) was administered via continuous aerosolization for up to 5 days in 364 patients with severe sepsis-induced ARDS.[126] There were no significant improvements in mortality, oxygenation, duration of mechanical ventilation, or duration of hospitalization in comparison with an aerosolized saline-treated control group. In a subsequent, albeit much smaller trial, the natural bovine surfactant Survanta, which contains some SP-B and SP-C, was administered via intratracheal instillation and compared with a group of patients receiving standard therapy. Surfactant resulted in both improved oxygenation and improved 30-day survival rates.[127] Based on the promising results of this trial, and suggestive preclinical studies, a series of subsequent clinical trials evaluated the efficacy of Venticute, a synthetic preparation containing recombinant SP-C and 50 mg PL/mL. After two phase II trials demonstrated safety of the treatment and improvements in gas exchange and ventilator-free days,[128] two larger phase III studies involving 221 and 227 patients, respectively, were conducted.[129] Although improvements in oxygenation in response to Venticute were shown in both studies, no differences in overall survival were noted in either study. A subgroup analysis, however, showed that patients with direct lung injuries, such as those caused by pneumonia and/or aspiration, had improved outcomes, including survival, when given Venticute. These observations led to a phase III trial assessing Venticute administration in patients with severe, direct lung injuries; however, that trial was stopped in 2008 due to lack of efficacy (personal communication, JFL). Interestingly, in a separate study, a natural, calf lung lavage surfactant call calfactant, was evaluated in pediatric patients with ARDS. This multicenter, randomized, blinded phase III trial included 153 patients ranging in age from infants to adolescents and showed that exogenous surfactant administration resulted in improvements in oxygenation and reduction in mortality (19.5% versus 36%), although the improved survival observed in this study was almost entirely due to the patients given surfactant who had direct lung injuries.[130] Currently, there is a larger phase II study under way evaluating calfactant in a prospective fashion in patients with direct injuries with ages ranging from 1 month to 85 years.

Surfactant Preparation and Dose

In general, animal studies suggest that natural surfactant preparations are superior to synthetic products, mainly due to the presence of hydrophobic surfactant proteins in the former compounds. Unfortunately, resource availability, cost, and the potential for variable composition are limiting factors of the natural products. For these reasons, more effective synthetic preparations are being developed. The newer synthetic compounds, including a novel recombinant SP-C–based surfactant (Venticute) and a SP-B–like peptide-based surfactant (Surfaxin) have been tested in phase I and II trials, and appear to have excellent biophysical activities, although none have shown consistently positive outcomes in Phase III studies to date, as noted earlier.[128] One area of current and future research is the evaluation of exogenous surfactant preparations that may affect bacterial growth and/or host-defense mechanisms. Although none of the commercially available surfactant preparations currently contain the collectins SP-A or SP-D, the addition of these components to exogenous surfactants, and recent studies focused on novel protein components of SP-B and SP-C, or peptoids, that will mimic the function of these proteins but are resistant to degradation, are being evaluated.[131–135]

The ideal dosage and dosing schedules are also unknown and will depend on the preparation used, the nature of the underlying illness, and the method used for delivery. For example, for severe disease with significant inhibition of surfactant function, relatively large amounts of exogenous surfactant will be required. Moreover, if surfactant is administered as a liquid bolus, relatively large dose volumes will be required for a more homogenous distribution.

Surfactant Delivery Methods

Animal studies have shown that surfactant administered via tracheal instillation is optimal if given as a rapid bolus rather than as slow infusion. In some studies, surfactant was administered via bronchoscopic instillation into individual lobes, and significant improvements in gas exchange were observed.[136] When directly compared in an animal model, bronchoscopic instillation was similar to tracheal instillation with regard to surfactant distribution patterns and physiologic outcomes, although the former technique took significantly longer and required a skilled bronchoscopist.[137] On the other hand, bronchoscopic instillation of surfactant associated with a lavage procedure aimed at removing inhibitory compounds from the air space may prove to be effective for some types of ARDS and/or meconium aspiration.[125,138]

Effects of Mechanical Ventilation

Animal studies have shown that the level of PEEP significantly influences the efficacy of surfactant replacement therapy. In addition, higher tidal volumes result in a greater conversion of exogenous LA surfactant forms to inferior functioning SA. The inherent conversion kinetics of a particular surfactant preparation, together with the specific mode of ventilation used, may well influence the duration of clinical response after surfactant is administered. Like endogenous surfactant, ventilatory modes that use smaller tidal volumes appear to be optimal, and when directly compared in an animal model of lung injury, high-frequency oscillation was superior to conventional modes utilizing low tidal volume and high PEEP with respect to physiologic outcomes and surfactant metabolism.[139]

Proposed Surfactant Treatment Strategies

The factors affecting a host's response to exogenous surfactant may all be influenced by the condition of the host's lungs at the time of administration. For example, a patient with severe ARDS would require large doses of a tracheally instilled surfactant to overcome protein inhibition. Another patient with relatively mild respiratory distress may respond to an aerosolized surfactant preparation, inasmuch as protein inhibition would not be as significant and smaller quantities of material would be sufficient. Moreover, the distribution of the injury at this stage would be relatively uniform so that aerosolization would be feasible. Although this early treatment strategy has not been used in humans, there is evidence from animal models of hyperoxia and ischemia-reperfusion that early administration of exogenous surfactant may prevent progressive lung dysfunction. These observations, together with animal data showing that surfactant is altered early in lung injury and in vitro data showing the importance of surfactant in host-defense properties, all provide a good rationale for pursuing early administration of exogenous surfactant in patients at high risk of developing ARDS. Until a reliable, early marker of impending ARDS is available, however, there still exists the problem of potentially treating patients who may not require or benefit from this intervention.

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KEY POINTS

- Pulmonary surfactant allows for the low surface tension in the gas-exchange portions of the lung, which prevents atelectasis, decreases the work of breathing, improves oxygenation, prevents alveolar flooding, and helps maintain patency of very small airways.
- SP-B is the only surfactant protein critical to surfactant formation in vivo.
- Mutations in SP-B and SP-C can lead to diffuse lung disease.
- SP-A and SP-D are thought to be important components of innate immunity and bind to both microorganisms and inflammatory cells.
- Surfactant replacement therapy in ARDS improves oxygenation but has not been shown to improve survival.

References

1. Pastva AM, Wright JR, Williams KL: Immunomodulatory roles of surfactant proteins A and D: Implications in lung disease. Proc Am Thorac Soc 4:252–257, 2007.
2. Neergaard, K: New interpretations of basic concepts of respiratory mechanisms. Z Gesamte Exp Med 66:373–394, 1929.
3. Clements J: Dependence of pressure-volume characteristics of lungs on intrinsic surface active material. Am J Physiol 187:592, 1956.
4. Pattle RE: Properties, function and origin of the alveolar lining layer. Nature 175:1125–1126, 1955.
5. Avery M, Mead J: Surface properties in relation to atelectasis and hyaline membrane disease. Am J Dis Child 97:517–523, 1959.
5a. Zuo YY, Veldhuizen RA, Neumann AW, et al: Current perspectives in pulmonary surfactant-inhibition, enhancement and evaluation. Biochim Biophys Acta 1778:1947–1977, 2008.
6. Williams MC, Hawgood S, Hamilton RL: Changes in lipid structure produced by surfactant proteins SP-A, SP-B, and SP-C. Am J Respir Cell Mol Biol 5:41–50, 1991.
7. Ikegami M, et al: Characteristics of surfactant from SP-A-deficient mice. Am J Physiol 275(2 Pt 1):L247–L254, 1998.
8. Enhorning G: Surfactant in airway disease. Chest 133:975–980, 2008.
9. Crouch E, Wright JR: Surfactant proteins A and D and pulmonary host defense. Annu Rev Physiol 63:521–554, 2001.
10. Wright JR: Immunoregulatory functions of surfactant proteins. Nat Rev Immunol 5:58–68, 2005.
11. Veldhuizen R, Nag K, Orgeig S, Possmayer F: The role of lipids in pulmonary surfactant. Biochim Biophys Acta 1408:90–108, 1998.
12. Clements JA, Nellenbogen J, Traham HJ: Pulmonary surfactant and evolution of the lungs. Science. 169:603–604, 1970.
13. Kuroki Y, Takahashi M, Nishitani C: Pulmonary collectins in innate immunity of the lung. Cell Microbiol 9:1871–1879, 2007.
14. Kishore U, et al: Surfactant proteins SP-A and SP-D: structure, function and receptors. Mol Immunol 43:1293–1315, 2006.
15. Sorensen GL, Husby S, Holmskov U: Surfactant protein A and surfactant protein D variation in pulmonary disease. Immunobiology 212:381–416, 2007.

16. Serrano AG, Perez-Gil J: Protein-lipid interactions and surface activity in the pulmonary surfactant system. Chem Phys Lipids 141:105–118, 2006.
17. Veldhuizen EJ, Haagsman HP: Role of pulmonary surfactant components in surface film formation and dynamics. Biochim Biophys Acta 1467:255–270, 2000.
18. Heinrich S, Hartl D, Griese M: Surfactant protein A—From genes to human lung diseases. Curr Med Chem 13:3239–3252, 2006.
19. Ikegami M, et al: Surfactant metabolism in surfactant protein A-deficient mice. Am J Physiol 272:L479–L485, 1997.
20. Bates S, et al: Surfactant protein-A plays an important role in lung surfactant clearance: Evidence using the surfactant protein-A gene-targeted mouse. Am J Physiol Lung Cell Mol Physiol 294: L325–L333, 2008.
21. Tino MJ, Wright JR: Surfactant protein A stimulates phagocytosis of specific pulmonary pathogens by alveolar macrophages. Am J Physiol 270:L677–L688, 1996.
22. van de Graaf EA, et al: Surfactant protein A in bronchoalveolar lavage fluid. J Lab Clin Med 120:252–263, 1992.
23. Gupta N, et al: Identification and characterization of p63 (CKAP4/ERGIC-63/CLIMP-63), a surfactant protein A binding protein, on type II pneumocytes. Am J Physiol Lung Cell Mol Physiol 291: L436–L446, 2006.
24. Bates S, et al: Role of P63 (CKAP4) in binding of surfactant protein-A to type II pneumocytes. Am J Physiol Lung Cell Mol Physiol 295:L658–L669, 2008.
25. Condon JC, et al: Surfactant protein secreted by the maturing mouse fetal lung acts as a hormone that signals the initiation of parturition. Proc Natl Acad Sci U S A 101:4978–4983, 2004.
26. Scavo LM, Ertsey R, Gao BQ: Human surfactant proteins A1 and A2 are differentially regulated during development and by soluble factors. Am J Physiol 275(4 Pt 1):L653–L669, 1998.
26a. Floros J, Wang G, Mikerov AN: Genetic complexity of the human innate host defense molecules, surfactant protein A1 (SP-A1) and SP-A2–impact on function. Crit Rev Eukaryot Gene Expr 19:125–137, 2009.
27. Ochs M, et al: Intracellular and intraalveolar localization of surfactant protein A (SP-A) in the parenchymal region of the human lung. Am J Respir Cell Mol Biol 26:91–98, 2002.
28. Osanai K, Mason RJ, Voelker DR: Trafficking of newly synthesized surfactant protein A in isolated rat alveolar type II cells. Am J Respir Cell Mol Biol 19:929–935, 1998.
29. Head JF, et al: Crystal structure of trimeric carbohydrate recognition and neck domains of surfactant protein A. J Biol Chem 278:43254–43260, 2003.
30. Haagsman HP: Structural and functional aspects of the collectin SP-A. Immunobiology. 205:476–489, 2002.
31. McCormack FX, Whitsett JA: The pulmonary collectins, SP-A and SP-D, orchestrate innate immunity in the lung. J Clin Invest 109:707–712, 2002.
32. Harrod KS, et al: SP-A enhances viral clearance and inhibits inflammation after pulmonary adenoviral infection. Am J Physiol 277(3 Pt 1):L580–L588, 1999.
33. Li G, et al: Surfactant protein-A–deficient mice display an exaggerated early inflammatory response to a beta-resistant strain of influenza A virus. Am J Respir Cell Mol Biol 26:277–282, 2002.
34. Wu H, et al: Surfactant proteins A and D inhibit the growth of Gram-negative bacteria by increasing membrane permeability. J Clin Invest 111:1589–1602, 2003.
35. Kabha K, et al: SP-A enhances phagocytosis of *Klebsiella* by interaction with capsular polysaccharides and alveolar macrophages. Am J Physiol 272:L344–L352, 1997.
36. Mariencheck WI, et al: Surfactant protein A enhances alveolar macrophage phagocytosis of a live, mucoid strain of *P. aeruginosa*. Am J Physiol 277(4 Pt 1):L777–L786, 1999.
37. Pasula R, et al: Surfactant protein A (SP-A) mediates attachment of *Mycobacterium tuberculosis* to murine alveolar macrophages. Am J Respir Cell Mol Biol 17:209–217, 1997.
38. Weikert LF, et al: SP-A enhances uptake of bacillus Calmette-Guérin by macrophages through a specific SP-A receptor. Am J Physiol 272:L989–L995, 1997.
39. Madan T, et al: Binding of pulmonary surfactant proteins A and D to *Aspergillus fumigatus* conidia enhances phagocytosis and killing by human neutrophils and alveolar macrophages. Infect Immunol 65:3171–3179, 1997.
40. McCormack FX, et al: Macrophage-independent fungicidal action of the pulmonary collectins. J Biol Chem 278:36250–36256, 2003.
41. Vandivier RW, et al: Role of surfactant proteins A, D, and C1q in the clearance of apoptotic cells in vivo and in vitro: Calreticulin and CD91 as a common collectin receptor complex. J Immunol 169:3978–3986, 2002.
42. Henning LN, et al: Pulmonary surfactant protein A regulates TLR expression and activity in human macrophages. J Immunol 180: 7847–7858, 2008.
42a. Gil M, McCormack FX, Levine AM: Surfactant protein A modulates cell surface expression of CR3 on alveolar macrophages and enhances CR3-mediated phagocytosis. J Biol Chem 284:7495–7504, 2009.
43. van Iwaarden F, et al: Pulmonary surfactant protein A enhances the host-defense mechanism of rat alveolar macrophages. Am J Respir Cell Mol Biol 2:91–98, 1990.
44. Weissbach S, et al: Surfactant protein A modulates release of reactive oxygen species from alveolar macrophages. Am J Physiol 267:L660–L666, 1994.
45. Wright JR, et al: Effects of endotoxin on surfactant protein A and D stimulation of NO production by alveolar macrophages. Am J Physiol 276(4 Pt 1):L650–L658, 1999.
46. Kunzmann S, et al: TGF-beta1 in SP-A preparations influence immune suppressive properties of SP-A on human CD4+ T lymphocytes. Am J Physiol Lung Cell Mol Physiol 291:L747–L756, 2006.
47. Gardai SJ, et al: By binding SIRPalpha or calreticulin/CD91, lung collectins act as dual function surveillance molecules to suppress or enhance inflammation. Cell 115:13–23, 2003.
48. Whitsett JA, Weaver TE: Hydrophobic surfactant proteins in lung function and disease. N Engl J Med 347:2141–2148, 2002.
49. Melton KR, et al: SP-B deficiency causes respiratory failure in adult mice. Am J Physiol Lung Cell Mol Physiol 285:L543–L549, 2003.
50. Tokieda K, et al: Pulmonary dysfunction in neonatal SP-B deficient mice. Am J Physiol 273:L875–L882, 1997.
51. Clark JC, et al: Decreased lung compliance and air trapping in heterozygous SP-B deficient mice. Am J Respir Cell Mol Biol 16:46–52, 1997.
52. Mulugeta S, Beers MF: Surfactant protein C: Its unique properties and emerging immunomodulatory role in the lung. Microbes Infect 8:2317–2323, 2006.
53. Beers MF, Mulugeta S: Surfactant protein C biosynthesis and its emerging role in conformational lung disease. Annu Rev Physiol 67:663–696, 2005.
54. Glasser SW, et al: Altered stability of pulmonary surfactant in SP-C-deficient mice. Proc Natl Acad Sci U S A 98:6366–6371, 2001.
55. Glasser SW, et al: Pneumonitis and emphysema in sp-C gene targeted mice. J Biol Chem 278:142911–142918, 2003.
56. Hartl D, Griese M: Surfactant protein D in human lung diseases. Eur J Clin Invest 36:423–435, 2006.
57. Palaniyar N, Nadesalingam J, Reid KB: Pulmonary innate immune proteins and receptors that interact with gram-positive bacterial ligands. Immunobiology 205:575–594, 2002.
58. Hansen S, Holmskov U: Lung surfactant protein D (SP-D) and the molecular diverted descendants: Conglutinin, CL-43 and CL-46. Immunobiology 205:498–517, 2002.
59. Akiyama J, et al: Tissue distribution of surfactant proteins A and D in the mouse. J Histochem Cytochem 50:993–996, 2002.
60. Wert SE, et al: Increased metalloproteinase activity, oxidant production, and emphysema in surfactant protein D gene-inactivated mice. Proc Natl Acad Sci U S A 97:5972–5977, 2000.
61. Allen MJ, et al: Polysaccharide recognition by surfactant protein D: Novel interactions of a C-type lectin with nonterminal glucosyl residues. Biochemistry 40:7789–7798, 2001.
62. Shrive AK, et al: High-resolution structural insights into ligand binding and immune cell recognition by human lung surfactant protein D. J Mol Biol 331:509–523, 2003.
63. Lawson PR, Reid KB: The roles of surfactant proteins A and D in innate immunity. Immunol Rev 173:66–78, 2000.

64. Reading PC, et al: Increased susceptibility of diabetic mice to influenza virus infection: Compromise of collectin-mediated host defense of the lung by glucose? J Virol 72:6884–6887, 1998.
65. White M, et al: Multimerization of surfactant protein D, but not its collagen domain, is required for antiviral and opsonic activities related to influenza virus. J Immunol 181:7936–7943, 2008.
66. Reading PC, et al: Collectin-mediated antiviral host defense of the lung: Evidence from influenza virus infection of mice. J Virol 71:8204–8212, 1997.
67. van de Wetering JK, et al: Characteristics of surfactant protein A and D binding to lipoteichoic acid and peptidoglycan, 2 major cell wall components of gram-positive bacteria. J Infect Dis 184: 1143–1151, 2001.
68. Bufler P, et al: Surfactant protein A and D differently regulate the immune response to nonmucoid *Pseudomonas aeruginosa* and its lipopolysaccharide. Am J Respir Cell Mol Biol 28:249–256, 2003.
69. Crouch E, Hartshorn K, Ofek I: Collectins and pulmonary innate immunity. Immunol Rev 173:52–65, 2000.
70. Clark H, Reid KB: Structural requirements for SP-D function in vitro and in vivo: Therapeutic potential of recombinant SP-D. Immunobiology 205:619–631, 2002.
71. Allen MJ, Voelker DR, Mason RJ: Interactions of surfactant proteins A and D with *Saccharomyces cerevisiae* and *Aspergillus fumigatus*. Infect Immun 69:2037–2044, 2001.
72. Ferguson JS, et al: Surfactant protein D increases fusion of *Mycobacterium tuberculosis*-containing phagosomes with lysosomes in human macrophages. Infect Immun 74:7005–7009, 2006.
73. Chiba H, et al: Human surfactant protein D (SP-D) binds *Mycoplasma pneumoniae* by high affinity interactions with lipids. J Biol Chem 277:20379–20385, 2002.
74. van Iwaarden JF, et al: Rat surfactant protein D enhances the production of oxygen radicals by rat alveolar macrophages. Biochem J 286:5–8, 1992.
75. Holmskov U, et al: Isolation and characterization of a new member of the scavenger receptor superfamily, glycoprotein-340 (gp-340), as a lung surfactant protein-D binding molecule. J Biol Chem 272:13743–13749, 1997.
76. Sano H, et al: Surfactant proteins A and D bind CD14 by different mechanisms. J Biol Chem. 275:22442–22451, 2000.
77. Andreeva AV, Kutuzov MA, Voyno-Yasenetskaya TA: Regulation of surfactant secretion in alveolar type II cells. Am J Physiol Lung Cell Mol Physiol 293:L259–L271, 2007.
78. Wright JR, Dobbs LG: Regulation of pulmonary surfactant secretion and clearance. Annu Rev Physiol 53:395–414, 1991.
79. Ueda T, et al: Clearance of surfactant protein B from rabbit lungs. Am J Physiol 268:L636–L641, 1995.
80. Wirtz HRW, Dobbs LG: Calcium mobilization and exocytosis after one mechanical stretch of lung epithelial cells. Science 250:1266–1269, 1990.
81. Frick M, et al: Ca^{2+} entry is essential for cell strain-induced lamellar body fusion in isolated rat type II pneumocytes. Am J Physiol Lung Cell Mol Physiol 286:L210–L220, 2004.
82. Krishnasamy S, et al: Molecular cloning, characterization, and differential expression pattern of mouse lung surfactant convertase. Am J Physiol 275:L969–L975, 1998.
83. Jacobs HC, et a: Reutilization of surfactant phosphatidylcholine in adult rabbits. Biochim Biophys Acta 837:77–84, 1985.
84. Magoon MW, et al: Subfractionation of lung surfactant. Implications for metabolism and surface activity. Biochim Biophys Acta 750:18–31, 1983.
85. Ikegami M, et al: Surfactant metabolism in transgenic mice after granulocyte macrophage-colony stimulating factor ablation. Am J Physiol 270:L650–L658, 1996.
86. Trapnell BC, Whitsett JA, Nakata K: Pulmonary alveolar proteinosis. N Engl J Med 349:2527–2539, 2003.
87. Kitamura T, et al: Idiopathic pulmonary alveolar proteinosis as an autoimmune disease with neutralizing antibody against granulocyte/macrophage colony-stimulating factor. J Exp Med 190:875–880, 1999.
88. Suzuki T, et al: Familial pulmonary alveolar proteinosis caused by mutations in CSF2RA. J Exp Med 205:2703–2710, 2008.
89. Martinez-Moczygemba M, et al: Pulmonary alveolar proteinosis caused by deletion of the GM-CSFRalpha gene in the X chromosome pseudoautosomal region 1. J Exp Med 205:2711–2716, 2008.
90. Fujiwara T, et al: Artificial surfactant therapy in hyaline-membrane disease. Lancet 79:31–37, 1980.
91. Cole FS, Hamvas A, Nogee LM: Genetic disorders of neonatal respiratory function. Pediatr Res 50:157–162, 2001.
92. Hamvas A: Inherited surfactant protein-B deficiency and surfactant protein-C associated disease: Clinical features and evaluation. Semin Perinatol 30:316–326, 2006.
93. Hamvas A, Cole FS, Nogee LM: Genetic disorders of surfactant proteins. Neonatology 91(4):311–317, 2007.
94. Nogee LM: Genetics of pediatric interstitial lung disease. Curr Opin Pediatr 18:287–292, 2006.
95. Nogee LM, et al: A mutation in the surfactant protein C gene associated with familial interstitial lung disease. N Engl J Med 344:573–579, 2001.
96. Hartl D, Griese M: Interstitial lung disease in children—Genetic background and associated phenotypes. Respir Res 6:32, 2005.
97. Thomas AQ, et al: Heterozygosity for a surfactant protein C gene mutation associated with usual interstitial pneumonitis and cellular nonspecific interstitial pneumonitis in one kindred. Am J Respir Crit Care Med 165:1322–1328, 2002.
97a. Guillot L, Epaud R, Thouvenin G, et al: New surfactant protein C gene mutations associated with diffuse lung disease. J Med Genet 46:490–494, 2009.
98. Petty TL, Ashbaugh DG: The adult respiratory distress syndrome: Clinical features factors influencing prognosis and principles of management. Chest 60:233–239, 1971.
99. Gunther A, et al: Surfactant alterations in severe pneumonia, acute respiratory distress syndrome, and cardiogenic lung edema. Am J Respir Crit Care Med 153:176–184, 1996.
100. Markart P, et al: Patients with ARDS show improvement but not normalisation of alveolar surface activity with surfactant treatment: putative role of neutral lipids. Thorax 62:588–594, 2007.
101. Savani RC, et al: Respiratory distress after intratracheal bleomycin: Selective deficiency of surfactant proteins B and C. Am J Physiol Lung Cell Mol Physiol 281:L685–L696, 2001.
102. Bernardino de la Serna J, et al: Cholesterol rules: Direct observation of the coexistence of two fluid phases in native pulmonary surfactant membranes at physiological temperatures. J Biol Chem 279:40715–40722, 2004.
103. Veldhuizen RA, et al: Alveolar surfactant aggregate conversion in ventilated normal and injured rabbits. Am J Physiol 270:L152–L158, 1996.
104. Amato MBP, et al: Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. N Engl J Med 339:347–354, 1998.
105. Eisner MD, et al: Efficacy of low tidal volume ventilation in patients with different clinical risk factors for acute lung injury and the acute respiratory distress syndrome. Am J Respir Crit Care Med 164:231–236, 2001.
106. Luchetti M, et al: Multicenter, randomized, controlled study of porcine surfactant in severe respiratory syncytial virus-induced respiratory failure. Pediatr Crit Care Med 3:261–268, 2002.
107. McCormack FX, et al: Idiopathic pulmonary fibrosis. Abnormalities in the bronchoalveolar lavage content of surfactant protein A. Am Rev Respir Dis 144:160–166, 1991.
108. Honda Y, et al: Pulmonary surfactant protein D in sera and bronchoalveolar lavage fluids. Am J Respir Crit Care Med 152:1860–1866, 1995.
109. McCormack FX, et al: Surfactant protein A predicts survival in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 152: 751–759, 1995.
110. Günther A, et al: Surfactant abnormalities in idiopathic pulmonary fibrosis, hypersensitivity pneumonitis and sarcoidosis. Eur Respir J 14:565–573, 1999.
111. Greene KE, et al: Serum SP-A and SP-D levels are elevated in patients with IPF. Am J Respir Crit Care Med 155:A216, 1997.
112. Kuroki Y, et al: Surfactant proteins A and D: disease markers. Biochim Biophys Acta 1408:334–345, 1998.
112a. Kinder BW, Brown KK, McCormack FX, et al: Serum surfactant protein-A is a strong predictor of early mortality in idiopathic pulmonary fibrosis. Chest 135:1557–1563, 2009.

113. Wang Y, et al: Genetic defects in surfactant protein A2 are associated with pulmonary fibrosis and lung cancer. Am J Hum Genet 84:52–59, 2009.
114. Enhorning G, Duffy LC, Welliver RC: Pulmonary surfactant maintains potency of conducting airways in the rat. Am J Respir Crit Care Med 151:534–556, 1995.
115. Hohlfeld J, Fabel H, Hamm H: The role of pulmonary surfactant in obstructive airway disease. Eur Respir J 10:482–491, 1997.
116. Lin M, et al: Pulmonary surfactant given prophylactically alleviates an asthma attack in guinea pigs. Clin Exp Allergy 26:270–275, 1996.
117. Babu KS, et al:, Inhaled synthetic surfactant abolishes the early allergen-induced response in asthma. Eur Respir J 21:1046–1049, 2003.
118. Haczku A, et al: *Aspergillus fumigatus*-induced allergic airway inflammation alters surfactant homeostasis and lung function in BALB/c mice. Am J Respir Cell Mol Biol 25:45–50, 2001.
119. Takeda K, et al: Surfactant protein D regulates airway function and allergic inflammation through modulation of macrophage function. Am J Respir Crit Care Med 168:783–789, 2003.
120. Strong P, et al: A recombinant fragment of human SP-D reduces allergic responses in mice sensitized to house dust mite allergens. Clin Exp Immunol 134:181–187, 2003.
121. Postle AD, et al: Deficient hydrophilic lung surfactant proteins A and D with normal surfactant phospholipid molecular species in cystic fibrosis. Am J Respir Cell Mol Biol 20(1):90–98, 1999.
121a. Lomas DA, Silverman EK, Edwards LD, et al: Serum surfactant protein D is steroid sensitive and associated with exacerbations of COPD. Eur Respir J 34:95–102, 2009.
121b. Huizar I, Kavuru M: Alveolar proteinosis syndrome: pathogenesis, diagnosis, and management. Curr Opin Pulm Med 15:491–498, 2009.
122. Shijubo N, et al: Pulmonary surfactant protein A in pleural effusions. Cancer 69:2905–2909, 1992.
123. Betz C, et al: Surfactant protein gene expression in metastatic and micrometastatic pulmonary adenocarcinomas and other non-small cell lung carcinomas: Detection by reverse transcriptase-polymerase chain reaction. Cancer Res 55:4283–4286, 1995.
124. Zhang F, et al: Serum levels of surfactant protein D are increased in mice with lung tumors. Cancer Res 63:5889–5894, 2003.
125. Lewis JF, Veldhuizen R: The role of exogenous surfactant in the treatment of acute lung injury. Annu Rev Physiol 65:613–642, 2003.
126. Anzueto A, et al: Aerosolized surfactant in adults with sepsis-induced acute respiratory distress syndrome. Exosurf Acute Respiratory Distress Syndrome Sepsis Study Group. N Engl J Med 334:1417–1421, 1996.
127. Gregory TJ, et al: Bovine surfactant therapy for patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 155:1309–1315, 1997.
128. Spragg RG, et al: Treatment of acute respiratory distress syndrome with recombinant surfactant protein C surfactant. Am J Respir Crit Care Med 167:1562–1566, 2003.
129. Spragg RG, et al: Effect of recombinant surfactant protein C-based surfactant on the acute respiratory distress syndrome. N Engl J Med 351:884–892, 2004.
130. Willson DF, et al: Effect of exogenous surfactant (calfactant) in pediatric acute lung injury: A randomized controlled trial. JAMA 293:470–476, 2005.
131. Blanco O, Perez-Gil J: Biochemical and pharmacological differences between preparations of exogenous natural surfactant used to treat respiratory distress syndrome: Role of the different components in an efficient pulmonary surfactant. Eur J Pharmacol 568:1–15, 2007.
132. Walther FJ, et al: Hydrophobic surfactant proteins and their analogues. Neonatology 91:303–310, 2007.
133. Almlen A, et al: Surfactant proteins B and C are both necessary for alveolar stability at end expiration in premature rabbits with respiratory distress syndrome. J Appl Physiol 104:1101–1108, 2008.
134. Seurynck-Servoss SL, et al: Lipid composition greatly affects the in vitro surface activity of lung surfactant protein mimics. Colloids Surf B Biointerfaces 57:37–55, 2007.
135. Wang Z, et al: Activity and inhibition resistance of a phospholipase-resistant synthetic surfactant in rat lungs. Am J Respir Cell Mol Biol 37:387–394, 2007.
136. Walmrath D, et al: Bronchoscopic surfactant administration in patients with severe adult respiratory distress syndrome and sepsis. Am J Respir Crit Care Med 154:57–62, 1996.
137. Veldhuizen RA, Yao LJ, Lewis JF: An examination of the different variables affecting surfactant aggregate conversion in vitro. Exp Lung Res 25:127–141, 1999.
138. Schlosser RL, et al: Comparison of effects of perflubron and surfactant lung lavage on pulmonary gas exchange in a piglet model of meconium aspiration. Biol Neonate 81:126–131, 2002.
139. Kerr CL, et al: High-frequency oscillation and exogenous surfactant administration in lung-injured adult sheep. Crit Care Med 31:2520–2526, 2003.

CHAPTER 10

Alveolar and Distal Airway Epithelial Fluid Transport

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INTRODUCTION

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EVIDENCE FOR ACTIVE FLUID TRANSPORT IN THE INTACT LUNG

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INTRODUCTION

This chapter discusses how the distal lung epithelium regulates lung fluid balance by active ion transport mechanisms across both the alveolar and the distal airway epithelium. Both experimental models of pulmonary edema and clinical studies are considered to illustrate how active sodium and chloride ion transport regulate the resolution of alveolar edema. Some of the material in this chapter has been included in recent reviews.[1,2]

For many years, it was generally believed that differences in hydrostatic and protein osmotic pressures (Starling forces) accounted for the removal of excess fluid from the air spaces of the lung. This misconception persisted in part because some experiments that measured solute flux across the epithelial and endothelial barriers of the lung were done at room temperature[3] and the studies were done in dogs, a species that turned out to have a very low rate of active sodium and fluid transport.[4] Although the removal of interstitial pulmonary edema by lung lymphatics and the lung microcirculation was known for a long time,[5] there was no information on how pulmonary edema was removed from the distal air spaces of the mature lung. New insight on active transport came from clearance of alveolar fluid at the time of birth and the development of culture systems to study pulmonary epithelial cells.

LUNG EPITHELIAL FLUID ABSORPTION

With few exceptions, the general model for transepithelial fluid movement is that active salt transport drives osmotic water transport. This paradigm is also correct for fluid clearance from the distal air spaces of the lung.[6,7] The results of several in vivo studies demonstrated that changes in hydrostatic or protein osmotic pressures cannot account for the removal of excess fluid from the distal air spaces. Furthermore, pharmacologic inhibitors of sodium transport can reduce the rate of fluid clearance in the lungs of several different species, including the human lung.[8] In addition, there is good evidence that isolated epithelial cells from the distal air spaces of the lung actively transport sodium and other ions, resulting in osmotic water absorption of fluid from the distal air spaces of the lung.

The large surface area of the alveoli favors the hypothesis that most fluid reabsorption occurs at the alveolar level, although active fluid reabsorption may occur across all of the different segments of the pulmonary epithelium of the distal air spaces of the lung. The precise contribution of each anatomic segment in the distal air spaces to fluid reabsorption is not firmly established. The distal airway epithelium is composed of terminal respiratory and bronchiolar units containing polarized epithelial cells that have the capacity to transport sodium and

chloride, including ciliated cells and nonciliated cuboidal Clara cells. The alveoli themselves are composed of a thin alveolar epithelium (0.1–0.2 μm) that covers 99% of the air space surface area in the lung and contains thin, squamous type I cells and cuboidal type II cells.[9] The alveolar type I cell covers 95% of the alveolar surface. The close apposition between the alveolar epithelium and the vascular endothelium facilitates efficient exchange of gases but also forms a tight barrier to movement of liquid and proteins from the interstitial and vascular spaces, thus assisting in maintaining relatively dry alveoli.

Ion transporters and other membrane proteins are asymmetrically distributed on opposing cell surfaces, conferring vectorial transport properties to the epithelium. Physiologic studies of the barrier properties of tight junctions in the alveolar epithelium indicate that diffusion of water-soluble solutes between alveolar epithelial cells is much slower than through the intercellular junctions of the adjacent lung capillaries.[10] Removal of large quantities of soluble protein from the air spaces appears to occur primarily by restricted diffusion, although there is evidence for some endocytosis and transcytosis of albumin across alveolar epithelium.[11]

EVIDENCE FOR ACTIVE FLUID TRANSPORT IN THE INTACT LUNG

A substantial number of innovative experimental methods have been used to study fluid and protein transport from the distal air spaces of the intact lung, including isolated perfused lung preparations, in situ lung preparations, surface fluorescence methods, and intact lung preparations in living animals for short time periods (30–240 min) or for extended time periods (24–144 hr). The advantages and disadvantages of these preparations have been reviewed in some detail.[7]

The first in vivo evidence that active ion transport could account for the removal of alveolar edema fluid across the distal pulmonary epithelium of the mature lung was obtained in studies of anesthetized, ventilated sheep.[12] In those studies, the critical discovery was that isosmolar fluid clearance of salt and water occurred in the face of a rising concentration of protein in the air spaces of the lung, whether the instilled solution was autologous serum or an isosmolar protein solution. The initial protein concentration of the instilled protein solution was the same as that of the circulating plasma. After 4 hours, the concentration of the protein had risen from approximately 6.5 g/100 mL to 8.4 g/100 mL, while the plasma protein concentration was unchanged. In longer-term studies in unanesthetized, spontaneously breathing sheep, alveolar protein concentrations increased to very high levels. After 12 and 24 hours, the alveolar protein concentrations increased to 10.2 and 12.9 g/100mL, respectively.[13] The overall rise in protein concentration was equivalent to an increase in distal air space protein osmotic pressure from 25 to 65 cm H_2O. Because the epithelial barrier was intact and thus prevented protein leak or a rapid protein absorption occurs in the lung, the only way that the protein concentration could have risen was if water had been removed (i.e., absorbed).

Other studies in the intact lung have supported the hypothesis that removal of alveolar fluid requires active transport.[14] For example, elimination of ventilation to one lung did not change the rate of fluid clearance in sheep, thus ruling out changes in transpulmonary airway pressure as a major determinant of fluid clearance, at least in the uninjured lung.[15] Furthermore, if active ion transport was responsible for fluid clearance, then fluid clearance should be temperature-dependent. In an in situ rat lung preparation, fluid clearance was inhibited by low temperature.[16] Similar results were obtained in ex vivo human lung studies,[8] in which hypothermia inhibited sodium and fluid transport.

Additional evidence for active ion transport was obtained in intact animals with the use of amiloride, an inhibitor of sodium uptake by the apical membrane of alveolar epithelium and distal airway epithelium. Amiloride inhibited 40% to 70% of basal fluid clearance in sheep, rabbits, rats, guinea pigs, and mice and in the human lung.[1] Amiloride also inhibited sodium uptake in distal airway epithelium from sheep and pigs.[17] To explore further the role of active sodium transport, experiments were designed to inhibit Na^+,K^+-ATPase. It has been difficult to study the effect of ouabain in intact animals because of cardiac toxicity. However, in the isolated rat lung, ouabain inhibited greater than 90% of fluid clearance.[18] Following the development of an in situ sheep preparation for measuring fluid clearance in the absence of blood flow, it was reported that ouabain inhibited 90% of fluid clearance over a 4-hour period.[14] Other investigators also established the likely role of active fluid transport for removal of fluid from the fetal lung.[15]

ION TRANSPORT IN ALVEOLAR AND DISTAL AIRWAY EPITHELIAL CELLS

The success in obtaining nearly pure cultures of alveolar epithelial type II cells from rats made it possible to study the transport properties of these cells and relate the results to the findings in the intact lung studies. The initial studies showed that, when type II cells were cultured on a nonporous surface such as plastic, they would form a continuous confluent layer of polarized cells after 2 to 3 days.[19,20] Interestingly, after 3 to 5 days, small domes of fluid could be appreciated below which the substratum was detached by the formation of the domes. The domes were thought to result from active ion transport from the apical to the basal surface, with water following passively, because they were inhibited by the replacement of sodium by another action or by pharmacologic inhibitors of sodium transport, such as amiloride and ouabain. More detailed information on the nature of ion transport across alveolar type II cells was obtained by culturing these cells on porous supports and mounting them in Ussing chambers and measuring short-

circuit current (Isc) and ion flux under voltage clamp conditions.[1,19,21]

The coordinated role of apical and basolateral sodium transport has been studied in several in vitro studies. Sodium ions that enter the epithelial cells at the apical membrane are pumped out of the cells at the basolateral membrane by the Na^+,K^+-ATPase enzyme. Because of the continuous pumping, sodium chemical potential is lower inside the cell. The entry step is passive, and sodium flows down a chemical potential gradient through specialized pathways, where basolateral transport requires energy to move ions against the gradient. Because of the pump activity, potassium electrochemical potential is larger inside the cell, and potassium leaks through the basolateral membrane and is then recycled by the Na^+,K^+-ATPase. The pathways for sodium entry into alveolar type II cells are numerous. Amiloride blocked dome formation[19,20] and decreased Isc in the in vitro studies,[21] a finding that supported the critical importance of sodium uptake through an amiloride-sensitive pathway in the apical membrane of alveolar epithelial cells. As already discussed, the efficacy of amiloride as an inhibitor of fluid clearance in the intact lung was demonstrated in several in vivo studies, although the fraction of amiloride-sensitive transport was as low as 40% to 50% in some lung preparations, particularly the rat and the human lung. The amiloride-insensitive sodium influx may be represented in vivo in part by the Na^+-glucose cotransport. A detailed discussion of the pharmacologic, biophysical, and molecular bases for fluid clearance across the alveolar and distal airway epithelium is available in other reviews.[1,22]

The role of the alveolar type I cell in vectorial fluid transport in the lung is unknown, although several investigators have tried to assess the potential contribution of the alveolar type I cell to vectorial fluid transport. On the basis of studies in freshly isolated type I cells, it is known that these cells have a high osmotic permeability to water with expression of aquaporin-5 on the apical surface.[23] Recent studies of freshly isolated alveolar type I cells from rats demonstrated that these cells express the Na^+,K^+-ATPaseα_1- and α_2-subunit isoforms.[24,25] In the same study, there was evidence for Na^+,K^+-ATPase α_1-subunit expression on the basolateral surface of the alveolar epithelial type I cells in situ in the rat lung. In addition, there is evidence for expression of all the subunits of the epithelial Na^+ channel (ENaC) in freshly isolated alveolar type I cells as well as in situ in the rat lung.[26] Finally, there is some evidence that ^{22}Na uptake can be partially inhibited by amiloride in freshly isolated rat alveolar type I cells, although definitive studies of cultured, polarized type I cells have not yet been achieved. Recent data demonstrate that the alveolar epithelial type I cells express a multitude of sodium transporting proteins, ENaC, cyclic nucleotide–gated sodium channels (CNG), and the Na^+,K^+-ATPase.[27] In addition, the cells express chloride transporters, that is, the cystic fibrosis transmembrane regulator (CFTR), and thus have the ion transporters necessary to participate in vectorial ion transport and clearance of alveolar fluid.[27a]

The alveolar epithelium comprises 99% of the surface area of the lung, a finding that suggests that removal of edema fluid from the lung might primarily occur across the alveolar epithelium. However, it has been demonstrated that the distal airway epithelium also actively transports sodium, a process that depends on amiloride-inhibitable uptake of sodium on the apical surface and extrusion of sodium through a basolateral Na^+,K^+-ATPase.[1,17] Clara cells actively absorb and transport sodium from the apical to the basal surface.[28] In addition, there are new data on the possible role of CFTR in upregulating cyclic 3′,5′-adenosine monophosphate (cAMP) fluid clearance (see next section, "Regulation of Lung Epithelial Fluid Transport"). This information provides support for a possible role of distal airway epithelia in fluid clearance, because CFTR is expressed abundantly in distal airway epithelial cells as well as in alveolar epithelial cells. Thus, even though their surface area is limited, a contribution from distal airway epithelia to the overall fluid transport is probable, especially as cells from the distal airway epithelium primarily transport salt from the apical to the basolateral surface. Figure 10-1 provides a schematic diagram of our current understanding of the location of ion transporters in the distal airway and alveolar epithelium that are responsible for vectorial fluid transport or net distal air space fluid clearance.

There are also new data confirming the importance of ENaC for alveolar fluid clearance using RNA interference (RNAi) against the αENaC subunit.[29] In those studies, inhibition of αENaC expression by specific small interfering RNA (siRNA) against αENaC attenuated the amiloride-sensitivity of both normal and stimulated alveolar fluid clearance, thus demonstrating the importance of ENaC.

REGULATION OF LUNG EPITHELIAL FLUID TRANSPORT

This section considers how the rate of vectorial fluid transport across the distal pulmonary epithelium can be increased by catecholamine or cAMP-dependent mechanisms. The potential relevance of these mechanisms under pathologic conditions is evaluated in the section "Alveolar Fluid Transport under Pathologic Conditions," later in this chapter.

Studies in newborn animals indicated that endogenous release of catecholamines, particularly epinephrine, may stimulate reabsorption of fetal lung fluid from the air spaces of the lung.[14,30,31] In most adult mammalian species, stimulation of β_2-adrenergic receptors by either salmeterol, terbutaline, or epinephrine increases fluid clearance.[32–35] This stimulatory effect occurs rapidly after intravenous administration of epinephrine or instillation of terbutaline into the alveolar space, and is completely prevented by either a nonspecific β_2-receptor antagonist (propranolol) or, in rats, by a specific β_2-antagonist.

The increased fluid clearance by β_2-agonists can be prevented by amiloride or RNAi against αENaC, indicating that the stimulation is related to an increased

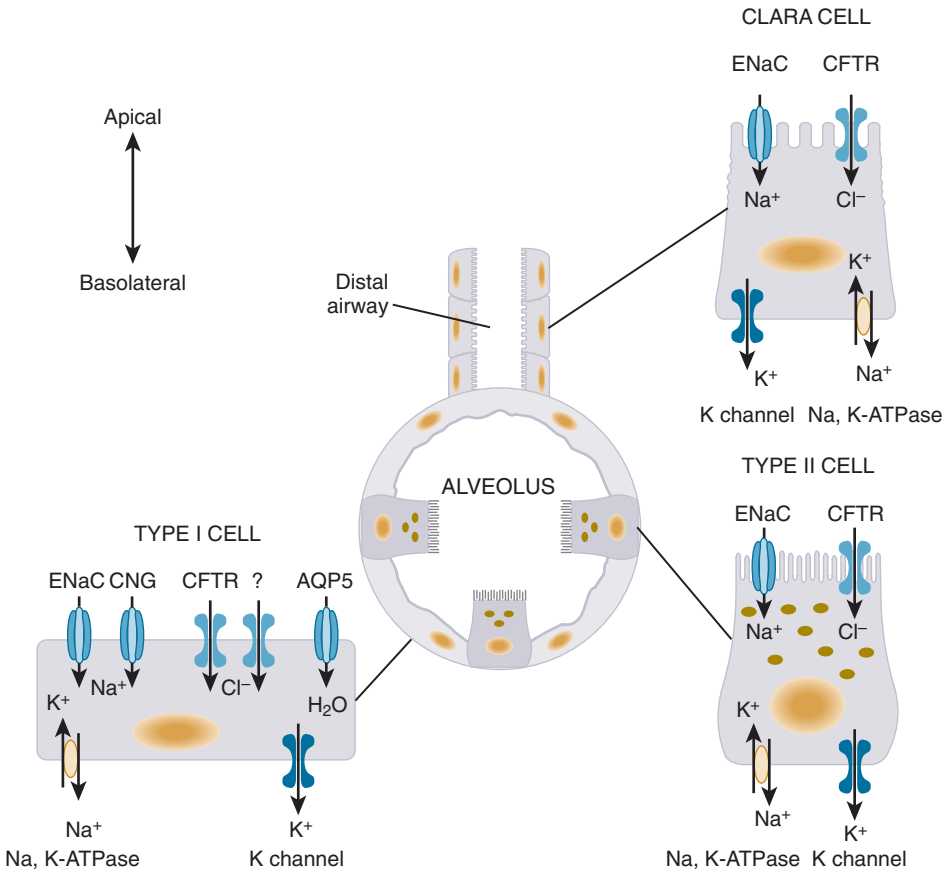

FIGURE 10-1 ■ A schematic diagram of the distal pulmonary epithelium that is relevant for salt and water transport. CFTR, cystic fibrosis transmembrane regulator; CNG, cyclic nucleotide–gated sodium channel; ENaC, epithelial Na^+ channel; AQP5, aquaporin-5. (Modified from Matthay MA, Folkesson HG, Clerici C: Lung epithelial fluid transport and the resolution of pulmonary edema. Physiol Rev 82:569–600, 2002.)

transepithelial sodium transport.[29,35] In anesthetized ventilated sheep, terbutaline-induced stimulation of fluid clearance was also associated with an increase in lung lymph flow, a finding that reflected increased removal of some of the alveolar fluid volume to the interstitium of the lung.[32] Although terbutaline increased pulmonary blood flow, this effect was not important, because control studies with nitroprusside, an agent that increased pulmonary blood flow, did not increase fluid clearance. Other studies have demonstrated that β-adrenergic agonists increased fluid clearance in rat, dog, guinea pig, and mouse as well as human lung.[1] The presence of β_1- and β_2-receptors on alveolar type II cells has been demonstrated in vivo by autoradiographic and immunochemistry techniques.[1]

It has been difficult to quantify the effect of catecholamines on the rate of alveolar fluid clearance and edema resolution in humans.[36] However, studies of fluid clearance in the isolated human lung have demonstrated that β-adrenergic agonist therapy increases fluid clearance, and the increased fluid clearance can be inhibited with propranolol or amiloride.[8] Subsequent studies suggested that long-acting lipid-soluble β-agonists may be more potent than hydrophilic β-agonists in the ex vivo human lung.[35] The magnitude of the stimulatory effect is similar to that observed in other species, with a β-agonist–dependent doubling of fluid clearance over baseline levels. These data are particularly important because aerosolized β-agonist treatment in some patients with pulmonary edema might accelerate the resolution of alveolar edema (see section "Alveolar Fluid Transport under Pathologic Conditions").

What has been learned about the basic mechanisms that mediate the catecholamine-dependent up-regulation of sodium transport in the lung? Based on in vitro studies, it was proposed that an increase in intracellular cAMP resulted in increased sodium transport across alveolar type II cells by an independent up-regulation of the apical sodium conductive pathways and the basolateral Na^+,K^+-ATPase. Proposed mechanisms for up-regulation of sodium transport proteins by cAMP include augmented sodium channel open probability,[1,37] increases in Na^+,K^+-ATPase α-subunit phosphorylation, and delivery of more ENaC channels to the apical membrane and more Na^+,K^+-ATPases to the basolateral cell membrane.[1]

Although most experimental studies have attributed a primary role for active sodium transport in the vectorial transport of salt and water from the apical to the basal surface of the alveolar epithelium of the lung, the potential role of chloride, especially in mediating the cAMP-

mediated up-regulation of fluid clearance across distal lung epithelium, has been the subject of a few recent studies. One older study of cultured alveolar epithelial cells concluded that vectorial transport of chloride across alveolar epithelium occurs by a paracellular route under basal conditions and perhaps by a transcellular route in the presence of cAMP stimulation.[38] Another study of cultured alveolar epithelial type II cells suggested that cAMP-mediated apical uptake of sodium might depend on an initial uptake of chloride.[39] A more recent study of cultured alveolar type II cells under apical surface–air interface conditions reported that β-adrenergic agonists produced acute activation of apical chloride channels with enhanced sodium absorption.[40] However, the results of these studies were considered to be inconclusive by some investigators,[41] partly because the data depend on cultured cells of an uncertain phenotype. Furthermore, studies of isolated alveolar epithelial type II cells do not address the possibility that vectorial fluid transport may be mediated by several different epithelial cells, including alveolar epithelial type I cells as well as distal airway epithelial cells.

In order to define the role of chloride transport in the active transport of salt and water across the distal pulmonary epithelium of the lung, one group has used in vivo lung studies to define the mechanisms and pathways that regulate chloride transport during the absorption of fluid from the distal air spaces of the lung.[42] This approach may be important because studies in several species, as already discussed, have indicated that distal airway epithelia are capable of ion transport and that both ENaC and CFTR are expressed in alveolar and distal airway epithelia.

Both inhibition and ion substitution studies demonstrated that chloride transport was necessary for basal fluid clearance. The potential role of CFTR under basal and cAMP-stimulated conditions was tested using intact lung studies in which CFTR was not functional because of failure in trafficking of CFTR to the cell membrane, the most common human mutation in cystic fibrosis (Δ1F508 mice). The results supported the hypothesis that CFTR was essential for cAMP-mediated up-regulation of isosmolar fluid clearance from the distal air spaces of the lung, because fluid clearance could not be increased in the Δ1F508 mice either with β-agonists or with forskolin, unlike in the wild-type control mice.[42] Additional studies using pharmacologic inhibition of CFTR in both mouse and human lungs with glibenclamide supported the same conclusion, namely that chloride uptake and CFTR-like transport seemed to be required for cAMP-stimulated fluid clearance from the distal air spaces of the lung.[42] Glibenclamide can also inhibit potassium channels so the inhibitory effects may not be specific for CFTR, but the Δ1F508 mouse studies have provided more direct evidence. Although the absence of CFTR in the upper airways results in enhanced sodium absorption, the data in these studies provide evidence that the absence of CFTR prevents cAMP–up-regulated fluid clearance from the distal air spaces of the lung, a finding that is similar to the results from studies on the importance of CFTR in mediating cAMP-stimulated sodium absorption in human sweat ducts.[43] Because CFTR is distributed throughout the distal pulmonary epithelium in distal airway epithelium as well as at the alveolar level in the human lung,[44] the data also suggest that the cAMP-mediated up-regulated reabsorption of pulmonary edema fluid may occur across distal airway epithelium as well as at the level of the alveolar epithelium. Finally, additional studies indicated that the lack of CFTR results in a greater accumulation of pulmonary edema in the presence of a hydrostatic stress, thus demonstrating the potential physiologic importance of CFTR in up-regulating fluid transport from the distal air spaces of the lung.[42] There is new evidence that functional CFTR chloride channels are present in adult rat alveolar epithelial type II cells based on whole cell patch-clamp experiments.[45] In addition, new data demonstrated expression of CFTR in both alveolar type I and II cells,[27,27a] as well as using a novel CFTR specific inhibitor, $CFTR_{Inh\text{-}172}$, in human lungs again demonstrated the importance of CFTR and chloride transport for cAMP-driven fluid absorption.[46]

In the last few years, several interesting catecholamine-independent mechanisms have been identified that can up-regulate fluid transport across the distal air spaces of the lung as well as in cultured alveolar type II cells. Hormonal factors such as glucocorticoids can up-regulate transport by transcriptional mechanisms, whereas thyroid hormone may work by a posttranslational mechanism. Some growth factors can work by either transcriptional or direct membrane effects, or by enhancing the number of alveolar type II cells. For example, keratinocyte growth factor (KGF) is a potent mitogen for alveolar type II cells. Administration of KGF (5 mg/kg) into the distal air spaces of the rat lung increases fluid clearance by 66% over baseline levels.[47] Other investigators have shown that KGF can enhance sodium and fluid transport in normal and injured rat lungs.[48,49] KGF may also work by enhancing the expression of sodium transport proteins.[50] There is also evidence that a proinflammatory cytokine, tumor necrosis factor-α (TNF-α), can rapidly up-regulate sodium uptake and fluid transport. The effect of TNF-α is amiloride inhibitable in both rats and isolated A549 human cells.[51,52] Finally, serine proteases can regulate the activity of ENaC and potentially increase fluid clearance across the distal airway epithelium. These catecholamine-independent mechanisms are explored in more detail in one review.[1]

MECHANISMS THAT CAN IMPAIR THE RESOLUTION OF ALVEOLAR EDEMA

Several mechanisms have been identified that can impair fluid transport from the distal air spaces of the lung. This section considers three conditions that have relevance to human disease: hypoxia, the use of anesthetics, and the presence of reactive oxygen and nitrogen species. The next section reviews mechanisms that impair fluid transport under specific pathologic conditions.

Hypoxia may occur during residence or recreation at high altitudes and under a variety of pathologic conditions associated with acute and chronic respiratory disease. Therefore, it is important to understand the effect of hypoxia on the ion and fluid transport capacity of the lung epithelium. The effect of hypoxia under in vivo conditions has been studied primarily in rats. In anesthetized rats, as well as in isolated perfused lungs, hypoxia decreased alveolar liquid clearance by inhibition of the amiloride-sensitive component.[53,54] The effect of hypoxia could not be explained by transcriptional effects on ENaC or Na^+,K^+-ATPase. The results suggested a post-translational mechanism such as a direct change of sodium transporter protein activity or transport to the plasma membrane. This latter hypothesis was supported by the normalization of fluid clearance by a cAMP agonist (terbutaline), which appears to increase the trafficking of sodium transporter proteins from the cytoplasm to the membrane.[55,56] Direct evidence for this mechanism in hypoxic alveolar epithelial type II cells was demonstrated for ENaC[57] as well as for an inhibitory effect of hypoxia on Na^+,K^+-ATPase activity in isolated A549 cells.[58]

In alveolar epithelial cells, the halogenated anesthetics affect sodium and fluid transport at the physiologic level as well as on a cellular level. In the rat, halothane and isoflurane decrease fluid clearance by inhibition of the amiloride-sensitive component. This effect was rapidly reversible after cessation of halothane exposure.[59] In vitro, exposure to a low concentration of halothane (1%) for a short time (30 min) induced a reversible decrease in Na^+,K^+-ATPase activity and amiloride-sensitive ^{22}Na influx in rat alveolar type II cells.[60] The mechanisms whereby halothane induced a decrease in sodium transport protein activity have not been yet elucidated, but they are not related in vitro to a decrease in intracellular adenosine triphosphate content or to a change in cytosolic free calcium. Taken together, these observations suggest that halogenated anesthetics may interfere with the clearance of alveolar edema.

Lidocaine is widely used in patients with acute cardiac disorders and has also been recently implicated as a possible cause of pulmonary edema following liposuction. In experimental studies in rats, either intravenous or intra-alveolar lidocaine reduced fluid clearance in rats by 50%.[61] Because lidocaine did not inhibit ENaC when expressed in oocytes, it seems that the inhibitory effect on vectorial fluid transport was primarily on the basal surface of alveolar epithelial cells, either through an effect on the activity of Na^+,K^+-ATPase or through an indirect effect via blockade of potassium channels, a well-known property of lidocaine. The effect of lidocaine was also completely reversible with β_2-agonist therapy.[61]

Under several pathologic conditions, in response to proinflammatory cytokines, activated neutrophils and macrophages can localize in the lung and migrate into the air spaces of the lung, and release reactive oxygen species by the membrane-bound enzyme complex nicotinamide adenine dinucleotide phosphate oxidase and nitric oxide (NO) via the calcium-insensitive inducible form of NO synthase. NO decreased Isc across cultured rat type II cells without affecting transepithelial resistance. NO also inhibited 60% of amiloride-sensitive Isc across type II cell monolayers following permeabilization of the basolateral membrane with amphotericin B.[62] NO reacted with superoxide ($\cdot O_2$) to form peroxynitrite ($ONOO^-$), a potent oxidant and nitrating species that directly oxidizes a wide spectrum of biologic molecules, such as DNA constituents, lipids, and proteins.[22] Boluses of peroxynitrite (0.5–1 mM) delivered into suspensions of freshly isolated type II cells from rabbits decreased amiloride-inhibitable sodium uptake to 68% and 56% of control values, respectively, without affecting cell viability. Some investigators reported that products of macrophages, including NO, can down-regulate sodium transport in fetal distal lung epithelium stimulated with endotoxin.[63] The data indicate that oxidation of critical amino acids residues in ENaC protein is probably responsible for this effect. This evidence matches well with other studies that have shown that protein nitration and oxidation by reactive oxygen and nitrogen species have been associated with diminished function of a variety of important proteins present in the alveolar space, including surfactant protein A.[64]

There is also new evidence that transforming growth factor-β_1 decreases expression of ENaC and alveolar epithelial sodium and fluid transport by an ERK 1/2-dependent mechanism in both primary rat and human alveolar type II cells.[65]

ALVEOLAR FLUID TRANSPORT UNDER PATHOLOGIC CONDITIONS

Fluid clearance from the distal air spaces of the lung has been measured in mechanically ventilated patients with acute respiratory failure from pulmonary edema as well as in several animal models designed to simulate clinically relevant pathologic conditions.

Studies of fluid clearance have been done in intubated, ventilated patients by measuring the concentration of total protein in sequential samples of undiluted pulmonary edema fluid aspirated from the distal air spaces of the lung with a standard suction catheter passed through the endotracheal tube into a wedged position in the distal airways of the lung.[36,66,67] This method for measuring fluid clearance in patients was adapted from the method for aspirating fluid from the distal air spaces of the lung in experimental studies in small and large animals.[7,32] The clinical procedure has been validated in patients by demonstrating that there is a relationship between fluid clearance and the improvement in oxygenation and the chest radiograph.[36,67]

In patients with severe hydrostatic pulmonary edema, there was net fluid clearance in the majority during the first 4 hours after endotracheal intubation and the onset of positive-pressure ventilation.[66] The rate of fluid clearance was 14%/hr in 38% of the patients. Overall, 75% of the patients had intact fluid clearance. There was no significant correlation between the levels of fluid clearance and endogenous plasma levels of epinephrine,

although twice as many of the patients with intact fluid clearance received aerosolized β-adrenergic therapy as did those with impaired fluid clearance; this difference did not reach statistical significance, perhaps because the total number of studied patients was modest. In a recent study of congestive heart failure in rats, it was demonstrated that β-adrenergic stimulation increased alveolar fluid clearance and that type II cell hyperplasia was likely responsible for the stimulation.[66a]

The majority of patients with increased permeability edema and acute lung injury have impaired alveolar epithelial fluid transport, a finding that is associated with more prolonged respiratory failure and a higher mortality (Fig. 10-2). In contrast, a minority of patients can remove alveolar edema fluid rapidly, and these patients have a higher survival rate.[36,67] These results indicate that a functional, intact distal lung epithelium is associated with a better prognosis in patients with acute lung injury, thus supporting the hypothesis that the degree of injury to the distal lung epithelium is an important determinant of the outcome in patients with increased permeability pulmonary edema from acute lung injury.

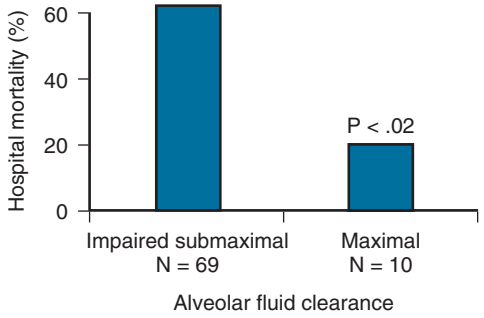

FIGURE 10-2 ■ Hospital mortality is increased in patients with acute lung injury or the acute respiratory distress syndrome with impaired fluid clearance. Impaired fluid clearance (<14%/hr) was compared with those with maximal fluid clearance (<14%/hr). The columns represent percent hospital mortality in each group. Hospital mortality of patients with maximal fluid clearance was significantly less ($P < .02$). N, number of patients. (Data from Ware LB, Matthay MA: Alveolar fluid clearance is impaired in the majority of patients with acute lung injury and the acute respiratory distress syndrome. Am J Respir Crit Care Med 163:1376–1383, 2001.)

What are the mechanisms that may impair fluid clearance from the air spaces of the lung in patients with acute lung injury? As already explained, alveolar hypoxia can depress alveolar epithelial fluid transport. Also, viral or bacterial lung infection can depress alveolar fluid transport, either by interfering with normal ion transport or by inducing apoptosis or necrosis of the distal lung epithelium. There are also some clinical data indicating that a decrease in fluid clearance may be associated with higher levels of nitrate and nitrite in pulmonary edema fluid, a finding that supports the hypothesis that nitration and oxidation of proteins essential to epithelial fluid transport may occur in some patients with lung injury, further depressing their ability to remove alveolar edema fluid.[64] Recent data suggest that elevated levels of the receptor for advanced glycation end-products (RAGE) may be a marker for alveolar type I cell injury and predict a reduced rate of clearing pulmonary edema fluid.[67a]

FUTURE DIRECTIONS

Recent progress demonstrates that it is feasible to quantify the rate of edema reabsorption from the distal air spaces of the lung in ventilated, critically ill patients with acute pulmonary edema. In conjunction with progress in experimental studies of lung fluid balance under clinically relevant pathologic conditions, further studies should be done to test the potential role of catecholamine-dependent and -independent therapies that might enhance the resolution of clinical pulmonary edema. Recent experimental data in a rat model of acute lung injury indicates that β_2-adrenergic agonist therapy can decrease lung endothelial permeability, increase alveolar fluid clearance, and decrease pulmonary edema when given after lung injury had developed.[68] The feasibility of delivering of therapeutic concentrations of aerosolized β-adrenergic agonist therapy to the distal air spaces of ventilated patients has been demonstrated.[69] Therefore, clinical trials are being conducted to test the potential value of this therapy for enhancing the resolution of pulmonary edema and improving clinical outcomes.[70]

KEY POINTS

- The distal conducting airways and alveolar surface are lined with epithelial cells that provide a tight barrier to protect the distal airspaces for gas exchange.
- The primary mechanism for reabsorption of excess alveolar fluid is active vectorial sodium and chloride transport.
- The best understood transporters are ENaC and CFTR.
- The resolution of alveolar edema is driven by active ion transport and can be up-regulated by cAMP stimulation.
- Alveolar fluid transport is impaired in patients with acute lung injury.

References

1. Matthay MA, Folkesson HG, Clerici C: Lung epithelial fluid transport and the resolution of pulmonary edema. Physiol Rev 82:569–600, 2002.
2. Folkesson HG, Matthay MA: Alveolar epithelial ion and fluid transport—Recent progress. Am J Respir Cell Mol Biol 35:10–19, 2006.
3. Taylor AE, Guyton AC, Bishop VS: Permeability of the alveolar epithelium to solutes. Circ Res 16:353–362, 1965.
4. Berthiaume Y, Broaddus VC, Gropper MA, et al: Alveolar liquid and protein clearance from normal dog lungs. J Appl Physiol 65:585–593, 1988.
5. Staub NC: Pulmonary edema. Physiol Rev 54:678–811, 1974.
6. Basset G, Crone C, Saumon G: Fluid absorption by rat lung in situ: Pathways for sodium entry in the luminal membrane of alveolar epithelium. J Physiol (Lond) 384:325–345, 1987.
7. Matthay MA, Folkesson HG, Verkman AS: Salt and water transport across alveolar and distal airway epithelium in the adult lung. Am J Physiol Lung Cell Mol Physiol 270:L487–L503, 1996.
8. Sakuma T, Okaniwa G, Nakada T, et al: Alveolar fluid clearance in the resected human lung. Am J Respir Crit Care Med 150:305–310, 1994.
9. Weibel ER: Lung morphometry and models in respiratory physiology. *In* Chang HK, Paiva M (eds): Respiratory Physiology: An Analytical Approach. New York: Marcel Dekker, 1989, pp 1–56.
10. Schneeberger-Keeley EE, Karnovsky MJ: The ultrastructural basis of alveolar-capillary membrane permeability to peroxidase used as a tracer. J Cell Biol 37:781–793, 1968.
11. Hastings RH, Folkesson HG, Matthay MA: Mechanisms of alveolar protein clearance in the intact lung. Am J Physiol Lung Cell Mol Physiol 286:L679–L689, 2004.
12. Matthay MA, Landolt CC, Staub NC: Differential liquid and protein clearance from the alveoli of anesthetized sheep. J Appl Physiol 53:96–104, 1982.
13. Matthay MA, Berthiaume Y, Staub NC: Long-term clearance of liquid and protein from the lungs of unanesthetized sheep. J Appl Physiol 59:928–934, 1985.
14. Walters DV, Olver RE: The role of catecholamines in lung liquid absorption at birth. Pediatr Res 12:239–242, 1978.
15. Sakuma T, Pittet JF, Jayr C, Matthay MA: Alveolar liquid and protein clearance in the absence of blood flow or ventilation in sheep. J Appl Physiol 74:176–185, 1993.
16. Rutschman DH, Olivera W, Sznajder JI: Active transport and passive liquid movement in isolated perfused rat lungs. J Appl Physiol 75:1574–1580, 1993.
17. Ballard ST, Schepens SM, Falcone JC, et al: Regional bioelectric properties of porcine airway epithelium. J Appl Physiol 73:2021–2027, 1992.
18. Olivera W, Ridge K, Wood LD, Sznajder JI: Active sodium transport and alveolar epithelial Na-K-ATPase increase during subacute hyperoxia in rats. Am J Physiol Lung Cell Mol Physiol 266:L577–L584, 1994.
19. Mason RJ, Williams MC, Widdicombe JH, et al: Transepithelial transport by pulmonary alveolar type II cells in primary culture. Proc Natl Acad Sci U S A 79:6033–6037, 1982.
20. Goodman BE, Crandall ED: Dome formation in primary cultured monolayers of alveolar epithelial cells. Am J Physiol Cell Physiol 243:C96–C100, 1982.
21. Cheek JM, Kim KJ, Crandall ED: Tight monolayers of rat alveolar epithelial cells: Bioelectric properties and active sodium transport. Am J Physiol Cell Physiol 256:C688–C693, 1989.
22. Matalon S, O'Brodovich H: Sodium channels in alveolar epithelial cells: Molecular characterization, biophysical properties, and physiological significance. Annu Rev Physiol 61:627–661, 1999.
23. Dobbs LG, Gonzalez R, Matthay MA, et al: Highly water permeable type I alveolar epithelial cells confer high water permeability between the airspace and vasculature in rat lung. Proc Natl Acad Sci U S A 95:2991–2996, 1998.
24. Ridge KM, Rutschman DH, Factor P, et al: Differential expression of Na-K-ATPase isoforms in rat alveolar epithelial cells. Am J Physiol Lung Cell Mol Physiol 273:L246–L255, 1997.
25. Borok Z, Liebler JM, Lubman RL, et al: Sodium transport proteins are expressed by rat alveolar epithelial type I cells. Am J Physiol Lung Cell Mol Physiol 282:L599–L608, 2002.
26. Johnson MD, Widdicombe JH, Allen L, et al: Alveolar epithelial type I cells contain transport proteins and transport sodium, supporting an active role for type I cells in regulation of lung liquid homeostasis. Proc Natl Acad Sci U S A 99:1966–1971, 2002.
27. Johnson MD, Bao HF, Helms MN, et al: Functional ion channels in pulmonary alveolar type I cells support a role for type I cells in lung ion transport. Proc Natl Acad Sci U S A 103:4964–4969, 2006.

27a. Johnson M, Allen L, Dobbs L: Characterizatics of Cl^- uptake in rat alveolar type I cells. Am J Physiol Lung Cell Mol Physiol 297:L816–L827, 2009.

28. van Scott MR, Davis CW, Boucher RC: Na^+ and Cl^- transport across rabbit nonciliated bronchiolar epithelial (Clara) cells. Am J Physiol Cell Physiol 256:C893–C901, 1989.
29. Li T, Folkesson HG: RNA interference for α-ENaC inhibits rat lung fluid absorption in vivo. Am J Physiol Lung Cell Mol Physiol 290: L649–L660, 2006.
30. Brown MJ, Olver RE, Ramsden CA, et al: Effects of adrenaline and of spontaneous labour on the secretion and absorption of lung liquid in the fetal lamb. J Physiol (Lond) 344:137–152, 1983.
31. Finley N, Norlin A, Baines DL, Folkesson HG: Alveolar epithelial fluid clearance is mediated by endogenous catecholamines at birth in guinea pigs. J Clin Invest 101:972–981, 1998.
32. Berthiaume Y, Staub NC, Matthay MA: Beta-adrenergic agonists increase lung liquid clearance in anesthetized sheep. J Clin Invest 79:335–343, 1987.
33. Charron PD, Fawley JP, Maron MB: Effect of epinephrine on alveolar liquid clearance in the rat. J Appl Physiol 87:611–618, 1999.
34. Crandall ED, Heming TH, Palombo RL, Goodman BE: Effect of terbutaline on sodium transport in isolated perfused rat lung. J Appl Physiol 60:289–294, 1986.
35. Sakuma T, Folkesson HG, Suzuki S, et al: Beta-adrenergic agonist stimulated alveolar fluid clearance in ex vivo human and rat lungs. Am J Respir Crit Care Med 155:506–512, 1997.
36. Matthay MA, Wiener-Kronish JP: Intact epithelial barrier function is critical for the resolution of alveolar edema in humans. Am Rev Respir Dis 142:1250–1257, 1990.
37. Matalon S: Mechanisms and regulation of ion transport in adult mammalian alveolar type II pneumocytes. Am J Physiol Cell Physiol 261:C727–C738, 1991.
38. Kim KJ, Cheek JM, Crandall ED: Contribution of active Na^+ and Cl^- fluxes to net ion transport by alveolar epithelium. Respir Physiol 85:245–256, 1991.
39. Jiang X, Ingbar DH, O'Grady SM: Adrenergic stimulation of Na^+ transport across alveolar epithelial cells involves activation of apical Cl^- channels. Am J Physiol Cell Physiol 275:C1610–C1620, 1998.
40. Jiang X, Ingbar DH, O'Grady SM: Adrenergic regulation of ion transport across adult alveolar epithelial cells: Effects on Cl^- channel activation and transport function in cultures with an apical air interface. J Membr Biol 181:195–204, 2001.
41. Lazrak A, Nielsen VG, Matalon S: Mechanisms of increased Na^+ transport in ATII cells by cAMP: We agree to disagree and do more experiments. Am J Physiol Lung Cell Mol Physiol 278:L233–L238, 2000.
42. Fang X, Fukuda N, Barbry P, et al: Novel role for CFTR in fluid absorption from the distal airspaces of the lung. J Gen Physiol 119:199–207, 2002.
43. Reddy MM, Light MJ, Quinton PM: Activation of the epithelial Na^+ channel (ENaC) requires CFTR Cl^- channel function. Nature 402:301–304, 1999.
44. Engelhardt JF, Zepeda M, Cohn JA, et al: Expression of the cystic fibrosis gene in adult human lung. J Clin Invest 93:737–749, 1994.
45. Brochiero E, Dagenais A, Prive A, et al: Evidence of a functional CFTR Cl(–) channel in adult alveolar epithelial cells. Am J Physiol Lung Cell Mol Physiol 287:L382–L392, 2004.
46. Fang X, Song Y, Hirsch J, et al: Contribution of CFTR to apical-basolateral fluid transport in cultured human alveolar epithelial type II cells. Am J Physiol Lung Cell Mol Physiol 290:L242–L249, 2006.
47. Wang Y, Folkesson HG, Jayr C, et al: Alveolar epithelial fluid transport can be simultaneously upregulated by both KGF and β-agonist therapy. J Appl Physiol 87:1852–1860, 1999.

48. Guery BPH, Mason CM, Dobard EP, et al: Keratinocyte growth factor increases transalveolar sodium reabsorption in normal and injured rat lungs. Am J Respir Crit Care Med 155:1777–1784, 1997.
49. Guo J, Yi ES, Havill AM, et al: Intravenous keratinocyte growth factor protects against experimental pulmonary injury. Am J Physiol Lung Cell Mol Physiol 275:L800–L805, 1998.
50. Borok Z, Lubman RL, Danto SI, et al: Keratinocyte growth factor modulates alveolar epithelial cell phenotype *in vitro*: Expression of aquaporin 5. Am J Respir Cell Mol Biol 18:C554–C561, 1998.
51. Börjesson A, Norlin A, Wang X, et al: TNFα stimulates alveolar liquid clearance during intestinal ischemia-reperfusion in rats. Am J Physiol Lung Cell Mol Physiol 278:L3–L12, 2000.
52. Fukuda N, Jayr C, Lazrak A, et al: Mechanisms of TNF-α stimulation of amiloride-sensitive sodium transport across alveolar epithelium. Am J Physiol Lung Cell Mol Physiol 280:L1258–L1265, 2001.
53. Vivona M, Matthay MA, Chabaud M, et al: Hypoxia reduces alveolar epithelial sodium and fluid transport in rats: Reversal by beta adrenergic treatment. Am J Respir Cell Mol Biol 25:554–561, 2001.
54. Suzuki S, Noda M, Sugita M, et al: Impairment of transalveolar fluid transport and lung Na, K-ATPase function by hypoxia in rats. J Appl Physiol 87:892–968, 1999.
55. Kleyman TR, Ernst SA, Coupaye-Gerard B: Arginine vasopressin and forskolin regulate apical cell surface expression of epithelial Na^+ channels in A6 cells. Am J Physiol Renal Physiol 266:F506–F511, 1994.
56. Snyder PM: Liddle's syndrome mutations disrupt cAMP-mediated translocation of the epithelial Na^+ channel to the cell surface. J Clin Invest 105:45–53, 2000.
57. Planes C, Blot-Chabaud M, Matthay MA, et al: Hypoxia and beta 2-agonists regulate cell surface expression of the epithelial sodium channel in native alveolar epithelial cells. J Biol Chem 277:47318–47324, 2002.
58. Dada LA, Chandel NS, Ridge KM, et al: Hypoxia-induced endocytosis of Na, K-ATPase in alveolar epithelial cells is mediated by mitochondrial reactive oxygen species and PKC-zeta. J Clin Invest 111:1057–1064, 2003.
59. Rezaiguia-Delclaux S, Jayr C, Luo DF, et al: Halothane and isoflurane decrease alveolar epithelial fluid clearance in rats. Anesthesiology 88:751–760, 1998.
60. Molliex S, Crestani B, Dureuil B, et al: Effects of halothane on surfactant biosynthesis by rat alveolar type II cells in primary culture. Anesthesiology 81:668–676, 1994.
61. Laffon M, Jayr C, Barbry P, et al: Lidocaine induces a reversible decrease in alveolar epithelial fluid clearance in rats. Anesthesiology 96:392–399, 2002.
62. Guo Y, DuVall MD, Crow JP, Matalon S: Nitric oxide inhibits Na^+ absorption across cultured alveolar type II monolayers. Am J Physiol Lung Cell Mol Physiol 274:L369–L377, 1998.
63. Compeau CG, Rotstein OD, Tohda H, et al: Endotoxin-stimulated alveolar macrophages impair lung epithelial Na^+ transport by an L-Arg-dependent mechanism. Am J Physiol Cell Physiol 266:C1330–C1341, 1994.
64. Zhu S, Ware LB, Geiser T, et al: Increased levels of nitrate and surfactant protein A nitration in the pulmonary edema fluid of patients with acute lung injury. Am J Respir Crit Care Med 163:166–172, 2001.
65. Frank J, Roux J, Kawakatsu H, et al: Transforming growth factor-β1 decreases expression of the epithelial sodium channel αENaC and alveolar epithelial vectorial sodium and fluid transport via an ERK 1/2-dependent mechanism. J Biol Chem 278:43939–43950, 2003.
66. Verghese GM, Ware LB, Matthay BA, Matthay MA: Alveolar epithelial fluid transport and the resolution of clinically severe hydrostatic pulmonary edema. J Appl Physiol 87:1301–1312, 1999.
66a. Maron MB, Luther DJ, Pilati CF, et al: β-adrenoceptor stimulation of alveolar fluid clearance is increased in rats with heart failure. Am J Physiol Lung Cell Mol Physiol 297:L487–L495, 2009.
67. Ware LB, Matthay MA: Alveolar fluid clearance is impaired in the majority of patients with acute lung injury and the acute respiratory distress syndrome. Am J Respir Crit Care Med 163:1376–1383, 2001.
67a. Briot B, Frank JA, Uchida T, et al: Elevated levels of the receptor for advanced glycation end products, a marker of alveolar epithelial type I cell injury, predict impaired alveolar fluid clearance in isolated perfused human lungs. Chest 135:269–275, 2009.
68. McAuley DF, Frank JA, Fang X, Matthay MA: Clinically relevant concentrations of beta2-adrenergic agonists stimulate maximal cyclic adenosine monophosphate-dependent airspace fluid clearance and decrease pulmonary edema in experimental acid-induced lung injury. Crit Care Med 32:1470–1476, 2004.
69. Atabai K, Ware LB, Snider ME, et al: Aerosolized beta$_2$-adrenergic agonists achieve therapeutic levels in the pulmonary edema fluid of ventilated patients with acute respiratory failure. Intensive Care Med 28:705–711, 2002.
70. Mutlu GM, Sznajder JI: β2-Agonists for treatment of pulmonary edema: ready for clinical studies? Crit Care Med 32:1607–1608, 2004.

CHAPTER 11

AIRWAY EPITHELIAL MUCINS AND MUCOUS HYPERSECRETION

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INTRODUCTION

COMPONENTS OF MUCUS

CHARACTERISTICS OF NORMAL AIRWAY MUCINS IN HEALTHY INDIVIDUALS

MUCOUS HYPERSECRETORY DISEASES AND THEIR CLINICAL CONSEQUENCES

IMPORTANCE OF MUCOUS HYPERSECRETION IN CHRONIC INFLAMMATORY AIRWAY DISEASES

Cystic Fibrosis

Asthma

Chronic Bronchitis and Chronic Obstructive Pulmonary Disease

EPITHELIAL SIGNALING PATHWAYS RESPONSIBLE FOR MUCIN PRODUCTION IN AIRWAYS

Early Studies of Mucins

Epidermal Growth Factor Receptor Activation Stimulates Mucin Production in Airways

Metalloproteases Cleave Membrane-Bound Epidermal Growth Factor Receptor Ligands to Produce Mucins

Roles of Reactive Oxygen Species in Airway Epithelial Mucin Production

Toll-like Receptors

THERAPEUTIC IMPLICATIONS

INTRODUCTION

When animals migrated from sea to land, gills were exchanged for lungs, thus increasing the surface area for gas exchange, and the respiratory exchange organ (lungs) was relocated deep within the thorax. This new apparatus required a connection from the areas of gas exchange in the alveoli to the external environment, which was provided by the airways. The airway epithelium is exposed to a wide array of environmental invaders, such as microbes and other inhaled irritants. The epithelium developed an early system for responses to the "invaders" as a first line of defense. Normally, when inhaled microbes deposit on the epithelial surface, the epithelium responds via a signaling cascade to trap and clear the invaders. The secretion of a thin layer of mucus plays an important role in the protection of the host, and this is normally accomplished without symptoms or significant pathologic changes. However, in chronic inflammatory airway diseases, overexuberant pathologic responses occur, impairing rather than protecting the host.

Mucous hypersecretion in large conducting airways leads to cough and excessive sputum production. Mucous hypersecretion also occurs in small peripheral airways, which become plugged. However, this peripheral plugging produces few or no symptoms early. Furthermore, no effective therapy is yet available. Therefore, this chapter focuses on mucus, mucins, and the effects of their hypersecretion. It is hoped that wide recognition of the effects and mechanisms of mucin hypersecretion will lead to important therapeutic progress.

COMPONENTS OF MUCUS

Mucus secretion normally plays a protective role in the epithelium. Airway mucus is a complex mixture of proteins and liquids and includes a sol phase composed of water and electrolytes.[1,2] Mucus contains water (95%), most of which is bound in a viscoelastic gel containing mucins.[3,4] The gel-forming mucins in mucus are high-molecular-weight glycoproteins that are key components of mucous cells and are rich in carbohydrates.[5] Mucin oligosaccharides are joined by an initial α_0-glycoside linkage of *N*-acetylgalactosamine to the hydroxyl moieties of serine or threonine of the mucin protein backbone.[6] Mucins produced intracellularly are packed tightly within granules. During exocytosis (secretion), the cells

secrete their granule contents in a condensed form, and the secreted mucins undergo rapid hydration to form a gel with unusual viscoelastic properties that allow the gel to interact with cilia to affect mucociliary clearance and effective cough. Various mucins may have very different biophysical properties, and future studies are needed to characterize these properties and their potential pathophysiologic implications. Currently, approximately 19 mucin (MUC) genes have been cloned. They are divided into two groups: membrane-associated– and gel-forming–secreted mucins.[7,8] Of the secreted mucins, two are especially prominent in inflammatory airway diseases: MUC5AC in airway goblet cells,[9–12] and MUC5B in submucosal gland mucous cells.[10,11,13,14]

CHARACTERISTICS OF NORMAL AIRWAY MUCINS IN HEALTHY INDIVIDUALS

Gel-forming mucins are produced by mucous tubules in submucosal glands in the large conducting airways and in goblet cells located in the surface epithelium in both large and small airways. MUC5AC is the predominant mucin produced by the surface epithelium[15] and by airway epithelial cells in culture.[12,16] The submucosal glands are normally small.[17] In the normal surface epithelium, goblet cells are sparse[12,18,19] but present at all levels, decreasing in number peripherally, presumably reflecting less contact of peripheral airways with environmental particulates. Pathogen-free animals also have few goblet cells in the airway epithelium.

On the surface of the airways is a periciliary sol phase, above which the mucous gel floats. The contracting cilia propel the mucous blanket mouthward, along with trapped environmental particles that have deposited on the epithelial surface. In addition, in the large conducting airways, clearance is assisted by cough. Interestingly, the cough receptors are preferentially located at the bifurcation of the airways,[20] adjacent to the gland ducts that exit on the epithelial luminal surface. The colocalization of cough receptors at sites of gland secretion on the airway surface facilitates cough-induced clearance. Activation of the cough receptors has been shown to stimulate submucosal gland secretion via vagal efferent nervous cholinergic pathways; these nerves also innervate airway smooth muscle in the conducting airways, and blockade of their efferent cholinergic pathways is the basis of anticholinergic therapy in chronic obstructive airway disease. The gland secretion that accompanies cough assists in the entrapment of deposited particulates and in their clearance from the major conducting airways.

MUCOUS HYPERSECRETORY DISEASES AND THEIR CLINICAL CONSEQUENCES

A variety of chronic inflammatory airway diseases are associated with mucous hypersecretion, and the stimuli involved may vary. For example, allergic factors are involved in asthma (see Chapter 38), genetic abnormalities dominate cystic fibrosis (CF; see Chapter 41), and chronic obstructive pulmonary disease (COPD; see Chapter 39) is linked closely to the inhalation of toxic components of cigarette smoke. Regardless of the variety of etiologies, the similarities that exist in cellular responses (such as mucous hypersecretion) among these various disease states suggest that some common mechanisms are likely to exist that could be useful in therapy.

The clinical manifestations of mucous hypersecretion depend, at least in part, on the anatomic location of the hypersecretory process. Hypersecretion of mucins by submucosal glands in proximal airways is associated with excessive sputum production.[21] Cough (described in Chapter 29) ensues because of the colocalization of the cough receptors and the gland duct openings.

Because of the large cross-sectional area of the conducting airways, obstructive plugging of these airways is rare. In contrast, the peripheral airways do not contain glands nor do they contain cough receptors to produce symptoms. Conversely, mucous hypersecretion in peripheral airways is due to secretion from goblet cells on the epithelial surface. The small diameters of the airways increase their tendency to become obstructed in many ways: First, secretion of mucins results in mucin hydration, which increases the volume more than a thousandfold.[22] Because of their small diameters, peripheral airways are more likely to become obstructed by mucin degranulation than are larger airways. In addition, chronic inflammation is associated with an increase in the volume of the epithelium, which occupies a larger percentage of the airway lumen than in healthy airways, thus exaggerating the obstructive effects of mucous hypersecretion. Contraction of airway smooth muscle adds to the narrowing, further exaggerating the effects of mucous hypersecretion. This is shown schematically in Figure 11-1. Mucous plugging may be the result of local hypersecretion by the peripheral airways themselves. However, it is also possible that mucus is aspirated retrograde into the periphery. Retrograde contamination of peripheral airways by bacteria-containing mucus (e.g., in intubated patients in the intensive care unit) could play a role in perpetuating chronic bacterial infection.

In spite of the fact that chronic progressive mucous plugging is common in chronic inflammatory airway diseases such as COPD,[23] CF,[18] and acute fatal asthma,[24–28] the detection of peripheral mucous plugging is very difficult.

IMPORTANCE OF MUCOUS HYPERSECRETION IN CHRONIC INFLAMMATORY AIRWAY DISEASES

In healthy subjects, mucous secretion is involved in innate immune defense of the host (see Chapter 13). These host responses defend against inhaled “invaders” (e.g., microbes, other inhaled irritants) efficiently, usually without obvious interference with function. However, in various chronic inflammatory airway diseases, there is evidence of abnormal inflammatory responses, which are believed to be importantly involved in the

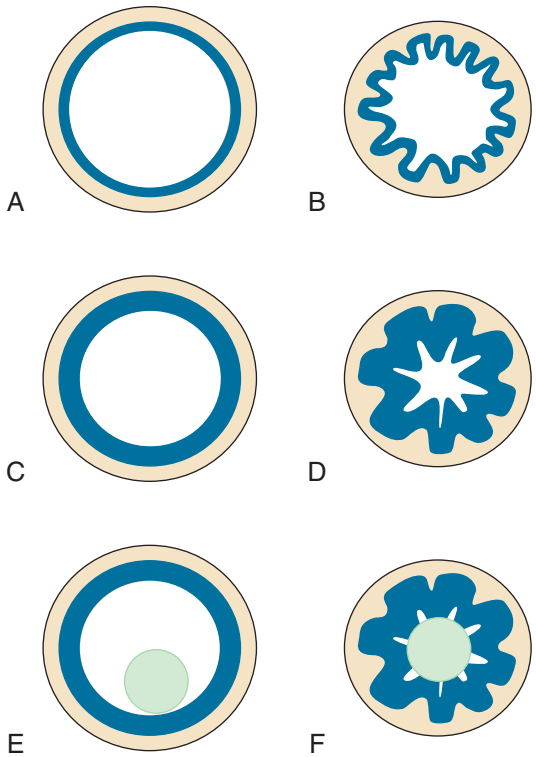

FIGURE 11-1 ■ Schematic representation of the potential impact of goblet cell hyperplasia and mucous plugging on small airway obstruction. In normal individuals, the surface epithelium covering small airways contains few goblet cells and is composed of a thin layer of epithelial cells. **A** and **B**, Normal, thin epithelium contributes little to luminal narrowing both when airway smooth muscle is relaxed (**A**) and when smooth muscle shortening occurs (**B**). **C** and **D**, In various airway inflammatory diseases (e.g., acute asthma, chronic obstructive pulmonary disease, and cystic fibrosis), epithelial cell hyperplasia is present in small airway epithelium, resulting in epithelial thickening. **C**, When airway smooth muscle is relaxed, thickened epithelium contributes little to airflow limitation. **D**, However, because the thickness of the airway wall (composed of epithelium, lamina propria, muscle, and adventitial compartments) is an important determinant of airflow limitation, when smooth muscle shortening occurs, hyperplastic epithelium is predicted to contribute to airflow obstruction. **E** and **F**, When hyperplastic goblet cells release mucins in the airway lumen, swelling of secreted mucins during hydration may result in mucous obstruction. **F**, The contribution of mucous secretions to airflow limitation is likely to be increased when smooth muscle shortening occurs. Thus, both goblet cell hyperplasia and mucous obstruction in small airways are predicted to contribute significantly to the airflow limitation that occurs in chronic inflammatory airway diseases. (Redrawn from Burgel PR, Montani D, Danel C, et al: A morphometric study of mucins and small airway plugging in cystic fibrosis. Thorax 62:153, 2007.)

pathophysiology of the diseases. Thus, whereas secretion of mucus normally plays a protective role in host defense, hypersecretion plays an important role in the pathophysiology of various chronic airway diseases. Below is a brief review of studies of mucous hypersecretion in CF, asthma, and chronic bronchitis/COPD. Other airway diseases can also cause mucous hypersecretion (e.g., bronchiectasis).

Cystic Fibrosis

CF, a life-shortening genetic disorder, is described in detail in Chapter 41. Mucous plugging has long been known to play a major role in the pathophysiology of the disease, but the extent and characteristics of plugging have long escaped analysis. It is of interest to understand why knowledge of peripheral airway disease is so limited: First, peripheral airways are too small to be visualized through a bronchoscope. Second, radiologic techniques have inadequate resolution to detect plugged airways. Biopsy material has been limited because of technical limitations. Finally, the peripheral airways are numerous (see Chapter 1), so obstruction of a large number of peripheral airways is required to cause clinically recognizable airway obstruction (see Chapter 24). Various investigators have reported that mucins contribute to the pathophysiology in CF.[10,29,30] A biopsy study of conducting airways in CF showed an increase in goblet cell size and an enlarged submucosal gland volume.[17] In a quantitative analysis of CF lungs removed at the time of lung transplantation, Burgel and coworkers[18] reported that in CF, most small airways contained extensive plugging, whereas control lungs contained only rare plugs (Fig. 11-2). Plugging was also present in small, noncartilaginous airways (Fig. 11-3). Pulmonary function studies in these CF patients prior to transplantation were indicative of severe airway obstruction, and the authors suggested that the extensive peripheral airway plugging contributed to the loss of lung function. In the airways with plugs, there was extensive goblet cell hyperplasia, with mucins streaming into the luminal plugs. These studies indicate that CF patients with late-stage disease and severe airway obstruction have extensive peripheral airway plugging, which contributes to the advanced obstruction present and the need for transplantation.

Although mucins play a role in the production of mucous plugs, other components (e.g., neutrophil products) including DNA and extravasated blood products (such as albumin) also contribute. It should be noted that the observation that mucin production is increased in CF and that mucins were seen streaming into lumens obstructed by plugs does not necessarily imply that CF epithelial cells have increased responsiveness to mucin production in CF, but only that in the area of plugs there are stimuli (e.g., *Pseudomonas* bacteria) that effectively stimulate production and secretion of mucins.

In CF, Burgel and coworkers[18] noted that the staining for mucins occupied approximately 20% of the plugged lumen volume, indicating that mucins contributed to the plugs but that other molecules were also importantly present. Neutrophils were also conspicuous in the plugs. Voynow and colleagues[31] reported that elastase, a product secreted by neutrophils, causes the degradation of mucin MUC5AC. Davies and associates[32] reported findings that suggested that one airway mucin (MUC5AC) is more vulnerable to proteolytic degradation than the other (MUC5B). The findings reported by Burgel and coworkers[18] confirmed this opinion. The prominent presence of neutrophils in plugged airways suggests the possibility that neutrophil-mediated effects could be

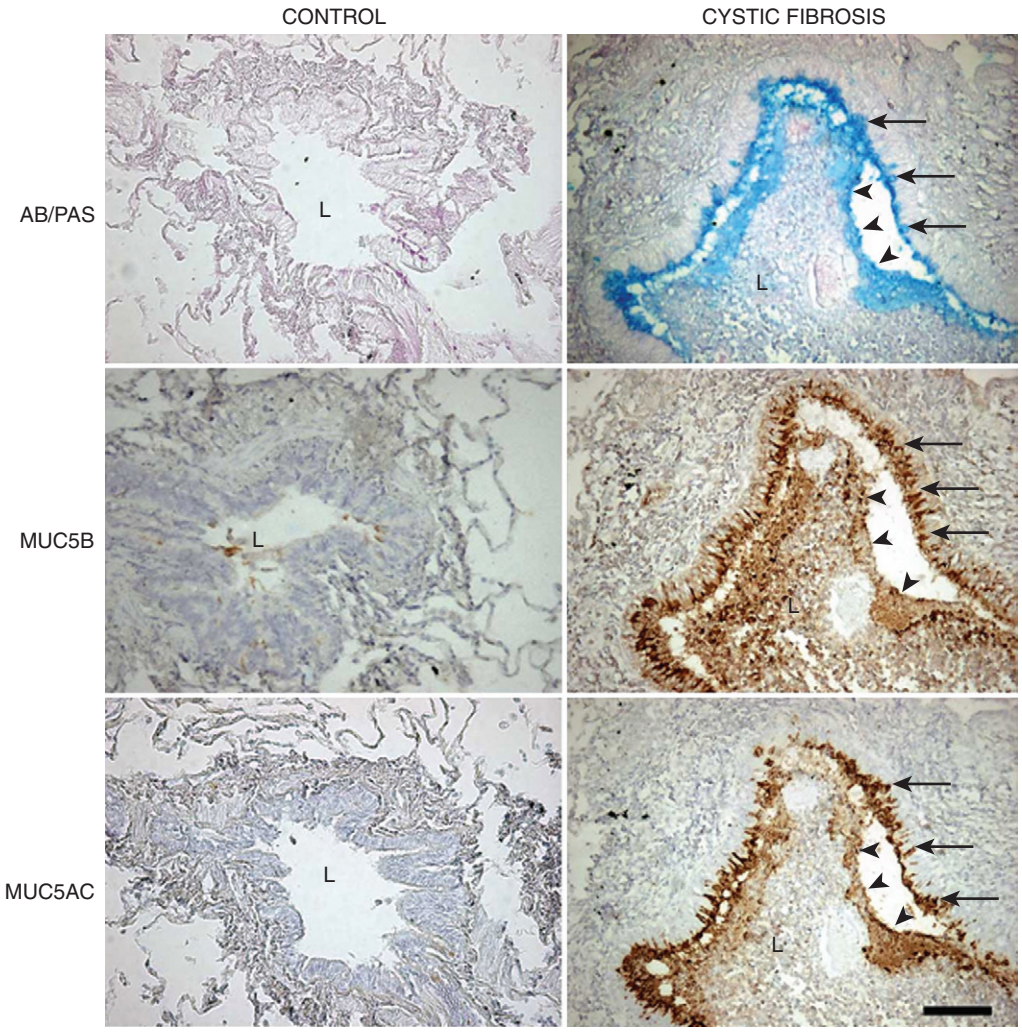

FIGURE 11-2 ■ Mucous glycoconjugates and mucins in airway lumens of controls and patients with cystic fibrosis. Representative photomicrographs. Sections containing small airways in a typical control subject (*left panels*) and in a patient with cystic fibrosis (*right panels*) were stained with Alcian blue/periodic acid–Schiff (AB/PAS) for mucous glycoconjugates, blue staining (*upper panels*) or with antibodies to mucin MUC5B (*brown staining; middle panels*) and MUC5AC (*brown staining, lower panels*). In the control subject, the airway lumen (L) is empty; no staining for AB/PAS, MUC5B, or MUC5AC is observed in the lumen or in the epithelium. In the patient with cystic fibrosis, the airway lumen is obstructed by a plug containing mucous glycoconjugates (AB/PAS), MUC5B, and MUC5AC only at the periphery of the plug (*arrowheads*), adjacent to the epithelium. Staining for mucins is absent in the center of the plug. Goblet cells in the epithelium are stained positively with AB/PAS and with MUC5AC and MUC5B antibodies (*arrows*). (Original magnification ×100; *bar* = 100 μm.) (From Burgel PR, Montani D, Danel C, et al: A morphometric study of mucins and small airway plugging in cystic fibrosis. Thorax 62:153, 2007.)

involved in proteolytic inactivation of secreted mucins. Many other molecules may also be components of mucous plugs. For example, albumin is a normal component of blood, but in states of inflammation with increased vascular permeability, albumin is reported to move from the vascular lumen to the airway lumen. Albumin is a plasma protein that can move across the endothelial surface via multiple mechanisms.[33] When albumin is present in renal tubular epithelial cells, it activates epidermal growth factor receptors (EGFRs) and causes the production of inflammatory mediators.[34] If albumin has similar actions in airways, perhaps in diseases with increased vascular permeability, albumin might play a role in activating EGFR and leading to mucous hypersecretion.

Asthma

In normal healthy subjects, airway mucins are sparse,[19] and only a thin layer of mucus exists on the airway luminal surface. Healthy subjects produce little sputum. However, in patients with asthma, a history of sputum overproduction is associated with an accelerated decline in maximal expiratory airflow.[35]

Sputum production is a frequent symptom of asthma and contributes to asthma morbidity. Turner-Warwick and Openshaw[36] reported that 77% of asthma patients had a history of sputum production, and 56% reported maximum sputum production at the peak of an asthma attack. Goblet cell numbers are increased even in mild asthma.[12] Mucous hypersecretion causes plugging,

especially in peripheral airways, which may not cause symptoms early. Widespread mucous hypersecretion was reported in fatal asthma by Cardell and Pearson in 1959[24] and was confirmed by other studies.[25–28] Thus, sputum secretion and cough, symptoms of hypersecretion in large airways, are common in asthma. Mortality in acute asthma is associated with mucous plugging, which is presumed to be a major cause of death. An example of mucous plugging in fatal asthma is shown in Figure 11-4.

In experimental models of allergic airway disease, mucous hypersecretion has been reported. For example, allergic sensitization by ovalbumin in rats increased mucin production in the airway epithelium.[37]

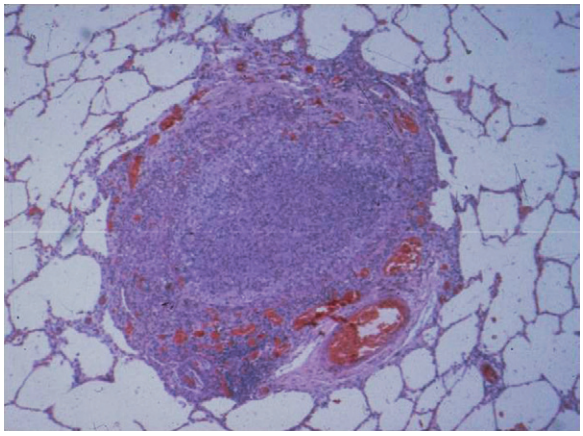

FIGURE 11-3 ■ Mucin plug in terminal bronchiole in a patient with cystic fibrosis. This section was stained with AB/PAS. The plugged bronchiole is surrounded by alveoli.

Chronic Bronchitis and Chronic Obstructive Pulmonary Disease

Mucous hypersecretion has often been considered to be an annoying but otherwise benign component of airway diseases associated with smoking. To understand the effects of mucin overproduction in chronic bronchitis and COPD, the anatomy of mucin-containing cells in airways is helpful. Submucosal glands are located in the large conducting airways but not in the peripheral, noncartilaginous airways. These glands are normally small and produce only small volumes of mucus. In tobacco-associated disease, the glands become enlarged and are capable of producing copious secretions. These secretions are cleared in the sputum, assisted by cough. If disease is limited to the large airways and airway obstruction is not prominent, symptoms of cough may disturb the patient but deterioration of lung function may not be conspicuous. Conversely, mucous hypersecretion in the peripheral airways (especially the noncartilaginous airways) is derived from goblet cells that form in the surface airway epithelium, where hypersecretion can cause airway obstruction. However, mucous secretions in the periphery are not detected early, so peripheral airways remain a relatively silent zone! Hogg and coworkers[23] and others were long convinced that peripheral airway changes occur early in the evolution of COPD. Many tests designed to diagnose peripheral airway obstruction have been devised (see Chapter 24), but these tests have not proved selective.

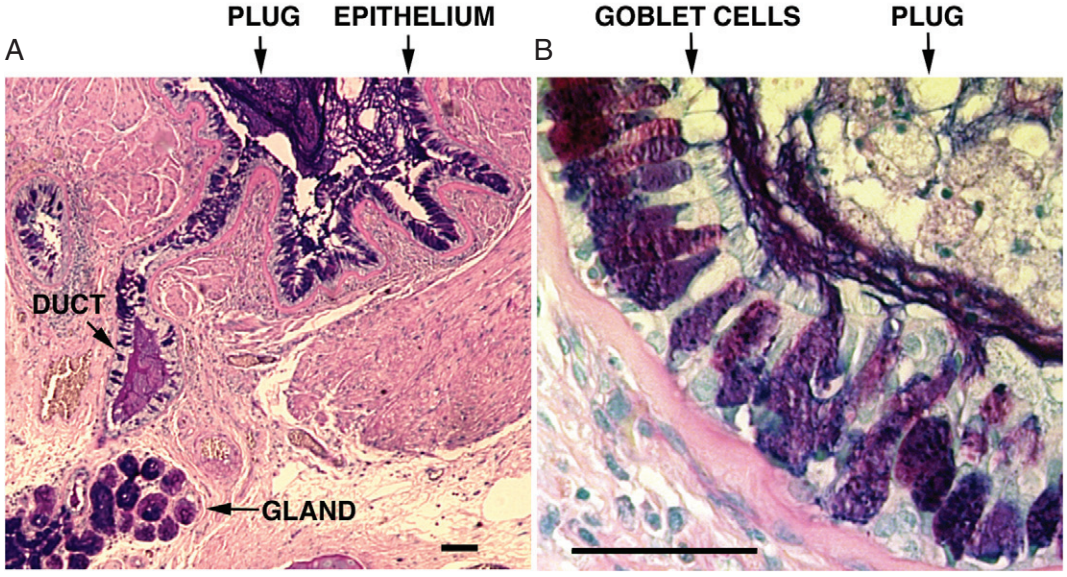

FIGURE 11-4 ■ Mucous hypersecretion in fatal asthma. **A**, AB/PAS staining for mucous glycoconjugates in a proximal airway section in a patient with fatal asthma. The airway lumen is plugged (PLUG) with mucus. The epithelium (EPITH.) shows marked goblet cell metaplasia. The submucosal gland (GLAND) has intense staining for mucous glycoconjugates and releases its contents into a gland duct (DUCT) that is filled with AB/PAS-stained material. **B**, Another AB/PAS-stained section of airway epithelium in the same patient at higher magnification. Although goblet cells (GC) here remain intact, mucus can be seen streaming from the luminal tips of the goblet cells into the lumen. The lumen is filled with mucus. Both scale *bars* = 50 μm.

In 2004, Hogg and coworkers[23] performed a quantitative assessment of small airways in surgically resected lung tissue in patients with COPD with different degrees of airway obstruction. The progression of COPD was strongly associated with an increase in inflammatory mucous exudates in the lumens of small airways. In addition, they reported an increase in the volume of tissue in the airway wall, which potentiates the effects of luminal plugging. Thus, in COPD, as well as in CF and in acute severe asthma, obstruction of peripheral airways plays a major role in the pathophysiology of the disease. Previous limited attempts at intervention are due to multiple factors: (1) most physicians associate mucous hypersecretion with large airways, where mucus can be visualized, and where the patients have complaints (cough and sputum production); (2) obstruction of the peripheral airways generally is not associated with symptoms early, decreasing the level of awareness; (3) peripheral airways are relatively inaccessible because of the limitations of present methodologies.

EPITHELIAL SIGNALING PATHWAYS RESPONSIBLE FOR MUCIN PRODUCTION IN AIRWAYS

The previous sections describe the characteristics of airway mucins (in "mucus") in airway diseases including CF, acute severe asthma, and COPD, where potentially lethal effects of mucous hypersecretion by obstruction of peripheral airways ("mucous plugging") are documented. Here the signaling pathways for mucin production are reviewed.

Early Studies of Mucins

Chronic airway diseases have long been associated with mucous hypersecretion. The gel-forming mucins, which are large-sized glycoproteins, became recognized as being responsible for the major characteristics of mucus. Cloning of mucin genes (reviewed by Rose and colleagues[38]) provided tools for studying mucin regulation. In the 1990s, intense research on mucins began, and many stimuli were shown to produce mucins in airway epithelial cells. Based on the newly available cell and molecular tools, rapid advances began to clarify the pathways involved in mucin production. In 1998, Li and associates[29] reported that *Pseudomonas* bacteria stimulate epithelial mucin production via a Src-dependent Ras/Raf/MAPK pathway.

Epidermal Growth Factor Receptor Activation Stimulates Mucin Production in Airways

Many of the stimuli that induce mucin production in airways such as microbes and cigarette smoke are derived from the environment and are inhaled, depositing on the airway epithelial surface. Takeyama and coworkers[37] hypothesized that receptors on the surface of the airway epithelium could be candidates for epithelial signaling, resulting in mucin production that occurs in response to the deposition of the inhaled foreign particulates. Epidermal growth factor (EGF), an EGFR ligand, was discovered by Cohen,[39] and subsequently, his group expanded the understanding of EGF and its receptor EGFR, focusing on epithelial cell proliferation and cancer. EGFR is a 170-kDa membrane glycoprotein that is activated by multiple ligands.

Takeyama and coworkers[37] hypothesized that epithelial responses to inhaled microbes such as *Pseudomonas* are initiated on the epithelial luminal surface, where the microbes are deposited, by activation of EGFR. The authors discovered that activation of EGFR by its ligands (such as EGF and transforming growth factor-α [TGF-α]) causes mucin production in cultured human airway epithelial cells, an effect that is prevented by EGFR inhibition. They confirmed these results in rats in vivo; they also found that ovalbumin sensitization increases MUC5AC mucin.

Perrais and colleagues[40] confirmed that EGFR ligands activate EGFR to produce mucins. They reported that the downstream pathways include a Ras/Raf/MAP kinase cascade. Subsequent reports identified EGFR as a key target for mucin synthesis/goblet cell metaplasia in response to multiple stimuli in vitro and in vivo (for a representative list, see Table 11-1).

TABLE 11-1. Examples of Stimuli That Induce Mucin Synthesis In Vitro or In Vivo by Epiderma Growth Factor Receptor Activation in Airways

In Vitro Experiments
- Bacterial products
  - *P aeruginosa* supernatant[45]
  - Lipopolysaccharide (LPS)[45,46]
  - Lipoteichoic acid (LTA)[63]
- Phorbol 12-myristate 13-acetate (PMA)[46]
- Cigarette smoke[64]
- Inflammatory cells
  - Neutrophils[16]
  - Eosinophils[65]
- Serine proteases
  - Human neutrophil elastase[55]
  - Human airway trypsin-like protease[66]

In Vivo Experiments
- T helper 2 (Th2) cells
- Antigen (ovalbumin)[37]
- Interleukin-13 (IL-13)[67]
- Mechanical damage of epithelium[68]
  - Cigarette smoke[64]
  - Leukotrienes[69]

From Burgel PR, Nadel JA: Roles of epidermal growth factor receptor activation in epithelial cell repair and mucin production in airway epithelium. Thorax 59:992, 2004.

Metalloproteases Cleave Membrane-Bound Epidermal Growth Factor Receptor Ligands to Produce Mucins

Airway epithelial cells themselves synthesize EGFR ligands in the airway epithelium[41] as transmembrane precursors that can be cleaved by metalloproteases, releasing soluble active growth factors.[42] In 1999, Dong and associates[43] reported that general metalloprotease inhibitors prevent the effects of EGFR proliferation in proportion to the release of the membrane-bound EGFR ligand TGF-α, and they concluded that the soluble ligand was responsible for the effects of EGFR activation. Prenzel and coworkers[44] similarly reported that a general metalloprotease inhibitor prevented EGFR ligand release and subsequent EGFR activation. These papers were the first to implicate cleavage of EGFR ligands by metalloprotease(s) in EGFR surface signaling. Subsequently, Kohri and colleagues[45] linked *Pseudomonas* bacterial supernatant to mucin production. EGFR activation was required, but the mode of EGFR signaling in the airway epithelium was unclear.

Tumor necrosis factor α–converting enzyme (TACE) is a member of the ADAM family of proteases. It is bound to the luminal surface of the airway epithelium. Shao and associates[46] recognized that TACE was capable of cleaving membrane-bound EGFR proligands (as shown previously).[47] Shao and associates[46] showed that *Pseudomonas* and their product lipopolysaccharide (LPS) increase mucin production in human airway epithelial cells, an effect that was reported to be EGFR-dependent and associated with the cleavage and release of the membrane-bound EGFR ligand TGF-α. Selective knockdown of TACE prevented the sequence leading to mucin production, establishing TACE as important in autocrine signaling involved in mucin production. These results established the role of TACE in the autocrine activation of EGFR and in mucin production in airways. Subsequently, many different stimuli were reported to cause mucin production via autocrine EGFR signaling by the airway epithelium. Other metalloproteases have also been reported to be involved in epithelial signaling. Because of the importance of the cleavage step in ligand-dependent EGFR activation, further exploration of various proteases in mucin production is recommended.

Roles of Reactive Oxygen Species in Airway Epithelial Mucin Production

Excess production of reactive oxygen species (ROS) is known to cause cell damage in chronic inflammatory diseases,[48] but ROS scavengers are also reported to inhibit interleukin-8 (IL-8) production.[49]

Several studies have contributed to the understanding of the role of ROS in epithelial signaling and mucin production. Thus, ROS stimulation (e.g., with H_2O_2) activates EGFR[50,51] and results in mucin production.[16]

Dual oxidase-1 (DUOX1) was found in human airway epithelial cells and was reported to generate ROS.[52,53] Shao and Nadel[54] suggested that DUOX1 could release ROS and thereby activate TACE. They used human neutrophil elastase (HNE) as the stimulus, because HNE had been previously reported to produce mucin via EGFR ligand-dependent activation.[55] Shao and Nadel[54] reported that HNE induced TACE activation, TGF-α release, and mucin expression, effects that were inhibited by ROS scavengers, implicating ROS in the response. Knockdown of DUOX1 expression with small interfering RNA prevented the responses. Furthermore, the PKC-δ/PKC-θ inhibitor rottlerin prevented the effects of HNE, suggesting that DUOX1 plays a critical role in mucin production via PKC-δ/PKC-θ-DUOX1-ROS–TACE-proligand-EGFR cascade. The scheme is shown diagrammatically in Figure 11-5. It is of interest that DUOX1 may release ROS in a limited cell compartment adjacent to TACE, thus producing a signal in defense of the host without harmful effects on epithelial cell viability. In fact, DUOX1 is now recognized to play a role in other epithelial defensive responses such as wound healing.[56] Activation of DUOX1 stimulates the production of the chemokine IL-8.[57] It is hoped that future studies in various epithelia will evaluate the importance of ROS and other aspects of the proinflammatory cascade in a variety of epithelial-based diseases, both inflammatory and malignant.

ROS liberated by inflammatory cells recruited to the epithelium may also play roles in mucin production. Thus, neutrophils recruited to the airways and activated are known to produce ROS.[58,59] When neutrophils were isolated from blood and activated and the neutrophil supernatant was added to human airway epithelial cells, the cells became EGFR phosphorylated and increased mucin synthesis occurred, effects that were shown to be due to EGFR phosphorylation.[16] However, neutrophils can also produce large amounts of ROS that may cause DNA damage and death of epithelial cells.[60] Thus, at low concentrations, molecules such as ROS produced by inflammatory cells can induce defensive responses such as mucin production, whereas higher concentrations can be destructive to the epithelium.

Because ROS appears to play important roles in mucin production, and because only limited studies of ROS-induced modulation exist, further examination of ROS effects on epithelial cell signaling are in order.

Toll-like Receptors

Multiple stimuli activate airway epithelial cell receptors and produce defensive responses. (For a discussion of innate immune responses, see Chapter 13.) Here we focus on mechanisms of mucin production. Because of their importance in studies performed on mucin production, Toll-like receptors (TLRs) are included here. Recognition of inhaled stimuli by the airway epithelium was initiated with studies of inhaled microorganisms. Recognition of pathogens is mediated by a set of germline-encoded receptors called "pattern recognition receptors," which recognize conserved molecular patterns shared by large groups of microorganisms. An important group of these receptors were discovered in fruit flies (so-called Toll receptors). When they were found in mammals, they were called "Toll-*like* receptors" (TLRs).[61]

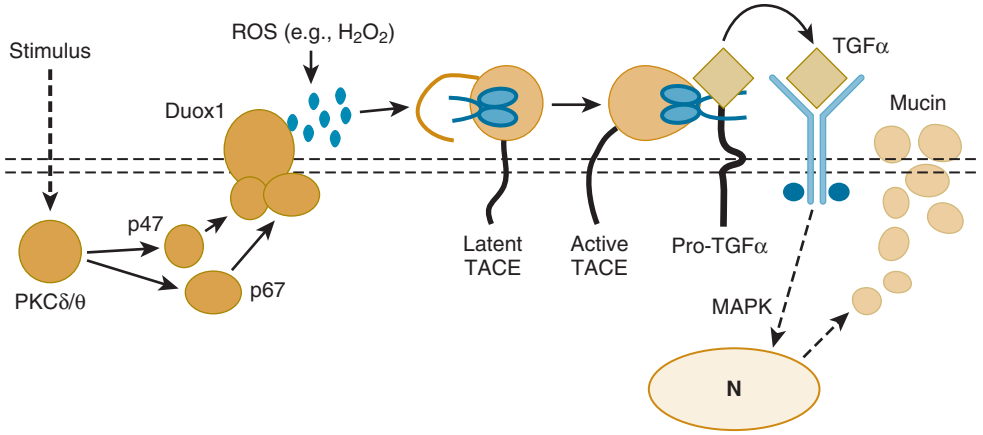

FIGURE 11-5 ■ Diagrammatic scheme of epidermal growth factor–dependent cascade that causes mucin production. Deposition of a stimulus on the airway epithelium activates an epithelial receptor (not shown), activates protein kinase C (PKC) isoforms PKCδ and PKCθ, which recruit cytosolic components (e.g., $p47^{phox}$) to plasma membrane (*double-dotted lines*) to join dual oxidase-1 (DUOX1) to form an active enzyme system for generating reactive oxygen species (ROS; e.g., H_2O_2; represented by *dark dots*). ROS activate the latent form of tumor necrosis factor-α–converting enzyme (TACE), which has an inhibitory prodomain (represented by a *curved line*) covering its catalytic domain (represented by *scissors*), removing the prodomain and exposing the catalytic domain to cleave pro-transforming growth factor-α (TGF-α; *yellow diamond with a dark tail*) into soluble TGF-α (*yellow diamond without a tail*), which binds to and activates epidermal growth factor receptor (EGFR), initiating mitogen-activated protein kinase signaling to the nucleus (*arrow* to nucleus), leading to mucin gene expression and mucin protein production. (Redrawn from Shao MX, Nadel JA: Dual oxidase 1–dependent MUC5AC mucin expression in cultured human airway epithelial cells. Proc Natl Acad Sci U S A 102:767, 2005.)

Early studies of TLRs were convincing in showing that these receptors are responsible for many of the pathophysiologic features of microbes. For example, the outer membranes of gram-negative bacteria contain the glycolipid LPS, which is responsible for many of the pathophysiologic features of these bacteria and is due to stimulation of TLR-4. Subsequently, many TLRs have been described in mammalian cells, including the airway epithelium. The discovery of TLRs provides a mechanism for microbes to bind to the host epithelium, and thus invade. Viral binding to these receptors is important for the entry of many viruses into epithelial cells and consequent multiplication. This binding is also an important sensing device, allowing the epithelium to detect the presence of the microbe and thence to initiate signaling that provides defensive responses. For example, multiple TLRs are involved in signaling responses to the effects of various viruses on IL-8 and vascular endothelial growth factor (VEGF) production.[62] These results show that multiple TLRs play roles in airway epithelial cell responses by activating EGF receptors via a complex epithelial cell cascade.

THERAPEUTIC IMPLICATIONS

The subject of deposition and clearance is discussed in Chapter 12, where effects of hypersecretion and inadequate clearance are discussed. Mucous hypersecretion occurs in the large conducting airways, where it causes cough and sputum secretion. In peripheral airways, hypersecretion can completely obstruct airway lumens. A most serious problem associated with mucous hypersecretion is peripheral mucous plugging. The peripheral airways remain a "silent zone" in the lungs, and novel methods are needed for adequate evaluation of these airways. Here, we have reviewed signaling pathways involved in mucin production. Multiple molecules are involved in the signaling process, providing multiple potential targets for therapy.

KEY POINTS

- Mucous hypersecretion is common in chronic inflammatory airway diseases (e.g., CF, chronic bronchitis and COPD, and asthma).
- In large conducting airways, hypersecretion is associated with cough and excess sputum production.
- In peripheral airways, hypersecretion is generally asymptomatic early but can lead to widespread plugging, incapacitation, and death.
- Many environmental microbes and other irritants stimulate mucin production by stimulating airway epithelial TLRs.
- A well-characterized epithelial surface pathway provides signals that induce mucin production and are candidates for therapy of mucous hypersecretion.

References

1. Creeth JM: Constituents of mucus and their separation. Br Med Bull 34:17, 1978.
2. Robinson NP, Kyle H, Webber SE, Widdicombe JG: Electrolyte and other chemical concentrations in tracheal airway surface liquid and mucus. J Appl Physiol 66:2129, 1989.
3. Reid LM, Bhaskar KR: Macromolecular and lipid constituents of bronchial epithelial mucus. Symp Soc Exp Biol 43:201, 1989.
4. Widdicombe JG: Airway mucus. Eur Respir J 2:107, 1989.
5. Lamblin G, Aubert JP, Perini JM, et al: Human respiratory mucins. Eur Respir J 5:247, 1992.
6. Seregni E, Botti C, Massaron S, et al: Structure, function and gene expression of epithelial mucins. Tumori 83:625, 1997.
7. Leikauf GD, Borchers MT, Prows DR, Simpson LG et al: Mucin apoprotein expression in COPD. Chest 121:166S, 2002.
8. Moniaux N, Escande F, Porchet N, et al: Structural organization and classification of the human mucin genes. Front Biosci 6:D1192, 2001.
9. Groneberg DA, Eynott PR, Lim S, et al: Expression of respiratory mucins in fatal status asthmaticus and mild asthma. Histopathology 40:367, 2002.
10. Groneberg DA, Eynott PR, Oates T, et al: Expression of MUC5AC and MUC5B mucins in normal and cystic fibrosis lung. Respir Med 96:81, 2002.
11. Davies JR, Hovenberg HW, Linden CJ, et al: Mucins in airway secretions from healthy and chronic bronchitic subjects. Biochem J 313:431, 1996.
12. Ordonez CL, Khashayar R, Wong HH, et al: Mild and moderate asthma is associated with airway goblet cell hyperplasia and abnormalities in mucin gene expression. Am J Respir Crit Care Med 163:517, 2001.
13. Sharma P, Dudus L, Nielsen PA, et al: MUC5B and MUC7 are differentially expressed in mucous and serous cells of submucosal glands in human bronchial airways. Am J Respir Cell Mol Biol 19:30, 1998.
14. Thornton DJ, Howard M, Khan N, Sheehan JK: Identification of two glycoforms of the MUC5B mucin in human respiratory mucus. Evidence for a cysteine-rich sequence repeated within the molecule. J Biol Chem 272:9561, 1997.
15. Meezaman D, Charles P, Daskal E, et al: Cloning and analysis of cDNA encoding a major airway glycoprotein, human tracheobronchial mucin (MUC5). J Biol Chem 269:12932, 1994.
16. Takeyama K, Dabbagh K, Jeong Shim J, et al: Oxidative stress causes mucin synthesis via transactivation of epidermal growth factor receptor: role of neutrophils. J Immunol 164:1546, 2000.
17. Hays SR, Fahy JV: Characterizing mucous cell remodeling in cystic fibrosis: Relationship to neutrophils. Am J Respir Crit Care Med 174:1018, 2006.
18. Burgel PR, Montani D, Danel C, et al: A morphometric study of mucins and small airway plugging in cystic fibrosis. Thorax 62:153, 2007.
19. Takeyama K, Fahy JV, Nadel JA: Relationship of epidermal growth factor receptors to goblet cell production in human bronchi. Am J Respir Crit Care Med 163:511, 2001.
20. Widdicombe JG: Neurophysiology of the cough reflex. Eur Respir J 8:1193, 1995.
21. Finkbeiner WE: Physiology and pathology of tracheobronchial glands. Respir Physiol 118:77, 1999.
22. Verdugo P: Goblet cells secretion and mucogenesis. Annu Rev Physiol 52:157, 1990.
23. Hogg JC, Chu F, Utokaparch S, et al: The nature of small-airway obstruction in chronic obstructive pulmonary disease. N Engl J Med 350:2645, 2004.
24. Cardell BS, Pearson RSB: Death in asthmatics. Thorax 14:341, 1959.
25. Aikawa T, Shimura S, Sasaki H, et al: Marked goblet cell hyperplasia with mucus accumulation in the airways of patients who died of severe acute asthma attack. Chest 101:916, 1992.
26. Earle BV: Fatal bronchial asthma: A series of fifteen cases with a review of the literature. Thorax 8:195, 1953.
27. Carroll N, Elliot J, Morton A, James A: The structure of large and small airways in nonfatal and fatal asthma. Am Rev Respir Dis 147:405, 1993.
28. Dunnill MS: The pathology of asthma, with special reference to changes in the bronchial mucosa. J Clin Pathol 13:27, 1960.
29. Li JD, Dohrman AF, Gallup M, et al: Transcriptional activation of mucin by *Pseudomonas aeruginosa* lipopolysaccharide in the pathogenesis of cystic fibrosis lung disease. Proc Natl Acad Sci U S A 94:967, 1997.
30. Dohrman A, Miyata S, Gallup M, et al: Mucin gene (MUC 2 and MUC 5AC) upregulation by Gram-positive and Gram-negative bacteria. Biochim Biophys Acta 1406:251, 1998.
31. Voynow JA, Young LR, Wang Y, et al: Neutrophil elastase increases MUC5AC mRNA and protein expression in respiratory epithelial cells. Am J Physiol 276:L835, 1999.
32. Davies JR, Svitacheva N, Lannefors L, et al: Identification of MUC5B, MUC5AC and small amounts of MUC2 mucins in cystic fibrosis airway secretions. Biochem J 344:321, 1999.
33. Minshall RD, Tiruppathi C, Vogel SM, et al: Endothelial cell-surface gp60 activates vesicle formation and trafficking via G(i)-coupled Src kinase signaling pathway. J Cell Biol 150:1057, 2000.
34. Reich H, Tritchler D, Herzenberg AM, et al: Albumin activates ERK via EGF receptor in human renal epithelial cells. J Am Soc Nephrol 16:1266, 2005.
35. Lange P, Parner J, Vestbo J, et al: A 15-year follow-up study of ventilatory function in adults with asthma. N Engl J Med 339:1194, 1998.
36. Turner-Warwick M, Openshaw P: Sputum in asthma. Postgrad Med J 63(Suppl 1):79, 1987.
37. Takeyama K, Dabbagh K, Lee HM, et al: Epidermal growth factor system regulates mucin production in airways. Proc Natl Acad Sci U S A 96:3081, 1999.
38. Rose MC, Nickola TJ, Voynow JA: Airway mucus obstruction: mucin glycoproteins, MUC gene regulation and goblet cell hyperplasia. Am J Respir Cell Mol Biol 25:533, 2001.
39. Cohen S: Nobel lecture. Epidermal growth factor. Biosci Rep 6:1017, 1986.
40. Perrais M, Pigny P, Copin MC, et al: Induction of MUC2 and MUC5AC mucins by factors of the epidermal growth factor (EGF) family is mediated by EGF receptor/Ras/Raf/extracellular signal-regulated kinase cascade and Sp1. J Biol Chem 277:32258, 2002.
41. Polosa R, Prosperini G, Leir SH, et al: Expression of c-erbB receptors and ligands in human bronchial mucosa. Am J Respir Cell Mol Biol 20:914, 1999.
42. Massague J, Pandiella A: Membrane-anchored growth factors. Annu Rev Biochem 62:515, 1993.
43. Dong J, Opresko LK, Dempsey PJ, et al: Metalloprotease-mediated ligand release regulates autocrine signaling through the epidermal growth factor receptor. Proc Natl Acad Sci U S A 96:6235, 1999.
44. Prenzel N, Zwick E, Daub H, et al: EGF receptor transactivation by G-protein-coupled receptors requires metalloproteinase cleavage of proHB-EGF. Nature 402:884, 1999.
45. Kohri K, Ueki I.F, Shim JJ, et al: *Pseudomonas aeruginosa* induces MUC5AC production via epidermal growth factor receptor. Eur Respir J 20:1263, 2002.
46. Shao MX, Ueki IF, Nadel JA: Tumor necrosis factor alpha–converting enzyme mediates MUC5AC mucin expression in cultured human airway epithelial cells. Proc Natl Acad Sci U S A 100:11618, 2003.
47. Peschon JJ, Slack JL, Reddy P, et al: An essential role for ectodomain shedding in mammalian development. Science 282:1281, 1998.
48. Rahman I, MacNee W: Oxidative stress and regulation of glutathione in lung inflammation. Eur Respir J 16:534, 2000.
49. Massion PP, Linden A, Inoue H, et al: Dimethyl sulfoxide decreases interleukin-8-mediated neutrophil recruitment in the airways. Am J Physiol 271:L838, 1996.
50. Goldkorn T, Balaban N, Matsukuma K, et al: EGF-Receptor phosphorylation and signaling are targeted by H_2O_2 redox stress. Am J Respir Cell Mol Biol 19:786, 1998.
51. Gamou S, Shimizu N: Hydrogen peroxide preferentially enhances the tyrosine phosphorylation of epidermal growth factor receptor. FEBS Lett 357:161, 1995.
52. De Deken X, Wang D, Many MC, et al: Cloning of two human thyroid cDNAs encoding new members of the NADPH oxidase family. J Biol Chem 275:23227, 2000.

53. Geiszt M, Witta J, Baffi J, et al: Dual oxidases represent novel hydrogen peroxide sources supporting mucosal surface host defense. FASEB J 17:1502, 2003.
54. Shao MX, Nadel JA: Dual oxidase 1–dependent MUC5AC mucin expression in cultured human airway epithelial cells. Proc Natl Acad Sci U S A 102:767, 2005.
55. Kohri, K, Ueki IF, Nadel JA: Neutrophil elastase induces mucin production by ligand-dependent epidermal growth factor receptor activation. Am J Physiol Lung Cell Mol Physiol 283:L531, 2002.
56. Koff JL, Shao MX, Kim S, et al: Pseudomonas lipopolysaccharide accelerates wound repair via activation of a novel epithelial cell signaling cascade. J Immunol 177:8693, 2006.
57. Boots AW, Hristova M, Kasahara DI, et al: ATP-mediated activation of the NADPH oxidase DUOX1 mediates airway epithelial responses to bacterial stimuli. J Biol Chem 284:17858, 2009.
58. Derevianko A, D'Amico R, Graeber T, et al: Endogenous PMN-derived reactive oxygen intermediates provide feedback regulation on respiratory burst signal transduction. J Leukoc Biol 62:268, 1997.
59. Kapp A, Zeck-Kapp G: Activation of the oxidative metabolism in human polymorphonuclear neutrophilic granulocytes: The role of immuno-modulating cytokines. J Invest Dermatol 95:94S, 1990.
60. Weissmann G, Smolen JE, Korchak HM: Release of inflammatory mediators from stimulated neutrophils. N Engl J Med 303:27, 1980.
61. Medzhitov R, Preston-Hurlburt P, Janeway CA Jr: A human homologue of the *Drosophila* Toll protein signals activation of adaptive immunity. Nature 388:394, 1997.
62. Koff JL, Shao MX, Ueki IF, Nadel JA: Multiple TLRs activate EGFR via a signaling cascade to produce innate immune responses in airway epithelium. Am J Physiol Lung Cell Mol Physiol 294:L1068, 2008.
63. Lemjabbar H, Basbaum C: Platelet-activating factor receptor and ADAM10 mediate responses to *Staphylococcus aureus* in epithelial cells. Nat Med 8:41, 2002.
64. Takeyama K, Jung B, Shim JJ, et al: Activation of epidermal growth factor receptors is responsible for mucin synthesis induced by cigarette smoke. Am J Physiol Lung Cell Mol Physiol 280:L165, 2001.
65. Burgel PR, Lazarus SC, Tam DC, et al: Human eosinophils induce mucin production in airway epithelial cells via epidermal growth factor receptor activation. J Immunol 167:5948, 2001.
66. Chokki M, Yamamura S, Eguchi H, et al: Human airway trypsin-like protease increases mucin gene expression in airway epithelial cells. Am J Respir Cell Mol Biol 30:470, 2004.
67. Shim JJ, Dabbagh K, Ueki IF, et al: IL-13 induces mucin production by stimulating epidermal growth factor receptors and by activating neutrophils. Am J Physiol Lung Cell Mol Physiol 280:L134, 2001.
68. Lee HM, Takeyama K, Dabbagh K, et al: Agarose plug instillation causes goblet cell metaplasia by activating EGF receptors in rat airways. Am J Physiol Lung Cell Mol Physiol 278:L185, 2000.
69. Vargaftig BB, Singer M: Leukotrienes mediate part of Ova-induced lung effects in mice via EGFR. Am J Physiol Lung Cell Mol Physiol 285:L808, 2003.
70. Burgel PR, Nadel JA: Roles of epidermal growth factor receptor activation in epithelial cell repair and mucin production in airway epithelium. Thorax 59:992, 2004.

CHAPTER 12

AEROSOL DEPOSITION AND CLEARANCE

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INTRODUCTION

The human lung has a large surface area, which for an average size person approximates half a doubles tennis court, thus maximizing the approximation and apposition of capillaries and alveolar tissue. Whereas this design optimizes gas exchange, it also has the intrinsic risk of exposing the delicate alveolar tissues to potentially noxious particles that may be present in the ambient air. There are various safeguards against the danger posed by inhaled particles. The first line of defense is that the configuration of the nasopharynx and serial branching of the airways causes particles to deposit proximal to the more vulnerable alveolar structures.[1,2] Second, if an insoluble particle deposits in the lung, there are processes by which it can be cleared from the airways or alveoli. There are also specific antimicrobial and antioxidant defenses, but these latter topics are beyond the scope of this chapter. Clearance of insoluble particles that deposit in the ciliated airways is achieved by mucociliary clearance.[3] The particles are trapped in a mucous blanket, which is then transported proximally by the beating of cilia. If the cilia are not functioning optimally or if the quantity/quality of the airway mucus is abnormal, the mucus and its entrapped particulates can be cleared by cough clearance. Particles that deposit distal to the ciliated airways are removed by alveolar clearance, mainly

by macrophages ingesting the particles and transporting them to regional lymph nodes.

The branching structure of the airways is a barrier not only to noxious environmental aerosols but also to therapeutic aerosols. However, the application of the principles of deposition facilitates the design of therapeutic aerosol development.[4] Therapeutic aerosols are given for two indications. The vast majority of these aerosols are prescribed for the treatment of respiratory disease, but there is increasing interest in availing of the lungs' large surface area to deliver nonrespiratory drugs via the lung as aerosols, usually peptides that cannot be given by oral route.

DEFINITION AND DESCRIPTION OF AN AEROSOL[1,2]

An *aerosol* can be defined as a system of solid particles or liquid droplets that can remain dispersed in a gas, usually air. Naturally occurring aerosols, as well as those emitted by clinical aerosol generators, almost always contain a wide range of particle sizes. Because the aerodynamic behavior of an aerosolized particle is critically influenced by its mass, it is important to be able to precisely describe the size distribution of aerosolized particles. In clinical studies, the mass median aerodynamic diameter (MMAD) and the geometric standard deviation (σg) are often used to characterize the dimensions of an aerosol. When the mass distribution of particles in an aerosol is fractionated and the cumulative particle distribution plotted as a lognormal distribution on probability paper, it often approximates a straight line. However, recent studies of clinical aerosols have indicated that nebulized particles are often not lognormal in distribution.[5] The MMAD represents the point in the distribution above which 50% of the mass resides, expressed as the diameter of a unit density (1 g/cc) sphere having the same terminal settling velocity as the aerosol particle in question, regardless of its shape and density.

The lognormal plot is convenient because, if linear, it defines a statistically "normal" distribution and the data can be described accurately by the MMAD and the standard deviation alone. For a lognormal distribution, one standard deviation is called the "geometric standard deviation" or σg. The σg is the ratio of the size at 84% (or 16%) to the MMAD and is an indicator of the variability in particle diameters. If the particle size varies over a wide range ($\sigma g > 1.2$), it is described as having a *polydisperse* particle distribution; if the particles are of similar size ($\sigma g < 1.2$), the particle distribution is described as *monodisperse*. Monodisperse aerosols are usually encountered only in research studies where specialized generators are used to create such aerosol.[6] For clinical aerosols that are not lognormal and are widely polydisperse, it is best to relate deposition studies to the entire distribution of particles and avoid focusing on simple descriptive terms like the MMAD and σg.[5,7]

The definition of the mass median diameter (MMD) is the same as that of the MMAD except that the data are not normalized to unit density.

PRINCIPLES OF DEPOSITION

The fraction of inhaled particles that deposit (as opposed to being exhaled) is called the "deposition fraction."[1,2] The likelihood that a particle will deposit in a particular airway depends on the interaction of three factors: the physical characteristics of the particle (e.g., mass, shape), the gas flow in which the particle is transported (the patient's breathing pattern[8] and any velocity impacted to the particle by a propellant), and the airway anatomy (especially the presence of airway obstruction[9]). In general, the greater the mass, the faster the velocity, and the narrower the airway, the greater the predisposition of the particle to deposit by a process called "inertial impaction." Inertial impaction is the dominant mechanism by which particles deposit in the nasopharynx and more proximal airways and describes the process by which a particle fails to follow the air stream in which it is suspended, thereby impacting on an obstacle instead of circumventing it. The probability of a particle undergoing inertial impaction (I) can be estimated using the following equation:

$$I = \alpha(V_t V_a \sin\theta / gR \quad (1)[1]$$

where V_t is the settling velocity of the entrained particle V_a = air stream velocity, θ = angle required to circumvent the obstacle, and R = airway radius. The settling velocity (defined in Equation 2) increases as particle size increases. This equation applies to situations in which laminar flow predominates. The presence of turbulent nonlaminar flow will tend to further increase impaction. Particles that fail to deposit in proximal airways by inertial impaction can deposit in peripheral airways and alveoli by a process called gravitational sedimentation.

Gravitational sedimentation is the process by which a particle accelerates under gravity until it reaches a terminal settling velocity (V_t), which is determined by the equation[1]

$$V_t = (\rho - \sigma) g d^2 / 18\gamma \quad (2)$$

where σ = density of air, γ = viscosity of air, ρ = density of particle, d = diameter of particle, and g = acceleration due to gravity. Therefore, for a given velocity, the greater the aerodynamic mass of an aerosol, the shorter the time it will remain suspended the air stream. Gravitational sedimentation is the main mechanism by which particles (0.5–5.0 μm in diameter) deposit in the peripheral regions of the lung.

Sedimentation is critically dependent on the patient's breathing pattern.[8] If there is a breath-hold before exhalation, particles are more likely to sediment; without a breath-hold, particles are more likely to be exhaled rather than deposited. It has also been suggested that alveolar volume may affect deposition fraction (larger air spaces require more time for sedimentation).

Very small particles (<0.2 μm) can deposit by diffusion.

The diffusion coefficient of a particle (D) can be expressed[2] as

$$D = kT / 3\pi\eta d \quad (3)$$

where k is the Boltzman constant, T is the temperature in Kelvin, η is the gas viscosity, and d is particle diameter.

These tiny particles are rarely important in therapeutic aerosols, but in inhalation toxicology studies, these particles can be produced by combustion and may be clinically relevant, even though they tend to be transient due to the tendency to agglomeration. In addition, manmade nanoparticles, which are of increasing interest in electronics and biomedical research, would, if inadvertently inhaled, be likely to deposit by diffusion (discussed later under "Environmental Aerosols").

Particles between 0.2 and 0.5 μm in diameter tend to be too small to deposit efficiently by sedimentation and yet too large to deposit efficiently by Brownian diffusion and tend to be exhaled rather than deposited in the lung.[1,2]

MEASUREMENTS OF PARTICLE SIZE

Evaluation of Aerosol Particle Size

Particle size is an important factor in determining whether a particle will undergo nasopharyngeal deposition, airway deposition, or alveolar deposition.[10] Particle size is usually measured by light scattering or cascade impaction. Light scattering measurement is based on the principle that there is differential scattering of polarized light by particles of different sizes. In cascade impaction, particles at a set flow rate go through a series of apertures of decreasing diameter and impact on a series of plates if they fail to follow the air stream. Cascade impactors with high flow rate (e.g., 28 L/min) devices were originally designed for environmental sampling of ambient air to collect 100% of the emitted dose. They have been adopted as the method of choice for monitoring quality control in a manufacturing plant for aerosol delivery. Cascade impaction has an advantage over light scattering in that it facilitates the correlation of different methods of quantifying the distribution of the active drug (e.g., chemical analysis of drug on each plate compared with radioactive label or weight).

However, measuring the emitted dose of aerosol using a high-flow cascade impactor is not ideal for predicting how an aerosol will perform in clinical practice. While low-flow cascade impactors sample only some of the output, they more closely duplicate in vivo conditions.[5,11,11a]

Application of In Vitro Measurements of Particle Size to Clinical Studies[5,7,11]

Particle size data obtained with different techniques are not necessarily interchangeable. Meaningful comparisons of the sizes of clinical aerosols, especially those produced by a pressurized metered-dose inhaler (MDI; which emits high-velocity particles), should be compared only if obtained with identical techniques. Nevertheless, despite the technical difficulties encountered in measuring the size of polydisperse clinical aerosols, some investigators have established that, when used with appropriate caution, data obtained by in vitro measurement of particle size do provide useful predictive data for subsequent clinical studies.[5,7,11]

The classic studies of the influence of particle size on lung deposition were performed with solid nonhygroscopic monodisperse aerosols.[6] In contrast, pharmaceutical aerosols tend to be polydisperse liquid droplets with the active pharmaceutical ingredient (as well as in some cases pharamaceutically inactive excipients such as preservatives and freon) being either in solution or suspended as micronized particles. Droplets can change size by exchanging water with either the dry carrier gas or the humid environment of the upper airway.[2,12] While some drug ingredients are hygroscopic and some diluent solutions are hypertonic, both of which could lead to an increase in particle size based on some theoretical models, the clinical significance of such changes is not known with certainty. It has been reported that hypotonic saline aerosols were associated with a slightly more peripheral deposition pattern on gamma scintigraphy compared with hypertonic saline aerosols.[13] Measuring the particle distribution of wet aerosols is difficult because the particles can be affected by ambient humidity. Therefore the predictive value of cascade impaction data from aqueous aerosols for in vivo deposition (e.g., for upper airway deposition as measured by gamma scintigraphy) is strongly dependent on the specific technique used for cascade impaction.[11a]

GENERATION OF THERAPEUTIC AEROSOLS[4]

There are three common ways in which therapeutic aerosols can be generated. First, the patient's inspiratory airflow may aerosolize a micronized dry powder (dry powder inhalers) Second, micronized particles are suspended in a volatile pressurized liquid that vaporizes when at atmospheric pressure, thus imparting velocity to the emitted particles. The third approach is to apply a dispersal force to a liquid and generate droplets, which are then inhaled by tidal breathing. The generation of the dispersal force can be as simple as using a compressed air source attached to a narrow orifice to generate a Venturi (i.e., jet nebulizer) or by more complex vibrating membranes and meshes. Figure 12-1 shows examples of commercial aerosol devices.

Dry Powder Devices[4,14,15]

Because dry powder inhaler aerosols are generated by the patient's inspiration, they are by definition coordinated with inspiration. The inspiratory flow rate tends be rapid and thus predisposes to extrapulmonary deposition. In optimizing design of new devices, there is a need to minimize resistance to flow so that weak and

FIGURE 12-1 ■ Examples of commercial aerosol devices. *From upper left, clockwise:* A pressurized metered-dose inhaler (pMDI; Proventil HFA, Schering-Plough, Kenilworth, NJ); a jet nebulizer and compressor (Pari, Midlothian, VA); a multidose dry powder inhaler (Diskus, GlaxoSmithKline, Research Triangle Park, NC); a single-dose dry powder inhaler (HandiHaler, Boehringer Ingelheim, Ridgefield, CT); a vibrating mesh nebulizer synchronized with breathing pattern (I-Neb, Philips/Respironics, Pittsburgh, PA); a valved-holding chamber (Forest Laboratories, St. Louis, MO), used in association with a pMDI.

tachypneic patents will be able to generate a threshold flow rate. Furthermore, it is desirable that the emitted dose should not vary significantly with changes in inspiratory flow so that intersubject dosing remains consistent. For high-potency drugs, lactose is often used as an excipient bulking agent. Devices can be single-dose devices in which a capsule of powder is perforated in the device (Spiriva HandiHaler, Boehringer Ingelheim, Ridgefield, CT), multidisk with individual doses wrapped in foil blisters (Advair/Seretide Diskus, GlaxoSmithKline, Research Triangle Park, NC), or multidose metered reservoir (Pulmicort Flexhaler, Astra Zeneca, Wilmington, DE,). For dry powder devices to maintain reproducible dosing over time, it is critical that the powder be protected from moisture. Despite these technical challenges, the design of dry powder inhalers has greatly improved and the devices described previously perform at high levels of efficiency and reproducibility.

A newer version of the dry powder device involves the incorporation of the drug particles into microspheres for more precise control of dose and particle size. This approach has been pioneered in the use of development of inhaled insulin.[16]

Pressurized Metered-Dose Inhalers[4,17–21]

Pressurized MDIs using chlorofluorocarbon propellants have been used in clinical practice for 50 years and remain the most popular method of administering short-acting rescue inhalers and inhaled corticosteroids. They are portable and discrete. The velocity of the emitted particles, however, requires that for adequate lung deposition, there must be precise coordination with a patient's respiration. Studies have shown that actuation technique is suboptimal in most patients. Even with optimal technique, 80% of the emitted dose may deposit on the pharynx and can cause local irritation. In addition, some orally bioavailable medications cause significant systemic exposure from swallowed medication. Valved holding chambers reduce pharyngeal deposition because high-velocity particles impact on the inside of the chamber and if the chamber has valves, the need for

precise coordination with respiration is obviated. For young children, a face mask can be used in conjunction with a valved holding chamber. Unfortunately, registration studies for MDI medications are almost always performed without a holding chamber because manufacturers do not want their product's prescription tied to a specific holding chamber. To make the chambers more acceptable to patients, effective small-volume chambers (140 mL) and collapsible chambers have been developed.

For the past decade, there has been a phase-out program for chlorofluorocarbon-containing pressurized MDIs because of concerns about the impact of chlorofluorocarbons on the environment. Short-acting β-agonists and corticosteroid pressurized MDIs have been reformulated using hydrofluoroalkane as a propellant. The U.S. Food and Drug Administration mandated that these new hydrofluoroalkane-containing pressurized MDIs have performance standards at least equal to existing chlorofluorocarbon-containing pressurized MDIs. While this task has been far more difficult and expensive than anticipated, the last remaining chlorofluorocarbon-containing pressurized MDIs were removed from the U.S. market in early 2009.

Jet Nebulizers[22]

The ubiquitous small-volume jet nebulizer is the mainstay of bronchodilator delivery in hospitalized patients and patients at the extremes of age. These devices are cheap and require little patient cooperation. In addition, they are useful for delivering medications that have a relatively large treatment mass such as antibiotics. Generation of the driving pressure requires either a tank of pressurized gas or an electric compressor. Although the manufacturers of compressors have made these devices more portable, they are far from convenient for ambulatory patients. In addition, nebulizers tend to take 10 to 20 minutes to deliver a single treatment, which negatively impacts adherence. Most generic nebulizers are inefficient and deliver less than 10% of the nebulizer charge to the lung. The remainder is left in the nebulizer chamber as dead volume, lost through the expiratory port because the device generates aerosol throughout the respiratory cycle, or deposited in the extrapulmonary upper airway because most of the emitted dose is contained in large, poorly respirable particles.

New Developments in Aerosol Delivery Systems[22–26]

Manufacturers have made enhancements in nebulizers. Internal recycling baffles reduce emitted particle size. Expiratory filters have been added for potentially hazardous aerosols to reduce collateral exposure. Significant enhancements in drug delivery by nebulizers are possible by coordinating nebulization with inspiration (e.g., "breath actuation") that essentially turns the nebulizer off during expiration. Another improvement in efficiency is called "breath enhancement," which utilizes the patient's inspiratory flow through the nebulizer to increase drug delivery (e.g., LC Star, Pari, Germany; Ventstream, Medicaid, Bognor Regis, UK).[24]

The newer devices include the AKITA (Activaero GMBH, Geunden, Germany), AER_X (Aradigm, Hayward, CA), eFlow (Pari, Midlothian, VA), I-neb (Philips/Respironics, Pittsburgh, PA), and On Q (Nektar, San Carlos, CA). Each device employs unique proprietary technologies that distinguish them from the traditional devices. Some tend to be more precise in their coordination with breathing patterns of individual patients (Akita, I-neb, AERx); they usually have a lower dead volume in the nebulizer chamber, a greater fraction of particles in the respirable range (i.e., <5 μm) and shorter treatment times. They eschew bulky compressors, use either vibrating mesh or crystal, or extrude the liquid through tiny holes or a combination of both vibration and microextrusion. They vary in their durability and the relative ease by which they can be cleaned between treatments.

Recently, the design of aerosol delivery systems has combined slow and deep inspiration with direct mechanical feedback to the patient for particles of relatively large MMAD. As discussed earlier, a "slow" inspiration reduces particle inertia and allows inhalation of particles that would otherwise deposit in the oropharynx during tidal breathing and will thus minimize oropharyngeal deposition.

PRINCIPLES OF ASSESSMENT OF DELIVERY SYSTEMS[22,23]

Assessing effects of an aerosolized drug requires the understanding of three major factors: the aerosol delivery system, the quality of the aerosol produced, and the quantification of deposition within the lungs. The latter measurement is performed in vivo and is time consuming and costly and involves some degree of risk and uncertainty to the patient. The other two components of the aerosol delivery process can be well characterized and studied in vitro. The field of aerosol delivery has advanced significantly in the last 10 years such that device characteristics and aerosol behavior can be significantly optimized on the bench before exposure to patients.

The Inhaled Mass

Figure 12-2 depicts a simple in vitro setup for measuring the quantity of aerosol produced by a nebulizer. An absolute filter that captures the aerosolized particles has replaced the mouthpiece. This system does not require an understanding of nebulizer function from first principles. Because the nebulizer is attached to a breathing device (Harvard pump, Harvard Apparatus, South Natick, MA), the conditions of delivery such as routine tidal breathing can be duplicated. The quantity of drug captured on the inspiratory filter represents the amount that passes the lips of the patient. To distinguish this quantity from a "dose" or deposited drug, the term *inhaled mass*

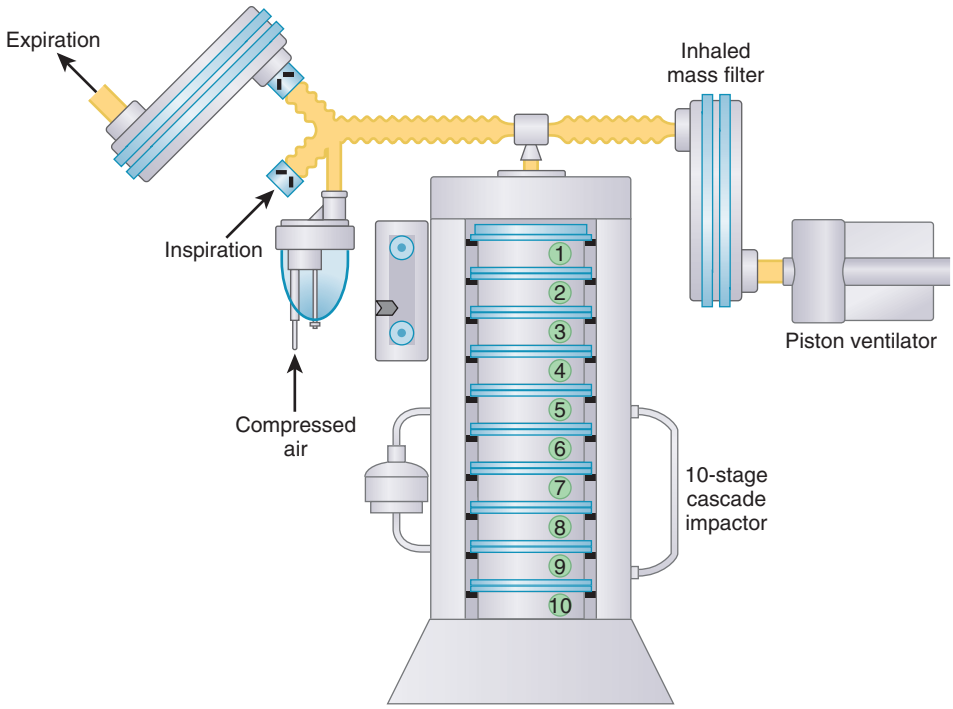

FIGURE 12-2 ■ The technique for bench measurements of inhaled mass and particle distribution: breathing pattern defined by settings on piston ventilator. Particles presented to "patient" (the ventilator) are captured on the inhaled mass filter. In separate experiments, the cascade impactor measures inspired aerosol. (Redrawn from Smaldone GC: Drug delivery via aerosol systems: concept of "aerosol inhaled." J Aerosol Med 4:229–235, 1991, with permission.)

has been coined. The *inhaled mass* represents "delivery" of drug to the patient constrained by conditions that should mimic actual clinical delivery.

Deposition

The term *deposition* begins to imply a "dose" to the patient. The term *deposition* needs to be further refined in a given situation (e.g., oropharyngeal versus parenchymal deposition, or central versus peripheral deposition within the lung). Each of these terms may be important depending upon the disease entity to be treated. Obviously, the measurement of deposition requires an in vivo experiment. However, deposition can be related to parameters that are measured in vitro as shown in Equation 4:

$$\text{Deposition} = \text{aerosol inhaled} - \text{aerosol exhaled} \quad (4)$$

Because the term "aerosol" is a little vague with respect to drug activity, Equation 4 can be rewritten as

$$\text{Deposition} = \textbf{\textit{inhaled mass}} - \text{exhaled mass} \quad (5)$$

Bench models are useful in identifying the parameters that define the *inhaled mass* for different devices and experimental conditions (Equation 5).[11] Investigators have developed protocols to test the output in vitro in ways that more closely replicate clinical practice. For example, bench testing of jet nebulizers can incorporate a piston ventilator to duplicate breathing patterns of spontaneously breathing patients or a ventilator circuit and endotracheal tube to duplicate aerosol delivery in the setting of mechanical ventilation. These in vitro protocols can be used to evaluate aerosolization protocols in ways that can optimize pulmonary drug deposition in subsequent clinical studies. For example, in patients undergoing mechanical ventilation, the brand of nebulizer, humidification, ventilator settings, and nebulizer volume fill are factors that can be optimized in vitro before proceeding to clinical studies.[27,28]

Because pulmonary anatomy is an important determinant of drug deposition, in vitro studies are a useful adjunct but not a substitute for clinical deposition studies. Clinical deposition studies are used to acquire two types of data: quantization of the mass of an inhaled drug deposited in the patient and an evaluation of regional distribution in the patient. Deposition can be divided into extrapulmonary deposition versus pulmonary deposition, whereas pulmonary deposition can be further subdivided into deposition in central airways versus peripheral airspaces. Gamma scintigraphy can be used to acquire both types of data. A radiotracer (usually technetium) is mixed with the study drug and aerosolized and inhaled. The drug deposition images on the gamma camera are superimposed on an outline of the patient's lung (obtained by a separate radioactive gas study[22,30] or a transmission image from an external standardized radioactive source[31]). Quantification of lung deposition can be obtained by expressing the radioactivity detected in the lungs to the radioactivity charge in the nebulizer. One must correct for the attenuation of radioactivity by the patient's body habitus using the transmission image. It is

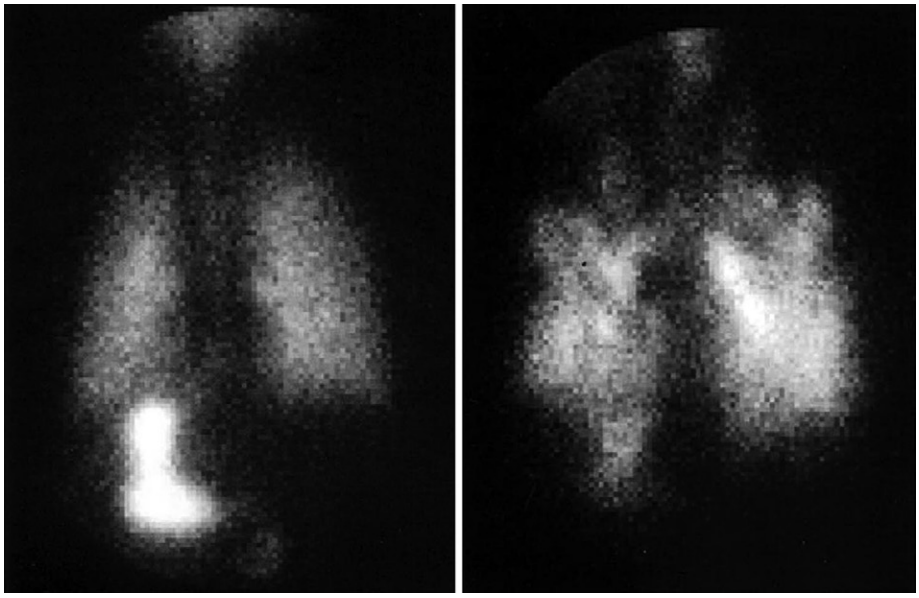

FIGURE 12-3 ■ Scans from patients with cystic fibrosis: *Left,* A 9-year-old boy with 48% upper airway (stomach) deposition. *Right,* A 31-year-old woman demonstrating a more peripheral but patchy distribution. (From Diot P, Palmer LB, Smaldone A, et al: RhDNase I aerosol deposition and related factors in cystic fibrosis. Am J Respir Crit Care Med 156:1662–1668, 1997, with permission.)

also necessary to confirm with a cascade impactor that the distribution of radiotracer and drug is identical throughout the range of particle sizes.[27]

There are other methods of measuring drug deposition that do not require gamma scintigraphy. A mass balance technique uses filters placed near a patient's mouth to measure the first amount inhaled and the amount exhaled, with the difference being what was deposited in the patient.[22,30] Pharmacokinetic approaches include comparison of blood levels of aminoglycosides obtained after an intravenous calibration standard to blood levels obtained after inhalation[32] or the urinary concentrations of pentamidine after inhalation.[33,33a] Oral charcoal can be used to block the absorption of swallowed pharyngeal deposited drug so that blood levels will be due entirely to drug absorbed through lung deposition and absorption.[14]

STRATEGIES TO OPTIMIZE DEPOSITION OF THERAPEUTIC AEROSOLS[19]

The determinants of aerosol deposition apply to both therapeutic and environmental inhaled particles. To optimize deposition of therapeutic aerosols, a number of strategies have been developed based on these principles, which are now discussed.

Getting Particles Past the Oropharynx

In clinical studies, predicting penetration of aerosol beyond the oropharynx and subsequent lung deposition is a major criterion for device selection. Deposition estimations are often based on particle size measurements defined by in vitro characterization of the aerosol produced by a given device. During tidal breathing, most investigators would expect aerosols below 5 μm to be deposited primarily in the lungs (the "fine particle fraction"). Conventional aerosol delivery devices (jet nebulizer, pressurized MDI, and dry powder inhaler) emit particles with a wide range of sizes and velocities. It is estimated that the combined effect of particle size, particle inertia, and the geometry of the oropharynx result in upper airway deposition ranging from 30% to 90% of the total deposition in the patient. Only nebulizers producing particles with particularly small MMAD (e.g., AeroTech II, Biodex, Shirley, NY; MMAD, 1.0 μm) bypass the upper airways (5% oropharyngeal deposition in adults).[34] In children, the smaller oropharyngeal airways make the task more difficult.[35] Thus, the demands placed on traditional devices can be overwhelming if the drug must efficiently bypass the upper airways (Fig. 12-3).

Control of Breathing Pattern and Aerosol Deposition

In normal subjects, the pattern of breathing is the most important factor affecting aerosol delivery and deposition. How the patient breathes affects the performance of the device, the penetration of particles past the oropharynx,and the deposition within the parenchyma. Earlier studies suggested that much of the variation in parenchymal deposition was related to differences in airway geometry between subjects. However, variability in deposition between subjects appears well controlled if the pattern of breathing is controlled. Figure 12-4 depicts data from 11 subjects inhaling 2.6-μm monodisperse particles. The fraction of particles depositing in the lung can be closely related to the period of breathing. In simplified form, points near the origin of the horizontal

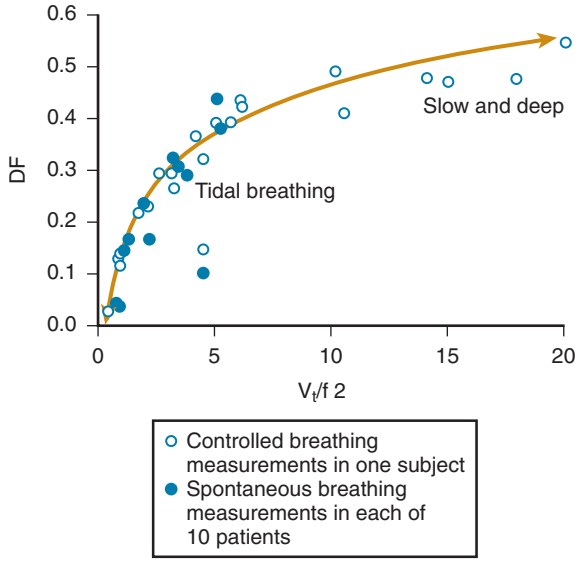

FIGURE 12-4 ■ Effect of breathing pattern on deposition; from 1 subject during controlled breathing (*filled circles*); from 10 patients during spontaneous breathing (*open circles*; data for 2.6-μm monodisperse particles). Breathing pattern was defined by a relationship that represents a measure of the period of breathing (tidal volume divided by breathing frequency squared or V_t/f'^2). Typical "tidal breathing" parameters found near origin, "slow and deep" inspirations away from the origin. (Modified from Bennet WD, Smaldone GC: Human variation in the peripheral airspace deposition of inhaled particles. J Appl Physiol 62:1603–1610, 1987, with permission.)

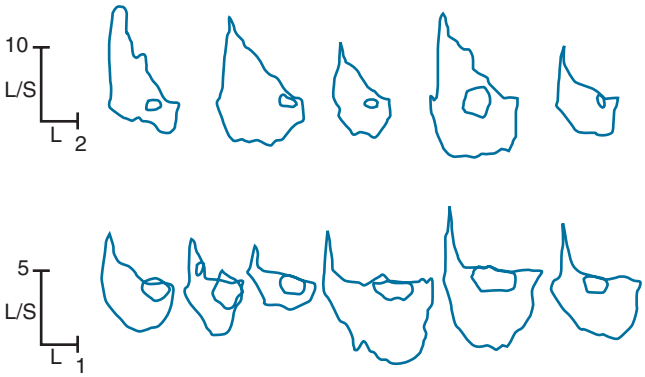

FIGURE 12-5 ■ Tracings of maximal flow and tidal flow versus volume for normal subjects (*upper panel*) and patients with severe obstructive lung disease (*lower panel*). Note the change in the sensitivity of the axes (ordinate: flow range from 0–10 or 0–5 L/S; abscissa: volume range from 0–2 or 0–1 L, respectively). *Lower panel*, For the patients, tidal loops are superimposed on maximal flow volume curves. (Modified from Smaldone GC, Messina M: Flow-limitation, cough and patterns of aerosol deposition in humans. J Appl Physiol 59:515–520, 1985, with permission.)

axis represent normal tidal volumes and frequencies. As tidal volume increases and breathing frequency decreases, the time of inspiration is prolonged (e.g., "slow and deep inspiration"). The curve depicted in Figure 12-4 represents maximum deposition with a slow and deep inspiration for particles of 2.6 μm. The curve would be shifted upward with deposition approaching 100% for larger particles.

Expiration and Problems with Aerosol Deposition

In normal subjects, those particles that do not deposit during inspiration are largely exhaled completely. Particles that pass through the oropharynx during inspiration enter the central airways and traverse them without difficulty because lobar and segmental bronchi are generally widely patent during inspiration. Then the particles enter alveoli with a few depositing by sedimentation, and like cigarette smoke, the bulk of the aerosol begins to be exhaled. Deposition is controlled by sedimentation in small airways and is influenced by local geometry and, to a strong degree, by the residence time (period of breathing).

In obstructive lung disease, maximal expiratory flows are diminished. With moderate disease, maximal flows can be superimposed on tidal breathing; as the disease progresses, maximal flows can be reduced even further. Therefore, it is common to observe that patients are often breathing on their maximal expiratory flow volume curves even during quiet tidal breathing[36] (Fig. 12-5). In these patients, flow-limiting segments exist in the same airways found in normal subjects during forced expiration, but in these patients, they form during every tidal breath. In patients with obstructive lung disease, the promotion of deposition in the peripheral lung poses a significant challenge as deposition of aerosol is enhanced during expiration at sites of flow limitation (Fig. 12-6). Based on these physiologic considerations, peripheral deposition of aerosol in these subjects would be favored by using a system that combines a slow prolonged inspiration (to promote deposition by settling) with a breath of long enough duration to minimize the particles available to the airways during expiration.

For many aerosol applications, inhaling particles "slowly and deeply" solves the problems outlined previously. A slow inhalation will minimize oropharyngeal deposition. "Slow" inspiration reduces particle inertia and allows inhalation of larger particles that would have deposited in the oropharynx during tidal breathing. This concept has been exploited in physiologic studies of mucociliary clearance in the distal airways utilizing particles as large as 6 μm.[37] More recently, commercial applications of these principles have combined slow and deep inspiration with direct mechanical feedback to the patient for particles of relatively large MMAD, resulting in more efficient delivery to the more distal airways (Fig. 12-7).[38]

Deposition and Dose versus Response[39–41]

For conventional bronchodilators and steroids, the dose and response are not critical for clinical efficacy because most delivery systems provide drug to the patient on the flat portion of the dose-response curve. Safety of most preparations is enhanced because of the high potency of most drugs and a high threshold for toxicity. The

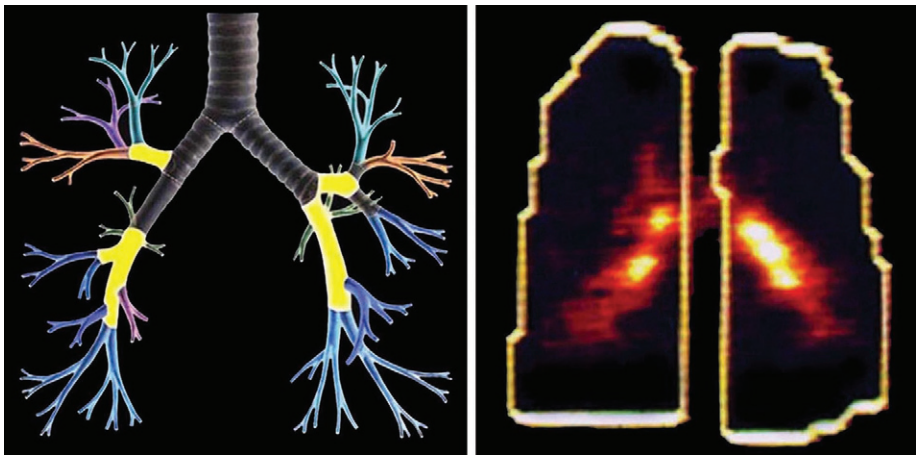

FIGURE 12-6 ■ Sites of flow-limiting segments in humans (*left panel*), corresponding deposition image in patient with severe chronic obstructive pulmonary disease (COPD; posterior view) with maximal expiratory flow volume curve superimposed on tidal loop (as shown for patients in *lower panel* of Figure 12-5). Particle deposition occurs preferentially at sites of flow-limiting segments. (Redrawn from Smaldone GC: Advances in aerosols: Adult respiratory disease. J Aerosol Med 19:36–46, 2006, with permission.)

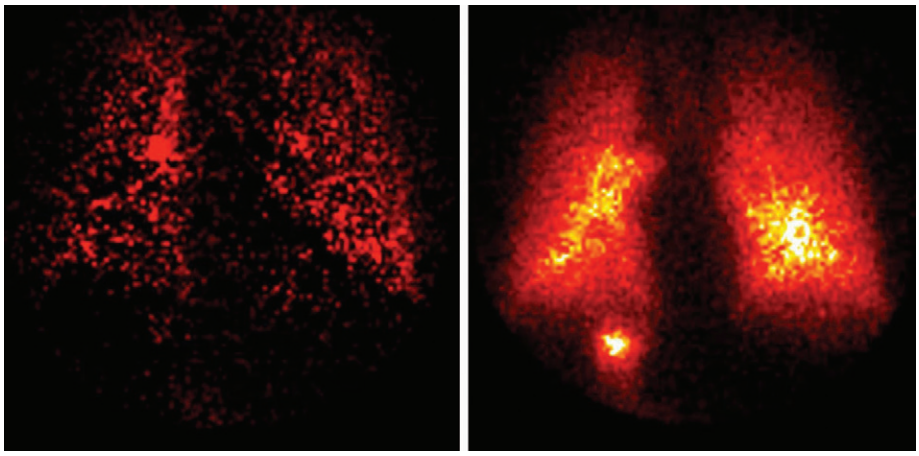

FIGURE 12-7 ■ Effect of slow and deep breathing on aerosol delivery and deposition. Deposition scans from normal subject following breathing from I-neb, a breath-actuated vibrating nebulizer (particles generated only during inspiration): *Left,* Following 20 breaths of normal tidal breathing. *Right,* Scan repeated after 3 breaths of very slow and deep inspiration (~7 sec/breath, see Fig. 12-1). For slow and deep breathing, deposition was 50 times more efficient per breath, a combination of enhanced delivery and more efficient deposition (unpublished data).

situation for bronchodilators and steroids may not carry over to newer drugs. For example, aerosolized cyclosporine used in the treatment of lung transplant rejection has recently been shown to significantly reduce mortality.[39] In vivo measurements of deposition have been related to clinical effects (dose vs. response). Figure 12-8 shows gamma camera images of individual patients from an early study assessing the effects of inhalation of aerosolized cyclosporine aerosol.[40] Analysis of cyclosporine deposition was related to clinical effects as shown in Figure 12-9. After institution of aerosolized cyclosporine therapy in patients with persistent acute rejection, pulmonary function improved (after 3 mo of therapy) as illustrated by increases in forced inspiratory volume in 1 second (FEV_1). However, there was a suggestion of a dose-response relationship with those patients receiving less than 20 mg of drug per allograft having minimal response.[40] A similar situation will exist for systemically absorbed drugs such as insulin where the dose to the lung parenchyma will be critical in patient management. Although clinical studies have shown that aerosolized cyclosporine appears to be effective overall in a population of patients,[39] the data from individual patients in Figure 12-9 suggest that conventional aerosol delivery systems leave some patients at risk for inadequate dosing, while others may be overdosed and exposed to potential toxicity.

ADDITIONAL FACTORS INFLUENCING DEVELOPMENT OF THERAPEUTIC AEROSOLS

In addition to efforts to bypass the oropharynx and optimize lung deposition, other factors influence the design

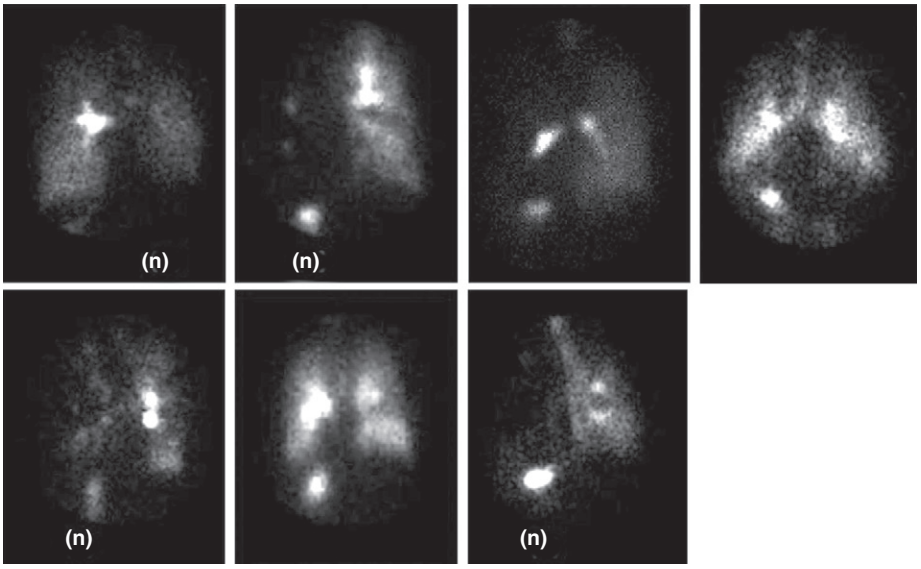

FIGURE 12-8 ■ Deposition of aerosolized radiolabeled cyclosporine aerosol. Lung images from seven patients with single- or double-lung transplants ("n" indicates native lungs). There was considerable variation in regional particle deposition (data from these images applied to Figure 12-9). (Modified from Smaldone GC: Advances in aerosols: Adult respiratory disease. J Aerosol Med 19:36–46, 2006, with permission.)

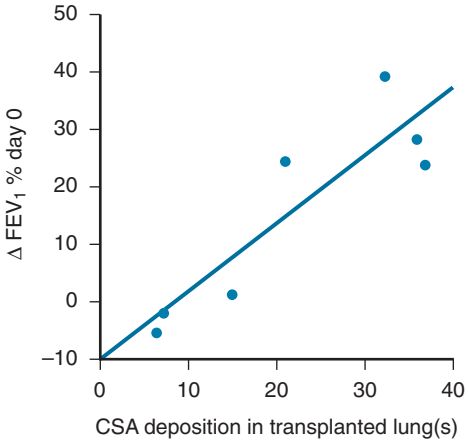

FIGURE 12-9 ■ Effects of aerosolized cyclosporine on airway function in transplant rejection. Change in spirometry (assessed by changes in FEV_1 (Δ FEV_1 %Day 0), from the initiation of aerosol cyclosporine to approximately 200 days of therapy, as a function of cyclosporine deposited in transplanted lung(s). (Redrawn from Iacono AT, Smaldone GC, Keenan RJ, et al: Dose-related reversal of acute lung rejection by aerosolized cyclosporine. Am J Respir Crit Care Med 155:1690–1698, 1997, with permission.)

of therapeutic aerosols. Some of these factors are disease related and others relate to specific populations.

Asthma[41–45]

One of the most important features of the commercial formulations of inhaled corticosteroids, the mainstay of maintenance therapy of asthma, is reduced oral bioavailability.[41–43] Many delivery systems for inhaled corticosteroids have high levels of oropharyngeal deposition (up to 80% with pressurized MDIs and dry powder inhalers), and it is crucial that when this oropharyngeal deposited drug is subsequently swallowed, its systemic exposure be kept as low as possible. The oral bioavailability of beclomethasone as one the oldest of the inhaled corticosteroids is about 20%, fluticasone is about 1%, and mometasone less than 1%. A newer drug, ciclesonide, does not become activated until it deposits in lung tissue.[43] However, even if there is no oral bioavailability, systemic exposure can still occur because of inhaled corticosteroids being absorbed directly into the lung after deposition. It appears that alveolar deposition may give rise to more systemic exposure because particles depositing in ciliated airways are subject to mucociliary clearance and because the barrier to diffusion may be more permeable in the alveolar air spaces than the airway. There are some pharmacodynamic data that suggest when fluticasone is administered to both normal subjects and asthmatics, the normal subjects are more susceptible to hypothalamic-pituitary-adrenal (HPA) axis suppression. This finding is most likely due to the more proximal deposition in the asthmatic subjects because of reduced airway caliber.[44] Most pharmaceutical manufacturers have therefore tried to target airway deposition over alveolar deposition. This appears reasonable because asthma is thought to be an airways disease. Some investigators, however, have suggested that there may be an alveolar inflammatory component in asthma, thus suggesting that alveolar deposition may be beneficial.[45] Nonetheless, this remains a minority viewpoint. Targeting of the airways in asthma is complicated by the polydisperse nature of therapeutic aerosols. Making average aerosol diameter smaller reduces oropharyngeal deposition but increases the amount of alveolar deposition. A low oral bioavailability is more important for polydisperse aerosols with larger MMADs in order to minimize systemic exposure from swallowed drug. Systemic exposure to inhaled corticosteroids can lead to

short-term growth suppression in children, decreases in bone mineral density, and possibly an increase in cataracts.[41–43] Whereas the potential role of inhaled corticosteroids in prevalence of cataracts is confounded by concomitant use of intermittent systemic corticosteroids, smoking, and ultraviolet light exposure,[46] an epidemiologic study from Australia that controlled for use of systemic and ocular steroid use found an association between inhaled steroids and the prevalence of cataract.[47] Cataracts could be theoretically due to inadvertent spraying of aerosol into the eyes in addition to systemic exposure.

While the search continues for the ideal method of delivery for inhaled steroids to patients with asthma, advances in drug design, formulation, and delivery now provide a wider array of options to the clinician. However, no delivery system can be considered to be intrinsically superior to all others. The delivery system should be judged instead by its ability to optimize the pharmacokinetic properties of the drug, most notably oral bioavailability, and by its suitability for the target subpopulation of asthmatics.[4]

Cystic Fibrosis

Antimicrobials are inhaled for the treatment of cystic fibrosis, for example, tobramycin, aztreonam, and polymyxin. Antibiotics usually require the aerosolization of several hundred milligrams of medication. Jet nebulizers or vibrating mesh devices are usually required to deliver such a large mass of medication. Aminoglycosides, when given systemically, have poor penetration and are limited by renal and ototoxicity. Inhalation of tobramycin, for example, can result in sputum levels two orders of magnitude higher than those associated with systemic delivery. For the purposes of inhalation, tobramycin was reformulated without the preservative present in the intravenous preparation.[48] Aztreonam was reformulated with a lysine side chain for inhalation instead of the methionine side chain found in the intravenous formulation, in order to reduce the risk of airway irritation.[49]

For patients with cystic fibrosis, antimicrobials and mucolytics (recombinant DNase and hypertonic saline) have been shown to be of benefit.[50] The multiplicity of inhaled treatments, however, is likely to have a negative impact on patient adherence and therefore creates the need to explore the use of devices with shorter treatment duration in order to improve adherence.

Delivery of Inhaled Medications to Young Children

Asthma is common in children and delivery of aerosols poses special challenges. The need for cooperation and coordination with breathing pattern and the need to generate a threshold inspiratory flow in children means that those younger than 4 years old cannot use a dry powder inhaler. Children 6 years and older can use a pressurized MDI, but under that age, a pressurized MDI should be used in association with a valved holding chamber because children have difficulty coordinating actuation with the respiratory cycle.[51] Face masks can be incorporated with holding chambers and jet nebulizers for children younger than 4. After age 6 years, children can be taught how to use a pressurized MDI without a spacer, although the use of spacers should continue to be encouraged.

For young children with asthma, nebulized treatment with a suspension of budesonide is an effective and well-tolerated alternative.[52] It should be noted that nebulizers tend to be less effective at aerosolizing suspensions than solutions, and clinicians are advised to prescribe budesonide only with the brand of nebulizers used in the clinical trials of this product.

Young children usually require a face mask to be used with either a nebulizer or a valved holding chamber. Recent studies suggest that clinically relevant in vitro modeling should include mimicking a child's breathing pattern and placing the face mask on a model of a child's face.[53] Using such a model, nebulizers appear to result in less variability in inhaled mass compared with the valved holding chamber. For a pressurized MDI used with a valved holding chamber, leaks around the face mask limit the exchange of tidal air with air in the chamber, thereby reducing the inhalation of aerosol by the patient. For nebulizers operated with compressors, the face mask can be kept filled with particles in spite of leaks because the compressor flow can exceed the minute ventilation of the child.[54] However, the very leaks that may preserve delivery to nebulizers result in deposition of drug on the face and in the eyes.

Recent experiments have indicated that deposition on the face and particularly in the eyes can be minimized if masks are designed such that linear velocity in the region of the leaks near the bridge of the nose is reduced. As can be seen in Figure 12-10, with such a modified face mask, deposition on the eyes and face was markedly reduced, while drug delivery to the patient (*inhaled mass*) was preserved.[53] Subsequent in vivo experiments confirmed the model's predictions[55] (Fig. 12-11). Even though the incidence of cataract in children receiving inhaled corticosteroids is very low, there is epidemiologic evidence linking inhaled steroid use in adults to an increased risk of cataract.[47]

Delivery of Therapeutic Aerosols to the Nasal Mucosa[56–58]

Corticosteroids, antihistamines, cromoglycate, and decongestants are inhaled nasally to treat rhinitis. These formulations use large particle sizes to maximize nasal deposition. For children who use inhaled corticosteroids for perennial rhinitis, formulations with low oral bioavailability such as fluticasone, mometasone, and ciclesonide are preferable to reduce the risk of growth suppression.

Among an increasing list of aerosolized medications that are being used to treat diseases of the nasal mucosa are corticosteroids, cromolyn, anticholinergics (ipratroprium bromide), saline, and decongestants. The particle

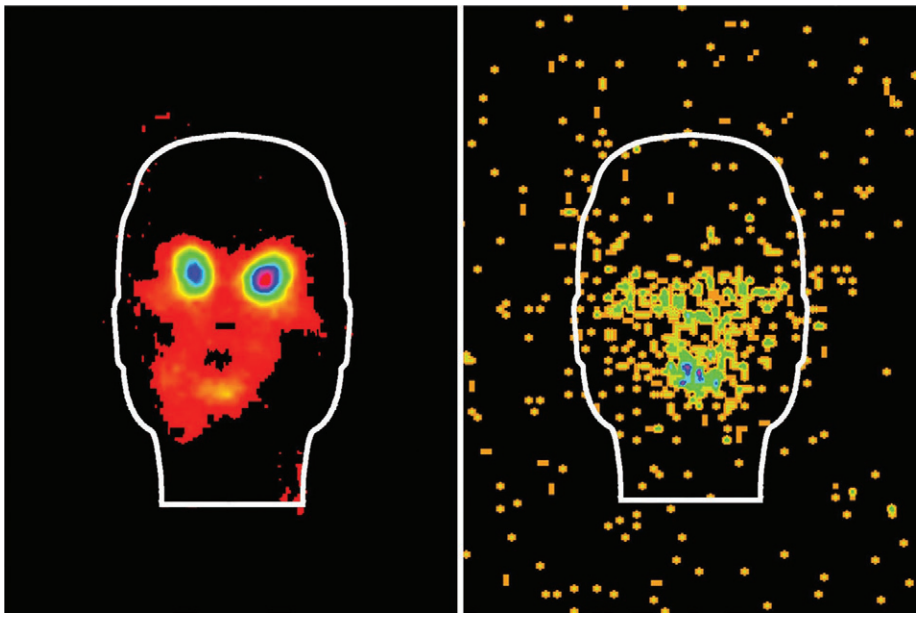

FIGURE 12-10 ■ In vitro example of facial and eye deposition during aerosol therapy: *Left,* Facial and eye deposition following nebulizer treatment with Pari nebulizer and tight-fitting face mask. *Right,* Reduced deposition with the same nebulizer and prototype face mask designed to reduce particle acceleration in the region of the eyes. (Modified from Smaldone GC: Assessing new technologies: Patient-device interactions and deposition. Respir Care 50:1151–1160, 2005, with permission.)

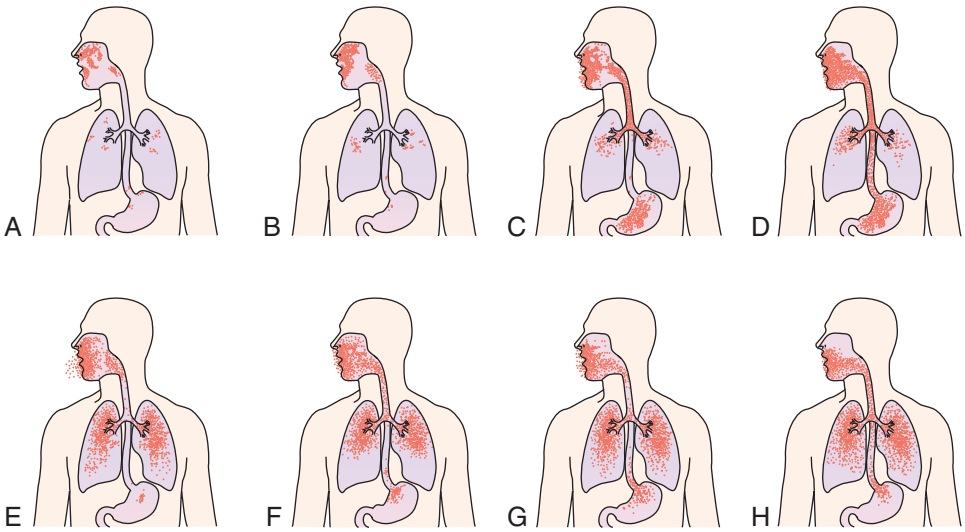

FIGURE 12-11 ■ Drug deposition of radiolabeled salbutamol in a young child: **A,** Inhaling from a pressurized metered dose inhaler/spacer through a non-tightly fitted facemask. **B,** Inhaling from a nebulizer through a non–tightly fitted face mask. **C,** Inhaling from a pressurized metered-dose inhaler/spacer through a tightly fitted face mask, screaming during inhalation. **D,** Inhaling from a nebulizer through a tightly fitted face mask, screaming during inhalation. **E** and **F,** Inhaling from a pressurized metered-dose inhaler/spacer through a tightly fitted face mask, quietly inhaling. **G** and **H,** Inhaling from a nebulizer through a tightly fitted face mask, quietly inhaling. Deposition on the face is apparent especially for the tight-fitting masks. (A-H, Redrawn from Erzinger S, Schuepp KG, Brooks-Wildhaber J, et al: Facemasks and aerosol delivery in vivo. J Aerosol Med 20(Suppl):S78–S84, 2007, with permission.)

size of nasal aerosols tends to be larger than pulmonary inhalers. Manual pumps that produce large, relatively low velocity particles are being used as an alternative to high-velocity, freon-based pressurized MDIs. There are isolated reports of nasal perforation occurring with high-velocity inhalers,[56] and patients should be advised to direct the spray in the direction of the ipsilateral ear and away from the nasal septum. In addition, actuating the inhaler against the lateral wall of the nares reduces the risk of epistaxis (caused by irritating the septum by medial orientation) or headache (caused by stimulating the olfactory nerve by a vertical delivery. In severe allergic sinusitis, the mucosa may be so congested that a short course of systemic corticosteroids may be needed

to allow penetration of aerosolized therapy. Prolonged use of topical decongestant sprays may lead to rebound hyperemia and intractable nasal congestion. In certain cases, systemic administration of decongestants may be preferable.

Intranasal corticosteroids are an effective therapy for seasonal and perennial rhinitis. While regular use of such an agent has been shown to lead to short-term growth suppression in children, it appears that this complication can be prevented by the use of a formulation with a low oral bioavailability (e.g., mometasone).[57,58]

Aerosol Delivery during Mechanical Ventilation[27,28,59–61]

Bronchodilators are used to treat patients with airway obstruction as they undergo mechanical ventilation. There is also interest in delivering topical antimicrobial therapy in patients with purulent tracheobronchitis. The dose delivered to this setting can be highly variable and subtherapeutic delivery can occur without optimizing certain factors. Humidification (temporary discontinuation of humidification doubles delivered dose through reduced rain out of medication), coordination with respiratory cycle, and the appropriate selection of delivery system can impact delivered dose. If optimized, consistent delivery can occur at doses that approximate those delivered in spontaneously breathing subjects.[27,28] Using such optimized delivery techniques in critically ill patients with ventilator-associated tracheobronchitis, aerosolized antibiotics decrease ventilator-associated pneumonia and other signs and symptoms of respiratory infection, facilitate weaning, and reduce bacterial resistance and use of systemic antibiotics.[59]

Aerosolized β-sympathomimetic agents are an essential component of the treatment of status asthmaticus. Such delivery is complicated if the patient is undergoing mechanical ventilation. Recent studies, however, have identified ways in which such delivery can be optimized. The use of pressurized MDI is feasible provided certain conditions are met.[60] For example, it is necessary to use a spacer/holding chamber when using a pressurized MDI in this setting. Not all holding chambers are equivalent in efficiency and different brands are not necessarily interchangeable. In contrast to the treatment of spontaneously breathing patients, delivery during mechanical ventilation must be synchronized with respiration. It is essential that a dose-escalation protocol be employed because doses far in excess of those used for maintenance therapy may be needed. Hence, efforts to obtain objective evidence on response to treatment (e.g., peak airway pressure, dynamic compliance) and toxicity (tachycardia, arrhythmias) should be sought. In endeavoring to maximize delivered doses, however, it must be remembered that the efficiency of pressurized MDI delivery decreases significantly if the interval between serial actuations is less than 1 minute and if the synchronization with the respiratory cycle is suboptimal.[61]

In conclusion, once technical factors have been identified and optimized, efficient delivery of aerosolized medications to patients undergoing mechanical ventilation is readily attainable.[28]

DIAGNOSTIC RADIOAEROSOLS

In this chapter, we primarily discuss the use of radioaerosols as research tools to measure lung deposition and mucociliary clearance. However, radioaerosols are also used in clinical practice.

The radiolabeled ventilation-perfusion scan is an important clinical tool for detection of pulmonary emboli. Perfusion is measured by injecting radiolabeled macroaggregates of protein that impact in capillaries while ventilation is evaluated by a radioactive gas or aerosol. Discrepancies between perfusion abnormalities and ventilation abnormalities are used to assess pulmonary emboli. The measurement of ventilation should ideally be performed by the use of radioactive gas (xenon or krypton). However, the use of these agents has significant disadvantages. Xenon has a relatively long half-life and needs to be trapped after exhalation. Krypton, in contrast, has a very short half-life and per-patient costs are high. In response to these concerns, technetium-labeled aerosols were developed on the assumption that if ventilation were absent from a lung region, then aerosol deposition would not occur in that region. In general, that assumption is true if submicron aerosols are inhaled, but it must be remembered that aerosol behavior is not identical to that of a gas.[62] For example, patients who are tachypneic with high inspiratory flows and who have airway obstruction will have central "hot spots" due to deposition by impaction.[36] This limits the use of these techniques in certain patient groups.

MUCOCILIARY CLEARANCE AND DISEASE

Inhaled particles that deposit in the ciliated airways are trapped in a blanket of mucus. Mucus is transported proximally by the rhythmic beating of the cilia (a fast, forward-power stroke and slower, backward-recovery stroke) to the pharynx where it is swallowed, a process called "mucociliary clearance."[3] The percentage of ciliated respiratory epithelial cells is highest in the tracheal and lobar bronchi and decreases progressively in more distal airways. Secretory cells are also more numerous in proximal airways. Goblet cells produce thick carbohydrate-rich secretions, while other cells produce more serous secretions. Diseases such as chronic bronchitis and bronchiectasis are associated with increased numbers of goblet cells in more distal airways. Airway secretions are also produced by submucosal glands. The latter are lined by mucinous and serous epithelial cells and become hypertrophic and hyperplastic in chronic bronchitis and other types of chronic airway inflammation.

Secretory dysfunction is common in many diseases but the pathophysiology of the dysfunction varies signifi-

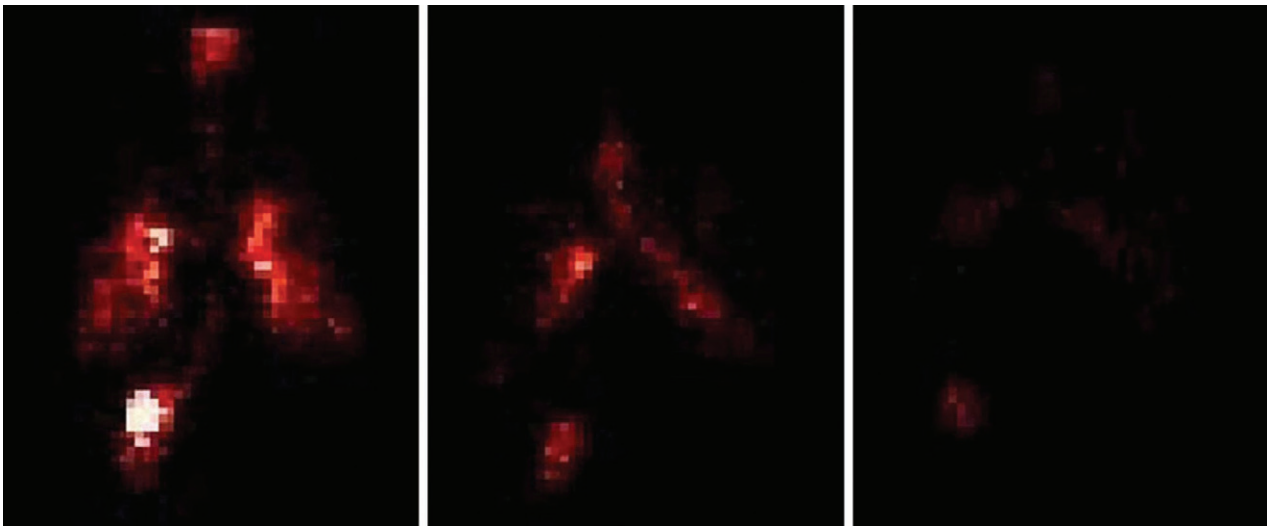

FIGURE 12-12 ■ Mucociliary clearance measured with the gamma camera. Serial scintigraphic images of the lungs, airways and oropharynx. *On the left* at 0 min, central airways activity is apparent (note esophagus and stomach outlined from swallowed oropharyngeal deposition), 60- and 120-min images seen (*middle* and *right*), most activity is cleared from the lungs in 120 min.

cantly. Mucociliary clearance can be impaired by intrinsic defects in ciliary function, which can be congenital (ciliary dyskinesias) or acquired (tobacco-smoking, influenza). Mucociliary clearance impairment can also be due to changes in the quantity and composition of airway secretions (chronic bronchitis, cystic fibrosis). When the mucociliary apparatus is significantly impaired, secretions can be cleared predominantly by cough clearance.

Mucociliary clearance in healthy subjects is usually completed within 24 hours of deposition.[3] The mucous path can be followed using radiolabeled aerosols (Fig. 12-12). Particles that deposit on ciliated airways containing ^{99m}Tc, bound to a molecule that prevents absorption into the circulation, will follow the clearing mucus. Particles deposit in proximal airways by inspiratory impaction (larynx, main stem, lobar and segmental bronchi). Extrapulmonary deposited particles will be swallowed and appear in the gamma scintigraphy as stomach "hot spots" overlying the left lower lung field. The interpretation of mucociliary clearance studies is complex and, in order to compare rates of mucociliary clearance between subjects or even to compare a series of studies in one subject, it is essential to consider a number of important variables.

The most important parameter affecting the rate of mucociliary clearance in healthy subjects is the initial pattern of particle deposition. We have already discussed the factors that determine this pattern and how it can be quantified (e.g., the specific central-to-peripheral ratio). The relevance of the initial pattern is that particles that are deposited in the central airways will be cleared more rapidly into the pharynx than more distally deposited particles. Therefore, if a normal subject with a central pattern of deposition is studied, the rate of mucociliary clearance will be faster than if it had been studied using a more peripheral initial deposition pattern. In addition, the fastest rates of mucous transport in normal subjects are believed to be in the trachea with a progressive decrease through more distal generations with the most peripherally deposited particles in the alveolar region not accessible to mucociliary clearance. Based on these principles, for data to be compared between studies, the initial pattern of deposition must be standardized.

Primary ciliary dyskinesia is a congenital disorder of the dynein arms of the cilia.[3] The normal cilium has nine pairs of dynein peripheral arms and two central pairs. Each pair consists of an inner and outer dynein arm. A variety of defects result in loss of the ciliary movement. The normal ciliary beat has a rapid forward stroke and a slower return stroke. In the absence of the ciliary movement, there will be mucous stasis and these patients develop bronchiectasis and sinusitis. In males, this can also lead to infertility due to immotile spermatozoa. There are associated abnormalities of visceral organs, situs inversus, and dextrocardia.

Cystic fibrosis, the most common fatal single gene genetic disease in Europe and North America, is associated with severe bronchiectasis.[3] The most persuasive causative theory is that the mucus is dehydrated and less easy to clear because of defective chloride channel (cystic fibrosis transmembrane receptor).[63] Hypertonic saline, when administered to the airways of patients with cystic fibrosis, creates an osmotic gradient that draws water into the airway lumen. Trials are underway to see if blocking epithelial sodium channels in the presence of hypertonic saline could increase water content of mucus. Epithelial sodium channel blockers are analogues of the amiloride molecule. While inhaled amiloride can block epithelial sodium channel receptors, its brief half-life at the airway epithelium limits its clinical effectiveness and leads to a search for newer agents with more favorable pharmacokinetics. Alternatively, stimulation of calcium-dependent chlorine channel with uridine triphosphate analogues can also increase airway hydration. The airway secretions in cystic fibrosis not only contain mucus secreted by the airway but also consist, predominantly,

of DNA and actin from dead neutrophils and recombinant DNase, administered by inhalation to facilitate clearance of secretions.

In chronic bronchitis. there is hypertrophy and hyperplasia of the submucosal glands as well as an increase in the number of goblet cells and the presence of goblet cells in more distal airways compared to normal. It appears that the mucous versus serous component increases and exacerbates the solid phase increases even more. This in effect means that the mucous layer is relatively dehydrated.[63,64]

In patients who die of status asthmaticus, the airways at autopsy are filled with inspissated mucus. Clearance of radiolabeled mucus is severely impaired in patients with status asthmaticus but recovery of mucociliary clearance occurs within weeks.[65]

Impairment of radiolabeled mucociliary clearance may be an index of disease severity in asthma,[65,66] chronic obstructive pulmonary disease (COPD),[67] and cystic fibrosis.[68] Serial measurements of mucociliary clearance can be useful in measuring pharmaceutical enhancement of mucociliary clearance both acutely and at a steady state, for example, the acute and sustained effects of hypertonic saline in cystic fibrosis.

In conclusion, mucociliary clearance is impaired in asthma, chronic bronchitis/COPD, cystic fibrosis, non–cystic fibrosis-bronchiectasis, and primary ciliary dyskinesia. Cough clearance augmented by physical therapy and other mechanical interventions (flutter valves, vibration vests) provides some treatment, but pharmaceutical interventions are limited. In asthma, there is improvement in mucociliary clearance and in sputum volume using guafenesin, but the data are sparse. In cystic fibrosis, benefits of DNAse are based on clinical data not mucociliary clearance.[50,69] β-Agonists increase mucociliary clearance after a single dose, but sustained enhancement on mucociliary clearance with β-agonists has yet to be demonstrated.[69] The epithelial sodium channel inhibitors show promise but clinical benefits are yet to be proven.[62,63]

ALVEOLAR CLEARANCE

Particle solubility affects clearance in alveoli. Soluble particulates may be absorbed through the thin membrane of the peripheral air spaces.[3,70,71] Insoluble particulates, however, tend to be phagocytosed by alveolar macrophages. Their metal content influences the free radical generating properties of the particle and can promote inflammation, especially as the particle is delivered to the lysosomes. Lysosomes have a very low pH designed to kill microorganisms but the low pH may promote solubility of transition metals such as ferrous iron and therefore be proinflammatory.

Responses to preexisting inflammation may be important because cells that are primed by one type of inflammation (e.g., by tobacco smoke or endotoxin) may be more reactive to a second stimulus from an inhaled particulate. Inhaled dose is important and excessive exposure can lead to overloading of alveolar macrophages, which can be proinflammatory even with relatively nonreactive particulates.[71] Macrophages migrate to regional lymph nodes and some particles are characterized by a distinctive adenopathy (e.g., silicosis and its eggshell calcifications).

ENVIRONMENTAL AEROSOLS

An appreciation of the principles of aerosol deposition and clearance is essential to both understanding the epidemiology of illness associated with exposure to environmental aerosols and in the development of rational strategies to reduce the impact of those exposures. This is a complex subject that overlaps with topics covered in several other chapters in this book. The impact of exposure to an aerosol depends on a number of factors, some of which are self-evident, and others that are less apparent. These factors include the total mass of particulates in the air, the size distribution, the shape and surface area of particles, the chemical composition of the particles, the level of ambient turbulence, the airway anatomy and breathing patterns of exposed individuals, and the immune response to inflammatory or infectious agents.[71,72] Exposure of rodents to high doses of low-toxicity, poorly soluble particulates results in pulmonary inflammation,[72] and impairment of alveolar clearance,[73] and an increased tendency to develop tumors.[72] It is, however, not yet clear if it is appropriate to extrapolate from high-dose rodent exposures to the determination of rational exposure thresholds for humans.[72] Unfortunately, it appears that in vitro exposure of cell cultures to environmental particulates correlates poorly with in vivo animal exposures.[74,75]

In December of 1952 in London, England, 4000 excess deaths were attributed to smog. This disaster had a huge impact on public health policy and led to efforts to reduce the impact of air pollution. At the time, it was assumed that it was the total concentration of particulates that was the most important determinant of mortality. However, retrospective analysis of stored autopsy specimens suggested that exposure to fine particulates and metals may have been more important than the total mass of exposure.[76] The increased emphasis on particle size was supported by a series of urban epidemiologic studies that found correlations between daily concentrations of particulates and mortality. Using data from urban sampling devices that can measure the amount of particles less than 10 μm in diameter (PM_{10}), it was demonstrated that even small increases in PM_{10} produced an increase in acute death rates.[77] Interestingly, it was cardiovascular deaths that seemed to dominate over respiratory death, leading to speculation that the deposition of particles in the lung could activate proinflammatory cascades. Later studies, using even more sophisticated samplers, found a correlation between mortality and fluctuations in the $PM_{2.5}$, fine particles less than 2.5 μm in diameter.[78] More recent research has focused on even smaller particles between 1 and 100 nm.[79] When these occur in the atmosphere, usually as result of combustion, they are referred to as ultrafine particles. When they are

manufactured in the semiconductor, pharmaceutical, or chemical industries, they are referred to as nanoparticles, even though their dimensions are also 1 to 100 nm. In contrast to ambient ultrafine particles, which tend to be polydisperse, nanoparticles are more monodisperse. Measuring particle size distributions in the nano spectrum requires more sophisticated techniques than conventional particles. Spectrophotometry, atomic force microscopy, and complex light scattering techniques have been developed to make these measurements. As particles approach the nano range, their behavior can be very different from the same material in bulk. Both ultrafine and nanoparticles can deposit by diffusion, have a very high deposition fraction, and are small enough to pass between epithelial cells in the lung and cause systemic toxicity. Surface area may become more important than mass. Metals may lose their malleability and become hard. For example, titanium is a relatively inert and nontoxic substance when inhaled as a typical respirable aerosol (0.5–5 μm particle size) but exposure to titanium particles within the nano range result in marked cytotoxicity and proinflammatory effects in the lungs of rats. These effects have led to calls for tighter regulation of nanoparticle manufacture and distribution of nanomaterials.

Application of the principles of aerosol deposition can reduce exposure to infectious or toxic environmental aerosols. For example, dust mite fecal aerosols tend to be large and have a relatively rapid settling velocity.[80] However, the energy imparted by a ceiling fan can prolong their residence time and facilitate their inhalation; hence, asthmatic patients are advised to eschew the use of ceiling fans in their bedrooms. Pulmonary tuberculosis is an infection spread exclusively through the inhalation of infected droplet nuclei that are present in ambient air.[81] The placement of a face mask on patients with suspected tuberculosis would intercept cough-generated aerosols by impaction before they have the opportunity to dry and settle in the air where they can remain ambient for hours. Individuals who wish to avoid inhaling ambient infected tuberculous aerosols need to wear tight-fitting masks such that all their inspired air is filtered by the mask because the aerosols are small enough to follow the air stream and pass around loosely fitting masks. Most naturally occurring aerosols have sufficient large particles to be filtered by the nose and the branching structure of the large central airways. Some aerosols, however, pose particular dangers. Asbestos fibers, despite being relatively large, can deposit in small peripheral air spaces because their cylindrical structure allows them to follow the air stream to the lung periphery.[82] As discussed previously, ultrafine aerosols pose an additional danger if inhaled. They can pass between the protective epithelial cells of the lung and cause systemic toxicity. Deposition of environmental aerosols are affected by particle size and shape, but also by breathing pattern; generation of aerosols by workers who are performing manual labor and have increased inspiratory flow rates and minute ventilation can result in increased lung-deposited dose. While larger particles have low peripheral deposition, these particles can nevertheless be hazardous because of their mass. For example, after the attack on the World Trade Center, particles greater than 50 μm were deposited in peripheral air spaces because they were present in very high concentrations in the air for hours after the collapse of the towers. Consequently, New York City firefighters who responded to the disaster site on the day the towers collapsed had significantly higher rates of lung injury than those who reported on day 2.[83] The toxicity of inhaled inorganic particles is complex and beyond the scope of this text. Factors influencing toxicity include the metal content of particles, especially transitional metals such as iron, which may influence free radical generation. It has been suggested that free radical generation may be greater in particulates that are freshly generated before they are oxidized by the air, thus potentially increasing the danger to workers who grind inorganic material.[84]

The most important indoor toxic environmental aerosol is tobacco smoke, a topic covered elsewhere in this text. However, some of the principles of aerosol delivery and deposition are useful in explaining some of the epidemiologic associations with different types of cigarettes.[85,86] Despite marked differences in "smoking-machine" generated concentrations of tar, cigarettes marked as medium-tar, low-tar ("lite"), and ultralow-tar ("ultralite") are associated with similar incidences of lung cancer. (High-tar unfiltered cigarettes are associated with an even higher incidence of lung cancer.) The explanation for this paradox appears to lie in part with the standardized smoke generator (ventilation holes in the "lite" cigarettes that dilute the machine- generated smoke may be occluded by human lips). However, a more important factor may be that people tend to inhale the smoke of the "lite" cigarettes more deeply and deposit carcinogenic particulates in the more distal airspaces. This latter theory is supported by the observation of a relative increase in the incidence of more peripheral adenocarcinomas relative to more central squamous carcinomas following the introduction of "lite/ultralite" cigarettes to the U.S. market where they now hold an 80% market share.[86]

In conclusion, further progress in understanding of the role of environmental aerosols in health and disease will be dependent on the collaboration of several disciplines, and an appreciation of the principles of deposition and clearance by the participating investigators should facilitate interdisciplinary communication and cooperation.

KEY POINTS

- The likelihood that a particle will deposit in an airway depends on the physical characteristics of the particle, the gas flow transporting the particle, and the airway anatomy. The greater the mass, the faster the flow, and the more narrow the airway, the greater the potential for inertial impaction.
- Particle deposition by sedimentation is dependent on a subject's breathing pattern. Breath-holding before exhalation increases deposition by sedimentation.
- Holding chambers reduce pharyngeal deposition and reduce the need for precise coordination to get the full dose.
- Most traditional jet nebulizers are inefficient and deliver less than 10% of the drugs to the lung.
- In normal subjects, the pattern of breathing is the most important factor affecting aerosol drug delivery to the lungs.
- Making the average aerosol diameter smaller reduces oropharyngeal deposition but increases the alveolar deposition, which may increase systemic absorption.
- Compared to parenteral therapy, medicines can be delivered by aerosol in greater concentration to the target organ, the lung, with fewer side effects.
- Directing the jet of high-velocity nasal sprays to the ipsilateral side avoids the side effects of headache when directed vertically and epistaxis when directed medially.
- Mucociliary disorders can be inherited and acquired. They can result from structural ciliary changes or changes in the composition or quantity of the mucus.
- Environmental aerosols, especially the fine particulates, result in excess acute deaths, often from cardiac causes.

References

1. Stuart BO: Deposition and clearance of inhaled particles. Environ Health Perspect 55:369–390, 1984.
2. Brain JD, Valberg PA, Sneddon S: Mechanisms of aerosol deposition and clearance. In Moren F, Newhouse MT, Dolovich MB (eds): Aerosols in Medicine. Amsterdam: Elsevier, 1985, pp 123–148.
3. Wanner A, Salathe M, O'Riordan TG: State of the art: Mucociliary dysfunction in airways disease. Am J Respir Crit Care Med 154:1868–1902, 1996.
4. Dolovich MB, Ahrens RC, Hess DR, et al: Device selection and outcomes of aerosol therapy: Evidence-based guidelines. American College of Chest Physicians/American College of Asthma, Allergy, and Immunology. Chest 127:335–371, 2005.
5. Sangwan S, Condos, R, Smaldone GC: Lung deposition and respirable mass during wet nebulization. J Aerosol Med 16:379–386, 2003.
6. Stahlhofen W, Gebhart J, Heyder J: Experimental determination of the regional deposition of aerosol particles in the human respiratory tract. Am Ind Hyg Assoc J 41:385–398, 1980.
7. Smaldone GC, Solomita M: Predicting in vivo deposition in vitro. J Aerosol Med Pulm Drug Deliv 22:9–10, 2009.
8. Bennet WD, Smaldone GC: Human variation in the peripheral airspace deposition of inhaled particles. J Appl Physiol 62:1603–1610 1987.
9. Pavia D, Thomson ML, Clarke SW, Shannon HS: Effect of lung function and mode of inhalation on penetration of aerosol in the human lung. Thorax 32:194–197, 1977.
10. Ziegler J, Wachtel H: Comparison of cascade impaction and laser diffraction for particle size distribution measurements. J Aerosol Med 18:311–324, 2005.
11. Smaldone GC: Drug delivery via aerosol systems: concept of "aerosol inhaled." J Aerosol Med 4:229–235, 1991.

11a. Solomita M, Smaldone GC: Reconciliation of cascade impaction during wet nebulization. J Aerosol Med Pulm Drug Deliv 22:11–18, 2009.

12. Finlay WH (ed): The Mechanics of Inhaled Pharmaceutical Aerosols. Academic Press, 2001, pp 47–85.
13. Phipps PR, Gonda I, Anderson SD, et al: Regional deposition of saline aerosols of different tonicities in normal and asthmatic subjects. Eur Respir J 7:1474–1482. 1994.
14. Thorsson L, Edsbäcker S, Conradson TB: Lung deposition of budesonide from Turbuhaler is twice that from a pressurized metered-dose inhaler P-MDI. Eur Resp J 7:1839–1844, 1994.
15. Fuller R: The Diskus. A new multidose dry powder device: Efficacy and comparison with Turbuhaler. J Aerosol Med 8:S11–S17, 1998.
16. Patton JS. Unlocking the opportunity of tight glycemic control. Innovative delivery of insulin via the lung. Diabetes Obes Metab 7(Suppl 1):S5–S8, 2005.
17. Fink JB: Metered-dose inhalers, dry powder inhalers, and transitions. Respir Care 45:623–635, 2000.
18. Nelson HS, Loffert DT: Comparison of the bronchodilator response to albuterol administered by the OptiHaler, the AeroChamber, or by metered dose inhaler alone. Ann Allergy 72:337–340, 1994.
19. Dolovich M: New propellant-free technologies under investigation. J Aerosol Med 12(Suppl 1):S9–S17, 1999.
20. Busse WW, Brazinsky S, Jacobson K, et al: Efficacy response of inhaled beclomethasone dipropionate in asthma is proportional to dose and is improved by formulation with a new propellant. J Allergy Clin Immunol 104:1215–1222, 1999.
21. Wildhaber JH, Devadson SG, Eber E, et al: Effect of electrostatic charge, flow, delay and multiple actuations on the in vitro delivery of salbutamol from different small volume spacers for infants. Thorax 51:985–988, 1996.
22. Smaldone GC, Fuhrer J, Steigbigel RT, McPeck M: Factors determining pulmonary deposition of aerosolized pentamidine in patients with human immunodeficiency virus infection. Am Rev Respir Dis 143:727–737, 1991.
23. Smaldone GC: Advances in aerosols: Adult respiratory disease. J Aerosol Med 19:36–46, 2006.
24. Devadason SG, Everard ML, Linto JM, Le Souef PN: Comparison of drug delivery from conventional versus "Venturi" nebulizers. Eur Respir J 10:2479–2483, 1997.
25. Nikander K: Adaptive aerosol deliver: The principles. Eur Respir Rev 7:385–387, 1997.

26. Sangwan S, Agosti J, Bauer L, et al: Aerosol protein delivery in asthma: Gamma camera analysis of regional deposition and perfusion. J Aerosol Med 14:185–195, 2001.
27. O'Riordan TG, Greco MJ, Perry RJ, Smaldone GC: Nebulizer function during mechanical ventilation. Am Rev Respir Dis 145:1117–1122, 1992.
28. Miller DD, Amin MM, Palmer LB, et al: Aerosol delivery and modern mechanical ventilation: In vitro/in vivo evaluation. Am J Respir Crit Care Med 168:1205–1209, 2003.
29. Itoh H, Smaldone GC, Swift DL, Wagner HN: Quantitative measurement of total aerosol deposition: Comparison of three different techniques. J Aerosol Sci 16:367–371, 1985.
30. Ilowite JS, Gorvoy JD, Smaldone GC: Quantitative deposition of aerosolized gentamicin in cystic fibrosis. Am Rev Respir Dis 136:1445–1449, 1987.
31. Macey DJ, Marshall R: Absolute quantitation of radiotracer uptake in the lungs using a gamma camera. J Nucl Med 23:731–734, 1982.
32. Le Conte P, Potel G, Peltier P, et al: Lung distribution and pharmakinetics of aerosolized tobramycin. Am Rev Respir Dis 147: 1279–1282, 1993.
33. Smaldone GC, Dickinson G, Marcial E, et al: Deposition of aerosolized pentamidine and failure of *Pneumocystis* prophylaxis. Chest 101:82–87, 1992.
33a. Smaldone GC, Vinciguerra C, Morra L: Urine pentamidine as an indicator of lung pentamidine in patients receiving aerosol therapy. Chest 100:1219–1223, 1991.
34. Smaldone GC, Diot P, Groth M, Ilowite J: Respirable mass: Vague and indefinable in disease. J Aerosol Med 11(Suppl 1):S105–S111, 1998.
35. Diot P, Palmer LB, Smaldone A, et al: RhDNase I aerosol deposition and related factors in cystic fibrosis. Am J Respir Crit Care Med 156:1662–1668, 1997.
36. Smaldone GC, Messina M: Flow-limitation, cough and patterns of aerosol deposition in humans. J Appl Physiol 59:515–520, 1985.
37. Anderson M, Philipson K, Svartengren M, Camner P: Human deposition and clearance of 6-μm particles inhaled with an extremely low flow rate. Exp Lung Res 21:187–195, 1995,
38. Smaldone GC: Assessing new technologies: Patient-device interactions and deposition. Respir Care 50:1151–1160, 2005.
39. Iacono AT, Johnson BA, Grgurich WF, et al: A randomized trial of inhaled cyclosporine in lung-transplant recipients. N Engl J Med 354:141–150, 2006.
40. Iacono AT, Smaldone GC, Keenan RJ, et al: Dose-related reversal of acute lung rejection by aerosolized cyclosporine. Am J Respir Crit Care Med 155:1690–1698, 1997.
41. O'Riordan TG: Optimizing delivery of inhaled corticosteroids: Matching drugs with devices. J Aerosol Med 15:245–250, 2002.
42. Peters SP: Safety of inhaled corticosteroids in the treatment of persistent asthma. J Natl Med Assoc 98:851–861, 2006.
43. Skoner JD, Schaffner TJ, Schad CA, et al: Addressing steroid phobia: Improving the risk-benefit ratio with new agents. Allergy Asthma Proc 29:358–364, 2008.
44. Brutsche MH, Brutsche IC, Munawar M, et al: Comparison of pharmacokinetics and systemic effects of inhaled fluticasone propionate in patients with asthma and healthy volunteers: A randomized crossover study. Lancet 356:556–561, 2000.
45. Kraft M, Pak J, Martin RJ, et al: Distal lung dysfunction at night in nocturnal asthma. Am J Respir Crit Care Med 163:1551–1556, 2001.
46. Hiller R, Sperduto RD, Podgor MJ, et al: Cigarette smoking and the risk of development of lens opacities. The Framingham studies. Arch Ophthalmol 115:1113–1118, 1997.
47. Cumming RG, Mitchell P, Leeder SR: Use of inhaled corticosteroids and the risk of cataracts. N Engl J Med 337:6–14, 1997.
48. Cheer SM, Waugh J, Noble S: Inhaled tobramycin (TOBI): A review of its use in the management of *Pseudomonas aeruginosa* infections in patients with cystic fibrosis. Drugs 63:2501–2520, 2003.
49. Retsch-Bogart GZ, Burns JL, Otto KL, et al, and AZLI Phase II Study Group: A phase 2 study of aztreonam lysine for inhalation to treat patients with cystic fibrosis and *Pseudomonas aeruginosa* infection. Pediatr Pulmonol 43:47–58, 2008.
50. Flume PA, O'Sullivan BP, Robinson KA, et al: Cystic fibrosis pulmonary guidelines. Chronic medications for maintenance of lung health. Am J Respir Crit Care Med 176:957–969, 2007.
51. Everard M: Aerosol delivery in infants and young children. J Aerosol Med 9:71–77, 1996.
52. Szefler SJ: Pharmacodynamics and pharmacokinetics of budesonide: A new nebulized corticosteroid. J Allergy Clin Immunol 104:175–183, 1999.
53. Smaldone GC, Sangwan S, Shah A: Facemask design, facial deposition, and delivered dose of nebulized aerosols. J Aerosol Med 20(Suppl 1):S66–S75, 2007.
54. Nikander K, Berg E, Smaldone GC: Jet nebulizers versus pressurized metered dose inhalers with valved holding chambers: Effects of the facemask on aerosol delivery. J Aerosol Med 20(Suppl 1):S46–S55, 2007.
55. Erzinger S, Schuepp KG, Brooks-Wildhaber J, et al: Facemasks and aerosol delivery in vivo. J Aerosol Med 20(Suppl):S78–S84, 2007.
56. Soderberg-Warner ML: Nasal septal perforation associated with topical corticosteroid therapy. J Pediatr 105:840–841, 1984.
57. Skoner DP, Rachelefsky GS, Meltzer EO, et al: Detection of growth suppression in children during treatment with intranasal beclomethasone dipropionate. Pediatrics 105:E23, 2000.
58. Schenkel EJ, Skoner DP, Bronsky EA, et al: Absence of growth retardation in children with perennial allergic rhinitis after one year of treatment with mometasone furoate aqueous nasal spray. Pediatrics 105:E22, 2000.
59. Palmer LB, Smaldone GC, Chen JJ, et al: Aerosolized antibiotics and ventilator-associated tracheobronchitis in the intensive care unit. Crit Care Med 36:2008–2013, 2008.
60. Dhand R, Tobin MJ: Inhaled bronchodilator therapy in mechanically ventilated patients. Am J Respir Crit Care Med 156:3–10, 1997,
61. Diot P, Morra L, Smaldone GC: Albuterol delivery in a model of mechanical ventilation: Comparison of MDI and nebulizer efficiency. Am J Respir Crit Care Med 152:1391–1394, 1995.
62. O'Riordan TG, Smaldone GC: Aerosols as indices of regional ventilation. J Aerosol Med 7:111–117, 1994.
63. Clunes MT, Boucher RC: Front-runners for pharmacotherapeutic correction of the airway ion transport defect in cystic fibrosis. Curr Opin Pharmacol 8:292–299, 2008.
64. Boucher RC: Relationship of airway epithelial ion transport to chronic bronchitis. Proc Am Thorac Soc 1:66–70, 2004.
65. Messina MS, O'Riordan TG, Smaldone GC: Changes in mucociliary clearance during acute exacerbations of asthma. Am Rev Respir Dis 143:993–997, 1991.
66. O'Riordan TG, Zwang J, Smaldone GC: Mucociliary clearance in adult asthma. Am Rev Respir Dis 146:598–603, 1992.
67. Smaldone G. Foster WM, O'Riordan TG, et al: Regional impairment of mucociliary clearance in chronic obstructive pulmonary disease. Chest 103:1390–1396, 1993.
68. Regnis JA, Robinson M, Bailey DL, et al: Mucociliary clearance in patients with cystic fibrosis and in normal subjects. Am J Respir Crit Care Med 150:66–71, 1994.
69. Salathe M, O'Riordan TG, Wanner A: Treatment of mucociliary dysfunction. Chest 110:1048–1057, 1996.
70. Jones JG: Clearance of inhaled particles from the alveoli. *In* Clarke S, Pavia D (eds): Aerosols and the Lung: Clinical and Experimental Aspects. London: Butterworths, 1984, pp 49–70.
71. Schoonen MA, Cohn CA, Roemer E, et al: Mineral-induced formation of reactive oxygen species. Rev Geochem Mineral 64:179–221, 2006.
72. Oberdorster G: Significance of particle parameters in the evaluation of exposure-dose-response relationships of inhaled particles. Inhal Toxicol 8(Suppl):73–89, 1996.
73. Warheit DB, Hansen JF, Yuen IS, et al: Inhalation of high concentrations of low toxicity dusts in rats results in pulmonary and macrophage clearance impairments. Toxicol Appl Pharmacol 145:10–22, 1997.
74. Sayes CM, Reed KL, Warheit DB: Assessing toxicity of fine and nanoparticles: Comparing in vitro measurements to in vivo pulmonary toxicity profiles. Toxicol Sci 97:163–180, 2007.
75. Seagrave JC, Mauderly JL, Seilkop SK: In vitro relative toxicity screening of combined particulate and semivolatile organic fractions of gasoline and diesel engine emissions. J Toxicol Environ Health Part A 66:1113–1132, 2003.
76. Hunt A, Abraham JL, Judson B, Berry CL: Toxicologic and epidemiologic clues from the characterization of the 1952 London smog

fine particulate matter in archival autopsy lung tissues. Environ Health Perspect 111:1209–1214, 2003.
77. Samet JM, Dominici F, Frank C, et al: Fine particulate air pollution and mortality in 20 U.S. cities, 1987–1994. N Engl J Med 343:1742–1740, 2000.
78. Miller KA. Siscovick DS, Sheppard L, et al: Long-term exposure to air pollution and incidence of cardiovascular events in women. N Engl J Med 356:447–458, 2007.
79. Oberdorster G, Oberdorster E, Oberdorster J: Nanotoxicology: An emerging discipline evolving from studies of ultrafine particles. Environ Health Perspect 113:823–839, 2005.
80. Arlian LG, Platts-Mills TA: The biology of dust mites and the remediation of mite allergens in allergic disease. J Allergy Clin Immunol 107(3 Suppl):S406–S413, 2001.
81. Fennelly KP, Martyny JW, Fulton KE, et al: Cough-generated aerosols of *Mycobacterium tuberculosis*: A new method to study infectiousness. Am J Respir Crit Care Med 169:604–609, 2004.
82. Baron PA: Measurement of airborne fibers: A review. Ind Health 39:39–50, 2001.
83. Prezant DJ, Weiden M, Banauch GI, et al: Cough and bronchial responsiveness in firefighters at the World Trade Center site. N Engl J Med 347:806–815, 2002.
84. Cohn CA, Laffers R, Simon SR, et al: Role of pyrite in formation of hydroxyl radicals in coal: Possible implications for human health. Part Fibre Toxicol 3:16, 2006.
85. Hecht SS, Murphy SE, Carmella SG, et al: Similar uptake of lung carcinogens by smokers of regular, light, and ultralight cigarettes. Cancer Epidemiol Biomarkers Prev 14:693–698, 2005.
86. Harris JE, Thun MJ, Mondul AM, Calle EE: Cigarette tar yields in relation to mortality from lung cancer in the cancer prevention study II prospective cohort, 1982–1988. BMJ 328:72, 2004.

CHAPTER 13

INNATE IMMUNITY IN THE LUNGS

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INTRODUCTION

OVERVIEW OF THE COMPONENTS OF LUNG INNATE IMMUNITY

INNATE RECOGNITION IN THE LUNG
Secreted Pattern Recognition Receptors
Cellular Pattern Recognition Receptors
Summary

EFFECTOR MECHANISMS
Epithelium
Neutrophils
Mononuclear Phagocytes

SYSTEM INTEGRATION

INTRODUCTION

The immune system is broadly conceptualized as having two separate but interconnected arms. In evolutionary terms, the *innate immune arm* is an older and more primitive system that has developed to provide early host defense against viruses, fungi, and bacteria. The fundamental basis of innate immunity is a system for pathogen detection that relies on the recognition of a range of pathogen-associated molecular patterns (PAMPs) that include complex lipids, carbohydrates, unmethylated CpG DNA sequences, and double-stranded RNAs. PAMPs are recognized by a series of secreted, cell surface and intracellular pattern recognition receptors (PRRs) that promote the recognition, phagocytosis, and killing of many microbes. In addition, recognition of PAMPs by PRRs initiates inflammation, which, in turn, leads to the recruitment of phagocytes, which kill and degrade microbes, promote the repair of damaged tissues, and assist in the restoration of tissue function. Though some organisms, for example, sea urchins, have evolved a system of host defense based exclusively on the innate immune system,[1] mammals and higher animals have evolved an *adaptive immune system* that differs from the innate immune system by its exquisite antigenic specificity. The adaptive immune system is also distinguished from its innate counterpart by the development of immunologic memory, thereby allowing a more rapid response to repeated exposure to previously encountered microbes and antigens. The initiation of adaptive immunity and the execution of some of its effector mechanisms are also dependent on the innate immune system. Thus, both the innate and the adaptive immune systems exist in a classic symbiotic relationship to provide optimal defense of the lung and other organs and tissues.

The broad concepts of innate and adaptive immunity outlined previously have evolved to protect most organs and tissues from *microbes*, a term we use to include bacteria, yeasts, fungi, protozoa, multicellular parasites, and viruses. However, most organs and tissues, including the lung, have adapted or evolved additional mechanisms to tailor the immune system to their own specific needs. The lung epithelium has a surface area approximately the size of a tennis court and represents the largest epithelial surface in the body. With an average respiratory rate of 15 breaths/min and an average tidal volume of 500 mL, the lungs are exposed to over 10,000 L of ambient air/day. The air that we breathe is a complex mixture of gases and particulates that can contain pollutants, oxidants, inorganic and organic dusts, pollens, toxins, bacteria and their constituents (e.g., bacterial endotoxin, lipopolysaccharides [LPS]), and viruses. In addition, the airways and gas-exchange surfaces of the lung can be exposed by aspiration to acidic gastric contents as well as to infected mucus from the nasal sinuses. Thus, all surfaces of the respiratory tract from the nasal passages to the alveoli are constantly exposed to a spectrum of harmless, harmful, and pathogenic agents, raising the important question of how the lung differentiates between what is harmful and what is essentially harmless.

Like the gut, the lung has evolved discriminative mechanisms to both suppress unwanted and potentially

harmful responses to harmless materials and retain the ability to vigorously activate innate and adaptive immunity when encountering harmful microbes and stressors. The overall goal of this chapter is to review current concepts of innate immune responses in the lung and their underlying mechanisms. Multiple cell lineages participate in innate protection of the lung, and many share similarities in the way they recognize and respond to microbes and other harmful agents. Therefore, we have organized the chapter into four broad sections. First, we provide an overview of lung innate immunity and its fundamental components. Second, we discuss general mechanisms of innate immune recognition. Third, we review innate lung cells and the effector mechanisms they utilize. Fourth, we discuss how these systems and mechanisms are integrated. Throughout the chapter, we also discuss how the innate immune system primes the adaptive immune system as a prelude to the chapter on adaptive immunity (see Chapter 14).

OVERVIEW OF THE COMPONENTS OF LUNG INNATE IMMUNITY

The innate immune system provides protection to the lungs against a diverse spectrum of inhaled particles and antigens that range from harmless nonmicrobial particles (e.g., dusts and pollens) to harmful pathogenic microbes (e.g., *Mycobacterium tuberculosis*). To accomplish the range of protection, the lungs have evolved multiple mechanisms to survey and respond to inhaled particles based primarily on their size and physicochemical properties, especially the presence and absence of PAMPs. As illustrated in Figure 13-1, innate immune protection in the lung can be broadly divided into considerations of (1) the conducting airways and (2) the gas-xchange surfaces of the alveoli. At the cellular level, innate protection is afforded by the coordinated functions of airway and alveolar epithelial cells, resident macrophages and

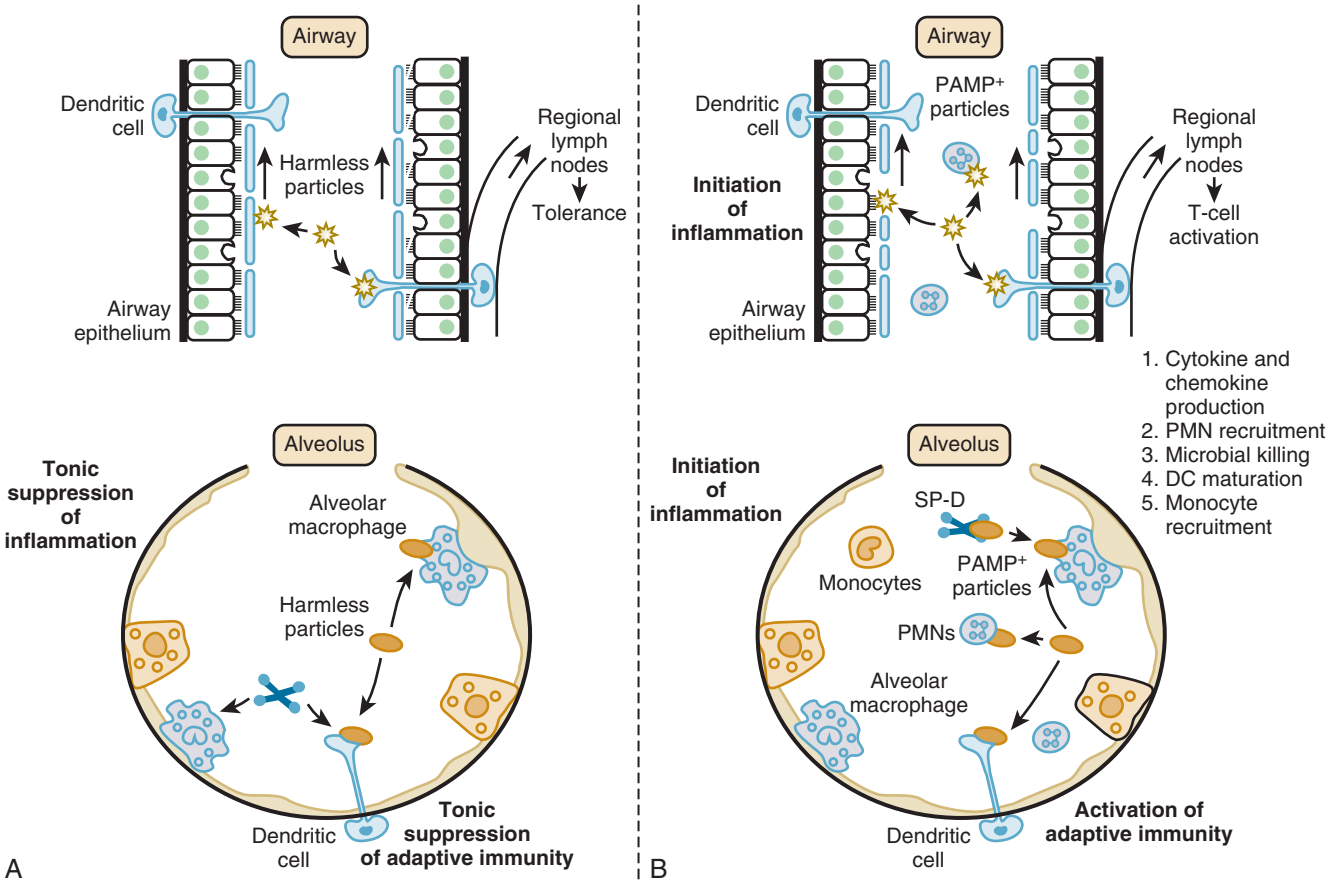


FIGURE 13-1 ■ Overview of innate immune protection in the conducting airways and alveoli of the lung. **A**, In the absence of pathogen-associated molecular patterns (PAMPs), that is, in the steady state, the airways are protected by mucus that captures harmless particulates and transports them along the mucociliary escalator. Dendritic cells also capture particles, traffic to regional lymph nodes, and promote tolerance to commonly inhaled antigens. Also in the absence of PAMPs, the alveoli are maintained in an anti-inflammatory and immunosuppressed state to prevent unwanted inflammation and immune activation toward commonly inhaled particles and antigens. **B**, Innate immunity is activated in the presence of PAMPs. PAMPs stimulate airway epithelial cells to express chemokines, cytokines, and lipid mediators that attract neutrophils (polymorphonuclear leukocytes [PMNs]), which, in turn, kill PAMP-expressing microbes. Airway dendritic cells response to PAMPs by maturing, migrating to regional lymph nodes, and stimulating T-cell proliferation. A similar program is activated in the alveoli upon PAMP detection by alveolar macrophages, alveolar epithelial cells and dendritic cells, resulting in the initiation of inflammation and activation of adaptive immunity.

dendritic cells (DCs), and recruited neutrophils (polymorphonuclear leukocytes [PMNs]), monocytes, and DC precursors.

Though often underestimated, an important component of airway host defense resides in the anatomic structure and epithelial cell lineages of the tracheobronchial tree. Air turbulence created by the nasal passages and the cartilaginous segmentation of the trachea and large airways ensures that particles in excess of 10 μm in diameter are deposited on the mucus-coated surfaces of the nose, pharynx, trachea, and descending airways. In turn, mucus, its ensnared particulates, and dissolved solutes are constantly wafted toward the pharynx by the coordinated beating of ciliated airway epithelial cells where their removal is aided by coughing, sneezing, and swallowing. In addition to the biophysical properties of mucus in innate host defense of the airways, the gel and pericellular liquid phases also contain an array of antimicrobial peptides and proteins, antioxidants, antiproteases, as well as specific immunoglobulin A (IgA) antibodies (Table 13-1), all of which are maintained at a modestly acidic pH (pH 6.6).[2] Principal among airway antimicrobial peptides in humans are salt-sensitive cysteine-rich cationic β-defensins and the cathelicidin, LL-37/hCAP-18.[3–7] β-Defensin-1 is constitutively secreted by airway epithelia and accumulates in airway surface liquid at microgram per milliliter concentrations.[8] Other β-defensins and LL-37/hCAP-18 are inducibly expressed following exposure to LPS and other proinflammatory mediators.[9–11] Antimicrobial proteins including lactoferrin and lysozyme are also present in airway epithelial secretions and contribute to the maintenance of normal airway sterility.[12,13]

The conducting airways are lined with ciliated and secretory epithelial cells that serve a key role in initially evaluating the surfaces of large particles with which they come into contact. In addition, a network of DCs resides throughout the airway epithelium and continuously samples the airway lumen (see Fig. 13-1). DCs are particularly abundant in the trachea and large conducting airways where most large particulates are deposited. In the absence of PAMPs, DCs capture airway antigen and migrate to regional lymph nodes where they induce $CD4^+$ and $CD8^+$ T-cell tolerance to harmless inhaled antigens.

TABLE 13-1. Some Constituents of Airway Epithelial Fluid

Lysozyme
Lactoferrin
Secretory leukoprotease inhibitor
Uric acid
Peroxidase
Aminopeptidases
Statherin
Secretory phospholipase A_2
β-defensins
Natural IgA antibodies
Reduced pH
SP-A*
SP-D*

*Restricted to alveoli.
IgA, immunoglobulin A; SP, surfactant protein.
Adapted from Diamond G, Legarda D, Ryan LK: The innate immune response of the respiratory epithelium. Immunol Rev 173:27–38, 2000.

In contrast to large particles, particles smaller than 5 μm in diameter are able to descend the entire tracheobronchial tree and lodge at bronchiolar-respiratory duct junctions or deposit onto the surfactant-rich surfaces of the alveoli. While sharing many similarities with innate protection of the airways—for example, the presence of antioxidants, antiproteases and antimicrobial enzymes—additional innate protection of the alveoli is afforded by the presence of resident alveolar macrophages and the lung specific collectins, surfactant protein A (SP-A) and SP-D (see Fig. 13-1). In addition to expressing Toll-like receptors (TLRs), resident alveolar macrophages express scavenger receptors that participate in the phagocytosis of microbial and nonmicrobial particles. SP-A and SP-D are secreted PRRs and are capable binding to microbial PAMPs, leading to opsonization and phagocytosis by alveolar macrophages and intraseptal DCs, which then either crawl into the airways and move up the mucociliary escalator or migrate to regional lymph nodes, respectively. In the absence of PAMPs, resident alveolar macrophages also play an important role in suppressing inflammation and adaptive immunity, thereby protecting the alveoli from unwanted responses to harmless inhaled particulates. SP-A and SP-D also play a key role in suppressing inflammation in the absence of PAMPs through tonic signaling effects on resident alveolar macrophages. Thus, the innate immune system not only protects the lungs from harmful microbes but also prevents inflammation, injury, and activation of the adaptive immune system in the steady state and in response to harmless inhaled particulates.

Next, we must consider how the airways and alveoli respond to the presence of potentially harmful microbes. As illustrated in Figure 13-1, resident airway and alveolar macrophages, DCs, and airway and alveolar epithelial cells are capable of recognizing different PAMPs through their repertoires of cell surface and intracellular PRRs, and by interaction of PAMP-bound secreted PRRs with specific receptors on epithelial cells, macrophages, and DCs. In turn, these interactions induce signaling responses that activate nuclear factor-κB (NF-κB), activator protein-1 (AP-1), and other key transcriptional switches to promote the expression of an array of innate response genes (Table 13-2). These gene products collectively promote the migration of PMNs and monocytes from the pulmonary circulation into the air spaces, facilitate changes in endothelial and epithelial permeability to facilitate inflammatory cell transmigration into the airspaces, and initiate the expression of specific genes involved in microbial killing. In addition to the activation of PMN and macrophage-dependent killing mechanisms, airway and alveolar DCs also respond to PAMPs, and following microbial phagocytosis, they undergo a process of maturation followed by migration to regional lymph

TABLE 13-2. Representative Genes Activated by Pattern Recognition Receptors

CXCL CHEMOKINES
CXCL1, CXCL2, CXCL4, CXCL9, CXCL10, CXCL11

CCL CHEMOKINES
CCL1, CCL2, CCL7

CYTOKINES
TNFα, IL-1β, TGF-β, IL-10

TLRS
TLR2, TLR4, TLR9

PROSURVIVAL
Bcl-2, cIAP1 and 2, Bcl-10

ANTIMICROBIAL
β-defensins, cathelicidins

DC MATURATION
CD40, CD80, CD86, Class II

Transcription of most of these genes is initiated by the activation of NF-κB and/or AP-1. Activation of NF-κB is initiated by most PRRs and involves the activation of IκB kinase. AP-1 is activated by MAPKs, especially JNK and p38. Activation of MAPKs also results in transactivation of NF-κB, and so activation of both pathways is usually required for optimal expression of genes involved in innate immunity.
AP-1, activator protein-1; CCL, CC chemokine ligand; CXCL, CXC chemokine ligand; DC, dendritic cell; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor-κB; PRR, pattern recognition receptor; TLR, Toll-like receptor.

nodes (see Fig. 13-1). During this process, ingested microbial products are digested, captured by major histocompatibility complex (MHC) class II molecules, and displayed on the DC plasma membrane together with co-stimulatory molecules such as CD40, CD80 and CD86 for effective presentation to naive $CD4^+$ and $CD8^+$ T-cells. Following activation and expansion in regional lymph nodes, effector $CD4^+$ and $CD8^+$ T-cells then migrate back to the site of microbial infection to augment specific host defense through their ability to activate macrophages and other effector cells by producing interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α), and other cytokines that increase host antimicrobial defenses.

In summary, innate immune mechanisms involving the airway and alveolar epithelium, secreted antimicrobial enzymes, PRRs and peptides, mucus and mucociliary transport, and resident macrophages and DCs protect the lung against inhaled microbial and nonmicrobial particulates to maintain lung sterility and health. In addition, in the steady state, the innate immune system actively suppresses inflammation and promotes tolerance to commonly inhaled harmless particulates. Above a certain threshold and upon sensing the presence of PAMPs, additional mechanisms are activated to protect the lungs by promoting inflammation and adaptive immunity and by establishing communication and cooperation between these systems. We should note that, although it is convenient to think of these events separately, it seems reasonable to suppose that in normal healthy individuals, responses to harmless nonmicrobial particulates and harmful microbes are occurring simultaneously, and silently, to maximally sustain lung health and protection.

INNATE RECOGNITION IN THE LUNG

With this broad overview of the key elements in innate host defense of the lung and their connections to adaptive immunity, we now consider in more detail how microbes are recognized by resident and recruited lung cells. For this purpose, we specifically focus on the mechanism of recognition by PRRs that are expressed by epithelial cells, macrophages, and DCs or are present in airway or alveolar surface liquids.

Secreted Pattern Recognition Receptors

Secreted PRRs have evolved to serve as bridges between certain PAMPs and specific receptors for these molecules. In the lung, secreted PRRs have particularly important roles in innate protection of the alveolar surfaces.

Collectins

The collectins are a family of secreted PRRs of which SP-A and SP-D are uniquely expressed in the distal lung.[14] All members of the collectin family are characterized by the presence of an N-terminal collagen-like domain, a coiled neck domain, and a globular C-type lectin domain that interacts with microbial PAMPs. SP-A and SP-D interact with a variety of PAMPs and stimulate microbial phagocytosis, the production of reactive oxidant species, the activation of NF-κB and AP-1 and the expression of proinflammatory cytokines.[15,16] Several studies have shown that activation of a proinflammatory response occurs when PAMP-bound SP-A and SP-D interact with macrophages via their collagenous tails through CD91.[17-19] Consistent with these findings, SP-A–deficient and SP-D–deficient mice have increased susceptibility to pulmonary infection with *Pseudomonas aeruginosa* and *Staphylococcus aureus*,[20,21] emphasizing the important contribution of these lung-specific collectins to innate lung host defense.

The lung is remarkable in that it maintains sterility of the alveolar surfaces while actively suppressing unwanted and potentially harmful inflammatory responses to harmless inhaled materials. Several studies have shed new light on this issue by revealing an additional role for SP-A and SP-D in the tonic suppression of lung inflammation. When initially created, SP-D–deficient mice were found to have increased numbers of foamy, activated alveolar macrophages and increased lung injury, suggesting that SP-D may somehow tonically suppress lung macrophage activation and lung inflammation.[22] As illustrated in Figure 13-2, some studies also suggest that in the steady state, that is, in the absence of PAMPs, SP-D and SP-A interact with alveolar macrophages via their globular head groups and signal via signal inhibitory regulatory protein-α (SIRPα) to tonically suppress proinflammatory responses.[19] Thus, SP-A and SP-D, through their ability to interact under different circumstances with CD91 and

SIRPα, play a pivotal role in the maintenance of the anti-inflammatory environment of the alveoli under steady-state conditions, while promoting an inflammatory and innate response when microbes are sensed. Interestingly, other studies also suggest that lipid and phospholipid constituents of surfactant significantly contribute to maintenance of the anti-inflammatory environment of the alveoli.[23]

Complement

The complement system functions as a pattern recognition system as well as a bridge to adaptive immunity through its ability to recognize repetitive structures on some microbes, and the Fc region of IgG and IgM antibodies. Complement activation is important in lung innate immunity because it promotes the opsonization of microbes and the generation of the potent chemotactic factor C5a, which, in turn, assists in the recruitment of phagocytic cells. Complement components of the classical, alternative, and mannose-binding lectin activation pathways are present in lung airway and alveolar fluids[24–26] and are synthesized by alveolar type II cells, macrophages, and DCs.[13,27–29] Many microbes can directly activate the alternative complement pathway, resulting in the covalent attachment of C3b to the microbial cell wall. Microbes expressing cell wall–associated mannose-rich polysaccharides can also bind mannose-binding lectin and activate the mannose-binding lectin pathway to promote C3b attachment to the microbial cell wall. Phagocytic cells, especially macrophages, PMNs, and DCs, express various receptors for C3b and C3bi and, together with other receptors, phagocytose and kill complement-opsonized microbes.

Pentraxins and Other Secreted Pattern Recognition Receptors

The pentraxins, including C-reactive protein, serum amyloid P, and pentraxin 3, also recognize PAMPs on microbes and activate the complement system to assist in their removal by phagocytic cells.[30,31] Similarly, ficolins promote phagocytosis and complement activation by binding to the gram-positive bacterial cell wall components *N*-acetylglucosamine and lipoteichoic acid.[32]

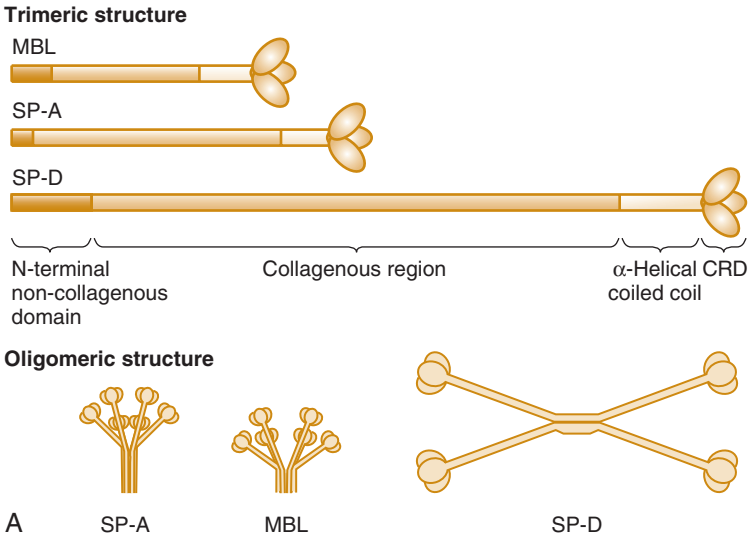
Cellular Pattern Recognition Receptors

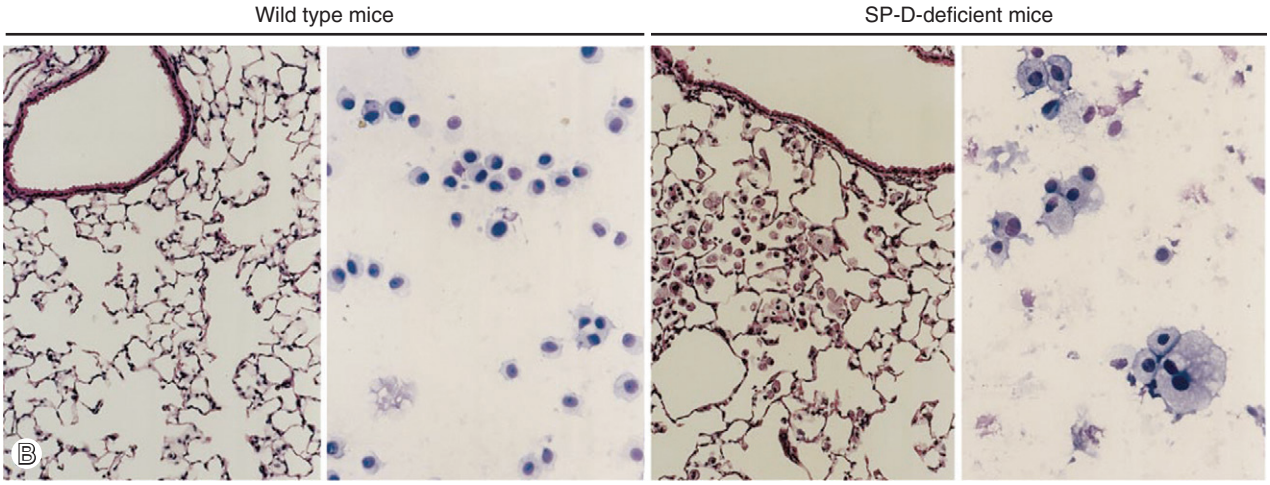
Different families of PRRs have evolved to enable the host to sense the presence of PAMPs in extracellular, endosomal, and cytoplasmic compartments in each of the lineages involved in lung innate immunity (Fig. 13-3). Key among the transmembrane cell surface and endosome-associated PRRs is the TLR family that is widely expressed on epithelial cells, macrophages, PMNs, and DCs. Members of the scavenger receptor family are primarily expressed on macrophages; whereas C-type lectin receptors are mainly expressed on DCs. Cytoplasmic PRRs are composed of nucleotide-binding and oligomerization domain (NOD)–like receptors (NLRs) of the NOD and neuronal apoptosis inhibitor protein (NACHT) leucine-rich domain and pyrin-containing protein (NALP) families and RNA helicases of the retinoic acid–inducible gene (RIG) family. Each of the cytoplasmic PRRs has evolved as a strategy to alert the host of the presence of PAMPs within the cytoplasm, as often occurs during the intracellular replication of facultative bacteria and viruses.

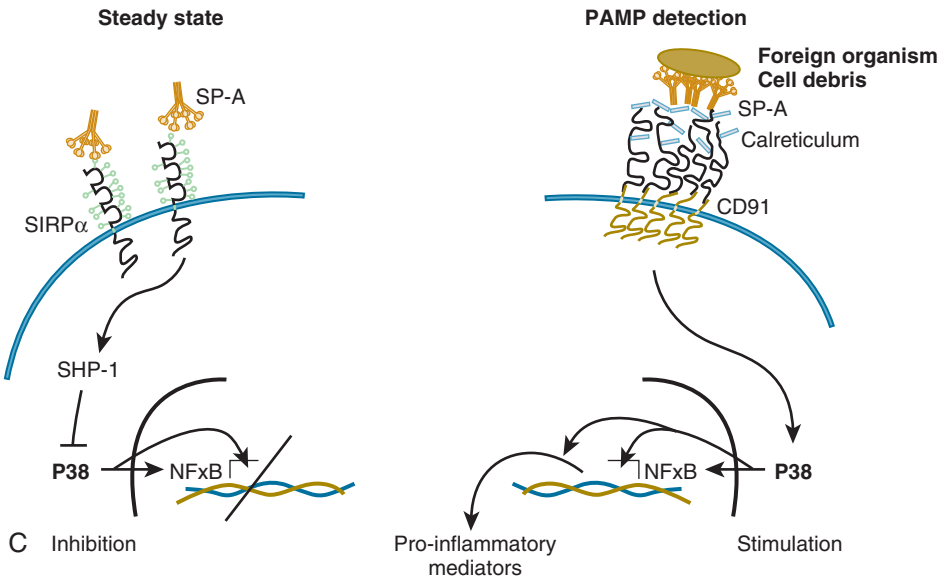
Plasma Membrane and Endosomal Pattern Recognition Receptors

Toll-like Receptors. TLRs are widely expressed throughout the body and are represented on airway and alveolar epithelial cells, macrophages, PMNs, and DCs.[33–36] Thirteen TLRs have been described in mice (TLR1-13) and 10 in humans (see Fig. 13-3). Although the ligands and biologic function of TLR10-13 remain unclear, significant progress has been made in understanding the functions and downstream signal transduction pathways of TLR1-9.[37–40] TLRs can be divided into those expressed on the cell surface (TLR1, 2, 4, 5, 6, and 11) and those expressed in intracellular compartments (TLR3, 7, 8, and 9). TLRs also recognize endogenous ligands called danger-associated molecular patterns (DAMPs) including heat shock proteins, low-molecular-weight hyaluronan, heparin sulfate, fibronectin, high mobility group-1 protein, and low-density lipoproteins (LDLs). Recognition of DAMPs by TLRs and other PRRs is usually associated with the initiation of noninfectious inflammation. Surface TLRs recognize a wide variety of PAMPs, while intracellular TLRs mainly recognize nucleic acid–based PAMPs. TLRs not only recognize their individual cognate PAMPs but also combine with other TLRs to form heteromeric complexes that recognize a broader range of PAMPs.[40–42] For example, TLR1 associates with TLR2 to recognize microbial lipopeptides,[43] TLR2 and TLR4 recognize the LPS-LPS-binding protein (LBP)/myeloid differentiation protein-2 (MD-2) complex when presented by CD14, and TLR2 recognizes broad patterns of lipoproteins in concert with either TLR1 and TLR6.[44] TLR5 recognizes flagellin and is particularly important in the response of airway epithelial cells to *P. aeruginosa* infection. Similarly, TLR6 can functionally associate with TLR2 to recognize a variety of microbial lipopeptides and peptidoglycan from gram-positive bacterial cell walls.[45]

In contrast to TLR1, 2, 4, 5, 6, and 11, TLR3, 7, 8, and 9 are not highly expressed at the cell surface but are expressed intracellularly in endosomal and endoplasmic reticulum membranes.[37–40] Intracellular destruction of ingested microbes results in the release of nucleic acids into the phagosome lumen. The ligand-binding regions of TLRs3, 7, 8, and 9 are also all expressed on the luminal side of the endosomal membrane. TLR3 recognizes viral double-stranded RNA and induces the production of type I IFNs (IFN-α/β).[46] In turn, type I IFNs play a vital role in antiviral immunity and in DC maturation.[47] TLR7 recognizes single-stranded RNA from viruses, whereas TLR9 recognizes unmethylated CpG-motifs in microbial DNA.[48,49] Synthetic ligands for TLR7 and 8, such as resiquimod and imiquimod, have been used therapeutically in the treatment of virally induced skin infections and skin tumors. The therapeutic efficacy of these agents


Trimeric structure
MBL
SP-A
SP-D
N-terminal non-collagenous domain
Collagenous region
α-Helical CRD coiled coil
Oligomeric structure
A
SP-A
MBL
SP-D


Wild type mice
SP-D-deficient mice
B


Steady state
SP-A
SIRPα
SHP-1
P38
NFxB
C
Inhibition
PAMP detection
Foreign organism
Cell debris
SP-A
Calreticulum
CD91
NFxB
P38
Pro-inflammatory mediators
Stimulation

is also believed to be a direct result of their ability to activate skin DCs to produce type I IFNs.[50]

Scavenger Receptors. The first macrophage scavenger receptor (SR) was described by Goldstein and coworkers in 1979[51] and Brown and colleagues in 1980[52] and was shown to bind and internalize acetylated-LDL. Since then, multiple SRs have been identified and shown to play diverse roles in the phagocytosis of a variety of particles and molecules ranging from bacteria to lipids (see Fig. 13-3). The SR family comprises eight classes (A-H) of which class A (SR-A) and class B (SR-B) are primarily involved in innate immunity through their ability to recognize and promote phagocytosis of a wide range of bacteria. Members of the SR-A and SR-B subfamilies are abundantly expressed on macrophages and DCs but do not appear to be expressed by airway or alveolar epithelial cells. This is in keeping with the notion that during exposure to inhaled microbes and particles, the lung epithelium has evolved mechanisms to respond to PAMPs by promoting inflammation but not to engage in phagocytosis, leaving this activity to professional phagocytes.

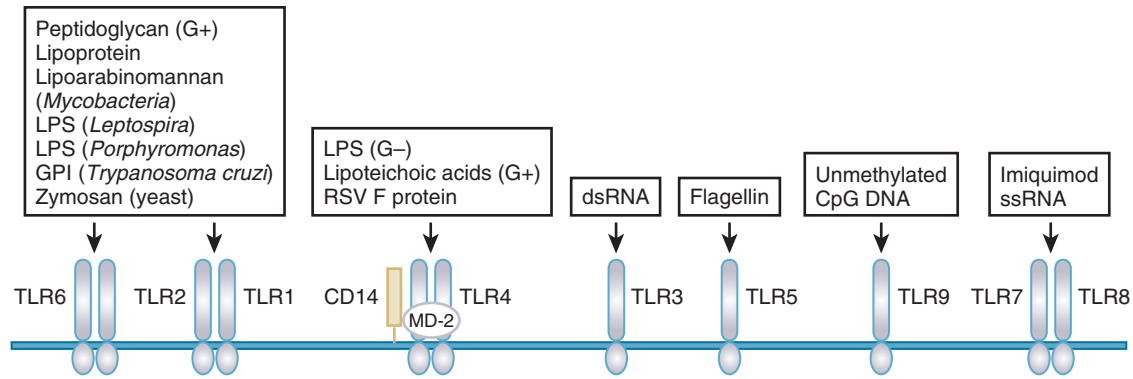
Class-A SRs are homotrimeric type II transmembrane proteins (extracellular C-terminal). SR-A exists as two splice variants (SR-AI and SR-AII) of a single gene and has been shown to recognize LPS, lipoteichoic acid, double-stranded RNA, and unmethylated CpG DNA sequences, suggesting that it may function in the recognition of PAMPs. However, studies with intact bacteria suggest that its primary function is to promote the phagocytosis of a range of nonopsonized bacteria including *S. aureus*, *Steptococcus pneumoniae* and *Escherichia coli*.[53] SR-A–deficient mice have increased susceptibility to systemic infections with *S. aureus* and *Listeria monocytogenes*[54,55] and pulmonary infections with *S. pneumonia*.[56] A second and equally important class-A SR involved in nonopsonic phagocytosis of bacteria is macrophage receptor with collagenous structure (MARCO). Initial studies suggested that MARCO has limited expression in splenic and lymph node macrophage subpopulations but was not expressed in lung macrophages.[57] However, later studies indicated that MARCO expression is induced following PAMP recognition, particularly by CpG DNA and LPS, and by proinflammatory cytokines such as TNF-α.[58,59] Studies in MARCO-deficient mice have also revealed its importance in innate pulmonary host defense against *S. pneumoniae*.[60] Furthermore, down-regulation of MARCO by IFN-γ increases susceptibility to *S. pneumoniae* in mice and may contribute to pulmonary bacterial pneumonias that occur following influenza infections.[61] MARCO is also thought to be a major receptor for unopsonized bacteria on human alveolar macrophages.[62] Interestingly, MARCO has also been implicated in the phagocytosis of inorganic dusts by pulmonary macrophages.[63,64] MARCO may also play a role in dampening pulmonary inflammation because MARCO-deficient mice exhibit increased lung inflammation in response to exposure to environmental stimuli such as crystalline silica and inhaled oxidants.[65,66]

Class-B SRs are primarily represented in the lung by CD36. CD36 is expressed on monocytes, macrophages, DCs, and vascular endothelium but does not appear to be expressed on airway or alveolar epithelial cells.[67–69] Like class-A SRs, CD36 has been implicated in PAMP recognition, especially lipoteichoic acid,[70] and in the phagocytosis of *S. aureus*.[71,72] However, whereas CD36 deficiency in mice results in impaired host defense against *S. aureus*,[70] naturally occurring genetic deficiency of CD36 in humans is associated with impaired responses to oxidized LDLs and the development of a metabolic syndrome–like state rather than a pulmonary phenotype.[73]

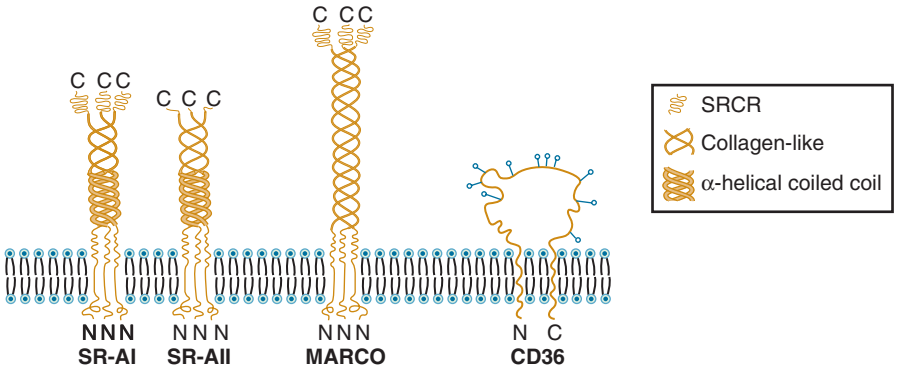
C-Type Lectin Receptors. In additional to their presence in the secreted PRRs SP-A and SP-D, C-type lectin domains are widely incorporated in a family of cell surface receptors that play an important role in the function of DCs and macrophages (see Fig. 13-3). As with SRs, C-type lectin receptors (CLRs) do not appear to be expressed on airway and alveolar epithelial cells. CLRs recognize high-density carbohydrate-based PAMPs on microbial cell walls and viral coats. Carbohydrate binding can be divided into mannose and galactose specificity.[74] Type I CLRs include dendritic and thymic epithelial cell-205 (DEC-205) and macrophage mannose receptor (MMR), and type II CLRs include dendritic cell-specific intracellular adhesion molecule (ICAM-3) grabbing nonintegrin (DC-SIGN) and dectin-1. As is discussed, studies in mice bearing targeted disruptions of CLR genes have emphasized their importance in innate host defense and particularly in DC maturation and antigen presentation.

DEC-205 is type 1 transmembrane receptor protein found on a variety of DC subsets, macrophages, and thymic epithelial cells.[75] The natural carbohydrate ligands of DEC-205 remain largely uncharacterized though the receptor has been shown to induce the endocytosis of experimental antigen-anti-DEC-205 receptor complexes and promote their delivery to endosomes prior to antigen processing and presentation. When DCs are treated with the antigen-anti-CD205 fusion protein alone, they induce tolerance to the antigen by deleting specific $CD4^+$ and

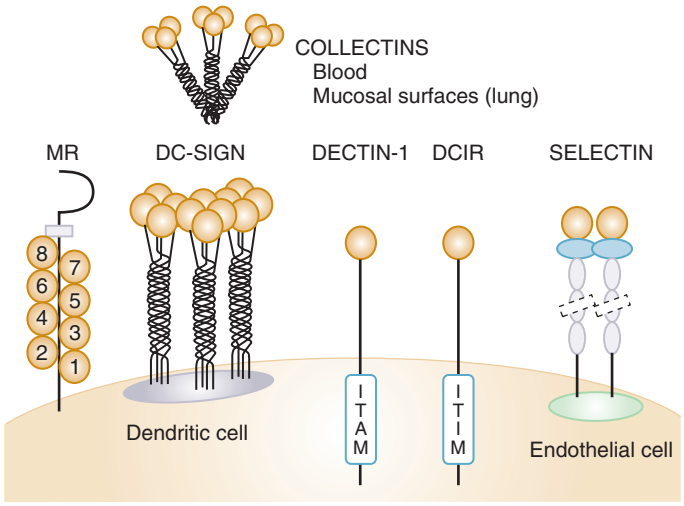
FIGURE 13-2 ■ Pulmonary collectins, especially surfactant protein A (SP-A) and SP-D, play a key role in suppressing inflammation in the absence of PAMPs, while stimulating inflammation in the presence of PAMPs. **A,** Structure of pulmonary collectins. **B,** The importance of SP-D in tonic suppression of lung inflammation is illustrated by the spontaneous proinflammatory phenotype of SP-D–deficient mice. **C,** Tonic suppression of inflammation is mediated by the binding of collectins to signal-inhibitory regulatory protein α (SIRPα) via their head groups, whereas activation of inflammation is mediated when PAMP-bound collectins interact with CD91 via their collagenous tail regions. (**A,** Adapted from Wright JR: Immunoregulatory functions of surfactant proteins. Nat Rev Immunol 5:58–86, 2005; **B,** adapted from Fisher JH, Sheftelyevich V, Ho YS, et al: Pulmonary-specific expression of SP-D corrects pulmonary lipid accumulation in SP-D gene-targeted mice. Am J Physiol Lung Cell Mol Physiol 278:L365–L373, 2000; **C,** adapted from Gardai SJ, Xiao YQ, Dickinson M, et al: By binding SIRPalpha or calreticulin/CD91, lung collectins act as dual function surveillance molecules to suppress or enhance inflammation. Cell 115:13–23, 2003.)



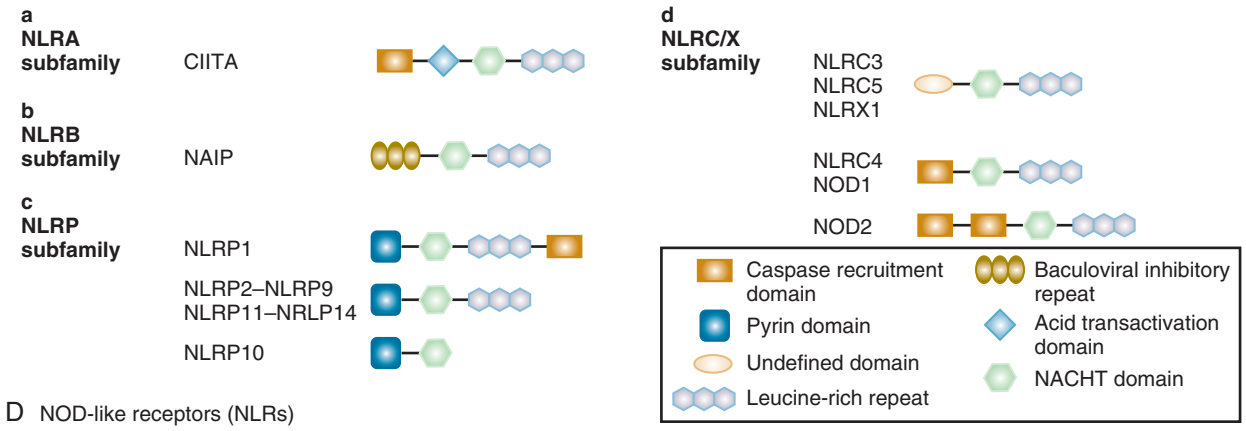
A Toll-like receptors (TLRs)



B Scavenger receptors



C C-type lectin receptors



D NOD-like receptors (NLRs)

$CD8^+$ T-cells and by promoting the development of T-regulatory (T_{Reg}) cells.[76] In the presence of an inflammatory stimulus, DCs exposed to the antigen-anti-DEC-205 fusion proteins promote long-lived immunity mediated by Ag-specific $CD4^+$ and $CD8^+$ T-cells.[77,78] Antigens delivered by targeting DEC-205 may be presented in association both with MHC class II molecules and by cross-presentation with MHC class I molecules.[79–81] Furthermore, a recent study showed that DEC-205 mediates the uptake of self-antigens via the endocytosis of apoptotic cells, thereby providing a possible mechanism for the cross-presentation of self-antigens resulting in the induction of both central and peripheral tolerance.[82]

Dendritic cell-specific receptor-1 (dectin-1) was initially thought to be a DC-specific CLR but was later shown to be expressed on macrophages, monocytes, PMNs, and some T-cell subsets.[83,84] Dectin-1 specifically recognizes β-(1,3)- and β-(1,6)-linked glucans[85] and is thought to play a key role in the nonopsonic phagocytosis of a number of pathogenic yeasts, fungi, and bacteria by macrophages and DCs.[86] Ligation of dectin-1 also stimulates the production of an array of proinflammatory cytokines, oxidants, and lipid mediators following recruitment of the Syk tyrosine kinase to the cytoplasmic tail of the receptor.[87–91] Dectin-1 also stimulates the proliferation of $CD4^+$ and $CD8^+$ T cells and serves as a costimulatory molecule.[83,92] In DCs, dectin-1 synergizes with TLR2 to induce TNF-α and interleukin (IL)-12 production but also promotes the production of IL-2 and IL-10 independent of the TLR2 pathway in a Syk kinase–dependent manner.[88] Recent studies have also begun to define the complex nature of the host's ability to recognize and clear foreign elements via dectin-1.[87] Whereas signals derived from dectin-1 can directly activate macrophages and DCs, the signaling patterns generated also influence the pattern and direction of DC activation through complex integrated signals derived from other systems such as TLRs.

DC-SIGN is also a type II CLR,[93,94] but differs from dectin-1 by its specificity for microbial mannose-rich carbohydrates.[93,95–97] Ligation of DC-SIGN activates Raf-1 kinase signaling and enhances TLR-induced cytokine expression.[98,99] DC-SIGN also mediates DC trafficking and DC–T-cell interactions through its ability to interact with ICAM-3 and ICAM-2, respectively. DC-SIGN is also expressed on the surface of a subset of peripheral blood and lung BDCA-2^+ plasmacytoid DCs (pDCs) and resident alveolar macrophages.[100] Interestingly, increased expression of DC-SIGN by alveolar macrophages has been reported in response to stimulation with IL-13, suggesting a possible role for DC-$SIGN^+$ cells in the pathogenesis of type 2 T helper (Th2)–mediated lung diseases.[100]

Cytoplasmic Pattern Recognition Receptors

Nucleotide-Binding and Oligomerization Domain–like Receptors. In humans, NLRs are a family of 22 intracellular PRRs that have evolved to sense PAMPs in the cytoplasm of most cells. Cytoplasmic PAMPs recognized by NLRs include bacterial peptidoglycans and flagellin from gram-positive and gram-negative bacteria as well as microbial toxins such as *Bacillus anthracis* lethal factor.[101–103] Earlier, we briefly introduced DAMPs as a collection of nuclear and cytoplasmic molecules including high mobility group box-1 (HMGB1), adenosine triphosphate (ATP), nicotinamide adenine dinucleotide (NAD^+), and adenosine that are released following tissue injury.[104] Though not technically DAMPs, recent studies have also shown that uric acid and crystalline silica are also sensed by NLRs and, like PAMPs, initiate noninfectious inflammatory responses.[105–107] In turn, the recognition of cytoplasmic PAMPs and DAMPs by NLRs activates an array of signal transduction pathways that lead to the activation of NF-κB and the consequent production of proinflammatory cytokines. NLRs also induce the assembly of intracellular protein-protein complexes called inflammasomes,[108–111] which stimulate IL-1β production and initiate several different forms of programmed cell death, including apoptosis, necrosis, pyroptosis, and pyronecrosis.[112]

NLRs are characterized by the presence of three functional domains: a C-terminal leucine-rich repeat domain (LRR), a core NOD or NACHT domain, and an N-terminal effector-binding domain consisting of either a pyrin-domain (PYD), a caspase activation and recruitment domain (CARD), or a baculovirus inhibitor of apoptosis protein repeat domain (Bir). NLRs are divided into subfamilies based on protein structure and include the NALPs (NACHT leucine-rich domain and pyrin-containing protein), NODs, CIITA (class II transactivator), IPAF (interleukin 1β-converting enzyme [ICE]-protease activating factor), and NAIP (neuronal apoptosis inhibitor protein) subfamilies.[113] More information about NLR structure and function is available in several recent reviews.[101,102,108,112–118]

NLRs may also play a role in the maturation of immature DCs after exposure to PAMPs or cytokines.[109] The precise mechanisms by which NLR signaling occurs is an area of intense investigation, but studies show that NLRs participate in the formation of three distinct inflammasomes including the NALP1-, NALP3- and IPAF-containing inflammasomes.[102,108] Although the role of

FIGURE 13-3 ■ Major classes of pattern recognition receptors (PRRs) expressed by lung cells. **A,** Toll-like receptors. **B,** Scavenger receptors. **C,** C-type lectin receptors. **D,** Nucleotide-binding and oligomerization domain (NOD)–like receptors. (**A,** Modified from Medzhitov R: Toll-like receptors and innate immunity. Nat Rev Immunol 1:135–145, 2001; **B,** modified from Taylor PR, Martinez-Pomares L, Stacey M, et al: Macrophage receptors and immune recognition. Annu Rev Immunol 23:901–944, 2005; **C,** redrawn from Gijzen K, Cambi A, Torensma R, Figdor CG: C-type lectins on dendritic cells and their interaction with pathogen-derived and endogenous glycoconjugates. Curr Protein Peptide Sci 7:283–294, 2006; **D,** redrawn from Geddes K, Magalhães JG, Girardin SE: Unleashing the therapeutic potential of NOD-like receptors. Nat Rev Drug Discovery 8:465–479, 2009.)

NLRs in a variety of human disorders has been characterized, the complete role of these molecules in lung homeostasis and defense is not yet fully understood.

Retinoic Acid–Inducible Gene-1–like Receptors. The last group of cytoplasmic PAMP sensors is the retinoic acid–inducible gene (RIG)-1–like receptors that have evolved to detect the presence of RNA from RNA viruses and replicating DNA viruses. Three family members, RIG-I, myeloma-differentiation associated gene 5 (MDA5), and laboratory of genetics and physiology 2 (LPG2), have been identified. All three family members contain a central ATPase and RNA-helicase domain and a C-terminal regulatory domain. The N-terminus of RIG-I and MDA5 contains a CARD domain (as recently reviewed by Nakhaei and associates).[119] RIG-1 has been shown to recognize viral RNA sequences from several viruses and is involved in the response of lung epithelial cells to influenza virus.[120,121] In contrast, MDA5 has been shown to respond to poly [I:C] and picornoviruses.[122] Upon sensing viral RNA sequences, RIG-like family members activate NF-κB and interferon regulatory factor (IRF) signaling pathways to promote the expression of type I IFNs and proinflammatory cytokines,[123] thereby inducing and augmenting host and lung innate immunity. This area of innate immunity is rapidly evolving, and it is likely that RIG-like receptors will be found to affect other areas of innate and adaptive immunity. Indeed, a recent study has implicated RIG-1 in lung tumor metastasis.[124]

Summary

Collectively, secreted, plasma membrane, endosomal, and cytosolic PRRs provide remarkable flexibility in innate protection of the lung. In the descending airways, plasma membrane PRRs, especially TLRs, are poised to sense PAMPs but are generally unable to phagocytose PAMP-containing microbes. However, TLR signaling in airway epithelial cells results in the production of proinflammatory mediators, especially chemokines and cytokines that call in PMNs and macrophages to the site of PAMP detection to enable microbial clearance. In addition, intraepithelial DCs constantly sample the airway lumen to maintain immunologic tolerance to commonly encountered antigens that do not express PAMPs while remaining poised to activate the adaptive immune system once PAMPs are sensed. It seems reasonable to suggest that in the steady state, responses to inhaled particulates and microbes occur continuously, but silently. The alveoli are also protected by epithelial cells, DCs, and resident alveolar macrophages that also sense PAMPs via plasma alveolar PRRs. However, two additional levels of protection exist. First, secreted PRRs, especially SP-A and SP-D, protect the alveolar surfaces by tonically suppressing unwanted inflammation in the steady state, while remaining poised to stimulate innate responses in the presence of PAMPs. Second, resident alveolar macrophages express an additional array of PRRs, especially SRs that promote the phagocytosis of microbes and other particulates. In the next section, we discuss how ligation of these various PRRs activate and regulate innate host defense responses in lung cells.

EFFECTOR MECHANISMS

Many cell lineages are committed to maintaining sterility and innate protection of the respiratory tract, and in this section we discuss the three broad cell types involved in protection in the steady state, namely (1) airway and alveolar epithelium, (2) macrophages and DCs, and (3) PMNs, which though not an abundant cell type in the steady state are rapidly recruited to augment lung phagocyte numbers once the presence of PAMPs is detected.

Epithelium

The lung epithelium has an important role in host defense against microbes that pass through the glottis to reach the conducting airways and gas-exchange parenchyma. The conducting airways of the lower respiratory tract are lined by ciliated columnar epithelial cells down to the terminal airways and respiratory bronchioles, which are nonciliated. In contrast, the alveolar epithelium consists of flattened type I epithelial cells that form most of the alveolar surface and type II cuboidal epithelial cells that produce surfactant and surfactant-related proteins and project into the subepithelial structures of the lungs. The classic antimicrobial defense mechanism in the conducting airways is the mucociliary system, which moves microbes deposited on the airway epithelial surface upward and out of the lungs. In addition to this physical removal system, the airway and alveolar epithelium participate actively in the innate defense of the lungs, with the major goal of protecting the critical gas-exchange surface from microbial invasion.[125] The mucociliary system provides for the removal of all particles that deposit on the airway epithelium, and the clearance times in the trachea and proximal airways are measured in minutes. The cilia on the epithelial surface beat in coordinated waves, directing the movement of particles upward toward the larynx. Epithelial cell activation is not required for optimal ciliary beating, although beat frequency can be speeded by β-agonists and slowed by opiates and other drugs.[126]

The normal constituents of airway epithelial fluid contribute to the initial inactivation of microbial particles on the airway surface (see Table 13-1). The major antibacterial components include lysozyme, lactoferrin, and β-defensins, but others are also present in lower concentrations. Lysozyme is lytic to bacterial cell walls and has broad activity. Lactoferrin binds iron, reducing its availability for microbial metabolism. The defensins have antimicrobial activity for gram-positive and gram-negative bacteria, fungi, mycobacteria, and some viruses.[127] The first member of the β-defensin family was actually identified as an expressed protein in bovine trachea.[128]

The mucociliary system and antimicrobial constituents of airway epithelial fluid can be thought of as constitutive host defenses, because they do not depend on specific microbial recognition mechanisms and do not need activation. However, the airway and alveolar epithelium also participate in innate immune mechanisms in that they express bacterial recognition molecules

common to innate immune cells and can be induced to produce an array of proinflammatory mediators that recruit leukocytes into the airways directly through the airway and alveolar epithelial walls. Airway and alveolar epithelial cells express PRRs and sense bacteria on the epithelial surface by the same TLR-dependent mechanisms used by leukocytes.[115] Among these are CD14, TLR-1, -2, -4, -6, and -9.[33,129,130] Signaling through PRRs on epithelial cells enhances the production of antimicrobial defensins by airway epithelial cells. For example, bacterial products such as LPS acting through TLR4 stimulate the release of β-defensins from human airway epithelial cells,[131] although the effect is much less than in macrophages, because human airway epithelial cells express very low amounts of the key TLR4 cofactor, MD-2.[132] Similarly, proinflammatory cytokines produced during innate immune responses, such as TNF-α, IL-1β and IFN-γ, amplify the production of β-defensins by airway epithelial cells in culture.[8,133]

In addition to defensins and other microbicidal proteins, bacterial products stimulate the airway epithelium to produce chemotactic signals that recruit inflammatory cells into the airways, and endogenous cytokines also stimulate airway and alveolar epithelial cells to amplify leukocyte migration. Bacterial LPS stimulates ciliated airway epithelial cells to produce CXC and CC chemokines, which recruit PMNs and monocytes, respectively, into the airway lumen.[131] Airway epithelial cells also produce IL-1β, IL-6, IL-8, RANTES (regulated on activation, normal T-cell expressed and secreted), granulocyte-macrophage colony-stimulating factor (GM-CSF), and transforming growth factor-β (TGF-β), in addition to other proinflammatory cytokines.[125] As with other cells involved in innate immunity, cytokine production in airway epithelial cells occurs via the activation of transcription factors NF-κB and NF-IL-6, among others.[134] Interestingly, noninfectious environmental agents like ozone,[135] asbestos,[136] diesel exhaust particles,[137] and air pollution particles[138] all lead to NF-κB activation in airway epithelial cells under experimental conditions, which is typically followed by IL-8 production and release. Airway epithelial cells also recognize unmethylated bacterial DNA by TLR9, leading to NF-κB activation and production of IL-6, IL-8, and β_2-defensin in the airways.[139] Unlike airway epithelial cells, alveolar epithelial cells do not respond directly to LPS but produce chemokines in response to TNF-α and IL-1β secreted by alveolar macrophages, which have encountered bacteria or their products in the alveolar spaces.

Studies with transgenic mice provide further support for the critical role of the lung epithelium in innate immunity and microbial defense. Skerrett and coworkers[140] showed that mice expressing a dominant negative IκB construct in distal airway epithelial cells, preventing NF-κB activation, have impaired airway PMN recruitment in response to inhaled LPS. This finding supports the importance of bacterial recognition by distal airway epithelial cells in vivo and shows that epithelium-derived cytokines produced by the NF-κB pathway probably are just as important as macrophage-derived cytokines in driving innate inflammatory responses in the airways and alveolar spaces. Hajjar and colleagues[140a] produced bone marrow chimeras in which either myeloid (leukocytes) or nonmyeloid (epithelial) cells lacked MyD88, a key adapter molecule required for signaling via all TLRs except TLR3. The mice lacking MyD88 (and, therefore, deficient TLR signaling) in nonmyeloid cells including the airway and alveolar epithelium had markedly impaired clearance of *P. aeruginosa*, whereas mice with or without MyD88 in myeloid cells had normal and equivalent bacterial clearance. This surprising result further supports the important role of the airway and alveolar epithelium in bacterial recognition and clearance from the lungs, a role that is perhaps equivalent to that of resident and recruited leukocytes.

Innate immune responses in the airway epithelium can generate or influence adaptive responses, because recognition of β-(1,3)-glucan in house dust mites stimulates the production of CCL20, a chemokine that recruits immature DCs into the airways.[141] The airway epithelium can directly influence the function of lung DCs, inducing adaptive Th2 responses that are thought to be important in the pathogenesis of asthma, and LPS responses in the airway epithelium are involved in some DC-driven Th2 cell responses.[142] Airway epithelial cells produce thymic stromal lymphopoietin, GM-CSF, IL-1β, IL-25, IL-33, and osteopontin, all of which activate DCs.[143]

An emerging concept is that deliberate stimulation of innate immunity in the airways and air spaces produces broad enhancement of antimicrobial defenses. Exposure of mice to a crude extract of nontypable *Haemophilus influenzae* bacteria via aerosol initially stimulated innate immunity and then protected the mice from lethal infection with *S. pneumoniae*.[144] This was associated with enhanced production of lysozyme, lactoferrin, and defensins in the lungs. Similarly, exposure to this crude bacterial extract protected mice from *S. aureus*, *P. aeruginosa*, and the fungus *A. fumigatus*.[145] Thus, prestimulation of innate immune mechanisms in the airway and perhaps alveolar epithelium enhances the antimicrobial activity and host defense of the lungs against a broad array of bacteria and fungi. The implication is that deliberate low-level stimulation of innate immunity in the lungs could be used as a protective strategy, but the emerging recognition of the important role of lung epithelial innate immunity in stimulating and regulating adaptive immune mechanisms raises the possibility that such a strategy might have unexpected effects.

Thus, innate immune mechanisms in the airways stimulate endogenous defenses by enhancing production of airway defensins and other antimicrobial products, by stimulating PMN and monocyte recruitment into the airways to augment antimicrobial defenses, and by setting the stage for DCs and Th2-mediated adaptive immune responses that could be important in the pathogenesis of allergic lung diseases.

Neutrophils

PMNs serve as the immediate effector arm of the innate immune system.[146,147] PMNs are produced from progenitor cells in the bone marrow, circulate for a short time

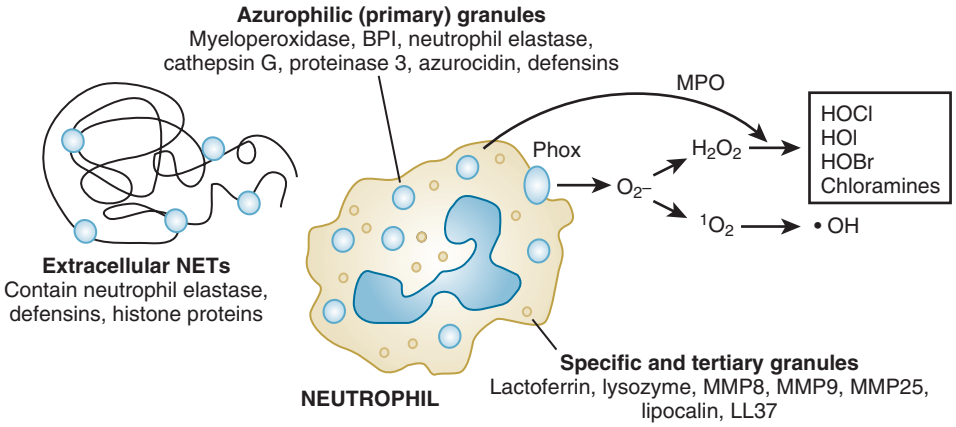


FIGURE 13-4 ■ Neutrophils use several mechanisms to kill microbes. (Mofified from Nathan C: Neutrophils and immunity: Challenges and opportunities. Nat Rev Immunol 6:173–182, 2006.)

in the bloodstream, and migrate to sites of tissue inflammation in response to signals produced by local innate immune mechanisms. The marrow progenitor cells that produce PMNs also produce monocytes, which mature into tissue macrophages and DCs. Mature PMNs are released from the marrow in response to granulocyte colony-stimulating factor (G-CSF) and other stimuli and circulate for up to 6 to 8 hours. The bone marrow releases between 10^9 and 10^{10} PMNs each day, and marrow release can increase severalfold in response to acute signals from the lungs and other tissues. PMNs contain several different kinds of cytoplasmic granules, which contain an array of proteins (Fig. 13-4). Small specific granules serve as a source of new membrane and fuse with the leading edge of the cell during migration. Primary (azurophilic) granules contain myeloperoxidase, which accounts for the green color of pus, bacterial permeability-increasing protein (BPI), PMN elastase, matrix metalloproteinases (MMPs), other proteinases, and defensins.

Circulating PMNs are spherical, with a diameter of approximately 8 μM, and must deform to make their way through the capillary microcirculation in the lungs and other organs. PMNs bear surface adhesion molecules that recognize carbohydrate and protein moieties expressed on activated endothelial cells. In the systemic circulation, PMNs migrate into tissue through postcapillary venules in a four-step process: weak adherence to the venular endothelium, rolling along the endothelial surface, arresting on the endothelial surface, and migration between endothelial junctions into tissue in response to local chemotactic gradients.[148] This paradigm is different in the lungs, where the pulmonary capillaries slow the transit of PMNs because of the small cross-sectional capillary diameter.[149,150] This produces a reservoir of capillary PMNs that are poised to respond directly to signals from the innate immune system in the air spaces. When bacteria or their products such as gram-negative LPS circulate in the bloodstream, PMNs undergo activation with cytoskeletal rearrangements that cause stiffening,[151] promoting increased entrapment of PMNs in the pulmonary capillaries.

When innate immunity is activated in the lungs, chemotactic factors are produced by resident alveolar macrophages and activated epithelium, which create soluble and tissue-fixed gradients that recruit PMNs into the alveolar spaces. Leukotriene B_4 (LTB_4) is a product of arachidonic acid metabolism in alveolar macrophages that produces an immediate and short-lived soluble gradient that recruits PMNs into the air spaces but dissipates within minutes.[152,153] Release of LTB_4 is followed closely by the release of IL-8, a chemotactic cytokine (chemokine) that binds to heparin residues on tissue matrix, creating a tissue reservoir that promotes long-lived gradients.[154,155] IL-8 is the dominant member of a group of CXC chemokines, which also include GRO-α, -β, and -γ, and ENA-78. The CXC chemokines have a C-X-C sequence at the N-terminus, which provides PMN specificity, and an N-terminal ELR peptide sequence, which is important in chemotactic receptor binding. The CXC chemokines recruit PMN to sites of inflammation, whereas chemokines with the CC N-terminal sequence recruit monocytes. IL-8 and related chemokines probably reach the endothelial luminal surface by diffusion from alveolar fluids, and bind to endothelial cell surface glycosaminoglycans to create a fixed local signal that guides PMNs sequestered in pulmonary capillaries into the air spaces. Whereas PMNs bear a single receptor for LTB_4, they express two different receptors with differing affinity for IL-8. The low-affinity receptor (CXCR2) is thought to localize PMNs at sites of inflammation, whereas the high-affinity receptor (CXCR1) is thought to guide PMN migration into tissues. The low-affinity receptor is shed from the surface of circulating PMNs in sepsis.[156] PMNs also have receptors for the complement component C5a and for formylated peptides produced by bacteria in the air spaces, so that endogenous as well as exogenous signals attract PMNs to sites of inflammation. The diversity of chemotactic stimuli recognized by PMNs promotes the formation of combinatorial gradients that guide PMN migration toward localized sites of inflammation in the lungs and other tissues.[157]

In the systemic circulation, PMN migration into tissues depends on the integrin CD11/CD18 on the PMN surface

recognizing the counterligand ICAM-1 on the endothelial surface. In the lungs, however, CD18-dependent and -independent mechanisms exist and the signals that determine whether or not PMN migration depends on CD18 are not clear.[158] For example, PMN migration into the lungs in response to *E. coli* and *P. aeruginosa* is CD18-dependent, whereas neutrophils do not require CD18 to emigrate into the air spaces in response to *S. pneumonia*. TNF-α and IL-1β appear to direct CD18-dependent migration, whereas IFN-γ is more important for CD18-independent emigration. Selectins like VLA-4 (very late antigen-4) and PECAM-1 (platelet–endothelial cell adhesion molecule-1) do not appear to regulate CD18-independent migration.

Under normal circumstances, PMN emigration is not associated with injury to the endothelial or epithelial barriers that separate the plasma compartment from the air spaces in the lungs. Endothelial cells undergo reversible contraction in response to thrombin and other inflammatory stimuli, opening endothelial junctions and allowing the passage of leukocytes. The alveolar epithelium is a much tighter barrier, and PMNs reach the air spaces with only minor and transient changes in epithelial permeability.[159,160] During migration, the spherical PMNs in the bloodstream change shape and small specific granules fuse with the leading edge of the cell membrane, providing new membrane material bearing specific adhesion molecules. PMNs in the air spaces are polarized, which is an initial sign of activation, but contain the full complement of primary azurophilic granules containing myeloperoxidase and defensins.[160] Metabolic studies of PMNs in rabbits with pneumococcal pneumonia and humans with bronchiectasis have shown that in these models, most PMN activation occurs in the air spaces and not during emigration into the lung.[161,162] However, when endothelial activation is intense, or when PMN activation signals are present within the circulation, PMNs become preactivated and migration can be associated with damage to the endothelial and epithelial barriers, with increased permeability pulmonary edema.[163]

Once in the air spaces, PMNs ingest bacteria and fungi that have been opsonized by complement and immunoglobulins that accumulate in the air spaces at sites of inflammation. PMNs contain a series of effector mechanisms to kill bacteria and fungi, including oxidant production, microbicidal proteins in primary azurophilic granules, and extracellular traps. As microbes are recognized and the phagosome begins to form, the subunits of a nicotinamide adenine dinucleotide phosphate, reduced form (NADPH) oxidase are assembled in the cell membrane and the cell undergoes a respiratory burst, in which an electron is transferred to molecular oxygen to form superoxide anion, which is reduced again to form hydrogen peroxide (H_2O_2). This happens on the invaginating phagosomal membrane, focusing oxidants on the contents of the developing phagosome. As the phagosome forms, the primary granules fuse with the phagosomal membrane, adding myeloperoxidase and cationic antimicrobial peptides to the phagolysosome. Myeloperoxidase catalyzes the formation of hypochlorous acid from H_2O_2 and a halide, typically chloride (Cl^-) because of its high concentration in the cellular environment. Hypochlorous acid is a highly reactive oxidant that oxidizes methionines, tyrosines, and other amino acids on proteins, killing the microbe.

In addition to their presence in airway surface liquid, PMN primary azurophilic granules also contain high concentrations of defensins.[127,164] Human neutrophil proteins (HNP)-1, -2, and -3 are α-defensins, so named because of the pattern of disulfide bonding in the tertiary structure of the proteins, and are abundant in azurophilic granules of PMNs. HNP-1 and -2 make up approximately 90% of the defensin proteins in PMNs. When defensins are added to the phagolysosomal space, they attach to negatively charged microbial membranes via electrostatic interactions and are thought to form lytic pores in the microbial cell wall. PMN defensins have antimicrobial activity for gram-positive and gram-negative organisms, fungi, and some viruses. Defensins are most active under conditions of low ionic strength and lose activity with increasing concentrations of salt or plasma proteins, which interfere with electrostatic interactions between the cationic defensins and the anionic microbial surface.[127] This has been proposed as a contributing factor for the pathogenesis of chronic airway infection in cystic fibrosis.[165] In addition to their antimicrobial activity, members of the defensin family participate directly in innate and adaptive immunity, because they stimulate IL-8 production by epithelial cells and modulate the responses of T-cells and immature DCs.[164,166,167]

When phagocytosis is appropriately regulated, microbial killing occurs within the protected environment of the PMN phagolysosome. However, at sites of intense inflammation, PMNs release superoxide anion, H_2O_2, and granular contents directly into the extracellular environment, leading to oxidant formation in the alveolar spaces with oxidation of structural proteins in the alveolar walls and intracellular proteins in leukocytes and the accumulation of defensins and other granular contents in the alveolar spaces.[168] These extracellular products contribute to indirect tissue injury by PMNs.

In addition to killing intracellular microbes using oxidants, chlorination, and antimicrobial peptides, as a final act, PMNs can project uncoiled nuclear DNA into the surrounding environment to form NETs (neutrophil extracellular traps) that ensnare and destroy bacteria[169,170] (Fig. 13-5). NET formation depends on the initial respiratory burst of the PMN and leads to the death of the PMN in a process that is distinct from apoptosis and necrosis.[171] The PMNs of patients with chronic granulomatous disease, which lack a functional membrane NADPH oxidase, do not form NETs with appropriate stimulation.[171] A variety of proinflammatory stimuli activate NET formation, including LPS and IL-8. C5a triggers NET formation in PMNs after priming with IFNs or GM-CSF. Some microbes, including *S. aureus*, *E. coli*, *P. aeruginosa*, and *M. tuberculosis*, directly stimulate NET formation by PMNs. The extracellular DNA mesh contains cationic proteins embedded in the negatively charged DNA net, including histones, defensins, and cathelicidin,

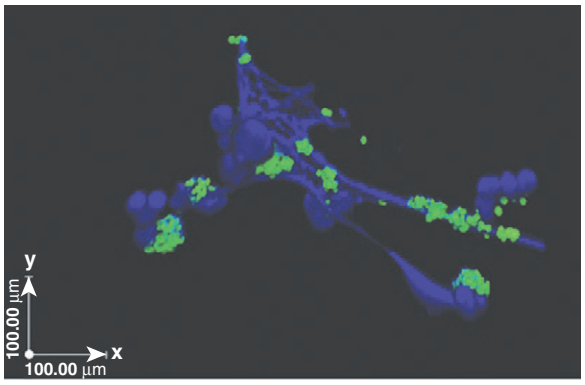


FIGURE 13-5 ■ Neutrophils can kill microbes by propelling uncoiled DNA into the surrounding environment. These have been termed neutrophil extracellular traps (NETs). (From von Kockritz-Blickwede M, Nizet V: Innate immunity turned inside-out: Antimicrobial defense by phagocyte extracellular traps. J Mol Med 87:775–783, 2009.)

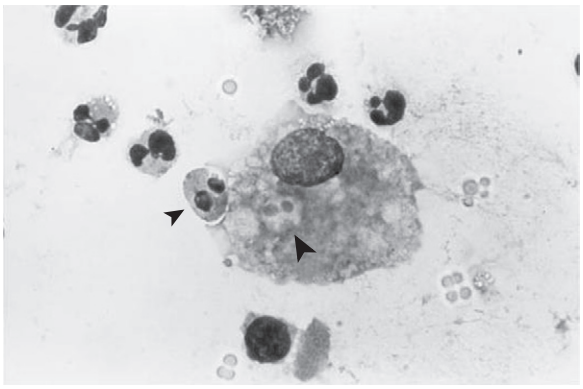


FIGURE 13-6 ■ Apoptotic PMN (*arrowheads*) being ingested by a lung macrophage in the bronchoalveolar lavage (BAL) of a patient with acute respiratory distress syndrome (ARDS). (From Matute-Bello G, Liles WC, Radella F, et al: Neutrophil apoptosis in the acute respiratory distress syndrome. Am J Respir Crit Care Med 156:1969–1977, 1997.)

which kill enmeshed bacteria. Similar extracellular traps are produced by eosinophils and mast cells, but unlike PMNs, eosinophils apparently survive NET formation. NET formation thickens secretions at sites of inflammation, creating a viscous pus that contains enmeshed microbes. As might be expected, some bacteria produce extracellular enzymes that degrade DNA NETs, including *S. pyogenes* (DNase Sda1/2) and *S. pneumoniae* (DNase EndA).[172,173] The mechanisms by which NETs are cleared from the air spaces during resolution of inflammation are not clear.

PMNs have an important role in signaling the activation of adaptive immunity. In rabbits with tuberculous pleurisy, PMNs were the first cells into the infected pleural space and were found to produce chemotactic factors that direct the subsequent wave of monocyte recruitment, which characterizes the full inflammatory reaction to *M. tuberculosis*.[174] PMN granule proteins cathepsin G and azurocidin are chemoattractants for mononuclear cells, which mature into macrophages and DCs at sites of inflammation, and neutrophil-derived CC chemokines recruit DCs.[175,176] PMNs release limited amounts of TNF-α and IFN-γ, which regulate macrophage, T-cell, and DC activation and maturation; however, the large numbers of PMNs at sites of inflammation can bring the concentrations of these PMN-derived cytokines into biologically relevant ranges. PMNs also produce CXCL-10 (IP-10, IFN-γ–inducible protein-10), which is a chemoattractant for natural killer cells and Th1 cells.[177]

At the same time that PMNs participate in and intensify inflammation in tissue, they also produce signals that control and begin the resolution of inflammation. PMNs, like macrophages and endothelial cells, release the secretory leukocyte protease inhibitor (SLPI), which inhibits PMN elastase.[178] After migration into tissues, PMNs produce lipoxins from membrane arachidonic acid, which inhibit PMN recruitment, superoxide anion generation, and NF-κB activation and enhance the uptake of apoptotic PMNs by macrophages.[179] PMN-derived oxidants inactivate proteases and other proteins at sites of inflammation.

PMNs and their products are cleared largely by macrophages during the resolution of inflammation. PMNs die primarily by apoptosis, necrosis, or NET formation. Apoptosis is a highly regulated form of cell death and is mediated by a series of intracellular caspases.[180,181] Apoptosis occurs via two major pathways: ligation of membrane death receptors, principally Fas/CD95 and TNFRI (p55), and mitochondrial stress that results in the release of cytochrome c into the cytoplasm. PMNs undergoing apoptosis express phosphatidylserine on the outer leaflet of the cell membrane and undergo nuclear chromatin condensation and cell shrinkage. Apoptotic PMNs are recognized via the CD36 receptor on macrophages and rapidly ingested, so that large numbers of apoptotic PMNs are usually not seen (Fig. 13-6). Macrophages that ingest apoptotic PMN produce TGF-β and IL-10, which have anti-inflammatory effects. This process results in the clearance of PMNs and their residual intracellular contents and dampening of inflammation. PMNs that are not ingested by macrophages undergo secondary necrosis with release of remaining intracellular contents into the inflammatory environment. When intracellular ATP levels fall to critically low levels, PMNs die by necrosis, with loss of membrane integrity, cytoplasmic swelling, and discharge of intracellular contents into the extracellular environment. Intracellular components are recognized as danger signals by macrophages, some of which have been included as "alarmins," or DAMPs.[182] DAMPs include the nuclear protein HMGB1, granular antimicrobial peptides, and other intracellular products. Macrophages that recognize these danger signals produce IL-1β, TNF-α, IL-8, and other proinflammatory cytokines, initiating or perpetuating inflammatory responses. Some PMNs recovered from the lungs of patients with acute respiratory distress syndrome (ARDS) have features of apoptosis, with small cytoplasmic features and nuclear pyknosis, whereas many have features of necrosis, including severe degranulation, membrane blebbing,

and cytoplasmic swelling. The signals that govern the balance between necrosis and apoptosis are incompletely understood.

Thus, PMNs are important effector cells in innate immunity, ideally designed to circulate through the body and accumulate rapidly at tissue sites of acute inflammation. Under normal circumstances, they arrive in tissue ready to ingest and kill microbes, then go quietly away by programmed cell death. PMN-derived signals regulate local inflammation and stimulate adaptive immune responses, providing a broader role for PMNs in host defense.

Mononuclear Phagocytes

The concept of the mononuclear phagocyte system as a functionally and phenotypically heterogeneous system of mononuclear phagocytes distributed throughout the body was developed in the 1960s and 1970s through a series of insightful studies pioneered by van Furth and Cohn[183] and Volkman and Gowans.[184] The central concept is that resident macrophages in all organs and tissues are derived from progenitor cells in the bone marrow. In turn, progenitor cells give rise to circulating blood monocytes and are recruited into organs and tissues where they differentiate into macrophages, thereby maintaining macrophage homeostasis. Heterogeneity in macrophage function and phenotype is thought to be an adaptive response to microenvironmental cues at the sites to which they have been recruited. For instance, in the lung, exposure to pulmonary surfactants and a high oxygen tension in the alveoli programs macrophages to express unique effector functions not seen in other organs. In response to additional needs during inflammation or infection, monocyte production in the bone marrow increases, thereby enabling increased monocyte recruitment to affected tissues.

In 1973, Steinman and Cohn[185] characterized a population of antigen-presenting cells in mouse spleen and, based on their morphology, coined the name *dendritic cells (DCs)*. Since the late 1980s, a vast array of monoclonal antibodies against monocytes, macrophages, and DC cell surface antigens has been developed and used in an attempt classify monocyte/macrophages and DCs as separate lineages. The issue is confusing for many reasons but particularly because macrophages exhibit many of the functions and antigenic markers of DCs, and vice versa. Indeed, in a recent position paper, David Hume[186] suggested that it is artificial to separate monocytes/macrophages and DCs into separate lineages and that the functional and antigenic divergence between these populations should be considered in the context of the known heterogeneity that occurs within the mononuclear phagocyte system. The issue of using cell surface markers to separate macrophages and DCs is particularly relevant in the lung, where CD11c is expressed at high levels on resident alveolar macrophages, interstitial macrophages, and DCs (as reviewed by Hume[186]). In addition, much of our initial understanding of the functions of resident lung mononuclear phagocytes came from studies conducted without the use of extensive cell surface marker panels or lineage tracing technologies. Thus, although it is clear that the cells described in many studies are mononuclear phagocytes, it is sometimes difficult to classify them further.

As illustrated in Figure 13-7, pulmonary mononuclear phagocytes can be broadly thought of as three overlapping subpopulations: (1) resident macrophages of the airway, alveolar surfaces, and alveolar interstitium, (2) monocytes that marginate in the lung microvasculature and are recruited into the air spaces in response to innate activation, and (3) resident and recruited DCs of the airways and lung parenchyma. In this section, we focus on the localization and innate immune functions of each group of cells.

Resident Macrophages

Resident airway and alveolar macrophages reside in the mixed environment of epithelial lining fluid and ambient inhaled air, whereas resident interstitial macrophages are located within the interstitial tissue or alveolar septae. Morphometric analyses indicate that the number of interstitial macrophages in normal lung is between one tenth and one half of the total number of alveolar macrophages.[187,188] Unlike resident alveolar and airway macrophages that can be obtained by bronchoalveolar lavage, interstitial macrophages can be obtained only by using tissue dispersion techniques. Consequently, considerably less is known about the biology and function of interstitial macrophages than about resident alveolar macrophages, especially in humans. In addition, interpreting current and past studies can be difficult because artifacts in cell phenotype and function can be introduced as a consequence of the tissue dispersion approach or by in vitro exposure to trace amounts of contaminating PAMPs during isolation. Despite these caveats, interstitial macrophages are thought to share many functional similarities with resident alveolar macrophages.

Functions of Resident and Interstitial Alveolar Macrophages. The primary functions of resident alveolar macrophages are (1) to dispose of inhaled microbes and particulates, (2) to clear pulmonary surfactant, and (3) to tonically suppress the development of inappropriate inflammatory and immune responses. Resident alveolar macrophages are capable of phagocytosing a wide spectrum of harmless and harmful microbes and other particulates. Under basal conditions, most ingested phagocytosed particulates are enclosed within phagosomes, which ultimately fuse with lysosomes, leading to their degradation by an array of acid-pH optimum hydrolytic enzymes. Some inhaled microbes (e.g., *M. tuberculosis*) and some environmental particulates (e.g., crystalline silica) are resistant to this process and become sequestered in secondary lysosomes where they remain for the lifespan of the macrophage. Most of these latter cells probably crawl into the airways and are cleared via the mucocilliary escalator, although a few probably migrate to regional draining lymph nodes, where their ultimate fate is uncertain.[189,190] Some particle-laden macrophages may remain in the lung for extended periods of time before either dying and releasing their particle burden, thereby rendering it available for phagocytosis

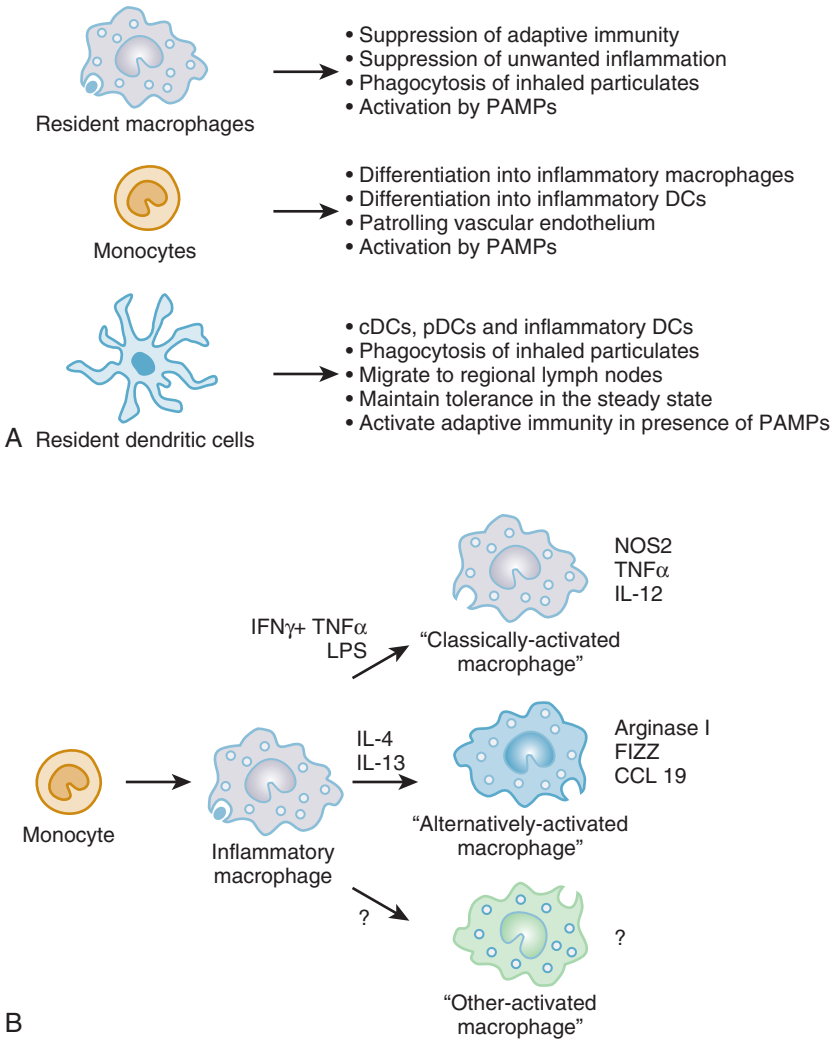


FIGURE 13-7 ■ **A,** In the steady state, lung mononuclear phagocytes can be considered to include: (i) resident macrophages of the alveoli and alveolar septae, (ii) marginating monocytes of the lung microvasculature, and (iii) resident dendritic cells. Each of these subsets exhibits overlapping and unique functions. **B,** Macrophages display distinct patterns of gene expression in response to type 1 T helper cells (Th1) and Th2 type cytokines and PAMPs. Prototypical are so-called classically and alternatively activated macrophages. It is likely that macrophages can exhibit a diverse repertoire of other states.

by other macrophages, or undergoing apoptosis and being cleared by other phagocytes.

Resident alveolar macrophages also actively contribute to the normal homeostasis of pulmonary surfactant. This point is most clearly emphasized in patients with pulmonary alveolar proteinosis (PAP), a disorder characterized by the accumulation of proteinaceous and lipid-rich surfactant in the alveoli leading to impaired gas exchange. A fundamental characteristic of the disorder is the finding that alveolar macrophage numbers are reduced, and those that are present are inefficient in clearing pulmonary surfactant.[191,192] Several studies have shown that PAP is associated with the development of autoantibodies against GM-CSF,[191–193] emphasizing the importance of GM-CSF in the activities of resident alveolar macrophages.

Last, resident alveolar macrophages play a critically important role in tonic suppression of alveolar inflammation and adaptive immunity. Based in part on studies by Maclean and associates,[194] the concept has evolved that the lung can deal with inhaled microbes and particulates until a certain threshold burden is reached. The threshold is, in part, determined by the phagocytic capacity of alveolar macrophages. Once the threshold is exceeded, microbes and other particulates are phagocytosed by resident DCs that "snorkel" through tight junctions of the alveolar epithelium to sample the alveolar compartment. Consistent with this concept, studies have shown that depletion of alveolar macrophages with liposome-encapsulated clodronate augments antigen presentation by pulmonary DCs, which in turn augments adaptive immune responses to intratracheal antigens.[195,196] Other studies have shown that resident alveolar macrophages suppress the functions of natural killer (NK) cells and plasma cells.[197,198]

The ability of resident alveolar macrophages to suppress inflammation and T-cell responses is specific to these cells and is not a characteristic of macrophages obtained from other locations or peripheral blood.[199–201] These findings suggest that the alveolar microenvironment may play an important role in the development of suppressive activity by resident alveolar macrophages. As noted earlier, the pulmonary collectins SP-A and SP-D inhibit PAMP-dependent production of proinflammatory cytokines through their interaction with SIRPα.[19] In addition, TGF-β, produced by alveolar macrophages and

activated at the surface of alveolar epithelial cells by the integrin αvβ6, has been shown to basally suppress alveolar inflammation.[202,203] Other studies have emphasized the importance of IL-10, prostaglandin E_2 and nitric oxide in the tonic suppression of alveolar inflammation and adaptive immunity.[204,205] Together, these studies suggest that resident alveolar macrophages have several mechanisms that actively suppress alveolar inflammation and the antigen-presenting activity of interstitial DCs, while remaining poised to reverse this response upon appropriate stimulation.

The tonic suppressive activity of alveolar macrophages can be relieved in several different ways. One mechanism involves exceeding the threshold phagocytic capacity of resident alveolar macrophages, thereby allowing microbes to interact with other lung cells, for example, pulmonary DCs or alveolar epithelial cells, which respond to PAMPs and other molecules by producing proinflammatory cytokines. Indeed, GM-CSF and TNF-α have been shown to reverse tonic suppression of adaptive immunity in vivo.[206] A second mechanism involves alveolar macrophages themselves. Here, PAMP recognition by the globular head groups of SP-A and SP-D enables lung collectins to interact with macrophages via calretiulin and CD91.[19] In contrast to the suppressive signal initiated when SP-A and SP-D interact with macrophages via SIRPα in the absence of PAMPs, CD91 signaling leads to the production of proinflammatory cytokines, which then augment inflammation and the recruitment of PMNs and monocytes. Thus, as summarized in Figure 13-7, resident alveolar macrophages are capable of suppressing inappropriate alveolar inflammation and adaptive immune responses to commonly encountered antigens. However, mechanisms exist to overcome this suppression to allow the recruitment of inflammatory cells, especially PMNs and monocytes, and to promote adaptive immunity.

Recruitment of Mononuclear Phagocytes

Bone-marrow–derived progenitor cells differentiate into monocytes, macrophages, and all DC subsets.[207–209] Two subsets of human and mouse circulating blood monocytes have been described that give rise to either resident macrophages or inflammatory macrophages and conventional DCs (cDCs).[210,211] In humans, these monocyte subsets are characterized as $CD14^{hi}CD16^{+}$ and $CD14^{lo}CD16^{+}$ monocytes.[212] The corresponding mouse subsets are defined as $CCR2^{hi}Ly6c^{hi}(Gr\text{-}1^{hi})CX_3CR1^{lo}$ and $CCR2^{lo}Ly6c^{lo}(Gr\text{-}1^{lo})CX_3CR1^{hi}$. Mouse $CCR2^{hi}$ and human $CD14^{hi}CD16^{+}$ monocytes are recruited to inflammatory sites in a CCR2-CCL2 (MCP-1)–dependent manner where they differentiate into inflammatory macrophages and cDCs. In contrast, $CD14^{lo}CD16^{+}$ human monocytes and $CCR2^{lo}$ mouse monocytes are considered as "resident" monocytes that patrol the lung microvasculature and contribute to the marginated monocyte pool.[213] This subset also expresses high levels of fractalkine receptor (CX_3CR1) and following interaction with fractalkine (CX_3CR1L) expressed on the luminal face of vascular endothelial cells, they transmigrate into tissues and differentiate into macrophages.[210,211] More information about the mechanisms of monocyte, macrophage, and DC migration can be found in several reviews.[214,215]

Functions of Recruited Monocytes and Macrophages. In contrast to resident alveolar macrophages, recruited monocytes and macrophages have important proinflammatory and host-defense activities including (1) microbial killing and (2) amplification of inflammation. Monocytes and macrophages kill microbes with reactive oxygen species and reactive nitrogen species. Superoxide anion (O_2^-) is mainly produced by the phagocyte NADPH oxidase.[216] Like PMNs, monocytes subsequently convert O_2^- into additional reactive oxygen species in a myeloperoxidase-dependent fashion,[217] but as they differentiate into macrophages, intracellular myeloperoxidase content declines and additional reactive oxygen species (e.g., hydroxyl radical [OH^-] are formed by the Fenton reaction.[218]

The generation of reactive oxygen species is critical to host defense against commonly encountered and pathogenic bacteria. Patients with chronic granulomatous disease and mice bearing a targeted disruption of the $p47^{phox}$ component of the NADPH oxidase[219,220] are deficient in their ability to control pulmonary and other infections.[219–222] However, inappropriate production of reactive oxygen species by macrophages (and other inflammatory cells) can result in epithelial injury that can lead to fibroproliferation as can be seen with survivors of ARDS and patients with idiopathic pulmonary fibrosis, asbestosis, or silicosis.[223–225] Thus, whereas reactive oxygen species play a vital role in the protection of the lung against microbes, inappropriate production in response to nonmicrobial particulates and pollutants including cigarette smoke[226] can result in a spectrum of injury to the airway and alveolar epithelium. Nitric oxide (NO) produced by inducible nitric oxide synthase (iNOS or NOS2) also contributes to macrophage-mediated microbial killing and epithelial injury following condensation with O_2^- to form peroxynitrite.[227,228] Whereas the importance of NO in microbial killing of *L. monocytogenes* and *M. tuberculosis* has been clearly demonstrated in mice,[229] the role of NO in host defense in humans is less clear.

Recruited monocytes and macrophages also amplify inflammation through the production of cytokines, chemokines, and lipid mediators. Studies conducted in the late 1970s indicated that macrophages hydrolyse arachidonyl-containing phospholipids in response to exposure to a variety of TLR agonists through the actions of cellular and secreted phospholipase A2 enzymes (PLA_2s).[230–233] The hydrolysis of arachidonyl-containing phospholipids by PLA_2s results in the formation of (1) lyso-phosphatidylcholine that, upon acetylation, leads to the production of platelet-activating factor (PAF)[234] and (2) arachidonic acid that serves as a substrate for the production of all eicosanoids (as reviewed by Riches and coworkers[235]).

PAF is produced within minutes of exposure of macrophages to TLR agonists and has broad proinflammatory activities that promote PMN recruitment, bronchoconstriction, and vasodilation. PAF also primes PMNs,

monocytes, and macrophages for enhanced production of proinflammatory cytokines in response to PAMPs.[236,237] Arachidonic acid is oxidized to prostaglandin E_2 (PGE_2), PGD_2, PGI_2 and thromboxane A_2 by cyclooxygenase-1 (COX-1) and COX-2, and these prostaglandins have important roles in the regulation of vascular tone and in the feedback inhibition of macrophage effector functions.[238] The principal leukotriene produced by macrophages is LTB_4, which is synthesized following TLR engagement and represents the major immediate PMN chemotactic factor produced in the lung prior to chemokine expression.[152,239]

Whereas the production of lipid mediators contributes to aspects of early lung inflammation, the production of cytokines and chemokines by macrophages and epithelial cells is necessary for the optimal recruitment of inflammatory cells and for their activation. The human chemokine family consists of four closely related subfamilies that have been classified on the basis of the presence and pattern of conserved cysteine residues and have been designated C, CC, CXC, and CXXXC families (as reviewed by Kunkel and coworkers[240] and Keane and Streiter[241]). The CXC and CC families are critical to the development of pulmonary inflammation. Members of the CXC family containing the ELR motif stimulate PMN chemotaxis, whereas family members that lack the ELR motif (e.g., CXCL10) are produced in response to IFN-γ and help regulate angiogenic responses.[242,243] In contrast, CC family members are involved primarily in the recruitment and activation of mononuclear cells. Macrophages are capable of producing CXC chemokines, especially IL-8, in the settings of acute and chronic lung inflammation in patients with bacterial pneumonia, ARDS, idiopathic pulmonary fibrosis, bronchiolitis obliterans with organizing pneumonia, and cystic fibrosis.[244–247] In addition, CC chemokines, such as macrophage inflammatory protein (MIP)–1α, are produced by macrophages in interstitial lung diseases.[248,249]

In addition to the programmed responses discussed previously, recruited monocytes differentiate into macrophages, which are capable of further differentiation. Based on earlier work in which different PAMPs were found to induce the expression of distinct patterns of macrophage gene expression,[29,250–252] the concept evolved that different patterns of gene expression could be induced in response to the conditions or stimuli that prevail at the sites to which macrophages have been recruited.[253,254] For example, exposure of macrophages to Th1 cytokines and LPS induces a pattern of gene expression characterized by increased expression of IL-12, IL-23, TNF-α, NOS2 and reduced expression of IL-10 and arginase. This response has been called "classic macrophage activation."[254] In contrast, exposure to Th2 cytokines, including IL-4 and IL-13, leads to a different pattern of gene expression characterized by increased synthesis of arginase, FIZZ, CCL19 and reduced expression of NOS2, a response often referred to as "alternative macrophage activation."[254] Defining these responses as distinct "phenotypes" can be useful in thinking about how macrophages participate in innate immunity and effector cells in the adaptive immune response (see Fig. 13-7). However, it is also more complicated than some of the simplistic schemes that have been proposed because there are often overlapping patterns of gene expression in response to other stimuli. Thus, it may be more appropriate to think about these adaptive responses as further evidence of the diversity of macrophage function. Regardless of these semantic issues, diversity in PAMP and stimulus-induced patterns of gene expression by macrophages contribute greatly to their diverse roles in innate protection of the lungs, lung cancer, repair, fibrosis, and microbial elimination.

In summary, macrophages play key roles in the maintenance of lung homeostasis through their abilities to suppress unwanted inflammation and immune responses to harmless, commonly encountered inhaled materials. However, they remain constantly poised to respond to harmful inhaled microbes and other substances. Part of this response involves calling in additional support through the recruitment of circulating blood PMNs and monocytes. In turn, recruited monocytes can differentiate into macrophages, which can then express appropriate responses to microenvironmental cues that they sense in the site to which they have been attracted.

Dendritic Cells

DCs represent an important group of phagocytic and antigen-presenting cells that act as a bridge between the innate and the adaptive immune systems. In the lung, DCs have been shown to form an extensive intra- and subepithelial network throughout the respiratory tract (Fig. 13-8). DCs are particularly abundant in the nose, trachea, large airways, and alveolar septae.[255–263] These cells continuously sample the airway and alveolar lumen by extending and retracting bulbous dendritic projections through the epithelium into the airway and alveolar lumen.[264,265] After encountering antigens and particulate matter in the airway, DCs then leave the epithelium and traffic into regional lymph nodes where they deliver stimulatory or tolerogenic signals to naïve T-cells.[266,267] This trafficking occurs constitutively in the steady state, and as such, lung DCs can be considered transient

FIGURE 13-8 ■ Airway dendritic cells exist as an interdigitating network within the epithelium and below the basement membrane. The section was stained for major histocompatibility complex (MHC) class II. (From Vermaelen K, Pauwels R: Pulmonary dendritic cells. Am J Respir Crit Care Med 172:530–551, 2005.)

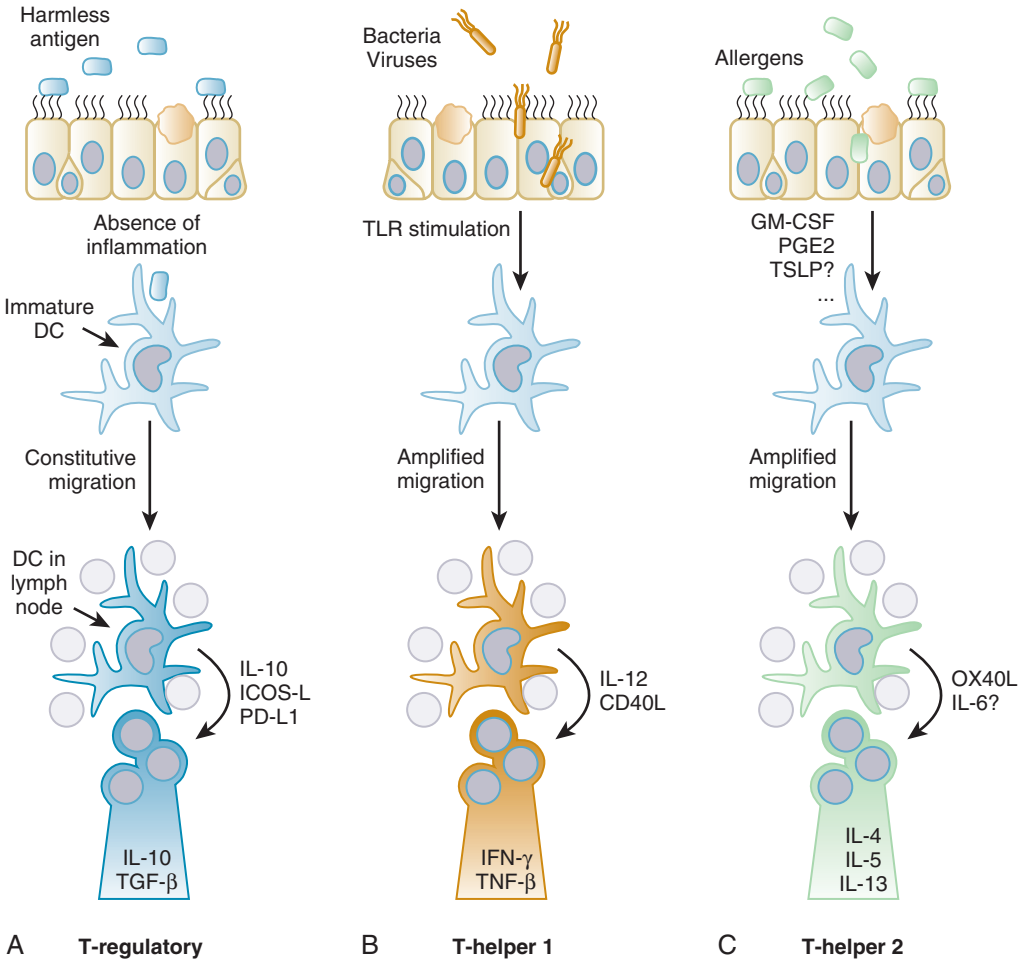


FIGURE 13-9 ■ Resident lung dendritic cells are capable of inducing the activation of CD4⁺ T-regulatory cells, as well as Th1 and Th2 CD4⁺ T-cells. (Redrawn from Vermaelen K, Pauwels R: Pulmonary dendritic cells. Am J Respir Crit Care Med 172:530–551, 2005.)

residents that are continuously replenished by bone marrow–derived precursors in the blood.[259,268,269]

Newly recruited resident DCs have an immature phenotype characterized by the expression of high levels of MHC class II and low levels of co-stimulatory molecules. These cells serve as the body's primary professional antigen-presenting cells that activate and initiate the clonal expansion of antigen-specific T-cells. DCs continually endocytose soluble and particulate materials that enter the respiratory tract. If these materials contain PAMPs, DCs will undergo a maturation program associated with the up-regulation of co-stimulatory molecules (such as CD40, CD80, and CD86), activate the expression of genes for cytokines and growth factors that promote naïve T-cell activation, and traffic to the regional lymph node (Fig. 13-9). Even in the absence of PAMPs, these DCs will not fully mature but will still traffic to lymph nodes. In the lymph nodes, DCs present MHC-peptide antigen complexes to T-cell receptors (TCRs) on naïve T-cells. TCR engagement by MHC-peptide complexes, in the presence of cytokines and co-stimulatory molecules expressed by DCs, leads to T-cell activation and expansion. The absence of the cytokines or co-stimulatory molecule engagement leads to the development of immunologic tolerance to the presented antigens (see Fig. 13-9). This is similar to the situation that occurs in the course of normal tissue turnover or following sterile injury, where DCs encounter and present self-antigen through their ability to phagocytose apoptotic cells and membrane vesicles generated by fragmenting apoptotic cells. In the absence of PAMPs, MHC-restricted presentation of self-antigens to naïve T-cells results in the delivery of a tolerogenic signal by self-antigens (see Fig. 13-9).

The ingestion of materials in the presence of PAMPs activates a program of DC maturation associated with the down-regulation of endocytic and phagocytic activities, the up-regulation of antigen-processing machinery, the up-regulation of co-stimulatory molecules expression, especially CD40, CD80, and CD86,[260,266,270] and the activation of genes encoding cytokines and growth factors that promote downstream naïve T-cell activation and maturation into T-effector cells,[271,272] which recirculate to the original site of PAMP activation to augment the development of adaptive immunity. With this general overview of DC function as a background, we now discuss in more detail the function and control of the multiple DC subsets represented in the lung. We focus largely on mouse lung DC subsets, because most

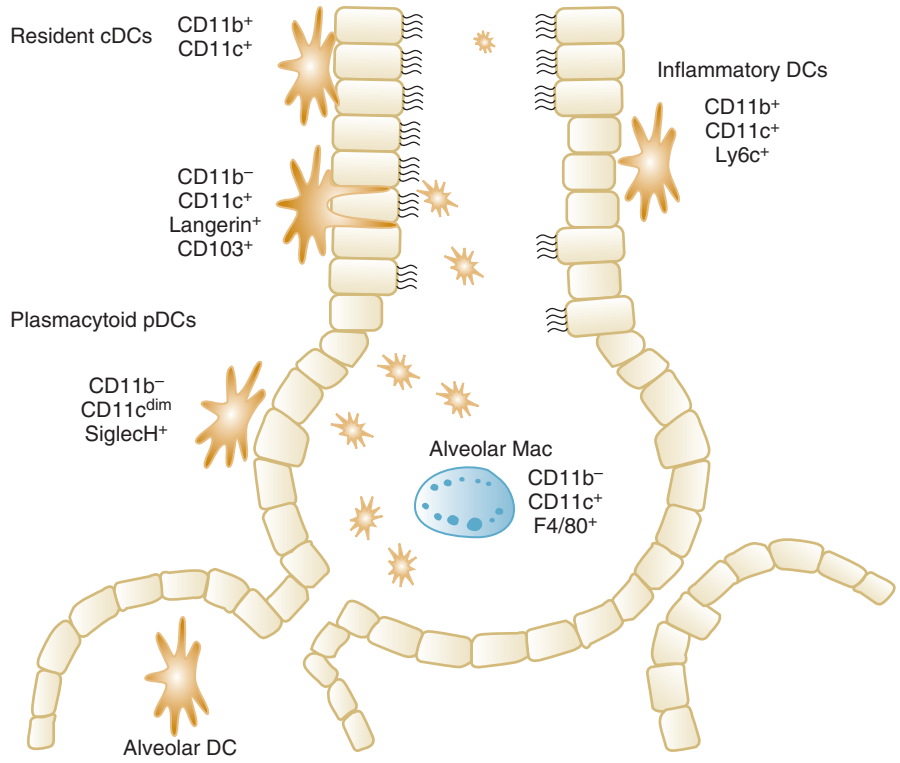


FIGURE 13-10 ■ Three major subsets of dendritic cells (DCs) exist in mouse lung: resident conventional DCs (cDCs), plasmacytoid DCs (pDCs) and inflammatory DCs. Each subset can be defined by the expression of distinct patterns of cell surface antigens recognized by monoclonal antibodies. (Redrawn from GeurtsvanKessel CH, Lambrecht BN: Division of labor between dendritic cell subsets of the lung. Mucosal Immunol 1:442–450, 2008.)

of the current knowledge has been developed in this species.

Mouse and Human Lung Dendritic Cell Subsets. Studies using cell surface markers, particularly CD11c and CD8α, initially suggested that DCs arose from both myeloid and lymphoid precursors that were thought to give rise to a bewildering array of DC subsets.[273] Recent studies in mice, however, suggest that DCs can be grouped into three major subsets, namely plasmacytoid DCs (pDCs), conventional DCs (cDCs), and inflammatory DCs (Fig. 13-10). pDCs are characterized by the presence of TLRs 7 and 9 and expression of the cell surface marker Siglec-H. They also secrete abundant quantities of type I IFNs in response to TLR ligation by PAMPs. Many TLR7 and TLR9 agonists are viral products, and their ability to stimulate type I IFN secretion by DCs is an important component in the early antiviral response. Typically, pDCs are present in low numbers in lung tissues in the steady state but are rapidly recruited into the lung when viral PAMPs are detected. Like other DCs, pDCs can also process antigens, traffic to regional lymph nodes, and participate in antigen presentation to naïve T-cells. In addition, pDCs can also restrain the activity of cDCs, thereby controlling both inflammation and the induction of adaptive immunity.

cDCs are the archetypal antigen-presenting DC and can be subdivided into migratory cDCs and lymphoid tissue resident cDCs. As their name implies, lymphoid tissue resident cDCs reside in spleen and lymph nodes and respond to antigens delivered by draining afferent lymphatic vessels. Migratory cDCs also have classic antigen-presenting functions but transiently reside in the airway epithelium and alveolar septae before migrating to regional draining lymph nodes via afferent lymphatics. Migratory cDCs extend their dendritic processes through the airway and alveolar epithelial tight junctions to capture, process, and present inhaled antigens in association with MHC class II molecules. Upon migration to lymph nodes, migratory cDCs present MHC-peptide antigen complexes and co-stimulatory molecules to naïve T cells.

In contrast to migratory cDCs and pDCs, inflammatory cDCs are absent from lymphoid and peripheral tissues under steady-state conditions. However, in response to local activation of innate immunity, peripheral blood monocytes home to sites of inflammation and/or infection and differentiate into inflammatory cDCs in response to specific cytokines, especially GM-CSF and Flt3 ligand.[208,209] The functions of inflammatory DCs are similar to those of migratory cDCs.

It is now recognized that all DCs and monocytes arise from a single myeloid progenitor cell called the macrophage and DC precursor (MDP).[274] The MDP differentiates to yield common DC precursor cells (CDPs) and monocytes. Whereas monocytes differentiate into macrophages, both monocytes and the CDPs can give rise to DCs. The CDPs can further differentiate into preconventional DCs (pre-DCs) and pDCs, whereas monocytes can

give rise to inflammatory DCs. In view of these findings, it has been suggested that the earlier classification of DCs into lymphoid DCs and myeloid DCs should be abandoned.[275]

Based on cell surface marker expression, mouse lung contains two major subsets of cDCs. All mouse lung cDCs express high levels of MHC class II proteins and the integrin CD11c, but the two subsets are differentiated by the presence or absence of CD8α (see Fig. 13-10). They can be further subdivided by the presence or absence of CD11b and/or langerin (see Fig. 13-10). Langerin$^+$ cDCs, which resemble Langerhans cells of the skin, exist together with langerin$^-$ subsets within the epithelium of the trachea and large airways.[260,276] The langerin$^+$ cDC subset also expresses CD103 and low levels of CD11b whereas the langerin$^-$ cDC subset is CD11b^{hi}CD103$^-$.[266] Ly-6C^{hi} blood monocyte progenitors give rise to both the Ly-6C^{hi} and Ly-6C^{lo} circulating monocyte subsets.[277,278] The Ly-6C^{lo} blood monocyte develops into the CD11b^{hi}CD103$^-$ lung DCs whereas the Ly-6C^{hi} blood monocytes develop into the CD11b^{lo}CD103$^+$ lung DCs.[212,279] Additional cDC subsets are found within the submucosa of the trachea and large airways. These cells are typically CD103$^-$CD11b^{hi}CD11c^{hi} and are efficient antigen-presenting cells. Though less well characterized, cDCs of the lung parenchyma are generally characterized as being CD11c^{hi}CD11b^{lo}CD8α$^-$CD205$^+$ Several excellent reviews on mouse lung DC subsets are available.[280,281]

Studies of human lung DC subsets are limited by difficulties in the availability of tissue samples, and as is the case for interstitial macrophages, there is always the possibility that methods for isolating DCs from lung tissue samples can activate and/or alter DC surface marker expression thereby introducing artifacts to the analysis. Human lung DCs are distinguished from resident alveolar macrophages by their expression of MHC class II, especially human leukocyte antigen (HLA)–DR4. In addition, human resident alveolar macrophages are highly autofluorescent whereas lung DCs exhibit low autofluorescence.[282] Human lung DCs can be distinguished from other myeloid and lymphoid cells by the absence of T-cell, B-cell, NK-cell, monocyte, and granulocyte lineage markers. MHC class II$^+$ DCs are found in normal human airway epithelium, lung parenchyma, and visceral pleura[256] and a langerin$^+$ DC subset is present in bronchioles.[283] Like the mouse, large numbers of DCs are present in alveolar septae.[255,258] Five subsets of pulmonary cDCs have been found in human lungs. Demedts and colleagues[284] identified three DC subsets in normal human lung specimens (Table 13-3). These include a CD1a$^+$MHCII$^+$BDCA-1 (blood dendritic cell antigen-1) cDC subset, another cDC subset that expresses BDCA-3$^+$ and CD11c$^+$, and a pDC subset that expresses BDCA-2$^+$ and CD123$^+$.[285] A fourth langerin$^+$ cDC subset is associated with airway mucosal epithelium. A fifth CD103$^+$Langerin$^+$CD11b^{lo} subset that express tight junction proteins, claudin 1, claudin 7, and zona occludins-2 resides beneath the basal lamina of both human and mouse mucosal epithelium.[284–287]

Inflammatory DCs arise by recruitment of blood monocyte and differentiation in response to activation of innate immune mechanisms. Inflammatory cDCs initially retain monocyte markers and are characterized as CD11c^{hi}CD11b^{hi}Ly6C^{hi}. Based on their ability to produce TNF-α and NOS2, these cells have also been called Tip-DCs,[288] though as noted earlier, this is also a property of macrophages, leading to the suggestion that DCs are really part of the broader mononuclear phagocyte system.[186]

TABLE 13-3. Subsets of Human Dendritic Cells

UPPER AIRWAY DC SUBSETS
CD8α$^-$ (CD11b$^+$CD11c$^+$MHCII$^+$)
CD8α$^-$ (CD11b$^-$ CD205$^+$)
pDC—controversial
LUNG INTERSTITIAL DC SUBSETS
CD8α$^-$ (CD11c$^+$CD11b$^+$ CD205$^+$MHCII^{hi})
CD103$^+$Langerin$^+$/CD207CD11b^{lo}—Langerhans DC
ALVEOLAR LUMEN DC SUBSETS
CD8α$^-$ (CD11c$^+$CD11b$^+$ Gr-1$^+$CD205$^+$MHCII$^+$)

DC, dendritic cell; MHC, major histocompatibility complex.

Functions of Lung Dendritic Cells. Lung DCs have the remarkable ability to change their phenotype upon exposure to PAMPs and other "danger" signals.[289,290] The maturation of immature lung DCs results in functional changes that "polarize" the DC subset. The term "polarization" is used here to indicate that the antigen-exposed DC subset acquires the ability to ultimately skew naïve T cells to become Th1, or Th2 (or possibly even Th17 or T_{Reg} cells). The ability to leave the epithelial barrier and migrate to regional lymph nodes is mediated in part by the expression of matrix MMP-9, and mice lacking MMP-9 fail to develop allergic airway inflammation.[291] When immature DCs are activated by chemokines they also down-regulate inflammatory chemokine pathways and traffic into draining lymph nodes by up-regulating CCR7. The CCR7 ligands, CCL19 and CCL21, are expressed on peripheral lymphatic endothelium and lymph node stromal cells. This mechanism serves to guide DCs from nonlymphoid into lymphoid tissues. The use of chemokines, chemoattractant receptors, selectins, and their ligands tightly regulates the migration of pDC and cDC subsets to, from, and within lung tissue. These various interactions have been reviewed by Springer[214] and Bromley and associates.[215]

Within draining regional lymph nodes, mature DCs that arrive from the lung are capable of delivering pathogen-specific signals to naïve T-cells. The further differentiation of these activated T-cells into functional T-cell subsets is driven by specific patterns of DC- and T-cell–derived cytokines that induce a fully mature T-cell response. These patterns of cytokines then sustain T-cell activation and downstream T-cell skewing.[289] For example, IL-12, IL-13, and IL-27, type 1 IFNs, and ICAM engagement drives the polarization of naïve T-cell into the Th1 phenotype. In contrast, CCL2 and OX40 ligand

promotes Th2 phenotype polarization, whereas IL-10 and TGF-β promote T_{Reg} development. The patterns of T-cell cytokine production that develop after exposure to a pathogen are relatively specific to that pathogen and determine in large part the resultant DC subset–driven T-cell response. This mixture of signaling molecules includes pro- and anti-inflammatory cytokines, reactive oxygen species, chemokines, eicosinoids, heat shock proteins, extracellular matrix proteins, and endogenous molecules such as histamine and PGE_2 that polarize the T-cell phenotype. However, T-cell polarization is not fixed and can change based on alterations in these signaling patterns, which can occur during the maturation of the host response to a pathogen. Nevertheless, in general, the concept that antigens plus PAMPs polarize lung DCs toward antigen-specific T-cell immunity whereas antigens alone polarize lung DCs toward antigen tolerance[292] appears to be correct. A major benefit of the ability of lung DCs to recognize and clear material present in inhaled air is to maintain efficient oxygen exchange in the lung. Even with chronic exposure, either the majority of harmless antigenic materials are eliminated and fail to trigger lung inflammation or they generate antigenic tolerance.[293] In this way, the lung both removes harmless substances from the airway and maintains tolerance to some antigens that are encountered daily by breathing while at the same time ensuring that the lung does not mount an inflammatory or immune response that could result in lung damage.

Most inhaled materials are exhaled.[294] Materials that are sampled by airway DCs are directed to intracellular compartments, resulting in the processing and presentation of their associated antigens and ultimately leading to the activation of naïve T-cells.[294–296] Endocytosed antigenic proteins are degraded into peptides and become associated with MHCII molecules within endolysosomal compartments that later fuse with the endplasmic reticulum. Antigen processing results in the generation of complexes consisting of antigenic peptides bound to MHC class I or class II molecules (MHCIp or MHCIIp). These complexes can engage naïve T-cell TCRs, which is followed by polarization of these T-cells into Th1, Th2, Th17, or T_{Reg} subsets.[297,298] DCs also present lipid antigens to naïve T-cells in complexes with the MHC-like molecule CD1. Both MHCII and CD1 molecules traffic within the same endosomal compartments where they are loaded with either peptides or lipids, respectively.[299] There are recent helpful reviews on the regulation and assembly of CD1-lipid, MHCIp, and MHCIIp complexes.[300,301] With the exception of viral antigens that are synthesized within the infected cell and host-derived intracellular antigens, extracellular antigens that ultimately become associated with MHCI initially gain entry to the DC via endocytosis or phagocytosis, but must escape the endosome. Once in the cytosol, these antigens are processed by the proteosome where they gain access to the transporter of antigenic peptide and endoplasmic reticulum. Subsequently, these antigens are degraded into peptides and then loaded into MHCI molecules to form MHCIp complexes for transport to the DC's surface.[302–305] Pinocytic uptake of exogenous antigens and phagocytosis of apoptotic cells that contain exogenous antigens (or even phagocytosis of exosomes, small vesicles released by apoptotic cells) promote entry of antigens into the cytosolic pathway and peptide loading into MHCI molecules for cross-presentation of MHCIp complexes to naive T-cells.[306,307]

Lung DCs can process and present viral antigens through phagocytosis of infected epithelial cells and cross-presentation. These cells also stimulate antiviral immunity via their ability to secrete antiviral type I IFNs (especially pDC), activate naïve Th lymphocytes, and induce T-effector memory cell responses.[308–310] The further differentiation of these activated T-cells into functional T-cell subsets is discussed in detail in Chapter 14.

SYSTEM INTEGRATION

The innate and adaptive immune systems have evolved to protect the lungs from harm by environmentally acquired microbes and other inhaled substances as well as from host-derived harmful stressors such as unwanted inflammation and inappropriate activation of adaptive immunity. A core concept is that innate immune protection in the lungs is not a consequence of individualized responses of individual cells but, rather, represents coordinated responses and collective cooperation between many resident and recruited lung cell types. These coordinated events result in maintenance of sterility of the airways and gas-exchange units, tolerance to harmless inhaled substances and self-antigens, and vigilance to respond to harmful microbes and substances. In addition, innate immune mechanisms assist in the rapid resolution of injury and restoration of lung homeostasis and function.

From the nose to the alveolus, the respiratory epithelium, interdigitating DCs, and resident and recruited macrophages have evolved exquisite, diverse, and overlapping mechanisms to distinguish between harmful and harmless. In its simplest form, this distinction is achieved by sensing the presence of microbial PAMPs. In the absence of PAMPs, the epithelium remains largely ignorant of inhaled particulates, whereas "snorkeling" DCs continuously sample the airways and alveoli for particles, antigens, and apoptotic cells to phagocytose, degrade, and present antigen to lymph node resident naïve $CD4^+$ and $CD8^+$ T-cells, thereby maintaining tolerance to harmless commonly encountered antigens and self-antigens. Similarly, resident macrophages phagocytose and dispose of particulates that reach the alveoli, while tonically maintaining an anti-inflammatory and immunosuppressive environment through the production of anti-inflammatory cytokines, especially TGF-β and IL-10, and eicoansoids such as PGE_2.

Integration of innate functions is dependent on cell-cell communication. In some settings, communication is fostered by proximity, as DCs exist as a network within airway epithelium and contact each other through tight junctions; whereas resident alveolar macrophages use integrins to communicate with alveolar epithelial cells.

In other settings, cell-cell communication is mediated through the secretion of a vast array of cytokines and lipid mediators, which can act in autocrine or paracrine fashions. Thus, different cell lineages can communicate with each other and among themselves. Communication between different cell types also plays an important role in the coordination of innate immunity and in the activation of adaptive immunity. For example, the finding that experimental or genetic depletion of resident alveolar macrophages results in the induction of alveolitis and lung injury, and diminishing tolerance to inhaled antigens,[311,312] emphasizes the importance of resident alveolar macrophages in suppressing inflammation and the activation of adaptive immunity. Integration of innate immunity in the lung is also associated with "coordinated burden sharing." For example, airway goblet cells and submucosal glands produce mucus, whereas ciliated epithelial cells propel mucus and entrapped particulates toward the pharynx. Similar coordinated burden sharing is exhibited by airway epithelial cells, which are poorly phagocytic but are highly capable of sensing PAMPs and calling in PMNs and monocytes, which in turn are highly phagocytic and microbicidal and eliminate an array of microbes. Together, these integrated systems have evolved to provide the lungs with maximum protection against harmful microbes while minimizing harmful responses against harmless inhaled substances. The net result is an exquisite system for protecting the gas-exchange parenchyma of the lungs, which is critical for survival.

KEY POINTS

The following is a brief summary that will help readers navigate the complex literature in this rapidly evolving, expanding, and important field of investigation:

Innate Immunity

- A primitive system of host defense system broadly based on the recognition of repetitive structures on microbes called "pathogen-associated molecular patterns" (PAMPs) by "pattern recognition receptors" (PRRs) expressed on lung cells.

Components of Lung Innate Immunity

- Airway epithelium
  - Tracheal and large airways are protected by mucus, which traps large inhaled particulates that are then transported to the pharynx by muciliary transport.
  - Airway surface liquid contains antibacterial proteins (e.g., lysozyme, lactoferrin) and peptide (e.g., defensins).
  - Airway epithelial cells respond to PAMPs by producing chemokines, cytokines, and lipid mediators, which recruit PMNs and monocytes.
- Alveolar epithelium
  - Alveoli are protected by SP-A and SP-D, which serve as microbial opsonins.
  - SP-A and SP-D also serve to suppress unwanted inflammation and adaptive immune responses to commonly encountered antigens.
- Neutrophils
  - Recruited to the airways and alveoli when airway and alveolar epithelial cells detect PAMPs.
  - Phagocytose and kill microbes by combined oxidative and nonoxidative mechanisms.
- Macrophages
  - Resident cells of the airway and alveolar lumen.
  - Suppress unwanted alveolar inflammation and adaptive immunity in the steady state.
  - Activated by PAMPs to amplify inflammation via the production of chemokines, cytokines, and lipid mediators.
  - Phagocytic cells capable of removing a wide range of microbial and nonmicrobial inhaled particulates.
- Dendritic cells
  - Three kinds of DCs, pDC, cDC, and inflammatory DC.
  - cDCs transiently reside in the airways and alveolar septae.

continued

KEY POINTS—CONT'D

- cDCs constantly sample airway and alveolar lumen contents by phagocytosis.
- In absence of PAMPs, immature cDCs traffic to regional lymph nodes and promote tolerance to inhaled antigens.
- In presence of PAMPs, cDCs mature, express co-stimulatory molecules, and activate effector T-cells.
- Depending on the mix of signals they receive, cDCs can polarize Th1, Th2, Th17, or T_{Reg} cell development

Integration of Innate Immunity

- The cell lineages of innate lung immunity collaborate to promote optimal responses to perceived danger signals (primarily PAMPs) while maintaining tolerance to inhaled antigens in the steady state.

References

1. Sodergren E, Weinstock GM, Davidson EH, et al: The genome of the sea urchin *Strongylocentrotus purpuratus*. Science 314:941–952, 2006.
2. Bodem CR, Lampton LM, Miller DP, et al: Endobronchial pH. Relevance of aminoglycoside activity in gram-negative bacillary pneumonia. Am Rev Respir Dis 127:39–41, 1983.
3. Goldman MJ, Anderson GM, Stolzenberg ED, et al: Human beta-defensin-1 is a salt-sensitive antibiotic in lung that is inactivated in cystic fibrosis. Cell 88:553–560, 1997.
4. Bals R, Wang X, Wu Z, et al: Human beta-defensin 2 is a salt-sensitive peptide antibiotic expressed in human lung. J Clin Invest 102:874–880, 1998.
5. Bals R, Wang X, Zasloff M, Wilson JM: The peptide antibiotic LL-37/hCAP-18 is expressed in epithelia of the human lung where it has broad antimicrobial activity at the airway surface. Proc Natl Acad Sci U S A 95:9541–9546, 1998.
6. Jia HP, Schutte BC, Schudy A, et al: Discovery of new human beta-defensins using a genomics-based approach. Gene 263:211–218, 2001.
7. Garcia JR, Krause A, Schulz S, et al: Human beta-defensin 4: A novel inducible peptide with a specific salt-sensitive spectrum of antimicrobial activity. FASEB J 15:1819–1821, 2001.
8. Singh PK, Jia HP, Wiles K, et al: Production of beta-defensins by human airway epithelia. Proc Natl Acad Sci U S A 95:14961–14966, 1998.
9. Harder J, Meyer-Hoffert U, Teran LM, et al: Mucoid *Pseudomonas aeruginosa*, TNF-alpha, and IL-1beta, but not IL-6, induce human beta-defensin-2 in respiratory epithelia. Am J Respir Cell Mol Biol 22:714–721, 2000.
10. Beisswenger C, Bals R: Functions of antimicrobial peptides in host defense and immunity. Curr Protein Pept Sci 6:255–264, 2005.
11. Alekseeva L, Huet D, Femenia F, et al: Inducible expression of beta defensins by human respiratory epithelial cells exposed to *Aspergillus fumigatus* organisms. BMC Microbiol 9:33, 2009.
12. Thompson AB, Bohling T, Payvandi F, Rennard SI: Lower respiratory tract lactoferrin and lysozyme arise primarily in the airways and are elevated in association with chronic bronchitis. J Lab Clin Med 115:148–158, 1990.
13. Zhao YX, Andoh A, Shimada M, et al: Secretion of complement components of the alternative pathway (C3 and factor B) by the human alveolar type II epithelial cell line A549. Int J Mol Med 5:415–419, 2000.
14. Haagsman HP, Hogenkamp A, van Eijk M, Veldhuizen EJ: Surfactant collectins and innate immunity. Neonatology 93:288–294, 2008.
15. McCormack FX, Whitsett JA: The pulmonary collectins, SP-A and SP-D, orchestrate innate immunity in the lung. J Clin Invest 109:707–712, 2002.
16. Crouch E, Hartshorn K, Ofek I: Collectins and pulmonary innate immunity. Immunol Rev 173:52–65, 2000.
17. Pikaar JC, Voorhout WF, van Golde LM, et al: Opsonic activities of surfactant proteins A and D in phagocytosis of gram-negative bacteria by alveolar macrophages. J Infect Dis 172:481–489, 1995.
18. Madan T, Eggleton P, Kishore U, et al: Binding of pulmonary surfactant proteins A and D to *Aspergillus fumigatus* conidia enhances phagocytosis and killing by human neutrophils and alveolar macrophages. Infect Immun 65:3171–3179, 1997.
19. Gardai SJ, Xiao YQ, Dickinson M, et al: By binding SIRPalpha or calreticulin/CD91, lung collectins act as dual function surveillance molecules to suppress or enhance inflammation. Cell 115:13–23, 2003.
20. LeVine AM, Kurak KE, Bruno MD, et al: Surfactant protein-A-deficient mice are susceptible to Pseudomonas aeruginosa infection. Am J Respir Cell Mol Biol 19:700–708, 1998.
21. Giannoni E, Sawa T, Allen L, et al: Surfactant proteins A and D enhance pulmonary clearance of *Pseudomonas aeruginosa*. Am J Respir Cell Mol Biol 34:704–710, 2006.
22. Botas C, Poulain F, Akiyama J, et al: Altered surfactant homeostasis and alveolar type II cell morphology in mice lacking surfactant protein D. Proc Natl Acad Sci U S A 95:11869–11874, 1998.
23. Kuronuma K, Mitsuzawa H, Takeda K, et al: Anionic pulmonary surfactant phospholipids inhibit inflammatory responses from alveolar macrophages and U937 cells by binding the lipopolysaccharide interacting proteins CD14 and MD2. J Biol Chem 284:488–500, 2009.
24. Roozendaal R, Carroll MC: Emerging patterns in complement-mediated pathogen recognition. Cell 125:29–32, 2006.
25. Walport MJ: Complement. First of two parts. N Engl J Med 344:1058–1066, 2001.
26. Walport MJ: Complement. Second of two parts. N Engl J Med 344:1140–1144, 2001.
27. Strunk RC, Eidlen DM, Mason RJ: Pulmonary alveolar type II epithelial cells synthesize and secrete proteins of the classical and alternative complement pathways. J Clin Invest 81:1419–1426, 1988.
28. van Kooten C, Fiore N, Trouw LA, et al: Complement production and regulation by dendritic cells: Molecular switches between tolerance and immunity. Mol Immunol 45:4064–4072, 2008.
29. Riches DW, Henson PM, Remigio LK, et al: Differential regulation of gene expression during macrophage activation with a polyribonucleotide. The role of endogenously derived IFN. J Immunol 141:180–188, 1988.
30. He X, Han B, Liu M: Long pentraxin 3 in pulmonary infection and acute lung injury. Am J Physiol Lung Cell Mol Physiol 292:L1039–L1049, 2007.
31. Manfredi AA, Rovere-Querini P, Bottazzi B, et al: Pentraxins, humoral innate immunity and tissue injury. Curr Opin Immunol 20:538–544, 2008.

32. Zhang XL, Ali MA: Ficolins: Structure, function and associated diseases. Adv Exp Med Biol 632:105–115, 2008.
33. Armstrong L, Medford AR, Uppington KM, et al: Expression of functional Toll-like receptor-2 and -4 on alveolar epithelial cells. Am J Respir Cell Mol Biol 31:241–245, 2004.
34. Sha Q, Truong-Tran AQ, Plitt JR, et al: Activation of airway epithelial cells by Toll-like receptor agonists. Am J Respir Cell Mol Biol 31:358–364, 2004.
35. Muir A, Soong G, Sokol S, et al: Toll-like receptors in normal and cystic fibrosis airway epithelial cells. Am J Respir Cell Mol Biol 30:777–783, 2004.
36. Underhill DM, Ozinsky A: Toll-like receptors: Key mediators of microbe detection. Curr Opin Immunol 14:103–110, 2002.
37. Jin MS, Lee JO: Structures of the Toll-like receptor family and its ligand complexes. Immunity 29:182–191, 2008.
38. Jin MS, Lee JO: Structures of TLR-ligand complexes. Curr Opin Immunol 20:414–419, 2008.
39. Kawai T, Akira S: TLR signaling. Semin Immunol 19:24–32, 2007.
40. Takeda K, Kaisho T, Akira S: Toll-like receptors. Annu Rev Immunol 21:335–376, 2003.
41. Takeuchi O, Kawai T, Sanjo H, et al: TLR6: A novel member of an expanding Toll-like receptor family. Gene 231:59–65, 1999.
42. Sugawara I, Yamada H, Li C, et al: Mycobacterial infection in TLR2 and TLR6 knockout mice. Microbiol Immunol 47:327–336, 2003.
43. Takeuchi O, Sato S, Horiuchi T, et al: Cutting edge: Role of Toll-like receptor 1 in mediating immune response to microbial lipoproteins. J Immunol 169:10–14, 2002.
44. Takeda K, Akira S: Toll-like receptors. *In* Coico R (ed): Current Protocols in Immunology. Malden, MA: John Wiley and Sons, Inc., 2007, pp. 14.12.11–14.12.13.
45. Ozinsky A, Underhill DM, Fontenot JD, et al: The repertoire for pattern recognition of pathogens by the innate immune system is defined by cooperation between Toll-like receptors. Proc Natl Acad Sci U S A 97:13766–13771, 2000.
46. Schulz O, Diebold SS, Chen M, et al: Toll-like receptor 3 promotes cross-priming to virus-infected cells. Nature 433:887–892, 2005.
47. Edelmann KH, Richardson-Burns S, Alexopoulou L, et al: Does Toll-like receptor 3 play a biological role in virus infections? Virology 322:231–238, 2004.
48. Diebold SS, Kaisho T, Hemmi H, et al: Innate antiviral responses by means of TLR7-mediated recognition of single-stranded RNA. Science 303:1529–1531, 2004.
49. Krug A, Rothenfusser S, Hornung V, et al: Identification of CpG oligonucleotide sequences with high induction of IFN-alpha/beta in plasmacytoid dendritic cells. Eur J Immunol 31:2154–2163, 2001.
50. Hengge UR, Benninghoff B, Ruzicka T, Goos M: Topical immunomodulators—Progress towards treating inflammation, infection, and cancer. Lancet Infect Dis 1:189–198, 2001.
51. Goldstein JL, Ho YK, Basu SK, Brown MS: Binding site on macrophages that mediates uptake and degradation of acetylated low density lipoprotein, producing massive cholesterol deposition. Proc Natl Acad Sci U S A 76:333–337, 1979.
52. Brown MS, Basu SK, Falck JR, et al: The scavenger cell pathway for lipoprotein degradation: Specificity of the binding site that mediates the uptake of negatively-charged LDL by macrophages. J Supramol Struct 13:67–81, 1980.
53. Peiser L, Gough PJ, Kodama T, Gordon S: Macrophage class A scavenger receptor-mediated phagocytosis of *Escherichia coli*: Role of cell heterogeneity, microbial strain, and culture conditions in vitro. Infect Immun 68:1953–1963, 2000.
54. Thomas CA, Li Y, Kodama T, et al: Protection from lethal gram-positive infection by macrophage scavenger receptor–dependent phagocytosis. J Exp Med 191:147–156, 2000.
55. Suzuki H, Kurihara Y, Takeya M, et al: A role for macrophage scavenger receptors in atherosclerosis and susceptibility to infection. Nature 386:292–296, 1997.
56. Arredouani MS, Yang Z, Imrich A, et al: The macrophage scavenger receptor SR-AI/II and lung defense against pneumococci and particles. Am J Respir Cell Mol Biol 35:474–478, 2006.
57. Elomaa O, Kangas M, Sahlberg C, et al: Cloning of a novel bacteria-binding receptor structurally related to scavenger receptors and expressed in a subset of macrophages. Cell 80:603–609, 1995.
58. Doyle SE, O'Connell RM, Miranda GA, et al: Toll-like receptors induce a phagocytic gene program through p38. J Exp Med 199:81–90, 2004.
59. van der Laan LJ, Dopp EA, Haworth R, et al: Regulation and functional involvement of macrophage scavenger receptor MARCO in clearance of bacteria in vivo. J Immunol 162:939–947, 1999.
60. Arredouani M, Yang Z, Ning Y, et al: The scavenger receptor MARCO is required for lung defense against pneumococcal pneumonia and inhaled particles. J Exp Med 200:267–272, 2004.
61. Sun K, Metzger DW: Inhibition of pulmonary antibacterial defense by interferon-gamma during recovery from influenza infection. Nat Med 14:558–564, 2008.
62. Arredouani MS, Palecanda A, Koziel H, et al: MARCO is the major binding receptor for unopsonized particles and bacteria on human alveolar macrophages. J Immunol 175:6058–6064, 2005.
63. Palecanda A, Paulauskis J, Al-Mutairi E, et al: Role of the scavenger receptor MARCO in alveolar macrophage binding of unopsonized environmental particles. J Exp Med 189:1497–1506, 1999.
64. Thakur SA, Hamilton R Jr, Pikkarainen T, Holian A: Differential binding of inorganic particles to MARCO. Toxicol Sci 107:238–246, 2009.
65. Dahl M, Bauer AK, Arredouani M, et al: Protection against inhaled oxidants through scavenging of oxidized lipids by macrophage receptors MARCO and SR-AI/II. J Clin Invest 117:757–764, 2007.
66. Thakur SA, Beamer CA, Migliaccio CT, Holian A: Critical role of MARCO in crystalline silica–induced pulmonary inflammation. Toxicol Sci 108:462–471, 2009.
67. Mayer AK, Muehmer M, Mages J, et al: Differential recognition of TLR-dependent microbial ligands in human bronchial epithelial cells. J Immunol 178:3134–3142, 2007.
68. Wintergerst ES, Jelk J, Asmis R: Differential expression of CD14, CD36 and the LDL receptor on human monocyte-derived macrophages. A novel cell culture system to study macrophage differentiation and heterogeneity. Histochem Cell Biol 110:231–241, 1998.
69. Urban BC, Willcox N, Roberts DJ: A role for CD36 in the regulation of dendritic cell function. Proc Natl Acad Sci U S A 98:8750–8755, 2001.
70. Hoebe K, Georgel P, Rutschmann S, et al: CD36 is a sensor of diacylglycerides. Nature 433:523–527, 2005.
71. Stuart LM, Deng J, Silver JM, et al: Response to *Staphylococcus aureus* requires CD36-mediated phagocytosis triggered by the COOH-terminal cytoplasmic domain. J Cell Biol 170:477–485, 2005.
72. Baranova IN, Kurlander R, Bocharov AV, et al: Role of human CD36 in bacterial recognition, phagocytosis, and pathogen-induced JNK-mediated signaling. J Immunol 181:7147–7156, 2008.
73. Hirano K, Kuwasako T, Nakagawa-Toyama Y, et al: Pathophysiology of human genetic CD36 deficiency. Trends Cardiovasc Med 13:136–141, 2003.
74. Gijzen K, Cambi A, Torensma R, Figdor CG: C-type lectins on dendritic cells and their interaction with pathogen-derived and endogenous glycoconjugates. Curr Protein Pept Sci 7:283–294, 2006.
75. Jiang W, Swiggard WJ, Heufler C, et al: The receptor DEC-205 expressed by dendritic cells and thymic epithelial cells is involved in antigen processing. Nature 375:151–155, 1995.
76. Mahnke K, Qian Y, Knop J, Enk AH: Induction of $CD4^+/CD25^+$ regulatory T cells by targeting of antigens to immature dendritic cells. Blood 101:4862–4869, 2003.
77. Bonifaz LC, Bonnyay DP, Charalambous A, et al: In vivo targeting of antigens to maturing dendritic cells via the DEC-205 receptor improves T cell vaccination. J Exp Med 199:815–824, 2004.
78. Hawiger D, Inaba K, Dorsett Y, et al: Dendritic cells induce peripheral T cell unresponsiveness under steady state conditions in vivo. J Exp Med 194:769–779, 2001.
79. Bonifaz L, Bonnyay D, Mahnke K, et al: Efficient targeting of protein antigen to the dendritic cell receptor DEC-205 in the steady state leads to antigen presentation on major histocompatibility complex class I products and peripheral $CD8^+$ T cell tolerance. J Exp Med 196:1627–1638, 2002.

80. Heath WR, Belz GT, Behrens GM, et al: Cross-presentation, dendritic cell subsets, and the generation of immunity to cellular antigens. Immunol Rev 199:9–26, 2004.
81. Mahnke K, Guo M, Lee S, et al: The dendritic cell receptor for endocytosis, DEC-205, can recycle and enhance antigen presentation via major histocompatibility complex class II–positive lysosomal compartments. J Cell Biol 151:673–684, 2000.
82. Shrimpton RE, Butler M, Morel AS, et al: CD205 (DEC-205): A recognition receptor for apoptotic and necrotic self. Mol Immunol 46:1229–1239, 2009.
83. Ariizumi K, Shen GL, Shikano S, et al: Identification of a novel, dendritic cell-associated molecule, dectin-1, by subtractive cDNA cloning. J Biol Chem 275:20157–20167, 2000.
84. Taylor PR, Brown GD, Reid DM, et al: The beta-glucan receptor, dectin-1, is predominantly expressed on the surface of cells of the monocyte/macrophage and neutrophil lineages. J Immunol 169:3876–3882, 2002.
85. Brown GD, Gordon S: Immune recognition. A new receptor for beta-glucans. Nature 413:36–37, 2001.
86. Herre J, Gordon S, Brown GD: Dectin-1 and its role in the recognition of beta-glucans by macrophages. Mol Immunol 40:869–876, 2004.
87. Gantner BN, Simmons RM, Canavera SJ, et al: Collaborative induction of inflammatory responses by dectin-1 and Toll-like receptor 2. J Exp Med 197:1107–1117, 2003.
88. Rogers NC, Slack EC, Edwards AD, et al: Syk-dependent cytokine induction by Dectin-1 reveals a novel pattern recognition pathway for C type lectins. Immunity 22:507–517, 2005.
89. Underhill DM, Rossnagle E, Lowell CA, Simmons RM: Dectin-1 activates Syk tyrosine kinase in a dynamic subset of macrophages for reactive oxygen production. Blood 106:2543–2550, 2005.
90. Gantner BN, Simmons RM, Underhill DM: Dectin-1 mediates macrophage recognition of *Candida albicans* yeast but not filaments. EMBO J 24:1277–1286, 2005.
91. Steele C, Marrero L, Swain S, et al: Alveolar macrophage-mediated killing of *Pneumocystis carinii* f. sp. muris involves molecular recognition by the Dectin-1 beta-glucan receptor. J Exp Med 198:1677–1688, 2003.
92. Grunebach F, Weck MM, Reichert J, Brossart P: Molecular and functional characterization of human Dectin-1. Exp Hematol 30:1309–1315, 2002.
93. Khoo US, Chan KY, Chan VS, Lin CL: DC-SIGN and L-SIGN: The SIGNs for infection. J Mol Med 86:861–874, 2008.
94. Serrano-Gomez D, Dominguez-Soto A, Ancochea J, et al: Dendritic cell–specific intercellular adhesion molecule 3–grabbing nonintegrin mediates binding and internalization of *Aspergillus fumigatus* conidia by dendritic cells and macrophages. J Immunol 173:5635–5643, 2004.
95. Cambi A, Koopman M, Figdor CG: How C-type lectins detect pathogens. Cell Microbiol 7:481–488, 2005.
96. Koppel EA, van Gisbergen KP, Geijtenbeek TB, van Kooyk Y: Distinct functions of DC-SIGN and its homologues L-SIGN (DC-SIGNR) and mSIGNR1 in pathogen recognition and immune regulation. Cell Microbiol 7:157–165, 2005.
97. Willment JA, Brown GD: C-type lectin receptors in antifungal immunity. Trends Microbiol 16:27–32, 2008.
98. Gringhuis SI, den Dunnen J, Litjens M, et al: C-type lectin DC-SIGN modulates Toll-like receptor signaling via Raf-1 kinase-dependent acetylation of transcription factor NF-kappaB. Immunity 26:605–616, 2007.
99. Hodges A, Sharrocks K, Edelmann M, et al: Activation of the lectin DC-SIGN induces an immature dendritic cell phenotype triggering Rho-GTPase activity required for HIV-1 replication. Nat Immunol 8:569–577, 2007.
100. Soilleux EJ, Morris LS, Leslie G, et al: Constitutive and induced expression of DC-SIGN on dendritic cell and macrophage subpopulations in situ and in vitro. J Leukoc Biol 71:445–457, 2002.
101. Rosenstiel P, Jacobs G, Till A, Schreiber S: NOD-like receptors: Ancient sentinels of the innate immune system. Cell Mol Life Sci 65:1361–1377, 2008.
102. Kanneganti TD, Lamkanfi M, Nunez G: Intracellular NOD-like receptors in host defense and disease. Immunity 27:549–559, 2007.
103. Martinon F, Tschopp J: NLRs join TLRs as innate sensors of pathogens. Trends Immunol 26:447–454, 2005.
104. Bianchi ME: DAMPs, PAMPs and alarmins: All we need to know about danger. J Leukoc Biol 81:1–5, 2007.
105. Petrilli V, Papin S, Dostert C, et al: Activation of the NALP3 inflammasome is triggered by low intracellular potassium concentration. Cell Death Differ 14:1583–1589, 2007.
106. Dostert C, Petrilli V, Van Bruggen R, et al: Innate immune activation through Nalp3 inflammasome sensing of asbestos and silica. Science 320:674–677, 2008.
107. Cassel SL, Eisenbarth SC, Iyer SS, et al: The Nalp3 inflammasome is essential for the development of silicosis. Proc Natl Acad Sci U S A 105:9035–9040, 2008.
108. Fritz JH, Ferrero RL, Philpott DJ, Girardin SE: Nod-like proteins in immunity, inflammation and disease. Nat Immunol 7:1250–1257, 2006.
109. Martinon F, Tschopp J: Inflammatory caspases: Linking an intracellular innate immune system to autoinflammatory diseases. Cell 117:561–574, 2004.
110. Chu ZL, Pio F, Xie Z, et al: A novel enhancer of the Apaf1 apoptosome involved in cytochrome c-dependent caspase activation and apoptosis. J Biol Chem 276:9239–9245, 2001.
111. Wong AW, Brickey WJ, Taxman DJ, et al: CIITA-regulated plexin-A1 affects T-cell–dendritic cell interactions. Nat Immunol 4:891–898, 2003.
112. Yu HB, Finlay BB: The caspase-1 inflammasome: A pilot of innate immune responses. Cell Host Microbe 4:198–208, 2008.
113. Ting JP, Davis BK: CATERPILLER: A novel gene family important in immunity, cell death, and diseases. Annu Rev Immunol 23:387–414, 2005.
114. Benko S, Philpott DJ, Girardin SE: The microbial and danger signals that activate Nod-like receptors. Cytokine 43:368–373, 2008.
115. Martin TR, Frevert CW: Innate immunity in the lungs. Proc Am Thorac Soc 2:403–411, 2005.
116. Ting JP, Willingham SB, Bergstralh DT: NLRs at the intersection of cell death and immunity. Nat Rev Immunol 8:372–379, 2008.
117. Kumar H, Kawai T, Akira S: Pathogen recognition in the innate immune response. Biochem J 420:1–16, 2009.
118. Geddes K, Magalhaes JG, Girardin SE: Unleashing the therapeutic potential of NOD-like receptors. Nat Rev Drug Discov 8:465–479, 2009.
119. Nakhaei P, Genin P, Civas A, Hiscott J: RIG-I-like receptors: Sensing and responding to RNA virus infection. Semin Immunol 21:215–222, 2009
120. Opitz B, Rejaibi A, Dauber B, et al: IFNbeta induction by influenza A virus is mediated by RIG-I which is regulated by the viral NS1 protein. Cell Microbiol 9:930–938, 2007.
121. Le Goffic R, Pothlichet J, Vitour D, et al: Cutting edge: Influenza A virus activates TLR3-dependent inflammatory and RIG-I–dependent antiviral responses in human lung epithelial cells. J Immunol 178:3368–3372, 2007.
122. Gitlin L, Barchet W, Gilfillan S, et al: Essential role of mda-5 in type I IFN responses to polyriboinosinic:polyribocytidylic acid and encephalomyocarditis picornavirus. Proc Natl Acad Sci U S A 103:8459–8464, 2006.
123. Yoneyama M, Kikuchi M, Natsukawa T, et al: The RNA helicase RIG-I has an essential function in double-stranded RNA-induced innate antiviral responses. Nat Immunol 5:730–737, 2004.
124. Poeck H, Besch R, Maihoefer C, et al: 5'-Triphosphate-siRNA: Turning gene silencing and Rig-I activation against melanoma. Nat Med 14:1256–1263, 2008.
125. Diamond G, Legarda D, Ryan LK: The innate immune response of the respiratory epithelium. Immunol Rev 173:27–38, 2000.
126. Salathe M: Effects of beta-agonists on airway epithelial cells. J Allergy Clin Immunol 110:S275–S281, 2002.
127. Ganz T: Defensins: Antimicrobial peptides of innate immunity. Nat Rev Immunol 3:710–720, 2003.
128. Diamond G, Zasloff M, Eck H, et al: Tracheal antimicrobial peptide, a cysteine-rich peptide from mammalian tracheal mucosa: Peptide isolation and cloning of a cDNA. Proc Natl Acad Sci U S A 88:3952–3956, 1991.
129. Hertz CJ, Wu Q, Porter EM, et al: Activation of Toll-like receptor 2 on human tracheobronchial epithelial cells induces the antimi-

crobial peptide human beta defensin-2. J Immunol 171:6820–6826, 2003.
130. Guillot L, Medjane S, Le-Barillec K, et al: Response of human pulmonary epithelial cells to lipopolysaccharide involves Toll-like receptor 4 (TLR4) –dependent signaling pathways: Evidence for an intracellular compartmentalization of TLR4. J Biol Chem 279:2712–2718, 2004.
131. Becker MN, Diamond G, Verghese MW, Randell SH: CD14-dependent lipopolysaccharide-induced beta-defensin-2 expression in human tracheobronchial epithelium. J Biol Chem 275:29731–29736, 2000.
132. Jia HP, Kline JN, Penisten A, et al: Endotoxin responsiveness of human airway epithelia is limited by low expression of MD-2. Am J Physiol Lung Cell Mol Physiol 287:L428–L437, 2004.
133. Russell JP, Diamond G, Tarver AP, et al: Coordinate induction of two antibiotic genes in tracheal epithelial cells exposed to the inflammatory mediators lipopolysaccharide and tumor necrosis factor alpha. Infect Immun 64:1565–1568, 1996.
134. Jany B, Betz R, Schreck R: Activation of the transcription factor NF-kappa B in human tracheobronchial epithelial cells by inflammatory stimuli. Eur Respir J 8:387–391, 1995.
135. Jaspers I, Flescher E, Chen LC: Ozone-induced IL-8 expression and transcription factor binding in respiratory epithelial cells. Am J Physiol 272:L504–L511, 1997.
136. Janssen YM, Barchowsky A, Treadwell M, et al: Asbestos induces nuclear factor kappa B (NF-kappa B) DNA-binding activity and NF-kappa B–dependent gene expression in tracheal epithelial cells. Proc Natl Acad Sci U S A 92:8458–8462, 1995.
137. Takizawa H, Ohtoshi T, Kawasaki S, et al: Diesel exhaust particles induce NF-kappa B activation in human bronchial epithelial cells in vitro: Importance in cytokine transcription. J Immunol 162:4705–4711, 1999.
138. Quay JL, Reed W, Samet J, Devlin RB: Air pollution particles induce IL-6 gene expression in human airway epithelial cells via NF-kappaB activation. Am J Respir Cell Mol Biol 19:98–106, 1998.
139. Platz J, Beisswenger C, Dalpke A, et al: Microbial DNA induces a host defense reaction of human respiratory epithelial cells. J Immunol 173:1219–1223, 2004.
140. Skerrett SJ, Liggitt HD, Hajjar AM, et al: Respiratory epithelial cells regulate lung inflammation in response to inhaled endotoxin. Am J Physiol Lung Cell Mol Physiol 287:L143–L152, 2004.
140a. Hajjar AM, Harowicz H, Liggitt HD, et al: An essential role for non-bone marrow-derived cells in control of Pseudomonas aeruginosa pneumonia. Am J Respir Cell Mol Biol 33:470–475, 2005.
141. Nathan AT, Peterson EA, Chakir J, Wills-Karp M: Innate immune responses of airway epithelium to house dust mite are mediated through beta-glucan–dependent pathways. J Allergy Clin Immunol 123:612–618, 2009.
142. Hammad H, Chieppa M, Perros F, et al: House dust mite allergen induces asthma via Toll-like receptor 4 triggering of airway structural cells. Nat Med 15:410–416, 2009.
143. Hammad H, Lambrecht BN: Dendritic cells and epithelial cells: Linking innate and adaptive immunity in asthma. Nat Rev Immunol 8:193–204, 2008.
144. Clement CG, Evans SE, Evans CM, et al: Stimulation of lung innate immunity protects against lethal pneumococcal pneumonia in mice. Am J Respir Crit Care Med 177:1322–1330, 2008.
145. Evans SE, Scott BL, Clement CG, et al: Stimulated innate resistance of lung epithelium protects mice broadly against bacteria and fungi. Am J Respir Cell Mol Biol Epub 2009;March 27 (ahead of print).
146. Nathan C: Neutrophils and immunity: Challenges and opportunities. Nat Rev Immunol 6:173–182, 2006.
147. Cowburn AS, Condliffe AM, Farahi N, et al: Advances in neutrophil biology: Clinical implications. Chest 134:606–612, 2008.
148. Zarbock A, Ley K: Neutrophil adhesion and activation under flow. Microcirculation 16:31–42, 2009.
149. Doerschuk CM, Beyers N, Coxson HO, et al: Comparison of neutrophil and capillary diameters and their relation to neutrophil sequestration in the lung. J Appl Physiol 74:3040–3045, 1993.
150. Burns AR, Smith CW, Walker DC: Unique structural features that influence neutrophil emigration into the lung. Physiol Rev 83:309–336, 2003.
151. Erzurum SC, Downey GP, Doherty DE, et al: Mechanisms of lipopolysaccharide-induced neutrophil retention. Relative contributions of adhesive and cellular mechanical properties. J Immunol 149:154–162, 1992.
152. Martin TR, Raugi G, Merritt TL, Henderson WR Jr: Relative contribution of leukotriene B4 to the neutrophil chemotactic activity produced by the resident human alveolar macrophage. J Clin Invest 80:1114–1124, 1987.
153. Westcott JY, McDonnell TJ, Voelkel NF: Alveolar transfer and metabolism of eicosanoids in the rat. Am Rev Respir Dis 139:80–87, 1989.
154. Frevert CW, Goodman RB, Kinsella MG, et al: Tissue-specific mechanisms control the retention of IL-8 in lungs and skin. J Immunol 168:3550–3556, 2002.
155. Frevert CW, Kinsella MG, Vathanaprida C, et al: Binding of interleukin-8 to heparan sulfate and chondroitin sulfate in lung tissue. Am J Respir Cell Mol Biol 28:464–472, 2003.
156. Cummings CJ, Martin TR, Frevert CW, et al: Expression and function of the chemokine receptors CXCR1 and CXCR2 in sepsis. J Immunol 162:2341–2346, 1999.
157. Foxman EF, Campbell JJ, Butcher EC: Multistep navigation and the combinatorial control of leukocyte chemotaxis. J Cell Biol 139:1349–1360, 1997.
158. Wang Q, Doerschuk CM, Mizgerd JP: Neutrophils in innate immunity. Semin Respir Crit Care Med 25:33–41, 2004.
159. Walker DC, Behzad AR, Chu F: Neutrophil migration through preexisting holes in the basal laminae of alveolar capillaries and epithelium during streptococcal pneumonia. Microvasc Res 50:397–416, 1995.
160. Martin TR, Pistorese BP, Chi EY, et al: Effects of leukotriene B4 in the human lung. Recruitment of neutrophils into the alveolar spaces without a change in protein permeability. J Clin Invest 84:1609–1619, 1989.
161. Jones HA, Sriskandan S, Peters AM, et al: Dissociation of neutrophil emigration and metabolic activity in lobar pneumonia and bronchiectasis. Eur Respir J 10:795–803, 1997.
162. Jones HA, Clark RJ, Rhodes CG, et al: In vivo measurement of neutrophil activity in experimental lung inflammation. Am J Respir Crit Care Med 149:1635–1639, 1994.
163. Hidalgo A, Chang J, Jang JE, et al: Heterotypic interactions enabled by polarized neutrophil microdomains mediate thromboinflammatory injury. Nat Med 15:384–391, 2009.
164. Voglis S, Quinn K, Tullis E, et al: Human neutrophil peptides and phagocytic deficiency in bronchiectatic lungs. Am J Respir Crit Care Med 180:159–166, 2009.
165. Smith JJ, Travis SM, Greenberg EP, Welsh MJ: Cystic fibrosis airway epithelia fail to kill bacteria because of abnormal airway surface fluid. Cell 85:229–236, 1996.
166. Yang D, Chertov O, Bykovskaia SN, et al: Beta-defensins: Linking innate and adaptive immunity through dendritic and T cell CCR6. Science 286:525–528, 1999.
167. Yang D, Liu ZH, Tewary P, et al: Defensin participation in innate and adaptive immunity. Curr Pharm Des 13:3131–3139, 2007.
168. Sittipunt C, Steinberg KP, Ruzinski JT, et al: Nitric oxide and nitrotyrosine in the lungs of patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 163:503–510, 2001.
169. Brinkmann V, Reichard U, Goosmann C, et al: Neutrophil extracellular traps kill bacteria. Science 303:1532–1535, 2004.
170. von Kockritz-Blickwede M, Nizet V: Innate immunity turned inside-out: Antimicrobial defense by phagocyte extracellular traps. J Mol Med 87:775–783, 2009.
171. Fuchs TA, Abed U, Goosmann C, et al: Novel cell death program leads to neutrophil extracellular traps. J Cell Biol 176:231–241, 2007.
172. Beiter K, Wartha F, Albiger B, et al: An endonuclease allows *Streptococcus pneumoniae* to escape from neutrophil extracellular traps. Curr Biol 16:401–407, 2006.
173. Sumby P, Barbian KD, Gardner DJ, et al: Extracellular deoxyribonuclease made by group A *Streptococcus* assists pathogenesis by enhancing evasion of the innate immune response. Proc Natl Acad Sci U S A 102:1679–1684, 2005.
174. Antony VB, Sahn SA, Antony AC, Repine JE: Bacillus Calmette-Guerin–stimulated neutrophils release chemotaxins for mono-

cytes in rabbit pleural spaces and in vitro. J Clin Invest 76:1514–1521, 1985.
175. Chertov O, Ueda H, Xu LL, et al: Identification of human neutrophil–derived cathepsin G and azurocidin/CAP37 as chemoattractants for mononuclear cells and neutrophils. J Exp Med 186:739–747, 1997.
176. Bennouna S, Bliss SK, Curiel TJ, Denkers EY: Cross-talk in the innate immune system: Neutrophils instruct recruitment and activation of dendritic cells during microbial infection. J Immunol 171:6052–6058, 2003.
177. Tamassia N, Calzetti F, Ear T, et al: Molecular mechanisms underlying the synergistic induction of CXCL10 by LPS and IFN-gamma in human neutrophils. Eur J Immunol 37:2627–2634, 2007.
178. Jin FY, Nathan C, Radzioch D, Ding A: Secretory leukocyte protease inhibitor: A macrophage product induced by and antagonistic to bacterial lipopolysaccharide. Cell 88:417–426, 1997.
179. Serhan CN, Chiang N, Van Dyke TE: Resolving inflammation: Dual anti-inflammatory and pro-resolution lipid mediators. Nat Rev Immunol 8:349–361, 2008.
180. Galluzzi L, Maiuri MC, Vitale I, et al: Cell death modalities: Classification and pathophysiological implications. Cell Death Differ 14:1237–1243, 2007.
181. Henson PM, Tuder RM: Apoptosis in the lung: Induction, clearance and detection. Am J Physiol Lung Cell Mol Physiol 294:L601–L611, 2008.
182. Oppenheim JJ, Tewary P, de la Rosa G, Yang D: Alarmins initiate host defense. Adv Exp Med Biol 601:185–194, 2007.
183. van Furth R, Cohn ZA: The origin and kinetics of mononuclear phagocytes. J Exp Med 128:415–435, 1968.
184. Volkman A, Gowans JL: The origin of macrophages from bone marrow in the rat. Br J Exp Pathol 46:62–70, 1965.
185. Steinman RM, Cohn ZA: Identification of a novel cell type in peripheral lymphoid organs of mice. I. Morphology, quantitation, tissue distribution. J Exp Med 137:1142–1162, 1973.
186. Hume DA: Macrophages as APC and the dendritic cell myth. J Immunol 181:5829–5835, 2008.
187. Crowell RE, Heaphy E, Valdez YE, et al: Alveolar and interstitial macrophage populations in the murine lung. Exp Lung Res 18:435–446, 1992.
188. Laskin DL, Weinberger B, Laskin JD: Functional heterogeneity in liver and lung macrophages. J Leukoc Biol 70:163–170, 2001.
189. Harmsen AG, Muggenburg BA, Snipes MB, Bice DE: The role of macrophages in particle translocation from lungs to lymph nodes. Science 230:1277–1280, 1985.
190. Doherty DE, Hirose N, Zagarella L, Cherniack RM: Prolonged monocyte accumulation in the lung during bleomycin-induced pulmonary fibrosis. A noninvasive assessment of monocyte kinetics by scintigraphy. Lab Invest 66:231–242, 1992.
191. Martin RJ, Coalson JJ, Rogers RM, et al: Pulmonary alveolar proteinosis: The diagnosis by segmental lavage. Am Rev Respir Dis 121:819–825, 1980.
192. Nugent KM, Pesanti EL: Macrophage function in pulmonary alveolar proteinosis. Am Rev Respir Dis 127:780–781, 1983.
193. Kitamura T, Tanaka N, Watanabe J, et al: Idiopathic pulmonary alveolar proteinosis as an autoimmune disease with neutralizing antibody against granulocyte/macrophage colony-stimulating factor. J Exp Med 190:875–880, 1999.
194. MacLean JA, Xia W, Pinto CE,et al: Sequestration of inhaled particulate antigens by lung phagocytes. A mechanism for the effective inhibition of pulmonary cell-mediated immunity. Am J Pathol 148:657–666, 1996.
195. Thepen T, Hoeben K, Breve J, Kraal G: Alveolar macrophage elimination in vivo is associated with an increase in pulmonary immune responses in mice. J Exp Med 170:499–509, 1989.
196. Thepen T, McMenamin C, Oliver J, et al: Regulation of immune response to inhaled antigen by alveolar macrophages: Differential effects of in vivo alveolar macrophage elimination on the induction of tolerance vs. immunity. Eur J Immunol 21:2845–2850, 1991.
197. Steele MG, Herscowitz HB: Suppression of murine IgM, IgG, IgA and IgE antibody responses by alveolar macrophages. Immunology 80:62–67, 1993.
198. Lauzon W, Lemaire I: Alveolar macrophage inhibition of lung-associated NK activity: involvement of prostaglandins and transforming growth factor-beta1. Exp Lung Res 20:331–349, 1994.
199. Holt PG: Inhibitor activity of unstimulated alveolar macrophages on T-lymphocyte blastogenic response. Am Rev Respir Dis 118:791–793, 1978.
200. Toews GB, Vial WC, Dunn MM, et al: The accessory cell function of human alveolar macrophages in specific T cell proliferation. J Immunol 132:181–186, 1984.
201. Shellito J, Kaltreider HB: Heterogeneity of immunologic function amongst subfracts of normal rat alveolar macrophages. Am Rev Respir Dis 129:747–753, 1984.
202. Morris DG, Huang X, Kaminski N, et al: Loss of integrin alpha(v) beta6–mediated TGF-beta activation causes Mmp12-dependent emphysema. Nature 422:169–173, 2003.
203. Munger JS, Huang X, Kawakatsu H, et al: The integrin alpha v beta 6 binds and activates latent TGF beta 1: a mechanism for regulating pulmonary inflammation and fibrosis. Cell 96:319–328, 1999.
204. Kawabe T, Isobe K-I, Hassegawa Y, et al: Immunosuppressive activity induced by nitric oxide in culture supernatant of activated rat alveolar macrophages. Immunology 76:72–78, 1992.
205. Roth MD, Golub SH: Human pulmonary macrophages utilize prostaglandins and transforming growth factor β1 to suppress lymphocyte activation. J Leuk Biol 53:366–371, 1993.
206. Bilyk N, Holt PG: Inhibition of the immunosuppressive activity of resident pulmonary alveolar macrophages by granulocyte/macrophage colony-stimulating factor. J Exp Med 177:1773–1777, 1993.
207. Fogg DK, Sibon C, Miled C, et al: A clonogenic bone marrow progenitor specific for macrophages and dendritic cells. Science 311:83–87, 2006.
208. Naik SH, Sathe P, Park HY, et al: Development of plasmacytoid and conventional dendritic cell subtypes from single precursor cells derived in vitro and in vivo. Nat Immunol 8:1217–1226, 2007.
209. Onai N, Obata-Onai A, Schmid MA, et al: Identification of clonogenic common Flt3+M-CSFR+ plasmacytoid and conventional dendritic cell progenitors in mouse bone marrow. Nat Immunol 8:1207–1216, 2007.
210. Auffray C, Fogg D, Garfa M, et al: Monitoring of blood vessels and tissues by a population of monocytes with patrolling behavior. Science 317:666–670, 2007.
211. Geissmann F, Jung S, Littman DR: Blood monocytes consist of two principal subsets with distinct migratory properties. Immunity 19:71–82, 2003.
212. Jakubzick C, Tacke F, Ginhoux F, et al: Blood monocyte subsets differentially give rise to $CD103^+$ and $CD103^-$ pulmonary dendritic cell populations. J Immunol 180:3019–3027, 2008.
213. Steppich B, Dayyani F, Gruber R, et al: Selective mobilization of CD14(+)CD16(+) monocytes by exercise. Am J Physiol Cell Physiol 279:C578–C586, 2000.
214. Springer TA: Traffic signals for lymphocyte recirculation and leukocyte emigration: The multistep paradigm. Cell 76:301–314, 1994.
215. Bromley SK, Mempel TR, Luster AD: Orchestrating the orchestrators: Chemokines in control of T cell traffic. Nat Immunol 9:970–980, 2008.
216. Vignais PV: The superoxide-generating NADPH oxidase: Structural aspects and activation mechanism. Cell Mol Life Sci 59:1428–1459, 2002.
217. Sasada M, Kubo A, Nishimura T, et al: Candidacidal activity of monocyte-derived human macrophages: Relationship between *Candida* killing and oxygen radical generation by human macrophages. J Leukocyte Biol 41:289–294, 1987.
218. Klebanoff SJ: Oxygen metabolites from phagocytes. *In* Gallin JI, Goldstein IM, Snyderman R (eds): Inflammation: Basic Principles and Clinical Correlates. New York: Raven, 1992, pp 541–588.
219. Chang YC, Segal BH, Holland SM, et al: Virulence of catalase-deficient aspergillus nidulans in p47phos −/− mice. Implications for fungal pathgoenicity and host defense in chronic granulomatous disease. J Clin Invest 101:1843–1850, 1998.
220. Jackson SH, Gallin JI, Holland SM: The p47phox mouse knock-out model of chronic granulomatous disease. J Exp Med 182:751–758, 1995.

221. Tauber AI, Borregaard N, Simons E, Wright J: Chronic granulomatous disease: A syndrome of phaogcyte oxidase deficiencies. Medicine 62:286–309, 1983.
222. Kelly JK, Pinto AR, Whitelaw WA, et al: Fatal *Aspergillus* pneumonia in chronic granulomatous disease. Am J Clin Pathol 86:235–240, 1986.
223. Castronova V: Generation of oxygen radicals and mechanisms of injury prevention. Environ Health Perspect 102:65–68, 1994.
224. Fireman E, Ben Efraim S, Greif J, et al: Suppressive activity of alveolar macropahges and blood monocytes from interstitial lung diseases: Role of released soluble factors. Int. J. Immunopharmacol. 11:751–760, 1989.
225. Gossart S, Cambon C, Orfila C, et al: Reactive oxygen intermediates as regulators of TNF-alpha production in rat lung inflammation induced by silica. J Immunol 156:1540–1548, 1996.
226. Kondo T, Tagami S, Yoshioka A, et al: Current smoking of elderly men reduces antioxidants in alveolar macrophages. Am J Respir Crit Care Med 149:178–182 1994.
227. Saleh D, Barnes PJ, Giaid A: Increased production of the potent oxidant peroxynitrite in the lungs of patients with idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 155:1763–1769, 1997.
228. Gow AJ, Thom SR, Ischiropoulos H: Nitric oxide and peroxynitrite-mediated pulmonary cell death. Am J Physiol 274:L112–L118, 1998.
229. MacMicking JD, Nathan C, Hom G, et al: Altered responses to bacterial infection and endotoxic shock in mice lacking inducible nitric oxide synthase. Cell 81:641–650, 1995.
230. Humes JL, Bonney RJ, Pelus L, et al: Macrophages synthesis and release prostaglandins in response to inflammatory stimuli. Nature 269:149–151, 1977.
231. Leslie CC: Properties and regulation of cytosolic phospholipase A2. J Biol Chem 272:16709–16712, 1997.
232. Ghosh M, Tucker DE, Burchett SA, Leslie CC: Properties of the group IV phospholipase A2 family. Prog Lipid Res 45:487–510, 2006.
233. Lambeau G, Gelb MH: Biochemistry and physiology of mammalian secreted phospholipases A2. Annu Rev Biochem 77:495–520, 2008.
234. Albert DH, Snyder F: Biosynthesis of 1-alkyl-2-acetyl-sn-glycero-3-phosphocholine (platelet-activating factor) from 1-alkyl-2-acyl-sn-glycero-3-phosphocholine by rat alveolar macrophages. Phospholipase A2 and acetyltransferase activities during phagocytosis and ionophore stimulation. J Biol Chem 258:97–102, 1983.
235. Riches DW, Channon JY, Leslie CC, Henson PM: Receptor-mediated signal transduction in mononuclear phagocytes. Prog Allergy 42:65–122, 1988.
236. Lo CJ, Cryer HG, Fu M, Kim B: Endotoxin-induced macrophage gene expression depends on platelet-activating factor. Arch Surg 132:1342–1347, 1997.
237. Maier RV, Hahnel GB, Fletcher JR: Platelet-activating factor augments tumor necrosis factor and procoagulant activity. J Surg Res 52:258–264, 1992.
238. Hsueh W: Prostaglandin biosynthesis in pulmonary macrophages. Am J Pathol 97:137–148, 1979.
239. Rankin JA, Sylvester I, Smith S, et al: Macrophages cultured in vitro release leukotriene B4 and neutrophil attractant/activation protein (interleukin 8) sequentially in response to stimulation with lipopolysaccharide and zymosan. J Clin Invest 86:1556–1564, 1990.
240. Kunkel SL, Lukacs NW, Strieter RM, Chensue SW: The role of chemokines in the immunopathology of pulmonary disease. Forum (Genova) 9:339–355, 1999.
241. Keane MP, Strieter RM: Chemokine signaling in inflammation. Crit Care Med 28:N13–N26, 2000.
242. Strieter RM, Polverini PJ, Kunkel SL, et al: The functional role of the ELR motif in CXC chemokine-mediated angiogenesis. J Biol Chem 270:27348–27357, 1995.
243. Moore BB, Keane MP, Addison CL, et al: CXC chemokine modulation of angiogenesis: The importance of balance between angiogenic and angiostatic members of the family. J Investig Med 46:113–120, 1998.
244. Carre PC, Mortenson RL, King TEJ, et al: Increased expression of the interleukin-8 gene by alveolar macrophages in idiopathic pulmonary fibrosis. A potential mechanism for the recruitment and activation of neutrophils in lung fibrosis. J Clin Invest 88:1802–1810, 1991.
245. Donnelly SC, Strieter RM, Kunkel SL, et al: Interleukin-8 and development of adult respiratory distress syndrome in at-risk patient groups. Lancet 341:643–647, 1993.
246. Carre PC, King TE Jr, Mortensen R, Riches DWH: Cryptogenic organizing pneumonia: Increased expression of interleukin-8 and fibronectin genes by alveolar macrophages. Am J Respir Cell Mol Biol 10:100–105, 1994.
247. Khan TZ, Wagener JS, Bost T, et al: Early pulmonary inflammation in infants with cystic fibrosis. Am J Respir Crit Care Med 151:1075–1082, 1995.
248. Standiford TJ, Rolfe MW, Kunkel SL, et al: Macrophage inflammatory protein-1 alpha expression in interstitial lung disease. J Immunol 151:2852–2863, 1993.
249. Smith RE, Strieter RM, Zhang K, et al: A role for C-C chemokines in fibrotic lung disease. J Leukoc Biol 57:782–787, 1995.
250. Noble PW, Lake FR, Henson PM, Riches DW: Hyaluronate activation of CD44 induces insulin-like growth factor-1 expression by a tumor necrosis factor-alpha–dependent mechanism in murine macrophages. J Clin Invest 91:2368–2377, 1993.
251. Lake FR, Noble PW, Henson PM, Riches DW: Functional switching of macrophage responses to tumor necrosis factor-alpha (TNF alpha) by interferons. Implications for the pleiotropic activities of TNF alpha. J Clin Invest 93:1661–1669, 1994.
252. Laszlo DJ, Henson PM, Weinstein L, et al: Development of functional diversity in mouse macrophages. Mutual exclusion of two phenotypic states. Am J Pathol 143:587–597, 1993.
253. Riches DW: Signalling heterogeneity as a contributing factor in macrophage functional diversity. Semin Cell Biol 6:377–384, 1995.
254. Gordon S: Alternative activation of macrophages. Nat Rev Immunol 3:23–35, 2002.
255. Holt PG, Schon-Hegrad MA: Localization of T cells, macrophages and dendritic cells in rat respiratory tract tissue: Implications for immune function studies. Immunology 62:349–356, 1987.
256. Sertl, K, Takemura T, Tschachler E, et al: Dendritic cells with antigen-presenting capability reside in airway epithelium, lung parenchyma, and visceral pleura. J Exp Med 163:436–451, 1986.
257. Nelson DJ, McMenamin C, McWilliam AS, et al: Development of the airway intraepithelial dendritic cell network in the rat from class II major histocompatibility (Ia) –negative precursors: Differential regulation of Ia expression at different levels of the respiratory tract. J Exp Med 179:203–212, 1994.
258. Schon-Hegrad MA, Oliver J, McMenamin PG, Holt PG: Studies on the density, distribution, and surface phenotype of intraepithelial class II major histocompatibility complex antigen (Ia) –bearing dendritic cells (DC) in the conducting airways. J Exp Med 173:1345–1356, 1991.
259. Holt PG, Haining S, Nelson DJ, Sedgwick JD: Origin and steady-state turnover of class II MHC-bearing dendritic cells in the epithelium of the conducting airways. J Immunol 153:256–261, 1994.
260. von Garnier C, Filgueira L, Wikstrom M, et al: Anatomical location determines the distribution and function of dendritic cells and other APCs in the respiratory tract. J Immunol 175:1609–1618, 2005.
261. Fokkens WJ, Vroom TM, Rijntjes E, Mulder PG: CD-1 (T6), HLA-DR-expressing cells, presumably Langerhans cells, in nasal mucosa. Allergy 44:167–172, 1989.
262. Gong JL, McCarthy KM, Telford J, et al: Intraepithelial airway dendritic cells: A distinct subset of pulmonary dendritic cells obtained by microdissection. J Exp Med 175:797–807, 1992.
263. Holt PG, Schon-Hegrad MA, Phillips MJ, McMenamin PG: Ia-positive dendritic cells form a tightly meshed network within the human airway epithelium. Clin Exp Allergy 19:597–601, 1989.
264. Blank F, Rothen-Rutishauser B, Gehr P: Dendritic cells and macrophages form a transepithelial network against foreign particulate antigens. Am J Respir Cell Mol Biol 36:669–677, 2007.
265. Jahnsen FL, Strickland DH, Thomas JA, et al: Accelerated antigen sampling and transport by airway mucosal dendritic cells following inhalation of a bacterial stimulus. J Immunol 177:5861–5867, 2006.

266. Sung SS, Fu SM, Rose CE Jr, et al: A major lung CD103 (alphaE)-beta7 integrin-positive epithelial dendritic cell population expressing Langerin and tight junction proteins. J Immunol 176:2161–2172, 2006.
267. Jakob T, Udey MC: Regulation of E-cadherin–mediated adhesion in Langerhans cell–like dendritic cells by inflammatory mediators that mobilize Langerhans cells in vivo. J Immunol 160:4067–4073, 1998.
268. Hintzen G, Ohl L, del Rio ML, et al: Induction of tolerance to innocuous inhaled antigen relies on a CCR7-dependent dendritic cell–mediated antigen transport to the bronchial lymph node. J Immunol 177:7346–7354, 2006.
269. McWilliam AS, Napoli S, Marsh AM, et al: Dendritic cells are recruited into the airway epithelium during the inflammatory response to a broad spectrum of stimuli. J Exp Med 184:2429–2432, 1996.
270. Iwasaki A: Mucosal dendritic cells. Annu Rev Immunol 25:381–418, 2007.
271. Jakubzick C, Tacke F, Llodra J, et al: Modulation of dendritic cell trafficking to and from the airways. J Immunol 176:3578–3584, 2006.
272. Chiu BC, Freeman CM, Stolberg VR, et al: Impaired lung dendritic cell activation in CCR2 knockout mice. Am J Pathol 165:1199–1209, 2004.
273. Vermaelen K, Pauwels R: Pulmonary dendritic cells. Am J Respir Crit Care Med 172:530–551, 2005.
274. Liu K, Victora GD, Schwickert TA, et al: In vivo analysis of dendritic cell development and homeostasis. Science 324:392–397, 2009.
275. Shortman K, Naik SH: Steady-state and inflammatory dendritic-cell development. Nat Rev Immunol 7:19–30, 2007.
276. Brokaw JJ, White GW, Baluk P, et al: Glucocorticoid-induced apoptosis of dendritic cells in the rat tracheal mucosa. Am J Respir Cell Mol Biol 19:598–605, 1998.
277. Tacke F, Ginhoux F, Jakubzick C, et al: Immature monocytes acquire antigens from other cells in the bone marrow and present them to T cells after maturing in the periphery. J Exp Med 203:583–597, 2006.
278. Varol C, Landsman L, Fogg DK, et al: Monocytes give rise to mucosal, but not splenic, conventional dendritic cells. J Exp Med 204:171–180, 2007.
279. Randolph GJ, Jakubzick C, Qu C: Antigen presentation by monocytes and monocyte-derived cells. Curr Opin Immunol 20:52–60, 2008.
280. GeurtsvanKessel CH, Lambrecht BN: Division of labor between dendritic cell subsets of the lung. Mucosal Immunol 1:442–450, 2008.
281. Hammad H, Lambrecht BN: Lung dendritic cell migration. Adv Immunol 93:265–278, 2007.
282. van Haarst JM, Verhoeven GT, de Wit HJ, et al: $CD1a^+$ and $CD1a^-$ accessory cells from human bronchoalveolar lavage differ in allostimulatory potential and cytokine production. Am J Respir Cell Mol Biol 15:752–759, 1996.
283. Valladeau J, Duvert-Frances V, Pin JJ, et al: The monoclonal antibody DCGM4 recognizes Langerin, a protein specific of Langerhans cells, and is rapidly internalized from the cell surface. Eur J Immunol 29:2695–2704, 1999.
284. Demedts IK, Brusselle GG, Vermaelen KY, Pauwels RA: Identification and characterization of human pulmonary dendritic cells. Am J Respir Cell Mol Biol 32:177–184, 2005.
285. Dzionek A, Fuchs A, Schmidt P, et al: BDCA-2, BDCA-3, and BDCA-4: three markers for distinct subsets of dendritic cells in human peripheral blood. J Immunol 165:6037–6046, 2000.
286. Bratke K, Lommatzsch M, Julius P, et al: Dendritic cell subsets in human bronchoalveolar lavage fluid after segmental allergen challenge. Thorax 62:168–175, 2007.
287. Lommatzsch M, Bratke K, Bier A, et al: Airway dendritic cell phenotypes in inflammatory diseases of the human lung. Eur Respir J 30:878–886, 2007.
288. Serbina NV, Salazar-Mather TP, Biron CA, et al: TNF/iNOS-producing dendritic cells mediate innate immune defense against bacterial infection. Immunity 19:59–70, 2003.
289. Kapsenberg ML: Dendritic-cell control of pathogen-driven T-cell polarization. Nat Rev Immunol 3:984–993, 2003.
290. Lambrecht BN: Lung dendritic cells: Targets for therapy in allergic disease. Curr Mol Med 8:393–400, 2008.
291. Vermaelen KY, Cataldo D, Tournoy K, et al: Matrix metalloproteinase-9–mediated dendritic cell recruitment into the airways is a critical step in a mouse model of asthma. J Immunol 171:1016–1022, 2003.
292. Herrick CA, Bottomly K: To respond or not to respond: T cells in allergic asthma. Nat Rev Immunol 3:405–412, 2003.
293. de Heer HJ, Hammad H, Soullie T, et al: Essential role of lung plasmacytoid dendritic cells in preventing asthmatic reactions to harmless inhaled antigen. J Exp Med 200:89–98, 2004.
294. Hastings RH, Folkesson HG, Matthay MA: Mechanisms of alveolar protein clearance in the intact lung. Am J Physiol Lung Cell Mol Physiol 286:L679–L689, 2004.
295. Wikstrom ME, Stumbles PA: Mouse respiratory tract dendritic cell subsets and the immunological fate of inhaled antigens. Immunol Cell Biol 85:182–188, 2007.
296. Villadangos JA, Schnorrer P: Intrinsic and cooperative antigen-presenting functions of dendritic-cell subsets in vivo. Nat Rev Immunol 7:543–555, 2007.
297. Steinman RM: Dendritic cells in vivo: A key target for a new vaccine science. Immunity 29:319–324, 2008.
298. Dudziak D, Kamphorst AO, Heidkamp GF, et al: Differential antigen processing by dendritic cell subsets in vivo. Science 315:107–111, 2007.
299. Sullivan BA, Nagarajan NA, Kronenberg M: CD1 and MHC II find different means to the same end. Trends Immunol 26:282–288, 2005.
300. Gelin C, Sloma I, Charron D, Mooney N: Regulation of MHC II and CD1 antigen presentation: From ubiquity to security. J Leukoc Biol 85:215–224, 2009.
301. Wearsch PA, Cresswell P: The quality control of MHC class I peptide loading. Curr Opin Cell Biol 20:624–631, 2008.
302. Cresswell P, Bangia N, Dick T, Diedrich G: The nature of the MHC class I peptide loading complex. Immunol Rev 172:21–28, 1999.
303. Germain RN: MHC-dependent antigen processing and peptide presentation: Providing ligands for T lymphocyte activation. Cell 76:287–299, 1994.
304. Shastri N, Cardinaud S, Schwab SR, et al: All the peptides that fit: The beginning, the middle, and the end of the MHC class I antigen-processing pathway. Immunol Rev 207:31–41, 2005.
305. Yewdell JW, Norbury CC, Bennink JR: Mechanisms of exogenous antigen presentation by MHC class I molecules in vitro and in vivo: Implications for generating $CD8^+$ T cell responses to infectious agents, tumors, transplants, and vaccines. Adv Immunol 73:1–77, 1999.
306. Hoeffel G, Ripoche AC, Matheoud D, et al: Antigen crosspresentation by human plasmacytoid dendritic cells. Immunity 27:481–492, 2007.
307. Di Pucchio T, Chatterjee B, Smed-Sorensen A, et al: Direct proteasome-independent cross-presentation of viral antigen by plasmacytoid dendritic cells on major histocompatibility complex class I. Nat Immunol 9:551–557, 2008.
308. Salio M, Palmowski MJ, Atzberger A, et al: CpG-matured murine plasmacytoid dendritic cells are capable of in vivo priming of functional CD8 T cell responses to endogenous but not exogenous antigens. J Exp Med 199:567–579, 2004.
309. Krug A, Veeraswamy R, Pekosz A, et al: Interferon-producing cells fail to induce proliferation of naive T cells but can promote expansion and T helper 1 differentiation of antigen-experienced unpolarized T cells. J Exp Med 197:899–906, 2003.
310. Villadangos JA, Young L: Antigen-presentation properties of plasmacytoid dendritic cells. Immunity 29:352–361, 2008.
311. Thepen T, Van Rooijen N, Kraal G: Alveolar macrophage elimination in vivo is associated with an increase in pulmonary immune response in mice. J Exp Med 170:499–509, 1989.
312. Shibata Y, Zsengeller Z, Otake K, et al: Alveolar macrophage deficiency in osteopetrotic mice deficient in macrophage colony-stimulating factor is spontaneously corrected with age and associated with matrix metalloproteinase expression and emphysema. Blood 98:2845–2852, 2001.

CHAPTER 14

ADAPTIVE IMMUNITY

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INTRODUCTION

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INTRODUCTION

The human immune system consists of many different cell types and organs that have evolved to destroy or control potentially harmful foreign substances. The immune response is essential for survival because it constitutes the principal means of defense against infection by pathogenic microorganisms, including those that enter through, and reside in, the respiratory tract. The immune response is also critically involved in pathologic processes of the lung and upper respiratory tract. This chapter provides an understanding of the adaptive (or acquired) immune response, which depends on the specific recognition of antigens by T and B lymphocytes. Immune recognition is highly specific for a particular pathogen, and yet an individual's immune cells can collectively respond to an almost unlimited number of foreign antigens. The molecular mechanisms underlying this specificity and diversity are unique to the immune system. The adaptive immune response also changes after successive encounters with the same pathogen. For example, memory of an antigen allows the immune response to occur faster and in greater magnitude compared with the initial encounter. This chapter also describes how primary and secondary immune responses are regulated by complex cellular interactions and the release of particular types of soluble mediators. Antigen-specific immune responses are also regulated and augmented by nonspecific inflammatory cells of the immune system, such as dendritic cells, macrophages, neutrophils, eosinophils, and mast cells.

COMPONENTS OF THE IMMUNE SYSTEM: OVERVIEW

All of the cells of the immune system arise from pluripotent hematopoietic stem cells through two main lines of differentiation that give rise to the lymphoid lineage and the myeloid lineage.[1] Specificity within the immune system is primarily provided by lymphocytes. The two major categories of lymphocytes are T cells, which are derived from bone marrow stem cells and primarily develop in the thymus, and B cells, which develop in the bone marrow in adult humans. A third population of lymphocytes is natural killer (NK) cells.

Lymphocytes and other cells of the immune system express a large number of different molecules on their surfaces. Some of these markers can be used to separate cells with different functions or to distinguish cells at particular stages of differentiation. Monoclonal antibodies to many different cell surface markers have been produced, and a systematic nomenclature has been

developed. The CD ("cluster of differentiation" or "cluster determinant") system provides a basis by which monoclonal antibodies that bind to the same surface molecule are grouped together, and the CD number is used to indicate the specific molecule recognized. Tables 14-1, 14-2, and 14-3 provide a partial list of surface antigens, particularly those mentioned in this chapter. The markers are partially grouped based on the cell type expressing them. It may be necessary to refer to this list of molecules throughout this chapter.

T cells are distinguished by the presence of the T-cell receptor for antigen (TCR).[2–4] Most T cells express a receptor composed of an α and a β chain, whereas a much smaller subset expresses a structurally similar receptor composed of a γ and a δ chain. Both receptors are associated with a complex of polypeptides, the CD3 complex, which provides a transmembrane signaling function and allows TCR engagement to be coupled to cellular activation. T cells expressing αβ TCRs can be divided into $CD4^+$ and $CD8^+$ T-cell subsets. $CD4^+$ T cells primarily recognize antigens presented by major histocompatibility complex (MHC) class II molecules. $CD8^+$ T cells primarily recognize antigens presented by MHC class I molecules. Functionally, T cells can be divided into several major subsets. For example, T helper cells may interact with B cells and help them to survive and divide, make antibody, and become memory B cells. T helper cells also may interact with cytotoxic T cells or with phagocytic cells and help them destroy intracellular pathogens. Different subsets of T helper cells can be distinguished by the pattern of cytokines that they secrete during an immune response. T helper cells are generally encompassed within the $CD4^+$ T-cell subset. Another subset of T cells is responsible for destruction of cells that have become infected by virus or other intracellular pathogens. These cells are called "cytotoxic T cells" and usually express the CD8 phenotypic marker. Although not clearly distinguished by phenotypic markers, separate subsets of T cells, within both the $CD4^+$ and the $CD8^+$ subsets, have been termed "T regulatory (or suppressor) cells" because they down-regulate immune responses.

TABLE 14-1. Selected Cell Surface Markers of Human T Cells

Cell Surface Markers	Identity/Function
TCR for antigen	Interacts with peptide/MHC complex on antigen-presenting cells
CD2	Binds to LFA-3; involved in co-stimulation and adhesion
CD3	T-cell signaling complex
CD4	Identifies T-cell subset with helper function; interacts with MHC class II molecule
CD8	Identifies T-cell subset with cytotoxic function; interacts with MHC class I molecule
CD25	α chain of IL-2 receptor; expressed on activated T cells and on a subset of regulatory $CD4^+$ T cells
CD28	Binds B7-1 (CD80) and B7-2 (CD86); co-stimulatory molecule involved in T-cell activation
CD45	Phosphatase involved in cellular activation and differentiation; different isoforms (CD45RA, CD45RO) mark naive versus previously activated T cells and stages of activation
CD62L	L-selectin; involved in lymphocyte adhesion; levels mark naive versus memory cells
CD69	Activation marker
CD95 (Fas)	Fas; receptor involved in apoptosis
CD95L (Fas ligand)	Ligand for Fas; involved in T-cell–mediated killing
CD152 (CTLA-4)	Binds to B7-1 (CD80) and B7-2 (CD86); involved in down-regulation of TCR signaling
CD154 (CD40 ligand)	Ligand for CD40; important for T-cell activation and T-cell–dependent B-cell activation
CD134 (OX40), CD137 (4-1BB), ICOS, PD-1	Additional co-stimulatory molecules in the TNF or CD28 family; involved in T-cell activation and regulation

CTLA-4, cytotoxic T lymphocyte antigen-4; ICOS, inducible co-stimulator; IL-2, interleukin-2; LFA-3, lymphocyte function antigen-3; MHC, major histocompatibility complex; PD-1, programmed cell death-1; TCR, T-cell receptor; TNF, tumor necrosis factor.

TABLE 14-2. Cell Surface Markers of Human B Cells

Cell Surface Markers	Identity/Function
BCR for antigen	Immunoglobulin molecules; recognizes antigen
CD5	Binds to CD72; regulation of cell proliferation/activation; identifies B1a cell subset
CD19	B-cell coreceptor subunit; involved in co-stimulation
CD20	B-cell marker
CD21	Complement receptor type II; B-cell coreceptor subunit; marks certain B-cell subsets; EBV receptor
CD22	Adhesion molecule; involved in B-cell activation
CD23	Identifies B-cell subset; low-affinity receptor for IgE
CD40	Binds CD40L; involved in T-cell–dependent B-cell activation
CD79a (Ig-α)	Involved in B-cell activation; signaling through BCR
CD79b (Ig-β)	Involved in B-cell activation; signaling through BCR
CD80 (B7-1)	Binds CD28 and CD152 (CTLA-4) on T cells
CD86 (B7-2)	Binds CD28 and CD152 (CTLA-4) on T cells

BCR, B-cell receptor; CD40L, CD40 ligand; CTLA-4, cytotoxic T lymphocyte antigen-4; EBV, Epstein-Barr virus; Ig, immunoglobulin.

TABLE 14-3. Other Cell Surface Markers of General Interest

Cell Surface Markers	Distribution	Identity/Function
CD1	Thymocytes, subset of lymphocytes, antigen-presenting cells	MHC class I–like molecule; involved in presentation of nonpeptide antigens
CD11a	Leukocytes	α chain of LFA-1; associates with CD18; interacts with ICAM-1; involved in adhesion and migration
CD11b	NK cells, monocytes, granulocytes	α chain of CR3; adhesion molecule
CD11c	Monocytes, granulocytes	α chain of CR4; adhesion molecule; identifies dendritic cells
CD14	Granulocytes, monocytes	Receptor for LPS/LPB complex; myeloid differentiation antigen; cell activation
CD16	NK cells, monocytes	FcγRIII; low-affinity receptor for IgG; involved in ADCC
CD18	Leukocytes	β chain of β_2 integrin molecules, including LFA-1, CR3, and CR4
CD29	Leukocytes	β chain of β_1 integrin molecules, including VLA1–VLA6
CD32	B cells, monocytes, granulocytes	FcγRII
CD35	B cells, subset of NK cells, monocytes, granulocytes	CR1
CD45	Leukocytes	Leukocyte common antigen; phosphatase; involved in cell signaling
CD46	Broad distribution	Membrane cofactor protein; regulates complement activation
CD54 (ICAM-1)	Broad distribution	Binds LFA-1; adhesion molecule
CD56	NK cells	Neural cell adhesion molecule
CD58 (LFA-3)	Broad distribution	Binds CD2; adhesion molecule; involved in cell signaling

ADCC, antibody-dependent cellular cytotoxicity; CR, complement receptor; ICAM-1, intercellular adhesion molecule-1; IgG, immunoglobulin G; LFA, leukocyte function antigen; LPB, LPB binding protein; LPS, lipopolysaccharide; MHC, major histocompatibility complex; NK, natural killer; VLA, vascular leukocyte adhesion molecule.

B cells are identified by the expression of surface immunoglobulin (Ig) or antibody molecules, which represent their specific B-cell receptor for antigen (BCR). Analogous to the CD3 complex on T cells, BCRs are also linked to accessory molecules, Ig-α (CD79a) and Ig-β (CD79b), which are required for cellular activation after antigen interaction.[5] After differentiation, B cells can develop the ability to produce high levels of antibody (soluble Ig). B cells also express a large number of other surface markers that are critically involved in their function and interaction with T cells. For example, most B cells express MHC class II molecules that allow them to present antigen to T helper cells. Other B-cell surface molecules are listed in Table 14-2.

A third population of lymphocytes is probably best defined as those cells that do not express either TCR or Ig and mostly includes NK cells.[6] A large proportion of this subset contains numerous electron-dense granules and is recognized morphologically as large granular lymphocytes. Markers on these cells are frequently shared with T cells (e.g., CD2 and CD8) or cells of the myelomonocytic series, for example, the integrin molecule CD11b or the low-affinity receptor for IgG (FcγRIII or CD16). NK cells appear to play an important role in the initial (innate) host defense against infection and tumor cells. Similar to certain phagocytes, they also have the capability to destroy target cells or pathogens, which have been coated with specific antibody, via a process known as "antibody-dependent cellular cytotoxicity."

The myeloid lineage consists primarily of monocytes (macrophages) and neutrophils, which provide nonspecific inflammatory mediators and phagocytic function. These cells are critically involved in the nonspecific component of the inflammatory response (see Chapters 13 and 16). In addition, macrophages and certain other nonlymphoid cells, such as dendritic cells, are specialized to present antigens to T cells and, thus, also contribute to specific immune responses.

The cells involved in the immune response are organized into tissues and organs. Primary lymphoid organs are the major sites of lymphopoiesis, in which stem cells and their committed precursor cells differentiate into lymphocytes and acquire specific functions. In humans, T lymphocytes mainly develop in the thymus, and B lymphocytes develop in the fetal liver and adult bone marrow. In the thymus, T-cell differentiation also includes acquiring the ability to recognize foreign antigens in the context of self-MHC molecules and the elimination of self-reactive cells (self-tolerance). B-cell acquisition of self-tolerance during development appears to take place in the bone marrow.

Differentiated lymphocytes migrate to secondary lymphoid organs that include lymph nodes, spleen, and mucosa-associated lymphoid tissues, such as the tonsils, lymph nodes of the respiratory tract, and Peyer's patches of the gut. These tissues provide an environment for lymphocytes to interact with each other, with antigen-presenting cells and other accessory cells, and with foreign antigens. The immune response occurs mostly within these secondary lymphoid organs, and lymphocytes migrate through the blood and lymph from one lymphoid organ to another and to nonlymphoid tissues. For example, foreign antigen exposure in the lung usually involves the movement of antigen to surrounding lymph nodes, where the specific immune response by T and B cells occurs. Generation of a cell-mediated immune response or antibody response allows

antigen-specific effector T cells or specific antibodies, respectively, to travel back to lung tissue for a direct assault on foreign antigens.

Under normal conditions, there is a continuous active flow of lymphocyte traffic through the lymph nodes. About 1% to 2% of the lymphocyte pool recirculates each hour, allowing a large number of antigen-specific lymphocytes to potentially come into contact with their appropriate antigen. Recirculating lymphocytes leave the blood and enter the lymph node through specialized postcapillary venules, known as high endothelial venules (HEVs). Specific interacting receptors on lymphocytes and HEV cells allow for this homing process to occur. Lymphocytes return to the circulation by way of afferent lymphatics that pass via the thoracic duct into the left subclavian vein. Lymphocytes also enter mucosa-associated lymphoid tissues, such as the tonsils and Peyer's patches, via HEVs. The recirculation and trafficking of memory and effector T and B cells is tightly regulated, determined by unique combinations of adhesion molecules and chemokines.[7] For example, certain lymphocytes may preferentially migrate across HEVs into intestinal lymphoid tissues (either Peyer's patches or mesenteric lymph nodes) or into respiratory tract tissues or may specifically home to the peripheral lymph nodes or the spleen.

Separate combinations of cell-surface adhesion molecules and chemokines allow activated lymphocytes and other leukocytes to migrate into nonlymphoid tissues, especially during inflammation and in response to the release of inflammatory cytokines.[7] The difference in trafficking patterns for nonactivated (resting) versus activated lymphocytes is striking and emphasizes the importance of particular adhesion molecules in the control of lymphocyte migration.

IMMUNE RECOGNITION

B Cells and Antibodies

Structure of Immunoglobulin and the B-Cell Receptor for Antigen

Immunoglobulin molecules, or antibodies, are a group of glycoproteins that act as BCRs. These molecules can also be secreted in large quantities by activated B cells and plasma cells. Figure 14-1 shows the basic structure of an Ig molecule. Each Ig molecule is bifunctional—one region (Fab) binds to antigen, and a different region (Fc) mediates various effector functions, such as binding to host tissues (via their cell surface Fc receptors) and binding to and activating the first component of the classic complement system.

The basic structure of all Ig molecules involves two identical light polypeptide chains and two identical heavy polypeptide chains linked together by disulfide bonds (see Fig. 14-1A). The isotype (class or subclass) of an Ig molecule is determined by its heavy chain type. There are five Ig classes—IgG, IgM, IgA, IgD, and IgE—corresponding to the γ, μ, α, δ, and ε heavy chain types. In humans, there are four IgG subclasses, IgG1 to IgG4. There are major differences in the structure and main functions of these different Ig classes and subtypes.

In Figure 14-1B, the IgG molecule is shown as an example of basic antibody structure. Each chain is composed of a series of globular regions or domains. Each domain encompasses about 60 to 70 amino acids and has an internal disulfide bond. The site of antigen binding is the amino (NH_2)-terminal domain for both the heavy (H) and the light (L) chains. This domain is characterized by remarkable sequence variability and is referred to as the variable region of the heavy and light chains (V_H and V_L region, respectively). The combination of V_H and V_L forms the antigen-binding site, and there are two such sites per IgG molecule (see Fig. 14-1B). The rest of each polypeptide has a relatively constant structure. The constant domain of the light chain is termed the C_L region, whereas the heavy chain has three constant domains: C_H1, C_H2, and C_H3. The hinge region, located between the C_H1 and C_H2 domains, provides flexibility and independence to the two antigen-binding sites. In both μ and ε heavy chains, there is an additional constant domain between C_H1 and C_H2, resulting in a total of four constant domains.

The greatest variability in antibody molecules occurs in the V_H and V_L domains, and these domains are responsible for the specificity in antigen binding.[8,9] Within the variable domains (see Fig. 14-1C), certain short segments show exceptional variability and are called "hypervariable regions." These regions are also referred to as "complementarity-determining regions" (CDRs) because they are directly involved in the binding to antigen. In both the V_H and the V_L regions, there are three CDRs (CDR1-CDR3) with intervening segments referred to as "framework regions" (see Fig. 14-1C). As discussed later, CDR3 (a component of the polypeptide V region) is formed by parts of the V (variable), D (diversity), and J (joining) gene segments. Variation within the V_H and V_L regions distinguishes one antibody molecule from another and is referred to as *idiotype* or *idiotypic variation*.

Genetic Mechanisms Involved in the Formation of the B-Cell Receptor Repertoire

Proteins are assembled by putting together functional regions, each coded by a gene segment. Most genes coding for a protein have a characteristic structure in which stretches of nucleotides (exons) encode the sequence of the protein. Exons are separated by noncoding regions (introns) (Fig. 14-2A). The entire stretch of deoxyribonucleic acid (DNA) is transcribed into a primary ribonucleic acid (RNA) transcript. Enzymes splice out the noncoding intron sequences to yield the mature messenger RNA segment, which is much shorter than the primary transcript. This messenger RNA is translated into protein on ribosomes. Preceding each gene that codes for a cell surface protein is a leader (L) sequence (at the 5′ coding end). The leader sequence codes for a signal peptide involved in the intracellular transport of the polypeptide chain, after which this polypeptide piece is removed. Figure 14-2B shows the corresponding structure of a rearranged Ig heavy chain

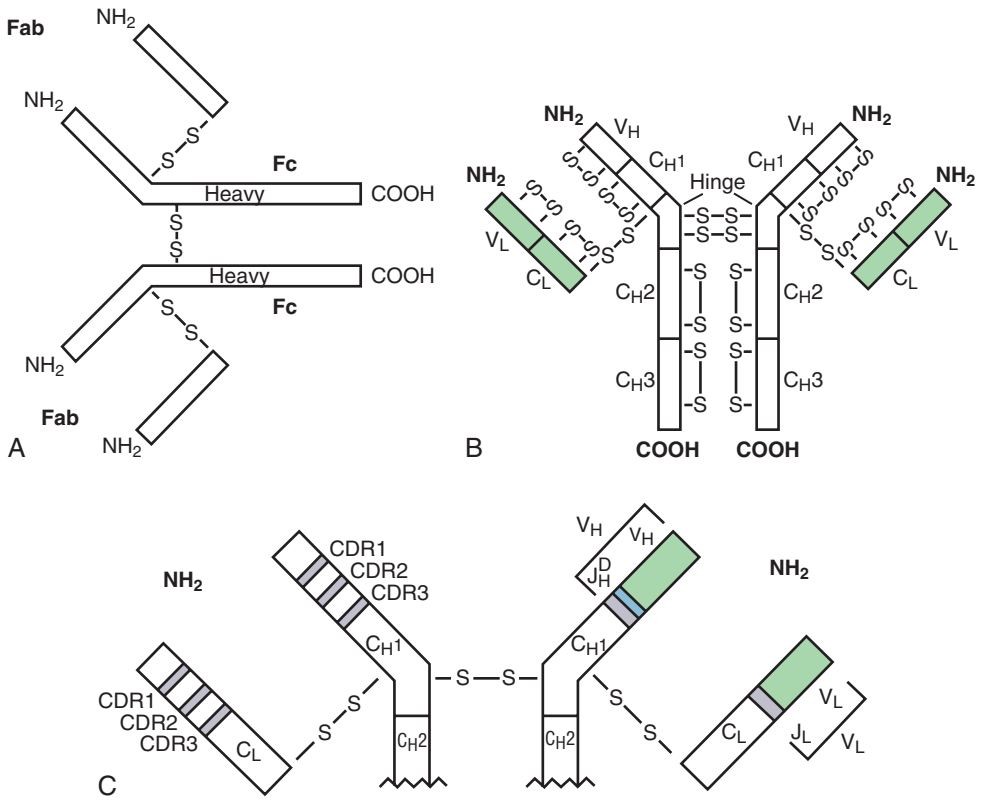

FIGURE 14-1 ■ The structure of immunoglobulin (Ig) molecules. **A,** Basic Ig structure with two heavy chains and two light chains linked together by disulfide bonds. The Fab region is involved in antigen binding, whereas the Fc region mediates various effector functions. **B,** Increasing detail of IgG molecule showing domains of both heavy and light chains. Each domain has an internal disulfide bond. The sites of antigen binding involve the NH_2-terminal domains of both the heavy and the light chains and are referred to as the *variable regions* (V_H and V_L, respectively). The rest of each chain has a relatively constant structure (C_H and C_L domains). **C,** Close-up of the antigen-binding variable regions. On the left, the complementarity-determining regions (CDRs) are *shaded* because they are the most variable components and are most involved in actual antigen binding. The CDRs are separated by intervening segments referred to as framework regions. On the right, the Ig polypeptide regions are correlated with the Ig gene segment (exons) that encode the variable region. Note that CDR3 corresponds to the $V_H/D_H/J_H$ junctional region of the rearranged heavy chain gene and the V_L/J_L junctional region of the rearranged light chain gene. (Adapted from MKSAP in the Specialty of Rheumatology. Philadelphia: American College of Physicians, 1993, p 6.)

gene. Note that each of the protein domains is encoded by an exon, which is separated by noncoding introns.

The BCR repertoire and the Ig molecules are characterized by enormous diversity. The principal genetic mechanisms that are used to generate this diversity include (1) genetic recombination of gene segments to form a functional Ig gene, (2) combinatorial diversity of heavy and light chain matching, and (3) somatic mutation of rearranged genes.[8-10] Another major force in shaping the antibody repertoire has been termed *receptor editing*, which allows receptors with self-reactive potential to be modified by additional recombination events during B-cell differentiation.[11,12]

Figure 14-3A illustrates the principle of genetic recombination for an Ig gene.[8,9] In this case, one of several variable (V) region gene segments (normally separated upstream from the constant [C] region gene segments on the same chromosome) can be linked to a single C region gene segment by genetic recombination. The combining of gene segments, rather than the existence of a single gene coding for every individual antibody molecule, considerably reduces the amount of genetic information required to encode many different antibody molecules. In Figure 14-3B, the different gene segments that encode a κ light polypeptide chain are shown. Note that in this case, a V region rearranges proximal to a J segment, which is linked to the C region segment. Rearrangement of κ or λ light chain genes involves V, J, and C region gene segments (Fig. 14-3A; see also Fig. 14-1C). In the formation of a functional heavy chain gene, a successful rearrangement of gene segments includes one V, one D, and one J region segment linked to a C region segment (compare Figs. 14-1C and 14-3B).

During genetic recombination, additional variability is provided by a process known as *junctional diversification*. When two gene segments are brought together during rearrangement, precise linking does not occur. Instead, some nucleotides are inserted or deleted randomly at the junctional site. This introduces new codons, and therefore new amino acids, into the junctional sequence. If an incorrect number of junctional nucleotides are added or deleted, functional molecules will

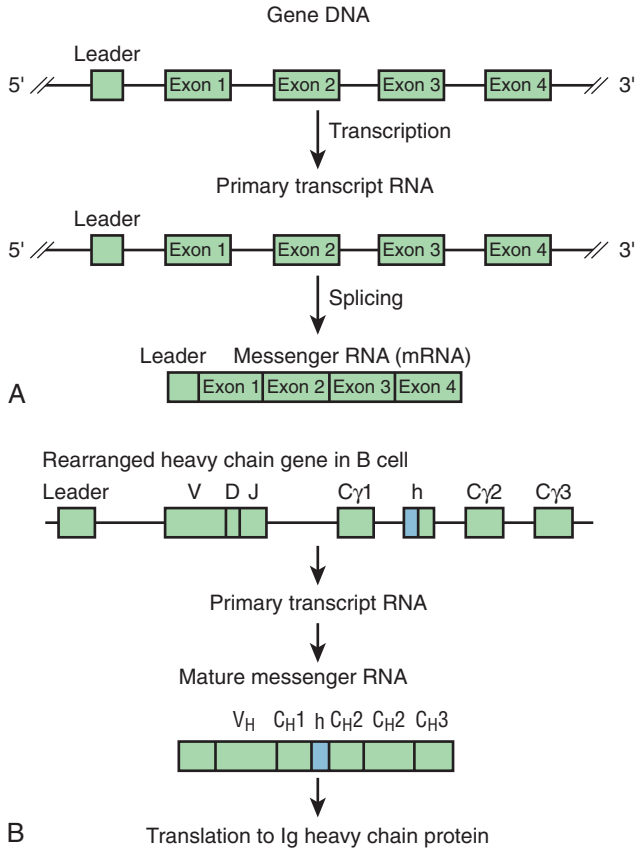

FIGURE 14-2 ■ Genes encoding Ig molecules. **A,** Characteristic structure of genes encoding a membrane protein. Note that the exons code for discrete structural regions of the protein, for example, an external domain, a transmembrane region, and a cytoplasmic tail. **B,** Corresponding structure of a rearranged IgG heavy chain gene. The leader-V region segment of DNA was initially located upstream on the same chromosome and has rearranged proximal to the DJ segment, which is proximal to the IgG Cγ exons. Processing of the primary transcript brings all of the coding regions together in the messenger RNA molecule for translation of the protein. (Adapted from MKSAP in the Specialty of Rheumatology. Philadelphia: American College of Physicians, 1993, p 7.)

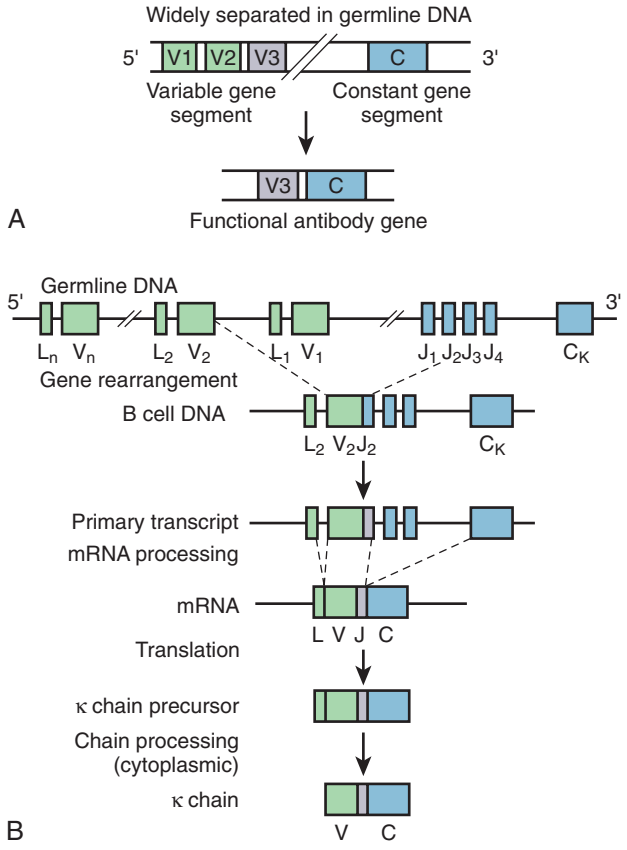

FIGURE 14-3 ■ Principles of genetic recombination. **A,** In the germline DNA, the V region segments are located upstream from the D, J, and C segments on the same chromosome. Recombination, which occurs only in lymphocytes, brings the V gene segments in proximity to the downstream segments. **B,** In the B cell, rearrangement of gene segments separated in the germline DNA allows for the formation of a functional immunoglobulin light chain gene (compare with Fig. 14-1C). mRNA, messenger RNA. (Adapted from MKSAP in the Specialty of Rheumatology. Philadelphia: American College of Physicians, 1993, p 8.)

not be encoded, because the rest of the gene will be "out of frame" or a "stop" sequence will be introduced. Junctional diversity occurs in the hypervariable CDR3 region of the molecule (see Fig. 14-1C).

In general, a single B cell usually expresses an Ig molecule of only one antigen specificity, composed of one heavy chain molecule and one light chain molecule. Even though there are two chromosomal copies of the heavy chain genes in each cell, only one is usually functionally expressed. This phenomenon of using genes on only one parental chromosome is known as *allelic exclusion*. Once a functional rearrangement of heavy chain genes has occurred on one parental chromosome, rearrangement of heavy chain genes on the other chromosome is mostly prevented. If the first rearrangement is not successful, the second one can occur. Allelic exclusion for light chain genes takes place in a similar fashion.

All of the genetic events described earlier occur before the B cell encounters its antigen. Further diversification of the B-cell (or antibody) response occurs after interaction with antigen by a process known as *somatic mutation*, primarily involving point mutations in the hypervariable regions of the V regions.[9,10] Somatic mutation can be viewed as "fine tuning" of the antibody response, occurring after the primary response to a stimulus and during the development of memory B cells. It is, therefore, mostly observed during a secondary immune response. Somatic mutation allows for the production of antibodies with higher affinity for antigen, that is, the ability to bind more strongly to an antigen. Although the mutations occur randomly, B cells with high affinity are selectively expanded (referred to as *affinity maturation*) because the stronger binding allows preferential stimulation by the target antigen, especially when concentrations of the antigen are limiting. Somatic mutation is closely tied to isotype switching, and T-cell help is almost always present. Somatic

mutation usually takes place at the site of T-cell–B-cell interaction in the germinal centers of lymph node or spleen.

Isotype Switching and Function of the Different Immunoglobulin Classes

As described earlier, one B cell usually makes antibody of a single specificity that is fixed by the nature of V_LJ_L and $V_HD_HJ_H$ rearrangements. During the lifetime of this cell, however, it can switch from making an IgM molecule to producing a different class of antibody, such as IgG or IgA, while retaining the same antigenic specificity. This phenomenon is known as *class switching* or *isotype switching*.[9,13]

Figure 14-4 shows the predominant mechanism by which a B cell switches from production of surface IgM to secretion of an IgG, IgA, or IgE molecule. The mechanism involves further DNA rearrangement (a process unique to Ig heavy chain genes), linking rearranged VDJ gene segments with a different heavy chain C region gene segment downstream. The switch (S) region is a stretch of repeating sequences 5′ to the C region that allows a VDJ unit (previously linked to the Cμ region gene segment) to rearrange to another C region downstream. In the process, the intervening DNA is deleted. The B cell, therefore, cannot return to IgM production. As described later, this form of class switching generally occurs after the B cell is stimulated by antigen and frequently is dependent on factors released by T helper cells. In Figure 14-4, it is noted that the Cδ region has no 5′ S region, and therefore the mechanism of class switching described previously is not used so a cell can express IgD on its surface. Another mechanism by which a B cell can express different isotypes is referred to as *alternative RNA splicing*. This mechanism is especially important for mature B cells to be able to express both surface IgM (μ chain) and IgD (δ chain) before B-cell stimulation. Alternative RNA splicing is also used when a B cell secretes IgM rather than expresses surface IgM.

The primary function of an antibody is to bind antigen. In some cases, this has a direct effect, for example, by neutralizing a toxin molecule. However, the interaction of antibody with antigen is usually not sufficient unless secondary effector functions are used.[9] For example, the antibody-antigen complex may activate the complement system, which may cause direct damage to the target or may attract inflammatory cells to the site of infection or injury. The activation of complement also allows inflammatory cells to bind antibody-coated molecules or antibody-coated cells via complement receptors.

Each class of secreted Ig has a different set of functions (Table 14-4).[9,14] IgG is the major antibody of secondary immune responses and is most important for obtaining effective immunization to various toxins, toxoids, and certain extracellular pathogens. IgG accounts for 70% to 75% of the total Ig pool and is the major Ig class in normal human serum. It also crosses the placenta and confers immunity to newborns and neonates for the first few months of life. The interaction

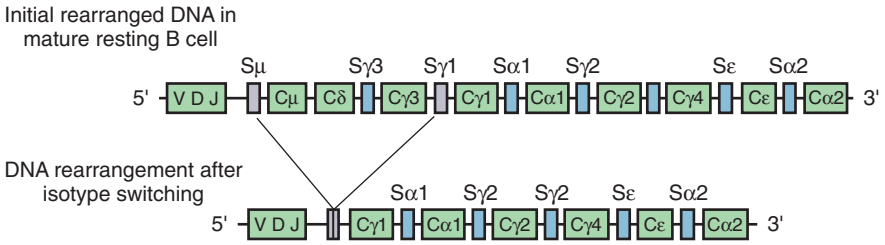

FIGURE 14-4 ■ Genetic mechanisms involved in Ig isotype switching. *Top,* The initial rearrangement of Ig heavy chain gene segments has already taken place in the B cell to put the V region proximal to the D, J, and Cμ segments. This latter genetic region contains other constant region gene segments farther downstream, including Cδ, various Cγ and Cα gene segments, and Cε. In the process of T-cell–dependent B-cell activation in the germinal centers, the B cell is signaled to undergo isotype switching to allow high-rate secretion of an IgG1 antibody. *Bottom,* This is accomplished by additional DNA rearrangements to allow the VDJ unit to rearrange to the Cγ1 segment downstream. The intervening DNA is deleted.

TABLE 14-4. Properties and Functional Characteristics of Immunoglobulin Classes and Subclasses

Effector Function	IgM	IgD	IgG1	IgG2	IgG3	IgG4	IgA	IgE
Mean serum levels (mg/mL)	1.5	0.04	9	3	1	0.5	2.1	0.00003
Opsonization	–	–	+++	–	++	+	+	–
Complement fixation	+++	–	++	+	+++	–	–	–
Binding of Fc receptor on phagocytic cells	–	–	++	+/–	++	+	–	–
Induction of mast cell degranulation	–	–	–	–	–	–	–	+++

Ig, immunoglobulin.

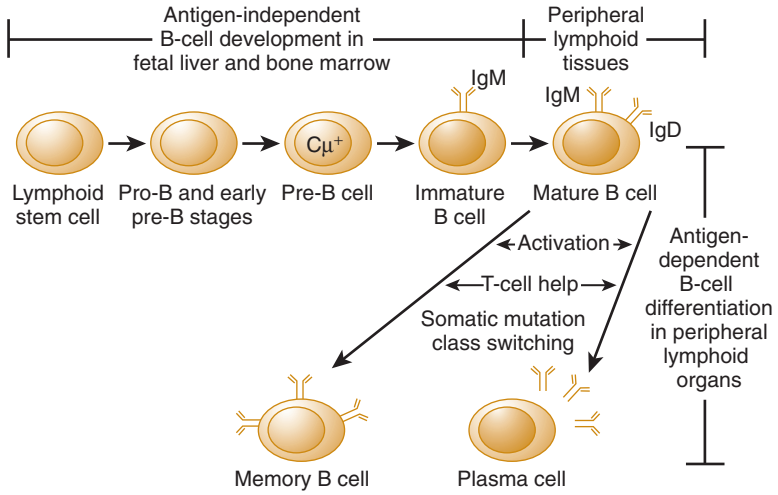

FIGURE 14-5 ■ B-cell development. Antigen-independent differentiation of the B cell in the adult bone marrow is shown from left to right. Pro-B and early pre-B stages involve the rearrangement of Ig heavy chain D-J and V-DJ gene segments and transient expression of a pre–B-cell receptor (BCR). Subsequent rearrangement of Ig light chain genes in the later pre-B cell allows for the development of a BCR-expressing immature B cell. The interaction of the mature naive B cell with antigen in the germinal centers of peripheral lymphoid organs and in the presence of T-cell help allows for somatic mutation of the Ig genes (affinity maturation), isotype switching, generation of B cells that are capable of high-rate IgG secretion, and generation of memory B cells.

of IgG antibodies with antigen can have numerous consequences, including precipitation, agglutination, complement activation, and various cellular effector functions via IgG (Fcγ) receptors.[9,14–17] Although not described at this time, an understanding of these processes is necessary to appreciate how IgG antibodies mediate the elimination or inactivation of pathogens and IgG-coated cells and how antibodies cause various types of immunopathologic processes. There are four IgG subclasses, with IgG1 and IgG3 being most effective at fixing complement and therefore activating complement-mediated effector functions. In addition, the structure of IgG3 is characterized by an elongated hinge region, which may account for its enhanced biologic activity.

IgM is the predominant early-secreted antibody, frequently seen in primary immune responses. IgM is important for effective responses to antigenically complex infectious organisms, especially those with polysaccharide-containing cell walls. IgM antibodies may also be extremely effective at precipitation, agglutination, and complement activation after binding to antigen. Secreted IgM is usually found as a pentamer of the basic (four-domain) Ig unit. Polymerization is facilitated by the binding of the heavy chain tailpieces to a J (joining) peptide.

IgA plays a major role in mucosal immunity and is the predominant Ig in secretions such as saliva and tracheobronchial secretions. Secretory IgA exists mainly in dimeric form and contains a secretory component, which is synthesized by epithelial cells and facilitates transport into secretions as well as protection from proteolysis. Secretory IgA is involved in the prevention of microbial adherence to mucosal cells and in the agglutination of microorganisms. IgA provides the first line of defense against a variety of pathogens.

IgE is scarce in the serum. Its major importance relates to its ability to bind to FcεR1 receptors on mast cells and basophils, and cross-linking of IgE bound to these cells results in cellular activation, degranulation, and release of mediators involved in allergic responses, such as histamine and various leukotrienes.[18] IgE plays a role in immunity to parasites, but in developed countries, it is more commonly associated with allergic responses and allergic diseases, such as hay fever and asthma (see Chapter 38).[19]

B-Cell Development

B cells are produced in the specialized microenvironments of the fetal liver and the adult bone marrow.[20] Figure 14-5 provides an overview of B-cell development, correlating the phenotype of a cell with antigen interactions and the various molecular events described earlier. Development of the stem cell through pro-B, pre-B, and immature B-cell stages occurs in the adult bone marrow. Early steps involve the expression of recombinase enzymes (e.g., recombination activating genes RAG-1 and RAG-2), rearrangement of Ig heavy chain DJ and VDJ gene segments, and transient expression of a pre–B-cell receptor.[20–22] The later pre–B cell is characterized by cytoplasmic μ heavy chain expression. The subsequent rearrangement of light chain genes allows for the expression of surface IgM (the BCR). Immature B cells express surface IgM, whereas mature naive B cells (present in the peripheral lymphoid tissues) usually express surface IgM and IgD. The rearrangement of variable region gene segments that allows for B-cell development in the bone marrow is independent of any antigen interaction and is relatively random. A number of growth and differentiation factors are required to drive B cells through the early stages of development in the bone marrow, and receptors for these factors are expressed on the developing B cells at various stages. Interleukin (IL)-3 and IL-7, for example, appear to be especially important in the early stages of B-cell development.[23,24]

After migration from the bone marrow, the life span of mature naive B cells is limited unless there is contact of the BCR with antigen. The interaction of B cells with foreign antigen occurs in the peripheral lymphoid tissues, particularly in the germinal centers of lymph nodes and spleen.[25] The interaction with antigen, in the setting of T-cell help, results in the generation of memory B cells and cells that secrete a large amount of Ig. This frequently involves class switching and somatic muta-

tion, which allows a secondary antibody response to generate antibodies of a different isotype with higher affinity for the stimulating antigen. These latter processes usually take place in the presence of factors released from T helper cells.

B-cell repertoire formation in the bone marrow is mostly random, and B cells with self-reactivity are generated. Negative selection of cells capable of strongly binding to self-antigens is an important part of B-cell development. This process of B-cell self-tolerance appears to involve both deletion (elimination) and functional inactivation (anergy) of self-reactive cells.[26] A separate mechanism has been described in which B cells with specificity for self-antigens can modify their receptors through a process called *receptor editing*.[11,12] These self-reactive B cells undergo a reversible arrest of development and appear to re-initiate light chain gene rearrangements to alter their BCR. If a B cell fails to successfully edit its BCR, it is destined for cell death (apoptosis). Immature B cells in the bone marrow appear to be capable of receptor editing, whereas mature B cells in the peripheral lymphoid tissues normally lose this ability to reexpress functional recombinase enzymes and to initiate a new round of Ig gene rearrangements.

Immunoglobulin Interactions with Antigen

An antigen is a molecule or molecular complex recognized by B cells or T cells. The term *immunogen* usually refers to a substance capable of eliciting an immune response, and therefore, it must also be capable of being recognized as an antigen. An antigen (e.g., a protein molecule) is usually much larger than the small region fitting into the combining site of an Ig molecule or the peptide piece recognized by a TCR. This smaller region is frequently referred to as an *antigenic determinant* or *epitope*. In a protein, a B-cell epitope can theoretically be constructed in two ways—as a continuous or a discontinuous epitope. In a continuous epitope, the amino acid residues are part of a single uninterrupted sequence, whereas in a discontinuous epitope, residues are not contiguous in the primary structure but are brought together by the folding of the polypeptide chain. Because this kind of epitope requires a special conformation of the antigen, it is frequently referred to as a "conformational epitope."

B cells and T cells usually recognize different parts of an antigen. B cells and their secreted Ig molecules most commonly recognize unprocessed or "native" antigens. These antigens have maintained their native configuration, and most of the epitopes are usually of the discontinuous or conformational type. In general, only a minor component of a B-cell response is directed to small linear peptide regions of the antigen. Studies indicate that epitopes recognized by B cells are not randomly distributed throughout the antigen, but rather reside in regions with particular structural features. One important feature is "accessibility," because epitopes normally must be on the outer surface of a protein and must even be able to protrude from an antigen's globular surface to be able to interact with the BCR.

T Cells and Antigen-Presenting Cells

In contrast to B cells, T cells recognize processed pieces of a protein antigen, which are presented to the TCR by MHC molecules on the surface of antigen-presenting cells.[3,4]

T-Cell Receptors

The TCR shows important structural similarities with Ig molecules (Fig. 14-6).[2] The αβ TCR is expressed by at least 90% of peripheral blood T cells. Essentially, all $CD4^+$ T cells and most $CD8^+$ T cells express this form of the TCR. A small percentage of αβ-expressing T cells have a double-negative ($CD4^-$, $CD8^-$) phenotype. As shown in Figure 14-6, each chain consists of two extracellular (external) Ig-like domains anchored into the plasma membrane by a transmembrane region and a short cytoplasmic tail. Similar to Ig molecules, the outer NH_2-terminal domain of each chain constitutes the variable region. Outside of the transmembrane region, the two chains are covalently linked together by disulfide bonds. The short cytoplasmic tail is consistent with the fact that the αβ heterodimer itself is not capable of transmitting a signal to the inside of the cell after receptor engagement. As discussed later, this function is accomplished by the CD3 complex of polypeptides and other signaling proteins that are associated with the TCR.

The γδ TCR is an alternative form of TCR that is similar in overall structure to the αβ receptor.[27] Although some γδ cells express CD8, most are $CD4^-$, $CD8^-$ (double negative). CD8 expression is largely confined to those

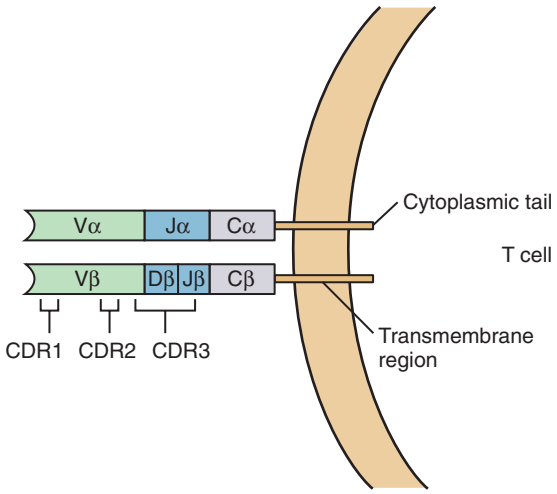

FIGURE 14-6 ■ The T-cell receptor (TCR) α and β chains indicate the regions encoded by different TCR gene segments. The positions of the CDRs of both the β and the α chains are also shown. These are the most variable parts of the TCR and the most important for TCR binding to peptide/major histocompatibility complex. CDR1 and CDR2 of both the α and the β chains are encoded within the variable region genes. CDR3 is formed by the rearrangement of V, D, and J gene segments of the β chain and V and J segments of the α chain and is encoded by the distal part of the V region segment through part of the J segment. The different parts of the TCR are not drawn to scale.

γδ cells residing in the small intestine. The γδ TCR is also expressed in association with the CD3 complex. Although γδ T cells form a minor proportion of the T cells in the thymus and secondary lymphoid organs, they are abundant in various intraepithelial populations, such as in the skin, intestines, and lung.[27,28]

Genetic Mechanisms Involved in T-Cell Receptor Structure and T-Cell Receptor Repertoire Formation

Genes encoding the TCR are organized similarly to Ig genes.[2,29] Figure 14-7 shows the germline organization of the TCR α and β chain gene complexes. In a manner similar to that described previously for B cells, rearrangement of gene segments, junctional diversity, and combinatorial joining of the two chains is responsible for the diversity of the TCR repertoire. However, in contrast to B cells, TCR genes do not undergo somatic mutation. Thus, nearly the entire TCR αβ repertoire is formed during T-cell development in the thymus and before any interaction with antigen. Because the T-cell repertoire is shaped to recognize self-MHC antigens, it is believed that extrathymic somatic mutation might too frequently result in deleterious self-reactive T cells. Thus, the absence of somatic mutation may protect against this potentially serious possibility.

Similar to B cells, T cells also show allelic exclusion for functional gene rearrangements. Thus, if one chromosome undergoes a functional rearrangement such that a functional polypeptide is produced, genes on the other parental chromosome are usually prevented from rearranging. Allelic exclusion is more complete for the β chain than for the α chain, and a small percentage of T cells express two functional TCR α chains (each paired with one β chain) and, therefore, two potential TCR specificities. However, in general, the great majority of mature T cells express only one αβ TCR and, therefore, only one specificity. This specificity does not change during the lifetime of a T cell.

The components of the αβ TCR heterodimer are shown in Figure 14-6, and the ribbon backbone structure of the Vα and Vβ portions of a human TCR are shown in Figure 14-8.[3,4,30,31] The upward-pointing loop structures are the CDRs. These regions are the most variable part of the TCR α and β chains and are most important for binding of the TCR to peptide/MHC complex. The CDR1 and CDR2 regions of the α chain and β chain are encoded within the germline *TCRAV* and *TCRBV* gene segments, and variability in their sequences distinguishes the different V region subfamilies. There are about 25 different Vβ (*TCRBV* gene) human subfamilies, which include about 50 functional gene segments, and about 40 to 50 different Vα (*TCRAV*) gene segments. The most diverse part of the β chain is the CDR3, which is formed during the rearrangement of *TCRB* gene segments and is encoded by the 3′-end of the V region, the diversity (D), and the joining (J) region gene segments (see Fig. 14-7). The expressed α chain gene (*TCRA*) is formed similarly, although there is no diversity (D) gene segment (see Fig. 14-7A). Just as in the rearrangement of Ig genes, random nucleotide additions and deletions as the TCR junctional

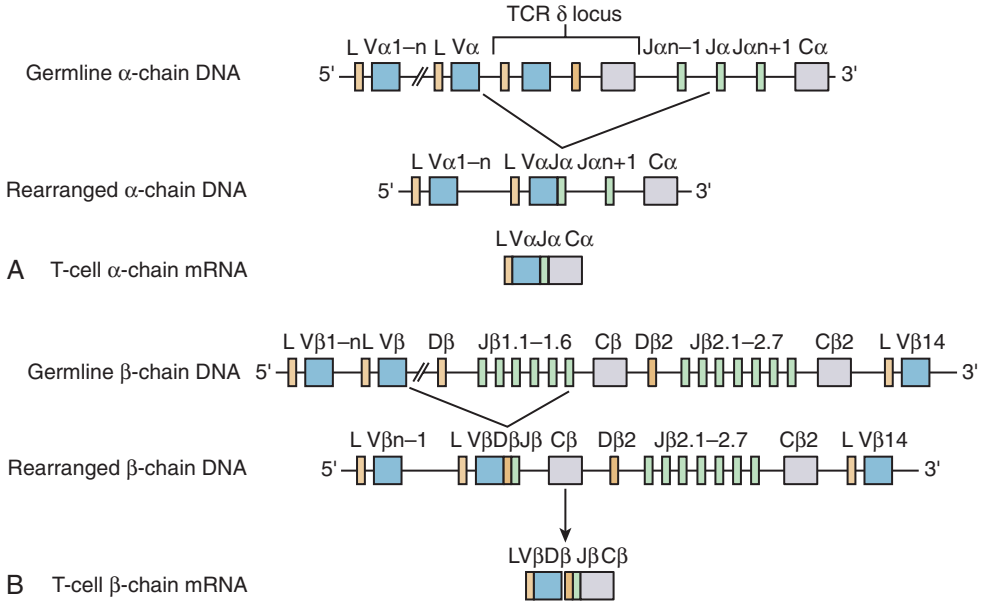

FIGURE 14-7 ■ Rearrangement of genes encoding the TCR. **A,** In the germline TCR α chain gene complex, before any rearrangement in T cells, approximately 40 to 50 Vα gene segments are located upstream of the multiple Jα and Cα gene segments. Within the TCR α chain locus is the TCR δ gene complex (expressed in γδ T cells), which is deleted when Vα genes are rearranged. During T-cell development, Vα genes are rearranged to downstream Jα gene segments to form a functional α chain gene. This process is similar to that described for immunoglobulin gene rearrangements. Expression of RNA and RNA processing allows for generation of TCR α chain messenger RNA (mRNA). **B,** A similar process allows for rearrangement of TCR β chain genes in the pre–T cell during T-cell development. In both **A** and **B**, nucleotide additions and deletions at the margins of the rearranging segments are not shown (see text).

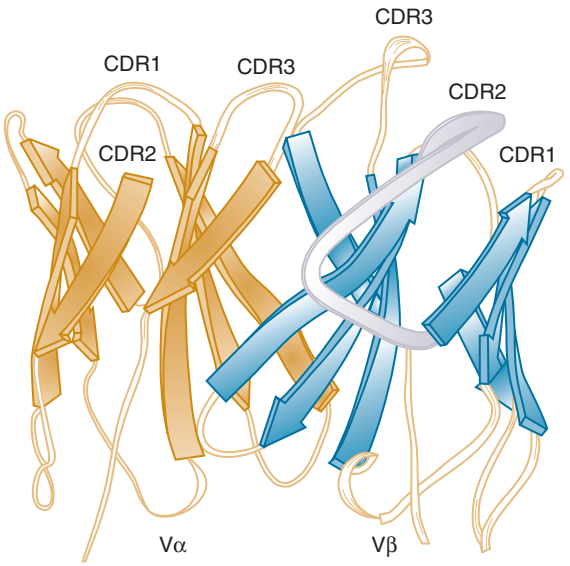

FIGURE 14-8 ■ A ribbon backbone structure of the Vα and Vβ portions of a human TCR. The upward-pointing loop structures are the CDRs. These regions are the most variable part of the TCR α and β chains and are most important for TCR binding to peptide/major histocompatibility complex. The CDR1 and CDR2 regions of the α chain and β chain are encoded within the germ-line TCRAV and TCRBV gene segments, respectively. The highly variable CDR3 region is formed by the rearrangement of V, (D), and J gene segments. Junctional nucleotide substitutions and deletions at the margins of rearrangement add to the potential diversity of the CDR3 region. (Adapted from Kotzin BL, Kappler J: Targeting the TCR in rheumatoid arthritis. Arthritis Rheum 41:1907, 1998.)

region gene segments join together create additional diversity. The CDR3 is the most important part of the TCR for direct interaction with peptide/MHC complexes.

Antigen-Presenting Cells and Molecules of the Major Histocompatibility Complex

There are two major varieties of MHC molecules (and genes) involved in the presentation of antigens to T cells.[32] MHC class I molecules include human leukocyte antigen (HLA)-A, HLA-B, and HLA-C molecules. MHC class II molecules include the HLA-DR, HLA-DQ, and HLA-DP molecules. Class I molecules are expressed on nearly all nucleated cells. In contrast, class II molecules have a limited distribution and are normally present only on cells involved in antigen presentation to T cells, including dendritic cells, macrophages, B cells, and thymic epithelial cells. The limited expression of class II antigens in different tissues may be extremely important in preventing various types of autoimmune reactions. After activation or after exposure to certain cytokines, such as interferon-γ (IFN-γ), other human cell types such as activated T cells and epithelial cells can express class II molecules.

The general structures of the two classes of MHC molecules are shown in Figure 14-9. For MHC class I antigens, the α chain (encoded within the MHC) is complexed to beta$_2$-microglobulin (encoded outside the MHC). As discussed later, the α chain is highly polymorphic (variable between individuals), whereas beta$_2$-microglobulin is invariant. The extracellular portion of the α chain is divided into three domains: α1, α2, and α3. The outer α1 and α2 domains represent the polymorphic components of the molecule, and the α3 domain is relatively constant. MHC class II molecules are composed of an α and a β chain, both of which are encoded within the MHC. The NH_2-terminal domains of

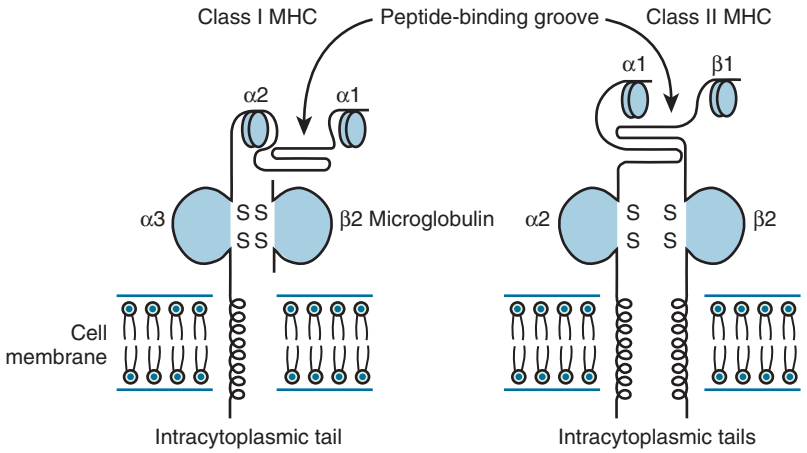

FIGURE 14-9 ■ Comparison of the composition of class I and class II major histocompatibility complex (MHC) molecules. The class I MHC α chain is variable (polymorphic) among different individuals. It is expressed with beta$_2$-microglobulin, which is encoded outside the MHC region, and does not differ among different individuals. The class II MHC molecules are composed of α and β chains. For HLA-DR molecules, only the β chain is variable, whereas for the HLA-DQ and HLA-DP molecules, both the α and the β chains are encoded by polymorphic alleles. In class I MHC molecules, the peptide-binding region is formed between the α1 and the α2 domains, which are polymorphic. The peptide-binding region of class II MHC molecules is formed between the α1 and the β1 domains of the α and β chains, respectively.

each chain (α1 and β1 domains) represent the polymorphic regions of the molecule and are important in antigen presentation, whereas the α2 and β2 domains are relatively constant.

MHC class I and class II molecules have been crystallized and their structures have been elucidated, providing remarkable insight into how antigenic peptides are bound and presented to T cells.[3,4,33–36] In Figure 14-10A, the peptide-binding pocket or groove of a class I molecule is viewed from the top, showing the surface that is contacted by a TCR. MHC class I pockets can usually only bind peptides of 8 to 10 amino acids, which are bound in a typical extended conformation with both the NH_2 terminus and the carboxy (COOH) terminus anchored in the peptide-binding groove. In the case of MHC class II, the peptide-binding groove is formed by the interaction of the NH_2-terminal domains of the α and β chains (see Fig. 14-10B). The structure of MHC class II allows peptides of varying lengths to bind because both ends of the peptide are free, and the peptide shown in the figure has the typical polyproline-like extended helical conformation seen in all class II MHC-bound peptides.

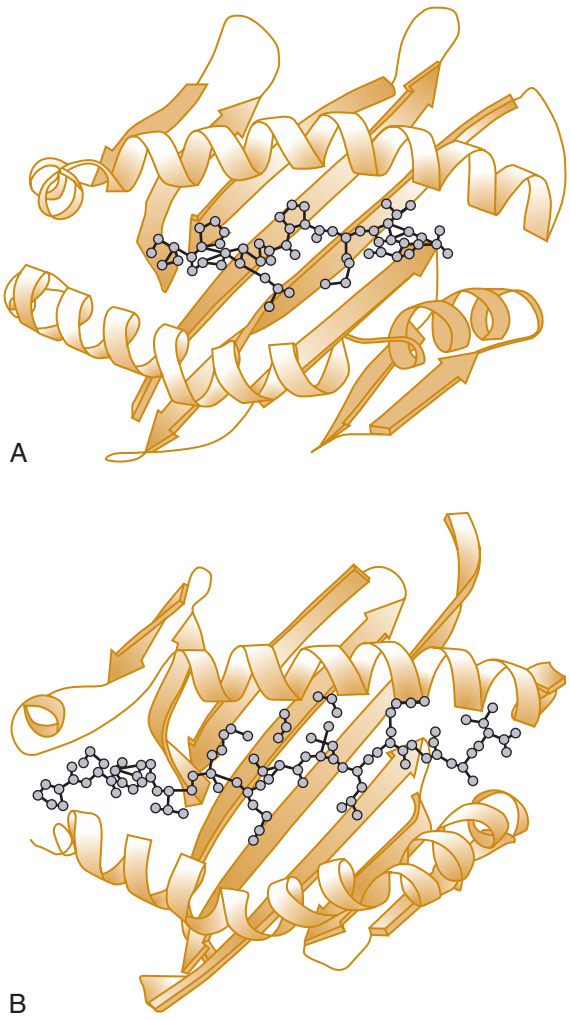

FIGURE 14-10 ■ Structure of the MHC/peptide complexes. **A,** A schematic view of a MHC class I binding groove with peptide. The peptide is shown in ball-and-stick representation. In class I molecules, the peptide is usually of fixed length (~9 amino acids) and bound such that the NH_2 and COOH termini are both anchored in the peptide-binding groove. **B,** A schematic view of a MHC class II (HLA-DR1) molecule with bound peptide in the groove. The peptide is shown in ball-and-stick representation. The peptide has the typical polyproline extended helical conformation seen in all class II bound peptides. The structure of class II allows peptide of varying lengths to bind because both ends of the peptide are free and can extend out of the groove on both sides. (From Jones EY: MHC class I and class II structures. Curr Opin Immunol 9:76–77, 1997.)

The aforementioned structural studies have important implications for understanding the interactions between the peptide/MHC complex and TCRs. For example, changes in amino acid residues on the floor of the peptide-binding pocket (which are covered up by the peptide) will likely affect peptide binding but not TCR binding directly. Amino acid residues on the α-helices facing into the groove are similarly likely to affect peptide binding, whereas residues facing up are candidates for interacting directly with the TCR.

Genetics and Nomenclature for the Human Leukocyte Antigen System

A description of the genetic organization of the MHC is important for understanding the basis for the association of certain HLA genes with disease.[32,37,38] The entire HLA region spans approximately 3.6 megabases and encompasses greater than 200 genes, many of which have important roles in the immune system. Figure 14-11 shows the general organization of class I, II, and III genes on human chromosome 6. The region located between the HLA-DR and HLA-B loci includes genes for complement (C) components (factor B, C2, C4A, and C4B) and genes encoding certain cytokines, such as tumor necrosis factor (TNF).

The combination of closely linked MHC genes on the same chromosome is referred to as the *MHC haplotype*; genes of the entire complex determine the haplotypes.[32] At many of the loci, there are multiple alternative forms (alleles) of a gene that can be inherited. For example, over 690 HLA-A, 1100 HLA-B, 690 HLA-DR, 95 HLA-DQ, and 130 HLA-DP alleles with official names are characterized at this time.[39] Allele numbers for the class II genes continue to increase with new molecular biologic typing techniques. Within the class II region (see Fig. 14-11), the DRA gene (encoding the DR α chain) is not polymorphic, and therefore, all of the allelic polymorphism is determined by DRB (DR β chain) gene variability. The DRB1 gene determines the DR1 to DR18 specificities; the DRB3 and DRB4 genes determine the DR52 and DR53 specificities, respectively. Within DQ, both the DQA1 and the DQB1 genes are polymorphic, and both contribute to DQ variability.

Because they are closely linked, MHC genes are frequently inherited as a unit (referred to as a *haplotype*).[32] Furthermore, meiotic recombination is unusual for certain regions within the MHC; for example, recombination is rare between the DRA and the DQA1 loci and

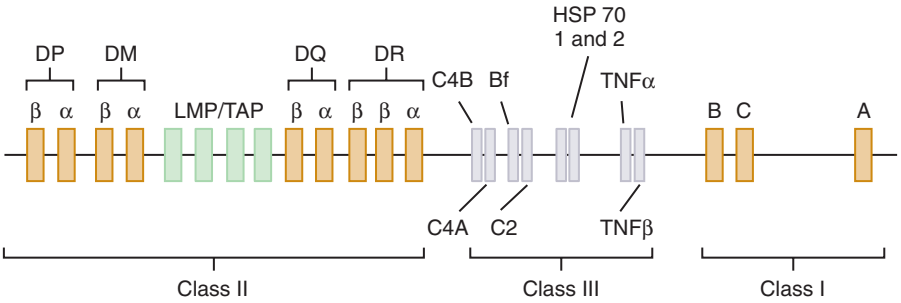

FIGURE 14-11 ■ Overview of the human leukocyte antigen (HLA) gene complex. The class I, II, and III regions of the gene complex are shown. In the class I region are the HLA-A, HLA-B, and HLA-C α chain genes. In the class II regions are the HLA-DR, HLA-DQ, and HLA-DP genes for the α and β chains. This region also contains the DM and LMP/TAP (transporters associated with antigen processing) genes, which encode molecules involved in the processing and transport of peptides to be presented with MHC molecules. The class III region in humans is located between the class I and class II regions and includes complement factors 4A (C4A) and 4B (C4B), factor B (Bf) of the alternate complement pathway, tumor necrosis factor-α and -β (TNF-α and TNF-β), and heat shock protein-70 (HSP70).

is much more common between the DQ and the DP regions. Therefore, in different ethnic populations, certain DR and DQ alleles appear to be inherited together to form part of a stable haplotype. Those associated DR and DQ alleles are inherited in linkage disequilibrium (e.g., DR3 and DQ2 [*DQA1*0501, DQB1*0201*] or DR4 and DQ8 [*DQA1*0301, DQB1*0302*] in whites).[40] On some chromosomes, certain HLA-B, class III, DR, and DQ gene alleles have been maintained as a unit, inherited in linkage disequilibrium, and are referred to as *extended haplotypes*. One extended haplotype associated with autoimmune diseases, such as systemic lupus erythematosus and type 1 diabetes, includes the alleles A1, B8, DR3, and DQ2.[40]

Presentation and T-Cell Recognition of Antigens

In contrast to B cells, T cells recognize processed peptides of a foreign antigen that are complexed to MHC molecules on antigen-presenting cells. Because of the process of thymic selection for self-MHC recognition, there is little capability for T cells to recognize intact or native protein antigens. $CD4^+$ T cells generally recognize peptides complexed to class II MHC molecules, whereas $CD8^+$ T cells interact with peptide/class I MHC molecules.[2–4,32] The purpose of this relatively complex antigen-presentation process may be to focus the T-cell response onto cells. For example, it is much easier for a T cell to kill a virus-infected cell before the pathogen has the opportunity to multiply than it is to kill individual virus particles. The class I MHC molecules, therefore, focus the cytotoxic T-cell response on cells infected with intracellular organisms, whereas free infectious particles are the targets of antibodies. Recognition of free (extracellular) organisms by T cells would only distract these cells from carrying out their true function of killing the infected targets. Class II MHC molecules similarly focus the delivery of T-cell help on the relevant antigen-specific B lymphocytes that eventually produce antibodies. Recognition of antigen only on the surface of MHC class II–expressing cells also allows for a system by which the activation of $CD4^+$ T cells can be closely regulated (see later discussion).

Peptide-containing MHC class I and class II molecules on the surface of antigen-presenting cells serve as ligands for engaging TCRs of $CD8^+$ and $CD4^+$ T cells, respectively. In order to effectively present antigenic peptides, antigen-presenting cells must be capable of performing at least two functions: (1) processing and displaying parts of antigens together with MHC molecules on their cell surface and (2) providing the other accessory signals necessary for T-cell activation. The second function is discussed later. Antigen processing refers to the series of steps that generate these peptide fragments, load them onto MHC molecules, and allow expression of the peptide/MHC complex on the cell surface.[41] MHC class I molecules are loaded with peptides derived from endogenously synthesized proteins in the endoplasmic reticulum, whereas MHC class II molecules are loaded with peptides derived from extracellular proteins in a specialized endosomal vesicle. Major differences exist in the manner in which endogenous and exogenous foreign antigens are prepared and presented to T cells (Table 14-5).[41–49]

All intracellular proteins can serve as sources of peptides for MHC class I molecules.[42–46] Endogenous foreign antigens are usually viral products that are synthesized within the cytoplasm. Some of the viral molecules produced in the cytoplasm are degraded into peptides by a multi-subunit proteasome complex. Transporters of antigenic peptides (TAP-1 and TAP-2) are required for the transport of peptides into the endoplasmic reticulum, where the association with class I molecules takes place. For stable expression on the cell surface, the MHC class I heavy chain and beta$_2$-microglobulin dimer must properly assemble with a peptide inserted into the MHC class I binding groove. This process occurs predominantly in the endoplasmic reticulum (ER) and is orchestrated by multiple ER-resident chaperone and accessory molecules that facilitate peptide loading and stabilization of the complex. After complete assembly of the MHC class I/peptide complex, it is transported to the surface via normal secretory pathways. On the cell

TABLE 14-5. Major Histocompatibility Complex Class I versus Class II Pathways of Antigen Presentation to T Cells

Characteristic	MHC Class I	MHC Class II
Expression	Nearly all nucleated cells	Antigen-presenting cells (B cells, macrophages, dendritic cells, thymic epithelial cells)
Responding cells	$CD8^+$ T cells	$CD4^+$ T cells
Peptides	~9 amino acids	~16–24 amino acids
Source of peptides	Endogenous antigens	Extracellular antigens
Site of peptide generation	Cytoplasm	Phagolysosome, endosome
Proteolytic mechanism	Cytosolic proteasome complex	Endosomal enzymes
Peptide loading compartment	Endoplasmic reticulum	Novel endosome (MHC II compartment)
Transport of MHC to loading area	Already in endoplasmic reticulum	Invariant chain acts as chaperone to carry to MHC compartment
Transport of peptide to loading area	Transporters associated with antigen	Fusion of vesicles processing (TAP-1 and TAP-2)
Loading of peptide into MHC	Complex of calreticulin, TAP-1/TAP-2, tapasin, and ERp57	HLA-DM–mediated release of CLIP and binding of new peptide
Transport of MHC/peptide complex to cell surface	Secretory pathway	Tubular transport

CLIP, class II–associated invariant chain peptide; HLA, human leukocyte antigen; MHC, major histocompatibility complex; TAP, transporter of antigenic peptide.

surface, the complex is recognized by a $CD8^+$ T cell, such as a cytotoxic T cell. In theory, because all cells appear to possess the processing apparatus, any class I–expressing cell can present antigen to a $CD8^+$ cytotoxic effector cell. However, antigen-presenting cells that are capable of activating resting $CD8^+$ T cells are more specialized.

Foreign antigens recognized by $CD4^+$ T cells are usually exogenous antigens that come from outside of the antigen-presenting cell (see Table 14-5).[47–49] In order for such an exogenous antigen to be presented to a $CD4^+$ T cell, it must be taken up (endocytosed or phagocytosed) and processed by an antigen-presenting cell, usually a B cell, macrophage, or dendritic cell. It is degraded into peptides in phagolysosomes. MHC class II molecules are bound to invariant chain immediately after their synthesis in the ER. A segment of invariant chain called class II–associated invariant chain peptide (CLIP) prevents premature binding of peptides in this intracellular compartment.[49] Transport to a multivesicular and multilamellar late endosomal compartments, called the MIIC compartments, allows for dissociation of CLIP and loading with peptide fragments. A nonclassic MHC class II–like molecule, HLA-DM, facilitates the release of CLIP and subsequent binding of other peptides to the empty MHC class II molecule. Like other MHC class II molecules, HLA-DM is a heterodimer of α and β chains. However, in contrast to other class II molecules, it is not polymorphic and is not expressed on the cell surface; rather it is predominantly located in the endocytic compartment. The MHC class II/peptide complex is subsequently displayed on the cell surface, where it is recognized by $CD4^+$ T lymphocytes. The mechanism by which this complex is transported to the cell surface is thought to involve the transformation of the MHCII compartments into tubular structures that are directed toward the site of T cell interaction with the plasma membrane, thus allowing control of the formation of the immunologic synapse.[47]

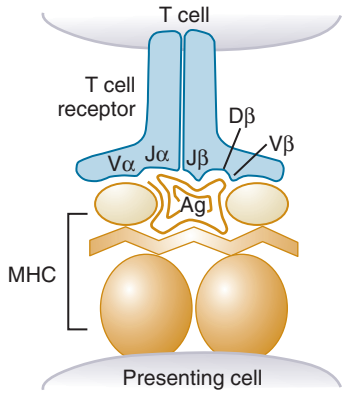

FIGURE 14-12 ■ T-cell recognition of a conventional peptide antigen. The MHC molecule on the antigen-presenting cell is *shaded* and shows the peptide-binding groove with a peptide in it. The interacting TCR is shown as a *pale* structure. Note that the junctional regions of the TCR α chain (Vα/Jα) and β chain ($V_\beta/D_\beta/J_\beta$) are depicted such that they appear to have the most important interaction with the peptide. These junctional regions form the CDR3 of the α and β chains, which is the most variable component of the TCR. The CDR1 and CDR2 loops are encoded within the Vα and Vβ regions, and these loops may have more interaction with the MHC parts of the complex compared with CDR3. A ribbon diagram of the TCR CDR loops is depicted in Figure 14-8. (Adapted from Drake CG, Kotzin BL: Superantigens: Biology, immunology, and potential role in disease. J Clin Immunol 12:140, 1992.)

Figure 14-12 shows a schematic view of antigen recognition by a $CD4^+$ T cell. A foreign peptide is contained within the antigen-binding groove of a class II MHC molecule, and the TCR simultaneously recognizes the complex of peptide and class II MHC molecule. Thus, residues of the variable region of the TCR interact with the peptide and MHC residues extending out from the

peptide-binding groove. As discussed earlier, the highly variable CDR3 region encompassing the Vβ/Dβ/Jβ and Vα/Jα junctions of the αβ TCR is frequently most important in the binding of peptide, whereas other parts of the variable regions are more involved in MHC residue interactions.[2–4]

T-cell superantigens are products of bacteria and viruses that differ in many ways from the conventional protein or peptide antigens described earlier.[50] Most striking is that their recognition by TCRs appears to depend almost entirely on the variable region of the β chain (Vβ). Thus, unlike recognition of conventional peptide antigens, the other components of the TCR (Dβ, Jβ, Vα, Jα) play little role in superantigen binding. Because the relative number of Vβ genes is limited, many T cells (~5%–30% of the entire repertoire) within an individual express responsive Vβ elements and are stimulated by a superantigen, whereas the responding frequency to a conventional antigen is usually much less than 1 in 10,000. The potential importance of superantigens in disease relates to their ability to stimulate T cells on a large scale. Although superantigens are presented by class II MHC molecules, they are not processed like conventional peptide antigens. Instead, they seem to bind directly to the outer walls of the peptide-binding cleft. Many different class II MHC molecules can usually present a particular superantigen, and thus its recognition is not MHC restricted. The best studied superantigens are the staphylococcal enterotoxins and toxic shock syndrome toxin-1. Superantigens have been noted to be produced by other bacteria, particularly group A streptococci, and occasional viruses. Studies suggest that superantigens and the massive T-cell activation induced by them play a role in diverse pathologic conditions, including toxic shock syndrome, Kawasaki disease, and possibly certain autoimmune diseases.

γδ T cells represent a separate lymphocyte subset, whose primary functional assignment is currently unknown.[27,28] Although in many ways similar to αβ T lymphocytes, they are clearly distinguished by their expression of a different set of TCR genes with different ligand specificities and by a different distribution in normal tissues. Although both αβ and γδ T cells circulate, αβ T cells tend to populate lymphoid tissues, whereas γδ T cells preferentially colonize nonlymphoid tissues, particularly epithelium-rich tissues such as skin, intestine, and reproductive tract. Bacterial antigens in general seem to be very good stimulators of γδ T cells, and it has been suggested that these cells function as a first line of defense against infectious pathogens. For example, it has been shown that the initial immune response to numerous pathogens is characterized by expansion of γδ cells. Furthermore, many γδ-cell subsets recognize mycobacterial antigens, and heat shock proteins have been shown to be the basis for the stimulation of certain clones. The ability of γδ T cells to respond to heat shock or stress proteins could provide a means of recognizing a wide variety of pathogens because these proteins are highly conserved among many species. γδ T cells have also been implicated in the regulation of various immune responses, especially in the lung.[51]

CD3 Complex and Intracellular Signaling after T-Cell Activation

An extensive description of the complex signaling events that occur in T cells[52] or B cells[53] after antigen receptor engagement and cellular activation is beyond the scope of this chapter. Briefly, in T cells, the CD3 complex of polypeptides and structurally distinct ζ chains are closely associated with the TCR heterodimer and are critical for transmitting a signal to the inside of the cell after TCR binding to antigen.[52] Triggering of the TCR/CD3 complex with effective co-stimulation is coupled to (1) protein tyrosine kinase activity associated with phosphorylation of particular tyrosine-based activation motifs within the CD3 and ζ chains and involving Lck, Fyn, and ZAP-70 protein tyrosine kinases and adapter proteins; (2) activation of phospholipase C-γ, resulting in phosphatidylinositol metabolism with generation of inositol triphosphate and diacylglycerol (DAG); (3) increase in intracellular calcium ion concentration; (4) activation of protein kinase C via DAG and calcium; and (5) activation of additional pathways involving calcineurin, Ras, and mitogen-associated protein kinase cascades, leading to the production of activated transcription factors (such as nuclear factor-κB, nuclear factor of activated T cells, and activator protein-1) to induce new gene expression and leading to cell proliferation and differentiation. In B cells, BCR aggregation by antigen initiates signal transduction by the receptor's associated CD79a and CD79b subunits.[53]

T-Cell Accessory Molecules CD4 and CD8

There are two major subpopulations of peripheral αβ-expressing T cells. The T-cell subset that expresses the CD4 molecule identifies cells that primarily recognize antigens in the context of class II MHC molecules (e.g., HLA-DR, HLA-DQ, and HLA-DP). Cells within the $CD8^+$ T-cell subset primarily recognize antigen in the context of class I MHC molecules (e.g., HLA-A and HLA-B). These accessory molecules appear to stabilize an interaction with the appropriate MHC molecule.[54–56] The CD4 molecule interacts with nonpolymorphic determinants on class II MHC molecules, whereas the CD8 molecule binds to analogous invariant residues on class I MHC molecules. The associated binding of CD8 may be especially important in stabilizing low-affinity TCR binding to the antigen/MHC complex. In addition, both CD4 and CD8 molecules participate in TCR-mediated signal transduction through associated Lck protein kinase.[52] In general, $CD4^+$ T cells have helper or inducer functions (e.g., help B cells in a T-cell–dependent antibody response), whereas $CD8^+$ T cells have cytotoxic or suppressor functions. Regulatory subsets expressing each of these coreceptors have also been described (see later discussion).

T-Cell Development and Selection of the T-Cell Repertoire

A general overview of important events in T-cell development is provided in Figure 14-13.[57] Stem cells pre-

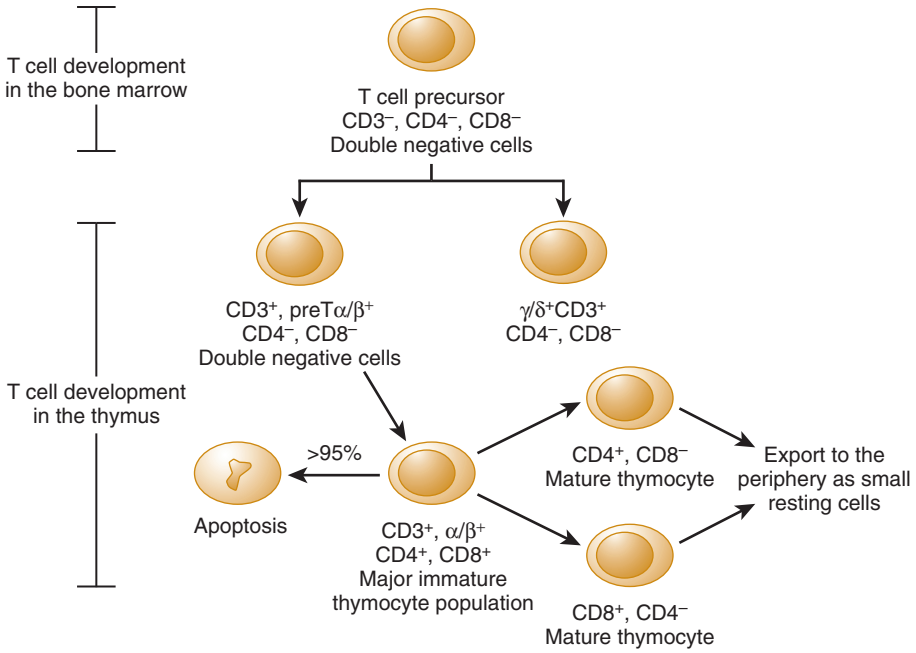

FIGURE 14-13 ■ T-cell development and maturation in the thymus. The rearrangement of the TCR β chain genes in the pre–T cell and then TCR α chain genes results in generation of a remarkably diverse TCR repertoire, expressed at the stage of the major immature thymocyte. These cells express TCR at relatively low density and are double positive for both CD4 and CD8. The repertoire is positively selected for (low) affinity to self-MHC (self-MHC restriction). Cells with TCR that do not undergo positive selection die in the thymus by apoptosis. Immature and mature thymocytes with high affinity for self-MHC peptide complexes are negatively selected and undergo apoptosis (deleted). Overall, greater than 95% of immature thymocytes fail to mature for export to the peripheral lymphoid organs. As immature thymocytes mature, they maintain CD4 expression and down-regulate CD8 (MHC class II restricted) or maintain CD8 expression and down-regulate CD4 (MHC class I restricted).

committed to the T-cell lineage arise in the bone marrow and migrate to the thymus. These cells do not express TCR molecules and do not express CD4 or CD8 molecules (i.e., they are double negative for CD4 and CD8). These cells develop by rearranging TCR β chain genes and generating a functional TCR β chain. A surrogate pre–T-cell α chain allows expression on the cell surface early in development.[58] Subsequently, the α chain genes are rearranged and TCR molecules are expressed at a relatively low density. The additional expression of both CD4 and CD8 (double-positive thymocytes) identifies the major immature thymocyte population.

The TCR repertoire of the early immature population appears to be dependent on the random rearrangement of TCR genes. Subsequently, in the thymus, two major processes modify this repertoire.[57,59,60] One process positively selects cells that have some TCR affinity for self-MHC molecules. Evidence suggests that an interaction with thymic cortical epithelial cells is involved in this positive selection step. This process allows mature cells to eventually recognize foreign antigens in the context of self-MHC antigens (a phenomenon termed *self-MHC restriction*). Cells that are not positively selected undergo programmed cell death (*apoptosis*) within the thymus. The other process deletes cells that have a high level of self-reactivity (termed *negative selection* or *self-tolerance*).[60] This deletion process primarily involves an interaction with bone marrow–derived cells (macrophages, dendritic cells, B cells) that have migrated to the thymus and specialized cells within the thymic medulla (medullary epithelial cells) that express a variety of organ-specific antigens.[61,62] The transcriptional regulator, Aire, plays an important role in T-cell tolerance induction in the thymus, mainly by promoting ectopic expression of a large repertoire of transcripts encoding proteins normally restricted to differentiated organs in the periphery.[62] Only a small percentage (~1%–3%) of thymocytes actually survive the processes of positive and negative selection and become mature thymocytes that have a relatively high level of TCR expression and express either $CD4^+$ or $CD8^+$ markers, but not both. In general, cells that are positively selected by an interaction with class II MHC molecules mature into the CD4 population, whereas cells that are positively selected on class I MHC molecules become the CD8 population.[63] Mature thymocytes subsequently migrate to peripheral lymphoid tissues, where they maintain these surface characteristics.

T-Cell Tolerance: The Prevention of Self-Reactivity

There is reason to believe that tolerance at the T-cell level is critical for the prevention of autoimmunity. Clonal deletion of self-reactive T cells in the thymus is discussed in the section on "T-Cell Development and Selection of the T-Cell Repertoire." This may be the major process for eliminating T cells that are reactive to non–organ-specific cellular proteins and to circulating

proteins, because these self-antigens are likely to be in the thymus during T-cell development. Some organ-sequestered antigens (e.g., certain uveal tract, brain, and endocrine organ antigens) are also expressed in the thymus.[61,62] However, studies have clearly shown that T cells to various self-antigens, including many organ-sequestered and posttranslationally modified antigens, are not completely deleted in the thymus. Therefore, self-tolerance must also involve the prevention of activation of these autoreactive T cells after they migrate from the thymus to the peripheral lymphoid tissues.[64,65]

Studies have shown that T cells with self-reactive TCRs are present in the peripheral lymphoid organs and the circulation of healthy individuals, but they are not sufficient for the development of autoimmune disease. Different peripheral mechanisms appear to help prevent autoimmune responses from occurring. One process appears to prevent the self-antigen from being effectively presented to a self-reactive T cell, which maintains that T cell in an ignorant state. For example, resting T cells with self-reactive potential may not be able to traffic to the tissue that expresses the antigen, or the antigen may not be presented by effective antigen-presenting cells. Some studies have suggested that inappropriate expression of class II antigens in a tissue can lead to autoimmunity, perhaps by circumventing this protective mechanism. T-cell activation triggered by a separate process (e.g., an infectious agent) may also bypass this protective mechanism by allowing cells with self-reactive potential to inappropriately traffic to tissues. T cells that do recognize antigen without effective antigen-presenting cells and co-stimulation may also be functionally deactivated (or anergized)[66] and prevented from any subsequent stimulation by that self-antigen. These cells continue to be present in the peripheral T-cell repertoire, but their prior contact with self-antigen prevents any subsequent response. Many investigators have worked on defining the intracellular mechanisms that lead to T-cell anergy, and current evidence indicates that anergic T cells activate some but not other signaling pathways after TCR engagement.[66] There is also evidence that the encounter of self-reactive T cells with antigen, but without effective presentation, sometimes leads to death of the autoreactive T cell rather than just anergy.

A final mechanism to prevent activation of self-reactive T cells involves regulatory (suppressor) T cells. In experimental animal models, there is evidence that $CD4^+$, $CD8^+$, and γδ T cells may be involved in the down-regulation of certain immune responses, and their absence may be associated with pathologic autoimmune responses. At least two subsets of regulatory $CD4^+$ T cell have been described that can inhibit cell-mediated immune responses and autoimmune pathologies: naturally occurring cells with suppressive activity and those induced by stimulation.[67,68] The naturally occurring regulatory $CD4^+$ T cells are characterized by constitutive CD25 expression and constitute 5% to 10% of the circulating $CD4^+$ population.[67–70] In murine model, depletion of these $CD4^+CD25^+$ T cells results in the spontaneous onset of multiorgan autoimmunity. These cells mediate their suppressive effects in a contact-dependent, antigen-independent manner in the absence of IL-10 or transforming growth factor-β (TGF-β). A novel member of the forkhead box/winged-helix family of transcription regulators, designated Foxp3, has been identified as a specific molecular marker for this type of regulatory T cell, and its expression is essential for programming both thymic development and function of these T cells.[67,71] In sarcoidosis, Foxp3-expressing regulatory T cells accumulate at the periphery of the granuloma in subjects with active disease.[72] However, despite suppressing mitogen-induced T cell proliferation, the regulatory T cells in lung could not completely suppress TNF-α and IFN-γ secretion, suggesting that the activity of this regulatory T-cell subset was incapable of controlling granulomatous inflammation. The other type of regulatory $CD4^+$ T cell is activation-induced, and these cells lack CD25 expression and are negative for Foxp3.[67] Much of the suppression from this group of regulatory cells can at least in part be attributable to cytokines such as TGF-β, because TGF-β is capable of suppressing both type 1 (Th1) and type 2 (Th2) T helper cell responses. It is relevant to note that mice made deficient in TGF-β by gene knockout techniques show evidence of progressive inflammation and autoimmunity involving multiple organs.[73] In some cases, regulatory $CD4^+$ T cells appear to release cytokines, such as IL-10 or even IL-4, that modulate the development and further activation of Th1-type cells involved in a cell-mediated response.[68,74,75]

GENERATION OF THE IMMUNE RESPONSE

T-Cell Activation and the Need for Co-stimulatory Molecules

Most immune responses depend on the activation of T cells, and normally, immune responses to foreign antigens are carefully orchestrated by a reciprocal communication between antigen-specific T cells and antigen-presenting cells. To be activated, naive T cells must receive several signals. One signal is antigen specific and is provided by engagement of the TCR. Additional signals are provided by co-stimulatory molecules and their interactions (Fig. 14-14). Resting antigen-presenting cells, such as resting B cells, frequently do not express significant levels of co-stimulatory molecules, and their interaction with T cells does not lead to T-cell activation. Furthermore, to be immunogenic, the antigen may need to be presented by antigen-presenting cells activated in an inflammatory context, such as during infection. Two of the most important co-stimulatory systems involve the interaction of CD28 with B7-1 (CD80) and B7-2 (CD86) and the interaction of CD40 ligand with CD40.[76] These two systems of interacting molecules also affect each other.

CD28 is constitutively expressed on $CD4^+$ T cells. Early in the immune response, B7-1 and B7-2 are up-regulated on the antigen-presenting cells. Binding of CD28 to B7 co-stimulates T-cell activation, leading to increased T-cell production of IL-2 and other cytokines,

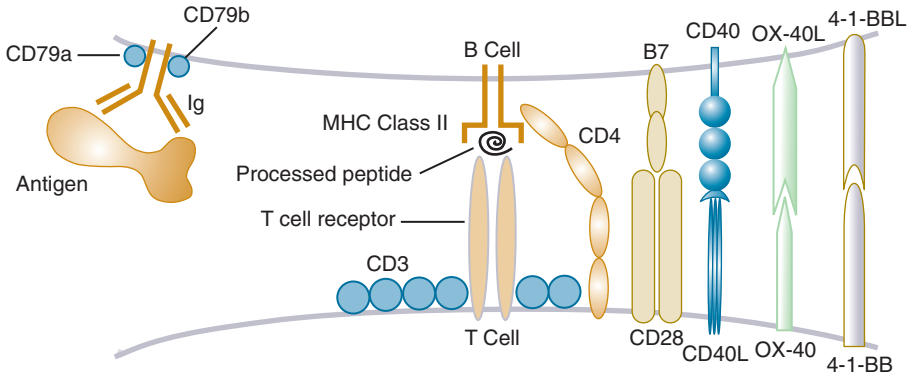

FIGURE 14-14 ■ T helper cell–B-cell interactions important for T-cell–dependent antibody production. Antigen cross-links membrane immunoglobulin (Ig) on the B cell (the BCR), which provides signal 1 for the B cell. CD79a (Ig-α) and CD79b (Ig-β) are Ig-accessory molecules necessary for transmitting the signal intracellularly. The antigen is internalized into an intracellular compartment in the B cell, processed to peptides, and combined with class II molecules for expression and presentation to the T helper cell. T-cell receptor (TCR) binding to the peptide/MHC provides signal 1 for the T cell. The CD3 complex and ζ chains allow for the TCR signal to be transmitted intracellularly. Activation of the T cell results in expression of CD40 ligand (CD40L), OX-40, and 4-1-BB. Interaction with CD40 provides the most important second signal to the B cell and is involved in T-cell activation. In addition, B7-1 (CD80) and B7-2 (CD86) are up-regulated on the B cell. Interaction with CD28 provides an important co-stimulatory signal to the T cell. This figure does not show the release of cytokines from the T helper cell that are necessary for full activation and differentiation of the B cell. In addition, this figure does not show other cellular interactions mediated by adhesion molecules. For example, the leukocyte function antigen (LFA)-1 integrin (CD11a, CD18) on the T cell interacts with intercellular adhesion molecule-1 (CD54) on the B cell. This interaction appears to be enhanced once the TCR and BCR have been engaged. CD2 on the T cell also interacts with LFA-3 on the B cell, which provides additional cell-cell adhesion.

increased cytokine receptor expression, increased cell survival, and increased T-cell proliferation.[77–79] Occupation of the CD28 receptor alone, without TCR engagement, appears to have little effect on T cells, and therefore, the signaling through CD28 is clearly a co-stimulatory event. The intracellular signaling events that occur after CD28 co-stimulation may overcome certain negative signals generated when the TCR is activated alone.[76,80,81]

Presentation in an inflammatory setting also leads to up-regulation of CD40 ligand (CD154) on the $CD4^+$ T cell.[82] CD40 ligand interacts with its counter-receptor, CD40, on B cells and other antigen-presenting cells, also inducing up-regulation of B7-1 and B7-2 as well as certain adhesion molecules and cytokine production by the presenting cell.[83] The interaction of CD40 ligand with CD40 is clearly bidirectional in that it provides signals important for T-cell and B-cell activation. CD40L is a member of the TNF receptor family, and a variety of other TNF receptor family members, such as CD134 (OX-40), CD137 (4-1BB), and CD27, have also been shown to possess co-stimulatory function following T-cell activation.[76,84] In chronic beryllium disease, CD137 has recently been shown to be the critical costimulatory molecule for the induction of T-cell proliferation and prevention of activation-induced cell death in effector $CD4^+$ T cells in lung.[85]

Other molecular interactions, especially involving adhesion molecules, have also been implicated in T-cell co-stimulation. For example, CD2 is expressed on T cells and binds to the lymphocyte function antigen (LFA)-3 molecule on antigen-presenting cells. CD2 also appears to be associated with the TCR complex and may be involved in signaling. CD2 is up-regulated on effector memory T cells, which has been used to allow selective targeting of this population by soluble LFA-3–Ig immunotherapy.[86] Other accessory molecules involved in adhesion of T cells to antigen-presenting cells, such as CD11a (LFA-1) and intercellular adhesion molecule (ICAM)-1, ICAM-2, and ICAM-3, are not specific for T-cell interactions but still may aid in achieving a threshold necessary for effective T-cell co-stimulation.

Following activation, T cells express cytotoxic T lymphocyte antigen-4 (CTLA-4) on their surface, which also binds B7-1 and B7-2 on the antigen-presenting cell and with stronger affinity than CD28.[87] This interaction appears to send a negative signal to down-regulate the T-cell response after its initial activation. CTLA-4 appears to be involved in the development of anergy and the generation of peripheral tolerance. CTLA-4–deficient mice develop a lymphoproliferative disorder and die early, and alterations in the gene encoding CTLA-4 have been associated with autoimmune endocrine diseases, further emphasizing the role of CTLA-4 in the control of lymphocyte homeostasis.[88,89] Programmed cell death 1 (PD-1) is another activation-induced inhibitory receptor that is expressed by T cells and binds B7 family members.[90] Similar to CTLA-4, PD-1 receptor engagement results in down-regulation of the immune response. Deficiencies of this gene have been associated with autoimmune diseases in animals and may be a possible gene contribution to human lupus.[91,92] In addition to these negative signals, down-regulation of the T-cell response may be further ensured by decreases in surface expression of CD40 ligand, OX-40, and 4-1BB after T-cell activation.[79,84]

As discussed earlier in the context of self-tolerance, engagement of the TCR on a naive T cell in the absence of co-stimulation can result in different outcomes.[76] In some situations, the outcome is a failure to stimulate,

and the T cell is oblivious to this encounter. At other times, recognition can induce death (apoptosis) of the responding T cells or anergy, in which case the T cells are unable to respond to a subsequent encounter with the same antigen (tolerance). Memory T cells appear to be less dependent on co-stimulatory molecules. However, antagonists that interrupt co-stimulatory interactions have been shown to have profound effects even later in the course of an established immune response. Blockers of the CD28-B7 interaction (with CTLA4-Ig, anti-B7, or anti-CD28 monoclonal antibodies) or of the CD40 ligand–CD40 interaction (with anti-CD40 ligand monoclonal antibodies), separately and together, are being investigated as therapies to treat autoimmune diseases and alloreactive responses after transplantation.[93–96] However, the recent development of cytokine storm in six healthy volunteers receiving the anti-CD28 monoclonal antibody TGN1412 as part of a phase 1 study demonstrates the potential risk of immunotherapy.[97]

Subsets of T Helper Cells

Although more sharply defined in mice than in humans, it is clear that T cells after activation may evolve into three major subsets of T helper cells, distinguished by the cytokines that they produce (Fig. 14-15).[57,74,75] Th1 cells mainly synthesize IL-2, IFN-γ and TNF-α, as well as other inflammatory cytokines, such as lymphotoxin and TNF. Th2 cells primarily are distinguished by their secretion of IL-4, IL-5, and IL-13. Th17 cells represent a distinct lineage of T cells from either Th1 or Th2 cells and express IL-17A, IL-17F, and IL-22.[98,99,99a,99b] These major types of T helper cells appear to serve very different functions. Th1 cells primarily enhance cell-mediated immune responses, such as delayed-type hypersensitivity reactions, which frequently involve activation of macrophages and effector T cells. Th2 cells mainly provide help for B cells by promoting class switching and enhancing the production of certain IgG isotypes and production of IgE. The ability to mediate an effective immune response against certain intracellular pathogens and the pathogenesis of certain diseases appears to be strongly influenced by the type of T helper cells involved. For example, in leishmaniasis and leprosy, the development of a response polarized toward the Th1 pathway is important for successful immune defense. The development of an early Th2 response may result in the inability to clear the offending organism. Inappropriately developed and activated Th1 cells have been implicated in the pathogenesis of certain autoimmune diseases, such as type 1 diabetes, multiple sclerosis, and rheumatoid arthritis. Th2 cells appear to be important for certain

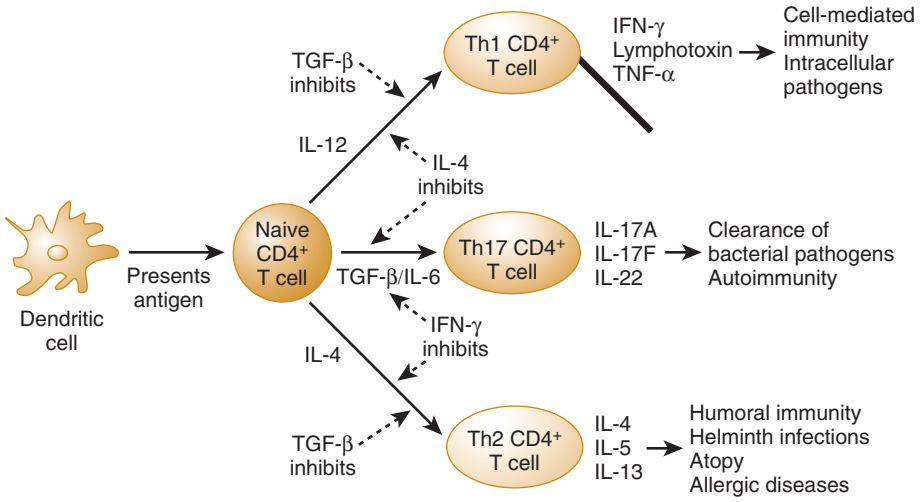

FIGURE 14-15 ■ Regulation of T helper cell activation and responses. Naive CD4⁺ T cells can develop into type 1T helper (Th1) cells if they are activated in the presence of interleukin (IL)-12, produced mostly by macrophages and other non–T cells. Interferon-γ (IFN-γ), increased by IFN-γ inducing factor (IL-18), also enhances the development toward a Th1 response. IFN-γ appears to increase the production of IL-12 and also the expression of receptors for IL-12. The generation of a Th1 response leads to the production of IL-2, IFN-γ, lymphotoxin (TNF-β), and TNF-α. These inflammatory cytokines are important for a successful immune response to intracellular pathogens. Inappropriate Th1 responses have also been implicated in organ-specific autoimmunity such as occurs in type 1 diabetes, multiple sclerosis, and rheumatoid arthritis. The early presence of IL-4 in the activation of a helper cell prevents Th1 responses and enhances the development of a type 2T helper cell (Th2) response. The source of the early IL-4 is not clear, but it may come from Th2 cells already present, NK1⁺ T cells, or non–T cells, such as mast cells and eosinophils. The Th2 response results in production of IL-4, IL-5, IL-10, and IL-13 and enhances humoral immunity. Although the Th2 cells are critical for the immune response to helminths, in the developed world, Th2 cells are probably most singled out for their important role in allergic disease and asthma. IL-4 and IFN-γ inhibit the development of a type 17 T helper cell (Th17) response that promotes bacterial clearance and may play a role in the development of autoimmunity. IL-6 and TGF-β promote the development of Th17 cells while IL-23 expressed by macrophages augments expression of Th17 cytokines by memory but not naive CD4⁺ T cells. Various regulatory CD4⁺ T cells have also been described. Regulatory CD4⁺ T cells secreting IL-10 have been shown to suppress Th1 responses. Regulatory T cells secreting transforming growth factor-β (TGF-β) have the capability to suppress both Th1 and Th2 responses. Evidence suggests that, in addition to the cytokines present at the time naive CD4⁺ T cells are stimulated, the type of dendritic cell may regulate the differentiation of CD4⁺ T cells into Th1, Th2, or Th17 subsets.

immune responses.[19] Eradication of helminths is Th2 dependent. However, Th2 cells also appear to be involved in disease by driving allergic responses, such as IgE production and eosinophil activation in asthma (see Chapter 38).[19] Th17 cells function at the interface between the innate and adaptive immune response, secreting cytokines that are important in bacterial clearance and in the pathogenesis of autoimmunity. Evidence suggests that in collagen-induced arthritis, T-cell–mediated colitis and experimental autoimmune encephalitis, Th17, as opposed to Th1, cytokines are critical for the induction and maintenance of inflammation.[100-102]

It has become clear that the Th1, Th2, and Th17 subsets develop from the same T-cell precursor, which is a naive $CD4^+$ T lymphocyte producing mainly IL-2 after stimulation with antigen. Considerable evidence indicates that the cytokine microenvironment is the primary determining factor for Th1, Th2, or Th17 differentiation (see Fig. 14-15).[57,74,75,98,99] IL-12 and IFN-γ have been shown to be most important in directing the development of Th1 cells that then go on to produce IFN-γ and TNF-α. IL-12 is produced by antigen-presenting cells (e.g., macrophages and dendritic cells) in response to Toll-like receptor stimulation by pathogens. IL-12 drives Th1 differentiation through signal transducer and activator of transcription 4 (STAT-4) and the activation of a unique Th1 transcription factor known as T-box expressed in T cells (T-bet).[103,104] Microbial products frequently induce macrophages and NK cells to release IFN-γ, which is involved in driving development of Th1 cells from their naive precursors. IFN-γ up-regulates a component of the IL-12 receptor on naive and differentiating T cells.[105] However, some organisms, such as the measles virus, have the ability to down-regulate IL-12 production by macrophages and therefore possibly evade destruction by cell-mediated immune responses. Early production of IFN-γ by Th1 cells and NK cells has been related to the production of IFN-γ–inducing factor (IL-18), and this cytokine may synergize with IL-12 for maximal early production of IFN-γ and Th1 development.

In a similar but opposite manner, the presence of IL-4 early in the immune response induces Th2 cell development from naive precursors through STAT-6, which leads to activation of the transcription factor GATA-3 and up-regulation of IL-4 and IL-5.[104,106] The effects of IL-4 in inducing Th2 development appear to be dominant over Th1- and Th17-polarizing cytokines.[74,75,107] Thus, if IL-4 levels exceed a threshold, Th2 development ensues, which leads to additional IL-4 production. Th2 cells do not respond to IL-12, which may be related to the ability of IL-4 to down-regulate expression of a component of the IL-12 receptor. The source of early IL-4 may include naive or differentiated $CD4^+$ T cells or both; the $NK1^+$ T-cell subset, which may be $CD4^+$ or double-negative; and various non–T-cell sources, such as mast cells, basophils, and eosinophils.[74,75,104]

TGF-β and IL-6 are necessary for the differentiation of naive $CD4^+$ T cells into Th17 cells.[107-109a] The orphan nuclear receptor, RORγt, is the master transcription factor in the differentiation of Th17 cells.[110] Expression of RORγt is TGF-β– and IL-6–dependent and is both necessary and sufficient to induce Th17 development in most $CD4^+$ T cells.[98] Unlike t-bet and GATA-3, the ligand of RORγt remains unknown. In the absence of IL-6, IL-21, in combination with TGF-β, can induce Th17 cells using an IL-6–independent pathway. IL-21 is also highly expressed by Th17 cells, and IL-21 production creates a positive feedback loop to further amplify Th17 responses in vivo.[107] Despite the finding that IL-23 signaling is not required for Th17 commitment and early IL-17 secretion, IL-23 is also important in amplifying and/or stabilizing the Th17 phenotype.[98]

The cytokines produced by Th1, Th2, and Th17 subsets cross-regulate one another's development and function. For example, IFN-γ produced by Th1 cells inhibits the development of Th2 and Th17 cells as well as certain humoral responses.[74,75,104] In a similar manner, IL-4 produced by Th2 cells inhibits Th1 and Th17 development and activation as well as macrophage activation by Th1 cytokines. IL-4 and IL-10 have the ability to inhibit both dendritic cell and macrophage IL-12 production. In addition, it is possible that the transcription factors GATA-3 and T-bet antagonize the development of the opposite T-cell subset by directly opposing each other's expression.[104,106] TGF-β also inhibits the development of Th1 and Th2 phenotypes.[104]

Following antigen exposure, naive T cells become activated, proliferate, and migrate to sites of inflammation. While the majority of antigen-primed cells die, a population of memory T cells develops, which allows for a more rapid and effective secondary immune response upon reexposure to antigen.[111,112] There appear to be at least two subsets of memory T cells, possessing different functional and migratory capabilities compared with naive lymphocytes. The effector memory T cell represents a terminally differentiated cell that immediately produces cytokine following antigen exposure and lacks the lymph node homing receptors L-selectin and CCR7. Conversely, central memory T cells express both L-selectin and CCR7, and these cells have the ability to differentiate into effector memory cells after restimulation. Thus, it is not surprising that the majority of $CD4^+$ T cells that localize to the lung express an effector memory phenotype.[113]

Signaling between cells of the immune system takes place both by direct cell-cell interactions involving surface molecules on interacting cells and by cytokines. In general, cytokines are designed to work at short distances and are frequently delivered in a directed fashion from the producing cell toward the cell receiving the communication. Cytokines are critically involved in both the generation and regulation of specific immune responses and the activation of nonspecific cells at sites of inflammation. The identification and detailed function of various inflammatory cytokines are described in Chapter 16.

$CD4^+$ T-Cell–B-Cell Collaboration and Regulation of Antibody Production

A central event in the immune response is the antigen-specific interaction between a T helper lymphocyte

and a B lymphocyte, which leads to their mutual activation. Although some antigens (usually nonproteins derived from bacteria) can activate B cells in a T-cell–independent fashion, the antibody response to most protein antigens requires that the relevant B cell must recognize antigen with its surface Ig receptor, and that it must also receive certain activation signals from a $CD4^+$ T helper cell. These signals include both secreted T-cell–derived lymphokines and those resulting from cell-cell contact. T-cell recognition of antigenic peptides bound to class II MHC molecules on the B-cell surface and co-stimulatory signals lead to T-cell activation and secretion of T helper lymphokines. Secretion is directed toward the site of contact with the B cell. Thus far, no combination of known T-cell–derived factors can fully replace contact with the T helper cell, indicating that the interaction of surface molecules provides additional signals to the B cell that promote its activation. Numerous interacting molecules have been identified that could transmit signals in the T-cell–B-cell interaction (see Fig. 14-14). This figure does not show the exchange of T-cell–derived helper cytokines and the binding to their corresponding receptors on the B cell.

Similar to the process of effective T-cell stimulation, which requires interaction of TCR with antigen/MHC and co-stimulatory signals, B cells also need more than one signal for activation to take place. The first signal is provided by antigen binding to surface Ig (BCR), and cross-linking of multiple receptors is usually required. The B cell then processes and presents the antigen via its class II MHC molecule to a cognate T helper cell that is specific for that peptide/MHC complex. A major second signal to the B cells occurs via CD40 on its surface through interaction with up-regulated CD40 ligand on the T helper cell. After receiving additional co-stimulatory signals from up-regulated B7-1 and B7-2 on the B cells, the activated T helper cell delivers cytokines in a focused manner to the antigen-specific B cell it is helping. Although many reciprocal receptor-ligand pairs are expressed on T cells and B cells, the signaling between CD40 ligand and CD40 has emerged as an obligatory and nonredundant interaction for functional T-cell–dependent B-cell activation to occur.[94] The signals transduced by CD40 are essential for the prevention of apoptosis of antigen-specific B cells in the germinal center and essential for B-cell proliferation and differentiation, isotype switching, and formation of memory B cells. Mutations in the CD40 ligand gene cause X-linked hyper-IgM syndrome, characterized by absent or low levels of IgG, IgA, and IgE (Ig isotypes that require T-cell help) but normal or elevated levels of IgM. Because T-cell activation also requires co-stimulatory signals through CD40 ligand, these individuals also demonstrate defects in T-cell–mediated immunity and defective T-cell activation.[114]

Interactions between LFA-1 and ICAM-1, as well as CD2 and LFA-3, are involved in T-cell–B-cell adhesion. Antigen receptor stimulation also increases the interaction between LFA-1 and ICAM-1 as well as the interaction between CD2 and LFA-3.

T-cell help is required for effective antibody responses, especially those involving specific high-affinity antibodies of the IgG, IgA, and IgE isotypes. However, as emphasized earlier, T-cell–B-cell signaling is clearly bidirectional. After resting T cells are activated, which frequently requires specialized antigen-presenting cells such as dendritic cells, antigen-specific B cells may be the most efficient presenters of determinants of a specific antigen.[115] The helper $CD4^+$ T cell recognizes a processed antigen presented on the B cell in the context of class II MHC antigens. The B cell focuses antigen for antigen-specific help by binding antigen through its Ig receptor, internalizing and processing the antigen, and presenting the derived peptides with class II MHC molecules (see Fig. 14-14). It is important to emphasize that the epitope on the native antigen recognized by the B cell is almost always different from the peptide epitope recognized by the helper T cell.

Subsequent to T-cell recognition, the T cell is activated, and help for B-cell proliferation and differentiation can be provided. T-cell help is critically dependent on the T-cell release of various cytokines, as described earlier. These cytokines have marked effects on B-cell maturation, especially in determining which isotypes will be produced by the B cell. The reciprocal surface molecular interactions, the directed nature of T cell cytokine release, and the controlled local action of these molecules result in "focused T-cell help" without generalized bystander activation of surrounding B cells.

Generation and Regulation of Cell-Mediated Immune Responses

Cell-mediated cytotoxicity is an essential defense against intracellular pathogens, including viruses and certain bacteria and parasites. Cytotoxic T cells are stimulated by presented endogenous antigens, most of them derived from intracellular pathogens and associated with class I MHC molecules. In contrast to most helper cells that express CD4, cytotoxic T cells are usually $CD4^-CD8^+$. The recognition of the antigen presented by class I MHC molecules triggers the T cell to express receptors for IL-2. Although some cytotoxic lymphocytes are able to produce their own IL-2, most depend on IL-2 produced by helper $CD4^+$ T cells of the Th1 type. The binding of IL-2 and possibly other cytokines leads to some proliferation and to the development of cytotoxic function. $CD4^+$ T helper cells (Th1 type) provide additional signals and cytokines for the generation of a maximal cytotoxic response.

Activated effector cells are capable of delivering a lethal message to a target cell, separating from their dying target, and going on to strike a new target. This creates a very efficient system of killing unwanted cells. Several mechanisms are involved in the actual killing process.[116–119] For example, cytotoxic T cells can directly signal their targets to undergo apoptosis through the interaction of Fas ligand, expressed on the surface of activated T cells, with Fas on the target cell. Stimulation of the Fas receptor results in recruitment of the caspase-8

through interaction with the adapter molecule, Fas-associated death domain protein (FADD).[116] Caspase-8 activation results in either direct caspase-3 activation or cleavage of BH3 interacting domain (BID) and translocation of BID and BCL-2 associated X protein (BAX) to the mitochondria. Once inserted into the mitochondrial membrane, BID and BAX induce the release of mitochondrial cytochrome c, which results in caspase-9 activation and ultimately activation of caspase-3. The cytotoxic T cell also produces substances such as lymphotoxin (TNF-β), trimers of which bind to receptors on the cellular targets and signal for apoptosis. During binding to the target cell, the cytotoxic $CD8^+$ T cells also release the contents of their granules, which include perforins and granule-associated serine esterases (granzymes), toward the adjacent membrane of the target cell. Released perforins assemble on the surface of the target cell and perforate the target cell plasma membrane, resulting in lysis and the entry of enzymes. The transmembrane channel created by the perforins resembles the membrane attack complex of the complement cascade. After entry into the target cell, activated granzymes released from the cytotoxic T cell activate proteins that mediate apoptosis as well as cause other types of cell damage.

SPECIFIC IMMUNE RESPONSES IN THE LUNG

Lymphocyte Populations and Trafficking in the Lung

The lung in healthy individuals usually harbors only a small number of lymphocytes.[120,121] The location of $CD4^+$ and $CD8^+$ αβ T cells can be arbitrarily separated into four compartments: bronchoalveolar space, bronchus-associated lymphoid tissue (BALT), lung interstitial tissues, and intravascular space. Although lymphocytes from these different positions may be involved in lung immune responses, there is no clear indication that these cells represent a resident lymphocyte population in the lung in humans. More likely, these lymphocytes belong to the recirculating lymphocyte pool. In contrast, γδ T cells have been localized to intraepithelial positions in the lung, and these cells may selectively reside in the lung.[28]

In a normal nonsmoking individual, lymphocytes account for approximately 10% to 15% of the bronchoalveolar cells obtained during bronchoalveolar lavage.[121] The number of bronchoalveolar lymphocytes can increase markedly in inflammatory diseases involving the alveoli and the interstitium, such as in sarcoidosis and hypersensitivity pneumonitis (see Chapters 59 and 66). Most bronchoalveolar lymphocytes are T cells, and essentially all of these cells express memory cell markers (e.g., CD45RO and low CD62L), indicating previous activation.[113] In disease, a significantly increased percentage of these T cells, compared with those in peripheral blood, also express markers of recent activation, such as HLA-DR, IL-2 receptor (CD25), and CD69.

BALT is a localized collection of lymphocytes in the subepithelial area of bronchi, analogous to gut-associated lymphoid tissue (e.g., Peyer's patches).[122] These lymphoid aggregates are separated from the airway lumen by a lymphoepithelium composed of flattened epithelial cells, which lack cilia. BALT also contains HEVs facilitating the recirculation of lymphocytes between blood and lymph. However, unlike gut-associated lymphoid tissues in the form of Peyer's patches, which are present in all mammals, BALT is only regularly present in some mammalian species. Indeed, it is usually absent in humans as long as there is no respiratory tract infection. Evidence suggests that BALT may appear in patients after chronic airway inflammation and chronic obstructive pulmonary disease.[123,124]

The interstitium of the normal lung contains few lymphoid cells, and most of these are not T cells. The majority of interstitial lymphocytes are NK cells, which constitute 10% to 15% of circulating lymphocytes. These cells do not express TCR or Ig but express markers characteristic of both T-cell and myelomonocytic lineages.[6] NK cells recognize and kill tumor cells and virus-infected cells in a nonspecific manner.[6] These cells also kill targets coated with antibodies via surface receptors for IgG (FcγRIII or CD16) in a process known as antibody-dependent cellular cytotoxicity. Furthermore, NK cells can also be an important source of cytokines (e.g., IFN-γ, TNF-α, and granulocyte-macrophage colony-stimulating factor [GM-CSF]) early in the immune response.

γδ T cells constitute only 0.5% to 10% of the peripheral blood lymphocyte population in humans.[28] However, they represent an enriched T-cell population in the pulmonary epithelium, intestinal epithelium, and skin. Unlike αβ T cells, epithelial γδ T cells do not recirculate and appear to represent resident pulmonary lymphocytes. The population of γδ T cells in the lung of normal adult C57BL/6 mice is approximately 2 to 5×10^4 cells, with the majority being either $V\gamma4^+$ or $V\gamma1^+$.[125] Importantly, the different γδ T cell subsets are thought to have different functional capabilities. For example, $V\gamma1^+$ γδ T cells enhance airway hyperresponsiveness while Vγ4 γδ T cells suppress this response in a murine model of asthma.[126] The pulmonary γδ T cells preferentially interact with $F4/80^+$ macrophages and MHC class II–expressing dendritic cells, suggesting that γδ T cells represent a primitive line of defense evolved to protect epithelial integrity and provide a possible bridge between innate immunity and acquired immune responses.

The distribution and trafficking of lymphocytes is governed by interactions between molecules on the lymphocyte surface and ligands present on vascular endothelial cells. The migration of lymphocytes from the bloodstream is not a random event, and this migration appears to be restricted to lymphoid tissue and areas of inflammation.[7] Naive T cells lack the ability to initiate an antigenic response until they are activated within a secondary lymphoid organ. Evidence indicates that their initial interaction with an antigen entering through the lung takes place in the surrounding lymphoid tissues and not in the lung directly. Naive and resting lymphocytes represent the major population that recirculates from blood to lymph via HEVs, with the initial attachment mediated by the homing receptor L-selectin (CD62L)

to peripheral lymph node addressin (PNAd) and glycosylation-dependent cell adhesion molecule-1 (GlyCAM-1) on the surface of endothelial cells.[7] This interaction results in lymphocyte tethering and rolling along the endothelial surface. Subsequent binding of chemokines (e.g., stromal cell–derived factor-1α, 6-C-kine, and macrophage inflammatory protein-3b) to G protein–coupled receptors on the lymphocyte surface leads to activation of integrin molecules (LFA-1).[7] After activation, LFA-1 binds to ICAM-1 on the vascular endothelium, resulting in firm adhesion.[7] This is followed by transendothelial migration of the lymphocyte into the lymphoid tissue. A second family of G protein–coupled receptors, known as sphingosine-1-phosphate receptor-1, is required for lymphocyte egress from the lymph node.[127] As stated earlier, BALT consists of diffuse lymphoid aggregates found in the bronchial mucosa of most mammals.[122] In contrast to HEVs in other secondary lymphoid organs, BALT HEVs express high levels of vascular cell adhesion molecule-1 (VCAM-1), which binds $\alpha_4\beta_1$ integrin on T cells. Thus, an adhesion cascade exists involving L-selectin/PNAd, $\alpha_4\beta_1$ integrin/VCAM-1, and LFA-1/ICAM-1, which targets specific lymphocyte populations to BALT and other bronchopulmonary tissues.[7,122]

Effector and memory T lymphocytes appear to have distinct pathways of lymphocyte recirculation compared with naive lymphocytes.[7] Effector T cells, especially after activation in the lymphoid tissues, travel to regions of inflammation where chemokines and other chemotactic molecules are generated by the underlying inflammatory process.[7] Expression of various adhesion molecules on the lymphocyte and binding to their appropriate molecular targets expressed on inflamed vascular endothelium allow cells to enter sites of inflammation.[7] The expression of ICAM-1, P-selectin, and VCAM-1 on the surface of inflamed vascular endothelium is involved in lymphocyte entry into areas of inflammation.[7] Tissue tropism is established by the expression of different combinations of adhesion molecules that allow a different subset of effector cells to home to different sites. For example, circulating memory lymphocytes specific for skin-associated antigens express the cutaneous lymphocyte antigen.[7] Conversely, memory for intestinal antigens has been localized to circulating lymphocytes expressing high levels of $\alpha_4\beta_7$ integrin.[7] Thus, memory T cells display selective homing to the tissue type where antigen encounter first occurred.

Antibody-Mediated Immune Responses in the Lung

Immune Response to Extracellular Pathogens

The humoral immune response is adapted for elimination of extracellular pathogens. An example of an antibody-mediated immune response is the response that occurs after exposure to *Streptococcus pneumoniae*. This bacterium frequently colonizes the nasopharynx and is the most common cause of community-acquired pneumonia.[128] Pneumococci gain access to the lower respiratory tract via aspiration. The upper airways are equipped with clearance mechanisms (e.g., mucociliary clearance and cough) that effectively eliminate most inhaled or aspirated bacteria from the airways (see Chapter 12). If the aspirated pneumococcus evades the upper airway defenses, the pathogen first encounters the mucosal humoral immune system. IgA provides the first line of defense against infectious agents, with IgG and IgM being less important in the bronchial secretions. The major functions of secretory IgA include the prevention of microbial adherence to the epithelial surface and the promotion of the agglutination of microorganisms. The combination of inhibition of adhesion and microbial agglutination favors the clearance of pneumococci via mechanical forces. Unlike IgG, IgA is unable to activate complement, and it is not an effective opsonin.

The first exposure of the host to the pneumococcus generates a primary humoral response. Bacteria in the lung are bound by antigen-presenting cells, which migrate to secondary lymphoid organs, where antigens are processed and presented with class II MHC molecules to $CD4^+$ T cells (Fig. 14-16). After TCR binding and effective co-stimulation enhanced by an inflammatory environment, activation of specific T cells occurs, and multiple T helper cytokines are elaborated. During this process, naive B cells in the lymph node bind unprocessed antigen via surface IgM and present peptide fragments to specific T helper cells via class II MHC molecules. T-cell–B-cell interactions in the germinal

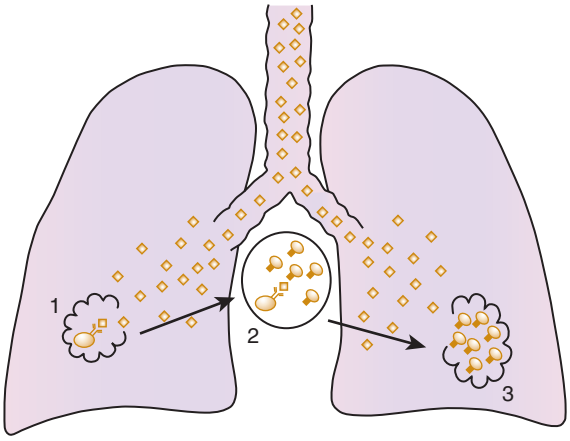

FIGURE 14-16 ■ Immune responses in the lung. Antigen (e.g., bacterial pathogen) enters the lung. Microbial products create an inflammatory environment. **1,** Antigen is taken up by nonspecific phagocytic cells and transported to regional lymph nodes. **2,** In the lymph nodes, a primary immune response is generated. Antigen-specific T cells are stimulated, and initial T helper cell–B-cell interactions and antibody production take place in the germinal centers. **3,** Antibodies, T helper cells, and effector cells circulate back to the lung for the immune response to target the pathogen. Trafficking of inflammatory cells is enhanced by the production of chemokines and other chemotactic factors and involves interactions of leukocytes with endothelial cells in the area of inflammation. In the process of the initial immune response, memory T cells and B cells are generated. This allows for a more effective secondary immune response to occur if the same pathogen is encountered at a later time.

centers lead to additional T-cell and full B-cell activation, characterized by clonal proliferation, isotype switching, and differentiation of B cells into secreting cells and memory cells. Subsequently, specific antibody, activated T cells, and perhaps some activated B cells circulate back to the lung to combat the pneumococcal infection.

In the area of infection, IgG1, IgG3, and IgM specific for intact pneumococcal antigens activate the complement system, resulting in some bacterial cell lysis. More important, antibody and complement act as opsonins, enhancing phagocytosis of encapsulated microorganisms. The release of mediators from activated T cells also enhances the antibacterial capacity of recruited nonspecific inflammatory cells in the lung. These events occur over a 4- to 7-day period and characterize the initial phase of a primary response. The time needed for peak response is approximately 7 to 10 days. The presence of memory B and T cells ensures that repeat exposure to *S. pneumoniae* results in a secondary immune response, which is characterized by a shorter lag phase and thus a more rapid response, a greater magnitude of antibody response, and a longer duration of response. Clinically, pneumococcal vaccination, which induces a primary humoral response, has decreased the rates of invasive pneumococcal disease in both children and adults.[129]

Immune Response to Autoantigens

Autoimmune disorders result when the normal mechanisms of immune self-tolerance fail. Essentially all autoimmune diseases, including antibody-mediated autoimmune diseases, appear to be dependent on the inappropriate activation of autoreactive $CD4^+$ T cells as well as on the autoreactive B cells responsible for the pathogenic autoantibodies. One example of an autoimmune disease involving the lung is Goodpasture's syndrome. This syndrome is characterized by pulmonary hemorrhage and glomerulonephritis, which are associated with elevated levels of IgG antibodies directed against basement membrane antigens. In various studies, pathologic damage has been shown to be directly dependent on the binding of these autoantibodies, which are primarily directed against the noncollagenous domain ($\alpha 3$ chain) of type IV collagen in basement membrane.[130-132] Immunofluorescent staining with anti–human IgG antibodies usually reveals a linear deposition of IgG in the glomerular and alveolar basement membranes. Despite the widespread distribution of type IV collagen in the body, disease expression is mostly limited to the lungs and kidneys. This limited disease expression suggests the possibility that other factors allow exposure of this autoantigen selectively in alveolar or glomerular basement membranes. In this regard, influenza A2 infection, hydrocarbon inhalation, and cigarette smoking have been associated with the initial episode of diffuse alveolar hemorrhage and exacerbation of disease in the setting of elevated levels of anti–basement membrane antibodies.[133] Much is now known regarding how autoantibodies cause damage in an autoimmune disease such as Goodpasture's syndrome. More recently, HLA associations and the B and T cell epitope have been identified.[134] HLA DRB1*1501 is strongly associated with the development of Goodpasture's disease whereas HLA DRB1*0701 and DRB1*0101 confer protection against development of this disease. In addition, the T-cell epitope has been mapped to the amino-terminal region of the $\alpha 3$ chain of type IV collagen.[135] As noted earlier, activation of both autoreactive $CD4^+$ T cells and autoreactive B cells appears to be necessary for a pathologic autoimmune response. These autoreactive $CD4^+$ T cells require CD28 co-stimulation, because blockade of this co-stimulatory molecule reduces anti–basement membrane antibody production and prevents the development of experimental autoimmune glomerulonephritis.[136]

Studies have identified an autoimmune etiology underlying the development of acquired pulmonary alveolar proteinosis.[137] This disorder is characterized by the accumulation of a periodic acid–Schiff staining, granular, eosinophilic material within the alveolar space (see Chapter 63). Based on the development of pulmonary alveolar proteinosis in mice rendered deficient in GM-CSF, a fundamental role of this factor in surfactant homeostasis has been discovered.[138] In addition, the presence of neutralizing IgG autoantibodies directed against GM-CSF have been identified in the bronchoalveolar lavage fluid and serum of all patients with acquired pulmonary alveolar proteinosis, but not in individuals with the congenital or secondary form of the disorder or in normal control subjects.[139] The detection of this IgG autoantibody is highly sensitive and specific and thus useful in the diagnosis of the acquired form of this disease. More recently, mutations in the ligand-binding α-chain of the GM-CSF receptor have been identified in patients with pulmonary alveolar proteinosis.[140]

Immune Response in Allergic Disease

Atopic asthma results when an immune response and IgE antibodies are directed against normally harmless proteins present in the environment (see Chapter 38). Numerous cell types, including mast cells, eosinophils, macrophages, and $CD4^+$ T lymphocytes, as well as the specific IgE-secreting B cells, are important in the development of allergy and asthma. The $CD4^+$ T cells, which accumulate in the lungs of asthmatics, display a Th2 phenotype,[141] and studies using murine asthma models have shown that allergic airway inflammation is dependent on Th2-type $CD4^+$ T cells. As discussed earlier, the development of a Th2 response is prompted by exposure of naive $CD4^+$ T cells to IL-4 at the beginning of an immune response.[74,75,104,106] In the presence of high expression of IL-4 and low IFN-γ, these Th2 $CD4^+$ T cells induce isotype switching in antigen-specific B cells to IgE.[142] The elevated levels of IgE in the asthmatic are essential for the immediate hypersensitivity response. The presence of IL-4 and IL-5 and the production of various chemokines during T-cell activation also enhance accumulation of eosinophils and basophils in the airways. Studies in murine models of allergic asthma have suggested an important role for another Th2 cytokine, IL-13, which was capable of inducing the pathologic features of asthma independent of IgE and eosinophils.[143] Related

to the Th2 dependence of asthma in humans, susceptibility to disease has been linked to loci on chromosome 5q, which contains the genes for IL-4 and IL-13.[144] Studies also suggest that genetically determined abnormalities in antigen-presenting cells may also play a role in the development of allergic reactions. In atopic individuals, antigen-presenting cells were shown to underproduce IL-12 or overproduce prostaglandin E_2, which favors a Th2 response.[145]

Cell-Mediated Inflammatory Responses in the Lung

Cell-mediated immune responses can be divided into two major categories: (1) $CD4^+$ T cells that mediate delayed-type hypersensitivity reactions and (2) $CD4^+$ T cells that help effector T cells with cytotoxic function.

Granulomatous Lung Disease

Granulomas are characteristic of infections that live at least partly intracellularly, such as *Mycobacterium tuberculosis*, *Mycobacterium leprae*, and organisms that are large and persistent. There is considerable evidence to suggest that $CD4^+$ T cells and the elaboration of Th1 cytokines are required for maximal granulomatous inflammation in the response to these infections. The triggering event in the development of noninfectious granulomatous lung disease is the deposition of antigen in the lung parenchyma. In the case of chronic beryllium disease[85,146] and hypersensitivity pneumonitis (see Chapter 66), the antigenic stimulus is known. In sarcoidosis, the inciting agent is unknown, although the immunopathogenic events are believed to be the same (see Chapter 59).[147] Thus, the unknown antigen is likely to be engulfed by antigen-presenting cells (i.e., dendritic cells and macrophages) in the lung parenchyma and presented to naive $CD4^+$ T cells in the peripheral lymphoid organs. Exposure of these activated naive $CD4^+$ T cells to IL-12 released by macrophages, and in the absence of IL-4, directs the T cell toward a Th1 response.[74,75,104,106] The development of a Th1 response is also influenced by early release of IFN-γ through the up-regulation of IL-12 production by macrophages and through the up-regulation of receptors for this cytokine on Th1 cells.

Production of chemokines and other chemotactic factors at the site of inflammation in the lung directs migration of activated effector $CD4^+$ T cells to the lung. The Th1 cytokines and other mediators produced by these T cells are responsible for the recruitment and activation of macrophages and other nonspecific inflammatory cells. The accumulation of inflammatory cells within the alveolus (alveolitis) appears to be the initial lesion characterizing sarcoidosis and other granulomatous lung diseases. In sarcoidosis, the accumulated $CD4^+$ T cells (obtained at bronchoalveolar lavage) include expanded subsets, identified by expression of particular TCR Vβ and Vα regions. Within these subsets are expansions of T-cell clones, each with a unique TCR β chain and α chain sequence. The presence of these oligoclonal expansions indicates a T-cell response to conventional peptide antigens, and the presence of different T-cell clones with related TCRs indicates a response to the same antigen. Both the HLA haplotype (the presenting class II MHC molecule) in an individual and stimulating antigen(s) will determine the TCRs utilized in these T-cell responses. In chronic beryllium disease, particular HLA-DP alleles (e.g., *HLA-DPB1* alleles expressing a glutamic acid residue at the 69th position of the β-chain) appear to be most important in the presentation of antigen to beryllium-specific T cells,[148] and this likely explains the increased disease susceptibility in individuals with the same HLA-DP alleles.[149] $CD4^+$ T-cell clones expressing similar TCRs (with the same V regions and highly similar CDR3 regions) have been noted to be expanded in the lungs of different individuals with chronic beryllium disease, reflecting similarities in presenting MHC class II molecules and the same stimulating antigen (beryllium).[146] In sarcoidosis, an association between the TCR usage of Vα2.3 and HLA-DR17 (DR3) expression has been reported.[150] It is important to emphasize that the pathologic T-cell responses in these diseases are compartmentalized to the lung, because the same T-cell clones are either absent or rare in the peripheral blood.[113]

The major effector cells of inflammation in chronic beryllium disease, sarcoidosis, and other granulomatous diseases appear to be macrophages primarily derived from circulating monocytes during the process of inflammation. Activated alveolar macrophages express MHC class II molecules and may contribute to antigen presentation. The formation of noncaseating granulomas occurs by coalescence of activated macrophages, which can also fuse to form multinucleated giant cells. $CD4^+$ T cells predominate in the center of the noncaseating granuloma, with $CD8^+$ T cells located at the periphery of the granulomatous response.

Cytotoxic T-Cell Reactions in the Lung

Cytotoxic T lymphocytes (CTLs) are critical in the recognition and elimination of virus-infected cells and tumor cells as well as in allograft rejection. These cells predominantly express CD8, although $CD4^+$ CTLs and NK cells may also be involved in cytotoxic T-cell responses. $CD4^+$ T helper cells are almost always required for full expression of a cytotoxic T-cell reaction. CTL responses have been detected in humans after infection with numerous viruses, including respiratory syncytial virus, parainfluenza, and influenzas A and B. Once a $CD8^+$ CTL recognizes a respiratory syncytial virus–infected cell, there are at least three distinct mechanisms by which the CTL can induce cell death.[116–119] Thus, as discussed earlier, the cytotoxic T cell can secrete cytotoxic cytokines such as TNF-α and IFN-γ in the vicinity of the target cell. In addition, direct contact between the activated CTL can be followed by the release of granule enzymes, including perforins and granzymes, which cause pore formation in the membrane of the target cell and enzyme-mediated apoptosis. The third mechanism

of CTL-induced cell death involves the interaction of Fas ligand on the surface of the CTL with Fas on the target cell. $CD4^+$ CTLs do not have cytotoxic granules and primarily utilize Fas-mediated apoptosis as their mechanism of cytotoxicity.

NK cells have a role complementary to that of CTLs in combating virus-infected cells or tumor cells.[6] NK cells constitute 5% to 10% of peripheral blood lymphocytes and appear to form the first line of defense against viral infection, providing nonspecific cytotoxic activity. These cells differ from CTLs in their lack of TCRs, and they recognize their targets in a non–MHC-restricted fashion. However, the mechanism of NK cell killing appears to be similar to that employed by $CD8^+$ CTLs. In addition, NK cells have receptors for IgG (FcγRIII; CD16) and can bind to the Fc region of antibody attached to the surface of a target cell and mediate antibody-dependent cellular cytotoxicity.

KEY POINTS

- The health of the lung and the individual depends on a functional immune system to protect against microbial invasion.
- Pathogens are targeted by both specific humoral immune responses and a variety of cell-mediated responses that result in the accumulation and activation of leukocytes.
- Although effector leukocytes may be both antigen specific and antigen nonspecific, essentially all of these immune responses are dependent on specific T (helper) cells for full expression and maximal effect.
- The vast array of pathogens and their large number of strategies to subvert the immune system is combated by a system of defense with remarkable specificity and yet enormous diversity. These capabilities are achieved through unique molecular mechanisms of BCR and TCR repertoire formation, which are fundamental for understanding the immune response.
- The generation and regulation of specific immune responses are also dependent on a complex series of molecular and cellular interactions.
- In occasional individuals, the defense system may break down, and in others, aberrant immune responses appear to contribute to various pathologies relevant to the lung and respiratory tract. With additional knowledge regarding the structure and function of the immune system, it is likely that new insight into these diseases will occur and that new therapeutic approaches will be conceived.

References

1. Kondo M, Wagers AJ, Manz MG, et al: Biology of hematopoietic stem cells and progenitors: Implications for clinical application. Annu Rev Immunol 21:759–806, 2003.
2. Marrack P, Kappler J: The T cell receptor. Science 238:1073–1078, 1987.
3. Davis MM, Boniface JJ, Reich Z, et al: Ligand recognition by alpha beta T cell receptors. Annu Rev Immunol 16:523–544, 1998.
4. Garcia KC, Teyton L, Wilson IA: Structural basis of T cell recognition. Annu Rev Immunol 17:369–397, 1999.
5. Gauld SB, Dal Porto JM, Cambier JC: B cell antigen receptor signaling: Roles in cell development and disease. Science 296:1641–1642, 2002.
6. Yokoyama WM, Kim S, French AR: Dynamic life of natural killer cells. Annu Rev Immunol 22:405–429, 2004.
7. Sigmundsdottir H, Butcher EC: Environmental cues, dendritic cells, and the programming of tissue-selective lymphocyte trafficking. Nat Immunol 9:981–987, 2008.
8. Alt FW, Blackwell TK, Yancopoulos GD: Development of the primary antibody repertoire. Science 238:1079–1087, 1987.
9. Torres RM, Imboden J, Schroeder HW Jr: Antigen receptor genes, gene products and co-receptors. *In* Rich RR, Fleisher TA, Shearer WT, et al (eds): Clinical Immunology: Principles and Practice. London: Mosby, 2008, pp 53–78.
10. Odegard VH, Schatz DG: Targeting of somatic hypermutation. Nat Rev Immunol 6:573–583, 2006.
11. Edry E, Melamed D: Receptor editing in positive and negative selection of B lymphopoiesis. J Immunol 173:4265–4271, 2004.
12. Nemazee D: Receptor editing in lymphocyte development and central tolerance. Nat Rev Immunol 6:724–740, 2006.
13. Stavnezer J, Guikema JE, Schrader CE: Mechanism and regulation of class switch recombination. Annu Rev Immunol 26:261–292, 2004.
14. Clark MR: IgG effector mechanisms. Chem Immunol 65:88–110, 1997.
15. Ravetch JV, Bolland S: IgG Fc receptors. Annu Rev Immunol 19:275–290, 2001.
16. Ravetch JV, Clynes RA: Divergent roles for Fc receptors and complement in vivo. Annu Rev Immunol 16:421–432, 1998.
17. Takai T: Roles of Fc receptors in autoimmunity. Nat Rev Immunol 2:580–592, 2002.
18. Kawakami T, Galli SJ: Regulation of mast-cell and basophil function and survival by IgE. Nat Rev Immunol 2:773–786, 2002.
19. Gould HJ, Sutton BJ: IgE in allergy and asthma today. Nat Rev Immunol 8:205–217, 2008.
20. Nagasawa T: Microenvironemtal niches in the bone marrow required for B-cell development. Nat Rev Immunol 6:107–116, 2006.
21. Brandt VL, Roth DB: A recombinase diversified: New functions of the RAG proteins. Curr Opin Immunol 14:224–229, 2002.
22. Jung D, Giallourakis C, Mostoslavsky R, Alt FW: Mechanism and control of V(D)J recombination at the immunoglobulin heavy chain locus. Annu Rev Immunol 24:541–570, 2006.
23. Rolink AG, Schaniel C, Busslinger M, et al: Fidelity and infidelity in commitment to B-lymphocyte lineage development. Immunol Rev 175:104–111, 2000.

24. Miller JP, Izon D, DeMuth W, et al: The earliest step in B lineage differentiation from common lymphoid progenitors is critically dependent upon interleukin 7. J Exp Med 196:705–711, 2002.
25. Klein U, Dalla-Favera R: Germinal centers: Role in B-cell physiology and malignancy. Nat Rev Immunol 8:22–33, 2008.
26. Wardemann H, Nussenzweig MC: B-cell self-tolerance in humans. Adv Immunol 95:83–110, 2007.
27. Adams EJ, Garcia KC: Structure of a γδ T cell receptor in complex with the nonclassical MHC T22. Science 308:227–231, 2005.
28. Born WK, Reardon CL, O'Brien RL: The function of γδ T cells in innate immunity. Curr Opin Immunol 18:31–38, 2006.
29. Sebzda E, Mariathasan S, Ohteki T, et al: Selection of the T cell repertoire. Annu Rev Immunol 17:829–874, 1999.
30. Garcia KC, Degano M, Stanfield RL, et al: An αβ T cell receptor structure at 2.5A and its orientation in the TCR-MHC complex. Science 274:209–219, 1996.
31. Garboczi DN, Ghosh P, Utz U, et al: Structure of the complex between human T-cell receptor, viral peptide and HLA-A2. Nature 384:134–141, 1996.
32. Winchester RJ: The major histocompatibility complex. *In* Rich RR, Fleisher TA, Shearer WT, et al (eds): Clinical Immunology: Principles and Practice. London: Mosby, 2008, pp 79–90.
33. Saper MA, Bjorkman PJ, Wiley DC: Refined structure of the human histocompatibility antigen HLA-A2 at 2.6A resolution. J Mol Biol 219:277–319, 1991.
34. Fremont DH, Hendrickson WA, Marrack P, et al: Structures of an MHC class II molecule with covalently bound single peptides. Science 272:1001–1004, 1996.
35. Dessen A, Lawrence CM, Cupo S, et al: X-ray crystal structure of HLA-DR4 (DRA*0101, DRB1*0401) complexed with a peptide from human collagen II. Immunity 7:473–481, 1997.
36. Jardetzky TS, Brown JH, Gorga JC, et al: Crystallographic analysis of endogenous peptides associated with HLA-DR1 suggests a common, polyproline II-like conformation for bound peptides. Proc Natl Acad Sci U S A 93:734–738, 1996.
37. Aguado B, Bahram S, Beck S, et al: Complete sequence and gene map of a human major histocompatibility complex. Nature 401:921–923, 1999.
38. Rhodes DA, Trowsdale J: Genetics and molecular genetics of the MHC. Rev Immunogenet 1:21–31, 1999.
39. Marsh SGE, Albert ED, Bodmer WF, et al: Nomenclature for factors of the HLA system. Tissue Antigens 60:407–464, 2002.
40. Graham RR, Ortmann WA, Langefeld CD, et al: Visualizing human leukocyte antigen class II risk haplotypes in human systemic lupus erythematosus. Am J Hum Genet 71:543–553, 2002.
41. Rodgers JR, Rich RR: Antigens and antigen processing. *In* Rich RR, Fleisher TA, Shearer WT, et al (eds): Clinical Immunology: Principles and Practice. London: Mosby, 2008, pp 91–102.
42. Cresswell P: Antigen processing and presentation. Immunol Rev 207:5–7, 2005.
43. Cresswell P, Ackerman AL, Giodini A, et al: Mechanisms of MHC class I-restricted processing and cross-presentation. Immunol Rev 207:145–157, 2005.
44. Hammer GE, Kanaseki T, Shastri N: The final touches make perfect the peptide-MHC class I repertoire. Immunity 26:397–406, 2007.
45. Purcell AW, Elliott T: Molecular machinations of the MHC I-peptide loading complex. Curr Opin Immunol 20:75–81, 2008.
46. van Endert P, Villadangos JA: Antigen processing and presentation. Curr Opin Immunol 19:63–65, 2007.
47. Vyas JM, Van der Veen AG, Ploegh HL: The knowns and unknowns of antigen processing and presentation. Nat Rev Immunol 8:607–618, 2008.
48. Li P, Gregg JL, Wang N, et al: Compartmentalization of class II antigen presentation: Contribution of cytoplasmic and endosomal processing. Immunol Rev 207:206–217, 2005.
49. Jensen PE: Recent advances in antigen processing and presentation. Nat Immunol 8:1041–1048, 2007.
50. Fraser JD, Proft T: The bacterial superantigens and superantigen-like proteins. Immunol Rev 225:226–243, 2008.
51. Simonian PL, Roark CL, Diaz del Valle F, et al: Regulatory role of γδ T cells in the recruitment of $CD4^+$ and $CD8^+$ T cells to lung and subsequent pulmonary fibrosis. J Immunol 177:4436–4443, 2006.
52. Smith-Gavin JE, Koretzky GA, Jordan MS: T cell activation. Annu Rev Immunol 27:591–619, 2009.
53. DeFranco AL: The complexity of signaling pathways activated by the BCR. Curr Opin Immunol 9:296–308, 1997.
54. Garcia KC, Scott CA, Brunmark A, et al: CD8 enhances formation of stable T-cell receptor/MHC class I molecule complexes. Nature 384:577–581, 1996.
55. Garcia KC: Molecular interaction between extracellular components of the T-cell receptor signaling complex. Immunity 172:73–85, 1999.
56. van der Merwe PA, Davis SJ: Molecular interactions mediating T cell antigen recognition. Annu Rev Immunol 21:659–684, 2003.
57. Budd RC, Fortner KA: T-cell development. *In* Rich RR, Fleisher TA, Shearer WT, et al (eds): Clinical Immunology: Principles and Practice. London: Mosby, 2008, pp 127–138.
58. von Boehmer H: Unique features of the pre-T-cell receptor α-chain: Not just a surrogate. Nat Rev Immunol 5:571–577, 2005.
59. Starr TK, Jameson SC, Hogquist KA: Positive and negative selection of T cells. Annu Rev Immunol 21:139–176, 2003.
60. Palmer E: Negative selection—Clearing out the bad apples from the T-cell repertoire. Nat Rev Immunol 3:383–391, 2003.
61. Anderson MS, Venanzi ES, Klein L, et al: Projection of an immunological self shadow within the thymus by the Aire protein. Science 298:1395–1400, 2002.
62. Mathis D, Benoist C: Aire. Annu Rev Immunol 27:287–312, 2009.
63. Singer A, Adoro S, Park JH: Lineage fate and intense debate: Myths, models and mechanisms of CD4- versus CD8-lineage choice. Nat Rev Immunol 8:788–801, 2008.
64. Walker LSK, Abbas AK: The enemy within: Keeping self-reactive T cells at bay in the periphery. Nat Rev Immunol 2:11–19, 2002.
65. Jiang H, Chess L: Regulation of immune responses by T cells. N Engl J Med 354:1166–1176, 2006.
66. Fathman CG, Lineberry NB: Molecular mechanisms of T cell anergy. Nat Rev Immunol 7:599–609, 2007.
67. Ramsdell F: Foxp3 and natural regulatory T cells: Key to a cell lineage? Immunity 19:165–168, 2003.
68. Maloy KJ, Powrie F: Regulatory T cells in the control of immune pathology. Nat Immunol 2:816–822, 2001.
69. Sakaguchi S, Sakaguchi N, Shimizu J, et al: Immunologic tolerance maintained by $CD25^+$ $CD4^+$ regulatory T cells: Their common role in controlling autoimmunity, tumor immunity, and transplantation tolerance. Immunol Rev 182:18–32, 2001.
70. Shevach EM, McHigh RS, Piccirillo CA, et al: Control of T cell activation by $CD4^+$ $CD25^+$ suppressor cells. Immunol Rev 182:58–78, 2001.
71. Sakaguchi S: The origin of FOXP3-expressing $CD4^+$ regulatory T cells: Thymus or periphery. J Clin Invest 112:1310–1312, 2003.
72. Miyara M, Amoura Z, Parizot C, et al: The immune paradox of sarcoidosis and regulatory T cells. J Exp Med 203:359–370, 2006.
73. Gorelik L, Flavell RA: Transforming growth factor-β in T cell biology. Nat Rev Immunol 2:46–53, 2002.
74. O'Garra A: Cytokines induce the development of functionally heterogeneous T helper cell subsets. Immunity 8:275–283, 1998.
75. Abbas AK, Murphy KM, Sher A: Functional diversity of helper T lymphocytes. Nature 383:787–793, 1996.
76. Frauwirth KA, Thompson CB: Activation and inhibition of lymphocytes by costimulation. J Clin Invest 109:295–299, 2002.
77. Alegre M-L, Frauwirth KA, Thompson CB: T-cell regulation by CD28 and CTLA-4. Nat Rev Immunol 1:220–228, 2001.
78. Greenwald RJ, Freeman GJ, Sharpe AH: The B7 family revisited. Annu Rev Immunol 23:515–548, 2005.
79. Sharpe AH, Freeman GJ: The B7-CD28 superfamily. Nat Rev Immunol 2:116–126, 2002.
80. Skalhegg BS, Tasken K, Hansson V, et al: Location of cAMP-dependent protein kinase type I with the TCR-CD3 complex. Science 263:84–87, 1994.
81. Li L, Yee C, Beavo JA: CD3- and CD28-dependent induction of PDE7 required for T cell activation. Science 283:848–851, 1999.
82. Grewal IS, Flavell RA: CD40 and CD154 in cell-mediated immunity. Annu Rev Immunol 16:111–135, 1998.
83. Yang Y, Wilson JM: CD40 ligand-dependent T cell activation: Requirement of B7-CD28 signaling through CD40. Science 273:1862–1864, 1996.

84. Watts TH: TNF/TNFR family members in costimulation of T cell responses. Annu Rev Immunol 23:23–68, 2005.
85. Mack DG, Lanham AK, Palmer BE, et al: 4-1BB enhances proliferation of beryllium-specific T cells in the lung of subjects with chronic beryllium disease. J Immunol 181:4381–4388, 2008.
86. Ellis CN, Krueger GG: Treatment of chronic plaque psoriasis by selective targeting of memory effector T lymphocytes. N Engl J Med 345:248–255, 2001.
87. Valk E, Rudd CE, Schneider H: CTLA-4 trafficking and surface expression. Trends Immunol 29:272–279, 2008.
88. Waterhouse P, Penninger JM, Timms E, et al: Lymphoproliferative disorders with early lethality in mice deficient in Ctla-4. Science 270:985–988, 1995.
89. Ueda H, Howson JMM, Esposito L, et al: Association of the T-cell regulatory gene *CTLA4* with susceptibility to autoimmune disease. Nature 423:506–511, 2003.
90. Keir ME, Butte MJ, Freeman GJ, Sharpe AH: PD-1 and its ligands in tolerance and immunity. Annu Rev Immunol 26:667–704, 2008.
91. Nishimura H, Nose M, Hiai H, et al: Development of lupus-like autoimmune diseases by disruption of the PD-1 gene encoding an ITIM motif-carrying immunoreceptor. Immunity 11:141–151, 1999.
92. Prokunina L, Castillejo-Lopez C, Oberg F, et al: A regulatory polymorphism in *PDCD1* is associated with susceptibility to systemic lupus erythematosus in humans. Nat Genet 32:666–669, 2002.
93. Kishimoto K, Dong VM, Issazadeh S, et al: The role of CD154-CD40 versus CD28-B7 costimulatory pathways in regulating allogeneic Th1 and Th2 responses in vivo. J Clin Invest 106:63–72, 2000.
94. Yamada A, Sayegh MH: The CD154-CD40 costimulatory pathway in transplantation. Transplantation 73:S36–S39, 2002.
95. Daikh DI, Wofsy D: Reversal of murine lupus nephritis with CTLA4Ig and cyclophosphamide. J Immunol 166:2913–2916, 2001.
96. Kremer JM, Westhovens R, Leon M, et al: Treatment of rheumatoid arthritis by selective inhibition of T-cell activation with fusion protein CTLA4Ig. N Engl J Med 349:1907–1915, 2003.
97. Suntharalingam G, Perry MR, Ward S, et al: Cytokine storm in a phase 1 trial of the anti-CD28 monoclonal antibody TGN1412. N Engl J Med 355:1018–1028, 2006.
98. Weaver CT, Hatton RD, Mangan PR, et al: IL-17 family cytokines and the expanding diversity of effector T cell lineages. Annu Rev Immunol 25:821–852, 2007.
99. Park H, Li Z, Yang XO, et al: A distinct lineage of CD4 T cells regulates tissue inflammation by producing interleukin 17. Nat Immunol 6:1133–1141, 2005.
99a. Nembrini C, Marsland BJ, Kopf M: IL-17-producing T cells in lung immunity and inflammation. J Allergy Clin Immunol 123:986–994, 2009.
99b. Gaffen SL: Structure and signaling in the IL-17 receptor family. Nat Rev Immunol 9:556–567, 2009.
100. Cua DJ, Sherlock J, Chen Y, et al: Interleukin-23 rather than IL-12 is the critical cytokine for autoimmune inflammation of the brain. Nature 421:744–748, 2003.
101. Murphy CA, Langrish CL, Chen Y, et al: Divergent pro- and anti-inflammatory roles of IL-23 and IL-12 in joint autoimmune inflammation. J Exp Med 198:1951–1957, 2003.
102. Yen D, Cheung J, Scheerens H, et al: IL-23 is essential for T cell-mediated colitis and promotes inflammation via IL-17 and IL-6. J Clin Invest 116:1317–1326, 2006.
103. Szabo SJ, Kim ST, Costa GL, et al: A novel transcription factor, T-bet, directs T_H1 lineage commitment. Cell 100:655–669, 2000.
104. Robinson DS, O'Garra A: Further checkpoints in Th1 development. Immunity 16:755–758, 2002.
105. Rogge L, Barberis-Maino L, Biffi M, et al: Selective expression of an interleukin-12 receptor component by human T helper 1 cells. J Exp Med 185:825–831, 1997.
106. Lee GR, Fields PE, Flavell RA: Regulation of IL-4 gene expression by distal regulatory elements and GATA-3 at the chromatin level. Immunity 14:447–459, 2001.
107. Betteli E, Korn T, Kuchroo VK: Th17: The third member of the effector T cell trilogy. Curr Opin Immunol 19:652–657, 2007.
108. Veldhoen M, Hocking RJ, Atkins CJ, et al: TGFbeta in the context of an inflammatory cytokine milieu supports de novo differentiation of IL-17-producing cells. Immunity 24:179–189, 2006.
109. Mangan PR, Harrington LE, O'Quinn DB, et al: Transforming growth factor-beta induces development of the T_H17 lineage. Nature 441:231–234, 2006.
109a. Korn T, Bettelli E, Oukka M, Kuchroo VK: IL-17 and Th17 cells. Annu Rev Immunol 27:485–517, 2009.
110. Ivanov II, McKnezie BS, Zhou L, et al: The orphan nuclear receptor RORγt directs the differentation program of proinflammatory IL-17+ T helper cells. Cell 126:1121–1133, 2006.
111. Sallusto F, Geginat J, Lanzavecchia A: Central memory and effector memory T cell subsets: Function, generation, and maintenance. Annu Rev Immunol 22:745–763, 2004.
112. Seder RA, Ahmed R: Similarities and differences in $CD4^+$ and $CD8^+$ effector and memory T cell generation. Nat Immunol 4:835–842, 2003.
113. Fontenot AP, Canavera SJ, Gharavi L, et al: Target organ localization of memory $CD4^+$ T cells in patients with chronic beryllium disease. J Clin Invest 110:1473–1482, 2002.
114. Lougaris V, Badolato R, Ferrari S, et al: Hyper immunoglobulin M syndrome due to CD40 deficiency: Clinical, molecular, and immunological features. Immunol Rev 203:48–66, 2005.
115. Lanzavecchia A: Antigen uptake and accumulation in antigen-specific B cells. Immunol Rev 99:39–51, 1987.
116. Barry M, Bleackley RC: Cytotoxic T lymphocyes: All roads lead to death. Nat Rev Immunol 2:401–409, 2002.
116a. Bouillet P, O'Rielly LA: CD95, BIM, and T cell homeostasis. Nat Rev Immunol 9:514–519, 2009.
117. Lieberman J: The ABCs of granule-mediated cytotoxicity: new weapons in the arsenal. Nat Rev Immunol 3:361–370, 2003.
118. Trapani JA, Smyth MJ: Functional significance of the perforin/granzyme cell death pathway. Nat Rev Immunol 2:735–747, 2002.
119. Cullen SP, Martin SJ: Mechanism of granule-dependent killing. Cell Death Differ 15:251–262, 2008.
120. D'Ambrosio D, Mariani M, Panina-Bordignon P, et al: Chemokines and their receptors guiding T lymphocyte recruitment in lung inflammation. Am J Respir Crit Care Med 164:1266–1275, 2001.
121. Reynolds HY: Bronchoalveolar lavage. Am Rev Respir Dis 135:250–263, 1987.
122. Tschering T, Pabst R: Bronchus-associated lymphoid tissue (BALT) is not present on the normal adult lung but in different diseases. Pathobiology 68:1–8, 2000.
123. Pabst R: Is BALT a major component of the human lung immune system? Immunol Today 13:119–122, 1992.
124. Hogg JC, Chu F, Utokaparch S, et al: The nature of small-airway obstruction in chronic obstructive pulmonary disease. N Engl J Med 350:2645–2653, 2004.
125. Wands JM, Roark CL, Aydintug MK, et al: Distribution and leukocyte contacts of γδ T cells in the lung. J Leuk Biol 78:1086–1096, 2005.
126. Hahn YS, Taube C, Jin N, et al: Different potentials of γδ T cell subsets in regulating airway hyperresponsiveness: Vγ1+ cells, but not Vγ4+ cells, promote airway hyperactivity. J Immunol 172:2894–2902, 2004.
127. Cyster JG: Chemokines, sphingosine-1-phosphate, and cell migration in secondary lymphoid organs. Annu Rev Immunol 23:127–159, 2005.
128. Tuomanen EI, Austrian R, Masure HR: Pathogenesis of pneumococcal infection. N Engl J Med 332:1280–1284, 1995.
129. Hsu H, Shutt KA, Moore MR, et al: Effect of pneumococcal conjugate vaccine on pneumococcal meningitis. N Engl J Med 360:244–256, 2009.
130. Hellmark T, Burkhardt H, Wieslander J: Goodpasture disease: Characterization of a single conformational epitope as the target of pathogenic autoantibodies. J Biol Chem 274:25862–25868, 1999.
131. Gunnarsson A, Hellmark T, Wieslander J: Molecular properties of the Goodpasture epitope. J Biol Chem 275:30844–30848, 2000.
132. Borza DB, Netzer KO, Leinonen A, et al: The Goodpasture autoantigen: Identification of multiple cryptic epitopes on the NC1 domain of the alpha3 (IV) collagen chain. J Biol Chem 275:6030–6037, 2000.

133. Fontenot AP, Schwarz MI: Diffuse alveolar hemorrhage. *In* Schwarz MI, King TE Jr (eds): Interstitial lung disease. Ontario: BC Decker, 2003, pp 632–656.
134. Ooi JD, Holdsworth SR, Kitching AR: Advances in the pathogenesis of Goodpasture's disease: From epitopes to autoantibodies to effector T cells. J Autoimmun 31:295–300, 2008.
135. Robertson J, Wu J Arends J, et al: Cigarette smoking and lung haemorrhage in glomerulonephritis caused by autoantibodies to glomerular basement membrane. Kidney Int 68:1061–1070, 2005.
136. Reynolds J, Tam FW, Chandraker A, et al: CD28-B7 blockade prevents the development of experimental autoimmune glomerulonephritis. J Clin Invest 105:643–651, 2000.
137. Trapnell BC, Whitsett JA, Nakata K: Pulmonary alveolar proteinosis. N Engl J Med 349:2527–2539, 2003.
138. Dranoff G, Crawford AD, Sadelain M, et al: Involvement of granulocyte-macrophage colony-stimulating factor in pulmonary homeostasis. Science 264:713–716, 1994.
139. Kitamura T, Tanaka N, Watanabe J, et al: Idiopathic pulmonary alveolar proteinosis as an autoimmune disease with neutralizing antibody against granulocyte/macrophage colony-stimulating factor. J Exp Med 190:875–880, 2003.
140. Notarangelo LD, Pessach I: Out of breath: GM-CSFRalpha mutations disrupt surfactant homeostasis. J Exp Med 205:2693–2697, 2008.
141. Herrick CA, Bottomly K: To respond or not to respond: T cells in allergic asthma. Nat Rev Immunol 3:405–412, 2003.
142. Kapsenberg ML, Hilkens CM, Wierenga EA, et al: The role of antigen-presenting cells in the regulation of allergen-specific T cell responses. Curr Opin Immunol 10:607–613, 1998.
143. Wynn TA: IL-13 effector functions. Annu Rev Immunol 21:425–456, 2003.
144. Marsh DG, Neely JD, Breazeale DR, et al: Linkage analysis of IL4 and other chromosome 5q31.1 markers and total serum immunoglobulin E concentrations. Science 264:1152–1156, 1994.
145. van der Pouw Kraan TC, Boeije LC, de Groot ER, et al: Reduced production of IL-12 and IL-12-dependent IFN-gamma release in patients with allergic asthma. J Immunol 158:5560–5565, 1997.
146. Fontenot AP, Maier LA: Genetic susceptibility and immune-mediated destruction in beryllium-induced disease. Trends Immunol 26:543–549, 2005.
147. Newman LS, Rose CS, Maier AL: Sarcoidosis. N Engl J Med 336:1224–1234, 1997.
148. Fontenot AP, Vollmer M, Newman LS, et al: HLA-DP restriction of $CD4^+$ T cells from the lungs of patients with beryllium-induced lung disease. Proc Natl Acad Sci U S A 97:12717–12722, 2000.
149. Richeldi L, Sorrentino R, Saltini C: HLA-DPB1 glutamate 69: A genetic marker of beryllium disease. Science 262:242–244, 1993.
150. Grunewald J, Wahlstrom J, Berlin M, et al: Lung restricted T cell receptor $AV2S3^+$ $CD4^+$ T cell expansions in sarcoidosis patients with a shared HLAS-DRbeta chain conformation. Thorax 57:348–352, 2002.

CHAPTER 15

GENERAL FEATURES OF NON-NEOPLASTIC RESPIRATORY PATHOLOGY

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INTRODUCTION

LUNG PROCESSING

ACUTE LUNG PROCESSES
Diffuse Alveolar Damage
Acute Bronchopneumonia
Diffuse Alveolar Hemorrhage
Acute Eosinophilic Lung Processes
Acute/Subacute Lymphocytic Lung Processes
Organizing Pneumonia

INTERSTITIAL LUNG FIBROTIC PATTERNS
Acute Interstitial Pneumonitis
Usual Interstitial Pneumonitis
Desquamative Interstitial Pneumonitis
Lymphocytic Interstitial Pneumonitis
Nonspecific Interstitial Pneumonitis
Other Forms of Idiopathic Interstitial Lung Pattern

GRANULOMATOUS LUNG PATTERNS

BRONCHIOLAR DISEASE PATTERNS
Chronic Bronchiolitis
Granulomatous Bronchiolitis
Obliterative Bronchiolitis

PULMONARY VASCULAR DISEASE PATTERNS

TRANSBRONCHIAL BIOPSY

INTRODUCTION

Pulmonary pathology plays a central role in the management and diagnosis of patients with lung diseases. Furthermore, the autopsy assessment of lungs provides important data regarding underlying acute or chronic disease in a high number of cases. Proper histopathologic interpretation of the lung requires a solid grasp of fundamental cellular processes, including inflammation and repair, neoplasia, and vascular alterations. Furthermore, the complexity of the normal gross and microscopic anatomy of the lung imposes significant challenges for the proper histopathologic alterations of lung diseases. The lung contains at least 30 different cells in the normal physiologic state, any of which can be increased or decreased in disease. The histopathologic identification of these cellular components and processes, their location, and overall interaction is often limited by the fact that the lung or biopsy fragments representative of lung tissue are subject to its state of inflation. In face of variable degrees of alveolar collapse present in histologic sections, the ensuing significant challenges can be overcome only with experience and a significant insight into clinical data regarding a given patient.

The widespread use of transbronchial and computed tomography–guided transthoracic needle biopsies has provided a formidable advance in the everyday clinical management of patients with lung diseases. However, the potential pitfalls outlined previously are exaggerated because of the potential for crush artifact and limited tissue sampling. The potential for misleading diagnosis has to be carefully considered throughout the histopathologic reading. As already stated, these limitations and the potential for errors can be significantly minimized with a solid knowledge of the fundamental cellular and pathologic processes in the lung allied to an open line of communication with the clinical team. This communication has to be established prior to the act of sampling the lung, because sampling accuracy can be significantly increased, and proper handling of lung fragments can be accomplished by the clinical team during the process of obtaining lung tissue. A summary of recommendations

are outlined in the sections that follow. This chapter also outlines a summary of relevant information regarding tissue processing and sections performed. Special histopathologic stains are described, with an emphasis on their utility in the histopathologic evaluation of the lung.

The pathologic interpretation can be broadly framed as aimed at either defining a "histopathologic pattern," reflecting the histopathologic alterations present in lung sections, or a conclusive final diagnosis. In the former, significant pathologic alterations are used to determine whether the lung is involved by an acute, granulomatous, or chronic and interstitial lung disease. Each histopathologic pattern carries a specific clinical differential diagnosis that warrants a detailed investigation. As an example, the diagnosis of alveolar hemorrhage with or without capillaritis entails the investigation of a set of diseases known to present with this particular pattern, including collagen vascular diseases and systemic vasculitides. The converse also applies in that specific diseases present with more than one pattern. For instance, scleroderma may present with acute lung injury (ALI), alveolar hemorrhage, bronchiolitis obliterans organizing pneumonia (BOOP), fibrosing pneumonias, and/or pulmonary vascular disease.[1] Patterns may occur in isolation or in combination; ALI and BOOP, for instance, may coexist. Therefore, proper interpretation of the predominant pattern is critical for proper patient management. Incorrect pathologic interpretation can result in delays or improper treatment. Conversely, what appears to represent a histopathologic process (e.g., ALI) may also carry a specific and final diagnosis. This is indeed the case with cytopathic lung viruses, including cytomegalovirus or herpesvirus infections, mycobacterial granulomatous inflammation, and *Pneumocystic jirovecii* infection. The converse also applies to infectious agents, that is, an infectious agent may be associated with several histopathologic patterns. This is also the case with *P. jirovecii* infection, which can produce the classic foamy or granular alveolar infiltrate or ALI pathology. The pathologic diagnosis of a neoplastic process is also a specific and final diagnosis; however, one should consider that inflammatory/repair-related histopathologic processes may accompany neoplastic processes, such as BOOP.

LUNG PROCESSING

Lung tissue requires some degree of inflation, which can be accomplished with instillation of formalin or any solution that can maintain the alveolar tissue open, preferably recapitulating alveolar structure at total lung capacity. Whole lungs should be inflated with a 10% buffered formalin solution under 25 cm H_2O pressure. Each lung will require approximately 2 to 4 L to achieve inflation, a volume that approximates total lung capacity. The advantages offered by formalin inflation are the immediate fixation (e.g., preservation of molecular and morphologic details) due to cross-linking of macromolecules and relative accessibility to immunohistochemical stains. Alternative approaches have been developed to also allow ease to perform frozen sections. These approaches rely on a 50% solution of OCT (optimal cutting temperature) or a buffered solution containing 0.5–2.0% agarose instilled at approximately 40°C to 60°C.[2] Lung biopsies are also amenable to inflation using 10% formalin injected with a syringe and a 15-gauge needle. Alternatively, gently tapping the fragment with a wooden stick in formalin can lead to air being expelled and improved infiltration by formalin. The staples can be removed on wedge biopsies and the tissue gently tapped in order to provide adequate infiltrate of formalin. Finally, the histopathologic interpretation of transbronchial biopsies can be enhanced by immediate placement in formalin and gently tapping each fragment against the vial wall, allowing the expansion of the periphery of the fragment. The general rules for proper fixation require that the relative volume relationship between tissue and the fixative should be 1:10; that is, the volume of formalin should be 10 times that of the target tissue. Furthermore, formalin penetrates and fixes tissues at a rate of 1 mm/hr. A maximum thickness of 4 mm is required for proper fixation, because thicker sections lose integrity and are not suitable for histopathologic analyses. The fragments are processed through gradients of alcohol (leading to loss of glycogen) and then sequential immersions in three containers with xylene, leading to dehydration of the tissue and clearing with removal of hydrophobic molecules, including lipids and fatty acids. The fragments are then embedded into molds of molten paraffin (at 60°C). This stage allows for proper orientation of the relevant samples. The bottom of the mold is then sectioned on a microtome and made into histologic slides. Most histopathologic interpretations are carried out using histologic slides stained by hematoxylin (an acidic nuclear stain that reacts with basic DNA histones) and eosin (for cytoplasmic details). Additional special stains used in the histopathologic evaluation of the lung are mentioned later under the specific topics.

ACUTE LUNG PROCESSES

Acute lung processes may appear within hours before a biopsy is obtained. Most of these involve early inflammation, which is usually characterized by varying degrees of edema, protein exudates, hemorrhages, inflammatory cell infiltrate including neutrophils, eosinophils, lymphocytes, occasionally multinucleated giant cells, and cellular damage to alveolar epithelial and endothelial cells. The relative contribution of each of these events and their preferential anatomic location in the alveolar unit allow one to diagnose a specific acute lung process. Predominance of red cells points toward alveolar hemorrhage, whereas predominance of intra-alveolar neutrophils strongly suggests bronchopneumonia. We included under the "acute" category the entities that present for several days that we opted to describe as "subacute." The correlation between the acute lung processes and specific clinical diagnoses is highlighted in Table 15-1.

TABLE 15-1. Acute Lung Processes and Underlying Clinical Entities

Acute lung injury (ALI): viral and bacterial infection, sepsis, hemorrhage and blood transfusions, drug toxicity, trauma, environmental exposures including hot or toxic fumes, aspiration, collagen vascular diseases, idiopathic (acute interstitial pneumonia [AIP]).

Diffuse alveolar hemorrhage (DAH) with or without capillaritis: idiopathic and restricted to the lung; collagen vascular diseases (rheumatoid arthritis, polymyositis, scleroderma, lupus erythematosus), transplant rejection, influenza virus infection, *Nocardia* infection, retinoid acid in acute myelogenous leukemia (M3), Wegener's granulomatosis, systemic vasculitis (perinuclear antineurophil cytoplasmic antibody [p-ANCA] vasculitis), Goodpasture's syndrome.

Acute eosinophilic lung processes: acute eosinophilic pneumonia, Löffler's syndrome, drug toxicity.

Acute/subacute lymphocytic lung processes: hypersensitivity pneumonitis, viral infections.

Organizing pneumonias: viral and bacterial pneumonias, drug toxicity, inhalational toxicity, collagen vascular disease, reaction to expansile tumors including granulomas and neoplastic processes, idiopathic.

Diffuse Alveolar Damage

Diffuse alveolar damage (DAD) is the pathologic presentation of ALI or acute respiratory distress syndrome (ARDS). An identical pathologic presentation is seen in acute interstitial pneumonia (AIP).[3] DAD always has an underlying causes, such as infections, drug reactions, transfusions, trauma, collagen vascular disease, or viral infections. AIP in its early stages describes the idiopathic form of DAD and, therefore, is a diagnosis of exclusion. The early events are characterized by alveolar edema, with leakage of plasma products, particularly of fibronectin, into the alveolar space (Figs. 15-1A and B and 15-2).[4] This results in the formation of hyaline membranes. Variable hemorrhage is present, but acute inflammation is not prominent. Type II cell hyperplasia and reactive atypia is a frequent finding, particularly when DAD is caused by drug toxicity. These acute events transition rapidly (i.e., 36–48 hr) to a macrophage and fibroproliferative process, which organizes the intra-alveolar exudate. The early organization is best appreciated with the Movat (or pentachrome) stain, which highlights the presence of mucopolysaccharides deposited by the proliferating fibroblasts. Fibrin is a common finding in thrombi in pulmonary arteries with ALI. The chronic stage entails alveolar collapse, fibrosis, and potential honeycombing, which are described in the next section. Most of the cases of DAD associated with ARDS or ALI will resolve, leaving some structural alterations that may underlie potential alterations in pulmonary performance. Infectious agents may lead to a DAD pattern, including *P. jirovecii*, and viral infections, including herpes and adenovirus infection (see Fig. 15-1B). Figure 15-1 outlines the histopathologic findings according to the evolution of ALI/DAD.

Acute Bronchopneumonia

Acute bronchopneumonia is the most frequent presentation of an acute lung process. It is a common finding at autopsy; however, it may be present in transbronchial or video-assisted thoracic surgery (VATS) biopsies, particularly in atypical clinical presentations. Bronchopneumonia is characterized by alveolar hemorrhage early in its course (i.e., ≤6 hr). This stage is followed by neutrophil accumulation in alveolar septa with prominent spilling into the alveolar spaces (see Fig. 15-1C). Most bacterial infections show predominance of neutrophil accumulation versus hemorrhage, yet we have observed cases with predominance of fresh alveolar hemorrhage, particularly in the setting of anaerobic or *Nocardia* infection. With the introduction of antibiotic therapy, the exudative component is rapidly (i.e., after 24 hr) organized with formation of fibroproliferative plugs, that is, the process becomes organizing pneumonia (OP).

Diffuse Alveolar Hemorrhage

Diffuse alveolar hemorrhage (DAH) is characterized by the presence of intra-alveolar hemorrhage. Red cells may be seen admixed with polymerized fibrin, often abutting the alveolar septum (see Fig. 15-1D). Red cells can permeate the alveolar septa and accumulate in the alveolar spaces or can be engulfed by alveolar macrophages. The differential diagnosis of artifactual bleeding due to surgical manipulation is sometimes difficult. In the latter case, red cells are usually less tightly packed within the alveolar space, hemosiderin in either the septa or within macrophages is absent, and red blood cells are not detected leaving the alveolar capillaries. Evidence of capillaritis can accompany alveolar hemorrhage (see Fig. 15-1E). Capillaritis is defined by the septal infiltration of neutrophils, with evidence of nuclear fragmentation. In the more advanced stages of capillaritis, microabscesses with septal necrosis may be identified. In comparison with bronchopneumonia, capillaritis shows less prominent intra-alveolar accumulation of neutrophils, whereas the converse applies to bronchopneumonia. Evidence of chronic hemorrhagic events is identified by hemosiderin accumulation in macrophages or in alveolar septa and variable degrees of septal fibrosis. This morphologic pattern is similar to that seen in chronic passive congestion due to left ventricular failure. An often difficult differential diagnosis is the distinction between DAH and desquamative interstitial pneumonitis (DIP) pattern. However, DIP lacks the features outlined earlier for DAH. The recognition of DAH carries important clinical implications as the differential diagnosis includes systemic vasculitis with high morbidity/mortality, such as Wegener's granulomatosis and Churg-Strauss vasculitis. In case the distinction of DAH/capillaritis versus bronchopneumonia is difficult, it is important to convey that a given case may represent the former, warranting a careful clinical screening of clinical conditions associated with this histologic pattern.[5] Frozen tissue may be suitable for immunofluorescence, particularly when

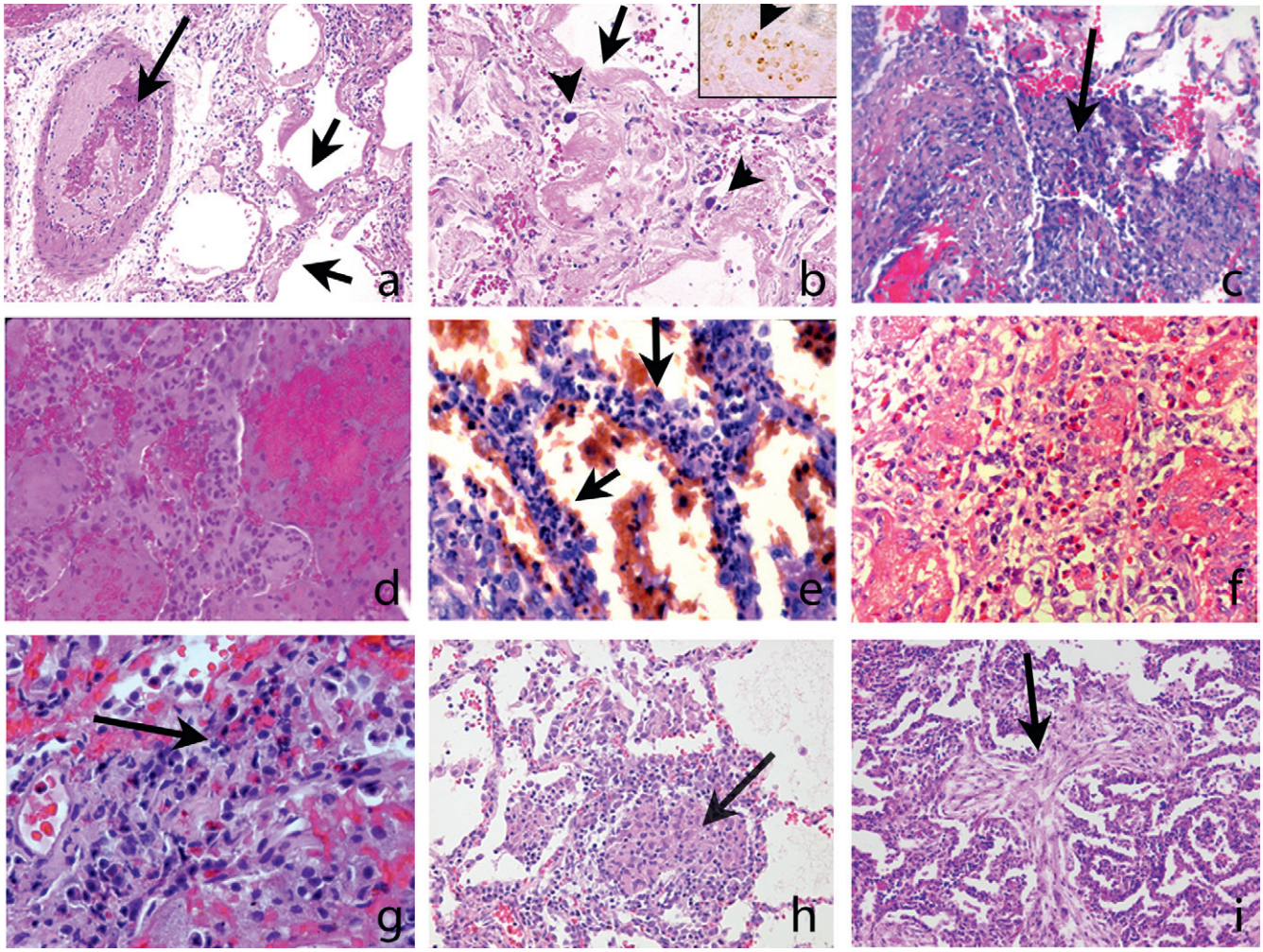

FIGURE 15-1 ■ Acute lung processes. **A,** Acute lung injury (ALI) with prominent hyaline membranes (*arrows*) lining alveolar septa. A medium-size pulmonary artery shows a recent thrombus (*long arrow*). **B,** ALI pattern with hyaline membranes (*arrow*) in a case of adenovirus infection, with the cytopathic effect (*arrowheads*). Viral identity is confirmed by immunohistochemistry (*inset, arrowhead*). **C,** Acute bronchopneumonia with accumulation of neutrophils in the intra-alveolar space (*arrow*). **D,** Diffuse alveolar hemorrhage (DAH). **E,** Capillaritis with septa infiltrated by neutrophils (*arrows*). **F,** Acute eosinophilic lung pattern with intra-alveolar accumulation of fibrinous exudates and eosinphils. **G,** Degranulated eosinophilic granules in eosinophilic lung disease (as reported by Gerhardt SG et al[29]) (*arrow*). **H,** A case of recent acute hypersensitivity pneumonitis with the presence of granulomas in the alveolar septa (*arrow*). **I,** Bronchiolitis obliterans with organizing pneumonia with a cast of granulation tissue in the alveolar duct (*arrow*).

associated with lupus erythematosus or Goodpasture's syndrome, and provide a final diagnosis.

Acute Eosinophilic Lung Processes

Acute eosinophilic processes are seen in idiopathic acute eosinophilic pneumonia, or in association with parasitic diseases (also known as Löffler's syndrome), bronchopulmonary aspergillosis, asthma, eosinophilic granuloma, cancer, and others. The typical finding is a dense infiltration of eosinophils in alveolar septa and intra-alveolar spaces (see Fig. 15-1F and G). The authors have often found large areas with cell-free eosinophilic granules, which likely represents the degranulation of infiltrating eosinophils (see Fig. 15-1G). Variable interstitial or perivascular infiltration of eosinophils can be seen with chronic diseases, including chronic eosinophilic pneumonia and Churg-Strauss vasculitis. The clinical history, radiologic presentation, and specific areas of histologic involvement aid in the proper differential diagnosis of the conditions associated with acute eosinophilic lung diseases.

Acute/Subacute Lymphocytic Lung Processes

Although most acute lung diseases show neutrophilic or eosinophilic infiltration, there are some clinical conditions in which a lymphocytic infiltration may

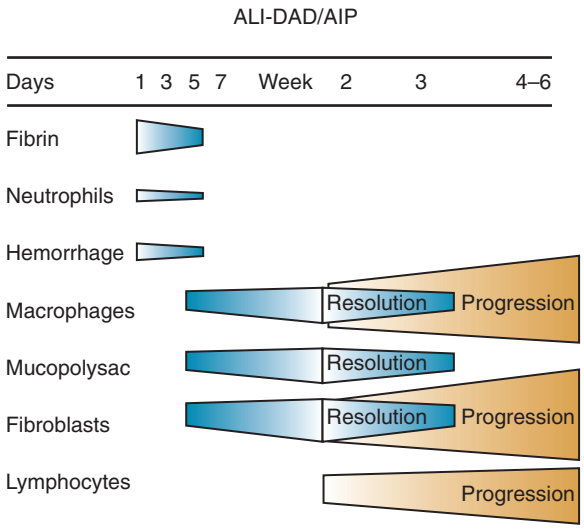

FIGURE 15-2 ■ Summary of histopathologic alterations present in ALI/diffuse alveolar damage through the course of the disease. These alterations can be followed either by resolution or with progression to a fibrotic lung with honeycombing. Color and thickness of the *horizontal bars* are proportional to the intensity of a particular histopathologic finding (based on Katzenstein's data[3]). Resolution of ALI between week 1 and 2 leads to progressive disappearance of the features present during the early stages of the disease. However, progression to chronicity leads to persistence or increase of features associated with interstitial inflammation and fibrosis.

predominate, including drug toxicity, viral infections, or immunologic reactions. In the latter condition, mycotoxins can cause an acute form of hypersensitivity pneumonitis (HP) in which granulomas may coexist with the lymphocytic infiltrate (see Fig. 15-1H). It is noteworthy that most of the lung lymphocytic processes are chronic, often accompanied by varying degrees of interstitial thickening by cells and fibrosis, as in lymphocytic interstitial pneumonitis (LIP) (see later), nonspecific interstitial pneumonitis (NSIP), and others.

Organizing Pneumonia

Organizing pneumonia (OP) is one of the most common acute/subacute patterns seen in lung biopsies, often being an accessory and therefore nonspecific pattern in several lung diseases. OP (also known as BOOP) is characterized by the presence of a loose, mucopolysaccharide-rich matrix, with young fibroblasts extending from an attachment site in the alveolar duct and filling the lumen (see Fig. 15-1I).[6] A central vessel and accumulation of centrally placed macrophages may also be seen. The alveolar septa may show varying numbers of lymphocytic or plasmacytic cell infiltrates. As mentioned, an interpretation of OP or BOOP should be considered with care prior to reaching a final clinical diagnosis. BOOP may occur in association with several clinical conditions (see Table 15-1). Once several of the more frequent conditions have been excluded by clinical workup, the final diagnosis of idiopathic BOOP should be considered.

TABLE 15-2. Interstitial Lung Diseases and Underlying Clinical Entities

Usual interstitial pneumonia (UIP)–like pattern: idiopathic (UIP), collagen vascular disease (scleroderma), asbestos interstitial lung disease.

Desquamative interstitial pneumonitis (DIP): idiopathic.

Lymphoid interstitial pneumonitis (LIP): idiopathic, collagen vascular disease (Sjögren's disease), AIDS, immunosuppression (acquired or hereditary), viral (Epstein-Barr virus [EBV] infection).

Nonspecific interstitial pneumonitis (NSIP): idiopathic; NSIP-like due to hypersensitivity pneumonitis, NSIP-like due to collagen vascular disease (i.e., scleroderma).

Giant cell interstitial pneumonitis (GIP): heavy metal exposure.

INTERSTITIAL LUNG FIBROTIC PATTERNS

This overall pattern, which encompasses most of the interstitial lung diseases (ILD), results from insults to the alveolar septa leading to a variable recruitment of lymphocytes, plasma cells, macrophages, and eosinophils. The key finding is the destruction of alveolar structures and/or thickening of alveolar septa by fibrosis. One study outlined the value of lung biopsy in the diagnosis of the clinical conditions associated with interstitial pneumonitis.[7] The patterns under this category are listed in Table 15-2 and illustrated in Figure 15-3.

Acute Interstitial Pneumonitis

AIP is the only entity that allies a component of acute lung disease with a rapidly evolving course with extensive alveolar collapse and replacement by collagenous tissue. The pathology of early disease is identical to that seen in DAD with hyaline membranes (see Figs. 15-1 and 15-2). The hallmark of this process is the uniformity of lung destruction, with little areas that are spared, which is not seen in usual interstitial pneumonia (UIP; see later). Furthermore, the process of fibrosis in AIP is distinctly irregular, because there are areas that show features of honeycombing, whereas other regions may show predominance of fibrosis admixed with chronic inflammatory infiltrate, with relative preservation of the overall septal outline.

Usual Interstitial Pneumonitis

UIP is a paradigmatic pattern of chronic and fibrotic lung disease that, in its idiopathic form, correlates with the clinical entity of idiopathic pulmonary fibrosis (IPF) (see Fig. 15-3A–C). The lung bases are predominantly involved with extensive alveolar replacement by fibrosis, chronic inflammatory infiltrates, and honeycombing. The extensive areas of fibrosis alternate with focally spared lung tissue (see Fig. 15-3A–C). Within the areas of fibrosis, focal organizing exudates protrude into the adjacent alveolar space to form the so-called fibroblastic foci, a

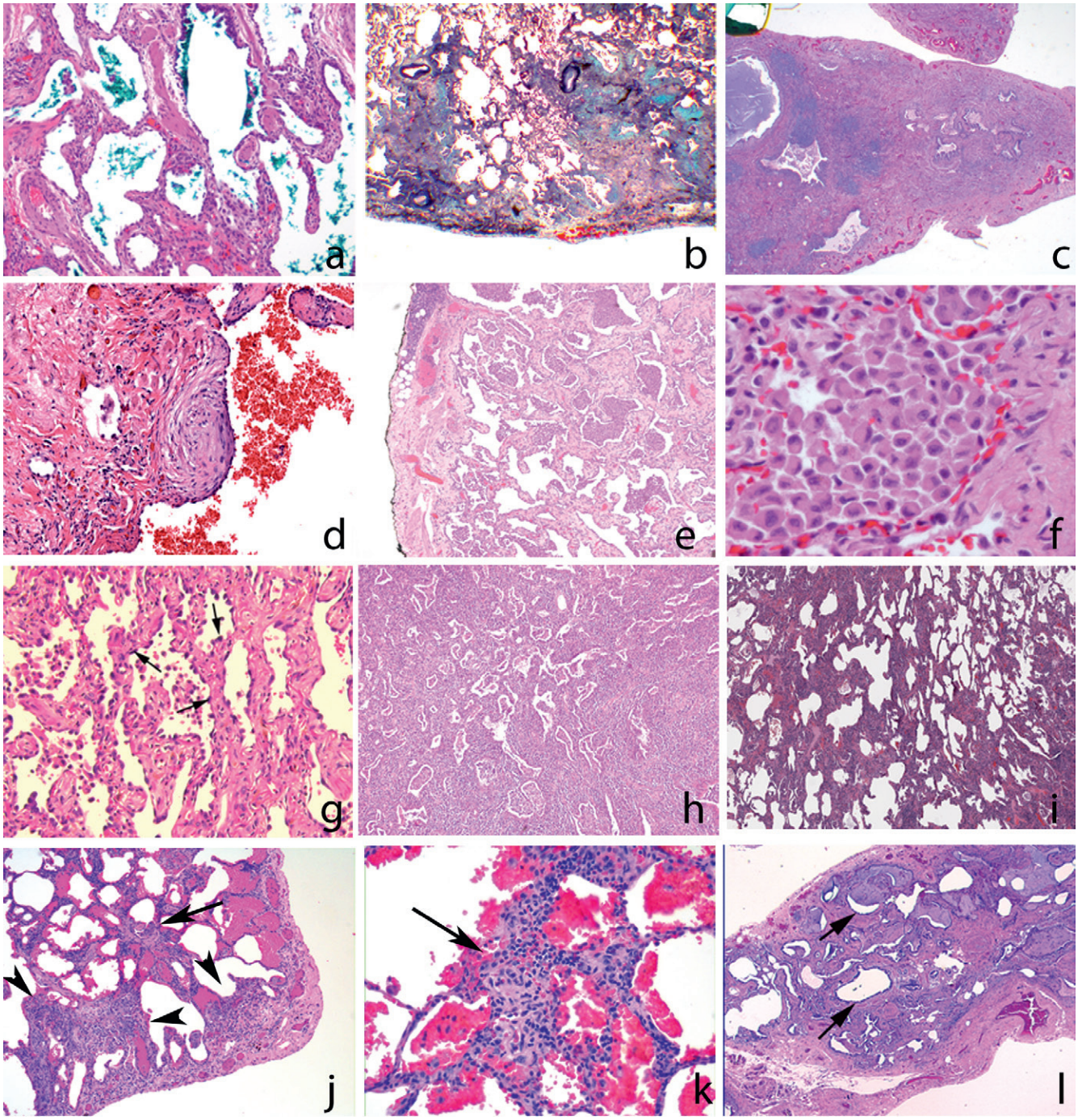

FIGURE 15-3 ■ Chronic interstitial lung patterns. **A,** Acute interstitial pneumonia (AIP) evolving into fibrotic stage with extensive and relatively diffuse septal thickening by fibrosis. **B–D,** Usual interstitial pneumonia (UIP), showing its heterogeneous presentation, with areas of alveolar collapse and replacement by active fibrogenic and inflammatory process (**B**), with areas of honeycombing (**C**), and presence of fibroblastic foci (**D**). **E–G,** Desquamative interstitial pneumonitis (DIP) with the characteristic uniform filling of alveolar spaces (**E**) with macrophages (**F**); once treated, DIP presents with a nonspecific type of regular interstitial thickening (*arrows*) (**G**). **H,** Lymphocytic interstitial pneumonitis (LIP) with dense and uniform infiltration by lymphocytes and plasma cells. **I** and **J,** Nonspecific interstitial pneumonitis (NSIP) type III with temporally homogeneous extensive fibrosis (**I** and **J**), alternating with areas with irregular interstitial inflammation (**I** and **K;** *arrows* in **J** and **K** highlight septal inflammation extending into intralobular septa—compare with **L;** *arrowheads* highlight similar inflammatory process but with alveolar collapse in the subpleural region). **L,** Honeycombing with lung parenchyma replaced by cystic areas surrounded by dense fibrosis and containing mucinous material (*arrows*).

key pathogenetic process involved in UIP (see Fig. 15-3D). These pathologic structures resemble the organization seen in BOOP, but in BOOP (or OP), the granulation tissue projects symmetrically from within an alveolar duct or respiratory bronchiole and fills the air space in a serpiginous manner (see Fig. 15-1I). UIP relatively spares the upper lobes; however, patients with advanced disease may show upper lobe involvement. If there is a predominance of upper lobe involvement, other etiologies such as fibrosing stage of HP or collagen vascular diseases should be considered in the differential diagnosis. UIP may be complicated by acute exacerbations with either an ALI pattern or areas of bronchopneumonia. There is a wide differential clinical diagnosis of entities that share the UIP pattern (see Table 15-2). Perhaps the most frequently encountered is the distinction between the idiopathic form of UIP, known as IPF, and that caused by collagen vascular disease, particularly scleroderma. Given the heterogeneity of the pathologic presentation in UIP, open-lung biopsies (two or three lobe biopsies) are necessary to provide accurate diagnosis. Transbronchial biopsies are generally not indicated for diagnosis. It is well recognized that the UIP pattern may have some common histopathologic features with those encountered in NSIP; thus, the final diagnosis may rely on the integration with the clinical presentation and radiologic features.

Desquamative Interstitial Pneumonitis

DIP is a well-recognized pathologic presentation of ILD, with several features in common with those encountered in respiratory bronchiolitis (RB) (see Fig. 15-3E–G). There is a spectrum of lesions that typify DIP. All include variable numbers of loosely clustered intra-alveolar macrophages (see Fig. 15-3E and F) and a range of fibrosis from mild airway fibrosis and interstitial thickening (similar to RB) to more diffuse, fibrotic interstitial thickening (see Fig. 15-3G). The alveolar macrophages, especially in those cases associated with cigarette smoking (>90% of cases), contain yellow-brown finely pigmented inclusions within their cytoplasm. Variable numbers of eosinophils may be admixed with the macrophages. The characteristic morphology may not be present in treated cases, in which case there is a reduction of the cellular interstitial inflammation and number of intra-alveolar macrophages. However, there may be residual interstitial thickening (see Fig. 15-3G).

Lymphocytic Interstitial Pneumonitis

LIP can present with a wide range of associated conditions, including collagen vascular disorders, immunosuppression (in cases of human immunodeficiency virus [HIV] infection), or inherited causes of immunosuppression (see Fig. 15-3H). LIP is characterized by extensive infiltration by a mixture of lymphocytes and plasma cells, often effacing the normal microscopic architecture of the alveolar septa. Secondary germinal centers may be observed, both in the parenchyma and in the peribronchiolar regions. Granulomas may be present in variable numbers and structural composition, sometimes leading one to consider the differential diagnosis of HP. Although some of these cases may represent a clonal (i.e., neoplastic) proliferation, the clinical progression is more often that of a chronic inflammatory condition. Transbronchial biopsies can be informative when evaluated in the context of the clinical and radiologic presentations. The immediate differential diagnosis involves conditions associated with lymphoplasmacytic infiltrates, including NSIP and HP, or conditions associated with granulomatous patterns, including HP, sarcoidosis, and mycobacterial infections.

Nonspecific Interstitial Pneumonitis

NSIP, a somewhat controversial pathologic and clinical presentation of interstitial lung diseases,[8] has been recently reviewed in a consensus conference[9] (see Figs. 15-3I–K). NSIP involves a spectrum of pathologic presentations that suggests there may be stages that progress from inflammation to fibrosis in patients. However, it is also conceivable that the different types of interstitial involvement represent static stages. The so-called type I,[8] or cellular variant, is characterized by prominent but irregular interstitial infiltrate by lymphocytes and plasma cells, with mild fibrosis, and focal areas of BOOP (see Fig. 15-3I). The differential diagnosis includes acute lymphocytic lung processes, which are of shorter duration and not associated with an increase in interstitial fibrosis. Granulomas are not in the spectrum of type I NSIP, but rather raise the suspicion of HP (Fig. 15-4G). Types II and III have variable degrees of fibrosis (see Fig. 15-3I–K). Type II has a uniform type of interstitial fibrosis accompanied by chronic inflammatory infiltrate (see Fig. 15-3K); although this overall pattern may again suggest HP, granulomas are not a feature of NSIP. Type III NSIP has marked areas of alveolar collapse, with replacement by extensive fibrosis (see Fig. 15-3L). There may be early microscopic honeycombing and low numbers of fibroblastic foci, but dense honeycombing or abundant fibroblastic foci are not observed in type III NSIP. All subtypes of NSIP are characterized by a uniform pattern of involvement within the secondary lobular unit, whereas UIP has a distinct heterogeneity, in which lobular areas vary between foci of honeycombing with areas of active inflammation or preserved alveolar structures. In our experience, lung involvement by a pathologic process akin to NSIP can be clearly seen in collagen vascular diseases, drug toxicity, and HP; thus, it is best to include these diseases in the differential diagnosis of NSIP.

Other Forms of Idiopathic Interstitial Lung Pattern

Other, rarer forms of ILD patterns include giant cell interstitial pneumonitis, reported in association with heavy metal exposures, end-stage sarcoidosis, and end-stage fibrotic lung (honeycombing pattern only). These patterns require a detailed clinical history and clinical correlation. In the case of end-stage sarcoidosis, it is

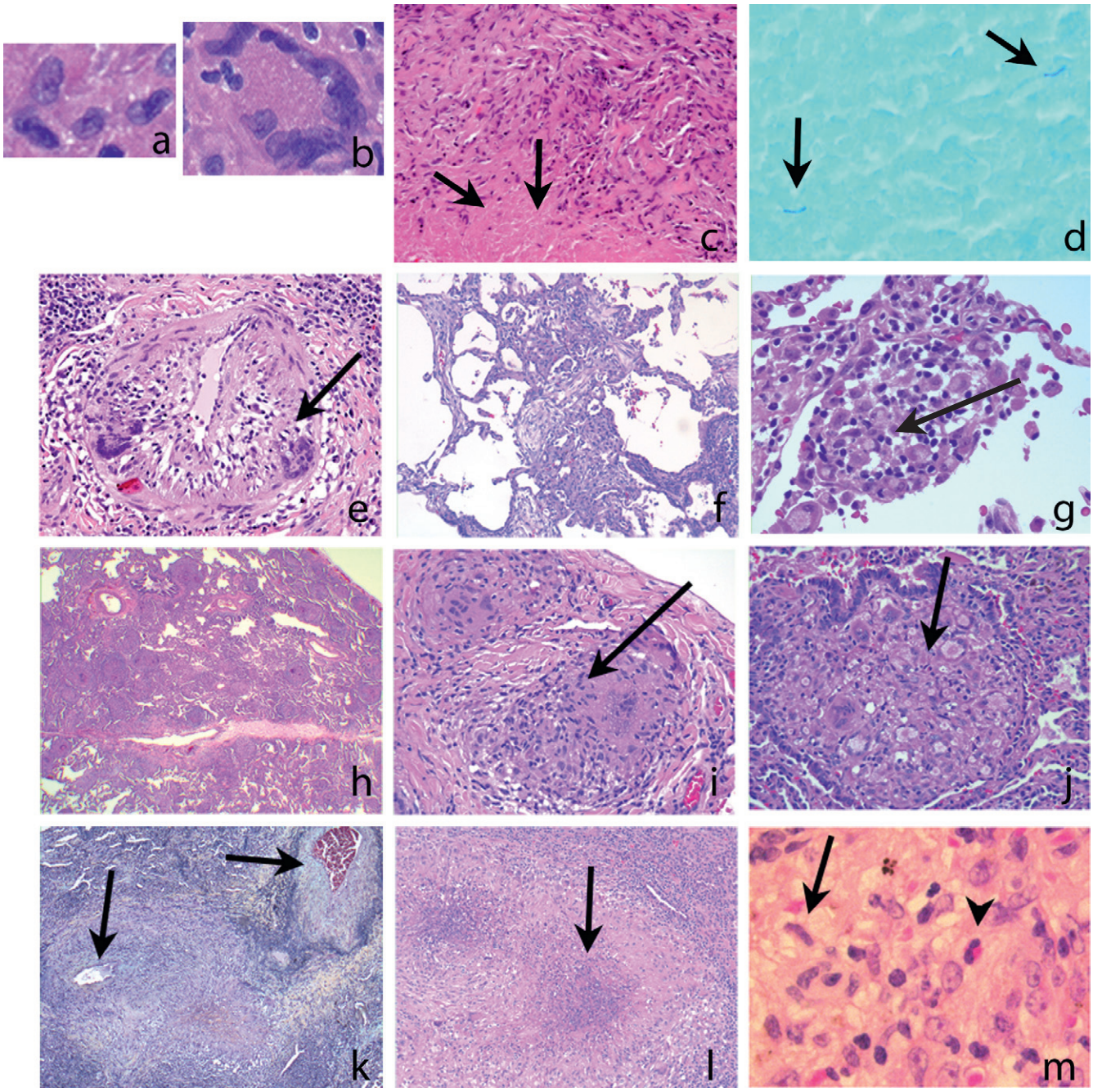

FIGURE 15-4 ■ Granulomatous lung patterns. **A,** High power of an epithelioid histiocyte. **B,** High power of multinucleated histiocyte. **C** and **D,** Tuberculous granulomas (**C**) with presence of caseous necrosis (*arrows* in **C**) and mycobacteria present in the acid-fast stain with methyl green counterstain (*arrows* in **D**). **E,** Atypical mycobacterial granulomas within the pulmonary artery (causing granulomatous vasculitis, *arrow*). **F** and **G,** Hypersensitivity pneumonitis showing an NSIP pattern of interstitial inflammation and fibrosis (**F**) and poorly formed granulomas in the septal-alveolar interface (*arrow* in **G**). **H–J,** Sarcoidosis, with extensive interstitial and alveolar involvement (**H**), with well-formed granulomas in subpleural (*arrow* in **I**) and intrabronchial locations (*arrow* in **J**). **K** and **L,** Wegener's granulomatosis, with necrotizing granulomas (*arrows* in **K**), seen invading the vessel wall in the Movat-stained section (*arrow* in **L**). **M,** High magnification of an eosinophilic granuloma lesion, with Langerhans histiocyte (*arrow*) and eosinophils (*arrowhead*).

possible to identify scattered active or hyalinized granulomas in the midst of the fibrous tissue as the remaining evidence of underlying sarcoidosis. Honeycombing is a terminal stage of ILDs in which the underlying cause may not be identified. It is characteristically seen in UIP and UIP-like conditions (see Fig. 15-3C).

GRANULOMATOUS LUNG PATTERNS

Granulomas are defined as organized conglomerates of histiocytes (macrophages). Most of the granulomatous lung diseases involve the formation of epithelioid granulomas, in which the characteristic cell is the epithelioid

TABLE 15-3. Conditions Associated with Granulomas

Typical and atypical mycobacterial infections:
Pattern: well-formed granulomas with variable caseous necrosis.
Fungal infections:
Pattern: well-formed granulomas with variable caseous necrosis
Hypersensitivity pneumonitis:
Pattern: nonspecific interstitial pneumonitis (NSIP)-like changes with poorly organized granulomas in alveolar-interstitial junction.
Sarcoidosis and berylium disease:
Pattern: well-formed granulomas along lymphatics; rarely with fibrinoid necrosis (in necrotizing sarcoidosis)
Immunodeficiencies:
Pattern: NSIP-like changes accompanied with poorly formed granulomas.
Lymphocytic interstitial pneumonitis (LIP):
Pattern: dense lymphoplasmacytic infiltrate with scattered well or poorly formed granulomas
Wegener's granulomatosis:
Pattern: necrotizing process with scattered giant cells and histiocytes in alveolar, vascular, and/or bronchiolar compartments.

histiocyte (see Fig. 15-4A and B). This cell is clustered within the granulomas and is characterized by an elongated profile with indistinct cytoplasmic membranes. Multinucleated giant cells may or may not be present. An outside rim of chronic inflammatory cells, predominantly lymphocytes, may be present in variable numbers. The differential diagnosis encompasses several potential entities, including infectious (mycobacterial or fungal), sarcoidosis, HP, interstitial pneumonitis not otherwise specified, NSIP-like due to immunosuppression, LIP, and granulomatous vasculitits (Table 15-3; see also Fig. 15-4). Some of the latter discussed entities present with a diffuse infiltration of macrophages, such as with areas of DIP-like lung pathology or a pseudo-DIP due to associated alveolar hemorrhage (which may occur in interstitial pneumonitis associated with collagen vascular diseases).

Central caseous necrosis (see Fig. 15-4B) points toward mycobacterial or fungal infection, which can be ascertained by acid-fast stain (see Fig. 15-4D) or Gomori silver methanamine stains, respectively, or tissue cultures. Caseating granulomas are usually well-formed with epithelioid macrophages, giant cells, and lymphocytes surrounding a centrally placed necrotic, eosinophilic core (see Fig. 15-4C). Calcifications may be present in chronic lesions. Miliary nodules may have less-well-formed organization, with areas of organizing exudate. Infectious granulomas, particularly atypical mycobacterial infection, can affect pulmonary arteries with a true granulomatous vasculitis, similar to Wegener's granulomatosis (see Fig. 15-4E).

Hypersensitivity pneumonitis (HP), which has a characteristic interstitial involvement (see Fig. 15-4F), also presents with granulomas, which are characteristically poorly organized, that is, the cells are loosely arranged without a clear rim of lymphocytes or connective tissue on the outside border. These granulomas are located in the alveolar septal–air space interface, often leading to a blurred outline of the alveolar structure (see Fig. 15-4G). As described previously, HP shows variable infiltration by lymphocytes and plasma cells, often in a centrilobular (bronchiolocentric) location.

Sarcoid granulomas are generally solid, well-formed granulomas, with no evidence of central necrosis (see Fig. 15-4H–J). Sarcoid granulomas are preferentially distributed along lymphatics, which are located in the pleura and along the bronchovascular tree (see Fig. 15-4H). Sarcoid granulomas may present as single structures, be located in the subpleural region or airway (see Fig. 15-4J) and vascular walls, but can coalesce when in abundant numbers. Focal fibrinoid necrosis may also occur and is characterized by a deep eosinophilic hue that resembles that of polymerized fibrin. Extensive central necrosis, however, is much more typical of infectious etiologies.

In conditions associated with alterations of immune responses, such as HIV infection, genetic causes, or immunodeficiency, a cellular interstitial pneumonitis can be identified in association with granulomas. These cases usually warrant in situ hybridization for Epstein-Barr viruses.

Systemic vasculitides can also present with granulomas. Wegener's granulomatosis shows poorly formed granulomas located in the interstitium (see Fig. 15-4K and L), surrounding areas of "dirty" necrosis containing necrotic neutrophils and cellular debris, interspersed with pockets of neutrophils and scattered multinucleated giant cells (see Fig. 15-4K). The edges of this process are effaced, giving it an appearance of a confluent pneumonic process, and the classic "geographic necrosis" outlines (see Fig. 15-4J). Alveolar hemorrhage with or without capillaritis may follow the granulomatous response in Wegener's granulomatosis. Clusters of Langerhans histiocytes (resembling granulomas) are characteristic of eosinophilic granulomas (Fig. 15-5I–L; see also Fig. 15-4M).

BRONCHIOLAR DISEASE PATTERNS

Terminal bronchioles account for the largest sectional area of airways. They branch dichotomously between cartilaginous bronchi and respiratory bronchioles for 20 to 24 generations. The terminal bronchioles are lined by a pseudostratified epithelium, lined predominantly by ciliated cells. The epithelium lies over a thin basement membrane (subbasal lamina). A submucosa brings blood supply within a mesh of loose connective tissue. The muscular layer accounts for approximately 20% of the thickness of the bronchiolar wall. The adventitial tissue surrounds the terminal bronchiole and connects it to the adjoining pulmonary artery.

Chronic Bronchiolitis

Chronic inflammatory processes involving the terminal bronchiole are frequent and relatively nonspecific because they are often associated with infectious

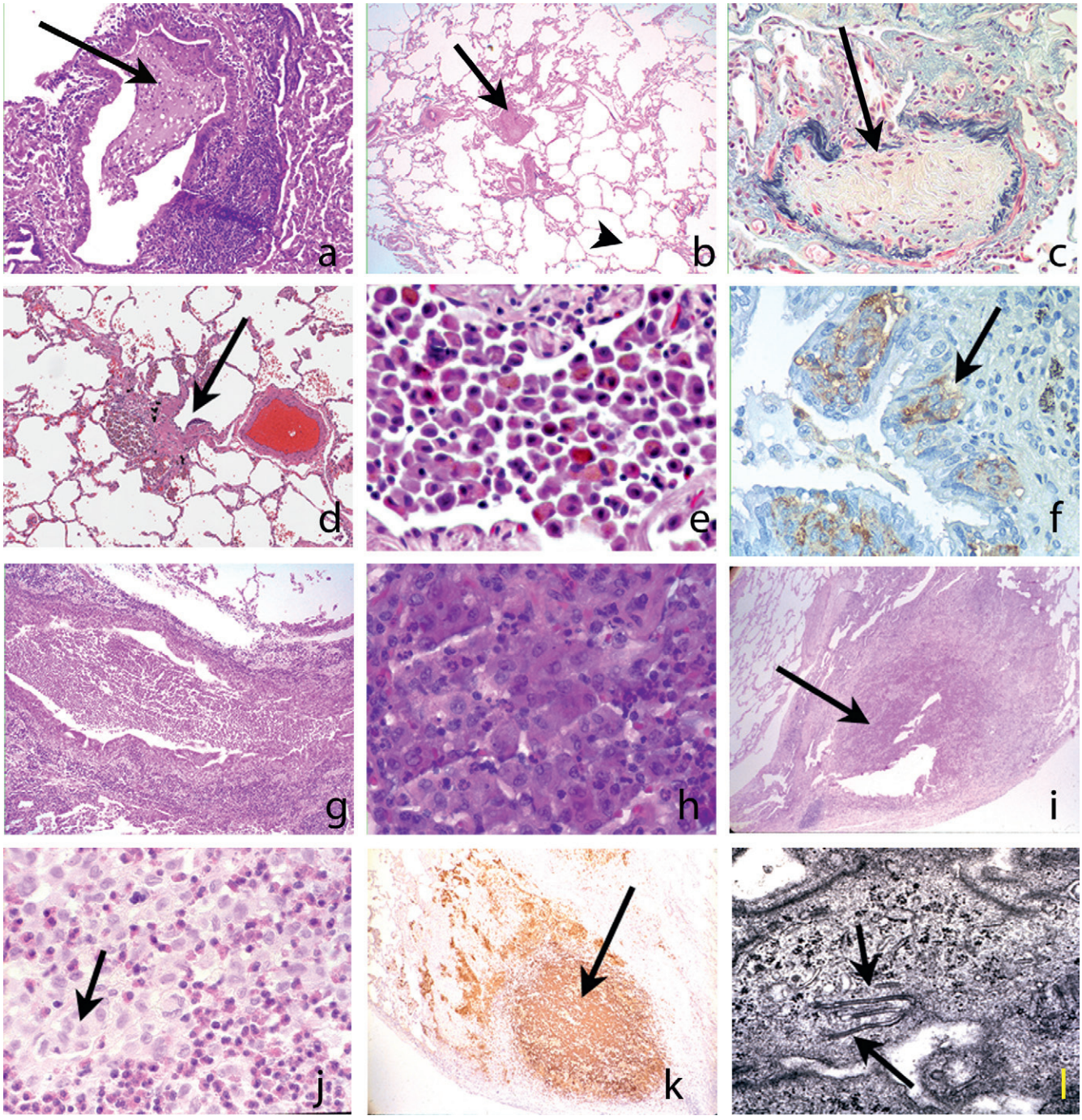

FIGURE 15-5 ■ Bronchiolar diseases. **A,** Chronic bronchiolitis with heavy lymphoplasmacytic infiltrate in bronchiolar wall, dilation of the lumen, and accumulation of mucus in bronchiolar lumen. This pattern can be seen in collagen vascular diseases, atypical presentation of cystic fibrosis, or chronic bronchitis in chronic obstructive pulmonary disease. **B** and **C,** Obliterative bronchiolitis showing areas of scarring in centrilobular regions, with a paucity of bronchioles (*arrow*). There is associated air space enlargement as seen in emphysema (*arrowhead*). **C,** Movat stain highlights disruption of the basement membrane and obliteration of the bronchiolar lumen (*arrow*). **D** and **E,** Respiratory bronchiolitis with distortion of terminal and respiratory bronchioles (**D**) and accumulation of pigmented macrophages in the affected airways (**E**). **F,** Neuroendocrine hyperplasia with increased numbers of chromogranin-positive cells (*arrow*). **G** and **H,** Diffuse panbronchiolitis with accumulation of neutrophils and mucus in the dilated bronchiolar lumen. Adjacent to the compromised airway, there is accumulation of foamy macrophages (**H**). **I–L,** Eosinophilic granulomas, with a cavitary lesion (*arrow* in **I**), surrounded by Langerhans histiocyte (*arrow* in **J**), which stain strongly with S100 antibody (*arrow* in **K**). These cells contain the characteristic tennis racket–shaped structures at electron microscopy (*arrows* in **L**).

processes (i.e., mycoplasma or viral infections), collagen vascular diseases, cigarette smoking, or asthma (see Fig. 15-5). In fact, this can the early and sole presentation of rheumatoid arthritis, even before serologic confirmation of the disease (see Fig. 15-5A[10]). This lymphocytic infiltrate can sometimes lead to the formation of lymphoid follicles that are characteristic of follicular bronchiolitis, which can be seen as the result of viral infections or collagen vascular diseases (such as Sjögren's disease) (see Fig. 15-5A). The Movat stain aids in the recognition of obliterative changes in which the airway is completely or partly obliterated by connective tissue (see Fig. 15-5B and C) (see later).

Bronchiolitis is frequently seen in association with cigarette smoking, which can cause RB and pulmonary Langerhans cell histiocytosis (or eosinophilic granuloma). RB is a nearly universal finding in chronic smokers, leading to the distortion of bronchiolar walls, increased wall fibrosis, and intraluminal accumulation of iron- and aluminum-containing pigmented macrophages (see Fig. 15-5D and E). RB is now interpreted as part of a spectrum that includes DIP.[11] Infrequently, pure respiratory bronchiolitis may be associated with a restrictive disease, known as respiratory bronchiolitis interstitial lung disease (RB-ILD). Although increased interstitial fibrosis is believed to underlie the clinical presentation of RB-ILD, it is unclear as to the extent of architectural changes of the bronchiolar wall and peribronchiolar tissue that can cause the alteration in lung function of this condition.

Distorted airways, like that seen in RB, can result from the accumulation of neuroendocrine cells staining positively for chromogranin (see Fig. 15-5F), characteristic of neuroendocrine hyperplasia. The pathologic changes can be subtle, although patients may show severe airway limitation.

Idiopathic small airway diseases include the entity of diffuse panbronchiolitis[12] (see Fig. 15-5G and H). Allied to a distinct tree-in-bud radiologic pattern, the morphology is characterized by intraluminal accumulation of large numbers of preserved and fragmented neutrophils amid abundant mucus and basophilic strands suggestive of degraded DNA. The bronchiolar wall is infiltrated by chronic lymphoplasmacytic infiltrates that extend into the adjacent alveolar tissue. A prominent and distinctive feature is the finding of interstitial foamy macrophages (see Fig. 15-5H). In our experience, a pattern quite similar to diffuse panbronchiolitis can be also seen in association with airway infections, including unusual cases of atypical mycobacteria. Therefore, clinical and radiologic correlation is warranted for a final diagnosis.

Pulmonary Langerhans cell histiocytosis (or eosinophilic granuloma) is seen almost exclusively in smokers and is characterized by bronchiolar fibrosis that radiates from the bronchiolar wall into the adjacent alveolar tissue, with accumulation of the distinctive histiocytes (Langerhans) that show indented kidney-shaped nuclei (see Figs. 15-4M and 15-5J). These cells form large clusters that stain positively for S100 protein, CD1a, and CD7 immunohistochemical markers and contain diagnostic Bierback structures at electron microscopy (see Fig. 15-5L). This infiltrative process is associated with increased numbers of eosinophils amid the Langherhans cells (see Fig. 15-5J). The lesions will evolve with progressive fibrosis and a marked decrease in the cellular infiltrate, imparting some difficulty in the diagnostic workup. However, the pattern of bronchiolar stellate fibrosis suggests the diagnosis of eosinophilic granuloma. Sometimes, a central cavitation can be seen (see Fig. 15-5I). A very similar fibrotic pattern is also seen in patients with chronic lesions due to tuberous sclerosis. Pulmonary arteries may be involved in association with severe pulmonary hypertension,[13] which carries a worse outcome.[14]

Granulomatous Bronchiolitis

Granulomatous lung diseases, such as mycobacterial, fungal, sarcoidosis (see Fig. 15-4J), and others, can also compromise the terminal bronchioles. The pattern of granulomatous involvement is similar to that described in the section on "Granulomatous Lung Patterns." A distinct form of granulomatous bronchiolitis is the bronchocentric granulomatosis, usually caused by infectious agents or by Wegener's granulomatosis.[15]

Obliterative Bronchiolitis

Inflammatory bronchiolitis can be associated with fibrous obliterative changes, which are centered in the submucosa and lead to progressive encroachment of the lumen. Obliterative bronchiolitis pattern can be seen in collagen vascular diseases, including rheumatoid arthritis, post lung transplant, and chronic graft-versus-host disease, or as an idiopathic disease. The characteristic feature is the evidence of active fibrogenesis with collagen and increased number of fibroblasts in a subepithelial location. The bronchiolar epithelium shows features of injury/regeneration, with flattened cytoplasm or areas of detachment from the underlying basement membrane. Inflammatory cell infiltrate is variable, but often seen migrating along penetrating blood vessels that insinuate from the outside bronchiolar wall through the bronchiolar smooth muscle cell layer. The smooth muscle layer is progressively disrupted, with residual clusters of fibers surrounded by collagenous tissue. The diagnosis is greatly aided by the identification that the bronchiole is of smaller diameter than the accompanying pulmonary artery, because these structures are of similar diameter throughout the lung, and by the pentachrome or Movat stain. This stain colors the elastic tissue black, the basement membrane and collagen yellow, the smooth muscle cell cytoplasm red, and any mucopolysaccharides blue. The pentachrome or Movat stain therefore highlights the disruption of the basement membrane and the collagenous infiltration of the lumen and bronchiolar wall. Chronic injury eventually leads to complete disappearance of the bronchiolar structure, replaced by a longitudinal scar that accompanies the adjacent pulmonary artery. Pentachrome stain reveals fragments of basement membrane, which are the reflection of a prior bronchiolar structure. Obliterative bronchiolitis can be diagnosed by transbronchial biopsy if the aforementioned criteria are applied stringently to the diagnostic workup.

Clinically, these cases present with airflow limitation and persistent hyperinflation in radiologic tests. In our experience, the correlation between clinical airflow limitation and degree of pathologic airway obstruction is poor.

PULMONARY VASCULAR DISEASE PATTERNS

The pulmonary arterial system is characterized histologically by a progressive loss of medial elastic layers in vessels smaller than 500 μm in diameter and diminution of a muscular layer that is present in vessels down to 70 μm in diameter.[16,17] As the arteries lose their muscular layer, they branch into precapillary segments, followed by capillaries. This unique anatomic organization allows for low alveolar perfusion pressures, which are represented by a low right ventricular afterload.

There is increased realization of the importance of pulmonary vascular disease and pulmonary hypertension in the outcome of several lung diseases.[17a] The pathology of pulmonary vascular disease was extensively documented in descriptive chapters[18] or independent reports of a series of cases.[19,20] Based on these descriptions, a pathologic classification emerged that was applied to all cases of pulmonary hypertension, although initially, the classification was intended to apply to cases of pulmonary hypertension associated with congenital heart malformations.[19] The "pulmonary vascular pathologic era" culminated with the 1973 World Symposium with a pathologically driven overall classification of the disease. The present clinical definition and classification of pulmonary hypertension has been outlined in the Venice International Symposium in 2004[21,22] and recently revised in the 2008 International Symposium in Dana Point, California.[22a] The role of pathology in the clinical workup of patients with potential pulmonary hypertension is quite limited, because the disease is defined hemodynamically as an elevation of pulmonary artery pressures in excess of 25 mm Hg. This reduced role of pulmonary vascular pathology has largely resulted from the difficulty of sampling of lung tissue of patients with the disease and the realization that the pulmonary vascular pathologist was not able to discriminate among the various clinical conditions associated with pulmonary hypertension (illustrated by the First International Pulmonary Hypertension Symposium in 1973[23]). The Second International Symposium of Pulmonary Hypertension in Evian, in 1998,[24] proposed a more descriptive role for pulmonary vascular pathology, aimed at a supportive role in the clinical workup, when biopsies were taken or autopsy material was available (with modification in Table 15-4[17]). The Third symposium in Venice proposed some changes in the pathologic consideration of pulmonary vascular disease,[25] particularly with emphasis in some changes in terminology, that is, complex vascular lesions for plexiform/dilation lesions and emphasis on the presence of venous pathology in conditions felt to compromise predominantly pulmonary arteries.

TABLE 15-4. Histopathological Classification of Pulmonary Hypertension Based on the Evian World Symposium

PRECAPILLARY CHANGES
Endothelial cell proliferation (based on endothelial cell immunostaining):
Small clusters
Plexiform lesions
Dilation lesions
Smooth muscle cell changes (based on smooth muscle cell immunostaining):
Intima
Media
Adventitia—fibroblasts
Thrombi
POSTCAPILLARY CHANGES
Vein wall thickening
CAPILLARY CHANGES
Capillary hemangioma
ASSOCIATED FINDINGS
Perivascular inflammation
Recent/old hemorrhage
Septal fibrosis

Given the limitations imposed by the assessment of pulmonary vascular pathology, the interaction with the clinical team is critical. The descriptive diagnosis should emphasize endothelial, smooth muscle and adventitial fibroblast-based remodeling[26] (Fig. 15-6). Each of these vascular types of remodeling should be correlated clinically and hemodynamically with the severity of the pulmonary vascular disease. Large pulmonary arteries show changes similar to those of atherosclerosis (see Fig. 15-6A). Intima lesions consist of smooth muscle–based lesions, which consist of eccentric and concentric intimal thickening. Endothelial cell–based lesions consist of plexiform (see Fig. 15-6C and D), dilation, and concentric lesions. Endothelial cell–based lesions and concentric thickening, with smooth muscle cell or endothelial cells, are associated with severe pulmonary hypertension, that is, in excess of 40 to 45 mm Hg and poor outcome. Intima thickening compromising most of the inner circumference of the pulmonary arteries is a relatively frequent finding when present in a few vessels of normal lung; however, cigarette smoking causes this pattern of vascular remodeling in a large number of pulmonary arteries.[27] These alterations are associated with pulmonary vascular dysfunction, including reduced nitric oxide–mediated vasodilation.[28] Medial lesions consist of smooth muscle cell hypertrophy/hyperplasia (see Fig. 15-6B). Medial thickening can be seen in conditions not related to pulmonary hypertension, including bystander remodeling in ILD or cigarette smoke–related lung disease (including RB and DIP). In our experience, the degree of intimal or medial thickening is a poor predictor of levels of pulmonary artery pressures, often

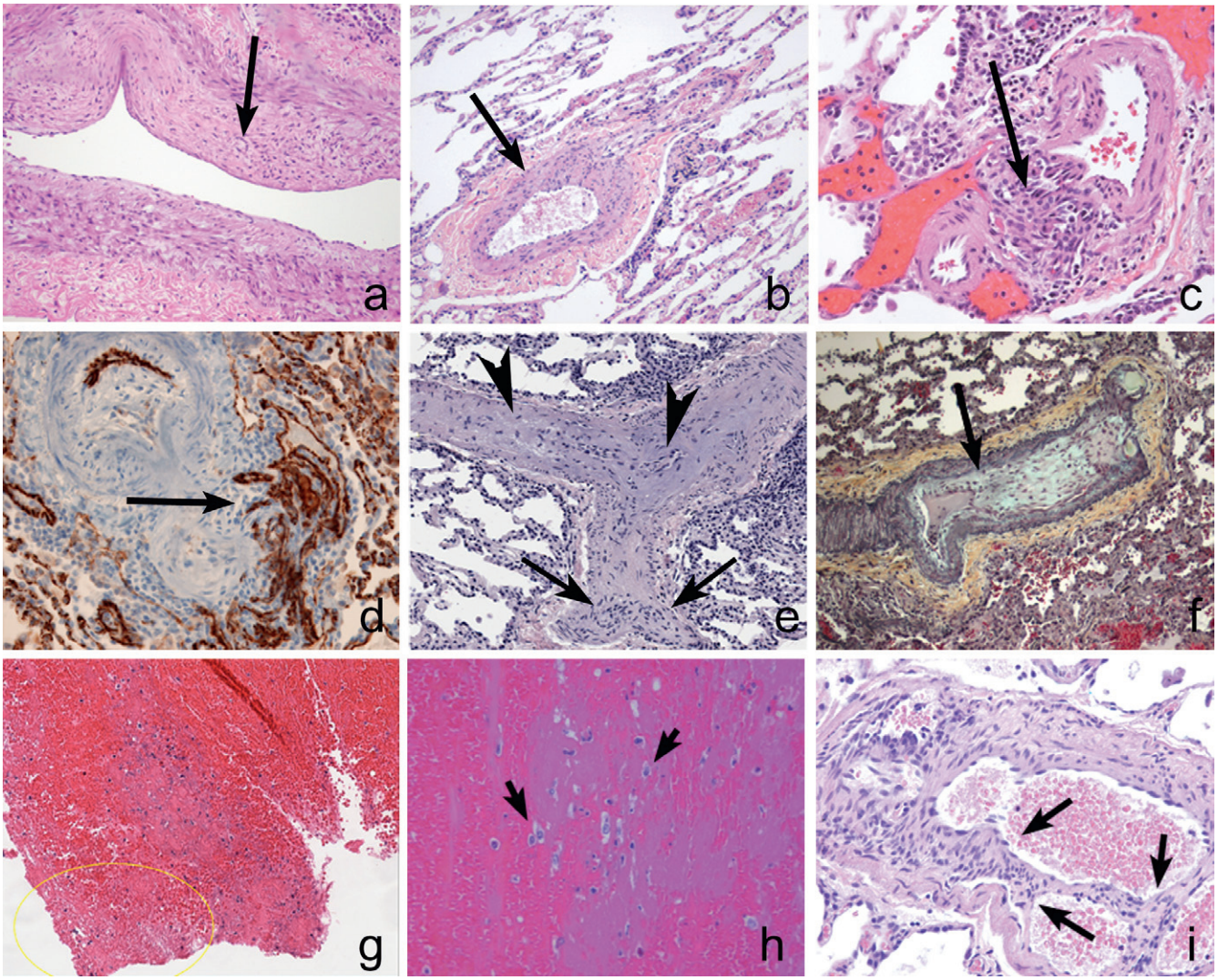

FIGURE 15-6 ■ Pulmonary vascular disease. **A,** Atherosclerotic-like changes with intima thickening in a large (elastic) pulmonary artery (*arrow*). **B,** Medial thickening (*arrow*) in a muscular pulmonary artery in idiopathic pulmonary hypertension. **C** and **D,** Plexiform lesion (*arrows*) consisting of intraluminal growth of endothelial cells highlighted by CD31 immunohistochemistry (*arrow* in **D**). **E,** Muscular artery with marked intima thickening (*arrowheads*), extending to branches (*arrows*) in a case of idiopathic pulmonary arterial hypertension. **F,** Pulmonary vein occluded by an organized thrombus, which is highlighted by the Movat stain (*arrow*) and diagnostic of veno-occlusive disease. **G–I,** Evolution of pulmonary thromboembolus with lines of Zhan in the circled area (**G**), and clearing around inflammatory cells trapped in the fibrin mesh (*arrows* in **H**). Organization of the thromboembolus leads to fibrotic bridges traversing the lumen of pulmonary artery (*arrows* in **I**).

needing a close correlation with clinical data. Occlusive lesions can also be found in pulmonary veins, characteristic of veno-occlusive disease[27a] (see Fig. 15-6F).

Adventitia thickening by fibroblasts and collagen is a relatively common occurrence, particularly in cases of pulmonary hypertension in neonates and in adults with scleroderma-associated pulmonary hypertension.

A common finding is pulmonary vascular remodeling due to localized or diffuse thromboembolic disease. Recent emboli are commonly encountered, because there are approximately 500,000 annual cases of pulmonary embolization, with an overall 20% mortality. Common risk factors are obesity, postoperative inactivity, and genetic alterations in anti- or procoagulant mediators. In lethal events, the histopathologic timing of clot formation in pulmonary arteries may be required for correlation with clinical events or for medicolegal reasons. Based on extensive experimental and histopathologic studies performed in the 1950s and 1960s, the morphologic events underlying the evolution of thrombi have been well delineated. Within minutes of formation of the platelet plug at the site of endothelial cell injury, fibrin is polymerized forming a mesh, which traps platelets, inflammatory cells, and red cells (see Fig. 15-6G and H). Thrombolysis starts immediately with activation of plasmin and therefore opposes the forces driving the formation and expansion of the thrombus. Up to 12 to 24 hours after formation of a thrombus, inflammatory

cells are still seen with preservation of the cellular structure. After this initial period, inflammatory cells undergo cell death and lysis, leading to the formation of a clear halo. In the first 48 hours, flattened cells (probably endothelial cells) expand from the intima into partially lysed fibrin strands (see Fig. 15-6G and H). After the first 48 hours, progressive organization occurs with fibrin lysis, incorporation of endothelial cells along fibrin stands, and early blood vessel formation. These processes, over the ensuing 2 to 3 weeks, progress with the incorporation of recanalized thrombi, in which the fibrin has been replaced by a collagenous background containing proliferated capillaries. Some thrombi may be extensively lysed, becoming a residual acellular, often eccentric, fibrotic intima thickening. Over months to years, luminal occlusions give rise to intraluminal bands of fibrous tissue (see Fig. 15-6I), with spaces in which blood flows. It is important to note that, in cases of emboli, the detached fragment will represent a potential extension rather than the early region of the thrombus. Therefore, precise timing of the pulmonary thromboembolus has to be interpreted with caution, with the caveat that its timing represents the events ongoing in the primary site and organizational events in the pulmonary arteries.

Pulmonary infarcts may complicate approximately 20% of pulmonary thromboemboli, particularly in patients with left heart failure. This low level of infarction is due to the dual lung circulation, including the bronchial circulation, which supplies an alternative to the pulmonary artery flow for lung structures.

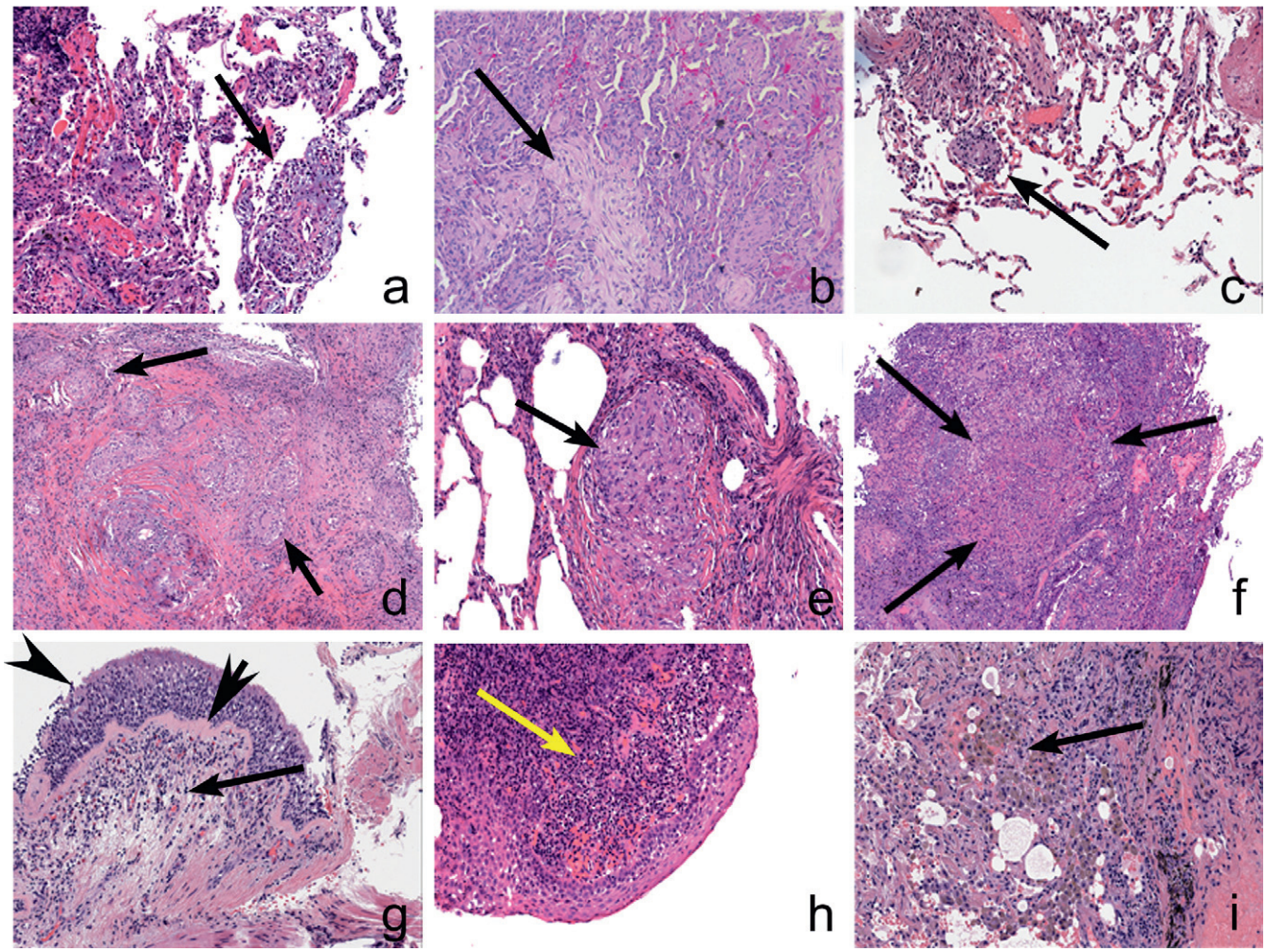

FIGURE 15-7 ■ Examples of pathologic processes identified in transbronchial biopsies. **A,** Acute bronchopneumonia with accumulation of neutrophils in the alveolar space (*arrow*). **B,** Organizing pneumonia organizing exudate (*arrow*) with granulation tissue in the alveolar space. **C,** Presence of poorly formed granulomas in biopsy of hypersensitivity pneumonitis (*arrow*). **D,** Example of confluent granulomas with extensive perigranulomatous fibrosis (*arrows*). **E,** Case of localized well-formed granuloma (*arrow*). **F,** Necrotizing granulomas with geographic necrosis (demarcated by *arrows*), consistent with Wegener's granulomatosis. **G,** Example of asthmatic large airway with thickened basement membrane (*short arrow*), detached superficial lining cells (*arrowhead*), and submucosal inflammation (*long arrow*). **H,** Intense chronic bronchiolitis (*arrow*). This process would be consistent with collagen vascular disease or graft-versus-host disease. **I,** Respiratory bronchiolitis with pigmented macrophages (*arrow*).

TRANSBRONCHIAL BIOPSY

Transbronchial biopsies have a central role in the management of patients with lung diseases. As mentioned previously, the accuracy of interpretation requires a deep knowledge of fundamental processes concerning inflammation, repair, scarring, proper tissue handling and processing, and an open line of communication with the clinical team. A poor indication for a transbronchial biopsy and inaccurate interpretation of the findings present in histologic slides can be avoided with these requirements. Figure 15-7 shows several examples of histopathologic patterns present in representative small fragments obtained from transbronchial biopsies.

KEY POINTS

- The interaction between the clinical team and the pathologist is critical for the proper pathologic interpretation of a lung biopsy.
- Most of the non-neoplastic lung diseases manifest histologically as particular pathologic patterns. The final diagnosis requires that the clinical team rules out/in clinical conditions associated with a particular pattern.
- Some non-neoplastic lung diseases, such as viral disease, may be associated with characteristic cytopathic alterations, which support a final pathologic diagnosis rather than the interpretation of a pattern of pulmonary disease.
- Histopathologic lung patterns are associated with multiple clinical diagnoses; conversely, specific diseases cause multiple lung patterns.
- Proper histopathologic recognition of patterns requires examination in low power to define which lung structures are predominantly compromised, followed by high-magnification examination of cellular features involved in specific lung patterns.

References

1. Highland KB, Garin MC, Brown KK: The spectrum of scleroderma lung disease. Semin Respir Crit Care Med 28:418–429, 2007.
2. Halbower AC, Mason RJ, Abman SH, et al: Agarose infiltration improves morphology of cryostat sections of lung. Lab Invest 71:149–153, 1994.
3. Katzenstein A-LA: Acute lung injury patterns: Diffuse alveolar damage and bronchiolitis obliterans-ongoing pneumonia. *In* Katzenstein A-LA (ed): Katzenstein's and Askin's Surgical Pathology of Non-neoplastic Lung Disease (3rd ed). Philadelphia: WB Saunders, 1998.
4. Katzenstein AL, Myers JL, Mazur MT: Acute interstitial pneumonia. A clinicopathologic, ultrastructural, and cell kinetic study. Am J Surg Pathol 10:256–267, 1986.
5. Zamora MR, Warner ML, Tuder R, et al: Diffuse alveolar hemorrhage and systemic lupus erythematosus. Clinical presentation, histology, survival, and outcome. Medicine (Baltimore) 76:192–202, 1997.
6. Yousem SA, Lohr RH, Colby TV: Idiopathic bronchiolitis obliterans organizing pneumonia/cryptogenic organizing pneumonia with unfavorable outcome: Pathologic predictors. Mod Pathol 10:864–871, 1997.
7. Hunninghake GW, Zimmerman MB, Schwartz DA, et al: Utility of a lung biopsy for the diagnosis of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 164:193–196, 2001.
8. Katzenstein AL, Myers JL: Nonspecific interstitial pneumonia and the other idiopathic interstitial pneumonias: Classification and diagnostic criteria. Am J Surg Pathol 24:1–3, 2000.
9. Travis WD, Hunninghake G, King TE Jr, et al: Idiopathic nonspecific interstitial pneumonia: Report of an American Thoracic Society project. Am J Respir Crit Care Med 177:1338–1347, 2008.
10. Schwarz MI, Lynch DA, Tuder R: Bronchiolitis obliterans: The lone manifestation of rheumatoid arthritis? Eur Resp J 7:817–820, 1994.
11. Myers JL, Veal CF Jr, Shin MS, et al: Respiratory bronchiolitis causing interstitial lung disease. A clinicopathologic study of six cases. Am Rev Respir Dis 135:880–884, 1987.
12. Fitzgerald JE, King TEJ, Lynch DA, et al: Diffuse panbronchiolitis in the United States. Am J Respir Crit Care Med 154:497–503, 1996.
13. Fartoukh M, Humbert M, Capron F, et al: Severe pulmonary hypertension in histiocytosis X. Am J Respir Crit Care Med 161:216–223, 2000.
14. Crausman RS, Jennings CA, Tuder RM, et al: Pulmonary histiocytosis X: Pulmonary function and exercise pathophysiology. Am J Respir Crit Care Med 153:426–435, 1996.
15. Myers JL, Katzenstein AL: Granulomatous infection mimicking bronchocentric granulomatosis. Am J Surg Pathol 10:317–322, 1986.
16. Wagenvoort CA, Wagenvoort N: Normal circulation of the lungs. *In* Wagenvoort CA, Wagenvoort N (eds): Pathology of Pulmonary Hypertension (1st ed). New York: John Wiley & Sons, 1977, pp 1–8.
17. Tuder RM, Marecki JC, Richter A, et al: Pathology of pulmonary hypertension. Clin Chest Med 28:23–42, vii, 2007.

17a. Tuder RM: Pathology of pulmonary arterial hypertension. Semin Respir Crit Care Med 30:376–385, 2009.

18. Wagenvoort CA, Wagenvoort N: Pulmonary hypertension: General remarks. *In* Wagenvoort CA, Wagenvoort N, (eds): Pathology of Pulmonary Hypertension (1st ed). New York: John Wiley & Sons, 1977, pp 9–16.
19. Heath D, Edwards JE: The pathology of pulmonary hypertensive disease. A description of six grades of structural changes in the pulmonary arteries with special reference to congenital cardiac septal changes. Circulation 18:533–547, 1958.
20. Wagenvoort CA, Wagenvoort N: Primary pulmonary hypertension. A pathologic study of the lung vessels in 156 clinically diagnosed cases. Circulation 42:1163–1184, 1970.
21. Galie N, Rubin LJ: Introduction: New insights into a challenging disease: A review of the Third World Symposium on Pulmonary Arterial Hypertension. J Am Coll Cardiol 43:S1, 2004.
22. Simonneau G, Galie N, Rubin LJ, et al: Clinical classification of pulmonary hypertension. J Am Coll Cardiol 43:S5–S12, 2004.

22a. Tuder RM, Abman SH, Braun T, et al: Development and pathology of pulmonary hypertension. J Am Coll Cardiol 54(1 Suppl):S3–S9, 2009.
23. Zaiman A, Fijalkowska I, Hassoun PM, et al: One hundred years of research in the pathogenesis of pulmonary hypertension. Am J Respir Cell Mol Biol 33:425–431, 2005.
24. Haworth SG, Rabinovitch M, Meyrick B, et al: Primary Pulmonary Hypertension: Executive Summary from the World Symposium—Primary Pulmonary Hypertension. Rich S (ed). 2–5. 1998. World Health Organization, Evian, September 6–10, 1998.
25. Pietra GG, Capron F, Stewart S, et al: Pathologic assessment of vasculopathies in pulmonary hypertension. J Am Coll Cardiol 43:25S–32S, 2004.
26. Tuder RM, Zaiman AL: Pathology of pulmonary vascular disease. *In* Peacock A, Rubin LJ, (eds): Pulmonary Circulation (2nd ed). London: Arnold, 2003, pp 25–32.
27. Barbera JA, Riverola A, Roca J, et al: Pulmonary vascular abnormalities and ventilation-perfusion relationships in mild chronic obstructive pulmonary disease. Am J Respir Crit Care Med 149:423–429, 1994.
27a. Montani D, Kemp K, Dorfmuller P, et al: Idiopathic pulmonary arterial hypertension and pulmonary veno-occlusive disease: similarities and differences. Semin Respir Crit Care Med 30:411–420, 2009.
28. Peinado VI, Barbera JA, Ramirez J, et al: Endothelial dysfunction in pulmonary arteries of patients with mild COPD. Am J Physiol 18:L908, 1998.
29. Gerhardt SG, Tuder RM, Girgis RE, et al: Pulmonary eosinophilia following lung transplantation for sarcoidosis in two patients. Chest 123:629–632, 2003.

CHAPTER 16

INJURY AND REPAIR OF THE LUNG

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Gregory P. Downey, MD • Marc Moss, MD

INTRODUCTION

CONCEPTS OF LUNG INJURY AND REPAIR

Lung Injury

Lung Repair

THE CLINICAL CONTEXT: HETEROGENEITY IN THE INJURY AND REPAIR PROCESS

Representative Example: ALI/ARDS

Physiology, Cell Biology, and Immunology of ALI

CAUSES AND MECHANISMS OF LUNG INJURY

Causes of Injury

Mechanisms and Pathways of Lung Cell Injury

Cell Death: Programmed Cell Death versus Toxic and Necrotic Cell Death

Protection of Cells from Damage

Assessing Programmed Cell Death

Manifestations of Lung Injury: Loss of Structure Leads to Loss of Function

Modeling Acute Lung Injury in Animals

REPAIR OF THE LUNG

Mechanisms and Pathways of Lung Cell Replacement

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Abnormal Cellular Repair

Does Lung Repair Recapitulate Lung Development?

INTRODUCTION

Much of pulmonary medicine is grounded in the concepts of injury and repair. However, neither of these terms is rigorously defined in the literature. Injury can be viewed at different levels—in the context of whole-organ function or at the level of individual cells or molecules. Similarly, repair can be considered at several levels—as a sequence of pathologic processes as in classical repair of a skin wound, at the level of single cell replacement, at the level of patching of holes physically torn in plasma membranes during injurious mechanical ventilation, and at the level of single molecules destroyed in the proteosome and replaced by new synthesis. Given this complexity and lack of consensus, we have provided our definition of the terms *injury* and *repair* with the aim of limiting what would otherwise be a very large subject. With this approach, we focus the discussion at a more conceptual level rather than on a detailed review of the primary literature. This chapter outlines challenges and questions that are inherent in the study of lung pathophysiology, and provides an overview of the essential concepts in lung injury and repair.

CONCEPTS OF LUNG INJURY AND REPAIR

The major physiologic function of the lungs is the uptake of oxygen and elimination of carbon dioxide from pulmonary capillaries. Respiratory failure reflects the inability of the breathing apparatus to provide adequate oxygenation of the arterial blood with or without adequate elimination of carbon dioxide. Dysfunction of various components of the respiratory system, alone or in combination, can result in respiratory failure, including in the airways (status asthmaticus), lung parenchyma (acute respiratory distress syndrome and acute interstitial pneumonitis), chest wall (trauma), and neuromuscular processes involved in respiration (Guillain-Barré syndrome).

Lung Injury

A broad definition of lung injury can be stated as: *the loss of normal lung function, structure, or architecture that results in respiratory failure or the inability of the lung to provide adequate oxygenation of the arterial blood and elimination of carbon dioxide.* Though deformities of the neuromuscular system and chest wall can result in alterations in oxygenation and carbon dioxide elimination, these disorders would not usually be considered to directly cause injury to the lung. We believe it is most appropriate to focus on lung structure and, in particular, to consider the issues of injury at the cellular and molecular level. Our concept of lung injury focuses primarily on cellular injury and destruction, with underlying diminution or loss of lung structure and function. Destruction here implies death of the cell, either by a variety of processes collectively termed *programmed cell death* and exemplified by apoptosis, or direct, externally mediated cell death, usually termed *necrosis.* Clearly, each of the more that 40 different types of cells known to reside in the lung performs individual functions, and injury should also be extended to abnormalities or loss of function to each type of cell, even if the cell is not overtly destroyed. In this chapter, we use as examples vascular endothelial cells, epithelial cells of the airways and alveoli, "interstitial" cells, nerves, and cells of the innate immune system. Loss or dysfunction of any of these cell types may also induce secondary effects on the tissue matrices, with further implications for overall lung function.

Whenever the term *injury* is used, we believe that the discussion should include specifics of what target is being injured, how the injury is mediated, how it is being assessed, and the overall effects on lung physiologic function. Thus we note as an example the attempt to define the concept of "acute lung injury" in animal models, which emphasize a multifaceted definition of lung injury that includes physiologic, histopathologic, and biochemical components.[1]

Lung Repair

The broad concept of lung repair includes *processes by which the function of the injured lung is restored to normal.* In regard to reparative processes, we focus on cellular aspects including replacement of both cells and supporting structures of the lung.

Repair and Homeostasis

The presumed function of reparative processes is to restore and maintain normal function (i.e., functional homeostasis). The healthy lung has an ample capacity to maintain its architecture and homeostatic activity through replacement of effete (expired) cells. In the absence of overt injury, the life span of lung cells (e.g., epithelial or endothelial cells) is thought to be long and their reparative potential high (see later). Under these conditions, *regeneration,* defined as complete restoration of any decline or abnormality of cell activity or numbers, would result in constant lung function over time[2] (Fig. 16-1, black line). However, the lung is a major portal to the environment and is exposed to diverse chemical and biologic agents that cause acute alterations in lung cellularity (i.e., loss of cell function or numbers). Normal aging can be viewed as a process in which steady and progressive declines in cell number and/or function reflect parallel decrements in the capacity of the epithelium or endothelium to heal itself (Fig. 16-1, blue line). Acute episodes of injury to the lung and its cellular and structural components, such as viral infection or chemical exposures, result in temporary fluctuations in lung function that reflect in part the ensuing response to exposure. *Repair,* therefore, can be defined as restitution of the cells and thus, the lung, to the preinjury level of structure and function. In aggregate, these processes would return the organ to a healthy state that is capable of responding to subsequent injuries (Fig. 16-1, green line).

Chronic lung disease is associated with a progressive loss of lung function that is exacerbated by environmental exposures. Individuals affected by chronic lung disease may be predisposed to repeated episodes of lung injury and may undergo cycles of injury that result in an accelerated decline in lung function (Fig. 16-1, yellow line). Chronic lung disease is often characterized by pathophysiologic alterations that can be considered *remodeling* processes, that is, fundamental alterations in cellular structure/function that modify interactions between the various types of cells. Classically, in the skin wound situation, this can involve the development of granulation tissue (inflammatory cells, fibroblasts, matrix deposition, neovascularization, etc.) that may or may not resolve to return the tissue to its original state. Similar processes occur in all tissues, including the lung.

Once a hypothetical functional threshold is reached (Fig. 16-1, red line), the lung may no longer have the

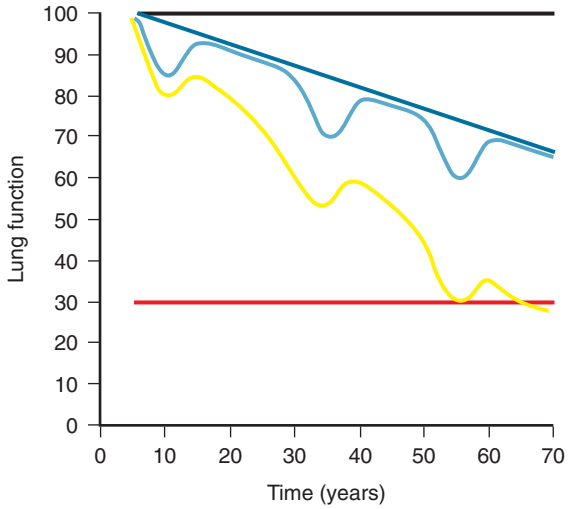

FIGURE 16-1 ■ Conceptual relationship between lung function and time. See text for discussion. (Adapted from Lazaar AL, Panettieri RA Jr: Is airway remodeling clinically relevant in asthma? Am J Med 115:652–659, 2003.)

capacity to repair itself and functionality is irreversibly lost. Under these conditions, an imbalance in the reparative capacity of adjacent tissues may result in *replacement,* that is, substitution of one tissue with another. A classic example of this is the development of fibrosis (sclerosis).

More Subtle Concepts of Injury and Repair

A more general concept of cellular injury might also include altered function such as secretion of surfactant, changes in the integrity of intercellular junctions, and effects of excessive biomechanical forces (stretch) on epithelial cells that may also lead to pathophysiologic effects but that may not be permanent (i.e., can be repaired without having to replace the cells). The effects of physical forces are of considerable importance in the lung, an organ that is constantly expanding and contracting, although these mechanisms are still poorly understood at the cellular and molecular levels.

Tissue Homeostasis and Cell Turnover

The underlying concept is that "injury" is occurring constantly but is normally mostly invisible due to protective and compensatory processes of avoidance or "repair." These processes range from blockade of the injurious stimulus to ongoing replacement of damaged and dead cells or structural components such as the basement membrane. As one of the key surfaces of the body that is exposed to the external environment, the respiratory tract is especially susceptible to environmental influences and injurious stimuli. Evolutionary forces have led to adaptation to this situation in other organs by creating rapidly replaceable and highly "plastic" structures such as the epithelium of the gut and skin. It is intriguing that the prevailing wisdom is that epithelial cells of the lung are long lived—a notion that may not be correct. The issue of rapidity of cell turnover has been addressed recently in cardiomyocytes (also considered to be long lived) utilizing an analysis based on the spike in radioactivity generated by atomic bomb testing in the 1950s. This analysis revealed a higher degree of turnover of these cells than had been formerly thought.[3] In fact, Shapiro and colleagues used this same approach to show that the lung matrix protein elastin turned over remarkably slowly.[4] However, lung cells were not examined.

Snapshot analyses of lung tissue from "normal" adult humans or experimental animals usually indicate only small scattered examples of replicating cells or of cells undergoing apoptosis (programmed cell death). Given the problems of sampling an organ such as the lung from tissue sections (one section usually represents only a minute percentage of the whole lung volume and only a single time point), the fact that evidence of cell turnover is detectable at all indicates a much higher degree of cellular turnover than used to be thought. Clearly this is an important area that needs more investigation with quantitative techniques and with attention to rates of turnover of the individual cell types. Thus we know that the resident alveolar macrophage (which is in fact located outside the body, i.e., on the surface of an exterior epithelium) is comparatively long lived (in comparison, for example, with macrophages at other sites in the body). In mice and dogs, the life span of these cells has been estimated in months, representing a significant proportion of the animal's life span. This raises questions about what maintains their persistence and the implications for the surveillance and protective functions of macrophages in the respiratory system.

Animal Models

It is important to recognize that much of our information about injury and repair comes from experimental animals, nearly all of which exhibit substantial differences from humans. This is especially important when we think about the plethora of human lung diseases that develop over years and in later life (e.g., after the lung has been in continuous operation for over 50 years). Most of our experimental animals are four footed, with consequently different lung orientation. The human upper respiratory tract is unique, as is the degree of mouth breathing by humans (most of our experimental animals are exclusive nose breathers, with significant implications for filtering and conditioning of the air that reaches the lower airways). Many studies are now carried out in mice, which, despite the high degree of common functional and evolutionary heritage with humans, differ from humans in many aspects. These differences should be carefully considered so that experimental observations in animals are not automatically applied to the human condition. Examples include the size, number of branches, composition, and vasculature of the airways. Mice have short airways, with a much higher proportion of bronchiolar structure and, allegedly, no bronchial circulation. However, there are many similarities between the anatomy (and presumable function) of small airways and subtended alveolar units between mice and humans, allowing cautious extrapolation of the results of experimental murine models to human disease.

THE CLINICAL CONTEXT: HETEROGENEITY IN THE INJURY AND REPAIR PROCESS

Many common pulmonary disorders, such as chronic obstructive pulmonary disease (COPD), interstitial lung diseases (ILDs), asthma, cystic fibrosis, acute lung injury (ALI), and the acute respiratory distress syndrome (ARDS), are characterized by injury to various cell types of the lung resulting in clinically significant physiologic abnormalities. The length of time from the onset of injury until the development of impairment depends on the intensity and duration of the insult. In ALI and ARDS, the degree of the initial injury is severe enough to result in respiratory failure over a period of hours or days. By contrast, patients with COPD usually require years of exposure to the offending agent (usually cigarette smoke in the developed world) prior to the development of

alterations in respiratory function. Finally, the clinical course of some lung diseases may reflect a complex mixture of both injury and repair. For example, patients with ILD often have a stuttering course with periods of rapidly declining lung function (thought to reflect injury to lung epithelium) interspersed with periods of relative quiescence (thought to reflect aberrant attempts at repair).

Representative Example: ALI/ARDS

ALI and its most severe form, ARDS, are frequent complications in critically ill patients and affect more than 200,000 individuals in the United States annually. Importantly, these conditions are responsible for significant morbidity and mortality, and the expenditure of more than $10 billion annually in direct health care costs.[5] Treatment of the underlying condition and excellent supportive care using "lung-protective" mechanical ventilation and conservative fluid management strategies contribute to successful clinical outcomes.[6] However, aside from the use of activated protein C[7] in the subset of ALI/ARDS patients with sepsis, and possibly treatment with glucocorticoids,[8] specific therapies are lacking and the cascade of events leading to ALI/ARDS, once in progression, is much less amenable to specific treatment.

Not all patients who are exposed to stimuli that can cause injury to the lung actually develop physiologic abnormalities. For example, smoking is the dominant risk factor for the development and progression of COPD; however, less than 25% of smokers develop COPD. Fortunately, not all critically ill patients develop ALI. Based on the results of several epidemiologic studies published over the last 2 decades, a variety of factors have been identified that can alter the susceptibility of an individual patient to the development of ALI. These factors can be separated into three general categories: the acute medical condition, preexisting acquired disorders, and genetic determinants (Fig. 16-2). The identification of such patient-specific characteristics could significantly improve both our understanding of the pathogenesis of ALI and our ability to care for these critically ill patients.

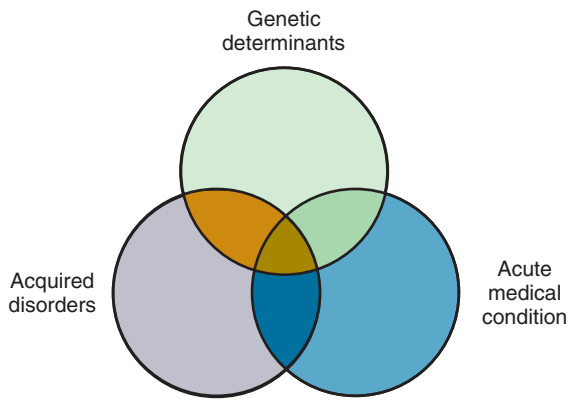

FIGURE 16-2 ■ Acute lung injury: clinical risk factors.

Characteristics of the Injurious Insult

The acute intensity of the injurious insult is a determining factor in the subsequent development of physiologic dysfunction in the lung. For example, acute damage to the lung caused by the inhalation of toxic agents can be caused by the accidental release of chemicals into an enclosed environment. The concentration of the toxic agent is a major determinant of the severity of the damage to the lung. Nitrogen dioxide is produced in silos and, when dissolved in water, creates nitrous acid and nitric acid, which are irritants to mucous membranes. Lower concentrations of nitrogen dioxide (50 to 100 ppm) can cause injury and the immediate onset of respiratory symptoms that may eventually be associated with the development of bronchiolitis obliterans. However, nitrogen dioxide concentrations of greater than 200 ppm can cause ALI and death within minutes. Another example showing the effect of the intensity of the insult is the increased likelihood of developing lung injury or pneumonitis from radiation exposure. The chance of developing radiation pneumonitis and the degree of impairment depend in part on the dose of radiation that is delivered, the dose per daily fraction, and the amount of lung volume that is treated.

For many types of injurious stimuli, the intensity and/or quantity of exposure correlates with the development of clinically significant pulmonary abnormalities. For example, longitudinal studies have shown accelerated decline in forced expiratory volume at 1 second (FEV_1) in a dose-response relationship to cigarette smoking, related to both the duration of smoking and the amount smoked. This dose-response relationship of pulmonary function with cigarette smoking accounts for the association of higher prevalence rates for COPD with increasing age. Similarly, in patients with cystic fibrosis, the number of acute exacerbations per year is strongly related to the decline in pulmonary function as measured by FEV_1. In ALI/ARDS, the number of transfusions or the severity of sepsis correlates with the risk for development of lung injury.

Characteristics of ALI/ARDS

Fowler and colleagues identified and monitored all patients who required mechanical ventilation for one of eight different conditions: cardiopulmonary bypass, burns, bacteremia, hypertransfusion, multiple long bone or pelvic fractures, disseminated intravascular coagulation, severe pneumonia, and aspiration of gastric contents.[9] In total, 88 of these patients developed ARDS, with an incidence ranging from 1.7% after cardiopulmonary bypass to 35.6% with pulmonary aspiration. Using a similar study design, Pepe and colleagues followed patients with a variety of diagnoses, including sepsis syndrome, aspiration of gastric contents, pulmonary contusion, hypertransfusion, and multiple fractures.[10] The incidence of ARDS among these at-risk diagnoses ranged from 8% for major fractures to 38% with sepsis syndrome.

These landmark studies identified several specific diagnoses that were common in critically ill patients and

were associated with an increased risk of developing ARDS (see Fig. 16-2). The majority of these patients can be classified into three common diagnoses: pneumonia, nonpulmonary sepsis, and aspiration of gastric contents. In one large population cohort study, pneumonia, severe sepsis, and witnessed aspiration accounted for 93% of the patients who developed ALI (46%, 36%, and 11%, respectively).[11] Major trauma was the fourth most common diagnosis associated with ALI. Additional studies have identified secondary factors that were associated with an increased risk for ARDS in trauma patients, including long bone fractures, chest trauma, and the requirement of blood transfusion during resuscitation. More recently, patients following pulmonary resection surgery were reported to be at increased risk for ARDS. In a study of 1139 patients who underwent lung surgery, 3.9% of the patients developed ALI or ARDS on average 4 days postoperatively.[12] Since lung surgery is a relatively common procedure, this relatively low percentage still represented nearly one new ARDS patient every 2 months following pulmonary resection at a single institution.

Preexisting Acquired Disorders

The presence of several preexisting medical disorders can modify the susceptibility to develop ALI in those patients who have developed one of the risk factors for ALI/ARDS described previously. Importantly, none of these conditions by itself is associated with the onset of ARDS. A history of alcohol abuse or dependence was the first reported comorbid condition that altered susceptibility to ARDS. In a study of 351 critically ill patients, 43% of the patients with a prior history of alcohol abuse developed ARDS, as compared with 22% in those patients without a history of alcohol abuse.[13] This initial association between alcohol abuse and an increased susceptibility for ALI/ARDS has been validated in several other populations, including patients with septic shock, critically ill patients requiring blood transfusions, surgical patients after lung resection, and intensive care unit patients in one epidemiologic survey in the Netherlands.[14–17]

Diabetes mellitus is another chronic medical condition that theoretically alters susceptibility for ARDS. Several different studies support the theory that proinflammatory cytokines, and more specifically the activation and recruitment of circulating neutrophils into the lung parenchyma, are an integral component of the pathogenesis of ARDS. The same alterations in the inflammatory cascade that predisposed diabetic patients to develop serious infections were hypothesized to be protective against the onset of ALI/ARDS. One study identified 113 patients with septic shock, of whom 28% had a history of diabetes.[18] In both univariate and multivariable analyses, the incidence of ARDS was significantly greater in the nondiabetic patients as compared with those who had a history of diabetes. These results also have been validated in a subsequent study of 688 patients at risk for ARDS, with a significantly reduced odds ratio for ARDS in patients with a history of diabetes (0.58).[19]

Older age has also been reported to be associated with an increased risk of developing ARDS, as it is for many different examples of lung injury and repair processes. Trauma patients over 70 were twice as likely to develop ARDS when compared to patients between 18 and 29 years of age.[20] Similarly, in patients with skin burns, increasing age has a positive association with ARDS.[21]

Several recent studies have reported that a delay in the initiation of specific therapies during the initial resuscitation period can also alter susceptibility for development of ALI/ARDS. In a study of 160 patients with septic shock, delayed initiation of early goal-directed therapy and antibiotic treatment during the first 6 hours were both independently associated with an increased risk for ALI/ARDS.[22] The delayed implementation of low tidal volume ventilation has also been reported to be a risk factor for ALI/ARDS. Several single-center studies and one secondary analysis of a large international survey have reported that the early use of high tidal volume is associated with the subsequent development of ALI/ARDS.[23] Finally, an association between the transfusion of blood products and the development of ALI/ARDS has been recognized for many years.[24]

Genetic Determinants

Discoveries about the genetic control of innate immunity and the inflammatory response have raised the question of whether polymorphic alleles of genes that encode cytokines and other mediators of inflammation can result in phenotypic differences in the host inflammatory response. These differences might account for some of the heterogeneity in individual susceptibility to develop ALI.[25] The possibility that genetic factors might be involved in the pathogenesis of ALI/ARDS was first raised when Marshall and colleagues reported an association between a specific polymorphism in the angiotensin-converting enzyme (ACE) gene and an increased mortality in patients with ARDS.[26] Experimental evidence suggests that activation of the pulmonary renin-angiotensin system might influence the pathogenesis of ARDS via mechanisms that include altered vascular permeability, vascular tone, and fibroblast activity, and by reducing alveolar epithelial cell survival and fibroblast activation. The human ACE gene (*DCP1*) is located on chromosome 17q23 and contains a restriction fragment length polymorphism consisting of the presence (insertion, I) or absence (deletion, D) of a 287-bp Alu repeat sequence in intron 16. Among 80 healthy white individuals, the I/D polymorphism accounted for 47% of the variance in plasma ACE, being highest in those with the DD genotype. When compared with a variety of controls, including patients with non-ARDS respiratory failure, those undergoing coronary artery bypass surgery, and the general population, the DD genotype frequency was highest in those patients with ALI/ARDS and was also associated with an increased ALI/ARDS-related mortality.

More recently, several other specific genetic polymorphisms have been associated with ARDS. Using the can-

didate gene approach, several studies have focused on the role of pre–B-cell colony-enhancing factor (PBEF), a cytokine involved in B-cell maturation, in the pathogenesis of ARDS. Of the 11 single nucleotide polymorphisms (SNPs) that were identified in the PBEF gene, the G allele of the 21001 T/G SNP both was associated with increased promoter activity and had a higher frequency in patients with sepsis-mediated ALI. In contrast, the T variant of the 21543 C/T SNP resulted in a twofold decrease in promoter activity and conferred protection from ALI. These two studies show that some of the differences in the degree of injury and the ability to repair the injured lung is related to genetic determinants. Ultimately, a clearer understanding of these genetic determinants will facilitate the development of more directed therapies that decrease the degree of injury and improve the reparative process in patients with ALI/ARDS.

Remarkably, the lung is capable of repairing the extensive amount of injury that occurs in most patients with ALI/ARDS. The majority of improvement in pulmonary physiologic measures and symptomatology occurs in the first 3 months after extubation. However, persistent respiratory symptoms and pulmonary function abnormalities are more common than initially appreciated in survivors of ALI/ARDS. Certain patients with ALI/ARDS are unable to normally repair their injured lungs and can develop persistent fibrotic changes in the lungs. Factors related to the severity of the ALI are the most accurate predictors of persistent respiratory compromise in survivors of ARDS, including increased fraction of inspired oxygen ($F_{I_{O_2}}$), higher levels of positive end-expiratory pressure, and decreased static pulmonary compliance during the acute clinical course of ARDS.

Physiology, Cell Biology, and Immunology of ALI

Common Pathway to ALI/ARDS

Regardless of the inciting event (acute medical condition), the clinical and pathologic manifestations of ALI/ARDS are similar, indicating the existence of common pathways that represent potential therapeutic targets.[27] ALI/ARDS reflects severe inflammatory injury to the endothelium and epithelium resulting in compromise of pulmonary barrier and transport functions leading to high-permeability pulmonary edema.[28]

Clinical and Pathologic Manifestations

Clinically, an initiating event (sepsis, shock, multiple transfusions, etc.) triggers a systemic inflammatory response with activation of macrophages, in turn leading to sequestration of large numbers of neutrophils in the lung. Histologically, ALI is characterized by large numbers of neutrophils in the vascular, interstitial, and alveolar spaces in association with endothelial and epithelial injury.[29] This, combined with the potential of neutrophils to induce tissue injury in diverse experimental systems, has led to the widely held concept that these potent phagocytes are central to the pathogenesis of ALI, a notion supported by numerous human and animal studies.[30] Further evidence points to specific pathogenic roles for neutrophil-derived microbicidal products, including reactive oxygen (O_2^-, H_2O_2) and nitrogen (NO, $ONOO^\bullet$) species and proteinases such as neutrophil elastase and matrix metalloproteinases. It is noteworthy that inflammation is inherently beneficial and may even actively participate in normal repair processes (see later); only when it becomes excessive or unregulated does host damage ensue.[31] Given the occurrence of ALI/ARDS in neutropenic patients, however, it is clear that other mechanisms also contribute to lung injury.[32]

Distinct Phases of Injury

Acute lung injury is a progressive and dynamic process that is characterized by distinct stages, each with different clinical, histopathologic, and radiographic features. The acute, or exudative, phase is characterized by the rapid onset of hypoxemic respiratory failure after an initiating event. Physiologically, at this stage the lungs have decreased compliance and there is significant ventilation-perfusion mismatch and shunting of venous blood, leading to profound arterial hypoxemia that is refractory to supplemental oxygen. The chest radiograph shows bilateral pulmonary infiltrates, which can be patchy or asymmetrical, and pleural effusions are often present. Importantly, studies involving computed tomographic scanning have revealed that the alveolar filling and atelectasis are not diffuse but rather tend to predominate in dependent lung zones with relative sparing of other areas. At this early stage, the histopathologic appearance is characterized by diffuse alveolar damage; the alveolar spaces are filled with protein-rich edema fluid, erythrocytes, neutrophils, and macrophages. Fibrin-rich hyaline membranes are prominent at this stage. This appearance reflects profound disruption of the integrity of the alveolar-capillary membrane, with loss of the barrier and transport functions of both the microvascular endothelium and epithelium.

Extent of Epithelial Injury Predicts Outcome

Injury to the distal lung epithelium is pivotal to the development of as well as the recovery from ALI. In fact, the extent of injury to the alveolar epithelium is an important predictor of the outcome of ALI/ARDS. In health, two types of alveolar epithelial cells exist in the lungs. Flattened type I cells form approximately 90% of the alveolar surface area and are most susceptible to injury. Cuboidal type II cells that are situated in the alveolar "corners" make up the remaining 10% of the alveolar surface area. Type II cells have several critical functions, including production of surfactant, ion and fluid transport, and—especially relevant to repair of the injured lung—proliferation and differentiation to type I cells after injury.

The loss of epithelial integrity and function in ALI is critically important not only to the genesis of pulmonary dysfunction, but also to repair of the injured lung. Under physiologic conditions, the alveolar epithelium is much

less permeable than the microvascular endothelium and, consequently, injury to the epithelium with loss of its barrier function contributes significantly to the formation of alveolar edema. Since alveolar epithelial cells contribute to fluid transport, injury to these cells also impairs the clearance of edema fluid from the alveolar space. Furthermore, dysfunction of alveolar type II cells compromises the production and turnover of surfactant, a factor that contributes to widespread atelectasis and further compromises the innate immune system of the lung. Lastly, the extent of injury to the alveolar epithelium has a major impact on repair of the injured lung.

In some patients, the acute phase of lung injury resolves completely, leaving these individuals with relatively normal lung function. However, in other patients, the process can be progressive, leading to diffuse pulmonary fibrosis with markedly diminished pulmonary compliance, persistent hypoxemia, and increased alveolar dead space. In the most severely affected individuals, pulmonary hypertension may develop, reflecting obliteration of the pulmonary capillary bed. The histolopathologic appearance of the lung in these patients includes the presence of excess collagen and other extracellular matrix proteins involving the alveolar and interstitial spaces, along with chronic inflammatory cells. In this phase, radiographic studies reveal diffuse interstitial linear opacities that are reflective of the fibrotic process. In addition, bullae and pneumothoraces sometimes occur.

Clinically, the recovery phase is characterized by gradual resolution of hypoxemia and radiographic infiltrates and improved pulmonary compliance. Interestingly, despite the presence of pulmonary fibrosis, the chronic phase resolves in many patients, and pulmonary function returns to normal.

CAUSES AND MECHANISMS OF LUNG INJURY

Causes of Injury

As would be expected for an organ that is open to the external environment, the lung is exposed to a wide variety of potentially injurious factors ranging from physical insults to infections to inhaled toxins or gases. In addition, the lung is also susceptible to injury from the vascular surface (e.g., blood-borne toxins or cell-derived products) as well as from mechanical effects generated during expansion and contraction. External insults will affect the epithelium with graded effects from the upper airways down to the alveolus, depending in particular on the physical size of the stimulus. Inhaled particles of less than 2 to 5 μm gain direct access to the alveolar surface, whereas larger particles are deposited in the airways, predominantly at bifurcations of the bronchial tree. However, materials inspired from the oropharynx reach all areas of the lung and can induce substantial epithelial injury. Hematogenous injury, initially to the endothelium, also occurs in many circumstances but particularly in sepsis, thrombotic conditions, and—perhaps more often than currently recognized—systemic autoimmune conditions. In most of these varied circumstances, the primary effects occur on the epithelial or endothelial cells.

A key contributor to lung injury, from either the vascular or epithelial surface, is the inflammatory process, including the effects of inflammatory mediators and the accumulation and activation of inflammatory cells. For example, Figure 16-3 depicts damage to endothelial and alveolar epithelial cells accompanying sequestration and activation of neutrophils in an acute inflammatory response. The process is usually associated with increased vascular and alveolar permeability (as illustrated in the figure), sometimes with sufficient damage to the alveolar wall to result in coagulation (fibrin) and erythrocyte accumulation in the air space. Importantly, in a "normal" and presumably protective local and self-limited inflammatory response, the fluid, debris, and other elements of the inflammation are rapidly removed and the epithelium and endothelium are quickly replaced and/or repaired. Inflammatory cells (e.g., neutrophils) can migrate into the alveolus in response to local chemoattractants without causing significant injury to the alveolar wall, unless they receive additional stimuli to release their toxic constituents.

Mechanisms and Pathways of Lung Cell Injury

Here again at the cellular level we encounter the issue of a reasonable definition of "injury." Externally or

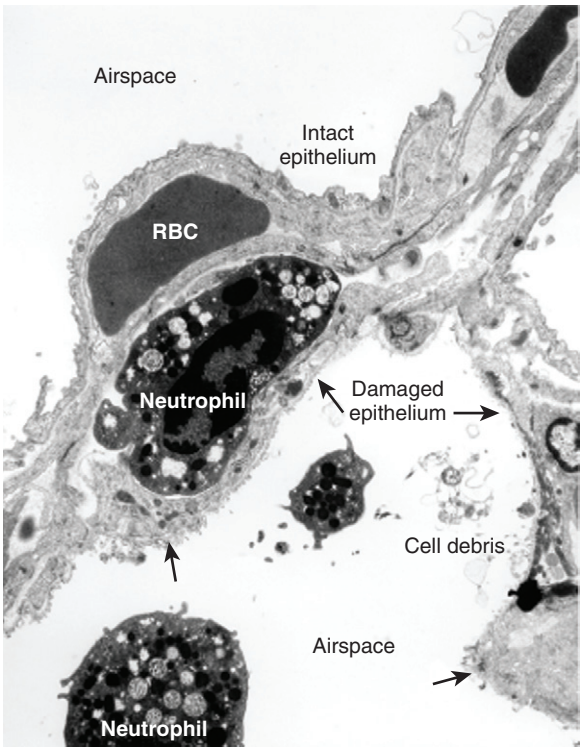

FIGURE 16-3 ■ Electron micrograph of inflammatory injury to the murine lung.

endogenously induced alterations of cell function could be considered injurious if they negatively affected the primary functions of that cell. For example, in broad terms, one key endothelial and epithelial function is maintenance of a barrier. Dysfunction would be manifest as increased permeability with egress of plasma constituents from the blood or access of environmental materials to the interstitium from the air spaces. Tight junctions between both epithelium and endothelium can "open" in response to stimuli or intracellular conditions without permanent destruction/death of the cells. In fact, such a transient permeability change is an important element of the host defense function of the inflammatory reaction and thus could be considered a physiologic response. This points out the fine line between what is often called injury, versus normal tissue responses—with a possible emphasis on how widely distributed the effect and how long the response persists. Local, transient barrier disruption and alveolar edema may thus occur to deal with a local inflammatory insult without substantial effect on whole-lung function, whereas the same mechanism applied across the entire tissue may lead to a condition (as in ALI/ARDS) that is clearly considered lung injury. However, in ALI/ARDS and such generalized inflammatory conditions, there is also overt epithelial cell death, so the concept of system-wide transient nonlethal cell "dysfunction" may be primarily hypothetical. Perhaps the most remarkable consideration is that, despite the myriad opportunities for damage, there is not more cellular injury or death in the lung, and/or that injury that does occur, perhaps all the time, is so readily and rapidly repaired that it is essentially invisible except in extreme situations.

Cell Death: Programmed Cell Death versus Toxic and Necrotic Cell Death

There has been a surge in interest in recent years about the mechanisms and importance of cell death, particularly the various forms of *programmed cell death* (PCD) in which processes intrinsic to the cell itself lead or contribute to death. Formerly, describing the mechanisms by which cells die fell largely to the pathologists and led to the recognition that cell death could be programmed (one form of which was termed *apoptosis*[33]). It is important to note that there are many forms of PCD,[34] so the term *apoptosis* is often used indiscriminately and thus erroneously in this regard. Originally a morphologic definition, apoptosis might best be defined currently not only on the basis of nuclear condensation and characteristic DNA fragmentation as well as other morphologic characters, but also based on its induction mechanisms and requirement for the action of a series of intracellular caspase proteases.

Many recent reviews address the various mechanisms and pathways leading to apoptosis and other forms of PCD.[34–37] However it is important to note two major pathways (as well as minor pathways) leading to apoptosis: the intrinsic pathway, involving signaling from the mitochondria; and the extrinsic pathway, deriving from signals generated from external stimulation of "death" receptors, usually members of the tumor necrosis factor receptor family such as Fas. The critical role played in apoptosis by the mitochondria cannot be overstated and has intriguing evolutionary implications, including pathways leading to cell death even in single-celled eukaryotes. In mammalian neutrophils, the mitochondria have essentially lost their energy-supplying function and could be considered primarily as an engine for the initiation of apoptosis in a cell that has an intrinsic life span of only a few hours. In other words, there are many ways by which cells may die, some arising from functional defects that cannot be repaired (e.g., DNA damage, the unfolded protein response, or an excessive autophagic response), and some from external stimuli.

Likewise, many different processes induce necrosis, that is, forms of cell death that do not normally require active participation of cellular processes and generally lead to disruption of the cell membrane with subsequent release of cellular contents. These would include physical effects of acid from inspiration of stomach contents, inhalation of toxic materials or fumes, infection with lytic viruses or bacterial products, mechanical disruption of cell membranes, and other effects.

Most forms of PCD, including apoptosis, are considered processes whose primary effect is silent (noninflammatory and nonimmunogenic) removal of cells from tissues. Normally the removal process is highly efficient, but if defective or overloaded, then apoptosis itself leads to loss of plasma membrane integrity and disruption of the cell—so-called secondary necrosis or post-apoptotic cytolysis. Because of the proinflammatory, and sometimes proimmunogenic, properties of intracellular constituents, this can lead to prolonged inflammation, as suggested in cystic fibrosis[38] or autoimmunity (as in systemic lupus erythematosus).

Protection of Cells from Damage

The lung has many mechanisms to protect cells from damage. The surfactant layer in the alveolus and the mucus barrier in the airways provide one such protection against external insults. A key issue for cells in the lung is the constant exposure to high oxygen tensions and oxidants, and lung cells contain abundant antioxidant defenses. The alveolar macrophages perform key scavenging functions for particles that do gain access to the alveolar compartment. An intriguing but understudied issue for the lung is the potential for mechanical injury to lung cells induced by the process of breathing. Studies in skeletal and cardiac muscle have shown that tears in the plasma membrane do occur in such mechanically stressed cells, and that there are substantial inbuilt repair processes involving the protein dysferlin that "plug" the holes with new membrane.[39] The effects of stretching can also be extended to other lung cell functions, and this is now receiving attention, for example, in the context of the potential damaging effects of mechanical ventilation with high tidal volumes as well as in normal breathing. PCD is also highly regulated and in many cases only occurs after the internal insult overcomes a threshold of the relative reparative or protective

activities. An example here is the autophagic response of cells to nutritional stress that can serve in the short term to keep the cell alive until the stress is relieved but that *in extremis* actually initiates PCD.

Assessing Programmed Cell Death

The inherent importance of cell injury and death in normal cell turnover and particularly in lung diseases implies a need to assess its presence. However, since these processes are part of normal tissue homeostasis, there are also potent mechanisms to either repair the cell or, if this is not possible, to remove it. Thus cells undergoing PCD are normally cleared so rapidly that it is hard to detect significant numbers of such cells in tissues, even if death and removal is actively ongoing.[40] For example, alveoli full of neutrophils in bacterial pneumonia can resolve the inflammation (i.e., clear these inflammatory cells) despite the fact that, at any given time, no more than 1% of the cells can be detected as apoptotic. This may lead to confusion, because the absence of detectable apoptosis does not necessarily mean cells are not dying and, in contrast, detectable apoptotic cells may reflect defective clearance mechanisms rather than increased cell death. These processes must be considered as well controlled and dynamic. A specific example may be in emphysema, where a number of investigators have shown increased numbers of detectable apoptotic cells in the pulmonary parenchyma that are likely to be both endothelial and epithelial cells. Whether this represents increased cell death or defective clearance, or both, is not clear. In emphysema, experimental evidence suggests that clearance processes are defective. Cigarette smoke can damage lung cells; however, the increase in numbers of apoptotic cells can be detected even years after a patient has stopped smoking. Therefore, if increased apoptosis is occurring, it must be attributed to other causes, or perhaps to persistence of toxins from earlier smoke exposure, or to an effect that only acts when the "long-lived" cells start to divide.

Manifestations of Lung Injury: Loss of Structure Leads to Loss of Function

There is increasing evidence for significant structural and functional interconnectivity between the various cellular layers of the alveolus.[41] This suggests that damage to the epithelium can be transmitted to interrelated injury to the endothelium as well as interstitial cells such as fibroblasts. Rapid repair of the cells might avoid significant damage to the alveolar matrix and thus preserve overall structure and function. However, injury to cells that is not readily reparable in an appropriate timeframe might also result in altered matrix, and derangement of the alveolar scaffold upon which cellular repair and maintenance of alveolar structure depend. These concepts tie together the proteolytic and cellular hypotheses of emphysema (destruction of the matrix versus epithelial or endothelial damage). Alterations in cell function, integrity, or presence can lead to overt manifestations of lung injury:

1. Alterations in alveolar-capillary barrier function with accumulation of alveolar exudate, as in ARDS
2. Accelerated cell death and/or loss of alveolar structure leading to loss of normal lung architecture, as in emphysema
3. Abnormalities of surfactant amount, composition, or function leading to altered structure through alveolar collapse
4. Dysfunction of the airways epithelium leading to abnormal mucus composition or amounts, ciliary function, etc.
5. Abnormal repair processes after injury, as in fibrosis of the airways or parenchyma

Each of these examples can lead to primary disruption of the gas exchange functions of the lung.

Modeling Acute Lung Injury in Animals

In humans, the diagnosis of ALI and ARDS is based on a well-defined set of clinical parameters that include: (1) acute onset of respiratory distress; (2) radiographic evidence of diffuse bilateral pulmonary infiltrates; (3) evidence of profound alterations in the gas-exchange function of the lung as assessed by the ratio of the arterial P_{O_2} to $F_{I_{O_2}}$ (ratio <300 mm Hg for ALI and <200 mm Hg for ARDS); and (4) absence of left ventricular dysfunction or other causes of elevated left atrial pressure (to exclude primary cardiogenic causes of pulmonary edema).[42] However, it is difficult to translate some of these criteria to experimental animal models. For example, although arterial blood gas analysis, radiographic assessment of pulmonary infiltrates, echocardiography, and even cardiac catheterization can all be performed in small animals, including mice, the equipment required to make all of these measurements is rarely available in all but the most highly specialized laboratories. Furthermore, the measurements are often incompatible with the design of experimental systems. Thus, it is not practical to use the human criteria in many experimental situations, particularly in studies involving small animals. An alternative approach is to define ALI in animals based on histopathologic criteria similar to those seen in humans with ALI and ARDS. In humans, the pathologic correlate of ALI/ARDS is diffuse alveolar damage (DAD), which is characterized by inflammatory infiltrates, thickened alveolar septae, and deposition of hyaline membranes. However, none of the available models of ALI in animals reproduces all the pathologic features of DAD. Therefore, the criteria used to define ALI and ARDS in humans should be translated to most animal models of ALI with appropriate caution.[1]

Feasible Assessment of Acute Lung Injury in Animal Models

The following represent the primary manifestations of pulmonary dysfunction that can be assessed in animal models of ALI.

Abnormalities of Gas Exchange. In humans, an elevated alveolar-to-arterial gradient, reflecting compromise of the gas-exchange function of the lungs, is one of the major parameters used to diagnose, stratify, and monitor patients with ALI/ARDS. While it is feasible to conduct arterial blood gas analysis in larger animals, it is more difficult in rodents and especially mice because of the difficulty obtaining a sufficient sample of arterialized blood. Noninvasive continuous monitoring of capillary or tissue oxygen saturation using conventional oximetry is a useful parameter to monitor if the appropriate instrumentation is available.

Decreased Lung Compliance. Decreased lung compliance due to pulmonary edema and atelectasis is a primary feature of human ALI/ARDS. It is important and easy to assess in animal models by determining the pressure-volume curve after a lung recruitment maneuver.

Assessment of Increased Permeability of the Alveolar-Capillary Membrane. This is a critical parameter and one that defines the pathophysiology of ALI in humans and in animal models. However, its measurement is subject to many potential technical difficulties that depend on the method used. The principal of this measurement is that, in ALI, the selective barrier function of the alveolar-capillary membrane (contributed to by the barrier functions of the pulmonary endothelium and epithelium) is compromised in response to injury. This is manifest by leakage of protein-rich fluid from the vascular to the interstitial and/or alveolar space and the accumulation of high-molecular-weight proteins that are normally excluded from the alveolar space. Many methods have been developed to assess lung permeability, but measurement of the concentration of albumin and higher molecular weight proteins in bronchoalveolar lavage fluid compared to their concentrations in plasma, and wet-todry weight of the excised lungs, are the most widely used.

Histologic Assessment of Lung Injury. One of the most challenging aspects of animal models of ALI is the histologic assessment of lung injury. In humans, the characteristic pathologic feature of ALI/ARDS is DAD. Key features of DAD include neutrophil accumulation in the vascular, interstitial, and alveolar spaces (evidence of an inflammatory response); deposition of hyaline membranes composed of fibrin and other proteinaceous debris (evidence of disruption of the alveolar/capillary membrane); interstitial thickening; and the formation of microthrombi (evidence of endothelial injury and intraluminal activation of the coagulation cascade). Animal models of ALI/ARDS should reflect some but not necessarily all of these features. It is important to bear in mind that some of the histologic features of human ALI/ARDS are not present or are present to a lesser degree in animal models of ALI, such as typical hyaline membranes and microvascular thrombi.

REPAIR OF THE LUNG

Repair of the damaged lung implies return to normal structure and function. In most cases of injury this would mean clearance of excess lung fluid; resorption of inflammatory exudate; removal of soluble and insoluble proteins, abnormal lipids, particles, and cell debris; apoptosis; removal of any inflammatory cells that have accumulated in response to the injury; and repopulation of the damaged structure with the appropriate cells and matrix. More persistent injury is often associated with fibroproliferative and neovasular responses (as in granulation tissue and wound healing in most sites in the body), which also has to be resolved if true repair is to be achieved, but which often may lead to more permanent scarring.

Mechanisms and Pathways of Lung Cell Replacement

Where do the replacement epithelial and endothelial cells come from? Studies completed in the 1970s clearly demonstrated that epithelial cells of the airways and alveolar space were replaced through proliferation and differentiation of endogenous lung progenitor cells.[43] These cells exhibit a secretory phenotype in the steady state, are most commonly referred to as airway Clara cells and alveolar type II cells, and function as the preferred precursor for replacement of injured cells. Some effort has been spent determining whether extrapulmonary cells can populate or replace injured epithelial cells. Although relevant for cell-based therapy for acute or chronic lung disease, the majority of studies failed to demonstrate functional restitution of the epithelium and/or significant epithelial reparative potential within the hematopoietic cell population.[44]

In contrast with the epithelium, repair of the endothelium can occur through two mechanisms. First, cells within existing vessels can act as progenitors for generation of new vessels. This process is termed *angiogenesis.* Alternatively, new vessels can form spontaneously through a process called *vasculogenesis.* This latter mechanism likely involves endothelial progenitor cells that are part of the hematopoietic cell lineage and are recruited to the injured lung.

Similar to the endothelium, the lung mesenchyme, which includes fibroblasts and smooth muscle, can be replaced by endogenous progenitors or recruited cells. Either cell type can contribute to productive repair of lung injury but may also participate in tissue remodeling under disease conditions. Several studies indicate that bone marrow–derived mesenchymal stem cells can modulate lung injury through regulation of inflammation. However, specific subtypes of bone marrow–derived cells may contribute to further lung injury. Consequently, more studies are needed to evaluate the pros and cons of lung cell replacement therapy focused on readily accessible cell sources such as the bone marrow.

Stem Cells, Constitutive Cell Turnover, and Reparative Cell Types

Hierarchies of Reparative Cells

The concept of injury and repair is fundamentally linked to the stem cell attributes of *mitotic potential* and

differentiation capacity. Mitotic potential has two components, the number of times a cell can undergo cell division and how these cell divisions are distributed over time. Differentiation potential is defined in terms of the number of differentiated cell types that can be generated by a mitotic cell.

Classical Stem Cell Hierarchy

Within a classical stem cell hierarchy (Fig. 16-4), the *stem cell* is defined as the reparative cell with the greatest mitotic and differentiation potential. A stem cell proliferates incrementally and thus distributes its mitotic potential over the life span of the organism. These attributes of "stemness" are controlled by interaction with the *stem cell microenvironment or niche.* The niche serves a protective function directed primarily toward sequestration of the stem cell from differentiation-promoting factors. Stem cell division produces two daughter cells whose fate is determined by interactions with the stem cell niche. *Symmetrical cell division* results in both daughter cells retaining contact with the niche and retention of these nascent cells as stem cells. This mechanism, which results in amplification of stem cell number, has been demonstrated in tissues with rapid cell turnover, such as the bone marrow and gut. In contrast, *asymmetric cell division* results in generation of one daughter cell that maintains contact with the niche and is retained as the stem cell. The second daughter cell loses contact with the niche and undergoes repeated cell division over a short period of time. This daughter cell is the founding cell for the *transit-amplifying* cell population. Transit-amplifying cells are transient constituents of the niche. They proliferate repeatedly over a short time period and withdraw from the cell cycle as they commit to a differentiation pathway. Thus, transit-amplifying cells serve to increase cell number and are destined to produce *terminally differentiated* cells. Terminally differentiated cells can have one or more phenotypes, constitute the majority of cells within a tissue, and provide functions characteristic of a specific tissue. Terminally differentiated cells are postmitotic and short lived. Thus, constant turnover of the terminally differentiated cell population acts as a stimulus for differentiation of transit-amplifying cells and resupply of this population via stem cell proliferation.

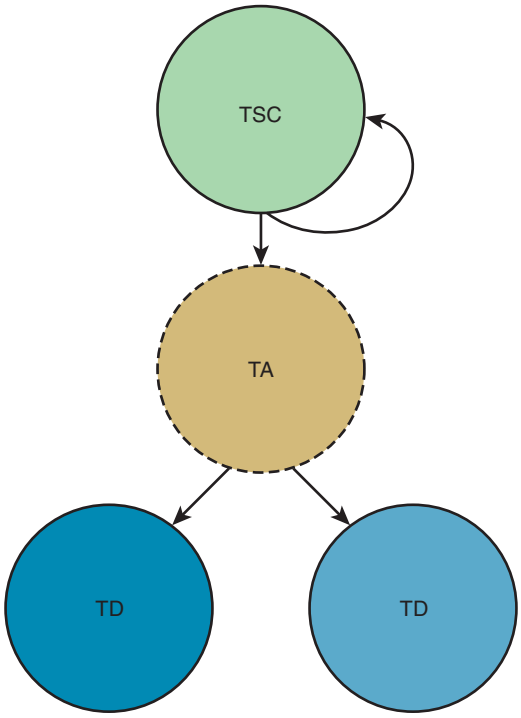

FIGURE 16-4 ■ Classical stem cell hierarchy: stem cell (TSC), transit-amplifying cell (TA), and terminally differentiated cell (TD).

Cells Involved in Lung Repair

Progenitor Cell. The term *progenitor cell* is a collective term used to describe any cell that has the capacity to proliferate. It is commonly used to indicate a cell that is in the process of cell division or has the potential to enter the cell cycle. The functional distinctions among lung progenitor cells are defined here.

Tissue-Specific Stem Cells. A tissue-specific stem cell is a rare cell type that is undifferentiated relative to its progeny. This cell has the capacity for unlimited self-renewal as a consequence of stable interactions with a stem cell niche. In the context of a hierarchy, the stem cell is defined as the reparative cell with the greatest mitotic and differentiation potential. Adult tissue stem cells have a differentiation potential equivalent to the cellular diversity of the tissue in which they reside.[45] Due to the relatively quiescent state of the pulmonary epithelium, lung stem cells are identified as cells that are activated in response to severe cell depletion. As a consequence of this experimental approach, the properties of lung stem cells must be viewed in the context of severe injury.

Tracheobronchial tissue-specific stem cells have been evaluated in humans and mice. These cells exhibit a low cuboidal to pyramidal morphology and are termed *basal cells.* Additional studies have suggested that the tracheobronchial tissue-specific stem cell resides within specialized microenvironments located at the submucosal gland duct junction and in intercartilagenous regions of the trachea and bronchial epithelium.[46] Within the bronchiole, tissue-specific stem cells have been identified within the neuroepithelial body and bronchiolar duct junction microenvironments. These cells are resistant to Clara cell–specific toxicants and express the molecular marker Clara cell secretory protein (CCSP).[43] Alveolar stem cells have not been identified. This deficiency is due in part to the lack of cell-selective injury methods that retain viability of the host. Several studies have used stem cell markers/activities such as telomerase, Hoechst efflux, label-retention, and CD43/Sca1 expression[47] to identify cells that fit one of the criteria used to define tissue-specific stem cells. These studies suggest that alveolar stem cells maintain individual alveolar saccules rather than broad regions of the parenchyma.

Facultative Progenitor Cell Pools. A facultative progenitor cell is one that exhibits differentiated features in the quiescent state yet has the capacity to proliferate for maintenance of normal tissue and in response to injury. In contrast with the bone marrow and gut, the lung epithelium is maintained and repaired under most conditions by an abundant, broadly distributed facultative progenitor cell pool. Facultative progenitor cells exist in two states: quiescent and reparative. In the steady state, facultative progenitor cells are nonmitotic and carry out differentiated functions necessary for tissue homeostasis. In response to injury, facultative progenitor cells dedifferentiate, enter the cell cycle, self-renew, and have a context-dependent probability of differentiating into regionally specific terminally differentiated cell types (ciliated epithelial cells and alveolar type II cells).[48–51] Pulmonary facultative progenitor cells are commonly known as the Clara cell and the alveolar type II cell (alveolus).[43]

Loss of Regenerative Potential: Depletion of the Facultative Progenitor Cell Pool

Multifunctional properties of pulmonary facultative progenitor cells also limit their ability to repair the injured epithelium. First, the metabolic pathways that allow the Clara cell to eliminate lipophilic agents also sensitize it to the toxic effects of these compounds.[52–54] Second, the phenotypic plasticity that is essential to the Clara cell's ability to detect and eliminate pathogens may compromise the reparative functions of this cell type.[55–57] Finally, repeated participation in epithelial repair may deplete the mitotic potential of the facultative progenitor cell pool. Depletion of this cell type would leave the epithelium deficient in both regenerative and differentiated functions and could result in a cascade of changes that contribute to epithelial fragility through loss of cellular autocrine/paracrine protective mechanisms, epithelial hypoplasia, and dysregulation of interactions between the epithelial, mesenchymal, and vascular compartments.

Histologic measures of the abundance of Clara cells and CCSP support the concept that the facultative progenitor cell type(s) are depleted in ALI and chronic lung diseases. These studies suggest that four processes lead to depletion of this critical cell type.

First, transition to a mucus-producing cell type may alter both progenitor function and cellular interactions. Within small airways of COPD patients and asthmatics, Clara cells undergo a metaplastic transition to a mucosecretory phenotype.[58] In severe disease, both Clara cells and mucosecretory cell types are depleted and the epithelium becomes hypoplastic.[59–61] Analysis of colony-forming cells within the human bronchial epithelium demonstrated that human mucus cells are postmitotic cells.[62] These data suggested that hyperplasia of mucus cells in the context of acute or chronic lung disease is a consequence of a phenotypic transition by non–mucus-producing cells.

Second, transition of progenitor cells from a facultative to an obligate progenitor state may also lead to depletion of reparative cells. Increased epithelial proliferation in lungs of smokers suggests an ongoing injury process and the potential for replicative senescence within the facultative progenitor cell pool.[63] Senescent cells persist and consequently inhibit activation of the remaining reparative cells. Thus, senescent cells would compromise differentiated functions while also acting to block cell replacement mechanisms.

Third, entry of the facultative progenitor cell into the cell cycle is accompanied by loss of differentiated functions such as secretion of CCSP or production of surfactant. Extensive analysis of CCSP levels in acute and chronic lung disease, including COPD, suggests that differentiated functions of the facultative progenitor cells are compromised[64,65] and that these cells are a direct target of toxic environmental agents. Thus, injuries that activate facultative progenitor cells may adversely affect protective mechanisms and render the epithelium susceptible to further injury.

Finally, defects in cellular maturation may also contribute to a failure to establish the facultative progenitor cell pool or to deplete it after injury. The lung undergoes extensive maturation during the postnatal period. The maturation process is interrupted by preterm birth and associated oxygen treatment, and is attenuated by postnatal exposure to environmental agents, including ozone and side-stream tobacco smoke in term infants.[66–68] These exposures are associated with depressed protective and reparative functions and morphologic and functional alterations to airway and alveolar facultative progenitor cells. These observations suggest an interaction between lung maturation and irritant exposure that leads to dysregulation of airway reparative processes.

These data support the concept that failure to establish or maintain an appropriately sized pool of facultative progenitor cells fosters environmentally induced chronic injury and repair cycles characteristic of lung disease. Hypoplasia of bronchial Clara cells is associated with tissue remodeling characterized by hyperplasia of an alternative progenitor, the basal cell, and consequent squamous metaplasia.[69–71] In contrast, Clara and alveolar type II cells are the sole progenitors of the bronchiolar and alveolar epithelium, respectively.[49,51] Depletion of either of these cell types leads to epithelial hypoplasia and remodeling of adjacent tissue compartments. Thus, changes in function and/or abundance of the facultative progenitor may be the nexus for the complex pathophysiologic alterations that occur in chronic lung diseases.

Gene-Environment Interactions in Lung Injury and Repair

The four Rs (regeneration, repair, remodeling, and replacement) are presented as distinct processes;

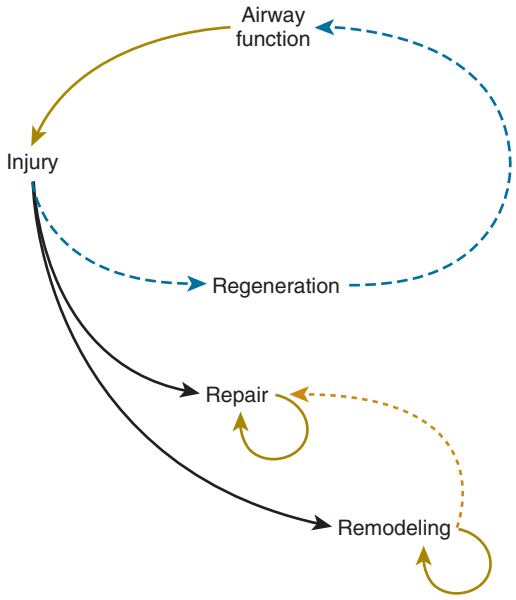

FIGURE 16-5 ■ Gene-environment interactions in lung injury, regeneration, repair, and remodeling. (Adapted from Lazaar AL, Panettieri RA Jr: Is airway remodeling clinically relevant in asthma? Am J Med 115:652–659, 2003.)

however, they are actually intertwined responses to acute or chronic lung injury[1] (Fig. 16-5). These relationships are modified by gene-environment interactions, the concept that genetic constitution determines the response to deleterious agents within the environment. Genetic predisposition has been associated with allelic variants that modify cellular susceptibility to environmental agents, including chemical (ozone, naphthalene) and bacterial (lipopolysaccharides, viral pathogens) agents. Such alleles can sensitize an individual to an initial or repeated injury but can also render him or her resistant to subsequent exposures through induction of tolerance.

Genotype is also a determinant of the cellular response to an agent. Specific genetic backgrounds are susceptible to metaplastic transitions such as conversion of airway secretory cells into a mucus-producing goblet cell phenotype (e.g., C57BL/6 vs. Balb/c strains of mice). Such transitions are associated with protection of the epithelium from further injury. Alterations in cellular phenotype may also extend to interactions between endogenous lung elements (epithelium, mesenchyme, nerves) and recruited elements such as inflammatory cells. Specific inbred strains of mice (e.g., C57Bl/6) are susceptible to bleomycin-induced inflammation and develop transient replacement of alveolar structures with mesenchymal cells (fibrosis). Thus, susceptibility to injury and the response to such an insult are determined by multiple factors, including the nature of the agent, dose and route of exposure, exposure history, and host genotype.

Abnormal Cellular Repair

The transition (transformation) of epithelial cells to a mesenchymal (myofibroblast) phenotype, termed *epithelial-mesenchymal transition* (EMT), is a key process in development as well as in pathologic processes such as neoplasia and fibrotic responses in the lung and other organs.[72] EMT involves the loss of epithelial phenotype, manifest by loss of intercellular junctions, cell spreading, and enhanced motility. This is accompanied by a loss of epithelial-specific proteins such as E-cadherin and cytokeratin and enhanced expression of mesenchymal proteins, including smooth muscle α-actin and vimentin. In the lung, EMT is believed to contribute to the peribronchial fibrosis that characterizes airway remodeling in chronic asthma and to fibrotic responses in the lung parenchyma, such as interstitial pulmonary fibrosis.[72,73]

Does Lung Repair Recapitulate Lung Development?

Numerous signaling processes are known to be involved in lung development (Wnt/β-catenin, notch-delta, sonic hedgehog-patched, FGF-FGFR, BMP/TGFβ).[74] These pathways are interactive and integrate formation and appropriate differentiation of tissues (epithelium, mesenchyme, vasculature) during lung development. During lung injury and repair, reactivation of many of these pathways has been reported. However, it is unclear whether integration of various signaling pathways occurs and whether this signaling results in productive cell replacement. An impediment to resolution of this question is the fact that analysis of damaged human lung tissue is descriptive at best, and cause and consequence usually cannot be separated. In contrast, analysis of signaling in animal models, which is the state of the art, relies on elimination of a specific pathway or profound mis-regulation of the targeted process. Consequently, feedback mechanisms are likely to be disrupted and may result in altered activation/inactivation of parallel or sequential signaling networks. Development of methods to simultaneously monitor alterations in multiple signaling cascades is needed to address this fundamental obstacle to understanding the molecular regulation of reparative processes.

KEY POINTS

- A typical definition of lung injury cites clinical endpoints that reflect decrements in gas exchange. But the mechanisms of injury are rooted in the cellular and molecular changes that *initiate* structural alterations and lead to compromised lung function.
  - Acute lung injury can be linked to specific inciting events, including infection, aspiration, and trauma, and results in decreased arterial P_{O_2}. At the tissue and cellular level, these stimuli result in increased vascular permeability and loss of alveolar epithelial barrier function consequent to cell alteration or death. These cellular changes result in edema which in turn compromises gas exchange.
  - Susceptibility to lung injury is determined by general health, previous exposures, and the individual's genetic constitution. This "gene-environment interaction" is the cornerstone of research initiatives directed at identification of susceptibility genes as well as those that modify the response to treatment.
- Repair of lung damage goes hand-in-glove with lung injury. The type of reparative process, be it cellular (migration, proliferation, metaplasia, or death) or molecular (metabolism, catabolism, macromolecule synthesis) is determined by the agent, dose, route, duration, and preexisting conditions within the lung. Consequently the reparative process reflects the current exposure in the context of past exposures.
  - The interface between the lung and the environment is reflected in a vast reparative capacity. Cells and macromolecules that are damaged are removed and replaced without disruption of lung function. This process occurs *silently* in normal individuals and is usually accompanied by processes that suppress both inflammation and incipient autoimmunity.
  - Tissue cell replacement is mediated primarily by facultative progenitor cells: those that perform critical homeostatic functions but retain the capacity to proliferate in response to injury. These cells are abundant and broadly distributed thereby forming a defensive shield against cellular injury.
  - Tissue-specific stem cells maintain themselves and have the capacity to regenerate all cell types within a specific tissue type. Such cells have been identified in the lung epithelium, endothelium, and mesenchyme of animals following extensive injury.
- When injury exceeds the ability of the lung to repair, a cascade of events results in remodeling of the target tissue as well as disruption of the interactions between adjacent tissues including the immune system. These *imbalances* may result in an exaggerated response that perpetuates the initial injury. One result of such lung remodeling is fibrotic lung disease which exhibits elements of epithelial, mesenchymal, and immune system disruption.

References

1. Matute-Bello G, Frevert CW, Martin TR: Animals models of acute lung injury. Am J Physiol Lung Cell Mol Physiol 295:L379–L399, 2008.
2. Lazaar AL, Panettieri RA Jr: Is airway remodeling clinically relevant in asthma? Am J Med 115:652–659, 2003.
3. Bergmann O, Bhardwaj RD, Bernard S, et al: Evidence for cardiomyocyte renewal in humans. Science 324:98–102, 2009.
4. Shapiro SD, Endicott SK, Province MA, et al: Marked longevity of human lung parenchymal elastic fibers deduced from prevalence of D-aspartate and nuclear weapons-related radiocarbon. J Clin Invest 87:1828–1834, 1991.
5. Rubenfeld GD, Herridge MS: Epidemiology and outcomes of acute lung injury. Chest 131:554–562, 2007.
6. Calfee CS, Matthay MA: Nonventilatory treatments for acute lung injury and ARDS. Chest 131:913–920, 2007.
7. Levi M: Activated protein C in sepsis: A critical review. Curr Opin Hematol 15:481–486, 2008.
8. Peter JV, John P, Graham PL, et al: Corticosteroids in the prevention and treatment of acute respiratory distress syndrome (ARDS) in adults: Meta-analysis. BMJ 336:1006–1009, 2008.
9. Fowler AA, Hamman RF, Good JT, et al: Adult respiratory distress syndrome: Risk with common predispositions. Ann Intern Med 98(5 Pt 1):593–597, 1983.
10. Pepe PE, Potkin RT, Reus DH, et al: Clinical predictors of the adult respiratory distress syndrome. Am J Surg 144:124–130, 1982.
11. Rubenfeld GD, Caldwell E, Peabody E, et al: Incidence and outcomes of acute lung injury. N Engl J Med 353:1685–1693, 2005.
12. Licker M, de Perrot M, Spiliopoulos A, et al: Risk factors for acute lung injury after thoracic surgery for lung cancer. Anesth Analg 97:1558–1565, 2003.
13. Moss M, Bucher B, Moore FA, et al: The role of chronic alcohol abuse in the development of acute respiratory distress syndrome in adults. JAMA 275:50–54, 1996.
14. Moss M, Burnham EL: Chronic alcohol abuse, acute respiratory distress syndrome, and multiple organ dysfunction. Crit Care Med 31(4 Suppl):S207–S212, 2003.
15. Licker M, Spiliopoulos A, Morel D, Chevalley C: Postextubation severe bronchospasm and hypotension triggered by exposure to a disinfectant spray. Anesthesiology 99:739–741, 2003.
16. Gajic O, Rana R, Winters JL, et al: Transfusion-related acute lung injury in the critically ill: Prospective nested case-control study. Am J Respir Crit Care Med 176:886–891, 2007.

17. Wind J, Versteegt J, Twisk J, et al: Epidemiology of acute lung injury and acute respiratory distress syndrome in The Netherlands: A survey. Respir Med 101:2091–2098, 2007.
18. Moss M, Guidot DM, Steinberg KP, et al: Diabetic patients have a decreased incidence of acute respiratory distress syndrome. Crit Care Med 28:2187–2192, 2000.
19. Gong MN, Thompson BT, Williams P, et al: Clinical predictors of and mortality in acute respiratory distress syndrome: Potential role of red cell transfusion. Crit Care Med 33:1191–1198, 2005.
20. Hudson LD, Milberg JA, Anardi D, Maunder RJ: Clinical risks for development of the acute respiratory distress syndrome. Am J Respir Crit Care Med 151(2 Pt 1):293–301, 1995.
21. Dancey DR, Hayes J, Gomez M, et al: ARDS in patients with thermal injury. Intensive Care Med 25:1231–1236, 1999.
22. Iscimen R, Cartin-Ceba R, Yilmaz M, et al: Risk factors for the development of acute lung injury in patients with septic shock: An observational cohort study. Crit Care Med 36:1518–1522, 2008.
23. Gajic O, Frutos-Vivar F, Esteban A, et al: Ventilator settings as a risk factor for acute respiratory distress syndrome in mechanically ventilated patients. Intensive Care Med 31:922–926, 2005.
24. Silliman CC, McLaughlin NJ: Transfusion-related acute lung injury. Blood Rev 20:139–159, 2006.
25. Gong MN: Genetic epidemiology of acute respiratory distress syndrome: Implications for future prevention and treatment [Abstract]. Clin Chest Med 27:705–724, 2006.
26. Marshall RP, Webb S, Bellingan GJ, et al: Angiotensin converting enzyme insertion/deletion polymorphism is associated with susceptibility and outcome in acute respiratory distress syndrome. Am J Respir Crit Care Med 166:646–650, 2002.
27. Ware LB, Matthay MA: The acute respiratory distress syndrome. N Engl J Med 342:1334–1349, 2000.
28. Lee WL, Downey GP: Neutrophil activation and acute lung injury. Curr Opin Crit Care 7:1–7, 2001.
29. Bachofen M, Weibel ER: Structural alterations of lung parenchyma in the adult respiratory distress syndrome. Clin Chest Med 3:35–56, 1982.
30. Martin TR: Neutrophils and lung injury: Getting it right. J Clin Invest 110:1603–1605, 2002.
31. Nathan C: Points of control in inflammation. Nature 420:846–852, 2002.
32. Ognibene FP, Martin SE, Parker MM, et al: Adult respiratory distress syndrome in patients with severe neutropenia. N Engl J Med 315:547–551, 1986.
33. Kerr JF, Wyllie AH, Currie AR: Apoptosis: A basic biological phenomenon with wide-ranging implications in tissue kinetics. Br J Cancer 26:239–257, 1972.
34. Galluzzi L, Maiuri MC, Vitale I, et al: Cell death modalities: Classification and pathophysiological implications. Cell Death Differ 14:1237–1243, 2007.
35. Green DR, Ferguson T, Zitvogel L, Kroemer G: Immunogenic and tolerogenic cell death. Nat Rev Immunol 9:353–363, 2009.
36. Pinheiro da Silva F, Nizet V: Cell death during sepsis: Integration of disintegration in the inflammatory response to overwhelming infection. Apoptosis 14:509–521, 2009.
37. Kim I, Xu W, Reed JC: Cell death and endoplasmic reticulum stress: Disease relevance and therapeutic opportunities. Nat Rev Drug Discov 7:1013–1030, 2008.
38. Vandivier RW, Fadok VA, Hoffmann PR, et al: Elastase-mediated phosphatidylserine receptor cleavage impairs apoptotic cell clearance in cystic fibrosis and bronchiectasis. J Clin Invest 109:661–670, 2002.
39. Han R, Campbell KP: Dysferlin and muscle membrane repair. Curr Opin Cell Biol 19:409–416, 2007.
40. Henson PM, Tuder RM: Apoptosis in the lung: Induction, clearance and detection. Am J Physiol Lung Cell Mol Physiol 294:L601–L611, 2008.
41. Sirianni FE, Chu FS, Walker DC: Human alveolar wall fibroblasts directly link epithelial type 2 cells to capillary endothelium. Am J Respir Crit Care Med 168:1532–1537, 2003.
42. Bernard GR, Artigas A, Brigham KL, et al: The American-European Consensus Conference on ARDS: Definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med 149(3 Pt 1):818–824, 1994.
43. Stripp BR, Reynolds SD: Maintenance and repair of the bronchiolar epithelium. Proc Am Thorac Soc 5:328–333, 2008.
44. Weiss DJ, Berberich MA, Borok Z, et al: Adult stem cells, lung biology, and lung disease. NHLBI/Cystic Fibrosis Foundation Workshop. Proc Am Thorac Soc 3:193–207, 2006.
45. Morrison SJ: Stem cell potential: Can anything make anything? Curr Biol 11:R7–R9, 2001.
46. Engelhardt JF: Stem cell niches in the mouse airway. Am J Respir Cell Mol Biol 24:649–652, 2001.
47. Rawlins EL, Hogan BL: Epithelial stem cells of the lung: Privileged few or opportunities for many? Development 133:2455–2465, 2006.
48. Evans MJ, Cabral-Anderson LJ, Freeman G: Role of the Clara cell in renewal of the bronchiolar epithelium. Lab Invest 38:648–653, 1978.
49. Evans MJ, Dekker NP, Cabral-Anderson LJ, Freeman G: Quantitation of damage to the alveolar epithelium by means of type 2 cell proliferation. Am Rev Respir Dis 118:787–790, 1978.
50. Evans MJ, Johnson LV, Stehens RJ, Freeman G: Renewal of the terminal bronchiolar epithelium in the rat following exposure to NO_2 or O_3. Lab Invest 35:246–257, 1976.
51. Evans MJ, Shami SG, Cabral-Anderson LJ, Dekker NP: Role of nonciliated cells in renewal of the bronchial epithelium of rats exposed to NO_2. Am J Pathol 123:126–133, 1986.
52. Plopper CG, Macklin J, Nishio SJ, et al: Relationship of cytochrome P-450 activity to Clara cell cytotoxicity. III. Morphometric comparison of changes in the epithelial populations of terminal bronchioles and lobar bronchi in mice, hamsters, and rats after parenteral administration of naphthalene. Lab Invest 67:553–565, 1992.
53. Plopper CG, Suverkropp C, Morin D, et al: Relationship of cytochrome P-450 activity to Clara cell cytotoxicity. I. Histopathologic comparison of the respiratory tract of mice, rats and hamsters after parenteral administration of naphthalene. J Pharmacol Exp Ther 261:353–363, 1992.
54. Buckpitt A, Buonarati M, Avey LB, et al: Relationship of cytochrome P450 activity to Clara cell cytotoxicity. II. Comparison of stereoselectivity of naphthalene epoxidation in lung and nasal mucosa of mouse, hamster, rat and rhesus monkey. J Pharmacol Exp Ther 261:364–372, 1992.
55. Larson SD, Plopper CG, Baker G, et al: Proximal airway mucous cells of ovalbumin-sensitized and -challenged Brown Norway rats accumulate the neuropeptide calcitonin gene-related peptide. Am J Physiol Lung Cell Mol Physiol 287:L286–L295, 2004.
56. Evans CM, Williams OW, Tuvim MJ, et al: Mucin is produced by clara cells in the proximal airways of antigen-challenged mice. Am J Respir Cell Mol Biol 31:382–394, 2004.
57. Tesfaigzi Y: Roles of apoptosis in airway epithelia. Am J Respir Cell Mol Biol 34:537–547, 2006.
58. Jeffery PK: Remodeling in asthma and chronic obstructive lung disease. Am J Respir Crit Care Med 164(10 Pt 2):S28–S38, 2001.
59. Shijubo N, Itoh Y, Yamaguchi T, et al: Clara cell protein-positive epithelial cells are reduced in small airways of asthmatics. Am J Respir Crit Care Med 160:930–933, 1999.
60. Mattsson J, Remberger M, Andersson O, et al: Decreased serum levels of Clara cell secretory protein (CC16) are associated with bronchiolitis obliterans and may permit early diagnosis in patients after allogeneic stem-cell transplantation. Transplantation 79:1411–1416, 2005.
61. Zhang Y, Wroblewski M, Hertz MI, et al: Analysis of chronic lung transplant rejection by MALDI-TOF profiles of bronchoalveolar lavage fluid. Proteomics 6:1001–1010, 2006.
62. Engelhardt JF, Schlossberg H, Yankaskas JR, Dudus L: Progenitor cells of the adult human airway involved in submucosal gland development. Development 121:2031–2046, 1995.
63. Miller YE, Blatchford P, Hyun DS, et al: Bronchial epithelial Ki-67 index is related to histology, smoking, and gender, but not lung cancer or chronic obstructive pulmonary disease. Cancer Epidemiol Biomarkers Prev 16:2425–2431, 2007.
64. Broeckaert F, Clippe A, Knoops B, et al: Clara cell secretory protein (CC16): Features as a peripheral lung biomarker. Ann N Y Acad Sci 923:68–77, 2000.
65. Mutti A, Corradi M, Goldoni M, et al: Exhaled metallic elements and serum pneumoproteins in asymptomatic smokers and patients with COPD or asthma. Chest 129:1288–1297, 2006.

66. Szefler SJ: Asthma progression: Can we and should we measure it? J Allergy Clin Immunol 121:598–600, 2008.
67. Bisgaard H, Szefler S: Prevalence of asthma-like symptoms in young children. Pediatr Pulmonol 42:723–728, 2007.
68. Rabinovitch N, Strand M, Gelfand EW: Particulate levels are associated with early asthma worsening in children with persistent disease. Am J Respir Crit Care Med 173:1098–1105, 2006.
69. Chilosi M, Poletti V, Zamò A, et al: Aberrant Wnt/beta-catenin pathway activation in idiopathic pulmonary fibrosis. Am J Pathol 162:1495–1502, 2003.
70. Voynow JA, Fischer BM, Roberts BC, Proia AD: Basal-like cells constitute the proliferating cell population in cystic fibrosis airways. Am J Respir Crit Care Med 172:1013–1018, 2005.
71. Wang H, Liu X, Umino T, et al: Cigarette smoke inhibits human bronchial epithelial cell repair processes. Am J Respir Cell Mol Biol 25:772–779, 2001.
72. Kim KK, Kugler MC, Wolters PJ, et al: Alveolar epithelial cell mesenchymal transition develops in vivo during pulmonary fibrosis and is regulated by the extracellular matrix. Proc Natl Acad Sci U S A 103:13180–13185, 2006.
73. Königshoff M, Balsara N, Pfaff EM, et al: Functional Wnt signaling is increased in idiopathic pulmonary fibrosis. PLoS One 3:e2142, 2008.
74. Cardoso WV: Molecular regulation of lung development. Annu Rev Physiol 63:471–494, 2001.

CHAPTER 17

HISTORY AND PHYSICAL EXAMINATION

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INTRODUCTION

Taking a careful and complete history and performing a thorough physical examination are hallmarks of the good internist and one of the distinguishing characteristics of a master clinician. The initial visit sets the tone of the immediate and future relationship with the patient and begins the process of diagnosing and managing the illness: a dynamic encounter with each of the patient's responses stimulating further probing and diagnostic hypotheses formation. The physician must be attentive to the patient's story, piecing together each bit of evidence to form a tentative preliminary diagnosis and differential diagnoses. Nothing should escape the eyes and ears of a watchful diagnostician. History taking is more than information gathering: it affords the opportunity to observe the patient's reactions as the inquiry proceeds. At this stage, no symptom or circumstance should be disregarded. With an understanding of biology and medicine coupled with past experience, the physician tries to connect the salient parts of the patient's story to develop a plausible explanation of the physiologic or pathologic events that lead to illness.

Although striving for a single diagnosis, the physician should realize that more than one disease may be present and that rare diseases are diagnosed only by those who consider them. Nevertheless, the maxim "uncommon presentations of common diseases are more frequent than common presentations of uncommon diseases" is likely to be true. It is important to continue both to gather information and to be open to reforming the diagnostic hypothesis as more information becomes available. Premature judgment or the failure to continue considering reasonable alternatives after an initial diagnosis is made is the single most common diagnostic error.[1,2]

Bayes' theorem implies that diagnostic tests will have a higher yield if their prior probability is high. Specific details from the history raise the probability of different diagnoses and direct further tests in a productive manner. Further diagnostic investigations—imaging, blood tests, pulmonary function studies, and even parts of the physical examination—depend on the history. Historic clues raise or lower probabilities, thereby improving the value of subsequent questions and evaluations. Test results plus findings from the history and physical examination may confirm or refute the main and differential diagnoses, setting up either management or need for an alternative hypothesis.

The assessment and plan, at the end of the initial write-up, should identify problems and a course of action that takes into account the patient's concerns and questions. The patient should feel satisfaction that the physician has done a thorough job of exploring his or her complaints, has provided a plausible explanation for them, and has planned a reasonable course of action.

Electronic Medical Record

The electronic medical record now allows documents of higher quality than written records, owing to improved organization, increased readability, use of supplementary

material, and better comparisons. It eliminates poor handwriting and lost or misplaced information. Additional benefits include cost saving for storage, easy accessibility, and quick transfer to another health care provider.[3] The electronic medical record facilitates a coordinated team approach and reduces duplication of tests. Patients with complicated illnesses often have several different physicians and electronic records can make it easier for one team to follow what another team is doing. Easy accessibility to a complete record is especially important in emergency situations for physicians who are unfamiliar with the presenting patient. Common electronic medications lists and reminders can save time and reduce errors. Electronic prescriptions provide greater patient safety.

Writing directly into the medical record, or initially through a word-processing program, makes a cogent summary and chronological story easier to produce. The ability to insert information where it belongs helps maintain a congruous timeline. Spelling and grammar checks and autocorrection of abbreviations should make the finished report an easily readable document.

The disadvantages of electronic medical records include "information overload" and potential loss of privacy. Software downtime can be crippling. Learning how to use the software and developing typing skills may require training. Most electronic medical record word processing software is less efficient than commonly used commercial word processing software.

The "cut-and-paste" technique, beginning where the last visit left off, both saves time and ensures that ongoing problems are not overlooked. The problem with the cut-and-paste approach is that too much and irrelevant information may get deposited and duplicated in the medical record. Such excess text can at times replace essential information and impair easy understanding and critical reasoning. Cutting-and-pasting of information from consultants and other involved persons should never substitute for one's own primary history gathering or clinical thought. Cutting-and-pasting information gathered by someone else implies agreement with the statements. Proofreading is essential, especially of electronic prescriptions, because of the different doses and means of delivery of certain drugs.

Transfer of electronic medical information is not foolproof. Patients and physicians find it easy and convenient to communicate and transfer information by email, but there is a risk that the record of these interchanges may not get placed in the patient's permanent medical record or may be the cause of misunderstanding. Physicians may send patients electronic copies of their record, but if these are in a word processing format, patients could alter the record for secondary gain. Many of these concerns could have medicolegal consequences.[3]

Communication Skills

The ability to listen skillfully, and to communicate clearly and empathetically with the patient, is the foundation for the physician-patient relationship. Communicating effectively with patients and peers underlies the success of a physician. The physician's communication should be objective, nonjudgmental, and empathic. Physicians are often better at obtaining medical information than they are at understanding how the illness affects the patients.[4]

Communication contains both verbal and nonverbal interactions.[5] A calm atmosphere, relaxed setting, and ample time are essential, particularly when disclosing bad news,[6] but even then, a physician with good communication skills should be able to make the patient pleased that she or he saw the physician. This can be accomplished by always stating the truth but by cushioning bald facts with hope. When realistic, the physician might say that the cancer was caught early, provide reassurance about a probable good outcome, or suggest a specific therapy.

MEDICAL INTERVIEW

There is much more to the medical history than a recitation of questions and recording of answers. Instead, the medical interview has been defined as the entire medium of patient-physician interaction.[7] From this interactive experience, both physicians and patients learn about each other: the knowledge shared and feelings imparted influence subsequent trust, understanding, concern, and adherence to the health plan. Experience is valuable in the acquisition of clinical pattern recognition and in cumulative clinical knowledge. Although interviewing skills can be systematically learned,[8] acquiring the art of adept history taking and physical examination is a lifelong process that is incrementally improved by careful practice.

The main purposes of the medical interview are to (1) gather useful information, (2) develop rapport, (3) respond to concerns, and (4) educate the patient. The ease with which patients can access information may lead to a more active role on their part. Patients may be well informed or misinformed about their actual or perceived diagnoses. Whatever their knowledge, most patients want to be accurately informed about their condition and to be involved in the deliberations and decision making.[9] At the same time, they generally want their physician to direct their health care in a reasoned manner. This entails taking into account the patients' background knowledge, prejudices, and culture in a sensitive manner. The physician's plan should take into account the individuality of the patient.

Encouraging the patient to take the lead in expressing his or her symptoms and relationships to these symptoms forms the basis for the patient-centered interview[10] and develops appropriate rapport. Even in this era of reliance on laboratory studies, Platt's[11] original claim that a diagnosis can be obtained by history taking alone in most patients has been reaffirmed by several subsequent investigations.[12–14]

Chief Complaint and Present Illness

The medical history has traditionally been subdivided into the chief complaint; present, past, family, and social histories; and systems review. Because of its relevance

and importance in the evaluation of patients with known or suspected pulmonary diseases, the occupational history is included as a separate component of the social history. Travel history, also included in the social history, is helpful in diagnosing certain lung diseases.

Only the chief complaint stands alone as a discrete response to a single question. It is generally recommended that the chief complaint be written in the patient's own words, lest the doctor's interpretation be substituted prematurely for the patient's unique concern. Each chief complaint must be explored in detail, and the resulting aggregate of information constitutes the history of the present illness. The various elements of the remainder of the history are sorted into their proper categories after the interview has been completed. The resulting history of present illness is a cogent chronological story that incorporates all the facts and their relationships that support the preliminary diagnosis and differential diagnoses. Although an open-ended and free-flowing encounter, the interview still should be focused and organized. Each new question is often linked to the answer to the previous one. At the end, the review of systems is a series of questions designed to cover previously unexamined territory.

Major Pulmonary Symptoms

Because dyspnea, cough, and chest pain are among the most common reasons for patients to visit physicians, and because these symptoms may result from serious underlying chest disease, careful questioning is needed to establish their etiology and significance. The anatomic and pathophysiologic basis of these cardinal symptoms is provided in Chapters 28 through 30. To aid the interviewer in obtaining a medical history, a brief overview of dyspnea, cough, and chest pain, as well as of hemoptysis, a corollary complaint is provided in this section.

Dyspnea

When healthy persons increase their physical activity, they eventually become aware of their breathing; if they increase the level of activity even further, this awareness increases and the sensation becomes progressively more unpleasant, until it finally causes them to slow down or stop.[15] Although dyspnea, shortness of breath and breathlessness are often used interchangeably, as in Chapter 28, some purists use the term dyspnea only when the symptom is abnormal, which implies that the awareness is disproportionate to the stimulus and that the sensation is pathologic. Many patients describe their breathing discomfort as "breathlessness," but many others will complain only of "tightness," "choking," "inability to take a deep breath," "suffocating," "can't get enough air," and occasionally even "tiredness."

The mechanisms that underlie the sensation of dyspnea remain poorly understood, and are reviewed in Chapter 28. In contrast to pain and cough, for which specific receptors and neural pathways have been identified, similar detailed knowledge is lacking for dyspnea, although evidence is mounting that links the symptom with pain.[15,15a] Studies of the neurophysiology of dyspnea are further complicated by the lack of objective tools to quantify a subjective sensation that has considerable interindividual variation. Rating instruments—such as the Borg scale,[16] and questionnaires, such as the British Medical Research Council questionnaire,[17] and Pulmonary Functional Status and Dyspnea Questionnaire[18]—have been validated as useful in measuring dyspnea. Self-administered, computerized versions of the Transitional Dyspnea Index (TDI) and Multidimensional Baseline Dyspnea Index (BDI) appear to be at least as good as interview questioning for this assessment.[19] Progress, though, is being made: recent studies have clearly shown that dyspnea during exercise in patients with chronic obstructive pulmonary disease (COPD) is closely linked to dynamic lung hyperinflation.[20]

Clinical Features. Patients with respiratory, cardiac, hematologic, metabolic, and neuromuscular disorders may all complain of dyspnea. A careful and detailed history is necessary to uncover the cause of the sensation. In addition, it is important to document the impact of the symptom on the patient's daily activities and to be alert to the "decreased activity phenomenon." The latter describes patients who say their dyspnea has not worsened, but only because they now walk more slowly or no longer climb stairs or engage in athletic activities. Sometimes, this slowing down occurs so gradually, patients may not be aware of it or attribute to aging. Assessing the activity required to bring about the dyspnea is important. How many stairs can be climbed before stopping? How far can someone walk on level ground at her or his own pace without stopping? Does talking on the phone, getting dressed, or eating cause dyspnea? Is the patient short of breath at rest?

The course over time should be noted. Sudden dyspnea without an obvious provocation suggests pulmonary embolism or pneumothorax, although myocardial ischemia and asthma also may have a rapid onset. Dyspnea caused by cigarette smoke, dusts, molds, perfumes, newly cut grass, cats, and strong odors is characteristic of the increased bronchial reactivity seen in asthma. Associated features, such as wheezing and the presence and type of chest tightness or pain, are important clues. Worsening dyspnea with cough productive of increased quantities of purulent sputum, occurring over 1 to 3 days, characterizes an exacerbation of COPD.

Special types of dyspnea are sufficiently distinctive to warrant separate designations. Episodes of breathlessness that wake persons from a sound sleep, *paroxysmal nocturnal dyspnea*, usually denote left ventricular failure, but may also occur in patients with chronic pulmonary diseases because of pooling of secretions, gravity-induced decreases in lung volumes, sleep-induced increases in airflow resistance, or nocturnal aspiration. *Orthopnea*, the onset or worsening of dyspnea on assuming the supine position, like paroxysmal nocturnal dyspnea, is found in patients with heart disease and chronic lung disease. Measurement of amino-terminal pro-B-type natriuretic peptide has proved useful in differentiating between a cardiac or a respiratory origin in patients with dyspnea.[21]

The inability to assume the supine position (*instant orthopnea*) is characteristic of paralysis of both leaves of the diaphragm. Dyspnea soon after assuming the supine position also may be associated with other conditions, such as arteriovenous malformation, bronchiectasis, and lung abscess. *Platypnea* denotes dyspnea that occurs in the upright position and *trepopnea*, an even rarer form of dyspnea that develops in either the right or the left lateral decubitus position, suggest lung vascular shunting. Both the terms *hyperpnea*, an increase in minute ventilation, and *hyperventilation*, an increase in alveolar ventilation in excess of carbon dioxide production, indicate that ventilation is abnormally increased. Neither term, however, carries any implication about the presence or absence of dyspnea.

Cough

The quantity of bronchial secretions produced each day by a nonsmoking healthy adult is not precisely known, but it is sufficiently small to be removed by mucociliary action alone: healthy persons seldom cough.[22] As described in Chapter 29, coughing is an essential mechanism that protects the airways from the adverse effects of inhaled noxious substances and defends the lungs by clearing excess secretions.[23] Coughing can be occasional, transient, and unimportant. By contrast, it may indicate the presence of severe intrathoracic disease.

Clinical Features. Most episodes of coughing are associated with short-lived upper respiratory tract infections or allergies, and patients, recognizing this, seldom visit their doctors. Nevertheless, cough is the most common complaint for which patients seek medical attention and the second most common reason for having a general medical examination.[24] Physicians should realize that when patients seek their help for cough, it is often out of concern for something new, different, and alarming about the symptom. The essential first step in evaluating a patient with cough is to obtain a thorough history, paying particular attention to the following aspects: acute or chronic, productive or nonproductive, character, time relationships, type and quantity of sputum, and associated features. It is noteworthy that, of the various components of the workup used by the authors of a systematic anatomic investigation to determine the causes of chronic cough, the medical history alone led to the correct diagnosis in 70% of 102 patients.[24]

Acute coughing is frequently associated with nasopharyngitis, laryngotracheobronchitis, or other, usually virus-induced, upper respiratory tract infections. Less commonly, it may be the chief manifestation heralding the onset of viral or bacterial bronchopulmonary infection or the inhalation of allergenic or irritating substances. The causes of cough that persisted for 3 weeks or longer in 102 patients were postnasal drip (41%), asthma (24%), gastroesophageal reflux (21%), chronic bronchitis (5%), and bronchiectasis (4%).[24] Other important but less common conditions were eosinophilic bronchitis[25] and the use of angiotensin-converting enzyme inhibitors.[26] The importance of the "big three"—postnasal drip, asthma, and gastroesophageal reflux—was verified by the results of another survey of the causes of chronic cough.[27] Not everyone agrees, however, and some experts claim that emphasis on the top three conditions is unwarranted and, moreover, that it stifles interest and research into other important causes and mechanisms of chronic cough.[28]

A careful history of patients with cough lasting at least 3 months revealed that nearly all the patients misdiagnosed as "psychogenic" had one of the conditions listed previously for chronic cough.[29] Even cough that is made worse with psychological stress is often caused by lung disease. Patients with exaggerated cough responses or habit cough may have a "psychogenic" component; nevertheless, even when chronic cough has a pulmonary etiology, it may respond to behavioral modification.[30]

Most physicians have heard that cough may be the initial signal of lung cancer; the diagnostic axiom that any change in the character or pattern of a chronic cough in a smoker demands a prompt chest radiographic evaluation for lung cancer bears remembering. Less well known is that cough may be the sole presenting manifestation of asthma[31] or gastroesophageal reflux disease.[32]

In low-income countries of the world, where the great majority of the global population lives, cough, usually productive but not always, of 3 weeks or longer has been the traditional (and reliable) clinical marker of possible pulmonary tuberculosis that should trigger examination of sputum specimens for *Mycobacterium tuberculosis*. Recent recommendations by partners of the Tuberculosis Coalition now include cough of "2 or 3 weeks," or longer, as an indication for sputum examination.[33]

Among the many complications of persistent or recurrent cough are tussive syncope; retinal vessel rupture; persistent headache; chest wall and abdominal muscle strains, including the development of abdominal wall hernia[34]; and even rib fractures. Severe chronic cough may cause devastating personal distress, causing patients to restrict their social and professional activities because of it.

Hemoptysis

The expectoration of any amount of blood denotes hemoptysis. Every patient with new-onset or appreciable hemoptysis deserves a thorough diagnostic workup, which generally includes computed tomography (CT) of the thorax and bronchoscopy. For centuries, hemoptysis was considered pathognomonic of pulmonary tuberculosis, a view that is summarized in the Hippocratic aphorism "the spitting of pus follows the spitting of blood, consumption follows the spitting of this and death follows consumption."[35] The frequency of the different conditions that cause hemoptysis depend to a large extent on the population studied, but bronchitis, lung cancer, tuberculosis, and bronchiectasis are usually the most common causes.[36–38] These are also the causes massive hemoptysis (defined in various series as >200 to >600 mL of blood in 24 hr). Lung cancer and bronchitis usually cause mild to moderate bleeding, whereas patients with bronchiectasis, lung abscess, fungal disease, and bleeding diathesis are more likely to have severe

bleeding.[36] Less common conditions associated with hemoptysis include arteriovenous malformations, broncholithiasis, foreign bodies, aspergilloma, mitral stenosis, trauma, anticoagulation excess, pulmonary hemorrhage syndromes, heart failure, pneumonia, and Wegener's granulomatosis.

Clinical Features. Prompt workup, beginning with a thorough history, is required in all patients. It is important to determine where the blood is coming from. Surprisingly, patients may not always be able to distinguish hemoptysis from hematemesis and nasopharyngeal bleeding. Vomiting blood may follow a prolonged coughing episode. Patients may swallow or aspirate blood from the upper airway. Some patients report only that the blood "welled up" in their throats. Others will say that it is mixed with sputum. Hematemesis can usually be differentiated from hemoptysis by the presence of symptoms of gastrointestinal involvement, such as nausea and vomiting, a history of peptic ulcer disease, alcoholism, or signs of cirrhosis; when in doubt, esophagoscopy is indicated.

Following physical examination, a chest radiograph and (often) a thoracic CT are required. Depending on the magnitude of the blood loss and the clinical circumstances, bronchoscopy is indicated to determine the location of the bleeding. Although these studies generally reveal which region of the lungs is the source, the cause of hemoptysis cannot be determined in 20% to 30% of cases.[39] Recent radiologic advances, particularly multidetector computed tomographic (MDCT) angiography, which enhance identification of the actual bleeding vessel, whether systemic or pulmonary, have greatly helped the interventionist when embolization is required to stop the bleeding.[40]

Chest Pain

Various types of chest pain are extremely common; their mechanisms and clinical patterns are described in Chapter 30. Chest pain is one of the most common symptoms that cause the sufferer to seek medical attention. Because there is no clear relationship between the intensity of the discomfort and the importance of its underlying cause, all complaints of chest pain must be carefully considered. The recent development of dedicated chest pain centers within emergency departments has improved the diagnosis, treatment, and survival of patients with this always troublesome symptom.[41]

Clinical Features. Pleurisy, or acute inflammation of the pleural surfaces, usually causes chest pain that has several distinctive features. Pleuritic pain is usually localized—nearly always on one side or the other—and tends to be distributed along the intercostal nerve zones. Pain from diaphragmatic pleurisy is often referred to the ipsilateral shoulder and side of the neck. The most striking and important characteristic of pleuritic pain is its clear relationship to respiratory movements. The pain may be variously described as "sharp," "burning," or simply "a catch," but it is typically worsened by taking a deep breath, and coughing or sneezing causes intense distress. Patients with pleurisy frequently also experience dyspnea because the aggravation of their pain during inspiration makes them conscious of every breath.

Acute pleuritic pain is found in patients with spontaneous pneumothorax, pulmonary embolism, and pneumonia, especially pneumococcal pneumonia, whereas a gradual onset over several days is observed in patients with tuberculosis; an even slower development is characteristic of primary or secondary malignancies. Chronic pleuritic pain is characteristic of mesothelioma. It may be difficult to distinguish pleuritic pain from the pain of a rib fracture, although point localization favors the latter. Pericardial pain is typically sharp, retrosternal in location, and relieved by sitting up and leaning forward.

The distribution and the superficial, knifelike quality of the pain of intercostal neuritis or radiculitis may resemble pleural pain because it is worsened by vigorous respiratory movements but, unlike pleurisy, not by ordinary breathing. A neuritic origin may be suggested by the presence of lancinating or electric shock–like sensations unrelated to movements, and hyperalgesia or anesthesia over the distribution of the affected intercostal nerve provides confirmatory evidence. In many instances of new-onset, neuritic chest wall pain, the diagnosis becomes clear a day or two later when the typical vesicular rash of herpes zoster breaks out.[42]

Among the most important types of chest pain is that of myocardial ischemia, which is usually caused by coronary artery atherosclerosis. These attacks, which are provoked by an inadequate oxygen supply to the myocardium, span a continuum of severity from chronic stable angina to classic acute myocardial infarction. Typical anginal pain is induced by exercise, heavy meals, and emotional upsets; the pain is usually described as a substernal "pressure," "constriction," or "squeezing" that, when intense, may radiate to the neck or down the ulnar aspect of one or both arms.[43] Pain from variant or Prinzmetal's angina is similar in location and quality to typical anginal pain but occurs in cycles at rest rather than during stressful episodes.[44] Both typical and variant types of angina are relieved by coronary vasodilator drugs, such as nitroglycerin. Typical angina also decreases with rest or removal of the inciting stress.

By contrast, the pain of acute myocardial infarction, although similar in location and character to anginal pain, is usually of greater intensity and duration, is not alleviated by rest or by nitroglycerin, may require large doses of opiates, and is often accompanied by profuse sweating, nausea, hypotension, and arrhythmias. During attacks of myocardial ischemia and myocardial infarction, patients are often short of breath from associated pulmonary edema, which may be severe, but the pain itself is not related to breathing. Pain similar to that of myocardial ischemia also occurs in patients with aortic valve disease, especially aortic stenosis, and other noncoronary heart disease and noncardiac disorders.

Inflammation of or trauma to the joints, muscles, cartilages, bones, and fasciae of the thoracic cage is a common cause of chest pain.[45] Redness, swelling, and soreness of the costochondral junctions is called Tietze's syndrome. All of these disorders are characterized by point tenderness over the affected area.

Most pulmonary thromboembolism is not associated with chest pain. The hallmark of pulmonary infarction, however, is typical pleuritic pain. Both acute and chronic causes of pulmonary hypertension may be associated with episodes of chest pain that resemble the pain of myocardial ischemia in their substernal location and pattern of radiation and in their being described as "crushing" or "constricting."[46] This type of chest pain is believed to result from right ventricular ischemia owing to impaired coronary blood flow secondary to increased right ventricular mass and elevated systolic and diastolic pressures or to compression of the left main coronary artery by the dilated pulmonary artery trunk.

Family and Social Histories

The family history provides important clues to the presence of heritable pulmonary diseases, such as cystic fibrosis, alpha$_1$-antitrypsin deficiency, hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu disease), immotile cilia syndrome, and immunodeficiency syndromes. Careful history taking also can uncover even more common familial disease associations, which are polygenic or in which the exact mode of genetic transmission has not yet been established. As the genetic profiles of more diseases are being uncovered, the family history assumes an even more important function. The family history should encompass at least three generations to account for sex-linked traits. Family history also can identify exposures such as to tuberculosis or other contagious diseases.

Of course, no evaluation of pulmonary symptoms is complete without a detailed history of smoking habits. The physician should ask, "Have you ever smoked?" A negative answer should prompt a confirmatory response such as, "So you are a lifelong nonsmoker?" and a complement if the second answer is yes. If the patient has smoked, the next questions should be, "When did you start?" "When did you quit?" and "How much did you smoke while you were at it?" Ask also about different forms of tobacco and exposure at home or workplace to other peoples' tobacco smoke. A history of exposure to environmental smoke is also important.[47] In many developing countries, smoke from indoor cooking and heating fires is a major cause of lung disease, especially in women. Risk factors for infection by the human immunodeficiency virus, such as homosexual activity, multiple sexual partners, transfusions, and injection drug abuse, should be specifically queried.

Medications and Allergies

A complete list of all medications is essential to a thorough history. Ideally, the patient should bring in all his or her medications and the physician should carefully go through each one, checking that the prescription has been properly written and filled and that the patient understands the benefit and possible side effects of each medicine. It is vital to note whether the patient has ever had an allergic or toxic reaction and what these reactions were. A complete listing of supplements and herbals should also be recorded and checked for potential interaction with medications. No drug history is complete without assessing whether the patient drinks alcoholic beverages or uses illicit drugs. The amount and frequency of their use should be recorded.

Occupational History

The occupational history, which is often included as part of the social history, is an integral part of a thorough medical interview. Unless a relationship is established between an occupationally related lung disease and the patient is removed from the exposure, the disease is likely to progress and may cause irreversible damage. Moreover, accurately diagnosed work-related illness can allow justifiable compensation for the patient and correction of the exposure by the industry.

The workup of suspected occupational lung disease is discussed in Chapters 64 through 66. Although only a few questions are asked in most initial medical interviews, if occupational illness is seriously considered, a detailed inquiry about each industry, profession, and job the patient has held needs to be carried out.[48,49] Because there are so many environmental agents and different illness, the diagnostician should consult online agencies such as the National Institute for Occupational Safety and Health (NIOSH), the Environmental Protection Agency (EPA), Hazardous Substances Data Bank, Occupational Safety and Health Administration (OSHA), or other online resources to learn more about the putative environmental toxicant.[50,51]

Travel History

The sites of residence help with the diagnosis of endemic fungal diseases, especially histoplasmosis and coccidioidomycosis. A history of recent travel may help establish the possibility of exposure to other infectious diseases, because several are restricted to specific geographic regions.[52] The physician should inquire into the duration of travel. Knowing about air travel is important because symptomless deep venous thrombosis, which can lead to pulmonary embolism, is reported to occur in up to 10% of passengers on long-haul flights.[53] It is important to consider events after travel: symptoms of pulmonary thromboembolism and infarction occur a variable time after the inciting event. The recent onset of severe acute respiratory syndrome (SARS) in Southeast China and its rapid spread throughout the world by airline passengers emphasizes the importance of obtaining a careful travel history.

Past History

Many pulmonary diseases tend to recur (e.g., tuberculosis), and new diseases may complicate old ones (e.g., bronchiectasis as a sequela of necrotizing pneumonia). Information about previous illnesses, operations, and trauma involving the respiratory system may be essential to understanding the current problem. Although these data may be gathered as part of past medical history,

much of the pertinent information will be absorbed into the chronological sequence of the history of present illness. An important aid in the evaluation of a patient with an abnormal chest radiograph is a previous radiograph for comparison. Patients should be asked to bring in past films, but if unavailable, physicians should make every effort to obtain them, because old radiographs may save needless costly and dangerous interventions.

Questionnaires, Computer-Assisted and Nursing History

Printed or computer-based questionnaires and histories taken by nurses or allied health professionals are often used to expedite history taking. They can identify problems that can be explored further in the medical interview. They are often used in certain clinical settings, such as preoperative anesthetic evaluation. Occupational questionnaires have been shown to enhance recognition of occupational illness and correlate well with the findings of an industrial hygienist.[54] Computer-based interviews can gather more information, allow more time to complete the interview, uncover sensitive information, and may be adaptable to persons speaking a language different from that of the physician and those with hearing impediments.[55]

These forms of information gathering should be considered adjuncts and not a substitute for the thorough history taken by the physician. The limitations of the programmed questions are that the patient may not understand or be able to express her or his concerns when confined by a form that does not allow the free exploration of symptoms that the open interview does. It, of course, lacks the benefits gained from the patient-physician interaction, such as the establishment of rapport and the ability to observe nonverbal behavior. The interview time is also important for the physician to fully comprehend the patient's illness and to contemplate the primary and differential diagnoses.

For monitoring the course of certain disorders such as asthma, daily recording of symptoms, such as wheezing and breathlessness, and objective assessments of severity of disease, such as peak expiratory flow, in a diary are preferable to a single questionnaire because recall of symptoms may be faulty and one measurement may not be representative. The electronic monitoring that now comes as standard equipment with most home noninvasive ventilation devices gives the date and time of the respiratory events and the use of these devices.

PHYSICAL EXAMINATION

Sadly, the declining emphasis on proficiency in physical examination during medical school and residency training and the ever-increasing reliance on technology-based diagnosis have led to a decreased interest in, some say even the "demise" of, the physical examination.[56] However, the old observation that 88% of all diagnoses in primary care were established by taking a thorough medical history and performing a complete physical examination[57] probably still holds today. At the very least, a carefully executed history and physical lead to more intelligent and cost-effective use of diagnostic technology. Plus, a physical examination can be performed virtually anywhere, may provide important information, lends itself to serial observations, and increases patients' confidence in their physicians.

Examination of the Chest

Physical examination of the chest employs the four classic techniques of inspection, palpation, percussion, and auscultation. Each is described subsequently, as are the constellations of abnormalities that allow the examiner to infer the presence and type of various pulmonary disorders. Apart from inspection, which is not only a visual, but also sometimes an olfactory and always a structured cognitive skill, the other three modalities depend on the generation and the perception of sound or tactile sensations and vibrations. As was true of the history, the environment in which the physical examination occurs must be appropriate to the needs of both the examiner and the examined. Privacy, warmth, good light, and quiet are all essential. The best light source is natural sunlight, which should be used if possible. An ill-lit, noisy, or distracting environment will likely result in a physical examination that is flawed or incomplete.

Inspection

The physical examination begins the moment the clinician first sees the patient, even before the introductions and beginning the medical interview. Keen observations, and the ability to pursue and interpret these observations, are the keys to skilled clinical diagnosis.

Inspection of the chest is carried out after sufficient clothing has been removed and the patient has been suitably draped to permit observation of the entire thorax. Ordinarily, inspection is performed with the patient sitting, but if the patient is too weak or cannot sit unaided, he or she should be supported in this position. Observing the shape and symmetry of the chest allows such abnormalities as kyphoscoliosis, pectus excavatum, pectus carinatum, ankylosing spondylitis, gynecomastia, and surgical scars or defects to become obvious.

Several classic patterns of ventilation can be readily recognized (Fig. 17-1). For example, *tachypnea*, which is almost uniform rapid shallow breathing; *Kussmaul's breathing*, which is relentless, rapid, and deep breathing (air-hunger); *Cheyne-Stokes respirations*, a cyclical waxing and waning of the depth of breathing with regularly recurring periods of apnea; and *Biot's breathing*, which is totally irregular breathing, both the size of breaths and the periods of apnea, which are sometimes prolonged. Impending respiratory failure from muscle fatigue can be detected by observing rapid shallow breathing, abdominal paradoxical motion, and alternation between rib cage and abdominal breathing, so-called *respiratory alternans*.[58] Hoover's sign is the paradoxical

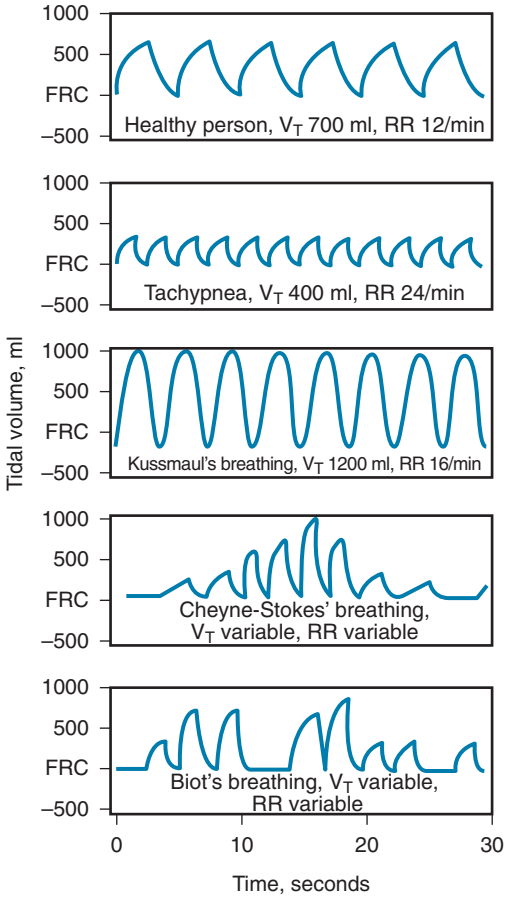

FIGURE 17-1 ■ Schematic drawing of different patterns of breathing. FRC, functional residual capacity, the normal lung volume at the end of expiration; RR, respiratory rate; VT, tidal volume.

inward displacement of the costal margin at the end of inspiration or throughout inspiration. Decreased regional ventilation can often be detected be seeing a lag in the motion of the affected part of the chest wall during breathing.

Palpation

Palpation of the thorax is a necessary part of the cardiac, breast, and lymph node examinations and often can detect bony abnormalities, such as a cervical rib, and subcutaneous calcinosis seen with systemic sclerosis. It is essential in examining causes of pain to determine point tenderness and thoracic spinal tenderness. It can detect fluctuant areas associated with empyema necessitans and crepitant areas associated with subcutaneous emphysema. Location by palpation of the trachea in the suprasternal notch is a useful way to detect shifts of the mediastinum. A spastic back muscle can be palpated as firm to identify a cause of pain. A lag in movement of the chest wall, suspected from inspection, can be confirmed by placing the two hands over opposite portions of each hemithorax and both feeling and observing whether or not the thorax moves symmetrically.[59] Symmetry is as important in palpation as it is in inspection.

A palpable vibration felt on the body, usually over the chest, is called *fremitus*. Vocal fremitus is elicited by having the patient speak "one, two, three," while the examiner's two palms or sides of the hands are moved horizontally from top to bottom of the two hemithoraces. Vocal fremitus is increased over regions of lungs through which there is increased transmission of sound, for example, consolidation from pneumonia. Conversely, fremitus is decreased in conditions in which sound transmission is impaired, for example, pleural effusion. Occasionally, fremitus over part of the chest wall can detect the presence of airway secretions (rhonchal fremitus) or an underlying pleural friction rub (friction fremitus).

In examining the heart, the examining physician should always search for an apical impulse, heaves and lifts, thrills, and palpable valve closure. In patients with severe COPD, abnormal cardiac movements are often better felt in the subxiphoid region than over the precordium.

Percussion

Skillful percussion depends on a uniform free and easy stroke of the striking finger (plexor) on the finger being struck (pleximeter), the ability to sense minor changes in pitch, and a keen sense of vibration—although the percussion note is heard, it is predominantly felt. Percussion of the thorax over normal air-containing lung produces a resonant note.

Sounds and tactile perception from percussion vary depending on the thickness of the skin, subcutaneous layer, breast tissue, and chest wall, as well as on the quality, distribution, and tension of the air under the area percussed. Pathologic processes may impair or enhance the resonating quality of the thorax. For example, the percussion note over a large pneumothorax is hyperresonant and becomes tympanitic when tension is present; in contrast, percussion over a pleural effusion or pneumonia produces dullness, which has been defined as a low-intensity sound of short duration, feeble carrying power, and rather high pitch.[60] Flatness is the unresonating sound obtained by percussing over the liver. Three different tonal zones can be detected when percussing large pleural effusions: normal resonance above the fluid, dullness in the middle, and flatness when completely below the fluid; these variations in sound may result from the presence of an internal meniscus or fluid wedge, which points upward into the lung above it. Carrying out a thoracentesis in the dull area offers the best chance of obtaining pleural fluid and avoids puncturing either an abdominal viscus or air-containing lung.

Auscultation

A stethoscope draped around the neck has long been the badge of the medical professional, and it is worn with pride by doctors, nurses, and respiratory therapists, despite predictions such as "it, too, will someday be relegated to a museum shelf."[61] Not for a long time, however, according to Murphy,[62] who mounts a spirited

TABLE 17-1. Classification of Common Lung Sounds

	Acoustic Characteristics	American Thoracic Society Nomenclature	Common Synonyms
Normal	200–600 Hz	Normal	Vesicular
	Decreasing power with increasing Hz		
	75–1600 Hz	Bronchial	Bronchial
	Flat until sharp decrease in power (900 Hz)		Tracheal
Adventitious		Adventitous	Abnormal
	Discontinuous, interrupted explosive sounds (loud, low in pitch), early inspiratory or expiratory	Coarse crackle	Coarse crackle
	Discontinuous, interrupted explosive sounds (less loud than above and of shorter duration; higher in pitch than coarse crackles or crackles), mid- to late inspiratory	Fine crackle	Fine crackle, crepitation
	Continuous sounds (>250 msec, high-pitched; dominant frequency of 400 Hz or more, a hissing sound)	Wheeze	Sibilant rhonchus
	Continuous sounds (>250 msec, low-pitched; dominant frequency about ≤200 Hz, a snoring sound)	Rhonchus	Sonorous rhonchus

defense in favor of stethoscopes, which he backs up with analyses of breath sounds obtained by respiratory acoustic recording. Indeed, mapping by computer-assisted imaging systems of breath sounds has provided new insights into their origin and clinical significance.[63] In addition, computerized multisensor breath sound imaging proved to be a sensitive and specific tool for differentiating pneumonia or pleural effusion from normal lungs.[64] Similarly, signal analysis of heart sounds recorded by digital electronic means has promising clinical applications and is useful for teaching cardiac auscultation.[65]

Stethoscopes are also helpful in picking up wheezes in asthmatics and crackles in patients with interstitial lung disease whose chest radiographs are normal. Moreover, patients expect their doctors to listen to their heart and lungs if they have cardiorespiratory complaints.

The terminology of breath sounds has been standardized and simplified to enhance understanding and communication (Table 17-1). Although a standardized nomenclature has been proposed by the American Thoracic Society[66] and the Tenth International Conference on Lung Sounds,[67] communication at the bedside often strays from recommended terminology.

The basic technique of auscultation with an ordinary stethoscope is well known to most physicians: the diaphragm detects higher-pitched sounds, and the bell lower-pitched, although if the bell is tightly pressed against the body, the taut underlying skin itself may serve as a "diaphragm" and improve perception of higher pitches. Conversely, the bell should be applied very lightly to hear, for example, the low-pitched rumble of mitral stenosis. Full contact with the skin is necessary for best listening, which may pose a problem in a patient whose intercostal spaces are sunken from weight loss. In addition, the skin or hairs may brush against the diaphragm and produce a sound that resembles a pleural friction rub. As with examiners' hands, a warm stethoscope head is appreciated by patients. The importance of a quiet room and of applying the stethoscope directly to the skin rather than through clothing has recently been reemphasized.[68] At times, especially in the intensive care unit, it is not always possible to sit patients up to listen carefully to their backs, which compromises the completeness of auscultation.

The recommended term for the ordinary breathing-associated sounds heard with a stethoscope placed on the chest of a healthy person is the *normal lung sound*, but, as shown in Table 17-1, many physicians prefer the older term "vesicular sound." The usually predominating inspiratory component arises from sounds generated by turbulent airflow within the lobar and segmental bronchi, whereas the weaker expiratory component arises within the larger, more central airways.[66] Sounds are attenuated as they move peripherally along the air passages, and are further damped by the large volume of the lungs' air spaces. The intensity of normal breath sounds varies with the magnitude of regional ventilation and, like percussion notes, diminishes with increasing thickness of the tissue overlying the chest wall. There is considerable variation among persons in the quality of breath sounds, which makes it essential to compare breath sounds from one side with those heard over the same location on the opposite hemithorax.

The transmission of normal lung sounds to the chest wall in pathologic conditions may be either attenuated or exaggerated. When the lung parenchyma is consolidated and the airway leading to the involved region is patent, breath sounds are overly well transmitted to the chest wall, and are termed *bronchial breath sounds*. Bronchial breath sounds are loud, high-pitched, tubular, or whistling sounds with expiration as loud as or louder than inspiration. Bronchial breath sounds are similar to tracheal breath sounds and their presence is the classic auscultatory sign of pneumonia. Similar sounds occur in patients with other types of consolidation, such as pulmonary edema and hemorrhage. The presence of this sign assumes that the sounds originate centrally and reach the chest wall. If the bronchus supplying the region of consolidation is not patent, the

central breath sounds tend to be attenuated, but voice-generated sounds, which are clearly of central origin, are increased.[69]

Interposition of a sound barrier between the central airways where sounds originate and the chest wall where they are heard also attenuates or interrupts transmission of normal lung sounds. Accordingly, normal breath sounds are diminished or absent over a pleural effusion, pneumothorax, and peripheral bullae, or distal to an obstructing mass lesion. Conversely, they may be increased if chest wall deformity or bronchial or tracheal derangement allows movement of air to be closer than usual to the stethoscope.

Adventitious Sounds

The major types of adventitious sounds are classified in Table 17-1. Two generic categories of adventitious sounds have been documented by high-speed recording techniques, and each of these has two subdivisions: discontinuous sounds, including fine crackles and coarse crackles, and continuous sounds, including wheezes and rhonchi.[70]

Discontinuous Sounds (Crackles)

Crackles, still often referred to as "rales" in the United States and "crepitations" in Great Britain, consist of a series of short explosive nonmusical sounds that punctuate the underlying breath sound; fine crackles are softer, shorter in duration, and higher in pitch than coarse crackles. There is general agreement that the brief recurrent detonations that characterize fine crackles are caused by the explosive openings of small airways that had closed owing to the surface forces within them.[66,71] This explains why fine crackles are much more common during inspiration than during expiration, and why they are best heard over dependent lung regions—where airways are more likely to close—than over uppermost regions. This is also compatible with the presence of crackles in healthy elderly persons in whom dependent airway closure occurs at resting lung volumes. Crackles, therefore, are best heard during the first deep breaths at the lung bases posteriorly; after several such breaths, the small airways may remain open for the time the patient is being examined.[71]

The timing of crackles is also important. Nath and Capel[72] have shown that late-inspiratory crackles are more often found in restrictive than obstructive lung disease. In a study by Pürilä and colleagues,[73] the crackles of fibrosing alveolitis began at 45% of inspiration, whereas those of COPD (25%), bronchiectasis (33%), and heart failure (37%) occurred earlier. The crackles of fibrosing alveolitis also lasted longer—88% of the inspiratory time.[73] This suggests that more tension is required to open individual airways in fibrosis than in lungs with secretions or edema, in which either obstruction with secretions or surfactant dilution may allow closure of the small airways. As inspiration progresses, radial traction on the airway wall increases until it suddenly pops open.[72] Expiratory crackles are much less frequent than inspiratory crackles and are often seen in obstructive lung disease.[71]

Continuous Sounds (Wheezes)

The American Thoracic Society Committee on Pulmonary Nomenclature defined wheezing as high-pitched (dominant frequency of ≥400 Hz) continuous adventitial lung sounds.[70] Continuous sounds are longer than 250 msec in duration. Wheezes are usually louder than the underlying breath sounds and frequently noted by patients. A leading theory is that wheezes are produced by fluttering of the airway walls and fluid together induced by a critical flow velocity.[74] The pitch of the wheeze is dependent on the mass and elasticity of the airway walls and the flow velocity. The degree of bronchial obstruction is proportional to the amount of the respiratory cycle that it occupies. There is no relationship to the intensity or pitch of the wheeze and pulmonary function. Wheezes are well heard over the trachea and listening over the trachea may be superior to listening over the lung in most asthmatic patients.[74] Wheezing with forced expiration can often be provoked in healthy subjects,[66] and does not establish a diagnosis of asthma. In fact, several disease states are associated with wheezing and additional information should be obtained to make the correct diagnosis.

Rhonchi are low-pitched continuous sounds with a dominant frequency about 200 Hz or less. These sounds are likely to originate from rupture of fluid films and airway wall vibrations.[66] Rhonchi may clear with cough and suctioning in intubated patients.

Voice-Generated Sounds

Another way of generating sounds for auscultation is to have patients speak while the examiner listens to their chests. Ordinarily, the patient is asked to say in a quiet voice "one, two, one, two," "ninety-nine, ninety-nine," or "E, E." If enhanced responses are heard, the patient repeats the words while whispering. Because sounds of central origin are attenuated as they are transmitted peripherally through normal air-filled lung, voice-generated sounds have a muffled quality and the words are indistinct. In contrast, in the presence of consolidation, the characteristics of the sounds are remarkably different. The term *egophony* indicates sounds that have a high-pitched, bleating quality; a change in sound-filtering properties of consolidated lungs accounts for the presence of egophony, which does not require, as often stated, the presence of an overlying pleural effusion. *Bronchophony* and *pectoriloquy* both mean that spoken sounds are transmitted with increased intensity and pitch; when each syllable of every word, especially when whispered, is distinct and easily recognized, pectoriloquy is the preferred description. An E to A sign occurs when the spoken letter "E" sounds like "A" while listened to over the lungs. Each of these auscultatory findings is a manifestation of the same acoustic property of consolidated lungs and thus has similar diagnostic significance.

Pleural Friction Rub

The small amount of liquid normally present in the pleural space separates the visceral and the parietal pleural layers and allows the lungs to expand and contract freely during breathing. In contrast, when the pleural surfaces are thickened and roughened by an inflammatory or neoplastic process, easy motion is prevented and a pleural friction rub may be produced. These sounds vary in intensity but often have a leathery or creaking quality that may be exaggerated by pressure with the stethoscope. Typically, rubs are heard during both inspiration and expiration, but they are evanescent and variable and may occur as a single component during any part of the respiratory cycle. Surprisingly, rubs may still be heard in the presence of a large pleural effusion, which prevents the coarsened pleural surfaces from actually rubbing against each other.

Nonpulmonary Sounds

The presence of air or other gas in the mediastinum may be associated with crunching, crackling sounds that are synchronous with cardiac contraction and are audible when breathing is momentarily stopped. The finding of a mediastinal crunch by auscultation usually signifies mediastinal emphysema, even when the chest radiograph shows no abnormalities. A pericardial friction rub is multiphasic and has a higher pitch, which usually makes it distinguishable.

Stridor is a high-pitched continuous sound produced by turbulent flow in the extrathoracic airway, which—in contrast to wheezing—is louder and longer during inspiration than expiration. Stridor has many causes,[74a] some of which are life-threatening and need immediate attention (see also Chapter 43).

As previously mentioned, various sounds may originate from the chest wall itself. Some of these have pathologic significance; others do not. Rubbing hairs trapped between the skin and the stethoscope produce intermittent crackling sounds that may be confused with crackles. Variable crackles are also produced when the stethoscope is placed over an area of subcutaneous emphysema and is rocked back and forth. Contracting chest wall muscles may generate sounds that have a muffled, distant, low-pitched, and rumbling quality. Occasionally, it is possible to hear a snapping sound during breathing from motion of a newly fractured rib.

Interpretation

When abnormalities are discovered on physical examination of the chest, it is useful to identify them by their anatomic location in the involved lung. This requires knowledge of the surface projections of the underlying bronchopulmonary lobes, which are shown in Figure 17-2. The upper and lower lobes of both lungs are separated by the two oblique fissures, which course from the spinous process of the third thoracic vertebra posteriorly to the level of the 6th rib in the midclavicular line anteriorly. On the right side anteriorly, the upper and middle lobes are separated by the horizontal fissure, which lies at about the level of the fourth costal cartilage. In the presence of either distortions of pulmonary anatomy or the shape of the rib cage, the surface projections of the underlying lung also change.

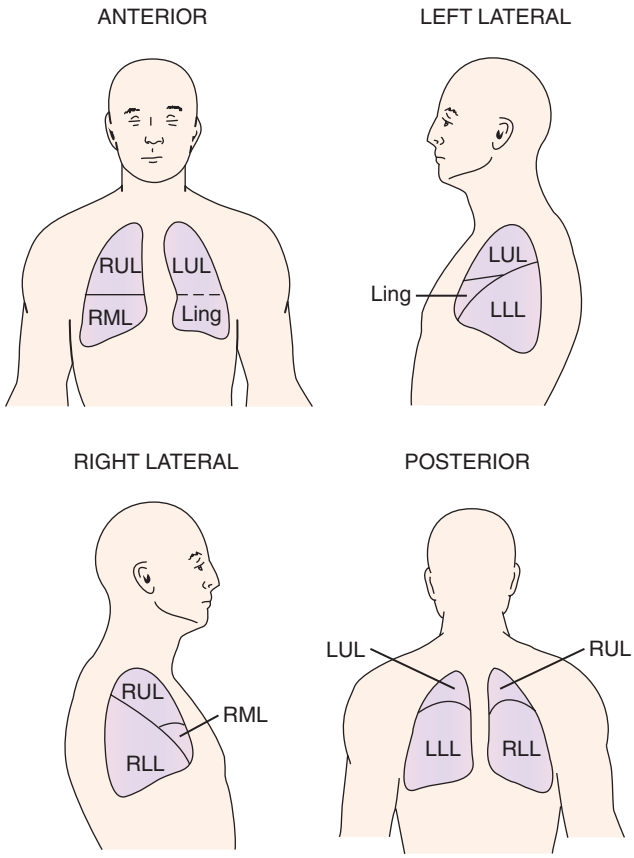

FIGURE 17-2 ■ Schematic drawing shows surface projections of underlying lobar anatomy of a healthy man. ling, lingular division of left upper lobe; LLL, left lower lobe; LUL, left upper lobe; RLL, right lower lobe; RML, right middle lobe; RUL, right upper lobe.

The classic findings on physical examination of the chest in some common pulmonary disorders are shown in Table 17-2. Ordinarily, consolidation must be within 1 or 2 cm of the costal surface to be reliably detected. Even then, physical examination alone cannot be relied upon to diagnose or exclude pneumonia.[75] Some pneumonias, such as mycoplasma pneumonia, typically cause surprisingly few physical abnormalities despite extensive radiographic involvement, but even in patients with classic lobar pneumonia, the findings may be nonspecific. Although unable to distinguish reliably between new-onset pneumonia and other pulmonary diseases, the findings from physical examination—vital signs, mental confusion, cyanosis, use of accessory muscles, and paradoxical breathing—are extremely important in assessing severity and in deciding whether or not to hospitalize patients with pneumonia.[76]

The distinction between pleural effusion and atelectasis, which depends on which side the heart and mediastinal contents have shifted toward, can usually be made only if the effusion is large or the atelectasis involves at

TABLE 17-2. Classic Physical Findings in Some Common Pulmonary Disorders

Disorder	Inspection	Palpation	Percussion	Auscultation
Bronchial asthma (acute attack)	Hyperinflation; use of accessory muscles	Impaired expansion; decreased fremitus	Hyperresonance; low diaphragm	Prolonged expiration: inspiratory and expiratory wheezes
Pneumothorax (complete)	Lag on affected side	Absent fremitus	Hyperresonant or tympanitic	Absent breath sounds
Pleural effusion (large)	Lag on affected side	Decreased fremitus; trachea and heart shifted away from affected side	Dullness or flatness	Absent breath sounds
Atelectasis (lobar obstruction)	Lag on affected side	Decreased fremitus; trachea and heart shifted toward affected side	Dullness or flatness	Absent breath sounds
Consolidation (pneumonia)	Possible lag or splinting	Increased fremitus on affected side	Dullness	Bronchial breath sounds; bronchophony; pectoriloquy; crackles

Modified from Hinshaw HC, Murray JF (eds): Diseases of the Chest (4th ed). Philadelphia: WB Saunders, 1980, p 23.

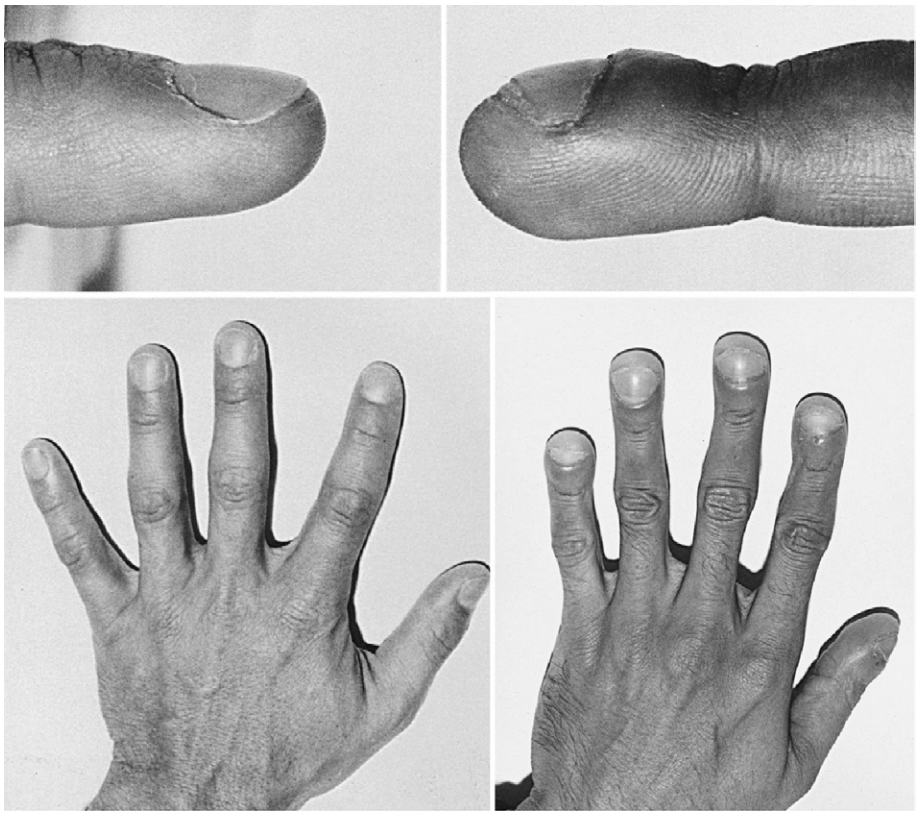

FIGURE 17-3 ■ Photographs show the hands and index fingers of a normal person (*left panels*) and a person with clubbing of the digits (*right panels*) secondary to severe diffuse pulmonary interstitial fibrosis.

least one lobe. When these full-blown manifestations are present, the presence of the causative disorder can be inferred with reasonable certainty. However, the absence of these findings does not exclude an abnormality, and a chest radiograph must always be taken as part of the complete pulmonary workup.

Extrapulmonary Manifestations

The examination of the lungs and pleura unlock only some of the clues to the presence of lung disease. Looking for extrapulmonary signs can often point toward a specific pulmonary disease, show that the lungs are involved in systemic diseases such lupus erythematosus, or demonstrate that the pulmonary abnormalities are secondary to diseases arising elsewhere in the body. Certain extrapulmonary manifestations are particularly useful.

Clubbing

The association of clubbing of the fingers or toes with disease has caught the attention of physicians since the time of Hippocrates. Clubbing is easy to recognize when

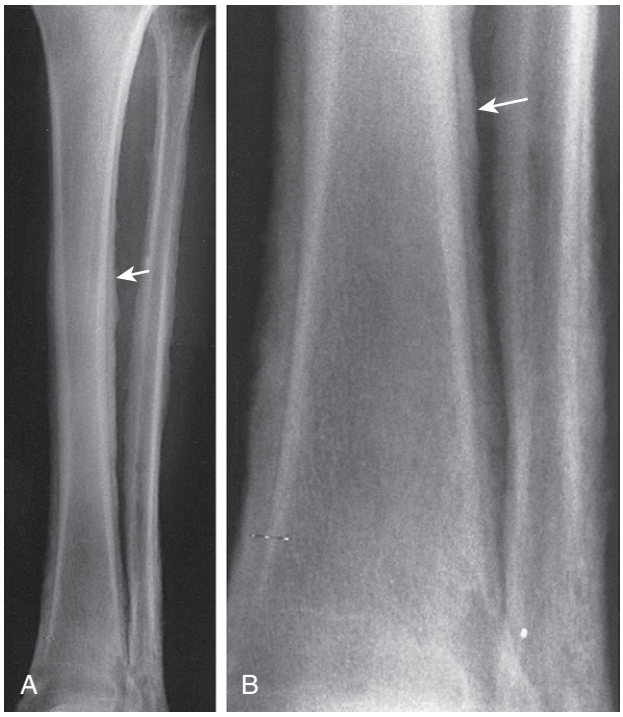

FIGURE 17-4 ■ Radiographs of the leg show marked subperiosteal new bone formation (*arrows*) that is diagnostic of hypertrophic osteoarthropathy. **A,** Most of tibia and fibula. **B,** Detailed view near the ankle.

it is severe (Fig. 17-3), but subtle changes are more common and less reliable. The hallmarks of clubbing are (1) a softening and periungual erythema of the nail beds, which causes the nails to seem to float rather than to be firmly attached, (2) an increase of the normal 165-degree angle that the nail makes with its cuticle, (3) an enlargement or bulging of the distal phalanx, which may be warm and erythematous, and (4) a curvature of the nails themselves. Of these features, the straightening of the nail cuticle angle appears to be the most sensitive measurement.[77]

Patients with clubbing may also have *hypertrophic osteoarthropathy*, a condition characterized by subperiosteal formation of new cancellous bone at the distal ends of long bones, especially the radius and ulna and the tibia and fibula. Hypertrophic osteoarthropathy (Fig. 17-4) is almost always associated with clubbing, particularly in patients with bronchogenic carcinoma, other intrathoracic malignancies, and cystic fibrosis. It occasionally occurs in patients with bronchiectasis, empyema, and lung abscess, but is rare in patients with most of the other conditions in which clubbing has been observed.[78] One of the striking features of clubbing is the speed with which it can develop, about 2 weeks in patients with new-onset empyema, and with which it can reverse, also about 2 weeks in patients after corrective cardiac surgery. The presence of clubbing, which was found in 1% of all admissions to an internal medicine department, was associated with "serious disease" in 40% of afflicted patients[79]; therefore, new-onset clubbing always warrants a chest radiograph, and if no abnormality is found, a CT to look for a pulmonary neoplasm or other lesion, which may still be localized and curable.

Clubbing has been found in many diverse conditions, such as children with human immunodeficiency virus,[80] hepatopulmonary syndrome,[81] and benign asbestos pleural disease[82] (Table 17-3). Both clubbing and hypertrophic osteoarthropathy can be idiopathic or familial; the familial form is often transmitted as a dominant trait. The hereditary form of hypertrophic osteoarthropathy is also called *pachydermoperiostosis*, a condition in which bone and joint involvement is often mild but furrowing of the skin of the face and scalp is usually marked.

The main pathologic finding in clubbing is increased capillary density. The most potent stimulus to new capillary growth is hypoxia, which causes an intense production of vascular growth factors, such as vascular endothelial growth factor (VEGF). With histochemical staining, Atkinson and Fox[83] showed increases in VEGF, platelet-derived growth factor, hypoxia-inducible factor (HIF)-1α, and HIF-2α along with increased microvessel density in the stroma of clubbed digits. The second common characteristic of patients with digital clubbing is shunting of blood past the capillary bed of either the lung or the liver, which suggests that lack of metabolism of angiogenic factors that bypass a critical organ may be involved. Several of the conditions associated with clubbing have inflammation and shunting, such as bronchiectasis and liver cirrhosis.

Other Extrapulmonary Associations

Besides clubbing, thoracic neoplasms may cause other extrathoracic abnormalities that may become evident on physical examination, including anemia, Cushing's syndrome, gynecomastia, and other paraneoplastic syndromes (Table 17-4). Other common extrathoracic manifestations that provide clues to the presence or state of an underlying malignancy are wasting, hoarseness, adenopathy (especially supraclavicular), and hepatomegaly. When evaluating patients with dyspnea, a thorough examination of the neck veins for evidence of increased central venous pressure and careful cardiac auscultation for the presence of a third heart sound or distinctive murmurs, are important findings in patients with heart failure.[84] The extremities should also be examined for evidence of peripheral edema, venous thrombosis, chronic venous stasis, and intravenous drug abuse.

The association of abnormalities in other organ systems with underlying lung disease can be very helpful in making a diagnosis. A wide variety of cutaneous or subcutaneous lesions (Table 17-5)[85] and ocular lesions (Table 17-6)[86] has been associated with various primary lung disorders. Likewise, persons presenting with a combination of lung and kidney disease (Table 17-7); lung and bone; joint, muscle, or nerve lesions (Table 17-8); and lung and gastrointestinal disease (Table 17-9) may denote a unifying disease process that can be detected by physical examination.

TABLE 17-3. Causes of Clubbing (partial listing)

NOT ASSOCIATED WITH OVERT DISEASE
Hereditary clubbing
Sporadic clubbing
Pachydermoperiostosis

THORACIC NEOPLASMS
Lung cancer especially fibrous tumors (accounts for most clubbing)
Benign and malignant pleural tumors
Other thoracic neoplasms, including esophageal cancer, and lymphoma

HEART AND VASCULAR DISEASE
Cyanotic congenital heart disease
Subacute bacterial endocarditis
Infected aortic graft
Aortic surgery
Takayasu's arteritis
Behçet's disease

PULMONARY AV SHUNTING
Cyanotic congenital heart disease
Acquired heart disease
Pulmonary AV fistula
Hereditary hemorrhagic telangiectasias

INTERSTITIAL LUNG DISEASE
Asbestosis
Idiopathic pulmonary fibrosis
Collagen vascular disease
Langerhans histiocytosis
Lipoid pneumonia

CHRONIC INFECTIONS
Bronchiectasis
Bronchiectasis from sarcoidosis or tuberculosis
Lung abscess
Empyema
Cystic fibrosis

GASTROINTESTINAL AND LIVER DISEASE
Inflammatory bowel disease
  Crohn's disease
  Ulcerative colitis
  Polyposis coli
Amebic colitis
  Bacillary dysentery
Liver disease
  Hepatoma
  Hepatopulmonary syndrome
  Biliary cirrhosis
Esophageal stricture

HEMOGLOBINOPATHY
Hemoglobinopathies
Congenital methemoglobinemia

OTHER
Thyroid acropathy
Secondary hyperparathyroidism
HIV related
  Lymphoid interstitial pneumonia
  Other infections
Prostaglandin infusion
Fabry's disease
Toxic exposure to arsenic, mercury or beryllium

UNILATERAL CLUBBING
Vascular disorders
  Subclavian artery aneurysm
  Brachial AV fistula
Subluxation of the shoulder
Median nerve injury
Local trauma
Hemiplegia

AV, arteriovenous; HIV, human immunodeficiency virus.

TABLE 17-4. Paraneoplastic Syndromes (partial listing)

PARANEOPLASTIC SYNDROMES
Acanthosis nigricans
Clubbing
Dermatomyositis-polymyositis
Hypertrophic osteoarthropathy
Intravascular thrombosis
Muscle weakness
Neuropathy
Phemphigoid
Raynaud's phenomenon

ENDOCRINE SYNDROMES ASSOCIATED WITH LUNG NEOPLASMS
Hypercalcemia (parathyroid-like substance)
Hyponatremia (inappropriate antidiuretic hormone)
Carcinoid syndrome (serotonin)
Cushing's syndrome (ACTH)
Hyper- and hypoglycemia (insulin)
Gynecomastia (gonodotropins) (prolactin)
Skin pigmentation (melanocyte-stimulating hormone, ACTH)
Acromegaly (growth hormone)
Diarrhea (vasoactive intestinal peptide)

ACTH, adrenocorticotropic hormone.

TABLE 17-5. Skin and Subcutaneous Lesions Associated with Lung Disease

SKIN LESIONS

Diffuse pigment change
- Acanthosis nigricans—lung neoplasm
- Albinism—Hermansky-Pudlak syndrome
- Bronze pigmentation—hemosiderosis
- Gray-brown—Whipple's disease

Cutaneous draining sinus
- Fungal infections (especially histoplasmosis)
- Mycobacterial infections (especially tuberculosis)
- Neoplasms (especially mesothelial tumors)
- Necrotizing vasculitis
- Other bacterial infections (especially actinomycosis)

Cutaneous ulcers
- Beryllium disease
- Chronic venous insufficiency
- Fungal infections (especially histoplasmosis)
- Mycobacterial disease
- Necrotizing vasculitis
- Parasitic disease
- Polycythemia
- Sickle cell disease
- Tularemia

Cutaneous vasculitis
- Behçet's syndrome
- Churg-Strauss syndrome
- Collagen vascular disease
- Sarcoidosis
- Wegener's granulomatosis

Erythema multiforme
- Drug reactions
- Fungi (especially coccidiomycosis)
- Mycoplasma and other infectious agents
- Neoplasms

Exfoliative dermatitis
- Adverse drug reactions
- Chemotherapy
- Disseminated malignancy
- Graft-versus-host disease
- Radiation therapy

Flushing
- Bronchial carcinoid, pheochromocytoma, other neoplasms
- Carbon dioxide, cyanide, and other toxins
- Drugs
- Foods and vasodilatory substances
- Hormones
- Mastocytosis
- Metabolic states (e.g., hyperthyroidism, fever)

Macular rash
- Anti-basement membrane disease
- Café-au-lait spots (neurofibromatosis)
- Coal miner's scars
- Collagen vascular disease
- Idiopathic pulmonary fibrosis
- Rose spots (psittacosis)
- Sarcoidosis
- Syphilis
- Viral pneumonia

Maculopapular rash
- Amyloidosis
- Drug-induced lung disease
- Collagen vascular disease
- Gaucher's disease
- Kaposi's sarcoma
- Lung neoplasm
- Lymphomatoid granulomatosis
- Lymphoma
- Parasites
- Sarcoidosis
- Syphilis
- Vasculitis
- Viral pneumonia

Sicca syndrome (dry mouth and eyes)
- Gaucher's disease
- Lymphocytic interstitial pneumonia
- Sjögren's syndrome

Telangiectasia
- Arteriovenous malformation
- Ataxia-telangiectasia
- Carcinoid syndrome
- Cushing's disease
- Hepatopulmonary syndrome and other chronic liver diseases
- Hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu)
- Mastocytosis
- Systemic sclerosis and other collagen vascular diseases

Urticaria
- Asthma
- Drug reactions
- Cystic fibrosis
- Exercise-induced urticaria
- Food allergy
- Hereditary angioneurotic edema
- Inhaled antigens
- Insect bites and stings
- Infectious agents, such as mycoplasma and helicobacter
- Mastocytosis
- Occupational sensitization
- Parasites
- Vasculitis

NAIL CHANGES WITH LUNG DISEASE

Color changes
- Cigarette smoking discoloration
- Splinter hemorrhages
- Yellow nail syndrome

Beau's lines (any severe illness)
- Dermatomyositis
- Sarcoidosis
- Seronegative arthropathies
- Systemic sclerosis

LUNG DISEASE WITH SUBCUTANEOUS INVOLVEMENT

Adenopathy
- Environmental mycobacteria
- Fungal infections
- HIV infections
- Metastatic neoplasm
- Leukemia
- Lymphoma
- Sarcoidosis
- Tuberculosis

Calcinosis
- Dermatomyositis
- Metastatic osteosarcoma
- Mixed connective tissue disease
- Scleroderma
- Tuberculosis
- Uremic metastatic calcification

Erythema induratum (Bazin's disease)
- Aortic stenosis
- Cryoglobulinemia
- Nodular vasculitis
- Panniculitis
- Peripheral neuropathy
- Takayasu's disease
- Streptococcus infection
- Tuberculosis and other mycobacterial disease
- Weber-Christian disease

Erythema nodosa
- Neoplasm
- Other infectious and inflammatory diseases
- Primary coccidiomycosis, histoplasmosis
- Primary tuberculosis
- Psittacosis
- Sarcoidosis

Subcutaneous nodules
- Amyloidosis
- Neoplasm
- Neurofibromatosis
- Rheumatoid arthritis
- Tuberous sclerosis (angiofibromas)
- von Recklinghausen's
- Weber-Christian disease

LUNG DISEASE WITH SALIVARY GLAND ENLARGEMENT

Bulimia and aspiration
Gaucher's disease
Lymphoid interstitial pneumonitis
Lymphatic carcinoma
Lymphoma
Other causes of lymphadenopathy
Sarcoidosis
Sjögren's disease

HIV, human immunodeficiency virus.

TABLE 17-6. Eye Involvement in Lung Disease

BLINDNESS
Giant cell arteritis
Late stage of many diseases
Sarcoidosis
Amaurosis fugax
  Antiphophospholipid syndrome
  Aspergillosis
  Churg-Strauss syndrome
  Temporal arteritis
  Wegener's granulomatosis

CHOROID
Toxoplasmosis
Histoplasmosis
Lupus erythematosis

CONJUNCTIVA
Allergic reaction
Chlamydia
Herpes
Kaposi's sarcoma
Sarcoidosis
Wegener's granulomatosis

CORNEA
Chlamydia
Herpes
Syphilis
Wegener's granulomatosis

IRIS
Neoplasm
Neurofibromatosis

LENS
Marfan's syndrome (dislocated)
Cataracts
  Tobacco smoking
  Steroid use

LIDS
Proptosis
  Graves' disease
  Neoplasm
  Leukemia
Ptosis
  Myasthenia gravis
  Muscular dystrophy

OPTIC NERVE
Cryptococcosis
Sarcoidosis
Graves' disease
Leukemia
Neurofibromatosis
Syphilis
Wegener's granulomatosis

RETINA
Antiphospholipid syndrome
Behçet's disease
Candidiasis
Cytomegalovirus, herpes, and other viruses
Diabetes
Disseminated intravascular coagulation
Dysproteinemia
Ehlers-Danlos syndrome
Embolic disease
Endocarditis
Fat emboli
Fungemia
Genetic metabolic deficiencies
HIV disease
Leukemia, lymphoma
Lupus erythematosis
Macroglobulinemia
Marfan's syndrome
Neoplasm (especially melanoma)
Polycythemia
Sarcoidosis
Sickle cell disease
Subacute bacterial endocarditis, sepsis (Roth spots)
Syphilis
Temporal arteritis
Toxoplasmosis
Trauma
Tuberous sclerosis
Wegener's granulomatosis

SCLERA AND EPISCLERA
Inflammatory bowel disease
Rheumatoid arthritis
Sarcoidosis
Scleroderma
Systemic vasculitis
Systemic lupus
Wegener's granulomatosis

SICCA
Graft-versus-host disease
Rheumatoid arthritis
Sjögren's syndrome

UVEA
Ankylosing spondylitis
Behçet's disease
Crohn's disease
Herpes zoster
Inflammatory bowel disease
Reactive arthritis
Rheumatoid arthritis
Sarcoidosis
Syphilis
Wegener's granulomatosis

HIV, human immunodeficiency virus.

TABLE 17-7. Lung Disease with Renal Involvement

GLOMERULONEPHRITIS
Systemic vasculitis
Collagen vascular disease
Antibasement membrane
Sarcoidosis

NEPHROTIC SYNDROME
Amyloidosis
Disseminated Langerhans cell histiocytosis
Drug-induced lung disease
Paraneoplastic syndrome
Post transplantation
Pulmonary hydatid disease
Systemic lupus erythematosis
Vasculitis
Venous thrombosis

RENAL MASS
Lymphangioleiomyomatosis
Metastasis neoplasm
Renal carcinoid
Tuberous sclerosis
Wegener's granulomatosis

NEPHROLITHIASIS
Alveolar proteinosis
Cystic fibrosis
Hypercalcemic syndromes
Osteolysis from mycobacteria or fungi
Sarcoidosis

SYSTEMIC HYPERTENSION
Collagen vascular disease
Diffuse alveolar hemorrhage
Pulmonary renal syndromes
Neurofibromatosis
Sleep apnea

TABLE 17-8. Lung Disease with Bone, Joint, Nerve, and Muscle Involvement

ARTHRITIS
Ankylosing spondylitis
Collagen vascular diseases
Reactive arthritis
Sarcoidosis
Systemic vasculitis
Tuberculosis

BONE LESIONS
Ankylosing spondylitis
Blastomycosis and other fungal disease
Collagen vascular diseases
Eosinophilic granulomatosis
Fibrous histiocytoma
Gaucher's disease
Neoplasm
Sarcoidosis
Tuberculosis

MUSCLE DISEASE
Collagen vascular disease
L-Tryptophan
Diabetes insipidus
Eosinophilic granulomatosis
Polymyositis
Sarcoidosis

NEUROLOGIC DISEASE
Acute inflammatory polyneuropathy
Amyotrophic lateral sclerosis
Aspiration
Botulism
Lambert-Eaton syndrome
Myasthenia gravis
Organophosphate poisoning
Polio and postpolio syndrome
Sarcoidosis
Churg-Strauss syndrome
Wegener's granulomatosis

TABLE 17-9. Lung Disease and Gastrointestinal and Liver Involvement

ESOPHAGEAL REFLUX
Aspiration pneumonia
Asthma
Scleroderma

INFLAMMATORY BOWEL DISEASE
Bronchitis
Bronchiectasis
Bronchiolitis
Colobronchial fistula
Desquamative interstitial lung disease
Drug reactions for agents that treat inflammatory bowel disease
Eosinophilic lung disease
Interstitial lung disease
Necrobiotic nodules
Obstructive lung disease
Organizing pneumonia
Reduced diffusing capacity
Sarcoidosis
Serositis affecting pleura or pericarditis
Tracheal stenosis

LIVER
$Alpha_1$-antitrypsin deficiency
Chronic active hepatitis
Hepatopulmonary syndrome
Portapulmonary hypertension
Primary biliary cirrhosis
Hepatosplenomegaly
- Amyloidosis
- Collagen vascular disease
- Eosinophilic granulomatosis
- Lymphatic interstitial pneumonia
- Sarcoidosis

Bronchitis
Bronchiectasis
Cough
Pulmonary fibrosis
Mycobacterial disease

KEY POINTS

- Taking a careful history and performing a thorough physical examination are essential first steps in formulating a preliminary differential diagnosis of the patient's complaints.
- After arriving at a tentative diagnosis, selected radiographic, laboratory, and other tests are ordered for further and confirmatory evaluation.
- The electronic medical record provides documents of higher quality than written records, owing to improved organization, increased readability, use of supplementary material, and better comparisons.
- Because dyspnea, cough with or without hemoptysis, and chest pain are among the most common reasons for patients to visit physicians, and because these symptoms may result from serious underlying chest disease, careful questioning and workup, as described, is mandatory.
- Physical examination can be performed virtually anywhere, provides important information, lends itself to serial observations, and increases patients' confidence in their physicians.
- New-onset clubbing of the digits warrants detection and investigation owing to its frequent association with serious underlying disease.

References

1. Graber ML, Franklin N, Gordon R: Diagnostic error in internal medicine. Arch Intern Med 165:1493–1499, 2005.
2. McSherry D: Avoiding premature closure in sequential diagnosis. Artif Intell Med 10:269–283, 1997.
3. Tsai J, Bond G: A comparison of electronic records to paper records in mental health centers. Int J Qual Health Care 20:136–143, 2008.
4. Argent J, Faulkner A, Jones A, O'Keeffe C: Communication skills in palliative care: Development and modification of a rating scale. Med Educ 28:559–565, 1994.
5. Kirscht JP: Communications between patients and physicians. Ann Intern Med 86:499–500, 1977.
6. Faulkner A: ABC of palliative care. Communication with patients, families, and other professionals. BMJ. 316:130–132, 1998.
7. Lipkin M Jr, Quill TE, Napodano RJ: The medical interview: A core curriculum for residencies in internal medicine. Ann Intern Med 100:277–284, 1984.
8. Lipkin M Jr, Putnam SM, Lazare A, et al (eds): The Medical Interview: Clinical Care, Education, and Research. New York: Springer Verlag, 1994.
9. Benaroia M, Elinson R, Zarnke K: Patient-directed intelligent and interactive computer medical history-gathering systems: A utility and feasibility study in the emergency department. Int J Med Inform 76:283–288, 2007.
10. Schattner A: The essence of patient care. J Intern Med. 254:1–4, 2003.
11. Platt R: Two essays on the practice of medicine. Manchester Univ Med Sch Gazet 27:139–145, 1947.
12. Hampton JR, Harrison MJ, Mitchell JR, et al: Relative contributions of history-taking, physical examination, and laboratory investigation to diagnosis and management of medical outpatients. Br Med J 2:486–489, 1975.
13. Sandler G: The importance of the history in the medical clinic and the cost of unnecessary tests. Am Heart J 100:928–931, 1980.
14. Peterson MC, Holbrook JH, Von HD, et al: Contributions of the history, physical examination, and laboratory investigation in making medical diagnoses. West J Med 156:163–165, 1992.
15. Morélet-Panzini C, Demoule A, Straus C, et al: Dyspnea as a noxious sensation: Inspiratory threshold loading may trigger diffuse noxious inhibitory controls in humans. J Neuophysiol 97:1396–1404, 2007.

15a. Yu J: Airway receptors and their reflex function–invited article. Adv Exp Med Biol 648:411–420, 2009.

16. Borg GA: Psychophysical bases of perceived exertion. Med Sci Sports Exerc 14:377–381, 1982.
17. Medical Research Council Committee on the Aetiology of Chronic Bronchitis: Standardized questionnaires on respiratory symptoms. Br Med J 2:1665, 1960.
18. Lareau SC, Carrieri-Kohlman V, Janson-Bjerklie S, Roos PJ: Development and testing of the Pulmonary Functional Status and Dyspnea Questionnaire (PFSDQ). Heart Lung 23:242–250, 1994.
19. Mahler DA, Waterman LA, Ward J, et al: Validity and responsiveness of the self-administered computerized versions of the baseline and transition dyspnea indexes. Chest 132:1283–1290, 2007.
20. O'Donnell DE, Laveneziana P: Dyspnea and activity limitation in COPD: Mechanical factors. COPD 4:225–236, 2007.
21. Baggish AL, van Kimmenade RR, Januzzi JL Jr: Amino-terminal pro-B-type natriuretic peptide testing and prognosis in patients with acute dyspnea, including those with acute heart failure. Am J Cardiol 101:49–55, 2008.
22. Bennett WD, Foster WM, Chapman WF: Cough-enhanced mucus clearance in the normal lung. J Appl Physiol 69:1670–1675, 1990.
23. Chang AB: The physiology of cough. Paediatr Respir Rev 7:2–8, 2006.
24. Irwin RS, Curley FJ, French CL: Chronic cough. The spectrum and frequency of causes, key components of the diagnostic evaluation, and outcome of specific therapy. Am Rev Respir Dis 141:640–647, 1990.
25. Brightling CE, Ward R, Goh KL, et al: Eosinophilic bronchitis is an important cause of chronic cough. Am J Respir Crit Care Med 160:406–410, 1999.
26. Lacourciere Y, Brunner H, Irwin R, et al: Effects of modulators of the renin-angiotensin-aldosterone system on cough. Losartan Cough Study Group. J Hypertens 12:1387–1393, 1994.
27. Palombini BC, Villanova CA, Araujo E, et al: A pathogenic triad in chronic cough: Asthma, postnasal drip syndrome, and gastroesophageal reflux disease. Chest 116:279–284, 1999.
28. Pavord ID, Chung KF: Chronic cough 2. Management of chronic cough. Lancet 373:1375–1384, 2008.
29. Irwin RS, Madison JM: The persistently troublesome cough. Am J Respir Crit Care Med 165:1469–1474, 2002.
30. Vertigan AE, Theodoros DG, Gibson PG, Winkworth AL: Review series: Chronic cough: Behaviour modification therapies for chronic cough. Chron Respir Dis 4:89–97, 2007.
31. Corrao WM, Braman SS, Irwin RS: Chronic cough as the sole presenting manifestation of bronchial asthma. N Engl J Med 300:633–637, 1979.
32. Ing AJ, Ngu MC: Cough and gastro-oesophageal reflux. Lancet 353:944–946, 1999.
33. Tuberculosis Coalition for Technical Assistance: International Standards for Tuberculosis Care (ISTC). The Hague, Netherlands: Tuberculosis Coalition for Technical Assistance, 2006.
34. Vasquez JC, Halasz NA, Chu P: Traumatic abdominal wall hernia caused by persistent cough. South Med J 92:907–908, 1999.
35. Pursel SE, Linkskog GE: Hemoptysis. A clinical evaluation of 105 patients examined consecutively on a thoracic surgical service. Am Rev Respir Dis 84:329–336, 1961.
36. Hirshberg B, Biran I, Glazer M, Kramer MR: Hemoptysis: Etiology, evaluation, and outcome in a tertiary referral hospital. Chest 112:440–444, 1997.
37. Santiago S, Tobias J, Williams AJ: A reappraisal of the causes of hemoptysis. Arch Intern Med 151:2449–2451, 1991.
38. Johnston H, Reisz G: Changing spectrum of hemoptysis. Underlying causes in 148 patients undergoing diagnostic flexible fiberoptic bronchoscopy. Arch Intern Med 149:1666–1668, 1989.
39. Anderson PE: Imaging and interventional radiological treatment of hemoptysis. Acta Radiol 47:780–792, 2006.
40. Khalil A, Fartoukh M, Tassart M, et al: Role of MDCT in identification of the bleeding site and vessels causing hemoptysis. AJR Am J Roentgenol 188:W117–W125, 2007.
41. Kost GJ, Tran NK: Point-of-care testing and cardiac biomarkers: The standard of care and vision for Chest Pain Centers. Cardiol Clin 23:467–490, 2005.
42. Gnann JW Jr, Whitley RJ: Clinical practice. Herpes zoster. N Engl J Med 347:340–346, 2002.
43. Davies SW: Clinical presentation and diagnosis of coronary artery disease: Stable angina. Br Med Bull 59:17–27, 2001.
44. Mayer S, Hillis LD: Prinzmetal's variant angina. Clin Cardiol 21:243–246, 1998.
45. Wise CM: Chest wall syndromes. Curr Opin Rheumatol 6:197–202, 1994.
46. Rubin LJ: Pulmonary arterial hypertension. Proc Am Thorac Soc 3:111–115, 2006.
47. Chan-Yeung M, Mich-Ward H: Respiratory health effects of exposure to environmental tobacco smoke. Respirology 8:131–139, 2003.
48. Begin R, Christman JW: Detailed occupational history: The cornerstone in diagnosis of asbestos-related lung disease. Am J Respir Crit Care Med 163:598–599, 2001.
49. Levy BS, Wegman DH: The occupational history in medical practice. What questions to ask and when to ask them. Postgrad Med 79:301–311, 1986.
50. Kuschner WG, Stark P: Occupational lung disease. Part 1. Identifying work-related asthma and other disorders. Postgrad Med 113: 70–78, 2003.
51. Kuschner WG, Stark P: Occupational lung disease. Part 2. Discovering the cause of diffuse parenchymal lung disease. Postgrad Med 113:81–88, 2003.
52. Spira AM: Assessment of travelers who return home ill. Lancet 361:1459–1469, 2003.
53. Scurr JH, Machin SJ, Bailey-King S, et al: Frequency and prevention of symptomless deep-vein thrombosis in long-haul flights: A randomised trial. Lancet 357:1485–1489, 2001.

54. Rosenstock L, Logerfo J, Heyer NJ, Carter WB: Development and validation of a self-administered occupational health history questionnaire. J Occup Med 26:50–54, 1984.
55. Bachman JW: The patient-computer interview: A neglected tool that can aid the clinician. Mayo Clin Proc 78:67–78, 2003.
56. Jauhar S: The demise of the physical exam. N Engl J Med 354:548–553, 2006.
57. Crombie DL: Diagnostic process. J Coll Gen Pract 6:579–589, 1963.
58. Roussos C, Macklem PT: The respiratory muscles. N Engl J Med 307:786–797, 1982.
59. Maitre B, Similowski T, Derenne JP: Physical examination of the adult patient with respiratory diseases: Inspection and palpation. Eur Respir J 8:1584–1593, 1995.
60. Yernault JC: History, symptoms and clinical examination in pleural disease. In Loddenkemper R, Antony VB (eds): Pleural Diseases. Sheffield, UK: European Respiratory Society Monograph. 7:60–75, 2002.
61. Markel H: The stethoscope and the art of listening. N Engl J Med 354:551–553, 2006.
62. Murphy RLH: In defense of the stethoscope. Respir Care 53:355–369, 2008.
63. Dellinger RP, Parrillo JE, Kushnir A, et al: Dynamic visualization of lung sounds with a vibration response device: A case series. Respiration 75:60–72, 2008.
64. Mor R, Kushnir I, Ekstein J, Ben-Dov I: Breath sound distribution images of patients with pneumonia and pleural effusion. Respir Care 52:1753–1760, 2007.
65. Tavel ME: Cardiac auscultation: A glorious past—And it does have a future! Circulation 113:1255–1259, 2006.
66. Pasterkamp H, Kraman SS, Wodicka GR: Respiratory sounds. Advances beyond the stethoscope. Am J Respir Crit Care Med 156:974–987, 1997.
67. Mikami R, Murao M, Cugell DW, et al: International Symposium on Lung Sounds. Synopsis of proceedings. Chest 92:342–345, 1987.
68. Kraman SS: Transmission of lung sounds through light clothing. Respiration 75:85–88, 2008.
69. Baughman RP, Loudon RG: Sound spectral analysis of voice-transmitted sound. Am Rev Respir Dis 134:167–169, 1986.
70. American Thoracic Society Ad Hoc Committee on Pulmonary Nomenclature: Updated nomenclature for membership reaction. ATS News 3:5–6, 1977.
71. Piirila P, Sovijarvi AR: Crackles: Recording, analysis and clinical significance. Eur Respir J 8:2139–2148, 1995.
72. Nath AR, Capel LH: Inspiratory crackles and mechanical events of breathing. Thorax 29:695–698, 1974.
73. Piirila P, Sovijarvi AR, Kaisla T, et al: Crackles in patients with fibrosing alveolitis, bronchiectasis, COPD, and heart failure. Chest 99:1076–1083, 1991.
74. Meslier N, Charbonneau G, Racineux JL: Wheezes. Eur Respir J 8:1942–1948, 1995.
74a. Ozgursoy OB, Batikhan H, Beton S, Dursun G: Sudden-onset life-threatening stridor in an adult caused by a laryngeal ductal cyst. Ear Nose Throat J 88:828–830, 2009.
75. Wipf JE, Lipsky BA, Hirschmann JV, et al: Diagnosing pneumonia by physical examination: Relevant or relic? Arch Intern Med 159:1082–1087, 1999.
76. Renaud B, Coma E, Labareree J, et al: Routine use of the pneumonia severity index for guiding the site-of-treatment decision of patients with pneumonia in the emergency department: A multicenter, prospective, observational, controlled cohort study. Clin Infect Dis 44:50–52, 2007.
77. Myers KA, Farquhar DR: The rational clinical examination. Does this patient have clubbing? JAMA 286:341–347, 2001.
78. Hansen-Flaschen J, Nordberg J: Clubbing and hypertrophic osteoarthropathy. Clin Chest Med 8:287–298, 1987.
79. Vandemergel X, Renneboog B: Prevalence, aetiologies and significance of clubbing in a department of general internal medicine. Eur J Intern Med 19:325–329, 2008.
80. Zar HJ, Hussey G: Finger clubbing in children with human immunodeficiency virus infection. Ann Trop Paediatr 21:15–19, 2001.
81. Rodriguez-Roisin R, Krowka MJ: Hepatopulmonary syndrome—A liver-induced vascular disorder. N Engl J Med 358:2378–2387, 2008.
82. McGavin C, Hughes P: Finger clubbing in malignant mesothelioma and benign asbestos pleural disease. Respir Med 92:691–692, 1998.
83. Atkinson S, Fox SB: Vascular endothelial growth factor (VEGF)-A and platelet-derived growth factor (PDGF) play a central role in the pathogenesis of digital clubbing. J Pathol 203:721–728, 2004.
84. Drazner MH, Rame JE, Dries DL: Third heart sound and elevated jugular venous pressure as markers of the subsequent development of heart failure in patients with asymptomatic left ventricular dysfunction. Am J Med 114:431–437, 2003.
85. Alper J, Kegel M: Skin signs in pulmonary disease. Clin Chest Med 8:299–311, 1987.
86. Sharma OP: Symptoms and signs in pulmonary medicine: Old observations and new interpretations. Dis Mon 41:577–638, 1995.

CHAPTER 18

MICROBIOLOGIC DIAGNOSIS OF LOWER RESPIRATORY TRACT INFECTION

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INTRODUCTION

SPECIMEN SELECTION AND COLLECTION

DIRECT EXAMINATION OF SPECIMENS

CULTURES, MICROBIAL ANTIGEN DETECTION, AND SUSCEPTIBILITY TESTING

Bacteria

Mycobacteria

Fungi

Viruses

Parasites

SEROLOGIC TESTS

MOLECULAR TESTS

INTRODUCTION

The laboratory diagnosis of lower respiratory infection poses a number of major challenges. First, the diversity of etiologic agents (Table 18-1) imposes diverse specimen requirements and laboratory approaches. Second, lower respiratory secretions are usually obtained through the oropharynx, which is normally heavily colonized with 10^{10} to 10^{12} colony-forming units (CFU) of aerobic and anaerobic bacteria and yeasts per milliliter of volume (Table 18-2). Some of these organisms can be pathogens in the lower respiratory tract, but the vast majority of them often contaminate lower respiratory secretions collected for microbiologic examination.[1]

A third problem is that the oropharyngeal secretions, which normally contain only a few gram-negative bacilli (such as Enterobacteriaceae, *Pseudomonas, Acinetobacter*), often become colonized with as many as 10^7 CFU of gram-negative bacilli per milliliter in seriously ill patients requiring intensive care (Fig. 18-1),[2] patients treated with antibiotics after hospitalization for acute pulmonary inflammatory disease,[3] chronic alcoholics and diabetics,[4] the institutionalized elderly and chronically ill,[5] and hospitalized patients with acute leukemia.[6] Thus, aspiration of even minute amounts (0.1 to 1 μL) of oropharyngeal secretions by such patients can deliver a bolus of 10^4 CFU of gram-negative bacilli per milliliter to the tracheobronchial tree.[7] The distinction in such cases between gram-negative bacillary colonization of the upper respiratory tract and gram-negative pneumonia cannot be easily made by sputum examination and culture. However, the former predisposes to the latter, and prevention of gram-negative bacillary colonization of the oropharynx reduces the risk of gram-negative pneumonia.[7–9] Despite this association, it is important to note that upper respiratory colonization with potentially pathogenic microorganisms, such as gram-negative bacilli, may not be related to the actual etiologic agents of lower respiratory infection. Thus, a fourth problem with the laboratory diagnosis of lower respiratory infections is that sputum specimens contaminated with Enterobacteriaceae or *Staphylococcus aureus* from oropharyngeal secretions may obscure the diagnosis of pneumococcal pneumonia, anaerobic pleuropulmonary infection, or even tuberculosis.[10–12]

The effects of prior antimicrobial therapy on bacteriologic test results in patients with primary pneumonia constitute a fifth problem. Spencer and Philp[13] found that not a single sputum specimen from 52 patients who had received antimicrobial therapy before hospitalization for primary pneumonia grew either *Streptococcus pneumoniae* or *Haemophilus influenzae,* whereas sputum specimens from 22 of 24 patients (92%) who had not received antimicrobial therapy before hospitalization for primary pneumonia did grow either *S. pneumoniae* (15 patients) or *H. influenzae* (7 patients). Presumably, sputum specimens from many of the patients who had been treated with antimicrobials would have grown either of these two organisms, given that they are primary pathogens in community-acquired pneumonia (CAP).

The last problem is that of proper sputum collection. Active participation of patients, when they are able to cooperate, is seldom requested but essential to produce

TABLE 18-1. Well-Known Microbial Pathogens That Cause Lower Respiratory Tract Infections

BACTERIA
Acinetobacter species
Actinomyces israelii
Bacillus anthracis
Enterobacteriaceae species
Francisella tularensis
Haemophilus influenzae
Klebsiella pneumoniae
Legionella species
Moraxella catarrhalis
Neisseria species
Nocardia asteroides group
Pseudomonas aeruginosa
Pseudomonas pseudomallei
Staphylococcus aureus
Streptococcus pneumoniae
Streptococcus pyogenes
Yersinia pestis

Chlamydiaceae
Chlamydia trachomatis
Chlamydophila pneumoniae
Chlamydophila psittaci

Mycoplasma
Mycoplasma pneumoniae

Rickettsieae
Coxiella burnetii

MYCOBACTERIA
Mycobacterium tuberculosis
Mycobacterium species other than *M. tuberculosis* (see Table 18-7)

FUNGI
Aspergillus species
Blastomyces dermatitidis
Candida species
Coccidioides immitis
Cryptococcus neoformans
Histoplasma capsulatum
Pneumocystis jirovecii
Zygomycetes

VIRUSES
Adenoviruses
Cytomegalovirus
Enteroviruses
Epstein-Barr virus
Herpes simplex viruses
Human metapneumovirus
Influenza A and B
Parainfluenza viruses
Respiratory syncytial virus
SARS-associated coronavirus
Varicella-zoster virus

PROTOZOA
Toxoplasma gondii

HELMINTHS
Ancylostoma duodenalis
Ascaris lumbricoides
Brugia species
Necator americanus
Paragonimus species
Strongyloides stercoralis
Trichinella spiralis
Wuchereria bancrofti

SARS, severe acute respiratory syndrome.

sputum specimens of good quality for microbiologic testing. The importance of proper sputum collection was documented by Laird 100 years ago in studies on the yield of *Mycobacterium tuberculosis* according to the appearance and cellular composition of the sputum examined (Table 18-3).[14] Once collected, the specimen should be delivered promptly to the laboratory for processing to prevent overgrowth of contaminating organisms.

SPECIMEN SELECTION AND COLLECTION

General guidelines for the types of specimen required and available tests according to etiologic agent are listed in Table 18-4. Expectorated sputum is the specimen most frequently obtained for the laboratory diagnosis of lower respiratory tract infection.[15,16] The first requirement for collection of a sputum specimen is an alert and cooperative patient who can rinse out his or her mouth with water or even brush his or her teeth before being instructed to produce a specimen resulting from a deep cough. The patient then must be encouraged to cough deeply to expectorate a specimen of lower respiratory secretions. Specimens are to be collected in sterile, leakproof, screw-capped containers. Containers with specimens from patients with suspected tuberculosis should be transported in a water-tight plastic biohazard bag to prevent contact with outside surfaces of the container.

Although a single sputum specimen may be sufficient for establishing the diagnosis of an acute bacterial inflammatory process, collection of a series of two or three single early morning sputum specimens obtained on successive days is recommended for patients suspected of having mycobacterial or fungal infections. Pooled specimens collected cumulatively over 12 to 24 hours are not satisfactory for this purpose because of excessive contamination with other bacteria. In patients with nonproductive cough or suspected mycobacterial, fungal, or *Pneumocystis jirovecii* infections, it may be helpful to induce sputum production with an inhaled aerosol of

hypertonic salt solution (3% to 10%). Specimens to be cultured for mycobacteria, if sent to a reference laboratory for processing, should be shipped refrigerated or treated first with cetylpyridinium chloride and sodium chloride in a screw-capped container,[17] which must be placed in a metal can with absorbent material and then packaged in an approved mailing container according to local specimen transport regulations. Although the recovery of fungi is optimal from cultures of fresh specimens, most clinically significant fungi appear to survive storage of 16 days or longer.[18] Specimens for viral cultures should be shipped refrigerated but not frozen, whereas specimens for chlamydial culture should be placed into sucrose-phosphate (2SP) medium and shipped frozen.

Sputum should be transported to the laboratory promptly after its collection to avoid overgrowth of contaminating flora and to improve isolation rates of pathogenic bacteria. Jefferson and associates[19] compared the results of respiratory specimens cultured immediately after specimen collection and after 2 to 5 hours of transportation, and found that fewer cultures yielded staphylococci, pneumococci, and gram-negative bacilli in the delayed group. Similarly, Penn and Silberman[20] found that organisms observed microscopically on Gram-stained smears of sputum specimens and their relative numbers in cultures changed dramatically between processing within an hour of collection and processing

TABLE 18-2. Microorganisms Normally Present in the Oral Cavity and Upper Respiratory Tract

Organism	Upper Respiratory Tract*	Mouth*
BACTERIA		
Actinomyces	+	+
Bacteroidiaceae	+	++
Bifidobacteria		+
Clostridia		±
Cocci, anaerobic	+	++
Corynebacteria	+	+
Enterobacteriaceae	±	±
Enterococci	±	±
Eubacteria	±	+
Fusobacteria	+	++
Haemophilus species	++	+
Mycoplasma species	+	+
Neisseria species	++	+
Propionibacteria	+	±
Pseudomonas species	±	±
Spirochetes		±
Staphylococci	+	+
Streptococci		
S. pyogenes	±	±
Viridans group	+	++
FUNGI		
Aspergillus		+
Candida	+	++
Cephalosporium	±	
Cryptococcus		±
Fusarium		±
Penicillium		+
Rhodotorula		+

*±, irregular or infrequent; +, common; ++, prominent.

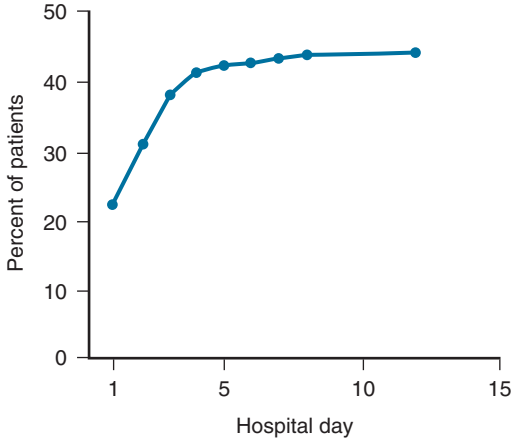

FIGURE 18-1 ■ Cumulative occurrence of colonization of the respiratory tract with gram-negative bacilli among patients in an intensive care unit. Gram-negative bacilli were isolated from either the pharynx or sputum (data from 1970 and 1971 combined). (Redrawn from Johanson WG Jr, Pierce AK, Sanford JP, et al: Nosocomial respiratory infections with gram-negative bacilli: The significance of colonization of the respiratory tract. Ann Intern Med 77:701–706, 1972.)

TABLE 18-3. Correlation Between Character of Sputum and Recovery of Bacteria from 541 Patients

SPUTUM		PATIENTS	
Appearance	**Predominant Cells**	**Total No.**	**No. of Positive (%)**
Watery or mucoid	Squamous epithelial	94	2 (2.1)
Mucopurulent, nonhomogeneous	Squamous epithelial	147	13 (8.8)
Mucopurulent, nonhomogeneous	Leukocytes	91	54 (59.3)
Mucopurulent, homogeneous	Leukocytes	144	110 (76.3)

Based on data from Laird AT: A method for increasing the diagnostic value of sputum reports. JAMA 52:294–296, 1909.

TABLE 18-4. Specimens for Isolation and Tests for Detection of Lower Respiratory Tract Pathogens

Organism	Specimen	Microscopy	Culture	Serology	Other
BACTERIA					
Aerobic and facultatively anaerobic	Expectorated sputum, blood, TTA, empyema fluid, protected catheter brush, BAL, lung aspirate or biopsy	Gram-stained smear	X		
Anaerobic	TTA, empyema fluid, tissue, abscess	Gram-stained smear	X		
Legionella species	Expectorated or induced sputum, BAL, bronchial washings, lung aspirate or biopsy, pleural fluid, serum (antibody EIA), urine (antigen EIA)	DFA		EIA	RIA or EIA (urine) PCR (throat swab, sputum)
Nocardia species	Expectorated or induced sputum, BAL, bronchial washings, lung aspirate or biopsy, tissue, abscess	Gram and/or modified carbolfuchsin stain	X		
Mycobacteria	Expectorated or induced sputum, BAL, bronchial washings, lung aspirate or biopsy, tissue, gastric washings	Fluorochrome or carbolfuchsin stain	X		Tuberculin skin test, PCR or TMA (sputum)
Chlamydiaceae	Nasopharyngeal swab, BAL, bronchial washings, lung aspirate or biopsy, serum	DFA	X	CF, EIA, MI	PCR (throat swab, sputum, BAL, bronchial washings)
Mycoplasma	Expectorated sputum, nasopharyngeal swab, BAL, lung aspirate or biopsy, serum		X	CF, EIA, MI	PCR (throat swab, sputum, BAL, bronchial washings)
FUNGI					
Deep-Seated Infections					
Blastomyces	Expectorated or induced sputum, BAL, bronchial washings, lung aspirate or biopsy, tissue, serum	KOH or calcofluor white with phase contrast; GMS stain	X	CF, ID	EIA (urine)
Coccidioides	Expectorated or induced sputum, BAL, bronchial washings, lung aspirate or biopsy, tissue, serum	KOH or calcofluor white with phase contrast; GMS stain	X	CF, ID, LA, EIA	
Histoplasma	Expectorated or induced sputum, BAL, bronchial washings, lung aspirate or biopsy, tissue, serum	KOH or calcofluor white with phase contrast; GMS stain	X	CF, ID	EIA (urine)
Opportunistic Infections					
Aspergillus	BAL, lung biopsy, serum	H & E, GMS stain	X	ID	
Candida	BAL, lung biopsy, serum	H & E, GMS stain	X		LA
Cryptococcus	Expectorated sputum, BAL, lung biopsy, serum	H & E, GMS stain	X	ID, LA, EIA	LA (urine)
Zygomycetes	Expectorated sputum, BAL, lung biopsy, tissue	H & E, GMS stain	X		
Pneumocystis	Lung biopsy, BAL, bronchial brushings or washings, induced sputum	GMS, calcofluor white, toluidine blue O, or Giemsa stain; DFA			PCR (induced sputum, BAL)
VIRUSES					
	Nasal washings, nasopharyngeal swab, BAL, lung aspirate or biopsy, serum	DFA, IFA	X	CF, EIA	PCR (throat swab, sputum, BAL, bronchial washings)

BAL, bronchoalveolar lavage; CF, complement fixation; DFA, direct fluorescent antibody; EIA, enzyme immunoassay; GMS, Gomori methenamine silver; H & E, hematoxylin and eosin; ID, immunodiffusion; IFA, indirect fluorescent antibody; KOH, potassium hydroxide; LA, latex agglutination; MI, micro-immunofluorescence; PCR, polymerase chain reaction; RIA, radioimmunoassay; TMA, transcription-mediated amplification; TTA, transtracheal aspirate.

Data from Miller JM: A Guide to Specimen Management in Clinical Microbiology, 2nd ed. Washington, DC: ASM Press, 1998; and Waites KB, Saubolle MA, Talkington DF, et al: Cumitech 10A: Laboratory Diagnosis of Upper Respiratory Tract Infections (Sharp SE, coord ed). Washington, DC: ASM Press, 2006.

after overnight refrigeration. While there were no significant differences in the culture results between the immediate and delayed cultures in this study, the loss of reliable microscopic features had significant impact on the interpretation of culture results.

Since sputum is usually not obtainable from children under 5 years of age, one or more invasive approaches may be necessary to obtain specimens in such cases. Specimens may include blood, pleural fluid, tracheal aspirate through a catheter inserted by direct laryngoscopy, and, in critically ill children, percutaneous lung aspirate.[16] Unfortunately, cultures of nasopharyngeal secretions or tracheal aspirates obtained via a catheter passed through the nose or mouth may be misleading because of frequent isolation of potentially pathogenic bacteria from the throats of healthy children. For example, *H. influenzae* has been recovered from selective cultures of the throat in 80% of healthy children.[21]

As shown in Table 18-4, there are several other instances in which examination of specimens other than sputum is indicated. For example, sputum is not a suitable specimen for the diagnosis of anaerobic pleuropulmonary disease because of the predominantly anaerobic composition of the bacterial flora in the oropharynx that may contaminate the specimen. In such instances, consideration may be given to obtaining transtracheal aspirates for culture. If saline or Ringer's lactate solution is instilled during transtracheal aspiration to facilitate specimen collection, one must be certain that the solution does not contain a preservative or bacteriostatic agent. Aerobic and anaerobic cultures of protected catheter brushes have also been recommended for identification of organisms causing anaerobic pleuropulmonary disease.[22] However, Bordelon and coworkers[23] found a poor correlation between the bacteriology of paired specimens obtained by protected catheter brush and by transtracheal aspirate in this setting. For detection of respiratory viruses, throat swabs or nasopharyngeal aspirates or washings are preferred over sputum samples.[24] Throat swabs may also be used for detecting *Chlamydophila pneumoniae,*[25–28] *Mycoplasma pneumoniae,*[28–31] *Legionella* species,[28] and respiratory viruses[32–37] by nucleic acid amplification assays. Blood cultures may be obtained in cases of suspected acute bacterial pneumonia but are positive only in 3% to 37% of cases.[38] If pleural fluid is present, thoracentesis should be performed to obtain fluid for aerobic and anaerobic cultures. A positive culture from blood or pleural fluid has a high predictive value in establishing the microbial cause of the infection. Urine may also be a useful specimen in certain situations. Pneumococci, for example, may be recovered from urine cultures in as many as 38% of patients with pneumococcal pneumonia.[39] Urine may also be tested for the presence of pneumococcal[40] and *Legionella pneumophila*[41,42] antigens. However, because antigenuria may persist for weeks or months following an acute bacterial infection, its presence may be indicative of past rather than current infection. Fungal antigen tests of urine are also available for diagnosis of histoplasmosis and blastomycosis.[43,44] Serologic tests of acute and/or convalescent serum samples are useful for the diagnosis of pulmonary infections caused by *Legionella* species, *M. pneumoniae, Chlamydia trachomatis, Chlamydophila psittaci, C. pneumoniae,* viruses, and fungi. These diagnostic approaches are discussed further in the Serologic Tests section of this chapter.

When easily obtained samples such as sputum, blood, and urine do not yield a diagnosis, more invasive techniques may be necessary. Bronchoscopy offers a safe approach to the collection of a specimen, although the inevitable contamination of the lower respiratory tract by oropharyngeal flora during insertion of the bronchoscope has generally invalidated the results of bacterial cultures obtained by suction through the inner channel or by an unprotected brush. An alternative fiberoptic bronchoscopic technique to obtain uncontaminated lower respiratory secretions is to use a distally occluded, telescoping, protected catheter brush.[45] Several studies have demonstrated the high sensitivity and specificity of quantitative cultures of secretions obtained by a protected brush in establishing the diagnosis of nosocomial pneumonia when the criterion of greater than 10^3 CFU/mL is used to define a positive or clinically significant culture result.[46,47]

Bronchoalveolar lavage (BAL) is widely used for the diagnosis of nonbacterial pulmonary infections in immunocompromised patients, but in more recent years its use has been expanded to include diagnosis of bacterial pneumonia, especially for nosocomial cases.[46–48] In most instances, paired specimens are obtained by both protected catheter brush and BAL, with numerous studies in the literature comparing the results of culture of these two types of specimens. In patients with CAP requiring admission to the hospital, use of these procedures has been shown to provide microbiologic diagnoses that are not obtainable otherwise by noninvasive means.[49] In some patients, these procedures have yielded additional pathogens not obtainable by noninvasive approaches. Much work has been done also with the use of BAL for the diagnosis of ventilator-associated pneumonia.[47,49] One of the problems in assessing the literature on the value of BAL culture results is the varied criteria used by different investigators to define a positive result. These criteria have included (1) intracellular organisms present in more than 7% of the cells and greater than 10^5 CFU/mL of unconcentrated lavage fluid, and (2) 10^5 CFU/mL of concentrated lavage fluid.[46,47] Consequently, valid comparison of published studies must be made cautiously. Additional variables include the different criteria in selecting study patients eligible for evaluation, and inclusion or exclusion of patients receiving prior antimicrobial therapy. Although the results of cultures from protected catheter brushes and BAL specimens are quantitatively similar, Meduri and Baselski[49] concluded that BAL specimens provided a larger and more representative volume of lower respiratory tract secretions than the protected catheter brushes, allowing microscopic analysis of the cytocentrifuged BAL fluid to identify the type of bacteria present and to demonstrate the presence of an active inflammatory response (neutrophils with intracellular organisms). The study also showed that the

diagnostic value of breakpoints of bacterial growth (i.e., 10^3 to 10^5 CFU/mL) depended not only on the type of microbiologic processing used but also on the relationship of two variables: the concentration of pathogens present in the BAL fluid, and the degree of contamination of the bronchoscopic channel through which lavage fluid was injected and aspirated. Other variables affecting the sensitivity of BAL specimens include the volume of lavage fluid injected and the volume of fluid retrieved. In contrast, diagnostic specificity depends greatly on techniques used to minimize contamination of the specimen by upper respiratory flora, such as discarding the first aliquot of aspirated fluid.

Topical anesthetics used for bronchoscopy can exhibit in vitro antimicrobial properties. However, this antimicrobial effect may be negligible in vivo because of the relatively short period between exposure of bronchial aspirates to lidocaine and inoculation of BAL specimens onto culture media.[50]

Finally, more aggressive techniques, such as transbronchial lung biopsy, video-assisted and open-lung biopsy, may be necessary for definitive diagnosis of pulmonary infections in certain populations, such as immunocompromised hosts. Fortunately, the use of such approaches has become less frequent since the advent of BAL and protected catheter brushes using fiberoptic bronchoscopic techniques. BAL often provides an alternative to biopsy procedures in the diagnosis of opportunistic lung infections[51] or when treatment fails.[48]

When deemed necessary, open-lung biopsy or video-assisted thoracoscopy provides the most direct approach for obtaining adequate amounts of tissue for histopathologic examinations and microbiologic testing. Such specimens provide a significant amount of information because they may contain evidence of the entire pathologic process. Material from an abscess should include not only pus but also tissue from the wall of the abscess. Pus should be withdrawn into a sterile syringe, which can be transported directly to the laboratory, or the contents may be injected into an anaerobic vial for transport to the laboratory. The use of a swab to obtain pus from an abscess is inadequate, and this practice is strongly discouraged. Ideally, a surgical specimen should be bisected aseptically in the operating room, with one half of the specimen submitted to surgical pathology and the other half placed in a sterile, leak-proof, screw-capped container for transport to the laboratory for processing.

Regardless of the particular invasive approach selected for obtaining specimens from immunocompromised hosts, such specimens are obtained usually at some risk and considerable expense to the patient. Therefore, laboratory test protocols such as that shown in Figure 18-2 should be established for processing specimens obtained by these invasive procedures to maximize the diagnostic yield and avoid the need to repeat such procedures. The surgical pathologist should work closely with the clinical microbiologist to ensure that specimen requirements for each laboratory are met and unnecessary duplication of specific examinations is avoided, especially when the amount of specimen material obtained is limited and must undergo multiple tests.

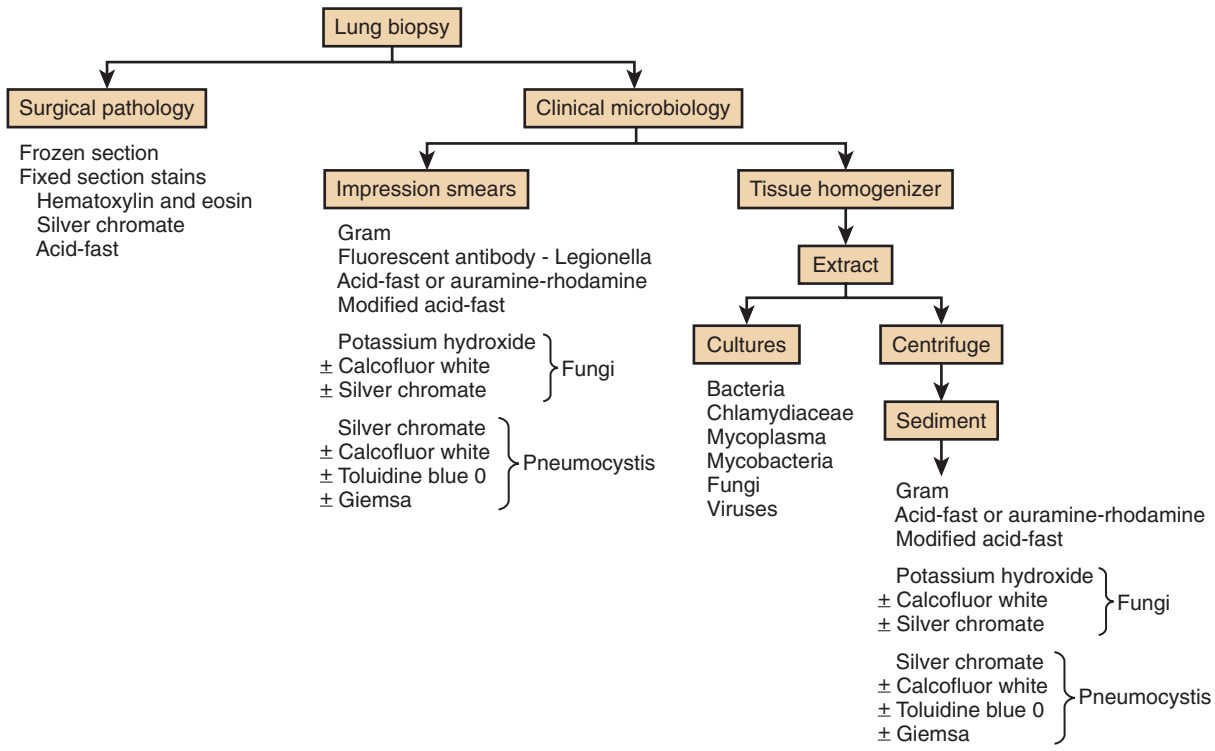

FIGURE 18-2 ■ Suggested protocol for processing video-assisted or open-lung biopsy specimens obtained from immunosuppressed patients. Variations on this protocol may be applicable in certain settings.

DIRECT EXAMINATION OF SPECIMENS

Microscopic or immunologic examination of specimens may offer a rapid approach to the diagnosis of lower respiratory infection and is an essential component of any laboratory protocol for processing BAL fluids and lung biopsy specimens from immunocompromised patients. The value of microscopic examination of the sputum to identify the nature of the inflammatory process was demonstrated in a beautiful series of illustrations in *Das Sputum,* by von Hoesslin, in 1921.[52] Similarly, Chodosh[53] and Baigelman and Chodosh[54] have urged examination of wet preparations of sputum stained with crystal violet to identify eosinophils and differentiate allergic from nonallergic inflammation. Microscopic examination of sputum cells has also been widely adopted as a screening procedure to determine the acceptability of a specimen for bacterial culture.[14]

The first step in the screening process is to select a purulent or opalescent area of the specimen and to transfer this portion of the sample to a sterile Petri dish. This sample is then used to prepare a wet mount or a Gram-stained smear for microscopic examination. The Gram stain is a rapid staining technique that differentiates bacteria based on the ability of their cell wall to retain a primary dye (typically crystal violet) following treatment with an iodine mordant and solvent. Bacteria that retain the dye are termed *gram positive,* while those that become decolorized and stain only with the subsequent counterstain (basic fuchsin or safranin) are termed *gram negative.* This staining method also stains squamous epithelial cells (Fig. 18-3A), ciliated columnar epithelial cells (see Fig. 18-3B), and alveolar macrophages or histiocytes (see Fig. 18-3C), which can be readily differentiated under high-power magnification (oil immersion, ≥ 630×) by an experienced microscopist. The presence of numerous squamous epithelial cells (>25 per low-power field, ≤ 100× magnification; Fig. 18-4AB) is indicative of oropharyngeal contamination. Such specimens should not be cultured for bacteria, and another specimen should be requested.

In contrast, specimens demonstrating a preponderance of polymorphonuclear leukocytes, ciliated columnar epithelial cells, or alveolar macrophages with few, if any, squamous epithelial cells (<10 per low-power field; see Fig. 18-4C) represent lower respiratory secretions that warrant further examination under high-power field and bacterial culture. The maximum recommended number of squamous epithelial cells per low-power field determining specimen acceptability for bacterial culture has been disputed in the literature.[55] However, Geckler et al.[56] found good overall agreement between the results of bacterial culture of paired sputa and transtracheal aspirates when the sputum contained fewer than 25 squamous epithelial cells per low-power field. The number of polymorphonuclear leukocytes had little effect on this correlation and should not be used alone to determine specimen adequacy for culture. The presence of alveolar macrophages is a more specific indicator of lower respiratory secretions than leukocytes and is more likely to be associated with a significantly lower incidence of oropharyngeal contamination.[57] These criteria have been established primarily to assess the quality of expectorated sputum samples suitable for bacterial culture. Similarly, endotracheal aspirates from adults and children should not be cultured for bacteria if the screening Gram-stained smears show no organisms or

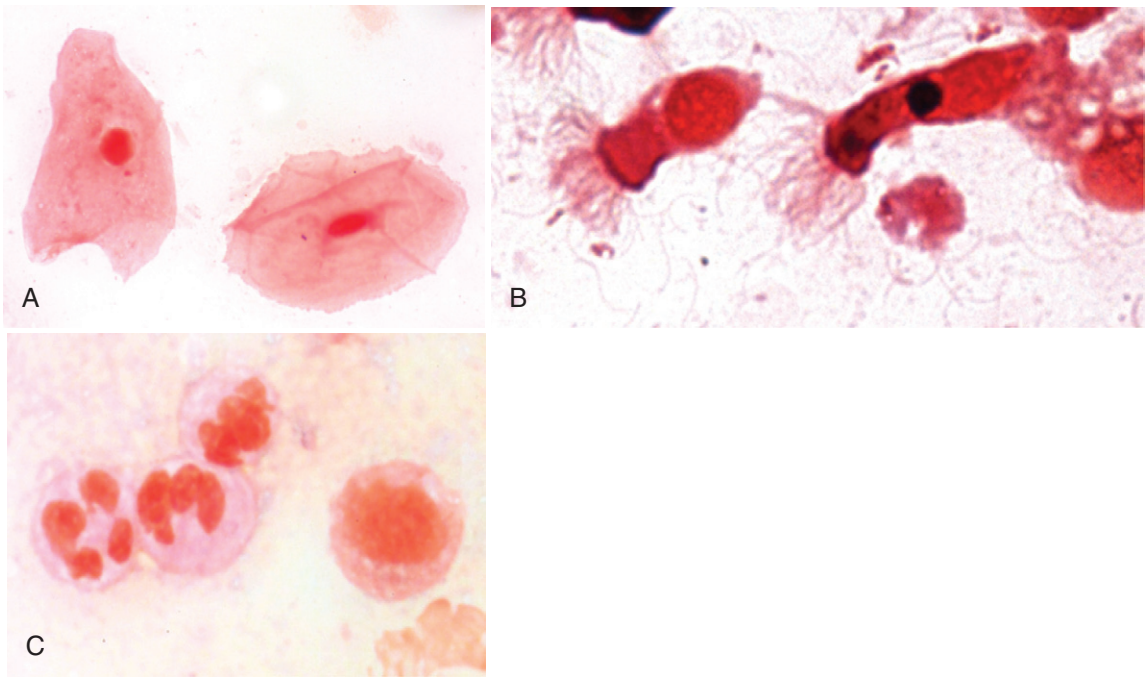

FIGURE 18-3 ■ Gram-stained appearance of typical cells in sputum smears (original magnification, ×630). **A,** Squamous epithelial cells. **B,** Ciliated columnar epithelial cells. **C,** Alveolar macrophage and three polymorphonuclear leukocytes.

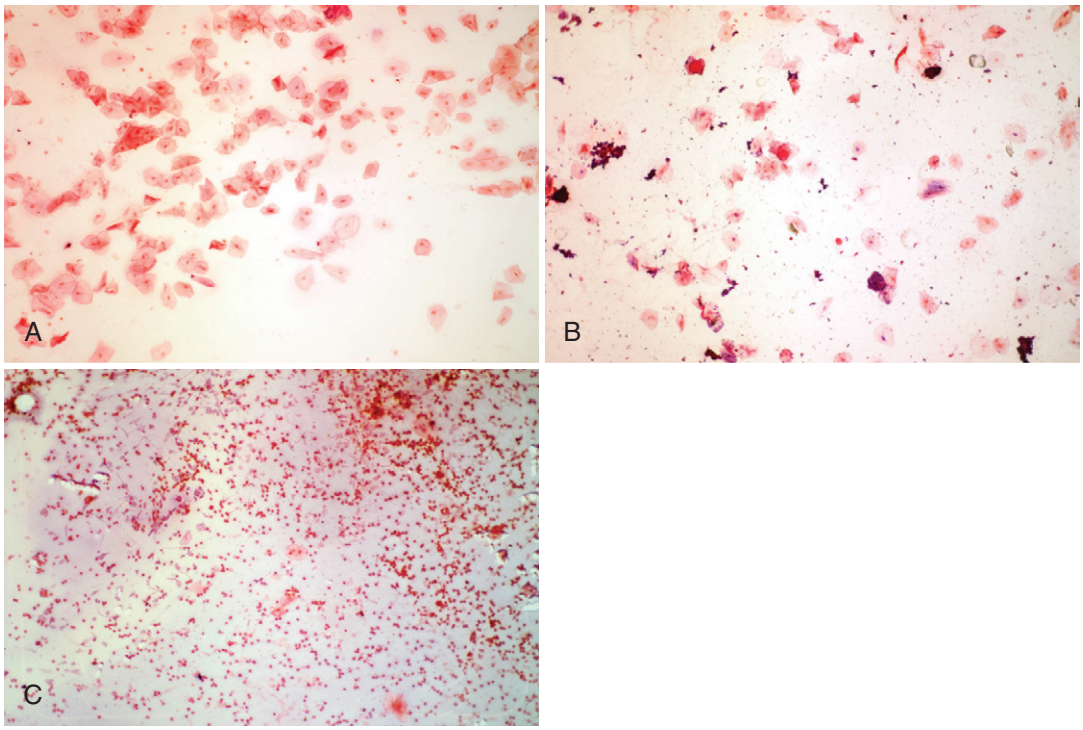

FIGURE 18-4 ■ Gram-stained smears of representative sputum specimens (original magnification, ×100; low-power field). **A,** <10 leukocytes, >25 epithelial cells. **B,** 10 to 25 leukocytes, >25 epithelial cells. **C,** >25 leukocytes, <10 epithelial cells.

leukocytes present.[58,59] Morris et al.[58] further showed that cultures for bacteria should not be performed if more than 10 squamous epithelial cells are present per low-power field in endotracheal aspirates from adults. However, cytologic screening to determine specimen acceptability is not indicated in respiratory specimens submitted for mycobacterial, fungal, and viral cultures because of the following reasons: (1) decontamination of these specimens is needed prior to these cultures, (2) selective culture media are used, and (3) little doubt exists regarding the clinical importance of mycobacterial, deep fungal, and viral isolates when they are present. Regardless of the type of cultures requested, direct correlation exists between quality of a given specimen and the yield of cultures (see Table 18-3).

Provided a specimen is acceptable for bacterial culture on the basis of cytologic screening, the smear should then be examined under high-power field to determine any predominance of a specific morphologic type of bacteria present. In general, high-power fields without any squamous epithelial cells and with at least three nonsquamous cells (e.g., polymorphonuclear leukocytes, macrophages, ciliated epithelial cells) should be examined for each stained smear.

In Gram-stained smears, *S. pneumoniae* (i.e., pneumococci) appear as lancet-shaped gram-positive diplococci. In assessing patients with acute CAP, Rein et al.[60] found that a preponderant flora of 10 or more gram-positive lancet-shaped diplococci per oil immersion field on a Gram-stained smear of sputum correctly predicted the presence of pneumococci in corresponding cultures in 90% of cases, with a sensitivity and specificity of 62% and 85%, respectively. As the criteria for defining the presence of pneumococci in the sputum Gram-stained smears were lowered, sensitivity increased but specificity decreased. Similar levels of sensitivity of Gram-stained smear have been reported by others in identifying pneumococci as well as *H. influenzae* in sputum specimens from patients with acute CAP.[61,62] For the diagnosis of pneumococcal pneumonia, a combination of Gram-stained smear and culture of sputum can yield the correct diagnosis in more than 80% of patients who received less than a 24-hour duration of effective antibiotic therapy.[63]

Diagnostic sensitivity and specificity also vary according to how strictly the criteria are set for defining a positive Gram-stained smear. If the presence of any lancet-shaped gram-positive diplococci is used as the criterion for positivity with *S. pneumoniae,* then the sensitivity of Gram-stained smear is excellent, but specificity is nil. Problems with such nonspecific criteria used by inexperienced microscopists such as house staff and medical students in examining Gram-stained smears of sputum were illustrated by several studies.[64,65] The use of the quellung reaction, in which *S. pneumoniae* capsule-specific antibodies enhance microscopic identification, has significantly improved the accuracy in detecting the presence of pneumococci in sputum.[66] However, the quellung reaction is subject to observer bias and has not been used widely in clinical laboratories.

Direct examination of sputum for identifying other pathogens causing acute bacterial pneumonia in adults, such as *H. influenzae, Moraxella catarrhalis,* and *Neisseria meningitidis,* may also be problematic. The presence of many pleomorphic, slender gram-negative

coccobacilli, especially within leukocytes, suggests the diagnosis of *H. influenzae.*[67–69] However, *H. influenzae* can often be found in the upper respiratory tract of asymptomatic patients,[21] and available data showed that Gram-stained smears of sputum are of variable diagnostic value.[67,68] Gram-stained smears of transtracheal aspirates have a higher diagnostic value in the diagnosis of *H. influenzae* pneumonia,[67,69] and should be considered when clinically indicated.

Similarly, *M. catarrhalis* and *N. meningitidis* may often be found in the upper respiratory tract. *Moraxella catarrhalis* is a normal commensal in this location, and nasopharyngeal carriage of *N. meningitidis* may range from 10% in healthy adults to 70% among healthy military recruits.[70] Their role as etiologic agents of pneumonia is strongly suggested by the finding of large numbers of gram-negative diplococci located within and outside of polymorphonuclear leukocytes in sputum specimens.[71–73] Furthermore, the correlation between sputum smear with these findings and transtracheal aspirate cultures is excellent.[73] However, *M. catarrhalis* cannot be distinguished from *N. meningitidis* on the basis of their microscopic morphology in Gram-stained smears of sputum specimens and should only be described morphologically (e.g., gram-negative diplococci) while awaiting culture results.

Because sputum microscopy (and subsequent culture) can give misleading results, the diagnosis of *Haemophilus, Moraxella,* or meningococcal pneumonia can only be confirmed by invasive techniques. And because invasive techniques are infrequently performed to identify the etiologic agents of acute CAP, the sensitivity and specificity of sputum Gram-stained smears cannot be determined reliably in such cases. Nevertheless, the presence of large numbers of organisms, intracellularly and extracellularly, resembling *Haemophilus, Moraxella,* or *Neisseria* in sputum Gram-stained smears should lead the clinical laboratory to identify these organisms in cultures and to test them for susceptibility to various commonly used antimicrobial agents.

A similar problem occurs in trying to distinguish between colonization and superinfection by gram-negative bacilli. Tillotson and Finland[3] found that the organisms considered responsible for bacterial secondary infection were present in moderate to large numbers in Gram-stained smears of sputum. Similarly, in a study of hospitalized patients with pneumonia, Noone and Rogers[74] found neutrophils and large numbers of gram-negative bacilli present in lower respiratory secretions that were collected by tracheobronchial suction and yielded 10^7 to 10^{10} CFU of gram-negative bacilli per milliliter. However, up to 10^8 CFU of gram-negative bacilli per milliliter may be found in respiratory secretions of patients on mechanical ventilation in intensive care unit without evidence of pneumonia,[2] and about 10^7 CFU of gram-negative bacilli per milliliter have been found in saline gargles from aspiration-prone patients.[4]

In summary, the Gram-stained smear is an essential and necessary part of the examination of sputum, for determining the quality and acceptability of sputum specimens for bacterial culture and for providing a rapid assessment of the most likely etiologic agent of the pneumonia. However, improper preparation and interpretation of Gram-stained smears by untrained health care providers do pose a serious limitation on the value of this diagnostic procedure.[60,75]

The Gram-stained smear may be used to assess the adequacy of specimens other than sputum, such as endotracheal aspirates from adults or children.[58,59] The Gram-stained smear of transtracheal aspirates is both sensitive and specific for the diagnosis of bacterial pneumonia and is especially useful in indicating the presence of anaerobic infections. Gram-stained smears of cytocentrifuged BAL fluids can also be helpful in identifying the type of bacteria causing the infection as well as the type of inflammatory reaction present, particularly with the finding of neutrophils with intracellular organisms.[49]

Many organisms, including the mycobacteria and *Legionella,* do not stain well or at all with Gram stain, and visualization requires the use of alternative methods. In particular, mycobacteria are visualized classically using fluorochrome and carbolfuchsin stains. Carbolfuchsin or "acid-fast" stains take advantage of the fact that most *Mycobacteria* species retain the primary carbolfuchsin stain following decolorization with acid-alcohol due to the high lipid content of their cell walls (i.e., they are acid-fast). Other bacteria will decolorize with this method and do not obscure the identity of the acid-fast organisms. Alternatively, fluorochrome stains selectively highlight mycobacteria with a fluorescent dye such as auramine-rhodamine. Microscopic examination of respiratory secretions stained with both fluorochrome and carbolfuchsin stains is about 50% sensitive and 99% specific in detecting *M. tuberculosis* in most clinical laboratories.[76,77] However, the percentage of smear-negative but culture-positive cases varies according to the severity of disease, ranging from 65% in patients with minimal disease to less than 10% in those with advanced disease, with overall incidence of 26% among hospitalized patients with pulmonary tuberculosis.[78] Among those initially smear-negative but culture-positive cases, 20% became smear-positive and culture-negative between 4 and 20 weeks after initiation of therapy. Thus, diagnostic value of the acid-fast stained smear is highly dependent on the types of populations studied and the prevalence of tuberculosis in those populations. Another variable influencing the sensitivity of the acid-fast stained smear is the relative centrifugal force used for concentration of the specimen.

Screening a slide for mycobacteria must be done in a careful and consistent manner. Approximately 10,000 acid-fast bacilli per milliliter of sputum must be present to be visualized under light microscopy using an acid-fast stain,[77] and detection can be time consuming and laborious. Fluorescence microscopic examination of sputum smears stained with the auramine-rhodamine fluorochrome rather than an acid-fast stain is more efficient in routine screening for mycobacteria in the diagnostic laboratory. Within the same amount of time, a much larger smear surface area can be examined with a 25× lens objective under fluorescence microscopy compared with the 100× lens objective required for screening

carbolfuchsin-stained smears under light microscopy. Because of the improved speed and ease of this laboratory technique, fluorescence microscopic examination is the method of choice for screening mycobacteria in sputum smears in high-volume clinical laboratories.

Immunofluorescence examination by direct fluorescent antibody (DFA) staining is an alternative method for direct visualization of organisms. The diagnosis of legionellosis is usually made by a combination of direct immunofluorescence examination and culture of respiratory specimens, and serologic testing of serum and urine. DFA staining can be done on sputum, transtracheal aspirate, bronchial washing, and lung tissue specimens, with sensitivities ranging from 25% to 66% for the diagnosis of *L. pneumophila* pneumonia, and specificities of more than 94%.[79] Both clinical and technical variables account for the broad range of sensitivity of this test, and accuracy of this method for detection of pneumonia due to other *Legionella* species is less precisely known. In the absence of other supporting evidence, a positive DFA result is generally not accepted as sufficient for the diagnosis of *Legionella* infection, and other confirmatory measures should be considered.

DFA has also been found to be sensitive and specific in detecting *C. trachomatis* in conjunctival and nasopharyngeal specimens from infants with conjunctivitis and pneumonia,[80,81] and has also been applied to respiratory secretions for diagnosis of respiratory infections due to respiratory syncytial virus (RSV), influenza A and B viruses, parainfluenza viruses, adenoviruses, and measles virus.[24] Although somewhat less sensitive than tissue culture techniques (as described later), these immunofluorescence microscopic methods offer rapid detection and a diagnostic approach for viral pathogens for which conventional viral culture techniques are tedious or not available.

Another method for direct examination makes use of phase-contrast microscopy of respiratory secretions mixed with 10% potassium hydroxide solution containing 10% glycerin. This important technique may provide immediate identification of *Blastomyces dermatitidis, Coccidioides immitis, Cryptococcus neoformans,* and *Aspergillus* species directly from clinical samples.[82] Calcofluor white, a fluorochrome that binds to chitin and cellulose present in fungal cell wall, can be added to potassium hydroxide or used alone to provide better delineation of fungal elements, including *P. jirovecii.*[83–85] Although calcofluor white stain may be used to detect *P. jirovecii,* other stains such as Giemsa, silver-based, or direct immunofluorescence are typically used for this purpose. Wolfson et al.[86] found the direct immunofluorescent monoclonal antibody staining method to be more sensitive and to require less screening time than the Giemsa staining method for detecting *P. jirovecii* in induced sputum and BAL specimens obtained from patients with human immunodeficiency virus. Cregan et al.[87] observed sensitivities of 95% with rapid silver stain, 97% with direct immunofluorescence, 97% with indirect immunofluorescence, and 92% with Diff-Quik (a modified Giemsa stain) for detecting *P. jirovecii* in sputum. All detection methods were slightly less sensitive for BAL fluid than sputum specimens. Kim et al.[83] found the rapid calcofluor white stain to be more sensitive than a modified methenamine silver stain in detecting *P. jirovecii* in various respiratory specimens, including BAL fluid, lung biopsy, induced sputum, expectorated sputum, tracheal secretions, and bronchial secretion.

TABLE 18-5. Detection of *Pneumocystis jirovecii* Cysts in Lung Tissue

Method	No. of Positive	No. of Cysts
Impression smear	18	1–320 ($P < .001$)*
Concentrate†	23 (<0.001)‡	2–1,900
Histopathological section	12	0

*Wilcoxon matched-pairs signed-rank test.
†Homogenate centrifuged at 2,525 × *g* for 15 minutes.
‡Sign test.
Based on Gay JD, Smith TF, Ilstrup DM: Comparison of processing techniques for detection of *Pneumocystis carinii* cysts in open-lung biopsy specimens. J Clin Microbiol 21:150–151, 1985.

As illustrated in Figure 18-2, direct microscopic examination is an essential component of the laboratory protocol for examining lung biopsy tissue specimens obtained from immunosuppressed patients. A variety of stains may be utilized depending on the organism(s) suspected, amount of tissue available, and capability of the processing laboratory. Like other respiratory specimens, the auramine-rhodamine fluorochrome stain is preferred over carbolfuchsin stains for screening mycobacteria in smears of lung tissue homogenate. Similarly, silver-based methods and calcofluor white may be used for staining fungi in tissue, although some prefer the toluidine blue O, Giemsa, or a fluorescent monoclonal antibody stain to detect *P. jirovecii.* Concentration of lung tissue homogenate by centrifugation has been shown to enhance the detection of *P. jirovecii* cysts (Table 18-5).[88] A laboratory protocol similar to that proposed for lung tissue samples should be followed when examining BAL fluids from immunosuppressed patients.

CULTURES, MICROBIAL ANTIGEN DETECTION, AND SUSCEPTIBILITY TESTING

Microbial culture of respiratory specimens should be performed to provide definitive identification of the pathogens and to permit determination of their susceptibility to antimicrobial agents. Numerous approaches to culture are available, with many culture media suitable for cultivation of particular groups of microorganisms. Such media may be "nonselective" to support the growth of a wide variety of organism or be "selective" to contain substances that favor growth of certain organisms to the exclusion of others. Media can also allow the differentiation of two different organisms growing on the same media (i.e., differential or indicator media). Selection of media optimal for isolation of suspected pathogens is a complex process and is beyond the scope of this chapter.

Bacteria

Over the years much laboratory effort has been directed to improving the sensitivity and specificity of bacterial cultures of sputum. In 1971, Barrett-Connor[11] suggested that routine sputum culture for the diagnosis of bacterial pneumonia had become a "sacred cow" (i.e., a laboratory test that is so highly regarded that it is not open to criticism). She challenged this notion by showing that only 45% of patients with bacteremic pneumococcal pneumonia had pneumococci isolated from their sputum cultures, whereas 27% of patients had moderate to heavy growth of another potential pathogen in these cultures. We now better understand how careful specimen collection, cytologic screening of specimens to obviate culture of those contaminated with oropharyngeal secretions, and use of the results of the Gram-stained smear to guide identification of isolates in culture all contribute to the diagnostic value of sputum culture in acute pneumococcal pneumonia. Anaerobic or microaerobic culture has also been shown to enhance the detection of pneumococci.[89,90] Usually, pneumococci can be isolated in culture when the organism is present at greater than 10^7 CFU/mL of sputum in acute pneumococcal pneumonia proven by cultures of transtracheal and bronchial aspirates.[91] However, such prediction of culture positivity of transtracheal aspirates based on number of organism present in expectorated sputum may not be reliable, due to differences in the laboratory methods used to process sputum.[10] Study of quantitative cultures of washed sputum specimens in which oropharyngeal contaminants were found in mean numbers of 10^4 CFU/mL and bacterial pathogens were present in mean numbers of 10^6 CFU/mL showed that few pathogens, such as *S. aureus, Klebsiella* spp., and *Pseudomonas aeruginosa,* were isolated from expectorated washed sputum but not from the corresponding transtracheal aspirate when they are present at 10^6 CFU or greater per milliliter of sputum.[92]

Due to the impracticality of the washed sputum–quantitative culture technique, equivocal results obtained from sputum cultures of hospitalized patients with serious CAP, or risks of opportunistic infections, diagnosis of bacterial pneumonia may occasionally require culture of clinical specimens obtained by invasive methods. Such samples include pleural or empyema fluids, transtracheal aspirates, and BAL. These should be cultured for aerobic, facultatively anaerobic, and anaerobic bacteria. Similar cultures should be performed on protected catheter brushes, although there is no universal agreement on the value of anaerobic culture.[23] In general, bacteria present in quantities of greater than 10^3 CFU/mL in cultures of protected catheter brushes[46] and in quantities of greater than 10^4 CFU/mL in cultures of BAL fluids[49] should be identified and tested for their susceptibility to appropriate antimicrobial agents.[93] Blood may also be cultured, although the yield in CAP is only up to 37% and less than 25% in nosocomial pneumonia.[38,94,95]

Specific pathogens require special culture media and incubation conditions. For example, respiratory specimens demonstrating a predominance of intra- and extracellular gram-negative diplococci in Gram-stained smears should be cultured on modified Thayer-Martin medium for the presence of *Neisseria* species. However, such culture medium is inhibitory to other potential pathogens such as *M. catarrhalis,* emphasizing the continued need for using nonselective culture media to detect other possible pathogens.

Legionella species also require special culture conditions. They can be recovered from lung tissue and other specimens of normally sterile anatomic sites when cultured on buffered charcoal yeast extract (BCYE) medium supplemented with α-ketoglutarate (BCYE-α). However, selective BCYE media containing polymyxin B, rifabutin, and either cefamandole (BMPA medium) or vancomycin (BVPA-α medium) are needed to recover *Legionella* from respiratory tract specimens (such as sputum) contaminated by oropharyngeal flora that will quickly outgrow and obscure *Legionella* isolates in culture.[79] Acid pretreatment of sputum as previously described may be of additional selective benefit.[96] Culture for *L. pneumophila* is about four times more sensitive than direct immunofluorescence examination by DFA staining of respiratory secretions, since the lower limit of detection by DFA staining is about 10^4 bacterial CFU/mL.[79] Urine is also useful for the detection of *L. pneumophila* antigens (see Serologic Tests section later).

Bacterial cultures of sputum should be performed only on specimens deemed acceptable by direct light microscopic screening of Gram-stained smears. If acceptable, sputum should be cultured on general purpose nonselective media (e.g., blood agar) that are suitable for the isolation of staphylococci, streptococci, pneumococci, and other nonfastidious bacteria. In addition, enriched media (e.g., chocolate agar) for culture of *Haemophilus* species and differential media (e.g., eosin–methylene blue or MacConkey's agar) for isolation of Enterobacteriaceae and *Pseudomonas* should be used. Any organism present in predominance with typical morphology in the Gram-stained smear should be specifically sought and identified in cultures and reported semiquantitatively (Table 18-6), whereas isolates from cultures of protected catheter brush specimens and BAL fluid should be reported quantitatively.[93] Sputum should never be

TABLE 18-6. Semiquantitative Scheme for Grading Bacterial Growth on Streaked Agar Plates

	NO. OF COLONIES PRESENT IN CONSECUTIVE STREAKED QUADRANTS		
Grade	First	Second	Third
1+	<10	0	0
2+	>10	<5	0
3+	>10	>5	<5
4+	>10	>5	>5

Based on data from Waites KB, Saubolle MA, Talkington DF, et al: Cumitech 10A: Laboratory Diagnosis of Upper Respiratory Tract Infections (Sharp SE, coord ed). Washington, DC: ASM Press, 2006.

cultured in broth medium or under anaerobic conditions given the predominance of anaerobic upper respiratory flora, but microaerobic condition (5% CO_2) can be used to enhance growth and detection of pneumococci. Enriched selective media, such as the modified Thayer-Martin and BCYE, should be inoculated when sputa demonstrate a predominance of intra- and extracellular gram-negative diplococci and when legionellosis is suspected. Transtracheal aspirates, pleural or empyema fluids, and lung abscess fluid should be processed for both aerobic and anaerobic cultures. *Neisseria* and *Haemophilus* species isolated from sputum cultures are often reported as usual oropharyneal flora. However, they may be clinically significant respiratory pathogens, especially when they are present predominantly both within and outside polymorphonuclear leukocytes on Gram-stained smears, emphasizing the importance of correlating the culture results with the Gram stain findings.

Antimicrobial susceptibility tests are performed usually on most bacterial pathogens of the lower respiratory tract, such as *S. pneumoniae, S. aureus, H. influenzae,* Enterobacteriaceae, and *Pseudomonas* species. Testing methods and interpretation of results should be done according to national laboratory standards for the various categories of organisms. Based on available personnel resources, commercial testing systems, and expertise in the clinical laboratory, antimicrobial susceptibility may be determined by disk diffusion, agar dilution, microbroth dilution, concentration gradient, or a combination of the four methods. Various automated and semi-automated antimicrobial susceptibility testing systems are commercially available (e.g., BD Phoenix Automated Microbiology System, Etest, MicroScan WalkAway *plus* System, Sensititre, VITEK 2), but detailed description of these methods is beyond the scope of this chapter. Susceptibility test results are reported typically as qualitative categories: "susceptible," "intermediate," and "resistant," based on comparisons of the minimum inhibitory concentration or zone size of bacterial growth inhibition with the criteria values set by national standards for the specific antimicrobial agents and testing method used. However, not all pathogens isolated in the laboratory can be tested reliably by these standard methods, and there are currently no national standards of susceptibility criteria set for these pathogens, such as Chlamydiaceae, *Mycoplasma, Bacillus,* and corynebacteria. In these instances, clinical judgment and careful assessment of patient improvement on antimicrobial therapy is essential for optimal patient management.

Chlamydiaceae

As shown in Table 18-1, the members of the Chlamydiaceae family that cause lower respiratory infection are *Chlamydia trachomatis, Chlamydophila pneumoniae,* and *Chlamydophila psittaci. Chlamydia trachomatis* pneumonia is most commonly seen in infants and young children, and the diagnosis may be made by direct immunofluorescence, culture, and serology. Unlike the other two pathogens in the same family, it is rarely a source of CAP in immunocompetent adults.[97] Clinical specimens for *C. trachomatis* culture are usually inoculated into cycloheximide-treated McCoy heteroploid mouse cells that are incubated for 40 to 72 hours before being examined for the presence of intracytoplasmic chlamydial inclusions.[98] These inclusion bodies are visualized under light microscopy after iodine staining of the glycogen produced by *C. trachomatis* in the infected cells. However, use of monoclonal DFA stain provides a more rapid and sensitive direct examination method than the iodine stain.

Chlamydophila psittaci does not synthesize glycogen, and its intracytoplasmic inclusions must be detected by another stain (e.g., Giemsa) usually after 5 to 10 days of incubation. Since *C. psittaci* is highly infectious and poses potential occupational hazards to laboratory personnel, cell cultures are rarely done for this organism, and the diagnosis of psittacosis is usually made by serologic tests.

As a known cause of CAP, *C. pneumoniae* can be detected by inoculating respiratory specimens into HeLa 229 monolayer cell culture. After 3 to 5 days of incubation, the cells are stained by a monoclonal DFA antibody specific for the organism.

Diagnosis of infections by all three organisms is made frequently by serologic testing (see later). However, cell culture and/or microbial DNA amplification tests on respiratory secretions or lung tissue may be needed to detect and confirm the presence of these pathogens in immunosuppressed patients who may not be able to mount antibody responses.[99–101] Antimicrobial susceptibility testing of Chlamydiaceae has little clinical utility presently because strain-to-strain variation in drug susceptibility and newly acquired drug resistance are both very rare. Methods for such testing have not been standardized and are used only for research purposes.

Mycoplasma

Like the Chlamydiaceae, *Mycoplasma* species are bacteria that do not grow on standard bacterial culture media. Culture media for isolation of *M. pneumoniae* generally contain fresh yeast extract, peptone, and animal serum, and are usually formulated as a biphasic preparation with an agar base overlaid with broth containing a pH indicator (for glucose fermentation) as well as penicillin and thallium acetate to inhibit bacterial overgrowth. Other additives may include amphotericin B to inhibit fungal overgrowth and a polymyxin to inhibit growth of *Pseudomonas* and other enteric bacilli. Optimal detection of *Mycoplasma* by culture can be achieved by inoculating clinical specimens into both selective and nonselective (biphasic) agar media. Upon incubation, the biphasic culture media are examined for the development of faint turbidity or a decrease in pH, while they are subcultured onto a selective agar media after 4 to 6 days and again after 8 to 12 days. The selective agar culture media are observed for the appearance of colonies typical of *M. pneumoniae.* Growth is usually visible by the end of 2 weeks of incubation, but biphasic culture media are incubated for 30 days before being discarded and

reported as negative for growth. Visible colonies of *M. pneumoniae* present in culture media are identified on the basis of hemadsorption, tetrazolium reduction, or growth inhibition by specific antiserum.[102,103]

Compared to the approximately 10^5 CFU/mL limit of detection by the culture method, direct antigen detection of *M. pneumoniae* in respiratory secretions by enzyme immunoassay (EIA) has a sensitivity of approximately 10^4 CFU/mL.[104] Due to the slow growth rate of this organism and insensitivity of the culture method (~60%), diagnosis of *M. pneumoniae* infection is more often made by the presence of specific antibodies in serum or by nucleic acid amplification of microbial gene targets in clinical specimens (see details in later sections).[103]

For the same reasons as those stated for Chlamydiaceae, drug susceptibility testing of mycoplasmas is not clinically indicated at present and is reserved only for research purposes, including in vitro evaluation of new antimicrobial agents. In general, both Chlamydiaceae and mycoplasmas are predictably susceptible to tetracyclines, macrolides, ketolides, and fluoroquinolone antibiotics.

Aerobic Actinomycetes

The pathogenic aerobic actinomycetes include the genera *Nocardia, Streptomyces, Actinomadura,* and *Rhodococcus.* Within this group, *Nocardia* species are the main respiratory pathogens. Although they grow well on mycobacterial culture media as well as on ordinary bacterial and fungal culture media, optimal recovery from clinical specimens is obtained by using the same culture medium (BCYE) as that for the isolation of *Legionella.*[105] Growth of nocardial colonies is usually visible within 3 to 7 days but may take up to 3 weeks of incubation to yield visible growth. The clinical significance of isolating *Nocardia asteroides* from sputum specimens remains controversial, since some studies comparing results between sputum culture and invasive methods (transtracheal aspirate and percutaneous lung aspiration) found colonization in as many as 51% of patients, while others reported absence of colonization.[106] Isolation of newly recognized *Nocardia* species and differences in the culture and identification methods used probably accounted for some of the differences in the findings of these studies. Distribution of *N. asteroides, N. farcinica,* and *N. nova* differs in various geographic areas, and differences exist in antimicrobial susceptibility among the species.[106]

Growth of *Nocardia* is suspected by the appearance of heaped folded colonies that may be covered by chalky aerial mycelia, but these characteristics and the organism's partial acid-fastness seen in acid-fast stained smears are not sufficient to identify the organism or to speciate it definitively. Definitive identification at the genus and species levels is based on results of biochemical tests, and speciation of *Nocardia* remains complex.[106] Among the various drug susceptibility testing methods available, the BACTEC radiometric method has been shown to be the most accurate method for testing *Nocardia* isolates.[107]

Rhodococcus equi is widely distributed in nature and is a rare cause of pulmonary infections in immunocompromised patients.[108] Rhodococci grow well on ordinary bacterial and fungal culture media. *Streptomyces* species are usually regarded as saprophytes and, therefore, as contaminants in cultures of respiratory tract specimens. However, since *Streptomyces* species closely resemble *Nocardia* in morphology of culture colonies, the two genera must be differentiated from one another on the basis of biochemical reactions in the laboratory.

Mycobacteria

Following the previously described digestion and concentration process in the laboratory, specimens are inoculated onto either egg-based (e.g., Löwenstein-Jensen) or agar-based (e.g., Middlebrook 7H10) culture media. Selective media containing antimicrobial agents, such as Gruft's modified Löwenstein-Jensen medium and Mitchison's selective 7H11 medium, are often used to suppress the growth of bacterial and fungal contaminants. Incubation in ambient atmospheric condition supplemented with 8% to 12% CO_2 increases the number and size of colonies of mycobacteria detected in these solid media. Specimens may also be inoculated into liquid medium of one of several commercially available semi-automated or automated culture systems, such as a radiometric method using ^{14}C-palmitic acid substrate (BACTEC 480TB System) or nonradiometric systems using a fluorescent indicator of O_2 consumption (BACTEC MGIT 960 System), colorimetric detection of CO_2 produced (BacT/ALERT 3D), or detection of pressure changes (due to O_2 consumption and/or CO_2 production from microbial growth) within the headspace above the liquid medium in a sealed bottle (VersaTREK Myco, formerly ESP Culture System II). The liquid culture media may be used with or without antimicrobial agents to detect mycobacterial growth and to determine susceptibility of *M. tuberculosis* isolates to antituberculous drugs. Because of their increased sensitivity and rapid detection of mycobacteria, these enriched selective broth culture systems are used widely, usually in combination with an agar-based medium, making them an important component of laboratory testing for *M. tuberculosis.*[77,109]

In contrast to the limit of detection of mycobacteria at approximately 10^4 organisms/mL by acid-fast stained smears, solid and liquid cultures are capable of detecting mycobacteria present at 10 CFU/mL of sputum.[110] Therefore, mycobacterial cultures should be performed on all respiratory secretions and other specimens from patients suspected of having tuberculosis or other mycobacterial diseases (see also Chapter 34). Cultures for mycobacteria are incubated typically for 8 weeks to detect the presence of slowly growing mycobacteria.

Mycobacterium tuberculosis usually requires 3 to 5 weeks of incubation for detectable growth in primary culture media, and another 1 to 2 weeks for niacin test to confirm its identification and for susceptibility testing. Studies of acid-fast smear-positive specimens found the mean durations from inoculation to culture positivity in

TABLE 18-7. Nontuberculous Mycobacteria Commonly Implicated in Lower Respiratory Tract Infections

RAPIDLY GROWING MYCOBACTERIA (visible growth in ≤7 days from dilute inoculum)

M. abscessus
M. chelonae
M. fortuitum group
M. mucogenicum

SLOWLY GROWING MYCOBACTERIA (visible growth in >7 days from dilute inoculum)

M. asiaticum
M. avium complex
M. celatum
M. chimaera
M. gastri
M. gordonae
M. haemophilum
M. kansasii
M. lentiflavum
M. malmoense
M. scrofulaceum
M. simiae
M. szulgai
M. terrae complex
M. triplex
M. xenopi

conventional solid media and by radiometric liquid culture method to be 19.4 and 8.3 days, respectively, for *M. tuberculosis* and 17.8 and 5.2 days, respectively, for nontuberculous mycobacteria (NTM).[111] On average, detection and drug susceptibility testing required 18 days by the radiometric method and 38 days by conventional methods. Time to culture positivity in acid-fast smear-negative specimens is usually longer, but the radiometric method remained faster than conventional methods. Once isolated in pure culture, identification of mycobacterial isolates can be done by the slower conventional biochemical methods or more rapidly either by gas-liquid chromatography or genetic methods.[77,109]

The NTM (also referred to as mycobacteria other than tuberculosis, or MOTT) have been classified as photochromogens, scotochromogens, nonphotochromogens, and rapid growers, according to their growth rates and pigmentation types. However, speciation by new and more precise diagnostic techniques, including molecular testing, has rendered this classification less meaningful (see also Chapter 35). From a clinical standpoint, these NTM are classified more usefully as rapidly growing or slowly growing mycobacteria, depending on the duration to culture positivity (Table 18-7), which aids the selection of additional testing and identification.

Fungi

The laboratory diagnosis of pulmonary fungal infections, especially the opportunistic invasive fungal infections, must often be based both on isolation of the organism from cultures and on histologic and serologic evidence of fungal infection (see also Chapter 36). Since pathogenic fungi are generally intolerant of decontamination and concentration procedures used to process specimens before culture for mycobacteria in the laboratory, specimens such as those submitted for mycobacterial cultures cannot be relied on for recovery of pathogenic fungi.[112] Clinical specimens should be sent specifically to the laboratory for the isolation of fungal pathogens. These specimens are typically inoculated onto nonselective media, such as potato dextrose agar, Sabouraud dextrose agar, or brain-heart infusion agar (BHIA), as well as selective media, such as BHIA-containing chloramphenicol and gentamicin with and without cycloheximide, and inhibitory mold agar. Fungal culture media that contain cycloheximide, which inhibits rapidly growing molds that commonly contaminate cultures, may be inhibitory to some pathogenic fungi, such as *C. neoformans* and *Aspergillus fumigatus*, thus emphasizing the importance of using a combination of selective and nonselective media in the isolation of fungal pathogens in culture. In contrast to bacterial cultures (usually incubated at 35°C), fungal cultures are incubated at 30°C.

In some instances, fungal pneumonia may be associated with fungemia. A variety of approaches have been used for detection of fungemia, including conventional blood culture bottles with or without radiometric or infrared spectrophotometric detection, biphasic medium bottles, lysis-filtration, and lysis-centrifugation. Because yeasts and many filamentous fungi are strictly aerobic in their growth requirements, aerobic culture bottles must be included in blood cultures obtained to detect fungemia. Failure to do so will result in significantly lower isolation rates of fungi from blood. Routine subculture of the aerobic blood culture bottles to fungal agar media has been advocated by some clinical microbiologists to improve sensitivity of fungal blood cultures. The commerically available but labor-intensive lysis-concentration method (Isolator) of blood culture has been shown also to be highly sensitive for detection of candidemia.[113,114] Although fungal blood culture is a relatively insensitive marker of disseminated fungal disease, the quantitative information provided by the lysis-concentration method may be useful in the management of patients with fungemia.[113,114] In general, the automated fluorometric (BACTEC) and colorimetric (BacT/ALERT 3D) detection methods of blood culture provide rates of recovering yeasts equivalent to those of aerobic cultures of the manual lysis-centrifugation method.[114-116] However, isolation of systemic fungal pathogens, such as *Histoplasma capsulatum,* from blood usually requires the lysis-centrifugation method or the use of special enriched fungal medium bottles for the BACTEC and BacT/ALERT 3D culture systems.[117,118]

Most yeasts, including *Candida* and *Cryptococcus* species, grow readily on most common fungal culture media, including Sabouraud or potato dextrose agar, inhibitory mold agar, BHIA, and Sabhi agar. Culture media containing antibiotics, such as chloramphenicol and gentamicin, are helpful when culturing respiratory

secretions containing contaminating bacteria, but cycloheximide may be inhibitory to *C. neoformans* and to some *Candida* species. Further complicating the isolation of fungal pathogens from respiratory specimens is that yeasts are frequently isolated from respiratory secretions. They have been reported in as many as 75% of sputum specimens and 25% of bronchial washings submitted for fungal culture.[1] Therefore, yeasts present in these specimens are considered to be of upper respiratory origin and need not be routinely identified unless when they are urease-positive. Urease-positive colonies require identification to rule out the possibility of *C. neoformans.* Urease-negative yeasts (e.g., *Candida* species) from sputa and bronchial washings may be reported as "yeasts present, not *C. neoformans*" in culture results. When isolated from other respiratory sources such as BAL fluid and normally sterile sites such as blood, such urease-negative yeasts should undergo further identification, which can be accomplished on the basis of colonial and microscopic morphology and biochemical reactions in commercially available tests.

Invasive pulmonary aspergillosis (IPA) also requires demonstration of parenchymal invasion for definitive diagnosis, due to colonization of the lower respiratory tract by *Aspergillus* in up to 90% of patients when defined as having at least one positive result from cultures of sputum, bronchial washing, or lung tissue.[119] Conversely, less than 10% of patients with proven IPA had *Aspergillus* recovered from cultures of sputum specimens. For optimal interpretation of culture results, both transbronchial lung biopsy and protected catheter brush should be used to obtain specimens for fungal cultures in order to decrease the frequency of false-negative and false-positive culture results.[120] Detection of fungal antigen in serum and various body fluids to aid in the diagnosis of infections due to *Aspergillus* species, *B. dermatitidis, C. neoformans,* and *H. capsulatum* are discussed later in the Serologic Tests section.

The unreliability of both positive and negative cultures in establishing or excluding a diagnosis of opportunistic fungal pulmonary disease, including aspergillosis, candidiasis, and zygomycosis, can be very problematic when evaluating the immunocompromised patient with pulmonary infiltrates. The two most reliable criteria for the definitive antemortem diagnosis of these opportunistic infections are (1) the presence of the fungus in otherwise viable lung tissue (by culture and/or histopathologic examination); and (2) a positive culture from cerebrospinal fluid, intraocular fluid, or other sterile body fluids (excluding blood and urine) in which the fungus is never normally present and when contamination in any manner is absolutely excluded.

In contrast to the fungi causing opportunistic pulmonary infections, isolation of pathogenic dimorphic fungi, such as *B. dermatitidis, C. immitis, H. capsulatum, Paracoccidioides brasiliensis,* and *Sporothrix schenckii* from respiratory secretions, antemortem or postmortem lung tissue, or any other site is invariably of clinical importance. Whereas zygomycetes may appear in cultures within 1 to 3 days and *Aspergillus* within 3 to 7 days, growth of the dimorphic fungi usually requires approximately 14 days of culture incubation. However, the time required for such fungal growth to be visible in culture is inoculum dependent, so that cultures of specimens with many organisms may become visible within 2 to 3 days while those with few organisms may not become positive even after 30 days. For this reason, fungal cultures are routinely incubated for 4 weeks or longer when the cultures are of specimens from patients who have serologic evidence of infection or who are being treated for an established fungal infection.[121] With adequate duration of incubation and proper laboratory techniques, fungal cultures of respiratory specimens were positive in approximately 85% of cases with disseminated or chronic pulmonary histoplasmosis.[122,123]

Since the presence of contaminating oropharyngeal flora does not interfere with the interpretation of culture results for dimorphic fungi, respiratory secretions are usually the best source for cultures of these organisms. Definitive diagnosis can often be made rapidly by direct microscopic examination of potassium hydroxide–stained or calcofluor white–stained smears of respiratory secretions, looking for cellular structures that are typical of members of this group of pathogenic fungi. Specimens that are negative by direct examination should still be submitted for fungal culture, since the latter is a more sensitive method for detection of fungi. Structures that are typical of the dimorphic fungi may be identified also in histopathologic tissue sections stained with Gomori methenamine silver. The presence of histiocytosis or a granulomatous reaction within lung tissue or a lymph node should prompt the performance of special stains and cultures for fungi as well as for mycobacteria, although chronic granulomatous lesions, especially those due to *H. capsulatum,* may be negative for fungal growth in culture. Close communication between the surgical pathologist and clinical microbiologist is of the utmost importance to ensure that an adequate amount of material is available for both direct microscopic and histologic examination and that appropriate cultures are performed to confirm the abnormal histopathologic findings.

Definitive identification of the pathogenic dimorphic fungi is based on one or more of the following methods: (1) recognition of characteristic microscopic features of the mold forms present in cultures; (2) conversion of the mold form to the yeast or spherule form that can be recognized microscopically; and (3) detection of cell-free exoantigens by a micro-immunodiffusion method. Conversion to the yeast form on culture is easily accomplished with *B. dermatitidis* and *S. schenckii,* whereas the immunodiffusion (ID) test for exoantigens is usually reserved for testing colonies suspected to be *C. immitis* or *H. capsulatum.* As an alternative to detection of exoantigens, molecular tests using oligonucleotide probes are available for rapid identification of these dimorphic fungi directly from cultures[124–126] or in histologic tissue sections.[127,128]

With the availability of new antifungal drugs and increasing recognition of drug resistance among certain pathogenic fungi, antifungal susceptibility testing has become important in the management of patients with

invasive fungal infections. Standard laboratory testing methods and interpretive criteria are available for clinical laboratories to examine clinically significant fungal isolates for resistance to the antifungal drugs currently used for treating such infections.[129–131] However, the need for such susceptibility testing is usually reserved for testing pathogenic fungi, such as *Candida* spp., *Aspergillus terrae, Fusarium, Scedosporium, Trichosporum,* and zygomycetes, that are known to be resistant to some of the commonly used antifungal drugs (e.g., amphotericin B, the azoles).

Viruses

As discussed previously in the section on direct specimen examination, nonculture techniques for detection of pathogenic viruses in respiratory specimens may include direct examination of specimens (e.g., nasopharyneal aspirates, sputum, BAL fluid) containing virus-infected epithelial cells using DFA staining and EIA. These methods provide a rapid means of viral antigen detection for influenza viruses, parainfluenza viruses, adenoviruses, and RSV (see also Chapter 31). The sensitivity of these direct detection methods depends on the type of specimen and the timing of specimen collection. Generally, the earlier in the course of disease the specimen is collected, the more likely that the virus will be detected. However, with the exception of RSV, conventional cell culture is usually the more sensitive method for detecting viruses in respiratory specimens, but it is usually slow, requiring an average of 3 to 4 days to detect cytopathic effects from influenza A virus and 8 to 9 days from CMV. The time required for detection of HSV, CMV, and respiratory viruses can be reduced to 16 to 48 hours after inoculation by using the rapid shell vial culture technique, which combines low-speed centrifugation (700× *g*) after inoculation of cell culture monolayers and immunofluorescent staining with virus-specific monoclonal antibody.[132,133]

The detection of viruses in respiratory secretions must be based on knowledge of their source of isolation, potential presence as colonizers in certain sites, and epidemiologic characteristics. Thus, isolation of influenza viruses, parainfluenza viruses, and RSV, as well as rhinoviruses and coronaviruses, from either respiratory secretions or lung tissue is clinically significant. In contrast, because of known asymptomatic secretion for periods ranging from weeks to months, isolation of adenoviruses, HSV, and CMV from respiratory secretions is of questionable significance, while positive cultures of lung tissue for these viruses are very important diagnostically. In addition, simultaneous isolation of adenovirus from both the throat and feces has a greater probability of association with febrile and respiratory illnesses in infants and children than when the virus is isolated only from the throat or feces. Although the isolation of CMV from lung tissue is important clinically, infection with CMV is often concurrent in immunocompromised hosts with infections caused by bacteria or fungi, including *P. jirovecii,* and in infants with *C. trachomatis* pneumonia.

Parasites

Identification of pulmonary parasites is typically made by microscopic examination of specimens (e.g., sputum, blood, feces) in conjunction with a detailed clinical history, radiologic imaging, and serologic testing.[134,135] Culture and direct antigen detection of the parasites are uncommonly used in this setting but are appropriate in certain circumstances and may be invaluable for confirming diagnosis (see also Chapter 37).

Fecal culture may be useful in cases of suspected pulmonary involvement with *Strongyloides stercoralis* when sputum cytology fails to identify larvae. The agar plate method is a useful adjunct to standard microscopic fecal examination and may be up to six times more sensitive.[136–139] Fecal culture may also enhance the sensitivity of *Entamoeba histolytica* identification from feces or aspirated lung abscess material, but is not routinely available in the diagnostic laboratory.[140] Serology is more commonly used for diagnosis of disseminated amebic disease and is discussed later.[140]

The identification of microfilariae causing tropical pulmonary eosinophilia poses a diagnostic challenge since these parasites typically circulate only at night. As an attractive alternative to nightly blood draws, antigen detection for bancroftian filariasis in peripheral blood has proven to be both sensitive and specific for the detection of microfilaria.[141,142] Antigen testing may also be used for identification of *Toxoplasma gondii* in peripheral blood, but is not yet widely available.[143–145]

SEROLOGIC TESTS

Serologic diagnosis of infection can be made by detecting (1) humoral immune responses (e.g., antibodies) of the infected individuals, and/or (2) microbial antigens present in sera or various body fluids. Immunologic assay methods frequently used to identify and quantify a specific antibody or a pathogen-specific antigen are based, respectively, on binding interactions between a known amount of pathogen-specific antigen and the specific antibody of interest or between a known amount of pathogen-specific antibody and the specific antigen of interest. The resultant antigen-antibody complexes can be detected directly by precipitation methods or by labeling of the antigen or the anti-antibody with a radioactive, fluorescent, or enzyme probe. The complexes can also be detected indirectly by measurement of an antibody-directed reaction, such as complement fixation (CF). The serologic methods commonly used in diagnostic laboratories include precipitation, ID, agglutination, hemagglutination inhibition, EIA, indirect immunofluorescence assay (IFA), CF, and immunoblotting (including Western blot).

Immunocompetent individuals produce both immunoglobulin M (IgM) and immunoglobulin G (IgG) antibodies specific against pathogens during infection. In general, IgM is produced during the first exposure to a given pathogen and is no longer detectable after this relatively short period of time. Over time, production of

IgG replaces that of IgM in the immunologic response of exposed patients. Serologic testing is used commonly to identify infections due to pathogens that are difficult to detect by other conventional methods, to evaluate the course of an infection, and to determine the nature of the infection (primary infection versus reinfection, acute versus chronic infection). Serologic results are usually expressed as a titer, which is the inverse of the greatest dilution, or lowest concentration (e.g., dilution of 1 : 16 = titer of 16), of a patient's serum that retains the specific antibody-antigen reactivity. Patient's specific IgM or IgG titers can be determined separately through the use of labeled anti-human antibody specific for the antibody isotype in the particular serologic assay.

Diagnosis of infection based on serologic responses of the infected host is confirmed usually by occurrence of seroconversion during a primary infection. Seroconversion is defined as a minimum fourfold increase in antibody titer between serum during the acute phase of infection and that during the convalescent phase (≥2 weeks later). Reinfection or recurrent infection later in life causes an anamnestic (secondary or booster) immune response that can be detected as increase in antibody titer. Although a fourfold or greater rise in antibody titer between acute and convalescent sera is usually required for diagnosis, an elevated pathogen-specific IgM antibody titer in a single serum sample suggests recent infection by the specific pathogen. A falling titer of the specific IgM antibody provides further support for the etiologic significance of this organism. However, serologic testing of pathogen-specific IgG antibody in acute and convalescent sera remains the approach to establish a specific microbial cause of the infection.

Various commercial assays—EIA and IFA—are available for detection of (1) specific IgM and/or IgG antibodies to respiratory tract pathogens, and/or (2) pathogen-specific antigens in serum or various body fluids. These assays are useful for supporting or confirming the diagnosis of bacterial infections caused by *Legionella* species, *Francisella tularensis, Yersinia pestis, M. pneumoniae, C. trachomatis, C. pneumoniae, C. psittaci,* and *Coxiella burnetii.* With these assays, infection is confirmed typically by observing a fourfold or greater rise in pathogen-specific IgG antibody titer between the acute and convalescent sera in a given patient.

For the diagnosis of *L. pneumophila* infection, urine can also be tested for *L. pneumophila* serogroup 1 antigens by EIA, with diagnostic specificity of 100% and sensitivity varying from 70% to 100%.[79] Antigen is detectable in more than 80% of patients at onset and after 14 days of symptoms before receiving treatment, as well as at 42 days or longer after onset of treatment.[41] However, these urinary antigen assays are specific only for diagnosis of infections due to *L. pneumophila* serogroup 1 and not other *Legionella* species. Detection of *H. influenzae* type B antigens in urine is of potential diagnostic value in pediatric patients with pneumonia, but such antigenuria may also follow routine immunization with *H. influenzae* type B conjugate vaccine.[146]

With the relative ease of serum collection and low sensitivity of culture methods, serologic tests are important adjunct tools for the diagnosis of *M. pneumoniae* infection. Cold agglutinins, detected by agglutination of type 0 Rh-negative red blood cells at 4°C, are present in the sera of approximately 50% of patients with *M. pneumoniae* infection, and levels decline to baseline within 6 weeks after acute infection. However, the formation of this nonspecific serologic marker may be induced by a wide variety of viral infections, lymphoid malignancies, and autoimmune disorders. Antibodies are detected by CF test in more than 85% of culture-positive patients, and a single elevated titer of greater than 1 : 80 or a greater than fourfold rise in titer between acute and convalescent sera is required to establish a diagnosis. EIAs to detect *M. pneumoniae*–specific IgM and immunoglobulin A (IgA) antibodies have been developed with improved sensitivity and specificity over the CF assay.[103] Specific IgM antibodies appear during the first week of illness and reach peak titers during the third week. However, the IgM antibodies are not constantly produced in adults, so that a negative IgM result does not rule out acute *M. pneumoniae* infection, particularly in the elderly. Detection of specific IgA antibodies in the serum has been shown to be a reliable approach for diagnosis, since these antibodies are also produced early in the course of disease and more reliably present in the infected individuals regardless of age.

Serologic testing also plays an important role in the diagnosis of fungal respiratory tract infections due to *Aspergillus* species, *C. immitis, C. neoformans,* and *H. capsulatum.* Detection of serum *Aspergillus* galactomannan (a major cell wall component of the fungus) antigen in serum by EIA can aid in the early diagnosis of IPA, with diagnostic sensitivity ranging from 60% to 100% in various patient groups.[119,147–149] Platelia *Aspergillus* EIA (Bio-Rad Laboratories, Redmond, WA), a commercially available assay that uses the rat monoclonal antibody EB-A2 directed against galactomannan in *A. fumigatus, A. flavus, A. niger, A. versicolor,* and *A. terres,* has been shown to yield positive results at an early stage of infection, with positive and negative predictive values of more than 90% in high-risk patients who were tested biweekly.[147] However, cross reactivity of this assay may occur in patients with histoplasmosis, paracoccidioidomycosis, and cryptococcosis,[149,150] and false-positive galactomannan antigen assay results can be observed in patients receiving certain foods or intravenous pipercillin-tazaobactam.[151–153] BAL fluid specimens from lung transplant recipients have been evaluated also for testing by *Aspergillus* galactomannan detection assay, with sensitivity of 82% and specificity of 96%.[154] Of note, the Plasma-Lyte (Baxter International Inc., Deerfield, IL) solution commonly used to perform BAL has been found to yield false-positive results with the Platelia *Aspergillus* EIA.[155]

Another fungal antigenic marker that is used increasingly for the diagnosis of invasive fungal infection is (1→3)-β-D-glucan, which is a component of the outer cell wall of saprophytic and pathogenic fungi except zygomycetes (*Mucor* and *Rhizopus* species) and *Cryptococcus* species.[147,156] This antigen has been detected in serum or other body fluids of patients with invasive aspergillosis, invasive candidiasis, and infections caused

by *Fusarium, Acremonium, Trichosporum, Scedosporium, Saccharomyces,* and *P. jirovecii.*[157,158] A multicenter trial of one assay method yielded diagnostic sensitivity of 70% and specificity of 87% in neutropenic patients with acute leukemia.[159] Use of different assay cutoff values may result in differences in sensitivity and specificity among the various commercially available assays for detecting this antigen.[156] Nonspecific cross reactivity of (1→3)-β-D-glucan detection assays has been reported with the use of cotton gauzes, swabs, packs, pads, or sponges for wound care or surgery; cellulose filters in hemodialysis patients; and various antimicrobial agents.[156,160]

Infection due to *C. immitis* can be based on detection of antibodies to antigens derived from the coccidioidal mycelia or spherules, although cross reactivity may occur with antibodies to other yeasts and dimorphic fungi. Precipitin-specific IgM antibodies develop in up to 75% of individuals within 2 to 3 weeks after primary *C. immitis* infection, and subsequently disappear except in patients with disseminated infection. Complement-fixing IgG antibodies appear later and persist in relation to the severity of disease, but decline with disease remission. Titers of 1 : 32 or higher should suggest the possibility of disseminated infection.[161,162] However, a single elevated titer obtained by CF, no matter how high, should not be used to make the diagnosis of disseminated disease.

Serologic assays to detect polysaccharides of *C. neoformans* cell wall in serum or cerebrospinal fluid are helpful to confirm the diagnosis of cryptococcosis. Commercially available assays show more than 95% diagnostic sensitivity and specificity for detection of cryptococcal antigen in serum, provided that proteolytic enzymes (pronases) are used to limit the false-positive and false-negative results due to the prozone effect, localized infection, infection with a poorly encapsulated strain, or low organism burden.[163] Cryptococcal antigen may also be detectable in pleural effusions and BAL fluid of patients with cryptococcal pneumonia,[164,165] but some patients with disseminated cryptococcosis may be negative by the serum cryptococcal antigen test. Serial measurement of serum antigen titers over time is not useful for the management of patients with pulmonary cryptococcosis.[166]

Serum antibodies to *H. capsulatum* are detected by CF test using both yeast and mycelial antigens and ID assay, showing positive titers in more than 90% of patients with pulmonary histoplasmosis and approximately 80% with disseminated disease.[123] The CF test is more sensitive but less specific than the ID test for the diagnosis of subclinical and acute pulmonary histoplasmosis, with CF titers of 1 : 8 or higher in 90% of patients versus ID test indicating M bands in 75% and H bands in only 25% of cases.[43] Cross-reactive antibodies are observed more commonly in CF than ID for patients with blastomycosis, coccidioidomycosis, and paracoccidioidomycosis. Antibodies become detectable first by CF test at 2 to 6 weeks after *Histoplasma* infection and then by ID test 2 to 4 weeks later. However, the ID test remains positive longer than the CF test after resolution of infection, becoming negative 2 to 5 years later. Presence of an M band by ID test with a negative CF test result suggests remote or past histoplasmosis. The M band remains positive much longer (several years) than does the H band, while the presence of the H band is indicative of active or acute infection, usually disappearing within 6 months. These serologic tests are less sensitive in immunosuppressed patients, and antibody titers are low, whereas antibody levels remain high in those with chronic pulmonary infection, progressive disseminated disease, or fibrosing mediastinitis. The polysaccharide antigen of *H. capsulatum* can be detected in urine by EIA in approximately 90% of patients with disseminated disease and 75% with diffuse acute pulmonary histoplasmosis.[122,123] Urinary *Histoplasma* antigen levels persist during ongoing active infection, and become undetectable with successful therapy and rise with relapse of infection. However, the urinary *Histoplasma* antigen assay is known to yield positive results in patients with disseminated infections caused by *B. dermatitidis, P. brasiliensis,* and *Penicillium marneffei.*[167] Cross reactivity of the assay has not been observed in patients with invasive candidiasis, cryptococcosis, coccidioidomycosis, aspergillosis, or other opportunistic systemic mycoses.

Serologic testing plays an important role as an aid to the diagnosis of parasitic and viral infections such as *T. gondii, Trichinella spiralis, S. stercoralis,* influenza viruses, parainfluenza viruses, RSV, adenoviruses, severe acute respiratory syndrome (SARS)–associated coronavirus, HSV, varicella-zoster virus, CMV, and Epstein-Barr virus (EBV). Serologic detection of fourfold rise in virus-specific antibody titers is also helpful when influenza, parainfluenza, RSV, or adenovirus infection is suspected but the virus is undetectable by cell cultures or by direct viral antigen testing of respiratory specimens.

In summary, serologic testing makes an important contribution to the diagnosis of infection with numerous respiratory pathogens, and is the test of choice for some organisms. It offers a relatively noninvasive alternative to direct examination and culture methods of tissues, and may play an essential role in the identification of microorganisms that grow poorly, or not at all, in culture.

MOLECULAR TESTS

In recent years, diagnostic approaches for the detection and identification of microbial pathogens in the clinical laboratory have moved rapidly toward use of molecular techniques, including in-house and commercially available tests.[168–170] Most of these methods are based on amplification, detection, and confirmation of certain nucleic acid targets (genes) specific to the pathogens of interest. Such molecular testing methods offer several advantages over conventional direct examination, microbiologic cultures, and serologic assays. First, molecular methods have the ability to detect and identify pathogens more rapidly (usually in ≤1 day) than traditional laboratory tests, and may be able to determine antimicrobial susceptibility directly from respiratory tract specimens. For example, detection of *M. tuberculosis* and its susceptibility to isoniazid and rifampin can be accomplished directly

from sputum (in ~2 hours) using polymerase chain reaction (PCR)–based technology.[171,172] Second, some microorganisms are difficult or impossible to grow in cultures, and molecular techniques provide the best, if not the only, means of directly detecting these organisms. Certain NTM, for example, are very difficult to cultivate by conventional culture-based methods, and nucleic acid amplification techniques would enable the detection of these organisms in clinical specimens.[173] Third, molecular tests lessen or eliminate the biohazard risk of exposure of laboratory personnel to highly contagious laboratory cultures of certain microorganisms, such as *M. tuberculosis* and *C. immitis,* if proper handling of specimens and cultures is not observed.

Among the available molecular assays are microbial detection and/or identification by oligonucleotide hybridization probes for use on pure culture isolates. For example, nucleic acid probes, such as AccuProbe (Gen-Probe, Inc., San Diego, CA), are commercially available for the identification of colonies of *H. capsulatum, B. dermatitidis,* and *C. immitis* grown in fungal cultures. Species-specific labeled probes are designed to hybridize to specific gene targets of the organisms in question after microbial nucleic acids were extracted from pure culture colonies. These tests are rapid (completed in <2 hours) and can be done on younger cultures, providing results sooner than exoantigen testing. Compared to conventional microscopic and biochemical techniques of identification, these nucleic acid probe methods are accurate, with diagnostic sensitivities and specificities of 98% to 100%.[124–126] Genetic probes are also available for identifying *M. tuberculosis, M. avium* complex, and *M. kansasii* isolated from mycobacterial culture media.[174,175]

Molecular tests may also be performed directly on respiratory specimens. Nucleic acid amplification–based tests are available currently for molecular detection of *M. tuberculosis,* and include a transcription-mediated amplification and hybridization protection assay to detect ribosomal RNA (rRNA) (Amplified MTD Test; Gen-Probe, Inc., San Diego, CA) and DNA hybridization of a conserved region of the 16S rRNA gene amplified by PCR (AMPLICOR MTB Test; Roche Molecular Diagnostics, Branchburg, NJ).[176,177] Both of these assays can yield results in 3 to 4 hours. In comparison to results of conventional culture methods, these nucleic acid testing methods showed the following sensitivities, specificities, and positive and negative predictive values: Amplified MTD Test, 86%, 100%, 100%, and 98%, respectively; AMPLICOR MTB test, 83%, 100%, 100%, and 98%, respectively.[178]

The CDC has recently published updated guidelines for the use of nucleic acid amplification (NAA) tests in the diagnosis of tuberculosis.[179] Compared with direct microscopic examination for acid-fast bacilli, NAA testing provides (1) a greater positive predictive value (>95%) with smear-positive specimens in settings where nontuberculous mycobacteria are common, and (2) the ability to rapidly confirm the presence of *M. tuberculosis* in 50% to 80% of smear-negative, culture-positive specimens, weeks earlier than culture.[180] The updated recommendation states "NAA testing should be performed on at least one respiratory specimen from each patient with signs and symptoms of pulmonary TB for whom a diagnosis of TB is being considered but has not yet been established, and for whom the test result would alter case management or TB control activities." In addition, the World Health Organization has recommended the use of NAA tests to screen for multidrug-resistant tuberculosis; two such kits are commercially available in Europe and elsewhere, but none have been approved by the FDA.

Diagnostic methods have also been described for detecting the nucleic acids of *S. pneumoniae,*[181] *C. pneumoniae,*[25–27] *M. pneumoniae,*[28–31] *L. pneumophila,*[28] dimorphic fungi,[182,183] *Aspergillus* species,[183,184] *P. jirovecii,*[185,186] *T. gondii,*[187] respiratory viruses, HSV,[188] and CMV[189,190] directly in respiratory specimens of normal and immuncompromised hosts. These tests may be done by conventional, labor-intensive amplification techniques (requiring 2 to 3 days of test turnaround time) or by rapid, real-time amplification methods yielding results in less than 3 hours. The latter approach is based on immediate, simultaneous fluorescence detection of amplified gene targets as they are generated by the in vitro assays. However, caution is needed to interpret the results of such test methods in differentiating between colonization (or latent forms) and infection by these organisms in the hosts. For example, *S. pneumoniae, C. pneumoniae, M. pneumoniae, Candida* species, and *P. jirovecii* may be carried by (colonize) some individuals without causing disease. Similarly, herpesviruses (HSV, CMV, EBV), *T. gondii,* and *P. jirovecii* may exist in a latent state (as cysts in the cases of *T. gondii* and *P. jirovecii*) in human tissues and may not cause disease. The detection of nucleic acid sequences of dimorphic fungi (e.g., *H. capsulatum*) or *M. tuberculosis* in lung or lymphatic tissue usually indicates disease, although such nucleic acids could be preserved in nonviable organisms contained in fibrotic granulomas from past/resolved infection. In addition, a notable concern with these direct rapid molecular tests is the lack of ability to do antimicrobial susceptibility testing.

Published studies of clinical validation of these molecular detection tests have indicated that most of these assays are at least comparable, if not better, in sensitivity and specificity to combination of conventional culture, direct antigen, and/or serologic detection methods, especially when examining respiratory specimens that contain low numbers of pathogens. For example, rapid PCR assay has been applied for the diagnosis of an outbreak of *C. psittaci* which occurred as a result of transmission of this infectious agent from birds purchased in stores to humans, showing a 50% increase in the rate of *C. psittaci* detection compared with culture.[191] Compared to culture and serologic tests, PCR was also shown to be the most sensitive method for detection of *C. pneumoniae* during an outbreak of CAP.[192]

Conventional and real-time nucleic acid–based tests are available for *P. jirovecii* and may be more sensitive than conventional microscopic methods.[193] However, they are usually more time-consuming and expensive, and may be less specific (especially nested PCR assays), than direct microscopic examination using various stain-

ing methods (methenamine silver, Giemsa, or toluidine blue O stains).[185] The lowered diagnostic specificity is likely due to the detection of *P. jirovecii* nucleic acid from cysts that are present in low numbers and in a latent state in pulmonary tissues of asymptomatic patients.[194] This could potentially be overcome through use of quantitative assays.[193] *Pneumocystis jirovecii* pneumonia may also be diagnosed by PCR analysis of serum and gastric wash fluid, although the clinical utility of these approaches is uncertain.[195,196]

Cytomegalovirus is frequently present in respiratory secretions of immunosuppressed patients in the absence of CMV pneumonitis. Quantitative PCR and expression of CMV proteins have been used in an attempt to differentiate between shedding of CMV and CMV disease. Higher copy numbers of CMV DNA can be found in cases of CMV pneumonia than in CMV shedding, and expression of CMV glycoprotein H messenger RNA was detected only in patients with disease.[189] However, these specialized PCR techniques must be used to maintain specificity of these sensitive assays.

Due to the various technical difficulties encountered by clinical laboratories in the isolation of respiratory viruses, molecular detection methods have become increasingly popular and important for the management of patients with these viral infections.[170,197] Different respiratory specimens, including throat swabs and nasopharyngeal swabs or aspirates, have been studied by various microbial gene amplification assays for the detection of influenza A and B viruses (including the H5N1 strain),[33,34,198,199] parainfluenza viruses,[32,33,198] RSV,[32,33,35,36,198] adenoviruses,[32,33,37,198,200] human metapneumovirus,[201] and SARS-associated coronavirus,[202,203] with diagnostic sensitivity and specificity that are greater than those of culture and direct antigen detection methods. These molecular tests also offer the advantage of detecting viral nucleic acid targets in patients who are already receiving antiviral therapy.[204]

Molecular assays have also allowed for the identification of previously unknown respiratory viruses, such as human metapneumovirus, novel coronaviruses, and human bocavirus. Some of these have been definitively linked with respiratory disease. For instance, human metapneumovirus is now recognized as an important agent of acute lower respiratory tract disease in infants and young children.[205] The roles of other viruses in respiratory disease, such as the human bocavirus, have yet to be elucidated.

Recently, several large-panel multiplex molecular assays for rapid, simultaneous detection of respiratory tract pathogens, including bacteria and viruses, have been developed and studied.[206–208] Use of such assays has led to the recognition that coinfections with two or more respiratory pathogens are more common than previously thought.[206,209] However, further studies are needed to determine the clinical significance of multiply detectable respiratory tract pathogens in clinical specimens from various patient populations and the cost-effective application of such molecular tests in clinical practice.

With the useful capabilities of molecular diagnostic tests and the need for rapid, sensitive detection of respiratory tract pathogens, molecular assays will gain an increasing role in the diagnosis and management of patients with opportunistic and community-acquired pneumonia. In many large clinical laboratories, these tests have replaced conventional, less sensitive diagnostic methods for routine use by health care providers.

KEY POINTS

- The clinical microbiology laboratory plays a vital role in the microbiologic diagnosis of the specific cause of lower respiratory tract infections.
- Reliable results depend on obtaining suitable and adequate specimens, transporting them promptly to the laboratory in appropriate media or containers, and then processing the material according to the organisms of interest.
- Information from the health care provider is equally crucial in guiding the laboratory to detect and identify the actual pathogens from among the many possible microorganisms that may cause infection in a given patient.
- The laboratory diagnosis of pulmonary infections is frequently based on a combination of histopathologic, microbiologic, and serologic examinations, which must always be interpreted in conjunction with the patient's clinical, radiographic, and other laboratory test findings.
- Newly available rapid molecular assays are playing an increasingly important role in the diagnosis of the cause of lower respiratory tract infections.

References

1. Waites KB, Saubolle MA, Talkington DF, et al: Cumitech 10A: Laboratory Diagnosis of Upper Respiratory Tract Infections (Sharp SE, coord ed). Washington, DC: ASM Press, 2006.
2. Johanson WG Jr, Pierce AK, Sanford JP, et al: Nosocomial respiratory infections with gram-negative bacilli: The significance of colonization of the respiratory tract. Ann Intern Med 77:701–706, 1972.
3. Tillotson JR, Finland M: Bacterial colonization and clinical superinfection of the respiratory tract complicating antibiotic treatment of pneumonia. J Infect Dis 119:597–624, 1969.
4. Mackowiak PA, Martin RM, Jones SR, et al: Pharyngeal colonization by gram-negative bacilli in aspiration-prone persons. Arch Intern Med 138:1224–1227, 1978.
5. Valenti WM, Trudell RG, Bentley DW: Factors predisposing to oropharyngeal colonization with gram-negative bacilli in the aged. N Engl J Med 298:1108–1111, 1978.
6. Fainstein V, Rodriguez V, Turck M, et al: Patterns of oropharyngeal and fecal flora in patients with acute leukemia. J Infect Dis 144:10–18, 1981.
7. Johanson WG Jr: Prevention of respiratory tract infection. Am J Med 76:69–77, 1984.
8. Stoutenbeek CP, van Saene HK, Miranda DR, et al: The effect of selective decontamination of the digestive tract on colonisation and infection rate in multiple trauma patients. Intensive Care Med 10:185–192, 1984.
9. Cockerill FR, Muller SR, Anhalt JP, et al: Prevention of infection in critically ill patients by selective decontamination of the digestive tract. Ann Intern Med 117:545–553, 1992.
10. Hahn HH, Beaty HN: Transtracheal aspiration in the evaluation of patients with pneumonia. Ann Intern Med 72:183–187, 1970.
11. Barrett-Connor E: The nonvalue of sputum culture in the diagnosis of pneumococcal pneumonia. Am Rev Respir Dis 103:845–848, 1971.
12. Bartlett JG, Finegold SM: Anaerobic pleuropulmonary infections. Medicine (Baltimore) 51:413–450, 1972.
13. Spencer RC, Philp JR: Effect of previous antimicrobial therapy on bacteriological findings in patients with primary pneumonia. Lancet 2:349–350, 1973.
14. Laird AT: A method for increasing the diagnostic value of sputum reports. JAMA 52:294–296, 1909.
15. Miller JM: A Guide to Specimen Management in Clinical Microbiology (2nd ed). Washington, DC: ASM Press, 1998.
16. Miller JM, Krisher K, Holmes HT: General principles of specimen collection and handling. *In* Murray PR, Baron EJ, Jorgensen JH, et al (eds): Manual of Clinical Microbiology (9th ed). Washington, DC: ASM Press, 2007, pp. 43–54.
17. Smithwick RW, Stratigos CB, David HL: Use of cetylpyridinium chloride and sodium chloride for the decontamination of sputum specimens that are transported to the laboratory for the isolation of *Mycobacterium tuberculosis*. J Clin Microbiol 1:411–413, 1975.
18. Hariri AR, Hempel HO, Kimberlin CL, et al: Effects of time lapse between sputum collection and culturing on isolation of clinically significant fungi. J Clin Microbiol 15:425–428, 1982.
19. Jefferson H, Dalton HP, Escobar MR, et al: Transportation delay and the microbiological quality of clinical specimens. Am J Clin Pathol 64:689–693, 1975.
20. Penn RL, Silberman R: Effects of overnight refrigeration on the microscopic evaluation of sputum. J Clin Microbiol 19:161–163, 1984.
21. Kuklinska D, Kilian M: Relative proportions of *Haemophilus* species in the throat of healthy children and adults. Eur J Clin Microbiol 3:249–252, 1984.
22. Broughton WA, Kirkpatrick MB, Bass JB: The technique of protected brush catheter bronchoscopy. J Crit Ill 2:63–70, 1987.
23. Bordelon JY, Legrand P, Gewin WC, et al: The telescoping plugged catheter in suspected anaerobic infections: A controlled series. Am Rev Respir Dis 128:465–468, 1983.
24. Costello M, Yungbluth M: Viral infections. *In* McPherson RA, Pincus MR (eds): Henry's Clinical Diagnosis and Management by Laboratory Methods (21st ed). Philadelphia: Saunders Elsevier, 2007, pp. 975–999.
25. Tondella ML, Talkington DF, Holloway BP, et al: Development and evaluation of real-time PCR-based fluorescence assays for detection of *Chlamydia pneumoniae*. J Clin Microbiol 40:575–583, 2002.
26. Kuoppa, Y, Boman J, Scott L, et al: Quantitative detection of respiratory *Chlamydia pneumoniae* infection by real-time PCR. J Clin Microbiol 40:2273–2274, 2002.
27. Reischl, U, Lehn N, Simnacher U, et al: Rapid and standardized detection of *Chlamydia pneumoniae* using LightCycler real-time fluorescence PCR. Eur J Clin Microbiol Infect Dis 22:54–57, 2003.
28. Welti M, Jaton K, Altwegg M, et al: Development of a multiplex real-time quantitative PCR assay to detect *Chlamydia pneumoniae, Legionella pneumophila* and *Mycoplasma pneumoniae* in respiratory tract secretions. Diagn Microbiol Infect Dis 45:85–95, 2003.
29. Hardegger D, Nadal D, Bossart W, et al: Rapid detection of *Mycoplasma pneumoniae* in clinical samples by real-time PCR. J Microbiol Methods 41:45–51, 2000.
30. Ursi D, Dirven K, Loens K, et al: Detection of *Mycoplasma pneumoniae* in respiratory samples by real-time PCR using an inhibition control. J Microbiol Methods 55:149–153, 2003.
31. Templeton KE, Scheltinga SA, Graffelman AW, et al: Comparison and evaluation of real-time PCR, real-time nucleic acid sequence-based amplification, conventional PCR, and serology for diagnosis of *Mycoplasma pneumoniae*. J Clin Microbiol 41:4366–4371, 2003.
32. Coiras MT, Aguilar JC, Garcia ML, et al: Simultaneous detection of fourteen respiratory viruses in clinical specimens by two multiplex reverse transcription nested-PCR assays. J Med Virol 72:484–495, 2004.
33. Templeton KE, Scheltinga SA, Beersma MF, et al: Rapid and sensitive method using multiplex real-time PCR for diagnosis of infections by influenza A and influenza B viruses, respiratory syncytial virus, and parainfluenza viruses 1, 2, 3, and 4. J Clin Microbiol 42:1564–1569, 2004.
34. Smith AB, Mock V, Melear R, et al: Rapid detection of influenza A and B viruses in clinical specimens by LightCycler real time RT-PCR. J Clin Virol 28:51–58, 2003.
35. Boivin G, Cote S, Dery P, et al: Multiplex real-time PCR assay for detection of influenza and human respiratory syncytial viruses. J Clin Microbiol 42:45–51, 2004.
36. van Elden LJ, van Loon AM, van der Beek A, et al: Applicability of a real-time quantitative PCR assay for diagnosis of respiratory syncytial virus infection in immunocompromised adults. J Clin Microbiol 41:4378–4381, 2003.
37. Mitchell S, O'Neill HJ, Ong GM, et al: Clinical assessment of a generic DNA amplification assay for the identification of respiratory adenovirus infections. J Clin Virol 26:331–338, 2003.
38. Metersky ML, Ma A, Bratzler DW, et al: Predicting bacteremia in patients with community-acquired pneumonia. Am J Respir Crit Care Med 169:342–347, 2004.
39. Mathers G: Bacteriology of the urine in lobar pneumonia. J Infect Dis 19:416–418, 1916.
40. Roson B, Fernandez-Sabe N, Carratala J, et al: Contribution of a urinary antigen assay (Binax NOW) to the early diagnosis of pneumococcal pneumonia. Clin Infect Dis 38:222–226, 2004.
41. Kohler RB, Winn WC, Wheat LJ: Onset and duration of urinary antigen excretion in Legionnaires disease. J Clin Microbiol 20:605–607, 1964.
42. Kashuba AD, Ballow CH: *Legionella* urinary antigen testing: Potential impact on diagnosis and antibiotic therapy. Diagn Microbiol Infect Dis 24:129–139, 1996.
43. Wheat LJ: Laboratory diagnosis of histoplasmosis: Update 2000. Semin Respir Infect 16:131–140, 2001.
44. Pappas PG: Blastomycosis. Semin Respir Crit Care Med 25:113–121, 2004.
45. Wimberley N, Faling LJ, Bartlett JG: A fiberoptic bronchoscopy technique to obtain uncontaminated lower airway secretions for bacterial culture. Am Rev Respir Dis 119:337–343, 1979.
46. Cook DJ, Fitzgerald JM, Guyatt GH, et al: Evaluation of the protected brush catheter and bronchoalveolar lavage in the diagnosis of nosocomial pneumonia. J Intensive Care Med 6:196–205, 1991.

47. Fagon JY: Hospital-acquired pneumonia. Diagnostic strategies: Lessons from clinical trials. Infect Dis Clin North Am 17:717–726, 2003.
48. van der Eerden MM, Vlaspolder F, de Graaff CS, et al: Value of intensive diagnostic microbiological investigation in low- and high-risk patients with community-acquired pneumonia. Eur J Clin Microbiol Infect Dis 24:241–249, 2005.
49. Meduri GU, Baselski V: The role of bronchoalveolar lavage in diagnosing nonopportunistic bacterial pneumonia. Chest 100:179–190, 1991.
50. Wimberley N, Willey S, Sullivan N, et al: Antibacterial properties of lidocaine. Chest 76:37–40, 1979.
51. Stover DE, Zaman MB, Hajdu SI, et al: Bronchoalveolar lavage in the diagnosis of diffuse pulmonary infiltrates in the immunosuppressed host. Ann Intern Med 101:1–7, 1984.
52. von Hoesslin H: Das Sputum. Berlin: Springer-Verlag, 1921.
53. Chodosh S: Examination of sputum cells. N Engl J Med 282:854–857, 1970.
54. Baigelman W, Chodosh S: Sputum wet preps: Window on the airways. J Respir Dis 5:59–70, 1984.
55. Van Scoy RE: Bacterial sputum cultures: A clinician's viewpoint. Mayo Clin Proc 52:39–41, 1977.
56. Geckler RW, Gremillion DH, McAllister CK, et al: Microscopic and bacteriological comparison of paired sputa and transtracheal aspirates. J Clin Microbiol 6:396–399, 1977.
57. Courcol RJ, Damien JM, Ramon P, et al: Presence of alveolar macrophages as a criterion for determining the suitability of sputum specimens for bacterial culture. Eur J Clin Microbiol 3:122–125, 1984.
58. Morris AJ, Tanner DC, Reller LB: Rejection criteria for endotracheal aspirates from adults. J Clin Microbiol 31:1027–1029, 1993.
59. Zaidi AK, Reller LB: Rejection criteria for endotracheal aspirates from pediatric patients. J Clin Microbiol 34:352–354, 1996.
60. Rein MF, Gwaltney JM, O'Brien WM, et al: Accuracy of Gram's stain in identifying pneumococci in sputum. JAMA 239:2671–2673, 1978.
61. Boerner DF, Zwadyk P: The value of the sputum Gram's stain in community-acquired pneumonia. JAMA 247:642–645, 1982.
62. Roson B, Carratala J, Verdaguer R, et al: Prospective study of the usefulness of sputum Gram stain in the initial approach to community-acquired pneumonia requiring hospitalization. Clin Infect Dis 31:869–874, 2000.
63. Musher DM, Montoya R, Wanahita A: Diagnostic value of microscopic examination of Gram-stained sputum and sputum cultures in patients with bacteremic pneumococcal pneumonia. Clin Infect Dis 39:165–169, 2004.
64. Merrill CW, Gwaltney JM, Hendley JW, et al: Rapid identification of pneumococci: Gram stain vs. the quellung reaction. N Engl J Med 288:510–512, 1973.
65. Dans PE, Charache P, Fahey M, et al: Management of pneumonia in the prospective payment era: A need for more clinician and support service interaction. Arch Intern Med 144:1392–1397, 1984.
66. Austrian R: The quellung reaction, a neglected microbiologic technique. Mt Sinai J Med 43:699–709, 1976.
67. Everett ED, Rham AE, Adaniya R, et al: *Haemophilus influenzae* pneumonia in adults. JAMA 238:319–321, 1977.
68. Levin DC, Schwarz MI, Matthay RA, et al: Bacteremic *Hemophilus influenzae* pneumonia in adults: A report of 24 cases and a review of the literature. Am J Med 62:219–224, 1977.
69. Verghese A, Berk SL: Bacterial pneumonia in the elderly. Medicine (Baltimore) 62:271–285, 1983.
70. Jones GR, Christodoulides M, Brooks JL, et al: Dynamics of carriage of *Neisseria meningitidis* in a group of military recruits: Subtype stability and specificity of the immune response following colonization. J Infect Dis 178:451–459, 1998.
71. Putsch RW, Hamilton JD, Wolinsky E: *Neisseria meningitidis,* a respiratory pathogen? J Infect Dis 121:48–54, 1970.
72. Johnson MA, Drew WL, Roberts M: *Branhamella* (*Neisseria*) *catarrhalis*—a lower respiratory tract pathogen? J Clin Microbiol 13:1066–1069, 1981.
73. Thornley PE, Aitken J, Drennan CJ, et al: *Branhamella catarrhalis* infection of the lower respiratory tract: Reliable diagnosis by sputum examination. Br Med J 285:1537–1538, 1982.
74. Noone P, Rogers BT: Pneumonia caused by coliforms and *Pseudomonas aeruginosa*. J Clin Pathol 29:652–656, 1976.
75. Fine MJ, Orloff JJ, Rihs JD, et al: Evaluation of housestaff physicians' preparation and interpretation of sputum Gram stains for community-acquired pneumonia. J Gen Intern Med 6:189–198, 1991.
76. Steingart KR, Henry M, Ng V, et al: Fluorescence versus conventional sputum smear microscopy for tuberculosis: A systematic review. Lancet Infect Dis 6:570–581, 2006.
77. Woods GL: Mycobacteria. *In* McPherson RA, Pincus MR (eds): Henry's Clinical Diagnosis and Management by Laboratory Methods (21st ed). Philadephia: Saunders Elsevier, 2007, pp. 1074–1085.
78. Kim TC, Blackman RS, Heatwole KM, et al: Acid-fast bacilli in sputum smears of patients with pulmonary tuberculosis: Prevalence and significance of negative smears pretreatment and positive smears post-treatment. Am Rev Respir Dis 129:264–268, 1984.
79. Murdoch DR: Diagnosis of *Legionella* infection. Clin Infect Dis 36:64–69, 2003.
80. Bell TA, Kuo CC, Stamm WE, et al: Direct fluorescent monoclonal antibody stain for rapid detection of infant *Chlamydia trachomatis* infections. Pediatrics 74:224–228, 1984.
81. Paisley JW, Lauer BA, Melinkovich P, et al: Rapid diagnosis of *Chlamydia trachomatis* pneumonia in infants by direct immunofluorescence microscopy of nasopharyngeal secretions. J Pediatr 109:653–655, 1986.
82. Roberts GD: Detection of fungi in clinical specimens by phase-contrast microscopy. J Clin Microbiol 2:261–265, 1975.
83. Kim YK, Parulekar S, Yu PK, et al: Evaluation of calcofluor white stain for detection of *Pneumocystis carinii*. Diagn Microbiol Infect Dis 13:307–310, 1990.
84. Hageage GJJ, Harrington BJ: Use of calcofluor white in clinical mycology. Lab Med 15:109–112, 1984.
85. Monheit JE, Cowan DF, Moore DG: Rapid detection of fungi in tissues using calcofluor white and fluorescence microscopy. Arch Pathol Lab Med 108:616–618, 1984.
86. Wolfson JS, Waldron MA, Sierra LS: Blinded comparison of a direct immunofluorescent monoclonal antibody staining method and a Giemsa staining method for identification of *Pneumocystis carinii* in induced sputum and bronchoalveolar lavage specimens of patients infected with human immunodeficiency virus. J Clin Microbiol 28:2136–2138, 1990.
87. Cregan P, Yamamoto A, Lum A, et al: Comparison of four methods for rapid detection of *Pneumocystis carinii* in respiratory specimens. J Clin Microbiol 28:2432–2436, 1990.
88. Gay JD, Smith TF, Ilstrup DM: Comparison of processing techniques for detection of *Pneumocystis carinii* cysts in open-lung biopsy specimens. J Clin Microbiol 21:150–151, 1985.
89. Drew WL: Value of sputum culture in diagnosis of pneumococcal pneumonia. J Clin Microbiol 6:62–65, 1977.
90. Howden R: Use of anaerobic culture for the improved isolation of *Streptococcus pneumoniae*. J Clin Pathol 29:50–53, 1976.
91. Thorsteinsson SB, Musher DM, Fagan T: The diagnostic value of sputum culture in acute pneumonia. JAMA 233:894–895, 1975.
92. Bartlett JG, Finegold SM: Bacteriology of expectorated sputum with quantitative culture and wash technique compared to transtracheal aspirates. Am Rev Respir Dis 117:1019–1027, 1978.
93. Niederman MS, Craven DE, Bonten MJ, et al: American Thoracic Society and Infectious Diseases Society of America (ATS/IDSA) guideline for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med 171:388–416, 2005.
94. Luna CM, Videla A, Mattera J, et al: Blood cultures have limited value in predicting severity of illness and as a diagnostic tool in ventilator-associated pneumonia. Chest 116:1075–1084, 1999.
95. Mayer J: Laboratory diagnosis of nosocomial pneumonia. Semin Respir Infect 15:119–131, 2000.
96. Wilson DA, Yen-Lieberman B, Reischl U, et al: Detection of *Legionella pneumophila* by real-time PCR for the *mip* gene. J Clin Microbiol 41:3327–3330, 2003.

97. Freidig EE, Smith TF, Wilson WR: Failure to recover *Chlamydia trachomatis* from open-lung biopsy tissue of adult immunosuppressed patients. Chest 86:649, 1984.
98. Woods GL, Walker DH: Chlamydial, rickettsial, and mycoplasmal infections. *In* McPherson RA, Pincus MR (eds): Henry's Clinical Diagnosis and Management by Laboratory Methods (21st ed). Philadelphia: Saunders Elsevier, 2007, pp. 1000–1015.
99. Komaroff AL, Aronson MD, Schachter J: *Chlamydia trachomatis* infection in adults with community-acquired pneumonia. JAMA 245:1319–1322, 1981.
100. Sundkvist T, Mardh PA: Serological evidence of C*hlamydia trachomatis* infection in non-immunocompromised adults with pneumonia. J Infect 9:143–147, 1984.
101. Tack KJ, Peterson PK, Rasp FL, et al: Isolation of *Chlamydia trachomatis* from the lower respiratory tract of adults. Lancet 1:116–120, 1980.
102. Waites KB, Bebear CM, Robertson JA, et al: Cumitech 34: Laboratory Diagnosis of Mycoplasmal Infections (Nolte FS, coord ed). Washington, DC: ASM Press, 2001.
103. Daxboeck F, Krause R, Wenisch C: Laboratory diagnosis of *Mycoplasma pneumoniae* infection. Clin Microbiol Infect 9:263–273, 2003.
104. Marmion BP, Williamson J, Worswick DA, et al: Experience with newer techniques for the laboratory detection of *Mycoplasma pneumoniae* infection, Adelaide, 1978–1992. Clin Infect Dis 17(Suppl 1):S90–S99, 1993.
105. Vickers RM, Rihs JD, Yu VL: Clinical demonstration of isolation of *Nocardia asteroides* on buffered charcoal-yeast extract media. J Clin Microbiol 30:227–228, 1992.
106. Corti ME, Villafane-Fioti MF: Nocardiosis: A review. Int J Infect Dis 7:243–250, 2003.
107. Ambaye A, Kohner PC, Wollan PC, et al: Comparison of agar dilution, broth microdilution, disk diffusion, E-test, and BACTEC radiometric methods for antimicrobial susceptibility testing of clinical isolates of the *Nocardia asteroides* complex. J Clin Microbiol 35:847–852, 1997.
108. Weinstock DM, Brown AE: *Rhodococcus equi:* An emerging pathogen. Clin Infect Dis 34:1379–1385, 2002.
109. Clinical and Laboratory Standards Institute: Laboratory Detection and Identification of Mycobacteria: Approved Guideline (M48-A). Wayne, PA: Clinical and Laboratory Standards Institute, 2008.
110. Yeager H, Lacy J, Smith LR, et al: Quantitative studies of mycobacterial populations in sputum and saliva. Am Rev Respir Dis 95:998–1004, 1967.
111. Roberts GD, Goodman NL, Heifets L, et al: Evaluation of the BACTEC radiometric method for recovery of mycobacteria and drug susceptibility testing of *Mycobacterium tuberculosis* from acid-fast smear-positive specimens. J Clin Microbiol 18:689–696, 1983.
112. Roberts GD, Karlson AG, DeYoung DR: Recovery of pathogenic fungi from clinical specimens submitted for mycobacteriological culture. J Clin Microbiol 3:47–48, 1976.
113. Bille J, Edson RS, Roberts GD: Clinical evaluation of the lysis-centrifugation blood culture system for the detection of fungemia and comparison with a conventional biphasic broth blood culture system. J Clin Microbiol 19:126–128, 1984.
114. Cockerill FR, Reed GS, Hughes JG, et al: Clinical comparison of BACTEC 9240 Plus Aerobic/F resin bottles and the Isolator aerobic culture system for detection of bloodstream infections. J Clin Microbiol 35:1469–1472, 1997.
115. Pohlman JK, Kirkley BA, Easley KA, et al: Controlled clinical comparison of Isolator and BACTEC 9240 Aerobic/F resin bottle for detection of bloodstream infections. J Clin Microbiol 33:2525–2529, 1995.
116. Hellinger WC, Cawley JJ, Alvarez S, et al: Clinical comparison of the Isolator and BacT/Alert aerobic blood culture systems. J Clin Microbiol 33:1787–1790, 1995.
117. Pohlman JK, Kirkley BA, Easley KA, et al: Controlled clinical evaluation of BACTEC Plus Aerobic/F and BacT/Alert aerobic fan bottles for detection of bloodstream infections. J Clin Microbiol 33:2856–2858, 1995.
118. Waite RT, Woods GL: Evaluation of BACTEC MYCO/F Lytic medium for recovery of mycobacteria and fungi from blood. J Clin Microbiol 36:1176–1179, 1998.
119. Hope WW, Walsh TJ, Denning DW: Laboratory diagnosis of invasive aspergillosis. Lancet Infect Dis 5:609–622, 2005.
120. Herbrecht R, Natarajan-Ame S, Letscher-Bru V, et al: Invasive pulmonary aspergillosis. Semin Respir Crit Care Med 25:191–202, 2004.
121. O'Shaughnessy EM, Shea YM, Witebsky FG: Laboratory diagnosis of invasive mycoses. Infect Dis Clin North Am 17:135–158, 2003.
122. Wheat LJ, Conces D, Allen SD, et al: Pulmonary histoplasmosis syndromes: Recognition, diagnosis, and management. Semin Respir Crit Care Med 25:129–144, 2004.
123. Wheat LJ, Kauffman CA: Histoplasmosis. Infect Dis Clin North Am 17:1–19, 2003.
124. Hall GS, Pratt-Rippin K, Washington JA: Evaluation of a chemiluminescent probe assay for identification of *Histoplasma capsulatum* isolates. J Clin Microbiol 30:3003–3004, 1992.
125. Huffnagle KE, Gander RM: Evaluation of Gen-Probe's *Histoplasma capsulatum* and *Cryptococcus neoformans* AccuProbes. J Clin Microbiol 31:419–421, 1993.
126. Padhye AA, Smith G, McLaughlin D, et al: Comparative evaluation of a chemiluminescent DNA probe and an exoantigen test for rapid identification of *Histoplasma capsulatum*. J Clin Microbiol 30:3108–3111, 1992.
127. Hayden RT, Isotalo PA, Parrett T, et al: In situ hybridization for the differentiation of *Aspergillus, Fusarium,* and *Pseudallescheria* species in tissue section. Diagn Mol Pathol 12:21–26, 2003.
128. Hayden RT, Qian X, Procop GW, et al: In situ hybridization for the identification of filamentous fungi in tissue section. Diagn Mol Pathol 11:119–126, 2002.
129. National Committee for Clinical Laboratory Standards: Method for Antifungal Disk Diffusion Susceptibility Testing of Yeasts: Approved Standard (M44-A). Wayne, PA: National Committee for Clinical Laboratory Standards, 2004.
130. Clinical and Laboratory Standards Institute: Reference Method for Broth Dilution Antifungal Susceptibility Testing of Yeasts: Approved Standard—Third Edition (M27-MA3). Wayne, PA: Clinical and Laboratory Standards Institute, 2008.
131. Clinical and Laboratory Standards Institute: Reference Method for Broth Dilution Antifungal Susceptibility Testing of Filamentous Fungi: Approved Standard—Second Edition (M38-MA2). Wayne, PA: Clinical and Laboratory Standards Institute, 2008.
132. Gleaves CA, Smith TF, Shuster EA, et al: Comparison of standard tube and shell vial cell culture techniques for the detection of cytomegalovirus in clinical specimens. J Clin Microbiol 21:217–221, 1985.
133. Navarro-Mari JM, Sanbonmatsu-Gamez S, Perez-Ruiz M, et al: Rapid detection of respiratory viruses by shell vial assay using simultaneous culture of Hep-2, LLC-MK2, and MDCK cells in a single vial. J Clin Microbiol 37:2346–2347, 1999.
134. Vijayan VK: How to diagnose and manage common parasitic pneumonias. Curr Opin Pulm Med 13:218–224, 2007.
135. Berk SL, Verghese A: Parasitic pneumonia. Semin Respir Infect 3:172–178, 1988.
136. Koga K, Kasuya S, Khamboonruang C, et al: An evaluation of the agar plate method for the detection of *Strongyloides stercoralis* in northern Thailand. J Trop Med Hyg 93:183–188, 1990.
137. Koga K, Kasuya S, Ohtomo H: How effective is the agar plate method for *Strongyloides stercoralis?* J Parasitol 78:155–156, 1992.
138. Intapan PM, Maleewong W, Wongsaroj T, et al: Comparison of the quantitative formalin ethyl acetate concentration technique and agar plate culture for diagnosis of human strongyloidiasis. J Clin Microbiol 43:1932–1933, 2005.
139. Arakaki T, Iwanaga M, Kinjo F, et al: Efficacy of agar-plate culture in detection of *Strongyloides stercoralis* infection. J Parasitol 76:425–428, 1990.
140. Fotedar R, Stark D, Beebe N, et al: Laboratory diagnostic techniques for *Entamoeba* species. Clin Microbiol Rev 20:511–532, 2007.
141. Chandrasena TG, Premaratna R, Abeyewickrema W, et al: Evaluation of the ICT whole-blood antigen card test to detect infection due to *Wuchereria bancrofti* in Sri Lanka. Trans R Soc Trop Med Hyg 96:60–63, 2002.

142. Wattal S, Dhariwal, AC, Ralhan PK, et al: Evaluation of OG4C3 antigen ELISA as a tool for detection of bancroftian filariasis under lymphatic filariasis elimination programme. J Commun Dis 39:75–84, 2007.
143. Hassan MM, Mansour SA, Atta M, et al: The importance of detecting circulating *Toxoplasma* antigens in human cases. J Egypt Soc Parasitol 27:27–34, 1997.
144. Hafid J, Tran Manh Sung R, Raberin H, et al: Detection of circulating antigens of *Toxoplasma gondii* in human infection. Am J Trop Med Hyg 52:336–339, 1995.
145. Chen R, Lu S, Lou D, et al: Evaluation of a rapid ELISA technique for detection of circulating antigens of *Toxoplasma gondii*. Microbiol Immunol 52:180–187, 2008.
146. Rothstein EP, Madore DV, Girone JA, et al: Comparison of antigenuria after immunization with three *Haemophilus influenzae* type B conjugate vaccines. Pediatr Infect Dis J 10:311–314, 1991.
147. Wheat LJ: Antigen detection, serology, and molecular diagnosis of invasive mycoses in the immunocompromised host. Transpl Infect Dis 8:128–139, 2006.
148. Wheat LJ, Walsh TJ: Diagnosis of invasive aspergillosis by galactomannan antigenemia detection using an enzyme immunoassay. Eur J Clin Microbiol Infect Dis 27:245–251, 2008.
149. Wheat LJ, Hackett E, Durkin M, et al: Histoplasmosis-associated cross-reactivity in the Bio-Rad Platelia *Aspergillus* enzyme immunoassay. Clin Vaccine Immunol 14:638–640, 2007.
150. Xavier MO, Pasqualotto AC, Cardoso IC, et al: Cross-reactivity of *Paracoccidioides brasiliensis, Histoplasma capsulatum,* and *Cryptococcus* species in the commercial Platelia *Aspergillus* enzyme immunoassay. Clin Vaccine Immunol 16:132–133, 2009.
151. Ansorg R, van den Boom R, Rath PM: Detection of *Aspergillus* galactomannan antigen in foods and antibiotics. Mycoses 40:353–357, 1997.
152. Viscoli C, Machetti M, Cappellano P, et al: False-positive galactomannan Platelia *Aspergillus* test results for patients receiving piperacillin-tazobactam. Clin Infect Dis 38:913–916, 2004.
153. Adam O, Auperin A, Wilquin F, et al: Treatment with piperacillin-tazobactam and false-positive *Aspergillus* galactomannan antigen test results for patients with hematological malignancies. Clin Infect Dis 38:917–920, 2004.
154. Husain S, Clancy CJ, Nguyen MH, et al: Performance characteristics of the Platelia *Aspergillus* enzyme immunoassay for detection of *Aspergillus* galactomannan antigen in bronchoalveolar lavage fluid. Clin Vaccine Immunol 15:1760–1763, 2008.
155. Hage CA, Reynolds JM, Durkin M et al: Plasmalyte as a cause of false-positive results for *Aspergillus* galactomannan in bronchoalveolar lavage fluid. J Clin Microbiol 45:676–677, 2007.
156. Kedzierska A, Kochan P, Pietrzyk A, et al: Current status of fungal cell wall components in the immunodiagnostics of invasive fungal infections in humans: Galactomannan, mannan and (1→3)-β-D-glucan antigens. Eur J Clin Microbiol Infect Dis 26:755–766, 2007.
157. Marty FM, Koo S, Bryar J, et al: (1→3)-β-D-glucan assay positivity in patients with *Pneumocystis* (*carinii*) *jirovecii* pneumonia. Ann Intern Med 147:70–72, 2007.
158. Cuetara MS, Alhambra A, Moragues MD, et al: Detection of (1→3)-β-D-glucan as an adjunct to diagnosis in a mixed population with uncommon proven invasive fungal diseases or with an unusual clinical presentation. Clin Vaccine Immunol 16:423–426, 2009.
159. Senn L, Robinson JO, Schmidt S, et al: (1→3)-β-D-glucan antigenemia for early diagnosis of invasive fungal infections in neutropenic patients with acute leukemia. Clin Infect Dis 46:878–885, 2008.
160. Marty FM, Lowry CM, Lempitski SJ, et al: Reactivity of (1→3)-β-D-glucan assay with commonly used intravenous antimicrobials. Antimicrob Agents Chemother 50:3450–3453, 2006.
161. Anstead GM, Graybill JR: Coccidioidomycosis. Infect Dis Clin North Am 20:621–643, 2006.
162. Catanzaro A: Coccidioidomycosis. Semin Respir Crit Care Med 25:123–128, 2004.
163. Currie BP, Freundlich LF, Soto MA, et al: False-negative cerebrospinal fluid cryptococcal latex agglutination tests for patients with culture-positive cryptococcal meningitis. J Clin Microbiol 31:2519–2522, 1993.
164. Young EJ, Hirsh DD, Fainstein V, et al: Pleural effusions due to *Cryptococcus neoformans:* A review of the literature and report of two cases with cryptococcal antigen determinations. Am Rev Respir Dis 121:743–747, 1980.
165. Baughman RP, Rhodes JC, Dohn MN, et al: Detection of cryptococcal antigen in bronchoalveolar lavage fluid: A prospective study of diagnostic utility. Am Rev Respir Dis 145:1226–1229, 1992.
166. Lortholary O, Nunez H, Brauner MW, et al: Pulmonary cryptococcosis. Semin Respir Crit Care Med 25:145–157, 2004.
167. Wheat J, Wheat H, Connolly P, et al: Cross-reactivity in *Histoplasma capsulatum* variety *capsulatum* antigen assays of urine samples from patients with endemic mycoses. Clin Infect Dis 24:1169–1171, 1997.
168. Murdoch DR: Nucleic acid amplification tests for the diagnosis of pneumonia. Clin Infect Dis 36:1162–1170, 2003.
169. Mackay IM: Real-time PCR in the microbiology laboratory. Clin Microbiol Infect 10:190–212, 2004.
170. Niesters HG: Molecular and diagnostic clinical virology in real time. Clin Microbiol Infect 10:5–11, 2004.
171. Ruiz M, Torres MJ, Llanos AC, et al: Direct detection of rifampin- and isoniazid-resistant *Mycobacterium tuberculosis* in auramine-rhodamine-positive sputum specimens by real-time PCR. J Clin Microbiol 42:1585–1589, 2004.
172. Wada T, Maeda S, Tamaru A, et al: Dual-probe assay for rapid detection of drug-resistant *Mycobacterium tuberculosis* by real-time PCR. J Clin Microbiol 42:5277–5285, 2004.
173. Emler S, Bottger EC, Broers B, et al: Growth-deficient mycobacteria in patients with AIDS: Diagnosis by analysis of DNA amplified from blood or tissue. Clin Infect Dis 20:772–775, 1995.
174. Woods GL: The mycobacteriology laboratory and new diagnostic techniques. Infect Dis Clin North Am 16:127–144, 2002.
175. Soini H, Musser JM: Molecular diagnosis of mycobacteria. Clin Chem 47:809–814, 2001.
176. Dorman SE: Coming-of-age of nucleic acid amplification tests for the diagnosis of tuberculosis. Clin Infect Dis 49:55–57, 2009.
177. Greco S, Girardi E, Navarra A, et al: Current evidence on diagnostic accuracy of commercially based nucleic acid amplification tests for the diagnosis of pulmonary tuberculosis. Thorax 61:783–790, 2006.
178. Vuorinen P, Miettinen A, Vuento R, et al: Direct detection of *Mycobacterium tuberculosis* complex in respiratory specimens by Gen-Probe Amplified *Mycobacterium tuberculosis* direct test and Roche AMPLICOR *Mycobacterium tuberculosis* test. J Clin Microbiol 33:1856–1859, 1995.
179. Centers for Disease Control and Prevention: Updated guidelines for the use of nucleic acid amplification tests in the diagnosis of tuberculosis. Morb Mortal Wkly Rep 58:7–10, 2009.
180. Guerra RL, Hooper NM, Baker JF, et al: Use of the Amplified *Mycobacterium tuberculosis* Direct Test in a public health laboratory: test performance and impact of clinical care. Chest 32:946–951, 2007.
181. Butler JC, Bosshardt SC, Phelan M, et al: Classical and latent class analysis evaluation of sputum polymerase chain reaction and urine antigen testing for diagnosis of pneumococcal pneumonia in adults. J Infect Dis 187:1416–1423, 2003.
182. Chen SC, Halliday CL, Meyer W: A review of nucleic acid-based diagnostic tests for systemic mycoses with an emphasis on polymerase chain reaction-based assays. Med Mycol 40:333–357, 2002.
183. Iwen PC: Molecular detection and typing of fungal pathogens. Clin Lab Med 23:781–799, 2003.
184. Mengoli C, Cruciani M, Barnes RA, et al: Use of PCR for diagnosis of invasive aspergillosis: Systematic review and meta-analysis. Lancet Infect Dis 9:89–96, 2009.
185. Torres J, Goldman M, Wheat LJ, et al: Diagnosis of *Pneumocystis carinii* pneumonia in human immunodeficiency virus-infected patients with polymerase chain reaction: A blinded comparison to standard methods. Clin Infect Dis 30:141–145, 2000.
186. Larsen HH, Masur H, Kovacs JA, et al: Development and evaluation of a quantitative, touch-down, real-time PCR assay for diagnosing *Pneumocystis carinii* pneumonia. J Clin Microbiol 40:490–494, 2002.

187. Bretagne S, Costa JM, Fleury-Feith J, et al: Quantitative competitive PCR with bronchoalveolar lavage fluid for diagnosis of toxoplasmosis in AIDS patients. J Clin Microbiol 33:1662–1664, 1995.
188. Espy MJ, Uhl JR, Mitchell PS, et al: Diagnosis of herpes simplex virus infections in the clinical laboratory by LightCycler PCR. J Clin Microbiol 38:795–799, 2000.
189. Boivin G, Olson CA, Quirk MR, et al: Quantitation of cytomegalovirus DNA and characterization of viral gene expression in bronchoalveolar cells of infected patients with and without pneumonitis. J Infect Dis 173:1304–1312, 1996.
190. Goto H, Yuasa K, Sakamaki H, et al: Rapid detection of cytomegalovirus pneumonia in recipients of bone marrow transplant: Evaluation and comparison of five survey methods for bronchoalveolar lavage fluid. Bone Marrow Transplant 17:855–860, 1996.
191. Messmer TO, Skelton SK, Moroney JF, et al: Application of a nested, multiplex PCR to psittacosis outbreaks. J Clin Microbiol 35:2043–2046, 1997.
192. Boman J, Allard A, Persson K, et al: Rapid diagnosis of respiratory *Chlamydia pneumoniae* infection by nested touchdown polymerase chain reaction compared with culture and antigen detection by EIA. J Infect Dis 175:1523–1526, 1997.
193. Fillaux J, Malvy S, Alvarez M, et al: Accuracy of a routine real-time PCR assay for the diagnosis of *Pneumocystis jirovecii* pneumonia. J Microbiol Methods 75:258–261, 2008.
194. Maskell NA, Waine DJ, Lindley A, et al: Asymptomatic carriage of *Pneumocystis jirovecii* in subjects undergoing bronchoscopy: A prospective study. Thorax 58:594–597, 2003.
195. Rabodonirina M, Cotte, L Boibieux A, et al: Detection of *Pneumocystis carinii* DNA in blood specimens from human immunodeficiency virus-infected patients by nested PCR. J Clin Microbiol 37:127–131, 1999.
196. Limawongpranee S, Wanachiwanawin D, Chokephaibulkit K, et al: Sensitive detection of *Pneumocystis jirovecii* DNA in gastric wash using nested polymerase chain reaction. Southeast Asian J Trop Med Public Health 38:892–896, 2007.
197. Henrickson KJ: Advances in the laboratory diagnosis of viral respiratory disease. Pediatr Infect Dis J 23(Suppl 1):S6–S10, 2004.
198. Hindiyeh M, Hillyard DR, Carroll KC: Evaluation of the Prodesse Hexaplex multiplex PCR assay for direct detection of seven respiratory viruses in clinical specimens. Am J Clin Pathol 116:218–224, 2001.
199. Ginocchio CC, Zhang F, Manji R, et al: Evaluation of multiple test methods for the detection of the novel 2009 influenza A (H1N1) during the New York City outbreak. J Clin Virol 45:191–195, 2009.
200. Gu Z, Belzer SW, Gibson CS, et al: Multiplexed, real-time PCR for quantitative detection of human adenovirus. J Clin Microbiol 41:4636–4641, 2003.
201. Maertzdorf J, Wang CK, Brown JB, et al: Real-time reverse transcriptase PCR assay for detection of human metapneumoviruses from all known genetic lineages. J Clin Microbiol 42:981–986, 2004.
202. Mahony JB, Petrich A, Louie L, et al: Performance and cost evaluation of one commercial and six in-house conventional and real-time reverse transcription-PCR assays for detection of severe acute respiratory syndrome coronavirus. J Clin Microbiol 42:1471–1476, 2004.
203. Ng LF, Wong M, Koh S, et al: Detection of severe acute respiratory syndrome coronavirus in blood of infected patients. J Clin Microbiol 42:347–350, 2004.
204. Fox JD: Nucleic acid amplification tests for detection of respiratory viruses. J Clin Virol 40(Suppl 1):S15–S23, 2007.
205. Caracciolo S, Minini C, Colombrita D, et al: Human metapneumovirus infection in young children hospitalized with acute respiratory tract disease: Virologic and clinical features. Pediatr Infect Dis J 27:406–412, 2008.
206. Freymuth F, Vabret A, Cuvillon-Nimal D, et al: Comparison of multiplex PCR assays and conventional techniques for the diagnostic of respiratory virus infections in children admitted to hospital with an acute respiratory illness. J Med Virol 78:1498–1504, 2006.
207. Lam WY, Yeung AC, Tang JW, et al: Rapid multiplex nested PCR for detection of respiratory viruses. J Clin Microbiol 45:3631–3640, 2007.
208. Lee WM, Grindle K, Pappas T, et al: High-throughput, sensitive, and accurate multiplex PCR-microsphere flow cytometry system for large-scale comprehensive detection of respiratory viruses. J Clin Microbiol 45:2626–2634, 2007.
209. Brunstein JD, Cline CL, McKinney S, et al: Evidence from multiplex molecular assays for complex multipathogen interactions in acute respiratory infections. J Clin Microbiol 46:97–102, 2008.

CHAPTER 19

RADIOGRAPHIC TECHNIQUES

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INTRODUCTION

CHEST RADIOGRAPHY: TECHNIQUES
Standard Film-Screen Radiography
American College of Radiology Standards
Portable Radiography
Digital (Computed) Radiography
Radiographic Views and Techniques
Fluoroscopy
Bronchography
Pulmonary Angiography
Aortography and Bronchial Angiography

ULTRASONOGRAPHY

COMPUTED TOMOGRAPHY
Physical Principles
Image Display
Spiral and Multislice Computed Tomography
Computed Tomography Scan Protocols
Computed Tomography and Radiation
Interventional Computed Tomography and Percutaneous Lung Biopsy
Positron Emission Tomography and Positron Emission Tomography Computed Tomography

MAGNETIC RESONANCE IMAGING
Physical Principles
Techniques

APPLICATIONS OF CONVENTIONAL CHEST RADIOGRAPHY
Screening and "Routine" Chest Radiographs
Detection of Lung Cancer and Assessment of Solitary Pulmonary Nodules
Evaluation of Intensive Care Unit Patients
Indications in Acute Lung Disease

APPLICATIONS OF CROSS-SECTIONAL IMAGING TECHNIQUES
Solitary Pulmonary Nodules
Multiple Pulmonary Nodules
Lung Cancer Staging
Lung Cancer Screening
Hilar and Mediastinal Masses
Diffuse Lung Disease
Intrathoracic Airway Disease
Cardiovascular Disease
Pleural Disease

INTRODUCTION

Chest radiographic techniques play a major role in the detection, diagnosis, and serial evaluation of thoracic disease. The appropriate use of radiographic methods requires some basic understanding of the technical aspects of imaging, of the abnormal findings visible with different techniques, and of the diagnostic accuracy of these techniques. It is not the intent of this chapter to provide a complete description of the techniques involved or an encyclopedic catalogue of radiographic abnormalities of chest diseases. Rather, this chapter is intended to provide a general survey of the imaging methods available, their most common indications, and certain principles concerning their use.

Since the late 1990s, remarkable advancements in the effectiveness of cross-sectional imaging techniques for the diagnosis of thoracic diseases has occurred, particularly the development of multislice computed tomography (MSCT) as well as improvements in magnetic resonance imaging (MRI) and ultrasonography. In many instances, cross-sectional methods have supplanted conventional radiography for the diagnosis of chest diseases. As with any radiographic method, the decision to utilize cross-sectional imaging should be based on consideration of the patient's clinical problem and the results of other imaging and laboratory testing.

Chest radiography still plays a fundamental role in the diagnosis of thoracic disease. Chest radiography is usually the initial imaging procedure performed when chest

disease is suspected, and despite the development of other imaging methods, chest radiography remains one of the most frequently performed radiographic examinations in the United States.

The thorax is difficult to image with conventional radiographic techniques because of large regional differences in tissue density and thickness. For example, with standard radiography, the number of x-ray photons passing through the lungs is more than 100 times greater than the number of x-ray photons penetrating the mediastinum.[1] The dynamic contrast range of conventional film-screen radiography is insufficient to properly demonstrate this range of x-ray photon transmission; with standard radiographic techniques, the use of exposure high enough to properly display the mediastinum and the subdiaphragmatic regions usually results in overexposure of the lungs.[1] Conversely, an exposure designed to provide the best visualization of the pulmonary parenchyma is normally too light for visualizing mediastinal anatomy. One of the advantages of digital imaging is that displayed contrast and brightness are largely independent of the kilovoltage and milliamperage values used to obtain the examination; both contrast and brightness can be manually adjusted by the user after the image has been obtained.[2] Furthermore, the dynamic contrast range (latitude) of digital radiographic techniques exceeds that of film-screen methods by a factor of 10 or more.[2]

Chest radiography has been in use since the discovery of x-rays, and evolutionary developments in radiographic technology have addressed some of the fundamental limitations of radiographic techniques.[1] Whereas film-screen projection radiography was the primary method by which chest radiography was performed for many years, digital radiography has largely supplanted film-screen techniques in many facilities, providing advantages such as image postprocessing and electronic storage of the radiographic data. The latter is particularly important because it allows for simultaneous access to imaging studies by multiple providers as well as transmission of the data over long distances in very short times.

Meticulous attention to technique is essential. Regardless of the method of recording the image, whether through standard film-screen radiography, image intensification, or digital recording, poor quality control leads to degradation of diagnostic information. Unfortunately, many technically inadequate radiographs are produced, leading either to repeat studies with additional patient exposure to ionizing radiation or to interpretation of the poor images, increasing the chance of diagnostic errors.

Indications for the use of chest radiography are protean and include the assessment of both acute (e.g., pneumonia) and chronic (e.g., chronic obstructive pulmonary disease [COPD]) lung diseases, assessment of dyspnea or other respiratory symptoms, evaluation of treatment success in patients with acute lung disease, follow-up of patients with a known chronic lung disease, monitoring of patients in intensive care units (ICUs), diagnosis of pleural effusion, screening for asymptomatic diseases in patients at risk, monitoring patients with industrial exposure, preoperative evaluation of surgical patients, and as the initial imaging study in patients with lung cancer and other tumors, vascular abnormalities, and hemoptysis. Abnormal radiographic findings can be quite subtle, however, and in many circumstances, the sensitivity and specificity of chest radiography is limited. In such situations, other imaging studies, especially thoracic computed tomography (CT), are performed to further investigate abnormalities visible on conventional radiographs or to evaluate patients considered high-risk for a particular condition, but with normal chest radiographic results.

The utility of chest radiographs has been studied in a number of clinical settings, and the appropriate criteria for their use have been determined by the American College of Radiology.[3] Although a detailed analysis of the diagnostic accuracy of chest radiographs in all instances is beyond the scope of this chapter, for illustrative purposes, their utility and limitations in several specific clinical settings are reviewed.

CHEST RADIOGRAPHY: TECHNIQUES

Standard Film-Screen Radiography

The goal of chest radiography is to optimize film quality and diagnostic information while limiting radiation exposure to the patient. Although there are minor disagreements among experts, virtually all definitions of image quality include three general factors: radiographic contrast, resolution, and image noise.[1,4] These are interrelated, and the ultimate quality of the radiograph is determined by the worst of the factors involved in its production.

Radiographic Contrast

With a standard film-screen system, radiographic contrast is principally determined by components of the system, chiefly the energy of the x-rays, and the degree to which secondary radiation (scatter) is eliminated. A film-screen combination possessing an intermediate or wide gray scale (latitude) is preferable to one producing extreme contrast.[1,4] Although very "white and black" radiographs appear to demonstrate excellent detail, differentiation of structures differing slightly in density, such as the pulmonary vessels and the background lung, is better achieved with a wide-latitude film-screen combination or digital radiography. Wide-latitude film-screen combinations or digital radiography also better displays the wide range of densities present in the thorax.[1] The use of a high-peak-kilovoltage (kVp) (120–150 kVp) technique reduces contrast between tissues of different densities and makes calcification more difficult to detect but provides considerably more information largely by allowing structures to be seen through the heart, mediastinum, and bones (Fig. 19-1).

When an object is radiographed, some photons are absorbed or scattered, whereas others pass unaffected through the object (Fig. 19-2A). If the object is close to the x-ray film or detector, exposure from scattered

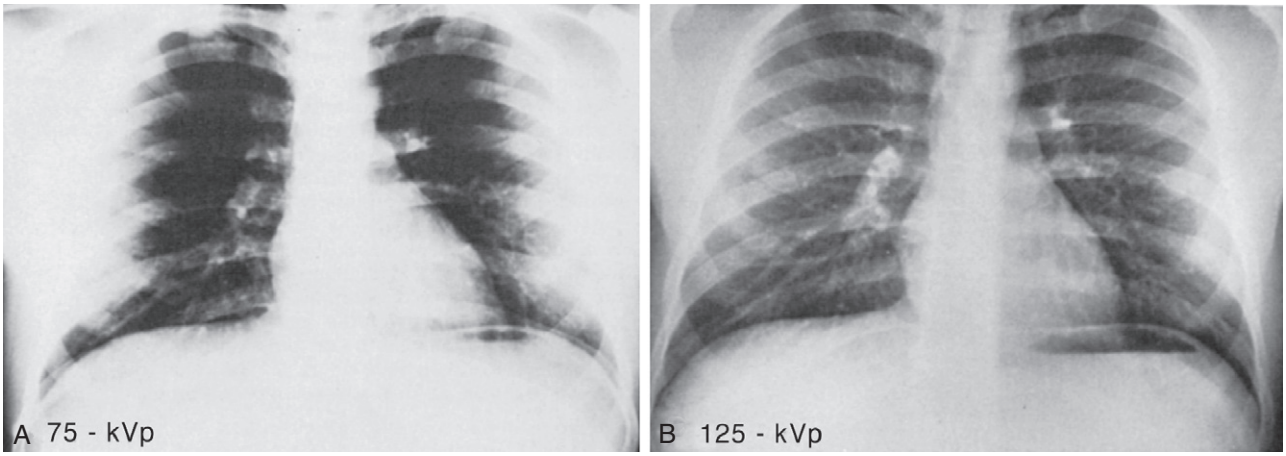

FIGURE 19-1 ■ **A,** This radiograph was made at 75 kVp. Note the lack of visibility of the peripheral lung and the area of the mediastinum. **B,** This radiograph was made at 125 kVp on the same patient. Note the improved definition of peripheral and mediastinal structures.

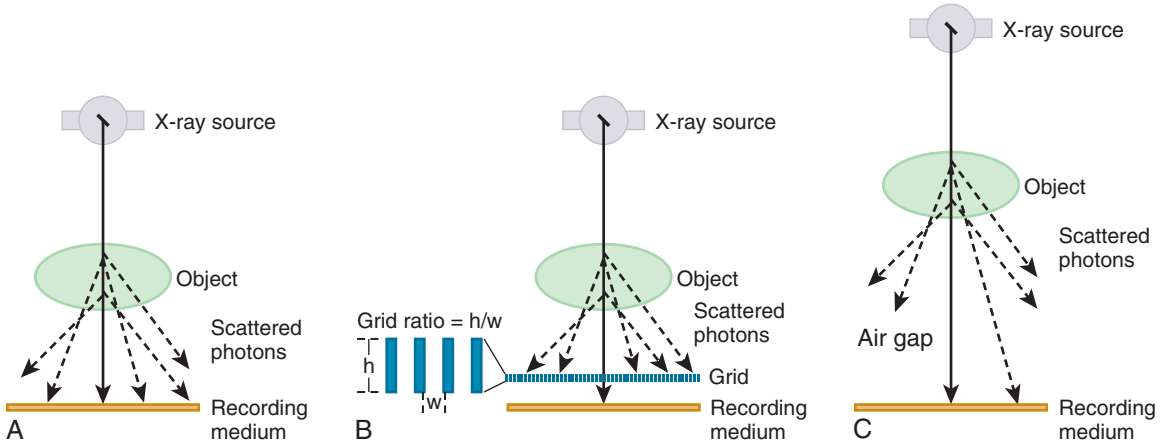

FIGURE 19-2 ■ Scattered radiation and scatter reduction. **A,** When an object is radiographed, some photons (the primary x-ray beam) (*solid line*) pass unaffected through the patient. Scattered or secondary radiation (*dashed lines*) arises at various angles to the primary beam and may expose the film or other recording medium, reducing image contrast and detail. **B,** Scatter can be reduced with a grid. An antiscatter grid placed between the object and the recording medium reduces exposure due to scattered radiation. A grid is made of thin layers of radiation absorber (e.g., lead). Scattered radiation traveling at an angle to the grid layers is absorbed, although some scattered radiation at shallow angles may pass through. The grid ratio is equal to the height of the radiation absorber strips divided by the distance between them. **C,** Scatter can be reduced with an air gap. When the distance between the object and the recording medium is increased, an air gap is created. With an air gap, scattered photons at sufficiently great angles miss the recording device or film.

radiation degrades image contrast and detail.[1,4] Because production of scatter radiation varies with the volume of tissue being imaged, the use of devices, referred to as "collimators," to restrict the beam size to the area being studied reduces scatter radiation. The further addition of filtration to the x-ray tube in the area of the collimator prevents low-kilovoltage radiation from reaching the patient, thus reducing the radiation absorbed by the patient without compromising diagnostic information.

Scattered radiation can also be removed by placing an antiscatter grid between the patient and the x-ray cassette (see Fig. 19-2B).[1,4-6] Such grids permit the passage of the parallel primary x-ray photons to expose the screen or detector while absorbing radiation scattered at an angle to the primary beam; the grid also absorbs some primary photons, making it necessary to increase the amount of radiation to which a patient is exposed. Care must be taken to ensure that the grid is of the proper type and is properly aligned to the x-ray beam. Placement off center, angulation, or the use of a grid focused at the wrong distance may affect the symmetry of radiograph exposure or even render it uninterpretable. Scatter radiation may also be reduced by increasing the distance between the x-ray cassette or detector and the patient, a process referred to as "creating an air gap" (Figs. 19-2C and 19-3).

Resolution

Spatial resolution of film-screen combinations in common use is 10 to 12 line pairs/mm. Many factors, however,

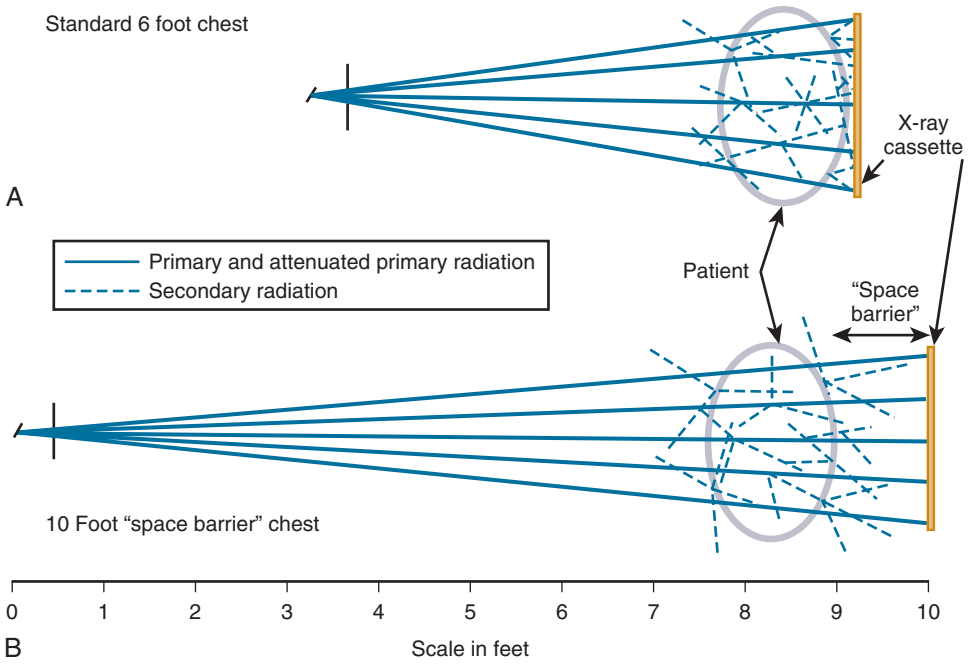

FIGURE 19-3 ■ **A,** The geometry of a standard 6-foot chest radiograph. For beam energies in the recommended range (≥120 kVp), a grid is necessary between the patient and the x-ray cassette or detector to diminish secondary radiation. **B,** A 10-foot air gap or "space barrier" can also be used. The air gap obviates the need for a grid. The 10-foot tube-to-film distance helps to minimize geometric enlargement. The avoidance of the grid diminishes patient radiation exposure.

can reduce the final resolution achieved on a chest radiograph. The use of large focal spots, particularly in thick body parts such as the thorax, degrades resolution by producing "edge unsharpness" or blur due to penumbra effects. Conversely, the limited capacity of a very small focal spot dictates a long x-ray exposure, and body motion can degrade spatial resolution, also causing edge unsharpness. A compromise choice in x-ray focal spot size of 1 mm or less is recommended. Lengthening of exposure duration causes degradation of spatial resolution because of insufficient power of the x-ray generator or deficiency of the heat capacity of the tube. Ideally, exposure duration should not exceed 25 msec and, for frontal projections, should be considerably less. A tube-film distance of at least 6 feet (1.8 m) is usually used to reduce magnification and image blurring (see Fig. 19-3).

Noise

All imaging systems are limited by noise. In radiography, noise is frequently referred to as "quantum mottle."[4] Image mottle is primarily determined by the number of x-ray photons used to produce the image. The fewer the number of photons, the noisier the image will be. With a given film-screen or digital system, attempts to increase speed generally result in decreased resolution because of mottle.

X-ray screens have been developed that employ rare earth phosphors and have the property of converting x-ray photons to light more efficiently. When used with properly matched films, these rare earth screens double or triple the speed at which a properly exposed radiograph can be made. They do not increase the noise of the system significantly, and they permit reduction of radiation exposure to the patient by one half or more.

American College of Radiology Standards

The American College of Radiology standards for performing adult chest radiography[7] specify the use of at least a 72-inch tube-film distance, a tube focal spot not to exceed 2.0 mm (0.6–1.2 mm recommended), rectangular collimation and beam filtration, a high-kilovoltage technique (120–150 kVp) appropriate to the characteristics of the film-screen combination, a film-screen speed of at least 200, an antiscatter technique (grid or air gap) equivalent to a 10:1 grid (preferably 12:1), and a maximum exposure time of 40 msec. The American College of Radiology also specifies a maximum mean skin entrance radiation dose (0.3 mGy/exposure).

Portable Radiography

The proliferation of ICUs and the increased use of patient monitoring for life-support devices have significantly increased the number of portable radiographs obtained.[1,8,9] As indicated earlier, these examinations are

necessary to determine whether catheters, endotracheal tubes, intra-aortic balloons, and various other devices have been correctly placed (Figs. 19-4 to 19-8).[10,11] Portable radiographs are also essential for assessing responses to therapy and for surveying for the presence of new thoracic disease.

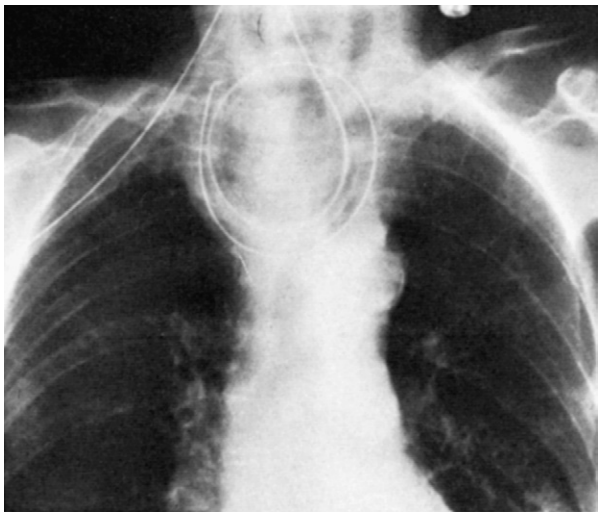

FIGURE 19-4 ■ An intensive care unit portable radiograph shows the nasogastric tube coiled in a Zenker's diverticulum, the existence of which was previously unknown.

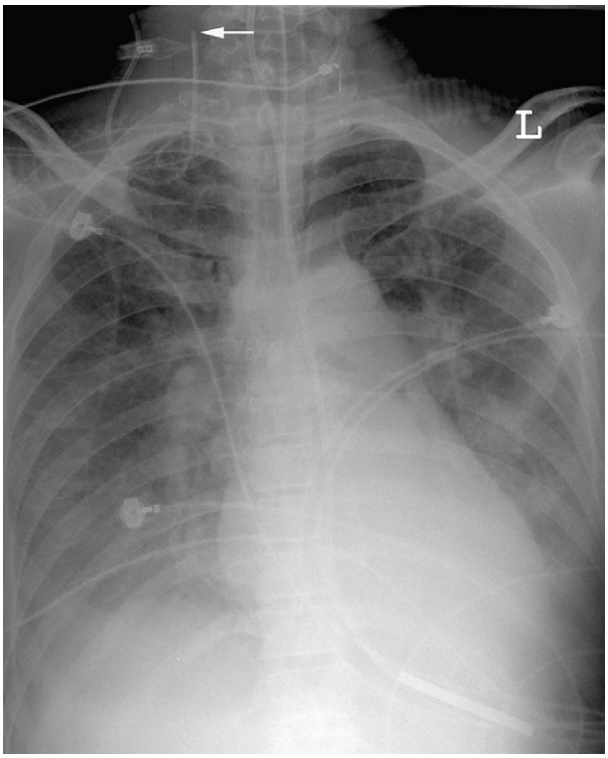

FIGURE 19-5 ■ A portable radiograph shows a misplaced central venous line. Note that the right external jugular venous catheter tip (*arrow*) is within the right internal jugular vein, rather than the superior vena cava. Extensive densities (pulmonary edema) are present in both lungs.

Even under ideal circumstances, the quality of the radiographs obtained with portable techniques does not approach the standard of those made in the radiology department (Fig. 19-9). Portable examinations are generally made at a focal spot–film distance of less than 72 inches, resulting in penumbral blurring, edge unsharpness, and degradation of fine detail.[4] The routine use of the anteroposterior (AP) projection, with the cassette adjacent to the patient's back, magnifies the cardiac silhouette and other anterior structures. When possible, the radiograph should be obtained with the patient in the sitting position, but this is frequently not feasible. Images obtained with the patient recumbent compromise the detection of pleural effusions and pneumothorax as well as the assessment of the gravitational distribution of pulmonary blood flow based on vessel size and lung zone opacity.

None of the several different types of mobile generators available is ideal. Exposure duration is difficult to control and is relatively long, and motion blurring degrades the image. Because of these limitations and the frequent need for immediate viewing of chest radiographs, storage phosphor-computed digital units are widely used for ICU radiography (see later discussion).[11] The storage plate phosphor's ability to provide relatively even density in overexposed and underexposed films and its ability to adjust the images digitally to better visualize mediastinal or pulmonary parenchymal areas are well suited for ICU portable radiography.

The American College of Radiology standards for performance of portable chest radiographs are relatively forgiving.[7] A tube-film distance of 40 to 72 inches is preferred. From 70 to 100 kVp is recommended if a grid is not used, whereas more than 100 kVp may be used in conjunction with a grid. Exposure times should be as short as feasible to reduce motion artifacts.

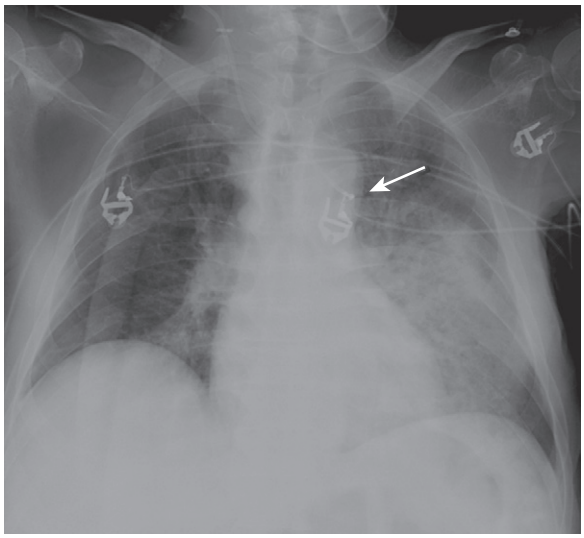

FIGURE 19-6 ■ An intensive care unit portable radiograph demonstrates malposition of a right central venous catheter. The catheter has been inadvertently inserted into the right carotid artery; the tip (*arrow*) resides in the aortic arch. A large area of consolidation is seen in the left lung.

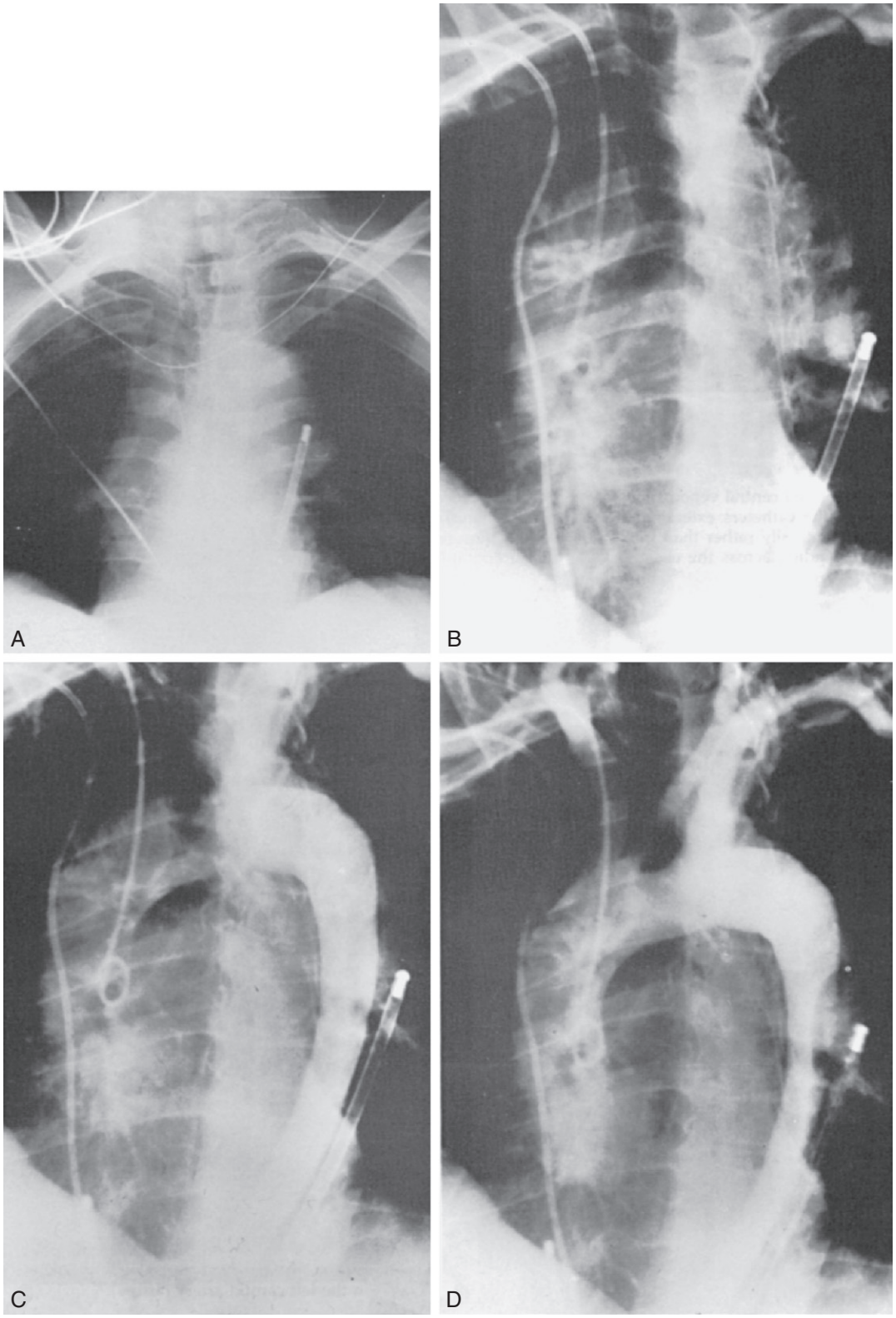

FIGURE 19-7 ■ Portable intensive care unit radiography is useful in several situations. **A,** A "routine" radiograph made after insertion of an intra-aortic balloon shows the catheter to be more lateral than usual. **B,** A portable oblique radiograph confirms the unusual position. The balloon-assist device appeared to be functioning adequately. **C,** An aortogram performed with a pigtail catheter in the ascending aorta reveals the balloon catheter to be outside of the lumen of the descending aorta. **D,** The diastolic cardiac phase is shown. The inflated balloon, which is in an aortic dissection, does partially occlude the aortic lumen, explaining why the balloon appeared to be functioning satisfactorily. The balloon had been inserted into the false lumen of an aortic dissection.

Digital (Computed) Radiography

The development of reusable radiation detectors along with advances in electronics and computer technology enabled the development of a new type of radiographic imaging: digital or computed radiography.[1,12] These systems are fundamentally different from film-screen radiography in that image detection can be completely separated from the method of image display, and because the images are digital in format, they can be subjected to significant postprocessing to improve diagnostic information. Also, digital image receptors have a much wider range of sensitivity or latitude compared with standard film-screen combinations (10,000:1 rather than 100:1), and their response to radiation is linear over this entire range.[1,2] Within these large limits, image contrast is independent of exposure. Furthermore, digital images can be displayed, transmitted, and stored electronically.[2,4]

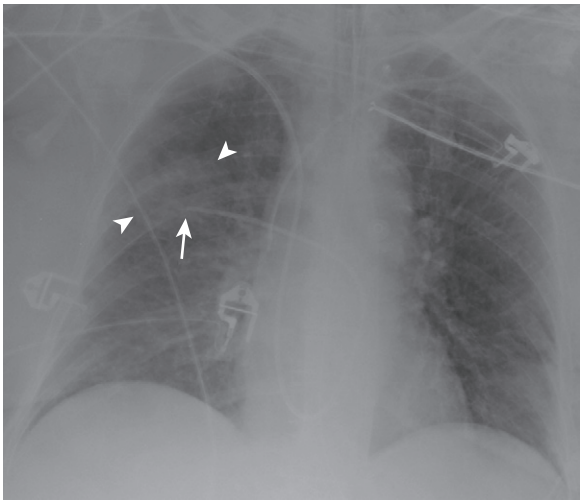

FIGURE 19-8 ■ Sequelae of a malpositioned Swan-Ganz catheter. The catheter (*arrow* = tip) extends too far peripherally into the segmental vessels of the right upper lobe artery. The catheter had been in this location for a number of hours. Note the opacity in the right upper lobe (*arrowheads*), representing pulmonary hemorrhage or infarction secondary to vessel obstruction by the Swan-Ganz catheter.

Storage Phosphor Systems

The most commonly employed system of digital radiography uses imaging plates that are exposed by conventional radiographic equipment and can be used like any x-ray cassette.[1,4] The reusable plates are coated with a photostimulatable phosphor that absorbs energy and retains a latent image when exposed to x-rays. The stored energy of the latent image is released as light when the plate is scanned by a laser in an image plate reader. The light produced is measured and digitized, yielding an image that can be subjected to contrast and spatial frequency enhancement and can be stored on magnetic or optical disks, viewed on monitors, or printed on film with a laser printer (Fig. 19-10). The imaging plates are erased by exposure to light and may be reused almost immediately.

The resolution of digital images depends on the matrix size used. Spatial resolution is less than that of film-screen combinations (2.5–5 line pairs/mm), depending on the size and type of plate used to capture the image.[1] The unit can be set to perform automatic processing by preprogramming parameters for certain examinations or may be postprocessed manually by the radiologist to enhance various specific image features.[13] The contrast

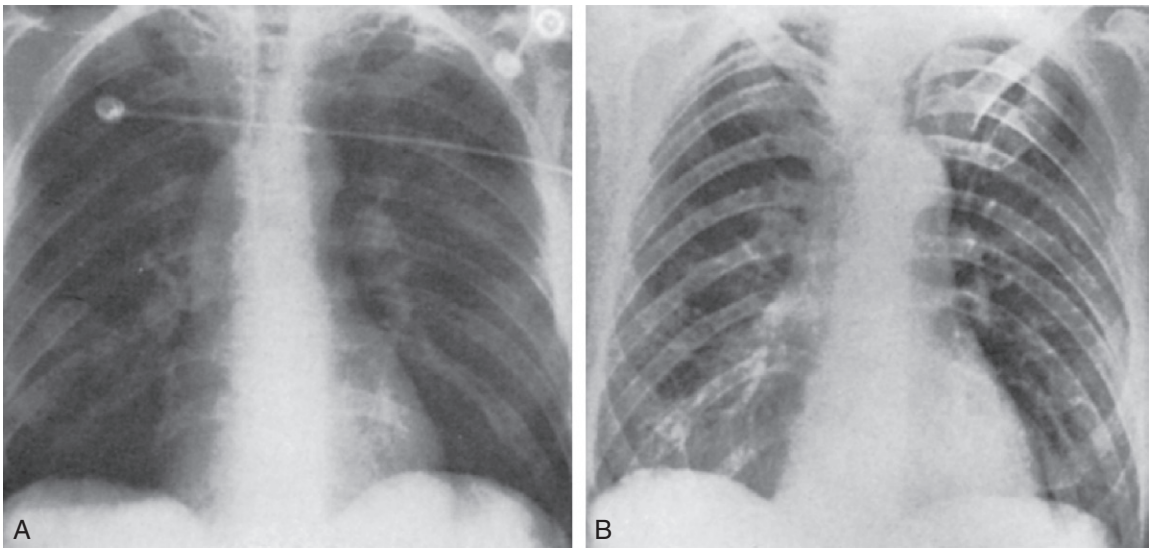

FIGURE 19-9 ■ Portable radiography has limitations. **A,** This anteroposterior (AP) supine portable radiograph was made in the intensive care unit. The energy of the beam was 100 kVp, and the focal spot–film distance was 40 inches. The pulmonary markings are poorly visualized because of a long exposure with motion blurring and a short focal spot–film distance with magnification and detail degradation. **B,** This radiograph was obtained from the same patient shortly after that shown in **A,** but in the main radiology department. The patient was sitting in a chair. The energy of the beam was 130 kVp, with a focal spot–film distance of 60 inches. Much better detail can be seen in the radiograph in **B.** It also has less magnification.

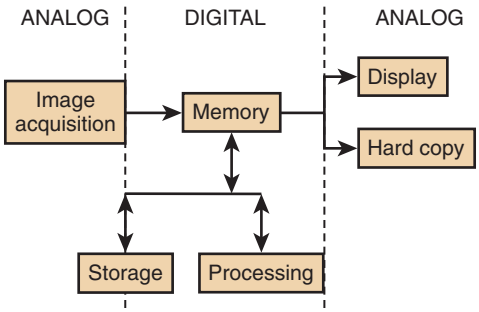

FIGURE 19-10 ■ This block diagram shows components of a digital radiographic system. Image manipulation, subtraction, and other such functions are performed during the digital phase. (From Nudelman S: *In* Digital Radiology—Physical and Clinical Aspects: Proceedings of Meeting Held at Middlesex Hospital and Medical School, London, England, March 9, 1983. London: Institute of Physical Sciences in Medicine, 1984, pp 1–43.)

scale can be altered, and the optical density of the entire image or of various areas can be changed. Edge enhancement can be obtained by amplifying high frequencies to visualize minute pulmonary detail. For the thorax, the automatic processing can be preset to produce a pair of images: one resembling a conventional film-screen radiograph and the other exhibiting varying amounts of edge enhancement (Fig. 19-11).

An obvious advantage is that the images can be immediately transmitted electronically and viewed at a workstation in the emergency room, ICU, operating room, or other area where online viewing is required.[1,4] Because the images are stored electronically, they may be recalled for comparison with subsequent studies, and they may be printed for conventional display at any time. High-resolution display units (2000-line) allow displayed images with excellent spatial resolution.

Clinical Efficacy

A large number of studies have compared digital imaging systems with conventional film-screen radiographs in both measured physical performance and interpretive accuracy. It is generally agreed that the denser portions of the thorax and the lung in front or behind these dense areas are seen significantly better with digital systems. There is disagreement concerning visualization of fine lung detail, line shadows, pneumothoraces, and interstitial lung disease.[14–18] An important consideration is that digital recording systems have a very wide exposure latitude, and adequate films can be obtained with a wide range of exposures, which reduces the need for repeated films.

Factors other than image quality are playing a preeminent role in the dissemination of digital techniques. Among these are immediate availability of the images, ease of storage and retrieval, interaction with hospital electronic information systems, and cost of film and file room operation. CT, MRI, ultrasonography, and nuclear medicine studies already are digital. The completely digital imaging department is increasingly common. In certain situations, digital images enables the use of computer-aided detection, particularly in the setting of mammography, chest radiography, and thoracic CT.[1]

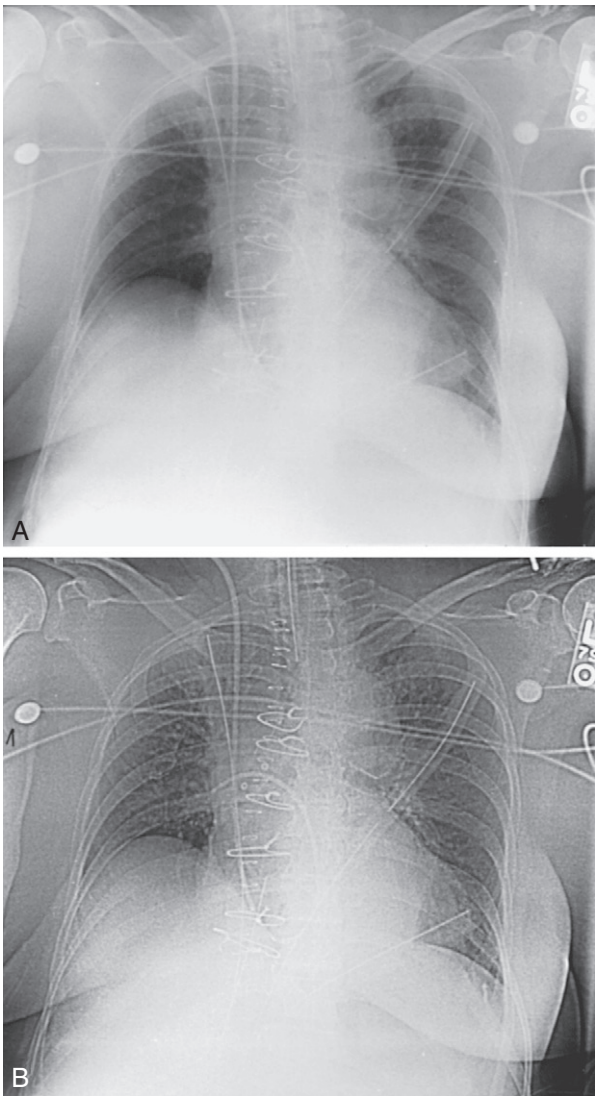

FIGURE 19-11 ■ This digital (computed radiography) study of the chest was made in an intensive care unit. **A,** This view resembles a "conventional" film-screen radiograph. **B,** This view was processed for edge enhancement.

Radiographic Views and Techniques

Routine Examination

A routine chest radiographic examination in an ambulatory patient usually consists of posteroanterior (PA) and left lateral projections. The utility of routine lateral radiographs, however, has been questioned. After analyzing over 10,000 radiographic chest examinations obtained routinely in a hospital-based population, Sagel and associates[19] concluded that the lateral radiograph could be safely eliminated in the routine examination of patients 20 to 39 years of age. Conversely, they and others[20] have concluded that the lateral radiograph should be obtained

in patients with suspected chest disease and in screening examinations of patients 40 years of age or older (Fig. 19-12).

Expiratory Views

Conventional radiographs are made at total lung capacity (i.e., full inspiration), thereby permitting the greatest volume of lung to be evaluated for possible pathology and providing the most contrast between intrapulmonary air and normal and abnormal intrathoracic structures (Fig. 19-13). However, localized or generalized air trapping in the lung or pleural space is more easily detected (and sometimes only detected) on a radiograph made during expiration. The normal lung diminishes in volume and increases in density with expiration. Areas of trapping usually retain their lucency and volume regardless of the phase of respiration. With unilateral or localized air trapping, mediastinal shift and failure of normal elevation of the hemidiaphragm on the affected side are frequently apparent only on expiration (Fig. 19-14). Small pneumothoraces, difficult to visualize and frequently overlooked on inspiratory radiographs, appear larger and more apparent on the expiratory study. As the thorax and underlying lung diminish in volume, the lung becomes denser, whereas the pneumothorax remains

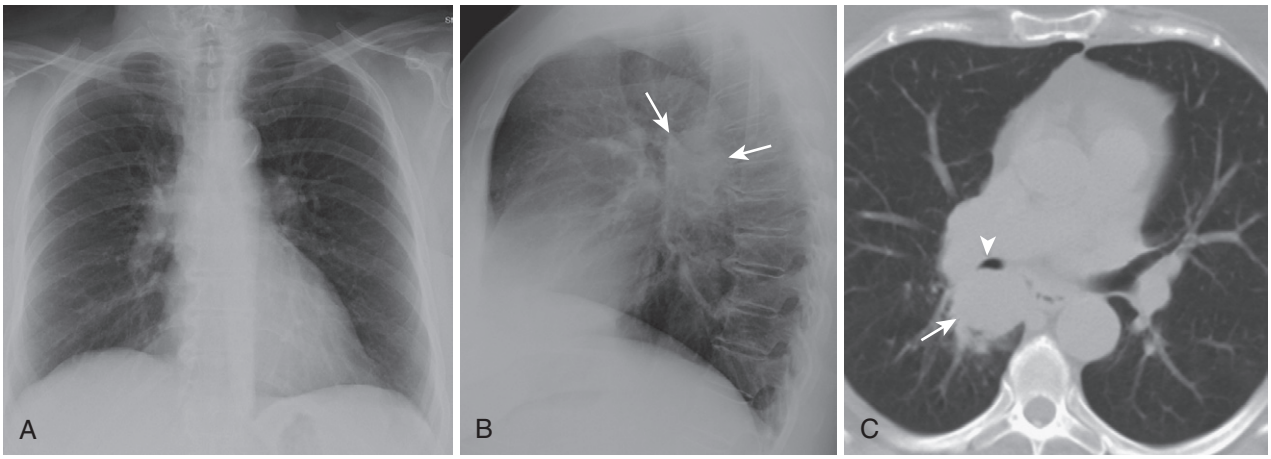

FIGURE 19-12 ■ The utility of the lateral radiograph. **A,** The posteroanterior (PA) radiograph shows no specific abnormalities. **B,** The lateral radiograph identifies a mass (*arrows*) projected over the hilum. **C,** Axial thoracic computed tomography (CT) confirms the presence of a mass (*arrow*) in the right lower lobe posterior to the bronchus intermedius (*arrowhead*). The lesion was shown to represent bronchogenic carcinoma.

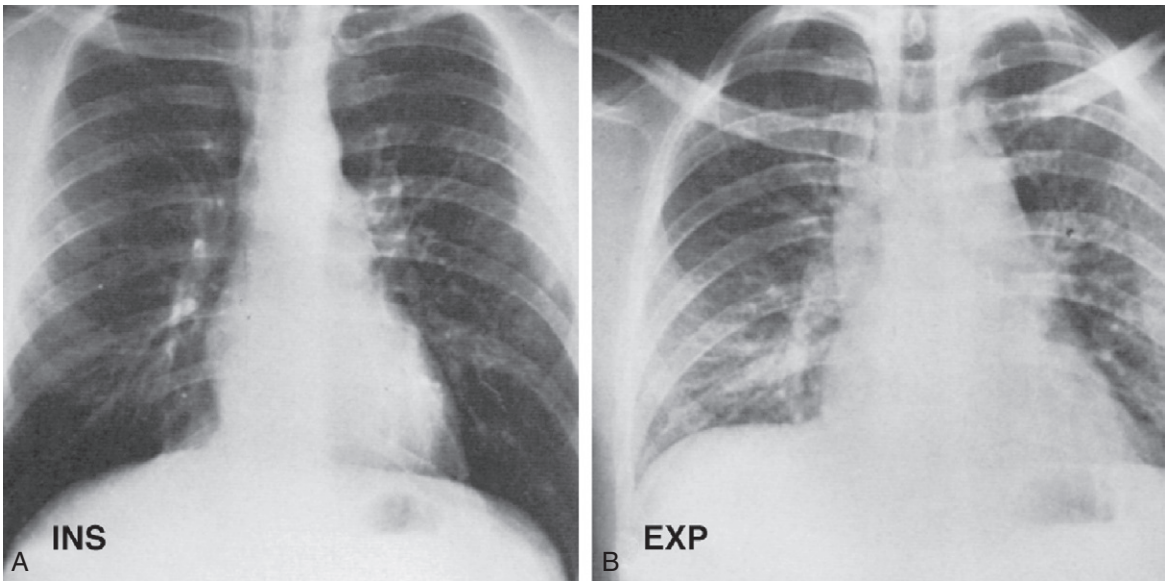

FIGURE 19-13 ■ These inspiration (INS) and expiration (EXP) radiographs are from a healthy man. **A,** With inspiration, the low level of the diaphragm permits visualization of the basal portions of the lung. There is normal radiolucency of the lung. The mediastinum is narrow, and the edges of the hilar structures are sharp. **B,** With expiration, the lung bases are obscured. The lung is dense. The mediastinum is wide and could be interpreted as abnormal if the fact that the film was made at residual volume was not appreciated.

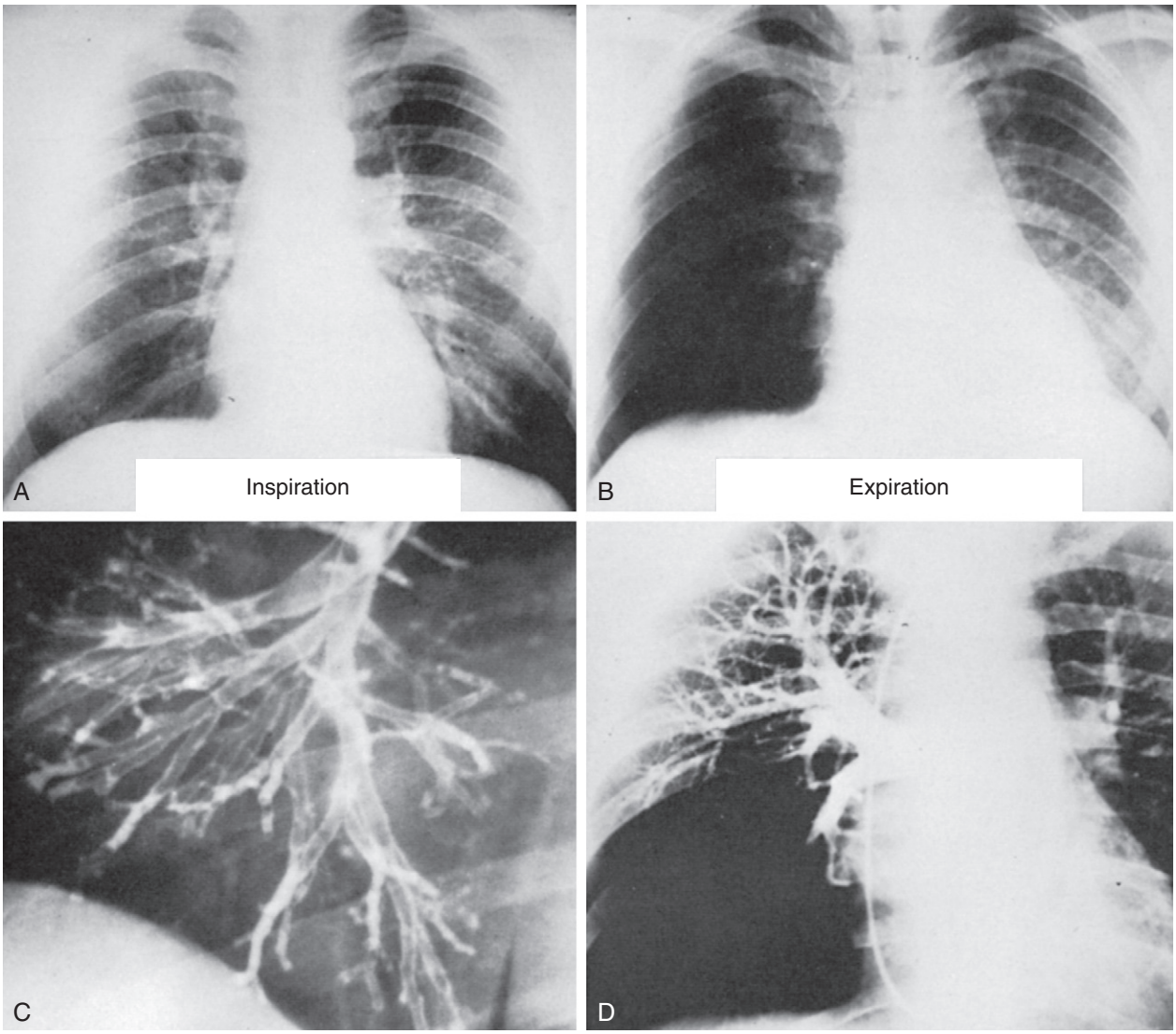

FIGURE 19-14 ■ The unilateral hyperlucent lung of an asymptomatic 32-year-old man. **A,** With inspiration, the vessels to the right lower lobe are smaller than those on the left, and the left hilus is prominent compared with the right. No radiographic evidence of air trapping is seen. **B,** With expiration, there is air trapping on the right. The left hemidiaphragm ascends normally, whereas the right remains low and fixed. The mediastinum shifts to the left. Lucency persists on the right. **C,** Bronchography with propyliodone fails to fill the small bronchi and bronchioles in the right lower lobe. Air movement is necessary to fill these small bronchi. The obliterative bronchiolitis causing the trapping (through collateral air drift) involves airways much smaller than those bronchi visualized on the study. Bronchiectasis, which may accompany this condition, is not present. **D,** Pulmonary angiography reveals a large perfusion defect in the involved area due to hypoxic vasospasm. This should not be mistaken for pulmonary embolism, because neither the trailing edge nor the wormlike defect of thrombi is seen. Neither bronchography nor angiography is indicated for asymptomatic patients with this condition.

essentially unchanged in size and occupies a greater proportion of the deflated hemithorax and is thereby outlined more clearly by denser pulmonary parenchyma (Fig. 19-15).

Other causes of localized or unilateral lucency on the radiograph are differentiated from air trapping by the expiratory study (Fig. 19-16). Among these are technical causes such as patient rotation, miscentered x-ray beam or grid, and "the anode-heel effect," an artifact of asymmetrical generation by the anode of the x-ray tube. Chest wall abnormalities, either congenital or postsurgical, can produce unilateral lucency. Undetected areas of atelectasis with compensatory overexpansion of portions of the lung and primary vascular disease, such as pulmonary embolus, may also produce lucency. None of these causes of pulmonary lucency will show trapped air on the expiratory radiograph.

Decubitus Views

Decubitus radiography is performed by placing the patient in the recumbent position, usually lying on one side and then the other. The x-ray exposure is made with a horizontal beam in either the AP or the PA projection.

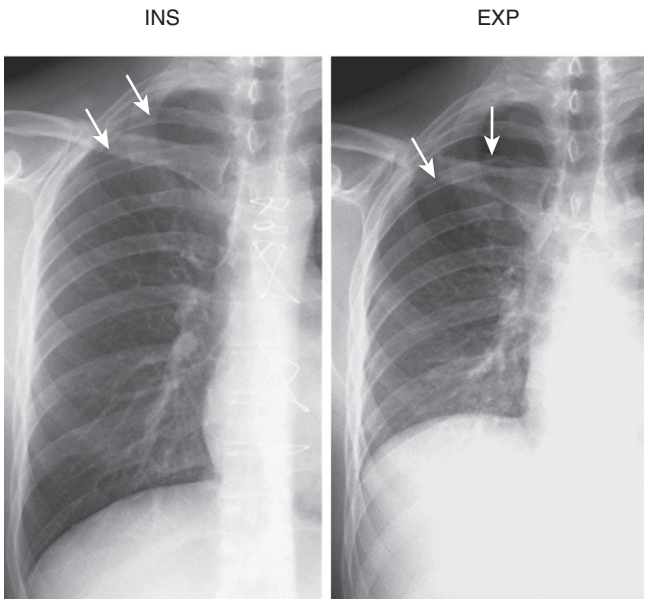

FIGURE 19-15 ■ Inspiration (INS) and expiration (EXP) films of a pneumothorax. **A,** With inspiration, the right pneumothorax is difficult to visualize but is faintly seen in the upper thorax (*arrows*). **B,** With expiration, the pneumothorax is outlined against denser lung. It appears to be considerably larger than in the inspiration study (*arrows*) (see text).

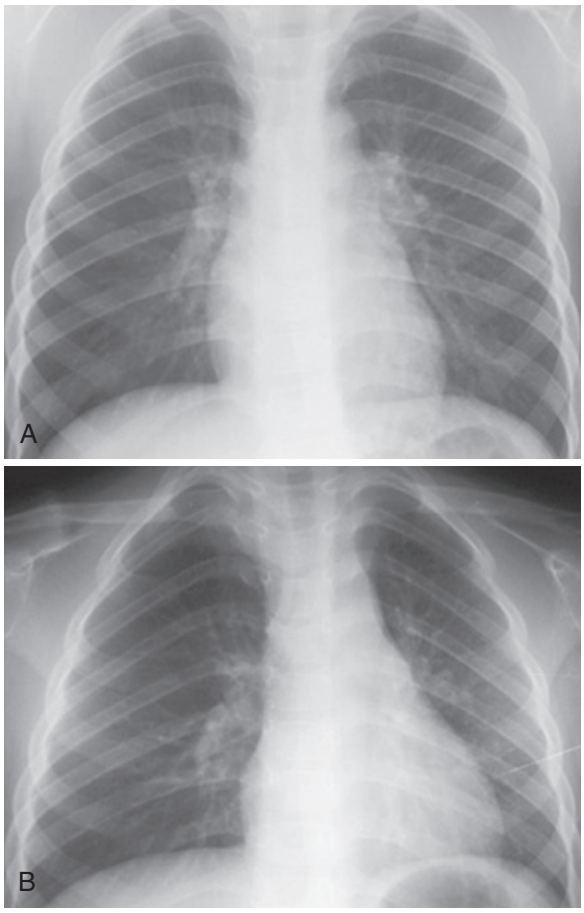

FIGURE 19-16 ■ Unilateral hyperlucent lung in an 8-year-old boy with a foreign body in the right main-stem bronchus. **A,** The inspiration radiograph shows mild hyperlucency of the right lung. **B,** The expiration film shows the right hemidiaphragm remains fixed in a low position, the right lung remains lucent, and the mediastinum is shifted to the left (air trapping). A foreign body was removed.

The technique is useful for determining the presence or absence of free fluid in the pleural space or parenchymal cavities, in estimating the size of effusions, and in diagnosing pneumothorax in patients who are unable to sit or stand. Free fluid gravitates to the dependent portion of the thorax, which in the decubitus patient lies against the lateral rib cage of the dependent hemithorax (Fig. 19-17) or the mediastinum of the contralateral side; pneumothorax does the opposite. In the typical AP supine chest radiograph, free fluid will layer posteriorly and manifest as an increase in density involving the entire hemithorax. Air within the pleural space will collect anteriorly and is often difficult to detect. The proper use of decubitus radiography will demonstrate the presence of free fluid, pneumothorax, or both (Figs. 19-18 and 19-19). When a portable study must be performed with the patient in bed, it may be technically difficult to obtain high-quality radiographs of the dependent portion of the hemithorax due to the underlying bed, clothes, or other inconveniences. For this reason, bilateral decubitus studies are advisable. Even in patients in whom PA and lateral erect radiographs can be performed, subpulmonic effusions may be difficult to detect, and no fluid meniscus may be visualized. Unless the fluid is completely loculated, a decubitus study will demonstrate its presence and size (see Fig. 19-19). As little as 20 mL of fluid can be seen in the decubitus position.

Lordotic Views

Radiographs made in the lordotic position can be of value in demonstrating lesions in the immediate subclavicular region or partially hidden by the clavicle. This is particularly true if these lesions are located posteriorly. In the lordotic view, which is most frequently obtained in the AP projection, the clavicle, being an anterior structure, is projected above the lung apex, and the subclavicular lung regions are well visualized. The lordotic view may also be used to confirm middle lobe or lingular atelectasis. A lordotic view centered over the lower portion of the chest will project the atelectatic lobe or segment so that it directly faces the x-ray beam, and it will be easily visualized as a dense triangular shadow.

Oblique Views

Occasionally, shallow oblique views are valuable in sorting out superimposed shadows and in visualizing pulmonary parenchymal opacities obscured by superimposition from the heart, mediastinum, or portions of the bony thorax. In general, it is more rewarding to study these opacities with CT.

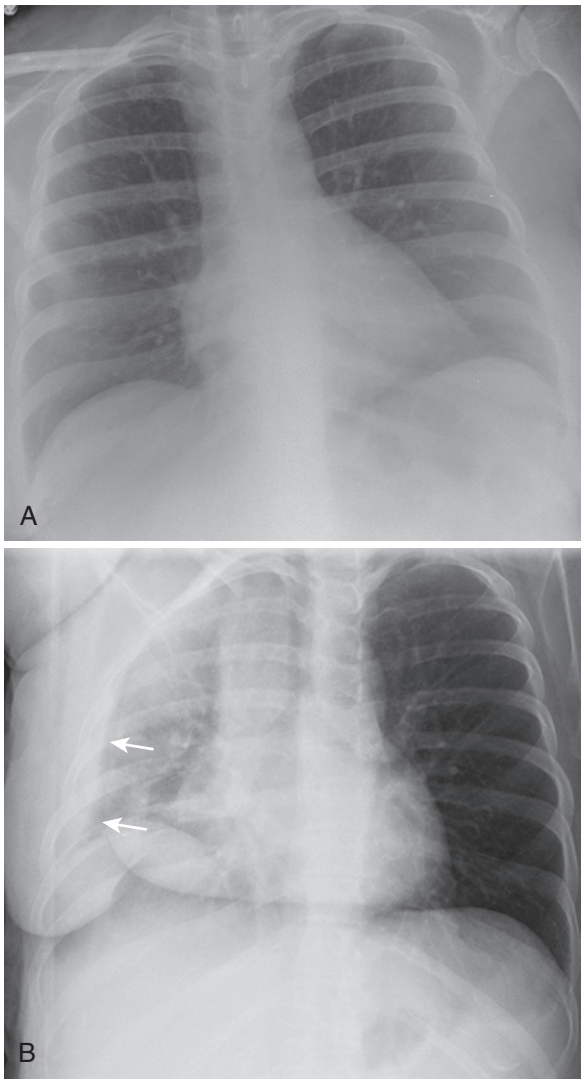

FIGURE 19-17 ■ The value of decubitus radiography. This patient had right pleuritic chest pain. **A,** A frontal chest radiograph shows no specific abnormalities; the right costophrenic angle is sharp. **B,** A right lateral decubitus radiograph shows a small right pleural effusion (*arrows*). Note that decubitus imaging causes collapse of the ipsilateral lung.

Fluoroscopy

Fluoroscopy at one time was commonly employed either as the primary method of radiologic examination of the chest or as an adjunct study to standard radiographs. Its use over the past several decades has diminished considerably. However, there remain a few situations in which fluoroscopy can provide information that is difficult to obtain by other means, such as for the detection of abnormalities of diaphragmatic motion that result from conditions affecting the phrenic nerve. The major use of chest fluoroscopy in current medical practice is as a guide for interventional procedures such as catheter angiography and needle or transbronchial biopsies.

Bronchography

Contrast bronchography, formerly a fairly common thoracic examination (see Fig. 19-14C), has been replaced by fiberoptic bronchoscopy and either CT or high-resolution computed tomography (HRCT) of the lung. In patients with suspected bronchiectasis, HRCT and spiral CT are as sensitive and are safer, more easily obtained, and much more pleasant to undergo than bronchography.[21]

Pulmonary Angiography

Pulmonary angiography has traditionally been employed primarily for the detection or exclusion of pulmonary embolism (Fig. 19-20; see also Fig. 19-14D). Although it has been traditionally regarded as the "gold standard" for making the diagnosis of pulmonary embolism, it has limitations and tends to be underutilized.[22] Other situations in which pulmonary angiography has been employed include the diagnosis and embolization of pulmonary arteriovenous malformations (Fig. 19-21), pulmonary arterial foreign body retrieval, pulmonary vasculitis (Fig. 19-22), and occasionally, the delineation of the anatomy of pulmonary vessels before lung surgery. The study is performed by rapidly injecting intravenous contrast material through a catheter and imaging the lung while the contrast material traverses the arteries and veins. Most frequently, the catheter is inserted into the femoral vein percutaneously and then guided into the pulmonary artery under fluoroscopic control.

Angiograms may be done with the catheter in a main branch of the pulmonary artery or more selectively in distal vessels. The radiographic contrast material is injected at the rate of approximately 10 to 25 mL/sec, depending on the vessel size. The volume of contrast depends on the location of the catheter. Between 40 and 60 mL of contrast material is usually injected into the right or left main pulmonary artery; half this amount of contrast is needed with digital subtraction techniques. Selective injections made within the more distal pulmonary arteries require smaller volumes. If the angiogram is performed for the detection or exclusion of pulmonary embolism after an abnormal but nondiagnostic perfusion scan, the location of the perfusion defect on the scan may act as a "road map" for the angiographer, and selective or superselective injections proximal to the area of perfusion deficit may be performed.

Unless the angiogram is done with a balloon occlusion technique, serial recording is necessary. In the past, rapid film changers were used with an exposure rate of 3 or 4/sec, but such "cut-film" techniques have been replaced by digital subtraction angiography. Filming is usually carried out for several seconds after injection to permit visualization of the pulmonary veins, the left side of the heart, and the thoracic aorta.

It is frequently necessary to image in several different projections to confirm or exclude pulmonary embolism. Oblique or lateral projections may be desirable. If the angiographic suite contains biplane equipment, the number of necessary contrast material injections can be

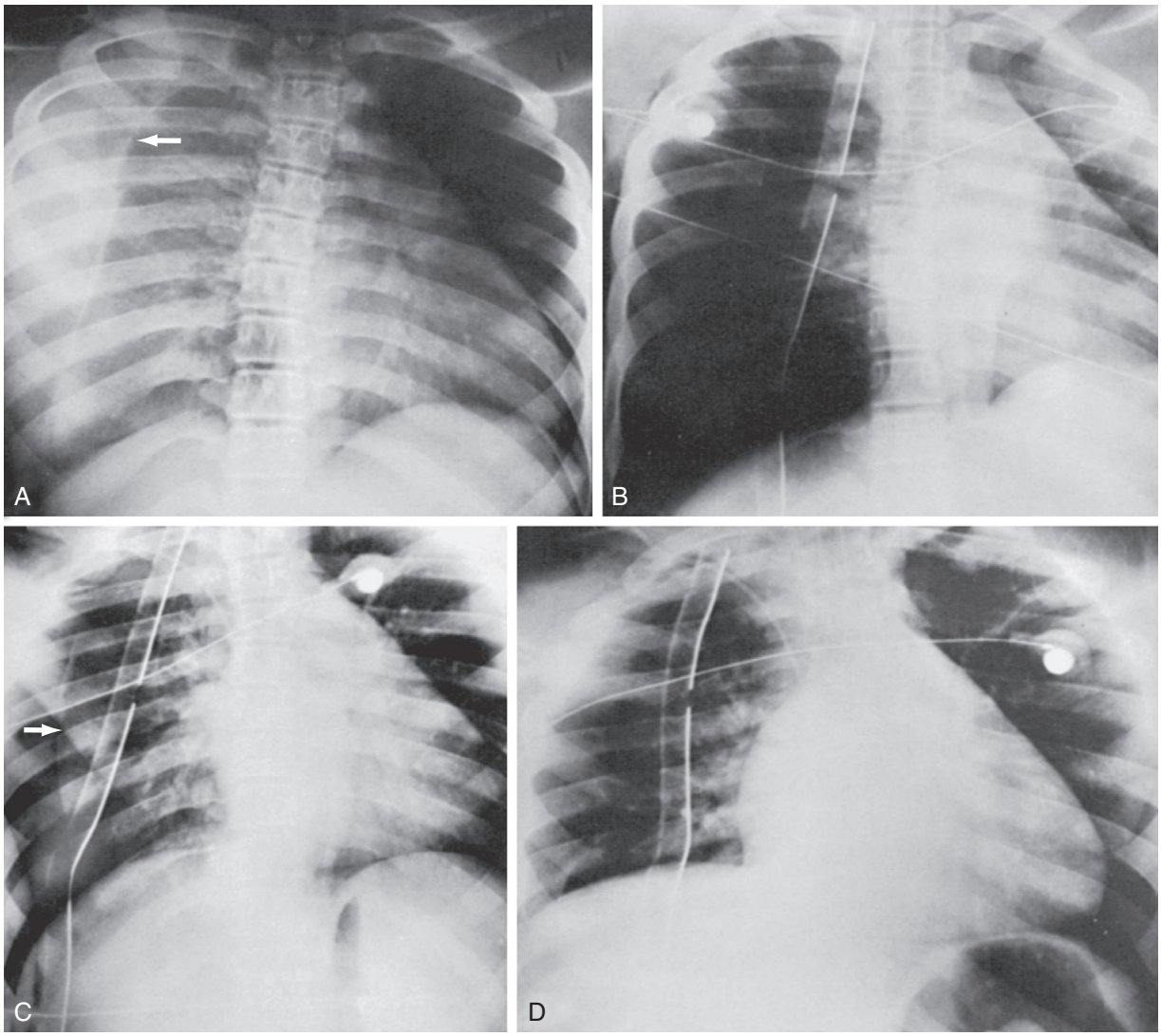

FIGURE 19-18 ■ The value of a decubitus film in portable radiography. A 20-year-old man was admitted to the hospital in shock after a knife wound to the right side of the chest. **A,** A supine AP portable radiograph shows a tension hemopneumothorax on the right. The mediastinum is deviated to the left. The right hemidiaphragm is depressed. The rib interspaces on the right are widened. The right lung is partially collapsed. No air-fluid levels are seen, but both sides of the pleural stripe are visualized, indicating that air is present along with fluid in the right hemithorax (*arrow*). **B,** A postoperative radiograph (AP supine) reveals air in the soft tissues. There is persistence of tension on the right despite the presence of a chest tube. It is not possible to determine whether the tension is due to air trapping within the lung or to a pneumothorax. **C,** A left lateral decubitus radiograph clearly shows the presence of a pneumothorax (*arrow*), even though the chest tube was draining small amounts of air out of the right hemithorax. The low position of the right hemidiaphragm is indicative of tension. **D,** An AP supine radiograph after reexploration shows no evidence of tension or of pneumothorax. The chest wound had been inadequately repaired at the first operation, permitting air to enter the right hemithorax on each inspiration. The tube, although draining small amounts of air, was partially obstructed with blood clot.

diminished by imaging in two orthogonal planes after a single injection of contrast medium. Magnification angiography may show emboli in vessels that are too small to be clearly seen on standard studies.

For a definite diagnosis of pulmonary embolism, it is necessary to visualize the embolus as either a filling defect (see Fig. 19-20) within a vessel or the trailing edge of a thrombus. Other abnormalities should not be regarded as diagnostic of embolism (see Fig. 19-14D).

Complications and death do occur, but fortunately are rare. Significant complications occur in less than 5% of patients, and death occurs in 0.1% to 0.5% of patients undergoing angiographic studies to evaluate suspected pulmonary embolism.[23] Minor arrhythmias are not infrequent when the catheter tip traverses the right ventricle. Ventricular fibrillation has been reported, as has refractory shock. Electrocardiographic monitoring and immediate availability of defibrillating equipment are necessary. Reactions to contrast material are most frequently minor and primarily consist of urticaria and vasovagal responses. However, major reactions with bronchospasm and cardiopulmonary collapse occasionally occur. Renal failure

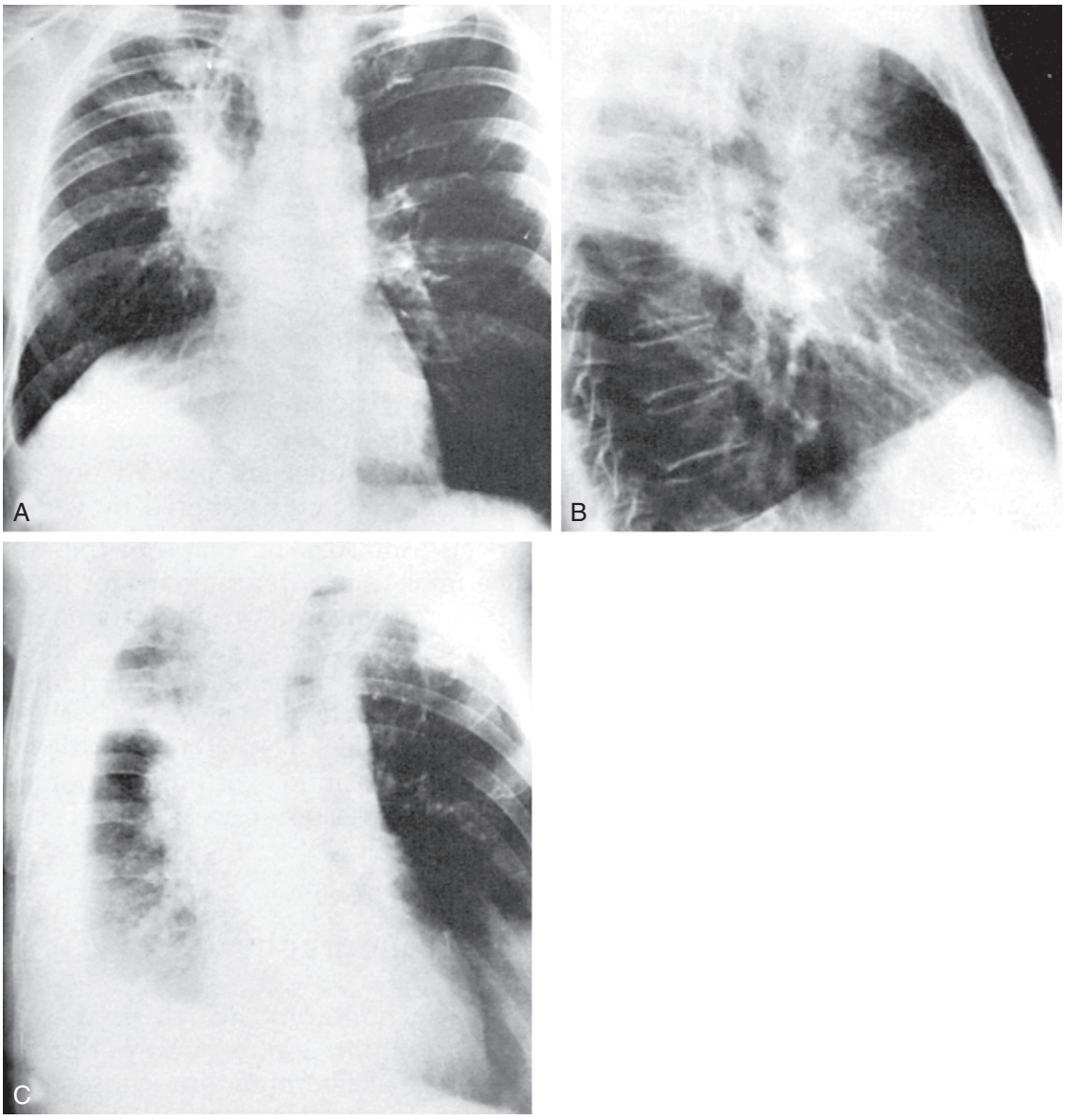

FIGURE 19-19 ■ The value of decubitus radiographs in a 55-year-old man with carcinoma of the right upper lobe. **A,** A PA radiograph shows an unusual configuration at the right base. Minimal blunting of the right costophrenic angle is present. The location of the hemidiaphragm cannot be determined. **B,** A lateral radiograph shows no definite evidence of fluid. The right hemidiaphragmatic shadow is elevated, particularly in its anterior portion. **C,** A right lateral decubitus projection reveals the presence of a large, free pleural effusion. The apparent elevation of the hemidiaphragm on the conventional PA and lateral films is due to subpulmonic effusion.

after administration of iodinated contrast material is a well-recognized complication, and preexisting renal disease manifested by elevated serum creatinine levels represents a relative contraindication to angiography. In all circumstances, the amount of contrast material injected should be the minimum required to produce diagnostic opacification of the pulmonary vessels. The use of nonionic or low-osmolar contrast material diminishes the number of minor reactions and increases patient comfort during the procedure and is now routine in most practices.

Aortography and Bronchial Angiography

Aortography is generally accomplished by the retrograde passage of a catheter from the femoral artery to the aorta or its branches after percutaneous insertion (Fig. 19-23). The study of the aorta and its branches plays a limited role in diseases of the lung. The imaging modalities of choice for diagnosing suspected aortic abnormalities, including aortic dissection, are MSCT, MRI, and in acute cases, transesophageal ultrasonography; aortography is seldom required. The diagnosis of pulmonary sequestra-

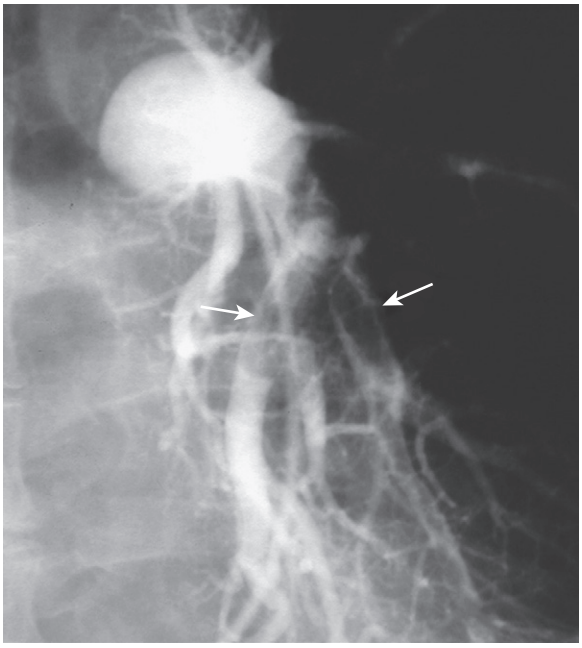

FIGURE 19-20 ■ Pulmonary angiography shows multiple emboli. Intraluminal filling defects (*arrows*) are present within the left pulmonary arterial vasculature, consistent with pulmonary emboli.

tion once depended on the demonstration of anomalous systemic blood supply by aortography, but in modern practice MSCT and MRI are often diagnostic and easily demonstrate the abnormal vascular supply (Fig. 19-24). Patients with severe hemoptysis may require bronchial arteriography and embolization of the bronchial artery or arteries supplying the bleeding site (Fig. 19-25). These studies require selective catheterization of the bronchial arteries. Angiographic technique is, for the most part, individualized to fit the particular clinical condition being studied.

Angiography can be performed with a technique termed "digital subtraction angiography." With digital subtraction angiography, an early image from the angiogram is recorded with an image intensifier and a high-resolution television camera and is digitized and stored. A later image in which vessels are opacified is handled in a similar manner. The first image is then subtracted from the second, and the resulting image is displayed. The background body structures are subtracted, leaving an image of the contrast-filled vessel (see Figs. 19-23 and 19-25). Because the body background does not obscure the final image, angiography can be accomplished with smaller amounts of contrast than otherwise necessary. Motion of structures in the area being studied may make subtraction of images difficult.

ULTRASONOGRAPHY

Ultrasonography, which is also discussed in Chapter 20, has limited usefulness in thoracic imaging, because the ultrasound beam is reflected at the air–soft-tissue interface around the lungs, but some specific uses have been recognized.[24-26] It is useful for studying vascular, cardiac, and some mediastinal abnormalities and for the localization of pleural fluid and air collections. Transesophageal sonography can allow imaging of some mediastinal structures and is often performed to assess the thoracic aorta and heart. The use of ultrasonography in lung imaging is largely limited to the pleura and immediate subpleural areas or to areas of consolidated lung or masses contacting or invading the chest wall. It is most commonly utilized for the detection, localization, and characterization of pleural effusions and to guide thoracentesis (Fig. 19-26).

Ultrasonography is also valuable in differentiating effusion from pleural thickening. Effusion is usually anechoic or hypoechoic, whereas pleural thickening results in an echogenic stripe within the enclosing rib margin.

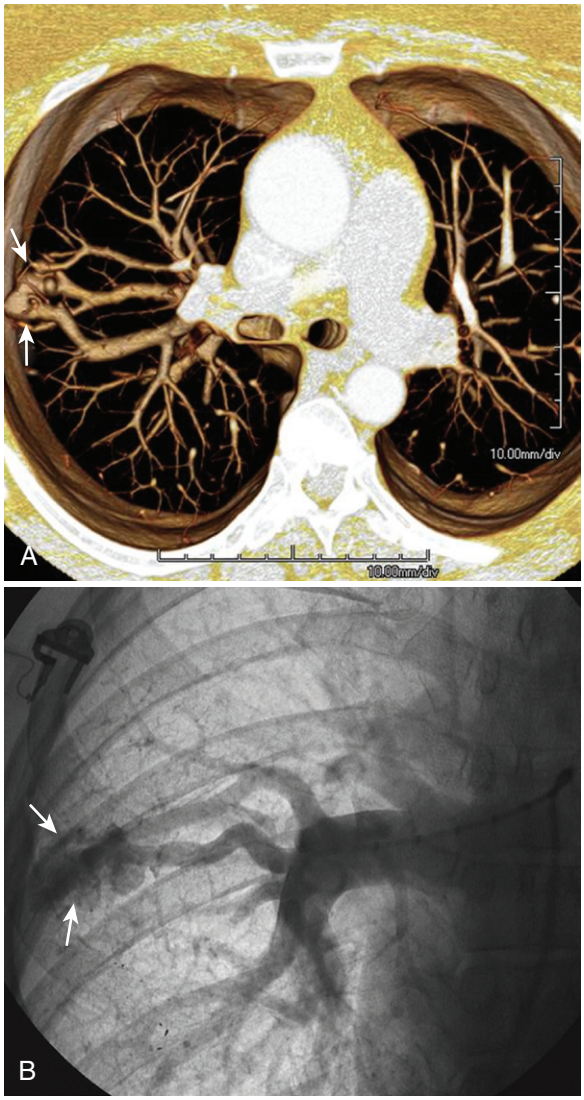

FIGURE 19-21 ■ Arteriovenous malformation. **A,** Axial thoracic volume rendered CT shows an arteriovenous malformation (*arrows*) in the peripheral right lung. **B,** Coronal pulmonary angiogram prior to embolization shows the arteriovenous malformation.

FIGURE 19-22 ■ Pulmonary arteriography in a patient with Takayasu arteritis shows a high-grade stenosis (*arrow*) of the right upper lobe pulmonary artery vasculature.

FIGURE 19-23 ■ Catheter aortography. Oblique coronal image from an aortogram shows the typical appearance of the aorta and great vessels.

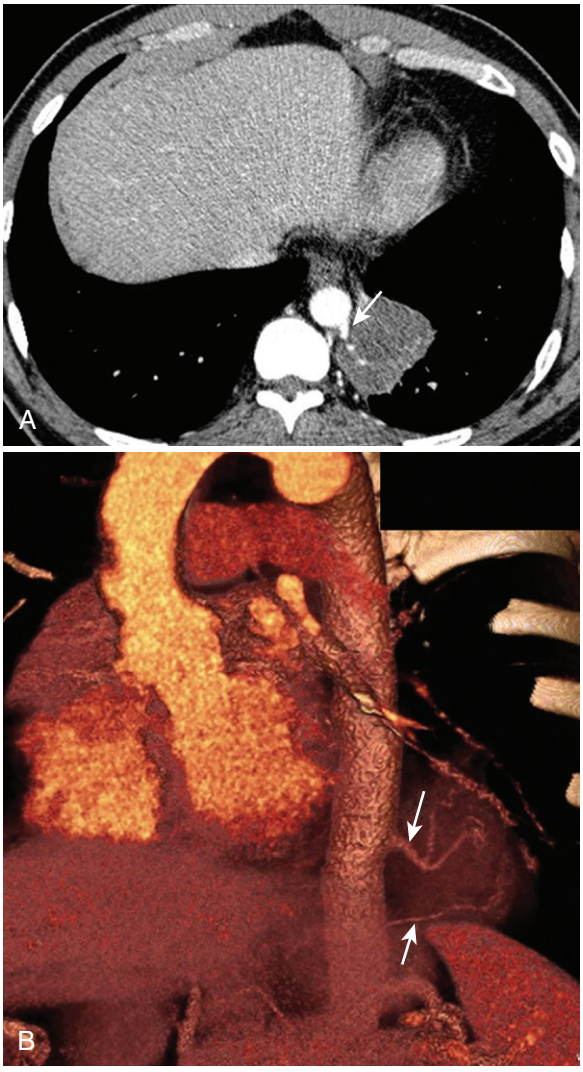

FIGURE 19-24 ■ Intralobar bronchopulmonary sequestration. **A,** Axial thoracic CT in a 24-year-old man with recurrent pneumonia shows a masslike opacity in the posterior basilar left lower lobe. Note the prominent aberrant vessel originating from the descending thoracic aorta (*arrow*) supplying the mass. **B,** Oblique coronal volume-rendered image shows the posterior basilar left lower lobe mass as well as two aberrant vessels (*arrows*) supplying the lesion.

When free-flowing or layering fluid is not demonstrated on decubitus radiographs in the presence of a thickened pleural stripe, ultrasound study may show collections of loculated fluid surrounded by pleural adhesions. Septations may be visualized within pleural collections, and their shape may change during the breathing cycle, confirming the presence of low-viscosity fluid. A complex echogenic fluid collection indicates the presence of exudate, empyema, or hemothorax, but an echo-free collection does not exclude these diagnoses. Ultrasound is also effective in differentiating subphrenic fluid from pleural effusion because the two hemidiaphragms are excellent reflectors of the ultrasound beam and therefore provide a visible boundary distinguishing intrathoracic from subdiaphragmatic spaces. The presence of a hypoechoic area caudal to the echogenic diaphragmatic stripe but cranial to the liver or spleen indicates ascites (Fig. 19-27).

FIGURE 19-25 ■ Bronchial arteriography in a patient with right lower lobe bronchiectasis and hemoptysis. **A,** Initial contrast injection into a hypertrophied bronchial artery. **B,** Injection into the same artery as in **A** shows significantly decreased blood flow following coil embolization.

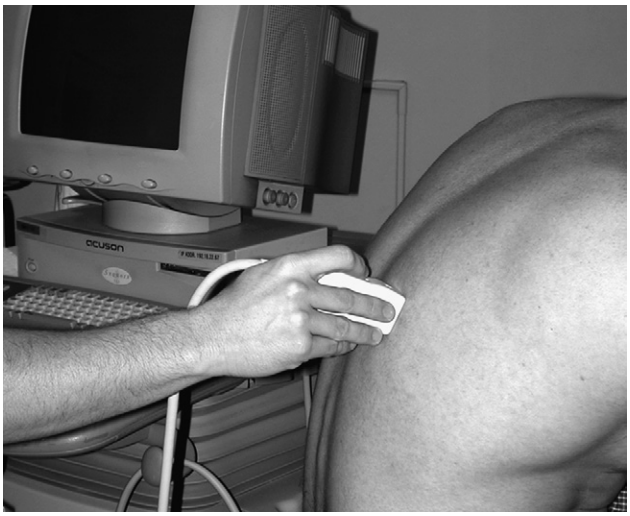

FIGURE 19-26 ■ The position of a patient for ultrasonically guided thoracentesis.

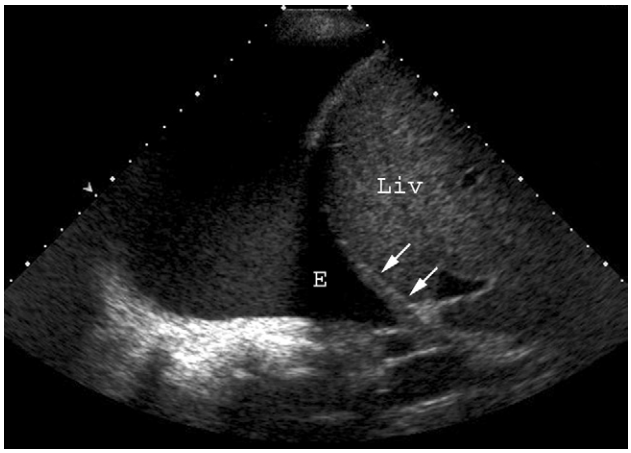

FIGURE 19-27 ■ Ultrasound examination of the lower left chest shows effusion (E) above the right hemidiaphragm (*arrows*). Liv, liver.

Ultrasound-guided thoracentesis is frequently performed when loculated fluid is suspected or after attempts at thoracentesis have failed.[27] The use of real-time equipment permits the performance of this procedure at the bedside (see Fig. 19-26). After locating the apparent fluid collection, the appropriate depth to which the needle should be inserted is displayed on the screen, and the aspiration is performed in the usual manner. Placement of catheters for drainage can be accomplished in a similar fashion.

Pleural neoplasms, mediastinal masses, or parenchymal masses that abut the pleural surface may be biopsied under ultrasonic guidance, provided that no aerated lung intervenes between the lesion and the pleura. The tip of the needle can be guided and identified within the mass, thus confirming appropriate placement before aspiration or biopsy.[28] However, CT or fluoroscopic guidance is more frequently employed for this purpose.

COMPUTED TOMOGRAPHY

Physical Principles

CT is based on the precise measurement of attenuation of a thinly collimated x-ray beam. Differential x-ray beam attenuation by different tissues forms the basis of image contrast on CT images. The advantages of CT are its axial

tomographic ("slicelike") format and its high sensitivity to differences in density between different tissues.

To obtain CT images, x-rays—produced by a modified standard x-ray tube—are passed through the patient, and the transmitted photons are measured by a series of x-ray detectors. The detectors produce an electric current that is proportional to the intensity of the beam of x-rays. The strength of this current is measured and digitized by an analog-to-digital converter and thus is available for computer manipulation. The reduction in the intensity of the beam as it passes through the patient's body is termed "attenuation" and is due to scattering and absorption of the x-ray photons by tissue. The attenuation (more precisely, the linear attenuation coefficient) of each point within the body can be calculated by the scanner's computer, provided that multiple measurements of x-ray attenuation can be made from different angles. The details of the x-ray beam and detector motion by which these multiple measurements are obtained vary considerably between scanners. Spiral or helical scanners, and more recently, MSCT scanners, use a continuously rotating gantry (containing the tube and detector array) and are capable of imaging the entire thorax in a single breath-hold. Because the x-ray attenuation measurements are stored in the computer, the image can be enhanced or manipulated mathematically with specific reconstruction algorithms. For example, the technique of HRCT combines thin collimation and image reconstruction with a high-spatial-frequency algorithm to produce increased sharpness in the final stage.

Image Display

The reconstructed CT image is made up of a matrix of picture elements or "pixels." The x-ray attenuation of each pixel is normalized to that of a test object containing pure water. The CT number is the ratio of tissue attenuation minus water attenuation relative to water attenuation multiplied by 1000, and is expressed in Hounsfield units (H). The CT number for lung is about –700 to –900H, whereas soft tissues have CT numbers ranging from approximately –100 (fat) to +100H (blood clot), with water measuring 0 H and most soft tissues in the 20- to 60-H range. The range of CT numbers encountered in patients is approximately 2000, ranging from –1000 (air) to +1000 (bone). However, although the computed image contains 2000 number levels, which could correspond to 2000 shades of gray, the human eye can perceive only about 16 to 20 distinct shades of gray. It is thus necessary when displaying CT images to restrict the image display to a small fraction of the actual range of attenuation values.

This restriction is done first by combining similar CT numbers into a single gray shade and second by setting the "window width" and "window level" display settings. The window width is the range of densities that will be displayed as shades of gray; all higher pixel values are shown as white, and all lower ones are shown as black. The window level is simply the median pixel value about which the display range is centered. Thus, to view the lungs, an appropriate window level is –700H, with a window width of 1000 to 1500 H. For viewing soft tissues, pleural space, mediastinum, or hila, a window level of 20 to 40 H with a width of 350 to 500 H is preferred. These are usually referred to, respectively, as "lung window" and "mediastinal or soft-tissue window" settings, and both should be displayed for a chest CT study.

Spiral and Multislice Computed Tomography

Spiral CT employs continuous scanning as the patient moves through the scanner gantry. In many patients, the entire thorax can be scanned during a single breath-hold. Spiral CT has the advantages of (1) volumetric imaging, which ensures contiguous image reconstruction and allows multiplanar or three-dimensional reconstructions to be performed; (2) more rapid scanning; and (3) more rapid contrast infusion with denser opacification of vessels.

MSCT markedly improves upon the advantages offered by single-slice spiral CT. MSCT scanners acquire scan information using multiple channels during a single tube rotation, thereby dramatically increasing the data acquisition rate. Current MSCT scanners may acquire up to 64 images per tube rotation for a given collimation, whereas routine single-slice spiral CT scanners may only acquire 1 image per tube rotation for a similar collimation. Scanners with even more detectors (as high as 320) are currently being introduced into the market. The speed advantage of MSCT scanning is obvious, and this tremendous speed allows for rapid imaging of large volumes of tissue in practically any phase of intravenous contrast enhancement. The image data sets provided by MSCT scanners also allow for improved-quality reformatted images.

Computed Tomography Scan Protocols

CT scans are obtained with different parameters, depending on the indication for the examination. Variables include scanning range, patient position, scan section thickness, table transport speed/pitch, and intravenous contrast injection rate, timing, and volume. These parameters are briefly reviewed later. The influence of table transport speed/pitch on CT protocols has evolved with the proliferation of MSCT scanners, and consideration of these variables is more relevant to cardiovascular imaging, and is not discussed here. The interested reader is referred to excellent reviews on the topic of MSCT scan parameters and the technical aspects of MSCT scanning.[29,30]

Scanning Range

In most instances, a chest CT study should encompass the entire thorax, from the lung apices to the posterior costophrenic angles. This is easily accomplished in a matter of a few seconds with MSCT. In patients with lung cancer, chest CT done for staging purposes may include the

adrenal glands and liver, although the liver acquisition should be timed properly to obtain images in the correct phase of liver enhancement. In practice, lung cancer staging studies are typically performed as dedicated examinations of the entire chest, abdomen, and pelvis.

Patient Position

Normally, patients are scanned in the supine position. However, decubitus positioning or prone positioning may be used to elucidate whether pleural fluid collections are free or loculated, to distinguish dependent atelectasis from parenchymal fibrosis, or to position lung lesions optimally for biopsy. Images are normally obtained at total lung capacity to obtain maximum air-tissue contrast and to spread anatomic structures and lesions over a larger area, thus minimizing volume averaging. Prone images are usually obtained with HRCT studies. Technical advances now permit the acquisition of CT images during, rather than after, forced expiratory vital capacity maneuvers.

Scan Section Thickness

In the era of single-slice spiral CT, the thickness of an individual CT section was set to a predetermined value before scanning by setting the x-ray beam to a certain thickness: a process referred to as "collimation." Typical slice thicknesses for single-slice spiral CT ranged from 1 to 10 mm, with 5- to 7-mm collimation employed for most "routine" thoracic CT applications. With the development of MSCT systems, although various collimation choices are still possible, most MSCT protocols employ certain detector configurations that either favor narrow detector width (to promote optimal spatial resolution) or wider detector widths (to facilitate rapid volume of coverage). As systems with greater numbers of detectors are developed, the choice of high spatial resolution at the expense of volume of coverage and total length of exposure—an age-old compromise in the era of single-slice spiral CT—is becoming less of a quandary. Modern MSCT systems now allow the entire thorax to be scanned with a narrow detector configuration (1-mm) in a matter of a few seconds. Once such images are acquired, they may be combined in various ways for optimal viewing. For example, a thoracic CT study obtained on an MSCT system with detector elements arranged in a manner resulting in 1-mm detector configuration would produce several hundred 1-mm images for the thorax of an averaged-sized patient. However, these 1-mm images can be "combined" to generate 5-mm images, and these images can be displayed for routine review; this results in about 50 to 70 images for a typical thoracic CT. Should the radiologist desire to view the high-resolution, 1-mm images, these images can be reconstructed from the original dataset as long as the original scan data are saved. For example, with single-slice spiral CT scanners, frequently the patient would need to return for additional thin-section (narrow-collimation) imaging to characterize any nodules encountered at the examination. The only way to avoid bringing patients back in this setting was to keep the patient on the scanner while the study was reviewed, but this approach seriously decreases scanner throughput. Even if the patient were held during the scan review, additional nodule characterization with single-slice CT would require repeat scanning with narrow collimation to optimally detect fat or calcium within the nodule, with requires additional radiation exposure. With MSCT, when a nodule is recognized on a study, images may be reconstructed according to the narrowest detector configuration to accomplish this goal long after the patient has left the scanner, without the need for additional scanning.

An additional benefit realized by the development of MSCT is the ability to image using isotropic voxels. The term *isotropic voxel* indicates that the resolution of the scan in the x-, y-, and z-planes is equal. In other words, MSCT scanning using isotropic voxels allows the CT data to be reconstructed in any plane with resolution equal to that of the axial scans. Most single-slice CT examinations did not possess this capability, and therefore non-axial reformatted images suffered from degraded quality compared with that of the axial scans. MSCT's ability to scan using isotropic voxels allows creation of images in any desired plane that are equal in resolution to the axial scans—this multiplanar capability was previously an advantage enjoyed by MRI and ultrasound over CT.

Contrast Enhancement

The injection of intravenous iodinated contrast material during chest CT is important in many situations. Administration of contrast material is not routine except for the diagnosis of vascular abnormalities such as aortic dissection, aneurysm, pulmonary embolism, when using a specific protocol in selected patients with pulmonary nodules, or for examinations performed for lung cancer staging (Fig. 19-28) or assessment of pleural of chest wall diseases. If possible, iodinated contrast materials are

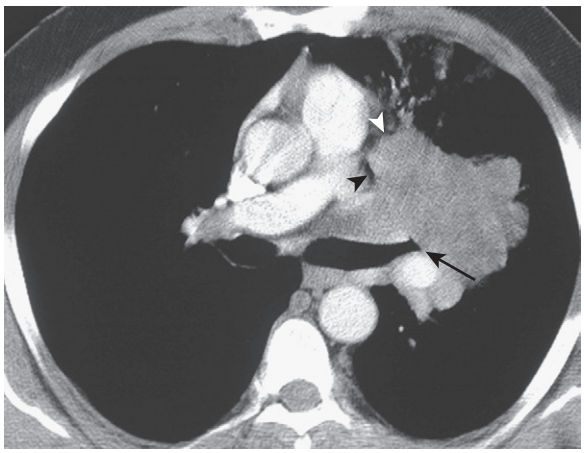

FIGURE 19-28 ■ CT was performed after contrast administration in a patient with left hilar bronchogenic carcinoma with mediastinal invasion. The primary hilar tumor obstructs the left upper lobe bronchus (*arrow*) and can be seen extending into the mediastinum anterior to the left main bronchus (*arrowheads*).

avoided, for they are expensive and are associated with a small but definite risk of serious reactions and toxicity. Although contrast infusion can be helpful in distinguishing vessels and soft-tissue masses in the mediastinum and hila, it is not considered necessary for diagnosis by all radiologists. For routine CT of the lungs (e.g., to rule out metastases), contrast material is rarely required.

Nonionic and low-osmolar contrast materials have proved to have a lower incidence of adverse reactions than high osmolar agents.[31] Patients with a prior history of contrast reaction should be treated with extreme care, as they are at higher risk for subsequent serious reactions, particularly those rare patients that have experienced contrast reactions despite proper premedication with corticosteroids and antihistamines.[31a] If vascular pathology is of interest in such patients, MRI is the preferred modality. If CT with contrast enhancement is necessary, pretreatment with corticosteroids is essential, and the referring physician should personally alert the radiologist to the patient's history.

The technique of intravenous contrast material administration is important. Peak opacification of vascular structures is desirable. To achieve this, a bolus of contrast material must be administered, preferably via a calibrated mechanical injector, and the area of interest must be scanned rapidly during the initial transit of the contrast agent. Timing of the delivery of intravenous contrast should be adjusted to the organ system of interest. For example, thoracic CT protocols designed for the detection of pulmonary embolism generally use rather short delays from the time of the beginning of contrast injection to the start of imaging (usually ~20 sec), whereas thoracic CT protocols designed for the evaluation of aortic dissection generally use slightly longer contrast injection delays.

The use of spiral CT and MSCT allows dense vascular opacification to be achieved because of the rapid scan time. In addition, because of the rapid nature of MSCT scanning, the volume of contrast required is less than with single-slice CT. Iodinated contrast materials distribute into the extracellular space rapidly; the time constant varies depending on the amount of contrast material and on the mode of administration, tissue perfusion, capillary permeability, and extracellular fluid volume. Scans obtained after this distribution has occurred are referred to as "equilibrium scans" and generally have less diagnostic value.

Computed Tomography and Radiation

The major drawback of the increased utilization of CT is radiation exposure. In 1980–1982, radiation from medical imaging accounted for approximately 18% of the per-capita effective radiation dose in the United States, but this value increased to 54% by 2006, due largely to increased radiation doses resulting from CT scanning and, to a much lesser extent, nuclear medicine procedures. Currently CT represents about 7% of all radiologic procedures in the world but accounts for more than 40% of the collective dose.[32] Given the continued increased use of CT since 2006, it is likely that these numbers are now even greater.

TABLE 19-1. Typical Radiation Doses Associated Background Sources and Common Thoracic Imaging Applications

Radiation Exposure	Effective Dose (mSv)
United States annual per-capita effective radiation dose 2006 (background/medical/total)	2.4/3.0/5.6[32]
Posteroanterior chest radiograph*	0.05
Ventilation/perfusion scan*	1.4[231]
Standard chest CT*	5–8[231]
High resolution chest CT (1 cm noncontiguous intervals)*	1
Catheter pulmonary angiography*	2.3–4.1
Whole-body ^{18}FDG-PET*	14[231]

*Values may vary according to individual equipment manufacturers, patient size, duration of study, use of dose-reduction techniques, and individual institutional protocols.
CT, computed tomography; ^{18}FDG-PET, [^{18}F]fluoro-2-deoxy-D-glucose positron emission tomography.

The two primary terms for describing the radiation imparted by a CT scan are *adsorbed* and *effective dose*. The adsorbed dose, measured in grays (Gy), is the energy absorbed per unit mass of a specific organ. In other words, it is the radiation imparted to a specific organ, and thus accounts for the future risk of developing a malignancy at that site. Effective dose, measured in sieverts (Sv) is an overall estimate of total-body radiation exposure. This is calculated by summing the individual adsorbed doses to each organ, each of which is multiplied by a weighting factor reflecting their individual radiosensitivities. Effective dose is useful for gross comparisons between different modalities and techniques.

Approximate effective doses for CT are given in Table 19-1. Of note, the values given are representative doses, but in fact, there is a wide range of exposures dependent upon CT technique and method of estimation. Also, indications such as pulmonary embolism, which require thinner sections, may involve greater amount of radiation. In addition, the radiation imparted by MSCT studies is generally higher than that of single-slice spiral CT, often in the range of 30% higher.

No large studies to date have attempted to quantify the cancer risk associated with CT radiation exposure. Most estimates are performed by extrapolating CT doses with reference to data on atomic bomb survivors. A slightly increased risk of malignancy was observed in the atomic bomb survivor group with an exposure of 5 to 20 mSv.[33] CT exposure doses are well within this range. Cancer risk also strongly depends upon age of exposure, with earlier exposure imparting a significantly greater risk.

Interventional Computed Tomography and Percutaneous Lung Biopsy

The indications for and contraindications to transthoracic needle biopsy (TNB) are presented in Tables 19-2 and 19-3.[34] The indications for TNB are changing as more data regarding the utility of alternative approaches to

TABLE 19-2. Indications for Transthoracic Needle Biopsy

Solitary pulmonary nodule or mass
Staging for lung carcinoma or extrathoracic malignancy
Mediastinal mass
Pleural lesion
Chest wall lesion
Hilar mass with negative bronchoscopic examinations
Focal lung opacity in an immunocompromised patient

TABLE 19-3. Contraindications to Transthoracic Needle Biopsy

Patient unable to cooperate with procedure:
Patient unable to lie in required position
Patient unable to hold breath consistently
Patient unable to give informed consent
Patient unable to follow directions
Coagulopathy: INR > 1.4 or platelets < 50,000/μL
Contralateral pneumonectomy or pneumothorax
Severe obstructive lung disease

INR, International Normalized Ratio for prothrombin time.

the management of thoracic lesions, such as positron emission tomography (PET; see Chapter 21) and video-assisted thoracoscopy (see Chapter 23), become available. Contraindications to TNB are usually relative. With proper evaluation and preprocedural care, the majority of thoracic lesions are amenable to TNB.

TNB procedures should be scheduled through a service dedicated to the performance of invasive procedures. Typically, such a group includes a nurse or nurse practitioner, an office assistant, CT technologists, radiologists experienced in the performance of TNB, and pathologists skilled in cytologic diagnosis. The service may then coordinate obtaining the relevant clinical information and reviewing any pertinent studies prior to the procedure.[34]

Preprocedural laboratory evaluation includes a complete blood count (including platelets), serum creatinine, and a coagulation profile. Abnormal results (see Table 19-3) should be corrected before the procedure is undertaken. Before the day of the procedure, the interventional service should contact the patient by phone to remind him or her of the procedure and to determine if the patient is taking any medications that should be discontinued prior to the procedure. Nonsteroidal anti-inflammatory agents should be discontinued 5 days prior to the procedure, and oral anticoagulants should be converted to shorter-acting parenteral agents, which may then be discontinued 4 to 12 hours before the procedure.[34]

The risks and benefits of the procedure, as well as alternative approaches to TNB, should be discussed with the patient prior to beginning the procedure, and the fact that informed consent was obtained should be documented in the medical record. A complete history and physical examination must be performed and documented if conscious sedation is to be used. Any allergies should be noted, and all questions should be answered before the procedure begins.[35]

Transthoracic lung biopsy may be performed using fine-needle aspiration (FNA) technique with or without the use of cutting needles for core biopsy.[35] Transthoracic FNA provides material for cytologic analysis and is usually sufficient for the diagnosis of carcinomas affecting the lung (primary or metastatic), whereas core biopsy utilizing cutting needles provides histopathologic material and is often required to definitively diagnose spindle cell neoplasms, most benign noninfectious pulmonary lesions, and pulmonary lymphomas and to distinguish certain histopathologic varieties of mesothelioma from metastatic adenocarcinoma affecting the pleura.[35]

Both percutaneous FNA and cutting-needle biopsy of pulmonary, mediastinal, or chest wall lesions may be performed using a single biopsy needle placed directly into the lesion or by using coaxial technique.[35] Either technique may be employed with CT, fluoroscopic, or sonographic guidance. CT-fluoroscopy, a technique that allows real-time CT imaging, provides tangible benefits for lung biopsy procedures compared with either CT or fluoroscopy alone, and is in common use for interventional radiology procedures at a number of centers. TNB performed using needles placed directly into the lesion typically employ 14- to 25-gauge aspiration needles (most often 22-gauge) or 18- to 22-gauge core biopsy devices, whereas biopsies performed using coaxial technique typically employ 22-gauge aspiration biopsy needles or 20-gauge core biopsy needles that are advanced through an outer sheath (often 19-gauge) that is initially placed within the lesion. The latter technique offers the advantage that, once the outer sheath needle is properly placed, repeated sampling of the lesion may be performed without need for additional manipulation of the needles.

All imaging studies should be reviewed prior to beginning the procedure to determine the best approach to the lesion. The best approach is one that is vertical and that does not cross bullae, interlobar fissures, or pulmonary vessels.[34]

Intravenous access should be established and hemodynamic monitoring should be begun before the procedure starts. When TNB is performed using CT guidance, the lesion is localized using narrowly collimated scans, with the patient holding her or his breath at functional residual capacity. The proposed skin entry site is established by identifying a clear path toward the lesion that avoids bullae, interlobar fissures, pulmonary vessels, and the undersurface of ribs and illuminating this site on the patient's skin using the table position laser lights on the CT scanner. The exact skin entry site may then be marked on the patient's skin using a permanent marker. The skin overlying this proposed entry site is cleansed and draped in sterile fashion, and the subcutaneous tissues in this region are liberally infiltrated with lidocaine for local anesthesia. The biopsy or sheath needle is then advanced under imaging guidance into the leading edge of the lesion (Fig. 19-29) during breath-holding.

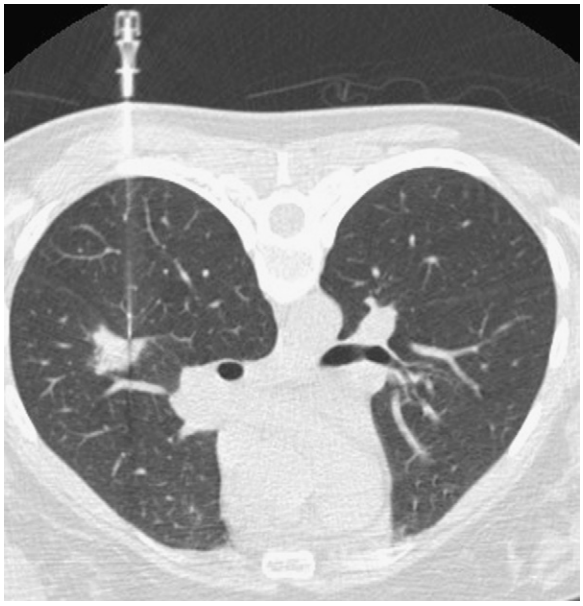

FIGURE 19-29 ■ CT-guided pulmonary nodule biopsy. With the patient in the prone position, a right upper lobe nodule was biopsied first with the placement of a 19-gauge outer sheath, with fine-needle aspiration biopsies performed using a 22-gauge needle placed through the sheath. Hodgkin's lymphoma was diagnosed.

Once the needle is properly positioned, the patient again holds her or his breath, the biopsy is performed, and the specimen is given to the cytopathologist for examination. A similar guidance approach can be used to localize fluid collections or pneumothoraces that are not responding to blindly placed thoracostomy tubes and then to guide percutaneously placed drains into the refractory collections.

Once material sufficient for diagnosis has been obtained, the needle is removed, hemostasis is achieved via local pressure, and the patient is imaged to exclude pneumothorax. Large or symptomatic pneumothoraces should be treated immediately with tube thoracostomy. Small pneumothoraces may be scanned sequentially over several minutes to ensure that the pneumothorax is not rapidly enlarging. Once a small pneumothorax is shown to be stable, the patient may be transferred to a gurney, and a chest radiograph is then obtained to establish the size of the postbiopsy pneumothorax for comparison with subsequent radiographs. The patient is then positioned on the gurney, whenever possible, with the biopsy site dependent to reduce the risk of air leak and to limit endobronchial spread of postbiopsy hemorrhage.[34]

The patient is then transferred to a recovery suite where vital signs and oxygen saturation are monitored for the next 3 hours. Supplemental oxygen may be administered to promote resorption of small pneumothoraces. If the patient remains asymptomatic, chest radiographs are obtained at 1.5 and 3 hours to assess for the development of a pneumothorax or the enlargement of a pneumothorax detected on the CT scanner immediately after biopsy. If no pneumothorax is seen on the 3-hour film, or if the pneumothorax is small, asymptomatic, and stable, the patient may be discharged. If the pneumothorax is enlarging or symptomatic, hospital admission and tube thoracostomy may be required. Assessment of the need for tube thoracostomy and/or hospital admission depends on the patient's underlying cardiopulmonary status, social support system, and proximity to an urgent care facility capable of properly treating the patient in a timely fashion.

The overall accuracy of TNB ranges from 70% to 100%, and approaches 90% to 95% for the diagnosis of thoracic malignancies.[35] The yield for TNB of benign lesions is less than that for malignancy, but may be enhanced with multiple samplings of the lesion, the use of cutting-needle biopsy, and routine culturing of aspirated specimens for biopsies preliminarily interpreted as negative for malignancy by the cytopathologist.[35]

Complications of TNB include pneumothorax, hemorrhage, hemoptysis, systemic air embolism, and malignant seeding of the biopsy tract. The mortality rate associated with TNB is approximately 0.02%, and fatalities are usually related to air embolism or massive hemorrhage. Pneumothoraces occur in approximately 30% of patients undergoing CT-guided procedures, but thoracostomy tube drainage is required in less than half of these patients. Factors associated with an increased likelihood of pneumothorax requiring thoracostomy tube drainage variably include severe COPD, the use of larger-gauge needles, small lesion size, intractable coughing, multiple needle passes through the pleura, the use of cutting needles, and prolonged procedure duration.[34]

Positron Emission Tomography and Positron Emission Tomography Computed Tomography

As with most nuclear medicine techniques, PET imaging begins with the injection of a radionuclide that localizes to a specific site in the body (see also Chapter 21). The most commonly used of these radioactive materials is [^{18}F]fluoro-2-deoxy-D-glucose (^{18}FDG). ^{18}FDG is a glucose analogue transported into metabolically active cells and, once phosphorylated, is fixed within the cell. The radionuclides used in PET imaging release a positron from their nucleus that subsequently undergoes an annihilation reaction with an electron. This process releases two coincidence 511-keV photons. These photons are detected by scintillation crystals in the PET camera. By using many of these coincidence detection events, a cross-sectional image can be obtained that demonstrates regions of activity. The amount of activity in a specific region of interest can be quantified by using a standard uptake value (SUV). The higher the SUV, the more metabolically active the tissue.

Compared to CT, ^{18}FDG-PET scanning is limited by relatively poor spatial resolution. To improve localization within the body, CT images may be obtained during the same scanning period, so-called PET-CT. These two separate data sets can then be colocalized to produce fusion images that contain data from both the PET and

FIGURE 19-30 ■ Whole-body coronal [^{18}F]fluoro-2-deoxy-D-glucose positron emission tomography computed tomography (^{18}FDG-PET-CT) shows intense left upper lobe tracer accumulation (*arrow*) in a patient with bronchogenic carcinoma. Note normal high tracer activity within the brain (*arrowheads*).

the CT portions of the examination (Fig. 19-30). This provides a more precise anatomic localization of the PET data to specific organs or abnormalities within the body.

^{18}FDG, as a glucose analogue, localizes to metabolically active cells. Tumor cells with their active division and growth typically acquire significantly greater amounts of ^{18}FDG than other cells, and thus are conspicuous on PET scanning (see Fig. 19-30). Common indications for PET and PET-CT of the thorax are the differentiation of benign versus malignant nodules and lung cancer staging. It is important to note, however, that active inflammatory processes, such as sarcoidosis, are also metabolically active and may concentrate ^{18}FDG. The final probability that an ^{18}FDG-PET-positive abnormality is malignancy is based upon a synthesis of the PET data, morphologic appearance of the lesion, and clinical presentation of the patient. It is also important to know the normal distribution of ^{18}FDG in the body, such as physiologically high tracer uptake in the heart and brain, and that high levels of activity in specific situations may be occasionally encountered, such as enhanced tracer uptake with muscular contraction.

Prior to the procedure, the patient should fast for at least 6 hours. This prevents competition between injected ^{18}FDG and glucose uptake from the gastrointestinal tract. For the same reason, a diabetic patient's glucose level should be well-controlled before the examination. Both a nonfasting state and hyperglycemia may cause false-negative examination results by producing artifactually low levels of uptake of ^{18}FDG in metabolically active tumors.

MAGNETIC RESONANCE IMAGING

Physical Principles

MRI is performed by magnetizing the patient's tissue slightly, generating a weak electromagnetic signal by applying a radiofrequency pulse, and spatially mapping that signal by manipulating its frequency and phase in a location-dependent manner with magnetic field gradients. Unlike CT, MRI does not require mechanical motions of the scanner and therefore can image directly in nonaxial planes.

Although MRI uses electromagnetic radiation, the energy levels used in MRI are quite low (i.e., nonionizing). MRI appears to be remarkably free of significant bioeffects. Potential safety hazards in MRI relate to the extremely strong static magnetic field and rapidly switched gradient magnetic fields used and to the possibility of tissue heating from radiofrequency energy absorbed by the body. Tissue heating is a theoretic concern but, in practice, is not significant when conventional MRI techniques are used. Theoretically, the rapidly varying gradient magnetic fields could stimulate electrically excitable tissue, but this does not occur with routine MRI techniques. In contrast, the powerful static magnetic field is a major safety hazard because the magnetic forces near a whole-body magnetic resonance (MR) imager are strong enough to cause significant projectile hazards. For example, an ordinary steel oxygen cylinder brought into an MRI examination room will fly into the bore of the magnet with a terminal velocity of about 45 mph. The possibility of displacements or torques on metallic implants within patients also must be considered. Although the margin of safety is high, there are rare documented instances of harm to patients from dislodging intracranial aneurysm clips or intraocular metallic foreign bodies. Finally, the magnetic field can operate reed relays in cardiac pacemakers and cause a change in the pacing mode. Accordingly, strict security around MRI facilities is essential to prevent patients with certain types of metallic implants from entering the scanner and to prevent medical personnel from carrying into the scan room objects that could become projectiles.

MRI produces extremely high contrast between different types of soft tissue. This soft-tissue contrast is based on intrinsic properties of the tissues, but it can be modified and exploited by appropriate use of operator-selectable imaging techniques. The tissue properties normally utilized in MRI are as follows: the concentration of protons available to produce an MR signal ("proton density"), the presence of motion or blood flow, and two properties known as T1 and T2, time constants that describe how quickly an MR signal can be generated

from a tissue (T1) and how quickly the MR signal, once generated, decays away (T2). In general, pathologic tissues have long T1 times and appear dark on those MR images whose appearance is conditioned primarily by T1 effects ("T1-weighted images"). Usually, pathologic tissues also have long T2 times and appear bright on T2-weighted images. The reason for this opposite behavior is that "T1" and "T2" describe processes that have opposite effects on the intensity of the MR signal. Flowing blood also can appear either bright or dark on MR images, depending on the examination technique used. The art of performing an MRI examination depends on appropriate manipulations of imaging techniques to capitalize on differences in proton density, flow, T1, and T2 between normal and pathologic tissue. In addition, the use of gadolinium-based MRI contrast materials, which alter the T1 and T2 of tissues semiselectively, has become important for numerous clinical applications, particularly MR angiography. MRI also can display other tissue properties such as molecular self-diffusion, temperature, and metabolites (MR spectroscopy), but these are less important for thoracic applications, although diffusion imaging and MR spectroscopy have recently shown some promise in lung cancer evaluation and staging.

Techniques

Motion during MRI causes artifacts that can degrade image quality severely. Motion compensation techniques, such as electrocardiographic gating and respiratory compensation, are widely used in thoracic MRI. High-speed techniques permit imaging in a matter of seconds, even fast enough to stop cardiac motion.

Direct MRI in sagittal, coronal, and oblique planes can provide superior depiction of structures that are oriented in the long axis of the body, such as the aorta, and of edges of structures that lie within the axial plane, such as lesions in the aortopulmonary window or lung apex.[36]

Flow has profound effects on the MR image. Two basic types of effects from flow occur in MRI; they are called "time-of-flight effects" and "spin-phase effects." The manifestations of flow effects in MR images strongly depend on the type of flow that is present and on the specific MRI techniques used. The clinical implication of this is that one can make blood in MR images either bright ("white-blood images") or dark ("black-blood images"). Most types of vascular pathology can be demonstrated with either white-blood or black-blood images, but there are usually clinical advantages to using one approach or the other in specific situations. Flow velocity can be estimated with MRI techniques, and thus noninvasive estimates of blood flow are potentially available.

Although high-speed imaging techniques are now available with MRI, it still is not an appropriate method to use for wide-ranging screening examinations of the entire trunk for metastatic disease. Such examinations normally should be performed with modern CT scanners. It usually is more rewarding to ask an anatomically focused question when requesting an MRI study.

APPLICATIONS OF CONVENTIONAL CHEST RADIOGRAPHY

Screening and "Routine" Chest Radiographs

It is now generally agreed that screening chest radiographs are not indicated except in specific high-risk populations.[37] Estimates as to possible iatrogenic disease caused by ionizing radiation from screening examinations, forecasts of possible genetic consequences, and financial concerns outweigh the medical value of such examinations. In 1973, the Department of Health, Education, and Welfare, in conjunction with the American College of Radiology and the American College of Chest Physicians, recommended the discontinuation of screening examinations. In 1985, recommendations of the American College of Radiology were more explicit: chest radiographs obtained for routine examination, preemployment screening, prenatal or obstetric screening, and hospital admission, and repeated examinations of patients with positive tuberculin tests and a negative initial chest radiograph, should be eliminated. From their analysis of over 10,000 chest radiographic examinations obtained in a hospital-based population, Sagel and associates[19] concluded that routine screening examinations done solely because of hospital admission or scheduled surgery are not warranted in patients under the age of 20 years. Even in selected high-risk populations, radiographic screening for carcinoma of the lung has failed to significantly increase longevity.

The value of the routine hospital admission chest radiograph is still controversial. Although the yield is low in asymptomatic patients, the examination can be extremely valuable as a baseline study for comparison with radiographs taken during or after the course of hospitalization in patients who develop pulmonary symptoms.

Detection of Lung Cancer and Assessment of Solitary Pulmonary Nodules

Although chest radiographs are clearly useful in the initial evaluation of patients suspected of having lung cancer, they are of limited accuracy in showing small or early cancers. At the time of their initial diagnosis, it is not uncommon for lung cancers to be visible retrospectively on prior radiographs.[38] Although additional radiographic studies, such as oblique views, are cost-effective for the initial evaluation of "nodular opacities" that do not clearly represent a lung nodule and are often of value in determining that a "nodular opacity" is not a true nodule, studies by CT are superior for the detailed evaluation of a known lung nodule.[39]

Evaluation of Intensive Care Unit Patients

Chest radiography is generally the most common imaging study performed in the most critically ill patients in the hospital—those in the ICU. ICU radiographs are taken with portable and, therefore, suboptimal technique; nonetheless, the information they provide often alters patient management.[9]

The overall incidence of abnormalities found on chest films in ICU patients is quite high; in a study of more than 1000 consecutive medical or surgical ICU films obtained routinely or after a change in clinical status, malposition of a monitoring device or a marked change in apparent cardiopulmonary status was found in 65%.[8] In a study of patients in a respiratory ICU,[40] chest radiographs showed at least one new, clinically unsuspected finding in 35% of patients that, in 29% of these patients, led to a change in management. Significant findings are even more likely when the study is obtained to assess a change in clinical status. In intubated patients in a medical ICU, 43% of radiographs showed significant worsening of a known process or development of a new abnormality.[41]

The value of obtaining chest radiographs on a daily basis in ICU patients is less clear. Strain and colleagues[42] found that routine morning radiographs revealed unsuspected abnormalities that led to a change in management in only about 15% of medical ICU patients, although this percentage was considerably higher (57%) in patients with pulmonary or unstable cardiac disease. Graat and coworkers[43] prospectively assessed the value of 2457 routine chest radiographs performed on patients in a combined medical and surgical ICU and found only 5.8% of routine chest radiographs showed new or unexpected findings; only 2.2% of patients required a change in management. Hall and colleagues[44] found that 18% of mechanically ventilated patients in a medical/surgical ICU had at least one radiograph that showed a clinically significant and unsuspected finding. Based on these results, the American College of Radiology has recommended that daily portable radiographs be obtained routinely in patients with acute cardiopulmonary problems, whereas only initial ICU admission chest radiography, and not routine daily chest radiography, is recommended for patients with stable cardiac disease or stable patients with extrathoracic disease prompting ICU admission. In the latter group of patients, additional chest radiography is recommended only for specific indications.[45]

The use of chest radiographs has also been recommended for assessing the placement of various support and monitoring devices, including endotracheal tubes, tracheostomy tubes, central venous catheters, pulmonary artery catheters, nasogastric tubes, chest tubes, pacemakers, and intra-aortic counterpulsation devices.[19,45] A significant frequency of clinically unsuspected endotracheal tube malposition detected by chest radiography, between 10% and 15%, has been reported.[19,45] In contrast, Hejblum and associates[45a] recently concluded that an on-demand strategy for ordering chest radiographs for mechanically ventilated patients in the intensive care unit is associated with a 32% reduction in the use of chest radiography compared with a routine daily strategy, but both strategies result in a similar rate of therapeutic or diagnostic intervention.

Indications in Acute Lung Disease

Dyspnea

Two studies suggest that chest radiography should be used routinely in patients with acute or chronic dyspnea.[46,47] In one study, new, clinically important radiographic abnormalities requiring acute intervention or follow-up evaluation were identified in 35% of 221 symptomatic patients.[46] Another study found that acute dyspnea was a strong predictor of a radiographic abnormality, but mainly in patients older than 40.[48] In this group, 86% of dyspneic patients had abnormal chest radiographs, whereas radiographs were abnormal in only 31% of patients younger than 40. Only 2% of patients younger than 40 with a normal physical examination had abnormal radiographs indicative of an acute abnormality. The American College of Radiology[49] recommends chest radiography when dyspnea is chronic or severe or when additional risk factors are present, such as age over 40; known cardiovascular, pulmonary, or neoplastic disease; or abnormal physical findings.

Acute Respiratory Symptoms

Opinions are also divided as to the utility of chest radiographs in patients with suspected acute lung disease and symptoms other than dyspnea. In a study of 1102 outpatients with acute respiratory disease, Benacerraf and coworkers[48] found patient age, results of physical examination, and presence or absence of hemoptysis to be important factors in predicting the value of radiographs. Only 4% of patients younger than 40, without hemoptysis and without detectable abnormalities on physical examination, had acute radiographic abnormalities. A much higher incidence of radiographic abnormalities was present if the patient was older than 40, had hemoptysis, or had abnormal physical findings. Heckerling,[50] in a study of 464 patients with acute respiratory symptoms, found a low incidence of pneumonia (3%) in patients with a negative physical examination, except in those with dementia. Whenever pneumonia is suspected in adults, the American Thoracic Society recommends PA (and lateral when possible) chest radiography. In this setting, chest radiography may be useful to determine which patients should be hospitalized and which patients should be classified as having "severe" pneumonia.[51]

Acute Asthma

Chest radiography is uncommonly used to make a diagnosis of asthma; radiographs are often normal, and visible abnormalities in this disease are usually nonspecific.[52] Although Petheram and associates[53] reported that 9% of 117 patients with severe acute asthma had unsuspected

radiographic abnormalities affecting management, the usefulness of radiography in patients with an established diagnosis of asthma who suffer an acute attack is limited. Correlation between the severity of radiographic findings and the severity or reversibility of an asthma attack is generally poor,[52-54] and radiographs provide significant information that alters treatment in 5% or fewer patients with acute asthma.[50,55,56] Although it is difficult to generalize regarding the role of radiographs in both adults and children with acute asthma, chest films should be used to exclude the presence of associated pneumonia or other complications when significant symptoms and/or appropriate clinical or laboratory findings are suggestive.[52,54,56]

Exacerbation of Chronic Obstructive Pulmonary Disease

Chest radiographs are often used in the initial assessment of patients with suspected COPD; however, they are of limited value in patients with known COPD who present with worsening of their disease.[56,57] In a study of 107 patients with COPD presenting with an exacerbation of symptoms, only 17 (16%) had an abnormal chest radiograph, and in only half of these did the radiographic findings result in a significant alteration in management.[56] In another study, including patients with both COPD and asthma, the management of 21% of patients was altered by radiographic findings.[57] It has been recommended that chest radiographs be obtained in patients with COPD only if certain clinical indicators are present; in various studies, these have included a history of heart disease or congestive heart failure, intravenous drug abuse, seizures, immunosuppression, other pulmonary disease, an elevated white blood cell count, fever, chest pain, and peripheral edema. When such indicators are used as a guide, nearly all patients with significant findings will have radiographs performed; however, it should be noted that more than two thirds of patients in one study met inclusion criteria for performing radiography.[57]

In most patients with an established diagnosis of cystic fibrosis, clinical findings and chest radiographs are sufficient for clinical management. Conversely, it should be recognized that patients with cystic fibrosis can have a significant exacerbation of their symptoms with little visible radiographic change.

APPLICATIONS OF CROSS-SECTIONAL IMAGING TECHNIQUES

Solitary Pulmonary Nodules

Assessment of a solitary pulmonary nodule (SPN) seen on chest radiographs is a common indication for CT.[39,58] CT is used to confirm that the SPN is real, to confirm that the SPN is solitary, to attempt further noninvasive characterization of the lesion, to guide percutaneous biopsy of the lesion, and to provide staging information if the SPN is found to represent a carcinoma. As discussed further in Chapter 47, the likelihood of malignancy in such nodules varies from less than 10% in mass screenings to about 50% in resected nodules.

In general, CT of a patient with an SPN should be performed with thin-section volumetric imaging to provide detailed analysis of nodule morphology and to allow identification of the presence of fat or calcium within the nodule, and when the latter is present, the

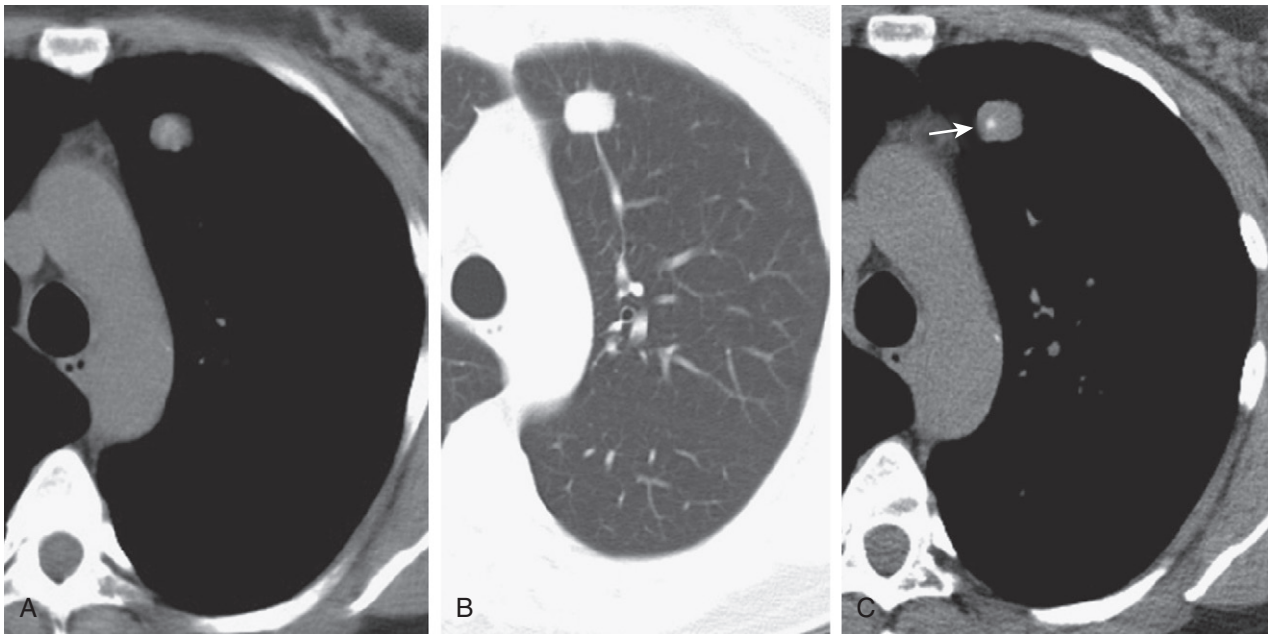

FIGURE 19-31 ■ Volumetric multislice computed tomography (MSCT) imaging of a pulmonary nodule detected at chest radiography. **A,** Axial 5-mm CT image shows a soft-tissue nodule in the left upper lobe. Vaguely increased attenuation is seen within the nodule suggesting calcification, but the finding is not well seen. **B,** Lung window images shows that the nodule is circumscribed. **C,** Thin-section (1-mm) soft-tissue image more clearly shows a small focus of calcification (*arrow*) within the lesion, suggesting a benign etiology.

pattern of calcification (Fig. 19-31); this is now fairly routine in the era of MSCT technology.

In up to 20% of instances, a "lung nodule" visible on chest radiographs actually represents an artifact, chest wall lesion, or pleural abnormality; in some cases, CT is essential to determine the true nature of the opacity. CT can be useful to define the morphology of the SPN and suggest whether it is benign, likely malignant, or indeterminate, having neither benign nor malignant characteristics. In some patients, a specific diagnosis of lesions such as rounded atelectasis (Fig. 19-32), a mucous plug, or arteriovenous malformation can be made based on CT findings, indicating the benign nature of the lesion.[39,58] Other CT appearances suggest the presence of malignancy.[39] These include a spiculated or irregular contour; the presence of air bronchograms within the nodule, bubbly air collections ("pseudocavitation"), or cavities; and a diameter of more than 2 cm (Fig. 19-33).[39,58] The presence of several patterns of calcification can indicate that the SPN is benign; "benign" patterns include diffuse, central, laminated, and "popcorn" calcification (Fig. 19-34).[39,58] In about 30% of benign nodules, calcium invisible on plain radiographs can be seen on thin-section CT. Carcinomas may occasionally show calcification, often in an eccentric or stippled pattern. The presence of fat within an SPN, indicated by a low CT attenuation coefficient (Fig. 19-35), strongly suggests the presence of hamartoma[39,58] or lipoid pneumonia; such nodules can be safely followed with serial radiographs.

Malignant tumors tend to show greater enhancement than benign nodules after the rapid injection of iodinated contrast material.[59–62] Because the degree of enhancement depends on the amount and rapidity of contrast infusion, it is important to use a consistent technique. Using a specific contrast enhancement CT protocol, a threshold for enhancement of 15 H or more typically is

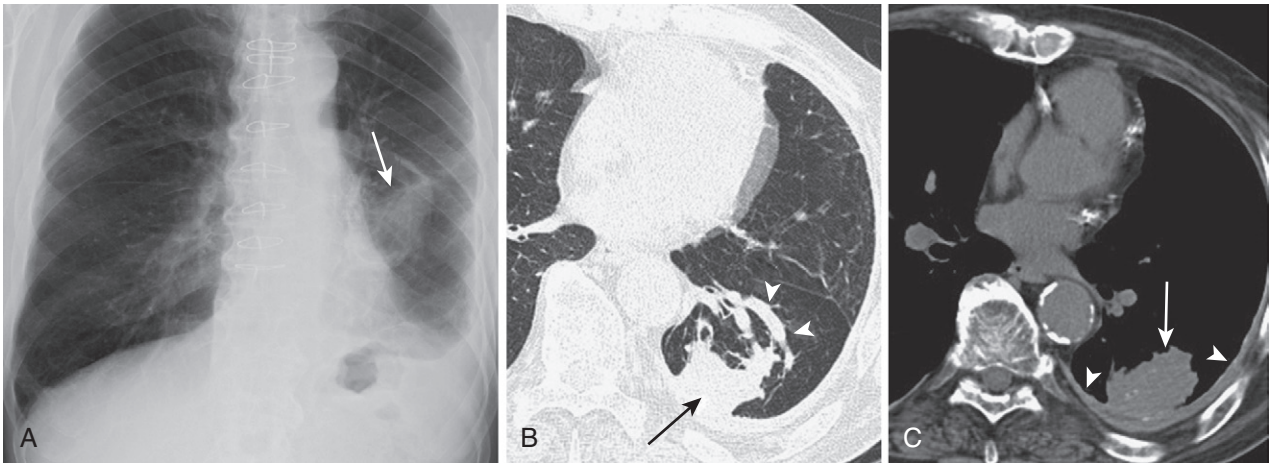

FIGURE 19-32 ■ Thoracic CT shows typical findings of rounded atelectasis. **A,** Frontal chest radiography shows volume loss in the left lower lobe associated with an oblong mass (*arrow*) and left-sided pleural abnormality. **B,** Axial thoracic CT in lung windows shows a subpleural left lower lobe mass (*arrow*) associated with left lower lobe volume loss (posterior displacement of left major fissure, small volume in the left lower lobe). Note "spiraling" appearance of left lower lobe bronchovascular bundles as they extend into the mass (*arrowheads*); this is the so-called comet-tail sign. **C,** Axial thoracic CT displayed in soft-tissue windows shows other features consistent with rounded atelectasis including abnormally thickened pleura (*arrowheads*) and contact of the mass (*arrow*) with the abnormal pleura.

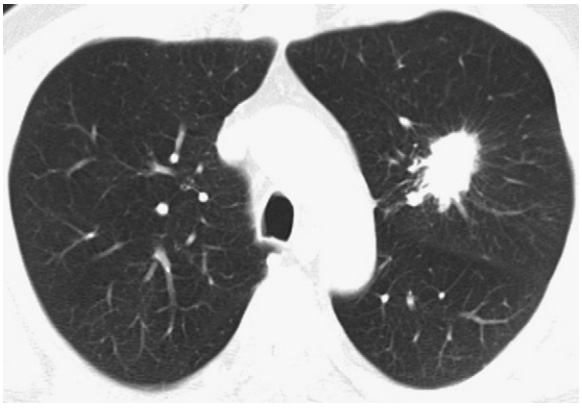

FIGURE 19-33 ■ Thoracic CT of bronchogenic carcinoma. Axial CT displayed in lung windows shows a spiculated lesion within the left upper lobe.

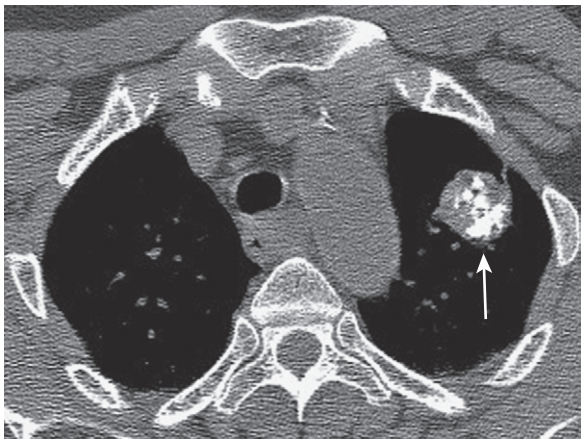

FIGURE 19-34 ■ Thoracic CT showing "popcorn" (chondroid) calcification within a left upper lobe nodule (*arrow*), consistent with hamartoma.

FIGURE 19-35 ■ This patient had a solitary nodule that proved to be a hamartoma. CT image showed low attenuation within the nodule (typical CT numbers within the lesion ranged from –90 to –100 HU), consistent with fat.

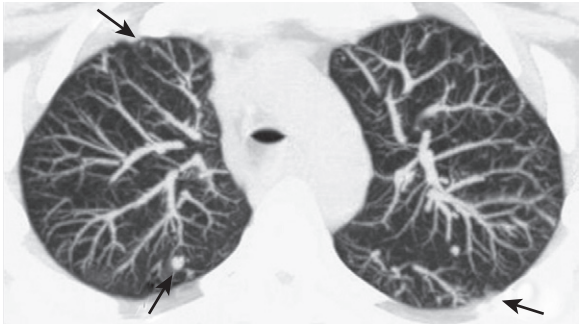

FIGURE 19-36 ■ This patient was diagnosed with metastatic cervical carcinoma. CT shows numerous bilateral pulmonary nodules (*arrows*) that were not visible on chest radiography. CT is more sensitive than radiography for detection of small nodules of any cause.

seen with malignancy, hamartoma, and some inflammatory lesions. Enhancement of less than 15 H almost always indicates a benign lesion, usually a granuloma. Therefore, whereas positive results (enhancement of ≥15 H at any time point during the study) are nonspecific, negative results are quite useful. This technique has been shown to have a sensitivity of 98% and a specificity of 58% in diagnosing carcinoma. More importantly, the negative predictive value of this technique is approximately 96%.[61] CT nodule enhancement studies are most appropriately used for patients who have indeterminate nodules (i.e., those without typical benign or malignant appearances). A similar use for dynamic, contrast-enhanced MRI has been reported, although data are limited.[63] The use of PET imaging (see Chapter 21) has also been shown to be very useful for distinguishing benign from malignant nodules,[64] and is generally favored over contrast-enhanced CT for additional imaging characterization of indeterminate lung nodules.

^{18}FDG-PET imaging may be used to differentiate between benign and malignant pulmonary nodules. In a recent meta-analysis,[63] ^{18}FDG-PET was shown to be 95% sensitive and 82% specific in the differentiation of benign from malignant nodules. The addition of PET-CT tends to increase sensitivity with no change in specificity compared with PET alone.[65] False-positive ^{18}FDG-PET results may be seen with inflammatory processes, particularly granulomatous diseases such as tuberculosis, histoplasmosis, and sarcoidosis. Tumors that may be ^{18}FDG-PET-negative include bronchoalveolar cell carcinoma, adenocarcinoma with predominant bronchoalveolar features, carcinoid tumors, and some metastases (e.g., renal cell carcinoma).[66] In addition, small nodules may not be of a sufficient size to produce a positive result with ^{18}FDG-PET scanning. The sensitivity of ^{18}FDG-PET imaging significantly decreases with nodules measuring less than 8 to 10 mm in diameter. As with any imaging modality, the correlation of the ^{18}FDG-PET results with morphologic features on CT, prior radiographic examinations, and the clinical presentation will improve the determination of the likelihood of malignancy.

Multiple Pulmonary Nodules

CT is the favored procedure for identifying multiple pulmonary nodules or masses. It detects more and smaller metastases (Fig. 19-36) than any other imaging technique, and 2- to 3-mm nodules are routinely visible.[67] This is most pertinent to patients with extrathoracic malignancies, in whom the detection of metastatic disease has a major impact on initial staging and assessment of response to therapy. The major sources of controversy regarding the use of CT for evaluation of possible metastases have been its limited specificity and cost-benefit ratio.[67]

CT is clearly more sensitive than chest radiographs in diagnosing multiple pulmonary nodules in patients with suspected metastasis. The sensitivity of CT for detecting surgically proven nodules ranges from 50% to 75% (i.e., 50%–75% of all resected nodules are seen on preoperative CT scans), whereas the sensitivity of chest radiographs is about 25% and that of conventional tomography about 35%. In some studies, most nodules (55%–60%) seen on CT and subsequently resected have proved to be benign (granulomas, intrapulmonary lymph nodes, and the like).[68] In other studies most CT-detected nodules (80%–95%) have proved to be metastatic lesions.[69] In a study involving radiologic-surgical correlation, Peuchot and Libshitz[69] evaluated 84 patients with previously

documented extrathoracic malignancies and newly identified pulmonary nodules. These authors noted important limitations in both the sensitivity and the specificity of CT. Of a total of 237 nodules resected, CT was able to identify only 173 (73%); 207 (87%) were metastatic tumors, 21 (9%) were benign, and 9 (4%) were bronchogenic carcinomas. Of 65 nodules interpreted as solitary on chest radiographs, CT disclosed multiple nodules in 46%, and 84% of these additional nodules were metastases.

Accordingly, CT results must be interpreted in light of the clinical characteristics of the patient. Primary tumors that commonly spread to the lungs, more advanced malignancies, and the absence of any simulators of metastases (silicosis, sarcoidosis, and prior granulomatous infection) would favor malignancy in pulmonary nodules detected by CT. Furthermore, smaller and less numerous nodules are more likely to be benign. The findings on CT are in themselves not specific, however, and follow-up may be necessary to demonstrate the growth or stability of small nodules.

Lung Cancer Staging

In patients with lung cancer, accurate anatomic staging is essential for planning the therapeutic approach.[70–72] CT is used in both assessment of primary tumor extent and detection of lymph node metastases. However, its accuracy in both situations is limited.[72]

Computed Tomography

The primary goal of CT is to help distinguish patients who likely have resectable tumors from those who do not. Pulmonary malignancy is considered to be likely unresectable (T4) if the primary tumor (1) involves the trachea or carina; (2) invades the mediastinum with involvement of mediastinal structures; (3) invades the chest wall with involvement of great vessels, brachial plexus, or vertebral column; or (4) results in a malignant pleural effusion or pleural implants.[72,73] The presence of satellite nodules in the same lobe as the primary tumor is now designated as T3 in the 7th edition of the TNM Classification of Malignant Tumors, and does not preclude surgical resection.[74]

Tracheal or carinal invasion can be suggested with CT but requires biopsy confirmation. The CT diagnosis of chest wall or mediastinal invasion can be problematic, although a CT scan should be obtained if these diagnoses are suspected. The sensitivity and specificity of CT in diagnosing T4 mediastinal or chest wall invasion are about 60% and 90%,[74] respectively, although some findings (e.g., vertebral body destruction, encasement of mediastinal structures, mediastinal fat infiltration) are virtually diagnostic.[71,74–79] Limited chest wall or mediastinal invasion is considered potentially resectable by many surgeons, but knowledge of tumor extent is nonetheless an important factor when planning therapy.

CT findings suggesting mediastinal invasion[74,76,77] include (1) replacement of mediastinal fat by soft-tissue attenuation, (2) compression or displacement of mediastinal vessels by tumor, (3) tumor contacting more than 90 degrees of the circumference of a structure such as the aorta or pulmonary artery (the greater the extent of circumferential contact, i.e., 180 degrees, the greater the likelihood of invasion), (4) more than 3 cm of contact between tumor and the mediastinum, and (5) obliteration of the mediastinal fat plane normally seen adjacent to most mediastinal structures (see Fig. 19-28). However, individually, these findings are unreliable for differentiating mediastinal invasion from anatomic contiguity.[74]

CT is of little value in the diagnosis of malignant pleural effusion, as this diagnosis requires cytologic confirmation.[80] However, in some patients, CT can show pleural implants with or without effusion or diffuse or nodular pleural thickening.[80,81] ^{18}FDG-PET may show tracer uptake in patients with malignant pleural effusion, even when CT does not show evidence of nodular pleural thickening and when cytologic analysis is negative.[82]

The diagnosis of mediastinal lymph node metastasis by CT is determined purely by node size. By convention, a nodal diameter of more than 1 cm is considered to be abnormal in all node stations (Fig. 19-37)[72,74] except the subcarinal space.[83,84] Tumor cannot be detected in normal-sized lymph nodes by CT, and there are no characteristic appearances allowing benign and malignant causes of nodal enlargement to be distinguished.[85–87] Pooled information from 35 studies published between 1991 and June 2006 evaluating the performance of CT scanning for noninvasive staging of the mediastinum has shown that this size threshold has a sensitivity of only about 51% and a specificity of 86% for diagnosing mediastinal lymph node metastases in patients with lung cancer.[71,88–90] Furthermore, the accuracy of CT for detecting involvement of individual node groups is low, perhaps as low as 40%.[88]

Despite its limited accuracy, CT, particularly in conjunction with ^{18}FDG-PET, is useful in determining the need for preoperative mediastinoscopy. Furthermore, CT may also be useful in guiding mediastinoscopy (e.g., suprasternal vs. left parasternal approach) or suggesting alternate procedures (e.g., needle biopsy, endoscopic ultrasound). If mediastinoscopy is not performed routinely before thoracotomy, CT can significantly reduce the number of thoracotomies performed in patients with gross mediastinal disease, but its use varies with practice patterns at individual institutions.[91]

Perhaps the most important potential contribution of CT to intrathoracic staging is precise mapping of nodes likely to be involved by tumor. For example, ipsilateral mediastinal lymphadenopathy places the patient in stage IIIA (potentially resectable), whereas contralateral lymphadenopathy (see Fig. 19-37B) renders the patient unresectable (stage IIIB). However, CT may have a limited role in this crucial staging distinction. The prognostic significance of N2 metastases appears to correlate with the method of their discovery, with those found at mediastinoscopy associated with only a 10% 5-year survival rate and those found at thoracotomy with a 25% 5-year survival rate.[92,93]

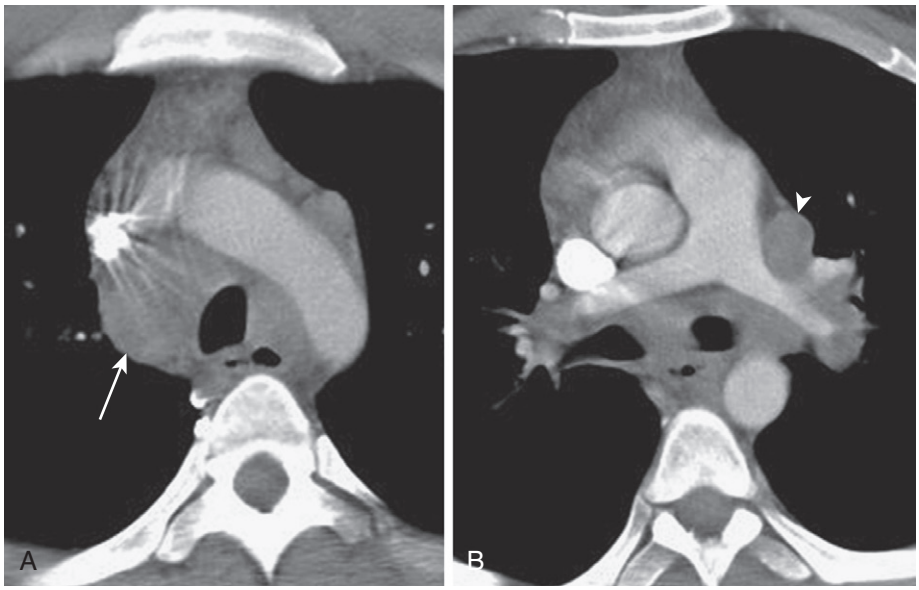

FIGURE 19-37 ■ This patient was diagnosed with non–small cell lung cancer, and CT was performed for staging. **A,** The primary tumor was present at another level in the right lung. Right paratracheal lymphadenopathy (*arrow*) is present; left mediastinal nodes also appear enlarged. **B,** Axial thoracic CT at a slightly lower level than **A** shows left hilar and subaortic (*arrowhead*) lymph nodes, which measure greater than 1 cm in short axis diameter, the most widely accepted size threshold for abnormality, and would be considered suspicious for metastasis. The radiographic staging thus would be IIIB.

Positron Emission Tomography and Positron Emission Tomography Computed Tomography

^{18}FDG-PET imaging has become an integral part of staging for lung cancer. The primary end point for using ^{18}FDG-PET is to increase the sensitivity for the detection of local and distant malignancy: to prevent patients with unresectable disease from undergoing unnecessary surgery. ^{18}FDG-PET and PET-CT are most useful for evaluating the N and M components of staging, although ^{18}FDG-PET activity in the primary tumor (T component) may provide insight into biologic aggressiveness and the chance of future spread of early localized tumors.[94] Characteristics of the primary tumor, however, are typically best evaluated using CT, given its superior spatial resolution.

In a meta-analysis, ^{18}FDG-PET showed a greater sensitivity and specificity for nodal disease compared with CT—79% versus 60% and 91% versus 77%, respectively.[95] The exact role of ^{18}FDG-PET with respect to more invasive diagnostic procedures, such as mediastinoscopy, is yet to be determined. Another recent study demonstrated that ^{18}FDG-PET has a relatively high false-positive rate for lung carcinoma lymph node metastases (26%),[96] suggesting that mediastinoscopy was still required for confirmation of mediastinal metastasis. ^{18}FDG-PET is still quite useful to identify potentially involved mediastinal groups (Fig. 19-38) and to evaluate mediastinal compartments that are typically inaccessible with mediastinoscopy. ^{18}FDG-PET is also useful in the evaluation of distant metastases and has the potential to supplant traditional imaging methods for this purpose. In a study by Weder and coworkers,[97] ^{18}FDG-PET detected unsuspected metastasis in 14% of patients with stage IIIa disease or less and in those who had already undergone CT of the chest and upper abdomen. The majority of these unsuspected metastases were osseous or adrenal in location. It is important to note that ^{18}FDG-PET has a decreased sensitivity for brain metastases compared to traditional techniques (CT and MRI) due to the fact that the high metabolic activity of the brain normally accumulates significant amounts of radiotracer activity.

Magnetic Resonance Imaging

There are few situations in which MRI is the preferred imaging modality for patients with primary lung cancer. The extent of chest wall invasion adjacent to a lung tumor sometimes may best be shown by MRI. However, MRI, like CT, still has imperfect sensitivity and specificity. MRI has been used for delineating additional chest wall involvement in patients with lymphoma.[98] Sagittal or coronal MR images can be advantageous in delineating the extent of tumors at the lung apex (Fig. 19-39).[72,99] Consequently, MRI is more accurate than CT for determining chest wall involvement in superior sulcus tumors; moreover, involvement of the neurovascular bundle[99] is better shown with coronal and sagittal MRI than with axial CT images.

In most patients with primary lung cancer, MRI has no unique information to offer, and CT is the preferred imaging procedure.[72] MRI is similar to CT in its ability to identify mediastinal lymph nodes[72] and to diagnose mediastinal metastases. Although it has been reported that MRI is more accurate than CT in detecting medi-

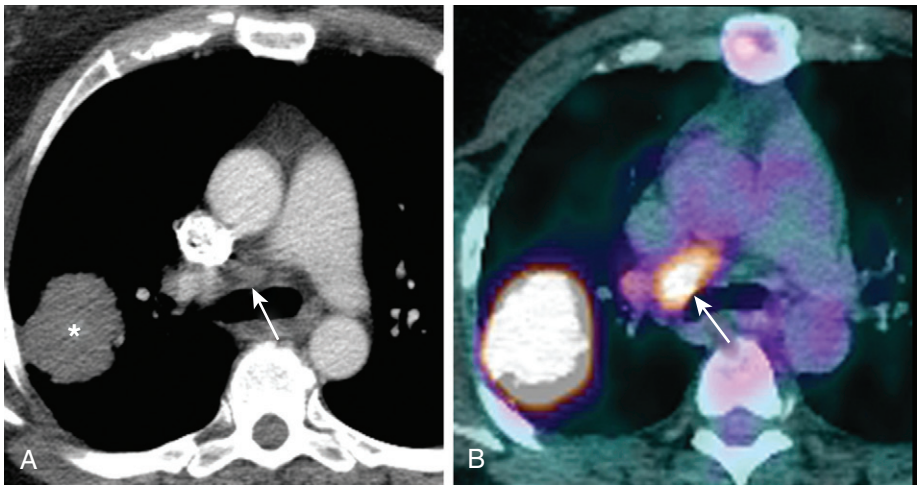

FIGURE 19-38 ■ Utility of PET-CT in the staging of pulmonary malignancy. This patient was diagnosed with non–small cell lung cancer, and CT and PET-CT were performed for staging. **A,** The primary tumor is visible in the peripheral right lung (*). Borderline right paratracheal lymph nodes (*arrow*) are present. **B,** PET-CT shows intense tracer uptake in the primary right lung neoplasm as well as within the right paratracheal lymph nodes (*arrow*). The latter finding prompted mediastinoscopy, which confirmed metastatic nodal disease.

astinal,[71,100] cardiac, or vascular invasion by lung cancer, the reported differences in accuracy are small. In general, the MR properties of benign and tumor-bearing mediastinal lymph nodes do not differ significantly in most patients,[101] and as with CT, node size is usually the only diagnostically useful discriminator. However, recent data with newer MR sequences, particularly diffusion-weighted imaging[102] and short tau inversion recovery imaging (STIR),[103,103a] as well as recent observations regarding findings at T2-weighted thoracic MRI,[103b] which may allow discrimination between benign and malignant lymph node involvement even for lymph nodes with short axis dimensions less than 1 cm. In addition, in some cases, MRI is able to demonstrate masses better than CT by imaging in the coronal or sagittal plane, and in some cases, MRI may be used as a problem-solving tool.

Brachial Plexopathy

Imaging of the brachial plexus is useful for patients with suspected metastatic disease, radiation injury, primary tumor, or traumatic injury. Clinical evaluation can suggest possible etiologies of brachial plexopathy and whether the neurologic deficit is more likely due to a central or a peripheral lesion.[104] However, clinical evaluation cannot demonstrate the pathology and localize precisely the site of involvement.

Metastatic disease and radiation injury are the most common causes of brachial plexopathy, and the clinical distinction between these is difficult, although pain, Horner's syndrome, and lower trunk involvement are characteristic of metastatic involvement.[105,106] CT is of proven value for patients with primary or metastatic tumors,[104,107] but it may be less useful for patients with radiation fibrosis. CT is superior for the detection of osseous involvement due to superior sulcus tumors.[99] Older data clearly indicated that MR is superior to CT for assessment of brachial plexus involvement by lesions within the superior sulcus, primarily due to the multiplanar capabilities of MR. However, as mentioned previously, advances in CT technology now allow imaging reconstruction in any plane, and it is likely that these improvements have enhanced the diagnostic capabilities of CT for assessment of superior sulcus tumors. Nevertheless, MR possesses inherently superior contrast resolution to CT, which is a valuable property for imaging the superior sulcus region. Therefore, MR is still considered the reference standard for evaluation of tumors within the superior sulcus and for assessment of brachial plexus involvement by tumors in this region.[99]

CT myelography, often in conjunction with conventional myleography and MR imaging, is the optimal imaging modality for the assessment of traumatic brachial plexus injury.[108]

Lung Cancer Screening

The utility of CT in screening for lung cancer remains uncertain. As with most screening issues, studies are subject to biases including lead-time bias, length-time bias, and overdiagnosis. Many of the screening studies performed have shown a high percentage of early stage cancers found, suggesting early detection and a greater chance of cure. For instance, in the International ELCAP study,[109] 85% of cancers detected were stage I. As none of these studies have had a control arm, the mortality benefit of early diagnosis assumes that lung cancer is an invariably fatal disease; however, this is not necessarily true. Currently, the National Lung Screening trial, which does include a control arm, is underway in an attempt to settle this debate.

A second potential issue with lung cancer screening is the high incidence of nonmalignant pulmonary nodules detected. According to the Mayo Clinic data,[110] 74% of patients had at least one nodule detected during the

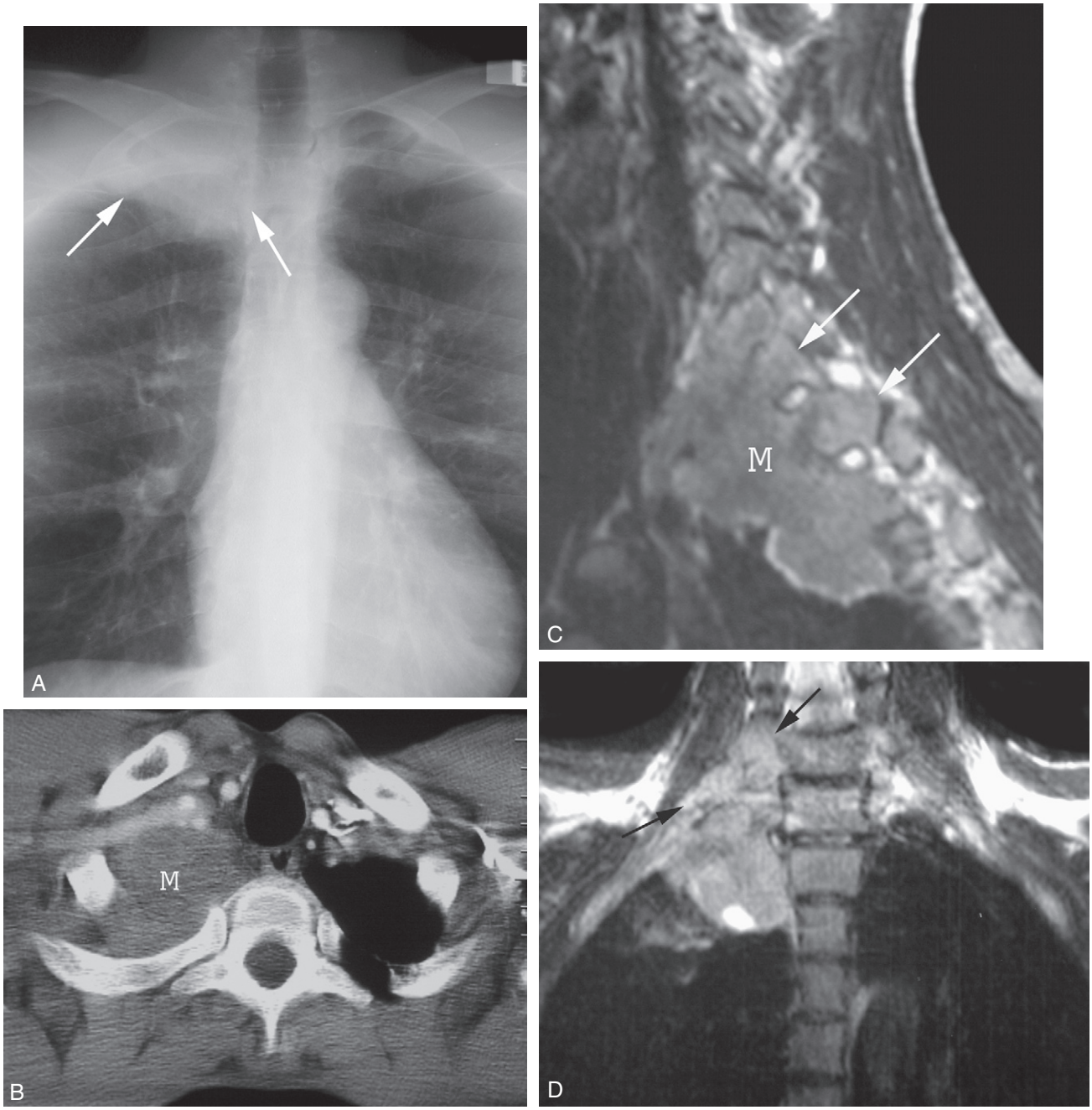

FIGURE 19-39 ■ This patient had primary non–small cell lung cancer with brachial plexopathy. **A,** Frontal chest radiography demonstrates right apical lung opacity (*arrows*) without clear chest wall involvement. **B,** An axial CT image through the lung apex delineates the lung mass (M), but chest wall involvement is not clearly identified. **C,** Sagittal T2-weighted magnetic resonance imaging (MRI) reveals the extension of the mass (M) into the vertebral body neural foramina (*arrows*). **D,** Coronal T2-weighted MRI shows extension of the mass into the right neck (*arrows*), in the region of the brachial plexus.

4-year study period and only 2% of noncalcified nodules were found to be malignant. Given that most patients with nodules are followed with CT to demonstrate 2 years of stability, the acceptance of lung cancer screening would undoubtedly result in a large number of subsequent CT scans that would not have otherwise be performed. This could have a significant impact on the cost-effectiveness of lung cancer screening and radiation exposure to this patient population.

Hilar and Mediastinal Masses

CT is indicated as the primary imaging modality in most patients with suspected hilar or mediastinal masses. The cross-sectional display and tissue discrimination of CT have revolutionized diagnostic imaging of the hilum and mediastinum.

Lesions can be detected with high sensitivity and located precisely to their structure of origin or anatomic

region (Fig. 19-40). By localizing a mass to a particular region of the mediastinum,[111,112] the differential diagnosis can be made more specific, and biopsy procedures can be planned with greater accuracy. In addition to the information gained from the location of the mass, the density discrimination of CT enables soft-tissue abnormalities, fluid collections, and fatty tissue to be distinguished accurately (Fig. 19-41).[113-115] With use of intravenous contrast material, masses and vascular anomalies can be accurately delineated. CT is useful in further evaluating a mass initially detected on chest radiography, in demonstrating pathology that is suspected on the basis of the clinical setting—but not visible on conventional imaging studies—and in precisely delineating the location of lesions for planning therapy.

MRI may be indicated as the primary imaging modality in patients with suspected mediastinal mass when the mediastinal abnormalities are thought to be vascular, with lesions at the thoracic inlet that may be advantageously displayed in the coronal plane, and for evaluation of posterior mediastinal masses and neurogenic tumors, which may have intraspinal components.[116,117] It has also been reported that MRI can be used to distinguish between a tumor mass and a benign fibrous mass[118-120] following radiation therapy, a distinction that can be difficult with CT. However, in practice, the differentiation of tumor from associated inflammation is difficult,[118,119] and ^{18}FDG-PET is generally preferred for this distinction.

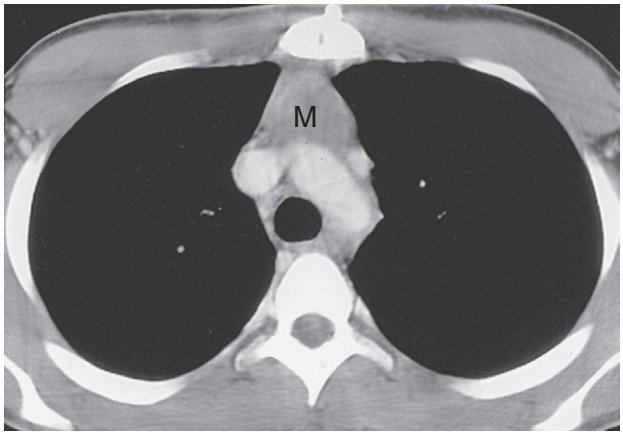

FIGURE 19-40 ■ This axial CT image shows an anterior mediastinal soft-tissue mass (M). There are no characteristic attenuation features (e.g., fat or calcium). The location of the mass, however, is precisely documented, and thus the differential diagnosis was limited and biopsy facilitated. The lesion was a seminoma.

MRI is rarely indicated for imaging hilar masses; CT is usually preferred for this application. Traditionally, contrast-enhanced MR would be considered as an alternative to contrast-enhanced thoracic CT for the assessment of hilar or mediastinal lesions in patients with impaired renal function, but recent recognition of a fibrosing dermopathy, referred to as nephrogenic systemic fibrosis, that may occur following intravenous administration of gadolinium-based contrast agents in patients with impaired renal function[121] gives pause to such an approach. Nevertheless, unenhanced MR, due to its inherent high contrast resolution, may still provide valuable information regarding hilar and mediastinal masses.

Primary and metastatic cardiac tumors usually are often detected initially by echocardiography, but MRI also is an accurate method of delineating such lesions.[122-127] It is thus appropriate as a problem-solving technique for patients with inconclusive ultrasound examinations and is of particular value for resolving false-positive echocardiographic findings, but it is also emerging as a first-line examination for a number of cardiovascular applications. Both MRI and CT can specifically demonstrate fat within cardiac lesions and fluid within pericardial cysts. Intracardiac tumor (Fig. 19-42) and thrombus frequently can be differentiated by MRI, particularly with contrast administration.

Diffuse Lung Disease

The clinical assessment of a patient with suspected diffuse infiltrative lung disease (DILD) can be a difficult

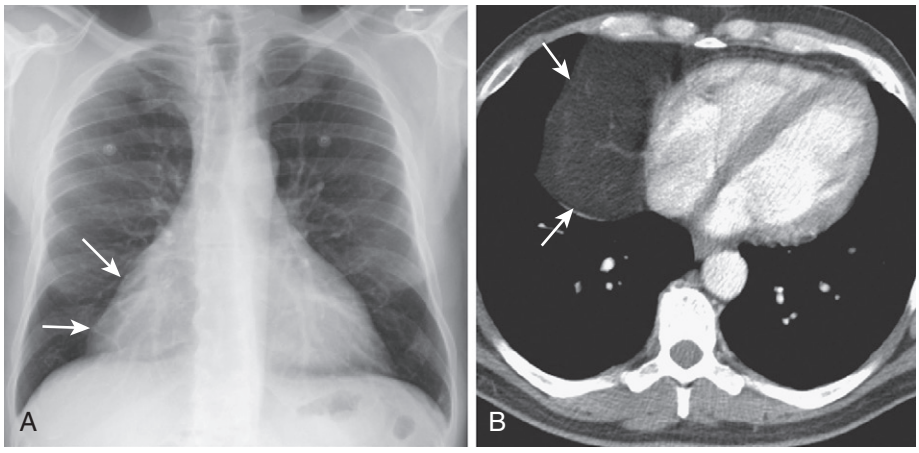

FIGURE 19-41 ■ CT characterization of fatty mediastinal masses. **A,** Frontal chest radiography shows a contour abnormality (*arrows*) along the right inferior mediastinum. **B,** Axial thoracic CT shows a fatty right paracardiac mass (*arrows*), consistent with thymolipoma.

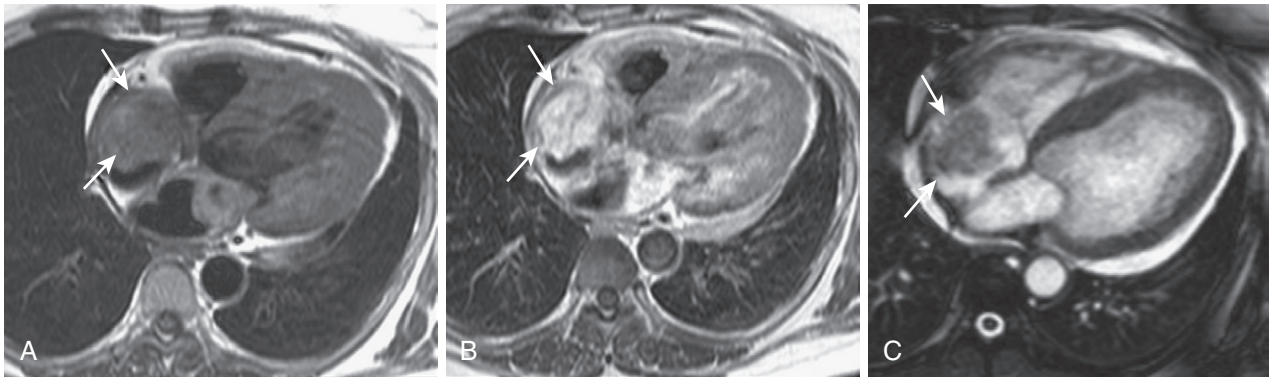

FIGURE 19-42 ■ MRI characterization of cardiac masses. **A,** Axial T1-weighted image shows a soft-tissue intensity mass (*arrows*) within the right atrium. **B,** Contrast-enhanced axial T1-weighted MRI shows intense enhancement of the mass (*arrows*), excluding thrombus as the diagnosis and suggesting neoplasm. **C,** Balanced fast-field echo image (obtained for function) shows the mass as a low-signal lesion (*arrows*) within the right atrium. Resection confirmed right atrial myxoma.

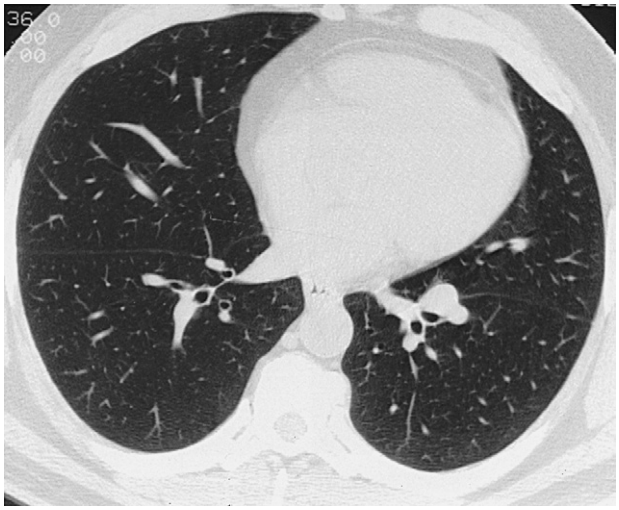

FIGURE 19-43 ■ This normal high-resolution computed tomography (HRCT) image at the level of the inferior pulmonary veins delineates the pulmonary vessels, major fissures, and lower lobe segmental bronchi.

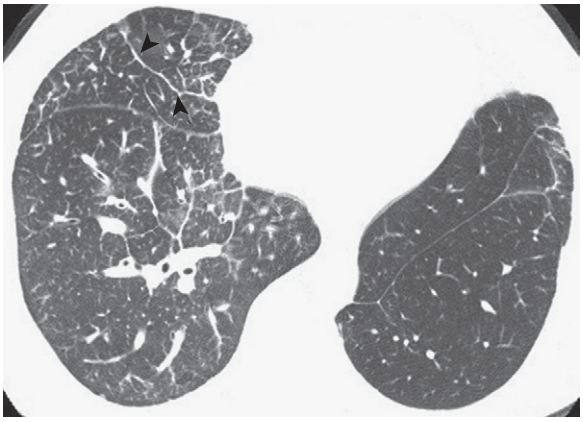

FIGURE 19-44 ■ This HRCT image in a patient with lymphangitic metastasis of breast carcinoma shows smoothly thickened interlobular septa (*arrowheads*); note asymmetry of the process.

and perplexing problem. Imaging studies are often important in reaching a final diagnosis, suggesting appropriate diagnostic procedures, and assessing the patient's course and prognosis.

In clinical practice, the imaging studies most frequently used to evaluate patients with suspected DILD are chest radiographs and HRCT. HRCT is typically used when the diagnosis is uncertain based on chest radiographs and clinical evaluation and further assessment is considered warranted and to assess treatment response in patients with established diagnoses.

HRCT findings in a wide variety of parenchymal diseases have been described, including the idiopathic interstitial pneumonias, sarcoidosis, diffuse neoplasms, pneumoconioses, infections, and numerous other disorders.[90,128–144] These studies have shown that HRCT delineates both normal anatomic structures (Fig. 19-43) and pathologic alterations in lung morphology more clearly than conventional or spiral CT or chest radiographs.[139,140,145,146] In general, HRCT findings of lung disease can be divided into increased lung opacity, including reticular, linear, and nodular opacities, consolidation, and ground-glass opacity; and decreased lung opacities, such as cysts, cavities, emphysema, and mosaic perfusion.[147]

Increased Lung Opacity

Linear and Reticular Opacities. Thickening of the interstitial fiber network of lung by fluid, fibrous tissue, or interstitial infiltration by cells results in an increase in both linear and reticular opacities as seen on HRCT.[147] Interlobular septal thickening occurs in patients with a variety of interstitial lung diseases, but most typically pulmonary edema, lymphangitic spread of tumor (Fig. 19-44),[147] and sarcoidosis, in addition to a small number of rarer causes.[148–150] Septal thickening is not common in patients with interstitial fibrosis, except for those with sarcoidosis and asbestosis.[151] Honeycombing reflects extensive fibrosis with lung destruction and results in a cystic, reticular appearance on HRCT that is characteristic (Fig. 19-45).[147,151] When honeycombing is present,

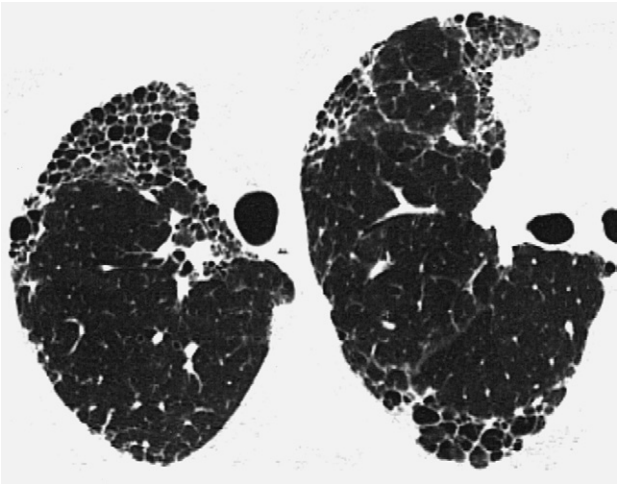

FIGURE 19-45 ■ HRCT at two levels shows rheumatoid lung disease with honeycombing. The appearance of multiple, contiguous, air-filled cystic structures having a subpleural predominance is typical.

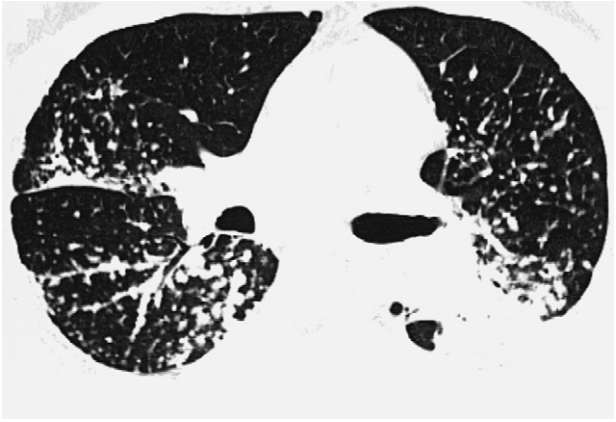

FIGURE 19-46 ■ HRCT in a patient with sarcoidosis shows a perilymphatic distribution of nodules. Note that numerous subpleural nodules are seen in relation to the right major fissure, and nodules also surround arteries in the right lower lobe. These findings, along with the patchy distribution of the nodules, are diagnostic of sarcoidosis in the appropriate clinical setting.

normal lung architecture is distorted, and secondary lobules are difficult or impossible to recognize. The cystic spaces of honeycombing can range from several millimeters to several centimeters in diameter and are characterized by thick, clearly definable, fibrous walls, and are often found stacked in several layers in the subpleural regions of lung.

Nodules. Well-defined nodules, as small as 1 to 2 mm in diameter, can be detected on HRCT in patients with a variety of diseases; these are usually interstitial in origin. Nodules can be classified according to their distribution as perilymphatic, random, or centrilobular according to their distribution within the secondary pulmonary lobule.[147] Recognition of one of these distributions is fundamental to the generation of differential diagnoses.[152,153] Perilymphatic nodules affect the peribronchovascular, interlobular septal, subpleural, and centrilobular interstitial compartments and are typical of sarcoidosis, which tends to have a peribronchovascular and subpleural predominance (Fig. 19-46)[148,152-154]; silicosis and coal worker's pneumoconiosis, which predominate in the subpleural and centrilobular regions[133,149,150]; and lymphangitic spread of tumor, which is usually peribronchovascular and septal.[147] Nodules with a random distribution are most typical of miliary infections (Fig. 19-47)[155] and hematogenous metastases.[147] Well-defined centrilobular nodules can be seen in silicosis and coalworker's pneumoconiosis,[156,157] asbestosis, and Langerhans cell histiocytosis.[158] Poorly defined centrilobular nodules often reflect bronchiolar or peribronchiolar abnormalities,[159] and can be seen in silicosis and coal worker's pneumoconiosis,[156] endobronchial spread of infection,[155] hypersensitivity pneumonitis,[160,161] and pulmonary edema.[159]

Consolidation and Ground-Glass Opacity. Air space consolidation, by definition, occurs when alveolar air is replaced by fluid, cells, or other material.[162] On HRCT, consolidation results in an increase in lung opacity

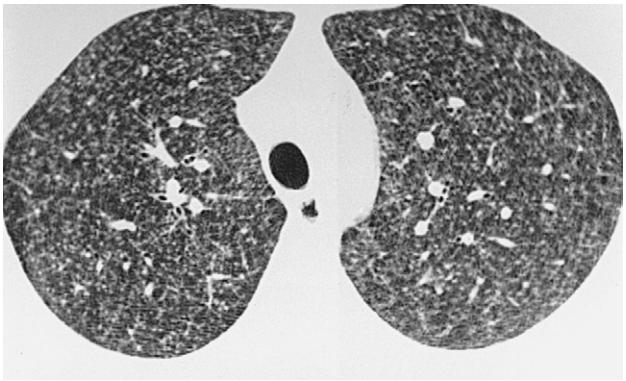

FIGURE 19-47 ■ This human immunodeficiency virus (HIV)–infected patient had miliary tuberculosis. Innumerable small nodules are visible on HRCT. These are evenly distributed throughout the lung in a "random" pattern. Note the dissimilarity to the distribution of nodules in Figure 19-46.

associated with obscuration of underlying vessels. Among patients with chronic DILD, the most common causes of this pattern include chronic eosinophilic pneumonia and cryptogenic organizing pneumonia.[163,164] The term *ground-glass opacity* refers to a hazy increase in lung opacity that is not associated with obscuration of underlying vessels (Fig. 19-48).[162] This finding can reflect the presence of a number of diseases and can be seen in patients with either minimal interstitial thickening or minimal air space filling.[137,140,165-168] It often reflects the presence of active disease, such as pulmonary edema, alveolitis associated with some idiopathic interstitial pneumonias, pulmonary hemorrhage (see Fig. 19-48), infectious pneumonias (particularly *Pneumocystis jirovecii* [formerly *P. carinii*] pneumonia), alveolar proteinosis, hypersensitivity pneumonitis (Fig. 19-49), and sarcoidosis.[169] However, ground-glass opacity may reflect the presence of fibrosis below the resolution of HRCT, particularly when the ground-glass opacity is associated

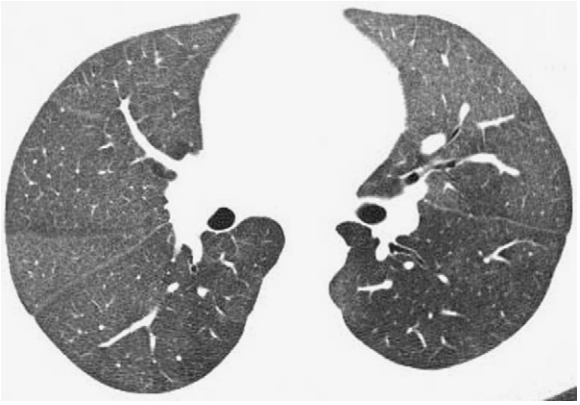

FIGURE 19-48 ■ In this patient with pulmonary hemorrhage in the setting of systemic lupus erythematosus, HRCT shows multifocal areas of geographic areas of opacity. The opacity does not obscure the normal lung markings (e.g., the vascular structures are still well delineated) and thus is considered ground-glass opacity.

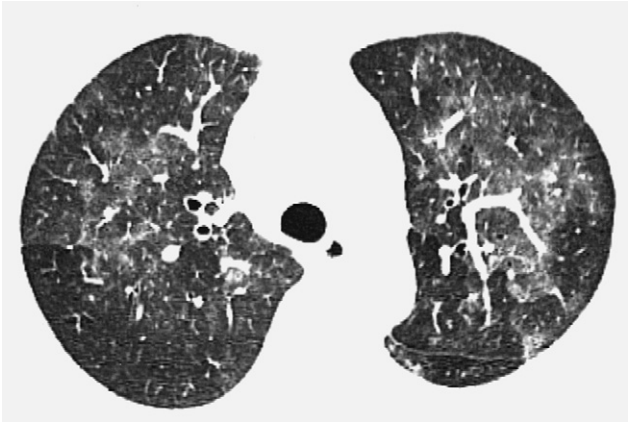

FIGURE 19-49 ■ In this patient with hypersensitivity pneumonitis, patchy ground-glass opacity is visible bilaterally.

with other findings of fibrotic lung disease, such as coarse reticulation, architectural distortion, traction bronchiectasis, and honeycombing.[166] Because of its potential reflection of active lung disease, the presence of ground-glass opacity may lead to surgical lung biopsy, depending on the clinical status of the patient.

Decreased Lung Opacity

Emphysema. Emphysema is accurately diagnosed with HRCT, and HRCT is more sensitive for the detection of emphysema than routine CT or chest radiographs.[141] Emphysema results in focal areas of very low attenuation that can be easily contrasted with surrounding, higher-attenuation, normal lung parenchyma (Fig. 19-50). In patients with centrilobular emphysema, areas of lucency can be seen surrounding the centrilobular artery and have a patchy, upper lobe distribution. In panlobular emphysema, focal areas of lucency are not usually present, but a diffuse simplification of lung architecture and a decrease in lung attenuation are present (see Fig. 19-50). In clinical practice, HRCT is rarely used in an attempt to diagnose emphysema. Usually, the combination of a smoking history, a low diffusing capacity, airway obstruction on pulmonary function tests, and an abnormal chest radiograph showing large lung volumes is sufficient to make the diagnosis. HRCT is useful in evaluating patients with COPD who are being considered as candidates for lung volume-reduction surgery. In addition, some patients with early emphysema can present with clinical findings more typical of infiltrative lung disease or pulmonary vascular disease, namely shortness of breath and low diffusing capacity, without evidence of airway obstruction on pulmonary function tests.[170] In such patients, HRCT can be valuable in detecting the presence of emphysema and excluding an interstitial abnormality. If significant emphysema is found on HRCT, no further workup is necessary; specifically, a lung biopsy is not needed.[171]

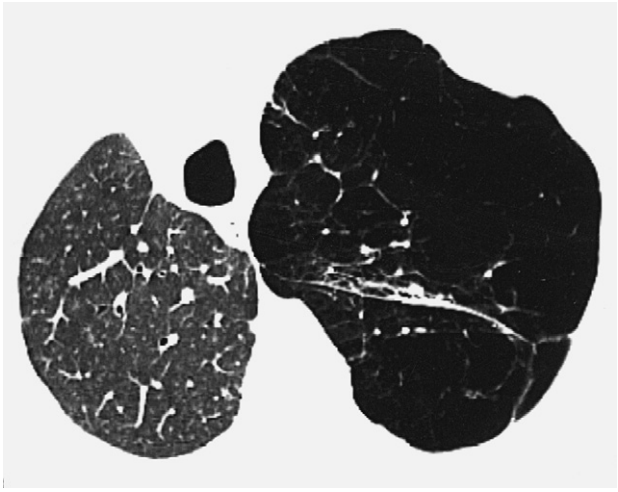

FIGURE 19-50 ■ This HRCT scan is from a patient with panlobular emphysema who underwent right lung transplantation. The emphysematous left lung is easily contrasted with the normal-appearing right lung. The left lung is less dense, is larger in volume, and contains fewer and smaller vessels.

Cystic Pulmonary Diseases. Lymphangiomyomatosis and Langerhans cell histiocytosis often result in multiple lung cysts (Fig. 19-51), which have a distinct appearance on HRCT.[158,172-174] The cysts have a thin but easily discernible wall, ranging up to a few millimeters in thickness. Associated findings of fibrosis are usually absent or much less conspicuous than they are in patients with honeycombing. In these diseases, the cysts are usually interspersed within areas of normal-appearing lung. In patients with Langerhans cell histiocytosis, the cysts can have bizarre shapes and an upper lobe predominance.

Mosaic Perfusion. Decreased lung attenuation not reflecting the presence of cystic lesions or emphysema can sometimes be recognized on HRCT in patients who have diseases that produce air trapping, poor ventilation, or poor perfusion.[141,163,165,167-176] The areas of decreased lung attenuation that are seen on HRCT can be focal, lobular or lobar, or multifocal. The term *mosaic*

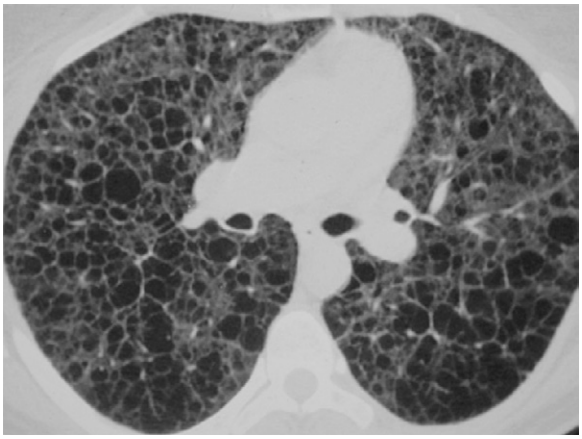

FIGURE 19-51 ■ A patient with lymphangiomyomatosis underwent HRCT. Note that the multiple cystic areas have clearly definable walls, in contrast to the appearance of emphysema (see Fig. 19-50).

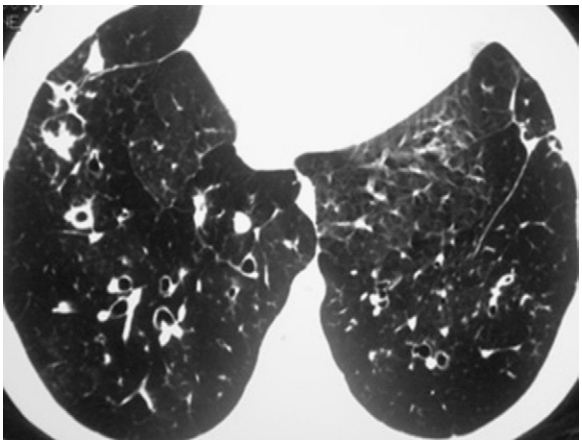

FIGURE 19-52 ■ HRCT in a patient with cystic fibrosis and mosaic perfusion shows inhomogeneous opacity in the lung bases bilaterally, somewhat geographically distributed. The areas of decreased attenuation represent mosaic perfusion, in this patient resulting from a combination of regional air trapping due to large airway disease and hypoperfusion in the affected areas of lung.

perfusion has been used to refer to patchy decreased lung attenuation resulting from perfusion abnormalities (Fig. 19-52). In patients with air trapping, this appearance can be enhanced with expiratory HRCT.[141,176–179]

Diagnostic Utility

The utility of chest radiographs and HRCT in the clinical diagnosis of diffuse lung disease relates to their ability to detect the presence of lung disease (sensitivity and specificity), characterize its nature, assess disease activity, and guide lung biopsy.

Sensitivity and Specificity. It is well documented that chest radiographs are limited in both their sensitivity and their specificity in patients with DILD.[144,180–182] For example, Gaensler and Carrington[181] reported that nearly 16% of patients with pathologic proof of interstitial lung disease had normal chest radiographs. The sensitivity of CT for detecting lung disease has been compared with that of chest radiography in a number of studies; without exception, these have shown that CT, and particularly HRCT, is more sensitive than chest radiography for detecting both acute and chronic diffuse lung diseases.[90,134,144,160,183–185] The average results of several studies show that the sensitivity of HRCT for detecting DILD is approximately 94% compared with 80% for chest radiographs.[182] The sensitivity of HRCT has also proved superior to that of routine CT obtained with wider collimation.[128,168,169]

It is important to note that the increased sensitivity of HRCT is not achieved at the expense of decreased specificity or diagnostic accuracy.[131,133,182] A specificity of 96% for HRCT compared with 82% for chest radiographs was reported by Padley and colleagues[182] in patients with DILD. In other studies, it has been shown that between 10% and 20% of patients with DILD suspected on chest radiographs subsequently prove to have normal lung biopsy results.[180,181] Although HRCT is clearly more sensitive than chest radiographs, its sensitivity in detecting lung disease is not 100%, and a negative HRCT cannot generally be used to rule out DILD. For example, in one study, although HRCT had very high sensitivity and specificity values, 4% of subjects with biopsy-proven lung disease were interpreted as having a normal HRCT.[182]

Diagnostic Accuracy. Even in the presence of definite abnormalities, chest radiographs have limited diagnostic accuracy for patients with DILD. In an attempt to improve the diagnostic accuracy of chest radiographs, McLoud and associates[186] employed a semiquantitative approach to the chest radiographic diagnosis of diffuse lung disease based on a modification of the International Labor Organization/Union Internationale Contre Cancer classification of chest radiographic abnormalities. In an evaluation of 365 patients with open lung biopsy–confirmed DILD, these investigators found that their first two diagnostic choices corresponded to the histologic diagnosis in only 50% of patients; this improved to only 78% when the first three choices were included. Furthermore, there was only 70% interobserver agreement as to the predominant type of parenchymal abnormality or its extent. Numerous reports have shown that HRCT is significantly more accurate than are chest radiographs in diagnosing both acute and chronic diffuse lung disease, usually allows a more confident diagnosis, and is subject to considerably less interobserver variation in its interpretation (Table 19-4).[131–133,141,151,168,187–193]

In an attempt to further refine diagnostic accuracy, Grenier and coworkers[131] used bayesian analysis to determine the relative value of clinical data, chest radiographs, and HRCT for patients with chronic DILD. For this study, two samples from the same population of patients with 27 different diffuse lung diseases were consecutively assessed: an initial retrospectively evaluated set of "training" cases (n = 208) and a subsequent prospectively evaluated set of "test" cases (n = 100) for validation. The results showed that for the test group an accurate diagnosis could be made in 27% of cases based on clinical

TABLE 19-4. Comparative Accuracy of Chest Radiographs and High-Resolution Computed Tomography

	CONFIDENT FIRST CHOICE DIAGNOSIS		CORRECTED FIRST CHOICE DIAGNOSIS WHEN CONFIDENT		CORRECT FIRST CHOICE DIAGNOSIS		CORRECT DIAGNOSIS IN FIRST THREE CHOICES	
Study	CXR	HRCT	CXR	HRCT	CXR	HRCT	CXR	HRCT
Mathieson et al[133]	23%	49%	77%	93%	57%	72%	73%	89%
Padley et al[182]	41%	49%	69%	82%	47%	56%	72%	81%
Grenier et al[131]	—	—	—	—	64%	76%	78%	83%
Nishimura et al[191]	—	—	60%	63%	38%	46%	49%	59%
Average	32%	49%	69%	79%	52%	63%	67%	78%

CXR, chest radiograph; HRCT, high-resolution computed tomography.

data only, increasing to 53% ($P < .0001$) with the addition of chest radiographs and to 61% ($P = .07$) with the further addition of HRCT scans. In some situations, HRCT findings are sufficiently diagnostic to obviate biopsy.[144,194]

Assessing Disease Activity. In addition to being more sensitive, specific, and accurate than chest radiographs, HRCT may also play a critical role in the evaluation of disease activity in patients with diffuse lung disease.[144,194] Available data suggest that, in certain cases, HRCT may be used to determine the presence or absence, and extent, of reversible (acute or active) lung disease compared with irreversible (fibrotic) lung disease. Furthermore, because HRCT may accurately identify subtle "active" lung disease, it can be used to study patients who are being treated in order to monitor the success or failure of the treatment being employed.[129,144,194–198]

Although a number of HRCT findings have been described as being indicative of active or reversible lung disease in patients with different disease entities, most attention has focused on the potential significance of ground-glass opacity in patients with chronic DILD.[137,166] This finding has been reported in a wide range of DILDs, including usual interstitial pneumonia, desquamative interstitial pneumonitis, lymphoid interstitial pneumonia, sarcoidosis, hypersensitivity pneumonitis, alveolar proteinosis, cryptogenic organizing pneumonia, respiratory bronchiolitis, and chronic eosinophilic pneumonia.[137] Ground-glass opacity also has been described in patients with neoplasms, in particular bronchoalveolar carcinoma, as well as a wide variety of acute lung processes, such as acute interstitial pneumonia; bacterial, fungal, viral, and *P. jirovecii* infections; pulmonary hemorrhage syndromes; and congestive heart failure and other causes of pulmonary edema.

Although ground-glass opacity is a nonspecific finding and can reflect various histologic abnormalities, in patients with chronic DILD, ground-glass opacity may represent active parenchymal inflammation. In a study of 26 patients with DILD in whom histopathologic correlation was obtained, biopsy specimens demonstrated that ground-glass opacity corresponded to inflammation in 24 cases (65%), and in 8 additional cases (22%), inflammation was present but fibrosis predominated[137,166]; in only 5 cases (13%) was fibrosis the sole histologic finding. Similarly, Leung and associates,[165] in a study of 22 patients with a variety of chronic DILDs and evidence of ground-glass opacity as either a predominant or an exclusive HRCT finding, showed that 18 (82%) had potentially active disease identified on lung biopsy.

Ground-glass opacity may also be seen in the presence of interstitial fibrosis without active inflammation.[137,165,166] To strongly suggest that ground-glass opacity indicates active disease, this finding should generally be unassociated with HRCT findings of fibrosis.[137,165,166] In patients with idiopathic pulmonary fibrosis, a significant correlation has been found between the presence of HRCT findings of ground-glass opacity and pathologic findings of active inflammation, the development of pulmonary fibrosis, the patient's prognosis,[142,196,198–200] and the likelihood of response to therapy.[195,196,198] HRCT has also been used to assess disease activity as well as the likelihood of response to therapy in patients with sarcoidosis.[129,138,154,167,197] In most series of patients with sarcoidosis, the main HRCT determinant of disease activity has been the presence and, to a lesser degree, the extent and distribution of small nodules.[138,167]

Guiding Lung Biopsy. Among the many indications for HRCT, perhaps the most important is as a potential guide for surgical lung biopsy. Many "diffuse" lung diseases are quite patchy in distribution, with areas of abnormal lung frequently interspersed among relatively normal areas of lung parenchyma. Furthermore, both active and fibrotic disease can be present in the same lung.[142,144,194,199–201] To establish a specific diagnosis and assess the clinical significance of the abnormalities present, it is critically important to selectively sample those portions of the lung that are the most abnormal and the most likely to be active. This can be accomplished with HRCT. Also, as a direct consequence of its ability to visualize, characterize, and determine the distribution of parenchymal disease, HRCT also provides a unique insight into the likely efficacy of transbronchial or surgical lung biopsy (via thoracotomy or video-assisted thoracoscopy) in patients with either acute or chronic diffuse lung disease. Surgical lung biopsy is often

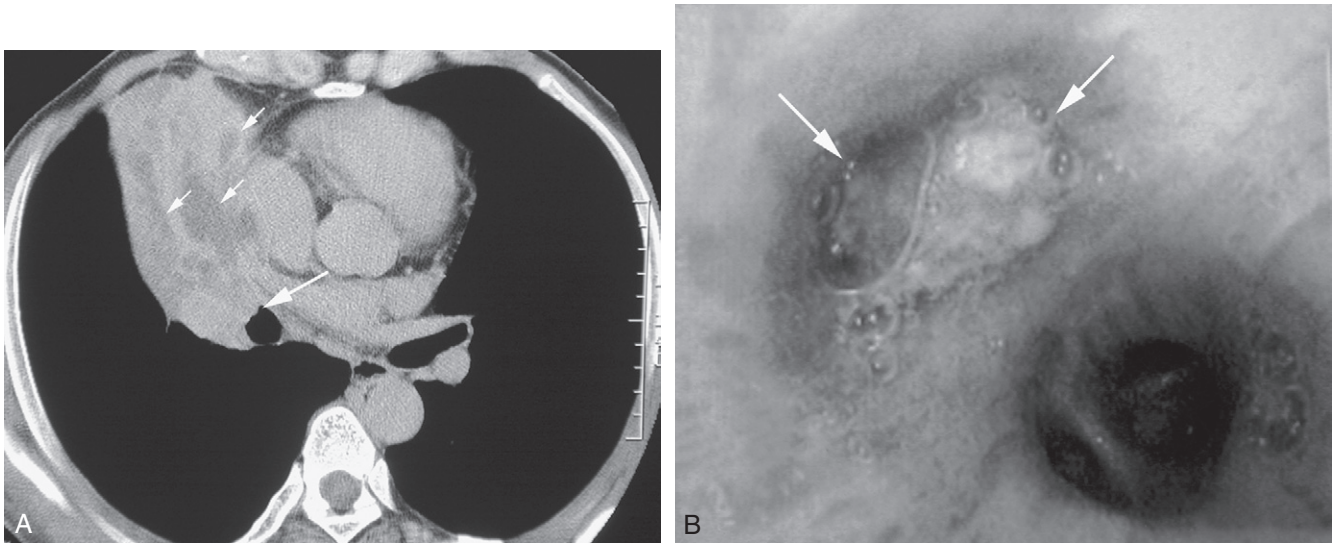

FIGURE 19-53 ■ **A,** Axial CT image shows a squamous carcinoma occluding the right middle lobe bronchial orifice (*large arrow*), producing complete collapse of the right middle lobe. Low-attenuation tubular foci (*small arrows*) visible within the collapsed right middle lobe represent mucus-impacted bronchi. **B,** Bronchoscopic image shows the carcinoma occluding the right middle lobe bronchus and protruding into the bronchus intermedius (*arrows*).

diagnostic, with accuracies greater than 90% generally reported,[144,181,194,202,203] but this procedure is also subject to sampling error. HRCT is of considerable value in determining the most appropriate sites for biopsy.[144,188,194]

Intrathoracic Airway Disease

Previously, spiral CT was used to evaluate the trachea or central airways and HRCT technique is more appropriate for imaging the peripheral airways. With the development of MSCT, volumetric HRCT is now possible, which allows simultaneously optimized evaluation of the central airways combined with HRCT technique for evaluation of the peripheral airways in a single examination.[204]

Central Airways

CT can effectively evaluate lesions (Fig. 19-53) of the trachea and central airways,[205] including strictures and stenoses, inflammatory diseases such as polychondritis (Fig. 19-54), some cases of extrinsic versus intrinsic obstruction,[206] aspirated foreign objects, tracheobronchomalacia, and neoplasms.[205] Multislice CT, with its ability to rapidly acquire images with equal resolution in all planes, is particularly useful in this assessment and can provide detailed three-dimensional analysis of the central airways. The ability to produce excellent quality three-dimensional images aids in the evaluation of subtle airway stenoses and complex airway lesions, particularly when they are oblique with respect to the imaging plane. In the assessment of tracheal and central bronchial neoplasms, CT does not substitute for bronchoscopy and biopsy, but it can be useful to determine the extent of invasion and to direct the bronchoscopist to a particular segment or to a precise location of peribronchial disease. The major value of CT imaging is its ability to visualize the luminal contents, the airway wall, and the surrounding soft tissue. Accordingly, the use of CT carries the greatest benefit in circumstances that require all three of these capabilities.

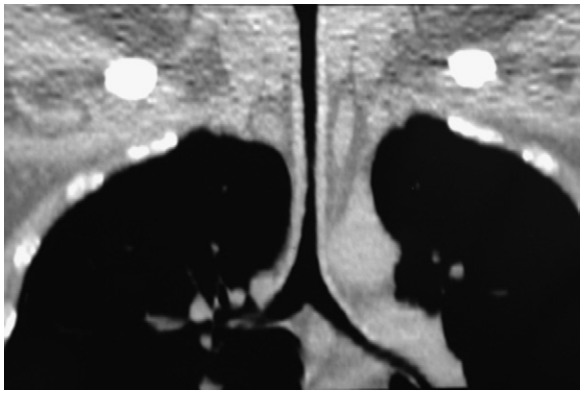

FIGURE 19-54 ■ Value of MSCT for central airway evaluation. Coronally reconstructed image shows diffuse thickening and narrowing of the trachea in a patient with relapsing polychondritis.

Bronchiectasis

CT should be the initial investigation in all patients with suspected bronchiectasis.[207–210] The sensitivity and specificity of HRCT (scans at 1-mm intervals) for diagnosing bronchiectasis to the segmental level are 95% to 98% (Figs. 19-55 and 19-56), whereas the sensitivity and specificity of thick-section CT are only about 80%. In current medical practice, CT has replaced bronchography. A review of the CT criteria for diagnosing bronchiectasis and the technical pitfalls that may intervene has been published.[211] MSCT scanning with narrow collimation

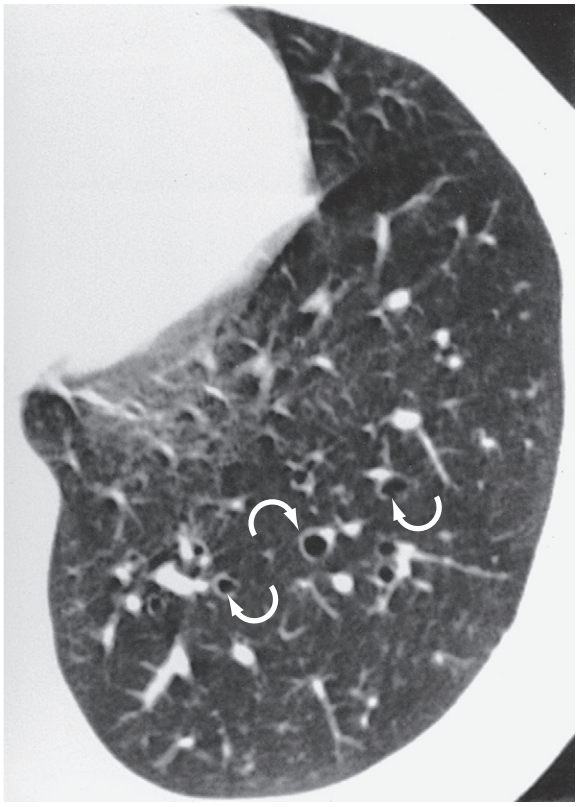

FIGURE 19-55 ■ HRCT image (performed with 1.5-mm collimation) shows obvious bronchiectasis (*arrows*).

(on the order of 1 mm) provides a larger volume of coverage with spatial resolution superior to routine single-slice spiral CT, yet also allows for volumetric imaging and the creation of exquisite reformatted images, including volume rendering.

Small Airway Disease

HRCT has the ability to demonstrate abnormalities of small airways having a diameter of a few millimeters or less.[141,153,159,163,176–178,212] Diagnosable abnormalities include (1) inflammatory forms of bronchiolitis, such as cellular bronchiolitis (usually due to infection, aspiration, or hypersensitivity pneumonitis), respiratory bronchiolitis, follicular bronchiolitis, and panbronchiolitis, and; (2) small airway diseases associated with airflow obstruction (e.g., constrictive bronchiolitis).[212] Cryptogenic organizing pneumonia has been previously classified as a disease of the small airways but is now considered an idiopathic interstitial pneumonia.[144,212] The use of postexpiratory HRCT is particularly important in the diagnosis of small airway diseases because air trapping may be visible in the absence of other abnormalities.[177,178] Postexpiratory HRCT may be performed by imaging after a forced vital capacity maneuver[213] or with lateral decubitus CT.[214] Recent data suggest that postexpiratory CT performed during a forced vital capacity maneuver, called "dynamic expiratory CT," is a more effective technique for the demonstration of subtle or transient air trapping.[213]

Cardiovascular Disease

Pulmonary Thromboembolism

Thoracic MSCT has emerged as the test of choice for the imaging evaluation of suspected pulmonary embolism. Ventilation-perfusion scintigraphy has long been used as the initial test for such patients. Its strengths and its limitations are well known and reviewed in Chapter 21. It is extremely safe, it is widely available, and it is exceedingly sensitive: a normal perfusion scintigram effectively rules out pulmonary embolism. A high-probability scan is quite specific (97% in the Prospective Investigation of Pulmonary Embolism Diagnosis [PIOPED] I study).[23] However, a substantial fraction of perfusion scintigrams yield results that are abnormal but nonspecific. In addition, it has been recognized increasingly that imaging the lower extremity veins can be useful and cost-effective for many patients suspected of having acute pulmonary embolism; thus, a single imaging procedure that evaluates both the lower extremity veins and the pulmonary arteries is quite useful.

Single-slice spiral CT, in pooled data from a number of studies, showed an overall sensitivity and specificity approaching 90% and 96%, respectively. Regardless, criticisms regarding the methodology employed in single-slice CT studies as well as the long-held faith in the diagnostic accuracy of catheter pulmonary angiography for suspected pulmonary embolism led to relatively slow adoption of the use of CT for this application in some centers. Once MSCT technology became available, however, it became clear that MSCT scans could demonstrate smaller vessels and, therefore by inference, should be more sensitive than single-slice CT for the detection of thromboembolic disease. Several studies investigating the incremental value of MSCT over single-slice CT for the diagnosis of thromboembolic disease were conducted shortly after the introduction of this technology, including the PIOPED II trial, the results of which were published in 2006. In PIOPED II, the sensitivity of MSCT for the diagnosis of pulmonary embolism was 83% (95% confidence limits, 76%–92%) and the specificity was 96%. The positive predictive value of a positive MSCT study was 86% and the negative predictive value was 95%. Although the sensitivity of MSCT in the PIOPED II trial has led some investigators to question the utility of MSCT for the evaluation of suspected pulmonary embolism, MSCT is nevertheless in widespread use as the first-line diagnostic modality for the investigation for such patients all across the world.

Ultimately, the main question that must be answered when patients suspected of thromboembolic disease undergo MSCT pulmonary angiography is, "can anticoagulation be safely withheld in such patients?" In other words, what is the negative predictive value of MSCT pulmonary angiography for thromboembolic disease? Several studies have addressed this question, and the negative predictive value of MSCT pulmonary angiography ranges

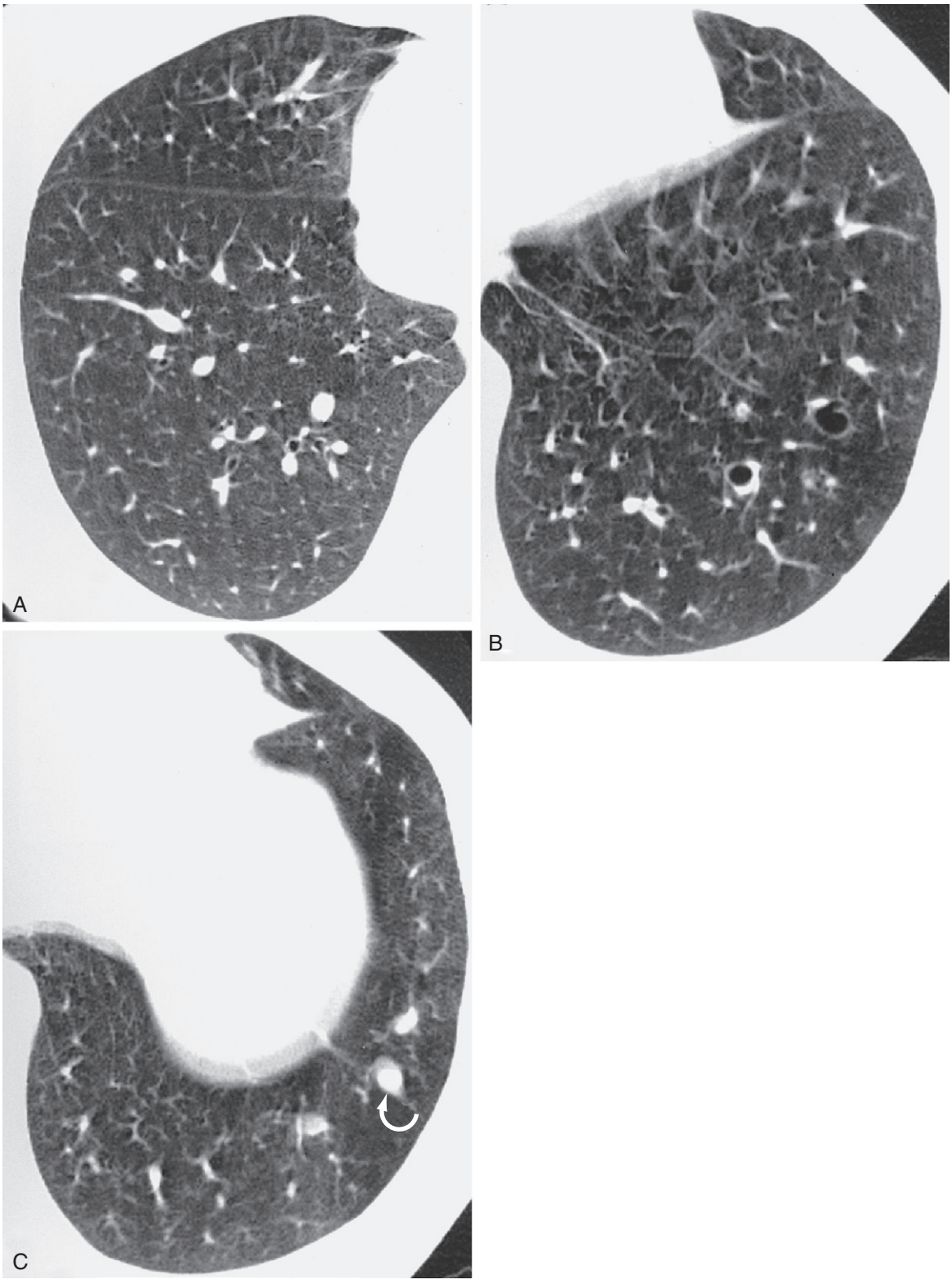

FIGURE 19-56 ■ **A,** HRCT shows the normal appearance of peripheral bronchi in the right lower lobe. In addition, note that there is a pulsation artifact anteriorly (middle lobe) due to transmitted cardiac pulsations. **B,** Focal bronchiectasis is present in the left lower lobe. Again, note that there is a pulsation artifact anteriorly (lingula and lower lobe). **C,** An image lower in the thorax demonstrates mucus-filled ectatic bronchi (*arrow*).

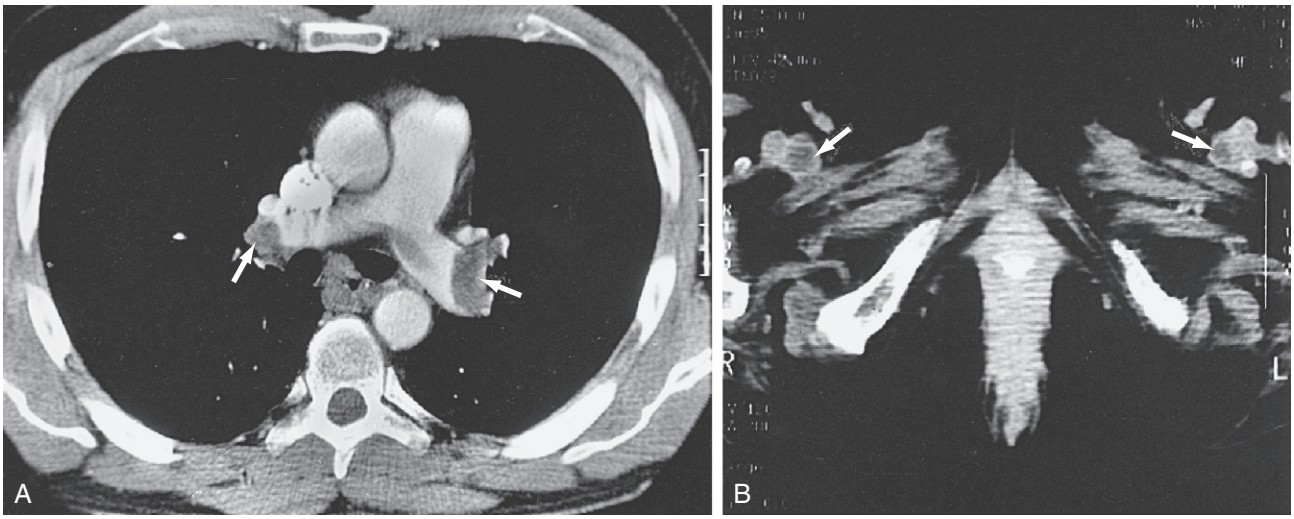

FIGURE 19-57 ■ CT images demonstrate pulmonary embolism and deep vein thrombosis. **A,** Contrast-enhanced helical CT shows bilateral large filling defects consistent with pulmonary emboli (*arrows*). **B,** A pelvic CT image made without additional contrast material shows bilateral filling defects in the common femoral veins consistent with venous thrombi (*arrows*).

from 95% to 99%.[215,216] Importantly, it has been suggested that further diagnostic testing should be pursued when MSCT pulmonary angiography results (with or without indirect CT venography, see later) are discordant with the clinical probability for pulmonary embolism, particularly when MSCT results are negative and the clinical probability of pulmonary embolism is considered high.[215]

Various investigations also suggest that both spiral CT and MSCT may also be able to detect deep venous thrombosis in the proximal leg and pelvic veins without injection of additional contrast material (Fig. 19-57), a technique known as indirect CT venography.[217,218] The addition of CT venography to thoracic MSCT studies obtained for the evaluation of suspected pulmonary embolism allows for the simultaneous evaluation of deep venous thrombosis and pulmonary embolism with a single test. Combining MSCT with CT venography increased the sensitivity for the diagnosis of pulmonary embolism to 90% and the negative predictive value of the combination of the examinations was 97% in the PIOPED II trial.[215]

Like MSCT, MRI can demonstrate pulmonary embolism directly as intravascular filling defects on cross-sectional images (Fig. 19-58).[219] Experience with MRI in patients suspected of having pulmonary embolism is far more limited than that with CT. The two techniques are probably overall roughly similar in accuracy for the detection of pulmonary embolism, although MRI may show more pronounced interobserver variability than CT and may show slightly decreased sensitivity compared with CT at the segmental and subsegmental vascular levels. MRI has been shown to be highly accurate for detecting deep venous thrombosis.[220,221]

The potential advantages of MRI are the lack of need for iodinated contrast material or ionizing radiation, ability to image the pulmonary arteries and deep venous system in a single examination, and potentially, the ability to perform perfusion imaging. The latter point is of particular significance in light of the imperfect sensitivity of CT. The advantages of MSCT are higher spatial resolution, wider availability, fewer artifacts, faster examination time, and simpler, more robust technology as well as, importantly, the availability of alternative diagnoses for patients with negative results. Currently, MSCT is a realistic option in the clinical management of patients with suspected pulmonary embolism; the clinical use of MRI is limited to medical centers with personnel who are highly skilled with advanced MRI technology.

Acquired Aortic Disease

Acquired aortic diseases, such as aortic dissection, can be imaged with aortography, CT angiography, echocardiography, and MRI.[222] Transthoracic echocardiography can assess the ascending aorta, but its limited field of view restricts its utility. Transesophageal echocardiography has produced definitive results,[223] but this technique requires sedation and carries the risk of esophageal injury. Aortography has previously been considered the standard method for demonstrating aortic dissection, but it is invasive, and both false-positive and (more commonly) false-negative results occur.[222] It has largely been replaced by cross-sectional imaging methods for the evaluation of aortic pathology.

CT angiography can accurately identify the intimal flap, the true and false lumens (Fig. 19-59), the vessels involved by dissection, and the presence of end-organ perfusion impairment; thus, CT angiography is used routinely for evaluating aortic dissection. Complications of dissection, such as mediastinal hematoma, hemothorax, and hemopericardium, can also be detected. Limitations of CT include the need for iodinated contrast material and its limited ability to assess aortic valve function (information that some surgeons require and others do not). The latter concern has been alleviated somewhat with the development of retrospectively

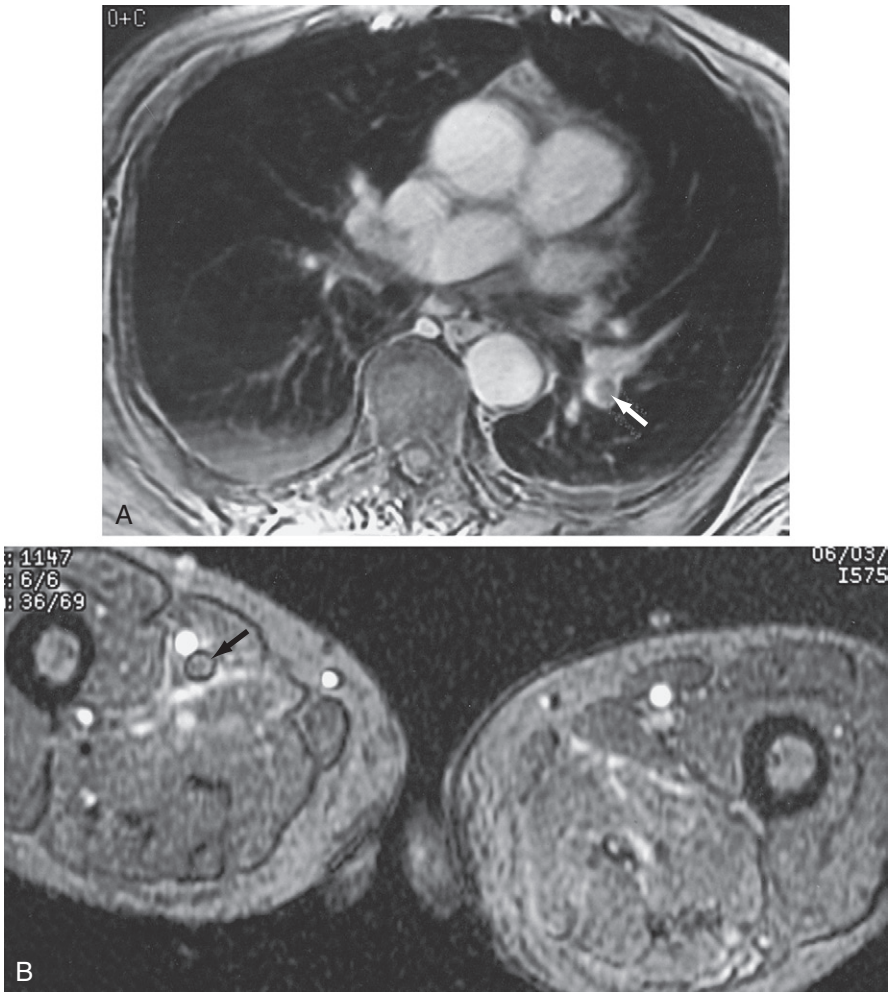

FIGURE 19-58 ■ MRI demonstrates pulmonary embolism and deep vein thrombosis. **A,** This contrast-enhanced magnetic resonance (MR) image shows a filling defect consistent with pulmonary embolus in the left lower lobe artery (*arrow*). **B,** This MR image made without contrast material shows a filling defect in the right superficial femoral vein consistent with venous thrombus (*arrow*), while the contralateral vein is patent and without filling defects.

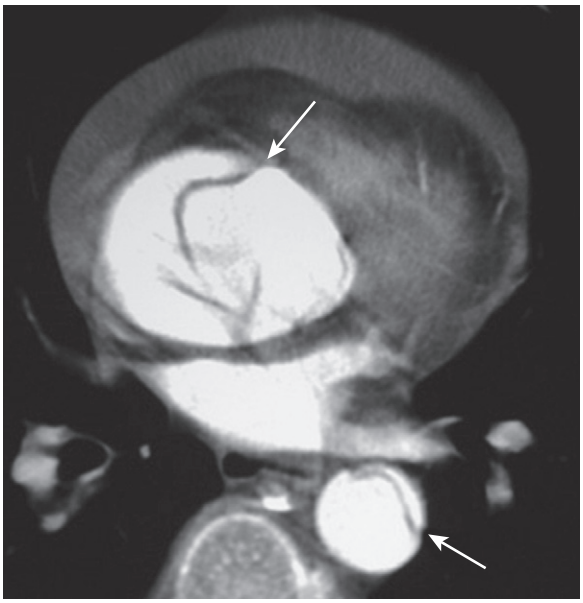

FIGURE 19-59 ■ Thoracic CT angiography in a patient with Stanford type A aortic dissection shows an intimal flap (*arrows*) in the ascending and descending thoracic aorta. Note dilation of the ascending aorta.

electrocardiographic-gated MSCT angiography of the aorta. With this technique, the imaging acquisition is conducted simultaneously with the electrocardiographic tracing, and data can then be reconstructed at any time during the cardiac cycle. Images reconstructed during late diastole often are motion free and allow assessment of the coronary arteries and aortic valve (Fig. 19-60).

MRI has several advantages in suspected aortic dissection. No iodinated contrast material is required (Fig. 19-61), and MRI does not require ionizing radiation. Cine-MRI can assess aortic valve and left ventricular function. However, MRI also has limitations in the assessment of dissections. Some patients are excluded from MRI for safety reasons. MRI examinations usually require more time than MSCT studies for dissection. Artifacts lead to nondiagnostic studies more often with MRI than with MSCT. Greater experience is required to interpret MR images accurately.

The relative accuracy of aortography, transesophageal echocardiography, MSCT, and MRI for detecting and characterizing dissections has not been established by definitive prospective clinical trials. For practical reasons, such a trial is not likely to be conducted. Accordingly, which technique is superior is arguable, and judgment

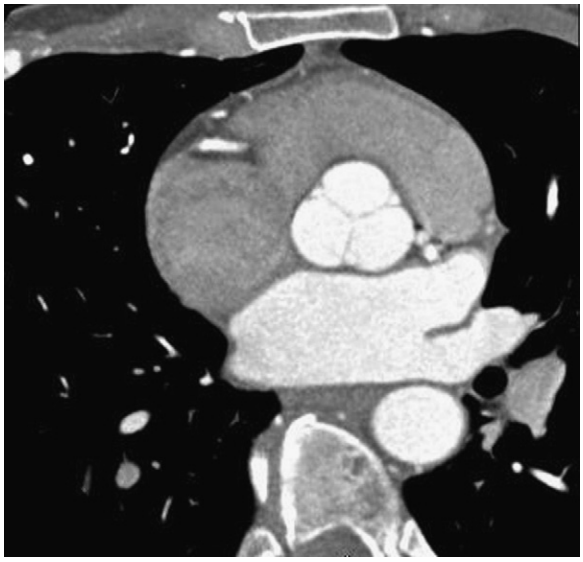

FIGURE 19-60 ■ Value of retrospectively gated thoracic CT angiography for the evaluation of the aorta. Axial CT angiography image obtained with retrospective electrocardiographic (ECG) gating (image reconstructed during diastole) shows a motion-free image. Note clarity of the aortic valve cusps. Compare with the nongated CT angiography image in Figure 19-59.

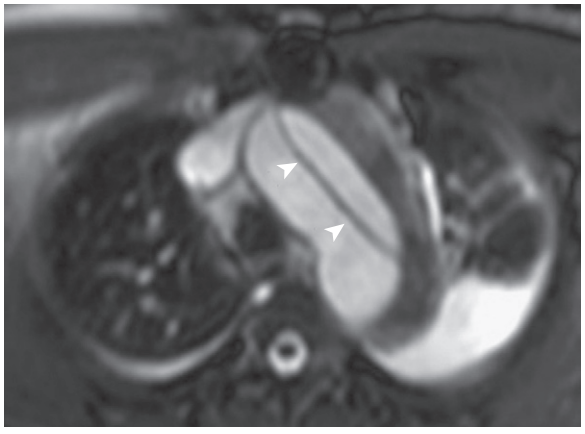

FIGURE 19-61 ■ This patient had symptoms classic for aortic dissection. "White blood" cine MR images show an intimal flap within the aortic arch (*arrowheads*), consistent with aortic dissection.

is required for individual cases. Aortography is the time-tested gold standard, but it is invasive and known to be inaccurate, particularly in cases with thrombosed false lumina, and has largely been replaced by cross-sectional methods. Extensive data indicate that both MSCT and MRI are accurate in evaluating dissections.[224] Our experience is that MSCT and MRI have equivalent accuracy for detecting dissection and that both are more sensitive than aortography. However, no single technique always fulfills all of the requirements for characterization of dissections. Several reports suggest that hemodynamically unstable patients with suspected aortic dissection should be studied with transesophageal echocardiography, whereas stable patients should be evaluated by MSCT or MRI.[223,225] MRI is also recommended for serial studies of patients with chronic dissection.

Both MSCT and MRI have advantages over aortography for evaluating thoracic aortic aneurysms. Both are noninvasive, can document that a mediastinal mass is an aneurysm, can assess the thickness of the aortic wall, and can measure accurately the diameter and longitudinal extent of the aneurysm. In most situations, MSCT is sufficient for diagnosis, and because it is less expensive and faster than MRI, it is the preferred study. MRI is particularly useful for patients with contraindications to iodinated contrast material.

In suspected traumatic aortic rupture, MSCT aortography has replaced catheter aortogtaphy for initial diagnosis.[226] Catheter aortography is generally reserved for indeterminate MSCT studies or problem-solving cases. Although MRI has been reported in this setting, it is not normally used because the problems of monitoring and sustaining the trauma patient are greater with MRI; in addition, MSCT examinations are substantially faster than MR examinations, and time is of the essence in traumatically injured patients. Chronic pseudoaneurysms (Fig. 19-62) in survivors of traumatic or iatrogenic aortic injury can be evaluated with either MRI or MSCT.

Congenital Anomalies of the Thoracic Great Vessels

Echocardiography, MRI, and angiography are commonly chosen modalities for demonstrating great vessel anomalies, associated cardiac malformations, and their physiologic sequelae in children. CT usefully can demonstrate simple vascular anomalies, such as an aberrant subclavian artery and persistence of the left superior vena cava. The vascular supply of sequestrations can be identified by MRI or CT, and angiography now is rarely needed (see Fig. 19-24). In adults with congenital anomalies of the great vessels, MRI is often the procedure of choice because its field of view is wider than that of echocardiography and it is noninvasive, but in complex lesions, these techniques often are complementary. MSCT is also a very effective tool for the investigation of adult and pediatric congenital cardiovascular abnormalities.

Published experience with MRI in developmental anomalies of the great vessels has focused on aortic coarctation and pulmonary artery obstruction, but extensive investigations of the utility of MR techniques for other vascular abnormalities, including extracardiac shunts and partial anomalous pulmonary venous return, have been performed. Coarctation is detected accurately by MRI (Fig. 19-63) or MSCT angiography. Complications of treatment, including restenosis and aneurysm, can be detected,[227,228] and the degree of collateral vascular supply, which affects the risk of surgery, can be established with either technique. The pressure gradient across the coarctation and the relative increase in blood flow distal to the coarctation may be quantified by MRI. Such calculations also provide quantitative data

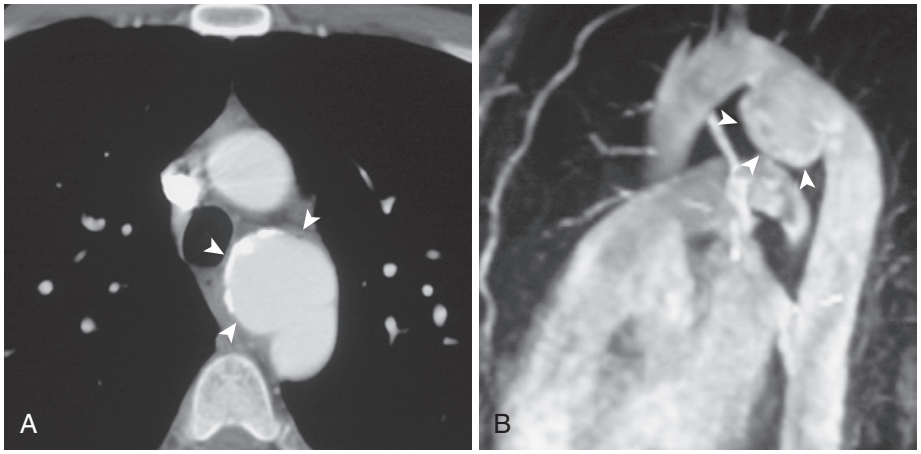

FIGURE 19-62 ■ Chronic pseudoaneurysm in a long-term survivor with undiagnosed traumatic aortic injury 17 years earlier. **A,** Contrast-enhanced CT image at the level of the aortic arch reveals a pseudoaneurysm (*arrowheads*); note calcification along the medial wall of the lesion. **B,** Oblique sagittal three-dimensional MR angiography image shows the pseudoaneurysm (*arrowheads*) to advantage.

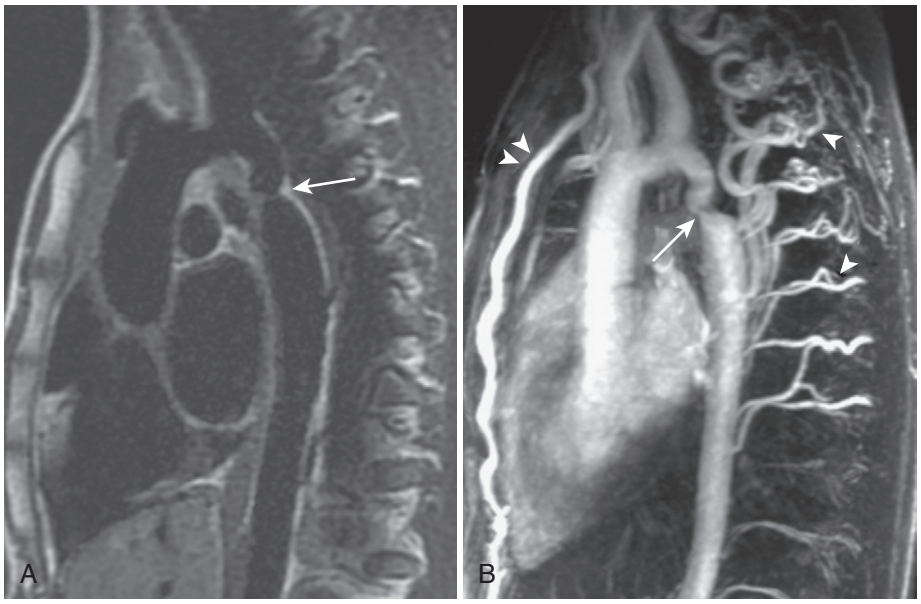

FIGURE 19-63 ■ Value of MRI in the assessment of congenital cardiovascular diseases: aortic coarctation. **A**, Oblique sagittal T1-weighted spin-echo image of the thoracic aorta shows focal, severe narrowing of the proximal descending thoracic aorta (*arrow*) consistent with aortic coarctation. **B,** Oblique sagittal volume-rendered image shows coarctation (*arrow*) as well as collateral vessel formation. The latter derive from intercostal (*single arrowheads*), internal mammary (*double arrowheads*), and chest wall arteries and indicate the presence of a significant pressure gradient across the coarctation.

regarding the efficacy of operative and percutaneous interventions.

MRI is the noninvasive imaging procedure of choice for detecting central pulmonary artery obstruction,[229] evaluating the potential for palliative shunts, and assessing the results of surgery,[228] although MSCT angiography is very useful as well. Comparisons of MRI with transthoracic echocardiography usually have shown MRI to be superior for demonstration of great vessel anomalies. Diagnosis of a variety of other congenital vascular anomalies by MRI and MSCT angiography also has been reported.

Pleural Disease

Most pleural processes can be imaged accurately and cost-effectively with conventional radiography or ultrasonography. However, CT, including single-slice spiral, multislice, and HR, can be useful in several clinical problems relating to the pleura.[24,80,230] These include differentiation of pleural and parenchymal disease (including the distinction between lung abscess and empyema); detection of subtle pleural abnormalities (such as early pleural plaques or small pneumothoraces); location of pleural fluid collections and pleural tumors, including

localization for interventional purposes (e.g., tube drainage or biopsy); determination of the extent of pleural tumors (in particular, metastases and mesothelioma); and occasionally, characterization of pleural lesions (Figs. 19-64 and 19-65; see also Fig. 19-32) or paradiaphragmatic lesions. MRI currently has a limited role in the evaluation of pleural abnormalities.

Type of Fluid

Most effusions appear to be near to water in attenuation. CT numbers cannot be used to predict the specific gravity of the fluid or its cause. One exception, however, is acute or subacute hemothorax. Hemothorax can sometimes appear inhomogeneous in attenuation, with some areas having an attenuation value higher than that of water.

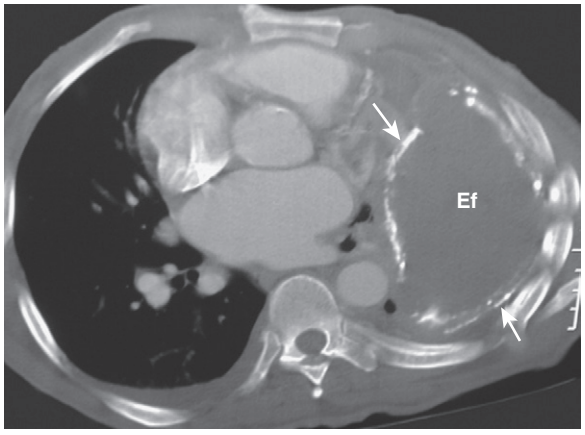

FIGURE 19-64 ■ Thoracic CT performed in a patient with a history of tuberculosis shows pleural thickening and calcification (*arrows*) and a residual pleural effusion (Ef) indicative of empyema.

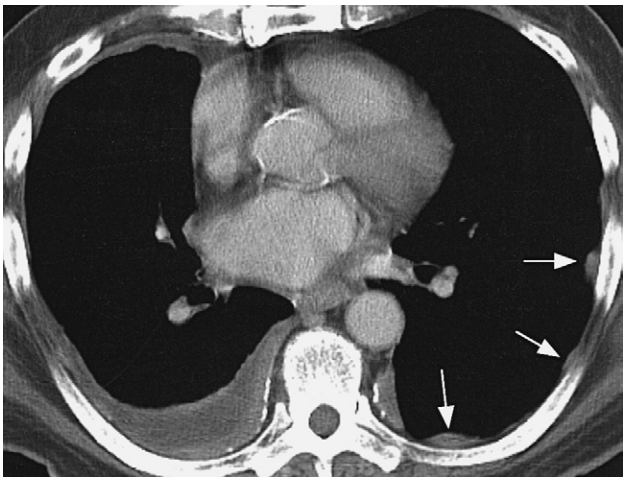

FIGURE 19-65 ■ A patient with prior asbestos exposure has focal areas of pleural thickening or pleural plaques within the left hemithorax (*arrows*). Pleural thickening on the right is associated with pleural effusion. This reflects the presence of early malignant mesothelioma.

The presence of pleural thickening is often of value in predicting the nature of the effusion. In patients with effusion, the presence of pleural thickening on CT indicates that the effusion is an exudate.[80] By definition, the pleura is considered thickened if it is visible on a contrast-enhanced or unenhanced CT. Transudates are never associated with pleural thickening. Conversely, the absence of pleural thickening on contrast-enhanced CT is less helpful. In this case, the effusion can be an exudate or transudate. Only about 60% of exudates are associated with visible pleural thickening. However, the absence of pleural thickening on a contrast-enhanced scan rules out empyema; empyema is always associated with parietal pleural thickening on contrast-enhanced CT.

Pleural versus Parenchymal Disease

Chest radiography may not be able to distinguish between parenchymal disease, pleural disease, and pathology affecting both compartments. CT can be useful in this setting. Pleural lesions typically have obtuse tapering margins and sharp interfaces with adjacent lung parenchyma, whereas parenchymal lesions tend to blend with lung parenchyma and have acute, irregular margins. One of the more common and therapeutically important problems in this category is differentiating lung abscess from empyema. Empyemas typically have smooth outer and inner margins, a lenticular shape, and a sharp interface with underlying lung; they tend to displace pulmonary vessels around them and often display prominent rim enhancement (the "split pleura sign") with intravenous administration of iodinated contrast material (see Fig. 19-64). Lung abscesses are characterized by spherical or polygonal shape, a thick wall with a shaggy or irregular inner margin, and permeation between adjacent pulmonary vessels. None of these features is unique, but when considered together, they permit categorization of the abnormality in most cases.

Early Detection

The contrast resolution and cross-sectional format of CT make it highly sensitive and accurate in detecting pleural thickening and early pleural plaques in patients with asbestos-related pleural disease (see Fig. 19-65).[24,128] Circumscribed plaques often are missed on chest radiographs unless they are calcified or attain a thickness of about 5 mm or more. Furthermore, normal extrapleural soft tissues and fat can be misinterpreted as plaques when they are prominent on chest radiography. Both standard CT and HRCT are accurate for detecting pleural plaques, but HRCT may be more accurate for characterizing subtle plaques.

CT has been shown to be accurate and more sensitive than conventional radiographs in detecting pneumothoraces. This can be of particular importance in trauma patients, who may require intubation and positive-pressure ventilation.

KEY POINTS

- After the medical history and physical examination, radiography is the most commonly used technique in the evaluation of patients with known or suspected thoracic disease.
- Most clinical questions can be answered by careful review of high-quality frontal and lateral chest radiographs. Currently available techniques of digital recording of images offer many interpretive and logistical advantages.
- When needed, higher-quality resolution of known or suspected abnormalities is available by CT, particularly by MSCT, which has rapid acquisition time and greatly improved resolution; MSCT has become the imaging method of choice for further evaluation of pulmonary nodule(s), lung cancer, mediastinal abnormalities, diffuse lung diseases, airway diseases, and suspected pulmonary embolism.
- MRI is useful in evaluating superior sulcus lesions, brachial plexopathy, and certain cardiac and mediastinal abnormalities. MRI is also useful, though less often used than MSCT, for evaluating suspected aortic dissection and pulmonary embolism.
- Further information about the application of radiographic techniques and the results of these studies is presented in the chapters concerning specific pulmonary diseases that appear later in this book.

References

1. Ravin CE, Chotas HG: Chest radiography. Radiology 204:593–600, 1997.
2. American College of Radiology: American College of Radiology practice guideline for digital radiography. *In* Practice Guidelines and Technical Standards. Reston, VA: American College of Radiology, 2007, pp 23–57.
3. American College of Radiology: American College of Radiology appropriateness criteria: Expert panels on thoracic imaging and cardiovascular imaging. *In* American College of Radiology Appropriateness Criteria. Reston, VA: American College of Radiology, 2005.
4. MacMahon H, Giger M: Portable chest radiography techniques and teleradiology. Radiol Clin North Am 34:1–20, 1996.
5. Butler PF, Conway BJ, Suleiman OH, et al: Chest radiography: A survey of techniques and exposure levels currently used. Radiology 156:533–536, 1985.
6. Revesz G, Shea FJ, Kundel HL: The effects of kilovoltage on diagnostic accuracy in chest radiography. Radiology 142:615–618, 1982.
7. American College of Radiology: American College of Radiology practice guideline for the performance of pediatric and adult chest radiography. *In* Practice Guidelines and Technical Standards. Reston, VA: American College of Radiology, 2007, pp 301–306.
8. Henschke CI, Pasternack GS, Schroeder S, et al: Bedside chest radiography: Diagnostic efficacy. Radiology 149:23–26, 1983.
9. Henschke CI, Yankelevitz DF, Wand A, et al: Accuracy and efficacy of chest radiography in the intensive care unit. Radiol Clin North Am 34:21–31, 1996.
10. Miller WT Sr: The chest radiograph in the intensive care unit. Semin Roentgenol 32:89–101, 1997.
11. Wiener MD, Garay SM, Leitman BS, et al: Imaging of the intensive care unit patient. Clin Chest Med 12:169–198, 1991.
12. Korner M, Weber CH, Wirth S, et al: Advances in digital radiography: Physical principles and system overview. Radiographics 27:675–686, 2007.
13. Volpe JP, Storto ML, Andriole KP, et al: Artifacts in chest radiographs with a third-generation computed radiography system. AJR Am J Roentgenol 166:653–657, 1996.
14. Aberle DR, Hansell D, Huang HK: Current status of digital projectional radiography of the chest. J Thorac Imaging 5:10–20, 1990.
15. Fuhrman CR, Gur D, Good B, et al: Storage phosphor radiographs vs conventional films: Interpreters' perceptions of diagnostic quality. AJR Am J Roentgenol 150:1011–1014, 1988.
16. Kido S, Ikezoe J, Takeuchi N, et al: Interpretation of subtle interstitial lung abnormalities: Conventional versus storage phosphor radiography. Radiology 187:527–533, 1993.
17. MacMahon H, Doi K, Sanada S, et al: Data compression: Effect on diagnostic accuracy in digital chest radiography. Radiology 178:175–179, 1991.
18. Schaefer CM, Greene R, Oestmann JW, et al: Digital storage phosphor imaging versus conventional film radiography in CT-documented chest disease. Radiology 174:207–210, 1990.
19. Sagel SS, Evens RG, Forrest JV, et al: Efficacy of routine screening and lateral chest radiographs in a hospital-based population. N Engl J Med 291:1001–1004, 1974.
20. Austin JH: The lateral chest radiograph in the assessment of nonpulmonary health and disease. Radiol Clin North Am 22:687–698, 1984.
21. Grenier P, Cordeau MP, Beigelman C: High-resolution computed tomography of the airways. J Thorac Imaging 8:213–229, 1993.
22. Goodman LR, Lipchik RJ, Kuzo RS: Acute pulmonary embolism: The role of computed tomographic imaging. J Thorac Imaging 12:83–86, 1997 [discussion 86–102].
23. Value of the ventilation/perfusion scan in acute pulmonary embolism. Results of the Prospective Investigation Of Pulmonary Embolism Diagnosis (PIOPED). The PIOPED Investigators. JAMA 263:2753–2759, 1990.
24. McLoud TC, Flower CD: Imaging the pleura: Sonography, CT, and MR imaging. AJR Am J Roentgenol 156:1145–1153, 1991.
25. Suzuki N, Saitoh T, Kitamura S: Tumor invasion of the chest wall in lung cancer: Diagnosis with US. Radiology 187:39–42, 1993.
26. Yang PC, Luh KT, Chang DB, et al: Value of sonography in determining the nature of pleural effusion: Analysis of 320 cases. AJR Am J Roentgenol 159:29–33, 1992.
27. vanSonnenberg E, Nakamoto SK, Mueller PR, et al: CT- and ultrasound-guided catheter drainage of empyemas after chest-tube failure. Radiology 151:349–353, 1984.
28. Yang PC, Luh KT, Sheu JC, et al: Peripheral pulmonary lesions: Ultrasonography and ultrasonically guided aspiration biopsy. Radiology 155:451–456, 1985.
29. Mahesh M: Search for isotropic resolution in CT from conventional through multiple-row detector. Radiographics 22:949–962, 2002.
30. Mahesh M, Cody DD: Physics of cardiac imaging with multiple-row detector CT. Radiographics 27:1495–1509, 2007.
31. Katayama H, Yamaguchi K, Kozuka T, et al: Adverse reactions to ionic and nonionic contrast media. A report from the Japanese Committee on the Safety of Contrast Media. Radiology 175:621–628, 1990.

31a. Davenport MS, Cohan RH, Caoili EM, et al: Repeat contrast medium reactions in premedicated patients: frequency and severity. Radiology 253:372–379, 2009.
32. Mettler FA Jr, Bhargavan M, Faulkner K, et al: Radiologic and nuclear medicine studies in the United States and worldwide: frequency, radiation dose, and comparison with other radiation sources—1950–2007. Radiology 253:520–531, 2009.
33. Pierce DA, Shimizu Y, Preston DL, et al: Studies of the mortality of atomic bomb survivors. Report 12, Part I. Cancer: 1950–1990. Radiat Res 146:1–27, 1996.
34. Klein JS, Zarka MA: Transthoracic needle biopsy. Radiol Clin North Am 38:235–266, vii, 2000.
35. Moore EH: Percutaneous lung biopsy: An ordering clinician's guide to current practice. Semin Respir Crit Care Med 29:323–334, 2008.
36. Heelan RT, Demas BE, Caravelli JF, et al: Superior sulcus tumors: CT and MR imaging. Radiology 170:637–641, 1989.
37. Tigges S, Roberts DL, Vydareny KH, et al: Routine chest radiography in a primary care setting. Radiology 233:575–578, 2004.
38. Muhm JR, Miller WE, Fontana RS, et al: Lung cancer detected during a screening program using four-month chest radiographs. Radiology 148:609–615, 1983.
39. Winer-Muram HT: The solitary pulmonary nodule. Radiology 239:34–49, 2006.
40. Bekemeyer WB, Crapo RO, Calhoon S, et al: Efficacy of chest radiography in a respiratory intensive care unit. A prospective study. Chest 88:691–696, 1985.
41. Greenbaum DM, Marschall KE: The value of routine daily chest x-rays in intubated patients in the medical intensive care unit. Crit Care Med 10:29–30, 1982.
42. Strain DS, Kinasewitz GT, Vereen LE, et al: Value of routine daily chest x-rays in the medical intensive care unit. Crit Care Med 13:534–536, 1985.
43. Graat ME, Hendrikse KA, Spronk PE, et al: Chest radiography practice in critically ill patients: A postal survey in the Netherlands. BMC Med Imaging 6:8, 2006.
44. Hall JB, White SR, Karrison T: Efficacy of daily routine chest radiographs in intubated, mechanically ventilated patients. Crit Care Med 19:689–693, 1991.
45. American College of Radiology: American College of Radiology apporpriateness criteria: Routine chest radiograph. *In* American College of Radiology Appropriateness Criteria. Reston, VA: American College of Radiology, 2008, pp 1–5.
45a. Hejblum G, Chalumeau-Lemonie L, Ioos V, et al: Comparison of routine and on-demand prescription of chest radiographs in mechanically ventilated adults: a multicentre, cluster-randomised, two-period crossover study. Lancet 374:1687–1693, 2009.
46. Butcher BL, Nichol KL, Parenti CM: High yield of chest radiography in walk-in clinic patients with chest symptoms. J Gen Intern Med 8:115–119, 1993.
47. Pratter MR, Curley FJ, Dubois J, et al: Cause and evaluation of chronic dyspnea in a pulmonary disease clinic. Arch Intern Med 149:2277–2282, 1989.
48. Benacerraf BR, McLoud TC, Rhea JT, et al: An assessment of the contribution of chest radiography in outpatients with acute chest complaints: A prospective study. Radiology 138:293–299, 1981.
49. American College of Radiology: American College of Radiology apporpriateness criteria: Chronic dyspnea-suspected pulmonary origin. *In* American College of Radiology Appropriateness Criteria. Reston, VA: American College of Radiology, 2009, pp 1–4.
50. Heckerling PS: The need for chest roentgenograms in adults with acute respiratory illness. Clinical predictors. Arch Intern Med 146:1321–1324, 1986.
51. Niederman MS, Mandell LA, Anzueto A, et al: Guidelines for the management of adults with community-acquired pneumonia. Diagnosis, assessment of severity, antimicrobial therapy, and prevention. Am J Respir Crit Care Med 163:1730–1754, 2001.
52. Zieverink SE, Harper AP, Holden RW, et al: Emergency room radiography of asthma: An efficacy study. Radiology 145:27–29, 1982.
53. Petheram IS, Kerr IH, Collins JV: Value of chest radiographs in severe acute asthma. Clin Radiol 32:281–282, 1981.
54. Blair DN, Coppage L, Shaw C: Medical imaging in asthma. J Thorac Imaging 1:23–35, 1986.
55. Gershel JC, Goldman HS, Stein RE, et al: The usefulness of chest radiographs in first asthma attacks. N Engl J Med 309:336–339, 1983.
56. Sherman S, Skoney JA, Ravikrishnan KP: Routine chest radiographs in exacerbations of chronic obstructive pulmonary disease. Diagnostic value. Arch Intern Med 149:2493–2496, 1989.
57. Tsai TW, Gallagher EJ, Lombardi G, et al: Guidelines for the selective ordering of admission chest radiography in adult obstructive airway disease. Ann Emerg Med 22:1854–1858, 1993.
58. Trotman-Dickenson B, Baumert B: Multidetector-row CT of the solitary pulmonary nodule. Semin Roentgenol 38:158–167, 2003.
59. Swensen SJ, Brown LR, Colby TV, et al: Pulmonary nodules: CT evaluation of enhancement with iodinated contrast material. Radiology 194:393–398, 1995.
60. Swensen SJ, Brown LR, Colby TV, et al: Lung nodule enhancement at CT: Prospective findings. Radiology 201:447–455, 1996.
61. Swensen SJ, Viggiano RW, Midthun DE, et al: Lung nodule enhancement at CT: Multicenter study. Radiology 214:73–80, 2000.
62. Zhang M, Kono M: Solitary pulmonary nodules: Evaluation of blood flow patterns with dynamic CT. Radiology 205:471–478, 1997.
63. Cronin P, Dwamena BA, Kelly AM, et al: Solitary pulmonary nodules: Meta-analytic comparison of cross-sectional imaging modalities for diagnosis of malignancy. Radiology 246:772–782, 2008.
64. Gould MK, Maclean CC, Kuschner WG, et al: Accuracy of positron emission tomography for diagnosis of pulmonary nodules and mass lesions: A meta-analysis. JAMA 285:914–924, 2001.
65. Kim SK, Allen-Auerbach M, Goldin J, et al: Accuracy of PET/CT in characterization of solitary pulmonary lesions. J Nucl Med 48:214–220, 2007.
66. Bryant AS, Cerfolio RJ: The maximum standardized uptake values on integrated FDG-PET/CT is useful in differentiating benign from malignant pulmonary nodules. Ann Thorac Surg 82:1016–1020, 2006.
67. Davis SD: CT evaluation for pulmonary metastases in patients with extrathoracic malignancy. Radiology 180:1–12, 1991.
68. Gross BH, Glazer GM, Bookstein FL: Multiple pulmonary nodules detected by computed tomography: Diagnostic implications. J Comput Assist Tomogr 9:880–885, 1985.
69. Peuchot M, Libshitz HI: Pulmonary metastatic disease: Radiologic-surgical correlation. Radiology 164:719–722, 1987.
70. Klein JS, Webb WR: The radiologic staging of lung cancer. J Thorac Imaging 7:29–47, 1991.
71. Webb WR, Gatsonis C, Zerhouni EA, et al: CT and MR imaging in staging non-small cell bronchogenic carcinoma: Report of the Radiologic Diagnostic Oncology Group. Radiology 178:705–713, 1991.
72. Silvestri GA, Gould MK, Margolis ML, et al: Noninvasive staging of non-small cell lung cancer: ACCP evidenced-based clinical practice guidelines (2nd ed). Chest 132:178S–201S, 2007.
73. Mountain CF: Revisions in the International System for Staging Lung Cancer. Chest 111:1710–1717, 1997.
74. Goldstraw P, Crowly J, Chansky K, et al: The IASLC Lung Cancer Staging Project: proposals for the revision of the TNM stage grouping in the forthcoming (seventh) edition of the TNM classification of malignant tumours. J Thor Oncol 2:706–714, 2007.
75. Glazer HS, Duncan-Meyer J, Aronberg DJ, et al: Pleural and chest wall invasion in bronchogenic carcinoma: CT evaluation. Radiology 157:191–194, 1985.
76. Glazer HS, Kaiser LR, Anderson DJ, et al: Indeterminate mediastinal invasion in bronchogenic carcinoma: CT evaluation. Radiology 173:37–42, 1989.
77. Herman SJ, Winton TL, Weisbrod GL, et al: Mediastinal invasion by bronchogenic carcinoma: CT signs. Radiology 190:841–846, 1994.
78. Pennes DR, Glazer GM, Wimbish KJ, et al: Chest wall invasion by lung cancer: Limitations of CT evaluation. AJR Am J Roentgenol 144:507–511, 1985.
79. Ratto GB, Piacenza G, Frola C, et al: Chest wall involvement by lung cancer: Computed tomographic detection and results of operation. Ann Thorac Surg 51:182–188, 1991.

80. Aquino SL, Webb WR, Gushiken BJ: Pleural exudates and transudates: Diagnosis with contrast-enhanced CT. Radiology 192:803–808, 1994.
81. Mori K, Hirose T, Machida S, et al: Helical computed tomography diagnosis of pleural dissemination in lung cancer: Comparison of thick-section and thin-section helical computed tomography. J Thorac Imaging 13:211–218, 1998.
82. Erasmus JJ, McAdams HP, Rossi SE, et al: FDG PET of pleural effusions in patients with non-small cell lung cancer. AJR Am J Roentgenol 175:245–249, 2000.
83. Kiyono K, Sone S, Sakai F, et al: The number and size of normal mediastinal lymph nodes: A postmortem study. AJR Am J Roentgenol 150:771–776, 1988.
84. Quint LE, Glazer GM, Orringer MB, et al: Mediastinal lymph node detection and sizing at CT and autopsy. AJR Am J Roentgenol 147:469–472, 1986.
85. Gross BH, Glazer GM, Orringer MB, et al: Bronchogenic carcinoma metastatic to normal-sized lymph nodes: Frequency and significance. Radiology 166:71–74, 1988.
86. Mori K, Yokoi K, Saito Y, et al: Diagnosis of mediastinal lymph node metastases in lung cancer. Jpn J Clin Oncol 22:35–40, 1992.
87. Staples CA, Muller NL, Miller RR, et al: Mediastinal nodes in bronchogenic carcinoma: Comparison between CT and mediastinoscopy. Radiology 167:367–372, 1988.
88. McLoud TC, Bourgouin PM, Greenberg RW, et al: Bronchogenic carcinoma: Analysis of staging in the mediastinum with CT by correlative lymph node mapping and sampling. Radiology 182:319–323, 1992.
89. Patterson GA, Ginsberg RJ, Poon PY, et al: A prospective evaluation of magnetic resonance imaging, computed tomography, and mediastinoscopy in the preoperative assessment of mediastinal node status in bronchogenic carcinoma. J Thorac Cardiovasc Surg 94:679–684, 1987.
90. Staples CA, Gamsu G, Ray CS, et al: High resolution computed tomography and lung function in asbestos-exposed workers with normal chest radiographs. Am Rev Respir Dis 139:1502–1508, 1989.
91. Friedman PJ: Lung cancer staging: efficacy of CT. Radiology 182:307–309, 1992.
92. Pearson FG, DeLarue NC, Ilves R, et al: Significance of positive superior mediastinal nodes identified at mediastinoscopy in patients with resectable cancer of the lung. J Thorac Cardiovasc Surg 83:1–11, 1982.
93. Smulders SA, Smeenk FW, Janssen-Heijnen ML, et al: Surgical mediastinal staging in daily practice. Lung Cancer 47:243–251, 2005.
94. Goodgame B, Pillot GA, Yang Z, et al: Prognostic value of preoperative positron emission tomography in resected stage I non-small cell lung cancer. J Thorac Oncol 3:130–134, 2008.
95. Dwamena BA, Sonnad SS, Angobaldo JO, et al: Metastases from non-small cell lung cancer: Mediastinal staging in the 1990s—Meta-analytic comparison of PET and CT. Radiology 213:530–536, 1999.
96. Melek H, Gunluoglu MZ, Demir A, et al: Role of positron emission tomography in mediastinal lymphatic staging of non-small cell lung cancer. Eur J Cardiothorac Surg 33:294–299, 2008.
97. Weder W, Schmid RA, Bruchhaus H, et al: Detection of extrathoracic metastases by positron emission tomography in lung cancer. Ann Thorac Surg 66:886–892, 1998 [discussion, 892–883].
98. Bergin CJ, Healy MV, Zincone GE, et al: MR evaluation of chest wall involvement in malignant lymphoma. J Comput Assist Tomogr 14:928–932, 1990.
99. Bruzzi JF, Komaki R, Walsh GL, et al: Imaging of non-small cell lung cancer of the superior sulcus: Part 2: Initial staging and assessment of resectability and therapeutic response. Radiographics 28:561–572, 2008.
100. Laurent F, Drouillard J, Dorcier F, et al: Bronchogenic carcinoma staging: CT versus MR imaging. Assessment with surgery. Eur J Cardiothorac Surg 2:31–36, 1988.
101. Glazer GM, Gross BH, Aisen AM, et al: Imaging of the pulmonary hilum: A prospective comparative study in patients with lung cancer. AJR Am J Roentgenol 145:245–248, 1985.
102. Hasegawa I, Boiselle PM, Kuwabara K, et al: Mediastinal lymph nodes in patients with non-small cell lung cancer: Ppreliminary experience with diffusion-weighted MR imaging. J Thorac Imaging 23:157–161, 2008.
103. Ohno Y, Hatabu H, Takenaka D, et al: Metastases in mediastinal and hilar lymph nodes in patients with non-small cell lung cancer: Quantitative and qualitative assessment with STIR turbo spin-echo MR imaging. Radiology 231:872–879, 2004.
103a. Morikawa M, Demura Y, Ishizaki T, et al: The effectiveness of 18F-FDG PET/CT combined with STIR MRI for diagnosing nodal involvement in the thorax. J Nucl Med 50:81–87, 2009.
103b. Yeh DW, Lee KS, Han J, et al: Mediastinal nodes in patients with non-small cell lung cancer: MRI findings with PET/CT and pathologic correlation. AJR Am J Roentgenol 193:813–821, 2009.
104. Armington WG, Harnsberger HR, Osborn AG, et al: Radiographic evaluation of brachial plexopathy. AJNR Am J Neuroradiol 8:361–367, 1987.
105. Kori SH, Foley KM, Posner JB: Brachial plexus lesions in patients with cancer: 100 cases. Neurology 31:45–50, 1981.
106. Lederman RJ, Wilbourn AJ: Brachial plexopathy: Recurrent cancer or radiation? Neurology 34:1331–1335, 1984.
107. Cascino TL, Kori S, Krol G, et al: CT of the brachial plexus in patients with cancer. Neurology 33:1553–1557, 1983.
108. Yoshikawa T, Hayashi N, Yamamoto S, et al: Brachial plexus injury: Clinical manifestations, conventional imaging findings, and the latest imaging techniques. Radiographics 26(Suppl 1)S133–S143, 2006.
109. Henschke CI, Yankelevitz DF, Libby DM, et al: Survival of patients with stage I lung cancer detected on CT screening. N Engl J Med 355:1763–1771, 2006.
110. Swensen SJ, Jett JR, Hartman TE, et al: CT screening for lung cancer: Five-year prospective experience. Radiology 235:259–265, 2005.
111. Ahn JM, Lee KS, Goo JM, et al: Predicting the histology of anterior mediastinal masses: Comparison of chest radiography and CT. J Thorac Imaging 11:265–271, 1996.
112. Brown LR, Aughenbaugh GL: Masses of the anterior mediastinum: CT and MR imaging. AJR Am J Roentgenol 157:1171–1180, 1991.
113. Glazer HS, Molina PL, Siegel MJ, et al: High-attenuation mediastinal masses on unenhanced CT. AJR Am J Roentgenol 156:45–50, 1991.
114. Glazer HS, Siegel MJ, Sagel SS: Low-attenuation mediastinal masses on CT. AJR Am J Roentgenol 152:1173–1177, 1989.
115. Glazer HS, Wick MR, Anderson DJ, et al: CT of fatty thoracic masses. AJR Am J Roentgenol 159:1181–1187, 1992.
116. Tanaka O, Kiryu T, Hirose Y, et al: Neurogenic tumors of the mediastinum and chest wall: MR imaging appearance. J Thorac Imaging 20:316–320, 2005.
117. Weinreb JC, Naidich DP: Thoracic magnetic resonance imaging. Clin Chest Med 12:33–54, 1991.
118. Glazer HS, Lee JK, Levitt RG, et al: Radiation fibrosis: Differentiation from recurrent tumor by MR imaging. Radiology 156:721–726, 1985.
119. Lee JK, Glazer HS: Controversy in the MR imaging appearance of fibrosis. Radiology 177:21–22, 1990.
120. Nyman RS, Rehn SM, Glimelius BL, et al: Residual mediastinal masses in Hodgkin disease: Prediction of size with MR imaging. Radiology 170:435–440, 1989.
121. Prince MR, Zhang H, Morris M, et al: Incidence of nephrogenic systemic fibrosis at two large medical centers. Radiology 248:807–816, 2008.
122. Araoz PA, Mulvagh SL, Tazelaar HD, et al: CT and MR imaging of benign primary cardiac neoplasms with echocardiographic correlation. Radiographics 20:1303–1319, 2000.
123. Barakos JA, Brown JJ, Higgins CB: MR imaging of secondary cardiac and paracardiac lesions. AJR Am J Roentgenol 153:47–50, 1989.
124. Casolo F, Biasi S, Balzarini L, et al: MRI as an adjunct to echocardiography for the diagnostic imaging of cardiac masses. Eur J Radiol 8:226–230, 1988.
125. Freedberg RS, Kronzon I, Rumancik WM, et al: The contribution of magnetic resonance imaging to the evaluation of intracardiac

tumors diagnosed by echocardiography. Circulation 77:96–103, 1988.
126. Lund JT, Ehman RL, Julsrud PR, et al: Cardiac masses: Assessment by MR imaging. AJR Am J Roentgenol 152:469–473, 1989.
127. Semelka RC, Shoenut JP, Wilson ME, et al: Cardiac masses: Signal intensity features on spin-echo, gradient-echo, gadolinium-enhanced spin-echo, and TurboFLASH images. J Magn Reson Imaging 2:415–420, 1992.
128. Aberle DR, Gamsu G, Ray CS, et al: Asbestos-related pleural and parenchymal fibrosis: Detection with high-resolution CT. Radiology 166:729–734, 1988.
129. Brauner MW, Grenier P, Mompoint D, et al: Pulmonary sarcoidosis: Evaluation with high-resolution CT. Radiology 172:467–471, 1989.
130. Grenier P, Chevret S, Beigelman C, et al: Chronic diffuse infiltrative lung disease: Determination of the diagnostic value of clinical data, chest radiography, and CT and Bayesian analysis. Radiology 191:383–390, 1994.
131. Grenier P, Valeyre D, Cluzel P, et al: Chronic diffuse interstitial lung disease: Diagnostic value of chest radiography and high-resolution CT. Radiology 179:123–132, 1991.
132. Hartman TE, Primack SL, Muller NL, et al: Diagnosis of thoracic complications in AIDS: Accuracy of CT. AJR Am J Roentgenol 162:547–553, 1994.
133. Mathieson JR, Mayo JR, Staples CA, et al: Chronic diffuse infiltrative lung disease: Comparison of diagnostic accuracy of CT and chest radiography. Radiology 171:111–116, 1989.
134. Muller NL: Computed tomography in chronic interstitial lung disease. Radiol Clin North Am 29:1085–1093, 1991.
135. Muller NL, Miller RR: Computed tomography of chronic diffuse infiltrative lung disease. Part 2. Am Rev Respir Dis 142:1440–1448, 1990.
136. Muller NL, Miller RR: Computed tomography of chronic diffuse infiltrative lung disease. Part 1. Am Rev Respir Dis 142:1206–1215, 1990.
137. Remy-Jardin M, Giraud F, Remy J, et al: Importance of ground-glass attenuation in chronic diffuse infiltrative lung disease: Pathologic-CT correlation. Radiology 189:693–698, 1993.
138. Remy-Jardin M, Giraud F, Remy J, et al: Pulmonary sarcoidosis: Role of CT in the evaluation of disease activity and functional impairment and in prognosis assessment. Radiology 191:675–680, 1994.
139. Webb WR: High resolution lung computed tomography. Normal anatomic and pathologic findings. Radiol Clin North Am 29:1051–1063, 1991.
140. Webb WR: High-resolution computed tomography of the lung: Normal and abnormal anatomy. Semin Roentgenol 26:110–117, 1991.
141. Webb WR: High-resolution computed tomography of obstructive lung disease. Radiol Clin North Am 32:745–757, 1994.
142. Wells AU, Rubens MB, du Bois RM, et al: Serial CT in fibrosing alveolitis: Prognostic significance of the initial pattern. AJR Am J Roentgenol 161:1159–1165, 1993.
143. Young K, Aspestrand F, Kolbenstvedt A: High resolution CT and bronchography in the assessment of bronchiectasis. Acta Radiol 32:439–441, 1991.
144. American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. This joint statement of the American Thoracic Society (ATS), and the European Respiratory Society (ERS) was adopted by the ATS board of directors, June 2001 and by the ERS Executive Committee, June 2001. Am J Respir Crit Care Med 165:277–304, 2002.
145. Itoh H, Murata K, Konishi J, et al: Diffuse lung disease: Pathologic basis for the high-resolution computed tomography findings. J Thorac Imaging 8:176–188, 1993.
146. Webb WR, Stein MG, Finkbeiner WE, et al: Normal and diseased isolated lungs: High-resolution CT. Radiology 166:81–87, 1988.
147. Gotway MB, Reddy GP, Webb WR, et al: High-resolution CT of the lung: Patterns of disease and differential diagnoses. Radiol Clin North Am 43:513–542, viii, 2005.
148. Lynch DA, Webb WR, Gamsu G, et al: Computed tomography in pulmonary sarcoidosis. J Comput Assist Tomogr 13:405–410, 1989.
149. Remy-Jardin M, Beuscart R, Sault MC, et al: Subpleural micronodules in diffuse infiltrative lung diseases: Evaluation with thin-section CT scans. Radiology 177:133–139, 1990.
150. Remy-Jardin M, Degreef JM, Beuscart R, et al: Coal worker's pneumoconiosis: CT assessment in exposed workers and correlation with radiographic findings. Radiology 177:363–371, 1990.
151. Primack SL, Hartman TE, Hansell DM, et al: End-stage lung disease: CT findings in 61 patients. Radiology 189:681–686, 1993.
152. Colby TV, Swensen SJ: Anatomic distribution and histopathologic patterns in diffuse lung disease: Correlation with HRCT. J Thorac Imaging 11:1–26, 1996.
153. Gruden JF, Webb WR, Naidich DP, et al: Multinodular disease: Anatomic localization at thin-section CT—Multireader evaluation of a simple algorithm. Radiology 210:711–720, 1999.
154. Muller NL, Kullnig P, Miller RR: The CT findings of pulmonary sarcoidosis: Analysis of 25 patients. AJR Am J Roentgenol 152:1179–1182, 1989.
155. Im JG, Itoh H, Shim YS, et al: Pulmonary tuberculosis: CT findings—Early active disease and sequential change with antituberculous therapy. Radiology 186:653–660, 1993.
156. Akira M, Higashihara T, Yokoyama K, et al: Radiographic type p pneumoconiosis: High-resolution CT. Radiology 171:117–123, 1989.
157. Akira M, Yokoyama K, Yamamoto S, et al: Early asbestosis: Evaluation with high-resolution CT. Radiology 178:409–416, 1991.
158. Brauner MW, Grenier P, Mouelhi MM, et al: Pulmonary histiocytosis X: Evaluation with high-resolution CT. Radiology 172:255–258, 1989.
159. Gruden JF, Webb WR, Warnock M: Centrilobular opacities in the lung on high-resolution CT: Diagnostic considerations and pathologic correlation. AJR Am J Roentgenol 162:569–574, 1994.
160. Lynch DA, Rose CS, Way D, et al: Hypersensitivity pneumonitis: Sensitivity of high-resolution CT in a population-based study. AJR Am J Roentgenol 159:469–472, 1992.
161. Silver SF, Muller NL, Miller RR, et al: Hypersensitivity pneumonitis: Evaluation with CT. Radiology 173:441–445, 1989.
162. Hansell DM, Bankier AA, MacMahon H, et al: Fleischner Society: Glossary of terms for thoracic imaging. Radiology 246:697–722, 2008.
163. Muller NL, Miller RR: Diseases of the bronchioles: CT and histopathologic findings. Radiology 196:3–12, 1995.
164. Nishimura K, Itoh H: High-resolution computed tomographic features of bronchiolitis obliterans organizing pneumonia. Chest 102:26S–31S, 1992.
165. Leung AN, Miller RR, Muller NL: Parenchymal opacification in chronic infiltrative lung diseases: CT-pathologic correlation. Radiology 188:209–214, 1993.
166. Lynch DA: Ground glass attenuation on CT in patients with idiopathic pulmonary fibrosis. Chest 110:312–313, 1996.
167. Muller NL, Miller RR: Ground-glass attenuation, nodules, alveolitis, and sarcoid granulomas. Radiology 189:31–32, 1993.
168. Remy-Jardin M, Remy J, Deffontaines C, et al: Assessment of diffuse infiltrative lung disease: Comparison of conventional CT and high-resolution CT. Radiology 181:157–162, 1991.
169. Leung AN, Staples CA, Muller NL: Chronic diffuse infiltrative lung disease: Comparison of diagnostic accuracy of high-resolution and conventional CT. AJR Am J Roentgenol 157:693–696, 1991.
170. Kuwano K, Matsuba K, Ikeda T, et al: The diagnosis of mild emphysema. Correlation of computed tomography and pathology scores. Am Rev Respir Dis 141:169–178, 1990.
171. Klein JS, Gamsu G, Webb WR, et al: High-resolution CT diagnosis of emphysema in symptomatic patients with normal chest radiographs and isolated low diffusing capacity. Radiology 182:817–821, 1992.
172. Lenoir S, Grenier P, Brauner MW, et al: Pulmonary lymphangiomyomatosis and tuberous sclerosis: Comparison of radiographic and thin-section CT findings. Radiology 175:329–334, 1990.
173. Moore AD, Godwin JD, Muller NL, et al: Pulmonary histiocytosis X: Comparison of radiographic and CT findings. Radiology 172:249–254, 1989.

174. Templeton PA, McLoud TC, Muller NL, et al: Pulmonary lymphangioleiomyomatosis: CT and pathologic findings. J Comput Assist Tomogr 13:54–57, 1989.
175. Lynch DA, Brasch RC, Hardy KA, et al: Pediatric pulmonary disease: Assessment with high-resolution ultrafast CT. Radiology 176:243–248, 1990.
176. Webb WR: Radiology of obstructive pulmonary disease. AJR Am J Roentgenol 169:637–647, 1997.
177. Arakawa H, Webb WR: Air trapping on expiratory high-resolution CT scans in the absence of inspiratory scan abnormalities: Correlation with pulmonary function tests and differential diagnosis. AJR Am J Roentgenol 170:1349–1353, 1998.
178. Arakawa H, Webb WR: Expiratory high-resolution CT scan. Radiol Clin North Am 36:189–209, 1998.
179. Arakawa H, Webb WR, McCowin M, et al: Inhomogeneous lung attenuation at thin-section CT: Diagnostic value of expiratory scans. Radiology 206:89–94, 1998.
180. Epler GR, McLoud TC, Gaensler EA, et al: Normal chest roentgenograms in chronic diffuse infiltrative lung disease. N Engl J Med 298:934–939, 1978.
181. Gaensler EA, Carrington CB: Open biopsy for chronic diffuse infiltrative lung disease: Clinical, roentgenographic, and physiological correlations in 502 patients. Ann Thorac Surg 30:411–426, 1980.
182. Padley SP, Hansell DM, Flower CD, et al: Comparative accuracy of high resolution computed tomography and chest radiography in the diagnosis of chronic diffuse infiltrative lung disease. Clin Radiol 44:222–226, 1991.
183. Brauner MW, Lenoir S, Grenier P, et al: Pulmonary sarcoidosis: CT assessment of lesion reversibility. Radiology 182:349–354, 1992.
184. Stein MG, Mayo J, Muller N, et al: Pulmonary lymphangitic spread of carcinoma: Appearance on CT scans. Radiology 162:371–375, 1987.
185. Strickland B, Strickland NH: The value of high definition, narrow section computed tomography in fibrosing alveolitis. Clin Radiol 39:589–594, 1988.
186. McLoud TC, Carrington CB, Gaensler EA: Diffuse infiltrative lung disease: A new scheme for description. Radiology 149:353–363, 1983.
187. Aberle DR: HRCT in acute diffuse lung disease. J Thorac Imaging 8:200–212, 1993.
188. Janzen DL, Padley SP, Adler BD, et al: Acute pulmonary complications in immunocompromised non-AIDS patients: Comparison of diagnostic accuracy of CT and chest radiography. Clin Radiol 47:159–165, 1993.
189. Johkoh T, Muller NL, Cartier Y, et al: Idiopathic interstitial pneumonias: Diagnostic accuracy of thin-section CT in 129 patients. Radiology 211:555–560, 1999.
190. Lee KS, Primack SL, Staples CA, et al: Chronic infiltrative lung disease: Comparison of diagnostic accuracies of radiography and low- and conventional-dose thin-section CT. Radiology 191:669–673, 1994.
191. Nishimura K, Izumi T, Kitaichi M, et al: The diagnostic accuracy of high-resolution computed tomography in diffuse infiltrative lung diseases. Chest 104:1149–1155, 1993.
192. Padley SP, Adler B, Muller NL: High-resolution computed tomography of the chest: Current indications. J Thorac Imaging 8:189–199, 1993.
193. Primack SL, Muller NL: High-resolution computed tomography in acute diffuse lung disease in the immunocompromised patient. Radiol Clin North Am 32:731–744, 1994.
194. Gotway MB, Freemer MM, King TE, Jr.: Challenges in pulmonary fibrosis. 1: Use of high resolution CT scanning of the lung for the evaluation of patients with idiopathic interstitial pneumonias. Thorax 62:546–553, 2007.
195. Akira M, Sakatani M, Ueda E: Idiopathic pulmonary fibrosis: Progression of honeycombing at thin-section CT. Radiology 189:687–691, 1993.
196. Lee JS, Im JG, Ahn JM, et al: Fibrosing alveolitis: Prognostic implication of ground-glass attenuation at high-resolution CT. Radiology 184:451–454, 1992.
197. Murdoch J, Muller NL: Pulmonary sarcoidosis: Changes on follow-up CT examination. AJR Am J Roentgenol 159:473–477, 1992.
198. Terriff BA, Kwan SY, Chan-Yeung MM, et al: Fibrosing alveolitis: Chest radiography and CT as predictors of clinical and functional impairment at follow-up in 26 patients. Radiology 184:445–449, 1992.
199. Wells AU, Hansell DM, Corrin B, et al: High resolution computed tomography as a predictor of lung histology in systemic sclerosis. Thorax 47:738–742, 1992.
200. Wells AU, Hansell DM, Rubens MB, et al: The predictive value of appearances on thin-section computed tomography in fibrosing alveolitis. Am Rev Respir Dis 148:1076–1082, 1993.
201. Flaherty KR, Travis WD, Colby TV, et al: Histopathologic variability in usual and nonspecific interstitial pneumonias. Am J Respir Crit Care Med 164:1722–1727, 2001.
202. Bensard DD, McIntyre RC, Jr., Waring BJ, et al: Comparison of video thoracoscopic lung biopsy to open lung biopsy in the diagnosis of interstitial lung disease. Chest 103:765–770, 1993.
203. Wall CP, Gaensler EA, Carrington CB, et al: Comparison of transbronchial and open biopsies in chronic infiltrative lung diseases. Am Rev Respir Dis 123:280–285, 1981.
204. Zompatori M, Sverzellati N, Poletti V, et al: High-resolution CT in diagnosis of diffuse infiltrative lung disease. Semin Ultrasound CT MR 26:332–347, 2005.
205. Boiselle PM: Imaging of the large airways. Clin Chest Med 29:181–193, vii, 2008.
206. Conces DJ Jr, Tarver RD, Vix VA: Broncholithiasis: CT features in 15 patients. AJR Am J Roentgenol 157:249–253, 1991.
207. Grenier P, Lenoir S, Brauner M: Computed tomographic assessment of bronchiectasis. Semin Ultrasound CT MR 11:430–441, 1990.
208. Grenier P, Maurice F, Musset D, et al: Bronchiectasis: assessment by thin-section CT. Radiology 161:95–99, 1986.
209. Hansell DM: Bronchiectasis. Radiol Clin North Am 36:107–128, 1998.
210. Kim JS, Muller NL, Park CS, et al: Cylindrical bronchiectasis: Diagnostic findings on thin-section CT. AJR Am J Roentgenol 168:751–754, 1997.
211. McGuinness G, Naidich DP, Leitman BS, et al: Bronchiectasis: CT evaluation. AJR Am J Roentgenol 160:253–259, 1993.
212. Lynch DA: Imaging of small airways disease and chronic obstructive pulmonary disease. Clin Chest Med 29:165–179, vii, 2008.
213. Gotway MB, Lee ES, Reddy GP, et al: Low-dose, dynamic, expiratory thin-section CT of the lungs using a spiral CT scanner. J Thorac Imaging 15:168–172, 2000.
214. Franquet T, Stern EJ, Gimenez A, et al: Lateral decubitus CT: A useful adjunct to standard inspiratory-expiratory CT for the detection of air-trapping. AJR Am J Roentgenol 174:528–530, 2000.
215. Stein PD, Fowler SE, Goodman LR, et al: Multidetector computed tomography for acute pulmonary embolism. N Engl J Med 354:2317–2327, 2006.
216. Swensen SJ, Sheedy PF 2nd, Ryu JH, et al: Outcomes after withholding anticoagulation from patients with suspected acute pulmonary embolism and negative computed tomographic findings: A cohort study. Mayo Clin Proc 77:130–138, 2002.
217. Goodman LR, Stein PD, Matta F, et al: CT venography and compression sonography are diagnostically equivalent: Data from PIOPED II. AJR Am J Roentgenol 189:1071–1076, 2007.
218. Loud PA, Katz DS, Bruce DA, et al: Deep venous thrombosis with suspected pulmonary embolism: Detection with combined CT venography and pulmonary angiography. Radiology 219:498–502, 2001.
219. Fink C, Ley S, Schoenberg SO, et al: Magnetic resonance imaging of acute pulmonary embolism. Eur Radiol 17:2546–2553, 2007.
220. Evans AJ, Sostman HD, Knelson MH, et al: 1992 ARRS Executive Council Award. Detection of deep venous thrombosis: prospective comparison of MR imaging with contrast venography. AJR Am J Roentgenol 161:131–139, 1993.
221. Evans AJ, Sostman HD, Witty LA, et al: Detection of deep venous thrombosis: Prospective comparison of MR imaging and sonography. J Magn Reson Imaging 6:44–51, 1996.
222. Cigarroa JE, Isselbacher EM, DeSanctis RW, et al: Diagnostic imaging in the evaluation of suspected aortic dissection. Old standards and new directions. N Engl J Med 328:35–43, 1993.

223. Sommer T, Fehske W, Holzknecht N, et al: Aortic dissection: A comparative study of diagnosis with spiral CT, multiplanar transesophageal echocardiography, and MR imaging. Radiology 199:347–352, 1996.
224. Gotway MB, Dawn SK: Thoracic aorta imaging with multisclice CT. Radiol Clin North Am 41:521–543, 2003.
225. Nienaber CA, von Kodolitsch Y, Nicolas V, et al: The diagnosis of thoracic aortic dissection by noninvasive imaging procedures. N Engl J Med 328:1–9, 1993.
226. Steenburg SD, Ravenel JG, Ikonomidis JS, et al: Acute traumatic aortic injury: Imaging evaluation and management. Radiology 248:748–762, 2008.
227. Knauth Meadows A, Ordovas K, Higgins CB, et al: Magnetic resonance imaging in the adult with congenital heart disease. Semin Roentgenol 43:246–258, 2008.
228. Kersting-Sommerhoff BA, Sechtem UP, Fisher MR, et al: MR imaging of congenital anomalies of the aortic arch. AJR Am J Roentgenol 149:9–13, 1987.
229. Strouse PJ, Hernandez RJ, Beekman RH 3rd: Assessment of central pulmonary arteries in patients with obstructive lesions of the right ventricle: Comparison of MR imaging and cineangiography. AJR Am J Roentgenol 167:1175–1183, 1996.
230. Leung AN, Muller NL, Miller RR: CT in differential diagnosis of diffuse pleural disease. AJR Am J Roentgenol 154:487–492, 1990.
231. Lockwood D, Einstein D, Davros W: Diagnostic imaging: Radiation dose and patients' concerns. Cleve Clin J Med 73:583–586, 2006.

CHAPTER 20

ULTRASONOGRAPHY

Devanand Anantham, MRCP • Armin Ernst, MD

INTRODUCTION

BASICS OF ULTRASOUND
Ultrasound Physics
Ultrasound Modes
Transducers
Doppler

ULTRASOUND IMAGE ACQUISITION
Positioning of Patients and Probe
Scan/Probe Orientation
Transducer Probe Handling
Image Acquisition

DIAGNOSTIC THORACIC ULTRASONOGRAPHY
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Pleural Effusions
Pneumothorax
Lung Atelectasis/Consolidation
Pulmonary Edema
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DOCUMENTATION

TRAINING

ADVANTAGES AND DISADVANTAGES OF ULTRASOUND

ENDOBRONCHIAL ULTRASOUND
Radial Endobronchial Ultrasound
Linear Endobronchial Ultrasound–Transbronchial Needle Aspiration Bronchoscope
Setting up an Endobronchial Ultrasound Service

INTRODUCTION

Ultrasonography is a diagnostic tool with expanding indications in pulmonary medicine. Indications include evaluation of pleural effusions and guidance for catheter insertion into the thorax. The analysis of image artifacts has further increased the range of ultrasound in diagnosing pulmonary pathology such as pneumothorax and pulmonary edema. Using endobronchial ultrasound (EBUS) during bronchoscopy, the airways can also be examined allowing sampling of lymph nodes and peripheral lung lesions. Although complete diagnostic ultrasound imaging of the thorax is still not available as part of a routine clinical examination, ultrasonography is being used to answer specific questions in point-of-care or goal-directed scanning.

Ultrasonography has the potential to revolutionize pulmonary practice by extending bedside diagnostic capabilities. Sonographically guided procedures increase the probability of success of procedures in the pleural space and improve diagnostic yields during bronchoscopy. Complications related to pleural interventions are also likely to be reduced. Ultrasonography is easily mastered once the image acquisition and interpretation, as well as the technical jargon (Table 20-1), are learned. These advantages coupled with the radiation-free, portable, and noninvasive properties of ultrasound place this technology in a position to gain widespread application in pulmonary medicine.

BASICS OF ULTRASOUND

Ultrasound Physics

Ultrasound is nonaudible sound energy used for medical applications in a frequency range of 2 to 20 MHz, frequencies that have been found to provide the best combination of penetration and resolution in the body. These frequencies are more than 1000 times greater than the audible range of sound, up to 20 kHz, but obey the same

TABLE 20-1. Glossary of Ultrasound Terminology

Acoustic enhancement	An artifact showing an increase in echogenicity in a region distal to a fluid collection.
Acoustic impedance	A measure of the "resistance" of the medium to the transmission of sound waves from one tissue to another. The difference in acoustic impedance (mismatch) between two tissues determines the reflection of waves at the interface.
Acoustic window	Pathway of an ultrasound beam between the probe and the target.
Acoustic shadow	Anechoic area behind bony structures.
Attenuation	The progressive reduction of amplitude and intensity of a transmitted signal as it moves through a medium.
Artifacts	Images created by physical effects on sound wave propagation not reflecting the presence of actual tissues.
Artifact lines	
Comet-tail artifacts	*Vertical* hyperechoic lines arising from the pleural line.
B lines	Comet-tail artifacts that spread all the way to the edge of the screen without fading.
Z lines	Comet-tail artifacts that fade quickly without reaching the edge of the screen.
Lines	
A lines	*Horizontal* hyperechoic echoes of the pleural line.
Doppler	Technique for imaging moving particles by the detection of a change in the frequency of the reflected ultrasound energy.
Echogenicity	
Hyperechoic	An appearance that is brighter or more white than that of normal solid organ structures such as the liver or spleen.
Hypoechoic	An appearance that is darker or more black than that of normal solid organ structures.
Lung sliding	The "to-and-fro" twinkling movement of the lung during respiration as it slides past the chest wall at the pleural line.
Modes	The means by which reflected ultrasound energy is displayed on the screen. In each case, the time for the energy to be reflected from an object determines the depth of the resultant image on the screen.
A-mode	Amplitude-mode—reflected energy is shown as peaks of different size; not used in thoracic ultrasound.
B-mode	Brightness-mode—reflected energy is displayed as areas of different brightness; used to generate the standard two-dimensional ultrasound image.
M-mode	Motion-mode—reflected energy is shown as areas of brightness traced from left to right on screen with time on the x-axis.
M-mode signs	
Sinusoid sign	A hyperechoic sinusoidal line deep to a pleural effusion that represents movement of the visceral pleura with respiration adjacent to a pleural effusion.
Seashore sign	A grainy "sandy" image with a few horizontal lines denoting the "sea" at the top, a sign that represents aerated lung.
Stratosphere sign	A series of prominent horizontal straight A lines that represent a pneumothorax.
Lung point	A sudden transition from a "seashore" to a "stratosphere" sign, representing the fleeting appearance of aerated lung expanding in inspiration into a pneumothorax. A positive ultrasound sign for pneumothorax.
Pleural line	Horizontal hyperechoic line that corresponds to the interface between the lung and the chest wall.
Resolution	The ability to display two tissue interfaces that are close to each other as separate images.
Time-variable gain	An amplification or gain of reflected ultrasound energy proportional to the timing of the returning signals to enable deeper objects to be as bright as those closer.

physics. As ultrasound waves travel through tissue, they undergo attenuation and are also deflected by scattering, refraction, and reflection; it is the reflection of the waves that forms the basis of the ultrasound images. Reflection depends on the difference in sound transmission characteristics of the tissue, or the impedance, which is a measure of the resistance to propagation of sound waves from one medium to another. In a completely homogeneous tissue, there would be no reflection; at the boundary between two tissue structures with different impedance (i.e., an impedance mismatch), an ultrasound pulse is partially reflected. The greater the difference in acoustic impedance, the greater will be the strength of the reflected ultrasound signal. The difference between acoustic impedance of air and tissue is very high and, at air-tissue interfaces, almost all energy is reflected back; thus a coupling gel is necessary to remove all air from the interface of the transducer and the body to allow ultrasound energy to enter the body. The more minor differences in impedance between body tissues allow partial reflection of waves to impart information about the location and characteristics of the tissues. Signal processing of the reflected energy into a gray-scale image on a screen forms the basis of ultrasound technology.

An ultrasound pulse is generated by the piezoelectric crystals within the transducer probe. When an alternating current is applied, these crystals vibrate to convert electrical energy into mechanical energy and produce an emitting pulse. After the pulse is transmitted, the system awaits the return of reflected signals, which are received by the same piezoelectric crystals in the transducer. Returning ultrasound energy provides two types of information: the amplitude of the signal, which indicates how much energy is reflected, and the timing of the returning signal, which is related to the distance of the target from the emitting probe.

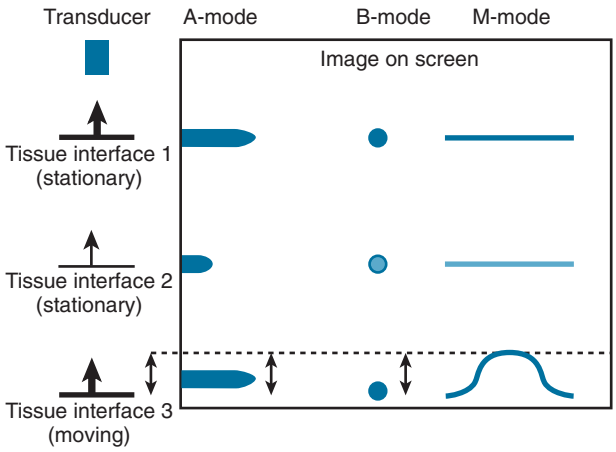

FIGURE 20-1 ■ Generation of images for each ultrasound mode depends on the amplitude of the reflected signal (size of arrow) and the timing of the returning signal (distance from transducer). The amplitude-mode (A-mode) is not currently used in thoracic ultrasonography. The brightness-mode (B-mode) is used to generate the standard two-dimensional image of ultrasound. The motion-mode (M-mode) provides a record of the position over time, allowing the recording of some signs of use in thoracic ultrasound such as the "seashore" sign of normal lung and the "stratosphere" sign of pneumothorax. (Adapted from Stoylen A: Basic ultrasound for clinicians. Available at http://folk.ntnu.no/stoylen/strainrate/Ultrasound. [accessed September 4, 2008].)

Ultrasound Modes

The processing of the reflected signals determines the type of image seen. In the A-mode (or *amplitude* mode), the received amplitude of energy from the transducer is displayed as peaks or waves shown at the distance determined by the depth of the image. This mode is not used currently in thoracic ultrasound. With the B-mode (or *brightness* mode), the amplitude of energy is instead displayed as spots of different brightness, so that a series of B-mode images can be used to produce a conventional two-dimensional ultrasound image. In the M-mode (or *motion* mode), the image of a particular object is traced across the screen by capturing a B-mode image as it sweeps across the screen against a time axis. This provides a single image in which relative positions of images are shown against time on the x-axis (Fig. 20-1).

Transducers

Thoracic ultrasound typically utilizes the 2- to 5-MHz frequency range that provides the optimal compromise between spatial resolution and depth of penetration for thoracic indications. Higher frequencies improve resolution but limit the depth of imaging; lower frequencies visualize with less resolution but to a greater depth. Thoracic ultrasound generally uses curvilinear or convex probes that employ a curved surface to create a scanned field that is wider than the footprint of the probe, producing a sector or fan-shaped image; small footprints can also be achieved with phased array probes with electronic steering. Small footprints enable better access through the narrow acoustic windows available between ribs through which the beam can access deeper tissues. Compared with linear probes, convex transducer probes have a reduced lateral resolution, but the resolution is acceptable for the relative sizes of structures imaged in the chest.

Doppler

Doppler imaging is used to detect motion. Doppler imaging is based on the principle that the frequency of sound increases as the source of sound moves toward an observer and decreases as the source of sound moves away. In pulsed wave Doppler, a pulse is transmitted and the change in frequency of the returning echo is measured at a certain time. Traditionally, a red color on the screen denotes objects moving toward the probe and blue denotes objects moving away from the probe. Optimal imaging for color Doppler is obtained when the transducer is aimed *parallel* to the flow of the target; in contrast, for B-mode and M-mode ultrasound, optimal imaging is produced when the transducer is aimed *perpendicular* to the target.

ULTRASOUND IMAGE ACQUISITION

Positioning of Patients and Probe

In a free pleural space without septations, effusions will collect in the dependent parts of the thorax whereas free air will collect in superior, nondependent locations. Therefore, the positions of the patient and of the ultrasound probe are crucially important to evaluate for these indications. In most thoracic evaluations, the patient is examined sitting upright. Patients who are ill may be examined in the supine or lateral decubitus position but, if so, the patient's position must be taken into consideration when images are interpreted. For systematic evaluation, the hemithorax can be divided into three zones: anterior, lateral, and posterior. These zones are demarcated by the anterior and posterior axillary lines.[1] The anterior zone spans from the anterior axillary line to the sternum, the posterior zone spans the posterior axillary line to the vertebral column, and the lateral zone lies between. For better access to the posterior thorax, supine patients who cannot sit up can be moved to the lateral edge of the bed.

Scan/Probe Orientation

Longitudinal scans through the intercostal spaces (i.e., parallel to the long axis of the body) are preferred to transverse scans both because of convention and because a longitudinal image will generally include the diaphragm for reference. To maintain orientation of the probe and the resulting image, the transducer probe has a ridge or groove. With the groove oriented toward the head of the patient, the resultant image will show the cephalad direction to the left of the screen.

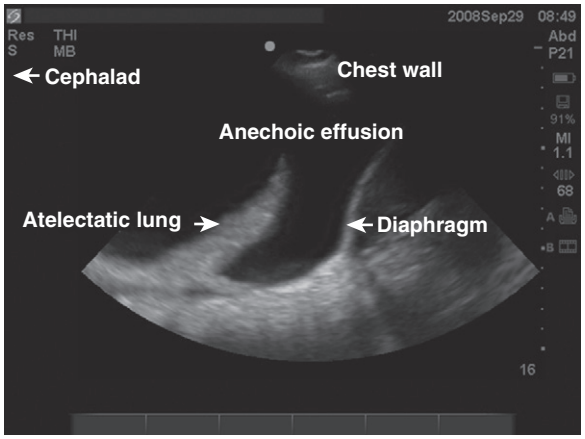

FIGURE 20-2 ■ B-mode image of an anechoic pleural effusion bordered by the hyperechoic diaphragm and an isoechoic atelectatic lung.

Superficial structures will be at the upper part of the screen with deep structures at the bottom of the screen (Fig. 20-2).

Transducer Probe Handling

The probe is held in the dominant hand as one would hold a pen, with the thumb on the orientation groove. The examiner's hand rests against the patient's skin as a support to stabilize the transducer. The probe is moved from intercostal space to intercostal space and moved transversely within intercostal spaces. Because air forms an almost impermeable barrier to ultrasound, air trapping is minimized by using a water-based coupling gel and by holding the probe firmly against the skin. The probe must be kept still during image acquisition to prevent confusion between the movement of the probe and dynamic signs within the thorax.

Image Acquisition

Two parameters need to be adjusted for optimal acquisition of the images: depth and gain. The depth of the field is set according to needs of the ultrasound examination: a 10-cm depth will usually suffice for most thoracic investigations. The gain is set to amplify signals relative to background noise. Increasing the gain makes an image whiter and decreasing the gain makes the image blacker. Time-variable gain enables the operator to amplify ultrasound signals proportional to the depth in order to make deeper structures appear as bright as more superficial structures. Because solid organs such as the normal liver are considered to be of intermediate density (isoechoic), gain can be adjusted with reference to the liver image to make it gray on the screen; other tissues can then be evaluated in comparison to this standard gray image. Although noise filters can improve the quality of imaging solid and liquid structures, the use of such filters can also obliterate the signal artifacts that are crucial to diagnostic analysis of aerated lung.

TABLE 20-2. Basic Interpretation of Ultrasound Images as Either Representing an Anatomic Structure or an Artifact

Image Appearance	Anatomic Structure	Artifact
Black (hypoechoic/ anechoic)	Uncomplicated fluid collection	Acoustic shadows
Gray (isoechoic)	Tissues (e.g., liver, spleen, lymph nodes, consolidation, atelectasis)	Acoustic enhancement (light gray)
	Complicated fluid collections (e.g., hemothorax, empyema)	
White (hyperechoic)	Fat	Aerated lung*
	Calculi	Pneumothorax

*Aerated lung is listed as an artifact in this table because the generated image does not conform to the size or shape of the actual tissue.

DIAGNOSTIC THORACIC ULTRASONOGRAPHY

Two types of images are visualized by ultrasound, either anatomic structures or artifacts[2] (Table 20-2). Anatomic structures are identified based on their location and echogenicity. Echogenicity of body structures can be referenced to solid organs such as the liver that are made to appear gray or isoechoic on the screen. Uncomplicated fluid collections appear darker than these solid organs and are termed "hypoechoic"; if they appear black, they are termed "anechoic." Air appears white and is "hyperechoic." The homogeneity or heterogeneity of echoes also contributes to the recognition of different issues.

Artifacts are images that do not correspond to specific anatomic structures but which can provide useful information if properly recognized. Examples of artifacts are acoustic shadows, acoustic enhancement, and reverberation echoes. Unlike anatomic structures, artifacts tend to move with the movement of the probe and converge toward the near field at the top of the screen. *Acoustic shadows* are anechoic regions that lie behind bony structures such as ribs. Because acoustic shadows provide no ultrasound information, the transducer probe should have an appropriately small footprint to transmit ultrasound pulses between the bony structures and thus avoid them. *Acoustic enhancement* is a hyperechoic region (lighter gray than liver) located distal to a cystic fluid collection; the enhanced region distal to the fluid should not be mistaken for another tissue structure. *Reverberation echoes* are alternating dark and white lines produced when ultrasound beams reflect back and forth between two surfaces, often at an air–soft tissue interface. These echoes produce multiple copy images seen at different depths depending on the number of times the beam was reflected (Fig. 20-3).

Normal Lungs

"Lung sliding" is the key sign used to identify normal lungs[1] (Table 20-3). To identify lung sliding, one first identifies the "pleural line" as a horizontal hyperechoic line located about 0.5 cm below the skin surface corresponding to the interface between the lung and the chest wall.[3] The pleural line is bordered cephalad and caudad by anechoic shadows caused by the ribs. "A lines" are deeper horizontal lines that are reverberation echo artifacts of the pleural line[3] (see Fig. 20-3). Once these lines are identified, lung sliding is seen as the to-and-fro twinkling and movement of the lung adjacent to the pleural line in rhythm with inspiration and expiration. The image above the pleural line on the screen is motionless. Therefore, lung sliding identifies visceral pleura sliding over parietal pleura. An M-mode image of this will show up as a grainy pattern that recedes distally and is termed the "seashore sign"[1] (Fig. 20-4).

Lung sliding is an important sign for identifying normal lung, but it is dependent on technical issues and interpretation. For example, the sign may not be detected

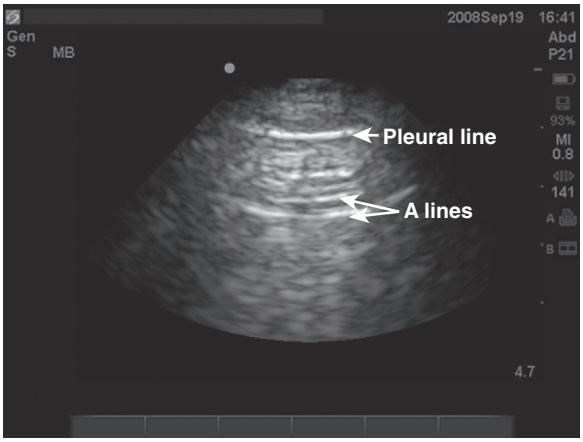

FIGURE 20-3 ■ B-mode image of normal lung with the pleural line and "A lines" indicated. "A lines" are echoes of the pleural line and indicate the presence of an air-soft tissue interface, whether the air is in aerated lung or free in the pleural space (e.g., pneumothorax).

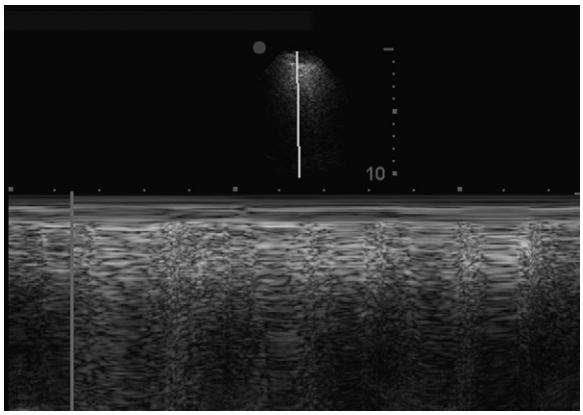

FIGURE 20-4 ■ M-mode image of normal lung show the "seashore sign." The seashore sign is recognized by the grainy texture and is distinguished from the stratosphere sign (see Fig. 20-8) where the grainy quality is absent and only the horizontal lines are seen. *Top,* The B-mode image from which the M-mode is generated.

TABLE 20-3. Ultrasound Signs of the Thorax in Health and Disease

Thoracic Condition	Ultrasound Image
Normal lungs	Lung sliding.
	Isolated comet-tail artifacts (B lines, Z lines).
	A lines.
	Seashore sign on M-mode.
Pleural effusion (free-flowing)	Static, usually anechoic collection that is bordered by the diaphragm, atelectatic lung, and the chest wall.
	Dynamic signs include flapping of atelectatic lung in the effusion and diaphragm movement with respiration allowing an effusion to be distinguished from ascites.
	Sinusoid sign on M-mode showing lung/visceral pleura motion adjacent to an effusion.
Pneumothorax	Absence of lung sliding sign.
	Absence of comet-tail artifacts.
	"Stratosphere" sign and "lung point" on M-mode.
Lung atelectasis/ consolidation	Isoechoic "hepatization" of lung with white lentiform/linear air bronchograms.
	Vascularity within consolidation preserved on color Doppler.
	Atelectasis may present with elevated hemidiaphragm and black (fluid-filled) bronchograms.
Pulmonary edema	Multiple "B lines" seen diffusely throughout thorax.
	Bilateral anechoic pleural effusions.
Diaphragm paresis or paralysis	Diaphragm moving <5 mm or paradoxically in inspiration.
	Loss of lung sliding sign.
	Intrathoracic location of liver or spleen.
Pulmonary embolism	Pulmonary infarcts appearing as peripheral wedge-shaped consolidation with diminished vascularity on color Doppler.
	Ipsilateral hyperechoic (hemorrhagic) effusion.
	(Supportive signs from echocardiography and compression vascular sonography of lower limbs.)

with low-frequency probes below 2.5 MHz.[1] In addition, the amplitude of lung sliding will decrease at the apex of the lung, where movement of the lung is less. Lung sliding can be mimicked by accessory respiratory muscle contractions, although unlike lung sliding, muscle movement will appear superficial to the pleural line. Lung sliding can also be absent in pathologic conditions in which lung motion is impaired such as pleurisy, pleurodesis, pneumothorax, subcutaneous emphysema, apnea and jet ventilation, extreme bronchospasm, extensive pneumonia, and the acute respiratory distress syndrome (ARDS).[3]

Pleural Effusions

Ultrasonography is more sensitive than chest radiography in diagnosing small pleural effusions[4] and is especially effective in distinguishing effusions from lung atelectasis. Pleural effusions can be identified by using both static and dynamic signs. *Static signs* for identifying pleural effusions are the anatomic boundaries of the diaphragm caudally, the chest wall superficially, and atelectatic lung at the bottom of the screen (see Fig. 20-2). Usually, the effusion is a hypoechoic region within these boundaries, but echogenicity cannot be the sole criterion for identifying a pleural effusion. All transudative effusions and some exudative effusions are anechoic in nature, but anechoic regions can also be seen with pleural thickening and abdominal ascites. Echogenic regions cannot be interpreted to mean a lack of effusion because echoes can be seen with complex pleural effusions such as hemothorax or empyema.

Dynamic signs used to identify pleural effusions include movement of the diaphragm adjacent to the effusion and of the lung within the effusion. The diaphragm is identified as a hyperechoic concave structure that descends with inspiration and is bordered caudally by either the liver or the spleen, both isoechoic structures. The position of the diaphragm helps distinguish a pleural effusion from ascites in the hepatorenal recess, where the diaphragm and its movement will not be seen. Of note, caution must be used in interpreting subcostal images because the concave diaphragm has high reflective properties that can lead to artifacts and because the spleen or liver can produce either acoustic shadows, which can be mistaken for effusions, or acoustic enhancement, which can be mistaken for consolidation.[1] Another dynamic sign of pleural effusions that can help avoid these misdiagnoses includes the movement of the lung within the effusion. The flapping of atelectatic lung secondary to cardiac contractions can sometimes be seen. The respiratory movement of the visceral pleura toward the chest wall can be captured on M-mode as a sinusoidal pattern.[1] Sometimes a "curtain" of aerated lung can be seen to slide into and out of smaller effusions.

In the evaluation of pleural effusions, the costal and diaphragmatic pleura should be carefully examined for nodules or masses that may be accessible to percutaneous biopsy (Fig. 20-5). The presence of swirling debris within an effusion in patients with cancer is a predictor of malignant effusions.[5] Color Doppler can be used to enhance the detection of this motion. The presence of pleural septations predicts an increased need for pleural interventions such as fibrinolysis and decortication[6] (Fig. 20-6).

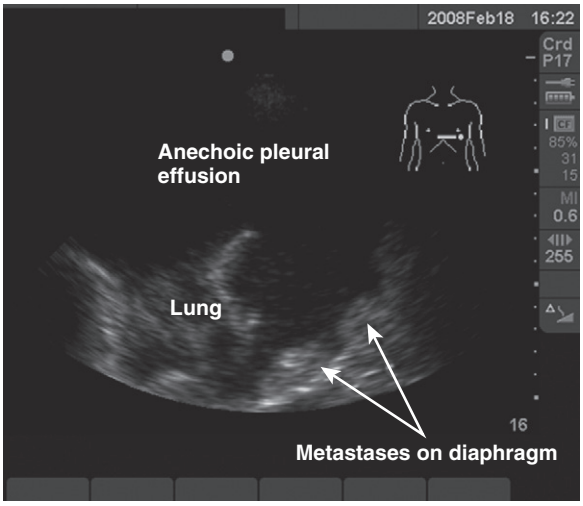

FIGURE 20-5 ■ Diaphragmatic metastases within a large anechoic pleural effusion. The metastases are seen as isoechoic nodules on the diaphragmatic surface.

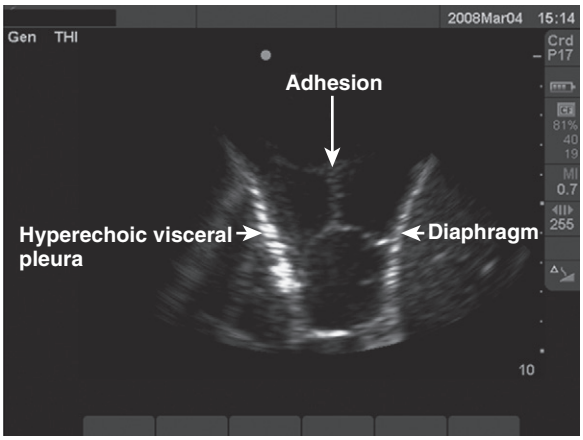

FIGURE 20-6 ■ B-mode image of complicated pleural effusion with adhesions between the hyperechogenic visceral pleura cephalad and the diaphragm caudally.

The use of ultrasonography to quantify the volume of pleural effusions has yet to be established in clinical practice. The size of the thoracic cavity, presence of loculations, position of the diaphragm, and degree of lung collapse all affect ultrasound measurements.[7] Despite these limitations, in supine patients with transverse scans at the posterior axillary line, the distance of maximum separation of parietal and visceral pleura on ultrasound has been shown to correlate better with the volume of thoracentesis drainage than measurements on lateral decubitus chest x-rays.[7,8] For comparison of the size of the same effusion over time, the transducer and the patient must be in exactly the same position for each measurement.

Pneumothorax

Pneumothorax itself has few positive findings; it is generally identified by the absence of the signs of normal aerated lung. As described previously, aerated lung is noted by the presence of the lung sliding sign; the lung is also noted by artifacts called "comet tails," including isolated B lines and Z lines, which are vertical hyperechoic lines that arise from the pleural line and move in synchrony with lung sliding.[1] "B lines" are comet-tail artifacts that spread from the pleural line all the way to edge of the screen without fading[1] (Fig. 20-7). Z lines are similar but, unlike B lines, fade quickly and do not reach the periphery of the screen.[1]

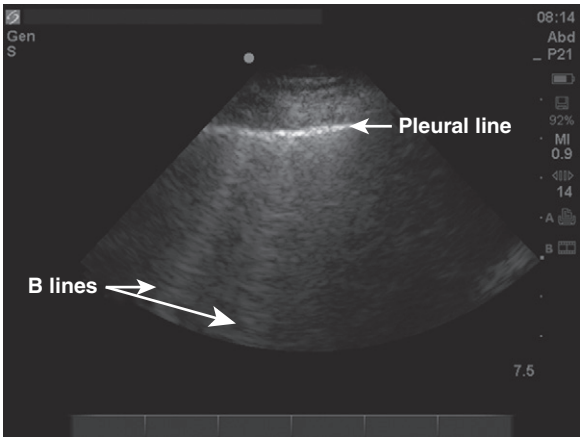

FIGURE 20-7 ■ B-mode ultrasound image shows B-line comet-tail artifacts emanating from the pleural line. Isolated B lines are artifacts found in normal aerated lung; when the B lines are multiple, they are thought to represent increased thickness of the interstitium; when multiple B lines are found diffusely throughout the thorax, they are thought to represent diffuse interstitial thickening as from pulmonary edema, interstitial lung disease, or acute respiratory distress syndrome.

In any ultrasound examination for pneumothorax, the nondependent part of the hemithorax should be scanned. In a pneumothorax, "A lines" representing reverberation echoes of the pleural line will still be seen, but there will be no movement at the pleural line and no evidence of lung sliding or comet-tail artifacts.[9-11] The absence of lung sliding and comet-tail artifacts indicates the presence of pneumothorax with a reported 100% sensitivity and 96.5% specificity.[12] Conversely, the presence of the lung sliding sign basically excludes a pneumothorax, with a reported 100% negative predictive value.[11] In a pneumothorax, multiple accentuated A lines may be seen and this can be captured on M-mode as a series of stratosphere-like horizontal lines (i.e., the stratosphere sign)[1] (Fig. 20-8). The horizontal lines seen in the stratosphere sign characteristic of free air can be contrasted with the grainy pattern prominent in the seashore sign of normal aerated lung (see Fig. 20-4). A pneumothorax can be grossly quantified as large if the loss of both lung sliding and comet tails extends to dependent parts of the thorax. The sudden and fleeting appearance of lung sliding and comet-tail artifacts in an area where they were previously absent may indicate aerated lung expanding intermittently into a moderate-sized pneumothorax. This fleeting appearance if captured on M-mode is termed the "lung point" and has been reported to have 66% sensitivity and 100% specificity for the diagnosis of a pneumothorax.[13] These ultrasound signs when used in combination may diagnose occult pneumothoraces not detected on supine chest x-rays[10,14] and are useful in the evaluation of patients after procedures such as central venous catheter placement, transbronchial lung biopsy, and chest tube clamping. The presence of a pneumothorax must be strongly suspected if comet-tail

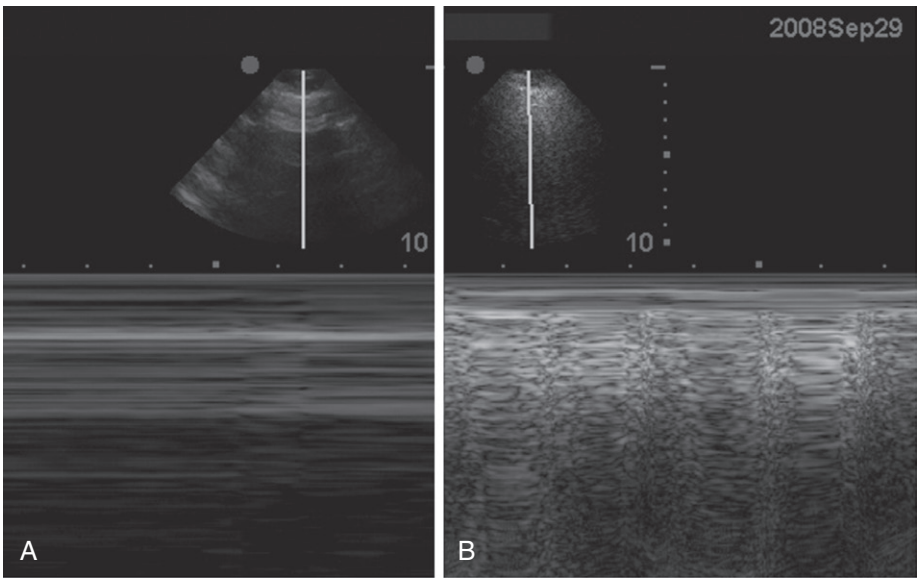

FIGURE 20-8 ■ M-mode image of a pneumothorax shows the "stratosphere sign" (**A**), characterized by multiple horizontal lines without the granularity seen with the normal aerated lung in the "seashore" sign (**B**). *Top,* The B-mode images from which the M-mode images were generated.

artifacts that were present before the procedure are not detected postprocedure.

Errors that can lead to a failure to diagnose pneumothorax include failure to scan in the nondependent parts of the thorax, failure to scan longitudinally, excessive use of noise filters, and an unsteady scanning hand that may give the false impression of lung sliding. A false diagnosis of pneumothorax may arise in patients with chronic obstructive pulmonary disease (COPD), which may mimic pneumothorax on ultrasound. In patients with COPD, the specificity of the diagnosis of pneumothorax is reduced to 71% even among experienced operators, indicating that additional imaging studies are required to confirm a pneumothorax in such patients.[15]

Lung Atelectasis/Consolidation

Alveolar consolidation can be identified on ultrasonography if the area of consolidation extends to the visceral pleura; if not, the intervening aerated lung will generate artifacts that make the diagnosis difficult. In alveolar consolidation, lung sliding will be abolished and a tissue pattern similar to the liver will develop due to the consolidation and "hepatization" of the lung. The superficial boundary of consolidated lung is usually regular and conforms to the visceral pleura whereas the deep border is invariably irregular depending on the extent of consolidation.[16] Air bronchograms may be seen as hyperechoic (white) lentiform or linear shadows that may vary with respiration[17–19] (Fig. 20-9). On color Doppler, branching pulmonary blood vessels may be visualized within the area of consolidation.[20]

These signs together with the absence of a sinusoidal pattern on M-mode indicative of pleural effusion give ultrasound a diagnostic sensitivity of 90% and specificity of 98% in detecting consolidation when compared with computed tomography (CT) scans.[21] A false-positive diagnosis of consolidation may result when complex echogenic pleural effusions or intrathoracic fat is mistaken for consolidation. The size of consolidation is typically smaller on ultrasound than on chest x-rays because the peripheries of a pneumonic area are usually partially air-filled.[22]

Atelectasis is imaged by ultrasound scanning in a way similar to consolidation (see Fig. 20-2). In addition, intercostal spaces may be observed to be narrowed and the hemidiaphragm elevated. If air bronchograms are seen, they do not change size with respiration. If the bronchi are filled with fluid in a postobstructive pneumonia/atelectasis, then fluid bronchograms may been seen as anechoic lentiform shadows within the area of consolidation.[23–25]

Lung abscesses will present as hypoechoic fluid collections with well-defined walls within an area of consolidation.[16] In the center of the abscess, septations or swirling of fluid may be identified.

Pulmonary Edema

The detection of thickened, edematous interlobular septae by ultrasonography can help make the diagnosis of pulmonary edema. Whereas single B lines are found in normal lungs as described, multiple B line comet-tail artifacts are thought to correspond to thickened interlobular septa[1] and multiple B lines that are identified diffusely and bilaterally are very suggestive of pulmonary edema.[16] The diagnosis can be confirmed by the disappearance of this finding with appropriate treatment of heart failure. Finding multiple and diffuse B lines has a diagnostic sensitivity and specificity of 93% when compared with chest radiographs in the diagnosis of alveolar-interstitial pulmonary abnormalities such as pulmonary edema.[26] This ultrasound pattern has also been shown to correlate with NT-ProBNP levels.[27] The total number of B line comet tails in the anterior and lateral chest of supine patients has also been shown to be cor-

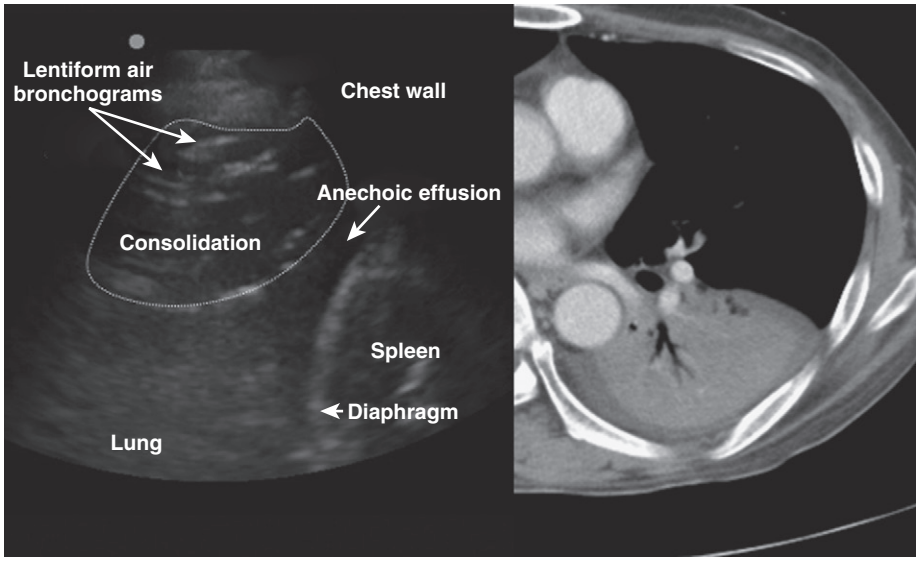

FIGURE 20-9 ■ B-mode image of subpleural consolidation with hyperechoic lentiform shadows corresponding to the air bronchograms seen on the adjacent computed tomography scan of the same patient.

relate with oxygenation levels in patients presenting with high-altitude pulmonary edema.[28]

Nonetheless, other lung diseases such as interstitial lung diseases and ARDS can present with these signs and be mistaken for pulmonary edema[16] because ultrasonography cannot distinguish between interlobular thickening due to edema and thickening due to inflammation or infiltration. Other ultrasonographic findings such as the presence of bilateral anechoic pleural effusions can contribute to the diagnosis of pulmonary edema. Using echocardiography, one can assess cardiac filling pressures, valve function, and left ventricular ejection fraction to confirm the diagnosis and possibly the etiology of the pulmonary edema.

Other Diagnoses

Diaphragmatic dysfunction can be assessed via ultrasound. This can be especially useful in evaluating patients with difficulties in weaning from mechanical ventilation. With inspiration, the normal diaphragm moves caudally 10 to 15 mm.[16] In diaphragmatic dysfunction, the movement of the diaphragm on inspiration may be less than 5 mm and signs of lung motion such as lung sliding may be lost.[16] The diaphragm may also be elevated as identified by an intrathoracic location of either the liver or the spleen.

Pulmonary embolism is suggested by the detection of pleural effusions that may be hyperechoic due to hemorrhage and by peripheral consolidations representing pulmonary infarction. Pulmonary infarcts typically appear as round or triangular pleural-based lesions[29] with evidence of reduced vascularity on color Doppler.[20] Thoracic ultrasonographic findings can be supplemented by compression vascular sonography of the lower limbs to identify deep venous thrombosis. Supportive echocardiographic evaluation would include assessment of right heart function, pulmonary artery pressure, and signs such as McConnell's sign: regional right ventricular dysfunction with akinesia of the mid-free wall but normal wall motion at the apex.[30]

Pulmonary contusion may be diagnosed based on the findings of focal alveolar-interstitial edema (focal area with multiple B lines) in patients within the appropriate clinical context.[31] However, the detection of peripheral parenchymal consolidation may have low sensitivity because the consolidation from contusion varies over time, becoming maximal 24 to 48 hours after the initial injury.[32]

Pleural-based lesions can also be evaluated by ultrasound. In fact, ultrasonography remains one of the best methods to distinguish pleural effusions from pleural thickening.[33] Pleural thickening is visualized as a peel of tissue with no mobile components (i.e., Doppler negative). Calcifications are visualized as hyperechoic regions and may indicate chronic inflammation as from previous tuberculosis. Pleural carcinomatosis is visualized as irregular thickening with isoechoic nodules that may infiltrate the chest wall.[34] In the assessment of patients after pleurodesis, the absence of lung sliding may also help evaluate the efficacy of pleural symphysis.[35]

Ultrasound has been shown to be more accurate than CT scans in assessing chest wall invasion of lung cancers, with a sensitivity and specificity of 89% and 95%.[36] Chest wall involvement can be diagnosed by evidence of tumor growth into the wall, invasion of the ribs with loss of the pleural line in that location, or the absence of lung sliding. Subpleural tumors typically have heterogeneous echogenicity and distorted vascularity as seen on color Doppler imaging.[20,37]

Algorithmic Evaluation of Acute/New-Onset Dyspnea[38] (Fig. 20-10)

Ultrasonography can be used in the evaluation of a patient with new-onset dyspnea. First, the nondependent portions of the thorax should be scanned for lung sliding and comet-tail artifacts as evidence for aerated lung. If absent, then a pneumothorax should be strongly suspected. If lung sliding is present, then the presence of multiple B lines diffusely throughout the thorax would suggest an alveolar-interstitial process such as pulmonary edema or ARDS. Evidence of alveolar consolidation or a large pleural effusion is sought by systematically scanning the thorax. Pulmonary embolism can also be considered based on the surrogate signs described earlier, particularly hyperchoic effusions and peripheral consolidation with decreased vascularity. Although thoracic ultrasound is of limited diagnostic value in airway diseases, there are emerging data supporting its use for diagnosing moderate bronchospasm based on the combination of predominant A lines with the presence of the lung sliding sign.[39] (In severe bronchospasm, lung sliding may be minimal or absent, as described earlier.) Unilateral bronchial intubation results in cessation of aeration

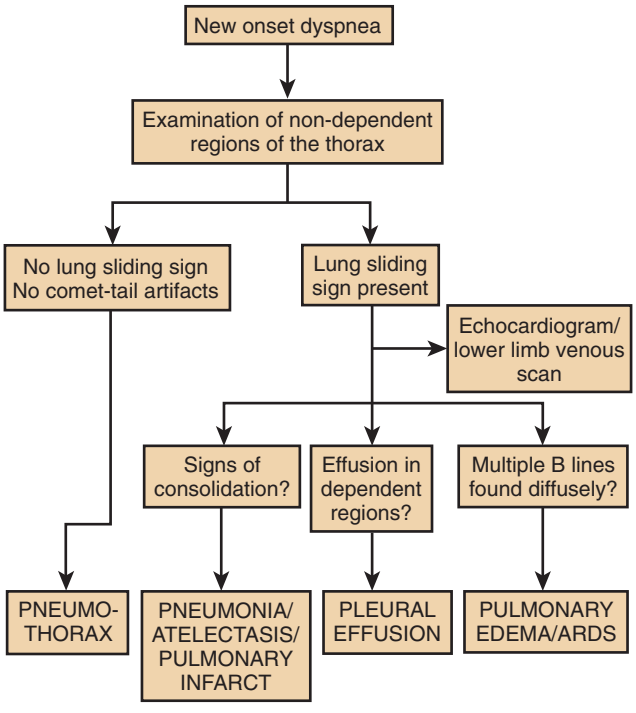

FIGURE 20-10 ■ Algorithmic evaluation of new-onset dyspnea.[38]

to one lung and consequently abolishes lung sliding while causing a transient pulsation of the pleural line in rhythm with cardiac contractions (lung pulse sign), probably caused by the transmission of cardiac contractions through the motionless lung.[40] The thoracic ultrasound evaluation of new-onset dyspnea can be supplemented by lower limb venous thrombosis scanning, as well as echocardiographic evaluation of right and left ventricular function and exclusion of pericardial effusion.

ULTRASOUND-GUIDED INTERVENTIONAL PROCEDURES

Thoracentesis and Pleural Catheter Placement

Ultrasound guidance can be valuable in increasing the success and safety of thoracentesis. Ultrasound-guided thoracentesis can successfully obtain fluid in up to 88% of cases following nonguided "blind" taps that were dry.[41] In the majority of failed blind pleural taps, subsequent examination by ultrasound has shown that the needle had been inserted subdiaphragmatically.[41] By using ultrasound guidance, therefore, operators can avoid puncturing intrathoracic organs such as the lungs, liver, spleen, and heart.[42] Ultrasound guidance can reduce the incidence of iatrogenic pneumothorax from up to 39% in blind thoracentesis to less than 5.4%.[43–48] With ultrasound-guided thoracentesis, the rate of pneumothorax can be kept to as low as 1.3% even in patients on positive-pressure ventilation.[49]

An ultrasonographically-directed thoracentesis is performed by first identifying and marking the target site with the patient positioned comfortably. To reduce the risk of complications, the operator should position the transducer probe so that the thickest portion of the target fluid collection is in the center of the screen. A separation of 10 to 15 mm between the visceral and the parietal pleura is usually deemed adequate to tap safely.[50]

The depth of needle insertion can be estimated on the ultrasound screen but, because the probe compresses near-field soft tissues, this distance can be misjudged. In a real-time procedure, the needle is usually directed at a downward angle of 45 degrees to the long axis of the probe over the rib; the operator attempts to keep the entire length of the needle in view along its trajectory. If the site is marked for a thoracentesis that will be performed at a later time, the patient position must be kept constant to avoid a change in location of the pleural fluid. The patient is then cleaned, draped, and anesthetized and the needle is placed at the same angle as the probe, usually perpendicular, at the target site. The point of entry is ideally superior to the rib to avoid injury to the neurovascular bundle. If catheters are inserted, ultrasonography can be used to confirm the position of catheters. The pleural catheter will appear as a hyperechoic linear structure within an anechoic fluid collection. Postprocedure ultrasound scans of the nondependent chest wall to identify lung sliding and comet-tail artifacts excludes an iatrogenic pneumothorax.[9–12]

Despite ultrasound guidance, taps can occasionally be unsuccessful. Reasons include plugging of the aspiration needle or the presence of loculations or septations preventing free drainage. Operator error due to compression artifacts may result in misjudging the depth of the effusion. The patient may have changed position between the scan and the tap. If a tap is dry, the thoracentesis needle should be withdrawn immediately and the patient rescanned. Repeat scanning enables repositioning of the entry point as well as exclusion of complications such as pneumothorax.

Transthoracic Needle Biopsy

Ultrasound guidance can be used to guide the biopsy of peripheral lung lesions, pleural masses, and anterior mediastinal tumors. Ultrasound enables the identification of the correct angle and depth of biopsy because it can distinguish solid from liquid components of pulmonary lesions. However, transthoracic needle biopsy should be performed only by physicians with expert knowledge both of ultrasonography and of needle biopsy techniques.[51]

Prerequisites for ultrasound-guided transthoracic needle biopsy are the presence of an acoustic window and the absence of overlying structures such as bone or aerated lung. Absolute contraindications include inability of patients to cooperate, to maintain an optimum position, or to control coughing. Uncorrected coagulopathy, thrombocytopenia (platelet count $< 50 \times 10^9$/L), uremia and severe pulmonary hypertension are relative contraindications. Bronchiectatic and chronic cavitary lesions are considered poor candidates for biopsy because of the limited capacity for local tamponade of any bleeding.[51]

The preferred method of biopsy is by the coaxial technique, in which a stylet with an introducer is inserted and biopsies are taken through the introducer when the stylet is removed. Patients are asked to hold their breath when the needle is advanced, during biopsy, and when the introducer is not occluded between biopsies. The needle should be visualized throughout its path, and failure to do so is usually the result of poor angulation. Any undue resistance should raise the suspicion of poor placement. Needle aspirates yield cytologic material; core biopsies for a tissue diagnosis are needed if tumors such as mesothelioma, lymphoma, teratoma, or thymoma are suspected.

Complications of biopsy include pneumothorax, hemoptysis, air embolism, or perforation of other organs. The pneumothorax rate in needle biopsy of lung lesions has been reported in less than 4%,[52–55] a low rate probably because most of the biopsied lesions were abutting the pleura. Air embolism can occur when a swing in intrathoracic pressure draws air into the pulmonary veins via the introducer.

DOCUMENTATION[56]

Appropriate documentation of ultrasonographic findings and interventional procedures is essential for research,

reimbursement, and communicating medical information. Capturing of images enables comparisons with future scans and assessment of a patient's progress. Standard documentation should include patient identification, time and date of procedure, ultrasound operator identification, patient position, transducer type and location, and indications and anatomic extent of the study. Reports should comment on normal findings, pathology, subjective measures of certainty (probable vs. possible), and changes compared with previous scans. Any limitations of the study should also be noted. If interventional procedures were performed, documentation usually includes the site, anaesthesia, specimens obtained, complications, and follow-up instructions.

TRAINING

The American Medical Association[57] has affirmed that ultrasound privileging is within the scope of appropriately trained physicians and that speciality-specific training standards should be developed. Such standards have yet to be developed within pulmonary or critical care medicine but are needed to maintain safety, accuracy, and credibility.[58] Guidelines from the American College of Emergency Physicians[59] suggest that there should be 3 to 4 hours of didactic instruction to cover basic physics and interpretation and 2 to 4 hours of practical demonstration/practice on basic handling, psychomotor skills, and "knobology" (the proper use of the dials on the ultrasound machine). In general emergency ultrasonography, 150 proctored scans are recommended.[59] Thus, for general thoracic ultrasonography, it would seem appropriate that 25 to 50 proctored examinations and logbook documentation would be appropriate for the acquisition of sufficient experience for each indication as, for example, in the diagnosis of pleural effusion. Novices should always be aware of both false-positive and false-negative signs. When scans do not correlate with clinical findings, the scans should be disregarded until confirmed by either an expert opinion or an alternative imaging method such as CT scanning. A realistic understanding of the limits of one's skill and knowledge will ensure continued safety and credibility.

ADVANTAGES AND DISADVANTAGES OF ULTRASOUND

The advantages of ultrasound imaging include bedside availability and the relative ease of performing repeated examinations. Imaging is real-time and free of harmful radiation. There are no documented side effects and discomfort is minimal. Despite the absence of randomized, controlled trials, ultrasonographic guidance for interventional procedures in the thorax is likely to improve diagnostic yield and reduce complications by providing visual guidance.[60] Bedside ultrasonography enables clinicians who understand the clinical context of patients to perform the most appropriate scans directed to address clinically relevant questions.

The disadvantages of ultrasonography are primarily related to the fact that it is heavily operator-dependent. Retrospective review of images provides only limited quality control. There is no scout scan to give a global picture for orientation. In addition, the basic ultrasound evaluation cannot determine the exact position of devices such as the endotracheal tube, central lines, and feeding tubes in the body. Ultrasonography is limited by bones, which prevent penetration of ultrasound waves, and by air, which largely reflects them. Full diagnostic imaging of the thorax can also be time-consuming. Costs include the capital investment for the purchase of the ultrasound machine and operating expenditures of consumables like the gel and sterile sheaths.[60]

The bedside nature of ultrasonography mandates that infection control issues be taken seriously. Portable machines should never be placed on patients' beds and should ideally have independent stands. Sterile sheaths should be employed in all real-time interventional procedures together with standard aseptic techniques. Ultrasound gel can be a culture medium for bacteria,[61] and it is a common courtesy to clean off all gel from the patient's body at the end of the procedure. The ultrasound machine should also be wiped clean between studies, with special attention given to components that may contribute to nosocomial transmission of infection: the transducer probe, cable, and keyboard.

ENDOBRONCHIAL ULTRASOUND

EBUS has revolutionized bronchoscopy because it extends the endoscopist's view beyond the mucosal surface of the airways. It enables a detailed assessment of the airway wall layers and facilitates guided biopsies of lymph nodes and tumors. EBUS is available in two general versions, based on either radial or linear transducer probes.[61a]

Radial EBUS and linear EBUS have contrasting features and applications. The radial EBUS probe produces high-resolution, 360-degree images and is inserted via a standard flexible bronchoscope. It facilitates the detailed evaluation of the central airway walls, as well as of peripheral lung lesions. However, any biopsy procedure guided by radial EBUS is not real-time but directed to the area identified previously by the radial EBUS image. Linear EBUS generates relatively lower resolution sector scans. Because the transducer is built into a dedicated bronchoscope, imaging is confined to lesions around the central airways and transbronchial needle aspirations (TBNA) are performed real-time.

Radial Endobronchial Ultrasound

Radial EBUS has a 20-MHz (12–30 MHz available) rotating transducer (external diameter 1.7–2.0 mm) that can be inserted together with a guidesheath through the working channel of a standard flexible bronchoscope (Fig. 20-11). Owing to the rotation of the transducer, a 360-degree image is produced that is perpendicular to the long axis of the bronchoscope. In the proximal

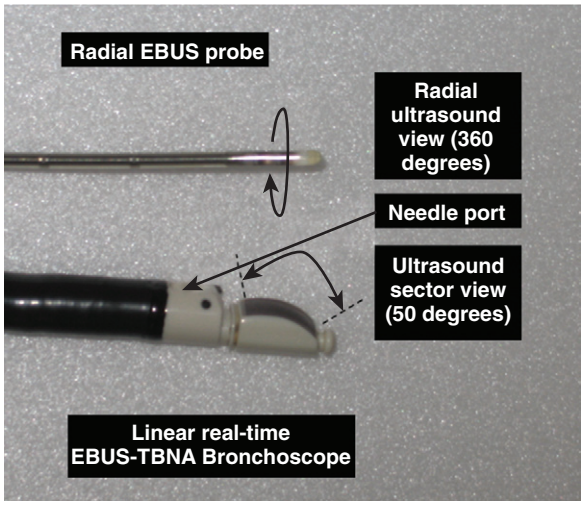

FIGURE 20-11 ■ Radial endobronchial ultrasound (EBUS) probe and linear real-time EBUS-TBNA (transbronchial needle aspiration) bronchoscope. Using a radial EBUS probe, transbronchial biopsies via a guidesheath or needle aspirates of lymph nodes are obtained after the probe is removed whereas, using a linear EBUS bronchoscope, needle aspirates are obtained via a needle advanced through the needle port along a trajectory similar to that shown for the *arrow*.

airways, coupling is achieved by inflating a balloon that surrounds the transducer with sterile water. Saline is avoided because it can result in salt crystallization. In the distal airways, such coupling is unnecessary because the smaller airway caliber allows direct contact between the transducer and the mucosal wall. The resulting scans penetrate to a depth of 4 to 5 cm with a lateral resolution of less than 1 mm.

Radial EBUS is typically performed after a standard bronchoscopic examination of the tracheobronchial tree. To avoid damaging the probe, the endoscopist should not insert the radial probe into the working channel of the bronchoscope when it is actively rotating. Most patients tolerate inflation of the balloon, even in the trachea, for short periods of time without ventilation problems. Once an image is obtained, the ultrasound view needs to be oriented and matched to the endoscopic view using familiar ultrasound landmarks such as major vessels, spine, and esophagus. In the trachea, the orientation of the image with EBUS is similar to that of axial CT scans. However, this orientation becomes more challenging for the operator as the scanning axis changes to an oblique angle in the main-stem bronchi and in more distal airways. Therefore, a detailed understanding of thoracic anatomy is mandatory for the successful use of EBUS.

Airway Assessment

Airway walls can be examined in detail using radial EBUS. Up to seven layers of the wall can be distinguished[62]: the mucosa, endochondium, perichondium, and adventitia are hyperechoic (white) whereas the intervening submucosa, cartilage, and connective tissue layer are hypoechoic (dark gray). Such detail allows assessment of airway invasion; EBUS has been reported to be superior to CT scanning in distinguishing airway wall invasion from extrinsic compression by a tumor.[62] By identifying evidence of tumor invasion into cartilage, patients can be excluded from endoscopic modalities such as photodynamic therapy or brachytherapy in favor of surgical resection.[63,64] EBUS can also guide interventional bronchoscopy: by identification of submucosal tumor involvement and airway malacia, one can avoid undersizing of stents, and by identification of adjacent blood vessels, one can avoid inducing hemoptysis via débridement or thermal ablation.[64,65]

Endobronchial Ultrasound–Guided Biopsies of Lymph Nodes

Radial EBUS can locate lymph nodes and extraluminal tumors relative to the airways. Once the target lesion is identified, the probe is removed and transbronchial biopsy or TBNA can be performed. The reported diagnostic yields with TBNA following radial EBUS range from 72% to 86%.[66–69] The use of EBUS guidance has been shown to improve diagnostic rates of TBNA in mediastinal lymph node stations 2, 3, and 4.[68] Preliminary data are also emerging about the use of Doppler to measure the vascular resistive index of lymph nodes.[70] Compared with normal nodes, malignant nodes may demonstrate a higher vascular resistive index to blood flow because of neovascularization; thus, it may be possible in the future to direct biopsies to those lymph nodes with the greatest likelihood of malignant involvement.

Endobronchial Ultrasound–Guided Biopsies of Peripheral Lung Lesions

Radial EBUS can increase the diagnostic yield of transbronchial lung biopsies of small (<30-mm) peripheral lung lesions[71] with diagnostic yields of 77% to 80%.[71–73a] Biopsy of fluoroscopically invisible nodules has also been possible with diagnostic yields of 70%.[74] The EBUS probe is inserted through a guidesheath into the bronchus where the lesion is suspected. Whereas normal air-filled alveoli produce a whitish snowstorm image with comet-tail artifacts, peripheral lung tumors are isoechoic and more homogeneous. When the image of the lesion is seen all around the probe, the probe is considered to be within the target. The transducer is then removed and a regular biopsy forcep is used to biopsy through the guidesheath. Biopsies of lesions at the site of the probe have been shown to have higher diagnostic rates when the probe is placed within rather than adjacent to the lesions.[75] The use of EBUS-guided transbronchial lung biopsy without fluoroscopic guidance is also safe and effective.[76,77] Electromagnetic navigation bronchoscopy or virtual bronchoscopy can be used to navigate the EBUS probes to peripheral lung lesions to improve diagnostic yields further.[77–79]

Linear Endobronchial Ultrasound–Transbronchial Needle Aspiration Bronchoscope

The linear EBUS probe has been built into a dedicated flexible bronchoscope to enable real-time TBNA biopsies. This EBUS bronchoscope (BF-UC260F-OL8; Olympus Ltd, Tokyo, Japan) has an external diameter of 6.9 mm and so requires insertion via an oral route or via an oral endotracheal tube (see Fig. 20-11). Because the endoscopic viewing optics are at a 30-degree angle from the long axis of the scope, the operator must compensate in order to interpret the view correctly. Particular attention is needed in intubating the trachea and often only the anterior apex of the vocal cords is visible as the scope enters the subglottic space. Usually endobronchial examination is limited and standard bronchoscopy may also be needed to complete a full airway examination. At the time of this writing, the only linear EBUS scope available has a convex 7.5-MHz EBUS transducer and a 50-degree sector view perpendicular to the long axis of the bronchoscope extending 20 to 50 mm in depth. This bronchoscope has a 2.0-mm working channel that can house a dedicated 22-gauge biopsy needle.

After insertion into the trachea, the EBUS-TBNA scope is maneuvered to the approximate location of the target lymph node or paratracheal tumor. The scope is flexed to contact the airway wall and then withdrawn while being rotated from side to side. Although there is a balloon that can be filled with normal saline to facilitate coupling, this is not always needed if good contact can be maintained between the airway mucosal surface and the probe. Simultaneous imaging of the endoscopic and ultrasound images aids localization. Lymph nodes appear more echoic (gray) than blood vessels and Doppler can be used to assist in making the distinction. The needle sheath is then visualized on the endoscopic image before the "jabbing" technique is used to perform TBNA under real-time guidance. Once the TBNA needle is within the target (Fig. 20-12), the stylet of the needle is removed and cellular material aspirated. Most mediastinal and hilar lymph nodes can be reached by the EBUS-TBNA bronchoscope except the aortopulmonary (station 5), subaortic (station 6), paraesophageal (station 8), and pulmonary ligament (station 9) nodes.

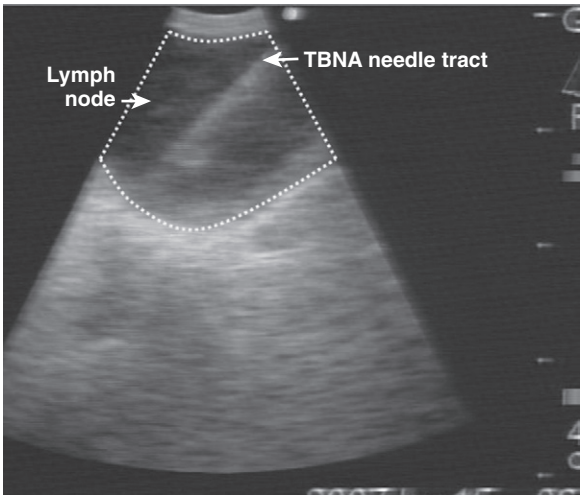

FIGURE 20-12 ■ Linear real-time EBUS-TBNA shows the biopsy needle within the lymph node (*outlined by dotted lines*).

Endobronchial Ultrasound–Transbronchial Needle Aspiration Mediastinal Staging

Compared with blind TBNA, real-time EBUS-TBNA has been shown to have a higher diagnostic yield in mediastinal staging[80] and may be comparable to cervical mediastinoscopy.[81] Even without the presence of rapid on-site cytology, diagnostic yields with definitive histology of 65% to 94% have been reported for real-time EBUS-TBNA.[82-84] The histologic staging of a radiologically normal mediastinum with lymph nodes of 10 mm or less has also been shown to be feasible.[85,86] The dedicated 22-gauge biopsy needle can obtain samples that are sufficient for genetic analysis (e.g., epidermal growth factor receptor mutations).[87] Although the pooled diagnostic sensitivity for EBUS-TBNA is 90% and the specificity is 100%, the false-negative rate can be over 20%.[88] Therefore, all negative results need to be followed up clinically or by alternative diagnostic modalities to confirm that the results are true negatives. When combined with transesophageal endoscopic ultrasound-guided fine needle aspiration (EUS-FNA), EBUS-TBNA can enable complete staging of the mediastinum with access to lymph node stations not accessible by either technique alone (diagnostic sensitivities of 93%–94%).[80,89] Such combined approaches may further extend the diagnostic options for mediastinal staging.

Other Applications

EBUS-TBNA has also been shown to have utility in diagnoses besides lung cancer. In patients with clinically suspected lymphoma, the reported diagnostic sensitivity is 90.9%.[90] In the demonstration of noncaseating granulomatous inflammation, EBUS-TBNA has a reported diagnostic yield for sarcoidosis of 85% to 93.8%.[91-93] Furthermore, real-time guided TBNA can potentially be used in the diagnostic workup of anterior mediastinal masses, paratracheal tumors, and mediastinal cysts.

Setting Up an Endobronchial Ultrasound Service

Training in EBUS covers image interpretation, knobology, orientation of endoscopic and ultrasound views, as well as biopsy techniques. Knowledge of thoracic anatomy and competence in basic flexible bronchoscopy and TBNA are prerequisites. The American College of Chest Physicians[94] recommends at least 50 proctored procedures to gain competence in EBUS and 5 to 10 procedures per year to maintain the skill. The European Respiratory Society and American Thoracic Society joint statement[95] suggests 40 supervised procedures to gain competence and 25 procedures per year to maintain the

skill. These guidelines are for radial EBUS and no similar recommendations are available for linear EBUS-TBNA. Other issues that need to be addressed when starting an EBUS service will be the costs of the equipment and disposables as well as the training of the endoscopy staff. EBUS can add to the time required for endoscopy initially and this has implications for what can be achieved under moderate sedation. However, in expert hands, radial EBUS adds less than 3 minutes to a TBNA procedure and about 60 seconds to the transbronchial biopsy of peripheral lesions.[68,73] Linear EBUS-TBNA has been reported to take a mean of 12.5 (range 8–21) minutes.[84]

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KEY POINTS

- Ultrasound offers the advantages of real-time, bedside, radiation-free imaging that will extend the possibilities for diagnosis and treatment by pulmonary and critical care physicians.
- Choice of transducer probes depends on frequency (compromise between spatial resolution and depth of scan) and footprint (acoustic window size).
- Patient and probe position must be considered when assessing gravitationally dependent pathology such as pneumothorax and pleural effusion.
- Anatomic structures are identified based on their location and echogenicity.
- Ultrasound-guidance for thoracentesis and pleural catheter placement has the potential to increase the success of these procedures and reduce complications.
- A key disadvantage of ultrasonography is that it is operator-dependent. Retrospective analysis of previously acquired images is limited.
- EBUS increases the diagnostic sensitivity for TBNA of mediastinal lymph nodes and for transbronchial lung biopsy of peripheral lung lesions.

References

1. Lichtenstein DA: Ultrasound in the management of thoracic disease. Crit Care Med 35(5 Suppl):S250–S261, 2007.
2. Lichtenstein D: Basic notions. *In* Lichtenstein D (ed): General Ultrasound in the Critically Ill. Heidelberg: Springer-Verlag, 2005, pp 3–8.
3. Lichtenstein D: Pneumothorax and introduction to ultrasound signs in the lung. *In* Lichtenstein D (ed): General Ultrasound in the Critically Ill. Heidelberg: Springer-Verlag, 2005, pp 105–115.
4. Colins JD, Burwell D, Furmanski S, et al: Minimal detectable pleural effusions. A roentgen pathology model. Radiology 105:51–53, 1972.
5. Chian CF, Su WL, Soh LH, et al: Echogenic swirling pattern as a predictor of malignant pleural effusions in patients with malignancies. Chest 126:129–134, 2004.
6. Chen KY, Liaw YS, Wang HC, et al: Sonographic septation: A useful prognostic indicator of acute thoracic empyema. J Ultrasound Med 19:837–843, 2000.
7. Eibenberger KL, Dock WI, Ammann ME, et al: Quantification of pleural effusions: Sonography versus radiography. Radiology 191:681–684, 1994.
8. Balik M, Plasil P, Waldauf P, et al: Ultrasound estimation of volume of pleural fluid in mechanically ventilated patients. Intensive Care Med 32:318–321, 2006.
9. Targhetta R, Bourgeois JM, Chavagneux R, et al: Ultrasonic signs of pneumothorax: Preliminary work. J Clin Ultrasound 21:245–250, 1993.
10. Lichtenstein DA, Mezière G, Lascols N, et al: Ultrasound diagnosis of occult pneumothorax. Crit Care Med 33:1231–1238, 2005.
11. Lichtenstein DA, Menu Y: A bedside ultrasound sign ruling out pneumothorax in the critically ill. Lung sliding. Chest 108:1345–1348, 1995.
12. Lichtenstein D, Mezière G, Biderman P, et al: The comet-tail artifact: An ultrasound sign ruling out pneumothorax. Intensive Care Med 25:383–388, 1999.
13. Lichtenstein D, Mezière G, Biderman P, et al: The "lung point": An ultrasound sign specific to pneumothorax. Intensive Care Med 26:1434–1440, 2000.
14. Soldati G, Testa A, Sher S, et al: Occult traumatic pneumothorax: Diagnostic accuracy of lung ultrasonography in the emergency department. Chest 133:204–211, 2008.
15. Slater A, Goodwin M, Anderson KE, et al: COPD can mimic the appearance of pneumothorax on thoracic ultrasound. Chest 129:545–550, 2006.
16. Lichtenstein D: Lung. *In* Lichtenstein D (ed): General Ultrasound in the Critically Ill. Heidelberg: Springer-Verlag, 2005, pp 116–128.
17. Yang PC, Luh KT, Chang DB, et al: Ultrasonographic evaluation of pulmonary consolidation. Am Rev Respir Dis 146:757–762, 1992.
18. Weinberg B, Diakoumakis EE, Kass EG, et al: The air bronchogram: Sonographic demonstration. AJR Am J Roentgenol 147:593–595, 1986.
19. Acunas B, Celik L, Acunas A: Chest sonography. Differentiation of pulmonary consolidation from pleural disease. Acta Radiol 30:273–275, 1989.
20. Mathis G: Subpleural lung consolidation. *In* Mathis G (ed): Chest Sonography. Heidelberg: Springer-Verlag, 2005, pp 50–106.
21. Lichtenstein DA, Lascols N, Mezière G, et al: Ultrasound diagnosis of alveolar consolidation in the critically ill. Intensive Care Med 30:276–281, 2004.
22. Mathis G: Thoraxsonography—Part II: Peripheral pulmonary consolidation. Ultrasound Med Biol 23:1141–1153, 1997.
23. Targhetta R, Chavagneux R, Bourgeois JM, et al: Sonographic approach to diagnosing pulmonary consolidation. J Ultrasound Med 11:667–672, 1992.

24. Gehmacher O, Mathis G, Kopf A, et al: Ultrasound imaging of pneumonia. Ultrasound Med Biol 21:1119–1122, 1995.
25. Dorne HL: Differentiation of pulmonary parenchymal consolidation from pleural disease using the sonographic fluid bronchogram. Radiology 158:41–42, 1986.
26. Lichtenstein D, Mézière G, Biderman P, et al: The comet-tail artifact. An ultrasound sign of alveolar-interstitial syndrome. Am J Respir Crit Care Med 156:1640–1646, 1997.
27. Gargani L, Frassi F, Soldati G, et al: Ultrasound lung comets for the differential diagnosis of acute cardiogenic dyspnoea: A comparison with natriuretic peptides. Eur J Heart Fail 10:70–77, 2008.
28. Fagenholz PJ, Gutman JA, Murray AF, et al: Chest ultrasonography for the diagnosis and monitoring of high-altitude pulmonary edema. Chest 131:1013–1018, 2007.
29. Mathis G, Blank W, Reissig A, et al: Thoracic ultrasound for diagnosing pulmonary embolism: A prospective multicenter study of 352 patients. Chest 128:1531–1538, 2005.
30. McConnell MV, Solomon SD, Rayan ME, et al: Regional right ventricular dysfunction detected by echocardiography in acute pulmonary embolism. Am J Cardiol 78:469–473, 1996.
31. Soldati G, Testa A, Silva FR, et al: Chest ultrasonography in lung contusion. Chest 130:533–538, 2006.
32. Cohn SM: Pulmonary contusion: Review of the clinical entity. J Trauma 42:973–979, 1997.
33. Beckh S, Bölcskei PL, Lessnau KD: Real-time chest ultrasonography: A comprehensive review for the pulmonologist. Chest 122:1759–1773, 2002.
34. Mathis G: Thoraxsonography—Part I: Chest wall and pleura. Ultrasound Med Biol 23:1131–1139, 1997.
35. Zhu Z, Donnelly E, Dikensoy O, et al: Efficacy of ultrasound in the diagnosis of pleurodesis in rabbits. Chest 128:934–939, 2005.
36. Bandi V, Lunn W, Ernst A, et al: Ultrasound vs CT in detecting chest wall invasion by tumor: A prospective study. Chest 133:881–886, 2008.
37. Hsu WH, Ikezoe J, Chen CY, et al: Color Doppler ultrasound signals of thoracic lesions. Am J Respir Crit Care Med 153:1938–1951, 1996.
38. Lichtenstein D: Analytic study of frequent and/or severe situations. *In* Lichtenstein D (ed): General Ultrasound in the Critically Ill. Heidelberg: Springer-Verlag, 2005, pp 177–183.
39. Lichtenstein DA, Mezière GA: Relevance of lung ultrasound in the diagnosis of acute respiratory failure: The BLUE protocol. Chest 134:117–125, 2008.
40. Lichtenstein DA, Lascols N, Prin S, et al: The "lung pulse": An early ultrasound sign of complete atelectasis. Intensive Care Med 29:2187–2192, 2003.
41. Weingardt JP, Guico RR, Nemcek AA Jr, et al: Ultrasound findings following failed, clinically directed thoracenteses. J Clin Ultrasound 22:419–426, 1994.
42. Diacon AH, Brutsche MH, Solèr M: Accuracy of pleural puncture sites: A prospective comparison of clinical examination with ultrasound. Chest 123:436–441, 2003.
43. Grogan DR, Irwin RS, Channick R, et al: Complications associated with thoracentesis. A prospective, randomized study comparing three different methods. Arch Intern Med 150:873–877, 1990.
44. Colt HG, Brewer N, Barbur E: Evaluation of patient-related and procedure-related factors contributing to pneumothorax following thoracentesis. Chest 116:134–138, 1999.
45. Barnes TW, Morgenthaler TI, Olson EJ, et al: Sonographically guided thoracentesis and rate of pneumothorax. J Clin Ultrasound 33:442–446, 2005.
46. Jones PW, Moyers JP, Rogers JT, et al: Ultrasound-guided thoracentesis: Is it a safer method? Chest 123:418–423, 2003.
47. Capizzi SA, Prakash UB: Chest roentgenography after outpatient thoracentesis. Mayo Clin Proc 73:948–950, 1998.
48. Doyle JJ, Hnatiuk OW, Torrington KG, et al: Necessity of routine chest roentgenography after thoracentesis. Ann Intern Med 124: 816–820, 1996.
49. Mayo PH, Goltz HR, Tafreshi M, et al: Safety of ultrasound-guided thoracentesis in patients receiving mechanical ventilation. Chest 125:1059–1062, 2004.
50. Lichtenstein D: Pleural effusion and introduction to the lung ultrasound technique. *In* Lichtenstein D (ed): General Ultrasound in the Critically Ill. Heidelberg: Springer-Verlag, 2005, pp 96–104.
51. Doelken P: Ultrasound-guided transthoracic needle biopsy. *In* Ernst A, Feller-Kopman D (eds): Ultrasound-Guided Procedures and Investigations. New York: Taylor and Francis, 2006, pp 63–74.
52. Pedersen OM, Aasen TB, Gulsvik A: Fine needle aspiration biopsy of mediastinal and peripheral pulmonary masses guided by real-time sonography. Chest 89:504–508, 1986.
53. Yang PC, Chang DB, Yu CJ, et al: Ultrasound-guided core biopsy of thoracic tumors. Am Rev Respir Dis 146:763–767, 1992.
54. Ikezoe J, Morimoto S, Arisawa J, et al: Percutaneous biopsy of thoracic lesions: Value of sonography for needle guidance. AJR Am J Roentgenol 154:1181–1185, 1990.
55. Yuan A, Yang PC, Chang DB, et al: Ultrasound-guided aspiration biopsy of small peripheral pulmonary nodules. Chest 101:926–930, 1992.
56. Simoff MJ: Documentation. *In* Ernst A, Feller-Kopman D (eds): Ultrasound-Guided Procedures and Investigations. New York: Taylor and Francis, 2006, pp 139–147.
57. American Medical Association: Res 802, I-99; Reaffirmed: Sub. Res. 108, A-00. Priviledging for ultrasound imaging. Available at http://www.ama-assn.org/apps/pf_new/pf_online?f_n=browse&doc=policyfiles/HnE/H-230.960.HTM (accessed February 5, 2008).
58. Langlois Sle P: Focused ultrasound training for clinicians. Crit Care Med 35(5 Suppl):S138–S143, 2007.
59. American College of Emergency Physicians: AECP Policy statement: Emergency ultrasound guidelines. 2001. Available at www.aecp.org/NR/rdonlyes/8024079E-28E8-4875-93E6-6867EA705A2A/0/ultrasound-guidelines.pdf (accessed February 6, 2008).
60. Feller-Kopman D: Ultrasound-guided thoracentesis. Chest 129: 1709–1714, 2006.
61. Lichtenstein D: Specific notions of ultrasound in the critically ill. *In* Lichtenstein D (ed): General Ultrasound in the Critically Ill. Heidelberg: Springer-Verlag, 2005, pp 13–18.

61a. Gomez M, Silvestri GA: Endobronchial ultrasound for the diagnosis and staging of lung cancer. Proc Am Thorac Soc 6:180–186, 2009.

62. Herth F, Ernst A, Schulz M, et al: Endobronchial ultrasound reliably differentiates between airway infiltration and compression by tumor. Chest 123:458–462, 2003.
63. Miyazu Y, Miyazawa T, Kurimoto N, et al: Endobronchial ultrasonography in the assessment of centrally located early-stage lung cancer before photodynamic therapy. Am J Respir Crit Care Med 165:832–837, 2002.
64. Herth F, Becker HD, LoCicero J 3rd, et al: Endobronchial ultrasound in therapeutic bronchoscopy. Eur Respir J 20:118–121, 2002.
65. Miyazawa T, Miyazu Y, Iwamoto Y, et al: Stenting at the flow-limiting segment in tracheobronchial stenosis due to lung cancer. Am J Respir Crit Care Med 169:1096–1102, 2004.
66. Shannon JJ, Bude RO, Orens JB, et al: Endobronchial ultrasound-guided needle aspiration of mediastinal adenopathy. Am J Respir Crit Care Med 153(4 Pt 1):1424–1430, 1996.
67. Plat G, Pierard P, Haller A, et al: Endobronchial ultrasound and positron emission tomography positive mediastinal lymph nodes. Eur Respir J 27:276–281, 2006.
68. Herth F, Becker HD, Ernst A: Conventional vs endobronchial ultrasound-guided transbronchial needle aspiration: A randomized trial. Chest 125:322–325, 2004.
69. Herth FJ, Becker HD, Ernst A: Ultrasound-guided transbronchial needle aspiration: An experience in 242 patients. Chest 123:604–607, 2003.
70. Herth FJ, Yasufuku K, Eberhardt R, et al: Resistance index in mediastinal lymph nodes: a feasibility study. J Thorac Oncol 3:348–350, 2008.
71. Paone G, Nicastri E, Lucantoni G, et al: Endobronchial ultrasound-driven biopsy in the diagnosis of peripheral lung lesions. Chest 128:3551–3557, 2005.
72. Herth FJ, Ernst A, Becker HD: Endobronchial ultrasound-guided transbronchial lung biopsy in solitary pulmonary nodules and peripheral lesions. Eur Respir J 20:972–974, 2002.
73. Kurimoto N, Miyazawa T, Okimasa S, et al: Endobronchial ultrasonography using a guide sheath increases the ability to diagnose peripheral pulmonary lesions endoscopically. Chest 126:959–965, 2004.

73a. Eberhardt R, Ernst A, Herth FJ: Ultrasound-guided transbronchial biopsies of solitary pulmonary nodules less than 20 mm. Eur Respir J 34:1284–1287, 2009.
74. Herth FJ, Eberhardt R, Becker HD, et al: Endobronchial ultrasound-guided transbronchial lung biopsy in fluoroscopically invisible solitary pulmonary nodules: A prospective trial. Chest 129:147–150, 2006.
75. Yamada N, Yamazaki K, Kurimoto N, et al: Factors related to diagnostic yield of transbronchial biopsy using endobronchial ultrasonography with a guide sheath in small peripheral pulmonary lesions. Chest 132:603–608, 2007.
76. Yoshikawa M, Sukoh N, Yamazaki K, et al: Diagnostic value of endobronchial ultrasonography with a guide sheath for peripheral pulmonary lesions without x-ray fluoroscopy. Chest 131:1788–1793, 2007.
77. Eberhardt R, Anantham D, Ernst A, et al: Multimodality bronchoscopic diagnosis of peripheral lung lesions: A randomized controlled trial. Am J Respir Crit Care Med 176:36–41, 2007.
78. Kikuchi E, Yamazaki K, Sukoh N, et al: Endobronchial ultrasonography with guide-sheath for peripheral pulmonary lesions. Eur Respir J 24:533–537, 2004.
79. Asahina H, Yamazaki K, Onodera Y, et al: Transbronchial biopsy using endobronchial ultrasonography with a guide sheath and virtual bronchoscopic navigation. Chest 128:1761–1765, 2005.
80. Wallace MB, Pascual JM, Raimondo M, et al: Minimally invasive endoscopic staging of suspected lung cancer. JAMA 299:540–546, 2008.
81. Ernst A, Anantham D, Eberhardt R, et al. Diagnosis of mediastinal adenopathy—Real-time endobronchial ultrasound guided needle aspiration versus mediastinoscopy. J Thorac Oncol 3:577–582, 2008.
82. Krasnik M, Vilmann P, Larsen SS, et al: Preliminary experience with a new method of endoscopic transbronchial real time ultrasound guided biopsy for diagnosis of mediastinal and hilar lesions. Thorax 58:1083–1086, 2003.
83. Rintoul RC, Skwarski KM, Murchison JT, et al: Endobronchial and endoscopic ultrasound-guided real-time fine-needle aspiration for mediastinal staging. Eur Respir J 25:416–421, 2005.
84. Herth FJ, Eberhardt R, Vilmann P, et al: Real-time endobronchial ultrasound guided transbronchial needle aspiration for sampling mediastinal lymph nodes. Thorax 61:795–798, 2006.
85. Herth FJ, Ernst A, Eberhardt R, et al: Endobronchial ultrasound-guided transbronchial needle aspiration of lymph nodes in the radiologically normal mediastinum. Eur Respir J 28:910–914, 2006.
86. Herth FJ, Eberhardt R, Krasnik M et al: Endobronchial ultrasound-guided transbronchial needle aspiration of lymph nodes in the radiologically and positron emission tomography-normal mediastinum in patients with lung cancer. Chest 133:887–891, 2008.
87. Nakajima T, Yasufuku K, Suzuki M, et al: Assessment of epidermal growth factor receptor mutation by endobronchial ultrasound-guided transbronchial needle aspiration. Chest 132:597–602, 2007.
88. Detterbeck FC, Jantz MA, Wallace M, et al: American College of Chest Physicians. Invasive mediastinal staging of lung cancer: ACCP evidence-based clinical practice guidelines (2nd ed). Chest 132(3 Suppl):202S–220S, 2007.
89. Herth FJ, Lunn W, Eberhardt R, et al: Transbronchial versus transesophageal ultrasound-guided aspiration of enlarged mediastinal lymph nodes. Am J Respir Crit Care Med 171:1164–1167, 2005.
90. Kennedy MP, Jimenez CA, Bruzzi JF et al: Endobronchial ultrasound-guided transbronchial needle aspiration in the diagnosis of lymphoma. Thorax 63:360–365, 2008.
91. Oki M, Saka H, Kitagawa C, et al: Real-time endobronchial ultrasound-guided transbronchial needle aspiration is useful for diagnosing sarcoidosis. Respirology 12:863–868, 2007.
92. Wong M, Yasufuku K, Nakajima T, et al: Endobronchial ultrasound: new insight for the diagnosis of sarcoidosis. Eur Respir J 29:1182–1186, 2007.
93. Garwood S, Judson MA, Silvestri G, et al: Endobronchial ultrasound for the diagnosis of pulmonary sarcoidosis. Chest 132:1298–1304, 2007.
94. Ernst A, Silvestri GA, Johnstone D: American College of Chest Physicians. Interventional pulmonary procedures: Guidelines from the American College of Chest Physicians. Chest 123:1693–1717, 2003.
95. Bolliger CT, Mathur PN, Beamis JF, et al: European Respiratory Society/American Thoracic Society. ERS/ATS statement on interventional pulmonology. European Respiratory Society/American Thoracic Society. Eur Respir J 19:356–373, 2002.

CHAPTER 21

NUCLEAR MEDICINE TECHNIQUES

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INTRODUCTION

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Pulmonary Embolism
Preoperative Evaluation

POSITRON EMISSION TOMOGRAPHY
Differentiating Benign and Malignant Lesions
Staging Lung Cancer
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INTRODUCTION

This chapter describes the two major applications of nuclear medicine techniques in the evaluation of diseases of the thorax: the ventilation-perfusion (V/Q) study to detect pulmonary embolism and [^{18}F]fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET) for evaluating patients with suspected or documented lung cancer. Virtually every hospital performs V/Q scans using single-photon–emitting radionuclides. Recently, however, multidetector computed tomographic angiography (CTA) has replaced V/Q imaging in some patients with suspected pulmonary embolism. FDG-PET imaging is being increasingly utilized for evaluation of solitary pulmonary nodules, initial staging of lung cancer, planning radiotherapy, and following lung cancer after treatment.

VENTILATION-PERFUSION IMAGING

The normally functioning lung demonstrates homogeneous patterns of ventilation and perfusion on the scintigraphic study.[1] V/Q imaging can be used to classify abnormalities in ventilation and perfusion according to the probable cause. The pathologic conditions affecting ventilation and perfusion may be divided into four functional categories: (1) the vascular occlusive state, (2) the consolidative state, (3) the obstructive state, and (4) the restrictive state.

Pulmonary emboli, extrinsic vascular compression, and pulmonary vasculitis are examples of the vascular occlusive state. In this state—in the absence of pulmonary infarction—ventilation is preserved within regions of pulmonary arterial vascular occlusion. Thus, most conditions causing a vascular occlusive state result in a V/Q mismatch.

Inflammatory and infectious lung diseases, pulmonary infarction, and atelectasis result in the consolidative state, which has two components. First, these disorders may result in alveolar collapse and atelectasis. Second, leakage of intravascular fluid into the alveolar space may occur secondary to capillary bed damage. In the consolidative state, both ventilation and perfusion are reduced and generally matched.

Acute asthma and chronic lung diseases such as emphysema, bronchitis, and bronchiectasis result in the obstructive state. With emphysema, there is loss of alveolar walls and their capillary beds, which increases alveolar volume and decreases the surface area for gas exchange. Airway obstruction occurs from either narrowing and/or closure of small airways or loss of structural support, excessive bronchial secretions, bronchial spasm, mucosal edema, or foreign bodies. The resultant decrease in alveolar P_{O_2} causes constriction in precapillary arterioles with redistribution of blood to better-ventilated alveoli. Thus, both ventilation and perfusion to involved areas are decreased but remain matched.

Chronic inflammation and fibrosis that eventually obliterate alveoli result in the restrictive state. Local ventilation may be preserved even though regional compliance is decreased. Overall alveolar ventilation is often increased because of associated increased respiratory drive. In the restrictive state, ventilation may be increased relative to perfusion, resulting in a V/Q mismatch.

Techniques

Ventilation imaging is performed using either a radiolabeled gas or a radiolabeled aerosol. The ventilation agent used has not resulted in a difference in the accuracy of V/Q imaging for the detection of pulmonary embolism. Most of the data in the literature are based on the use of xenon-133 (^{133}Xe) gas. The major alternative ventilation imaging agent is technetium-99m (^{99m}Tc)–labeled aerosol, which some institutions find easier to use than a radiolabeled gas.

The ^{133}Xe ventilation studies are performed using commercially available ventilation devices. The patient breathes through either a face mask or a mouthpiece with the nose clamped. A first-breath or breath-hold image is obtained as the ^{133}Xe is administered at the mouthpiece during a deep inspiration and breath-hold. The patient then performs normal tidal breathing while inhaling the ^{133}Xe-air mixture for at least 4 minutes while equilibrium images are obtained. Regions of the lung that appear as areas of decreased accumulation on the breath-hold image may normalize on the equilibrium image because of slow equilibrium through the airways or because of collateral air drift. After the equilibrium images are obtained, washout imaging is performed while the patient breathes in room air and exhales the ^{133}Xe into a storage container or a system that exhausts the radiolabeled gas into the atmosphere. Abnormalities on the breath-hold and equilibrium images are areas of decreased ^{133}Xe accumulation. Abnormalities on the washout phase are determined by asymmetry of the washout images. Focal areas of retained activity represent regional air trapping. ^{133}Xe studies are preferably performed in the sitting position, but the studies can be performed in the supine position. These studies can be performed on patients on a ventilator by using an elastic bag to deliver the gas during the study. Because the photon energy of ^{133}Xe is lower than that of ^{99m}Tc, which is used for the perfusion study, the ventilation study is performed prior to the perfusion study.

Radiolabeled aerosols are also used for imaging regional ventilation and are available commercially in the form of small and efficient aerosol nebulizers. Although several different radiopharmaceuticals have been used, ^{99m}Tc-labeled diethylenetriaminepenta-acetic acid (^{99m}Tc-DTPA) is most commonly used. The radioaerosols are typically between 0.5 and 3 μm in size. For the study, 1.11 GBq (30 mCi) of ^{99m}Tc-DTPA in 3 mL of saline is placed in the nebulizer. Oxygen is used with the nebulizer to produce the aerosol, which is inhaled by the patient through either a face mask or a mouthpiece with a nose clip. The patient inhales the aerosol until 37 MBq (1 mCi) is in the lungs, which generally takes 3 to 5 minutes. The distribution of the aerosol within the lungs is proportional to regional ventilation. The radiolabeled aerosol study is performed prior to the perfusion study. Typically a 200,000- to 250,000-count posterior image is made and the time recorded. Other views are obtained for the same time interval except for the lateral images, which are obtained for shorter periods of time. The count rate for the aerosol ventilation study should be approximately 20% of the count rate for the perfusion study. The advantages of the radioaerosol study over the ^{133}Xe study are that the radioaerosol study requires minimal patient cooperation and it can be performed as a portable study. These studies can also be performed relatively easily in patients on ventilators. A major disadvantage of the radioaerosol study is the central deposition of radioactivity that occurs in patients with chronic obstructive pulmonary disease (COPD). Newer radioaerosols have been developed that overcome some of the limitations of the ^{99m}Tc-DTPA aerosol. These agents include ^{99m}Tc technegas and ^{99m}Tc pertechnegas. These agents, which are not available in the United States at this time, are produced by burning ^{99m}Tc pertechnetate in a carbon crucible at extremely high temperatures, producing an ultrafine aerosol.

Perfusion lung imaging is accomplished by intravenous injection of radiolabeled particles that embolize within the pulmonary vasculature. The number of particles that impact in a volume of the lung is proportional to the pulmonary arterial blood flow to that region. Because the radiolabeled particles are administered intravenously, they are well mixed with venous blood in the right atrium and ventricle before being distributed into the lung in direct proportion to local pulmonary arterial blood flow. Thus, the perfusion images represent regional distribution of pulmonary arterial blood flow at the time of radiopharmaceutical administration.

Technetium-99m–labeled macroaggregated albumin (^{99m}Tc-MAA) is the radiopharmaceutical used for perfusion imaging. More than 90% of the particles are between 10 and 90 μm in size. The typical administered dose is 74 to 148 MBq (2-4 mCi) of ^{99m}Tc (140-keV photon)-MAA that contains approximately 500,000 particles. To obtain an even distribution of the radioactivity in the pulmonary vascular bed, 60,000 or more particles are needed. Because the normal human lung contains approximately 300 million precapillary arterioles, only approximately 0.1% of these vessels are blocked during this study. The pulmonary perfusion study is extremely safe even in patients with severe COPD in whom the precapillary arterioles are smaller in diameter and the number of precapillary arterioles and capillaries is diminished. The biologic half-life of the ^{99m}Tc-MAA in the lung is 2 to 6 hours owing to metabolism of MAA in the lungs. Patients who have right-to-left shunts tolerate the procedure well, even though the presence of a right-to-left shunt has been considered a relative contraindication to the procedure. But there have been no reported consequences of administering the particles in these patients. In fact, radiolabeled particles have been directly injected into a coronary artery or carotid artery without any adverse effects, and as pointed out in Chapter 54, injection of ^{99m}Tc-MAA is a useful way of quantifying the magnitude of right-to-left shunting of blood in patients with pulmonary arteriovenous malformations.

For perfusion scintigraphy, at least eight views of the thorax are obtained, including the anterior, posterior, left and right posterior and anterior obliques, and right and left lateral views. For each view, 750,000 counts are obtained except for the lateral views. The lateral view

with the best perfusion is imaged for 500,000 counts, the time is recorded, and the other lateral view is acquired for the same length of time.

Perfusion scintigraphy is sensitive but not specific for diagnosing pulmonary diseases. Almost all pulmonary diseases cause decrease in pulmonary perfusion to affected lungs zones. Ventilation imaging is used to improve the specificity for diagnosing pulmonary embolism. Pulmonary embolism and other vascular occlusive states result in perfusion abnormalities without abnormalities in ventilation (mismatched defects). In consolidative states, such as pneumonia, ventilation and perfusion are decreased in the same region as the radiographic abnormality (matched defects). Airway obstruction, mucus plugging, atelectasis, and pneumonia may result in ventilation abnormalities larger than the perfusion abnormalities (reverse mismatch).

Pulmonary Embolism

As emphasized in Chapter 51, there is a strong association between pulmonary embolism and deep venous thrombosis (DVT) because pulmonary embolism usually begins with DVT. Patients with suspected pulmonary embolism should have their initial evaluation directed at the chest. Afterward, if the diagnosis remains uncertain, venous imaging can be performed.[2]

Multidetector CTA is being increasingly used to evaluate patients with suspected pulmonary embolism.[2a,2b] The use of CTA has been adopted in clinical practice at many centers, and V/Q scintigraphy is being used in a secondary role. Although the initial studies demonstrated a lower sensitivity for computed tomography (CT) than for perfusion scintigraphy, recent studies with improved CT techniques demonstrate better results. The technical improvements include multidetector scanners with thin collimation and high pitch, which improve the sensitivity of CT for detecting subsegmental emboli. Increasing observer experience will also likely further improve the results.

The second Prospective Investigation Of Pulmonary Embolism Diagnosis (PIOPED II), was a large multicenter study evaluating the accuracy of multidetector CTA in patients with suspected acute pulmonary embolism.[3] The purpose of PIOPED II was to determine the extent to which multidetector CT is an efficacious, minimally invasive test for pulmonary embolism and thereby to reduce the need for pulmonary angiography and V/Q scanning. The added information from computed tomographic venography (CTV) and a validated clinical assessment (the Wells score) were also evaluated. Each patient in the study underwent both a V/Q scan and a multidetector CTA for suspected pulmonary embolism. The final determination of pulmonary embolism status was being made by the combination of V/Q scintigraphy, venous ultrasonography of the lower extremities, pulmonary angiography, and venography. In this study of 824 patients who had a reference diagnosis and CTA, 51 were excluded because of poor image quality. In the remaining patients with adequate CTA, the sensitivity was 83% and the specificity was 96%. The sensitivity for combined CTA-CTV was 90% and the specificity was 95%. A concordant clinical assessment increased the prediction value.

Sostman and coworkers[4] evaluated the sensitivity and specificity of V/Q scintigraphy for detecting acute pulmonary embolism in patients in the PIOPED II study. They used the V/Q scan interpretation of high probability for pulmonary embolism to indicate "pulmonary embolism present," of normal or very low probability as "pulmonary embolism absent," and low or intermediate probability as "nondiagnostic of pulmonary embolism": 27% of patients had nondiagnostic scan interpretations and were excluded. The sensitivity of a pulmonary embolism present scan finding was 78% and the specificity of a pulmonary embolism absent scan finding was 98%. They concluded that in a population similar to that in PIOPED II, V/Q scintigraphy was diagnostically definitive in a majority of patients and could be appropriately utilized in patients in whom CTA may be disadvantageous. Although CTA is the primary procedure that is currently used to evaluate patients with suspected pulmonary embolism at many centers, V/Q scintigraphy still has an important role in the diagnostic workup. The reasons that V/Q scintigraphy is performed instead of CTA are that the patients have renal dysfunction, are allergic to the contrast material, are too large to be scanned in the CT scanner, have low clinical suspicion of pulmonary embolism and a normal chest radiograph, or are young women in whom radiation dose to the breasts is of concern.

Pulmonary angiography has been considered the "gold standard" for clinical diagnosis of pulmonary embolism. The intravascular filling defect seen on pulmonary angiography may be acute, but the actual age of the pulmonary embolus cannot be determined. There are angiographic findings of chronic pulmonary embolism, but the significance of chronic emboli, unless discovered in patients with pulmonary hypertension, is uncertain. The accuracy of pulmonary angiography interpretation has not been adequately studied. In the National Urokinase Pulmonary Embolism Trial,[5] the angiographers agreed that pulmonary embolism was present 94% of the time. In the first PIOPED study,[6] interobserver agreement about the presence of pulmonary embolism was 92%. If the embolus was large and was in the main pulmonary artery or lobar artery, agreement was 98%. The agreement was 80% in segmental arteries and 40% in peripheral arteries.

The PIOPED I study prospectively compared the results of V/Q scintigraphy with the results from pulmonary angiography.[6] None of the patients in the PIOPED study with a normal lung scan interpretation and pulmonary angiography was found to have pulmonary embolism. A normal perfusion study has long been accepted to exclude the diagnosis of pulmonary embolism.[7] Never has a patient had a documented pulmonary embolus with a normal perfusion lung scan. Accordingly, a normal scan stops the evaluation for pulmonary embolism.

Perfusion scintigraphy is not specific for pulmonary embolism because almost all pulmonary diseases produce perfusion abnormalities.[8] The diagnostic accuracy of

scintigraphy for the detection of pulmonary emboli was significantly improved when ^{133}Xe ventilation studies were added to the perfusion lung scan and chest radiograph.[9] The concept of segmental equivalents—that is, that two subsegmental perfusion defects can be added to produce the same diagnostic significance as a single segmental defect—contributed to the diagnostic accuracy of the interpretation of V/Q scintigraphy.[10] Additional studies improved the categorization of perfusion defects matched by ventilatory or radiographic abnormality to reduce the number of intermediate-probability diagnoses.[11,12] The categorization of perfusion defects as small (<25% of the area of an average-sized pulmonary artery segment), moderate (equivalent to 25%=75% of the area of a segment), and large (>75% of a segment) has led to the more accurate criteria that are used to categorize V/Q scans today. Bronchopulmonary segments are typically of different sizes. Although the reader of a V/Q scan could attempt to individualize the evaluation of defect size to the particular segment, in practice, most experienced readers utilize an average, idealized segment to evaluate the defects in any location.

Diagnostic Criteria

Different sets of criteria have been developed for interpreting V/Q scans. Several studies have demonstrated that experienced readers are more accurate in their interpretations when using their experience than when using reference criteria.[13–15] Although the gestalt interpretation works for highly experienced readers, reference criteria are helpful for those readers with less experience in interpreting V/Q scans. The PIOPED I studies have set the standard for reference criteria (Table 21-1). These multicenter studies have been sponsored by the National Heart, Lung, and Blood Institute.[6] In the original study that was performed to evaluate the accuracy of V/Q scanning as compared with contrast angiography, 933 patients were recruited, 931 had V/Q scans, and 755 had pulmonary angiograms. Pulmonary embolism was present in 251 patients (33%). Thus, the prevalence of pulmonary embolism in the population being referred for V/Q scans at multiple large tertiary care medical centers was 33%. When using the PIOPED I criteria for interpreting V/Q scans to determine the likelihood of pulmonary embolism, it is important to consider the prevalence of disease in the population. If the prevalence of disease is less than in the PIOPED I study, then the likelihood of pulmonary embolism in each category would be lower than it was in the PIOPED I study. In the PIOPED II study, Sostman and coworkers[4] found the prevalence of pulmonary embolism to be 18%. Because the number of patients with suspected pulmonary embolism is increasing without a concordant increase in the incidence of pulmonary embolism, the prevalence of pulmonary embolism in patients having imaging studies is decreasing. We estimate the prevalence of pulmonary embolism in the patients being studied at our institution to be 5%.

The interpretations of the V/Q scans were entered into a database so that the major findings could be compared with abnormalities found on the chest radiograph and angiogram. The criteria that had been used for the original interpretations of the PIOPED V/Q scans were then revised based on the findings of the computerized comparisons (see Table 21-1). The revised PIOPED criteria were then compared with the original PIOPED criteria and gestalt interpretations of two experts in a prospective study.[16] In this study of 104 patients who had V/Q scans and pulmonary angiography, the gestalt percent probability estimate was the most accurate for assessing the likelihood of pulmonary embolism, with an area under the receiver operating characteristic (ROC) curve of 0.836. The revised PIOPED criteria had an area under the ROC curve of 0.753, which was larger than the area under the ROC curve using the original PIOPED criteria.

After the publication of the revised PIOPED criteria, they were accepted as the standard criteria for interpreting V/Q scans.[14] The typical finding of pulmonary embolism on V/Q imaging is large, wedge-shaped, peripheral perfusion defects in areas that have normal ventilation and that are normal on plain radiographs. The larger the number of these defects, the more likely it is that the patient has pulmonary embolism. It is important to keep in mind that in patients who have a prior history of pulmonary embolism, the finding of large mismatched defects is not as accurate as in patients who do not have a previous history of pulmonary embolism.[1] For a V/Q scan to be considered high probability (≥80% in the PIOPED study), two or more large mismatched segmental perfusion defects or the equivalent in moderate or large and moderate mismatched defects must be present. Two large mismatched perfusion defects are borderline for high probability, but generally should be categorized as high probability.

Patients who had intermediate-probability V/Q scans had pulmonary embolism detected by pulmonary angiography 20% to 79% of the time. The criteria for an intermediate-probability scan include the following: one moderate to two large mismatched segmental perfusion defects or the equivalent in moderate or large and moderate defects, one matched V/Q defect with a clear chest radiograph, and difficult to categorize as low or high probability.

Patients with a low-probability V/Q scan had a 19% or less probability of having a positive pulmonary angiogram. The criteria for low probability included the following: nonsegmental perfusion defects, perfusion defect with substantially larger abnormality on chest radiography, perfusion defects matched by ventilation abnormality, and any number of small perfusion defects with a normal chest radiograph. Thus, patients with extensive COPD with matched ventilation and perfusion were categorized as low probability.

The normal perfusion study excludes pulmonary embolism (Fig. 21-1). Criteria for normality included no perfusion defects and perfusion outlining exactly the shape of the lungs seen on chest radiograph. Hilar and aortic impressions may be seen, and the chest radiograph, the ventilation scan, or both may be abnormal.

The PIOPED II V/Q scan criteria include revisions from the revised PIOPED criteria based on continuing analysis of the original PIOPED data and the input of the

TABLE 21-1. Ventilation-Perfusion (V/Q) Scan Interpretation Criteria

Revised PIOPED Criteria	PIOPED II Ventilation-Perfusion (V/Q) Scan Criteria
HIGH PROBABILITY (≥80%)	**HIGH SCAN PROBABILITY**
Two or more large mismatched segmental perfusion defects or the equivalent in moderate or large and moderate mismatched defects*	Two or more large mismatched segmental defects or the equivalent in moderate or large and moderate defects
INTERMEDIATE PROBABILITY (20%–79%)	**INTERMEDIATE-INDETERMINATE SCAN PROBABILITY**
One moderate to one and one-half large mismatched segmental perfusion defects or the equivalent in moderate segmental perfusion defects	One-half to one and one-half segmental equivalents
Single matched V/Q defect with clear chest radiograph†	Difficult to categorize as high or low
Difficult to categorize as low or high, or not described as low or high	Solitary moderate or large segmental size triple match in lower lobe (zone)
	Multiple opacities with associated perfusion defects
LOW PROBABILITY (≤19%)	**LOW SCAN PROBABILITY**
Nonsegmental perfusion defects (e.g., cardiomegaly, enlarged aorta, enlarged hila, elevated diaphragm)	A single matched V/Q defect
Any perfusion defect with a substantially larger chest radiographic abnormality	More than three small segmental lesions
Perfusion defects matched by ventilation abnormality† provided that there are (a) a clear chest radiograph and (b) some areas of normal perfusion in the lungs	Probable pulmonary embolism mimic:
Any number of small perfusion defects with a normal chest radiograph	One lung mismatched (whiteout) with absent perfusion
	Solitary lobar mismatch
	Mass or other radiographic lesion causing all mismatch
	Moderate-sized pleural effusion (greater than costophrenic angle but less than one third of pleural cavity with no other perfusion defect in either lung)
	Marked heterogeneous perfusion
	VERY LOW SCAN PROBABILITY
	Nonsegmental lesion (e.g., prominent hilum, cardiomegaly, elevated diaphragm, linear atelectasis, costophrenic angle effusion with no other perfusion defect in either lung)
	Perfusion defect smaller than radiographic lesion
	Two or more V/Q matched defects with regionally normal chest radiograph and some areas of normal perfusion elsewhere in the lungs
	One to three small segmental perfusion defects
	A solitary matched triple defect in the mid or upper lung zone confined to a single segment
	Stripe sign present around the perfusion defect (best tangential view)
	Pleural effusion of one third or more of the pleural cavity with no other perfusion defect in either lung
NORMAL	**NORMAL PERFUSION SCAN**
No perfusion defects—perfusion outlines exactly the shape of the lungs seen on the chest radiograph (note that hilar and aortic impressions may be seen, and the chest radiograph and/or ventilation study may be abnormal)	No perfusion defect. Perfusion scan must outline the shape of the lungs seen on chest radiograph, which could be abnormal (e.g., scoliosis).

*Two large mismatched perfusion defects are borderline for high probability. Individual readers may correctly interpret individual scans with this pattern as high probability. In general, it is recommended that more than this degree of mismatch be present for the high-probability category.
†Very extensive matched defects can be categorized as low probability. Single V/Q matches are borderline for low probability and should be considered for intermediate probability in most cases by most readers, although individual readers may correctly interpret individual scans with this pattern as low probability.
PIOPED, Prospective Investigation of Pulmonary Embolism Diagnosis (study); V/Q, ventilation-perfusion.

PIOPED II nuclear medicine working group (Figs. 21-1 to 21-5). In the PIOPED II criteria, the criteria for high probability have remained the same. The intermediate-probability criteria and the low-probability criteria have been revised, and a very low probability category has been added. These changes result in fewer patients having intermediate-probability scans and provide more definitive diagnoses within the very low probability category, but are not well understood by clinicians.[17]

The revised intermediate-probability criteria include scans that had 0.5 to 1.5 segmental equivalent defects, scans that were difficult to categorize as high or low probability, scans that had a solitary moderate or large segmental size triple match in the lower zone, and multiple opacities with associated perfusion defects.

The revised low-probability criteria include a single matched V/Q defect, more than three small (<25% of a segment) lesions, probable pulmonary embolism mimic, moderate-sized pleural effusion, and marked heterogeneous perfusion pattern. The very low probability criteria

Text continued on p. 477

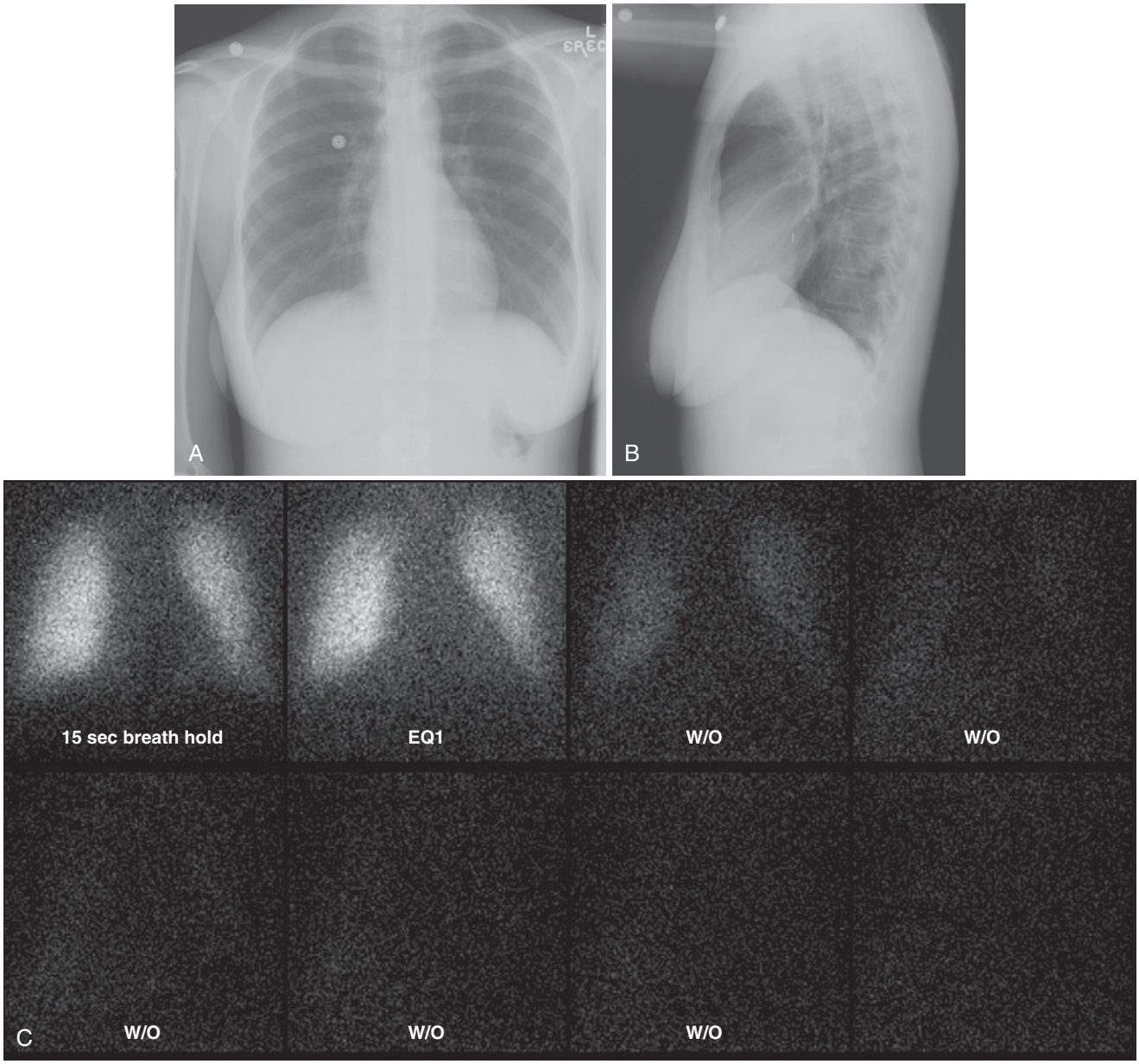
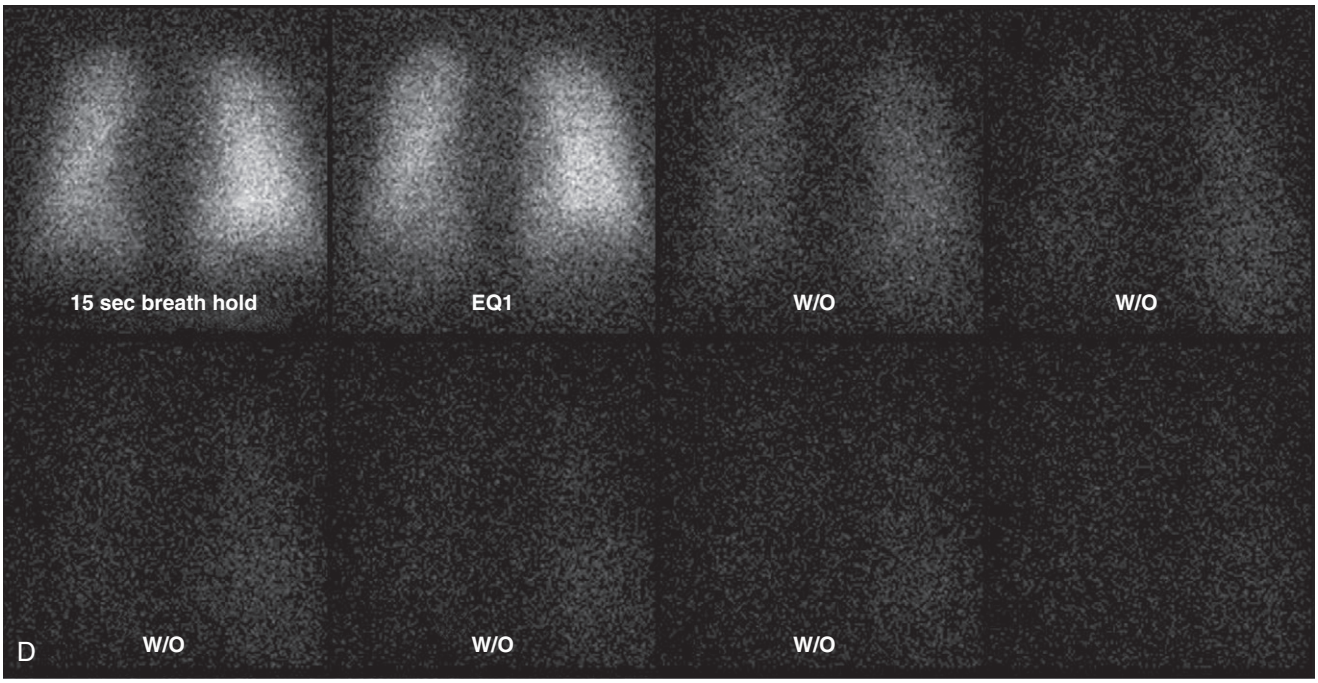


FIGURE 21-1 ■ Example of a normal ventilation-perfusion (V/Q) scan. The posteroanterior (**A**) and lateral (**B**) chest radiographs are normal. A ^{133}Xe ventilation study obtained in the anterior (**C**) and



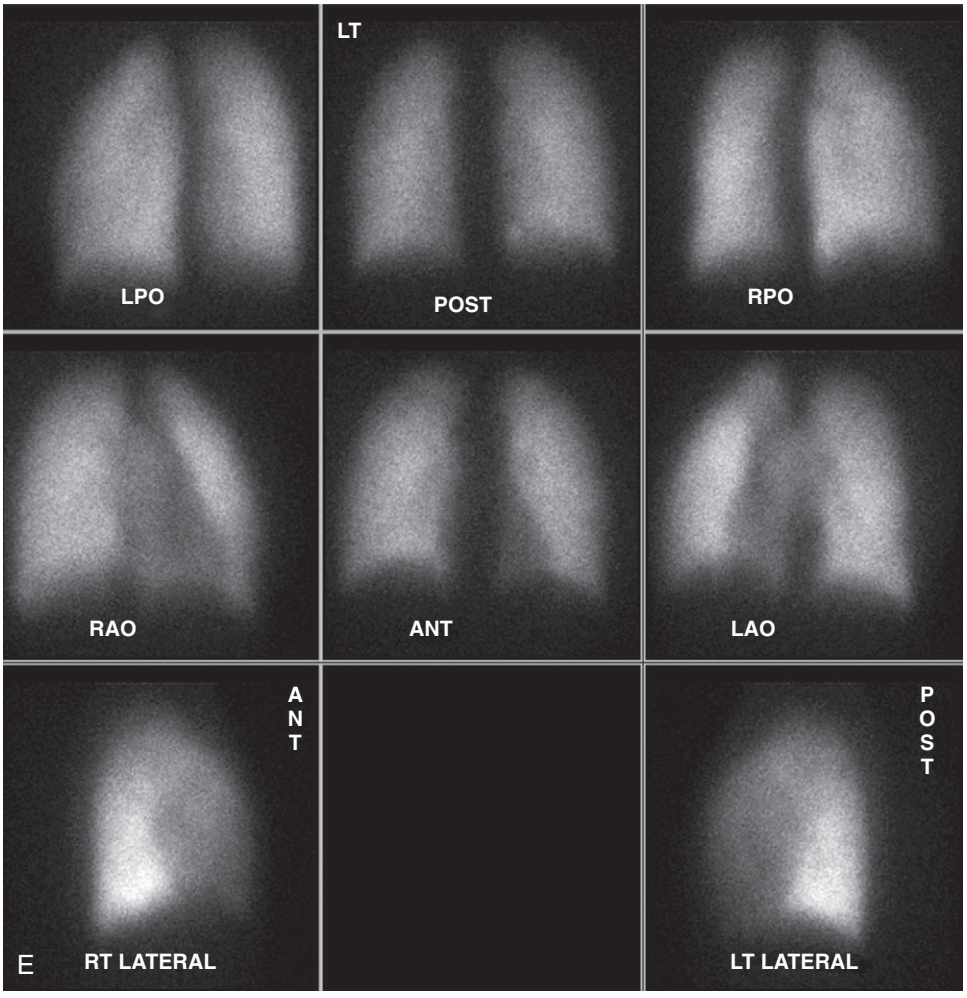


FIGURE 21-1 ■ cont'd. posterior (**D**) views demonstrates a normal breath-hold image and a single wash-in to equilibrium image. No retention is seen on washout (W/O) images. **E,** The technetium-99m–labeled albumin macroaggregates (^{99m}Tc-MAA) perfusion images are normal, with the perfusion outlining the heart and mediastinal structures.

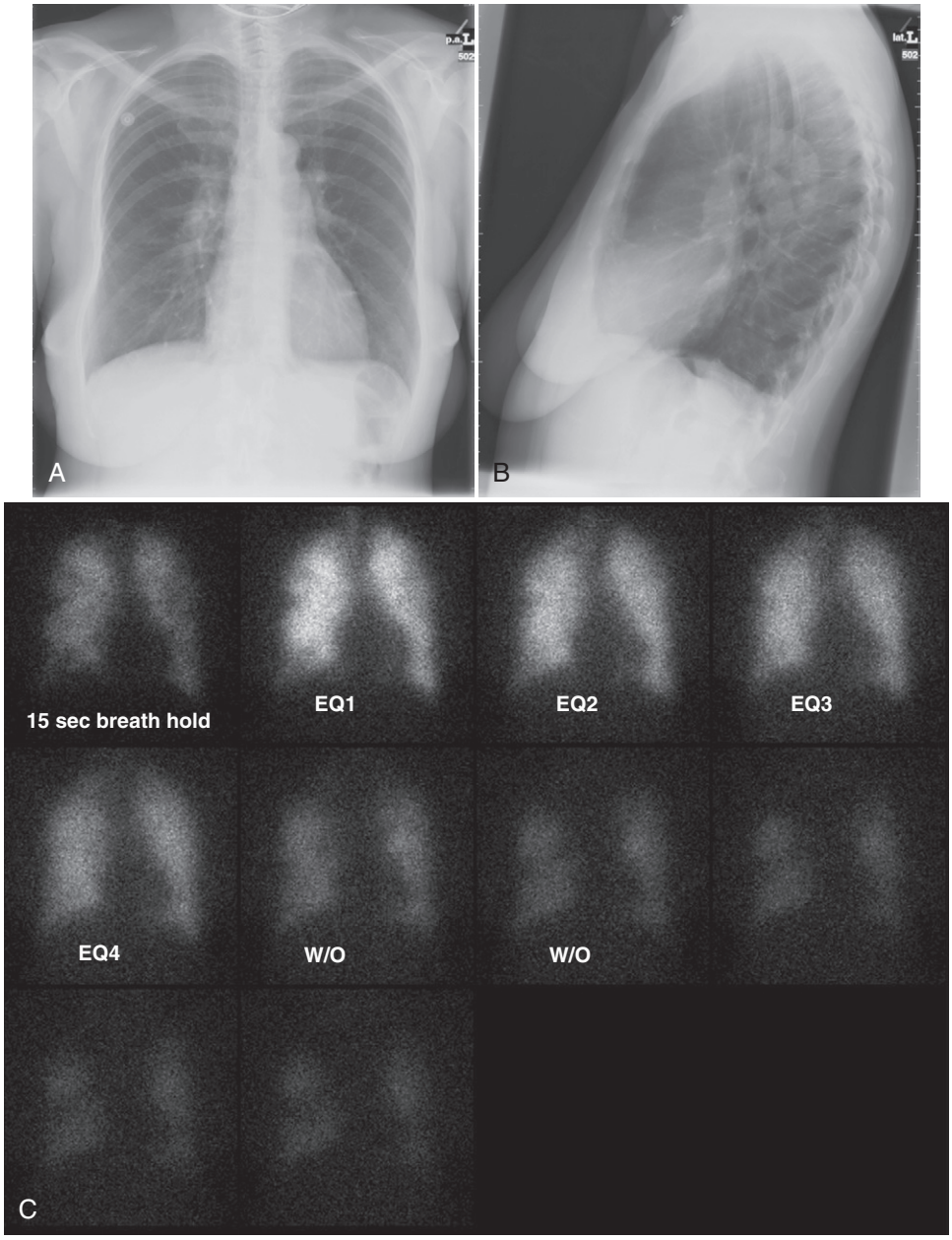


FIGURE 21-2 ■ Example of a very-low-probability V/Q scan. The posteroanterior (**A**) and lateral (**B**) chest radiographs reveal hyperinflated lungs with flattened hemidiaphragms. **C,** Anterior and

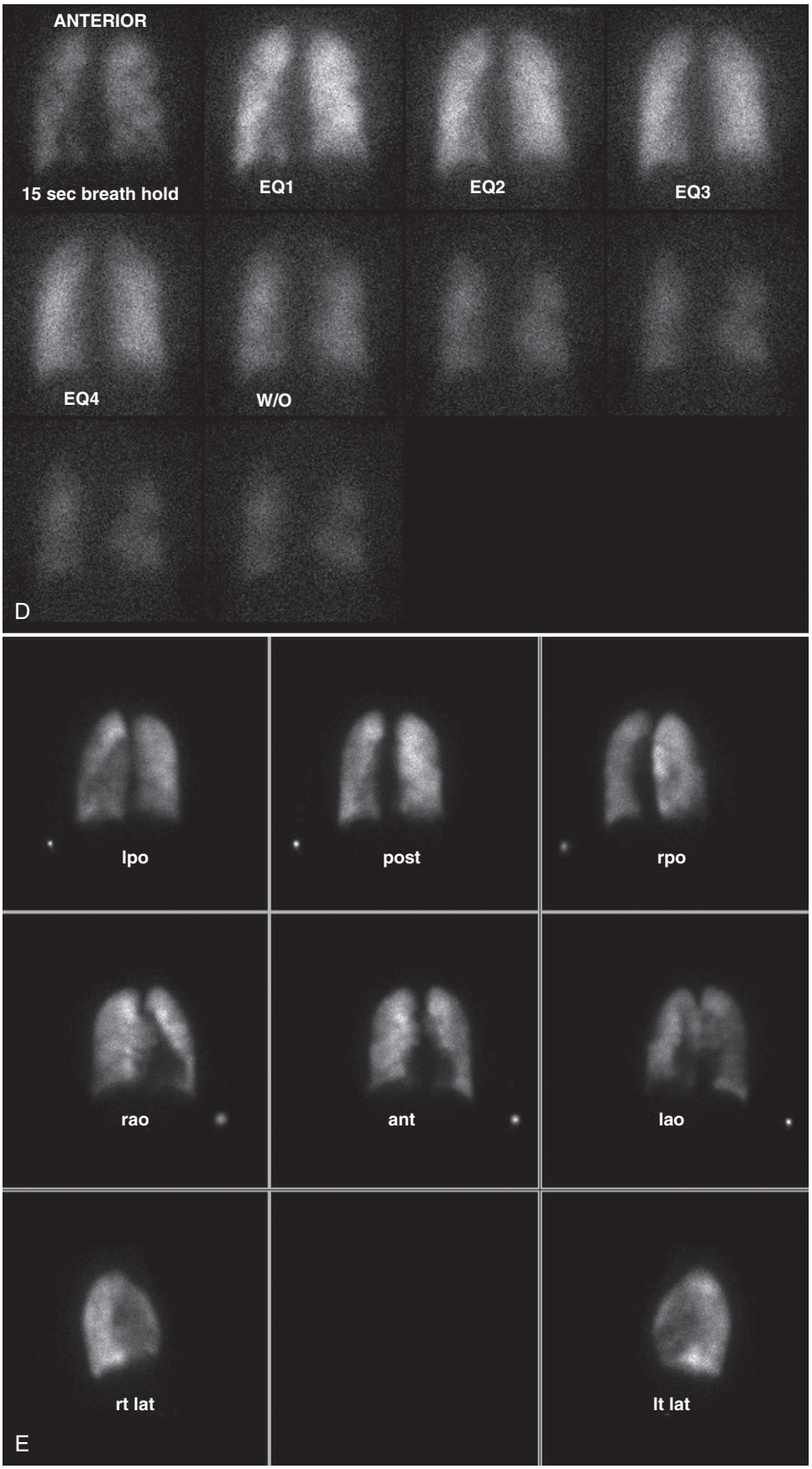
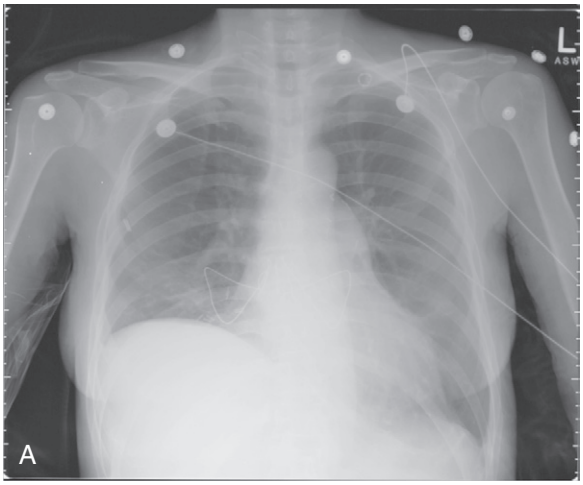


FIGURE 21-2 ■ cont'd. (**D**) posterior ^{133}Xe ventilation images reveal multiple areas of decreased accumulation on the breath-hold images and retention on the washout (w/o) images. **E,** The ^{99m}Tc-MAA perfusion images demonstrate perfusion abnormalities corresponding to the ventilation abnormalities. These are the findings of chronic obstructive pulmonary disease (COPD).



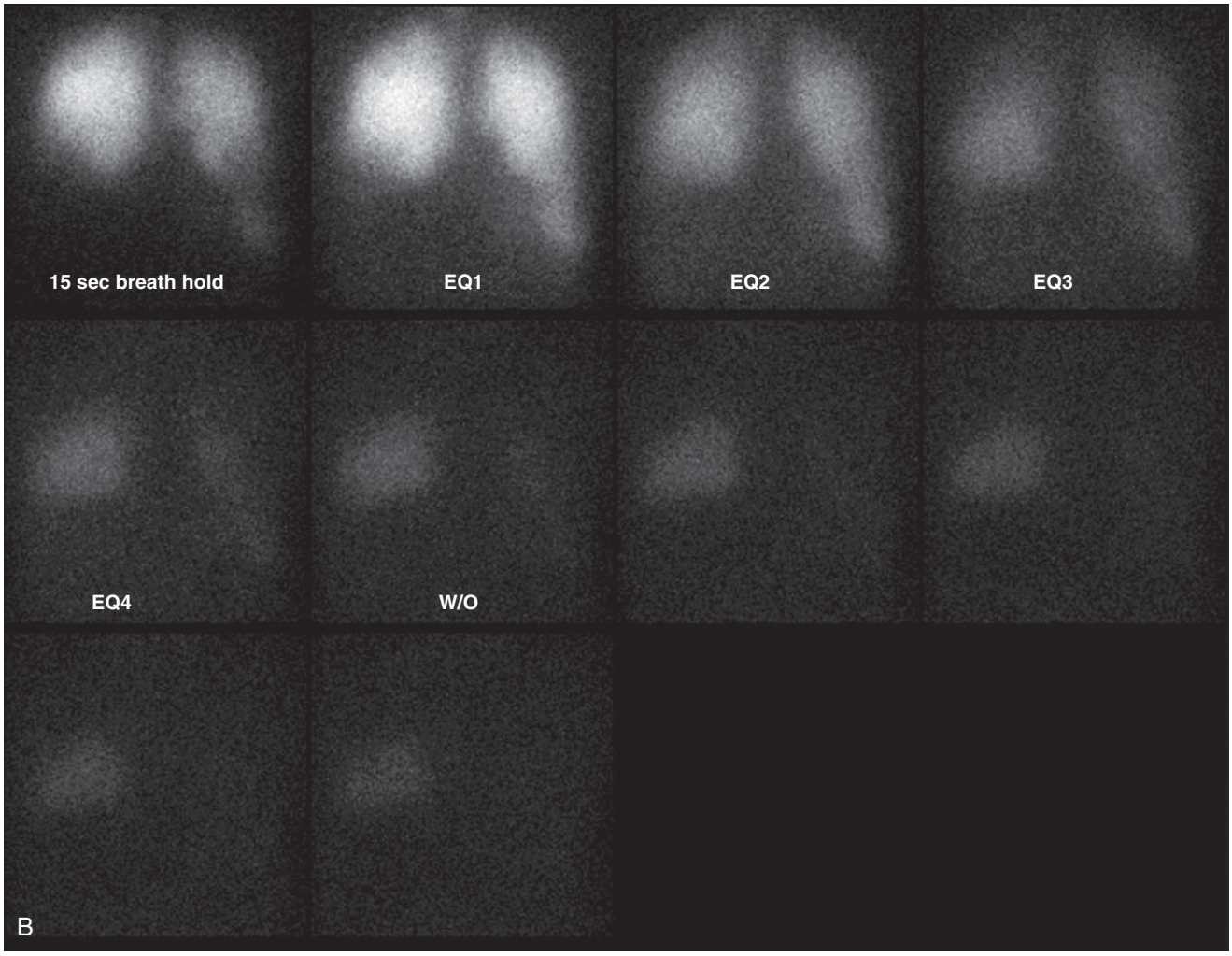


FIGURE 21-3 ■ Example of a low-probability V/Q scan. **A,** An anteroposterior chest radiograph in a patient after bilateral lung transplantation reveals an elevated right hemidiaphragm and small bilateral pleural effusions. Anterior (**B**) and

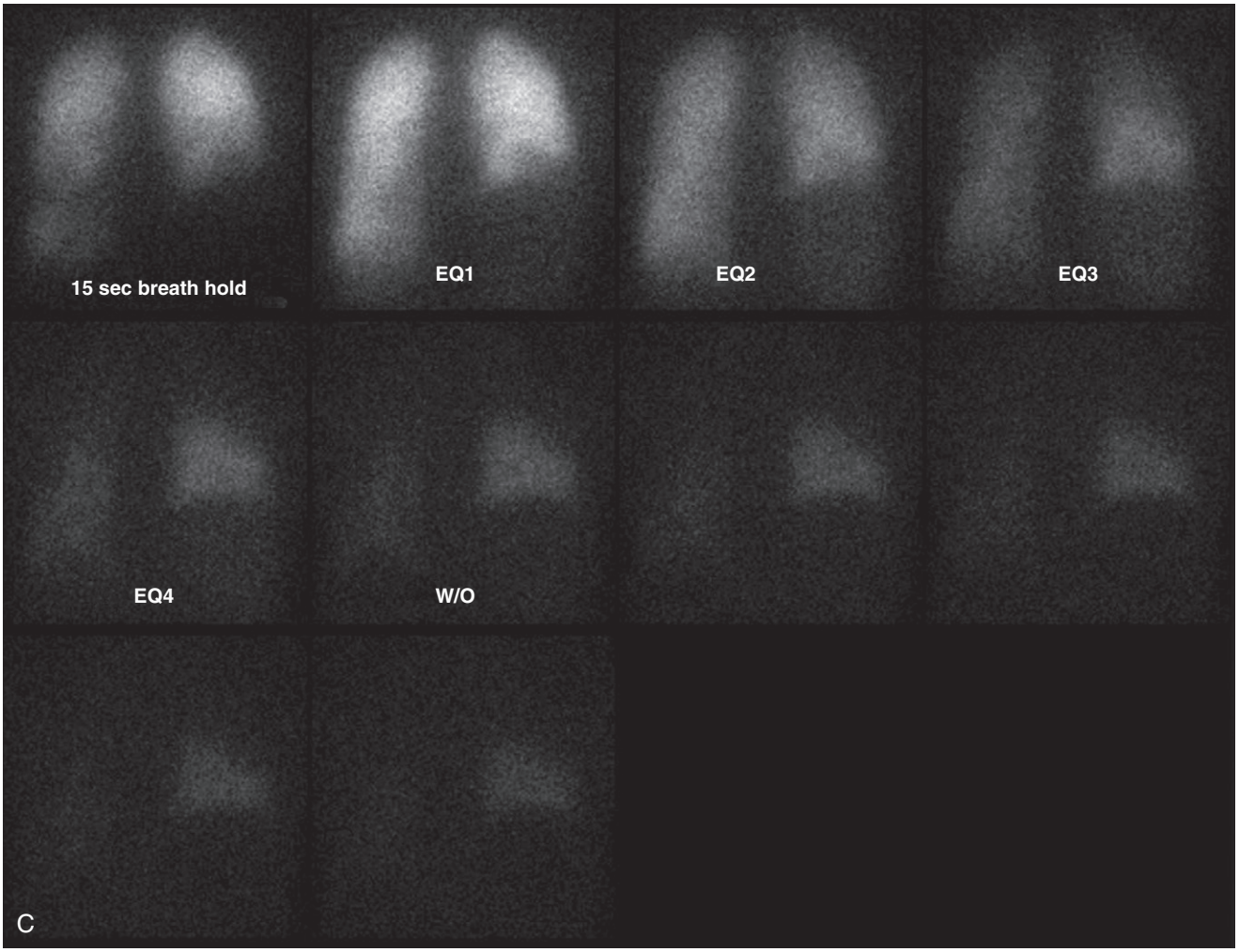


FIGURE 21-3 ■ cont'd. posterior (**C**) ^{133}Xe ventilation images reveal absent ventilation in the right lung base because of the elevated hemidiaphragm, and evidence of decreased ventilation in the right mid-lung and left lower lung.

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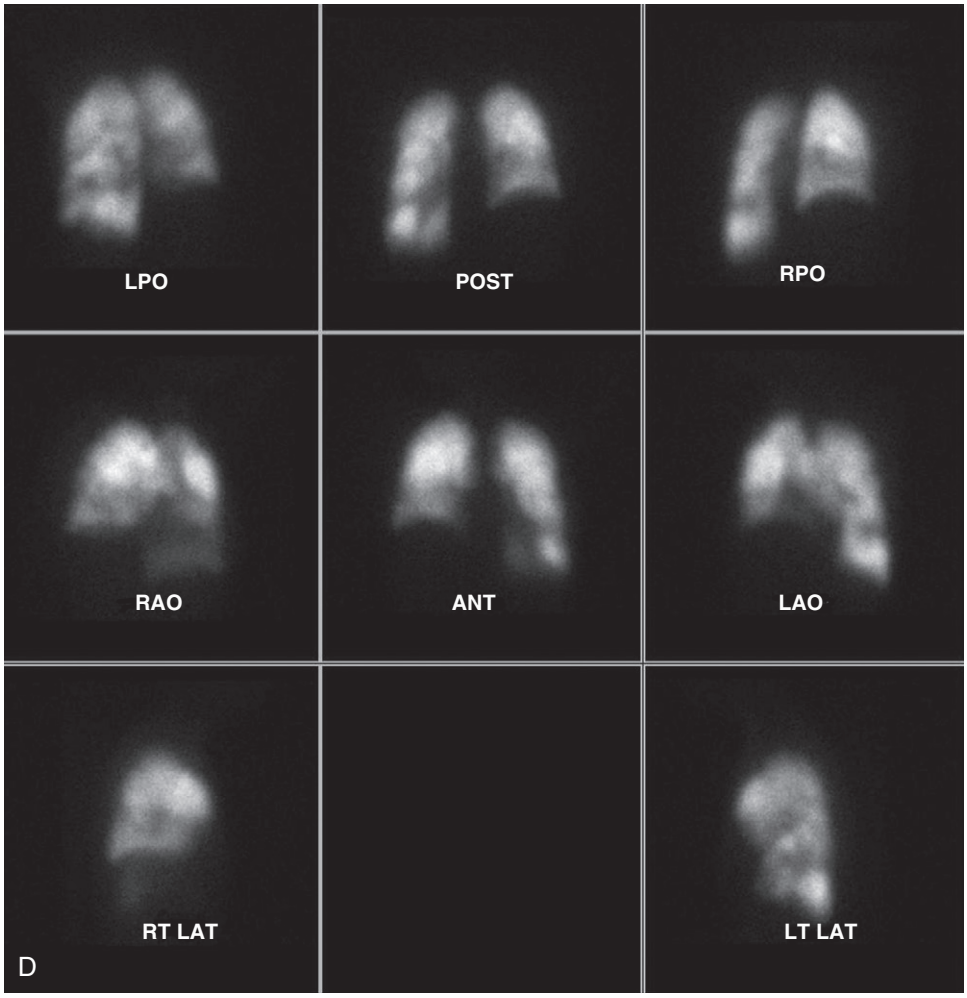

FIGURE 21-3 ■ cont'd. D, The ^{99m}Tc-MAA perfusion images reveal decreased perfusion in the areas of abnormal ventilation and marked heterogeneity without segmental-appearing defects.

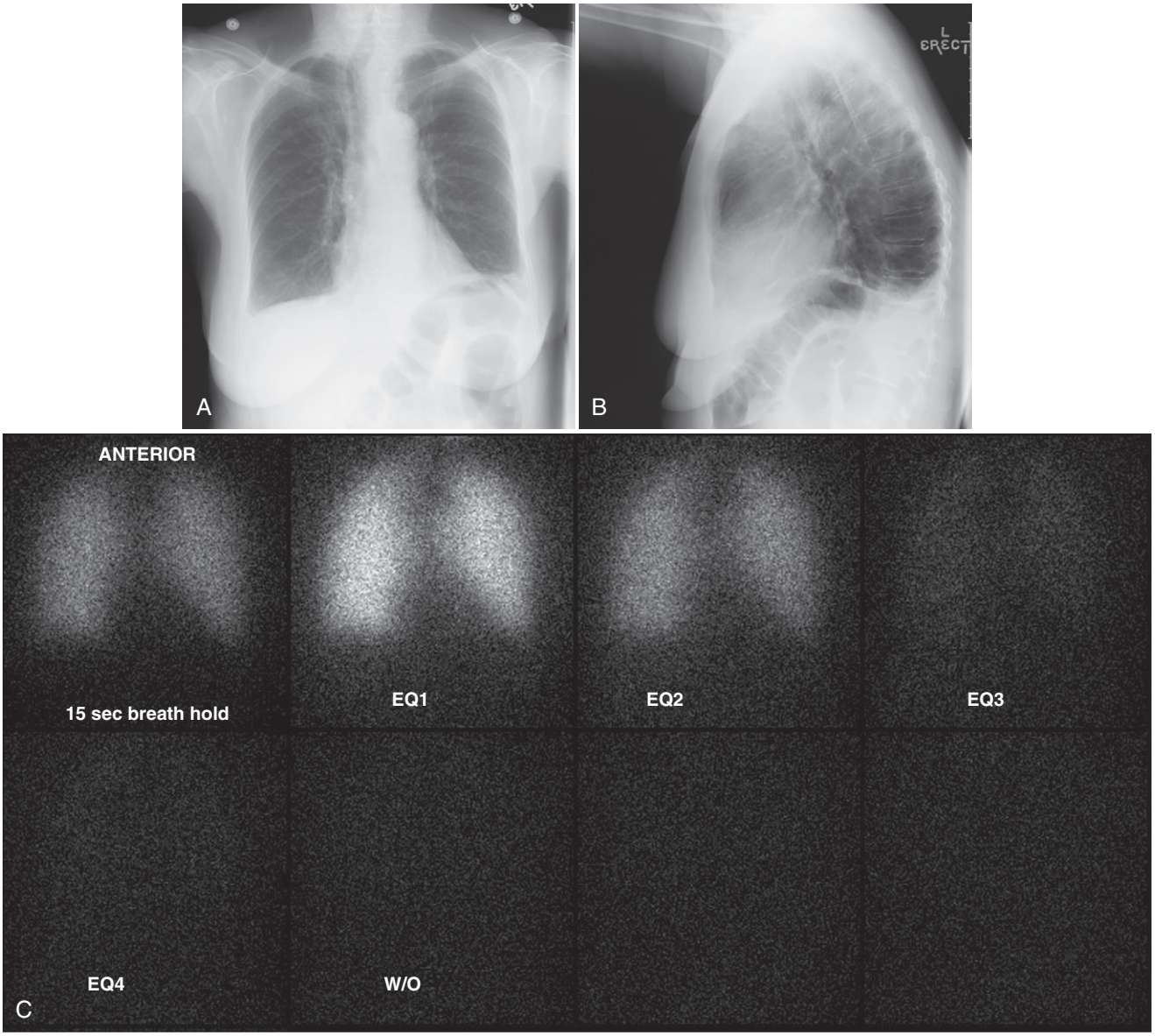

FIGURE 21-4 ■ Example of an intermediate-probability V/Q scan. Posteroanterior (**A**) and lateral (**B**) chest radiographs reveal spiral pleural thickening, small bilateral pleural effusions, and left lower lobe subsegmental atelectasis. Anterior (**C**) and

Continued

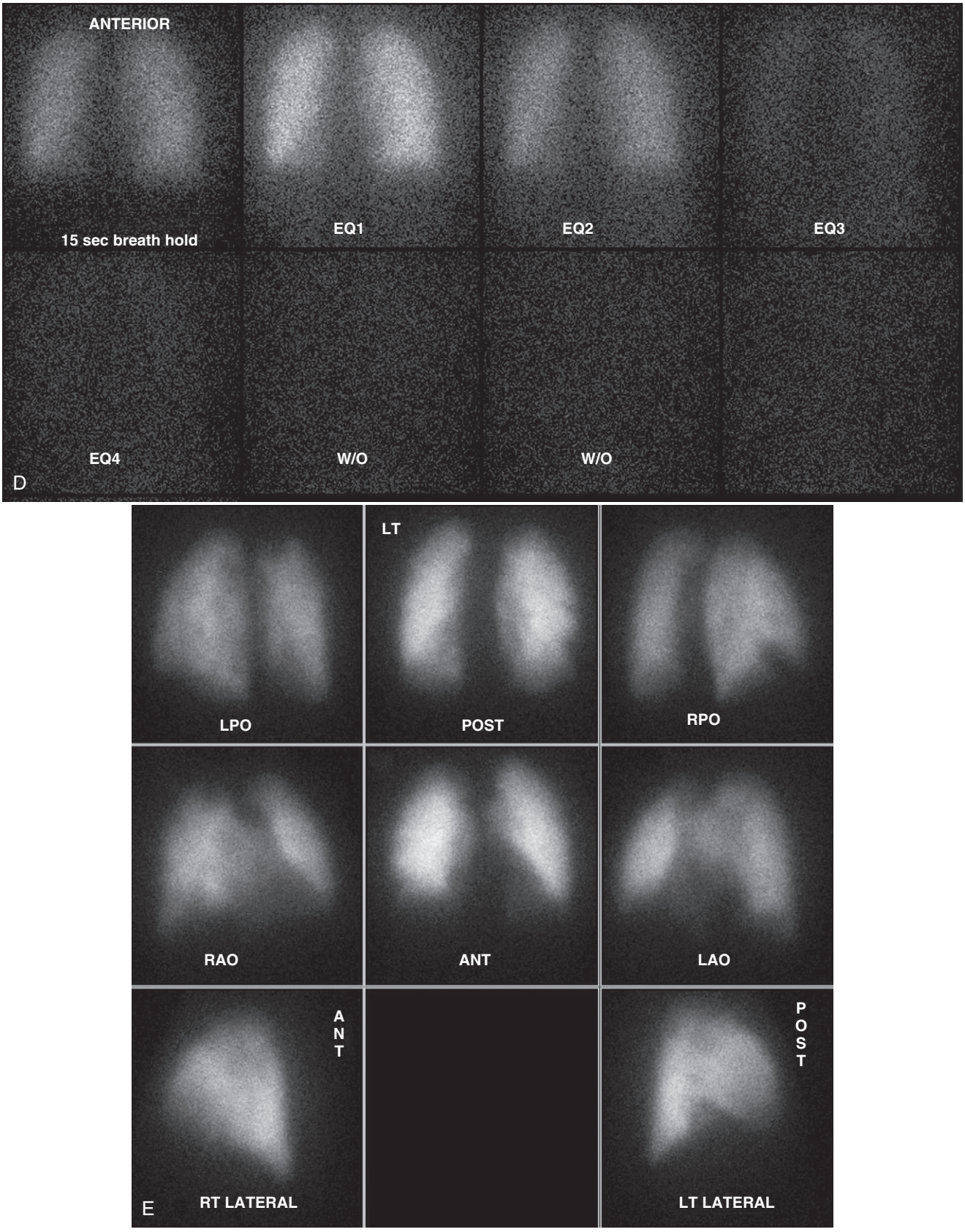

FIGURE 21-4 ■ cont'd. posterior (**D**) ^{133}Xe ventilation images reveal uniform ventilation without definite abnormalities (limited number of equilibrium [EQ] and washout [W/O] images). **E,** The ^{99m}Tc-MAA perfusion images reveal a segmental defect in the lateral basilar segment of the right lower lobe and a moderate defect in the right apex.

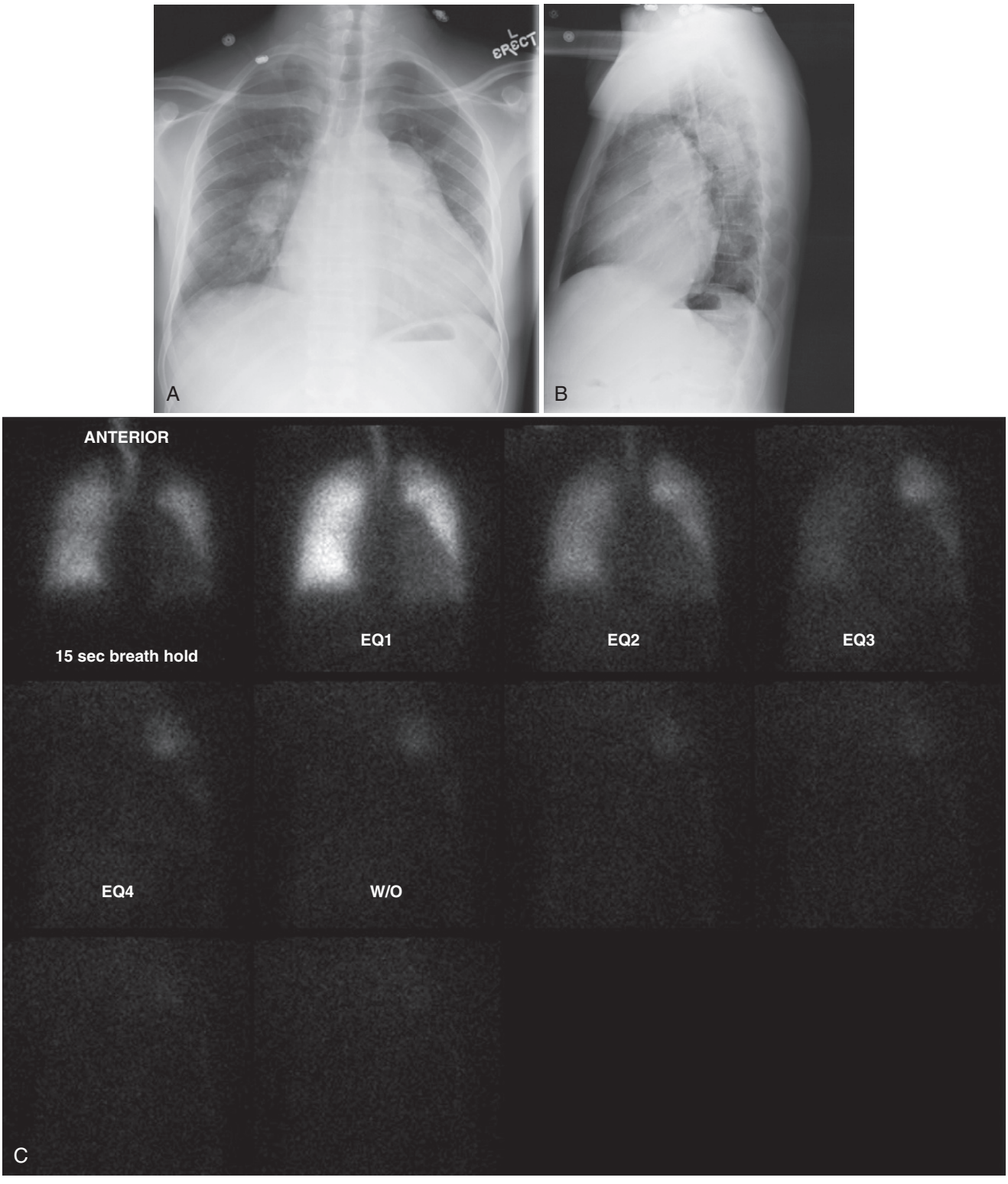

FIGURE 21-5 ■ Example of a high-probability V/Q scan. Posteroanterior (**A**) and lateral (**B**) chest radiographs reveal cardiomegaly with enlarged right and left pulmonary arteries consistent with pulmonary hypertension. Anterior (**C**) and

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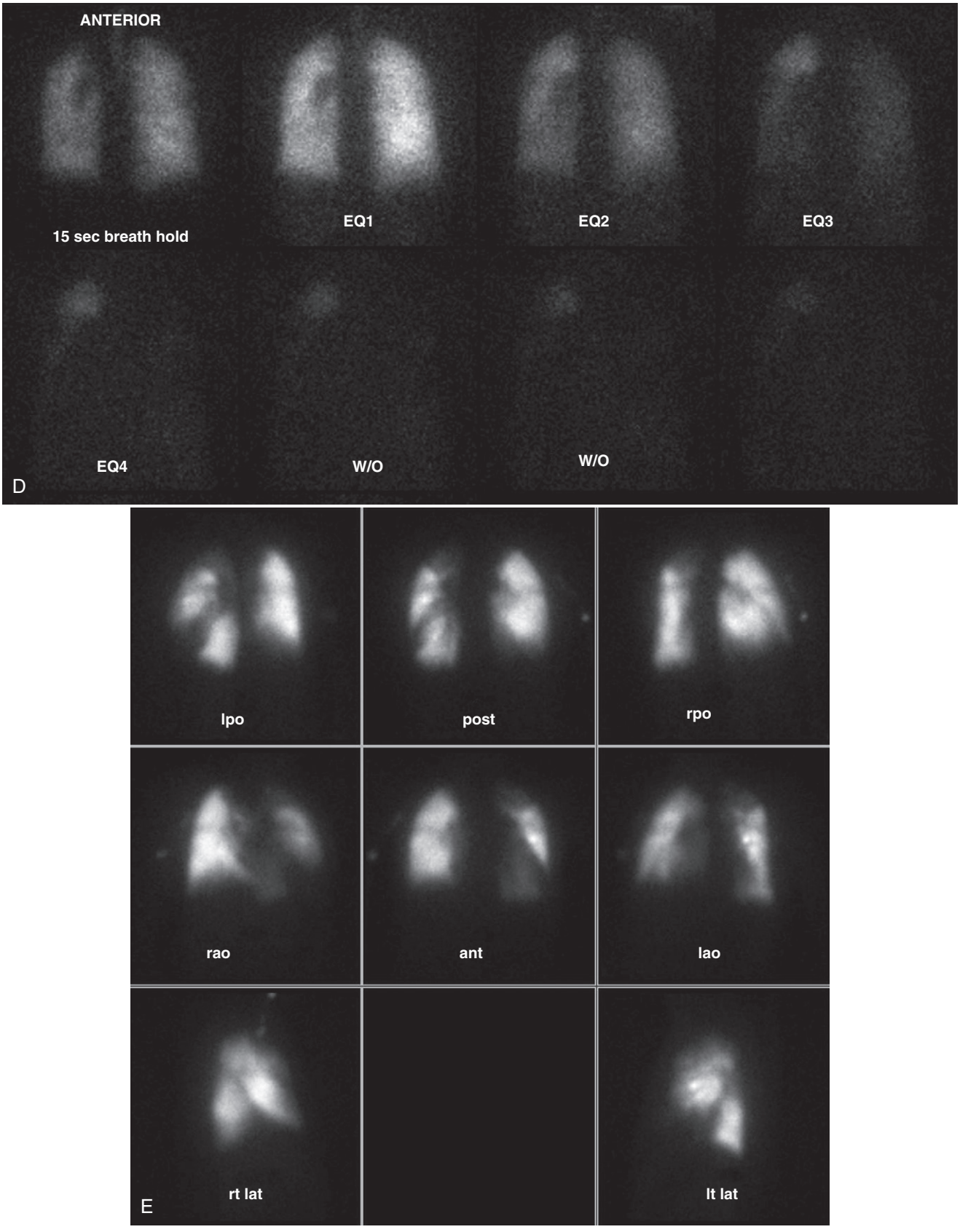

FIGURE 21-5 ■ cont'd. posterior (**D**) ^{133}Xe ventilation images at equilibrium (EQ) and during washout (W/O) reveal evidence of air trapping in the left upper zone. **E,** The ^{99m}Tc-MAA perfusion images reveal multiple bilateral segmental defects.

include the following: nonsegmental lesion, a perfusion defect smaller than a radiographic lesion, two or more V/Q matched defects with regionally normal chest radiograph, one to three small segmental perfusion defects, a solitary triple-matched defect in the mid or upper lung zone confined to a single segment, a stripe sign present around the perfusion defect, and a large pleural effusion.

Pulmonary embolism mimics are included in the low-probability category. These diseases result in V/Q mismatch and are quite uncommon.[18] The disease processes that result in pulmonary embolism mimics involve the pulmonary vessels, producing vascular occlusive physiologic findings including normal ventilation. Most mimics of pulmonary embolism are caused by chronic perfusion deficits from previous pulmonary embolism, intravenous drug abuse, and hilar or mediastinal involvement by bronchogenic carcinoma.[2] Less common causes include vasculitis or other connective tissue disorder, tuberculosis, irradiation, vascular anomalies such as pulmonary arterial agenesis and peripheral coarctation, arteriovenous malformation, surgical pulmonic-systemic shunts, and extrinsic compression of pulmonary arteries or veins from mediastinal malignancy or fibrosis.

Other Diagnostic Patterns

As noted in the PIOPED II criteria (see Table 21-1), a stripe sign results in the defect being considered very low probability for pulmonary embolism. The stripe sign is a rim of activity along the pleura that is greater than the rest of a segmental-appearing defect.[19] This sign has been found to be between 90% and 95% reliable as an indication of nonembolic disease.[20] Another diagnostic pattern on V/Q scans is the segmental contour pattern that is considered to be the result of lymphangitic spread of tumors.[21] The venules and arterioles may also be involved with tumor microemboli. With this pattern, the segments are outlined by the defects, and the defects are not the segments themselves. The pattern of diffuse pulmonary edema on the chest radiograph generally results in minimal, if any, perfusion abnormality.[22] Frequently, whenever a chest radiograph is shown to have diffuse abnormality, it is assumed that the V/Q scan would be intermediate probability for pulmonary embolism. However, in a study of 55 patients with diffuse radiographic opacities, 73% had normal or near-normal perfusion images.[22]

Preoperative Evaluation

Ventilation and perfusion imaging by the methods used to study patients suspected of having pulmonary embolism has also proved useful in the preoperative evaluation of patients with cancer of the lung. Because many patients with newly diagnosed and potentially curable bronchogenic carcinoma have coexisting COPD, both being complications of inveterate cigarette smoking, the issue sometimes arises as to whether the patient can tolerate lung resection and, if so, how much lung can be removed (e.g., lobectomy or pneumonectomy). Scintigraphic studies of regional lung function are probably not warranted if the patient's preoperative forced vital capacity (FVC) is greater than 2 L and the FEV_1 is greater than 50%. Lower values raise questions, however, because the functional limitations of lung resection, in general, begin to affect daily life when postoperative FEV_1 is reduced to 0.8 L or less.

Postoperative lung function can be reasonably well estimated by either ventilation or perfusion lung scanning, but perfusion with ^{99m}Tc-MAA is the preferred method owing to its simplicity and slight theoretical advantage. After summing the radioactivity over each lung in the anterior and posterior views, the postoperative FEV_1 is predicted by multiplying the preoperative value by the ratio of the counts in all the lung to be preserved to the total activity.[23,24] Recently, studies using dynamic perfusion magnetic resonance imaging (MRI) were shown to be as accurate (but more costly and complicated) as perfusion scintigraphy for predicting postoperative lung function in patients with lung cancer.[24]

POSITRON EMISSION TOMOGRAPHY

Imaging evaluation of a thoracic abnormality depends on a variety of factors, including patient symptoms and history. Plain chest radiographs are still the most common radiographic examination as they provide enormous amounts of anatomic information and often dictate whether additional imaging is required. Whereas CT is usually the next study performed, PET with FDG has emerged as an invaluable tool for in patients with suspected cancer. More recently, the combination of CT-PET has been used, primarily to differentiate benign from malignant pulmonary lesions that are indeterminate on conventional studies, to stage non–small cell lung cancer (NSCLC), to assist in planning radiotherapy, and to distinguish recurrent or persistent cancer from post-treatment fibrosis. In early stage NSCLC, FDG uptake correlates with survival and thus provides prognostic information. Most importantly, PET is a new direction for radiology and was the genesis of a molecular imaging approach, complementing more traditional anatomic and morphologic radiographic studies. This section focuses on the current clinical indications and utility of PET imaging in the thorax.[24a]

Differentiating Benign and Malignant Lesions

Diagnostic imaging plays a central role in evaluating patients with or suspected lung cancer, but unfortunately, conventional studies do not always provide the information necessary to establish a diagnosis or plan treatment. The etiology of a lung lesion may be suggested on conventional imaging studies, but further invasive evaluation is often required.[25] Thus, in an effort to improve diagnostic accuracy while reducing the necessity of follow-up studies and biopsies, new noninvasive techniques are constantly being explored. Since the mid 1990s, PET has become a routine procedure for

differentiating benign from malignant lesions. The rationale for using FDG, a glucose analogue, as the imaging probe is that increased glucose metabolism is a fundamental property of malignancies, and that FDG preferentially accumulates in malignant tumors as compared with benign abnormalities.[26,27]

The radiologic manifestations of NSCLC are variable, although it typically presents as a focal pulmonary opacity or solitary pulmonary nodule. However, not all pulmonary lesions are malignant, and differentiating benign from malignant lesions is a common radiologic dilemma. Once an abnormality is detected, comparison with prior radiographs or CT is suggested to determine growth. If the lesion is stable over a 2-year period, then it is highly suggestive of a benign abnormality.[28] Many lesions remain indeterminate, and a decision to follow the lesion for growth, or alternatively to intervene (i.e., biopsy or resection), depends on clinical factors such as age, past medical and smoking history, and suspicious radiologic findings.

PET with FDG is now commonly used for indeterminate pulmonary lesions.[29,30] The results from these studies have been consistent, with an overall accuracy around 85%. Those patients with increased FDG uptake—a positive PET scan—require further attention, as these lesions are considered malignant until proven otherwise (Figs. 21-6 and 21-7). Unfortunately, not all lesions with increased FDG uptake are malignant. False-positive scans (positive PET scans that prove benign) have been reported with a number of entities, including infectious and inflammatory processes such as tuberculosis, histoplasmosis, and rheumatoid nodules.[31–34]

Lesions that do not have increased FDG uptake are usually benign. These patients can be followed with sequential imaging to determine resolution or stability. False-negative studies are unusual, but may be seen with some small (<10 mm) lung cancers, bronchoalveolar cell cancers, or carcinoid tumors.[35,36] If the lesion grows, then it should be considered malignant, and a biopsy or resection is recommended. The rare patient with a negative PET scan who later proves to have NSCLC typically has a biologically indolent tumor. The short delay before a diagnosis is made does not appear to change prognostic outcome.[37,38]

Several studies have shown that a diagnostic strategy that incorporates PET is cost-effective and will reduce

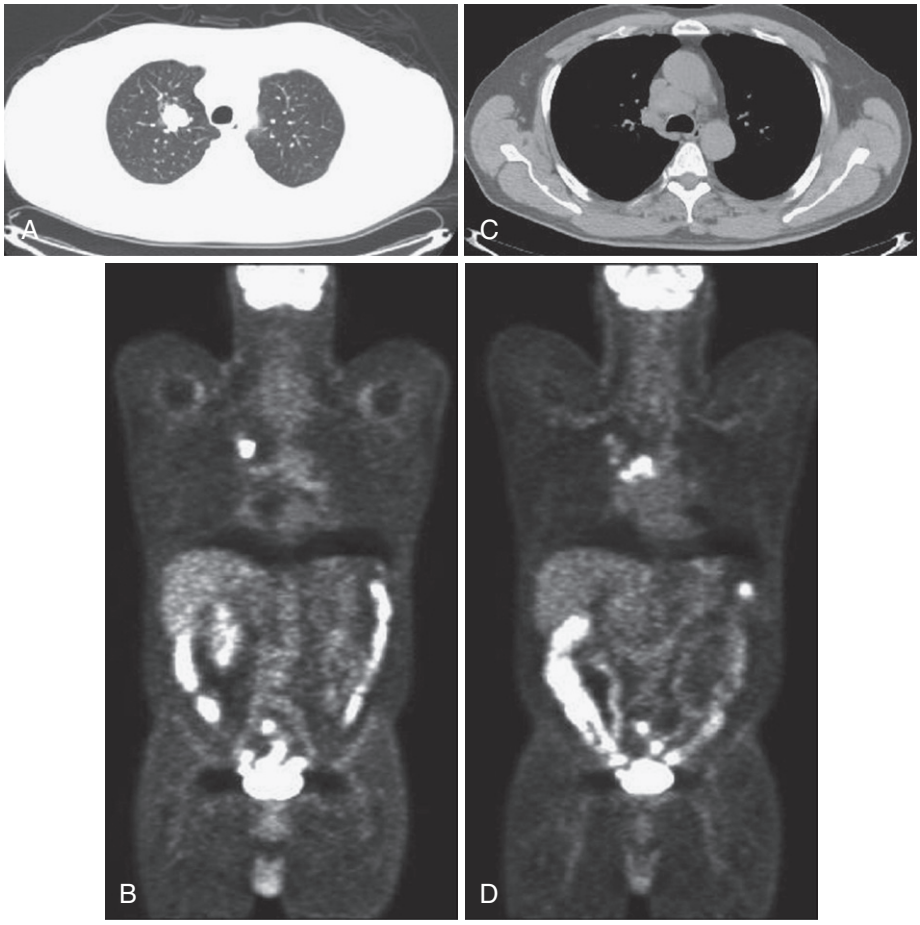

FIGURE 21-6 ■ A 63-year-old man with a right upper nodule on chest radiograph. **A,** Axial computed tomography (CT) image confirms an indeterminate nodule. **B,** Coronal positron emission tomography (PET) image shows increased [^{18}F]fluoro-2-deoxy-D-glucose (FDG) uptake consistent with a malignant lesion. **C,** CT shows enlarged pretracheal lymph nodes. **D,** Coronal PET image demonstrates increased FDG activity in the pretracheal and right paratracheal regions suggestive of lymph node metastasis. Mediasternoscopy confirmed stage IIIA non–small cell lung cancer (NSCLC).

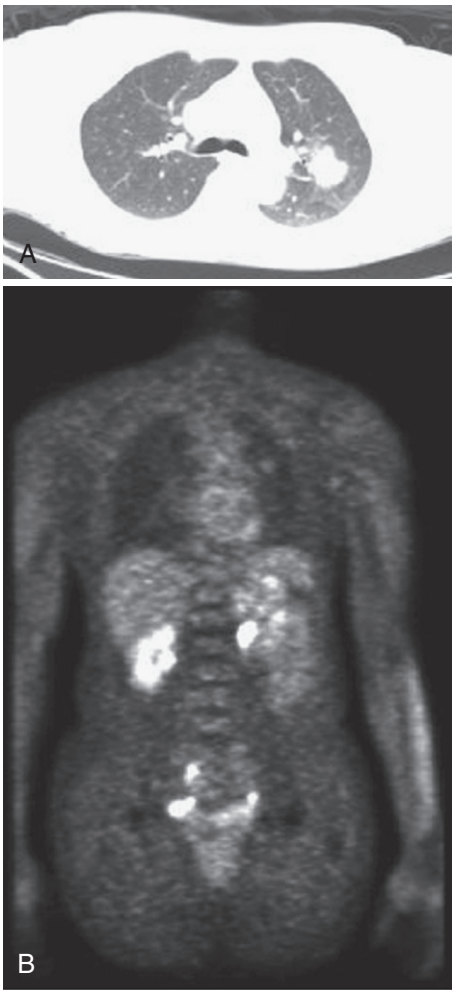

FIGURE 21-7 ■ A 65-year-old woman presented with an irregular left upper lobe mass. **A,** Axial CT confirms the irregular left upper lobe nodule. **B,** Coronal PET shows no significant increased FDG activity consistent with a benign lesion. This was followed for over 2 years and did not change in size consistent with a benign abnormality.

the number of patients who undergo resections of indeterminate lesions that prove to be benign by 15%.[39,40] It was estimated that the combination of PET and CT to evaluate indeterminate focal pulmonary lesions could save almost $1,200 per patient as compared with the use of CT alone.[41,42]

Staging Lung Cancer

Once a diagnosis of lung cancer has been made, accurate staging is essential in determining therapeutic options and prognosis. The primary goal of radiologic studies is to help distinguish those patients in whom the tumor is potentially resectable (stages I to IIIA) from those in whom the tumor is not resectable (stages IIIB and IV). Imaging evaluation typically includes thoracic CT, a radionuclide bone scan, and brain imaging (CT or MRI) in the search for extrathoracic metastases. Unfortunately, despite careful clinical evaluation, conventional staging techniques are suboptimal: some patients are overstaged and others are understaged. Tissue sampling is required for histologic confirmation prior to initiation of therapy, but this is limited by the imaging studies' ability to detect an anatomic abnormality suggestive of tumor.

With the addition of PET, more accurate lung cancer staging can be achieved. Several studies have reported changes in patient management in up to 40% of cases as compared with conventional imaging alone. Some patients first considered to be resectable had more advanced disease, whereas others with anatomic abnormalities suggestive of metastases were found to have localized, resectable disease.[43–46]

The tumor-node-metastasis (TNM) descriptors used to stage tumors were designed for anatomic assessment and are not always applicable to PET imaging. PET assessment of tumor (T) status differs from conventional anatomic imaging in that lung lesions are typically interpreted as either positive or negative for malignancy.

Although CT, and occasionally MRI, is used to evaluate hilar and mediastinal nodes, the accuracy of detecting nodal metastases with conventional studies using a short axis diameter (>1 cm) is approximately 60%.[47] Normal-sized lymph nodes may harbor malignant cells, and enlarged nodes may be benign.[48,49] However, PET is more sensitive and specific than CT alone, with accuracy reported to be greater than 80% (Fig. 21-8).[44,50] In one study, PET correctly changed nodal staging as determined by CT in 24% of presurgical patients. In another report of patients with clinical stage I disease, mediastinoscopy was deemed unnecessary if the PET showed normal mediastinal nodal activity.[51] In those patients with increased FDG uptake in hilar and mediastinal lymph nodes, PET provides a road map for surgical nodal sampling and should reduce the number of patients with unresectable mediastinal nodal metastases who, in the absence of histologic diagnosis, undergo resection.

Lung cancer most commonly metastasizes to the regional lymph nodes, adrenal glands, bones, brain, and liver.[47] Whereas routine radiologic evaluation remains controversial, PET imaging appears to improve the noninvasive detection of extrathoracic disease. Whole-body PET has the capability to stage both intra- and extrathoracic disease in a single examination with more improved accuracy than conventional imaging alone.[46,52]

The adrenal glands are a common site of metastasis in NSCLC.[53] These lesions are occasionally difficult to distinguish from benign abnormalities, as up to two thirds of adrenal lesions detected by CT in patients with lung cancer are benign. Consequently, PET has been advocated to evaluate adrenal masses as the sensitivity and specificity for detecting adrenal metastases in lung cancer patients are reported to be over 80%.[54]

The bones are another common site of metastatic disease, and metastases are found in up to 20% of patients at presentation.[55] At least 20% of these patients are asymptomatic, but bone scans using ^{99m}Tc-MDP are only 60% specific, with a sensitivity of 90%. PET imaging in patients

FIGURE 21-8 ■ A 75-year-old presented with cough and hemoptysis. **A,** Axial CT demonstrates a thick-walled right upper lobe cavitary lesion. **B,** Coronal PET image demonstrates significant FDG activity suggestive of a malignancy. Biopsy revealed NSCLC.

with lung cancer has been shown to detect lesions not found on these other studies. The accuracy, sensitivity, specificity, and positive and negative predictive values for bone metastases are all reported to be over 90%.

Lung cancer also metastasizes to the brain, and up to 12% of patients with brain metastases are asymptomatic at presentation. Either CT or MRI is typically used to search for central nervous system lesions. Because the normal brain has significant glucose uptake, metastases may be difficult to detect on PET.[56] For this reason, PET imaging has a low sensitivity (68%) in detecting brain metastases and should not be used to replace CT or MRI.

Although lung cancer commonly metastasizes to the liver, it is an unusual isolated site of disease, particularly in the absence of metastatic disease to regional lymph nodes. Nevertheless, whole-body PET scanning may be useful in the evaluation of hepatic lesions that are indeterminate by conventional imaging. Several small series have suggested that PET is more specific than CT in detecting liver metastases.[46,57] False-positive PET studies can rarely occur with other lesions, such as liver abscesses or other malignant primary liver lesions (cholangiocarcinoma and hepatocellular carcinoma).[58]

In summary, the use of PET for routine staging of non–small cell lung cancer appears to improve detection of metastases and reduces both cost and morbidity. With the use of PET, preliminary data suggest that bone scintigraphy may be eliminated, although brain imaging is required, if clinically indicated.

Posttreatment Follow-up

After patients have been treated for lung cancer, anatomic changes including airway distortion, focal pulmonary opacities, and soft-tissue abnormalities often develop within the thorax and chest wall. Depending on the therapeutic intervention (surgical or radiation), benign abnormalities including posttreatment scarring and fibrosis may be impossible to distinguish from residual cancer on conventional imaging studies.

Unfortunately, once patients have had first-line therapy, it remains uncertain if detecting early recurrence will improve survival. If therapeutic options improve, it may become important to distinguish benign posttreatment changes from residual or recurrent malignancy. PET studies have shown accuracy of 78% to 98%, sensitivity of 97% to 100%, and specificity of 62% to 100%.[59–62] However, false-positive results may occur immediately following surgery or irradiation. It is therefore recommended that FDG-PET studies in this situation be obtained approximately 4 to 5 months after completion of the therapy, which allows inflammatory changes to subside and provides a more accurate assessment of tumor viability (Fig. 21-9).

Planning Radiotherapy

Planning for radiation treatment traditionally uses conventional imaging, including chest radiographs, CT, or MRI for an anatomic description of the extent of the tumor. This treatment planning relies on morphologic features, which do not always provide a clear distinction between benign and malignant tissue. Several preliminary studies suggest that CT-PET is more accurate than other imaging studies in making this distinction.

Radiation ports are typically planned to treat the primary lesion, with prophylactic doses to the mediastinum to treat microscopic tumor foci not identified by conventional imaging studies.[63–65] It is common to use small margins on CT-defined targets when planning three-dimensional treatment to minimize radiation damage to adjacent normal tissues. The use of CT-PET when planning radiation ports has been shown to influence treatment in approximately 30% of patients, resulting in enlarging portions of the irradiated margins up to 15 cm.[65,66] The use of anatomic imaging alone would have meant inadequate radiation coverage and a higher

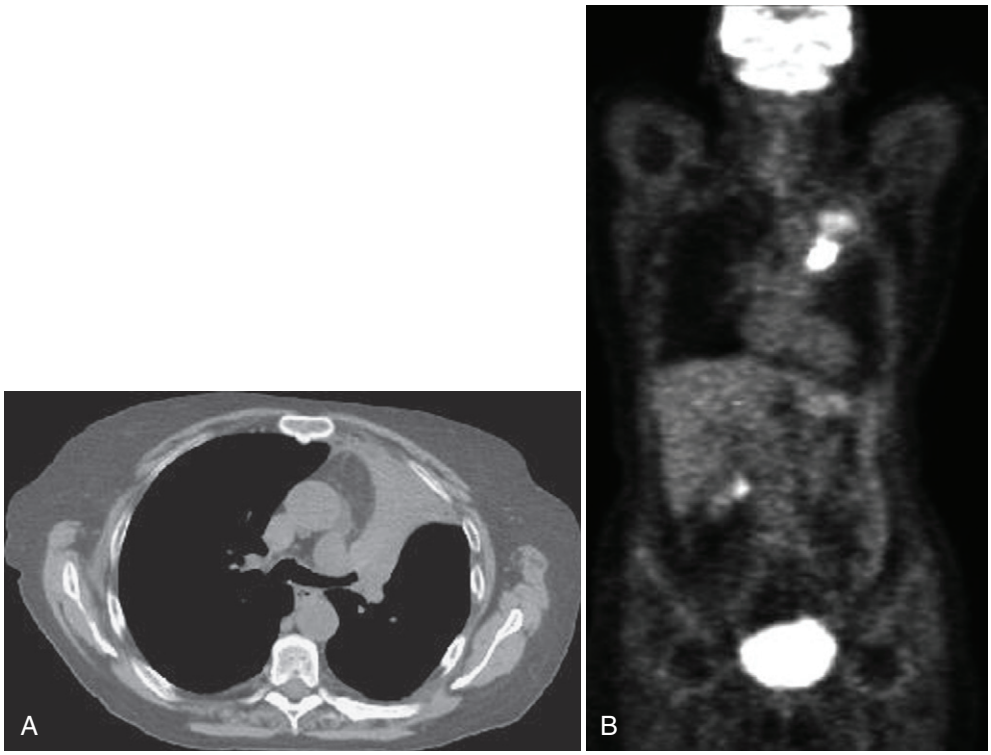

FIGURE 21-9 ■ A 57-year-old man with treated NSCLC presented with increasing cough. **A,** Axial CT image showed obstruction of the left upper lobe bronchus with associated left upper lobe atelectasis. **B,** Coronal PET image demonstrates significant activity in the left hilum consistent with recurrent lung cancer. Bronchoscopy proved recurrent NSCLC.

chance of local recurrence. In addition, in poorly demarcated tumors, PET scans can identify the neoplastic focus to be smaller than suspected by conventional imaging,[67,68] potentially allowing irradiation of smaller portals with less morbidity. Thus, for radiation planning, integrating CT-PET appears to be more accurate than CT alone in defining tumor extent. Future studies will show if this indeed is associated with increased survival and reduced morbidity.

Prognostic Information

Although conventional imaging studies elucidate anatomic detail, there is minimal prognostic information. However, several recent PET studies suggest that PET may be usefully employed as a marker that predicts response to therapy and outcomes.[37,69-71] The amount of FDG uptake in the primary lesion at the time of diagnosis in patients with early-stage NSCLC correlates with survival, but no definite correlation exists between FDG uptake and late-stage disease.[70] Once patients have been treated for lung cancer, a positive PET scan in the thorax is associated with a statistically worse survival than a negative study. Other prospective trials suggest that complete reduction in metabolic activity of the tumor site to background activity (complete response) is indicative of true local remission of the disease.[61,71]

When assessing a patient's operability following induction chemotherapy (stage IIIA-N2), some preliminary studies have suggested PET as a noninvasive method for selecting those patients who should proceed to surgical resection.[72,72a] Repeat mediastinoscopy in irradiated patients is difficult due to fibrosis, and neither the disappearance of lymphadenopathy nor a greater than 50% decrease of the primary tumor diameter on CT was significantly associated with improved survival. Similarly, in a recent study in potentially resectable patients receiving neoadjuvant chemotherapy, a change in FDG activity on PET did not correlate with survival. Therefore, PET to predict long-term response is not indicated in these patients.

FUTURE DEVELOPMENTS

PET provides a new direction for tumor imaging, and with an increased understanding of tumor biology, accompanied by improvements in detection, characterization, and staging, this type of noninvasive molecular assessment of tumors is likely to improve patient outcome. Future developments include technologic improvements in scanner design and resolution, in addition to the design of novel tumor-specific imaging probes. Although FDG has a high sensitivity, the lack in specificity places limits on its clinical utility. A series of tumor-specific probes could then be used to produce a noninvasive "tumor profile." Such molecular imaging characterization of a thoracic abnormality could have significant diagnostic, prognostic, and therapeutic implications.

KEY POINTS

- Although multidetector CTA is being increasingly used to evaluate patients with suspected pulmonary embolism, V/Q scintigraphy plays an important backup role in patients with renal dysfunction, contrast allergy, massive obesity, and low clinical suspicion of embolism and when radiation is contraindicated.
- Newly revised criteria for evaluating V/Q scintigraphic findings in patients with suspected pulmonary embolism show that the sensitivity of a "pulmonary embolism present" interpretation was 77% and that the specificity of a "pulmonary embolism absent" was 98%: thus confirming the diagnostic efficacy of the method.
- V/Q scintigraphy is also useful for predicting the level of pulmonary function that will remain postoperatively in patients with cancer of the lung who have abnormal function to begin with and are being considered for resectional surgery.
- Since the mid 1990s, PET imaging in the thorax has become an invaluable tool in managing patients with cancer. It is particularly valuable in evaluating patients with an indeterminate pulmonary nodule and in staging patients with NSCLC.
- PET appears useful in providing prognostic information in early-stage NSCLC, in suggesting recurrent disease following treatment, and in planning radiotherapy. PET does not appear useful as a prognostic marker in patients with advanced-stage disease nor in predicting survival following neoadjuvant therapy.

References

1. Worsley D, Gottschalk A: Nuclear medicine techniques and applications. *In* Murray JF, Nadel JA, Mason RJ, Boushey HA (eds): Textbook of Respiratory Medicine (3rd ed). Philadelphia: Lippincott Williams & Wilkins, 1990, pp 697–723.
2. Sostman HD, Gottschalk A: Evaluation of patients with suspected venous thromboembolism. *In* Sandler MP, Coleman RE, Patton IA, et al (eds): Diagnostic Nuclear Medicine. Philadelphia: Lippincott Williams & Wilkins, 2003, pp 345–366.

2a. Bhargavan M, Sunshine JH, Hervey SL, et al: The actual role of CT and ventilation-perfusion scanning in workup for suspected pulmonary embolism: evidence from hospitals. AJR Am J Roentgenol 193:1324–1332, 2009.

2b. Anderson DR, Barnes DC: Computerized tomographic pulmonary angiography versus ventilation-perfusion lung scanning for the diagnosis of pulmonary embolism. Curr Opin Pulm Med 15:425–429, 2009.

3. Stein PD, Fowler SE, Goodman LR, et al: Multidetector computed tomography for acute pulmonary embolism. N Engl J Med 354:2317–2327, 2006.
4. Sostman HD, Stein PD, Gottschalk A, et al: Acute pulmonary embolism: Sensitivity and specificity of ventilation-perfusion scintigraphy in PIOPED II study. Radiology 246:941–946, 2008.
5. Walsh P, Greenspan RH, Simon M, et al: Angiographic severity index for pulmonary embolism. Circulation 18(Suppl):101–108, 1973.
6. Investigators PIOPED: Value of the ventilation/perfusion scan in acute pulmonary embolism: Results of the Prospective Investigation Of Pulmonary Embolism Diagnosis (PIOPED). JAMA 268:2753–2759, 1990.
7. Kipper MS, Moser KM, Kortman KE, Ashburn WL: Long-term follow-up of patients with suspected pulmonary embolism and a normal lung scan. Perfusion scans in embolic suspects. Chest 82:411–415, 1982.
8. Miniati M, Sostman HD, Gottschalk A, et al: Perfusion lung scintigraphy for the diagnosis of pulmonary embolism: a reappraisal and review of the Prospective Investigative Study of Acute Pulmonary Embolism Diagnosis methods. Semin Nucl Med 38:450–461, 2008.
9. Alderson PO, Rujanavech N, Secker-Walker RH, McKnight RC: The role of ^{133}Xe ventilation studies in the scintigraphic detection of pulmonary embolism. Radiology 120:633–640, 1976.
10. Neumann RD, Sostman HD, Gottschalk A: Current status of ventilation-perfusion imaging. Semin Nucl Med 10:198–217, 1980.
11. Alderson PO, Biello DR, Sachariah KG, Siegel BA: Scintigraphic detection of pulmonary embolism in patients with obstructive pulmonary disease. Radiology 138:661–666, 1981.
12. Biello DR, Mattar AG, McKnight RC, Siegel BA: Ventilation-perfusion studies in suspected pulmonary embolism. AJR Am J Roentgenol 133:1033–1037, 1979.
13. Gottschalk A, Sostman HD, Coleman RE, et al: Ventilation-perfusion scintigraphy in the PIOPED study. Part II. Evaluation of the scintigraphic criteria and interpretations. J Nucl Med 34:1119–1126, 1993.
14. Sullivan DC, Coleman RE, Mills SR, et al: Lung scan interpretation: Effect of different observers and different criteria. Radiology 149:803–807, 1983.
15. Freeman LM, Krynyckyi B, Zuckier LS: Enhanced lung scan diagnosis of pulmonary embolism with the use of ancillary scintigraphic findings and clinical correlation. Semin Nucl Med 31: 143–157, 2001.
16. Sostman HD, Coleman RE, DeLong DM, et al: Evaluation of revised criteria for ventilation-perfusion scintigraphy in patients with suspected pulmonary embolism. Radiology 193:103–107, 1994.
17. Siegel A, Holtzman SR, Bettmann MA, Black WC: Clinicians' perceptions of the value of ventilation-perfusion scans. Clin Nucl Med 29:419–425, 2004.
18. Pope CF, Sostman HD: Venous thrombosis and pulmonary embolism. *In* Putman CE, Ravin CE (eds): Textbook of Diagnostic Imaging. Philadelphia: WB Saunders, 1988, pp 584–604.
19. Sostman HD, Gottschalk A: The stripe sign: A new sign for diagnosis of nonembolic defects on pulmonary perfusion scintigraphy. Radiology 142:737–741, 1982.
20. Sostman HD, Gottschalk A: Prospective validation of the stripe sign in ventilation-perfusion scintigraphy. Radiology 184:455–459, 1992.
21. Sostman HD, Brown M, Toole A, et al: Perfusion scan in pulmonary vascular/lymphangitic carcinomatosis: The segmental contour pattern. AJR Am J Roentgenol 137:1072–1074, 1981.
22. Newman GE, Sullivan DC, Gottschalk A, Putman CE: Scintigraphic perfusion patterns in patients with diffuse lung disease. Radiology 143:227–231, 1982.
23. Leonard CT, Whyte RI, Lillington GA: Primary non–small-cell lung cancer: Determining the suitability of the patient and tumor for resection. Curr Opin Pulm Med 6:391–395, 2000.

24. Ohno Y, Hatabu H, Higashino T, et al: Dynamic perfusion MRI versus perfusion scintigraphy: Prediction of postoperative lung function in patients with lung cancer. AJR Am J Roentgenol 182:73–78, 2004.
24a. Levine M, Julian J: Imaging: PET-CT imaging in non-small-cell lung cancer. Nat Rev Clin Oncol 6:619–620, 2009.
25. Patz EF Jr, Erasmus JJ: Positron emission tomography imaging in lung cancer. Clin Lung Cancer 1:42–48, 1999 [discussion 49].
26. Cronin P, Dwamena BA, Kelly AM, Carlos RC: Solitary pulmonary nodules: Meta-analytic comparison of cross-sectional imaging modalities for diagnosis of malignancy. Radiology 246:772–782, 2008.
27. Fletcher JW, Kymes SM, Gould M, et al: A comparison of the diagnostic accuracy of 18F-FDG PET and CT in the characterization of solitary pulmonary nodules. J Nucl Med 49:179–185, 2008.
28. Swensen SJ, Viggiano RW, Midthun DE, et al: Lung nodule enhancement at CT: Multicenter study. Radiology 214:73–80, 2000.
29. Vansteenkiste J, Dooms C: Positron emission tomography in nonsmall cell lung cancer. Curr Opin Oncol 19:78–83, 2007.
30. Khandani AH, Fielding JR: PET in management of small pulmonary nodules. Radiology 242:948–949, 2007 [author reply 949].
31. Fletcher JW, Djulbegovic B, Soares HP, et al: Recommendations on the use of 18F-FDG PET in oncology. J Nucl Med 49:480–508, 2008.
32. Christensen JA, Nathan MA, Mullan BP, et al: Characterization of the solitary pulmonary nodule: 18F-FDG PET versus nodule-enhancement CT. AJR Am J Roentgenol 187:1361–1367, 2006.
33. Bryant AS, Cerfolio RJ: The maximum standardized uptake values on integrated FDG-PET/CT is useful in differentiating benign from malignant pulmonary nodules. Ann Thorac Surg 82:1016–1020, 2006.
34. Patz EF Jr, Goodman PC: Positron emission tomography imaging of the thorax. Radiol Clin North Am 32:811–823, 1994.
35. Heyneman LE, Patz EF: PET imaging in patients with bronchioloalveolar cell carcinoma. Lung Cancer 38:261–266, 2002.
36. Erasmus JJ, McAdams HP, Patz EF Jr, et al: Evaluation of primary pulmonary carcinoid tumors using FDG PET. AJR Am J Roentgenol 170:1369–1373, 1998.
37. Ahuja V, Coleman RE, Herndon J, Patz EF Jr: The prognostic significance of fluorodeoxyglucose positron emission tomography imaging for patients with nonsmall cell lung carcinoma. Cancer 83:918–924, 1998.
38. Cheran SK, Nielsen ND, Patz EF Jr: False-negative findings for primary lung tumors on FDG positron emission tomography: Staging and prognostic implications. AJR Am J Roentgenol 182:1129–1132, 2004.
39. Gambhir SS, Shepherd JE, Shah BD, et al: Analytical decision model for the cost-effective management of solitary pulmonary nodules. J Clin Oncol 16:2113–2125, 1998.
40. Scott WJ, Shepherd J, Gambhir SS: Cost-effectiveness of FDG-PET for staging non–small cell lung cancer: A decision analysis. Ann Thorac Surg 66:1876–1883, 1998 [discussion 83–85].
41. Buscombe J, O'Rourke E: Is 18F FDG PET-CT cost effective in lung cancer? Expert Rev Anticancer Ther 7:471–476, 2007.
42. Bashir H, Shabo G, Nunan TO: Positron emission tomography scanning is coming to a hospital near you soon! Clin Med 8:134–139, 2008.
43. Quaia E, Tona G, Gelain F, et al: Integrated fluorine-18 fluorodeoxyglucose (18F-FDG) PET/CT compared to standard contrast-enhanced CT for characterization and staging of pulmonary tumors eligible for surgical resection. Acta Radiol 49:995–1004, 2008.
44. Yi CA, Shin KM, Lee KS, et al: Non–small cell lung cancer staging: Efficacy comparison of integrated PET/CT versus 3.0-T whole-body MR imaging. Radiology 248:632–642, 2008.
45. Ohno Y, Koyama H, Nogami M, et al: Whole-body MR imaging vs. FDG-PET: Comparison of accuracy of M-stage diagnosis for lung cancer patients. J Magn Reson Imaging 26:498–509, 2007.
46. Marom EM, McAdams HP, Erasmus JJ, et al: Staging non–small cell lung cancer with whole-body PET. Radiology 212:803–809, 1999.
47. Patz EF Jr: Imaging bronchogenic carcinoma. Chest 117(4 Suppl 1):90S–95S, 2000.
48. Boiselle PM, Patz EF Jr, Vining DJ, et al: Imaging of mediastinal lymph nodes: CT, MR, and FDG PET. Radiographics 18:1061–1069, 1998.
49. Gauger J, Patz EF Jr, Coleman RE, Herndon JE 2nd: Clinical stage I non–small cell lung cancer including FDG-PET imaging: Sites and time to recurrence. J Thorac Oncol 2:499–505, 2007.
50. Patz EF Jr, Lowe VJ, Goodman PC, Herndon J: Thoracic nodal staging with PET imaging with 18FDG in patients with bronchogenic carcinoma. Chest 108:1617–1621, 1995.
51. Farrell MA, McAdams HP, Herndon JE, Patz EF Jr: Non–small cell lung cancer: FDG PET for nodal staging in patients with stage I disease. Radiology 215:886–890, 2000.
52. Marom EM, Bruzzi JF, Truong MT: Extrathoracic PET/CT findings in thoracic malignancies. J Thorac Imaging 21:154–166, 2006.
53. Oliver TW Jr, Bernardino ME, Miller JI, et al: Isolated adrenal masses in nonsmall-cell bronchogenic carcinoma. Radiology 153:217–218, 1984.
54. Erasmus JJ, Patz EF Jr, McAdams HP, et al: Evaluation of adrenal masses in patients with bronchogenic carcinoma using 18F-fluorodeoxyglucose positron emission tomography. AJR Am J Roentgenol 168:1357–1360, 1997.
55. Bury T, Barreto A, Daenen F, et al: Fluorine-18 deoxyglucose positron emission tomography for the detection of bone metastases in patients with non–small cell lung cancer. Eur J Nucl Med 25:1244–1247, 1998.
56. Larcos G, Maisey MN: FDG-PET screening for cerebral metastases in patients with suspected malignancy. Nucl Med Commun 17:197–198, 1996.
57. Weder W, Schmid RA, Bruchhaus H, et al: Detection of extrathoracic metastases by positron emission tomography in lung cancer. Ann Thorac Surg 66:886–892, 1998 [discussion 892–893].
58. Delbeke D, Martin WH, Sandler MP, et al: Evaluation of benign vs malignant hepatic lesions with positron emission tomography. Arch Surg 133:510–515, 1998 [discussion 515–516].
59. Von Schulthess GK, Hany TF: Imaging and PET-PET/CT imaging. J Radiol 89(3 Pt 2):438–447, 2008 [quiz 448].
60. de Geus-Oei LF, van Krieken JH, Aliredjo RP, et al: Biological correlates of FDG uptake in non–small cell lung cancer. Lung Cancer 55:79–87, 2007.
61. Patz EF Jr, Connolly J, Herndon J: Prognostic value of thoracic FDG PET imaging after treatment for non–small cell lung cancer. AJR Am J Roentgenol 174:769–774, 2000.
62. Patz EF Jr, Lowe VJ, Hoffman JM, et al: Persistent or recurrent bronchogenic carcinoma: Detection with PET and 2-[F-18]-2-deoxy-D-glucose. Radiology 191:379–382, 1994.
63. Park SJ, Ionascu D, Killoran J, et al: Evaluation of the combined effects of target size, respiratory motion and background activity on 3D and 4D PET/CT images. Phys Med Biol 53:3661–3679, 2008.
64. Gillham C, Zips D, Ponisch F, et al: Additional PET/CT in week 5-6 of radiotherapy for patients with stage III non–small cell lung cancer as a means of dose escalation planning? Radiother Oncol 88:335–341, 2008.
65. Munley MT, Marks LB, Scarfone C, et al: Multimodality nuclear medicine imaging in three-dimensional radiation treatment planning for lung cancer: Challenges and prospects. Lung Cancer 23:105–114, 1999.
66. Kiffer JD, Berlangieri SU, Scott AM, et al: The contribution of 18F-fluoro-2-deoxy-glucose positron emission tomographic imaging to radiotherapy planning in lung cancer. Lung Cancer 19:167–177, 1998.
67. Hebert ME, Lowe VJ, Hoffman JM, et al: Positron emission tomography in the pretreatment evaluation and follow-up of non–small cell lung cancer patients treated with radiotherapy: preliminary findings. Am J Clin Oncol 19:416–421, 1996.
68. Nestle U, Walter K, Schmidt S, et al: 18F-Deoxyglucose positron emission tomography (FDG-PET) for the planning of radiotherapy in lung cancer: High impact in patients with atelectasis. Int J Radiat Oncol Biol Phys 44:593–597, 1999.
69. Dooms C, Verbeken E, Stroobants S, et al: Prognostic stratification of stage IIIA-N2 non–small-cell lung cancer after induction chemotherapy: A model based on the combination of morphometric-pathologic response in mediastinal nodes and primary tumor response on serial 18-fluoro-2-deoxy-glucose positron emission tomography. J Clin Oncol 26:1128–1134, 2008.
70. Hoang JK, Hoagland LF, Coleman RE, et al: Prognostic value of fluorine-18 fluorodeoxyglucose positron emission tomography

imaging in patients with advanced-stage non–small-cell lung carcinoma. J Clin Oncol 26:1459–1464, 2008.
71. Duhaylongsod FG, Lowe VJ, Patz EF Jr, et al: Detection of primary and recurrent lung cancer by means of F-18 fluorodeoxyglucose positron emission tomography (FDG PET). J Thorac Cardiovasc Surg 110:130–139, 1995 [discussion 139–140].
72. Vansteenkiste JF, Stroobants SG, De Leyn PR, et al: Potential use of FDG-PET scan after induction chemotherapy in surgically staged IIIa-N2 non–small-cell lung cancer: A prospective pilot study. The Leuven Lung Cancer Group. Ann Oncol 9:1193–1198, 1998.
72a. Hicks RJ: Role of 18F-FDG PET in assessment of response in non-small cell lung cancer. J Nucl Med 50(Suppl 1):31S–42S, 2009.

CHAPTER 22

FLEXIBLE BRONCHOSCOPY

Elif Kupeli, MD • Demet Karnak, MD • Atul C. Mehta, MB, BS

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Narrow-Band Imaging

THERAPEUTIC BRONCHOSCOPY

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Electrosurgery
Argon Plasma Coagulation
Cryotherapy
Laser Photoresection
Photodynamic Therapy
Brachytherapy
Stent Placement
Bronchial Thermoplasty

INTRODUCTION AND HISTORICAL BACKGROUND

Among the many areas in pulmonary medicine that have been revolutionized by technological advances, flexible bronchoscopy (FB) is one of the prime examples. Today, it has become one of the most frequently performed invasive procedures in pulmonary medicine.

Gustav Killian performed the first bronchoscopy in 1897 to extract a piece of a pork bone from the right main bronchus.[1] From that meager beginning, the technology in bronchoscopy has advanced exponentially. In 1966, the flexible bronchoscope was introduced into clinical practice by Shigeto Ikeda.[2] Currently, this instrument is one of the most important tools for diagnosis and treatment of pulmonary diseases.

Since its introduction the flexible bronchoscope has become the instrument of choice owing to its diagnostic accuracy, safety, and ease of use. The procedure can be easily performed in an outpatient setting, under moderate sedation and local anesthesia. Compared with FB, rigid bronchoscopy is now used only for selective indications such as massive hemoptysis.[3–6]

The indications for fiberoptic bronchoscopy are broad and growing (Table 22-1). Nonetheless, certain conditions are not considered indications for FB. For example, FB is not indicated in patients with cough unless the cough fails to respond to conventional treatment or if there is a change in its character. Similarly, bronchoscopy is not indicated in patients with isolated pleural effusion or atelectasis,[7–9] and its use to remove secretions during acute exacerbations of chronic obstructive lung disease is also considered inappropriate.[10] FB also has little role in finding synchronous lesions in patients undergoing lung resection of a solitary pulmonary nodule suspected to be primary bronchogenic carcinoma.[11] There are also contraindications to its use, both absolute and relative (Table 22-2).

PROCEDURE

FB is usually performed via the oral or the nasal route.[12] Either route provides excellent access to the lower airways. By either route, attention should also be given to the upper airways. In particular, bronchoscopy performed for the evaluation of hemoptysis or wheezing should include a careful evaluation of the upper airways.

The need for sedation during FB remains a matter of some debate in the literature.[13–15] The purpose of

TABLE 22-1. Indications for Diagnostic Flexible Bronchoscopy (Adult)

Hemoptysis
Wheeze and stridor: suspected stricture, upper airway obstruction
Lung infiltrates of unknown cause
- Suspected pulmonary infections not responding to conventional treatment
  (a) Localized
  (b) Diffuse
- Lung infiltrates in an immunocompromised host
- Recurrent or unresolved pneumonia
- Cavitary lesion
- Interstitial infiltrates
- New pulmonary nodule

Unexplained lung collapse
Suspected or known bronchogenic carcinoma
- Positive or suspicious sputum cytology
- Staging
- Follow-up after endobronchial treatments

Mediastinal and hilar lymphadenopathy and masses
Lung transplantation
- Inspect airway anastomosis
- Rejection surveillance

Esophageal cancer evaluation
Endotracheal intubation
- Confirm tube position
- Evaluate for tube-related injury

Evaluation for foreign body aspiration
Chest trauma
- Rule out rupture of central airways
- Examine for aspirated contents

Evaluation following burns or chemical injury to the airways
Unexplained superior vena cava syndrome
Unexplained vocal cord paralysis or hoarseness
Suspected fistulas
- Bronchopleural
- Tracheoesophageal and bronchoesophageal
- Tracheo- or bronchoaortic
- Iatrogenic (postsurgical)

TABLE 22-2. Contraindications for Flexible Bronchoscopy

ABSOLUTE
Uncorrectable hypoxemia
Lack of patient cooperation
Lack of skilled personnel
Lack of appropriate equipment and facilities
Unstable angina
Uncontrolled arrhythmias

RELATIVE
Unexplained or severe hypercarbia
Uncontrolled asthma
Uncorrectable coagulopathy
Unstable cervical spine
Need for a large-size tissue specimen for diagnosis
Debility, advanced age, malnutrition

sedation is to improve patient comfort and add to the ease of the procedure for the bronchoscopist.[16] Although bronchoscopy can be carried out without sedation,[17,18] most are performed under moderate sedation.[19,20] Interestingly, according to some surveys, 16% to 21% of physicians use general anesthesia for FB.[19,21] Intravenous preparations of various sedatives such as diazepam, midazolam, lorezapam, morphine sulfate, fentanyl, and hydrocodone have been used either singly or in combination based on the bronchoscopist's preference and the availability of the drug.[22–27] Fentanyl has a greater analgesic potency than morphine.[23] Hydrocodone has a greater antitussive property than codeine but less than that of morphine.[28] The combination of a benzodiazepine and an opioid has been shown to be safe and synergistic for the purposes of sedation during FB.[26,29] The combination of hydrocodone and midazolam reduces cough during FB without causing significant desaturation and improves the overall well-being of the patient.[26,29] Dextromethorphan can be given orally 90 minutes before the procedure to improve cough suppression.[30] Patients suffering with human immunodeficiency virus (HIV) infection, recipients of stem cell transplantation, lung transplant recipients for cystic fibrosis, and drug abusers usually require higher doses of sedatives than other patients.[31–33]

Although nerve blocks can be used to provide excellent analgesia to the airway, physicians generally rely on topical administration of local anesthetic agents. Lidocaine is the most commonly used drug for the purpose.[34] It offers a relatively wide margin of safety with a rapid onset and sufficient duration of action to allow completion of most bronchoscopic procedures. The gel preparation of lidocaine is preferred over the spray for nasal anesthesia.[35–37] The oropharynx can be anesthetized with 2% to 4% lidocaine applied as a spray, nebulized solution, or gargles. The vocal cords as well as the endobronchial tree are anesthetized by direct instillation of 1% to 2% lidocaine via the working channel of the bronchoscope. The total dose of lidocaine should be limited to 8.2 mg/kg in adults, with extra caution in the elderly or those with liver or cardiac impairments.[22]

Anticholinergic agents such as atropine and glycopyrrolate have been commonly used as premedication for FB[38,39] with the aim to reduce the bronchial secretions and suppress vagal overactivity. Several studies have shown that anticholinergics offer little advantage as premedications and their use should be avoided.[40–42]

MONITORING

To ensure adequate oxygenation (oxygen saturation >92%) and hemodynamic stability, pulse oximetry, heart rate and blood pressure are monitored throughout the procedure. All FB procedures are performed observing universal precautions. Following each procedure, the instrument is thoroughly disinfected or sterilized according to the published consensus statement.[43]

DIAGNOSTIC BRONCHOSCOPY

Examination of the upper airways can be instructive. The vocal cords may be involved with infections (Fig. 22-1) or malignancy or may show paralysis as a result of interruption of the recurrent laryngeal nerve. The trachea may be abnormal owing to either congenital or acquired conditions (Fig. 22-2A and B). The endobronchial mucosa exhibit characteristic changes due to infiltrative or systemic conditions (see Fig. 22-2C and D). Endobronchial lesions may be caused by a multitude of conditions including malignant or infectious disease or by foreign bodies (Fig. 22-3).

Bronchoalveolar Lavage

Bronchoalveolar lavage (BAL) has become an important clinical and investigational tool.[44,45] It is a standard diagnostic procedure in all patients with diffuse lung abnormalities of unknown cause whether an infectious, noninfectious, immunologic, or malignant etiology is suspected.[46] BAL allows the recovery of both cellular and noncellular components of the alveolar lining fluid and epithelial surface of the lower respiratory tract. Components of the BAL fluid represent the inflammatory and immune status of the lower respiratory tract and alveoli[44,47] (Fig. 22-4). BAL, which samples the distal air spaces, differs significantly from a bronchial washing, which samples the large airways via aspiration of small amounts of instilled saline.[48,49] BAL should be considered when the bleeding risk prohibits bronchial

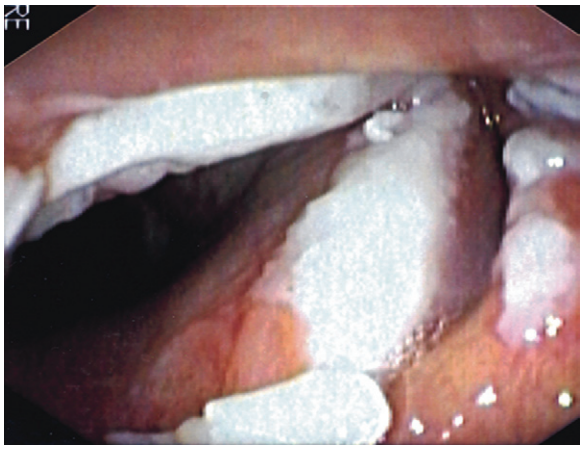

FIGURE 22-1 ■ Vocal cord candidiasis in an immunocompromised host.

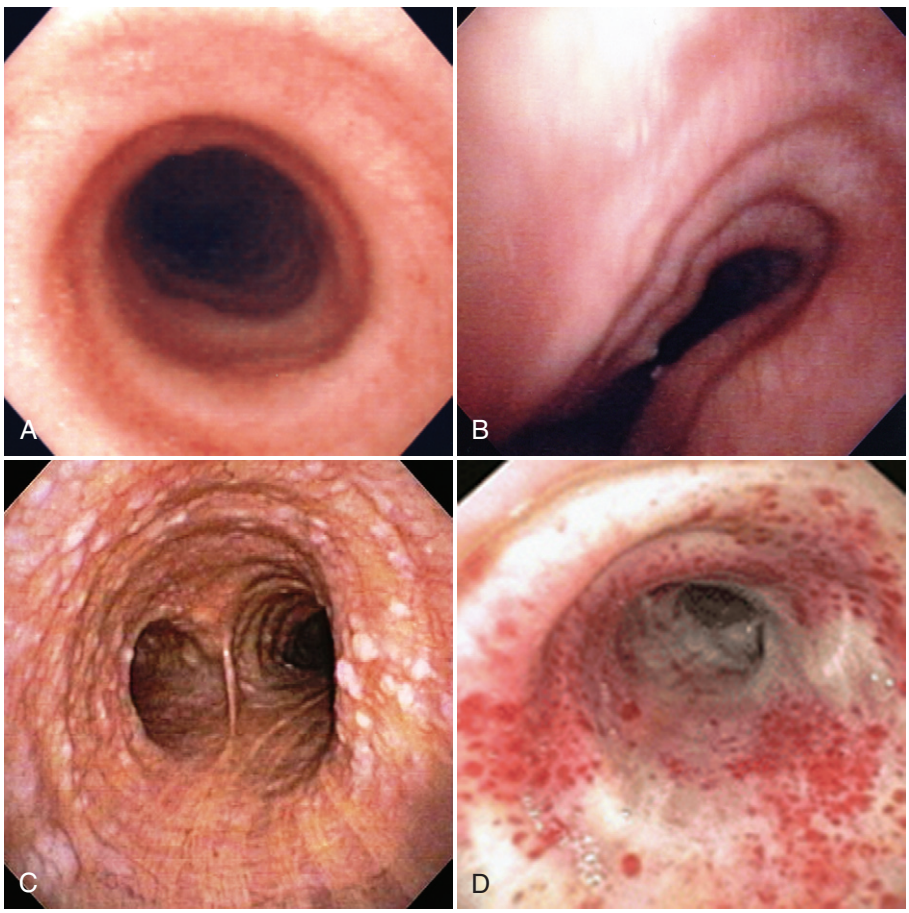

FIGURE 22-2 ■ **A,** Complete tracheal ring, also called a "stovepipe trachea." Note the absence of the posterior membrane. **B,** A "saber-sheath" trachea in a patient with emphysema. **C,** Diffuse "pebbly mural" appearance of endobronchial sarcoidosis. **D,** Endobronchial petechiae in a patient receiving clopidogrel. (A, Image courtesy of Dr. James Stoller.)

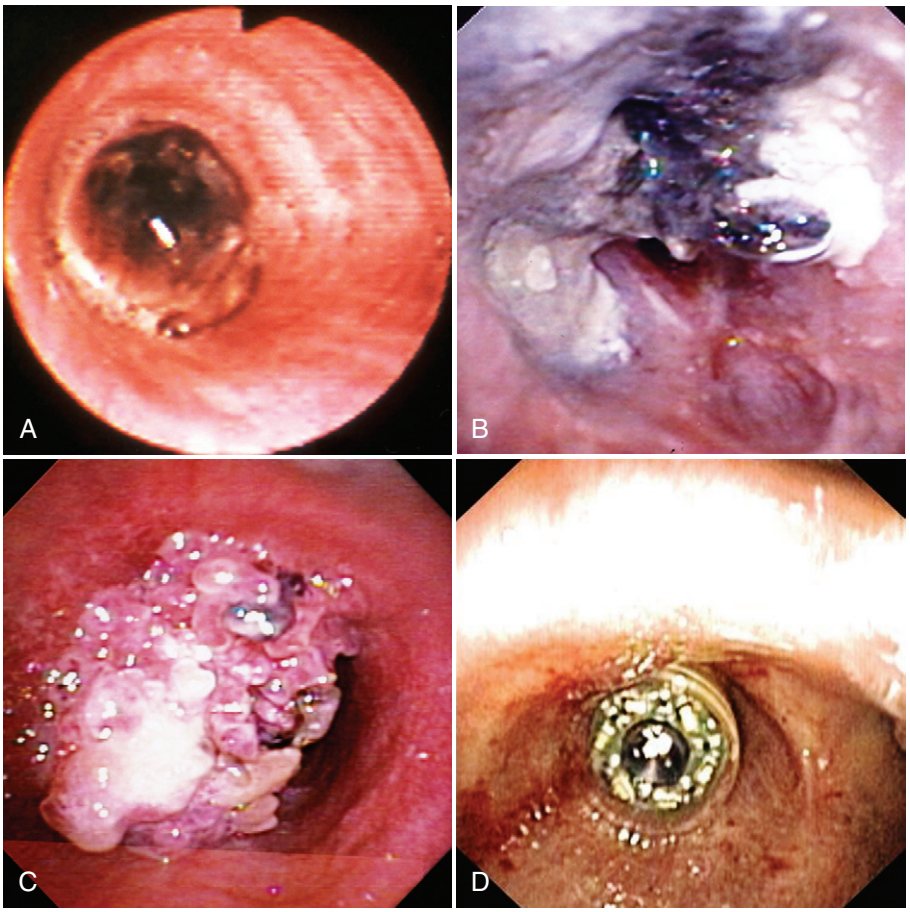

FIGURE 22-3 ■ Endobronchial lesions. **A,** Metastatic melanoma involving the left main bronchus. Note the black pigmentation of the tumor. **B,** *Aspergillus niger* infection in a lung transplant recipient. The black pigment indicates the fungus and the white pigment indicates calcium oxalate crystals produced by the fungus. **C,** Recurrent respiratory papillomatosis involving the trachea. Note the typical mulberry appearance. **D,** A foreign body in the left main bronchus. The object is a camera used for capsule endoscopy that was aspirated into the lungs. (D, Image courtesy of Dr. Thomas Gildea.)

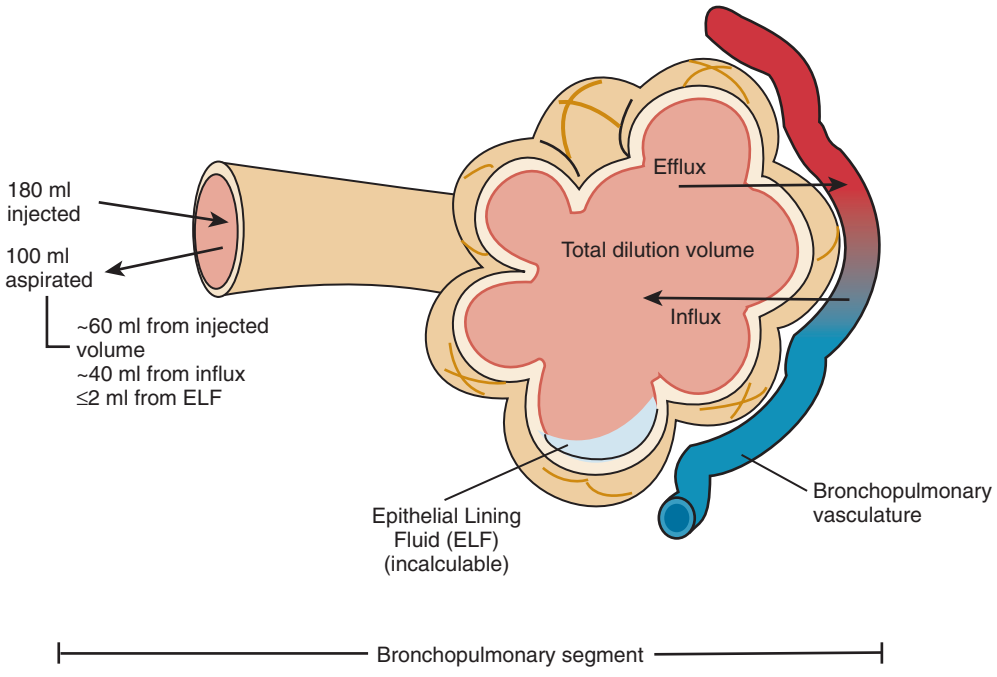

FIGURE 22-4 ■ Schematic presentation of the constituents of the bronchoalveolar lavage fluid. (Courtesy of Dr. Raed Dweik.)

brushing, transbronchial biopsy, or transbronchial needle aspiration or when fluoroscopy is not available.

For diffuse infiltrates, any area can be chosen for BAL. Thus, in the case of diffuse abnormalities, the right middle lobe or the lingula is usually sampled because, for a supine patient, gravity assists the recovery of a maximal amount of BAL fluid return.[45,46,50] In the case of localized disease, lavage should be performed from the area of focal radiographic abnormality,[48,50] and for maximal recovery, the patient can be positioned to improve recovery from the desired segment. "Good wedge" position usually means that the bronchoscope is advanced as far as possible without losing the view of the distal lumen. In this optimal position, a slow, gradual, manual aspiration, without allowing the airway walls to collapse, tends to maximize the lavage return.

BAL has significantly improved the diagnostic workup of lung diseases, whether diffuse or localized. In pulmonary alveolar proteinosis, it has both diagnostic and therapeutic value.[46,51-54] In an international statement on the major interstitial lung diseases, BAL is considered to be helpful in strengthening the diagnosis of sarcoidosis in the absence of a tissue diagnosis.[55] BAL and/or transbronchial biopsy (TBB) are considered valuable in excluding other diseases in a patient with suspected idiopathic pulmonary fibrosis who cannot undergo surgical biopsy.[56] BAL may be a useful tool in the diagnosis of peripherally located primary lung cancer, with an overall diagnostic yield range of 33% to 69%, being exclusively diagnostic in 9% to 11% of cases.[57-60] It also has value in patients suspected to have bronchoalveolar cell carcinoma[57,59,61] and lymphangitic carcinomatosis.[62-64] Numerous case reports confirm the ability of BAL to diagnose leukemia and lymphomatous pulmonary involvement as well as plasma cell dyscrasia.[65-67] Finding asbestos bodies in BAL fluid may correlate with occupational exposure, yet in itself, it is not proof of an asbestos-related disease.[68,69] The presence of more than 25% eosinophils in the BAL fluid confirms the diagnosis of eosinophilic lung diseases and the presence of more than 4% $CD1^+$ Langerhans cells confirms a diagnosis of Langerhans cell histiocytosis, albeit with low sensitivity.[70] In chronic beryllium disease, lymphocytes from the BAL proliferate when stimulated in vitro with soluble beryllium salts, with a sensitivity and specificity approaching 100%; this lymphocyte test has become a valuable diagnostic tool for this condition and has replaced open lung biopsy.[71,72] In patients with ventilator-associated pneumonia, a positive quantitative culture ($>10^4$ colony-forming units/mL) on BAL fluid may be clinically useful with a sensitivity of 22% to 93% and a specificity of 45% to 100%, depending upon the clinical status of the patient.[73-80] BAL is also a useful tool in the diagnosis of pulmonary infections in immunocompromised patients with the reported yield as high as 93%[81-87] (Fig. 22-5). Thus, in certain conditions, BAL findings can be diagnostic and thereby avoid the need for either TBB or open-lung biopsy (Table 22-3). In other settings, although not diagnostic, BAL can be used as an adjunct to the diagnosis when interpreted in the context of the entire clinical picture.

FIGURE 22-5 ■ Bronchoalveolar lavage specimen reveals a larva of *Strongyloides stercoralis*. (Courtesy of Dr. Suhail Raoof.)

TABLE 22-3. Diseases in which Bronchoalveolar Lavage can be Diagnostic

Opportunistic infections (*Pneumocystis jirovecii*, fungi)
Pulmonary alveolar proteinosis
Alveolar hemorrhage syndrome
Malignant infiltrates (solid tumors, lymphoma, leukemia)
Dust exposure
Eosinophilic lung disease
Chronic beryllium disease
Langerhans cell histiocytosis

Bronchial Washings

The utility for bronchial washings is largely for the diagnosis of airway diseases including primary or metastatic lung carcinoma and fungal or mycobacterial infection. Broncial washing is the easiest to perform but has the lowest yield of the various bronchoscopy procedures (sensitivity, 27%–90%),[88-93] with a higher yield for central lesions.[91,94-96] Bronchial washings are an inexpensive adjunct and should be collected during a diagnostic bronchoscopy when appropriate because, even though by a small percentage, they can increase the overall diagnostic yield of the procedure.[91]

Bronchial Brushings

Bronchial Brush Biopsy. Bronchial brush biopsies (BBBs) were analyzed for the first time in 1973 and showed highly suspicious cytology in most of the cases with lung cancer.[97] In general, BBB provides diagnostic material in 72% (range, 44%–94%) of patients with central lung cancers and 45% of patients with peripheral lesions under fluoroscopic guidance.[98] When it is combined with endobronchial biopsy (EBB) of central lesions, the diagnostic yield of FB increases to between 79% to 96%.[99] We usually perform brushing after obtaining all the other bronchoscopy specimens to avoid bleeding or cell distortion interfering with obtaining or interpreting the overall results. The size or the length of the brush has not been shown to affect the diagnostic yield from BBB.

Protected Specimen Brush. Protected specimen brush (PSB) was first described in 1979 by Wimberley and coworkers[100] as a technique to establish an accurate diagnosis in patients with suspected pneumonia. In ventilator-associated pneumonia (VAP), the sensitivity of PSB ranges from 58% to 86% and the specificity from 71% to 100%.[101] For now, the procedure appears to have lost popularity against empiricism for the diagnosis of VAP (see Chapter 33).

Endobronchial Biopsy

EBB is an essential and technically simple tool in the diagnosis of endobronchial neoplasm. It is used for lesions directly visualized during bronchoscopy. It provides histologic specimens, whereas bronchial washing provides only cytologic samples. The reported diagnostic yield from EBB is 80% with a range of 51% to 97% depending upon the patient population.[88,89,98,102] The number of biopsies required for optimal diagnostic yield varies according to the suspected diagnosis. Three biopsy specimens of an endobronchial lesion suspected to be bronchogenic carcinoma can provide a diagnostic yield of over 97%.[103] Biopsies of the surface of endobronchial tumors may be falsely negative if there is peripheral necrosis; in such circumstances, a Wang needle sampling deeper into the mass may be diagnostic.

Transbronchial Biopsy

TBB is the technique by which a piece of lung parenchyma is obtained by using flexible forceps positioned distally via FB. In many instances, TBB can replace open-lung biopsy. TBB is diagnostically useful in 38% to 79% of patients (average sensitivity, 52%) depending upon the underlying disease.[104–108] TBB has a diagnostic yield of 40% to 90% in sarcoidosis,[109] 10% to 40% in Langerhans cell histiocytosis,[110] 88% to 97% in *Pneumocystis jirovecii* pneumonia,[111] and 57% to 79% in lung infections caused by *Mycobacterium tuberculosis*.[112] In patients suspected to have pulmonary alveolar proteinosis, its diagnostic yield has been reported to be as high as 100% (Fig. 22-6). The diagnostic yield of TBB increases with the number of the biopsy specimens obtained.[113]

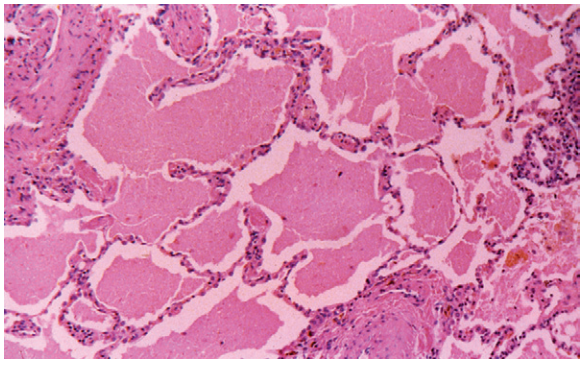

FIGURE 22-6 ■ Transbronchial biopsy specimen confirms the diagnosis of pulmonary alveolar proteinosis. Note periodic acid–Schiff (PAS) stain–positive material filling up the alveolar spaces.

Usually 6 to 10 biopsy specimens are obtained under fluoroscopic guidance. However, use of the fluoroscopy is not mandatory in patients with diffuse parenchymal disease, and biopsies can be obtained by assessing the proximity to the pleura as guided by the patient's perception of chest pain. When performed in association with bronchial brushings and transbronchial needle aspiration (TBNA), TBB adds to the diagnostic yield of FB for peripheral lung cancers.[95,98,114–119]

Pneumothorax and hemorrhage are the most feared complications following TBB, with an incidence of up to 3% of cases.[120] Renal insufficiency (blood urea nitrogen [BUN] > 30 mg/dL [10.7 mmol/L] and creatinine of >3 mg/dL [265 µmol/L]), coagulopathies, and pulmonary hypertension are considered risk factors for bleeding following TBB.[121] TBB can be safely performed while patients are receiving aspirin or nonsteroidal anti-inflammatory drugs; however, use of clopidogrel bisulfate should be withheld for at least 5 to 7 days before the procedure.[122,123]

Transbronchial Needle Aspiration

TBNA is a sensitive, accurate, safe, and cost-effective technique in the diagnosis and staging of lung cancer[119,124–130]; in selected cases, it can also be applied for the diagnosis of benign diseases.[131–135] Despite proven advantages, the practice of TBNA remains underutilized.[136] There is no absolute contraindication for TBNA. Superior vena cava obstruction has been considered as a relative contraindication by some because of a potential increased risk of bleeding[119]; however, the opposite view also exists.[137]

Diagnosis and staging of bronchogenic carcinoma can be established using 21- or 22-gauge cytology needles; diagnosis of benign conditions and lymphomas may require a larger-bore histology (19-gauge) needle.[136,138] The reported sensitivity, specificity, and accuracy of TBNA in lung cancer patients are 60% to 90%, 98% to 100%, and 60% to 90%, respectively.[138–142] The overall sensitivity, specificity, and accuracy of TBNA for mediastinal staging are 50%, 96%, and 78%, respectively.[98] Judicious use of TBNA can thus reduce the need for mediastinoscopy. In the diagnosis of involvement of mediastinal or hilar lymph nodes by sarcoidosis or tuberculosis, TBNA can be useful as well[131–135] (Fig. 22-7). In cases with pulmonary nodules, TBNA increases the diagnostic yield of FB by 25%.[141] TBNA can be safely performed in mechanically ventilated patients.[142]

The procedure of TBNA is safe, with an overall major complication rate of approximately 0.26%. Complications include damage of the working channel of the bronchoscope, fever, bacteremia, and bleeding from the puncture site (Fig. 22-8).[119,136,142] Use of computed tomography (CT), fluoroscopy, and ultrasonic guidance has been shown to improve the TBNA yield[143,144] (see Chapter 20).

Ultrathin Bronchoscopy

The ultrathin bronchoscope currently being studied has an outer diameter of 2.8 mm and an inner channel diam-

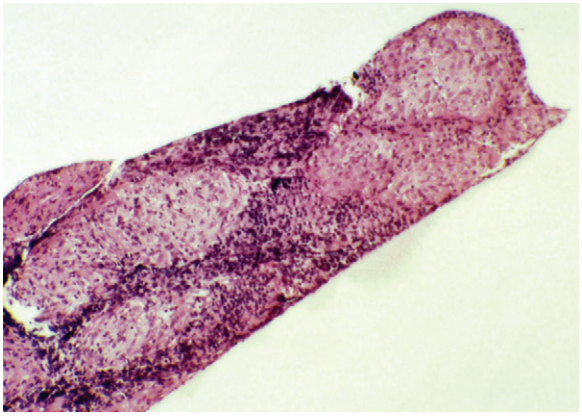

FIGURE 22-7 ■ Transbronchial needle aspiration specimen obtained using a 19-gauge histology needle reveals noncaseating granulomas under high-power magnification (×200) and hematoxylin and eosin stain.

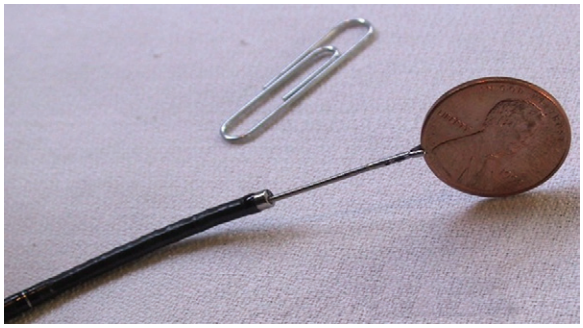

FIGURE 22-9 ■ Ultrathin bronchoscope with a flexible forceps inserted through the working channel. (Courtesy of Dr. Rex Yung.)

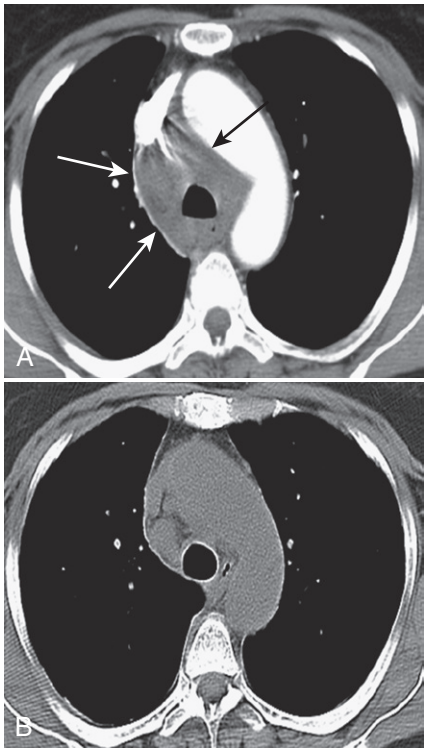

FIGURE 22-8 ■ Complication of transbronchial needle aspiration. **A,** On day 1, mediastinal hemorrhage is noted (*arrows*). **B,** By day 6, the abnormality has resolved. (Courtesy of Dr. Stefano Gasparini.)

eter of 1.2 mm and is made up mainly of fiberoptic bundles. This device has been developed to overcome the low diagnostic yield of FB for small lesions less than 20 mm in diameter.[145-148] Complexities of the distal airway anatomy requires fluoroscopic or CT guidance to maneuver the scope to the peripheral lesions. These bronchoscopes also can be used with ease in mechanically ventilated patients with small endotracheal tubes in place. Ultrathin bronchoscopes help in evaluating the nature and the extent of the upper airway obstruction where there is a risk for completely compromising the airways with standard bronchoscopes.[148] Over time, miniaturization of the instrument is likely to continue (Fig. 22-9).

Confocal Bronchoscopy

Fibered confocal fluorescence microscopy (FCFM) is a new technique that produces microscopic imaging of a living tissue via a 1-mm fiberoptic probe that can be introduced through the working channel of the conventional bronchoscope. In a recent study, bronchial FCFM was performed at 488-nm excitation wavelength on two bronchial specimens ex vivo and in 29 individuals at high risk for lung cancer in vivo; the alterations in fluorescent signal appeared to originate from the elastin component of the basement membrane zone.[149] Alterations of the autofluorescence microstructure were observed in 19 of 22 metaplastic or dysplastic samples, 5 of 5 carcinomas in situ, and 2 of 2 invasive lesions, representing a minimally invasive method to study specific basement membrane alterations associated with premalignant bronchial lesions in vivo. In the future, the technique may be used to study bronchial wall remodeling in nonmalignant chronic bronchial diseases.

Electromagnetic Navigation

Electromagnetic navigation (EMN) can be used to guide the bronchoscopist to lesions that cannot be visualized in the airways, either because they are distal or paratracheal. The EMN creates an electromagnetic field around the chest of a patient undergoing FB, superimposes the field upon previously acquired three-dimensional CT images, and uses a microsensor to determine the

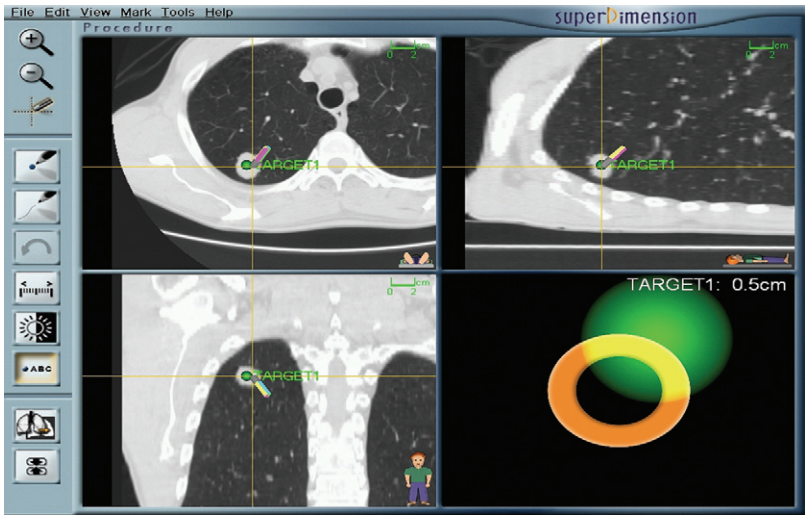

FIGURE 22-10 ■ Electromagnetic navigation monitor. Note: Location of the pulmonary nodule is depicted in three different views. Right lower quadrant image exhibits the position of the microsensor (*orange ring*) in relation to the virtual pulmonary nodule (*green circle*).

bronchoscopist's position within the endobronchial tree. EMN can then guide placement of endoscopic accessories to peripheral lung lesions or to mediastinal lymph nodes. In principle, the device is similar to the global positioning system used in automobiles and air planes.

The diagnostic yield of FB for peripheral lung lesions and solitary pulmonary nodules is limited and dependent upon lesion size and location.[142] Recent studies have shown that EMN increases this yield.[150–157] EMN is well-tolerated and has proved to be both safe and useful in localizing small or fluoroscopically invisible lung lesions with a sufficient level of accuracy (Fig. 22-10).

Autofluorescence Bronchoscopy

In the treatment of lung cancer, the best outcome is achieved if the lesion is discovered in the intraepithelial stage. However, intraepithelial neoplastic lesions are difficult to localize by conventional white-light bronchoscopy (WLB). Autofluorescence bronchoscopy (AFB) has been in use since 1988 as an aid to the diagnosis of bronchial precancerous lesions and early lung cancers.[158–163] In this method, airways are illuminated by blue light. Fluorescence emitted from the mucosal surface is partially quenched in areas of dysplasia, a result that can be enhanced by video signal processing. Normal areas are usually exhibited in a green color whereas the suspicious areas appear in a reddish to brown discoloration (Fig. 22-11). The lesions detected by AFB include squamous cell cancer and the "premalignant" dysplasias of the squamous epithelium.[164] AFB can also capture the endobronchial extent of tumor; thus it is helpful to decide the line of resection preoperatively or plan endobronchial therapies.

However, discrimination between cancerous/precancerous lesions and inflammation is not possible by endoscopic images alone and the histologic diagnosis is still necessary.[158] In a multicenter study, the combination of WLB and AFB had greater sensitivity (82.3%) for detecting dysplasia than WLB (57.9%) alone, although the benefit for detecting carcinoma in situ was not significant.[161] The low specificity of the technique, the lack of evidence for a decrease in disease-specific mortality, and the lack of cost analyses are some of the drawbacks of this technique.[164] Therefore, AFB is not yet considered a screening tool for lung cancer[161,164] (Fig. 22-12).

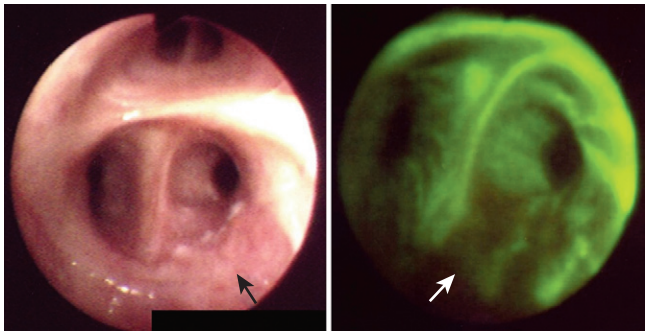

FIGURE 22-11 ■ Autofluorescence bronchoscopy: White-light image (*left*) versus autofluorescent image (*right*). A lesion that is poorly seen using white light (*black arrow, left*) becomes more evident under fluorescent light (*white arrow, right*). This brownish discoloration involving the posterior airway wall depicts an area suspicious for early lung cancer.

Narrow-Band Imaging

Visualizing the vascular pattern of the bronchial epithelial surface promises to advance the understanding of angiogenesis in the early phases of carcinogenesis of lung tissue and to advance the diagnosis of premalignant lesions. Narrow-band imaging (NBI) is a new, alternative light-wavelength capture system that can be used to detect the altered blood vessel morphology of bronchial dysplasia. Wavelengths of light in the visible spectrum (400–700 nm) are filtered to narrow the wavelength to bands in the blue and green spectrum (415 and 540 nm), coinciding with the peak absorption spectrum of oxyhemoglobin and thereby enhancing detection of blood

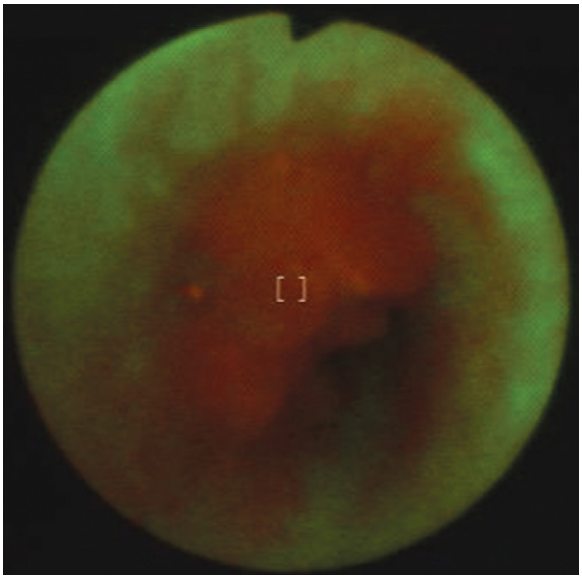

FIGURE 22-12 ■ False-positive autofluorescence bronchoscopy in patients with recurrent respiratory papillomatosis involving the trachea. All endobronchial biopsies from the suspicious areas were negative for malignancy.

TABLE 22-4. Indications for Therapeutic Flexible Bronchoscopy

Removal of central airway neoplasm (malignant/benign)
• Laser photoresection
• Endobronchial electrosurgery
• Argon plasma coagulation
• Brachytherapy
• Cryotherapy
• Photodynamic therapy
Dilation of stricture and stenosis: balloon bronchoplasty
Stent placement
Intralesional injection: cidofovir, mitomycin, steroid
Removal of foreign body, mucous plug, blood clot
Bronchoalveolar lavage for pulmonary alveolar proteinosis
Aspiration of cysts: mediastinal or bronchogenic
Drainage of lung abscess
Hemoptysis
Pulmonary toilet
Difficult endotracheal intubation
Percutaneous dilational tracheostomy
Pneumothorax/bronchopleural fistula (fibrin glue therapy)
Bronchoscopic volume reduction
Gene therapy

vessels. It may be helpful to detect severely dysplastic lesions; it is estimated that invasive carcinoma will develop in 40% to 83% of patients with severely dysplastic lesions.[165,166] NBI in combination with high-magnification bronchoscopy can be useful in characterizing capillary loop patterns of dysplastic airway lesions.[167] Also, NBI may be more specific than AFB for dysplasia when used as an adjunct to AFB to evaluate vascular patterns of autofluorescence-abnormal areas.[156] When NBI is used with WLB, detection of bronchial dysplasia is significantly improved compared with WLB alone. At the same time, NBI requires closer examination both as a stand-alone technology and in comparison with other imaging strategies including AFB in the setting of clinical trials.[168]

Because both AFB and NBI are "technologies in search of an indication," they remain largely research tools and should not be routinely performed outside well-designed clinical trials or special clinical circumstances.[164,168] In one study, high-magnification bronchovideoscopy combined with NBI was found useful in the detection of capillary blood vessels in angiogenic squamous dysplasia lesions at sites of abnormal fluorescence. This may enable the discrimination between angiogenic squamous dysplasia and other preinvasive bronchial lesions.[167]

THERAPEUTIC BRONCHOSCOPY

Even though FB is most often employed for diagnostic indications, its therapeutic spectrum has also expanded significantly since its initial inception (Table 22-4).[169] With the development of fiberoptic bronchoscopy, rigid bronchoscopy has become less popular. Nonetheless, rigid bronchoscopy remains an invaluable tool and should be considered for control of the compromised airway, massive hemoptysis, silicone stent placement, and removal of large foreign bodies, especially in the pediatric age group.[169] There are several therapeutic techniques with overlapping indications, with both advantages and disadvantages, for which the best uses may become clear in the future (Table 22-5).

Therapeutic applications of FB are discussed below.

Foreign Body Removal

Indications

Foreign body aspiration is one of the most common indications for therapeutic bronchoscopy. The diagnosis and removal of foreign bodies has long been performed using a rigid bronchoscope in children as well as in adults; however, in recent years, FB has reduced the need for rigid bronchoscopy, and a trained bronchoscopist can successfully confirm and remove a foreign body in a single sitting using an FB. Moreover, a flexible bronchoscope with a large suction channel may permit suctioning of small foreign bodies from distal airways and allow the retrieval of foreign bodies from deep in subsegmental bronchi.[170-174] In adults, foreign bodies are usually right-sided, but in children, this is not necessarily true owing to the equal size and angulations of the main bronchi. In children, aspiration usually results from their tendency to place objects in the mouth, and also from their use of incisive teeth that forcefully send the object to the back of the throat. Nuts account for the majority of aspirated foreign bodies among children. In adults, removal of foreign bodies was reported in fewer than 9 events out of 4500 bronchoscopies/yr (0.2%).

TABLE 22-5. Advantages and Disadvantages of Various Therapeutic Bronchoscopic Techniques

Treatment	Equipment/Technique	Result	Complications
Mechanical removal	Standard/GA/LA	Short-term, immediate	Bleeding
Electrosurgery	Standard, GA/LA, rigid and fiberscope	Immediate and superficial, very cheap	Endobronchial fire
Argon plasma coagulation	Special probes, GA/LA, fiberscope	Immediate and superficial, effective hemostasis, low cost	Damage to bronchoscope, gas embolism, no vaporization effect
Cryotherapy	Special applicators, GA or LA	Delayed effect, safe for the cartilage	Rare
Nd:YAG laser	Laser, mostly GA, or fiber through rigid	Immediate effect	Perforation, endobronchial fire
Photodynamic therapy	Dye and diode laser, LA	Delayed effect, safe for the cartilage	Skin photosensitivity, secondary necrosis, perforation risk
Brachytherapy	High-dose therapy requires remote control after loading, LA	Delayed effect	Radiation bronchitis, stenosis, fistula

GA, general anesthesia; LA, local anesthesia; Nd:YAG, neodymium:yttrium aluminum garnet.
From Sutedja G, Bolliger CT: Endobronchial electrocautery and argon plasma coagulation. *In* Bolliger CT, Mathur PN (eds): Progress in Respiratory Research. Vol 30: Interventional Bronchology. Basel: S Karger, 2000, pp 120–131.

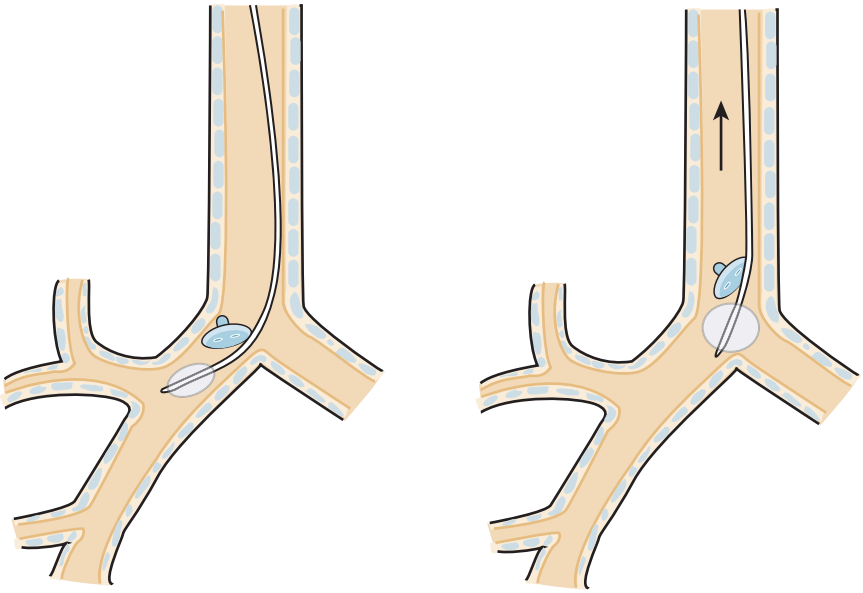

FIGURE 22-13 ■ Schematic representation of the use of a balloon catheter for dislodging a foreign body by a retrograde pull. (Courtesy of Dr. Eric Folch.)

Risk factors for aspiration in adults include alcohol intoxication, sedative and hypnotic drugs, poor dentition, senility, mental retardation, seizure, trauma with loss of consciousness, swallowing impairment, parkinsonism, and general anesthesia.[169,170]

Contraindications, Procedure, Results, and Complications

All contraindications that apply to the routine FB apply to the removal of a foreign body. Lack of experience and lack of availability of all necessary endobronchial accessories are the more important contraindications. Removal of a foreign body using FB should be attempted only by or under the supervision of an expert bronchologist. Acute respiratory distress caused by the foreign body indicates need for rigid bronchoscopy. There are not enough data to support use of FB in infants with foreign body aspiration.[170] Published reports indicate that FB is successful in 87% of patients with foreign body aspiration.[172,173,175–180] FB can thus be used as an alternative to rigid bronchoscopy avoiding the need for general anesthesia and its related cost and complications.[170]

Foreign body removal using FB is carried out in stages: first, dislodging the foreign body, then, grasping or securing the object, and finally, removing it along with the flexible bronchoscope as single unit. A balloon catheter is usually used to dislodge the foreign body from the distal airways and to pull it into the proximal airways (Fig. 22-13). Once the object is grasped and secured with an appropriate accessory, it is kept very close to the tip of the flexible bronchoscope to reduce danger of losing it in the subglottic area or at the level of vocal cords. A variety of ancillary accessories (forceps, grasping claws, snares, baskets [dormia, fishnet], and magnets) are available for foreign body extraction.[169] Once the object is in

the trachea, the patient can also be asked to cough to expel the foreign body. Lasers and cryoprobes can also be used if a significant amount of granulation tissue is present. A cryoprobe passed through the flexible bronchoscope can be used to retrieve the foreign body by placing the tip in contact with the object until the point of contact is frozen, leading to adhesion (cryoadhesion). This allows for en bloc removal of the object with the cryoprobe and the flexible bronchoscope. This approach is especially useful for the removal of blood clots, mucous plugs, friable organic material, and small inorganic objects. Occasionally, laser instruments can assist in the removal of large objects by breaking them up into smaller pieces. Self-expanding metallic stents embedded in the bronchial mucosa can be extracted by fracturing the wires using laser energy.[169]

Serious complications can accompany removal of a foreign body, including central airway obstruction, airway wall perforation, or flooding of the airways with secretions or blood. Other less serious complications are hypoxia, bronchospasm, arrhythmias, laryngeal edema, bacteremia, fever, migration of the object to distal airways, object fragmentation, and loss of the object at the glottis during removal efforts. The key for the success in foreign body removal is airway protection, an experienced operator, adequate equipment, and availability of a rigid bronchoscope for an emergent situation.[181]

Electrosurgery

Endobronchial electrosurgery (ES) is the application of heat produced by high-frequency electrical current to treat tumor tissue using special accessories such as coagulation probes, knives, and snares introduced through a bronchoscope. A small probe functions as an active electrode that focuses heat to a tiny spot at the point of contact, leading to tissue coagulation or vaporization. The electrical current can also cut or blend cutting and coagulation. The degree of tissue destruction depends on the power used, duration of contact, surface area of contact, and water content of the tissue.

To avoid endobronchial ignition, the fractional concentration of oxygen in inspired gas (FIO_2) should be kept below 40%. Insulated bronchoscopes, compatible with ES, are used to prevent leakage of electrical current, avoiding burns or electrical shock to the patient and the bronchoscopist.[182,183]

Indications and Contraindications

ES is used for immediate debulking of intraluminal tumor and has a curative potential in patients with occult carcinomas, benign tumors, or polypoid lesions. Coagulation is achieved by gently touching the tumor tissue and applying 20 to 40W until blanching of the mucosa becomes apparent. The tumor area should be kept free of blood or mucus by continuous suctioning or the electrical current will be conveyed through these liquids. The coagulated tissue can be removed using biopsy forceps. The process can be repeated until the desired lumen size is achieved. In cases of large tumor, ES can be used to coagulate the tumor base to devascularize the lesion and reduce the risk for bleeding while the tumor tissue is débrided mechanically. The procedure is contraindicated in patients with pacemakers and defibrillators to avoid cardiac consequences.[182,183]

Results and Complications

In vivo studies have shown that a monopolar flexible electrocautery probe produces predictable yet superficial coagulative necrosis by blanching the mucosa with relative sparing of cartilage. After a relatively short learning period, the bronchoscopist can create a shallow necrosis of 2 to 3 mm, avoiding damage to the tracheobronchial wall. Moreover, electrocautery is a cost-effective bronchoscopic intervention.[182,184] Coulter and Mehta[185] showed that a high success rate (89%) could be achieved by using ES under local anesthesia in a selected group of the patients with small, polypoid endobronchial lesions. Outcomes of ES in both malignant and benign diseases have been promising.[186–194] Although complications are rare in experienced hands, the most common ones are bleeding (2%–5%), endobronchial ignition while using high FIO_2, and electrical shock to the operator when inappropriate grounding is used. Although airway perforation has not been reported, it is a tangible risk.

Argon Plasma Coagulation

Argon plasma coagulation (APC) uses ionized argon gas to conduct electrical current from the probe to the tissue, transferring heat in a homogeneous but superficial way to the conductive surface lying closest to the probe. The argon gas spreads out into the airway lumen, and the portion that is activated and ionized becomes the plasma jet. A spark through the plasma jet desiccates tissues to a specific depth. Because positively charged argon gas automatically flows toward the negatively charged bleeding tissue, treatment can be directed in an axial, a radial, or a retrograde fashion (Fig. 22-14). As the tissue gets desiccated, it offers more resistance to the electrical current. Argon plasma automatically moves toward untreated areas with lesser degree of tissue resistance, thus producing little vaporization and limiting the depth of penetration.[183,184,195]

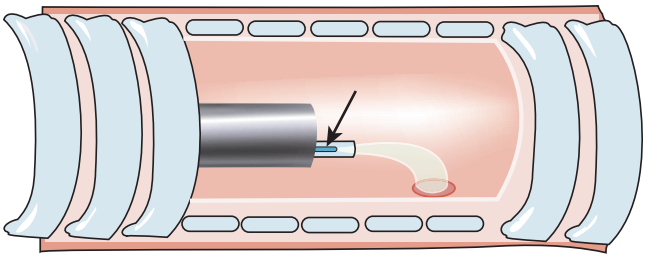

FIGURE 22-14 ■ Schematic presentation of argon plasma coagulation. *Arrow* shows the tungsten carbide electrode. Positively charged argon gas automatically flows radially to the negatively charged bleeding tissue. (Courtesy of Dr. Eric Folch.)

Indications and Contraindications

APC is frequently used for palliation of malignant obstruction as part of multimodality treatment and also in benign conditions such as hemorrhage and treatment of excess granulation tissue (including stent-related granuloma), papillomatosis, and postinfectious airway stenosis.[182-184] The most important advantages of this technique are its ability to treat lesions at sharp angles from the tip of the electrode and to treat lesions in close proximity to airway stents, and its superiority in achieving hemostasis. Its major limitation is the depth of penetration of less than 3 mm, thus limiting its use in large bulky tumors obstructing the airways. Conversely, APC offers good protection against perforation of the airways. Its only absolute contraindication is the presence a pacemaker susceptible to electrical interference.[195]

Results and Complications

APC provides effective hemostasis, self-limited depth of penetration, no damage to uncovered stents, and minimal smoke. In properly selected cases, it provides symptomatic relief in almost 90% of the patients. It is also portable, less expensive than laser, and easy to use with a flexible bronchoscope. The potential complications include gas embolism with argon, bleeding, endobronchial ignition with possible damage to the bronchoscope, postprocedure stenosis, and injury to deeper structures, as previously described for electrocautery (Fig. 22-15). The need for an expensive, disposable probe is also a drawback associated with the procedure. FIO_2 should be kept below 40% during APC. The observed mortality and overall complication rate are 0.4% and 3.7% of cases, respectively.[195,196]

Cryotherapy

Cryotherapy causes freezing of the tissue, leading to extracellular ice crystal formation, hypertonicity, and withdrawal of the intracellular water to cause tissue damage and necrosis. It employs gas decompression or the "Joule-Thompson principle" to cause thermal tissue destruction by direct contact. The three cooling agents (cryogen) available are liquid nitrogen, nitrous oxide, and carbon dioxide (N_2, N_2O, and CO_2). The cryoprobe can be used through rigid or flexible bronchoscopes. When the cryogen is released from very high pressure to the normal atmospheric pressure, at the tip of the cryoprobe, it expands. This expansion lowers its temperature to between –80°C to –160°C at the tip of the probe. The probe is placed in contact with the tissue being treated, reaching tissue temperature as low as –80°C. The temperature increases approximately 10°C per mm from the tip ("warming effect"), so the effective killing zone is approximately 5 to 8 mm. The cryoprobe is activated with a foot pedal and is advanced approximately 5 mm distal from the tip of the flexible bronchoscope. Repeated cycles of freezing and thawing are applied to the endobronchial tissue in a contiguous fashion to cover the entire surface of the lesion. Tissue necrosis and sloughing takes place within 24 to 48 hours, and a "cleanup" bronchoscopy is usually required to remove necrotic tissue. This delayed tissue effect is one of the shortcomings of cryotherapy.[197,198]

FIGURE 22-15 ■ Damage to the tip of the bronchoscope caused during argon plasma coagulation. Note the charred tip along with the frayed rubber sheath. (Image courtesy of Dr. Praveen Mathur.)

Indications and Contraindications

Cryotherapy has been used for the destruction of endobronchial lesions when immediate results are not mandatory and "hot" therapies are contraindicated; for example, cryotherapy is ideal for treating stent-related granulomas when the stent is made of a flammable material. The tissue effects depend upon the length and the duration of the freezing-thawing cycles, temperature attained, and type of the tissue. Skin, nerves, endothelium, granulation tissue, and mucous membranes are sensitive to cryotherapy, and connective and fibrous tissues, nerve sheath, cartilage, and fatty tissue are cryoresistant. Proper selection of the cryosensitive tumor is essential for a successful outcome.[184,197,198] Cryotherapy has been shown to have beneficial effect in conjunction with radiation therapy. Under special circumstances, cryotherapy can be used with excellent results in removing organic foreign objects, blood clots, and mucus plugs by "cryoadhesion," as described earlier. Advantages of cryotherapy include its ability to be used in a high oxygen environment and under local anesthesia and its limited bronchial wall damage.[197,198] Cryotherapy may enhance the effect of chemotherapy in a mouse lung cancer model.[199,199a]

Results and Complications

In most cases, cryotherapy offers a safe and inexpensive alternative for ablation of endobronchial tumor. The most common side effects are airway sloughing requiring a repeat bronchoscopy and a postprocedure fever. On a rare occasion, cryoadhesion to a necrotic tumor can cause excessive damage to the airway wall. Moderate bleeding, mediastinitis, and fistula formation following cryotherapy have also been encountered in few cases.[197,198]

Laser Photoresection

Laser light has three unique characteristics—monochromaticity, coherence, and collimation—that permit a controlled delivery of a well-defined energy. Laser light causes thermal, photodynamic, and electromagnetic changes in the living tissue. Although many types of laser systems exist, neodymium:yttrium-aluminum-garnet (Nd:YAG) laser with an invisible infrared beam exhibits a number of advantages for bronchoscopic use. It can deliver up to 100 W of output in the beam through a flexible quartz fiber. At lower watts, the Nd:YAG laser photocoagulates, whereas at higher settings, it vaporizes tissue. Use of energy higher than 40 W is seldom needed. It is also a durable and reliable laser with minimal maintenance. Another version, neodymium:yttrium-aluminum-perovskite (Nd:YAP), achieves particularly good coagulation owing to its high absorption rate within the tissue (20 times > Nd:YAG).[184,200,201]

Indications

The main indications of laser photoresection (LPR) are relief of central airway obstruction from exophytic obstructive neoplasms and from tracheal stenosis. An ideal lesion for the laser LPR is an endobronchial tumor, less than 4 cm in length, which arises from a single wall of a central airway, has a visible distal lumen, and distal lung collapse of less than 4 to 6 weeks[169,200] (Table 22-6).

Contraindications

Lesions not amenable to LPR are extrinsic or submucosal, primarily involving lobar or segmental bronchi and contiguous with the esophagus. Other contraindications to LPR include abnormal coagulation profile, unstable cardiovascular status, and a high oxygen requirement.[184]

Results and Complications

LPR can restore airway patency with immediate symptomatic improvement in 93% of cases[200–202] (Fig. 22-16). This technique palliates symptoms of cough, dyspnea, and hemoptysis along with documented benefits in radiographic, spirometric, and quality of life parameters. Studies have shown a small survival benefit when emergent LPR is compared with emergent radiotherapy. LPR is associated with the following complications (range, 0%–2.2%): exsanguination (2%), endobronchial ignition, pneumothorax or barotrauma, bronchopleural or bronchoesophageal fistula, and hypoxemia.[201,203] Extensive knowledge of the anatomy of the tracheobronchial tree is mandatory prior to performing the procedure. Accumulation of blood and secretions can lead to rapid desaturation. Tracheobronchial tree perforation can be fatal owing to its close proximity with the great vessels. While performing the procedure, one must take precautions to avoid fire, which can severely damage the airways, bronchoscope, suction catheter, or the endotracheal tube. Care should be taken to avoid ocular (mainly retinal) or skin damage by the direct laser beam.[169,201,203]

Photodynamic Therapy

Photodynamic therapy (PDT) is a three-step process that involves the intravenous administration of a photosensitizing agent known as dihematoporphyrin ether/ester (DHE; Photofrin II), exposure to a laser light of a specific wavelength, and finally, a cleanup bronchoscopy.[169] After 48 hours, the DHE is preferentially retained by tumor cells and cleared from most healthy tissues; the tumor is then exposed to a particular laser light introduced via a flexible bronchoscope. Exposure of DHE to light of a proper wavelength results in tumor destruction caused by a photochemical reaction including generation of oxygen radical species, direct damage to cells and organelles, indirect ischemic effects, apoptosis, and

TABLE 22-6. Factors Influencing Outcome of Nd:YAG Laser Photoresection

Factors	Favorable	Unfavorable
Location	Trachea, main bronchi	Lobar and segmental bronchi
Type of lesion	Endobronchial	Extrinsic
Appearance	Polypoid, exophytic, pedunculated	Submucosal
Extent of involvement	Localized (1 wall)	Extensive (>1 wall)
Length of lesion	<4 cm	>4 cm
Distal lumen	Visible	Not visible
Duration of collapse	<4–6 wk	>4–6 wk
Clinical status		
Hemodynamics	Stable	Unstable
Oxygen requirement	<0.4 FIO_2	>0.4 FIO_2
Coagulation profile	Normal	Abnormal
Pulmonary vascular supply	Intact	Compromised

FIO_2, fractional concentration of oxygen in inspired gas; Nd:YAG, neodymium:yttrium-aluminum-garnet.
From Lee P, Mehta AC: Therapeutic flexible bronchoscopy. In Beams JF, Mathur PN, Mehta AC (eds): Interventional Pulmonary Medicine, Lung Biology in Health and Disease. Leflant C (executive ed). New York: Marcel Dekker, 2004, pp 49–78.

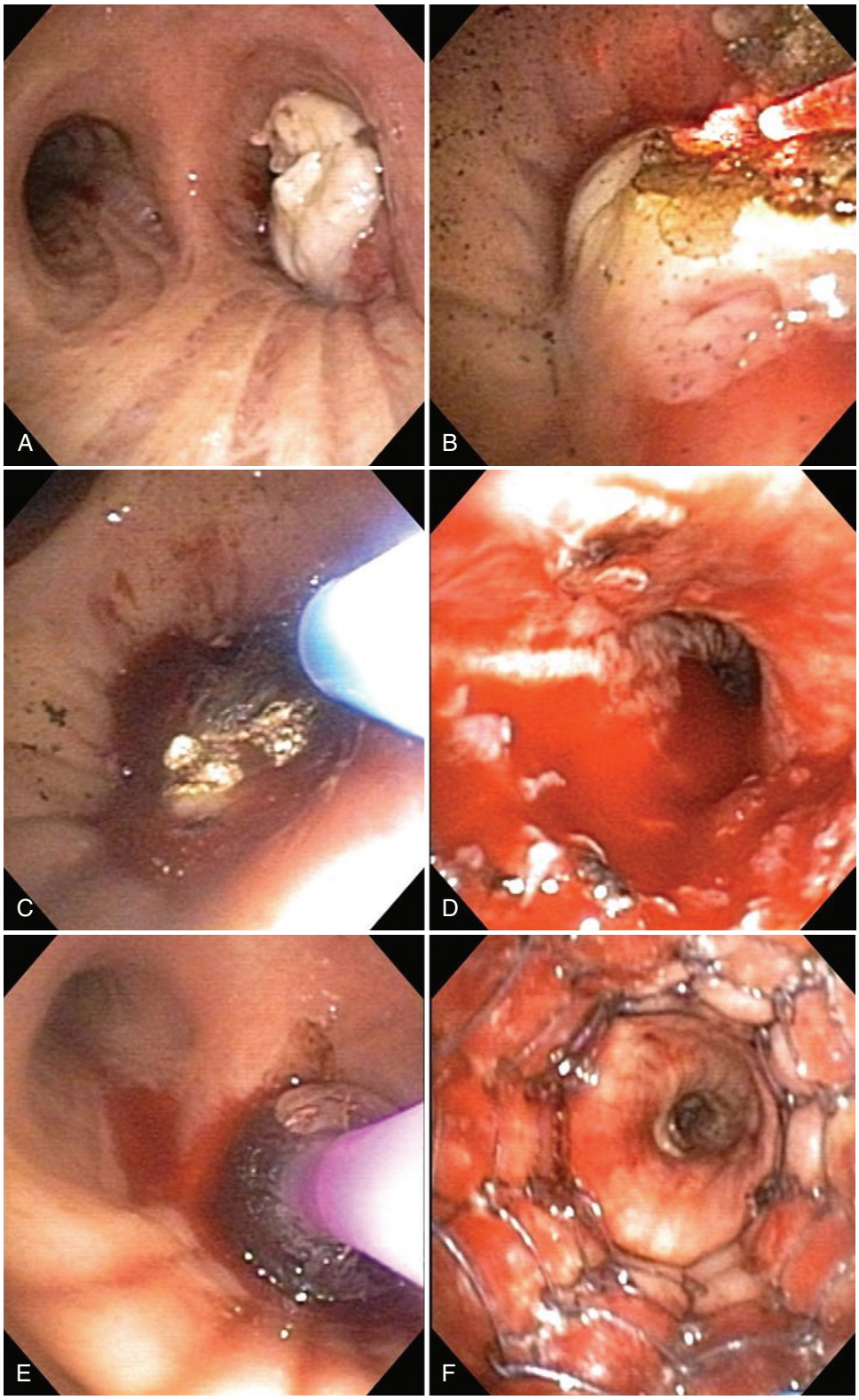

FIGURE 22-16 ■ Multimodality palliative therapy for a patient with a malignant lesion obstructing the right main stem bronchus. **A,** Pretreatment. **B,** Laser photoresection (note the laser fiber). **C,** Debulking using argon plasma coagulation (note the blue argon plasma coagulation [APC] catheter). **D,** Postmechanical debulking. **E,** Balloon dilation. A silicone balloon is fully inflated in the right main stem bronchus location. **F,** Stent placement. Note the self-expanding metallic stent in place. (Images courtesy of Dr. Eric Folch.)

inflammatory effects. Cleanup bronchoscopy is often necessary to avoid complications such as postobstructive pneumonia or respiratory distress or failure.[169,184,204]

Indications and Contraindications

PDT is indicated for the palliation of advanced obstructing cancers of the tracheobronchial tree and appears to be effective for superficial as well as submucosal disease. Curative treatment for asymptomatic multiple and early lung cancers is another indication for PDT. Occasionally, it is also used preoperatively to reduce the extent of surgical resection by rendering the line of resection free of the disease. In high-risk surgical patients or in those who refuse surgery, PDT may represent an alternative treatment as long as the malignancy satisfies the following criteria: (1) radiographically occult, (2) superficial, less than 3 cm^2 in surface area and 1 mm in depth, and (3) squamous cell carcinoma.

Owing to its delayed effect and possible swelling of the lesion following the therapy, tracheal-carinal lesions and lesions in post-pneumonectomy patients are considered contraindications. PDT is contraindicated if the tumor invades vascular structures or if there is a history of porphyria and/or porphyrin hypersensitivity.[169,204]

Results and Complications

PDT has been used to treat advanced lung cancer,[205] to treat multiple malignancies alone or in combination with surgery,[206] and to pretreat in order to reduce the extent of the surgical resection.[207] In superficial tumors, a complete remission rate between 64% to 98% with PDT has been described.[205,206,208]

PDT has a slow onset of action, requires frequent cleanup bronchoscopies, and mandates that the patient avoid sunlight for 4 to 6 weeks.[209] The most common complications include skin photosensitivity, up to 4 to 6 weeks after the procedure; local airway edema; strictures; hemorrhage; and fistula formation. The major limitation of PDT, as with brachytherapy and cryotherapy, is the delayed response to therapy.[169,184,204]

Brachytherapy

Endobronchial brachytherapy ("brachy" meaning "short"; short-distance radiotherapy) requires implantation or insertion of a radioactive source adjacent to the lesion in a patient's airway. A polyethylene catheter is placed adjacent to the lesion via FB and its position verified by radiography (or fluoroscopy). The catheter is then loaded with the radioactive source, usually radium in capsules for low dose (1–2 gray/hr) or iridium for high-dose radiotherapy (10 gray/hr) reaching the total dose of 500 to 4000 gray directly to the lesion.[210,211]

Indications

Patients with unresectable primary carcinoma of the lung, recurrent carcinoma of the lung, or cancers metastatic to the airway are potential candidates for brachytherapy. The lesion can be either extrinsic or intrinsic to the airway.[210] It may also be benign obstruction such as granulation tissue.[211] The main goal of brachytherapy is palliation of symptoms of airway obstruction caused by tumor. Brachytherapy can also be used as an adjunct to external beam radiotherapy for curative treatment of primary non–small cell tumors. Occasionally, brachytherapy has been used as a curative treatment of a residual tumor following surgery.[210]

Contraindications

A few absolute contraindications for endobronchial brachytherapy exist, such as known fistulas involving the airways. To avoid life-threatening complications, one should exclude tumors directly involving the major arteries and mediastinal structures. CT, magnetic resonance imaging, or digital subtraction angiography of the chest should be performed before instituting endobronchial therapy in patients suspected to have mediastinal extension of tumor. Patients with endotracheal carcinoma causing high-grade obstruction should be treated with Nd:YAG laser and possible placement of stent prior to brachytherapy because of the potential postradiation edema and total airway obstruction.[210]

Results and Complications

The studies that combined external radiation with brachytherapy showed that even if quick airway response was gained, there was no survival benefit[210]; thus, its role is mainly for palliation. High-dose brachytherapy has been used safely for granulation tissue caused by metallic stents[211] and may be more effective when used prophylactically than therapeutically.

Complications include respiratory compromise, massive hemoptysis, fistula formation, radiation bronchitis, airway stenosis, and pulmonary artery erosion. The combined rate of massive hemoptysis and airway-mediastinal fistula formation ranges from 0% to 42%. Risk of late exsanguinations has been found to be high in patients receiving brachytherapy to the right upper lobe, anterior segment area, probably owing to its close proximity to the pulmonary artery.[210,211]

Brachytherapy may be an effective palliative treatment for endobronchial malignancies, but further investigations are necessary to determine the optimal dose and its efficacy in bronchogenic carcinoma alone and in combination with either external beam radiation therapy, surgery, or other endobronchial therapeutics.

Stent Placement

Stents are devices used for the internal splinting of luminal structures.[184] The first stents that were used in the trachea were the T-tubes developed by Montgomery. Though they require a tracheostomy for their placement, these silicone stents are still widely used by otolaryngologists and are considered to be the safest approach in cases with high tracheal stenoses. Westaby and colleagues modified this stent and designed a T-Y

prosthesis, which enabled splinting of the carinal region. Using the same tissue-friendly silicone material, Dumon developed the first stents that could be inserted through a bronchoscope without a tracheostomy. Over the years, several other polymer stents have been developed and commercialized. However, all polymer prostheses require use of a rigid bronchoscope and general anesthesia for their deployment.[184]

A family of stents have been developed that can be inserted using FB. These stents are made from metal, such as steel and nitinol (nickel-titanium), and are the direct offspring of its vascular counterpart. There seem to be many advantages to metal construction over the polymer prostheses; metal stents have thinner walls and are thus easier to place using FB under moderate sedation and local anesthesia as an outpatient procedure.

They are available as self-expanding or balloon expandable versions and as covered or uncovered versions. Covered stents are designed mainly to prevent tumor growth or the prosthesis-related granulation tissue invading the airways (Fig. 22-17A). In recent years, fully covered stents have also been introduced to the armamentarium of the therapeutic bronchoscopist (see Fig. 22-17B).[184]

Indications and Contraindications

Indications for the placement of the SEMS include (1) counteracting extrinsic compression from tumors or lymph nodes; (2) stabilizing airway patency after endoscopic removal of intraluminally growing cancer; and (3) sealing malignant fistulas (e.g., stump dehiscences) or fistulas between the trachea and esophagus.[184,212] The U.S. Food and Drug Administration has issued a warning against use of metallic stents in patients with benign conditions until all therapeutic options, including use of silicone stent and surgery, have been explored.

Results and Complications

Stents can be used temporarily in a multimodality concept of cancer care and as a last palliative measure. The efficacy regarding functional improvement and quality of life has been demonstrated.[184]

Retained secretions, bacterial colonization of stent material, migration, stent fractures, and development of granulation tissue are the frequent complications. Metallic stents have a significantly lower rate of migration than silicone stents. Granulation tissue formation especially at either end of the stents, even months after their insertion, can significantly obstruct the internal lumen; the obstruction can ultimately be worse than the primary disease. Removal of the granulation tissue can be very difficult and require use of laser photoresection, APC, or cryotherapy (in the case of covered stents). On occasion, a granulated stent may need to be permanently removed using rigid bronchoscopy or by surgical methods. It is agreed by all experts that there is currently no ideal endobronchial stent. Newer materials, a better understanding of airway biomechanics, and other approaches, such as bioabsorbable stents, may lead to improvements in stent technology.[169,184,212]

Bronchial Thermoplasty

Recently, Cox and associates[213,214] reported their experience with bronchial thermoplasty in asthmatic patients. This novel technique involves treatment of airways with a specially designed, four-wired, thermoplasty probe that ablates airway smooth muscle. The thermal effect appears to remain confined to the airway wall and the immediate peribronchial area without associated fibrosis. The procedure seems to be well tolerated and patients demonstrate an improvement in airway hyperresponsiveness, quality of life and symptom-free days, and peak flow measurements. Even in patients with severe asthma, thermoplasty has been reported to improve quality of life and to decrease severe exacerbations, emergency department visits and days missed from work for up to 12 months.[215] At this early stage, the procedure remains an intriguing subject for research.

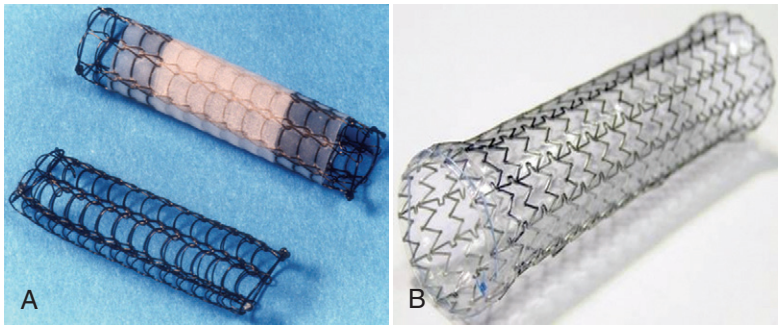

FIGURE 22-17 ■ A, Covered (*top*) and uncovered (*bottom*) versions of a self-expanding metallic stent. **B,** Fully covered self-expanding hybrid stent.

KEY POINTS

- Since its introduction in 1966, FB has replaced rigid bronchoscopy for most diagnostic and therapeutic indications; rigid bronchoscopy has a continued role for a few indications such as massive hemoptysis and removal of large foreign bodies, especially in the pediatric population.
- BAL, which samples the distal air spaces, can diagnose several diseases that involve the air spaces, including opportunistic infections, bronchoalveolar carcinoma, and pulmonary alveolar proteinosis.
- TBB has value in the diagnosis of infiltrative diffuse pulmonary diseases; with the advent of novel guidance techniques, such as EMN, TBB may become accurate at sampling distal focal lesions.
- TBNA has a role in sampling the mediastinal nodes to assist in staging of lung cancer and in making diagnoses of nodal involvement with sarcoidosis or tuberculosis.
- New developments in bronchoscopy, including confocal bronchoscopy, AFB, and NBI bronchoscopy, may prove valuable in evaluating early lesions of the large airways.
- Therapeutic bronchoscopy with the standard flexible bronchoscope has long been used for removal of foreign bodies and stent placement; now, with many new technologies, bronchoscopy can be used for the relief of large airway obstruction.
- Each therapeutic bronchoscopic technique has overlapping indications and its own advantages and disadvantages; it is hoped that, with ongoing research, the best use of these techniques will be determined (see Table 22-5).

References

1. Becker HD: Gustav Killian: A biographical sketch. J Bronchol 2:77–83, 1995.
2. Ikeda S, Yanai N, Ioshikawa S: Flexible bronchofiberoscope. Keio J Med 17:1–16, 1968.
3. Prakash UBS, Diaz Jimenes JP: The rigid bronchoscope. In Prakash UBS (ed): Bronchoscopy. New York: Raven, 1994, pp 53–69.
4. Helmers RA, Sanderson DR: Rigid bronchscopy. The forgotten art. Clin Med 16:393–399, 1995.
5. Beamis JF: Rigid bronchoscopy. *In* Beamis JF, Mathur PN (eds): Interventional Pulmonology. New York: McGraw-Hill, 1999.
6. Miller JI Jr: Rigid bronchoscopy. Chest Surg Clin North Am 6:161–167, 1996.
7. Upham JW, Mitchell CA, Armstrong JG, Kelly WT: Investigation of pleural effusion: The role of bronchoscopy. Aust N Z J Med 22:41–43, 1992.
8. Chang SC, Perng RP: The role of fiberoptic bronchoscopy in evaluating the causes of pleural effusions. Arch Intern Med 149:855–857, 1989.
9. Marini JJ, Pierson DJ, Hudson LD: Acute lobar atelectasis: A prospective comparison of fiberoptic bronchoscopy and respiratory therapy. Am Rev Respir Dis 119:971–978, 1979.
10. Wiedemann HP: Bronchoscopy in severe chronic obstructive pulmonary disease. J Bronchol 1:177–178, 1994.
11. Liam CK, Pang YK, Poosparajah S: Diagnostic yield of flexible bronchoscopic procedures in lung cancer patients according to tumor location. Singapore Med J 48:625–631, 2007.
12. Mehta AC, Dweik RA: Controversies in bronchoscopy. Nasal versus oral insertion of the flexible bronchoscope: Pronasal insertion. J Bronchol 3:224–228, 1996.
13. Kvale PA: Is sedation necessary for bronchoscopy? Pro sedation. J Bronchol 1:246–249, 1994.
14. Colt HG: Is sedation necessary for bronchoscopy? Con sedation. J Bronchol 1:250–253, 1994.
15. Gonzalez R, De-La-Rosa-Ramirez I, Maldonado-Hernandez A, Dominguez-Cherit G: Should patients undergoing a bronchoscopy be sedated? Acta Anaesthesiol Scand 47:411–415, 2003.
16. Mehta AC: Don't lose the forest for the trees: Satisfaction and success in bronchoscopy. Am J Respir Crit Care Med 166:1306–1307, 2002.
17. Pearce S: Fiberoptic bronchoscopy: Is sedation necessary? BMJ 281:79–80, 1980.
18. Colt HG, Morris JF: Fiberoptic bronchoscopy without premedication. A retrospective study. Chest 98;1327–1330, 1990.
19. Prakash UB, Offord KP, Stubbs SE: Bronchoscopy in North America: The ACCP survey. Chest 100:1668–1675, 1991.
20. Reed A: Preparation of the patient for awake flexible bronchoscopy. Chest 101:244–253, 1992.
21. Prakash UB, Stubbs SE: The bronchoscopy survey: Some reflections. Chest 100:1660–1667, 1991.
22. British Thoracic Society guidelines on diagnostic flexible bronchoscopy. Thorax 56(Suppl 1):i1–i21, 2001.
23. Chhajed PN, Aboyoun C, Malouf MA, et al: Management of acute hypoxemia during flexible bronchoscopy with insertion of a nasopharyngeal tube in lung transplant recipients. Chest 121:1350–1354, 2002.
24. Maltias F, Laberge F, Laviolette M: A randomized double-blind, placebo-controlled study of lorazepam as premedication for bronchoscopy. Chest 109:1195–1198, 1996.
25. Rab-Khan A, MacLeod D, Prichard JS: Marked increase in benzodiazepine requirements during bronchoscopy in HIV positive intravenous drug abusers. Ir Med J 85:37–38, 1992.
26. Stolz D, Chhajed PN, Leuppi JD, et al: Cough suppression during flexible bronchoscopy using combined sedation with midazolam and hydrocodone: A randomized, double-blind, placebo-controlled trial. Thorax 59:773–776, 2004.
27. Tüller C, Tüller D, Tamm M, Brutsche MH: Hemodynamic effects of endobronchial application of ornipressin versus terlipressin. Respiration 71:397–401, 2004.
28. Braga PC, Allegra L (eds): Centrally Acting Opioid Drugs. New York: Raven Press, 1989.
29. Vincent BD, Silvestri GA: An update on sedation and analgesia during flexible bronchoscopy. J Bronchol 14:173–180, 2007.
30. Schwarz Y, Greif J, Lurie O, et al: Dextrometorphan premedication reduces midazolam requirement: Objective and subjective parameters in peribronchoscopy. Respiration 74:314–319, 2007.

31. Borer H, Chhajed PN, Mueller P: Assessment of patient satisfaction with bronchoscopy. The Solothurn Questionnaire. Eur Respir J 26(Suppl 49):530S, 2005.
32. Chhajed PN, Wallner J, Stolz D, et al: Sedative drug requirements during flexible bronchoscopy. Respiration 72:617–621, 2005.
33. Chhajed PN, Aboyoun C, Chhajed TP, et al: Sedative drug requirements during bronchoscopy are higher in cystic fibrosis after lung transplantation. Transplantation 80:1081–1085, 2005.
34. Teale C, Gomes PJ, Muers MF, Pearson SB: Local anesthesia for fiberoptic bronchoscopy: Comparison between cocaine and lidocaine. Respir Med 84:407–408, 1990.
35. Webb AR, Woodhead MA, Dalton HR, et al: Topical nasal anesthesia for fiberoptic bronchoscopy: Patients' preference for lignocaine gel. Thorax 44:674–675, 1989.
36. Efthimiou J, Higenbottam T, Holt D, Cochrane GM: Plasma concentrations of lignocaine during fiberoptic bronchoscopy. Thorax 37:68–71, 1982.
37. Randell T, Yli-Hankala A, Valli H, Lindgren L: Topical anesthesia of the nasal mucosa for fiberoptic airway endoscopy. Br J Anaesth 68:164–167, 1992.
38. Honeybourne D, Neuman C: An audit of bronchoscopy practice in the United Kingdom: A survey of adherence to national guidelines. Thorax 52:709–713, 1997.
39. Roffe C, Smith MJ, Basran GS: Anticholonergic premedication for fiberoptic bronchoscopy. Monaldi Arch Chest Dis 49:101–106, 1994.
40. Cowl CT, Prakash UB, Kruger BR: The role of anticholinergics in bronchoscopy. A randomized clinical trial. Chest 118:188–192, 2000.
41. Williams T, Brooks T, Ward C: The role of atropine premedication in fiberoptic bronchoscopy using intravenous midazolam sedation. Chest 133:1394–1398, 1998.
42. Makker H, Kishen R, O'Driscoll R: Atropine as premedication for bronchoscopy. Lancet 345:724–725, 1995.
43. Mehta AC, Prakash UBS, Garland R, et al: American Collage of Chest Physicians and American Association for Bronchoscopy Consensus Statement: Prevention of flexible bronchoscopy-associated infection. Chest 128:1742–1755, 2005.
44. Hunninghake GW, Gadek JE, Kwanami O, et al: Inflammatory and immune processes in the human in health and disease: Evaluation by bronchoalveolar lavage. Am J Pathol 97:149–198, 1979.
45. Reynolds HY, Newball HH: Analyses of proteins and respiratory cells from human lungs by bronchial lavage. J Lab Clin Med 84:559–573, 1974.
46. Costabel U, Guzman J: Bronchoalveolar lavage in interstitial lung disease. Curr Opin Pulm Med 7:255–261, 2001.
47. American Thoracic Society: Clinical role of bronchoalveolar lavage in adults with pulmonary disease. Am Rev Respir Dis 142:481, 1990.
48. Helmers RA, Hunninghake GW: Bronchoalveolar lavage. *In* Wang KP (ed): Biopsy Techniques in Pulmonary Disorders. New York: Raven, 1989, pp 15–28.
49. Pingleton SK, Harrison GF, Stechschulte DJ, et al: Effect of location, pH and temperature of instillate in bronchoalveolar lavage in normal volunteer. Am Rev Respir Dis 128:1035–1037, 1983.
50. Helmers RA, Hunninghake GW: Bronchoscopy: Bronchoalveolar lavage in the non-immunecompromised patient Chest 96:1184–1190, 1989.
51. Meyer KC: The role of bronchoalveolar lavage in interstitial lung disease. Clin Chest Med 25:637–649, 2005.
52. Enomoto K, Takada T, Suzuki E, et al: Bronchoalveolar fluid cells in mixed connective tissue disease. Respirology 8:149–156, 2003.
53. Ryu RJ, Chung MP, Han J, et al: Bronchoalveolar lavage in fibrotic idiopathic interstitial pneumonias. Respir Med 101:655–660, 2007.
54. Costabel U, Uzaslan E, Guzman J: Bronchoalveoalr lavage in drug-induced lung disease. Clin Chest Med 25:25–35, 2004.
55. Hunninghake GW, Costabel U, Ando M, et al: ATS/ERS/WASOG statement on sarcoidosis. American Thoracic Society/European Respiratory Society/World Association of Sarcoidosis and other Granulomatous Disorders. Sarc Vasc Diffuse Lung Dis 16:149–173, 1999.
56. ATS/ERS Statement: Idiopathic pulmonary fibrosis: Diagnosis and treatment. Am J Respir Crit Care Med 161:646–664, 2000.
57. de Gracia J, Bravo C, Miravitlles M, et al: Diagnostic value of bronchoalveolar lavage in peripheral lung cancer. Am Rev Respir Dis 147:649–652, 1993.
58. Linder J, Radio SJ, Robbins RA, et al: Bronchoalveolar lavage in the cytologic diagnosis of carcinoma of the lung. Acta Cytol 31:796–801, 1987.
59. Pirozynski M: Bronchoalveolar lavage in the diagnosis of peripheral, primary lung cancer. Chest 102:372–374, 1992.
60. Liam CK, Pang YK, Poosparajah S: Diagnostic yield of flexible bronchoscopic procedures in lung cancer patients according to tumor location. Singapore Med J 48:625–631, 2007.
61. Sestini P, Rottoli L, Gotti G, et al: Bronchoalveolar lavage diagnosis of bronchoalveolar carcinoma. Eur J Respir Dis 66:55–58, 1985.
62. Fedullo AJ, Ettensohn DB: Bronchoalveolar lavage in the lymphangitic spread of adenocarcinoma to the lung. Chest 87:129–131, 1985.
63. Levy H, Horak DA, Lewis MI: The value of bronchial washings and bronchoalveolar lavage in the diagnosis of lymphangitic carcinamatosis. Chest 94:1028–1230, 1988.
64. Lowe EE, Baughman RP: Pulmonary lymphangitic metastasis from breast cancer. Lymphocytic alveolitis is associated with favorable prognosis. Chest 102:1113–1117, 1992.
65. Wisecarver C, Ness MJ, Rennard SI, et al: Bronchoalveolar lavage in the assessment of pulmonary Hodgkin's disease. Acta Cytol 33:528–529, 1989.
66. Menashe P, Stenson W, Reynoso G, et al: Bronchoalveolar lavage plasmacytosis in a patient with a plasma cell dyscrasia. Chest 95:226–231, 1989.
67. Rossini GA, Balbi B, Risso M, et al: Acute myelomonocytic leukemia. Demonstration of pulmonary involvement by bronchoalveolar lavage. Chest 87:259, 1985.
68. DeVuyst P, DuMortier P, Moulin E, et al: Diagnostic value of asbestos bodies in bronchoalveolar lavage fluid. Am Rev Respir Dis 136:1219–1224, 1987.
69. Cordeiro CR, Jones JC, Alfaro T, Ferreira AJ: Broncoalveolar lavage in occupational lung diseases. Semin Respir Crit Care Med 28:504–513, 2007.
70. Costabel U, Guzman J, Bonella F, Oshimo S: Bronchoalveolar lavage in other interstitial lung diseases. Semin Respir Crit Care Med 28:514–524, 2007.
71. Fontenot AP, Canavera SJ, Gharavi L, et al: Target organ localization of memory CD4+ T cells in patients with chronic beryllium disease. J Clin Invest 110:1473–1482, 2002.
72. Rossman MD, Kern JA, Elias JA, et al: Proliferative response of bronchoalveolar lymphocytes to beryllium: A test for chronic beryllium disease. Ann Intern Med 108:687–693, 1988.
73. Thorpe JE, Baughman RP, Frame BT, et al: Bronchoalveolar lavage for diagnostic acute bacterial pneumonia. J Infect Dis 155:855–861, 1987.
74. American Thoracic Society: Clinical role of bronchoalveolar lavage in adults with pulmonary disease. Am Rev Respir Dis 142:481–486, 1990.
75. Clech C, Jaureguy F, Hamza L, et al: Agreement between quantitative cultures of post-intubation of tracheal aspiration and plugged telescoping catheter, protected specimen brush, or BAL for the diagnosis of nosocomial pneumonia. Chest 130:956–961, 2006.
76. Veber B, Souweine B, Gachot B, et al: Comparison of direct examination of three types of bronchoscopy specimens used to diagnose nosocomial pneumonia. Crit Care Med 28:962–968, 2000.
77. Leong JR, Huang DT: Ventilator associated pneumonia. Surg Clin North Am 86:1409–1429, 2006.
78. Torres A, El-Ebiary M: Bronchoscopic BAL in the diagnosis of ventilatory associated pneumonia. Chest 117:198S–202S, 2000.
79. Porzecanski I, Bawton D: Diagnosis and treatment of ventilator-associated pneumonia. Chest 130:597–604, 2006.
80. The Canadian Critical Care Trials Group: A randomized trial of diagnostic techniques for ventilator-associated pneumonia. N Engl J Med 355:2619–2632, 2006.
81. White P, Bonacum JT, Miller CB: Utility of fiberoptic bronchoscopy in bone marrow transplant patients. Bone Marrow Transplant 20:681–687, 1997.

82. Stover DE, Zaman MB, Hajdu SI, et al: Bronchoalveolar lavage in the diagnosis of diffuse pulmonary infiltrates in the immunosuppressed host. Ann Intern Med 101:1–7, 1984.
83. Jain P, Sandur S, Meli Y, et al: Role of flexible bronchoscopy in immunocompromised patients with lung infiltrates. Chest 125:712–722, 2004.
84. Feller Kopman D, Ernst A: The role of bronchoalveolar lavage in the immunocompromised host. Semin Respir Infect 18:87–94, 2003.
85. Joos L, Chhajed PN, Wallner J, et al: Pulmonary infections diagnosed by BAL: A 12-year experience in 1066 immunocompromised patients. Respir Med 101:93–97, 2007.
86. Boersma WG, Erjavec Z, van der Werf TS, et al: Bronchoscopic diagnosis of pulmonary infiltrates in granulocytopenic patients with hematologic malignancies: BAL versus PSB and PBAL. Respir Med 101:317–325, 2007.
87. Hohenthal U, Itala M, Salonen J, Spila J, et al: Bronchoalveolar lavage in immunocompromised patients with haematological malignancy—Value of new microbiological methods. Eur J Haematol 74:203–211, 2005.
88. Buccheri G, Barberis P, Delfino M: Diagnostic, morphologic, and histopathologic correlates in bronchogenic carcinoma: A review of 1,045 bronchoscopic examinations. Chest 99:809–814, 1991.
89. Dasgupta A, Jain P, Minai O, et al: Utility of transbronchial needle aspiration in the diagnosis of endobronchial lesions. Chest 115:1237–1241, 1999.
90. Govert JA, Dodd LG, Kussin PS, Samuelson WM: A prospective comparison of fiberoptic transbronchial needle aspiration and bronchial biopsy for bronchoscopically visible lung carcinoma. Cancer 87:129–134, 1999.
91. Mak V, Johnston I, Hetzel M, Grubb C: Value of washings and brushings at fiberoptic bronchoscopy in the diagnosis of lung cancer. Thorax 45:373–376, 1990.
92. Rosell A, Monso E, Lores L, et al: Cytology of bronchial biopsy rinse fluid to improve the diagnostic yield for lung cancer. Eur Respir J 12:1415–1418, 1998.
93. Yung RCW: Tissue diagnosis of suspected lung cancer: Selecting between bronchoscopy, transthorasic needle aspiration and resectional biopsy. Respir Care Clin North Am 9:51–76, 2003.
94. Henschke C, Yankelevitz D, Libby D, Kimmel M: CT screening for lung cancer: The first ten years. Cancer J 8(Suppl 1):S47–S54, 2002.
95. Baaklini WA, Reinoso MA, Gorin AB, et al: Diagnostic yield of fiberoptic bronchoscopy in evaluating solitary pulmonary nodules. Chest 117:1049–1054, 2000.
96. Reichenberger F, Weber J, Tamm M, et al: The value of transbronchial needle aspiration in the diagnosis of peripheral pulmonary lesions. Chest 116:704–708, 1999.
97. Zavala DC, Richardson RH, Mukerjee PK, et al: Use of the bronchofiberoscope for bronchial brush biopsy. Chest 63:889–892, 1973.
98. Mazzone P, Jain P, Arroliga A, Matthay RA: Bronchoscopy and needle biopsy techniques for diagnosis and staging of lung cancer. Clin Chest Med 23:137–158, 2002.
99. Saita S, Tanzillo A, Riscica C, et al: Bronchial brushing and biopsy: A comparative evaluation in diagnosing visible bronchial lesions. Eur J Cardiothorac Surg 4:270–272, 1990.
100. Wimberley N, Faling LC, Barlett JG: A fiberoptic bronchoscopy technique to obtain uncontaminated lower airway secretions for bacterial culture. Am Rev Respir Dis 119:337–343, 1979.
101. Campbell GD: Blinded invasive diagnostic procedures in ventilator-associated pneumonia. Chest 117(4 Suppl):207S–211S, 2000.
102. Chaudhary B, Yoneda K, Burki N: Fiberoptic bronchoscopy: Comparison of procedures used in the diagnosis of lung cancer. J Thorac Cardiovasc Surg 76:33–37, 1978.
103. Rivera MP, Mehta AC: Initial diagnosis of lung cancer: ACCP evidence based clinical practice guidelines (2nd ed). Chest 132(3 Suppl):131S–148S, 2007.
104. Hunninghake GW, Zimmerman MB, Schwartz DA, et al: Utility of a lung biopsy for the diagnosis of idiopathic pulmonary fibrosis. Am J Respir Care Med 164:193–196, 2001.
105. Thorax DPLD Committee: Diagnosis and assessment of diffuse parenchymal lung disease. Thorax 54(Suppl):S1–S14, 1999.
106. Green FHY: Overview of pulmonary fibrosis. Chest 122(6 Suppl):334S–339S, 2002.
107. Berbescu EA, Katzenstein AL, Snow JL, Zisman DA: Transbronchial biopsy in usual interstitial pneumonia. Chest 129:1126–1131, 2006.
108. Tokuda A, Katayama N, Nakatsumi Y, Fujimura M: Asymptomatic pulmonary actinomycosis diagnosed by transbronchial biopsy. Nihon Kokyuki Gakkai Zasshi 45:494–498, 2007.
109. American Thoracic Society: Statement on sarcoidosis. Am J Respir Crit Care Med 160:736–755, 1999.
110. Green MB, Allen JN: Cough, dyspnea and reticulonodular opacities in a 58-year-old smoker Chest 132:700–703, 2007.
111. Mones JM, Salvana MJ, Oldham SA: Diagnosis of *Pneumocystis carinii* pneumonia. Roetgenographic-pathologic correlates based on fiberoptic bronchoscopy specimens from patients with the acquired immunodeficiency syndrome. Chest 89:522–526, 1986.
112. Venkateshiah S, Mehta AC: Role of flexible bronchoscopy in the diagnosis of pulmonary tuberculosis in immunocompetent individuals. J Bronchol 10:300–308, 2003.
113. Szlubowski A, Soja J, Kuzdzal J, et al: Transbronchial lung biopsy as a diagnostic method of peripheral lesions. Pneumonol Alergol Pol 72:482–486, 2004.
114. Chechani V: Bronchoscopic diagnosis of solitary pulmonary nodules and lung masses in the absence of endobronchial abnormality. Chest 109:620–625, 1996.
115. Hanson RR, Zavala DC, Rhodes ML, et al: Transbronchial biopsy via flexible fiberoptic bronchoscope: Result in 164 patients. Am Rev Respir Dis 114:67–72, 1976.
116. Milman N, Faurschou P, Munch EP, Grode G: Transbronchial lung biopsy through the fiberoptic bronchoscope: Results and complications in 452 examinations. Respir Med 88:749–753, 1994.
117. Torrington TG, Kern JD: The utility of fiberoptic bronchoscopy in the evaluation of the soltary pulmonary nodule. Chest 104:1021–1024, 1993.
118. Descombes E, Gardiol D, Leuenberger PH: Transbronchial lung biopsy: An analyses of 530 cases with reference to the number of samples. Monaldi Arch Chest Dis 53;324–329, 1997.
119. Sharafkhaneh A, Baaklini W, Gorin AB, Gren L: Yield of transbronchial needle aspiration in the diagnosis of mediastinal lesions. Chest 124:2131–2135, 2003.
120. Hernández Blasco L, Sánchez Hernández IM, Villena Garrido V, et al: Safety of the transbronchial biopsy in outpatients. Chest 99:562–565, 1991.
121. Wahidi MM, Rocho AT, Hollingsworth JW, et al: Contraindications and safety of the transbronchial lung biopsy via flexible bronchoscopy. Respiration 72:285–295, 2005.
122. Herth FJ, Becker HD, Ernst A: Aspirin does not increase bleeding complications after transbronchial biopsy. Chest 122:1461–1464, 2002.
123. Ernst A, Eberhardt R, Wahidi M, et al: Effect of routine clopidogrel use on bleeding complications after transbronchial biopsy in humans. Chest 129:734–737, 2006.
124. Bilaçeroğlu S, Çağırıcı U, Günel O, et al: Comparision of rigid and flexible transbronchial needle aspiration in the staging of bronchogenic carcinoma. Respiration 65:441–449, 1998.
125. Harrow EM, Abi-Saleh W, Blum J, et al: The utility of transbronchial needle aspiration in the staging of bronchogenic carcinoma. Am J Respir Crit Care Med 161:601–607, 2000.
126. Hermens FHW, Van Engelenburg TCA, Visser FJ, et al: Diagnostic yield of transbronchial histology needle aspiration in patients with mediastinal lymph node enlargement. Respiration 70:631–635, 2003.
127. Shah PL, Singh S, Bower M, et al: The role of transbronchial fine needle aspiration in an integrated care pathway for the assessment of patients with suspected lung cancer. J Thorac Oncol 1:324–327, 2006.
128. Aono H, Okamoto H, Kunikane H, et al: Transbronchial needle aspiration cytology of subcarinal lymphnodes for the staging procedure in the diagnosis of lung cancer. Respirology 11:782–785, 2006.
129. Le Jeune I, Baldwin D: Measuring the success of transbronchial needle aspiration in every clinical practice. Respir Med 101:670–675, 2007.

130. Reichenberger F, Weber T, Tamm M, et al: The value of transbronchial needle aspiration in the diagnosis of peripheral pulmonary nodules. Chest 116:704–708, 1999.
131. Trisolini R, Agli LL, Cancellieri A, et al: The value of flexible needle aspiration in the diagnosis of stage I sarcoidosis. Chest 124:2126–2130, 2003.
132. Smojver-Jezek S, Peros-Golubicic T, Tekavec-Trkanjec J, et al: Transbronchial fine needle aspiration cytology in the diagnosis of mediastinal/hilar sarcoidosis. Cytopathology 18:3–7, 2007.
133. Çetinkaya E, Yıldız P, Altın S, Yılmaz V: Diagnostic value of transbronchial needle aspiration by Wang 22-gauge cytology needle in intrathoracic lymphadenopathy. Chest 125:527–531, 2004.
134. Bilaçeroğlu S, Gunel O, Eriş N, et al: Transbronchial needle aspiration in diagnosis intrathoracic tuberculous lymphadenitis. Chest 126:259–267, 2004.
135. Garg S, Handa U, Mohan H, Janmeja AK: Comparative analyses of various cytohistological techniques in the diagnosis of lung diseases. Diagn Cytopatol 35:26–31, 2007.
136. Dasgupta A, Mehta AC: Transbronchial needle aspiration: An underused diagnostic technique. Clin Chest Med 20:39–51, 1999.
137. Wang KP, Haponik EF, Britt EJ, et al: Transbronchial needle aspiration of peripheral pulmonary nodules. Chest 86:819–823, 1984.
138. Bilaçeroğlu S, Chhajed P: Transbronchial needle aspiration: A diagnostic tool in routine bronchoscopy. J Assoc Physicians India 53:797–802, 2005.
139. Toloza EM, Harpole L, Detterbeck F, McCrory DC: Invasive staging of non-small cell lung cancer: A review of the current evidence. Chest 123(Suppl):137S–146S, 2003.
140. Schreiber G, McCrory DC: Performance characteristics of different modalities for diagnosis of suspected lung cancer summary of published evidence. Chest 123(Suppl):115S–128S, 2003.
141. Diacon AC, Schuurmans MM, Theron J, et al: Transbronchial needle aspirates: Comparison of two preparation methods. Chest 127:2015–2018, 2005.
142. Ghamande SA, Rafanan A, Dweik RA, et al: Role of transbronchial needle aspiration in mechanically ventilated patients. Chest 122: 985–989, 2002.
143. White CS, Weiner EA, Patel P, Britt EJ: Transbronchial needle aspiration: Guidance with CT fluoroscopy. Chest 118:1630–1638, 2000.
144. Garpestad E, Goldberg S, Herth F, et al: CT fluoroscopy guidance for transbronchial needle aspiration: An experience in 35 patients. Chest 119:329–332, 2001.
145. Rooney CP, Wolf K, McLennan G: Ultrathin bronchoscopy as an adjunct to standard bronchoscopy in the diagnosis of peripheral lung lesions. Respiration 69:63–68, 2002.
146. Yamamoto S, Ueno K, Imamura F, et al: Usefulness of ultrathin bronchoscopy in diagnosis of lung cancer. Lung Cancer 46:43–48, 2004.
147. Shinagawa N, Yamazaki K, Onodera Y, et al: Factors related to diagnostic sensitivity using an ultrathin bronchoscope under CT-guidance. Chest 131:549–553, 2007.
148. Raoof S, Mehrishi S, Prakash UB: Role of bronchoscopy in modern medical intensive care unit. Clin Chest Med 22:241–261, 2001.
149. Thiberville L, Moreno-Swirc S, Vercauteren T, et al: In vivo imaging of the bronchial wall microstructure using fibered confocal fluorescence microscopy. Am J Respir Crit Care Med 175:22–31, 2007.
150. Becker HC, Herth F, Ernst A, Schwarz Y: Bronchoscopic biopsy of peripheral lung lesions under electromagnetic guidance: A pilot study. J Bronchol 12:9–13, 2005.
151. Schwarz Y, Greif J, Becker HD, et al: Real time electromagnetic navigation bronchoscopy to peripheral lung lesions using overlaid CT images: The first human study. Chest 129:998–994, 2006.
152. Gildea TR, Mazzone PJ, Karnak D, et al: Electromagnetic navigation diagnostic bronchoscopy: A prospective study. Am J Respir Crit Care Med 174:982–989, 2006.
153. Eberhardt R, Anantham D, Herth F, et al: Electromagnetic navigation diagnostic bronchoscopy in peripheral lung lesions. Chest 131:1800–1805, 2007.
154. Eberhardt R, Anantham D, Ernst A, et al: Multimodality bronchoscopic diagnosis of peripheral lung lesions: A randomized controlled trial. Am J Respir Crit Care Med 176:36–41, 2007.
155. Makris D, Scherpereel A, Leroy S, et al: Electromagnetic navigation diagnostic bronchoscopy for small peripheral lung lesions. Eur Respir J 29:1187–1192, 2007.
156. Herth FJ, Eberhardt R, Ananthan D, et al: Narrow-band imaging bronchoscopy increases the specificity of bronchoscopic early lung cancer detection. J Thorac Oncol 4:1060–1065, 2009.
157. Herth FJ, Ernst A: Innovative bronchoscopic diagnostic techniques: Endobronchial ultrasound and electromagnetic navigation. Curr Opin Pulm Med 11:278–281, 2005.
158. Lam S, Kennedy T, Unger M, et al: Localization of bronchial intraepithelial neoplastic lesions by fluorescence bronchoscopy. Chest 113:696–702, 1998.
159. Moro-Sibilot D, Jeanmart M, Lantuejoul S, et al: Cigarette smoking, preinvasive bronchial lesions and autofluorescence bronchoscopy. Chest 122:1902–1908, 2002.
160. Franklin WA: Premalignant evaluation of lung cancer: Gilles F Filley lecture. Chest 125(5 Suppl):90S–94S, 2004.
161. Häussinger K, Becker H, Stanzel F, et al: Autofluorescence bronchoscopy with white light bronchoscopy compared with white light bronchoscopy alone for the detection of precancerous lesions: A European randomised controlled multicenter trial. Thorax 60:496–503, 2005.
162. Nakanishi K, Ohsaki Y, Kurihara M, et al: Color auto-fluoroscence from cancer lesions: Improved detection of central type lung cancer. Lung Cancer 58:214–219, 2007.
163. Baba M, Iyoda A, Nomoto Y, et al: Cytological findings of preinvasive bronchial lesions detected by light induced fluorescence endoscopy in a lung cancer screening system. Oncol Resp 17:579–583, 2007.
164. Mehta AC, Gildae TR: Is autofluorescence bronchoscopy needed to diagnose early bronchogenic carcinoma? J Bronchol 10:70–74, 2003.
165. Band PR, Feldstein M, Saccomanno G: Reversibility of bronchial marked atypia: Implication for chemopreventation. Cancer Detect Prev 9:157–160, 1986.
166. Frost JK, Ball WC Jr, Levin ML, et al: Sputum cytopathology: Use and potential in monitoring the workplace environment by screening for biological effects of exposure. J Occup Med 28:692–703, 1986.
167. Shibuya K, Hoshino H, Chiyo M, et al: High magnification bronchovideoscopy combined with narrow band imaging could detect capillary loops of angiogenic squamous dysplasia in heavy smokers at high risk for lung cancer. Thorax 58:989–995, 2003.
168. Vincent BD, Fraig M, Silvestri GA: A pilot study of narrow-band imaging compared with white light bronchoscopy for evaluation of normal airways and premalignant and malignant airway disease. Chest 131:1794–1799, 2007.
169. Lee P, Mehta AC: Therapeutic flexible bronchoscopy. *In* Beams JF, Mathur PN, Mehta AC (eds): Interventional Pulmonary Medicine, Lung Biology in Health and Disease. Leflant C (executive ed). New York: Marcel Dekker, 2004, pp 49–78.
170. Marquette CH, Martinot A: Foreign body removal in adults and children. *In* Bolliger CT, Mathur PN (eds): Progress in Respiratory Research. Vol 30: Interventional Bronchology. Basel: S Karger, 2000, pp 96–107.
171. Mehta AC, Rafanan AL: Extraction of airway foreign bodies in adults: "How I do it." J Bronchol 8:123–131, 2001.
172. Rafanan A, Mehta AC: Adult airway FB removal: What is new? Clin Chest Med 22:319, 2001.
173. Swanson KL, Prakash UB, Midthun DE, et al: Flexible bronchoscopic management of airway foreign bodies in children. Chest 121:1695–1700, 2002.
174. Martinot A, Closset M, Marquette CH, et al: Indications for flexible versus rigid bronchoscopy in children with suspected foreign-body aspiration. Am J Respir Crit Care Med 155:1676–1679, 1997.
175. El-Khushman HM, Sharara AM, Sa Ada MA, Hijazi MA: Tracheobronchial straight metallic pin aspiration in young Jordanian females. Saudi Med J 28:913–916, 2007.
176. Gencer M, Ceylan E, Koksal N: Extraction of pins from the airway with flexible bronchoscopy. Respiration 74:674–679, 2007.
177. Karakoc F, Cakir E, Ersu R, et al: Late diagnosis of foreign body aspiration in children with chronic respiratory symptoms. Int J Pediatr Otorhinolaryngol 71:241–246, 2007.

178. Debeljak A, Sorli J, Music E, Kecelj P: Bronchoscopic removal of foreign bodies in adults: Experience with 62 patients from 1974–1998. Eur Respir J 14:792–795, 1999.
179. Ramírez-Figueroa JL, Gochicoa-Rangel LG, Ramírez-San Juan DH, Vargas MH: Foreign body removal by flexible fiberoptic bronchoscopy in infants and children. Pediatr Pulmonol 40:392–397, 2005.
180. Tariq SM, George J, Srinivasan S: Inhaled foreign bodies in adolescents and adults. Monaldi Arch Chest Dis 63:193–198, 2005.
181. Kovitz KL, Mayse ML: Foreign body removal. *In* Beams JF, Mathur PN, Mehta AC (eds): Interventional Pulmonary Medicine, Lung Biology in Health and Disease. Leflant C (executive ed). New York: Marcel Dekker, 2004, pp 259–270.
182. Sutedja G, Bolliger CT: Endobronchial electrocautery and argon plasma coagulation. *In* Bolliger CT, Mathur PN (eds): Progress in Respiratory Research. Vol 30: Interventional Bronchology. Basel: S Karger, 2000, pp 120–131.
183. Seijo LM, Sterman DH: Interventional pulmonology. N Engl J Med 344:740–749, 2001.
184. Bolliger CT, Sutedja TG, Strausz J, Freitag L: Therapeutic bronchoscopy with immediate effect: Laser, electrocautery, argon plasma coagulation and stents. Eur Respir J 27:1258–1271, 2006.
185. Coulter T, Mehta AC: The hHeat is on: Impact of endobronchial electrosurgery on the need for Nd-YAG laser photoresection. Chest 118:516–521, 2000.
186. Gerasin VA, Shafirovsky BB: Endobronchial electrosurgery. Chest 93:270–274, 1988.
187. Ledingham SJ, Goldstraw P: Diathermy resection and radioactive gold grains for palliation of obstruction due to recurrence of bronchial carcinoma after external irradiation. Thorax 44:48–51, 1989.
188. Petrou M, Kaplan D, Goldstraw P: Bronchoscopic diathermy resection and stent insertion: A cost effective treatment for tracheobronchial obstruction. Thorax 48:1156–1159, 1993.
189. Sutedja G, van Kralingen K, Schramel FM, Postmus PE: Fibreoptic bronchoscopic electrosurgery under local anaesthesia for rapid palliation in patients with central airway malignancies: A preliminary report. Thorax 49:1243–1246, 1994.
190. Homasson JP, Roden S, Angebault M, et al: [Treatment of bronchial tumors with high-frequency thermocoagulation. Preliminary studies] (French). Rev Pneumol Clin 51:77–81, 1995.
191. Sutedja TG, van Boxem TJ, Schramel FM, et al: Endobronchial electrocautery is an excellent alternative for Nd:YAG laser to treat airway tumors. J Bronchol 4:101–105, 1997.
192. Hooper RG, Jackson FN: Endobronchial electrocautery. Chest 94:595–598, 1988.
193. Saenghirunvattana S, Buakham C, Masakul N, Saenghirunvattana R: Management of endobronchial cancer using bronchoscopic electrocautery J Med Assoc Thai 89:459–461, 2006.
194. Kamal I, Quadri T, Lane SJ, Cullen JP: The role of endobronchial electrocautery in the management of malignant airway obstruction. Ir Med J 99:148–150, 2006.
195. Freitag L, Reichle G: Argon plasma coagulator. *In* Beams JF, Mathur PN, Mehta AC (eds): Interventional Pulmonary Medicine, Lung Biology in Health and Disease. Leflant C (executive ed). New York: Marcel Dekker, 2004, pp 203–213.
196. Reichle G, Frietag L, Kullmann HJ, et al: Argon plasma coagulation in bronchology: A new method-alternative and complementery. J Bronchol 7:109–117, 2000.
197. Vergnon JM, Mathur PN: Cryotherapy for endobronchial disorders. *In* Bolliger CT, Mathur PN (eds): Progress in Respiratory Research. Vol 30: Interventional Bronchology. Basel: S Karger, 2000, pp 133–145.
198. Sheski FD, Mathur PN: Cryotherapy, electrocautery, and brachytherapy. Clin Chest Med 20:123–138, 1999.
199. Forest V, Peoc'h M, Campos L, et al: Benefit of a combined treatment of cryotherapy and chemotherapy on tumour growth and late cryo-induced angiogenesis in a non-small-cell lung cancer model. Lung Cancer 54:79–86, 2006.
199a. Forest V, Hadjeres R, Bertrand R, et al: Optimisation and molecular signalling of apoptosis in sequential cryotherapy and chemotherapy combination in human A549 lung cancer xenografts in SCID mice. Br J Cancer 100:1896–1902, 2009.
200. Cavaliere S, Dumon JF: Laser bronchoscopy. *In* Bolliger CT, Mathur PN (eds): Progress in Respiratory Research. Vol 30: Interventional Bronchology. Basel: S Karger, 2000, pp 108–119.
201. Diaz-Jımenez JB, Rodriguez AN: Laser bronchoscopy for malignant disease. *In* Beams JF, Mathur PN, Mehta AC (eds): Interventional Pulmonary Medicine, Lung Biology in Health and Disease. Leflant C (executive ed). New York: Marcel Dekker, 2004, pp 89–125.
202. Colt H: Laser bronchoscopy for benign disease. *In* Beams JF, Mathur PN, Mehta AC (eds): Interventional Pulmonary Medicine, Lung Biology in Health and Disease. Leflant C (executive ed). New York: Marcel Dekker, 2004, pp 127–155.
203. Turner JF Jr, Wang KP: Endobronchial laser therapy. Clin Chest Med 20:107–122, 1999.
204. Häussinger K, Diaz-Jimenez JP, Rodriguez AN, et al: Photodynamic therapy: Palliative and curative aspects. *In* Bolliger CT, Mathur PN (eds): Progress in Respiratory Research. Vol 30: Interventional Bronchology. Basel: S Karger, 2000, pp 159–170.
205. Moghissi K, Dixon K, Stringer M, et al: The place of bronchoscopic photodynamic therapy in advanced unresectable lung cancer: Experience of 100 cases. Eur J Cardiothorac Surg 15:1–6, 1999.
206. Okunaka T, Kato H, Konaka C, et al: Photodynamic therapy for multiple primary bronchogenic carcinoma. Cancer 68:253–258, 1991.
207. Kato H, Konaka C, Ono J, et al: Preoperative laser photodynamic therapy in combination with operation in lung cancer. J Thorac Cardiovasc Surg 90:420–429, 1985.
208. Moghissi K, Dixon K: Is bronchoscopic photodynamic therapy a therapeutic option in lung cancer? Eur Respir J 22:535–541, 2003.
209. Usuda J, Kato H, Okunaka T, et al:. Photodynamic therapy (PDT) for lung cancers. J Thorac Oncol 1:489–493, 2006.
210. Sheski FD, Mathur PN: Cryotherapy, electrocautery and brachytherapy. *In* Mehta AC (ed): Clinics in Chest Medicine. Philadelphia: WB Saunders, 1999, pp 134–136.
211. Brenner B, Kramer MR, Katz A, et al: High dose rate brachytherapy for nonmalignant airway obstruction: New treatment option. Chest 124:1605–1610, 2003.
212. Freitag L: Tracheobronchial stents. In Bolliger CT, Mathur PN (eds): Progress in Respiratory Research. Vol 30: Interventional Bronchology. Basel: S Karger, 2000, pp 171–185.
213. Cox G, Miller JD, McWilliams A, et al: Bronchial thermoplasty for asthma. Am J Respir Crit Care Med 173:965–969, 2006.
214. Cox G, Thomson NC, Rubin AS, et al: AIR Trial Study Group. Asthma control during the year after bronchial thermoplasty. N Engl J Med 356:1327–1337, 2007.
215. Castro M, Rubin AS, Laviolette M, et al: Effectiveness and safety of bronchial thermoplasty in the treatment of severe asthma: a multicenter, randomized, double-blind, sham-controlled clinical trial. Am J Respir Crit Care Med Oct 8 (Epub ahead of print) 2009.

CHAPTER 23

PLEUROSCOPY AND MEDICAL THORACOSCOPY

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INTRODUCTION

PLEUROSCOPY (MEDICAL THORACOSCOPY)
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DIFFERENCES BETWEEN PLEUROSCOPY AND VIDEO-ASSISTED THORACIC SURGERY (SURGICAL THORACOSCOPY)

INTRODUCTION

Biopsy procedures play an essential role in the diagnostic evaluation of patients with respiratory diseases. Most of the basic techniques we use today were mainly developed and refined during the 20th century. Recently, significant advances in endoscopic technology have provided sophisticated endoscopic instruments and endoscopic telescopes with extremely high optical resolution and small diameters. In addition, developments in anesthesiology offer a wide range of alternatives, from procedures performed under local anesthesia to selective double-lumen intubation under general anesthesia.

As with all medical procedures, the risk-benefit ratio of more invasive methods has to be considered for each individual patient, weighing the risk of morbidity and mortality against the benefit of obtaining an early diagnosis to guide correct therapy. Usually, the more invasive procedures are used if simpler, less invasive methods have failed, if the latter are not very promising for obtaining a reliable diagnosis, or if additional therapeutic options can be combined with the diagnostic approach.

This chapter reviews these more invasive procedures, such as pleuroscopy and medical thoracoscopy. Other biopsy methods, such as bronchoscopic biopsies, thoracentesis, needle biopsy of lung lesions, and closed-needle biopsy of the pleura, are described in other chapters.

PLEUROSCOPY (MEDICAL THORACOSCOPY)

Historical Development

Thoracoscopy was introduced together with laparoscopy in 1910 by Hans-Christian Jacobaeus, who at that time worked as an internist in Stockholm, Sweden. He published his first experiences in a paper entitled "On the possibility to use cystoscopy in the examination of serous cavities."[1] It was recently reported that, as early as 1866, F.-R. Cruise in Ireland had possibly been the first to perform a thoracoscopy, examining the pleural space of a girl with empyema through a pleurocutaneous fistula that had developed after spontaneous pleural drainage.[2] Jacobaeus, in his pioneering paper,[1] mentions two cases of pleuritis exsudativa (tuberculous pleurisy), in which he studied the pleural surfaces after replacing the fluid with air. Although not able to get a clear impression of the pleural changes, he was confident that the method would be successful in the future and might eventually yield prognostic information. Jacobaeus[3] himself initiated the therapeutic application of thoracoscopy for lysis

of pleural adhesions by means of thoracocautery to facilitate pneumothorax treatment of tuberculosis ("Jacobaeus operation"). During the ensuing 40 years, his technique of using a single entry site for the thoracoscope and another for the electrocautery device under local anesthesia was applied worldwide for this specific therapeutic purpose, until antibiotic therapy of tuberculosis was introduced and made the procedure obsolete.[4] Between 1950 and 1960, a generation of chest physicians familiar with the therapeutic application of thoracoscopy began to use the technique for biopsy diagnosis of pleural and even pulmonary disease.[5] Today, pleuroscopy is considered as an integral part of interventional pulmonology.[6]

At the same time, the excellent results of laparoscopic surgery and the tremendous advances in endoscopic technology stimulated many thoracic surgeons almost simultaneously in Europe and the United States to develop minimally invasive techniques, which were termed *therapeutic* or *surgical thoracoscopy*, as well as video-controlled or video-thoracoscopic surgery, or video-assisted thoracic surgery (VATS).[7–10]

To clarify the difference between the two methods, the term *medical thoracoscopy* was introduced.[11] This is performed using the Jacobaeus technique under local anesthesia or conscious sedation, via a single or two sites of entry, by the pulmonary physician in an endoscopy suite using nondisposable rigid instruments.[12] Its main indications are the diagnosis and treatment of recurrent pleural exudative effusions and the treatment of spontaneous pneumothorax. However, because the term *thoracoscopy* is used for both the medical and the surgical procedures, a degree of uncertainty has arisen, which may lead to unnecessary surgical interventions for what are, in fact, medical indications. To avoid confusion in the future, it has been suggested that the old term *pleuroscopy*, as used in 1923[4] and as proposed by Weissberg for the sake of clarity,[4] should be favored over *medical thoracoscopy*.

Finally, in some countries, interventional pulmonologists have broadened their field of expertise to include more elaborate interventions (e.g., sympathectomy, splanchnicectomy, treatment of empyema)[13–15] and to perform thoracoscopy in the operating theater, under total intravenous anaesthesia and spontaneous ventilation (with a laryngeal mask or simple endotracheal tube protecting the airway) or mechanical ventilation. Hence, one can consider "thoracoscopy" to encompass a spectrum of interventions from "simple pleuroscopy," performed under local anesthesia outside the operating theater, to "thoracoscopy," performed by experienced pulmonologists in an operating theater, to "video-assisted thoracic surgery," performed by thoracic surgeons in the operating theater.

In Europe, pleuroscopy/medical thoracoscopy (P/MT) is part of the training program of pulmonary medicine,[16] and it is becoming more popular in the United States. According to a national survey in 1994, pleuroscopy was used frequently by 5% of all pulmonary physicians.[17] Although newer data are not yet available, the interest in the technique seems to be increasing.[18] However, training is lagging: in an American College of Chest Physicians (ACCP) survey of U.S. pulmonary/critical care fellowship programs in 2002/2003, only 12% of the directors stated that P/MT was offered in their programs.[19] In the United Kingdom, where medical thoracoscopy has been underutilized compared with the rest of Europe, there is also growing interest.[20,21] Meanwhile, the technique has been introduced successfully in many Asian countries and in other parts of the world, particularly with the introduction of the semirigid (semiflexible) pleuroscope.[22–24]

Techniques

Pleuroscopy is an invasive technique that should be used to obtain a diagnosis when other, simpler methods are nondiagnostic (in case of pleural exudates) or to achieve pleurodesis (in case of recurrent pleural effusion or pneumothorax).[25] As with all technical procedures, there is a learning curve before full competence is achieved.[26,27] Appropriate training is therefore mandatory.[12,27] The technique is actually very similar to chest tube insertion by means of a trocar, the difference being that, with pleuroscopy, the pleural cavity can be visualized and biopsies can be taken from all areas of the pleural cavity, including the chest wall, diaphragm, mediastinum, and lung under direct visual control. When indicated, talc poudrage can be performed. In general, pleuroscopy is easier to learn than flexible bronchoscopy if sufficient expertise in thoracentesis and chest tube placement has already been gained.[12]

There are two different techniques of diagnostic and therapeutic pleuroscopy, as performed by the pulmonary physician.[12,28] In the first method, as first described by Jacobaeus for diagnostic purposes, a single entry site is usually produced with a 7- or 9-mm trocar for a thoracoscope with a working channel for accessory instruments and optical biopsy forceps; for this technique, local anesthesia is usually employed.[5] This approach can be modified for use of a semirigid pleuroscope.[22–24] In the other technique, as used by Jacobaeus for lysis of adhesions, two entry sites are used: one with a 7-mm trocar for the examination telescope and the other with a 5-mm trocar for accessory instruments, including the biopsy forceps. For this technique, neuroleptic or general anesthesia is preferred.[28]

Equipment

Rigid instruments are still in use, as they were from the beginning. Compared with the rigid thoracoscopes, flexible bronchoscopes or other flexible endoscopes have several disadvantages, mainly less adequate orientation within the pleural cavity and small and frequently inadequate biopsy specimens. A recently modified semirigid pleuroscope with a flexible tip has become an acceptable alternative.[22–24] As mentioned, the single-entry-site technique is usually performed via a 7- or 9-mm diameter trocar and a cannula with valve. Optical devices exist with various fields of view (0, 30, and 90 degrees) (Fig. 23-1). Trocars are also available with diameters of 5 and 3.75 mm for performing thoracoscopy in children. In

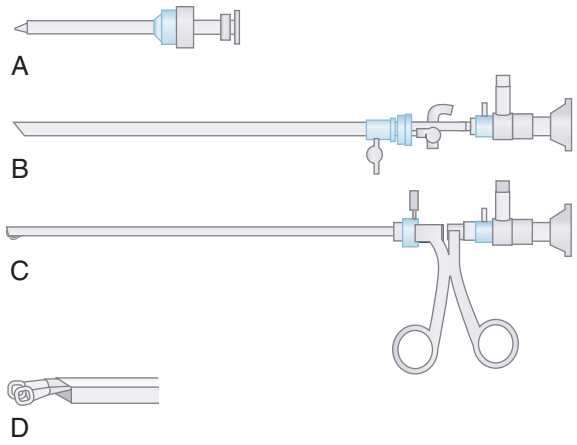

FIGURE 23-1 ■ Instruments for pleuroscopy (medical thoracoscopy). **A,** Trocar and cannula with valve. **B,** Single-incision thoracoscope (9 mm diameter). **C,** Biopsy forceps with straight optics. **D,** Magnified view of optical device and forceps in the thoracoscope shaft ready for biopsy. (A–D, Redrawn from Loddenkemper R: Thoracoscopy—State of the art. Eur Respir J 11:213–221, 1998.)

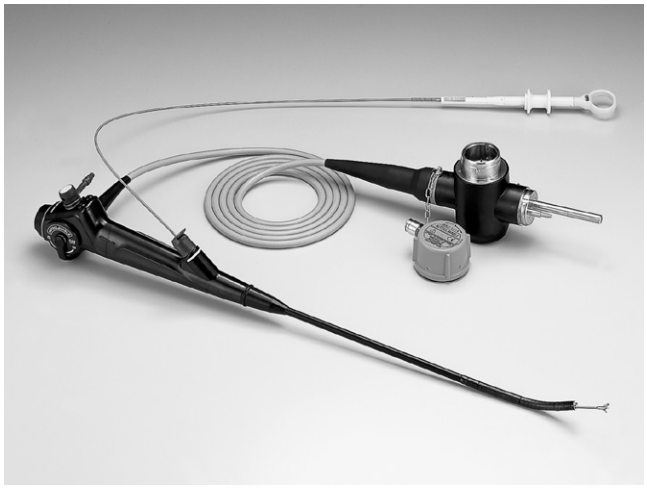

FIGURE 23-2 ■ Semirigid (semiflexible) pleuroscope with biopsy forceps.

infants, instruments similar to those used in rigid bronchoscopy are employed. Biopsy forceps with straight viewing as well as accessory instruments such as puncture needle, cautery electrode, probe, combined suction and cautery cannula with valves, and various biopsy forceps and scissors are available. For talc pleurodesis, a talc atomizer is used.[28]

The two-entry-site technique uses a 7-mm trocar for the first site of entry for appropriate telescopes and forceps and similar accessory instruments. For the second site of entry, a 5-mm trocar is used for insertion of instruments designed for its smaller bore, including a loop for dividing adhesions and a double-lumen insufflator.[28]

As stated earlier, a semirigid (semiflexible) pleuroscope was developed recently.[22–24] The design, including the handle, is similar to that of a standard flexible bronchoscope; however, the proximal 22 cm is stiff and the distal 5 cm is bendable with an angulation of 160 and 130 degrees (Fig. 23-2). The outer diameter of the shaft is 7 mm and a working channel of a diameter of 2.8 mm allows the use of standard instruments available for flexible bronchoscopy. The semirigid pleuroscope has several advantages: The skills involved in operating the instrument are already familiar to the practicing bronchoscopist. Because the shaft is rigid, it can be moved like the rigid thoracoscope without losing the orientation, and it is compatible with the existing video processors and light sources. Its disadvantages compared with rigid thoracoscopic instruments are the smaller biopsy specimens, although its diagnostic yield in pleural disease has been shown to be comparable with that of the conventional rigid thoracoscope.[24] Its flexible tip allows very homogeneous distribution of talc on all pleural surfaces.

The procedure suite should be equipped with monopolar and, if possible, bipolar electrocoagulation as well as equipment for resuscitation and assisted ventilation, electrocardiography, and blood pressure monitoring, and a defibrillator, as well as an oxygen source and vacuum generators.[5,28]

Pleuroscopy can be performed in the operating room or in an environment dedicated to invasive procedures.[11,12,23] The personnel required to perform pleuroscopy include an endoscopy nurse (or an endoscopy assistant) to assist with the instrumentation, an additional assistant outside the sterile field to bring necessary equipment, and the physician performing the pleuroscopy.[27] Ideally, an additional person sits at the patient's head and monitors his or her overall condition. In an emergency, pleuroscopy can be performed with only a physician and a nurse, but this is less efficient and prolongs the procedure.[5]

Indications

Pleuroscopy today is primarily a diagnostic procedure, but it can also be applied for therapeutic purposes (Table 23-1).[11,12,15] Pleuroscopy is mainly used for diagnosis of exudates of unknown etiology, for staging of diffuse malignant mesothelioma or lung cancer, and for treatment by talc pleurodesis of malignant or other recurrent effusions.[29,30] Pleuroscopy is also useful for evaluation and possible treatment of spontaneous pneumothorax and empyema.[11] For those familiar with the technique, pleuroscopy is also indicated for diagnostic biopsies from the diaphragm, lung, mediastinum, and pericardium and for more elaborate procedures.[13–15] As mentioned earlier, there is an overlap of indications between pleuroscopy and VATS (see later discussion and Table 23-1). In addition, pleuroscopy offers a remarkable tool for research as a "gold standard" in the study of pleural effusions.

The diagnosis of pleural effusions is the main and oldest indication for pleuroscopy, as described by

TABLE 23-1. Indications for Pleuroscopy versus Surgical Thoracoscopy (VATS)

Pleuroscopy	Pleuroscopy or VATS (Gray Area)	VATS
Pleural effusions • Pleural effusions of unknown etiology • Staging of lung cancer • Staging of diffuse malignant mesothelioma • Pleurodesis by talc poudrage	Spontaneous pneumothorax • Staging • Pleurodesis by talc poudrage • Decortication • Empyema (stage I/II) • Drainage Diffuse pulmonary diseases • Biopsy Localized lesions • Chest wall, diaphragm Sympathectomy, splanchnicectomy	Lung procedures • Lung biopsy • Lobectomy • Lung volume reduction surgery Pleural procedures • Pleurectomy (pneumothorax) • Drainage/decortication (empyema stage III) Esophageal procedures • Excision of cyst, benign tumors • Esophagectomy • Antireflux procedures Mediastinal procedures • Resection of mediastinal mass • Thoracic lymphadenectomy • Thoracic duct ligation • Pericardial window • Sympathectomy

VATS, video-assisted thoracic surgery.

Jacobaeus himself in his earliest articles.[1,4] However, even in the therapeutic era, publications from many countries emphasized the diagnostic value of pleuroscopy in spontaneous pneumothorax, focal pulmonary disease, diseases of the chest wall, mediastinal tumors, diseases of the heart and great vessels, and thoracic trauma.[4] Later, these indications were expanded to include performing biopsies for localized and diffuse lung diseases.[11,12] Today, the use of pleuroscopy for diagnosis of lung diseases has decreased owing to the improvements in less invasive pulmonary biopsy techniques such as flexible bronchoscopic biopsy and computed tomography (CT)–guided biopsy.[4,12]

In the past, therapeutic pleuroscopy was used extensively for collapse treatment of tuberculosis in order to sever adhesions that prevented a complete artificial pneumothorax.[3] This indication disappeared after the successful introduction of chemotherapy for tuberculosis.[4] Today, the main indication for therapeutic pleuroscopy is talc poudrage in malignant or other chronic and recurrent pleural effusions.[30] The first report on *talcage* was published in 1935[30] and, in 1963, it was first used for treating recurrent effusions.[4] Since then, talc poudrage performed during pleuroscopy for pleurodesis in malignant pleural effusions has been widely applied, especially in Europe.[4] Talc pleurodesis via pleuroscopy has several advantages over pleurodesis via a thoracostomy tube: simultaneous drainage of pleural fluid, visualization of the visceral pleura to ensure that the lung is not encased by pleural thickening or tumor that could prevent reexpansion, and guidance of chest tube placement.[31] In addition, talc pleurodesis can also be used to prevent recurrent pneumothorax.[32]

Other indications for therapeutic pleuroscopy are the drainage of empyema[15] or dorsal sympathectomy in hyperhidrosis patients.[13,14] Anecdotal reports describe its use for removal of foreign bodies, for removal of benign tumors, and for production of pericardial fenestrations.[12]

Contraindications

Contraindications to pleuroscopy are few and rarely absolute. The main limitation is the size of the free pleural space, which must be at least 6 to 10 cm in width.[12] If extensive adhesions prevent the lung from collapsing away from the chest wall, thoracoscopy can still be performed, but this requires special skill and should not be undertaken without special training.[33]

Several factors may make it necessary to postpone pleuroscopy but are rarely prohibitive; these include a persistent cough, hypoxemia, hypocoagulability (prolonged International Normalized Ratio or platelet count less than 40,000–60,000/mm^3), and cardiac abnormalities. Great care should be taken, particularly in the presence of hypercarbia. Depending on the severity of respiratory failure, this may prove to be an absolute contraindication, except in patients with a tension pneumothorax or massive pleural effusion, in whom it can be anticipated that pleuroscopy would provide therapeutic benefit in addition to a possible diagnosis. Under these conditions, premedication should be administered judiciously to minimize respiratory center depression. Even in very ill patients on a ventilator, diagnostic pleuroscopy has been carried out without significant complications.[5,28]

Contraindications for pulmonary biopsy are suspicion of arteriovenous pulmonary aneurysm, vascular tumors, hydatid cysts, and a stiff fibrotic lung.[26,34] Relative contraindications for pulmonary biopsy would include previous systemic steroid or immunosuppressive therapy

because, under these circumstances, bronchopleural fistulas resulting from lung biopsy may heal poorly.

The thoracoscopist must consider the risk-benefit ratio in each case. Pleuroscopy should be performed only after careful evaluation aimed at answering specific questions.

Complications

Pleuroscopy is a safe and effective modality in the diagnosis and treatment of several pleuropulmonary diseases if certain standard criteria are fulfilled.[5,28,35] In the most thorough review, only 1 death occurred among 8000 cases, for a mortality rate of 0.01%.[34] In another series reviewing 4300 cases, the mortality rate was 0.09%.[28] The reported mortality rate of pleuroscopy is thus roughly equivalent to or less than that of transbronchial biopsies. In another report of 817 pleuroscopy procedures using conscious sedation and local anesthesia, the complications were persistent air leak of more than 7 days' duration in 2%, subcutaneous emphysema in 2%, and postoperative fever in 16%.[36] The major complication rate in a series of 102 patients was 1.9% and included ventricular tachycardia responding to resuscitation, subcutaneous emphysema, and persistent air leak.[37] The minor complication rate was 7.5%, including transient air leak, fever, and minor bleeding at a biopsy site. Another large series including 360 patients reported morbidities of fever in 9.8%, empyema in 2.5%, pulmonary infection in 0.8%, and malignant invasion of the scar in 0.3%.[38] Major uncontrollable bleeding requiring thoracotomy was not reported in any of these large series and appears to be extremely rare. During the procedure, cardiorespiratory functions should be monitored. Many complications such as benign arrhythmias, low-grade hypotension, and hypoxemia can be prevented by administration of oxygen.[39] In case of persistent bleeding, electrocoagulation may become necessary.[28]

As much as several liters of pleural fluid can be removed completely during pleuroscopy with little risk of pulmonary edema, because immediate equilibration of pressure is provided by direct entrance of air through the cannula into the pleural space. Following lung biopsies, a bronchopleural fistula may result. Particularly if the lungs are stiff, a fistula may require longer to heal than the usual period of applied pleural suction of 3 to 5 days.[28] Local site infection is uncommon, and empyema has been reported only very rarely.[34] In cases of mesothelioma, the late complication of tumor growth at the site of entry has been observed after pleuroscopy and also after thoracentesis or closed-needle biopsy. Radiotherapy 10 to 12 days after pleuroscopy has been reported to prevent this late complication.[40] The standard use of prophylactic radiotherapy in these cases is controversial, however.[41] After talc poudrage, any postprocedure fever, as a nonspecific inflammatory reaction, and pain can be treated symptomatically. In conclusion, the overall mortality rate with pleuroscopy is low. Morbidity which is mainly due to benign postprocedural fever, is also minimal. Pleuroscopy in the hands of the appropriately trained pulmonologist is safe.[35]

Patient Preparation

Before pleuroscopy, radiologic evaluation should routinely include a posteroanterior and a lateral chest radiograph. Ultrasound for localization of the pleural fluid and for diagnosis of potential fibrinous membranes or adhesions in the pleural space is helpful. A CT scan is not mandatory but can be helpful to localize abnormalities such as loculated empyema or localized lesions (tumors) of the chest wall or diaphragm.

Evaluation of the patient's respiratory status requires, at a minimum, arterial or capillary blood gas analysis. An electrocardiogram should be obtained to exclude recent myocardial infarction or significant arrhythmia. The clinical laboratory will provide the coagulation parameters, serum electrolytes, and blood glucose as well as blood group typing, platelet count, liver function studies, and serum creatinine.

The planned technique, the management of possible postoperative complications, and the expected diagnostic or therapeutic results should be explained to the patient. It is only then that the patient can truly provide informed consent.[5]

The site of introduction of the pleuroscope depends in part on the location of abnormalities to access and the location of potentially hazardous areas to avoid. Pleuroscopy is usually performed with the patient in the lateral decubitus position with the intended procedural site facing upward.[5,11,28,42] A pillow is placed under the patient's flank, causing the spine to flex laterally and widening the intercostal spaces at the procedural site.

Access to the Pleural Space

Because it is impossible to perform the procedure if the pleural cavity is completely obliterated, a sufficiently large pleural space is an essential prerequisite, allowing the introduction of the trocar and thoracoscope/pleuroscope without injuring the lung or other organs.

The simplest access is available in case of a preexisting complete pneumothorax, in which the trocar can be introduced directly into the pleural space without risk of injuring the lung. In the presence of a large pleural effusion, the trocar can also be introduced directly. In case of a smaller pleural effusion, a needle puncture should be performed at the level of greatest opacification/dullness or, ideally, under sonographic or fluoroscopic guidance. When pleural fluid is aspirated, the syringe is removed from the needle and air enters the pleural space either spontaneously or after the patient takes a few deep breaths. The entry of air causes the lung to collapse away from the chest wall and creates a pleural space for safe trocar insertion. Alternatively, if one is certain that the needle is well positioned in the pleural fluid (e.g., not in the lung), air can be injected into the pleural space by means of a syringe. Most often, a few milliliters of air are sufficient to create a good separation of the lung from the chest wall. A greater safety is provided under ultrasound guidance, which allows the operator to localize the pleural effusion and to avoid transecting significant adhesions.[43] Another option is

fluoroscopy "on the table," which can show the air-fluid level caused after injection of air as well as adhesions, if present.

If neither effusion nor pneumothorax is present, an artificial pneumothorax must be created either by the blunt dissection technique using the finger[33] or by the technique of pneumothorax induction. The blunt dissection technique (extended thoracoscopy) involves gentle dissection of the pleural adhesions with a finger in order to advance the pleuroscope into the pleural space.[33,42] If carbon dioxide is introduced instead of air, for faster absorption in case of gas embolism, the pneumothorax should be induced immediately before undertaking P/MT, because the pneumothorax will be absorbed rapidly.[5,12] Some pleuroscopists induce the pneumothorax the day before the procedure, allowing more time to obtain pressure measurements and to determine if the pleural space is patent. It can also reduce the actual time spent in a busy operating/endoscopy room. When general anesthesia is planned, it may also be desirable to induce the pneumothorax on the previous day, so that a general anesthetic is not given unnecessarily to a patient who cannot undergo pleuroscopy owing to an obliterated pleural space.[28]

However, some experienced teams regularly perform pleuroscopy without any form of image-guided induction of a pneumothorax. In one series of more than 700 pleuroscopies conducted without preprocedural imaging of the entry site, induction of a pneumothorax was impossible in only 10 patients, due to extensive adhesions.[44] In this series, no major complications such as bleeding were observed.

Anesthesia

Pleuroscopy by the single-entry-site technique is usually done under local anesthesia with premedication, together with an antianxiolytic, a narcotic, or both (e.g., midazolam and hydrocodone). If necessary, additional pain medication should be given during the procedure, as required. With this conscious sedation, an anesthetist is not needed. Exceptions are rare idiosyncratic or allergic sensitivities to typical anesthetics, very anxious or uncooperative patients including children, and severe hypercarbia. An excellent alternative today is sedation by propofol with or without premedication. General anesthesia with intratracheal intubation and ventilation is used in some centers[45] but is not generally necessary for pleuroscopy.[12,42]

Monitoring devices such as a cardiac monitor, oxygen saturation monitor, and automatic blood pressure monitor are applied. An intravenous line is maintained, both for intravenous sedation as well as possible resuscitation medications.

Pleuroscopic Technique

The site of introduction of the thoracoscope should be chosen to access the location of presumed abnormalities and to avoid potentially hazardous areas such as the midanterior line where one finds the internal mammary artery, the axillary region with the lateral thoracic artery, and the infraclavicular region with the subclavian artery. The region of the diaphragm is unsuitable, not only because adhesions are frequent but also because the liver or spleen may be injured.[5,12,42] The trocar is introduced for general applications in the lateral thoracic region between the mid- and the anterior axillary line in the 4th to 7th intercostal space ("safety triangle"), for pleural effusions in the 6th or 7th intercostal space, and for pneumothorax in the 4th intercostal space. Following preparation with a surgical disinfectant, local anesthesia using 1% or 2% lidocaïne is performed, and after making a small skin incision, the trocar is advanced with a fairly forceful corkscrew motion until the detectable resistance of the internal thoracic fascia has been overcome. The cannula of the trocar should lie at least 0.5 cm within the pleural space. Pleural effusions should be removed by using a suction tube that does not occlude the cannula, so that air may rapidly enter the pleural space to equalize pressures. After complete removal of the effusion, or in cases without effusion, the optical device is introduced through the cannula, and the pleural space is then inspected (Fig. 23-3).

The pleural space can be inspected through the thoracoscope either directly or indirectly by video. Anatomic relationships and intrathoracic structures are usually well recognized. Biopsies of the pleura and, if needed, of the lungs, can be performed easily and safely by means of the lung biopsy forceps. In the presence of undiagnosed pleural effusions, biopsies should be taken from macroscopic lesions at the anterior chest wall, the diaphragm, and the posterior chest wall for histologic evaluation and, if suspicious of tuberculosis, for mycobacterial culture. If no macroscopic abnormalities are visible, several biopsies should be taken from different sites of the parietal pleura. Biopsies from the lung are not taken routinely to avoid creation of a fistula, but may be necessary when the abnormalities are seen only on the lung surface. Especially in cases of inflammatory pleural exudates or when several therapeutic thoracenteses have already been performed, fibrinous membranes or adhesions may be present that hinder examination. These can be severed by using a blunt forceps or by cutting with electrocautery.

Although a single site of entry is generally sufficient, a second site may be useful for biopsies or to coagulate.[28] The position of the second site of entry is determined by viewing through the 50-degree scope while depressing the possible entry site with the index finger. It is sometimes helpful to insert a needle through the same site while viewing its precise location through the thoracoscope. After administration of a local anesthetic, a 5-mm incision is made and the 5-mm trocar is inserted directly. Its cannula will accommodate many instruments designed for its smaller bore.

Talc Pleurodesis

Talc poudrage is the most widely reported method of talc instillation into the pleural space.[30] It is mainly used for pleurodesis in malignant or recurrent pleural

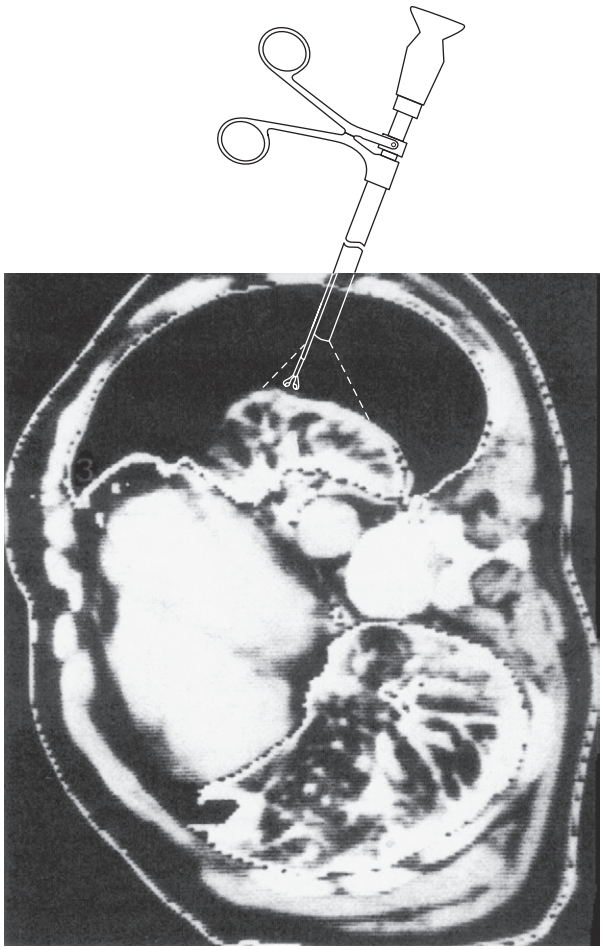

FIGURE 23-3 ■ Computed tomography representation of pleuroscopy in the right thoracic cavity with the patient in the left lateral decubitus position. Visualization of the chest wall, pleura, diaphragm, lung, and anterior (and part of posterior) mediastinum is possible. (From Loddenkemper R: Thoracoscopy—State of the art. Eur Respir J 11:213–221, 1998.)

effusions[23,30,34] but is also used in persistent or recurrent spontaneous pneumothorax.[32] Thoracoscopic talc pleurodesis can be performed under local anesthesia but generally requires additional pain medication.

In cases of pleural effusion, it is important to remove all pleural fluid before spraying with talc. The complete removal of pleural fluid is easily accomplished during pleuroscopy because air promptly enters the pleural cavity, thus creating the desired equilibrium of pressures. Complete collapse of the lung is desirable, because it permits wide and uniform distribution of the talc. A complete lung expansion is necessary for successful pleurodesis.[30,31] A trapped lung caused by thickening of the visceral pleura can be determined at pleuroscopy. The lung can also fail to reexpand if there is main-stem bronchial occlusion by a tumor or extensive pleural tumor infiltration that "traps" the lung. If the chest radiographs fail to show a contralateral mediastinal shift in the presence of a large pleural effusion, an endobronchial obstruction should be suspected and excluded by bronchoscopy before the thoracoscopy.

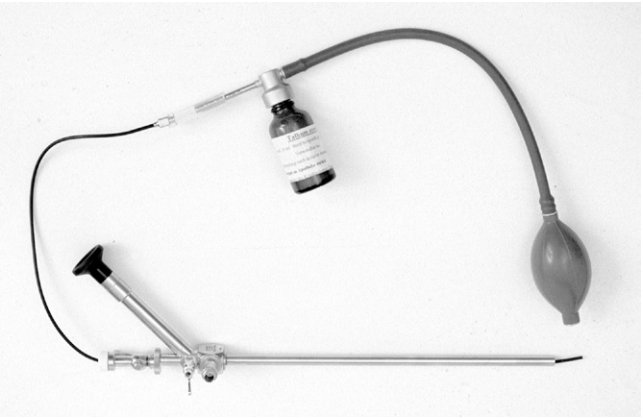

FIGURE 23-4 ■ Insufflator and bottle containing talc powder attached to a catheter that is introduced through the working channel of the rigid thoracoscope (with an angled optic).

The optimal dose of talc for poudrage is not known, but usually a dose of about 5 g is recommended for malignant or recurrent effusions[31] whereas, for pneumothorax patients, 2 g is usually sufficient.[32] The pleural cavity should be inspected during talc insufflation to ensure that the talc is uniformly distributed. For this purpose, one can use a thoracoscope with an angled optical device and a flexible suction catheter that is connected to a small bottle containing talc and to a pneumatic atomizer introduced through the working channel either of the thoracoscope[28,42] (Fig. 23-4) or of the semirigid pleuroscope.[23]

After talc poudrage, an 8- to 10-mm (24- to 30-French) chest tube should always be inserted, and pointed toward the posterior costovertebral gutter in case of effusions or toward the apex in case of pneumothorax. Suction should be applied carefully and progressively (–5 to –20 cm H_2O) to avoid creation of air leaks, which can develop because of diseased, necrotic tissue in the visceral pleura. Following the procedure, the chest tube can be removed when the daily amount of fluid production is less than 100 mL or when an air leak associated with a pneumothorax has stopped. One recent report suggests that the chest tube can be removed within 24 hours without regard to daily fluid production.[46] A potential advantage of talc poudrage via pleuroscopy compared with slurry delivered via chest tubes is the more even distribution of talc over the whole pleural surface.[31] In three head-to-head studies[47–49] comparing talc poudrage with talc slurry instillation, talc poudrage was at least equally and, in some studies, significantly more effective than talc slurry; slurry has never been shown to be superior to poudrage. In patients undergoing pleuroscopy, talc poudrage should therefore be the preferred method. In patients with a poor Karnofsky index, or when thoracoscopy is refused or impossible, talc slurry represents a valid alternative.

Talc is inexpensive and highly effective.[50] Its most common short-term adverse effects include fever and pain. Cardiovascular complications such as arrhythmias, cardiac arrest, chest pain, myocardial infarction, and

hypertension have been noted[51]; whether these complications result from the procedures or are related to talc per se has not been determined.[52] Acute respiratory distress syndrome (ARDS), acute pneumonitis, and respiratory failure have also been reported after talc poudrage and slurry. The development of respiratory failure may be due to the dose and especially to smaller particle sizes of talc, which can distribute via the pleural lymphatics to the rest of the body. The use of size-calibrated, larger-size talc appears to be absolutely safe in the treatment of recurrent pleural effusions and spontaneous pneumothorax.[53,54,54a]

Results

Pleural Effusions

Even after extensive diagnostic workup of the pleural fluid, the etiology of a number of pleural effusions may remain undetermined.[12,55] Blind needle biopsies may establish the diagnosis in some additional cases, particularly in tuberculous pleurisy. In a series by Boutin and colleagues of 1000 consecutive patients with pleural effusion,[26] 215 cases remained undiagnosed after repeated pleural fluid analysis and performance of pleural biopsies. This is in agreement with the results of several other authors who, without the use of pleuroscopy, report that at least 20% to 25% of pleural effusions remain undiagnosed, although this certainly depends strongly on the particular patient populations.[12]

Several studies have tried to determine the diagnostic accuracy of pleuroscopy in the setting of undiagnosed pleural effusion, but the results vary widely, with a range of about 60% to 90%.[26,37,56] Closer evaluation of the study designs reveals that the duration of follow-up was occasionally short and frequently not mentioned at all. One well-designed study of 102 patients reported by Menzies and Charbonneau,[37] with follow-up periods between 1 and 2 years, found a sensitivity of 91%, a specificity of 100%, accuracy of 96%, and a negative predictive value of 93%. Boutin and colleagues[26] reported a false-negative rate of 15% within 1 year of follow-up. In a retrospective study of 709 patients who underwent pleuroscopy for diagnosis of unexplained exudative effusions, Janssen and coworkers[56] also found a 15% false-negative rate in a long-term follow-up (minimum, 24 mo) of 208 patients with initial negative results; the overall sensitivity of pleuroscopy was 91%, the specificity was 100%, the positive predictive value was 100%, and the negative predictive value was 92%.[56] Of note, even thoracotomy can miss the diagnosis. In a study of the results of thoracotomy in patients with pleural effusion of undetermined etiology, even after a pathologic diagnosis of a benign pleural process, 25% of patients were diagnosed with a malignancy.[57] The diagnoses most often missed were malignant pleural mesothelioma and lymphoma (mesothelioma in 10 and lymphoma in 4 out of 31 cases,[56] and lymphoma in 6 and mesothelioma in 4 of 13 cases[57]). Autofluorescence videothoracoscopy may help in the future to avoid some of the false-negative results.[58]

Because of its high diagnostic accuracy, diagnostic pleuroscopy is an excellent option in cases of exudates in which the etiology remains undetermined after pleural fluid analysis.[23,31,34] The procedure allows fast and more definite biopsy diagnosis, including a high yield for tuberculosis cultures, and determination of hormone receptors in some malignancies. Furthermore, staging in lung cancer and diffuse mesothelioma is possible. The exclusion of an underlying malignancy or of *Mycobacterium tuberculosis* is provided with high probability. Surgery, including surgical thoracoscopy, not only is more invasive and expensive but also does not produce better results than pleuroscopy and should therefore be reserved for very selected cases.

Malignant Pleural Effusions

Diagnosis. Malignant pleural effusions are today the leading diagnostic and therapeutic indication for pleuroscopy[12,23,59] (Figs. 23-5 and 23-6). In a prospective comparison of different diagnostic tests performed in the same patients, the diagnostic yield of nonsurgical biopsy methods in malignant pleural effusions was studied simultaneously in 208 patients, including 116 metastatic pleural effusions (from 28 breast cancers, 30 cancers of various other organs, and 58 cancers of undetermined origin); 29 cancers of the lung; 58 diffuse malignant mesotheliomas; and 5 malignant lymphomas.[34] The diagnostic yield of pleural fluid cytology was 62%, of closed pleural biopsy was 44%, and of pleuroscopy was 95%. The sensitivity of pleuroscopy was higher than that of cytology and closed pleural biopsy combined (95% vs. 74%, $P < .001$). The combined methods were diagnostic in 97% of malignant pleural effusions (Fig. 23-7). In 6 of the 208 cases (2.8%), an underlying neoplasm was suspected at pleuroscopy, but confirmed only by thoracotomy or autopsy. Similar results have been reported by a number of other investigators.[21,25,56]

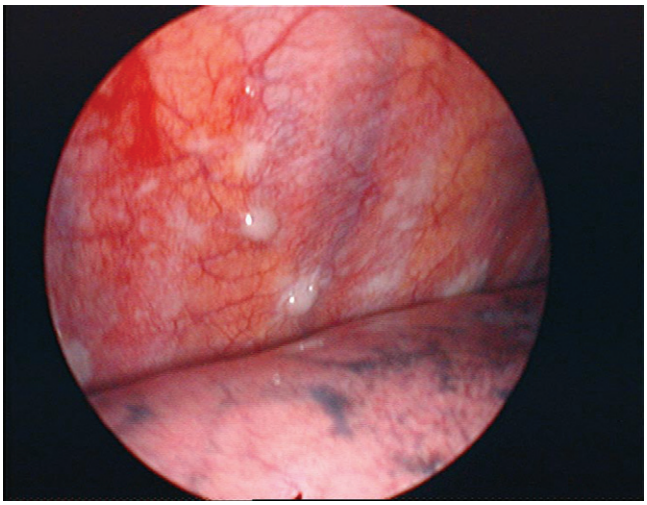

FIGURE 23-5 ■ View through the thoracoscope in a patient with a malignant pleural effusion due to breast cancer. One can see small whitish tumor nodules on the parietal (chest wall) pleura (*upper part of photo*). The lung surface (*lower part of photo*) demonstrates some anthracosis. (From Loddenkemper R, Mathur PN, Noppen M, Lee P: Medical Thoracoscopy/Pleuroscopy: Manual and Atlas. New York: Thieme, 2010.)

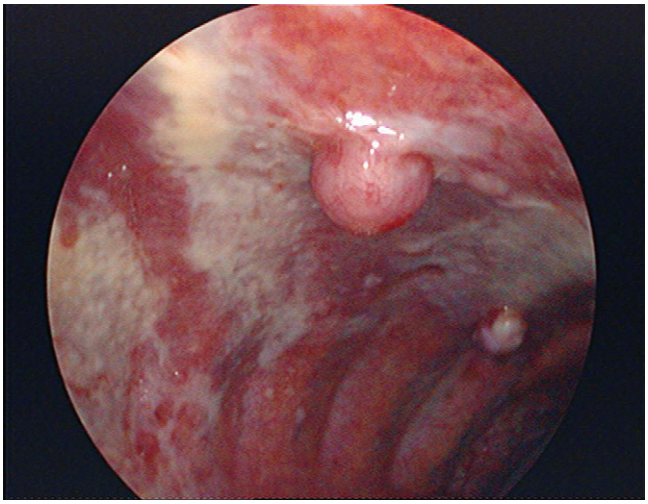

FIGURE 23-6 ■ View through the thoracoscope in a patient with diffuse malignant mesothelioma following occupational asbestos exposure. One can see tumor nodules and whitish areas with pleural thickening on the parietal (chest wall) pleura (*upper part of photo*). Histology revealed a sarcomatoid cell type. (From Loddenkemper R, Mathur PN, Noppen M, Lee P: Medical Thoracoscopy/Pleuroscopy: Manual and Atlas. New York: Thieme, 2010.)

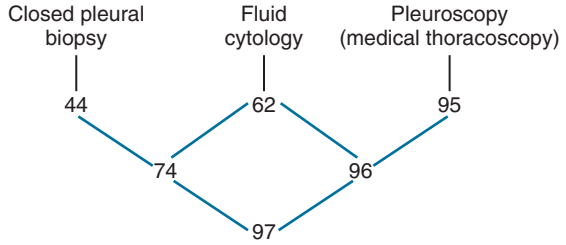

FIGURE 23-7 ■ Sensitivity of different biopsy methods (cytologic and histologic results combined) for the diagnosis of malignant pleural effusions. Numbers represent sensitivity (%) of tests, either alone or combined, in a prospective intrapatient comparison of 208 patients. (Redrawn from Loddenkemper R, Boutin C: Thoracoscopy: Present diagnostic and therapeutic indications. Eur Respir J 6:1544–1555, 1993.)

The reasons for false-negative results of pleuroscopy include insufficient and nonrepresentative biopsies, probably due to lack of experience of the thoracoscopist or the presence of adhesions preventing access to neoplastic tissue.[28,34] Adhesions may often be a consequence of repeated therapeutic removal of large amounts of fluid by thoracentesis.

The diagnostic sensitivity of pleuroscopy is similar for all types of malignant effusion. In one study, the overall yield in 287 cases was 62% for cytology and 95% for pleuroscopy; the relative yields for cytology and pleuroscopy did not vary greatly for lung carcinomas (n = 67), at 67% and 96%, respectively, for extrathoracic primaries (n = 154), at 62% and 95.5%, or for diffuse malignant mesotheliomas (n = 66), at 58% and 92%.[12]

Staging. Pleuroscopy may be useful in staging lung cancer, diffuse malignant mesothelioma, and metastatic cancer. In lung cancer patients, pleuroscopy can help to determine whether the effusion is malignant or paramalignant.[34] As a result, it may be possible to avoid exploratory thoracotomy for tumor staging. Canto and associates[60] found no thoracoscopic evidence of pleural involvement in 8 of 44 patients with lung cancer and pleural effusion; 6 proceeded to resection, where the lack of pleural involvement was confirmed.

In diffuse malignant mesothelioma, pleuroscopy can provide an earlier diagnosis and better histologic classification than closed pleural biopsy because of larger and more representative biopsies and more accurate staging.[61] Earlier diagnosis and staging may have important therapeutic implications either for surgery or for local immunotherapy or local chemotherapy, because better clinical outcomes have been observed for patients detected in the early stages (I and II).[61]

Pleuroscopy is also helpful in the diagnosis of benign asbestos-related pleural effusion by excluding mesothelioma or malignancies. Fibrohyaline or calcified, thick, and pearly white pleural plaques may be found, indicating possible asbestos exposure.[61] Thoracoscopic pulmonary biopsies and even biopsies from special lesions on the parietal pleura may demonstrate high concentrations of asbestos fibers, and thereby provide further support for a diagnosis of asbestos-induced disease.[62]

A further advantage of pleuroscopy in metastatic pleural disease is that biopsies of the visceral and diaphragmatic pleura are possible under direct observation. In addition, the larger size of pleuroscopic biopsies may provide easier identification of primary tumor, including hormone receptor determination in breast cancer,[63] and improved morphologic classification in lymphomas.[64,64a] In addition, the extent of intrapleural tumor spread can be described using a scoring system that has been shown to correlate well with survival[65] and with response to talc poudrage.[66]

Therapy. In malignant pleural effusions, talc pleurodesis achieves success rates of more than 90% as reported in several series.[31] Although there is a lack of randomized, controlled studies, talc poudrage seems to be the most efficient method of pleurodesis.[31] Diacon and colleagues,[67] in a prospective randomized trial, compared pleuroscopic talc poudrage under local anesthesia to bleomycin instillation. In 36 patients, they found much lower recurrence rates of effusion after talc poudrage (13% compared with 41% with bleomycin after 30 days; 13% and 59%, respectively, after 90 days; and 13% and 65%, respectively, after 180 days). A cost estimation also favored talc poudrage, both for initial hospitalization and with regard to recurrences. Boutin and associates[28] randomly compared talc poudrage and tetracycline instillation in 40 patients. The success rate after 1 month was 90% for talc and 80% for tetracycline. However, after 9 months, talc pleurodesis persisted whereas, with tetracycline, malignant effusions recurred in 50% of cases. Fentiman and coworkers[68] found talc superior to tetracycline for control of pleural effusions secondary to breast cancer. Viallat and associates,[38] in a retrospective study of over 300 patients, found that talc poudrage achieved a 90% success rate at 1 month and, in 82%, produced a lifelong symphysis. The success rate in metastatic cases was higher than in mesothelioma cases. Weissberg and BenZeev[69] reported similar results

in another large series with 360 cases. Aelony,[70] in a case series, observed prolonged survival averaging 22.4 months after treatment with talc poudrage pleurodesis. In vitro studies suggest that talc produces apoptosis in human malignant mesothelioma cells and might therefore have an antitumor[71] as well as an antiangiogenic effect.[72]

In chylothorax due to lymphoma, Mares and Mathur[73] showed excellent results of talc poudrage, all in cases refractory to chemotherapy or radiation therapy. All 19 patients with 24 hemithoraces involved had no recurrence after 30, 60, and 90 days (8 patients died during the 90 days of follow-up).

Tuberculous Pleural Effusions. Although the diagnostic yield of pleural fluid *M. tuberculosis* culture combined with closed-needle biopsy is quite high, there may be indications for pleuroscopy in otherwise uncertain pleural effusions[12,29] (Fig. 23-8). The diagnostic accuracy of pleuroscopy is almost 100% because the pathologist is provided with multiple, selected biopsies and there is a higher likelihood of obtaining the tubercle bacilli on culture.[12,34] In this prospective intrapatient comparison, an immediate diagnosis of *M. tuberculosis* infection in 100 cases was established histologically in 94% with pleuroscopy, but in only 38% with needle biopsy.[12,34] This may be of clinical importance, because a proper histopathologic diagnosis allows antituberculous chemotherapy to be started without delay. The combined yield of histology and bacteriologic culture was 99% for pleuroscopy and 51% for needle biopsy, increasing to 61% when culture results from effusions were added (Fig. 23-9). The percentage of positive *M. tuberculosis* cultures from pleuroscopic biopsies (78%) was twice as high as that from pleural fluid and needle biopsies combined (39%), allowing bacteriologic confirmation of the diagnosis and, importantly, drug susceptibility testing. In 5 of the 78 positive cases (6.4%), resistance to one or multiple antituberculous drugs was found and influenced therapy and prognosis.

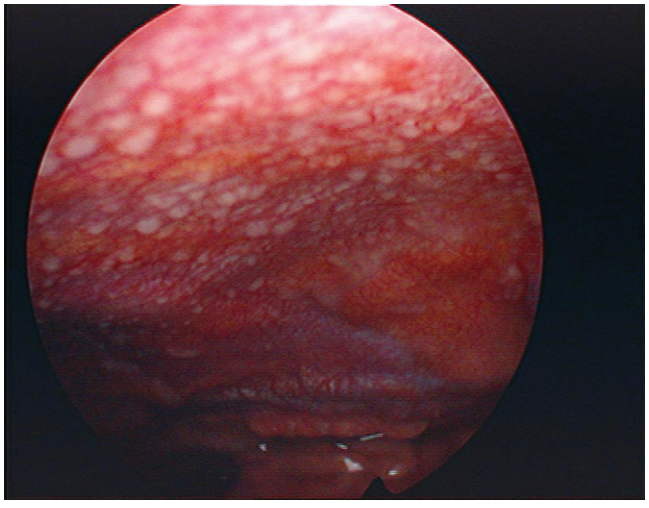

FIGURE 23-8 ■ View through the thoracoscope in a patient with a tuberculous pleural effusion. Note the numerous small whitish nodules on the parietal (chest wall) pleura (*upper part of photo*). The histology revealed florid exudative tuberculous pleurisy with epithelioid cell granulomas, numerous multinucleated giant cells of the Langerhans type, and necrosis. *Mycobacterium tuberculosis* cultures from the biopsies were positive, whereas those from the effusion were negative. (From Loddenkemper R, Mathur PN, Noppen M, Lee P: Medical Thoracoscopy/Pleuroscopy: Manual and Atlas. New York: Thieme, 2010.)

Closed-needle biopsy can have high yield in areas with a high prevalence of tuberculosis but, even then, pleuroscopy can have other benefits. In a prospective study of 40 cases from South Africa, pleuroscopy had a diagnostic yield of 98% in comparison with an 80% diagnostic yield from pleural biopsies performed with an Abrams needle.[74] The value of blind pleural biopsy for diagnosis was confirmed by another prospective study that demonstrated a high diagnostic accuracy with a high pleural fluid adenosine deaminase, differential lymphocytic cell count, as well as closed-needle biopsy in an area with a high incidence of tuberculosis.[75] However, pleuroscopy can lead to complete drainage of the effusion; initial complete drainage of the effusion, performed during and after pleuroscopy, was associated with greater symptomatic improvement than any subsequent therapy.[76] The positive role of early removal of the pleural fluid has also been shown recently in a double-blind, randomized, placebo-controlled trial from Taiwan.[77] No studies are known that compare the potential benefits of pleuroscopy, allowing early diagnosis, complete drainage, and early drug treatment, with drug treatment alone.

It is debatable whether to treat patients with antituberculous drugs merely on the suspicion of tuberculous pleurisy if they present with a high lymphocyte count in the pleural fluid and a positive skin test. At least in countries with a low prevalence of tuberculosis, where other laboratory tests such as adenosine deaminase may not be specific, pleuroscopy may be indicated when needle biopsies show negative results, in order to prove or exclude tuberculosis. In addition, the high yield for positive tuberculosis cultures from pleuroscopic biopsies increases the possibility of obtaining susceptibility tests, which, in cases of drug resistance, may influence therapy and prognosis.[12,75]

Other Pleural Effusions. In cases with effusions that are neither malignant nor tuberculous, pleuroscopy may give visual clues to the etiology such as by revealing

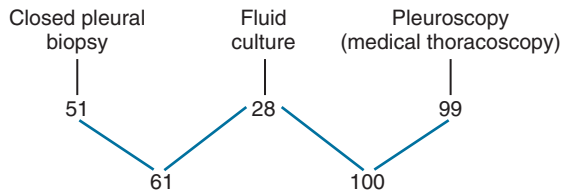

FIGURE 23-9 ■ Sensitivity of different biopsy methods (histologic and bacteriologic results combined) for the diagnosis of *Mycobacterium tuberculosis* infection. Numbers represent sensitivity (%) of tests, either alone or combined, in a prospective intrapatient comparison of 100 patients. (Redrawn from Loddenkemper R, Boutin C: Thoracoscopy: Present diagnostic and therapeutic indications. Eur Respir J 6:1544–1555, 1993.)

the thick white fibrin deposits seen in rheumatoid effusions, calcifications in effusions following pancreatitis, dilated veins in liver cirrhosis, or signs of trauma.[5,34] Although, in these entities, the history, pleural fluid analysis, and physical and other examinations are usually helpful, pleuroscopy may be indicated to confirm the clinical suspicion.[55] If pleural effusion is secondary to underlying lung diseases such as pulmonary infarct or pneumonia, the diagnosis can frequently be made on visual examination and be confirmed by biopsy of the lung.[5,28,34] As already mentioned, pleuroscopy is well suited for diagnosis of benign asbestos-related pleural effusion, which, by definition, is a diagnosis of exclusion.[61]

In other undiagnosed pleural effusions, when the cause is unsuspected, the main diagnostic value of pleuroscopy lies in its ability to exclude malignant and tuberculous disease.[12,55] By means of pleuroscopy, the proportion of so-called idiopathic pleural effusions usually falls below 10%, whereas, in studies that have not used pleuroscopy, failure to obtain a diagnosis can exceed 20% of cases.[53] However, this certainly also depends on the selection of patients and on the definition of "idiopathic." Even after surgical exploration—the gold standard—there are still undiagnosed effusions.[57,78]

Dense pleuropulmonary adhesions may prevent successful pleuroscopy. If so, multiple closed-needle biopsies should be performed or more invasive surgical procedures should be considered.

Talc pleurodesis can be considered in some cases of nonmalignant pleural effusions that are recurrent and symptomatic and do not respond to medical therapy. Such effusions may include those due to hepatic and renal hydrothorax, chylothorax, and systemic lupus erythematosus.[79–81] In such patients with recurrent benign undiagnosed effusions, Vargas and colleagues[82] achieved successful pleurodesis in 20 of 22 by talc insufflation using a thoracoscopic technique with a mediastinoscope performed under general anesthesia.

Empyema

Pleuroscopy can also be used in the management of early empyema, mainly to achieve early and complete drainage.[15,28,83,84] Intermediate between tube thoracostomy and VATS, pleuroscopy is effective and, compared with surgical drainage, costs significantly less and avoids general anesthesia. It is particularly advisable for frail patients at high surgical risk.[15,84a] In cases with multiple loculations, it is possible to open these spaces to remove the fibrinopurulent membranes by forceps and to create a single cavity that can then be successfully drained and irrigated.[85] If performed for this indication, pleuroscopy should be carried out early in the course of empyema, before the adhesions become too fibrous and adherent to perform pleuroscopy. Thus, if the indication for placement of a chest tube is present and if the facilities are available, pleuroscopy can be performed at the time of chest tube insertion. Overall, pleuroscopy is a procedure similar to chest tube placement but one that enables the creation of a single pleural cavity, allowing much better local treatment.[83,85] However, prospective studies on the role of pleuroscopy in the treatment of early empyema in adults have not yet been published.

Spontaneous Pneumothorax

In spontaneous pneumothorax, pleuroscopy has both diagnostic and therapeutic purposes[5,28,32,34,86–88] (Fig. 23-10). In particular, if a chest tube is introduced by the trocar technique, it is easy to use an optical device for visual inspection of the lung and pleural cavity, before insertion of the chest tube through this cannula. By inspection during pleuroscopy, the underlying lesions can be directly assessed according to the classification of Vanderschueren and coworkers[87]: stage I, with an endoscopically normal lung; stage II, with pleuropulmonary adhesions; stage III, with small bullae and blebs (<2 cm in diameter); and stage IV, with numerous large bullae (>2 cm in diameter). In 1047 cases of pneumothorax in which pleuroscopy was used by three different teams, pathologic lesions were detected in about 70%, with similar percentages for stages II through IV.[12] Blebs and bullae were detected in 45% to 62% of cases. Although the detection rates of blebs and bullae are reported to be higher (76%–100%) in series using VATS or thoracotomy,[87] it is unlikely that large bullae and blebs or fistulas would be overlooked during pleuroscopy.

Pleuroscopy offers the possibility of combining chest drainage with treatment by electrocautery of blebs and bullae if the site of the air leak is visible and by pleurodesis using talc poudrage.[32,86] Sattler in Vienna in 1937 was the first to use pleuroscopy to treat pneumothorax

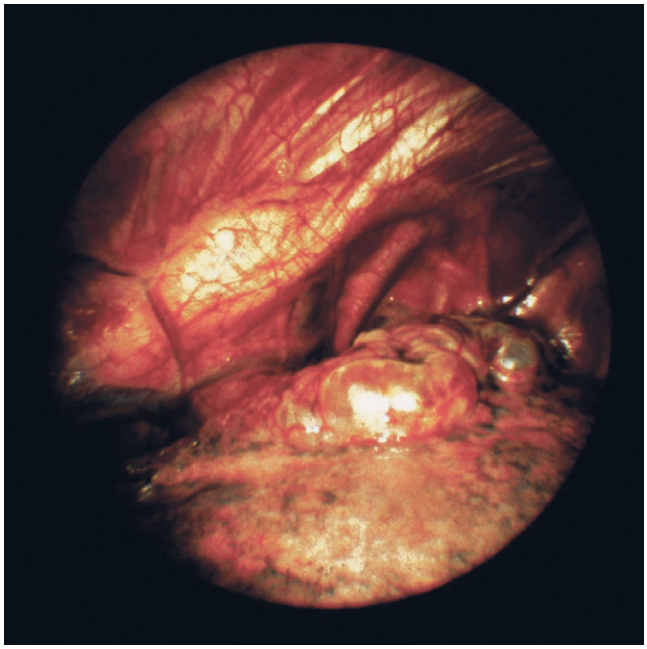

FIGURE 23-10 ■ View through the thoracoscope in a patient with a spontaneous pneumothorax. On the surface of the lung (*lower part of photo*), large apical blebs are visible.

by cauterization of adhesions that prevented the closure of bronchopleural fistulas.[4] Talc poudrage achieves excellent results, with recurrence rates reported below 10%.[32] A prospective study showed that, for complicated pneumothorax, defined as recurring or persistent pneumothorax, simple talc poudrage under local anesthesia prevented a recurrence of pneumothorax.[89] In a prospective, randomized, multicenter comparison, talc poudrage for primary spontaneous pneumothorax proved more efficient (only 1 of 61 patients with talc poudrage had a recurrence, compared with 10 of 47 with simple pleural drainage) and more cost-effective than drainage alone.[90] In stage III/IV cases with numerous blebs or bullae, usually there is an indication for VATS or thoracotomy in order to perform a bullectomy or stapling of blebs/bullae, and these patients should be transferred directly to the surgical department after insertion of a chest tube.[86] Other types of pneumothorax treated successfully by pleuroscopy have included those due to *Pneumocystis jirovecii* (formerly *P. carinii*) pneumonia, metastatic osteosarcoma, pleural endometriosis, lymphangioleiomyomatosis, and cystic fibrosis.[55]

In talc poudrage for pneumothorax, a mere 2 to 4 mL of talc can be sufficient for effective pleurodesis.[32] No long-term sequelae were observed 22 to 35 years after talc poudrage. Total lung capacity averaged 89% of the predicted value in 46 patients, whereas it was 97% of the predicted value in 29 patients treated with tube thoracostomy alone.[91] None of the poudrage group developed mesothelioma over the 22- to 35-year follow-up. Although talc poudrage may result in minimally reduced total lung capacity, as well as pleural thickening on chest radiography, these changes appear to be clinically unimportant.[54,92] Talc poudrage may be relatively contraindicated for patients who may become candidates for lung transplantation, although currently it is not considered an absolute contraindication to lung transplantation.[93]

Therefore, if the facilities are available, pleuroscopy may be performed in all patients with spontaneous pneumothorax in whom tube drainage is indicated. Several advantages are offered: precise assessment of underlying lesions under direct visual control, choice of best (conservative or surgical) treatment measures, direct treatment by electrocautery of small blebs and bullae, and severing of adhesions, if necessary, followed by talc poudrage, as well as selection of the best location for subsequent chest tube placement.[34]

Diffuse Pulmonary Diseases

Diffuse lung diseases provide a good indication for diagnostic pleuroscopy[5,28,34,93–95] (Fig. 23-11). An overview of the entire lung surface, assisted by the magnification of the thoracoscope, allows harvesting of representative samples of abnormal areas of parenchyma. In a review of the literature, the sensitivity of pleuroscopic lung biopsies was 93% in 1031 cases with varying etiologies.[28] In a large series of 419 patients with diffuse lung diseases, the overall sensitivity was 85% with different yields depending upon the underlying disease: 98% in sarcoidosis stage II and III, 88% in malignant diseases, 85% in diffuse pulmonary fibrosis/interstitial pneumonia and 42% in histiocytosis X.[34] Pleuroscopy has also been used with a high diagnostic yield in immunocompromized patients.[94]

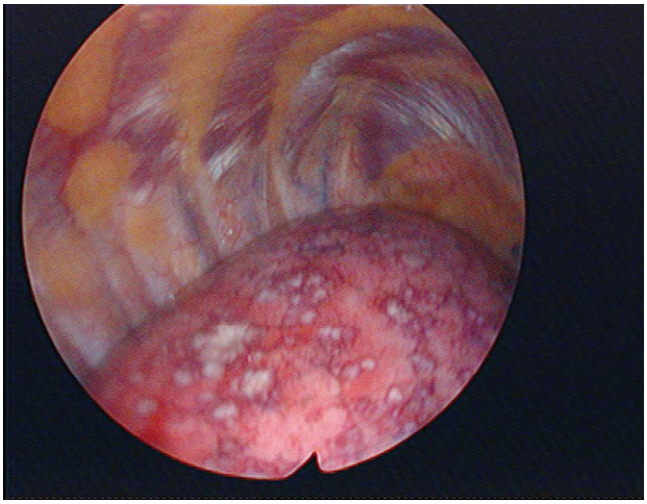

FIGURE 23-11 ■ A view through the thoracoscope in a patient with multiple pulmonary metastases due to ovarian cancer (*lower part of photo*).

In comparison with bronchoscopy, pleuroscopy is more invasive (see "Contraindications") but presents several advantages. It provides significantly larger samples and allows the physician to choose the biopsy site. Unlike transbronchial biopsy, pleuroscopy enables electrocautery, so that bleeding following pleuroscopic parenchymal biopsy can be managed without difficulty. With regard to sensitivity and invasiveness, pleuroscopy ranks between transbronchial biopsy and open-lung biopsy.[34]

Localized Diseases

Localized abnormalities of the chest wall, diaphragm, and thoracic spine may be diagnosed using pleuroscopy if the pleural space is not obliterated.[5,34] Hyaline pleural plaques, localized pleural mesothelioma, lipoma, neurinoma, rib metastasis, rib erosions, and the like can be examined and, if necessary, biopsied. Very discrete metastases are sometimes found in the region of the diaphragm and the posterior chest wall, with or without associated pleural effusion. Chest wall lesions may be easier to diagnose than lung lesions: In a retrospective study in which 109 cases with chest wall lesions of different etiologies were analyzed, the diagnostic sensitivity was 83%[34] whereas, in solitary lung lesions, the overall diagnostic sensitivity was only 46%.

Currently, the application of pleuroscopy has decreased substantially for localized disease due to better imaging techniques such as CT, magnetic resonance imaging, and ultrasound, which allow image-guided biopsies. For example, such biopsies have proved useful for diagnosis of pleural plaques, lipomas, and cysts.[12]

Alternatively, surgical thoracoscopy, or VATS, may now be used for these indications, because the technique not only is diagnostic but also allows the removal of benign or malignant lesions.

Use of Pleuroscopy/Medical Thoracoscopy for Research

Pleuroscopy/medical thoracoscopy (P/MT) is a valuable tool for research in pleural diseases. It allows microscopic inspection of the whole pleural cavity including the surface of the lungs, selective sampling of biopsies from the pleura or lung under visual control, and thus can diagnose or exclude several pathologies with high sensitivity and specificity. P/MT is the pulmonologist's gold standard for diagnosis of pleural effusions.

Research domains for pleuroscopy in normal subjects include performance of pleural lavage in otherwise normal subjects undergoing pleuroscopy for reasons other than pleuropulmonary diseases (e.g., for treatment of essential hyperhdrosis), which enables the examination of the normal pleura and its contents,[96–98] as well as the examination of pleural changes in pleuropulmonary diseases not associated with pleural effusions (e.g., spontaneous pneumothorax).[99]

There are numerous examples of the research value of P/MT in the diagnosis of pleural effusions. Prospective studies have been performed in malignant pleural effusion,[12,26,60] which showed the high diagnostic yield compared with pleural cytology and closed-needle biopsy. Prospective studies in tuberculous pleurisy have also shown the superiority of P/MT in comparison with pleural fluid examinations and closed pleural biopsies.[12,74,75]

P/MT is also superior in the diagnosis of diffuse malignant mesothelioma.[34,61] The technique of autofluorescence thoracoscopy is evaluated for the improved detection of otherwise invisible pleural lesions.[58] P/MT allows better staging and has prognostic implications in malignant mesothelioma.[34,61] P/MT allows the grading of pleural involvement, which is correlated with survival[65] and also with the success of talc pleurodesis.[30,49,66] It allows us to study the mechanisms of talc pleurodesis in malignant pleural effusion.[66,71,72]

Research on the role of P/MT in the management of pneumothorax has been performed,[32,87–90] including the role of talc poudrage in comparison with other pleurodesis techniques.[32,87,90] New techniques have expanded our understanding of the abnormalities associated with pneumothorax, such as fluorescein-enhanced autofluorescence thoracoscopy.[100]

Future Areas of Research

- Prospective studies of the diagnostic accuracy of pleuroscopy for so-called idiopathic pleural effusions.
- The value of new visualization methods such as autofluorescence or narrow-band imaging in the early diagnosis of malignant pleural effusions, particularly when diffuse malignant mesothelioma is suspected.[101,102]
- Prospective studies of the role of pleuroscopy in tuberculous pleurisy for early diagnosis, complete drainage, and early drug treatment compared with drug treatment alone.
- Prospective studies on the role of pleuroscopy in the management of empyema.
- Potential role of pleuroscopy for intrapleural gene therapy.

DIFFERENCES BETWEEN PLEUROSCOPY AND VIDEO-ASSISTED THORACIC SURGERY (SURGICAL THORACOSCOPY)

As described in the preceding sections, P/MT is used mainly for diagnosis of pleural diseases. The most common indications for pleuroscopy are diagnosis of pleural effusion with inspection of the pleural cavity, combined with biopsies from the parietal and visceral pleura, as well as treatment of malignant or other therapy-refractory effusions by talc pleurodesis (poudrage). It is a relatively simple and inexpensive technique because it can be performed in an endoscopy room, under local anesthesia or conscious sedation through a single entry site with nondisposable instruments.

VATS, conversely, which takes its roots from pleuroscopy, has now been technically developed to the point that it can replace thoracotomy for most indications, if certain limitations such as dense pleural symphysis are not present. VATS requires an operating room, general anesthesia with single-lung ventilation, more than two (usually three) entry sites, and complex instruments. Overall, it is a more invasive and expensive technique with a higher risk than pleuroscopy; however, in experienced hands and in the proper setting, VATS is less invasive, is less expensive, and has a lower risk than open procedures.

The different clear-cut indications for either pleuroscopy or VATS are listed in Table 23-1. However, there remains a gray area of indications for which either method can be used (see Table 23-1). Gray areas include treatment of pneumothorax stages I to III, drainage of empyema stages I and II, biopsies in diffuse parenchymal lung diseases, and sympathetic interventions. For these indications, the choice of the medical or the surgical approach depends on local expertise, availability of the technique, and performance status and prognosis of the patient.

The choice of the medical or the surgical approach depends on local expertise, availability of the technique, and performance status and prognosis of the patient. More details are given in the book Manual and Atlas of Medical Thoracoscopy/Pleuroscopy.[103]

KEY POINTS

- P/MT is less invasive than surgical thoracoscopy (VATS) because it is performed under local anesthesia and conscious sedation, most commonly through a single entry. It is also less expensive because it can be performed in an endoscopy suite, using nondisposable rigid or semirigid endoscopes, and usually does not require an anesthesiologist.
- P/MT is used today mainly for diagnostic purposes, in particular in pleural effusions of otherwise indeterminate origin, owing to its high sensitivity and specificity for the diagnosis of malignant and tuberculous etiologies.
- P/MT is useful in staging diffuse malignant mesothelioma and lung cancer with pleural effusion.
- P/MT allows talc poudrage, which is today the most successful conservative method for pleurodesis in malignant and recurrent pleural effusions.
- P/MT can be useful for treatment of spontaneous pneumothorax; the introduction of the scope by the trocar technique is similar to the introduction of a chest tube, and an optical device can be used to inspect the pleural space followed by coagulation of blebs and bullae and talc poudrage.
- P/MT can be used in the management of early empyema, for biopsy diagnosis of diffuse pulmonary diseases as well as for sympathectomy in hyperhidrosis patients. As an invasive procedure, it should be used only if other, simpler methods fail or are not available.
- P/MT is a safe procedure that is even easier to learn than flexible bronchoscopy, if sufficient expertise in thoracentesis and chest tube placement has already been gained. As part of interventional pulmonology, it should be included in the training program of pulmonologists.

References

1. Jacobaeus HC: Über die Möglichkeit, die Zystoskopie bei Untersuchung seröser Höhlungen anzuwenden. Munch Med Wochenschr 57:2090–2092, 1910.
2. Hoksch B, Birken-Bertsch H, Müller JM: Thoracoscopy before Jacobaeus. Ann Thorac Surg 74:1288–1290, 2002.
3. Jacobaeus HC: The cauterization of adhesions in artificial pneumothorax therapy of tuberculosis. Am Rev Tuberc 6:871, 1922.
4. Loddenkemper R: Medical thoracoscopy—Historical perspective. *In* Beamis JF Jr, Mathur PN, Mehta AC (eds): Interventional Pulmonary Medicine. New York: Marcel Dekker, 2004, pp 411–429.
5. Brandt HJ, Loddenkemper R, Mai J (eds): Atlas of Diagnostic Thoracoscopy: Indications—Technique. New York: Thieme, 1985.
6. Seijo LM, Sterman DH: Interventional pulmonology. N Engl J Med 344:740–749, 2001.
7. Inderbitzi R, Althaus U: Therapeutic thoracoscopy, a new surgical technique (abstract). Thorac Cardiovasc Surg 39(Suppl):89, 1991.
8. Miller JI Jr: Therapeutic thoracoscopy: New horizons for an established procedure (editorial). Ann Thorac Surg 52:1036–1037, 1991.
9. Landreneau RI, Mack MI, Hazelrigg SR, et al: Video assisted thoracic surgery: Basic technical concepts and intercostal approach strategies. Ann Thorac Surg 54:800–807, 1992.
10. LoCicero J: Minimally invasive thoracic surgery, video-assisted thoracic surgery and thoracoscopy (editorial). Chest 102:330–331, 1992.
11. Mathur PN, Boutin C, Loddenkemper R: "Medical" thoracoscopy: Technique and indications in pulmonary medicine. J Bronchol 1:228–239, 1994.
12. Loddenkemper R: Thoracoscopy—State of the art. Eur Respir J 11:213–221, 1998.
13. Noppen M, Herregodts P, D'haese J, et al: A simplified T2-T3 sympathicolysis technique for the treatment of essential hyperhidrosis: Short- term results in 100 patients. J Laparoendosc Surg 6:151–159,1996.
14. Noppen M, Meysman M, D'Haese J, Vincken W: Thoracoscopic splanchnolysis for the relief of chronic pancreatitis pain: Experience from a group of pneumologists. Chest 113:528–531, 1998.
15. Tassi GF, Davies RJO, Noppen M: Advanced techniques in medical thoracoscopy. Eur Respir J 28:1051–1059, 2006.
16. Dijkman JH, Martinez Gonzales del Rio J, Loddenkemper R, et al: Report of the working party of the "UEMS Monospecialty Section on Pneumology" on training requirements and facilities in Europe. Eur Respir J 7:1019–1022, 1994.
17. Tape TG, Blank LL, Wigton RS: Procedural skills of practicing pulmonologists: A national survey of 1,000 members of the American College of Physicians. Am J Respir Crit Care Med 151:282–287, 1995.
18. Lee P, Lan RS, Colt HG: Survey of pulmonologists' perspectives on thoracoscopy. J Bronchol 10:99–106, 2003.
19. Pastis NJ, Nietert PJ, Silvestri GA: Variation in training for interventional pulmonary procedures among US pulmonary/critical care fellowships—A survey of fellowship directors. Chest 127:1614–1618, 2005.
20. Burrows NJ, Ali NJ, Cox GM: The use and development of medical thoracoscopy in the United Kingdom over the past 5 years. Respir Med 7:1234–1238, 2006.
21. Buchanan DR, Neville E (eds): Thoracoscopy for Physicians: A Practical Guide. London: Arnold, 2004.
22. Ernst A, Hersh CP, Herth F, et al: A novel instrument for the evaluation of the pleural space: An experience in 34 patients. Chest 122:1530–1534, 2002.
23. Lee P, Colt HG: Rigid and semirigid pleuroscopy: The future is bright. Respirology 10: 418–425, 2005.
24. Munawar M, Khan MA, Edwards J, et al: The autoclavable semirigid thoracoscope: The way forward in pleural disease? Eur Respir J 29:571–574, 2007.
25. Rodriguez-Panadero F, Janssen JP, Astoul P: Thoracoscopy: General overview and place in the diagnosis and management of pleural effusion. Eur Respir J 28:409–421, 2006.
26. Boutin C, Viallat JR, Cargnino C, et al: Thoracoscopy in malignant pleural effusions. Am Rev Respir Dis 124:588–592, 1981.

27. Ernst A, Silvestri GA, Johnstone D: Interventional pulmonary procedures: Guidelines from the American College of Chest Physicians. Chest 123:1693–1717, 2003.
28. Boutin C, Viallat JR, Aelony Y (eds): Practical Thoracoscopy. New York: Springer, 1991.
29. Loddenkemper R: Medical thoracoscopy. *In* Light RW, Lee YCG (eds): Textbook of Pleural Diseases (2nd ed.). London: Hodder Arnold, 2008, pp 583–597.
30. Rodriguez-Panadero F, Antony VB: Pleurodesis: State of the art. Eur Respir J 10:1648–1654, 1997.
31. Antony VB, Loddenkemper R, Astoul P, et al: Management of malignant pleural effusions (ATS/ERS statement). Am J Respir Crit Care Med 162:1987–2001, 2000.
32. Boutin C, Astoul P, Rey F, et al: Thoracoscopy in the diagnosis and treatment of spontaneous pneumothorax. Clin Chest Med 16:497–503, 1995.
33. Janssen JP, Boutin C: Extended thoracoscopy: A biopsy method to be used in case of pleural adhesions. Eur Respir J 5:763–766, 1992.
34. Loddenkemper R, Boutin C: Thoracoscopy: Present diagnostic and therapeutic indications. Eur Respir J 6:1544–1555, 1993.
35. Colt HG: Thoracoscopy: A prospective study of safety and outcome. Chest 108:324–329, 1995.
36. Boutin C, Viallat JR, Cargnino P, et al: Thoracoscopy. *In* Chrétien J, Bignon J, Hirsch A (eds): Lung Biology in Health and Disease. Vol 30: The Pleura in Health and Disease. New York: Marcel Dekker, 1985, pp 587–622.
37. Menzies R, Charbonneau M: Thoracoscopy for the diagnosis of pleural disease. Ann Intern Med 114:271–276, 1991.
38. Viallat JR, Rey F, Astoul P, et al: Thoracoscopic talc poudrage. Pleurodesis for malignant effusions: A review of 360 cases. Chest 110:1387–1393, 1996.
39. Cho K, Ozawa S, Kuzihara M, et al: Cardiorespiratory changes in thoracoscopy under local anesthesia. J Bronchol 7:215–220, 2000.
40. Boutin C, Rey F, Viallat JR: Prevention of malignant seeding after invasive diagnostic procedures in patients with pleural mesothelioma: A randomized trial of local radiotherapy. Chest 108:754–758, 1995.
41. Davies HE, Musk AW, Lee YC: Prophylactic radiotherapy for pleural puncture sites in mesothelioma: The controversy continues. Curr Opin Pulm Med 14:326–330, 2008.
42. Mares DC, Mathur PN: Medical thoracoscopy: The pulmonologist's perspective. Semin Respir Crit Care Med 18:603–615, 1997.
43. Hersh CP, Feller-Kopman D, Wahidi M, et al: Ultrasound guidance for medical thoracoscopy: A novel approach. Respiration 70:299–301, 2003.
44. Noppen M: Chest ultrasound is o.k. for mountaineers and astronauts … and for pulmonologists? (editorial). Respiration 70:240–241, 2003.
45. D'haese J, Camu F, Noppen M, et al: Total intravenous anaesthesia and high frequency jet ventilation during transthoracic endoscopic sympathectomy for treatment of essential hyperhidrosis palmaris: A new approach. J Cardiothorac Vasc Anesth 10:767–771, 1996.
46. Goodman A, Davies CW: Efficacy of short-term versus long-term chest tube drainage following talc slurry pleurodesis in patients with malignant pleural effusions: A randomized trial. Lung Cancer 54:51–55, 2006.
47. Yim AP, Chan AT, Lee TW, et al: Thoracoscopic talc insufflation versus talc slurry for symptomatic malignant pleural effusion. Ann Thorac Surg 62:1655–1658, 1996.
48. Stefani A, Natali P, Casali C, Morandi U: Talc poudrage versus talc slurry in the treatment of malignant pleural effusion. A prospective comparative study. Eur J Cardiothorac Surg 30:827–832, 2006.
49. Dressler CM, Olak J, Herndon JE, et al: Phase III intergroup study of talc poudrage vs talc slurry sclerosis for malignant pleural effusion. Chest 127:909–915, 2007.
50. Kennedy L, Sahn SA: Talc pleurodesis for the treatment of pneumothorax and pleural effusion. Chest 106:1215–1222, 1984.
51. Light RW: Talc should not be used for pleurodesis. Am J Respir Crit Care Med 162:2024–2026, 2000.
52. Sahn SA: Talc should be used for pleurodesis. Am J Respir Crit Care Med 162:2023–2024, 2000.
53. Janssen J, Collier G, Astoul P, et al: Safety of pleurodesis with talc poudrage in malignant pleural effusion: A prospective cohort study. Lancet 369:1535–1539, 2007.
54. Noppen M: Who's (still) afraid of talc? Eur Respir J 29:619–621, 2007.
54a. Tschopp JM, Schnyder JM, Astoul P, et al: Pleurodesis by talc poudrage under simple medical thoracoscopy: an international opinion. Thorax 64:273–274, 2009.
55. Light RW: The undiagnosed pleural effusion. Clin Chest Med 27:309–319, 2006.
56. Janssen JP, Ramlal S, Mravumac M: The long-term follow-up of exudative pleural effusion after nondiagnostic thoracoscopy. J Bronchol 11:169–174, 2004.
57. Ryan CJ, Rodgers RF, Unni UK, et al: The outcome of patients with pleural effusion of indeterminate cause at thoracotomy. Mayo Clin Proc 56:145–149, 1981.
58. Chrysanthidis MG, Janssen JP: Autofluorescence videothoracoscopy in exudative pleural effusions: Preliminary results. Eur Respir J 26:989–992, 2005.
59. Harris RJ, Kavuru MS, Rice TW: The diagnostic and therapeutic utility of thoracoscopy. A review. Chest 108:828–841, 1995.
60. Canto A, Ferrer G, Romagosa V, et al: Lung cancer and pleural effusion: Clinical significance and study of pleural metastatic locations. Chest 87:649–652, 1985.
61. Greillier L, Astoul P: Mesothelioma and asbestos-related pleural diseases. Respiration 76:1–15, 2008.
62. Boutin C, Dumortier P, Rey F, et al: Black spots concentrate oncogenic asbestosis fibers in the parietal pleura: Thoracoscopic and mineralogic study. Am J Respir Crit Care Med 153:111–119, 1996.
63. Schwarz C, Lübbert H, Rahn W, et al: Medical thoracoscopy: Hormone receptor content in pleural metastases due to breast cancer. Eur Respir J 24:728–730, 2004.
64. Celikoglu F, Teirstein AS, Krellenstein DJ: Pleural effusion in non-Hodgkins lymphoma. Chest 101:1357–1360, 1992.
64a. Schwarz C, Bittner R, Kirsch A, et al: A 62-year-old woman with bilateral pleural effusions and pulmonary infiltrates caused by extramedullary hematopoiesis. Respiration 78:110–113, 2009.
65. Sanchez-Armengol A, Rodriguez-Panadero F: Survival and talc pleurodesis in metastatic pleural carcinoma, revisited: Report of 125 cases. Chest 104:1482–1485, 1993.
66. Antony VB, Nasreen N, Mohammed KA, et al: Talc pleurodesis: Basic fibroblast growth factor mediates pleural fibrosis. Chest 126:1522–1528, 2004.
67. Diacon AH, Wyser C, Bolliger CT, et al: Prospective randomized comparison of thoracoscopic talc poudrage under local anaesthesia versus bleomycin instillation for pleurodesis in malignant pleural effusions. Am J Respir Crit Care Med 162:1445–1449, 2000.
68. Fentiman IS, Rubens RD, Hayward JL: A comparison of intracavitary talc and tetracycline for the control of pleural effusions secondary to breast cancer. Eur J Cancer Clin Oncol 22:1079–1081, 1986.
69. Weissberg D, BenZeev I: Talc pleurodesis: Experience with 360 patients. J Thorac Cardiovasc Surg 106:689–695, 1993.
70. Aelony Y: Treatment of mesotheliomatous pleural effusion: Experimental therapy versus thoracoscopic talc poudrage? Pro: Talc poudrage therapy. J Bronchol 8:54–59, 2001.
71. Nasreen N, Mohammed KA, Dowling PA: Talc induces apoptosis in human malignant mesothelioma cells in vitro. Am J Respir Crit Care Med 161:595–600, 2000.
72. Najmunnisa N, Mohammed KA, Brown S, et al: Talc mediates angiostasis in malignant pleural effusions via endostatin induction. Eur Respir J 29:761–769, 2007.
73. Mares CC, Mathur PN: Thoracoscopic talc pleurodesis for lymphoma induced chylothorax, a case series of twenty-two treated hemithoraces in eighteen patients. Am J Respir Crit Care Med 155:A481, 1997.
74. Walzl G, Wyser C, Smedema J, et al: Comparing the diagnostic yield of Abrams needle pleural biopsy and thoracoscopy. Am J Respir Crit Care Med 153:A460, 1996.

75. Diacon AH, van de Wal BW, Wyser C, et al: Diagnostic tools in tuberculous pleurisy: A direct comparative study. Eur Respir J 22:589–591, 2003.
76. Wyser C, Walzl G, Smedema JP, et al: Corticosteroids in the treatment of tuberculous pleurisy: A double-blind, placebo-controlled, randomized study. Chest 110:333–338, 1996.
77. Chung C-L, Chen C-H, Yeh C-H, et al: Early effective drainage in the treatment of loculated tuberculous pleurisy. Eur Respir J 31:1261–1267, 2008.
78. Venekamp LN, Velkeniers B, Noppen M: Does "idiopathic pleuritis" exist? Natural history of non-specific pleuritis diagnosed after thoracoscopy. Respiration 72:74–78, 2005.
79. Sudduth C, Sahn SA: Pleurodesis for non-malignant pleural effusions: Recommendations. Chest 102:1855–1860, 1992.
80. Aelony Y, King R, Boutin C: Thoracoscopic talc poudrage pleurodesis for chronic recurrent pleural effusions. Ann Intern Med 115:778–782, 1991.
81. Glazer M, Berkman N, Lafair JS, et al: Successful talc slurry pleurodesis in patients with non-malignant pleural effusion: Report of 16 cases and review of the literature. Chest 117:1404–1409, 2000.
82. Vargas FS, Milanez JRC, Filomeno LTB, et al: Intrapleural talc for the prevention of recurrences in benign or undiagnosed pleural effusions. Chest 106:1771–1775, 1994.
83. Soler M, Wyser C, Bolliger CT, et al: Treatment of early parapneumonic empyema by "medical" thoracoscopy. Schweiz Med Wochenschr 127:1748–1753, 1997.
84. Loddenkemper R, Kaiser D, Frank W: Treatment of parapneumonic pleural effusion and empyema—Conservative view. Eur Respir Mon 29:199–207, 2004.
84a. Heffner JE, Klein JS, Hampson C: Interventional management of pleural infections. Chest 136:1148–1159, 2009.
85. Brutsche MH, Tassi GF, Györik S, et al: Treatment of sonographically stratified multiloculated thoracic empyema by medical thoracoscopy. Chest 128:3303–3309, 2005.
86. Tschopp J-M, Rami-Porta R, Noppen M, Astoul P: Management of spontaneous pneumothorax: State of the art. Eur Respir J 28:637–650, 2006.
87. Schramel FMNH, Postmus PE, Vanderschueren RG: Current aspects of spontaneous pneumothorax. Eur Respir J 10:1372–1379, 1997.
88. van de Brekel JA, Duurkens VA, Vanderschueren RG: Pneumothorax: Results of thoracoscopy and pleurodesis with talc poudrage and thoracotomy. Chest 103:345–347, 1993.
89. Tschopp J-M, Brutsche M, Frey JG: Treatment of complicated spontaneous pneumothorax by simple talc pleurodesis under thoracoscopy and local anaesthesia. Thorax 52:329–332, 1997.
90. Tschopp J-M, Boutin C, Astoul P, et al: Talcage by medical thoracoscopy for primary spontaneous pneumothorax is more cost-effective than drainage: A randomised study. Eur Respir J 20:1003–1009, 2002.
91. Lange P, Mortensen J, Groth S: Lung function 22–35 years after treatment of idiopathic spontaneous pneumothorax with talc poudrage or simple drainage. Thorax 43:559–561, 1988.
92. Györik S, Erni S, Studler U, et al: Long-term follow-up of thoracoscopic talc pleurodesis for primary spontaneous pneumothorax. Eur Respir J 29:757–760, 2007.
93. Judson MA, Sahn SA: The pleural space and organ transplantation. Am J Respir Crit Care Med 153:1153–1165, 1996.
94. Dijkman JH, Van der Meer JW, Bakker W, et al: Transpleural lung biopsy by the thoracoscopic route in patients with diffuse interstitial pulmonary disease. Chest 82:76–83, 1982.
95. Vansteenkiste J, Verbeken E, Thomeer M, et al: Medical thoracoscopic lung biopsy in interstitial lung disease: A prospective study of biopsy quality. Eur Respir J 14:585–590, 1999.
96. Noppen M, De Waele M, Li R, et al: Volume and cellular content of normal pleural fluid in humans examined by pleural lavage. Am J Respir Crit Care Med 162:1023–1026, 2000.
97. Noppen M: Normal volume and cellular contents of pleural fluid. Paediatr Respir Rev 5:S201–S205, 2004.
98. Amjadi K, Alvarez GG, Vanderhelst E, et al: The prevalence of blebs or bullae among young healthy adults: A thoracoscopic investigation. Chest 132:1140–1145, 2007.
99. Desmedt A, Vanderlinden E, Demanet C, et al: Characterization of pleural inflammation occurring after primary spontaneous pneumothorax. Eur Respir J 23:896–900, 2004.
100. Noppen M, De Keukeleire T, Hanon S, et al: Fluorescein enhanced autofluorescence thoracoscopy in primary spontaneous pneumothorax and normal subjects. Am J Respir Crit Care Med 174:26–30, 2006.
101. Schönfeld N, Schwarz C, Kollmeier J, et al: Narrow band imaging (NBI) during medical thoracoscopy: first impressions. J Occup Med Toxicol 26:24, 2009.
102. Ishida A, Ishikawa F, Nakamura M, et al: Narrow band imaging applied to pleuroscopy for the assessment of vascular patterns of the pleura. Respiration 78:432–439, 2009.
103. Loddenkemper R, Mathur PN, Noppen M, Lee P: Medical Thoracoscopy/Pleuroscopy: Manual and Atlas. New York: Thieme, 2010.

CHAPTER 24

PULMONARY FUNCTION TESTING

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INTRODUCTION

Pulmonary function tests (PFTs) are an integral part of diagnosing and managing patients with respiratory disease. PFTs play an important role in respiratory medicine but they are only one piece of the puzzle and are not diagnostic of any given disease: many pathologic processes share similar pulmonary function patterns. PFTs are most useful when interpreted in conjunction with other clinical information including history, physical examination, imaging studies, and laboratory data.

PFTs provide clinically useful information under the following conditions: (1) measurements are accurate and precise, (2) patient data are compared with high-quality reference values appropriate for the patient population, (3) the interpretation is made according to a standardized interpretation strategy, (4) the report is configured to highlight important data and to avoid interpretive errors.

The commonly performed and most clinically useful PFTs are discussed: spirometry, diffusing capacity, lung volume tests, tests of respiratory muscle strength, and bronchial provocation tests.

SPIROMETRY

Spirometry is the most useful and readily available PFT. It is an essential tool for any health care provider who cares for patients with respiratory disease. Even tests as well established as spirometry are not entirely straightforward. This section addresses those controversies along with the practicalities of performing and interpreting the test.

Indications

The common clinical indications for spirometry are listed in Table 24-1. Spirometry is a valuable screening test for evaluating respiratory symptoms (cough, wheeze, dyspnea, and chest tightness), abnormal physical examination findings (wheeze, crackles, cyanosis, hyperinflation) and abnormal laboratory tests (chest radiographs, arterial blood gases, oximetry). It is also useful in diagnosing and monitoring many common respiratory diseases including asthma, chronic obstructive pulmonary disease (COPD), various diffuse parenchymal lung diseases, and neuromuscular disorders.

The role of spirometry in populations without respiratory symptoms or pulmonary disease is less clear. A number of proposals have recommended screening asymptomatic smokers and ex-smokers with spirometry, although there is no clear evidence of benefit. The concept is controversial. The U.S. Preventive Services Task Force recommends against screening spirometry for asymptomatic adults including smokers and ex-smokers[1] because it found no evidence that lung function testing improved health care outcomes. In contrast, the National Lung Health Education Program recommends spirometry for all current and past smokers over age 45 years.[2] Their rationale is not evidence based. Screening spirometry would be beneficial if the results encouraged asymptomatic smokers to quit. Studies are conflicting as to whether performing spirometry results in increased smoking-cessation rates.[3,4]

The appropriate use of preoperative spirometry for risk stratification is also controversial. There are good data that spirometry is valuable in predicting postoperative pulmonary complications in patients undergoing thoracic surgery[5]; there is no such evidence for patients undergoing extrathoracic surgery.[6,7] There is no defined threshold at which surgical risk is prohibitive, and spirometry alone should not preclude extrathoracic surgery.[7] Spirometry should be performed in patients undergoing lung resection surgery and cardiac surgery and in selected patients undergoing extrathoracic surgery who have respiratory symptoms or known lung disease.[8]

Spirometry is a safe test with minimal associated risks and there are few contraindications to its performance. Inability to follow technician instructions due to altered mental status or patient unwillingness and subjective discomforts such as pain and nausea may affect test quality and are relative contraindications. Testing should be terminated if the patient develops significant lightheadedness or syncope. Testing should also be terminated if sequential spirometric measurements show a greater than 20% reduction in FEV_1 that is not explained by procedural problems, suggesting maneuver induced bronchoconstriction.[8a]

TABLE 24-1. Indications for Spirometry

Evaluate respiratory symptoms, signs, abnormal laboratory or radiographic findings
Assist in diagnosing respiratory diseases
Monitor respiratory disease activity and response to therapy
Determine respiratory disease prognosis
Evaluate the pulmonary effects of occupational, environmental, and drug exposures
Provide objective assessment of impairment or disability
Evaluate risk prior to lung resection surgery
Assist in smoking-cessation efforts

Spirometry Measurements

Although spirometry measures many physiologic parameters, the important clinical measures are the forced vital capacity (FVC) (the maximal volume of air forcefully exhaled after a maximal inspiration) and forced expiratory volume in 1 second (FEV_1) (the amount of air exhaled during the first second of a FVC maneuver). Both FVC and FEV_1 are expressed in liters at body temperature (37°C) and ambient pressure saturated with water vapor (BTPS). Many other measurements can be obtained from the FVC maneuver. Two of these include the mean forced expiratory flow between 25% and 75% of the FVC ($FEF_{25\%-75\%}$) and peak expiratory flow (PEF), which is the maximum flow achieved during forced exhalation. Both are measured in liters per second. There is evidence that a reduction in $FEF_{25\%-75\%}$ is a spirographic manifestation of small airway dysfunction.[9] However, $FEF_{25\%-75\%}$ is a highly variable test that is dependent on exhalation time and is not specific for small airway disease in individual patients.[10] PEF reflects the caliber of the large airways and is highly effort dependent. Although PEF is attractive because it can be measured using inexpensive handheld devices, it is a more variable measure than FEV_1 and the correlation between PEF and FEV_1 in patients with airway obstruction is poor.[11,12] Neither $FEF_{25\%-75\%}$ or PEF offers any advantage over FEV_1.

Spirometry Performance

Spirometry is commonly performed in the primary care setting and can be completed in less than 15 minutes. Robust testing devices costing less than $2,000 are available for office use. Equipment performance standards and quality control recommendations are discussed in detail elsewhere.[13] The volume accuracy of the spirometer should be checked at least daily with a 3-L syringe.[13] The instrument should display both flow-volume and volume-time tracings, and inspections of these tracings are needed for optimal quality control. Figure 24-1 provides examples of flow-volume and volume-time

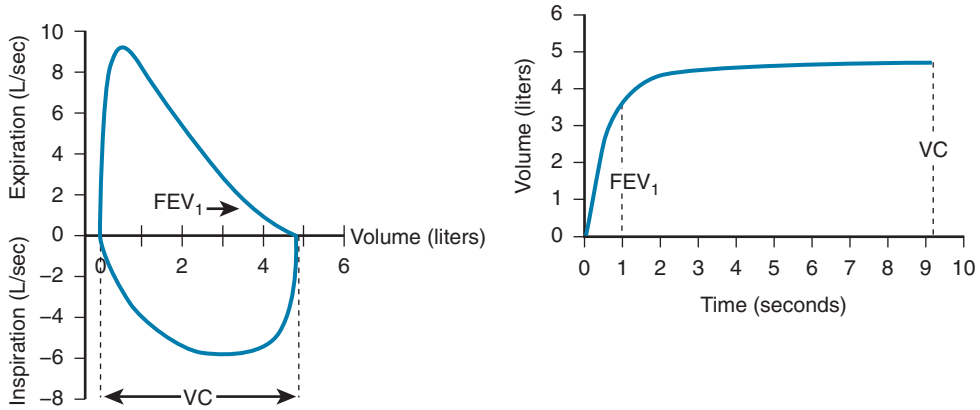


FIGURE 24-1 ■ Examples of flow-volume (*left*) and volume-time (*right*) tracings for a healthy subject are illustrated. FEV_1, forced expiratory volume in 1 second.

TABLE 24-2. Spirometry Acceptability (Within-Maneuver) Criteria

1. Good start of test
   a. Sharp take-off without hesitation
   b. Extrapolated volume < 5% or 0.15 L, whichever is greater
2. Meet end-of-test criteria
   a. Complete exhalation to RV
   b. Plateau on volume-time curve
   c. Exhalation time ≥ 6 seconds (3 sec for children)
3. Absence of artifacts
   a. Cough, especially during first second of exhalation
   b. Glottis closure
   c. Hesitation or submaximal effort
   d. Air leak
   e. Obstructed mouthpiece

RV, residual volume.
Modified from Miller MR, Hankinson J, Brusasco V, et al: Standardisation of spirometry. Eur Respir J 26:319–338, 2005.

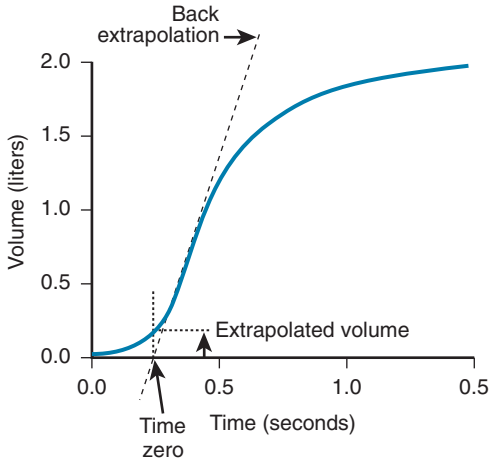


FIGURE 24-2 ■ The back extrapolation method for determining time zero (the adjusted start time) and extrapolated volume are illustrated. The extrapolated volume must be less than 5% of the FVC or 0.150 L, whichever is greater.

tracings. An adequate FVC maneuver requires (1) maximal inspiration to total lung capacity (TLC); (2) an abrupt, maximally forceful exhalation; and (3) exhalation continuing to residual volume. In older patients and in patients with airway obstruction, an unforced or slow vital capacity (SVC) may be useful. In these patients, the SVC may be larger than the FVC due to dynamic air trapping with the forced maneuver. The largest vital capacity (VC) obtained should be used for interpretation.[14,15]

The initial step in spirometry interpretation is to assess test acceptability and repeatability. The American Thoracic Society/European Respiratory Society (ATS/ERS) Task Force on Standardization of Lung Function Testing[13] provides clear guidelines for assessing test acceptability and repeatability. An acceptable study requires the visual examination of each individual effort to determine whether specific within-maneuver criteria are met (Table 24-2). This should include direct inspection of both the volume-time and the flow-volume tracings. Based on this examination, the technician can adjust coaching for the next maneuver. Poorly performed or submaximal maneuvers may mimic disease patterns, leading to interpretive errors.

The start of test criteria requires an abrupt, sharp rise in flow with no hesitation. This is quantified by assessing the back extrapolated volume as illustrated in Figure 24-2. At the onset of forced exhalation, inertial forces must be overcome; PEF is not achieved until approximately 150 msec after the exhalation maneuver begins. The extrapolated volume, calculated using the new "time zero," must be less than 5% of the FVC or 0.150 L, whichever is greater.[13] Most modern spirometers provide rapid computerized feedback to alert the technician when start-of-test criteria are not met. An inaccurate "start-of-test" with a large back extrapolated volume could overreport FEV_1 relative to FVC, resulting in an increased FEV_1/FVC ratio, possibly missing an obstructive pattern.

The end-of-test criteria ensures that the patient has exhaled completely to residual volume (RV). The end-of-test criteria are met at an exhalation time of greater than 6 seconds (3 seconds for children < 10 years of age) or

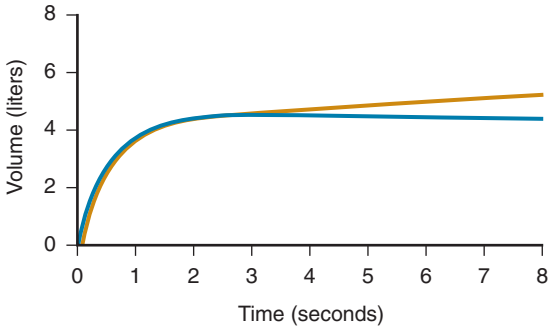


FIGURE 24-3 ■ Premature closure of the glottis is exhibited. This will result in an underestimation of FVC.

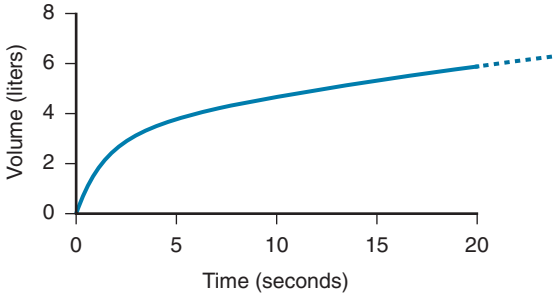


FIGURE 24-4 ■ A volume-time tracing for a patient with COPD who does not meet end of test criteria despite an exhalation time exceeding 20 seconds.

a plateau on the volume-time curve (defined as a change in volume < 25 mL for the last second of exhalation). Most currently available spirometers alert the technician if end-of-test criteria are not met. Visual inspection of the tracings is necessary to exclude a trial with premature closure of the glottis, because this can erroneously be reported as meeting end-of-test criteria (Fig. 24-3). Two situations exist in which end-of-test criteria may not be met despite being acceptable maneuvers. Patients with severe airway obstruction may not meet the plateau end-of-test criteria despite very long exhalations, often exceeding 15 seconds (Fig. 24-4). Prolonged exhalations in this setting generally do not result in misinterpretation and may cause unnecessary discomfort, lightheadedness, or, rarely, syncope.[16] Young children and adults with severe restriction may have difficulty meeting the specified exhalation time requirements. Visual inspection of the volume-time curves is useful in these situations to confirm the presence of a plateau. The technician can use this information to stop the test.

Failing to adhere to the end-of-test criteria and complete exhalation to RV will result in a falsely low FVC. This may have two consequences. A restrictive ventilatory defect may be suggested and lead to further testing.[17] A low FVC can falsely elevate the FEV_1/FVC ratio, which could obscure an obstructive abnormality.[18]

Other elements of an acceptable test include the absence of cough, glottic closure, or hesitation during the maneuver; an air leak from the mouth or nose; and obstruction of the mouthpiece. Maximal effort throughout the maneuver is suggested, although the consequences of a submaximal effort are not clear-cut. Some

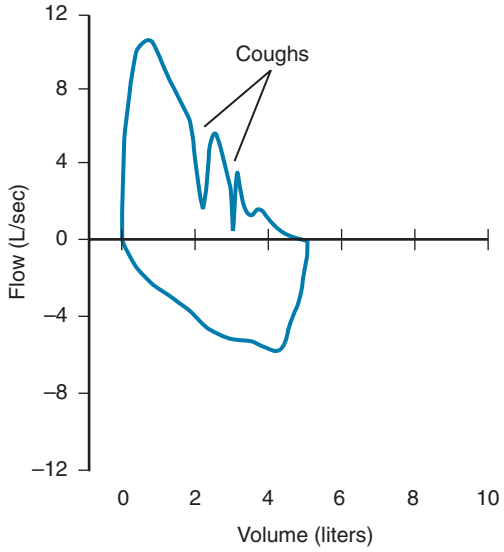


FIGURE 24-5 ■ An unacceptable spirogram due to coughing. Useful information may be obtained from spirograms with cough. If the cough occurs after the first second of exhalation, FEV_1 will be reliable.

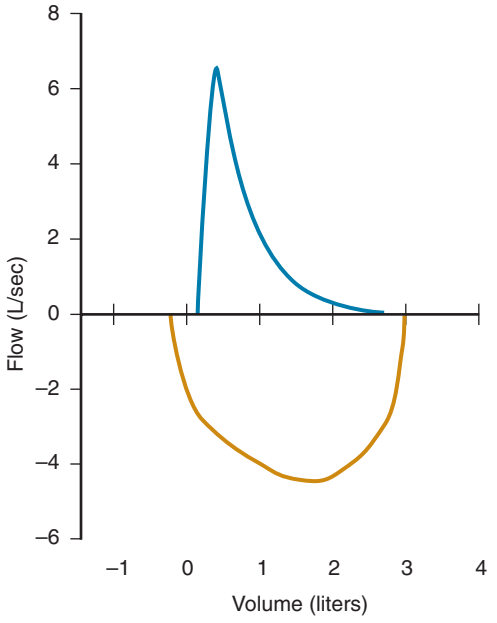


FIGURE 24-6 ■ An unacceptable spirogram due to expiratory leak. Note expiratory vital capacity is less than inspiratory vital capacity.

patients exhibit "negative effort dependence" in which maximal effort is associated with a reduced FEV_1 due to thoracic gas compression.[11,19] Negative effort dependence is classically seen in disease processes in which there is a loss of cartilage in the trachea or bronchi such as tracheomalacia, although it can also be observed in individuals without airway pathology. Reducing the effort after approximately 2 to 3 seconds of forceful exhalation does not appear to change the results and lessens discomfort and the risk of syncope.[20] Examples of unacceptable tests are shown in Figures 24-5 to 24-10.

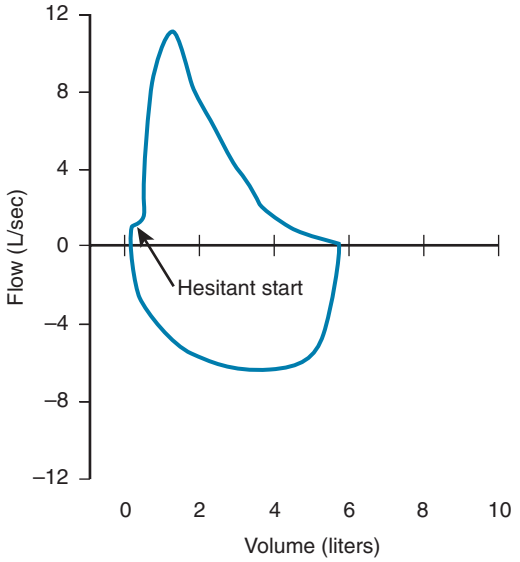


FIGURE 24-7 ■ An unacceptable spirogram due to hesitant start. This will result in an underestimation of FEV_1.

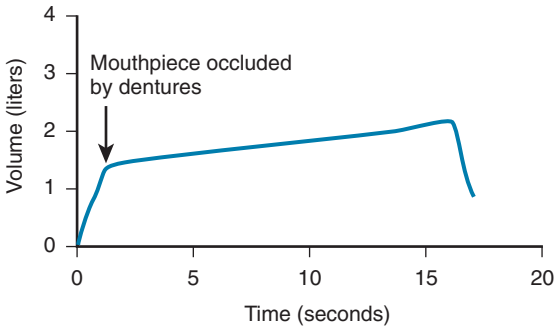


FIGURE 24-8 ■ An unacceptable spirogram due to partial mouthpiece obstruction by denture.

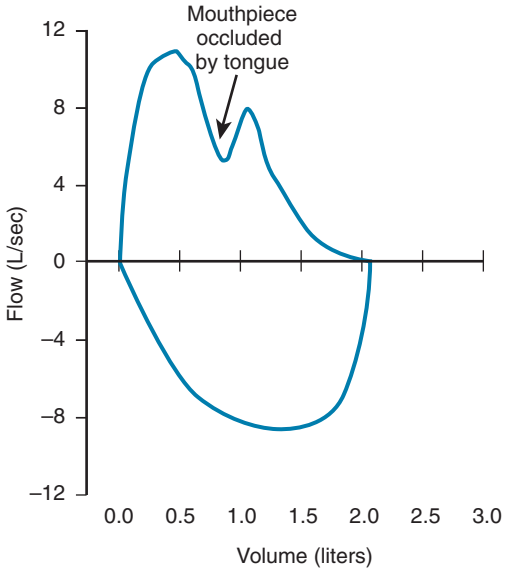


FIGURE 24-9 ■ An unacceptable spirogram due to transient occlusion of mouthpiece by tongue.

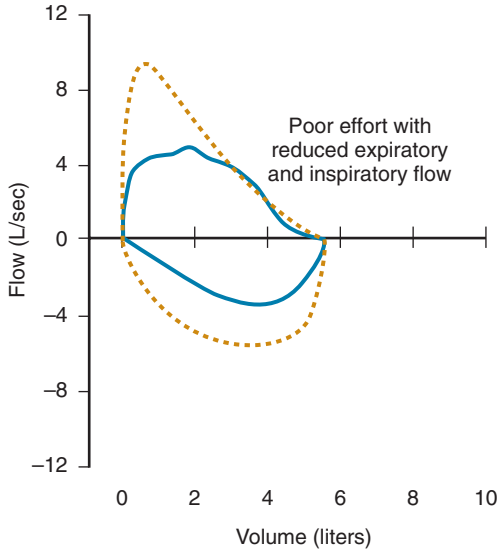


FIGURE 24-10 ■ An unacceptable spirogram due to submaximal effort is illustrated. Flattening of both the inspiratory and the expiratory limbs (*solid line*) is present. Inspiratory limb flattening due to submaximal effort is a common problem and needs to be distinguished from upper airway obstruction. A normal spirogram is superimposed (*dotted line*).

TABLE 24-3. Spirometry Repeatability (Between-Maneuver) Criteria

After three acceptable spirograms, apply the following criteria:

1. Are the two largest values of FVC within 0.15 L of each other?
2. Are the two largest values of FEV_1 within 0.15 L of each other?

If both criteria are met, conclude test session.

If criteria are not met, continue testing until criteria are met, patient is fatigued, or eight tests have been performed.

FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity.
Modified from Miller MR, Hankinson J, Brusasco V, et al: Standardisation of spirometry. Eur Respir J 26:319–338, 2005.

An adequate test requires a minimum of three acceptable maneuvers, that is, maneuvers that meet the criteria described previously. The next step in interpretation is to determine whether the repeatability or between-maneuver criteria are met (Table 24-3). Specifically, the two largest values of FVC and FEV_1 must be within 0.15 L of one another. If the FVC value is less than 1.0 L, the highest and next highest FVC and FEV_1 should be within 0.10 L. In a study of 18,000 consecutive patients, 95% met these repeatability criteria and repeatability was not significantly influenced by patient characteristics such as sex, age, height, and smoking status.[21] If the repeatability criteria are not met after three acceptable tests, testing should continue until repeatability criteria are met or eight attempts have been made.[13] More than eight maneuvers is generally not useful.[22,23] From all acceptable tests, the largest FVC (or SVC if larger than FVC) and FEV_1 are selected for analysis, even if they come from different maneuvers. At least three maneuvers that meet the acceptability and repeatability criteria should be

saved. If the tests do not meet the acceptability and repeatability criteria, they may still have some clinical utility. The interpreting physician needs to comment in the report that the data should be considered minimum values for the patient.

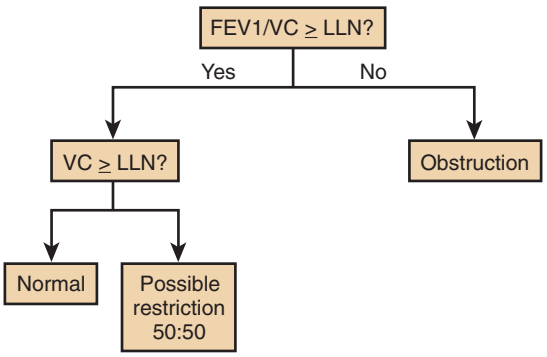
Spirometry Interpretation

After acceptable and repeatable studies are obtained, interpretation can proceed using a systematic approach. Using the FVC, FEV_1, and FEV_1/FVC ratio, an obstructive, restrictive, or normal pattern is determined. A simple approach for interpreting spirometry is shown in Figure 24-11. The first step is to assess the FEV_1/FVC ratio. Narrowing of either the large or the small airways will result in a larger reduction in FEV_1 relative to FVC, resulting in a reduced FEV_1/FVC ratio. The pathophysiologic processes in asthma and COPD primarily affect the mid to smaller airways and show a proportionally greater reduction in flow in the middle and later parts of exhalation. This produces the characteristic concave shape on the flow-volume curve.

Whereas obstruction is always defined as a low FEV_1/FVC, the definition of "low" is not consistent. The ATS/ERS Task Force on Standardization of Lung Function Testing[14] defines an obstructive ventilatory defect as a FEV_1/FVC ratio below the 5th percentile of the predicted value—a statistically defined lower limit of normal (LLN). The Global Initiative for Chronic Obstructive Lung Disease (GOLD) defines airway obstruction as a post-bronchodilator FEV_1/FVC less than 70%.[24] Both approaches use the FEV_1 percent predicted to grade the severity of airway obstruction. The ATS/ERS Task Force and GOLD criteria for defining and classifying airflow obstruction are listed in Figure 24-12.

The GOLD guidelines advocate the use of the fixed ratio for FEV_1/FVC for reasons of simplicity and ease of remembrance, while acknowledging that the FEV_1/FVC decreases with age and may result in the overdiagnosis of COPD in the elderly.[24] The process of aging results in a loss of elastic recoil; FEV_1 decreases more rapidly than FVC, resulting in a progressive reduction in the FEV_1/FVC ratio with advancing age. Figure 24-13 provides examples of flow-volume curves for normal subjects aged 20, 50, and 80 years. The ATS/ERS Task Force[14] emphasizes the importance of using the 5th percentile LLN to prevent overdiagnosis in the elderly and underdiagnosis in the younger population. This is depicted graphically in Figure 24-14. Using National Health and Nutrition Examination Survey (NHANES) III reference equations for white males for FEV_1/FVC, the LLN is less than 70% at ages older than 41 years. For white females, the LLN is below 70% at ages older than 52 years.[25] The risk of overdiagnosing an obstructive ventilatory pattern when using the fixed ratio of FEV_1/FVC less than 70% is evident in two studies both showing approximately 20% of elderly subjects misidentified as abnormal with the fixed ratio compared with the 5th percentile LLN method.[26,27] In our laboratory, we interpret the presence and severity of obstruction using the ATS/ERS criteria to avoid the misclassification of older and younger patients.

Another controversy arises in classifying those whose FEV_1/FVC ratio is reduced but the FEV_1 is in the normal range. Patients with this pattern have been identified as obstructed[14] or a "normal physiologic variant" when FEV_1 was greater than 100% of predicted.[28] Accurate interpretation of subjects with a reduced FEV_1/FVC ratio and a preserved FEV_1 requires clinical information, because it depends on the prior probability of obstructive disease. In healthy individuals, this pattern may represent unequal



Severity classification	FEV1 % predicted
Normal physiologic variant	>100
Mild	70–100
Moderate	60–69
Moderately severe	50–59
Severe	35–49
Very severe	<35

FIGURE 24-11 ■ A simple algorithm for interpreting spirometry beginning with the FEV_1/FVC ratio is shown. A reduced FEV_1/FVC ratio, less than the lower limit of normal (LLN), is diagnostic of obstruction, and the severity of obstruction is determined by the FEV_1 percent predicted. Restriction is suggested if the FVC is reduced, although a reduced FVC is not specific for a restrictive pattern.

DEFINITION OF OBSTRUCTION AND CLASSIFICATION OF SEVERITY BY SPIROMETRY

ATS/ERS FEV_1/FVC <LLN		GOLD FEV_1/FVC <0.70	
FEV_1 % predicted			FEV_1 % predicted
>70	Mild	Stage I: Mild	≥80
60–69	Moderate	Stage II: Moderate	<80
50–59	Moderately severe	Stage III: Severe	<50
35–49	Severe		
<35	Very severe	Stage IV: Very severe	<30

FIGURE 24-12 ■ The American Thoracic Society and European Respiratory Society (ATS/ERS) defines obstruction as an FEV_1/FVC ratio below the lower limit of normal (LLN) defined as below the 5th percentile of the predicted value. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) defines obstruction as a FEV_1/FVC ratio less than 0.70. Both grade the severity of obstruction based on the FEV_1 percent predicted.

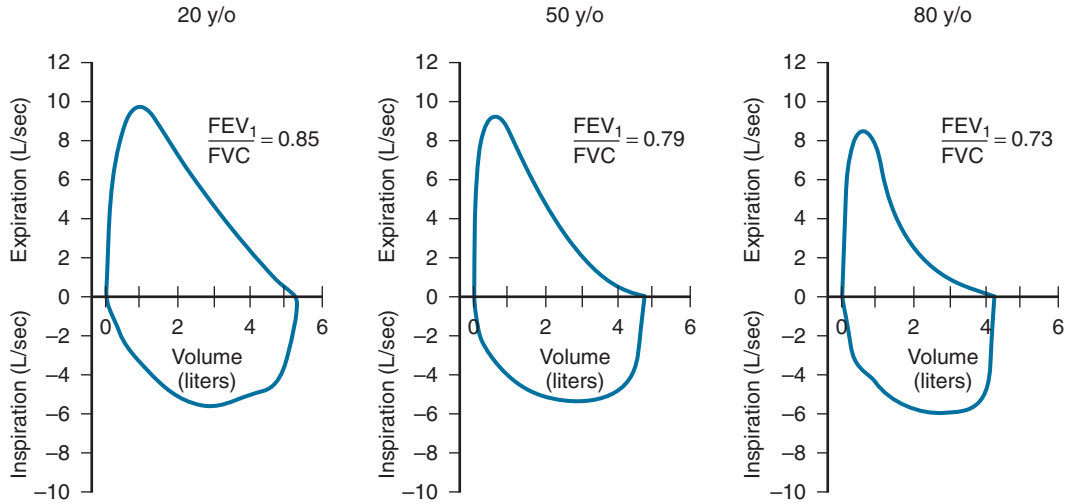


FIGURE 24-13 ■ Examples of flow-volume curves for healthy subjects aged 20, 50, and 80 years. The FEV_1/FVC ratio decreases with age, primarily due to a loss of elastic recoil. The changes in flow with ageing are most evident at lower lung volumes.

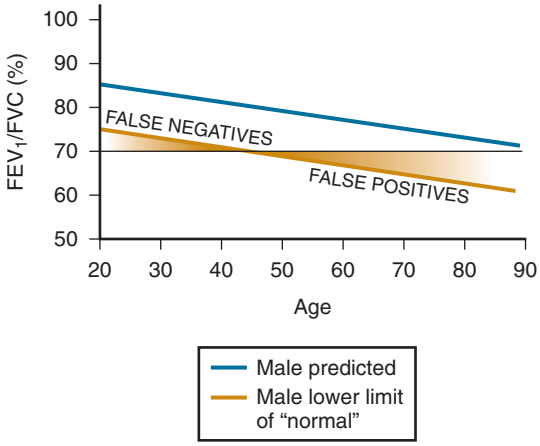


FIGURE 24-14 ■ The reduction in FEV_1/FVC with age for a white male is represented graphically. The *blue line* represents the predicted value and the *brown line* represents the LLN. After approximately age 41, the lower limit of normal is less than the 70% limit that the GOLD guidelines recommend as the threshold for obstruction. The *dark area* represents false positives and false negatives associated with using the 70% limit.

growth of the airways relative to the lung parenchyma, but in people with respiratory symptoms or exposures, it probably represents airway obstruction.

A restrictive ventilatory defect is defined as a total lung capacity (TLC) below the 5th percentile of the predicted value.[14] Because spirometry is much more readily available, technically easier, and less costly to perform than measurements of lung volumes (plethysmography, nitrogen washout, or inert gas techniques), FVC is often used as a surrogate for TLC to diagnose a restrictive abnormality. Spirometry-based algorithms can exclude a restrictive process with greater than 95% accuracy if the FVC is normal.[17,29] However, a low FVC cannot reliably diagnose restriction. A reduced FVC has a positive predictive value of only approximately 50% for confirming a restrictive process with only modest improvements in accuracy if reserved for patients with a normal FEV_1/FVC ratio.[30-32] Spirometry is helpful in excluding but not predicting a restrictive defect. VC will be reduced despite a normal TLC if inspiratory or expiratory efforts are submaximal and if there is air trapping associated with small airway closure or noncommunicating bullae.

It is not uncommon to identify patients with a reduced FEV_1 and FVC with a normal FEV_1/FVC ratio and normal TLC. This has been referred to as a "nonspecific pattern" and was found in approximately 10% of patients in a large academic PFT lab.[32a] The majority of patients with this pattern had either airway hyperresponsiveness or abnormalities that restrict the normal expansion of the lung or thorax such as obesity.

A mixed or combined ventilatory defect is present when both the FEV_1/FVC ratio and the TLC are below the 5th percentiles of their predicted values. A reduced FVC associated with a reduced FEV_1/FVC ratio is most likely due to hyperinflation, although a concomitant restrictive process cannot be ruled out without measurement of TLC by plethysmography. In a study of nearly 5000 patients with airway obstruction, approximately 40% had a reduced VC; less than 10% of this subgroup met the definition of restriction (reduced TLC measured with plethysmography).[33]

Though the FEV_1/FVC ratio is the spirometric standard for diagnosing obstruction, the FEV_1/FEV_6 ratio is an acceptable surrogate. The FEV_6 maneuver, which allows cessation of exhalation after 6 seconds, has several advantages over the standard FVC maneuver. It is less physically demanding for the patient. It simplifies spirometric testing for the technician, shortens testing time, and has superior reproducibility.[34] The FEV_1/FEV_6 ratio performs well in categorizing patients with obstruction with a sensitivity and specificity greater than 90% compared with the FEV_1/FVC ratio.[16,34,35,35a] Based on these findings, the National Lung Health Education Program has recommended replacement of FVC with FEV_6.[2] However, FEV_6 is not as sensitive as FVC at determining the presence of a restrictive respiratory impairment (sensitivities 83%-88%).[16,36] Reference values are available for FEV_1/FEV_6 and FEV_6.[25]

Bronchodilator Testing

Bronchodilator administration in the pulmonary function laboratory is commonly performed to determine acute reversibility of airflow limitation. The ATS/ERS Task Force[13] recommends the administration of four separate puffs at 30-second intervals of the short acting β_2-agonist albuterol (total of 400 mcg) using a spacer device. For pre- and postbronchodilator spirometry studies, a minimum of three acceptable and repeatable tests should be obtained at baseline and 15 minutes after bronchodilator administration. If the short-acting anticholinergic drug ipratropium bromide is used, testing should be repeated 30 minutes after administration. The combination of albuterol and ipratropium produces a greater response than either medication alone.[37] The ordering physician's purpose is paramount in determining the conditions of testing: If the aim of the study is to determine whether there is any evidence of reversible airflow obstruction, the patient should not take short-acting bronchodilators for 4 to 6 hours prior to testing and long-acting bronchodilators 12 to 24 hours before testing. However, if the goal is to determine whether lung function can be improved above that achieved with baseline treatment, medications should be taken as prescribed.[13]

There is no consensus as to what defines acute reversibility in patients with airflow limitation. Certainly, improvement in lung function must exceed the changes observed in healthy individuals administered bronchodilator. The 95th percentile for percent change from baseline in healthy nonsmokers for FEV_1 is 9%.[38] The ATS/ERS Task Force[14] defines a positive bronchodilator response as an increase in FEV_1 and/or FVC greater than or equal to 12% and 200 mL of the baseline value.

The clinical utility of acute bronchodilator testing is not well defined. The National Asthma Education and Prevention Program Expert Panel Report 3[39] recommends measuring pre- and postbronchodilator pulmonary function in asthmatics. The GOLD guidelines[24] recommend the use of postbronchodilator spirometry for diagnosis and staging of COPD. It is not clear how an acute response to bronchodilator in the laboratory influences the management of patients with asthma or COPD. One reported benefit of bronchodilator testing is to distinguish between asthma and COPD. Reversible airflow obstruction is the hallmark for asthma and irreversible obstruction is often a characteristic of COPD.[40] However, it is not uncommon for patients with COPD to respond acutely to bronchodilator; some studies report more than 50% of subjects met criteria for reversibility.[41–43] There is significant overlap between response to bronchodilator for patients with asthma and those with COPD, and it cannot reliably differentiate between asthma and COPD.[37] There are some quantitative and qualitative patterns more commonly associated with one than the other. In general, asthmatics have a larger absolute increase in FEV_1 than patients with COPD. In COPD patients who respond to bronchodilator, there often is an increase in FVC, whereas individuals with asthma more often respond with an increase in FEV_1.[44] Asthma is a disease characterized by variability in bronchial responsiveness and in bronchodilator reversibility. Similarly, bronchodilator responsiveness in COPD patients is not static. In one study, 52% of COPD patients changed their responder/nonresponder status over an 8-week period.[45] Bronchodilator reversibility cannot be the sole criteria for differentiation of asthma from COPD, and clinical information is necessary for making this distinction.

Another possible benefit of bronchodilator testing is the association between bronchodilator reversibility and prognosis. In asthma, larger responses to bronchodilator have been associated with an increased risk of accelerated loss of lung function and the development of fixed airflow obstruction.[46] For COPD patients, the importance of bronchodilator reversibility with regard to lung function decline and mortality is not clear; some studies suggest that it is a marker of more rapid disease progression[43,50] and others find no effect[47–49] or a positive impact on disease progression.[51]

Bronchodilator testing is not useful in predicting symptomatic improvement in patients with obstructive lung disease treated with bronchodilator therapy. The absence of a response to a bronchodilator given in the laboratory should not preclude a trial of bronchodilator medications.[52] The reason for the lack of correlation between traditional acute bronchodilator response (increase in FEV_1 and in FVC) and subsequent clinical benefit with use of bronchodilator may be due to a reduction in hyperinflation with bronchodilator use. Obstructed patients treated with bronchodilators have less hyperinflation, as measured by increased inspiratory capacity. The beneficial effect on hyperinflation is especially prominent with exercise.[53] A 10% improvement in inspiratory capacity with bronchodilator is a better predictor of improvement in dyspnea and in exercise tolerance in patients with COPD than is an improvement in FEV_1 or FVC.[54–57] Bronchodilator responses exhibiting an improvement in FEV_1 and FVC and an improvement in inspiratory capacity without an improvement in expiratory flows are illustrated in Figure 24-15. A positive bronchodilator response in COPD patients does not distinguish those patients who will clinically improve when treated with inhaled steroids from those who will not.[41]

Spirometry in Upper Airway Obstruction

The upper airway extends from the nose or mouth to the main carina of the trachea. The upper airway is further subdivided into the extrathoracic and intrathoracic components. The extrathoracic airway includes the nose, mouth, pharynx, larynx, and the 2 to 4 cm of the trachea cephalad to the thoracic inlet. The intrathoracic component comprises the 6 to 9 cm of trachea extending from the thoracic inlet caudal to the main carina. Spirometry is very useful in identifying upper airway obstruction (UAO).[58] UAO may present in a similar manner to the more common causes of airway obstruction such as asthma and COPD. Differentiating UAO from these more common causes of airway obstruction is important because treatment is very different and confirmatory diagnostic tests are required.

The flow-volume loop is the single best PFT for diagnosing UAO. The importance of the flow-volume tracing in diagnosing UAO was demonstrated by Miller and

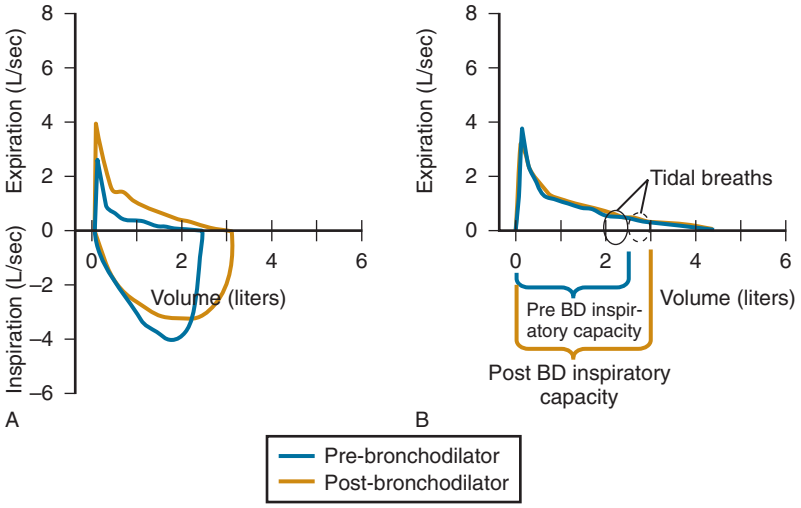


FIGURE 24-15 ■ Patients with airflow obstruction may improve following the administration of bronchodilator in two ways: FEV_1 and/or FVC may improve by 12% and 200 mL (**A**), or there may be a reduction in hyperinflation manifest by an increase in inspiratory capacity (**B**). A reduction in hyperinflation is associated with clinical improvement.

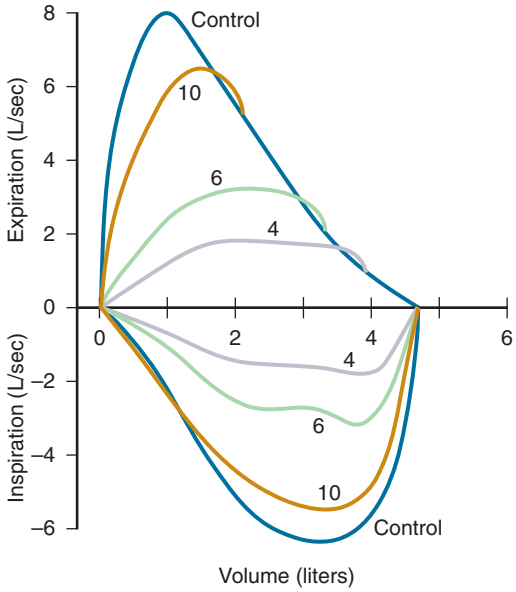


FIGURE 24-16 ■ Reductions in inspiratory and expiratory flows with a healthy subject breathing through progressively smaller calibrated fixed orifices (from 10 mm to 4 mm) are shown. Breathing through the orifices did not affect FVC and FEV_1 remained above 90% of control value until the 6 mm orifice was used. (Modified from Miller RD, Hyatt RE: Obstructing lesions of the larynx and trachea: Clinical and physiologic characteristics. Mayo Clin Proc 44:145–161, 1969.)

Hyatt.[59] They obtained flow-volume tracings with normal volunteers breathing through calibrated orifices. With decreasing orifice diameter, a prominent plateau was noted throughout inhalation and exhalation as shown in Figure 24-16. Their study also confirmed the poor sensitivity of FVC and FEV_1 for detecting UAO and affirmed the need to examine the flow-volume curve when UAO is suspected. FVC was not affected by the orifices and FEV_1 remained above 90% of the control value until the 6-mm orifice was used.[59]

Three patterns of UAO can be identified by examining the inspiratory and expiratory components of the flow-volume tracing.[59–61] The UAO pattern is determined by the location of the obstruction (intrathoracic or extrathoracic) and whether the obstruction is fixed or variable. Reviewing the physiologic principles that govern air movement into and out of the airways can identify the pattern of obstruction observed with the flow-volume curve. Transmural pressure gradients develop across the upper airway wall with inhalation and exhalation. Whether the transmural pressure is positive or negative depends on the phase of respiration (inhalation or exhalation) and on the location of the obstruction. Under normal circumstances, the integrity of the airway wall prevents crimping or expansion, preserving airflow. With variable extrathoracic obstruction, as depicted in Figure 24-17, transmural pressure is negative with inhalation, resulting in crimping of the airway at the site of the lesion, reducing airflow and flattening the inspiratory limb of the flow-volume tracing. With exhalation, transmural pressure is positive, decreasing the degree of obstruction and improving flow. Patient effort is especially important when using the flow-volume curve to diagnose UAO. In our experience, the most common cause of inspiratory limb flattening is submaximal inspiratory effort. Causes of extrathoracic UAO include tracheomalacia; vocal cord abnormalities (paralysis, edema, neoplasms, vocal cord dysfunction); thyroid tumors; laryngeal edema (angioedema, post-extubation, burns); epiglottitis, tonsillar, and retropharyngeal abscesses; and foreign bodies.[62] While the reduction in inspiratory flow is most pronounced with these causes of variable extrathoracic obstruction, PEF is also decreased but to a smaller degree. The flow-volume curve reveals a more pronounced decrease in the inspiratory limb flattening than in the expiratory limb. The exception is extrathoracic tracheomalacia, which exhibits only inspiratory limb flattening with a normal expiratory limb.

Variable intrathoracic obstruction is shown in Figure 24-18. Transmural pressure is negative with exhalation as pleural pressure exceeds intratracheal pressure, crimping the airway downstream of the site of the lesion, reducing airflow and flattening the expiratory limb of the flow-volume curve. With inhalation, tracheal pressure exceeds surrounding pleural pressure, no compression

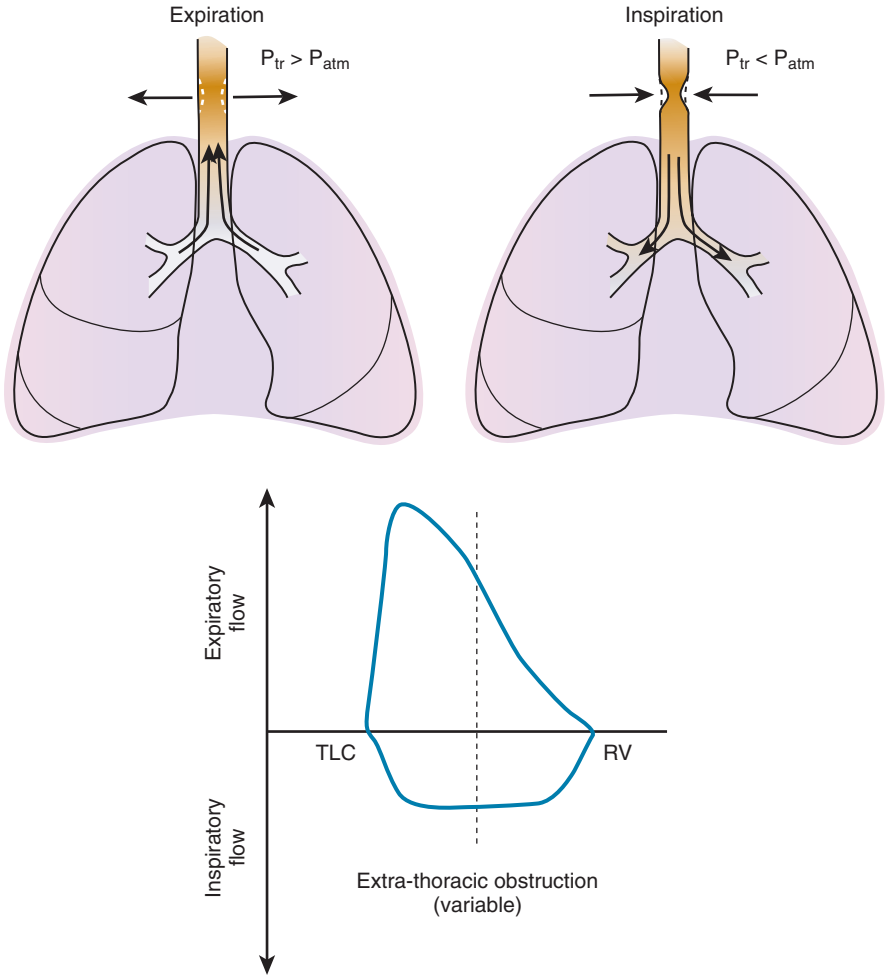


FIGURE 24-17 ■ Characteristic changes in upper airway diameter with variable extrathoracic obstruction. Inspiratory limb flattening is seen on the flow-volume curve. Forced expiratory flow at 50% of lung volume ($FEF_{50\%}$) is greater than forced inspiratory flow at 50% of lung volume ($FIF_{50\%}$).

downstream occurs, resulting in greater inspiratory flow. Causes of variable intrathoracic obstruction include tracheomalacia, tracheal tumors, tracheal inflammatory processes (Wegener's granulomatosis, tracheitis), and mediastinal adenopathy.[62] Similar to variable extrathoracic obstruction discussed previously, most causes of variable intrathoracic obstruction result in reductions of both expiratory and inspiratory flows with more pronounced reductions in expiratory flows. The exception is intrathoracic tracheomalacia, which exhibits only expiratory limb flattening with a preserved inspiratory limb. Fixed lesions of the upper airway are firm and relatively resistant to the effects of transmural pressure changes. They do not change significantly with the phase of respiration and both the inspiratory and the expiratory limbs of the flow-volume curve are similarly flattened (as illustrated in Fig. 24-19). The most common cause of fixed UAO is subglottic stenosis from prior intubation or tracheostomy. Other causes include benign and malignant tumors anywhere in the upper airway, large thyroid goiters, and large foreign bodies.[62] Tracheomalacia located at the thoracic inlet will also result in near-equal reduction in both inspiratory and expiratory flows.

The ratio of forced expiratory flow at 50% of lung volume to forced inspiratory flow at 50% of lung volume (FEF_{50}/FIF_{50}) is a simple test for determining the type of UAO. Miller and Hyatt[60] documented the following ratios for $FEF_{50\%}/FIF_{50\%}$: normal individuals of 1.0 or greater; fixed upper airway obstruction 0.9; variable extrathoracic UAO 2.2; and variable intrathoracic obstruction 0.3.

The diagnosis of UAO is more difficult when there is concomitant "lower" airway obstruction associated with asthma or COPD.[63] Rotman and coworkers[64] found four variables derived from the FVC maneuver to be useful in distinguishing UAO from normal subjects and patients with COPD. These included: $FIF_{50\%}$ of 100 L/min or less; $FEF_{50\%}/FIF_{50\%}$ of 1.0 or greater; FEV_1/PEF of 10 mL/L/min or greater; and $FEV_1/FEV_{0.5}$ of 1.5 or greater. However, there was significant overlap between the groups, and others have proposed measuring the maximum voluntary ventilation (MVV) and then using the MVV/FEV_1 ratio of 25 or less as a criterion for diagnosing UAO or concomitant UAO and COPD.[65,66] However, MVV is highly dependent on patient effort and more variable, making this test less clinically useful.

While spirometry is very helpful in evaluating UAO, visual inspection of the flow-volume curve or any of the values derived from the FVC maneuver can be misleading when patient effort is submaximal and when there is concomitant obstructive lung disease. Confirmatory tests such as ultrafast cinetomographic computed

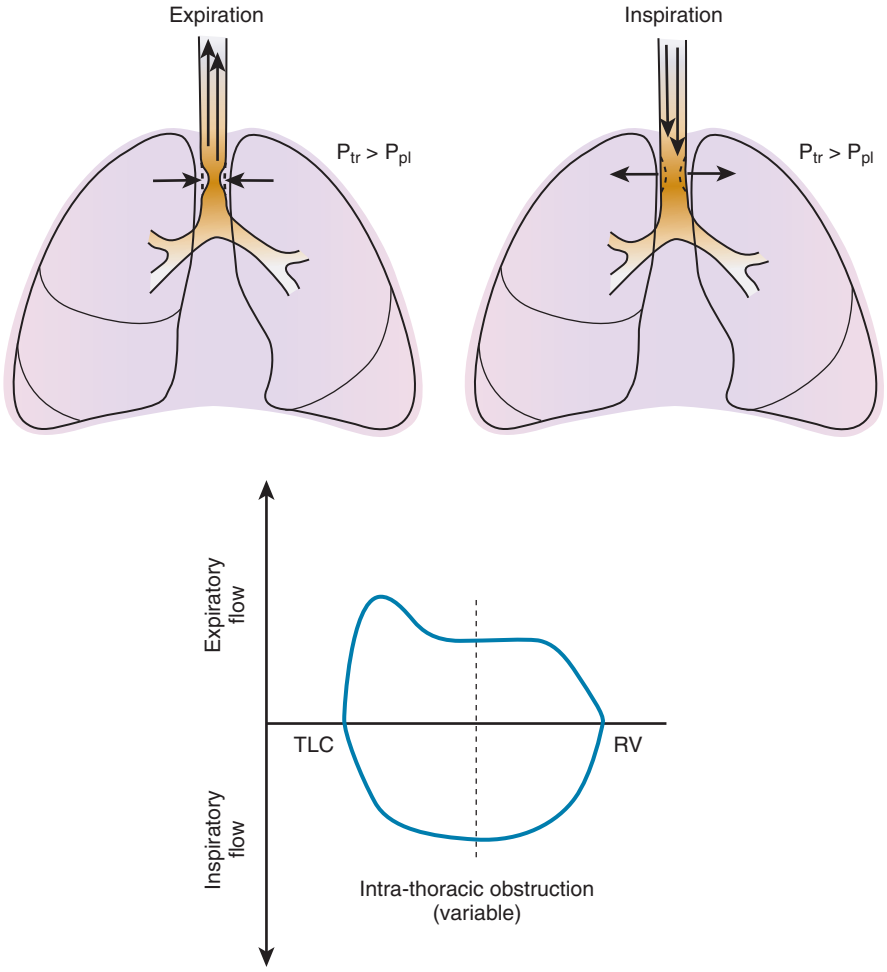


FIGURE 24-18 ■ Characteristic changes in upper airway diameter with variable intrathoracic obstruction. Expiratory limb flattening is seen on the flow-volume curve. $FEF_{50\%}$ is less than $FIF_{50\%}$.

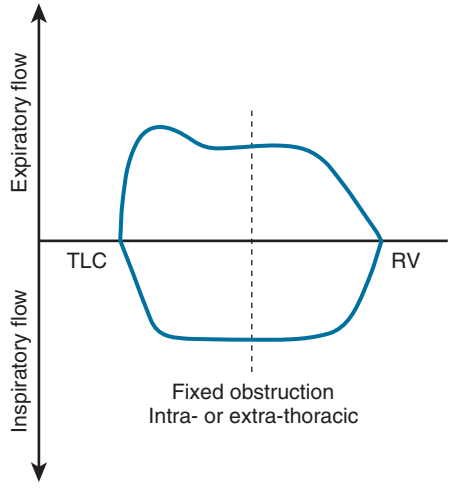


FIGURE 24-19 ■ With fixed upper airway obstruction, there is flattening of both the inspiratory and the expiratory limbs of the flow-volume curve. $FEF_{50\%}$ is approximately equal to $FIF_{50\%}$.

tomography (cine-CT) and laryngoscopy or bronchoscopy are necessary to confirm the diagnosis.

DIFFUSING CAPACITY

The diffusing capacity for carbon monoxide (D_{LCO}) is a common and clinically useful test that provides a quantitative measure of gas transfer in the lungs. D_{LCO}, along with spirometry, is a core PFT used to evaluate and manage patients with respiratory diseases. Diffusing capacity is often abnormal in patients with interstitial lung disease, pulmonary vascular disease, and COPD. Because D_{LCO} is a measure of the transfer of gas from the airways to the reaction with hemoglobin in the pulmonary capillaries, D_{LCO} has been called a "window on the pulmonary microcirculation."[67] Diffusing capacity is influenced by processes in addition to diffusion and is usually obtained at rest when it is submaximal so it is not a true capacity measurement. Transfer factor (T_{LCO}), the term commonly used outside of North America, is technically a more accurate name for the test. However, because of its historical use and for the sake of uniformity, the ATS/ERS Task Force[68] continues to endorse the term D_{LCO}.

Diffusing Capacity Physiology

Measuring $D_{L_{CO}}$ provides information on the transfer of gas from the airways to hemoglobin. This is depicted in Figure 24-20. The gas essential to cellular metabolism is O_2 but CO is used in the test. Why is the diffusion of CO measured rather than the diffusion of O_2? Both CO and O_2 readily diffuse across the alveolar capillary membrane and bind tightly with hemoglobin. However, CO has a binding affinity for hemoglobin 200 to 250 times greater than that of O_2. Because of the high affinity combined with the abundance of CO binding sites on the hemoglobin molecule, the pulmonary capillary CO tension remains near zero when low concentrations of CO are inhaled. The CO uptake is therefore diffusion limited. In contrast, the pulmonary capillary O_2 tension or partial pressure rises along the length of the capillary, creating appreciable back tension (Fig. 24-21). Oxygen is perfusion-limited in normoxic conditions and perfusion and diffusion-limited in hypoxic conditions. Despite the fact that O_2 is the primary gas of interest, technical factors preclude measurement of $D_{L_{O_2}}$. At the present time, CO is the best gas to measure the diffusion properties of the lung.

Fick's law describes the diffusion of a gas through tissue. The amount of gas transferred across a membrane is directly proportional to the tissue surface area, diffusion constant, and the difference in gas partial pressure and is inversely proportional to the tissue thickness. The diffusion constant is proportional to the solubility of a gas and is inversely proportional to the square root of the molecular weight of the gas. This relationship is shown in Figure 24-22. It is not possible to determine the tissue area or thickness of the alveolar capillary membrane for the entire lung so area, thickness, and the diffusion constant are replaced by a single constant, D_L, which represents the diffusing capacity for the lung.

$$\dot{V}_{gas} = D_L \times (P_1 - P_2)$$

where D_L is the diffusing capacity of the lung and P_1 and P_2 are the gas concentrations in the alveolus and pulmonary capillary, respectively. When CO is the gas being

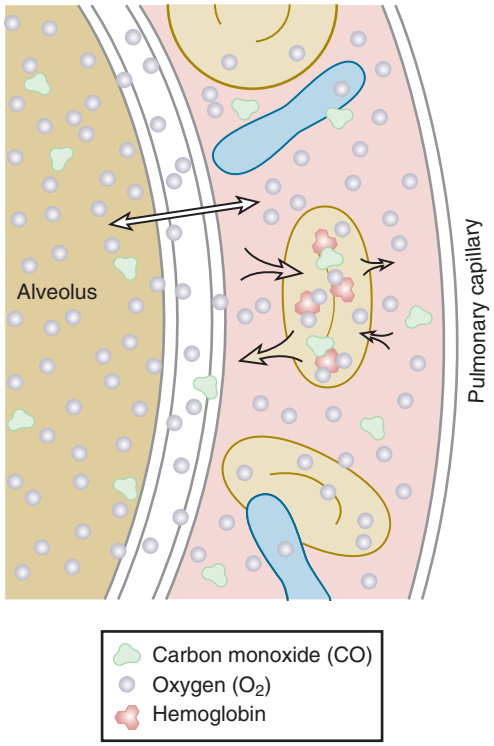


FIGURE 24-20 ■ The transfer of carbon monoxide and oxygen molecules across the alveolar-capillary membrane, through plasma, across the red blood cell membrane and the reaction with hemoglobin is represented.

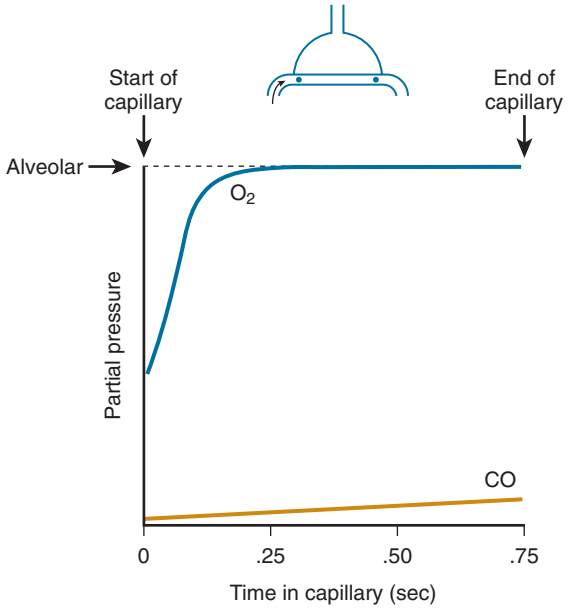


FIGURE 24-21 ■ This figure illustrates why oxygen (O_2) uptake is perfusion limited under most clinical circumstances, because the capillary partial pressure of O_2 rapidly increases along the length of the pulmonary capillary, while the capillary partial pressure of carbon monoxide, at low concentrations, remains near zero and its uptake is limited by diffusion.

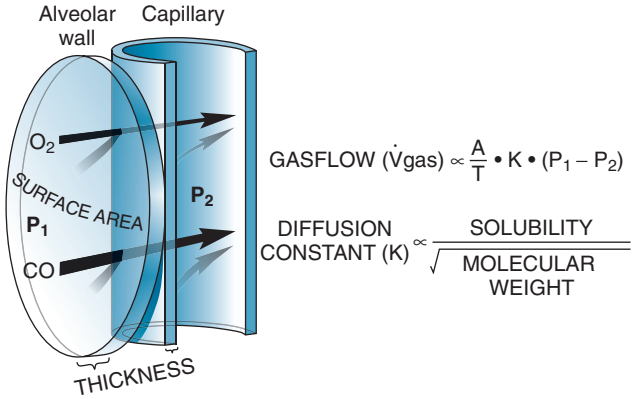


FIGURE 24-22 ■ Fick's law describes the factors that determine diffusion of a gas ($\dot{V}_{GAS}$) through tissue including tissue surface area (A), a diffusion constant (K), the difference in gas partial pressure across the tissue ($P_1 - P_2$) and tissue thickness (T).

measured, P_2 is assumed to be small and is ignored. The equation then becomes

$$D_{L_{CO}} = \dot{V}_{CO} / P_{A_{CO}}$$

Or, in words, the quantity of CO transferred from the alveolar gas to the capillary blood, or the $D_{L_{CO}}$, is equal to the volume of CO transferred per minute per millimeter of mercury of alveolar partial pressure of CO. The traditional units for $D_{L_{CO}}$ are millimeters CO at STPD (standard temperature, pressure, and dry) conditions/min/mm Hg; SI units are moles CO/min/kPa.[68]

As illustrated in Figure 24-20, the pathway for diffusion of CO and O_2 involves diffusion across the alveolar capillary membrane (consisting of the alveolar cell, the basement membrane, a potential interstitial space, and the capillary endothelium), across a thin layer of plasma, across a red blood cell membrane, and within the red blood cell until they bind with hemoglobin. Roughton and Forster[69] simplified this process into two stages: (1) diffusion of CO from the alveolus to the red cell interior, described as the membrane component (D_M), and (2) the rate of uptake of CO by binding with hemoglobin in the red cells per mm Hg CO tension (θ) and the blood volume of the pulmonary capillary bed (V_C). The basic equation for $D_{L_{CO}}$ is a conductance, flow divided by pressure change ($\dot{V}/\Delta P$). The reciprocal of conductance is resistance and resistances can be added in series. Roughton and Forster[69] proposed the following equation to describe the diffusion of CO in the lung:

$$1/D_{L_{CO}} = 1/D_M + 1/\theta V_C$$

The relative contribution of each component can be determined by measuring $D_{L_{CO}}$ with high concentrations of inspired O_2. With increasing partial pressure of O_2, CO competes with O_2 for hemoglobin binding, reducing the θV_C component. While this is conceptually important in determining the pathophysiologic mechanism for reduced $D_{L_{CO}}$ in various conditions, it has not been found to be clinically useful because of technical difficulties and poor reproducibility.[70]

Diffusing Capacity Test Performance

The single-breath technique is the most common method for measuring $D_{L_{CO}}$ and is the focus of this discussion. Its advantages are that it has been standardized by the ATS/ERS Task Force, there are well-defined reference values for healthy subjects, and the majority of clinical studies have used this method.[68] Diffusing capacity can be measured using other techniques including the steady state, rebreathing, intrabreath, and multiple inert gas methods. These are more technically demanding and are reviewed elsewhere.[71]

The single-breath $D_{L_{CO}}$ technique requires a subject to inhale a gas mixture containing a low concentration of CO and an inert gas, usually helium, methane, or neon. The inert gas is essentially insoluble and cannot cross the alveolar capillary membrane. Because the inhaled concentration of inert gas is known, the alveolar volume (VA) can be determined by measuring the exhaled concentration. The initial alveolar concentration of CO (PA_{CO}) can be determined by making the assumption that CO is diluted to the same extent as the inert gas. The advantage of this method is that it only requires knowing the concentrations of the inhaled CO and inert gas and the concentrations of the same gases in an alveolar sample. This method allows the measurement of VA as well as $D_{L_{CO}}$.

The measurement of the single-breath $D_{L_{CO}}$ measurement is more complex than spirometry. It requires a higher level of commitment and expertise for test performance, maintenance, and quality control. In addition, the instrument is considerably more expensive than a spirometer, often costing more than $30,000. For these reasons, $D_{L_{CO}}$ is not commonly performed in the outpatient office setting. The basic instrument consists of a source of test gas, a device for measuring inspired and expired volume, and gas analyzers. The test gas is usually a mixture of 0.3% CO, an inert gas (often either 0.3% methane, 10% helium, or 0.5% neon), 17% or 21% O_2, and the balance nitrogen. At altitudes above sea level, gas mixtures with a higher concentration of O_2 are often used to achieve an inspired O_2 partial pressure similar to that at sea level.[72,73] The gas analyzer can be a single-sample slow-responding analyzer or a continuous high-speed analyzer. The high-speed analyzers allow the washout volume and alveolar sample volume to be adjusted and appear to improve the accuracy and reproducibility of $D_{L_{CO}}$ measurements.[74]

Performance standards for $D_{L_{CO}}$ equipment and quality control measures are discussed in detail elsewhere.[68] The methods for determining instrument accuracy vary from instrument to instrument, and specific instructions provided by the manufacturer must be followed. Standard recommendations suggest that before each test, the gas-analyzer should be zeroed. Each day, volume accuracy should be tested with a 3-L syringe. In addition, the system should be tested weekly with a biologic control or a commercially available $D_{L_{CO}}$ simulator (Hans Rudolph, Inc., Kansas City, MO).

Standardizing test performance is important to minimize variability. The patient should be instructed not to smoke or exercise vigorously on the day of the test, and if clinically safe, supplemental oxygen should be discontinued 10 minutes prior to testing. The patient should inspire the test gas in less than 4 seconds. The inhaled volume should be at least 85% of the largest known VC. The patient then holds his or her breath for 10 (±2) seconds, maintaining near-atmospheric pressure during the breath-hold (performing neither a Valsalva nor a Müller maneuver). Breath-hold time is calculated using the Jones-Meade method (two thirds of the time for inspiration and continuing until halfway through the sample collection).[75] After the breath-hold, the patient is instructed to exhale smoothly without hesitation. Total exhalation time for clearing the washout volume and collecting the alveolar sample should not exceed 4 seconds. Measurement of $D_{L_{CO}}$ requires an adequate alveolar sample. The alveolar sample is the gas volume obtained after the anatomic and mechanical dead-space volumes are cleared or "washed out." It is the volume of gas used to analyze the CO and tracer gas concentrations.

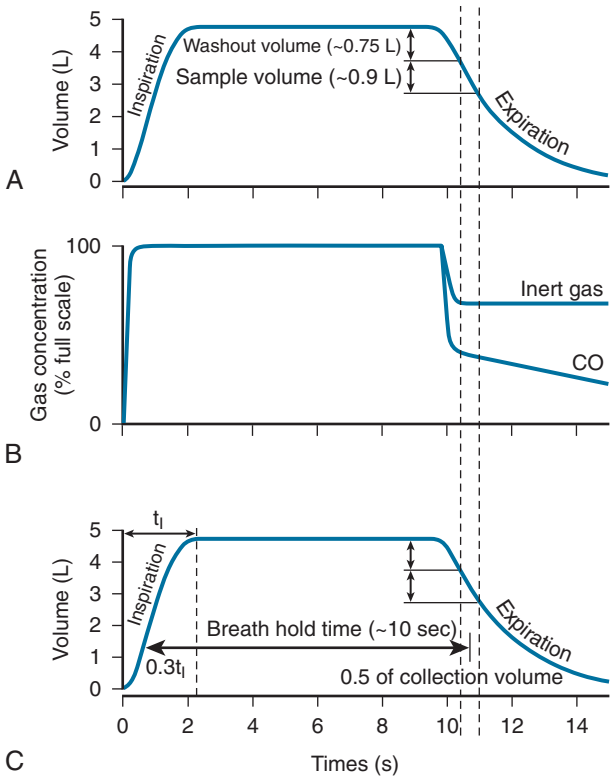


FIGURE 24-23 ■ Diffusing capacity tracings are represented including lung volumes (**A**) with washout and sample volumes; inert gas and carbon monoxide (CO) concentrations (**B**); and Jones-Meade method for calculating breath-hold time (**C**), which begins at 0.30 of inspiratory time and continues to 0.50 of sample collection.

The washout volume needed to clear the dead space confidently is 0.75 to 1.0 L.[74] In patients with a VC of less than 2.0 L, the washout volume may be reduced to 0.50 L. If all lung units emptied simultaneously, it would not matter where the alveolar sample was collected as long as the dead space was appropriately cleared. However, in patients with lung units that empty with different time constants, a suitable volume is needed to represent multiple lung units. The recommended alveolar sample gas volume collected for analysis is 0.50 to 1.00 L. In patients with a VC of less than 2.0 L, an alveolar sample gas volume of less than 0.50 L is acceptable if the dead-space volume has been adequately cleared. This can be done by visually adjusting the alveolar sample collection at a point where the inert gas concentration has started to plateau. It requires a system with a rapid gas analyzer. The single-breath DL_{CO} maneuver is illustrated in Figure 24-23.

The DL_{CO} maneuver should be repeated until there are at least two technically acceptable and repeatable tests or until five tests have been performed. The ATS/ERS Task Force suggests the average of at least two acceptable tests be reported. The tests should be repeatable within 3 mL CO (STPD)/min/mm Hg of each other or within 10% of the highest value.[68] Many laboratories require a higher degree of intrasession repeatability. See the section on "Interpreting Change in Lung Function," later. A DL_{CO} maneuver checklist is included as Table 24-4.

TABLE 24-4. DL_{CO} Maneuver Checklist

V_I is at least 85% of largest VC
Rapid inspiration – V_I inspired in <4.0 seconds
Breath-hold time of 10 ± 2 seconds; no evidence for air leak during breath-hold
Intrapulmonary pressure during breath-hold is near atmospheric; no Valsalva or Müller
Smooth unforced exhalation in < 4 seconds
Washout (dead-space) volume is 0.75 to 1.0 L (0.50 L is acceptable if VC < 2.0 L)
Sample (alveolar) volume is 0.50 to 1.0 L and collected on plateau of inert gas tracing (<0.50 L is acceptable if VC < 2.0 L)
A minimum of two acceptable tests within two units

DL_{CO}, diffusing capacity for carbon monoxide; VC, vital capacity; V_I, inhaled volume.
Modified from Macintyre N, Crapo RO, Viegi G, et al: Standardisation of the single-breath determination of carbon monoxide uptake in the lung. Eur Respir J 26:720–735, 2005.

Variability in Diffusing Capacity Measurements

Many technical and physiologic factors influence DL_{CO} variability. These sources of variability must be minimized to obtain clinically useful results. As noted previously, the ATS/ERS Task Force recommended that two acceptable tests be within 3 mL CO (STPD)/min/mm Hg of each other or within 10% of the highest value and laboratories should strive to meet a repeatability criteria of 2 mL CO (STPD)/min/mm Hg. Strict adherence to guideline recommendations will reduce variation. Interlaboratory variability for DL_{CO} can be very large and comparing results from different laboratories should be done cautiously.[76] If technical factors are tightly controlled, intra-individual variability can be within 5%. This is comparable with the accepted intra-individual variability for FVC and FEV_1.[77–79]

The most important technical sources of variation in the measurement of DL_{CO} include the inspired volume of test gas, rate of inspiration, breath-hold duration, method of calculating breath-hold time, the condition of the breath-hold, dead-space washout volume, and gas analysis. The measurement of inspired and expired volumes must be accurate. Inspiratory volume should be within 85% of another independent measure of VC. A submaximal inspiratory volume will reduce the DL_{CO}[80] as will prolonging inspiration beyond 4 seconds. Breath-hold time should be 10 ± 2 seconds using the Jones-Meade method described earlier. An underreported breath-hold time will result in an overestimation of DL_{CO}. During the breath-hold, intrapulmonary pressure should be near atmospheric[81]; a Valsalva maneuver (expiratory efforts against a closed airway) will decrease venous return and thoracic blood volume, resulting in a decrease in DL_{CO} of

up to 17%.[82] A Müller maneuver (inspiratory efforts against a closed airway) will have the opposite effect on venous return and thoracic blood volume and may increase DL_{CO} up to 6%.[82] If the dead-space volume is not cleared, the resulting contamination of the alveolar gas sample will result in an underestimation of DL_{CO}. Gas analyzer instability is a frequently unrecognized technical source of increased variability.

Physiologic sources of variability may be more difficult to control than technical sources of variability but must be considered when interpreting changes in an individual's DL_{CO}. The most important physiologic sources of variability in the measurement of DL_{CO} are listed in Table 24-5. Cross-sectional reference studies have shown that DL_{CO} is primarily influenced by age, height, sex, and race.[72,83] Diffusing capacity is lower with advancing age and shorter height. It is lower in women than in men for any given height and hemoglobin level. In African Americans, DL_{CO} is lower by an average of 1.96 mL CO (STPD)/min/mm Hg compared with whites for a given height.[84] Reduced hemoglobin (anemia) results in a reduction in DL_{CO} and an adjustment for hemoglobin concentration is important for interpretation.[68] An elevated carboxyhemoglobin level lowers DL_{CO} by reducing the available hemoglobin binding sites and by increasing the back-pressure of CO in alveolar capillary blood. In general, a 1% increase in carboxyhemoglobin reduces the measured DL_{CO} by 1%.[68] Because cigarette smoking is the most common reason for increased carboxyhemoglobin, patients should not smoke on the day of the test. Changes in inspired O_2 concentration (increased with the use of supplemental O_2, decreased at higher altitude) affect DL_{CO}. Diffusing capacity increases with lower inspired O_2 pressure (P_{O_2}), because O_2 and CO compete for the same binding sites on the hemoglobin molecule. The altitude effects on DL_{CO} can be corrected by either increasing the test gas O_2 concentration or by using an altitude adjustment equation.[73] For example, in Salt Lake City, UT (altitude 1400 m), 25% O_2 is commonly used in the DL_{CO} test gas mixtures to produce a PO_2 similar to that at sea level (150 mm Hg).[72]

TABLE 24-5. Physiologic Sources of Variability in Measurement of DL_{CO}

Age
Gender
Ethnicity
Hemoglobin concentration
Carboxyhemoglobin concentration
Altitude and inspired oxygen concentration
Circadian rhythm
Menstrual cycle
Smoking history
Exercise
Body position
Bronchodilation

Other physiologic conditions can affect DL_{CO}. Diffusing capacity decreases from morning to evening, a finding likely explained by small changes in hemoglobin during the course of the day.[85] Diffusing capacity can vary about 9% throughout a woman's menstrual cycle, with the highest level occurring just before menses and the lowest occurring 5 to 10 days after the onset of menses. This monthly variation is not explained by changes in hemoglobin concentration.[86] Current and former cigarette smokers have small reductions in DL_{CO} compared with never smokers that is proportional to the number of pack-years.[84] The effects of exercise on DL_{CO} are complex. During exercise, DL_{CO} increases and is associated with increased capillary blood flow.[87,88] Following intense exercise, DL_{CO} falls below preexercise levels, perhaps representing a redistribution of pulmonary capillary blood volume to peripheral muscles.[89] Diffusing capacity decreases as a patient moves from the supine to sitting to standing positions,[87] and it is recommended that patients be sitting at least 10 minutes prior to testing and remain sitting during testing. Bronchodilator administration increases DL_{CO} as much as 6% in patients with obstructive lung disease.[90] The use of bronchodilator drugs prior to testing should be noted in the interpretation.

Diffusing Capacity Interpretation

As with all PFTs, the first step in interpreting a DL_{CO} study is to review and comment on test quality and repeatability. The results from two acceptable tests should be within 3 mL CO (STPD)/min/mm Hg of each other and the mean value reported. Adjustments for hemoglobin and carboxyhemoglobin should be reported. The test is judged abnormal if it is below the lower 5th percentile of the reference population. The ATS/ERS Task Force criteria[14] for grading the severity of reductions in DL_{CO} are listed in Table 24-6.

A common practice is to adjust or "correct" DL_{CO} for lung volume by using DL_{CO}/VA. The clinical utility of this measurement is questionable primarily because the relationship between DL_{CO} and VA is not linear. In some circumstances, including postpneumonectomy patients and normal subjects with incomplete inhalation, the reduction in DL_{CO} is less than the concomitant decrease in VA and the DL_{CO}/VA will be increased. In patients with pulmonary vascular disease and in some patients with

TABLE 24-6. Degree of Severity of Decrease in DL_{CO}

Degree of Severity	DL_{CO} % Predicted
Mild	>60% and <LLN
Moderate	40%–60%
Severe	<40%

DL_{CO}, diffusing capacity for carbon dioxide; LLN, lower limits of normal.
Modified from Pellegrino R, Viegi G, Brusasco V, et al: Interpretative strategies for lung function tests. Eur Respir J 26:948–968, 2005.

hyperinflation, the reduction in D_{LCO} is greater than the concomitant change in VA, resulting in a decrease in D_{LCO}/VA.[80,91] When ventilation is maldistributed and VA is altered, it cannot be assumed that the diffusion properties of the maldistributed lung units are the same as the more normal lung units. In summary, the measurement D_{LCO}/VA is commonly misleading and cannot be relied upon to make clinical decisions.

The single-breath D_{LCO} test requires the measurement of VA. VA minus dead-space volume approximates TLC. However, VA is determined by the inert gas dilution method and measures only those areas of the lung that communicate with the mouth. Lung units that contain "trapped" gas are not measured. In patients with obstructive lung disease, VA results in a significant underestimation of TLC as compared with a TLC measured by body plethysmography.[92,93] Relying on VA to assess lung volumes may wrongly classify patients with obstructive lung disease as having a mixed obstructive/restrictive abnormality (see "Techniques for Measuring Lung Volumes," later).

Clinical Utility of Diffusing Capacity

The main objective of pulmonary function testing is to provide useful information to help answer the clinical question for which the test was ordered. Diffusing capacity interpretation is most clinically useful when it is performed in conjunction with measurements of spirometry and lung volumes. A low D_{LCO} with normal spirometry suggests the presence of pulmonary vascular disease, early interstitial lung disease, emphysema associated with a restrictive lung process, anemia (reduced hemoglobin), or elevated carboxyhemoglobin level. Pulmonary vascular diseases such as idiopathic pulmonary artery hypertension, pulmonary embolism, chronic thromboembolic pulmonary hypertension, and pulmonary vasculitis should be considered in a patient with a significant reduction in D_{LCO} and normal spirometry and lung volumes.[94,95] Early interstitial lung disease can cause mild to moderate reductions in D_{LCO} before the development of abnormal spirometry and lung volumes. A reduced D_{LCO} is often an early manifestation of interstitial lung disease, and a low D_{LCO} in a patient with dyspnea should lead to further evaluation such as a high-resolution CT scan of the chest.[96] Emphysema with a concomitant restrictive process such as idiopathic pulmonary fibrosis, amiodarone-induced interstitial lung disease, and hypersensitivity pneumonitis has been associated with a reduced D_{LCO} and normal spirometry and lung volumes.[97]

A low D_{LCO} in the setting of obstruction, defined as a FEV_1/FVC ratio below the LLN, suggests a diagnosis of emphysema. In emphysema, the magnitude of the reduction in D_{LCO} correlates with the severity of airway obstruction, exercise capacity, and the degree of emphysema scored pathologically or radiologically with CT scans.[98–100]

The clinical value of D_{LCO} in diagnosing COPD in an individual patient is limited because patients can have early emphysema while D_{LCO} is preserved and the chronic bronchitis phenotype is often associated with a normal D_{LCO}.[98] In addition, D_{LCO} has not been proved to be better than FEV_1 in predicting symptoms or mortality. In children and young adults, a low D_{LCO} in the presence of airway obstruction should raise the possibility of cystic fibrosis or alpha$_1$-antitrypsin deficiency. One of the uses of D_{LCO} measurement in patients with obstructive lung disease is distinguishing asthma from COPD: diffusing capacity is preserved and often elevated in asthma.[101,102] This is probably due to improved ventilation-perfusion relationships in the apices of the lungs.[103]

A low D_{LCO} in the setting of restriction, defined as an FVC or TLC below the LLN, is seen in various interstitial lung diseases, neuromuscular disease, chest wall abnormalities, and severe congestive heart failure. Most interstitial lung diseases, such as idiopathic pulmonary fibrosis,[104] nonspecific interstitial pneumonitis,[104] sarcoidosis,[105] cryptogenic organizing pneumonitis,[106] and drug-induced pulmonary toxicity (e.g., amiodarone, bleomycin, cyclophosphamide, methotrexate, and nitrofurantoin),[107,108] are associated with a disproportionately larger reduction in D_{LCO} than in lung volumes. Pulmonary processes associated with significant restriction that do not affect the lung parenchyma, such as neuromuscular disease, chest wall abnormalities, and pleural abnormalities, generally cause only a small reduction in D_{LCO}.

Diffusing capacity is valuable in monitoring disease progression in patients with idiopathic pulmonary fibrosis and sarcoidosis.[109,110] While commonly used to screen patients for amiodarone pulmonary toxicity, serial D_{LCO} measurement may not be effective due to poor specificity.[111]

Congestive heart failure has variable effects on both D_{LCO} and lung volumes depending on disease severity. In advanced heart failure, D_{LCO} and lung volumes are often reduced.[112] In early heart failure, lung volumes are preserved and D_{LCO} is also usually normal, although it may be mildly elevated because of increased pulmonary capillary blood volume.[113]

Most disease processes reduce D_{LCO}. A few disorders are associated with an elevated D_{LCO}, defined as a D_{LCO} greater than 140% of predicted value. The most common cause of an elevated D_{LCO} is obesity, probably due to increased pulmonary capillary blood volume.[114] Other disease processes associated with an elevated D_{LCO} include pulmonary hemorrhage syndromes (e.g., Wegener's granulomatosis, Goodpasture's syndrome, idiopathic pulmonary hemosiderosis), polycythemia, left-to-right intracardiac shunts, and asthma.[114–116]

LUNG VOLUMES

Lung volumes are useful for detecting and physiologically characterizing the nature and severity of lung diseases.[117] While spirometry measures inhaled and exhaled lung volumes, the term "lung volumes" is generally reserved for the measurements TLC, functional residual capacity (FRC), and RV.[117] A reduced TLC defines a restrictive pattern.[14] Four techniques are commonly used to measure lung volumes: body plethysmography, nitro-

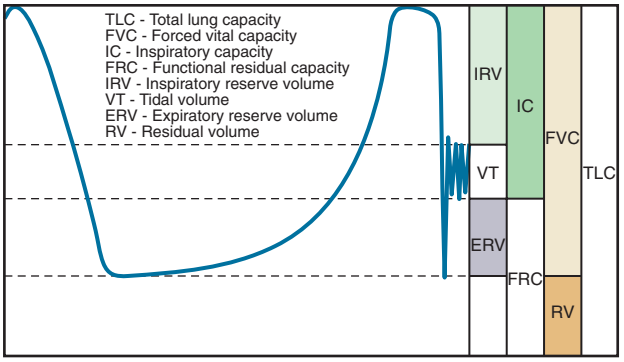


FIGURE 24-24 ■ The four basic lung volumes are: inspiratory reserve volume (IRV), tidal volume (VT), expiratory reserve volume (ERV), and residual volume (RV). The four basic lung capacities are: total lung capacity (TLC), forced vital capacity (FVC), inspiratory capacity (IC), and functional residual capacity (FRC).

gen washout, inert gas dilution, and radiographic imaging methods.

Definitions of "Volumes" and "Capacities"

TLC can be divided into several subdivisions grouped as "volumes" and "capacities." Two or more "volumes" make up a "capacity." The four basic volumes are tidal volume, inspiratory reserve volume, expiratory reserve volume, and residual volume. The four basic capacities are TLC, VC, inspiratory capacity, and FRC. Figure 24-24 illustrates the most commonly measured lung volumes and capacities.

TLC is the amount of air in the lungs at the end of a maximal inhalation. It is attained when the recoil forces of the lung and chest wall counterbalance the maximal inspiratory muscle force. RV is the amount of air in the lungs at the end of a maximal exhalation. It is determined by the balance of the forces tending to reduce lung volume (maximal expiratory muscle force and inward lung recoil) against the outward recoil of the chest wall. VC is the volume of air that can be exhaled after a maximal inhalation. TLC is, therefore, the sum of RV and VC. Inspiratory capacity is the amount of air that can be inhaled from the end of a tidal exhalation. FRC is the volume of air in the lungs at the end of a relaxed exhalation and is the critical measurement obtained with lung volume testing. Expiratory reserve volume is the volume of air that can be exhaled from the end of a tidal exhalation; inspiratory reserve volume is the volume of air that can be inhaled from the end of a tidal inspiration.

Indications for Lung Volume Testing

Lung volumes are indicated to confirm a restrictive pattern in a patient with a reduced VC. As noted in the "Spirometry" section, a reduced VC suggests restriction but has a poor positive predictive value for confirming a restrictive process.[29,30,32] That is, a normal VC excludes a restrictive process but a reduced VC accurately predicts restriction in only approximately 50% of patients.[14]

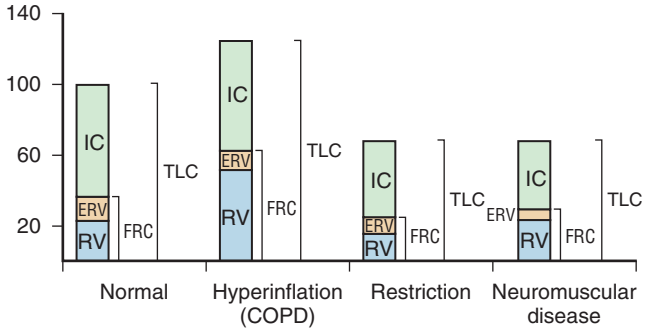


FIGURE 24-25 ■ Four basic lung volume patterns are illustrated: normal, hyperinflation, restriction, and neuromuscular disease.

Four basic lung volume patterns can be identified based on pathophysiology: normal, hyperinflation, restriction, and associated with neuromuscular disease. These are illustrated in Figure 24-25. Measurement of lung volumes is necessary to definitively characterize these patterns. In young healthy adults, RV constitutes about 25% of TLC and FRC about 40% of TLC. In hyperinflation, often present in patients with COPD, decreased elastic recoil results in an increased TLC, RV, and FRC.[53] Restrictive processes are characterized by reduced lung or chest wall compliance and appear as proportional reductions in TLC, RV, and FRC. Neuromuscular diseases also cause a restrictive pattern. The characteristic pattern of neuromuscular disease is a reduced TLC associated with an increased RV.[118,119]

Clinical Utility of Lung Volume Testing

While lung volume measurements are necessary to confirm a restrictive pattern and to characterize pathophysiologic processes,[120] their role in clinical management is unclear.[117] Lung volume measurements are often helpful in the evaluation of patients with a reduced VC. A restrictive pattern caused by decreased lung compliance is seen in patients with interstitial lung disease and lung volume measurements are suggested in the evaluation of patients with interstitial lung disease.[121,122] A restrictive pattern is also seen in patients with decreased chest wall compliance.[119] Decreased chest wall compliance is present in many different disease processes including kyphoscoliosis, ankylosing spondylitis, pleural effusions, fibrothorax, thoracoplasty, and morbid obesity.[119] Neuromuscular diseases also result in a restrictive pattern.[118] Expiratory muscle weakness causes an increase in RV, while inspiratory muscle weakness limits inspiration to TLC.[123]

All of these restrictive processes have characteristic lung volume patterns, and measuring lung volumes may help determine the specific pathophysiologic process. Lung volume measurement may be useful when more than one abnormality is suspected. For example, while obesity does cause restriction by reducing chest wall compliance, the TLC is not reduced below the LLN until the weight-to-height ratio (calculated as kg/cm) is greater than 1.0.[124] Obese patients whose weight-to-height ratio is less than 1.0 and who have a low TLC should be

evaluated for other causes of restriction, such as intrinsic lung disease.

Measurement of lung volumes can be clinically useful in patients with COPD. A reduced VC is common in patients with COPD. The causes of this reduction include submaximal effort or air trapping associated with small airway closure or noncommunicating bullae.[33] Measuring TLC with plethysmography in patients with COPD and a reduced VC can exclude a concomitant restrictive process.[33] Moderate to severe airway obstruction is associated with air trapping, which leads to hyperinflation. Hyperinflation causes dyspnea at rest that worsens with even mild exertion. Air trapping and overinflation of the lungs reduces inspiratory capacity and is a primary hallmark of hyperinflation. In patients with COPD, inspiratory capacity predicts symptoms, quality of life, and exercise capacity better than spirometry.[54-56] Hyperinflation, manifested by a reduced IC/TLC ratio is an independent risk factor for mortality in patients with COPD.[125] The IC/TLC ratio is a better predictor of mortality than FEV_1 and it predicts mortality independent of the multi-dimensional grading system that includes the body mass index, measure of airflow obstruction, dyspnea score and exercise capacity commonly referred to as the BODE index.[125] An IC/TLC threshold of 25% provides the best power to predict mortality; an IC/TLC ratio less than 25% was associated with an all-cause mortality of 70% in a cohort of COPD patients followed for a median of 34 months.[125]

Abnormal lung volume values may help focus the diagnostic evaluation of patients with respiratory symptoms. A restrictive pattern in a patient with dyspnea should lead to further diagnostic testing to evaluate for interstitial lung disease even if the chest radiograph is normal.[96]

The clinical utility of serial measurements of lung volumes in disease processes other than COPD has not been established. Lung volume measurements are not as useful as spirometry or diffusing capacity for following disease activity or response to therapy in idiopathic pulmonary fibrosis or sarcoidosis.[109,110]

Techniques for Measuring Lung Volumes

All techniques used to measure lung volumes have technical limitations. The laboratory-based tests require a two-step process. FRC is measured with body plethysmography, nitrogen washout, or inert gas dilution techniques. The inspiratory capacity obtained from spirometry is added to FRC to determine TLC. In healthy subjects and patients with interstitial lung disease, all three methods provide similar results. However, in patients with obstructive lung disease, nitrogen washout and gas dilution methods will significantly underestimate the lung volume obtained with body plethysmography.[117,126] In patients with severe obstructive lung disease, the difference in TLC can exceed 3 L. A comparison of lung volumes measured by the various techniques in healthy subjects, patients with interstitial lung disease, asthma, and mild and severe COPD are reported in Table 24-7.

Body plethysmography is considered the "gold standard" technique for measuring lung volumes. The test can be performed quickly, and repeated measurements can be obtained in a single session. It is, however, technically demanding and requires expensive, complex, and space-consuming instruments, and for these reasons, it is usually not performed in physician's offices. Measurement technique, equipment, and quality control are reviewed in detail elsewhere.[117,127] Plethysmography measures compressible gas volume in the chest based on Boyle's law (i.e., at a constant temperature, the product of gas volume and pressure is a constant). The patient sits in a sealed box connected to a mouthpiece and gently pants against a closed shutter at FRC. The panting frequency should not exceed 1 pant/sec. If the pants are too rapid, mouth pressure and alveolar pressure will not equilibrate and TLC will be overestimated. The thoracic gas volume is calculated from the slope of

TABLE 24-7. Total Lung Capacity by Five Methods in 100 Persons*

	Healthy Subjects	Interstitial Lung Disease	Asthma	Slight COPD	Severe COPD
N	23	17	25	21	14
Male/female	4.8	1.4	2.1	6.0	1.8
Age (yr)	29.1 ± 7.9	43.1 ± 17.5	21.1 ± 11.4	50.9 ± 10.4	53.0 ± 10.7
Height (inches)	69.5 ± 3.3	67.4 ± 4.1	67.7 ± 2.8	67.4 ± 3.2	65.4 ± 4.3
Average D_{LCO} mL/min/mm Hg	32.2 ± 5.31	17.4 ± 6.2	30.0 ± 6.6	19.2 ± 6.44	13.1 ± 5.65
TLC METHOD (DATA IN L)					
Plethysmographic	6.71 ± 1.20	4.90 ± 1.16	6.78 ± 1.23	6.52 ± 1.23	7.40 ± 1.45
7-Minute helium	6.61 ± 1.21	4.68 ± 1.06	5.99 ± 0.75	6.11 ± 1.35	5.91 ± 1.14
Single-breath helium	6.31 ± 1.06	4.40 ± 1.04	5.66 ± 0.99	5.54 ± 1.08	4.62 ± 1.23
Nitrogen single breath	6.25 ± 0.99	4.12 ± 0.96	5.38 ± 0.84	5.31 ± 1.03	4.31 ± 1.21
Radiographic	6.19 ± 1.23	4.89 ± 1.15	6.49 ± 1.04	6.22 ± 1.24	6.28 ± 1.44

*TLC measured by five methods (plethysmography, single breath and 7-minute helium dilution, nitrogen single breath and radiographic) in 100 persons.
D_{LCO}, diffusing capacity for carbon monoxide; TLC, total lung capacity.
From Ferris BG: Epidemiology standardization project (American Thoracic Society). Am Rev Respir Dis 118:1–120, 1978.

the pressure-volume curve obtained by the compression and decompression of the gas in the chest during the panting maneuver. A total of three to five loops should be recorded with similar slopes. The interpreting physician must examine the slopes that are determined automatically by computerized systems. The criteria for an adequate test are at least three plethysmographic FRC values that agree within 5%; the mean value is reported.[117]

Inert gas dilution techniques are another common technique used to measure lung volumes. These tests use the mass balance approach to calculate lung volumes. The patient inhales a known concentration and volume of an inert gas, usually helium, methane, or neon, and the gas is allowed to mix. Because the initial volume and concentration of the inert gas are known, determining the exhaled concentration of the inert gas allows the calculation of the volume present in the patient's lungs at the moment tracer gas breathing began. The major limitation of this method is that it measures only the gas volume in the lungs that directly communicates with the mouth. Unlike body plethysmography, which measures total thoracic gas volume, inert gas dilution methods can underestimate TLC in obstructed patients with "air trapping."[126,128–130] Testing technique, equipment, and quality control are discussed in detail elsewhere.[117]

Gas dilution methods can be performed with either a single- or a multiple-breath technique. The single-breath technique is usually performed in conjunction with diffusing capacity measurement (see "Diffusing Capacity" section). It requires inhalation to TLC and a 10-second breath-hold. After gas from the dead space is cleared, the exhaled gas is collected and alveolar volume measured. Alveolar volume minus dead-space volume approximates TLC.

The multiple-breath technique requires the patient to rebreathe the inert gas mixture (usually helium) at FRC until helium reaches equilibrium in the lungs, a process that takes less than 10 minutes in most patients. FRC is determined based on the stable concentration of helium. The multiple-breath technique requires minimal patient effort and coordination. Usually only a single measurement will be made because a waiting period of at least 15 minutes is required between tests in patients without airway obstruction and up to 1 hour in patients with airway obstruction. TLCs measured by the single-breath and multiple-breath techniques show good agreement in patients without airway obstruction, but the single-breath technique significantly underestimates the TLC obtained by the multiple-breath technique when the FEV_1/FVC ratio is less than 0.70.[92]

A third method for determining lung volumes is nitrogen washout. Nitrogen washout techniques also use a mass balance approach to estimate TLC and, as with the inert gas dilution techniques, the test measures only the lung gas volume that communicates directly with the mouth. Trapped gas is not measured and TLC is underestimated in patients with obstructive lung disease.[93,126] The testing method is described in detail elsewhere.[117] Nitrogen washout lung volumes can be obtained using either a single-breath or a multiple-breath technique. The single-breath technique requires the inhalation of 100% O_2 with measurement of the nitrogen concentration in the exhaled gas. The single-breath technique allows the determination of closing volume. This was thought to have potential as a sensitive test for early airway disease but has not been found to be clinically useful.[131] The single-breath technique significantly underestimates TLC compared with the multiple-breath technique. Most laboratories that use nitrogen washout rely on the multiple-breath technique to determine lung volumes.[132] In the multiple-breath nitrogen washout method, the patient breathes 100% O_2 at FRC with continuous collection and monitoring of the exhaled nitrogen gas. FRC is calculated based on the assumption that the mass of displaced nitrogen is equal to the mass of nitrogen in the lungs at the beginning of the test and that the initial concentration of nitrogen in the lungs was 80%. The multiple-breath nitrogen washout test requires minimal patient effort and coordination. It is very sensitive to leaks in the system. A prolonged waiting period is required before the test can be repeated in patients with airflow obstruction, making it difficult to perform more than one measurement in a test session.

TLC can also be calculated from a standard posteroanterior and lateral chest radiograph. The calculation can be done rapidly using a computerized algorithm and the result is comparable with those of plethysmography and gas dilution techniques in many clinical settings.[133–135] However, radiographic TLC does not correlate well with gas dilution techniques in patients with interstitial lung disease and is dependent on complete inhalation.[136] The technique is not widely used and obtaining a chest radiograph for the sole purpose of measuring TLC cannot be justified. However, the radiographic method can be quite useful to evaluate change in lung volumes over time, because prior chest radiographs are often available and can provide lung volume information from a patient's past.

REFERENCE VALUES FOR PULMONARY FUNCTION TESTS

Reference values play a role in pulmonary function testing that is as important as making high-quality measurements. Interpretation of lung function tests requires the selection of appropriate reference values and their limits. The patient's results are compared with the reference values to determine whether the patient's values are normal (within boundaries established for healthy subjects) or abnormal (outside the statistically defined limits of the nomal subject range).

Defining the Lower Limits of Normal

In pulmonary function testing, reference values are typically calculated from equations using test results from a reasonably large sample of healthy individuals. The reference ranges are set statistically, assuming gaussian distributions. This assumption is correct for most lung function measurements. The lower limit of the "normal" range is

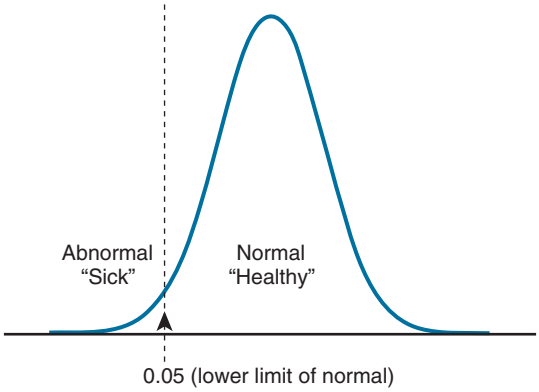


FIGURE 24-26 ■ In pulmonary function testing, the LLN is defined as the lower 5th percentile: Patients with values below the 5th percentile are reported as abnormal.

commonly defined as the lower 95% confidence interval or the lower 5th percentile. The practice of using 80% of the predicted mean value for the LLN can lead to interpretive errors, especially when age and height diverge from the average, and should be avoided.[28] As represented in Figure 24-26, patient values above the 5th percentile are labeled normal or "healthy" and those below are labeled abnormal. The terms "normal" and "abnormal" are problematic because they carry a connotation of health or disease. It is important to note that 5% of a healthy reference population is categorized as "abnormal." Using only an LLN is appropriate for spirometry because the clinical question being asked is whether the measured value is too low. For lung volumes and diffusing capacity, the clinical questions involve values that are both larger and smaller than the predicted value and both upper and lower limits of normal should be available.

Use of Reference Values in Interpretation

When the prior probability of disease is low (i.e., healthy individuals), increasing the number of tests will increase the likelihood of errors in interpretation. One study detected a false-positive rate of 24% when a full set (14 comparisons) of PFTs was applied to healthy individuals.[137] With results near the threshold, the clinician needs to be cautious with interpretation (Fig. 24-27). Clinical information and the prior probability of disease need to be considered to avoid errors near the lower or upper limit of normal.

Reference comparisons can be made using a representative sample of healthy subjects for which a reference range has been determined (reference equations) or, even better, by comparison with a patient's own prior measurement as illustrated in Figure 24-28. For an individual, the ideal reference comparison is a good-quality baseline test obtained when she or he is healthy. Such a reference allows the comparison to be switched from group to self.[138] As illustrated in Figure 24-29, most reference values have a distribution that is roughly ± 20%

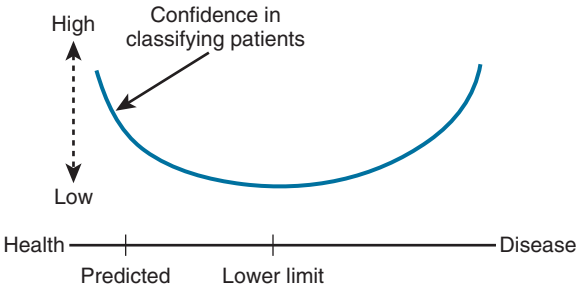


FIGURE 24-27 ■ Confidence in classifying patients as normal ("healthy") or abnormal ("diseased") increases the further the test deviates from the LLN.

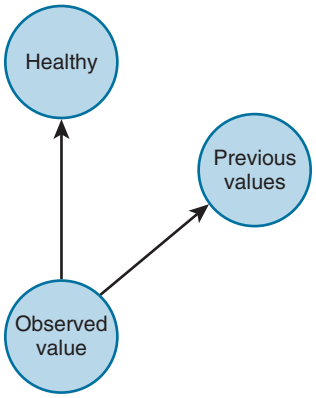


FIGURE 24-28 ■ The patient's test result (observed value) is ideally compared with a previous value obtained using similar technique or to a representative sample of healthy "normal" subjects.

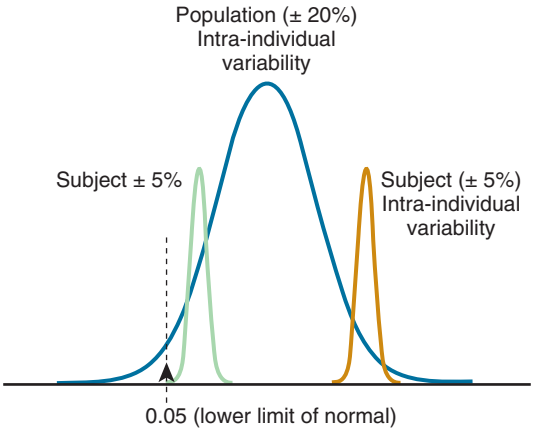


FIGURE 24-29 ■ It is preferable to compare the patient's result with a prior measurement, because the intra-individual variability is much less than the population variability.

(a 40% range) of predicted about a mean of 100%. A person who started at 120% of predicted would have to lose 33% of her or his lung function before the values fell off the "cliff of abnormality." In contrast, a person whose baseline lung function is near the LLN would be classified as abnormal with a trivial decrease in her or his lung function simply because the baseline numbers

are near the lower limit threshold of the normal distribution.[139] Once an individual's baseline has been established, intra-individual variability may be as little as ± 5% and decline is more easily detected. Therefore, if it is important to assess change over time or change with a response to an exposure or a therapy, baseline tests are critical. Although it is not practical to obtain baseline measurements for everyone, measurement of baseline values is reasonable for individuals at risk for respiratory illness or injury, including workers exposed to potential lung toxins and patients receiving treatments that may cause lung injury.

Criteria for Selecting Reference Values

Pulmonary function laboratories should select reference values based on the following principles:

1. The reference population must be biologically similar to the population of patients likely to be tested in the laboratory. Critical elements are gender, age, height, weight, and ethnic considerations.
2. Test quality in the reference population must be high. Instruments and procedures used to generate reference values should meet current standards.
3. The sample size in the reference study must be reasonably large because uncertainty in a comparison increases when the number of subjects in the reference value study is small.
4. Appropriate statistical limits of the normal range should be used. Fixed limits such as 80% of predicted should not be used unless they have been demonstrated to work on a study population that is appropriate for the individual being tested.
5. Reference equations should not be extrapolated beyond the reported ranges of the age and stature of the reference population. This is especially important when choosing reference values for children.[140]

A model for a study designed to create reference equations for spirometry is the NHANES III reported by Hankinson and colleagues.[25] Their reference values are based on a very large (7429 participants, ages 8-80) random sample of the United States that included three ethnic groups: whites, African Americans, and Mexican Americans. Spirometry was measured with high-quality instruments and procedures. Equations were created to predict "normal" values and lower limits of the normal range for an individual. An advantage of this study is the availability of race-/ethnic-specific reference equations. Race-/ethnic-specific equations are not available or as robust for lung volume measurements and diffusing capacity. Although adjustment factors have been reported, these are not as accurate as specific race/ethnic equations.[14] Limitations of the NHANES equations are the lack of information for Asian Americans and for children younger than 8 years of age. Reference equations for spirometry, lung volume measurements, and diffusing capacity for various populations are listed in the ATS/ERS Task Force publication.[14]

INTERPRETING CHANGE IN LUNG FUNCTION TESTS

In patients with lung disease, lung function measurements are often repeated over time to monitor disease activity or to assess response to therapy. Important clinical decisions are made based on changes in lung function. To determine whether a change in lung function is significant, the variability or reproducibility of the lung function test must be known. Sources of variability include (1) technical factors from either the instrument, the technician, or the subject; (2) biologic factors; and (3) disease-related changes.[141] It is essential to determine whether a change in lung function represents a change related to the disease or treatment (signal) rather than technical or biologic sources of intra-individual variability (noise). Lung function variability increases over time and is generally greater in subjects with disease than in normal subjects.

Within-Session Repeatability

Within-session test repeatability recommended by the ATS/ERS Task Force is listed in Table 24-8.[14,68,117] Our laboratory deviates from these recommendations only for DL_{CO}. Based on the results from two large studies that found that more than 91% of DL_{CO} tests had two results within 2.0 mL/min/mm Hg of each other. Our laboratory requires this level of reproducibility.[77,142]

Intersession Variability

Significant changes in PFTs when obtained weeks, months, and years apart have not been extensively studied in normal subjects or patients with underlying lung diseases. The information on variability over time comes from several sources and inconsistencies are present due to limited data, varied technical quality, and varied patient populations. Changes can be expressed as an absolute value or as a percentage change from an earlier measurement. Table 24-9 provides clinically significant changes over time in common PFTs for normal subjects and for patients with COPD. The limits provided in Table 24-9 roughly indicate the 90% to 95% confidence limits of the intersession variation of the tests.[78,142–144] Changes greater than those listed in Table

TABLE 24-8. Within-Session Repeatability Criteria per ATS/ERS Task Force

FVC	FEV_1	DL_{CO}	TLC_{PL}
150 mL (100 mL if FVC < 2 L)	150 mL (100 mL if FVC < 2 L)	3.0 mL CO/min/mm Hg	5%

ATS/ERS, American Thoracic Society/European Respiratory Society; DL_{CO}, diffusing capacity for carbon monoxide; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 second; TLC_{PL}, total lung capacity measured with plethysmography.

TABLE 24-9. Clinically Significant Changes in FEV_1, FVC, DL_{CO}, and TLC_{PL} over Time

	FVC	FEV_1	DL_{CO}	TLC_{PL}
Week to week				
Normal subjects	11%	12%	3 units	8%
COPD patients	20% or 400 mL	20% or 225 mL	4 units	↑
Year to year				
Normal subjects	15%	15%	10%	NA

COPD, chronic obstructive pulmonary disease; DL_{CO}, diffusing capacity for carbon monoxide; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; TLC_{PL}, total lung capacity measured with plethysmography.

24-9 over the specified time period are outside the expected variability of the test measurement and imply a clinically relevant change in pulmonary function.

Spirometry is more variable over time in patients with COPD than in normal subjects. In normal subjects, a change in FEV_1 over weeks to months greater than 12% is significant; for COPD patients, the threshold is a change of greater than 20%.[143] More recent data from the Lung Health Study and National Emphysema Treatment Trial reported that more than 90% of participants had an intersession (averaging 25–86 days) FEV_1 difference less than 225 mL.[144]

Data regarding significant changes in DL_{CO} are relatively weak. Variability in DL_{CO} in normal subjects for weeks to months involved 11 subjects. In well-performing instruments, a change in DL_{CO} over 24 weeks of greater than 3.0 mL/min/mm Hg was significant.[78] Approximately 40% of the variability was attributed to the instrument and the remainder to the subject. A change in DL_{CO} of greater than 10% was significant in eight normal subjects tested over 1 year with well-performing equipment.[145] In COPD patients tested over 1 week, a change in DL_{CO} of greater than 4.0 mL/min/mm Hg was significant.[79]

Data from the same laboratory with a well-maintained, constant instrument are likely to be associated with less variability over time. Observed changes over time are more likely to represent clinically significant changes rather than noise from technical factors. In the setting of a stable laboratory environment, a smaller change over time may be considered clinically important. Also, it is more likely that a significant change has occurred when more than two measurements are made over time.

TESTS OF RESPIRATORY MUSCLE STRENGTH

Measurements of respiratory muscle strength are important in the evaluation and management of patients with neuromuscular disease and selected patients with unexplained dyspnea. Respiratory muscle dysfunction is common in a variety of neuromuscular disorders. Identifying respiratory muscle weakness is clinically important. It predicts adverse clinical sequelae and may lead to interventions that improve outcomes.

A number of tests are available to assess respiratory muscle strength. These are usually used in conjunction with standard PFTs. Multiple tests are recommended to make a confident diagnosis of respiratory muscle weakness, because single tests of respiratory muscle strength tend to overdiagnose respiratory muscle weakness.[146] The advantages and disadvantages of the respiratory muscle function tests are listed in Table 24-10.

Spirometry

Spirometry with examination of the flow-volume loop should be performed on all patients with suspected respiratory muscle weakness. A reduced VC is a sensitive test for diagnosing moderate to severe respiratory muscle weakness, and serial testing is useful for monitoring disease progression.[147] Spirometry findings are not specific for respiratory muscle weakness and are less sensitive in mild disease than measures of maximum mouth pressures; respiratory muscle strength needs to decrease by approximately 50% before VC is significantly reduced.[123,147] Measurement of upright and supine VC is useful for diagnosing diaphragm weakness. In normal subjects, VC is less than 10% lower in the supine than in the upright position. A reduction of greater than 30% suggests severe diaphragm weakness.[147] The maximum flow-volume loop also exhibits characteristic changes with moderate to severe respiratory muscle weakness as illustrated in Figure 24-30. The contour of the expiratory limb is blunted with a decreased PEF and decreased slope of the ascending limb, abrupt cessation of flow occurs near RV, and pronounced flattening of the inspiratory limb is seen.[147,148] This pattern may be confused with extrathoracic UAO.

Maximal Inspiratory and Expiratory Pressures

The primary tests for assessing respiratory muscle strength in the laboratory are maximal inspiratory pressure (MIP) or P_{Imax} (also referred to as negative inspiratory force[99]) and maximal expiratory pressure (MEP) or P_{Emax}. P_{Imax} and P_{Emax} are obtained at the mouth with use of either a flanged mouthpiece or a tube mouthpiece that is connected to a mechanical pressure gauge. The system requires a small leak (1- to 2-mm hole) to prevent glottis closure and to reduce the use of buccal muscles.[147] The inspiratory or expiratory pressure should be maintained for at least 1.5 seconds and the maximum pressure sustained for 1 second recorded. The maneuver should be repeated at least five times with the maximum value of three maneuvers that vary by less than 20% reported.[147] Although the criteria permit variation of up to 20%, intrasession repeatability of less than 5% is achievable and preferable.[149] The lung volume at which the maneuver is performed is critically important. P_{Imax} is a measure of the diaphragm and other inspiratory muscles and is highest when obtained from residual volume. P_{Emax} reflects the strength of the expiratory muscles (primarily

TABLE 24-10. Tests of Respiratory Muscle Weakness: Advantages and Disadvantages

Test	Advantages	Disadvantages
VC	• Widely available • Easy to perform • Inexpensive • Reproducible • Supine and upright measurement sensitive for diaphragm weakness	• Poor specificity • Less sensitive for early weakness than P_{Imax} or P_{Emax} • Difficult to perform with bulbar dysfunction
P_{Imax}	• Widely used • Noninvasive • Can obtain at bedside • Reference values available • Predicts clinical consequences • Good negative predictive value	• Effort and technique dependent • Poor positive predictive value • Difficult to perform with bulbar dysfunction • Low values occur with lung hyperinflation
P_{Emax}	• Widely used • Noninvasive • Can obtain at bedside • Reference values available • Predicts clinical consequences	• Effort and technique dependent • Poor positive predictive value • Difficult to perform with bulbar dysfunction
SNIP	• Noninvasive • Can obtain at bedside • Easier than P_{Imax} or P_{Emax} with severe disease or bulbar dysfunction • Predicts outcomes in ALS	• Effort dependent • Provides no information about expiratory muscle strength • Unreliable if upper airway distortion/nasal obstruction
MVV	• None	• No advantage over VC • Poor specificity • Highly effort dependent • Uncomfortable to perform
Esophageal, gastric, transdiaphragmatic pressure measurements; phrenic nerve stimulation pressure measurements	• Best measures of respiratory muscle strength • Improves specificity compared with P_{Imax} or P_{Emax}	• Invasive • Difficult to perform • Performed only at specialty centers

ALS, amyotrophic lateral sclerosis; MVV, maximum voluntary ventilation; P_{Emax}, maximal expiratory pressure; P_{Imax}, maximal inspiratory pressure; SNIP, sniff nasal inspiratory pressure; VC, vital capacity.

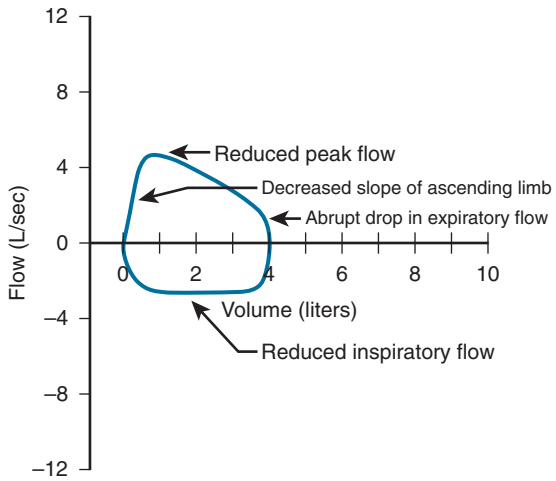


FIGURE 24-30 ■ The characteristic changes in the flow-volume curve with moderate or severe respiratory muscle weakness are illustrated. The slope of the ascending segment of the expiratory limb is reduced, peak expiratory flow is reduced, there is an abrupt drop in expiratory flow near the end of exhalation, and inspiratory flow is reduced.

abdominal muscles) and is highest when obtained at TLC. Because P_{Imax} and P_{Emax} are dependent on lung volumes, they are altered by diseases that affect lung volumes. For example, COPD results in an increase in RV due to hyperinflation, and P_{Imax} may be reduced in COPD because of the change in lung volume and not because of respiratory muscle weakness. Similarly, in restrictive disorders of the lung or chest wall such as kyphoscoliosis and pulmonary fibrosis, TLC is decreased, resulting in a reduced P_{Emax} even in the absence of muscle weakness. These tests are also dependent on maximum effort and proper technique. As in most PFTs, maximum effort and proper technique are critical. Patients with bulbar dysfunction may not be able to obtain a good seal on the mouthpiece, which will reduce maximum mouth pressures. Because of these factors, the positive predictive value of P_{Imax} and P_{Emax} is relatively low. Normal values exclude significant respiratory muscle weakness, but low values may reflect poor effort or technique or may be due to alterations in lung volumes rather than respiratory muscle dysfunction.

Definitive reference values for P_{IMAX} and P_{EMAX} have not been established. Differences in technique, mouth-

TABLE 24-11. Reference Values with Lower Limits of Normal for Maximal Inspiratory Pressure and Maximal Expiratory Pressure

Age (yr)	P_{Imax} (cm H_2O) (LLN)	P_{Emax} (cm H_2O) (LLN)
20–54	Male: 124 (80)	Male: 233 (149)
	Female: 87 (55)	Female: 152 (98)
55–59	Male: 103 (71)	Male: 218 (144)
	Female: 77 (51)	Female: 145 (105)
60–64	Male: 103 (71)	Male: 209 (135)
	Female: 73 (47)	Female: 140 (100)
65–85	Male: 83 (65)	Male: 174 (140)
	Female: 57 (45)	Female: 116 (90)

LLN, lower limits of normal; P_{Emax}, maximal expiratory pressure; P_{Imax}, maximal inspiratory pressure.

piece design and lung volumes at which the measurement was obtained contribute to differences in published reference ranges.[150–155] Our laboratory uses the references ranges determined by Black[150] for ages less than 65 years and Enright for ages greater than 65 years, because they are based on well designed trials and standardized technique[152] (Table 24-11).

Though not diagnostically definitive, measurement of P_{Imax} and P_{Emax} are clinically useful in many different neuromuscular diseases. Serial monitoring of pulmonary function in Guillain-Barré syndrome predicts the development of respiratory failure and need for mechanical ventilation.[156] Specifically, respiratory failure is likely when VC is less than 20 mL/kg; P_{Imax} is less negative than (–)30 cm H_2O; and P_{Emax} is less than 40 cm H_2O (the "20–30–40 rule").[156] P_{Imax} and P_{Emax} less than 30% of normal predicts respiratory failure in patients with other neuromuscular disorders.[157,158] A P_{Emax} less than 60 cm H_2O predicts an ineffective cough.[159]

Sniff Nasal Inspiratory Pressure

Sniff nasal inspiratory pressure (SNIP) is another noninvasive test for assessing inspiratory muscle strength. It is a technically simple test to perform. A plug, connected to a pressure transducer, is wedged into one nostril. The patient is instructed to make short, sharp, maximal inspiratory efforts (sniffs) through the unobstructed nostril.[147] Up to 10 maximal sniffs should be obtained until a consistent value is achieved. SNIP correlates well with sniff transdiaphragmatic pressures and LLN are available.[160–162] Significant inspiratory muscle weakness is unlikely if the values are greater than (–) 70 cm H_2O for males and (–) 60 cm H_2O for females.[147] The SNIP is easier to obtain than P_{Imax} or P_{Emax} in patients with bulbar dysfunction. It is useful in monitoring respiratory muscle strength in patients with amyotrophic lateral sclerosis (ALS)[160,163]; a value less than 40 cm H_2O is a sensitive test for predicting mortality.[160] Combining the SNIP measurement with P_{Imax} reduces the number of false-positive diagnoses of inspiratory muscle weakness by 19%.[146] The SNIP test is unreliable in patients with upper airway distortion and nasal congestion.

Maximum Voluntary Ventilation

The MVV is commonly used for assessing respiratory muscle strength. The test can be performed on most office spirometers. The patient is instructed to breathe as deep and fast as he or she can for 15 seconds. The respiratory rate should be 70 to 110 breaths/min with a tidal volume approximately 50% of VC. The maximal ventilation in 12 seconds is calculated and multiplied by 5. If MVV divided by $FEV_1 \times 41$ is less than 0.80, the test is abnormal and suggests neuromuscular weakness or poor effort.[164] MVV was once touted as a specific test for respiratory muscle weakness. However, it is highly effort dependent and is influenced by factors other than respiratory muscle function (these include airway resistance and respiratory system compliance).[123] In those patients who do have respiratory muscle weakness, MVV is reduced in proportion to VC. Because it is a difficult and strenuous test to perform and adds little to more simple tests such as VC, it is no longer recommended in the evaluation and management of patients with respiratory muscle weakness.[147]

Invasive Tests for Measuring Respiratory Muscle Strength

Several invasive tests are available to more precisely determine the presence of respiratory muscle weakness. These tests overcome the inherent problems associated with measuring mouth or nasal pressures by directly measuring esophageal or gastric pressures with a balloon catheter. Pressures can be measured with the patient sniffing or coughing or by electrically stimulating the phrenic nerve.[146,162,165] Measuring sniff esophageal or sniff transdiaphragmatic pressures reduces the number of patients diagnosed with inspiratory muscle weakness by approximately 30% to 40% compared with P_{Imax} alone.[146,162] Measuring cough gastric pressure reduces the number of patients diagnosed with expiratory muscle weakness by approximately 40% compared with P_{Emax} alone.[165] Measuring twitch transdiaphragmatic or twitch gastric pressure by electrically stimulating the phrenic nerve further improves diagnostic accuracy.[146] Although these are the gold standard for diagnosing respiratory muscle weakness, the tests are invasive and difficult to perform. They are only performed in specialized laboratories and are not widely used clinically.

BRONCHIAL PROVOCATION TESTS

Bronchial provocation (bronchoprovocation) tests are performed to assess bronchial hyperresponsiveness (BHR). They involve the administration of a stimulus that causes airway narrowing in susceptible patients. Bronchoprovocation tests are primarily used to confirm a diagnosis of asthma but are most clinically useful when the diagnosis is not clear-cut. Asthma is a chronic

disorder of the airways characterized by variable and recurring symptoms, airflow obstruction, BHR, and underlying inflammation.[39] The diagnosis of asthma is most often made with a history of intermittent respiratory symptoms in combination with variable airflow obstruction. While BHR is a key feature of asthma, bronchoprovocation tests are not often necessary to establish the diagnosis.

Indications

Indications for bronchoprovocation include

1. Establishing a diagnosis of asthma when atypical features are present: Asthma symptoms with normal spirometry, a presumptive diagnosis of asthma that does not improve with asthma therapy, or nonspecific asthma symptoms such as persistent cough are common reasons to obtain the test.[166]
2. Evaluating the possibility of occupational asthma: Bronchoprovocation testing is generally a sensitive but not specific test for diagnosing occupational asthma.[167,168]
3. Excluding a diagnosis of asthma in patients for whom an erroneous diagnosis has significant social impact (military recruits, divers, firefighters, and other high-risk occupations).[169,170]
4. Monitoring asthma therapy: Symptoms and lung function may normalize despite ongoing airway inflammation; BHR correlates well with airway inflammation, and adjusting therapy based on BHR may improve outcomes.[171,172]
5. Identifying specific asthma triggers. It is rarely necessary to perform specific bronchial challenge testing with the suspected offending agent, although it may be performed for research or legal purposes.
6. Objectively assessing asthma severity.[173]

Contraindications

Contraindications to bronchoprovocation testing are listed in Table 24-12. Bronchoprovocation can elicit severe bronchoconstriction in susceptible individuals. In patients with severely reduced lung function at baseline, worsening airway obstruction can be dangerous. An FEV_1 less than 50% of predicted (or <1.0 L) is an absolute contraindication and a FEV_1 less than 60% to 70% of predicted (or <1.5 L) is a relative contraindication to test performance.[166,173] Because of the potential to precipitate severe airway obstruction, trained personnel and medications to treat bronchospasm (albuterol and ipratropium) should be immediately available.

A relative contraindication for performing bronchial challenge tests is the failure of patients to withhold medications that may affect the test result, causing a false-negative study. Medications affecting the test should be held for an appropriate period of time determined by the drugs' duration of effect.[166] Short-acting β-agonists (albuterol) should be held for 8 hours; medium-acting bronchodilators (ipratropium) should be held for 24 hours, and long-acting bronchodilators (salmeterol, formoterol, and tiotropium) should be held for 48 hours. Theophylline preparations should be held for 12 to 48 hours depending on the duration of effect. Leukotriene modifiers should be held for 24 hours. Antihistamines have a variable effect of BHR and should be held for 24 to 72 hours depending on their duration of effect. Coffee, tea, cola drinks, and chocolate have small effects on BHR and should be withheld on the day of the study.[174]

TABLE 24-12. Contraindications for Bronchial Provocation Testing

ABSOLUTE
Severe airflow limitation (FEV_1 < 50% predicted or <1.0 L)
Acute coronary syndrome or stroke within 3 months
Severe hypertension (systolic BP > 200 mm Hg or diastolic BP > 100 mm Hg)
Cerebral or aortic aneurysm
RELATIVE
Moderate airflow limitation (FEV_1 < 60% predicted or <1.5 L)
Inability to perform acceptable and repeatable spirometry
Pregnancy*
Nursing mothers*
Current use of cholinesterase inhibitor medication for myasthenia gravis*
Significant hypoxemia (Pa_{O_2} < 60)
Recent upper or lower respiratory tract infection (within 6 wk)
Failure to withhold medication that may affect test results
Vigorous exercise on day of test

*Relative contraindications for methacholine administration.
BP, blood pressure; FEV_1, forced expiratory volume in 1 second; Pa_{O_2}, arterial oxygen pressure.
Modified from Crapo RO, Casaburi R, Coates AL, et al: Guidelines for methacholine and exercise challenge testing—1999. This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999. Am J Respir Crit Care Med 161:309–329, 2000.

Categories of Bronchoprovocation Tests

There are three broad categories of bronchoprovocation tests. Bronchial hyperreactivity can be elicited using specific airway irritants, "direct" stimuli using nonspecific pharmacologic agents (methacholine and histamine), and "indirect" stimuli (exercise, eucapnic voluntary hyperventilation, cold air hyperventilation, hypertonic saline, mannitol, and adenosine monophosphate [AMP]). The direct airway challenges cause airway narrowing via a direct effect on airway smooth muscle whereas indirect airway challenges cause airflow obstruction by acting on airway inflammatory and neuronal cells, which release mediators or cytokines that provoke bronchoconstriction.[173]

Specific inhalation challenge tests with substances found in the workplace are considered the gold standard for confirming or diagnosing occupational asthma.[167,175] However, a negative test may not definitively exclude the diagnosis of occupational asthma if the wrong agent or too low a concentration is used. Moreover, these tests require specialized equipment and have the potential to trigger severe life-threatening asthmatic reactions. They should be performed only at specialized centers and are not widely available.

Methacholine Inhalation Challenge

Methacholine inhalation challenge testing is the most widely used method to assess BHR. Methacholine acts by directly stimulating specific receptors on bronchial smooth muscle, causing bronchoconstriction and airway narrowing. Histamine is an alternative direct bronchial smooth muscle stimulant that gives similar results but is not commonly used because it is not U.S. Food and Drug Administration (FDA) approved and causes more side effects, including headache, hoarseness, and flushing.[166] Methacholine inhalation challenge is a sensitive test (sensitivity 85%-90%) for diagnosing asthma, including occupational asthma, cough variant asthma, and exercise-induced bronchoconstriction.[166,167,176–178] The sensitivity of the test is probably even greater than reported because the gold standard for asthma diagnosis in most studies is clinical improvement with specific asthma therapy. The problem with using response to therapy as the definitive test for diagnosing asthma is that eosinophilic bronchitis is similar to asthma in clinical presentation and responds favorably to inhaled corticosteroids but is not associated with variable airflow obstruction or BHR.[179,180] It is likely that some of the "false-negative" methacholine tests represent eosinophilic bronchitis. The specificity of methacholine testing is relatively poor, especially in general population studies.[181] Allergic rhinitis, COPD, patients who smoke, cystic fibrosis, bronchiectasis, bronchiolitis, and recent respiratory tract infections can all result in false-positive tests.[166,173]

Standardized protocols for methacholine testing are available.[166] The test consists of performing spirometry at baseline and then after each dose of nebulized methacholine. An initial methacholine concentration of 0.031 mg/mL or 0.0625 mg/mL is used and subsequent doses are increased by two- to fourfold until the FEV_1 falls by 20% from the baseline value or a concentration of 16 mg/mL is reached. If the FEV_1 falls by 20% from the baseline value, bronchodilator (albuterol 2 puffs) should be administered and the FEV_1 repeated in 10 minutes. The technician should record the patient's symptoms during the test. The reproduction of the symptoms that prompted the study is especially important (e.g., cough, dyspnea) as this suggests the symptoms are due to asthma. Methacholine can be administered using the 2-minute tidal-breathing method or the five-breath dosimeter protocol.[166] The 2-minute tidal breathing method appears to be more sensitive.[182]

Change in FEV_1 is the primary outcome measure for methacholine challenge testing. Spirometry must be acceptable and reproducible for the test to be meaningful. Maximal inspiratory maneuvers need to be performed if vocal cord dysfunction is being considered. If the patient cannot perform spirometry adequately, body plethysmography can be used to determine specific airway conductance. Plethysmography is more complicated than spirometry and does not improve test accuracy.[166] If plethysmography is used, the outcome measurement is specific airway conductance, and a reduction of 35% to 40% defines a positive result.

The provocative concentration that results in a 20% reduction in FEV_1 (PC_{20}) is determined by interpolation.[166] The categorization of BHR based on PC_{20} is listed in Table 24-13. The results are most accurately interpreted if clinical information is available. When the pretest probability of asthma is between 30% and 70%, a PC_{20} less than 1.0 mg/dL strongly suggests asthma. Conversely, a PC_{20} greater than 16 mg/dL suggests the patient does not have asthma and alternative diagnoses need to be considered. Results in the borderline area (between 4.0 and 16 mg/mL) require clinical information for meaningful interpretation.[183] Many laboratories use a threshold of 8 mg/mL for diagnosing asthma when the clinical index of suspicion is moderate. However, the positive predictive value of a PC_{20} less than 8 mg/dL was less than 50% when histamine challenge was performed in a sample of the general population.[181] Direct bronchoprovocation studies are highly sensitive when current asthma symptoms are present but are not specific.

TABLE 24-13. Categorization of Bronchial Responsiveness for Methacholine Inhalation Challenge

PC_{20} (mg/mL)	Interpretation
>16	Normal BHR
4.0–16	Borderline BHR
1.0–4.0	Mild BHR (positive test)
<1.0	Moderate to severe BHR

BHR, bronchial hyperresponsiveness; FEV_1, forced expiratory volume in 1 second; PC_{20}, provocative concentration that results in a 20% reduction in FEV_1.

Modified from Crapo RO, Casaburi R, Coates AL, et al: Guidelines for methacholine and exercise challenge testing—1999. This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999. Am J Respir Crit Care Med 161:309–329, 2000.

Indirect Bronchoprovocation Tests

Bronchoprovocation testing can be performed using indirect challenges that act by stimulating inflammatory cells and sensory nerves to release mediators that result in bronchial smooth muscle contraction and airway narrowing.[171,173] Indirect challenges include exercise, eucapnic voluntary hyperventilation (EVH), cold air hyperventilation, hypertonic saline, mannitol, and AMP. Indirect challenges may be less sensitive than direct challenges for the diagnosis of asthma but are more specific.[173,184–186] Some asthmatics, especially those with mild BHR, respond to direct challenges but not indirect challenges.[173] Indirect challenges are better tests for assessing airway inflammation and determining response to an inhaled corticosteroid than methacholine testing.[171,173,186,187] In asthmatics, symptoms and lung function improve rapidly with inhaled corticosteroid therapy despite ongoing airway inflammation. An improvement in BHR to indirect stimuli correlates well with airway inflammation and may be a useful target for titrating the dose of inhaled corticosteroid.[171] While BHR to direct stimuli also improves with inhaled corticosteroid use, it is not as sensitive a marker of airway inflammation, and BHR persists even after there has been significant improvement in airway inflammation.[188]

Of the indirect methods, standard exercise tests are less useful for diagnosing asthma. Exercise testing is most commonly performed in the evaluation of exercise-induced bronchospasm. In this setting, it is less sensitive than other indirect challenge tests and direct challenge tests.[178,189–192] The lack of sensitivity is likely due to the inability of some patients to achieve adequate exercise levels due to deconditioning, musculoskeletal limitations, or submaximal effort. Exercise testing is highly specific in differentiating asthma from normal.[173]

If exercise is chosen as the provoking agent, testing can be performed in the laboratory, using a treadmill or bicycle ergometer, or performing specific exercise tests in the field. Whichever method is used, the patient should exercise for a total duration of 6 to 8 minutes with 4 to 6 minutes of exercise at near-maximum levels.[166] The minute ventilation should achieve 50% to 60% of MVV and the heart rate should reach 90% of predicted maximum.[173] Sensitivity improves if dry air, rather than ambient air, is inhaled.[193] FEV_1 is the primary outcome variable and it should be obtained 5, 10, 15, 20, and 30 minutes postexercise. A reduction in FEV_1 of 10% compared with baseline is considered a positive test.[166]

EVH is a useful test for diagnosing asthma.[184,194] It is the most sensitive test for diagnosing exercise-induced bronchospasm.[178,189–191] The test is performed by having the patient breathe deep and fast a gas mixture of 5% CO_2 and the balance room air for 6 to 8 minutes. A target minute ventilation is set at $30 \times FEV_1$.[195] Spirometry is measured immediately, 5, 10, and 20 minutes after the hyperventilation. A positive test is defined as a 10% reduction in FEV_1.

Hypertonic saline and mannitol are indirect challenge tests that cause an increase in airway osmolarity, resulting in mediator release and bronchoconstriction.[173,185] Hypertonic saline challenge tests involve the nebulization of 4.5% saline. Mannitol capsules are inhaled using a dry powder inhaler that has recently been FDA approved for bronchoprovocation testing. Spirometry is performed serially after inhalation of these agents at 0, 5, 10, and 20 minutes, and a 10% reduction in FEV_1 compared with baseline is considered a positive study.[173] Mannitol may be more sensitive than the other indirect challenges for detecting mild BHR.[196] Inhalation of hypertonic saline or mannitol is a sensitive stimuli for provoking exercise-induced bronchospasm.[197,198] Mannitol is a more clinically useful test than is histamine for determining improvement with inhaled corticosteroids.[185]

AMP is a purine nucleotide that acts as an indirect bronchoprovocation agent. Airway response to adenosine appears to be a sensitive marker of mast cell priming; atopic asthmatics are more responsive to AMP than to methacholine.[173] There are limited data comparing AMP with other indirect agents and with methacholine. However, AMP appears to be more specific than methacholine for distinguishing pediatric asthma from other obstructive diseases such as bronchiectasis and bronchiolitis obliterans. It may also be useful in separating nonsmoking adults with COPD from those with asthma. Methacholine is often positive in both groups whereas AMP is more often positive only in the patients with asthma.[199] AMP is administered with a nebulizer using either the five-breath dosimeter or 2-minute tidal breathing technique. Similar to methacholine challenge testing described previously, the concentration of inhaled AMP is gradually increased, with measurement of FEV_1 after each dose. A 20% reduction in FEV_1 is considered a positive test. AMP is not FDA approved for bronchoprovocation.

KEY POINTS

- Pulmonary function testing plays an important role in the diagnosis and management of patients with respiratory disease. The major types of PFTs are spirometry, diffusing capacity, lung volume, respiratory muscle strength, and bronchoprovocation tests.
- Spirometry is the most commonly performed and clinically useful PFT. FEV_1 and FVC are the primary measurements obtained during spirometry and a reduced FEV_1/FVC ratio is necessary to diagnose airflow obstruction.
- DL_{CO} provides a quantitative measure of gas transfer in the lungs and is an important test in managing patients with interstitial lung disease.
- Lung volume testing allows the measurement of TLC, which is required to confirm the presence of a restrictive pattern.
- Pulmonary function testing interpretation requires examination of the tracings to determine acceptability and repeatability. Meaningful interpretation also requires comparison with a patient's prior result or an appropriate reference value.
- Bronchial provocation testing is clinically useful in confirming a diagnosis of asthma when atypical features are present.
- Measurement of P_{Imax} and P_{Emax} are sensitive but not specific tests for detecting respiratory muscle weakness as low values may be due to poor technique or effort and alterations in lung volumes.

References

1. Lin K, Watkins B, Johnson T, et al: Screening for chronic obstructive pulmonary disease using spirometry: Summary of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med 148:535–543, 2008.
2. Ferguson GT, Enright PL, Buist AS, et al: Office spirometry for lung health assessment in adults: A consensus statement from the National Lung Health Education Program. Chest 117:1146–1161, 2000.
3. Wilt TJ, Niewoehner D, Kane RL, et al: Spirometry as a motivational tool to improve smoking cessation rates: A systematic review of the literature. Nicotine Tob Res 9:21–32, 2007.
4. Parkes G, Greenhalgh T, Griffin M, et al: Effect on smoking quit rate of telling patients their lung age: The Step2quit randomised controlled trial. BMJ 336:598–600, 2008.
5. Colice GL, Shafazand S, Griffin JP, et al: Physiologic evaluation of the patient with lung cancer being considered for resectional surgery: ACCP evidenced-based clinical practice guidelines (2nd ed). Chest 132:161S–177S, 2007.
6. Zibrak JD, O'Donnell CR, Marton K: Indications for pulmonary function testing. Ann Intern Med 112:763–771, 1990.
7. Smetana GW, Lawrence VA, Cornell JE: Preoperative pulmonary risk stratification for noncardiothoracic surgery: Systematic review for the American College of Physicians. Ann Intern Med 144:581–595, 2006.
8. Qaseem A, Snow V, Fitterman N, et al: Risk assessment for and strategies to reduce perioperative pulmonary complications for patients undergoing noncardiothoracic surgery: A guideline from the American College of Physicians. Ann Intern Med 144:575–580, 2006.

8a. Lange NE, Mulholland M, Kreider ME: Spirometry: Don't blow it. Chest 136:608–614, 2009.

9. McFadden ER Jr, Linden DA: A reduction in maximum mid-expiratory flow rate. A spirographic manifestation of small airway disease. Am J Med 52:725–737, 1972.
10. Brusasco V, Crapo R, Viegi G: Coming together: The ATS/ERS consensus on clinical pulmonary function testing. Eur Respir J 26:1–2, 2005.
11. Hegewald MJ, Lefor MJ, Jensen RL, et al: Peak expiratory flow is not a quality indicator for spirometry: Peak expiratory flow variability and FEV_1 are poorly correlated in an elderly population. Chest 131:1494–1499, 2007.
12. Aggarwal AN, Gupta D, Jindal SK: The relationship between FEV_1 and peak expiratory flow in patients with airways obstruction is poor. Chest 130:1454–1461, 2006.
13. Miller MR, Hankinson J, Brusasco V, et al: Standardisation of spirometry. Eur Respir J 26:319–338, 2005.
14. Pellegrino R, Viegi G, Brusasco V, et al: Interpretative strategies for lung function tests. Eur Respir J 26:948–968, 2005
15. Nathell L, Nathell M, Malmberg P, et al: COPD diagnosis related to different guidelines and spirometry techniques. Respir Res 8:89, 2007.
16. Vandevoorde J, Verbanck S, Schuermans D, et al: FEV_1/FEV_6 and FEV_6 as an alternative for FEV_1/FVC and FVC in the spirometric detection of airway obstruction and restriction. Chest 127:1560–1564, 2005.
17. Swanney MP, Beckert LE, Frampton CM, et al: Validity of the American Thoracic Society and other spirometric algorithms using FVC and forced expiratory volume at 6 s for predicting a reduced total lung capacity. Chest 126:1861–1866, 2004.
18. Townsend MC, Du Chene AG, Fallat RJ: The effects of underrecorded forced expirations on spirometric lung function indexes. Am Rev Respir Dis 126:734–737, 1982.
19. Krowka MJ, Enright PL, Rodarte JR, et al: Effect of effort on measurement of forced expiratory volume in one second. Am Rev Respir Dis 136:829–833, 1987.
20. Ioachimescu OC, Venkateshiah SB, Kavuru MS, et al: Estimating FVC from FEV_2 and FEV_3: Assessment of a surrogate spirometric parameter. Chest 128:1274–1281, 2005.
21. Enright PL, Beck KC, Sherrill DL: Repeatability of spirometry in 18,000 adult patients. Am J Respir Crit Care Med 169:235–238, 2004.
22. Ferris BG Jr, Speizer FE, Bishop Y, et al: Spirometry for an epidemiologic study: Deriving optimum summary statistics for each subject. Bull Eur Physiopathol Respir 14:145–166, 1978.
23. Kanner RE, Schenker MB, Munoz A, et al: Spirometry in children. Methodology for obtaining optimal results for clinical and epidemiologic studies. Am Rev Respir Dis 127:720–724, 1983.
24. Rabe KF, Beghe B, Luppi F, et al: Update in chronic obstructive pulmonary disease 2006. Am J Respir Crit Care Med 175:1222–1232, 2007.
25. Hankinson JL, Odencrantz JR, Fedan KB: Spirometric reference values from a sample of the general U.S. population. Am J Respir Crit Care Med 159:179–187, 1999.
26. Hansen JE, Sun XG, Wasserman K: Spirometric criteria for airway obstruction: Use percentage of FEV_1/FVC ratio below the fifth percentile, not < 70%. Chest 131:349–355, 2007.
27. Roberts SD, Farber MO, Knox KS, et al: FEV_1/FVC ratio of 70% misclassifies patients with obstruction at the extremes of age. Chest 130:200–206, 2006.
28. American Thoracic Society: Lung function testing: Selection of reference values and interpretative strategies. Am Rev Respir Dis 144:1202–1218, 1991.
29. Glady CA, Aaron SD, Lunau M, et al: A spirometry-based algorithm to direct lung function testing in the pulmonary function laboratory. Chest 123:1939–1946, 2003.
30. Aaron SD, Dales RE, Cardinal P: How accurate is spirometry at predicting restrictive pulmonary impairment? Chest 115:869–873, 1999.
31. Venkateshiah SB, Ioachimescu OC, McCarthy K, et al: The utility of spirometry in diagnosing pulmonary restriction. Lung 186:19–25, 2008.
32. Vandevoorde J, Verbanck S, Schuermans D, et al: Forced vital capacity and forced expiratory volume in six seconds as predictors of reduced total lung capacity. Eur Respir J 31:391–395, 2008.

32a. Hyatt RE, Cowl CT, Bjoraker JA, et al: Conditions associated with an abnormal nonspecific pattern of pulmonary function tests. Chest 135:419–424, 2009.

33. Dykstra BJ, Scanlon PD, Kester MM, et al: Lung volumes in 4,774 patients with obstructive lung disease. Chest 115:68–74, 1999.
34. Swanney MP, Jensen RL, Crichton DA, et al: FEV(6) is an acceptable surrogate for FVC in the spirometric diagnosis of airway obstruction and restriction. Am J Respir Crit Care Med 162:917–919, 2000.
35. Akpinar-Elci M, Fedan KB, Enright PL: FEV_6 as a surrogate for FVC in detecting airways obstruction and restriction in the workplace. Eur Respir J 27:374–377, 2006.

35a. Jing J, Huang T, Cui W, et al: Should FEV_1/FEV_6 replace FEV_1/FEV ratio to detect airway obstruction? A metaanalysis. Chest 135:991–998, 2009.

36. Jensen RL, Crapo RO, Enright P: A statistical rationale for the use of forced expired volume in 6 s. Chest 130:1650–1656, 2006.
37. Donohue JF: Therapeutic responses in asthma and COPD. Bronchodilators. Chest 126:125S–137S, 2004 [discussion 159S–161S].
38. Dales RE, Spitzer WO, Tousignant P, et al: Clinical interpretation of airway response to a bronchodilator. Epidemiologic considerations. Am Rev Respir Dis 138:317–320, 1988,
39. Expert Panel Report 3 (EPR-3): Guidelines for the diagnosis and management of asthma—Summary report 2007. J Allergy Clin Immunol 120:S94–S138, 2007.
40. Buist AS: Similarities and differences between asthma and chronic obstructive pulmonary disease: Treatment and early outcomes. Eur Respir J Suppl 39:30s–35s, 2003.
41. Mahler DA, Wire P, Horstman D, et al: Effectiveness of fluticasone propionate and salmeterol combination delivered via the Diskus device in the treatment of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 166:1084–1091, 2002.
42. Rennard SI, Anderson W, ZuWallack R, et al: Use of a long-acting inhaled $beta_2$-adrenergic agonist, salmeterol xinafoate, in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 163:1087–1092, 2001.
43. Anthonisen NR, Wright EC: Bronchodilator response in chronic obstructive pulmonary disease. Am Rev Respir Dis 133:814–819, 1986.

44. Chhabra SK, Bhatnagar S: Comparison of bronchodilator responsiveness in asthma and chronic obstructive pulmonary disease. Indian J Chest Dis Allied Sci 44:91–97, 2002.
45. Calverley PM, Burge PS, Spencer S, et al: Bronchodilator reversibility testing in chronic obstructive pulmonary disease. Thorax 58:659–664, 2003.
46. Ulrik CS, Backer V: Nonreversible airflow obstruction in life-long nonsmokers with moderate to severe asthma. Eur Respir J 14:892–896, 1999.
47. Hansen EF, Phanareth K, Laursen LC, et al: Reversible and irreversible airflow obstruction as predictor of overall mortality in asthma and chronic obstructive pulmonary disease. Am J Respir Crit Care Med 159:1267–1271, 1999.
48. Anthonisen NR, Lindgren PG, Tashkin DP, et al: Bronchodilator response in the Lung Health Study over 11 yrs. Eur Respir J 26:45–51, 2005.
49. Postma DS, Gimeno F, van der Weele LT, et al: Assessment of ventilatory variables in survival prediction of patients with chronic airflow obstruction: The importance of reversibility. Eur J Respir Dis 67:360–368, 1985.
50. Kanner RE: The relationship between airways responsiveness and chronic airflow limitation. Chest 86:54–57, 1984.
51. Postma DS, de Vries K, Koeter GH, et al: Independent influence of reversibility of air-flow obstruction and nonspecific hyperreactivity on the long-term course of lung function in chronic air-flow obstruction. Am Rev Respir Dis 134:276–280, 1986.
52. Guyatt GH, Townsend M, Nogradi S, et al: Acute response to bronchodilator. An imperfect guide for bronchodilator therapy in chronic airflow limitation. Arch Intern Med 148:1949–1952, 1988.
53. Ferguson GT: Why does the lung hyperinflate? Proc Am Thorac Soc 3:176–179, 2006.
54. O'Donnell DE, Lam M, Webb KA: Spirometric correlates of improvement in exercise performance after anticholinergic therapy in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 160:542–549, 1999.
55. Di Marco F, Milic-Emili J, Boveri B, et al: Effect of inhaled bronchodilators on inspiratory capacity and dyspnoea at rest in COPD. Eur Respir J 21:86–94, 2003.
56. Cooper CB: The connection between chronic obstructive pulmonary disease symptoms and hyperinflation and its impact on exercise and function. Am J Med 119:21–31, 2006.
57. Newton MF, O'Donnell DE, Forkert L: Response of lung volumes to inhaled salbutamol in a large population of patients with severe hyperinflation. Chest 121:1042–1050, 2002.
58. Guntupalli KK, Bandi V, Sirgi C, et al: Usefulness of flow volume loops in emergency center and ICU settings. Chest 111:481–488, 1997.
59. Miller RD, Hyatt RE: Obstructing lesions of the larynx and trachea: Clinical and physiologic characteristics. Mayo Clin Proc 44:145–161, 1969.
60. Miller RD, Hyatt RE: Evaluation of obstructing lesions of the trachea and larynx by flow-volume loops. Am Rev Respir Dis 108:475–481, 1973.
61. Acres JC, Kryger MH: Clinical significance of pulmonary function tests: Upper airway obstruction. Chest 80:207–211, 1981.
62. Aboussouan LS, Stoller JK: Diagnosis and management of upper airway obstruction. Clin Chest Med 15:35–53, 1994.
63. Gelb AF, Tashkin DP, Epstein JD, et al: Diagnosis and Nd-YAG laser treatment of unsuspected malignant tracheal obstruction. Chest 94:767–771, 1988.
64. Rotman HH, Liss HP, Weg JG: Diagnosis of upper airway obstruction by pulmonary function testing. Chest 68:796–799, 1975.
65. Owens GR, Murphy DM: Spirometric diagnosis of upper airway obstruction. Arch Intern Med 143:1331–1334, 1983.
66. Garcia-Pachon E, Casan P, Sanchis J: Indices of upper airway obstruction in patients with simultaneous chronic airflow limitation. Respiration 61:121–125, 1994.
67. Hughes JMB: The single breath transfer factor (TL,CO) and the transfer coefficient (KCO): A window onto the pulmonary microcirculation. Clin Physiol Funct Imaging 23:63–71, 2003.
68. Macintyre N, Crapo RO, Viegi G, et al: Standardisation of the single-breath determination of carbon monoxide uptake in the lung. Eur Respir J 26:720–735, 2005.
69. Roughton FJ, Forster RE: Relative importance of diffusion and chemical reaction rates in determining rate of exchange of gases in the human lung, with special reference to true diffusing capacity of pulmonary membrane and volume of blood in the lung capillaries. J Appl Physiol 11:290–302, 1957.
70. Crapo RO, Jensen RL, Wanger JS: Single-breath carbon monoxide diffusing capacity. Clin Chest Med 22:637–649, 2001.
71. Cotes JE, Chinn DJ, Miller MR: Transfer factor (diffusing capacity) for carbon monoxide and nitric oxide. *In* Cotes JE, Miller MR (eds): Lung Function: Physiology, Measurement and Application in Medicine, 6th ed. Oxford: Blackwell Publishing, 2006.
72. Crapo RO, Morris AH: Standardized single breath normal values for carbon monoxide diffusing capacity. Am Rev Respir Dis 123: 185–189, 1981.
73. Kanner RE, Crapo RO: The relationship between alveolar oxygen tension and the single-breath carbon monoxide diffusing capacity. Am Rev Respir Dis 133:676–678, 1986.
74. Huang YC, Macintyre NR: Real-time gas analysis improves the measurement of single-breath diffusing capacity. Am Rev Respir Dis 146:946–950, 1992.
75. Jones RS, Meade F: A theoretical and experimental analysis of anomalies in the estimation of pulmonary diffusing capacity by the single breath method. Q J Exp Physiol Cogn Med Sci 46:131–143, 1961.
76. Kangalee KM, Abboud RT: Interlaboratory and intralaboratory variability in pulmonary function testing. A 13-year study using a normal biologic control. Chest 101:88–92, 1992.
77. Punjabi NM, Shade D, Patel AM, et al: Measurement variability in single-breath diffusing capacity of the lung. Chest 123:1082–1089, 2003.
78. Jensen RL, Teeter JG, England RD, et al: Sources of long-term variability in measurements of lung function: Implications for interpretation and clinical trial design. Chest 132:396–402, 2007.
79. Robson AG, Innes JA: Short term variability of single breath carbon monoxide transfer factor. Thorax 56:358–361, 2001.
80. Johnson DC: Importance of adjusting carbon monoxide diffusing capacity ($D_{L_{CO}}$) and carbon monoxide transfer coefficient (KCO) for alveolar volume. Respir Med 94:28–37, 2000.
81. Normand H, Lavigne F, Mouadil A: Performing the apnea of the single-breath carbon monoxide diffusing capacity: Relaxation on the shutter or full inspiration with near atmospheric intrapulmonary pressure? Chest 130:207–213, 2006.
82. Smith TC, Rankin J: Pulmonary diffusing capacity and the capillary bed during Valsalva and Müller maneuvers. J Appl Physiol 27:826–833, 1969.
83. Cotes JE, Chinn DJ, Quanjer PH, et al: Standardization of the measurement of transfer factor (diffusing capacity). Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. Eur Respir J Suppl 16:41–52, 1993.
84. Neas LM, Schwartz J: The determinants of pulmonary diffusing capacity in a national sample of U.S. adults. Am J Respir Crit Care Med 153:656–664, 1996.
85. Frey TM, Crapo RO, Jensen RL, et al: Diurnal variation of the diffusing capacity of the lung: Is it real? Am Rev Respir Dis 136:1381–1384, 1987.
86. Sansores RH, Abboud RT, Kennell C, et al: The effect of menstruation on the pulmonary carbon monoxide diffusing capacity. Am J Respir Crit Care Med 152:381–384, 1995.
87. Huang YC, Helms MJ, MacIntyre NR: Normal values for single exhalation diffusing capacity and pulmonary capillary blood flow in sitting, supine positions, and during mild exercise. Chest 105:501–508, 1994.
88. Zavorsky GS, Quiron KB, Massarelli PS, et al: The relationship between single-breath diffusion capacity of the lung for nitric oxide and carbon monoxide during various exercise intensities. Chest 125:1019–1027, 2004.
89. Johns DP, Berry D, Maskrey M, et al: Decreased lung capillary blood volume post-exercise is compensated by increased membrane diffusing capacity. Eur J Appl Physiol 93:96–101, 2004.
90. Iversen ET, Sorensen T, Heckscher T, et al: Effect of terbutaline on exercise capacity and pulmonary function in patients with chronic obstructive pulmonary disease. Lung 177:263–271, 1999.

91. Frans A, Nemery B, Veriter C, et al: Effect of alveolar volume on the interpretation of single breath $D_{L_{CO}}$. Respir Med 91:263–273, 1997.
92. Punjabi NM, Shade D, Wise RA: Correction of single-breath helium lung volumes in patients with airflow obstruction. Chest 114:907–918, 1998.
93. Kendrick AH: Comparison of methods of measuring static lung volumes. Monaldi Arch Chest Dis 51:431–439, 1996.
94. Steenhuis LH, Groen HJ, Koeter GH, et al: Diffusion capacity and haemodynamics in primary and chronic thromboembolic pulmonary hypertension. Eur Respir J 16:276–281, 2000.
95. Sun XG, Hansen JE, Oudiz RJ, et al: Pulmonary function in primary pulmonary hypertension. J Am Coll Cardiol 41:1028–1035, 2003.
96. Epler GR, McLoud TC, Gaensler EA, et al: Normal chest roentgenograms in chronic diffuse infiltrative lung disease. N Engl J Med 298:934–939, 1978.
97. Aduen JF, Zisman DA, Mobin SI, et al: Retrospective study of pulmonary function tests in patients presenting with isolated reduction in single-breath diffusion capacity: Implications for the diagnosis of combined obstructive and restrictive lung disease. Mayo Clin Proc 82:48–54, 2007.
98. Cotton DJ, Soparkar GR, Grahan BL: Diffusing capacity in the clinical assessment of chronic airflow limitation. Med Clin North Am 80:549–564, 1996.
99. Mohsenifar Z, Lee SM, Diaz P, et al: Single-breath diffusing capacity of the lung for carbon monoxide: A predictor of Pa_{O_2}, maximum work rate, and walking distance in patients with emphysema. Chest 123:1394–1400, 2003.
100. Cerveri I, Dore R, Corsico A, et al: Assessment of emphysema in COPD: A functional and radiologic study. Chest 125:1714–1718, 2004.
101. Goedhart DM, Zanen P, Lammers JW: Relevant and redundant lung function parameters in discriminating asthma from COPD. COPD 3:33–39, 2006.
102. Knudson RJ, Kaltenborn WT, Burrows B: Single breath carbon monoxide transfer factor in different forms of chronic airflow obstruction in a general population sample. Thorax 45:514–519, 1990.
103. Collard P, Njinou B, Nejadnik B, et al: Single breath diffusing capacity for carbon monoxide in stable asthma. Chest 105:1426–1429, 1994.
104. Martinez FJ, Flaherty K: Pulmonary function testing in idiopathic interstitial pneumonias. Proc Am Thorac Soc 3:315–321, 2006.
105. Wasfi YS, Rose CS, Murphy JR, et al: A new tool to assess sarcoidosis severity. Chest 129:1234–1245, 2006.
106. Nagai S, Kitaichi M, Itoh H, et al: Idiopathic nonspecific interstitial pneumonia/fibrosis: Comparison with idiopathic pulmonary fibrosis and BOOP. Eur Respir J 12:1010–1019, 1998.
107. Dimopoulou I, Galani H, Dafni U, et al: A prospective study of pulmonary function in patients treated with paclitaxel and carboplatin. Cancer 94:452–458, 2002.
108. Ngan HY, Liang RH, Lam WK, et al: Pulmonary toxicity in patients with non-Hodgkin's lymphoma treated with bleomycin-containing combination chemotherapy. Cancer Chemother Pharmacol 32:407–409, 1993.
109. Flaherty KR, Andrei AC, Murray S, et al: Idiopathic pulmonary fibrosis: Prognostic value of changes in physiology and six-minute-walk test. Am J Respir Crit Care Med 174:803–809, 2006.
110. Sietsma K: Sarcoidosis and the diffusing capacity for carbon monoxide. Sarcoidosis 7:12–14, 1990.
111. Camus P, Martin WJ 2nd, Rosenow EC 3rd: Amiodarone pulmonary toxicity. Clin Chest Med 25:65–75, 2004.
112. Puri S, Baker BL, Dutka DP, et al: Reduced alveolar-capillary membrane diffusing capacity in chronic heart failure. Its pathophysiological relevance and relationship to exercise performance. Circulation 91:2769–2774, 1995.
113. Gehlbach BK, Geppert E: The pulmonary manifestations of left heart failure. Chest 125:669–682, 2004.
114. Saydain G, Beck KC, Decker PA, et al: Clinical significance of elevated diffusing capacity. Chest 125:446–452, 2004.
115. Coulter TD, Stoller JK: What causes an elevated diffusing capacity? Respir Care 45:531–532, 2000.
116. Stewart RI: Carbon monoxide diffusing capacity in asthmatic patients with mild airflow limitation. Chest 94:332–336, 1988.
117. Wanger J, Clausen JL, Coates A, et al: Standardisation of the measurement of lung volumes. Eur Respir J 26:511–522, 2005.
118. De Troyer A, Borenstein S, Cordier R: Analysis of lung volume restriction in patients with respiratory muscle weakness. Thorax 35:603–610, 1980.
119. Bergofsky EH: Respiratory failure in disorders of the thoracic cage. Am Rev Respir Dis 119:643–669, 1979.
120. Bancalari E, Clausen J: Pathophysiology of changes in absolute lung volumes. Eur Respir J 12:248–258, 1998.
121. Chetta A, Marangio E, Olivieri D: Pulmonary function testing in interstitial lung diseases. Respiration 71:209–213, 2004.
122. American Thoracic Society: Idiopathic pulmonary fibrosis: Diagnosis and treatment. International consensus statement. American Thoracic Society (ATS), and the European Respiratory Society (ERS). Am J Respir Crit Care Med 161:646–664, 2000.
123. Ward NS, Hill NS: Pulmonary function testing in neuromuscular disease. Clin Chest Med 22:769–781, 2001.
124. Ray CS, Sue DY, Bray G, et al: Effects of obesity on respiratory function. Am Rev Respir Dis 128:501–506, 1983.
125. Casanova C, Cote C, de Torres JP, et al: Inspiratory-to-total lung capacity ratio predicts mortality in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 171:591–597, 2005.
126. Ferris BG: Epidemiology standardization project (American Thoracic Society). Am Rev Respir Dis 118:1–120, 1978.
127. Coates AL, Peslin R, Rodenstein D, et al: Measurement of lung volumes by plethysmography. Eur Respir J 10:1415–1427, 1997.
128. Rodenstein DO, Stanescu DC: Reassessment of lung volume measurement by helium dilution and by body plethysmography in chronic air-flow obstruction. Am Rev Respir Dis 126:1040–1044, 1982.
129. Pare PD, Wiggs BJ, Coppin CA: Errors in the measurement of total lung capacity in chronic obstructive lung disease. Thorax 38:468–471, 1983.
130. Schaanning CG, Gulsvik A: Accuracy and precision of helium dilution technique and body plethysmography in measuring lung volumes. Scand J Clin Lab Invest 32:271–277, 1973.
131. Rodarte JR, Hyatt RE, Rehder K, et al: New tests for the detection of obstructive pulmonary disease. Chest 72:762–768, 1977.
132. Brugman TM, Morris JF, Temple WP: Comparison of lung volume measurements by single breath helium and multiple breath nitrogen equilibration methods in normal subjects and COPD patients. Respiration 49:52–60, 1986.
133. Glenn WV Jr, Greene R: Rapid computer-aided radiographic calculation of total lung capacity (TLC). Radiology 117:269–273, 1975.
134. Reger RB, Young A, Morgan WK: An accurate and rapid radiographic method of determining total lung capacity. Thorax 27:163–168, 1972.
135. Loyd HM, String ST, DuBois AB: Radiographic and plethysmographic determination of total lung capacity. Radiology 86:7–14, 1966.
136. Pappas GP, Brodkin CA, Sheppard L, et al: The validity of radiographic estimation of total lung capacity in patients with respiratory disease. Chest 114:513–520, 1998.
137. Vedal S, Crapo RO: False positive rates of multiple pulmonary function tests in healthy subjects. Bull Eur Physiopathol Respir 19:263–266, 1983.
138. Crapo RO: The role of reference values in interpreting lung function tests. Eur Respir J 24:341–342, 2004.
139. Crapo RO: Role of reference values in making medical decisions. Indian J Med Res 122:100–102, 2005.
140. Subbarao P, Lebecque P, Corey M, et al: Comparison of spirometric reference values. Pediatr Pulmonol 37:515–522, 2004.
141. Hankinson JL, Stocks J, Peslin R: Reproducibility of lung volume measurements. Eur Respir J 11:787–790, 1998.
142. Wise RA, Teeter JG, Jensen RL, et al: Standardization of the single-breath diffusing capacity in a multicenter clinical trial. Chest 132:1191–1197, 2007.
143. Pennock BE, Rogers RM, McCaffree DR: Changes in measured spirometric indices. What is significant? Chest 80:97–99, 1981.
144. Herpel LB, Kanner RE, Lee SM, et al: Variability of spirometry in chronic obstructive pulmonary disease: Results from two clinical trials. Am J Respir Crit Care Med 173:1106–1113, 2006.

145. Hathaway EH, Tashkin DP, Simmons MS: Intraindividual variability in serial measurements of D_{LCO} and alveolar volume over one year in eight healthy subjects using three independent measuring systems. Am Rev Respir Dis 140:1818–1822, 1989.
146. Steier J, Kaul S, Seymour J, et al: The value of multiple tests of respiratory muscle strength. Thorax 62:975–980, 2007.
147. ATS/ERS Statement on respiratory muscle testing. Am J Respir Crit Care Med 166:518–624, 2002.
148. Vincken WG, Elleker MG, Cosio MG: Flow-volume loop changes reflecting respiratory muscle weakness in chronic neuromuscular disorders. Am J Med 83:673–680, 1987.
149. Wen AS, Woo MS, Keens TG: How many maneuvers are required to measure maximal inspiratory pressure accurately. Chest 111:802–807, 1997.
150. Black LF, Hyatt RE: Maximal respiratory pressures: Normal values and relationship to age and sex. Am Rev Respir Dis 99:696–702, 1969.
151. Harik-Khan RI, Wise RA, Fozard JL: Determinants of maximal inspiratory pressure. The Baltimore Longitudinal Study of Aging. Am J Respir Crit Care Med 158:1459–1464, 1998.
152. Enright PL, Kronmal RA, Manolio TA, et al: Respiratory muscle strength in the elderly. Correlates and reference values. Cardiovascular Health Study Research Group. Am J Respir Crit Care Med 149:430–438, 1994.
153. Bruschi C, Cerveri I, Zoia MC, et al: Reference values of maximal respiratory mouth pressures: A population-based study. Am Rev Respir Dis 146:790–793, 1992.
154. Leech JA, Ghezzo H, Stevens D, et al: Respiratory pressures and function in young adults. Am Rev Respir Dis 128:17–23, 1983.
155. Wilson SH, Cooke NT, Edwards RH, et al: Predicted normal values for maximal respiratory pressures in Caucasian adults and children. Thorax 39:535–538, 1984.
156. Lawn ND, Fletcher DD, Henderson RD, et al: Anticipating mechanical ventilation in Guillain-Barré syndrome. Arch Neurol 58:893–898, 2001.
157. Braun NM, Arora NS, Rochester DF: Respiratory muscle and pulmonary function in polymyositis and other proximal myopathies. Thorax 38:616–623, 1983.
158. Lyall RA, Donaldson N, Polkey MI, et al: Respiratory muscle strength and ventilatory failure in amyotrophic lateral sclerosis. Brain 124:2000–2013, 2001.
159. Szeinberg A, Tabachnik E, Rashed N, et al: Cough capacity in patients with muscular dystrophy. Chest 94:1232–1235, 1988.
160. Morgan RK, McNally S, Alexander M, et al: Use of sniff nasal-inspiratory force to predict survival in amyotrophic lateral sclerosis. Am J Respir Crit Care Med 171:269–274, 2005.
161. Heritier F, Rahm F, Pasche P, et al: Sniff nasal inspiratory pressure. A noninvasive assessment of inspiratory muscle strength. Am J Respir Crit Care Med 150:1678–1683, 1994.
162. Laroche CM, Mier AK, Moxham J, et al: The value of sniff esophageal pressures in the assessment of global inspiratory muscle strength. Am Rev Respir Dis 138:598–603, 1988.
163. Fitting JW, Paillex R, Hirt L, et al: Sniff nasal pressure: A sensitive respiratory test to assess progression of amyotrophic lateral sclerosis. Ann Neurol 46:887–893, 1999.
164. Morris AHK, Crapo RO, Gardner RM (eds): Clinical Pulmonary Function Testing (2nd ed). Salt Lake City, UT: Intermountain Thoracic Society, 1984.
165. Man WD, Kyroussis D, Fleming TA, et al: Cough gastric pressure and maximum expiratory mouth pressure in humans. Am J Respir Crit Care Med 168:714–717, 2003.
166. Crapo RO, Casaburi R, Coates AL, et al: Guidelines for methacholine and exercise challenge testing—1999. This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999. Am J Respir Crit Care Med 161:309–329, 2000.
167. Mapp CE, Boschetto P, Maestrelli P, et al: Occupational asthma. Am J Respir Crit Care Med 172:280–305, 2005.
168. Tan RA, Spector SL: Provocation studies in the diagnosis of occupational asthma. Immunol Allergy Clin North Am 23:251–267, 2003.
169. Miedinger D, Chhajed PN, Tamm M, et al: Diagnostic tests for asthma in firefighters. Chest 131:1760–1767, 2007.
170. Anderson SD, Brannan JD, Trevillion L, et al: Lung function and bronchial provocation tests for intending divers with a history of asthma. SPUMS J 25:233–248, 1995.
171. Brannan JD, Koskela H, Anderson SD: Monitoring asthma therapy using indirect bronchial provocation tests. Clin Respir J 4:4–15, 2007.
172. Sont JK, Willems LN, Bel EH, et al: Clinical control and histopathologic outcome of asthma when using airway hyperresponsiveness as an additional guide to long-term treatment. The AMPUL Study Group. Am J Respir Crit Care Med 159:1043–1051, 1999.
173. Joos GF, O'Connor B, Anderson SD, et al: Indirect airway challenges. Eur Respir J 21:1050–1068, 2003.
174. Henderson JC, O'Connell F, Fuller RW: Decrease of histamine induced bronchoconstriction by caffeine in mild asthma. Thorax 48:824–826, 1993.
175. Cartier A, Bernstein IL, Burge PS, et al: Guidelines for bronchoprovocation on the investigation of occupational asthma. Report of the Subcommittee on Bronchoprovocation for Occupational Asthma. J Allergy Clin Immunol 84:823–829, 1989.
176. Goldstein MF, Veza BA, Dunsky EH, et al: Comparisons of peak diurnal expiratory flow variation, postbronchodilator FEV(1) responses, and methacholine inhalation challenges in the evaluation of suspected asthma. Chest 119:1001–1010, 2001.
177. Irwin RS, French CT, Smyrnios NA, et al: Interpretation of positive results of a methacholine inhalation challenge and 1 week of inhaled bronchodilator use in diagnosing and treating cough-variant asthma. Arch Intern Med 157:1981–1987, 1997.
178. Eliasson AH, Phillips YY, Rajagopal KR, et al: Sensitivity and specificity of bronchial provocation testing. An evaluation of four techniques in exercise-induced bronchospasm. Chest 102:347–355, 1992.
179. Brightling CE, Ward R, Woltmann G, et al: Induced sputum inflammatory mediator concentrations in eosinophilic bronchitis and asthma. Am J Respir Crit Care Med 162:878–882, 2000.
180. Gibson PG, Fujimura M, Niimi A: Eosinophilic bronchitis: Clinical manifestations and implications for treatment. Thorax 57:178–182, 2002.
181. Cockcroft DW, Murdock KY, Berscheid BA, et al: Sensitivity and specificity of histamine PC20 determination in a random selection of young college students. J Allergy Clin Immunol 89:23–30, 1992.
182. Cockcroft DW, Davis BE, Todd DC, et al: Methacholine challenge: Comparison of two methods. Chest 127:839–844, 2005.
183. Gilbert R, Auchincloss JH Jr: Post-test probability of asthma following methacholine challenge. Chest 97:562–565, 1990.
184. Roach JM, Hurwitz KM, Argyros GJ, et al: Eucapnic voluntary hyperventilation as a bronchoprovocation technique. Comparison with methacholine inhalation in asthmatics. Chest 105:667–672, 1994.
185. Koskela HO, Hyvarinen L, Brannan JD, et al: Sensitivity and validity of three bronchial provocation tests to demonstrate the effect of inhaled corticosteroids in asthma. Chest 124:1341–1349, 2003.
186. van den Berge M, Kerstjens HA, Meijer RJ, et al. Corticosteroid-induced improvement in the PC20 of adenosine monophosphate is more closely associated with reduction in airway inflammation than improvement in the PC20 of methacholine. Am J Respir Crit Care Med 164:1127–1132, 2001.
187. Barnes PJ, Pedersen S, Busse WW: Efficacy and safety of inhaled corticosteroids. New developments. Am J Respir Crit Care Med 157:S1–S53, 1998.
188. Boulet LP, Turcotte H, Brochu A: Persistence of airway obstruction and hyperresponsiveness in subjects with asthma remission. Chest 105:1024–1031, 1994.
189. Mannix ET, Manfredi F, Farber MO: A comparison of two challenge tests for identifying exercise-induced bronchospasm in figure skaters. Chest 115:649–653, 1999.
190. Rundell KW, Anderson SD, Spiering BA, et al: Field exercise vs laboratory eucapnic voluntary hyperventilation to identify airway hyperresponsiveness in elite cold weather athletes. Chest 125:909–915, 2004.
191. Dickinson JW, Whyte GP, McConnell AK, et al: Screening elite winter athletes for exercise induced asthma: A comparison of three challenge methods. Br J Sports Med 40:179–182, 2006 [discussion 179–182].

192. Brown LL, Martin BL, Morris MJ: Airway hyperresponsiveness by methacholine challenge testing following negative exercise challenge. J Asthma 41:553–558, 2004.
193. Anderson SD, Schoeffel RE, Follet R, et al: Sensitivity to heat and water loss at rest and during exercise in asthmatic patients. Eur J Respir Dis 63:459–471, 1982.
194. Hurwitz KM, Argyros GJ, Roach JM, et al: Interpretation of eucapnic voluntary hyperventilation in the diagnosis of asthma. Chest 108:1240–1245, 1995.
195. Argyros GJ, Roach JM, Hurwitz KM, et al: Eucapnic voluntary hyperventilation as a bronchoprovocation technique: Development of a standarized dosing schedule in asthmatics. Chest 109:1520–1524, 1996.
196. Brannan JD, Koskela H, Anderson SD, et al: Responsiveness to mannitol in asthmatic subjects with exercise- and hyperventilation-induced asthma. Am J Respir Crit Care Med 158:1120–1126, 1998.
197. Holzer K, Anderson SD, Chan HK, et al: Mannitol as a challenge test to identify exercise-induced bronchoconstriction in elite athletes. Am J Respir Crit Care Med 167:534–537, 2003.
198. Smith CM, Anderson SD: Inhalational challenge using hypertonic saline in asthmatic subjects: A comparison with responses to hyperpnoea, methacholine and water. Eur Respir J 3:144–151, 1990.
199. Oosterhoff Y, de Jong JW, Jansen MA, et al: Airway responsiveness to adenosine 5′-monophosphate in chronic obstructive pulmonary disease is determined by smoking. Am Rev Respir Dis 147:553–558, 1993.

CHAPTER 25

CLINICAL EXERCISE TESTING

Kathy E. Sietsema, MD

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INTRODUCTION

Many chronic conditions that affect lung function, either directly or indirectly, are first manifest as symptoms or limitations during exercise. Examinations performed at rest may fail to identify the defect, or may inadequately predict the impact of organ system impairment on the overall ability to perform work. Exercise tests have thus long been part of medical practice, both as diagnostic tools and as means of assessing functional capacity. These range from simple functional performance measures to standardized graded profiles of work with measurement of multiple physiologic variables. An appreciation of the physiologic processes subserving exercise and their integrated function provides a basis for applying data from exercise tests to the evaluation and management of patients.

PHYSIOLOGY OF EXERCISE

Any physical activity in which work is performed by skeletal muscle can be regarded as exercise. A broad distinction is made between resistance and endurance exercises, resistance exercise referring to activities consisting of brief periods of muscle contraction at high forces, such as weight lifting, and endurance exercise referring to lower intensity contractions performed rhythmically for extended periods of time, such as in walking or running. Though both forms of exercise are relevant to clinical assessments of disability and rehabilitation, it is endurance, also referred to as aerobic, exercise that is the primary focus of most clinical exercise testing, and of this discussion.

Overview of Cellular Energetics Relevant to Clinical Exercise Testing

Oxygen Uptake as a Measure of Exercise

Contraction of skeletal muscle is accomplished by the ratcheting of overlapping segments of actin and myosin filaments relative to one another within muscle fibers, powered by hydrolysis of adenosine triphosphate (ATP). The major pathway for ATP generation is aerobic metabolism in the mitochondria via the Krebs tricarboxylic acid cycle and electron transport chain, as illustrated in Figure 25-1. Carbon dioxide (CO_2) is generated from breakdown of substrate, and oxygen (O_2) is consumed in the final step of the electron transport chain. Under steady-state conditions, the ratio of CO_2 production to O_2 consumption (respiratory quotient, or RQ) reflects substrate utilization, ranging from 0.7 for fat to 1.0 for carbohydrate. Glycogen is the predominant substrate

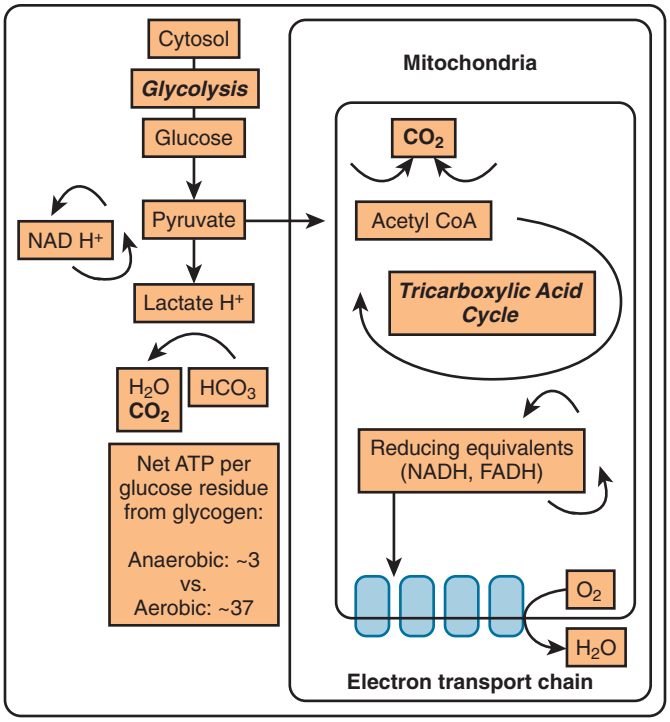

FIGURE 25-1 ■ Simplified schematic of cellular energetics and gas exchange. Glycolysis is the splitting of 6 carbon glucose equivalents into 3 carbon pyruvate molecules. Complete oxidation (*blue arrows*) to CO_2 and water is accomplished by transport of pyruvate into the mitochondria after conversion to acetyl CoA (also derived from lipid metabolism, not shown) to enter the tricarboxylic acid cycle. As each carbon is removed from pyruvate, CO_2 is released as a by-product and hydrogen ions are complexed to the cofactors nicotinamide adenine dinucleotide (NAD) and flavin adenine dinucleotide (FAD) for delivery to the electron transport chain on the inner mitochondrial membrane. Hydrogen ions are passed through a series of four complexes and concentrated in the intermembrane space, forming the electrochemical gradient that drives ATP synthase. This process is called oxidative phosphorylation because oxygen is required to serve as the final electron acceptor in the electron transport chain. In its absence, the upstream reactions cannot proceed and pyruvate is instead converted to lactate (*orange arrows*) to regenerate the cofactor NAD, allowing glycolysis to continue anaerobically. The resulting lactic acid is buffered by bicarbonate, with the evolution of CO_2. Energy released at multiple steps in these processes is captured in the form of ATP, though the net gain per molecule of glucose is far lower for anaerobic glycolysis than for complete oxidation.

utilized during short-duration exercise, so that O_2 and CO_2 are exchanged in roughly equal volumes in muscle during short bouts of moderate exercise. Ultimately this cellular gas exchange must be matched by similar levels of gas exchange in the lung.

The relationship between the amounts of oxygen consumed and work performed is predictable within a relatively narrow range. And since the body has limited capacity for storing oxygen, the rate of *oxygen uptake* at the lung ($\dot{V}O_2$) can be taken as the rate of cellular *oxygen consumption.* $\dot{V}O_2$ is thus proportional to the external work of physical activities, as illustrated by the examples in Table 25-1, though the exact relationships are complicated by factors such as biomechanical economy and body weight, which can alter the actual oxygen cost of an exercise task. Progressively higher rates of exercise work require higher $\dot{V}O_2$, and the maximum $\dot{V}O_2$ that an individual can attain is the conventional expression of exercise capacity.

Lactate or Anaerobic Threshold

Though most energy for endurance exercise is derived from oxidative metabolism, it has long been recognized that there is a critical or threshold level of work above which exercise is associated with a systemic lactic acidosis,[1] indicative of nonoxidative glycolysis. Among healthy individuals, the threshold for lactate accumulation occurs at $\dot{V}O_2$ values averaging around 50% to 60%, but ranging widely from 40% to over 80% of maximum $\dot{V}O_2$. The magnitude of cardiac and ventilatory stress that a task represents and its tolerability to the patient are affected by whether the work is above or below the individual's lactate threshold. The lactate threshold is therefore an important characteristic of exercise function that is relevant to the clinical evaluation of patients.

Lactate is the product of anaerobic glycolysis in the myocyte cytosol (see Fig. 25-1). This is a rapidly available source of ATP for muscle contraction, but it is an inefficient source of energy for endurance exercise, because the energy yield is only a fraction what is possible by full oxidation of carbohydrate to CO_2 and water. To sustain glycolysis in the absence of oxygen, the cofactor nicotinamide adenine dinucleotide (NAD) is regenerated during the conversion of pyruvate to lactate. The occurrence of progressive lactic acidosis is a marker of exercise that cannot be sustained for very long; however, lactate per se is not what causes the muscle to fatigue, and in fact, there are local effects of the acidosis that appear important for exercise performance.[2] In particular, oxygen delivery is enhanced by the Bohr effect, by which a fall in pH causes rightward shift of the oxyhemoglobin dissociation curve and a release of oxygen from hemoglobin. This is illustrated in Figure 25-2, which shows that venous P_{O_2} remains constant but hemoglobin unloads oxygen and reduces oxygen saturation as the pH drops during lactic acidosis–inducing exercise.[3]

Despite extensive investigation over a period of many decades, the mechanisms[4-6] and effects[2,7] of lactic acid accumulation during exercise continue to be debated. Conflicting interpretations of this process are reflected in the varied nomenclature for its description. The term *anaerobic threshold,* introduced by Wasserman and McIlroy in 1964,[8] reflects the view that lactate production occurs when a critical rate of oxygen delivery is reached relative to oxygen demand.[9,10] This view is consonant with a large body of data showing that the lactate threshold can be experimentally shifted by factors altering oxygen availability,[11] such as hemoglobin concentration, arterial P_{O_2}, and blood flow, and that it occurs at a low level of exercise when oxygen delivery is impaired by cardiac dysfunction, or utilization is impaired due to metabolic defects.[4]

TABLE 25-1. Estimated Metabolic Costs for Selected Physical Activities* and the Corresponding $\dot{V}O_2$ Values for a 70-kg Adult of Normal Body Habitus

	Activities	Estimated METs	$\dot{V}O_2$ for ~70-kg Adult (mL/min)
Walking, Running, Climbing	Rest, seated	1.0	250
	Walking slowly with children while pushing stroller	2.5	625
	Walking, 3 mph on level ground	3.3	825
	Walking, 3 mph carrying load of <25 lbs	4.0	1000
	Jogging, <5 mph	7.0	1750
	Running, 7 mph	11.5	2875
	Walking up stairs or climbing ladder	8.0	2000
	Running up stairs	15.0	3750
Home and Self-Care	Dressing and undressing	2.0	500
	Grooming: washing, shaving, hairstyling	2.0–2.5	500–625
	Light cleaning, dusting	2.5	625
	Vacuuming	3.5	875
	Sweeping garage or sidewalk	4.0	1000
	Mowing lawn, walking power mower	5.5	1375
Occupational and Recreational	Light work standing: bartending, filing	2.3	575
	Pressing clothes	4.0	1000
	Playing golf, general	4.5	1125
	Machine tool operation	2.5–5.0	625–1250
	Swimming leisurely	6.0	1500
	Playing tennis, general	7.0	1750
	Shoveling, digging dirt	6.0–8.5	1500–2125
	Firefighting: climbing ladder with gear	11.0	2750

*Expressed as multiples of the resting metabolic rate (METs, defined as 3.5 mL/min/kg), METs values were abstracted from The Compendium of Physical Activities,[147,148] a compilation of data derived from various sources, including questionnaires, laboratory simulations, and field measurements.
mph, miles per hour.

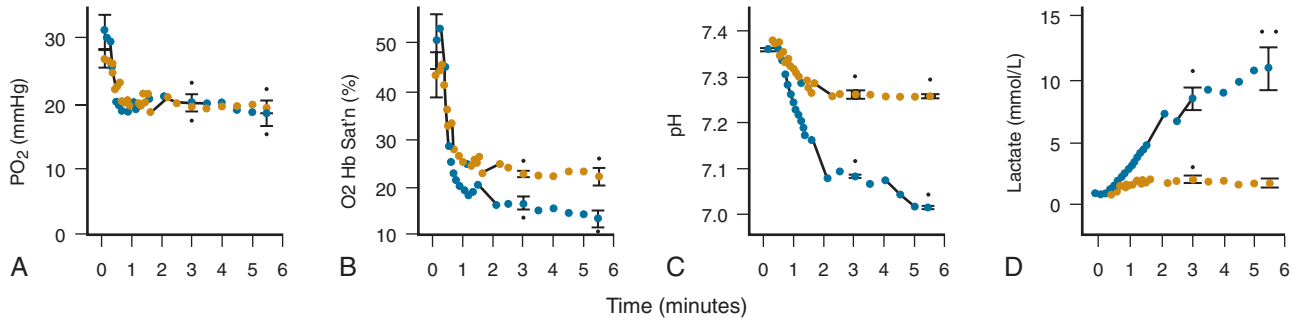

FIGURE 25-2 ■ Femoral blood P_{O_2}, S_{O_2}, and pH during constant work rate exercise at moderate- and high-intensity work rates. In each panel, mean values for five subjects are shown; orange symbols are for moderate-intensity and blue symbols high-intensity exercise; Bars indicate SE for samples drawn at 3-minute and 6-minute time points. **A,** Venous P_{O_2} fell from rest during exercise and reached stable values, which were similar for both exercise intensities. **B,** S_{O_2} and O_2 content were lower during high-intensity compared to moderate-intensity exercise. This was due to a right shift in the oxyhemoglobin dissociation induced by lactic acidosis (Bohr effect) **(C and D).** (Modified from Stringer W, Wasserman K, Casaburi R, et al: Lactic acidosis as a facilitator of oxyhemoglobin dissociation during exercise. J Appl Physiol 76:1462–1467, 1994.)

Alternative perspectives challenge the notion that oxygen availability determines the lactate threshold, since lactate accumulation begins at levels well below maximum $\dot{V}O_2$. Some attribute the rise of lactate to progressive changes in muscle fiber types being recruited as exercise intensity increases, with highly oxidative type I fibers recruited at low levels of exercise and type II fibers with greater glycolytic capacity increasingly recruited at higher work rates.[12] From this observation, it has been inferred that lactate accumulation results from increasing flux of substrate through glycolytic pathways in type II fibers, independent of oxygen availability. Rate limitation of oxygen utilization by enzymatic steps prior to the electron transport chain[13] or saturation of mechanisms for clearance of lactate have also been proposed as the basis for lactate accumulation.[5] The increase in the ratio

of lactate to its precursor pyruvate in blood,[14] and in the ratio of nicotinamide adenine dinucleotide, reduced (NADH) to NAD in muscle,[15] indicates a change in the cellular redox state associated with lactic acidosis, which argues against it resulting solely from greater flux through nonoxidative pathways or impaired clearance.

The lack of consensus concerning its mechanism has given rise to a variety of terms to describe the onset of exercise lactic acidosis, including "ventilatory threshold," "gas exchange threshold," and "lactic acidosis threshold." Importantly, neither its significance as a parameter of exercise function nor its utility in clinical exercise testing is diminished by these differences in perspective. The terms *lactate threshold* and *anaerobic threshold* are used in this chapter when referring to the underlying metabolic processes, and the resulting changes in respiratory gas-exchange variables, respectively.

Domains of Exercise Intensity

In diagnostic testing, the significance of the lactate threshold lies in its relationship to oxygen delivery processes, and in the assessment of function, its significance lies in its relationship to endurance ability.[16] Exercise below the lactate threshold can be continued for prolonged periods of time without discomfort or fatigue, but exercise above this level is associated with systemic acidosis and augmented ventilatory demand. Consistent with this, there is a very limited range above the lactate threshold for which steady-state responses for oxygen transport and utilization can be established. Above this, exercise leads to fatigue and inability to continue exercise due to reaching physiologic limits (see Fig. 25-3). It is thus possible to define discrete domains of exercise intensity,[17,18] with exercise below the lactate threshold designated as "moderate," above the lactate threshold as "heavy," and exercise unsustainable because it leads to attainment of physiologic limits termed "very heavy" or "severe." Although the concept of different intensity domains is relevant to the clinical evaluation of patients, the kind of testing required to precisely distinguish between heavy and very heavy exercise is not well suited to clinical exercise testing. The anaerobic threshold is readily determined using standard testing protocols,

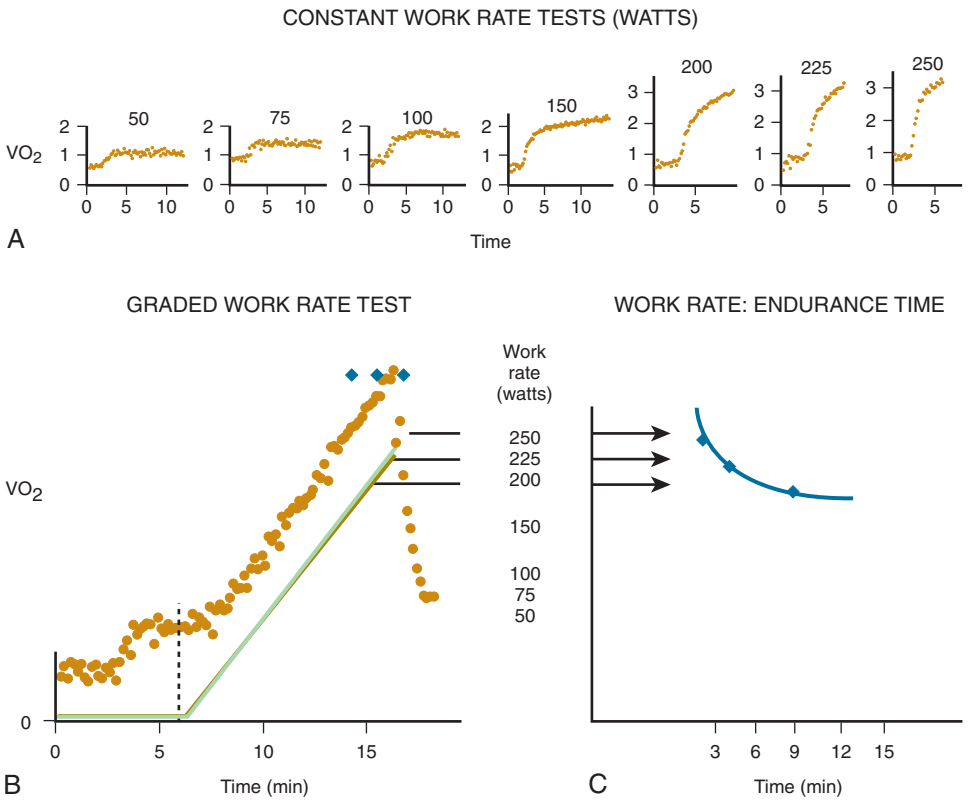

FIGURE 25-3 ■ Data from a healthy man showing relationships between $\dot{V}O_2$, work rate, and time during constant work rate and graded exercise tests. **A,** The profile of $\dot{V}O_2$ for a series of constant work rates ranging from 50 to 250 watts, each test targeted to be 10 minutes long. The lowest three work rates were moderate intensity (i.e., below lactate threshold), and resulted in $\dot{V}O_2$ reaching a steady state within 2 to 3 minutes. The 150-watt work rate represented heavy intensity, slightly above lactate threshold, and attaining a steady state $\dot{V}O_2$ took longer. The three highest work rate tests were very heavy intensity, and all were ended prior to the targeted time due to the subject reaching his maximum $\dot{V}O_2$. **B,** $\dot{V}O_2$ and work rate increased as function of time during a graded test consisting of 3 minutes of rest, then 3 minutes of unresisted cycling, followed by a progressive increase in work rate (*solid line*). Peak $\dot{V}O_2$ reached on the graded test was similar to the end exercise $\dot{V}O_2$ values for the three very heavy constant work rate tests (*blue diamonds*). **C,** The curvilinear relationship of endurance time for these three work rates. The lower intensity tests would not result in maximal $\dot{V}O_2$ and would be sustainable for extended times.

however, and provides a facile measure of endurance capacity.

Organ Systems Supporting Exercise and Limiting Functions

Integrated function of multiple organ systems is required to successfully support exercise while maintaining other vital functions. Impairment in any of these systems can limit maximal exercise or can impose increased requirements on other systems, altering the overall efficiency of exercise. Discrimination of these effects and their contribution to functional impairment is a central goal of clinical exercise testing. The major organ systems supporting exercise are briefly outlined in this section.

Skeletal Muscle

When a small enough mass of muscle is exercised that the cardiac output is not maximally stressed, the maximal oxygen consumption of the muscle is determined by its metabolic capacity. During exercise involving a large muscle mass, however, such as running or cycling, the ability of the active muscle to utilize oxygen exceeds the capacity of the cardiovascular system for oxygen delivery.[19] For the kind of exercise used in clinical exercise testing, therefore, skeletal muscle is viewed as having a "metabolic reserve" and is not normally the proximal limiting factor to maximum $\dot{V}O_2$. Despite this, exercise training is associated with structural and functional adaptations in muscle that allow a given level of work to be accomplished using a lower proportion of the cellular metabolic capacity and with more rapid adjustments to changes in metabolic state. These adaptations include increases in mitochondrial and capillary densities, and increases in the activity of oxidative enzymes.

The existence of a metabolic reserve in the muscle is conditional on there being sufficient muscle mass to accept the increased blood flow of maximal cardiac output and on the muscle having normal metabolic function. Muscle disorders that are limiting to exercise function are diverse and include conditions characterized by decreased mass, impaired capacity for activation or contraction, or decreased energy metabolism. In addition, it is increasingly recognized that reduced muscle mass or function can complicate many chronic disease states,[20,21] such as chronic obstructive pulmonary disease (COPD),[22,23] and their treatments (e.g., corticosteroid therapy), and can contribute importantly to exercise impairment.

Cardiovascular System

The direct relationship between exercise capacity and hemodynamic capacity is underscored by expressing $\dot{V}O_2$ in the terms of the Fick relationship for oxygen:

$$\dot{V}O_2 = \dot{Q} \times C(a-v)O_2$$

where $\dot{Q}$ represents cardiac output and $C(a-v)O_2$ the arterial-venous difference in oxygen content. The increase in exercise cardiac output is coordinated with mechanisms that direct increased blood flow to exercising muscle and minimize flow to less metabolically active tissues, while maintaining blood pressure and flow to vital organs.[24,25] Factors initiating the increase in cardiac output at exercise onset include an augmented venous return due to the action of the skeletal muscle pump and neurally mediated changes in heart rate. Heart rate increases initially by withdrawal of resting parasympathetic tone, and subsequently by progressive sympathetic stimulation. Peak heart rate is dependent on age, with maximal values decreasing by an average of 1 beat/min per year. Stroke volume increases primarily through the Starling mechanism of augmented contractility associated with the stretch of myocardium by higher venous return along with sympathetic augmentation of contractility. Most of the increase in stroke volume occurs relatively early in graded exercise such that increasing cardiac output becomes increasingly dependent on heart rate during heavy exercise.[26] Stroke volume may actually peak prior to maximal exercise and decrease at the highest levels of work due to limited diastolic filling time at high heart rates.[27]

These changes result in systemic blood flow increasing nearly linearly with $\dot{V}O_2$ at a rate of 5 to 6 liters of blood flow for each increment of 1 L/min in $\dot{V}O_2$, with little variation by age or fitness level.[28] For healthy young adults, maximal exercise cardiac output may be in the range of 25 or 30 L/min, and for highly trained endurance athletes, up to 35 to 40 L/min. Most of the exercise-induced increase in cardiac output is attributable to heart rate, which increases two- to threefold, while stroke volume only increases by 20% to 50%. As training does not affect maximum heart rate, training-related increases in cardiac output are mediated entirely by augmented stroke volume. After training stroke volume is higher, and heart rate is lower, at a given $\dot{V}O_2$. The linear decrease in $\dot{V}O_2$ with normal aging is due at least in part to the age-related decline in maximal heart rate and cardiac output. Because cardiac output is normally the limiting factor to maximal aerobic capacity, any attenuation of cardiac function reduces exercise capacity.

Hematologic and Neuroendocrine Systems

The Fick relationship identifies the maximal $C(a-v)O_2$ as the other factor, along with cardiac output, determining maximal $\dot{V}O_2$. This factor is largely a function of hematologic and neuroendocrine processes. While it is not routinely measured during clinical exercise testing, studies of normal subjects and patients with heart failure show that $C(a-v)O_2$ increases linearly across the range of exercise capacity of an individual, reaching peak values at maximum $\dot{V}O_2$.[29]

In health, the arterial oxygen content is primarily a function of hemoglobin concentration, so is lower in women than men, accounting for some of the gender difference in exercise capacity. Additional factors determining mixed venous oxygen content are the distribution of cardiac output and the extraction of oxygen

by perfused tissues. Local extraction of oxygen from capillary blood is a function both of muscle's metabolic capacity and of the microvascular structures that determine diffusion distance from capillary to mitochondria. Distribution of blood flow to and within the muscle is mediated by increases in sympathetic outflow to vascular beds of nonexercising tissues and paracrine factors in exercising muscle mediating local vasodilation.[30] Despite the number of factors contributing to peripheral oxygen extraction, there is far less variability in maximal $C(a-v)O_2$ among healthy persons than there is in maximal cardiac output, with small systematic differences reported due to gender, age, and training status. Consequently the most common clinical disorders limiting $C(a-v)O_2$ are those reducing arterial concentration of oxygen, namely anemia and hypoxemia. Less commonly, extraction of oxygen at the tissue level can be impaired due to metabolic defects in the muscle, or due to disturbances of distribution of blood flow resulting from autonomic dysfunction or regional vascular disease.

Pulmonary System

Control of Breathing. During moderate exercise, the volume per time of pulmonary ventilation ($\dot{V}_E$) matches the rate of carbon dioxide output at the lung ($\dot{V}_{CO_2}$) so closely that there are no more than trivial changes in arterial P_{CO_2} and pH despite large excursions in $\dot{V}_{CO_2}$, $\dot{V}_E$, and venous P_{CO_2}. During higher intensity exercise, lactic acidosis induces a partially compensatory respiratory alkalosis.[31] Although the subject of investigation for over a century, the integration and hierarchy of the factors that contribute to the precise control of $\dot{V}_E$ during exercise remain incompletely understood.[32–35] Ventilatory stimuli originating in the central nervous system and reflexes triggered by mechanical and metabolic processes in exercising limbs and vascular structures are postulated to contribute to the rapid adaptation of ventilation to the start of exercise. The importance of mechanisms related to chemo-sensing processes for "fine-tuning" ventilatory control is evidenced by the remarkable consistency of arterial acid-base homeostasis during rest and exercise.

Breathing Mechanics. In healthy persons, $\dot{V}_E$ may increase 20-fold or more relative to resting levels at maximal exercise. Tidal volume (V_T) increases predominately at low levels of exercise, followed by progressive increases in breathing frequency. V_T approaches, but usually does not reach, inspiratory capacity (IC), and breathing frequencies greater than 50 per minute are unusual. The combination of V_T and breathing frequency at any level of $\dot{V}_E$ appears to be chosen to optimally utilize lung and chest wall mechanics to minimize work of breathing.[36] The increases in V_T result primarily from increases in the volume inspired above resting functional residual capacity, with smaller incursions during exhalation into expiratory reserve volume (ERV)[37] (see Fig. 25-8). Healthy nonathletes generally use less than 75% of breathing capacity, represented by maximal voluntary ventilation (MVV) at peak exercise, and so are not limited by their breathing mechanics. The difference between MVV and $\dot{V}_E$ at peak exercise during a graded exercise test has been termed the exercise "breathing reserve."

Increasing the capacity of the cardiovascular system by training allows healthy persons to attain levels of exercise requiring more of their breathing capacity, so that breathing reserve may be reduced or exhausted.[38] Diseases reducing breathing capacity or increasing breathing requirements can also reduce the normal breathing reserve and, if severe enough, impose limits to exercise due to inability to ventilate sufficiently to keep pace with the rate of CO_2 production.

Gas Exchange. As noted earlier, arterial P_{CO_2} normally remains very close to resting levels during moderate exercise, decreasing at higher intensities due to metabolic acidosis. Because $\dot{V}_E$ increases disproportionately to cardiac output during exercise, the overall ratio of ventilation to perfusion ($\dot{V}/\dot{Q}$) is higher during exercise than at rest. Despite this, the relative efficiency of CO_2 elimination is improved as reflected by the decrease in the ratio of $\dot{V}_E$ to $\dot{V}_{CO_2}$ and decrease in effective dead space–to–tidal volume ratio (V_D/V_T) calculated from the modified Bohr equation. The alveolar-arterial difference in P_{O_2}, or $P(A-a)O_2$, increases during exercise; however, arterial P_{O_2} remains similar to resting levels, almost always above 80 torr at sea level, in healthy nonathletes.[39,40]

Endurance-trained individuals may demonstrate decreased arterial P_{O_2} during high levels of exercise, attributed to both $\dot{V}/\dot{Q}$ mismatch and diffusion limitation due to rapid pulmonary capillary transit time.[41] Thus, the capacity for pulmonary gas exchange, like breathing mechanics, may become limiting to exercise in athletes.

EXERCISE TESTS

Types of Exercise Tests

Functional Performance Tests

A wide assortment of low-complexity or field tests have been devised to test the ability to perform tasks that mimic activities important to home life or to occupation. In clinical contexts, these most commonly simulate elements of activities of daily living using measures such as walking speed, balance, and time required (e.g., to rise from a chair or ascend a flight of stairs). These can be predictive of success in independent living or need for various levels of assistance.[42] In the context of occupation and work fitness, functional tests might instead involve carrying a fire hose up a ladder or running a mile within predetermined times, and are used to predict capacity for job performance.

Walk Tests

Less task-specific tests involving walking on a course or track are applied more broadly to clinical populations with chronic diseases or disabilities.[43] Examples include timed walking tests for which the distance covered in a set time is measured, and fixed-distance tests in which the time required to cover a defined course is measured. Incremental walking tests cue the patient to walk at a

progressively faster pace, and so have the profile of graded exercise tests commonly used in diagnostic laboratories. Because they require little equipment, walking tests are inexpensive to perform and are adaptable to many different environments.

The 6-minute walk test is the most widely used and well-characterized of the walking tests and is frequently utilized in clinical research trials.[44] It and other self-paced tests are subject to "ceiling effects" and may be expected to be relevant primarily to patients whose disease is severe enough to interfere with maintaining a normal or brisk walking pace. In some conditions, such as pulmonary hypertension, these tests have been shown to elicit maximal or near-maximal physiologic responses.[45] In this population, the 6-minute walk test has proven to be sensitive in discriminating between-subject differences in prognosis,[46] and for identifying within-subject changes in performance associated with interventions.[47] Experience with the responsiveness of the 6-minute walk test to change in some other clinical populations, including chronic heart,[48] lung,[44] and kidney[49] diseases, has been less consistent. Published recommendations for administering the 6-minute walk test[50] highlight the importance of standardizing test procedures to account for effects of learning, verbal encouragement, and variations in course layout. Because physiologic measures are not generally made during this kind of testing, these tests have little or no role in diagnostic evaluations.

Laboratory-Based Exercise Testing

Testing in a laboratory allows more extensive monitoring of clinical variables and use of specialized equipment for physiologic measures. *Cardiopulmonary exercise testing* is the term applied to testing when ventilation and pulmonary gas exchange are measured in addition to the electrocardiogram (ECG) and blood pressure, and is the focus of discussion in the following sections. A wide range of other diagnostic instruments may be used to compliment these basic measurements for specific clinical purposes.

APPLICATIONS OF EXERCISE TESTING

Applications of exercise testing can be broadly classified under the headings of tests done for quantitative purposes—that is, to measure exercise capacity or the degree of impairment in persons with known conditions—and tests done for diagnostic purposes (Table 25-2).

Exercise Testing to Quantify Capacity or Impairment

Objective measures of exercise capacity are useful for determining disability, for assessing prognosis, for grading and longitudinal tracking of disease severity, and

TABLE 25-2. Clinical Applications of Cardiopulmonary Exercise Testing with Selected Examples

Category	Goal	Examples
Quantitative Assessments	Quantify functional capacity	• Athletic training assessment
		• Disability assessment
		• Disease severity rating
		• Evaluation of response to therapy or disease progression
	Establish prognosis	• Cardiac transplantation priority and timing
		• Preoperative risk assessment for lung resection
		• General preoperative risk assessment
	Exercise prescription	• Pulmonary rehabilitation
		• Weight loss or other health benefits
	Pacemaker evaluation	• Optimize settings
Diagnostic Assessments	Confirm a suspected disorder	• Document dynamic hyperinflation in chronic obstructive pulmonary disease
		• Provoke exercise-induced bronchoconstriction
		• Evaluate for ischemia as cause of chest pain
	Attribute symptoms or limitation to a cause	• Distinguish between two or more established diagnoses as cause of change in symptoms
	Evaluate significance of abnormal finding on resting study	• Echocardiogram finding of uncertain significance
		• Abnormal pulmonary function test
	Evaluate exercise intolerance: Specific diagnoses	• Cardiac ischemia
		• Heart rate insufficiency
		• Ventilatory limitation
	Evaluate exercise intolerance: Narrow differential diagnosis	• Distinguish between cardiovascular, pulmonary, or metabolic pattern of abnormality
	Evaluate exercise intolerance: Limit diagnostic workup	• Confirm normalcy of age- or weight-referenced responses

for prescribing exercise training. Disability assessment of patients with lung disease is addressed in Chapter 27 of this text and is not discussed here. Similarly, exercise testing to guide athletic training of healthy persons is beyond the scope of this discussion.

Prognosis

Exercise capacity is an independent predictor of survival in many different clinical populations, including apparently healthy persons and patients with chronic cardiovascular conditions.[51–55] Exercise capacity also provides prognostic information for patients with chronic lung diseases, including COPD,[56] cystic fibrosis,[57,58] and parenchymal lung diseases.[59,60,60a]

The prognostic value of exercise capacity has proven to have utility in clinical decision making in a number of contexts. The most extensively studied is the estimation of prognosis among patients with chronic heart failure for the purpose of prioritizing heart transplant waiting lists. Early reports of this application used a peak $\dot{V}O_2$ value of less than 14 ml/min per kg of body weight as a criterion for consideration of transplantation, based on demonstration that patients referred for transplantation with exercise capacity above this level had 2-year survival rates similar to those of transplant recipients.[61,62] Since then, additional exercise variables have been found to add to the prognostic value of peak $\dot{V}O_2$ in this population,[63,64] and important covariants affecting their interpretation have been identified.[65,66] Tailoring of other advanced therapies for heart failure to individual patients is likely to incorporate a number of variables measured during exercise testing.

There is relatively less experience with the use of exercise data for decision making regarding lung transplantation. The 6-minute walk distance has been found to predict mortality among patients awaiting lung transplantation,[60,67,68] and has been used in allocation algorithms. Similarly, the National Emphysema Treatment Trial found peak exercise work rate to be a key factor identifying those patients with severe emphysema who could benefit from lung volume reduction surgery.[69] These contexts are analogous to that of heart transplantation, in that exercise capacity is used to identify a subset of patients whose disease puts them at sufficiently high risk to justify the risk of aggressive interventions.

Another application of the prognostic value of exercise data is in preoperative risk assessment. In contrast to the decision making related to transplants, here low exercise capacity is used to identify those for whom the risk of surgery may be considered prohibitive. Among patients with anatomically resectable lung cancer, peak $\dot{V}O_2$ values less than 12–15 mL/min/kg predict increased risk of perioperative morbidity and mortality.[70,70a] As a result, exercise testing is included in algorithms for guiding the choice and extent of lung cancer surgery, especially for patients with marginal pulmonary function.[71,72] Because unresected lung cancer has a poor prognosis itself, in this context exercise capacity serves more to inform the risk-benefit discussion than as an absolute criterion of operability.[73] Fewer data are reported for the use of exercise testing in preoperative assessment for nonthoracic surgery.[73a] An anaerobic threshold of less than 11 mL/min/kg has been reported to predict increased risk of mortality following elective abdominal procedures, and has been used effectively to plan the intensity of perioperative care for patients who are elderly or have comorbid conditions.[74]

Grading and Tracking of Disease Severity

When disease limits exercise function, it is rational to grade the severity of disease by the degree of exercise impairment. Weber and colleagues in 1982 demonstrated the predicted relationship between peak cardiac output and peak $\dot{V}O_2$ among patients with chronic heart failure and proposed a functional severity classification (termed classes A through D) based on stratifying peak $\dot{V}O_2$ at 20, 16, and 10 mL/min/kg.[75] The validity of this approach is borne out by the relationship of Weber class to prognosis and to the New York Heart Association symptom-based classification.[76] In addition, longitudinal changes in peak $\dot{V}O_2$ appear to accurately reflect changes in status of patients with heart failure referred for transplantation.[77] Functional capacity is increasingly used in the grading of severity of chronic lung disease as well. Exercise capacity, expressed as either 6-minute walk distance or peak $\dot{V}O_2$, is used along with body mass index, airflow obstruction, and dyspnea scores to calculate the BODE index of COPD severity,[78] and among patients with moderate to severe disease, longitudinal changes in this index identify changes in clinical status and mortality risk.[79] Longitudinal exercise testing is also an important tool in clinical research trials evaluating interventions, including drugs or rehabilitation, aimed at improving physical function.

Exercise Prescription

Quantifying exercise capacity is an integral component of exercise prescription.[80] Pre–pulmonary rehabilitation testing is used to identify maximal capacity and anaerobic threshold as measures of baseline impairment, select initial work rates for training, and calibrate training guides such as heart rate or symptoms to physiologic targets.[81] In addition to these quantitative measures, the nature of exercise limitation can be confirmed and patients screened for exercise hypoxemia or adverse responses to exercise that should be addressed prior to exercise conditioning.[82]

Exercise Testing for Diagnostic Purposes

Historically the most common diagnostic use of exercise testing has been to identify exercise-induced myocardial ischemia as the cause of exertional chest pain. An extensive literature defines the utility of exercise testing for this purpose and is not reviewed here. Like stress testing for coronary disease, cardiopulmonary testing is sometimes performed to verify a specific condition as a cause

of symptoms. This may be the case, for example, if a condition such as exercise-induced bronchoconstriction is suspected. Design of the test protocol to optimize the chance of provoking that abnormality, and use of specific ancillary measurements to identify it, enhance the test's diagnostic specificity.

Often cardiopulmonary exercise testing is performed to evaluate patients with unexplained exercise intolerance without the a priori intent of confirming a specific condition.[83] Standardized test protocols that span the range of an individual's capability allow exercise function to be characterized in terms of major parameters and response patterns.[84] The results are then compared with normal reference values and interpreted in the context of the patient's history and symptoms. In some cases a specific diagnosis will be established by the finding of a unique abnormality. The underlying causes of dyspnea and exercise intolerance are diverse, however,[85,86] and not all potential diagnoses have unique findings in the measurements made using standard test protocols. Often, therefore, diagnostic exercise testing aims to narrow the differential diagnosis and provide a focus for further evaluations based on the patterns of exercise responses.[87] No less important, in some cases support for limiting further diagnostic testing can be obtained by finding normal results or by exclusion of specific conditions that would otherwise require more invasive testing to evaluate. A general approach to diagnostic testing is discussed below in the section on clinical exercise data and interpretation.

CONDUCTING CARDIOPULMONARY EXERCISE TESTS IN CLINICAL PRACTICE

Practice Standards and Risks

The risk of serious complications during medical exercise testing has been estimated in the range of less than 1 to 5 per 10,000 tests, and the risk of death at 0.5 per 10,000 tests based on surveys of laboratory testing in patients with known or suspected cardiac disease.[88,89] This means that exercise testing is a relatively safe procedure, but not without risk. Consensus recommendations published by several professional societies[40,80,90] include guidelines for reducing risk by setting standards related to contraindications to testing, monitoring procedures, criteria for interrupting a test, and availability of emergency resources. Absolute contraindications to maximal exercise testing include temporal proximity to acute myocardial infarction or other major event, decompensated state of chronic disease, acute infectious illness, or instability of cardiac rhythm or hemodynamics. Additional relative contraindications may apply in the context of the indication for testing and the staffing of the laboratory. There is presently no certification process required for physicians to perform exercise tests, but minimal training and skills needed for supervising tests and interpreting the ECG are published.[91]

Instrumentation and Measurements

Instruments for conducting clinical cardiopulmonary exercise tests have become widely available. Specific methods and performance characteristics of equipment vary between devices, but all use similar component measurements for calculation of gas exchange. Patients breathe through either a mask or a mouthpiece, and ventilatory and gas-exchange variables are calculated from analyses of expired breath from a mixing chamber or breath-by-breath.[92] Respired volumes are derived from volume or flow transducers interfaced with the breathing apparatus, and partial pressures of CO_2 and O_2 in the exhalate are measured by gas analyzers with rapid response times.[40] Measurements must be precisely time-aligned for accurate calculation of gas-exchange rates. Calibration routines therefore include calibrating signals from the flow or volume transducer and gas analyzers, and determining transit and analysis times and environmental factors such as temperature and humidity.

Calculation of gas exchange is based on mass balance equations having the general form:

$$\dot{V}_{O_2} = \dot{V}_E \times (F_{I_{O_2}} - F_{E_{O_2}})$$

and

$$\dot{V}_{CO_2} = \dot{V}_E \times F_{E_{CO_2}}$$

with correction factors to adjust for water vapor and other factors.[10] By convention, $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ are expressed at standard temperature and pressure, dry (STPD) because they reflect metabolic processes and so are most meaningful as molar equivalents. For the above calculations, therefore, $\dot{V}_E$ is expressed in STPD and $F_{E_{CO_2}}$ and $F_{E_{O_2}}$ are fractional concentrations of the dry exhaled gas volumes. When reporting $\dot{V}_E$, however, it is expressed at body temperature and pressure, fully saturated with water vapor (BTPS), because this is the form in which air is breathed, and the significance of $\dot{V}_E$ is more related to the mechanical requirements of breathing than to the molar equivalents of the gases. Profiles of instantaneous measures of gas tension, flow, and volume over individual breaths may also be recorded.

Heart rate is determined from the 12-lead ECG, which is monitored continuously for changes in rhythm or repolarization. Blood pressure is determined intermittently by cuff, and arterial saturation is estimated by pulse oximetry. Periodic assessment of ratings of perceived exertion and dyspnea are frequently included in test procedures. Arterial blood may be sampled for blood gas analyses either from an indwelling catheter or by discrete punctures. In addition to blood gas tensions, this allows calculation of $P(A-a)_{O_2}$ from the alveolar gas equation and V_D/V_T from the modified Bohr equation,[10,40] which represent the most sensitive measures of the efficiency of pulmonary gas exchange routinely available for clinical assessments.

Test Design Issues

Ergometers

The most commonly used ergometers are treadmills and stationary cycles. Treadmills offer the advantage of

simulating a universal component of daily activities. For most subjects, treadmill exercise also elicits a slightly higher peak $\dot{V}O_2$ than cycling, and so a more likely true physiologic maximum. Conversely, cycles offer the practical advantages of less motion artifact in signals from monitoring devices, easier performance of blood draws or other procedures, and lesser chance of injury due to falls. Because seated exercise allows very low initial work rates and the ability to discontinue work at any time, cycles may be favored in laboratories that frequently evaluate very frail patients. In addition, the imposed work rate is more accurately defined for cycling because the biomechanics are relatively less complicated than those of walking. Portable gas-exchange measurement systems make it feasible to use other modalities of exercise simulating occupational or sports activities, or to accommodate populations for whom conventional ergometers may not be appropriate.

Protocols

Both fixed work rate and graded work rate protocols have utility in clinical testing. The relationship between the responses of $\dot{V}O_2$ to these two different profiles of work is illustrated in Figure 25-3, page 557.

Graded or Incremental Exercise. Graded tests begin with a low level of difficulty and work rate is progressively increased until maximal tolerance is reached or some other end point occurs. Numerous graded protocols have been developed for cycles or treadmills.[40,84,93] Work rate is increased on a cycle by raising resistance to pedaling and on a treadmill by changes in grade and/or speed. Some protocols call for a specific series of ergometer settings, though individualizing the settings allows targeting the incremental portion of the test to an 8- to 12-minute duration, increasing the likelihood of optimal patient performance.[94] Because physiologic responses take time to fully develop, measurements of $\dot{V}O_2$ and other variables during graded tests lag behind the steady-state requirements of the instantaneous work rate being performed. Despite this, key variables such as the anaerobic threshold—as well as $P(A-a)O_2$ and V_D/V_T, reflecting gas-exchange efficiency—are similar to those obtained during steady-state exercise.[95] In most cases too, the $\dot{V}O_2$ at peak exercise of a graded exercise test is comparable to the maximal $\dot{V}O_2$ that is classically derived from having subjects perform a series of very-heavy-intensity fixed work rate tests to exhaustion.[18,96] The term *peak* $\dot{V}O_2$ is customarily used to distinguish the results of a graded test from the latter, more rigorously defined, maximum $\dot{V}O_2$.

Constant Work Rate Exercise. Though graded tests are most common in clinical testing, fixed or constant work rate tests are also useful. Constant work rates elicit markedly different responses depending on the intensity that work rate represents to the patient.[97,98]

Work rates of moderate intensity result in most measured variables reaching steady states within a few minutes and are appropriate, for example, for assessing the need for ambulatory oxygen therapy in patients with COPD. Tests of higher intensity with measurement of endurance time as the primary variable are increasingly used in clinical research trials, particularly in COPD. With appropriate selection of the testing work rate, changes in endurance time are more responsive to changes in function induced by rehabilitation[99] or drug therapy[100] than are parameters from graded testing. This results from the complex dynamic pattern of cardiorespiratory responses to heavy and very heavy exercise, as shown in Figure 25-3. In these ranges, $\dot{V}O_2$ and other variables do not reach new steady states in the 2 to 3 minutes required to adapt to moderate exercise; in fact, the trajectory of $\dot{V}O_2$ paradoxically extends to a higher level than would be expected if the exercise were only a moderate stress. The basis for this is incompletely understood.[101] The consequence, however, is that in this range of exercise, maximal $\dot{V}O_2$ is approached asymptotically over an extended period of time. Interventions increasing maximal $\dot{V}O_2$ or the lactate threshold by even small amounts can substantially prolong the time required to reach physiologic limits at that work rate. Aside from providing a useful form of testing in clinical trials, this observation underscores how a modest increment in exercise capacity (e.g., due to exercise training) can disproportionately improve tolerance for exercise in the range of work rates around a patient's lactate threshold.

CLINICAL EXERCISE DATA AND INTERPRETATION

Organization of Exercise Data and Comparison with Normal Values

Results of exercise function tests include discreet values, such as peak $\dot{V}O_2$, and slopes or ratios of variables reflecting their interrelationships and dynamic changes occurring with exercise. Interpreting these data includes comparisons with reference values from healthy populations (Table 25-3). As is the case for pulmonary function tests, comparative data for all variables of interest are rarely available from a single source, so reference data are selected from a number of sources.[40] For some measured variables, normal responses are relatively invariant, whereas others are affected by demographic, genetic, and behavioral factors and have wide ranges within healthy populations. For the latter, which include peak $\dot{V}O_2$ and anaerobic threshold, predicted values vary considerably depending on the characteristics of the population sample on which the regression equations are based. Equations derived from volunteers tend to predict higher values than those derived from randomly selected sedentary subjects. Selection and use of reference sets therefore requires consideration of the characteristics of the patient population being tested as well as the methodology of the laboratory. Graphical displays are used to identify the anaerobic threshold and facilitate identification of patterns of responses in other variables that are characteristic of different clinical conditions (Figs. 25-4, 25-5, and 25-6).

Table 25-3. Normal Values for Variables from Clinical Exercise Testing and Factors Contributing to Their Variability Among Healthy Adults*

		OTHER FACTORS CONTRIBUTING TO VARIABILITY†				
	Normal Values or Equations	Age	Gender	Fitness	Effort	References
Peak $\dot{V}O_2$‡ (ml/min)				+++	+++	39, 113, 149, 150
Men	= (Height [cm] − age [yr]) × 21					
Women	= (Height [cm] − age [yr]) × 14					
	LLN: 83% of predicted					
Anaerobic threshold $\dot{V}O_2$	= 50–60% of normal peak $\dot{V}O_2$	+	+	+++		39, 113, 150
	LLN: 40–55% of normal peak $\dot{V}O_2$					
$\Delta\dot{V}O_2/\Delta WR$ (ml/min/watt)	= 10.0					104, 151
	LLN: 8.5					
Peak HR (beat/min)	= (220 − age [yr])				+++	40, 150
	LLN: (predicted − 20 beats/min)					
Peak $\dot{V}O_2$/HR (ml O_2/beat)	= Predicted peak $\dot{V}O_2$ ÷ Predicted peak HR			++	++	113
	LLN: ~ (predicted − 2.7)					
$\dot{V}E/\dot{V}CO_2$ @ AT§	LLN: 28–32	+	+			39, 152
Breathing reserve (L/min)	28% of MVV			+	+++	39, 153
	LLN: 11 L/min					
PaO_2, heavy exercise (mm Hg)	>80	+				39
$P(A-a)O_2$, heavy exercise (mm Hg)	<34	+				39
VD/VT, rest	<0.4	+				39
VD/VT, heavy exercise	<0.3 *and* lower than VD/VT at rest	+				39

*Representative values or equations for sedentary adults are shown. Values expressed as "<" or ">" represent estimates of the upper or lower limits of normal; otherwise values are averages with lower limits of normal (LLN) indicated where available. Sources and selected alternatives can be found in the references listed.

†Potential sources of significant variability in the values of healthy persons represented by the listed ranges or not accounted for in the reference equations, with +, ++, and +++ indicating increasing magnitude of the potential effect.

‡Equations for peak $\dot{V}O_2$ are simplified equations based on unpublished analyses (J.E. Hansen, personal communication). See references cited for detailed regressions.

§Ratio of $\dot{V}E$ to $\dot{V}CO_2$ measured at the anaerobic threshold (AT).

Heavy exercise, exercise above anaerobic threshold; HR, heart rate; MVV, maximal voluntary ventilation measured at rest; VD/VT, dead space–to–tidal volume ratio calculated by the Enghoff modification of the Bohr equation using arterial PCO_2 and simultaneous measures of $\dot{V}CO_2$ and respiratory exchange ratio (RER).

Interpreting Exercise Data to Quantify Exercise Capacity

Variables for Quantifying Exercise Capacity

Exercise capacity can be quantified by the amount of external work performed, expressed as watts or as the stage of a standard test protocol, or by the level of metabolic work (i.e., $\dot{V}O_2$) that can be attained. Which of these is of greater relevance depends on context. Capacity for external work may be most relevant to occupational ability assessment, but normalcy of cardiorespiratory capacity for metabolic work is the focus of tests assessing disease severity or prognosis. Ergonomic efficiency may alter the expected relationship between external and metabolic work. In addition, the peak work rate attained on a graded test is affected by the rate at which the work rate is increased, and so is only meaningful in the context of a standardized protocol.

Maximal or peak $\dot{V}O_2$ is the standard metabolic expression of exercise capacity. It is systematically higher in men than women, declines linearly with age throughout adulthood, and is modified by activity level, so reference equations typically include some or all of these factors.[40] The common practice of expressing peak $\dot{V}O_2$ in ml/min/kg of body mass as means of normalizing for size has the advantage of combining an expression of cardiorespiratory capacity with an expression of the weight that needs to be supported during ambulatory activities. The quotient may be low if either peak $\dot{V}O_2$ is abnormally low or weight is abnormally high, however, with obvious differences in clinical implications.

The anaerobic threshold is the $\dot{V}O_2$ above which gas exchange and ventilation reflect an accelerated rate of $\dot{V}CO_2$ due to the buffering of lactic acid. It is most readily determined graphically from a plot of $\dot{V}CO_2$ against $\dot{V}O_2$ (see Fig. 25-4). It is expressed in milliliters per

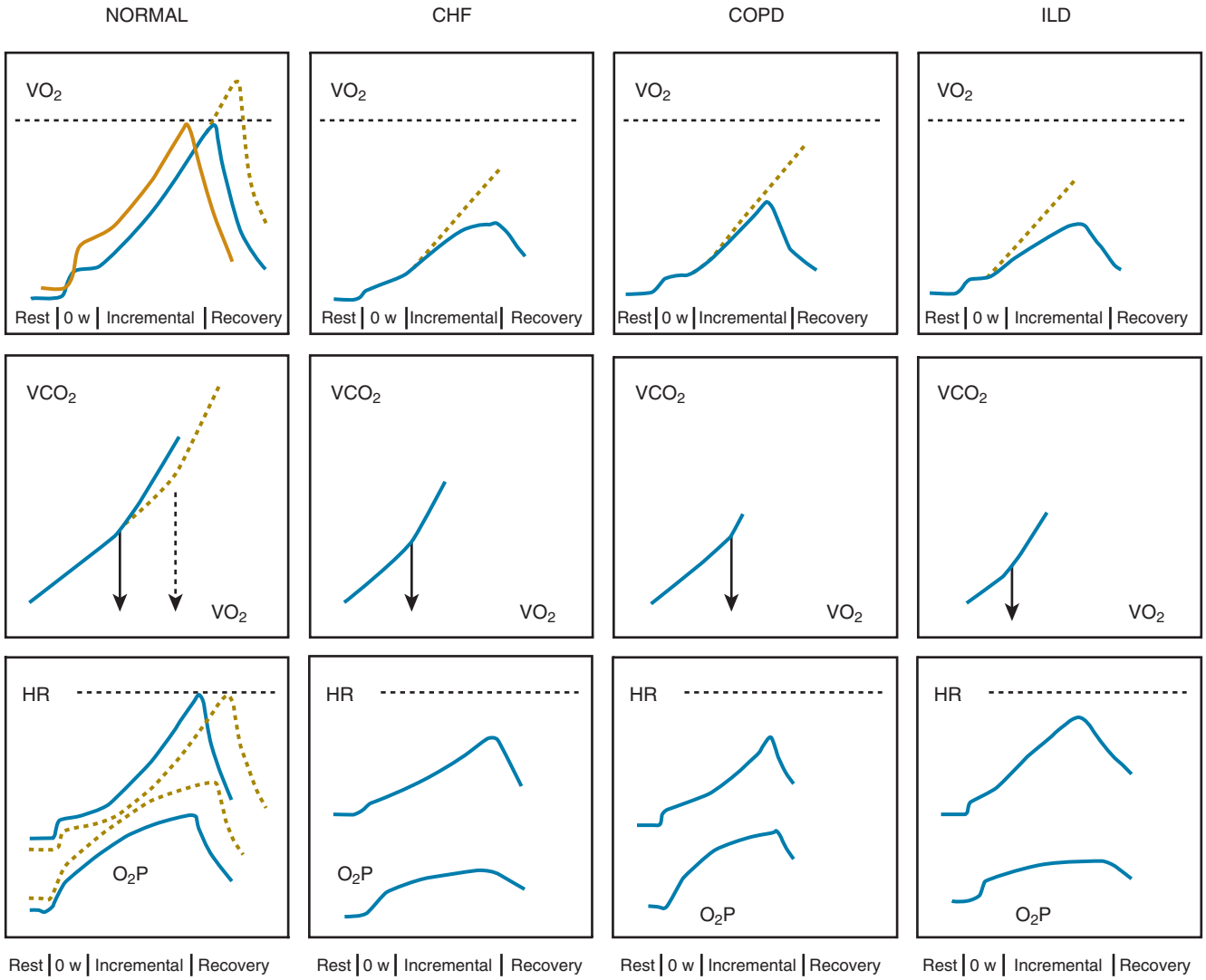

FIGURE 25-4 ■ Typical response patterns to graded cycle exercise test performed by a normal subject compared to sample patients with chronic heart failure (CHF), chronic obstructive pulmonary disease (COPD), and interstitial lung disease (ILD), all scaled identically: Variables reflecting oxygen delivery and utilization. *Top row,* $\dot{V}o_2$ as a function of time for a protocol consisting of 3 minutes of rest, 3 minutes of unresisted cycling (0 watts), incremental increase in work rate, and recovery. *Horizontal dashed lines* indicate predicted maximal $\dot{V}o_2$, which is approached as a linear function of work rate in the normal subject (*left panel, solid blue line*). A more fit subject (*dashed line*) demonstrates the same relationship between work rate and $\dot{V}o_2$ but reaches higher values for both, whereas an obese subject (*solid orange line*) has a higher $\dot{V}o_2$ at any given work rate. In the patients with CHF and ILD, the rate of increase in $\dot{V}o_2$ relative to work rate is lower than normal (*dashed lines*) due to impaired cardiac output response, and recovery of $\dot{V}o_2$ following exercise is also slower. *Middle row,* $\dot{V}co_2$ is plotted as function of $\dot{V}o_2$ (omitting data from rest and recovery) to identify the anaerobic threshold[154] as the $\dot{V}o_2$ above which there is a disproportionate increase of $\dot{V}co_2$ (*vertical arrows*) indicating buffering of lactic acid. Anaerobic threshold is higher $\dot{V}o_2$ in the fit subject (*first panel, dashed line*), and is lower in the patients with CHF and ILD, though relatively normal in the COPD patient, for whom it thus is a high percentage of peak $\dot{V}o_2$. *Bottom row,* Heart rate (HR) and oxygen pulse (O_2P, calculated as $\dot{V}o_2$/HR) as a function of time. *Horizontal dashed lines* indicate predicted maximal HR. Both normal subjects reach the same peak HR, but HR is lower and O_2P higher for the fit subject (*dashed lines*) at a given work rate. In the patient with CHF, peak HR is reduced and O_2P is low and reaches an asymptote early, reflecting limited increase in stroke volume. Peak HR and O_2P are also low in the patient with COPD, though the pattern is closer to normal with truncation of the test prior to reaching peak cardiovascular responses. The ILD pattern reflects reduced oxygen delivery due to limited right ventricular stroke volume and arterial hypoxemia, and so resembles CHF more than COPD.

minute (mL/min) or as a percentage of maximal $\dot{V}o_2$. For middle-aged men it should be at least 40% peak $\dot{V}o_2$, and for women a slightly higher percentage. The anaerobic threshold declines less steeply with aging than peak $\dot{V}o_2$, so it becomes a progressively higher percentage of peak with age. In clinical testing, both the predicted and measured anaerobic thresholds are expressed as a percentage of the *predicted* peak $\dot{V}o_2$ to avoid misinterpreting a low value as normal because of a concomitant decrease in maximal capacity or an underestimation of peak $\dot{V}o_2$ due to submaximal effort or some other factor.

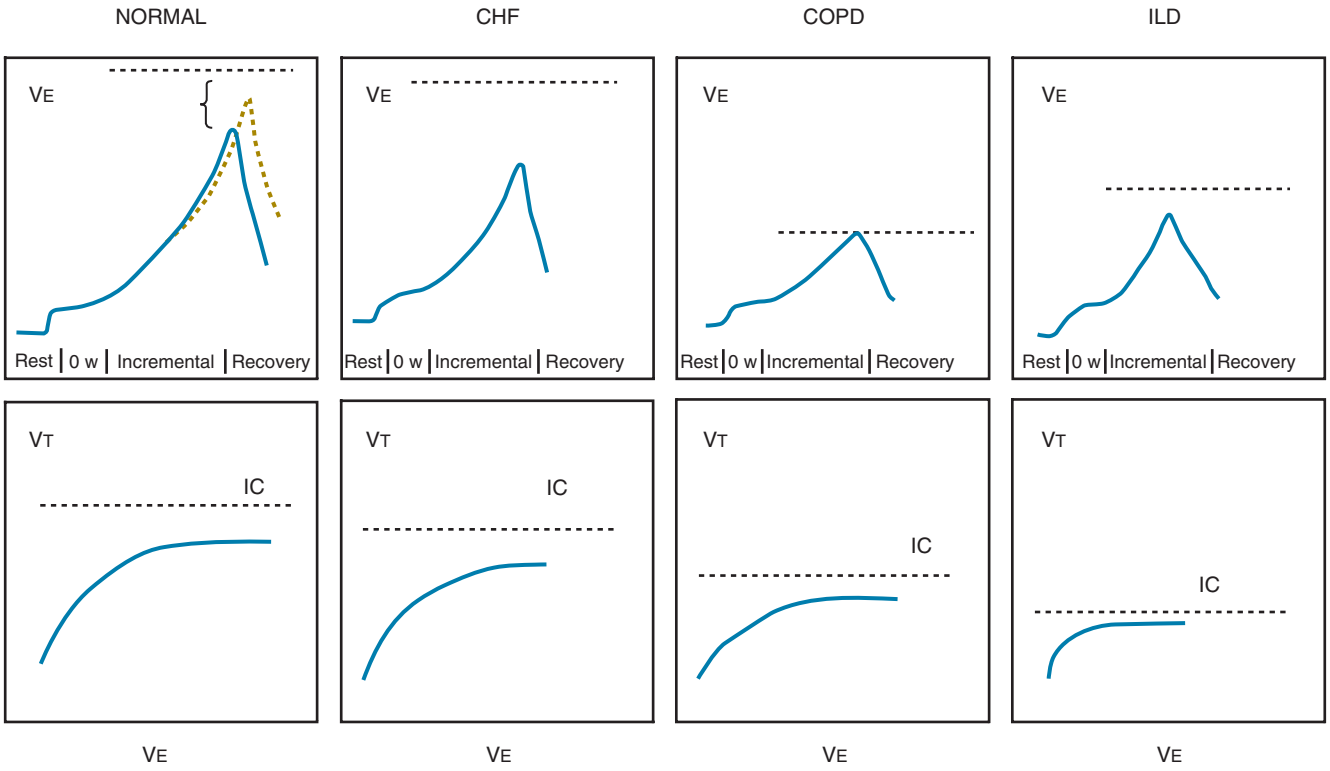

FIGURE 25-5 ■ Exercise variables reflecting ventilatory variables for the same protocol and subjects shown in Figure 25-4. *Top row,* $\dot{V}_E$ as a function of time. *Horizontal dashed lines* indicate the subjects' MVV values. The normal subject has a breathing reserve (*bracket*) at end exercise, which is smaller for the fit individual (*dashed line*), who reached a higher peak $\dot{V}_E$ but had lower $\dot{V}_E$ at a given work rate in the range above the anaerobic threshold. The COPD patient has no breathing reserve and ends exercise on reaching MVV. *Bottom row,* Tidal volume (V_T) as a function of $\dot{V}_E$. *Horizontal dashed lines* indicate subjects' inspiratory capacities (IC). All subjects increase tidal volume early in exercise, with V_T approximating IC early in exercise in the patient with ILD.

Utilizing Data from Quantitative Testing

Prognosis. Using exercise data in the estimation of prognosis requires comparison with data from the relevant clinical population. For example, peak $\dot{V}_{O_2}$ predicts mortality risk in both COPD and idiopathic pulmonary fibrosis (IPF), but for a given value, mortality is higher in IPF. Testing modality and protocol should also be comparable to those used in the reference studies. The treatment of data of obese patients can be problematic in this context. Using actual weight to define peak $\dot{V}_{O_2}$ in ml/min/kg lowers values for obese subjects independent of disease severity and should be avoided, for example, in transplantation assessments, where the value of peak $\dot{V}_{O_2}$ presumably derives from its relationship to cardiac function. The appropriate approach in preoperative risk assessments is less clear as obesity may constitute a component of the estimated risk.

Exercise Training. Prescriptions for endurance training include elements of exercise frequency, duration, and intensity. Exercise tests are particularly helpful in guiding selection of a work rate matching the desired intensity. Prescribing guidelines often define intensity in terms of percentages of peak heart rate, $\dot{V}_{O_2}$, or work rate,[80] though referencing the work rate to the anaerobic threshold results in more uniform training stimulus. Work rates corresponding to the subject's anaerobic threshold are effective and are usually tolerated for the 30- to 45-minute durations commonly targeted in the prescriptions. Higher intensities, up to about midway between anaerobic and peak, are also suitable and can result in greater effects for a given time.

Longitudinal Assessments. Using exercise tests to monitor changes in patients' condition over time depends on an appreciation of the repeatability of the key variables. The within-subject coefficient of variation for peak $\dot{V}_{O_2}$ is reported to be in the range of 4% to 8% for a number of clinical populations.[102,103] Somewhat more variability is usually reported for determination of the anaerobic threshold from gas-exchange variables, despite it being independent of maximal effort. There appear to be minimal learning effects on the results of graded tests. Six-minute walk distance, in contrast, is systematically longer on the second compared to the first trial, with subsequent tests showing progressively less change and coefficients of variation in the range of 6% to 8%.[50]

Interpreting Exercise Data for Diagnostic Purposes: Typical Response Patterns

For tests targeting the confirmation of a specific diagnosis, interpretation may be based on ancillary measures

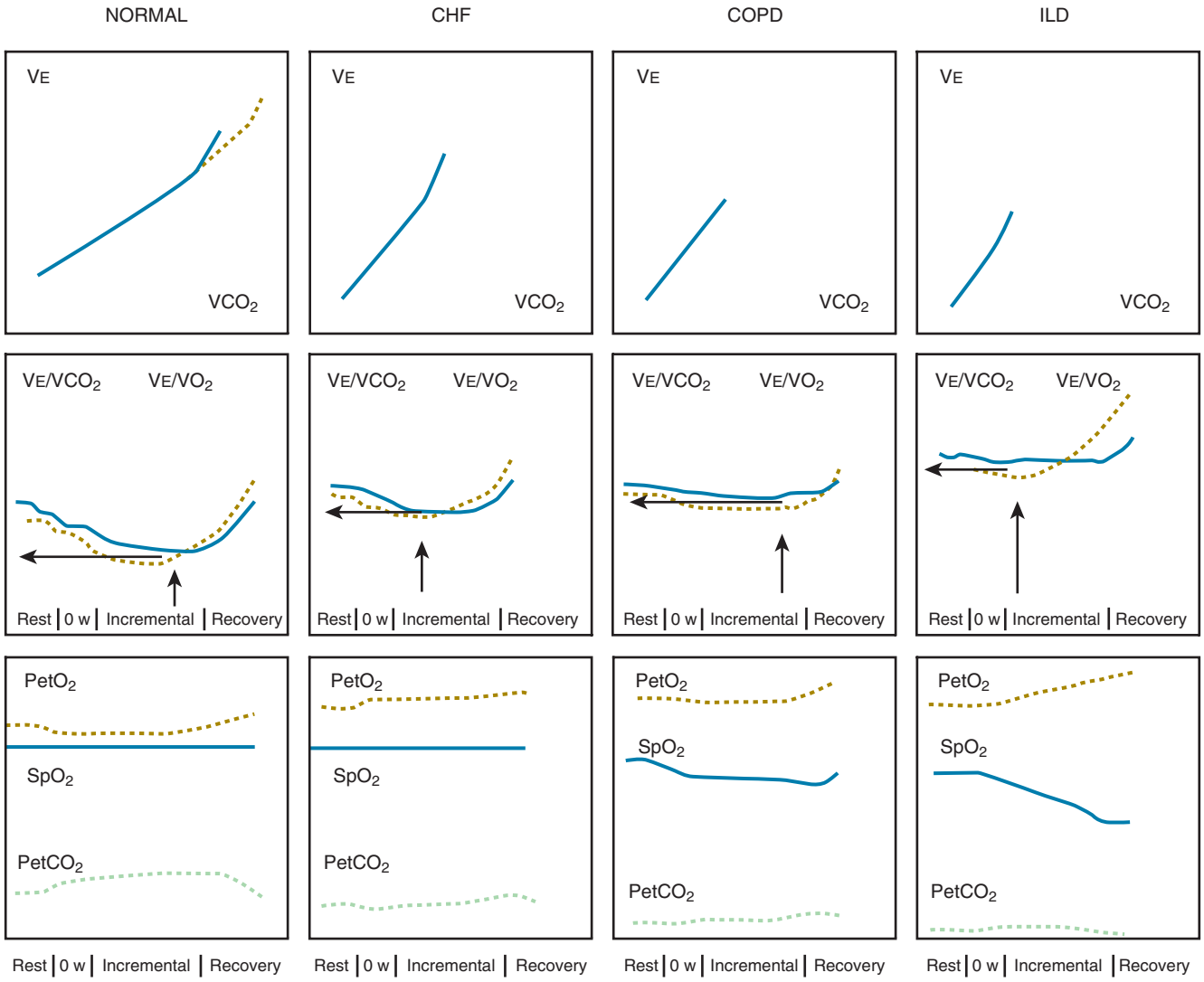

FIGURE 25-6 ■ Exercise variables reflecting gas-exchange efficiency for the same protocol and subjects as in Figure 25-4. *Top row,* $\dot{V}_E$ as a function of $\dot{V}_{CO_2}$. $\dot{V}_E$ and $\dot{V}_{CO_2}$ are linearly related over most of exercise, but the slope is steeper for all patient groups shown due to the effects of high ventilation-to-perfusion relationships in the lung. Late in exercise, an increase in slope marks ventilatory compensation for metabolic acidosis, which may not be evident in patients with reduced chemoresponsiveness or severe ventilatory limitation, or when exercise is limited soon after the anaerobic threshold, as shown for COPD. *Middle row,* $\dot{V}_E/\dot{V}_{CO_2}$ (*solid blue lines*) and $\dot{V}_E/\dot{V}_{O_2}$ (*dotted brown lines*) ratios as a function of time. An increase in $\dot{V}_E/\dot{V}_{O_2}$ marks the anaerobic threshold (*vertical arrows*); the $\dot{V}_E/\dot{V}_{CO_2}$ at this point (*horizontal arrows*) is an index of efficiency of gas exchange. *Bottom row,* End-tidal P_{O_2} (P_{ETO_2}, *dashed brown lines*) and P_{CO_2} (P_{ETCO_2}, *dashed blue lines*) and pulse oximeter O_2 saturation (S_{PO_2}, *solid blue lines*). Arterial desaturation is often progressive and more severe in ILD than COPD, but is not typical of CHF.

such as posttest spirometry or cardiac imaging. In the more broadly focused evaluation of dyspnea or exercise intolerance, interpretation focuses on classifying responses as characteristic of cardiovascular, ventilatory, or metabolic abnormalities. Patterns of findings in test variables that are typical of some common cardiorespiratory disorders are illustrated in Figures 25-4 through 25-6 and further described below.

Limitation due to Cardiovascular Disorders

Any condition abnormally limiting cardiac output reduces peak $\dot{V}_{O_2}$ and can affect other $\dot{V}_{O_2}$-related variables. The anaerobic threshold is often low, and the slope of change of $\dot{V}_{O_2}$ relative to work rate ($\Delta\dot{V}_{O_2}/\Delta WR$) may be less than normal, particularly in the range above anaerobic threshold.[104] This reflects an abnormal reliance on anaerobic metabolism due to failure of cardiac output to appropriately respond to the oxygen requirement,[105] resulting in an abnormal "oxygen deficit" as evidenced by a delayed recovery of $\dot{V}_{O_2}$ and heart rate to resting levels when exercise ends.[106] Impairments in stroke volume require an augmented heart rate response reflected in a steeper slope of the linear relationship of heart rate (HR) to $\dot{V}_{O_2}$. Conversely, the ratio $\dot{V}_{O_2}$/HR, termed the *oxygen pulse,* is lower. This expression has

units of milliliters of oxygen (mL O_2)/heart beat and by derivation from the Fick relationship is equal to the product of stroke volume and $C(a-v)O_2$. Normal values at peak exercise vary by the same factors affecting peak $\dot{V}O_2$, depend on effort, and are increased when heart rate is limited by pharmacologic agents, so the pattern of change is often more informative than the peak value. Attainment of a constant value prior to the end of a graded test implies attainment of maximal values for both stroke volume and $C(a-v)O_2$.[29] Decreasing values as work rate progresses are distinctly abnormal but may be seen in settings in which stroke volume falls during exercise, such as in hypertrophic cardiomyopathy or exercise-induced cardiac ischemia.

Chronic Heart Failure. Reduction of peak $\dot{V}O_2$ and anaerobic threshold are characteristic of heart failure. A rather unique finding of afterload dependence of left ventricular function sometimes observed is a transient rise in $\dot{V}O_2$ and $\dot{V}O_2$/HR in the early seconds of recovery following cessation of exercise, as the acute reduction in systemic vascular resistance allows stroke volume to increase above peak exercise levels. Peak heart rate is frequently low in chronic heart failure (termed *chronotropic incompetence*), even in the absence of therapeutic β-adrenergic blockade.

Heart failure is also associated with inefficiency of pulmonary gas exchange manifest as high levels of $\dot{V}E$ for a given metabolic rate. This can be characterized as the slope of the relationship of $\dot{V}E$ to $\dot{V}CO_2$, ($\Delta\dot{V}E/\Delta\dot{V}CO_2$) or the ratio of $\dot{V}E/\dot{V}CO_2$ measured at the anaerobic threshold, both of which have upper limits of normal in the range of 28 to 32. High ventilatory requirements do not result solely from the early onset of lactic acidosis, but are due at least in part to increased effective VD/VT. In contrast, arterial oxygenation and the $P(A-a)O_2$ are usually normal in heart failure in the absence of concomitant lung disease. A proportion of patients with severe left heart failure demonstrate an oscillatory pattern of pulmonary gas exchange and ventilation, having a periodicity of 45 to 60 seconds similar to Cheyne-Stokes respiration. Values of peak $\dot{V}O_2$ and $\Delta\dot{V}E/\Delta\dot{V}CO_2$, and findings of chronotropic incompetence and oscillatory breathing all have prognostic significance in chronic systolic heart failure. Diastolic heart failure is characterized by many of these same findings.[107,108]

Pulmonary Vascular Disease. Pulmonary vascular diseases limit cardiac output due to constraints on right ventricular performance with a resulting reduction of peak $\dot{V}O_2$. Because the gas-exchanging structures themselves are often affected, evidence of pulmonary V:Q abnormalities are almost universal.[109,110] If VD/VT is calculated, it may be normal or high at rest but generally does not decrease normally during exercise. This gas-exchange inefficiency is reflected in $\dot{V}E/\dot{V}CO_2$, which remains abnormally high at the anaerobic threshold. In contrast to the findings in left ventricular failure, impaired oxygenation is common. There are several potential mechanisms for exercise hypoxemia in pulmonary vascular disease, including V:Q mismatch, diffusion limitation, and intra-atrial shunting through a patent foramen ovale. The latter may be suspected from a characteristic pattern of acute changes in ventilatory variables induced by hyperventilation of the alveolar capillary blood to compensate for right-to-left shunting of venous CO_2.[111,112]

Deconditioning. Though normal reference data sets often include measurements of subjects characterized as sedentary, the degree of inactivity in clinical populations may be more extreme than represented in many reference samples.[113] Conditioning involves changes in cardiac stroke volume and peripheral vascular structures, so it is not surprising that it can be difficult to distinguish between deconditioning and mild cardiovascular disease on the basis of peak $\dot{V}O_2$ and anaerobic threshold. In deconditioning alone, the $\Delta\dot{V}O_2/\Delta WR$, measures of gas-exchange efficiency, and the ECG and blood pressure responses to exercise should be normal, however, so that abnormalities in these variables warrants further cardiovascular evaluation.

Limitation due to Ventilatory Disorders

Because there is normally some reserve function of the lung, exercise capacity may be maintained in early pulmonary disease. As lung impairment increases, whether due to obstructive or parenchymal disorders, exercise may be limited by the combined effects of impaired lung mechanics, reducing breathing capacity, and impaired gas exchange, increasing breathing requirements, as illustrated in Figure 25-7. Cardiovascular responses may also be constrained by the secondary effects of lung disease on the pulmonary circulation, respiratory muscle blood flow, and altered intrathoracic pressures. Alterations in work of breathing and gas exchange can precipitate dyspnea disproportionate to the level of exercise, which can cause patients to stop exercise due to symptoms. Which of these various factors has the dominant effect on exercise varies among different disorders, and among patients with a given lung disease.

Chronic Obstructive Pulmonary Disease. Typical findings on exercise with COPD include elevated $\dot{V}E$ relative to $\dot{V}CO_2$, reflecting high pulmonary V:Q relationships as described previously for heart failure and pulmonary vascular disease. Abnormally high ventilatory requirements and reduced ventilatory capacity can result in patients reaching their maximal capacity to breathe at relatively low levels of exercise. Exercise must be limited at this point because progressively higher rates of CO_2 production and O_2 consumption without corresponding increases in $\dot{V}E$ would rapidly lead to intolerable derangements of arterial blood gases. Such ventilatory limitation is readily evident if exercise is terminated at the point at which the patient approaches maximum breathing capacity, as represented by the MVV.[114] The MVV does not necessarily represent a physiologic breathing pattern, however, and some patients are limited by dyspnea at $\dot{V}E$ levels below MVV, indicating a need for additional ways of identifying limitation of exercise by ventilatory factors.

Analysis of the flow-volume relationship during tidal respiration by patients with COPD often demonstrates attainment of the patient's maximal expiratory flow rates even at low levels of exercise.[115] While this does not necessarily cause exercise to be terminated, further

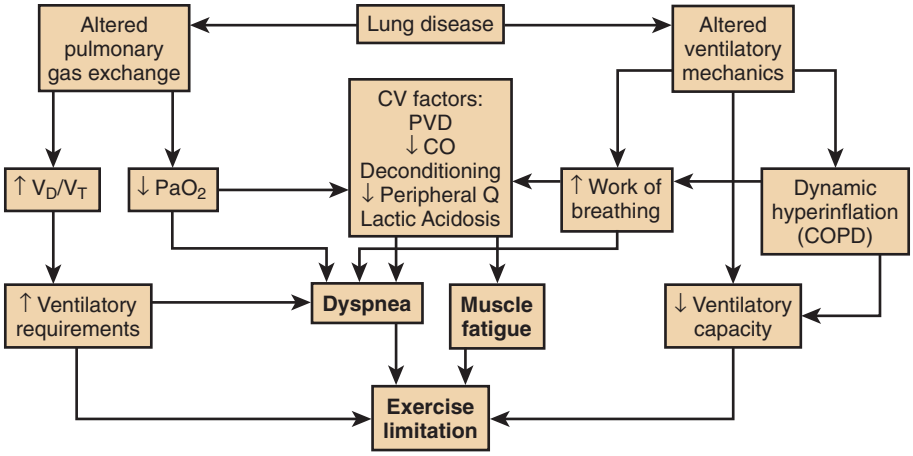

FIGURE 25-7 ■ Interaction of pulmonary and cardiovascular factors contributing to exercise intolerance in lung disease. In simplest terms, lung diseases lead to exercise limitation due to dual effects of altered gas-exchange efficiency and altered breathing mechanics, which increase ventilatory requirements and decrease ventilatory capacity, respectively. This leads to exercise limitation when the limits of ventilation are attained. Cardiovascular and skeletal muscle effects can contribute to exercise limitation by a number of mechanisms. Cardiac output may be limited by the presence of secondary pulmonary vascular disease, or the effects of lung mechanics on systemic venous return. Altered breathing mechanics also increase work of breathing, which can distribute more cardiac output to the muscles of respiration and away from locomotor muscles. These effects, together with deconditioning or other muscle dysfunction associated with lung disease, result in early onset of lactic acidosis, further increasing ventilatory requirements. Symptoms of dyspnea and muscle fatigue (not illustrated) arise from multiple of the processes shown, and can limit the tolerability of exercise even at levels below absolute physiologic limitation.

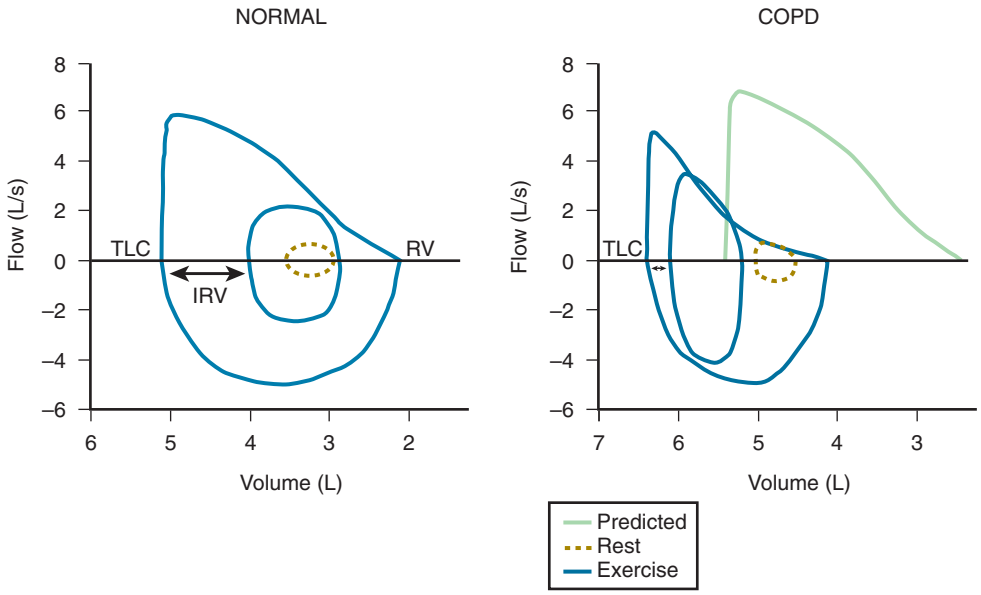

FIGURE 25-8 ■ Flow-volume relationships for tidal breathing during exercise compared with the maximal flow-volume loop measured at rest prior to exercise. Placement of the tidal loops on the horizontal axis is based on periodic measures of IC during exercise. *Left,* Data from a normal subject showing the normal expansion of tidal volume within the maximal flow-volume loop over the range of exercise. *Right,* Similar data from a patient with COPD demonstrating marked increase in end-expiratory lung volume, or dynamic hyperinflation, during exercise with attainment of maximal expiratory flow rates over much of exhalation and reduction of inspiratory reserve volume (IRV). (Modified from O'Donnell DE, Banzett RB, Carrieri-Kohlman V, et al: Pathophysiology of dyspnea in chronic obstructive pulmonary disease: a roundtable. Proc Am Thorac Soc 4:145–168, 2007.)

increases in $\dot{V}_E$ can require or induce a shift to higher end-expiratory lung volumes, which has been termed *dynamic hyperinflation,* as illustrated in Figure 25-8. The higher operational lung volumes place the respiratory muscles in less favorable operating length, which can increase the work of breathing and predispose to respiratory muscle fatigue, particularly in patients with COPD who have hyperinflation at rest. O'Donnell and colleagues have demonstrated the importance of dynamic hyperinflation to exercise intolerance in COPD by showing that the severity of dyspnea in this population is closely related to encroachment on inspiratory reserve

volume (IRV), with marked increases in dyspnea occurring once IRV is less than 500 mL.[116] It may thus be useful to identify these findings in patients with COPD whose symptoms seem disproportionate to abnormalities of resting lung function. Expiratory flow limitation and increases in end-expiratory lung volume have also been demonstrated in patients without COPD, including obese persons, who have low ERV at rest, and the elderly, who have relatively low expiratory flow rates at low lung volumes. The relationship of these findings to dyspnea and exercise impairment in conditions other than COPD is not well defined, and their measurement during clinical testing of unselected populations is not routine.[117]

Patients with COPD also have variable degrees of exercise hypoxemia and, less commonly, may develop hypercapnia and/or blunted ventilatory response to metabolic acidosis. Despite the predisposition to ventilatory limitation and gas-exchange abnormalities, a significant proportion of patients with COPD report leg fatigue, rather than dyspnea, as their primary symptom limiting exercise.[118] Reductions in muscle mass and function are increasingly recognized as intrinsic or confounding impairments in COPD.[22,119] These may be the proximal cause of exercise limitation[119] and/or contribute to ventilatory limitation due to the increased ventilatory requirements represented by early onset of lactic acidosis. Recognition of muscular impairment in patients with lung disease is important because it represents a treatable target for exercise training, an integral component of pulmonary rehabilitation.[120]

COPD can also limit cardiovascular responses to exercise.[121] Loss of recruitable pulmonary capillary bed predisposes to exaggerated increases in pulmonary artery pressures during exercise, and elevated intrathoracic pressures can impair venous return, either of which may constrain cardiac output. The augmented work of breathing associated with abnormal breathing mechanics obligates a higher blood flow to the respiratory muscles, potentially reducing available blood flow to the locomotor muscles.[122]

A general correlation between exercise capacity and the degree of resting lung function abnormalities can be demonstrated in patients with moderate to severe COPD.[123] However, prediction of functional impairment for individual patients from resting measurements is imperfect. This is in keeping with the heterogenous abnormalities in ventilatory, cardiovascular, and muscular function already referred to that can occur in this condition.[124] Thus, while diagnosis of COPD is based on resting lung function, exercise testing can be diagnostically helpful in the differential diagnosis of how a particular patient's disease impacts exercise tolerance.[82]

Episodic Airflow Obstruction: Asthma and Laryngeal Dysfunction. Provocation of bronchoconstriction by exercise is an important diagnostic application of clinical testing. Commonly used graded protocols may not be the most effective for inducing bronchoconstriction, however, which is associated with airway cooling or dehydration during high levels of ventilation. Protocols recommended for exercise broncho-provocation utilize a rapid increase in work rate to attain a heart rate of 80% to 90% maximal and a $\dot{V}_E$ of 40% to 60% of MVV, which are then maintained for a minimum of 4 minutes.[125,126] Prolonged protocols and lower intensities are avoided as they may induce a refractory state in which there is resistance to bronchoconstriction. Exercise-induced bronchoconstriction is typically manifest in the postexercise period, identified by a 10% or greater decrease in forced expiratory volume in 1 second (FEV_1) relative to the preexercise period. FEV_1 is measured serially every 5 minutes postexercise for 30 minutes or until a positive result is obtained and reversed with β-agonists. When well-controlled, asthmatics can have normal responses to graded exercise testing, though flow limitation and dynamic hyperinflation have been demonstrated even with relatively normal resting spirometry and may reduce exercise tolerance.[127]

Graded exercise protocols have been reported to be effective for precipitating symptoms in patients with exercise-associated upper airway dysfunction as a cause of dyspnea.[128] In contrast to asthma, upper airway obstruction is more likely to occur during exercise rather than recovery, and is associated with stridor. It may be possible to differentiate these conditions from abnormal inspiratory flow rates on exercise flow-volume loops, though definitive diagnosis and identification of the structures involved are based on visualizing the upper airway by laryngoscopy.

Interstitial Lung Disease. As is the case for COPD, diffuse parenchymal lung disease is marked by abnormalities in both breathing mechanics and gas exchange. Restrictive lung mechanics result in exercise tidal volumes that approach the resting measure of IC early in exercise. End-expiratory lung volume is usually maintained at resting levels.[129] Even though breathing capacity may be significantly reduced, exercise limitation often appears consequent to the secondary effects of interstitial disease on cardiovascular responses,[130] or the effects of hypoxemia, rather than due to ventilatory mechanics. Consistent with this, the patterns of abnormalities in $\dot{V}_{O_2}$ and related variables during graded testing may be indistinguishable from those of intrinsic pulmonary vascular disease, described above. Both oxygenation and CO_2 elimination are abnormal, reflected in high $\dot{V}_E/\dot{V}_{CO_2}$ and V_D/V_T and widened $p(A-a)O_2$. The latter measures may be the earliest abnormalities in exercise responses related to interstitial disease.[131,132] Although a feature of any condition altering V:Q, isolated abnormalities of $p(A-a)O_2$ or V_D/V_T, in the absence of clinical findings of chronic heart failure or airflow obstruction to account for them, suggests either interstitial or pulmonary vascular disease. Among patients with established interstitial disease, hypoxemia tends to be more severe than in COPD. The degree of exercise impairment varies both within and between conditions, with more severe impairment reported among patients with idiopathic interstitial fibrosis than among those with a similar degree of restriction due to chronic pneumoconiosis.[133] Extrapulmonary manifestations of conditions such as collagen vascular disease may dominate exercise findings.

Hyperventilation Syndromes. Hyperventilation syndromes are reported among the conditions leading to

referral for evaluation of dyspnea, and in some series represent a substantial proportion of patients undergoing exercise testing for this reason.[134] Erratic patterns of tidal volume and frequency are suggestive of this condition, but the sensitivity of this finding is not clear. Precipitation of typical symptoms in conjunction with evidence of acute hyperventilation, with no other apparent abnormality, is supportive of the diagnosis. One study has reported systematically higher respiratory rate and smaller tidal volumes during exercise among patients believed to have hyperventilation syndromes compared to controls, but the differences were small.[135]

Limitation due to Muscle or Metabolic Factors

Among the systemic and metabolic conditions that may affect exercise function, obesity and muscle metabolic disorders are frequently under consideration in the differential diagnosis of unexplained dyspnea.

Obesity. Obesity increases the metabolic cost of weight-bearing exercise and thus decreases the amount of external relative to internal work that can be performed. This is reflected in higher values for $\dot{V}O_2$ at a given work rate compared to lean individuals (see Fig. 25-3), but does not alter the relationship between the increment in $\dot{V}O_2$ for a given increment in work rate ($\Delta\dot{V}O_2/\Delta WR$), or relationships between $\dot{V}O_2$ and other variables. Similarly, the relationship between $\dot{V}E$ and $\dot{V}CO_2$ is normal. In addition to incurring higher $\dot{V}O_2$ due to the work of supporting excess weight, the work of breathing may be increased due to effects on chest wall mechanics.[136,137] Exercise testing may be useful in the evaluation of the obese patient for exclusion of other coexisting conditions causing exercise intolerance.

Metabolic Myopathies. Muscle metabolic disorders include a spectrum of conditions that may sometimes present in adolescence or adulthood as exertional dyspnea with, or instead of, muscle-specific symptoms. These are classified as defects in carbohydrate metabolism, fat metabolism, or mitochondrial oxidation.

The prototypic disorder of carbohydrate metabolism is McArdle's syndrome, in which a deficiency of myophosphorylase prevents metabolism of glycogen. This results in dependence on fatty acids or circulating glucose as substrate and is identified by the unique inability to produce lactate under ischemic conditions, such as hand grip exercise performed with a blood pressure cuff inflated to a suprasystolic level. During lower extremity exercise, peak $\dot{V}O_2$ is limited to levels that would correspond to a normal lactate threshold, but with little or no increase in blood lactate. The $C(a-v)O_2$ fails to widen normally, so the cardiovascular response to exercise is hyperdynamic,[138] reflected in a high heart rate relative to $\dot{V}O_2$.

Disorders of fatty acid metabolism, such as defects in carnitine palmitoyltransferase, result in dependence on carbohydrate metabolism. Symptom of muscle pain and cramping occur under conditions of fasting or prolonged exercise. Short-duration tests commonly used in clinical testing can be supported by carbohydrate metabolism, so peak $\dot{V}O_2$ and other responses to graded testing may be normal.[139]

Mitochondrial myopathies constitute diverse conditions resulting from defects of any of the nuclear- or mitochondrial DNA–encoded proteins involved in oxidative phosphorylation.[140] They are most readily recognized when presenting as characteristic syndromes affecting multiple tissues with high energy needs. Clinical findings vary from one patient to another, however, due to differing burdens of affected mitochondria between and within tissues, so exercise intolerance may occur as an apparently isolated finding without a recognizable syndrome. In one clinical series,[141] mitochondrial defects were reported to account for over 8% of patients undergoing exercise testing to evaluate unexplained dyspnea. Common exercise findings include a high heart rate and cardiac output relative to $\dot{V}O_2$ due to impaired oxygen extraction in the muscle. Peak $\dot{V}O_2$ is reduced in proportion to the mutational burden in muscle,[142] and lactate concentrations may be elevated at rest or early in exercise. In addition, $\dot{V}E$ has been reported to be high relative to metabolic rate,[141,143] although the basis for this in these conditions is not established.

Interpretive Strategies

A number of strategies have been proposed for the diagnostic interpretation of exercise data. These are based on comparison of the patient's response patterns with those that are typical of patients with known disorders either using a series of categorical assessments or a stepwise algorithm.[10,144,145] Limited data are available to define the diagnostic yield of these analyses for each of the conditions potentially causing dyspnea. It is widely agreed, however, that exercise testing is useful for distinguishing between cardiac and pulmonary disorders[83] and so narrowing the differential diagnosis and providing direction for further evaluation.[146]

An approach to systematically summarizing test results is shown in Table 25-4, which organizes the test data into four components.

Summary of Overall Quality of the Test and Peak Exercise Performance

Peak $\dot{V}O_2$ is expressed in absolute terms and in comparison to reference values. The symptom or finding that limited exercise is identified and an assessment made of whether the test can be interpreted as a valid measure of the patient's exercise capacity. The latter can be based on several lines of evidence, including the tester's impression of the patient's effort. Objective evidence of maximal or near-maximal exercise includes reaching or approaching any physiologic maxima, such as $\dot{V}E$ greater than 80% of MVV, heart rate within 10 beats/min (1 standard deviation) of predicted maximum, or a plateau of $\dot{V}O_2$ or heart rate in the face of increasing work rate. An approximation of maximum is also implied by findings that the patient did exercise in the very-heavy-intensity range, that is, well beyond the lactate threshold. Peak exercise respiratory exchange ratio (RER) values

TABLE 25-4. Approach to Organization of Exercise Test Data for Summary and Interpretation*

General Areas of Analysis	Specific Questions	Variables	Relevant Conditions
Test quality and performance	Does the test represent maximal capacity?	Peak HR and RER	
		AT	
		Symptoms	
	What was the limiting symptom? Were the patient's complaints reproduced?	Symptoms	Diagnostic value may be reduced if symptoms not reproduced
	What is maximal capacity? How does it compare with reference values?	Peak $\dot{V}O_2$	
	Is metabolic requirement higher than normal?	Peak $\dot{V}O_2$	Obesity
		Peak WR	
	Is endurance capacity low?	AT	Deconditioning
			Cardiovascular disease
			Myopathy
Ventilatory mechanics	Is there limitation due to lung mechanics?	$\dot{V}E$ Exercise IC	COPD
			Respiratory muscle weakness
			ILD
	Is the pattern of breathing abnormal?	VT	Hyperventilation syndrome
		Respiratory rate	
		Flow-volume relationship	Laryngeal dysfunction
		Postexercise FEV_1	Exercise-induced bronchoconstriction
Efficiency of gas exchange	Is $\dot{V}E$ high relative to metabolic rate?	$\dot{V}E/\dot{V}CO_2$	Chronic heart failure
			Chronic lung disease
			Pulmonary vascular disease
			Acid-base disturbance
	Are there other findings of abnormal pulmonary gas exchange?	SpO_2	ILD
		ABGs	COPD
		$P(A-a)O_2$ and VD/VT	Pulmonary vascular disease
Oxygen delivery and utilization	Is endurance capacity abnormal?	AT	Cardiovascular disease
			Myopathy
			Severe deconditioning
	Does $\dot{V}O_2$ increase appropriately?	$\Delta\dot{V}O_2/\Delta WR$	Cardiovascular disease
			Myopathy
	Does heart rate increase as expected relative to $\dot{V}O_2$?	High $\dot{V}O_2/HR$	Chronotropic insufficiency
		Low $\dot{V}O_2/HR$	Low SV
			Reduced HbO_2 content
			Impaired O_2 extraction
	Are there abnormalities of ECG or blood pressure?	ECG	Myocardial ischemia
		BP	Arrhythmia
			Hypertension
			Autonomic dysfunction

*Four major areas of analysis are shown along with examples of the form of questions used in analyzing each area, the pertinent exercise variables, and examples of relevant clinical conditions.

ABGs, arterial blood gases; AT, anaerobic threshold; BP, blood pressure; COPD, chronic obstructive pulmonary disease; ECG, electrocardiogram; HbO_2, oxyhemoglobin; HR, heart rate; IC, inspiratory capacity; ILD, interstitial lung disease; RER, respiratory exchange ratio; SpO_2, pulse oximeter O_2 saturation; SV, stroke volume; WR, work rate.

above 1.10 or 1.15 imply significant lactic acidosis, and have been used as criteria of effort, but since peak RER depends on the resting value and the rate of increase of work rate, no single value can be defined as a necessary criterion of an adequate test. Since the lactate threshold is usually in the midrange of exercise, however, a peak $\dot{V}O_2$ that exceeds the anaerobic threshold by 80% or more supports a high degree of effort.

Description of Ventilatory Response and Assessment of Whether or Not Breathing Mechanics Limited Exercise Performance

An absent breathing reserve indicates ventilatory limitation, and a low reserve (<20% of MVV) is suggestive of the same. It has been proposed that the degree to which ventilation is constrained during exercise be

quantified as the percentage of exhaled tidal volume that reaches or exceeds maximal flow rates.[115] As noted previously, the utility of this practice in clinical testing has not been systematically evaluated. Changes in breathing mechanics occurring during exercise are not reflected in the calculated breathing reserve, however, so that findings on flow-volume loop or physical examination, such as inspiratory stridor or reduction of IC and IRV, indicate potential ventilatory limitation even if breathing reserve appears normal. Erratic patterns of tidal volume and frequency suggest hyperventilation or malingering.

Analysis of Efficiency of Pulmonary Gas Exchange

Inefficiency of oxygenation is identified by abnormally low arterial $P_{A}O_2$ or high $P(A-a)O_2$, and inefficiency of CO_2 elimination by failure of V_D/V_T to decrease normally. These measures are based on analyses of exercise arterial blood gases. Inefficient gas exchange may alternatively be inferred from pulse oximetry findings of desaturation by more than 3% or by abnormally high $\dot{V}_E$ relative to $\dot{V}CO_2$. Because noninvasive oximetry is not always precise and high $\dot{V}_E/\dot{V}CO_2$ relationships can reflect acute or chronic hyperventilation (e.g., due to anxiety or compensation for chronic metabolic acidosis), an exercise arterial blood gas can be useful in confirming or excluding defects in gas exchange when the noninvasive measures are unexpectedly abnormal.

Analysis of Oxygen Delivery and Utilization

Abnormalities of oxygen delivery and/or utilization are reflected in the responses related to $\dot{V}O_2$, including low anaerobic threshold, low $\Delta\dot{V}O_2/\Delta WR$, or plateau of $\dot{V}O_2/HR$. Any cardiovascular disorder or muscle metabolic disorder can cause these abnormalities, so attribution of the findings to a particular condition involves consideration of history, physical findings, ECG, and blood pressure responses. For example, the onset or progression of cardiac arrhythmias, failure of blood pressure to increase, or ST segment displacement on ECG all suggest myocardial ischemia. Similarly, examination and ECG findings can provide clues to valve stenosis as the cause of $\dot{V}O_2$ abnormalities. The association of abnormal $\dot{V}O_2$ responses with impaired pulmonary gas exchange is characteristic of pulmonary vascular disease, including idiopathic pulmonary hypertension. Pulmonary venous hypertension can result in an identical pattern of findings, so when the patient is at risk for diastolic dysfunction, distinguishing between these conditions requires measurement of central circulatory pressures by right heart catheterization. Although the same constellation of exercise findings is typical of systolic heart failure, this is usually readily distinguished by clinical or echocardiogram findings.

Peripheral processes can also impair the $\dot{V}O_2$ response to exercise. Muscle symptoms are typical of both myopathies and peripheral arterial disease, but the latter may be suspected by risk factors and is confirmed or excluded by measurement of the ankle-brachial pressure index. Metabolic myopathies may be suggested by a history of rhabdomyolysis, use of myotoxic drugs, or family history compatible with mitochondrial disorder. Confirmation ultimately depends on histologic and biochemical analysis of a muscle biopsy specimen. Disorders of the regulation of blood flow distribution to muscle are suggested by blood pressure abnormalities or other manifestations of autonomic dysfunction.

KEY POINTS

- Exercise capacity and tolerance for exercise tasks are determined by the integrative function of multiple organ systems and so can be adversely affected by diverse diseases.
- Clinical exercise testing protocols range from simple task-based performance tests to more comprehensive procedures that quantify the imposed work rate and the associated physiologic responses.
- Cardiopulmonary exercise testing combines measures of ventilation, pulmonary gas exchange, electrocardiogram, and blood pressure to quantify exercise function and to characterize the range and pattern of cardiorespiratory adaptations to the exercise stress.
- Major parameters of exercise function derived from cardiopulmonary exercise testing include maximum oxygen uptake ($\dot{V}O_2$), which is the conventional measure of exercise capacity, and the lactate or anaerobic threshold, which is a marker of endurance capacity.
- Exercise testing is indicated to quantify exercise capacity for the purpose of defining functional capacity or impairment, grading the severity of cardiovascular diseases, assessing prognosis in chronic heart or lung disease, and designing exercise prescriptions for rehabilitation.
- Exercise testing is useful diagnostically in the evaluation of patients with unexplained dyspnea or exercise intolerance by identifying or excluding certain specific conditions, or helping direct further diagnostic evaluations.

References

1. Owles WH: Alterations in the lactic acid content of the blood as a result of light exercise, and associated changes in the CO_2-combining power of the blood and in the alveolar CO_2 pressure. J Physiol (Lond) 69:214–237, 1930.
2. Lamb GD, Stephenson DG: Point: Lactic acid accumulation is an advantage during muscle activity. J Appl Physiol 100:1410–1412, 2006.
3. Stringer W, Wasserman K, Casaburi R, et al: Lactic acidosis as a facilitator of oxyhemoglobin dissociation during exercise. J Appl Physiol 76:1462–1467, 1994.
4. Wasserman K, Beaver WL, Whipp BJ: Gas exchange theory and the lactic acidosis (anaerobic) threshold. Circulation 81(Suppl II):II14–II30, 1990.
5. Brooks GA: Anaerobic threshold: Review of the concept and directions for future research. Med Sci Sports Exerc 17:22–34, 1985.
6. Robergs RA, Ghiasvand F, Parker D: Biochemistry of exercise-induced metabolic acidosis. Am J Physiol Regul Integr Comp Physiol 287:R502–R516, 2004.
7. Bangsbo J, Juel C: Counterpoint: Lactic acid accumulation is a disadvantage during muscle activity. J Appl Physiol 100:1412–1413, 2006.
8. Wasserman K, McIlroy MB: Detecting the threshold of anaerobic metabolism in cardiac patients during exercise. Am J Cardiol 14:844–852, 1964.
9. Wasserman K: Coupling of external to cellular respiration during exercise: The wisdom of the body revisited. Am J Physiol 266:E519–E539, 1994.
10. Wasserman K, Hansen JE, Sue DY, et al: Principles of Exercise Testing and Interpretation, 4th ed. Philadelphia: Lippincott Williams & Wilkins, 2005.
11. Katz A, Sahlin K: Regulation of lactic acid production during exercise. J Appl Physiol 65:509–518, 1988.
12. Ivy JL, Withers RT, Van Handel PJ, et al: Muscle respiratory capacity and fiber type as determinants of the lactate threshold. J Appl Physiol 48:523–527, 1980.
13. Putman CT, Jones NL, Lands LC, et al: Skeletal muscle pyruvate dehydrogenase activity during maximal exercise in humans. Am J Physiol 269:E458–E468, 1995.
14. Wasserman K, Beaver WL, Davis JA, et al: Lactate, pyruvate, and lactate-to-pyruvate ratio during exercise and recovery. J Appl Physiol 59:935–940, 1985.
15. Sahlin K, Katz A, Henriksson J: Redox state and lactate accumulation in human skeletal muscle during dynamic exercise. Biochem J 245:551–556, 1987.
16. Coyle EF: Integration of the physiological factors determining endurance performance ability. Exerc Sport Sci Rev 23:25–63, 1995.
17. Wells JG, Balke B, Van Fossan DD: Lactic acid accumulation during work; a suggested standardization of work classification. J Appl Physiol 10:51–55, 1957.
18. Meyer T, Lucia A, Earnest CP, et al: A conceptual framework for performance diagnosis and training prescription from submaximal gas exchange parameters—theory and application. Int J Sports Med 26(Suppl 1):S38–S48, 2005.
19. Mortensen SP, Dawson EA, Yoshiga CC, et al: Limitations to systemic and locomotor limb muscle oxygen delivery and uptake during maximal exercise in humans. J Physiol (Lond) 566:273–285, 2005.
20. Moylan JS, Reid MB: Oxidative stress, chronic disease, and muscle wasting. Muscle Nerve 35:411–429, 2007.
21. Gosker HR, Wouters EF, van der Vusse GJ, et al: Skeletal muscle dysfunction in chronic obstructive pulmonary disease and chronic heart failure: Underlying mechanisms and therapy perspectives. Am J Clin Nutr 71:1033–1047, 2000.
22. Maltais F, LeBlanc P, Jobin J, et al: Peripheral muscle dysfunction in chronic obstructive pulmonary disease. Clin Chest Med 21:665–677, 2000.
23. Man WD, Kemp P, Moxham J, Polkey MI: Skeletal muscle dysfunction in COPD: Clinical and laboratory observations. Clin Sci (London) 117:251–264, 2009.
24. Rowell LB: Ideas about control of skeletal and cardiac muscle blood flow (1876–2003): Cycles of revision and new vision. J Appl Physiol 97:384–392, 2004.
25. Thomas GD, Segal SS: Neural control of muscle blood flow during exercise. J Appl Physiol 97:731–-738, 2004.
26. Higginbotham MB, Morris KG, Williams RS, et al: Regulation of stroke volume during submaximal and maximal upright exercise in normal man. Circ Res 58:281–291, 1986.
27. Stringer WW, Whipp BJ, Wasserman K, et al: Non-linear cardiac output dynamics during ramp-incremental cycle ergometry. Eur J Appl Physiol 93:634–639, 2005.
28. Astrand PO, Cuddy TE, Saltin B, et al: Cardiac output during submaximal and maximal work. J Appl Physiol 19:268–274, 1964.
29. Stringer WW, Hansen JE, Wasserman K: Cardiac output estimated noninvasively from oxygen uptake during exercise. J Appl Physiol 82:908–912, 1997.
30. Duling BR: Control of striated muscle blood flow. *In* Crystal RG, West JB (eds): The Lung: Scientific Foundations. New York: Raven Press, 1991, pp 1497–1505.
31. Stringer W, Casaburi R, Wasserman K: Acid-base regulation during exercise and recovery in humans. J Appl Physiol 72:954–961, 1992.
32. Haouzi P: Theories on the nature of the coupling between ventilation and gas exchange during exercise. Respir Physiol Neurobiol 151:267–279, 2006.
33. Dempsey JA, Vidruk EH, Mitchell GS: Pulmonary control systems in exercise: update. Fed Proc 44:2260–2270, 1985.
34. Whipp BJ, Ward SA: Determinants and control of breathing during muscular exercise. Br J Sports Med 32:199–211, 1998.
35. Mitchell GS, Babb TG: Layers of exercise hyperpnea: Modulation and plasticity. Respir Physiol Neurobiol 151:251–266, 2006.
36. Otis AB, Fenn WO, Rahn H: Mechanics of breathing in man. J Appl Physiol 2:592–607, 1950.
37. Henke KG, Sharratt M, Pegelow D, et al: Regulation of end-expiratory lung volume during exercise. J Appl Physiol 64:135–146, 1988.
38. Johnson BD, Saupe KW, Dempsey JA: Mechanical constraints on exercise hyperpnea in endurance athletes. J Appl Physiol 73:874–886, 1992.
39. Hansen JE, Sue DY, Wasserman K: Predicted values for clinical exercise testing. Am Rev Respir Dis 129(Suppl):S49–S55, 1984.
40. ATS/ACCP statement on cardiopulmonary exercise testing. Am J Respir Crit Care Med 167:211–277, 2003.
41. Hopkins SR, McKenzie DC, Schoene RB, et al: Pulmonary gas exchange during exercise in athletes. I. Ventilation-perfusion mismatch and diffusion limitation. J Appl Physiol 77:912–917, 1994.
42. Guralnik JM, Ferrucci L, Pieper CF, et al: Lower extremity function and subsequent disability: Consistency across studies, predictive models, and value of gait speed alone compared with the short physical performance battery. J Gerontol A Biol Sci Med Sci 55:M221–M231, 2000.
43. Solway S, Brooks D, Lacasse Y, et al: A qualitative systematic overview of the measurement properties of functional walk tests used in the cardiorespiratory domain. Chest 119:256–270, 2001.
44. Brown CD, Wise RA: Field tests of exercise in COPD: The six-minute walk test and the shuttle walk test. COPD 4:217–223, 2007.
45. Deboeck G, Niset G, Vachiery JL, et al: Physiological response to the six-minute walk test in pulmonary arterial hypertension. Eur Respir J 26:667–672, 2005.
46. Miyamoto S, Nagaya N, Satoh T, et al: Clinical correlates and prognostic significance of six-minute walk test in patients with primary pulmonary hypertension: Comparison with cardiopulmonary exercise testing. Am J Respir Crit Care Med 161:487–492, 2000.
47. Paramothayan NS, Lasserson TJ, Wells AU, et al: Prostacyclin for pulmonary hypertension in adults. Cochrane Database Syst Rev (2):CD002994, 2005.
48. Olsson LG, Swedberg K, Clark AL, et al: Six minute corridor walk test as an outcome measure for the assessment of treatment in randomized, blinded intervention trials of chronic heart failure: A systematic review. Eur Heart J 26:778–793, 2005.

49. Association between recombinant human erythropoietin and quality of life and exercise capacity of patients receiving haemodialysis. Canadian Erythropoietin Study Group. BMJ 300:573–578, 1990.
50. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med 166:111–117, 2002.
51. Szlachcic J, Massie BM, Kramer BL, et al: Correlates and prognostic implication of exercise capacity in chronic congestive heart failure. Am J Cardiol 55:1037–1042, 1985.
52. Keteyian SJ, Brawner CA, Savage PD, et al: Peak aerobic capacity predicts prognosis in patients with coronary heart disease. Am Heart J 156:292–300, 2008.
53. Kavanagh T, Mertens DJ, Hamm LF, et al: Peak oxygen intake and cardiac mortality in women referred for cardiac rehabilitation. J Am Coll Cardiol 42:2139–2143, 2003.
54. Kavanagh T, Mertens DJ, Hamm LF, et al: Prediction of long-term prognosis in 12,169 men referred for cardiac rehabilitation. Circulation 106:666–671, 2002.
55. Wensel R, Opitz CF, Anker SD, et al: Assessment of survival in patients with primary pulmonary hypertension: Importance of cardiopulmonary exercise testing. Circulation 106:319–324, 2002.
56. Oga T, Nishimura K, Tsukino M, et al: Analysis of the factors related to mortality in chronic obstructive pulmonary disease: Role of exercise capacity and health status. Am J Respir Crit Care Med 167:544–549, 2003.
57. Nixon PA, Orenstein DM, Kelsey SF, et al: The prognostic value of exercise testing in patients with cystic fibrosis. N Engl J Med 327:1785–1788, 1992.
58. Pianosi P, Leblanc J, Almudevar A: Peak oxygen uptake and mortality in children with cystic fibrosis. Thorax 60:50–54, 2005.
59. Kawut SM, O'Shea MK, Bartels MN, et al: Exercise testing determines survival in patients with diffuse parenchymal lung disease evaluated for lung transplantation. Respir Med 99:1431–1439, 2005.
60. Lederer DJ, Arcasoy SM, Wilt JS, et al: Six-minute-walk distance predicts waiting list survival in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 174:659–664, 2006.
60a. Fell CD, Liu LX, Motika C, et al: The prognostic value of cardiopulmonary exercise testing in idiopathic pulmonary fibrosis. Am J Resp Crit Care Med 179:402–407, 2009.
61. Mancini DM, Eisen H, Kussmaul W, et al: Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. Circulation 83:778–786, 1991.
62. Costanzo MR, Augustine S, Bourge R, et al: Selection and treatment of candidates for heart transplantation: A statement for health professionals from the Committee on Heart Failure and Cardiac Transplantation of the Council on Clinical Cardiology, American Heart Association. Circulation 92:3593–3612, 1995.
63. Guazzi M, Myers J, Abella J, et al: The added prognostic value of ventilatory efficiency to the Weber classification system in patients with heart failure. Int J Cardiol 129:86–92, 2008.
64. Gitt AK, Wasserman K, Kilkowski C, et al: Exercise anaerobic threshold and ventilatory efficiency identify heart failure patients for high risk of early death. Circulation 106:3079–3084, 2002.
65. Elmariah S, Goldberg LR, Allen MT, et al: Effects of gender on peak oxygen consumption and the timing of cardiac transplantation. J Am Coll Cardiol 47:2237–2242, 2006.
66. O'Neill JO, Young JB, Pothier CE, et al: Peak oxygen consumption as a predictor of death in patients with heart failure receiving beta-blockers. Circulation 111:2313–2318, 2005.
67. Tuppin MP, Paratz JD, Chang AT, et al: Predictive utility of the 6-minute walk distance on survival in patients awaiting lung transplantation. J Heart Lung Transplant 27:729–734, 2008.
68. Martinu T, Babyak MA, O'Connell CF, et al: Baseline 6-min walk distance predicts survival in lung transplant candidates. Am J Transplant 8:1498–1505, 2008.
69. Fishman A, Martinez F, Naunheim K, et al: A randomized trial comparing lung-volume-reduction surgery with medical therapy for severe emphysema. N Engl J Med 348:2059–2073, 2003.
70. Beckles MA, Spiro SG, Colice GL, et al: The physiologic evaluation of patients with lung cancer being considered for resectional surgery. Chest 123:105S–114S, 2003.
70a. Brunelli A, Belardinelli R, Refai M, et al: Peak oxygen consumption during cardiopulmonary exercise test improves risk stratification in candidates to major lung resection. Chest 135:1260–1267, 2009.
71. Wyser C, Stulz P, Soler M, et al: Prospective evaluation of an algorithm for the functional assessment of lung resection candidates. Am J Respir Crit Care Med 159:1450–1456, 1999.
72. Colice GL, Shafazand S, Griffin JP, et al: Physiologic evaluation of the patient with lung cancer being considered for resectional surgery: ACCP evidenced-based clinical practice guidelines (2nd edition). Chest 132:161S–177S, 2007.
73. Loewen GM, Watson D, Kohman L, et al: Preoperative exercise Vo_2 measurement for lung resection candidates: Results of Cancer and Leukemia Group B Protocol 9238. J Thorac Oncol 2:619–625, 2007.
73a. Smith TB, Stonell C, Purkayastha S, Paraskevas P: Cardiopulmonary exercise testing as a risk assessment method in non cardiopulmonary surgery: a systematic review. Anesthesia 64:883–893, 2009.
74. Older P, Hall A, Hader R: Cardiopulmonary exercise testing as a screening test for perioperative management of major surgery in the elderly. Chest 116:355–362, 1999.
75. Weber KT, Kinasewitz GT, Janicki JS, et al: Oxygen utilization and ventilation during exercise in patients with chronic cardiac failure. Circulation 65:1213–1223, 1982.
76. van den Broek SA, van Veldhuisen DJ, de Graeff PA, et al: Comparison between New York Heart Association classification and peak oxygen consumption in the assessment of functional status and prognosis in patients with mild to moderate chronic congestive heart failure secondary to either ischemic or idiopathic dilated cardiomyopathy. Am J Cardiol 70:359–363, 1992.
77. Stevenson LW, Steimle AE, Fonarow G, et al: Improvement in exercise capacity of candidates awaiting heart transplantation. J Am Coll Cardiol 25:163–170, 1995.
78. Celli BR, Cote CG, Marin JM, et al: The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. N Engl J Med 350:1005–1012, 2004.
79. Martinez FJ, Han MK, Andrei AC, et al: Longitudinal change in the BODE index predicts mortality in severe emphysema. Am J Respir Crit Care Med 178:491–499, 2008.
80. ACSM's Guidelines for Exercise Training and Prescription, 8th ed. Philadelphia: Lippincott Williams & Wilkins, 2009.
81. Durstine JL, Moore GE, Painter PL, Roberts SO (eds): ACSM's Exercise Management for Persons with Chronic Diseases and Disabilities, 3rd ed. Champaign, IL: Human Kinetics, 2009.
82. Marciniuk DD, Gallagher CG: Clinical exercise testing in chronic airflow limitation. Med Clin North Am 80:565–587, 1996.
83. Martinez FJ, Stanopoulos I, Acero R, et al: Graded comprehensive cardiopulmonary exercise testing in the evaluation of dyspnea unexplained by routine evaluation. Chest 105:168–174, 1994.
84. Whipp BJ, Davis JA, Torres F, et al: A test to determine parameters of aerobic function during exercise. J Appl Physiol 50:217–221, 1981.
85. Pratter MR, Curley FJ, Dubois J, et al: Cause and evaluation of chronic dyspnea in a pulmonary disease clinic. Arch Intern Med 149:2277–2282, 1989.
86. DePaso WJ, Winterbauer RH, Lusk JA, et al: Chronic dyspnea unexplained by history, physical examination, chest roentgenogram, and spirometry: Analysis of a seven-year experience. Chest 100:1293–1299, 1991.
87. Palange P, Carlone S, Forte S, et al: Cardiopulmonary exercise testing in the evaluation of patients with ventilatory vs circulatory causes of reduced exercise tolerance. Chest 105:1122–1126, 1994.
88. Gibbons L, Blair SN, Kohl HW, et al: The safety of maximal exercise testing. Circulation 80:846–852, 1989.
89. Arena R, Myers J, Williams MA, et al: Assessment of functional capacity in clinical and research settings: A scientific statement from the American Heart Association Committee on Exercise, Rehabilitation, and Prevention of the Council on Clinical Cardiology and the Council on Cardiovascular Nursing. Circulation 116:329–343, 2007.

90. Fletcher GF, Balady GJ, Amsterdam EA, et al: Exercise standards for testing and training: A statement for healthcare professionals from the American Heart Association. Circulation 104:1694–1740, 2001.
91. Rodgers GP, Ayanian JZ, Balady G, et al: American College of Cardiology/American Heart Association Clinical Competence statement on stress testing: A report of the American College of Cardiology/American Heart Association/American College of Physicians–American Society of Internal Medicine Task Force on Clinical Competence. J Am Coll Cardiol 36:1441–1453, 2000.
92. Beaver WL, Lamarra M, Wasserman K: Breath-by-breath measurement of true alveolar gas exchange. J Appl Physiol 51:1662–1675, 1981.
93. Porszasz J, Casaburi R, Somfay A, et al: A treadmill ramp protocol using simultaneous changes in speed and grade. Med Sci Sports Exerc 35:1596–1603, 2003.
94. Buchfuhrer MJ, Hansen JE, Robinson TE, et al: Optimizing the exercise protocol for cardiopulmonary assessment. J Appl Physiol 55:1558–1564, 1983.
95. Furuike AN, Sue DY, Hansen JE, et al: Comparison of physiologic dead space/tidal volume ratio and alveolar-arterial P_{O_2} difference during incremental and constant work exercise. Am Rev Respir Dis 126:579–583, 1982.
96. Hill DW: The critical power concept: A review. Sports Med 16:237–254, 1993.
97. Whipp BJ, Wasserman K: Oxygen uptake kinetics for various intensities of constant-load exercise. J Appl Physiol 33:351–356, 1972.
98. Roston WL, Whipp BJ, Davis JA, et al: Oxygen uptake kinetics and lactate concentration during exercise in humans. Am Rev Respir Dis 135:1080–1084, 1987.
99. Ong KC, Chong WF, Soh C, et al: Comparison of different exercise tests in assessing outcomes of pulmonary rehabilitation. Respir Care 49:1498–1503, 2004.
100. O'Donnell DE, Lam M, Webb, KA: Measurement of symptoms, lung hyperinflation, and endurance during exercise in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 158:1557–1565, 1998.
101. Poole DC, Barstow TJ, Gaesser GA, et al: V_{O_2} slow component: Physiological and functional significance. Med Sci Sports Exerc 26:1354–1358, 1994.
102. Hansen JE, Sun XG, Yasunobu Y, et al: Reproducibility of cardiopulmonary exercise measurements in patients with pulmonary arterial hypertension. Chest 126:816–824, 2004.
103. Bensimhon DR, Leifer ES, Ellis SJ, et al: Reproducibility of peak oxygen uptake and other cardiopulmonary exercise testing parameters in patients with heart failure (from the Heart Failure and A Controlled Trial Investigating Outcomes of exercise training). Am J Cardiol 102:712–717, 2008.
104. Hansen JE, Sue DY, Oren A, et al: Relation of oxygen uptake to work rate in normal men and men with circulatory disorders. Am J Cardiol 59:669–674, 1987.
105. Tanabe Y, Nakagawa I, Ito E, et al: Hemodynamic basis of the reduced oxygen uptake relative to work rate during incremental exercise in patients with chronic heart failure. Int J Cardiol 83:57–62, 2002.
106. Cohen-Solal A, Laperche T, Morvan D, et al: Prolonged kinetics of recovery of oxygen consumption after maximal graded exercise in patients with chronic heart failure: Analysis with gas exchange measurements and NMR spectroscopy. Circulation 91:2924–2932, 1995.
107. Guazzi M, Myers J, Peberdy MA, et al: Exercise oscillatory breathing in diastolic heart failure: prevalence and prognostic insights. Eur Heart J 29:2751–2759, 2008.
108. Farr MJ, Lang CC, Lamanca JJ, et al: Cardiopulmonary exercise variables in diastolic versus systolic heart failure. Am J Cardiol 102:203–206, 2008.
109. Riley MS, Porszasz J, Engelen MP, et al: Gas exchange responses to continuous incremental cycle ergometry exercise in primary pulmonary hypertension in humans. Eur J Appl Physiol 83:63–70, 2000.
110. Sun XG, Hansen JE, Oudiz RJ, et al: Exercise pathophysiology in patients with primary pulmonary hypertension. Circulation 104:429–435, 2001.
111. Sun XG, Hansen JE, Oudiz RJ, et al: Gas exchange detection of exercise-induced right-to-left shunt in patients with primary pulmonary hypertension. Circulation;105:54–60, 2002.
112. Sietsema KE, Cooper DM, Perloff JK, et al: Control of ventilation during exercise in patients with central venous to systemic arterial shunts. J Appl Physiol 64:234–242, 1988.
113. Neder JA, Nery LE, Castelo A, et al: Prediction of metabolic and cardiopulmonary responses to maximum cycle ergometry: A randomised study. Eur Respir J 14:1304–1313, 1999.
114. Brown HV, Wasserman K: Exercise performance in chronic obstructive pulmonary diseases. Med Clin North Am 65:525–547, 1981.
115. Johnson BD, Weisman IM, Zeballos RJ, et al: Emerging concepts in the evaluation of ventilatory limitation during exercise: The exercise tidal flow-volume loop. Chest 116:488–503, 1999.
116. O'Donnell DE, Revill SM, Webb KA: Dynamic hyperinflation and exercise intolerance in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 164:770–777, 2001.
117. Calverley PM: Dynamic hyperinflation: Is it worth measuring? Proc Am Thorac Soc 3:239–244, 2006.
118. Killian KJ, LeBlanc P, Martin DH, et al: Exercise capacity and ventilatory, circulatory, and symptom limitation in patients with chronic airflow limitation. Am Rev Respir Dis 146:935–940, 1992.
119. Gosselink R, Troosters T, Decramer M: Peripheral muscle weakness contributes to exercise limitation in COPD. Am J Respir Crit Care Med 153:976–980, 1996.
120. Casaburi R, Patessio A, Ioli F, et al: Reductions in exercise lactic acidosis and ventilation as a result of exercise training in patients with obstructive lung disease. Am Rev Respir Dis 143:9–18, 1991.
121. Sietsema K: Cardiovascular limitations in chronic pulmonary disease. Med Sci Sports Exerc 33:S656–S661, 2001.
122. Dempsey JA, Romer L, Rodman J, et al: Consequences of exercise-induced respiratory muscle work. Respir Physiol Neurobiol 151:242–250, 2006.
123. Pinto-Plata VM, Celli-Cruz RA, Vassaux C, et al: Differences in cardiopulmonary exercise test results by American Thoracic Society/European Respiratory Society–Global Initiative for Chronic Obstructive Lung Disease stage categories and gender. Chest 132:1204–1211, 2007.
124. West JB, Wagner PD, Neder JA, et al: The major limitation to exercise performance in COPD is inadequate energy supply to the respiratory and locomotor muscles vs. lower limb muscle dysfunction vs. dynamic hyperinflation. J Appl Physiol 105:758–762, 2008.
125. Crapo RO, Casaburi R, Coates AL, et al: Guidelines for methacholine and exercise challenge testing—1999. Am J Respir Crit Care Med 161:309–329, 2000.
126. Weiler JM, Bonini S, Coifman R, et al: American Academy of Allergy, Asthma & Immunology Work Group report: Exercise-induced asthma. J Allergy Clin Immunol 119:1349–1358, 2007.
127. Kosmas EN, Milic-Emili J, Polychronaki A, et al: Exercise-induced flow limitation, dynamic hyperinflation and exercise capacity in patients with bronchial asthma. Eur Respir J 24:378–384, 2004.
128. Heimdal JH, Roksund OD, Halvorsen T, et al: Continuous laryngoscopy exercise test: A method for visualizing laryngeal dysfunction during exercise. Laryngoscope 116:52–57, 2006.
129. Marciniuk DD, Sridhar G, Clemens RE, et al: Lung volumes and expiratory flow limitation during exercise in interstitial lung disease. J Appl Physiol 77:963–973, 1994.
130. Hansen JE, Wasserman K: Pathophysiology of activity limitation in patients with interstitial lung disease. Chest 109:1566–1576, 1996.
131. Pappas GP, Newman LS: Early pulmonary physiologic abnormalities in beryllium disease. Am Rev Respir Dis 148:661–666, 1993.
132. Miller A, Brown LK, Sloane MF, et al: Cardiorespiratory responses to incremental exercise in sarcoidosis patients with normal spirometry. Chest 107:323–329, 1995.
133. Marciniuk DD, Gallagher CG: Clinical exercise testing in interstitial lung disease. Clin Chest Med 15:287–303, 1994.
134. Sridhar MK, Carter R, Banham SW, et al: An evaluation of integrated cardiopulmonary exercise testing in a pulmonary function laboratory. Scott Med J 40:113–116, 1995.

135. Troosters T, Verstraete A, Ramon K, et al: Physical performance of patients with numerous psychosomatic complaints suggestive of hyperventilation. Eur Respir J 14:1314–1319, 1999.
136. Gilbert R, Sipple JH, Auchincloss JH Jr: Respiratory control and work of breathing in obese subjects. J Appl Physiol 16:21–26, 1961.
137. Babb TG, Ranasinghe KG, Comeau LA, et al: Dyspnea on exertion in obese women: Association with an increased oxygen cost of breathing. Am J Respir Crit Care Med 178:116–123, 2008.
138. Lewis SF, Haller RG: The pathophysiology of McArdle's disease: Clues to regulation in exercise and fatigue. J Appl Physiol 61:391–401, 1986.
139. Orngreen MC, Duno M, Ejstrup R, et al: Fuel utilization in subjects with carnitine palmitoyltransferase 2 gene mutations. Ann Neurol 57:60–66, 2005.
140. Larsson NG, Oldfors A: Mitochondrial myopathies. Acta Physiol Scand 171:385–393, 2001.
141. Flaherty KR, Wald J, Weisman IM, et al: Unexplained exertional limitation: Characterization of patients with a mitochondrial myopathy. Am J Respir Crit Care Med 164:425–432, 2001.
142. Taivassalo T, Jensen TD, Kennaway N, et al: The spectrum of exercise tolerance in mitochondrial myopathies: A study of 40 patients. Brain 126:413–423, 2003.
143. Lindholm H, Lofberg M, Somer H, et al: Abnormal blood lactate accumulation after exercise in patients with multiple mitochondrial DNA deletions and minor muscular symptoms. Clin Physiol Funct Imaging 24:109–115, 2004.
144. Eschenbacher WL, Mannina A: An algorithm for the interpretation of cardiopulmonary exercise tests. Chest 97:263–267, 1990.
145. Weisman IM, Zeballos RJ. Clinical exercise testing. Clin Chest Med 2001;22:679–701, viii.
146. Palange P, Ward SA, Carlsen KH, et al: Recommendations on the use of exercise testing in clinical practice. Eur Respir J 29:185–209, 2007.
147. Ainsworth BE, Haskell WL, Leon AS, et al: Compendium of physical activities: Classification of energy costs of human physical activities. Med Sci Sports Exerc 25:71–80, 1993.
148. Ainsworth BE, Haskell WL, Whitt MC, et al: Compendium of physical activities: An update of activity codes and MET intensities. Med Sci Sports Exerc 32:S498–S504, 2000.
149. Bruce RA, Kusumi F, Hosmer D: Maximal oxygen intake and nomographic assessment of functional aerobic impairment in cardiovascular disease. Am Heart J 85:546–562, 1973.
150. Jones NL, Makrides L, Hitchcock C, et al: Normal standards for an incremental progressive cycle ergometer test. Am Rev Resp Dis 131:700–708, 1985.
151. Neder JA, Nery LE, Peres C, et al: Reference values for dynamic responses to incremental cycle ergometry in males and females aged 20 to 80. Am J Respir Crit Care Med 164:1481–1486, 2001.
152. Sun XG, Hansen JE, Garatachea N, et al: Ventilatory efficiency during exercise in healthy subjects. Am J Respir Crit Care Med 166:1443–1448, 2002.
153. Blackie SP, Fairbarn MS, McElvaney NG, et al. Normal values and ranges for ventilation and breathing pattern at maximal exercise. Chest 100:136–142, 1991.
154. Beaver WL, Wasserman K, Whipp BJ: A new method for detecting anaerobic threshold by gas exchange. J Appl Physiol 60:2020–2027, 1986.

CHAPTER 26

PREOPERATIVE EVALUATION

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INTRODUCTION

Until recently, few studies had rigorously evaluated the ability of preoperative variables to predict postoperative pulmonary complications (PPCs). Recent investigations supplemented by a meta-analysis of the perioperative outcomes of large numbers of patients, however, now allow generation of indices that can better predict a patient's risk for mortality.[1-5] New investigations have also improved the ability to predict an individual's risk of developing postoperative pneumonia and respiratory failure (see Tables 26-1 and 26-2 as an example).

PPCs rival cardiovascular complications as a cause of perioperative morbidity in high-risk surgical procedures in patients with lung disease. Because surgical procedure–related risk factors contribute to overall risk, modifying the surgical approach may help reduce this risk (see later discussion on laparoscopic procedures as an example). Although patients with lung disease, even when it is quite severe, tend to tolerate anesthesia and surgery without excessive mortality or excessive morbidity, and although postoperative complications can be minimized by identifying high-risk patients preoperatively and treating them aggressively,[6,7] postoperative care should include approaches designed to reduce PPCs in all patients, regardless of their potential risk.

This chapter discusses the importance of the assessment of cardiac disease in patients with lung disease, the recent modifications in surgical and perioperative practices that have improved perioperative outcome, and preoperative assessment of patients with lung disease for specific procedures.

ASSESSMENT OF CARDIAC RISK IN PATIENTS WITH LUNG DISEASE

One of the most important risk factors predicting perioperative mortality after noncardiac surgery in patients with lung disease, especially lung disease due to smoking, is myocardial ischemia and infarction in the immediate postoperative period.[8,9] Many investigations have characterized the risk factors for perioperative cardiac events.[8,9] Practice guidelines have been published by the American College of Cardiology, the American Heart Association,[5] and the American College of Physicians.[10] The specific guidelines for preoperative assessment are designed to identify preexisting heart disease, to define the severity and stability of that disease, and to determine the risk of having a cardiac event (e.g., myocardial infarction, congestive heart failure, death) when the patient undergoes a specific surgical procedure.[6,10] To summarize the guidelines[5] briefly, there are defined clinical predictors of increased cardiovascular risk. Notably, pulmonary disease would influence these predictors if the patient had associated pulmonary hypertension, coronary artery disease, arrhythmias, or a low functional status. Surgical procedures have been classified as to

their risk of causing cardiac death or nonfatal myocardial infarction. High-risk procedures are those that have a 5% or higher risk of these cardiac events, intermediate procedures have a risk of more than 1% but less than 5%, and low-risk procedures have a risk less than 1%.[5,10]

Reduction of cardiac risk involves medical therapy with perioperative β-blockers, such as metoprolol, the administration of a central-acting α-agonist, such as clonidine or dexmedetomidine, and possibly statin medication.[11–15]

Although not shown in all studies,[12] several investigations have documented the efficacy of perioperative β-blockade or α-agonist therapy in decreasing perioperative ischemia and cardiac mortality.[11–15] In fact, investigations have shown that β-blockers can be administered to patients with chronic obstructive lung disease (COPD) without increasing airway obstruction.[14,16] Atrial arrhythmias are frequently observed in patients with COPD,[14–18] especially after cardiac operations[19,20]; and they are associated with prolonged hospitalization and an increased incidence of strokes, poorer cognitive dysfunction, and death.[19,20] These atrial arrhythmias can be prevented by perioperative administration of β-blockers.[19,21] Patients with COPD and elderly patients who have had previous myocardial infarctions have a 40% increase in survival if β-blockers are administered, but because of physician bias, these patients are often not treated with these lifesaving medications.[22] Therefore, current data still suggest that β-blockers should be used in patients with COPD who are at risk for cardiac events perioperatively or in patients who have had myocardial infarctions.

Long-acting inhaled β-agonists may have adverse cardiac effects in patients with COPD, particularly if these patients have preexisting cardiac arrhythmias, hypoxemia, or left ventricular systolic dysfunction.[23] Patients were found to have increased heart rates and more supraventricular and ventricular premature beats when they were given 24 mg of formoterol.[23] In patients hospitalized for heart failure, there was an increased, dose-response–related risk between the use of inhaled β-agonists and all causes of mortality.[16] Patients with hypoxemic COPD can have an autonomic neuropathy, which has been associated with a prolonged QTc interval and an increased risk of ventricular arrhythmias and death.[24,25] The QTc interval can be further prolonged by more severe hypoxemia, and β-agonists can increase hypoxemia transiently, in some instances by worsening ventilation-perfusion heterogeneity.[25] The incidence of perioperative arrhythmias in patients given long-acting β-agonists has not been compared with those occurring in patients receiving shorter-acting β-agonists. Long-acting β-agonists should, however, be utilized with caution in COPD patients who are having arrhythmias or ischemia.[16]

CHANGES IN ANESTHETICS AND SURGICAL PRACTICES

Anesthesia and Analgesia

Atelectasis has been noted in 90% of the patients given any anesthetic except ketamine and epidural anesthetics.[26] The atelectasis develops whether the patient is breathing spontaneously or is paralyzed and ventilated mechanically.[27] The atelectasis occurs in the dorsal, caudal lung regions in supine patients and can comprise 10% of the total lung tissue.[27] It is attributed to compression of lung tissue by mediastinal organs and abdominal pressure, is reduced by phrenic nerve stimulation, and is believed to result from loss of inspiratory muscle tone, changes in thoracic geometry, and alterations in diaphragm position and motion.[26–28] The atelectasis persists for up to 2 days after major surgery (see later) but resolves within 24 hours after laparoscopy in nonobese patients.[26–28] Morbidly obese patients have more atelectasis than nonobese patients, and the atelectasis persists longer.[29] A vital capacity maneuver (i.e., applying an airway pressure of 40 cm H_2O for 8 sec) reexpands atelectactic lung tissue, alleviates the atelectasis (as seen on computed tomography [CT] scans), and improves oxygenation.[29,30] Greater pressures and even the beach-chair position[31] as well as using pressure-controlled ventilation intraoperatively[32] may be needed in obese patients and those with low abdominal and/or chest wall compliance. Newer volatile anesthetics (i.e., desflurane, sevoflurane) with a shorter half-life are now utilized.[33] Within 10 minutes after discontinuing either desflurane or sevoflurane, patients have normal ventilatory responses.[33] These agents may not be associated with the same changes seen with older volatile anesthetics.[33]

Despite the documented effects of the volatile anesthetics on pulmonary function, there is no clear evidence that regional anesthesia results in better intraoperative or postoperative pulmonary function.[34–36] A number of investigators report preserved lung compliance and arterial oxygenation with use of epidural anesthesia. Others, however, find a decrease in the expiratory reserve volume and cough efficacy with both spinal and epidural anesthesia.[34–36]

A number of studies have compared the effects of regional and general anesthesia in patients with lung disease. Ravin[35] examined 20 patients with a maximal voluntary ventilation (MVV) value of less than 68 L/min and a residual volume–to–total lung capacity ratio greater than 45% who underwent lower abdominal surgery. Intraoperatively and postoperatively, there was no difference in arterial P_{O_2} between patients receiving spinal anesthesia and those given general anesthesia. Similar results were obtained by Boutros and Weisel.[36] Thus, there does not appear to be an advantage in using regional anesthesia to maintain intraoperative or immediate postoperative arterial blood gas values. Postoperative respiratory failure, however, may possibly occur less frequently in selected patients receiving epidural analgesia.[37] Furthermore, there does not seem to be any difference in other organ function, including cognition, after regional anesthesia compared with general anesthesia.[37,38] At a minimum, it appears that epidural analgesia can produce superior pain relief, particularly if it is initiated prior to the surgical incision,[39] and it may be associated with fewer complications and a lower incidence of respiratory failure than parenteral narcotics in selected patients. Thus, the decision to use regional or general

anesthesia should be made on the basis of the location of the surgery, the surgical technique (laparoscopy), and whether controlling the airway is advantageous.

Abdominal Surgeries

Upper abdominal surgery carries more risk for pulmonary complications than does lower abdominal surgery (which, in turn, carries more risk than peripheral surgery). Diaphragm dysfunction induced by upper abdominal surgery has been identified as an important factor in the development of postoperative pulmonary problems.[40] The pulmonary dysfunction observed after open upper abdominal surgery is characterized by a long-lasting decrease in lung volumes, leading to the development of atelectasis and hypoxemia.[40] Postoperatively, patients use rib cage breathing rather than abdominal breathing. These abnormalities have been attributed to dysfunction of the diaphragm and/or the phrenic nerve. A number of studies indicate, however, that phrenic nerve stimulation generates normal transdiaphragmatic pressures after upper abdominal surgery. Accordingly, the nerve seems to work, and the strength of the diaphragm seems to be normal. These findings imply that the activity of the nerve may be reduced by transmission of inhibitory signals resulting from visceral or somatic afferents. In support of this idea is the observation that administering local anesthetics to the epidural space improves diaphragmatic function after upper abdominal surgery. Other investigators, however, found that epidural and subarachnoid administration of opiates achieved pain relief but did *not* improve diaphragmatic function.[41,42] Although pain relief and/or postoperative maneuvers designed to improve lung volumes (e.g., intermittent positive-pressure treatments, incentive spirometry, deep-breathing exercises) seem to decrease the incidence of postoperative pulmonary dysfunction, neither intervention completely prevents the problem.[41,42] It appears that most of the maneuvers designed to increase lung volumes and expand atelectatic lung segments are equally effective,[43] but intermittent positive-pressure breathing seems to be less comfortable and is more expensive.[43]

Laparoscopic procedures were introduced to the U.S. military hospitals in 1990; within 2 years, 87% of the cholecystectomies performed were done laparoscopically with only a 10% or less conversion rate to an open procedure.[44] The number of complications observed after laparoscopic procedures depends on the experience of both the surgeon and the institution with the procedure. The number of perioperative complications decreases after approximately 20 procedures, and the risk of adverse outcomes stabilizes after 50 laparoscopic procedures have been performed at an institution.[45,45a]

The advantages of the laparoscopic technique are that much smaller abdominal incisions are made, less postoperative pain is created, there is less disruption of diaphragmatic or abdominal muscle activity, and the patients can often leave the hospital within 1 day of the surgery.[46] Patients with lung disease who would have had difficulty with the PPCs associated with open abdominal procedures have now successfully undergone laparoscopic abdominal procedures.[46]

Cardiac Surgeries

The postoperative period following cardiac surgery is characterized by a high incidence of respiratory complications.[47] Atelectasis is more prominent when cardiopulmonary bypass is used, occurring even more commonly than after thoracotomy. A randomized investigation of 78 patients undergoing cardiopulmonary bypass documented that the delivery of positive end-expiratory pressure up to 15 cm H_2O (until a peak inspiratory pressure of 40 cm H_2O was reached) resulted in significant improvement in oxygenation during the first hour after bypass; however, the improvement was not sustained.[30]

Intraoperative variables that have been associated with severe atelectasis include the number of grafts, longer bypass times, and use of internal mammary grafts, which requires opening the pleural space.[47] Phrenic nerve paralysis is not commonly found in these patients (<10%) and is therefore not a common cause of atelectasis after cardiac surgery.[48] The mechanisms for the atelectasis may be that the blood supply to the alveolar epithelium is inadequate during cardiopulmonary bypass. Lungs that are ventilated without positive end-expiratory pressure and that are exposed to the atmosphere tend to develop atelectasis. The cold temperature used in these surgical procedures may also produce abnormalities in surfactant production or function.

The patients undergoing cardiac surgery in the current decade are older and have more comorbidities than patients in the 1990s.[49] However, the perioperative mortality rate for this procedure has decreased to 3% in 1999 from nearly 4% in 1990.[49] Short-term mortality after coronary artery bypass graf (CABG; <30 days) is primarily affected by cardiac variables, including age, history of previous heart operation, prior myocardial infarction, extent of noncardiac comorbidity, and urgency of the operation.[50,51] In contrast, intermediate-term survival (>30 days postoperatively) is affected by noncardiac variables, including functional status, COPD, and renal dysfunction.[50]

Recently, CABG procedures are being done off cardiopulmonary bypass (OPCAB). Retrospective analyses suggest that these patients had fewer perioperative myocardial infarctions and shorter ICU stays.[51-53] The Octopus Study Group documented the equivalence of off-pump and on-pump bypass surgery with respect to perioperative and 1-year survival; however, only low-risk patients were assessed.[54] Furthermore, cognitive declines and the incidence of atrial fibrillation were not different between the patients who had been on bypass and those who had been OPCAB.[54,55] Therefore, preliminary data do not document a superiority of OPCAB compared with the conventional bypass procedure.

Thoracic Surgeries

The atelectasis seen after thoracic surgery seems to have different mechanisms. Cardiopulmonary bypass is not

routinely used for thoracic surgery, so it is not a cause of the atelectasis. Diaphragm dysfunction does not appear to be a problem, although the maximal strength of the diaphragm may be somewhat reduced after thoracotomy.[56] Phrenic nerve dysfunction is not uncommon after thoracotomy, but the abnormalities are usually mild and account for only half of the diaphragmatic motion disturbances.[57] Pleural or mediastinal drainage tubes do not appear to contribute to postoperative lung dysfunction.[58] Mechanical compression of the lung, accumulation of secretions, increased lung water, alterations in chest wall mechanics due to the thoracotomy itself, and reduced surfactant activity may lead to atelectasis of the lung after thoracotomy.

Esophagectomy is associated with an extremely high risk of PPCs. A multicenter prospective study of 1777 patients undergoing surgical resection of the esophagus reported a 21% incidence of pneumonia and a 16% incidence of respiratory failure.[59] Preoperative factors associated with PPCs were increasing age, dyspnea, diabetes mellitus, COPD, alkaline phosphatase greater than 125 U/L, lower serum albumin concentrations, increased complexity scores, and decreased functional status. Intraoperative risk factors included the need for blood transfusion and longer operative time. A trial of 220 patients with adenocarcinoma of the mid-to-distal esophagus or the gastric cardia involving the distal esophagus randomized to esophagectomy via transhiatal versus a transthoracic approach showed lower incidence of PPCs (27% vs. 57%, $P < .001$) with the transhiatal approach.[60]

PREOPERATIVE EVALUATION OF HIGH-RISK PATIENTS

Patients Who Smoke

Patients with moderate to severe COPD, and smokers without demonstrable airflow limitation are at high risk for PPCs. Patients with asthma should also be carefully evaluated. This section considers these three groups of patients.

One third of all patients who undergo surgery are smokers.[61] Chronic exposure to cigarette smoke produces profound changes in physiology that may alter responses to perioperative interventions and contribute to perioperative morbidity and mortality, mainly because of the effects of smoking on the cardiovascular and respiratory systems.[61,61a] Such alterations may also predispose to postoperative renal failure in smokers with severe COPD.[62]

Smokers may have increased levels of carboxyhemoglobin as a function of their brand of cigarette, how deeply they inhale, the number of puffs they take, and the level of ventilation during smoking.[63] The level of carboxyhemoglobin in smokers usually ranges from 3% to 15%, and the major effects are (1) to reduce the amount of hemoglobin available to bind with oxygen (which decreases arterial oxygen content) and (2) to shift the oxygen-hemoglobin saturation curve to the left (which facilitates loading of oxygen onto hemoglobin but impairs unloading at the tissues). Smoking has been shown to increase the carboxyhemoglobin measured during surgery, even after the initiation of mechanical ventilation.[64] Smokers have decreased oxygen delivery and increased tissue oxygen extraction, manifested by a reduced mixed venous oxygen content. Patients at greater risk for elevated carboxyhemoglobin levels are those who smoke avidly late at night and then undergo an early morning operation. Therefore, it is recommended that smokers stop smoking 12 to 18 hours preoperatively (if not permanently) to allow three half-lives of time for carboxyhemoglobin clearance.

Nicotine has concentration-dependent effects on the cardiovascular system. It can cause systemic vasoconstriction and increase both heart rate and systemic blood pressure. Abstinence from smoking for 20 minutes is followed by a decrease in heart rate, blood pressure, and systemic catecholamine levels.[65] These cardiovascular effects of nicotine may contribute to perioperative morbidity in smokers, and short-term abstinence may be beneficial.

Several investigators have evaluated PPCs in smokers.[61,66,67] These studies suggest that smoking may be associated with increased pulmonary complications when the patient is older, has smoked longer, is currently smoking, and perhaps already has significant underlying lung disease. Several investigators have documented that an optimal period of abstinence is 8 weeks prior to surgery, as this duration of cessation is associated with fewer pulmonary complications, better wound healing, and shorter length of stay in the ICU.[61] Also, patients who stop smoking before or immediately after percutaneous cardiac revascularization have a lower risk of Q-wave infarctions and death.[67] A smoking-intervention program targeted at smokers who are hospitalized for surgery produces higher long-term quit rates.[68] Accordingly, the preoperative evaluation of smokers should include enrolling them in smoking-cessation programs[68] or, at a minimum, provide a time when a serious discussion can occur regarding smoking. At least 12 to 24 hours of preoperative abstinence should be sought to achieve possible cardiovascular benefits and perhaps optimally 6 to 8 weeks of preoperative abstinence to decrease the incidence of PPCs.[61]

Patients with Obstructive Sleep Apnea and Chronic Obstructive Pulmonary Disease

Risk factors for PPCs are related to general health and nutritional status and include advanced age, COPD, congestive heart failure, lower albumin level, dependent functional status, and weight loss.[69] Obesity itself has not been clearly identify as a risk factor for PPCs. Pulmonary problems associated with PPCs include COPD, pneumonia, and sleep apnea.[69] Patients with obstructive sleep apnea (OSA) patients have a higher incidence of (mainly respiratory) PPCs than those who do not.[70] In a more defined surgical population, 39% of patients with OSA

who had hip or knee replacements developed PPCs or cardiac complications compared with 18% of patients without OSA; 24% of the patients with OSA required ICU admissions compared with 9% of patients without OSA.[71] Few investigations have identified the perioperative risks for OSA surgical patients,[72,72a] but left heart failure or right heart dysfunction due to pulmonary hypertension should be sought. Pulmonary hypertension is particularly associated with a significant perioperative risk.[73,74] As cardiovascular dysfunction in OSA patients can be modified by treatment,[75–77] it seems important to identify patients not known to have OSA and have them treated. However, to date, owing to lack of appropriate studies, it is not known whether establishing the diagnosis of OSA prior to surgery and instituting/optimizing therapy will improve perioperative outcomes.

A large retrospective observational review of patient data (mainly men) in Veterans Affairs hospitals allowed risk stratification for postoperative pneumonia and postoperative respiratory failure. Each risk factor was assigned a point value, and the total number of points was associated with a predicted probability for the development of these complications.[1,3] For example, a history of COPD conferred 5 points for the risk of postoperative pneumonia and 6 points on the respiratory failure risk index. Pulmonary function tests were not done for these investigations, and the investigators stated that "pulmonary function tests do not appear to predict PPCs."[69] Accordingly, the diagnosis of COPD was based on clinical assessment. Having more than 55 points on the Postoperative Pneumonia Risk Index gave the patient a predicted probability of pneumonia of 15% and of perioperative mortality of about 25%.[3] A point total over 40 on the Respiratory Failure Risk Index was associated with a predicted probability of 31% of respiratory failure.[1] Of note, the newer study from Arozullah's group[2] is more broadly applicable becaue it was developed in patients from the private sector as well as from the Veterans Affairs hospitals and involved patients undergoing vascular and general surgical operations. Although individual point scores differed from the original study, a similar incidence of postoperative respiratory failure was found compared with the original risk model. This congruence between the studies validates the original study and, notably, still identifies COPD as a relevant risk factor for postoperative respiratory failure (Tables 26-1 and 26-2).

Preoperative spirometry or other pulmonary function tests have not been uniformly useful in identifying those who will develop severe pulmonary complications.[78–81] The presence of preoperative hypoxemia identified those who required mechanical ventilation postoperatively in two studies (Fig. 26-1),[80,81] and intraoperative blood administration was associated with those who require mechanical ventilation and develop postoperative pneumonia.[82] Perioperative transfusions are associated with increased mortality, postoperative pneumonia, and hospital length of stay.[82]

TABLE 26-1. Independent Predictors of Respiratory Failure after General and Vascular Surgery

Effect	Odds Ratio (95% CI)	Score
ASA class (3 vs. 1–2)	2.88 (2.46–3.36)	3
ASA class (4–5 vs. 1–2)	4.90 (4.11–5.85)	5
Emergency	2.42 (2.17–2.69)	2
Work RVU (10–17 vs. <10)	2.30 (1.94–2.73)	2
Work RVU (>17 vs. <10)	4.45 (3.72–5.31)	4
Preop albumin (<3.5 vs. >3.5)	1.49 (1.34–1.64)	1
Integumentary versus hernia	1.14 (0.87–1.50)	1
Respiratory versus hernia	3.12 (2.18–4.47)	3
Heart versus hernia	2.31 (1.67–3.20)	2
Aneurysm versus hernia	1.55 (1.20–2.00)	2
Mouth, palate versus hernia	6.64 (4.78–9.21)	7
Stomach, intestines versus hernia	2.13 (1.66–2.73)	2
Endocrine versus hernia	1.54 (0.99–2.38)	2
Preop sepsis	2.00 (1.71–2.34)	2
Preop creatinine > 1.5	1.65 (1.49–1.82)	2
History of severe COPD	1.52 (1.36–1.69)	2
Ascites	1.85 (1.50–2.28)	2
Dyspnea (yes vs. no)	1.32 (1.19–1.46)	1
Impaired sensorium	1.50 (1.22–1.84)	1
Preop bilirubin > 1.0	1.21 (1.08–1.35)	1
>2 alcoholic drinks/day	1.30 (1.14–1.49)	1
Bleeding disorders	1.25 (1.07–1.46)	1
Age (40–65 vs. <40 yr)	1.70 (0.86–3.37)	2
Age (>65 vs. <40 yr)	2.06 (1.54–2.77)	2
Preop WBC (<2.5 vs. 2.5–10)	1.48 (0.89–2.47)	1
Preop WBC (>10 vs. 2.5–10)	1.20 (1.09–1.33)	1
Preop serum sodium (>145)	1.56 (1.21–2.03)	2
Weight loss > 10%	1.26 (1.10–1.44)	1
Preop acute renal failure	1.51 (1.17–1.94)	2
Gender (male vs. female)	1.19 (1.06–1.35)	1
CHF < 30 days before operation	1.30 (1.09–1.55)	1
Smoker	1.15 (1.05–1.26)	1
Preop platelet count < 150	1.21 (1.06–1.38)	1
CVA with neurologic deficit	1.27 (1.10–1.47)	1
CVA without neurologic deficit	1.23 (1.02–1.48)	1
Wound class (clean/contaminated)	1.16 (1.02–1.30)	1
Wound class (contaminated)	1.36 (1.15–1.61)	1
Wound class (infected)	1.25 (1.04–1.50)	1
Preop SGOT > 40	1.16 (1.04–1.30)	1
Preop hematocrit < 38	1.11 (1.01–1.23)	1

ASA, American Society of Anesthesiologists; CHF, congestive heart failure; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident (stroke); Preop, preoperative; RVU, relative value unit; SGOT, serum glutamic-oxalacetic transaminase; WBC, white blood count.

Adapted from Johnson RG, Arozullah AM, Neumayer L, et al: Multivariable predictors of postoperative respiratory failure after general and vascular surgery: Results from the patient safety in surgery study. J Am Coll Surg 204:1189–1198, 2007.

Patients with Asthma

Patients with acute bronchospasm are rarely subjected to elective surgery, and they are almost certainly at

increased risk for perioperative complications. Unfortunately, there are no data available on how long after resolution of an acute exacerbation of asthma that patients remain at increased risk. Giving anesthesia to, and performing surgery on, stable, well-treated asthmatic patients is associated with a low incidence of complications.[83]

Several maneuvers associated with anesthesia may aggravate bronchospasm, particularly if the patient has a history of severe asthma. First, tracheal intubation can initiate bronchospasm.[84] Thus, in moderate to severe asthmatics, regional anesthesia should be considered. When general anesthesia is necessary, endotracheal intubation should be avoided, if possible. Shnider and Papper[85] showed that patients who received general anesthesia but were not intubated had an incidence of bronchospasm similar to that of patients who received regional anesthesia compared with a 6% to 7% incidence of bronchospasm in those who were intubated.

All of the volatile anesthetics are effective in preventing[86] and reversing bronchospasm. However, the volatile agents do not have a normal bronchodilatory effect when the epithelium is disrupted, as their bronchodilatory effects appear to depend at least in part on prostanoid and nitric oxide generation from the epithelium.[87] Halothane is associated with ventricular arrhythmias when toxic aminophylline levels are present. Therefore, if there is any concern about the aminophylline level, halothane should probably be avoided. Sevoflurane has proved to be a safe clinical alternative to halothane.

Some of the fixed agents used for anesthesia induction improve bronchomotor tone. Ketamine prevents antigen-induced increases in pulmonary resistance in experimental models of asthma[88] and decreases calcium influx into airway smooth muscle.[89] In contrast, thiopental has no effect on bronchomotor tone. Propofol decreases respiratory resistance in nonasthmatic patients who smoke and is associated with lower respiratory resistance than either thiopental or etomidate in these patients.[90] However, propofol was not compared with ketamine and is probably not as good a bronchodilator as ketamine.

Narcotics have not been well studied regarding their effects on asthmatics. Because morphine has been associated with histamine release, some investigators have recommended against its use in patients with asthma.[84] Some have also advised against using the nondepolarizing neuromuscular blocking agent *d*-tubocurarine because it also releases histamine.[84]

TABLE 26-2. Respiratory Risk Index for Respiratory Failure after General and Vascular Surgery

Risk Level	Score Range*	Respiratory Failure (%)
Low	<8	0.08
Medium	8–12	0.84
High	>12	6.75

*Score derived from independent predictors of respiratory failure (see Table 26-1).

Adapted from Johnson RG, Arozullah AM, Neumayer L, et al: Multivariable predictors of postoperative respiratory failure after general and vascular surgery: Results from the patient safety in surgery study. J Am Coll Surg 204:1189–1198, 2007.

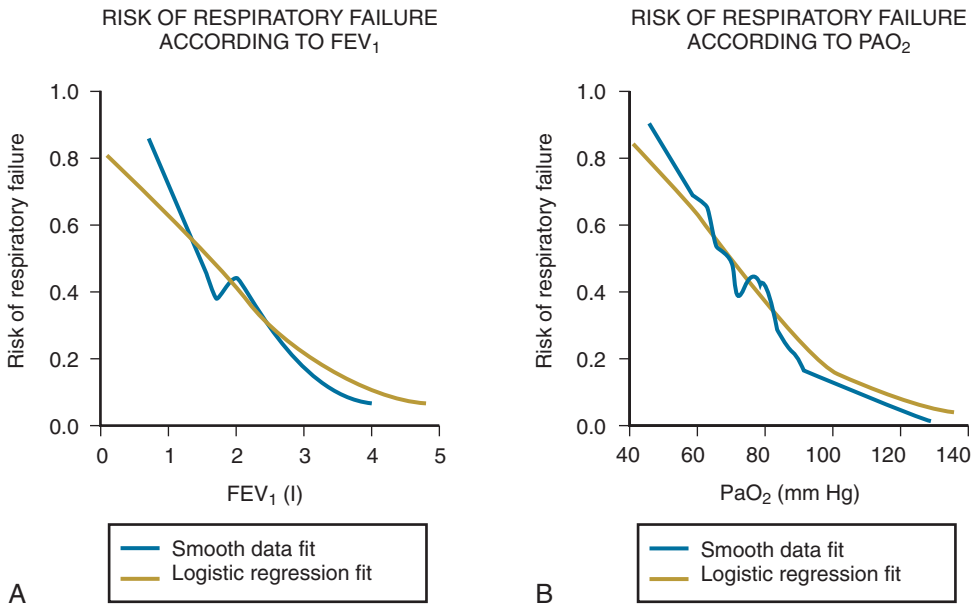

FIGURE 26-1 ■ The risk for postoperative respiratory failure after thoracoabdominal aorta surgery. Assessment of risk was done by testing the forced expiratory volume in 1 second (FEV_1) (**A**) as well as testing preoperative arterial oxygen tension (Pa_{O_2}) (**B**). The *blue lines* have been generated from a smooth fit of the data, and the *brown lines* have been generated from a univariate logistic linear regression analysis of the data. Note the similarities between the two preoperative tests in predicting subsequent respiratory failure. (Redrawn from Svensson LG, Hess KR, Coselli JS, et al: A prospective study of respiratory failure after high-risk surgery on the thoracoabdominal aorta. J Vasc Surg 14:271–282, 1991.)

PULMONARY RESECTION

Surgery remains the only chance for a cure of lung cancer and is especially useful for patients with stage IA or IB non–small cell malignancies, as 5-year survivals that range as high as 77% and 60%, respectively, have been reported (see Chapter 47). Lung resection surgery can now be done with smaller incisions (2 cm for closed thoracoscopy), muscle-sparing incisions (8 cm), less rib damage (no rib spreader utilized), and thoracoscopy. These new surgical techniques have decreased the mortality, morbidity, and length of stay associated with thoracic surgery.[91,92] In several reports, for example, the surgical mortality rate for elderly patients (≥70 years) who underwent thoracic procedures was 1.5%, the median length of stay was 4 days, and the conversion rate to open thoracotomy was low, 1%.[93–95] Although the risks associated with these surgeries have decreased, there has not been a direct comparison of minimally invasive versus standard thoracotomy on the long-term outcome of patients with lung cancer. Accordingly, many suggest that thoracotomy should be the preferred approach in those without underlying comorbidities, indicating an increased risk of the operation. The preoperative evaluation required for the newer techniques has yet to be defined.

The morbidity and mortality associated with standard lung resection procedures have also improved; operative mortality overall for lung resection is now 3.7% in some medical centers, whereas in the 1980s, the mortality was 6.2% for pneumonectomy.[95] High-volume hospitals have better outcomes than do medical centers where fewer procedures are performed,[96,97] but a more recent study suggests that the number of procedures done by an individual physician is not correlated with hospital mortality.[98]

Physiologic Changes Postresection

A number of physiologic changes occur after pneumonectomy. Hsia and colleagues[99–101] exercised three conditioned foxhounds before and 6 to 12 months after pneumonectomy and found postoperative impairment of ventilatory responses to carbon dioxide at all levels of work along with arterial hypoxemia during heavy exercise. The physiologic mechanism in part responsible for the latter abnormality was an increase in exercise-induced ventilation-perfusion heterogeneity and a diffusion limitation. Together, these problems accounted for 58% of the hypoxemia. Cardiac output was also reduced after pneumonectomy, and the hemoglobin concentration increased to compensate for the decrease in oxygen delivery. Further studies that were designed to determine why removing 42% of the total lung tissue (the left lung) decreased the diffusing capacity by only 30% suggested that the remaining lung increases its diffusing capacity by recruiting new vessels.[101] Interestingly, there is a greater degree of diffusion capacity compensation with right versus left pneumonectomy. Mechanisms proposed to explain the recruitment of new vessels implied by these compensatory changes include the effects of the resulting pulmonary hypertension and/or the expansion of the remaining lung that occurs, which could open new alveolar septal and corner capillaries, respectively.

Patients have a 15% decrease in vital capacity after lobectomy, and a 35% to 40% decrease following pneumonectomy.[102] The decrease in lung function is usually less than expected from the number of segments removed, suggesting that the tumor decreased the function of the resected lung and/or that the remaining lung expanded. Patients also have a decrease in oxygen consumption, arterial P_{O_2}, cardiac output, stroke volume, and heart rate at maximum exercise, and they are not able to achieve their preoperative maximal workload and they have a decrease in stroke volume at all levels of exercise and an increase in systemic vascular resistance.[102] The patients who had had a lobectomy had changes similar to those seen in patients with a pneumonectomy, but the differences were less pronounced.

Resection Procedures

Preoperative assessment of patients in need of pulmonary resectional surgery should address two questions: (1) Is the likelihood of perioperative mortality or a postoperative complication so high that the surgery should not be performed? (2) Will the postoperative pulmonary function be sufficient to allow reasonable quality of life?

Is the Likelihood of Perioperative Mortality or a Postoperative Complication So High the Surgery Should Not Be Performed? Because most pulmonary resectional surgery is done with the hope of curing lung cancer, the risks of postoperative complications would have to be extraordinarily high before they would dissuade most patients, or their physicians, from undertaking the operation.[103] Not surprisingly, no studies have suggested that preoperative evaluation aids in making this decision.

The mortality associated with lobectomy and pneumonectomy may be increased in patients over 70 years of age (4%–7% and 14%, respectively), although the effect of age is debated.[104,105] The suggestion has been made that the increased risk is related to increased comorbidities rather than to age alone. Data on patients over age 80 are limited, but selected patients also seem to be reasonable surgical candidates. Lobectomy should not be excluded solely on the basis of age alone. The British Thoracic Society guidelines[106] indicate that age should be taken into account when considering pneumonectomy.

Because of the combined morbidities attributable to smoking, patients who are candidates for pulmonary resection require complete cardiac and pulmonary evaluation. There are numerous clinical predictors of coronary artery disease, and its presence certainly increases the risk of death or of having a nonfatal myocardial infarction within 30 days of surgery. With appropriate pre- and perioperative management, however,

these risks may be reduced considerably. Nonetheless, patients with unstable coronary syndromes, unstable or severe angina, a recent myocardial infarction with residual ischemic risk, decompensated congestive heart failure, uncorrectable life-threatening arrhythmias, or severe valvular disease can generally be excluded from surgery, as their 5-year survival is much more likely to depend on their cardiac abnormalities than on the lung cancer. To expand on this concept further, coronary angioplasty and stenting like conventional CABG surgery are problematic because of the time restrictions limiting the management of bronchogenic carcinoma. Combining conventional CABG surgery with the lung surgery has led to increased risk of morbidity and mortality.[107] However, one small study that looked at minimally invasive ("off-pump") direct coronary artery bypass concurrently with the lung resection surgery found that complications were comparable with resection alone and noted no postoperative myocardial infarctions or episodes of myocardial ischemia.[108] Thus, in certain instances, it may soon be possible to approach some patients with coexisting significant coronary artery disease that would have been previously excluded from lung resection surgery, if further studies confirm these findings.

In reviewing older studies done to predict PPCs after lung resection, it becomes clear that patients develop both pulmonary and cardiac complications (e.g., arrhythmias, myocardial infarction, pulmonary embolism, pneumonia, empyema) that can influence the duration of mechanical ventilation and outcome. Although none of these complications can be accurately predicted by preoperative studies of pulmonary function, a mortality rate under 5% can be expected if the preoperative postbronchodilator forced expiratory volume in 1 second (FEV_1) is more than 1.5 Ls in patients scheduled for lobectomy. A similar mortality rate, about 5%, should be seen if patients scheduled for pneumonectomy have a preoperative postbronchodilator FEV_1 of more than 2 L. Accordingly, if the FEV_1 exceeds these limits (in the absence of symptoms, dyspnea, or chest radiographic evidence of interstitial lung disease), the British Thoracic Society recommends that no additional pulmonary testing is needed. There has been increased use of preoperative exercise studies in an attempt to detect patients likely to have postoperative complications; but there are, as yet, no convincing data that this approach is more sensitive or specific. Mortality from respiratory problems is somewhat more common in older patients who have more serious airflow limitation.

Will the Postoperative Pulmonary Function Be Sufficient to Allow Reasonable Quality of Life? Fear of creating pulmonary insufficiency by lung resection is an important concern; and, accordingly, numerous studies have been conducted to find the lowest limit of pulmonary function that allows surgery to be performed while maintaining adequate pulmonary function postoperatively. Many older studies compared pulmonary function before and after operations for pulmonary tuberculosis.[109] More recent studies have examined patients with bronchogenic carcinoma. Boushy and associates[110] followed 142 patients for 3 months postoperatively and found that 10 died in the immediate postoperative period from myocardial infarction or pulmonary emboli. As would be expected, these patients had pulmonary function studies similar to those of patients who survived their operations.

Recent consensus statements suggest that all patients should have their FEV_1 measured. Those who have no dyspnea on exertion or interstitial lung disease on chest radiographs, and those who have an FEV_1 of more than 1.5 L are deemed suitable for a lobectomy. Those with an FEV_1 of more than 2.0 L are deemed at low risk for a pneumonectomy. Patients whose FEV_1 values are below these limits, and those who have dyspnea on exertion or interstitial lung disease on chest radiographs (regardless of their FEV_1) should have their diffusing capacity for carbon monoxide (DL_{CO}) measured along with pulse oximetry.[106,111] The postoperative DL_{CO} and FEV_1 should then be estimated by multiplying the preoperative FEV_1 by the percentage of lung segments that will remain in the scenario of the most extensive resection possible. The method of estimation is based on the number of segments in each lobe.

Lobe	*Segments*
Right upper	3
Right middle	2
Right lower	5
Left upper	3
Lingula	2
Left lower	4
Total	19

If the expectation is that the right lower lobe will be resected, the remaining segments would be 19 – 5 = 14, which represents 74% of the segments (14/19). The predicted postoperative FEV_1 would thus be 74% of the preoperative value. The postoperative FEV_1, can then be used to predict operative risk and to aid in decision making in the fashion[106] outlined in Table 26-3. Expressing the postoperative data as a percent predicted, rather than a raw value, avoids any possible bias that

TABLE 26-3. Postoperative FEV_1 and DL_{CO} for Predicting Operative Risk and Aiding in Decision Making

Predicted Postoperative FEV_1 and DL_{CO}	Risk	Recommendation
>40% predicted	Average	No further testing needed
<40% predicted	High	16%–60% mortality
		Consider less extensive resection
		Consider radiotherapy
Any other combination	Intermediate	Exercise testing needed

DL_{CO}, diffusing capacity for carbon monoxide; FEV_1, forced expiratory volume in 1 second.

might result for older patients, patients of small stature, and women who might tolerate a lower FEV_1 after surgery while still having these values exceed 40% predicted.

Other ways to estimate the degree of functional lung that might remain following resectional surgery include measuring differential lung function by bronchospirometry, perfusion lung scanning, or more recently, xenon radiospirometry. The latter technique involves intravenous injection of radioactive xenon that has been dissolved in sodium chloride. Because of its low solubility in blood, xenon escapes from pulmonary capillary blood into accessible alveoli as blood flows through the lungs. A gamma camera detects the isotope, and the relative distribution to each lung may be calculated.[112] Using this method, Kristersson and coworkers[113] compared preoperative and postoperative pulmonary function in 19 supine patients who underwent pneumonectomy. They concluded that xenon radiospirometry predicted postoperative ventilatory capacity as well as did the older technique of bronchospirometry. Other studies have compared regional ventilation and perfusion studies with standard lung scanning methods and found a similar good correlation between predicted and actual postoperative pulmonary function. In fact, little difference was found when either ventilation or perfusion was used as the basis for the postoperative prediction of postoperative pulmonary function.[112] Accordingly, radionuclide perfusion lung scanning is also accepted as a useful and simple method with which to predict postoperative function. It does not, however, seem to offer any better ability to predict outcome than the simpler calculation of remaining segments described previously. Quantitative CT scans may provide this data[107] as well as delineate the extent and distribution of emphematous lung changes that often accompany the lung cancer. Using such data in patients with resectable lung cancer situated in the area of the severe emphysema (i.e., those with favorable anatomy) may allow combined resection and lung volume resection surgery. This approach has been shown to carry an acceptable risk and give long-term survival in patients that might otherwise have been excluded on the basis of poor lung function.[114]

Both of the more recently published guidelines agree that cardiopulmonary exercise testing allows accurate stratification of postoperative complications.[106,111] A summary of numerous studies indicates that patients with maximum oxygen consumption ($\dot{V}o_2max$) of more than 20 mL/kg (and possibly >15 mL/kg) have no increased risk of death or of developing postoperative complications, whereas those with a $\dot{V}o_2max$ of less than 10 mL/kg have an extremely high risk of death (as high as 50%).

Pulmonary arterial pressure measurements, with occlusion of the pulmonary artery supplying the lung to be resected, have also been used to predict outcome but do not appear to give any better indication of which patients will not tolerate resection.[115]

Combined cardiopulmonary risk indices have also been proposed for the purpose of predicting both pulmonary and cardiac complications.[116] Neither these indices nor spirometry seems to accurately predict complications, however.[117]

Lung Volume Reduction Surgery

The effects of lung volume reduction surgery (LVRS) on the morbidity and mortality of patients with emphysema have been described. The initial report of the National Emphysema Treatment Trial (NETT)[118] found that in 69 patients with an FEV_1 of 20% or less of the predicted value, and either a homogeneous distribution of emphysema or a DL_{CO} of 20% or less of the predicted value, the 30-day mortality was 16% compared with 0% in 70 patients treated medically ($P < .001$). In addition, those treated surgically had little functional improvement. Accordingly, patients meeting these criteria were subsequently excluded from the ongoing trial.[118,118a]

The report of the completed trial of 1078 patients indicated that exercise capacity, dyspnea, and quality of life improved in those randomized to undergo surgery compared with those treated medically, but no survival benefit was observed.[119] Secondary analyses indicated that the beneficial effects were strongest in patients with predominantly upper lobe disease who had low exercise capacity (i.e., ≤25 W for females and ≤40 Ws for males) measured preoperatively, at the end of a 6- to 10-week period of rehabilitation. Conversely, those with predominantly lower lobe emphysema and an exercise capacity *exceeding* these limits had a greater risk of death if treated surgically.

Based on these findings, the Centers for Medicare and Medicaid Services (CMS) issued a national coverage analysis indicating that LVRS is not indicated, and will not be included as a covered procedure, for the high-risk group described previously. CMS also stated that they intend to cover LVRS for non–high-risk patients who (1) satisfy the entry criteria of the NETT and who present with severe upper lobe emphysema, or (2) have severe *non*–upper lobe emphysema along with a low exercise capacity. LVRS will *not* be a covered benefit for patients with severe non–upper lobe emphysema who have an exercise capacity exceeding the previously discussed limits. CMS also stipulated that the procedure will be covered only at one of the facilities that participated in the NETT and at sites that have previously been approved for lung transplantation.

KEY POINTS

- Patients with pulmonary disease are at increased risk of postoperative cardiovascular, renal, and pulmonary complications.
- Indices are available to identify patients at risk for postoperative complications after abdominal, cardiac, and pulmonary resection surgeries.
- High-risk patients include those who smoke and/or have COPD, sleep apnea, and/or uncontrolled asthma.
- The incidence of complications, especially pulmonary, is influenced by the type, site, and duration of the surgical procedure (i.e., procedure-related factors).
- Postoperative pulmonary complications (PPCs) in all types of procedures can be reduced in ALL patients, regardless of risk, by optimizing medical therapy preoperatively, by modifying anesthetic/surgical approach when indicated, and by delivering aggressive postoperative care with emphasis on analgesia and lung expansion.

References

1. Arozullah A, Daley J, Henderson W, et al: Multifactorial risk index for predicting postoperative respiratory failure in men after noncardiac surgery. Ann Surg 232:243–253, 2000.
2. Johnson RG, Arozullah AM, Neumayer L, et al: Multivariable predictors of postoperative respiratory failure after general and vascular surgery: Results from the patient safety in surgery study. J Am Coll Surg 204:1188–1198, 2007.
3. Arozullah AM, Khuri SF, Henderson WG, et al: Development and validation of a multifactorial risk index for predicting postoperative pneumonia after major noncardiac surgery. Ann Intern Med 135:847–857, 2001.
4. Smetana GW, Lawrence VA, Cornell JE: Preoperative pulmonary risk stratification for noncardiothoracic surgery: Systematic review for the American College of Physicians. Ann Intern Med 144:581–595, 2006.
5. Fleischer LA, Beckman JA, Brown KA, et al: ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery: Executive summary. Circulation 116:1971–1996, 2007.
6. Kroenke K, Lawrence VA, Theroux, JF, Tuley MR: Operative risk in patients with severe obstructive pulmonary disease. Arch Intern Med 152:967–971, 1992.
7. Nunn JF, Milledge JS, Chen D, et al: Respiratory criteria of fitness for surgery and anaesthesia. Anaesthesia 43:543–551, 1988.
8. Chassot PG, Delabays A, Spahn DR: Preoperative evaluation of patients with, or at risk of, coronary artery disease undergoing non-cardiac surgery. Br J Anaesth 89:747–759, 2002.
9. Fleisher LA, Eagle KA: Lowering cardiac risk in noncardiac surgery. N Engl J Med 345:1677–1682, 2001.
10. Eagle KA, Brundage BH, Chaitman BR, et al: Guidelines for perioperative cardiovascular evaluation for noncardiac surgery. Circulation 93:1278–1317, 1996.
11. Wallace AW, Galindez D, Salahieh A, et al: Effect of clonidine on cardiovascular morbidity and mortality after noncardiac surgery. Anesthesiology 101:284–293, 2004.
12. POISE Study Group: Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): A randomized controlled trial. Lancet 371:1839–1847, 2008.
13. Hindler K, Shaw AD, Samuels J, et al: Improved postoperative outcomes associated with preoperative statin therapy. Anesthesiology 105:1260–1272, 2006.
14. Ferguson TB, Coombs LP, Peterson ED: Preoperative beta blocker use and mortality and morbidity following CABG surgery in North America. JAMA 287:2221–2227, 2002.
15. Auerbach AD, Goldman L: Beta blockers and reduction of cardiac events in noncardiac surgery. JAMA 287:1435–1444, 2002.
16. Kotlyar E, Keogh AM, Macdonald PS, et al: Tolerability of carvedilol in patients with heart failure and concomitant chronic obstructive pulmonary disease or asthma. J Heart Lung Transplant 21:1290–1295, 2002.
17. Seider N, Abinader EG, Oliven A: Cardiac arrhythmias after inhaled bronchodilators in patients with COPD and ischemic heart disease. Chest 104:1070–1074, 1993.
18. Brathwaite D, Weissman C: The new onset of atrial arrhythmias following major noncardiothoracic surgery is associated with increased mortality. Chest 114:462–468, 1998.
19. Samuels LE, Kaufman MS, Morris RJ, et al: Coronary artery bypass grafting in patients with COPD. Chest 113:878–882, 1998.
20. Ommen SR, Odell JA, Stanton MS: Atrial arrhythmias after cardiothoracic surgery. N Engl J Med 336:1429–1434, 1997.
21. Gottlieb SS, McCarter RJ, Vogel RA: Effect of beta-blockade on mortality among high-risk and low-risk patients after myocardial infarction. N Engl J Med 339:489–497, 1998.
22. Viskin S, Barron HV: Beta blockers prevent cardiac death following a myocardial infarction: So why are so many infarct survivors discharged without beta blockers? Am J Cardiol 78:821–822, 1996.
23. Cazzola M, Imperatore F, Salzillo A, et al: Cardiac effects of formoterol and salmeterol in patients suffering from COPD with preexisting cardiac arrhythmias and hypoxemia. Chest 114:411–415, 1998.
24. Sarubbi B, Esposito V, Ducceschi V, et al: Effect of blood gas derangement on QTc dispersion in severe chronic obstructive pulmonary disease: Evidence of an electropathy? Int J Cardiol 58:287–292, 1997.
25. Stewart AG, Waterhouse JC, Howard T: The QTc interval, autonomic neuropathy and mortality in hypoxaemic COPD. Respir Med 89:79–84, 1995.
26. Hedenstierna G: Alveolar collapse and closure of airways: Regular effects of anaesthesia. Clin Physiol Func Imaging 23:123–129, 2003.
27. Magnusson L, Spahn DR: New concepts of atelectasis during general anaesthesia. Br J Anaesth 91:61–72, 2003.
28. Hedenstierna G, Tokics L, Lundquist H, et al: Phrenic nerve stimulation during halothane anesthesia: Effects of atelectasis. Anesthesiology 80:751–760, 1994.
29. Eichenberger A-S, Proietti S, Wicky S, et al: Morbid obesity and postoperative pulmonary atelectasis: An underestimated problem. Anesth Analg 95:1788–1792, 2002.
30. Claxton BA, Morgan P, McKeague H, et al: Alveolar recruitment strategy improves arterial oxygenation after cardiopulmonary bypass. Anaesthesia 58:111–116, 2003.
31. Valenza F, Vagginelli F, Tiby A, et al: Effects of the beach chair position, positive end-expiratory pressure, and pneumoperitoneum on respiratory function in morbidly obese patients during anesthesia and paralysis. Anesthesiology 107:725–732, 2007.
32. Cadi P, Guenon T, Journois D, et al: Pressure-controlled ventilation improves oxygenation during laparoscopic obesity surgery

compared with volume-controlled ventilation. Br J Anaesth 100:706-716, 2008.
33. Eger EI: New inhaled anesthetics. Anesthesiology 80:906–922, 1994.
34. Wahba WM, Craig DB, Don HF, Becklake MR: The cardiorespiratory effects of thoracic epidural anesthesia. Can Anaesth Soc J 19:8–19, 1972.
35. Ravin MB: Comparison of spinal and general anesthesia for lower abdominal surgery in patients with chronic obstructive pulmonary disease. Anesthesiology 35:319–322, 1971.
36. Boutros AR, Weisel M: Comparison of effects of three anaesthetic techniques on patients with severe pulmonary obstructive disease. Can Anaesth Soc J 18:286–292, 1971.
37. Park WY, Thompson JS, Lee KK: Effect of epidural anesthesia and analgesia on perioperative outcome. Ann Surg 234:560–571, 2001.
38. Rasmussen LS, Johnson T, Kuipers HM, et al: Does anaesthesia cause postoperative cognitive dysfunction? A randomized study of regional versus general anaesthesia in 438 elderly patients. Acta Anaesthesiol Scand 47:260–266, 2003.
39. Block BM, Liu SS, Rowlingson AJ, et al: Efficacy of postoperative epidural analagesia: A meta analysis. JAMA 290:2455–2463, 2003.
40. Dureuil B, Viires N, Cantineau JP, et al: Diaphragmatic contractility after upper abdominal surgery. J Appl Physiol 61:1775–1780, 1986.
41. Liu S, Carpenter RL, Neal JM: Epidural anesthesia and analgesia: Their role in postoperative outcome. Anesthesiology 82:1474–1506, 1995.
42. Liu SS, Carpenter RL, Mackey DC, et al: Effects of perioperative analgesic technique on rate of recovery after colon surgery. Anesthesiology 83:757–765, 1995.
43. Celli BR, Rodriguez KS, Snider GL: A controlled trial of intermittent positive pressure breathing, incentive spirometry and deep breathing exercises in preventing pulmonary complications after abdominal surgery. Am Rev Respir Dis 130:12–15, 1984.
44. Wherry DC, Marohn MR, Malanoski MP, et al: An external audit of laparoscopic cholecystectomy in the steady state performed in medical treatment facilities of the Department of Defense. Ann Surg 224:145–154, 1996.
45. Watson DI, Baigrie RJ, Jamieson GG: A learning curve for laparoscopic fundoplication: Definable, avoidable, or a waste of time? Ann Surg 224:198–203, 1996.
45a. Jencks SF, Williams MV, Coleman EA: Rehospitalizations among patients in the medicare fee-for-service program. N Engl J Med 360:1418–1428, 2009.
46. Putensen-Himmer G, Putensen C, Lammer H, et al: Comparison of postoperative respiratory function after laparoscopy or open laparotomy for cholecystectomy. Anesthesiology 77:675–680, 1992.
47. Tenling A, Hachenberg T, Tyden H, et al: Atelectasis and gas exchange after cardiac surgery. Anesthesiology 89:371–378, 1998.
48. Markand ON, Moorthy SS, Mahomed Y, et al: Postoperative phrenic nerve palsy in patients with open heart surgery. Ann Thorac Surg 39:68–73, 1985.
49. Ferguson TB, Hammill BG, Peterson ED, et al: A decade of change-risk profiles and outcomes for isolated coronary artery bypass grafting procedures 1990–1999: A report from the STS National Database Committee and the Duke Clinical Research Institute. Ann Thorac Surg 73:480–490, 2002.
50. Gardner SC, Grunwald GK, Rumsfeld JS, et al: Risk factors for intermediate-term survival after coronary artery bypass grafting. Ann Thorac Surg 72:2033–2037, 2001.
51. Al-Ruzzeh S, Nakamura K, Athanasiou T, et al: Does off-pump coronary artery bypass (OPCAB) surgery improve the outcome in high-risk patients? A comparative study of 1398 high-risk patients. Eur J Cardiothorac Surg 23:50–55, 2003.
52. Nathoe HM, van Dijk D, Jansen EWL, et al: A comparison of on-pump and off-pump coronary bypass surgery in low-risk patients. N Engl J Med 348:394–402, 2003.
53. Khan NE, DeSouza A, Mister R, et al: A randomized comparison of off-pump and on-pump multivessel coronary-artery bypass surgery. N Engl J Med 350:21–28, 2004.
54. Keizer AMA, Hijman R, van Dijk D, et al: Cognitive self-assessment one year after on-pump and off-pump coronary artery bypass grafting. Ann Thorac Surg 75:835–839, 2003.
55. Puskas JD, Williams WH, Mahoney EM, et al: Off-pump vs conventional coronary artery bypass grafting: Early and 1-year graft patency, cost and quality-of-life outcomes. JAMA 291:1841–1849, 2004.
56. Maeda H, Nakahara K, Ohno K, et al: Diaphragm function after pulmonary resection: Relationship to postoperative respiratory failure. Am Rev Respir Dis 137:678–681, 1988.
57. DeVita M, Robinson L, Rehder J, et al: Incidence and natural history of phrenic neuropathy occurring during open heart surgery. Chest 103:850–856, 1993.
58. Gilbert T, McGrath B, Soberman M: Chest tubes: Indication, placement, management, and complications. J Intensive Care Med 8:73–86, 1993.
59. Bailey SH, Bull DA, Harpole DH, et al: Outcomes after esophagectomy: A ten-year prospective cohort. Ann Thorac Surg 75:217–222, 2003.
60. Hulscher JB, van Sandick JW, de Boer AG, et al: Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the esophagus. N Engl J Med 347:1662–1669, 2002.
61. Moller AM, Villebro N, Pedersen T, et al: Effect of preoperative smoking intervention on postoperative complications: A randomized clinical trial. Lancet 359:114–117, 2002.
61a. Warner DO: American Society of Anesthesiologists Smoking Cessation Initiative Task Force: Feasibility of tobacco interventions in anesthesiology practices: a pilot study. Anesthesiology 110:1223–1228, 2009.
62. Kheterpal S, Tremperk K, Englesbe MJ, et al: Predictors of postoperative acute renal failure after noncardiac surgery in patients with previously normal renal function. Anesthesiology 107:892–902, 2007.
63. Wald N, Howard S, Smith PG, Bailey A: Use of carboxyhaemoglobin levels to predict the development of diseases associated with cigarette smoking. Thorax 30:133–139, 1975.
64. Takeda R, Tanaka A, Maeda T, et al: Role of CO during abdominal surgery: Perioperative changes in carbonylhemoglobin and methemoglobin during abdominal surgery: Alteration in endogenous generation of carbon monoxide. J Gastroenterol Hepatol 17:535–541, 2002.
65. Roth GM, Shick RM: The cardiovascular effects of smoking with special reference to hypertension. Ann N Y Acad Sci 90:308–316, 1960.
66. Bluman LG, Mosca L, Newman N, et al: Preoperative smoking habits and postoperative pulmonary complications. Chest 113: 883–889, 1998.
67. Hasdai D, Garratt KN, Grill DE, et al: Effect of smoking status on the long-term outcome after successful percutaneous coronary revascularization. N Engl J Med 336:755–761, 1997.
68. Simon JA, Solkowitz SN, Carmody TP, et al: Smoking cessation after surgery, a randomized trial. Arch Intern Med 157:1371–1376, 1997.
69. Arozullah AM, Conde MV, Lawrence VA: Preoperative evaluation for postoperative pulmonary complications. Med Clin North Am 87:153–173, 2003.
70. Chung F, Yegneswaran B, Liao P, et al: Higher postoperative complications in obstructive sleep apnea (OSA) patients. Anesthesiology 107:A935, 2007.
71. Gupta RM, Parvizi J, Hanssen AD, et al: Postoperative complications in patients with obstructive sleep apnea syndrome undergoing hip or knee replacement: A case-control study. Mayo Clin Proc 76:897–905, 2001.
72. Benumof JL: Obstructive sleep apnea in the adult obese patient: Implications for airway management. Anesthesiol Clin North Am 20:789–811, 2002.
72a. Longitudinal Assessment of Bariatric Surgery (LABS) Consortium, Flum DR, Belle SH, et al: Perioperative safety in the longitudinal assessment of bariatric surgery. N Engl J Med 361:445–454, 2009.
73. Kirsch M, Guesnier L, LeBesnerais P, et al: Cardiac operations in octogenarians: Perioperative risk factors for death and impaired autonomy. Ann Thorac Surg 66:60–67, 1998.

74. Lai HC, Lai HC, Wang KY, et al: Severe pulmonary hypertension complicates postoperative outcome of non-cardiac surgery. Br J Anaesth 99:184–190, 2007.
75. Garrigue S, Bordier P, Jais P, et al: Benefit of atrial pacing in sleep apnea syndrome. N Engl J Med 346:404–412, 2002.
76. Cloward TV, Walker JM, Farney RJ, et al: Left ventricular hypertrophy is a common echocardiographic abnormality in severe obstructive sleep apnea and reverses with nasal continuous positive airway pressure. Chest 124:594–601, 2003.
77. Wolk R, Kara T, Somers VK: Sleep-disordered breathing and cardiovascular disease. Circulation 108:9–12, 2003.
78. Williams-Russo P, Charlson ME, MacKenzie R, et al: Predicting postoperative pulmonary complications. Arch Intern Med 152: 1209–1213, 1992.
79. Lawrence VA, Dhanda R, Hilsenbeck SG, et al: Risk of pulmonary complications after elective abdominal surgery. Chest 110:744–750, 1996.
80. Jayr C, Matthay MA, Goldstone J et al: Preoperative and intraoperative factors associated with prolonged mechanical ventilation: A study in patients following major abdominal vascular surgery. Chest 103:1231–1236, 1993.
81. Fujita T, Sakurai K: Multivariate analysis of risk factors for postoperative pneumonia. Am J Surg 169:304–307, 1995.
82. Dunne JR, Malone D, Tracy JK, et al: Perioperative anemia: An independent risk factor for infection, mortality and resource utilization in surgery. J Surg Res 102:237–244, 2002.
83. Warner DO, Warner MA, Barnes RD, et al: Perioperative respiratory complications in patients with asthma. Anesthesiology 85:460–467, 1996.
84. Kingston HGG, Hirshman CA: Perioperative management of the patient with asthma. Anesth Analg 63:844–855, 1984.
85. Shnider SM, Papper EM: Anesthesia for the asthmatic patient. Anesthesiology 22:886–892, 1961.
86. Rooke GR, Choi J-H, Bishop MJ: The effect of isoflurane, halothane, sevoflurane, and thiopental/nitrous oxide on respiratory system resistance after tracheal intubation. Anesthesiology 86: 1294–1299, 1997.
87. Park KW, Dai HB, Lowenstein E, et al: Isoflurane- and halothane-mediated dilation of distal bronchi in the rat depends on the epithelium. Anesthesiology 86:1078–1087, 1997.
88. Hirshman CA, Downes H, Farbood A, Bergman NA: Ketamine block of bronchospasm in experimental canine asthma. Br J Anaesth 51:713–716, 1979.
89. Pabelick CM, Jones KA, Street K, et al: Calcium concentration-dependent mechanisms through which ketamine relaxes canine airway smooth muscle. Anesthesiology 86:1104–1111, 1997.
90. Eames WO, Rooke GA, Wu RS-C, et al: Comparison of the effects of etomidate, propofol, and thiopental on respiratory resistance after tracheal intubation. Anesthesiology 84:1307–1311, 1996.
91. Landreneau RJ, Mack MJ, Dowling RD, et al: The role of thoracoscopy in lung cancer management: International symposium on thoracic malignancies. Chest 113:6S–12S, 1998.
92. Gottschalk A, Cohen SP, Yang S, Ochroch EA: Preventing and treating pain after thoracic surgery. Anesthesiology 104:594–600, 2006.
93. Pagni S, Federico JA, Ponn RB: Pulmonary resection for lung cancer in octogenarians. Ann Thorac Surg 63:785–789, 1997.
93a. Lucangelo U, Antonaglia V, Zin WA, et al: High-frequency percussive ventilation improves perioperatively clinical evolution in pulmonary resection. Crit Care Med 37:1663–1669, 2009.
94. Jaklitsch MT, DeCamp MM, Liptay MJ, et al: Video-assisted thoracic surgery in the elderly: A review of 307 cases. Chest 110: 751–758, 1996.
95. Flehinger BJ, Kimmel M, Melamed MR: The effect of surgical treatment on survival from early lung cancer. Chest 101:1013–1018, 1992.
96. Romano PS, Mark DH: Patient and hospital characteristics related to in-hospital mortality after lung cancer resection. Chest 101: 1332–1337, 1992.
97. Bach PB, Cramer LD, Schrag D, et al: The influence of hospital volume on survival after resection for lung cancer. N Engl J Med 345:181–188, 2001.
98. Treasure T, Utley M, Bailey A: Assessment of whether in-hospital mortality for lobectomy is a useful standard for the quality of lung cancer surgery: Retrospective study. BMJ 327:73–74, 2003.
99. Hsia CCW, Carlin JI, Wagner PD, et al: Gas exchange abnormalities after pneumonectomy in conditioned foxhounds. J Appl Physiol 68:94–104, 1990.
100. Carlin JI, Hsia CCW, Cassidy SS, et al: Recruitment of lung diffusing capacity with exercise before and after pneumonectomy in dogs. J Appl Physiol 70:135–142, 1991.
101. Hsia CCW, Herazo LF, Ramanathan M, et al: Cardiopulmonary adaptations to pneumonectomy in dogs. IV. Membrane diffusing capacity and capillary blood volume. J Appl Physiol 77:998–1005, 1994.
102. Van Mieghem W, Demedts M: Cardiopulmonary function after lobectomy or pneumonectomy for pulmonary neoplasm. Respir Med 83:199–206, 1989.
103. Burke JR, Duarte IG, Thourani VH, Miller JI Jr: Preoperative risk assessment for marginal patients requiring pulmonary resection. Ann Thorac Surg 76:1767–1773, 2003.
104. Damhuis RA, Schutte PR: Resection rates and postoperative mortality in 7899 patients with lung cancer. Eur Respir J 9:7–10, 1996.
105. Massard G, Moog R, Wihlm JM, et al: Bronchogenic cancer in the elderly: Operative risk and long term prognosis. Thorac Cardiovasc Surg 44:40–45, 1996.
106. British Thoracic Society and Society of Cardiothoracic Surgeons of Great Britain and Ireland Working Party: Guidelines on the selection of patients with lung cancer for surgery. Thorax 56:89–108, 2001.
107. Bolliger CT, Koegelenberg CFN, Kendal R: Preoperative assessment for lung cancer surgery. Curr Opin Pulm Med 11:301–306, 2005.
108. Dyszkiewicz W, Jemielity MM, Piwkowski CT, et al: Simulataneous lung resection for cancer and myocardial revascularization without cardiopulmonary bypass (off-pump coronary artery bypass grafting). Ann Thorac Surg 77:1023–1027, 2004.
109. Curtis JK, Bauer H, Rasmussen HK, et al: Studies of pulmonary function before and after pulmonary surgery in 450 tuberculosis patients. J Thorac Surg 37:598–605, 1959.
110. Boushy SF, Billig DM, North LB, et al: Clinical course related to preoperative and postoperative pulmonary function in patients with bronchogenic carcinoma. Chest 59:383–391, 1971.
111. Beckles MA, Spiro SG, Colice GL, Rudd RM: The physiologic evaluation of patients with lung cancer being considered for resectional surgery. Chest 123(Suppl):105S–114S, 2003.
112. Ali MK, Mountain CF, Ewer MS, et al: Predicting loss of pulmonary function after pulmonary resection for bronchogenic carcinoma. Chest 77:337–342, 1980.
113. Kristersson S, Arburelius M, Jungquist G, et al: Prediction of ventilatory capacity after lobectomy. Scand J Respir Dis 54:315–325, 1973.
114. Choong CK, Meyers BF, Battafarno RJ: Lung cancer resection combined with lung volume reduction in patients with severe emphysema. J Thorac Cardiovasc Surg 127:1323–1331, 2004.
115. Ribas J, Diaz O, Barbera JA, et al: Invasive exercise testing in the evaluation of patients at high-risk for lung resection. Eur Respir J 12:1429–1435, 1998.
116. Wyser C, Stulz P, Soler M, et al: Prospective evaluation of an algorithm for the functional assessment of lung resection candidates. Am J Respir Crit Care Med 159:1450–1456, 1999.
117. Melendez JA, Carlon VA: Cardiopulmonary risk index does not predict complications after thoracic surgery. Chest 114:69–75, 1998.
118. National Emphysema Treatment Trial Research Group: Patients at high risk of death after lung-volume-reduction surgery. N Engl J Med 345:1075–1083, 2001.
118a. Benzo R, Farrell MH, Chang C-CH, et al: Integrating health status and survival data: the palliative effect of lung volume reduction surgery. Am J Respir Crit Care Med 180:239–246, 2009.
119. National Emphysema Treatment Trial Research Group: A randomized trial comparing lung-volume-reduction surgery with medical therapy for severe emphysema. N Engl J Med 348:2059–2073, 2003.

CHAPTER 27

EVALUATION OF RESPIRATORY IMPAIRMENT AND DISABILITY

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INTRODUCTION

Respiratory impairment refers to an alteration in lung structure and/or lung function that results in decreased or limited functional ability and is usually manifested by dyspnea on exertion. Many respiratory diseases may cause impairment, from airways disease such as asthma and chronic obstructive pulmonary disease (COPD) to interstitial lung diseases. A pulmonary physician may be asked to evaluate impairment and/or disability, either for his or her own patients or for others in the context of an independent medical examination through a benefits or compensation program.

This chapter reviews the elements of an impairment evaluation and then provides an overview of the major programs in the United States and how disability and/or impairment is determined under each. Impairment ratings are described using the framework for the assessment of respiratory impairment set forth by the American Thoracic Society (ATS)[1,2] along with the most commonly used rating methodology contained in the American Medical Association (AMA) *Guides to*

the Evaluation of Permanent Impairment, hereafter referred to as the AMA *Guides*. However, the AMA *Guides* are not used by every system. It is incumbent on the evaluating physician to be sure she or he understands and follows the rules and specific requirements of the program under which the patient is being evaluated. The final determination on the award is usually made by personnel in the program or a judge, but the thoroughness of the medical report and its consistency with the program requirements will increase the weight given to the physician's medical opinion.

DEFINITIONS

There is a critical distinction between the terms *impairment* and *disability*. The terms *impairment* and *disability* are often used interchangeably, perhaps made more confusing by the fact that different benefits and compensation programs may use both terms but focus on one more than the other. *Impairment* occurs at the organ or organ system level. *Whole-person impairment* refers to the loss relative to the functioning of the body as a whole. *Disability*, in contrast, refers to the person in terms of limitation in the ability to perform normal activities, including personal, social, and work activities.

Physicians should understand that such determinations are medicolegal decisions, and they can have additional ramifications for the patient beyond that of providing a diagnosis. The physician may be asked to address causation; that is the physician may need to opine whether the respiratory condition was caused or at least aggravated by a certain factor, most commonly work, on a more-likely-than-not basis.

Although several of these terms are related, it is important that each term be applied in accordance with its precise definition. The definitions that follow are those based on the traditional World Health Organization's (WHO's) International Classification of Impairment, Disability, and Handicap (ICIDH) model, which has formed the classic paradigm through which these terms have been defined since 1980.[3] It is important to note that although this model is no longer used by the WHO, programs within the United States are only just beginning to recognize the paradigm shift put forth in the revised International Classification of Functioning, Disability, and Health (ICF).[4] Because most of the existing U.S. programs continue to use the traditional ICIDH definitions, these are reviewed first. To avoid confusion, the International Classification of Functioning, Disability, and Health (ICF) is described later in the chapter under the "Future Directions" section.

Impairment

Impairment refers to the degree of loss of normal use or function of a body part or organ. It was defined by the WHO as "any loss or abnormality of psychological, physiologic, or anatomic structure or function."[3] It was defined by the AMA as "a loss, loss of use, or derangement of any body part, organ system or organ function."[5a]

The essential elements that make up an impairment evaluation will vary to some degree according to the program or system through which the evaluation is being performed. Standard components typically include history, with occupational and environmental history and description of limitations in activities of daily living (ADLs); physical examination; and review of medical records and diagnostic test results that establish the respiratory condition.

Whereas pulmonary function test (PFT) results are the primary factor that determine the presence and degree of pulmonary impairment, some systems will specify that particular tests should be used for assessment of impairment or disability, whereas others allow physician discretion in choosing another test if he or she believes it to be a more accurate reflection of the patient's true respiratory impairment. Some programs will only allow physicians with certain qualifications to perform impairment ratings. Additional elements that may need to be addressed can include delineation of permanent work restrictions, outline of future medical treatment requirements, and/or consideration of apportionment.

Before a physician can determine that a condition has resulted in permanent impairment or disability, the diagnosis should be well defined, the condition stable, and medical treatment either optimized or reasonable options exhausted. When these criteria are met, this is termed *maximum medical improvement* (MMI).

Disability

Disability refers to any resulting alteration in the individual's capacity to perform customary activities. It was defined by the WHO as "any restriction or lack of ability to perform any activity within the range considered normal for a human being."[3] The AMA defined *disability* as an "alteration of an individual's capacity to meet or perform personal, social, or occupational demands or statutory or regulatory requirements because of an impairment."[5a]

Although the degree of impairment frequently correlates with the degree of disability, this is not always the case. The classic example of this is the loss of the fifth finger of the nondominant hand. Under the typical impairment rating system, the loss of this finger would be associated with a very small impairment of the whole person. For the average person, this small impairment would result in a correspondingly small disability. For a concert pianist, this small impairment would be associated with significant disability, particularly in the context of work activities.

Handicap

Handicap refers to the societal disadvantage caused by the impairment or disability. It was defined by the WHO as "a disadvantage for a given individual that limits or prevents fulfillment of that person's normal role depending on sex, age, social and cultural factors."[3]

Additional Terms

Temporary impairment refers to impairment that exists only for a limited period of time after an injury or illness.

Temporary disability insurance covers partial compensation for loss of wages due to a non–work-related injury or illness. Partial compensation for lost wages as well as medical benefits are covered by Workers' Compensation for work-related injuries and illness.

Permanent impairment can be assessed only once the patient has reached MMI. MMI is defined in the AMA *Guides*, Sixth Edition,[6a] as the "point in time in the recovery process … when further formal medical or surgical intervention cannot be expected to improve the underlying impairment" and "symptoms can be expected to remain stable with the passage of time, or can be managed with palliative measures that do not alter the underlying impairment substantially." This is termed "permanent and stationary" in some systems.

W*hole-person impairment* refers to the alteration in the functioning of the body as a whole, so can range from 0% (no impairment) to 100% (essential cessation of all body functions).

Permanent partial impairment is the numeric percentage of the loss of body functioning due to the loss or limitation in the functioning of the organ or organ systems affected. For most respiratory conditions, the primary organ involved is the lung, but at times, the pulmonary arteries or nose and throat may be affected.

Permanent total disability is the medicolegal determination that a person's impairment precludes future gainful employment.

CLINICAL APPROACH TO IMPAIRMENT EVALUATIONS

Although the term *impairment rating* is sometimes used interchangeably with the term *impairment evaluation*, the impairment rating itself is but a small part of what should be a comprehensive medical evaluation[7] (Table 27-1). The physician must first fully understand the purpose and the requirements of the program for which the evaluation is being conducted. The initial goal of the impairment evaluation should be to confirm the medical diagnosis,[2] through a thorough, detailed patient history, physical examination, and review of diagnostic testing results that established the diagnosis. The diagnosis or diagnoses should be clearly stated, along with extrapulmonary conditions that may be contributory to symptoms, limitations in ADLs, and/or impairment. A statement of MMI is often required. Factors important to the impairment rating itself include items from history, physical examination, and diagnostic testing results that reflect disease severity, including impact on normal ADLs,[5a] and current treatment requirements. The physician may be asked to make a statement on causation or apportionment. An outline of reasonably anticipated future medical course and treatment requirements should be given. The following sections describe the various aspects of an impairment evaluation, including the history to be taken, the examination to be conducted, and the testing to be obtained depending on the diagnosis considered and the type of evaluation being performed.

TABLE 27-1. Components of a Respiratory Impairment Evaluation

1. Clear understanding of the rules and specific requirements of the program under which the individual is being evaluated.
2. Complete medical history
   a. Complete occupational and environmental exposure history
   b. Limitations in activities of daily living (ADLs)
3. Physical examination
4. Diagnostic testing
   a. Tests that establish the diagnosis
   b. Tests that identify extra-pulmonary conditions contributing to impairment
   c. Results used in the assessment of impairment
      i. Pulmonary function tests
         A. Spirometry
         B. Single-breath diffusing capacity (DL_{COsb})
      ii. Cardiopulmonary exercise test (when indicated)
      iii. Arterial blood gas measurement (when indicated)
5. Diagnosis
   a. Assessment of causation, usually relationship to work (when indicated)
6. Impairment assessment
   a. Statement of maximum medical improvement (MMI)
   b. Impairment rating
   c. Ability to work/work restrictions (when indicated)
   d. Apportionment (if requested)
   e. Future medical treatment

History

The history of present illness (HPI) is the standard, detailed respiratory history used by most pulmonologists, including symptoms of cough, cough with phlegm, wheeze, chest tightness, and shortness of breath. If present, details should be provided that include when the symptom started, exacerbating and alleviating factors along with temporal relationship, progression over time and current status including frequency, severity, and response to any medication that is used. A scale for the rating of dyspnea is suggested in the AMA *Guides*, based on the Epidemiology Standardization Project,[8] which also provides standardized questions for the assessment of other symptoms. Questions about conditions such as chronic rhinitis, postnasal drip, gastroesophageal reflux disease, cardiac disease, and other lung diseases, including smoking-related lung disease, may help the physician understand other possible contributors to respiratory symptoms. Although dyspnea is the primary limiting symptom of respiratory impairment, dyspnea can also result from nonpulmonary causes including, cardiovascular disease, obesity, and deconditioning. Frequency, severity, treatment requirements, and duration of

periodic exacerbations of diseases such as asthma and bronchiectasis should be well documented. Medications used or tried in the past for the treatment of the respiratory conditions should be described, along with a description of the relief afforded.

Constitutional symptoms are relevant in the HPI in patients with certain diseases, such as fever, sweats, chills, and fatigue in patients with hypersensitivity pneumonitis, chest pain, weight loss, and malaise in patients with asbestos-related lung disease, and night sweats and fatigue in patients with chronic beryllium disease.

A standard detailed past medical and surgical history, list of medications and allergies, family history, and review of systems will provide a good understanding of the patient as a whole. It will also allow the physician to identify other possible diseases that may be contributory to the patient's current status, as well as assess potential treatment-related side effects. The standard social history should include smoking history, including amount, duration, and current smoking status.

An element that may be new to most pulmonologists is the need to obtain a detailed occupational and environmental history. This is necessary to help the physician address whether there is a relationship between a respiratory condition and past or ongoing workplace exposures. The occupational history is most easily performed in chronological order starting from childhood. Details about the period of time spent at each job, the job title, description of the work performed, and details about jobs or processes that may have produced dust, fumes, gas, or smoke should be described, including estimation of intensity, frequency, and duration of exposure. Questions about ventilation and use of respiratory protection can provide helpful clues, as well as whether or not there were any immediate symptoms noted. Chemical exposures, particularly any heavy exposures or exposures that resulted in symptoms, should be detailed. If available, the Material Safety Data Sheet (MSDS) may be reviewed, as it can provide helpful information on the components of the chemicals used in the workplace and potential associated health effects. Unfortunately, MSDSs are not required to provide complete information, and thus some are more reliable than others.

An environmental history includes questions about heating, cooling, and humidification sources; pets including birds; hot tubs; water-damaged areas; and exposures from hobbies should also be obtained to determine whether there is a relationship between the disease and any environmental exposures.

In addition to the just-discussed components, the history should also include a description of how the condition affects the person's ability to perform normal *activities of daily living* (ADLs). Questions most relevant to patients with pulmonary disease include ability to perform basic self-care such as showering; ability to walk, including estimated distance at own pace and at a fast pace or up a hill, estimated pace compared with others one's own age, and number of flights of stairs that can be climbed; and ability to perform indoor and outdoor home maintenance chores, as well as customary hobby, exercise, and job-related activities. There are a number of standardized methods by which to assess ability to perform ADLs, some of which are disease-specific. A list of ADLs suitable for all conditions is outlined in the AMA *Guides*.[5a] Symptoms and limitations in ADLs that are consistent with the lung disease and objective testing data provide useful supporting information for the impairment rating. Dyspnea scales are often used, and can be a helpful way to summarize the relative degree of symptomatology or activity limitation.[8] However, the degree to which dyspnea correlates with objective measures of pulmonary function and exercise performance is variable.[9–12]

Physical Examination

A complete physical examination should be performed, with focus on the respiratory and cardiovascular systems.[2,6,7] A detailed description of the chest should be made, including any deformities or scars, abnormal motion, respiratory rate and effort, breath sounds, and percussion, which can help support the diagnosis. Vital signs should be documented including blood pressure and heart rate, which may affect ability to perform pulmonary function and exercise tests, as well as height and weight, as obesity can cause PFT and exercise test abnormalities and contribute to pulmonary symptoms. Signs of hypoxemia, such as cyanosis and clubbing, should be documented. Signs of cor pulmonale, such as jugular venous distention, right ventricular heave, and liver engorgement, and peripheral edema provide evidence of severe respiratory impairment in patients with respiratory disease.[2]

Diagnosis, Causation, and Maximum Medical Improvement

Any available or provided medical records should be summarized, with focus on the results of the diagnostic testing that help establish the diagnosis and/or severity of the condition. Medicolegal cases may often involve the review and summarization of large volumes of records. Some independent medical examinations require that only the records provided through the program be reviewed.

The list of medical diagnoses should start with the diagnosis of the condition for which the patient is being evaluated, including disease severity. The diagnosis of asthma associated with workplace exposures may fall under one of three different diagnoses: occupational asthma (new-onset asthma caused by a workplace exposure), work-aggravated asthma (existing asthma aggravated by a workplace exposure), and reactive airways dysfunction syndrome (RADS), which can result from a single high-level exposure irritant exposure. Other diagnoses that may be contributory to symptoms, limitations in activities of daily living, or testing abnormalities should be clearly delineated.

If relevant, the diagnosis should also include a statement on *causation*, the physician's opinion as to whether or not a given workplace exposure has caused

or aggravated an illness. This is a medicolegal determination, also known as attribution, made on a medically probable basis, also known as a "more-likely-than-not" basis. That is, the physician should be able to opine with greater than 50% certainty that the exposure(s) in the workplace caused the respiratory condition or worsened an underlying condition based on objective criteria, such as change in treatment requirements. This criterion is less rigorous than would be required for scientific proof of a hypothesis (i.e., 95% certainty). This is important, because in cases of respiratory illness, there may be multifactorial causation, frequently a long latency between initial exposure and clinical onset of disease, nonspecific clinical manifestations, incomplete understanding of dose-response relationships from epidemiologic studies, and lack of individual exposure data. Although recognition of these limitations is necessary, causation can be attributed in most cases on a more-probable-than-not basis by simply applying reasonable judgment. This process is easier when the exposure is known, the dose-response relationship is well characterized, and competing diagnoses are unlikely. The physician should clearly describe the specific substances at the workplace; their known health effects according to the medical literature; the relative dose, in terms of estimated intensity, frequency, and/or duration of exposure; and finally, why it is medically probable that the exposure(s) caused or resulted in permanent aggravation of the diagnosed medical condition in this worker. When one or more of these conditions are not met, attribution should be based on the answers to the following questions.

- Is the diagnosis clearly established, and is it biologically plausible (or consistent with the available epidemiologic data) that the disease could have been caused or aggravated by the exposure in question?
- Have competing diagnoses been adequately considered?
- Is the exposure of sufficient intensity and duration to have caused or aggravated the disease?
- Has there been an adequately long latent period, or is there a temporal relationship between onset of exposure and clinical manifestation of disease?

Some systems, such as most state workers' compensation and a Department of Labor Program, the Energy Employees Occupational Illness Compensation Program (EEOICP) require the physician to make a statement that the patient has reached MMI before performing an impairment rating. If the examining physician believes the condition is not stable or believes that there may be additional treatment reasonably likely to improve the condition, it is medically prudent to state this. What will happen logistically following determination of the MMI will depend on the specific program requirements. The examining physician should be aware of the ramifications of making these medicolegal determinations. For example, in the state workers' compensation system, determination of MMI will allow the worker to be awarded permanent impairment, but will also result in the cessation of temporary benefits such as compensation for lost wages, as the case is closed by the workers' compensation insurance company.

GUIDES TO RESPIRATORY IMPAIRMENT RATINGS

American Thoracic Society Guidelines for Evaluation of Impairment or Disability

There are a number of systems that have been used to determine respiratory impairment. Most base impairment primarily on lung function. In their "Guidelines for the Evaluation of Impairment/Disability Secondary to Respiratory Disorders," the ATS recommends that impairment due to most lung diseases be rated based on PFT results.[2] The results of the ATS impairment system, based on PFTs, places individuals into four impairment categories. Each of these categories provides a corresponding description of the associated ability to perform job demands (Table 27-2). This system does not lend itself

TABLE 27-2. American Thoracic Society Impairment Categories, with Corresponding Description of Ability to Perform Job Demands

Category	Criteria	Ability to Perform Job Demands
Normal	FVC ≥ 80% of predicted, ***and*** FEV_1 ≥ 80% of predicted, ***and*** $FEV_1/FVC \times 100 \geq 75\%$, ***and*** DL_{COsb} ≥ 80% of predicted	
Mildly impaired	FVC 60%–79% of predicted, ***or*** FEV_1 60%–79% of predicted, ***or*** $FEV_1/FVC \times 100$ 60% to 74%, ***or*** DL_{COsb} 60%–79% of predicted	Usually not correlated with diminished ability to perform most jobs
Moderately impaired	FVC 51%–59% of predicted, ***or*** FEV_1 41%–59% of predicted, ***or*** $FEV_1/FVC \times 100$ 41% to 59%, ***or*** DL_{COsb} 41%–59% of predicted	Progressively lower levels of lung function correlated with diminishing ability to meet the physical demands of many jobs
Severely impaired	FVC ≤ 50% of predicted, ***or*** FEV_1 ≤ 40% of predicted, ***or*** $FEV_1/FVC \times 100 \leq 40\%$, ***or*** DL_{COsb} ≤ 40% of predicted	Unable to meet the physical demands of most jobs, including travel to work

DL_{COsb}, single-breath diffusing capacity; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity.
From American Thoracic Society (ATS): Evaluation of impairment/disability secondary to respiratory disorders. American Thoracic Society. Am Rev Respir Dis 133:1205–1209, 1986.

to use in most compensation systems, in which monetary awards are typically based on a numerically derived percentage of whole-person impairment, as it does not provide such a paradigm.

American Medical Association Guides to the Evaluation of Permanent Impairment

The most commonly used methodology by which to calculate an actual numeric value for permanent partial impairment is set forth in the AMA *Guides*. Although the Fifth Edition is no longer the most current edition since the recent publication of the Sixth Edition in 2008, most compensation systems have not yet adopted the Sixth Edition. Therefore, the methodology of the still widely used AMA *Guides*, Fifth Edition, is presented in this section. The methodology of the Sixth Edition is described under "Future Directions."

The AMA *Guides*, Fifth Edition and earlier, delineate methodology similar to ATS by which to place individuals into one of four impairment categories, as shown in Table 27-3, but also provide an associated range of percentage whole-person impairment: Class 1 impairment is equal to 0% whole-person impairment, Class 2 impairment ranges from 10% to 25% impairment, Class 3 ranges from 26% to 50% impairment, and Class 4 ranges from 51% to 100% whole-person impairment. The physician can then determine a final numeric percentage whole-person impairment, based on where the test results fall within that range of impairment, as well as other factors, including impact of the respiratory condition on the ability to perform ADLs. Because a person can never have more than 100% impairment of the body, impairment in any additional organ system needs to be combined rather than added to the respiratory impairment. The AMA *Guides* contain a special combining table for this purpose.

Classification of Impairment Resulting from Specific Pulmonary Diseases

In the classification of impairment, the greatest weight should be placed on objective data.

Asthma

Rating asthma according to the standard respiratory disorder methodology can both under- and overestimate impairment, given the episodic and variable nature of airflow limitation and bronchial hyperresponsiveness.[13] The AMA *Guides*, Fifth Edition, incorporated the methodology of the ATS Guidelines for the Evaluation of Permanent Impairment and Disability updated in 1993,[1] to more accurately reflect the true impairment due to this condition. First, a worker with objectively confirmed asthma must be determined to be at MMI or to have achieved optimal therapeutic goals (i.e., minimum medication that obtains the best overall outcome).[6b] To rate asthma impairment according to the AMA *Guides*, Fifth Edition, a postbronchodilator forced expiratory volume in 1 second (FEV_1), reversibility (% change with bronchodilator), or methacholine challenge results (provocative concentration of methacholine inducing a 20% drop in FEV_1 [PC_{20} mg/mL]), and minimum medications required to maintain this status are needed (Table 27-4).

Bronchiectasis

Rating conditions such as bronchiectasis by the standard pulmonary function testing methods also can underestimate impairment, as it is the recurrent episodes of infection and inflammation that cause intermittent respiratory symptoms, respiratory dysfunction, and limitations in ADLs, often with normal lung function in between episodes. The AMA *Guides*, Fifth Edition, acknowledge that this method will be applicable only in "limited cases,"

TABLE 27-3. American Medical Association Classification of Respiratory Impairment

Class 1, 0%–9%: No Impairment of the Whole Person	Class 2, 10%–25%: Mild Impairment of the Whole Person	Class 3, 26%–50%: Moderate Impairment of the Whole Person	Class 4, 51%–100%: Severe Impairment of the Whole Person
FVC ≥ lower limit of normal,* ***and*** FEV_1 ≥ lower limit of normal,† ***and*** FEV_1/FVC ≥ lower limit of normal ***and*** D_{LCO} ≥ lower limit of normal,‡ ***or*** $\dot{V}O_2$max > 25 mL/kg/min	FVC between 60% and lower limit of normal, ***or*** FEV_1 between 60% and lower limit of normal, ***or*** $\dot{V}O_2$max between 20 and 25 mL/kg/min	FVC between 51% and 59% of predicted, ***or*** FEV_1 between 41% and 59% of predicted, ***or*** $\dot{V}O_2$max between 15 and 20 mL/kg/min	FVC ≤ 50% of predicted, ***or*** FEV_1 ≤ 40% of predicted, ***or*** D_{LCO} ≤ 40% of predicted, ***or*** $\dot{V}O_2$max < 15 mL/kg/min

*Lower limit of normal FVC for men is predicted normal FVC—1.115 L; lower limit of normal FVC for women is predicted normal FVC—0.676 L (adapted from Crapo et al[19]).
†Lower limit of normal FEV_1 for men is predicted normal minus 0.842 L; lower limit of normal FEV_1 for women is predicted normal minus 0.561 L (adapted from Crapo et al[19]).
‡Lower limit of normal D_{LCO} from men is predicted normal—8.2 mL/min/mm Hg; lower limit of normal D_{LCO} for women is predicted normal—5.74 mL/min/mm Hg (adapted from Crapo et al[22]).
D_{LCO}, diffusing capacity for carbon monoxide; FVC, forced vital capacity; $\dot{V}O_2$max, maximal oxygen consumption.
Used with permission from the American Medical Association: Cocchiarella L, Andersson GBJ (eds): The respiratory system. *In*: Guides to the Evaluation of Permanent Impairment, Fifth Edition. Chicago: AMA Press, 2001, pp 87–116.

TABLE 27-4. American Medical Association Impairment Classification for Asthma Severity

A. POSTBRONCHODILATOR FEV_1*

Score	FEV_1 (% predicted)
0	Lower limit of normal
1	70–Lower limit of normal
2	60–69
3	50–59
4	<50

B. REVERSIBILITY OF FEV_1 OR DEGREE OF AIRWAY HYPERRESPONSIVENESS*

Score	% FEV_1 Change	PC_{20}† (mg/mL)
0	<10	>8
1	10–19	8–>0.6
2	20–29	0.6–>0.125
3	>30	≤0.125

C. MINIMUM MEDICATION NEED‡

Score	Medication
0	No medication
1	Occasional bronchodilator, not daily, and/or occasional cromolyn, not daily
2	Daily bronchodilator and/or daily cromolyn and/or daily low-dose inhaled steroid (<800 µg beclomethasone or equivalent)
3	Bronchodilator on demand and daily high-dose inhaled steroid (>800 µg beclomethasone or equivalent) or occasional course (1–3/yr) systemic steroid
4	Bronchodilator on demand and daily high-dose inhaled steroid (>1000 µg beclomethasone or equivalent) and daily or every other day systemic steroid

D. SUMMARY OF IMPAIRMENT RATING CLASSES§

Impairment Class	Total Score	% Impairment of the Whole Person
I	0	0–9
II	1–5	10–25
III	6–9	20–50
IV	7–9	51–100
V	10–11 or asthma not controlled despite maximal treatment (i.e., FEV_1 remaining < 50% despite use of ≥ 20 mg prednisone/day)	

*When the postbronchodilator FEV_1 value is above the lower limit of normal, the PC_{20} value should be determined and used for rating impairment; when the postbronchodilator FEV_1 value is less than 70% of the predicted value, the degree of reversibility should be used; when the FEV_1 value is between 70% of the predicted value and the lower limit of normal, either the degree of reversibility of FEV_1 or the PC_{20} can be used.

†PC_{20}, the provocative concentration of methacholine that causes a 20% decrease in FEV_1 from the prechallenge baseline.

‡The need for minimum medication should be demonstrated by the treating physician (e.g., previous records of exacerbation when medications have been reduced).

§The impairment rating is calculated as the sum of the patient's scores from parts A, B, and C.

FEV_1, forced expiratory volume in 1 second.

From the American Medical Association: Cocchiarella L, Andersson GBJ (eds): The respiratory system. *In*: Guides to the Evaluation of Permanent Impairment, Fifth Edition. Chicago: AMA Press, 2001, pp 87–116.

but will allow the physician to assign a rating based on the extent and severity of these episodes and their impact on ADLs, with objective supporting evidence documented.[5b]

Lung Cancer

The AMA *Guides*, Fifth Edition, recommends one of two methods be used for rating permanent impairment due to lung cancer.[5b] All individuals with lung cancer are considered severely impaired at the time of diagnosis. At 1 year after diagnosis, if there is still evidence of tumor or tumor recurrence, the person is considered to be severely impaired. If there is no residual tumor or recurrence, the impairment rating is performed according to the standard rating methodology for respiratory diseases.

Diseases of the Pulmonary Arteries

This category includes pulmonary artery hypertension, cor pulmonale, and pulmonary emboli. The rating is determined by the presence or absence of physical examination signs (right ventricular heave, increased pulmonic component [P_2] of the second heart sound [S_2], peripheral edema) and symptoms of right heart failure (dyspnea), as well as the observed pulmonary artery pressure (PAP), as shown in Table 27-5.

Conditions of the Upper Airway

The AMA *Guides*, Fifth Edition,[5d] contain methodology by which to assign impairment due to obstruction of the upper airway, larynx, trachea, and/or bronchi, based on degree and location(s) of the obstruction, nature of the activities that trigger dyspnea, as well as need for ventilation. There is also methodology for the rating of voice/speech impairment, based on audibility, intelligibility, and functional efficiency.

ROLE OF DIAGNOSTIC TEST RESULTS IN IMPAIRMENT RATINGS

Radiographic Data

Documentation of chest radiograph or computed tomography (CT) scan abnormalities consistent with the lung disorder is frequently required to establish evidence of disease, particularly for diseases like pneumoconiosis. The chest imaging findings may correlate poorly with the physiologic findings, especially in patients with obstructive lung disease.

Some programs require that chest x-rays be read by a National Institute of Occupational Safety and Heath (NIOSH)–certified B-reader and classified according to the International Labour Organization's (ILO's) classification system.[14] This radiographic interpretation system was devised to attempt to objectively and consistently report the presence, appearance, and extent of radiographic changes consistent with pleural and parenchymal evidence of pneumoconiosis. Chest radiograph

TABLE 27-5. Criteria for Rating Permanent Impairment Due to Pulmonary Hypertension

Class 1 0%–9% Impairment of the Whole Person	Class 2 10%–29% Impairment of the Whole Person	Class 3 30%–49% Impairment of the Whole Person	Class 4 50%–100% Impairment of the Whole Person
No symptoms or signs of right heart failure and mild pulmonary hypertension (P_{PA} 40–50 mm Hg) or a Doppler echocardiography–derived peak tricuspid velocity of 3.0–3.5 m/sec	No symptoms or signs of right heart failure and moderate PA hypertension (P_{PA} 51–75 mm Hg)	Moderate pulmonary hypertension (P_{PA} < 75 mm Hg) ***and*** Signs and symptoms of right HF ***or*** Symptoms of mild limitation (class 2) with any degree of pulmonary hypertension	Severe pulmonary hypertension (P_{PA} > 75 mm Hg) ***or*** Symptoms of severe limitation (class 3 or 4) with any degree of pulmonary hypertension

PA, pulmonary artery; P_{PA}, pulmonary artery pressure.
From the American Medical Association: Cocchiarella L, Andersson GBJ (eds): The cardiovascular system: Systemic and pulmonary arteries. *In*: Guides to the Evaluation of Permanent Impairment, Fifth Edition. Chicago: AMA Press, 2001, pp 65–86.

findings of opacities with an ILO profusion score of at least 1/0 are "consistent with" asbestosis and will be accepted for compensation purposes by programs such as the Department of Labor for that condition. If the opacities are small and irregular (classified as "s" and "t") and are found predominantly in the middle and lower lobes or are found in conjunction with pleural plaques, these findings are highly consistent with a diagnosis of asbestosis.

Whereas the ILO interpretation may help raise suspicion of pneumoconiosis, or provide sufficient evidence of disease in the correct clinical situation, the physician needs to determine on a clinical basis whether additional testing is needed to definitively establish a medical diagnosis and determine whether treatment is needed. The physician should note that additional testing may or may not be covered by the benefits or compensation program. Because of the variability in the extent of radiographic findings and the degree of physiologic impairment, none of the major programs or rating systems uses radiographic findings in the assessment of impairment due to the lung disease. The NIOSH website provides a search tool by which to find certified B-readers by state and country.[15]

Pulmonary Function Testing

PFTs are the most important tests, both from a diagnostic standpoint and in their use to determine impairment for most respiratory conditions. Both the ATS[2] and the AMA *Guides*,[5,6] specify the use of forced vital capacity (FVC), FEV_1, FEV_1/FVC, and single-breath diffusing capacity (DL_{COsb}). Some programs mandate that pulmonary function testing be performed pre- and postbronchodilator and should be done in patients with low FEV_1 or diagnoses of reversible airflow limitation. The ATS specifies that individuals should be evaluated only after they have received an accurate diagnosis and while they are receiving optimal therapy.[2] This is consistent with the AMA *Guides'* requirement that the patient be at MMI, as described previously.[5] Measurement of height in stocking feet is recommended, as is use of arm span (distance from the tips of the middle fingers with arms outstretched) in cases of spinal deformity.[2,16]

Both ATS and the AMA *Guides* emphasize the importance of only using test results that meet the quality standards defined in the latest ATS statement "Standardization of lung function testing."[17] This document governs the equipment, quality assurance, and technique that should be used to perform lung function testing, in addition to the assessment of the quality of the test and the method of interpretation. If a physician has concern that the PFTs were not performed in a manner consistent with the ATS Guidelines, including acceptability and reproducibility, then she or he should request that a repeat test be obtained. One exception is when a patient has consistently demonstrated less than optimal technique on past tests despite language-appropriate education and encouragement. This consistent unacceptable test performance may be due to overall debilitation, pain, or language barrier, and it is unlikely that repeating the test will yield improved results. Test results that are markedly worse than those of prior tests raise concern for an exacerbation of the underlying condition and that the patient is not at MMI, or it may be that the patient gave less than full effort; regardless, such results would not be considered to reflect the patient's permanent impairment status. Options include informing the subject of the discrepancy and repeating the test or using the results "as a subsidiary and not the main criterion."[18]

When evaluating PFTs for impairment, the normal values of the laboratory performing the test should not be used, but rather the normal values of the impairment rating system. For example, the ATS and AMA *Guides*, Fifth Edition, reference population normal values derived from Crapo and coworkers,[19] while the AMA *Guides*, Sixth Edition, reference National Health and Nutrition Examination Survey (NHANES) III–derived prediction equations.[20]

DL_{COsb}, measured by the single-breath method of Ogilvie and colleagues[21] and interpreted according to Crapo and Morris,[22] is suggested by both ATS and the AMA *Guides*. Both recommend correction by the methodology of others for factors including hemoglobin, carboxyhemoglobin,[2,5b] and altitude and alveolar volume,[2] but correction methodology and interpretive strategies are not explicitly described in the rating criteria. The

most recent ATS statement on DL_{COsb} describes explicit criteria for evaluating acceptability and repeatability, as well as adjustment for hemoglobin, supplemental oxygen, altitude, carboxyhemoglobin, while noting that further study is needed before specific recommendations for lung volume adjustment can be made.[23] In a separate statement, the ATS has noted that low DL_{COsb} along with low DL_{COsb} corrected for alveolar volume (DL_{COsb}/VA) suggests parenchymal abnormalities as the cause of the impairment, but recommends examining the two separately.[17] Neither the ATS nor the AMA *Guides* utilize DL_{COsb}/VA in assessing impairment.

Maximal voluntary ventilation (MVV) and FEV_{25-75} are not recommended for use by ATS or the AMA *Guides* in impairment evaluation. ATS defines a restrictive ventilatory defect as a reduction in total lung capacity (TLC) below the fifth percentile of the predicted value, with a normal FEV_1/FVC ratio.[17] TLC is not included in the standard rating criteria in either the ATS or the AMA *Guides*. Although the AMA *Guides*, Sixth Edition, caution that a true restrictive defect may not be present even with a reduced FVC in the setting of a normal or increased FEV_1/FVC,[6] FVC continues to be the test used in the rating of impairment. Low FVC can be caused by submaximal inspiratory or expiratory effort and/or patchy peripheral airflow obstruction.[17] One study showed the predictive value of reduced FVC to be less than 60% for the presence of true restrictive deficit.[24] Others report concern about reduced lung function test results, including FVC, in obesity,[25,26] but there are no established criteria by which to account for obesity in testing.

Cardiopulmonary Exercise Testing

Neither the ATS nor the AMA *Guides* recommend the routine use of exercise test results in the determination of permanent impairment, but do note that maximal exercise test results, specifically $\dot{V}O_2max$, should be used in specific circumstances. ATS recommended that exercise test results be used in cases where the static PFTs do not reflect the true impairment present.[2] For example, studies have demonstrated that alveolar-arterial oxygen pressure difference ($P(A—a)O_2$) during exercise is a better reflection of impairment due to gas exchange abnormality than DL_{COsb}.[27] Although exercise limitation does not necessarily correlate with static lung function testing,[28,29] exercise testing can be very helpful in cases where there is a large discrepancy between symptoms and resting physiology,[27] providing a more precise measurement of work capacity.[30]

Airflow limitation and gas exchange abnormality help define the relative degree to which respiratory disease is contributing to exercise limitation. When exercise limitation is present, nonrespiratory causes of exercise limitation should be considered as well, including cardiovascular disease, deconditioning, and neuromuscular disease.[31] The ATS guidelines for respiratory impairment note that exercise testing can be used as a valid measure of respiratory impairment when the following criteria are met: (1) if exercise testing is not terminated for other nonpulmonary reason, (2) if there is low breathing reserve at termination, and (3) if there is absence of or erratic overventilation at submaximal levels with failure to achieve anaerobic threshold. However, there are no details provided on how these criteria should be met and the AMA *Guides* do not delineate a specific methodology. The reason for test termination should be noted, as tests terminated early due to nonrespiratory causes such as excessive blood pressure, cardiac abnormality, or leg pain do not reflect maximum exercise tolerance.

To determine work capacity, and thus impairment, ATS requires use of $\dot{V}O_2max$ to place workers into one of three categories of work tolerance, assuming that workers can comfortably perform sustained work at 40% of $\dot{V}O_2max$ and that $\dot{V}O_2$ requirements of the workers' job are known (Table 27-6). Major limitations to this approach include the following: (1) little published data that substantiate its use; (2) heterogeneous methods of assessing maximal oxygen uptake[32]; (3) the fact that actual work performed by workers with the same job title can vary markedly from employer to employer or among employees with differing seniority at the same employer; (4) the questionable relationship between exercise tolerance on the treadmill or bicycle and performance on the job[33]; and (5) the lack of consideration of modifying factors such as the need to talk or use personal protective equipment (PPE) while performing the work.[34] The average energy requirements of a number of jobs are listed in Table 27-7. The AMA *Guides*, Fifth and Sixth Editions, both consider a $\dot{V}O_2max$ greater than 25 mL/kg/min to place one into the lowest (least) category of impairment (class 1 and class 0, respectively), and a $\dot{V}O_2max$ less than 15 mL/kg/min to place one into the highest (greatest) category of impairment (class 4). The use of exercise testing and $\dot{V}O_2max$ overestimates impairment in older workers. As an alternative,

TABLE 27-6. American Thoracic Society Interpretation of Exercise Test Results Using $\dot{V}O_2max$

$\dot{V}O_2max$	METS	Estimated Work Ability
≥25 mL/kg/min	≥7.1	Continuous heavy exertion throughout an 8-hour day in all but the most physically demanding jobs
15–25 mL/kg/min ***and*** Metabolic demands of the work ≤ $\dot{V}O_2max$		Able to perform that job comfortably, assuming there are no frequent or extended periods (5 min) requiring exertion substantially >40% $\dot{V}O_2max$
≤ 15 ml/kg/min	≤4.3	Unable to perform most jobs because they would be uncomfortable traveling back and forth

METS, the energy demand in liters of oxygen consumption per minute/basal oxygen consumption (3.5 mL/kg/min); $\dot{V}O_2max$, maximal oxygen consumption.

From American Thoracic Society (ATS): Evaluation of impairment/disability secondary to respiratory disorders. American Thoracic Society. Am Rev Respir Dis 133:1205–1209, 1986.

TABLE 27-7. Energy Requirements Expressed as Oxygen Uptake ($\dot{V}O_2$) of Various Types of Work

Level of Work	$\dot{V}O_2$ (APPROXIMATE)		
	mL/kg/min	L/min	METS
Light to moderate work (sitting)			
Clerical	5.6	0.42	1.6
Using repair tools	6.3	0.47	1.8
Operating heavy equipment	8.8	0.66	2.5
Heavy truck driving	12.6	0.95	3.0
Moderate work (standing)			
Light work, own pace	8.8	0.66	2.5
Janitorial work	10.5	0.79	3.0
Assembly line (lifts ≥ 45 lb)	12.3	0.92	3.5
Paper hanging	14.0	1.05	4.0
Standing and/or walking (arm work)			
General heavy labor	15.8	1.19	4.5
Using heavy tools	21.0	1.58	6.0
Lift and carry 60–80 lb	26.2	1.97	7.5

METS, the energy demand in liters of oxygen consumption per minute/basal oxygen consumption (3.5 mL/kg/min); $\dot{V}O_2$max, maximal oxygen consumption.
Adapted from Becklake M: Organic or functional impairment. Am Rev Respir Dis 129:S96-S100, 1984.

it has been proposed that $\dot{V}O_2$max be expressed as percent of predicted,[35] although this is not in standard use at this time. Although advances have been made, the recent ATS Statement on Cardiopulmonary Exercise Testing[31] noted a comprehensive updated framework for impairment/disability is urgently needed.

Blood Gas Analysis

Arterial blood gas analysis is not used for impairment rating purposes on a routine basis. Resting arterial P_{O_2} does not correlate with exercise capacity. As a result, arterial hypoxemia at rest is, by itself, not evidence of severe impairment in exercise tolerance. ATS recommends it only be used in "selected patients" under "rigidly controlled laboratory conditions," and should be documented on at least two occasions separated by at least 4 weeks.[2] They consider hypoxemia to be evidence of severe impairment only when accompanied by evidence of cor pulmonale. Arterial blood gas analysis was also considered to be a test infrequently indicated in the evaluation of impairment in the AMA *Guides*, Fifth Edition.[5b] It is not included in the Sixth Edition.

Addressing Discrepancies between Objective and Subjective Data

A description of the severity of the disease or condition should be given. This can be difficult when there is a discrepancy between the severity reported by the patient and the severity of the disease based on the results of the diagnostic testing. It is important that the physician distinguish between data that are *objective* (findings evident to the examiner in a reproducible manner and not dependent on only the patient's perceptions), including physical signs and diagnostic testing results, and the *subjective* data, which are reported by the patient, such as symptoms perceived by the patient only and not evident to the examiner. Normally, the two will be very similar, making the history, physical examination, and diagnostic testing findings all helpful in the assessment of true functional impairment. If the subjective complaints are not consistent with the objective findings, the physician should first be sure there is no coexisting disease process responsible for the symptoms. For example, dyspnea may also be caused by nonrespiratory disorders such as cardiac disease and anemia. *Organic impairment* refers to the presence of objective findings of respiratory dysfunction or disease. *Functional impairment* refers to dyspnea for which an objectively measured abnormality of organ function cannot be identified. Recognizing that tests for organic impairment are not perfectly sensitive, the contribution of functional impairment can range from "negligible" to "perhaps accounting for the entire extent of a patient's dyspnea." When there is a discrepancy between the subjective and the objective data, and other medical conditions have been excluded as possible contributors to the subjective complaints, there are several steps that should be taken. The first and foremost is to review the purpose of the evaluation with the patient to ensure that a lack of comprehension of either questions or performance of PFTs does not exist. Second, an evaluation of test performance, including cooperation and the results of effort-independent tests such as functional residual capacity, may be of some use. Examination of test results for comparability over time may show evidence of consistency or the lack thereof. Finally, exercise testing may shed considerable light on a patient's level of effort by demonstrating the relationships of heart rate and ventilatory rate at workloads actually achieved to the predicted maximal values.

Dyspnea due to functional impairment may result from subconscious effects on the perception of symptoms or from outright malingering. Because of the inability of PFTs and other tests to be perfectly sensitive in diagnosing organic causes of impairment, the diagnosis of malingering should be made with caution. The *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR), classifies malingering as a condition "that may be a focus of clinical attention."[36] Furthermore, malingering is described as "the intentional production of false or grossly exaggerated physical or psychological symptoms, motivated by external incentives." Specific listed examples of these external incentives include avoiding work and obtaining financial compensation. The DSM-IV-TR recommends that malingering should be strongly suspected if any combination of the following is noted: (1) there is a medicolegal context of presentation, (2) a marked discrepancy between the person's claimed stress or disability and the objective findings is noted, (3) a lack of

cooperation during the diagnostic evaluation and compliance with the prescribed treatment regimen are observed, and (4) there is the presence of antisocial personality disorder. Malingering is differentiated from a factitious disorder in that the motivation for the symptom production is external, rather than an intrinsic need to maintain the sick role. Malingering may also be differentiated from conversion disorder and other somatoform disorders by the intentional production of symptoms and the obvious external incentives associated with it.

Although it is important to identify frank malingering, which represents fraud, it must be emphasized that malingering is relatively rare and should remain a diagnosis that is made through exclusion and with extreme caution.

WORK RESTRICTIONS, APPORTIONMENT, AND FUTURE MEDICAL TREATMENT

Work Restrictions

Some compensation systems, such as workers' compensation, require a statement on ability to work, that is, are there any physical activities or exposures the worker should avoid? Inability to work may be due to inability to perform a specific physical activity, perform it safely on a sustained or repeated basis, and/or perform it in the presence of certain dust, fume, gas, chemical, and/or antigen exposures, as in the case of occupational allergic asthma and hypersensitivity pneumonitis.

The NIOSH recommends the following hierarchical approach to reducing workplace exposures: elimination; substitution; engineering controls, such as improving ventilation or enclosing exposures; and administrative controls, before using personal protective equipment, such as respirators.[37] Medical clearance for the use of respirators is mandated by the OSHA, either through their standard questionnaire or through a comparable medical examination.[38] Before using a respirator, the worker should undergo fit testing with the specific make and model of the respirator to be used, to ensure proper fit and protection. Fit testing is also regulated by OSHA.

In order for the physician to determine whether or not the worker can perform the full scope of the job tasks, both the physical requirements of the job and the worker's capabilities need to be known. Exercise testing, with its limitations noted previously, is a standard approach used in this assessment. Although submaximal testing has been used, and does have some advantages in terms of administration and merits in terms of demonstrating a workers' ability to sustain activity at a predetermined level of exertion, maximal exercise testing is normally used. Accuracy of exercise testing to predict functional performance can be increased by combining exercise testing with measures of pulmonary function[28] and with heart rate monitoring during the performance of work activities.[39] Actual simulation of work may be performed by a physical or occupational therapist, called a Functional Capacity Evaluation (FCE). Interpretation of results and formulation of formal work restrictions should be performed in a manner consistent with Americans with Disabilities Act (ADA) considerations, including suggesting possible methods of reasonable accommodation in the workplace.

Apportionment

When multiple disease processes are present that may contribute to respiratory impairment, the physician may be asked to apportion, or make a statement of the relative contribution of each disease process to the total impairment. This is usually performed in the context of workers' compensation in an effort to limit the amount of the monetary award to that specifically attributed to the workplace exposure or event. It does not typically reduce medical treatment benefits or wage compensation. Unfortunately, the scientific basis for this level of precision is rarely present and thus must be acknowledged as arbitrary even if required by the entitlement system.

Cigarette smoking and its sequelae is the most common condition taken into account when considering apportionment of respiratory impairment. For example, much has been written about the difference in symptoms and physical limitations in smoking compared with nonsmoking asbestos workers,[40] and the observation that the most common cause of exercise limitation in one group studied was the cardiovascular system rather than the respiratory system.[41] Specific methods for apportionment have been proposed,[42] but none has been validated scientifically or considered generally accepted. If objective evidence of prior impairment exists, such as diagnostic testing results performed before the work-related exposure or development of disease, some states will allow apportionment to be performed by subtracting the preexisting impairment from the current total impairment.

Expected Future Medical Treatment

A description of the expected natural history of the condition, that is, if the condition is expected to remain stable or potentially deteriorate over time, should be provided. In addition, the recommended medical follow-up and anticipated treatment requirements can provide a helpful measure of reasonably anticipated future medical expenses. This is of value to the worker, as well as insurance adjusters and attorneys.

MAJOR STATE AND FEDERAL BENEFIT AND COMPENSATION PROGRAMS

Most impairment and disability evaluations will be performed under the context of a particular state or federal program. A number of different programs exist for individuals and workers in specific employment settings. Most programs reference both impairment and disability. In some programs, the primary determination to be made by the physician is disability, usually in the context

of making the dichotomous determination of "disabled" or "not disabled." Systems in which the primary role of physicians is to determine impairment will also be discussed. Most major compensation systems require physicians undergo special training and/or approval before they are permitted to perform these evaluations for benefits programs. A few of the larger programs are reviewed in the following sections.

Programs in Which Physicians Primarily Determine Disability

These are programs that provide benefits to individuals who are determined to be unable to work due to a medical condition. The role of the physician is to determine if there is evidence of an illness and, if so, provide medical evidence that supports the determination that the worker cannot engage either in a particular occupation or in any type of gainful employment. These are typically all or none systems; either the worker is totally disabled due to the condition or he or she is not. No benefits are awarded unless the worker is determined to be totally disabled.

Federal Black Lung Program

The Federal Black Lung Program is a medical treatment program for miners, administered through the Department of Labor (DOL).[43] It arose out of the Federal Coal Mine and Safety Act of 1969, with amendments made in 1977, 1981, and 2000. The Act established mandatory safety and health standards in mines, and included provisions for research and training. Title IV of the Act established black lung benefits, recognizing that there are many coal miners who are disabled or deceased because of mining-related lung disease, primarily pneumoconiosis. The amendments that followed the initial act broadened the scope of workers covered and lung diseases. A *miner* is now defined as "any person who works or has worked in or around a coal mine or coal preparation facility in the extraction, preparation or transportation of coal, and any person who works or has worked in coal mine construction or maintenance in or around a coal mine or coal preparation facility." In addition, the amendments also broadened the disease covered, so that *pneumoconiosis* is now defined as any "chronic dust disease of the lung and its sequelae including respiratory and pulmonary impairments, arising out of coal mine employment." Thus, the Federal Black Lung program covers not only coal miners with silicosis or coal worker's pneumoconiosis but also airways disease due to coal mining, such as chronic airways obstruction.

Benefits are awarded to the miners or to their *surviving dependents*, defined as the wife or dependent child, parents, or siblings of the miner. Each miner who applies for benefits is afforded the opportunity to undergo a medical evaluation paid for by the DOL to ascertain if she or he is eligible for benefits. The testing must be performed in the manner outlined in the Federal regulations. Only physicians who have been approved by the DOL may perform the examination; they cannot be related to the miner or have examined or treated the miner within the preceding 12 months. Miners may apply for benefits under state workers' compensation as well.

There are strict eligibility requirements. This normally requires the miner to have been employed for a minimum of 10 years in underground mine work. Once determined to be eligible, the physician must then determine if the miner has lung disease due to mining, as defined by the statute. This is most commonly determined on the basis of chest x-ray findings of pneumoconiosis, specifically large or small opacities of profusion 1/0 or greater, read by a NIOSH-certified B-reader and classified according to the ILO's classification system.[14] A determination may also be made by biopsy or autopsy evidence of pneumoconiosis, or through a reasoned medical opinion that there was a condition that would be reasonably expected to yield the previously discussed chest x-ray or pathology findings. The regulations also specify criteria for posthumous determinations.

The physician will next determine if the miner meets the definition of *totally disabled*, defined as being unable to work as a miner or perform comparable work due to respiratory impairment. The medical criteria that establish total disability are pulmonary function test results with FVC, FEV_1, or MVV below values listed in the tables contained in the regulations (60% of predicted), FEV_1/FVC ratio 55% or less, or ABG analysis based on a P_{O_2} at or below a value specified for concurrently measured P_{CO_2}, listed in one of three tables provided for different ranges of altitude. If these criteria are met, the physician must also establish that the miner is unable to perform his or her usual job in the coal mine, or unable to be employed in the area of their residence with the skills used in the mines over a period of time. The specific tables noted previously may be accessed at the U.S. DOL's Division of Coal Mine Workers Compensation page[44] through the Pulmonary Functions Standards and Tables link. This website also contains a link to the specific standards that must be used for the administration and interpretation of PFTs contained in the legislation.

If not covered under state workers' compensation, medical treatment expenses for black lung–related conditions, including medication, will be covered. Home oxygen, pulmonary rehabilitation, and home health care may be covered after special approval.

Social Security Disability

Amendments to the Social Security Act in 1950 established the first legislation for financial assistance "to aid the permanently and totally disabled." Numerous changes in this system have occurred since that time. The Social Security Administration (SSA) oversees two programs: the Social Security Disability Insurance (SSDI) program, which pays monthly cash benefits to former workers now unable to work for at least a year due to disability; and the Supplemental Security Income (SSI) program, which provides benefits to disabled persons who meet financial need criteria. Former workers are eligible for

SSDI if they have earned a sufficient number of work credits while working in the past, based on past contributions made to Social Security. What constitutes a credit is variable, as is number of credits required, and with workers aged 62 years or older requiring the greatest number of credits to qualify.

In this program, the physician must first determine whether an applicant is disabled. *Disability* is defined as not being able to do any substantial gainful work activity because of a medically determined physical or mental impairment, which is expected to last at least 12 months or which may result in death. The determination may be made based on information submitted by treating physicians and/or through an evaluation by an approved physician. There are strict eligibility criteria. The categories of impairments of the respiratory system and an overview of the impairment criteria are listed in Table 27-8. The SSA outlines the specific tests and testing criteria, including quality considerations, which form the basis for the determination as to whether or not the degree of impairment would be expected to prevent an individual from working. Up-to-date Blue Book information can be freely accessed at the SSA website (http://www.ssa.gov/disability/professionals/bluebook/).

Programs in Which Physicians Primarily Determine Impairment

In addition to the programs outlined previously, there are programs that compensate workers for permanent impairment remaining after treatment of a medical condition that developed as a direct result of a workplace exposure or activity. A description of a few of these programs follows.

Workers' Compensation

State workers' compensation systems are state-specific, as they are governed by the rules and laws of each individual state. States began to adopt this European "no-fault" model in the early 1900s in a piecemeal manner.[45]

TABLE 27-8. Social Security Administration Respiratory System Impairment Categories and Criteria by Which to Establish Sufficient Impairment to Result in Disability

Category		Impairment Rating Criteria to Establish Disability
Chronic pulmonary insufficiency	Obstructive disease, any cause	Based on FEV_1 in liters (BTPS) and height without shoes (Table I)[1]
	Restrictive disease, any cause	Based on FVC in liters (BTPS) and height without shoes (Table II)[2]
	Pulmonary disease causing gas exchange abnormality	DL_{CO} < 10.5 ml/min/mm Hg, or DL_{CO} < 40% predicted, or ABG result based on P_{O_2} for a specified P_{CO_2}, at rest or steady state exercise ≤5 METS[3]
Asthma		Based on Table I criteria, or based on frequency of attacks[4]
Cystic fibrosis		As per COPD or based on frequency of infections or exacerbations[5] or based on infection treatment requirements[5]
Pneumoconiosis		Based on Table II criteria
Bronchiectasis		Based on Table II criteria or based on frequency of infections or exacerbations[6]
Mycobacterial, mycotic, or other chronic infection		Based on Table II criteria
Cor pulmonale	Secondary to pulmonary vascular hypertension	Mean pulmonary artery pressure > 40 mm Hg Arterial hypoxemia[3] or based on Section 4.02 (chronic heart failure)
Sleep disorders		As per cor pulmonale
Lung transplant		

ABG, arterial blood gas; BTPS, body temperature, ambient pressure, saturated with water vapor; COPD, chronic obstructive pulmonary disease; DL_{CO}, diffusing capacity for carbon monoxide; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; P_{CO_2}, pressure of carbon dioxide; P_{O_2}, pressure of oxygen.
Adapted from the Social Security Administration. Updated Blue Book information can be obtained on the SSA website (http://www.ssa.gov/disability/professionals/bluebook/) under the links to the Adult Listings, and the link to Section 3.00 Respiratory system.
[1]SSA Blue Book Section 3.02 Table I.
[2]SSA Blue Book Section 3.02 Table II.
[3]SSA Blue Book Section 3.02 Table III-A, III-B, or III-C, depending on altitude.
[4]Frequency of attacks, defined as occurring every 2 months or at least six times a year despite treatment. Attacks requiring in-patient hospitalizations are counted as two attacks.
[5]Infection treatment requirements, defined as persistent infection accompanied by bacterial infections occurring at least once every 6 months requiring intravenous or nebulization antimicrobial therapy.
[6]Frequency of infections or exacerbations, defined as number of episodes of bronchitis, pneumonia, hemoptysis, or respiratory failure requiring treatment occurring at least every 2 months or six times per year. In-patient hospitalizations are counted as two episodes.

This system affords employees the right to guaranteed treatment and benefits for an injury or illness that occurs "in the course and scope" of their work, regardless of fault, but in exchange for the ability to sue their employers for negligence.[46] The determination that a worker has a work-related condition is usually made by a physician on a medically probable basis, that is, it is at least 51% likely that work event caused or substantially worsened the condition or illness. Whereas the state workers' compensation systems remain highly variable from state to state, commonalities include employer funding of the system; coverage of medical treatment expenses; temporary wage replacement compensation, usually about two thirds of salary; vocational rehabilitation training (some states only); and compensation for permanent impairment that remains after the worker has completed medical treatment, that is, is at MMI. There is usually a statute of limitation, or a time period that a claim must be made after the worker has received a diagnosis of a work-related disease. In many states, the statute of limitations is 2 years.

The monies a worker may be paid in compensation for persistent permanent impairment of the respiratory system are usually based on the impairment rating provided by the physician. Most states designate the specific system by which permanent impairment is to be determined. Forty-four states and two commonwealths use the AMA *Guides*.[6a] Some states mandate the use of the "most recent" or "most current" edition, whereas others specifically mandate that the Fifth Edition, the Fourth Edition, or the Third Edition, revised be used. Some states, such as Minnesota, have developed their own guidelines for the rating of permanent impairment. Some states, such as Colorado, require that a physician have undergone training and become "accredited" before performing impairment evaluations. Because of the variability of the systems used, as well as concerns for validity and internal consistency within some editions of the *Guides* themselves,[47] significant variability exists in impairment ratings performed across the country.[48] Physicians should consult their state regulations or workers' compensation agencies to learn about the system and statutes used in their state.

There are other workers' compensation programs that cover specific workers groups. For example, the Office of Workers' Compensation (OWCP) administers medical treatment and benefits to current federal workers through the Federal Employees' Compensation Program, Department of Energy (DOE) workers through the EEOICP (as described in the next section), and through the Longshore and Harbor Workers' Compensation Program for workers in these industries. Under the Federal Employers' Liability Act (FELA), enacted in the beginning of the 20th century, federal railroad workers must establish that negligence of the railroad or other railroad personnel contributed to the injury or illness through a legal claim before full treatment and other benefits are awarded. If there is "contributory negligence" on the part of the worker, partial benefits are awarded. The Merchant Marine Act (Jones Act) is a similar system.

Veterans Administration

Department of Veterans Affairs provides medical care for military personnel who have a service-connected condition. Veterans who meet the service requirements and were discharged under other than dishonorable conditions may apply for compensation for disability due to service-connected conditions, defined as injury or illness incurred or aggravated during active military service. Veterans with disabilities can qualify for severance with disability pay or monthly disability compensation. Those veterans who are permanently and totally disabled or 65 years of age and older, had wartime service, and meet the financial eligibility requirement may receive a monthly pension.

Disability ratings are performed according to the Rating Schedule that contains over 700 diagnostic codes under 14 different body systems.[49] Although it is called a disability rating, the listed criteria reflect symptoms, impairment, and treatment requirements by which the rater determines the rating, given in 10% increments ranging from 0% to 100%, rather than a determination of ability or inability to work.

The respiratory system is divided into diseases of the nose and throat, diseases of the trachea and bronchi, and diseases of the lung and pleura. Veterans Affairs–affiliated and –designated physicians review medical records, and are asked to provide medical history, including current treatment requirements, physical examination findings, and results of diagnostic and clinical tests that support the diagnosis along with any associated conditions, and PFT results. The major criteria that the raters use in the determination of the disability rating for the specified respiratory diseases are shown in Table 27-9, adapted from the U.S. Department of Veteran's Affairs Web Automated Reference Materials Systems (WARMS) website, which contains the up-to-date Book C Schedule for Rating Disabilities.[49] Specific illnesses and medical conditions are presumed to be service-connected for select groups of veterans, including prisoners of war, veterans exposed to radiation, Vietnam veterans exposed to agent orange or other herbicides, and Gulf War veterans. These veterans are eligible for disability compensation for those conditions without burden of proof.

Energy Employees Occupational Illness Compensation Program

This is a federal program available as an adjunct or alternative to state workers' compensation for workers who were or are employed by or were subcontractors at DOE sites or who worked for businesses that functioned as vendors providing services or goods for the DOE. The compensation program is outlined in the EEOICP Act of 2000, as amended (EEOICPA or Act), which also established the DOL's responsibility for the administration of this program.[50] Part B of the Act provides compensation to current and former workers who meet DOL criteria for beryllium sensitization, chronic beryllium disease

TABLE 27-9. Veterans Administration: Specific Lower Respiratory Diseases for Which Veterans May Be Eligible for Service-Related Disability and General Criteria Used

Disease	Rating Based on the Following Criteria
Bronchitis, chronic	FEV_1, FEV_1/FVC, DL_{CO}
Bronchiectasis	Cough frequency, number and frequency of infections requiring antibiotics and incapacitating episodes per year
Bronchial asthma	Frequency and type of treatment, physician visits, severity of attacks, FEV_1, FEV_1/FVC
COPD, emphysema	FEV_1, FEV_1/FVC, DL_{CO}, $\dot{V}O_2$max (with cardiorespiratory limit), use of oxygen, evidence of secondary cardiovascular dysfunction[4]
TB	Active vs. inactive disease, respiratory status, x-ray findings, residual lung disease, thoracoplasty
Pulmonary vascular disease	Pulmonary embolism with residual symptoms, ongoing treatment needs, IVC surgery, evidence of secondary cardiovascular dysfunction[4]
Neoplasm	If in remission 6 months after ending treatment, rating will be reassessed and may decrease from 100% based on residuals.
ILD[1]	FVC, DL_{CO}, $\dot{V}O_2$max (with cardiorespiratory limit), evidence of secondary cardiovascular dysfunction,[4] use of oxygen
Mycotic lung disease[2]	Active vs. inactive disease, respiratory symptoms, constitutional symptoms
Restrictive lung diseases[3]	FEV_1, FEV_1/FVC, DL_{CO}, $\dot{V}O_2$max (with cardiorespiratory limit), use of oxygen, evidence of secondary cardiovascular dysfunction[4]
Sarcoidosis	Radiographic involvement, frequency and type of treatment, cardiac involvement, respiratory and systemic symptoms
Sleep apnea	Sleep study results, symptoms, CPAP treatment, respiratory failure

[1]ILD: diffuse interstitial fibrosis, DIP, pulmonary alveolar proteinosis, drug-induced pulmonary pneumonitis and fibrosis, radiation-induced pulmonary pneumonitis and fibrosis, HP, pneumoconiosis (silicosis, anthracosis), asbestosis.

[2]Mycotic lung disease: histoplasmosis, coccidiomycosis, blastomycosis, cryptococcosis, aspergillosis, mucormycosis.

[3]Restrictive lung diseases: diaphragm paralysis/paresis, spinal cord injury with respiratory insufficiency, chest wall deformities, postsurgical residua, chronic pleural fibrosis or effusions.

[4]Evidence of secondary cardiovascular dysfunction: evidence of cor pulmonale, RVH, or pulmonary hypertension.

COPD, chronic obstructive pulmonary disease; CPAP, continuous positive airway pressure; DIP, desquamative interstitial pneumonia; DL_{CO}, diffusing capacity for carbon monoxide; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; HP, hypersensitivity pneumonitis; ILD, interstitial lung disease; IVC, inferior vena cava; RVH, right ventricular hypertrophy; TB, tuberculosis; $\dot{V}O_2$max, maximal oxygen consumption.

Veteran's Affairs Web Automated Reference Materials Systems (WARMS) website: http://www.warms.vba.va.gov/regs/38CFR/BOOKC/PART4/S4_97.DOC (Accessed June 15, 2008).

TABLE 27-10. EEOICPA Part B Requirements for Eligibility and Diagnosis under the Act for Beryllium-Related Illness and Silicosis*

Condition	Eligible Workers	Requirements for Diagnosis under Part B
Beryllium sensitization	See Chronic beryllium disease	Abnormal Beryllium Lymphocyte Proliferation test (BeLPT) performed on blood or BAL cells
Chronic beryllium disease	Employees of the DOE, its predecessor agencies, contractors, and subcontractors, designated atomic weapons workers, and beryllium vendors.	For diagnoses made on or after 1/01/1993† An abnormal BeLPT and at least one of the following: 1. Lung biopsy showing a process consistent with CBD. 2. A CT scan showing changes consistent with CBD. 3. A pulmonary function or exercise tolerance test showing pulmonary deficits consistent with CBD.
Chronic silicosis	DOE employee or contractor who worked at least 250 days in underground tunnel operations at the Nevada or Alaska nuclear test sites.	One of the following: 1. A chest x-ray B-reading confirming pneumoconiosis with a profusion score of 1/0 or greater. 2. Results from a CT or other imaging study consistent with silicosis. 3. A lung biopsy consistent with silicosis.

*The final decision as to whether or not the patient meets the requirements is made by the Department of Labor.

†If the diagnosis was made before 1/01/1993, at least three of the following must be documented: characteristic chest radiograph or CT scan denoting abnormalities; a test showing restrictive, obstructive, or diffusion abnormality; lung pathology consistent with CBD; a clinical course consistent with a chronic respiratory disorder; an immunologic test showing beryllium sensitivity (skin patch test or beryllium test preferred).

BAL, bronchoalveolar lavage; CBD, chronic beryllium disease; CT, computed tomography; DOE, U.S. Department of Energy; EEOICPA, Energy Employees Occupational Illness Compensation Program.

Adapted from U.S. Department of Labor Medical Requirements under the Energy Employees Occupational Illness Compensation Program Act OMB No. 1215-0197 Expiration date: 08/31/2010 Form EE-7 April 2005.

(CBD) and silicosis (Table 27-10). Individuals with beryllium sensitization are awarded medical monitoring for possible progression to CBD, whereas those with CBD and silicosis are awarded medical evaluation to follow-up and monitor disease, and coverage of medications and consequential illness evaluation and treatment as needed, along with a one-time lump-sum payment of $150,000.

DOE employees, contractors, and subcontractors and atomic weapons employees diagnosed with cancer are compensated in a manner similar to that of CBD and silicosis, if that cancer is determined to have developed

as a result of working at a covered facility, based on DOL criteria. Members of special cohorts, composed of workers at specific sites during certain time periods, are afforded compensation for specific cancers without further burden of proof. The Radiation Exposure Commission Act (RECA) provides compensation to individuals who develop these specific cancers and other serious diseases as a result of exposure to radiation during above-ground nuclear weapons testing or during work as uranium miners, millers, and ore transporters. Eligibility is largely determined on the basis of having worked in certain locations during specified periods of time, a minimum duration of exposure, and having a specific type of cancer. A lump-sum payment and medical expenses will be awarded to individuals who have been awarded compensation by the Department of Justice (DOJ). Because the DOL makes the final determination as to whether or not the worker meets the requirements for the diagnosis, the evaluating physician should clearly document the history of the claimed illness(es), physical examination findings, the clinical testing data supporting the diagnosis, and the date the illness was first documented. Consequential illness or injury may be accepted if sufficient medical documentation of its relationship to the covered illness is submitted. There are provisions for survivor eligibility provided as part of this compensation program.

The EEOICP Act established Part E, and replaced Part D, a program that had been administered by the DOE in which panels of physicians made medical determinations as to whether or not a particular illness was related to DOE work. Under Part E, DOE employees, contractors, and subcontractors, as well as eligible RECA claimants, are awarded payment of medical expenses, as well as a maximum of $250,000 compensation for permanent impairment and loss of wages, if they are determined to have developed an illness as a result of occupational exposure to a toxic substance at a covered DOE facility. Workers with conditions accepted under Part B will be automatically accepted under Part E for compensation for impairment. Unfortunately, DOE vendors are eligible under Part B but are not eligible for compensation under Part E. There is survivor eligibility provided under Part E. Impairment ratings may be performed by physicians who are certified by the American Board of Independent Medical Examiners (ABIME) or American Academy of Disability Evaluating Physicians (AADEP), or who are otherwise considered by the DOL to have the requisite experience or knowledge. Not all physicians approved to provide care for workers under Part B of the program are eligible to provide impairment ratings under Part E. Physicians will be asked to submit such credentials for approval by the DOL to confirm their ability to provide impairment ratings. Alternatively, medical consultants to the DOL may perform the ratings. Currently, the ratings are still performed under the AMA *Guides*, Fifth Edition, which had been the most recent edition at the time the legislation was passed. Each percent whole-person impairment determined through an impairment rating is compensated $2,500. Compensation for lost wages is based on the number of years that the employee was unable to work or sustained a reduction in wages because of the illness up to 65 years of age.

The Americans with Disabilities Act

The ADA of 1990 prohibits discrimination against a qualified individual with a *disability*, defined as "a physical or mental impairment that substantially limits a major life activity."[51] Some, but not all, individuals with permanent respiratory impairment will meet the ADA definition of disability, depending on whether or not the impairment is severe enough to "substantially limit a major life activity." "Substantially limits" means being unable to perform or significantly restricted in performing a major life activity that the average person in the general population can perform.[52] Major life activities include, but are not limited to, functions such as caring for oneself, performing manual tasks, walking, seeing, hearing, speaking, breathing, learning, and working. The act applies to individuals who have, have a record of, or are regarded as having a physical or mental impairment. A qualified individual is a person who has the requisite skills and experience to do the job and "can perform the essential job tasks with or without reasonable accommodation" without risk of direct threat to self or others. Knowing what the essential job tasks are and what is required to do them physically is essential for the physician to be able to make this determination. This information is often contained in the workers' position description. The worker's job title typically provides insufficient information.

Essential job tasks are defined as the specific functions that an individual in that position must be able to perform without aid or with the assistance of reasonable accommodation. Factors involved in determining whether or not a job activity is an "essential function" include whether or not all employees in the position are required to perform the task, the position exists to perform the function, the frequency and duration of the job function, and whether or not there are other employees available and qualified to perform the function. A "preemployment" physical is not permitted under the ADA; an employer may not ask questions about disability or require a medical examination until after a conditional job offer has been made. A postoffer, preplacement medical evaluation is permitted, as long as: the employer does this for all employees entering the same job category; if doing so is job-related and consistent with business necessity, based on objective evidence that a worker will be unable to perform essential job functions or will pose a direct threat because of a medical condition; or when an employer receives a request for reasonable accommodation and the disability or the need for the accommodation is not obvious.

Reasonable accommodation is defined as a modification or adjustment to the job, work environment, or the way things are usually done that enables a person with a disability to perform the essential job function. Physicians may suggest means by which reasonable accommodation may be made, but the employer decides whether or not the accommodation is reasonable on a case-by-case basis. Examples of reasonable accommoda-

tion for individuals with respiratory impairment can include modification of the workstation to allow use of a wheelchair, scooter, or oxygen equipment; decreasing the need to travel distances, lift or push objects; and/or allowing written rather than lengthy verbal communication. A direct threat occurs when an individual poses a significant risk of substantial harm to the health or safety of herself/himself or others, and the risk cannot be reduced to an acceptable level with reasonable accommodation. The risk needs to be defined in terms of the specific behavior or physical limitation that would pose the direct threat, the duration of the risk, the nature and severity of the potential harm, and the likelihood and imminence of the potential harm. An example of direct threat would be use of oxygen in an area with open flames or sparking materials.

FUTURE DIRECTIONS

International Classification of Functioning, Disability, and Health

The WHO's ICIDH model was recognized as problematic in a number of respects, including an implied unidirectional relationship from impairment to handicap, limited definition of the role of the environment, and focus on the disablement, rather than on factors that may enable. The WHO put forth the International Classification of Functioning, Disability, and Health (ICF) in 2001,[4] designed to be used in conjunction with International Classification of Diseases (ICD)–10 codes to put forth a uniform description of health and well-being in two parts.

Part 1 is the part most relevant to most physicians, and combines the consideration of body structure and function, activities, and participation into a unified concept. Essentially, the term *functioning* combines the positive aspects of body functions, activities, and participation, whereas the term *disability* is now used to describe the combination the negative aspects of functional loss (impairment), activity limitation (disability), and participation restriction (handicap).

Part 2 consists of Contextual Factors, divided into personal factors, such as age, education, attitudes, and environmental factors. *Facilitators* are contextual factors that enhance functioning and *barriers* are contextual factors that restrict or limit functioning. As its purpose is to serve as a method to describe functioning and disability in a uniform manner across a wide range of medical disorders on the international level, it certainly holds promise as a system that may improve the reliability, accuracy, and validity of determinations of impairment compared with the systems currently in use, although the only major impairment rating system that references the ICF is the AMA *Guides*, Sixth Edition, which is not yet in widespread use.

American Medical Association *Guides*, Sixth Edition

The methodology for rating general respiratory impairment in the AMA *Guides*, Sixth Edition, is shown in Table 27-11. Based on the "key factor," which is an objective test result (spirometry, DL_{CO}, or $\dot{V}o_2max$), the individual is placed into one of five classes of impairment and assigned the default amount of impairment in the middle of that category. "Non-key factors," such as functional history and physical examination, are then considered, which may or may not serve to move the individual into the higher or lower range of impairment for that category, which determines the final percent whole-person impairment. One major change is that the maximum whole-person impairment for most respiratory disorders is 65% whole-person impairment, rather than 100% whole-person impairment in previous editions, although this impairment may still be combined with impairment in other organ systems.

Americans with Disabilities Act Amendments Act of 2008

The ADA Amendments Act of 2008[53] has just been implemented. This amendment effectively expands the

TABLE 27-11. Overview of AMA *Guides*, 6th Edition, Impairment Rating Scheme, Based on the WHO International Classification of Functioning, Disability, and Health (ICF) Model

Class	Description	Default Impairment (% Whole Person)*	Range of Impairment (% Whole Person)†
0	No symptoms or intermittent symptoms not requiring treatment	0	0
1	Minimal	6	2,4,6,8,10
2	Mild	17	11,14,17,20,23
3	Moderate	32	24,28,32,36,40
4	Severe	55	45,50,55,60,65

*Based on "Key Factor" (spirometry, DL_{COsb}, or $\dot{V}o_2max$).
†Possible final impairment after consideration of "Non-key Factors" (functional history and physical examination findings).
AMA, American Medical Association; DL_{COsb}, single-breath diffusing capacity; $\dot{V}o_2max$, maximal oxygen consumption; WHO, World Health Organization.
Adapted from the American Medical Association: Rondinelli RD (ed): The pulmonary system. *In*: Guides to the Evaluation of Permanent Impairment, Sixth Edition. Chicago: AMA Press, 2008, pp 77–100.

number of workers who will qualify for coverage under the Act. While retaining the original definitions of disability, it expands the definition of "major life activities," to include activities such as sleeping, standing, lifting, bending, concentrating, communicating, thinking, and working.[54] A list of "major bodily functions" are now included, such as functions of the immune system, normal cell growth, and respiratory. A disease that causes intermittent impairment or that is in remission is considered a disability if it would substantially limit a major life activity when active. The impact of these changes on Equal Employment Opportunity Commission (EEOC) enforcement guidance and the resulting changes in the workplace have yet to be determined.

KEY POINTS

- *Impairment* refers to the degree of loss of normal use or function of a body part or organ.
- *Disability* refers to any resulting alteration in the individual's capacity to perform customary activities.
- *Handicap* refers to the societal disadvantage caused by the impairment or disability, unless obstacles to performing customary activities can be overcome by means of accommodation or compensation.
- *MMI* is the time at which permanent impairment can be assessed. It is achieved when the diagnosis has been well defined, the condition is stable, and medical treatment has either optimized or reasonable options have been exhausted.
- The *Americans with Disabilities Act of 1990* prohibits discrimination against a qualified individual with a disability, defined as "a physical or mental impairment that substantially limits a major life activity." The definition of major life activities was greatly expanded and a list of "major bodily functions" was added through the ADA Amendments Act of 2008.
- *Reasonable accommodation* is defined as a modification or adjustment to the job, work environment, or the way things are usually done that enables a person with a disability to perform an essential job function.
- An *impairment evaluation* is a medical evaluation. The essential elements that compose an impairment evaluation will vary to some degree according to the program or system through which the evaluation is being performed. Standard components typically include history, including a detailed occupational and environmental history and description of limitations in ADLs; physical examination; and review of medical records and diagnostic test results that establish the respiratory condition. If the worker is at maximum medical improvement (MMI), a permanent impairment rating can be performed. The physician may be asked to address causation, which is usually the disease relationship to workplace exposures, the need for work restrictions, future medical needs, and possibly apportionment of impairment.
- An *impairment rating* is a numeric value from 0% to 100% that represents the percent loss of total body function due to the respiratory system. This numeric value helps form the basis for the monetary award given to workers with permanent impairment that remains after reaching MMI.
- *Workers' compensation* is the system through which employees are afforded guaranteed treatment and benefits for an injury or illness that occurs "in the course and scope" of their work. Whereas the state workers' compensation systems remain highly variable from state to state, commonalities include employer funding of the system; coverage of medical treatment expenses; temporary wage replacement compensation, usually about two thirds of salary; vocational rehabilitation training (some states only); and compensation for permanent impairment. Separate federal workers' compensation programs exist, which also vary considerably program to program.
- Specific benefit and compensation programs exist for certain groups of workers, including miners, DOE workers, veterans, and radiation-exposed workers.

References

1. American Thoracic Society (ATS): Guidelines for the evaluation of impairment/disability in patients with asthma. Am Rev Respir Dis 147:1056–1061, 1993.
2. American Thoracic Society (ATS): Evaluation of impairment/disability secondary to respiratory disorders. American Thoracic Society. Am Rev Respir Dis 133:1205–1209, 1986.
3. World Health Organization (WHO): International Classification of Impairment, Disability, and Handicap (ICIDH). Geneva: WHO Press, 1980.

4. World Health Organization (WHO): International Classification of Functioning, Disability, and Health (ICF). Geneva: WHO Press, 2001.
5a. Cocchiarella L, Andersson GBJ (eds): Philosophy, purpose, and appropriate use of the guides. *In*: Guides to the Evaluation of Permanent Impairment, Fifth Edition. Chicago: AMA Press, 2001, pp 1–16.
5b. Cocchiarella L, Andersson GBJ (eds): The respiratory system. *In*: Guides to the Evaluation of Permanent Impairment, Fifth Edition. Chicago: AMA Press, 2001, pp 87–116.
5c. Cocchiarella L, Andersson GBJ (eds): The cardiovascular system: Systemic and pulmonary arteries. *In*: Guides to the Evaluation of Permanent Impairment, Fifth Edition. Chicago: AMA Press, 2001, pp 65–86.
5d. Cocchiarella L, Andersson GBJ (eds): Ear, nose, throat, and related structures. *In*: Guides to the Evaluation of Permanent Impairment, Fifth Edition. Chicago: AMA Press, 2001, pp 245–276.
6a. Rondinelli RD (ed): Practical application of the guides. *In*: Guides to the Evaluation of Permanent Impairment, Sixth Edition. Chicago: AMA Press, 2008, pp 19–30.
6b. Rondinelli RD (ed): The pulmonary system. *In*: Guides to the Evaluation of Permanent Impairment, Sixth Edition. Chicago: AMA Press, 2008, pp 77–100.
7. Taiwo OA, Cain HC: Pulmonary impairment and disability. Clin Chest Med 23:841–851, 2002.
8. Ferris BG: Epidemiology standardization project (American Thoracic Society). Am Rev Respir Dis 118:1–120, 1978.
9. Bestall JC, Paul EA, Garrod R, et al: Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. Thorax 54:581–586, 1999.
10. Epler GR, Saber FA, Gaensler EA: Determination of severe impairment (disability) in interstitial lung disease. Am Rev Respir Dis 121:647–659, 1980.
11. McGavin CR, Artvinli M, Naoe H, McHardy GJ: Dyspnoea, disability, and distance walked: Comparison of estimates of exercise performance in respiratory disease. Br Med J 2:241–243, 1978.
12. Mador MJ, Kufel TJ: Reproducibility of visual analog scale measurements of dyspnea in patients with chronic obstructive pulmonary disease. Am Rev Respir Dis 146:82–87, 1992.
13. Chan-Yeung M: Evaluation of impairment/disability in patients with occupational asthma. Am Rev Respir Dis 135:950–951, 1987.
14. International Labour Office (ILO): Guidelines for the Use of the ILO International Classification of Radiographs of Pneumoconioses (rev. ed 2000). Occupational Safety and Health Series, No. 22. Geneva: International Labour Office, 2002.
15. National Institute for Safety and Health (NIOSH): NIOSH Safety and Health Topic: Chest Radiography. NIOSH B-reader list. Available at http://www.cdc.gov/niosh/topics/chestradiography/breader-list.html.
16. Hepper NG, Black LF, Fowler WS: Relationships of lung volume to height and arm span in normal subjects and in patients with spinal deformity. Am Rev Respir Dis 91:356–362, 1965.
17. Pellegrino R, Viegi G, Brusasco V, et al: Interpretative strategies for lung function tests. Eur Respir J 26:948–968, 2005.
18. Cotes JE II: Assessment of disablement due to impaired respiratory function. Bull Physiopathol Respir (Nancy) 11:210P–217P, 1975.
19. Crapo RO, Morris AH, Gardner RM: Reference spirometric values using techniques and equipment that meet ATS recommendations. Am Rev Respir Dis 123:659–664, 1981.
20. Hankinson JL, Odencrantz JR, Fedan KB: Spirometric reference values from a sample of the general U.S. population. Am J Respir Crit Care Med 159:179–187, 1999.
21. Ogilvie CM, Forster RE, Blakemore WS, et al: A standardized breath-holding technique for the clinical measurement of the diffusing capacity of the lung for carbon monoxide. J Clin Invest 36:1–17, 1956.
22. Crapo RO, Morris AH: Standardized single breath normal values for carbon monoxide diffusing capacity. Am Rev Respir Dis 123:185–189, 1981.
23. Macintyre N, Crapo RO, Viegi G, et al: Standardisation of the single-breath determination of carbon monoxide uptake in the lung. Eur Respir J 26:720–735, 2005.
24. Aaron SD, Dales RE, Cardinal P: How accurate is spirometry at predicting restrictive pulmonary impairment? Chest 115:869–873, 1999.
25. Canoy D, Luben R, Welch A, et al: Abdominal obesity and respiratory function in men and women in the EPIC-Norfolk Study, United Kingdom. Am J Epidemiol 159:1140–1149, 2004.
26. Aaron SD, Fergusson D, Dent R, et al: Effect of weight reduction on respiratory function and airway reactivity in obese women. Chest 125:2046–2052, 2004.
27. Risk C, Epler GR, Gaensler EA: Exercise alveolar-arterial oxygen pressure difference in interstitial lung disease. Chest 85:69–74, 1984.
28. Cotes JE, Zejda J, King B: Lung function impairment as a guide to exercise limitation in work-related lung disorders. Am Rev Respir Dis 137:1089–1093, 1988.
29. Fink G, Moshe S, Goshen J, et al: Functional evaluation in patients with chronic obstructive pulmonary disease: Pulmonary function test versus cardiopulmonary exercise test. J Occup Environ Med 44:54–58, 2002.
30. Sue DY: Exercise testing in the evaluation of impairment and disability. Clin Chest Med 15:369–387, 1994.
31. ATS/ACCP Statement on cardiopulmonary exercise testing. Am J Respir Crit Care Med 167:211–277, 2003.
32. Weller JJ, el-Gamal FM, Parker L, et al. Indirect estimation of maximal oxygen uptake for study of working populations. Br J Ind Med 45:532–537, 1988.
33. Becklake MR, Rodarte JR, Kalica AR: NHLBI workshop summary. Scientific issues in the assessment of respiratory impairment. Am Rev Respir Dis 137:1505–1510, 1988.
34. Becklake MR: Organic or functional impairment. Overall perspective. Am Rev Respir Dis 129:S96–S100, 1984.
35. Neder JA, Nery LE, Bagatin E, et al: Differences between remaining ability and loss of capacity in maximum aerobic impairment. Braz J Med Biol Res 31:639–646, 1998.
36. American Psychiatric Association: Additional conditions that may be a focus of clinical attention. *In*: Diagnostic and Statistical Manual of Mental Disorders (4th ed, text rev). Washington, DC: American Psychiatric Association, 2000, pp 739–740.
37. NIOSH. National Institute for Occupational Safety and Health. Available at www.cdc.gov/niosh.
38. Occupational Safety and Health Administration (OSHA): Respiratory Protection Standard 29CFR 1910.134. Available at http://www.osha.gov/SLTC/respiratoryprotection/standards.html.
39. Harber P, Tamimie J, Emory J, et al. Effects of exercise using industrial respirators. Am Ind Hyg Assoc J 45:603–609, 1984.
40. Sue DY, Oren A, Hansen JE, Wasserman K: Lung function and exercise performance in smoking and nonsmoking asbestos-exposed workers. Am Rev Respir Dis 132:612–618, 1985.
41. Agostoni P, Smith DD, Schoene RB, et al: Evaluation of breathlessness in asbestos workers. Results of exercise testing. Am Rev Respir Dis 135:812–816, 1987.
42. Guidotti TL: Apportionment in asbestos-related disease for purposes of compensation. Ind Health 40:295–311, 2002.
43. Department of Labor (DOL): Regulations implementing the Federal coal mine health and safety act of 1969, as amended; final rule. Fed Reg 65:80045–80053, 2000.
44. United States Department of Labor (DOL): 20 CFR 718 Appendix B—Standards for Administration and Interpretation of Pulmonary Function Tests. Tables B1, B2, B3, B4, B5, B6. Available at http://www.dol.gov/dol/allcfr/Title_20/Part_718/Appendix_B.htm.
45. Clayton A: Workers' compensation: A background for Social Security professionals. Soc Secur Bull 65:7–15, 2003.
46. Guyton GP: A brief history of workers' compensation. Iowa Orthop J 19:106–110, 1999.
47. Spieler EA, Barth PS, Burton JF Jr, et al: Recommendations to guide revision of the Guides to the Evaluation of Permanent Impairment. American Medical Association. JAMA 283:519–523, 2000.
48. Patel B, Buschbacher R, Crawford J: National variability in permanent partial impairment ratings. Am J Phys Med Rehabil 82:302–306, 2003.
49. Veterans Administration (VA): Code of Federal Regulations: Pensions, Bonuses, and Veterans Relief [38CFR Book C: Schedule for Rating Respiratory System]. Available at http://www.warms.vba.va.gov/BookC.html.

50. Energy Employees Occupational Illness Compensation Program (EEOICP): Performance of functions; claims for compensation under the Energy Employees Occupational Illness Compensation Program Act of 2000, as amended. Final rule. Fed Reg 71:78519–78568, 2006.
51. Americans with Disabilities Act of 1990 42 USC 12101 et seq, 1990.
52. United States Equal Employment Opportunity Commission (EEOC): Discrimination by type: Facts and Guidance: Disability. Available at http://www.eeoc.gov/index.html.
53. Notice Concerning The Americans With Disabilities Act (ADA) Amendments Act of 2008: U.S. Equal Employment Opportunity Commission. Available at http://www.eeoc.gov/ada/amendments_notice.html.
54. ADA Amendments Act of 2008; 42 USCA § 12101 note: U.S. Equal Employment Opportunity Commission. Available at http://www.eeoc.gov/policy/adaaa.html.

CHAPTER 28
DYSPNEA

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INTRODUCTION

Dyspnea (Greek *dys,* meaning "painful," "difficult," and *pneuma,* meaning "breath") is a clinical term for the sensation of breathlessness or shortness of breath experienced by both normal subjects and patients with diseases affecting the respiratory system. Its importance has been recognized by the release of an American Thoracic Society Statement[1] and, more recently, a roundtable discussion by experts in the field.[2] Dyspnea assumes clinical significance when it occurs at a level of exertion that is unacceptably low for the individual. It is increasingly regarded as an important outcome for both prognostic and therapeutic purposes across a wide range of clinical conditions and principally chronic obstructive pulmonary disease (COPD),[3] heart failure,[4] and advanced cancer.[5]

There are no precise data on the prevalence of dyspnea.[6] A recent meta-analysis suggests a worldwide prevalence of 10% for COPD in adults older than 40 years,[7] making its cardinal symptom, dyspnea, a substantial cause of morbidity, especially in older people. A greater prevalence of dyspnea due to all causes is indicated by a survey of 4900 middle-aged and older adults with 27.2% reporting dyspnea relative to 12.5% reporting COPD.[6] A survey of 1556 seriously ill patients admitted to hospital 49% reported dyspnea compared with the 51% reporting pain.[8] Morbidity associated with dyspnea is variable, ranging from minor annoyance to functional incapacity.[9] Moreover, it is now clear that dyspnea is a strong independent predicator of mortality in both COPD[10] and heart failure.[11] Compared with pain, dyspnea is relatively refractory to effective symptom management, likely affecting not only patients but also their care providers (including health professionals) during terminal or severe chronic conditions.[12]

Dyspnea encompasses a variety of sensations experienced when breathing feels uncomfortable, labored, and unsatisfying,[1] sensations likely to be linked to discrete physiologic mechanisms.[13] It is distinct from objective findings associated with physical examination, such as tachypnea, hyperinflation, and cyanosis. Dyspnea is multifactorial, and although it results from some pathophysiologic event, it is likely to be influenced by such factors as psychological state, bodily preoccupation, level of awareness, usual level of physical activity, body weight, state of nutrition, and medications. These many modifying factors may explain the variable correlation between dyspnea ratings and airflow limitation or exercise performance.[13] Because most diseases in

which dyspnea occurs are essentially irreversible (e.g., chronic lung disease, heart failure, cancer), management of the dyspnea to improve quality of life is a desirable goal.

DEFINITION OF DYSPNEA

Over the years, there have been many attempts to define dyspnea and these have shared a common theme of an uncomfortable perception associated with the act of breathing. However, the more formalized definition given in the consensus statement of the American Thoracic Society is now widely accepted and has provided a sound basis for researchers and clinicians concerned with understanding and managing this symptom.[1] This states that "*Dyspnea* is a term used to characterize a subjective experience of breathing discomfort that is comprised of qualitatively distinct sensations that vary in intensity. The experience derives from interactions among multiple physiological, psychological, social, and environmental factors, and it may induce secondary physiological and behavioral responses."

LANGUAGE OF DYSPNEA

When patients complain of being short of breath, they are usually reporting sensations with which they are familiar but that have become noticeable on low levels of exertion. When questioned further, patients may volunteer comments such as "hard to breathe," "can't get enough air," or "feeling tight" but often have difficulty being more specific. Overlaying this, cultural or language differences may result in patients using different words to describe the same sensory experience.[14] Modeled on the proven clinical utility of evaluating the language of pain (e.g., assessing ischemic heart disease), researchers have begun to ask if the language of dyspnea might be similarly useful.

Since the early 1980s, studies in healthy subjects and dyspneic patients have identified distinctive clusters of descriptors from commonly used expressions of breathing discomfort. In general, four primary categories of breathing discomfort can be identified: "tightness," "need or urge to breathe," (often labeled "air hunger"), "work or effort of breathing," and "depth and frequency of breathing." In patient populations, "tightness" appears to be clearly associated with asthma, whereas "urge to breathe" and "effort of breathing" are more characteristic of chronic lung disease. The perception of changes in breathing depth and frequency probably relates more to awareness of chest wall movement than to awareness of breathing discomfort but may nonetheless be worrisome to the patient.

Although there are few cross-cultural studies of the language of dyspnea, the basic categories of phrases noted previously appear consistent across countries.[13] A summary of studies that have defined and explored the utility of qualitative descriptors of dyspnea has recently been published.[13] Recently, the pain model of symptom attributes has been further applied to explore the importance of the affective component (i.e., unpleasantness) of dyspnea in addition to its intensity and quality. One publication has summarized existing research in this area and reported that for a given intensity of dyspnea, that with a greater "air hunger" component is perceived as a substantially more unpleasant experience than that with a strong "work/effort" component.[15] These authors have developed a multidimensional profile for dyspnea, based on an analogous instrument for pain, which should be useful in better understanding the affective component of dyspnea with a view to developing more targeted therapeutic approaches.[15] In conclusion, it seems that a more careful consideration of the language and emotional impact of dyspnea by health practitioners might yield important diagnostic insights or improved management of breathless patients.

MECHANISMS OF DYSPNEA

The neurophysiologic mechanisms that give rise to the perception of dyspnea are incompletely understood (Fig. 28-1). Current thinking suggests that the discomfort of dyspnea comprises two primary components: (1) an "urge to breathe" (often referred to as "air hunger") and (2) a "sense of excessive effort" associated with breathing. Although sensations of effort and urge to breathe normally increase together, they can be separated experimentally.[16] A third quality of respiratory discomfort, chest tightness, is commonly reported by asthmatics.[17] Dyspnea in an individual patient may well represent

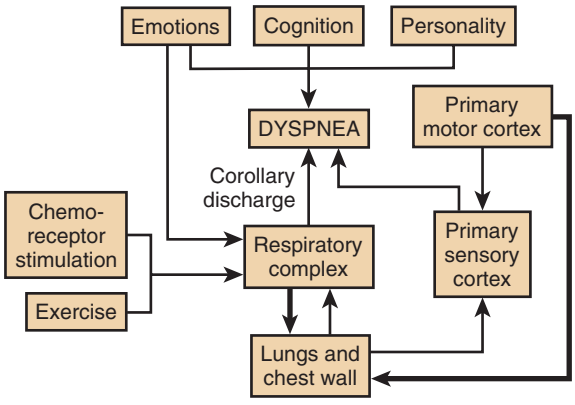

FIGURE 28-1 ■ The respiratory complex in the brain stem is central to our understanding of dyspnea. Activation of the respiratory complex by afferent input from a variety of receptors or by emotions, with input from the lungs and chest wall, determines the efferent command to breathe to the lungs and chest wall. The brain is made aware of this as dyspnea by a simultaneous corollary discharge. Alternatively, ventilation may occur as a result of voluntary output from the primary motor cortex with coactivation of the primary sensory cortex, which contributes to dyspnea. The primary sensory cortex also receives input from the lungs and chest wall that may affect the perception of dyspnea. The central experience of dyspnea may also be affected by emotions, cognition, and personality.

a combination of these component sensations and account for the different qualities of dyspnea mentioned previously.

As with all sensations, the experience of dyspnea must result from changes in neural activity within the cortical structures of the brain that are responsible for sensory perception. Unlike localized sensations, such as touch and temperature, that arise predominantly from peripheral receptor stimulation, dyspnea is a vague visceral sensation analogous to thirst or hunger, sensations that are more dependent on neural activity arising from within the central nervous system. Indeed, dyspnea arises in situations (e.g., exercise, breath-holding, anemia) that do not have a common pattern of peripheral receptor stimulation. Because dyspnea is a perception, studies on its mechanisms must be confined to humans and are limited by the difficulty of measuring a subjective experience and the neural activity that underlies it. New technologies, principally positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), allow imaging of brain function associated with sensory, motor, and cognitive processes, and in recent years, these have been applied to identify the neural basis of dyspnea perception in healthy subjects. Different investigators have induced dyspnea in different ways, with varying degrees of "urge to breathe" and "sense of effort." Despite this, a consistent pattern of neural activity associated with dyspnea perception is emerging from these studies. Of particular note is the activation of limbic and paralimbic structures, especially the anterior insular cortex, anterior cingulate gyrus, amygdale, and cerebellum. Activation of these phylogenically ancient regions of the cerebral cortex has been seen in brain imaging studies of pain,[18] thirst,[19] and hunger[20] and is consistent with the idea that dyspnea is a primal experience associated with behaviors intended to counteract a threat to survival.[21,22] This body of work has been the subject of a review.[23]

There is good evidence that the "urge to breathe" component of the dyspnea sensation depends to a large extent on the degree to which respiratory-related neurons in the brain stem are stimulated. Stimulation of ventilation with exercise, hypoxia, hypercapnia, and metabolic acidosis induces dyspnea[24,25] whereas a voluntary increase in ventilation induces little dyspnea, even in patients with respiratory mechanical limitation.[26] Moreover, dyspnea is felt strongly when respiratory stimulation occurs in the absence of a possible ventilatory response, as with transaction experimental respiratory muscle paralysis.[27,28] By contrast, the "sense of effort" aspect of dyspnea is likely to reflect efferent activity from the motor area of the cerebral cortex to respiratory muscles, as has been demonstrated for perception of peripheral muscle function in general.[13]

The role of afferent feedback from the lungs and chest wall in the genesis of dyspnea is complex. Conditions thought to activate lung irritant receptors and/or pulmonary C-fibers (e.g., pulmonary edema, atelectasis, congestive heart failure) may well contribute to dyspnea via vagal nerve afferents either directly or by modulating other sensory inputs that give rise to dyspnea.[28] Conversely, physiologic activation of slowly adapting stretch receptors (SARs) during lung inflation may inhibit the central respiratory drive and in this way ameliorate dyspnea. The immediate relief of dyspnea observed with thoracic movements following breath-holding but without improvements in blood gas status is consistent with this concept.[29]

In their recent review of the roles of airway nerves in inflammatory airway disease, Undem and Nassenstein[28] implicate vagal mechanisms in the production of dyspnea, both directly by neural signaling and indirectly by increasing the work of breathing via the release of acetylcholine (which stimulates airway smooth muscle contraction and mucus secretion). Nishino[30] suggested that vagal mechanisms associated with coughing affected the sensation of dyspnea, although the author agreed that other neural mechanisms could play roles. Further support for this comes from the observation in quadriplegic patients (lacking afferent information from the chest wall) that carbon dioxide–induced dyspnea is reduced as the tidal volume is increased without any change in blood gas levels.[31] Moreover, recent studies of inhaled furosemide (which potentiates SAR activity in an animal model) on experimental dyspnea in healthy subjects[32] and exertional dyspnea in COPD patients[33] have shown evidence of amelioration of the dyspneic sensation. With respect to "sense of effort" proprioceptive feedback from muscle, joint, and metaboreceptors probably integrates with the motor cortical output in the genesis of this perception.[13]

In light of the previous discussion, exertional dyspnea in patients with lung disease can usefully be considered a manifestation of the increased central respiratory drive necessary to achieve adequate ventilation by a mechanically constrained respiratory apparatus. This concept fits with the observation that in COPD patients, progressive hyperinflation is associated with increasing dyspnea as ventilatory demands require greater respiratory muscle activity to overcome increased elastic work at high lung volumes and to offset the foreshortening of inspiratory muscles that places them at a mechanical disadvantage.[13] Following from this, the lessening of dyspnea that follows successful lung volume reduction surgery is consistent with improvement in both lung and respiratory muscle mechanics. Support of this concept comes from a study showing that a decrease in dyspnea after volume reduction was associated with alleviation of hyperinflation of the lungs and a decrease in neural drive to the diaphragm.[34] Moreover, the concept is supported by the observation that noninvasive ventilatory support during exercise relieves dyspnea in patients with COPD,[34] presumably by reducing the work of breathing and consequently the efferent neural activity to respiratory muscles. The utility of this concept of dyspneogenesis extends to conditions in which lung disease is not the primary problem. In particular, the dyspnea of heart failure might be accounted for in terms of a heightened respiratory drive secondary to expiratory flow limitation[35] or peripheral muscle dysfunction.[36] A similar phenomenon may occur with deconditioning. The benefits of exercise training for those with dyspnea may be mediated in

part by changes in peripheral muscle function. Other conditions in which dyspnea in the absence of lung disease could be accounted for by increased respiratory drive include motoneuron disease/respiratory muscle weakness,[37] late-stage pregnancy,[38] anemia,[39] thyroid disorders, panic disorder, and anxiety.[40]

The sensation of dyspnea, like pain, has a psychological dimension.[41] An individual's emotional state, personality, previous experience, and cognitive function are likely to influence the experience and reporting of dyspnea. Dyspnea is worse when it is unexpected, when it occurs in inappropriate situations, and when it is perceived by the patient to be dangerous.[42] Studies in both healthy subjects and patients with underlying disease have suggested that perception of the intensity of breathlessness may be influenced by prior experience of the sensation.[43,44] Whether such observations are related to the frequency of prior experience of dyspnea (e.g., with exercise) or to some ill-defined psychological factor is unknown. In patients with the hyperventilation syndrome, both dyspnea and ventilation may dramatically increase in the absence of any known physiologic stimulus to breathe.[40] Dyspnea is a particular problem in patients with panic attacks. An Internet-based survey found that 95% of the respondents reported breathing problems during panic attacks, and 68% reported "remarkable" dyspnea.[45] An interesting example of clinically significant activity-related breathlessness in healthy human pregnancy is reported.[46] Jensen and colleagues[46] reported that variability in perceptual response to exercise could not be explained by variation in central ventilatory drive or in respiratory mechanical/muscular factors, but ultimately reflected a difference in awareness of increased ventilation. The source of that variation in perception is not clear. O'Donnell and coworkers[2] have recently reviewed the role of "higher center" neural processing on dyspnea perception and its relevance to self-management of this symptom.

In sum, dyspnea may occur when there is (1) increased central respiratory drive secondary to hypoxia, hypercapnia, or other afferent input; (2) augmented requirement for the respiratory drive to overcome mechanical constraints or weakness; and (3) altered central perception.

ASSESSMENT OF DYSPNEA

Clinicians generally rely on a combination of patients' reports and physiologic measurements (e.g., forced expiratory volume in 1 second [FEV_1]) to evaluate dyspnea. By assessing the nature and severity of symptoms, such as dyspnea, physicians quickly gain an advantage in the decision-making process. With a better understanding of the physiologic basis of symptoms, physicians can target the types and extent of diagnostic testing as well as the urgency with which a diagnosis must be made. Understanding the mechanisms of dyspnea or the responses to interventions, however, requires objective measurement of the symptom. Although primarily used for clinical investigation, there is increasing interest in applying dyspnea measurements to clinical practice.[47] For a recent review of factors that limit exercise performance in COPD and the identification of factors that contribute to the variability in dyspnea during exercise, see Stendardi and associates.[48] O'Donnell and coworkers[13] present a hypothetical model for exertional dyspnea based on current neurophysiologic concepts that were developed to explain the origins of "effort," "air hunger," and the accompanying affective "distress" response.

Exercise Performance as an Indication of Dyspnea

Exercise testing is commonly used to better understand dyspnea,[49] although there are discrepancies in the available diagnostic algorithms.[50] This form of testing focuses more on physiologic limitations than on the symptoms that limit exercise and might not be necessary for all patient groups. Two widely used field tests are the 6-minute walk distance and shuttle walking tests,[51] which are easy to perform, requiring minimal equipment; more sophisticated cardiopulmonary exercise testing (CPET) can be particularly helpful when it is unclear whether the patient is limited by the respiratory versus the cardiovascular system.[52]

Exercise Limitation Due to Dyspnea

Early attempts to evaluate the severity of dyspnea involved patient assessments of their own exercise tolerance (e.g., the five-point Medical Research Council [MRC] scale[53] and its modified version the American Thoracic Society [ATS] scale). Although such scales are simple, they are insensitive, require individuals to make comparisons with others, and cannot readily measure changes with therapeutic interventions. The Baseline Dyspnea Index, a rater-administered test, was developed to rate patients with regard not only to the "magnitude of the task" that elicits dyspnea (e.g., hills compared with level ground) but also to the impact of dyspnea on activities of daily living and the effort expended before dyspnea occurs.[54] Measurements can be repeated over time or in response to interventions. A number of easy-to-use self-administered questionnaires to assess functional limitation due to dyspnea have been developed but in general have not found widespread use.[55]

Quality of Life and Dyspnea

The negative impact of dyspnea on an individual's quality of life has been increasingly recognized since the mid 1980s and now is an important outcome measure in studies of therapeutic intervention for COPD/dyspnea. Two questionnaires, the St. George's Respiratory Questionnaire (SGRQ) and the Chronic Respiratory Disease Questionnaire (CRQ), are the most used. The CRQ is a rater-administered questionnaire with 20 items that focus on four aspects of illness: dyspnea, fatigue, emotional function, and the patient's feeling of control over

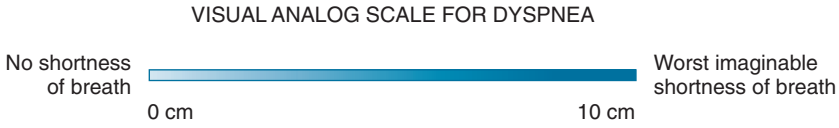

FIGURE 28-2 ■ Visual analogue scales, such as the horizontal one shown here, can be used for measuring dyspnea during an activity (e.g., exercise testing) or in response to questions. Such scales may be depicted vertically as well. On request, the subject marks a point on the line in response to a question (e.g., How short of breath are you right now?). The score is determined by the length of the line from "no shortness of breath" to the point marked by the patient. The scales are usually 10 cm long to facilitate scoring, and electronic scales may be used to allow online scoring (e.g., during exercise testing). Instructions about what is meant by the terms used to describe a sensation (e.g., "extremely breathless") must be clear and must be presented in a uniform fashion to provide meaningful result.

the disease.[56] Dyspnea is evaluated on a seven-point scale in relation to the five most important activities provoking dyspnea during the previous 2 weeks. The SGRQ is a self-administered questionnaire with 76 items addressing symptoms, activity, and the impact of disease on daily life. Dyspnea is not evaluated specifically but is included with other respiratory symptoms such as cough, sputum, and wheezing.[57] These instruments have been shown to be reasonably reproducible, to correlate with each other, and to relate appropriately to physiologic measurements.[58–60] Although important for clinical investigation, these tools are somewhat demanding to use, often requiring trained health personnel, and are of unproven value for routine clinical care.

Psychometric Measurement of Dyspnea

Several instruments are available for rating the symptom dyspnea directly; they allow reasonably reproducible rating of the intensity of dyspnea on a simple linear or numeric scale during exercise or in response to specific questions. The visual analogue scale (VAS) is a horizontal or vertical line, usually 10 cm long, anchored at either end with words such as "no dyspnea" and "maximal dyspnea" (Fig. 28-2). In response to a question (e.g., "How short of breath are you?"), the subject marks a point along the line so the length reflects the intensity of the sensation. The Borg Scale is a 10-point scale with extremes of "nothing at all" and "maximal."[61] Unlike the VAS, the Borg Scale (Table 28-1) includes verbal descriptors (e.g., "slight," "severe") to assist in rating the symptom. Both scales demonstrate good reproducibility,[62,63] but the proximity of the terms "slight" and "severe" on the Borg scale may reduce its sensitivity and discourage subjects from using the whole scale as they do with the VAS.[64] A valid approach, which has perhaps better clinical utility, has been to employ a simple numeric rating scale ranging from 0 to 10.[65] Additional scales continue to be developed.[55] Any of these validated instruments may be appropriate when designing research studies, but it is critical that they be administered in a standardized way. Recently, researchers have begun to extend dyspnea assessment beyond the intensity domain to explore the qualitative and affective components using a multidimensional dyspnea profile instrument,[15] modeled on an approach widely used in pain research.

TABLE 28-1. Modified Borg Category Scale for Rating Dyspnea

Rating	Intensity of Sensation
0	Nothing at all
0.5	Very, very slight (just noticeable)
1	Very slight
2	Slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximal

DIAGNOSTIC APPROACH TO THE PATIENT WITH DYSPNEA

Overview: Physiologic Categories of Dyspnea

The differential diagnosis of dyspnea includes neuromuscular, renal, endocrine, rheumatologic, hematologic, and psychiatric diseases, as well as diseases of the lungs, heart, and chest wall. The diagnostic approach is determined by the acuity of the problem. For acute dyspnea, the differential diagnosis is relatively narrow and the cause is generally easily identified (e.g., pneumonia, pulmonary embolism, congestive heart failure, asthma), although psychogenic dyspnea or hyperventilation syndrome can pose a diagnostic challenge.[66] For subacute or chronic dyspnea, a systematic, physiologically based approach enables one to make sense of what otherwise becomes a long list of potential diagnoses.

At its core, the goal of the respiratory and cardiovascular systems is to take oxygen from the air we breathe, transfer it to hemoglobin, deliver it to metabolically active tissue, and transport carbon dioxide, the primary product of metabolism, back to the lung, where it can be eliminated. Dyspnea arises when this goal has not been met (and the patient becomes hypoxemic,

hypercapnic, and/or acidemic with consequent stimulation of the chemoreceptors), when achieving this goal produces stress within the cardiorespiratory system (e.g., increased work of breathing or elevated left ventricular and pulmonary capillary pressures, secondary to pathologic abnormalities), or because of direct stimulation of pulmonary receptors (e.g., irritant receptors, again resulting from a pathologic process). Ultimately, dyspnea can be conceived as originating from the respiratory or cardiovascular systems, including derangements in oxygen delivery, such as in anemia, and problems with uptake and utilization of oxygen, such as in mitochondrial disorders.

To facilitate a systematic approach to this problem, one can divide the process of respiration into three components:

1. A controller, which determines the rate and depth of breathing;
2. A ventilatory pump, which facilitates the movement of gas into and out of the alveolus; and
3. A gas exchanger, which consists of the pulmonary vasculature and the alveolus (Table 28-2).

Abnormalities in any one of these elements can lead to dyspnea. Similarly, one can consider the derangements of the cardiovascular system within three categories: conditions characterized by high cardiac output, normal cardiac output, and low cardiac output.

Diseases that mechanically interfere with ventilation (i.e., derangements of the ventilatory pump) increase the effort of breathing, whether because of narrowing of the airway or because of a change in the elastic properties of the lungs or chest wall. If the respiratory muscles are weakened, the effort of breathing seems greater because a larger fraction of maximal available muscle force is required. (This is analogous to peripheral muscle function, in which, for example, it would be more difficult to lift a weight after an arm has just been liberated from being in a cast.) Any stimulus of ventilation (e.g., exercise, hypoxia, acidosis, interstitial edema, pulmonary hypertension), which can be considered abnormalities of the controller, may provoke the sensation of dyspnea. Psychological dysfunction may cause or exaggerate dyspnea and is thought to be an alteration in behavioral control of breathing.[67] In many conditions, the origin of dyspnea is only partially understood (e.g., pulmonary embolism without hypoxemia) or is due to multiple factors (e.g., abnormalities of the ventilatory pump and gas exchanger in a patient with COPD).

History

A comprehensive medical history is important for a diagnosis of dyspnea.[68] It is important to identify

TABLE 28-2. Diseases that Cause Dyspnea Grouped by Physiological Mechanism of Action*

VENTILATORY CONTROLLER AND GAS EXCHANGER—INCREASED RESPIRATORY DRIVE
Simulation of Chemoreceptors
Conditions leading to acute hypoxemia
Impaired gas exchanger (e.g., asthma, pulmonary embolism, pneumonia, congestive heart failure†)
Environmental hypoxia (e.g., altitude, contained space with fire)
Conditions leading to increased dead space and/or acute hypercapnia
Impaired gas exchanger (e.g., acute, severe asthma, exacerbations of COPD, severe pulmonary edema)
Impaired ventilatory pump (see below) (e.g., muscle weakness, airflow obstruction)
Metabolic Acidosis
Renal disease (renal failure, renal tubular acidosis)
Decreased oxygen carrying capacity (e.g., anemia)
Decreased release of oxygen to tissues (e.g., hemoglobinopathy)
Decreased cardiac output
Stimulation of Pulmonary Receptors (Irritant, Mechanical, Vascular)‡
Interstitial lung disease
Pleural effusion (compressive atelectasis)
Pulmonary vascular disease (e.g., thromboembolism, idiopathic pulmonary hypertension)
Congestive heart failure
Mild asthma
Behavioral Factors
Hyperventilation syndrome, anxiety disorders, panic attacks
VENTILATORY PUMP—INCREASED EFFORT OR WORK OF BREATHING
Muscle Weakness
Myesthenia gravis, Guillain-Barré, spinal cord injury, myopathy, postpoliomyelitis syndrome
Decreased Compliance of the Chest Wall
Severe kyphoscoliosis, obesity, pleural effusion
Airflow Obstruction (Includes Increased Resistive Load from Narrowing of Airways and Increased Elastic Load from Hyperinflation)
Asthma, COPD, laryngospasm, aspiration of foreign body, bronchitis

*Some diseases appear in more than one category. They act via several physiologic mechanisms.
†Heart failure includes both systolic and diastolic dysfunction. Systolic dysfunction may produce dyspnea at rest and with activity. Diastolic dysfunction typically leads to symptoms primarily with exercise. In addition to the mechanisms noted above, systolic heart failure may also produce dyspnea via metaboreceptors; these are receptors that are postulated to lie in muscles and are stimulated by changes in the metabolic milieu of the tissue that result when oxygen delivery does not meet oxygen demand.
‡These conditions probably produce dyspnea by a combination of increased ventilatory drive and primary sensory input from the receptors.
COPD, chronic obstructive pulmonary disease.

activities that precipitate it and to understand its impact on the patient's life. Because decreased exercise tolerance may go unrecognized by the patient owing to alterations in lifestyle (e.g., a patient who develops dyspnea climbing stairs may move from a two-story house to a single-level apartment) that do not tax the respiratory and cardiovascular systems, input from close acquaintances may be helpful. Although most patients with severe lung disease report that their activities are limited by dyspnea, some patients are actually more limited by fatigue, weakness, joint pain, or chest pain than by dyspnea.

The key areas of inquiry are (1) quality of the symptom, (2) persistence or variability of the symptom, (3) aggravating or precipitating symptom. As noted previously (in the section on "Mechanisms of Dyspnea"), the sensation of "chest tightness" is commonly associated with bronchoconstriction, an increased sense of "effort or work of breathing" is typical of derangements of the ventilatory pump, and a sense of "air hunger" or "urge to breathe" is characteristic of problems that stimulate the respiratory controller. The sense of difficulty getting a deep breath may be associated with hyperinflation due to obstructive lung disease or with the hyperventilation syndrome.

Intermittent dyspnea is probably due to reversible conditions (e.g., bronchoconstriction, congestive heart failure, pleural effusion, acute pulmonary emboli, hyperventilation syndrome), whereas persistent or progressive dyspnea is more characteristic of chronic conditions (e.g., COPD, interstitial fibrosis, chronic pulmonary emboli, dysfunction of the diaphragm or chest wall). Nocturnal dyspnea may be brought on by asthma, congestive heart failure, gastroesophageal reflux,[69] obstructive sleep apnea, or even nasal obstruction. Dyspnea in the recumbent position is classically associated with left ventricular failure but may also occur with abdominal processes (e.g., ascites) or diaphragmatic dysfunction. Dyspnea that worsens in the upright position (i.e., platypnea) may be related to orthodeoxia, a decrease in arterial oxygen pressure (P_{O_2}) in the upright position, which occurs with cirrhosis, pulmonary arteriovenous malformations, or interatrial shunts.[70–73] Physical activity generally accentuates dyspnea of physiologic origin, as when ventilation is stimulated by lactic acid production at relatively low levels of exercise (e.g., anemia, cardiac disease, deconditioning). Dyspnea after exercise may be affected by a number of factors (e.g., activity, time of day, position, exposures, meals, medications). To the extent that post-exercise dyspnea may be mitigated by warm-up activities or use of inhaled bronchodilators, exercise-induced asthma should be considered. Although emotional states may affect dyspnea of any cause,[66] psychogenic dyspnea should be suspected when dyspnea varies on a daily or hourly basis, especially when it is unrelated to exertion or if litigation is involved.[67]

Recognition of factors that may precipitate (e.g., cigarettes, allergens, smog) or relieve (e.g., position, medications) breathlessness is helpful. Obesity may aggravate dyspnea because of increased metabolic and ventilatory demands as well as mechanical interference with chest movement.[74] Severe weight loss may weaken the respiratory muscles.[75] Symptoms of right ventricular failure (e.g., abdominal swelling, edema of the extremities) suggest hypoxemia, pulmonary vascular problems (e.g., pulmonary hypertension of any cause, obstructive sleep apnea), or left ventricular failure. Neuromuscular diseases, such as amyotrophic lateral sclerosis (ALS), may present with dyspnea as a result of respiratory muscle weakness.[76] Raynaud's phenomenon alone or in combination with skin, joint, or swallowing problems suggests collagen vascular disease.

Physical Examination

Pattern of breathing (e.g., splinting, use of pursed lips or accessory muscles), body habitus (e.g., cachexia, obesity), posture (e.g., leaning forward on elbows to recruit pectoralis muscles as ventilatory muscles, as in COPD), skeletal deformity, and emotional state may be important clues to the diagnosis. Cough on deep inspiration or expiration suggests asthma or interstitial lung disease. A generalized decrease in the intensity of breath sounds suggests emphysema or moderate to severe bronchoconstriction, whereas a localized decrease may occur in pneumothorax, pleural effusion, localized airway obstruction, or elevated hemidiaphragm of any cause. Forced expiratory maneuvers may elicit focal or diffuse wheezing. Cardiac examination may suggest pulmonary hypertension (e.g., right ventricular heave or prominent P_2) or right ventricular failure (e.g., jugular venous distention, right-sided S_3 gallop). Clubbing of the digits is an easily overlooked sign of many processes, notably cancer or purulent lung disease (e.g., bronchiectasis). Cyanosis, a bluish coloration of the perioral region or nails, indicates there are 5 gm of deoxygenated hemoglobin/100 mL of blood (note: hypoxemia in the presence of significant anemia may not cause cyanosis because of insufficient hemoglobin). Edema of the lower extremities suggests congestive heart failure if symmetrical and thromboembolic disease if asymmetrical. Assessment of the patient's emotional status may be helpful.[66]

If a patient's history includes a report that he or she develops dyspnea walking a short distance (e.g., ≤200 yards), one should consider walking the patient in a corridor near the examination room to elicit his or her symptoms. When dyspnea occurs, observe the patient, repeat the vital signs, reexamine the chest and heart, and check the oxygen saturation with pulse oximetry. The development of an abrupt increase pulse-pressure product, basilar crackles, or acute wheezing suggests a rapid increase in pulmonary capillary pressure and interstitial edema. Rapid shallow breathing may be a sign of stiff lungs or chest wall. Occasionally, the patient will walk farther than one would expect from the history; motivation and the inability of the patient to tolerate any respiratory discomfort may, in fact, be the cause of the patient's limitation. It is not uncommon for patients who lead extremely sedentary lives, especially if they have been told they have a condition that may cause shortness of breath, to equate any increase in ventilation as pathologic.

Laboratory Assessment

The laboratory is only occasionally of help in the diagnosis of dyspnea. Anemia of any cause may contribute to dyspnea. Polycythemia may be the only clue to chronic hypoxemia. Elevation of the erythrocyte sedimentation rate may suggest occult infection or autoimmune disease. A chemistry panel may reveal occult renal disease or acid-base derangement. More elaborate screening may uncover collagen vascular or thyroid disease. A new laboratory test, measurement of B-type natriuretic peptide (BNP), is finding wide acceptance in the differential diagnosis of acute dyspnea,[77,78] primarily in the emergency department setting.[79] The ventricle secretes BNP in response to elevated pressure. Therefore, it is usually elevated in patients with left ventricular failure or cor pulmonale but not in patients with exacerbations of obstructive lung disease. It has been shown to be more accurate than echocardiography in recognizing left ventricular dysfunction as a cause of acute dyspnea.[80]

The database should include chest radiography, spirometry, and possibly electrocardiography. Chest roentgenograms are useful when abnormal but are insensitive for detecting early obstructive and interstitial diseases; approximately 10% of patients with interstitial disease will have a normal chest radiograph. Computed tomography (CT) angiogram has become the standard modality for assessment of suspected thromboemoblic disease. Although it is not recommended as a general screening test, it can be used to assess for both occult interstitial lung disease and thromboemoblic disease in patients with evidence of gas-exchange abnormalities, for example, low diffusing capacity and/or hypoxemia at rest or with exercise (desaturation on exercise oximetry), or pulmonary hypertension on echocardiography.

Spirometry is a useful screening test for both airway and parenchymal disease. Because airway obstruction in asthma may be intermittent, monitoring of peak flow at home or in the workplace may be productive. The yield of routine electrocardiography is low, although it may reveal previously unsuspected coronary artery disease, occult valvular disease, or diastolic dysfunction, and can suggest pulmonary hypertension (i.e., if signs of right ventricular hypertrophy or tricuspid regurgitation are present).

Special Studies (Including Pulmonary Function Tests)

An array of special studies may be required for diagnosis of dyspnea (Table 28-3).[1] Pulmonary function tests are useful but correlate only moderately with the severity of the dyspnea.[81] In the patient with episodic dyspnea, but normal spirometry, methacholine inhalation testing can aid in the diagnosis of asthma. Patients with dyspnea characterized as "chest tightness" are most likely to have a positive study.[82]

Pulse oximetry may reveal previously unrecognized hypoxemia, a possible clue to many diseases; because the lungs have significant reserve capacity for diffusion at rest, exercise oximetry may be necessary to elicit hypoxemia in patients with abnormalities of the gas exchanger. Oximetry should always be assessed in patients with a low diffusing capacity, which may be seen in individuals with emphysema, pulmonary vascular disease, and interstitial lung disease. Orthodeoxia (i.e., hypoxemia worse in the upright position) leads to a search for one of the many causes of this unusual condition.[72,73,83]

If ventilatory muscle weakness is suggested by the patient's history, physical examination, or measurement of lung volumes, ventilatory muscle strength should be assessed. Maximal inspiratory and expiratory pressures can be measured easily and followed sequentially over time.

Cardiopulmonary exercise testing (CPET) helps determine whether exercise is limited by the pulmonary, cardiovascular, or musculoskeletal system.[52] To the extent that patients with lung disease are frequently at risk for or have concurrent cardiac problems due to cigarette smoking, CPET can be very useful. Unfortunately, exercise testing is insensitive for distinguishing cardiac disease from deconditioning.[84] Therefore, additional cardiac evaluation may be required. Spiral CT scanning of the chest with iodinated contrast has replaced ventilation-perfusion lung scanning as the screening procedure of choice for the diagnosis of pulmonary embolic disease.[85–90] One should remember that patients

TABLE 28-3. Special Studies for Evaluation of Dyspnea

PULMONARY FUNCTION STUDIES
Lung volumes and flow rates
D_{LCO}
Arterial blood gases
Cardiopulmonary exercise testing
Bronchial challenge
Maximal inspiratory pressure
IMAGING TECHNIQUES
Ventilation-perfusion lung scanning
Chest CT scanning (high-resolution or contrast)
Gallium scanning
Diaphragmatic fluoroscopy
CARDIAC EVALUATION
Echocardiographic or radionuclide ventriculography
Thallium scan
Holter monitoring (occult ischemia or arrhythmia)
Cardiac catheterization (preferably with exercise)
ESOPHAGEAL EXAMINATION OR pH MONITORING
OTOLARYNGOLOGIC ASSESSMENT
SLEEP STUDIES
PSYCHOLOGICAL ASSESSMENT

CT, computed tomography; D_{LCO}, diffusing capacity for carbon dioxide.

with chronic thromboemoblic disease often present with gradually worsening dyspnea in the absence of episodic breathlessness characteristic of acute pulmonary embolism.

If exercise testing suggests cardiac dysfunction, echocardiography, radionuclide scanning, measurement of BNP, or even cardiac catheterization (preferably combined with supine exercise) may identify unsuspected ventricular dysfunction, valvular disease, or pulmonary hypertension.[80,91] Diastolic dysfunction, characterized by normal ventricular pressures at rest but marked elevations during exercise, is a common cause of heart failure but is frequently missed as the etiology of exertional dyspnea. In a patient with a history of hypertension and/or left ventricular hypertrophy, this diagnosis should be considered, even in the presence of normal systolic function on an echocardiogram. A stage III CPET (with pulmonary artery catheter in place) might be necessary to confirm the role of diastolic dysfunction in the patient's symptoms.

Gallium and high-resolution CT scanning are sensitive but not specific for occult infectious and inflammatory lung disease.[90]

It is clear that a cascade of special studies might be necessary before reaching a specific diagnosis. If extensive testing is unrevealing, psychiatric evaluation may be valuable, especially if there is a strong psychological component. However, it is more likely that the patient has an early stage of an as-yet-undiagnosed condition that serial testing may reveal.

TABLE 28-4. Symptomatic Treatment of Dyspnea

REDUCE SENSE OF EFFORT AND IMPROVE RESPIRATORY MUSCLE FUNCTION
Energy conservation (e.g., pacing)
Breathing strategies (e.g., pursed-lip breathing)
Position (e.g., leaning forward)
Correct obesity or malnutrition
Inspiratory muscle exercise
Respiratory muscle rest (e.g., cuirass, nasal ventilation, transtracheal oxygen)
Medications (e.g., theophylline)
DECREASE RESPIRATORY DRIVE
Oxygen
Opiates and sedatives
Exercise conditioning
Vagal nerve section (not done)
Carotid body resection (not done)
ALTER CENTRAL NERVOUS SYSTEM FUNCTION
Education
Psychological interventions (e.g., coping strategies, psychotherapy, group support)
Opiates and sedatives
USE EXERCISE TRAINING ALONE OR WITH PULMONARY REHABILITATION
Enhance self-esteem and self-confidence in ability to perform
Improve efficiency of movement
Desensitization to dyspnea (e.g., from repeated exercise)

SYMPTOMATIC TREATMENT OF DYSPNEA

Dyspnea can be most effectively alleviated by treatment of the underlying disease and its complications. The focus should be on alleviating symptoms as well as improving pulmonary function.[92] Lung volume reduction surgery for relief of dyspnea in advanced emphysema deserves special mention. Removal of multiple bullous or emphysematous portions of the lungs reduces hyperinflation and improves lung recoil, potentially leading to dramatic improvement in pulmonary function and dyspnea for some individulas.[93] As experience with this approach continues to develop, it is likely that increasing numbers of patients will gain substantial benefit as optimal selection criteria are refined.

When dyspnea persists despite optimal treatment of the underlying disease, treatment should focus on the symptom rather than the disease and particularly on the specific mechanisms contributing to an individual's dyspnea (e.g., respiratory muscle dysfunction, hypoxemia, anxiety).[1] Until guidelines for specific therapy are established, one must take a generic approach to treatment, with a focus on improving respiratory muscle function, thereby decreasing the sense of effort, decreasing the drive to breathe, altering the central experience, and instituting exercise training (Table 28-4 and Fig. 28-3).

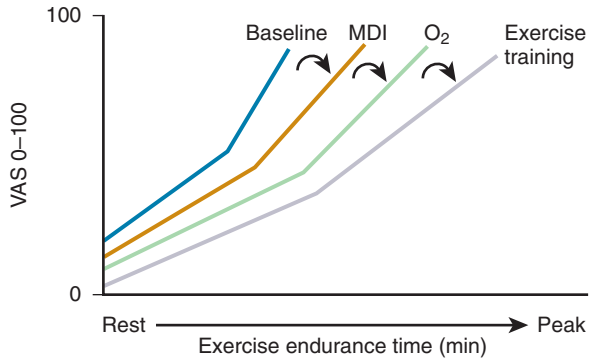

FIGURE 28-3 ■ The cumulative effects of treatment on exercise endurance time at a set workload and dyspnea measured by a visual analogue scale (VAS) are depicted here. The endurance time gradually improves with cumulative treatment using a bronchodilator by metered-dose inhaler (MDI), oxygen (O_2), and exercise training. Dyspnea relative to the workload is gradually relieved both at rest and relative to time on the treadmill, even though maximum dyspnea remains about the same. Improvement on exercise testing should translate into improvement with activities of daily living so the patient should experience less dyspnea with activities of daily living.

Reducing Respiratory Effort and Improving Respiratory Muscle Function

Energy conservation techniques reduce physical effort (e.g., walking more slowly) so less ventilatory effort is necessary. Breathing techniques (e.g., pursed lips) may reduce respiratory discomfort by slowing breathing, reducing hyperinflation, and improving oxygen saturation.[94] If ventilation limits exercise, strengthening the respiratory muscles should improve maximal ventilation and exercise performance, thereby alleviating the dyspnea. Unfortunately, the results of this approach have been inconsistent,[95,96] although one meta-analysis concluded that it can be of value especially in patients with documented respiratory muscle weakness.[97]

Nutritional repletion of cachectic patients can improve respiratory muscle strength and decrease dyspnea, although the clinical effectiveness of this therapy is unclear.[95,98] It is intuitively appealing to "rest" chronically "fatigued" respiratory muscles with mechanically assisted ventilation (positive or negative pressure) so they perform better with less dyspnea, and although not all studies have shown much benefit,[99] there is increasing evidence in support of this management strategy in patients with exacerbations[100] or respiratory failure.[101] In less acute circumstances, a meta-analysis concluded that acute noninvasive ventilatory support during exercise does relieve dyspnea and improves exercise performance in COPD.[34] Studies of medications to relieve dyspnea by increasing muscle contractility have been unconvincing.[102]

Decreasing the Respiratory Drive

Because dyspnea is so closely related to the respiratory drive, treatments that reduce the drive should reduce dyspnea. Supplemental oxygen can reduce carotid body activation and decrease dyspnea by decreasing ventilation and reducing hyperinflation during exercise.[103] Other benefits of oxygen that may decrease dyspnea include improved ventilatory muscle function,[104] stimulation of left ventricular contractility and reduced pulmonary artery pressure.[105] The amount of oxygen should be titrated to prevent desaturation below 90%, although even higher amounts may be advantageous for preventing dyspnea and improving exercise performance. Indeed, oxygen supplementation can improve exercise capacity in individuals without exercise hypoxaemia.[106] Oxygen supplementation is recommended for use during pulmonary rehabilitation programs.[96]

Treatments aimed at peripheral receptors or reflex pathways have shown some positive results. In healthy subjects, topical anesthesia of airway receptors[107] or buccal mucosa[108] reduced experimentally induced breathlessness. Inhalation of furosemide, proposed to potentiate activity of SARs, has been shown to reduce dyspnea in some individuals with COPD.[32,33] In studies in COPD patients, a fan blowing air on the face has been shown to decrease dyspnea[109] and chest wall vibration[110] has been shown to reduce exertional dyspnea, raising hope for treatments directed at peripheral receptors. More drastic surgical approaches, including vagal nerve section and carotid body resection, have always been controversial and are not currently available.

Altering Central Perception

The experience of dyspnea is affected by many factors, including education, cultural background, knowledge, emotional state, bodily preoccupation, and prior experience. Some recent studies of dyspnea relief emphasize the importance of central processes in decreasing dyspnea.[111] Altering the central experience of dyspnea may be helpful even when physiologic approaches are inadequate.[1] Education, including specific coping strategies (e.g., muscle relaxation[112]), helps patients understand their disease and develop feelings of mastery over it.[113] Sharing experiences with others or psychotherapy may reduce the intensity of the dyspnea and the distress associated with it.[114,115] These educational and psychosocial strategies for symptom management have been comprehensively reviewed and their use, in conjunction with exercise training, is recommended.[96]

Most discussions of centrally acting drugs for dyspnea focus on opiates. Opiates do have pharmacologic effects that should reduce the severity of the dyspnea (including reduction in ventilation), and it is likely that opiates would affect an individual's experience of dyspnea as they do pain.[116] However, fear of side effects, especially respiratory depression, has discouraged their use in patients with COPD.[117–120] Nonetheless, laboratory studies in COPD patients has produced modest improvement in exercise performance and dyspnea scores and only slight and infrequent side effects (e.g., drowsiness) with benefits that have been related both to decreases in ventilatory requirements for a given workload and to reductions in the perception of breathlessness at each level of ventilation.[116,121] Conversely, placebo-controlled outpatient studies have shown inconsistent benefits and frequent side effects.[117,119,122,123] For example, in a 14-week controlled crossover study of 16 patients with severe stable COPD,[122] long-acting morphine produced no relief of the dyspnea as measured by the CRQ or during walking. Moreover, there was a deterioration in the CRQ Mastery subscale and in the 6-minute walk distance. Almost all of the subjects experienced significant, although not life-threatening, side effects, although the authors emphasized that one subject had a "spectacular" response and continued treatment. Thus, opiates may be appropriate for dyspnea in an occasional carefully selected patient with far-advanced disease.[124]

Opiates are less controversial for palliation of dyspnea in terminal malignant disease or chronic respiratory failure. In this setting, the importance of relieving suffering despite the risk of shortening life is more widely accepted. Recent systematic reviews clearly demonstrate the efficacy of this approach in the palliation of refractory dyspnea.[125,126]

Based on the concept of opiate receptors in the airways, inhalation of opiates has been examined as a

way of relieving dyspnea without the side effects seen with systemic administration. Despite earlier reports of that inhaled opiates increased submaximal exercise endurance time in patients with severe COPD[127] and reduced dyspnea in patients with terminal lung disease and heart failure,[128] recent systematic reviews based on controlled trials have failed to demonstrate any real benefit of administering opiates by this route.[125,126]

Centrally acting pharmacologic agents have a limited role in the treatment of dyspnea, although controlled studies of unselected COPD patients have shown no benefit of anxiolytics on dyspnea.[117,129] Similarly, there is little experimental evidence to support the use of antidepressants in the management of dyspnea, although positive results have been reported in case studies.[130,131] Despite a lack of evidence, there is widespread recognition that there are clear clinical associations between dyspnea, anxiety, and depression, and a view that individual patients with chronic dyspnea can benefit by targeting psychomorbidity with appropriate therapies.[132,133]

Role of Exercise Training in Relieving Dyspnea

There is now convincing evidence that pulmonary rehabilitation programs, along with improving exercise capacity and health-related quality of life, improve the symptom of dyspnea in patients with COPD.[96] Exercise training appears to be a critical part of pulmonary rehabilitation programs for reduction of dyspnea and, although one randomized, controlled study reported a better outcome with high-intensity compared with moderate-intensity training,[134] further studies are needed to clarify the impact of training intensity on dyspnea outcomes. Although most studies have employed endurance training using treadmills or cycles in supervised clinical environments, there is accumulating evidence that pulmonary rehabilitation programs can yield dyspnea-related benefits with (1) interval training,[135] (2) strength training,[136] and (3) home-based exercise training.[137] It is not certain how important the educational component of pulmonary rehabilitation is in relieving dyspnea. A program of dyspnea management (including relaxation, breathing retraining, pacing, self-talk, and panic control) without an exercise component was compared with general health education; neither measure alleviated the dyspnea or improved the 6-minute walking distance.[138] By contrast, it has been shown that treadmill training with or without nurse coaching is equally effective in reducing dyspnea during exercise testing and activities of daily living.[139] Despite uncertainty about the impact of education per se on dyspnea outcomes, current recommendations strongly endorse the inclusion of an educational component as part of a pulmonary rehabilitation program.[96]

Exercise training may relieve dyspnea by many mechanisms. Neither pulmonary mechanics nor respiratory muscle strength is usually affected.[96,140] True conditioning with decreased lactate production and resulting decreased stimulation of ventilation may occur even in patients with severe disease.[141] Relaxation and increased mechanical efficiency (e.g., longer stride length[142]) may lower oxygen consumption and ventilation for a given activity.[143] Exercise training may improve self-confidence, thereby reducing anxiety and dyspnea.[144,145] Repeated exercise may result in desensitization to the symptom (i.e., the same ventilatory stimulus results in less dyspnea[43,139,146,147]). In any one patient, it is difficult to know which of these mechanisms is operant, but for clinical purposes, it may not matter.

Relief of Dyspnea in End-Stage Lung Disease

Dyspnea is one of the most devastating symptoms known to human beings. In no area of medicine is relief more important than when dealing with dyspnea in end-stage lung disease. The severity of this symptom is well recognized in terminal malignancy, interfering with both physical and psychological function.[148] More than half of patients dying of cancer described their dyspnea as moderate or worse.[148] This awareness is lacking in other areas of terminal lung disease, where most information is anecdotal.[149] One exception is the treatment of the terminal phase of ALS. The value of opiates and anxiolytics for relief of symptoms (especially dyspnea) in the last 24 hours of life of patients with ALS has been documented by postmortem telephone interviews with family members in both the United Kingdom and Germany.[150]

Although patients with chronic lung disease are normally encouraged to exercise to maintain their state of fitness, there comes a time when a different approach is required and the focus shifts from prolongation of life to relief of distress.[149] When dyspnea with exertion is extreme, it may be more appropriate to restrict activity and to focus on modifying treatments such as oxygen, opiates, and anxiolytics. Palliative treatment may include partial ventilatory support or, under rare circumstances, a tracheostomy with mechanical ventilation. Such dramatic steps to relieve dyspnea must be taken with full understanding of the ramifications and complications. Some patients might choose a morphine drip to allow a comfortable death, whereas others might choose an aggressive approach focused on prolongation of life as well as relief of discomfort. It is up to the health care provider to help the individual patient understand these choices.

KEY POINTS

- Dyspnea is a complex symptom arising from the central processing of information relayed from the respiratory complex, with modifying information from numerous afferent sources.
- The information is integrated within the psychological and intellectual makeup of the individual. It is still unclear whether there is a final common pathway for the sensation.
- Dyspnea may be due to diseases in virtually any organ system, whether caused by interference with breathing, increased demand for breathing, or weakening of the respiratory pump. In most cases, however, one is dealing with a disorder of the respiratory or cardiovascular system.
- Diagnosis of dyspnea requires a comprehensive database. Cardiopulmonary exercise testing may be particularly useful when a patient has concomitant cardiopulmonary diseases or when cardiovascular deconditioning is suspected.
- When the cause is not obvious, a series of studies analyzing cardiopulmonary function at rest and with exercise usually uncovers a specific diagnosis. Sophisticated studies of the heart, pulmonary vascular bed, lung parenchyma, and even esophagus may be necessary.
- Treatment of dyspnea is most effective when it is based on a specific diagnosis. When treatment of the underlying disease is inadequate, treatment should focus on the symptom.
- A combination of education, exercise training, oxygen, and muscle strengthening aids most patients; but in far-advanced disease, compassion may require the use of agents that directly blunt the sensation even though they may shorten life.

References

1. American Thoracic Society: Dyspnea. Mechanisms, assessment, and management: A consensus statement. Am J Respir Crit Care Med 159:321–340, 1999.
2. O'Donnell DE, Banzett RB, Carrieri-Kohlman V, et al: Pathophysiology of dyspnea in chronic obstructive pulmonary disease: A roundtable. Proc Am Thorac Soc 4:145–168, 2007.
3. Celli BR, Cote CG, Lareau SC, Meek PM: Predictors of survival in COPD: More than just the FEV_1. Respir Med 102(Suppl 1):S27–S35, 2008.
4. Oxberry SG, Johnson MJ: Review of the evidence for the management of dyspnoea in people with chronic heart failure. Curr Opin Support Palliat Care 2:84–88, 2008.
5. Dy SM, Lorenz KA, Naeim A, et al: Evidence-based recommendations for cancer fatigue, anorexia, depression, and dyspnea. J Clin Oncol 26:3886–3895, 2008.
6. Abramson M, Matheson M, Wharton C, et al: Prevalence of respiratory symptoms related to chronic obstructive pulmonary disease and asthma among middle-aged and older adults. Respirology 7:325–331, 2002.
7. Halbert RJ, Natoli JL, Gano A, et al: Global burden of COPD: Systematic review and meta-analysis. Eur Respir J 28:523–532, 2006.
8. Desbiens NA, Mueller-Rizner N, Connors AF, Wenger NS: The relationship of nausea and dyspnea to pain in seriously ill patients. Pain 71:149–156, 1997.
9. Ho SF, O'Mahony MS, Steward JA, et al: Dyspnoea and quality of life in older people at home. Age Ageing 30:155–159, 2001.
10. Esteban C, Quintana JM, Aburto M, et al: Predictors of mortality in patients with stable COPD. J Gen Intern Med 23:1829–1834, 2008.
11. Ekman I, Cleland JG, Swedberg K, et al: Symptoms in patients with heart failure are prognostic predictors: Insights from comet. J Card Fail 11:288–292, 2005.
12. Caress AL, Luker KA, Chalmers KI, Salmon MP: A review of the information and support needs of family carers of patients with chronic obstructive pulmonary disease. J Clin Nurs 18:479–491, 2009.
13. O'Donnell DE, Ora J, Webb KA, et al: Mechanisms of activity-related dyspnea in pulmonary diseases. Respir Physiol Neurobiol 167:116–132, 2009.
14. Hardie GE, Janson S, Gold WM, et al: Ethnic differences: Word descriptors used by African-American and white asthma patients during induced bronchoconstriction. Chest 117:935–943, 2000.
15. Banzett RB, Pedersen SH, Schwartzstein RM, Lansing RW: The affective dimension of laboratory dyspnea: Air hunger is more unpleasant than work/effort. Am J Respir Crit Care Med 177:1384–1390, 2008.
16. Lansing RW, Im BS, Thwing JI, et al: The perception of respiratory work and effort can be independent of the perception of air hunger. Am J Respir Crit Care Med 162:1690–1696, 2000.
17. Phankingthongkum S, Daengsuwan T, Visitsunthorn N, et al: How do Thai children and adolescents describe asthma symptoms? Pediatr Allergy Immunol 13:119–124, 2002.
18. Casey KL: Forebrain mechanisms of nociception and pain: Analysis through imaging. Proc Natl Acad Sci U S A 96:7668–7674, 1999.
19. Denton D, Shade R, Zamarippa F, et al: Neuroimaging of genesis and satiation of thirst and an interoceptor-driven theory of origins of primary consciousness. Proc Natl Acad Sci U S A 96:5304–5309, 1999.
20. Del Parigi A, Gautier JF, Chen K, et al: Neuroimaging and obesity: Mapping the brain responses to hunger and satiation in humans using positron emission tomography. Ann N Y Acad Sci 967:389–397, 2002.
21. Isaev G, Murphy K, Guz A, Adams L: Areas of the brain concerned with ventilatory load compensation in awake man. J Physiol 539:935–945, 2002.
22. Fink GR, Corfield DR, Murphy K, et al: Human cerebral activity with increasing inspiratory force: A study using positron emission tomography. J Appl Physiol 81:1295–1305, 1996.
23. von Leupoldt A, Dahme B: Cortical substrates for the perception of dyspnea. Chest 128:345–354, 2005.
24. Adams L, Lane R, Shea SA, et al: Breathlessness during different forms of ventilatory stimulation: A study of mechanisms in normal subjects and respiratory patients. Clin Sci (Lond) 69:663–672, 1985.
25. Lane R, Adams L: Metabolic acidosis and breathlessness during exercise and hypercapnia in man. J Physiol 461:47–61, 1993.
26. Freedman S, Lane R, Guz A: Breathlessness and respiratory mechanics during reflex or voluntary hyperventilation in patients

with chronic airflow limitation. Clin Sci (Lond) 73:311–318, 1987.
27. Banzett RB, Lansing RW, Brown R, et al: "Air hunger" from increased P_{CO_2} persists after complete neuromuscular block in humans. Respir Physiol 81:1–17, 1990.
28. Undem BJ, Nassenstein C: Airway nerves and dyspnea associated with inflammatory airway disease. Respir Physiol Neurobiol 167:36–44, 2009.
29. Flume PA, Eldridge FL, Edwards LJ, Houser LM: The Fowler breathholding study revisited: Continuous rating of respiratory sensation. Respir Physiol 95:53–66, 1994.
30. Nishino T: Aggravation of dyspnoea by coughing: Vagal mechanisms. Pulm Pharmacol Ther 22:102–107, 2009.
31. Banzett RB, Lansing RW, Reid MB, et al: "Air hunger" arising from increased P_{CO_2} in mechanically ventilated quadriplegics. Respir Physiol 76:53–67, 1989.
32. Moosavi SH, Binks AP, Lansing RW, et al: Effect of inhaled furosemide on air hunger induced in healthy humans. Respir Physiol Neurobiol 156:1–8, 2007.
33. Jensen D, Amjadi K, Harris-McAllister V, et al: Mechanisms of dyspnoea relief and improved exercise endurance after furosemide inhalation in COPD. Thorax 63:606–613, 2008.
34. van't Hul A, Kwakkel G, Gosselink R: The acute effects of noninvasive ventilatory support during exercise on exercise endurance and dyspnea in patients with chronic obstructive pulmonary disease: A systematic review. J Cardiopulm Rehabil 22:290–297, 2002.
35. Duguet A, Tantucci C, Lozinguez O, et al: Expiratory flow limitation as a determinant of orthopnea in acute left heart failure. J Am Coll Cardiol 35:690–700, 2000.
36. Piepoli MF: Exercise training in heart failure. Curr Heart Fail Rep 3:189–196, 2006.
37. Tripodoro VA, De Vito EL: Management of dyspnea in advanced motor neuron diseases. Curr Opin Support Palliat Care 2:173–179, 2008.
38. Choi HS, Han SS, Choi HA, et al: Dyspnea and palpitation during pregnancy. Korean J Intern Med 16:247–249, 2001.
39. Wasserman K, Casaburi R: Dyspnea: Physiological and pathophysiological mechanisms. Annu Rev Med 39:503–515, 1988.
40. Smoller JW, Pollack MH, Otto MW, et al: Panic anxiety, dyspnea, and respiratory disease. Theoretical and clinical considerations. Am J Respir Crit Care Med 154:6–17, 1996.
41. Craig KD: Emotional aspects of pain. *In* Wall PD, Melzack R (eds): Textbook of Pain (2nd ed). Edinburgh: Churchill Livingstone, 1989, pp. 220–230.
42. Chetta A, Gerra G, Foresi A, et al: Personality profiles and breathlessness perception in outpatients with different gradings of asthma. Am J Respir Crit Care Med 157:116–122, 1998.
43. Belman MJ, Brooks LR, Ross DJ, Mohsenifar Z: Variability of breathlessness measurement in patients with chronic obstructive pulmonary disease. Chest 99:566–571, 1991.
44. Jones PW, Oldfield WLG, Wilson RC: Reduction in breathlessness during exercise at sea level after 4 weeks at an altitude of 4000 metres. J Physiol (Lond) 422:105P, 1990.
45. Anderson B, Ley R: Dyspnea during panic attacks. An internet survey of incidences of changes in breathing. Behav Modif 25:546–554, 2001.
46. Jensen D, Webb KA, Davies GA, O'Donnell DE: Mechanisms of activity-related breathlessness in healthy human pregnancy. Eur J Appl Physiol 106:253–265, 2009.
47. Cullen DL, Rodak B: Clinical utility of measures of breathlessness. Respir Care 47:986–993, 2002.
48. Stendardi L, Binazzi B, Scano G: Exercise dyspnea in patients with COPD. Int J Chron Obstruct Pulmon Dis 2:429–439, 2007.
49. O'Donnell DE, Lam M, Webb KA: Measurement of symptoms, lung hyperinflation, and endurance during exercise in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 158:1557–1565, 1998.
50. Medinger AE, Chan TW, Arabian A, Rohatgi PK: Interpretive algorithms for the symptom-limited exercise test: Assessing dyspnea in Persian Gulf war veterans. Chest 113:612–618, 1998.
51. Brown CD, Wise RA: Field tests of exercise in COPD: The six-minute walk test and the shuttle walk test. COPD 4:217–223, 2007.
52. Ferrazza AM, Martolini D, Valli G, Palange P: Cardiopulmonary exercise testing in the functional and prognostic evaluation of patients with pulmonary diseases. Respiration 77:3–17, 2009.
53. Comstock GW, Tockman MS, Helsing KJ, Hennesy KM: Standardized respiratory questionnaires: Comparison of the old with the new. Am Rev Respir Dis 119:45–53, 1979.
54. Mahler DA, Weinberg DH, Wells CK, Feinstein AR: The measurement of dyspnea. Contents, interobserver agreement, and physiologic correlates of two new clinical indexes. Chest 85:751–758, 1984.
55. Dorman S, Byrne A, Edwards A: Which measurement scales should we use to measure breathlessness in palliative care? A systematic review. Palliat Med 21:177–191, 2007.
56. Guyatt GH, Berman LB, Townsend M, et al: A measure of quality of life for clinical trials in chronic lung disease. Thorax 42:773–778, 1987.
57. Jones PW, Quirk FH, Baveystock CM, Littlejohns P: A self-complete measure of health status for chronic airflow limitation. The St. George's Respiratory Questionnaire. Am Rev Respir Dis 145:1321–1327, 1992.
58. Harper R, Brazier JE, Waterhouse JC, et al: Comparison of outcome measures for patients with chronic obstructive pulmonary disease (COPD) in an outpatient setting. Thorax 52:879–887, 1997.
59. Eakin EG, Resnikoff PM, Prewitt LM, et al: Validation of a new dyspnea measure: The UCSD Shortness of Breath Questionnaire. University of California, San Diego. Chest 113:619–624, 1998.
60. Weaver TE, Narsavage GL, Guilfoyle MJ: The development and psychometric evaluation of the Pulmonary Functional Status Scale: An instrument to assess functional status in pulmonary disease. J Cardiopulm Rehabil 18:105–111, 1998.
61. Borg GA: Psychophysical bases of perceived exertion. Med Sci Sports Exerc 14:377–381, 1982.
62. Wilson RC, Jones PW: A comparison of the visual analogue scale and modified Borg scale for the measurement of dyspnoea during exercise. Clin Sci (Lond) 76:277–282, 1989.
63. Wilson RC, Jones PW: Long-term reproducibility of Borg scale estimates of breathlessness during exercise. Clin Sci (Lond) 80:309–312, 1991.
64. Muza SR, Silverman MT, Gilmore GC, et al: Comparison of scales used to quantitate the sense of effort to breathe in patients with chronic obstructive pulmonary disease. Am Rev Respir Dis 141:909–913, 1990.
65. Gift AG, Narsavage G: Validity of the numeric rating scale as a measure of dyspnea. Am J Crit Care 7:200–204, 1998.
66. Saisch SG, Wessely S, Gardner WN: Patients with acute hyperventilation presenting to an inner-city emergency department. Chest 110:952–957, 1996.
67. Howell JB: Behavioural breathlessness. Thorax 45:287–292, 1990.
68. Mahler DA, Horowitz MB: Clinical evaluation of exertional dyspnea. Clin Chest Med 15:259–269, 1994.
69. Field SK: Underlying mechanisms of respiratory symptoms with esophageal acid when there is no evidence of airway response. Am J Med 111(Suppl 8A):37S–40S, 2001.
70. Kubler P, Gibbs H, Garrahy P: Platypnoea-orthodeoxia syndrome. Heart 83:221–223, 2000.
71. Isaac J: Hypoxaemia, platypnoea, orthodeoxia and right-to-left shunts. Br J Anaesth 86:596–597, 2001.
72. Hirai N, Fukunaga T, Kawano H, et al: Platypnea-orthodeoxia syndrome with atrial septal defect. Circ J 67:172–175, 2003.
73. Godart F, Rey C: Platypnea-orthodeoxia syndrome: A probably underestimated syndrome? Chest 119:1624–1625, 2001.
74. Parameswaran K, Todd DC, Soth M: Altered respiratory physiology in obesity. Can Respir J 13:203–210, 2006.
75. Efthimiou J, Fleming J, Gomes C, Spiro SG: The effect of supplementary oral nutrition in poorly nourished patients with chronic obstructive pulmonary disease. Am Rev Respir Dis 137:1075–1082, 1988.
76. Ganzini L, Johnston WS, Silveira MJ: The final month of life in patients with ALS. Neurology 59:428–431, 2002.
77. Morrison LK, Harrison A, Krishnaswamy P, et al: Utility of a rapid B-natriuretic peptide assay in differentiating congestive heart failure from lung disease in patients presenting with dyspnea. J Am Coll Cardiol 39:202–209, 2002.

78. Pesola GR: The use of B-type natriuretic peptide (BNP) to distinguish heart failure from lung disease in patients presenting with dyspnea to the emergency department. Acad Emerg Med 10:275–277, 2003.
79. Ray P, Delerme S, Jourdain P, Chenevier-Gobeaux C: Differential diagnosis of acute dyspnea: The value of B natriuretic peptides in the emergency department. QJM 101:831–843, 2008.
80. Logeart D, Saudubray C, Beyne P, et al: Comparative value of Doppler echocardiography and B-type natriuretic peptide assay in the etiologic diagnosis of acute dyspnea. J Am Coll Cardiol 40:1794–1800, 2002.
81. Morris MJ, Grbach VX, Deal LE, et al: Evaluation of exertional dyspnea in the active duty patient: The diagnostic approach and the utility of clinical testing. Mil Med 167:281–288, 2002.
82. Chevalier B, Schwartzstein R: The role of the methacholine inhalation challenge: Avoiding a misdiagnosis of asthma. J Respir Dis 22:153–160, 2001.
83. Newton PN, Wakefield AE, Goldin R, Govan J: *Pneumocystis carinii* pneumonia with pleurisy, platypnoea and orthodeoxia. Thorax 58:185–186, 2003.
84. Martinez FJ, Stanopoulos I, Acero R, et al: Graded comprehensive cardiopulmonary exercise testing in the evaluation of dyspnea unexplained by routine evaluation. Chest 105:168–174, 1994.
85. Matsui K, Beasley MB, Nelson WK, et al: Prognostic significance of pulmonary lymphangioleiomyomatosis histologic score. Am J Surg Pathol 25:479–484, 2001.
86. Mayo JR, Remy-Jardin M, Muller NL, et al: Pulmonary embolism: Prospective comparison of spiral CT with ventilation-perfusion scintigraphy. Radiology 205:447–452, 1997.
87. Cross JJ, Kemp PM, Walsh CG, et al: A randomized trial of spiral CT and ventilation perfusion scintigraphy for the diagnosis of pulmonary embolism. Clin Radiol 53:177–182, 1998.
88. Ghaye B, Remy J, Remy-Jardin M: Non-traumatic thoracic emergencies: CT diagnosis of acute pulmonary embolism: The first 10 years. Eur Radiol 12:1886–1905, 2002.
89. Adams FG: The role of spiral computed tomography and D-dimer in pulmonary embolism. Scott Med J 46:7–8, 2001.
90. Witt C, Dorner T, Hiepe F, et al: Diagnosis of alveolitis in interstitial lung manifestation in connective tissue diseases: Importance of late inspiratory crackles, 67 gallium scan and bronchoalveolar lavage. Lupus 5:606–612, 1996.
91. Ilia R, Carmel S, Carlos C, Gueron M: Relation between shortness of breath, left ventricular end-diastolic pressure and severity of coronary artery disease. Int J Cardiol 52:153–155, 1995.
92. Pino-Garcia JM, Garcia-Rio F, Gomez L, et al: Short-term effects of inhaled beta-adrenergic agonist on breathlessness and central inspiratory drive in patients with nonreversible COPD. Chest 110:637–641, 1996.
93. Patel N, DeCamp M, Criner GJ: Lung transplantation and lung volume reduction surgery versus transplantation in chronic obstructive pulmonary disease. Proc Am Thorac Soc 5:447–453, 2008.
94. Puente-Maestu L, Stringer WW: Hyperinflation and its management in COPD. Int J Chron Obstruct Pulmon Dis 1:381–400, 2006.
95. Nici L, Donner C, Wouters E, et al: American Thoracic Society/European Respiratory Society statement on pulmonary rehabilitation. Am J Respir Crit Care Med 173:1390–1413, 2006.
96. Ries AL, Bauldoff GS, Carlin BW, et al: Pulmonary rehabilitation: Joint ACCp/AACVPR evidence-based clinical practice guidelines. Chest 131:4S–42S, 2007.
97. Lotters F, van Tol B, Kwakkel G, Gosselink R: Effects of controlled inspiratory muscle training in patients with COPD: A meta-analysis. Eur Respir J 20:570–576, 2002.
98. King DA, Cordova F, Scharf SM: Nutritional aspects of chronic obstructive pulmonary disease. Proc Am Thorac Soc 5:519–523, 2008.
99. Celli B, Lee H, Criner G, et al: Controlled trial of external negative pressure ventilation in patients with severe chronic airflow obstruction. Am Rev Respir Dis 140:1251–1256, 1989.
100. Wedzicha JA, Seemungal TA: COPD exacerbations: Defining their cause and prevention. Lancet 370:786–796, 2007.
101. Roberts CM, Brown JL, Reinhardt AK, et al: Non-invasive ventilation in chronic obstructive pulmonary disease: Management of acute type 2 respiratory failure. Clin Med 8:517–521, 2008.
102. ZuWallack RL, Mahler DA, Reilly D, et al: Salmeterol plus theophylline combination therapy in the treatment of COPD. Chest 119:1661–1670, 2001.
103. Peters MM, Webb KA, O'Donnell DE: Combined physiological effects of bronchodilators and hyperoxia on exertional dyspnoea in normoxic COPD. Thorax 61:559–567, 2006.
104. Bye PT, Esau SA, Levy RD, et al: Ventilatory muscle function during exercise in air and oxygen in patients with chronic airflow limitation. Am Rev Respir Dis 132:236–240, 1985.
105. Dean NC, Brown JK, Himelman RB, et al: Oxygen may improve dyspnea and endurance in patients with chronic obstructive pulmonary disease and only mild hypoxemia. Am Rev Respir Dis 146:941–945, 1992.
106. Emtner M, Porszasz J, Burns M, et al: Benefits of supplemental oxygen in exercise training in nonhypoxemic chronic obstructive pulmonary disease patients. Am J Respir Crit Care Med 168:1034–1042, 2003.
107. Taguchi O, Kikuchi Y, Hida W, et al: Effects of bronchoconstriction and external resistive loading on the sensation of dyspnea. J Appl Physiol 71:2183–2190, 1991.
108. Simon PM, Basner RC, Weinberger SE, et al: Oral mucosal stimulation modulates intensity of breathlessness induced in normal subjects. Am Rev Respir Dis 144:419–422, 1991.
109. Spence DP, Graham DR, Ahmed J, et al: Does cold air affect exercise capacity and dyspnea in stable chronic obstructive pulmonary disease? Chest 103:693–696, 1993.
110. Cristiano LM, Schwartzstein RM: Effect of chest wall vibration on dyspnea during hypercapnia and exercise in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 155:1552–1559, 1997.
111. Peiffer C: Dyspnea relief: More than just the perception of a decrease in dyspnea. Respir Physiol Neurobiol 167:61–71, 2009.
112. Renfroe KL: Effect of progressive relaxation on dyspnea and state anxiety in patients with chronic obstructive pulmonary disease. Heart Lung 17:408–413, 1988.
113. Carrieri-Kohlman V, Gormley J: Coping strategies for dyspnea. *In* Mahler D (ed): Dyspnea. New York: Marcel Dekker, 1998, pp. 287–313.
114. Dudley DL, Glaser EM, Jorgenson BN, Logan DL: Psychosocial concomitants to rehabilitation in chronic obstructive pulmonary disease. Part I. Psychosocial and psychological considerations. Chest 77:413–420, 1980.
115. Levine S, Weiser P, Gillen J: Evaluation of a ventilatory muscle endurance training program in the rehabilitation of patients with chronic obstructive pulmonary disease. Am Rev Respir Dis 133:400–406, 1986.
116. Light RW, Muro JR, Sato RI, et al: Effects of oral morphine on breathlessness and exercise tolerance in patients with chronic obstructive pulmonary disease. Am Rev Respir Dis 139:126–133, 1989.
117. Rice KL, Kronenberg RS, Hedemark LL, Niewoehner DE: Effects of chronic administration of codeine and promethazine on breathlessness and exercise tolerance in patients with chronic airflow obstruction. Br J Dis Chest 81:287–292, 1987.
118. Woodcock AA, Gross ER, Gellert A, et al: Effects of dihydrocodeine, alcohol, and caffeine on breathlessness and exercise tolerance in patients with chronic obstructive lung disease and normal blood gases. N Engl J Med 305:1611–1616, 1981.
119. Woodcock AA, Johnson M, Geddes DM: Breathlessness, alcohol and opiates. N Engl J Med 306:1363–1364, 1982.
120. Timmis AD, Rothman MT, Henderson MA, et al: Haemodynamic effects of intravenous morphine in patients with acute myocardial infarction complicated by severe left ventricular failure. Br Med J 280:980–982, 1980.
121. Sackner MA: Effects of hydrocodone bitartrate on breathing pattern of patients with chronic obstructive pulmonary disease and restrictive lung disease. Mt Sinai J Med 51:222–226, 1984.
122. Poole PJ, Veale AG, Black PN: The effect of sustained-release morphine on breathlessness and quality of life in severe chronic obstructive pulmonary disease. Am J Respir Crit Care Med 157:1877–1880, 1998.
123. Johnson MA, Woodcock AA, Geddes DM: Dihydrocodeine for breathlessness in "pink puffers." Br Med J (Clin Res Ed) 286:675–677, 1983.

124. Robin ED, Burke CM: Single-patient randomized clinical trial. Opiates for intractable dyspnea. Chest 90:888–892, 1986.
125. Ben-Aharon I, Gafter-Gvili A, Paul M, et al: Interventions for alleviating cancer-related dyspnea: A systematic review. J Clin Oncol 26:2396–2404, 2008.
126. Currow DC, Abernethy AP: Pharmacological management of dyspnoea. Curr Opin Support Palliat Care 1:96–101, 2007.
127. Young IH, Daviskas E, Keena VA: Effect of low-dose nebulised morphine on exercise endurance in patients with chronic lung disease. Thorax 44:387–390, 1989.
128. Westphal CG, Campbell ML: Nebulized morphine for terminal dyspnea. Am J Nurs Suppl 11–15, 2002.
129. Man GC, Hsu K, Sproule BJ: Effect of alprazolam on exercise and dyspnea in patients with chronic obstructive pulmonary disease. Chest 90:832–836, 1986.
130. Smoller JW, Pollack MH, Systrom D, Kradin RL: Sertraline effects on dyspnea in patients with obstructive airways disease. Psychosomatics 39:24–29, 1998.
131. Weiss DJ, Kreck T, Albert RK: Dyspnea resulting from fibromyalgia. Chest 113:246–249, 1998.
132. Booth S, Moosavi SH, Higginson IJ: The etiology and management of intractable breathlessness in patients with advanced cancer: A systematic review of pharmacological therapy. Nat Clin Pract Oncol 5:90–100, 2008.
133. Hill K, Geist R, Goldstein RS, Lacasse Y: Anxiety and depression in end-stage COPD. Eur Respir J 31:667–677, 2008.
134. Gimenez M, Servera E, Vergara P, et al: Endurance training in patients with chronic obstructive pulmonary disease: A comparison of high versus moderate intensity. Arch Phys Med Rehabil 81:102–109, 2000.
135. Sabapathy S, Kingsley RA, Schneider DA, et al: Continuous and intermittent exercise responses in individuals with chronic obstructive pulmonary disease. Thorax 59:1026–1031, 2004.
136. Simpson K, Killian K, McCartney N, et al: Randomised controlled trial of weightlifting exercise in patients with chronic airflow limitation. Thorax 47:70–75, 1992.
137. Hernandez MT, Rubio TM, Ruiz FO, et al: Results of a home-based training program for patients with COPD. Chest 118:106–114, 2000.
138. Sassi-Dambron DE, Eakin EG, Ries AL, Kaplan RM: Treatment of dyspnea in COPD. A controlled clinical trial of dyspnea management strategies. Chest 107:724–729, 1995.
139. Carrieri-Kohlman V, Gormley JM, Douglas MK, et al: Exercise training decreases dyspnea and the distress and anxiety associated with it. Monitoring alone may be as effective as coaching. Chest 110:1526–1535, 1996.
140. Ramirez-Venegas A, Ward JL, Olmstead EM, et al: Effect of exercise training on dyspnea measures in patients with chronic obstructive pulmonary disease. J Cardiopulm Rehabil 17:103–109, 1997.
141. Casaburi R, Patessio A, Ioli F, et al: Reductions in exercise lactic acidosis and ventilation as a result of exercise training in patients with obstructive lung disease. Am Rev Respir Dis 143:9–18, 1991.
142. McGavin CR, Gupta SP, Lloyd EL, McHardy GJ: Physical rehabilitation for the chronic bronchitic: Results of a controlled trial of exercises in the home. Thorax 32:307–311, 1977.
143. Ries AL, Kaplan RM, Limberg TM, Prewitt LM: Effects of pulmonary rehabilitation on physiologic and psychosocial outcomes in patients with chronic obstructive pulmonary disease. Ann Intern Med 122:823–832, 1995.
144. Scherer YK, Schmieder LE: The effect of a pulmonary rehabilitation program on self-efficacy, perception of dyspnea, and physical endurance. Heart Lung 26:15–22, 1997.
145. Gormley JM, Carrieri-Kohlman V, Douglas MK, Stulbarg MS: Treadmill self-efficacy and walking performance in patients with COPD. J Cardiopulm Rehabil Prev 13:424–431, 1993.
146. O'Donnell DE, McGuire M, Samis L, Webb KA: The impact of exercise reconditioning on breathlessness in severe chronic airflow limitation. Am J Respir Crit Care Med 152:2005–2013, 1995.
147. Carrieri-Kohlman V, Douglas MK, Gormley JM, Stulbarg MS: Desensitization and guided mastery: Treatment approaches for the management of dyspnea. Heart Lung 22:226–234, 1993.
148. Bruera E, Schmitz B, Pither J, et al: The frequency and correlates of dyspnea in patients with advanced cancer. J Pain Symptom Manage 19:357–362, 2000.
149. Luce JM, Luce JA: Perspectives on care at the close of life. Management of dyspnea in patients with far-advanced lung disease: "Once I lose it, it's kind of hard to catch it…." JAMA 285:1331–1337, 2001.
150. Neudert C, Oliver D, Wasner M, Borasio GD: The course of the terminal phase in patients with amyotrophic lateral sclerosis. J Neurol 248:612–616, 2001.

CHAPTER 29

COUGH

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INTRODUCTION

Cough is a symptom that has been experienced by every human and is an essential innate protective mechanism that ensures the removal of mucus, noxious substances, and infections from the larynx, trachea, and large bronchi. Cough also minimizes the inhalation of toxic material. Impairment or absence of coughing can be harmful or even fatal in disease. Cough may also be a sign of disease in or outside the airways and lungs and a useful indicator for both patient and physician for initiating diagnosis and treatment of disease processes. When cough itself is persistent and excessive, it can be harmful and deleterious and may need to be suppressed directly.

Because cough is a normal defensive mechanism, it is a symptom experienced by healthy individuals. Epidemiologic surveys have shown that between 11% to 18% of the general population report a persistent cough,[1-3] but it is not known how much this cough is "normal" or is associated with disease. This reporting of chronic cough may be due to the presence of cigarette smokers in these surveys or to the exposure of an urbanized population to environmental indoor and outdoor irritants and air pollution. There may also be undiagnosed illnesses associated with cough within these populations. The potential contribution of irritants to cough is illustrated by the report of excessive cough in New York firefighters who worked in the dust fall-out of the World Trade Center bombing on September 11, 2001.[4] Cough is also a common presenting symptom to the clinician. In the United States, cough is the most common complaint for which patients seek medical attention and the second most common reason for a general medical

consultation; patients with persistent cough constitute about 10% to 38% of a chest specialist outpatient practice. In the United Kingdom, about 3 million prescriptions are written annually for cough preparations by general practitioners, representing a cost of $3 million; this is an underestimate because a vast number of cough mixtures are also bought over-the-counter without a medical prescription. Cough medicines represent $1 billion yearly sales in the world.

Recent books,[5,6] reviews,[7,8] reports from expert groups on cough management[9,10] and symposium proceedings[11,12] provide excellent accounts of the physiology, pathology, and clinical science of cough in healthy subjects and in those with airway diseases.

DEFINITION OF COUGH

Cough is usually initiated as a series of respiratory maneuvers that lead to a characteristic cough sound. It usually starts as a deep inspiration, followed by a strong expiration against a closed glottis, which then opens with an expulsive flow of air, followed by a restorative inspiration; these are the inspiratory, compressive, expulsive, and recovery phases of cough (Fig. 29-1). The first cough sound is heard during the expulsive phase. This definition is valuable but may be restrictive for several reasons: (1) In the expulsive phase of cough, there may be a secondary closure of the glottis, which generates the second cough sound; this is usually present in airway disease, but may be absent in health. Its mechanisms are unknown. (2) The initial inspiration of cough may be followed by a series of expiratory efforts, with closures of the glottis but not intervening inspirations—a "cough bout." (3) Punctate mechanical stimulation of the trachea or larynx causes a brief but strong expiratory effort—the "expiration reflex"—and, in the case of the glottis, reflex glottal closure[13–15]; these reflexes presumably act to prevent or minimize entry of foreign material into the trachea and lungs. Throat clearing, as in postnasal drip, consists more of this expiration reflex or "huff" than a full cough.

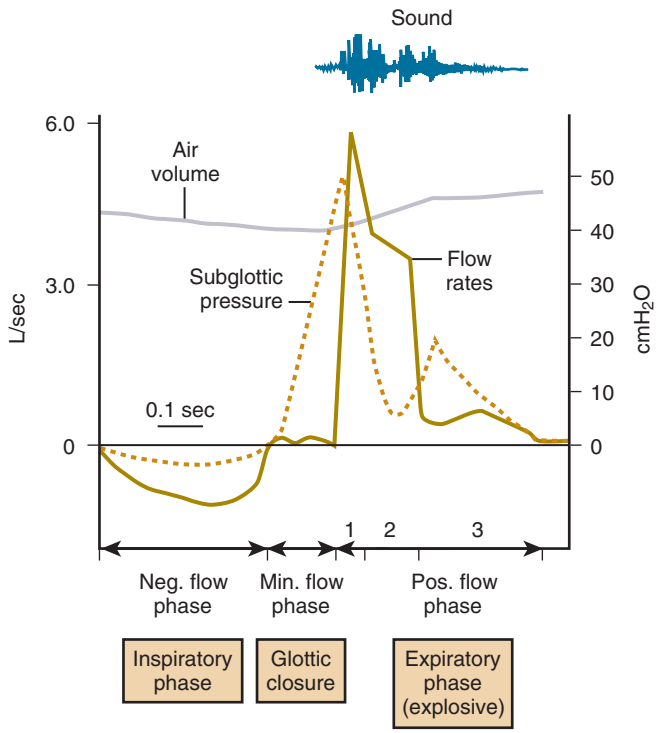


FIGURE 29-1 ■ Diagrammatic representation of the changes of the following variables during a representative cough: sound level, lung volume, flow rate, subglottic pressure. During inspiration, the flow rate is negative; at the glottic closure, the flow rate is zero; and during the expiratory phase, the flow rate is positive. The last phase can be divided into three parts: growing, constant, and decreasing. (Redrawn from Bianco S, Robuschi M: Mechanisms of cough. *In* Braga PC, Allegra L [eds]: Cough. New York: Raven, 1989, pp 29–36.)

Not only are there different patterns of "cough," but these patterns may be differently affected by pharmacologic and physiologic inputs.[13–15] The picture is complicated by the use of different semantics for cough components. Thus, the second phase may be called "expulsive," "explosive," or "expiratory," the second cough sound may be called "voiced" or "glottal," and a cough bout may be called an "epoch," "burst," or "peal." The confusion is probably not important provided the terms are clearly defined. Cough sounds may have clear harmonic patterns,[16] but the basis of these patterns has been little analyzed, and their significance, if any, has not been established. Induced cough is usually preceded by an "urge-to-cough,"[17] involving activation of the cerebral cortex.[18] Voluntary cough and habit cough presumably originate in the cortex. Once a cough has been induced, there will be secondary feedbacks both from the lungs and from the higher parts of the brain, which do not seem to have been analyzed.

Thus, the definition of cough may need to be extended to embrace, or at least consider, these different patterns and neural circuits. This consideration is not a semantic quibble. The reflexes have different afferent and central nervous pathways, but clinical descriptions of cough have seldom differentiated between them. Antitussive drugs could have selective actions on the different afferent pathways.

PHYSIOLOGY

Experimentally, involuntary coughing appears to be initiated only from those structures innervated by the vagus nerve and its branches.[13,19] These are especially the larynx and the proximal tracheobronchial tree, but they also include the lower part of the oropharynx and the smaller bronchi, as well as the tympanic membrane and the external auditory meatus. Irritation of all these sites can cause coughing. The one clear exception to vagally mediated coughing is that caused voluntarily[20,21] (Fig. 29-2); of all the highly complex defense mechanisms, cough is the only one that we can mimic voluntarily and accurately. We can also inhibit it voluntarily. Most patients can suppress their cough for 5 to 20 minutes if they try hard.[20]

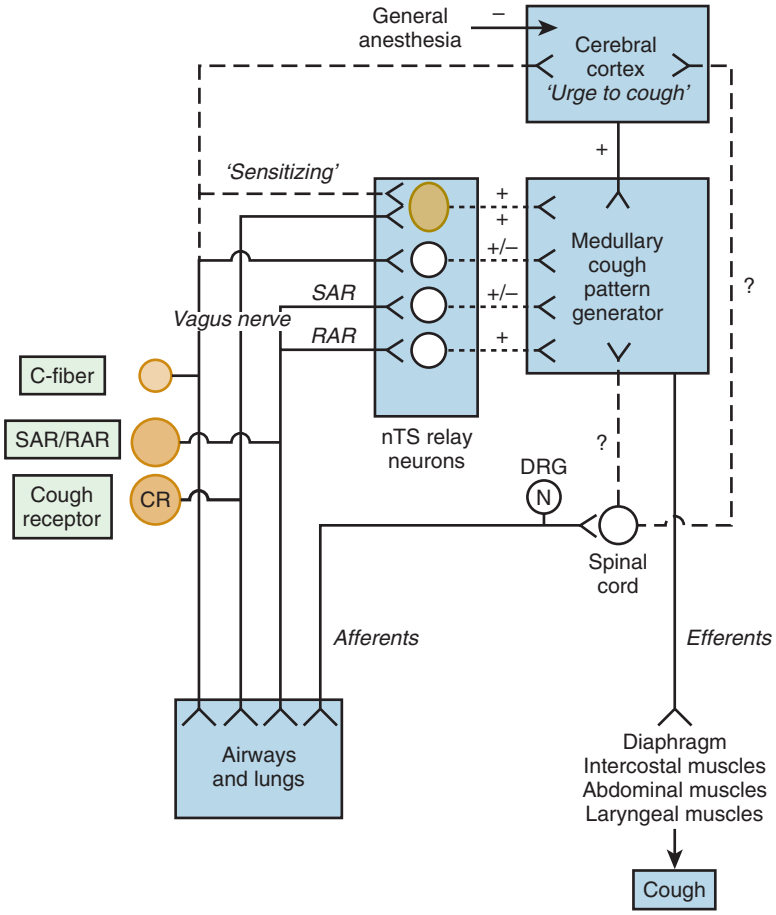


FIGURE 29-2 ■ Model illustrating the afferent and efferent pathways in the control of cough. Rapidly adapting receptors (RARs), slow-adapting receptors (SARs) and C-fibers may modulate the cough responses, and a distinct set of cough receptors has been described in the guinea pig. There may be promotion of coughing through interactions with cortical and brain-stem structures, in addition to putative contributions via spinal airway afferents. The cough pattern generator coordinates the output to muscles and effectors that results in the cough response. DRG, dorsal root ganglion; nTS, nucleus tractus solitarius; +, enhancing; –, inhibitory; ?, putative. (Adapted from Mazzone SB: Sensory regulation of the cough reflex. Pulm Pharmacol Ther 17:361–368, 2004.)

Spontaneous coughing can be initiated by a wide variety of inflammatory or mechanical changes in the airways and by inhalation of a large number of chemical and mechanical irritants. Rapid and large changes in lung volume can cause cough, as can psychological effects such as laughter. The extremely wide variety of stimuli that can trigger cough points to a similarly wide range of properties of the sensory receptors that are the starting point of the cough reflex.[13,19,22]

Receptors for the Cough Reflex

The most sensitive sites for initiating cough are the larynx and the tracheobronchial tree, especially the carina and the points of bronchial branching.[13,19,22–24] Inhaled materials impinge on these points. In experimental animals and humans, it is difficult or impossible to induce coughing from the smaller airways and alveoli. This is teleologically understandable because in the smaller airways even a vigorous cough would not move gas fast enough to cause turbulence and shearing forces at the airway wall, so the cough would be ineffective. In view of the wide range of stimuli for coughing, one would expect the sensory nerve receptors to be "polymodal" (i.e., to respond to a variety of chemical and pharmacologic mediators and to mechanical stimulation). Such receptors are found throughout the respiratory tract.

Larynx and Pharynx

Nerve receptors (or perhaps better termed "sensors") in the laryngeal mucosa are activated by the mechanical and chemical stimuli for cough; their fibers run mainly in the superior and recurrent laryngeal nerves before joining the vagus nerves. Many studies of laryngeal afferent innervation suggest that the sensors for cough belong to the broad group of "rapidly adapting 'irritant' receptors" (RARs) found there and in the tracheobronchial tree.[25–27] The RARs are normally silent, as would be expected and, when activated, cause rapidly adapting discharges with an irregular pattern that are conducted in fast-velocity vagal myelinated (Aδ) fibers. Their many stimuli include cigarette smoke, ammonia, ether vapor, acid and alkaline solutions, hypotonic and hypertonic saline, and mechanical stimulation by catheter, mucus, or dust; all these stimuli can provoke cough. Although strong cough can be induced from the larynx, its denervation or bypass makes little difference to the strength of cough caused by inhaled irritants. As with many protective/defensive mechanisms, the cough reflex displays much "redundancy"—that is, a doubled sensory input for cough does not result in a doubling of the motor response.

Activation of receptors in the larynx or pharynx may cause either a "typical" cough, starting with an inspiration, or the expiration reflex, starting with an expiratory

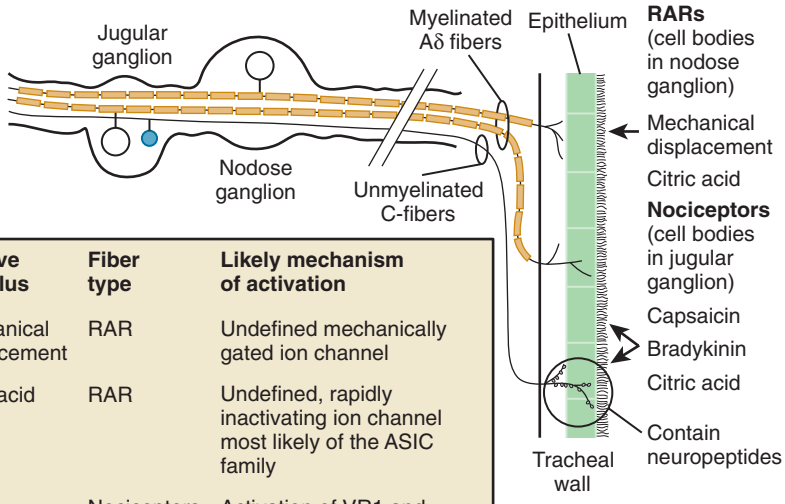
effort.[13–15] The difference is presumably due to various types of cough sensors in the mucosa. Although cough induced from the pharynx may seem to be the exception to the vagal rule, in that the pharynx is supplied mainly by the glossopharyngeal nerve, there is a small pharyngeal branch of the superior laryngeal (vagal) nerve that could mediate cough, and this seems to be especially active in humans.[28] Furthermore, postnasal drip associated with, for example, inflammation due to nasopharyngitis and sinusitis, can induce cough possibly due to spread of inflammatory mediators into the larynx.

Tracheobronchial Tree

Similar RARs are found in the trachea and large bronchi of those species that cough. The sensors have nerve terminals under or within the epithelium (Fig. 29-3), concentrated at points of airway branching; some of them lie close (1 μm) to the epithelium.[29–31] Their appearance and location suggest that they might be sensitive to intraluminal irritants. They are activated, like those in the larynx, by an extremely wide range of chemical and mechanical irritants and by many inflammatory and immunologic mediators, such as histamine, bradykinin, prostaglandins, and substance P. In experimental animals, RAR activity is enhanced by pulmonary congestion, atelectasis, bronchoconstriction, and decreases in lung compliance, all of which can cause cough in patients.

Although the evidence that the RARs are primarily responsible for coughing is convincing, other lung reflexes may interact with them. C-fiber receptors, which have thin nonmyelinated vagal afferent fibers, are found in the laryngeal, bronchial, and alveolar walls. They are activated by much the same range of stimuli as are the RARs, but their responses, at least for those in the alveolar walls, do not include cough.[22,31,32] The C-fiber receptors may release tachykinins, such as substance P, which in turn stimulate RARs to cause cough and can also cause neurogenic inflammation by an axon reflex. This may explain the effect of tachykinin antagonists in inhibiting cough. However, there is no convincing evidence that C-fiber receptors can be a primary sensory input to the cough reflex. A new group of Aδ-nociceptors has been identified in the guinea pig, and electrophysiologic and immunohistochemical studies indicate that this may represent an airway afferent nerve subtype distinct from RARs and C fibers that play an essential role in regulating the cough reflex, termed "cough receptors."[33] Airway C-fiber receptors have been differentiated into two groups.[30,34] The precise actions of these new groups of sensors on cough have not yet been determined.

Thus, the fact that the other receptors, such as the C-fiber endings, also respond like RARs to many of the same stimuli suggests that the total pattern of cough may be due to the interaction of several reflexes. This view,



Tussive stimulus	Fiber type	Likely mechanism of activation
Mechanical displacement	RAR	Undefined mechanically gated ion channel
Citric acid	RAR	Undefined, rapidly inactivating ion channel most likely of the ASIC family
	Nociceptors	Activation of VR1 and activation of undefined ASIC
Capsaicin*	Nociceptors	Activation of VR1 channels
Bradykinin	Nociceptors	B2 receptor-mediated activation of VR1 channels. This may involve protein kinase C and lipoxygenase enzymes

*Capsaicin activates RAR indirectly by including neuropeptides release; neuropeptide-mediated smooth muscle contraction and increase in vascular permeability activate RAR.

FIGURE 29-3 ■ Vagal afferent innervation of guinea pig trachea. Mechanism of sensory nerve stimulation by various cough-inducing stimuli (*inset*). ASIC, acid-sensing ion channel; RAR, rapidly adapting receptors; VR-1, transient receptor vanniloid-1. (Redrawn from Undem BJ, Carr MJ, Kollarik M: Physiology and plasticity of putative cough fibers in the guinea pig. Pulm Pharmacol Ther 15:193–198, 2002.)

together with the variety of physiologic patterns of sensitivities and responses of RARs in various parts of the respiratory tract, could explain the great divergence of cough patterns in different conditions and in different patients. The effectiveness of antitussive drugs that act at peripheral sites (e.g., by the inhalation of anesthetic aerosols) may depend on their relative actions on the different groups of receptors that affect cough or on their central connections.

Plasticity of the Cough Sensors

In disease, the sensory receptors for cough can show an exaggerated response to stimuli that would normally be harmless or mildly irritating. This increase in sensitivity of RARs and C-fiber receptors can be caused, inter alia, by allergen challenge, viral infections, ozone, cigarette smoke, and a variety of inflammatory mediators.[35] RARs can also be sensitized by mucus in the airways, underlying smooth muscle contraction, and mucosal edema.[31,32,36–38] Structural changes in the nervous receptors, in particular in their intracellular mediators, have been related to the increases in sensitivity. Similar changes have been seen in the nerve cell bodies in the jugular and nodose ganglia and in the afferent pathways entering the brain stem (see later). The relevance of these plasticity changes to human airway disease is apparent.

Membrane Receptors/Channels on Sensory Endings for Cough

The last decade has seen extensive studies on the membrane/channel receptors in sensory nerves involved in coughing.[31,35,38–40] The details are complex and most conclusions tentative, so they are summarized only briefly; however, the results are of considerable importance not only in indicating how coughing may be induced but also by pointing to possible future targets in antitussive therapy.

Cough sensors, especially the RARs and Aδ-nociceptors, are stimulated by touch and stretch and are thought to have stretch-activated membrane channels, as do similar receptors elsewhere (e.g., baroreceptors). In addition, they have voltage-gated sodium channels that can be activated by acid and belong to the acid-sensing ion channel (ASIC) family. However, the RAR membranes lack transient receptor potential vanilloid (TRPV-1) receptors, which are found in C- and Aδ-nociceptors. The TRPV-1 receptors are activated especially by capsaicin, much used as a tussive agent, and are sensitized or activated by (inter alia) heat, protons, bradykinin, arachidonic acid derivatives, adenosine triphosphate (ATP) and phosphokinase C. Recently, cannabinoid (CB2) membrane receptors have also been identified.[41] Thus, the way in which a large variety of tussive stimulants activate the sensory nerves responsible for cough is beginning to be clarified. The membrane receptors on cough sensors have been studied mainly in experimental animals,[35,42] but their relevance to human cough is still unclear.

Central Nervous System Control

A (possible) circuit diagram for the interaction of cough inputs and outputs and the respiratory rhythm generator in the brain stem has been proposed.[43–46] Coughing is integrated in the medulla oblongata where the afferent fibers for coughing first relay in or near the nucleus of the tractus solitarius; the motor outputs are in the nucleus retroambigualis, sending motoneurons to the respiratory muscles, and in the nucleus ambiguous, sending motoneurons to the larynx and bronchial tree. In the cat, brain-stem pathways for the expiration reflex differ from those for a typical cough,[46,47] and pathways for cough from the larynx differ from those from the tracheobronchial tree.[48] These observations, if true for humans, point to different antitussive agents appropriate to the two sites.

The voluntary control of coughing can probably bypass these integrative centers[20,21] (see Fig. 29-3), because some patients with brain-stem damage lack a spontaneous cough reflex but can consciously induce coughing to clear the airways.[49] Greater understanding of the central control of coughing is desirable because most antitussive drugs act centrally, and we know little about how they do this. However, research has shown that central nervous membrane receptors for cough include serotonin, gamma-animobutyric acid, *N*-methyl-D-aspartate, neurokinins, and dopamine, results that could have considerable therapeutic implications.[43,50] Studies with functional magnetic resonance imaging of the human cerebral cortex and upper brain during induced cough and the urge-to-cough are delineating those areas involved[18,51] (Fig. 29-4).

The central nervous pathways for cough show interactions and plasticity, as do the peripheral mechanisms already described.[37,52,53] For example, afferent fibers from RARs and C-fiber receptors converge in the nucleus of the solitary tract. Neurokinins released from the latter potentiate the activity of the former, especially cough and reflex bronchoconstriction, and this potentiation is enhanced by continued C-fiber activity. An example of such central plasticity may also be seen in some cases of gastroesophageal reflux (GER), where activity in esophageal afferents, which do not normally cause cough, may activate the cough reflex when sensitization takes place.

Motor Outputs

Although glottic closure is usually regarded as an essential and definitive component of cough, in both human and experimental animals, the closure may be incomplete or even absent, and this does not seem greatly to limit the effectiveness of the cough in terms of airway clearance. In addition, the glottal closure reflex has a lower threshold to irritants than does the expiration and cough reflexes and may therefore depend on different pathways.[23,24]

Coughing is associated with respiratory actions other than those of the respiratory skeletal muscles.[13,19,22] There is usually bronchoconstriction, although this may be masked or reversed by the dramatic changes in lung

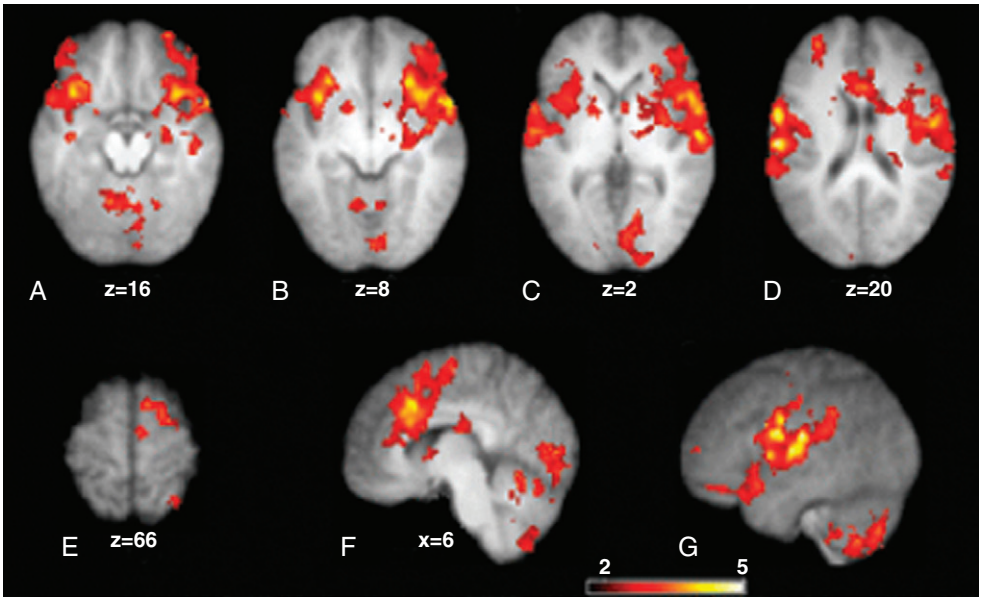


FIGURE 29-4 ■ Activation of brain pathways associated with inhalation of capsaicin to cause an "urge-to-cough" shown by functional magnetic resonance imaging. The majority of regional activations were distributed in both hemispheres, including the orbitofrontal cortex (**A**), inferior frontal gyrus (**A** and **B**), anterior insula (**B** and **C**), superior temporal gyrus (**C**), and primary motor and somatosensory cortices (**D** and **G**). Midline capsaicin activations include the supplementary motor area (**E**) and the anterior midcingulate cortex (**F**). The locations of capsaicin activations in the primary motor and somatosensory cortices were at the caudal end of the central sulci in both hemispheres (**D**) and are clearly discernable on the three-dimensional rendering of the left hemisphere. (A-G, From Mazzone SB, McLennan L, McGovern AE, et al: Representation of capsaicin-evoked urge-to-cough in the human brain using functional magnetic resonance imaging. Am J Respir Crit Care Med 176:327–332, 2007.)

volume. The afferent mechanisms for reflex cough and reflex bronchoconstriction may be different. Cough may be caused mainly by RARs and Aδ-nociceptors and the bronchoconstriction mainly by C-fiber sensors. In practice, coughing, like laughter, can precipitate an attack of asthma, and asthma attacks are often associated with a hyperreactive cough reflex. The possibility of vicious circles exists. Bronchoconstriction would increase linear velocity of airflow and lessen the inflow of irritant and tussigenic material to deeper parts of the airways.

The afferent sensors for cough also cause reflex secretion of mucus from airway submucosal glands.[13,19,22,54] Mucus entraps inhaled particles and irritant chemicals, and the material is thus cleared from the airways by mucociliary transport and by the cough itself. Mucus could also act as a physicochemical barrier between the luminal irritants and the airway wall. However, an increase in mucus secretion in conditions associated with cough has never been accurately measured, perhaps because of lack of appropriate methods.

Mechanics of Coughing

The inspiratory phase of cough consists of a deep inspiration through a widely opened glottis. The inhaled volume varies greatly, from a nearly complete vital capacity to much lower values. The inspiration may draw material into the lungs; however, the large lung volume provides a better mechanical efficiency for the expiratory muscles of cough because they are initially stretched, because their stretch reflex is activated, and because there is a stronger elastic recoil of the lung to aid expiration. Furthermore, the deep inspiration opens the airways in preparation for their clearance during the expiratory phase.[52]

In the compressive phase of cough, which lasts about 200 ms, the glottis closes while the expiratory muscles contract, and the intrapleural and intra-alveolar pressures rise rapidly to values as high as 300 mm Hg (40 kPa).[52,55] The expulsive phase follows when the glottis opens. The expiratory flow rate depends both on air leaving the central airways during dynamic collapse as a result of the high intrathoracic pressure and on the effect of high alveolar pressure, increased during the compressive phase and maintained at a high level by the contraction of the expiratory muscles. The expulsive phase of coughing may be long-lasting, with a large expiratory tidal volume, or it may be interrupted by glottic closures into a series of short expiratory efforts, each having a compressive and an expulsive phase. What determines which pattern of coughing has not been established, but may depend on the anatomic site of origin of the cough, on the different nerve types of receptor activated, and on the strength of their activation.

Maximum expiratory flow is effort-independent because it is limited by dynamic compression of the airways.[52] This compression starts immediately downstream from the "equal pressure point" at which intraluminal and extraluminal pressures around the bronchial wall are equal, so that transbronchial pressure is zero. The effectiveness of cough depends on peak airflow and will therefore be greater with a larger elastic recoil of

the lung and a greater elasticity of the central airways. Dynamic compression of the airways downstream from the equal pressure point increases velocity, kinetic energy, and turbulence of the air passing through the proximal airways. Thus, the clearing capacity of the cough is improved. If cough consists of a series of expiratory efforts, with lung volume decreasing with each effort, dynamic compression is predicted to move into the more peripheral bronchi, which will be progressively cleared of intraluminal material. However, at present this description is largely theoretical and needs to be established experimentally. Determinants of maximal airflow are discussed in Chapter 24.

Whereas mucociliary transport is the major method of clearing the airway lumen in healthy subjects, cough is an important reserve mechanism, especially in patients with lung disease. In many lung diseases, mucociliary clearance is impeded and cough is necessary to remove the increased amount of secretions and debris. Healthy subjects have twice the mucociliary clearance rate of that in patients with chronic bronchitis, but when cough is permitted or encouraged, the patients increase their clearance by 20%, whereas healthy subjects increase their clearance by only 2.5%. As would be expected, all studies point to the fact that cough is effective in causing clearance if there is hypersecretion of mucus; by definition, a dry cough is an unproductive one.

APPROACH TO THE PATIENT WITH COUGH

In the management of a patient with cough, the first step is to identify the cause of the cough and then treat the cause. Cough may be indicative of trivial to very serious airway or lung diseases and also of extrapulmonary processes. Often, the cause may not be delineated or treatment of the putative cause may not lead to suppression or improvement of the cough, or there is no effective treatment of the cause available. Therapy that suppresses cough by inhibiting the cough pathway without treating the cause ("symptomatic," "nonspecific," or "indirect" antitussives) is needed if the cough is very severe, if treatment of the cause does not lead to sufficient cough suppression, or if treatment of the cause is not possible or successful.

The differential diagnosis of cough is extensive and includes infections, inflammatory and neoplastic conditions, and many pulmonary as well as extrapulmonary conditions (Table 29-1). The protocol for investigating a chronic cough that has persisted for more than 3 weeks takes into account several factors pertaining to the pathophysiology of cough and the most common causes of cough. Persistent cough may be due to the presence of excessive secretions, to airway damage and infection, or to the establishment of a hypersensitive cough reflex. A protocol based on systematic evaluation using history, examination, and laboratory investigations focusing at the anatomic sites of cough receptors that constitute the afferent limb of the cough reflex is a most widely advocated approach to diagnosis and treatment.[9,10]

The foremost consideration for the clinician at the first visit is to (1) determine the severity, (2) assess the cause of the cough, and (3) plan investigations and treatment. Various indicators in the history and examination of the patient may provide clues to the diagnosis, although these may not be entirely reliable or specific and may be absent in many cases.

A period of 3 weeks has been taken as a cutoff point for an acute cough usually due to an upper respiratory virus infection, although some postviral coughs may persist for many weeks or months. The only caveat to this is that sometimes such a cough may last for more than 3 weeks and many patients with an "idiopathic" cough often state that their cough originated during an upper respiratory tract infection. A cough that has lasted for more than 2 to 3 months is less likely to be due to an upper respiratory tract infection, and further investigations in terms of other associated causes must be looked for.

TABLE 29-1. Common Causes of Cough

ACUTE INFECTIONS
Tracheobronchitis
Bronchopneumonia
Viral pneumonia
Acute-on-chronic bronchitis
Pertussis

CHRONIC INFECTIONS
Bronchiectasis
Tuberculosis
Cystic fibrosis

AIRWAY DISEASES
Asthma
Chronic bronchitis
Chronic postnasal drip

PARENCHYMAL DISEASES
Chronic interstitial lung fibrosis
Emphysema
Sarcoidosis

TUMORS
Bronchogenic carcinoma
Alveolar cell carcinoma
Benign airway tumors
Mediastinal tumors

FOREIGN BODIES

MIDDLE EAR PATHOLOGY

CARDIOVASCULAR DISEASES
Left ventricular failure
Pulmonary infarction
Aortic aneurysm

OTHER DISEASES
Reflux esophagitis
Recurrent aspiration
Endobronchial sutures

DRUGS
Angiotensin-converting enzyme inhibitors

Cough with sputum production usually points toward conditions such as chronic bronchitis and bronchiectasis or other causes of bronchorrhea. The diagnostic value of knowing that the cough is productive is probably limited. One study indicates that similar causes are often found for both productive and dry cough.[56] In addition, the volume of sputum produced is difficult to estimate accurately (usually depending on sputum cups and block of salivary contamination), and coughing itself leads to sputum production. The concept of a dry versus a productive cough as delineating a cough secondary to an increased cough reflex for the former and a cough secondary to excessive mucus production for the latter is not entirely correct. An enhanced cough reflex may be present in both productive and nonproductive cough. Features that are associated with an increased cough reflex include cough triggered by taking a deep breath, laughing, inhalation of cold air, and prolonged talking. Therefore, the diagnostic approach remains similar as to whether the cough is productive or not.

The characteristics of the cough may sometimes help. Throat clearing may be associated with a postnasal drip, a predominantly nocturnal cough may be attributed to asthma rather than to other causes, or cough after meals may be related to coexistent GER. However, the predictive values of these characteristics are low.[57] A cough with a "honking" or "barking" quality, particularly in a child, has been associated with a psychogenic or habit cough.

Many cigarette smokers have a chronic cough, but rarely seek medical advice regarding their cough as they expect the irritant effect of cigarette smoke is the cause of their cough. A change in the pattern or characteristics of their cough, such as an increase in intensity (usually after an upper respiratory tract infection), or accompanying hemoptysis may force a smoker to seek medical attention. A chest radiograph is mandatory in this situation.

TABLE 29-2. Potential Complications from Excessive Cough

RESPIRATORY
Pneumothorax
Subcutaneous emphysema
Pneumomediastinum
Pneumoperitoneum
Laryngeal damage
CARDIOVASCULAR
Cardiac dysrhythmias
Loss of consciousness
Subconjunctival hemorrhage
CENTRAL NERVOUS SYSTEM
Syncope
Headaches
Cerebral air embolism
MUSCULOSKELETAL
Intercostal muscle pain
Rupture of rectus abdominis muscle
Increase in serum creatine phosphokinase
Cervical disc prolapse
GASTROINTESTINAL
Esophageal perforation
OTHER
Social embarrassment
Depression
Urinary incontinence
Disruption of surgical wounds
Petechiae
Purpura

Measuring Cough

Assessment of cough frequency and severity rests mainly on history taking. In very severe cough, complications arising from cough such as vomiting, rib fractures, tiredness, incontinence, and syncope may be experienced (Table 29-2), and their presence indicates that the chronicity and intensity of the cough are severe. The effect of cough on the patient's lifestyle and psychological well-being may also provide an idea of the severity of the cough. Questionnaires that are specifically devised to measure these effects have been developed.[58,59] For the assessment of the response of the cough to various treatment modalities, tools to measure the frequency and severity of cough have also been developed.[16,60,61] In many published studies, the effectiveness of particular interventions have been determined qualitatively at the clinic, but use of more quantitative tools is gradually being introduced.

Cough can be measured in several ways: (1) The severity of cough can be judged by the patient recording her or his perception on a visual analogue scale ranging from mild to severe or on a nominal scale from 0 to 10; (2) cough-specific health-related quality of life questionnaires can provide a quantitative measure of the impact of chronic cough on the patient; (3) measurement of the cough reflex can be done by counting the cough responses to inhalation of tussive agents such as capsaicin, the pungent extract of peppers, or citric acid– or low-chloride–content solutions; and (4) quantitative ambulatory recording of the frequency and intensity of cough.[62] What should be the "gold standard" for measuring the severity of the cough is not clear yet, but it will need to be a combination of both subjective and objective measurements and, ideally, should include both frequency and intensity of cough and the extent to which it is divided into individual cough and cough epochs. All these features are of concern to the patient.

Measurement of the Cough Reflex

Persistent cough may result from an increase in the sensitivity of the cough sensors. This can be measured with inhalation of an aerosol of capsaicin or of citric acid. Most patients with a persistent cough due to a range of

causes have an enhanced cough reflex to capsaicin when compared with healthy noncoughing subjects.[63] Successful treatment of the primary condition underlying the chronic cough (specific or disease-orientated treatment) often leads to a normalization of the cough reflex.[64] The degree of the cough responsiveness to inhaled capsaicin may be a reflection of the severity of the cough, but this has not been examined yet. Of relevance to the evaluation and treatment strategies for persistent dry cough is the fact that the cough response can be augmented by various mediators of inflammation such as the prostaglandins PGE_2 and $PGF_{2\alpha}$ and bradykinin through a process of sensitization.[65,66] Measurement of the cough reflex response to such agents may be useful in confirming the presence of a persistent cough or in assessing the response to treatment. At the moment, only centers with an interest in cough use it for clinical and research purposes.

Measurement of Cough Frequency and Intensity

Advances in computer technology and in digital sound recording have led to the development of ambulatory systems for audio or audiovisual recording of cough, with the ultimate objective of automatically obtaining cough counts and possibly intensity in a real-life setting. Several devices have been described.[16,61,67] Although none has been tested in the context of treatment studies, their availability represents a major progress in the assessment of cough. A recent study indicated that the number of cough sounds and the cough seconds, a measurement of the time of coughing, correlated strongly with scores on a Leicester Cough Questionnaire (LCQ) and cough visual analogue scale.[16]

Although the methods are valuable in counting the number of expiratory efforts associated with cough, they do not allow assessment of cough intensity (because this need not correlate with intensity of expiratory sound). They can be used to differentiate between individual coughs and those associated with a cough epoch, although the definition of the distinction is arbitrary. Both intensity of cough efforts and whether they occur are groups are features of importance to the patient. Nor do current methods allow a distinction between a "true" cough and an expiration reflex, a feature that should be important to the investigator.

Quality of Life Questionnaires

Quality of life questionnaires specific for the evaluation of the impact of chronic cough[59] provide subjective measurements that are likely to reflect the severity of cough from the viewpoint of the patient. Such measurements integrate both the impact of frequency and the intensity of cough. The LCQ uses a seven-point Likert response scale for 19 items from three domains (physical, psychological, and social) and is shown to be repeatable and responsive in patients with chronic cough.[68] This is increasingly becoming a useful clinical tool.

Diagnosis and Investigations of Chronic Cough

The history and examination will sometimes indicate likely associated diagnosis or diagnoses, and the timing of various investigations may vary according to presentation (Table 29-3). Initial investigations may be limited to a chest radiograph, particularly in a cigarette smoker. Abnormalities have been reported in 10% to 30% of chest radiographs of cigarette smokers, although the yield of tumors is likely to be lower. Further investigations (e.g., computed tomography or fiberoptic bronchoscopy) may be pursued despite a "normal" chest radiograph.

Patients on angiotensin-converting enzyme (ACE) inhibitor therapy should discontinue such therapy, with replacement by other appropriate treatments. A period of observation of 3 to 4 weeks in a patient who provides a good history of an upper respiratory tract infection prior to further investigation or therapeutic trial is adequate, although institution of an anti-inflammatory therapy such as inhaled corticosteroids can be useful in controlling this type of cough.

Postnasal drip ("nasal catarrh" or "upper airway cough syndrome"), asthma, and GER are the three most common conditions associated with a chronic cough, and a diagnostic approach to exclude these conditions first is sensible. Examination of the nose and sinuses with a computed axial tomogram of the sinuses may be indicated with a history of postnasal drip or rhinosinusitis, with ambulatory esophageal pH monitoring to exclude GER. The diagnosis of asthma is supported by the

TABLE 29-3. Diagnostic Evaluation of Chronic Cough

1. History and physical examination.
2. Chest radiograph, particularly in smokers.
3. Initial evaluation may lead to diagnosis of chronic bronchitis in cigarette smokers and of angiotensin-converting enzyme inhibitor cough. Discontinue cigarette smoking and offending drug.
4. Further diagnostic evaluation on basis of initial evaluation:
   i. If suggestive of postnasal drip, order a computed tomographic scan of sinuses, and allergy tests
   ii. If suggestive of asthma, request a record of peak expiratory flow measurements at home for 2 weeks and a bronchoprovocation test with histamine or methacholine and/or a trial of antiasthma treatment.
   iii. If suggestive of gastroesophageal reflux disease, request 24-hr pH monitoring and, if necessary, an endoscopic examination of the esophagus or a barium swallow series.
   iv. If the chest radiograph is abnormal, consider examination of sputum and a fiberoptic bronchoscopy. A high-resolution computed tomographic scan of the thorax and further lung function evaluation may be necessary.
5. Treat specifically for associated conditions. The cause(s) of cough is (are) determined when specific therapies eliminate or improve the cough. There may be more than one associated cause for the cough.

presence of diurnal variation in peak flow measurements, bronchial hyperresponsiveness to histamine or methacholine challenge, and the presence of eosinophils in sputum. Under the umbrella of "asthma" would also be included cough-variant asthma and eosinophilic bronchitis. However, a therapeutic trial may be the best initial approach, particularly when the history and examination provide supportive clues. It is important that effective doses of medication over a sufficient period of time are given. Often, a longer-than-usual period of treatment is necessary to control the cough. Postnasal drip is an often overlooked condition and aggressive treatment consists of corticosteroid nasal drops together with an antihistamine, with the possibility of adding antibiotic therapy and a short period of treatment with a nasal decongestant. Often, more than one of these conditions may coexist and cough may respond only with concomitant treatment of these. For example, inhaled steroid therapy and gastric acid suppression with a proton pump inhibitor or H_2-histamine blockers would be indicated for the coexistence of asthma and GER.

Bearing in mind that there are a myriad of other less common causes of a chronic cough, investigations must proceed further if the just-discussed causes have been excluded. Lung function tests to include lung volumes and gas transfer factor, and a computed axial tomogram of the lungs should be considered in case of bronchiolar or parenchymal disease or unsuspected bronchiectasis. Fiberoptic bronchoscopy should be considered and, apart from excluding small central tumors, provides mucosal biopsies for histologic examination.

CAUSES AND TREATMENT OF ACUTE AND CHRONIC COUGH

Acute Cough

Acute cough is usually due to a viral or bacterial upper respiratory tract infection. The cough of the common cold is usually self-limiting and accompanies the cold in the majority of sufferers within the first 48 hours.[69] Other symptoms of postnasal drip, throat-clearing, irritation of the throat, sore throat, nasal obstruction, and nasal discharge also accompany the cough, which usually resolves within 2 weeks, although it can be sometimes prolonged. Pertussis should be considered in the differential diagnosis, particularly with a whooping characteristic of the cough, and is often associated with vomiting. Other causes of acute cough are pneumonia, congestive cardiac failure, exacerbation of chronic obstructive pulmonary disease (COPD), aspiration, or pulmonary embolism. These conditions are usually accompanied by other symptoms such as shortness of breath and fever, but cough may be the predominant or, rarely, the only symptom.

Patients with the common cold usually self-medicate with over-the-counter antitussive preparations. A Cochrane review reported no good evidence for or against the effectiveness of over-the-counter medicines such as antitussives and antihistamines in acute cough. "Satisfactory" responses to pediatric cough syrups was reported in 46% and 56% of children compared with 21% of children in the placebo group.[70] Codeine was ineffective compared with placebo against the acute cough of the common cold,[71] while dextromethorphan has some effect in a meta-analysis,[72] but not in two smaller studies.[73,74] In a study of 100 children, dextromethorphan or diphenhydramine given as a single dose before bedtime was found to be no better than placebo in providing nocturnal symptom relief for children with cough and sleep difficulty from an upper respiratory tract infection.[75] Instead, a subsequent study showed that buckwheat honey provided symptomatic relief,[76] but a placebo effect was not excluded. The American Academy of Pediatrics has highlighted the fact that the efficacy of antitussive preparations in children is lacking and that these medications may be potentially harmful.[77] Their recommendation is that cough due to acute viral airway infections is self-limiting and may be treated with fluids and humidity.

A first-generation antihistamine and decongestant has been proposed for the treatment of cough associated with a postnasal drip in acute cough,[69] but a study using a newer-generation antihistamine, loratidine, in combination with a decongestant showed no effect.[78] The rhinitis associated with the common cold may become mucopurulent, but this is not an indication for antibiotic therapy unless this persists for more than 10 to 14 days.

Chronic Cough

Chronic cough (cough that persists for more than 3 weeks) can be caused by many diseases, but according to several series, it is most commonly due to asthma, GER, postnasal drip (rhinosinusitis), chronic bronchitis, and bronchiectasis.[64,79]

Postnasal Drip (Rhinosinusitis, Upper Respiratory Tract Syndrome)

Postnasal drip has been reported as being the most common cause of chronic cough.[79,80] The strong association between postnasal drip and chronic persistent cough is based on epidemiologic evidence and on a prospective study in adults. Postnasal drip ("nasal catarrh") is characterized by a sensation of nasal secretions or of a "drip" at the back of the throat, accompanied very often by frequent need to clear the throat ("throat-clearing"). There may be a nasal quality to the voice due to concomitant nasal blockage and congestion, and there may be hoarseness of the voice. Physical examination of the pharynx is often unremarkable although a "cobblestoning" appearance of the mucosa and draining secretions may be observed. Computed tomography of the sinuses may reveal mucosal thickening or sinus opacification and air-fluid levels. Extrathoracic variable upper airway obstruction is not invariably present.[81] Testing for allergens may be helpful, and the presence of allergy to pollens supports the presence of seasonal allergic rhinitis.

Topical administration of corticosteroid drops in the head-down position is the best treatment, often with the concomitant use of antihistamines. Topical steroids offer a local effect with the minimum of side effects. Occasionally, severe symptoms may be controlled initially by a short course of oral steroids, followed by topical therapy. A topical anticholinergic spray to the nose (such as ipratropium bromide) to dry excessive nasal secretions may provide additional benefit. Topical decongestant vasoconstrictor sprays may be useful adjunct therapy for a few days, but rebound nasal obstruction may occur after prolonged use. Antibiotic therapy is necessary in the presence of acute sinusitis involving bacterial infection with the presence of mucopurulent secretions that has persisted for at least 10 days.

Asthma and Associated Eosinophilic Conditions

Chronic cough may occur in asthma under different clinical settings. Asthma may present predominantly with cough, often nocturnal, and the diagnosis is supported by the presence of reversible airflow limitation and bronchial hyperresponsiveness.[82] This condition of "cough-variant" asthma is a common type of asthma in children. Elderly asthmatics may also give a history of chronic cough prior to a diagnosis of asthma made on the basis of episodic wheeze. Cough as the only presenting symptom of asthma has been reported in up to 57% of patients and is often its most prominent symptom.[83] Atopic cough is recognized in Japan as an isolated chronic cough characterized by an atopic background, sputum eosinophilia, cough hypersensitivity, normal pulmonary function, and airway hyperresponsiveness.[84]

Eosinophilic bronchitis is characterized by cough without asthma symptoms or bronchial hyperresponsiveness but with eosinophilia in sputum.[85] Cough may also occur as a first sign of worsening of asthma usually presenting first at night, associated with other symptoms such as wheeze and shortness of breath with falls in early morning peak flows. Some patients with asthma may also develop a persistent dry cough despite good control of their asthma with antiasthma therapy.

Patients with asthma do not usually have an enhanced cough reflex, although a subgroup with a persistent cough may do so.[86] In these latter patients, cough sensors may be sensitized by inflammatory mediators such as bradykinin, tachykinins, and prostaglandins. Cough in asthma may also be due to bronchial smooth muscle contraction, which may activate cough receptors through physical deformation. Indeed, in some patients with cough-variant asthma, β-adrenergic bronchodilators are effective antitussives.[87] A predominance of eosinophils in induced sputum and bronchial biopsies, together with a thickened basement membrane and bronchial hyperresponsiveness, is present in cough-variant asthma. In eosinophilic bronchitis, conversely, cough responsiveness to capsaicin is increased without bronchial hyperresponsiveness, but the immunopathologic abnormalities are similar to those of asthma.[88]

Cough associated with asthma should be treated with antiasthma medication including inhaled corticosteroid therapy and bronchodilators such as β_2-adrenergic agonists. Such treatment should be given over a prolonged period of time (3–6 months) at a minimum dose that controls the cough. Often, a trial of oral corticosteroids (e.g., prednisolone 40 mg/day for 2 weeks) may be recommended, particularly in those asthmatics that have had a cough despite being on adequate antiasthma medication. A combination of inhaled corticosteroids and a long-acting β-agonist is now the best available maintenance treatment for moderate-to-severe asthma. Leukotriene receptor antagonists may control cough-variant asthma. Eosinophilic bronchitis responds well to inhaled or oral corticosteroid therapy.

Gastroesophageal Reflux

GER, the movement of acid and other components of gastric contents from the esophagus into the larynx and trachea, is one of the most commonly associated causes of chronic cough in all age groups. GER may lead to symptoms of physical complications such as heartburn, chest pain, a sour taste, or regurgitation, and also a chronic persistent cough. There may also be no symptoms associated with GER or impaired clearance of esophageal acid. Prolonged exposure of the lower esophagus to acid may lead to esophagitis, Barrett's esophagus, esophageal ulceration and stricture, and bleeding. An esophageal-tracheobronchial cough reflex mechanism has been proposed on the basis of studies in which distal esophageal acid perfusion induced coughing episodes in such patients that was suppressed by local distal esophageal perfusion of lidocaine and by an inhaled anticholinergic agent, ipratropium bromide.[89] Over 90% of the cough episodes have been shown to be temporally related to reflux episodes. Significant reflux occurs in both supine and upright positions. A high proportion of patients with GER also appear to have gastrohypopharyngeal reflux, and there may be a direct effect of acid reflux on cough receptors in the larynx and trachea. Coughing itself may precipitate reflux, setting a vicious circle of acid inducing–cough that in turn induces acid reflux. Continuous monitoring of tracheal and esophageal pH in patients with symptomatic GER has demonstrated significant increases in tracheal acidity with pH's falling down to 4 or less during episodes of reflux.[90] Other components of the refluxate, apart from acid, such as the content of pepsin or other enzymes may also contribute to cough, but the importance of this contribution is not yet established.

There is no particular specific pattern of the cough of GER. The cough may be long-standing and may be productive. In the presence of reflux and microaspiration, laryngeal symptoms may be present with dysphonia, hoarseness, and sore throat; often, posterior vocal cord laryngeal inflammation is visible. There may be associated esophageal dysmotility characterized by heart burn, water brash, and oral regurgitation, worse in the supine position. Esophageal dysmotility may occur in the absence of acid reflux.[91]

The most specific test for GER is a 24-hour ambulatory esophageal pH monitoring examining for episodes of pH below 4 and for the temporal relationship between cough and falls in pH. However, there is a low frequency of acid reflux episodes associated in time with cough with only up to 13% of coughs occurring shortly after an acid reflux episode.[92] Positive predictive values for the use of esophageal pH monitoring are reported to be between 68% and 100%, and a negative test nearly excludes GER as the cause of cough. Other tests that may be used are esophageal manometry to measure dysmotility, particularly associated with reflux episodes; upper gastrointestinal contrast series to detect reflux of barium into the esophagus; or an upper gastrointestinal endoscopy. A trial of antireflux treatment with a proton pump inhibitor or a histamine H_2-antagonist may be used in patients as a diagnostic measure where ambulatory 24-hour pH esophageal monitoring is not available. This may also be indicated in patients with chronic cough that remains unexplained after diagnostic workup or exclusion of other associated causes.

The aim of treatment of GER is to decrease the frequency and duration of the events. Conservative measures such as weight reduction; high-protein, low-fat diet; elevation of the head of the bed; avoidance of coffee and smoking should be advocated. Reduction of acid production by the stomach can be achieved with either H_2-histamine blockers or proton pump inhibitors, but there have been no comparative studies. Given the increasing use of proton pump inhibitors and their superior effect in acid suppression and in treating GER, these drugs will remain the preferred choice. Although initial uncontrolled studies have provided very optimistic effects of histamine H2-receptor antagonists or proton pump inhibitors in controlling the cough associated with GER, double-blind placebo studies[93,94] report more limited effects. Of 17 patients with a positive pH test, 6 had improvement or resolution of cough with omeprazole treatment for 12 weeks within the first 2 weeks of treatment.[93] In another trial, omeprazole 40 mg/day for 8 weeks partly relieved GER-related cough.[94] A 3 months, treatment at the highest recommended dose of a proton pump inhibitor is usually advocated. Not all patients respond and, in some, the response is only partial. One of the reasons for this failure may be the effect of the nonacid refluxate. Antireflux surgery such as open or laparoscopic fundoplication may be considered for patients with proven GER disease whose cough has failed to respond to medical therapy.[95] The effect of specific treatments for esophageal dysmotility is not known.

Chronic Bronchitis/Chronic Obstructive Pulmonary Disease

Although 30% to 40% of the community smokes, chronic bronchitis is only reported in 5% of the patients seeking medical attention for cough. Chronic bronchitis should be considered in a patient who produces sputum on most days over at least 3 consecutive months, particularly during the winter months, over at least 2 consecutive years. In a smoker, the presence of chronic bronchitis may be predictive of progressive irreversible airflow obstruction.[96] The cough of chronic bronchitis may result from excessive sputum production associated with mucus cell hyperplasia and bronchiolar inflammation. The presence of airflow obstruction diagnosed on the basis of a ratio of forced expiratory volume in 1 second to forced vital capacity (FEV_1/FVC) of less than 70% or of an FEV_1 of less than 70% of the predicted value indicates the onset of COPD.[97]

The productive cough in chronic bronchitis is exacerbated by upper respiratory infections with common viruses or by exposure to irritating dusts or environmental pollutants. Other causes of productive cough should be excluded such as bronchiectasis or postnasal drip. It is important to exclude also the presence of an endobronchial tumor. Cessation of cigarette smoking is usually accompanied by a reduction in cough, occurring most often within 4 to 5 weeks.[98] Various adjuncts such as nicotine replacement or bupropion or varenicline, a nicotine receptor partial agonist, may help smoke cessation.[99] Treatment of any associated chronic airflow obstruction with short-acting or/and long-acting β_2-adrenoceptor agonists and anticholinergic agents should be considered particularly in the presence of dyspnea. Suppression of the inflammatory process in the small airways may be tried with the combination of inhaled corticosteroids and long-acting β-agonist. Oral or systemic corticosteroids are effective in the treatment of exacerbations of COPD. Mucolytic therapy may reduce the incidence of exacerbations. Use of indirect (symptomatic) antitussive therapies is not recommended but may be needed in excessive coughing.

Bronchiectasis

The cough of bronchiectasis is associated with overproduction of airway secretions together with a reduced clearance, often with a vicious circle of recurrent bacterial infections. Usually, the patient produces 30 mL or more of mucoid or mucopurulent sputum per day, sometimes accompanied by fever, hemoptysis, and weight loss. In early cases of bronchiectasis, the condition may be present only with a persistent productive cough. Bronchiectasis may be associated with postnasal drip and rhinosinusitis, asthma, GER disease, and chronic bronchitis. Common pathogens cultured from sputum include *Haemophilus influenzae*, *Staphyloccocus aureus*, and *Pseudomonas aeroginusa*. The chest radiograph may show increased bronchial wall thickening, particularly in the lower lobes in advanced cases, but thin-section computed axial tomography of the chest can reveal early changes of intrapulmonary airway wall thickening, dilation, and distortion, with mucus plugging, and evidence of bronchiolitis.[100]

Cough in bronchiectasis is the most effective mechanism for clearing airway secretions. In addiction, there is an increased capsaicin cough response in bronchiectasis.[101] Cough during infective exacerbations of bronchiectasis may become a tiring symptom, and specific treatment of the exacerbation leads to a reduction of

cough. The cough due to bronchiectasis may be controlled with inhaled β_2-agonists that improve mucociliary clearance and reverse any associated bronchoconstriction by postural drainage of airway secretions and by the use of intermittent antibiotic therapy. Use of antitussives is not recommended, but in the context of severe cough, some suppressive effect may be clinically beneficial.

Angiotensin-Converting Enzyme Inhibitor Cough

ACE inhibitors are often prescribed for the treatment of hypertension and heart failure, and cough has been observed in 2% to 33% of patients.[102,103] The cough is typically described as "dry," associated with a tickly irritating sensation in the throat. It may appear within a few hours of taking the drug, but may also become apparent only after weeks or even months. The cough disappears within days or weeks following withdrawal of drug. Patients with ACE inhibitor cough demonstrate an enhanced response to capsaicin inhalation challenge. Accumulation of bradykinin and prostaglandins, which sensitize cough receptors directly, has been implicated. The best course of action for ACE inhibitor cough is to discontinue the treatment and to replace it with alternative therapies such as angiotensin II receptor antagonists, which are not associated with cough.

Postinfectious Cough

Postinfectious cough has been reported from 11% to 25% of patients with chronic cough.[104,105] A persistent cough occurs in 25% to 50% of patients following *Mycoplasma* or *Bordetella pertussis* infection.[106] *B. pertussis* infection has now been increasingly recognized as a cause of both acute and chronic cough, particularly in older children and in adults.[107] In children, other respiratory infections associated with chronic cough include viruses (respiratory syncytial virus and parainfluenzae), *Mycoplasma*, and *Chlamydiae*.[108] The cough of *B. pertussis* usually lasts for only 4 to 6 weeks, is spasmodic with a typical whoop, but can last for a longer period of time. In most patients with a postinfectious cough, the initial trigger is usually an upper respiratory tract infection, and cough that is expected to have lasted for only a week at most persists for many months, often severe. Such patients are often referred to a cough clinic and are usually investigated for the more commonly associated cause of cough. It is assumed that there may have been persistent damage to the airways containing the cough sensors or persistent airway inflammation induced initially by the virus. Bronchial epithelial inflammation and damage are present in children with chronic cough following lower respiratory tract illness. Irritants may penetrate more readily through the damaged epithelium. This may represent a vicious circle of events of coughing-induced damage that maintains and triggers further cough. Inhaled corticosteroids are often prescribed, but with variable success. Oral steroids may be successful.[104] Inhaled ipratropium bromide was reported to be effective in a small study.[109] Macrolide antibiotics or trimethoprin/sulfamethoxazole are effective in eliminating *B. pertussis* but do not alter subsequent clinical course.[110]

Other Conditions

Other conditions causing cough include bronchogenic carcinoma, metastatic carcinoma, sarcoidosis, chronic aspiration, interstitial lung disease, or left ventricular failure, conditions that can usually be excluded by performing a chest radiograph. Psychogenic or habit cough is not uncommon particularly in children, and is usually a diagnosis arrived at after exclusion of other causes. Habit cough is a throat-clearing noise made by a person who is nervous and self-conscious. Cough may be associated with a depressive illness and long-standing cough may cause depression. In the pediatric population, other cough etiologies specific for this age group need to be considered such as congenital abnormalities, for example, vascular rings, tracheobronchomalacia, pulmonary sequestration or mediastinal tumors, foreign bodies in the airway or esophagus, aspiration due to poor coordination of swallowing or esophageal dysmotility, and heart disease.

Chronic Persistent Cough of Unknown Cause ("Idiopathic" Cough)

Identification of a potential cause of cough has been reported in 78% to 99% of patients presenting at a cough clinic, and specific treatment of identifiable causes has also been reported to be successful in up to 69% to 99% of cases.[79,111] However, more recent series have identified 7% to 46% of patients with chronic cough as having idiopathic cough, despite undergoing thorough diagnostic evaluation.[8] The high success rates reported in some centers versus the lower success rates in others remain unexplained, but possibly relates to the definition of successful treatment and the case mix. The patient with idiopathic cough should be diagnosed as such only after an intensive diagnostic evaluation with empirical trial of therap(ies) has (have) been carried out.

These patients with a persistent cough of unknown cause or not responding to treatment of associated causes present in a similar way as others in terms of their cough symptoms where a cause has been identified. However, it is reported that they tend to be middle-aged women who frequently give a history of cough onset at the menopause and can have associated autoimmune disorders such as autoimmune hypothyroidism.[112] An enhanced cough reflex is usually found, and this usually improves when the associated cause has been successfully treated. Patients with an enhanced cough reflex often complain of a persistent tickling sensation in the throat that often leads to paroxysms of coughing. This sensation can be triggered by factors such as changes in ambient temperature, taking a deep breath, laughing, talking over the phone for a few minutes, and exposure to cigarette smoke or other irritants such as aerosol sprays or perfumes or to certain odors. Mucosal biopsies taken from a group of nonasthmatic patients with idiopathic cough showed evidence of increased mast cells

and of airway wall remodeling features such as increased subbasement membrane thickening, increased airway smooth muscle mass, goblet cell hyperplasia, and increased blood vessels.[113] These changes could represent the sequelae of chronic trauma to the airway wall following intractable cough, and could in turn lead to sensitization of the cough reflex. There is an increase in neural profiles that express the neuropeptide, calcitonin gene–related peptide (CGRP), and the calcium channel, TRPV1, in the airway epithelium of chronic coughers that could contribute to the increased cough reflex.[114,115]

COUGH SUPPRESSION THERAPIES

"Symptomatic," "Indirect," or "Nonspecific" Antitussives

When the treatment of the cause of cough is not effective or not available, therapies directed at eliminating the symptom of cough irrespective of the cause of the cough may be tried (Table 29-4). These therapies are also termed "symptomatic," "indirect," or "nonspecific" antitussives. This is particularly relevant to patients with lung cancer with a persistent cough, of whom 50% rate their cough as moderate to severe,[116] and in many other conditions with chronic cough where specific therapies do not lead to cough control or do not exist. Drugs that affect the complex mechanism of the cough reflex may act by inhibition of central mechanisms within the brain stem or of peripheral mechanisms on the cough sensors in the airways. Because of the relative low efficacy of current antitussives, several new classes of antitussives are being developed, based on our understanding of the cough reflex and of the membrane receptors and channels on cough sensors.[7,117,118] A summary of the existing direct and indirect antitussives and their potential modes and sites of actions are shown in Figure 29-5.

TABLE 29-4. Treatments for Cough

1. TREATING THE SPECIFIC UNDERLYING CAUSE(S)	
Asthma, cough-variant asthma	Bronchodilators and inhaled corticosteroids
Eosinophilic bronchitis	Inhaled corticosteroids; leukotriene inhibitors
Allergic rhinitis and postnasal drip	Topical nasal steroids and antihistamines
	Topical nasal anticholinergics (with antibiotics, if indicated)
Gastroesophageal reflux	Conservative measures
	Histamine H_2 antagonist or proton pump inhibitor
Angiotensin-converting enzyme inhibitor	Discontinue and replace with alternative drug such as angiotensin II receptor antagonist
Chronic bronchitis/COPD	Smoking cessation.
	Treat for COPD
Bronchiectasis	Postural drainage. Treat infective exacerbation and airflow obstruction.
Infective tracheobronchitis	Appropriate antibiotic therapy
	Treat any postnasal drip
2. SYMPTOMATIC TREATMENT (ONLY AFTER CONSIDERATION OF CAUSE OF COUGH)	
Acute cough likely to be transient (e.g., upper respiratory viral infection)	Simple linctus
Persistent cough particularly nocturnal	Opiates (codeine or pholcodeine)
Persistent intractable cough due to terminal incurable disease	Opiates (morphine or diamorphine)
	Local anesthetic aerosol
Cough in children	Simple linctus (pediatric)

COPD, chronic obstructive pulmonary disease.

Narcotic and Non-narcotic Antitussives

Opiates including morphine, diamorphine, and codeine are the most effective antitussive agents.* At their effective doses, they cause physical dependence, respiratory depression, and gastrointestinal colic. Morphine and diamorphine are reserved for the control of cough and pain of terminal bronchial cancer patients, but codeine, dihydrocodeine, and pholcodeine can be tried in other cases of chronic cough. Codeine is the methylether of morphine and has long been the standard centrally acting antitussive drug against which the pharmacologic and clinical effects of newer drugs have been measured. Codeine is probably the most commonly prescribed antitussive. It has some antitussive activity, compared with placebo when given orally. Although codeine possesses antitussive activity against pathologic cough[118] and against induced cough in normal volunteers,[119] a recent study suggested, contrary to earlier evidence, that it had little effect on cough in selected COPD patients[120] or against acute cough of the common cold[71] compared with placebo.

It should be used cautiously in patients with reduced hepatic function, but it can be used without dose modification in patients with renal failure. Drowsiness may be an incapacitating side effect, together with nausea, vomiting, and constipation. Rarely, allergic cutaneous reactions such as erythema multiforme have been described. Codeine can cause physical dependence, but on a smaller scale than morphine. Dihydrocodeine has no particular advantage over codeine and may cause more addiction than codeine. Pholcodeine is also as effective as codeine but has little or no analgesic effect.

Morphine and diamorphine should be used only for severe distressing cough that cannot be relieved by other less potent antitussives and are therefore usually confined to patients with terminal illness such as bronchial carcinoma. These opioids also relieve anxiety and pain. They cause sedation, respiratory depression, and constipation. Opioids can exacerbate wheezing through the release of histamine, but this is rare. Diamorphine may be preferred to morphine because of its lower incidence

*Diamorphine is not prescribable in the United States.

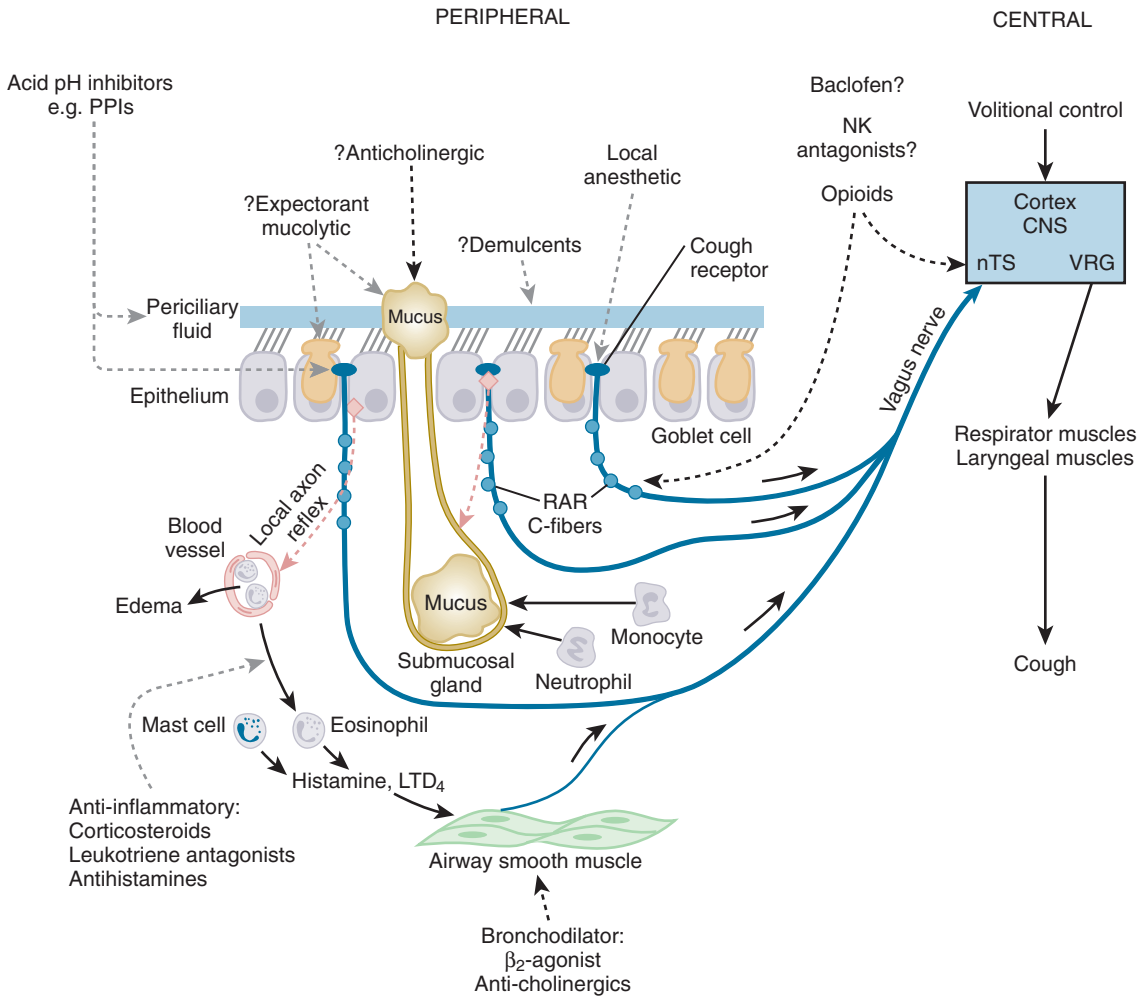


FIGURE 29-5 ■ Afferent pathways of the cough reflex and some potential sites of action of direct and indirect antitussive drugs. Drugs may be divided according to their peripheral effects on airways or to their central effects in the central nervous system (CNS). LTD_4, leukotriene D_4; NK, neurokinin; nTS, nucleus tractus solitarius; PPI, proton pump inhibitor; RAR, rapidly adapting receptors; VRG, ventral respiratory group. (Redrawn from Chung KF: Management of cough. *In* Chung KF, Widdicombe JG, Boushey HA [eds]: Cough: Causes, Mechanisms and Therapy. Oxford: Blackwell, 2003, pp 283–297.)

of nausea and vomiting. Morphine is usually given as a slow-release oral preparation, and has been shown to be efficacious in severe intractable cough.[121] Diamorphine is preferably given by injection.

Dextromethorphan is a non-narcotic antitussive, a synthetic derivative of morphine with no analgesic or sedative properties, and is usually included as a constituent of many compound cough preparations sold over the counter. It is as effective as codeine in suppressing acute and chronic cough when given orally,[122,123] with one study showing its superiority over codeine.[124] Antitussive efficacy of a single 30-mg dose has been demonstrated against cough associated with upper respiratory tract infections.[72] However, in children, dextromethorphan has been shown to be ineffective in providing any symptomatic relief in cough due to upper respiratory tract infections.[75,76] It is commonly used as a constituent of many compound cough preparations that are sold over the counter. Side effects are few at the usual dose, but at higher doses, dizziness, nausea, vomiting, and headaches may occur. It should be avoided in patients with hepatic insufficiency as it undergoes metabolic degradation in the liver. The American Academy of Pediatrics has highlighted the potential adverse effects and overdosage associated with antitussive preparations containing dextromethorphan in children,[77] where dextromethorphan has been shown to be ineffective in cough due to upper respiratory tract infections.[75,76] Dextromethorphan should be used with caution also in patients on monoamine oxidase inhibitors as cases of central nervous depression and death have occurred.

Other non-narcotic preparations include noscapine and levopropoxyphene, although their antitussive efficacy has not been proved. Levodropropizine, a nonopioid antitussive with peripheral inhibition of sensory cough receptors, has a favorable benefit/risk profile compared with dextromethorphan.[125] Other drugs acting on cough receptors include benzonatate, which inhibits vagal stretch lung receptors, with a possible central effect.

Of the potentially new antitussives is baclofen which is an agonist of gamma-aminobutyric acid, an inhibitory neurotransmitter. It showed demonstrable inhibitory effects in two patients with chronic cough[126] and against ACE inhibitor cough,[127] but there have been no clinical trials yet.

Local Anesthetics

Lidocaine aerosol inhaled from a nebulizer has been administered to cases of intractable cough with variable results, and should be reserved for such individual cases.[128] It works by inhibiting sensory neural activity, but also removes reflexes that protect the lung from noxious substances. Its effects are transient and they should be avoided in patients with asthma or a past history of asthma because they can induce severe bronchoconstriction. There have been no controlled trials of local anesthetics, but their efficacy in controlling cough is not ideal because of their short duration of effect.

Expectorants and Mucolytics

Expectorants and mucolytics may alter the volume of secretions or their composition. Despite the lack of proof, mucolytic agents such as acetylcysteine, carbocisteine, bromhexine, and methylcysteine are often used to facilitate expectoration by reducing sputum viscosity in patients with chronic bronchitis. A small reduction in the exacerbation of bronchitis has been reported with oral acetylcysteine, accompanied by small improvement in cough, a decrease in volume of sputum, and some ease of expectoration. Aromatic agents such as eucalyptus and menthol have decongestant effects in the nose and can be useful in short-term relief of cough. Menthol inhibits capsaicin-induced cough in normal volunteers[129] and acts on a cold-sensitive receptor. Demulcents also form an important component of many proprietary cough preparations and may be useful because the thick sugary preparation may act as a protective layer on the mucosal surface.

Potential New Antitussives

The medical literature contains reports of potential antitussive activities of several existing drugs marketed for other purposes. Positive reports of the effects of the tricyclic antidepressant amitriptyline in open studies have been reported, but a proper blind, placebo-controlled study is needed. The antidepressant paroxetine, a serotonin reuptake inhibitor, the antiepileptic therapies gabapentin and carbamazepine, and the antispasticity agent baclofen, an agonist of the $GABA_B$ receptor have also been reported to be beneficial in some reports. New cough suppressants[130] are also being developed that include new opioids or blockers of TRPV-1 and other vanniloid receptors[117,131] or of specific sodium channels.[132] The search for newer effective antitussives is ongoing.

KEY POINTS

- Cough may also be a sign of disease in or outside the airways and lungs and a useful indicator for both patient and physician for initiating diagnosis and treatment of disease processes.
- Impairment or absence of coughing can be harmful or even fatal in disease.
- When cough itself is persistent and excessive, it can be harmful and deleterious and may need to be suppressed directly.
- The most sensitive sites for initiating cough are the larynx and the tracheobronchial tree.
- In the management of a patient with cough, the first step is to identify the cause of the cough and then treat the cause.
- Many cigarette smokers have a chronic cough, a change in the pattern or characteristics of their cough such as an increase in intensity (usually after an upper respiratory tract infection), or accompanying hemoptysis may force a smoker to seek medical attention. A chest radiograph is mandatory in this situation.
- Patients on ACE inhibitor therapy should discontinue such therapy, with replacement by other appropriate treatments.
- Postnasal drip, asthma, and GER are the three most common conditions associated with a chronic cough, and a diagnostic approach to exclude these conditions first is sensible.
- When the treatment of the cause of cough is not effective, therapies directed at eliminating the symptom of cough irrespective of the cause of the cough may be tried (see Table 29-4).

References

1. Cullinan P: Persistent cough and sputum: Prevalence and clinical characteristics in south east England. Respir Med 86:143–149, 1992.
2. Barbee RA, Halonen M, Kaltenborn WT, Burrows B: A longitudinal study of respiratory symptoms in a community population sample. Correlations with smoking, allergen skin-test reactivity, and serum IgE. Chest 99:20–26, 1991.
3. Lundback B, Nystrom L, Rosenhall L, Stjernberg N: Obstructive lung disease in northern Sweden: Respiratory symptoms assessed in a postal survey. Eur Respir J 4:257–266, 1991.
4. Prezant DJ: World Trade Center Cough Syndrome and its treatment. Lung 186(Suppl 1):S94–S102, 2008.
5. Chung KF, Widdicombe JG (eds): Pharmacology of cough. Berlin: Springer-Verlag, 2009, pp 1–389.
6. Chung KF, Widdicombe JG, Boushey H (eds): Cough: Causes, Mechanisms and Therapy. Oxford: Blackwell Publishing, 2003, pp 1–304.
7. Pavord ID, Chung KF: Management of chronic cough. Lancet 371:1375–1384, 2008.
8. Chung KF, Pavord ID: Prevalence, pathogenesis, and causes of chronic cough. Lancet 371:1364–1374, 2008.
9. Morice AH, Fontana GA, Sovijarvi AR, et al: The diagnosis and management of chronic cough. Eur Respir J 24:481–492, 2004.
10. Irwin RS: Assessing cough severity and efficacy of therapy in clinical research: ACCP evidence-based clinical practice guidelines. Chest 129:232S–237S, 2006.
11. Dicpinigaitis PV: The First American Cough Conference. New York City, June 8–9, 2007. Lung 186(Suppl 1):S1–S2, 2008.
12. Chung KF, Widdicombe JG (eds): The 2008 Fifth International Symposium on Cough. Pulm Pharmacol Ther 22:57–165, 2009.
13. Widdicombe JG: Neurophysiology of the cough reflex. Eur Respir J 8:1193–1202, 1995.
14. Widdicombe J, Fontana G: Cough: What's in a name? Eur Respir J 28:10–15, 2006.
15. Tatar M, Hanacek J, Widdicombe J: The expiration reflex from the trachea and bronchi. Eur Respir J 31:385–390, 2008.
16. Kelsall A, Decalmer S, Webster D, et al: How to quantify coughing: Correlations with quality of life in chronic cough. Eur Respir J 32:175–179, 2008.
17. Davenport PW: Urge-to-cough: What can it teach us about cough? Lung 186(Suppl 1):S107–S111, 2008.
18. Mazzone SB, McLennan L, McGovern AE, et al: Representation of capsaicin-evoked urge-to-cough in the human brain using functional magnetic resonance imaging. Am J Respir Crit Care Med 176:327–332, 2007.
19. Widdicombe JG: Afferent receptors in the airways and cough. Respir Physiol 114:5–15, 1998.
20. Lee PC, Cotterill-Jones C, Eccles R: Voluntary control of cough. Pulm Pharmacol Ther 15:317–320, 2002.
21. Eccles R: Placebo effects of antitussive treatments on cough associated with upper respiratory tract infection. *In* Chung KF, Widdicombe JG, Boushey HA (eds): Cough: Causes, Mechanisms and Therapy. Oxford: Blackwell, 2003, pp 259–268.
22. Karlsson J-A, Sant'Ambrogio G, Widdicombe J: Afferent neural pathways in cough and reflex bronchoconstriction. J Appl Physiol 65:1007–1023, 1988.
23. Sant'Ambrogio G, Sant'Ambrogio FB: Role of laryngeal afferents in cough. Pulm Pharmacol 9:309–314, 1996.
24. Nishino T, Tagaito Y, Isono S: Cough and other reflexes on irritation of airway mucosa in man. Pulm Pharmacol 9:285–292, 1996.
25. Widdicombe JG: Functional morphology and physiology of pulmonary rapidly adapting receptors (RARs). Anat Rec 270A:2–10, 2003.
26. Sant'Ambrogio G: Nervous receptors of the tracheobronchial tree. Annu Rev Physiol 49:611–627, 1987.
27. Widdicombe JG: Reflexes from the upper respiratory tract. *In* Cherniack NS, Widdicombe JGE (eds): Handbook of Physiology. Section 3. Respiration. Vol 2: Control of Breathing. Bethesda, MD: American Physiological Society, 1986, pp 363–394.
28. Addington WR, Stephens RE, Gilliland K, Miller SP: Tartaric acid-induced cough and the superior laryngeal nerve evoked potential. Am J Phys Med Rehabil 77:523–526, 1998.
29. Undem BJ, Carr MJ, Kollarik M: Physiology and plasticity of putative cough fibres in the Guinea pig. Pulm Pharmacol Ther 15:193–198, 2002.
30. Undem BJ, Chuaychoo B, Lee MG, et al: Subtypes of vagal afferent C-fibres in guinea-pig lungs. J Physiol 556:905–917, 2004.
31. Mazzone SB, Canning BJ: Plasticity of the cough reflex. Eur Respir Rev 12:236–242, 2002.
32. Mazzone SB, Canning BJ, Widdicombe JG: Sensory pathways for the cough reflex. *In* Chung KF, Widdicombe JG, Boushey HA (eds): Cough: Causes, Mechanisms and Therapy. Oxford: Blackwell, 2003, pp 161–172.
33. Canning BJ, Mori N, Mazzone SB: Vagal afferent nerves regulating the cough reflex. Respir Physiol Neurobiol 152:223–242, 2006.
34. Canning BJ: Encoding of the cough reflex. Pulm Pharmacol Ther 20:396–401, 2007.
35. Carr MJ: Plasticity of the afferent innervation of the airways: the role of ion channels. Pulm Pharmacol Ther 20:412–415, 2007.
36. Canning BJ: Interactions between vagal afferent nerve subtypes mediating cough. Pulm Pharmacol Ther 15:187–192, 2002.
37. Kollarik M, Undem BJ: Plasticity of vagal afferent fibres mediating cough. *In* Chung KF, Widdicombe JG, Boushey HA (eds): Cough: Causes, Mechanisms and Therapy. Oxford: Blackwell, 2003, pp 181–192.
38. Carr MJ, Ellis JL: The study of airway primary afferent neuron excitability. Curr Opin Pharmacol 2:216–219, 2002.
39. Undem BJ, Kollarik M: Characterization of the vanilloid receptor 1 antagonist iodo-resiniferatoxin on the afferent and efferent function of vagal sensory C-fibers. J Pharmacol Exp Ther 303:716–722, 2002.
40. Hwang SW, Oh U: Hot channels in airways: pharmacology of the vanilloid receptor. Curr Opin Pharmacol 2:235–242, 2002.
41. Belvisi MG: Preclinical assessment of novel therapeutics on the cough reflex: Cannabinoid agonists as potential antitussives. Lung 186(Suppl 1):S66–S69, 2008.
42. Mazzone SB, Undem BJ: Cough sensors. V: Pharmacological modulation of cough sensors. *In* Chung KF, Widdicombe JG (eds): Pharmacology of Cough. Berlin: Springer Verlag, 2009, pp 99–128.
43. Bolser DC, Davenport PW, Golder FJ, et al: Neurogenesis of cough. *In* Chung KF, Widdicombe JG, Boushey HA (ed): Cough: Causes, Mechanisms and Therapy. Oxford: Blackwell, 2003, pp 173–180.
44. Shannon R, Baekey DM, Morris KF, Lindsey BG: Ventrolateral medullary respiratory network and a model of cough motor pattern generation. J Appl Physiol 84:2020–2035, 1998.
45. Shannon R, Baekey DM, Morris KF, et al: Functional connectivity among ventrolateral medullary respiratory neurones and responses during fictive cough in the cat. J Physiol 525(Pt 1):207–224, 2000.
46. Bolser DC, Davenport PW: Expiratory muscle control during the cough reflex. Eur Respir Rev 12:243–248. 2002.
47. Baekey DM, Morris KF, Nuding SC, et al: Ventrolateral medullary respiratory network participation in the expiration reflex in the cat. J Appl Physiol 96:2057–2072, 2004.
48. Bolser DC: Experimental models and mechanisms of enhanced coughing. Pulm Pharmacol Ther 17:383–388, 2004.
49. Addington WR, Stephens RE, Gilliland KA: Assessing the laryngeal cough reflex and the risk of developing pneumonia after stroke: An interhospital comparison. Stroke 30:1203–1207, 1999.
50. Widdicombe J: Neuroregulation of cough: implications for drug therapy. Curr Opin Pharmacol 2:256–263, 2002.
51. Simonyan K, Saad ZS, Loucks TM, et al: Functional neuroanatomy of human voluntary cough and sniff production. Neuroimage 37:401–409, 2007.
52. Fontana GA: Motor mechanisms and the mechanics of cough. *In* Chung KF, Widdicombe JG, Boushey HA (eds): Cough: Causes, Mechanisms and Therapy. Oxford: Blackwell, 2003, pp 193–206.
53. Bonham AC, Sekizawa SI, Joad JP: Plasticity of central mechanisms for cough. Pulm Pharmacol Ther 17:453–457, 2004.
54. German VF, Ueki IF, Nadel JA: Micropipette measurement of airway submucosal gland secretion: Laryngeal reflex. Am Rev Respir Dis 122:413–416, 1980.
55. Leith DE, Butler JP, Sneddon SI: Cough. *In* Cherniack NS, Fishman AP, Widdicombe JG (eds): Handbook of Physiology. Section 3:

Respiration. Vol 3: Mechanisms of Breathing (Part 1). Baltimore: American Physiological Society, 1986, pp 315–336.
56. Smyrnios NA, Irwin RS, Curley FJ: Chronic cough with a history of excessive sputum production. The spectrum and frequency of causes, key components of the diagnostic evaluation, and outcome of specific therapy. Chest 108:991–997, 1995.
57. McGarvey LP, Heaney LG, Lawson JT, et al: Evaluation and outcome of patients with chronic non-productive cough using a comprehensive diagnostic protocol. Thorax 53:738–743, 1998.
58. French CT, Irwin RS, Fletcher KE, Adams TM: Evaluation of a cough-specific quality-of-life questionnaire. Chest 121:1123–1131, 2002.
59. Birring SS, Prudon B, Carr AJ, et al: Development of a symptom specific health status measure for patients with chronic cough: Leicester Cough Questionnaire (LCQ). Thorax 58:339–343, 2003.
60. Matos S, Birring SS, Pavord ID, Evans DH: An automated system for 24-h monitoring of cough frequency: the Leicester cough monitor. IEEE Trans. Biomed. Eng 54:1472–1479, 2007.
61. Coyle MA, Keenan DB, Henderson LS, et al: Evaluation of an ambulatory system for the quantification of cough frequency in patients with chronic obstructive pulmonary disease. Cough 1:3, 2005.
62. Chung KF: Measurement of cough. Respir Physiol Neurobiol 152:329–339, 2006.
63. Choudry NB, Fuller RW: Sensitivity of the cough reflex in patients with chronic cough. Eur Respir J 5:296–300, 1992.
64. O'Connell F, Thomas VE, Pride NB, Fuller RW: Capsaicin cough sensitivity decreases with successful treatment of chronic cough. Am J Respir Crit Care Med 150:374–380, 1994.
65. Nichol G, Nix A, Barnes PJ, Chung KF: Prostaglandin F2 alpha enhancement of capsaicin induced cough in man: Modulation by beta 2 adrenergic and anticholinergic drugs. Thorax 45:694–698, 1990.
66. Fox AJ, Lalloo UG, Bernareggi M, et al: Bradykinin and captopril-induced cough in guinea-pigs. Nat Med 2:814–817, 1996.
67. Birring SS, Fleming T, Matos S, et al: The Leicester Cough Monitor: Preliminary validation of an automated cough detection system in chronic cough. Eur Respir J 31:1013–1018, 2008.
68. Birring SS, Matos S, Patel RB, Prudon B, et al: Cough frequency, cough sensitivity and health status in patients with chronic cough. Respir Med 100:1105–1109, 2006.
69. Curley FJ, Irwin RS, Pratter MR, et al: Cough and the common cold. Am Rev Respir Dis 138:305–311, 1988.
70. Smith SM, Schroeder K, Fahey T: Over-the-counter medications for acute cough in children and adults in ambulatory settings. Cochrane Database Syst Rev 1:CD001831, 2008.
71. Freestone C, Eccles R: Assessment of the antitussive efficacy of codeine in cough associated with common cold. J Pharm Pharmacol 49:1045–1049, 1997.
72. Pavesi L, Subburaj S, Porter-Shaw K: Application and validation of a computerized cough acquisition system for objective monitoring of acute cough: A meta-analysis. Chest 120:1121–1128, 2001.
73. Tukiainen H, Karttunen P, Silvasti M, et al: The treatment of acute transient cough: A placebo-controlled comparison of dextromethorphan and dextromethorphan-beta 2-sympathomimetic combination. Eur J Respir Dis 69:95–99, 1986.
74. Lee PCL, Jawad MS, Eccles R: Antitussive efficacy of dextromethorphan in cough associated with acute upper respiratory tract infection. J Pharm Pharmacol 52:1137–1142, 2000.
75. Paul IM, Yoder KE, Crowell KR, et al: Effect of dextromethorphan, diphenhydramine, and placebo on nocturnal cough and sleep quality for coughing children and their parents. Pediatrics 114:e85–e90, 2004.
76. Paul IM, Beiler J, McMonagle A, et al: Effect of honey, dextromethorphan, and no treatment on nocturnal cough and sleep quality for coughing children and their parents. Arch Pediatr Adolesc Med 161:1140–1146, 2007.
77. Committee on Drugs: Use of codeine- and dextromethorphan-containing cough remedies in children. Pediatrics 99:918–920, 1997.
78. Berkowitz RB, Connell JT, Dietz AJ, et al: The effectiveness of the nonsedating antihistamine loratadine plus pseudoephedrine in the symptomatic management of the common cold. Ann Allergy 63:336–339, 1989.
79. Irwin RS, Curley FJ, French CL: Chronic cough: the spectrum and frequency of causes, key components of the diagnostic evaluation, and outcome of specific therapy. Am Rev Respir Dis 141:640–647, 1990.
80. Mello CJ, Irwin RS, Curley FJ: Predictive values of the character, timing, and complications of chronic cough in diagnosing its cause. Arch Intern Med 156:997–1003, 1996.
81. Irwin RS, Pratter MR, Holland PS, et al: Postnasal drip causes cough and is associated with reversible upper airway obstruction. Chest 85:346–352, 1984.
82. Carrao WM, Braman SS, Irwin RS: Chronic cough as the sole presenting manifestation of bronchial asthma. N Engl J Med 300:633–637, 1979.
83. Osman LM, McKenzie L, Cairns J, et al: Patient weighting of importance of asthma symptoms. Thorax 56:138–142, 2001.
84. Fujimura M, Ogawa H, Nishizawa Y, Nishi K: Comparison of atopic cough with cough variant asthma: Is atopic cough a precursor of asthma? Thorax 58:14–18, 2003.
85. Gibson PG, Dolovich J, Denburgh J, et al: Chronic cough: Eosinophilic bronchitis without asthma. Lancet 1:1246–1247, 1989.
86. Doherty MJ, Mister R, Pearson MG, Calverley PM: Capsaicin responsiveness and cough in asthma and chronic obstructive pulmonary disease. Thorax 55:643–649, 2000.
87. Fujimura M, Kamio Y, Hashimoto T, Matsuda T: Cough receptor sensitivity and bronchial responsiveness in patients with only chronic non-productive cough: Effect of bronchodilator therapy. J Asthma 31:463–472, 1994.
88. Brightling CE, Ward R, Wardlaw AJ, Pavord ID: Airway inflammation, airway responsiveness and cough before and after inhaled budesonide in patients with eosinophilic bronchitis. Eur Respir J 15:682–686, 2000.
89. Ing AJ, Ngu MC, Breslin AB: Pathogenesis of chronic persistent cough associated with gastroesophageal reflux. Am J Respir Crit Care Med 149:160–167, 1994.
90. Jack CIA, Calverley PMA, Donnelly RJ, et al: Simultaneous tracheal and oesophageal pH measurements in asthmatic patients with gastroesophageal reflux. Thorax 50:201–204, 1995.
91. Kastelik JA, Redington AE, Aziz I, et al: Abnormal oesophageal motility in patients with chronic cough. Thorax 58:699–702, 2003.
92. Paterson WG, Murat BW: Combined ambulatory esophageal manometry and dual-probe pH-metry in evaluation of patients with chronic unexplained cough. Dig Dis Sci 39:1117–1125, 1994.
93. Ours TM, Kavuru MS, Schilz RJ, Richter JE: A prospective evaluation of esophageal testing and a double-blind, randomized study of omeprazole in a diagnostic and therapeutic algorithm for chronic cough. Am J Gastroenterol 94:3131–3138, 1999.
94. Kiljander TO, Salomaa ER, Hietanen EK, Terho EO: Chronic cough and gastro-oesophageal reflux: A double-blind placebo-controlled study with omeprazole. Eur Respir J 16:633–638, 2000.
95. Novitsky YW, Zawacki JK, Irwin RS, et al: Chronic cough due to gastroesophageal reflux disease: Efficacy of antireflux surgery. Surg Endosc 16:567–571, 2002.
96. Vestbo J, Lange P: Can GOLD stage 0 provide information of prognostic value in chronic obstructive pulmonary disease? Am J Respir Crit Care Med 166:329–332, 2002.
97. Rabe KF, Hurd S, Anzueto A, et al: Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med 176:532–555, 2007.
98. Wynder EL, Kaufman PL, Lesser RL: A short-term follow-up study on ex-cigarette smokers. With special emphasis on persistent cough and weight gain. Am Rev Respir Dis 96:645–655, 1967.
99. Jorenby DE, Leischow SJ, Nides MA, et al: A controlled trial of sustained-release bupropion, a nicotine patch, or both for smoking cessation. N Engl J Med 340:685–691, 1999.
100. Roberts HR, Wells AU, Milne DG, et al: Airflow obstruction in bronchiectasis: Correlation between computed tomography features and pulmonary function tests. Thorax 55:198–204, 2000.
101. Torrego A, Haque RA, Nguyen LT, et al: Capsaicin cough sensitivity in bronchiectasis. Thorax 61:706–709, 2006.

102. Israili ZH, Hall WD: Cough and angioneurotic edema associated with angiotensin-converting enzyme inhibitor therapy. A review of the literature and pathophysiology. Ann Intern Med 117:234–242, 1992.
103. Berkin KE, Ball SG: Cough and angiotensin converting enzyme inhibition. Br Med J (Clin Res Ed) 296:1279, 1988.
104. Poe RH, Harder RV, Israel RH, Kallay MC: Chronic persistent cough. Experience in diagnosis and outcome using an anatomic diagnostic protocol. Chest 95:723–728, 1989.
105. Hoffstein V: Persistent cough in nonsmoker. Can Respir J 1:40–47, 1994.
106. Davis SF, Sutter RW, Strebel PM, et al: Concurrent outbreaks of pertussis and *Mycoplasma pneumoniae* infection: Clinical and epidemiological characteristics of illnesses manifested by cough. Clin Infect Dis 20:621–628, 1995.
107. Gilberg S, Njamkepo E, Du C, et al: Evidence of *Bordetella pertussis* infection in adults presenting with persistent cough in a French area with very high whole-cell vaccine coverage. J Infect Dis 186:415–418, 2002.
108. Kamei RK: Chronic cough in children. Pediatr Clin North Am 38:593–605, 1991.
109. Holmes PW, Barter CE, Pierce RJ: Chronic persistent cough: Use of ipratropium bromide in undiagnosed cases following upper respiratory tract infection. Respir Med 86:425–429, 1992.
110. Altunaiji S, Kukuruzovic R, Curtis N, Massie J: Antibiotics for whooping cough (pertussis). Cochrane Database Syst Rev 3:CD004404, 2007.
111. O'Connell F, Thomas VE, Pride NB, Fuller RW: Capsaicin cough sensitivity decreases with successful treatment of chronic cough. Am J Respir Crit Care Med 150:374–380, 1994.
112. Birring SS, Brightling CE, Symon FA, et al: Idiopathic chronic cough: Association with organ specific autoimmune disease and bronchoalveolar lymphocytosis. Thorax 58:1066–1070, 2003.
113. Niimi A, Torrego A, Nicholson AG, et al: Nature of airway inflammation and remodeling in chronic cough. J Allergy Clin Immunol 116:565–570, 2005.
114. Groneberg DA, Niimi A, Dinh QT, et al: Increased expression of transient receptor potential vanilloid-1 in airway nerves of chronic cough. Am J Respir Crit Care Med 170:1276–1280, 2004.
115. O'Connell F, Springall DR, Krausz T, et al: Abnormal intraepithelial airway nerves in persistent unexplained cough? Am J Respir Crit Care Med 152:2068–2075, 1995.
116. Muers MF, Round CE: Palliation of symptoms in non–small cell lung cancer: A study by the Yorkshire Regional Cancer Organisation Thoracic Group. Thorax 48:339–343, 1993.
117. McLeod RL, Correll CC, Jia Y, Anthes JC: TRPV1 antagonists as potential antitussive agents. Lung 186(Suppl 1):S59–S65, 2008.
118. Eddy NB, Friebel H, Hahn KJ, Halbach H: Codeine and its alternates for pain and cough relief. 3. The antitussive action of codeine—Mechanism, methodology and evaluation. Bull World Health Organ 40:425–454, 1969.
119. Empey DW, Laitinen LA, Young GA, et al: Comparison of the antitussive effects of codeine phosphate 20 mg, dextromethorphan 30 mg and noscapine 30 mg using citric acid–induced cough in normal subjects. Eur J Clin Pharmacol 16:393–397, 1979.
120. Smith J, Owen E, Earis J, Woodcock A: Effect of codeine on objective measurement of cough in chronic obstructive pulmonary disease. J Allergy Clin Immunol 117:831–835, 2006.
121. Morice AH, Menon MS, Mulrennan SA, et al: Opiate therapy in chronic cough. Am J Respir Crit Care Med 175:312–315, 2007.
122. Eddy NB, Friebel H, Hahn KJ, Halbach H: Codeine and its alternates for pain and cough relief. 4. Potential alternates for cough relief. Bull World Health Organ 40:639–719, 1969.
123. Aylward M, Maddock J, Davies DE, et al: Dextromethorphan and codeine: Comparison of plasma kinetics and antitussive effects. Eur J Respir Dis 65:283–291, 1984.
124. Matthys H, Bleicher B, Bleicher U: Dextromethorphan and codeine: Objective assessment of antitussive activity in patients with chronic cough. J Int Med Res 11:92–100, 1983.
125. Catena E, Daffonchio L: Efficacy and tolerability of levodropropizine in adult patients with non-productive cough. Comparison with dextromethorphan. Pulm Pharmacol Ther 10:89–96, 1997.
126. Dicpinigaitis PV, Rauf K: Treatment of chronic, refractory cough with baclofen. Respiration. 65:86–88, 1998.
127. Dicpinigaitis PV: Use of baclofen to suppress cough induced by angiotensin-converting enzyme inhibitors. Ann Pharmacother 30:1242–1245, 1996.
128. Udezue E: Lidocaine inhalation for cough suppression. Am J Emerg Med 19:206–207, 2001.
129. Morice AH, Marshall AE, Higgins KS, Grattan TJ: Effect of inhaled menthol on citric acid induced cough in normal subjects. Thorax 49:1024–1026, 1994.
130. Chung KF: The need for new therapies for cough: Disease-specific and symptom-related antitussives. *In* Chung KF, Widdicombe JG (eds): Pharmacology of Cough. Berlin: Springer Verlag, 2009, pp 345–370.
131. Taylor-Clark TE, Nassenstein C, McAlexander MA, Undem BJ: TRPA1: A potential target for anti-tussive therapy. Pulm Pharmacol Ther 22:71–74, 2009.
132. Carr MJ: Plasticity of the afferent innervation of the airways: The role of ion channels. Pulm Pharmacol Ther 20:412–415, 2007.

CHAPTER 30

CHEST PAIN

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INTRODUCTION

Pain is a complex subjective experience that varies from person to person in its quality, intensity, duration, location, frequency, and associated features. Its perception is influenced by a subject's culture, emotional and cognitive contributions, socioeconomic status, familial background, prevailing psychological factors, anticipation and previous experience, and the context in which the symptom occurs.

Chest pain is characterized by an unpleasant sensation that is either localized to the thorax or believed to originate from structures located in the latter. It may announce the presence of severe, occasionally life-threatening, disease. Diagnosis of chest pain is often complicated by the vague presentations and indistinct anatomic localization of many of its causes.

EPIDEMIOLOGY

There are uncertainties about the exact prevalence of chest pain. In a study of 500 randomly selected households in Burlington, Canada, 16% of 827 respondents reported experiencing pain within the 2 weeks preceding the survey.[1] Persistent pain was approximately twice as common as temporary pain, and chest pain was the fifth most common type of temporary pain. In studies of acute pain that was sufficient to warrant medical attention, chest pain is always an important factor.

A survey of 1016 randomly selected enrollees of a health care plan in Seattle, Washington, revealed a high incidence of pain that lasted a whole day or more or that occurred several times during the previous 6 months[2]; the most common complaint was back pain, followed by headache, abdominal pain, facial pain, and chest pain. Chest pain accounted for 12% of the reported cases, but was the most common site of pain that prompted respondents (35%) to seek medical attention. Pain is also a common reason for persons to visit hospital emergency departments. In a survey of 36,271 random evaluations, stomach pain, other abdominal pain, and chest pain were the most often cited reasons; they occurred with almost equal frequency and, together, accounted for 10.7% of all emergency department visits.[3]

NEUROBIOLOGY OF PAIN

Pain is not a simple sensation. The neurobiologic and functional components of the sensory channels for pain are neither fixed nor immutable. The nervous system, from the level of the nociceptor (the receptor that responds to noxious stimuli) to the supraspinal sites of integration, is characterized by its dynamic response (plasticity) to tissue insult.

Pain arising from visceral organs (e.g., heart or gastrointestinal tract) differs in many ways from that arising from somatic structures, such as the skin. Visceral pain is difficult to localize, is diffuse in character, and is typically referred to somatic structures. In addition, it is often associated with greater autonomic and motor responses than is somatic pain. These differences between somatic and visceral pain are associated with characteristic features of sensory innervations that are unique to the viscera.

SOMATIC PAIN

Somatic structures, such as the skin, are invested with a wide variety of nociceptors, each with selective sensitivities to mechanical, thermal, or chemical stimuli, in addition to the polymodal nociceptor that responds to multiple modalities of noxious stimuli.[4,5] Cutaneous nociceptors are characterized by high activation thresholds, very infrequent or no spontaneous discharges, an ability to encode stimulus intensities in the noxious (but not innocuous) range, and most importantly, sensitization. *Sensitization* refers to an increase in the magnitude of response after tissue insult, sometimes associated with an increase in spontaneous activity as well as a decrease in response threshold. This attribute of nociceptors contributes to development of hyperalgesia, or an increased response to a stimulus that is normally painful.

When a tissue is injured, a host of sensitizing chemicals are synthesized at the site of injury or released from circulating cells that are attracted to the site of injury. These include amines (e.g., histamine and serotonin), peptides (e.g., substance P and calcitonin gene–related peptide), kinins (e.g., bradykinin), neurotrophins, cytokines, prostaglandins, leukotrienes, excitatory amino acids (e.g., glutamate), and free radicals. However, it is unlikely that any one putative chemical mediator is responsible for nociceptor sensitization. Although substance P, for example, is contained in most nociceptor cell bodies, it is also present in a significant number of non-nociceptor cell bodies. Similarly, other peptides, such as calcitonin gene–related peptide, somatostatin, and galanin, are found more commonly in small to intermediate-sized dorsal root ganglion cell bodies.

VISCERAL PAIN

Whether visceral nociceptors exist is uncertain. Input to the central nervous system (CNS) from aortic baroreceptors, gastric chemoreceptors, and pulmonary stretch receptors is rarely perceived. Nevertheless, it is evident that visceral afferents possess many of the characteristics of nociceptors.

All viscera possess a dual innervation. Organs of the thoracic cavity are innervated by vagal afferent fibers with cell bodies in the nodose and jugular ganglia as well as by spinal afferent fibers with cell bodies in thoracic dorsal root ganglia. Unlike their somatic counterpart, spinal visceral afferent fibers typically traverse either or both prevertebral and paravertebral ganglia en route to the spinal cord. Thus, in contrast to somatic input to the CNS, which has a single, usually spinal, destination, input to the CNS from organs in the thoracic cavity arrives at two locations, namely the brain-stem nucleus tractus solitarii (vagal afferent input) and the thoracic spinal cord. Accordingly, the potential exists for interaction in the CNS of inputs from the same thoracic organ. The esophagus and heart also possess an intrinsic nervous system with cell bodies in the organ wall or in ganglia in the epicardial fat.[6]

Further differences between somatic and visceral innervation relate to the density of innervation and spinal pattern of termination. In general, the number of visceral afferent fibers is disproportionately less than the number of somatic afferent fibers, although the rostrocaudal spread of visceral afferent fiber terminals in the spinal cord is considerably greater than the spread of central terminals from somatic afferent fibers. Although this means that there are fewer central visceral terminals in the spinal cord, visceral afferent fiber terminals have many more terminal swellings (suggestive of synapses) than somatic nociceptor terminals and they spread over several spinal cord segments.[7] The obvious consequence of the low number of visceral afferents and greater intraspinal spread is loss of spatial discrimination, consistent with the diffuse, difficult-to-localize, nature of visceral pain.

The axons of visceral sensory neurons are, with rare exception, either thinly myelinated Aδ fibers or unmyelinated C fibers. Generally, the proportion of C fibers in visceral sensory nerves is greater than the proportion of Aδ fibers. However, high-threshold fibers are not uniformly C fibers, and low-threshold fibers are not uniformly Aδ fibers.

Unlike tissue-damaging stimuli that produce pain in somatic structures, tissue injury is not required for production of pain in the viscera. For the lower airways, irritants contained in smoke, ammonia, and other inhaled substances are capable of producing discomfort and pain. For the heart and mesentery, ischemia can be an adequate stimulus.[8] For hollow organs of the gastrointestinal tract, the adequate stimulus is typically distention of the lumen of the organ, which activates stretch and tension receptors in the smooth muscles.

Hollow viscera, including the esophagus, are innervated by two populations of mechanosensitive afferent fibers, namely a larger group (70%–80%) of fibers that have low thresholds for response (i.e., within the physiologic range), and a smaller group (20%–30%) of fibers that have thresholds for response that fall in the noxious range.[9] All mechanosensitive visceral afferent fibers may function in some circumstances as nociceptors, and low- and high-threshold mechanosensitive fibers contribute to discomfort and pain that arise from the viscera.

"*Silent nociceptors,*" a relatively new category of receptor/afferent fibers, may also contribute to altered sensations from somatic structures. Silent nociceptors have no spontaneous activity and do not respond to acute, high-intensity mechanical stimulation in normal circumstances. After tissue insult, these afferent fibers typically begin to discharge spontaneously and acquire sensitivity to mechanical stimulation. However, the contribution of such "silent" or "sleeping" afferent fibers to altered sensations that arise from the viscera is uncertain at present.

HYPERALGESIA

Some individuals are uniformly more sensitive (i.e., have lowered thresholds for stimulus-produced pain) than others. *Hyperalgesia*, the enhanced response to a stimulus that is normally noxious, consists of primary and secondary components. *Primary hyperalgesia* refers to enhanced sensitivity to stimuli applied at the site of tissue injury (e.g., an incision). *Secondary hyperalgesia*, conversely, pertains to enhanced sensitivity to stimuli applied to uninjured tissue adjacent to the site of injury. Both peripheral mechanisms (sensitization of nociceptors and afferent fibers innervating the insulted tissue) and central mechanisms (changes in the excitability of spinal and supraspinal neurons) contribute to primary and secondary hyperalgesia. Afferent fibers that innervate the pelvic viscera have been shown to sensitize when organs are experimentally inflamed. Both low-threshold and high-threshold mechanosensitive afferent fibers in the pelvic nerve exhibit exaggerated responses to distention relative to responses of the same afferent fibers before inflammation. This change in neuron excitability is believed to arise principally through the action of glutamate at the *N*-methyl-D-aspartate (NMDA) receptor. Contributions of non-NMDA receptors, AMPA or kainite, and of the receptor at which substance P acts (neurokinin 1 [NK1] receptor) are also likely.[10] Glutamate and substance P are co-contained in many small-diameter dorsal root ganglion cells and presumably are concurrently released in the spinal dorsal horn, where NMDA receptors on nociceptor terminals may act as autoreceptors to facilitate the further release of both glutamate and substance P.[11] In addition, there is evidence that substance P can act synergistically with glutamate to enhance the responses of spinal neurons.[12]

Virtually all spinal cord neurons that receive a visceral input also receive input from somatic structures, including the skin, muscle, and joints. This convergence of inputs in the spinal dorsal horn includes both viscerosomatic and visceravisceral pathways and is believed to be the basis of referred sensation that characterizes visceral pain. Such convergence also suggests that injury to somatic tissue could lead to visceral hyperalgesia and, conversely, that injury to a viscus could lead to somatic hyperalgesia.

Spinal nociceptive transmission can be modulated by electrical or chemical stimulation in the midbrain or medulla.[13] Both inhibitory and facilitatory influences on spinal nociceptive transmission are present and likely play an important role in the maintenance of secondary hyperalgesia.[14] Electrical activation of vagal afferent fibers similarly engages descending facilitatory and inhibitory modulation of spinal nociceptive transmission. Responses of neurons in the thoracic dorsal horn to either esophageal distention[15] or lower airway irritation caused by ammonia or smoke[16] are altered when the cervical spinal cord is blocked or transected or when the vagi are cut. It would be expected that responses to esophageal or respiratory stimulation would increase when the cervical spinal cord was blocked because tonic descending inhibitory influences are usually present; unexpectedly, responses were more commonly reduced, suggesting the presence of a descending facilitatory influence that is associated with vagal input to the brain stem. In a related work, both vagal afferent input and cardiac sympathetic afferent inputs contribute to the sensation of cardiac pain, particularly referral of such pain to the neck and jaw.[17]

MEASURING PAIN

Pain has proved to be both hard to define as well as difficult to measure. Because pain can only be quantified indirectly, it has been difficult to determine the optimal measuring tool for all types of pain sensations. Two widely used techniques, namely rating scales and questionnaires, are often used in clinical and epidemiologic studies of chest pain.

Rating scales constitute the simplest measurement of pain. One of the easiest to use is the quantification of pain intensity by a graded rating scale, such as the popular Visual Analogue Scale.[18] However, the sensation of pain has many more components than just its intensity; thus, a single dimensional rating scale leaves many aspects of the sensation undocumented.

To address the multidimensional qualities of pain, questionnaires have been developed.[19] The McGill Pain Questionnaire, the most widely used method in the

English language for studying the epidemiology of pain, was developed in the 1970s[20] and has been shown to be reliable and useful.[21] Although questionnaires are a powerful way of obtaining data on both the qualitative and the quantitative aspects of pain, it is not always possible to compare the results of studies with the same questionnaire because of differences in the way they have been employed.

CHEST PAIN SYNDROMES

Pain arising from the various viscera in the thoracic cavity and from the chest wall is often qualitatively similar and exhibits overlapping patterns of referral, localization, and quality, given the proximity of the various organs and the vagaries of perception of pain of visceral origin. This leads to difficulty in the differential diagnosis of chest pain (Table 30-1). Nevertheless, many chest pain syndromes are sufficiently distinctive clinically such that diagnostic efforts often rely on accurate description of the characteristic pattern of pain. The importance of the medical history in unraveling the various causes of chest pain cannot be overemphasized.

PLEUROPULMONARY DISORDERS

The lung parenchyma and visceral pleura are considered to be insensitive to ordinary painful stimuli, but pain does arise from stimulation of the mucosa of the trachea and main bronchi.[22] The lungs and bronchi are populated with mechanoreceptors that respond to stretch (inflation or deflation of the lungs) as well as chemoreceptors called J receptors that respond to a variety of algogenic chemicals, including bradykinin, prostaglandins, serotonin, and capsaicin.[23,24] Inhalation of irritant substances, such as ammonia, can trigger a cough reflex and can produce a sense of rawness, tightness in the chest, and pain. In addition, rapidly adapting mechanoreceptors that respond to lung deflation are also "irritant receptors" and signal respiratory pain. J receptors have been proposed to contribute to discomfort and pain that accompanies breathlessness.[23–25]

These receptors are, in turn, innervated by vagal and sympathetic afferent fibers. Nerve fibers that travel in the vagus nerves, including myelinated axons that carry impulses from slowly adapting stretch receptors in the conducting airways, myelinated axons that lead from rapidly adapting irritant cough receptors in the trachea and bronchi, and unmyelinated axons that subserve the extensive network of C fiber receptors (e.g., "pulmonary" J receptors and "bronchial" C fibers), are, by far, more important.[26]

The pulmonary causes of chest pain may be related to the pleural tissue, pulmonary vessels, or lung parenchyma. Causes of chest pain related to the lung parenchyma include infection, cancer, or chronic diseases such as sarcoidosis. These are discussed in more detail elsewhere in the textbook.

Pleurisy

Pleurisy results from inflammation of the parietal pleura. The visceral pleura is not innervated by nociceptors, but inflammatory processes in the periphery of the lung that involve the overlying visceral pleura (e.g., pneumonia) frequently cause inflammation of the adjacent parietal pleura that, in turn, provokes pleuritic pain conveyed by somatic nerves. The parietal pleura that lines the interior of the rib cage and covers the outer portion of each hemidiaphragm is innervated by the neighboring intercostal nerves; when pain fibers in these regions are

TABLE 30-1. Common Causes of Chest Pain

PLEUROPULMONARY DISORDERS
- Pleurisy
  - Infection
  - Pulmonary embolism
  - Spontaneous pneumothorax
  - Collagen vascular disease
  - Sickle cell disease
  - Familial Mediterranean fever
  - Malignancy (e.g., mesothelioma)
- Pulmonary hypertension
  - Pulmonary embolism
  - Primary pulmonary hypertension
  - Eisenmenger's syndrome

TRACHEOBRONCHITIS
- Infection
- Inhalation of irritants
- Malignancy

INFLAMMATION OR TRAUMA OF THE CHEST WALL
- Rib fracture
- Muscle injury (myalgia)
- Infection
- Malignancy
- Sickle cell disease
- Neuritis-radiculitis
- Herpes zoster infection

CARDIOVASCULAR DISORDERS
- Angina pectoris
- Variant angina
- Myocardial infarction
- Aortic valve disease
- Mitral valve prolapse
- Hypertrophic cardiomyopathy
- Pericarditis
- Cocaine toxicity

DISORDERS OF THE AORTA
- Aortic dissection

GASTROINTESTINAL DISORDERS
- Reflux esophagitis
- Esophageal motility disorders
- Cholecystitis
- Peptic ulcer disease
- Pancreatitis
- Disorders of intestinal motility

MISCELLANEOUS CAUSES OF CHEST PAIN
- Thoracic outlet obstruction
- Mediastinal emphysema
- Iatrogenic

stimulated, pleuritic pain is localized to the cutaneous distributions of the involved neurons over the chest wall. In contrast, the parietal pleura that lines the central region of each hemidiaphragm is innervated by fibers that travel with the phrenic nerves; when this portion of the diaphragm is stimulated (e.g., by contiguous inflammation), the resulting pain is referred to the ipsilateral shoulder or neck.

Because of the somatic innervation of the parietal pleura as well as the localization of most diseases of the lungs or chest wall to one hemithorax or the other, pleuritic pain tends to be limited to the affected region rather than be diffuse, with the exception of referral to the ipsilateral neck or shoulder. Pain may be variously described as "sharp," "dull," "achy," "burning," or simply a "catch." There is a distinctive and unmistakable relationship to breathing movements, and taking a deep breath typically aggravates pleuritic pain.[27] Coughing and sneezing can cause intense distress. Movements of the trunk, such as bending, stooping, or turning in bed, worsen pleuritic pain, so much so that patients often prefer the body position in which motion of the affected region is least.

An immediate onset of pleuritic pain suggests traumatic injuries or spontaneous pneumothorax. A sudden onset, often associated with dyspnea and tachypnea, also characterizes the clinical presentation of pulmonary embolism.[28] A slower but still acute onset over minutes to a few hours often heralds the development of community-acquired bacterial (typically pneumococcal) pneumonia, especially when accompanied by fever and chills. Recurrent acute pleuritic pain is a feature of familial Mediterranean fever.[29] Finally, a gradual onset over days or weeks, often associated with features of chronic illness, such as low-grade fever, weakness, and weight loss, suggests tuberculosis or malignancy.

Pulmonary Hypertension

Persons with pulmonary hypertension may experience crushing or constricting substernal pain that, at times, radiates to the neck or arms, thus resembling the pain of myocardial ischemia.[30] Pain from pulmonary hypertension has been reported in patients with both acute (e.g., multiple or massive pulmonary emboli) and chronic (e.g., Eisenmenger's syndrome, pulmonary vasculitis, or mitral stenosis) conditions. In addition, about half of the patients with primary pulmonary hypertension may have precordial chest pain.[31]

In acute pulmonary hypertension resulting from massive pulmonary embolism, the pain may be caused by sudden distention of the main pulmonary artery and stimulation of mechanoreceptors.

In primary pulmonary hypertension, chest pain may be related to either (1) right ventricular ischemia because coronary blood flow is unable to meet the metabolic needs of the overloaded right ventricular muscle mass as the latter strives to maintain sufficient systolic and diastolic pulmonary arterial pressures[32] or (2) compression of the left main coronary artery by the dilated pulmonary artery trunk.[33]

Although precordial pain related to the sudden onset of pulmonary hypertension can develop in cases of acute pulmonary embolism, embolism-associated pain is much more likely to be pleuritic in character, whether or not pulmonary infarction occurs.[34]

Pulmonary artery stenosis may also cause substernal pain, presumably by the same pressure-overload mechanism through which pulmonary hypertension with right ventricular hypertrophy provokes pain.[35]

TRACHEOBRONCHITIS

Pain of tracheal origin is generally felt in the midline, anteriorly, from the larynx to the xyphoid. Conversely, pain from either main bronchus is felt in the ipsilateral anterior chest near the sternum or in the anterior neck near the midline.[22] Whatever its origin, pain related to tracheobronchitis is typically described as "raw" or "burning" but may be "dull" or "achy," and exaggerated by deep breathing. This type of discomfort usually denotes the presence of viral or bacterial tracheobronchitis or, less often, a malignancy, but can also be experienced during exposure to noxious gases. Tracheobronchial pain is thought to be mediated by bronchial C fibers. Experimentally induced tracheal pain can be abolished by vagal blockade[36] or by vagotomy.[37]

INFLAMMATION OR TRAUMA OF THE CHEST WALL

Inflammation of, or trauma to, the joints, muscles, cartilages, bones, and fasciae that constitute the thoracic cage can cause chest pain.[38–40] Fibromyalgia, fibrositis, and other rheumatologic disorders of the thoracic cage, such as ankylosing spondylitis, are known to cause pain and discomfort in the chest.[41] Acute or chronic inflammation of the xyphoid process (xyphodynia)[42] and superficial "jumping" thrombophlebitis of the chest wall (Mondor's syndrome)[43] may also be uncommon sources of chest pain. Occasionally, pain related to respiration may be experienced along the costal margins after vigorous exercise.[44] In addition, metastatic malignancy may present as painful lesions of the chest wall, sometimes with spontaneous rib fractures. Another confusing source of chest pain is infectious arthritis of the sternoclavicular joint or costochondral junctions, which is an increasing problem among injection drug users.[45]

With *costochondritis*, chest wall pain arises from the costochondral cartilaginous junctions. It is usually described as "dull with a gnawing, aching quality." There is little, if any, relationship to respiratory or other body movements. Tenderness to palpation is clearly localized to one or more of the costal cartilages.[46] There may be redness, swelling, and enlargement of the costal bridges (Tietze's syndrome). The most common sites of costosternal perichondritis are the second, third, and fourth cartilages, but any part of the large cartilaginous shield along the central and lower portions of the anterior thoracic cage may be involved.

The pain of *intercostal neuritis* or *radiculitis*, which often originates from disorders of the cervicodorsal spine or nerve roots, is usually perceived in the rib cage. The superficial, spontaneous lancinating or electric shock–like pain of intercostal neuritis is typically felt over the cutaneous distribution of the involved nerves and may be worsened by taking deep breaths, coughing, and sneezing; unlike pleurisy, neuritic pain is usually not aggravated by ordinary breathing; the diagnosis is supported by the presence of hyperalgesia or anesthesia on examination of the skin. In some patients with neuritis/radiculitis, the diagnosis becomes evident 2 or 3 days later with the development of the characteristic vesicular rash of herpes zoster over the involved dermatome. Painful radiculitis is also recognized as an important early manifestation of Lyme disease.[47]

Injuries to the ribs (fracture) and thoracic cage muscles (strain, tears, or hematoma) are common causes of localized chest pain. The relationship of the pain to trauma is obvious in most instances, but diagnosis may be elusive, particularly if the inciting event is relatively minor (e.g., unnoticed episode of coughing) or when onset of pain is delayed.

CARDIOVASCULAR DISORDERS

Mechanosensitive and chemosensitive afferent fibers are present in the myocardium.[23,48] Chemical stimuli are believed to be the most important actuators of cardiac pain, but mechanical distention or distortion may also play a role.[49] Sensory fibers travel from the heart to the spinal cord through the several cardiac nerves, the upper five thoracic sympathetic ganglia, and finally, the upper five thoracic dorsal roots; afferent fibers also reach the brain through the vagus nerves.[50] Cardiac pain is likely associated with activity in afferent fibers contained in the sympathetic afferent innervation of the heart.

Myocardial Ischemia

Angina pectoris due to myocardial ischemia is typically described as severe "pressure," "squeezing," or "constriction" with maximal intensity retrosternally or over the left parasternal border. Radiation to the neck, jaw, shoulder, or down the inner aspect of one or both arms may be present. It is usually induced by exercise but may be provoked by heavy meals, excitement, or extreme emotion. Pain tends to recur with repeated provocation, although its severity may vary. Pain usually subsides within 2 to 10 minutes with rest, and relief is accelerated by treatment with sublingual nitroglycerin.[51] A majority of patients with stable angina pectoris have significant reduction of at least one major coronary artery.[52] Prinzmetal's or variant angina is similar in quality and location to typical angina pectoris but occurs at rest rather than during exercise or increased myocardial oxygen needs.[53] In this syndrome, the imbalance between myocardial oxygen supply and demand is postulated to arise from epicardial coronary artery vasospasm, usually superimposed on noncritical atheromatous vessel narrowing. Pain does not always accompany myocardial ischemia, and many electrocardiographically detectable episodes of ischemia in patients with stable angina pectoris are asymptomatic ("silent" ischemia).[54] Conversely, many individuals with angina-like chest pain have normal or nearly normal coronary arteries when studied by arteriography. As many as 30% of these noncoronary cases are classified as "syndrome X,"[55] with the development of chest pain attributed to either coronary microvascular spasm or heightened pain perception.[55,56]

The pain of *acute myocardial infarction* is similar in location to that of angina pectoris, but is typically much more severe in intensity, is not relieved by rest or nitroglycerin, often requires large doses of opiates for control, and is frequently associated with profuse sweating, nausea, dyspnea, and profound weakness.[51] During episodes of myocardial ischemia, the involved myocardium stiffens; when severe, this decrease in compliance may increase left ventricular end-diastolic filling pressure sufficiently to raise left atrial and pulmonary vascular pressures and to cause pulmonary edema. Massive myocardial infarction may also lead to intractable hypotension and shock. Acute myocardial infarction may also be silent,[57] especially in patients with diabetes mellitus.[58]

Valvular Heart Disease

Chest pain can also arise from other *non-coronary artery disorders*, including mitral valve prolapse, myocarditis,[51] pericarditis, and hypertrophic cardiomyopathy.[59] It can also be related to cocaine use.

Patients with aortic stenosis may complain of angina-like pain on exertion. The frequency of chest pain is higher with aortic stenosis than with any other valvular heart disease and occurs in two thirds of patients with severe disease.[51] Whenever a patient presents with progressive angina, dyspnea, or syncope, aortic stenosis should be considered.

Patients with mitral stenosis or pulmonic stenosis infrequently experience chest pain.

Pericarditis

The pain of *pericarditis* is most commonly pleuritic and arises from spread of the inflammatory process across the pericardium to the adjacent parietal pleura. Typically, pain is worse in the recumbent position and while lying on the left side and is partially or completely relieved by sitting up, leaning forward, or lying on the right side. Occasionally, pericardial pain may be confused with anginal pain, but radiation to the arms is uncommon. Although there are few afferent nociceptors in the pericardium, there appear to be some pain receptors in the diaphragmatic portion of its parietal layer, which is innervated by sensory axons that travel in the phrenic nerves.[60] Stimulation of these fibers causes pain that may be sharp and steady and referred to the upper margins (ridge) of the trapezius muscles. Pain in this location is claimed to be specific for pericarditis because other diseases seldom cause discomfort in that area.[51]

Pericardial friction rubs, presumably indicating underlying pericarditis, occur more often than pericardial pain during the first few days after acute myocardial infarction and with worsening uremia.[51,61] Other causes of pericarditis, usually associated with pericardial pain, are infections, often viral but also bacterial,[62] and connective tissue diseases (e.g., lupus erythematosus). Pericarditis, usually with fever, also occurs after open heart surgery (post-pericardiotomy syndrome) and after myocardial infarction (Dressler's syndrome), both of which are considered to be autoimmune disorders.[63] Often, no diagnosis can he made and pericarditis is considered idiopathic.

Cocaine Toxicity

Cocaine toxicity is associated with more visits to the emergency department for adverse reactions than any other illicit drug, and chief among the presenting complaints is chest pain.[64] Cocaine-associated chest pains typically begin about 60 minutes after injection or inhalation of the substance and lasts for 120 minutes.[65] The pain is most frequently substernal in location and pressure-like in character; it may be accompanied by shortness of breath and diaphoresis. Interestingly, clinical presentation may not differ among persons who develop myocardial infarction documented by biochemical markers and those who do not.

Cocaine-induced chest pain is undoubtedly provoked by the combined effects of an increase in myocardial oxygen demand owing to an increase in heart rate and in systolic and mean arterial pressures and a decrease in myocardial oxygen supply due to vasoconstriction of the epicardial coronary arteries.[66]

Despite its widespread use and the frequent causal association (even among casual users), patients with chest pain who are seeking medical assistance are seldom queried about recent use of cocaine. Consequently, in the setting of cardiac symptoms, identification of cocaine exposure is a legitimate goal of cardiovascular history taking. In addition this is an important question to ask because there is consensus that β-adrenergic blocking agents, which are indicated in acute coronary artery syndromes, may aggravate cocaine-induced myocardial ischemia and that nitroglycerin and calcium-channel blocking drugs (e.g., verapamil) constitute the treatments of choice. Cessation of cocaine use is essential for secondary prevention.

Disorders of the Aorta

Dissection of the aorta is usually associated with pain that is nearly always sudden and extremely severe at onset. Pain may be described, aptly, as "tearing" or "ripping" and often spreads widely, to the neck, throat, jaw, back, or abdomen, as the dissection extends from its point of origin.[67] Frequent associated features are drenching sweats, nausea and vomiting, and lightheadedness. Angina-like chest pain can also arise secondary to reduced coronary artery blood flow as a result of syphilitic aortitis or Takayasu's vasculitis.

NONCARDIAC CHEST PAIN

The term *noncardiac chest pain* is used to describe an entity that in the United States has an estimated annual incidence as high as 450,000 cases and that causes considerable long-term morbidity and health care utilization. There are three main categories of extracardiac disease that cause angina-like chest pain: (1) musculoskeletal disorders of the chest wall (see previous section), which may account for 10% to 20% of cases[125]; (2) a variety of esophageal disorders, particularly gastroesophageal reflux, which may cause 30% to 40%; and (3) psychiatric disorders (discussed later), which may explain 30% to 50% of the total.

Gastrointestinal Disorders

Receptors are present in the esophagus and may cause pain when activated by mechanical (spasm), chemical (acid reflux), or thermal (hot liquids) stimuli. Afferent nerves travel in both vagal and sympathetic (T3 to T12) pathways.[68] Pain originating from the esophagus is usually referred to midline structures, such as the throat, neck, and sternal regions, but may involve the arms as well. Stimulation of the distal end of the esophagus can cause pain directly over the heart.

Chest pain may arise either from esophageal reflux (the most common identifiable esophageal cause of chest pain) or from disorders of esophageal motility, such as diffuse esophageal spasm, achalasia, hyperactive lower esophageal sphincter, or nutcracker esophagus.[69,70] Esophageal pain may mimic angina pectoris by its radiation to the neck and arms as well as relief by nitroglycerin.[51] Chest discomfort that lasts an hour or more, that leaves a residual dull achy discomfort, or that is associated with pyrosis, odynophagia, or dysphagia should suggest pain of esophageal origin. Clinical history alone, however, cannot reliably distinguish pain originating from the esophagus from cardiac pain.

Lastly, other gastrointestinal disorders, such as cholecystitis, peptic ulcer disease, and acute pancreatitis, may present with pain that is perceived in the lower thorax.[60]

Miscellaneous Causes of Chest Pain

Obstructive lesions at the thoracic outlet may compress the brachial plexus and subclavian artery and can cause pain in the anterior chest and arms. *Thoracic outlet syndrome* is usually caused by compression of the neurovascular bundle by a cervical rib or a structural abnormality of the 1st rib or clavicle. Associated neuronal abnormalities have been described,[71] and electrophysiologic studies are useful not only to assist with the diagnosis but also to define which patients will respond to surgical decompression.[72] Chest pain may also arise from *iatrogenic causes*, such as pneumothorax following bronchoscopy or central venous catheter malposition.[73]

Psychological Factors

Many patients experience chest pain for which no cause is ever found even after careful and thorough evaluation. Psychological factors clearly affect each person's interpretation of bodily sensations, and a psychiatric cause should be excluded in undiagnosed cases of chest pain.

An association between noncardiac chest pain and anxiety disorders, particularly panic disorder, has been reported. This is particularly well described in patients with mitral valve prolapse.[74] Patients with demonstrable heart disease may also have panic attacks. Alternatively, persons with chest pain may have psychological distress that is related to the panic syndrome and not the cardiac condition.

EVALUATION AND TREATMENT OF CHEST PAIN

Given the wide variety of causes and seriousness of chest pain, considerable clinical judgment is required to decide which patients should be thoroughly evaluated and which tests should be used in the workup. In many instances, empirical therapy may need to be initiated even as evaluation proceeds, with subsequent readjustments in treatment protocols as more information is obtained that clarifies the clinical picture.

The evaluation of chest pain begins with a complete medical interview. The history may reveal nuances in the quality, location, duration, provoking events, and relieving measures, which serve to accurately focus the subsequent evaluation. However, with few exceptions, such as evident injury to the chest wall, a specific diagnosis cannot be made with complete confidence from the clinical history alone. Physical examination may reveal evidence of pleural, lung parenchymal, or airway disease; localized chest wall involvement; or signs of mitral valve prolapse, aortic valve stenosis, or other cardiac abnormalities.

For adults who present to the emergency department with new-onset chest pain, the immediate concern is to properly identify and characterize potentially life-threatening condition, such as myocardial infarction, acute pulmonary embolism, or tension pneumothorax, that requires urgent management. Some diagnostic features are listed in Table 30-2.

A standard 12-lead electrocardiogram (ECG), appropriate chest imaging, measurement of oxygen saturation and arterial blood gases, and blood chemistry profiles (e.g., troponin, D-dimer) often provide important data. In the appropriate clinical setting, some patients may require echocardiography or pulmonary function testing. Many other noninvasive or invasive tests are available for the evaluation of pain believed to be of respiratory, cardiac, or gastrointestinal origin. If diagnosis remains uncertain, admission to chest pain observation units that offer a safe and effective means of care for patients with possible unstable angina who are considered to be at intermediate risk for cardiovascular events may be considered.

TABLE 30-2. Differential Diagnosis of Chest Pain

Diagnosis	Pain	Characteristics	ECG	CXR	Associated Features
Angina pectoris	Substernal, constricting	Transient, effort-related	Local ST depression; occasional elevation	Normal	Relief with NTG
MI	Substernal, crushing	Persistent, severe	Local ST elevation or depression	Possible vascular congestion or cardiomegaly	Relief with opiates; possible hypotension; ↑ troponin
Pulmonary embolism	Pleuritic	Sudden onset with dyspnea	Nonspecific; occasional RV strain	Normal or opacities ± small pleural effusion	Risk factor/s for venous thrombosis
Pulmonary artery hypertension	Gradual onset	Associated with dyspnea, fatigue and edema	Tall right precordial R waves, right axis deviation, RV strain	Prominent pulmonary arteries	Exclude pulmonary thromboembolism and interstitial lung disease
Bacterial pneumonia	Pleuritic	Onset in minutes to hours	Normal	Consolidation	Fever, productive cough
Pneumothorax	Sharp, unilateral	Sudden onset with dyspnea	Normal	Collapsed lung	Asthenic habitus, recurrence
Pericarditis	Pleuritic	Either side; gradual onset	Generalized ST elevation	Possible enlarged silhouette	Friction rub
Aortic dissection	Substernal, severe	Radiation to the back	Nonspecific; LVH or inferior MI	Widened mediastinum	Prostration, loss of pulse, aortic insufficiency
Esophageal spasm/reflux	Substernal	May mimic angina; burning	Normal or ST-T changes	Normal	Relief with NTG or antacids
Costochondritis	Dull-achy, localized	↑ by cough or deep breath	Normal	Normal	Localized tenderness
Herpes zoster	Sharp, unilateral	Dysesthesia	Normal	Normal	Vesicular rash

CXR, chest x-ray; ECG, electrocardiogram; LVH, left ventricular hypertrophy; MI, myocardial infarction; NTG, nitroglycerin; RV, right ventricular.

The most definitive treatment for chest pain, whatever its origin, is to find its cause and to cure it. The general principles of therapy of respiratory, cardiac, musculoskeletal, esophageal, and panic disorders are available and the clinician is encouraged to refer to them. Chronic noncardiac chest pain is more difficult to manage, especially when its trigger cannot be found. Because of the complexities and difficulties in dealing with those few patients who have chronic, severe, and often refractory pain, referral to special pain centers staffed by a multidisciplinary team of specialists is recommended. At times, psychiatric consultation for specific treatment may be helpful.

Cardiac Ischemia

Evaluation of patients with suspected *unstable angina or non-ST elevation myocardial infarction* should include a 12-lead ECG (serial tests may be considered if the initial ECG is not diagnostic), and biomarker determination (creatine kinase-MB, myoglobin, or cardiac-specific troponin [preferred]). Other helpful tests include B-type natriuretic peptide (BNP), stress testing (if ECG and cardiac biomarker measurements are normal),[75] noninvasive coronary imaging tests (cardiac computed tomography [CT] or magnetic resonance imaging [MRI] techniques), echocardiography, radionuclide angiography, or coronary angiography. The indication for stress echocardiography has recently been clarified and includes the evaluation of acute chest pain and other chest pain syndromes, such as anginal equivalent, with or without heart failure, as well as risk assessment in symptomatic patients following revascularization procedures.[76,76a]

Acute ECG changes, such as ST segment deviations or deep T wave inversions, positive cardiac biomarkers or stress test results, or hemodynamic instability should prompt admission to an intensive care unit. Hospital admission may also be considered if diagnosis remains uncertain despite initial limited evaluations. Available risk stratification models, such as the Thrombolysis in Myocardial Infarction (TIMI) score, may aid diagnosis and management. Aspirin, preferably non–enteric-coated formulations, should be provided unless contraindicated or already taken by the patient. Other medications that may be useful in the acute management of ischemic heart disease include nitroglycerin (sublingual or intravenous), β-blockers, angiotensin-converting enzyme (ACE) inhibitors, non-dihydropyridine calcium channel blocker, morphine sulfate (for persistent chest discomfort), antiplatelet agents (clopidogrel or GP II/IIIa inhibitor), and anticoagulant therapy (e.g., unfractionated heparin, enoxaparin, or fondaparinux). Patients should be placed on strict bed rest and supplemental oxygen should be provided, particularly if the patient is in respiratory distress or if oxygen saturation is less than 90%. Every patient with acute coronary syndrome should be evaluated for possible reperfusion therapy (fibrinolytic agents) or revascularization (coronary artery bypass graft surgery or percutaneous coronary intervention) unless contraindicated.[75–81b] A recently published meta-analysis revealed that management of non–ST segment elevation acute coronary syndromes by early invasive therapy improves long-term survival and reduces adverse cardiovascular events (late myocardial infarction and rehospitalization for unstable angina) compared with a more conservative approach.[82]

Evaluation and management of *variant* or *Prinzmetal's angina* consists of coronary angiography in patients with chest pain accompanied by transient ST segment elevation. Nitrates and calcium channel blockers may be given if no obstructive coronary artery lesions are evident on coronary angiography, with percutaneous coronary intervention reserved for those with significant coronary artery stenosis. Provocative testing may be considered in cases of diagnostic uncertainty if no contraindications exist.[77]

For cardiac ischemic chest pain related to the use of *cocaine* or *methamphetamine*, nitroglycerin and calcium channel blockers or may be considered as are immediate coronary angiography (preferred) or fibrinolytic therapy (if coronary angiography is not possible) if electrocardiographic ST elevation (or new ST segment depression or T wave changes) persists despite pharmacologic intervention. A combined α- and β-blocking agent, such as labetalol, may be helpful in patients with sinus tachycardia related to cocaine use if a vasodilator (nitroglycerin or calcium channel blocker) has been administered within the previous hour.[77]

Patients with *cardiovascular syndrome X* may also benefit from medical intervention with nitrates, calcium channel blockers, and/or β-blockers. Intracoronary ultrasound, coronary angiography, 24-hour ambulatory ECG, provocative testing, or coronary flow reserve measurement may be considered to aid with diagnosis.[77]

Risk stratification with exercise ECG (using the Bruce protocol or Duke treadmill score), exercise perfusion imaging, or exercise echocardiography should be considered for patients with symptomatic chronic stable angina who are able to exercise and have no contraindications to such testing. For those who are unable to exercise, myocardial perfusion imaging with dipyridamole or adenosine or dobutamine echocardiography is recommended unless contraindications to such testing exist.[83]

Pulmonary Embolism

Pulmonary embolism is a life-threatening feature of venous thromboembolism and most frequently originates from deep venous thrombosis in the lower extremities.

Patients with acute pulmonary embolism who have elevated levels of troponin are at high risk for short-term mortality and adverse outcome events.[84] A recent meta-analysis of the different diagnostic strategies for suspected pulmonary embolism disclosed the positive likelihood ratios for high-probability ventilation-perfusion (V/Q) lung scan (18.3), spiral CT (24.1), and lower extremity venous ultrasonography (16.2). The corresponding negative likelihood ratios were 0.05 for a normal or near-normal lung scan, 0.04 for a negative

spiral CT along with a negative result on ultrasonography, and 0.08 for a D-dimer concentration less than 500 μg/L by quantitative enzyme-linked immunosorbent assay. With these tests, the posttest probability of pulmonary embolism was greater than 85% in patients with a moderate or high pretest probability and below 5% in patients with a low or moderate pretest probability. Because of higher negative likelihood ratios, spiral CT alone, a low-probability V/Q lung scan, magnetic resonance angiography, a quantitative latex D-dimer test, and hemagglutination D-dimers can only exclude pulmonary embolism in those with a low pretest probability.[85] Patients with pulmonary embolism can be treated with either unfractionated heparin or low-molecular-weight heparin. Anticoagulation is maintained either for 3 to 6 months for events related to a transient risk factor or for greater than 12 months for recurrent venous thromboembolism.[86]

Pericardial Disease

Acute pericarditis is often, but not always, accompanied by pericardial effusion that can be detected by echocardiography. Therapy of acute pericarditis involves identification and management of any underlying cause/s of the condition (e.g., infection or malignancy). In constrictive pericarditis, echocardiography can demonstrate the presence of pericardial thickening and calcification that limits diastolic filling of the ventricles (restrictive filling) and causes a characteristic biphasic pattern of venous return with a diastolic component that is equal to or greater than the systolic component. In selected patients, pericardectomy is a highly effective treatment for constrictive pericarditis.[87]

Cardiac Tamponade

Cardiac tamponade is diagnosed by the presence of cardiac compression by fluid within the pericardial sac. This, in turn, impairs ventricular diastolic filling and gives rise to the sensation of chest pain, dyspnea, tachycardia, falling systemic blood pressure, elevated venous pressure (characteristic loss of the atrial Y descent with maintenance of both the systolic atrial filling wave and the X descent), and pulsus paradoxus (an exaggerated inspiratory decrease in arterial systolic pressure > 10 mm Hg). Cardiac tamponade should be suspected whenever a patient presents with unexplained hypotension or pulsus paradoxus, especially following myocardial infarction, chest trauma, percutaneous coronary intervention, or cardiac surgery. Other risk factors include anticoagulation therapy, malignancy, or an underlying connective tissue disease. A pericardial rub may be appreciated during physical examination. ECG changes compatible with acute pericarditis may be present as is an enlarged cardiac silhouette on chest films. Diagnosis is generally determined by two-dimensional echocardiography that demonstrates an inspiratory increase of right ventricular dimensions and decrease of left ventricular dimensions, compression of the right atrium, right ventricular diastolic collapse, and a heart that swings with cardiac contractions. Left atrial collapse is less common than right atrial collapse but is very specific of cardiac tamponade. There is commonly also an abnormal inspiratory increase of blood flow velocity through the tricuspid valve accompanied by a decrease in mitral valve flow velocity as well as dilation of the inferior vena cava with lack of inspiratory collapse. Rapid infusion of fluid and percutaneous or surgical pericardial fluid drainage leads to immediate relief of chest discomfort, dyspnea, venous hypertension, and pulsus paradoxus.[87,88]

Pulmonary Arterial Hypertension

Evaluation of suspected pulmonary arterial hypertension generally consists of ECG, an arterial blood gas, a chest radiograph, pulmonary function testing, exercise capacity (6-min walk test), noninvasive Doppler echocardiography (with and without contrast), V/Q scanning (to rule out chronic thromboembolic disease), pulmonary angiography, and right heart catheterization to both confirm the diagnosis as well as identify any associated disorders. Testing for connective tissue disease or human immunodeficiency virus (HIV) infection may be considered in patients with suggestive clinical histories for these disorders.[89] Acute vasoreactivity testing (using intravenous epoprostenol or adenosine or inhaled nitric oxide) should be performed for patients with idiopathic pulmonary arterial hypertension. Polysomnography is indicated for patients with a clinical history suggestive of obstructive sleep apnea. Current and investigational agents for pulmonary arterial hypertension include potent vasodilators such as prostacyclin and its analogues (iloprost and treprostinil), endothelin receptor antagonists (bosentan and ambrisentan), sildenafil, a cylcic guanosine monophosphate (cGMP)–specific phosphodiesterase type 5 inhibitor, and high-dose calcium channel blockers. Pulmonary thromboendarterectomy may benefit patients with chronic thromboembolic pulmonary hypertension. Lung (preferably bilateral) transplantation or heart-lung transplantation may be considered for selected patients with New York Heart Association functional class III and IV symptoms.[90]

Thoracic Aortic Dissection

Rapid diagnosis and management are critical for patients with thoracic aortic dissection. Aortography, as a method of diagnosing thoracic aortic dissection, has been replaced by less invasive imaging techniques, such as transesophageal echocardiography, helical CT, and MRI, all of which yield clinically reliable data for both confirming as well as ruling out this condition. In one review, pooled sensitivity (98%–100%) and specificity (95%–98%) from 16 studies involving 1139 patients were comparable between these three less invasive imaging tools. Pooled positive likelihood ratio was higher for MRI than for transesophageal echocardiography or helical CT. The posttest probability of thoracic aortic

dissection following a positive result of each of these imaging tests is 93% to 96% if a patient has a high-risk (i.e., 50%) pretest probability of the condition, and 0.1% to 0.3% if a patient has a low-risk (i.e., 5%) pretest probability following a negative result from each of the imaging tests.[91]

Pneumothorax

Spontaneous pneumothorax can be either primary or secondary. Patients with small primary pneumothoraces may be observed closely for either progression or resolution if they are clinically stable. Chest catheter or tube insertion is indicated if the pneumothorax enlarges or if clinical deterioration occurs, as well as in patients with large primary or secondary pneumothoraces. Patients with small secondary spontaneous pneumothoraces who are clinically stable may be either observed or managed with a chest tube depending on clinical severity and course of the pneumothorax.[92,93]

Tension Pneumothorax

A tension pneumothorax is a life-threatening condition that requires urgent management. High intrathoracic pressures develop because of ingress of air into the pleural space via a one-way valve process, which, in turn, prevents egress of air; this gives rise to vena caval compression, reduction in venous return, and diminished cardiac output. Radiographically, a tension pneumothorax presents as a collapse of the ipsilateral lung, depression/flattening of the ipsilateral hemidiaphragm, and shift of the mediastinum to the contralateral hemithorax. Therapy consists of emergency percutaneous aspiration or chest tube insertion.[93]

Pancoast Tumors

Pancoast's (superior sulcus) tumors require a definitive tissue diagnosis prior to initiation of therapy, which may, in selected patients, include resection and/or chemoradiotherapy. MRI, both mediastinal and extrathoracic, is frequently performed to rule out involvement of adjacent neurovascular structures (brachial plexus, vertebral column, or subclavian vessels) that will influence surgical approaches.[94]

Chest Trauma

Blunt and penetrating chest trauma can give rise to chest pain related to hemothorax (bleeding into the pleural space), pneumothorax, rib, sternal or clavicular fractures, or injury to the chest wall musculature.

As little as 5 mL of hemothorax can be appreciated on a decubitus chest radiograph, but a size of about 200 mL is required for it to be readily identified on an upright chest radiograph, where it will appear as blunting or, with greater volume of bleeding, a concave upward sloping of the fluid, in the ipsilateral costophrenic angle. The presence of an air-fluid level indicates a hemopneumothorax. Chest CT is more sensitive than chest radiographs in detecting a small hemothorax; in addition, it may occasionally offer clues to the origin of the bleeding.

Rib fractures may be associated with injuries to the brachial plexus and subclavian veins (upper rib fractures) or spleen and liver (lower rib fractures). A flail chest resulting from at least two fracture sites on at least three consecutive ribs can create regional chest wall instability and respiratory distress. A sternal fracture occurs most commonly at the body or manubrium, generally following direct trauma to the anterior chest or from deceleration. Significant posterior displacement of the sternum may be associated with trauma to the underlying cardiovascular structures. Chest CT is more sensitive than plain chest radiographs for detecting rib and sternal fractures.[93]

Gastroesophageal Reflux

Dyspepsia secondary to gastroesophageal reflux can be managed with proton pump inhibitors, histamine$_2$ receptor antagonists, or prokinetic agents. An empirical trial with these medications may be considered if the clinical history strongly supports the diagnosis of gastroesophageal reflux and if the patient is not at high risk for a gastrointestinal malignancy. Risk factors, such as use of nonsteroidal anti-inflammatory agents, should be investigated. Endoscopy may be necessary in some patients with unexplained dyspepsia and persistent symptoms. Recommendations for eradication therapy of *Helicobacter pylori*–positive dyspepsia have been published.[95]

Pancreatitis

Common causes of acute pancreatitis include gallstone disease (about 50% of cases) and alcohol abuse (20%–25%). Patients typically complain of abdominal pain and vomiting, but chest pain may develop as well. Lipase determination, with its higher sensitivity and specificity over amylase, is preferred over the latter for the diagnosis of acute pancreatitis; the former is produced only by the pancreas. In addition, the half-life of lipase is longer than that of amylase. Other helpful laboratory tests include liver chemistries, triglyceride, and calcium. When diagnostic doubt exists, abdominal imaging by contrast enhanced CT may be beneficial. In additional to supportive measures, therapeutic endoscopic retrograde cholangiopancreatography (ERCP) may be considered, particularly if the acute pancreatitis is severe, due to gallstones, or when cholangitis, jaundice, or a dilated common bile duct is present. The presence of cholangitis is an indication for endoscopic sphincterotomy or duct drainage by stenting. Image-guided fine-needle aspiration is recommended for patients with significant pancreatic necrosis, who may require débridement if infection is present.[96,97]

KEY POINTS

- Chest pain is characterized by an unpleasant sensation that is either localized to the thorax or believed to originate from structures located in the latter. It may announce the presence of severe, occasionally life-threatening, disease.
- Pain arising from visceral organs (e.g., heart or gastrointestinal tract) differs in many ways from that arising from somatic structures, such as the skin. Visceral pain is difficult to localize, is diffuse in character, and is typically referred to somatic structures. It is also often associated with greater autonomic and motor responses than is somatic pain.
- Somatic and visceral innervations differ in relation to the density of innervations and spinal pattern of termination. In general, the number of visceral afferent fibers is disproportionately less than the number of somatic afferent fibers, although the rostrocaudal spread of visceral afferent fiber terminals in the spinal cord is considerably greater than the spread of central terminals from somatic afferent fibers. The low number of visceral afferents and greater intraspinal spread is responsible for loss of spatial discrimination, consistent with the diffuse, difficult-to-localize, nature of visceral pain.
- Pain is both hard to define as well as difficult to measure. Two widely used techniques, namely rating scales and questionnaires, are often used in clinical and epidemiologic studies of chest pain. Although rating scales constitute the simplest measurement of pain, the sensation of pain has many more components than just its intensity; thus, a single-dimensional rating scale leaves many aspects of the sensation undocumented.
- Pain arising from the various viscera in the thoracic cavity and from the chest wall is often qualitatively similar and exhibits overlapping patterns of referral, localization, and quality, given the proximity of the various organs and the vagaries of perception of pain of visceral origin. This leads to difficulty in the differential diagnosis of chest pain.

References

1. Crook J, Rideout E, Browne G: The prevalence of pain complaints in a general population. Pain 18:299–314, 1984.
2. Von Kroff M, Dworkin SF, Le Resch L, et al: An epidemiologic comparison of pain complaints. Pain 32:173–183, 1988.
3. Schappert SM: National Hospital Ambulatory Medical Survey: 1992 Emergency department summary. Data from the National Health Survey. Vital Health Stat 13. 125:1–108, 1997.
4. Perl ER: Pain and the discovery of nociceptors. *In* Belmonte C, Cervero F (eds): Neurobiology of Nociceptors. Oxford: Oxford University Press, 1996, pp 5–36.
5. Torebjork HE, Schmelz M, Handwerker HO: Functional properties of human cutaneous nociceptors and their role in pain and hyperalgesia. *In* Belmonte C, Cervero F (eds): Neurobiology of Nociceptors. Oxford: Oxford University Press, 1996, pp 349–369.
6. Sylven C: Mechanisms of pain in angina pectoris: A critical review of the adenosine hypothesis. Cardiovasc Drugs Ther 7:745–759, 1993.
7. Sugiura Y, Tonosaki Y: Spinal organization of unmyelinated visceral afferent fibers in comparison with somatic afferent fibers. *In* Gebhart GF (ed): Visceral Pain. Progress in Pain Research and Management Series (Vol 5). Seattle: IASP Press, 1995, pp 41–59.
8. Longhurst JC: Chemosensitive abdominal visceral afferents. *In* Gebhart GF (ed): Visceral Pain. Progress in Pain Research and Management Series (Vol 5). Seattle: IASP Press, 1995. pp 99–132.
9. Sengupta JN, Gebhart GF: Mechanosensitive afferent fibers in the gastrointestinal and lower urinary tracts. *In* Gebhart GF (ed): Visceral Pain. Progress in Pain Research and Management Series (Vol 5). Seattle: lASP Press, 1995, pp 75–98.
10. Urban MO, Gebhart GF: The glutamate synapse: A target in the pharmacologic management of hyperalgesic pain states. Prog Brain Res 116:382–395, 1998.
11. Liu H, Mantyh PW, Basbaum AI: NMDA receptor regulation of substance P release from primary afferent nociceptors. Nature 386:721–724, 1997.
12. Dougherly PM, Willis WD: Enhancement of spinothalamic neuron responses to chemical and mechanical stimuli following combined microiontophoretic application of *N*-methyl-D-aspartic acid and substance P. Pain 47:85–93, 1991.
13. Fields HL, Basbaum AI: Central nervous system mechanisms of pain modulation. *In* Wall PD, Melzack R (eds): Textbook of Pain (3rd ed). New York: Churchill Livingstone, 1993. pp 243–257.
14. Urban MO, Gebhart GF: Central mechanisms in pain. Med Clin North Am 83:585–596, 1999.
15. Euchner-Wamser I, Sengupta JN, Gebhart GF, et al: Characterization of responses of T2-T4 spinal cord neurons to esophageal distension in the rat. J Neurophysiol 69:868–883, 1993.
16. Hummel T, Sengupta JN, Meller ST, et al: Responses of T2-4 spinal cord neurons to irritation of the lower airways in the rat. Am J Physiol 273:R1147–R1157, 1997.
17. Chandler MJ, Zhang J, Foreman RD: Vagal, sympathetic and somatic sensory inputs to upper cervical (C1-C3) spinothalamic tract neurons in monkeys. J Neurophysiol 76:2555–2567, 1996.
18. Huskisson EC: Visual analogue scales. *In* Melzack R (ed): Pain Measurement and Assessment. New York: Raven, 1983, pp 33–37.
19. Kerns RD, Turk DC, Rudy TE: The West Haven-Yale Multidimensional Pain Inventory (WHYMPJ). Pain 23:345–356, 1985.
20. Melzack R: The McGill Pain Questionnaire: Major properties and scoring methods. Pain 1:277–299, 1975.
21. Graham C, Bond SS, Gerkousch MM, et al: Use of the McGill Pain Questionnaire in the assessment of cancer pain: Replicability and consistency. Pain 8:377–387, 1980.
22. Morton DR, Klassen KP, Curtis GM: The clinical physiology of the human bronchi. I. Pain of tracheobronchial origin. Surgery 28:699–704, 1950.
23. Cervero F: Sensory innervation of the viscera: Peripheral basis of visceral pain. Physiol Rev 74:95–138, 1994.
24. Widdicomb JG: Sensory innervation of the lungs and airways. Prog Brain Res 67:49–64, 1986.
25. Paintal AS: The visceral sensations: Some basic mechanisms. Prog Brain Res 67:3–20, 1986.

26. Coleridge JC, Coleridge HM: Afferent vagal C fibre innervation of the lungs and airways and its functional significance. Rev Physiol Biochem Pharmacol 99:1–110, 1984.
27. Light RW (ed): Clinical manifestations and useful tests. *In*: Pleural Disease (5th ed). Philadelphia: Lippincott Williams & Wilkins, 2007, pp 73–108.
28. Manganelli D, Palla A, Donnamaria V, et al: Clinical features of pulmonary embolism: Doubts and certainties. Chest 107:25S–32S, 1995.
29. Livneh A, Langevitz P, Pras M: Pulmonary associations in familial Mediterranean fever. Curr Opin Pulm Med 5:326–331, 1999.
30. Viar WN, Harrison TR: Chest pain in association with pulmonary hypertension: Its similarity to the pain of coronary disease. Circulation 5:1–11, 1952.
31. Rich S, Dantzker DR, Ayres SM, et al: Primary pulmonary hypertension: A national prospective study. Ann Intern Med 107:216–223, 1987.
32. Rubin LJ: Pathology and pathophysiology of primary pulmonary hypertension. Am J Cardiol 75:51A–54A, 1995.
33. Patrat J-F, Jondreau G, Dubourg O, et al: Left main coronary artery compression during primary pulmonary hypertension. Chest 112:842–843, 1997.
34. Bell WR, Simon TL, DeMets DL: The clinical features of submassive and massive pulmonary emboli. Am J Med 62:355–360, 1977.
35. Lasser RP, Genkins G: Chest pain in patients with isolated pulmonary stenosis. Circulation 15:258–266, 1957.
36. Guz A: Respiratory sensations in man. Br Med Bull 33:175–177, 1977.
37. Morton DR, Klassen KP, Curtis GM: The clinical physiology of the human bronchi. II. The effect of vagus section upon pain of tracheobronchial origin. Surgery 30:800–809, 1951.
38. Epstein SE, Gerber LH, Borer JS: Chest wall syndrome. JAMA 241:2793–2797, 1979.
39. Wise CM: Chest wall syndromes (editorial). Curr Opin Rheumatol 6:197–202, 1994.
40. Fruergaard P, Launbjerg J, Hesse B, et al: The diagnosis of patients admitted with acute chest pain but without myocardial infarction. Eur Heart J 17:1028–1034, 1996.
41. Mukerji B, Mukerji V, Alpert MA, et al: The prevalence of rheumatologic disorders in patients with chest pain and angiographically normal coronary arteries. Angiology 46:425–430, 1995.
42. Sklaroff HJ: Xyphodynia—Another cause of atypical chest pain: Six case reports. Mt Sinai J Med 46:546–548, 1979.
43. Alberti P, Antoci G, Rivadossi E, et al: Mondor syndrome: Etiopathogenesis and case report. Minerva Ginecol 44:541–544, 1992.
44. Roussos CS, Macklem PT: Diaphragmatic fatigue in man, J Appl Physiol 43:189–197, 1977.
45. Heckenkamp J, Helling HJ, Rehm KE: Post-traumatic costochondritis caused by *Candida albicans*: Aetiology, diagnosis and treatment. Scand Cardiovasc J 31:165–167, 1997.
46. Kamel M, Kotob H: Ultrasonographic assessment of local steroid injection in Tietze's syndrome. Br J Rheumatol 36:547–550, 1997.
47. Halperin JJ: Nervous system Lyme disease. J Neurol Sci 153:182–191, 1998.
48. Foreman RD: Organization of the spinothalamic tract as a relay for cardiopulmonary sympathelic afferent fiber activity. Prog Sens Physiol 9:2–51, 1989.
49. Crea F, Gaspardone A: New look at an old symptom: Angina pectoris. Circulation 96:3766–3773, 1997.
50. Malliani A, Lombardi F, Pagani M: Sensory innervaton of the heart. Prog Brain Res 67:39–48, 1986.
51. Donat WE: Chest pain: Cardiac and noncardiac causes. Clin Chest Med 8:241–252, 1987.
52. Campbell J, King SB, Douglas JS, et al: Prevalence and distribution of disease in patients catheterized for suspected coronary disease. *In* King SB, Douglas JS (eds): Coronary Arteriography and Angioplasty. New York: McGraw-Hill, 1985, p 365.
53. Mayer S, Hillis LD: Prinzmetal's variant angina. Clin Cardiol 21:243–246, 1998.
54. Lambert CR: Pathophysiology of stable angina pectoris. Cardiol Clin 9:1–10, 1991.
55. Kaski JC: Chest pain and normal coronary arteriograms: Role of "microvascular spasm." Lancet 351:1144–1145, 1998.
56. Mohri M, Koyanagi M, Egashira K, el al: Angina pectoris caused by coronary microvascular spasm. Lancet 351:1165–1169, 1998.
57. Myrtek M, Fichtler A, Konig K, et al: Differences between patients with asymptomatic and symptomatic myocardial infarction: The relevance of psychological factors. Eur Heart J 15:311–317, 1994.
58. Rutter MK, McComb JM, Brady S, et al: Silent myocardial ischemia and microalbuminuria in asymptomatic subjects with non-insulin dependent diabetes mellitus. Am J Cardiol 83:27–31, 1999.
59. Shirey EK, Proudfit WL, Hawk WA: Primary myocardial disease: Correlation with clinical findings, angiographic, and biopsy diagnosis: Follow-up of 139 patients. Am Heart J 99:198–207, 1980.
60. Schneider RR, Seckler SG: Evaluation of acute chest pain. Med Clin North Am 65:53–66, 1981.
61. Gregoratos G: Pericardial involvement in myocardial infarction. Cardiol Clin 8:601–608, 1990.
62. Brook I, Frazier EH: Microbiology of acute purulent pericarditis: A 12-year experience in a military hospital. Arch Intern Med 156:1857–1860, 1996.
63. Prince SE, Cunha BA: Postpericardiotomy syndrome. Heart Lung 26:165–168, 1997.
64. Hoffman RS, Hollander JE: Evaluation of patients with chest pain after cocaine use. Crit Care Clin 13:809–828, 1997.
65. Hollander JE, Hoffman RS, Gennis P, et al: Prospective multicenter evaluation of cocaine-associated chest pain. Acad Emerg Med 1:330–339, 1994.
66. Pitts WR, Lange RA, Cigarroa JE, et al: Cocaine-induced myocardial ischemia and infarction: Pathophysiology, recognition, and management. Prog Cardiovasc Dis 40:65–76, 1997.
67. Eagle KA, DeSanctis RW: Aortic dissection. Curr Probl Cardiol 14:227–278, 1989.
68. Christensen J: Origin of sensation in the esophagus. Am J Physiol 246:G221–G225, 1984.
69. Richter JE: Gastroesophageal reflux as a cause of chest pain. Med Clin North Am 75:1065–1080, 1991.
70. Pasricha PJ: Noncardiac chest pain: From nutcrackers to nociceptors. Gastroenterology 112:309–310, 1997.
71. Lewin KH, Wilbourn AJ, Maggiano HJ: Cervical rib and median sternotomy–related brachial plexopathies: A reassessment. Neurology 50:1407–1413, 1998.
72. Jordan SE, Machleder HI: Diagnosis of thoracic outlet syndrome using electrophysiologically guided anterior scalene blocks. Ann Vasc Surg 121:260–264, 1998.
73. Webb JG, Simmonds SD, Chan-Yan C: Central catheter malposition presenting as chest pain. Chest 89:309–312, 1986.
74. Fleet RP, Dupuis G, Marchand A, et al: Panic disorder in coronary artery disease patients with noncardiac chest pain. J Psychosom Res 44:81–90, 1998.
75. Gibbons RJ, Balady GJ, Bricker JT, et al: ACC/AHA 2002 guideline update for exercise testing: Summary article. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines). J Am Coll Cardiol 40:1531–1540, 2002.
76. Douglas PS, Khandheria B, Stainback RF, et al: ACCF/ASE/ACEP/AHA/ASNC/SCAI/SCCT/SCMR 2008 appropriateness criteria for stress echocardiography: a report of the American College of Cardiology Foundation Appropriateness Criteria Task Force, American Society of Echocardiography, American College of Emergency Physicians, American Heart Association, American Society of Nuclear Cardiology, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, and Society for Cardiovascular Magnetic Resonance: Endorsed by the Heart Rhythm Society and the Society of Critical Care Medicine. Circulation 117:1478–1497, 2008.

76a. Hendel RC, Berman DS, Di Carli MF, et al: CCF/ASNC/ACR/AHA/ASE/SCCT/SCMR/SNM 2009 appropriate use criteria for cardiac radionuclide imaging: A report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, the American Society of Nuclear Cardiology, the American College of Radiology, the American Heart Association, the American Society of Echocardiography, the Society of Cardiovascular Computed Tomography, the Society for Cardiovascular Magnetic Resonance, and the Society of Nuclear Medicine. Endorsed by the American College of Emergency Physicians. J Am Coll Cardiol 53:2201–2229, 2009.

77. Anderson JL, Adams CD, Antman EM, et al: ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction) developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. J Am Coll Cardiol 50:e1–e157, 2007.
78. King SB 3rd, Smith SC Jr, Hirshfeld JW Jr, et al: 2007 focused update of the ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice guidelines. J Am Coll Cardiol 51:172–209, 2008.
79. Eagle KA, Guyton RA, Davidoff R, et al: ACC/AHA 2004 guideline update for coronary artery bypass graft surgery: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1999 Guidelines for Coronary Artery Bypass Graft Surgery). Circulation 110:e340–e437, 2004.
80. Fraker TD Jr, Fihn SD, 2002 Chronic Stable Angina Writing Committee, et al: 2007 chronic angina focused update of the ACC/AHA 2002 guidelines for the management of patients with chronic stable angina: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines Writing Group to develop the focused update of the 2002 guidelines for the management of patients with chronic stable angina. J Am Coll Cardiol 50:2264–2274, 2007.
81. Snow V, Barry P, Fihn SD, et al: Primary care management of chronic stable angina and asymptomatic suspected or known coronary artery disease: A clinical practice guideline from the American College of Physicians. Ann Intern Med 141:562–567, 2004.
81a. Verheugt FW: Acute myocardial infarction associated with ST segment elevation and the new European Society of Cardiology guidelines. Heart 95:1112–1117, 2009.
81b. Campbell-Scherer DL, Green LA: ACC/AHA guideline update for the management of ST-segment elevation myocardial infarction. Am Fam Physician 79:1080–1086, 2009.
82. Bavry AA, Kumbhani DJ, Rassi AN, et al: Benefit of early invasive therapy in acute coronary syndromes: A meta-analysis of contemporary randomized clinical trials. J Am Coll Cardiol 48:1319–1325, 2006.
83. Snow V, Barry P, Fihn SD, et al: Evaluation of primary care patients with chronic stable angina: Guidelines from the American College of Physicians. Ann Intern Med 141:57–64, 2004.
84. Becattini C, Vedovati MC, Agnelli G: Prognostic value of troponins in acute pulmonary embolism: A meta-analysis. Circulation 116:427–433, 2007.
85. Roy PM, Colombet I, Durieux P, et al: Systematic review and meta-analysis of strategies for the diagnosis of suspected pulmonary embolism. BMJ 331(7511):259, 2005.
86. Snow V, Qaseem A, Barry P, et al: Management of venous thromboembolism: A clinical practice guideline from the American College of Physicians and the American Academy of Family Physicians. Ann Intern Med 146:204–210, 2007.
87. Hoit BD: Pericardial disease and pericardial tamponade. Crit Care Med 35(8 Suppl):S355–S364, 2007.
88. Fowler NO: Cardiac tamponade. A clinical or an echocardiographic diagnosis? Circulation 87:1738–1741, 1993.
89. McGoon M, Gutterman D, Steen V, et al: Screening, early detection, and diagnosis of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. Chest 126(1 Suppl):14S–34S, 2004.
90. Rubin LJ: American College of Chest Physicians: Diagnosis and management of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. Chest 126(1 Suppl):7S–10S, 2003.
91. Shiga T, Wajima Z, Apfel CC, et al: Diagnostic accuracy of transesophageal echocardiography, helical computed tomography, and magnetic resonance imaging for suspected thoracic aortic dissection: Systematic review and meta-analysis. Arch Intern Med 166:1350–1356, 2006.
92. Baumann MH, Strange C, Heffner JE, et al: Management of spontaneous pneumothorax: An American College of Chest Physicians Delphi consensus statement. Chest 119:590–602, 2001.
93. Miller LA: Chest wall, lung, and pleural space trauma. Radiol Clin North Am 44:213–224, viii, 2006.
94. Shen KR, Meyers BF, Larner JM, et al: Special treatment issues in lung cancer: ACCP evidence-based clinical practice guidelines (2nd ed). Chest 132(3 Suppl):290S–305S, 2007.
95. Veldhuyzen van Zanten SJ, Flook N, Chiba N, et al. An evidence-based approach to the management of uninvestigated dyspepsia in the era of *Helicobacter pylori*. Canadian Dyspepsia Working Group. CMAJ 162(12 Suppl):S3–S23, 2000.
96. Working Party of the British Society of Gastroenterology; Association of Surgeons of Great Britain and Ireland; Pancreatic Society of Great Britain and Ireland; Association of Upper GI Surgeons of Great Britain and Ireland: UK guidelines for the management of acute pancreatitis. Gut 54(Suppl 3):iii1–iii9, 2005.
97. American Gastroenterological Association (AGA) Institute on "Management of Acute Pancreatitis" Clinical Practice and Economics Committee; AGA Institute Governing Board: AGA Institute medical position statement on acute pancreatitis. Gastroenterology 132:2019–2021, 2007.

CHAPTER 31

VIRAL INFECTIONS

F. Eun-Hyung Lee, MD • John Treanor, MD

INTRODUCTION
Classification
Transmission
Pathogenesis of Infection

CLINICAL SYNDROMES
Common Cold
Pharyngitis
Acute Bronchitis
Influenza-like Illness
Croup
Bronchiolitis
Pneumonia

MAJOR VIRAL PATHOGENS
Adenoviruses
Coronaviruses
Cytomegalovirus
Hantaviruses
Herpes Simplex Viruses
Influenza Viruses
Measles Virus
Metapneumoviruses
Parainfluenza Viruses
Respiratory Syncytial Virus
Rhinovirus
Varicella-Zoster Virus

INTRODUCTION

Viral infections are important causes of disease of the respiratory tract. The common cold is the most frequently encountered infectious syndrome of humans, while influenza continues to be a major cause of mortality and serious morbidity on a worldwide basis. Respiratory viral infections frequently complicate the course of patients with chronic obstructive pulmonary disease and asthma. As the number of immunocompromised persons in the population has increased, infections due to cytomegalovirus and other herpesviruses, adenoviruses, and paramyxoviruses have assumed increasing importance in pulmonary medicine. Finally, recent years have seen the continuing emergence of new viral respiratory pathogens, including hantaviruses, human metapneumovirus, avian and porcine influenza A viruses, and the SARS coronavirus. This introductory section outlines general concepts of respiratory viral infections and their associated clinical syndromes. The following sections then provide a review of the major viral pathogens infecting the respiratory tract.

Classification

Viruses of importance in the respiratory tract (Table 31-1) include both those considered to be principal respiratory viruses—whose replication is generally restricted to the respiratory tract—and others in which respiratory involvement is part of a generalized infection. Virus classification depends in part on the type and configuration of the nucleic acids in the viral genome, the characteristics of the viral structural proteins, and the presence or absence of an envelope surrounding the virus particle. The number of distinct antigenic types within each virus family also varies.

Transmission

The routes by which the different respiratory viruses spread from person to person are variable and include combinations of contact, droplet, and aerosol transmission. For example, rhinovirus and respiratory syncytial virus are primarily spread by direct contact with contaminated skin and environmental surfaces, followed by self-inoculation of virus onto the nasal mucosa or conjunctiva. Others viruses, such as measles and varicella-zoster viruses, spread as small-particle aerosols. Other viruses may spread by means of larger-particle aerosols over short distances (1 meter). The relative importance of the various transmission routes under natural conditions for each virus varies and in many cases is unknown.

TABLE 31-1. Viral Infections of the Respiratory Tract

Group	Nucleic Acid	Envelope	Types	Disease/Syndrome*
Adenovirus	DNA	No	1–47	Common cold; bronchitis; bronchiolitis; pharyngoconjunctival fever; acute respiratory disease (ARD) in military recruits; pneumonia
Coronavirus	RNA	Yes	229E, OC43, HuCoV-SARS	Common cold, severe acute respiratory syndrome (SARS)
Hantavirus	RNA	Yes	Multiple	Acute respiratory distress, pneumonitis
Orthomyxovirus	RNA	Yes		
Influenza virus			A, B, C	Influenza; common cold; pharyngitis; croup; bronchitis; bronchiolitis; pneumonia
Paramyxoviruses	RNA	Yes		
Measles virus				Measles; pneumonia; bronchiectasis
Parainfluenza virus			1–4	Common cold; croup; bronchitis; bronchiolitis; pneumonia
Respiratory syncytial virus			A, B	Common cold; croup; bronchitis; bronchiolitis; pneumonia
Human metapneumovirus			A, B	Bronchiolitis, common cold
Picornaviruses	RNA	No		
Enterovirus				
Coxsackievirus			1–24	Type A21 (Coe virus) colds and ARD; others (types 2, 4, 5, 6, 8, 10); herpangina
Echovirus			1–34	Common cold (importance uncertain)
Rhinovirus			1–100	Common cold
Herpes viruses	DNA	Yes		
Herpes simplex virus			1, 2	Acute pharyngitis in normal persons; chronic ulcerative pharyngitis; tracheitis; pneumonia in immunosuppressed patients
Cytomegalovirus			1	Mononucleosis; acute and chronic pharyngitis; pneumonia in immunosuppressed patients
Varicella-zoster virus			1	Pneumonia in normal persons and immunosuppressed patients
Epstein-Barr virus			1	Mononucleosis; acute and chronic pharyngitis
Human herpesvirus 6			1	Pneumonia in immunosuppressed patients
Filovirus	RNA	Yes	Marburg; Ebola 1, 2	Pharyngitis as an early manifestation of hemorrhagic fever
Human immunodeficiency virus	RNA	Yes	1, 2	Pharyngitis with primary infection; secondary pulmonary infections
Papillomavirus	DNA	No	>60	Laryngeal and tracheobronchial papillomatosis

*Bacterial infections, including sinusitis, otitis media, and pneumonia, complicate respiratory virus infection. Also, infection with the respiratory viruses may precipitate attacks of asthma and cause exacerbations in patients with chronic obstructive pulmonary disease.

Pathogenesis of Infection

The initial sites of infection and pathogenesis differ for the various virus groups. Some, such as rhinovirus, are associated mainly with upper respiratory tract involvement. Others, such as influenza, commonly invade the lower airways and sometimes the pulmonary parenchyma in addition to causing upper airway disease. The viruses also differ in the extent that virus-induced cell damage and host immune response and inflammation contribute to the clinical manifestations of disease.

An additional important feature of respiratory virus infections is their effect on the resident bacterial flora of the upper airways. Respiratory virus infections have been found to alter bacterial colonization patterns, increase bacterial adhesion to respiratory epithelium, and reduce mucociliary clearance and phagocytosis. These impairments of host defenses by virus allow colonization by pathogenic bacteria and invasion of normally sterile areas, such as the paranasal sinuses, middle ear, and lower respiratory tract, often resulting in secondary infection.

CLINICAL SYNDROMES

As shown in Table 31-1, infection by one of the respiratory viruses may result in more than one clinical syn-

drome. Similarly, a particular syndrome can result from infection with one of several different viruses. The poor correlation of agent and syndrome makes specific etiologic diagnosis on clinical grounds inaccurate, although knowledge of the seasonal patterns of infection may be helpful. Moreover, infection with a single virus may cause disease at multiple levels of the respiratory tract.

Common Cold

There is no universally accepted, standard definition of a "cold," but the term is usually used to refer to acute rhinitis with variable degrees of pharyngitis. Systemic complaints are absent or modest in severity, and fever is unusual. Allergic diseases of the upper airway often have clinical manifestations similar to those of colds. Colds are frequently associated with involvement of the middle ear, presumably due to eustachian tube dysfunction. Colds are associated with symptomatic otitis media in approximately 2% of cases in adults, and in a higher proportion in young children. Colds are frequently associated with sinus mucosal thickening or secretions on computed tomography (CT) scans, but rarely result in symptomatic sinusitis. Vertigo associated with viral labyrinthitis may also be seen.

The common cold syndrome is caused by any one of a large number of antigenically distinct viruses found in four principal groups (Table 31-2). Epidemiologic studies have indicated that, on an annual basis, any one antigenic type of virus is responsible for less than 1% of all colds. Since the discovery of the respiratory viruses in the 1960s, rhinovirus has emerged as the prototype common cold virus (Fig. 31-1).

The recommended treatment for colds is to use individual remedies to treat specific symptoms. Nasal sprays containing decongestants should be used for no more than 3 days to prevent a rebound vasomotor rhinitis. Cough syrups containing expectorants are of unproven value in common colds. Symptoms of sneezing and rhinorrhea can be alleviated with nonselective sedating antihistamines such as brompheniramine, chlorpheniramine, or clemastine fumarate,[1] but treatment with selective histamine$_1$ inhibitors is not effective. Studies of pseudoephedrine have demonstrated measurable improvements in nasal airflow consistent with a decongestant effect.[2] Nonsteroidal anti-inflammatory drugs such as naproxen moderate the systemic symptoms of rhinovirus infection. However, the use of the decongestant phenylpropanolamine has been shown to be associated with an increased risk of hemorrhagic stroke.[3] Topical application of ipratropium, a quaternary anticholinergic agent that is minimally absorbed across biologic membranes, reduces rhinorrhea significantly in naturally occurring colds. This agent probably exerts its major effect on the parasympathetic regulation of mucous and seromucous glands. Importantly, most over-the-counter cough and cold remedies have not been studied in pediatric populations, in which they may be associated with significant side effects.[4]

TABLE 31-2. Viruses Associated with the Common Cold

Virus	Percentage of Cases*
Rhinovirus	40
Coronavirus	10
Parainfluenza virus Respiratory syncytial virus Influenza virus Adenovirus	10–15
Other viruses (enterovirus, rubeola, rubella, varicella)	5
Presumed undiscovered viruses	20–30
Group A β-hemolytic streptococci†	5–10

*Estimated percentage of colds annually.
†Included because differentiation of streptococcal and viral pharyngitis is not possible by clinical means.

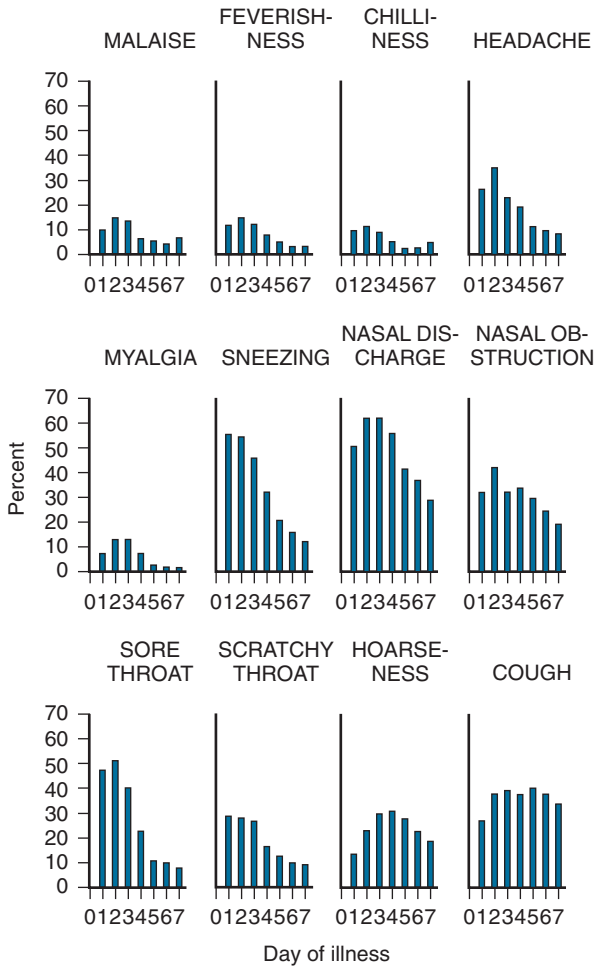

FIGURE 31-1 ■ Graphs showing the clinical features of rhinovirus colds (139 natural infections). (Adapted from Gwaltney JM Jr, Hendley JO, Simon G, Jordan WS Jr: Rhinovirus infections in an industrial population. II. Characteristics of illness and antibody response. JAMA 202:494–500, 1967.)

Pharyngitis

Pharyngitis occurs most often as part of the common cold syndrome and thus is usually associated with the same viruses that cause colds. In some cases, pharyngeal symptoms predominate to a degree that overshadows other complaints; the soreness may be attributable to the presence of kinins, which are potent stimulators of pain nerve endings. High levels of bradykinin and lysylbradykinin are present in nasal secretions of patients with rhinovirus colds; furthermore, intranasal application of bradykinin promotes sore throat and nasal symptoms in volunteers, supporting a role for these agents in the pathogenesis of cold symptoms.[5]

The respiratory viruses causing pharyngitis can be divided into two groups: those associated with a pharyngeal or tonsillar exudate and those in which such an exudate does not occur (Table 31-3). Pharyngitis is often a prominent complaint with adenovirus and influenza virus infection. Also, some viruses are associated with other types of enanthema, such as vesicles and ulcers. Coxsackie A viruses are associated with the condition herpangina, a painful, often febrile pharyngitis of children and young adults characterized by vesicular lesions of the soft palate.

Viruses in the herpes family cause a small proportion of cases of pharyngitis. Primary infection with herpes simplex virus manifests as an acute vesiculoulcerative pharyngitis or gingivostomatitis that may have an exudative character. In immunocompromised patients, herpes simplex virus causes large, shallow ulcers of the mucosa that are chronic and progressive if untreated (Fig. 31-2). Epstein-Barr virus mononucleosis characteristically has an acute exudative pharyngitis. Mononucleosis due to cytomegalovirus infection may have a nonexudative pharyngitis that is acute or chronic, and cytomegalovirus also rarely causes oral ulcerations in immunosuppressed patients. Pharyngitis occurs in primary infection with human immunodeficiency virus (HIV). Viruses in the hemorrhagic fever group produce an acute pharyngitis that occurs early in the disease, before skin lesions appear. Also, exudative pharyngitis is a common clinical manifestation in Lassa fever.

TABLE 31-3. Important Microbial Agents Associated with Acute Pharyngitis

Pharyngitis with colds and influenzal illness (no exudate)	Rhinovirus Influenza virus Coronavirus Respiratory syncytial virus
Exudative pharyngitis (exudate is not present in all cases)	*Streptococcus pyogenes* (group A β-hemolytic streptococcus) Mixed anaerobic infection (Vincent's angina and peritonsillar abscess) Adenovirus Herpes simplex virus Epstein-Barr virus *Corynebacterium diphtheriae* (pseudomembrane)

Typically, sore throat accompanied by nasal symptoms is more likely to be viral in nature. Infection with mixed anaerobic bacteria (Vincent's angina) or with *Corynebacterium diphtheria* are also in the differential diagnosis of exudative pharyngitis. The treatment of most cases of viral pharyngitis is symptomatic.

Acute Bronchitis

The diagnosis of acute bronchitis is usually applied to cases of acute respiratory disease with severe and prolonged cough that continues after other signs and symptoms of the acute infection have subsided. Cough occurs during the first week of illness in 30% of rhinovirus colds in young adults and in 80% or more of cases of influenza A virus infection, in which it is often prolonged. Adenovirus infections characteristically involve the tracheobronchial tree, with resultant bronchitis, which in military populations is part of the syndrome of *acute respiratory disease.*

The mechanisms of cough production in viral infection are not well understood, but may include direct damage to the respiratory mucosa, release of inflammatory substances in response to the infection, increased production and/or decreased clearance of respiratory secretions, and stimulation of airway irritant receptors. Intranasal application of several prostaglandins also produces cough in uninfected volunteers.[5] Infection may also enhance airway reactivity, leading to increased sensitivity to cold air and pollutants such as cigarette smoke.

The differential diagnosis of acute bronchitis includes nonviral infections and noninfectious etiologies such as cough-variant asthma. *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* infections cause prolonged cough; *Bordetella pertussis* infection should also be considered in the differential diagnosis. In otherwise healthy persons, workup of acute cough should be directed toward determining the presence of pneumonia; if this

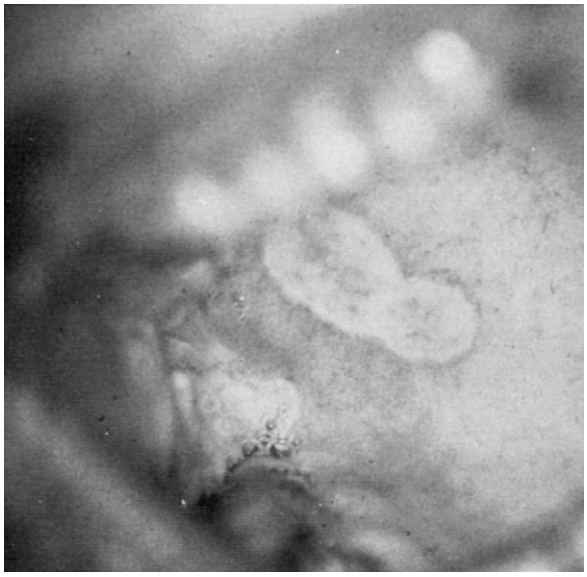

FIGURE 31-2 ■ Chronic herpetic ulcerations overlying the hard palate in an immunosuppressed patient.

is not present, then treatment with antibacterial agents is of no benefit.[6] Symptomatic treatment is directed at the suppression of cough. In children, a single nocturnal dose of honey is as effective as dextromethorphan in suppressing nighttime coughing.[7]

Influenza-like Illness

The clinical syndrome of influenza is characterized by the rapid onset of constitutional symptoms, including fever, chills, prostration, muscle aches, and headache, concurrent with or followed by upper and lower respiratory tract symptoms. Systemic symptoms tend to dominate the first several days of illness, whereas respiratory complaints, particularly cough, predominate later in the first week of illness. Photophobia, excess tearing, and pain with eye movement are common early in the illness. Mild conjunctivitis, clear nasal discharge without obstruction, pharyngeal injection, and small, tender cervical lymph nodes are frequently present. Fever, peaking at 39°C to 40°C or higher, may occur and can last for 1 to 5 days. Persistent nonproductive cough, easy fatigability, and asthenia are common in the second week of illness.

Influenza type A and B viruses are the most important causes of the influenza syndrome, particularly when it occurs in epidemic form. However, the syndrome can occur in association with infection by other viruses, including adenoviruses, parainfluenza viruses, and respiratory syncytial virus. The characteristic clinical features of influenza and its epidemic nature permit the practitioner to make an accurate diagnosis in most cases seen during recognized epidemics of influenza virus infection, particularly if cough and fever are present.[8] Specific antiviral therapy is effective if given early in the course of the illness (see the section on influenza viruses). Symptomatic treatment (bed rest, oral hydration, antipyretics, and antitussives) is also beneficial. Fever should be treated in certain clinical situations, such as in children with previous febrile convulsions or patients with preexisting cardiac disease. Because of its possible association with Reye's syndrome, aspirin should be avoided in pediatric patients.

Croup

The croup syndrome of children is characterized by an unusual brassy or barking cough that may be accompanied by inspiratory stridor, dyspnea, and hoarseness. The symptoms are often preceded by several days of upper respiratory illness and are typically worse at night. Croup is seen primarily in children under the age of 6 years. The term *acute infectious croup* or *laryngotracheobronchitis* is applied to a contagious disease that affects otherwise healthy children and that is often associated with a respiratory illness in the family. The term *acute spasmodic croup* is applied to a similar syndrome that is most common in young children who are prone to recurrent attacks, which may be precipitated by respiratory viral infections and possibly allergic or other factors. In these children, fever is frequently absent, and symptoms often abate within several hours.

Most children with acute laryngotracheobronchitis have symptoms of decreasing intensity over several days and can be managed at home. However, increasing laryngeal obstruction can be associated with respiratory insufficiency, which is manifested by restlessness, air hunger, stridor at rest, use of accessory muscles, and intercostal retractions, and which may be followed by development of exhaustion with severe hypoventilation, cyanosis, and cardiovascular collapse. A fluctuating course is typical.

Radiologic examination of the upper airway shows glottic and subglottic edema (Fig. 31-3) and helps to differentiate the disorder from acute bacterial epiglottitis.

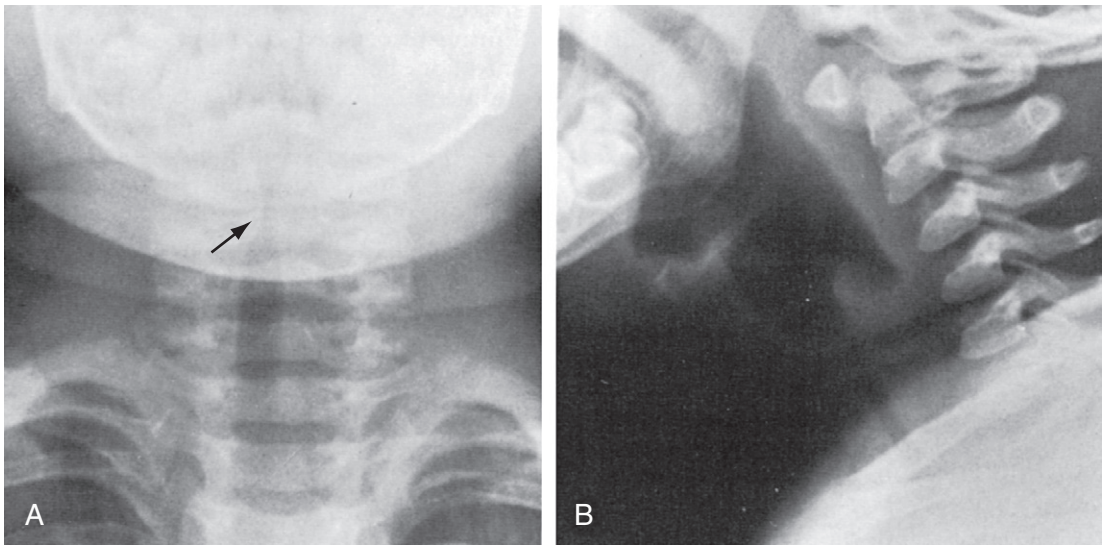

FIGURE 31-3 ■ Anteroposterior **(A)** and lateral **(B)** neck roentgenograms of a 2-year-old child with croupy cough, inspiratory stridor, and fever. The anteroposterior view shows subglottic narrowing in the steeple pattern (*arrow*) characteristic of laryngotracheobronchitis caused by parainfluenza virus. The lateral view shows ballooning of the hypopharynx resulting from laryngeal obstruction. (Courtesy of Joan McIlhenny, MD, Department of Radiology, University of Virginia Medical Center, Charlottesville, Virginia.)

However, radiographs are limited in accuracy, and when the diagnosis is uncertain, radiologic and pharyngeal examination should be avoided because of the risk of cardiorespiratory arrest in acute epiglottitis. Emergency assessment by an otolaryngologist or an anesthesiologist is indicated in this situation.

The acute infectious croup syndrome has been associated principally with infection by one of the parainfluenza viruses, as well as respiratory syncytial virus, influenza A and B viruses, adenoviruses, and rhinovirus. Measles is an important cause of severe croup in the developing world, and influenza A epidemics also are associated with severe croup. The differential diagnosis of croup includes acute bacterial epiglottitis, diphtheritic croup, asthma, and intrinsic or extrinsic upper airway obstruction related to an aspirated foreign body, allergic angioedema, and retropharyngeal abscess.

Because the majority of hospitalized children are hypoxic, oxygen is the mainstay of treatment for severe disease. Humidified air or mist therapy is commonly used, but the value of mist therapy has not been proven, and removal of the child from the parents and placement in a mist tent can be more distressing to the child than beneficial.

Nebulized racemic epinephrine is commonly used for symptomatic relief in croup. It is believed that α-adrenergic stimulation by this drug causes mucosal vasoconstriction, leading in turn to decreased subglottic edema. The onset of action is rapid, often within minutes, but the duration of relief is also limited, lasting 2 hours or less. Therefore, treated subjects should be observed closely for clinical deterioration. While symptomatic relief is considerable, use of epinephrine is not associated with improvements in oxygenation. Steroids have been shown to confer significant benefits in the management of mild, moderate, and severe croup, including more rapid improvement in symptoms, reduced length of hospital stay, and reduced rates of intubation. Administration of single-dose steroid therapy in this setting has not been associated with significant side effects, and should probably be used in any patient with significant enough illness to require an emergency room or clinic visit.[9]

Antiviral agents have not been tested for efficacy in this situation, although the potential benefit of the use of an antiviral in the typical self-limited course of croup would likely be limited. Because croup is a viral illness, antibiotic therapy is of no benefit.

Bronchiolitis

Bronchiolitis is an acute inflammatory disorder of the small airways characterized by obstruction with air trapping, hyperinflation of the lungs, and atelectasis that typically occurs in children under the age of 2 years. After a several-day prodrome of mild upper respiratory tract symptoms, patients typically present with inspiratory and expiratory wheezing. The clinical features, which include tachypnea, intercostal and suprasternal retractions, nasal flaring, hyperresonant chest, wheezing, and inspiratory crackles, usually lead to an accurate clinical diagnosis. The infant is often afebrile, and in mild cases symptoms resolve within several days. Chest roentgenograms show hyperinflated lungs with flattening of the diaphragms, peribronchial thickening, and often atelectasis or parenchymal consolidation indicative of concurrent bronchopneumonia (Fig. 31-4). The white blood cell count and differential count are usually within normal limits.

The majority of cases in which an etiologic agent has been demonstrated are associated with respiratory syncytial virus. Other viruses associated with bronchiolitis include human metapneumovirus, parainfluenza viruses, influenza A and B viruses, adenoviruses, measles virus, and rhinovirus. The major differential diagnostic consideration is asthma, which is uncommon under the age of 1 year.

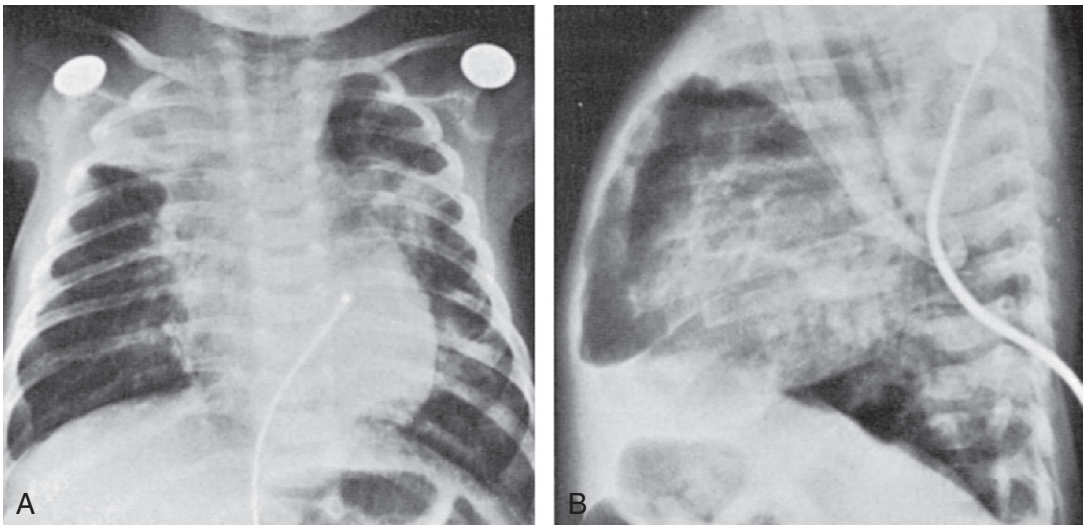

FIGURE 31-4 ■ Anteroposterior **(A)** and lateral supine **(B)** chest roentgenograms of a 1-month-old child with respiratory syncytial virus pneumonia. Note the marked overexpansion and patchy infiltrates in both upper and left lower lung zones. (Courtesy of Thomas Lee Pope, Jr., MD, Department of Radiology, University of Virginia Medical Center, Charlottesville, Virginia.)

Correction of hypoxemia is the most important aspect of managing lower respiratory tract disease. Studies of corticosteroid therapies have found no consistent benefit, and bronchodilating drugs are not effective and may contribute to increased restlessness and cardiovascular stress. Because of the dehydrating effect of tachypnea and reduced oral intake in some hospitalized infants, parenteral rehydration is often needed, but care must be taken to avoid inducing hyponatremia. Aerosol treatment with the synthetic nucleoside ribavirin has been associated with reductions in virus titers but inconsistent clinical benefits.

Pneumonia

Viruses are important causes of pneumonia in both adults and children. They have been associated with up to 40% of radiographically proven pneumonias in hospitalized adults and are estimated to cause 16% of total pneumonias in pediatric outpatients and up to 49% in hospitalized infants. These figures may underestimate the importance of viral infections as a cause of pneumonia, particularly in outpatients, because of the insensitivity of viral diagnostic methods and because of the lack of chest roentgenograms in many patients with acute viral infections. Also, because viral infections may be complicated by secondary bacterial pneumonias, invasive procedures would be needed to accurately differentiate among pure viral pneumonias, secondary bacterial pneumonias, and mixed viral and bacterial infections.

Normal Host

The relative importance of the different viruses as causes of pneumonia in otherwise healthy people depends on the season in which illness occurs and the age distribution of the population under study. During outbreaks, influenza virus accounts for over 50% of viral pneumonia in adults. In addition, respiratory syncytial virus, adenoviruses, parainfluenza viruses, and varicella virus can all cause pneumonia in healthy adults. Unusual viruses continue to emerge in epidemics of severe acute pneumonitis, including hantaviruses, coronavirus (that causing severe acute respiratory syndrome [SARS]), and both avian and porcine influenza A viruses.

In children, respiratory syncytial virus, parainfluenza viruses, and adenoviruses—in addition to influenza viruses—are the most important causes of pneumonia. Measles virus pneumonia occurs in children and adults during epidemics in susceptible populations. There are reports of cases of pneumonia in adults and children attributable to rhinovirus, but the evidence that these viruses are definite causes of pneumonia is circumstantial.

The clinical and radiographic features of sporadic cases of viral pneumonia are usually not sufficiently characteristic to permit specific viral diagnosis or differentiation from bacterial pneumonias on clinical grounds alone. Exceptions include measles and varicella pneumonia, in which the associated rash establishes the diagnosis. Therefore, attention is first directed at excluding primary or secondary bacterial pneumonia. If available, viral cultures of respiratory secretions and tests to detect viral antigens or nucleic acids may provide a specific diagnosis. Serologic testing may be useful.

Treatment of viral pneumonia in the normal host is supportive in nature and is directed at early antimicrobial therapy of secondary bacterial infections. Specific antiviral therapy may be beneficial and is discussed with the individual pathogens later in the chapter. Viral pneumonias with extensive involvement of lung tissue may require prolonged ventilatory assistance and pulmonary rehabilitation. Some cases of viral pneumonia have a rapid and relentless fatal course, with generalized alveolar and interstitial infiltrates, development of the acute respiratory distress syndrome (ARDS), and progressive respiratory failure.

Immunocompromised Host

Viral pneumonia is an important problem in the increasing number of persons in the population who have deficiencies in immunity as the result of cytotoxic chemotherapy, organ transplantation, and the acquired immunodeficiency syndrome (AIDS). The major respiratory viruses that affect healthy persons may also cause pneumonia in immunodeficient hosts, and severe and prolonged pneumonias due to adenovirus, respiratory syncytial, influenza, measles, or parainfluenza viruses may develop in such patients. In addition, these individuals may develop pneumonia due to viruses that rarely cause lower respiratory tract disease in normal hosts, such as cytomegalovirus, which causes severe primary viral pneumonia as well as predisposing patients to bacterial and fungal superinfections because of its added immunosuppressive effects. Also, varicella-zoster and herpes simplex virus pneumonias are relatively uncommon but serious infections in immunosuppressed patients.

MAJOR VIRAL PATHOGENS

Adenoviruses

Adenoviruses are medium-sized (65 to 80 nm), nonenveloped viruses with a genome composed of linear double-stranded deoxyribonucleic acid (DNA)[10] (Fig. 31-5). Currently, 47 antigenic types of adenovirus are associated with human infection, although not all types have been associated with human disease. The protein coat of the virus is composed of 252 hexagonal and pentagonal capsomeres in an icosahedral array with long projecting fibers at each vertex. These fibers are thought to be the site of host cell attachment. Adenovirus types 2 and 5 and Coxsackie B viruses utilize the same receptor, designated the Coxsackie-adeno receptor (CAR). Interaction of the penton base with α_5 integrins also promotes virus entry into the cell. Type-specific antigens, which give rise to neutralizing antibody, are present on the hexons and fibers of the capsid. The hexons also contain a complement fixation antigen with cross reactivity among the mammalian adenoviruses.

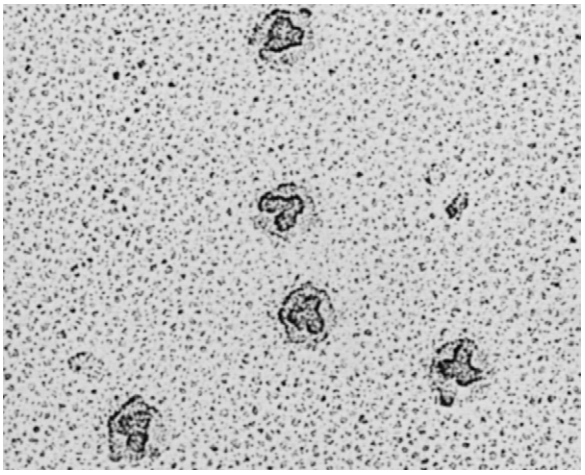

FIGURE 31-5 ■ Photoelectron micrograph showing human adenovirus type 2. Each virion contains a lobulated group of three adenosomes, which are composed of DNA and protein. Full virion particles contain a total of 12 adenosomes, each of which is found below one vertex of the icosahedral capsid. (Courtesy of J. Brown and W. Newcomb, University of Virginia, Charlottesville, Virginia.)

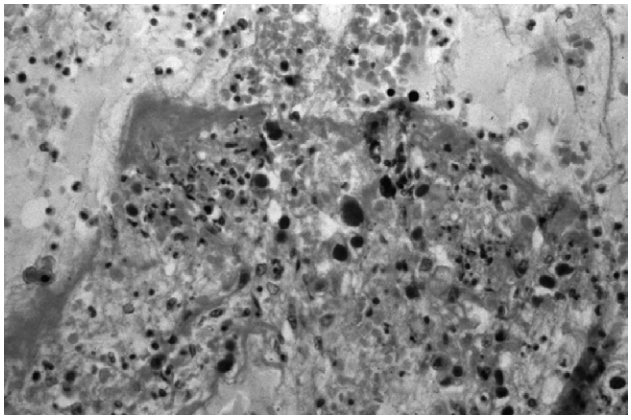

FIGURE 31-6 ■ Photomicrograph of lung tissue from a fatal case of adenovirus pneumonia, illustrating the characteristic "smudge" cells.

Epidemiology and Transmission

Humans are the reservoir of the adenoviruses that cause human disease, although nonhuman adenoviruses are found in other species. Some serotypes, especially types 1 and 2, routinely infect infants and young children, who then have prolonged asymptomatic viral shedding from the respiratory and gastrointestinal tracts. Other types, including those that have been most often implicated in respiratory disease (e.g., types 3, 4, and 7), are acquired later in life, characteristically in epidemic settings. In most instances, viral transmission probably occurs by direct contact with infectious secretions. However, the explosive nature of adenoviral acute respiratory disease in military recruits probably reflects airborne spread.

Most community adenovirus respiratory disease has been recognized in the summer months in association with outbreaks or sporadic cases of febrile pharyngitis or bronchitis. Nosocomial outbreaks of adenovirus infection have occurred in hospital wards, special care units, and psychiatric facilities. Since 1996, a specific variant of adenovirus type 7 (Ad7d2) has been responsible for several civilian outbreaks and a large military outbreak.[11] The appearance of this new Ad7 genotype may herald a shift in the predominant strains with greater disease impact.

Pathogenesis

Adenoviruses have been isolated from the upper airway, eye, urine, stool, and, rarely, blood. The incubation period for naturally acquired adenovirus disease of the respiratory tract is in the range of 4 to 7 days but may be up to 2 weeks.

Cytopathologic changes have also been observed in bronchial epithelium cells,[12] and crystalline arrays of virus particles have been found in alveolar lining cells of infected persons with severe illness.[13] The extent of damage to the respiratory tract in nonfatal adenovirus respiratory disease is not well defined, but may result from a combination of virus-related cytopathology and host-related inflammatory responses to infection. In cases of fatal adenovirus pneumonia, bronchial epithelial necrosis, bronchial obstruction, and interstitial pneumonia have been seen.[14] Cells containing large basophilic, intranuclear inclusions—so-called smudge cells—appear to be characteristic (Fig. 31-6). In lung transplant recipients, a necrotizing bronchocentric pneumonia with diffuse alveolar damage has been reported.[15]

Clinical Illness

Adenovirus Respiratory Disease. The nonpneumonic respiratory syndromes associated with adenovirus infection include acute respiratory disease of military recruits and *pharyngoconjunctival fever* of civilians, which have similar characteristics (Fig. 31-7). Adenovirus respiratory disease typically involves the pharynx as a moderate to severe, sometimes purulent, pharyngitis. Also characteristic of this disease is marked tracheitis, bronchitis, or tracheobronchitis, plus rhinitis and conjunctivitis. Conjunctivitis is not a feature of infection with the other major respiratory viruses and therefore, when present, is a useful diagnostic finding in adenovirus respiratory disease. With adenovirus respiratory disease, the conjunctivitis is typically mild and follicular, although some adenovirus types also cause the more severe condition, epidemic keratoconjunctivitis. Fever, chills, myalgia, and prostration are prominent features of adenovirus infection, so it is often perceived by the patient as a "flulike" illness or an unusually severe cold.

Cases of acute respiratory disease tend to have more tracheobronchitis, perhaps reflecting acquisition of infection by the airborne route. Conversely, in pharyngoconjunctival fever, the infrequency of cough and other tracheobronchial complaints in some outbreaks may reflect infection contracted by pharyngeal and/or conjunctival inoculation with virus from contaminated

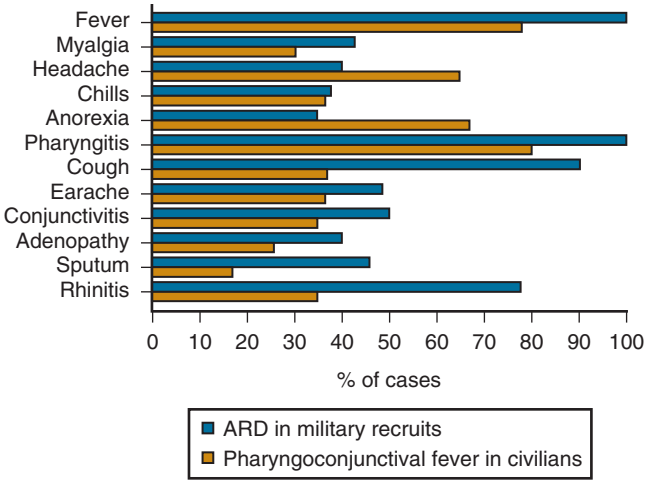

FIGURE 31-7 ■ Graph showing comparison of the clinical characteristics of acute respiratory disease (ARD) of military recruits and pharyngoconjunctival fever of civilians. (Adapted from Dascomb HE, Hilleman MR: Clinical and laboratory studies in patients with respiratory disease caused by adenoviruses. Am J Med 21:161–174, 1956; and Martone WJ, Hierholzer JC, Keenlyside RA, et al: An outbreak of adenovirus type 3 disease at a private recreation center swimming pool. Am J Epidemiol 111:229–237, 1980.)

water. The two syndromes are associated with the same viral serotypes, and in civilian populations, both occur as sporadic cases. In young children, adenovirus infection has been associated with both mild and febrile respiratory illness; concomitant otitis media occurred in approximately 40% of these cases.

Adenovirus Pneumonia. Adenovirus was first recognized as a cause of viral pneumonia in military recruits and has since been recognized as a rare cause of pneumonia in civilian adults and children. The clinical characteristics of adenovirus pneumonia are similar to those of other pneumonias, so that it is difficult to make an accurate etiologic diagnosis on the basis of clinical features. In fatal cases there has been extensive pulmonary damage, with death occurring 2 to 3 weeks into the illness. Intravascular coagulopathy has also been a late feature of some cases, and a septic-shock picture has been described.[16] Adenoviruses cause a particularly aggressive form of pneumonia in neonates, characterized by necrotizing bronchiolitis and alveolitis.[17] Viral acquisition from the mother, perhaps via the birth canal, may occur. Long-term sequelae of adenovirus infection may include persistent radiographic abnormalities, abnormal pulmonary function tests, bronchiectasis, and hyperlucent lung.

Adenovirus Infection in Persons with Impaired Immunity. Adenoviruses can cause fatal pneumonia and disseminated infection, with hepatitis, hemorrhagic cystitis, and renal failure, in transplant patients and other persons with immunodeficiency.[18] A variety of immunotypes have been recovered from these patients (Table 31-4), including higher numbered serotypes that are only seen in such patients. Types seen with particular frequency include 1, 2, 5, 6, 7, 11, 21, 31, 34, and 35. The clinical importance of the recovery of an adenovirus from these patients, particularly from stool samples, is often difficult to determine because of the multifactorial nature of their disease.

TABLE 31-4. Adenoviruses Associated with Respiratory Tract Disease in Immunocompromised Patients*

PRIMARY IMMUNODEFICIENCIES	
Upper Respiratory Tract Infection	
Group B	Type 34
Bronchitis	
Group C	Type 1
Bronchiolitis	
Group C	Type 2
Pneumonia	
Group A	Type 31
Group B	Types 7, 11, 35
Group C	Type 2
ORGAN TRANSPLANT RECIPIENTS	
Upper Respiratory Tract Infection	
Group B	Type 7
Group C	Type 2
Pneumonia	
Group A	Type 31
Group B	Types 7, 11, 34, 35
Group C	Types 1, 2, 5, 6
Group E	Type 4
CANCER IMMUNOSUPPRESSION PATIENTS	
Upper Respiratory Tract Infection	
Group A	Type 31
Group B	Type 35
Pneumonia	
Group B	Type 21
Group C	Types 1, 2
Group E	Type 4
AIDS PATIENTS	
Upper Respiratory Tract Infection	
Group A	Type 31
Group D	Type 29
Pneumonia	
Group B	Types 3, 11, 16, 21, 34, 35
Group C	Types 1, 2, 5
Group D	Types 8, 22, 29, 30, 37, 43, 44, 45, 46, 47

*Adapted from Hierholzer JC: Adenoviruses in the immunocompromised host. Clin Microbiol Rev 5:262–274, 1992.

Diagnosis

Diagnosis may be achieved either by virus isolation or by direct detection of viral antigens or nucleic acids from appropriate specimens of respiratory secretions, conjunctival swabs, stool, and urine, depending on the clinical syndrome. Rapid detection of viral antigens in clinical specimens by enzyme-linked immunosorbent

assay or immunoflorescence and of viral DNA by nucleic acid amplification techniques is increasingly used, because of the fastidiousness of some serotypes and the slow rate of isolation. Quantitative measurement of adenovirus DNA levels in plasma may be useful for diagnosis and response to therapy.[19]

Frozen specimens (−70°C) are satisfactory for testing because of the relative stability of adenoviruses. Cytopathic effect usually appears in cell culture in 3 to 7 days, but may take several weeks. The time required to detect virus in cell culture can be shortened to as little as 2 days by employing centrifugation culture systems. Serodiagnosis has relied primarily on testing for a group-specific complement fixation antibody response, using acute and convalescent serum specimens. Infection with some adenovirus types is not detected by the complement fixation test. In biopsy specimens, the appearance of characteristic intranuclear basophilic inclusion bodies seen by light microscopy or of crystalline arrays of virus seen by electron microscopy are useful in histopathologic diagnosis.

Treatment and Prevention

Antiviral treatment of proven value for adenovirus infection is not available. Both the broad-spectrum antiviral agents ganciclovir and cidofovir, and ribavirin for group C adenoviruses, are active in vitro, and an increasing number of reports indicate that intravenous gancyclovir may be useful in seriously ill patients, although at the expense of significant renal toxicity.[20] Cidofovir has also been used for preemptive therapy in high-risk immunocompromised patients.[21] While intravenous ribavirin[22] or ribavirin combined with immunoglobulin[23] has been administered in individual patients, failures are common.[24] Donor leukocyte infusions have also been tried.

Because of the prominent fever and systemic complaints associated with adenovirus respiratory disease, analgesics, such as aspirin and acetaminophen, are needed more often than with a milder coryzal illness such as a rhinovirus cold. Warm saline gargles are helpful for relieving throat pain, which does not usually require narcotics. The presence of pharyngeal exudate may sometimes lead to an incorrect diagnosis of streptococcal pharyngitis, resulting in the initiation of antimicrobial therapy.

Effective and safe live oral vaccines for adenovirus types 4 and 7 were developed for military use, and, when delivered in enteric-coated capsules, controlled acute respiratory disease in recruit populations. Of note, use of these vaccines was not associated with replacement by nonvaccine serotypes. Because the manufacturer no longer produces these vaccines, they are not currently used in the military. Consequently, adenoviruses have reemerged as important causes of lower respiratory tract disease in this population.

Coronaviruses

Coronaviruses are enveloped viruses containing a single-stranded, positive-sense ribonucleic acid (RNA) genome of approximately 29,000 nucleotides. Distinctive club-shaped projections are present on the virus surface, giving the appearance of a crown or corona, from which it derives its name. Coronaviruses can be classified into three main groups, two mammalian (I and II) and one avian (III), based on genetic and antigenic differences. The group I strains include coronavirus strain 229E (HCoV 229E) and HCoV NL63, while group II includes strains HCoV OC43 and HKU1. In addition, the novel coronavirus responsible for *severe acute respiratory syndrome* (SARS), denoted HuCoV-SARS, is also a member of group II.

The virus contains five structural proteins: spike or Sprotein, hemagglutinin-esterase (HE), M (matrix), E (envelope), and N (nucleocapsid). The S protein is the major envelope glycoprotein and mediates both attachment to cells and fusion with the cell membrane. Antibodies to the spike protein are thought to be associated with protection and thus candidates for therapeutic and vaccine targets. A second envelope protein, HE, is only found in some coronavirus strains, but is not present on HuCoV-SARS. Nonstructural proteins such as the viral replicases and proteinases, particularly the 3C-like proteinase, are also antiviral targets.

Epidemiology and Transmission

Human coronaviruses OC43 and 229E have been recognized as causes of the common cold for many years and cause frequent reinfections throughout life. In adults these viruses have accounted for 4% to 15% of acute respiratory disease annually and up to 35% during peak periods. Annual illness rates in children reach 8%, with peak rates of up to 20%.[25] The reported frequency of infection in adults for 229E and OC43 viruses has ranged from 15 to 25 per 100 persons per year, with up to 80% of infections occurring in persons with prior antibody to the infecting virus.[26] Coronaviruses usually circulate during winter and early spring, but can be detected year-round.[27]

For all coronaviruses, transmission involves inoculation of the respiratory tract with infectious secretions via large droplets and close contact, as demonstrated in human challenge experiments for OC43[28] and animal studies for HuCoV-SARS.[29] In the spring of 2003, the emergence of HuCoV-SARS occurred in southern China, and the virus rapidly spread worldwide.[30] Virus shedding for HuCoV-SARS peaked at day 10 of symptom onset, which was at the height of disease severity.[31] This phenomenon accounted for the preponderance of transmission in hospitals. The incubation period for SARS is estimated from 2 to 10 days, and for conventional human coronaviruses 3 to 4 days.

Pathogenesis

Conventional coronavirus antigen has been detected in epithelial cells shed from the nasopharynx of infected volunteers,[32] and during experimental infection, nasal airway resistance, mucosal temperature, and the albumin content of nasal secretions increase.[33] However, relatively little is known about the pathogenesis of

the common cold induced by conventional human coronaviruses.

The hallmark of the pulmonary pathology in fatal cases of SARS was diffuse alveolar damage,[34] type II pneumocyte hyperplasia, squamous metaplasia, and multinucleated giant cells. Hemophagocytosis has been reported, potentially as a consequence of cytokine dysregulation.[35] Furthermore, virus was detected within pulmonary epithelial cells.[36] From these findings, it is postulated that disease pathogenesis involves direct damage to pulmonary epithelia by the virus in combination with an overly enthusiastic host immune response.

Clinical Illness

Conventional human coronaviruses produce a typical coryzal illness that is indistinguishable from colds due to other viruses. Coronaviruses have also been linked with acute otitis media, exacerbations of asthma in children, and exacerbations of chronic bronchitis and pneumonia in adults.

In contrast, SARS has a nonspecific presentation that is difficult to distinguish from other viral acute respiratory illnesses, particularly influenza. Common symptoms on presentation are fever, chills and/or rigors, myalgias, and occasionally diarrhea. Cough and dyspnea are the predominant respiratory symptoms but may not be present initially. Respiratory disease becomes more severe over 4 to 7 days, and about 20% of patients require respiratory support. SARS fatality rates were 11% for all ages but much higher in older adults[37]; children generally had mild disease.[38] SARS laboratory abnormalities include elevations in lactate dehydrogenase, transaminases, and creatine kinase, and hematologic abnormalities, particularly lymphopenia (depletion of CD4 and CD8 T cells), and thrombocytopenia.

Common findings on chest CT include unilateral or bilateral ground-glass opacifications, and interlobular septal and intralobular interstitial thickening. In most patients, peripheral involvement in the lower lung zones has been observed. In some cases, after recovery from acute illness, pulmonary fibrosis has developed.[39] Clinical features predictive of poor outcomes included the presence of bilateral disease at presentation, peak level of lactate dehydrogenase, older age, and other comorbid conditions.

Diagnosis

The main site of viral replication of HuCoV-SARS appears to be the lower respiratory tract[36]; therefore, polymerase chain reaction (PCR) detection is the most reliable in the sputum, but virus can also be detected in the blood and stool.[40] Serum antibodies rise within 2 to 3 weeks of illness, although measurements at 4 weeks have become the standard to exclude SARS.

Treatment and Prevention

Current available human antiviral treatments for HuCoV-SARS include chloroquine, protease inhibitors, ribavirin, type I interferons, niclosamide, and anti-inflammatory agents such as indomethacin.[41–43] Ribavirin, a purine nucleoside analogue, was used early during the SARS epidemic. Then, ribavirin in combination with lopinavir/ritonavir (protease inhibitors commonly used in HIV disease) was associated with a lower incidence of adverse outcomes compared to historical controls of ribavirin alone. Nelfinavir, another protease inhibitor, also has demonstrated in vitro antiviral activity. Other targets for controlling SARS viral replication have included interferons. In an uncontrolled clinical study, the use of corticosteroids with interferon alfacon-1 (synthetic interferon-α) demonstrated improvements in oxygenation.[44] Although the mechanisms are unknown, chloroquine, niclosamide, and indomethacin all have activity inhibitory to HuCoV-SARS in vitro.[45–47] Neutralizing antibodies to the S1 protein contained in convalescent plasma (stocked by the Hong Kong Red Cross) may also be important in preventing viral entry.[43]

For conventional coronoviruses, immunity is short lived. Epidemiologic studies of coronovirus infection have demonstrated high reinfection rates.[48] In human volunteer experiments, infection with a 229E-like coronavirus only induced effective immunity short term because rechallenge with homotypic virus, the 229E serotype, resulted in infection and illness.[49] In addition, under certain circumstances, vaccines against animal coronaviruses have led to enhanced disease.[50] Thus, efforts to derive a coronavirus vaccine for humans may be difficult.

Cytomegalovirus

Cytomegalovirus (CMV) is a member of the gammaherpesvirus subfamily of the herpesviruses and has the same structural and biochemical characteristics, which include an internal core containing linear double-stranded DNA, an icosadeltahedral capsid containing 162 capsomeres, and an envelope derived from the host-cell nuclear membrane. However, the large size of the CMV virion (200 nm) and larger genome distinguish it from the other human herpesviruses. There is approximately 80% homology between the genomes of various strains of CMV, but sufficient differences exist to permit strain identification by restriction endonuclease analysis. The CMV genome codes for approximately 33 structural proteins, the functions of many of which are currently unknown. In addition, clinical isolates often encode multiple gene products not seen in laboratory strains. Envelope glycoproteins B and H have been identified as a major antigens eliciting neutralizing antibody. Glycoprotein B may also be a target for cytotoxic T-lymphocyte responses,[51] while multiple proteins serve as targets for T-cell responses. Cytomegalovirus-specific, cytotoxic T-cell responses are an important host defense mechanism that has been shown to be associated with survival from CMV infection in bone marrow transplant recipients.[52] However, CMV uses multiple mechanisms, including down-regulation of human leukocyte antigen on the cell surface and interference with antigen processing, to evade recognition by the host.

Epidemiology and Transmission

Infection with CMV, whether disease associated or asymptomatic, is followed by prolonged excretion of virus in urine, saliva, stool, tears, breast milk, vaginal secretions, and semen. Thus, the major community reservoir for CMV is asymptomatic infected persons. Virus shedding persists for years in children with congenital and perinatal CMV infections. Transmission of the virus is believed to occur by direct contact, especially under conditions of intimacy such as found in child care centers[53] and the family setting. Thus, the rate of acquisition of infection is greater in populations with high density, leading to infection at an early age. In addition to transmission by sexual intercourse, passage through a contaminated birth canal, and ingestion of breast milk, CMV infection can be acquired from transfused blood products and from transplanted organs. No seasonal patterns of CMV infection have been observed.

Pathogenesis

In human fibroblast cell cultures, CMV produces a slowly progressive lytic infection. Infected cells contain large irregular basophilic intranuclear inclusions and also eosinophilic inclusions in paranuclear areas. The intranuclear inclusions are a hallmark of CMV infection and have been found in cells of a number of organs, including kidney, liver, lung, and the gastrointestinal tract (Fig. 31-8). In the lung, fibroblasts, epithelial cells, endothelial cells, and smooth muscle cells are all targets for CMV infection.[54]

In immunocompetent persons, most infections are subclinical. If symptoms occur, the most typical manifestation is acute pharyngitis with features similar to mononucleosis. In immunocompromised hosts there may be a variety of clinical syndromes, whose severity is affected by whether infection is acquired de novo or represents reactivation of endogenous virus. The risk of severe disease is particularly high in transplant patients when a CMV-seronegative recipient receives an organ from a seropositive donor.

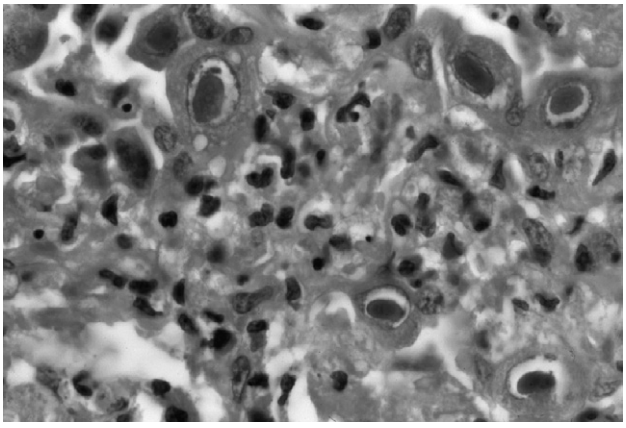

FIGURE 31-8 ■ Photomicrograph of lung tissue from an individual with CMV pneumonia, showing eosinophilic intranuclear inclusions.

The pathogenesis of CMV pneumonia is partly related to viral replication but also is thought to have an immunopathologic basis.[55] The development of CMV pneumonitis reflects a complex interaction between viral infection and graft-versus-host disease, particularly in marrow transplant recipients.[56,57] Two patterns of histopathology have been described in the lung tissue of bone marrow transplant patients with serious pneumonia.[58] One is a miliary pattern, with multiple focal lesions showing extensive cytomegaly with localized necrobiosis, alveolar hemorrhage, fibrin deposition, and neutrophilic response (see Fig. 31-8). The other is of interstitial character, with alveolar cell hyperplasia, interstitial edema, lymphoid infiltration, and diffusely distributed cytomegalic cells.

Clinical Illness

Cytomegalovirus causes a variety of human diseases, including congenital and perinatal infections, infectious mononucleosis, hepatitis, posttransfusion infection, and invasive infection in patients with impaired immunity. In transplant populations, CMV infection often involves multiple organ systems in conjunction with other opportunistic infectious agents.

The main impact of CMV is as a respiratory pathogen is in immunocompromised patients because the virus rarely causes pneumonia in healthy hosts. In recipients of allogeneic bone marrow transplants, CMV is recognized as the most common infectious cause of interstitial pneumonia and, untreated, is responsible for the highest fatality rate. The risk of CMV pneumonia is greatest between 30 and 90 days after bone marrow transplantation. However, late occurrence of CMV syndromes posttransplantation (i.e., at >180 days) has been increasingly recognized with effective control of earlier onset disease.

Risk factors for the disease include advanced age, the presence of acute graft-versus-host disease, intensive conditioning regimens, and allografts. Cytomegalovirus infection and pneumonitis also develop in the majority of isolated lung transplant recipients who are serologically at risk, usually in the transplanted lung.[59] In these patients, CMV pneumonitis may be a factor in the development of *bronchiolitis obliterans* reactions, a serious posttransplantation complication. Cytomegalovirus can also be a primary pathogen in persons with AIDS, although it is more often encountered in conjunction with other pulmonary pathogens.

Characteristically, patients with CMV pneumonia have sustained fever, nonproductive cough, and dyspnea. Crackles and tachypnea are often present, and marked hypoxemia is an indicator of life-threatening infection. Pneumonitis may be accompanied by mild neutropenia, thrombocytopenia, and elevated liver enzymes, which may be helpful in differential diagnosis. Chest radiographic changes are usually bilateral, with diffuse or focal haziness involving the middle and lower lung fields. Both miliary and interstitial radiographic patterns have been described (Fig. 31-9). Patients with a miliary pattern of lung pathology may have a sudden onset of tachypnea, severe respiratory distress, and hypoxemia resulting in a

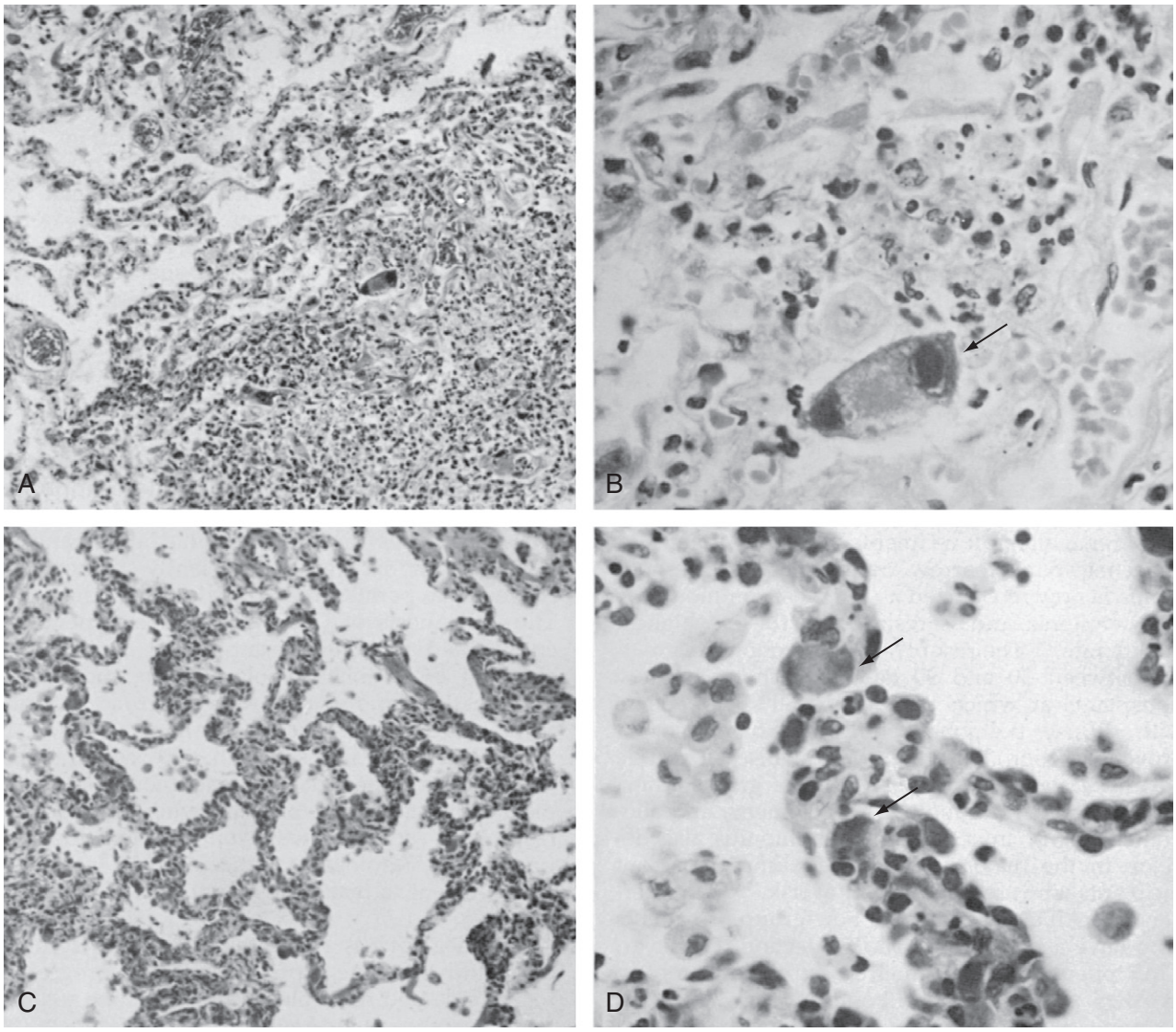

FIGURE 31-9 ■ Multifocal or miliary pattern and diffuse interstitial pneumonitis patterns of CMV pneumonia. **A,** The multifocal pattern has well-circumscribed lesions adjacent to relatively normal pulmonary tissue. **B,** Within these lesions are numerous cells with cytomegaly and intranuclear inclusions (*arrow*), a neutrophilic response, and cellular necrosis. **C,** The diffuse interstitial pneumonitis pattern of CMV pneumonia shows alveolar cell hyperplasia, interstitial thickening, and mild mononuclear cell infiltrate. **D,** Interspersed with the alveolar lining cells are cells with characteristic cytomegaly (*arrows*). (Hematoxylin and eosin stain; **A** and **C,** magnification ×150; **B** and **D,** ×600.) (Courtesy of W. E. Beschorner, Johns Hopkins University, Baltimore, Maryland.)

rapidly fatal course,[60] whereas patients with an interstitial pattern of disease often have an insidious onset of pneumonia with slowly progressive hypoxemia. In these patients, pulmonary infiltrates may be initially localized, with bilateral spread over days or weeks. Often the perihilar distribution of the infiltrate is suggestive of pulmonary edema.[59] Common CT scan findings include small nodules, consolidation, and ground-glass attenuation.[61]

Reactivation of CMV recently has been demonstrated to play a role in critically ill previously immunocompetent patients. During the critical illness, some recent evidence suggests a transient and vulnerable period of "immunoparalysis," indicating reactivation and not exogenous infection of CMV. In these patients, CMV viremia occurred with frequencies of 33% and was associated with prolonged hospitalization and death.[62] At this time, however, it is unclear if CMV prophylaxis would be beneficial.

Diagnosis

Cytomegalovirus pneumonia should be in the differential diagnosis for any immunosuppressed patient with unexplained lower respiratory complaints or pulmonary infiltrates. However, the clinical assessment of patients with suspected CMV pneumonia is complicated by their frequently having simultaneous pulmonary infections with other microbial agents and because the clinical features and radiographic appearance of CMV pneumonia are not

sufficiently characteristic to permit an accurate etiologic diagnosis. Because of its generally immunosuppressive properties, CMV predisposes to infections with bacterial[63] and fungal pathogens, such as *Aspergillus.*[64] In addition, noninfectious pulmonary conditions are also common in the population at risk for CMV pneumonitis, including pulmonary malignancy or hemorrhage and posttransplant lymphoproliferative disorder. Culture and pathologic examination of specimens obtained by bronchoalveolar lavage and biopsy are diagnostic. However, the detection of virus in respiratory secretions, urine, or blood does not establish with certainty that CMV is responsible for a particular clinical syndrome. This is particularly true in patients with AIDS, in whom detection of CMV in bronchoalveolar lavage fluid is often not associated with pulmonary pathology. However, in transplant recipients, detection of CMV in blood does increase the risk of subsequent development of CMV pneumonia, and may be useful in guiding preemptive therapy.

The time required for appearance of viral cytopathic effect in cell culture depends on the quantity of virus in the specimen tested and ranges from 2 to more than 35 days, with a median of approximately 1 week. Laboratory diagnosis can be expedited by a technique of centrifugation of the specimen onto cell monolayers in shell vials coupled with immunofluorescent staining for viral antigen. However, direct detection of the CMV antigen (pp67 antigen) in leukocytes or plasma, as well as detection of viral DNA or messenger RNA by nucleic acid amplification, are the most rapid and sensitive techniques.[65] The CMV viral load by quantitative PCR is a good predictor of development of CMV disease in transplant recipients. Serologic testing has no role in diagnosis of acute infection and is used only to determine the serologic status of donors and recipients prior to transplantation.

Treatment and Prevention

Once CMV pneumonitis is established, particularly in allogeneic bone marrow transplant patients, it is very difficult to treat. Ganciclovir is highly active against CMV in vitro, but monotherapy is not effective in pneumonitis in bone marrow transplant recipients. The combination of ganciclovir therapy and intravenous CMV immune globulin can reduce mortality from approximately 90% to 50% or lower in these patients.[66] The effect of the immune globulin in this situation may mostly be to ameliorate graft-versus-host disease. Whether combination therapy is required in solid organ transplant recipients with CMV pneumonia is uncertain. Cidofovir and foscarnet are other antiviral drugs with activity against CMV; both have been used to successfully treat CMV retinitis, but their effectiveness for treating CMV pneumonia has not been established. All of the available CMV antivirals have serious side effects that limit their usefulness.

Guidelines for reducing the risk of CMV disease in stem cell transplant recipients have recently been published.[67] Transplant candidates should be screened for evidence of CMV immunity, and CMV-seronegative recipients of allogeneic stem cell transplants from CMV-seronegative donors should receive only leukocyte-reduced or CMV-seronegative red blood cells and/or leukocyte-reduced platelets. In mismatched solid organ transplant recipients (donor+/recipient−), posttransplant prophylaxis with oral ganciclovir or its prodrug valganciclovir significantly reduces the risk of CMV disease, although late-onset disease still occurs.[68] Another strategy is preemptive therapy with ganciclovir or another anti-CMV agent when screening detects infection, but before disease develops. This strategy requires the use of sensitive and specific laboratory tests for diagnosis.

No vaccines are available for prevention of CMV infection or disease, although several strategies are being actively pursued, including live, attenuated virus vaccines and inactivated subunit vaccines.

Hantaviruses

Hantaviruses are members of the Bunyavirus family and include a number of genetically diverse viruses. By electron microscopy, one of the hantaviruses—Sin Nombre virus (SNV)—is roughly spherical, with a mean diameter of 112 nm. The virions contain a dense envelope, surrounded by fine surface projections. Filamentous nucleocapsids are present within the virions. The genome consists of negative-sense single-stranded RNA arranged in three physically discrete gene segments. The smallest segment (S) encodes the nucleoprotein; the middle-sized segment (M), the two envelope glycoproteins, G1 and G2; and the largest (L), the putative polymerase protein.[69]

These viruses are difficult to isolate from clinical material in cell culture, and grow slowly. Viral entry into the cell is mediated by a variety of cell surface integrins,[70] which may be related to the patterns of pathogenicity of the virus. The genome is segmented, and genetic reassortments in dually infected cells are common. It is believed that new pathogenic strains arise by this mechanism.

Epidemiology and Transmission

The *hantavirus pulmonary syndrome* (HPS) is a zoonosis in which rodents experience prolonged asymptomatic infection, and humans experience severe, often fatal disease. Each of the individual hantavirus strains appears to be associated with a specific rodent host: for example, SNV with the deer mouse (*Peromyscus maniculatus*), Bayou virus with the rice rat (*Oryzomys palustris*), Black Creek Canal virus with the cotton rat (*Sigmodon hispidus*), New York virus with the white-footed mouse (*Peromycus leucopus*), and so on. The features that are associated with maintenance of these viruses in rodent populations and with rodent-to-rodent transmission are unclear. However, serologic studies suggest that hantaviral infection of feral rodents is widespread throughout North America.[71]

Transmission to humans is presumed to be the result of contact with infected rodent excreta. Virus can be

isolated from urine, feces, and wet cage bedding for as long as 150 days postinfection in asymptomatic cotton rats.[72] Risk factors for acquisition of HPS include peridomestic cleaning, agricultural activities, and other forms of occupational exposure to rodent droppings, as well as high densities of rodents in the household. In the Four Corners region, the occurrence of El Nino–southern oscillation events have been linked to increased rainfall, rodent population densities, and thus cases of hantavirus cardiopulmonary syndrome (HCPS).[73]

Person-to-person transmission was not seen in the North American outbreaks.[74] In contrast, a recent outbreak of HPS in South America has suggested that, under certain circumstances, person-to-person transmission can occur.[75] Whether this feature is unique to the particular hantavirus implicated in that outbreak (Andes virus) or will be a feature in future outbreaks is unknown at present.

Pathogenesis

Infection with SNV or other agents of HPS have relatively long incubation periods (approximately 8 to 20 days), and antibody and cellular responses in humans are usually detectable at the time of presentation.[76] Neutralizing antibody is directed against the surface glycoproteins G1 and G2, and lower titers on presentation correlate with greater disease severity.[77] Viremia is detectable at presentation and declines promptly after resolution of fever.

Pathologic findings in fatal cases include pleural effusions, alveolar edema and fibrin, and interstitial mononuclear cell infiltrate[78] with little necrosis or polymorphonuclear leukocyte infiltration. These findings are believed to be most consistent with a capillary leak syndrome with subsequent noncardiogenic pulmonary edema as the major mechanism of disease. Immunopathologic responses play a major role in HCPS.[79] Infection of humans with SNV and other hantaviruses results in widespread expression of viral antigens in endothelial cells of pulmonary and cardiac tissues,[80] and CD8 T-cell responses peak at the time of maximal clinical symptoms, implicating these responses in the pathogenesis of disease.[81] Myocardial depression has also been ascribed to induction of nitric oxide and locally secreted cytokines in response to infection.[82] Evidence has also suggested a role for antagonism of the host innate immune response by the hantavirus G1 tail as a pathogenic mechanism.[83]

Clinical Features

Presentation of HPS begins with a prodrome of fever, chills, and myalgias, occasionally accompanied by abdominal discomfort and gastrointestinal symptoms, and generalized malaise. Upper respiratory symptoms are usually absent. After a variable period of several days, the patient presents with mild, nonproductive cough and progressive dyspnea resulting from leakage of high-protein edema fluid into the alveoli. On physical examination, patients are febrile, with tachypnea and tachycardia with mild hypotension. Examination of the chest may reveal crackles but is otherwise unremarkable.

Laboratory studies generally reveal hemoconcentration, mild thrombocytopenia, and mildly elevated liver function test results. The triad of thrombocytopenia, left shift with circulating myeloblasts, and circulating immunoblasts is highly suggestive of HPS.[84] Multivariate analysis has identified dizziness, nausea, and the absence of cough as clinical symptoms predictive of HPS, as well as thrombocytopenia, elevated hematocrit, and decreased serum bicarbonate as features that help distinguish HPS from other causes of acute respiratory distress such as pneumococcal pneumonia and influenza.[85] Mild renal abnormalities may be detected, but unlike hantavirus-related *hemorrhagic fever with renal disease syndrome* (HFRS), do not progress to renal failure. Renal dysfunction may be more common in HPS associated with Bayou virus than with other hantaviruses.[86]

Chest radiographs are typical of pulmonary edema, without consolidation. Pleural effusions are present in most cases. Early in the course of HPS these effusions are transudative, while later they develop higher fluid protein content and in severe cases have the protein characteristics of plasma.[87] Cardiopulmonary manifestations in severe cases include a shock state with low cardiac index, low stroke volume index, and high systemic vascular resistance.[87] Progression is associated with worsening cardiac dysfunction and development of lactic acidosis. The case-fatality rate averages approximately 30% to 40%. In those patients who survive, recovery is usually complete, but some patients have manifested long-term pulmonary and cognitive dysfunction.[88]

Diagnosis

Patients universally have detectable serum immunoglobulin M (IgM) and immunoglobulin G antibody at the time of admission, and serologic techniques are the mainstay of diagnosis. In low-prevalence areas, a positive IgM antibody test is diagnostic.[89] Virus can also be detected in blood by reverse transcriptase–PCR during the first 10 days of illness.[90] In contrast, isolation of virus from tissue is laborious and time-consuming and must be undertaken in suitable containment facilities, and so is not useful diagnostically.

Treatment and Prevention

Treatment is supportive, and requires careful management of fluid status to maintain perfusion without exacerbating pulmonary edema. It has been suggested that high-dose steroid therapy may be useful[79] because of the pathogenesis of the disease and the use of steroids in systemic capillary leak syndrome. In severe cases, extracorporeal membrane oxygenation has been shown to be potentially beneficial.[91] The broad-spectrum antiviral agent ribavirin is active against hantavirus in vitro, and was demonstrated to be effective in HFRS in Korea. However, trials of ribavirin in HPS have not supported efficacy in this situation.[92]

Herpes Simplex Viruses

Both herpes simplex viruses (HSV) types 1 and 2 belong to the alphaherpesvirus subfamily of herpesviruses and share the same basic structural features. HSV-1 is most commonly associated with respiratory infection, while HSV-2 is more commonly associated with genital infection. The two HSV types were originally differentiated by neutralization assay and have been found to differ in a number of biologic and biochemical properties as well. Infection with either type results in production of both type-specific and cross-reactive antibodies, with higher concentrations of antibodies being produced against the homologous type.

Epidemiology and Transmission

Humans are the reservoir for HSV-1 and HSV-2 viruses. With primary infection, infectious virus is produced in the skin and mucous membranes, being present in vesicle fluid and cellular debris from herpetic ulcers. After establishment of latency in nerve ganglia, virus is intermittently shed in respiratory, vaginal, and urethral secretions in the absence of clinical disease. Asymptomatic respiratory tract shedding can be detected in about 1% to 2% of seropositive children and adults.

HSV-1 spreads by means of transfer of virus-containing respiratory secretions, vesicle fluid, and cell debris under conditions of close personal contact. The portal of entry for primary infections is the mucous membranes of the oropharynx and possibly the eye. Virus deposited onto areas of burned or abraded skin, and exogenous inoculation or autoinoculation of virus, also lead to clinical lesions. Cases of HSV-1 occur sporadically throughout the year and occasionally in small clusters. HSV-1 infection is usually acquired in childhood or adolescence, with epidemiologic surveys showing a prevalence of HSV antibody of 30% to 100% in adults.

Pathogenesis

Primary HSV infection has a mean incubation period of approximately 1 week. The events involved in primary infection occur at a local site and are related to viral replication in parabasal and intermediate epithelial cells, with resultant cell destruction and initiation of host inflammatory responses. Cells containing characteristic nuclear inclusions and sometimes multinucleation may be observed in lesions. In normal individuals, clinical involvement of regional lymph nodes may occur during primary infection, but otherwise the disease is usually contained at the primary site by the host's natural defenses. In neonates and others with deficient or impaired immune systems, local infection may be followed by viremic spread to multiple organs, including skin, liver, brain, adrenals, and lungs. Disseminated disease may also occur in such individuals following reactivation of latent infection. Visceral infection is characterized by a highly destructive coagulation necrosis of involved sites.[93] In a series of fatal cases of HSV pneumonia, inflammatory infiltrates, parenchymal necrosis, and hemorrhage are found in lung tissue at autopsy.[94] Patients with associated herpetic laryngotracheitis have necrotizing lesions in these areas.

Latent infection is established in sensory nerve ganglia, and is followed by lifelong recurrences of virus shedding and often lesions on skin and mucous membranes of the involved dermatomes. Cellular immunity is of primary importance in controlling HSV infection, although the specific responses are under study. In animal models, the stage of maturity of macrophages, interferon production, and the presence of natural killer cells and of sensitized killer lymphocytes have all appeared to be involved in resistance to infection.

Clinical Illness

Acute Gingivostomatitis and Pharyngitis. Herpetic disease of the oral cavity and pharynx is the most common overt manifestation of primary infection with HSV-1. Scattered or clustered vesicles and ulcers of various sizes (3 to 7 mm) are located on the buccal mucosa, tongue, gingiva, or floor of the mouth. Individual lesions usually appear as a shallow, white-based ulcer surrounded by a thin rim of erythema. Pain is prominent in involved areas of the mouth and pharynx, and regional nodes are tender and enlarged, particularly with pharyngitis. Fever, malaise, and reduced oral intake may add to the overall severity of these illnesses, which last up to 2 weeks.

Chronic Ulcerative Pharyngitis and Laryngotracheitis. In immunocompromised patients, including those with AIDS, both primary and recurrent HSV infection may present as a chronic erosive process of the mucous membranes of the oral cavity and upper airway. Characteristically, the lesions appear as large (5- to 15-mm) individual ulcerations that are slowly progressive and may coalesce when present in adjacent sites (see Fig. 31-2). The base of the ulcer is white or gray. Although shallow, the lesions are usually painful and may reduce oral intake. Herpetic lesions are sometimes present on the lips and the skin of the face. Infection may spread to the esophagus and lower airway, possibly facilitated by instrumentation, resulting in the development of similar lesions at these sites. Clinical features of herpetic tracheobronchitis include dyspnea, cough, fever, chills, diaphoresis, chest pain, wheezes, hypotension, and hypoxemia.[95] Herpetic tracheobronchitis has also been reported to occur in elderly patients presenting with bronchospasm who did not have histories of chronic lung disease or of immunosuppression.[96]

Pneumonia. Herpes simplex virus causes pneumonia in neonates with congenital and peripartum infections and in patients with malignancy, burns, organ transplantation, and other conditions leading to mechanical ventilation and impaired immunity. Neonatal herpes simplex pneumonia has been reported to occur between the 3rd and 14th days of life and to be associated with prominent hila and central interstitial infiltrate on radiographs.[97] Other associated findings have been thrombocytopenia, disseminated intravascular coagulation, abnormalities in liver function, vesicular skin lesions, and

deterioration during antimicrobial treatment. The pathologic findings in infants, children, and adults suggest that the disease may occur either as the result of direct extension of infection from the tracheobronchial tree to the lung or as the result of hematogenous dissemination of virus from mucocutaneous lesions of the upper airway or genitourinary tract. CT scan findings include multifocal segmental and subsegmental ground-glass opacities, but are not distinctive.[98] In one study, more than one half of the patients had concomitant pulmonary infection with other microorganisms, including bacterial, candidal, and *Aspergillus* species and cytomegalovirus.[94] Histologic evidence of herpetic esophagitis was present in 10 of 16 patients with herpes pneumonia in whom esophageal examination was performed. Many cases are nosocomially acquired.[99]

Herpes simplex virus infection of the lower airway has also been found in association with ARDS. The relationship of HSV infection to ARDS is unclear, but the presence of HSV in the lower respiratory tract was associated with the need for prolonged respiratory support and an increased late mortality. Isolation of HSV from lower respiratory tract secretions has also been common in mechanically ventilated patients and may be associated with a poor outcome,[100,101] although it is unclear whether this represents reactivation as a consequence of overall illness or whether the virus plays a direct role in mortality.[102]

Diagnosis

The clinical features of herpetic gingivostomatitis are sufficiently characteristic to permit accurate diagnosis in most cases. Other conditions with similar oral lesions are limited and include herpangina, aphthous stomatitis, Stevens-Johnson syndrome, and other enanthems resulting from infection and drug sensitivities. In herpangina, the lesions are smaller (1 to 3 mm), more often vesicular, and usually localized to the soft palate. The ulcers in aphthous stomatitis are few, relatively deep, and well circumscribed. Aphthosis is characterized by periodic recurrence, whereas acute herpetic gingivostomatitis and pharyngitis are limited to a single occurrence. Herpetic pharyngitis, when exudative, must be distinguished from pharyngitis due to *Streptococcus pyogenes,* adenovirus, Epstein-Barr virus, and diphtheria. Laboratory confirmation of the diagnosis of acute herpetic disease of the oropharynx can be made by examination of Giemsa- or Wright-stained smears of scrapings from the base of a fresh lesion (Tzanck test) and by culture of scrapings or swab specimens. Techniques for the rapid detection of viral antigens or DNA are widely available.

Chronic ulcerative pharyngitis due to HSV has a characteristic clinical appearance that is highly suggestive of the diagnosis (see Fig. 31-2). The white color of the candidal lesion may lead to confusion, but the lesion of thrush is an easily removable plaque, not an ulcer. Thrush and chronic herpetic pharyngitis may coexist in the same patient. The lesions of aphthous stomatitis are not characteristically found in the back of the oropharynx and are relatively small (2 to 5 mm), with a fixed diameter.

The diagnosis of herpetic laryngotracheitis may be difficult because of the inaccessibility of the lesions. The disease should be suspected in any immunocompromised patient with herpetic lesions of the mouth, upper airway, or skin of the face, especially if endotracheal intubation has been performed. In such patients, bronchoscopic examination is indicated for sampling of suspected areas for cytology and viral culture.

The diagnosis of HSV pneumonia should be suspected in any immunocompromised patient with unexplained pulmonary infiltrates, especially in the presence of herpetic laryngotracheitis or herpetic lesions of other mucocutaneous sites, including the genital area. Definitive diagnosis of HSV pneumonia depends on obtaining a sample of involved lung for viral culture and testing for HSV antigen or nucleic acids. Limited experience with lung biopsy in patients with HSV pneumonia suggests that obtaining adequate samples for culture and histologic examination may be a problem[94] and that, when possible, generous biopsy specimens should be obtained.

Treatment and Prevention

No vaccines of proven value are currently available. Primary HSV gingivostomatitis in immunocompetent persons responds to oral acyclovir treatment. Specific therapy of herpes simplex pneumonia has not been evaluated in controlled trials, but most clinicians would use intravenous acyclovir in this situation. In immunosuppressed patients with chronic mucocutaneous HSV infection, including pharyngitis and laryngotracheitis, prompt treatment with acyclovir is recommended both to control the local infection and to prevent possible dissemination to the lung. Valacyclovir, the valine ester prodrug of acyclovir, and famciclovir, the prodrug of penciclovir, are orally administered drugs that are also effective for mucocutaneous HSV.

Antiviral susceptibility testing should be considered in patients with serious HSV infection who do not respond to initial treatment with oral valacyclovir or intravenous acyclovir. Foscarnet is probably the best available alternative therapy. Prophylactic intravenous and oral acyclovir regimens have been shown to be effective in preventing recurrences of mucocutaneous HSV infection in seropositive patients undergoing intense periods of immunosuppression, such as bone marrow transplant recipients or patients receiving combination chemotherapy for leukemia.

Influenza Viruses

Influenza viruses belong to the family Orthomyxoviridae, and are classified into three distinct types, influenza A, influenza B, and influenza C virus, based on major antigenic differences. All three viruses share the presence of a host cell–derived envelope, envelope glycoproteins important for entry and egress from cells, and a segmented negative-sense, single-stranded RNA genome. The standard nomenclature for influenza viruses includes the influenza type, place of initial isolation, strain designation, and year of isolation. For example, an influenza

A virus isolated from a patient in Puerto Rico in 1934 is given the strain designation A/Puerto Rico/8/34, sometimes referred to as "PR8" virus.

The envelope glycoproteins are hemagglutinins (HAs) and neuraminidases (NAs). At least 15 highly divergent, antigenically distinct HAs have been described in influenza A viruses (H1 to H15) as well as at least 9 distinct NAs (N1 to N9). Influenza A viruses are further divided into subtypes based on the hemagglutinin (H) and neuraminidase (N), e.g., H1N1 or H3N2. Infection with influenza virus results in long-lived resistance to reinfection with the homologous virus. Infection induces both systemic and local antibody, as well as cytotoxic T-cell responses, each of which plays a role in recovery from infection and resistance to reinfection.

Epidemiology and Transmission

Influenza virus infection is acquired by transfer of virus-containing respiratory secretions. Both small-particle aerosols and droplets probably play a role in this transmission, but for infection control purposes influenza is generally considered to be transmitted by droplets. In temperate climates in either hemisphere, epidemics occur almost exclusively in the winter months (generally October to April in the Northern hemisphere and May to September in the Southern hemisphere), while influenza may be seen year round in the tropics.

Influenza epidemics are regularly associated with excess morbidity and mortality, usually expressed in the form of excess rates of pneumonia and influenza-associated hospitalizations and deaths, with potentially as many as 51,000 deaths annually in the United States.[103] Attack rates are generally highest in the young, whereas mortality is generally highest in the elderly. Excess morbidity and mortality are particularly high in those with medical conditions including pulmonary conditions such as asthma or COPD. Rates of influenza-related hospitalizations are particularly high in healthy children under 2 years of age, in whom rates approach those of older children with high-risk conditions.[104,105]

A high frequency of antigenic variation is a unique feature of influenza virus that helps to explain why this virus continues to cause epidemic disease. Antigenic variation involves principally the two external glycoproteins of the virus, HA and NA, and is referred to as "antigenic drift" or "antigenic shift," depending on whether the variation is small or great. Antigenic drift refers to relatively minor antigenic changes that result from amino acid changes in one or more of the five identified major antigenic sites on the HA molecule.[106] Antigenic shift refers to the complete replacement of the HA or NA with a novel HA or NA. These viruses are "new" viruses to which the population has no immunity. When such a new virus is introduced into a population, a severe, worldwide epidemic, or pandemic, of influenza results. Recent pandemics of influenza include the H1N1 pandemic of 1918, the H2N2 pandemic of 1957, and the H3N2 pandemic of 1968. Extensive surveillance and sequence information suggests that these new HA and NA genes are introduced into viruses circulating in humans from resident populations of influenza A viruses in birds.[107]

In the spring of 2009, a novel H1N1 influenza A virus emerged in Mexico and the United States. This triple-reassortant swine influenza A (H1) virus contains genes from avian, human and swine influenza viruses and is causing the pandemic of 2009, which has already infected millions of people worldwide.[107a-107c] Unlike seasonal influenza viruses, which cause greatest morbidity and mortality in infants and the elderly, high-risk populations for the novel H1N1 virus appear to be infants, young children, previously healthy adults ages 24–49 years, women who are pregnant or postpartum (28 days), and patients who are immunocompromised.[107d] Other conditions such as obesity, diabetes mellitus, COPD and asthma have also been described among hospitalized patients with this infection.[107e,107f]

Pathogenesis

Infection with influenza virus in humans is generally limited to the respiratory tract. After inoculation, the incubation period is thought to be from 18 to 72 hours, depending in part on the inoculum dose. Virus shedding is maximal at the onset of illness and may continue for 5 to 7 days or longer in children.

Bronchoscopy of individuals with typical, uncomplicated acute influenza typically reveals diffuse inflammation of the larynx, trachea, and bronchi, and a range of histologic findings (Fig. 31-10), from vacuolization of columnar cells with cell loss, to extensive desquamation of the ciliated columnar epithelium down to the basal layer of cells.[108,109] Generally, the tissue response becomes more prominent as one moves distally in the airway. Recovery is associated with rapid regeneration of the epithelial cell layer, and pseudometaplasia.

Abnormalities of pulmonary function are frequently demonstrated in otherwise healthy, nonasthmatic young adults with uncomplicated (nonpneumonic) acute influenza. Demonstrated defects include diminished expiratory forced flow rates, increased total pulmonary resistance, and decreased density-dependent forced flow rates consistent with generalized increased resistance in airways less than 2 mm in diameter,[110,111] as well as hyperresponsiveness to bronchoprovocation.[110] In addition, abnormalities of carbon monoxide diffusing capacity[112] and increases in the alveolar-arterial oxygen difference[113] have been seen. Of note, pulmonary function defects can persist for weeks after clinical recovery. Influenza in asthmatics or patients with COPD with influenza may result in acute declines in forced vital capacity or forced expiratory volume in 1 second. Individuals with acute influenza may be more susceptible to bronchoconstriction from air pollutants such as nitrates.[114]

Clinical Illness

Typical uncomplicated influenza often begins with an abrupt onset of symptoms after an incubation period of 1 to 2 days. Systemic symptoms include feverishness, chilliness or frank shaking chills, headaches, myalgia,

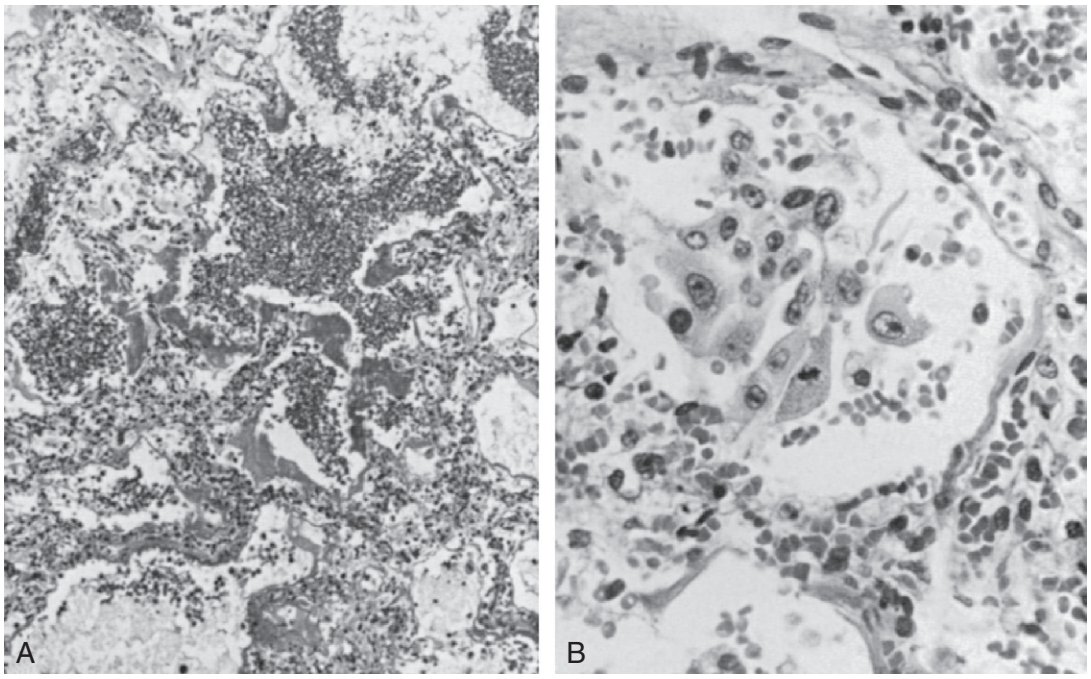

FIGURE 31-10 ■ Photomicrographs of lung tissue from a patient who died with primary influenza A viral pneumonia without recognized bacterial superinfection. The patient did not receive assisted ventilation prior to death. **A,** Histologic section showing intra-alveolar hemorrhage with numerous erythrocytes and exudate filling alveoli, hyaline membranes, and alveolitis. (Hematoxylin and eosin stain; original magnification ×125.) **B,** Histologic section showing desquamated reactive alveolar lining cells, admixed with lymphocytes, macrophages, and erythrocytes in the alveolar space. One alveolar lining cell contains a mitotic figure. (Hematoxylin and eosin, original magnification ×500.) (Courtesy of Philip Feldman, MD, Department of Pathology, University of Virginia Medical Center, Charlottesville, Virginia.)

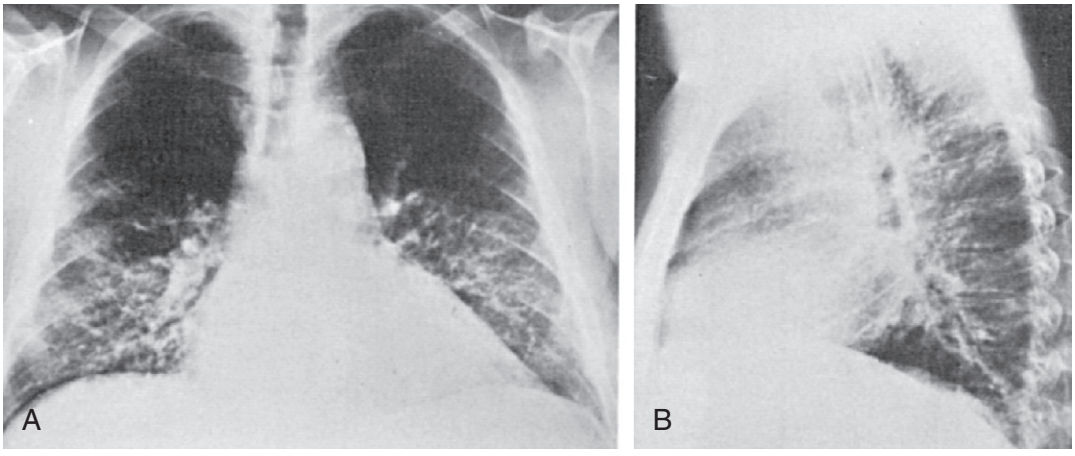

FIGURE 31-11 ■ Posteroanterior **(A)** and lateral **(B)** chest roentgenograms of a 55-year-old man with febrile illness showing bilateral diffuse reticulonodular infiltrates with a lower zone predominance and some hyperexpansion. These findings are typical, although not specific, for influenza viral pneumonia. (Courtesy of Thomas L. Pope, Jr., MD, Department of Radiology, University of Virginia School of Medicine, Charlottesville, Virginia.)

malaise, and anorexia. Typical respiratory symptoms include dry cough, severe pharyngeal pain, and nasal obstruction and discharge. Elderly individuals may simply present with fever, lassitude, and confusion without the characteristic respiratory complaints, which may not occur at all. There is a wide range of symptomatology, but the presence of fever plus either sore throat or cough is predictive of positive culture results in adults.

The syndrome of primary influenza viral pneumonia was first well documented in the 1957–1958 outbreak. The illness begins with a typical onset of influenza, followed quickly by a rapid progression of fever, cough, dyspnea, and cyanosis. Physical examination and chest radiographs (Fig. 31-11) reveal bilateral findings consistent with ARDS. Gram staining of the sputum fails to reveal significant bacteria, and bacterial culture yields

sparse growth of normal flora, whereas viral cultures yield high titers of influenza A virus. Such patients do not respond to antibiotics, and their mortality is high.

Secondary bacterial pneumonia has primarily been described in patients who are elderly or who have chronic pulmonary, cardiac, and metabolic or other disease. The classic description is of an influenza illness followed by a period of improvement lasting usually 4 to 14 days. Recrudescence of fever is associated with symptoms and signs of bacterial pneumonia such as cough, sputum production, and an area of consolidation detected on physical examination and chest radiographs. The most common bacterium implicated is *Streptococcus pneumoniae,* with a significantly increased frequency of *Staphylococcus aureus.*[115,116] Many patients present with mixed viral and bacterial pneumonia. Bacterial superinfections of influenza have been postulated as a major cause of death during the pandemic of 1918.[117]

Similar to previously circulating seasonal influenza virus, most cases of infection with the novel H1N1 influenza virus result in mild disease. However, severe disease in hospitalized patients due to pneumonia and acute respiratory distress syndrome has been reported during this H1N1 pandemic, from both viral pneumonitis and superinfections with bacterial pneumonia.[107e,107f] In agreement with seasonal influenza virus infections, the most common complicating bacterial organisms include *Streptococcus pneumoniae, Staphylococcus aureus*, and Group A streptococci. Mortality rates in hospitalized patients with the novel H1N1 influenza infection range from 7% to 17%.[107d,107e] Interestingly, in one small study of 10 patients in Intensive Care Units in Michigan, nearly 50% had evidence of thromboembolic disease.[117a]

Diagnosis

Virus can be isolated readily from nasal swab specimens, nasal aspirates, or combined nose and throat swab specimens. Virus can also be isolated readily from sputum or endotracheal aspirate samples. Over 90% of positive cultures can be detected within 3 days of inoculation.[118] Immunologic detection of influenza antigens in respiratory samples can be used for rapid diagnosis, and a large number of such tests are commercially available. The reported sensitivities of each test in comparison to cell culture has varied between 40% and 80% and is somewhat dependent on the nature of the samples tested and the patients from whom they were derived. In general, sensitivities in adults and elderly patients tend to be lower than those reported in young children, who shed much larger quantities of virus in nasal secretions and therefore have much higher concentrations of antigen in their samples.[119] Similarly, sensitivity is likely to be higher early in the course of illness, when viral shedding is maximal. PCR techniques have also been developed and are highly sensitive and specific.

Diagnosis of the novel H1N1 influenza virus can be made by rapid antigen detection, viral culture and PCR methods. The current rapid diagnostic tests have not been very sensitive in identifying H1N1 virus infections, and are worse in adults than in pediatric cases,[119a] which means that many influenza-like illnesses due to the novel H1N1 are not being confirmed. By contrast, PCR-based tests for the virus are highly sensitive and specific but may not always be readily available.[119b]

Treatment and Prevention

Vaccines. Two types of vaccine are available for prevention of influenza. Inactivated virus vaccines consist of either inactivated purified virions (whole virus vaccines) or partially purified HA and NA preparations (split-product or subvirion vaccines). These vaccines are administered intramuscularly without adjuvant and are intended to induce formation of antibody against the viral HA and NA, which are associated with protection. Cellular immune responses also occur, and may also be associated with protection. Inactivated vaccines are well tolerated in all age groups, although hypersensitivity to hens' eggs, in which the vaccine virus is grown, is a contraindication to vaccination. Generally, if persons can eat eggs or egg-containing products, vaccination is safe. If necessary, individuals with anapylaxis can be desensitized and safely vaccinated.[120]

Increases in HAI antibody are seen in about 90% of healthy adult recipients of vaccine. Only a single dose of vaccine is required in individuals who been previously vaccinated or who have experienced prior infection with a related subtype, but a two-dose schedule is required in unprimed individuals. This includes children up to age 9 who have not previously been vaccinated or who were vaccinated for the first time with only a single dose in the previous season.[121] Diminished responses are seen in elderly and immunocompromised populations.

The protective efficacy of inactivated influenza vaccine is estimated to be in the range of 70% to 90% in healthy adults and children when there is a good antigenic match between vaccine and epidemic viruses.[122,123] Relatively few prospective trials of protective efficacy have been conducted in high-risk populations. In one placebo-controlled prospective trial, inactivated vaccine was approximately 58% effective in preventing laboratory-documented influenza among adults over 60, and 29% in those over 70.[124] Retrospective cohort studies have shown vaccine to be protective against influenza- and pneumonia-related hospitalization in the elderly, and to be associated with decreases in all-cause winter mortality.[125] However, these results have been called into question, and doubts remain regarding the level of effectiveness of inactivated vaccine in this age group.[126]

Live, attenuated vaccine induces a limited, asymptomatic infection of the upper respiratory tract and induces a variety of immune response designed to mimic the protective immunity induced by natural infection.[127,128] The vaccine is well tolerated and highly effective in children, but is associated with an increased frequency of wheezing in children under the age of 2 years. Live vaccine is protective in adults as well, resulting in decreased laboratory-confirmed influenza in challenge studies and reduced frequencies of influenza-like illness in the field.[129] Although the vaccine is well tolerated in the elderly and in those with chronic lung disease,

immune responses are very infrequent in older recipients, and the vaccine is therefore not licensed for use in those over 49 years.

Although vaccine virus can be recovered from vaccinated individuals, particularly children, for several days following vaccine, transmission is extremely unusual.[130] Live vaccine can be administered safely to health care workers except for those caring for immunosuppressed individuals requiring barrier precautions.

Randomized controlled comparisons of the efficacy of inactivated and live, attenuated vaccine in children have consistently shown that live vaccine provides superior efficacy in this population, with an approximately 50% lower cumulative incidence of influenza in those receiving live vaccine.[131] Similar comparisons in adults have suggested slightly superior efficacy of inactivated vaccine,[132] and large cohort studies are also consistent with the interpretation that inactivated vaccine has slightly better efficacy than live vaccine in adults, particularly in those who have received vaccines in previous years.[133]

Current target groups for influenza vaccination[121] are focused on two complementary strategies: targeting vaccine to those at the highest risk for influenza-related complications, and preventing transmission of influenza to such individuals by vaccinating their close contacts, including health care workers (Table 31-5).

TABLE 31-5. Target Groups for Influenza Immunization

PERSONS AT INCREASED RISK FOR COMPLICATIONS

- Persons > 65 years of age
- Residents of nursing homes and other chronic care facilities
- Adults and children with chronic pulmonary or cardiovascular diseases, including asthma
- Adults and children with chronic metabolic diseases (including diabetes mellitus), renal dysfunction, hemoglobinopathies, or immunosuppression (including human immunodeficiency virus infection)
- Children and adolescents receiving long-term aspirin therapy
- Women who will be in the second or third trimester of pregnancy during the influenza season
- Children ages 6–23 months

PERSONS AGES 50–64 YEARS

- Influenza vaccine has been recommended for this entire age group to increase vaccination rates among persons in this age group with high-risk conditions.

PERSONS WHO CAN TRANSMIT INFLUENZA TO THOSE AT HIGH RISK

- Physicians, nurses, and other personnel in both hospital and outpatient care settings, including medical emergency response workers
- Employees of nursing homes, assisted living facilities, and other chronic care facilities who have contact with patients or residents
- Persons who provide home care to persons in groups at high risk
- Household contacts (including children) of persons in groups at high risk
- Household contacts of children ages 0–23 months

In the fall of 2009, vaccines to the novel H1N1 virus became available as a single inoculation separate from the seasonal trivalent vaccine. Due to limited supply of the new vaccine, priority has been given to populations at high risk of developing influenza-related complications, including pregnant women, caretakers who live with or care for infants younger than 6 months, health care and emergency medical personnel, infants and young adults age 6 months through 24 years, and adults from 25 to 64 years with chronic medical conditions that put them at high risk of influenza-related complications.

Antivirals. Two classes of antiviral agents are currently available for the treatment and prevention of influenza, the M2 inhibitors (M2Is) amantadine and rimantadine, and the neuraminidase inhibitors (NIs) oseltamivir and zanamivir. The M2Is are active against all strains of influenza A virus in a variety of cell culture systems and animal models. However, these drugs have no activity against influenza B viruses, and resistance to their antiviral effects emerges readily. The NIs are active against both influenza A and B viruses. Antiviral resistance has emerged as an important problem for these agents as well.

The most common side effects of amantadine are minor and reversible central nervous system (CNS) side effects such as insomnia, dizziness, or difficulty in concentrating. These dose-related side effects may be more troublesome in the elderly, in whom confusion is noted in about 18% of recipients.[134] In addition, amantadine use has been associated with seizures in individuals with prior seizure disorder. The CNS effects of amantadine are increased when these drugs are coadministered with anticholinergics or antihistamines, or drugs such as trimethoprim-sulfamethoxazole that inhibit tubular secretion of amantadine and increase the potential for CNS toxicity.[135] There are no other known significant drug interactions with amantadine. Rimantadine is associated with a considerably reduced rate of CNS side effects.[136] There are no known drug interactions that significantly affect the levels or metabolism of rimantadine.

When used as therapy, the M2Is are effective in reducing the severity and duration of illness due to susceptible strains of influenza A virus in both adults and children. Treatment with amantadine also results in significantly more rapid improvement in small airways dysfunction in previously healthy adults with uncomplicated H3N2 influenza.[110,137] Effective use of these drugs requires that they be administered within 48 hours of symptom onset, when viral replication is at its peak. The M2Is are also effective in prevention of influenza when administered prior to exposure, either by giving the drug throughout the influenza season or by giving short courses of prophylaxis upon exposure in an institutional or family outbreak. In this latter setting, it is important to avoid both treatment and prophylaxis to prevent the emergence and transmission of resistant viruses.

Resistance is the result of single point mutations in the membrane-spanning region of the M2 protein, and confers complete cross-resistance between amantadine and rimantadine.[138] Resistant viruses emerge in the

majority of treated individuals, particularly children,[139] and prolonged shedding of resistant viruses may occur in immunocompromised patients even after therapy is terminated.[140] While resistant viruses were initially detected very infrequently in untreated patients in the years following introduction of these drugs, the first decade of this century has seen the emergence and spread of resistant influenza A (H3N2) viruses such that almost all such viruses isolated worldwide exhibit resistance to the M2Is.[141] The novel H1N1 viruses causing the 2009 pandemic are also resistant.

Neuraminidase inhibitors (NIs) are potent inhibitors of influenza virus in vitro and in vivo. Influenza B viruses are somewhat less sensitive than influenza A viruses but are well within clinically achievable concentrations. Activity against influenza viruses includes avian viruses with all nine known NA subtypes. While zanamivir and oseltamivir have an identical mechanism of action and similar profile of antiviral activity, they have differing pharmacologic properties. Zanamivir is not orally bioavailable and is administered as a dry powder for oral inhalation, using the so-called diskhaler device. Oseltamivir phosphate is an orally bioavailable ethyl ester prodrug that is rapidly absorbed from the gastrointestinal tract and is converted in the liver by hepatic esterases to the active metabolite, oseltamivir carboxylate. The metabolite is excreted unchanged in the urine by tubular secretion, with a serum half-life of 6 to 10 hours. Administration of the drug with food may improve tolerability without impacting drug levels.

The major adverse effects reported for oseltamivir have been gastrointestinal upset in about 10% to 15% of recipients, probably due to irritation as a result of rapid release of the drug in the stomach. Rates of nausea can be substantially reduced if the drug is taken with food. Adverse effects in individuals treated with zanamivir have occurred at essentially the same rate as in placebo recipients. However, postmarketing surveillance has found that inhaled zanamivir may be very uncommonly associated with bronchospasm, sometimes severe or fatal, in influenza patients, particularly those with underlying airways disease.

Because zanamivir has no significant systemic absorption, there are no recommended dosage reductions. The dose of oseltamivir should be reduced to 75 mg once daily in individuals with renal impairment (i.e., with creatinine clearance of less than 30 mL/min). No data are available regarding the use of the drug in individuals with more significant levels of renal impairment. Likewise, no information is available regarding the use of oseltamivir in individuals with hepatic impairment. Clinically significant drug interactions have not been reported. Because the drug is eliminated by tubular secretion, probenecid increases serum levels of the active metabolite approximately twofold. However, dosage adjustments are not necessary in individuals taking probenecid. Coadministration of cimetidine, amoxacillin, or acetaminophen has no effect on serum levels of oseltamivir or oseltamivir carboxylate.[142]

Both NIs are effective in the treatment of influenza due to either influenza A or B virus if administered within the first 48 hours of symptom onset, with reduced duration of illness and earlier return to work or normal activities. Meta-analysis of results of these trials has also suggested that early treatment may reduce the frequency of influenza-related complications, with reductions in the use of antibacterials and in hospitalization.[143] Only oseltamivir is currently licensed for use in children under 5. Administration of oseltamivir liquid at a dosage of 2 mg/kg/dose twice daily for 5 days was well tolerated and resulted in a 36-hour reduction in the duration of symptoms in children with influenza A.[144] NIs have also been used successfully for seasonal or contact prophylaxis.

Mutations within the catalytic framework of NA that abolish binding of the drugs have been described.[145,146] Depending on the location of the mutation, these viruses may be specifically resistant to only one inhibitor.[147] Resistance mutations in NA may be associated with altered characteristics of the enzyme, with significantly reduced activity.[148,149] Drug-resistant viruses are most commonly isolated from treated children.[150] Viral fitness appears to be less compromised by oseltamivir resistance mutations in the N1 neuraminidase.[151] N1-resistant viruses have emerged and become predominant among N1 viruses isolated worldwide, while N2 viruses remain sensitive to oseltamivir. Both N1 and N2 viruses are sensitive to zanamivir.

In the fall of 2009, the CDC reported that most circulating strains of the novel H1N1 influenza A virus were sensitive to the neuraminidase inhibitors oseltamivir and zanamivir, but that nearly all strains were resistant to the amantadines. Although antiviral therapy is not recommended for mild influenza infections, early treatment of hospitalized patients within 2 days of the onset of symptoms suggested clinical benefit.[107e] Therefore, antiviral drugs should be considered in seriously ill patients with both confirmed and suspected H1N1 viral infections. Reports of oseltamivir-resistance in H1N1 virus with the H275Y mutation have recently appeared[151a]; resistance has also cropped up in several countries and is being monitored closely for its clinical impact. Intravenous formulations of peramivir, a neuraminidase inhibitor, have been released though not approved by the FDA and can be considered for patients unable to take oral or inhaled medications.

Measles Virus

Measles virus is classified in the *Morbillivirus* genus of the Paramyxoviridae family and is structurally similar to parainfluenza viruses and respiratory syncytial virus. Its surface glycoproteins include a hemagglutinin responsible for attachment to cells, as well as a fusion (F) protein responsible for cell membrane fusion and virus penetration of cells, but no neuraminidase. The cell surface molecule SLAM (signaling lymphocyte activation molecule) serves as a receptor for entry of the virus into susceptible cells.[152] In addition, the membrane cofactor CD46 can also serve as a receptor, particularly for the vaccine strain.[153] Only one serotype of wild measles virus is recognized, although minor antigenic differences are

detectable by monoclonal antibodies. The human is the natural host for measles virus.

Epidemiology and Transmission

Measles occurs worldwide, but epidemic patterns vary depending on population density and levels of acquired immunity. Prior to vaccine use, measles occurred in epidemics of 3 to 4 months in duration every 2 to 5 years in temperate regions.[154] Except in isolated areas, most people experienced infection by 20 years of age, and 90% of reported cases occurred in those less than 10 years of age. Infection confers lifelong protection against measles, although asymptomatic reinfections may occur.

Measles virus infection is highly contagious and can spread despite high levels of acquired immunity in the population. Airborne transmission via small-particle aerosols and possible spread by fomites appear to account for its high communicability. The virus remains infectious in small-particle aerosols for several hours at low relative humidity and has caused secondary infections in the absence of face-to-face contact with an index case.[155] The incubation period is usually 9 to 14 days but may be longer in adults. Patients are most infectious during the late prodrome, when respiratory involvement contributes to creation of infectious aerosols. The virus may be shed for several days after the onset of rash in normal hosts.

Measles-associated mortality in developed countries is usually 0.1% or less but approaches 2% of cases in the developing world. Case-fatality rates have been as high as 25% in some areas. Most deaths result from respiratory tract involvement, neurologic complications, or both and are related to various combinations of malnutrition, young age, and immunosuppression induced by measles virus infection.

Pathogenesis

The respiratory tract and possibly the conjunctival epithelium are the portals of entry and initial sites of replication of measles virus, as well as subsequent target organs of disease expression. An initial viremic phase leads to infection of reticuloendothelial cells, and a second phase of viremia, corresponding to the prodromal stage of illness, results in dissemination of virus to the epithelial cells of the skin, respiratory tract, gut, bile duct, and bladder and to lymphoid organs.

Measles-induced giant cells may be present in the tonsils, appendix, other lymphoid organs, and various epithelial surfaces, including those of the respiratory tract. The effects of infection on the lymphoid system include leukopenia and immune suppression manifested by cutaneous anergy and depressed natural killer cell activity for weeks after the onset of the rash.[156] The mechanisms by which measles induces immunosuppression are incompletely understood, but infection of dendritic cells and suppression of the interleukin (IL)-12 response are thought to play an important role.[157]

The onset of the rash correlates temporally with the development of host immune responses and subsequent termination of virus shedding. Skin rash develops in agammaglobulinemic patients with measles, whereas progressive giant cell (measles virus) pneumonia without rash may occur in those with deficient cell-mediated immune function. The pathologic changes in involved organs include lymphoid hyperplasia, mononuclear cell infiltration, and the presence of multinucleated giant cells. Lower respiratory tract involvement may be associated with the destruction of ciliated respiratory epithelium, interstitial pneumonia, epithelial cell hyperplasia, and syncytial cell formation.

Clinical Illness

Typical Measles. The prodrome of typical measles lasts 2 to 8 days and is characterized by fever, malaise, anorexia, cough, coryza, and conjunctivitis. Koplik's spots, which are erythematous macular lesions with central white-yellow or gray puncta, appear on the buccal or labial mucous membranes toward the end of the prodromal period. The maculopapular, erythematous eruption begins about the face and neck and progresses to involve the upper body, trunk, and extremities. The rash typically disappears after 5 to 6 days in the order in which it appeared. Defervescence and symptom improvement occur several days after the appearance of the rash, although persistent cough is common. Leukopenia is common during the prodromal and early exanthematous stages of measles. Pronounced leukopenia (less than 2000 cells/μL) is associated with a poor prognosis. The development of neutrophilic leukocytosis suggests the possibility of bacterial superinfection or other complications.

Lower respiratory tract complications develop in 4% to 50% of patients. These include bronchitis, pneumonia, and, less often, croup or bronchiolitis. In young adults, a multilobar reticulonodular infiltrate is the most common radiographic abnormality.[158] In the absence of bacterial superinfection or atypical measles, pleural effusion or lobar consolidation is uncommon. In patients with altered cell-mediated immune function, and rarely in apparently normal persons, infection by wild measles virus can cause a lethal giant-cell pneumonia with or, in about 30% of patients, without rash.[159] Severe virus-induced pneumonia has been recognized during measles in pregnant women[160] and in those infected with HIV.[161] In hospitalized patients, mortality rates are approximately 70% in oncology patients and 40% in HIV-infected patients.[159]

Secondary bacterial infection has been found in 30% to 50% of young adults with measles-related pneumonia. Symptoms and signs indicative of bacterial infection usually begin 5 to 10 days after onset of the rash. One study employing transtracheal aspiration found a range of bacterial pathogens in adults, most commonly *Haemophilus influenzae, Neisseria meningitidis,* and *S. pneumoniae.*[158] Up to 30% of cases are complicated by otitis media or sinusitis. Acute nonrespiratory complications include hepatitis, encephalitis, keratitis, and

mesenteric adenitis, as well as a high rate of severe diarrheal disease in children in developed countries. Measles infection or vaccination may be followed by conversion of a positive tuberculin skin reaction to negative for weeks. Measles may exacerbate active tuberculosis, but whether measles reactivates dormant tuberculosis is unresolved.[162]

Atypical Measles. An unusual clinical syndrome has been recognized in adolescents and young adults who received the inactivated measles vaccine between 1963 and 1968 and who have been subsequently reexposed to the wild virus. The illness begins abruptly, with high fever, headache, myalgia, vomiting, abdominal pain, and nonproductive cough. Respiratory symptoms, including dyspnea, coryza, sore throat, and pleuritic chest pain, are common. A polymorphous eruption, which may include vesicles, petechiae, purpura, and urticarial lesions, begins typically on the distal extremities and spreads proximally over 3 to 5 days. Although Koplik's spots are absent, conjunctivitis and glossitis with strawberry tongue have been described.

Pulmonary abnormalities occur in most cases, and acute respiratory failure has been described. Chest radiographic changes include patchy, diffuse, or dense lobar infiltrates, pleural effusions, and hilar adenopathy.[163] Residual nodular pulmonary infiltrates may persist for years and lead to diagnostic confusion. The fever and other symptoms usually resolve in 1 to 3 weeks. The pulmonary function changes in atypical measles include transient hypoxemia and significantly reduced lung volumes.

Diagnosis

Measles virus may be isolated from the blood, urine, or respiratory secretions during the prodrome and up to several days after the exanthem appears. Isolation of virus from clinical specimens has been performed in several types of human and monkey cell cultures but is slow and inefficient. Respiratory and conjunctival secretions or urine sediment stained by various techniques reveals multinucleated giant cells in most cases. Immunofluorescent staining of skin biopsy specimens, cells from combined nasopharyngeal and throat swab samples, and, less often, exfoliated cells in the urine demonstrates measles virus antigens early in the disease.

Treatment and Prevention

The treatment of measles involves supportive care and specific therapy for bacterial complications. No antiviral agents have proven clinical value, but aerosol and intravenous ribavirin and immunoglobulin have been used in treating measles pneumonia.[160,164] Vitamin A therapy reduces morbidity and mortality in severe measles in children.[165] Patients suspected of having measles should be placed in respiratory isolation.

The live, attenuated measles vaccine currently used in the United States provides durable immunity in over 90% of recipients. The vaccine is safe, and it has been conclusively shown to have no association with autism.[166,167]

Metapneumoviruses

The human metapneumoviruses (hMPV) are pleiomorphic particles with short envelope projections, resembling other paramyxoviruses.[168] These viruses are closely related to the pneumoviruses (of which respiratory syncytial virus [RSV] is the human example), differing only by the absence of two nonstructural proteins and a slightly different arrangement of gene order on the negative-sense, single-stranded RNA genome. The basic virology of these viruses closely resembles that of RSV. Envelope glycoproteins include the SH (sulfhydryl), F (fusion), and G (glycosylated) proteins, although there is little sequence homology in these genes between RSV and hMPV.[169] By analogy, it is expected that antibody to the F and G proteins of hMPV would play a role in protection against reinfection. At least two major genetic groups have been identified, roughly corresponding to subgroups A and B of RSV.[170] Sequential infections of the same individual tend to involve different genogroups. The role of cell-mediated immunity in this infection is largely unexplored.

Epidemiology and Transmission

Human metapneumovirus infections are distributed worldwide, and have been documented in about 12% of children with lower respiratory tract illness in an outpatient setting[171] and in about 6% to 7% of hospitalized children during the winter respiratory season.[172] As with many other respiratory viruses, infection is linked to daycare attendance.[173] The peak age incidence is 11 months, and serologic studies suggest that essentially all children have been infected by age 5.[168] Similar to the case with RSV, disease has also been documented in adults and in the elderly,[174] although asymptomatic infection is also common in adults. The mode of transmission has not been documented, but is likely to be via droplet spread as with RSV. There is a clear seasonal variation in incidence, with the majority of cases occurring during the winter months.[171]

An interesting feature of the epidemiology of these viruses is that children with hMPV are often coinfected with other respiratory viral pathogens, especially RSV.[175] Dual infections with both viruses may result in more intense bronchiolitis in some infants.[176] hMPV was also detected in many cases of SARS, but did not appear to exacerbate this illness.[177]

Clinical Features

Human metapneumoviruses appear to be responsible for a spectrum of acute respiratory illnesses ranging from very mild or asymptomatic infection to severe bronchiolitis and pneumonitis. The clinical picture most closely resembles that of RSV, and bronchiolitis is the major manifestation in children.[171,178] Clinical features include wheezing and hypoxia in hospitalized children.[179] A variety of other lower and upper respiratory tract syndromes are also associated with hMPV infection, including croup and pneumonitis.[171,172] There are no clinical

features that can reliably distinguish between disease caused by hMPV and RSV, although in general RSV is more severe.

Symptomatic infection in adults and in the elderly has also been described.[174] hMPV infections of young adults had features of the common cold, with nasal congestion, rhinorrhea, cough, and hoarseness predominating. Frail elderly and high-risk adults had lower rates of hMPV infection than healthy adults but more severe clinical symptoms, with significantly higher frequencies of dyspnea and wheezing, and more prolonged illness.[174] Elderly patients with hMPV infection were hospitalized with diagnoses of COPD, bronchitis, and pneumonia. hMPV appears to be a leading cause of respiratory tract infection after lung transplantation.[180] In one study, hMPV was the most commonly detected RNA virus in bronchoalveolar lavage samples from immunocompromised patients.[181]

Pathogenesis

Relatively little is known about the pathogenesis of this disease. In hospitalized children with hMPV, levels of nasal secretion of the RANTES (regulated on activation, normal T-cell expressed and secreted) chemokine have been reported to be suppressed, while levels of nasal IL-8 were increased.[182] The immune responses elicited by hMPV are similar to those of RSV but often less vigorous.[183]

Diagnosis

Viral culture is slow and unpredictable. Most infections have been detected by nucleic acid amplification techniques.

Prevention and Treatment

Treatment is supportive. No antiviral agents or vaccines are currently licensed for treatment or prevention of hMPV infections, and this is unlikely to change in the near future. Ribavirin is as active in vitro against hMPV as it is against RSV.[184]

Parainfluenza Viruses

Parainfluenza viruses belong to the *Paramyxovirus* genus of the Paramyxoviridae family, which includes mumps virus and important veterinary pathogens. This group of medium-sized (150 to 200 nm), pleomorphic, enveloped viruses has a nonsegmented, single-stranded RNA genome contained in a helical nucleocapsid. The human parainfluenza viruses are separated into types 1 to 4, and type 4 is further divided into subtypes A and B, on the basis of antigenic differences. One envelope glycoprotein (HN) has hemagglutinin and neuraminidase activity and mediates for adsorption of virus to host cell receptors and release. The F glycoprotein has membrane-fusing activity and is responsible for viral penetration into cells and for the formation of multinucleated syncytial cells. Antibody against the HN and F proteins is involved in protective immunity.

Epidemiology and Transmission

Parainfluenza viruses have a worldwide distribution, and almost all persons are infected initially during childhood. Infections by parainfluenza type 3 virus may occur in infancy, whereas infections by type 1 and 2 viruses appear to be prevented by maternal antibody and usually occur later. National surveillance has demonstrated distinct seasonality for type 1 viruses, occurring in biennial outbreaks in the fall of odd-numbered years. In contrast, yearly outbreaks of type 3 virus occurred annually in the spring, with smaller fall outbreaks in those years when type 1 outbreaks did not occur. Type 2 viruses are detected much less frequently, but appeared to be more prevalent in the fall; type 4 does not exhibit notable seasonality.[185]

Parainfluenza viruses appear to be transmitted from person to person by direct contact with infectious respiratory secretions or by large-particle aerosols. The incubation period is approximately 3 to 6 days. Transmission occurs readily in families. Outbreaks of infection have occurred in closed populations, such as nurseries, daycare centers, and hospitals, in which high attack rates (40% to 80%) occur in susceptible persons.

Parainfluenza virus infections, most commonly type 1 virus, are associated with approximately 40% of croup cases and up to 75% of those with a documented viral cause, with smaller proportions of pneumonia or bronchiolitis cases in children. The incidence of croup and lower respiratory tract disease due to type 1 or 2 infections is highest between 6 months and 3 years of age, whereas parainfluenza type 3 is an important cause of bronchiolitis or pneumonia in infants less than 6 months old. Reinfections with parainfluenza viruses are common and may occur within several months of each other in young children. Parainfluenza virus type 1 infections are estimated to account for up to 28,900 annual hospitalizations in the United States, and parainfluenza virus type 3 for up to 52,000.[186]

Pathogenesis

Although viremia has been described, replication of the virus is generally restricted to the respiratory tract mucosa. The quantity of virus shed in respiratory secretions tends to parallel the severity of illness.[187] Virus shedding commonly continues for periods of 8 to 10 days in initial infections but may last for 3 weeks or longer. Prolonged shedding (months) of parainfluenza virus type 1 or 3 has been reported in apparently normal hosts,[188] as well as in immunodeficient children.[189]

The pathologic findings in fatal cases are typical of other viral pneumonias and include peribronchiolar and alveolar lymphocytic infiltration.[190] Infection of the tracheal epithelium with localized edema and fibrinous exudate contributes to airway narrowing in croup. The reasons for the laryngotracheal localization of parainfluenza virus–induced disease are unresolved. Virus–host

cell interactions (specifically cleavage of the F protein) and other host factors, including the nature of the immune response, are postulated to play contributory roles in the pathogenesis of croup. The nasopharyngeal secretion concentrations of parainfluenza virus–specific immunoglobulin E and of histamine and leukotriene C4, and cellular responses to viral antigen, are higher in patients with wheezing than in those with upper respiratory tract illness alone.[191]

Clinical Illness

Primary infections are usually symptomatic and associated with the most severe forms of illness. Initial infections with parainfluenza virus types 1 to 3 cause febrile rhinitis, pharyngitis, laryngitis, and bronchitis in children. Depending on the serotype causing infection, 50% to 80% of primary infections are associated with fever, and up to one third of children have evidence of lower respiratory tract involvement. In parainfluenza virus type 1 and 2 infections, lower respiratory disease is principally manifested as croup, whereas type 3 infection has been associated with croup, bronchiolitis, and pneumonia.

In adults and older children, reinfections are frequently asymptomatic. Symptomatic infections are manifested as common colds, usually without fever, and less often pharyngitis, tracheobronchitis, or influenza-like illness. Pneumonia and exacerbations of COPD have been described following parainfluenza virus infection in adults and the elderly.[192]

Although uncommon, parainfluenza viruses can cause serious lower respiratory tract disease, including fatal pneumonia with or without giant cells, in children with immunodeficiency or leukemia, and in adults and children who are bone marrow or stem cell transplant recipients.[193] Nosocomial outbreaks in immunosuppressed patients have been reported.[194] Because upper respiratory illness may be absent and nasopharyngeal cultures negative, bronchoalveolar lavage is often required for diagnosis.

Diagnosis

Throat and nasopharyngeal secretions contain the virus at the onset of symptoms. Virus can be isolated as early as 3 days and usually within 10 days after inoculation of cell culture with specimens from infants and children. Virus replication in cell culture is usually detected by hemadsorption of guinea pig erythrocytes or immunofluorescence. Rapid diagnosis by detection of parainfluenza antigens in respiratory secretions or PCR-based tests has also been developed.

Treatment and Prevention

There are currently no available antiviral agents of proven effectiveness against parainfluenza virus. Ribavirin is active against parainfluenza viruses in vitro, and would theoretically be expected to be active in vivo as well. Anecdotal reports in immunodeficient children with severe parainfluenza virus infections suggest that aerosolized ribavirin may be associated with antiviral effects and clinical benefit,[195] although delayed treatment with aerosolized ribavirin was not associated with improved survival in bone marrow transplant recipients.[196]

Initial attempts to develop vaccines for the prevention of parainfluenza virus infections involved use of formalin-inactivated virus. However, these vaccines failed to provide protection in field trials carried out in the 1960s, despite being modestly immunogenic. In contrast to RSV vaccines, the use of formalin-inactivated parainfluenza virus vaccine was not associated with enhanced disease upon subsequent infection. Several approaches have been explored subsequently to develop an effective parainfluenza vaccine, including use of subunit vaccines and development of live, attenuated viruses as potential parainfluenza virus vaccines.[197]

Respiratory Syncytial Virus

Respiratory syncytial virus (RSV) is classified in the *Pneumovirus* genus of the Paramyxoviridae family. Similar in structure to parainfluenza viruses, RSV is a pleomorphic (150 to 300 nm), enveloped virus with a single-stranded, nonsegmented RNA genome. The surface proteins include the F protein responsible for fusion of the viral envelope with the host cell membranes and formation of syncytium, and the G protein, a heavily glycosylated protein responsible for attachment to cells. Antibodies against the F and G proteins neutralize RSV in vitro, but antibodies against the G protein do not do not prevent syncytium formation. Two major antigenic groups (designated A and B) are distinguished primarily by differences in the G glycoprotein.[198] The clinical and epidemiologic importance of strain variation are under study, but infections by group A strains appear to be more severe.[199] Further antigenic subgroups and genomic heterogeneity are recognized among circulating RSV strains.

Epidemiology and Transmission

Respiratory syncytial virus is worldwide in distribution and, in temperate climates, causes annual outbreaks of infection in the late fall, winter, or spring. Epidemics are associated with increases in pediatric hospitalizations and deaths due to lower respiratory tract illness in infants and young children.[200] Nearly 50% of children are infected within the first year, and almost all within 3 years of age. Reinfections in children and adults are quite common even with the same strain, suggesting immunity is only partial at best.[201] Epidemiologic factors related to serious illness in infected infants include low socioeconomic status, crowding, maternal smoking, lack of breastfeeding, daycare center attendance, and history of allergic disease. RSV is also recognized as a cause of severe disease in older adults,[202] and may result in a greater total burden of mortality in the elderly than in infants.[103]

Virus spreads by large-particle aerosols during close personal contact and by hand contamination with infectious secretions and subsequent self-inoculation of the

eye or nose. RSV is a major nosocomial pathogen on pediatric wards, and high attack rates occur during outbreaks in hospitals, transplantation units, daycare centers, and geriatric residential homes. Attack rates in children have approached 100% during outbreaks in daycare centers and are commonly 20% to 50% in hospital staff and patients during epidemic periods. In the family setting, secondary infection develops in approximately one half of infants and up to one third of adult contacts after introduction of virus by an older sibling.[203]

Pathogenesis

Viral replication generally begins in the upper respiratory tract with gradual (4- to 5-day) progression to involve the lower respiratory tract. In normal children, the duration of viral shedding ranges from 1 to 3 weeks. Clinical signs of bronchiolitis include air trapping and wheezing. Pathologic findings in RSV bronchiolitis include necrosis of bronchiolar epithelium, loss of ciliated epithelial cells, and marked peribronchiolar mononuclear inflammation.[204] Virus-induced cytopathology and associated submucosal edema lead to obstruction of smaller bronchioles, particularly in infants, with distal collapse or air trapping.

Both serum and mucosal antibody responses occur but are associated with only partial protection. The magnitude of the antibody response is related to the age at primary infection, with infants less than 8 months of age having approximately 10-fold lower antibody levels than older ones.[205] Reinfection may occur within weeks after primary infection and as early as 8 weeks in adults with secondary infections.[201] Increasing levels of circulating and mucosal antibody occur with each successive infection and appear to be associated with milder illness. High titers of serum neutralizing antibody are generally associated with a lower risk of severe illness in infants and children.[206]

Cell-mediated immunity appears to be important in viral clearance, and may also be involved in pathogenesis. For example, adult bone marrow transplant populations are at high risk of severe lower respiratory disease from RSV, which is likely due to prolonged periods of decreased cellular immunity.[207,208] In contrast, in AIDS patients with decreased cellular immunity, viral shedding can continue for up to 6 months with only mild disease.[209]

Studies investigating the association of severe RSV disease in infants with genetic polymorphisms have implicated several candidate innate and adaptive immune genes, including surfactants, TLR4, and several cytokine and chemokine genes, as modulating the severity of RSV disease.

Clinical Illness

The clinical manifestations of infection are dependent upon both the age and the immunologic state of the host. In infants and young children, upper respiratory illness accompanied by fever and otitis media is common. Respiratory syncytial virus is the major cause of lower respiratory tract illness in infants and young children and accounts for 45% to 90% of bronchiolitis, up to 40% of pneumonia, and smaller proportions of croup and bronchitis cases in this age group. Most severe infections occur in infants less than 6 months of age, and almost all primary infections are symptomatic, with 40% or more associated with bronchiolitis or pneumonia. Approximately 1% to 2% of infections result in hospitalization, and about one tenth of hospitalized infants require ventilatory support.

The risk of hospitalization and severe bronchiolitis is particularly high in infants with congenital heart disease, chronic lung disease, or immunodeficiency. In addition, infants born prematurely are also at risk for severe disease because they lack maternal antibody. Mortality is usually 0.5% to 1.5% in previously healthy infants hospitalized with RSV disease but is 15% to 40% in those with primary immunodeficiency, cancer chemotherapy, or pulmonary and heart disease; pulmonary hypertension, in particular, is associated with poor outcome. Severe disease in children has also been associated with a family history of asthma, and those exposed to cigarette smoke in the family household.[210]

Radiographic findings in lower respiratory tract disease include bronchial wall thickening, peribronchial shadowing, air trapping, and, in pneumonia, multilobar patchy shadowing or poorly defined nodularity (see Fig. 31-4). Although no radiographic pattern is specific, air trapping, alone or with other abnormalities, is highly associated with RSV infection in hospitalized children.[211]

The most common physiologic abnormality is hypoxemia that may persist for weeks after apparent recovery.[212] Prolonged pulmonary function abnormalities, including increased airway resistance, peripheral airway obstruction, and decreased arterial oxygen saturation, have been detected in children years after bouts of RSV-related bronchiolitis.[213] Bronchiolitis in infancy has also been associated with an increased risk of subsequent recurrent wheezing and cough and airway hyperreactivity. However, whether or not adults develop asthma after severe RSV disease during infancy has not been established.

One half or more of recurrent infections in adults are associated with upper respiratory tract illness. Adults typically experience coryza, pharyngitis, and cough, sometimes accompanied by low-grade fever. Bronchitis, influenza-like illness, pneumonia, and exacerbations of asthma and chronic bronchitis have also been described in adults with RSV infection. In the United States, approximately 170,000 hospitalizations and over 10,000 deaths are associated with RSV annually in adults over 65 years of age.[103] In elderly adults, the clinical features of RSV infection can mimic those of influenza, although fever is less and wheezing is more frequent.[214] In one study, rates of RSV infection were from 3% to 7% among healthy elderly and 4% to 10% in high-risk adults, and compared to influenza, intensive care unit (ICU) admissions were higher and mortality similar at 7% to 8%.[202] RSV also plays a substantial role in causing exacerbations of COPD, with rates from 5% to 10%.[215]

Respiratory syncytial virus, often nosocomially acquired, causes severe lower respiratory tract disease in immunosuppressed children and adults. Upper respiratory tract illness usually precedes the development of pneumonia, and complicating sinusitis and otitis media are common. Two thirds or more of the bone marrow transplant recipients who develop RSV pneumonia succumb without treatment.

Diagnosis

Respiratory syncytial virus grows well in several human cell lines, in which it causes formation of characteristic syncytia. Virus can be detected as early as 2 days and usually within 7 days on primary isolation from specimens collected from children. A variety of antigen detection tests have been developed for more rapid diagnosis. The sensitivity of such techniques is dependent on the quality of the nasopharyngeal specimen, with nasopharyngeal aspirates superior to brushings or swabs.[216] In addition, sensitivity is related to the amount of antigen being shed, and so is generally greater in children than adults. In transplant patients with suspected RSV pneumonia, samples of the lower respiratory tract by bronchoalveolar lavage are more sensitive than throat swabs for detection of RSV antigens.[217] A PCR-based respiratory viral multiplex assay for detection of RSV and other respiratory viruses has also been approved by the Food and Drug Administration.

Treatment and Prevention

Correction of hypoxemia is the most important aspect of managing RSV lower respiratory tract disease. Ribavirin is highly active against RSV in vitro, and aerosolized ribavirin has been shown to reduce viral shedding and shorten the course of illness in some but not all studies. Aerosolized ribavirin is currently recommended for use only in selected infants and young children who are at high risk for serious RSV disease.[218]

In immunosuppressed patients, particularly human stem cell transplant recipients, both aerosolized ribavirin and high-dose oral ribavirin have been used for early treatment to prevent progression to pneumonia.[219] Once RSV pneumonia has developed, intravenous ribavirin alone is ineffective, but combinations of aerosolized ribavirin with intravenous immune globulin (RSV-IVIG), and particularly paluvizumab (see later), may be beneficial if treatment is initiated prior to the onset of respiratory failure.[220,221]

Vaccines for prevention of RSV have not been developed. In a study of formalin-inactivated RSV vaccine conducted in the 1960s, vaccinated infants developed more severe disease compared to unvaccinated children.[222] The mechanism of this enhancement remains unknown, although an unbalanced immune response in which the majority of immunity is directed against nonprotective and/or denatured epitopes generated by the inactivation process, a lack of antibody maturation, and enhanced immune complex deposition are some current hypotheses.[223,224]

In contrast, passive transfer of antibody to the RSV F protein has been shown to be a highly effective means to prevent RSV morbidity in high-risk children. The currently commercially available product, paluvizumab, is a humanized monoclonal antibody to the F protein.[225] Administration of paluvizumab to infants with prematurity or bronchopulmonary dysplasia resulted in a 55% reduction in RSV-related hospitalizations, and a lower incidence of ICU admissions.[226] In a second trial, administration of paluvizumab to infants and children with hemodynamically significant congenital heart disease was well tolerated and resulted in a 45% decrease in RSV-associated hospitalizations.[227] A new higher affinity anti-RSV monoclonal antibody, motavizumab, is in clinical trials for RSV prophylaxis of high-risk infant populations.

Prophylaxis with paluvizumab should be considered for infants younger than 24 months old with chronic lung disease severe enough to require medical therapy within 6 months of the anticipated start of the RSV season.[228] Prophylaxis with paluvizumab (and not RSV-IVIG) should be given to infants with hemodynamically significant congenital heart disease and infants born before 32 weeks of gestation. Prophylaxis for infants born between 32 and 35 weeks of gestation should depend on the presence of other RSV risk factors, such as tobacco smoke, attendance at daycare, school-aged siblings, and congenital airway abnormalities. Paluvizumab has not been shown to be effective in the therapy of established RSV disease.

Recommendations for interruption of nosocomial transmission include handwashing, decontamination of surfaces and inanimate objects, and isolation of infected patients. Use of disposable eye-nose goggles by pediatric staff reduces the risk of nosocomial RSV infection in both staff and patients.[229] Regular use of gowns, gloves, and possibly masks by hospital staff caring for infected children may also reduce the risk of nosocomial RSV spread. Protective isolation of high-risk infants or deferring their elective admission has been recommended during institutional outbreaks of RSV.

Rhinovirus

The rhinovirus (RV) virion is a nonenveloped particle 30 nm in diameter with four major structural proteins. The genome of RV consists of single-stranded RNA of approximately 2.5×10^6 daltons and codes for a 240-kD protein that is cleaved into the structural units of the virion. Rhinovirus genomes have been found to have 45% to 62% homology with poliovirus genomes. Poliovirus and RV differ, however, in the construction of their protein shells: that of RV being loosely packed with a resultant sensitivity to inactivation at low pH, and that of poliovirus being tightly packed, providing the virion with resistance to acid inactivation. The acid sensitivity of RV and its optimum growth at 32°C to 34°C are thought to account for its replication in the nasal passages (and possibly large airways) but not in the gastrointestinal tract.

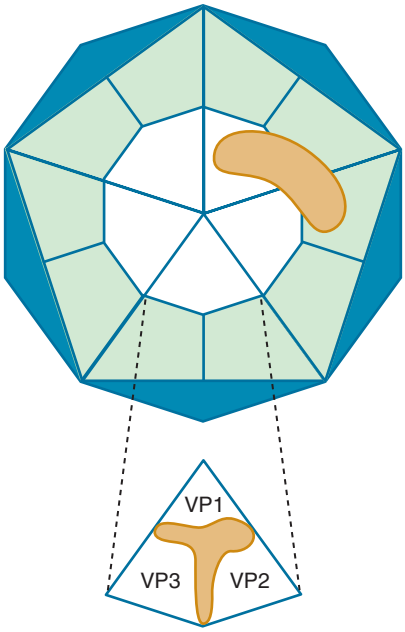

FIGURE 31-12 ■ Organization of rhinovirus shell drawn to scale with attached antibody molecule. *Top,* The protein shell is built of 12 pentamers, one of which is highlighted (*white*). Each of the five wedge-shaped subunits of the pentamer is called a "protomer." The antibody molecule (*beige*) bridges protomers of two adjacent pentamers. *Bottom,* Surface organization of the protomer. Three of the polypeptide chains (VP1, VP2, VP3) making up each protomer are exposed on the virus surface, while the smallest polypeptide (VP4) is buried at the bottom of the protomer. The host-cell receptor is thought to bind near the base of the cleft formed by antigenic plateaus forming VP1, VP2, and VP3. The blunt-nosed binding site of the antibody is too wide to fit into the base of the cleft. (Courtesy of Roland Rueckert, MD, University of Wisconsin, Madison, Wisconsin.)

Three of the four proteins in the RV shell (VP1, VP2, and VP3) react with neutralizing antibody, forming the basis on which 100 antigenic types and one subtype have been numbered. The presence of neutralizing antibody in serum and nasal secretions correlates with protection from infection. X-ray diffraction studies of RV have disclosed the presence of a large depression on the surface of the virus shell at a junction between the plateaus of the three proteins (Fig. 31-12).[230] This depression contains the recognition site for the host cell receptor, which is intracellular adhesion molecule-1 (ICAM-1) for 91 of 102 known rhinovirus serotypes.[231] Rhinovirus serotypes that do not bind to ICAM-1 are referred to as the minor receptor group viruses, and appear to utilize the low-density lipoprotein receptor.[232] Manipulations of these receptor proteins have been explored as a potential control measure for rhinovirus infection.

Epidemiology and Transmission

Rhinoviruses are worldwide in distribution. In the United States, RV has been observed to cause 0.74 to 0.77 infections per person per year in adults. Rhinovirus is believed to produce even higher infection rates in children, leading to acquisition of antibody to the different RV types throughout childhood and adolescence, with peak antibody prevalence occurring in young adults. Immunity to rhinovirus is type specific and relatively solid following infection, although second infections with the same virus type can occur. The different immunotypes circulate in a given population in an apparently random manner. In the United States, RV infections are most prevalent in the early fall and late spring.

The major reservoir for RV is schoolchildren, who transmit RV infection among their peers in the classroom and introduce it into their homes, infecting other family members. Studies of experimental RV colds in volunteers have shown that RV is most efficiently spread by contaminated fingers accidentally depositing virus into the nose or eye. Also, experimental RV transmission has been achieved by the airborne route, presumably by large-particle aerosol. The relative importance of these two routes of RV transmission under natural conditions has not been determined.

Pathogenesis

Approximately two thirds of both natural and experimental RV infections result in overt illness. The incubation period of RV colds is usually 2 days but may be up to a week. Symptoms begin within 1 day following experimental infection. Small doses of RV instilled into the nose or eye of susceptible volunteers regularly lead to infection, indicating that mucociliary clearance is not effective against the virus. During the period of illness, sloughed ciliated epithelial cells containing viral antigen are present in nasal secretions.[233]

In general, the number of RV-infected cells in the nasopharynx appears to be quite limited,[234] and infection does not lead to detectable damage to the epithelium of the nasal passages. These results have suggested that virus-induced cellular injury is not the direct cause of symptoms in rhinovirus colds, and that inflammatory mediators play an important role. Nasal secretions during the initial response to rhinovirus infection are predominantly the result of increased vascular permeability, as demonstrated by elevated levels of plasma proteins in nasal secretions; glandular secretions (lactoferrin, lysozyme, and secretory immunoglobulin A) predominate late in colds.[235] In contrast to the situation in allergic rhinitis, histamine does not appear to play a role in the induction of symptoms in colds. Nasal secretion kinin levels correlate with symptoms in natural and experimental colds, and intranasal administration of bradykinin causes increased nasal vascular permeability, rhinitis, and sore throat.[236] Interleukin-1, -6, and -8 levels also increase in experimental rhinovirus colds and correlate well with symptom severity.[237] Enhanced synthesis of proinflammatory cytokines and cell adhesion molecules in the middle ear may also contribute to the pathogenesis of otitis media associated with colds.[238]

Clinical Illness

Rhinovirus colds vary in severity from mild episodes characterized by a day or two of coryza or scratchy throat to full-blown illnesses with profuse and prolonged rhinorrhea, pharyngitis, and bronchitis. The profile of a typical RV cold, based on composite results from young adults with natural infection, is shown in Figure 31-1. The median length of illness is 1 week, with symptoms lasting up to 2 weeks in one quarter of cases. Peak symptoms are usually seen on the second and third days of illness. The characteristics of RV illness are not distinctive enough to permit its differentiation from colds due to other respiratory viruses. Rhinovirus is among the respiratory viruses implicated in the development of acute sinusitis and represents about half of all viruses recovered from middle ear effusions in children with acute otitis media.[239] Recently, a clinical presentation indistinguishable from that of influenza has also been reported in healthy adults.[240]

Rhinovirus alone or in combination with bacteria has been recovered from aspirates obtained by direct puncture of the maxillary sinuses of patients with acute sinusitis.[241] Mucosal thickening and/or sinus exudates have been observed in as many as 77% of subjects with acute colds.[242] These abnormalities are transient, and in uncomplicated cases resolve within 21 days. However, clinically manifest acute bacterial sinusitis is seen in a small (0.5% to 5%) proportion of individuals with naturally occurring colds. It is presumed that the RV infection impairs mucociliary clearance and other local defenses in the sinus cavity, allowing secondary bacterial invasion.

There is increasing evidence for an important role of rhinoviruses in lower respiratory tract disease in adults and children. Rhinovirus is the second most frequently recognized agent associated with pneumonia and bronchiolitis in infants and young children and commonly causes exacerbations of preexisting airways disease in older patients with COPD or cystic fibrosis.[243] Colds are generally more severe in atopic individuals, and rhinoviruses are major causes of asthma exacerbation.[244] Children with a history of wheezing/asthma had significantly more RV-associated hospitalizations than those without such history.[245]

Rhinovirus infections may also be associated with severe lower respiratory tract disease in transplant recipients,[246] and in some cases can be associated with prolonged viral shedding.[247] These viruses can also be detected in lower respiratory tract disease in individuals with hematologic malignancy, often in conjunction with other pathogens.[248]

Diagnosis

Rhinoviruses can be isolated in cell culture, usually within 2 to 7 days after inoculation. Virus is present in nasopharyngeal secretions in highest concentrations during the first and second days of illness but may be shed for as long as 3 weeks. Identification of the specific serotype of a rhinovirus isolate is made by neutralization test. Rapid tests for detecting RV antigen or nucleic acids by PCR have been developed and are more sensitive than culture.

Treatment and Prevention

The only effective therapy for RV colds currently available is symptomatic treatment of individual complaints. Remedies recommended for such treatment are described in the section on the common cold earlier in this chapter. As mentioned, the plethora of rhinovirus serotypes suggests that an effective vaccine will not be forthcoming in the foreseeable future. Advances in understanding of the structural and molecular biology of the rhinoviruses has led to development of a number of strategies for antiviral intervention, including receptor blockade and capsid-binding agents. However, none of these agents has reached approval for clinical use.

Varicella-Zoster Virus

Varicella, or *chickenpox,* is a highly contagious childhood disease that typically causes community outbreaks in late winter and early spring months in temperate regions. Varicella spreads rapidly to household contacts, with an attack rate of nearly 90% within 2 weeks. Consequently, most adults in temperate areas have experienced infection during childhood, but a high proportion of adults in semitropical and tropical areas remain susceptible to primary infection.[249] Herpes zoster, or *shingles,* is nonseasonal in occurrence and is seen in persons of all ages, although its incidence increases almost linearly over the age of 30 years. About 10% to 20% of adults experience zoster, typically as a single episode after the fifth decade of life. Clinically apparent reinfections with varicella-zoster virus (VZV) may occur.

Although the virus has been infrequently recovered from respiratory secretions of varicella patients, epidemiologic evidence indicates that the virus is spread from person to person through airborne transmission. Cutaneous lesions may be the source of infectious virus. Infection of susceptible persons has occurred after contact with patients with varicella, or, less often, herpes zoster. Prior to the implementation of vaccination, VZV was an important cause of nosocomial outbreaks on pediatric wards, during which spread could occur by small-particle aerosols.

Pathogenesis

The incubation period of varicella averages 2 weeks, and almost all cases of varicella develop within 11 to 20 days after exposure. The initial portal of infection is the respiratory tract, with viremic dissemination leading to the extensive cutaneous and mucous membrane lesions. Following infection, VZV establishes latency in the posterior dorsal root ganglia. Reactivation of virus replication and centrifugal spread along sensory nerves lead to the unique dermatomal distribution of shingles (zoster). Viremic dissemination to other sites may occur in immunocompromised hosts with zoster.

Clinical Illness

Varicella. In normal children, varicella is usually not associated with significant systemic or respiratory manifestations. The exanthem typically begins around the scalp and head, with subsequent involvement of the trunk and extremities. Lesions progress through various stages (erythematous macules, vesicles, pustules, crusts), so that an area will have lesions in different stages of evolution. In contrast, in smallpox, a disease with which varicella was often confused, lesions begin on the face and spread outwardly to the extremities, and adjacent lesions are at the same stage of development.

In children and susceptible adults who are immunocompromised, particularly those with defects in cell-mediated immune function, including HIV infection,[250] varicella follows a more severe course. Continued lesion development particularly involving the extremities, high fever, and visceral involvement with pneumonia, meningoencephalitis, and hepatitis are common. Severe pneumonia occurs in approximately 10% of varicella cases during pregnancy.

Viral pneumonia is the major complication of varicella in previously healthy adults, in whom it occurs with an estimated 25-fold higher frequency than in children.[251] Smoking is a significant risk factor. Pneumonia associated with varicella is usually apparent 1 to 6 days after the onset of rash. Symptoms include cough, dyspnea, pleuritic chest pain, and hemoptysis. Physical findings other than fever and tachypnea are often modest. The intensity of the rash does not necessarily correlate with the severity of pneumonia. The characteristic radiographic pattern is that of diffuse nodular (1- to 10-mm) infiltrates (Fig. 31-13), which may resolve with miliary calcific densities.[252] Hilar adenopathy, pleural effusions, and peribronchial infiltrates are frequently present. Pulmonary infarction may complicate the clinical picture. Pulmonary function studies have found normal spirometric values but decreased carbon monoxide diffusing capacity, which may persist for months. However, many individuals with radiographic changes are relatively asymptomatic.

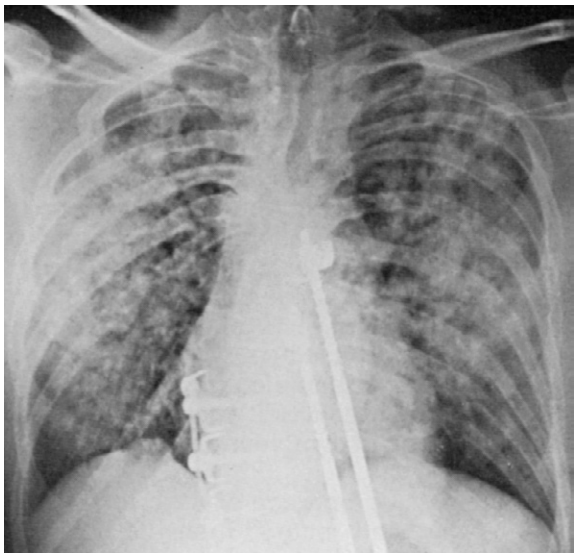

FIGURE 31-13 ■ Anteroposterior chest roentgenogram of a 23-year-old paraplegic man showing bilateral fluffy infiltrates ("pulmonary edema" pattern) with areas of nodular coalescence. This patient died of varicella pneumonia. (Courtesy of Thomas L. Pope, Jr., MD, Department of Radiology, University of Virginia School of Medicine, Charlottesville, Virginia.)

Herpes Zoster. Zoster represents reactivation of latent virus along one to three dermatomes, and in adults is usually associated with acute pain in the involved areas. The thoracic dermatomes are involved in about one half of cases. Prolonged severe pain, or *postherpetic neuralgia,* occurs with increased frequency in those over the age of 50 years.

Zoster occurs more often in those receiving immunosuppressive therapy or combination chemotherapy for malignancies and at anatomic sites irradiated for treatment of malignancies. Depending on the degree of immunosuppression, herpes zoster occurs in 30% or more of patients. Cutaneous dissemination (defined as more than 20 lesions outside the primary dermatome) occurs in 25% to 50% of immunosuppressed patients and in up to 2% of apparently healthy patients with zoster. It is associated with visceral involvement, including pneumonitis as well as hepatitis, meningoencephalitis, and uveitis, in approximately one half of those affected. Mortality depends on the degree of immunosuppression and has ranged from zero to 10%.

Diagnosis

The virus is very labile but can be isolated from vesicular fluid during the first 3 days of varicella in normal hosts and for up to 10 days in immunocompromised hosts or patients with disseminated zoster. Direct inoculation of vesicular fluid onto monolayers of cell culture (human embryonic lung fibroblasts) at the bedside increases the likelihood of isolation. A rapid diagnosis of herpes group infection can be established by cytologic examination of lesion scrapings (Tzank smear and others), which has a sensitivity of 70% to 85% when lesions are in the vesicular stage. Direct immunofluorescence for VZV antigen in lesions is the most sensitive rapid laboratory test.

Treatment and Prevention

Live, attenuated varicella vaccine generates neutralizing antibody in over 95% of recipients, and long-lived cytotoxic T-lymphocyte responses against varicella virus.[253] Vaccination of immunosuppressed children, mostly those with leukemia, is also safe, although a small proportion of children will experience a mild, varicella-like clinical syndrome approximately 1 month after vaccination.[254] In both healthy and immunosuppressed children, the vaccine is highly effective at preventing varicella, with efficacy rates of 50% to 90%. Two doses of varicella vaccine administered subcutaneously are recommended for children 12 months and older, adolescents, and adults without evidence of prior immunity.[255] Second-dose catch-up vaccination is recommended for those who previously received only a single dose of vaccine.

A higher dose live vaccine effectively restimulates cellular immunity in adults and can reduce the frequency of reactivation as well as the clinical severity of zoster.[256] The high-dose live vaccine is recommended as a single dose in all healthy individuals 60 and above.[257]

Although uncomplicated varicella in children usually requires no specific treatment, oral acyclovir initiated within 24 hours of rash onset reduces the number of lesions, duration of fever, and healing time compared with placebo in children, adolescents, and adults.[258] In certain circumstances, sequential intravenous and oral acyclovir has been used in therapy of varicella in immunocompromised children.[259] In immunocompromised patients with localized zoster, intravenous acyclovir has been found to halt dissemination. In addition, oral acyclovir, valacyclovir, and famcyclovir are effective for the treatment of zoster, and may reduce the duration of postherpetic neuralgia in healthy adults.[260] Intravenous acyclovir (10 mg/kg every 8 hours for 5 to 7 days) appears efficacious in varicella pneumonia in previously healthy adults if started early.[261]

KEY POINTS

- Viral infections are extremely important causes of disease of the respiratory tract, which are associated with considerable morbidity and, at times, mortality.
- Clinical syndromes—such as the common cold, pharyngitis, acute bronchitis, influenza-like illness, croup, bronchiolitis, and pneumonia—may be caused by several different viruses, and most of the major respiratory viruses may cause more than one clinical syndrome.
- Adenoviruses of many antigenic types cause sporadic, epidemic, or nosocomial disease both in previously healthy children and adults and in persons with impaired immunity.
- Human coronaviruses have long been recognized as causes of the common cold, and a novel strain was identified as the cause of the recent pandemic of severe acute respiratory syndrome (SARS).
- In immunocompetent persons, infection with cytomegalovirus is usually asymptomatic, but severe pneumonia and extrapulmonary disease occur in immunocompromised patients.
- Hantaviruses cause severe, often fatal pneumonia in addition to a cardiopulmonary and hemorrhagic fever with renal disease syndrome.
- Herpes simplex virus, especially type 1, causes acute gingivostomatitis and pharyngitis in healthy persons and chronic ulcerative pharyngitis and laryngotracheitis and pneumonia in immunocompromised patients.
- Influenza virus, especially types A and B, regularly causes seasonal epidemics of pneumonia, which are associated with substantial excess morbidity and need for hospitalization that are at least partially preventable by vaccination.
- Measles virus occurs worldwide but has largely been curtailed by vaccination in industrialized countries; in resource-poor countries, death from associated pneumonia is common.
- Human metapneumoviruses and respiratory syncytial virus (RSV) both cause a spectrum of acute respiratory illnesses ranging from mild or asymptomatic infection to severe bronchiolits and pneumonia. Disease from RSV is generally more severe than from metapneumoviruses, and may also occur in adults, especially those with chronic lung disease or immunosuppression.
- Parainfluenza viruses occur worldwide and commonly infect young children, who may present with croup or, less often, bronchiolitis or pneumonia.
- The numerous strains of rhinovirus are the most common cause of the common cold.
- Varicella-zoster virus causes two distinct clinical syndromes, varicella, which in adults is often associated with pneumonia, and zoster, a painful skin eruption that is common in immunocompromised patients and increases with age in otherwise healthy adults. Effective vaccines are available for each condition.

References

1. Gwaltney JM Jr, Druce HM: Efficacy of brompheniramine maleate for the treatment of rhinovirus colds. Clin Infect Dis 25:1188–1194, 1997.
2. Taverner D, Danz C, Econimos D: The effects of oral pseudoephedrine on nasal patency in the common cold: A double-blind single-dose placebo-controlled trial. Clin Otolaryngol Allied Sci 24:47–51, 1999.
3. Yoon BW, Bae HJ, Hong KS, et al: Phenylpropanolamine contained in cold remedies and risk of hemorrhagic stroke. Neurology 68:146–149, 2007.
4. Sharfstein JM, North M, Serwint JR: Over the counter but no longer under the radar—pediatric cough and cold medications. N Engl J Med 357:2321–2324, 2007.
5. Doyle WJ, Boehm S, Skoner DP: Physiologic responses to intranasal dose-response challenges with histamine, methacholine, bradykinin, and prostaglandin in adult volunteers with and without nasal allergy. J Allergy Clin Immunol 81:924–935, 1990.
6. Wenzel RP, Fowler AA: Acute bronchitis. N Engl J Med 355:2125–2130, 2006.
7. Paul IM, Beiler J, McMonagle A, et al: Effect of honey, dextromethorphan, and no treatment on nocturnal cough and sleep quality for coughing children and their parents. Arch Pediatr Adolesc Med 161:1140–1146, 2007.
8. Monto AS, Gravenstein S, Elliott M, et al: Clinical signs and symptoms predicting influenza infection. Arch Intern Med 160:3243–3247, 2000.
9. Bjornson CL, Klassen TP, Williamson J, et al: A randomized trial of a single dose of oral dexamethasone for mild croup. N Engl J Med 351:1306–1313, 2004.
10. Horwitz MS. Adenoviruses. *In* Fields BN, Knipe DM, Chanock RM (eds): Virology. New York: Raven Press, 1990, pp 1723–1740.
11. Erdman DD, Xu W, Gerber SI, et al: Molecular epidemiology of adenovirus type 7 in the United States, 1966–2000. Emerg Infect Dis 8:269–277, 2002.
12. Steen-Johnsen J, Orstavik I, Attramadal A: Severe illness due to adenovirus type 7 in children. Acta Paediatr Scand 58:157–163, 1969.
13. Myerowitz RL, Stalder H, Oxman MN, et al: Fatal disseminated adenovirus infection in a renal transplant recipient. Am J Med 59:591–598, 1975.
14. Rosman FC, Mistchenko AS, Ladenheim HS, et al: Acute and chronic human adenovirus pneumonia: Cellular and extracellular matrix components. Pediatr Pathol Lab Med 16:521–541, 1996.
15. Ohori NP, Michaels MG, Jaffe R, et al: Adenovirus pneumonia in lung transplant recipients. Hum Pathol 26:1073–1079, 1995.
16. Klinger JR, Sanchez MP, Curtin LA, et al: Multiple cases of life-threatening adenovirus pneumonia in a mental health care center. Am J Respir Crit Care Med 157:645–649, 1998.
17. Pinto A, Beck R, Jadavji T: Fatal neonatal pneumonia caused by adenovirus type 35: Report of one case and review of the literature. Arch Pathol Lab Med 116:95–99, 1992.
18. Leen AM, Rooney CM: Adenovirus as an emerging pathogen in immunocompromised patients. Br J Haematol 128:135–144, 2005.
19. Miura-Ochiai R, Shimada Y, Konno T, et al: Quantitative detection and rapid identification of human adenoviruses. J Clin Microbiol 45:958–967, 2007.
20. Leruez-Ville M, Minard V, Lacaille F, et al: Real-time blood plasma polymerase chain reaction for management of disseminated adenovirus infection. Clin Infect Dis 38:45–52, 2004.
21. Ljungman P, Ribaoud P, Eyrich M, et al: Cidofovir for adnovirus infections after allogeneic hematopoietic stem cell transplantation: A survey by the Infectious Diseases Working Party of the European Group for Blood and Marrow Transplantation. Bone Marrow Transplant 31:481–483, 2003.
22. Cassano WF: Intravenous ribavirin therapy for adenovirus cystitis after allogeneic bone marrow transplantation. Bone Marrow Transplant 7:247–248, 1991.
23. Sabroe I, McHale J, Tait DR, et al: Treatment of adenoviral pneumonitis with intravenous ribavirin and immunoglobulin. Thorax 50:1219–1220, 1995.
24. La Rosa AM, Champlin RE, Mirza NB, et al: Adenovirus infections in adult recipients of blood and marrow transplants. Clin Infect Dis 32:871–875, 2001.
25. Kaye HS, Dowdle WR: Seroepidemiologic survey of coronavirus (strain 229E) infections in a population of children. Am J Epidemiol 101:238–244, 1975.
26. Hamre D, Beem M: Virologic studies of acute respiratory disease in young adults. V. Coronavirus 229E infections during six years of surveillance. Am J Epidemiol 96:94–106, 1972.
27. Monto AS. Coronaviruses. *In* Evans AS (ed): Viral Infections of Humans. New York: Plenum, 1997, pp 211–227.
28. Tyrrell DAJ, Bynoe ML, Hoorn B: Cultivation of "difficult" viruses from patients with organ cultures. Br Med J 1:606–610, 1968.
29. Fouchier RA, Kuiken T, Schutten M, et al: Aetiology: Koch's postulates fulfilled for SARS virus. Nature 423:240, 2003.
30. Peiris JS, Lai ST, Poon LL, et al: Coronavirus as a possible cause of severe acute respiratory syndrome. Lancet 361:1319–1325, 2003.
31. Peiris JS, Chu CM, Cheng VC, et al: Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: A prospective study. Lancet 361:1767–1772, 2003.
32. McIntosh K, McQuillin J Jr, Reed SE, Gardner PS: Diagnosis of human coronavirus infection by immunofluorescence: Method and application to respiratory disease in hospitalized children. J Med Virol 2:341–346, 1978.
33. Bende M, Barrow I, Heptonstall J, et al: Changes in human nasal mucosa during experimental coronavirus common colds. Acta Otolaryngol 107:262–269, 1989.
34. Franks TJ, Chong PY, Chui P, et al: Lung pathology of severe acute respiratory syndrome (SARS): A study of 8 autopsy cases from Singapore. Hum Pathol 34:743–748, 2003.
35. Nicholls JM, Poon LL, Lee KC, et al: Lung pathology of fatal severe acute respiratory syndrome. Lancet 361:1773–1778, 2003.
36. Drosten C, Gunther S, Preiser W, et al: Identification of a novel coronavirus in patients with severe acute respiratory syndrome [see comment]. N Engl J Med 348:1967–1976, 2003.
37. Summary of probable SARS cases with onset of illness from 1 November 2002 to 31 July 2003. WHO Press Release. Geneva: World Health Organization, 2004.
38. Hon KL, Leung CW, Cheng WT, et al: Clinical presentations and outcome of severe acute respiratory syndrome in children. Lancet 361:1701–1703, 2003.
39. Antonio GE, Wong KT, Hui DS, et al: Thin-section CT in patients with severe acute respiratory syndrome following hospital discharge: Preliminary experience. Radiology 228:810–815, 2003.
40. Thiel V, Ivanov KA, Putics A, et al: Mechanisms and enzymes involved in SARS coronavirus genome expression. J Gen Virol 84:2305–2315, 2003.
41. Haagmans BL, Osterhaus AD: Coronaviruses and their therapy. Antiviral Res 71:397–403, 2006.
42. Osterhaus AD: New respiratory viruses of humans. Pediatr Infect Dis J 27:S71–S74, 2008.
43. Wong SS, Yuen KY: The management of coronavirus infections with particular reference to SARS. J Antimicrob Chemother 62:437–441, 2008.
44. Loutfy MR, Blatt LM, Siminovitch KA, et al: Interferon alfacon-1 plus corticosteroids in severe acute respiratory syndrome: A preliminary study. JAMA 290:3222–3228, 2003.
45. Wu CJ, Jan JT, Chen CM, et al: Inhibition of severe acute respiratory syndrome coronavirus replication by niclosamide. Antimicrob Agents Chemother 48:2693–2696, 2004.
46. Keyaerts E, Vijgen L, Maes P, et al: In vitro inhibition of severe acute respiratory syndrome coronavirus by chloroquine. Biochem Biophys Res Commun 323:264–268, 2004.
47. Amici C, Di Coro A, Ciucci A, et al: Indomethacin has a potent antiviral activity against SARS coronavirus. Antiviral Ther 11:1021–1030, 2006.
48. Callow KA, Parry HG, Sergeant M, Tyrell DA: The time course of the immune response to experimental coronavirus infection of man. Epidemiol Infect 103:435–446, 1990.
49. Reed SE: The behavior of recent isolates of human respiratory coronavirus in vitro in volunteers: Evidence of heterogeneity among 229E-related strains. J Med Virol 13:179–192, 1984.

50. Glansbeek HL, Haagmans BL, te Lintelo EG, et al: Adverse effects of feline IL-12 during DNA vaccination against feline infectious peritonitis virus. J Gen Virol 83:1–10, 2002.
51. Hopkins JI, Fiander AN, Evans AS, et al: Cytotoxic T cell immunity to human cytomegalovirus glycoprotein. Br J Med Virol 49:124–131, 1996.
52. Quinnan GV Jr, Burns WH, Kirmani N, et al: HLA-restricted cytotoxic T lymphocytes are an early immune response and important defense mechanism in cytomegalovirus infections. Rev Infect Dis 6:156–163, 1984.
53. Adler SP: Cytomegalovirus and child day care: Evidence for an increased infection rate among day-care workers. N Engl J Med 321:1290–1296, 1989.
54. Sinzger C, Grefte A, Plachter B, et al: Fibroblasts, epithelial cells, endothelial cells and smooth muscle cells are major targets of human cytomegalovirus infection in lung and gastrointestinal tissues. J Gen Virol 76:741–750, 1995.
55. Grundy JE: Virologic and pathogenetic aspects of cytomegalovirus infection. Rev Infect Dis 12:S711–S719, 1990.
56. Muller CA, Hebart H, Roos A, et al: Correlation of interstitial pneumonia with human cytomegalovirus-induced lung infection and graft-versus-host disease after bone marrow transplantation. Med Microbiol Immunol 184:115–121, 1995.
57. Smith MA, Sundaresan S, Mohanakumar T, et al: Effect of development of antibodies to HLA and cytomegalovirus mismatch on lung transplantation survival and development of bronchiolitis obliterans syndrome. J Thorac Cardiovasc Surg 116:812–820, 1998.
58. Beschorner WE, Hutchins GM, Burns WH, et al: Cytomegalovirus pneumonia in bone marrow transplant recipients: Miliary and diffuse patterns. Am Rev Respir Dis 122:107–114, 1980.
59. Shreeniwas R, Schulman LL, Berkmen YM, et al: Opportunistic bronchopulmonary infections after lung transplantation: Clinical and radiographic findings. Radiology 200:349–356, 1996.
60. Abdallah PS, Mark JBD, Merigan TC: Diagnosis of cytomegalovirus pneumonia in compromised hosts. Am J Med 61:326–332, 1976.
61. Kang EY, Patz EF Jr, Muller NL: Cytomegalovirus pneumonia in transplant patients: CT findings. J Comput Assist Tomogr 20:295–299, 1996.
62. Limaye AP, Kirby KA, Rubenfeld GD, et al: Cytomegalovirus reactivation in critically ill immunocompetent patients. JAMA 300:413–422, 2008.
63. van den Berg AP, Klompmaker IJ, Haagsma EB, et al: Evidence for an increased rate of bacterial infections in liver transplant patients with cytomegalovirus infection. Clin Transpl 10:224–231, 1996.
64. Husni RN, Gordon SM, Longworth DL, et al: Cytomegalovirus infection is a risk factor for invasive aspergillosis in lung transplant recipients. Clin Infect Dis 26:753–755, 1998.
65. Barrett-Muir WY, Aitken C, Templeton K, et al: Evaluation of the murex hybrid capture cytomegalovirus DNA assay versus plasma PCR and shell vial assay for diagnosis of human cytomegalovirus viremia in immunocompromised patients. J Clin Microbiol 36:2554–2556, 1998.
66. Emmanuel D, Cummingham I, Jules-Elysee K, et al: Cytomegalovirus pneumonia after bone marrow transplantation successfully treated with the combination of ganciclovir and high-dose intravenous immune globulin. Ann Intern Med 109:777–782, 1988.
67. Dykewicz C: Summary of the guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. Clin Infect Dis 33:139–144, 2001.
68. Akalin E, Sehgal V, Ames S, et al: Cytomegalovirus disease in high-risk transplant recipients despite ganciclovir or valganciclovir prophylaxis. Am J Transplant 3:731–735, 2003.
69. Chizhikov VE, Spiropoulou CF, Morzunov SP, et al: Complete genetic characterization and analysis of isolation of Sin Nombre virus. J Virol 69:8132–8136, 1995.
70. Mackow ER, Gavrilovskaya IN: Cellular receptors and hantavirus pathogenesis. Curr Top Microbiol Immunol 256:91–115, 2001.
71. Mills JN, Johnson JM, Ksiazek TG, et al: A survey of hantavirus antibody in small-mammal populations in selected United States National Parks. Am J Trop Med Hyg 58:525–532, 1998.
72. Hutchinson KL, Rollin PE, Peters CJ: Pathogenesis of a North American hantavirus, Black Creek Canal virus, in experimentally infected *Sigmodon hispidus*. Am J Trop Med Hyg 59:58–65, 1998.
73. Hjelle B, Glass GE: Outbreak of hantavirus infection in the Four Corners region of the United States in the wake of the 1997–1998 El Nino-southern oscillation. J Infect Dis 181:1569–1573, 2000.
74. Vitek CR, Breiman RF, Ksiazek TG, et al: Evidence against person-to-person transmission of hantavirus to health care workers. Clin Infect Dis 22:824–826, 1996.
75. Ferres M, Vial P, Marco C, et al: Prospective evaluation of household contacts of persons with hantavirus cardiopulmonary syndrome in Chile. J Infect Dis 195:1563–1571, 2007.
76. Khan AS, Khabbaz RF, Armstrong LR, et al: Hantavirus pulmonary syndrome: The first 100 US cases. J Infect Dis 173:1297–1303, 1996.
77. Bhardwaj M, Nofchissey R, Goade D, et al: Humoral immune response in hantavirus cardiopulmonary syndrome. J Infect Dis 182:43–48, 2000.
78. Nolte KB, Feddersen RM, Foucar K, et al: Hantavirus pulmonary syndrome in the United States: A pathological description of a disease caused by a new agent. Hum Pathol 26:110–120, 1995.
79. Peters CJ, Khan AS: Hantavirus pulmonary syndrome: The new American hemorrhagic fever. Clin Infect Dis 34:1224–1231, 2002.
80. Green W, Feddersen R, Yousef O, et al: Tissue distribution of hantavirus antigen in naturally infected humans and deer mice. J Infect Dis 177:1696–1700, 1998.
81. Tuuminen T, Kekalainen E, Makela S, et al: Human CD8+ T cell memory generation in *Puumala* hantavirus infection occurs after the acute phase and is associated with boosting of EBV-specific CD8+ memory T cells. J Immunol 179:1988–1995, 2007.
82. Saggioro FP, Rossi MA, Duarte MI, et al: Hantavirus infection induces a typical myocarditis that may be responsible for myocardial depression and shock in hantavirus pulmonary syndrome. J Infect Dis 195:1541–1549, 2007.
83. Prescott J, Ye C, Sen G, Hjelle B: Induction of innate immune response genes by Sin Nombre hantavirus does not require viral replication. J Virol 79:15007–15015, 2005.
84. Peters CJ: Hantavirus pulmonary syndrome in the Americas. *In* Scheld WM, Craig WA, Hughes JM (eds): Emerging Infections 2. Washington, DC: ASM Press, 1998, pp 17–64.
85. Moolenaar RL, Dalton C, Lipman HB, et al: Clinical features that differentiate hantavirus pulmonary syndrome from three other acute respiratory illnesses. Clin Infect Dis 21:643–649, 1995.
86. Hjelle B, Jenison S, Torrez-Martinez N, et al: Rapid and specific detection of Sin Nombre virus antibodies in patients with hantavirus pulmonary syndrome by a strip immunoblot assay suitable for field diagnosis. J Clin Microbiol 35:600–608, 1997.
87. Hallin GW, Simpson SQ, Crowell RE, et al: Cardiopulmonary manifestations of hantavirus pulmonary syndrome. Crit Care Med 24:252–258, 1996.
88. Hopkins RO, Larson-Lohr V, Weaver LK, Bigler ED: Neuropsychological impairments following hantavirus pulmonary syndrome. J Int Neuropsychol Soc 4:190–196, 1998.
89. Padula PJ, Colavecchia SB, Martinez VP, et al: Genetic diversity, distribution, and serological features of hantavirus infection in five countries in South America. J Clin Microbiol 38:3029–3035, 2000.
90. Terajima M, Hendershot JD 3rd, Kariwa H, et al: High levels of viremia in patients with the Hantavirus pulmonary syndrome. J Infect Dis 180:2030–2034, 1999.
91. Mertz GJ, Hjelle B, Crowley M, et al: Diagnosis and treatment of new world hantavirus infections. Curr Opin Infect Dis 19:437–442, 2006.
92. Mertz GJ, Miedzinski L, Goade D, et al: Placebo-controlled, double-blind trial of intravenous ribavirin for the treatment of hantavirus cardiopulmonary syndrome in North America. Clin Infect Dis 39:1307–1313, 2004.
93. Whitley RJ: Herpes simplex viruses. *In* Fields BN, Knipe DM, Chanock RM (eds): Virology. New York: Raven, 1990, pp 1843–1887.
94. Ramsey PG, Fife KH, Hackman RC, et al: Herpes simplex virus pneumonia: Clinical, virologic, and pathologic features in 20 patients. Ann Intern Med 97:813–820, 1982.

95. Legge RH, Thompson AB, Linder J, et al: Acyclovir-responsive herpetic tracheobronchitis. Am J Med 85:561–563, 1988.
96. Sherry MK, Klainer AS, Wolff M, Gerhard H: Herpetic tracheobronchitis. Ann Intern Med 109:229–233, 1988.
97. Hubbell C, Dominguez R, Kohl S: Neonatal herpes simplex pneumonitis. Rev Infect Dis 10:431–438, 1988.
98. Aquino SL, Dunagan DP, Chiles C, Haponik EF: Herpes simplex virus 1 pneumonia: Patterns on CT scans and conventional chest radiographs. J Comput Assist Tomogr 22:795–800, 1998.
99. Engelmann I, Gottlieb J, Meier A, et al: Clinical relevance of and risk factors for HSV-related tracheobronchitis or pneumonia: Results of an outbreak investigation. Crit Care 11:R119, 2007.
100. Ong GM, Lowry K, Mahajan S, et al: Herpes simplex type 1 shedding is associated with reduced hospital survival in patients receiving assisted ventilation in a tertiary referral intensive care unit. J Med Virol 72:121–125, 2004.
101. Bruynseels P, Jorens PG, Demey HE, et al: Herpes simplex virus in the respiratory tract of critical care patients: A prospective study. Lancet 362:1536–1541, 2003.
102. Verheij J, Groeneveld AB, Beishuizen A, et al: Herpes simplex virus type 1 and normal protein permeability in the lungs of critically ill patients: A case for low pathogenicity? Crit Care 8: R139, 2004.
103. Thompson WW, Shay DK, Weintraub E, et al: Mortality associated with influenza and respiratory syncytial virus in the United States. JAMA 289:179–186, 2003.
104. Neuzil KM, Mellen BG, Wright PF, et al: The effect of influenza on hospitalizations, outpatient visitis, and courses of antibiotics in children. N Engl J Med 342:225–231, 2000.
105. Izurieta HS, Thompson WW, Kramarz P, et al: Influenza and the rates of hospitalization for respiratory disease among infants and young children [see comments]. N Engl J Med 342:232–239, 2000.
106. Wilson IA, Cox NJ: Structural basis of immune recognition of influenza virus hemagglutinin. Annu Rev Immunol 8:737–771, 1990.
107. Webster RG, Bean WJ, Gorman OT, et al: Evolution and ecology of influenza A viruses. Microbiol Rev 56:152–179, 1992.
107a. Shinde V, Bridges CB, Uyeki TM, et al: Triple-reassortant swine influenza A (H1) in humans in the United States, 2005–2009. N Engl J Med 360:2616–2625, 2009.
107b. Perez-Padilla R, de la Rosa-Zamboni D, Ponce de Leon S, et al: Pneumonia and respiratory failure from swine-origin influenza A (H1N1) in Mexico. N Engl J Med 361:680–689, 2009.
107c. Dawood FS, Jain S, Finelli L, et al: Emergence of a novel swine-origin influenza A (H1N1) virus in humans. N Engl J Med 360:2605–2615, 2009.
107d. Webb SA, Pettila V, Seppelt I, et al: Critical care services and 2009 H1N1 influenza in Australia and New Zealand. N Engl J Med 361:1925–1934, 2009.
107e. Jain S, Kamimoto L, Bramley AM, et al: Hospitalized patients with 2009 H1N1 influenza in the United States, April–June 2009. N Engl J Med 361:1935–1944, 2009.
107f. Kumar A, Zarychanski R, Pinto R, et al: Critically ill patients with 2009 influenza A (H1N1) infection in Canada. JAMA 302:1872–1879, 2009.
108. Walsh JJ, Dietlein LF, Low FN, et al: Bronchotracheal response in human influenza. Arch Intern Med 108:376–388, 1961.
109. Hers JFP, Mulder J, Masurel N, et al: Studies on the pathogenesis of influenza virus pneumonia in mice. J Pathol Bacteriol 83:207–217, 1962.
110. Little JW, Hall WJ, Douglas RG Jr, et al: Airway hyperreactivity and peripheral airway dysfunction in influenza A infection. Am Rev Respir Dis 118:295–303, 1978.
111. Hall WJ, Douglas RG Jr, Hyde RW, et al: Pulmonary mechanics after uncomplicated influenza A infection. Am Rev Respir Dis 113:141–147, 1976.
112. Horner GJ, Gray FD Jr: Effect of uncomplicated, presumptive influenza on the diffusing capacity of the lung. Am Rev Respir Dis 108:866–869, 1973.
113. Johanson WGJ, Pierce AK, Sanford JP: Pulmonary function in uncomplicated influenza. Am Rev Respir Dis 100:141–146, 1969.
114. Utell MJ, Aquilina AT, Hall WJ, et al: Development of airway reactivity to nitrates in subjects with influenza. Am Rev Respir Dis 121:233–241, 1980.
115. Schwarzmann SW, Adler JL, Sullivan RFJ, Marine WM: Bacterial pneumonia during the Hong Kong influenza epidemic of 1968–1969. Arch Intern Med 127:1037–1041, 1971.
116. Bisno AL, Griffin JP, VanEpps KA: Pneumonia and Hong Kong influenza: A prospective study of the 1968–1969 epidemic. Am J Med Sci 261:251–274, 1971.
117. Morens DM, Taubenberger JK, Fauci AS: Predominant role of bacterial pneumonia as a cause of death in pandemic influenza: Implications for pandemic influenza preparedness. J Infect Dis 198:962–970, 2008.
117a. Intensive-care patients with severe novel influenza A (H1N1) virus infection—Michigan, June 2009. MMWR Morb Mortal Wkly Rep 58:749–752, 2009.
118. Newton DW, Mellen CF, Baxter BD, et al: Practical and sensitive screening strategy for detection of influenza virus. J Clin Microbiol 40:4353–4356, 2002.
119. Chan KH, Maldeis N, Pope W, et al: Evaluation of the Directigen FluA+B test for rapid diagnosis of influenza virus type A and B infections. J Clin Microbiol 40:1675–1680, 2002.
119a. Faix DJ, Sherman SS, Waterman SH: Rapid-test sensitivity for novel swine-origin influenza A (H1N1) virus in humans. N Engl J Med 361:728–729, 2009.
119b. Hurt AC, Baas C, Deng YM, et al: Performance of influenza rapid point-of-care tests in the detection of swine lineage A (H1N1) influenza viruses. Influenza Other Respi Viruses 3:171–176, 2009.
120. Murphy DR, Strunk RC: Safe administration of influenza vaccine in asthmatic children hypersensitive to egg proteins. J Pediatr 106:931–933, 1985.
121. Centers for Disease Control and Prevention: Prevention and control of influenza: Recommendations of the Advisory Committee on Immunization Practice (ACIP), 2008. MMWR Morb Mortal Wkly Rep 57:1–60, 2008.
122. Edwards KM, Dupont WD, Westrich MK, et al: A randomized controlled trial of cold-adapted and inactivated vaccines for the prevention of influenza A disease. J Infect Dis 169:68–76, 1994.
123. Neuzil KM, Dupont WD, Wright PF, Edwards KM: Efficacy of inactivated and cold-adapted vaccines against influenza A infection, 1985 to 1990: The pediatric experience. Pediatr Infect Dis J 20:733–740, 2001.
124. Govaert TM, Thijs CT, Masurel N, et al: The efficacy of influenza vaccination in elderly individuals: A randomized double-blind placebo-controlled trial. JAMA 272:1956–1961, 1994.
125. Nichol KL, Nordin J, Nelson DB, et al: Effectiveness of influenza vaccine in the community-dwelling elderly. N Engl J Med 357:1373–1381, 2007.
126. Jackson LA, Nelson JC, Benson P, et al: Functional status is a confounder of the association of influenza vaccine and risk of all cause mortality in seniors. Int J Epidemiol 35:345–352, 2006.
127. Belshe RB, Mendelman PM, Treanor J, et al: The efficacy of live attenuated cold-adapted trivalent, intranasal influenzavirus vaccine in children. N Engl J Med 358:1405–1412, 1998.
128. Belshe RB, Gruber WC, Mendelman PM, et al: Efficacy of vaccination with live attenuated, cold-adapted, trivalent, intranasal influenza virus vaccine against a variant (A/Sydney) not contained in the vaccine. J Pediatr 136:168–175, 2000.
129. Nichol KL, Mendelman PM, Mallon KP, et al: Effectiveness of live, attenuated intranasal influenza virus vaccine in healthy, working adults: A randomized controlled trial. JAMA 282:137–144, 1999.
130. Vesikari T, Karvonen A, Korhonen T, et al: A randomized, double-blind study of the safety, transmissibility, and phenotypic and genotypic stability of cold-adapted influenza virus vaccine. Pediatr Infect Dis J 25:590–597, 2006.
131. Belshe RB, Edwards KM, Vesikari T, et al: Live attenuated versus inactivated influenza vaccine in infants and young children. N Engl J Med 356:685–696, 2007.
132. Ohmit SE, Victor JC, Rotthoff JR, et al: Prevention of antigenically drifted influenza by inactivated and live attenuated vaccines. N Engl J Med 355:2513–2522, 2006.
133. Wang Z, Tobler S, Roayaei J, Eick A: Live attenuated or inactivated influenza vaccines and medical encounters for respiratory illnesses among US military personnel. JAMA 301:945–953, 2009.

134. Keyser LA, Karl M, Nafziger AN, Bertino JS Jr: Comparison of central nervous system adverse effects of amantadine and rimantadine used as sequential prophylaxis of influenza A in elderly nursing home patients. Arch Intern Med 160:1485–1488, 2000.
135. Speeg KV, Leighton JA, Maldonado AL: Case report: Toxic delerium in a patient taking amantadine and trimethoprim-sulfamethoxazole. Am J Med Sci 298:410–412, 1989.
136. Dolin R, Reichman RC, Madore HP, et al: A controlled trial of amantadine and rimantadine in the prophylaxis of influenza A in humans. N Engl J Med 307:580–584, 1982.
137. Little J, Hall W, Douglas RG Jr, et al: Amantadine effect on peripheral airways abnormalities in influenza. Ann Intern Med 85:177–182, 1976.
138. Hay AJ, Wolstenholme AJ, Skehel JJ, Smith MH: The molecular basis of the specific anti-influenza action of amantadine. EMBO J 4:3021–3024, 1985.
139. Shiraishi K, Mitamura K, Sakai Y, et al: High frequency of resistant viruses harboring different mutations in amantadine-treated children with influenza. J Infect Dis 188:57–61, 2003.
140. Boivin G, Goyette N, Bernatchez H: Prolonged excretion of amantadine-resistant influenza A virus quasi species after cessation of antiviral therapy in an immunocompromised patient. Clin Infect Dis 34:E23–E25, 2002.
141. Bright RA, Medina M-J, Xu X, et al: Incidence of adamantane resistance among influenza A (H3N2) viruses isolated worldwide from 1994 to 2005: A cause for concern. Lancet 366:1175–1181, 2005.
142. Hill G, Cihlar T, Oo C, et al: The anti-influenza drug oseltamivir exhibits low potential to induce pharmacokinetic drug interactions via renal secretion—correlation of in vivo and in vitro studies. Drug Metabol Dispos 30:13–19, 2002.
143. Kaiser L, Wat C, Mills T, et al: Impact of oseltamivir treatment on influenza-related lower respiratory tract complications and hospitalizations. Arch Intern Med 163:1667–1672, 2003.
144. Whitley RJ, Hayden FG, Reisinger KS, et al: Oral oseltamivir treatment of influenza in children. Pediatr Infect Dis J 20:127–133, 2001.
145. Gubareva LV, Bethell R, Hart GJ, et al: Characterization of mutants of influenza A selected with the neuramindase inhibitor 4-guanidino-Neu5Ac2en. J Virol 70:1818–1827, 1996.
146. Gubareva LV, Robinson MJ, Bethell RC, Webster RG: Catalytic and framework mutations in the neuraminidase active site of influenza viruses that are resistant to 4-guanidino-neu5ac2en. J Virol 71:3385–3390, 1997.
147. Moscona A: Oseltamivir resistance—disabling our influenza defenses. N Engl J Med 353:2633–2636, 2005.
148. McKimm-Breschkin JL, Sahasrabudhe A, Blick TJ, et al: Mutations in a conserved residue in the influenza virus neuraminidase active site decreases sensitivity to neu5acen-derived inhibitors. J Virol 72:2456–2462, 1998.
149. Goto H, Bethell RC, Kawaoka Y: Mutations affecting the sensitivity of the influenza virus neuraminidase to 4-guanidino-2,4-dideoxy-2,3-dehydro-N-acetylneuraminic acid. Virology 238: 265–272, 1997.
150. Kiso M, Mitamura K, Sakai-Tagawa Y, et al: Resistant influenza A viruses in children treated with oseltamivir: Descriptive study. Lancet 364:759–765, 2004.
151. Ives JA, Carr JA, Mendel DB, et al: The H274Y mutation in the influenza A/H1N1 neuraminidase active site following oseltamivir phosphate treatment leaves virus severely compromised both in vitro and in vivo. Antiviral Res 55:307–317, 2002.
151a. Baz M, Abed Y, Papenburg J, et al: Emergence of oseltamivir-resistant pandemic H1N1 virus during prophylaxis. N Engl J Med 361:2296–2297, 2009.
152. Tatsuo H, Ono N, Tanaka K, Yanagi Y: SLAM (CDw150) is a cellular receptor for measles virus. Nature 406:893–897, 2000.
153. Nussbaum O, Broder CC, Moss B, et al: Functional and structural interactions between measles virus hemagglutinin and CD46. J Virol 69:3341–3349, 1995.
154. Black FL: Measles. *In* Evans AS (ed): Viral Infections in Humans, 3rd ed. New York: Plenum, 1989, pp 451–469.
155. Chen RT, Goldbaum GM, Wassilak SGF, et al: An explosive point-source measles outbreak in a highly vaccinated population. Am J Epidemiol 129:173–182, 1989.
156. Griffin DE, Ward BJ, Jauregui E, et al: Natural killer cell activity during measles. Clin Exp Immunol 81:218–224, 1990.
157. Rall GF: Measles virus 1998–2002: Progress and controversy. Annu Rev Microbiol 57:343–367, 2003.
158. Gremillion DH, Crawford GE: Measles pneumonia in young adults: An analysis of 106 cases. Am J Med 71:539–542, 1981.
159. Kaplan LJ, Daum RS, Smaron M, McCarthy CA: Severe measles in immunocompromised patients. JAMA 267:1237–1241, 1992.
160. Atmar RJ, Englund JA, Hammill H: Complications of measles during pregnancy. Clin Infect Dis 14:217–226, 1992.
161. Krasinski K, Borkowsky W: Measles immunity in children infected with human immunodeficiency virus. JAMA 261:2512–2516, 1989.
162. Flick JA: Does measles really predispose to tuberculosis? Am Rev Respir Dis 114:257–265, 1976.
163. Hall WJ, Hall CB: Atypical measles in adolescents: Evaluation of clinical and pulmonary function. Ann Intern Med 90:882–886, 1979.
164. Nadel S, McGann K, Hodinka RL, et al: Measles giant cell pneumonia in a child with human immunodeficiency virus infection. Pediatr Infect Dis J 10:542–544, 1991.
165. Hussey GD, Klein M: A randomized, controlled trial of vitamin A in children with severe measles. N Engl J Med 323:160–164, 1990.
166. Madsen KM, Hviid A, Vestergaard M, et al: A population-based study of measles, mumps, and rubella vaccination and autism. N Engl J Med 347:1477–1482, 2002.
167. Wilson K, Mills E, Ross C, et al: Association of autistic spectrum disorder and the measles, mumps, and rubella vaccine: A systematic review of current epidemiological evidence. Arch Pediatr Adolesc Med 157:628–634, 2003.
168. van den Hoogen BG, de Jong JC, Groen J, et al: A newly discovered human pneumovirus isolated from young children with respiratory tract disease. Nat Med 7:719–724, 2001.
169. Biacchesi S, Skiadopoulos MH, Boivin G, et al: Genetic diversity between human metapneumovirus subgroups. Virology 315:1–9, 2003.
170. Boivin G, Abed Y, Pelletier G, et al: Virological features and clinical manifestations associated with human metapneumovirus: A new paramyxovirus responsible for acute respiratory-tract infections in all age groups. J Infect Dis 186:1330–1334, 2002.
171. Williams JV, Harris PA, Tollefson SJ, et al: Human metapneumovirus and lower respiratory tract disease in otherwise healthy infants and children. N Engl J Med 350:443–450, 2004.
172. Boivin G, De Serres G, Cote S, et al: Human metapneumovirus infections in hospitalized children. Emerg Infect Dis 9:634–640, 2003.
173. Lambert SB, Allen KM, Druce JD, et al: Community epidemiology of human metapneumovirus, human coronavirus NL63, and other respiratory viruses in healthy preschool-aged children using parent-collected specimens. Pediatrics 120:e929–e937, 2007.
174. Falsey AR, Erdman D, Anderson LJ, Walsh EE: Human metapneumovirus infections in young and elderly adults. J Infect Dis 187:785–790, 2003.
175. Greensill J, McNamara PS, Dove W, et al: Human metapneumovirus in severe respiratory syncytial virus bronchiolitis. Emerg Infect Dis 9:372–375, 2003.
176. Semple MG, Cowell A, Dove W, et al: Dual infection of infants by human metapneumovirus and human respiratory syncytial virus is strongly associated with severe bronchiolitis. J Infect Dis 191:382–386, 2005.
177. Chan PK, Tam JS, Lam CW, et al: Human metapneumovirus detection in patients with severe acute respiratory syndrome. Emerg Infect Dis 9:1058–1063, 2003.
178. van den Hoogen BG, van Doornum GJ, Fockens JC, et al: Prevalence and clinical symptoms of human metapneumovirus infection in hospitalized patients. J Infect Dis 188:1571–1577, 2003.
179. Esper F, Boucher D, Weibel C, et al: Human metapneumovirus infection in the United States: Clinical manifestations associated with a newly emerging respiratory infection in children. Pediatrics 111:1407–1410, 2003.
180. Hopkins P, McNeil K, Kermeen F, et al: Human metapneumovirus in lung transplant recipients and comparison to respiratory syncytial virus. Am J Respir Crit Care Med 178:876–881, 2008.

181. Gerna G, Vitulo P, Rovida F, et al: Impact of human metapneumovirus and human cytomegalovirus versus other respiratory viruses on the lower respiratory tract infections of lung transplant recipients. J Med Virol 78:408–416, 2006.
182. Jartti T, van den Hoogen B, Garofalo RP, et al: Metapneumovirus and acute wheezing in children. Lancet 360:1393–1394, 2002.
183. Douville RN, Bastien N, Li Y, et al: Human metapneumovirus elicits weak IFN-gamma memory responses compared with respiratory syncytial virus. J Immunol 176:5848–5855, 2006.
184. Wyde PR, Chetty SN, Jewell AM, et al: Comparison of the inhibition of human metapneumovirus and respiratory syncytial virus by ribavirin and immune serum globulin in vitro. Antiviral Res 60:51–59, 2003.
185. Fry AM, Curns AT, Harbour K, et al: Seasonal trends of human parainfluenza viral infections: United States, 1990–2004. Clin Infect Dis 43:1016–1022, 2006.
186. Counihan ME, Shay DK, Holman RC, et al: Human parainfluenza virus-associated hospitalizations among children less than five years of age in the United States. Pediatr Infect Dis J 20:646–653, 2001.
187. Hall CB, Geiman JM, Breese BB, Douglas RG Jr: Parainfluenza viral infections in children: Correlation of shedding with clinical manifestations. J Pediatr 91:194–198, 1977.
188. Muchmore HG, Parkinson AJ, Humphries JE, et al: Persistent parainfluenza virus shedding during isolation at the South Pole. Nature 289:187–189, 1981.
189. Fishaut M, Tubergen D, McIntosh K: Prolonged fatal respiratory viral infections in children with disorders of cell mediated immunity. Pediatr Res 13:447, 1979.
190. Downham MAPS, Gardner PS, McQuillin J, Ferris JAJ: Role of respiratory viruses in childhood mortality. Br Med J 1:235–239, 1975.
191. Volovitz B, Faden H, Ogra PL: Release of leukotriene C4 in respiratory tract during acute viral infection. J Pediatr 112:218–222, 1988.
192. Parainfluenza infections in the elderly 1976–1982. Can Med Assoc J 287:1619, 1983.
193. Dignan F, Alvares C, Riley U, et al: Parainfluenza type 3 infection post stem cell transplant: High prevalence but low mortality. J Hosp Infect 63:452–458, 2006.
194. Jalal H, Bibby DF, Bennett J, et al: Molecular investigations of an outbreak of parainfluenza virus type 3 and respiratory syncytial virus infections in a hematology unit. J Clin Microbiol 45:1690–1696, 2007.
195. Stankova J, Carret AS, Moore D, et al: Long-term therapy with aerosolized ribavirin for parainfluenza 3 virus respiratory tract infection in an infant with severe combined immunodeficiency [see comment]. Pediatr Transpl 11:209–213, 2007.
196. Wendt CH, Weisdorf DJ, Jordan MC, et al: Parainfluenza virus respiratory infection after bone marrow transplantation. N Engl J Med 326:921–926, 1992.
197. Sato M, Wright PF: Current status of vaccines for parainfluenza virus infections. Pediatr Infect Dis J 27(10 Suppl):S123–S125, 2008.
198. Hall CR, Walsh EE, Schnabel KC, et al: Occurrence of groups A and B of respiratory syncytial virus over 15 years: Associated epidemiologic and clinical characteristics in hospitalized and ambulatory children. J Infect Dis 162:1283–1290, 1990.
199. Walsh Ee, McConnochie KM, Long CE, Hall CB: Severity of respiratory syncytial virus infection is related to virus strain. J Infect Dis 175:814–820, 1997.
200. Hall CB, Weinberg GA, Iwane MK, et al: The burden of respiratory syncytial virus infection in young children. N Engl J Med 360:588–598, 2009.
201. Hall CB, Walsh EE, Long CE, Schnabel KC: Immunity to and frequency of reinfection with respiratory syncytial virus. J Infect Dis 163:693–698, 1991.
202. Falsey A, Hennessey PA, Formica MA, et al: Respiratory syncytial virus in elderly and high-risk adults. N Engl J Med 352:1749–1759, 2005.
203. Hall CG, Geiman JM, Biggar R, et al: Respiratory syncytial virus infections within families. N Engl J Med 294:414–419, 1976.
204. Wohl MEB, Chernick V: Bronchiolitis. Am Rev Respir Dis 118:759–781, 1978.
205. Holberg CJ, Wright AL, Martinez FD, et al: Risk factors for respiratory syncytial virus-associated lower respiratory illnesses in the first year of life. Am J Epidemiol 133:1135–1151, 1991.
206. Piedra PA, Jewell AM, Cron SG, et al: Correlates of immunity to respiratory syncytial virus (RSV) associated-hospitalization: Establishment of minimum protective threshold levels of serum neutralizing antibodies. Vaccine 21:3479–3482, 2003.
207. Khushalani NI, Bakri FG, Wentling D, et al: Respiratory syncytial virus infection in the late bone marrow transplant period: Report of three cases and review. Bone Marrow Transplant 27:1071–1073, 2001.
208. Machado CM, Boas LS, Mendes AV, et al: Low mortality rates related to respiratory virus infections after bone marrow transplantation. Bone Marrow Transplant 31:695–700, 2003.
209. King JC Jr: Community respiratory viruses in individuals with human immunodeficiency virus infection. Am J Med 102:19–24, 1997 [discussion appears in Am J Med 102:25–26, 1997].
210. McConnochie KM, Roghmann KJ: Parental smoking, presence of older siblings, and family history of asthma increase risk of bronchiolitis. Am J Dis Child 140:806–812, 1986.
211. Simpson W, Hacking PM, Court SDM, Gardner PS: The radiological findings in respiratory syncytial virus infections in children II. The correlation of radiological categories with clinical and virological findings. Pediatr Radiol 2:155–162, 1974.
212. Hall CB, Hall WJ, Speers DM: Clinical and physiological manifestations of bronchiolitis and pneumonia: Outcome of respiratory syncytial virus. Am J Dis Child 133:798–802, 1979.
213. Hall CB, Hall WJ, Gala CL, et al: Long-term prospective study in children after respiratory syncytial virus infection. J Pediatr 105:358–364, 1984.
214. Falsey AR, Cunningham CK, Barker WH, et al: Respiratory syncytial virus and influenza A virus infections in the hospitalized elderly. J Infect Dis 172:389–394, 1995.
215. Sethi S, Murphy TF: Infection in the pathogenesis and course of chronic obstructive pulmonary disease. N Engl J Med 359:2355–2365, 2008.
216. Barnes SD, Leclair JM, Forman MS, et al: Comparison of nasal brush and nasopharyngeal aspirate techniques in obtaining specimens for detection of respiratory syncytial viral antigen by immunofluorescence. Pediatr Infect Dis J 8:598–601, 1989.
217. Englund JA, Piedra PA, Jewell A, et al: Rapid diagnosis of respiratory syncytial virus infections in immunocompromised adults. J Clin Microbiol 34:1649–1653, 1996.
218. American Academy of Pediatrics. Respiratory syncytial virus. *In* Peter G (ed): 1997 Red Book: Report of the Committee on Infectious Diseases, 24th ed. Elk Grove Village, IL: American Academy of Pediatrics, 1997, pp 443–447.
219. Chakrabarti S, Collingham KE, Holder K, et al: Pre-emptive oral ribavirin therapy of paramyxovirus infections after haematopoietic stem cell transplantation: A pilot study. Bone Marrow Transplant 28:759–763, 2001.
220. Small TN, Casson A, Malak SF, et al: Respiratory syncytial virus infection following hematopoietic stem cell transplantation. Bone Marrow Transplant 29:321–327, 2002.
221. Boeckh M, Berrey MM, Bowden RA, et al: Phase I evaluation of the respiratory syncytial virus-specific monoclonal antibody palivizumab in recipients of hematopoietic stem cell transplants. J Infect Dis 184:350–354, 2001.
222. Fulginiti VA, Eller JJ, Sieber OF, et al: Respiratory virus immunization. I. A field trial of two inactivated respiratory virus vaccines: An aqueous trivalent parainfluenza virus vaccine and an alum-precipitated respriratory syncytial virus vaccine. Am Epidemiol 89:435–448, 1969.
223. Polack FP, Teng MN, Collins PL, et al: A role for immune complexes in enhanced respiratory syncytial virus disease. J Exp Med 196:859–865, 2002.
224. Delgado MF, Coviello S, Monsalvo AC, et al: Lack of antibody affinity maturation due to poor Toll-like receptor stimulation leads to enhanced respiratory syncytial virus disease. Nat Med 15:34–41, 2009.
225. Johnson S, Oliver C, Prince GA, et al: Development of a humanized monoclonal antibody (MEDI-493) with potent in vitro and in vivo activity against respiratory syncytial virus. J Infect Dis 176:1215–1224, 1997.

226. IMpact RSV Study Group: Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. Pediatrics 102:531–537, 1998.
227. Feltes TF, Cabalka AK, Meissner HC, et al: Palivizumab prophylaxis reduces hospitalization due to respiratory syncytial virus in young children with hemodynamically significant congenital heart disease. J Pediatr 143:532–540, 2003.
228. Diagnosis and management of bronchiolitis. Pediatrics 118:1774–1793, 2006.
229. Gala CL, Hall CB, Schnabel KC, et al: The use of eye-nose goggles to control nosocomial respiratory syncytial virus infection. JAMA 256:2706–2708, 1986.
230. Rossman MG, Arnold E, Erickson JW, et al: Structure of a human common cold virus and functional relationship to other picornaviruses. Nature 317:145–153, 1985.
231. Uncapher CR, DeWitt CM, Colonno RJ: The major and minor group receptor families contain all but one human rhinovirus serotype. Virology 180:814–817, 1991.
232. Hofer F, Gruenberger M, Kowalski H, et al: Members of the low-density lipoprotein receptor family mediate entry of a minor-group cold virus. Proc Natl Acad Sci U S A 91:1839–1842, 1994.
233. Turner RB, Hendley JO, Gwaltney JM Jr: Shedding of infected ciliated epitheilial cells in rhinovirus colds. J Infect Dis 145:849–853, 1982.
234. Arruda E, Boyle TR, Winther B, et al: Localization of human rhinovirus replication in the upper respiratory tract by in situ hybridization. J Infect Dis 171:1329–1333, 1995.
235. Igarashi Y, Skoner DP, Doyle WJ, et al: Analysis of nasal secretions during experimental rhinovirus upper respiratory infections. J Allergy Clin Immunol 92:722–731, 1993.
236. Rees GL, Eccles R: Sore throat following nasal and orophayrngeal bradykinin challenge. Acta Otolaryngol 114:311–314, 1994.
237. Turner RB, Weingand KW, Hwa-Chyon Y, Leedy DW: Association between interleukin-8 concentration in nasal secretions and severity of symptoms of experimental rhinovirus colds. Clin Infect Dis 26:840–846, 1998.
238. Okamoto Y, Kudo K, Ishikawa K, et al: Presence of respiratory syncytial virus genomic sequences in middle ear fluid and its relationship to expression of cytokines and cell adhesion molecules. J Infect Dis 168:1277–1281, 1993.
239. Nokso-Koivisto J, Raty R, Blomqvist S, et al: Presence of specific viruses in the middle ear fluids and respiratory secretions of young children with acute otitis media. J Med Virol 72:241–248, 2004.
240. Lamson D, Renwick N, Kapoor V, et al: MassTag polymerase-chain-reaction detection of respiratory pathogens, including a new rhinovirus genotype, that caused influenza-like illness in New York State during 2004–2005. J Infect Dis 194:1398–1402, 2006.
241. Pitkaranta A, Arruda E, Malmberg H, Hayden FG: Detection of rhinovirus in sinus brushings of patients with acute community-acquired sinusitis by reverse transcription-PCR. J Clin Microbiol 35:1791–1793, 1997.
242. Gwaltney JM Jr, Phillips CD, Miller RD, Riker DK: Computed tomographic study of the common cold. N Engl J Med 330:25–30, 1994.
243. Wilkinson TM, Hurst JR, Perera WR, et al: Effect of interactions between lower airway bacterial and rhinoviral infection in exacerbations of COPD. Chest 129:317–324, 2006.
244. Friedlander SL, Busse WW: The role of rhinovirus in asthma exacerbations. J Allerg Clin Immunol 116:267–273, 2005.
245. Miller EK, Lu X, Erdman D, et al: Rhinovirus-associated hospitalizations in young children. J Infect Dis 195:773–781, 2007.
246. Ison MG, Hayden FG, Kaiser L, et al: Rhinovirus infections in hematopoietic stem cell transplant recipients with pneumonia. Clin Infect Dis 36:1139–1143, 2003.
247. Kaiser L, Aubert JD, Pache JC, et al: Chronic rhinoviral infection in lung transplant recipients [see comment]. Am J Respir Crit Care Med 174:1392–1399, 2006.
248. Parody R, Rabella N, Martino R, et al: Upper and lower respiratory tract infections by human enterovirus and rhinovirus in adult patients with hematological malignancies. Am J Hematol 82:807–811, 2007.
249. Longfield JN, Winn RE, Gibson RL, et al: Varicella outbreaks in army recruits from Puerto Rico. Arch Intern Med 150:970–973, 1990.
250. Jura E, Chadwick EG, Josephs SH, et al: Varicella-zoster virus infections in children infected with human immunodeficiency virus. Pediatr Infect J 8:586–590, 1989.
251. Mohsen AH, McKendrick M: Varicella pneumonia in adults. Eur Resp J 21:886–891, 2003.
252. Raider L: Calcification in chickenpox pneumonia. Chest 60:504–507, 1971.
253. Zerboni L, Nader S, Aoki K, Arvin AM: Analysis of the persistence of humoral and cellular immunity in children and adults immunized with varicella vaccine. J Infect Dis 177:1701–1704, 1998.
254. Gershon AA, LaRussa P, Steinberg S: The varicella vaccine: Clinical trials in immunocompromised individuals. Infect Dis Clin North Am 10:583–594, 1996.
255. Centers for Disease Control and Prevention: Prevention of varicella: Recommendations of the Advisory Committee on Immunization Practice (ACIP). MMWR Morb Mortal Wkly Rep 56:1–38, 2007.
256. Oxman MN, Levin MJ, Johnson GR, et al: A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. N Engl J Med 352:2271–2284, 2005.
257. Centers for Disease Control and Prevention: Prevention of herpes zoster: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep 57:1–23, 2008.
258. Dunkle LM, Arvin AM, Whitley RJ, et al: A controlled trial of acyclovir for chickenpox in normal children. N Engl J Med 325:1539–1544, 1991.
259. Carcao MD, Lau RC, Gupta A, et al: Sequential use of intravenous and oral acyclovir in the therapy of varicella in immunocompromised children. Pediatr Infect Dis J 17:626–631, 1998.
260. Beutner KR, Friedman DJ, Forszpaniak C, et al: Valaciclovir compared with acyclovir for improved therapy for herpes zoster in immunocompetent adults. Antimicrob Agents Chemother 39:1546–1553, 1995.
261. Haake DA, Zakowski PC, Haake DL, Bryson YJ: Early treatment with acyclovir for varicella pneumonia in otherwize healthy adults: Retrospective controlled study and review. Rev Infect Dis 12:788–798, 1990.

CHAPTER 32

PYOGENIC BACTERIAL PNEUMONIA AND LUNG ABSCESS

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INTRODUCTION

PATHOPHYSIOLOGY

EPIDEMIOLOGY
Community-Acquired Pneumonia
Hospital-Acquired (Nosocomial) Pneumonia
Health Care–Associated Pneumonia

CLINICAL PRESENTATION
"Typical" versus "Atypical" Pneumonia

PATIENT EVALUATION
Clinical Evaluation
Laboratory Evaluation
Radiographic Evaluation
Microbiologic Evaluation
Invasive Diagnostic Techniques
Differential Diagnosis

THERAPEUTIC APPROACH TO PNEUMONIA
Assessment of Severity
Selection of Antimicrobial Agents
Adjustments in Antimicrobial Therapy

COMMON CAUSES OF PYOGENIC PNEUMONIA
Streptococcus pneumoniae (Pneumococcal Pneumonia)
Other Streptococci
Haemophilus influenzae
Mycoplasma pneumoniae
Chlamydophila pneumoniae (Formerly *Chlamydia pneumoniae*)
Staphylococcus aureus
Gram-negative Bacillary Pneumonia
Legionella
Anaerobic Bacteria

OTHER LESS COMMON CAUSES OF PNEUMONIA
Actinomycoses
Chlamydophila psittaci (Formerly *Chlamydia psittaci*)—Psittacosis
Coxiella burnetti—Q Fever
Nocardiosis
Melioidosis (*Burkholderia pseudomallei*)
Rhodococcus equi
Anthrax *(Bacillus anthracis)*
Tularemia *(Francisella tularensis)*
Plague *(Yersinia pestis)*
Moraxella catarrhalis
Neisseria meningitidis
Pasteurella multocida

LUNG ABSCESS

CAUSES OF NONRESPONDING PNEUMONIA
Infectious Causes
Noninfectious Causes
Diagnostic Evaluation
Therapeutic Management

PREVENTION
Vaccinations
Strategies to Prevent Hospital-Acquired Pneumonia and Ventilator-Associated Pneumonia

INTRODUCTION

There are an estimated 4 million cases of community-acquired pneumonia (CAP)/yr in the United States that result in approximately 10 million physician visits, 1 million hospitalizations, and 45,000 deaths.[1] The mortality of CAP in hospitalized patients is 14% but increases to 20% to 50% in patients who require intensive care unit (ICU) care. In addition, pneumonia is the second most common and most frequently fatal nosocomial infection among hospitalized patients.

A clinical diagnosis of pneumonia can usually be readily established on the basis of signs, symptoms, and chest radiographs, although distinguishing CAP from conditions such as congestive heart failure, pulmonary embolism, and chemical pneumonia from aspiration is sometimes difficult. Unfortunately, defining an etiologic agent is much more challenging. Although early empirical therapy is often necessary, it is still important to identify the causative pathogen in order to confirm the appropriateness of therapy and reduce unnecessary antimicrobial use. In hospitalized cases, up to 10% of patients do not respond to initial antibiotic therapy.

Adequate diagnosis and management of pneumonia is complicated by the growing proportion of aged and comorbid, debilitated, institutionalized, and immunocompromised individuals, by the increasingly diverse array of microorganisms that cause pneumonia, and by evolving antimicrobial resistance.

PATHOPHYSIOLOGY

Inhalation pneumonia is most often due to microorganisms that (1) survive long enough while suspended in the air to be transported far from the initial source, (2) have a size less than 5 μm and carry a high inoculum, and (3) evade local host defenses.

In contrast, aspiration of oropharyngeal secretions is the main mechanism of contamination of lower airways by large bacteria. While a person is awake, normal glottal reflexes prevent aspiration; however, during sleep, 50% of normal persons aspirate small volumes of pharyngeal secretions. Healthy adults have 10 to 100 million bacteria/mL of oropharyngeal secretions. This may increase 100- to 1000-fold in patients with periodontal disease. Therefore, aspiration of 0.001 mL may carry an inoculum of greater than 100,000 microorganisms.

Normal oropharynx is predominated by a mixed flora of low virulence. The ability of virulent microorganisms such as *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae* to colonize the oropharynx is determined by the interaction of specific microbial adhesins with cellular receptors. For example, glycoproteins such as fibronectin in oral mucus promote the adherence of viridans streptococci and prevent colonization of the oropharynx by gram-negative bacilli. Colonization by gram-negative bacilli is increased in persons with lower levels of salivary fibronectin, which occurs consequent to alcoholism, diabetes, malnutrition, and other severe comorbidities. The presence of local immunoglobulins (particularly immunoglobulin A [IgA]), complement, and normal flora also prevents colonization of the oropharynx by more virulent organisms. Antimicrobial-mediated depression of the normal oral flora facilitates colonization by resistant gram-negative bacilli. Gram-negative bacillus colonization also occurs when new receptors appear in the surface of epithelial cells. This occurs following influenza infection or in chronic obstructive pulmonary disease (COPD).

Complex interactions between the virulence and quantity of inhaled or aspirated microorganisms and the integrity of mechanical barriers as well as of innate and adaptive immunity determine whether pneumonia develops.[2] Disruption of the factors that regulate bacterial adherence to mucosal surfaces facilitates oropharyngeal colonization by more pathogenic microorganisms. Aerosolization is the route of infection by intracellular bacteria such as *Mycoplasma pneumoniae*, *Chlamydophila* spp., and *Coxiella burnetii*, whereas disease due to *S. pneumoniae*, *Haemophilus influenzae*, gram-negative bacilli, and related organisms is due to aspiration. Aside from inhalational pneumonia due to *Legionella* or contaminated medical aerosols, aspiration is the cause of hospital-acquired pneumonia (HAP),[2] especially in intubated patients. Biofilms are a well-recognized reservoir of bacteria that facilitate the development of HAP.[2,2a]

EPIDEMIOLOGY

Community-Acquired Pneumonia

The true incidence of CAP is uncertain because the illness is not reportable and only 20% to 50% of patients require hospitalization. Estimates of the incidence of CAP range from 2 to 15 cases/1000 persons/yr, with substantially higher rates in the elderly.[3]

For any given pathogen, the severity of disease is largely determined by the subject's age and the presence and type of any coexisting illness.[4–7] Nevertheless, the likely microbial causes of CAP differ according to the severity of disease at clinical presentation. *S. pneumoniae*, *M. pneumoniae*, *Chlamydophila pneumoniae*, and viruses are likely to cause mild CAP (Table 32-1),

TABLE 32-1. Common Causes of Community-Acquired Pneumonia in Patients Who Do Not Require Hospitalization*

Mycoplasma pneumoniae
Streptococcus pneumoniae
Chlamydophila pneumoniae
Haemophilus influenzae
Respiratory viruses

*Organisms are listed in the general order of frequency.

whereas in patients with CAP severe enough to warrant hospitalization, *S. pneumoniae* is the most commonly identified etiologic agent followed by *H. influenzae* and *M. pneumoniae* (Table 32-2).[7,8] Gram-negative enteric bacilli, *S. aureus*, *Legionella* spp., and respiratory viruses other than the influenza virus are uncommon, with an incidence of less than 5%. Polymicrobial infections account for 10% to 20% of episodes.

The most frequently identified pathogens causing severe CAP (i.e., CAP requiring immediate ICU care) include *S. pneumoniae*, *Legionella pneumophila*, *H. influenzae*, gram-negative bacilli, *S. aureus*, *M. pneumoniae*, and respiratory tract viruses (Table 32-3).[7,9,10] *P. aeruginosa* infection is relatively uncommon except in patients with specific risk factors (previous antibiotic treatment and severe pulmonary comorbidity, especially bronchiectasis, cystic fibrosis, and severe COPD).[7,9] Up to 20% of severe CAP episodes are caused by polymicrobial infection; however, even if extensive diagnostic procedures are performed, the responsible pathogen is not isolated in up to 50% to 60% of patients with severe CAP.

Methicilin-resistant *Staphylococcus aureus* (MRSA), originally a nosocomial pathogen, appeared in recent times in the community and are referred to community-acquired MRSA. Community-acquired MRSA can lead to severe pulmonary infections, including necrotizing and hemorrhagic pneumonia.[11]

The likely etiology of severe CAP in differing patient populations is shown in Table 32-4.[12-14]

Age-Related Factors

Pneumonia remains one of the major causes of morbidity in children. In Europe, more than 2.5 million cases of childhood pneumonia occur yearly, which account for around 50% of hospital admissions for children. Radiographically defined pneumonia is present in 7.5% of febrile illnesses in infants up to 3 months old and in 13% of infectious illnesses during the first 2 years of life. In children younger than 2 years, *S. pneumoniae* and respiratory syncytial virus (RSV) are the most frequent microorganisms, whereas *M. pneumoniae* is a leading

TABLE 32-2. Common Causes of Community-Acquired Pneumonia in Patients Who Require Hospitalization*

Streptococcus pneumoniae
Mycoplasma pneumoniae
Chlamydophila pneumoniae
Haemophilus influenzae
Mixed infections
Enteric gram-negative bacilli
Aspiration (anaerobes)
Respiratory viruses
Legionella spp.

*Organisms are listed in the general order of frequency.

TABLE 32-3. Common Causes of Severe Community-Acquired Pneumonia*†

Streptococcus pneumoniae
Enteric gram-negative bacilli
Staphylococcus aureus
Legionella spp.
Mycoplasma pneumoniae
Respiratory viruses
Pseudomonas aeruginosa (relative frequency determined by the presence or absence of specific risk factors)

*Severity of disease warranting treatment in an intensive care unit.
†Organisms are listed in the general order of frequency.

TABLE 32-4. Distribution of Pathogens in Severe Community-Acquired Pneumonia According to the Presence of Modifying Factors*

	ELDERLY		NURSING HOME	HUMAN IMMUNODEFICIENCY VIRUS	
Parameter	**Metlay & Fine[41]**	**Blasi et al[42]**		**Menendez et al[43]**	**Menendez et al[44]**
Country	United States	Spain	United States	Spain	United States
Year	2001	1996	2001	2000	2001
No. of patients	57	95	47	214	20
Streptococcus pneumoniae	21%	49%	9%	33%	4%
Haemophilus influenzae	13%	11%	—	14%	—
Legionella	10%	8%	31%	—	4%
Staphylococcus aureus	10%	3%	2%	8%	—
Enteric gram-negative bacilli	21%	8%	15%	6%	4%
Pseudomonas aeruginosa	3%	8%	4%	20%	14%
Atypical pathogens†	5%	11%	—	2%	23%

*Results are expressed as the percentage of isolated pathogens.
†*Mycoplasma pneumonia* and *Chlamydophila pneumoniae.*

cause of pneumonia in older children and young adults.

In adults, increased age is associated with a change in the distribution of microbial causes and an increase in the frequency and severity of pneumonia.[15] The annual incidence of CAP in noninstitutionalized elderly people is estimated to be between 18/1000 and 44/1000 compared with 4.7/1000 and 11.6/1000 in the general population.[3,16] Although the elderly are particularly at risk for pneumococcal pneumonia, they also have increased rates of pneumonia due to group B streptococci, *Moraxella catarrhalis*, *H. influenzae*, *L. pneumophila*, gram-negative bacilli, *C. pneumoniae*, and polymicrobial infections.[3,9,17] Moreover, although the absolute rate of infection by *M. pneumonia* does not decrease with age, this pathogen accounts for a smaller proportion of pneumonia in the elderly than in younger populations. In patients older than 80 years, there is a higher incidence of aspiration pneumonia and lower incidence of *Legionella* spp. than in patients younger than 80 years.[18]

Personal Habits

Alcohol consumption is an important risk factor for CAP owing to its immunosuppressive effects and its potential to lower consciousness level, thus, increasing the risk of aspiration pneumonia. Alcoholism per se has been shown to be an independent risk factor for an increased rate and severity of pneumonia, especially that due to *S. pneumoniae*.[19,20] This predisposition persists several months after cessation of alcohol consumption.[21]

Smoking is one of the most important risk factors for CAP. It is also associated with an increased frequency of CAP due to *S. pneumoniae*, *L. pneumophila*, and influenza.[15] Smoking alters mucociliary transport and humoral and cellular defenses, affects epithelial cells, and increases adhesion of *S. pneumonia* and *H. influenzae* to the oropharyngeal epithelium.

Comorbidities

The most frequent comorbidity associated with CAP is COPD. Patients with COPD have an increased risk for CAP. Microorganisms frequently colonize the lower airways of patients with COPD. In addition, such patients have important alterations in mechanical and cellular defenses. Although the etiology of CAP may not generally be different in patients with COPD, persons with severe COPD (forced expiratory volume in 1 second [FEV_1] < 30% of predicted) and bronchiectasis have an increased risk for pneumonias caused by *H. influenzae* and *P. aeruginosa*.[9]

In COPD patients treated with oral corticosteroids for long periods, the risk of infection by *Aspergillus* spp. is increased.[22]

Bronchitis and pneumonia remain the major causes of morbidity and mortality in patients with cystic fibrosis. During the first decade of life, *S. aureus* and nontypeable *H. influenza* are the most common pathogens, although *P. aeruginosa* is occasionally isolated in infants. By 18 years of age, 80% of patients with cystic fibrosis harbor *P. aeruginosa* and 3.5% harbor *Burkholderia cepacia*.[23] *Stenotrophomonas maltophilia*, *Achromobacter xylosoxidans*, and nontuberculous mycobacteria are emerging pathogens in this population.[24]

Other comorbidities associated with increased rates of CAP and subsequent mortality include congestive heart failure, chronic kidney or liver disease, cancer, diabetes, dementia, cerebrovascular diseases, and immunodeficiency states (e.g., neutropenia, lymphoproliferative diseases, immunoglobulin deficiencies, human immunodeficency virus [HIV] infection).

Susceptibility to infection is increased by a number of malnutrition-related phenomena such as a decreased level of secretory IgA, a failure of macrophage recruitment, and alterations in cellular immunity. As a result, the frequency of respiratory tract colonization by gram-negative bacilli is increased in patients with malnutrition and the incidence and severity of respiratory infections are increased.

Geographic and Occupational Considerations

Geographic setting, seasonal timing, travel history, and occupational or unusual exposures modify the risk of various microbial etiologies of CAP. For example, an increased frequency of *S. pneumoniae* occurs in soldiers, painters, and South African gold miners. *Burkholderia pseudomallei* (melioidosis) is endemic in the rural tropics.[25] Animal exposure may prompt a diagnostic evaluation for agents of zoonotic pneumonia including psittacosis (birds) and *Rhodococcus* (horses). Rodent contact suggests the possibility of infection by *Yersinia pestis* (plague) in the rural southwestern United States[26] and *Francisella tularensis* (tularemia) in rural Arkansas or Nantucket, Massachusetts.[27] Exposure to sheep, dogs, and cats may prompt evaluation for *C. burnetii* (Q fever) in Nova Scotia, Australia, or the Basque region of Spain.[28] The role of seasonal timing is illustrated by the increased incidence of lower respiratory tract infections due to *S. pneumoniae* and *H. influenzae* in winter months. More recently, pneumonia caused by a novel coronavirus causing the severe acute respiratory syndrome (SARS) has emerged in epidemic form in southeast Asia.[29,30] Sporadic human infections by avian influenza A/H5N1 in various places in the world increase the risk of future pandemics.[31] Finally, the infectious agents that cause anthrax, tularemia, and plague may be used for bioterrorism or biowarfare purposes and cause lower respiratory tract infections.[32–34]

Hospital-Acquired (Nosocomial) Pneumonia

Early-onset HAP (<5 days of hospitalization) is most often due "community" microorganisms such as *S. pneumoniae*, *H. influenzae*, and anaerobes. Late-onset HAP (>5 days of hospitalization) is mainly caused by MRSA, enteric gram-negative bacilli, *P. aeruginosa*, nonfermenters such as *Acinetobacter baumanii* and *S. maltophilia*,

and polymicrobial infections.[35] Factors that increase the risk of HAP include antibiotic exposure, old age, severe comorbidities, underlying immunosuppression, colonization of the oropharynx by virulent microorganisms, conditions that promote pulmonary aspiration or inhibit coughing (e.g., thoracoabdominal surgery, endotracheal intubation, insertion of nasogastric tube, supine position), and exposure to contaminated respiratory equipment.

Health Care–Associated Pneumonia

Health care now reflects a continuum of care with many traditional inpatient services provided in outpatient settings. In each of these instances, physicians often categorize new infections in such subjects as "community-acquired." Data indicate, however, that these health care associated infections have a unique epidemiology more like that of traditional hospital-acquired infections. Accumulating evidence pointing to the potential impact of health care–acquired pneumonia (HCAP) results in its recognition as a separate entity by the American Thoracic Society (ATS) and Infectious Diseases Society of America (IDSA).[36] Results from a large database of culture-positive pneumonia justify this new category. *S. aureus* (both methicillin-sensitive and -resistant) and *P. aeruginosa* were the most frequent microorganisms. Compared with CAP, HCAP patients have more severe disease, higher mortality, greater length of stay, and increased cost.[37] Although there is no doubt that HCAP has to be classified differently from CAP, risk factors and particularly the microbiology of HCAP are not consistent when comparing the United States and other countries outside the United States.

CLINICAL PRESENTATION

Pneumonia is characterized by the presence of fever, altered general well-being, and respiratory symptoms such as cough (90%), expectoration (66%), dyspnea (66%), pleuritic pain (50%), and hemoptysis (15%). In elderly and immunocompromised patients, the signs and symptoms of pulmonary infection may be muted and overshadowed by nonspecific complaints. Fever higher than 38.5°C or accompanied by chills should never be attributed to bronchitis without examining a chest radiograph.

Occasionally, there is a "classic" history, such as that of the patient with pneumococcal infection who presents with sudden onset of rigor followed by pleuritic chest pain, dyspnea, and rusty sputum. Similarly, a patient with *Legionella* pneumonia may complain predominantly of diarrhea, fever, headache, confusion, and myalgia. For *M. pneumoniae* infection, extrapulmonary manifestations such as myringitis, encephalitis, uveitis, iritis, and myocarditis may be present. However, only rarely does the clinical history clearly suggest a specific etiologic diagnosis.

Unfortunately, information obtained from the clinical history and physical examination is not sufficient to confirm the diagnosis of pneumonia. A definitive diagnosis requires the presence of new opacity on the chest radiograph.

In elderly patients, especially those with multiple comorbidities, pneumonia may present with general weakness, decreased appetite, altered mental status, incontinence, or decompensation due to underlying diseases. The presence of tachypnea may precede other signs of pneumonia by 1 to 2 days. Tachycardia is another common initial sign but is less frequent and specific than tachypnea. Fever is absent in 30% to 40% of patients. Owing to the lack of specific symptoms, the diagnosis of CAP is frequently delayed in the elderly.[3,17] Elderly patients with pneumonia who present with altered mental status without fever have a delay in receiving antibiotics by more than 4 hours after arrival, and this delay affects mortality.[38]

"Typical" versus "Atypical" Pneumonia

The division of CAP into typical and atypical syndromes has been used to predict the likely pathogens and select appropriate empirical therapy.[4–7] The clinical picture of "typical" CAP is that of disease characteristically caused by bacteria such as *S. pneumoniae*, *H. influenzae*, and *K. pneumoniae*. The initial presentation is frequently acute, with an intense and unique chill. Productive cough is present, and the expectoration is purulent or bloody. Pleuritic pain may be present and it is a very specific finding of *S. pneumoniae*. Physical examination reveals typical findings of pulmonary consolidation. There is leukocytosis with neutrophilia and the presence of band forms. Chest radiography shows lobar condensation with air bronchograms.

In contrast, the syndrome of gradual onset of fever, nonproductive cough, and a relatively normal white blood cell count in a patient without a demonstrable bacterial pathogen has been called "atypical pneumonia." Frequently, systemic complaints are more prominent than the respiratory ones. The atypical syndrome is characteristic of infections by pathogens such as *M. pneumoniae*, *Chlamydophila* spp., *C. burnetii*, and viruses. Unfortunately, several studies, including one that included patients with mild CAP treated on an outpatient basis,[39] have found that neither the clinical symptoms nor the radiographic manifestations are sufficiently sensitive or specific to reliably guide pathogen-directed antibiotic treatment against "typical" versus "atypical" microorganisms.[39] Therefore, current guidelines do not emphasize the use of the typical versus atypical classification to determine initial empirical antibiotic treatment for CAP.[4–7,40]

PATIENT EVALUATION

Clinical Evaluation

The clinical findings that best differentiate CAP from other acute respiratory tract infections are cough, fever, tachypnea, tachycardia, and pulmonary crackles.[41] CAP

is present in 20% to 50% of persons who have all four factors.[41] Specific signs of pulmonary consolidation are present in only one third of the cases that warrant hospitalization and are less frequently observed in less ill patients. Early in the evolution of disease, pain and cough may be absent and the physical examination may be normal other than the presence of fever. In debilitated elderly patients, vague clinical manifestations of pneumonia are common and the presence of fever with no apparent source, especially when accompanied by confusion or tachypnea, justifies obtaining a chest radiograph.

Clues to the etiologic diagnosis may lie outside the respiratory tract. Bradycardia in relation to the amount of fever (pulse should increase by 10 beats/min/°C of temperature elevation) has been associated with pneumonia secondary to *Legionella*, *Chlamydophila psittaci*, *Mycoplasma*, and tularemia. Specifically *M. pneumoniae* may present with a variety of extrapulmonary manifestations including arthralgia, cervical lymphadenopathy, bullous myringitis, diarrhea, myalgia, myocarditis, hepatitis, nausea, pericarditis, and vomiting.[42] Skin lesions of erythema multiforme or erythema nodosum suggest *Mycoplasma* infection (as well as tuberculosis and fungal infection), whereas lesions of ecthyma gangrenosum are seen most commonly with *P. aeruginosa* infection. Finally, the examiner must look for the presence of complications such as pleural effusion, pericarditis, endocarditis, arthritis, and central nervous system involvement, which may necessitate further diagnostic procedures and, potentially, a change in therapy.[43]

Laboratory Evaluation

Once the patient is found to have pneumonia, laboratory studies should be performed that include blood cell counts, serum glucose and electrolyte measurements, and pulse oximetry or arterial blood gas assays.[4–7] These data provide a logical basis for making decisions regarding the need for hospitalization. HIV testing should be offered to hospitalized adults with CAP in areas where the rate of newly detected HIV infection exceeds 1/1000 hospital discharges.

Marked leukocytosis with leftward shift is more often encountered with infections caused by *S. pneumoniae*, *H. influenzae*, and gram-negative bacilli than with infections by *M. pneumoniae*, *Chlamydophila* spp., *Coxiella*, or nonbacterial causes of pneumonia. Leukopenia may be seen with overwhelming pneumococcal or gram-negative bacillary pneumonia. The serum level of C-reactive protein and the erythrocyte sedimentation rate are increased to higher values with bacterial than with viral pneumonias.

New promising information suggests that procalcitonin, a precursor of calcitonin, is released into the blood of persons with bacterial infections. This biomarker measured in blood has been useful to evaluate the severity and prognosis of the patients and to deescalate antibiotic treatments.[44,45] The routine use of procalcitonin in the initial evaluation of CAP needs further evaluation.

Radiographic Evaluation

Radiographic evaluation is necessary to establish the presence of pneumonia, because there is no combination of historical data, physical findings, or laboratory results that reliably confirms the diagnosis.[4,7,41,46] Limitations of chest radiography include suboptimal specificity, particularly in patients with the acute respiratory distress syndrome (ARDS), and interobserver variability.[7] Frequently, the emergency department admissions with radiographic pneumonia are subsequently proved not to have pneumonia. Conversely, the sensitivity of the chest radiograph is decreased in (1) patients with emphysema, bullae, or structural abnormalities of the lung, who may present with delayed or subtle radiographic changes; (2) obese patients, in whom it may be difficult to discern the existence of pneumonia; and (3) patients with very early infection, severe dehydration, or profound granulocytopenia. Failure to detect an abnormal opacity on the plain chest radiograph essentially rules out pneumonia,[41] even though computed tomography (CT) of the chest provides a more sensitive means of detecting minor radiographic abnormalities.[41] In routine clinical practice, a thoracic CT scan is not recommended for patients with suspected pneumonia who have an apparently normal chest radiograph.[7]

Although several radiologic patterns have been associated with pneumonia caused by specific microorganisms, this is not a reliable method for diagnosing a specific pathogen.[47,48] Nonetheless, the presence of air bronchograms and a lobar or segmental pattern is more characteristic of typical than atypical causes of pneumonia. In contrast, a mixed pattern (alveolar and interstitial disease) is more frequently observed with atypical pneumonias. Pneumonia complicating aspiration (frequently from anaerobes) most often involves the superior segment of the right lower lobe or posterior segment of the right upper lobe, or both, as well as the corresponding segments on the left. Infections developing from hematogenous seeding often appear as multiple rounded shadows sometimes with cavities in the greatest distribution of blood flow. Demonstration of a lung abscess, cavitation, or necrotizing pneumonia suggests infection by anaerobes, *S. aureus*, or gram-negative bacilli. Pleural effusion frequently accompanies pneumonia and has management implications. The size of pleural effusion on the chest radiograph helps decide whether to perform a thoracentesis.

Microbiologic Evaluation

Identification of the infecting microorganism serves to verify the clinical diagnosis of infection and facilitates the use of specific therapy instead of unnecessarily broad-spectrum antimicrobial agents. Although the utility of sputum examination is much debated (see later), pleural fluid (if present) and two sets of blood cultures should be obtained in patients hospitalized for CAP. Optimization of culture results require that specimens be obtained before initiation of antimicrobial therapy. Sputum samples must be carefully collected,

TABLE 32-5. Recommended Microbiologic Evaluation in Patients with Community-Acquired Pneumonia

PATIENTS WHO DO NOT REQUIRE HOSPITALIZATION

None*

PATIENTS WHO DO REQUIRE HOSPITALIZATION

- Two sets of blood cultures
- Gram stain and culture of a valid sputum sample
- Urinary antigen test for detection of *Legionella pneumophila* (in endemic areas or during outbreaks)
- Stain for acid-fast bacilli and culture of sputum (if tuberculosis is suggested by clinical history or radiologic findings)
- Fungal stain and culture of sputum, and fungal serologies (if infection by an endemic mycosis is suggested by the clinical history or radiologic findings)
- Sputum examination for *Pneumocystis jirovecii* (if suggested by clinical history or radiologic findings)
- Serologies for *Mycoplasma pneumoniae, Chlamydophila pneumoniae, Chlamydophila psittaci, Coxiella burnetii, Legionella* spp., and respiratory viruses (in endemic areas or during outbreaks)
- Culture and microscopic evaluation of pleural fluid (if significant fluid is present)

PATIENTS WHO REQUIRE TREATMENT IN AN ICU

- Gram stain and culture of valid sputum sample, endotracheal aspirate, or bronchoscopically obtained specimens using a protected specimen brush or BAL
- Other procedures as for other hospitalized patients

*Gram stain and culture should be strongly considered in patients with risk factors for infection by an antimicrobial-resistant organism or unusual pathogen.

BAL, bronchoalveolar lavage; ICU, intensive care unit.

TABLE 32-6. Recommended Microbiologic Evaluation in Patients with Hospital-Acquired Pneumonia

Two sets of blood cultures

Gram stain and culture of a valid sputum sample*

Urinary antigen test for detection of *Legionella pneumophila* (in endemic areas or during outbreaks)

*Gram stain and culture of valid sputum sample, endotracheal aspirate, or bronchoscopically obtained specimens using a protected specimen brush or bronchoalveolar lavage (if patient is intubated).

transported, and processed in order to optimize the recovery of common bacterial pathogens. These recommendations are summarized in Tables 32-5 and 32-6.

Examination of the Sputum

Microscopic examination of expectorated sputum is the easiest and most rapidly available method of evaluating the microbiology of lower respiratory tract infections. A valid expectorated sputum specimen can be obtained from about 40% of patients hospitalized with CAP. When interpreting sputum cultures, it is crucial to ensure that oropharyngeal materials do not unduly contaminate the specimens. The presence of more than 10 squamous epithelial cells per low-power field (×100 magnification) indicates excessive oropharyngeal contamination; consequently, the specimen should be discarded because it is not representative of the pulmonary milieu.[4] A specimen with few or no squamous cells and many polymorphonuclear white blood cells (>25 cells/low-power field) is ideal (see Fig. 32-3). These criteria may not be reliable in patients who are granulocytopenic.[49] Gram-stained acceptable expectorated sputum specimens should be carefully examined using ×1000 magnification (oil immersion lens). In addition, specific fluorescent antibodies can be used to help evaluate sputum or other respiratory tract specimens for the presence of *Legionella*.

When valid sputum is obtained, the specificity of the Gram stain for pneumococcal pneumonia is estimated to be greater than 80%.[50] Because the fastidious nature of *S. pneumoniae* and *H. influenzae* leads to the death of these organisms, the sensitivity of sputum culture is less than that of sputum Gram stain examination for *S. pneumoniae* (50%–60%) and *H. influenzae*. The reverse is true for *S. aureus* and gram-negative bacilli because these bacteria are much hardier and may proliferate during sputum transport and processing. Because of contamination by oral flora, true pneumonia due to *S. aureus* and gram-negative bacilli is doubtful if the Gram stain of a valid sputum specimen does not corroborate the presence of these bacteria. In good quality gram-stained sputum, the presence of a single or a preponderant morphotype of bacteria (+90%) is diagnostic. Sputum with a mixed flora in the Gram stain has no diagnostic value. In contrast with widely held opinion, sputum culture results are convincing only when the organism isolated is compatible with the morphology of the organism present in greater than 90% of the Gram stain. In the absence of an informative Gram stain, the predictive value of sputum culture is very low.

The last IDSA/ATS guidelines[40] recommend to obtain a sputum sample for stain and culture in hospitalized patients with the clinical indications listed in Table 32-7 but are optional for patients without these conditions.

For patients with HAP or ventilator-associated pneumonia (VAP), the range of potential pathogens is so broad and antimicrobial susceptibility patterns so diverse that vigorous diagnostic measures are justified. In ventilated patients, the equivalent of sputum is the endotracheal aspirate. The criteria for a valid sample are the same as those for sputum. Unfortunately, although the Gram stain and qualitative cultures of endotracheal aspirates have excellent sensitivity, they have poor specificity.[51] Quantitative cultures of endotracheal aspirate samples, with a threshold of more than 10^5 colony-forming units (CFU)/mL to distinguish colonization from infection, have been recommended in the diagnosis of VAP.[52] The diagnostic value of the quantitative cultures of endotracheal aspirates is similar to quantitative cultures of invasive techniques.

Some bacterial agents of pneumonia cannot be cultivated on conventional laboratory media. For example, *Legionella* requires special charcoal yeast extract agar

TABLE 32-7. Clinical Indications for More Extensive Testing in Community-Acquired Pneumonia

Intensive care unit admission
Failure of outpatient antibiotic therapy
Radiographic cavities
Leukopenia
Active alcohol abuse
Chronic severe liver disease
Severe obstructive/structural lung disease
Asplenia
Recent travel (within past 2 wk)
Positive *Legionella* UAT result
Positive pneumococcal UAT result
Pleural effusion

UAT, urinary antigen test.
From Mandell LA, Wunderink RG, Anzueto A: Infectious Society of America/American Thoracic Society Consensus Guidelines on the Management of Community-Acquired Pneumonia. Clin Infect Dis 44(Suppl 2):S27–S72, 2007.

for isolation, whereas recovery of *Chlamydophila* spp. and *C. burnetii* requires culture in tissue systems. When necessary, specimens can be referred to specialized or reference laboratories for appropriate handling. Culture of certain rare agents of bacterial pneumonia poses major health risks to laboratory workers (e.g., *F. tularensis*, *Bacillus anthracis*, *C. burnetii*). Specimens suspected to harbor one of these agents should be dealt with carefully in a biologic safety hood, and isolation of the pathogens should be reserved for specialized laboratories.

Blood and Pleural Fluid Cultures

Although the overall yield of blood cultures is probably less than 20% in patients hospitalized for CAP, a positive culture of blood or pleural fluid definitively establishes the etiologic diagnosis of pneumonia.[53] Not only are sputum cultures frequently contaminated by oral flora, but *S. pneumoniae* is successfully recovered from sputum cultures in only 40% to 50% of cases of bacteremic pneumococcal pneumonia.[54] Not surprisingly, the detected rate of bacteremia is reduced in patients with mild CAP and higher in patients with severe CAP, especially those warranting ICU care. The latest IDSA/ATS guidelines[40] recommend obtaining blood samples for culture in hospitalized patients with the clinical indications listed in Table 32-9 but are optional for patients without these conditions.

In up to 40% of CAP, an accompanying pleural effusion may be present. Although specificity of pleural exudates culture is very high, the sensitivity is low because of the low incidence of invasion of the pleura. Gram stain or cultures yielding bacterial pathogens from pleural fluid are likely to be an accurate reflection of the microbial cause of pneumonia. Diagnostic thoracentesis should, therefore, be performed when a significant pleural effusion is present. Gram stain of pleural fluid may produce an indication of the nature of the infecting organisms within 1 hour, with culture and identification requiring 24 to 48 hours.

Antigen Detection

Commercial assays can be used to rapidly detect capsular polysaccharide antigens of *S. pneumonia* or *L. pneumophila* serogroup 1 in urine.[50,55,56] The sensitivity of these tests is little affected by prior antibiotic treatment. Indeed, results may remain positive several weeks after successful treatment. These assays require less than 1 hour, although the diagnostic value improves after further processing (centrifuging the urine), which can delay test results for at least 2 additional hours. For *L. pneumophila* serogroup 1, the sensitivity is 60% to 80%, and the specificity is greater than 95%.[57] Urinary antigen testing is currently the most helpful rapid test for the diagnosis of *Legionella* infections. The major limitation of urinary antigen tests is that currently available tests are intended to detect *L. pneumophila* serogroup 1 antigen only, although this is the most common cause of *Legionella* infection.

The sensitivity of the *S. pneumoniae* urinary antigen kits is 50% to 80% and the specificity 90%.[58] The effect of pretreatment with antibiotics resulted in contradictory reports. The urinary antigen test may also be applied on pleural fluid with a sensitivity and specificity of almost 100%. There is a relation between the degree of positivity for the *S. pneumoniae* urinary antigen test positivity and the Pneumonia Severity Index (PSI).[59] Urine specimens of children, frequent carriers of *S. pneumoniae* in the nasopharynx, may test positive in the absence of evidence of pneumonia, and the test should therefore be interpreted with caution in children.[60]

The most recent IDSA/ATS guidelines[40] recommend *S. pneumoniae* and *L. pneumophila* urinary antigen detection in hospitalized patients with the clinical indications listed in Table 32-11 but are optional for patients without these conditions.

Antigens for the many common respiratory viruses, influenza virus, RSV, adenovirus, and parainfluenza viruses can be detected by direct immunofluorescence or by commercially available enzyme immunoassay. A rapid antigen detection test for influenza can also provide an etiologic diagnosis within 15 to 30 minutes. Test performance varies according to the test used, sample type, duration of illness, and patient age. Most show a sensitivity ranging from 50% to 70% in adults and a specificity approaching 100%. The sensitivity for immunofluorescence can be increased by inoculation of the clinical sample on appropriate cells, followed by immunofluorescence after 48 hours.[40]

Nucleic Acid for Amplification Tests

Culture procedures for viruses and fastidious bacteria, *M. pneumoniae, C. pneumoniae, L. pneumophila*, and *Bordetella pertussis*, which normally do not colonize the human respiratory tract, are too insensitive and too slow

to be therapeutically relevant and should be detected by nucleic acid amplification tests. Their sensitivity is almost superior to that of the traditional procedures and are considered as the "gold standard."[61] Traditional tests that require at least 1 to 2 days produce results that are unavailable in time to have any impact on patient management. Real-time multiplex polymerase chain reaction (PCR) assays detect respiratory viruses in both immunocompetent and immunosuppressed hosts.[62]

Serologic Evaluation

Serologic techniques are often the most practical means to establish a microbiologic diagnosis for pneumonia caused by pathogens that cannot be readily cultured. Examples include common pathogens such as *M. pneumoniae*, *C. pneumoniae*, and *L. pneumophila*; less common causes of pneumonia such as those caused by the agents of tularemia, brucellosis, and psittacosis; and viral infections. Diagnosis usually requires that a convalescent specimen demonstrate a fourfold rise in IgG titer above that present in an acute specimen. These tests are not usually helpful in initial patient management but are of greater utility in detecting epidemics and defining the epidemiology of the pertinent infectious agents. Because IgM antibodies appear earlier than IgG antibodies, the detection of IgM in serum is a widely used approach for the early serologic diagnosis of many acute infections. It should be realized that IgM antibodies are often not produced in children younger than 6 months of age. The IgM response may also appear late and wanes with age. Because the microorganisms mentioned previously rarely cause HAP, serologies are not indicated in this type of respiratory infection, except when *Legionella* spp. is suspected.

Invasive Diagnostic Techniques

Because of problems encountered with the use of expectorated sputum, it may be necessary to perform an invasive procedure to obtain suitable material for microscopy and cultures. This may be important in the management of patients with life-threatening CAP in whom diagnostic materials cannot otherwise be obtained rapidly, patients with progressive pneumonia despite seemingly appropriate antimicrobial therapy, immunocompromised patients, and patients with HAP, especially in the setting of endotracheal intubation.[43,63]

Bronchoscopic Samples

The reliability of using bronchoscopic procedures to determine the microbial etiology of pneumonia depends on the technique used and the organism sought. When compared with sputum cultures, routinely processed bronchoscopic specimens demonstrate improved sensitivity and equal specificity for the culture of pathogenic fungi and mycobacteria. However, such materials have unacceptably poor specificity for routine bacterial cultures owing to oropharyngeal contamination. In contrast, semiquantitative or quantitative cultures of materials obtained bronchoscopically with a protected sheath brush or through bronchoalveolar lavage (BAL) and by direct lung aspiration have been successfully used for aerobic and anaerobic bacterial cultures[64–66] (see Chapter 22).

For protected sheath brush cultures, a threshold of 10^3 CFU/mL has been recommended to distinguish colonization from infection. However, 14% to 40% of duplicate samples yield disparate quantitative results, which might lead to differences in patient management. The quality of these samples can be determined by the number of epithelial squamous cells in nonintubated patients.

BAL fluid can be cultured quantitatively for bacteria and qualitatively for fungi, mycobacteria, and viruses. A concentrate can be stained for histochemical and fluorescence evaluation.[66] The recommended threshold of 10^4 CFU/mL for diagnosing bacterial pneumonia shows excellent correlation with diagnoses based on protected sheath brush results and histologic examination of the lung.[67] BAL permits identification of contaminated specimens (i.e., those with >1% squamous epithelial cells), the immediate diagnosis of infection (i.e., intracellular bacteria in >2%–5% of examined polymorphonuclear leukocytes), and the exclusion of infection (i.e., <50% polymorphonuclear leukocytes among the recovered cells).[68]

Other procedures that have been used to diagnose VAP include quantitative cultures of materials obtained by nondirected ("blind") protected sheath brush and nondirected ("mini") BAL.[69] The advantages of both procedures are the ease of performance, greater availability, decreased costs, and fewer side effects. Finally, although qualitative culture of materials obtained by endotracheal suction has excellent sensitivity (>85%), the specificity of such cultures is poor (<35%); thus, overreliance on these cultures may lead to antibiotic overtreatment.[52] In some studies, quantitation with a threshold of 10^5 CFU/mL has improved the specificity of endotracheal suction specimens, but this has been at the cost of decreased sensitivity.[52,70]

Although semiquantitative protected sheath brush and BAL procedures have sensitivities and specificities in the range of 60% to 90%, the sensitivity of bronchoscopic procedures is substantially reduced by the prior administration of antimicrobial agents.[71] Furthermore, the use of a sophisticated algorithm (i.e., Clinical Pulmonary Infection Score) increases the diagnostic accuracy of clinical judgment.[72] Finally, measurement of inflammatory markers such as the triggering receptor expressed on myeloid cells (TREM-1) may provide powerful, independent diagnostic information.[73]

The use of quantitative cultures obtained by protected sheath brush and BAL, compared with qualitative cultures of endotracheal aspirates and clinical evaluation, was associated with lower 14-day mortality rates, earlier reversal of organ dysfunction, and less antibiotic use. However, other randomized trials on the use of quantitative cultures of protected sheath brush and BAL specimens, rather than quantitative cultures of endotracheal aspirates, in patients with VAP have not replicated these findings.[74,75]

In conclusion, the place of quantitative cultures and endotracheal aspirates in determining whether to initiate or withdraw antimicrobial therapy in patients with VAP is unsettled.[76] Currently, two different strategies are proposed: (1) The *clinical strategy* is to administer broad-spectrum antibiotics if new pulmonary radiographic opacities are accompanied by two of three clinical parameters (fever, leukocytosis or leukopenia, purulent secretions) or when the Clinical Pulmonary Infection Score is higher than 6.[73] (2) The *quantitative strategy* is to withhold antimicrobials in patients with suspected VAP if a Gram stain of material obtained at bronchoscopy does not support the diagnosis of pneumonia; or if antibiotics have been started, the quantitative culture results are used to either withdraw the antibiotics or adjust therapy to specifically treat the recovered pathogen.[77]

Transthoracic Lung Aspiration

Transthoracic lung aspiration obtains specimens suitable for microbiologic and cytologic examination directly from lung parenchyma. It is a more successful method for diagnosing malignant pulmonary lesions than infectious diseases, for which, in immunocompetent hosts, the diagnostic yield by transthoracic lung aspiration is approximately 50%. For diagnosis of pulmonary infections, the false-positive rate is 5% to 20% with a sensitivity of 35% to 82%. The variable sensitivity may be due to the small volumes of material retrieved on aspiration, the inevitable aeration of the specimen and consequent loss of viable anaerobes, or poor localization of the site to be aspirated. Serious complications of transthoracic lung aspiration include pneumothorax (2%–5%) and hemoptysis (2%–5%), which occur even when small-gauge needles are used.

Differential Diagnosis

Several diseases may present with fever and chest radiographic opacities and mimic CAP (Table 32-8)[41]; such diseases should be suspected when the chest radiographic resolution is unusually quick or when there is a lack of response to initial or subsequent antibiotic treatments. In patients with HAP, and particularly in those with VAP, the classic signs and symptoms of pneumonia (including new radiographic changes, fever, leukocytosis or leukopenia, and purulent pulmonary secretions) are neither sufficiently sensitive nor specific to confirm the presence of a pulmonary infection. In patients suspected of having VAP, the presence of chest radiographic opacities plus two of the clinical signs mentioned previously has a sensitivity of 30% to 70% and a specificity of 70%. Atelectasis, pulmonary hemorrhage, ARDS, and pulmonary embolism—among others—are causes that may mimic pneumonia. In patients with suspected HAP or VAP, the microbiologic confirmation of pneumonia is important in order to avoid unnecessary treatments and a potential future increase of microbial resistance.

TABLE 32-8. Noninfectious Causes of Fever and Radiographic Changes That May Mimic Community-Acquired Pneumonia

Pulmonary edema
Pulmonary infarction
Acute respiratory distress syndrome
Pulmonary hemorrhage
Lung cancer or metastatic cancer
Atelectasis
Radiation pneumonitis
Drug reactions involving the lung
Extrinsic allergic alveolitis
Pulmonary vasculitis
Pulmonary eosinophilia
Bronchiolitis obliterans and organizing pneumonia

THERAPEUTIC APPROACH TO PNEUMONIA

Once the diagnosis of pneumonia has been made, the clinician must decide whether the patient can be managed in the outpatient setting. Applying a prediction rule can facilitate this decision. The second key decision is selection of the initial antimicrobial therapy.[78]

Assessment of Severity

The PSI (Table 32-9) is a point scoring system derived from a retrospective analysis of a cohort of 14,199 patients with CAP in 1989 and prospectively validated in a separate cohort of 38,039 patients with CAP in 1991. Age is the most significant risk factor, with 1 point given for each year of age (−10 points in women). Other risk factors include patient demographics, comorbid conditions, physical examination findings, and laboratory results. Prospective studies in community and teaching hospitals have shown that the PSI may be safely and effectively applied in clinical practice.[79–81] Because these criteria are less useful at the extremes of age, aged-based criteria have been developed for assessing the severity of pneumonia in children and the elderly.

Patients who have a PSI score of 70 or less (class I or II) have an attributable risk of death within 30 days of less than 1% and outpatient treatment is recommended. Patients with a PSI score of 71 to 90 (class III) have a 30-day mortality rate of up to 2.8% and may benefit from brief hospitalization. Hospital care is appropriate for patients with scores of 91 to 130 (class IV), who have a 30-day risk of death of 8.2% to 9.3%, and for patients with a score of more than 130 (class V), who have a 30-day risk of death of 27.0% to 31.1%.

Similar rules for grading the severity of CAP have been developed by the British Thoracic Society.[10,82] Their algorithm assigns 1 point for each of the following findings upon presentation: (1) confusion; (2) urea higher than 7 mmol/L; (3) respiratory rate of 30/min or more; (4) low systolic (<90 mm Hg) or low diastolic (≤60 mm Hg) blood pressure; and (5) age 65 years or older. The 30-day mortality rates for patients with scores of 0 or 1 (group

TABLE 32-9. Scoring System for Determining Risk of Complications in Patients with Community-Acquired Pneumonia*

Patient Characteristic	Points Assigned
DEMOGRAPHIC FACTORS	
Males	Age (in yr)
Females	Age (in yr) −10
Nursing home residents	Age (in yr) +10
COMORBID ILLNESSES	
Neoplastic disease	+30
Liver disease	+20
Congestive heart failure	+10
Cerebrovascular disease	+10
Renal disease	+10
PHYSICAL EXAMINATION FINDINGS	
Altered mental status	+20
Respiratory rate 30/min or more	+20
Systolic blood pressure < 90 mm Hg	+20
Temperature < 35°C or ≥40°C	+15
Pulse 125/min or more	+10
LABORATORY FINDINGS	
pH < 7.35	+30
BUN > 10.7 mmol/L	+20
Sodium < 130 mEq/L	+20
Glucose > 13.9 mmol/L	+10
Hematocrit < 30%	+10
Po_2 < 60 mm Hg or O_2 saturation < 90%	+10
Pleural effusion	+10

*A risk score is obtained by summing the patient's age in years (age −10 for females) and the points for each applicable patient characteristic. Patients with a score < 50 are candidates for outpatient treatment, whereas those with scores > 90 warrant hospitalization. Proper management of patients with scores of 70–90 requires careful application of clinical judgment.

BUN, blood urea nitrogen; Po_2, oxygen pressure.

Adapted from Fine MJ, Auble TE, Yealy DM, et al: A prediction rule to identify low-risk patients with community-acquired pneumonia. N Engl J Med 336:243–250, 1997.

TABLE 32-10. American Thoracic Society Criteria for Admission of Patients with Community-Acquired Pneumonia to an Intensive Care Unit

MINOR CRITERIA

Respiratory rate ≥ 30 breaths/min

Pao_2/Fio_2 ratio < 250

Multilobar radiographic involvement

Confusion or disorientation

Uremia (BUN level > 20 mg/dL)

Leukopenia (WBC count < 4000 cells/dL)

Thrombocytopenia (platelet count < 100,000 cells/dL)

Hypothermia (core temperature < 36°C)

Hypotension requiring aggressive fluid resuscitation

MAJOR CRITERIA

Invasive mechanical ventilation

Septic shock with need for vasopressors

BUN, blood urea nitrogen; Fio_2, fractional concentration of oxygen in inspired gas; Pao_2, arterial oxygen pressure; WBC, white blood cell.

1), 2 (group 2), and 3 to 5 (group 3) are 1.5%, 9.2%, and 22%, respectively.[10] Outpatient treatment is recommended for group 1, brief inpatient or supervised outpatient care is recommended for group 2, and hospitalization is recommended for group 3 (with consideration of ICU care for group 3 patients with scores of 4 or 5).

The IDSA and the ATS have published ICU admission criteria for patients with CAP.[40] According to these criteria (Table 32-10), ICU admission is warranted for patients who fulfill three minor criteria or one major criterion. Management of severe CAP per these guidelines has been associated with decreased mortality.[83]

Selection of Antimicrobial Agents

Whenever possible, the initial treatment for pneumonia should be pathogen-directed. Unfortunately, pathogens are rarely identified at the time of presentation, especially when patients are seen in the outpatient setting. Because optimal outcomes are associated with rapid initiation of treatment, the initial antibiotic treatment for patients with pneumonia must often be empirical. When selecting initial empirical antimicrobial therapy, physicians should consider the setting in which the pneumonia occurs (e.g., community, hospital, nursing home), the severity of the disease, the age of the patient, the presence of comorbidities and immunosuppression, previous antimicrobial therapy, and specific clinical manifestations of the illness. Geographic and facility-specific factors such as the endemicity of specific microorganisms (e.g., *C. burnetii*, *L. pneumophila*, endemic mycoses, antimicrobial-resistant pathogens) may also affect the initial treatment choice.

In hospitalized patients, specimens for cultures of blood, sputum, and pleural fluid (if present) should be obtained prior to treatment. On occasion, a brief delay in starting therapy while awaiting the results of an invasive diagnostic procedure is reasonable in patients who are not severely ill. However, delays of more than 8 hours, which unfortunately are common, have been shown to be associated with increased mortality and may otherwise increase the length of hospitalization.[84,85]

Community-Acquired Pneumonia

CAP may be defined as pneumonia occurring in patients who have not been hospitalized or living in a nursing home during the 2 weeks prior to the onset of symptoms.[4] *S. pneumoniae* is the most common pathogen in moderate to severe CAP[7] and accounts for up to 60% of all bacteremic pneumonia. Therapy should be effective against penicillin-resistant *S. pneumoniae* unless there are specific epidemiologic or clinical characteristics that strongly suggest pneumonia due to an "atypical" organism (e.g., mild CAP warranting outpatient care in a previously healthy individual), mixed aerobic-anaerobic flora due to aspiration, or the presence of gram-negative

bacilli or *P. aeruginosa* in a patient with specified risk factors.[4–7,86,87] The ATS,[6] Canadian Infectious Diseases Society/Canadian Thoracic Society,[7] and IDSA[5] also recommend that any empirical regimen for CAP should be active against "atypical" pathogens such as *M. pneumoniae*, *C. pneumoniae*, and *L. pneumophila*. Where the guidelines vary most is in the specific criteria warranting more aggressive care and preferences for the use of specific antimicrobial agents. It is important to recognize that all these guidelines are based on broad epidemiologic considerations that may not pertain to all locations.[88] If the epidemiology of antimicrobial resistance within a facility is such that drug resistance is known to be rare, less aggressive selection of antimicrobial therapy may be appropriate.[89]

The appropriate role of fluoroquinolones in the treatment of CAP has attracted particular attention and controversy. Some experts recommend that use of respiratory fluoroquinolones should be strictly limited to adults for whom another regimen has already failed (e.g., an oral agent for outpatient management of CAP), those who are allergic to alternative agents, or those for whom there are no other effective treatment options.[87] Fluoroquinolone resistance and subsequent treatment failures are well reported in patients with community-acquired pneumococcal pneumonia.[90–94] Widespread fluoroquinolone use, especially in subtherapeutic doses, has been associated with pneumococcal-fluoroquinolone resistance rates of up to 13% in Hong Kong.[25]

Retrospective analyses of patients hospitalized with CAP indicate that regimens that cover "atypical" pathogens and those that follow recommendations made by the ATS and the IDSA are associated with improved clinical outcomes.[4,6,83,89,95] There have been no prospective, randomized, head-to-head studies that directly compare the utility of these guidelines. Summaries of the outpatient and inpatient CAP antibiotic recommendations are presented in Tables 32-11 and 32-12, respectively.[96]

Hospital-Acquired Pneumonia

Hospital-acquired, or nosocomial, pneumonia is defined as pneumonia occurring 48 hours or more after admission to the hospital.[6] Severe HAP is defined by the concomitant occurrence of sepsis syndrome, respiratory failure, rapid progression of chest radiographic shadows, multilobar involvement, or cavity formation.[6] VAP is a subset of HAP and is defined as pneumonia in a mechanically ventilated patient that occurs more than 48 hours after intubation.

Antibiotic regimens recommended for the empirical treatment of HAP typically include expanded-spectrum β-lactam agents, often given in combination with aminoglycosides or vancomycin. If aspiration is likely, specific treatment for anaerobes (e.g., metronidazole, clindamycin) must be strongly considered. Unless *Legionella* is known to be endemic in the institution, targeted therapy for this pathogen is seldom necessary

TABLE 32-11. Guidelines for Empirical Oral Outpatient Treatment of Immunocompetent Adults with Community-Acquired Pneumonia

BRITISH THORACIC SOCIETY

Primary: amoxicillin

Alternatives: erythromycin or clarithromycin

AMERICAN THORACIC SOCIETY

No modifying factors*

Advanced macrolide† or doxycycline‡

Comorbidities*: β-lactam§ macrolide‖ or doxycycline,‡ or fluoroquinolone¶ alone

INFECTIOUS DISEASES SOCIETY OF AMERICA

No modifying factors*: advanced macrolide† or doxycycline

Comorbidities*: fluoroquinolone¶ or advanced macrolide†

Antibiotics within 3 mo: fluoroquinolone¶ alone or advanced macrolide† β-lactam§

Suspected aspiration: clindamycin or amoxicillin-clavulanate

Influenza with bacterial superinfection: β-lactam§ or fluoroquinolone¶

Nursing home patient: fluoroquinolone¶ alone or amoxicillin-clavulanate advanced macrolide

DRUG-RESISTANT *STREPTOCOCCUS PNEUMONIAE* THERAPEUTIC WORKING GROUP

Primary: macrolide, doxycycline, cefuroxime, amoxicillin, amoxicillin-clavulanate

Alternative: fluoroquinolone#

CANADIAN INFECTIOUS DISEASE SOCIETY AND CANADIAN THORACIC SOCIETY

No modifying factors: macrolide or doxycycline‡

COPD: advanced macrolide† or doxycycline‡

COPD plus recent antibiotics or steroids: fluoroquinolone¶ alone, amoxicillin-clavulanate macrolide,‡ or second-generation cephalosporin** macrolide‡

Suspected aspiration: amoxicillin-clavulanate, macrolide, or fluoroquinolone‡¶ clindamycin or metronidazole

Nursing home patient: fluoroquinolone¶ alone *or* macrolide‡ plus amoxicillin-clavulanate *or* second-generation cephalosporin

*American Thoracic Society comorbidities (modifying factors) include cardiopulmonary disease and age > 65 years, receipt of a β-lactam antimicrobial within the prior 3 mo, alcoholism, prior immunosuppressive therapy, multiple medical comorbidities, exposure to a child in a daycare center, residence in a nursing home, underlying cardiopulmonary disease, multiple comorbidities or recent antimicrobial therapy. Infectious Diseases Society of America comorbidities include only COPD, diabetes, renal or congestive heart failure, and malignancy.

†Advanced macrolides are azithromycin and clarithromycin. Telithromycin has similar antimicrobial activity.

‡Second-choice agent.

§High-dose amoxicillin (3–4 g/day), high-dose amoxicillin-clavulanate (2 g amoxicillin plus 125 mg clavulanic acid every 12 hr), cefopodoxime, cefprozil, or cefuroxime.

‖To ensure coverage of β-lactamase producing *Haemophilus influenzae*, erythromycin should not be used in combination with amoxicillin.

¶Antipneumococcal fluoroquinolones include levofloxacin, gatifloxacin, moxifloxacin, and gemifloxacin.

#Levofloxacin or moxifloxacin.

**Available oral second-generation cephalosporins include cefaclor, cefuroxime axetil, cefprozil, cefonocid, and loracarbef.

COPD, chronic obstructive pulmonary disease.

TABLE 32-12. Guidelines for Empirical Parenteral Inpatient Treatment of Immunocompetent Adults with Community-Acquired Pneumonia

MILD TO MODERATE DISEASE

British Thoracic Society

Mild to moderate disease

Primary: (ampicillin or penicillin) a macrolide

Alternative: fluoroquinolone*

American Thoracic Society

No modifying factors†: azithromycin alone, doxycycline, β-lactam or fluoroquinolone* alone

With modifying factors‡: (cefotaxime *or* ceftriaxone *or* ampicillin-sulbactam *or* high-dose ampicillin) (macrolide or doxycycline) *or* fluoroquinolone* alone

Infectious Diseases Society of America

Primary§: (cefotaxime, ceftriaxone, ertapenem, or ampicillin/sulbactam) advanced macrolide† *or* fluoroquinolone* alone

Suspected aspiration: fluoroquinolone* ± antianaerobic agent‖

Drug-Resistant *Streptococcus pneumoniae* Therapeutic Working Group

Primary: (cefuroxime, cefotaxime, ceftriaxone, or ampicillin-sulbactam) macrolide

Alternative: fluoroquinolone*

Canadian Infectious Diseases Society and Canadian Thoracic Society

Fluoroquinolone* *or* (cephalosporin¶ macrolide)**

SEVERE DISEASE

British Thoracic Society

Primary: (cefuroxime, cefotaxime, or ceftriaxone) macrolide, rifampin

Alternative: fluoroquinolone* ± penicillin IV

American Thoracic Society

Standard: (cefotaxime or ceftriaxone) (azithromycin or fluoroquinolone*)

At risk for *Pseudomonas aeruginosa*††: antipseudomonal β-lactam‡‡ ciprofloxacin or antipseudomonal β-lactam aminoglycoside plus (azithromycin or fluoroquinolone*)

Infectious Diseases Society of America

Primary: (cefotaxime, ceftriaxone, ertapenem, or ampicillin/sulbactam) (advanced macrolide† or fluoroquinolone*)

β-Lactam allergy: fluoroquinolone* ± clindamycin

Pseudomonas risks††: (antipseudomonal β-lactam‡‡ ciprofloxacin) or antipseudomonal β-lactam‡‡ aminoglycoside (fluoroquinolone* or a macrolide)

Pseudomonas risks†† and β-lactam allergy: (aztreonam levofloxacin) *or* aztreonam (moxifloxacin or gatifloxacin) ± an aminoglycoside

Drug-Resistant *Streptococcus pneumoniae* Therapeutic Working Group

Primary: (ceftriaxone or cefotaxime) macrolide; or (ceftriaxone or cefotaxime) fluoroquinolone*

Alternative (with caution): fluoroquinolone*

Infectious Diseases Society and Canadian Thoracic Society

Standard: (cefotaxime, ceftriaxone or β-lactam–β-lactamase inhibitor) (fluoroquinolone* or macrolide**)

Pseudomonas risks††: Ciprofloxacin (antipseudomonal β-lactam‡‡ or aminoglycoside) *or* antipseudomonal β-lactam‡‡ aminoglycoside macrolide**

*Antipneumococcal fluoroquinolones include levofloxacin, gatifloxacin, and moxifloxacin.

†Advanced macrolides are azithromycin and clarithromycin.

‡Modifying factors include those considered to increase the risk of infection by a penicillin-resistant pneumococcus (age > 65 yr, exposure to a β-lactam antimicrobial within the prior 3 mo, alcoholism, prior immunosuppressive therapy, multiple medical comorbidities, exposure to a child in a daycare center or to infection by an enteric gram-negative bacillus (residence in a nursing home, underlying cardiopulmonary disease, multiple comorbidities, or recent antimicrobial therapy).

§Preferred regimen may be determined by whether the patient has received antibiotics within the prior 3 mo.

‖Antianaerobic agents include clindamycin, metronidazole, and β-lactam–β-lactamase inhibitor combinations.

¶Acceptable cephalosporins include second-generation agents (e.g., cefuroxime, cefamandole), third-generation agents (cefotaxime or ceftriaxone), or fourth-generation agents (cefepime or cefpirome, neither of which is available in the United States).

**Second-choice agent.

††American Thoracic Society risk factors for *Pseudomonas aeruginosa* are structural lung disease (i.e., bronchiectasis, cystic fibrosis), corticosteroid use (>10 mg prednisone/day), broad-spectrum antibiotic therapy for more than 7 days in the past month, or malnutrition. The Infectious Diseases Society of American risk factors for *P. aeruginosa* include only structural lung disease or recent completion of a course of antibiotics or steroids. The Canadian risk factors include only structural lung disease, recent antibiotic therapy, or recent hospitalization in an intensive care unit.

‡‡Antipseudomonal β-lactams include ceftazidime, cefepime, imipenem, meropenem, mezocillin, piperacillin, and piperacillin-tazobactam.

in the treatment of HAP. Empirical therapy for VAP is necessarily broad because the range of potential pathogens is large and mortality is significantly increased when the responsible pathogen is resistant to the initial antibiotic regimen (Table 32-13).

Nursing Home–Acquired Pneumonia

The etiology of bacterial pneumonia in nursing home residents is diverse and includes HAP-associated pathogens (e.g., aerobic gram-negative rods, *S. aureus*), CAP-associated pathogens (e.g., *S. pneumoniae*, *H. influenzae*, "atypicals"), and anaerobes (due to the aspiration risk in these patients).[3,12,97] Consequently, treatment recommendations for acute pneumonia in nursing home patients represent a hybrid between recommendations for CAP and HAP.[4–7] Particular attention should be paid to providing adequate treatment for *S. pneumoniae* in all patients and to gram-negative bacilli, especially in patients with severe CAP in the setting of significant medical comorbidities or recent antimicrobial therapy.

Other Pneumonia Syndromes

On initial presentation, a variety of other infectious pulmonary syndromes may not be readily differentiated

TABLE 32-13. Guidelines for Empirical Antibiotic Treatment of Nosocomial Pneumonia*

Setting	Core Pathogens	Antimicrobial Choices
2–5 DAYS IN HOSPITAL		
Mild to moderate pneumonia Severe pneumonia "low-risk"	Enterobacteriaceae *Streptococcus pneumoniae* *Haemophilus influenzae* Methicillin-sensitive *Staphylococcus aureus*	β-Lactam–β-lactamase inhibitor† *or* ceftriaxone *or* fluoroquinolone‡ All ± an aminoglycoside
≥5 DAYS IN HOSPITAL		
Mild to moderate pneumonia	As above	As above
≥5 DAYS IN HOSPITAL		
Severe HAP "low risk"	*Pseudomonas aeruginosa, Enterobacter* spp., *Acinetobacter* spp.	Carbapenem *or* β-lactam–β_1-lactamase inhibitor† *or* cefepime All plus amikacin or fluoroquinolone‡
≥2 DAYS IN HOSPITAL		
Severe HAP "high risk"	As above	As above
SPECIAL CIRCUMSTANCES§		
Recent abdominal surgery *or* witnessed aspiration	Anaerobes	As per Table 32-14
Other sites of infection with MRSA or prior use of antistaphylococcal antibiotics	MRSA	As per Table 32-14
Prolonged ICU stay or prior use of broad-spectrum antibiotics or structural lung disease (cystic fibrosis, bronchiectasis)	*Pseudomonas aeruginosa*	As per Table 32-14
Endemicity within facility *and* either impaired cell-mediated immunity or failure to respond to antibiotics	*Legionella*	As per Table 32-14

*High-risk criteria include age ≥ 65 years, pancreatitis, chronic obstructive pulmonary disease, central nervous system dysfunction (stroke, drug overdose, coma, status epilepticus), congestive heart failure, malnutrition, diabetes mellitus, endotracheal intubation, renal failure, complicated thoracoabdominal surgery, alcoholism, and pancreatitis. All other patients are considered to be at low risk.
This protocol does not address the treatment of neutropenic or HIV-infected persons.
Severe pneumonia requiring care in an ICU is characterized by rapid radiographic progression, multilobar disease, or cavitation. All other cases of nosocomial pneumonia are considered *mild to moderate.*
†Ticarcillin-clavulanate and piperacillin-tazobactam are the preferred β-lactam–β-lactamase inhibitors for the treatment of nosocomial pneumonia. Ampicillin-sulbactam lacks adequate activity against many nosocomial enteric gram-negative bacilli.
‡Levofloxacin (IV or PO), gatifloxacin (IV or PO), moxifloxacin (IV or PO), or gemifloxacin (PO only) are preferred for *Streptococcus pneumoniae*. When used for severe HAP, levofloxacin should be dosed at 750 mg IV daily. Ciprofloxacin has the best in vitro activity against *Pseudomonas aeruginosa*.
§Antimicrobial treatment should also be sufficient to cover core pathogens.
HAP, hospital-acquired pneumonia; HIV, human immunodeficiency virus; ICU, intensive care unit; MRSA, methicillin-resistant *Staphylococcus aureus*.
Modified from American Thoracic Society: Hospital-acquired pneumonia in adults: Diagnosis assessment of severity, initial antimicrobial therapy, and preventative strategies. Am J Respir Crit Care Med 153:1711–1725, 1995.

from acute bacterial pneumonia. Examples include influenza A, SARS,[29,30] and hantavirus pulmonary syndrome.

Concerns about potential bioterrorism or biowarfare require that attention be paid to the epidemiologic, clinical, and microbiologic significance of pneumonia due to *B. anthracis* (anthrax),[33] *F. tularensis* (tularemia),[34] and *Y. pestis* (plague).[32] These infectious agents are individually discussed later in this chapter. Further information may be obtained from organizations such as the Centers for Disease Control and Prevention (www.cdc.gov), IDSA (www.idsociety.org), and the World Health Organization (www.who.org).

Adjustments in Antimicrobial Therapy

Organisms recovered from normally sterile sites, such as blood, pleural fluid, cerebrospinal fluid, or transthoracic lung aspiration specimens, are presumed to be pathogens. Because of problems introduced by contamination with oropharyngeal secretions, expectorated sputum culture results must be interpreted in light of the quality of the specimen, correlation with pathogens identified by Gram stain, and the clinical impression.

If the etiologic agent of pneumonia has been reliably identified, the initial antimicrobial regimen should be adjusted based on the results of in vitro susceptibility testing. The ideal drug for a known pathogen has the narrowest spectrum of activity and is the most efficacious, least toxic, and least costly. Pathogen-based modification of therapy is particularly important in HAP because prolonged use of broad-spectrum empirical agents promotes the emergence of pathogens with multidrug resistance.[98] Recommendations for specific drug choices and duration of therapy for specific microorganisms are discussed under the sections devoted to individual microorganisms and are summarized in Table 32-14.

TABLE 32-14. Agents for Specific Therapy of Selected Respiratory Pathogens

Type of Infection	Preferred Agent(s)	Alternative Agent(s)
COMMUNITY-ACQUIRED PNEUMONIA		
Streptococcus pneumoniae		
PCN-susceptible	Penicillin G, amoxicillin, clindamycin, doxycycline, telithromycin	Cephalosporin, macrolide,* (MIC < 2.0 g/mL) fluoroquinolone,†
PCN-resistant	Agents identified using in vitro susceptibility tests, including cefotaxime, ceftriaxone, vancomycin, and fluoroquinolone†	Telithromycin (MIC ≥ 2.0 g/mL)
Mycoplasma	Doxycycline, macrolide	Fluoroquinolone,† telithromycin
Chlamydophila pneumoniae	Doxycycline, macrolide	Fluoroquinolone,† telithromycin
Legionella	Azithromycin, fluoroquinolone (including ciprofloxacin),† erythromycin (± rifampin)	Doxycycline ± rifampin
Haemophilus influenzae	Second- or third-generation cephalosporin, clarithromycin, doxycycline, β-lactam/β-lactamase inhibitor, trimethoprim/sulfamethoxazole, azithromycin, telithromycin	Fluoroquinolone†
Moraxella catarrhalis	Second- or third-generation cephalosporin, trimethoprim-sulfamethoxazole, macrolide doxycycline, β-lactam–β-lactamase inhibitor	Fluoroquinolone†
Neisseria meningitidis	Penicillin	Ceftriaxone, cefotaxime, cefuroxime, chloramphenicol, fluoroquinolone†
Streptococci (other than *S. pneumoniae*)	Penicillin, first-generation cephalosporin	Clindamycin (susceptibility should be confirmed), vancomycin
Anaerobes	Clindamycin, β-lactam–β-lactamase inhibitor, β-lactam plus metronidazole	Carbapenem
Staphylococcus aureus Methicillin-susceptible	Oxacillin, nafcillin, cefazolin; all ± rifampin or gentamicin‡	Cefuroxime, cefotaxime, ceftriaxone, fluoroquinolones,† clindamycin, vancomycin
Methicillin-resistant	Vancomycin‡ ± rifampin or gentamicin	Linezolid, quinupristin-dalfopristin; trimethoprim-sulfamethoxazole, fluoroquinolones,† and tetracyclines may also show activity (in vitro testing required)
Klebsiella pneumoniae and other Enterobacteriaceae (excluding *Enterobacter* spp.)	Third-generation cephalosporin or cefepime (all ± aminoglycoside) carbapenem	Aztreonam, β-lactam–β-lactamase inhibitor,§ fluoroquinolone†
HOSPITAL-ACQUIRED INFECTIONS		
Enterobacter spp.	Carbapenem, β-lactam–β-lactamase inhibitor,§ cefepime, fluoroquinolone; all + aminoglycoside in seriously ill patients	Third-generation cephalosporin + aminoglycoside
Pseudomonas aeruginosa	Anti-pseudomonal β-lactam‖ + aminoglycoside, carbapenem + aminoglycoside	Ciprofloxacin + aminoglycoside, ciprofloxacin + antipseudomonal β-lactam‖
Acinetobacter	Aminoglycoside + piperacillin or a carbapenem	Doxycycline, ampicillin-sulbactam, colistin
LESS COMMON PATHOGENS		
Nocardia	Trimethoprim-sulfamethoxazole	Imipenem ± amikacin, doxycycline or minocycline, sulfonamide ± minocycline or amikacin
Coxiella burnetii (Q fever)	Doxycycline	Fluoroquinolone
Chlamydophila psittaci (psittacosis)	Doxycycline	Erythromycin, chloramphenicol
Eikenella corrodens	Penicillin	Tetracyclines, β-lactam–β-lactamase inhibitor, second- and third-generation cephalosporins, fluoroquinolones

*Azithromycin (IV or PO) is the preferred macrolide; clarithromycin (PO) or erythromycin (IV or PO) may also be used.
†Levofloxacin (IV or PO), gatifloxacin (IV or PO), moxifloxacin (IV or PO), or gemifloxacin (PO only) are preferred for *Streptococcus pneumoniae*. Ciprofloxacin has the best in vitro activity against *Pseudomonas aeruginosa*.
‡Rifampin and gentamicin should be reserved for cases of bacteremic *Staphylococcus aureus* pneumonia, empyema formation, or lung abscesses. Activity of rifampin and gentamicin requires laboratory confirmation for methicillin-resistant *S. aureus*.
§Ticarcillin-clavulanate and piperacillin-tazobactam are the preferred β-lactam–β-lactamase inhibitors for the treatment of nosocomial pneumonia due to Enterobacteriaceae. Ampicillin-sulbactam lacks adequate activity against many nosocomial enteric gram-negative bacilli.
‖Antipseudomonal β-lactams ceftazidime, cefepime, imipenem, meropenem, mezlocillin, piperacillin, or piperacillin-tazobactam.
MIC, minimum inhibitory concentration.
Modified from Bartlett JG, Dowell SF, Mandell LA, et al: Practice guidelines for the management of community-acquired pneumonia in adults: Infectious Diseases Society of America. Clin Infect Dis 31:347–382, 2000.

If a pathogen is not identified, reevaluation of the initial therapeutic regimen must take into account the patient's response to therapy. Failing empirical antibiotic regimen warrants complete reappraisal. Usually, a more aggressive effort to obtain respiratory specimens is needed along with a search for empyema or other complications of pneumonia. If still no diagnosis is established, empirically broadening the spectrum of antimicrobial coverage may be wise.

The change from parenteral to oral antimicrobial therapy can safely be made in CAP patients who are clinically stable and able to absorb effective oral antimicrobials[99,100]; often, this is achieved within 3 days of the initiation of parenteral therapy in hospitalized patients. No clinical benefit is found for in-hospital observation after switching from intravenous to oral antibiotics for CAP patients. Because HAP pathogens are frequently resistant to all available oral antimicrobial agents and because the severity of illness is so much greater, oral antimicrobial therapy is much less frequently appropriate.

COMMON CAUSES OF PYOGENIC PNEUMONIA

Streptococcus pneumoniae (Pneumococcal Pneumonia)

Epidemiology

S. pneumoniae is the most frequent cause of CAP among patients who require hospitalization.[7,8,100a] The overall incidence of pneumococcal pneumonia is approximately 200 cases/100,000 persons/yr, with 9 to 14 cases/100,000 cases of bacteremia. This infection accounts for 40,000 deaths annually in the United States. Risk factors for infection include male sex, chronic liver or kidney disease, congestive heart failure, age younger than 2 years or older than 65 years, African American or Native American ancestry, heavy alcohol use, cigarette smoking, malnutrition, dementia, institutionalization, COPD, immunoglobulin deficiency, HIV infection, and organ transplantation.[101–103] Organisms are transmitted by aerosolized droplets and direct physical contact.[104] Therefore, increased rates of carriage occur under circumstances of crowding and inadequate ventilation. Pneumococcal infections occur predominantly in the winter and early spring and are often associated with prior infection by influenza or RSV.[105]

Clinical Manifestations

The classic presentation of pneumococcal pneumonia consists of a single rigor followed within a few hours by sustained fever and the development of cough, dyspnea, and production of rusty or mucoid sputum. Severe pleuritic chest pain is common. Chest examination may find localized crackles and focal decreased breath sounds at early stages of infection. Eventually, signs of consolidation evolve. Neutropenia may occur in patients with overwhelming infection. The radiographic appearance of pneumococcal pneumonia is often either lobar consolidation or patchy bronchopneumonia (Fig. 32-1). Bacteremia is more likely with lobar opacities than with multilobar or bilateral disease. Cavitation rarely if ever develops. Small, sterile parapneumonic effusions are frequently found.

Microbiologic Diagnosis

Although Gram stain of purulent sputum that reveals numerous, characteristic "lancet-shaped" diplococci with blunted ends (commonly seen in pairs and short chains) in the absence of other predominant flora is strongly suggestive of the diagnosis (Fig. 32-2), a valid sputum specimen cannot always be obtained.[106,107] The organism is recovered from sputum culture in fewer than half of the cases. Even a single dose of antibiotics affects the yield of sputum cultures, the likely explanation for the discrepancy between sputum Gram stain and culture results. Furthermore, pneumococci may be part of the oral flora. Blood cultures are positive in 10% to 30% of hospitalized patients.[6] The rapid, commercial urinary antigen *S. pneumoniae* test has a sensitivity of 50% to 80% and a specificity of approximately 90%; the sensitivity is higher in bacteremic cases.

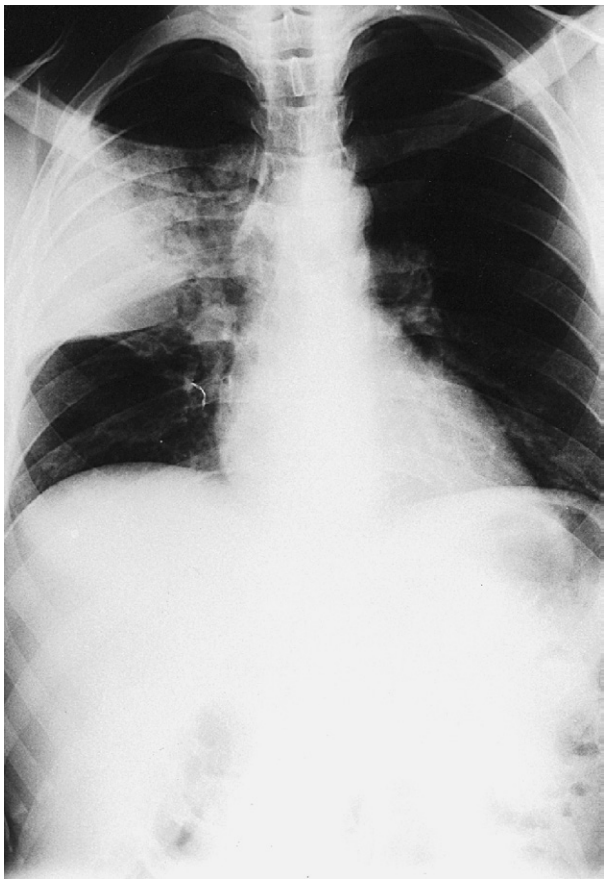

FIGURE 32-1 ■ Pneumococcal pneumonia presenting with lobar consolidation.

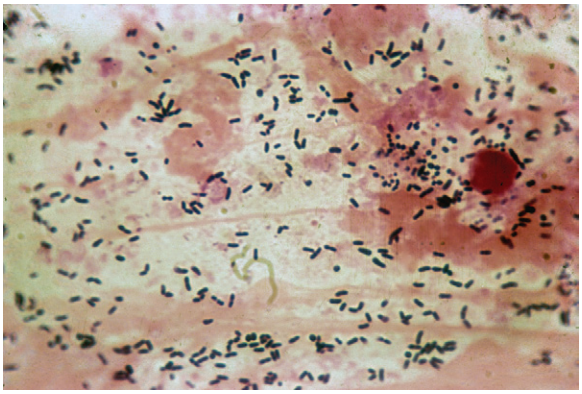

FIGURE 32-2 ■ Gram stain of sputum from a patient with pneumococcal pneumonia. The predominant organisms are gram-positive, lancet-shaped diplococci.

Clinical Course

With an appropriate antibiotic, a salutary clinical response usually occurs within 24 to 48 hours. Fever may persist for up to 5 days without signifying therapeutic failure or complication of the infection. Resolution of radiographic changes usually occurs within 4 to 8 weeks, but up to 12 weeks may be required in patients with extensive underlying lung disease. Complications such as empyema, purulent pericarditis, meningitis, endocarditis, arthritis, and cellulitis are uncommon in the modern era. In asplenic individuals, fulminant septicemia and disseminated intravascular coagulation may be the first signs of pneumococcal pneumonia. The overall mortality of bacteremic pneumococcal pneumonia is 11% to 20%,[108] increasing to 20% to 40% in persons over 65 years of age.

Treatment

Antimicrobial resistance, particularly to penicillin, has complicated the treatment for *S. pneumoniae* in much of the world.[109] For nonmeningeal isolates of *S. pneumoniae*, the recent redefinition of full susceptibility as a minimum inhibitory concentration (MIC) of penicillin 2.0 μg/mL or less and high-level resistance as an MIC 8.0 μg/mL or higher has dramatically changed the incidence of penicillin resistance. This redefinition was driven by the discordance between the previous lower MIC levels and clinical success rates. Resistant isolates are more commonly isolated from attendees of daycare centers, residents of long-term care facilities, and persons who have received antimicrobial therapy within the preceding 3 months. In recent years, the rates of penicillin resistance have stabilized or even started to decrease.[110] Several explanations for this trend exist, including the effect of the pediatric conjugate vaccine and a shift in the outpatient antibiotic prescription patterns away from β-lactams.

Resistance to other β-lactams is due to alterations in penicillin-binding proteins of *S. pneumoniae* rather than to β-lactamase production. Unlike other β-lactams, cefotaxime, ceftriaxone, and cefepime retain activity against 75% to 95% of nonmeningeal isolates of *S. pneumoniae*.[111–113] *S. pneumoniae* resistance rates to other antimicrobials are up to 30% for trimethoprim-sulfamethoxazole (TMP-SMX), 16% for tetracyclines, 26% for macrolides, and 9% for clindamycin; these rates are higher among penicillin-resistant pneumococci.[109,112] Failures of azithromycin treatment of *S. pneumoniae* isolates expressing moderate-level macrolide resistance (MIC ≤ 32 μg/mL or less) are well documented.[114–116] High-level resistance with MIC greater than 64 μg/mL (MLSB [macrolides, lincosamides, or streptogramin B] phenotype) is more common in Europe[117] and has been associated with in vitro resistance to clindamycin. *S. pneumoniae* resistance to fluoroquinolones has also emerged (with rates of ≤13% in Hong Kong) with resultant clinical treatment failures.[25,90–94]

The potential for resistance to all the major classes of antibiotics complicates the choice of empirical antibiotic for suspected *S. pneumoniae*. By far the most important determinant of appropriate therapy is to avoid antibiotics used in the prior 90 days.[118] Severity of illness also may play a role. Whereas only limited data are available and the number of documented *S. pneumoniae* cases is small, combination therapy appears to have slightly better outcomes than fluoroquinolone monotherapy requiring ICU admission.[119] Retrospective and prospective observational studies have suggested a benefit to treating severely ill patients with proven pneumococcal infections with both a β-lactam and a macrolide agent.[57,110,120–122] Although this warrants further validation,[110,122] the most likely explanation is that the macrolides exert a immunomodulatory effect. Improved outcome for bacteremic CAP cases due to pathogens not usually susceptible to a macrolide supports the findings of these studies.[123]

Other Streptococci

Epidemiology

S. pyogenes (group A β-hemolytic streptococcus) can be found in the oropharynx of over 20% of children and a smaller percentage of adults. In the United States, the incidence of pneumonia due to *S. pyogenes* was 0.15 to 0.35/100,000 persons/year, accounting for 0.3% of CAP cases with an identified pathogen.[124,125] Carriage rates increase greatly during epidemics and in crowded conditions.[104,126] The organism is easily transferred between contacts, leading to epidemics of group A streptococcal pneumonia in military recruits, nursing homes, and other crowding situations.[124,126] Pneumonia due to *S. pyogenes* most often occurs during the late winter and spring months, may follow an episode of influenza, measles, or varicella, and has been associated with increased age, alcohol abuse, diabetes mellitus, cancer, and HIV infection.[124]

Group B streptococci (*S. agalactiae*) are a major cause of neonatal sepsis and pneumonia. Pneumonia accounts for approximately 15% of adult infections by group B streptococcal infections in adults.[127] Most adults with group B streptococcal pneumonia are debilitated and develop pneumonia as a consequence of aspiration.[127] Diabetes, hepatic cirrhosis, stroke, breast cancer,

decubitus ulcer, and neurogenic bladder are also risk factors.[127]

The *Streptococcus milleri* group C streptococci (which include *S. intermedius*, *S. anginosis*, and *S. constellatus*) have emerged as significant respiratory pathogens, predominantly causing empyema and lung abscesses. Infections with this group share many of the features of anaerobic infections, including increased risk in males, periodontal disease, and alcoholism. Viridans and microaerophilic streptococci (α-hemolytic, nonpneumococcal) are rarely the sole pathogens in patients with pneumonia. They are more commonly found mixed with other facultative and anaerobic organisms in cases of aspiration pneumonia.

Clinical Manifestations

CAP from these pathogens is nearly identical to pneumococcal pneumonia. Exudative pharyngitis may be evident and unilobar involvement is common with group A streptococcal pneumonia.[126] Pleural effusions in group A streptococcal pneumonia are frequent, may be large, accumulate rapidly, and appear early in the course of the disease. Pneumonia caused by other β-hemolytic streptococci is usually less abrupt and milder; pleural effusions are uncommon, and lung tissue necrosis is rare[127] despite frequent bacteremia.[124] Disease resulting from α-hemolytic streptococci resembles aspiration pneumonia. *S. milleri* infection is predominantly empyema, with or without concomitant pneumonia.[128] Pneumothorax at the time of initial presentation appears to be more common with *S. milleri* than with other streptococcal empyemas. Lung abscesses can also be found.

Microbiologic Diagnosis

Because the organisms are indistinguishable from streptococci in the normal oral flora, documentation of infection from these organisms requires isolation from a culture of blood, pleural fluid, or respiratory specimen obtained by means of an invasive procedure (Fig. 32-3). Pleural fluid cultures of children with *S. pyogenes* pneumonia are frequently positive.[129] PCR technology holds great promise for aiding diagnosis, especially of group A streptococcal infections[130] and *S. milleri* empyema.[131]

Clinical Course

Empyema and/or pericarditis occur in 5% to 30% of patients with group A streptococcal pneumonia[124,126]; other complications include pneumothorax, mediastinitis, and bronchopleural fistula formation. The only classic nonsuppurative complication that follows *S. pyogenes* pneumonia is glomerulonephritis. The overall mortality rate is 24% to 38%, with an 18% mortality rate in previously healthy patients.[124,125]

Treatment

Most of these streptococci are susceptible to penicillin G, ampicillin, and many cephalosporins. α-Hemolytic streptococci may require high dosage (8–18 million units/day). Because resistance to clindamycin and erythromycin is found in up to 15% to 20% of isolates,[132] susceptibility testing is advisable before therapy with a macrolide or clindamycin.[133] Drainage of empyema fluid is an important part of therapy.

Haemophilus influenzae

Epidemiology

H. influenzae is the third most common cause of CAP requiring hospitalization in adults and accounts for approximately 1.2 cases/100,000 adults/yr in the United States.[7] Chronic lung disease, malignancy, HIV infection, and alcoholism are among the most common predisposing conditions to *Haemophilus* pneumonia. Active smoking appears to particularly increase the risk of *H. influenzae* pneumonia. Because unvaccinated young children lack specific immunity to capsular material, they are prone to bacteremic pneumonia with encapsulated strains as well as noninvasive (nonbacteremic) infection by unencapsulated (or nontypeable) strains. Noninvasive infection by unencapsulated strains is the most common *H. influenzae* pneumonia in adults.

Clinical Manifestations

The clinical presentation of *Haemophilus* pneumonia is indistinguishable from other bacterial pneumonias.

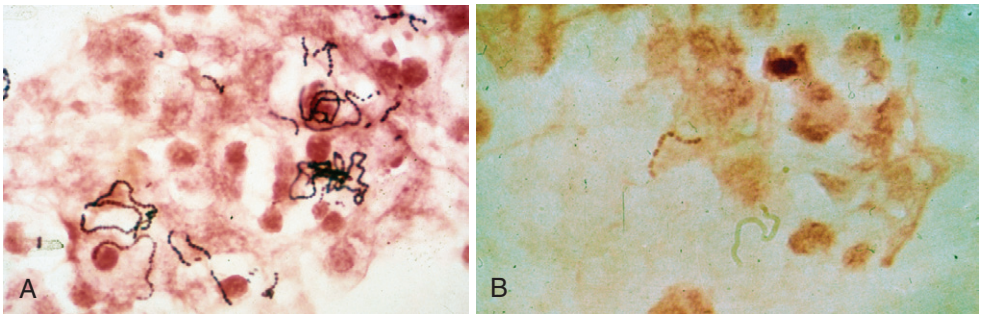

FIGURE 32-3 ■ **A,** Group A streptococcus (*Streptococcus pyogenes,* β-hemolytic streptococcus). **B,** Group B streptococcus (*Streptococcus agalactiae*) are indistinguishable from *Streptococcus pneumoniae* on Gram stain.

Bacteremia is more common in children than in adults. On radiographs, *Haemophilus* pneumonia may be multilobar, patchy bronchopneumonia or have areas of frank consolidation. Spherical radiographic shadows ("round pneumonia") have been described but cavitation is uncommon. Small parapneumonic effusions may occasionally progress to empyema.

Microbiologic Diagnosis

Diagnosing *H. influenzae* pneumonia by a Gram stain of sputum is difficult. The small, pleomorphic coccobacilli are often overlooked or are misidentified as *S. pneumoniae* because of poor staining. Culture of expectorated sputum reveals *H. influenzae* in only half of well-documented cases of pneumonia. Moreover, asymptomatic colonization with nontypeable strains in COPD patients complicates analysis of Gram stain and sputum cultures (Fig. 32-4).

Clinical Course

The overall mortality rate of *H. influenzae* pneumonia is 5% to 7% but is much higher in patients with bacteremia or extrapulmonary disease. Associated foci of infection, such as empyema, meningitis, arthritis, pericarditis, and epiglottitis are more common with infection by encapsulated organisms.

Treatment

About 20% to 50% of *H. influenzae* isolates produce β-lactamase and are therefore resistant to ampicillin. Consequently, patients with serious respiratory tract infections requiring parenteral therapy should be empirically treated with a cephalosporin, or a β-lactam–β-lactamase inhibitor combination. Azithromycin, fluoroquinolones, tetracyclines, and telithromycin also have excellent activity against *H. influenzae*. About 7% to 10% of isolates are resistant to TMP-SMX.

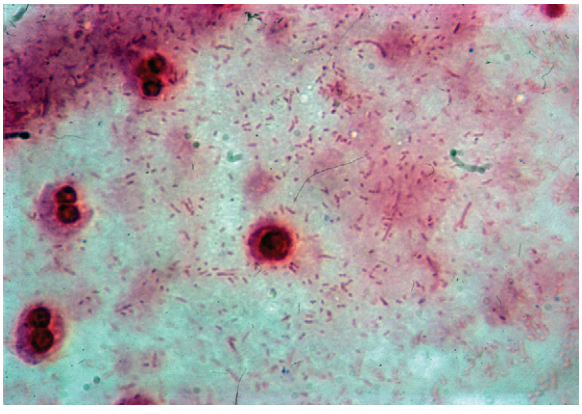

FIGURE 32-4 ■ Gram stain of *Haemophilus influenzae* shows small pleomorphic coccobacilli that can be missed on sputum examination.

Mycoplasma pneumoniae

Epidemiology

M. pneumoniae accounts for up to 37% of CAP in persons treated as outpatients and 10% of pneumonia in persons requiring hospitalization.[6,8] An estimated 2 cases/yr/1000 individuals occur in the United States. *Mycoplasma* infections occur year-round, but outbreaks are most common in the fall. The frequency of *M. pneumoniae* CAP appears to vary from year to year. Because *Mycoplasma* is readily transmitted from person to person via aerosolized respiratory droplets, outbreaks are common in families or closed populations.[134]

Clinical Manifestations

The clinical picture of *M. pneumoniae* pneumonia is the paradigm of atypical CAP[4,7] as described previously. Chest auscultation may be normal. Sometimes crackles and decreased breath sounds are present. Pharyngitis and cervical adenopathy may be encountered. Bullous myringitis is not more common with *Mycoplasma* pneumonia than with pneumococcal pneumonia/otitis. A wide variety of exanthems, including maculopapular eruptions, urticaria, erythema multiforme, and erythema nodosum, occur in 10% to 25% of patients. Laboratory studies may reveal mild to moderate leukocytosis. The chest radiograph usually shows an interstitial or a mixed pattern that is often more striking than would be expected based on chest physical findings (Fig. 32-5).

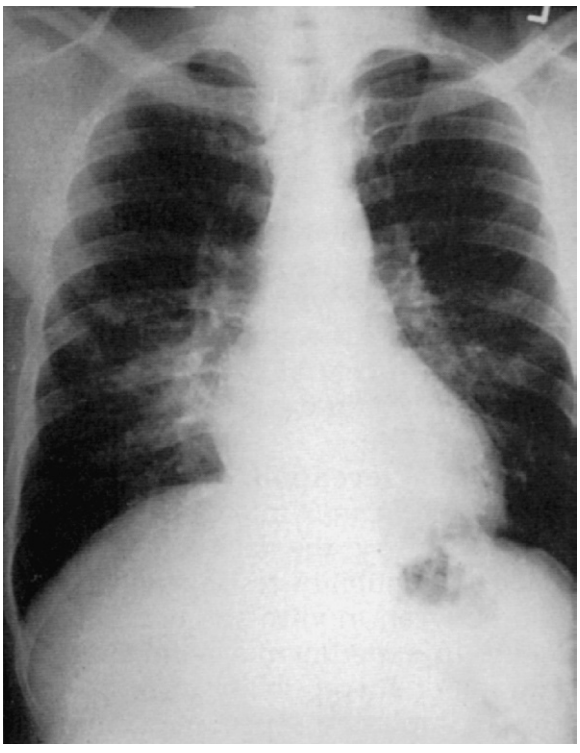

FIGURE 32-5 ■ Radiographic findings in *Mycoplasma pneumoniae* pneumonia are nonspecific. Bilateral bronchopneumonia occurred in this patient.

Small pleural effusions may occur. There are many reports of other radiologic presentations as well.

Microbiologic Diagnosis

Acute *Mycoplasma* pneumonia may stimulate cold agglutinin production in a titer 1:32 or greater. This nonspecific finding also occurs in various other infectious and noninfectious conditions including pneumonia due to *Legionella*, adenovirus, and influenza.[4] When obtained, sputum generally displays moderate numbers of polymorphonuclear leukocytes without a predominant organism. Recovery of *M. pneumoniae* from culture of clinical specimens requires special cultures and takes approximately 10 days. Demonstration of a fourfold rise in specific *M. pneumoniae* complement fixation titer for paired acute and convalescent serum samples confirms the diagnosis. The results of culture and serologic tests are rarely helpful in clinical management but are useful for epidemiologic purposes. A DNA probe test for rapid detection of *M. pneumoniae* in sputum is available, but its role in patient management is still ill-defined.[135]

Clinical Course

Mycoplasma pneumonia is usually a benign, often self-limited infection with an excellent prognosis for complete recovery. ARDS and death have been reported but are rare. Other complications of *M. pneumoniae* infection include fulminant intravascular hemolysis, the Stevens-Johnson syndrome, aseptic meningitis, meningoencephalitis, pericarditis, and myocarditis.[136]

Treatment

Antimicrobial therapy with a tetracycline, macrolide, or fluoroquinolone shortens the course of clinical symptoms and hastens resolution of radiographic abnormalities. To prevent clinical relapse, 2 weeks is the minimum recommended duration for treatment.[4] Early in the course of illness, patients with *Mycoplasma* pneumonia should be isolated to prevent transmission of the organism by respiratory droplets. Azithromycin prophylaxis can prevent infection in close contacts of patients.[137] Despite adequate therapy and resolution of symptoms, *M. pneumoniae* may persist in sputum cultures of infected patients for many weeks but do not appear to readily transmit infection.

Chlamydophila pneumoniae (Formerly *Chlamydia pneumoniae*)

Epidemiology

C. pneumoniae accounts for 5% to 15% of cases of CAP and is generally the second most common cause of CAP requiring hospitalization.[8] Seroepidemiologic studies suggest that *C. pneumoniae* infection eventually occurs in 40% to 50% of the general population, including nursing home residents. Acquisition of *C. pneumoniae* occurs via airborne transmission of infected respiratory droplets.[137a]

Clinical Manifestations

Primary infection by *C. pneumoniae* is usually asymptomatic. An acute, mild respiratory tract infection is observed in only 10% of infected adolescents and young adults. Bronchitis, sinusitis, laryngitis, tonsillitis, or exacerbations of asthma may occur with or without associated pneumonia. Sore throat with hoarseness is often severe and may precede pneumonia by up to a week and resolve prior to pneumonia onset, resulting in a biphasic illness. Diarrhea is common in hospitalized patients. The erythrocyte sedimentation rate is elevated, but there is little leukocytosis. Chest radiographs often reveal nonspecific alveolar opacities. Pleural effusions are rare.

Microbiologic Diagnosis

C. pneumoniae cannot be visualized by Gram stain, and tissue culture is required to grow the pathogen. Criteria for serologic diagnosis of acute infection are a microimmunofluorescence IgM titer of 1:16 or higher, IgG titer of 1:512 or higher, or a fourfold rise in antibody titer following acute infection. IgG may not be elevated until 3 to 6 weeks after the onset of illness.[4] Many patients are concomitantly infected by *C. pneumoniae* and other pathogens (especially *S. pneumoniae*).

Clinical Course and Treatment

Complete recovery following *C. pneumoniae* infection is the rule.[138] When associated with an exacerbation of asthma, *C. pneumoniae* can cause a prolonged recovery time. A minimum of 2 weeks treatment with a macrolide, tetracycline, doxycycline, or fluoroquinolone is recommended.[4,139] Fatalities occur principally in patients with mixed infection and preexisting illness. Reinfection by *C. pneumoniae* in older patients is associated with more severe symptoms, perhaps due to antigenic sensitization.

Staphylococcus aureus

Epidemiology

S. aureus accounts for less than 10% of cases of CAP[7] but is the second or third most common etiology in patients with CAP requiring ICU admission. *S. aureus*, especially MRSA, accounts for up to 30% of nosocomial pneumonias.[12] Nasal or skin colonization is the major source for pneumonia: 30% to 50% of healthy adults carry the organism transiently in the anterior nares. Patients who develop MRSA pneumonia have nasal colonization on admission in 67% of cases whereas noncolonized patients have less than a 5% risk of subsequent MRSA pneumonia.[140] Health care workers may have even higher carriage rates. The organism is easily transferred from person to person by direct hand contact.

A community-acquired strain of MRSA has recently become an important CAP pathogen in the United States.

In addition to antibiotic resistance, the DNA cassette containing the mecA gene also included other virulence factors, such as the Panton-Valentine leukocidin (PVL). The combination of antibiotic resistance and increased virulence factors has been associated with significantly higher mortality.[141] Typical hospital-acquired strains of MRSA have also caused episodes of CAP but usually occur in patients with risk factors for HCAP.[142] The ability to differentiate clinically between nosocomial- and community-acquired cases is increasingly difficult because risk factors, such as prior antibiotic therapy, often overlap.

Factors that predispose patients to acquire staphylococcal pneumonia include underlying pulmonary disease (e.g., COPD, carcinoma, cystic fibrosis), chronic illness (e.g., diabetes mellitus, renal failure), or viral infection (e.g., influenza, measles). *S. aureus*, including community-acquired MRSA, is second in frequency to *S. pneumoniae* as a cause of postinfluenza bacterial pneumonia. Postinfluenza CAP due to community-acquired MRSA is particularly virulent. Pneumonia caused by hematogenous spread of *Staphylococcus* usually occurs as a consequence of intravenous drug abuse or septic embolization in the setting of endocarditis or an infected vascular site.

Clinical Manifestations

In cases of acquired hematogenously, signs and symptoms related to the underlying endovascular infection predominate; if pulmonary infarction results from a septic embolism, pleuritic chest pain and hemoptysis are often noted. Otherwise, respiratory tract symptoms are mild or absent despite radiographic evidence of multiple pulmonary opacities. Severe manifestations, including high-grade fever, massive hemoptysis, neutropenia, pulmonary necrosis, and mortality, are more common among persons infected by *S. aureus* organisms that carry the PVL toxin.[143,144] These toxin-producing strains often demonstrate cavitary disease already at the time of presentation, initially causing confusion with lung abscess or hematogenous spread of *S. aureus*. Rapid progression of pulmonary opacities and massive pleural effusions is also common. The chest radiograph in patients with hematogenous staphylococcal pneumonia often reveals multiple, discrete, and often cavitary shadows with a predilection for the lower lobes (Fig. 32-6).[144a]

Microbiologic Diagnosis

Purulent sputum with multiple clusters of large gram-positive cocci, particularly if intracellular, is strongly suggestive of *S. aureus* pneumonia (Fig. 32-7). The organism is easily recovered from sputum cultures. The absence of MRSA, even after several doses of antibiotics, is strong evidence that MRSA is not the causative pathogen. Less than 25% of infections due to aspiration are associated with positive blood cultures. In contrast, staphylococcal pneumonia resulting from hematogenous spread usually yields multiple positive blood cultures. This is especially true when MRSA causes CAP. Pleural effusions are often watery rather than grossly purulent but are still high yield on culture. An important clue is a concomitant skin lesion, which is often positive on Gram stain.

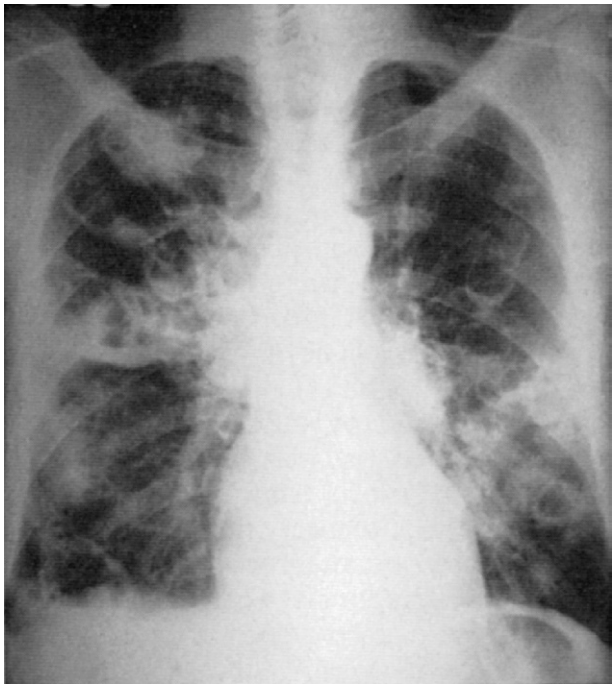

FIGURE 32-6 ■ Chest radiograph shows hematogenous staphylococcal pneumonia associated with bacterial endocarditis. The pneumonia is characterized by many cavities.

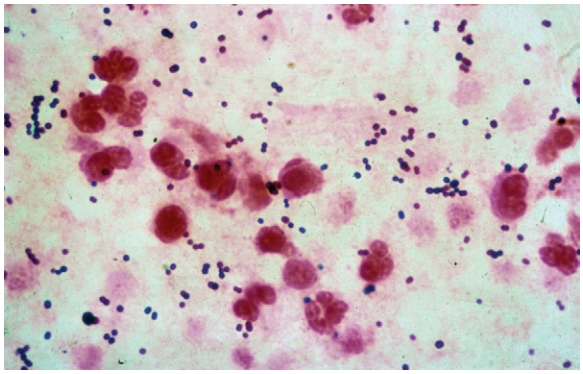

FIGURE 32-7 ■ Gram stain of sputum from a patient with staphylococcal pneumonia shows abundant large, round gram-positive cocci in clusters.

Clinical Course

Local complications of staphylococcal pneumonia include empyema and abscess formation. Metastatic infection to the central nervous system, bones, joints, skin, and kidneys occurs in association with hematogenous infection. Most of these manifestations are due to strains secreting PVL or one of the other large numbers of exotoxins produced by *S. aureus*. Even with appropriate antibiotics, the duration of fever and need for ICU

care is often prolonged. Cavities may prevent adequate local antibiotic levels, whereas unrecognized or incompletely drained empyema may prolong fever. Pleuroscopy or decortication is required in a large percentage of cases. The mortality of *S. aureus* CAP is generally higher than most etiologies, with the mortality in methicillin-sensitive strains about 30%. *S. aureus* CAP following influenza has a reported mortality of greater than 60%, even if not methicillin-resistant.[2]

Treatment

The treatment of choice for methicillin-susceptible *S. aureus* (MSSA) pneumonia is a penicillinase-resistant penicillin (e.g., oxacillin 8–12 g/day) or a first-generation cephalosporin. Duration of therapy of 7 to 10 days is adequate in uncomplicated cases, but 4 to 6 weeks of treatment has been suggested for patients with bacteremia or cavitation. In the penicillin-allergic patient, clindamycin or linezolid can be used.

Treatment is increasingly problematic because of the increasing incidence of CAP caused by both nosocomial MRSA and community-acquired MRSA strains.[144,145] Although outright resistance to vancomycin is still rare, the MIC has been shifting upward and MICs of greater than 1 μg/mL have been associated with frequent clinical failure. In higher-risk patients, such as those with VAP or with underlying renal insufficiency, linezolid may be a better choice for treatment. For community-acquired MRSA, vancomycin therapy alone has been associated with a significant failure rate,[141] most likely because it does not block exotoxin production.[146] Addition of clindamycin or use of linezolid has been associated with improved outcomes in small case series. Clindamycin monotherapy is probably not adequate because of the rapid development of resistance, especially with the high inoculum in cavitary disease. Although often sensitive to other antibiotics such as fluoroquinolones, TMP-SMX, and aminoglycosides, these antibiotics are unreliable in severe community-acquired MRSA cases.

Tricuspid valve débridement may be required in patients with recurrent septic pulmonary emboli. Infected vascular access lines and grafts must be removed.

Gram-Negative Bacillary Pneumonia

The term *gram-negative bacillary pneumonia* refers to infections caused by members of two groups, the Enterobacteriaceae and Pseudomonaceae and other aerobic, nonfermentative gram-negative bacilli. Infections caused by *Haemophilus*, *Legionella*, and anaerobes are usually excluded from this categorization.

Enterobacteriaceae

Epidemiology. Although more common in HAP, gram-negative bacilli also cause 5% to 10% of CAP.[7,9] CAP due to gram-negative bacilli is often severe and frequently requires ICU care. At least 40% to 45% of HAPs are caused by Enterobacteriaceae, such as *Escherichia*, *Klebsiella*, *Proteus*, *Morganella*, *Enterobacter*, *Providencia*, *Serratia*, *Salmonella*, and *Citrobacter*. Patients in an ICU, and especially those undergoing mechanical ventilation, have the highest risk of developing gram-negative bacillary pneumonia.

The Enterobacteriaceae normally colonize the digestive tract, and pneumonia usually results from aspiration of oropharyngeal flora. Although uncommon in healthy, nonhospitalized individuals, the prevalence of oropharyngeal colonization by gram-negative bacilli is greatly increased by serious comorbidities, hospitalization, antimicrobial use, and risk for aspiration, such as cerebrovascular accidents, seizures, or anesthesia.[9] Occasionally, use of contaminated home respiratory therapy equipment directly introduces gram-negative rods into the respiratory tract. Finally, Enterobacteriaceae pneumonia may result from hematogenous seeding from infection at other anatomic sites.

Among the Enterobacteriaceae, *Escherichia coli* is the single most frequent cause of CAP.[9] The classic cause of community-acquired gram-negative bacillary pneumonia, *K. pneumoniae* (Friedlander's pneumonia), causes fewer than 10% of CAPs, but more than 20% of nosocomial pneumonias. Alcohol abuse is the most common underlying condition, with some contribution from diabetes mellitus and chronic pulmonary disease, for community-acquired *K. pneumoniae* pneumonia because it colonizes the pharynx in up to 30% of ambulatory alcoholics.

Clinical Manifestations. The classic clinical features of Enterobacteriaceae pneumonia are abrupt onset of dyspnea, fever, chills, and cough in an older patient who is either hospitalized or chronically ill. In CAP due to *Klebsiella* pneumonia, pleuritic chest pain, hemoptysis, and bloody sputum (occasionally with a "currant jelly" appearance) may be noted. With *Serratia* pneumonia, sputum occasionally is pink or red as a result of bacterial pigments (so-called pseudohemoptysis). However, these classic findings are often absent, and the epidemiology and clinical manifestations of Enterobacteriaceae pneumonias are not sufficiently unique to distinguish these infections from pneumonias due to other causes.[9] Most laboratory abnormalities are nonspecific but neutropenia is an ominous sign. Chest radiographs often demonstrate lower lobe bronchopneumonia, which is often bilateral. A classic radiographic appearance of *Klebsiella* pneumonia is that of lobar consolidation with a predilection for the upper lobes (especially on the right) (Fig. 32-8) with a bulging or bowed fissure due to the heavy gelatinous exudate.

Microbiologic Diagnosis. Enterobacteriaceae pneumonia should be suspected when expectorated sputum is purulent and the Gram stain reveals large numbers of uniform-appearing gram-negative rods (Fig. 32-9). Sputum culture alone is notoriously nonspecific for Enterobacteriaceae in endotracheal intubated patients and is one of the major reasons for interest in quantitative culture diagnosis. Even in nonintubated patients, gram-negative bacilli found in the sputum may represent contamination by oropharyngeal contents rather than being the cause of the pneumonia. Polymicrobial infections involving gram-negative bacilli, anaerobes,

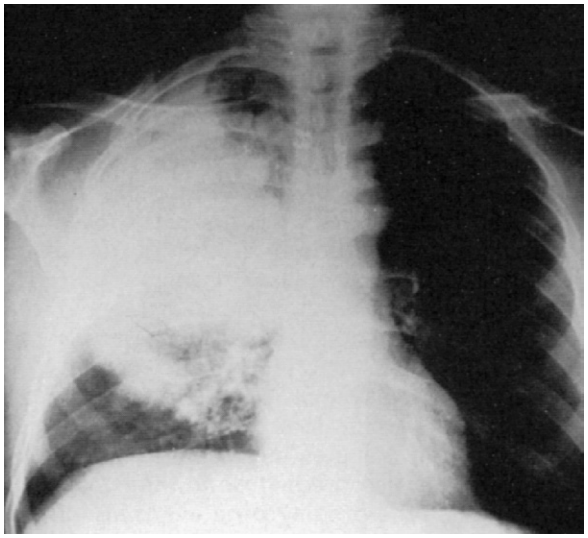

FIGURE 32-8 ■ Dense infiltration of the right upper lobe produced the radiographic appearance of a "bowed" fissure in this patient with *Klebsiella pneumoniae* pneumonia.

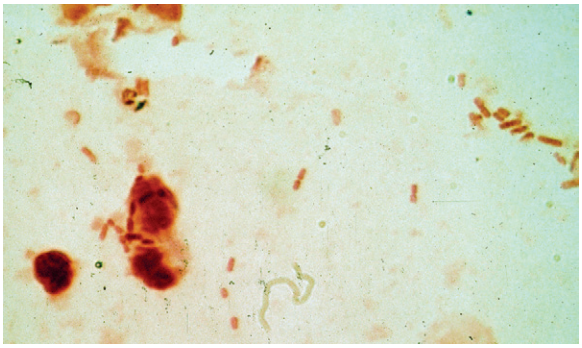

FIGURE 32-9 ■ Large gram-negative rods seen in the sputum of a patient with *K. pneumoniae* pneumonia.

streptococci, and *S. aureus* are common. Severe Enterobacteriaceae pneumonia is accompanied by bacteremia in 20% to 30% of patients.[9]

Clinical Course. Enterobacteriaceae pneumonia fatality rates are 25% to 50%.[9] Presence of bacteremia, neutropenia, and old age points to a poor prognosis. Respiratory failure is a common complication. Destruction of pulmonary alveolar septa may lead to cavitation and, at worst, lobar gangrene.

Treatment. Treatment of serious infections due to Enterobacteriaceae is complicated by the emergence of multidrug antimicrobial resistance. *Enterobacter* spp., *Citrobacter freundii*, *Serratia* spp., and *Providencia* spp. often possess type I chromosomal β-lactamases that mediate resistance to third-generation cephalosporins, cephamycins (e.g., cefoxitin) and β-lactam–β-lactamase combinations. These β-lactamases may be induced by prior use of third-generation cephalosporins and, to a lesser extent, piperacillin. In addition, *K. pneumoniae* and *E. coli* may harbor extended-spectrum β-lactamases that inactivate third- and fourth-generation cephalosporins (i.e., cefepime). Many of these isolates also carry determinants for fluoroquinolone and aminoglycoside resistance, and some are resistant to β-lactam–β-lactamase combinations. Emergence of extended-spectrum β-lactamases has been linked to the widespread use of ceftazidime. Only the carbapenems (imipenem and meropenem) and aminoglycosides (especially amikacin) are consistently active in the presence of both type I chromosomal β-lactamases and extended-spectrum β-lactamases.

Considering the range of antimicrobial resistance, initial therapy of life-threatening pneumonia thought to be due to Enterobacteriaceae must be carefully selected. In patients with serious infection, a two-drug regimen of an aminoglycoside with a broad-spectrum β-lactam or carbapenem is recommended for empirical treatment. Monotherapy may be reasonable for immunocompetent patients with mild to moderate diseases who are known or likely to be infected by susceptible strains of *Proteus*, *Morganella*, *K. pneumoniae*, or *E. coli*. The excellent absorption of oral fluoroquinolones allows these agents to be used as follow-up to initial intravenous therapy when active against the relevant pathogens. Recommendations for empirical therapy for HAP are provided in Table 32-13.

Pseudomonas aeruginosa *and Related Organisms*

Epidemiology. *P. aeruginosa* is an uncommon cause of CAP. Although one large Spanish study found that 7% of CAP was due to *P. aeruginosa*, most studies have found substantially lower rates.[9] The major risk factor for *Pseudomonas* CAP is structural lung disease, such as cystic fibrosis, bronchiectasis, and severe COPD (FEV_1 < 30%). Another common risk factor with these outpatient entities is frequent antibiotic use. Very rarely, such infections develop in normal hosts, perhaps related to aerosols of contaminated water.[7,9,23,49,147,148]

In contrast, *P. aeruginosa* is a leading cause of nosocomial pneumonia and a particularly frequent cause of VAP.[149] Prolonged endotracheal intubation and prior antibiotic therapy, especially with broad-spectrum antibiotics, are the primary risk factors for *Pseudomonas* VAP. Pneumonia may also occur following the administration of aerosols produced by contaminated respiratory therapy equipment. Other nonfermenters, such as *S. maltophilia* and *B. cepacia*, carry the same nosocomial risk factors, most commonly cause pneumonia in patients after prolonged broad-spectrum antibiotic therapy, and are associated with a high mortality rate. *B. cepacia* is also found in outpatients with cystic fibrosis.[150]

Clinical Manifestations. The clinical picture of pneumonia due to *P. aeruginosa* is largely indistinguishable from that of pneumonia due to one of the Enterobacteriaceae. Patients with bacteremic pneumonia appear much more toxic. Physical examination may reveal ecthyma gangrenosum, and leukopenia is common. The chest radiographic appearance is often that of bilateral patchy bronchopneumonia in the lower lobes. Because of its propensity to invade vascular tissue, the clinical and laboratory manifestations of *Pseudomonas*

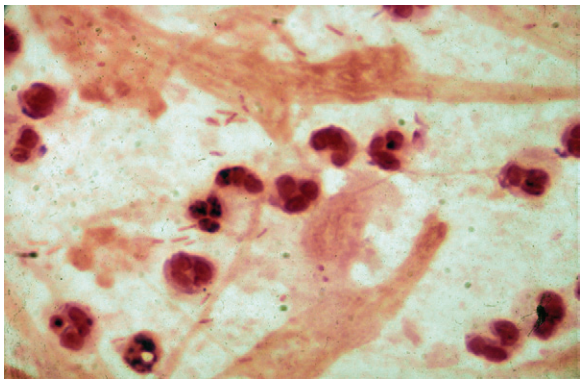

FIGURE 32-10 ■ Gram stain of sputum of *Pseudomonas* seen as slender gram-negative bacilli.

bacteremic pneumonia may resemble pulmonary thromboembolism. *Pseudomonas* HAP is the most common cause of cavitary pneumonia in hospitalized or immunocompromised patients, and empyema is not uncommon.

Microbiologic Diagnosis. Gram stain of sputum from patients with *Pseudomonas* pneumonia typically shows purulence and many slender, gram-negative bacilli (Fig. 32-10). Colonization of the oropharynx in hospitalized or debilitated patients complicates the Gram stain interpretation. In endotracheally intubated patients, absence of *Pseudomonas* on culture is strong evidence that it is not involved in the pneumonia. An invasive diagnostic procedure is especially useful in immunocompromised or neutropenic patients, in whom sputum may be minimal or nondiagnostic.[49] Blood cultures are often positive in neutropenic patients.

Clinical Course. Mortality from community-acquired *P. aeruginosa* pneumonia is up to 28%[9]; and in persons with VAP due to *P. aeruginosa*, mortality rates are 40% to 70%.[151] The prognosis in neutropenic patients with *P. aeruginosa* pneumonia is particularly poor.[152,152a]

Treatment. *P. aeruginosa* pneumonia should initially be treated with two potentially synergistic antimicrobial agents, such as an aminoglycoside and an antipseudomonal β-lactam antibiotic; this is especially true for bacteremic or neutropenic patients.[152] Amikacin is the most reliably active aminoglycoside. The β-lactam antibiotics, in order of probable activity against *P. aeruginosa*, are the carbapenems (imipenem and meropenem), the acylureidopenicillins (e.g., piperacillin), ceftazidime, and cefepime.[153] Although fluoroquinolones (particularly ciprofloxacin) possess good intrinsic activity against *P. aeruginosa*, resistance is common, making empirical monotherapy hazardous. Specific antibiotic choices can be changed when the in vitro susceptibility pattern is known. Emergence of resistance during the course of monotherapy is common.

S. maltophilia is inherently resistant to most standard antibiotics.[154] TMP-SMX is the most reliable agent, and fluoroquinolones or ticarcillin-clavulanate occasionally have activity.[152] Isolates of *S. maltophilia* may become resistant in the face of seemingly effective therapy. *B. cepacia* isolates may be susceptible to acylureidopenicillins, ceftazidime, TMP-SMX, fluoroquinolones, minocycline, and chloramphenicol. Resistance rates are higher in isolates from patients with cystic fibrosis.

Acinetobacter baumanii

Epidemiology. *A. baumanii*, a member of the family Achromobacteriaceae, is a gram-negative bacillary cause of pneumonia that may be either community- or hospital-acquired. In the United States, *Acinetobacter* CAP is most commonly seen in men who abuse alcohol. *Acinetobacter* has also been associated with CAP in hot climates, both dry[155] and humid.[156] Additional risk factors include old age, alcoholism, and severe medical comorbidities.[25] Nosocomial pneumonia is not uncommon and results from aspiration of endogenous flora or by exposure to contaminated respiratory equipment. In the United States, the overall risk of *Acinetobacter* pneumonia is 7.6/10,000 ventilator-days. Nosocomial infections caused by *Acinetobacter* show seasonal variation, peaking in late summer.

Clinical Manifestations. Patients with community-acquired *Acinetobacter* pneumonia often present with the acute onset of severe respiratory distress, tachypnea, fever, productive cough, and pleuritic pain.[25] Leukopenia, pleural effusions, and empyema are common. Nosocomial *Acinetobacter* pneumonia has a less dramatic presentation, similar to those of other hospital-acquired gram-negative bacillary pneumonias.[25]

Microbiologic Diagnosis. Examination of expectorated sputum, which is usually purulent, may reveal a predominance of paired gram-negative coccobacilli that resemble *Neisseria*, *Haemophilus*, and *Moraxella* spp. Bacteremia more often complicates community-acquired than nosocomial *Acinetobacter* pneumonia.

Clinical Course. The mortality rate of community-acquired *Acinetobacter* pneumonia is close to 50%.[25] Patients at greatest risk of death are those with leukopenia or empyema. The fatality rate for nosocomial *Acinetobacter* pneumonia is determined by the severity of underlying disease.

Treatment. Amikacin, tobramycin, ceftazidime, carbapenems, and doxycycline are active against most community isolates.[157] Nosocomial *Acinetobacter* spp. are resistant to most β-lactams and aminoglycosides and therefore are most reliably treated with carbapenems.[158] Some investigators have reported successful treatment of highly resistant isolates with ampicillin-sulbactam or colistin.[159,160] Unfortunately, resistance to β-lactam antimicrobials, carbapenems, aminoglycosides, and fluoroquinolones, and even polymyxin B and colistin[159] is increasingly common among nosocomial isolates.

Legionella

Epidemiology

L. pneumophila causes both epidemic and sporadic infections; both patterns may occur in the community or in hospitals. Outbreaks have been linked to contaminated potable water systems, ultrasonic mist devices,

whirlpool baths, air-conditioning condensates, and water-evaporative systems.[161] Recent travel is the most significant historical clue to the possibility of *Legionella* CAP. The route of transmission is probably through both inhalation of contaminated aerosols and aspiration. Sporadic cases of *L. pneumophila* pneumonia (50%–80% of which are due to serogroup 1) account for 2% to 6% of CAPs in immunocompetent hosts.[7] Importantly, *L. pneumophila* is one of the most common causes of severe CAP. Risk factors include immunosuppression, male gender, cigarette use, diabetes, cancer and end-stage renal disease, alcohol use, and exposure to contaminated drinking water. Infection by *L. pneumophila* is more common in some specific geographic regions, such as the Mediterranean or western Pennsylvania.

In addition to *L. pneumophila*, 40 other *Legionella* species have been identified. The species *L. micdadei*, *L. bozemanii*, *L. dumoffi*, *L. gormanii*, *L. longbeachae*, *L. jordanis*, and *L. wadsworthii* produce a pneumonic illness indistinguishable from that of *L. pneumophila*. Much less is known about the epidemiology of nonpneumophila *Legionella* infections, but they also appear to be water-related. Immunosuppressed patients are predominantly affected.

Clinical Manifestations

The incubation period for *Legionella* pneumonia is 2 to 10 days. Early complaints of lethargy, headache, fever, recurring rigors, anorexia, and myalgias are frequent. After several days, the cough becomes more pronounced; occasionally, watery or purulent sputum develops. Dyspnea becomes prominent in half of the cases, and one third of patients complain of pleuritic chest pain. Hemoptysis may occur. Among the myriad common extrapulmonary manifestations that may completely overshadow the respiratory complaints, gastrointestinal (watery diarrhea, nausea, vomiting, abdominal pain) and neurologic complaints (headache, confusion, obtundation, seizures, hallucinations) are particularly noteworthy.

Patients appear acutely ill. Temperatures reach 40.5°C in one third of patients, are typically sustained, and may be accompanied by relative bradycardia. Physical findings are usually limited to the chest. Crackles and rhonchi are prominent early but usually give way to impressive signs of consolidation. Pleural friction rubs are not unusual. Generalized abdominal tenderness, hepatomegaly, splenomegaly, cutaneous rash, nuchal rigidity, and focal neurologic deficits have all been described.

The sputum becomes more purulent as the disease progresses. Hyponatremia and hypophosphatemia are present in more than half of severe cases. Mild elevations of serum creatinine, creatine phosphokinase, and liver enzymes are also common, as are hematuria and proteinuria. Leukocytosis with a shift to the left is characteristic, but leukopenia and thrombocytopenia occur in severely ill patients. Cold agglutinins may be present.

Chest radiographic findings typically lag behind the early clinical illness. An alveolar pattern with lobar, nodular, or subsegmental involvement that spares the apices is most common (Fig. 32-11). Small pleural effusions are found in 50% of patients and may precede development of the parenchymal process. Frank cavitation rarely occurs.[47]

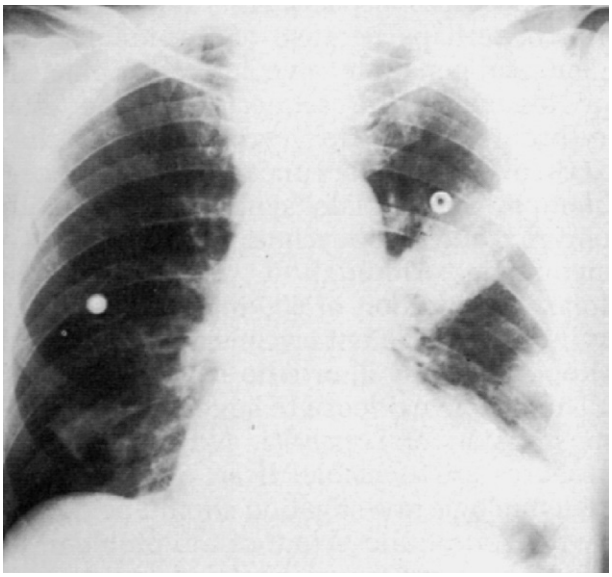

FIGURE 32-11 ■ Multilobar involvement occurring with *Legionella pneumophila* pneumonia.

Microbiologic Diagnosis

Legionella are obligatory aerobic, fastidious, gram-negative bacilli that do not stain well with the ordinary Gram stain or grow well on conventional media. *L. micdadei* and some other *Legionella* spp. may stain weakly acid-fast. Early in the infection, a Gram stain of sputum from patients with *Legionella* pneumonia discloses few or no polymorphonuclear leukocytes. Furthermore, despite use of appropriate media, the sensitivity of cultures of respiratory specimens in clinical practice is as low as 10%. The diagnosis of *L. pneumophila* infection often requires invasive procedures to obtain respiratory secretions, because at least 25% of patients with *Legionella* infection do not produce sputum.[57] Rarely, *Legionella* has been recovered from blood, pleural fluid, and other extrapulmonary sites. The *Legionella* urinary antigen test has a sensitivity of 60% to 80% and specificity of greater than 95% for *L. pneumophila* serogroup 1.[57] The sensitivity of the direct fluorescent antibody (DFA) assay for sputum ranges from 33% to 68%, with specificity greater than 95%,[57] but its use is hindered by the expertise required for interpretation and the multiplicity of *Legionella* spp. and serogroups that require specific antiserum. PCR-based assays for sputum have greater than 80% sensitivity and greater than 90% specificity.[57] A fourfold rise in antibody titer occurs in most patients within 8 weeks of the onset of illness.[57] Even in appropriate clinical circumstances, a single acute titer of 1:256 has a positive predictive value of only 15%.

Clinical Course

A dramatic clinical response to appropriate antibiotic therapy is usually observed within the first 48 hours. In contrast, radiographic findings may temporarily continue to progress despite observed clinical improvement and may take months to resolve.[47] Acute renal failure and oliguria, often independent of shock and myoglobinuria, are noted in approximately 10% of patients and dialysis may be transiently required. Many patients note lingering fatigue and weakness for months following *Legionella* pneumonia. The mortality of community-acquired cases is approximately 15%. Clinical outcome is related primarily to the host immunocompetence, presence of preexisting comorbidities, early initiation of appropriate therapy, and development of complications. The need for ventilatory support or dialysis is a grim determinant of a poor outcome.

Treatment

Azithromycin and fluoroquinolones are superior to erythromycin and clarithromycin. Although it should never be used alone, the addition of rifampin is advised for patients who are severely ill or immunocompromised, especially if the primary therapy is not with azithromycin or a fluoroquinolone.[4] Antibiotics should be continued for 10 to 21 days in immunocompetent patients to decrease the rate of relapse.[4]

Anaerobic Bacteria

Epidemiology

Mixed aerobic and anaerobic infection is usually a complication of macroaspiration of oropharyngeal contents. Rare causes include rupture of the esophagus and intra-abdominal abscesses. Underlying pulmonary conditions such as malignancy, bronchiectasis, and pulmonary infarction are present in 20% of patients who have an anaerobic lung infection. Although acute complications of macroaspiration are largely due to a chemical injury pneumonitis (Mendelson's syndrome) and/or infection by pathogenic aerobes in the oral flora, many of these episodes later result in the clinical emergence of mixed aerobic and anaerobic pneumonia.

Clinical Manifestations

Important clues to the diagnosis of anaerobic pleuropulmonary infection are predisposition to aspiration, the presence of periodontal disease, a subacute or chronic presentation, foul-smelling sputum or empyema fluid, involvement of dependent lung segments, and the presence of lung cavitation. These infections present as four different syndromes: pneumonitis, necrotizing pneumonia, lung abscess, and empyema (which almost always overlaps one of the other syndromes). These entities are probably different expressions of the same fundamental pathologic process and may be regarded as a continuum of changes.

Anaerobic pneumonitis is characterized by the acute onset of fever, cough (often dry), and pleuritic pain. The foul sputum and hemoptysis that are characteristic of anaerobic lung abscess are often absent in cases of uncomplicated pneumonitis. Physical findings may include evidence of chronic alcoholism, pharyngeal dysfunction, or periodontal disease. Crackles and decreased breath sounds are localized over the involved lung fields. Chest radiographs demonstrate bronchopneumonic shadows, but usually not lobar consolidation, in the aspiration-prone segments of the lung (e.g., posterior segment of the right upper lobe and superior segment of the right lower lobe).

Necrosis and suppuration of lung parenchyma characterize *anaerobic necrotizing pneumonia*. These patients tend to be toxic, with prominent complaints of fever, dyspnea, pleuritic pain, and productive cough. Sputum is often purulent. Most patients have tachycardia, tachypnea, and temperatures well above 39°C. Chest radiographs demonstrate dense segmental opacification with multiple small lucent areas of lung necrosis (<2 cm in diameter), usually without air-fluid levels (Fig. 32-12). Multilobar involvement may occur.

In the absence of appropriate treatment, anaerobic pneumonitis may evolve into a *primary lung abscess*. Patients commonly experience fatigue, low-grade fever, weight loss, and productive cough for several weeks after an episode of loss of consciousness and before seeking medical attention. Approximately half of the patients describe putrid sputum, and hemoptysis may occur. On examination, patients appear chronically ill, with temperatures up to 39°C. Breath sounds may be either diminished or amphoric. Anemia of chronic disease is frequent. In most patients, a single lung abscess of more than 2 cm in diameter is detected in a dependent lung segment on radiography (Fig. 32-13). The abscess may be multilocular; occasionally, multiple abscesses are located in different lung segments.

Empyema commonly complicates each of the preceding three syndromes. The incidence of anaerobes as a cause of community-acquired empyema is generally overestimated and is only present in 20%.[131] Most primary empyemas are due to *S. milleri/intermedius*. When anaerobic empyema occurs in the absence of parenchymal lung infection, the presence of a subphrenic or other intra-abdominal abscess is suggested.

Microbiologic Diagnosis

Distinguishing aspiration pneumonia (infection) from aspiration pneumonitis (Mendelson's syndrome), which represents chemical injury by acidic gastric contents,[162] is important. Gram stain of sputum or examination of a bronchoscopically obtained specimen from a patient with anaerobic infection reveals numerous polymorphonuclear leukocytes with an abundance of intracellular and extracellular bacteria. Typically, the microorganisms present a variety of Gram stain reactions and morphologies that may include pale-staining gram-negative rods with tapered ends (suggestive of *Fusobacterium nucleatum*), small, pale-staining gram-negative coccobacilli,

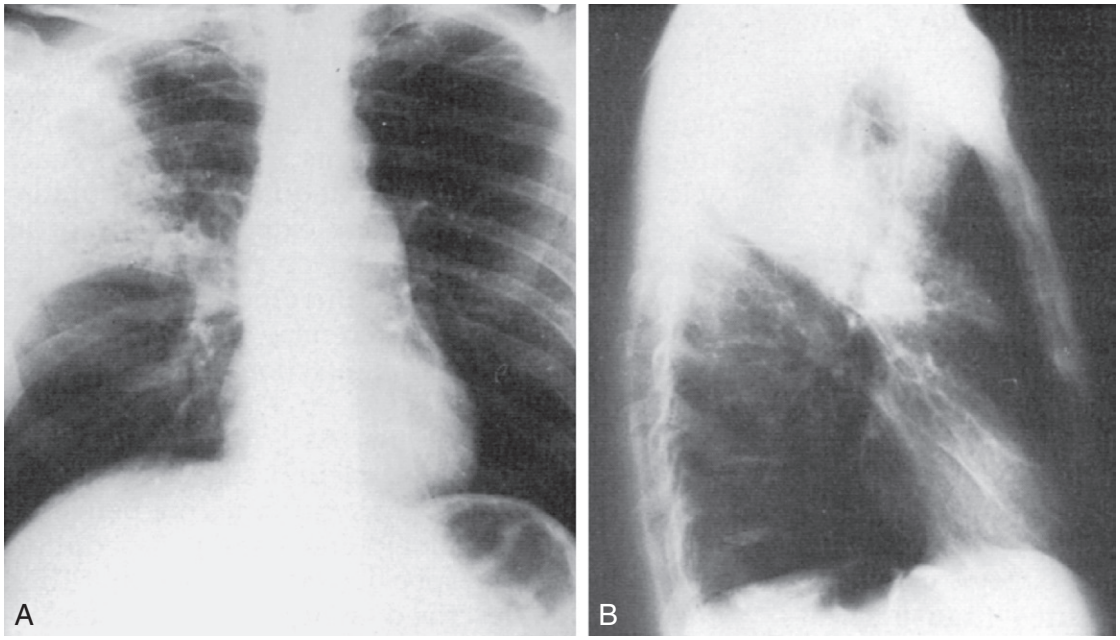

FIGURE 32-12 ■ Anaerobic necrotizing pneumonia following aspiration of oropharyngeal secretions. Multiple, small (<2 cm) radiolucencies are seen throughout the posterior segment of the right upper lobe on the posteroanterior (**A**) and lateral (**B**) projections.

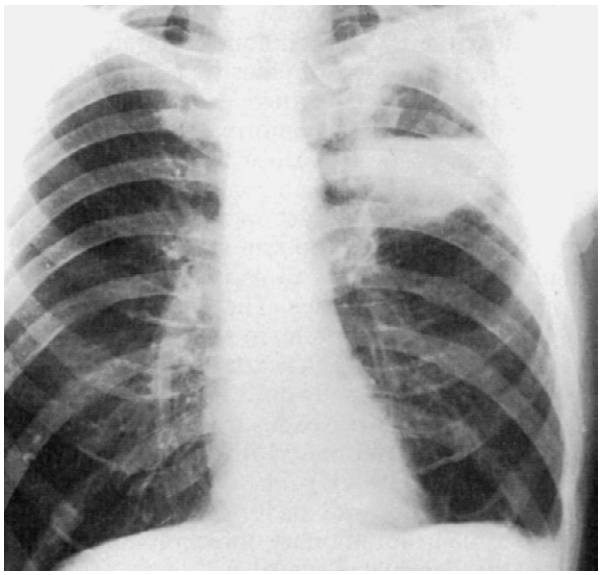

FIGURE 32-13 ■ A single parenchymal cavity with an air-fluid level typifies an anaerobic lung abscess. Most often, these lesions are located in the dependent, aspiration-prone lung segments (superior segment of the right lower lobe and left lower lobe and posterior segments of the upper lobes). This patient also has a small left empyema.

and chains of tiny gram-positive cocci. Because the indigenous flora of the upper respiratory tract consists predominantly of anaerobic bacteria, cultures of expectorated sputum are not appropriate for diagnosis of anaerobic infections. With careful attention to technique, recovery on average of 3.2 bacterial isolates/case of aerobic/anaerobic pneumonia, of which 80% are anaerobes, is possible. The most commonly encountered anaerobes in pleuropulmonary infections include *F. nucleatum*, *Prevotella*, *Porphymonas*, *Peptostreptococcus*, and microaerophilic *Streptococcus*. The major aerobic and facultative organisms recovered in conjunction with anaerobes are *Streptococcus* spp. Although *S. aureus*, various enteric gram-negative bacilli, and *Pseudomonas* may also be isolated, their significance is often questionable. Use of molecular techniques can often identify anaerobes in culture negative cases.[131]

Clinical Course

Uncomplicated pneumonitis generally responds promptly to appropriate antibiotics. Fever should resolve within a few days, and the chest radiograph normalizes within 3 weeks. Fever resolves more slowly in the other types of anaerobic pleuropulmonary infection. Closure of abscess cavities and resorbtion of empyema collections may require many months. Fatality rates are low in adequately treated patients, except those with necrotizing pneumonia, in which mortality approaches 20%.[131] Chronic lung abscess may be complicated by brain abscess, other metastatic abscess, secondary amyloidosis, life-threatening hemoptysis, or bronchopleural fistula. Inadequately treated acute empyema may result in chronic empyema or *empyema necessitans* (rupture through the chest wall).

Treatment

Emergence of β-lactamase–mediated resistance indicates that penicillin G and ampicillin are no longer the drugs of choice for treatment of patients with serious anaerobic pleuropulmonary infection. Such resistance occurs not only among *Bacteroides* spp. but also among

Prevotella and even some *F. nucleatum* strains. Empirical treatment for serious anaerobic pleuropulmonary infection therefore requires the use of a β-lactam–β-lactamase inhibitor (e.g., ampicillin-sulbactam, ticarcillin-clavulanate, or piperacillin-tazobactam) or metronidazole combined with either penicillin or ampicillin. Because of the very frequent presence of aerobes, metronidazole monotherapy is not adequate for suspected anaerobic pneumonia. For mild to moderate disease, clindamycin or an antianaerobic cephalosporin can suffice, although occasional pulmonary isolates are resistant to one or more of these agents. For example, *Eikenella corrodens* is resistant to clindamycin. Carbapenem monotherapy is also effective but generally provides unnecessarily broad coverage. When complete identification and susceptibility testing of anaerobes are available, therapy can be specifically tailored. Ten days of total treatment is usually adequate for uncomplicated pneumonitis. Necrotizing pneumonia, abscess, and empyema require prolonged parenteral therapy to achieve clinical improvement; and extended courses of oral therapy, often requiring several months, may be required for cure.

Standard drainage of empyema fluid is required. Percutaneous drainage or surgical resection of anaerobic lung abscess is almost never indicated. Bronchoscopy is useful for excluding an underlying malignancy in patients without other risk factors for development of lung abscess, such as edentulous patients.

OTHER LESS COMMON CAUSES OF PNEUMONIA

A variety of less common pathogens can cause pneumonia. These agents are usually suspected by either unique risk factors or presentations or are diagnosed by surprising results on culture. The unique aspects of these pneumonia pathogens are discussed.

Actinomycoses

A variety of species within the two genera of the Actinomycetaceae family (*Actinomyces* and *Propionibacterium*), which normally are harmless commensals in the oropharynx, can cause subacute to chronic pulmonary infections that are virtually indistinguishable. Pulmonary actinomycosis infection follows aspiration of oropharyngeal material. Periodontitis and other dental disease clearly increase the risk of cervicofacial invasion and likely also for pneumonia. Most patients are 30 to 60 years old. Cases in men outnumber those in women by four to one. Bronchiectasis and COPD are common underlying conditions.

Patients with actinomycosis appear chronically ill but not toxic. Constitutional symptoms, including fatigue, weight loss, and low-grade fever, may be present for weeks to months prior to diagnosis and often mimic the presentation of chronic fungal infection, tuberculosis, and malignancy. Fever may be absent. Most patients gradually develop productive cough and pleuritic chest pain, but hemoptysis and putrid sputum are unusual.

The classic physical finding of actinomycoses is a sinus tract on the chest with discharge of characteristic "sulfur granule" –containing pus. These distinctive 2 mm, gritty, yellow granules consist of masses of intertwined filaments of *Actinomyces* or *Propionibacterium* that have been mineralized by host-derived calcium phosphate. Cervicofacial involvement is rarely observed in patients with thoracic involvement. Radiographic findings most commonly demonstrate fibrotic changes confined to a single lobe with one or more small cavitary lesions. In advanced cases, the findings are more distinctive, with penetration through the chest wall, destruction of adjacent bone tissue, or direct extension through an interlobar fissure. Laboratory abnormalities are often limited to those of anemia of chronic disease.

Members of the *Actinomyces* and *Propionibacterium* genera are gram-positive, diphtheroidal or filamentous, branching bacilli. Most strains grow best in anaerobic conditions, although some also grow aerobically. In patients with a cutaneous chest wall sinus, the best means of establishing a diagnosis of actinomycosis is the sulfur granules that, when crushed and stained, form a characteristic pattern of gram-positive, branching filaments (Fig. 32-14). The organism can usually be recovered from culture of this material, provided anaerobic conditions are maintained for the specimen. Diagnosis of an actinomycotic parenchymal lesion is more difficult. Sulfur granules are rarely present in sputum, and recovery of the organism in sputum cultures is unreliable because

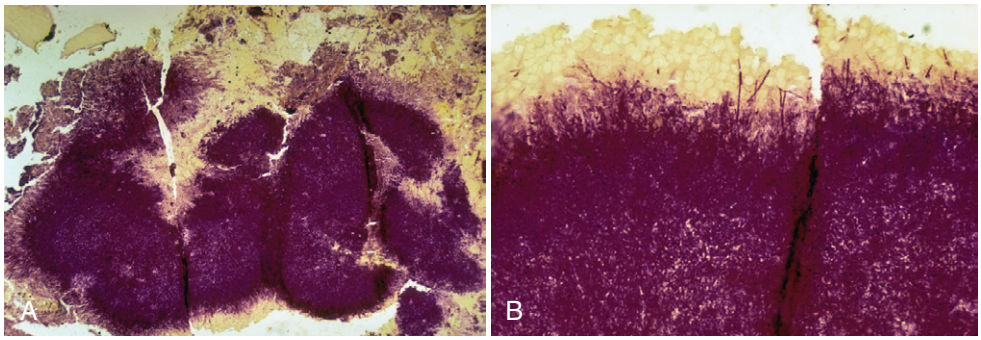

FIGURE 32-14 ■ Gram stain of an actinomycotic sulfur granule. **A,** ×100, **B,** ×400.

colonization without invasion may occur along any mucosal surface. Definitive diagnosis depends on demonstrating the characteristic histopathology and culture from a sterile body fluid or tissue biopsy. It is common to identify other organisms, including *Haemophilus (Actinobacillus) actinomycetemcomitans* and *Prevotella*, in addition to *Actinomyces* or *Propionibacterium*.

Complications of pulmonary actinomycosis relate to its ability to invade across anatomic barriers. Pleural empyema, cutaneous thoracic sinuses, mediastinitis, pericarditis, and vertebral osteomyelitis are not infrequent. Metastatic infection, including brain, skin, and bone, occurs more commonly with pulmonary actinomycosis than with other variants (e.g., cervicofacial disease) but is still unusual. With adequate therapy, death from actinomycosis is rare.

Prolonged antibiotic treatment is the key to curing actinomycosis. *Actinomyces* are universally susceptible to penicillin G, which should be given in intravenous doses of 12 to 20 million units daily for 4 to 6 weeks. Ceftriaxone has also been successfully used to provide prolonged parenteral therapy. This should be followed by at least 6 months of oral penicillin V or ampicillin. In cases with polymicrobial infection, the presence of other organisms may require modification of therapy. If β-lactamase–producing anaerobes are present, treatment choices as described for anaerobic pneumonia are recommended. On occasion, clindamycin fails because of concomitant infection by *H. actinomycetemcomitans*.

Chlamydophila psittaci (Formerly *Chlamydia psittaci*)—Psittacosis

Exposure to birds is the classic risk factor for psitticosis. Multiple species harbor the organism, but most cases have been acquired from canaries, parakeets, cockatiels, parrots, and pigeons. Although infected birds are typically ill, asymptomatic fecal carriage is well reported. *C. psittaci* can be detected in blood, tissues, feathers, and feces of infected birds. The organism is acquired by humans via inhalation of contaminated bird excreta. Although approximately 50% of cases are reported in owners of infected pet birds, 25% of sporadic cases and occasional outbreaks occur without a history of bird exposure. Psittacosis is also an occupational hazard in poultry business workers, especially those exposed to turkeys.

The symptoms of psittacosis may develop abruptly, with high fever and chills, or they may evolve slowly. Headache, arthralgia, and painful myalgia (especially in the head and neck) are prominent features. A severe cough develops that may be either dry and hacking or productive of mucoid sputum. Chest pain and dyspnea are present with extensive pulmonary involvement. Temperatures are 38°C to 40°C and are frequently accompanied by relative bradycardia. Splenomegaly or occasionally a pale macular rash (Horder's spots) can be seen. Laboratory findings are nonspecific, except occasionally for findings consistent with granulomatous hepatitis. The chest radiograph shows unilateral or bilateral bronchopneumonia in the lower lobes, often seeming to radiate out from the hilar areas.

C. psittaci is an obligate intracellular parasite that does not stain by the Gram method but can be seen as large intracytoplasmic inclusions in infected cells when stained with Giemsa stain. Cultivation of the organism, which requires tissue culture for growth, poses a threat to laboratory personnel and should be performed only in specialized facilities. The diagnosis of psittacosis is best made by demonstrating a fourfold rise in complement-fixing antibodies in paired acute and convalescent serum samples. A single titer of 1:16 or greater can be considered presumptive evidence of infection in a patient with compatible illness. Cross reaction of the antibody with *C. burnetii* or *Brucella* may occur.

The case-fatality rate is about 1% with antimicrobial therapy. Unusual complications include respiratory failure, encephalitis, hepatitis, disseminated intravascular coagulation, renal failure, and endocarditis. Treatment with doxycycline is recommended, but the clinical response may be slow. Because of the risk of relapse, therapy should be given for a minimum of 2 weeks after fever has resolved. Chloramphenicol, erythromycin, azithromycin, and moxifloxacin have shown in vitro activity.

Coxiella burnetti—Q Fever

Q fever occurs worldwide and is a particular public health problem in farming communities in Europe, North America, and Australia. *C. burnetii* asymptomatically infects a wide variety of domestic and wild animals as well as insects. The organism is highly resistant to drying and maintains infectivity after months of dormancy in contaminated soil. Transmission to humans occurs primarily via exposure to the urine, feces, placenta, or unpasteurized milk of an infected animal: cows, sheep, and goats are most common. Outbreaks have occurred in tanneries, dairies, and wool-rendering plants, among laboratory personnel, and in household members exposed to an infected cat or dog during parturition.[163,164]

Following an incubation period of 2 to 4 weeks, 10% to 20% of infected persons develop an atypical pneumonia syndrome.[163] On examination, high fever (≥40°C), relative bradycardia, conjunctivitis, hepatosplenomegaly, and chest crackles may be detected. Unlike other rickettsial infections, a rash is typically absent.[164] Laboratory studies often show a normal white blood cell count, decreased platelet count, and liver function tests suggestive of granulomatous hepatitis.[163] Chest radiography often reveals segmental opacities.

C. burnetii is a small, obligate intracellular bacterium that cannot be cultured on standard media or visualized with the Gram stain. Because of the high infectivity of the organism, cultures should be attempted only by experienced personnel in Biosafety Level 3 laboratory facilities. Diagnosis usually relies on demonstrating a fourfold rise in specific antibody titer from acute to convalescent serum samples or on pathologic findings, which may be augmented by immunohistochemical detection techniques or DNA amplification.

Although patients may be acutely ill on presentation, the disease is rarely fatal and generally runs its course in 1 to 2 weeks.[163] Some patients, however, particularly the elderly, have a very prolonged illness. Tetracyclines, especially doxycycline, are first-line therapy for Q fever. Quinolones have excellent in vitro activity and may be advantageous in the treatment of meningoencephalitis.[164] No special isolation procedures are recommended.

Nocardioisis

Although several other species (e.g., *Nocardia brasiliensis*) have also been associated with human infection, *N. asteroides* is the etiologic agent in over 80% of pulmonary or disseminated cases. The organism is widespread in nature, primarily in soil. The respiratory tract, skin, and gastrointestinal tract are portals of infection. Dysfunction of cell-mediated immunity and, to a lesser extent, immunoglobulin defects are predisposing factors. Thus, the rate of disease appearance is increased in patients who have a lymphoreticular malignancy, Cushing's disease, or acquired immunodeficiency syndrome (AIDS) or who are receiving immunosuppressive medications. Most reported cases recently have occurred in transplant patients, with the greatest risk in lung or heart transplant recipients and stem cell transplants. Persons with pulmonary alveolar proteinosis are also at increased risk. Nonetheless, approximately half of the patients who develop nocardiosis have no known underlying medical disorder.

Although nocardiosis and actinomycosis are clinically similar infections of the lower respiratory tract, nocardiosis can be distinguished by a lesser proclivity for sinus tract formation and a greater tendency for hematogenous dissemination in both healthy and impaired hosts. Dissemination occurs and may involve almost every organ system, but the central nervous system and skin are most commonly involved.[165] Many patients with pulmonary nocardiosis have low-grade fever, fatigue, weight loss, productive cough, and pleuritic chest pain for weeks prior to seeking medical attention. However, some immunosuppressed patients present with acute, fulminant pneumonia. Physical examination is nonspecific unless sites of dissemination are obvious. Neurologic signs of a mass lesion may be present. Cutaneous dissemination appears as multiple subcutaneous abscesses with or without sinus tracts. Chest radiographs commonly demonstrate localized bronchopneumonia or lobar consolidation, but solitary, multiple, or miliary nodules, abscesses, and pleural effusion also occur.

Nocardia spp. are gram-positive bacilli that appear as beaded, branching filaments. Unlike the anaerobic Actinomycetaceae, *Nocardia* requires aerobic growth conditions and is usually weakly acid-fast when stained by the modified Ziehl-Neelsen method with 1.0% sulfuric acid as the decolorizing agent (Fig. 32-15). Although the organism can be cultivated on conventional blood agar or Sabouraud medium, growth may not be apparent for 3 to 21 days. Although the organism occasionally colonizes the upper respiratory tract, recovery of *Nocardia* from a culture of sputum or invasively obtained material is highly predictive of the diagnosis. Extension of the pulmonary infection to the pleural cavity, with or without chest wall involvement, occurs in 10% of patients.

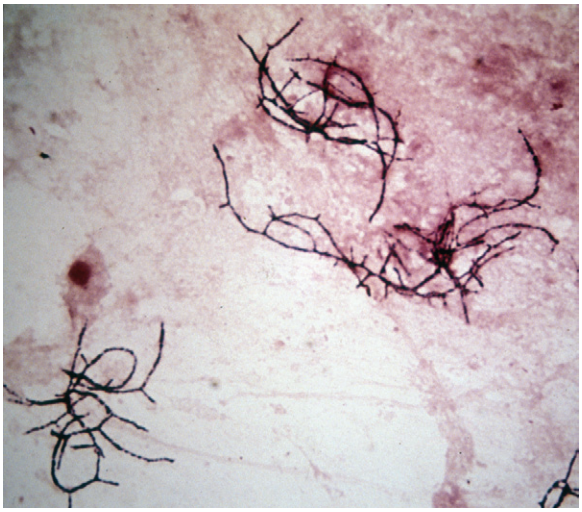

FIGURE 32-15 ■ Modified acid-fast stain of sputum containing *Nocardia asteroides* shows filamentous branching organisms.

Mortality approaches 50% in those with central nervous system lesions but is less than 10% in those with only pulmonary disease.[165] Because of in vitro synergy, TMP-SMX has become the standard treatment.[165] In case of sulfa allergy or a resistant organism, minocycline, amikacin, cefotaxime, imipenem, or linezolid may be useful, but choices should always be guided by the results of susceptibility testing.[165,166] Therapy must be prolonged to prevent relapses. Adequate drainage or excision of abscesses and empyema is a crucial adjunct to antimicrobial therapy.

Melioidosis (*Burkholderia pseudomallei*)

In the most highly endemic areas, melioidosis may be the most common cause of severe CAP.[167] *B. pseudomallei* is found in soil, vegetation, and water throughout tropical regions between latitudes 20°N and 20°S, especially in Southeast Asia.[28,168] In the indigenous population of northern Australia, the yearly incidence is 25 cases/100,000.[169] Acquisition of the organism is through cutaneous inoculation or inhalation.[28] The incubation period of acute pneumonia is 1 to 21 days.[168] The infection may remain latent for months to years.[168] Risk factors for clinical disease include diabetes, alcohol-related problems, and renal disease. Meteorologic conditions, such as typhoons or episodic heavy rain, may increase the risk of acute fulminant pneumonia.

Melioidosis can produce either acute fulminant pneumonia or indolent, cavitary disease. Clinical manifestations of acute melioidosis include high fever, prostration, dyspnea, pleuritic chest pain, purulent sputum, and hemoptysis. Cellulitis and lymphangitis often occur at the site of cutaneous inoculation. Concomitant bacteremia is common.[167] The chest radiograph typically shows

diffuse miliary nodules, which may expand and cavitate. Subacute or chronic *B. pseudomallei* pneumonia is milder and often occurs after a period of latency. Patients may be entirely asymptomatic (e.g., disease demonstrated by radiograph only), or they may present with an illness that is clinically and radiographically indistinguishable from chronic pulmonary tuberculosis.

B. pseudomallei is an aerobic, gram-negative bacillus that grows readily on routine culture media. Specific IgM to *B. pseudomallei* can be demonstrated by indirect immunofluorescence in the serum of patients who have active infection. Fourfold rises in hemagglutination and complement fixation antibodies are other serologic aids for diagnosing melioidosis. Low-titer hemagglutinating antibodies may be found in persons with prior exposure to soil and water in endemic areas. Without evidence of active infection, such persons do not warrant therapy.

Despite improvements in recognition and treatment, melioidosis is still associated with high morbidity and mortality.[167] *B. pseudomallei* is usually susceptible to carbenems, ceftazidime, piperacillin-tazobactam, tetracyclines, sulfonamides, chloramphenicol, and TMP-SMX. Optimal treatment for disseminated or life-threatening melioidosis requires initial intensive therapy with a carbapenem or ceftazidime followed by 3 months of TMP-SMX.[28,167]

Rhodococcus equi

Rhodococcus equi may cause lung abscess and pneumonia. Most cases occur in the setting of impaired cell-mediated immunity (e.g., high doses of corticosteroids, HIV infection, solid organ transplantation),[170] and a history of animal exposure is common. Illness develops subacutely, mimicking mycobacterial or fungal infection. Bacteremia can occur despite the intracellular location. Chest radiographs often show nodules that gradually cavitate.

The organism is a gram-positive bacillus. It may stain weakly acid-fast but is much smaller than mycobacteria. The most effective regimens appear to be vancomycin or erythromycin. The addition of rifampin may be useful. Development of resistance has occurred with β-lactam antibiotics. Prolonged therapy is necessary to prevent relapse.

Anthrax (*Bacillus anthracis*)

Although *B. anthracis* is detected in many agricultural regions, anthrax is a rare infection in the developed world. The spores are the transmissible agent of infection. Spores reside in soil, water, and vegetation and primarily infect large herbivorous animals (e.g., cows, sheep, and horses). Humans are often infected via contact with contaminated animals or animal products (e.g., animal hides and wools).[33] Ominously, anthrax has become a proven agent of bioterrorism.[171–173]

The manifestations of anthrax are cutaneous, gastrointestinal, and inhalational (woolsorters' disease). The inhalational form is the most severe. Disease follows inhalation and germination of *B. anthracis* spores and production of toxin. Clinical illness begins insidiously with fever, malaise, nonproductive cough, and precordial pain. This stage is followed by rapid pulmonary deterioration with dyspnea, stridor, chest pain, tachypnea, cyanosis, nausea, vomiting, and drenching night sweats. Diffuse edema of the neck and anterior chest may be evident. Meningitis is a common complication.

Radiographically, the lung parenchyma is initially clear. A widened mediastinum and bilateral pleural effusions are clues to the diagnosis of inhalational anthrax. Mediastinal widening occurs in 100% of inhalational anthrax cases but only 8% of control CAP patients.[174] CT scans of the chest may be required to define these characteristics.[33] Later findings include vascular engorgement and lung parenchymal opacities, although usually not a typical bronchopneumonia.

B. anthracis is a large, facultative, gram-positive rod that forms centrally located spores. The organism grows readily on routine culture media and can be rapidly recovered from cultures of blood, sputum, and pleural fluid. In advanced disease, the organism can be demonstrated by Gram stain of peripheral blood.[33] Anthrax can be detected in nasal swabs of persons exposed to anthrax spores. However, the predictive value of this test for diagnosing clinical disease is ill-defined.[33]

Treatment recommendations for inhalational anthrax may be affected by resistance patterns and the potential need to treat mass casualties. Current recommendations for inhalational anthrax call for initial treatment with ciprofloxacin plus one or two additional antibiotics that have in vitro activity, such as clindamycin, vancomycin, imipenem, meropenem, chloramphenicol, penicillin, ampicillin, rifampin, and clarithromycin.[175] If the recovered isolate is susceptible, therapy can be changed from the fluoroquinolone to maximum doses of penicillin G or doxycycline. Intravenous therapy may be converted to oral therapy once the patient's condition stabilizes for 60 days total. Although the reported mortality rate has been as high as 90%, 6 of 11 patients with inhalational anthrax survived during the 2001 anthrax attacks in the United States.[33]

Tularemia (*Francisella tularensis*)

Although *F. tularensis* has been recovered from numerous insects and species of wild or domestic mammals throughout the temperate zones of the Northern Hemisphere, fewer than 200 cases of tularemia/yr are reported in the United States.[34] Humans acquire infection following direct contact with tissues of an infected animal (as when skinning or eating an infected animal), through the bite of an infected tick or deerfly, or by inhalation of contaminated aerosols.[27,34,176] Persons who engage in landscaping or agricultural activities that generate aerosols in highly endemic areas are at particular risk of developing pneumonic tularaemia.[27] Because of the efficiency of aerosol transmission, *F. tularensis* is regarded as a potential biowarfare weapon.[34]

Pneumonia occurs as a consequence of inhalation of contaminated aerosols or as a complication of bacteremia. Clinical manifestations of inhalational pneumonia

typically begin abruptly with fever, chills, malaise, and headache. Shortly thereafter, dyspnea, cough, and chest pain develop.[34] Chest radiographs are usually normal at the onset of systemic symptoms (i.e., 3 to 5 days following aerosol exposure) but ultimately show diffuse bronchopneumonia, often with hilar adenopathy.[34] Pleural effusion is relatively common and may occur without parenchymal involvement.[34]

F. tularensis is a fastidious, pleomorphic, gram-negative bacillus that is rarely visualized on Gram stain of sputum and requires specially enriched media for optimal recovery by culture. Because of the hazardous nature of the organism, culture is best undertaken by reference laboratories. The organism can also be rapidly identified in tissues, secretions, and exudates by use of immunohistochemical techniques.[34] Retrospective diagnosis can be accomplished by demonstrating a fourfold rise in agglutinating titers. A single titer of 1:160 or greater is compatible with past or current infection.

Mortality can be as high as 60% if pneumonic tularemia is not suspected and treated appropriately. Although gentamicin has been used successfully, streptomycin remains the preferred therapy.[34] Ciprofloxacin is an acceptable alternative agent, but doxycycline and chloramphenicol are associated with higher relapse rates and require a longer duration of therapy.[34] Ceftriaxone is unsatisfactory despite its demonstrated in vitro activity. In the event of known aerosol exposure to *F. tularensis*, antimicrobial prophylaxis with doxycycline or ciprofloxacin for 14 days is recommended.[34]

Plague (*Yersinia pestis*)

Zoonotic plague is typically associated with ground squirrels, rabbits, prairie dogs, rats, and other small ground animals. Rodent fleas are responsible for transmission of the organism between animal hosts. Humans become infected when bitten by an infected rodent flea, by handling an infected animal carcass, or less frequently by inhaling an aerosol from a human or animal with pulmonary involvement. Most cases of plague in the United States occur in rural regions of New Mexico, Arizona, and California.[26] Because of the disease severity and potential for aerosol transmission, *Y. pestis* is regarded as a potential biowarfare weapon.[32]

Three clinical forms of infection exist: bubonic, septicemic, and pneumonic. Although the latter presents as a primary pneumonia, pulmonary involvement may also complicate bubonic and septicemic infections. Plague pneumonia may develop 2 to 7 days after the initial exposure. Fever and toxicity occur early, followed by chest pain, productive cough, dyspnea, and hemoptysis. The hemoptysis causes confusion with the hantavirus pulmonary syndrome, which overlaps with plague geographically in the United States. If pulmonary disease complicates bubonic plague, painful adenopathy is also noted. In the septicemic form, the patient may show only signs of septic shock in association with pneumonia. Chest radiographs commonly reveal bilateral lower lobe alveolar opacities, but nodules, adenopathy, and pleural effusions have been described.

Y. pestis is a short, nonmotile, gram-negative rod. Most patients with plague have positive blood cultures. In addition, the organism can be recovered from sputum and lymph node aspirates by routine bacteriologic techniques. Fluorescent antibody staining of sputum and tissues facilitates the rapid diagnosis of plague but is available only in specialized laboratories.

Because of the potential for person-to-person transmission, all patients with plague pneumonia should be isolated. Recommended treatment consists of gentamicin or doxycycline.[32,177] Alternative treatments include fluoroquinolones, streptomycin, or chloramphenicol. For all regimens, the duration of treatment should be at least 10 days.

Moraxella catarrhalis

M. catarrhalis causes pneumonia, acute exacerbations of COPD, otitis media, and maxillary sinusitis.[178] Pneumonia typically occurs in patients with underlying COPD, although alcoholism, malnutrition, increased age, congestive heart failure, and malignancy are also frequent accompaniments.[178]

Moraxella pneumonia is heralded by several days of dyspnea and cough before pneumonia is diagnosed. Pleuritic chest pain and blood-tinged sputum may occur. High fever, toxic states, and empyema are uncommon.[178] Chest radiographs show bronchopneumonia or lobar pneumonia that usually involves a single lobe. Pleural effusion and cavitation may occur.

Because *M. catarrhalis* may be a part of the normal upper respiratory tract flora, only adequately screened sputum samples provide useful diagnostic information. A purulent specimen that contains many intracellular Gram-negative diplococci and yields heavy growth of *M. catarrhalis* is highly suggestive of true pneumonia. Blood cultures are rarely positive.[178]

The mortality of *M. catarrhalis* is approximately 10% and is attributable primarily to exacerbations of severe underlying pulmonary disease.[178] Effective agents include TMP-SMX or a cephalosporin, macrolide, tetracycline, quinolone, or β-lactam–β-lactamase inhibitor combination. Virtually all isolates are resistant to penicillin and ampicillin because of β-lactamase production.

Neisseria meningitidis

Neisseria meningitidis pneumonia is often a surprise culture diagnosis because clinical manifestations of meningococcal pneumonia resemble those of pneumococcal pneumonia or an acute exacerbation of COPD. The estimated incidence of sporadic primary meningococcal pneumonia is 0.4 cases/100,000 adults/yr; pneumonia also complicates 5% to 15% of invasive meningococcal infections.[179] Rates of asymptomatic carriage vary according to the season and are increased under conditions of crowding.[179] Person-to-person transmission occurs largely through droplet aerosols. Nosocomial clusters of meningococcal pneumonia are well described.

The Gram stain appearance of *Neisseria* in sputum is similar to that of *Moraxella* and *Acinetobacter*. Rates of

isolation of the organism from blood, cerebrospinal fluid, and pleural fluid from patients with meningococcal pneumonia are highly variable.

Aqueous penicillin G for 10 days, in daily doses of 4 to 6 million units intravenously, is adequate therapy for isolated pneumonia. Coexistence of septicemia or meningitis warrants increasing the dose to 18 to 24 million units/day. Chloramphenicol remains a useful drug in developing countries.[179] Isolates with decreased susceptibility to penicillin are not yet a significant problem in the United States.[180]

Because meningococci can be transmitted from patients with pneumonia to susceptible contacts, respiratory droplet isolation should be implemented during the initial days of treatment. Chemoprophylaxis with rifampin is advised for household and other intimate contacts of the patient. Alternative regimens for prophylaxis include ceftriaxone or ciprofloxacin. These prophylaxis recommendations are based on those for meningitis; however, the epidemiology of meningococcal infections suggests that a similar benefit can be derived by prophylaxis of pneumonia contacts.

Pasteurella multocida

Pasteurella multocida is part of the normal oral flora of many domestic and wild mammals. Although skin and soft tissue infections following a cat or dog bite are more common manifestations of human disease, sporadic cases of pneumonia, lung abscess, and empyema occur in patients with chronic respiratory diseases, including COPD, carcinoma, and bronchiectasis. Most patients recall prior exposure to animals.

Pasteurella pneumonia is indistinguishable from other etiologies of CAP, although empyema may occur more frequently with it. The organism is a small, gram-negative coccobacillus that cannot be distinguished from other gram-negative rods by Gram stain of sputum. Identification of the organism by sputum culture is easily accomplished. Blood and pleural fluid may also yield the organism.

The treatment of choice for *P. multocida* pneumonia is penicillin G, 4 to 12 million units daily for 10 to 14 days. Tetracycline, amoxicillin-clavulanate, second- and third-generation cephalosporins, TMP-SMX, fluoroquinolones, and chloramphenicol are also active.

LUNG ABSCESS

Lung abscesses are pus-containing necrotic lesions of the lung parenchyma that often contain an air-fluid level. A similar process with multiple small cavities less than 2 cm in diameter has been designated necrotizing pneumonia by some clinicians. Lung abscess may be associated with infections caused by pyogenic bacteria, mycobacteria (see Chapters 34 and 35), fungi (see Chapter 36), and parasites (see Chapter 37). Lung abscess, often infected but sometimes bland, may also complicate pulmonary infarction (see Chapter 51), primary and metastatic malignancies (see Chapters 47 and 49), and the necrotic conglomerate lesions of silicosis and coal miners' pneumoconiosis (see Chapter 65). Empyema is covered in Chapter 74. Information about treatment of lung abscess is covered in a previous section of this chapter.

CAUSES OF NONRESPONDING PNEUMONIA

The causes of nonresponding pneumonia are classified according to the etiology as infectious, noninfectious, and of unknown origin.[181] Table 32-15 shows common infectious and noninfectious causes.

Infectious Causes

In hospitalized CAP, infections are responsible for 40% of nonresponding CAP. The most frequent microorganisms found are *S. pneumoniae*, *Legionella*, *P. aeruginosa* and *S. aureus*. Microorganisms found may show resistance against antibiotics prescribed. Resistance, although infrequent, may also develop during treatment specially related to the new fluoroquinolones, levofloxacin, and macrolides.[114] Recently, pleuropulmonary complications PVL-positive community-acquired MRSA pneumonia have been reported.[141]

Patients with CAP or HAP may also fail to respond adequately because of an unusual microbial etiology not adequately covered with the standard empirical therapeutic regimens. For example, *P. aeruginosa* causes

TABLE 32-15. Causes of Nonresponding Pneumonia

INFECTIOUS PNEUMONIA
Resistant microorganisms
Community-acquired pneumonia (e.g., *Streptococcus pneumoniae*, *Staphylococcus aureus*)
Nosocomial pneumonia (e.g., *Acinetobacter*, MRSA, *Pseudomonas aeruginosa*)
Uncommon microorganisms (e.g., *Mycobacterium tuberculosis, Nocardia* spp., fungi, *Pneumocystis jirovecii*)
Complications of pneumonia
Empyema
Abscess or necrotizing pneumonia
Metastatic infection
NONINFECTIOUS PNEUMONIA
Neoplasms
Pulmonary hemorrhage
Pulmonary embolism
Sarcoidosis
Eosinophilic pneumonia
Pulmonary edema
Acute respiratory distress syndrome
Bronchiolitis obliterans with organizing pneumonia
Drug-induced pulmonary disease
Pulmonary vasculitis

MRSA, methicillin-resistant *Staphylococcus aureus.*

about 10% of cases of nonresponding CAPs, whether due to persistent infection or to subsequent nosocomial superinfection.[182] Similarly, the most common causative organisms in an elderly nursing home population with CAP who failed to respond to treatment after 72 hours of antimicrobial therapy were MRSA (33%), enteric gram-negative bacilli (24%), and *P. aeruginosa* (14%).[183] In nonresponding VAP, up to 50% of the episodes are caused by multiresistant microorganisms, with the most frequent being MRSA, *P. aeruginosa*, and *Acinetobacter* spp.[184,185]

Unusual microorganisms to be considered in patients who fail to respond to initial antimicrobial therapy include *Mycobacteria*, *Nocardia* spp., anaerobes, fungi, *Pneumocystis jirovecii*, and other microorganisms requiring specific antibiotic treatment other than that recommended in the guidelines for CAP or HAP. Investigation of the etiology of some of these microorganisms requires exhaustive review to search for risk factors, including epidemiology, personal habits (e.g., illicit drug use), environmental factors, professional, leisure, pets, and journeys.

Local or metastatic infectious complications also contribute to a clinical response. The incidence of metastatic infections such as endocarditis, arthritis, pericarditis, meningitis, or peritonitis is greater in bacteremic pneumonia. Empyema is one of the most frequent complications in pneumonia and is thus a common cause of nonresponse that must be ruled out with thoracentesis when a pleural effusion is present. Another cause of nonresponse is abscess formation or necrotizing pneumonia because antibiotics have a decreased activity in necrotic tissues.

Last, it should be recognized that in 30% of the cases, no specific cause for lack of response can be identified despite adequate antibiotic treatment. This may be due to the presence of comorbidities or to an exaggerated or diminished inflammatory response.

Noninfectious Causes

Noninfectious diseases with acute involvement of the pulmonary parenchyma may simulate pneumonia. This category includes neoplasms, pulmonary infarction, pulmonary hemorrhages, bronchiolitis obliterans and organizing pneumonia, eosinophilic pneumonia, hypersensitivity pneumonitis, and drug-induced lung disease. Alveolar cell lung cancer may be particularly difficult to distinguish radiographically from pyogenic pneumonia. The frequency of noninfectious etiologies has been reported to be 22% in CAP and 19% in nosocomial pneumonia. Table 32-15 summarizes infectious and noninfectious causes of nonresponding pneumonia.

Diagnostic Evaluation

In patients with nonresponding or progressive pneumonia, complete reevaluation of the history, physical examination, and laboratory studies is required.[181] In the evaluation of possible causes, important epidemiologic clues mentioned elsewhere in this chapter may suggest unusual microorganisms, unexpected resistance to antimicrobials, or host immune disorders such as HIV infection.

Microbiologic Studies

The microbiologic investigation requires comprehensive culture and microscopic examination of the sputum, urinary antigen detection, blood cultures, and serum antibody detection (Table 32-16).

If simpler procedures do not provide a rapid diagnosis, invasive techniques (i.e., bronchoscopy) are recommended in most cases of nonresponding pneumonia. Both protected sheath brush and BAL sampling should be done during the same procedure. Quantitative bacterial cultures of these samples are preferred. The sensitivity is around 40% in the context of nonresponding CAP and 70% in nosocomial ICU pneumonia[185]; sensitivity is reduced by the previous administration of antibiotics.[71] In patients undergoing mechanical ventilation, the tracheal aspirate provides a good diagnostic yield in nonresponding pneumonia (sensitivity of 93% and specificity of 80% for a cutoff of 10^5 CFU/ml). Gram stain of cytocentrifuged BAL fluid can rapidly identify intracellular microorganisms and may guide decisions regarding changes in antimicrobial therapy. As with sputum, comprehensive microbiologic studies should be performed

TABLE 32-16. Recommended Microbiologic Evaluation in Patients with Nonresolving Pneumonia*

BLOOD CULTURES (TWO SETS)
URINE
Antigen test for detection of *Legionella pneumophila*
SPUTUM
Gram stain, Giemsa stain, immunofluorescence stains for *Legionella*; normal and modified Ziehl-Neelsen stain for *Mycobacterium* spp. and *Nocardia* spp.
Cultures for conventional bacteria, *Legionella*, mycobacteria, and fungi
BRONCHOSCOPY SPECIMENS (USING PSB OR BAL)
Gram stain, Giemsa stain, immunofluorescence stains for *Legionella* and *Pneumocystis jirovecii*; normal and modified Ziehl-Neelsen stain for *Mycobacteria* spp. and *Nocardia* spp.
Cultures for aerobic and anaerobic bacteria,† *Legionella*, mycobacteria, and fungi
PLEURAL FLUID
Gram stain, Giemsa stain, immunofluorescence stains for *Legionella*; normal and modified Ziehl-Neelsen stain for *Mycobacteria* spp. and *Nocardia* spp.
Cultures for aerobic and anaerobic bacteria, *Legionella*, mycobacteria, and fungi

*In endemic areas, serologic and/or antigen detection tests should be done to evaluate for the presence of *Histoplasma capsulatum*, *Cryptococcus neoformans*, *Coccidioides immitis*, and *Blastomyces dermatitidis*.
†Quantitative criteria for the interpretation of PSB and BAL specimens are described in the text.
BAL, bronchoalveolar lavage; PSB, protected specimen brush.

TABLE 32-17. Possible Diseases Depending on Differential Cell Count in Bronchoalveolar Lavage Fluid

PREDOMINANCE OF POLYMORPHONUCLEAR LEUKOCYTES
Bacterial infection
Bronchiolitis obliterans with organizing pneumonia
PREDOMINANCE OF LYMPHOCYTES
Tuberculosis
Hypersensitivity pneumonitis
Sarcoidosis
Fibrosis
HEMOSIDERIN-LADEN MACROPHAGES
Alveolar hemorrhage
EOSINOPHILS
Pulmonary eosinophilia
Fungal infection
Pneumocystis jirovecii
Systemic diseases
Drug-induced disease

(Table 32-17). Complete processing of BAL cells may provide other useful information. DNA amplification and hybridization procedures may be warranted. When present, pleural fluid should be obtained and subjected to a full array of studies.

Imaging Studies

In nonresolving pneumonia, a simple chest radiograph may demonstrate pleural effusion, cavitation, or new changes. In progressive pneumonia, clinical deterioration and the extension of the radiographic image may appear during the first 72 hours after the initiation of satisfactory treatment.

Pulmonary CT scans provide a more detailed study of the parenchyma, interstitium, pleura, and mediastinum. In the right clinical setting, the appearance of nodular images with the halo sign (i.e., a nodule surrounded by a halo of ground-glass attenuation, especially near the pleura) on CT scan is suggestive of pulmonary aspergillosis or mucormycosis.[186,187] Nodules of similar appearance have also been described in cytomegalovirus infection, Wegener's granulomatosis, Kaposi's sarcoma, and hemorrhagic metastasis. Chest radiography of *P. jirovecii* pneumonia shows characteristic ground-glass opacities consistent with interstitial pneumonia. Infection by *Nocardia* spp., *M. tuberculosis*, or Q fever may result in nodules or multiple masses with or without cavitation. Diffuse or mixed interstitial and alveolar opacities may be due to viral infections or *M. pneumoniae*.

Other imaging studies, such as perfusion-ventilation scintigraphy, may be performed according to the clinical suspicion of pulmonary embolism. Spiral CT scans and pulmonary arteriography complement this diagnostic procedure.

Therapeutic Management

Correction of Host Abnormalities

Defects related to the host's immune system may impede recovery from pneumonia. Immunodeficiency may occur as a complication of cancer chemotherapy, immunosuppressive therapy, or corticosteroid use; or it may result from a congenital (e.g., agammaglobulinemia) or acquired (e.g., HIV infection) immune defect. Many of these immune system deficiencies are not remediable; however, drug-related immunosuppression may be improved by discontinuing the offending agent. Even if complete discontinuation is not medically feasible, tapering or intermittent dosage may improve immune function, particularly with corticosteroids.

Granulocytopenia (absolute granulocyte count << 500/μL) has been associated with fulminate, antibiotic-unresponsive pneumonia. Although the use of granulocyte colony-stimulating factor or granulocyte-macrophage colony-stimulating factor has not been shown to decrease infectious mortality in patients with established infections,[188] use of these agents is reasonable in the treatment of profoundly neutropenic patients with severe pneumonia unresponsive to antimicrobial therapy.[189] Administration of activated protein C has been shown to improve survival in selected critically ill patients with septic shock.[190]

Antimicrobial Adjustment

Unless there is undrained pus, infectious causes of nonresponding pneumonia require a diagnostic evaluation and adjustment in empirical treatment.[181] The ideal time to make these changes is unknown, although it has been suggested that one should wait until 72 hours after the initiation of treatment except in the presence of severe clinical deterioration or dramatic progression as determined by chest radiology. Prior to initiating the new therapeutic schedule, new samples should be obtained for microbiologic studies.

In nonresponding CAP, strong consideration should be given to extending the antibacterial spectrum to ensure coverage of resistant *S. pneumoniae*, *P. aeruginosa*, *S. aureus*, and anaerobes. Such broad-spectrum therapy should be undertaken after all abscesses or empyemas have been drained, the results of all previous cultures are reviewed, and whenever possible, vigorous new efforts have been made to identify the offending microorganisms. The specific antimicrobial regimen chosen depends on patient risk factors, disease severity, and the local epidemiology of antimicrobial resistance. In community MRSA (PVL strains), antimicrobial treatments may include, depending on susceptibility tests, linezolid or clindamycin plus vancomycin.[4,7,141]

In nonresponding nosocomial pneumonia, combinations of up to three antibiotics may be necessary to cover *P. aeruginosa*, MRSA, and the endemic flora of each hospital, such as *Acinetobacter* spp. or other microorganisms.[184] Occasionally, empirical coverage against *Aspergillus* spp. should be considered (i.e., severe

COPD, significant immunosuppressive therapy, corticosteroids treatments), especially if supported by clinical, radiologic,[186] or laboratory data.[191]

PREVENTION

Vaccinations

Prevention of pneumonia may be possible by administering the pneumococcal and influenza (during flu season) vaccines for eligible patients. Criteria for administration of pneumococcal and influenza[192] vaccines are presented in Tables 32-18 and 32-19, respectively. The recommendations for administration of live, attenuated influenza vaccine are healthy persons from 5 to 49 years including health care providers and household contacts of high-risk patients. This intranasally live vaccine is an alternative for healthy persons and must be avoided in high-risk persons with chronic underlying diseases or immunodeficiencies.[40] Data from meta-analyses of randomized, controlled trials show that pneumococcal vaccination reduces the incidence of definitive and presumptive pneumococcal pneumonia but differ as to the degree to which this benefit occurs in the elderly (i.e., ≥65 yr) or other high-risk patients.[193] Data from randomized clinical trials also demonstrate that the influenza vaccine reduces the incidence of clinical influenza in the elderly, and a meta-analysis of other trials and a population-based analysis show that the influenza vaccine reduces mortality and hospitalizations for any cause in the elderly.[194]

Strategies to Prevent Hospital-Acquired Pneumonia and Ventilator-Associated Pneumonia

The most successful strategies to prevent HAP are those that increase staff handwashing, ensure aseptic

TABLE 32-18. Recommendations for Administration of Polysaccharide Pneumococcal Vaccine*†

Indications	Revaccination
Age > 65 yr	If the patient < 65 yr at the time of the initial vaccination, provide the second vaccination dose ≥5 yr after the first dose. If the patient ≥ 65 at the time of initial vaccination, revaccination is not recommended.
Age 2-64 yr with: sickle cell disease, asplenia, or immunocompromised state (HIV infection, leukemia, lymphoma, multiple myeloma, generalized malignancy, chronic renal failure, nephrotic syndrome, organ or bone marrow transplant, or receiving immunosuppressive therapy).	For patients ≤ 10 yr, provide revaccination 3 yr after the previous dose. For patients > 10 yr, provide a single revaccination dose ≥5 yr after the previous dose.
Age 2-64 yr with: chronic cardiopulmonary disease (CHF, cardiomyopathy, COPD, emphysema), diabetes mellitus, alcoholism, chronic liver disease, cerebrospinal fluid leak, or from high-risk ethnic community (e.g., Alaska Natives)	No revaccination

*Although there is no specific precaution, the currently available polysaccharide vaccine generally lacks efficacy in persons < 2 yr of age.
†Although the safety of the currently available polysaccharide vaccine has not been assessed during the first trimester of pregnancy, no adverse consequences have been reported.
CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus.
Modified from Centers for Disease Control and Prevention: Prevention of pneumococcal disease: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep 46:1–24, 1997.

TABLE 32-19. Recommendations for Administration of Influenza Vaccine*

Age ≥ 50 yr
Nursing home resident
Chronic cardiopulmonary disease (including asthma)
Chronic metabolic diseases (including diabetes mellitus), renal dysfunction, hemoglobinopathies
Immunosuppression (including immunosuppressive therapy and HIV)
Children and adolescents (aged 6 months to 18 years) receiving long-term aspirin therapy
Women who will be in the second or third trimester of pregnancy during the influenza season
Health care workers (primarily to avoid transmission of influenza virus to high-risk patients)
Close contacts of high-risk persons (primarily to avoid transmission of influenza virus to high-risk patients)

**Note*: Avoid giving vaccine to patients with anaphylactic allergy to eggs or to other influenza vaccine components. The optimal period for vaccination is October to November. However, it is acceptable to provide vaccine from September up to early March.
Modified from Bridges CB, Harper SA, Fukuda K, et al: Prevention and control of influenza: Recommendations of the Advisory Committee on Immmunization Practices (ACIP). MMWR Recomm Rep 52:1–34, 2003.

suctioning techniques, and prevent aspiration. The greatest attention and highest-quality studies have focused on patients undergoing mechanical ventilation in whom elevation of the head of the bed, aspiration of subglottic secretions, and use of oscillating beds for surgical and neurologic patients may prevent VAP.[195] Although selective gut decontamination with antibiotics may also decrease the incidence of VAP, it has not been consistently associated with a shorter duration of ventilation or ICU stay or with better survival.[196] This strategy is not generally recommended, because this approach may increase antimicrobial resistance.[195]

The choice of an antimicrobial agent for treating pneumonia should target the likely causative organism, which may be identified by Gram stains and cultures of sputum, pleural fluid, other respiratory tract specimen and blood.

However, it is often not possible to determine the etiology of pneumonia on clinical grounds and bodily fluid samples. The clinical presentation, risk factors, and epidemiology considerations as well as Gram stain of sputum may not be diagnostic. Thus, prompt initiation of effective antimicrobial therapy often requires the use of empirical regimens. Once the offending pathogenic organism has been identified and its antimicrobial susceptibility determined, more specific therapy should be given unless there are compelling clinical contraindications. Thoughtful application of these simple principles can minimize the morbidity, mortality, and socioeconomic cost of pyogenic bacterial pneumonias.

KEY POINTS

- All patients with suspected pneumonia should have a chest radiograph. Gram stains and cultures of blood, sputum, and other sites should be obtained in hospitalized patients prior to treatment. Specialized serologic or urinary markers are essential for certain microbial infections. *S. pneumoniae* and *L. pneumophila* urinary antigens can make an etiologic diagnosis with reasonable sensitivity and specificity.
- Infection by the aerosolization route occurs with the intracellular bacteria such as *M. pneumoniae*, *Chlamydophila* spp., and *C. burnetii*, whereas infection occurs by aspiration with *S. pneumoniae*, *H. influenzae*, gram-negative bacilli, and other organisms. Aside from inhalational pneumonia due to *Legionella* or contaminated medical aerosols, aspiration is the cause of HAP, especially in intubated patients.
- Culture procedures for viruses and fastidious bacteria, *M. pneumoniae, C. pneumoniae, L. pneumophila*, and *B. pertussis* are too insensitive and too slow to be therapeutically relevant and should be detected by nucleic acid amplification tests.
- In elderly and immunocompromised patients, the signs and symptoms of pneumonia may be muted and overshadowed by nonspecific complaints. Fever higher than 38.5°C or accompanied by chills should never be attributed to bronchitis without examining a chest radiograph. Elderly patients with pneumonia who present with altered mental status without fever have a delay in receiving antibiotics and this delay affects mortality.
- The treatment for pneumonia should be pathogen-directed, but pathogens are rarely identified initially. Therefore, the setting in which the patient resides (e.g., community, hospital, nursing home), the severity of the disease, the age of the patient, the presence of comorbidities and immunosuppression, previous antimicrobial therapy, and specific clinical and radiologic manifestations of the illness must be considered.
- If the etiologic agent has been reliably identified, the antimicrobial regimen should be adjusted based on the results of in vitro susceptibility testing. The ideal drug for a known pathogen has the narrowest spectrum of activity and is the most efficacious, least toxic, and least costly.

References

1. Halm EA, Teirstein AS: Clinical practice. Management of community-acquired pneumonia. N Engl J Med 347:2039–2045, 2002.
2. Welsh D, Mason C: Host defense in respiratory infections. Med Clin North Am 85:1329–1347, 2001.

2a. Hall-Stoodley L, Stoodley P: Evolving concepts in biofilm infections. Cell Microbiol 11:1034–1043, 2009.

3. Marrie T: Community-acquired pneumonia in the elderly. Clin Infect Dis 31:1066–1078, 2000.
4. Bartlett JG, Dowell SF, Mandell LA, et al: Practice guidelines for the management of community-acquired pneumonia. Clin Infect Dis 31:347–382, 2000.
5. Mandell LA, Bartlett JG, Dowell SF, et al: Update of practice guidelines for the management of community-acquired pneumonia in immunocompetent adults. Clin Infect Dis 37:1405–1433, 2003.
6. Niederman M, Mandell L, Anzueto A, et al: Guidelines for the management of adults with community-acquired pneumonia. Diagnosis, assessment of severity, antimicrobial therapy, and prevention. Am J Respir Crit Care Med 163:1730–1754, 2001.

7. Mandell LA, Marrie TJ, Grossman RF, et al: Canadian guidelines for the initial management of community-acquired pneumonia: An evidence-based update by the Canadian Infectious Diseases Society and the Canadian Thoracic Society. The Canadian Community-Acquired Pneumonia Working Group. Clin Infect Dis 31:383–421, 2000.
8. Falguera M, Sacristan O, Nogues A, et al: Nonsevere community-acquired pneumonia: Correlation between cause and severity or comorbidity. Arch Intern Med 161:1866–1872, 2001.
9. Arancibia F, Bauer T, Ewig S, et al: Community acquired pneumonia due to Gram-negative bacteria and *Pseudomonas aeruginosa*: Incidence, risk and prognosis. Arch Intern Med 162: 1849–1858, 2002.
10. Lim W, van der Eerden M, Laing R, et al: Defining community acquired pneumonia severity on presentation to hospital: An international derivation and validation study. Thorax 58:377–382. 2003.
11. Hyvernat H, Pulcini C, Carles D, et al: Fatal *Staphylococcus aureus* hemorrhagic pneumonia producing Panton-Valentine leucocidin. Scand J Infect Dis 39:183–185, 2007.
12. El Solh A, Sikka P, Ramadan F, et al: Etiology of severe pneumonia in the very elderly. Am J Respir Crit Care Med 163:645–651, 2001.
13. Cordero E, Pachon J, Rivero A, et al: Community-acquired bacterial pneumonia in human immunodeficiency virus–infected patients: Validation of severity criteria. Am J Respir Crit Care Med 162:2063–2068, 2000.
14. Park D, Sherbin V, Goodman M, et al: The etiology of community-acquired pneumonia at an urban public hospital: Influence of human immunodeficiency virus infection and initial severity of illness. J Infect Dis 184:268–277, 2001.
15. Baik I, Curhan GC, Rimm EB, et al: A prospective study of age and lifestyle factors in relation to community-acquired pneumonia in US men and women. Arch Intern Med 160:3082–3088, 2000.
16. Kaplan V, Angus DC, Griffin MF, et al: Hospitalized community-acquired pneumonia in the elderly: Age- and sex-related patterns of care and outcome in the United States. Am J Respir Crit Care Med 165:766–772, 2002.
17. Zalacain R, Torres A, Celis R, et al: Community-acquired pneumonia in the elderly: Spanish multicenter study. Eur Respir J 21:294–302, 2003.
18. Fernandez-Sabe N, Carratala J, Roson B, et al: Community-acquired pneumonia in very elderly patients: Causative organisms, clinical characteristics, and outcomes. Medicine (Baltimore) 82:159–169, 2003.
19. Feldman C: The role of alcohol in severe pneumonia and acute lung injury. In Rello J, Leeper K (eds): Severe Community Acquired Pneumonia. Boston: Kluwer Academic, 2001, pp 139–152.
20. Moss M: The role of alcohol in severe pneumonia and acute lung injury: North American prespective. In Rello J, Leeper K (eds): Severe Community Acquired Pneumonia. Boston: Kluwer Academic; 2001, pp 119–138.
21. de Roux A, Ewig S, Garcia E, et al: Mixed community-acquired pneumonia in hospitalised patients. Eur Respir J 27:795–800, 2006.
22. Agusti C, Rano A, Filella X, et al: Pulmonary infiltrates in patients receiving long-term glucocorticoid treatment: Etiology, prognostic factors, and associated inflammatory response. Chest 123:488–498, 2003.
23. Saiman L, Siegel J: Infection control recommendations for patients with cystic fibrosis: Microbiology, important pathogens, and infection control practices to prevent patient-to-patient transmission. Infect Control Hosp Epidemiol 24(5 Suppl):S6–S52, 2003.
24. Schidlow D, Fiel S: Cystic fibrosis. In Albert R, Spiro S, Jett J (eds): Comprehensive Respiratory Medicine. Philadelphia: Elsevier, 2008, pp 42.1–42.14.
25. Chen MZ, Hsueh PR, Lee LN, et al: Severe community-acquired pneumonia due to *Acinetobacter baumannii*. Chest 120:1072–1077, 2001.
26. Imported plague—New York City, 2002. MMWR Morb Mortal Wkly Rep 52:725–728, 2003.
27. Feldman KA, Stiles-Enos D, Julian K et al: Tularemia on Martha's Vineyard: Seroprevalence and occupational risk. Emerg Infect Dis 9:350–354, 2003.
28. White NJ: Melioidosis. Lancet 361:1715–1722, 2003.
29. Poutanen SM, Low DE, Henry B, et al: Identification of severe acute respiratory syndrome in Canada. N Engl J Med 348:1995–2005, 2003.
30. Tsang KW, Ho PL, Ooi GC, et al: A cluster of cases of severe acute respiratory syndrome in Hong Kong. N Engl J Med 348:1977–1985, 2003.
31. Rajagopal S, Treanor J: Pandemic (avian) influenza. Semin Respir Crit Care Med 28:159–170, 2007.
32. Inglesby TV, Dennis DT, Henderson DA, et al: Plague as a biological weapon: Medical and public health management. Working Group on Civilian Biodefense. JAMA 283:2281–2290, 2000.
33. Inglesby TV, O'Toole T, Henderson DA, et al: Anthrax as a biological weapon, 2002: Updated recommendations for management. JAMA 287:2236–2252, 2002.
34. Dennis DT, Inglesby TV, Henderson DA, et al: Tularemia as a biological weapon: Medical and public health management. JAMA 285:2763–2773, 2001.
35. Ibrahim EH, Ward S, Sherman G, Kollef MH: A comparative analysis of patients with early-onset vs late-onset nosocomial pneumonia in the ICU setting. Chest 117:1434–1442, 2000.
36. American Thoracic Society: Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med 171:388–416, 2008.
37. Kollef MH, Shorr A, Tabak YP, et al: Epidemiology and outcomes of health-care–associated pneumonia: results from a large US database of culture-positive pneumonia. Chest 128:3854–3862, 2005.
38. Waterer GW, Kessler LA, Wunderink RG: Delayed administration of antibiotics and atypical presentation in community-acquired pneumonia. Chest 130:11–15, 2006.
39. Bochud PY, Moser F, Erard P, et al: Community-acquired pneumonia. A prospective outpatient study. Medicine (Baltimore) 80:75–87, 2001.
40. Mandell LA, Wunderink RG, Anzueto A, et al: Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis 44(Suppl 2):S27–S72, 2007.
41. Metlay JP, Fine MJ: Testing strategies in the initial management of patients with community-acquired pneumonia. Ann Intern Med 138:109–118, 2003.
42. Blasi F, Tarsia P, Aliberti S, et al: *Chlamydia pneumoniae* and *Mycoplasma pneumoniae*. Semin Respir Crit Care Med 26:617–624, 2005.
43. Menendez R, Perpiña M, Torres A: Evaluation of nonresolving and progressive pneumonia. Semin Respir Infect 18:103–111, 2003.
44. Menendez R, Cavalcanti M, Reyes S, et al: Markers of treatment failure in hospitalised community acquired pneumonia. Thorax 63:447–452, 2008.
45. Christ-Crain M, Stolz D, Bingisser R, et al: Procalcitonin guidance of antibiotic therapy in community-acquired pneumonia: A randomized trial. Am J Respir Crit Care Med 174:84–93, 2006.
46. American Thoracic Society: Diagnostic standards and classification of tuberculosis in adults and children. Am J Respir Crit Care Med 161:1376–1395, 2000.
47. Tan MJ, Tan JS, Hamor RH, et al: The radiologic manifestations of Legionnaire's disease. The Ohio Community-Based Pneumonia Incidence Study Group. Chest 117:398–403, 2000.
48. Virkki R, Juven T, Rikalainen H, et al: Differentiation of bacterial and viral pneumonia in children. Thorax 57:438–441, 2002.
49. Garau J, Gomez L: *Pseudomonas aeruginosa* pneumonia. Curr Opin Infect Dis 16:135–143, 2003.
50. Roson B, Carratala J, Verdaguer R, et al: Prospective study of the usefulness of sputum Gram stain in the initial approach to community-acquired pneumonia requiring hospitalization. Clin Infect Dis 31:869–874, 2000.
51. Blot F, Raynard B, Chachaty E, et al: Value of Gram stain examination of lower respiratory tract secretions for early diagnosis of nosocomial pneumonia. Am J Respir Crit Care Med 162:1731–1737, 2000.
52. Cook D, Mandell L: Endotracheal aspiration in the diagnosis of ventilator-associated pneumonia. Chest 117:195S–197S, 2000.

53. Metersky ML, Ma A, Bratzler DW, Houck PM: Predicting bacteremia in patients with community-acquired pneumonia. Am J Respir Crit Care Med 169:342–347, 2004.
54. Campbell G, Marrie T, Anstey R, et al: The contribution of blood cultures to the clinical management of adult patients admitted to the hospital with community-acquired pneumonia: A prospective observational study. Chest 123:1142–1150, 2003.
55. Marcos M, Jimenez de Anta M, Puig de la Bellacasa J, et al: Rapid urinary antigen test for diagnosis of pneumococcal community-acquired pneumonia in adults. Eur Respir J 21:209–214, 2003.
56. Murdoch DR, Laing RT, Cook JM: The NOW *S. pneumoniae* urinary antigen test positivity rate 6 weeks after pneumonia onset and among patients with COPD. Clin Infect Dis 37:153–154, 2003.
57. Waterer GW, Somes GW, Wunderink RG: Monotherapy may be suboptimal for severe bacteremic pneumococcal pneumonia. Arch Intern Med 161:1837–1842, 2001.
58. Gutierrez F, Masia M, Rodriguez JC, et al: Evaluation of the immunochromatographic Binax NOW assay for detection of *Streptococcus pneumoniae* urinary antigen in a prospective study of community-acquired pneumonia in Spain. Clin Infect Dis 36:286–292, 2003.
59. Ortega L, Sierra M, Dominguez J, et al: Utility of a pneumonia severity index in the optimization of the diagnostic and therapeutic effort for community-acquired pneumonia. Scand J Infect Dis 37:657–663, 2005.
60. Esposito S, Bosis S, Colombo R, et al: Evaluation of rapid assay for detection of *Streptococcus pneumoniae* urinary antigen among infants and young children with possible invasive pneumococcal disease. Pediatr Infect Dis J 23:365–367, 2004.
61. Weinberg GA, Erdman DD, Edwards KM, et al: Superiority of reverse-transcription polymerase chain reaction to conventional viral culture in the diagnosis of acute respiratory tract infections in children. J Infect Dis 189:706–710, 2004.
62. Templeton KE, Scheltinga SA, van den Eeden WC, et al: Improved diagnosis of the etiology of community-acquired pneumonia with real-time polymerase chain reaction. Clin Infect Dis 41:345–351, 2005.
63. Rano A, Agusti C, Jimenez P, et al: Pulmonary infiltrates in non-HIV immunocompromised patients: A diagnostic approach using non-invasive and bronchoscopic procedures. Thorax 56:379–387, 2001.
64. Baughman R: Protected-specimen brush technique in the diagnosis of ventilator-associated pneumonia. Chest 117:203S–206S, 2000.
65. Grossman R, Fein A: Evidence based assessment of diagnostic tests for ventilator-associated pneumonia. Executive summary. Chest 117:177S–181S, 2000.
66. Torres A, El-Ebiary M: Bronchoscopic BAL in the diagnosis of ventilator-associated pneumonial. Chest 117:198S–202S, 2000.
67. Torres A, Fabregas N, Ewig S, et al: Sampling methods for ventilator-associated pneumonia: Validation using different histologic and microbiological references. Crit Care Med 28:2799–2804, 2000.
68. Hubmayr R, Burchardi H, Elliot M, et al: Statement of the 4th International Consensus Conference in Critical Care on ICU Acquired Pneumonia. Intensive Care Med 28:1521–1536, 2002.
69. Campbell G: Blinded invasive diagnostic procedures in ventilator-associated pneumonia. Chest 117:207S–211S, 2000.
70. Wu CL, Yang DI, Wang NY, et al: Quantitative culture of endotracheal aspirates in the diagnosis of ventilator-associated pneumonia in patients with treatment failure. Chest 122:662–668, 2002.
71. Sirvent JM, Vidaur L, Gonzalez S, et al: Microscopic examination of intracellular organisms in protected bronchoalveolar mini-lavage fluid for the diagnosis of ventilator-associated pneumonia. Chest 123:518–523, 2003.
72. Singh N, Rogers P, Atwood C, et al: Short-course empiric antibiotic therapy for patients with pulmonary infiltrates in the intensive care unit. A proposed solution for indiscriminate antibiotic prescription. Am J Respir Crit Care Med 162:505–511, 2000.
73. Gibot S, Cravoisy A, Levy B, et al: Soluble triggering receptor expressed on myeloid cells and the diagnosis of pneumonia. N Engl J Med 350:451–458, 2004.
74. Sole-Violant J, Fernandez J, Benitez A, et al: Impact of quanitative invasive diagnostic techniques in the management and outcome of mechanically ventilated patients with suspected pneumonia. Crit Care Med 28:2737–2741, 2000.
75. The Canadian Critical Care Trial Group: A randomized trial of diagnostic techniques for ventilator-associated pneumonia. N Engl J Med 355:2619–2630, 2006.
76. Waterer GW, Wunderink RG: Controversies in the diagnosis of ventilator-acquired pneumonia. Med Clin North Am 85:1565–1581, 2001.
77. Torres A, Ewig S: Diagnosing ventilator-associated pneumonia. N Engl J Med 350:433–435, 2004.
78. Barlow GD, Lamping DL, Davey PG, Nathwani D: Evaluation of outcomes in community-acquired pneumonia: A guide for patients, physicians, and policy-makers. Lancet Infect Dis 3:476–488, 2003.
79. Marrie TJ, Lau CY, Wheeler SL et al: A controlled trial of a critical pathway for treatment of community-acquired pneumonia. CAPITAL Study Investigators. Community-Acquired Pneumonia Intervention Trial Assessing Levofloxacin. JAMA 283:749–755, 2000.
80. Dean NC, Suchyta MR, Bateman KA, et al: Implementation of admission decision support for community-acquired pneumonia. Chest 117:1368–1377, 2000.
81. Chan SS, Yuen EH, Kew J, et al: Community-acquired pneumonia—Implementation of a prediction rule to guide selection of patients for outpatient treatment. Eur J Emerg Med 8:279–86, 2001.
82. British Thoracic Society: Guidelines for the Management of Community Acquired Pneumonia in Adults. Thorax 56(Suppl 4):IV1–IV64, 2001.
83. Menendez R, Ferrando D, Valles JM, Vallterra J: Influence of deviation from guidelines on the outcome of community-acquired pneumonia. Chest 122:612–617, 2002.
84. Battleman DS, Callahan M, Thaler HT: Rapid antibiotic delivery and appropriate antibiotic selection reduce length of hospital stay of patients with community-acquired pneumonia: Link between quality of care and resource utilization. Arch Intern Med 162:682–688, 2002.
85. Houck PM, Bratzler DW, Nsa W, et al: Timing of antibiotic administration and outcomes for Medicare patients hospitalized with community-acquired pneumonia. Arch Intern Med 164:637–644, 2004.
86. Thornsberry C, Sahm DF, Kelly LJ, et al: Regional trends in antimicrobial resistance among clinical isolates of *Streptococcus pneumoniae, Haemophilus influenzae*, and *Moraxella catarrhalis* in the United States: Results from the TRUST Surveillance Program, 1999–2000. Clin Infect Dis 34(Suppl 1):S4–S16, 2002.
87. Heffelfinger JD, Dowell SF, Jorgensen JH, et al: Management of community-acquired pneumonia in the era of pneumococcal resistance: A report from the Drug-Resistant *Streptococcus pneumoniae* Therapeutic Working Group. Arch Intern Med 160:1399–1408, 2000.
88. Angus D, Marrie T, Obrosky D, et al: Severe community-acquired pneumonia: Use of intensive care services and evaluation of American and British Thoracic Society Diagnostic criteria. Am J Crit Care Med 166:717–723, 2002.
89. Feldman RB, Rhew DC, Wong JY, et al: Azithromycin monotherapy for patients hospitalized with community-acquired pneumonia: A 3½-year experience from a Veterans Affairs hospital. Arch Intern Med 163:1718–1726, 2003.
90. Ho PL, Yung RW, Tsang DN, et al: Increasing resistance of *Streptococcus pneumoniae* to fluoroquinolones: Results of a Hong Kong multicentre study in 2000. J Antimicrob Chemother 48:659–665, 2001.
91. Low DE, de Azavedo J, Weiss K, et al: Antimicrobial resistance among clinical isolates of *Streptococcus pneumoniae* in Canada during 2000. Antimicrob Agents Chemother 46:1295–1301, 2002.
92. Brueggemann AB, Coffman SL, Rhomberg P, et al: Fluoroquinolone resistance in *Streptococcus pneumoniae* in United States since 1994–1995. Antimicrob Agents Chemother 46:680–6688, 2002.
93. Davidson R, Cavalcanti R, Brunton JL, et al: Resistance to levofloxacin and failure of treatment of pneumococcal pneumonia. N Engl J Med 346:747–750, 2002.

94. Anderson KB, Tan JS, File TM Jr, et al: Emergence of levofloxacin-resistant pneumococci in immunocompromised adults after therapy for community-acquired pneumonia. Clin Infect Dis 37:376–381, 2003.
95. Houck PM, MacLehose RF, Niederman MS, Lowery JK: Empiric antibiotic therapy and mortality among medicare pneumonia inpatients in 10 western states: 1993, 1995, and 1997. Chest 119:1420–1426, 2001.
96. Rhew DC, Goetz MB, Shekelle PG: Evaluating quality indicators for patients with community-acquired pneumonia. Jt Comm J Qual Improv 27:575–590, 2001.
97. Marrie TJ: Pneumonia in the long-term-care facility. Infect Control Hosp Epidemiol 23:159–164, 2002.
98. Hoffken G, Niederman MS: Nosocomial pneumonia: The importance of a de-escalating strategy for antibiotic treatment of pneumonia in the ICU. Chest 122:2183–2196, 2002.
99. Rhew DC, Tu GS, Ofman J, et al: Early switch and early discharge strategies in patients with community-acquired pneumonia: A meta-analysis. Arch Intern Med 161:722–727, 2001.
100. Castro-Guardiola A, Viejo-Rodriguez AL, Soler-Simon S, et al: Efficacy and safety of oral and early-switch therapy for community-acquired pneumonia: A randomized controlled trial. Am J Med 111:367–374, 2001.
100a. van der Poll T, Opal SM: Pathogenesis, treatment, and prevention of pneumococcal pneumonia. Lancet 374:1543–1556, 2009.
101. Nuorti JP, Butler JC, Farley MM, et al: Cigarette smoking and invasive pneumococcal disease. Active Bacterial Core Surveillance Team. N Engl J Med 342:681–689, 2000.
102. Musher DM, Alexandraki I, Graviss EA, et al: Bacteremic and nonbacteremic pneumococcal pneumonia. A prospective study. Medicine (Baltimore) 79:210–221 2000.
103. Robinson KA, Baughman W, Rothrock G, et al: Epidemiology of invasive *Streptococcus pneumoniae* infections in the United States, 1995–1998: Opportunities for prevention in the conjugate vaccine era. JAMA 285:1729–1735, 2001.
104. Musher DM: How contagious are common respiratory tract infections? N Engl J Med 348:1256–1266, 2003.
105. Dowell SF, Whitney CG, Wright C, et al: Seasonal patterns of invasive pneumococcal disease. Emerg Infect Dis 9:573–579, 2003.
106. Musher DM, Montoya R, Wanahita A: Diagnostic value of microscopic examination of Gram-stained sputum and sputum cultures in patients with bacteremic pneumococcal pneumonia. Clin Infect Dis 39:165–169, 2004.
107. Garcia-Vazquez E, Marcos MA, Mensa J, et al: Assessment of the usefulness of sputum culture for diagnosis of community-acquired pneumonia using the PORT predictive scoring system. Arch Intern Med 164:1807–1811, 2004.
108. Kalin M, Ortqvist A, Almela M, et al: Prospective study of prognostic factors in community-acquired bacteremic pneumococcal disease in 5 countries. J Infect Dis 182:840–847, 2000.
109. Whitney CG, Farley MM, Hadler J, et al: Increasing prevalence of multidrug-resistant *Streptococcus pneumoniae* in the United States. N Engl J Med 343:1917–1924, 2000.
110. Waterer GW: Combination antibiotic therapy with macrolides in community-acquired pneumonia: More smoke but is there any fire? Chest 123:1328, 2003.
111. National Committee for Clinical Laboratory Standards: Twelfth Informational Supplement. M100-S12. Performance Standards for Antimicrobial Susceptibility Testing. Wayne, PA: NCCLS, 2002.
112. Doern GV, Heilmann KP, Huynh HK: Antimicrobial resistance among clinical isolates of *Streptococcus pneumoniae* in the United States during 1999–2000, including a comparison of resistance rates since 1994–1995. Antimicrob Agents Chemother 45:1721–1729, 2001.
113. Sahm DF, Thornsberry C, Mayfield DC, et al: In vitro activities of broad-spectrum cephalosporins against nonmeningeal isolates of *Streptococcus pneumoniae*: MIC interpretation using NCCLS M100-S12 recommendations. J Clin Microbiol 40:669–674, 2002.
114. Kelley MA, Weber DJ, Gilligan P, Cohen MS: Breakthrough pneumococcal bacteremia in patients being treated with azithromycin and clarithromycin. Clin Infect Dis 31:1008–1011, 2000.
115. Musher DM, Dowell ME, Shortridge VD, et al: Emergence of macrolide resistance during treatment of pneumococcal pneumonia. N Engl J Med 346:630–631, 2002.
116. Lonks JR, Garau J, Gomez L, et al: Failure of macrolide antibiotic treatment in patients with bacteremia due to erythromycin-resistant *Streptococcus pneumoniae*. Clin Infect Dis 35:556–564, 2002.
117. Lagrou K, Peetermans WE, Verhaegen J, et al: Macrolide resistance in Belgian *Streptococcus pneumoniae*. J Antimicrob Chemother 45:119–121, 2000.
118. Vanderkooi OG, Low DE, Green K, et al: Predicting antimicrobial resistance in invasive pneumococcal infections. Clin Infect Dis 40:1288–1297, 2005.
119. Leroy O, Saux P, Bedos JP, Caulin E: Comparison of levofloxacin and cefotaxime combined with ofloxacin for ICU patients with community-acquired pneumonia who do not require vasopressors. Chest 128:172–183, 2005.
120. Martinez JA, Horcajada JP, Almela M, et al: Addition of a macrolide to a beta-lactam–based empirical antibiotic regimen is associated with lower in-hospital mortality for patients with bacteremic pneumococcal pneumonia. Clin Infect Dis 36:389–395, 2003.
121. Brown RB, Iannini P, Gross P, Kunkel M: Impact of initial antibiotic choice on clinical outcomes in community-acquired pneumonia: Analysis of a hospital claims–made database. Chest 123:1503, 2003.
122. File TM Jr, Mandell LA: What is optimal antimicrobial therapy for bacteremic pneumococcal pneumonia? Clin Infect Dis 36:396–398, 2003.
123. Metersky ML, Ma A, Houck PM, Bratzler DW: Antibiotics for bacteremic pneumonia: Improved outcomes with macrolides but not fluoroquinolones. Chest 131:466–473, 2007.
124. Muller MP, Low DE, Green KA, et al: Clinical and epidemiologic features of group A streptococcal pneumonia in Ontario, Canada. Arch Intern Med 163:467–72, 2003.
125. O'Brien KL, Beall B, Barrett NL, et al: Epidemiology of invasive group A streptococcus disease in the United States, 1995–1999. Clin Infect Dis 35:268–276, 2002.
126. Outbreak of group A streptococcal pneumonia among Marine Corps recruits—California, November 1–December 20, 2002. MMWR Morb Mortal Wkly Rep 52:106–109, 2003.
127. Farley MM: Group B streptococcal disease in nonpregnant adults. Clin Infect Dis 33:556–561, 2001.
128. Ahmed RA, Marrie TJ, Huang JQ: Thoracic empyema in patients with community-acquired pneumonia. Am J Med 119:877–883, 2006.
129. Al Kaabi N, Solh Z, Pacheco S, et al: A Comparison of group A streptococcus versus *Streptococcus pneumoniae* pneumonia. Pediatr Infect Dis J 25:1008–1012, 2006.
130. Morozumi M, Nakayama E, Iwata S, et al: Simultaneous detection of pathogens in clinical samples from patients with community-acquired pneumonia by real-time PCR with pathogen-specific molecular beacon probes. J Clin Microbiol 44:1440–1446, 2006.
131. Maskell NA, Batt S, Hedley EL, et al: The bacteriology of pleural infection by genetic and standard methods and its mortality significance. Am J Respir Crit Care Med 174:817–823, 2006.
132. Lin FY, Azimi PH, Weisman LE, et al: Antibiotic susceptibility profiles for group B streptococci isolated from neonates, 1995–1998. Clin Infect Dis 31:76–79, 2000.
133. Alos JI, Aracil B, Oteo J, Gomez-Garces JL: Significant increase in the prevalence of erythromycin-resistant, clindamycin- and miocamycin-susceptible (M phenotype) *Streptococcus pyogenes* in Spain. J Antimicrob Chemother 51:333–337, 2003.
134. Hammerschlag MR: *Mycoplasma pneumoniae* infections. Curr Opin Infect Dis 14:181–186, 2001.
135. Murdoch DR: Nucleic acid amplification tests for the diagnosis of pneumonia. Clin Infect Dis 36:1162–1170, 2003.
136. Smith R, Eviatar L: Neurologic manifestations of *Mycoplasma pneumoniae* infections: Diverse spectrum of diseases. A report of six cases and review of the literature. Clin Pediatr (Phila) 39:195–201, 2000.
137. Hyde TB, Gilbert M, Schwartz SB, et al: Azithromycin prophylaxis during a hospital outbreak of *Mycoplasma pneumoniae* pneumonia. J Infect Dis 183:907–912, 2001.

137a. Blasi F, Tarsia P, Aliberti S: Chlamydophila pneumoniae. Clin Microbiol Infect 15:29–35, 2009.
138. Miyashita N, Saito A, Kohno S, et al: Community-acquired *Chlamydia pneumoniae* pneumonia in Japan: a prospective multicenter community-acquired pneumonia study. Intern Med 41:943–949, 2002.
139. Monno R, De Vito D, Losito G, et al: *Chlamydia pneumoniae* in community-acquired pneumonia: sSeven years of experience. J Infect 45:135–138, 2002.
140. Robicsek A, Suseno M, Beaumont JL, et al: Prediction of methicillin-resistant *Staphylococcus aureus* involvement in disease sites by concomitant nasal sampling. J Clin Microbiol 46:588–592, 2008.
141. Micek ST, Dunne M, Kollef MH: Pleuropulmonary complications of Panton-Valentine leukocidin-positive community-acquired methicillin-resistant *Staphylococcus aureus*: Importance of treatment with antimicrobials inhibiting exotoxin production. Chest 128:2732–2738, 2005.
142. Micek ST, Kollef KE, Reichley RM, et al: Health care-associated pneumonia and community-acquired pneumonia: A single-center experience. Antimicrob Agents Chemother 51:3568–3573, 2007.
143. Dufour P, Gillet Y, Bes M, et al: Community-acquired methicillin-resistant *Staphylococcus aureus* infections in France: Emergence of a single clone that produces Panton-Valentine leukocidin. Clin Infect Dis 35:819–824, 2002.
144. Gillet Y, Issartel B, Vanhems P, et al: Association between *Staphylococcus aureus* strains carrying gene for Panton-Valentine leukocidin and highly lethal necrotising pneumonia in young immunocompetent patients. Lancet 359:753–759, 2002.
144a. DeLeo FR, Chambers HF: Reemergence of antibiotic-resistant Staphylococcus aureus in the genomics era. J Clin Invest 119:2464–2474, 2009.
145. Outbreaks of community-associated methicillin-resistant *Staphylococcus aureus* skin infections—Los Angeles County, California, 2002–2003. MMWR Morb Mortal Wkly Rep 52:88, 2003.
146. Stevens DL, Ma Y, Salmi DB, et al: Impact of antibiotics on expression of virulence-associated exotoxin genes in methicillin-sensitive and methicillin-resistant *Staphylococcus aureus*. J Infect Dis 195:202–211, 2007.
147. Hatchette TF, Gupta R, Marrie TJ: *Pseudomonas aeruginosa* community-acquired pneumonia in previously healthy adults: Case report and review of the literature. Clin Infect Dis 31:1349–1356, 2000.
148. Crnich CJ, Gordon B, Andes D: Hot tub–associated necrotizing pneumonia due to *Pseudomonas aeruginosa*. Clin Infect Dis 36:e55–e57, 2003.
149. Chastre J, Fagon J: Ventilator-associated pneumonia. Am J Respir Crit Care Med 165:867–903, 2002.
150. Walsh NM, Casano AA, Manangan LP, et al: Risk factors for *Burkholderia cepacia* complex colonization and infection among patients with cystic fibrosis. J Pediatr 141:512–517, 2002.
151. Ewig S, Torres A: *Pseudomonas aeruginosa* and initial antibiotic choices. In Rello J, Leeper K (eds): Perspectives on Severe Community-Acquired Pneumonia. Norwell, MA: Kluwer Academic Publishers; 2001, pp 105–118.
152. Chatzinikolaou I, Abi-Said D, Bodey GP, et al: Recent experience with *Pseudomonas aeruginosa* bacteremia in patients with cancer: Retrospective analysis of 245 episodes. Arch Intern Med 160:501–509, 2000.
152a. El Solh AA, Alhajhusain A: Update on the treatment of Pseudomonas aeruginosa pneumonia. J Antimicrob Chemother 64:229–238, 2009.
153. Giamarellou H, Antoniadou A: Antipseudomonal antibiotics. Med Clin North Am 85:19–42, v, 2001.
154. Valdezate S, Vindel A, Loza E, et al: Antimicrobial susceptibilities of unique *Stenotrophomonas maltophilia* clinical strains. Antimicrob Agents Chemother 45:1581–1584, 2001.
155. Scott P, Deye G, Srinivasan A, et al: An outbreak of multidrug-resistant *Acinetobacter baumannii-calcoaceticus* complex infection in the US military health care system associated with military operations in Iraq. Clin Infect Dis 44:1577–1584, 2007.
156. Leung WS, Chu CM, Tsang KY, et al: Fulminant community-acquired *Acinetobacter baumannii* pneumonia as a distinct clinical syndrome. Chest 129(1):102–109, 2006.
157. Wisplinghoff H, Edmond MB, Pfaller MA, et al: Nosocomial bloodstream infections caused by *Acinetobacter* species in United States hospitals: Clinical features, molecular epidemiology, and antimicrobial susceptibility. Clin Infect Dis 31:690–697, 2000.
158. Garnacho-Montero J, Ortiz-Leyba C, Fernandez-Hinojosa E, et al: *Acinetobacter baumannii* ventilator-associated pneumonia: Epidemiological and clinical findings. Intensive Care Med 31:649–655, 2005.
159. Urban C, Segal-Maurer S, Rahal JJ: Considerations in control and treatment of nosocomial infections due to multidrug-resistant *Acinetobacter baumannii*. Clin Infect Dis 36:1268–1274, 2003.
160. Garnacho-Montero J, Ortiz-Leyba C, Jimenez-Jimenez FJm, et al: Treatment of multidrug-resistant *Acinetobacter baumannii* ventilator-associated pneumonia (VAP) with intravenous colistin: A comparison with imipenem-susceptible VAP. Clin Infect Dis 36:1111–1118, 2003.
161. Pedro-Botet ML, Stout JE, Yu VL: Legionnaires' disease contracted from patient homes: The coming of the third plague? Eur J Clin Microbiol Infect Dis 21:699–705, 2002.
162. Marik PE. Aspiration pneumonitis and aspiration pneumonia. N Engl J Med 344:665–671, 2001.
163. Raoult D, Tissot-Dupont H, Foucault C, et al: Q fever 1985–1998. Clinical and epidemiologic features of 1,383 infections. Medicine (Baltimore) 79:109–123, 2000.
164. Marrie TJ, Raoult D: Update on Q fever, including Q fever endocarditis. Curr Clin Top Infect Dis 22:97–124, 2002.
165. Torres HA, Reddy BT, Raad II, et al: Nocardiosis in cancer patients. Medicine (Baltimore) 81:388–397, 2002.
166. Brown-Elliott BA, Ward SC, Crist CJ, et al: In vitro activities of linezolid against multiple *Nocardia* species. Antimicrob Agents Chemother 45:1295–1297, 2001.
167. Currie BJ, Fisher DA, Howard DM, et al: Endemic melioidosis in tropical northern Australia: A 10-year prospective study and review of the literature. Clin Infect Dis 31:981–986, 2000.
168. Currie BJ, Fisher DA, Howard DM, et al: The epidemiology of melioidosis in Australia and Papua New Guinea. Acta Trop 74:121–127, 2000.
169. Cheng AC, Hanna JN, Norton R, et al: Melioidosis in northern Australia, 2001–02. Commun Dis Intell 27:272–277, 2003.
170. Kedlaya I, Ing MB, Wong SS: *Rhodococcus equi* infections in immunocompetent hosts: Case report and review. Clin Infect Dis 32:E39–E46, 2001.
171. Bush LM, Abrams BH, Beall A, Johnson CC: Index case of fatal inhalational anthrax due to bioterrorism in the United States. N Engl J Med 345:1607–1610, 2001.
172. Borio L, Frank D, Mani V, et al: Death due to bioterrorism-related inhalational anthrax: Report of 2 patients. JAMA 286:2554–2559, 2001.
173. Mayer TA, Bersoff-Matcha S, Murphy C, et al: Clinical presentation of inhalational anthrax following bioterrorism exposure: Report of 2 surviving patients. JAMA 286:2549–2553, 2001.
174. Kyriacou DN, Yarnold PR, Stein AC, et al: Discriminating inhalational anthrax from community-acquired pneumonia using chest radiograph findings and a clinical algorithm. Chest 131:489–496, 2007.
175. Bartlett JG, Inglesby TV Jr, Borio L: Management of anthrax. Clin Infect Dis 35:851–858, 2002.
176. Feldman KA, Enscore RE, Lathrop SL, et al: An outbreak of primary pneumonic tularemia on Martha's Vineyard. N Engl J Med 345:1601–1606, 2001.
177. Mwengee W, Butler T, Mgema S, et al: Treatment of plague with gentamicin or doxycycline in a randomized clinical trial in Tanzania. Clin Infect Dis 42:614–621, 2006.
178. Verduin CM, Hol C, Fleer A, et al: *Moraxella catarrhalis*: From emerging to established pathogen. Clin Microbiol Rev 15:125–144, 2002.
179. Rosenstein NE, Perkins BA, Stephens DS, et al: Meningococcal disease. N Engl J Med 344:1378–1388, 2001.
180. Richter SS, Gordon KA, Rhomberg PR, et al: *Neisseria meningitidis* with decreased susceptibility to penicillin: Report from the SENTRY antimicrobial surveillance program, North America, 1998–99. Diagn Microbiol Infect Dis 41:83–88, 2001.
181. Menendez R, Torres A: Treatment failure in community-acquired pneumonia. Chest 132:1348–1355, 2007.

182. Arancibia F, Ewig S, Martinez J, et al: Antimicrobial treatment failures in patients with community-acquired pneumonia: Causes and prognostic implications. Am J Respir Crit Care Med 162:154–160, 2000.
183. El Solh A, Aquilina A, Dhillon R, et al: Impact of invasive strategy on management of antimicrobial treatment failure in institutionalized older people with severe pneumonia. Am J Respir Crit Care Med 166:1038–1043, 2002.
184. Ferrer M, Ioanas M, Torres A: The evaluation of the non-responding patients with ventilator-associated pneumonia. Clin Pulm Med 8:290–295, 2001.
185. Pereira Gomes J, Pedreira W Jr, Araujo E, et al: Impact of BAL in the management of pneumonia with treatment failure: Positivity of BAL culture under antibiotic therapy. Chest 118:1739–1746, 2000.
186. Yeghen T, Kibbler CC, Prentice HG, et al: Management of invasive pulmonary aspergillosis in hematology patients: A review of 87 consecutive cases at a single institution. Clin Infect Dis 31: 859–868, 2000.
187. Franquet T: Imaging of pneumonia: Trends and algorithms. Eur Respir J 18:196–208, 2001.
188. Hughes WT, Armstrong D, Bodey GP, et al: 2002 guidelines for the use of antimicrobial agents in neutropenic patients with cancer. Clin Infect Dis 34:730–751, 2002.
189. Ozer H, Armitage JO, Bennett CL, et al: 2000 update of recommendations for the use of hematopoietic colony-stimulating factors: Evidence-based, clinical practice guidelines. American Society of Clinical Oncology Growth Factors Expert Panel. J Clin Oncol 18:3558–3585, 2000.
190. Bernard GR, Vincent JL, Laterre PF, et al: Efficacy and safety of recombinant human activated protein C for severe sepsis. N Engl J Med 344:699–709, 2001.
191. Herbrecht R, Letscher-Bru V, Oprea C, et al: *Aspergillus galactomannan* detection in the diagnosis of invasive aspergillosis in cancer patients. J Clin Oncol 207:1898–1906, 2002.
192. Bridges CB, Harper SA, Fukuda K, et al: Prevention and control of influenza. Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 52:1–34, 2003.
193. Cornu C, Yzebe D, Leophonte P, et al: Efficacy of pneumococcal polysaccharide vaccine in immunocompetent adults: A meta-analysis of randomized trials. Vaccine 19:4780–4790, 2001.
194. Nichol KL, Nordin J, Mullooly J, et al: Influenza vaccination and reduction in hospitalizations for cardiac disease and stroke among the elderly. N Engl J Med 348:1322–1332, 2003.
195. Collard HR, Saint S, Matthay MA: Prevention of ventilator-associated pneumonia: An evidence-based systematic review. Ann Intern Med 138:494–501, 2003.
196. Bergmans DC, Bonten MJ, Gaillard CA, et al: Prevention of ventilator-associated pneumonia by oral decontamination: A prospective, randomized, double-blind, placebo-controlled study. Am J Respir Crit Care Med 164:382–388, 2001.

CHAPTER 33

VENTILATOR-ASSOCIATED PNEUMONIA

Jean Chastre, MD • Charles-Edouard Luyt, MD, PhD

INTRODUCTION

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INTRODUCTION

Ventilator-associated pneumonia (VAP) is the most frequent intensive care unit (ICU)–acquired infection among patients who are treated with mechanical ventilation.[1,2] In contrast to infections of other organs (e.g., urinary tract and skin), for which mortality ranges from 1% to 4%, the mortality rate for VAP, defined as pneumonia occurring more than 48 hours after the onset of mechanical ventilation, ranges from 20% to 50%, and can even be higher when lung infection is caused by high-risk pathogens.[1–3] Although the attributable mortality rate for VAP is still debated, good evidence indicates that VAP prolongs the duration of mechanical ventilation and the ICU stay.[1,2] Approximately 50% of all antibiotics prescribed in an ICU are administered for respiratory tract infections.[4] Because several studies have shown that appropriate antimicrobial treatment of patients with VAP significantly improves outcome, rapid identification of infected patients and accurate selection of antimicrobial agents are important clinical goals.[1] Agreement is lacking, however, about the appropriate diagnostic, therapeutic, and preventive strategies for VAP.

PATHOGENESIS

Normally, a variety of defense mechanisms protect the normal human respiratory tract from infection. Examples include anatomic barriers, such as the glottis and larynx; cough reflexes; constituents of tracheobronchial secretions; mucociliary clearance; epithelial lining fluid and surfactant components; cell-mediated and humoral immunity; a phagocytic system that involves alveolar macrophages and recruited neutrophils; and both humoral and cell-mediated immunity.[5,6] When these coordinated components function properly, invading microbes are eliminated and clinical disease is avoided. When these defenses are impaired, however, or if they are overcome by virtue of a high inoculum of organisms or organisms of unusual virulence, pneumonitis results.

As suggested by the infrequent association of VAP with bacteremia, most of these infections appear to result from aspiration of potential pathogens that have colonized the mucosal surfaces of the oropharyngeal airways, the dental plaque, and/or the paranasal sinuses.[6] Endotracheal intubation not only compromises the natural barrier between the oropharynx and trachea, but also facilitates the entry of bacteria into the lungs by pooling and leakage of contaminated secretions around the endotracheal tube cuff from the subglottic area below the true vocal cords.[7] This phenomenon occurs in most intubated patients, whose supine position may facilitate its occurrence.[8] Moreover, biofilm formation on the inner and outer surfaces of the endotracheal tube provides a protected environment for pathogens. Bacterial aggregates in biofilm dislodged during suctioning are

dangerous for the lung, because they are difficult to clear by host immune defenses and difficult to eradicate with antibiotics.

Tracheobronchial colonization with gram-negative bacilli (GNB) usually precedes the onset of VAP. Risk factors for tracheobronchial colonization appear to be the same as those that favor pneumonia and include advanced age, more severe illness, longer hospitalization, prior or concomitant use of antibiotics, malnutrition, endotracheal intubation, depressed level of consciousness, immune suppression from disease or medication, azotemia, underlying pulmonary disease, and longer duration of mechanical ventilation.[1,9,10] Experimental studies have linked some of these risk factors with changes in adherence of GNB to respiratory epithelial cells. Although formerly attributed to losses of cell surface fibronectin, these changes in adherence also reflect alterations of cell surface carbohydrates. Bacterial adhesins and prior antimicrobial therapy appear to facilitate the process. Interestingly, Enterobacteriaceae usually appear in the oropharynx first, whereas *Psuedomonas aeruginosa* more often appear first in the trachea.[11]

Although the stomach can be a reservoir for pneumonia pathogens, the gastropulmonary route of infection is not always the primary route of infection in critically ill patients.[12] Progression of colonization from the stomach to the upper respiratory tract with subsequent episodes of VAP could not be demonstrated in several studies, and efforts to eliminate the gastric reservoir with antimicrobial therapy without decontaminating the oropharyngeal cavity have generally failed to prevent VAP.[13] In fact, there is more than one potential pathway for colonization of the oropharynx and trachea in such a setting, including cross infection from the hands of health care personnel, and contaminated respiratory therapy equipment. Patient care activities, such as bathing, oral care, tracheal suctioning, enteral feeding and tube manipulations, provide many opportunities for transmission of pathogens when meticulous infection control practices are not followed.

EPIDEMIOLOGY

Incidence

The exact incidence of VAP varies widely depending on the case definition of pneumonia and the population being evaluated. For example, the incidence may be up to two times higher in patients diagnosed by qualitative or semiquantitative sputum cultures compared to quantitative cultures of lower respiratory tract secretions. However, all studies confirmed that nosocomial pneumonia is considerably more frequent in ventilated patients than in other ICU patients, with the incidence increasing by as much as 6- to 20-fold in this subset of patients.[14,15] VAP occurs in 9% to 27% of all intubated patients, and its incidence increases with duration of ventilation.[10] The risk of VAP is highest early in the course of the hospital stay, and is estimated to be 3% per day during the first 5 days of ventilation, 2% per day during days 5 to 10 of ventilation, and 1% per day after this.[10] Since most mechanical ventilation is short term, approximately half of all episodes of VAP occur within the first 4 days of mechanical ventilation. In a large epidemiologic study, independent predictors of VAP retained by multivariate analysis were a primary admitting diagnosis of burns, trauma, central nervous system disease, respiratory disease, or cardiac disease; mechanical ventilation during the preceding 24 hours; witnessed aspiration; and use of paralytic agents. Exposure to antibiotics conferred protection, but this effect was attenuated over time.[10] According to four studies, the VAP rate was higher in patients with acute respiratory distress syndrome (ARDS) than other ventilated patients, affecting between 34% and greater than 70% of patients with ARDS and often leading to the development of sepsis, multiple organ failure, and death.[16–19]

Attributable Mortality, Morbidity, and Costs

Mechanically ventilated patients in the ICU with VAP appear to have a 2- to 10-fold higher risk of death as compared with patients without pneumonia. Although these statistics indicate that VAP can be lethal, previous studies have not demonstrated clearly that pneumonia is responsible for the higher mortality rate of these patients. It is often difficult to determine whether ICU patients with severe underlying illness would have survived if VAP had not occurred. VAP, however, has been recognized in several case-control studies or studies using multivariate analysis as an important prognostic factor for different groups of critically ill patients.[20–24]

Other factors beyond the simple development of VAP, such as the severity of the disease or the responsible pathogens, may be more important determinants of outcome for patients in whom pneumonia develops. Indeed, it may be that VAP increases mortality only in the subset of patients with intermediate severity of illness,[24] when initial treatment is inappropriate,[25–29] and/or in patients with VAP caused by high-risk pathogens, such as *P. aeruginosa.*[30] Patients with very low severity and early-onset pneumonia caused by organisms such as *Haemophilus influenzae* or *Streptococcus pneumoniae* have excellent prognoses with or without VAP, whereas very ill patients with late-onset VAP occurring while they are in a quasi-terminal state would be unlikely to survive.

All studies have shown clearly that patients with VAP have prolonged duration of mechanical ventilation and lengthened ICU and hospital stay as compared with patients who do not have VAP.[1,2] Summarizing available data, VAP appears to extend the ICU stay by at least 4 days, with the attributable ICU length of stay being longer for medical than surgical patients and for patients infected with "high-risk" as opposed to "low-risk" organisms.[31] The prolonged hospitalization of patients with VAP underscores the considerable financial burden

imposed on the health care system by the development of VAP.[32,33]

Etiologic Agents

Microorganisms responsible for VAP differ according to the population of ICU patients, the durations of hospital and ICU stays, and the specific diagnostic method(s) used to establish the responsible pathogens. A number of studies have shown that GNB cause many of the respiratory infections in this setting.[1,2] The data from 24 studies conducted on ventilated patients, for whom bacteriologic studies were restricted to uncontaminated specimens, confirmed these results: GNB represented 58% of recovered organisms (Fig. 33-1). The predominant GNB were *P. aeruginosa* and *Acinetobacter* spp., followed by *Proteus* spp., *Escherichia coli, Klebsiella* spp., and *H. influenzae.* A relatively high rate of gram-positive pneumonias was also reported in those studies, with *Staphylococcus aureus* involved in 20% of the cases. Many episodes of VAP are caused by multiple pathogens.[34]

Underlying diseases may predispose patients to infection with specific organisms. Patients with chronic obstructive pulmonary disease are at increased risk for *H. influenzae, Moraxella catarrhalis,* or *S. pneumoniae* infections; cystic fibrosis increases the risk of *P. aeruginosa* and/or *S. aureus* infections, while trauma and neurologic disease increase the risk for *S. aureus* infection. Furthermore, the causative agent for pneumonia differs among ICU surgical populations, with 18% of the nosocomial pneumonias caused by *Haemophilus* or pneumococci, particularly in patients with trauma, but not in patients with malignancy, transplantation, or abdominal or cardiovascular surgery.[1,2]

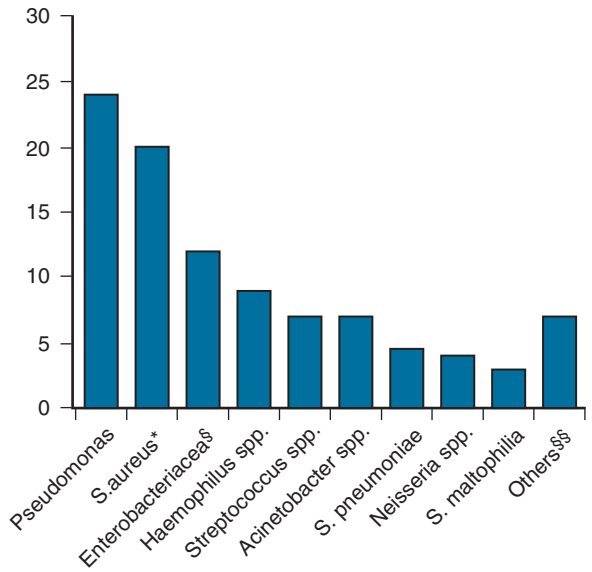

FIGURE 33-1 ■ Etiology of VAP as documented by bronchoscopic techniques in 24 studies for a total of 1689 episodes and 2490 pathogens. *Methicillin-resistant *Staphylococcus aureus* (MRSA), 56%; methicillin-sensitive *S. aureus* (MSSA), 44%. §*Klebsiella* spp., 16%; *Escherichia coli,* 24%; *Proteus* spp., 22%; *Enterobacter* spp., 19%; *Serratia* spp., 12%; *Citrobacter* spp., 5%. §§Including *Corynebacterium* spp., *Moraxella* spp., and *Enterococcus* spp. (Adapted from Chastre J, Fagon JY: Ventilator-associated pneumonia. Am J Respir Crit Care Med 165:867–903, 2002.)

Despite somewhat different definitions of early-onset pneumonia, varying from onset of less than 3 to less than 7 days, high rates of *H. influenzae, S. pneumoniae,* methicillin-sensitive *S. aureus,* or susceptible Enterobacteriaceae were constantly found in early-onset VAP, whereas *P. aeruginosa, Acinetobacter* spp., methicillin-resistant *S. aureus* (MRSA), and multiresistant GNB were significantly more frequent in late-onset VAP.[1] The different pattern of distribution of etiologic agents between early- and late-onset VAP is linked to prior antimicrobial therapy in many patients with late-onset VAP. When multivariate analysis was used to identify risk factors for VAP caused by potentially drug-resistant bacteria such as MRSA, *P. aeruginosa, Acinetobacter baumannii,* and/or *Stenotrophomonas maltophilia* in 135 consecutive episodes of VAP, only three variables remained significant: duration of mechanical ventilation of longer than 7 days before onset of VAP, prior antibiotic use, and prior use of broad-spectrum drugs (third-generation cephalosporins, fluoroquinolones, and/or imipenem).[35] Not all studies have confirmed this distribution pattern, and in some studies the most common pathogens associated with early-onset VAP were *P. aeruginosa*, MRSA, and *Enterobacter* spp., with similar pathogens associated with late-onset VAP.[36,37] These findings might be explained in part by prior hospitalization and the use of antibiotics prior to transfer to the ICU.

Legionella species, anaerobes, fungi, viruses, and even *Pneumocystis jirovecii* should be mentioned as potential causative agents, but these microbes are not commonly found when pneumonia is acquired during mechanical ventilation. Several of these causative agents might be more common than reported, because of difficulties with the diagnostic techniques used to identify them, including viruses.[38,39] Isolation of fungi, most frequently *Candida* species, at significant concentrations poses interpretative problems. Invasive disease has been reported in VAP, but yeasts are isolated more frequently from respiratory tract specimens in the absence of apparent disease. Based on current data,[40] the use of the commonly available respiratory sampling methods (bronchoscopic or nonbronchoscopic) in ventilated patients is not sufficient to make the diagnosis of *Candida* pneumonia, and evidence of bloodstream invasion is also needed.

DIAGNOSIS

Two diagnostic algorithms can be used when VAP is suspected, typically when a patient has new or progressive radiographic infiltrates and clinical findings suggesting infection, such as the new onset of fever, purulent sputum, leukocytosis, and a decline in arterial oxygenation. The first option is to treat every patient clinically suspected of having a pulmonary infection with new

antibiotics, even when the likelihood of infection is low, arguing that several studies showed that immediate initiation of appropriate antibiotics was associated with reduced mortality.[41] The second option is to use an invasive diagnostic strategy based on quantitative cultures of distal respiratory specimens obtained using bronchoscopic or nonbronchoscopic techniques, such as bronchoalveolar lavage (BAL) or a protected specimen brush (PSB), in order to improve the identification of patients with true VAP and facilitate decisions about whether or not to treat with antibiotics.[2,42,43] Although no consensus exists on the best diagnostic strategy for patients clinically suspected of having VAP, the goals are early, appropriate use of antibiotics in patients with true VAP and withholding them in others.[1,2]

The Clinical Strategy

Using this strategy, all patients suspected of having VAP are treated with new antibiotics. The selection of appropriate empirical therapy is based on risk factors and local microbiologic and resistance patterns, and involves qualitative testing to identify possible pathogens. The initial antimicrobial therapy is adjusted according to culture results or clinical response (Fig. 33-2). Antimicrobial treatment is discontinued if and only if the following three criteria are fulfilled on day 3: (1) clinical diagnosis of VAP is unlikely (there are no definite infiltrates found on chest radiography at follow-up and no more than one of the three following findings is present: temperature greater than 38.3°C, leukocytosis or leukopenia, and purulent tracheobronchial secretions) or an alternative noninfectious diagnosis is confirmed; (2) tracheobronchial aspirate culture results are nonsignificant; and (3) severe sepsis or shock is not present.[44]

This clinical approach has two undisputable advantages: first, no specialized microbiologic techniques are required, and, second, the risk of missing a patient who needs antimicrobial treatment is minimal when all suspected patients are treated with new antibiotics.

While the simple qualitative culture of endotracheal aspirates (EAs) is a technique with a high percentage of false-positive results due to bacterial colonization of the proximal airways in many ICU patients, recent studies using quantitative culture techniques suggest that the diagnostic accuracy of EA cultures is similar to the accuracy of more invasive techniques.[45] The inherent advantages of these techniques are that they are less invasive, they are available to nonbronchoscopists, they are less expensive than bronchoscopy, they are less likely to compromise gas exchange, and they can be performed in patients with small endotracheal tubes. The disadvantages include the potential sampling errors inherent in a blind technique and lower specificity for distinguishing airway colonization from true pneumonia.

Another option when using the clinical approach is to follow the strategy described by Singh et al., in which decisions regarding initial antibiotic therapy are based on a clinical score constructed from seven variables, the Clinical Pulmonary Infection Score (CPIS).[46] Patients with a CPIS greater than 6 are treated as having VAP with antibiotics for 10 to 21 days, and antibiotics are discontinued after 3 days if the CPIS is 6 or less (Fig. 33-3). Such an approach avoids prolonged treatment of patients who have a low likelihood of infection, while allowing immediate treatment of patients who are more likely to have VAP. Two conditions must be fulfilled when using this strategy. First, the selection of initial antimicrobial therapy should be based on the most common microbes responsible for VAP at each institution. For example, ciprofloxacin would not be the right choice in hospitals with a high prevalence of MRSA infections. Second, physicians should reevaluate antimicrobial treatment on day 3, when susceptibility patterns of the microorganism(s) recovered from pulmonary secretions are available, in order to select treatment with a narrower spectrum antibiotic.

The Invasive Strategy

This strategy uses quantitative cultures of lower respiratory secretions (BAL or PSB collected with or without a bronchoscope) to define both the presence of pneumonia and the etiologic pathogen. Growth above a threshold concentration is required to make a diagnosis of VAP and determine the causative microorganism(s).[47] Growth below the threshold is assumed to be due to colonization or contamination. Using this strategy, therapeutic decisions are tightly protocolized, using the results of direct examination of distal pulmonary samples and results of quantitative cultures in deciding whether to start antibiotic therapy, which pathogens are responsible for infection, which antimicrobial agents to use, and whether to continue therapy (Fig. 33-4).

Quantitative cultures of BAL and/or PSB specimens consistently yield fewer microorganisms growing above the diagnostic threshold than are present in qualitative cultures of tracheal aspirates.[2,48] Thus, when therapeutic decisions have been based on these data, fewer patients have been treated with antibiotics, and a potentially narrower spectrum of therapy was used, as compared with the clinical approach, thereby limiting the emergence and dissemination of drug-resistant strains and minimizing antibiotic-related toxicity.[43,49]

Another compelling argument in favor of the invasive strategy is that this approach directs attention away from the lungs as the source of fever when BAL/PSB quantitative culture results are negative. Many ICU patients with negative bronchoscopic cultures have other potential sites of infection that need to be identified in order to avoid delays in initiating appropriate treatment.[50]

The accuracy of bronchoscopic techniques is questionable in patients who have received prior antibiotics, particularly when new antibiotics have been introduced after the onset of the symptoms suggestive of nosocomial pneumonia and before pulmonary secretions were collected. However, several investigators have found that cultures of respiratory secretions are not modified in a major way when pneumonia develops in patients who have been receiving systemic antibiotics for several

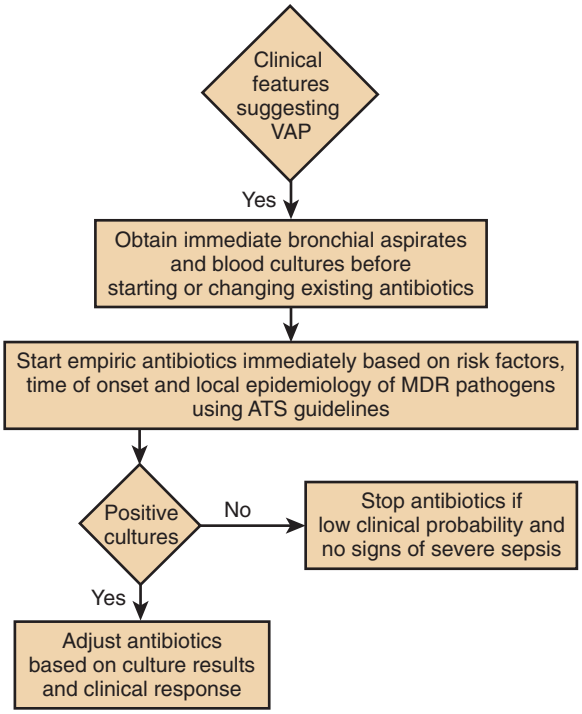

FIGURE 33-2 ■ Diagnostic and therapeutic strategy applied to patients managed with the "clinical" strategy.

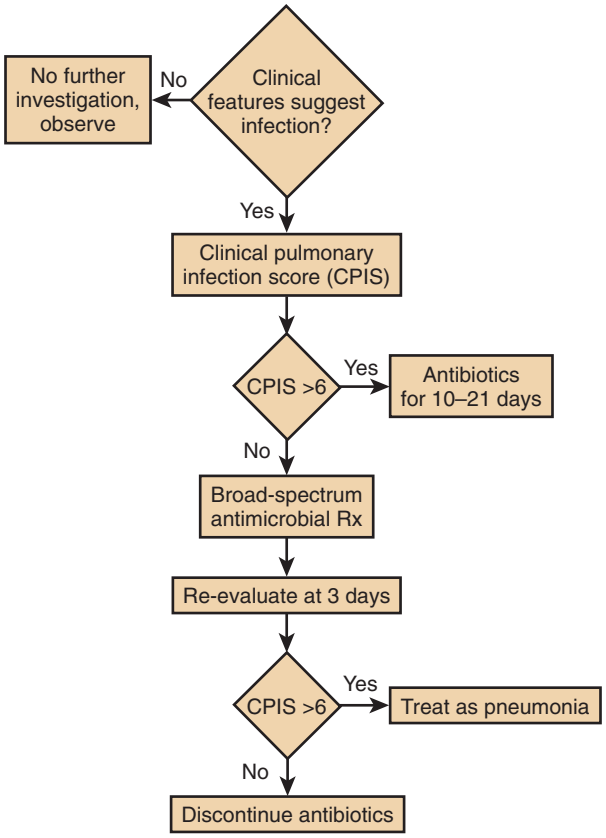

FIGURE 33-3 ■ Diagnostic and therapeutic strategy applied to patients managed with the strategy proposed by Singh et al.[46]

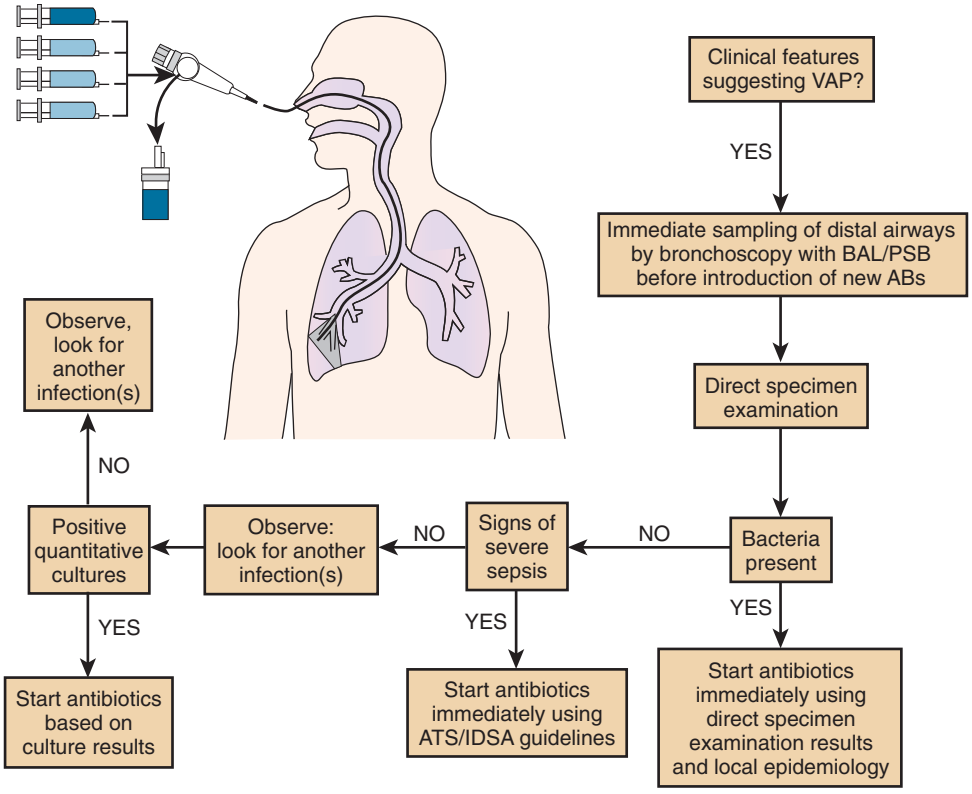

FIGURE 33-4 ■ Diagnostic and therapeutic strategy applied to patients with a clinical suspicion of VAP managed according to the "invasive" strategy.

days before the appearance of the new pulmonary infiltrates. The reason for this appears to be that the bacteria responsible for the new infection are likely to be resistant to the antibiotics that have been used.[51,52] The problem with performing microbiologic cultures of pulmonary secretions after initiation of new antibiotics in patients suspected of having VAP is that the antibiotics can increase the number of false-negative results, regardless of the way in which these secretions are obtained.[52-54]

One major technical problem with all bronchoscopic techniques is proper selection of the sampling area in the tracheobronchial tree. The sampling area is usually selected based on the location of the radiographic infiltrate, or the bronchoscopic identification of a pulmonary segment that has purulent secretions.[55] In patients with diffuse pulmonary infiltrates or minimal new changes in a previously abnormal chest radiograph, determining the correct segment to sample can be difficult. In such cases, sampling should be directed to the area where endobronchial abnormalities are maximal. Because autopsy studies indicate that VAP frequently involves the posterior portion of the right lower lobe, this area should probably be given priority for sampling.[56]

Summary of the Evidence

Aside from decision-analysis studies[57,58] and a single retrospective study,[59] five trials have used a randomized scheme to assess the effect of a diagnostic strategy on antibiotic use and outcome in patients suspected of having VAP.[26,27,43,60,61] In three randomized studies conducted in Spain, no differences were found in mortality and morbidity when either invasive (PSB and/or BAL) or noninvasive (quantitative endotracheal aspirate cultures) techniques were used to diagnose VAP.[26,27,60] These studies were relatively small, ranging from 51 to 88 patients. Antibiotics were continued in all patients despite negative cultures, thereby offsetting the potential advantage of the specific diagnostic test in patients with suspected VAP. Several prospective studies have concluded that antibiotics can be stopped in patients with negative quantitative cultures, without adversely affecting the recurrence of pneumonia and mortality.[42,62,63]

In a French study in which 413 patients were randomized, those receiving bacteriologic management using BAL and/or PSB had a lower mortality rate on day 14, lower sepsis-related organ failure assessment scores on day 3 and 7, and less antibiotic use.[43] Pertinently, 22 nonpulmonary infections were diagnosed in the bacteriologic strategy group and only 5 in the clinical strategy group, suggesting that overdiagnosis of VAP can lead to errors in identifying nonpulmonary infections. A recent randomized trial conducted by the Canadian Critical Care Trials Group investigated the effect of different diagnostic approaches on outcomes of 740 patients suspected of having VAP.[61] There was no difference in the 28-day mortality rate in patients in whom BAL was used, versus those in whom endotracheal aspiration was used as the diagnostic strategy. The BAL group and the endotracheal aspiration group also had similar rates of targeted antibiotic therapy on day 6, days alive without antibiotics, and maximum organ dysfunction scores. Unfortunately, information about how the decision algorithms were followed in the two diagnostic arms once cultures were available was not provided, raising uncertainties about how de-escalation of antibiotic therapy was pursued in patients with negative BAL cultures. Obviously, the potential benefit of using a diagnostic tool such as BAL for safely restricting unnecessary antimicrobial therapy in such a setting can only be obtained when decisions regarding antibiotics are closely linked to bacteriologic results, including both direct examination and cultures of respiratory specimens.

TREATMENT

Antimicrobial therapy of patients with VAP is a two-stage process. The first stage involves administering broad-spectrum antibiotics to avoid inappropriate treatment in patients with true bacterial pneumonia.[1] The second stage focuses on trying to achieve this objective without overusing or abusing antibiotics. In general, the first goal can be accomplished by identifying patients with pneumonia in a rapid fashion and starting therapy with an empirical regimen that is likely to treat the most common etiologic agents in a particular institution. This requires that the initial antibiotic choice be driven by knowledge of the likely etiologic pathogens, and the local patterns of antimicrobial resistance. The second goal involves stopping therapy in patients with a low probability of VAP, focusing and narrowing treatment once the etiologic agent is known, switching to monotherapy after day 3 whenever possible, and shortening the duration of therapy to 7 to 8 days in most patients, as determined by the patient's clinical response and information about the bacteriology (Table 33-1).

Initial Treatment

Failure to initiate prompt appropriate therapy (i.e., using an agent to which the etiologic organism is sensitive, with the optimal dose and route of administration) has been consistently linked with increased mortality in patients with VAP.[28,41,64] Due to the emergence of multiresistant GNB, such as *P. aeruginosa* and/or extended-spectrum β-lactamase–producing Enterobacteriaceae in many institutions and the increasing role of gram-positive bacteria, such as MRSA, empiric treatment with broad-spectrum antibiotics is justified in most patients with a clinical suspicion of VAP.[2,3] The choice of agents should be based on local patterns of antimicrobial susceptibility and anticipated side effects, and should also take into account the antibiotics that the patients have received within the prior 2 weeks, striving not to use the same antimicrobial classes, if possible.[65,66] Having

TABLE 33-1. Proposed Strategy for Conducting Antimicrobial Therapy in Patients with VAP

Proposed Strategy	Rationale
Step 1: Start therapy using broad-spectrum antibiotics	Due to the emergence of multiresistant GNB, such as *P. aeruginosa* and ESBL-producing GNB in many institutions, and the increasing role of MRSA, empiric treatment with broad-spectrum antibiotics is justified in most patients with a clinical suspicion of VAP.
Step 2: Stop therapy if the diagnosis of infection becomes unlikely	The goal is to ensure that ICU patients with true bacterial infection receive immediate appropriate treatment. However, this can result in more patients receiving antimicrobial therapy than necessary, because clinical signs of infection are nonspecific.
Step 3: Use narrower spectrum antibiotics, once the etiologic agent is identified	For many patients with VAP, including those with late-onset infection, therapy can be narrowed once the results of respiratory tract and blood cultures are available, either because an anticipated organism (such as *P. aeruginosa* and *Acinetobacter* spp. or MRSA) was not recovered, or because the organism isolated is sensitive to a more narrow-spectrum antibiotic than used in the initial regimen.[63,64]
Step 4: Use pharmacokinetic-pharmacodynamic data to optimize treatment	Clinical and bacteriologic outcomes can be improved by optimizing the therapeutic regimen according to pharmacokinetic and pharmacodynamic properties of the agent(s) selected for treatment.
Step 5: Switch to monotherapy on days 3–5	There are no clinical benefits to using a regimen combining two antibiotics for more than days 3–5, provided that initial therapy was appropriate, the clinical course appears favorable, and microbiologic data do not point to a very difficult-to-treat microorganism.
Step 6: Shorten the duration of therapy	Reducing duration of therapy in patients with VAP has led to good outcomes with less antibiotic use. Prolonged therapy leads to colonization with antibiotic-resistant bacteria, which may precede a recurrent episode of VAP.

ESBL, extended-spectrum β-lactamase; GNB, gram-negative bacteria; ICU, intensive care unit; MRSA, methicillin-resistant *Staphylococcus aureus;* VAP, ventilator-associated pneumonia.

current knowledge about local bacteriologic patterns can increase the likelihood that appropriate initial antibiotic treatment will be prescribed.[67] Only patients with early-onset infection and no specific risk factors, such as prolonged duration of hospitalization, admission from a health care–related facility, and recent prolonged antibiotic therapy, can be treated with a relatively narrow-spectrum drug, such as a nonpseudomonal third-generation cephalosporin.[1]

Several published reports have shown a relationship among serum concentrations of β-lactams or other antibiotics, the minimal inhibitory concentration (MIC) of the infecting organism, and the rate of bacterial eradication from respiratory secretions in patients with lung infection.[68–70] Consequently, clinical and bacteriologic outcomes can be improved by optimizing the therapeutic regimen according to pharmacokinetic properties of the antimicrobial(s) selected for treatment. Development of dosing algorithms based on a drug's MIC, the patient's creatinine clearance and weight, and pharmacokinetic-pharmacodynamic parameters might be a way to improve treatment of these patients, because this overall approach is more precise than current guidelines for use of antimicrobial agents.

Avoiding the Overuse of Antibiotics

The need to ensure that ICU patients with true bacterial infections promptly receive an appropriate antibiotic regimen can lead to many more patients receiving antimicrobial therapy than is actually necessary, because clinical signs of infection are relatively nonspecific. Thus, when a clinical approach to VAP is used, it is important to perform serial clinical and microbiologic evaluations, and reevaluate therapy after 48 to 72 hours so that therapy can be stopped if infection is unlikely. To accomplish this, all diagnostic strategies that are designed for managing patients with a clinical suspicion of VAP should make explicit the decision tree that is used to identify patients with a low probability of infection, in whom therapy can be stopped when infection appears improbable.

For many patients with VAP, including those with late-onset infection, therapy can be narrowed once the results of respiratory tract and blood cultures are available, because a resistant organism (such as *P. aeruginosa* and *Acinetobacter* spp. or MRSA) is not recovered or because the organism isolated is sensitive to a narrower spectrum antibiotic than used in the initial regimen. For example, vancomycin and linezolid should be stopped if MRSA is not identified, unless the patient is allergic to β-lactams or has developed an infection caused by a gram-positive microorganism. Very-broad-spectrum agents, such as carbapenems, piperacillin-tazobactam, and/or cefepime, should also be restricted to patients with infection caused by pathogens that are only susceptible to these agents. Clinicians must be aware that the emergence of resistant mutants may lead to treatment failure when third-generation cephalosporins are chosen to treat infections caused by *Enterobacter, Citrobacter, Morganella morgannii,* indole-positive *Proteus,* and *Serratia* spp., even if the isolate is initially susceptible.

The most common reason to use combination therapy in initial management of patients with VAP is to achieve synergy in treating *P. aeruginosa* or other difficult-to-treat GNB. However, antibiotic synergy has only been

shown to be valuable in vitro and in patients with neutropenia[71] or bacteremic infection,[72] which is uncommon in VAP. A recent meta-analysis evaluated all prospective randomized trials of β-lactam monotherapy as compared with β-lactam/aminoglycoside combination regimens in 7586 patients with sepsis, of whom at least 1200 patients had VAP.[73] The clinical success rates were similar with monotherapy versus combination therapy, and combination therapy had no advantage in the treatment of *P. aeruginosa* infections. Importantly, combination therapy did not prevent the emergence of antimicrobial resistance during treatment, but it was associated with a significantly higher rate of nephrotoxicity. Based on these data, therapy could be switched to monotherapy in most patients after 3 or 5 days, provided that initial therapy was appropriate, the clinical course is favorable, and microbiologic data do not identify a difficult-to-treat microorganism with a high in vitro MIC, as is found with some lactose-nonfermenting GNB.

Efforts to reduce the duration of therapy for VAP are justified by studies of the natural history of the response to therapy. Most patients with VAP who receive appropriate antimicrobial therapy have a good clinical response within the first 6 days.[74–76] Prolonged therapy leads to colonization with antibiotic-resistant bacteria, which may precede a recurrent episode of VAP. A multicenter, randomized, controlled trial in 401 patients with microbiologically proven VAP showed that the clinical outcomes of patients who received appropriate empiric therapy for 8 days were similar to those of patients who received therapy for 15 days.[77] A trend to greater rates of relapse for short-duration therapy was seen if the etiologic agent was *P. aeruginosa* or *Acinetobacter* spp., but the clinical outcomes were exactly the same. These results have been confirmed in two later studies, including a prospective, randomized trial of 290 patients evaluating an antibiotic discontinuation policy.[78,79]

PREVENTION

Because VAP is associated with increased morbidity, longer hospital stay, increased health care costs, and higher mortality rates, prevention is a major challenge for all ICU personnel.[1,80,81]

Conventional Infection Control Approaches

Conventional approaches should be the first steps taken in all prevention programs. The design of the ICU has a direct effect on the potential for nosocomial infections. Adequate space and lighting, properly functioning ventilation systems, and appropriate handwashing facilities all lead to lower infection rates.[82] It is important to note, however, that upgrading the physical environment does not reduce the infection rate unless the attitudes and practices of health care personnel are also improved. In any ICU, one of the most important factors is the health care staff, including the number, quality, and motivation of medical, nursing, and ancillary members. The team should include a sufficient number of nurses to minimize their movement from one patient to another and to avoid having them work under constant pressure.[83–85] The importance of personal cleanliness and attention to aseptic procedures must be emphasized at every opportunity. It is clear that careful monitoring, decontamination, and compliance with guidelines for the use of respiratory equipment all reduce the incidence of nosocomial pneumonia.[86] In particular, handwashing and handrubbing with alcohol-based solutions remain the most important components of effective infection control practices in the ICU.[87,88]

Environmental and patient-oriented microbiologic monitoring facilitates the early recognition of colonization and infection, and has been associated with significant reductions in nosocomial infection rates.[89] The focal point for infection control activities in the ICU is a surveillance system designed to establish and maintain a database that identifies endemic rates of nosocomial infections. This information facilitates the recognition of epidemics, when infection rates rise above the endemic threshold for a specific type of nosocomial infection.

Adoption of an antibiotic policy that restricts the prescription of broad-spectrum agents and inappropriate antibiotics is of major importance. Better use of antibiotics in the ICU can be achieved by implementing strict guidelines, avoiding the treatment of patients who do not have bacterial infections, using narrow-spectrum antibiotics whenever possible, and reducing the duration of treatment.[90,91] Similarly, transfusion of red blood cells and other allogenic blood products should follow a strict policy, because several studies have identified exposure to allogenic blood products as a risk factor for postoperative infection and pneumonia.[92,93]

Specific Prophylaxis against VAP

Specific strategies aimed at reducing the duration of mechanical ventilation (a major risk factor for VAP), such as improved methods of sedation,[94] use of protocols to facilitate and accelerate weaning,[94–96] using adequate levels of positive end-expiratory pressure,[97] and also using intensive insulin therapy to control blood glucose[98] should be considered as integral parts of any infection control program. All are based on the application of strict protocols. Similarly, noninvasive positive-pressure ventilation using a face mask should be employed whenever possible.[99]

Some very simple, safe, inexpensive, and logical measures may have major effects on the frequency of VAP in mechanically ventilated patients.[1,88] These include avoiding nasal insertion of endotracheal and gastric tubes[100]; maintaining the endotracheal tube cuff pressure above 20 cm H_2O to prevent leakage of bacteria around the cuff

into the lower respiratory tract[101]; promptly reintubating patients who are likely to fail extubation[102]; keeping patients in the semirecumbent position, especially when enteral nutrition is used[103]; removing tubing condensate[104]; and providing meticulous oral hygiene[105] or using an antiseptic such as chlorhexidine.[106]

Continuous or intermittent suctioning of oropharyngeal secretions using a specially designed endotracheal tube with a separate lumen that opens into the subglottic region has been proposed as a means to avoid chronic aspiration of secretions around the endotracheal cuff of intubated patients.[107,108] While most studies that have evaluated this approach demonstrated that VAP development was delayed, the incidence of VAP caused by *P. aeruginosa* or Enterobacteriaceae did not differ with or without subglottic suctioning, and no difference in mortality rates was observed. Recent data from animal models and randomized human studies, including a large trial, support the hypothesis that an endotracheal tube coated externally and internally with a potent antiseptic product such as silver has a sustained antimicrobial effect in the proximal airways, blocking biofilm formation at its surface and significantly reducing the VAP rate.[109–112]

Gastric colonization by potentially pathogenic organisms increases with decreasing gastric acidity.[113] Thus, medications that decrease gastric acidity (antacids, histamine$_2$ [H_2] blockers) can increase the gastric bacterial burden and increase the risk of VAP. In contrast, medications that do not affect gastric acidity (e.g., sucralfate) do not appear to increase this risk. Several meta-analyses of more than 20 randomized trials have evaluated the risk for VAP associated with methods used to prevent gastrointestinal bleeding in critically ill patients.[114] The largest randomized trial comparing ranitidine to sucralfate showed that ranitidine was superior in preventing gastrointestinal bleeding and did not increase the risk of VAP.[115] Therefore, despite the potential advantage of sucralfate (potentially less VAP with more gastrointestinal bleeding) over H_2 blockers (potentially more VAP with less gastrointestinal bleeding) in preventing VAP, stress ulcer prophylaxis with H_2 blockers appears to be safe in patients who are at high risk for bleeding as well as VAP.

Several groups have used topical prophylactic antibiotics for selective decontamination of the oropharynx and digestive tract (SDD) in patients at high risk for nosocomial pneumonia. The SDD regimen usually includes a short course of systemic antibiotic therapy, such as cefotaxime, trimethoprim, or a fluoroquinolone, combined with nonabsorbable local antibiotic prophylaxis, consisting of a combination of an aminoglycoside, polymyxin B, and amphotericin. Since the original study published by Stoutenbeek et al. in 1984,[116] which demonstrated a decrease of the overall infection rate in patients receiving the SDD regimen, more than 40 randomized, controlled trials, and 7 meta-analyses have been published.[117,118] All seven meta-analyses reported a significant reduction in the risk of VAP, and four reported a significant reduction in mortality. No mortality benefit was seen with topical prophylaxis alone. A clear consensus as to the effectiveness of SDD has not developed, however, because of discordances among the meta-analyses related to limitations and methodologic deficiencies of the analyzed studies. Particular problems include the use of clinical diagnosis of pneumonia as a study end point, the heterogeneity of the populations studied, the wide variety of oral regimens, the inconsistent addition of systemic antibiotics (cefotaxime or ceftazidime), and differences in analytic methods.[80,81] Recently, De Jonge et al. were able to show, in a large, prospective, randomized, unblinded clinical trial of 934 patients, that SDD decreases ICU and hospital mortality and colonization with resistant aerobic GNB in settings with a low prevalence of vancomycin-resistant enterococci and MRSA.[119]

Implementing a Structured Prevention Policy

The application of consistent evidence-based interventions to prevent VAP has been highly variable from one ICU to another, and often suboptimal. Furthermore, no single preventive measure can succeed alone, emphasizing the need to use multifaceted and multidisciplinary programs to prevent VAP. Such programs are frequently referred to as "care bundles." A care bundle is a set of readily implementable interventions that are required to be undertaken for each patient on a regular basis.[120] The key goal is that every intervention must be implemented for every patient on every day of his or her stay in the ICU. Compliance is assessed for the bundle as a whole, so failure to complete even a single intervention means failure of the whole bundle at a particular assessment. The interventions need to be packaged in such a way that they are easy to assess for compliance, which usually means that no more than five interventions are included in each care bundle. The performance goal is to routinely achieve over 95% compliance. Care bundles make it possible to introduce evidence-based preventive measures, including appropriate nurse staffing levels, hand hygiene with alcohol-based formulations, standardized weaning protocols and daily interruption of sedation, oral care with chlorhexidine, and keeping patients who receive enteral nutrition in a semirecumbent position.[121] All of these measures can be consistently applied to all patients in a coordinated way. Recent experience confirms the positive effects of these approaches in reducing the frequency of VAP.[122–125] The newer emphasis on care bundles in the ICU is shifting the focus from the diagnosis and treatment of VAP to the more important goal of preventing VAP from occurring in the first place.

KEY POINTS

- VAP is associated with mortality in excess of that caused by the underlying disease alone, particularly in the case of infection due to high-risk pathogens, such as *P. aeruginosa* and MRSA.
- The predominant organisms responsible for infection are *S. aureus, P. aeruginosa,* and Enterobacteriaceae, but etiologic agents widely differ according to the population of hospital patients, the duration of hospital stay, and prior antimicrobial therapy.
- Because even a few doses of a new antimicrobial agent can negate results of microbiologic cultures, pulmonary secretions in patients suspected of having developed VAP should always be obtained before new antibiotics are administered.
- Antimicrobial therapy of patients with VAP should follow a two-stage process. The first stage involves administering broad-spectrum antibiotics to avoid inappropriate treatment in patients with true bacterial pneumonia.
- The second stage focuses on trying to achieve this objective without overusing and abusing antibiotics, combining a number of different steps, such as stopping therapy in patients with a low probability of VAP, streamlining treatment once the etiologic agent is known, switching to monotherapy after days 3 to 5, and shortening duration of therapy to 7 to 8 days, as dictated by the patient's clinical response to therapy and information about the bacteriology of the infection.
- Some very simple, no-cost measures, such as maintaining the endotracheal tube cuff pressure above 20 cm H_2O to prevent leakage of bacteria around the cuff into the lower respiratory tract, promptly reintubating patients who are failing extubation, oral care with chlorhexidine, keeping patients in the semirecumbent position especially in the case of enteral nutrition, removal of ventilator tubing condensates with minimal exposure to patients, and reducing the duration of ventilation have an important effect on decreasing the frequency of VAP.

References

1. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med 171:388–416, 2005.
2. Chastre J, Fagon JY: Ventilator-associated pneumonia. Am J Respir Crit Care Med 165:867–903, 2002.
3. National Nosocomial Infections Surveillance (NNIS) System report, data summary from January 1990–May 1999, issued June 1999. Am J Infect Control 27:520–532, 1999.
4. Bergmans DC, Bonten MJ, Gaillard CA, et al: Indications for antibiotic use in ICU patients: A one-year prospective surveillance. J Antimicrob Chemother 39:527–535, 1997.
5. Estes RJ, Meduri GU: The pathogenesis of ventilator-associated pneumonia: I. Mechanisms of bacterial transcolonization and airway inoculation. Intensive Care Med 21:365–383, 1995.
6. Meduri GU, Estes RJ: The pathogenesis of ventilator-associated pneumonia: II. The lower respiratory tract. Intensive Care Med 21:452–461, 1995.
7. Craven DE, De Rosa FG, Thornton D: Nosocomial pneumonia: Emerging concepts in diagnosis, management, and prophylaxis. Curr Opin Crit Care 8:421–429, 2002.
8. Torres A, Serra-Batlles J, Ros E, et al: Pulmonary aspiration of gastric contents in patients receiving mechanical ventilation: The effect of body position. Ann Intern Med 116:540–543, 1992.
9. Bonten MJ, Gaillard CA, de Leeuw PW, et al: Role of colonization of the upper intestinal tract in the pathogenesis of ventilator-associated pneumonia. Clin Infect Dis 24:309–319, 1997.
10. Cook DJ, Walter SD, Cook RJ, et al: Incidence of and risk factors for ventilator-associated pneumonia in critically ill patients. Ann Intern Med 129:433–440, 1998.
11. Bonten MJ, Bergmans DC, Speijer H, et al: Characteristics of polyclonal endemicity of *Pseudomonas aeruginosa* colonization in intensive care units: Implications for infection control. Am J Respir Crit Care Med 160:1212–1219, 1999.
12. Bonten MJ, Gaillard CA, van Tiel FH, et al: The stomach is not a source for colonization of the upper respiratory tract and pneumonia in ICU patients. Chest 105:878–884, 1994.
13. Bonten MJ, Kullberg BJ, van Dalen R, et al: Selective digestive decontamination in patients in intensive care. J Antimicrob Chemother 46:351–362, 2000.
14. Cross AS, Roup B: Role of respiratory assistance devices in endemic nosocomial pneumonia. Am J Med 70:681–685, 1981.
15. Horan TC, Culver DH, Gaynes RP, et al: Nosocomial infections in surgical patients in the United States, January 1986–June 1992. National Nosocomial Infections Surveillance (NNIS) System. Infect Control Hosp Epidemiol 14:73–80, 1993.
16. Chastre J, Trouillet JL, Vuagnat A, et al: Nosocomial pneumonia in patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 157:1165–1172, 1998.
17. Delclaux C, Roupie E, Blot F, et al: Lower respiratory tract colonization and infection during severe acute respiratory distress syndrome: Incidence and diagnosis. Am J Respir Crit Care Med 156:1092–1098, 1997.
18. Markowicz P, Wolff M, Djedaini K, et al: Multicenter prospective study of ventilator-associated pneumonia during acute respiratory distress syndrome: Incidence, prognosis, and risk factors. ARDS Study Group. Am J Respir Crit Care Med 161:1942–1948, 2000.
19. Meduri GU, Reddy RC, Stanley T, et al: Pneumonia in acute respiratory distress syndrome: A prospective evaluation of bilateral bronchoscopic sampling. Am J Respir Crit Care Med 158:870–875, 1998.
20. Fagon JY, Chastre J, Vuagnat A, et al: Nosocomial pneumonia and mortality among patients in intensive care units. JAMA 275:866–869, 1996.
21. Vincent JL, Bihari DJ, Suter PM, et al: The prevalence of nosocomial infection in intensive care units in Europe: Results of the European Prevalence of Infection in Intensive Care (EPIC) Study. EPIC International Advisory Committee. JAMA 274:639–644, 1995.

22. Melsen WG, Rovers MM, Bonten MJ: Ventilator-associated pneumonia and mortality: a systematic review of observational studies. Crit Care Med 37:2709–2718, 2009.
23. Falagas ME, Kouranos VD, Michalopoulos A, et al: Inadequate statistical power of published comparative cohort studies on ventilator-associated pneumonia to detect mortality differences. Clin Infect Dis 15:468–472, 2010.
24. Bueno-Cavanillas A, Delgado-Rodriguez M, Lopez-Luque A, et al: Influence of nosocomial infection on mortality rate in an intensive care unit. Crit Care Med 22:55–60, 1994.
25. Rello J, Ausina V, Ricart M, et al: Impact of previous antimicrobial therapy on the etiology and outcome of ventilator-associated pneumonia. Chest 104:1230–1235, 1993.
26. Sanchez-Nieto JM, Torres A, Garcia-Cordoba F, et al: Impact of invasive and noninvasive quantitative culture sampling on outcome of ventilator-associated pneumonia: A pilot study [see comments]. Am J Respir Crit Care Med 157:371–376, 1998 [published erratum appears in Am J Respir Crit Care Med 157(3 Pt 1):1005, 1998].
27. Ruiz M, Torres A, Ewig S, et al: Noninvasive versus invasive microbial investigation in ventilator-associated pneumonia: Evaluation of outcome. Am J Respir Crit Care Med 162:119–125, 2000.
28. Alvarez-Lerma F: Modification of empiric antibiotic treatment in patients with pneumonia acquired in the intensive care unit. ICU-Acquired Pneumonia Study Group. Intensive Care Med 22:387–394, 1996.
29. Kollef MH: Antimicrobial therapy of ventilator-associated pneumonia: How to select an appropriate drug regimen. Chest 115:8–11, 1999.
30. Combes A, Luyt CE, Fagon JY, et al: Early predictors for infection recurrence and death in patients with ventilator-associated pneumonia. Crit Care Med 35:146–154, 2007.
31. Heyland DK, Cook DJ, Griffith L, et al: The attributable morbidity and mortality of ventilator-associated pneumonia in the critically ill patient. The Canadian Critical Trials Group. Am J Respir Crit Care Med 159:1249–1256, 1999.
32. Baker AM, Meredith JW, Haponik EF: Pneumonia in intubated trauma patients: Microbiology and outcomes. Am J Respir Crit Care Med 153:343–349, 1996.
33. Muscedere JG, Martin CM, Heyland DK: The impact of ventilator-associated pneumonia on the Canadian health care system. J Crit Care 23:5–10, 2008.
34. Combes A, Figliolini C, Trouillet JL, et al: Incidence and outcome of polymicrobial ventilator-associated pneumonia. Chest 121:1618–1623, 2002.
35. Trouillet JL, Chastre J, Vuagnat A, et al: Ventilator-associated pneumonia caused by potentially drug-resistant bacteria. Am J Respir Crit Care Med 157:531–539, 1998.
36. Ibrahim EH, Ward S, Sherman G, et al: A comparative analysis of patients with early-onset vs late-onset nosocomial pneumonia in the ICU setting. Chest 117:1434–1442, 2000.
37. Giantsou E, Liratzopoulos N, Efraimidou E, et al: Both early-onset and late-onset ventilator-associated pneumonia are caused mainly by potentially multiresistant bacteria. Intensive Care Med 31:1488–1494, 2005.
38. Bruynseels P, Jorens PG, Demey HE, et al: Herpes simplex virus in the respiratory tract of critical care patients: A prospective study. Lancet 362:1536–1541, 2003.
39. Luyt CE, Combes A, Deback C, et al: Herpes simplex virus lung infection in patients undergoing prolonged mechanical ventilation. Am J Respir Crit Care Med 175:935–942, 2007.
40. Rello J, Esandi ME, Diaz E, et al: The role of *Candida* sp isolated from bronchoscopic samples in nonneutropenic patients. Chest 114:146–149, 1998.
41. Iregui M, Ward S, Sherman G, et al: Clinical importance of delays in the initiation of appropriate antibiotic treatment for ventilator-associated pneumonia. Chest 122:262–268, 2002.
42. Bonten MJ, Bergmans DC, Stobberingh EE, et al: Implementation of bronchoscopic techniques in the diagnosis of ventilator-associated pneumonia to reduce antibiotic use. Am J Respir Crit Care Med 156:1820–1824, 1997.
43. Combes A, Luyt CE, Trouillet JL, Chastre J: Controversies in ventilator-associated pneumonia. Semin Respir Crit Care Med 31:47–54, 2010.
44. Torres A, Ewig S: Diagnosing ventilator-associated pneumonia. N Engl J Med 350:433–435, 2004.
45. Cook D, Mandell L: Endotracheal aspiration in the diagnosis of ventilator-associated pneumonia. Chest 117:195S–197S, 2000.
46. Singh N, Rogers P, Atwood CW, et al: Short-course empiric antibiotic therapy for patients with pulmonary infiltrates in the intensive care unit: A proposed solution for indiscriminate antibiotic prescription. Am J Respir Crit Care Med 162:505–511, 2000.
47. Chastre J, Fagon JY, Bornet-Lecso M, et al: Evaluation of bronchoscopic techniques for the diagnosis of nosocomial pneumonia. Am J Respir Crit Care Med 152:231–240, 1995.
48. Baselski VS, Wunderink RG: Bronchoscopic diagnosis of pneumonia. Clin Microbiol Rev 7:533–558, 1994.
49. Shorr AF, Sherner JH, Jackson WL, et al: Invasive approaches to the diagnosis of ventilator-associated pneumonia: A meta-analysis. Crit Care Med 33:46–53, 2005.
50. Meduri GU, Mauldin GL, Wunderink RG, et al: Causes of fever and pulmonary densities in patients with clinical manifestations of ventilator-associated pneumonia. Chest 106:221–235, 1994.
51. Johanson WG Jr, Seidenfeld JJ, Gomez P, et al: Bacteriologic diagnosis of nosocomial pneumonia following prolonged mechanical ventilation. Am Rev Respir Dis 137:259–264, 1988.
52. Souweine B, Mom T, Traore O, et al: Ventilator-associated sinusitis: Microbiological results of sinus aspirates in patients on antibiotics. Anesthesiology 93:1255–1260, 2000.
53. Montravers P, Fagon JY, Chastre J, et al: Follow-up protected specimen brushes to assess treatment in nosocomial pneumonia. Am Rev Respir Dis 147:38–44, 1993.
54. Prats E, Dorca J, Pujol M, et al: Effects of antibiotics on protected specimen brush sampling in ventilator-associated pneumonia. Eur Respir J 19:944–951, 2002.
55. Meduri GU, Chastre J: The standardization of bronchoscopic techniques for ventilator- associated pneumonia. Chest 102:557S–564S, 1992.
56. Rouby JJ, Martin De Lassale E, Poete P, et al: Nosocomial bronchopneumonia in the critically ill: Histologic and bacteriologic aspects [see comments]. Am Rev Respir Dis 146:1059–1066, 1992.
57. Baker AM, Bowton DL, Haponik EF: Decision making in nosocomial pneumonia: An analytic approach to the interpretation of quantitative bronchoscopic cultures. Chest 107:85–95, 1995.
58. Sterling TR, Ho EJ, Brehm WT, et al: Diagnosis and treatment of ventilator-associated pneumonia—impact on survival: A decision analysis. Chest 110:1025–1034, 1996.
59. Heyland DK, Cook DJ, Marshall J, et al: The clinical utility of invasive diagnostic techniques in the setting of ventilator-associated pneumonia. Canadian Critical Care Trials Group. Chest 115:1076–1084, 1999.
60. Sole Violan J, Fernandez JA, Benitez AB, et al: Impact of quantitative invasive diagnostic techniques in the management and outcome of mechanically ventilated patients with suspected pneumonia. Crit Care Med 28:2737–2741, 2000.
61. Heyland D, Dodek P, Muscedere J, et al: A randomized trial of diagnostic techniques for ventilator-associated pneumonia. N Engl J Med 355:2619–2630, 2006.
62. Croce MA, Fabian TC, Waddle-Smith L, et al: Utility of Gram's stain and efficacy of quantitative cultures for posttraumatic pneumonia: A prospective study. Ann Surg 227:743–751, 1998 [discussion appears in Ann Surg 227:751–755, 1998].
63. Joffe AR, Muscedere J, Marshall JC, et al: The safety of targeted antibiotic therapy for ventilator-associated pneumonia: A multicenter observational study. J Crit Care 23:82–90, 2008.
64. Rello J, Gallego M, Mariscal D, et al: The value of routine microbial investigation in ventilator-associated pneumonia. Am J Respir Crit Care Med 156:196–200, 1997.
65. Trouillet JL, Vuagnat A, Combes A, et al: *Pseudomonas aeruginosa* ventilator-associated pneumonia: Comparison of episodes due to piperacillin-resistant versus piperacillin-susceptible organisms. Clin Infect Dis 34:1047–1054, 2002.
66. Bhat S, Fujitani S, Potoski BA, et al: *Pseudomonas aeruginosa* infections in the intensive care unit: Can the adequacy of empirical beta-lactam antibiotic therapy be improved? Int J Antimicrob Agents 30:458–462, 2007.
67. Rello J, Sa-Borges M, Correa H, et al: Variations in etiology of ventilator-associated pneumonia across four treatment sites:

Implications for antimicrobial prescribing practices. Am J Respir Crit Care Med 160:608–613, 1999.
68. Forrest A, Nix DE, Ballow CH, et al: Pharmacodynamics of intravenous ciprofloxacin in seriously ill patients. Antimicrob Agents Chemother 37:1073–1081, 1993.
69. Kashuba AD, Nafziger AN, Drusano GL, et al: Optimizing aminoglycoside therapy for nosocomial pneumonia caused by gram-negative bacteria. Antimicrob Agents Chemother 43:623–629, 1999.
70. Schentag JJ: Pharmacokinetic and pharmacodynamic surrogate markers: Studies with fluoroquinolones in patients. Am J Health Syst Pharm 56:S21–S24, 1999.
71. Ceftazidime combined with a short or long course of amikacin for empirical therapy of gram-negative bacteremia in cancer patients with granulocytopenia. The EORTC International Antimicrobial Therapy Cooperative Group. N Engl J Med 317:1692–1698, 1987.
72. Korvick JA, Bryan CS, Farber B, et al: Prospective observational study of *Klebsiella* bacteremia in 230 patients: Outcome for antibiotic combinations versus monotherapy. Antimicrob Agents Chemother 36:2639–2644, 1992.
73. Paul M, Soares-Weiser K, Leibovici L: Beta lactam monotherapy versus beta lactam-aminoglycoside combination therapy for fever with neutropenia: Systematic review and meta-analysis. BMJ 326:1111, 2003.
74. Dennesen PJ, van der Ven AJ, Kessels AG, et al: Resolution of infectious parameters after antimicrobial therapy in patients with ventilator-associated pneumonia. Am J Respir Crit Care Med 163:1371–1375, 2001.
75. Luna CM, Blanzaco D, Niederman MS, et al: Resolution of ventilator-associated pneumonia: Prospective evaluation of the Clinical Pulmonary Infection Score as an early clinical predictor of outcome. Crit Care Med 31:676–682, 2003.
76. Combes A, Figliolini C, Trouillet JL, et al: Factors predicting ventilator-associated pneumonia recurrence. Crit Care Med 31:1102–1107, 2003.
77. Chastre J, Wolff M, Fagon JY, et al: Comparison of 8 vs 15 days of antibiotic therapy for ventilator-associated pneumonia in adults: a randomized trial. JAMA 290:2588–2598, 2003.
78. Micek ST, Ward S, Fraser VJ, et al: A randomized controlled trial of an antibiotic discontinuation policy for clinically suspected ventilator-associated pneumonia. Chest 125:1791–1799, 2004.
79. Ibrahim EH, Ward S, Sherman G, et al: Experience with a clinical guideline for the treatment of ventilator-associated pneumonia. Crit Care Med 29:1109–1115, 2001.
80. Dodek P, Keenan S, Cook D, et al: Evidence-based clinical practice guideline for the prevention of ventilator-associated pneumonia. Ann Intern Med 141:305–313, 2004.
81. Collard HR, Saint S, Matthay MA: Prevention of ventilator-associated pneumonia: an evidence-based systematic review. Ann Intern Med 138:494–501, 2003.
82. du Moulin G: Minimizing the potential for nosocomial pneumonia: Architectural, engineering, and environmental considerations for the intensive care unit. Eur J Clin Microbiol Infect Dis 8:69–74, 1989.
83. Needleman J, Buerhaus P, Mattke S, et al: Nurse-staffing levels and the quality of care in hospitals. N Engl J Med 346:1715–1722, 2002.
84. Aiken LH, Clarke SP, Cheung RB, et al: Educational levels of hospital nurses and surgical patient mortality. JAMA 290:1617–1623, 2003.
85. Hugonnet S, Uckay I, Pittet D: Staffing level: A determinant of late-onset ventilator-associated pneumonia. Crit Care 11:R80, 2007.
86. Guidelines for prevention of nosocomial pneumonia. Centers for Disease Control and Prevention. MMWR Morb Mortal Wkly Rep 46:1–79, 1997.
87. Pittet D, Mourouga P, Perneger TV: Compliance with handwashing in a teaching hospital. Infection Control Program. Ann Intern Med 130:126–130, 1999.
88. Tablan OC, Anderson LJ, Besser R, et al: Guidelines for preventing health-care–associated pneumonia, 2003: Recommendations of CDC and the Healthcare Infection Control Practices Advisory Committee. MMWR Recomm Rep 53:1–36, 2004.
89. Haley RW, Culver DH, White JW, et al: The efficacy of infection surveillance and control programs in preventing nosocomial infections in US hospitals. Am J Epidemiol 121:182–205, 1985.
90. Kollef MH: Optimizing antibiotic therapy in the intensive care unit setting. Crit Care 5:189–195, 2001.
91. Struelens MJ, Byl B, Vincent JL: Antibiotic policy: A tool for controlling resistance of hospital pathogens. Clin Microbiol Infect 5:S19–S24, 1999.
92. Leal-Noval SR, Marquez-Vacaro JA, Garcia-Curiel A, et al: Nosocomial pneumonia in patients undergoing heart surgery. Crit Care Med 28:935–940, 2000.
93. Shorr AF, Duh MS, Kelly KM, et al: Red blood cell transfusion and ventilator-associated pneumonia: A potential link? Crit Care Med 32:666–674, 2004.
94. Kress JP, Pohlman AS, O'Connor MF, et al: Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. N Engl J Med 342:1471–1477, 2000.
95. Girard TD, Kress JP, Fuchs BD, et al: Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): A randomised controlled trial. Lancet 371:126–134, 2008.
96. Ely EW, Baker AM, Dunagan DP, et al: Effect on the duration of mechanical ventilation of identifying patients capable of breathing spontaneously. N Engl J Med 335:1864–1869, 1996.
97. Manzano F, Fernandez-Mondejar E, Colmenero M, et al: Positive-end expiratory pressure reduces incidence of ventilator-associated pneumonia in nonhypoxemic patients. Crit Care Med 36:2225–2231, 2008.
98. van den Berghe G, Wouters P, Weekers F, et al: Intensive insulin therapy in the critically ill patients. N Engl J Med 345:1359–1367, 2001.
99. Girou E, Schortgen F, Delclaux C, et al: Association of noninvasive ventilation with nosocomial infections and survival in critically ill patients. JAMA 284:2361–2367, 2000.
100. Rouby JJ, Laurent P, Gosnach M, et al: Risk factors and clinical relevance of nosocomial maxillary sinusitis in the critically ill. Am J Respir Crit Care Med 150:776–783, 1994.
101. Rello J, Sonora R, Jubert P, et al: Pneumonia in intubated patients: Role of respiratory airway care. Am J Respir Crit Care Med 154:111–115, 1996.
102. Torres A, Gatell JM, Aznar E, et al: Re-intubation increases the risk of nosocomial pneumonia in patients needing mechanical ventilation. Am J Respir Crit Care Med 152:137–141, 1995.
103. Drakulovic MB, Torres A, Bauer TT, et al: Supine body position as a risk factor for nosocomial pneumonia in mechanically ventilated patients: A randomised trial. Lancet 354:1851–1858, 1999.
104. Craven DE, Goularte TA, Make BJ: Contaminated condensate in mechanical ventilator circuits: A risk factor for nosocomial pneumonia? Am Rev Respir Dis 129:625–628, 1984.
105. Panchabhia TS, Dangayach NS, Krishnan A, et al: Oropharyngeal cleansing with 0.2% chlorhexidine for prevention of nosocomial pneumonia in critically ill patients: an open-label randomized trial with 0.01% potassium permanganate as control. Chest 135:1150–1158, 2010.
106. Tantipong H, Morkchareonpong C, Jaiyindee S, et al: Randomized controlled trial and meta-analysis of oral decontamination with 2% chlorhexidine solution for the prevention of ventilator-associated pneumonia. Infect Control Hosp Epidemiol 29:131–136, 2008.
107. Dezfulian C, Shojania K, Collard HR, et al: Subglottic secretion drainage for preventing ventilator-associated pneumonia: A meta-analysis. Am J Med 118:11–18, 2005.
108. Lorente L, Lecuona M, Jimenez A, et al: Influence of an endotracheal tube with polyurethane cuff and subglottic secretion drainage on pneumonia. Am J Respir Crit Care Med 176:1079–1083, 2007.
109. Kollef MH, Afessa B, Anzueto A, et al: Silver-coated endotracheal tubes and incidence of ventilator-associated pneumonia: The NASCENT randomized trial. JAMA 300:805–813, 2008.
110. Olson ME, Harmon BG, Kollef MH: Silver-coated endotracheal tubes associated with reduced bacterial burden in the lungs of mechanically ventilated dogs. Chest 121:863–870, 2002.

111. Rello J, Kollef M, Diaz E, et al: Reduced burden of bacterial airway colonization with a novel silver-coated endotracheal tube in a randomized multiple-center feasibility study. Crit Care Med 34:2766–2772, 2006.
112. Berra L, Kolobow T, Laquerriere P, et al: Internally coated endotracheal tubes with silver sulfadiazine in polyurethane to prevent bacterial colonization: A clinical trial. Intensive Care Med 34:1030–1037, 2008.
113. Donowitz LG, Page MC, Mileur BL, et al: Alteration of normal gastric flora in critical care patients receiving antacid and cimetidine therapy. Infect Control 7:23–26, 1986.
114. Messori A, Trippoli S, Vaiani M, et al: Bleeding and pneumonia in intensive care patients given ranitidine and sucralfate for prevention of stress ulcer: Meta-analysis of randomised controlled trials. BMJ 321:1103–1106, 2000.
115. Cook D, Guyatt G, Marshall J, et al: A comparison of sucralfate and ranitidine for the prevention of upper gastrointestinal bleeding in patients requiring mechanical ventilation. Canadian Critical Care Trials Group [see comments]. N Engl J Med 338:791–797, 1998.
116. Stoutenbeek CP, van Saene HK, Miranda DR, et al: The effect of selective decontamination of the digestive tract on colonisation and infection rate in multiple trauma patients. Intensive Care Med 10:185–192, 1984.
117. D'Amico R, Pifferi S, Leonetti C, et al: Effectiveness of antibiotic prophylaxis in critically ill adult patients: Systematic review of randomised controlled trials. BMJ 316:1275–1285, 1998.
118. Nathens AB, Marshall JC: Selective decontamination of the digestive tract in surgical patients: A systematic review of the evidence. Arch Surg 134:170–176, 1999.
119. de Jonge E, Schultz MJ, Spanjaard L, et al: Effects of selective decontamination of digestive tract on mortality and acquisition of resistant bacteria in intensive care: A randomised controlled trial. Lancet 362:1011–1016, 2003.
120. Pronovost P, Needham D, Berenholtz S, et al: An intervention to decrease catheter-related bloodstream infections in the ICU. N Engl J Med 355:2725–2732, 2006.
121. Chastre J: Conference summary: Ventilator-associated pneumonia. Respir Care 50:975–983, 2005.
122. Zack JE, Garrison T, Trovillion E, et al: Effect of an education program aimed at reducing the occurrence of ventilator-associated pneumonia. Crit Care Med 30:2407–2412, 2002.
123. Resar R, Pronovost P, Haraden C, et al: Using a bundle approach to improve ventilator care processes and reduce ventilator-associated pneumonia. Jt Comm J Qual Patient Saf 31:243–248, 2005.
124. Apisarnthanarak A, Pinitchai U, Thongphubeth K, et al: Effectiveness of an educational program to reduce ventilator-associated pneumonia in a tertiary care center in Thailand: A 4-year study. Clin Infect Dis 45:704–711, 2007.
125. Babcock HM, Zack JE, Garrison T, et al: An educational intervention to reduce ventilator-associated pneumonia in an integrated health system: A comparison of effects. Chest 125:2224–2231, 2004.

CHAPTER 34

TUBERCULOSIS

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INTRODUCTION

Mycobacteria have played an extremely important role in influencing society throughout history. Tuberculosis and Hansen's disease (leprosy), the two most prominent mycobacterial diseases, have been recognized as scourges of humanity since antiquity. Whereas leprosy was most apparent as a metaphor for the destitute, disabled, and disfigured, tuberculosis was the "captain of all these men of death," according to John Bunyan, a plague that carried away the young and talented members of society. Currently, although the resurgence of tuberculosis in industrialized countries that began in the mid-1980s has subsided, the disease continues to ravage much of the developing world and to kill or disable many young, productive members of society.[1–3] Because of the frequency with which both pulmonary and extrapulmonary tuberculosis occur together, and because the general manifestations and microbiologic features are the same with all sites of disease, this chapter addresses both pulmonary and extrapulmonary tuberculosis.

Because tuberculous infection is so prevalent throughout much of the developing world, the conflicts and upheavals that result in immigration from low-income to developed countries will have a continuing influence on the incidence of tuberculosis everywhere. For this reason, tuberculosis must be viewed as a global problem, one that is not contained by national boundaries and

whose effects are felt in all countries regardless of their state of development.[4] More recently, in addition to human immunodeficiency virus (HIV) infection, drug resistance is providing new challenges to tuberculosis control efforts.[5] Both multidrug-resistant (MDR) tuberculosis (caused by organisms resistant to at least isoniazid and rifampin) and extensively drug-resistant (XDR) tuberculosis (caused by MDR organisms that are also resistant to one of the fluoroquinolones and to at least one of the injectable second-line agents) pose significant difficulties for tuberculosis control programs in most of the world.

CHARACTERISTICS OF *MYCOBACTERIUM TUBERCULOSIS*

The main defining characteristic of the genus *Mycobacterium* is the property of "acid-fastness," the ability to withstand decolorization with an acid-alcohol mixture after coloration with such stains as Ziehl-Neelsen or auramine O (Fig. 34-1).[6] In addition to their being acid fast, the mycobacteria are primarily intracellular parasites, have slow rates of growth (except for the "rapid grower" category), are obligate aerobes, and in normal hosts induce a granulomatous response in tissue (see Chapter 15, Fig. 15-4C).

Details about the means of obtaining specimens for studies of mycobacteria and their differentiation are provided in Chapter 18. *Mycobacterium tuberculosis* produces characteristic buff-colored colonies. Biochemical testing or deoxyribonucleic acid (DNA) probes serve to identify the species. Ninety-nine percent of *M. tuberculosis* strains produce niacin.[7] In radiometric systems, a culture of *M. tuberculosis* can be identified by testing for resistance to *para*-nitro-acetylamino-hydroxypropiophenone (NAP), a precursor in the synthesis of chloramphenicol.[8] Growth of *M. tuberculosis* is not inhibited by this antimicrobial compound, in contrast with other mycobacterial species that do not grow in its presence.

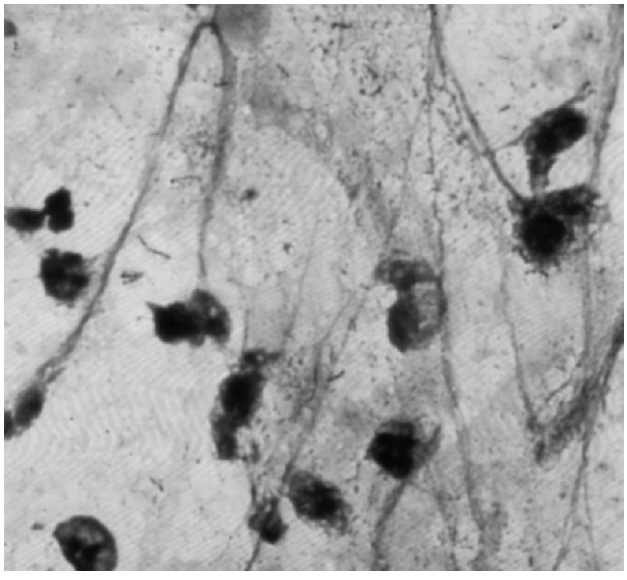

FIGURE 34-1 ■ Ziehl-Neelsen–stained smear of sputum showing acid-fast bacilli (in this instance *Mycobacterium tuberculosis*). (Original magnification ×960.)

Tuberculosis is caused by any one of three mycobacterial pathogens that form part of the *M. tuberculosis* complex: *M. tuberculosis, Mycobacterium bovis,* and *Mycobacterium africanum. Mycobacterium microti, Mycobacterium pinnipedii,* and *Mycobacterium caprae* are also members of the *M. tuberculosis* complex but only rarely cause disease in humans. Because *M. bovis* and *M. africanum* produce relatively few cases of human tuberculosis, they are not considered separately in this chapter.

The complete genomes of six *M. tuberculosis* strains have been sequenced, including two laboratory strains: H37Rv,[9] the first strain to be sequenced, and H37Ra,[10] the attenuated strain; the genome of H37Rv is composed of 4.41 million base pairs containing 4009 genes (http://genolist.pasteur.fr/TubercuList/). The *M. tuberculosis* genome differs from other bacterial genomes in that it contains a large number of genes for enzymes involved in lipogenesis and lipolysis that are presumably related to synthesis and maintenance of the bacterial cell wall. Functions have been attributed to approximately 52% of the predicted proteins encoded by the genes, and similarities were found with other genes for an additional 39%.[11] The remaining 9% may represent genes encoding proteins with *M. tuberculosis*–specific functions and, thus, are of particular interest. It is clear from the genetic makeup of the organism that it has the potential to survive in a variety of environments, including those with very low oxygen tension. This latter capability is consistent with the ability of the organism to remain viable but dormant in sequestered sites in the body, only to again become active under the proper conditions. The potential for developing new drugs, vaccines, and diagnostic tests on the basis of the knowledge of the complete array of genes in *M. tuberculosis* is enormous and is only beginning to be realized.[12,13] It is anticipated that additional information about virulence factors, drug and vaccine targets, and the pathogenesis of latency and active disease will be provided by the analysis and comparison of the whole-genome sequences.[10,14,15]

EPIDEMIOLOGY

For most of recorded history, tuberculosis has been a problem of enormous dimensions worldwide—and it still is. The World Health Organization (WHO) estimates that nearly one third (1.9 billion people) of all the people in the world are infected with *M. tuberculosis.* According to the latest (2009) WHO Global report,[3] in 2007 there were an estimated 9.27 million new cases, of which 4.1 million (44%) were sputum smear positive for acid-fast bacilli and, therefore, highly infectious; the total number of prevalent cases (new and old) in the world was estimated to be 13.7 million, from which there were an estimated 1.78 million deaths. Most of the persons with clinically active tuberculosis (>95%) and nearly all

of those who die from it (98%) reside in developing countries.

Since 1990 there has been a progressive decrease in the incidence of tuberculosis in all nine WHO regions of the world except Eastern Europe and Africa, although rates in both of these areas have recently begun to show a downward trend.[3] Because of the limitations in the global surveillance and reporting system for tuberculosis, only 5.3 of the estimated 9.2 million new cases were actually reported to WHO in 2007.[3] In 2004 (the last year for which worldwide information is available), tuberculosis accounted for approximately 2.5% of all deaths in the world, nearly 20% of deaths of persons between 15 and 59 years of age, and 26% of avoidable adult deaths.[16]

Also in 2007, it was estimated that there were 1.37 million new cases and 456,000 deaths from tuberculosis in persons with HIV infection.[3] The distribution of persons with coexisting HIV and tuberculosis varies considerably around the world, but the great majority (79%) live in sub-Saharan Africa. Although the rates of tuberculosis in Africa have increased steeply since 1992,[3] with the rapid spread of HIV infection in Asia, a similar—perhaps even greater—impact of HIV infection on the incidence of tuberculosis will almost certainly occur there, too.

In spite of the staggering impact of tuberculosis in developing countries, it was believed that the disease was well on its way to being eliminated in most of the developed world, including the United States, where from at least the beginning of the 20th century, tuberculosis death rates were steadily decreasing, a decline that was accelerated by the introduction of antituberculosis chemotherapy in the late 1940s. Following the introduction of effective chemotherapy, rates of new cases of tuberculosis decreased steadily at an average annual rate of approximately 5%. However, from 1984 to 1992, the number of tuberculosis cases increased by 20%. With renewed effort and considerably increased funding, case rates once again began to decline in 1993, as shown in Figure 34-2. In 2008, 12,898 cases of tuberculosis (4.2 cases per 100,000 population) were reported in the United States, the lowest number since systematic national reporting began in 1953. However, the rate of decline in cases has slowed since 2000: from an average annual decline of 7.3% from 1993 to 2000 to 3.8% from 2000 to 2008.[17]

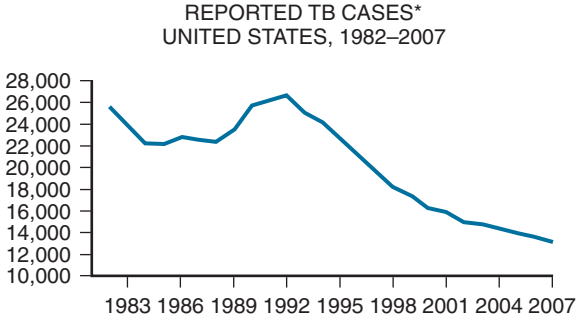

FIGURE 34-2 ■ Reported cases of tuberculosis in the United States, 1982–2007. (From Centers for Disease Control and Prevention: Reported Tuberculosis in the United States, 2007. Atlanta: Centers for Disease Control and Prevention, 2008.)

The reasons for the resurgence of tuberculosis in the late 1980s and early 1990s in the United States, as well as in western Europe, are complex but revolve largely around two major factors: the epidemic of infection with HIV and the deterioration of public health systems.[18] Interacting with and amplifying these two major factors were two additional circumstances: (1) socioeconomic conditions, particularly homelessness that led to crowding; and (2) immigration of persons from countries in the world where the prevalence of tuberculous infection was high. Although the prevalence of HIV infection has decreased in the United States and the use of antiretroviral therapy has diminished the risk of tuberculosis among persons with HIV infection, the conditions that fueled the resurgence of tuberculosis remain largely unchanged.[4,19] Notably, while the number of cases of tuberculosis decreased overall by 49% from 1993 to 2008,[17] the reduction occurred mainly among the U.S.-born population, in which cases decreased by 72%. In 2008, 58.8% of newly diagnosed cases of tuberculosis in United States were reported among foreign-born persons. A recent review demonstrated that, among this group, the rates of tuberculosis are the highest during the first 2 years after entry into the country, regardless of age, with annual rates especially high (>250/100,000 persons) among immigrants from sub-Saharan Africa and Southeast Asia.[4] By contrast, in the United States and other developed countries, tuberculosis case rates in persons born in these countries tend to increase with increasing age, because the older a person is, the more likely he or she is to have acquired tuberculous infection, having lived during a time when the disease was far more prevalent than it is today.

TRANSMISSION OF *MYCOBACTERIUM TUBERCULOSIS*

Knowledge of the factors that govern transmission of *M. tuberculosis* from a source case and of the sequence by which the disease develops in a potential new host is vital, both for devising strategies for tuberculosis control and for evaluating the risk of a person becoming infected after exposure to a patient with tuberculosis.[20] Transmission of *M. tuberculosis* is influenced by features of the source case, particularly the bacillary load, the closeness of the potential recipient of the organism to the source, and the condition of the environmental air they share. A possible additional factor is the infectivity of the organism: the degree to which *M. tuberculosis* has the ability to establish itself within the lung or other sites in the new host once transmission has occurred.

Source Case

Transmission of *M. tuberculosis* is a classic example of an airborne infection.[21] In nearly all instances, tuberculous infection is acquired by inhalation of one or more

tubercle bacilli contained in an airborne particle small enough (1 to 5 μm) to reach an alveolus. For a person with tuberculosis to be infectious, the organisms must have access to environmental air and be aerosolized. By and large, this means that only patients with pulmonary tuberculosis can be regarded as infectious. However, respirable particles containing *M. tuberculosis* may rarely be generated from other sources: for example, irrigation of a tuberculous abscess.[22] After aerosolized respiratory secretions are expelled from the nose or mouth, their water content evaporates rapidly, leaving only a small residue of solid matter—the *droplet nucleus*—which may include tubercle bacilli and which may remain suspended in the air for several hours.[23] A single bacillus in a tiny droplet nucleus is more hazardous than several bacilli in larger airborne particles, which when inhaled deposit in airways rather than alveoli and which then are quickly removed by mucociliary clearance.

Coughing is the most effective mechanism for generating aerosols that create droplet nuclei. Forced expiratory maneuvers other than coughing—such as sneezing, yelling, singing, and loud talking—all involve, to a greater or lesser extent, the sudden acceleration of air required to disrupt a liquid surface or mucous strands, thereby aerosolizing particles. Thin, watery secretions are more easily fragmented into small respirable droplets than is more viscous mucus. In general, the greater the volume of respiratory secretions, the greater the number of potentially infectious droplets.

Riley and coworkers[24] demonstrated marked variability in the infectious potential of tuberculosis patients that, in part, could be related to the severity of coughing. One patient with exceptionally infectious disease not only had severe pulmonary tuberculosis but tuberculous laryngitis as well. It was calculated that this patient was as contagious as a child with measles is to other susceptible children. Similar studies by Escombe and coworkers,[25] which described the infectiousness of HIV-infected patients with tuberculosis, reported that infectiousness was very heterogeneous. Of 97 patients (118 admissions) hospitalized in an HIV-tuberculosis ward, 10 caused 90% of the infections in guinea pigs exposed to air exhausted from the ward. Of the 10 infectious patients, 6 had MDR tuberculosis that was inadequately treated; in addition to having MDR tuberculosis, being sputum smear positive and being on suboptimal treatment both contributed to the degree of infectiousness.

Simple maneuvers, such as covering the mouth while coughing, can reduce formation of droplet nuclei by deflecting droplets from the air stream. Similarly, a mask worn by the patient is effective because particles are trapped while they are still large, before the water content has evaporated. Masks (disposable particulate respirators) worn by persons exposed to an infectious source are less effective than are masks worn by patients, because most airborne droplet nuclei are much smaller than their parent droplets. However, properly constructed, well-fitting masks are very efficient in removing respirable particles of 1 to 5 μm.[26]

An important factor to be considered in determining infectiousness is the number of organisms contained in the lungs of the source case. This can be inferred from the extent and morphology of the disease, as determined by the chest roentgenogram and more directly estimated by microscopic examination of sputum. Canetti[27] demonstrated that the bacillary population of tuberculous lesions varies greatly, depending on the morphology of the lesion. The number of bacilli in solid nodular lesions ranges from 10^2 to 10^4 organisms, whereas in cavitary lesions, populations are on the order of 10^7 to 10^9 bacilli. Loudon and Spohn,[28] among others, demonstrated that the prevalence of tuberculin reactors among young contacts of patients with newly discovered tuberculosis increased as the radiographic extent of involvement increased. Thus, in tuberculosis control, the contacts of persons with more extensive tuberculosis should be accorded a higher priority for epidemiologic investigations than should the contacts of persons with less severe disease.

The most direct means of estimating bacillary population is microscopic examination of properly stained sputum smears. An average viable bacillary population of 5000 to 10,000 organisms per milliliter of sputum is required for the organisms to be seen in an acid-fast–stained sputum smear.[29] Data from a variety of sources consistently demonstrate that contacts of patients who have organisms present in sputum smears have a much higher prevalence of infection than do contacts of patients with negative smears and either positive or negative cultures.[30] However, it should be noted that the contacts of sputum smear–negative patients may acquire tuberculous infection and develop tuberculosis. Transmission from smear-negative patients was estimated to be the cause of approximately 17% of newly diagnosed cases in San Francisco.[31]

A third important factor in determining the infectiousness of a source case is the use of chemotherapy. In a series of studies designed to identify and quantify factors influencing transmissibility of *M. tuberculosis,* Sultan and associates[32] and Riley and coworkers[24] noted that patients who had positive sputum smears but who were receiving antituberculosis drugs were much less infectious for guinea pigs than were untreated patients. By their calculations, the relative infectiousness of untreated patients in comparison with treated patients was 50 : 1. Escombe and coworkers,[25] as already noted, came to a similar conclusion. Consistent with these experimental observations, a substantial body of clinical data has accumulated that indicates that, once treatment to which the organisms are susceptible is begun, transmission of *M. tuberculosis* decreases quickly. The quantification of the infectiousness of cough-generated aerosols has shown the same result—that the major factor associated with persistent culture-positive aerosols was lack of effective treatment during the previous week.[33]

The most important mechanism by which chemotherapy reduces infectiousness is the direct effect of the drug on the bacillary population in the lungs. Hobby and associates[29] found that, after an average of 15.6 days of multidrug chemotherapy, there was a reduction in the number of tubercle bacilli per milliliter of sputum of at least 2 logs, from approximately 10^6 to approximately

10^4, or a 99% decrease. These data are similar to those reported by Jindani and coworkers,[33] who demonstrated a reduction in colony counts of nearly 2 logs per milliliter of sputum in the first 2 days of treatment, and a further reduction of 1 log during the next 12 days. Thus, in the initial 2 weeks of treatment, there was a decrease from approximately 10^7 to 10^4 organisms per milliliter of sputum, or a reduction of 99.9%. However, even with this profound reduction in the bacillary population, the remaining number of organisms (10,000 per milliliter of sputum) would still be sufficient to produce a positive acid-fast sputum smear. In addition to reducing the number of viable bacilli, chemotherapy also promptly decreases coughing. Loudon and Spohn[28] noted that coughing was reduced by 40% after 1 week of treatment and by 65% after 2 weeks.

The sum of these effects is that, once a patient with tuberculosis is placed on effective therapy, transmission of tubercle bacilli ceases to be a concern. The decline in infectiousness is caused mainly by the rapid reduction in bacillary population in the lungs as a result of antituberculosis chemotherapy, particularly isoniazid. Drug regimens that do not include isoniazid probably should not be expected to render the patient noninfectious as rapidly as do those containing isoniazid. Likewise, the prompt reduction in infectiousness cannot be assumed to occur in patients harboring organisms that are resistant to isoniazid.

The operational implications of these assumptions concerning infectiousness should be modified in accordance with the patient's living and working circumstances. The general principles of infection control entail an assessment of the vulnerability to tuberculous infection of persons who will potentially be exposed and the consequences should those who are exposed become infected.

Data from several sources indicate that strains of *M. tuberculosis* resistant to isoniazid may be less pathogenic than fully susceptible organisms.[34,35] Molecular epidemiologic studies suggest that the mutation conferring resistance may have a role in the pathogenicity of *M. tuberculosis,* especially mutations associated with isoniazid resistance.[36] Isolates harboring the most common mutation, *katG* S315T and the *inhA* promoter 15c-t, were able to cause secondary cases of tuberculosis (defined by genotyping of strains in a population). In contrast, mutations in *katG* other than the common S315T mutation did not cause secondary cases. Although more information is needed to confirm this association, this finding may explain the different results regarding the pathogenicity of drug-resistant strains. It is also clear that the lesser pathogenicity can easily be offset by a prolonged period of infectiousness, as might occur with ineffective treatment, as suggested by Escombe and associates,[25] or by exposure of an immunocompromised host. Outbreaks of tuberculosis caused by MDR and XDR strains of tubercle bacilli have taken place in hospitals or correctional facilities and largely have involved HIV-infected persons.[37] Through the use of DNA fingerprinting, nosocomial transmission has been clearly documented. However, the outbreak described by Reves and associates[38] did not involve persons with evident immunocompromise. Moreover, in the outbreak that was described by Nardell and colleagues,[39] the patients were homeless and, though many of them were alcoholic, no other potential cause of immunodeficiency was recognized.

Environmental Factors

The physical laws that apply to aerosolized particles, described in detail in Chapter 12, dictate that droplet nuclei essentially become part of the environmental air; thus, environmental factors are of extreme importance in influencing transmission of tubercle bacilli. Studies by Loudon and associates[40] showed that, under standard conditions of temperature and humidity indoors, 60% to 71% of aerosolized *M. tuberculosis* organisms survived for 3 hours, 48% to 56% for 6 hours, and 28% to 32% for 9 hours. Apart from the natural death rate, the only factors influencing the infectiousness of organisms in a droplet nucleus under ordinary circumstances are its removal by venting or filtering and the death of the organisms from exposure to ultraviolet light. Environmental factors may be manipulated to dilute the concentration of tubercle bacilli, mainly removing them by effective filtration, killing them with ultraviolet light, or both.[41]

The influence of the concentration of organisms in environmental air in transmission of *M. tuberculosis* has been well illustrated in several microepidemics in which recirculation of air played an important role. The most dramatic example occurred on board a U.S. Navy vessel that had a closed, recirculating ventilation system.[42] The index case had a positive sputum smear and a brisk cough and therefore was highly infectious. As a result of this one case, 53 of 60 persons (88%) in his berthing compartment acquired tuberculous infections, and 6 developed tuberculosis. In a second compartment connected to the same ventilation system, 43 of 81 persons (53%) became infected and 1 developed tuberculosis. Smaller epidemics, one caused by a patient who underwent bronchoscopy in an intensive care unit, have been described.[43,44]

Since early in the 20th century, it has been known that exposure to ultraviolet radiation kills tubercle bacilli. Riley and coworkers,[24] in their classic studies of infectiousness in a series of patients, demonstrated that ultraviolet irradiation of air passing through an air-conditioning duct completely eliminated transmission of *M. tuberculosis* to guinea pigs housed beyond the ultraviolet lights. The major usefulness of ultraviolet lights is in hospital areas or clinics where patients with untreated tuberculosis are likely to be encountered. This is especially important in open areas such as waiting rooms, where ventilation may not be adequate to remove infectious particles, and within ventilation systems.[41]

Circumstances of Exposure

The conditions under which the exposure occurs have a major influence on the number of infectious particles inhaled. If the exposure is of long duration and takes

place under conditions that would be associated with a high concentration of droplet nuclei in the air inhaled by the contact, there is obviously a greater likelihood that transmission will occur. This is simply a restatement of what has been known for many years: crowding and intimacy of contact are important determinants of transmission of *M. tuberculosis.*[45] This is reflected in data from the United States showing that rates of both clinical tuberculosis and tuberculin reactivity are much higher among close (generally household) than among nonclose (generally out-of-household) contacts.[17] In general, the rate of tuberculosis is in the range of 15 per 1000 close contacts and 3 per 1000 nonclose contacts examined. Of close contacts, approximately 30% are infected, in comparison with approximately 15% of nonclose contacts. Because the risk of tuberculosis is higher among close contacts, they should also be considered high-priority candidates for isoniazid preventive therapy.

Host Factors

It has generally been thought that risk factors for acquisition of tuberculous infection have been exogenous to the contact; in other words, the likelihood of becoming infected with *M. tuberculosis* is related mainly to features of the index case and of the environment shared by the index case and the contact. Nevertheless, endogenous factors, especially the immune responsiveness of the newly infected person, do influence whether or not tuberculosis will develop. For example, the data indicating that the risk of acquiring tuberculous infection is greater among blacks than among whites, given equal levels of exposure,[46] suggest endogenous factors play a role in affecting the response to an encounter with *M. tuberculosis.* This may be true of HIV-infected persons as well. The possible factors have not yet been defined, although in the presence of HIV infection, any of several abnormalities could account for an increased likelihood of infection.

Once viable *M. tuberculosis* organisms have been deposited in the lungs, both nonimmunologic and immunologic factors defend the potential host against the development of infection. Of these, the more potent by far is the specific immunologic response mounted after the first successful invasion of tubercle bacilli.[47,48] The most commonly measured evidence of this response is reactivity to tuberculoprotein, assessed by the tuberculin skin test or by a positive interferon-γ (IFN-γ) release assay. In immunocompetent persons, the cell-mediated immune response to the first tuberculous infection generally checks the proliferation of the organisms. In addition, external challenges from inhaled mycobacteria are met with substantially increased resistance that greatly reduces the likelihood that any new exogenous infection will occur. For this reason, an already infected person who is in contact with an infectious case is less likely to acquire a new infection than is a previously uninfected contact. The cell-mediated immunity that develops in response to mycobacterial infection is species-specific for the infecting organisms. However, sensitization with heterologous mycobacterial antigens, such as the bacillus of Calmette and Guérin (BCG) or nontuberculous mycobacteria, increases the responsiveness of lymphocytes and macrophages to *M. tuberculosis* and, thus, may afford some protection against subsequent infection with *M. tuberculosis.*[49]

In people with impaired immune responses, such as those with HIV infection, the mechanisms by which infection, both initial and latent, is contained are substantially less effective than in those with normal immunity, which explains why persons with HIV infection who acquire a new tuberculous infection so often develop tuberculosis. Moreover, previous tuberculous infection in an HIV-infected person is less likely than in healthy persons to provide protection against a new exogenous infection.[50] The risk of reinfection in persons with HIV infection is higher among those with a CD4 cell count less than 200 cells/μL.[51] It has also been demonstrated that the risk of reinfection is higher in areas where the incidence of tuberculosis is high.[52]

Although there are specific genetic defects, such as polymorphisms in the genes for the natural resistance-associated membrane protein-1 (NRAMP-1) and the vitamin D receptor, that have been found to predispose to mycobacterial diseases, their contribution to the total burden of tuberculosis appears to be small in relationship to the much more dominant social and environmental factors.[53]

PATHOGENESIS

The genesis of the pathologic reactions in tuberculosis is inextricably linked with the response of the host to the invading tubercle bacillus. In most individuals infected with *M. tuberculosis,* the host response—both nonspecific and specific—restricts the growth of the pathogen, thereby containing the infection.[48,54] Paradoxically, however, a major component of the tissue damage associated with tuberculosis is thought to result from the immunologic responses to *M. tuberculosis.* The near absence of cell-mediated immunity that occurs in patients with advanced HIV infection is assumed to be responsible for the atypical presentations of tuberculosis in HIV-infected patients. Such patients tend not to have cavitary lung lesions and to have multisystem involvement with tuberculosis. Although the lack of immune response minimizes tissue necrosis, the organism is not met with an effective protective response; thus, proliferation and dissemination are facilitated.

Figure 34-3 describes schematically the pathogenesis of tuberculosis. As can be seen, the process occurs in two phases: the acquisition of tuberculous infection and the subsequent development of tuberculosis. Tuberculosis may develop as a direct progression from infection to disease (3% to 10% probability within 1 year of infection) or from late progression occurring many years after infection (up to 5% probability for the lifetime of an infected person after the first year of infection).[55] These percentages were derived from data collected before the HIV epidemic. In HIV-infected populations, the rate of developing disease is considerably higher.

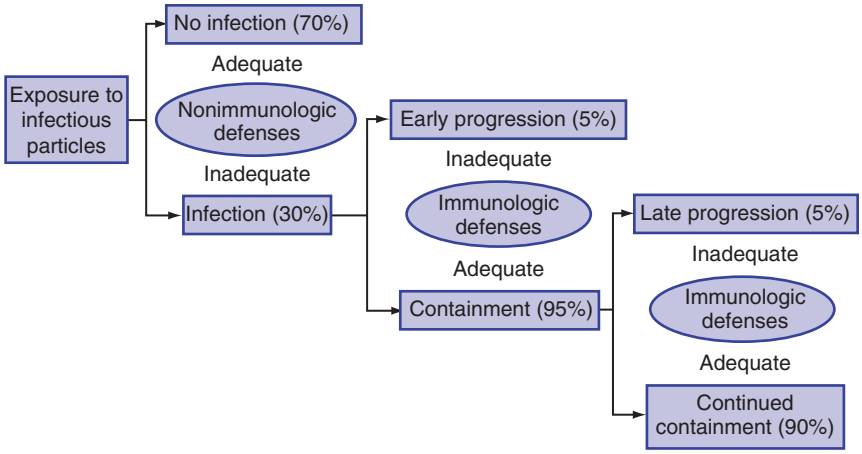

FIGURE 34-3 ■ Consequences of exposure to an infectious source case of tuberculosis. Exposure to a patient with infectious tuberculosis causes tuberculous infection in approximately 30% of those exposed. Of those who are infected, 3% to 10% develop tuberculosis within 1 year of their becoming infected. Beyond 1 year, an additional 3% to 5% develop tuberculosis during the remainder of their lifetimes.

Events in the Nonimmunized Host

Tiny droplet nuclei are efficient vehicles for conveying *M. tuberculosis* deeply into the lungs owing to their aerodynamic properties, which enable them to avoid the mechanical barriers that prevent larger particles from penetrating beyond conducting airways (see further discussion in Chapter 12). Tubercle bacilli within particles that reach the respiratory bronchioles and alveoli are generally ingested by alveolar macrophages and removed from the alveolar space by migration of the phagocytes along the alveolar surface to the origin of the mucociliary transport system. Macrophages, even from individuals with no prior immunologic experience with mycobacterial infection, possess some killing or growth-inhibiting capability. Thus, once alveolar macrophages phagocytose a small number of invading mycobacteria, killing and digestion of the organism probably follow in the majority of exposures to *M. tuberculosis.*

Clearance by alveolar macrophages may completely eradicate all the bacilli—if only a few organisms are implanted on the alveolar surface; however, when many infected droplet nuclei are deposited, the number of bacilli ingested by an individual macrophage can overwhelm the microbicidal system of the phagocyte. When the nonspecific defenses are insufficient to kill all of the organisms, the surviving bacilli multiply, causing a localized tuberculous pneumonia. In general, after the development of specific cell-mediated immune response, this lesion heals spontaneously, leaving only a calcified parenchymal focus (*Ghon lesion*), which may be accompanied by calcification in hilar nodes, the two lesions together forming the *Ranke complex.*

During the phase of tissue invasion, *M. tuberculosis*–laden macrophages enter the bloodstream via the lymphatics, which then provides access to all organs of the body; this invariable dissemination sets the stage for the development of pulmonary and extrapulmonary tuberculosis that occurs by reactivation many years later. It has been postulated that the sites in which the organisms thrive best are those in which the prevailing oxygen tension is high. Support for this theory comes from the observations that the apical portions of the lungs, the most favored location of persistence and subsequent proliferation of tubercle bacilli, are known to have the highest oxygen tension in the body, whereas organs such as the heart and spleen have much lower values and are seldom clinically involved.

Immunologic Responses to *Mycobacterium tuberculosis*

The principal immune response associated with protection against tuberculosis in experimental animals and presumably humans is cell-mediated immunity involving T lymphocytes and macrophages.[47,48,54] Studies in BCG-immunized animals indicate that, although immunization does not prevent infection with *M. tuberculosis,* the growth of the organism within macrophages is reduced by several orders of magnitude. In dramatic contrast, immunodeficiency, such as that produced by HIV infection or selective depletion of T cells or cytokines—especially IFN-γ—in experimental animals, results in a weakening of defenses against *M. tuberculosis.*[48] However, because *M. tuberculosis* is a virulent organism, little if any immunodeficiency is necessary for disease to develop. Thus, tuberculosis, which commonly occurs with a lesser degree of immunodeficiency than other HIV-associated "opportunistic" infections, has become a sentinel disease for the presence of HIV infection.

Once *M. tuberculosis* antigens are internalized, the macrophages digest them into small fragments. Particular fragments (epitopes) are able to bind to the major histocompatibility complex (human leukocyte antigen) molecules of infected macrophages and other antigen-presenting cells, which can transport the epitopes to the macrophage surface for presentation to T cells. With time, the number of T cells with specificity for antigens and epitopes of *M. tuberculosis* expands and establishes a state of delayed-type hypersensitivity in most healthy individuals.[48] Delayed-type hypersensitivity to the antigens of *M. tuberculosis* is measured by a person's ability to produce an indurated reaction to the intracutaneous injection of tuberculin purified protein derivative (PPD) or a positive IFN-γ release assay. Specific $CD4^+$ T cells secrete a characteristic pattern of lymphokines, including interleukin-2, a growth factor for T cells that stimulates their clonal expansion, and IFN-γ, a major mediator of

macrophage activation.[48] It is known that IFN-γ is necessary for the activation of microbicidal mechanisms in macrophages. One of the major cytotoxic mechanisms of phagocytic cells is the production of reactive oxygen intermediates from molecular oxygen, the most potent of which are hydrogen peroxide and the hydroxyl radical. Not surprisingly for a pathogen with a preference for growth in the lungs, tubercle bacilli are found to be extraordinarily resistant in vitro to the cytotoxic activity of reactive oxygen intermediates.[56] The production of reactive nitrogen intermediates, particularly nitric oxide, is also thought to play an important role in killing *M. tuberculosis*. Evidence indicates that murine macrophages that produce nitric oxide both inhibit growth and actually kill virulent human tubercle bacilli in vitro.[57,58] Nitric oxide is produced by murine macrophages activated by two cytokines, IFN-γ, and tumor necrosis factor-α (TNF-α). $CD4^+$ T cells produce IFN-γ, and mycobacteria-infected macrophages produce large amounts of TNF-α.

Lymphokines and cytokines also have the ability to organize granulomas that then serve to wall off the infection, kill or reduce the growth of bacilli, and restrict the mobility of infected macrophages and the spread of the infection within the body.[56,59] In immunodeficient individuals or animals deprived of TNF-α, there is a lack of organized granulomas and generally unrestricted spread of infected macrophages throughout the body, which may explain the pathogenesis of miliary tuberculosis. Essentially, each macrophage that cannot kill its internalized bacilli becomes an infectious seed enabling the growth and spread of bacilli.

Similarly, it is becoming increasingly clear that activated T cells, activated macrophages, and production of a variety of lymphokines and cytokines are also involved in tissue damage in tuberculosis. If the macrophages fail to kill or contain the organisms initially, antigens diffuse from the cells, leading to a greater influx of blood monocytes to the site of the lesion, increased macrophage activation, a larger granuloma, and ultimately greater necrosis. At some point in sensitized individuals, there is killing of the infected macrophages by products of the intracellular tubercle bacilli or possibly cytotoxic T lymphocytes. This killing results in release of tissue-dissolving enzymes that can cause caseous necrosis and cavitation. The extracellular liquid milieu serves as an ideal culture medium in which tubercle bacilli can proliferate to very large numbers.

Exogenous Versus Endogenous Infection

One of the historical controversies in tuberculosis has been the extent to which clinical tuberculosis can be attributed to new infection by recently inhaled exogenous organisms (i.e., from the environment) as opposed to a reactivation of viable bacilli that have been maintained for many years in a dormant or growth-restricted state within the body.[60] Data related to this issue are largely inferential; however, the concept is very important in that, as discussed subsequently, current tuberculosis control efforts are based largely on the idea that most tuberculosis in low-incidence areas is the result of endogenous reactivation. Thus, prevention entails identification of infected persons and giving them preventive therapy with isoniazid.

Stead,[60] after an extensive review of the literature, concluded that the data provided strong—albeit inferential—evidence that chronic (so-called adult) pulmonary tuberculosis results from proliferation of organisms in foci that were seeded during primary infection. The data presented showed that, in tuberculin-negative persons, rates of tuberculosis were proportional to the degree of exposure (49.4 cases per 1000 person-years of observation with heavy exposure and 10.8 cases per 1000 person-years in those "not particularly exposed"). In contrast, rates of disease in persons known to be tuberculin-positive at the beginning of the observation period were not so clearly related to exposure (7.6 cases per 1000 person-years with heavy exposure and 4.3 cases per 1000 person-years in those "not particularly exposed"). If exogenous reinfection were the predominant mechanism by which tuberculosis developed, rates of disease should have varied with the degree of exposure in both the tuberculin-positive and tuberculin-negative groups. This obviously was not the case.

DNA restriction fragment length polymorphism (RFLP) analysis has provided more direct evidence on transmission pathways and on the question of reinfection. For example, isolates of tubercle bacilli from HIV-positive individuals, in health care facilities or correctional institutions, frequently show identical DNA fingerprints (Fig. 34-4), indicating that these individuals were prob-

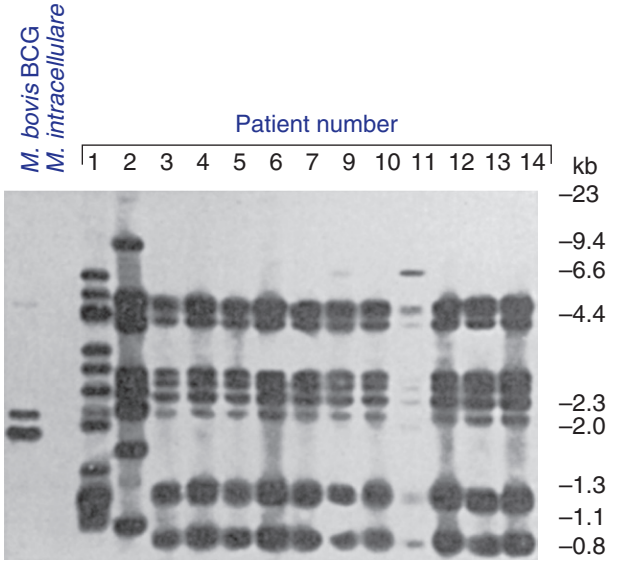

FIGURE 34-4 ■ Gel electrophoresis of DNA extracted from organisms isolated from patients in an outbreak of tuberculosis in San Francisco. Cases 3 through 14 were linked epidemiologically, whereas cases 1 and 2 were not. This is an example of the use of restriction fragment length polymorphism analysis to track strains of *Mycobacterium tuberculosis*. (From Daley CL, Small PM, Schecter GF, et al: An outbreak of tuberculosis with accelerated progression among persons infected with the human immunodeficiency virus: An analysis using restriction fragment length polymorphisms. N Engl J Med 326:231–235, 1992.)

ably infected by the same source.[50,61,62] Thus, molecular technology—by identifying organisms that are genetically related—can suggest the source of infection. Regarding reinfection, the results of a study using RFLP analysis conducted in a high-incidence community showed that exogenous reinfection accounted for 75% of the cases of recurrent tuberculosis in persons who had had apparently curative treatment.[63] However, this study was limited by a relatively low sampling rate of recurrent cases. Molecular epidemiologic analyses from other areas have shown lower rates of apparent reinfection.[64,65] Thus, although it is clear that reinfection does occur and may account for a certain proportion of cases, the magnitude of the contribution to the overall incidence of tuberculosis is not known, but probably varies considerably depending on local epidemiologic circumstances.

The overall implication of the results of experimental infection in animals, results of clinical studies, and epidemiologic data is that specific immunity to antigens of the tubercle bacillus provides considerable resistance against disease, but protection is incomplete. Heavy exposure to tubercle bacilli may result in new disease, even in individuals who are tuberculin-positive and, hence, have considerable immunologic protection. Lapses or deficiencies in immune responses can lead to reactivation or endogenous infection.

RISK FACTORS

Although the factors involved in the pathogenesis of tuberculosis, described previously, apply in all instances in which the disease develops, not all persons are at equal risk of developing disease after acquiring an infection. Many conditions that either influence the likelihood of tuberculosis or serve as markers of increased risk have been identified. As noted previously, in generally healthy populations the risk of developing tuberculosis is much higher during the first year after infection has occurred; between 3% and 10% of newly infected persons develop tuberculosis during this period. The two factors presumably involved are the adequacy of the host response in countering the invasion and the dose of bacilli implanted in the lungs. The "inoculum effect" has not been clearly demonstrated in humans but is strongly suggested by results of animal experiments.[21] Presumably, beyond the first year after infection has taken place, the immune response has matured and the number of organisms present has been substantially reduced.

Among persons with tuberculous infection, case rates vary markedly with age. Rates are considerably increased in infants and relatively increased in adolescents and young adults.[66] The reasons for the variations are as yet undetermined but may relate to age-dependent influences on the effectiveness of the immune response.

Clearly, the most potent condition that increases the risk of tuberculosis is infection with HIV. Selwyn and coworkers[67] found that 8 of 212 HIV-infected intravenous drug users developed tuberculosis in a 2-year period of observation, a case rate of 8 per 100 person-years of observation. Of these, 7 cases developed within a subset of 49 persons who were known to be tuberculin-positive. Thus, the case rate for persons who were dually infected with both HIV and *M. tuberculosis* was 7.9 per 100 person-years. This exceeds the lifetime risk of a person with tuberculous infection who is not HIV-infected. It also appears that the risk of rapid progression of tuberculosis among persons who are infected with HIV and who then become infected with *M. tuberculosis* is tremendously increased, as has been demonstrated in descriptions of two such outbreaks.[61,68] The reported rates of tuberculosis in cohorts of persons with HIV infection vary widely, and depend on the prevalence of tuberculosis in the environment, particularly the presence of infectious cases; the frequency with which treatment for latent tuberculous infection is used; the severity of immune compromise within the HIV-infected group; and whether dually infected persons are receiving antiretroviral therapy, which substantially reduces the risk.[69,70]

The only study conducted to address the incidence of tuberculosis prospectively in a broad-based group of persons with HIV infection in the United States—before the widespread use of combined antiretroviral therapy—was the Pulmonary Complications of HIV Infection study.[71] In this cohort, drawn from six centers across the country, the rate of tuberculosis was 0.71 per 100 person-years of observation. In multivariate analyses, the factors that were associated with increased rates were residence in New York City or Newark (the two East Coast centers), being tuberculin positive (reaction > 5 mm), and having a $CD4^+$ cell count below 200 cells/μL.

In persons with both HIV and tuberculous infections, antiretroviral therapy and preventive treatment with isoniazid substantially decrease the incidence of tuberculosis. In a retrospective analysis of the incidence of tuberculosis among persons with HIV infection in Rio de Janeiro, Brazil, among patients who received neither antiretroviral treatment nor isoniazid preventive therapy, the incidence of tuberculosis was 4.01/100 person-years.[72] Among patients who received antiretroviral therapy, the incidence was 1.90/100 person-years (95% confidence interval [CI], 1.66 to 2.17), and those treated with isoniazid had a rate of 1.27/100 person-years (95% CI, 0.41 to 2.95). The incidence among patients who received both antiretroviral therapy and isoniazid was 0.80/100 person-years (95% CI, 0.38 to 1.47). Overall, there was a 76% reduction in tuberculosis risk among patients receiving both antiretroviral treatment and isoniazid. (Isoniazid preventive therapy is discussed in a later section.)

Other conditions or therapies that interfere with cell-mediated immunity also increase the risk of tuberculosis. These relationships, although well described and generally accepted, are poorly quantified. Examples of these disorders include hematologic malignancies and cancer chemotherapy. In addition, conditions such as diabetes mellitus and uremia are thought to fit into this general category of risk-enhancing diseases, although the basis for this effect is not established. The risk of tuberculosis is also increased considerably in persons with silicosis,[73]

presumably owing to the effect of silica on the function of alveolar macrophages.

Genetic factors had been suggested by twin studies in which there was a greater concordance of disease in monozygotic than in dizygotic twins.[74] However, it is difficult to separate them from linked environmental factors. Case rates among persons infected with *M. tuberculosis* living in Denmark in the 1950s were only 28 per 100,000 per year.[75] This contrasts strikingly with annual rates of 1500 to 1800 per 100,000 in Eskimo populations in Alaska and Greenland.[76] Genetic differences are also suggested by the pattern of tuberculosis noted among Filipinos in the U.S. Navy.[77] Their rate of disease tended to increase with duration of enlistment rather than to decrease, unlike the pattern seen in blacks and whites. The apparently decreased ability of Filipinos to develop potent cell-mediated immunity is also suggested by their increased rates of developing symptomatic coccidioidomycosis.

Undernutrition is known to interfere with cell-mediated responses and thus is thought to account for the increased frequency of tuberculosis in malnourished persons.[78] In addition to overt malnutrition, other factors related to specific but poorly defined nutritional deficiencies may also be associated with an increased risk of tuberculosis. For example, observations suggest that risk is increased in persons who have had a gastrectomy or an intestinal bypass procedure for weight control.[79] Body build has also been related to the risk of disease among infected persons. In U.S. Navy personnel, rates of tuberculosis were nearly three times greater among men who were thin for their height; the increased incidence of tuberculosis did not appear to be related to nutritional status.[77]

In spite of the number of risk factors for developing tuberculosis that have been identified, the majority of cases diagnosed each year have none of these abnormalities or characteristics.

TUBERCULOUS INFECTION

As indicated previously, infection may or may not follow exposure to *M. tuberculosis* in otherwise healthy individuals, but when infection occurs, it causes a cell-mediated immune response to the organisms whose presence can then be identified by a positive response to testing with an appropriate skin test antigen or INF-γ release assay. Until recently, the only standardized test available to identify this reactivity was the tuberculin skin test utilizing tuberculin PPD. Although the tuberculin skin test remains the "gold standard" for detecting latent tuberculous infection in persons who do not have clinical tuberculosis, tests that measure release of INF-γ from whole blood in response to exposure to specific *M. tuberculosis* antigens are now available commercially.[80]

Tuberculin Skin Test

Tuberculin was first prepared by Robert Koch in 1890 and was touted by him as being therapeutic for tuberculosis. Shortly thereafter, the diagnostic capabilities of the material were recognized through its use in animals. In 1934, Seibert and Glenn[81] prepared the first batch of a much more purified preparation, which they termed *purified protein derivative.* The antigen is prepared in liquid form containing the detergent Tween 80 to decrease adsorption of protein to the glass of the vial. The standard intermediate tuberculin test consists of the intracutaneous injection (Mantoux's method) of 0.1 mL of material, which contains 0.0001 mg of PPD (5 TU). The site usually chosen is the volar surface of the forearm, but any accessible area can be used. A short-beveled 26- or 27-gauge needle should be used with a 1-mL graduated syringe. A properly placed intracutaneous injection should cause a well-demarcated wheal 6 to 10 mm in diameter in which the hair follicles form dimples. Conventionally, the reading is done 48 to 72 hours after the injection, but it may be delayed for up to 1 week.[82]

In persons such as hospital employees, who are likely to be tested repeatedly—if tuberculin-negative at the outset—a two-step testing procedure is recommended to avoid confusing a boosted reaction with a true conversion.[83] Boosting occurs when a person who was infected and would have tested positive in the past loses skin test reactivity over the course of several years. When this occurs, a single tuberculin test is falsely negative, but the test itself is capable of recalling (i.e., boosting) the waned reactivity. A subsequent test would then elicit a positive reaction and may cause the person tested to be classified as a tuberculin converter. To elicit the boosted response and to categorize the person more accurately as infected or not infected, a second 5-TU tuberculin test is applied within 1 to 2 weeks of the first (spuriously negative) test. If the second test shows a positive reaction, it is interpreted as a boosted response indicative of prior infection; if the reaction remains negative, it is assumed to be truly negative.

The reaction to the test should be read by inspecting and palpating the area where the tuberculin was injected. The reaction size is determined by measuring the diameter of any induration with a ruler. The amount of erythema should not be taken into account; only the extent of induration is important. Readings must be recorded accurately in millimeters.

The interpretation of tuberculin tests requires clinical judgment as well as understanding of the test. In a population in which the only mycobacterial species causing infection was *M. tuberculosis,* the curve describing the distribution of reaction sizes in otherwise healthy infected persons given 5-TU PPD would be bell shaped, having a mode of 17 to 18 mm, with very few reactions less than 10 mm. Thus, defining the minimum reaction size indicative of tuberculous infection would be simple.[84] Unfortunately, in many parts of the world, a portion of the population is infected with nontuberculous mycobacteria, which induce some degree of sensitization to tuberculin; inoculation with BCG, for many years the world's most commonly used vaccination, has the same enhancing effect on tuberculin reactivity. Although these reactions are on the whole smaller than

those caused by *M. tuberculosis,* they nevertheless smudge the distinction between reactions in persons infected with *M. tuberculosis* and those not infected. On the basis of a large amount of epidemiologic data and skin testing with antigens prepared from nontuberculous mycobacteria, the best compromise between false-positive and false-negative readings to 5-TU PPD tuberculin tests is 10 mm. Thus, under most circumstances, a reading of 10 mm or more is considered indicative of infection with *M. tuberculosis.* However, in some situations, smaller reactions should be taken to indicate tuberculous infection. For example, a reaction of 5 mm in a child who is a contact of a person with smear-positive tuberculosis would probably indicate tuberculous infection and be considered positive. Likewise, a 5-mm reaction in a person with known HIV infection should be considered positive. In the United States, the history of BCG administration is generally ignored in interpreting the results of the tuberculin skin test.[85]

There are several reasons why the tuberculin reaction may be interpreted as negative in the presence of tuberculous infection. These include errors in application or reading of the test result, usually related to the inexperience of the tester/reader, and should be easily correctable with proper training. Problems with the antigen are infrequent unless it has been improperly handled. Many disease states, especially HIV infection, interfere with cell-mediated immune responses. Lymphoreticular malignancies such as Hodgkin's disease are potent suppressors of cell-mediated immunity. Corticosteroids and immunosuppressive drugs decrease tuberculin reactivity if the patient is on a sufficient dose for a sufficient period of time. For corticosteroids, the minimum dose is 15 to 20 mg of prednisone or the equivalent of another preparation, given daily for 2 to 3 weeks.[86] As stated previously, advancing age is associated with loss of tuberculin reactivity, although it may be recalled.[82] Malnutrition also may cause defects in cell-mediated immunity with consequent diminished tuberculin reactivity. Finally, overwhelming tuberculosis itself may cause diminished or absent tuberculin responsiveness.

Even when the test is applied and the result is read with particular care in patients with proven tuberculosis and no apparent immunosuppression at the time they are admitted to a hospital, only 80% to 85% have reactions of 10 mm or more to 5-TU PPD.[87] Thus, a negative tuberculin test result cannot be used to exclude tuberculosis as a diagnostic possibility.

The interpretation of tuberculin skin test results in persons with HIV infection is particularly problematic, because of the progressive immunosuppression that occurs as HIV disease advances. Individuals infected with HIV are less likely to have a positive tuberculin reaction. In a cross-sectional study of persons with HIV infection and a wide range of $CD4^+$ lymphocyte counts, anergy—defined as lack of any reaction to tuberculin (5 TU) plus mumps and *Candida* antigens—occurred more frequently when the $CD4^+$ count was less than 400 cells/μL.[88]

Interferon-γ Release Assays

Two INF-γ release assays are currently approved for marketing in the United States, the QuantiFERON-TB test and the T-Spot TB test. The QuantiFERON-TB (Cellestis Limited, Carnegie, Victoria, Australia) test, specifically QuantiFERON-TB Gold and QuantiFERON-TB Gold In-tube, measure the amount of INF-γ released from sensitized lymphocytes in whole blood incubated overnight with mixtures of *M. tuberculosis* antigens, early secreted antigenic target (ESAT)-6 and culture filtrate protein (CFP)-10.[80] The other approved test, the T-Spot TB (or ELISPOT), utilizes an elispot format to quantify the number of cells in peripheral blood that secrete INF-γ when stimulated with ESAT-6 and CFP-10 (Oxford Immunotec, Abingdon, United Kingdom).[89]

Compared with the tuberculin skin test, the INF-γ release assays have the advantage of being accomplished with one patient visit, being more specific in the presence of BCG vaccination or infection with nontuberculous mycobacteria, having less reader variability, and not recalling waned immunity (the booster reaction described earlier).[89] A recent systematic review showed that the INF-γ release assays have excellent specificity and are not affected by BCG vaccination.[90] The sensitivity to diagnose infection (using culture-positive *M. tuberculosis* cases as the reference) was variable in the different studies, but T-SPOT TB appeared to be more sensitive than QuantiFERON-TB Gold and QuantiFERON-TB Gold In-tube and the tuberculin skin test.[90,91] In patients with HIV infection, the responses to TST and QuantiFERON-TB Gold In-tube correlated with the degree of immunodeficiency, whereas results of the T-SPORT TB are independent of the level of CD4 T-cell depletion,[91a] which may explain the variable results of the different INF-γ-release assays and TST among patients with HIV infection.[91b]

INF-γ release assays have disadvantages that include the need to draw blood and process it within a specific time and there being far less experience with the test than with PPD and, therefore, much less evidence to characterize the performance of the test for diagnosing latent tuberculous infection and for epidemiologic studies. The risk factors for conversion and reversion were different for ELISPOT and the tuberculin skin test.[92] The authors attributed these findings to a lack of understanding of the dynamics of the INF-γ response to ESAT-6 and CFP-10. Also, because there is no knowledge about the time required for the INF-γ release assays to become positive after the onset of infection, the interpretation of a negative ELISPOT requires caution, especially when there is no reference point in time for exposure to *M. tuberculosis.*

Other authors, who also found a substantial proportion of reversions, attributed their findings to the decrease of the bacterial load due to treatment, and to the natural resolution of the infection.[93] In a study in the United Kingdom, Wilkinson et al.,[94] using ELISPOT, showed an early rise in spot-forming counts in patients given isoniazid and rifampin, then a reduction at month 3. No changes were observed in those without treatment. In

India, Pai et al.[95] followed 216 nursing and medical students and observed that 9 (24%) of the 38 individuals with an initial positive QuantiFERON Gold In-tube test had reversion, which was associated with an initial tuberculin skin test negative result. Interestingly, those with skin test conversion also had increase in levels of INF-γ, Taken together, these data underscore the uncertainty regarding the interpretation of the INF-γ release assays in providing information about the outcome of infection with *M. tuberculosis,* both treated and untreated.

Currently, the CDC recommends using the QuantiFERON-TB Gold test for the same indications as the tuberculin skin test: for evaluating persons suspected of having tuberculosis and for screening, including contacts of an infectious case of tuberculosis, children younger than 17 years of age, pregnant woman, and persons at increased risk of tuberculosis, particularly those with HIV infection, recent immigrants who have had BCG vaccination, and health care workers. The QuantiFERON-TB Gold test usually can be used in place of—and not in addition to—the tuberculin skin test.[96]

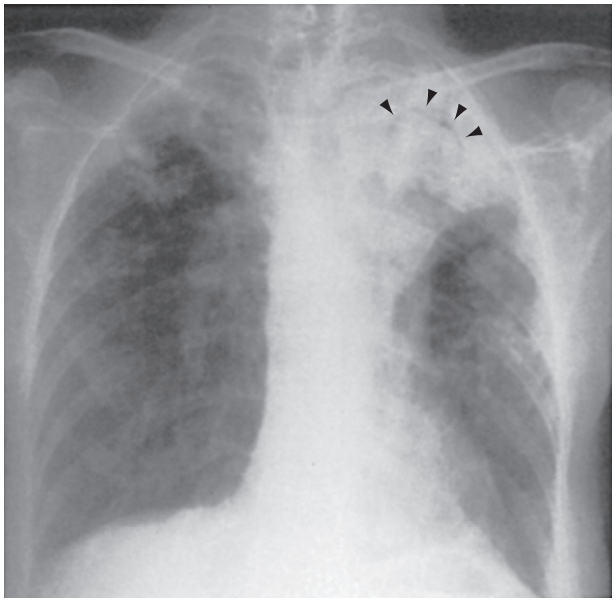

FIGURE 34-5 ■ Frontal-view chest roentgenogram showing a fungus ball (mycetoma or aspergilloma) in a preexisting tuberculous cavity. Note the characteristic crescent of air (*arrowheads*) over the superior margin of the fungus ball.

PULMONARY TUBERCULOSIS

Currently, in the United States approximately 71% of new cases of tuberculosis involve the lungs only, 20% involve extrapulmonary sites only, and 8% involve both locations.[17] Although extrapulmonary involvement is common in persons with HIV infection, the lungs are also involved in 60% to 70% of such patients.[97]

History, Physical, and Laboratory Examinations

Cough is the most common symptom of pulmonary tuberculosis. Early in the course of the illness it may be nonproductive, but subsequently, as tissue necrosis ensues, sputum is usually produced. Inflammation of the lung parenchyma adjacent to a pleural surface may cause pleuritic pain without evident pleural disease. Spontaneous pneumothorax may also occur, often with chest pain and perhaps dyspnea. *Dyspnea* that results from parenchymal lung involvement is unusual unless there is extensive disease, which may occur, however, and may be associated with severe respiratory failure. *Hemoptysis* usually occurs with more extensive involvement but does not necessarily indicate an active tuberculous process. Hemoptysis may also result from bronchiectasis left as a residual of healed tuberculosis; from rupture of a dilated vessel in the wall of an old cavity (*Rasmussen's aneurysm*); from bacterial or fungal infection (especially in the form of a fungus ball [*aspergilloma* or mycetoma]) in an old residual cavity (Fig. 34-5); or from erosion of calcified lesions into the lumen of an airway (*broncholithiasis*).

The systemic features of tuberculosis include fever in approximately 35% to 80%[98,99]; malaise and weight loss; a variety of hematologic abnormalities, especially leukocytosis and anemia[100]; and metabolic disorders, including hyponatremia, which in one series was found to occur in 11% of patients.[101] Subsequently, hyponatremia was determined to be caused by production of an antidiuretic hormone–like substance found within affected lung tissue.[102]

Physical findings are not particularly helpful. Crackles may be heard in the area of involvement, along with bronchial breath sounds, when lung consolidation is close to the chest wall. Amphoric breath sounds may be indicative of a cavity.

Radiographic Features

In developed countries, radiographic examination of the chest is usually the first diagnostic study undertaken, after the history and physical examination. In resource-limited settings, a chest radiograph is not necessarily included as part of the routine evaluation because of cost, complexity, and nonspecificity of the findings.[103] Pulmonary tuberculosis nearly always causes detectable abnormalities on the chest film, although in patients with HIV infection, a normal chest radiograph occurred in as many as 11% of patients with positive sputum cultures.[71] In primary tuberculosis, occurring as a result of recent infection, the process is generally seen as a middle or lower lung zone infiltrate, often associated with ipsilateral hilar adenopathy (Fig. 34-6). Atelectasis may result from compression of airways by enlarged lymph nodes. If the primary process persists beyond the time when specific cell-mediated immunity develops, cavitation may occur (so-called progressive primary tuberculosis).

Tuberculosis that develops many years after the original infection (endogenous reactivation) usually involves the upper lobes of one or both lungs. Cavitation is common in this form of tuberculosis. The most frequent

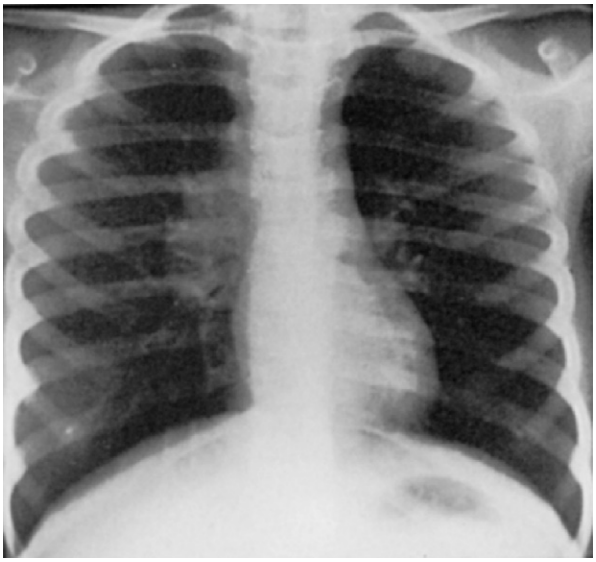

FIGURE 34-6 ■ Frontal-view chest roentgenogram showing right hilar adenopathy from primary tuberculosis.

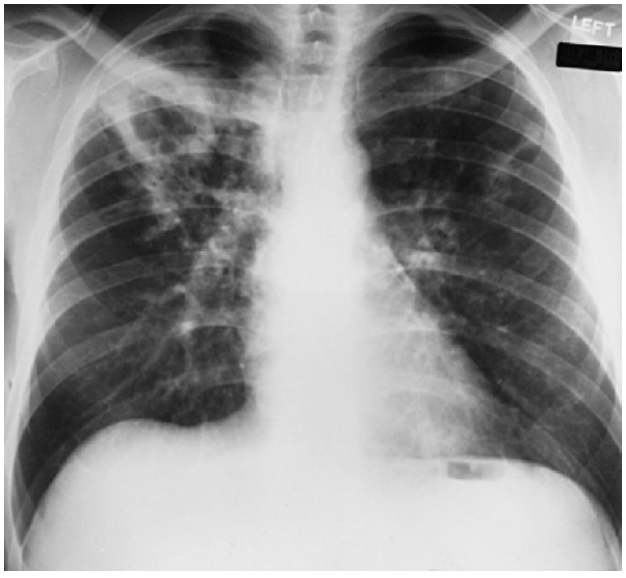

FIGURE 34-7 ■ Frontal-view chest film showing upper lobe cavitary lesion typical of endogenous reactivation tuberculosis.

sites are the apical and posterior segments of the right upper lobe (Fig. 34-7) and the apical-posterior segment of the left upper lobe. Healing of the tuberculous lesions usually results in development of a fibrotic scar with shrinkage of the lung parenchyma and, often, calcification. Involvement of the anterior segments alone is unusual. In the immunocompetent adult with tuberculosis, intrathoracic adenopathy is uncommon. When the disease progresses, infected material may be spread via the airways (i.e., "bronchogenic" spread) into the lower portions of the involved lung or to the other lung. Erosion of a parenchymal focus of tuberculosis into a blood or lymph vessel may result in dissemination of the organism and a miliary pattern on the chest film (Fig. 34-8).

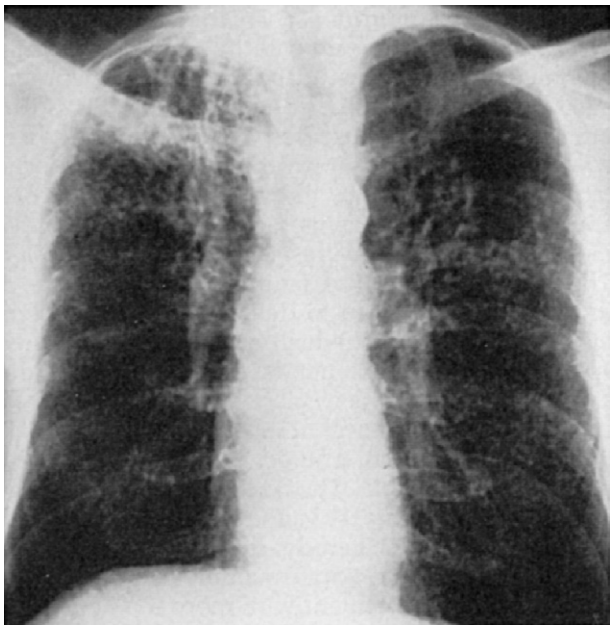

FIGURE 34-8 ■ Frontal-view chest film showing focal infiltration in the right upper lobe and scattered miliary lesions throughout both lungs.

Radiographic findings in HIV-infected patients are affected by the degree of immunosuppression. As further explained and illustrated in Chapter 80, tuberculosis occurring relatively early in the course of HIV infection tends to produce typical radiographic findings with predominantly upper lobe infiltration and cavitation.[104] With more advanced HIV disease, the radiographic findings become more "atypical": cavitation is uncommon, and lower lung zone or diffuse infiltrates and intrathoracic adenopathy are frequent (Fig. 34-9). Surprisingly, a substantial number of HIV-infected patients with pulmonary tuberculosis had normal radiographs at the end of their course of treatment.[105]

The activity of a presumed tuberculous process cannot be determined simply from a single radiographic examination of the chest. A cavity might be a sterile residual of an old infection, whereas a fibrotic-appearing lesion may be active. Conversely, not all radiographic worsening of the residua of prior tuberculous lesions can be ascribed to reactivation of the disease, although such worsening should always be of concern. Superimposed infections with other organisms or bleeding from bronchiectasis or from residual cavities may cause new infiltrations to appear. In addition, carcinomas may arise from within the area of scarring (so-called scar carcinomas) and be the cause of radiographic changes.

From this discussion, it should be obvious that the chest radiograph, although extremely valuable, cannot provide a definitive diagnosis of tuberculosis. Because of the radiographic similarities among the other disorders in the differential diagnosis, and because of the uncertainties in assessing disease activity and in determining the reasons for progressive radiographic changes, careful microbiologic evaluation is always indicated. A nondiagnostic microbiologic evaluation should prompt

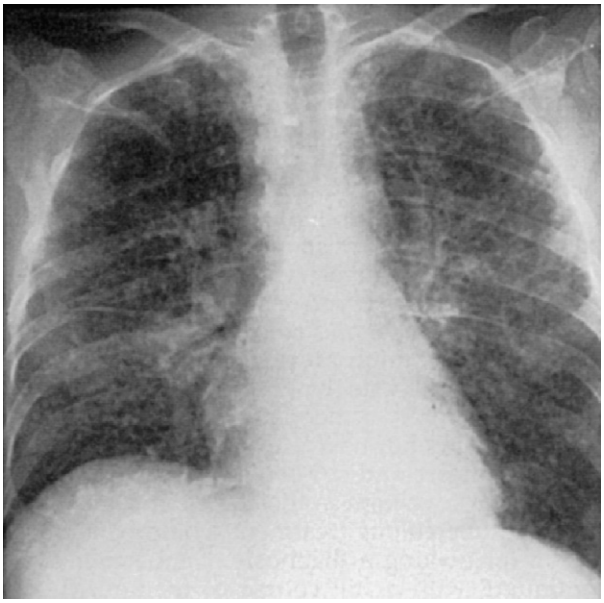

FIGURE 34-9 ■ Frontal-view chest film in a patient with acquired immunodeficiency syndrome and tuberculosis. Note the diffuse lung involvement and the bilateral hilar and right paratracheal adenopathy.

a careful assessment for other causes of the radiographic abnormality.

Bacteriologic Evaluation

As noted previously, a definitive diagnosis of tuberculosis can be established only by isolation of tubercle bacilli in culture or identification of specific nucleic acid sequences. Obviously, when the lung is involved, sputum is the initial specimen of choice. Sputum specimens should be collected at the time of the initial evaluation, and if they are found to be negative by microscopy, additional specimens should be collected. Single early-morning specimens have a higher yield and a lower rate of contamination than do pooled specimens.[106] Collecting more than two sputum specimens increases the yield only slightly.[107]

There are several options for obtaining specimens from patients who are not producing sputum. The first and most useful in terms of yield and avoidance of patient discomfort is inducing sputum production by the inhalation of a hypertonic (3% to 5%) saline mist generated by an ultrasonic nebulizer. Sputum induced by this technique is clear and resembles saliva; thus, it must be properly labeled or it may be discarded by the laboratory. This is a benign and well-tolerated procedure, although bronchospasm may be precipitated in asthmatic patients.

Sampling of gastric contents via a nasogastric tube has a lower yield than sputum induction and is more complicated and uncomfortable for the patient. However, in children and some adults, gastric contents may be the only specimen that can be obtained. Gastric lavage should be performed early in the morning before the patient has gotten out of bed, eaten, or brushed teeth. Once the specimen is obtained, prompt neutralization of the gastric acid is necessary to ensure a maximum yield.

Depending on the clinical circumstances, if the sputum is negative or cannot be obtained, the next diagnostic step is usually fiberoptic bronchoscopy with bronchoalveolar lavage, and in some instances transbronchial lung biopsy. The yield of bronchoscopy has been high in miliary tuberculosis and in local disease as well.[108,109] Bronchoscopic procedures have been especially helpful in the diagnostic evaluations of patients with HIV infection.[110,111] Needle aspiration biopsy may also provide specimens from which mycobacteria are isolated, but the technique is especially suited to the evaluation of peripheral nodular lesions for which there is a suspicion of malignancy.

In some situations, a therapeutic trial of antituberculosis chemotherapy may be indicated before more invasive studies are undertaken.[112] For example, in a tuberculin-positive person who is under 40 years of age, is a nonsmoker, and comes from a country where there is a high prevalence of tuberculosis, either current or past tuberculosis is much more likely than a neoplasm to be a cause for a radiographic abnormality, even in the presence of negative smears and cultures of sputum. In such a patient, improvement in the chest film concomitant with antituberculosis treatment would be sufficient reason for making a diagnosis of tuberculosis and continuing with a full course of therapy. If a response is going to occur, it should be seen within 2 months of starting treatment. If no improvement is noted, the abnormality is the result of either old tuberculosis or another process. An algorithm illustrating this approach is shown in Figure 34-10.

Because of the potentially disastrous consequences of delays in diagnosis of tuberculosis, it is essential that the identification of *M. tuberculosis* be performed rapidly and the results be reported promptly. Waiting days for the results of microscopic examinations, weeks for culture results, and months for speciation and susceptibility studies, as has commonly been the practice, is no longer acceptable.

Acid-Fast Staining

A systematic review of the different diagnostic tests for tuberculosis was recently published.[113] As pointed out, the first step in the diagnostic sequence is nearly always staining and examining readily available specimens for acid-fast bacilli (AFB). Finding AFB is very specific for mycobacteria (except in rare instances), but provides no information about species. In addition, the sensitivity of microscopic examination is relatively low; the level of detection is approximately 10,000 bacilli per milliliter of secretions, if 100 oil immersion microscopic fields are examined. In practice, 40% to 70% of patients with *M. tuberculosis* isolated in culture have positive smears.[114]

Sensitivity of detection of AFB is increased by about 10% when using a fluorochrome staining procedure with auramine O, a fluorescent stain.[115] This procedure requires use of a fluorescent microscope but is faster

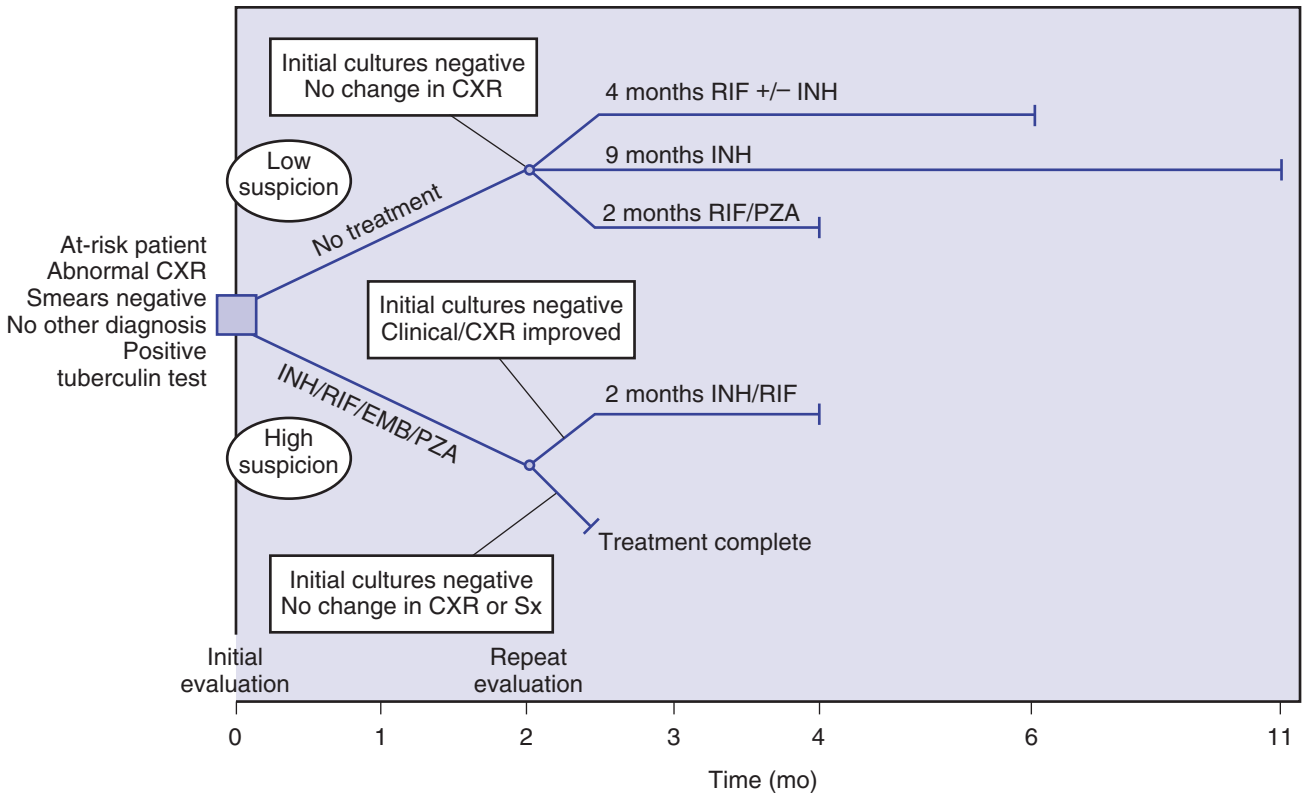

FIGURE 34-10 ■ Treatment algorithm for active, culture-negative pulmonary tuberculosis and inactive tuberculosis. The decision to begin treatment for a patient with sputum smears that are negative depends on the degree of suspicion that the patient has tuberculosis. If the clinical suspicion is high (lower portion of figure), then multidrug therapy should be initiated before acid-fast smear/culture results are known. If the diagnosis is confirmed by a positive culture (see Fig. 34-11), treatment can be continued to complete a standard course of therapy. If initial cultures remain negative and treatment has been with multiple drugs for 2 months, then there are two options depending on repeat evaluation at 2 months (lower portion of figure). In option 1, if the patient demonstrates symptomatic or radiographic improvement without another apparent diagnosis, then a diagnosis of culture-negative tuberculosis can be inferred. Treatment should be continued with isoniazid and rifampin alone for an additional 2 months. In option 2, if the patient demonstrates neither symptomatic nor radiographic improvement, then prior tuberculosis is unlikely, and treatment is complete once treatment including at least 2 months of rifampin and pyrazinamide has been taken. In low-suspicion patients not initially on treatment (upper portion of figure), if cultures remain negative, the patient has no symptoms, and the chest radiograph is unchanged at 2 to 3 months, there are three treatment options: (1) isoniazid for 9 months; (2) rifampin with or without isoniazid for 4 months; or (3) rifampin and pyrazinamide for 2 months. (See later discussion of latent tuberculous infection.) CXR, chest radiograph; EMB, ethambutol; INH, isoniazid; PZA, pyrazinamide; RIF, rifampin; Sx, symptoms. (From Blumberg HM, Burman WJ, Chaisson RE, et al, for the American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: Treatment of tuberculosis. Am J Respir Crit Care Med 167:603–662, 2003.)

than acid-fast staining because the intensity of the fluorescent signal enables slides to be scanned at lower magnification. Smears generally are interpreted as negative, or, if positive, are reported as rare (3 to 9 organisms per slide), few (10 or more per slide), or numerous (1 or more per high-power oil immersion field). A limitation of this method is the need of a short-arc mercury vapor lamp (MVP) used as the excitatory light source. This has a limited lifespan (200 to 300 hours), is costly, requires high maintenance, and is potentially toxic due to its mercury content. Recently, a light-emitting diode (LED) has been substituted as the light source. The LED has a life span of more than 50,000 hours, and a recent study demonstrated that its performance was similar to the MVP-based microscopy; because of its considerably lower cost, the LED is a feasible option for laboratories with limited resources.[116]

In most situations in which acid-fast organisms are detected by microscopy, they should be assumed to be *M. tuberculosis* until proven otherwise. Assuming the patient has tuberculosis will trigger the appropriate prompt responses from the physicians responsible for treatment and from public health agencies.

Mycobacterial Culture

Although definitive identification of *M. tuberculosis* can be accomplished by rapid amplification tests, determination of drug susceptibility generally still requires isolation of the organism in culture. However, rapid polymerase chain reaction (PCR)–based tests that identify resistance-conferring mutations have recently been developed and validated, although they are not yet marketed in the United States.[117] Many of the mutations that cause drug

resistance have been identified, but there have not yet been evaluations of the utility of tests designed to detect these mutations in routine clinical practice.[118]

Culturing of mycobacteria from clinical specimens requires a higher level of technical capability than that needed for microscopy. The need for infection control precautions, constant-temperature incubators, and a constant power supply restricts the use of culture in many developing countries. At a minimum, laboratories performing culture should be able to identify *M. tuberculosis.* Isolates that are not *M. tuberculosis* or are of questionable identity should then be sent to a more specialized laboratory for definitive speciation.

Solid Media. Culture of sputum usually involves digestion, decontamination, and concentration of the specimen before inoculating media. This process enables more uniform plating of the specimen and decreases bacterial overgrowth. For specimens other than sputum, digestion and decontamination are not required. It is generally recommended that two different kinds of media be inoculated: usually an egg-based one, such as Löwenstein-Jensen, and an agar-based one, such as Middlebrook-Cohn 7H10. Egg-based media are generally regarded as the reference standard and may result in a larger number of positive cultures, whereas agar-based media enable earlier detection of growth.[119] *Mycobacterium tuberculosis* colonies appear in 2 to 6 weeks. Cultures showing no growth at 6 weeks are reported as negative, although they generally are kept for another 2 to 4 weeks before being discarded.

Liquid Media with Radiometric and Colorimetric Detection Systems. Because early identification of patients with tuberculosis is important and because of concern regarding multidrug-resistant organisms, radiometric or colorimetric detection and sensitivity test systems should be used in hospitals in which large numbers of patients with tuberculosis are managed. Radiometric culture systems incorporate ^{14}C-labeled palmitic acid into a liquid culture medium[8]; accordingly, as mycobacteria grow in this medium, they liberate $^{14}CO_2$ that can be measured by the detection device. The increased sensitivity of the system enables growth to be detected sooner, usually in 10 to 14 days. As noted earlier, a positive NAP test or DNA probe testing confirms an isolate as being *M. tuberculosis.* A limitation of the method is the need for safe disposal of the radioactive waste. Therefore, currently, it is more common to see nonradiometric methods based on fluorescent or colorimetric (based on the reduction of a colored redox indicator present in the culture medium) signals.[120]

Nucleic Acid Amplification Tests. Nucleic acid amplification tests include those that involve PCR amplification, transcription-mediated amplification, strand-displacement amplification, ligase chain reaction, Q Beta replicase amplification, transcription-mediated amplification, and peptide nucleic acid assay.[120] Each of these approaches has strengths and weaknesses, descriptions of which are beyond the scope of this discussion. In each test, either DNA or ribonucleic acid (RNA) within as few as 1 to 10 organisms is amplified to detectable levels. Currently, rapid amplification tests are mainly used with specimens in which AFB have been found, although one available test has been licensed for use with AFB smear-negative specimens. The updated recommendations by the CDC indicate that a nucleic acid amplification test should be performed on at least one specimen, preferably the first diagnostic specimen, and that the results should be available within 48 hours of collection. The recommended interpretation algorithm includes the use of clinical judgment when the nucleic acid amplification test is negative.[121] This limitation has been applied because the sensitivity of the tests for specimens that are smear negative but culture positive is not sufficiently high to exclude *M. tuberculosis* with a negative result of a rapid test.[113,121]

Other Diagnostic Methods

Several antigens, including highly purified and recombinant antigens specific for *M. tuberculosis* complex, have been used in serologic antibody tests with variable results. A recent systematic review found that the results of serologic tests are highly variable, but there is no commercial test that is better than the sputum smear microscopy; therefore, the use of these methods is very limited.[122]

Drug Susceptibility Testing

Determination of susceptibility to antimicrobial agents is of considerable clinical importance. Because of concerns regarding tuberculosis caused by drug-resistant organisms, drug susceptibility testing is recommended for all initial *M. tuberculosis* isolates. Although several techniques are used for determining resistance, the proportion method remains the reference standard.[123] This involves inoculating one or more dilutions of cultured mycobacteria on drug-free media and on media containing appropriate concentrations of antimycobacterial agents. Resistance is generally considered to be present when the growth on the drug-containing medium is 1% or more of the control growth. The standard drug concentrations used for defining resistance of *M. tuberculosis* to the first-line drugs are as follows: isoniazid, 0.2 g/mL; rifampin, 1.0 g/mL; ethambutol, 5.0 g/mL; and streptomycin, 2.0 g/mL. Susceptibility testing for pyrazinamide has been done mainly in a radiometric system,[124] and more recently with nonradiometric methods, which have shown comparable results.[125] Testing for susceptibility to second-line drugs is generally performed only in reference laboratories and recommended mainly for MDR strains. Rapid radiometric measurements have been used to determine drug susceptibility and can provide results much more quickly than from cultures on solid media,[124] but definitive results still take weeks.

Recent studies have demonstrated that the Microscopic-Observation Drug Susceptibility (MODS) assay is a simple, fast, and reliable method to detect *M. tuberculosis* and determine the drug susceptibility at the same time.[126] MODS incorporates the antituberculosis drugs from the beginning of the assay. The method uses a

sealed 24-well tissue-culture plate with liquid culture media containing different antibiotics and controls that are examined periodically under an inverted light microscope. When compared with culture on Löwenstein-Jensen medium and an automated mycobacterial culture system (MBBacT), the sensitivity to detect *M. tuberculosis* growth was 97.5% to 97.8% for MODS, 89% for MBBacT, and 84% for Löwenstein-Jensen. The median times for a positive culture were 7, 22, and 68 days, respectively. The agreement with the proportional method for susceptibility test was 100% for rifampin, 97% for isoniazid, 95% for ethambutol, and 92% for streptomycin.[126,127]

Molecular methods that provide results much more quickly than conventional tests are now available and attracting increasing attention.[121] These techniques are based on the detection of drug-resistant associated mutations that are present in 90% to 95% of the isolates that are phenotypically resistant to isoniazid and rifampin. Currently there are several commercial methods. The Genotype MTBDR*plus* (Hain Lifescience, Nehren, Germany) is a PCR-based reverse hybridization assay to detect rifampin and isoniazid resistance directly in smear-positive sputum.[128] A recent study in South Africa demonstrated that 97% of the specimens gave a useful result within 1 to 2 days, with a sensitivity of 98.8% and specificity of 100% for the detection of multidrug resistance when compared with conventional results. Interestingly, the assay performed well on contaminated cultures, which cannot be used for susceptibility test by conventional methods.[129] The INNO-LiPA Rif.TB kit (Innogenetics, Gent, Belgium) is also based on PCR and hybridization of the PCR product on strips that identify *M. tuberculosis* as well as the mutations responsible for the resistance to rifampin.[130] Other methods based on real-time PCR using different probes, such as the molecular beacons and bacteriophage-based assays, are promising but currently are not commercially available.[131,132]

Genetic Polymorphisms

As noted earlier in this chapter, analysis of the genetic polymorphisms in genomic DNA of *M. tuberculosis* has been shown to be a useful tool for studying the epidemiology and transmission dynamics of tuberculosis.[34,50,67,133–135] RFLP analysis is based on the finding that tubercle bacilli possess repetitive DNA sequences. Of these sequences, IS*6110* is found in 2 to 25 copies per individual isolate or strain with enough polymorphism to study the dynamics of the transmission of tuberculosis in a population. The polymorphism based on IS*6110* is considered the standard method; however, secondary typing methods such as spoligotyping, mycobacterial interspersed repeat unit (MIRU) typing, and polymorphic guanine cytosine-rich sequence (PGRS) are required to increase the resolving power when the number of IS*6110* bands is less than 6.[62] The IS*6110* and PGRS are based on determining RFLPs and involve extracting DNA from cultured *M. tuberculosis,* digesting it with restriction endonucleases, separating the resulting fragments by gel electrophoresis, and using Southern blot analysis with labeled components of these sequences to create a unique, strain-specific DNA fingerprint.

Spoligotyping is a PCR-based method that detects polymorphisms in the direct repeat locus, and has enabled the demonstration that different genotypes of *M. tuberculosis* predominate in different parts of the world.[136] This technique is relatively simple, highly reproducible, and suited to high-throughput approaches. A second PCR-based genotyping method, MIRU typing, is based on minisatellite-like loci containing a variable number of tandem repeats (VNTR) present in different loci in the genome.[137] Like spoligotyping, MIRU/VNTR typing is highly reproducible. In contrast to RFLP, spoligotyping, and MIRU/VNTR typing, single nucleotide polymorphisms (SNPs) and large sequence polymorphisms represent unique event polymorphisms especially suited for inferring evolutionary history,[138] and are easily incorporated into high-throughput formats. However, except for the comparison of a few whole-genome sequences,[139–141] SNP data are still very limited in *M. tuberculosis.*[142]

Treatment

Further information about the introduction and development of chemotherapy for pulmonary tuberculosis is provided in Appendix 1 for this chapter, which can be found in the electronic version of this textbook on its Website. The Appendix also provides important details about the means of action, genetic basis of resistance, and chief adverse effects of each of the main first- and second-line antituberculosis agents that are currently in use; also included is Table 34A.1, which lists the available preparations and their recommended doses.

Current Standard Regimens

The treatment regimens that are recommended currently by the American Thoracic Society, the CDC, and the Infectious Diseases Society of America are shown in Table 34-1.[143]

The recommended basic treatment regimen for previously untreated patients with pulmonary tuberculosis consists of an initial phase of isoniazid, rifampin, pyrazinamide, and ethambutol given for 2 months, followed by a 4-month continuation phase of isoniazid and rifampin.[143,144] As shown in Table 34-1, there are several variations in the pattern of administration of the basic regimen, which are largely designed to enable health care personnel (or their surrogates) to provide closer supervision of treatment.

Several caveats apply to these recommendations for treatment to be successful. First, the organisms must be susceptible to the drugs used. Second, patients must take all or nearly all of the prescribed treatment. Third, success should be documented by bacteriologic evaluation; that is, sputum cultures should be negative by the end of 3 months of treatment. If the sputum still contains *M. tuberculosis* after 2 to 3 months of therapy, the patient should be reassessed carefully to determine whether a change in treatment is necessary.

Table 34-1. Drug Regimens for Culture-Positive Pulmonary Tuberculosis Caused by Drug-Susceptible Organisms

INITIAL PHASE			CONTINUATION PHASE			Range to Total Doses (Minimum Duration)	RATING* (EVIDENCE)†	
Regimen	Drugs	Interval and Doses‡ (Minimum Duration)	Regimen	Drugs	Interval and Doses‡§ (Minimum Duration)		HIV+	HIV−
1	INH RIF PZA EMB	Seven days/wk for 56 doses (8 wk) or 5 days/wk for 40 doses (8 wk)§	1a	INH/RIF	Seven days/wk for 126 doses (18 wk) or 5 days/wk for 90 doses (18 wk)§	182–130 (26 wk)	A (I)	A (II)
			1b	INH/RIF	Twice weekly for 36 doses (18 wk)	92–76 (26 wk)	A (I)	A (II)¶
			1c**	INH/RPT	Once weekly for 18 doses (18 wk)	74 or 58 (26 wk)	B (I)	E (I)
2	INH RIF PZA EMB	Seven days/wk for 14 doses (2 wk) then twice weekly for 12 doses (6 wk) *or* 5 days/wk for 10 doses (2 wk)§ then twice weekly for 12 doses (6 wk)	2a	INH/RIF	Twice weekly for 36 doses (18 wk)	62–58 (26 wk)	A (II)	B(II)¶
			2b**	INH/RPT	Once weekly for 18 doses (18 wk)	44 or 40 (26 wk)	B (I)	E (I)
3	INH RIF PZA EMB	Thrice weekly for 24 doses (8 wk)	3a	INH/RIF	Thrice weekly for 54 doses (18 wk)	78 (26 wk)	B (I)	B (II)
4	INH RIF EMB	Seven days/wk for 56 doses (8 wk) or 5 days/wk for 40 doses (8 wk)§	4a	INH/RIF	Seven days/wk for 217 doses (31 wk) or 5 days/wk for 155 doses (28 wk)§	273–195 (39 wk)	C (I)	C (II)
			4b	INH/RIF	Twice weekly for 62 doses (31 wk)	118–102 (39 wk)	C (I)	C (II)

Definitions of evidence ratings:
*A, preferred; B, acceptable alternative; C, offer when A and B cannot be given; E, should never be given.
†I, randomized clinical trial; II, data from clinical trials that were not randomized or were conducted in other populations; III, expert opinion.
‡When directly observed therapy (DOT) is used, drugs may be given 5 days/wk and the necessary number of doses adjusted accordingly. Although there are no studies that compare 5 with 7 daily doses, extensive experience indicates this would be an effective practice.
§Patients with cavitation on initial chest radiograph and positive cultures at completion of 2 months of therapy should receive a 7-month (28-week; either 196 doses [daily] or 56 doses [twice-weekly]) continuation phase.
§Five-day-a-week administration is always given by DOT. Rating for 5-day-a-week regimens is AIII.
¶Not recommended for human immunodeficiency virus (HIV)–infected patients with $CD4^+$ cell counts less than 100 cells/μL.
**Options 1c and 2b should only be used in HIV-negative patients who have negative sputum smears at the time of completion of 2 months of therapy and who do not have cavitation on the initial chest radiograph (see text). For patients started on this regimen and found to have a positive culture at 2 months, treatment should be extended an extra 3 months.
EMB, ethambutol; INH, isoniazid, PZA, pyrazinamide, RIF, rifampin, RPT, rifapentine.
Modified from Blumberg HM, Burman WJ, Chaisson RE, et al, for the American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: Treatment of tuberculosis. Am J Respir Crit Care Med 167:604–662, 2003.

Because of concerns with drug resistance, initial isolates from patients with tuberculosis should have drug susceptibility tests performed and the results should be used to guide treatment. Drug susceptibility tests should be repeated for specimens that are positive after 3 months of treatment.

The recommendation of a four-drug intensive phase is based, in part, on findings of the British Medical Research Council[145,146] concerning the outcome in countries or regions where the prevalence of initial resistance to isoniazid is likely to be high, in which case treatment regimens should include a 2-month, four-drug initial phase, and a 4-month continuation phase of rifampin plus isoniazid. However, a recent meta-analysis of clinical trials indicates that treatment failures and relapses are inordinately high when there is initial isoniazid resistance, suggesting that ethambutol should be continued for the duration of the regimen.[147] The risk of not taking this approach is the development of rifampin resistance.

Several factors have been found to be predictive of a poor therapeutic outcome, including extensive tuberculosis and a large population of bacilli, the rapidity or slowness with which sputum becomes negative after treatment is begun, and several factors associated with adherence.[143,148–150] In U.S. Public Health Service Study 22, the presence of cavitation on the initial chest film and sputum culture positivity at the end of the 2-month

intensive phase of treatment were highly predictive of an adverse outcome—either treatment failure or relapse.[148] For this reason, in patients with cavitation on the initial chest film and who have positive sputum cultures at the end of the initial phase of treatment, prolongation of the continuation phase to 7 months, making a total of 9 months of treatment, is recommended.[143] Factors that have been associated with poor clinic attendance and, therefore, with a less likely chance of favorable response, include use of alcohol, younger age (but above 18 years), and unmarried status. Patients with any of these characteristics should be monitored especially carefully. Although directly observed therapy (DOT) is labor intensive, the improved outcomes shown in retrospective analyses justify its use in preventing treatment failure and relapse, both of which have striking cost as well as public health implications.[151–153]

Special Situations

The algorithm shown in Figure 34-11 presents the approach to treatment of pulmonary tuberculosis in patients with *M. tuberculosis* isolated from sputum, and Figure 34-10 shows a treatment algorithm for patients with radiographic evidence of tuberculosis but negative bacteriologic examinations. In the absence of bacteriologic confirmation, treatment depends first on the degree of suspicion of active disease, and second on whether or not initial treatment causes clinical or radiographic improvement.

HIV Infection. The recommended treatment regimen for HIV-infected patients with tuberculosis consists of the same 6-month regimen as described for non–HIV-infected persons, although there are several important areas in which therapy may differ. Although

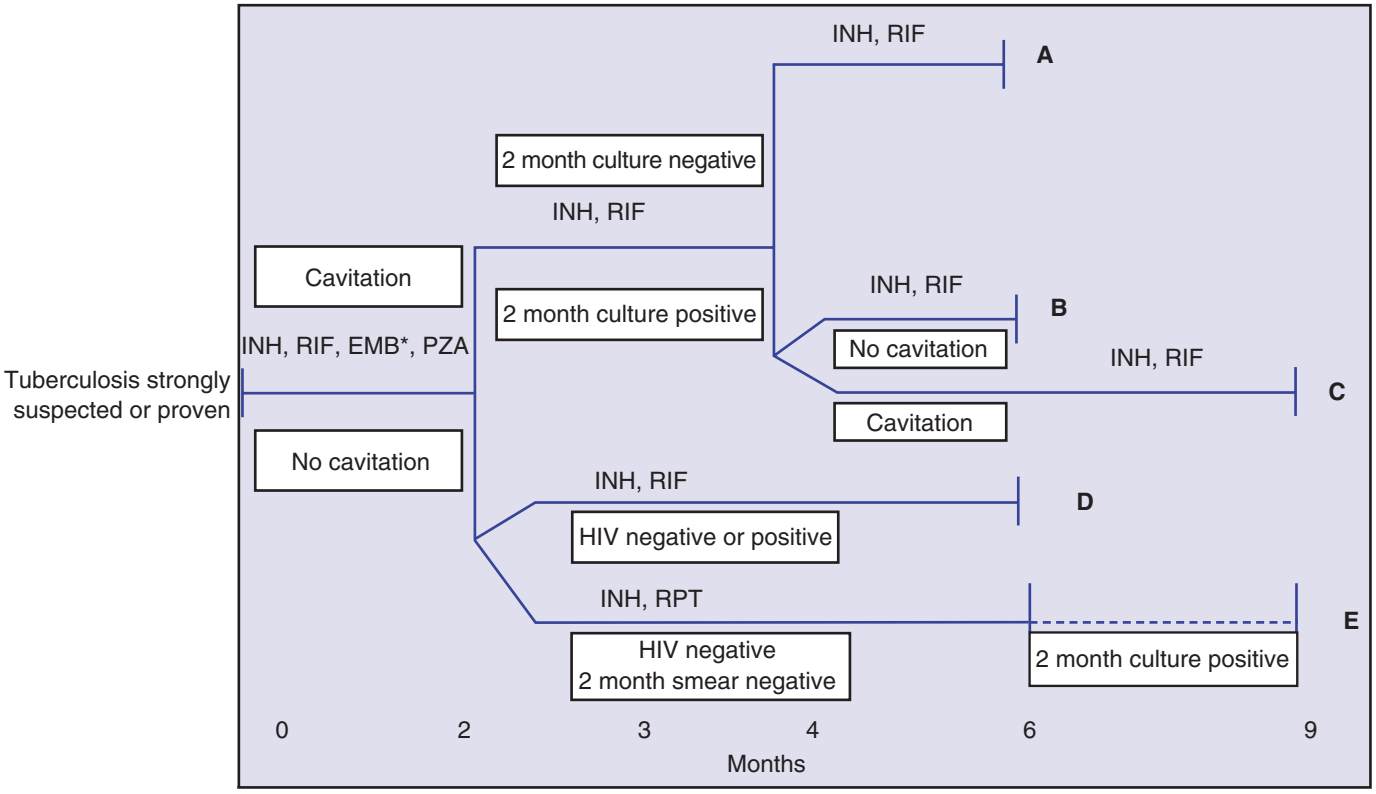

FIGURE 34-11 ■ Treatment algorithm for patients with sputum-culture positive tuberculosis. Patients in whom tuberculosis is proven or strongly suspected should have treatment initiated with isoniazid, rifampin, pyrazinamide, and ethambutol daily or thrice weekly for the initial 2 months (*intensive phase*). A repeat smear and culture should be performed at the time 2 months of treatment is completed. The *continuation phase* of treatment should consist of isoniazid and rifampin daily or twice weekly for 4 months to complete a total of 6 months of treatment (arm A of figure). If the patient has HIV infection and the $CD4^+$ cell count is less than 100/μL, the *continuation phase* should consist of daily or thrice-weekly isoniazid and rifampin. Twice-weekly therapy should not be used for patients with advanced HIV infection. If the culture at completion of 2 months of treatment is positive but there was no cavitation on the initial chest film or the culture is negative (with or without cavitation on the initial film), a 4-month continuation phase should be used (arms B and D of figure). If cavitation was present on the initial chest radiograph and the culture from the time of completion of 2 months of therapy is positive, the continuation phase should be lengthened to 7 months (total of 9 months of treatment—arm C of figure). In non–HIV-infected patients having *no* cavitation on chest radiograph *and negative* acid-fast smears at completion of 2 months of treatment, the *continuation phase* may consist of either once-weekly isoniazid and rifapentine, or daily or twice-weekly isoniazid and rifampin, to complete a total of 6 months of treatment (arm D of figure). Patients receiving isoniazid/rifapentine whose 2-month cultures are positive should have treatment extended by 3 additional months (total of 9 months of treatment—arm E of figure). EMB, ethambutol; INH, isoniazid; PZA, pyrazinamide; RIF, rifampin; RPT, rifapentine. (Modified from Blumberg HM, Burman WJ, Chaisson RE, et al, for the American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: Treatment of tuberculosis. Am J Respir Crit Care Med 167:603–662, 2003.)

rates of relapse are not increased among HIV-infected patients who take a standard 6-month regimen in the United States, there is an association with acquiring rifampin resistance.[154–156] In sub-Saharan Africa, however, where different regimens are often used, the likelihood of death, especially during the first 2 months of therapy, and of relapse following apparently successful treatment is considerably higher in HIV-infected than in non–HIV-infected patients.[157] The cause of rifampin monoresistance is not clear but has been associated with the use of once- or twice-weekly drug administration in the continuation phase and prior use of rifabutin as prophylaxis for *Mycobacterium avium* complex infections.[154,156,158] For this reason, the rifapentine once-weekly regimen is contraindicated for all patients with HIV infection, and a twice-weekly regimen is not recommended for HIV-infected patients with $CD4^+$ counts less than 100 cells/μL.[143]

An important concern in treating tuberculosis in patients with HIV infection is the potential for interactions with other drugs, especially antiretroviral agents, as discussed in detail in Chapter 80. The most practical means of minimizing the effects of interactions is to use a regimen consisting of two nucleoside reverse transcriptase inhibitors plus efavirenz or, in pregnant women, nevirapine in the HIV treatment regimen, and rifabutin in place of rifampin in the antituberculosis regimen. Monitoring of serum drug concentrations may be useful in avoiding the adverse consequences of the interactions. The timing of initiation of an antiretroviral regimen in patients being treated for tuberculosis has not been determined. The general recommendation is that, for patients with tuberculosis and HIV infection having a $CD4^+$ count less than 200 cells/μL, an antiretroviral regimen should be started[159]; for patients with $CD4^+$ counts of 200 to 350 cells/μL, the possible benefits are less clear, but treatment should be considered. However, this is an area that is changing rapidly.

Another feature of the treatment of tuberculosis, as well as of other opportunistic infections, is the paradoxical worsening that may occur in HIV-infected persons who are also receiving antiretroviral therapy, a clinical phenomenon known as the immune reconstitution inflammatory syndrome (IRIS). The frequency of tuberculosis-related IRIS varies depending on the study, mainly because of the different case definitions used. Recently, the International Network for the Study of HIV-associated IRIS published the case definitions for the two main syndromes of tuberculosis.[160] The more common syndrome is the paradoxical tuberculosis–associated IRIS, which occurs within the first weeks or months after the start of antiretroviral therapy in patients already being treated for tuberculosis. Characteristic features include new or exacerbated symptoms or signs of tuberculosis and worsening of its radiologic manifestations; usually, the syndrome is self-limiting, with a median duration of 2 months. Risk factors for the development of this form of IRIS include advanced HIV disease, disseminated and extrapulmonary tuberculosis, and a short interval between starting antituberculosis and antiretroviral treatments.

The second IRIS syndrome, known as antiretroviral therapy–associated tuberculosis, occurs when tuberculosis (or some other lurking undiagnosed HIV-linked complication) is "unmasked" and flares up not long after beginning antiretroviral therapy and, therefore, can be diagnosed.

Drug Resistance. Patients who do not have a favorable bacteriologic response early during treatment present a difficult problem. After 3 months of chemotherapy, more than 90% of patients taking regimens containing isoniazid and rifampin should have negative sputum cultures. Failure of the sputum to become negative generally means that either the organisms are resistant to the agents being used or the patient is not taking the drugs. Patients who continue to have *M. tuberculosis* in their sputum after 2 to 3 months of treatment should be started on DOT, if not already being supervised, and should have drug susceptibility testing performed. If resistance is found, the regimen should be modified accordingly. If sputum samples are still positive after 4 months of therapy, the regimen should be considered to have failed and a new regimen should be begun, ideally based on recent drug susceptibility test results. A list of possible regimens for non-MDR tuberculosis is shown in Table 34-2.

The basic principle of treatment for patients whose organisms are resistant to one or more of the first-line drugs is the administration of at least two (but generally three or four) agents to which there is demonstrated sensitivity.[143,161] Unfortunately, there are no data to provide evidence-based guidelines as to the relative effectiveness of various regimens and the necessary duration of treatment. Clearly, if the organism is susceptible to isoniazid and rifampin, a usual regimen can be expected to be successful. In the presence of resistance to isoniazid, treatment with rifampin and ethambutol, supplemented by pyrazinamide, also is likely to be successful. There are data that suggest that 12 months of treatment with rifampin and ethambutol is sufficient[162]; however, in patients with organisms resistant to isoniazid, such decisions should be made on a case-by-case basis.

The fourth Global Drug Resistance Surveillance Project conducted between 2002 and 2007 by the WHO and the International Union Against Tuberculosis and Lung Disease included 91,577 patients from 81 countries, representing 35% of the global notified new smear-positive cases.[163] Drug resistance was found in all countries surveyed, except for Iceland, with a weighted mean of 17% of new cases having resistance to at least one antituberculosis drug and 2.9% having multiple drug resistance (resistance to at least isoniazid and rifampin). According to the most recent WHO estimates, in 2007, 511,000 cases of MDR tuberculosis occurred worldwide: 289,000 (3.1%) among all new, never-treated patients, and 221,000 (19%) among all previously treated patients.[3] There were areas of the world in which rates of multiple drug resistance are truly alarming, such as Baku, Azerbaijan, where 56.3% of new cases were resistant to any drug and 22.3% were MDR,[163] a considerable worsening since the previous report.[164]

Table 34-2. Selected Treatment Regimens for non-MDR Drug-Resistant Tuberculosis

Resistance to	Treatment Regimen	Duration of Therapy	Comments
Isoniazid (± streptomycin)	Rifampin Ethambutol Pyrazinamide	6–9 months	A fluoroquinolone may strengthen the regimen for patients with extensive disease.
Isoniazid and pyrazinamide	Rifampin Ethambutol Fluoroquinolone*	9–12 months	A longer duration of treatment should be used for patients with extensive disease.
Isoniazid and ethambutol	Rifampin Pyrazinamide Fluoroquinolone	9–12 months	A longer duration of treatment should be used for patients with extensive disease.
Rifampin	Isoniazid Ethambutol Fluoroquinolone plus at least 2 months of pyrazinamide	12–18 months	An injectable drug may strengthen the regimen for patients with extensive disease.
Rifampin and ethambutol (± streptomycin)	Isoniazid Pyrazinamide Fluoroquinolone plus injectable drug† for at least the first 2–3 months	18 months	A longer course (6 months) of the injectable may strengthen the regimen for patients with extensive disease.
Rifampin and pyrazinamide (± streptomycin)	Isoniazid Ethambutol Fluoroquinolone plus injectable drug for at least the first 2–3 months	18 months	A longer course (6 months) of the injectable may strengthen the regimen for patients with extensive disease.
Isoniazid, ethambutol pyrazinamide (± streptomycin)	Rifampin Fluoroquinolone plus an oral second-line agent,‡ plus injectable drug for at least the first 2–3 months	18 months	A longer course (6 months) of the injectable may strengthen the regimen for patients with extensive disease.
Pyrazinamide	Isoniazid, rifampin plus at least 2 months of ethambutol	9 months	Most commonly seen in *M. bovi* infection.

*Fluoroquinolones: levofloxacin or moxifloxacin.
†Injectable drugs: streptomycin, amikacin, kanamycin, or capreomycin.
‡Oral second-line drugs: ethionamide, cycloserine, or *p*-aminosalicylic acid.
From Francis J, for the Curry National Tuberculosis Center and California Department of Public Health, Drug-Resistant Tuberculosis: A Survival Guide for Clinicians, 2nd ed. Sacramento: California Department of Public Health, 2008, pp 34–35.

Patients with MDR tuberculosis should be treated with a minimum of 4—and preferably more—drugs to which the isolate is susceptible, including any susceptible first-line agents, a fluoroquinolone, an injectable aminoglycoside, and oral second-line drugs to create a regimen of 4 to 6 agents. Treatment should be directly observed, either in the hospital or domiciliary setting.[164a]

The outcome of treatment in persons with tuberculosis caused by MDR organisms is generally less good than that of treatment of disease caused by susceptible organisms, although data are sparse. At least in part, the outcome depends on the number of agents to which the organisms are susceptible, the promptness and appropriateness of therapy, the number of previous courses of therapy, and the HIV status of the patient. For example, in a group of patients with MDR tuberculosis who had undergone multiple previous courses of chemotherapy, the rate of successful outcome was only slightly better than 50%.[164] However, both in New York and in San Francisco, non–HIV-infected patients with MDR tuberculosis who had not been extensively treated previously had a much better rate of success (92% and 97%, respectively), albeit with a much shorter follow-up time.[165,166] In the report from San Francisco, the prognosis for patients with HIV infection and MDR tuberculosis was very poor: all 11 patients died during the period of the study, although no patients received antiretroviral therapy,[165] but whether or not it would have improved the outcome is unknown.

In 2006, XDR tuberculosis—defined as tuberculosis caused by *M. tuberculosis* that are not only MDR but resistant as well as to any one of the fluoroquinolones and to at least one of three injectable second-line drugs (amikacin, capreomycin, or kanamycin)—was identified and was rapidly recognized as a serious emerging threat to global public health.[37,167] Subsequent reports have identified XDR tuberculosis in all regions of the world, with countries from the former Soviet Union reporting as high as 24% XDR tuberculosis among the MDR cases.[163] The two strongest risk factors for XDR tuberculosis are failure of a tuberculosis treatment regimen that contains second-line drugs, including an injectable agent and a fluoroquinolone, and close contact with an individual with documented XDR tuberculosis or with an individual for whom treatment with a regimen including second-line drugs is failing or has failed.

The outcome of treatment of patients with XDR tuberculosis is generally less good than the outcome for

patients with MDR disease.[168] In one cohort from KwaZulu-Natal, 98% of XDR tuberculosis patients coinfected with HIV died, with a median time of death of only 16 days from time of specimen collection.[37] Rates of successful completion of treatment among patients with XDR tuberculosis but without HIV infection range from approximately 30% to 60%. Consultation with an expert is advised in treating patients with MDR/XDR tuberculosis, because the regimen chosen often represents the last best chance for cure, and treatment must be done correctly. The regimen should be based on the results of drug susceptibility tests when available. In most instances, however, the results are not known until several weeks after therapy is started. In such instances, treatment should be determined on the basis of the patient's history of prior therapy, avoiding reliance on agents taken previously, and on the prevailing resistance patterns in the community or subpopulation of which the patient is a member.

Children. The basic principles that apply in the management of adults with pulmonary tuberculosis are equally applicable in children. Although children have been excluded from nearly all clinical trials of short durations of chemotherapy, there are several reports documenting the usefulness of 6- and 9-month regimens in children.[143,169,170] The most frequent difference between treating children and adults is the more limited use of ethambutol. Because children tend to have forms of tuberculosis that are associated with lower bacillary populations, the likelihood of drug resistance is less. Moreover, young children generally cannot have visual acuity testing performed accurately, and thus cannot be monitored for toxicity. However, if ethambutol is used, the dose is 20 mg/kg because of differences in pharmacokinetics between adults and children.[171]

At least in younger children, sputum specimens for bacteriologic evaluations cannot usually be obtained. Consequently, the response to treatment is assessed by clinical and radiographic criteria. For this same reason, drug susceptibility or resistance often must be inferred from the pattern of the presumed source case or community data rather than being determined in the laboratory.

Pregnancy and Breast-feeding. Active untreated tuberculosis represents a far greater hazard to a pregnant woman and her fetus than does treatment for the disease. Pregnant women or mothers of young infants, therefore, should be started on treatment with isoniazid, rifampin, and ethambutol. Pyrazinamide is included in recommendations for treating tuberculosis in pregnant women by the WHO, but it has not been included in recommendations in the United States because of insufficient information about possible harm to the fetus.[143,144] Streptomycin, which interferes with development of the ear and may cause congenital deafness, is the only antituberculosis drug documented to have harmful effects on the fetus.[172] This potential is presumably shared by amikacin, kanamycin, and capreomycin; however, there is little or no information about the effects of these drugs on the fetus, or about the potential hazards of cycloserine, ethionamide, and pyrazinamide.

Although several antituberculosis drugs are present in breast milk, their concentrations and the total amounts that could possibly be ingested by a nursing infant are such that adverse effects would be unlikely. Thus, no modifications of treatment regimens are necessary for nursing mothers.[143]

Associated Conditions. Tuberculosis commonly occurs in association with other conditions, either because an underlying disease or its treatment alters immune responsiveness, thereby predisposing to tuberculosis (e.g., HIV infection, hematologic or reticuloendothelial malignancies, chronic renal disease or type 2 diabetes mellitus), or because the accompanying condition occurs frequently in the same social and cultural milieu as tuberculosis, particularly alcoholism and all its complications and other forms of substance abuse. Because all of these conditions may affect the response to and outcome of treatment, therapeutic decisions must be made on an individualized basis, and when possible, steps must be taken to correct the immunosuppression.

In patients with impaired renal function, streptomycin, kanamycin, amikacin, and capreomycin should be avoided if at all possible or given two to three times per week in the usual dose. If there is severe impairment of renal function, reduction in frequency of administration of ethambutol and pyrazinamide to two to three times per week may be necessary.[143]

Liver disease, particularly alcoholic hepatitis and cirrhosis, is commonly associated with tuberculosis. In general, the complications of potentially hepatotoxic antituberculosis drugs have not been greater in patients with liver disease.[173] However, detecting such adverse effects if they occur may be difficult because of the preexisting disorder of hepatic function. Moreover, what in a person with normal liver function would be minor hepatotoxicity could have major consequences in a patient with severe liver disease. Options in treating patients with severe liver disease include treatment without isoniazid, using rifampin, ethambutol, and pyrazinamide for 6 months; treatment without pyrazinamide for a total duration of 9 months; treatment with only one potentially hepatotoxic drug, usually retaining rifampin and adding ethambutol and a fluoroquinolone for a total of 12 to 18 months; and treatment with a regimen that contains no hepatotoxic drugs, such as streptomycin, ethambutol, a fluoroquinolone, and perhaps another second-line drug for 18 to 24 months.[143] In patients with severe liver disease, routine testing of liver function should be performed at baseline and during treatment.

Finally, in patients with psychiatric disorders, close supervision of treatment with DOT of all medications is essential.

Adjuctive Therapy

Currently, the adjunctive therapies for pulmonary tuberculosis include surgery and corticosteroid treatment. Although surgery was once a mainstay of treatment for pulmonary tuberculosis, since the advent of chemotherapy it has rarely been indicated. Artificial pneumothorax,

pneumoperitoneum, phrenic nerve interruption, plombage, and thoracoplasty—procedures designed to collapse portions of the lung and close cavities—were common interventions until the 1960s,[174] but then rendered obsolete by the effectiveness of chemotherapy. Rarely, patients with MDR pulmonary tuberculosis are treated with either pneumoperitoneum or thoracoplasty.

Resection. Currently, surgical resection may be indicated in several situations. In patients with tuberculosis caused by MDR or XDR organisms that is anatomically limited within the lung, resection may be an effective therapeutic option.[175] Before operating on such patients, the bacillary population should be reduced as much as possible with drugs to which the organism is susceptible. However, the timing of surgery can be difficult, in that the effectiveness of a limited second-line drug regimen cannot always be predicted. Resection may also be necessary because of massive hemoptysis associated with current or old tuberculosis, because of residual lung damage (e.g., bronchiectasis) exacerbated by recurrent bacterial infections, or because of a bronchopleural fistula with (usually) a tuberculous empyema. In addition to these therapeutic indications for surgery, tuberculosis is sometimes diagnosed by examination of a pulmonary mass or nodule that was resected owing to suspicion of malignancy.

In any situation involving possible lung surgery in patients with or suspected of having tuberculosis, including the resection of a solitary nodule in a patient with a positive tuberculin reaction, it is desirable for the patient to have been receiving adequate antituberculosis chemotherapy before the operation. This will minimize the possibility of spread of tuberculosis within the lung and of bronchial stump infection and empyema. The optimum amount of time before operation that treatment should be given is not clear, but in emergencies, such as massive hemoptysis, at least single doses of the drugs should be given, whereas with elective procedures, it is desirable to wait at least until the sputum smear is negative. If the sputum smear is negative to begin with, 2 weeks of treatment is reasonable.

Corticosteroids. The use of corticosteroids in pulmonary tuberculosis has been and remains controversial. In view of the well-known effects of corticosteroids in decreasing cell-mediated immune responses, it seems counterintuitive that these same agents could be beneficial. Nevertheless, corticosteroids, by interfering with the tissue-damaging immune response, may minimize the adverse effects of the inflammatory reaction. For this reason, corticosteroids may under certain conditions be of benefit in patients with pulmonary tuberculosis who are receiving adequate chemotherapy. These conditions were defined by a controlled trial reported by Johnson and colleagues[176] in which all patients were treated with effective antituberculosis chemotherapy (although rifampin was not yet available) and were assigned at random to receive either methylprednisolone or placebo. This study demonstrated that corticosteroid treatment most benefited the seriously ill patient (defined by low serum albumin concentration, low body weight, and severe weight loss) who had extensive tuberculosis. This benefit was evidenced mainly by an increase in the rate of radiographic clearing; there was no adverse effect on the bacteriologic response. In less severely ill patients, methylprednisolone either was of no benefit or actually decreased the speed of sputum conversion. These data suggest that the major role of corticosteroid treatment is in patients with severe tuberculosis and severe systemic effects.

Although not considered in the study by Johnson and colleagues, steroids may also be of benefit in patients with marked abnormalities of gas exchange and respiratory failure.[177] A more recent systematic review examined the results of clinical trials of corticosteroids as adjunctive therapy for pulmonary tuberculosis and came to essentially the same conclusions as the Johnson et al. study (which was included in the review).[178] In addition, dexamethasone is recommended in tuberculous meningitis and, although the evidence is less persuasive, corticosteroids are often given in tuberculous pericarditis.

EXTRAPULMONARY TUBERCULOSIS

Extrapulmonary tuberculosis presents more of a diagnostic and therapeutic problem than does pulmonary tuberculosis. In part this relates to its being less common and therefore less familiar to most clinicians.[179,180] In addition, extrapulmonary tuberculosis involves relatively inaccessible sites, and often, because of the vulnerability of the areas involved, much greater damage can be caused by fewer bacilli. The combination of small numbers of bacilli in inaccessible sites causes bacteriologic confirmation of a diagnosis to be more difficult, and invasive procedures are frequently necessary to establish a diagnosis. In addition to the need for invasive diagnostic procedures, surgery may be an important component of management.

In 2007 in the United States, 20% of newly reported cases of tuberculosis involved extrapulmonary sites only.[181] The proportion of patients with extrapulmonary involvement is greater among patients with HIV infection. In one large retrospective study of tuberculosis occurring in patients with HIV infection, approximately one third of the patients had only extrapulmonary sites of involvement, one third had both pulmonary and extrapulmonary disease, and one third had only pulmonary involvement.[97] Because of the frequency of extrapulmonary tuberculosis among HIV-infected patients, diagnostic specimens from any suspected site of disease should be cultured for mycobacteria, including blood and bone marrow from patients who do not have an obvious localized site of disease but who are febrile.

Disseminated Tuberculosis

Miliary tuberculosis, although it nearly always involves the lungs, is considered among the extrapulmonary forms of the disease because of the multiplicity of organs affected. In the past, miliary tuberculosis occurred mainly in young children, as an early consequence of initial infection and bacillemia; currently, however, except among HIV-infected persons, it is more common

among older persons, as a result of endogenous reactivation and bloodstream invasion. The shift in age-specific incidence presumably has been caused at least in part by the paucity of new infections in relation to the number of endogenous reactivations that take place in the United States. The incidences in both sexes are nearly equal except in the HIV-infected population, in which the disease predominates among men.

The term *miliary* is derived from the similarity of the lesions to millet seeds. Grossly, these lesions are 1- to 2-mm yellowish nodules that on histologic examination are granulomas (see Chapter 15, Fig. 15-4C). As noted previously, HIV-infected patients may not be able to form granulomas; thus, discrete individual lesions may not be present, but a diffuse uniform pattern of infiltration is seen.

Because of the multisystem involvement in disseminated tuberculosis, the clinical manifestations are protean. Initial screening laboratory studies are not particularly helpful either. The chest film, however, is abnormal in most but not all patients with disseminated tuberculosis: the frequency of a classic military pattern has ranged from 50% to 90%. Overall, it appears that, at the time of diagnosis, approximately 85% of patients have the diffuse tiny nodules characteristic of miliary tuberculosis. Other abnormalities may be present as well. These include upper lobe infiltrates with or without cavitation, pleural effusion, and pericardial effusion. In patients with HIV infection, the radiographic pattern is one of diffuse infiltration rather than discrete nodules.

Autopsy series have shown the liver, lungs, bone marrow, kidneys, adrenal glands, and spleen to be the organs most frequently involved in miliary tuberculosis, but any organ can be the site of disease.[182] Because of the multiplicity of sites involved, there are many potential sources of material to provide a diagnosis. Acid-fast smears of sputum are positive in 20% to 25% of patients, and *M. tuberculosis* is cultured from sputum in 30% to 65%.[183–185] Smears of induced sputum may be positive when the patient is not expectorating spontaneously. In a patient with an abnormal chest film and negative sputum examinations, bronchoscopy should be the next step. Combinations of bronchoalveolar lavage and transbronchial biopsy would be expected to have a high yield.[109] Other potential sites for biopsy include liver and bone marrow, each of which has a high likelihood of showing granulomas (70% to 80%), but only a 25% to 40% chance of providing bacteriologic confirmation; urine is easy to obtain, and cultures may be positive in up to 25% of patients.[184,185] Selection of other potential sources of diagnostic material should be guided by specific findings.

The role of rapid nucleic acid amplification tests for identification of *M. tuberculosis* in patients with miliary tuberculosis has not been defined, and neither of the two tests licensed by the U.S. Food and Drug Administration is approved for nonrespiratory specimens. The reported data are difficult to interpret because, often, the results of specimens from different sites are combined, patients are selected by a variety of criteria, and test performance varies.[186–188]

In the prechemotherapy era, disseminated tuberculosis was uniformly fatal. With treatment, however, the reported case-fatality rates vary, ranging from 29% to 64%, depending in part on the frequency of meningitis in the series.[185] When meningitis is present, the duration of standard chemotherapy should be extended from 6 to 9 or 12 months.[143] Corticosteroids may be useful, as discussed previously, for severe pulmonary disease with respiratory failure and if there is involvement of the central nervous system.[189]

Lymphatic Tuberculosis

Lymphatic tuberculosis accounts for approximately 42% of the cases of extrapulmonary tuberculosis in the United States.[181] Although the basic descriptive epidemiology of tuberculosis applies to lymphatic tuberculosis, there are a few differences. This form of tuberculosis is relatively more common among children than adults. In addition, lymphatic tuberculosis differs from the overall pattern in that it occurs more frequently in women. It also appears to be more common among Asians and Pacific Islanders than among blacks and whites. Among HIV-infected persons, the incidence of tuberculous lymphadenitis increases as the level of $CD4^+$ T cells decreases.[190]

Tuberculous lymphadenitis usually presents as painless swelling of one or more lymph nodes (Fig. 34-12). The nodes most commonly involved are those of the posterior or anterior cervical chain or those in the supraclavicular fossa. Frequently the process is bilateral, and other noncontiguous groups of nodes can be involved. At least initially, the nodes are discrete and the overlying skin is normal. With ongoing disease, the nodes may become matted and the overlying skin inflamed. Rupture of the node can result in formation of a sinus tract, which may persist for years. Intrathoracic adenopathy may compress bronchi, causing atelectasis, thereby leading to lung infection and perhaps bronchiectasis. Although rare, upper airway obstruction may result from cervical node enlargement. Both chylous pleural effusion and ascites have occurred because of intrathoracic or abdominal node involvement with obstruction of retroperitoneal lymphatics or the thoracic duct.

The diagnosis of tuberculous lymphadenopathy is established by lymph node biopsy or aspiration with histologic examination, including stains for acid-fast organisms and culture of the material. Smears show acid-fast organisms in approximately 25% to 50% of biopsy specimens, and *M. tuberculosis* is isolated in approximately 70% of instances in which the final diagnosis is considered to be tuberculosis.[191] Caseating granulomas are seen in nearly all biopsy specimens from immunocompetent patients. In immunodeficiency states, granulomas may be poorly formed or absent.[192]

The rate of response of tuberculous lymphadenitis to the standard 6-month regimen is much slower than that of pulmonary tuberculosis. Nodes may enlarge, new nodes may appear, and fistulas may develop during treatment that ultimately proves effective, but true bacteriologic relapse after completion of therapy is unusual.[193]

FIGURE 34-12 ■ Tuberculous lymphadenitis. There is swelling of an anterior cervical node and a chronic sinus tract with cutaneous scarring in the supraclavicular area. (Courtesy of Dr. Austin Brewin, University of California, San Francisco.)

Corticosteroid treatment has been used to shrink intrathoracic nodes and relieve bronchial obstruction, primarily in children. In a controlled study, Nemir and coworkers[194] demonstrated that corticosteroids increase the rate of resolution of radiographic changes thought to be due to bronchial narrowing by lymph nodes or endobronchial lesions in children with primary tuberculosis. Apart from this indication, there is no clear role for corticosteroids in lymphatic tuberculosis.

Surgical intervention may be necessary to make a diagnosis of tuberculous lymphadenitis, and on occasion surgical incision and drainage are needed to prevent spontaneous drainage and fistula formation. Surgical excision of involved nodes, strictly as an adjunct to chemotherapy, is associated with perhaps a slightly worse outcome than medical treatment with aspiration of the node or medical treatment alone.[195]

Pleural Tuberculosis

Although the pleural space is within the thorax, it is considered an extrapulmonary site of tuberculosis. Tuberculous pleuritis accounts for 17% of the extrapulmonary cases in the United States.[181] The epidemiology of pleural tuberculosis parallels that of the overall pattern for tuberculosis, being more common among men and increasing in incidence with increasing age between ages 5 and 45 years. As noted previously, this epidemiologic pattern is modified by the occurrence of HIV infection, although pleural involvement seems relatively less frequent among HIV-infected persons.

There are two mechanisms by which the pleural space becomes involved in tuberculosis. The difference in pathogenesis results in different clinical presentations, approaches to diagnosis, treatment, and sequelae. The first mechanism occurs early in the course of a tuberculous infection—a few tubercle bacilli may gain access to the pleural space and, in the presence of cell-mediated immunity, can cause a hypersensitivity response.[196,197] This form of tuberculous pleuritis commonly goes unnoticed, and the process resolves spontaneously. However, in some patients, the tuberculous involvement of the pleura is manifested as an acute illness with fever and pleuritic pain.[198] If the effusion is large enough, dyspnea may occur, although the effusions are generally rather small and are rarely bilateral.

The diagnosis of pleural tuberculosis is generally established by analysis of pleural fluid and pleural biopsy. In a patient with a pleural effusion that might be tuberculous, a diagnostic thoracentesis should be performed. Sufficient fluid should be obtained for cell count, cytologic examination, biochemical analysis, and microbiologic evaluation (all described in detail in Chapter 73), but enough fluid should be left to allow a needle biopsy to be performed if the original specimen proves to be exudative and no diagnosis is evident. The fluid is nearly always straw-colored, although it may be slightly bloody. Leukocyte counts are usually in the range of 100 to 5000 cells/μL.[199] Early in the course of the process, polymorphonuclear leukocytes may predominate, but mononuclear cells soon become the majority. The fluid is exudative, with a protein concentration greater than 50% of the serum protein concentration, and the glucose level may be normal to low. The presence of more than 10% eosinophils or 5% mesothelial cells is evidence against a tuberculous etiology.[200]

Adenosine deaminase has been shown to have high sensitivity, except in HIV-infected patients, but variable specificity, for diagnosing tuberculous pleural effusion.[201] Interferon-γ has been reported to have both high sensitivity (0.99) and high specificity (0.98) and to be equally reliable in HIV-infected and -uninfected patients[202,203]: further studies are needed to define the diagnostic role of this potentially useful test. Because few organisms are present in the pleural space, acid-fast smears of pleural fluid are rarely positive, and *M. tuberculosis* is isolated by culture in only 20% to 40% of patients with proven tuberculous pleuritis.[198,204] A single closed-needle biopsy

of the pleura with a Cope or an Abrams needle, with collection of three or four specimens for histologic examination, acid-fast staining, and culture of the tissue, confirms the diagnosis in approximately 65% to 75% of patients in whom tuberculous pleuritis is ultimately diagnosed. A second set of specimens in patients whose initial biopsy is negative increases the yield to 80% to 90%.[204] The results of thoracoscopy are nearly always diagnostic, but the procedure is invasive, costly, and not always available. In a patient with an exudative mononuclear pleural effusion that remains undiagnosed after a full evaluation, including pleural biopsy, and who has a positive tuberculin reaction, antituberculosis treatment should be initiated.

Treatment of the hypersensitivity variety of tuberculous pleural effusion consists of standard antituberculosis drug regimens.[143] Drainage via tube thoracostomy is rarely necessary, although repeat thoracenteses may be required to relieve symptoms. The use of corticosteroids may increase the rate of resolution and decrease the residual fluid, but such treatment is rarely indicated.[205]

The second variety of tuberculous involvement of the pleura, which is much less common than tuberculous pleurisy with effusion, is a true empyema that follows the spilling into the pleural space of a large number of organisms, usually from rupture of a cavity or an adjacent parenchymal focus via a bronchopleural fistula.[206] Tuberculous empyema is usually associated with evident pulmonary parenchymal disease on chest films. In this situation the fluid generally is thick and cloudy and may contain cholesterol, which causes the fluid to look like chyle (pseudochylous effusion). The fluid is exudative and usually has a relatively high white blood cell count, nearly all of which are lymphocytes. Acid-fast smears and mycobacterial cultures are usually positive, making pleural biopsy unnecessary.

In addition to standard antituberculosis chemotherapy, surgical drainage with an ordinary thoracostomy tube is often necessary and may be required for a prolonged period of time. In selected patients, creation of an Eloesser flap, in which a small portion of rib overlying the empyema space is resected and the skin is sutured to the pleura, is the procedure of choice.[207]

Genitourinary Tuberculosis

The epidemiologic pattern of genitourinary tuberculosis parallels that of tuberculosis in general, with the exception of HIV-infected patients. The pathogenesis appears to be one of seeding of the kidney at the time of the initial infection and bacillemia. This mechanism is supported by the finding that, with careful study, tuberculous lesions can be found in both kidneys in 90% of patients with renal tuberculosis, even though the disease is clinically evident in only one kidney.[208] Lower genitourinary tract involvement is thought to represent spread from the kidneys, but hematogenous seeding may also occur. Genital lesions were reported by Medlar and coworkers[209] in 13% of men with disseminated renal lesions, 52% of those with caseating lesions, and 100% of those with cavitary lesions in the kidney. Genital involvement without renal involvement occurred in 11%.

In patients with genitourinary tuberculosis, local symptoms predominate and systemic symptoms are less common.[210,211] Dysuria, hematuria, and frequent urination are common, and flank pain may also be noted. However, in general the symptoms are very subtle, and often there is advanced destruction of the kidneys by the time a diagnosis is established.[212] In women, genital involvement is more common without renal tuberculosis than in men and may cause pelvic pain, menstrual irregularities, and infertility as presenting complaints.[211] In men, a painless or only slightly painful scrotal mass is probably the most common presenting symptom of genital involvement, but symptoms of prostatitis, orchitis, or epididymitis may also occur.[210] A substantial number of patients with any form of genitourinary tuberculosis are asymptomatic, and the disease is detected because of an evaluation for an abnormal routine urinalysis. In patients with renal or genital tuberculosis, urinalyses are abnormal in more than 90%, the main finding being pyuria, hematuria, or mixed pyuria and hematuria. The finding of pyuria in an acidic urine with no organisms isolated from a routine urine culture should prompt an evaluation for tuberculosis. Occasionally, when there is an isolated genital focus of disease or when a tuberculous kidney is blocked by a ureteral stricture, the urinalysis may be normal and cultures may be sterile.

The suspicion of genitourinary tuberculosis should be heightened by the presence of abnormalities on the chest film. In most series, 50% to 75% of patients have chest radiographic abnormalities, although many of these may be the result of previous, not current, tuberculosis.[210,211]

When genitourinary tuberculosis is suspected, at least three first-voided early morning urine specimens should be collected and stained for AFB and cultured for mycobacteria. In men, saprophytic *Mycobacterium smegmatis* may cause a positive smear. However, in the presence of abnormalities suggesting tuberculosis, the finding of a positive smear should be interpreted as confirming the diagnosis of genitourinary tuberculosis until the results of cultures are known. *M. tuberculosis* is isolated from the urine in 80% to 95% of cases of genitourinary tuberculosis.[210,211] Diagnosis of isolated genital lesions usually requires biopsy, because the differential diagnosis often includes neoplasia as well as other infectious processes.

Positive urine cultures may occur in the absence of any clinical, laboratory, or radiographic findings on intravenous pyelograms, which suggests concomitant genitourinary tuberculosis in patients with other forms of tuberculosis. Bentz and coworkers[213] found unanticipated positive urine cultures in 21% of patients with other extrapulmonary forms of tuberculosis and in 5% of those with pulmonary tuberculosis alone.

Renal tuberculosis, at least as indicated by a positive urine culture, may occur in patients with HIV infection. In one series, positive urine cultures were found in 12 (71%) of 17 cultures submitted in patients with tuberculosis and advanced HIV infection, although this was not a systematic sampling.[97]

There are several treatment considerations for genitourinary tuberculosis apart from standard chemotherapy. Nephrectomy, formerly a mainstay of therapy for renal tuberculosis, now is seldom indicated; however, in patients who have tuberculosis caused by MDR organisms and who can tolerate removal of a kidney, nephrectomy may be indicated. Nephrectomy may also be indicated for patients who have recurrent pyogenic bacterial infections in a kidney destroyed by tuberculosis, for patients with persistent pain, and for those with massive hematuria. Surgical or endoscopic procedures may also be necessary to correct ureteral strictures and to augment the capacity of a contracted bladder.

Bone and Joint Tuberculosis

The incidence of tuberculosis involving the joints and bones increases with increasing age and is equally frequent among men and women. In comparison with blacks and whites, other racial groups are less likely to have skeletal involvement. Skeletal tuberculosis does not appear to be particularly frequent in persons with HIV infection.

It is presumed that most osteoarticular tuberculosis results from endogenous reactivation of foci of infection seeded during the initial bacillemia, although spread from paravertebral lymph nodes has been postulated to account for the common localization of spinal tuberculosis to the lower thoracic and upper lumbar vertebrae. It is also postulated that the predilection for tuberculosis to localize in the metaphyses of long bones is due to the relatively rich blood supply and scarcity of phagocytic cells in this portion of the bone.[214] After beginning in the subchondral region of the bone, the infection spreads to involve the cartilage, synovium, and joint space. This produces the typical findings of metaphyseal erosion and cysts and loss of cartilage with narrowing of the joint space. Typically, in the spine these changes involve two adjacent vertebrae and the intervertebral disk (Fig. 34-13). An interesting observation was made in 103 cases of spinal tuberculosis: an "atypical" form of spondylitis without evidence of disk involvement occurred in slightly more than half (52%) of the patients.[215–217] Paravertebral or other para-articular abscesses may develop with occasional formation of sinus tracts. Although weight-bearing joints are the most common sites for skeletal tuberculosis, any bone or joint may be involved.[214] In most series of osteoarticular tuberculosis, tuberculosis of the spine (Pott's disease) makes up 50% to 70% of the cases reported. In adults the lower thoracic and upper lumbar vertebrae are most commonly involved, whereas in children the upper thoracic spine is the most frequent site. The hip or knee is involved in 15% to 20% of cases, and shoulders, elbows, ankles, wrists, and other bones or joints also make up 15% to 20%. Usually only one bone or joint is involved, but occasionally the process may be multifocal. Evidence of either previous or current pulmonary tuberculosis is found in approximately half the reported patients, and other extrapulmonary sites may be involved as well.

The first diagnostic test undertaken is usually a radiograph of the involved area. Early in the process, the only abnormality noted may be soft-tissue swelling. Computed tomography (CT) scans and magnetic resonance imaging of the spine are considerably more sensitive than routine films and should be obtained when there is a high index of suspicion of an infectious process. Radionuclide bone scanning with technetium-99m can demonstrate occult skeletal involvement in patients with normal radiographs. Likewise, gallium-67 scanning may define unsuspected sites, especially soft-tissue involvement not seen on the bone scan.

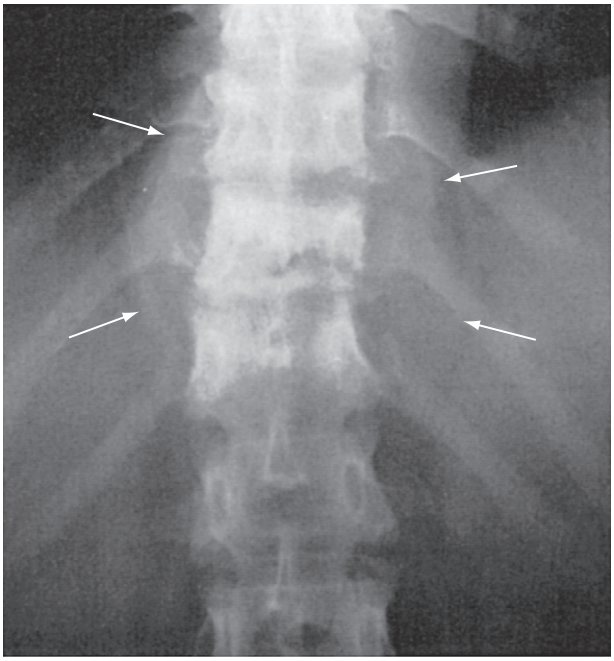

FIGURE 34-13 ■ Radiograph of lower thoracic and upper lumbar spine, showing tuberculous involvement of the 10th, 11th, and 12th thoracic vertebrae and a paraspinous abscess (*arrows*). Note loss of intervertebral disk space.

Confirmation of the diagnosis is obtained by aspiration of joint fluid or periarticular abscesses or by biopsy of bone or synovium with histologic and microbiologic evaluation of the material obtained. Acid-fast stains are positive in 20% to 25% of samples of joint fluid, and *M. tuberculosis* is isolated in approximately 60% to 80% of them.[214] Biopsy specimens of synovium or bone have a higher yield and enable histologic examination as well. Evidence of granulomatous inflammation even in the absence of bacteriologic proof of the diagnosis is sufficient evidence of tuberculosis to begin therapy unless another cause is found.

Standard chemotherapy of 6 to 9 months' duration is highly successful in skeletal tuberculosis, but surgery is occasionally a necessary adjunct.[215] The longer duration of treatment has been suggested because of the difficulties in assessing response. Several controlled studies have documented that chemotherapy conducted largely on an ambulatory basis is effective in curing spinal tuberculosis without the need for immobilization.[216] The role of emergency spinal cord decompression in patients with Pott's disease and early neurologic findings is not clear, and, if paraplegia is already present, the benefit of surgical intervention is even less clear. Moreover, there

is no well-defined surgical procedure of choice. An "all-or-none" approach has been advocated by several surgeons,[217–219] which means that surgery is not performed except in patients with progressive neurologic deterioration unresponsive to chemotherapy—in whom all affected bone is removed and an anterior spinal fusion is performed; there is no role for simple débridement other than for diagnosis. Surgery may be indicated in other forms of articular tuberculosis when there is extensive destruction of the joint or surrounding soft tissues, in which case synovectomy and joint fusions may be necessary.

Central Nervous System Tuberculosis

Meningitis is the most frequent form of central nervous system tuberculosis; solitary or multiple tuberculomas occur less commonly. The epidemiologic pattern of central nervous system tuberculosis is quite different from that of either pulmonary or other forms of extrapulmonary tuberculosis, in that the peak incidence is in infants and children up to 4 years of age. Although an appreciable number of cases occur in adults, meningitis accounts for only approximately 6% of all cases of extrapulmonary tuberculosis, which are equally divided between males and females.[181]

Central nervous system tuberculosis, especially tuberculomas, seems to occur with greater frequency among HIV-infected persons. Central nervous system tuberculomas have been reported even in patients who are receiving what should be adequate chemotherapy.[220] Because tuberculomas may be indistinguishable on CT scan from the lesions of toxoplasmosis, specific diagnosis is necessary.

Meningitis presumably can result from direct meningeal seeding and proliferation during a tuberculous bacillemia either at the time of initial infection or at the time of reactivation of an old pulmonary focus, or it can also result from reactivation of an old parameningeal focus with rupture into the subarachnoid space.[221] The consequences of the subarachnoid space contamination include diffuse meningitis, a localized arteritis, encephalitis, and myelitis. The symptoms depend primarily on which of these processes predominates. With meningitis, the process is primarily located at the base of the brain.[222] Symptoms therefore include those related to cranial nerve involvement in addition to headache, decreased level of consciousness, and neck stiffness. The duration of illness before diagnosis is quite variable and is related partly to the presence or absence of other sites of involvement. In a large series of patients, the average duration of illness was 12 days.[223] In most series, over 50% of patients with meningitis have abnormalities on chest film that are consistent with an old or current tuberculous process, often miliary tuberculosis. At autopsy, disseminated disease is found in a very high percentage of patients with meningitis. In patients with tuberculous meningitis, sputum cultures have been positive in 40% to 50%; thus, a substantial number of patients have pulmonary and systemic symptoms in addition to those referable to the central nervous system. Patients in whom arteritis is the predominant manifestation of meningitis can present with a variety of focal central nervous system ischemic syndromes in addition to the symptoms already described.

In tuberculous meningitis, the lumbar puncture usually shows increased opening pressure, and the cerebrospinal fluid (CSF) usually contains between 100 and 1000 cells/μL.[179,223] In approximately 65% to 75% of patients, lymphocytes predominate, whereas polymorphonuclear leukocytes predominate in the remainder, generally early in the course of the illness. The protein concentration is elevated in nearly all patients. Very high (>3300 mg/dL) protein concentrations have been associated with a poor prognosis; the glucose concentration in CSF is usually low, but not as low as that often found in pyogenic bacterial meningitis.[223] Acid-fast organisms are seen on smears of CSF in only 10% to 20% of patients, and the rate of culture positivity varies from 25% to 80%, but is generally in the lower end of the range.[223] In a substantial number of patients, *M. tuberculosis* is isolated from other sources, which, in the presence of compatible CSF findings, is sufficient to diagnose tuberculous meningitis. In view of the severity of tuberculous meningitis, a presumptive diagnosis justifies empirical treatment if no other diagnosis can be established promptly. Because of the difficulty with establishing a diagnosis of tuberculous meningitis by bacteriologic methods, Thwaites and associates[223] developed and validated a clinical scoring system by which tuberculous meningitis could be separated from pyogenic bacterial meningitis. Younger age (<36 years), lower white blood cell count (<15,000/μl), longer duration of illness (>6 days), lower CSF white blood cell count (<900/μL), and lower percentage (<75%) of neutrophils in the CSF were associated with a greater likelihood of a tuberculous etiology.

A recent meta-analysis of 14 studies of nucleic acid amplification tests for the diagnosis of tuberculous meningitis found a combined sensitivity of 56% and a specificity of 98%.[187] Thus, when a nucleic acid amplification test is positive, one can assume that the etiology is tuberculous, but a negative result does not exclude the diagnosis.

If there are no epidemiologic indicators of possible resistance, a treatment regimen of isoniazid, rifampin, pyrazinamide, and ethambutol should be effective. The recommended length of the continuation phase is at least 7 months, for a total treatment duration of 9 to 12 months, although there are no clinical trials that serve to define the optimum treatment duration.[143]

Corticosteroid treatment has a beneficial effect in patients with tuberculous meningitis and cerebral edema,[189] and decreases the frequency of adverse sequelae in children with less advanced disease.[224] Given the poor prognosis of tuberculous meningitis, the reasonably good data supporting corticosteroid use in more severe forms of the disease, and the paucity of information in patients with less advanced disease, corticosteroid treatment, specifically with dexamethasone, is recommended for all patients[189] at a dosage of 12 mg/day for 3 weeks, then decreased gradually during the next 3 weeks. Even with effective chemotherapy and corticosteroids, however, both the mortality rate and

rate of residual neurologic abnormalities from tuberculous meningitis remain high.

The other major central nervous system form of tuberculosis, the tuberculoma, presents a more subtle clinical picture than does tuberculous meningitis.[225] The usual presentation is that of a slowly growing focal lesion, although a few patients have increased intracranial pressure and no focal findings. The CSF is usually normal, and the diagnosis is established by CT scanning or magnetic resonance imaging and subsequent resection, biopsy, or aspiration of any ring-enhancing lesion. The response to antituberculosis chemotherapy is good, and corticosteroids are indicated only if there is an increase in intracranial pressure.

Abdominal Tuberculosis

Tuberculosis can involve any intra-abdominal organ as well as the peritoneum. The age distribution of abdominal tuberculosis shows a relatively higher incidence in young adults and a second peak in older persons. Men and women have similar incidences. The abdomen is a relatively common site of disease in HIV-infected persons.

Abdominal tuberculosis presumably results from seeding at the time of initial infection and then either direct or late progression to clinical disease. Peritonitis can also be caused by rupture of tuberculous lymph nodes within the abdomen, and intestinal tuberculosis may result from direct implantation in the gut of ingested tubercle bacilli. Before the advent of chemotherapy, tuberculous enteritis was common in patients with advanced pulmonary tuberculosis, presumably being caused by swallowed bacilli from the lungs. In a prospective study conducted between 1924 and 1949, intestinal abnormalities compatible with tuberculous enteritis were found by contrast radiography in 1%, 4.5%, and 24.7% of patients with minimal, moderately advanced, and far advanced pulmonary tuberculosis, respectively.[226]

The clinical manifestations of abdominal tuberculosis depend on the areas of involvement. In the gut itself, tuberculosis may occur in any location from the mouth to the anus, although lesions proximal to the terminal ileum are unusual. The most common sites of involvement are the terminal ileum and cecum; other portions of the colon and the rectum are involved less frequently.[227] In the terminal ileum or cecum, the most common manifestations are pain (which may lead to a misdiagnosis of appendicitis) and intestinal obstruction. A palpable mass may be noted that, together with its radiographic appearance, can easily be mistaken as a carcinoma. Rectal lesions usually present as anal fissures or fistulas or perirectal abscesses. In addition to carcinoma, the differential diagnosis of these findings includes inflammatory bowel disease. Because of the concern regarding carcinoma, the diagnosis often is made through surgery.[228]

Tuberculous peritonitis commonly causes pain as its presenting manifestation, often accompanied by abdominal swelling. Fever, weight loss, and anorexia are also common. Active pulmonary tuberculosis is uncommon in patients with tuberculous peritonitis. Because the process frequently coexists with other disorders, especially cirrhosis with ascites, the symptoms of tuberculosis may be obscured. The combination of fever and abdominal tenderness in a person with ascites should always prompt an evaluation for intra-abdominal infection, and paracentesis should be performed. Ascitic fluid in tuberculous peritonitis is exudative and contains between 50 and 10,000 leukocytes per microliter, the majority of which are lymphocytes, although polymorphonuclear leukocytes occasionally predominate.[229] Acid-fast organisms are rarely seen on smears of the fluid, and cultures are positive in only approximately 50%, although the yield increases if a large volume of fluid is submitted for culture. Because of the generally low yield from culture of the fluid, laparoscopic biopsy is often necessary to confirm the diagnosis.

Standard chemotherapy is quite effective in abdominal tuberculosis. Corticosteroids have been advocated in tuberculous peritonitis to reduce the risk of adhesions causing intestinal obstructions, but this recommendation is controversial because of the low frequency of obstruction. As discussed previously, surgery is often necessary to establish a diagnosis and, in addition, may be necessary to relieve intestinal obstruction.

Pericardial Tuberculosis

The descriptive epidemiology of pericardial tuberculosis is not well defined, but in general it tends to occur among older persons, particularly nonwhites and men. The pericardium may become involved during the initial bacillemia, with early progression to clinically evident disease or recrudescence after a quiescent period. Hematogenous seeding may also occur during the course of endogenous reactivation. Alternatively, there may be direct extension of an adjacent focus of disease from the lung parenchyma, pleura, or tracheobronchial lymph nodes into the pericardium. Like the pleura, the pericardium is a serosal surface capable of exuding large amounts of fluid in response to inflammation. As presumably occurs in tuberculous pleuritis with effusion, it is likely that tuberculin hypersensitivity plays a role in producing the intense inflammatory response and abundant effusion in the pericardium. This would account for the relative infrequency of isolation of tubercle bacilli from pericardial fluid, the nonpurulent nature of the fluid, and the generally prompt response to antituberculosis chemotherapy in most instances. Conversely, rupture of a caseous lymph node into the pericardium may cause contamination with a much greater number of organisms; a greater inflammatory response with thicker, more purulent fluid; and a greater likelihood of either early or late hemodynamic effects.

The most common form or stage of tuberculous pericarditis is characterized by pericardial effusion with little pericardial thickening or epicardial involvement. Because in most instances the fluid accumulates slowly, the pericardium can expand to accommodate very large

volumes (2 to 4 L) with little apparent hemodynamic compromise. Symptoms of cardiopulmonary origin tend to occur later and include cough, dyspnea, orthopnea, ankle swelling, and chest pain. The chest pain may occasionally mimic angina but usually is described as being dull, aching, and often affected by position and by inspiration.

The fluid itself is usually serosanguineous or occasionally grossly bloody, is exudative, and has a white blood cell count ranging from 500 to 50,000 cells/μL, with an average of 5000 to 7000 cells/μL.[230] The cells are predominantly mononuclear, although polymorphonuclear leukocytes occasionally predominate. Tubercle bacilli have been identified in pericardial fluid in approximately 25% to 30% of cases (smear and culture combined).[230] Biopsy of the pericardium with both histologic and bacteriologic evaluation is much more likely to provide a diagnosis, although a nonspecific histologic pattern and failure to recover the organisms do not exclude a tuberculous cause.

Although not well documented, it appears that, if the patient survives the subacute phase without treatment, chronic fibrotic pericarditis nearly always follows. Before the advent of antituberculosis therapy, 88% of one series of patients who had tuberculous pericarditis developed evidence of chronic constriction.[231] Constriction has also been observed to develop during the course of antituberculosis chemotherapy, although this appears to be uncommon in patients who have had symptoms for less than 3 months; it is frequent in patients who have had symptoms for more than 6 months.

The fibrotic reaction progresses to complete fusion of visceral and parietal pericardium and encasement of the heart in a rigid scar that often becomes calcified. Impairment of coronary circulation is common. At this point the histologic pattern is usually nonspecific; thus, confirmation of a tuberculous etiology is infrequent.

The definitive diagnosis of tuberculous pericarditis requires identification of tubercle bacilli in pericardial fluid or tissue. Although not conclusive, demonstration of caseating granulomata in the pericardium and consistent clinical circumstances provide convincing evidence of a tuberculous etiology. Less conclusive but still persuasive evidence is the finding of another form of tuberculosis in a patient with pericarditis of undetermined cause. Approximately 25% to 50% of patients with tuberculous pericarditis have evidence of other organ involvement, particularly pleuritis, at the time pericarditis is diagnosed.[232] Still less direct and more circumstantial evidence of a tuberculous etiology is the combination of a positive intermediate-strength tuberculin skin test reaction and pericarditis of unproved cause.

Because of the potentially life-threatening nature of pericardial tuberculosis, treatment with antituberculosis agents should be instituted promptly once the diagnosis is made or strongly suggested. It appears that the likelihood of constriction is greater in patients who have had symptoms longer; thus, early therapy may reduce the incidence of this complication. Several studies have suggested that corticosteroids have a beneficial effect in treating both tuberculous pericarditis with effusion and constrictive pericarditis.[233–235] However, a meta-analysis of studies examining the effects of corticosteroids in tuberculous pericarditis concluded that, although steroids could have an important effect, the studies were too small to be conclusive.[233] Nevertheless, patients with proven tuberculous pericarditis who are receiving adequate antituberculosis therapy and who have no major contraindications should receive corticosteroids. The optimum regimen is not known, but daily prednisone, 60 mg/day for 4 weeks, followed by 30 mg/day for 4 weeks, 15 mg/day for 2 weeks, and 5 mg/day for 1 week, is the recommended regimen.[143] Corticosteroid therapy should not be used if there is a strong suspicion that the infection is caused by a drug-resistant organism unless adequate antituberculosis chemotherapy can be ensured.

In general, if hemodynamic compromise occurs, pericardiectomy is necessary. Although pericardiocentesis generally improves the circulatory status, the improvement is usually temporary. Pericardial windows with drainage into the left pleural space also generally provide only temporary relief. The criteria for selecting patients for pericardiectomy are not clear, apart from those patients who have refractory hemodynamic compromise.

LATENT TUBERCULOUS INFECTION

The concept of latent tuberculous infection and the observations on which its treatment are based were made in the 1950s during the course of experimental studies on the chemotherapeutic effect of isoniazid: animals given isoniazid before being challenged by *M. tuberculosis* had a much lower frequency of tuberculosis.[236] Subsequently, it was found that isoniazid given to children with primary tuberculosis nearly eliminated extrapulmonary spread of the disease.[237] These results provided the rationale for several large U.S. Public Health Service studies of the effectiveness of isoniazid in preventing tuberculosis. These studies were double-blind, placebo-controlled clinical trials that involved approximately 70,000 participants who were in a number of different settings and who had a variety of different risk factors for tuberculosis. The design and results of these studies are described in detail by Ferebee.[238] The findings were remarkably similar in all groups studied; participants given isoniazid had a reduction of approximately 80% in the incidence of tuberculosis during the year the medication was given, in comparison with those given placebo. The protective effect decreased during subsequent years, but the treated groups still showed approximately 50% less tuberculosis than did the control groups each year after the medication year through 10 to 12 years of observation. Overall, isoniazid reduced the incidence of tuberculosis by approximately 60%.

The effectiveness of antituberculosis drugs in preventing tuberculosis is presumably a result of the reduction of the viable population of sequestered bacilli in inactive

or radiographically invisible lesions in the lungs and elsewhere. However, on occasion treatment may be given to persons who have been exposed to tuberculosis but do not have a positive tuberculin reaction. In this situation, treatment is assumed to prevent the establishment of a tuberculous infection, an example of "primary prophylaxis."

Indications for Treatment

The recommendations for testing for and treatment of latent tuberculous infection reflect the concept that only persons who are at increased risk of tuberculosis should be tested for latent infection; thus, any person who is tested and is found to have a positive test should be considered for treatment.[239] The two broad categories of persons in whom the risk of tuberculosis is substantially higher than that of the general population of the United States are persons who are either known or presumed to have been recently infected with *M. tuberculosis* and persons who have clinical conditions that increase the risk of progressing from latent infection to active tuberculosis. The specific groups in which treatment is indicated are as follows (in order of decreasing degree of risk for developing tuberculosis).

Persons with HIV Infection

Several studies have shown that the rates of tuberculosis among persons who are infected with both *M. tuberculosis* and HIV are extremely high, ranging from 3% to 10% per year.[67,240–245] The effectiveness of preventive therapy among persons with HIV infection has been examined in 11 trials with a total of 8130 randomized participants.[241,244,245] Preventive therapy with any antituberculosis drug versus placebo was associated with a lower incidence of active tuberculosis (relative risk [RR], 0.64; 95% CI, 0.51 to 0.81). Among persons with a positive tuberculin skin test, the reduction in risk was even greater (RR, 0.38; 95% CI, 0.25 to 0.57) compared with persons having negative skin test, in whom the reduction was not statistically significant (RR, 0.83; 95% CI, 0.58 to 1.18). The efficacy was similar for all regimens, regardless of drug type, frequency, or duration of treatment. However, compared to isoniazid monotherapy, short-course multidrug regimens were much more likely to require discontinuation of treatment due to adverse effects.

Pape and colleagues[241] reported a rate of 1.7 cases per 100 person-years among HIV-infected, tuberculin-positive (>5-mm induration) adults given isoniazid, 300 mg/day for 12 months, in comparison with a rate of 10.0 cases per 100 person-years in those given placebo. Whalen and associates[244] reported similar rates (1.1 per 100 person-years) among tuberculin-positive, HIV-infected Ugandan adults given isoniazid, 300 mg/day for 6 months, in comparison with a rate of 3.1 cases per 100 person-years in those given placebo. In neither of these studies was benefit found among anergic subjects. The study by Pape and colleagues[241] also demonstrated a reduction in the rate of progression to AIDS and in death rates among those tuberculin-positive subjects given isoniazid. The lack of benefit for anergic subjects was subsequently corroborated in a study conducted in the United States by Gordin and coworkers.[245] Although the optimum duration of preventive therapy with isoniazid in persons with HIV infection is not known, 9 months is currently recommended.[239]

Close Contacts of New Cases

Two percent to 4% of these persons develop tuberculosis in the year after exposure has occurred.[246,247] In young children and adolescents, the risk is perhaps twice that in adults. Because the tuberculin reaction may be negative if infection has recently occurred, all close contacts should be treated.[239] Those with a reaction of 5 mm or more should be considered to be infected and should receive a full course of preventive therapy. Close contacts who have negative tuberculin reactions should be retested 2 to 3 months after the index case has ceased being infectious or after contact has been broken. If the tuberculin reaction at that time is less than 5 mm, isoniazid can be discontinued, and if the reaction is 5 mm or more, the drug should be continued for a full course. Contacts who are known to be HIV-infected should be treated even if the tuberculin test result is negative.

Persons with Recent Infection

As discussed in the section describing the pathogenesis of tuberculosis, the risk of developing tuberculosis is greatest during the initial 1 to 2 years after acquisition of the infection. Any person who is documented to have had a conversion of the skin test reaction from negative to positive should be considered newly infected and receive treatment. A skin test conversion is defined as an increase in reaction size of 10 mm or more within a 2-year period for persons under 35 years of age and a 15-mm or more increase for persons over 35 years of age. Tuberculin skin test reactors younger than 5 years of age should be accorded a high priority for preventive therapy, both because they obviously have been infected relatively recently and because of the potential for severe disease in this age group.

Persons with Stable Radiographic Findings Consistent with Previous Tuberculosis

This group includes persons with a history of tuberculosis who never received chemotherapy or who were not treated adequately, and persons with no known history of the disease. The rate at which new episodes of tuberculosis develop in these groups ranges from approximately 0.4% to 3.5% per year.[238,248–250] The risk is lowest in persons with small lesions that have been stable for a long period.[250] In persons with radiographic abnormalities, it is essential that current tuberculosis be excluded by a careful clinical and bacteriologic evaluation. Because exclusion of active tuberculosis might not be feasible or possible at the initiation of therapy, an alternative

approach is to begin therapy with multiple drugs: isoniazid, rifampin, and pyrazinamide, sometimes with ethambutol. If active disease is present as determined by a positive culture or by radiographic improvement, therapy should be continued for 6 months. If there is no suggestion of active disease, therapy can be stopped after 4 months and the course of treatment will be sufficient for preventive purposes.[239]

Persons with Other Conditions That Increase the Risk of Tuberculosis

Although the risk of tuberculosis is not always quantifiable, there is sufficient evidence to warrant preventive therapy in certain situations[239]: silicosis or coal worker's pneumoconiosis; prolonged therapy with adrenocorticosteroids (usually 15 mg or more of prednisone daily, or its equivalent, for more than 2 to 3 weeks); immunosuppressive therapy; hematologic or reticuloendothelial malignancies, and perhaps certain solid tumors; end-stage renal disease; clinical conditions associated with rapid weight loss (including intestinal bypass for obesity and inadequate nutritional intake); after gastrectomy; and after treatment with anti-TNF agents.[251] In addition, even in the absence of any of these risk factors, persons in the following circumstances who have tuberculin skin test readings of 10 mm or more should be considered for preventive therapy[239]: foreign-born persons from areas of high tuberculosis prevalence; medically underserved, low-income populations, including high-risk racial and ethnic groups; residents of long-term care facilities (e.g., correctional institutions and nursing homes); and other groups that, on the basis of local epidemiologic patterns, have been shown to have a high incidence of tuberculosis (e.g., migrant workers, homeless persons).

Current Treatment Regimens

Three regimens are currently recommended for treating latent tuberculous infection in adults.[239] The regimen that is supported most strongly is isoniazid given daily for 9 months. A 6-month regimen has also been shown to produce considerable protection and may provide the best balance between cost and benefit. Both the 6-month and the 9-month isoniazid regimens may be given twice weekly under direct observation. A regimen of rifampin and pyrazinamide given daily for 2 months was recommended as an alternative to isoniazid,[252] but owing to its significantly greater risk of hepatotoxicity than isoniazid alone, currently it is recommended only for persons thought not likely to complete a 6- to 9-month course of therapy and who can be monitored closely.[253,254] A third option, although the supporting data are not so strong, is rifampin given daily for 4 months.

Isoniazid is given in a single daily dose of 300 mg for adults and 5 to 10 mg/kg body weight (up to 300 mg/day) for children. The drug may also be given in doses of 15 mg/kg twice a week, which may facilitate direct observation of treatment. The minimum duration of treatment is 6 months; 9 months of treatment is considered optimum. Rifampin is given in a single dose of approximately 10 mg/kg body weight for both adults and children, up to a total daily dose of 600 mg. The same dose is used when the drug is given twice weekly. If rifabutin is substituted for rifampin, the dose is 5 mg/kg/day or 300 mg/day.

Treatment of latent tuberculous infection with isoniazid or rifampin should not be undertaken in persons who have active, unstable liver disease. Stable chronic liver disease is not a contraindication, but such patients deserve careful consideration regarding the indications and need close attention during the course of treatment. Other persons who should be monitored especially closely during the administration of preventive therapy include persons over 35 years of age; those taking other medications with which there may be interactions (such as phenytoin, disulfuram, or antiretroviral drugs); and persons with other disorders such as alcoholism, diabetes mellitus, or renal insufficiency that may increase the risk of adverse reactions, mainly hepatitis and peripheral neuropathy.

Pregnancy is not a contraindication to isoniazid; however, in view of the concern with elective administration of any drug during the course of pregnancy, it is generally prudent to wait until after delivery to give isoniazid. The exceptions to this generality are women who have a documented tuberculin conversion during pregnancy or who are HIV-infected and have a positive tuberculin reaction.

Management of Exposure to Drug-Resistant Organisms

Providing preventive therapy for persons exposed to MDR or XDR organisms is especially problematic because there are no regimens of proven efficacy. The options that are available include observation only and administration of two drugs to which the source case isolate was shown to be susceptible (e.g., a 6-month regimen of ethambutol and pyrazinamide or of pyrazinamide and a fluoroquinolone).[239] It should be noted that there are no data to guide the choice of an option. In such situations consultation should be obtained. Regardless of the approach that is chosen, if evidence suggesting tuberculosis arises, the patient should be treated promptly with a multidrug regimen to which the organism would be predicted, on the basis of susceptibility testing of the index case isolate, to be susceptible.

Immunization with Bacille Calmette-Guérin

Administration of BCG vaccine has been the major preventive technique used for many years throughout much of the world, and yet no vaccine has been the subject of greater controversy.[49] BCG is an attenuated tubercle bacillus (*Mycobacterium bovis*) that was created beginning in 1908 by Calmette and Guérin in France and that

was found to protect a variety of animal species against tuberculosis. It was first used in humans in 1921 and has since become the most widely used vaccine in the world: As many as 80% of infants in developing countries receive BCG immunizations. The controversy related to results in prevention of tuberculosis in adult populations should not obscure the fact that BCG has been demonstrated to prevent disseminated and miliary tuberculosis and tuberculosis meningitis in children. Controversy stems from the fact that, of eight controlled clinical trials of BCG against pulmonary tuberculosis in adults, protection has ranged from 0 to 70%.[49] Interestingly, when two different vaccines were used in a Medical Research Council Trial in the United Kingdom, one of which produced only very poor tuberculin skin test reactivity, equal degrees of protection were seen. Conversely, no protection was seen in the South Indian Trial of over 200,000 people monitored for 15 years, although all patients who developed tuberculosis had been converted to skin test positivity by the vaccine.[255] It is unclear why BCG appears to be effective in some parts of the world and not in others (a finding that is also evident in protection against leprosy). Clearly, there is a great deal that has yet to be elucidated about the nature of protective host immune responses, host genetic factors, variations in pathogenicity of tubercle bacilli, and the role of exposure to environmental nontuberculous mycobacteria that may provide resistance or enhance susceptibility.

There are many variables that potentially could account for the discordant results. These include variations in potency of the strains of BCG used, technique of administration, handling of the vaccine, and prevalence of infection with nontuberculous mycobacteria, which may in themselves confer some degree of protection.[256] Partly because of these factors, it is now generally accepted that BCG is not a tool that can be used to decrease the overall incidence of tuberculosis in a population. However, it appears that BCG reduces the likelihood of the more severe forms of the disease in children, and it is with this goal in mind that it continues to be a component of WHO immunization recommendations for developing countries.

In the United States, BCG has very limited applicability. It is recommended only for tuberculin-negative persons who are repeatedly exposed to potentially infectious patients who are being ineffectively treated. In general, the recommendation is limited to children. BCG should not be given to immunocompromised persons, including those with symptomatic HIV infection, or to pregnant women.

TACKLING CURRENT PROBLEMS

Tuberculosis is becoming a more complicated disease globally because of the occurrence of MDR and XDR organisms and the increasing frequency of comorbidities, particularly HIV infection but also other risk-enhancing factors such as diabetes, renal insufficiency, immunosuppressive drugs, and tobacco and other substance addiction. No longer can it be said that tuberculosis control is mainly a management issue rather than a technical problem. Nor can it continue to be said that all that is needed to solve current problems is more assiduous application of the tools that are already widely available. Yet, the most extensively used diagnostic methods around the world, both for active tuberculosis (sputum smear microscopy) and for latent tuberculosis (tuberculin skin test), were invented at end of the 19th century. Similarly, BCG vaccine, despite its wide use, does not provide the needed protection. Today's standard treatment with four drugs (isoniazid, rifampin, ethambutol, and pyrazinamide) has remained unchanged for more than 30 years and is insufficient to treat patients with MDR or XDR tuberculosis. Although there are new diagnostic methods, all of them are either an improvement of the old techniques or based on the detection of nucleic acids. Neither are point-of-care diagnostic tests as are urgently needed.

The increase of drug-resistant tuberculosis and the detection of XDR cases underscores the need for new drugs as well as means to decrease the risk of developing resistance to new drugs.[257] Also high on the list is the availability of a test for the rapid detection of drug resistance suitable for field use. The current technology has identified drug targets and has enabled testing of new compounds with high-throughput screening methods. Several drugs for active tuberculosis are now being tested in clinical trials.[258,259] Some of them are candidates for first-line drugs that can reduce the treatment time, such as moxifloxacin. Others drugs have less drug-drug interaction, with the potential benefit of being used with antiretroviral drugs such as rialazil. Other drugs have a different target, such as TMC207.[260–262] However, we are still far from having a truly short treatment (currently the term *short course* is used for the 6-month regimen!).

Better understanding of the protective immune response to *M. tuberculosis* and of the pathogenesis of the disease, the availability of whole genomic sequences of several clinical strains of *M. tuberculosis,* and the recent evidence of the importance of the coevolution of the host and organism have led to the design of different vaccination approaches.[263,264] Although substantial knowledge has been developed as a consequence of vaccine research, we are still far from having an understanding of why the natural immune system (which prevents 90% of persons infected from developing active tuberculosis) fails in 10% of those infected, and why the adaptive immune response in tuberculosis does not protect us from repeated infections. In spite of these gaps in knowledge, several vaccine candidates are now being tested.[12]

Although important scientific advances have been made recently, major gaps in understanding the basic biology of the organism and the human response to infection with *M. tuberculosis* remain. The rapidly emerging new challenges to the care and control of tuberculosis, such as HIV, MDR tuberculosis, and more recently XDR tuberculosis, may outstrip the advances and threaten our ability to control the disease.

Appendix can be found on Expert Consult

KEY POINTS

- Although tuberculosis cases and case rates are consistently declining in high- and most middle-income countries, the disease continues to be highly prevalent in low- and some middle-income countries.
- The epidemic of HIV infection, especially in sub-Saharan Africa, is leading to extremely high tuberculosis case rates.
- Both HIV infection and resistance to antituberculosis drugs, especially multidrug resistance and extensive drug resistance, present major problems in worldwide tuberculosis control.
- Adequate treatment for tuberculosis, both drug susceptible and drug resistant, is the major intervention for decreasing transmission of *M. tuberculosis.*
- Assuming an adequate regimen is prescribed, patient adherence is the critical factor that determines the success of treatment.
- The treatment of extrapulmonary tuberculosis is largely the same as the treatment of pulmonary tuberculosis. The exceptions are central nervous system tuberculosis and tuberculosis involving bones and joints, in which treatment of longer duration is recommended.
- Treating latent tuberculous infection in persons at increased risk of progressing to active tuberculosis significantly reduces the risk of disease.

References

1. Bloom BR, Murray CJ: Tuberculosis: Commentary on a reemergent killer. Science 257:1055–1064, 1992.
2. Corbett EL, Watt CJ, Walker N, et al: The growing burden of tuberculosis: Global trends and interactions with the HIV epidemic. Arch Intern Med 163:1009–1021, 2003.
3. World Health Organization: Global tuberculosis control 2009: Epidemiology, strategy, financing (WHO/HTM/TB/2009.411). Geneva: World Health Organization, 2009.
4. Cain KP, Benoit SR, Winston CA, et al: Tuberculosis among foreign-born persons in the United States. JAMA 300:405–412, 2008.
5. Raviglione MC: Facing extensively drug-resistant tuberculosis—a hope and a challenge. N Engl J Med 359:636–638, 2008.
6. Barksdale L, Kim KS: Mycobacterium. Bacteriol Rev 41:217–372, 1977.
7. Wayne LG: Microbiology of tubercle bacilli. Am Rev Respir Dis 125:31–41, 1982.
8. Siddiqi SH, Hwangbo CC, Silcox V, et al: Rapid radiometric methods to detect and differentiate *Mycobacterium tuberculosis/M. bovis* from other mycobacterial species. Am Rev Respir Dis 130:634–640, 1984.
9. Cole ST, Brosch R, Parkhill J, et al: Deciphering the biology of *Mycobacterium tuberculosis* from the complete genome sequence. Nature 393:537–544, 1998.
10. Zheng H, Lu L, Wang B, et al: Genetic basis of virulence attenuation revealed by comparative genomic analysis of *Mycobacterium tuberculosis* strain H37Ra versus H37Rv. PLoS ONE 3:e2375, 2008.
11. Camus JC, Pryor MJ, Medigue C, et al: Re-annotation of the genome sequence of *Mycobacterium tuberculosis* H37Rv. Microbiology 148:2967–2973, 2002.
12. Young DB, Perkins MD, Duncan K, et al: Confronting the scientific obstacles to global control of tuberculosis. J Clin Invest 118: 1255–1265, 2008.
13. Williams KJ, Duncan K: Current strategies for identifying and validating targets for new treatment-shortening drugs for TB. Curr Mol Med 7:297–307, 2007.
14. Golby P, Hatch KA, Bacon J, et al: Comparative transcriptomics reveals key gene expression differences between the human and bovine pathogens of the *Mycobacterium tuberculosis* complex. Microbiology 153:3323–3336, 2007.
15. Vishnoi A, Srivastava A, Roy R, et al: MGDD: *Mycobacterium tuberculosis* genome divergence database. BMC Genomics 9:373, 2008.
16. World Health Organization: The top 10 causes of death. *In* Fact Sheet No. 310. Geneva: World Health Organization, 2008.
17. Trends in tuberculosis—United States, 2008. MMWR Morb Mortal Wkly Rep 58:249–253, 2009.
18. Brudney K, Dobkin J: Resurgent tuberculosis in New York City: Human immunodeficiency virus, homelessness, and the decline of tuberculosis control programs. Am Rev Respir Dis 144:745–749, 1991.
19. Burzynski J, Schluger NW: The epidemiology of tuberculosis in the United States. Semin Respir Crit Care Med 29:492–498, 2008.
20. Hopewell PC: Factors influencing the transmission and infectivity of *Mycobacterium tuberculosis:* Implications for clinical and public health management of tuberculosis. *In* Sande MA, Hudson L, Root R (eds): Respiratory Infections. New York: Churchill Livingstone, 1986, pp 191–216.
21. Wells WF: Airborne Contagion and Air Hygiene. Cambridge, MA: Harvard University Press, 1955.
22. Hutton MD, Stead WW, Cauthen GM, et al: Nosocomial transmission of tuberculosis associated with a draining abscess. J Infect Dis 161:286–295, 1990.
23. Riley RL: Airborne infection. Am J Med 57:466–475, 1974.
24. Riley RL, Mills CC, O'Grady F, et al: Infectiousness of air from a tuberculosis ward. Ultraviolet irradiation of infected air: Comparative infectiousness of different patients. Am Rev Respir Dis 85:511–525, 1962.
25. Escombe AR, Moore DA, Gilman RH, et al: The infectiousness of tuberculosis patients coinfected with HIV. PLoS Med 5:e188, 2008.
26. Fennelly KP: Personal respiratory protection against *Mycobacterium tuberculosis*. Clin Chest Med 18:1–17, 1997.
27. Canetti G: Present aspects of bacterial resistance in tuberculosis. Am Rev Respir Dis 92:687–703, 1965.
28. Loudon RG, Spohn SK: Cough frequency and infectivity in patients with pulmonary tuberculosis. Am Rev Respir Dis 99:109–111, 1969.
29. Hobby GL, Holman AP, Iseman MD, et al: Enumeration of tubercle bacilli in sputum of patients with pulmonary tuberculosis. Antimicrob Agents Chemother 4:94–104, 1973.
30. Rouillon A, Perdrizet S, Parrot R: Transmission of tubercle bacilli: The effects of chemotherapy. Tubercle 57:275–299, 1976.
31. Behr MA, Warren SA, Salamon H, et al: Transmission of *Mycobacterium tuberculosis* from patients smear-negative for acid-fast bacilli [see comments]. Lancet 353:444–449, 1999. [published erratum appears in Lancet 1999;353:1714]

32. Sultan L, Nyka W, Mills C, et al: Tuberculosis disseminators: A study of the variability of aerial infectivity of tuberculous patients. Am Rev Respir Dis 82:358–369, 1960.
33. Jindani A, Aber VR, Edwards EA, et al: The early bactericidal activity of drugs in patients with pulmonary tuberculosis. Am Rev Respir Dis 121:939–949, 1980.
34. Burgos M, DeRiemer K, Small PM, et al: Effect of drug resistance on the generation of secondary cases of tuberculosis. J Infect Dis 188:1878–1884, 2003.
35. Cohen T, Sommers B, Murray M: The effect of drug resistance on the fitness of *Mycobacterium tuberculosis*. Lancet Infect Dis 3:13–21, 2003.
36. Gagneux S, Burgos MV, DeRiemer K, et al: Impact of bacterial genetics on the transmission of isoniazid-resistant *Mycobacterium tuberculosis*. PLoS Pathog 2:e61, 2006.
37. Gandhi NR, Moll A, Sturm AW, et al: Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa. Lancet 368:1575–1580, 2006.
38. Reves R, Blakey D, Snider DE Jr, et al: Transmission of multiple drug-resistant tuberculosis: Report of a school and community outbreak. Am J Epidemiol 113:423–435, 1981.
39. Nardell E, McInnis B, Thomas B, et al: Exogenous reinfection with tuberculosis in a shelter for the homeless. N Engl J Med 315:1570–1575, 1986.
40. Loudon RG, Bumgarner LR, Lacy J, et al: Aerial transmission of mycobacteria. Am Rev Respir Dis 100:165–171, 1969.
41. Riley RL, Nardell EA: Clearing the air: The theory and application of ultraviolet air disinfection. Am Rev Respir Dis 139:1286–1294, 1989.
42. Houk VN, Baker JH, Sorensen K, et al: The epidemiology of tuberculosis infection in a closed environment. Arch Environ Health 16:26–35, 1968.
43. Ehrenkranz NJ, Kicklighter JL: Tuberculosis outbreak in a general hospital: Evidence for airborne spread of infection. Ann Intern Med 77:377–382, 1972.
44. Catanzaro A: Nosocomial tuberculosis. Am Rev Respir Dis 125:559–562, 1982.
45. Kuemmerer JM, Comstock GW: Sociologic concomitants of tuberculin sensitivity. Am Rev Respir Dis 96:885–892, 1967.
46. Stead WW, Senner JW, Reddick WT, et al: Racial differences in susceptibility to infection by *Mycobacterium tuberculosis*. N Engl J Med 322:422–427, 1990.
47. Arentz M, Hawn TR: Tuberculosis infection: Insight from immunogenomics. Drug Discov Today Dis Mech 4:231–236, 2007.
48. Flynn JL, Chan J: Immunology of tuberculosis. Annu Rev Immunol 19:93–129, 2001.
49. Bloom BR, Fine PEM: The BCG experience: Implications for future vaccines against tuberculosis. *In* Bloom BR (ed): Tuberculosis: Pathogenesis, Protection and Control. Washington, DC: ASM Press, 1994, pp 531–557.
50. Small PM, Shafer RW, Hopewell PC, et al: Exogenous reinfection with multidrug-resistant *Mycobacterium tuberculosis* in patients with advanced HIV infection. N Engl J Med 328:1137–1144, 1993.
51. Charalambous S, Grant AD, Moloi V, et al: Contribution of reinfection to recurrent tuberculosis in South African gold miners. Int J Tuberc Lung Dis 12:942–948, 2008.
52. Dobler CC, Marks GB, Simpson SE, et al: Recurrence of tuberculosis at a Sydney chest clinic between 1994 and 2006: Reactivation or reinfection? Med J Aust 188:153–155, 2008.
53. Berrington WR, Hawn TR: *Mycobacterium tuberculosis,* macrophages, and the innate immune response: Does common variation matter? Immunol Rev 219:167–186, 2007.
54. Russell DG: Who puts the tubercle in tuberculosis? Nat Rev Microbiol 5:39–47, 2007.
55. Sutherland I: Recent studies in the epidemiology of tuberculosis, based on the risk of being infected with tubercle bacilli. Adv Tuberc Res 19:1–63, 1976.
56. Ulrichs T, Kaufmann SH: New insights into the function of granulomas in human tuberculosis. J Pathol 208:261–269, 2006.
57. Chan J, Tanaka K, Carroll D, et al: Effects of nitric oxide synthase inhibitors on murine infection with *Mycobacterium tuberculosis*. Infect Immun 63:736–740, 1995.
58. Denis M: Interferon-gamma-treated murine macrophages inhibit growth of tubercle bacilli via the generation of reactive nitrogen intermediates. Cell Immunol 132:150–157, 1991.
59. Kindler V, Sappino AP, Grau GE, et al: The inducing role of tumor necrosis factor in the development of bactericidal granulomas during BCG infection. Cell 56:731–740, 1989.
60. Stead WW: Pathogenesis of a first episode of chronic pulmonary tuberculosis in man: Recrudescence of residuals of the primary infection or exogenous reinfection? Am Rev Respir Dis 95:729–745, 1967.
61. Daley CL, Small PM, Schecter GF, et al: An outbreak of tuberculosis with accelerated progression among persons infected with the human immunodeficiency virus: An analysis using restriction-fragment-length polymorphisms. N Engl J Med 326:231–235, 1992.
62. Kanduma E, McHugh TD, Gillespie SH: Molecular methods for *Mycobacterium tuberculosis* strain typing: A users guide. J Appl Microbiol 94:781–791, 2003.
63. van Rie A, Warren R, Richardson M, et al: Exogenous reinfection as a cause of recurrent tuberculosis after curative treatment. N Engl J Med 341:1174–1179, 1999.
64. Caminero JA, Pena MJ, Campos-Herrero MI, et al: Exogenous reinfection with tuberculosis on a European island with a moderate incidence of disease. Am J Respir Crit Care Med 163:717–720, 2001.
65. Lambert ML, Hasker E, Van Deun A, et al: Recurrence in tuberculosis: Relapse or reinfection? Lancet Infect Dis 3:282–287, 2003.
66. Comstock GW, Livesay VT, Woolpert SF: The prognosis of a positive tuberculin reaction in childhood and adolescence. Am J Epidemiol 99:131–138, 1974.
67. Selwyn PA, Hartel D, Lewis VA, et al: A prospective study of the risk of tuberculosis among intravenous drug users with human immunodeficiency virus infection. N Engl J Med 320:545–550, 1989.
68. Di Perri G, Cruciani M, Danzi MC, et al: Nosocomial epidemic of active tuberculosis among HIV-infected patients. Lancet 2:1502–1504, 1989.
69. Santoro-Lopes G, de Pinho AM, Harrison LH, et al: Reduced risk of tuberculosis among Brazilian patients with advanced human immunodeficiency virus infection treated with highly active antiretroviral therapy. Clin Infect Dis 34:543–546, 2002.
70. Badri M, Wilson D, Wood R: Effect of highly active antiretroviral therapy on incidence of tuberculosis in South Africa: A cohort study. Lancet 359:2059–2064, 2002.
71. Markowitz N, Hansen NI, Hopewell PC, et al: Incidence of tuberculosis in the United States among HIV-infected persons. The Pulmonary Complications of HIV Infection Study Group. Ann Intern Med 126:123–132, 1997.
72. Golub JE, Saraceni V, Cavalcante SC, et al: The impact of antiretroviral therapy and isoniazid preventive therapy on tuberculosis incidence in HIV-infected patients in Rio de Janeiro, Brazil. AIDS 21:1441–1448, 2007.
73. Balmes J: Silica exposure and tuberculosis: An old problem with some new twists. J Occup Med 32:114–115, 1990.
74. Comstock GW: Tuberculosis in twins: A re-analysis of the Prophit survey. Am Rev Respir Dis 117:621–624, 1978.
75. Horwitz O, Wilbek E, Erickson PA: Epidemiological basis of tuberculosis eradication. 10. Longitudinal studies on the risk of tuberculosis in the general population of a low-prevalence area. Bull World Health Organ 41:95–113, 1969.
76. Grzybowski S, Styblo K, Dorken E: Tuberculosis in Eskimos. Tubercle 57:S1–58, 1976.
77. Comstock GW, Edwards LB, Livesay VT: Tuberculosis morbidity in the U.S. Navy: Its distribution and decline. Am Rev Respir Dis 110:572–580, 1974.
78. Chandra RK: Nutrition and immunology: From the clinic to cellular biology and back again. Proc Nutr Soc 58:681–683, 1999.
79. DiBenedetto A, Diamond P, Essig HC: Tuberculosis following subtotal gastrectomy. Surg Gynecol Obstet 134:586–588, 1972.
80. Mazurek GH, Weis SE, Moonan PK, et al: Prospective comparison of the tuberculin skin test and 2 whole-blood interferon-gamma release assays in persons with suspected tuberculosis. Clin Infect Dis 45:837–845, 2007.

81. Seibert FB, Glenn JT: Tuberculin purified derivative: Preparation and analysis of a large quantity for standard. Am Rev Tuberc 44:9–25, 1941.
82. Slutkin G, Perez-Stable EJ, Hopewell PC: Time course and boosting of tuberculin reactions in nursing home residents. Am Rev Respir Dis 134:1048–1051, 1986.
83. Thompson NJ, Glassroth JL, Snider DE Jr, et al: The booster phenomenon in serial tuberculin testing. Am Rev Respir Dis 119:587–597, 1979.
84. Edwards PG, Edwards LB: Quantitative aspects of tuberculin sensitivity. Am Rev Respir Dis 81:24–32, 1960.
85. Snider DE Jr: Bacille Calmette-Guerin vaccinations and tuberculin skin tests. JAMA 253:3438–3439, 1985.
86. Bovornkitti S, Kangsadal P, Sathirapat P, et al: Reversion and reconversion rate of tuberculin skin reactions in connection with the use of prednisone. Dis Chest 38:51–55, 1960.
87. Holden M, Dubin MR, Diamond PH: Frequency of negative intermediate-strength tuberculin sensitivity in patients with active tuberculosis. N Engl J Med 285:1506–1509, 1971.
88. Markowitz N, Hansen NI, Wilcosky TC, et al: Tuberculin and anergy testing in HIV-seropositive and HIV-seronegative persons. Pulmonary Complications of HIV Infection Study Group. Ann Intern Med 119:185–193, 1993.
89. Pai M, Riley LW, Colford JM Jr: Interferon-gamma assays in the immunodiagnosis of tuberculosis: A systematic review. Lancet Infect Dis 4:761–776, 2004.
90. Pai M, Zwerling A, Menzies D: Systematic review. T-cell-based assays for the diagnosis of latent tuberculosis infection: An update. Ann Intern Med 149:177–184, 2008.
91. Chee CB, Gan SH, Khinmar KW, et al: Comparison of sensitivities of two commercial gamma interferon release assays for pulmonary tuberculosis. J Clin Microbiol 46:1935–1940, 2008.
91a. Lalvani A, Pareek M: Interferon gamma release assays: principles and practice. Enferm Infecc Microbiol Clin 2009. [Epub ahead of print].
91b. Leidl L, Mayanja-Kizza H, Sotgiu G, et al: Relationship of immunodiagnostic assays for tuberculosis and numbers of circulating CD4+ T-cells in HIV-infection. Eur Respir J 2009. [Epub ahead of print].
92. Hill PC, Brookes RH, Fox A, et al: Longitudinal assessment of an ELISPOT test for *Mycobacterium tuberculosis* infection. PLoS Med 4:e192, 2007.
93. Ewer K, Millington KA, Deeks JJ, et al: Dynamic antigen-specific T-cell responses after point-source exposure to *Mycobacterium tuberculosis*. Am J Respir Crit Care Med 174:831–839, 2006.
94. Wilkinson KA, Kon OM, Newton SM, et al: Effect of treatment of latent tuberculosis infection on the T cell response to *Mycobacterium tuberculosis* antigens. J Infect Dis 193:354–359, 2006.
95. Pai M, Joshi R, Dogra S, et al: Serial testing of health care workers for tuberculosis using interferon-gamma assay. Am J Respir Crit Care Med 174:349–355, 2006.
96. Mazurek GH, Jereb J, LoBue P, et al: Guidelines for using the QuantiFERON®-TB Gold Test for detecting *Mycobacterium tuberculosis* infection, United States. MMWR Recomm Rep 54:49–55, 2005.
97. Small PM, Schecter GF, Goodman PC, et al: Treatment of tuberculosis in patients with advanced human immunodeficiency virus infection. N Engl J Med 324:289–294, 1991.
98. Kiblawi SS, Jay SJ, Stonehill RB, et al: Fever response of patients on therapy for pulmonary tuberculosis. Am Rev Respir Dis 123:20–24, 1981.
99. Arango L, Brewin AW, Murray JF: The spectrum of tuberculosis as currently seen in a metropolitan hospital. Am Rev Respir Dis 108:805–812, 1973.
100. Cameron SJ: Tuberculosis and the blood—a special relationship? Tubercle 55:55–72, 1974.
101. Chung DK, Hubbard WW: Hyponatremia in untreated active pulmonary tuberculosis. Am Rev Respir Dis 99:595–597, 1969.
102. Vorherr H, Massry SG, Fallet R, et al: Antidiuretic principle in tuberculous lung tissue of a patient with pulmonary tuberculosis and hyponatremia. Ann Intern Med 72:383–387, 1970.
103. Hopewell PC, Pai M, Maher D, et al: International standards for tuberculosis care. Lancet Infect Dis 6:710–725, 2006.
104. Pitchenik AE, Rubinson HA: The radiographic appearance of tuberculosis in patients with the acquired immune deficiency syndrome (AIDS) and pre-AIDS. Am Rev Respir Dis 131:393–396, 1985.
105. Small PM, Hopewell PC, Schecter GF, et al: Evolution of chest radiographs in treated patients with pulmonary tuberculosis and HIV infection. J Thorac Imaging 9:74–77, 1994.
106. Kubica GP, Gross WM, Hawkins JE, et al: Laboratory services for mycobacterial diseases. Am Rev Respir Dis 112:773–787, 1975.
107. Mase SR, Ramsay A, Ng V, et al: Yield of serial sputum specimen examinations in the diagnosis of pulmonary tuberculosis: A systematic review. Int J Tuberc Lung Dis 11:485–495, 2007.
108. Danek SJ, Bower JS: Diagnosis of pulmonary tuberculosis by flexible fiberoptic bronchoscopy. Am Rev Respir Dis 119:677–679, 1979.
109. Burk JR, Viroslav J, Bynum LJ: Miliary tuberculosis diagnosed by fibreoptic bronchoscopy and transbronchial biopsy. Tubercle 59:107–109, 1978.
110. Broaddus C, Dake MD, Stulbarg MS, et al: Bronchoalveolar lavage and transbronchial biopsy for the diagnosis of pulmonary infections in the acquired immunodeficiency syndrome. Ann Intern Med 102:747–752, 1985.
111. Barnes PF: Role of fiberoptic bronchoscopy in diagnosis of pulmonary tuberculosis in patients at risk for AIDS. Chest 103:1923–1924, 1993.
112. Gordin FM, Slutkin G, Schecter G, et al: Presumptive diagnosis and treatment of pulmonary tuberculosis based on radiographic findings. Am Rev Respir Dis 139:1090–1093, 1989.
113. Pai M, Ramsay A, O'Brien R: Evidence-based tuberculosis diagnosis. PLoS Med 5:e156, 2008.
114. Pio A, Chaulet P: Tuberculosis Handbook, 2nd ed. Geneva: World Health Organization, 1998, pp 65–78.
115. Steingart KR, Henry M, Ng V, et al: Fluorescence versus conventional sputum smear microscopy for tuberculosis: A systematic review. Lancet Infect Dis 6:570–581, 2006.
116. Marais BJ, Brittle W, Painczyk K, et al: Use of light-emitting diode fluorescence microscopy to detect acid-fast bacilli in sputum. Clin Infect Dis 47:203–207, 2008.
117. Ling DI, Zwerling AA, Pai M: GenoType MTBDR assays for the diagnosis of multidrug-resistant tuberculosis: A meta-analysis. Eur Respir J 32:1165–1174, 2008.
118. Victor TC, Lee H, Cho SN, et al: Molecular detection of early appearance of drug resistance during *Mycobacterium tuberculosis* infection. Clin Chem Lab Med 40:876–881, 2002.
119. Krasnow I, Wayne LG: Comparison of methods for tuberculosis bacteriology. Appl Microbiol 18:915–917, 1969.
120. Tiwari RP, Hattikudur NS, Bharmal RN, et al: Modern approaches to a rapid diagnosis of tuberculosis: Promises and challenges ahead. Tuberculosis (Edinb) 87:193–201, 2007.
121. Updated guidelines for the use of nucleic acid amplification tests in the diagnosis of tuberculosis. MMWR Morb Mortal Wkly Rep 58:7–10, 2009.
122. Steingart KR, Henry M, Laal S, et al: Commercial serological antibody detection tests for the diagnosis of pulmonary tuberculosis: A systematic review. PLoS Med 4:e202, 2007.
123. Vestal AL: Procedures for the Isolation and Identification of Mycobacteria. Washington, DC: Department of Health, Education and Welfare, 1976, pp 97–115.
124. Siddiqi SH, Libonati JP, Middlebrook G: Evaluation of rapid radiometric method for drug susceptibility testing of *Mycobacterium tuberculosis*. J Clin Microbiol 13:908–912, 1981.
125. Aragon LM, Garrigo M, Moreno C, et al: Evaluation of the BacT/ALERT PZA kit in comparison with the BACTEC 460TB PZA for testing *Mycobacterium tuberculosis* susceptibility to pyrazinamide. J Antimicrob Chemother 60:655–657, 2007.
126. Arias M, Mello FC, Pavon A, et al: Clinical evaluation of the microscopic-observation drug-susceptibility assay for detection of tuberculosis. Clin Infect Dis 44:674–680, 2007.
127. Moore DA, Evans CA, Gilman RH, et al: Microscopic-observation drug-susceptibility assay for the diagnosis of TB. N Engl J Med 355:1539–1550, 2006.
128. Miotto P, Piana F, Cirillo DM, et al: Genotype MTBDR*plus*: a further step toward rapid identification of drug-resistant *Mycobacterium tuberculosis*. J Clin Microbiol 46:393–394, 2008.

129. Barnard M, Albert H, Coetzee G, et al: Rapid molecular screening for multidrug-resistant tuberculosis in a high-volume public health laboratory in South Africa. Am J Respir Crit Care Med 177:787–792, 2008.
130. Quezada CM, Kamanzi E, Mukamutara J, et al: Implementation validation performed in Rwanda to determine whether the INNO-LiPA Rif.TB line probe assay can be used for detection of multidrug-resistant *Mycobacterium tuberculosis* in low-resource countries. J Clin Microbiol 45:3111–3114, 2007.
131. Lin SY, Probert W, Lo M, et al: Rapid detection of isoniazid and rifampin resistance mutations in *Mycobacterium tuberculosis* complex from cultures or smear-positive sputa by use of molecular beacons. J Clin Microbiol 42:4204–4208, 2004.
132. Pai M, Kalantri S, Pascopella L, et al: Bacteriophage-based assays for the rapid detection of rifampicin resistance in *Mycobacterium tuberculosis:* A meta-analysis. J Infect 51:175–187, 2005.
133. Jasmer RM, Hahn JA, Small PM, et al: A molecular epidemiologic analysis of tuberculosis trends in San Francisco, 1991–1997. Ann Intern Med 130:971–978, 1999.
134. Mathema B, Kurepina NE, Bifani PJ, et al: Molecular epidemiology of tuberculosis: Current insights. Clin Microbiol Rev 19:658–685, 2006.
135. Ong A, Rudoy I, Gonzalez LC, et al: Tuberculosis in healthcare workers: A molecular epidemiologic study in San Francisco. Infect Control Hosp Epidemiol 27:453–458, 2006.
136. Filliol I, Driscoll JR, van Soolingen D, et al: Snapshot of moving and expanding clones of *Mycobacterium tuberculosis* and their global distribution assessed by spoligotyping in an international study. J Clin Microbiol 41:1963–1970, 2003.
137. Mazars E, Lesjean S, Banuls AL, et al: High-resolution minisatellite-based typing as a portable approach to global analysis of *Mycobacterium tuberculosis* molecular epidemiology. Proc Natl Acad Sci U S A 98:1901–1906, 2001.
138. Gagneux S, Small PM: Global phylogeography of *Mycobacterium tuberculosis* and implications for tuberculosis product development. Lancet Infect Dis 7:328–337, 2007.
139. Cubillos-Ruiz A, Morales J, Zambrano MM: Analysis of the genetic variation in *Mycobacterium tuberculosis* strains by multiple genome alignments. BMC Res Notes 1:110, 2008.
140. Gutacker MM, Smoot JC, Migliaccio CA, et al: Genome-wide analysis of synonymous single nucleotide polymorphisms in *Mycobacterium tuberculosis* complex organisms: Resolution of genetic relationships among closely related microbial strains. Genetics 162:1533–1543, 2002.
141. Fleischmann RD, Alland D, Eisen JA, et al: Whole-genome comparison of *Mycobacterium tuberculosis* clinical and laboratory strains. J Bacteriol 184:5479–5490, 2002.
142. Baker L, Brown T, Maiden MC, et al: Silent nucleotide polymorphisms and a phylogeny for *Mycobacterium tuberculosis*. Emerg Infect Dis 10:1568–1577, 2004.
143. Blumberg HM, Burman WJ, Chaisson RE, et al, for the American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: Treatment of tuberculosis. Am J Respir Crit Care Med 167:603–662, 2003.
144. World Health Organization: Treatment of Tuberculosis: Guidelines for National Programmes, 3rd ed. Geneva: World Health Organization, 2003, pp 1–108.
145. Fox W, Ellard GA, Mitchison DA: Studies on the treatment of tuberculosis undertaken by the British Medical Research Council tuberculosis units, 1946–1986, with relevant subsequent publications. Int J Tuberc Lung Dis 3:S231–S279, 1999.
146. Mitchison DA, Nunn AJ: Influence of initial drug resistance on the response to short-course chemotherapy of pulmonary tuberculosis. Am Rev Respir Dis 133:423–430, 1986.
147. Lew W, Pai M, Oxlade O, et al: Initial drug resistance and tuberculosis treatment outcomes: Systematic review and meta-analysis. Ann Intern Med 149:123–134, 2008.
148. Benator D, Bhattacharya M, Bozeman L, et al: Rifapentine and isoniazid once a week versus rifampicin and isoniazid twice a week for treatment of drug-susceptible pulmonary tuberculosis in HIV-negative patients: A randomised clinical trial. Lancet 360:528–534, 2002.
149. Mitchison DA: Assessment of new sterilizing drugs for treating pulmonary tuberculosis by culture at 2 months. Am Rev Respir Dis 147:1062–1063, 1993.
150. Singla R, Osman MM, Khan N, et al: Factors predicting persistent sputum smear positivity among pulmonary tuberculosis patients 2 months after treatment. Int J Tuberc Lung Dis 7:58–64, 2003.
151. Chaulk CP, Moore-Rice K, Rizzo R, et al: Eleven years of community-based directly observed therapy for tuberculosis. JAMA 274:945–951, 1995.
152. Moore RD, Chaulk CP, Griffiths R, et al: Cost-effectiveness of directly observed versus self-administered therapy for tuberculosis. Am J Respir Crit Care Med 154:1013–1019, 1996.
153. Burman WJ, Dalton CB, Cohn DL, et al: A cost-effectiveness analysis of directly observed therapy vs self-administered therapy for treatment of tuberculosis. Chest 112:63–70, 1997.
154. Acquired rifamycin resistance in persons with advanced HIV disease being treated for active tuberculosis with intermittent rifamycin-based regimens. MMWR Morb Mortal Wkly Rep 51:214–215, 2002.
155. Bradford WZ, Martin JN, Reingold AL, et al: The changing epidemiology of acquired drug-resistant tuberculosis in San Francisco, USA. Lancet 348:928–931, 1996.
156. Vernon A, Burman W, Benator D, et al: Acquired rifamycin monoresistance in patients with HIV-related tuberculosis treated with once-weekly rifapentine and isoniazid. Tuberculosis Trials Consortium. Lancet 353:1843–1847, 1999.
157. Kang'ombe CT, Harries AD, Ito K, et al: Long-term outcome in patients registered with tuberculosis in Zomba, Malawi: Mortality at 7 years according to initial HIV status and type of TB. Int J Tuberc Lung Dis 8:829–836, 2004.
158. Bishai WR, Graham NM, Harrington S, et al: Brief report: Rifampin-resistant tuberculosis in a patient receiving rifabutin prophylaxis. N Engl J Med 334:1573–1576, 1996.
159. Hammer SM, Turmen T, Vareldzis B, et al: Antiretroviral guidelines for resource-limited settings: The WHO's public health approach. Nat Med 8:649–650, 2002.
160. Meintjes G, Lawn SD, Scano F, et al: Tuberculosis-associated immune reconstitution inflammatory syndrome: Case definitions for use in resource-limited settings. Lancet Infect Dis 8:516–523, 2008.
161. World Health Organization: Guidelines for the Programmatic Management of Drug-Resistant Tuberculosis: Emergency Update. Geneva: World Health Organization, 2008, pp 50–271.
162. Zierski M: Prospects of retreatment of chronic resistant pulmonary tuberculosis patients: A critical review. Lung 154:91–102, 1977.
163. World Health Organization: Anti-tuberculosis Drug Resistance in the World: Report no. 4 (WHO/HTM/TB/2004.343). Geneva: World Health Organization, 2008.
164. Goble M, Iseman MD, Madsen LA, et al: Treatment of 171 patients with pulmonary tuberculosis resistant to isoniazid and rifampin. N Engl J Med 328:527–532, 1993.
164a. Francis J. Curry National Tuberculosis Center and California Department of Public Health: Treatment. *In* Drug-Resistant Tuberculosis: A Survival Guide for Clinicians. Francis J. Curry National Tuberculosis Center, 2008, pp 32–56.
165. Burgos M, Gonzalez LC, Paz EA, et al: Treatment of multidrug-resistant tuberculosis in San Francisco: An outpatient-based approach. Clin Infect Dis 40:968–975, 2005.
166. Telzak EE, Sepkowitz K, Alpert P, et al: Multidrug-resistant tuberculosis in patients without HIV infection. N Engl J Med 333:907–911, 1995.
167. Emergence of *Mycobacterium tuberculosis* with extensive resistance to second-line drugs—worldwide, 2000–2004. MMWR Morb Mortal Wkly Rep 55:301–305, 2006.
168. Mitnick CD, Shin SS, Seung KJ, et al: Comprehensive treatment of extensively drug-resistant tuberculosis. N Engl J Med 359:563–574, 2008.
169. Kumar L, Dhand R, Singhi PD, et al: A randomized trial of fully intermittent vs. daily followed by intermittent short course chemotherapy for childhood tuberculosis. Pediatr Infect Dis J 9:802–806, 1990.

170. Al-Dossary FS, Ong LT, Correa AG, et al: Treatment of childhood tuberculosis with a six month directly observed regimen of only two weeks of daily therapy. Pediatr Infect Dis J 21:91–97, 2002.
171. World Health Organization: Guidance for National Tuberculosis Programmes on the Management of Tuberculosis in Children. Geneva: World Health Organization, 2006, pp 2–41.
172. Robinson GC, Cambon KG: Hearing loss in infants of tuberculous mothers treated with streptomycin during pregnancy. N Engl J Med 271:949–951, 1964.
173. Girling DJ: Adverse effects of antituberculosis drugs. Drugs 23:56–74, 1982.
174. Gaensler EA: The surgery for pulmonary tuberculosis. Am Rev Respir Dis 125:73–84, 1982.
175. Iseman MD, Madsen L, Goble M, et al: Surgical intervention in the treatment of pulmonary disease caused by drug-resistant *Mycobacterium tuberculosis*. Am Rev Respir Dis 141:623–625, 1990.
176. Johnson JR, Turk TL, MacDonald FM: Corticosteroids in pulmonary tuberculosis. II. Importance of background factors. Am Rev Respir Dis 96:43–61, 1967.
177. Huseby JS, Hudson LD: Miliary tuberculosis and adult respiratory distress syndrome. Ann Intern Med 85:609–611, 1976.
178. Smego RA, Ahmed N: A systematic review of the adjunctive use of systemic corticosteroids for pulmonary tuberculosis. Int J Tuberc Lung Dis 7:208–213, 2003.
179. Alvarez S, McCabe WR: Extrapulmonary tuberculosis revisited: A review of experience at Boston City and other hospitals. Medicine (Baltimore) 63:25–55, 1984.
180. Ebdrup L, Storgaard M, Jensen-Fangel S, et al: Ten years of extrapulmonary tuberculosis in a Danish university clinic. Scand J Infect Dis 35:244–246, 2003.
181. Centers for Disease Control and Prevention: Reported Tuberculosis in the United States, 2007. Atlanta: Centers for Disease Control and Prevention, 2007.
182. Slavin RE, Walsh TJ, Pollack AD: Late generalized tuberculosis: A clinical pathologic analysis and comparison of 100 cases in the preantibiotic and antibiotic eras. Medicine (Baltimore) 59:352–366, 1980.
183. Munt PW: Miliary tuberculosis in the chemotherapy era: With a clinical review in 69 American adults. Medicine (Baltimore) 51:139–155, 1972.
184. Sahn SA, Neff TA: Miliary tuberculosis. Am J Med 56:494–505, 1974.
185. Gelb AF, Leffler C, Brewin A, et al: Miliary tuberculosis. Am Rev Respir Dis 108:1327–1333, 1973.
186. Pai M, Ling DI: Rapid diagnosis of extrapulmonary tuberculosis using nucleic acid amplification tests: What is the evidence? Future Microbiol 3:1–4, 2008.
187. Pai M, Flores LL, Pai N, et al: Diagnostic accuracy of nucleic acid amplification tests for tuberculous meningitis: A systematic review and meta-analysis. Lancet Infect Dis 3:633–643, 2003.
188. Pai M, Flores LL, Hubbard A, et al: Nucleic acid amplification tests in the diagnosis of tuberculous pleuritis: A systematic review and meta-analysis. BMC Infect Dis 4:6, 2004.
189. Prasad K, Singh MB: Corticosteroids for managing tuberculous meningitis. Cochrane Database Syst Rev (1):CD002244, 2008.
190. Jones BE, Young SM, Antoniskis D, et al: Relationship of the manifestations of tuberculosis to CD4 cell counts in patients with human immunodeficiency virus infection. Am Rev Respir Dis 148:1292–1297, 1993.
191. Huhti E, Brander E, Paloheimo S, et al: Tuberculosis of the cervical lymph nodes: A clinical, pathological and bacteriological study. Tubercle 56:27–36, 1975.
192. Marchevsky A, Rosen MJ, Chrystal G, et al: Pulmonary complications of the acquired immunodeficiency syndrome: A clinicopathologic study of 70 cases. Hum Pathol 16:659–670, 1985.
193. Campbell IA: The treatment of superficial tuberculous lymphadenitis. Tubercle 71:1–3, 1990.
194. Nemir RL, Cardona J, Vaziri F, et al: Prednisone as an adjunct in the chemotherapy of lymph node-bronchial tuberculosis in childhood: A double-blind study. II. Further term observation. Am Rev Respir Dis 95:402–410, 1967.
195. Campbell IA, Dyson AJ: Lymph node tuberculosis: A comparison of various methods of treatment. Tubercle 58:171–179, 1977.
196. Stead WW, Eichenholz A, Stauss HK: Operative and pathologic findings in twenty-four patients with syndrome of idiopathic pleurisy with effusion, presumably tuberculous. Am Rev Tuberc 71:473–502, 1955.
197. Ellner JJ, Barnes PF, Wallis RS, et al: The immunology of tuberculous pleurisy. Semin Respir Infect 3:335–342, 1988.
198. Berger HW, Mejia E: Tuberculous pleurisy. Chest 63:88–92, 1973.
199. Jay SJ: Diagnostic procedures for pleural disease. Clin Chest Med 6:33–48, 1985.
200. Light RW: Pleural Diseases, 5th ed. Philadelphia: Lippincott Williams & Wilkins, 2007, pp 73–108.
201. Jimenez Castro D, Diaz Nuevo G, Perez-Rodriguez E, et al: Diagnostic value of adenosine deaminase in nontuberculous lymphocytic pleural effusions. Eur Respir J 21:220–224, 2003.
202. Villena V, Lopez-Encuentra A, Pozo F, et al: Interferon gamma levels in pleural fluid for the diagnosis of tuberculosis. Am J Med 115:365–370, 2003.
203. Villena V, Lopez-Encuentra A, Echave-Sustaeta J, et al: Interferon-gamma in 388 immunocompromised and immunocompetent patients for diagnosing pleural tuberculosis. Eur Respir J 9:2635–2639, 1996.
204. Scharer L, McClement JH: Isolation of tubercle bacilli from needle biopsy specimens of parietal pleura. Am Rev Respir Dis 97:466–468, 1968.
205. Engel ME, Matchaba PT, Volmink J: Corticosteroids for tuberculous pleurisy. Cochrane Database Syst Rev (4):CD001876, 2007.
206. Johnson TM, McCann W, Davey WN: Tuberculous bronchopleural fistula. Am Rev Respir Dis 107:30–41, 1973.
207. Eloesser L: Of an operation for tuberculous empyema. Ann Thorac Surg 8:355–357, 1969.
208. Medlar EM: Cases of renal infection in pulmonary tuberculosis: Evidence of healed tuberculous lesions. Am J Pathol 2:401–419, 1926.
209. Medlar EM, Spain DM, Holliday WR: Post-mortem compared with clinical diagnoses of genitourinary tuberculosis in adult males. J Urol 61:1078–1088, 1949.
210. Christensen WI: Genitourinary tuberculosis: Review of 102 cases. Medicine (Baltimore) 53:377–390, 1974.
211. Simon HB, Weinstein AJ, Pasternak MS, et al: Genitourinary tuberculosis: Clinical features in a general hospital population. Am J Med 63:410–420, 1977.
212. Lattimer JK: Renal tuberculosis. N Engl J Med 273:208–211, 1965.
213. Bentz RR, Dimcheff DG, Nemiroff MJ, et al: The incidence of urine cultures positive for *Mycobacterium tuberculosis* in a general tuberculosis patient population. Am Rev Respir Dis 111:647–650, 1975.
214. Berney S, Goldstein M, Bishko F: Clinical and diagnostic features of tuberculous arthritis. Am J Med 53:36–42, 1972.
215. Pertuiset E, Beaudreuil J, Liote F, et al: Spinal tuberculosis in adults: A study of 103 cases in a developed country, 1980–1994. Medicine (Baltimore) 78:309–320, 1999.
216. A 15-year assessment of controlled trials of the management of tuberculosis of the spine in Korea and Hong Kong. Thirteenth Report of the Medical Research Council Working Party on Tuberculosis of the Spine. J Bone Joint Surg Br 80:456–462, 1998.
217. Jain AK, Dhammi IK: Tuberculosis of the spine: A review. Clin Orthop Relat Res (460):39–49, 2007.
218. Tuli SM: Results of treatment of spinal tuberculosis by "middle-path" regime. J Bone Joint Surg Br 57:13–23, 1975.
219. Tuli SM: Tuberculosis of the spine: A historical review. Clin Orthop Relat Res (460):29–38, 2007.
220. Bishburg E, Sunderam G, Reichman LB, et al: Central nervous system tuberculosis with the acquired immunodeficiency syndrome and its related complex. Ann Intern Med 105:210–213, 1986.
221. Auerbach O: Tuberculous meningitis: Correlation of therapeutic results with the pathogenesis and pathologic changes. I. General considerations and pathogenesis. Am Rev Tuberc 64:408–418, 1951.

222. Auerbach O: Tuberculous meningitis: Correlation of therapeutic results with the pathogenesis and pathologic changes. II. Pathologic changes in untreated and treated cases. Am Rev Tuberc 64:419–429, 1951.
223. Thwaites GE, Chau TT, Stepniewska K, et al: Diagnosis of adult tuberculous meningitis by use of clinical and laboratory features. Lancet 360:1287–1292, 2002.
224. Girgis NI, Farid Z, Kilpatrick ME, et al: Dexamethasone adjunctive treatment for tuberculous meningitis. Pediatr Infect Dis J 10:179–183, 1991.
225. Damergis JA, Leftwich EI, Curtin JA, et al: Tuberculoma of the brain. JAMA 239:413–415, 1978.
226. Mitchell RS, Bristol LJ: Intestinal tuberculosis: An analysis of 346 cases diagnosed by routine intestinal radiography on 5,529 admissions for pulmonary tuberculosis, 1924–49. Am J Med Sci 227:241–249, 1954.
227. Carrera GF, Young S, Lewicki AM: Intestinal tuberculosis. Gastrointest Radiol 1:147–155, 1976.
228. Bhansali SK: Abdominal tuberculosis: Experiences with 300 cases. Am J Gastroenterol 67:324–337, 1977.
229. Burack WR, Hollister RM: Tuberculous peritonitis: A study of forty-seven proved cases encountered by a general medical unit in twenty-five years. Am J Med 28:510–523, 1960.
230. Schepers GW: Tuberculous pericarditis. Am J Cardiol 9:248–276, 1962.
231. Harvey AM, Whitehill MR: Tuberculous pericarditis. Medicine 16:45–94, 1937.
232. Gooi HC, Smith JM: Tuberculous pericarditis in Birmingham. Thorax 33:94–96, 1978.
233. Mayosi BM, Ntsekhe M, Volmink JA, et al: Interventions for treating tuberculous pericarditis. Cochrane Database Syst Rev (4):CD000526, 2002.
234. Strang JI, Kakaza HH, Gibson DG, et al: Controlled trial of prednisolone as adjuvant in treatment of tuberculous constrictive pericarditis in Transkei. Lancet 2:1418–1422, 1987.
235. Strang JI, Kakaza HH, Gibson DG, et al: Controlled clinical trial of complete open surgical drainage and of prednisolone in treatment of tuberculous pericardial effusion in Transkei. Lancet 2:759–764, 1988.
236. Ferebee SH, Hopwood L, Palmer CE: Studies on prevention of experimental tuberculosis with isoniazid. II. Effects of different dosage regimens. Am Rev Tuberc 74:917–939, 1956.
237. Mount FW, Ferebee SH: Preventive effects of isoniazid in the treatment of primary tuberculosis in children. N Engl J Med 265:713–721, 1961.
238. Ferebee SH: Controlled chemoprophylaxis trials in tuberculosis: A general review. Bibl Tuberc 26:28–106, 1970.
239. Targeted tuberculin testing and treatment of latent tuberculosis infection. This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999. This is a Joint Statement of the American Thoracic Society (ATS) and the Centers for Disease Control and Prevention (CDC). This statement was endorsed by the Council of the Infectious Diseases Society of America (IDSA), September 1999, and the sections of this statement. Am J Respir Crit Care Med 161:S221–S247, 2000.
240. Allen S, Batungwanayo J, Kerlikowske K, et al: Two-year incidence of tuberculosis in cohorts of HIV-infected and uninfected urban Rwandan women. Am Rev Respir Dis 146:1439–1444, 1992.
241. Pape JW, Jean SS, Ho JL, et al: Effect of isoniazid prophylaxis on incidence of active tuberculosis and progression of HIV infection. Lancet 342:268–272, 1993.
242. Antonucci G, Girardi E, Raviglione MC, et al: Risk factors for tuberculosis in HIV-infected persons: A prospective cohort study. The Gruppo Italiano di Studio Tubercolosi e AIDS (GISTA). JAMA 274:143–148, 1995.
243. Guelar A, Gatell JM, Verdejo J, et al: A prospective study of the risk of tuberculosis among HIV-infected patients. AIDS 7:1345–1349, 1993.
244. Whalen CC, Johnson JL, Okwera A, et al: A trial of three regimens to prevent tuberculosis in Ugandan adults infected with the human immunodeficiency virus. Uganda–Case Western Reserve University Research Collaboration. N Engl J Med 337:801–808, 1997.
245. Gordin FM, Matts JP, Miller C, et al: A controlled trial of isoniazid in persons with anergy and human immunodeficiency virus infection who are at high risk for tuberculosis. Terry Beirn Community Programs for Clinical Research on AIDS. N Engl J Med 337:315–320, 1997.
246. Ferebee SH, Mount FW: Tuberculosis morbidity in a controlled trial of the prophylactic use of isoniazid among household contacts. Am Rev Respir Dis 85:490–510, 1962.
247. Egsmose T, Ang'awa JO, Poti SJ: The use of isoniazid among household contacts of open cases of pulmonary tuberculosis. Bull World Health Organ 33:419–433, 1965.
248. Katz J, Kunofsky S, Damijonaitis V, et al: Effect of isoniazid upon the reactivation of inactive tuberculosis: Final report. Am Rev Respir Dis 91:345–350, 1965.
249. Grzybowski S, Ashley MJ, Pinkus G: Chemoprophylaxis in inactive tuberculosis: Long-term evaluation of a Canadian trial. Can Med Assoc J 114:607–611, 1976.
250. International Union Against Tuberculosis: Efficacy of various durations of isoniazid preventive therapy for tuberculosis: Five years of follow-up in the IUAT trial. Bull World Health Organ 60:555–564, 1982.
251. Gomez-Reino JJ, Carmona L, Valverde VR, et al: Treatment of rheumatoid arthritis with tumor necrosis factor inhibitors may predispose to significant increase in tuberculosis risk: A multicenter active-surveillance report. Arthritis Rheum 48:2122–2127, 2003.
252. Halsey NA, Coberly JS, Desormeaux J, et al: Randomised trial of isoniazid versus rifampicin and pyrazinamide for prevention of tuberculosis in HIV-1 infection. Lancet 351:786–792, 1998.
253. Jasmer RM, Saukkonen JJ, Blumberg HM, et al: Short-course rifampin and pyrazinamide compared with isoniazid for latent tuberculosis infection: A multicenter clinical trial. Ann Intern Med 137:640–647, 2002.
254. Centers for Disease Control and Prevention: Use of short-course tuberculosis preventive therapy regimens in HIV-seronegative persons. JAMA 280:1736, 1998.
255. Second East African/British Medical Research Councils: Trial of BCG vaccines in South India for tuberculosis prevention: First report. Bull Int Union Tuberc 55:14–22, 1980.
256. Palmer CE, Long MW: Effects of infection with atypical mycobacteria on BCG vaccination and tuberculosis. Am Rev Respir Dis 94:553–568, 1966.
257. Lonnroth K, Raviglione M: Global epidemiology of tuberculosis: Prospects for control. Semin Respir Crit Care Med 29:481–491, 2008.
258. Zhang Y: Advances in the treatment of tuberculosis. Clin Pharmacol Ther 82:595–600, 2007.
259. Mitsuyama M, McMurray DN: Tuberculosis: Vaccine and drug development. Tuberculosis (Edinb) 87(Suppl 1):S10–S13, 2007.
260. Nuermberger E, Tyagi S, Tasneen R, et al: Powerful bactericidal and sterilizing activity of a regimen containing PA-824, moxifloxacin, and pyrazinamide in a murine model of tuberculosis. Antimicrob Agents Chemother 52:1522–1524, 2008.
261. Rustomjee R, Diacon AH, Allen J, et al: Early bactericidal activity and pharmacokinetics of the diarylquinoline TMC207 in treatment of pulmonary tuberculosis. Antimicrob Agents Chemother 52:2831–2835, 2008.
262. Spigelman MK: New tuberculosis therapeutics: A growing pipeline. J Infect Dis 196(Suppl 1):S28–S34, 2007.
263. Reece ST, Kaufmann SH: Rational design of vaccines against tuberculosis directed by basic immunology. Int J Med Microbiol 298:143–150, 2008.
264. Hoft DF: Tuberculosis vaccine development: Goals, immunological design, and evaluation. Lancet 372:164–175, 2008.

CHAPTER 34
APPENDIX

ESSENTIALS OF CHEMOTHERAPY

INTRODUCTION

The development of successful chemotherapy for tuberculosis must rank as one of the greatest achievements of medical science. Beginning in the late 1940s, chemotherapy began to slow down—little by little—the centuries' long and ever-growing toll from the incurable "captain of all these men of death," John Bunyan's name for the plague that has killed an estimated 2 billion human beings: more, by far, than any other disease. Notable victims included kings and princes, cardinals, famous poets, writers, musicians, and artists, and, of course, countless anonymous poor people. Finding a cure for this scourge did not happen easily, quickly, or by serendipity. It was the cumulative work over decades by many men and women dedicated to that single purpose, and—keep this in mind—these efforts are ongoing. The history of the initial taming of tuberculosis and why the task remains unfinished makes fascinating reading, especially in the accounts of Dubos and Dubos,[1] Ryan,[2] and Daniel.[3]

Even though effective treatment has been available for more than 50 years, tuberculosis continues to plague vulnerable regions of the world. More and more strains of disease-producing *Mycobacterium tuberculosis* are resistant to standard antituberculosis regimens: some strains are resistant to nearly all available agents. A glance at the most recent statistics—an estimated 9.27 million new cases; 1.3 million deaths among human immunodeficiency virus (HIV)–uninfected persons and 456,000 among HIV-infected persons; and 511,000 cases of multiresistant disease in the year 2007—reveals how much work remains to be done.[4]

BEGINNINGS

To understand where we currently stand and to appreciate the enormity of the task ahead, this appendix provides a brief chronology of the use of chemotherapy for treating tuberculosis, starting with streptomycin, the original breakthrough agent, which was first injected into a desperately ill young woman in November 1944. To everyone's astonishment and relief, she did not die but slowly began to recover. Then, miraculously, so did others.[5]

But within a few years, after many more patients with tuberculosis had been treated with streptomycin, it became apparent that the striking clinical and radiographic improvement observed initially did not always last; after several months of treatment, patients began to worsen and the reason was immediately obvious: their tubercle bacilli had become resistant to streptomycin.[6] The findings of clinical failure and emergence of drug resistance served to define the major bacteriologic principle on which successful chemotherapy for tuberculosis depends: bacillary populations are not uniform in their susceptibility to antituberculosis agents; hence, it is always necessary to treat active disease with more than one drug to which the organisms are susceptible.

The concept of multiple-drug chemotherapy was first validated in 1950 by a British Medical Research Council study in which streptomycin was partnered with *para*-aminosalicylic acid, better known as PAS: long-lasting success occurred because PAS prevented organisms from becoming resistant to streptomycin and vice versa, and two drugs have more clinical clout than only one.[7] Since that time, treatment with more than one drug has been standard in the management of patients with tuberculosis. Although the combination of streptomycin and PAS was effective, neither agent was well tolerated and clinical improvement was slow and hampered by side effects. The long-sought solution to antituberculosis chemotherapy arrived in 1952 with the introduction of isoniazid, a powerful drug that was not only highly effective, but well tolerated and inexpensive.[8] However, once again it was learned that single-drug treatment with isoniazid was inadequate because resistance to the agent developed quickly. The solution was clear: combine isoniazid with both streptomycin and PAS. This triple therapy became the standard treatment for tuberculosis until 1967, when a new antituberculosis agent, ethambutol, an easily tolerated and minimally toxic drug, was welcomed as a substitute for PAS.[9]

Subsequent experiments have shown that, in any wild strain of *M. tuberculosis,* the frequency of drug-resistant mutants is 1 in 3.5×10^6 for isoniazid, 1 in 3.8×10^6 for streptomycin, 1 in 3.1×10^8 for rifampin, and 1 in $0.5 \times$

10^4 for ethambutol.[10] Thus, a bacillary population of more than 10^{12} organisms would be required before one would expect to find (statistically) a single bacillus resistant to both isoniazid and streptomycin.

Once optimum doses of each component were established, wide use of triple therapy revolutionized the care of patients with tuberculosis. Springett[11] reviewed death rates from tuberculosis for cohorts of patients in Birmingham, England, for the years 1947, 1950, 1953, 1956, and 1959. With increasing use of antituberculosis chemotherapy, deaths decreased dramatically during the 10 years after diagnosis, and nearly all of the reduction was accounted for by improvements in survival during the first year after diagnosis. In addition, not only were survivors more numerous, but among survivors, far fewer than in the prechemotherapy era continued to be potential sources of new infections. In the Springett study, both the decrease in mortality rate and the reduction in the prevalence of chronically infectious patients reached their maximum in 1956, with no further improvement in 1959.

The next major advance in chemotherapy for pulmonary tuberculosis resulted from the discovery of rifampin (or rifampicin, as it is known in many parts of the world) and the demonstration that the combination of isoniazid and rifampin, generally with ethambutol or streptomycin, could dramatically shorten the necessary duration of treatment.[12] In a series of important studies from East Africa during the 1970s, the British Medical Research Council established that a 6-month regimen consisting of isoniazid, streptomycin, and rifampin was as effective as the standard regimen used at the time in developing countries (18 months of isoniazid and thiacetazone, plus streptomycin given during the first 2 months).[13]

A critical factor influencing the effectiveness of chemotherapy was, and continues to be, the adherence (or lack thereof) of patients to the prescribed regimen, a fact well documented both in the United States and in developing countries.[14,15] In spite of initial high rates of success elsewhere, the results of a U.S. Public Health Service multicenter cooperative trial indicated that a 6-month regimen of isoniazid and rifampin did not have an acceptable rate of favorable outcome.[16] Positive cultures were found in 6.1% of the patients between 3 and 6 months after treatment began. Of greater importance was that 9.2% experienced relapse after completion of treatment. Strikingly, 16.8% of the patients were withdrawn from the study because they had been delinquent about clinic visits during the 6 months of treatment. This outcome was a setback for efforts to shorten the duration of treatment to 6 months, which—assuming equal effectiveness and tolerance—would have considerable clinical and logistical advantages over 18- to 24-month regimens.

Studies of chemotherapy then began to focus on the possible benefits of pyrazinamide.[17] Dickinson and coworkers[18] demonstrated that streptomycin, rifampin, and isoniazid are quickly bactericidal for rapidly growing *M. tuberculosis* in vitro. The in vitro conditions could be likened to the conditions under which the extracellular organisms in tuberculous lesions are living. Although both rifampin and isoniazid are rapidly bactericidal, Mitchison and Dickinson[19] demonstrated that rifampin is more effective in killing organisms that grow in spurts rather than continuously. Although both isoniazid and rifampin are effective in killing intracellular organisms, pyrazinamide is especially effective for this purpose, suggesting that the addition of pyrazinamide would strengthen the isoniazid-rifampin combination. Subsequently, two studies substantiated the fact that the addition of pyrazinamide for 2 months to a regimen of isoniazid and rifampin does indeed improve the effectiveness of a 6-month regimen.[20,21] Thus, a 6-month regimen of isoniazid and rifampin supplemented by pyrazinamide and ethambutol for the initial 2 months is now recommended as standard treatment for most patients with newly diagnosed pulmonary tuberculosis.[22,23]

DRUGS IN CURRENT USE

As shown in Table 34A-1, 10 drugs currently are approved by the U.S. Food and Drug Administration for treating tuberculosis, and 6 other drugs are effective but not approved for this indication. The table lists both first- and second-line drugs, the available preparations, and the doses currently used to treat tuberculosis.

First-Line Drugs

Isoniazid is the most widely used of all antituberculosis agents. It is very effective, specific for some mycobacteria, relatively nontoxic, easily administered, and inexpensive. Isoniazid is highly active against *M. tuberculosis:* most strains are inhibited by concentrations of 0.05 to 0.20 μg/mL, and it has profound early bactericidal activity. The drug is readily absorbed from the gastrointestinal tract; peak blood concentrations of approximately 5 μg/mL occur 1 to 2 hours after administration of 3 to 5 mg/kg of body weight. The serum half-life varies depending on whether a person is a rapid or slow acetylator: half-lives are 2 to 4 hours in slow acetylators and 0.5 to 1.5 hours in rapid acetylators.[24] The drug penetrates well into all body fluids and cavities, producing concentrations similar to those found in serum. Isoniazid presumably exerts its effect by inhibiting an enzyme, mycolate synthetase. The genetic bases for the action of isoniazid and for microbial resistance to the drug have been at least partially explained. Zhang and coworkers[25] and Heym and associates[26] demonstrated that the gene for the catalase-peroxidase enzyme (*katG*) was deleted in some isoniazid-resistant strains of *M. tuberculosis,* which suggests that isoniazid requires intracellular conversion to an active form by the enzyme. However, subsequent studies have shown that most isoniazid-resistant strains have not lost the *katG* gene. Rather, a number of *katG* polymorphisms have been identified, at least some of which are associated with isoniazid resistance.[27,28]

Mutations in the *inhA* gene provide a second genetic mechanism for isoniazid resistance. The product of this gene is thought to be an enoyl reductase that is involved

TABLE 34A-1. Doses* of Antituberculosis Drugs for Adults and Children†

Drug	Preparation		Daily	WEEKLY 1×	WEEKLY 2×	WEEKLY 3×
FIRST-LINE DRUGS						
Isoniazid	Tablets (50 mg, 100 mg, 300 mg); elixir (50 mg/5 mL); aqueous solution (100 mg/mL) for IV or IM injection.	Adults (max.)	5 mg/kg (300 mg)	15 mg/kg (900 mg)	15 mg/kg (900 mg)	15 mg/kg (900 mg)
		Children (max.)	10–15 mg/kg (300 mg)	—	20–30 mg/kg (900 mg)	—
Rifampin	Capsule (150 mg, 300 mg). Powder may be suspended for oral administration. Aqueous solution for IV injection.	Adults‡ (max.)	10 mg/kg (600 mg)	—	10 mg/kg (600 mg)	10 mg/kg (600 mg)
		Children (max.)	10–20 mg/kg (600 mg)	—	10–20 mg/kg (600 mg)	—
Rifabutin	Capsule (150 mg)	Adults‡ (max.)	5 mg/kg (300 mg)	—	5 mg/kg (300 mg)	5 mg/kg (300 mg)
		Children	Appropriate dosing for children is unknown.			
Rifapentine	Tablet (150 mg film coated)	Adults	—	10 mg/kg (continuation phase) (600 mg)	—	—
		Children	The drug is not approved for use in children.			
Pyrazinamide	Tablet (500 mg scored)	Adults	20–30 mg/kg (2 g)	—	40–50 mg/kg (4 g)	30–45 mg/kg (3 g)
		Children (max.)	15–30 mg/kg (2 g)	—	50 mg/kg (4 g)	—
Ethambutol	Tablet (100 mg, 400 mg)	Adults	15–20 mg/kg (1.6 g)	—	40–50 mg/kg (2.4 g)	25–35 mg/kg (2.4 g)
		Children§ (max.)	20 mg/kg daily (1 g)	—	50 mg/kg (4 g)	—
SECOND-LINE DRUGS						
Cycloserine	Capsule (250 mg)	Adults (max.)	10–15 mg/kg/day (1.0 g in two doses), usually 500–750 mg/day in two doses¶	There are no data to support intermittent administration.		
		Children (max.)	10–15 mg/kg/day (1.0 g/day)	—	—	—
Ethionamide	Tablet (250 mg)	Adults (max.)	15–20 mg/kg/day (1.0 g/day), usually 500–750 mg/day in a single daily dose or two divided doses¶	There are no data to support intermittent administration.		
		Children (max.)	15–20 mg/kg/day (1.0 g/day)			

*Dose per weight is based on ideal body weight. Children weighing more that 40 kg should be dosed as adults.
†For purposes of this document, adult dosing begins at age 15 years.
‡Dose may need to be adjusted when there is concomitant use of protease inhibitors or non-nucleoside reverse transcriptase inhibitors.
§The drug can likely be used safely in older children but should be used with caution in children under 5 years, in whom visual acuity cannot be monitored. In younger children, ethambutol at the dose of 15 mg/kg/day can be used if there is suspected or proven resistance to isoniazid or rifampin.
¶It should be noted that, although this is the dose recommended generally, most clinicians with experience using cycloserine indicate that it is unusual for patients to be able to tolerate this amount. Serum concentration measurements are often useful in determining the optimum dose for a given patient.
¶The single daily dose can be given at bedtime or with the main meal.

continued

TABLE 34A-1. Doses* of Antituberculosis Drugs for Adults and Children†—cont'd

Drug	Preparation		Daily	WEEKLY 1×	WEEKLY 2×	WEEKLY 3×
Streptomycin	Aqueous solution (1-g vials) for IM or IV administration.	Adults (max.)	15 mg/kg/day (1 g), and 10 mg/kg in persons >59 years of age (750 mg). Usual dose 750 mg–1.0 g IM or IV typically given as a single dose 5–7 days a week and reduced to 2–3 times a week after first 2–4 months or after culture conversion, depending on the efficacy of the other drugs in the regimen.			
		Children (max.)	20–40 mg/kg/day (1.0 g)	—	20 mg/kg	—
Amikacin/ Kanamycin	Aqueous solution (500-mg and 1-g vials) for IM or IV administration.	Adults (max.)	15 mg/kg/day (1 g), and 10 mg/kg in persons >59 years of age (750 mg). Usual dose 750 mg–1.0 g IM or IV typically given as a single dose 5–7 days a week and reduced to 2–3 times a week after first 2–4 months or after culture conversion, depending on the efficacy of the other drugs in the regimen.			
		Children (max.)	15–30 mg/kg/day (1.0 g) IM or IV as a single daily dose	—	15–30 mg/kg	—
Capreomycin	Aqueous solution (1-g vials) for IM or IV administration.	Adults (max.)	15 mg/kg/day (1 g), and 10 mg/kg in persons >59 years of age (750 mg). Usual dose 750 mg–1.0 g IM or IV typically given as a single dose 5–7 days a week and reduced to 2–3 times a week after first 2–4 months or after culture conversion, depending on the efficacy of the other drugs in the regimen.			
		Children (max.)	15–30 mg/kg/day (1.0 g) as a single daily dose	—	15–30 mg/kg	—
***para*-Aminosalicylic Acid (PAS)**	Granules (4-g packets) can be mixed with food. Tablets (500 mg) are still available in some countries, but not in the United States. A solution for IV administration is available in Europe.	Adults	8–12 g/day in 2 or 3 doses	There are no data to support intermittent administration.		
		Children	200–300 mg/kg/day in 2–4 divided doses (10 g)			
Levofloxacin	Tablets (250 mg, 500 mg, 750 mg); aqueous solution (500-mg vials) for IV injection.	Adults	500–1000 mg daily	There are no data to support intermittent administration.		
		Children	The long-term (>several weeks) use of levofloxacin in children and adolescents has not been approved because of concerns about effects on bone and cartilage growth. However, most experts agree that the drug should be considered for children with tuberculosis caused by organisms resistant to both isoniazid and rifampin. The optimal dose is not known.			
Moxifloxacin	Tablets (400 mg); aqueous solution (400 mg/250 mL) for IV injection.	Adults	400 mg daily	There are no data to support intermittent administration.		
		Children	The long-term (>several weeks) use of moxifloxacin in children and adolescents has not been approved because of concerns about effects on bone and cartilage growth. The optimal dose is not known.			
Gatifloxacin	Tablets (400 mg); aqueous solution (200 mg/20 mL; 400 mg/40 mL) for IV injection.	Adults	400 mg daily	There are no data to support intermittent administration.		
		Children	The long-term (>several weeks) use of gatifloxacin in children and adolescents has not been approved because of concerns about effects on bone and cartilage growth. The optimal dose is not known.			

Drugs in **bold** are approved by the U.S. Food and Drug Administration for treatment of tuberculosis.
Modified from Blumberg HM, Burman WJ, Chaisson RE, et al: American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: Treatment of tuberculosis. Am J Respir Crit Care Med 167:604–662, 2003.

in mycolic acid biosynthesis. Mutations of *inhA* usually are associated with low-level resistance to isoniazid and resistance to ethionamide as well, which suggests that the *inhA* product is also a target for ethionamide.[27]

When isoniazid is used alone, a population of organisms resistant to the drug emerges rapidly. This was demonstrated in an early clinical trial in which 11%, 52%, and 71% of patients to whom isoniazid alone was given developed resistant strains after 1, 2, and 3 months of treatment, respectively.[29]

Hepatitis is the major toxic effect of isoniazid.[22,30,31] Asymptomatic elevations of aminotransferase—up to five times the upper limit of normal—occur in 10% to 20% of persons receiving isoniazid alone for treatment of latent tuberculous infection.[32] The enzyme levels usually return to normal even with continued administration of the drug. Recent data indicate that the incidence of clinical hepatitis is lower than was previously thought. In 11,141 patients managed in an urban tuberculosis control program who were receiving isoniazid alone as treatment for latent tuberculous infection, hepatitis occurred in only 0.1% to 0.15%.[33] A meta-analysis of six studies estimated the rate of clinical hepatitis in patients given isoniazid to be only 0.6%.[34] The rate of clinical hepatitis was 1.6% when isoniazid was given with other agents, *not* including rifampin.[34] When isoniazid was given in combination with rifampin, the rate of clinical hepatitis averaged 2.7% in 19 reports. For isoniazid alone, the risk increases with increasing age; it is uncommon in persons under 20 years old but is nearly 2% in persons ages 50 to 64 years.[35] The risk may also be increased in persons with underlying liver disease, in those with a history of heavy alcohol consumption, and in the postpartum period, particularly among Hispanic women.[35,36] A large survey estimated the rate of fatal hepatitis to be 0.023%,[37] but more recent studies suggest the rate is substantially lower.[33] The risk may be increased in women. Death has been associated with continued administration of isoniazid well after the onset of symptoms of hepatitis.

Peripheral neuropathy, the second most frequent adverse reaction associated with isoniazid administration, occurs especially in persons with other disorders that may cause neuropathy (HIV infection, diabetes mellitus, uremia, and alcoholism). The neuropathy can be prevented or reversed by administration of pyridoxine 25 mg/day.

Rifampin is also rapidly bactericidal for *M. tuberculosis.* The drug is easily administered and is relatively nontoxic. It is quickly absorbed from the gastrointestinal tract; serum concentrations of 6 to 7 μg/mL occur 1.5 to 2 hours after ingestion. The half-time in blood is 3 to 3.5 hours, although this may be decreased in persons who have been taking the drug for several weeks.[38] The half-time increases with increasing doses of the drug. For sensitive strains of *M. tuberculosis,* the minimum inhibitory concentration of rifampin is approximately 0.5 μg/mL, although there is variation among strains.[39] Approximately 75% of the drug is protein bound, but it penetrates well into tissues and cells. Penetration through noninflamed meninges is poor; however, therapeutic concentrations are achieved in cerebrospinal fluid when the meninges are inflamed.[40]

Among susceptible strains of *M. tuberculosis,* the rate of mutation seems to be less for rifampin than for isoniazid. David[10] reported the rate of mutation to rifampin resistance to be approximately 10×10^{10} per bacterium per generation. In spite of this rather low rate of in vitro mutation, resistance rapidly develops when rifampin is used alone in vivo.[41] Resistance to rifampin unaccompanied by resistance to other antituberculosis drugs has been reported to occur almost exclusively among patients with HIV infection, particularly among patients being treated with once- or twice-weekly intermittent regimens.[42–44]

Rifampin exerts its effect by binding to the β-subunit of RNA polymerase.[27] For this reason, it has activity against many bacteria other than *M. tuberculosis.* Resistance to rifampin results from mutations in the *rpoB* gene, the product of which is the β-subunit of RNA polymerase. Although many different mutations may be involved, alterations in *rpoB* have been shown to account for approximately 96% of the rifampin-resistant strains isolated from patients in many different parts of the world.[27] The mechanism for resistance in the remaining 4% is not known.

Adverse reactions to rifampin when it is given daily include rashes, hepatitis, gastrointestinal upset, and, rarely, thrombocytopenia. The rates of these reactions have been variable, but in general are quite low.[22] Hepatitis occurred in 3.1% of the patients in the U.S. Public Health Service study of 6-month isoniazid-rifampin treatment.[16] Intermittent (twice-weekly) administration of higher doses of rifampin is associated with several immunologically mediated reactions, including thrombocytopenia, an influenza-like syndrome, hemolytic anemia, and acute renal failure.[45]

Drug-drug interactions due to induction of hepatic microsomal enzymes by rifampin are relatively common and are of particular concern in patients with HIV infection. The rifamycins—rifampin, rifabutin, and rifapentine—interact with the protease inhibitor and nonnucleoside reverse transcriptase inhibitor classes of antiretroviral agents.[22] The interaction of these classes of drugs is bidirectional: protease inhibitors decrease clearance of rifamycins, and rifamycins accelerate clearance of protease inhibitors by inducing hepatic P-450 cytochrome oxidases.[46] Of the rifamycin derivatives, rifabutin has the least effect on the concentration of antiretroviral agents. The practical implications of these interactions on treatment regimens are discussed in both Chapters 34 and 80. Rifampin induces the metabolism of a number of other drugs, including methadone, warfarin, oral contraceptives, digoxin, macrolide antibiotics, and ketoconazole.[22] (A complete list of interactions with the rifamycins is found in Blumberg and colleagues.[22]) Doses of these drugs need to be adjusted when rifampin is given. Ketoconazole and, to a lesser extent, fluconazole interfere with absorption of rifampin, thereby decreasing its serum concentration.

Rifabutin, although not approved by the U.S. Food and Drug Administration for the treatment of tuberculo-

sis, may be used as a substitute for rifampin in most treatment regimens.[22] Because of its lesser propensity to induce cytochrome P-450 enzymes, rifabutin is generally reserved for patients who are taking any medication for which there are unacceptable interactions with rifampin. It may also be used for patients who are intolerant of rifampin. There is nearly complete cross-resistance among the rifamycins for *M. tuberculosis.* The toxicity profile of rifabutin is similar to that of rifampin except that, in some studies with HIV-infected patients, neutropenia has been reported and uveitis has been described when the drug is given with a macrolide antibiotic that reduces rifabutin clearance.[22]

Rifapentine, which has the longest serum half-life of the rifamycins, has been shown to be effective in combination with isoniazid given once weekly in the continuation phase of treatment for pulmonary tuberculosis.[47] However, it should be emphasized that this regimen is *not* to be used for patients with HIV infection, patients who have cavitary lesions on chest film, or patients who have positive sputum smears at the end of the 2-month initial phase of treatment. The toxicity profile is similar to that of rifampin.

Ethambutol in usual doses of 15 mg/kg of body weight is generally considered to have a static effect on *M. tuberculosis.* The drug is easily administered and has a low frequency of adverse reactions. Its main effect is to reduce the risk of rifampin resistance in patients with tuberculosis caused by strains that have primary resistance to isoniazid. Peak plasma concentrations occur 2 to 4 hours after ingestion. With doses of 15 mg/kg, the peak concentration is approximately 4 μg/mL.[48] The concentration increases proportionally with increasing doses. In persons with normal renal function, the half-time in blood is approximately 4 hours. Minimum inhibitory concentrations of the drug for *M. tuberculosis* range from 1 to 5 μg/mL. Protein binding is minimal, but penetration into cells is thought to be poor. Cerebrospinal fluid concentrations of ethambutol, even in the presence of meningeal inflammation, are low, averaging 1 to 2 μg/mL after a dose of 25 mg/kg.[49] Like isoniazid, ethambutol appears to exert its effect by interfering with cell wall biosynthesis. Specifically, the target for ethambutol is thought to be an arabinosyltransferase. Mutations in the *embB* gene that, together with *embA* and *embC,* codes for arabinosyltransferases are found in approximately 70% of ethambutol-resistant strains.[27]

Retrobulbar neuritis is the main adverse effect of ethambutol. Symptoms include blurred vision, central scotomata, and red-green color blindness. This complication is dose related, occurring in 15% of patients given 50 mg/kg, 1% to 5% of those given 25 mg/kg, and less than 1% in those given 15 mg/kg.[22] The frequency of ocular effects is increased in patients with renal failure, presumably owing to increased serum concentrations of the drug.

Streptomycin is rapidly bactericidal, although its effectiveness is inhibited by an acid pH.[22] Because the drug is not absorbed from the gut, it must be given parenterally. Peak serum concentrations occur approximately 1 hour after an intramuscular dose. With a dose of 15 mg/kg, the peak concentration is in the range of 40 μg/mL. The half-time in blood is approximately 5 hours. Sensitive strains of *M. tuberculosis* are inhibited by streptomycin in a concentration of 8 μg/mL. The drug has good tissue penetration; however, it enters the cerebrospinal fluid only in the presence of meningeal inflammation. Streptomycin and ethambutol have been found to be of approximately equal effectiveness in combination regimens; however, because of a relatively high prevalence of resistance to streptomycin, particularly in patients from developing countries, its usefulness is limited. For this reason and because it requires parenteral administration, streptomycin is no longer considered a first-line agent in treating tuberculosis.[22]

Streptomycin exerts its effect by interfering with ribosomal protein synthesis. This effect is mediated by binding of the drug to 16S ribosomal RNA (rRNA), thereby inhibiting initiation of translation. Mutations in the genes that code for 16S rRNA (*rrs* and *rpsL*) have been found in 65% to 77% of resistant strains. Mutations in *rpsL* have been associated with high-level streptomycin resistance, whereas low-level resistance has been associated with *rrs* mutations.[27] More recently, mutations in the gene *gid*B were found to be associated with low-level streptomycin resistance. This gene encodes a methyltransferase specific for the 16S rRNA. The available data indicate that *gid*B mutations emerge spontaneously at a high frequency of 10^{-6}.[50]

The most serious adverse effect of streptomycin is ototoxicity.[22] This usually results in vertigo, but hearing loss may also occur. The risk of ototoxicity is related both to cumulative dosage and to peak serum concentrations. In general, peak concentrations of greater than 40 to 50 μg/mL should be avoided, and the total dose should not exceed 100 to 120 g.[22] Because of its effect on fetal auditory system development, streptomycin is contraindicated in pregnancy. Streptomycin should be used with caution in patients with renal insufficiency, in whom dosing frequency should be reduced to two to three times a week, because of increased risk of nephrotoxicity and ototoxicity.[22]

Pyrazinamide is active against *M. tuberculosis* at an acid pH, which suggests that the drug is activated under these conditions.[51] The drug is particularly active against dormant or semidormant *M. tuberculosis* in macrophages or in the acidic environment within areas of caseation, and is rapidly bacteriostatic but only slowly bactericidal. Absorption from the gastrointestinal tract is nearly complete; peak serum concentrations occur approximately 2 hours after ingestion. Concentrations generally range from 30 to 50 μg/mL with doses of 20 to 25 mg/kg. The serum half-life is 9 to 10 hours. At a pH of 5.5, the minimal inhibitory concentration of pyrazinamide for *M. tuberculosis* is 20 μg/mL. Penetration of the drug into cells and tissues seems to be fairly good, although data with regard to tissue concentrations are limited. Data suggest that there is no specific cellular target but that pyrazinamide disrupts the membrane energetics and acidification of cytoplasm.[52]

The genetic mechanism of mycobacterial resistance to pyrazinamide appears to be any of a large number of

mutations in the *pncA* gene, which encodes the enzyme pyrazinamidase. This enzyme appears to be necessary for the intracellular conversion of pyrazinamide to its active form. Mutations in the *pncA* gene are found in approximately 70% of pyrazinamide-resistant strains.[27,52]

The most important adverse reaction to pyrazinamide is liver injury. This appears to be a dose-related occurrence. In a large U.S. Public Health Service study in which pyrazinamide was given in a dose of 25 mg/kg daily for 6 months, hepatotoxicity occurred in 2% to 3% of patients.[53] At a dose of 40 mg/kg per day, also given for 6 months, 6% of patients developed hepatitis. All patients were also receiving isoniazid and PAS in addition to pyrazinamide. An increased frequency of hepatotoxicity has been reported in studies of pyrazinamide combined with rifampin in a 2-month treatment regimen for latent tuberculous infection in persons without HIV infection; accordingly, the indications for this regimen are very limited.

Because pyrazinamide impairs renal urate clearance, hyperuricemia occurs in nearly all patients taking the drug. Clinical gout is not common, but diffuse arthralgias, apparently unrelated to the hyperuricemia, occur frequently. The drug may also cause nausea and vomiting and skin rashes, especially photosensitive dermatitis.

Second-Line Drugs

Four additional agents approved for treating tuberculosis are available in the United States: PAS, ethionamide, cycloserine, and capreomycin. In addition, the fluoroquinolones, amikacin, and kanamycin have antituberculosis effects and have been used to a greater or lesser extent, generally in treating patients with tuberculosis caused by drug-resistant organisms. All these second-line drugs have important limitations—effectiveness, toxicity, and cost—that interfere with their general applicability in treating tuberculosis.[22]

Of the second-line drugs, the fluoroquinolones—levofloxacin, moxifloxacin, and gatifloxacin—are the most widely used, because all three agents possess good in vitro bactericidal activity and gatifloxacin and moxifloxacin have good in vivo bactericidal activity against *M. tuberculosis.*[54,55] The fluoroquinolones should not be considered as first-line agents but should be reserved either for patients with drug-resistant organisms or those who cannot tolerate first-line drugs.[22] A systematic analysis of the randomized controlled trials published until July of 2007 concluded that ciprofloxacin cannot be recommended for treating tuberculosis, and that information regarding other fluoroquinolones was too limited to make any recommendation.[56] However, results from a recent clinical study showed that an intensive phase with isoniazid, rifampin, pyrazinamide, and moxifloxacin was associated with a greater likelihood of negative culture after 4 weeks of treatment than the standard regimen of isoniazid, rifampin, pyrazinamide, and ethambutol, although the culture status at 2 months was similar in both groups.[57]

The target of the fluoroquinolones is DNA gyrase, an enzyme that operates to increase coiling of DNA. Resistance to these agents is mediated by mutations in *gyrA* and *gyrB* genes that encode for DNA gyrase.[27] Not many strains have been sequenced, but *gyrA* mutations have been found in 42% to 85% of resistant isolates.[27,58]

The quinolones are generally well tolerated. The most frequent adverse effects include nausea, vomiting, dizziness, anxiety, and other central nervous system effects. Photosensitivity and arthropathy may also occur. There are few clinical studies of the usefulness of quinolones in multiple-drug regimens. Optimal dosages and durations of quinolone administration are not known.

All of the other oral agents are difficult to administer because of adverse effects. It is strongly recommended that consultation with an expert be obtained before treatment with these drugs is undertaken.[22] Administration of PAS causes a high frequency of gastrointestinal upset plus hypersensitivity reactions in another 5% to 10% of patients. In addition, the usual dose of 10 to 12 g/day requires ingestion of 20 to 24 tablets, although administration has been made somewhat easier by the availability of a granular formulation. Ethionamide likewise causes a high frequency of gastrointestinal side effects, often necessitating discontinuation of the drug. Cycloserine causes behavioral disturbances, ranging from irritability and depression to frank psychosis, in a large percentage of patients taking the drug; moreover, seizures and peripheral neuropathy occur, especially with high doses and when cycloserine and isoniazid are given together. In addition to the adverse effects of PAS, ethionamide, and cycloserine, none of these drugs is particularly potent against *M. tuberculosis.* Kanamycin, amikacin, and capreomycin are not absorbed from the gastrointestinal tract and thus necessitate parenteral administration. All three drugs may cause hearing loss related both to peak concentrations and to cumulative doses and, in addition, may impair renal function.

Other unapproved but possibly useful antituberculosis agents include the β-lactam imipenem, the β-lactam/β-lactamase combination amoxicillin-clavulanate, and linezolid.[59-61] These agents have been used in small numbers of patients with tuberculosis caused by multidrug-resistant organisms. However, their role in the treatment of tuberculosis has not been precisely determined. The currently available compounds of the macrolide class of agents, which are useful against *Mycobacterium avium* complex, do not have antituberculosis effects.

PROGRAMMATIC CONSIDERATIONS

The availability of powerful antituberculosis medications made it possible to cure around 95% patients with disease caused by susceptible organisms, but it soon became apparent that drugs alone are insufficient: they are but one key element in a comprehensive tuberculosis control program. As far back as 1959, at the landmark Arden House Conference, the basic components of a national public health program were defined with, as a long-range goal, the eradication of tuberculosis in the United States.[62] Twenty years later, another conference

reviewed and refined the objectives and proposed new control strategies.[63] At practically the same time, effective national tuberculosis control programs were introduced into resource-poor countries by the International Union Against Tuberculosis and Lung Disease[64]; much later, the concepts that made these programs so efficacious were adopted, updated, and promoted by the World Health Organization (WHO) under the rubric Directly Observed Treatment Short-course, more familiarly known as DOTS.

Not surprisingly, the lessons from all these activities were similar. Among them, the most important programmatic principle is the obligation of the health care system or treating physician to provide effective supervision of therapy *from beginning to end.* Because of inadequacies both in the provision of tuberculosis control services and in private physician supervision of treatment, completion of therapy is often problematic.[65] As perhaps an extreme example, at Harlem Hospital in New York during the late 1980s, 89% of patients with tuberculosis who had been started on appropriate treatment were lost to follow-up after discharge, in large part owing to cutbacks in funding of outpatient services.[66] Obviously, failure to continue medications precludes successful therapy and promotes the emergence of drug-resistant organisms as, in fact, occurred in New York City.

Even in well-organized tuberculosis control programs, ensuring patient adherence to therapy often presents a difficult problem. The reasons for poor adherence are complex and numerous. Prediction of who will be compliant and who will not is difficult and generally unreliable. To improve adherence, a number of modifications in the organization of treatment have been tried, with varying degrees of success.[67] These include setting clinic hours to suit the patient's schedule; directly observing treatment in the clinic, the patient's home, or another location; and offering incentives and enablers, such as meals and transportation reimbursements.[22] Although all of these approaches, as well as others, have had their successes, it is obvious that compliance will remain a major problem as long as treatment regimens continue to be lengthy and cumbersome. It has come to be generally accepted that the best means of ensuring completion of therapy is giving the drugs under "directly observed therapy," or DOT,[22,23] which is one of the essential elements of the WHO's DOTS global tuberculosis control strategy, mentioned earlier.[68] Globally it was estimated that, in 2007, 93% of the world's population had access to DOTS services but only 63% of the estimated total number of smear-positive cases were reported by DOTS programs.[4] The use of the DOTS strategy has been associated with improved treatment outcomes in several cohort analyses.[15,69,70] However, a Cochrane review of 11 trials with 5609 patients did not show a significant difference in the cure of patients who were treated with observed therapy compared with self-administration.[71] These results highlight the fact that simply observing medication ingestion does not ensure successful completion of treatment and that the full range of measures for supporting patients in completion of treatment must be employed.[72]

Because of heightened public health concerns regarding transmission of *M. tuberculosis* by noncompliant patients and, in particular, concern about multidrug-resistant organisms, public health statutes that could require DOT or, in some instances, confinement until treatment is completed were strengthened in the early 1990s.[73,74] A review of the use and usefulness of these laws in New York City has shown that they were not abused and added significantly to the ability of health authorities to improve treatment outcome and minimize spread of tuberculous infection.[74]

IMPORTANCE OF COMPLETION

Effective chemotherapy is the major mechanism by which the spread of tuberculous infection is halted; thus, treatment of tuberculosis serves as an important public health measure.[72] For antituberculosis chemotherapy to be effective in this public health role, it must be carried out properly. Tuberculosis is one of the few diseases for which a little treatment may be worse than no treatment. Grzybowski and Enarson[75] reviewed the literature and determined the outcome of treatment for tuberculosis in three groups of patients who had positive acid-fast bacillus (AFB) smears: patients who had no chemotherapy at all; patients who were treated in poorly organized programs; and patients who were treated individually with the best available regimens. Among untreated patients, approximately 50% died in 4 to 5 years; 25% remained chronically ill with positive sputum smears and thus continued to be infectious; and the disease resolved spontaneously in the remaining 25%. The outcome in poorly organized programs differed in that the death rate was decreased, but the percentage of patients who continued to have *M. tuberculosis* in their sputum was actually increased; because poor treatment is a major factor in causing drug resistance, it is likely that a large proportion of the patients with chronically positive sputum had drug-resistant organisms. Top-notch programs, in contrast, hugely reduced both the death rate from tuberculosis *and* the number of chronically infectious patients with AFB-positive sputum.

References

1. Dubos R, Dobos J: The White Plague: Tuberculosis, Man, and Society. New Brunswick, NJ: Rutgers University Press, 1996.
2. Ryan F: The Forgotten Plague: How the Battle Against Tuberculosis Was Won and Lost. Boston: Little Brown, 1992.
3. Daniel TM: Captain of Death: The Story of Tuberculosis. Rochester, NY: University of Rochester Press, 1997.
4. World Health Organization: Global tuberculosis control 2008: epidemiology, strategy, financing. WHO Report 2009 (WHO/HTM/TB/2009.411). Geneva: World Health Organization, 2009.
5. Hinshaw HC, Feldman WH: Streptomycin in the treatment of clinical tuberculosis: A preliminary report. Proc Staff Meet Mayo Clin 20:313–318, 1945.
6. McDermott W, Muschenheim C, Hadley SJ: Streptomycin in the treatment of tuberculosis in humans: I. Meningitis and generalized hematogenous tuberculosis. Ann Intern Med 27:769–822, 1947.
7. Treatment of pulmonary tuberculosis with streptomycin and para-aminosalicylic acid; a Medical Research Council investigation. Br Med J 2:1073–1085, 1950.

8. Robitzek EH, Selikoff IJ: Hydrazine derivatives of isonicotinic acid (rimifon marsilid) in the treatment of active progressive caseous-pneumonic tuberculosis; a preliminary report. Am Rev Tuberc 65:402–428, 1952.
9. Bobrowitz ID, Robins DE: Ethambutol-isoniazid versus PAS-isoniazid in original treatment of pulmonary tuberculosis. Am Rev Respir Dis 96:428–438, 1967.
10. David HL: Probability distribution of drug-resistant mutants in unselected populations of *Mycobacterium tuberculosis*. Appl Microbiol 20:810–814, 1970.
11. Springett VH: Ten-year results during the introduction of chemotherapy for tuberculosis. Tubercle 52:73–87, 1971.
12. Fox W, Mitchison DA: Short-course chemotherapy for pulmonary tuberculosis. Am Rev Respir Dis 111:325–353, 1975 [published erratum appears in Am Rev Respir Dis 111:845–848, 1975].
13. Fox W, Ellard GA, Mitchison DA: Studies on the treatment of tuberculosis undertaken by the British Medical Research Council tuberculosis units, 1946–1986, with relevant subsequent publications. Int J Tuberc Lung Dis 3:S231–S279, 1999.
14. Volmink J, Matchaba P, Garner P: Directly observed therapy and treatment adherence. Lancet 355:1345–1350, 2000.
15. Chaulk CP, Moore-Rice K, Rizzo R, et al: Eleven years of community-based directly observed therapy for tuberculosis. JAMA 274:945–951, 1995.
16. Snider DE Jr, Long MW, Cross FS, et al: Six-months isoniazid-rifampin therapy for pulmonary tuberculosis: Report of a United States Public Health Service Cooperative Trial. Am Rev Respir Dis 129:573–579, 1984.
17. Mackaness GB: The intracellular activation of pyrazinamide and nicotinamide. Am Rev Tuberc 74:718–728, 1956.
18. Dickinson JM, Aber VR, Mitchison DA: Bactericidal activity of streptomycin, isoniazid, rifampin, ethambutol, and pyrazinamide alone and in combination against *Mycobacterium tuberculosis*. Am Rev Respir Dis 116:627–635, 1977.
19. Mitchison DA, Dickinson JM: Short term chemotherapy of tuberculosis: Bactericidal mechanisms in short term chemotherapy. Bull Int Union Tuberc 53:270–275, 1978.
20. Snider DE, Graczyk J, Bek E, et al: Supervised six-months treatment of newly diagnosed pulmonary tuberculosis using isoniazid, rifampin, and pyrazinamide with and without streptomycin. Am Rev Respir Dis 130:1091–1094, 1984.
21. Combs DL, O'Brien RJ, Geiter LJ: USPHS Tuberculosis Short-Course Chemotherapy Trial 21: Effectiveness, toxicity, and acceptability. The report of final results. Ann Intern Med 112:397–406, 1990.
22. Blumberg HM, Burman WJ, Chaisson RE, et al: American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: Treatment of tuberculosis. Am J Respir Crit Care Med 167:603–662, 2003.
23. World Health Organization: Treatment of Tuberculosis: Guidelines for National Programmes (3rd ed). Geneva: World Health Organization, 2003.
24. Ellard GA: Variations between individuals and populations in the acetylation of isoniazid and its significance for the treatment of pulmonary tuberculosis. Clin Pharmacol Ther 19:610–625, 1976.
25. Zhang Y, Heym B, Allen B, et al: The catalase-peroxidase gene and isoniazid resistance of *Mycobacterium tuberculosis*. Nature 358:591–593, 1992.
26. Heym B, Zhang Y, Poulet S, et al: Characterization of the katG gene encoding a catalase-peroxidase required for the isoniazid susceptibility of *Mycobacterium tuberculosis*. J Bacteriol 175:4255–4259, 1993.
27. Ramaswamy S, Musser JM: Molecular genetic basis of antimicrobial agent resistance in *Mycobacterium tuberculosis:* 1998 update. Tuber Lung Dis 79:3–29, 1998.
28. Wei CJ, Lei B, Musser JM, et al: Isoniazid activation defects in recombinant *Mycobacterium tuberculosis* catalase-peroxidase (KatG) mutants evident in InhA inhibitor production. Antimicrob Agents Chemother 47:670–675, 2003.
29. Treatment of pulmonary tuberculosis with isoniazid; an interim report to the Medical Research Council by their Tuberculosis Chemotherapy Trials Committee. Br Med J 2:735–746, 1952.
30. Menzies D, Long R, Trajman A, et al: Adverse events with 4 months of rifampin therapy or 9 months of isoniazid therapy for latent tuberculosis infection: A randomized trial. Ann Intern Med 149:689–697, 2008.
31. Saukkonen JJ, Cohn DL, Jasmer RM, et al: An official ATS statement: Hepatotoxicity of antituberculosis therapy. Am J Respir Crit Care Med 174:935–952, 2006.
32. Mitchell JR, Zimmerman HJ, Ishak KG, et al: Isoniazid liver injury: Clinical spectrum, pathology, and probable pathogenesis. Ann Intern Med 84:181–192, 1976.
33. Nolan CM, Goldberg SV, Buskin SE: Hepatotoxicity associated with isoniazid preventive therapy: A 7-year survey from a public health tuberculosis clinic. JAMA 281:1014–1018, 1999.
34. Steele MA, Burk RF, DesPrez RM: Toxic hepatitis with isoniazid and rifampin: A meta-analysis. Chest 99:465–471, 1991.
35. Kopanoff DE, Snider DE Jr, Caras GJ: Isoniazid-related hepatitis: A U.S. Public Health Service cooperative surveillance study. Am Rev Respir Dis 117:991–1001, 1978.
36. Franks AL, Binkin NJ, Snider DE Jr, et al: Isoniazid hepatitis among pregnant and postpartum Hispanic patients. Public Health Rep 104:151–155, 1989.
37. Snider DE Jr, Caras GJ: Isoniazid-associated hepatitis deaths: A review of available information. Am Rev Respir Dis 145:494–497, 1992.
38. Acocella G, Pagani V, Marchetti M, et al: Kinetic studies on rifampicin. I. Serum concentration analysis in subjects treated with different oral doses over a period of two weeks. Chemotherapy 16:356–370, 1971.
39. Lorian V, Finland M: In vitro effect of rifampin on mycobacteria. Appl Microbiol 17:202–207, 1969.
40. D'Oliveira JJ: Cerebrospinal fluid concentrations of rifampin in meningeal tuberculosis. Am Rev Respir Dis 106:432–437, 1972.
41. Hobby GL, Lenert TF: The action of rifampin alone and in combination with other antituberculous drugs. Am Rev Respir Dis 102:462–465, 1970.
42. Acquired rifamycin resistance in persons with advanced HIV disease being treated for active tuberculosis with intermittent rifamycin-based regimens. MMWR Morb Mortal Wkly Rep 51:214–215, 2002.
43. Bradford WZ, Martin JN, Reingold AL, et al: The changing epidemiology of acquired drug-resistant tuberculosis in San Francisco, USA. Lancet 348:928–931, 1996.
44. Vernon A, Burman W, Benator D, et al: Acquired rifamycin monoresistance in patients with HIV-related tuberculosis treated with once-weekly rifapentine and isoniazid. Tuberculosis Trials Consortium. Lancet 353:1843–1847, 1999.
45. Girling DJ, Hitze KL: Adverse reactions to rifampicin. Bull World Health Organ 57:45–49, 1979.
46. Burman WJ, Jones BE: Treatment of HIV-related tuberculosis in the era of effective antiretroviral therapy. Am J Respir Crit Care Med 164:7–12, 2001.
47. Benator D, Bhattacharya M, Bozeman L, et al: Rifapentine and isoniazid once a week versus rifampicin and isoniazid twice a week for treatment of drug-susceptible pulmonary tuberculosis in HIV-negative patients: A randomised clinical trial. Lancet 360:528–534, 2002.
48. Lee CS, Gambertoglio JG, Brater DC, et al: Kinetics of oral ethambutol in the normal subject. Clin Pharmacol Ther 22:615–621, 1977.
49. Bobrowitz ID: Ethambutol in tuberculous meningitis. Chest 61:629–632, 1972.
50. Okamoto S, Tamaru A, Nakajima C, et al: Loss of a conserved 7-methylguanosine modification in 16S rRNA confers low-level streptomycin resistance in bacteria. Mol Microbiol 63:1096–1106, 2007.
51. McDermott W, Tompsett R: Activation of pyrazinamide and nicotinamide in acidic environments in vitro. Am Rev Tuberc 70:748–754, 1954.
52. Singh P, Mishra AK, Malonia SK, et al: The paradox of pyrazinamide: An update on the molecular mechanisms of pyrazinamide resistance in *Mycobacteria*. J Commun Dis 38:288–298, 2006.
53. United States Public Health Service Tuberculosis Therapy Trial: Hepatic toxicity of pyrazinamide used with isoniazid in tuberculous patients. Am Rev Respir Dis 80:371–387, 1959.
54. Moadebi S, Harder CK, Fitzgerald MJ, et al: Fluoroquinolones for the treatment of pulmonary tuberculosis. Drugs 67:2077–2099, 2007.

55. Zhang Y: Advances in the treatment of tuberculosis. Clin Pharmacol Ther 82:595–600, 2007.
56. Ziganshina LE, Squire SB: Fluoroquinolones for treating tuberculosis. Cochrane Database Syst Rev 1:CD004795, 2008.
57. Burman WJ, Goldberg S, Johnson JL, et al: Moxifloxacin versus ethambutol in the first 2 months of treatment for pulmonary tuberculosis. Am J Respir Crit Care Med 174:331–338, 2006.
58. Ginsburg AS, Grosset JH, Bishai WR: Fluoroquinolones, tuberculosis, and resistance. Lancet Infect Dis 3:432–442, 2003.
59. Chambers HF, Kocagoz T, Sipit T, et al: Activity of amoxicillin/clavulanate in patients with tuberculosis. Clin Infect Dis 26:874–877, 1998.
60. Chambers HF, Turner J, Schecter GF, et al: Imipenem for treatment of tuberculosis in mice and humans. Antimicrob Agents Chemother 49:2816–2821, 2005.
61. Condos R, Hadgiangelis N, Leibert E, et al: Case series report of a linezolid-containing regimen for extensively drug-resistant tuberculosis. Chest 134:187–192, 2008.
62. Arden House Conference on Tuberculosis. (DHEW Publication No. PHS784). Washington, DC: U.S. Department of Health, Education and Welfare, 1960.
63. Kearns TJ, Russo PK: The control and eradication of tuberculosis: A summary report. N Engl J Med 303:812–814, 1980.
64. Enarson DA: Principles of IUATLD collaborative tuberculosis programmes. Bull Int Union Tuberc 66:195–200, 1991.
65. Munro SA, Lewin SA, Smith HJ, et al: Patient adherence to tuberculosis treatment: A systematic review of qualitative research. PLoS Med 4:e238, 2007.
66. Brudney K, Dobkin J: Resurgent tuberculosis in New York City: Human immunodeficiency virus, homelessness, and the decline of tuberculosis control programs. Am Rev Respir Dis 144:745–749, 1991.
67. Garner P, Smith H, Munro S, et al: Promoting adherence to tuberculosis treatment. Bull World Health Organ 85:404–406, 2007.
68. Raviglione MC, Uplekar MW: WHO's new Stop TB strategy. Lancet 367:952–955, 2006.
69. Results of directly observed short-course chemotherapy in 112,842 Chinese patients with smear-positive tuberculosis. China Tuberculosis Control Collaboration. Lancet 347:358–362, 1996.
70. Weis SE, Slocum PC, Blais FX, et al: The effect of directly observed therapy on the rates of drug resistance and relapse in tuberculosis. N Engl J Med 330:1179–1184, 1994.
71. Volmink J, Garner P: Directly observed therapy for treating tuberculosis. Cochrane Database Syst Rev 4:CD003343, 2007.
72. Hopewell PC, Pai M, Maher D, et al: International standards for tuberculosis care. Lancet Infect Dis 6:710–725, 2006.
73. Gostin LO: Controlling the resurgent tuberculosis epidemic: A 50-state survey of TB statutes and proposals for reform. JAMA 269:255–261, 1993.
74. Gasner MR, Maw KL, Feldman GE, et al: The use of legal action in New York City to ensure treatment of tuberculosis. N Engl J Med 340:359–366, 1999.
75. Grzybowski S, Enarson DA: Results in pulmonary tuberculosis patients under various treatment program conditions. Bull Int Union Tuberc 53:70–75, 1978.

CHAPTER 35

NONTUBERCULOUS MYCOBACTERIAL INFECTIONS

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INTRODUCTION

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INTRODUCTION

Soon after the discovery of *Mycobacterium tuberculosis* in 1882 by Robert Koch, several other species of mycobacteria were described. It was not until half a century later, however, that these mycobacteria were recognized to cause disease in humans, and by the 1980s they were recognized as causing a broad spectrum of disease.[1] Over the years, these organisms have gone by many names, including "mycobacteria other than tuberculosis," "environmental mycobacteria," "anonymous or atypical mycobacteria," and "nontuberculous mycobacteria" (NTM), the preferred term in the United States. The epidemic of the human immunodeficiency virus (HIV) heralded a new awareness of NTM infections because of the highs rates of disseminated infections due to *Mycobacterium avium* complex[2] (or, as commonly abbreviated, MAC) and other species.[3] On the one hand, disseminated NTM infections have declined significantly in HIV-infected populations following the advent of antiretroviral drugs; on the other hand, rates of NTM disease in HIV-uninfected populations appear to be on the increase.

NTM represent a broad array of organisms that are ubiquitous in our environment. They have been isolated from natural and drinking waters as well as soil, and exposure to these reservoirs is thought to be the source of human infection. At least 140 species of NTM have been identified, and many of these have been reported to cause disease in both immunocompetent and immunocompromised patients. Unlike *M. tuberculosis,* NTM do not appear to be transmitted from human to human, they vary greatly in their ability to cause disease, and evidence for latency is lacking. Unfortunately, NTM are difficult to treat because of high levels of in vitro resistance to antimicrobial drugs, which requires long courses of therapy with relatively poor outcomes when compared to tuberculosis. To date, our lack of understanding of the transmission and pathogenesis of these increasingly important infections has limited out ability to develop public health measures aimed at preventing infection.

TAXONOMY

In 1997, approximately 50 species of NTM had been identified, with approximately 13 described as respiratory pathogens.[4] Currently, there are more than 140 identified NTM species with at least 40 that are associated with lung infection[5] (Table 35-1). Thus, it is reasonable to ask why there appears to be such a profusion of NTM species in general and those associated with lung disease in particular.

The primary explanation can be found in the mycobacteriology laboratory. Prior to the era of DNA sequencing for organism identification, NTM were identified

TABLE 35-1. Slowly Growing and Rapidly Growing Nontuberculous Mycobacteria That Have Been Reported to Cause Lung Disease

Slowly Growing Mycobacteria		Rapidly Growing Mycobacteria	
M. arupense	*M. kubicae*	*M. abscessus*	*M. goodii*
M. avium	*M. lentiflavum*	*M. alvei*	*M. holsaticum*
M. asiaticum	*M. malmoense*	*M. boenickei*	*M. mageritense*
M. branderi	*M. palustre*	*M. bollettii*	*M. massiliense*
M. chimaera	*M. saskatchewanse*	*M. brumae*	*M. mucogenicum*
M. celatum	*M. scrofulaceum*	*M. chelonae*	*M. peregrinum*
M. florentinum	*M. shimodei*	*M. confluentis*	*M. phocaicum*
M. beckeshornense	*M. simiae*	*M. elephantis*	*M. septicum*
M. intermedium	*M. szulgai*	*M. fortuitum*	*M. thermoresistible*
M. interjectum	*M. triplex*		
M. intracellulare	*M. xenopi*		
M. kansasii			

Data from references 5, 143, 144.

based on their morphologic and biochemical characteristics as well as in vitro susceptibility patterns. The inadequacy or insensitivity of these techniques was reflected in the number of organisms that were grouped as "complexes," such as the "*Mycobacterium fortuitum* complex," which included multiple rapidly growing species such as *M. fortuitum, Mycobacterium chelonae,* and *Mycobacterium abscessus.* Although, it was apparent that multiple species were present with similar growth and morphologic properties, standard laboratory techniques were not adequate to reliably separate them to the species level.

Currently, there are multiple techniques for NTM species identification, including DNA probes for the most commonly isolated NTM species and high-performance liquid chromatography (HPLC).[5] HPLC has been especially useful in the identification of new NTM species but lacks the sensitivity of molecular techniques. The revolutionary change in NTM identification was the advent of readily available DNA sequencing, especially the sequencing of the 16S ribosomal RNA gene, which is highly conserved so that 1% or greater differences in this gene sequence can define an NTM species. Publicly available databases of 16S ribosomal RNA gene sequences allow relatively easy comparison of mycobacterial isolates to determine if a new NTM species is present. Alternatively, sequences of the heat shock protein 65 (hsp65) gene, or the entire genomic DNA sequence of an NTM species, can be compared to other publicly available gene sequence databases. For practical purposes, anyone with access to DNA sequencing can potentially identify a new sequence and species of NTM.

The expansion of new NTM species in the past 15 years is, therefore, primarily a consequence of more sensitive identification techniques capable of separating closely related NTM species rather than a proliferation of new NTM species. Predictably, many of these newly identified species have microbiologic properties very similar to other closely related NTM, so that identification of the new NTM species may not be associated with any new or surprising clinical properties. It remains to be seen if this revolution in NTM species identification will have an equally profound impact on clinical NTM disease. What is certain, however, is that clinicians will have to become familiar with many more NTM species names as new NTM species are identified by increasingly more laboratories.

EPIDEMIOLOGY

Incidence and Prevalence

The epidemiology of NTM disease has been difficult to determine because reporting is not mandatory in most countries and differentiation between infection and disease is often difficult. The incidence and prevalence of NTM infections have varied significantly across studies, partially because the studies have used different methodologies and studied different populations.[6] Although not definitive, the existing data suggest that the incidence and prevalence of NTM infections are increasing.

Epidemiologic studies of NTM infection and disease use one of three approaches: (1) the use of antigens to examine the reactivity to delayed-typed hypersensitivity; (2) the reported isolation rate of NTM from laboratories; or (3) the use of both clinical and laboratory data to define disease more accurately.[6] Studies utilizing delayed-type hypersensitivity reaction to subcutaneously injected mycobacterial antigens have estimated that 11% to 33.5% of the population in the United States has been exposed to NTM.[6–8] A recent study used data from the National Health and Nutritional Examination Survey (NHANES) cohort to describe skin reactivity to purified protein derivative-B (PPD-B) during two time periods. For the years 1971–1972 and 1999–2000, rates of a positive skin

test were 11.2% and 16.6%, respectively.[9] Skin test reactivity was noted to increase between the two time periods in foreign-born but not in U.S.-born individuals, suggesting a higher rate of exposure and infection in the foreign-born individuals.

Laboratory-based studies utilize consecutive isolates from a well-defined catchment area to estimate the frequency of infection. Survey data from state laboratories in the early 1980s estimated a prevalence of NTM infection of 1 to 2 cases per 100,000 population.[10] A similar follow-up survey from 1993 to 1996 reported an annual case rate of 7 to 8 per 100,000, documenting an increase in isolation of NTM when compared to the previous survey.[11] Although these surveys reported an increase in the number of isolates of NTM between the two time periods, it is important to point out that laboratory-based surveys suffer from the fact that they provide isolate-based information but may not take into account the number of patients and whether or not the patients have disease.

Studies that combine cultural and clinical data may be more useful for estimating disease incidence and prevalence. Studies since the 1950s from Czechoslovakia,[12] Wales,[13] Ireland,[14] Australia,[15] and the United States[10] have reported increases in incidence or prevalence. In some reports, the increase in the rate of NTM infection was associated with a decline in the rate of tuberculosis. For example, in Japan from 1971 to 1984, the incidence of pulmonary tuberculosis decreased from 133.1 to 46.3 per 100,000 while the incidence of NTM pulmonary disease increased from 0.89 to 2.15.[16] Similarly, in Switzerland, the incidence of pulmonary tuberculosis decreased from 16.2 to 13.2 per 100,000 over 6 years while the incidence of pulmonary NTM increased from 0.4 to 0.9 per 100,000.[17] Marras and coworkers[18] reported an increase in the number of pulmonary NTM isolates in Ontario from 9.1 per 100,000 in 1997 to 14.1 per 100,000 in 2003 (Fig. 35-1); during this same time period, the rate of tuberculosis declined. In a subsequent analysis of these data, Iseman and Marras[19] noted that the prevalence was likely to be in the range of 14 to 35 per 100,000, far exceeding the prevalence of tuberculosis in Ontario. A recent study reported a significant increase in the annual prevalence of NTM pulmonary disease in patients hospitalized in 11 states between 1998 and 2005.[19a] Annual prevalence increased among men and women in Florida (3.2%/year and 6.5%/year, respectively) and among women in New York (4.6%/year) but there was no significant increase in California. While not all studies have documented an increase in NTM prevalence,[20] the preponderance of evidence suggests that pulmonary disease due to NTM is increasing.

The reasons for the increase in incidence and prevalence have not been explained, although increased awareness of the disease and improved diagnostic techniques could be a factor. A true increase in incidence could be related to changes in the host such as an aging population, an increased prevalence of chronic lung disease, or an increase in the number of immunocompromised individuals. The observation of a decreased incidence of pulmonary tuberculosis and an increased incidence of pulmonary NTM, as noted previously, could be explained by cross-immunity between mycobacterial species. Finally, an increase in the prevalence or virulence of environmental organisms or changes in human behavior that would lead to increased exposure to organisms could be contributing factors.

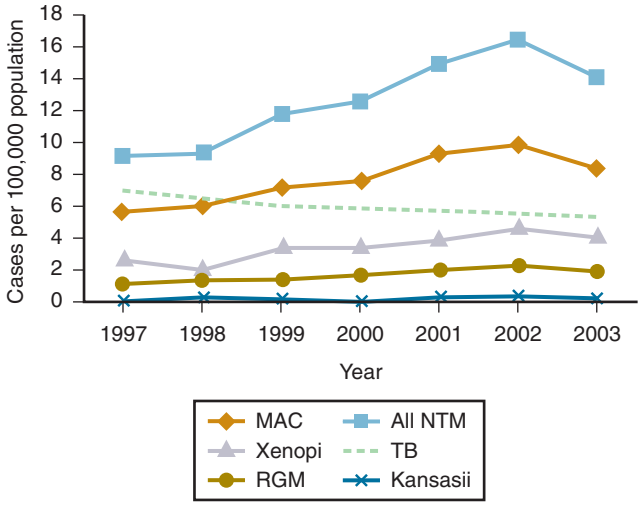

FIGURE 35-1 ■ Prevalence of pulmonary nontuberculous mycobacteria (NTM) infections and tuberculosis (TB) case rates in Ontario, 1997–2003. All NTM prevalence rates increased significantly (all $P \leq 0.001$). Tuberculosis rates were calculated from the total number of tuberculosis cases and population data from Statistics Canada for 1999–2003 (from http://www.statcan.ca/english/Pgdb/demo02.htm, accessed October 4, 2004) and estimated by back-extrapolation for 1997 and 1998. MAC, *M. avium* complex; RGM, rapidly growing mycobacteria. (Reproduced with permission from Marras TK, Chedore P, Ying AM, Jamieson F: Isolation prevalence of pulmonary non-tuberculous mycobacteria in Ontario 1997–2003. Thorax 62:661–666, 2007.)

Geographic Distribution and Variation

NTM have been reported to cause pulmonary disease around the globe, although there is marked variation in the prevalence of disease and in which species predominates. In the United States, the southeastern region seems to have the highest rates of infection.[10,21,22] NTM have been recovered with higher frequency from water samples in the southeastern versus northern United States, so exposure is likely higher in these regions.[23] The predominant species in North America have been MAC, followed by *Mycobacterium kansasii, M. abscessus, M. fortuitum, M. chelonae,* and *M. scrofulaceum.*[10,21] MAC has also been reported as the predominant species in Central and South America, Europe, and Asia. *Mycobacterium xenopi* is common in Europe and Canada, whereas *Mycobacterium malmoense* is more common in Northern than Southern Europe. Populations of miners in Czechoslovakia[12] and South Africa[24,25] have been reported to have high rates of *M. kansasii* infection.

TRANSMISSION AND PATHOGENESIS

Transmission

NTM are ubiquitous in the environment and have been found in natural and drinking waters, biofilms, soil, and aerosols.[26] The presumed source of infection is exposure to these environmental reservoirs because human-to-human transmission has never been documented. Studies using genotyping techniques, such as pulsed-field gel electrophoresis, have been able to isolate the same strains of NTM from patients and their environment.[27–29] Although, the mechanism by which an environmental exposure eventually leads to pulmonary infection is poorly understood,[30] it has been hypothesized that exposure to infected aerosols can lead to infection and possibly disease. In at least two cases, the same strain of MAC was isolated from the patients' respiratory specimens and water from their shower head.[27,28] In another report, the patient's strain of MAC was isolated from potting soil in the home.[29] There have also been reports of outbreaks in which patients' isolates matched environmental isolates of NTM.[31] Extrapulmonary NTM infections are usually the result of a puncture wound or surgery.

Factors Associated with Infection

A prospective study using skin testing data from Palm Beach, Florida, reported that 32.9% of 447 participants in a population-based random household survey had a positive reaction to *M. avium* sensitin.[32] Independent predictors of a positive reaction included black race, birth outside the United States, and more than 6 years' cumulative exposure to soil. Exposure to water, food, and pets was not associated with skin test reactivity. Using NHANES data, investigators reported similar findings with regard to sensitization to *Mycobacterium intracellulare*[9]: male gender, non-Hispanic black race, and birth outside the United States were each independently associated with sensitization. The highest rate of skin test reactivity occurred in persons who were 20 to 39 years of age, and among individuals who were 20 years of age and older, working in agriculture or construction was strongly associated with sensitization. These two studies are interesting in that skin test reactivity to either *M. avium* or *M. intracellulare* sensitin was associated with factors likely associated with soil exposure and were more common in men and foreign-born individuals. However, disease seems to be more common in older women and, at least in the United States, in U.S.-born individuals. Thus, it is likely that the risk factors for exposure and infection are different from those associated with disease.

Factors Associated with Disease

Most NTM are significantly less pathogenic than *M. tuberculosis* and likely require some degree of host impairment to establish infection. A number of risk factors for disease have been described, and these can be subdivided broadly into three groups: (1) factors impairing host immunity, (2) factors leading to impaired local (lung) immunity, and (3) factors relating to host demographics. Increasing age has been consistently described as a risk factor for pulmonary NTM, in patients both with and without underlying lung disease.[8,10,33,34] The most consistently reported risk factor is male gender, though there is also a population of elderly females who are at risk for nodular bronchiectatic lung disease. Perhaps the most important risk factor for the development of pulmonary NTM disease is underlying chronic lung disease. NTM disease has been described in association with cystic fibrosis, chronic obstructive pulmonary disease (including alpha$_1$-antitrypsin deficiency), cavitary lung disease, pneumoconiosis, bronchiectasis, prior tuberculosis, and pulmonary alveolar proteinosis.[35] Studies have documented a high prevalence of NTM in sputum cultures from patients with cystic fibrosis, with estimates ranging from 3% to 19.5%, the majority of which were MAC.[36,37]

Patients with NTM lung disease often have associated gastroesophageal reflux disease (GERD) or other esophageal disorders. Historically, it has been reported that patients with rapidly growing mycobacteria often have associated esophageal disorders[38–40]; recent reports have also described a high frequency of GERD in patients with MAC lung disease.[41,42] In a report from South Korea that used pH probes to diagnose GERD, the authors reported the prevalence of GERD was 26%, although only 27% of the patients were symptomatic.[41] Patients with *M. abscessus* infection were more likely to have GERD than those with MAC, although the difference did not reach statistical significance.

One of the most interesting patient populations to develop NTM pulmonary disease consists of postmenopausal women who often have certain associated morphologic features. This constellation was first described by Prince and colleagues[33] in 1989 and later referred to as the "Lady Windermere syndrome," after the lead in Oscar Wilde's play *Lady Windermere's Fan,* who was characterized by her fastidious behavior.[43] The morphologic features such as pectus excavatum, scoliosis, thin body habitus, and mitral valve prolapse were described subsequently by Iseman and others.[44] Recently, investigators reported that women with pulmonary NTM disease were taller and thinner and weighed less than matched control subjects[45] (Fig. 35-2): 51% had scoliosis, 11% pectus excavatum, and 9% mitral valve prolapse, all significantly more common than in reference populations. Another interesting feature of this syndrome is the predilection for right middle lobe and lingular bronchietasis. To date, extensive evaluation of the immune system of these patients has been unrevealing, but mutations in the cystic fibrosis transmembrane regulator (CFTR) gene are common.[45,46]

NTM in acquired immunodeficiency syndrome (AIDS) most commonly causes disseminated disease that presents with nonspecific symptoms such as fever, night sweats, diarrhea, abdominal pain, and lymphadenopathy, with MAC being the most frequent isolate.[47] Despite the fact that MAC is isolated from the sputum in up to

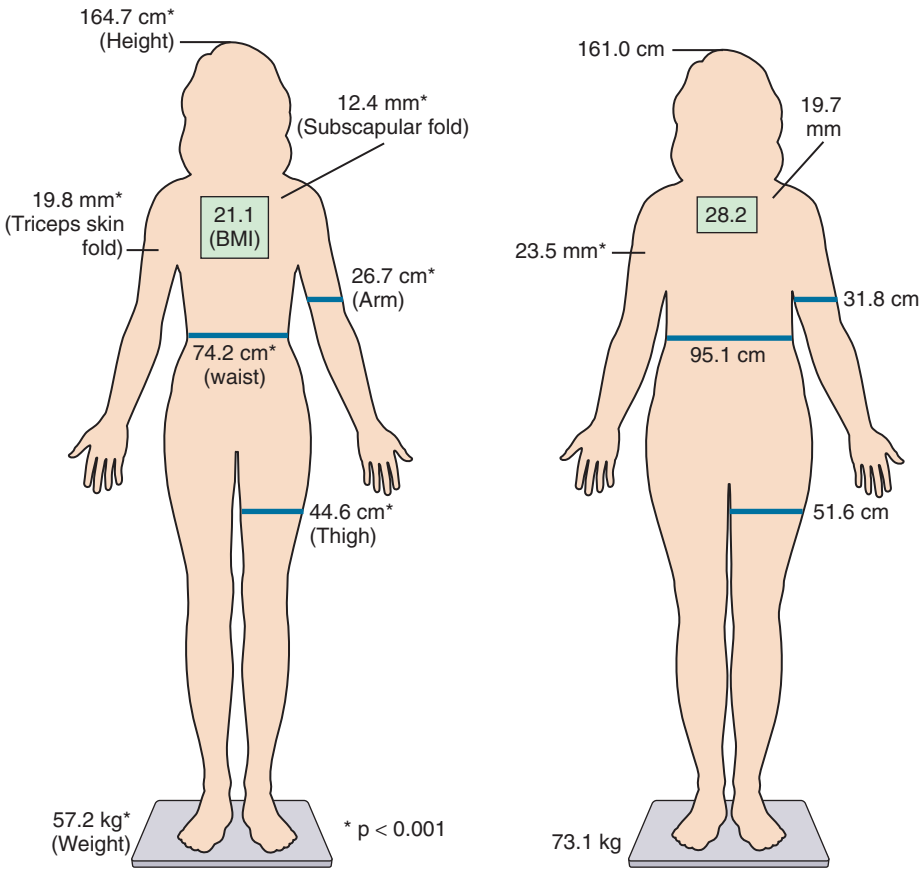

FIGURE 35-2 ■ Schematic depiction of the anthropometrics of women with pulmonary nontuberculous mycobacterial disease (n = 60) (*left*) compared with National Health and Nutrition Examination Survey age-, sex-, and race-matched control subjects (*right*). *P < 0.001. (Reproduced with permission from Kim RD, Greenberg DE, Ehrmantraut ME, et al: Pulmonary nontuberculous mycobacterial disease: Prospective study of a distinct preexisting syndrome. Am J Respir Crit Care Med 178:1006–1074, 2008.)

10% of AIDS patients with CD4 T-cell counts less than 50 cells/μL, pulmonary disease due to MAC is uncommon.[48] Pulmonary disease been reported in 2.5% to 8% of patients with disseminated MAC[49] and, rarely, has also been reported in the absence of dissemination.[49,50] Patients with pulmonary disease tend to have higher CD4 counts and focal alveolar infiltrates, which rarely cavitate. *Mycobacterium kansasii* can also cause disease in patients with HIV and AIDS. In one study, the risk for infection with *M. kansasii* was increased 150-fold in HIV-infected patients and 900-fold in those with AIDS.[51] In contrast to MAC, *M. kansasii* only rarely causes indolent disease and should almost always be treated as a pathogen.[52]

Pulmonary disease due to NTM has been described in several other immunocompromised patient populations, including transplant recipients. Rates may be as high as 6.5% following heart or lung transplantation,[53] and 2.9% following bone marrow transplantation,[54] but are probably much lower in patients following liver or kidney transplantation.[55,56] *Mycobacterium abscessus* infection in patients with cystic fibrosis who have undergone lung transplantation has been associated with severe and sometimes fatal disease.[57–59]

Multiple cytokines are necessary for granuloma formation and eventual containment of mycobacterial infections. The most important among these are interferon-γ (IFN-γ), interleukin-12 (IL-12), and tumor necrosis factor-α (TNF-α). Patient populations with defects in each cytokine are susceptible to infection with NTM. Mutations in IFN-γ receptor 1 (IFN-γR1), IFN-γ receptor 2, IL-12 p40, and the IL-12 receptor have all been shown to lead to human disease.[60] The dominant and recessive IFN-γR1 deficiencies have distinct clinical presentations.[60] Large numbers of patients with inflammatory bowel disease, rheumatoid arthritis, or psoriatic arthritis are treated with infusions of the TNF-α inhibitors. Although initially demonstrated to predispose to tuberculosis,[61] recent reports have linked these therapies to NTM infections as well.[62] Patients with suspected or known mycobacterial infections should not receive these medications without proper antimycobacterial therapy.

Most studies have focused on evaluating possible host abnormalities that could lead to NTM disease, although microbial factors are likely to be important as well. Recent studies have identified isolates and phenotypes associated with increased virulence in in vitro

models.[62a,62b] Moreover, a recent population-based assessment of the clinical significance of NTM in a region of the Netherlands demonstrated a wide range of pathogenicity among different NTM species.[62c]

DIAGNOSIS AND MANAGEMENT OF SPECIFIC PATHOGENS

NTM lung infection presents with diverse manifestations (Table 35-2). This chapter focuses on the most common clinical presentations in the immune-competent host: chiefly, tuberculosis-like (cavitary) disease and disease associated with nodules and bronchiectasis (nodular/bronchiectatic disease). The diagnostic evaluation usually consists of (1) assessment for the presence of one or more compatible symptoms, which are usually insidious in onset (cough, sputum production, fatigue, weight loss, fever, hemoptysis); (2) radiographic evaluation, which frequently includes high-resolution computed tomography (HRCT) scans of the chest; and (3) microbiologic evaluation, which usually consists of three or more sputum specimens for microscopy and mycobacterial culture and/or collection of specimens bronchoscopically. The most important diagnosis for exclusion is tuberculosis.

The diagnosis of NTM lung disease can be challenging. Unlike pulmonary tuberculosis, in which a single positive culture of sputum or bronchoscopic specimen, barring laboratory contamination, establishes the diagnosis, confirmation of the diagnosis of NTM lung disease usually requires repeated isolation of a particular NTM species. Diagnostic criteria have been developed—and recently revised—to aid the clinician in the diagnostic evaluation of persons suspected of having pulmonary NTM disease.[5] The NTM diagnostic criteria outlined in Table 35-3 are based on experience with common and well-described respiratory pathogens such as MAC, *M. kansasii,* and *M. abscessus.* However, it is important to note that because of the varying pathogenicity among the many NTM species, no single diagnostic approach will work for all cases.[62c] Diagnostic criteria that are too sensitive promote overdiagnosis and the unnecessary exposure of patients to potentially toxic antimicrobial medications. By contrast, overly rigid diagnostic criteria put patients at risk for undertreatment and progressive NTM disease. Fortunately, NTM lung disease is usually sufficiently indolent for a careful patient assessment to determine with confidence the presence or absence of significant disease.

The difficulty in determining the clinical significance of an NTM respiratory isolate results from several factors. NTM isolates can contaminate clinical specimens, usually from environmental sources. Many NTM species, such as *Mycobacterium gordonae,* are generally nonpathogenic and almost invariably represent specimen contamination rather than true infection. NTM can be found in potable (municipal or tap) water (*M. kansasii,* MAC, *Mycobacterium simiae, M. abscessus, M. xenopi*), so that their presence in a clinical specimen can be due to waterborne contamination of the specimen, even if the isolated species is sometimes associated with significant clinical disease. And sometimes, the recovery of even potentially virulent and pathogenic NTM may not be associated with active or progressive disease, for reasons that are not understood. Unfortunately, no easily applied algorithm addresses all NTM species in all clinical circumstances. The clinician must have not only some knowledge of the disease-producing potential of NTM species, but also an awareness of the circumstances associated with the isolation of the NTM species.

A single positive sputum culture for NTM is usually regarded as indeterminate for the diagnosis of NTM lung disease. In contrast, when two or more sputum cultures are positive, the diagnosis of disease is more likely. For example, 98% of patients with two or more positive sputum cultures for MAC had evidence of progressive disease during follow-up in a study from Japan.[63] A single positive NTM culture from bronchoscopy can be diagnostic for disease (see Table 35-3), but the clinician must keep in mind those NTM species that are usually respiratory contaminants (especially *M. gordonae*) and those NTM species that can be found in tap water (discussed earlier) since "pseudo-outbreaks" of NTM disease can be

TABLE 35-2. Diversity of NTM Pulmonary Disease

- Tuberculosis-like (cavitary) disease
- Disease associated with nodules/bronchiectasis
  - Disease associated with genetic airway abnormalities and abnormal airway clearance (cystic fibrosis, primary ciliary dyskinesia, alpha$_1$-antitrypsin deficiency)
- Hypersensitivity-like lung disease
- Disease associated with esophageal motility disorders
- Disease associated with disseminated disease and immune suppression
  - HIV/AIDS
  - Defects in interferon-γ and interleukin-12 pathways
  - Tumor necrosis factor-α antagonists

TABLE 35-3. Microbiologic Criteria for Diagnosis of NTM Lung Disease

At least three sputum results available	• Two positive cultures regardless of the results of AFB smear
Single available bronchial wash or lavage	• One positive culture regardless of the results of AFB smear
Tissue biopsy	• Compatible histopathology (granulomatous inflammation) and a positive biopsy culture for NTM • Compatible histopathology (granulomatous inflammation) and a positive sputum or bronchial wash culture for NTM

AFB, acid-fast bacillus; NTM, nontuberculous mycobacteria.
Data from Griffith DE, Aksamit T, Brown-Elliott BA, et al: An official ATS/IDSA statement: Diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. Am J Respir Crit Care Med 175:367–416, 2007.

the consequence of bronchoscopic equipment that has been inappropriately rinsed with tap water.[64] This latter criterion does not mean that bronchoscopy has a better yield for detection of NTM, but rather that it would be inappropriate to subject a patient to multiple bronchoscopic procedures simply to obtain multiple respiratory specimens. Patients who are suspected of having NTM lung disease but do not meet the diagnostic criteria should be followed clinically until the diagnosis is either firmly established or excluded, a process that can literally take months to years.

Making the diagnosis of NTM lung disease does not necessitate the institution of therapy, which is a decision based on potential risks and benefits of therapy for individual patients. Factors that might influence the decision to treat NTM lung disease include the virulence of the NTM pathogen and the potential for disease progression, the severity (or lack of severity) of symptoms and radiographic findings, the presence of known indolent disease, and the presence of advanced age and/or severe comorbid conditions (with limited life expectancy); another factor is the inability to tolerate the prolonged and sometimes toxic antimicrobial regimens for NTM disease. Again, there is no substitute for physician familiarity with NTM pathogens and the individual patient for optimal management of NTM lung disease.

Other clinical manifestations of NTM infection include lymphadenitis, disseminated disease, and skin, soft tissue, and bone disease. Lymphadenitis is the most common NTM disease manifestation in children and is usually due to MAC or, less commonly, *M. scrofulaceum.*[65] The most important differential diagnosis is tuberculosis lymphadenitis, although NTM account for approximately 90% of mycobacterial lymphadenitis in American children (but only 10% in adults).[66] Symptoms are usually minimal, with frequent unilateral involvement of submandibular, submaxillary, preauricular, or cervical lymph nodes. Skin and soft tissue infections are usually due to the "rapidly growing mycobacteria," *M. abscessus, M. fortuitum, M. chelonae,* or *M. marinum,* and are the result of direct inoculation after either trauma or surgery.[1,67] Dissemination of NTM pathogens is most often associated with the severe immunosuppression of advanced AIDS and is caused by MAC.[47,68–70] Disseminated NTM infections can occur in other immune-compromised states, such as organ transplantation, or in association with indwelling foreign bodies such as venous catheters, dialysis catheters, or other prosthetic devices.[71–74]

Laboratory Diagnosis

The diagnosis of NTM disease is based on isolation of these organisms from diagnostic specimens. Cultures should include both solid and broth media for detection of mycobacteria, and a semiquantitative reporting of colony counts is recommended.[5] The optimal temperature for growth of most NTM species is between 28°C and 37°C, although some species require either higher or lower temperatures for optimal growth and some species require special supplementation for recovery from culture.[5] Most NTM grow within 2 to 3 weeks of subculture but the group of rapidly growing NTM appear within 7 days of subculture.

Identification of specific species can be based on phenotypic, chemotaxonomic, and molecular methods.[5] NTM can be categorized by their growth rate and pigmentation, although these characteristics are not specific enough for final speciation. In addition, biochemical testing can be used to help speciate the NTM. However, none of these procedures is sufficient to differentiate all NTM, particularly some of the newly identified species.

Additional techniques for speciation include nucleic acid probes, polymerase chain reaction and other amplification methods, HPLC, and nucleic acid sequencing.[75–80] The commercially available AccuProbe technology (GenProbe, San Diego, CA) is currently recommended for identification of *M. tuberculosis* complex, *M. avium* complex (as well as *M. avium* and *M. intracellulare* separately), *M. kansasii,* and *M. gordonae.* HPLC, which analyzes the chromatographic profile of the mycolic acids extracted from the bacterial cell wall, can be used to speciate a large number of NTM.[81] Identification of mycobacteria by 16S ribosomal DNA sequencing[75,76] provides more accurate determination of the species, although neither HPLC nor 16S ribosomal DNA sequencing can differentiate all species of NTM.

The clinical usefulness of drug susceptibility testing in the management of patients with NTM disease remains controversial, stemming from the fact that in vitro results do not correlate well with clinical outcomes for some mycobacterial species. No single susceptibility method is recommended for all species of slowly growing mycobacteria. For MAC, a broth-based culture method—with both microdilution and macrodilution methods—is considered acceptable.[5] Initial isolates should be tested for response to clarithromycin, as should isolates from treatment failures and relapses, patients who have taken macrolides previously, and AIDS patients who develop bacteremia on macrolide prophylaxis. Isolates of *M. kansasii* should be tested for response to rifampin (rifampicin) because resistance to rifampin is associated with treatment failure or relapse. If rifampin resistance is documented, additional drugs should be tested.[5] Broth microdilution minimal inhibitory concentration (MIC) determination for susceptibility testing is recommended for rapidly growing mycobacteria.

Slowly Growing Mycobacteria

Although there are fewer species of slowly growing NTM than rapidly growing species, the slow growers are more common causes of lung disease (see Table 35-1). The slow growers include over 40 species with a wide range of pathogenicity, from organisms such as *M. kansasii* that are probably second only to *M. tuberculosis* in terms of disease-producing capability to *M. gordonae,* which rarely causes lung disease.

Mycobacterium avium *Complex*

Mycobacterium avium complex includes the NTM species *M. avium,* of which there are several subspecies,

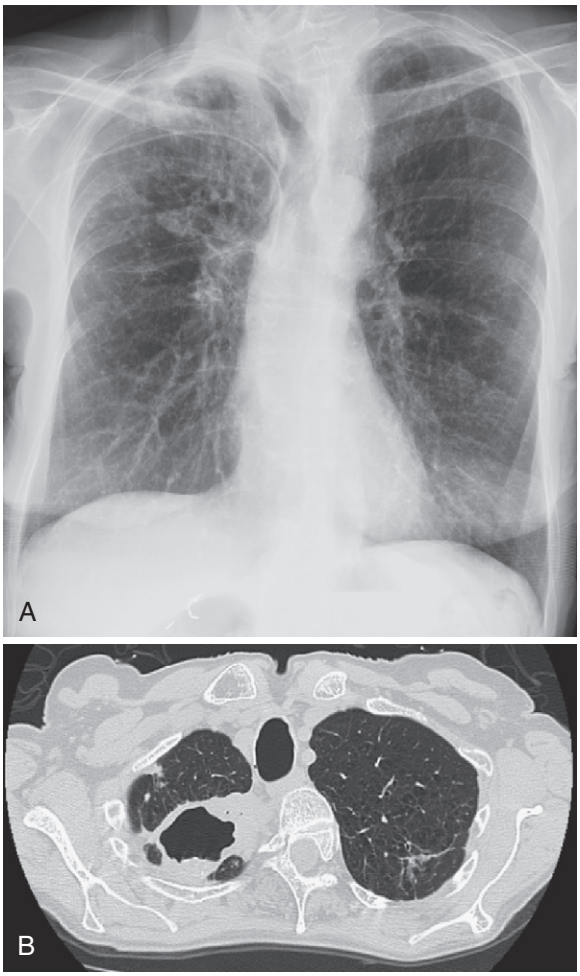

FIGURE 35-3 ■ A 63-year-old female smoker with cavitary MAC lung disease. The patient, who presented with cough, fatigue, weight loss, and intermittent hemoptysis, was diagnosed with MAC in 2004. She failed two courses of multidrug therapy, and her sputum remains strongly culture positive for MAC. **A,** Chest radiograph showing cavitary consolidation in the right apex and scattered nodular and reticulonodular densities in both lungs. **B,** Computed tomography scan showing large cavity in right upper lung field.

as well as *M. intracellulare* and some as yet poorly described species, which explains why MAC has sometimes also been referred to as *Mycobacterium avium-intracellulare* (MAI). Differentiation of the separate MAC species is not possible with routine laboratory techniques, although DNA probes are available for *M. avium* and *M. intracellulare.* Currently, in most circumstances, the differentiation of *M. avium* and *M. intracellulare* does not make a significant difference clinically or therapeutically (although *M. avium* is more often seen with disseminated disease, and in the United States *M. intracellulare* is more often isolated as a respiratory pathogen).

The traditionally recognized presentation of MAC lung disease has been as apical fibrocavitary lung disease similar to tuberculosis, sometimes with large cavities, usually in males but also in females in their fifth and sixth decades who have a history of cigarette smoking and alcohol abuse (Fig. 35-3). If left untreated, this form of disease is generally progressive and can result in extensive cavitary lung destruction.

MAC lung disease also presents with nodular and interstitial nodular infiltrates, which frequently involve the right middle lobe or lingula, predominantly in postmenopausal nonsmoking white females (Fig. 35-4). This form of disease, termed *nodular/bronchiectatic disease,* tends to have a much slower progression than cavitary disease, such that long-term follow-up may be necessary to demonstrate clinical or radiographic changes. Even with this more indolent form of disease, however, death may result from progressive disease.[33] Nodular/bronchiectatic MAC lung disease is radiographically characterized by HRCT findings that include multiple small peripheral pulmonary nodules centered on the bronchovascular tree and cylindrical bronchiectasis (see Fig. 35-4). The HRCT pattern of these predominantly peripheral small nodular densities has been described as "tree-in-bud," and reflects inflammatory changes including bronchiolitis.

Patients with nodular/bronchiectatic MAC lung disease often have additional microbiologic findings associated with bronchiectasis, including respiratory

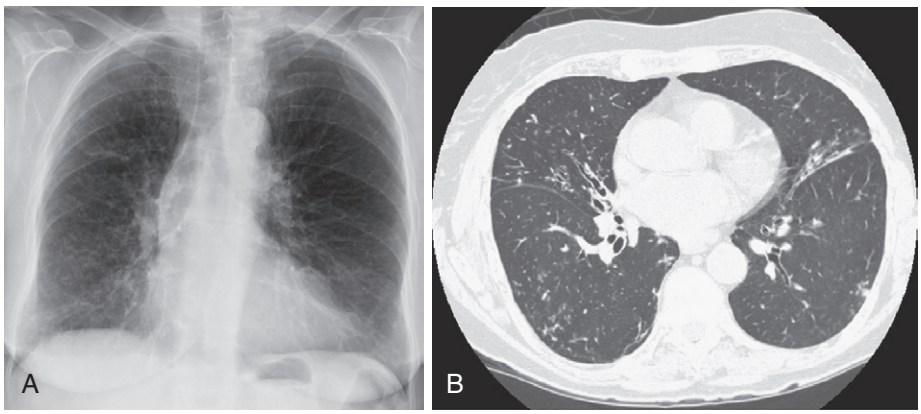

FIGURE 35-4 ■ A 78-year-old nonsmoking female with a several-year history of cough and increasing fatigue. Her sputum was consistently culture positive for MAC. **A,** Chest radiograph showing bilateral, primarily mid–lung field reticular and reticulonodular densities; **B,** Chest computed tomography (CT) scan showing bilateral small nodules and "tree-in-bud" appearance and bronchiectasis in the right middle lobe and lingula.

cultures positive for *Pseudomonas aeruginosa, Nocardia* species, and occasionally other NTM such as *M. abscessus.* Nonmycobacterial exacerbations of bronchiectasis often complicate the assessment and management of MAC disease such that strategies aimed at treatment of the bronchiectasis may improve patients' symptoms.

For many patients, perhaps the majority of patients with nodular/bronchiectatic disease, it is unknown if bronchiectasis is the result of the mycobacterial infection or due to some other process that predisposes to subsequent mycobacterial infection. In some patients with NTM lung disease, bronchiectasis is the result of diseases such as cystic fibrosis, primary ciliary dyskinesia, or alpha$_1$-antitrypsin deficiency, so that the bronchiectasis clearly antedates the MAC disease.[46,82,83] The routine evaluation of underlying causes of bronchiectasis, such as cystic fibrosis and alpha$_1$-antitrypsin deficiency, in patients with nodular/bronchiectatic MAC disease is currently controversial, and no consensus exists concerning routine testing for these possible underlying conditions in all patients with nodular/bronchiectatic MAC disease.

Therapy of MAC Lung Disease. Several aspects of treatment for MAC lung disease are frustrating, difficult to explain, and even counterintuitive. The greatest misunderstanding about treatment regimens for NTM pathogens is the result of the expectation that all NTM infections should respond in a predictable manner to antimicrobial therapy, similar to *M. tuberculosis.* In reality, when treatment regimens are based on in vitro susceptibility testing, the NTM pathogen very often does not respond to antimicrobial agents as predicted from the susceptibility results. The most difficult and frustrating aspect of NTM therapy for many clinicians is the lack of a clear association between the in vitro susceptibility results and the clinical (in vivo) response. For many NTM, including MAC, laboratory cutoffs for "susceptible" and "resistant" do not have a demonstrable clinical correlate and have not been confirmed to be clinically meaningful. Response to treatment of disease caused by MAC correlates only with in vitro susceptibility to macrolides (clarithromycin and azithromycin), and not to other agents.[84–89] Several other NTM species (*M. abscessus, M. simiae, M. malomoense, M. xenopi,* etc.) lack established correlation between in vitro susceptibilities and in vivo responsiveness to any antimicrobial agent. The explanation(s) for the dichotomy between laboratory susceptibility testing results and clinical benefit for many NTM is (are) currently not known. Accordingly, clinicians must use in vitro susceptibility data for many NTM with the awareness that, unlike tuberculosis, the results are an imperfect guide to treatment outcome.

Because the macrolides—clarithromycin and azithromycin—are the only antimicrobial agents for which there is a demonstrated correlation between in vitro susceptibility and in vivo response for MAC lung disease, these agents, partnered with ethambutol, serve as the cornerstones of MAC therapy (Table 35-4). As also shown, this regimen must be reinforced with a rifamycin and, possibly, an injectable aminoglycoside (amikacin or streptomycin), because companion drugs are necessary to prevent the emergence of macrolide-resistant MAC isolates. Macrolides should *never* be used as monotherapy for treatment of MAC disease, either pulmonary or disseminated.[90]

TABLE 35-4. Treatment of Pulmonary Disease due to *M. avium* Complex Infections

Type of Disease	Regimen
Nodular/ bronchiectatic disease	1) clarithromycin 1000 mg tiw or azithromycin 500–600 mg tiw *and* 2) ethambutol 25 mg/kg tiw *and* 3) rifampin 600 mg tiw
Cavitary disease	1) clarithromycin 500–1000 mg/day or azithromycin 250–300 mg/day *and* 2) ethambutol 15 mg/kg daily *and* 3) rifampin 450–600 mg daily *and* 4) consider streptomycin or amikacin 15 mg/kg tiw for first 2–3 months
Advance or previously treated disease	1) clarithromycin 500–1000 mg/day or azithromycin 250–300 mg/day *and* 2) ethambutol 15 mg/kg daily *and* 3) rifabutin 150–300 mg daily or rifampin 450–600 mg daily *and* 4) include streptomycin or amikacin 15 mg/kg tiw for first 2–3 months

tiw, three times per week.
Data from Griffith DE, Aksamit T, Brown-Elliott BA, et al: An official ATS/IDSA statement: Diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. Am J Respir Crit Care Med 175:367–416, 2007.

There is another difficult-to-explain phenomenon associated with MAC drug therapy. Patients who have failed prior MAC therapy, with or without a macrolide, have lower sputum conversion rates with macrolide-containing treatment regimens, even with macrolide-susceptible MAC isolates, than do patients with no prior therapy.[85,88,91,92] Although the explanation for this observation is also not clear, it is evident that the best chance for treatment success in MAC lung disease is the first treatment effort. Finally, patients who are successfully treated for nodular/bronchiectatic MAC disease can be reinfected by new MAC isolates, sometimes with renewal of progressive disease.[93]

The recommended duration of treatment for MAC pulmonary disease is to continue therapy until 12 months of sputum culture negativity,[5] a goal that requires patients to have sputum collected for mycobacterial culture on a regular basis throughout the course of treatment.

For some patients who are taking clarithromycin, the doses may need to be split (e.g., 500 mg twice daily) because of gastrointestinal intolerance. For patients of low body weight (<50 kg) or older age, the clarithromycin dose for daily regimens may need to be reduced to 500 mg/day or 250 mg twice daily because of gastrointestinal intolerance. Patients receiving clarithromycin and rifabutin should be carefully monitored for rifabutin-

related toxicity, especially hematologic (leukopenia) and ocular (uveitis) toxicity.

Macrolide-resistant MAC lung disease is associated with a poor prognosis.[90] The two major risk factors for macrolide-resistant MAC disease are macrolide monotherapy or treatment with a macrolide and inadequate companion medications. The treatment strategy associated with the most success for macrolide-resistant MAC lung disease includes both the use of a multidrug regimen, including a parenteral aminoglycoside (streptomycin or amikacin), and surgical resection ("debulking") of diseased lung.[90] The optimal drug regimen for treating macrolide-resistant strains is unknown, but some experts recommend ethambutol, rifabutin, an injectable agent, and possibly another oral drug such as an 8-methoxyfluoroquinolone or clofazimine.

Patients whose disease is predominantly localized to one lung and who can tolerate resectional surgery should be considered for surgery under the following conditions: (1) poor response to drug therapy, (2) development of macrolide-resistant MAC disease, or (3) presence of significant disease-related complications, such as hemoptysis. Whenever possible, surgery should be performed by thoracic surgeons who have had considerable experience with resectional lung surgery for mycobacterial disease.[94]

Therapy of Disseminated MAC Disease. Successful treatment of disseminated MAC in persons with AIDS is based on treatment of both the mycobacterial and HIV infections. Clinicians must therefore be aware of the drug-drug interactions between the antimycobacterial and antiretroviral medications. Current guidelines for the use of antimycobacterial drugs with HIV therapies can be found at www.cdc.gov/nchstp/tb/TB_HIV_DRUGS/TOC.htm.

Patients with disseminated MAC disease should be treated with clarithromycin, 1000 mg/day or 500 mg twice daily (or, as an alternative, azithromycin at a dose of 500 mg daily), and ethambutol at a dose of 15 mg/kg daily.[95–97] Rifabutin, if added, should be used at a dose of 300 mg daily, with adjustments for interactions with antiretroviral drugs. As with macrolide-resistant MAC lung disease, patients with disseminated disease from macrolide-resistant strains are far less likely to be successfully treated[84]; clofazimine has been associated with excess mortality and should not be used.[98] Treatment of MAC in patients with AIDS should be considered lifelong, unless immune restoration is achieved by antiretroviral therapy. MAC treatment may be stopped for patients who are asymptomatic, have completed 12 months or more of therapy, and have maintained a $CD4^+$ T-cell count over 100 cells/μL for at least 12 months.[99]

Preventive therapy for disseminated MAC is recommended for all HIV-infected patients with less than 50 $CD4^+$ T-cells/μL.[100] Based on efficacy and ease of use, azithromycin—given as 1200 mg once weekly—is the preferred agent.[101] Clarithromycin is also effective; however, it is considered an alternative agent because it must be given twice daily and the risk of breakthrough with macrolide-resistant strains is higher with daily clarithromycin than with weekly azithromycin. Rifabutin is also effective but should only be used when a macrolide cannot be tolerated. Primary MAC prophylaxis should be discontinued among adult and adolescent patients who have responded to antiretroviral therapy with an increase in $CD4^+$ T-lymphocyte counts to more than 100 cells/μL for more than 3 months. Primary prophylaxis should be reintroduced if the $CD4^+$ T-lymphocyte count decreases to less than 50 to 100 cells/μL.

Therapy of MAC Lymphadenopathy. The treatment of choice for MAC lymphadenopathy, as well as localized lymphadenopathy due to most NTM pathogens, is complete surgical resection of the involved lymph nodes.[65,66,102,103] When complete surgical resection is not possible, due for instance to nerve impingement or encasement by infected nodes, then chemotherapy with MAC treatment regimens similar to those for lung and disseminated disease is necessary.[104]

Mycobacterium kansasii *Pulmonary Disease*

Tap water is the major reservoir for *M. kansasii.*[105–107] *Mycobacterium kansasii* is the second most common cause of NTM lung disease in the United States, but has also been reported in Europe, Asia, and Africa. *Mycobacterium kansasii* lung disease most closely parallels the clinical course of *M. tuberculosis,* including radiographic abnormalities (Fig. 35-5). While most patients with *M. kansasii* lung disease have upper lobe fibrocavitary findings, some patients have been reported with nodular/bronchiectatic radiographic abnormalities. In HIV-infected patients, *M. kansasii* can present with essentially any pattern of radiographic abnormality.[108]

Therapy of *M. kansasii* Pulmonary Disease. The recommended regimen for treating pulmonary *M. kansasii* disease includes daily rifampin (600 mg/day), isoniazid (300 mg/day), and ethambutol (15 mg/kg/day) for a duration that includes 12 months of negative sputum cultures.[5] Limited data suggest that therapy with rifampin, ethambutol, and clarithromycin for *M. kansasii* disease can also be successful,[109] including intermittent therapy.[110] The recommended treatment duration, as with MAC lung disease, is a duration that includes 12 months of sputum mycobacterial culture negativity.

Patients whose *M. kansasii* isolates have become resistant to rifampin as a result of previous therapy have been treated successfully with a regimen that consists of high-dose daily isoniazid (900 mg), high-dose ethambutol (25 mg/kg per day), and sulfamethoxazole (1.0 gm three times per day) combined with several months of streptomycin or amikacin.[111] The excellent in vitro activity of clarithromycin and moxifloxacin against *M. kansasii* suggests that multidrug regimens containing these agents and at least one other agent based on in vitro susceptibilities, such as ethambutol or sulfamethoxazole, are likely to be even more effective for treatment of a patient with rifampin-resistant *M. kansasii* disease.

Therapy of Disseminated *M. kansasii* Disease. The treatment regimen for disseminated disease, as usually observed in patients with AIDS, should be the same as for pulmonary disease.[5] Because of the critically important role of rifamycins in the treatment of *M. kansasii* disease,

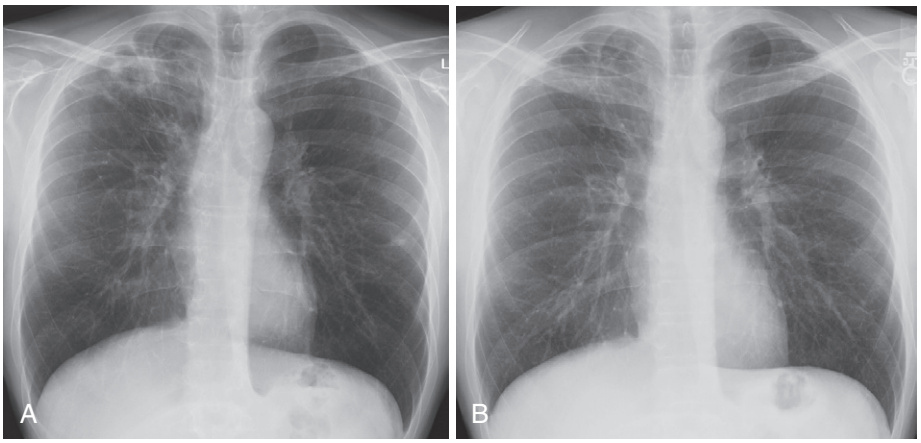

FIGURE 35-5 ■ A 46-year-old male smoker with *M. kansasii* lung disease. The patient presented with cough and weight loss. He was treated as a tuberculosis suspect initially, but his sputum specimen was strongly culture positive for *M. kansasii.* **A,** Chest radiograph showing right upper lobe (RUL) cavitary consolidation. **B,** Chest radiograph with improvement in RUL abnormalities after completing therapy.

it is important to construct *M. kansasii* and antiretroviral treatment regimens that are compatible (see website mentioned in disseminated MAC disease discussion earlier). An option for treating HIV-infected patients who receive an antiretroviral regimen not compatible with rifamycins is to substitute a macrolide or moxifloxacin for the rifamycin. There is no recommended prophylaxis regimen for disseminated *M. kansasii* disease.

Mycobacterium xenopi

Mycobacterium xenopi is a thermophile that survives in hot water systems and natural hot water resevoirs. Its survival in flowing water systems and resistance to common disinfectants enable *M. xenopi* to contaminate laboratory samples and medical devices such as bronchoscopes, thus causing health care–acquired disease (pseudoinfections) and laboratory contamination of specimens. Clusters of hospital isolates have been reported from the United States and Europe.[112] Because of its environmental presence, the differentiation of true clinical infection from pseudoinfection may be difficult but is of paramount importance.

Mycobacterium xenopi is rarely isolated in the United States; however, it is the second most common cause of NTM lung disease in Canada, the United Kingdom, and Europe.[113] Pulmonary *M. xenopi* infections are most common, but extrapulmonary and disseminated infections have been reported. Impaired immunity, either local (preexisting pulmonary disease) or systemic (HIV, immunosuppressive medications) appear to predispose to *M. xenopi* infections. Radiographic findings with *M. xenopi* pulmonary disease are variable but most often include upper lobe cavitary abnormalities compatible with tuberculosis.

In one recent report of therapy for *M. xenopi* infections, overall mortality was high—and mostly unrelated to *M. xenopi* disease—and the response to chemotherapy was not correlated with in vitro susceptibility results.[114] In another recent report from Europe, *M. xenopi* isolates demonstrated favorable in vitro MICs to isoniazid, rifampin, and ethambutol.[113] Even with variable treatment regimens, antimicrobial treatment cured 58% of patients who met American Thoracic Society (ATS) criteria for *M. xenopi* lung disease.[113] Again, there was no correlation between failure or treatment relapse and in vitro susceptibility results. In the most recent published treatment results, a regimen of clarithromycin, rifampin, and ethambutol was compared to ciprofloxacin, rifampin, and ethambutol; treatment success, failure, or relapse did not differ between the two groups.[115] All-cause mortality was again relatively high, and somewhat higher in the ciprofloxacin + rifampin + ethambutol arm. Overall, the optimal pharmacologic management has yet to be determined; however, a regimen consisting of clarithromycin, rifampin, and ethambutol ± isoniazid, administered for a duration of therapy that includes 12 months of sputum culture negativity, seems reasonable. The unusually high overall mortality with this infection is difficult to explain, but may be a reflection of the comorbidities of the patients with *M. xenopi* disease. For whatever reason, it appears to be a consistent observation.

Mycobacterium malmoense

Mycobacterium malmoense is considered the second most serious pathogen after MAC in Northern Europe. The clinical relevance of *M. malmoense* isolates has been described as 70% to 80% in Europe, although clinical isolates in the United States are not nearly as often deemed clinically significant.[116] Patients with *M. malmoense* lung disease frequently have preexisting obstructive lung disease. Not surprisingly, *M. malmoense* lung disease often presents in a manner similar to other cavitary NTM lung disease pathogens. Overall, in vivo response to antimicrobials does not correlate with in vitro susceptibility to antimicrobial agents. In a recent report, clarithromycin, rifampin, and ethambutol were compared to a regimen consisting of ciprofloxacin, rifampin, and ethambutol.[115] Although a more favorable

response to therapy was attained with the macrolide-containing regimen, overall mortality did not differ between the two regimens. The optimal pharmacologic management of *M. malmoense* has yet to be determined.[115–117] Currently, a reasonable regimen for *M. malmoense* might consist of rifampin, ethambutol, and clarithromycin with or without isoniazid for a duration to include 12 months of sputum culture negativity.[116]

Mycobacterium simiae

Recovery of *M. simiae* from clinical specimens has been reported in three geographic regions, Israel, Cuba, and the Southwestern United States, including Texas, Arizona, and New Mexico. The organism is most often isolated as a single positive specimen that is smear negative and not associated with clinical disease. For several clusters of isolates, organisms were also recovered from the local tap water, suggesting it as the likely source.[118,119] A large pseudo-outbreak of *M. simiae* isolates from an urban hospital in Texas has been reported.[120] The source for most of the recovered organisms was a hot water holding area. In most published series, the majority of *M. simiae* isolates have been judged to be not clinically significant.[120,121] In a recent publication, the authors noted, "The available diagnostic criteria are inadequate for the selection of patients for whom drug treatment for true *M. simiae* infection would be beneficial."[121] When *M. simiae* is a significant pathogen, it is most often associated with pulmonary disease or, in immune-compromised hosts, disseminated disease.

As with other NTM, there is no established correlation between in vitro susceptibility of the organism and in vivo clinical response to antimicrobial agents, nor is there an established, predictably reliable treatment regimen for *M. simiae* disease. In a study from Israel,[122] there were no recurrences reported in 102 patients with pulmonary *M. simiae* disease after treatment with rifampin, ethambutol, and clarithromycin given daily for at least 12 months of negative sputum cultures. Some experts suggest using macrolide-based regimens similar to those used for MAC; in addition, other agents such as 8-methoxyfluoroquinolones, sulfamethoxazole, and linezolid may have some activity against this organism.

Mycobacterium szulgai

Mycobacterium szulgai is characterized primarily by cavitary lung disease in patients with underlying chronic lung disease that resembles disease due to *M. tuberculosis.* As with other NTM pathogens, it can also be associated with nodular/bronchiectatic disease. Most respiratory isolates of *M. szulgai* are associated with significant lung disease: 11 of 15 patients (73%) in the Netherlands who grew *M. szulgai* from their sputum met current ATS criteria for disease.[123] In vitro susceptibilities demonstrate susceptibility to rifampin, isoniazid, ethambutol, and clarithromycin. A recent study suggested that regimens containing rifamycin, ethambutol, and clarithromycin with or without a fluoroquinolone for approximately 12 months have almost 100% treatment success.[123] Unlike many other NTM pathogens, the in vitro susceptibilities for *M. szulgai* appear to predict favorable treatment response.

Rapidly Growing Mycobacteria

Rapidly growing mycobacteria (RGM) are distinguished by growth in culture in less than 7 days and comprise over 70 distinct species, 17 of which have been associated with lung disease (see Table 35-1). Because many RGM are not pathogenic in humans, it is important to subclassify organisms within this group to the species level since this affects both treatment and prognosis. Although RGM can produce pulmonary disease, they have a propensity to produce skin and soft tissue infections.

Mycobacterium abscessus

Mycobacterium abscessus is the third most common NTM infection in the United States and causes 80% of infections due to RGM.[38] Most patients with pulmonary disease due to *M. abscessus* are nonsmoking, white women older than 60 years who have no predisposing conditions. The usual clinical presentation is similar that of other NTM pulmonary infections and includes cough and easy fatigability. For most patients with no predisposing conditions, the disease is slowly progressive; however, more fulminant, rapidly progressive disease has been seen in patients with gastroesophageal disorders and cystic fibrosis. The chest radiograph usually shows multilobar, patchy, reticulonodular or mixed reticulonodular-alveolar opacities[38] (Fig. 35-6). HRCT findings include the presence of cylindrical bronchiectasis with multiple small nodules, similar to MAC lung disease.[38,82,124] Cavitation has been reported in 10% to 20% of patients. Death occurred as a consequence of *M. abscessus* in 20% of patients in one report.[38]

Therapy of *M. abscessus* Pulmonary Disease. *Mycobacterium abscessus* is typically resistant in vitro to most of the medications used to treat tuberculosis, and has demonstrated in vitro activity to only a few antimicrobial agents. Cure with medical therapy may be unrealistic for *M. abscessus.* Therapy usually consists of 2 to 4 months of intravenous agents such as imipenem or cefoxitin plus amikacin given daily or three times weekly.[5] Any oral agents that have demonstrated in vitro activity should be included in the treatment regimen. Unfortunately, the macrolides are the only readily available oral agents typically active in vitro against *M. abscessus.* Linezolid, an oxazolidinone, is active against some strains of *M. abscessus,* but is frequently associated with significant hematologic toxicity and peripheral neuropathy.[125,126] Tigecycline has significant in vitro activity against *M. abscessus,* but is available only as an intravenous preparation and is associated with significant nausea and vomiting.

Once the patient has demonstrated a clinical response to therapy, there are several possible choices for continued treatment: (1) stop therapy after 2 to 4 months and follow the patient for signs of progression of disease and, if present, periodically reinstitute treatment; (2) stop the

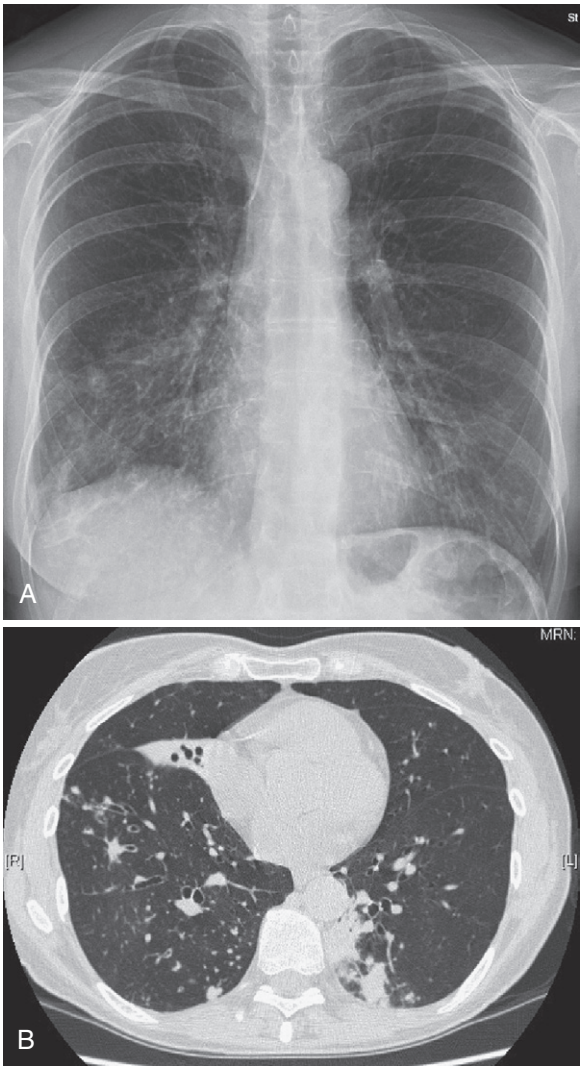

FIGURE 35-6 ■ A 68-year-old nonsmoking female with several-year history of cough, fatigue, and weight loss. Her sputum cultures were consistently positive for *M. abscessus*. **A,** Chest radiograph showing middle and lower lung zone nodular opacities and bronchiectasis. **B,** Chest computed tomography scan showing right middle lobe atelectasis and bronchiectasis with bilateral lower lobe bronchiectasis and nodular opacities. Note the left lower lobe air space opacity in this patient with severe reflux and probable chronic aspiration.

aminoglycoside and continue the cefoxitin or imipenem for a longer period along with an oral agent; and (3) continue an oral agent and institute inhaled amikacin. Unfortunately, none of these choices is evidence-based so, ultimately, treatment decisions will need to be individualized and often some form of therapy will be given periodically on a lifelong basis.

A combination of surgical resection and chemotherapy may increase the chance of cure in patients who have focal lung disease and who can tolerate resection. Patients should be treated with an initial period of antimicrobial drug therapy prior to surgery to lessen the bacillary load.[5] As with MAC lung disease, surgery should be performed by thoracic surgeons experienced in performing this type of surgery.[94]

Therapy of *M. abscessus* Skin, Soft Tissue, and Bone Infections. Serious infections should be treated with a regimen similar to that used for pulmonary disease. Skin and soft tissue infections should be treated for a minimum of 4 months and bone infections for 6 months. Surgery is generally indicated for extensive disease, abscess formation, or when drug therapy is difficult.[5] Foreign bodies such as prosthetic joints, percutaneous catheters, and breast implants should be removed, and the patient treated with a prolonged antimicrobial treatment regimen.

Mycobacterium chelonae

Mycobacterium chelonae is more likely to produce skin, soft tissue, and bone infections than pulmonary disease. Keratitis due to *M. chelonae* has been associated with wearing contact lenses and with ocular surgery such as laser-assisted in situ keratomileusis (LASIK).[127,128] Disseminated disease has been reported in immunecompromised patients and usually presents with characteristic cutaneous lesions.[129] The clinical and radiographic presentation of *M. chelonae* pulmonary disease is similar to that of other rapidly growing mycobacteria.

Isolates of *M. chelonae* are usually susceptible to tobramycin, the macrolides, linezolid, and imipenem.[73,130,131] Other active drugs may include amikacin, clofazimine, doxycycline, and the fluoroquinolones. *Mycobacterium chelonae* isolates are uniformly resistant to cefoxitin. Treatment of *M. chelonae* infections should be based on in vitro susceptibility results. Administration of clarithromycin 500 mg twice daily for 6 months was reported to have a high cure rate in patients with cutaneous lesions associated with disseminated disease.[132] The one patient who relapsed did so with a macrolide-resistant strain. Patients have also responded to linezolid with or without clarithromycin.[133,134] Patients with serious skin, soft tissue, and bone infections should be treated similarly to those with *M. abscessus* disease. For corneal infections, both topical and oral agents are often used, and many patients may require corneal transplants for recovery of vision or cure.

Mycobacterium fortuitum

Mycobacterium fortuitum is responsible for 15% of RGM cases in the United States but is a relatively uncommon cause of lung disease except in patients with disorders associated with chronic aspiration.[38] The clinical and radiographic presentation of patients with pulmonary disease is similar to that of other RGM. Skin, soft tissue, and bone infections are more common than pulmonary disease. Both sporadic and clustered outbreaks of furunculosis due to *M. fortuitum* (and other RGM) have been reported after exposure to contaminated water during pedicures.[135-137]

In contrast to *M. abscessus, M. fortuitum* demonstrates broader in vitro susceptibility to both oral and intravenous antimicrobial drugs, including the newer mac-

rolides, the fluoroquinolones, doxycycline, minocycline, the sulfonamides, and two intravenous drugs, imipenem and cefoxitin.[5] Although most isolates of *M. fortuitum* are susceptible in vitro to the macrolides, these drugs should be used with caution because of the presence of an inducible erythromycin methylase (*erm*) gene.[138]

Mycobacterium fortuitum lung disease should be treated with at least two drugs to which in vitro susceptibility has been demonstrated.[5] As with other NTM lung infections, treatment should be continued for at least 12 months of negative sputum cultures. Skin, soft tissue, and bone infections should be treated similarly to *M. abscessus* infections, although more effective oral agents are usually available.

Hypersensitivity Pneumonitis–Like NTM Pulmonary Disease

Most reports describing the development of a typical pattern of hypersensitivity pneumonitis–like lung disease have been in patients associated with hot-tub exposure, although similar clinical presentations have been associated with other indoor standing water sources and exposures.[28,139,140] In one case report, hypersensitivity-like lung disease was observed in association with an indoor shower.[28] Some investigators have used the phrase "hot-tub lung" to describe the presentation associated with standing water sources. In the cases of exposure to hot tubs, MAC has been the mycobacterial organism isolated from sputum, bronchoalveolar lavage, tissue, and hot-tub water. Furthermore, when assessed by genotyping methods, MAC isolates from both the hot-tub water and the lung specimens have demonstrated identical patterns. Controversy still exists, however, as to whether hot-tub lung is an infectious process, inflammatory process, or combination of processes.

Patients with hypersensitivity pneumonitis–like lung disease tend to be young and without preexisting lung disease. The clinical presentation varies from mild respiratory symptoms to respiratory failure requiring mechanical ventilatory support.[141] Key elements to the diagnosis of MAC hypersensitivity-like lung disease include a compatible clinical history (subacute onset of respiratory symptoms, hot-tub exposure), characteristic radiographic findings, and MAC isolates in sputum, bronchoalveolar lavage, tissue, and hot-tub water (and compatible histopathology when available).

Patient prognosis is generally excellent independent of severity on presentation.[139] The most benefit is gained by simply removing the patient from further antigen exposure. In the case of hot-tub lung, removal from antigen exposure generally involves drainage of hot-tub water and complete avoidance of hot-tub use. Whether continued exposure to ambient environmental MAC organisms can propagate the hypersensitivity pulmonary reaction is uncertain. For selected patients with hypersensitivity pneumonitis–like lung disease, use of systemic corticosteroids may be of benefit and hasten recovery of pulmonary symptoms, gas-exchange abnormalities, and radiographic abnormalities. Likewise, antimycobacterial therapy, with the same medications as for standard pulmonary MAC lung disease, may be required in some patients but for shorter durations of therapy, usually 3 to 6 months. Most patients can be expected to have nearly complete resolution of respiratory symptoms as well as of pulmonary function and radiographic abnormalities.

HEALTH CARE–ASSOCIATED NTM DISEASE AND PREVENTION OF NTM INFECTIONS

NTM are ubiquitous in the environment, so that complete avoidance is difficult if not impossible. The organisms generally have very low virulence for humans compared with *M. tuberculosis,* so NTM disease may be more a problem with host susceptibility than with organism contact. With some notable exceptions previously discussed, the specific susceptibility of an individual patient to NTM infection may be impossible to determine at this point; accordingly, disease prevention remains problematic. The question remains, however, should patients with known vulnerabilities to NTM infection be advised to avoid known environmental sources of NTM? For instance, should vulnerable patients be advised not to take showers, which are known to be associated with aerosolized NTM?[27] Currently the answer is unknown, and prevention of most environmentally acquired NTM infection remains a challenge.

Progress has been made, however, in the prevention of nosocomial NTM infections, which will prove to be the first step in the inevitable subsequent progress that will be made in the prevention of NTM infections as a whole. Transmission of NTM disease in the health care setting has most frequently been linked to tap (municipal) water exposure.[64] While various NTM species (including MAC, *M. kansasii, M. xenopi,* and *M. simiae*) have been isolated from municipal water supplies, *M. fortuitum* and *M. abscessus* have most often been implicated in health care–associated NTM disease. Even with use of potent disinfectants, including organomercurials, chlorine, bromine, 2% formaldehyde, and glutaraldehyde, NTM organisms may persist on equipment or devices after tap water exposure. The inability to eliminate these organisms underscores the importance of avoidance of tap water for preventing health care–associated NTM diseases, such as those following median sternotomy, plastic surgery procedures, liposuction, LASIK, dialysis, and the implantation of long-term central intravenous catheters, tympanostomy tubes, and prosthetic devices such as heart valves, knee and hip joints, lens implants, and metal rod bone stabilizers.[5] Pseudoutbreaks have involved bronchoscopes contaminated with *M. abscessus* and *M. immunogenum.* Documented outbreaks of hygiene-associated *M. fortuitum* and *M. mageritense* furunculosis in association with use of contaminated whirlpool footbaths have been described in nail salons.[137,142]

As a result of the increased understanding of environmental NTM reservoirs and reports linking the use of tap water to health care–associated NTM infections, it is recommended that tap water not be used in preparation of surgical procedures, prosthetics, and intravascular catheters; not be used in cleaning of fiberoptic endoscopes; and not be used to rinse the mouth out before collecting expectorated sputum samples. Moreover, recognition that alternative medicines or unapproved substances for injection may also be at risk of contamination by NTM warrants caution against use of these products as well.

KEY POINTS

- Nontuberculous mycobacteria (NTM) comprise over 140 different species that are ubiquitous in our environment. Members of the *Mycobacterium avium* complex (MAC) are the most common causes of NTM lung disease.
- Infection occurs after exposure to NTM in the environment: human-to-human transmission has not been described.
- Epidemiologic studies suggest that NTM infections are increasing in some areas of the world.
- Risk factors for pulmonary NTM disease include underlying chronic lung diseases such as chronic obstructive pulmonary diseases, cystic fibrosis, alpha$_1$-antitrypsin deficiency, prior tuberculosis, and bronchiectasis.
- Diagnosis of pulmonary NTM infections requires that the patient meet certain clinical, radiographic, and microbiologic criteria.
- The recommended treatment for MAC pulmonary disease is a macrolide, plus ethambutol and a rifamycin, with or without an aminoglycoside administered for at least 12 months of culture negativity.
- The recommended treatment for *Mycobacterium kansasii* pulmonary disease is isoniazid (or macrolide), rifamycin, and ethambutol administered for at least 12 months of culture negativity.
- Treatment of rapidly growing mycobacterial infections should be based on the results of in vitro drug susceptibility testing, but the clinical outcome varies significantly depending on the causative species.

REFERENCES

1. Wolinsky E: Nontuberculous mycobacteria and associated diseases. Am Rev Respir Dis 110:107–159, 1979.
2. Zakowski P, Fligiel S, Berlin OGW, et al: Disseminated *Mycobacterium avium-intracellulare* infection in homosexual men dying of acquired immunodeficiency. JAMA 248:2980–2982, 1982.
3. Levine B, Chaisson RE: *Mycobacterium kansasii:* A cause of treatable pulmonary disease associated with advanced human immunodeficiency virus (HIV) infection. Ann Intern Med 114:861–868, 1991.
4. Wallace RJ Jr, Cook JL, Glassroth J, et al: American Thoracic Society statement: Diagnosis and treatment of disease caused by nontuberculous mycobacteria. Am J Respir Crit Care Med 156:S1–S25, 1997.
5. Griffith DE, Aksamit T, Brown-Elliott BA, et al: An official ATS/IDSA statement: Diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. Am J Respir Crit Care Med 175:367–416, 2007.
6. Marras TK, Daley CL: Epidemiology of human pulmonary infection with nontuberculous mycobacteria. Clin Chest Med 23:553–567, 2002.
7. Palmer CE: Tuberculin sensitivity and contact with tuberculosis; further evidence of nonspecific sensitivity. Am Rev Tuberculosis 68:678–694, 1953.
8. Edwards FG: Disease caused by "atypical" (opportunist) mycobacteria: A whole population review. Tubercle 51:285–295, 1970.
9. Khan K, Wang J, Marras TK: Nontuberculous mycobacterial sensitization in the United States: National trends over three decades. Am J Respir Crit Care Med 176:306–313, 2007.
10. O'Brien RJ, Geiter LJ, Snider DE: The epidemiology of nontuberculous mycobacterial diseases in the United States: Results from a national survey. Am Rev Respir Dis 135:1007–1014, 1987.
11. CDC: Nontuberculous mycobacteria reported to the Public Health Laboratory Information System by state public health laboratories, United States 1993–1996. Atlanta, Georgia: U.S. Department of Health and Human Services, CDC, 1999. Available at www.cdc.gov/eid/content/14/3/390.htm.
12. Kubin M, Svandova E, Medek B, et al: *Mycobacterium kansasii* infection in an endemic area of Czechoslovakia. Tubercle 61:207–212, 1980.
13. Jenkins PA: The epidemiology of opportunistic mycobacterial infections in Wales, 1952–1978. Rev Infect Dis 3:1021–1023, 1981.
14. Kennedy MP, O'Connor TM, Ryan C, et al: Nontuberculous mycobacteria: Incidence in Southwest Ireland from 1987 to 2000. Respir Med 97:257–263, 2003.
15. O'Brien DP, Currie BJ, Krause VL: Nontuberculous mycobacterial disease in northern Australia: A case series and review of the literature. Clin Infect Dis 31:958–967, 2000.
16. Tsukamura M, Kita N, Shimoide H, et al: Studies on the epidemiology of nontuberculous mycobacteriosis in Japan. Am Rev Respir Dis 137:1280–1284, 1988.
17. Debrunner M, Salfinger M, Brandli O, et al: Epidemiology and clinical significance of nontuberculous mycobacteria in patients

negative for human immunodeficiency virus in Switzerland. Clin Infect Dis 15:330–345, 1992.
18. Marras TK, Chedore P, Ying AM, et al: Isolation prevalence of pulmonary non-tuberculous mycobacteria in Ontario 1997–2003. Thorax 62:661–666, 2007.
19. Iseman MD, Marras TK: The importance of nontuberculous mycobacterial lung disease. Am J Respir Crit Care Med 178:999–1000, 2008.
19a. Billinger ME, Olivier KN, Viboud C, et al: Nontuberculous mycobacterial-associated lung disease in hospitalized persons, United States, 1998–2005. Emerg Infect Dis 15:1562–1569, 2009.
20. Dailloux M, Abalain ML, Laurain C, et al: Respiratory infections associated with nontuberculous mycobacteria in non-HIV patients. Eur Respir J 28:1211–1215, 2006.
21. Good RC, for the Centers for Disease Control: Isolation of nontuberculous mycobacteria in the United States, 1979. J Infect Dis 142:779–783, 1980.
22. Good RC, Snider DE Jr: Isolation of nontuberculous mycobacteria in the United States, 1980. J Infect Dis 146:829–833, 1982.
23. Falkinham JO 3rd, Parker BC, Gruft H: Epidemiology of infection by nontuberculous mycobacteria. I. Geographic distribution in the eastern United States. Am Rev Respir Dis 121:931–937, 1980.
24. Corbett EL, Blumberg L, Churchyard GJ, et al: Nontuberculous mycobacteria: Defining disease in a prospective cohort of South African miners. Am J Respir Crit Care Med 160:15–21, 1999.
25. Corbett EL, Churchyard GJ, Clayton T, et al: Risk factors for pulmonary mycobacterial disease in South African gold miners: A case-control study. Am J Respir Crit Care Med 159:94–99, 1999.
26. Falkinham JO: Nontuberculous mycobacteria in the environment. Clin Chest Med 23:529–551, 2002.
27. Falkinham JO 3rd, Iseman MD, de Haas P, et al: *Mycobacterium avium* in a shower linked to pulmonary disease. J Water Health 6:209–213, 2008.
28. Marras TK, Wallace RJ Jr, Koth LL, et al: Hypersensitivity pneumonitis reaction to *Mycobacterium avium* in household water. Chest 127:664–671, 2005.
29. De Groote MA, Pace NR, Fulton K, et al: Relationships between *Mycobacterium* isolates from patients with pulmonary mycobacterial infection and potting soils. Appl Environ Microbiol 72: 7602–7606, 2006.
30. Corpe RF, Stergus I: Is the histopathology of nonphotochromogenic mycobacterial infections distinguishable from that caused by *Mycobacterium tuberculosis?* Am Rev Respir Dis 87:289–291, 1963.
31. Phillips MS, von Reyn CF: Nosocomial infections due to nontuberculous mycobacteria. Clin Infect Dis 33:1363–1374, 2001.
32. Reed C, von Reyn CF, Chamblee S, et al: Environmental risk factors for infection with *Mycobacterium avium* complex. Am J Epidemiol 164:32–40, 2006.
33. Prince DS, Peterson DD, Steiner RM, et al: Infection with *Mycobacterium avium* complex in patients without predisposing conditions [see comments]. N Engl J Med 321:863, 1989.
34. Robakiewicz M, Grzybowski S: Epidemiologic aspects of nontuberculous mycobacterial disease and of tuberculosis in British Columbia. Am Rev Respir Dis 109:613–620, 1974.
35. Field SK, Cowie RL: Lung disease due to the more common nontuberculous mycobacteria. Chest 129:1653–1672, 2006.
36. Kilby JM, Gilligan PH, Yankaskas JR, et al: Nontuberculous mycobacteria in adult patients with cystic fibrosis. Chest 102:70–75, 1992.
37. Olivier KN, Weber DJ, Wallace RJ Jr, et al, for the Nontuberculous Mycobacteria in Cystic Fibrosis Study Group: Nontuberculous mycobacteria. I: Multicenter prevalence study in cystic fibrosis. Am J Respir Crit Care Med 167:828–834, 2003.
38. Griffith DE, Girard WM, Wallace RJ Jr: Clinical features of pulmonary disease caused by rapidly growing mycobacteria: An analysis of 154 patients. Am Rev Respir Dis 147:1271–1278, 1993.
39. Varghese G, Shepherd R, Watt P, et al: Fatal infection with *Mycobacterium fortuitum* associated with oesophageal achalasia. Thorax 43:151–152, 1988.
40. Hadjiliadis D, Adlakha A, Prakash UB: Rapidly growing mycobacterial lung infection in association with esophageal disorders. Mayo Clin Proc 74:45–51, 1999.
41. Koh WJ, Lee JH, Kwon YS, et al: Prevalence of gastroesophageal reflux disease in patients with nontuberculous mycobacterial lung disease. Chest 131:1825–1830, 2007.
42. Thomson RM, Armstrong JG, Looke DF: Gastroesophageal reflux disease, acid suppression, and *Mycobacterium avium* complex pulmonary disease. Chest 131:1166–1172, 2007.
43. Reich JM, Johnson RE: *Mycobacterium avium* complex pulmonary disease presenting as an isolated lingular or middle lobe pattern: The Lady Windermere syndrome. Chest 101:1605–1609, 1992.
44. Iseman MD, Buschman DL, Ackerson LM: Pectus excavatum and scoliosis: Thoracic anomalies associated with pulmonary disease caused by *Mycobacterium avium* complex. Am Rev Respir Dis 144:914–916, 1991.
45. Kim RD, Greenberg DE, Ehrmantraut ME, et al: Pulmonary nontuberculous mycobacterial disease: Prospective study of a distinct preexisting syndrome. Am J Respir Crit Care Med 178:1066–1074, 2008.
46. Ziedalski TM, Kao PN, Henig NR, et al: Prospective analysis of cystic fibrosis transmembrane regulator mutations in adults with bronchiectasis or pulmonary nontuberculous mycobacterial infection. Chest 130:995–1002, 2006.
47. Nightingale SD, Byrd LT, Southern PM, et al: Incidence of *Mycobacterium avium-intracellulare* complex bacteremia in human immunodeficiency virus-positive patients. J Infect Dis 165:1082–1085, 1992.
48. Chin DP, Hopewell PC, Yajko DM, et al: *Mycobacterium avium* complex in the respiratory or gastrointestinal tract and the risk of *Mycobacterium avium* complex bacteremia in patients with human immunodeficiency virus infection. J Infect Dis 169:289–295, 1994.
49. Kalayjian RC, Toossi Z, Tomashefski JF Jr, et al: Pulmonary disease due to infection by *Mycobacterium avium* complex in patients with AIDS. Clin Infect Dis 20:1186–1194, 1995.
50. Hocqueloux L, Lesprit P, Herrmann JL, et al: Pulmonary *Mycobacterium avium* complex disease without dissemination in HIV-infected patients. Chest 113:542–548, 1998.
51. Bloch KC, Zwerling L, Pletcher MJ, et al: Incidence and clinical implications of isolation of *Mycobacterium kansasii:* Results of a 5-year, population-based study. Ann Intern Med 129:698–704, 1998.
52. Marras TK, Daley CL: A systematic review of the clinical significance of pulmonary *Mycobacterium kansasii* isolates in HIV infection. J Acquir Immune Defic Syndr 36:883–889, 2004.
53. Malouf MA, Glanville AR: The spectrum of mycobacterial infection after lung transplantation. Am J Respir Crit Care Med 160: 1611–1616, 1999.
54. Weinstock DM, Feinstein MB, Sepkowitz KA, et al: High rates of infection and colonization by nontuberculous mycobacteria after allogeneic hematopoietic stem cell transplantation. Bone Marrow Transplant 31:1015–1021, 2003.
55. Quejpo JA, Broseta E, Santos M, et al: Mycobacterial infection in a series of 1261 renal transplant recipients. Clin Microbiol Infect 9:518–525, 2003.
56. Doucette K, Fishman JA: Nontuberculous mycobacterial infection in hematopoietic stem cell and solid organ transplant recipients. Clin Infect Dis 38:1428–1439, 2004.
57. Sanguinetti M, Ardito F, Fiscarelli E, et al: Fatal pulmonary infection due to multidrug-resistant *Mycobacterium abscessus* in a patient with cystic fibrosis. J Clin Microbiol 39:816–819, 2001.
58. Morales P, Ros JA, Blanes M, et al: Successful recovery after disseminated infection due to *Mycobacterium abscessus* in a lung transplant patient: Subcutaneous nodule as first manifestation—a case report. Transplant Proc 39:2413–2415, 2007.
59. Taylor JL, Palmer SM: *Mycobacterium abscessus* chest wall and pulmonary infection in a cystic fibrosis lung transplant recipient. J Heart Lung Transplant 25:985–988, 2006.
60. Dorman SE, Holland SM: Interferon-gamma and interleukin-12 pathway defects and human disease. Cytokine Growth Factor Rev 11:321–333, 2000.
61. Keane J: Tumor necrosis factor blockers and reactivation of latent tuberculosis. Clin Infect Dis 39:300–302, 2004.

62. Salvana EM, Cooper GS, Salata RA: *Mycobacterium* other than tuberculosis (MOTT) infection: An emerging disease in infliximab-treated patients. J Infect 55:484–487, 2007.
62a. Rhoades ER, Archambault AS, Greendyke R, et al: *Mycobacterium abscessus* glycopeptidolipids mask underlying cell wall phosphatidyl-myo-inositol mannosides blocking induction of human macrophages TNF-alpha by preventing interaction with TLR2. J Immunol 183:1997–2007, 2009.
62b. Tateishi Y, Hirayama Y, Ozeki Y, et al: Virulence of *Mycobacterium avium* complex strains isolated from immunocompetent patients. Microb Pathog 46:6–12, 2009.
62c. van Ingen J, Bendien SA, de Lange WC, et al: Clinical relevance of non-tuberculous mycobacteria isolates in the Nijmegen-Arnheim region, The Netherlands. Thorax 64:502–506, 2009.
63. Tsukamura M: Diagnosis of disease caused by *Mycobacterium avium* complex. Chest 99:667–669, 1991.
64. Wallace RJ Jr, Brown A, Griffith DE: Nosocomial outbreaks/pseudo-outbreaks caused by nontuberculous mycobacteria. Annu Rev Microbiol 52:453–490, 1998.
65. Schaad UB, Votteler TP, McCracken GH, et al: Management of atypical mycobacterial lymphadenitis in childhood: A review based on 30 cases. J Pediatr 95:356–360, 1979.
66. Wolinsky E: Mycobacterial lymphadenitis in children: A prospective study of 105 nontuberculous cases with long-term follow-up. Clin Infect Dis 20:954–963, 1995.
67. Wallace RJ Jr, Swenson JM, Silcox VA, et al: Spectrum of disease due to rapidly growing mycobacteria. Rev Infect Dis 5:657–679, 1983.
68. Horsburgh CR: *Mycobacterium avium* complex infection in the acquired immunodeficiency syndrome. N Engl J Med 324:1332–1338, 1991.
69. Horsburgh CR Jr, Gettings J, Alexander LN, et al: Disseminated *Mycobacterium avium*-complex disease among patients infected with human immunodeficiency virus, 1985–2000. Clin Infect Dis 33:1938–1943, 2001.
70. Horsburgh CR Jr, Selik RM: The epidemiology of disseminated nontuberculous mycobacterial infection in the acquired immunodeficiency syndrome (AIDS). Am Rev Respir Dis 139:4–7, 1989.
71. Ingram CW, Tanner DC, Durack DT, et al: Disseminated infection with rapidly growing mycobacteria. Clin Infect Dis 16:463–471, 1993.
72. Chetchotisakd P, Kiertiburanakul S, Mootsikapun P, et al: Disseminated nontuberculous mycobacterial infection in patients who are not infected with HIV in Thailand. Clin Infect Dis 45:421–427, 2007.
73. Wallace RJ Jr, Brown BA, Onyi GO: Skin, soft tissue, and bone infections due to *Mycobacterium chelonae:* importance of prior corticosteroid therapy, frequency of disseminated infections, and resistance to oral antimicrobials other than clarithromycin. J Infect Dis 166:405–412, 1982.
74. Falkinham JO: Epidemiology of infection by nontuberculous mycobacteria. Clin Microbiol Rev 9:177–215, 1996.
75. Hall L, Doerr KA, Wohlfiel SL, et al: Evaluation of the MicroSeq system for identification of mycobacteria by 16S ribosomal DNA sequencing and its integration into a routine clinical mycobacteriology laboratory. J Clin Microbiol 41:1447–1453, 2003.
76. Claud JL, Neal J, Rosenberry R, et al: Identification of *Mycobacterium* spp. by using a commercial 16S ribosomal DNA sequencing kit and additional sequencing libraries. J Clin Microbiol 40:400–406, 2002.
77. El Amin NM, Hanson HS, Pettersson B, et al: 16S rRNA gene sequence analysis vs. conventional methods. Scand J Infect Dis 32:47–50, 2000.
78. Butler WR, Jost KC, Kilburn JO: Identification of mycobacteria by high-performance liquid chromatography. J Clin Microbiol 29:2468–2472, 1991.
79. Rogall T, Flohr T, Bottger EC: Differentiation of *Mycobacterium* species by direct sequencing of amplified DNA. J Gen Microbiol 136:1915–1920, 1990.
80. Kirschner P, Springer B, Vogel U, et al: Genotypic identification of mycobacteria by nucleic acid sequence determination: Report of a two year experience in a clinical laboratory. J Clin Microbiol 31:2882–2889, 1993.
81. Butler WR, Guthertz LS: Mycolic acid analysis by high-performance liquid chromatography for identification of *Mycobacterium* species. Clin Microbiol Rev 14:704–726, 2001.
82. Kim JS, Tanaka N, Newell JD, et al: Nontuberculous mycobacterial infection: CT scan findings, genotype, and treatment responsiveness. Chest 128:3863–3869, 2005.
83. Chan ED, Kaminska AM, Gill W, et al: Alpha-1-antitrypsin (AAT) anomalies are associated with lung disease due to rapidly growing mycobacteria and AAT inhibits *Mycobacterium abscessus* infection of macrophages. Scand J Infect Dis 39:690–696, 2007.
84. Chaisson RE, Benson CA, Dube MP, et al: Clarithromycin therapy for bacteremic *Mycobacterium avium* complex disease: A randomized, double-blind, dose-ranging study in patients with AIDS. Ann Intern Med 121:905–911, 1994.
85. Griffith DE, Brown BA, Girard WM, et al: Azithromycin activity against *Mycobacterium avium* complex lung disease in patients who were not infected with human immunodeficiency virus. Clin Infect Dis 23:983–989, 1996.
86. Wallace RJ Jr, Brown BA, Griffith DE, et al: Initial clarithromycin monotherapy for *Mycobacterium avium-intracellulare* complex lung disease. Am J Respir Crit Care Med 149:1335–1341, 1994.
87. Dautzenberg BD, Piperno P, Diot C, et al: Clarithromycin in the treatment of *Mycobacterium avium* lung infections in patients without AIDS. Chest 107:1035–1040, 1995.
88. Wallace RJ Jr, Brown BA, Griffith DE, et al: Clarithromycin regimens for pulmonary *Mycobacterium avium* complex: The first 50 patients. Am J Respir Crit Care Med 153:1766–1772, 1996.
89. Kobashi Y, Yoshida K, Miyashita N, et al: Relationship between clinical efficacy of treatment of pulmonary *Mycobacterium avium* complex disease and drug-sensitivity testing of Mycobacterium avium complex isolates. J Infect Chemother 12:195–202, 2006.
90. Griffith DE, Brown-Elliott BA, Langsjoen B, et al: Clinical and molecular analysis of macrolide resistance in *Mycobacterium avium* complex lung disease. Am J Respir Crit Care Med 174:928–934, 2006.
91. Tanaka E, Kimoto T, Tsuyuguchi K, et al: Effect of clarithromycin regimen for *Mycobacterium avium* complex pulmonary disease. Am J Respir Crit Care Med 160:866–872, 1999.
92. Griffith DE, Brown BA, Girard WM, et al: Azithromycin-containing regimens for treatment of *Mycobacterium avium* complex lung disease. Clin Infect Dis 32:1547–1553, 2001.
93. Wallace RJ Jr, Zhang Y, Brown-Elliot BA, et al: Repeat positive cultures in *Mycobacterium intracellulare* lung disease after macrolide therapy represent new infections in patients with nodular bronchiectasis. J Infect Dis 186:266–273, 2002.
94. Mitchell JD, Bishop A, Cafaro A, et al: Anatomic lung resection for nontuberculous mycobacterial disease. Ann Thorac Surg 85:1887–1892; discussion 1892–1883, 2008.
95. Gordin FM, Sullam PM, Shafran SD, et al: A randomized, placebo-controlled study of rifabutin added to a regimen of clarithromycin and ethambutol for treatment of disseminated infection with *Mycobacterium avium* complex. Clin Infect Dis 28:1080–1085, 1999.
96. Ward TT, Rimland D, Kauffman C, et al: Randomized, open-label trial of azithromycin plus ethambutol vs. clarithromycin plus ethambutol as therapy for *Mycobacterium avium* complex bacteremia in patients with human immunodeficiency virus infection. Clin Infect Dis 27:1278–1285, 1998.
97. Shafran SD, Singer J, Zarowny DP, et al: A comparison of two regimens for the treatment of *Mycobacterium avium* complex bacteremia in AIDS: Rifabutin, ethambutol, and clarithromycin versus rifampin, ethambutol, clofazimine and ciprofloxacin. N Engl J Med 335:377–383, 1996.
98. Chaisson RE, Keiser P, Pierce M, et al: Clarithromycin and ethambutol with or without clofazimine for the treatment of bacteremic *Mycobacterium avium* complex disease in patients with HIV infection. AIDS 11:311–317, 1997.
99. Benson CA, Kaplan JE, Masur H, et al: Treating opportunistic infections among HIV-infected adults and adolescents: Recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association/Infectious Diseases Society of America. MMWR Recomm Rep 53(RR-15):1–112, 2004.

100. Kaplan JE, Masur H, Holmes KK: Guidelines for preventing opportunistic infections among HIV-infected persons. MMWR Morb Mortal Wkly Rep 51(RR-8):1–52, 2002.
101. Oldfield EC 3rd, Fessel WJ, Dunne MW, et al: Once weekly azithromycin therapy for prevention of *Mycobacterium avium* complex infection in patients with AIDS: A randomized, double-blind, placebo-controlled multicenter trial. Clin Infect Dis 26:611–619, 1998.
102. Taha AM, Davidson PT, Bailey WC: Surgical treatment of atypical mycobacterial lymphadenitis in children. Pediatr Infect Dis 4:664–667, 1985.
103. Castro DJ, Hoover L, Castro DJ, et al: Cervical mycobacterial lymphadenitis: Medical vs. surgical management. Arch Otolaryngol 111:816–819, 1985.
104. Berger C, Pfyffer GE, Nadal D: Treatment of nontuberculous mycobacterial lymphadenitis with clarithromycin plus rifabutin. J Pediatr 128:383–386, 1996.
105. Engel HWB, Berwald LG, Havelaar AH: The occurrence of *Mycobacterium kansasii* in tap water. Tubercle 61:21–26, 1980.
106. MacSwiggan DA, Collins CH: The isolation of *M. kansasii* and *M. xenopi* from water systems. Tubercle 55:291–297, 1974.
107. Baily RK, Wyles S, Dingley M, et al: The isolation of high catalase *Mycobacterium kansasii* from tap water. Am Rev Respir Dis 101:430–431, 1970.
108. Cattamanchi A, Nahid P, Marras TK, et al: Detailed analysis of the radiographic presentation of *Mycobacterium kansasii* lung disease in patients with HIV infection. Chest 133:875–880, 2008.
109. Shitrit D, Baum GL, Priess R, et al: Pulmonary *Mycobacterium kansasii* infection in Israel, 1999–2004: Clinical features, drug susceptibility, and outcome. Chest 129:771–776, 2006.
110. Griffith DE, Brown-Elliot BA, Wallace RJ Jr: Thrice-weekly clarithromycin-containing regimen for treatment of *Mycobacterium kansasii* lung disease: Results of a preliminary study. Clin Infect Dis 37:1178–1182, 2003.
111. Wallace RJ Jr, Dunbar DF, Brown BA, et al: Rifampin-resistant *Mycobacterium kansasii*. Clin Infect Dis 18:1736–1743, 1994.
112. Bennett SN, Peterson DE, Johnson DR, et al: Bronchoscopy-associated *Mycobacterium xenopi* pseudoinfections. Am J Respir Crit Care Med 150:245–250, 1994.
113. van Ingen J, Boeree MJ, de Lange WC, et al: *Mycobacterium xenopi* clinical relevance and determinants, the Netherlands. Emerg Infect Dis 14:385–389, 2008.
114. Jenkins PA, Campbell IA, for the Research Committee of the British Thoracic Society: Pulmonary disease caused by *Mycobacterium xenopi* in HIV-negative patients: Five year follow-up of patients receiving standardized treatment. Respir Med 97:439–444, 2003.
115. Jenkins PA, Campbell IA, Banks J, et al: Clarithromycin vs ciprofloxacin as adjuncts to rifampicin and ethambutol in treating opportunist mycobacterial lung diseases and an assessment of *Mycobacterium vaccae* immunotherapy. Thorax 63:627–634, 2008.
116. Hoefsloot W, Boeree MJ, van Ingen J, et al: The rising incidence and clinical relevance of *Mycobacterium malmoense:* A review of the literature. Int J Tuberc Lung Dis 12:987–993, 2008.
117. Research Committee of the British Thoracic Society: Pulmonary disease caused by *M. malmoense* in HIV negative patients: 5-year follow-up of patients receiving standardized treatment. Eur Respir J 21:478–482, 2003.
118. El Sahly HM, Septimus E, Soini H, et al: *Mycobacterium simiae* pseudo-outbreak resulting from a contaminated hospital water supply in Houston, Texas. Clin Infect Dis 35:802–807, 2002.
119. Conger NG, O'Connell RJ, Laurel VL, et al: *Mycobacterium simiae* outbreak associated with a hospital water supply. Infect Control Hosp Epidemiol 25:1050–1055, 2004.
120. Valero G, Peters J, Jorgensen H, et al: Clinical isolates of *Mycobacterium simiae* in San Antonio, Texas. Am J Respir Crit Care Med 152:1555–1557, 1995.
121. van Ingen J, Boeree MJ, Dekhuijzen PN, et al: Clinical relevance of *Mycobacterium simiae* in pulmonary samples. Eur Respir J 31:106–109, 2008.
122. Shitrit D, Peled N, Bishara J, et al: Clinical and radiological features of *Mycobacterium kansasii* infection and *Mycobacterium simiae* infection. Respir Med 102:1598–1603, 2008.
123. van Ingen J, Boeree MJ, de Lange WC, et al: Clinical relevance of *Mycobacterium szulgai* in The Netherlands. Clin Infect Dis 46:1200–1205, 2008.
124. Han D, Lee KS, Koh WJ, et al: Radiographic and CT findings of nontuberculous mycobacterial pulmonary infection caused by Mycobacterium abscessus. AJR Am J Roentgenol 181:513–517, 2003.
125. Wallace RJ Jr, Brown-Elliott BA, Ward SC, et al: Activities of linezolid against rapidly growing mycobacteria. Antimicrob Agents Chemother 45:764–767, 2001.
126. Ntziora F, Falagas ME: Linezolid for the treatment of patients with [corrected] mycobacterial infections [corrected] a systematic review. Int J Tuberc Lung Dis 11:606–611, 2007.
127. Freitas D, Alvarenga L, Sampaio J, et al: An outbreak of *Mycobacterium chelonae* infection after LASIK. Ophthalmology 110:276–285, 2003.
128. Winthrop KL, Steinberg EB, Holmes G, et al: Epidemic and sporadic cases of nontuberculous mycobacterial keratitis associated with laser in situ keratomileusis. Am J Ophthalmol 135:223–224, 2003.
129. Fournier S, Pialoux G, Vincent V: *Mycobacterium genavense* and cutaneous disease in AIDS. Ann Intern Med 128:409, 1998.
130. Brown BA, Wallace RJ Jr, Onyi GO, et al: Activities of four macrolides, including clarithromycin, against *Mycobacterium fortuitum, Mycobacterium chelonae,* and *Mycobacterium chelonae*-like organisms. Antimicrob Agents Chemother 36:180–184, 1992.
131. Swenson JM, Wallace RJ Jr, Silcox VA, et al: Antimicrobial susceptibility testing of 5 subgroups of *Mycobacterium fortuitum* and *Mycobacterium chelonae*. Antimicrob Agents Chemother 28:807–811, 1985.
132. Wallace RJ Jr, Swenson JM, Silcox VA, et al: Treatment of nonpulmonary infections due to *Mycobacterium fortuitum* and *Mycobacterium chelonei* on the basis of *in vitro* susceptibilities. J Infect Dis 152:500–514, 1985.
133. Brown-Elliott BA, Wallace RJ Jr, Blinkhorn R, et al: Successful treatment of disseminated *Mycobacterium chelonae* infection with linezolid. Clin Infect Dis 33:1433–1434, 2001.
134. Kyle SD, Porter WM: *Mycobacterium chelonae* infection successfully treated with oral clarithromycin and linezolid. Br J Dermatol 151:1101, 2004.
135. Sniezak PJ, Graham BS, Busch HB, et al: Rapidly growing mycobacterium infections following pedicures. Arch Dermatol 139:629–634, 2003.
136. Winthrop KL, Albridge K, South D, et al: The clinical management and outcome of nail salon-acquired *Mycobacterium fortuitum* skin infection. Clin Infect Dis 38:38–44, 2004.
137. Winthrop KL, Abrams M, Yakrus MA, et al: An outbreak of mycobacterial furunculosis associated with footbaths at a nail salon. N Engl J Med 346:1366–1371, 2002.
138. Nash KA: Intrinsic macrolide resistance in *Mycobacterium smegmatis* is conferred by a novel erm gene, erm(38). Antimicrob Agents Chemother 47:3053–3060, 2003.
139. Hanak V, Kalra S, Aksamit TR, et al: Hot tub lung: Presenting features and clinical course of 21 patients. Respir Med 100:610–615, 2006.
140. Aksamit TR: Hot tub lung: Infection, inflammation, or both? Semin Respir Infect 18:33–39, 2003.
141. Mangione EJ, Huitt G, Lenaway D, et al: Nontuberculous mycobacterial disease following hot tub exposure. Emerg Infect Dis 7:1039–1042, 2001.
142. Vugia DJ, Jang Y, Zizek C, et al: Mycobacteria in nail salon whirlpool footbaths, California. Emerg Infect Dis 11:616–618, 2005.
143. Tortoli E: The new mycobacteria: An update. FEMS Immunol Med Microbiol 48:159–178, 2006.
144. Tortoli E: Impact of genotypic studies on mycobacterial taxonomy: The new mycobacteria of the 1990's. Clin Microbiol Rev 16:319–354, 2003.

CHAPTER 36

FUNGAL INFECTIONS

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INTRODUCTION

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UNCOMMON PULMONARY FUNGAL INFECTIONS
Pulmonary Infections Due to *Scedosporium* (Formerly Pseudallescheriosis, Allescheriosis, Maduromycosis of the Lung)
Pulmonary Sporotrichosis
Other Fungi

INTRODUCTION

From the standpoint of fungal diseases, North America is unique among the continents because it is the "home" of three of the major endemic mycoses: histoplasmosis, blastomycosis, and coccidioidomycosis. Although histoplasmosis is also found in all the other continents except Antarctica, coccidioidomycosis in South America, and blastomycosis in Africa, only in North America are these illnesses common.

These three fungal diseases share many characteristics. The causative agents are mycelial soil organisms. Illness is acquired by inhaling aerosolized spores. In the infected host, the organisms change their form, a characteristic called "dimorphism." *Histoplasma capsulatum* and *Blastomyces dermatitidis* convert to a yeast

form at 37°C (thermal dimorphism), whereas *Coccidioides immitis* converts in tissue to a spherule that replicates by forming endospores (tissue dimorphism).

The endemic areas are large. Most of the midwest and south-central United States is endemic for both histoplasmosis[1] and blastomycosis,[2] and a large area in the southwest United States and an adjacent area of Mexico are endemic for coccidioidomycosis.[3] All three illnesses occur in normal hosts, although histoplasmosis and coccidioidomycosis are also major opportunistic mycoses in patients with depressed cell-mediated immunity, and especially in patients with acquired immunodeficiency syndrome (AIDS).[4,5] Paracoccidioidomycosis is the major endemic mycosis in South America.[6] The causative organism is also a thermally dimorphic soil organism. Cryptococcosis occurs worldwide. The causative organism is not dimorphic. It is always a yeast form both in nature and in the infected host. The disease is acquired by inhalation, but the organism evokes little inflammatory response in the lung. It has an unusual trophism for the central nervous system (CNS), so most diagnosed cases of cryptococcosis are chronic meningitis rather than pneumonia.

The endemic mycoses and cryptococcosis all share one important feature: inhaled spores cannot be killed by neutrophils either because they resist intracellular killing[7] or, in the case of cryptococcosis, because they escape phagocytosis. Thus, intact cell-mediated immunity is crucial to prevent progressive infection. The result is a high likelihood of benign self-limited infection when cellular immunity is intact and a high likelihood of progressive primary infection when it is not. There is also epidemiologic evidence of relapse after long dormancy (similar to tuberculosis) when T-cell function becomes very depressed. Cryptococcosis, histoplasmosis, and coccidioidomycosis are major T-cell opportunistic infections, as demonstrated by their very aggressive courses in patients with AIDS, in whom T-cell deficiency is most severe. Blastomycosis and paracoccidioidomycosis also exploit T-cell deficiency.

Aspergillosis and mucormycosis occur worldwide; their causative agents are ubiquitous soil organisms that are always mycelial (growing as branching hyphae) both in nature and in infected mammalian tissue. Spores are regularly inhaled, but the fungi have low virulence and almost no ability to invade a normal host. In fact, adequate phagocyte function is sufficient for protection, even without specific cellular immunity. The risk factors for infection include prolonged neutropenia and use of high-dose corticosteroids (which depress phagocyte as well as T-cell function). Patients with human immunodeficiency virus (HIV) infection have no major problem with these organisms unless phagocyte number, phagocyte function, or both are reduced, either by the disease, by comorbid illness, or by the toxicity of various therapies.

Candidiasis is unlike other fungal infections in many ways. *Candida albicans* is not a soil organism and is not acquired by inhalation. Rather, it is part of the normal pharyngeal and gastrointestinal flora of humans. T-cell function is required to prevent mucosal overgrowth, which occurs in mucocutaneous candidiasis and especially with HIV infection. However, normal phagocyte function and intact skin and mucosal barriers are adequate to prevent deep infection, which usually occurs across the bowel wall or through the skin (often aided by intravascular catheters). Pulmonary disease usually results from hematogenous spread to the lung. Primary pulmonary infections, from aspiration of pharyngeal material, are rare.

A variety of other soil organisms rarely causes pulmonary or systemic infections when phagocyte defects are present. They are best thought of as aspergillosis-like infections and are discussed only briefly in this chapter. Sporotrichosis is also caused by a soil fungus. Usually, it is an inoculation disease with lesions of the skin and draining lymphatics. Rarely, sporotrichosis presents as pneumonia, likely following inhalation of aerosolized fungal spores.

In view of their important linkage with immunologic and nonimmunologic defenses, it is possible to classify pulmonary fungal diseases according to the major impairment of host defenses that contributes to their pathogenesis (Table 36-1). The diseases are discussed in this chapter in the order in which they appear in the table. *Pneumocystis jirovecii* (formerly *carinii*) was formerly considered a protozoan but is presently classified as a fungus. *P. jirovecii* pneumonia and the other fungal complications of AIDS and non-AIDS immunosuppressive disorders are discussed in Chapters 80 and 82.

HISTOPLASMOSIS

Histoplasmosis is the illness caused by the thermal dimorphic fungus *H. capsulatum*. The spectrum of disease caused by the fungus ranges from the asymptomatic acquisition of a positive histoplasmin skin test reaction to a rapidly fatal pulmonary or disseminated illness.

TABLE 36-1. Classification of Pulmonary Fungal Diseases According to the Major Impairment of Host Defenses That Contributes to Their Pathogenesis

DEFECTS OF T-CELL FUNCTION
Histoplasmosis
Blastomycosis
Coccidioidomycosis
Paracoccidioidomycosis
Cryptococcosis
DEFECTS OF PHAGOCYTIC FUNCTION
Aspergillosis
Mucormycosis
Candidiasis
Pseudoallescheriosis
Other (rare) fungi

History and Epidemiology

The first case of histoplasmosis was recognized by Samuel Darling in Panama in 1906.[8] Darling, a U.S. Army pathologist, performed an autopsy on a man who had died of a progressive systemic infection. Darling identified an organism that resembled *Leishmania donovani* microscopically in the tissue sections. He assumed that the organism was a protozoan, and he named it *Histoplasma capsulatum*. During the next 2 years, Darling found two similar cases, also at autopsy. The name *H. capsulatum*, unfortunate because it implies a protozoan, persists to this date, even though daRocha-Lima[9] correctly surmised as early as 1912 that the organism was actually a fungus. There is no capsule; the lucent areas Darling saw surrounding the organisms probably were due to an artifact of tissue preparation.

In 1926, Riley and Watson,[10] the latter a first-year resident in pathology, reported the next case from Minnesota, also at autopsy, and rekindled awareness of the disease. Histoplasmosis was first diagnosed during life by Dodd and Tompkins,[11] who identified intracellular organisms on the peripheral blood smear of a leukemic child from Tennessee dying of a systemic febrile illness with hepatosplenomegaly and anemia. DeMonbreun[12] successfully isolated the organism using animal inoculation. He proved that the organism was a fungus and demonstrated its thermal dimorphism. For the next few years, scattered similar cases were reported from the central United States, maintaining the general perception that histoplasmosis was a rare and uniformly fatal illness.

About that time, it was recognized that many tuberculin-negative individuals in the central United States had unexplained pulmonary calcifications. A major advance in understanding histoplasmosis came when Christie and Peterson[13] hypothesized that these calcifications might be caused by healed *H. capsulatum* infection. Using the original De-Monbreum isolate, they prepared histoplasmin, a complex skin test antigen. They tested tuberculin-negative persons in Nashville, Tennessee, who had pulmonary calcifications on their chest radiograph: All had positive histoplasmin skin tests. Their findings were quickly confirmed and extended by Palmer[14] of the U.S. Public Health Service. Shortly thereafter, Emmons[15] was able to grow the fungus from the soil in the endemic area, especially soil enriched by bird droppings.

Thus, during a period of only a few years, histoplasmosis, formerly considered rare and uniformly fatal, became recognized as common and almost invariably benign. The natural habitat for the fungus was the soil, and human and animal infections occurred after inhalation of the infecting particle. Extensive skin test surveys suggest that as many as 50 million people in the United States have been infected by *H. capsulatum* and that there are up to 500,000 new infections yearly.[16]

The organism requires organic nitrogen for growth and is frequently isolated from soil heavily contaminated by bird or bat feces.[15,17] In nature, the fungus grows as an aerial mycelium with many small spores on specialized side branches. When a site harboring the fungus is disturbed, an aerosol is formed. Infection often follows exposure because the spores, when inhaled, are almost the perfect size to reach the alveoli.

During the 1950s, many small outbreaks of histoplasmosis were linked to exposure to (usually abandoned) chicken houses. With the shift of the U.S. population from predominantly rural to urban and suburban and the abandonment of household raising of chickens, the epidemiology of histoplasmosis has changed.[18] For decades, most outbreaks have occurred in urban settings, frequently in areas of relatively low endemicity. A large community-wide outbreak in Montreal and two separate outbreaks in Mason City, Iowa, occurred in areas where histoplasmosis had seldom been recognized.[18] All were associated with construction projects that disturbed contaminated soil.[18] The most recent (and largest ever) outbreak occurred in Indianapolis, Indiana,[19] associated with downtown construction of a swimming pool complex. Indianapolis is within the endemic area. The huge number of primary infections during the Indianapolis outbreak suggests that urban dwellers, even in endemic areas, do not regularly become infected with *H. capsulatum*. Thus, they remain susceptible when exposed to aerosolized spores during construction activity.

The source of the fungus has also changed. Small contaminated sites associated with chicken houses have been replaced by large contaminated sites associated with blackbird roosts. Blackbirds (grackles, starlings, red-winged blackbirds, and others) are gregarious and often roost in large aggregations of birds, producing enormous amounts of droppings. Tree-lined river banks are favorite roosting sites. When such sites are disturbed by construction activities, immense numbers of spores can be aerosolized, leading to community-wide outbreaks involving hundreds or thousands of people. Mini-outbreaks also still occur. Cutting up fallen trees for firewood is a more modern cause of histoplasmosis than entering a chicken coop. The chain saw creates an excellent aerosol.

Pathogenesis

The lung is the portal of entry in almost every case.[20] Direct percutaneous inoculation of the spores may occur, but only a few such cases have ever been reported. Also, rarely, the organism can be transmitted by organ transplantation from a donor with unrecognized active histoplasmosis in the donated organ.[21]

When the spores of *H. capsulatum* are inhaled, some elude the nonspecific defenses of the lung. Spores that reach the alveoli convert to the yeast phase and multiply by binary fission. The initial tissue response to the organism is predominantly neutrophilic, followed by an increase in alveolar macrophages.[22] The yeast forms are phagocytosed by the macrophages but are not killed. In fact, they multiply rapidly within the macrophages and spread to hilar lymph nodes and then throughout the body. During this time, metastatic foci of infection develop in many organs, such as the liver and spleen.[23]

When lymphocyte-mediated cellular immunity develops, usually about 2 weeks after the original inhalation, there is an increase in immune lymphocytes in the lung

and other infected organs. These lymphocytes arm macrophages, which improves their ability to control the fungus. In mice, interleukin-12 is an important signal, leading to increased interferon-γ production that confers protection against primary infection.[23–26] Tumor necrosis factor (TNF)-α is also increased and provides additional protective effects.[23–27] Granuloma formation depends on complex cellular interactions between immune lymphocytes and armed macrophages. As the intensity of cellular inflammation increases, necrosis occurs, which is often caseous and at times is indistinguishable from the necrosis seen in tuberculosis.[28] Areas of caseation necrosis occur not only in the lung but also at all distant sites.

Healing of these lesions is accompanied by peripheral fibrosis. Central areas of encapsulated, necrotic material frequently calcify. These calcified foci manifest on chest radiograph as single or multiple calcified nodules or as a classic Ranke complex with peripheral and hilar calcifications. Calcified lesions are often seen in the liver and the spleen.[29]

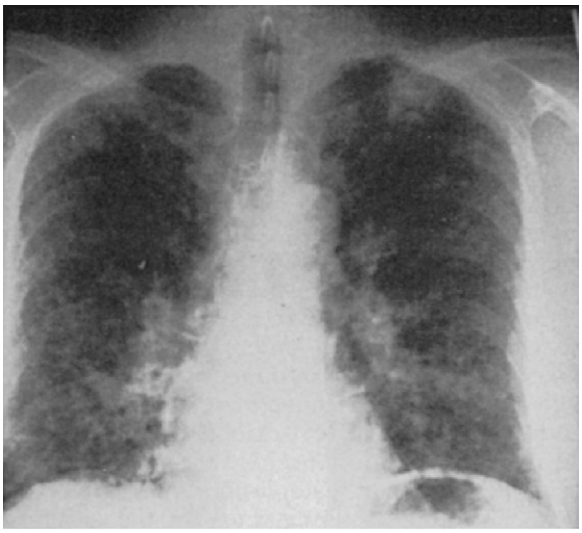

FIGURE 36-1 ■ Chest radiograph shows acute pulmonary histoplasmosis. Note the bilateral opacities and bilateral hilar adenopathy.

Clinical Manifestations

Most normal persons who are infected by the fungus remain asymptomatic. Even when symptoms do occur, they are usually nonspecific; hence, ordinary sporadic, mild infections are seldom diagnosed. Most of what is known about symptomatic primary histoplasmosis comes from the study of outbreaks of the disease. Many of the first reported outbreaks were small, involving only a few individuals. Frequently, the exposure to the fungus took place in a confined place, such as a storm cellar, a chicken house, or a bat cave. In these small outbreaks, symptoms were very common. The severity of illness ranged from mild respiratory illness to overwhelming pneumonia with diffuse nodular opacities and severe gas-exchange abnormalities.[30]

In more recent community-wide outbreaks, exposure to the fungus has been not in enclosed spaces but in open air, where fewer infectious spores are inhaled.[31,32] In these groups, the frequency of symptomatic illness is lower (<50% of infected individuals as determined by skin test conversion). Even when illness is symptomatic, the severity of symptoms is less.

The incubation time of acute histoplasmosis in previously nonimmune individuals ranges between 9 and 17 days. In an open-air outbreak in Minneapolis, Minnesota (low background endemicity), the mean incubation time was 14 days. In that outbreak, the day and the hour of exposure were known, because all patients visited the infectious site for less than 2 hours.

When present, symptoms vary widely from brief periods of malaise to severe, life-threatening illness. In a typical patient, the illness resembles influenza. The onset is abrupt, with fever, chills, and substernal chest discomfort. A harsh, nonproductive cough develops along with headache, arthralgias, and myalgias. Erythema nodusum may occur, drawing attention.

Whether symptomatic or not, normal hosts recover uneventfully from primary pulmonary infection more than 99% of the time.[20] Only rarely, when the infective dose is unusually high, does severe pulmonary illness develop, which may progress rapidly to the acute respiratory distress syndrome, and may lead to death from respiratory insufficiency if not treated promptly.[1]

Even though the portal of entry is the lung, many patients, even those with symptoms, have a normal chest radiograph. When the chest radiograph is abnormal, the characteristic finding is a single area (or occasionally multiple areas) of pneumonitis, usually in better-ventilated lower lung zones. The draining hilar and mediastinal lymph nodes are often enlarged on the ipsilateral side (Fig. 36-1).[1,20] Unfortunately, this parenchymal–hilar node complex may be incomplete, with either component being absent, making the radiographic diagnosis more difficult. Furthermore, these abnormalities on chest radiograph may occur in asymptomatic individuals, causing diagnostic problems when they are discovered accidentally.

Healing of histoplasma pulmonary lesions may be complete, with total resolution of the previously noted pneumonitis. However, in some patients, the lesion contracts into a round nodule concurrent with the pathologic sequence of central necrosis, fibrous encapsulation, and variable calcification (Fig. 36-2). These residual "coin" lesions are common in endemic areas. If the lesions do not calcify, then differentiation from bronchogenic carcinoma is sometimes difficult.[20] Early in the course, they may be metabolically active, even lighting up on positron emission tomography (PET) computed tomography (CT) scans. Later, they have low metabolic activity, are less likely to enhance on contrast CT, and have increased density compared with lung neoplasms. In general, lesions calcify more often and more quickly in children and young adults than in older individuals.

Similarly, healing of caseation necrosis in the hilar and mediastinal lymph nodes may lead to calcifications, often larger than similar calcifications in tuberculosis. Follow-

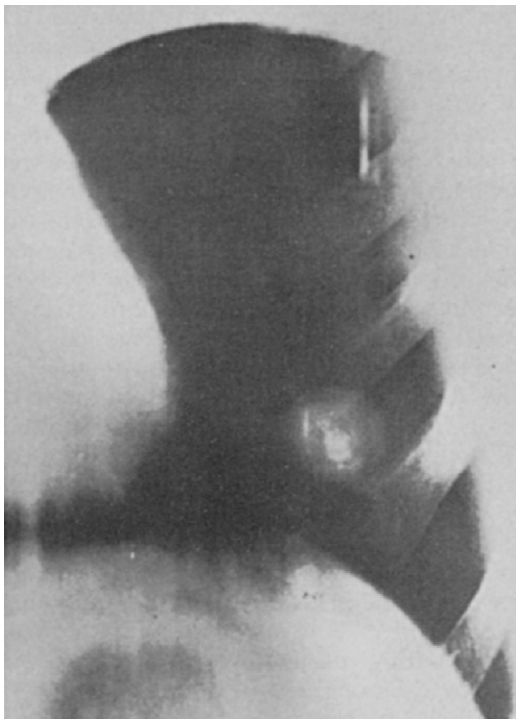

FIGURE 36-2 ■ Tomogram shows dense central calcification as well as concentric circles of laminar calcifications in a "coin" lesion of histoplasmosis.

ing heavy exposure, typical diffuse nodular opacities may develop, which are different from miliary tuberculosis because the individual lesions are larger and not as sharply defined. When healing occurs, the necrotic central areas of all these lesions may calcify, producing characteristic buckshot calcifications throughout the lungs.[20]

Physical examination during acute histoplasmosis is usually negative, except for fever. Hepatosplenomegaly usually implies disseminated disease and is discussed later. However, there are several syndromes associated with acute histoplasmosis that present with striking signs and symptoms. Perhaps the most impressive is the arthralgia–erythema nodosum–erythema multiforme complex. Arthralgias may occur during the acute symptomatic phase of the illness and may be severe enough to interfere with walking and other activities of daily living. Arthralgias usually resolve within a week or so. In several large outbreaks, erythema nodosum and erythema multiforme were noted, usually in patients with arthralgias.[33] These allergic skin manifestations occurred most often in women with normal or mildly abnormal chest radiographs, at the height of the cell-mediated immune response. The overall incidence of erythema nodosum, erythema multiforme, or both, in primary histoplasmosis is less than 1%.

Local Complications

Acute histoplasmosis is usually a benign and self-limited infection in persons with normal immunity. Serious complications occur occasionally and are usually caused by involvement of strategically located structures. Marked enlargement of the paratracheal lymph nodes may compress the trachea or one of the main-stem bronchi, causing an irritative cough, dyspnea, or both. Enlarged mediastinal lymph nodes may impinge on the esophagus (causing dysphagia) or on the superior vena cava (causing edema of the head and upper extremities).[20,34] These complications are encompassed within the term *mediastinal granuloma*. A surgical approach to isolated large nodes may improve symptoms but may not be necessary because the natural history is slow improvement. When surgery is done, the back wall of the resected nodal mass can be left in place to avoid too-aggressive dissection into adjacent vascular structures. Endovascular stenting has been used successfully to relieve superior vena caval obstruction.

Lymph nodes that calcify during healing may also impinge on adjacent structures or may even erode into various tissues. Erosion through the wall of the trachea or bronchi may cause broncholithiasis. Patients present with obstructive pneumonia, with expectoration of stones, or with hemoptysis. Rarely, calcified nodes may create tracheoesophageal fistulas when they erode into both adjacent structures.

Another rare manifestation of histoplasmosis is mediastinal fibrosis, which accompanies the healing of involved mediastinal lymph nodes, entrapping contiguous mediastinal structures. Bronchi may be entrapped, as may branches of pulmonary arteries and veins. In extreme cases, progressive obliteration of pulmonary vessels leads to pulmonary hypertension and death from cor pulmonale. Unfortunately, a surgical approach to diffuse mediastinal fibrosis is risky and not usually helpful, even though the course of illness is progressive. There have been anecdotal reports of endovascular stenting of focally narrowed arteries and pulmonary veins with some symptomatic improvement.[34a]

During the large outbreak of histoplasmosis in Indianapolis, pericarditis was identified as a relatively common complication of primary histoplasmosis, occurring in 45 of 712 patients (6.3%).[35] The pericardial effusions were usually sterile exudates. The pericardial inflammation is probably due to histoplasma involvement of adjacent mediastinal structures rather than to hematogenous spread of the fungus to the pericardium.

Chronic Pulmonary (Cavitary) Histoplasmosis

When primary histoplasmosis occurs in individuals with structurally abnormal lungs, such as heavy smokers with established emphysema, the infection often involves the upper lobes, which are most abnormal. Radiographically, the infection frequently mimics reinfection tuberculosis because bullae in radiographically involved lung may mimic cavitary disease.

Because of the resemblance to tuberculosis, it is not surprising that this form of histoplasmosis was first discovered in tuberculosis sanatoriums.[36] Many patients were chronically ill, and many died quickly, often in part

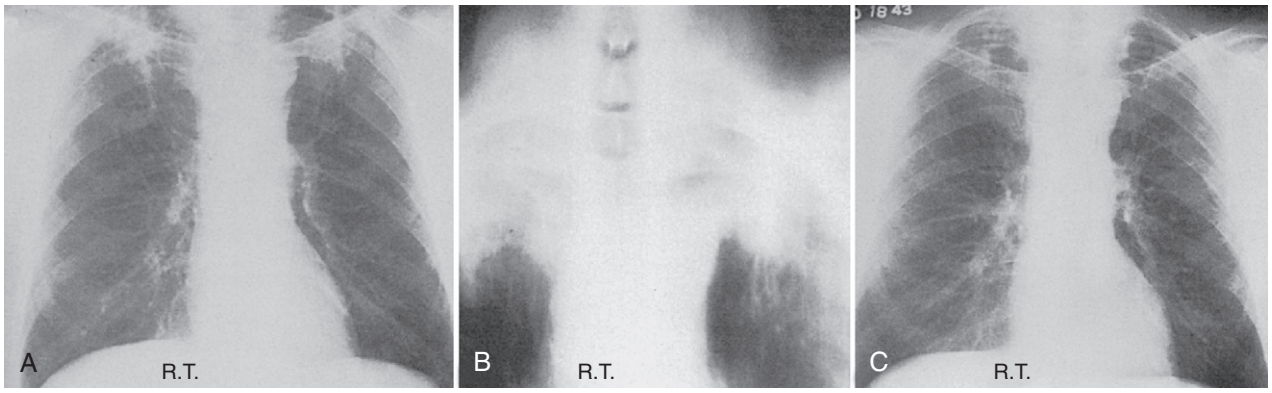

FIGURE 36-3 ■ Acute, self-limited upper lobe histoplasmosis in a 48-year-old cigarette smoker. **A,** The admission chest radiograph shows bilateral apical disease. **B,** The apical tomograms demonstrate multiple small cavities. **C,** The follow-up chest radiograph shows clearing.

from their underlying diseases. This led to the impression, subsequently proved false, that this form of histoplasmosis had a poor prognosis.

Goodwin and colleagues[37] were the first to point out that not all such patients have a progressive, destructive pulmonary infection. Virtually all have underlying chronic obstructive pulmonary disease. The infection smolders in the abnormal lung. Even in this setting, acute histoplasma infection often slowly resolves spontaneously, though more slowly (Fig. 36-3).[37,38] Occasionally, however, infection in these abnormal air spaces persists and progresses, enlarging existing emphysematous spaces and destroying adjacent, more normal pulmonary parenchyma.[37]

Clinically as well as radiographically, the symptoms of this progressive form of upper lobe histoplasmosis mimic those of tuberculosis. Low-grade fever and anorexia with weight loss are common. Most patients develop a productive cough, with variable amounts of mucopurulent sputum. Night sweats also occur but are not as prominent as in tuberculosis. As mentioned, the chest radiographic findings are usually similar to those of reinfection tuberculosis, showing fibrocavitary disease, sometimes with volume loss (Fig. 36-4).

Progressive Disseminated Histoplasmosis

During the early phase of acute histoplasmosis, the fungus gains access to the circulation via the hilar lymph nodes. It is likely that transient self-limited fungemia occurs in most, if not all, patients. Evidence for this comes from postmortem studies in the most highly endemic areas, in which careful search reveals healed, often calcified, granulomas in the spleen in more than 70% of autopsies.[29]

The circulating yeasts are phagocytosed by cells of the reticuloendothelial system. Killing of the fungus does not occur at first, and there is further multiplication intracellularly. With the advent of T-lymphocyte–mediated immunity, fungal replication is checked and granuloma formation begins. If the cell-mediated immune response is poor, the yeast continue to multiply. More macrophages are recruited, which in turn become parasitized and eventually disrupted, perpetuating the cycle.[5] A severe systemic illness develops, which invariably leads to death unless treated promptly and aggressively.

On physical examination, patients are febrile and acutely ill. Hepatosplenomegaly may be present. Laboratory evaluation may show anemia, leukopenia, and thrombocytopenia. In extremely ill patients, disseminated intravascular coagulation may be seen. The chest radiographic findings are variable, ranging from normal to diffusely abnormal (Fig. 36-5).[39] Biopsy material from the bone marrow and other involved tissue shows collections of macrophages full of intracellular yeast (Fig. 36-6) or, in the most severe instances, widespread necrosis with large numbers of organisms lying loose in the extracellular debris with little, if any, evidence of granuloma formation.[40] Virtually all patients with this form of the illness have some degree of T-cell defect. Before the modern era of widespread use of cytotoxic agents and glucocorticoids, many patients had underlying Hodgkin's disease, a well-known example of naturally occurring T-cell immune deficiency.[5,39]

The most severe form of progressive disseminated histoplasmosis (PDH) occurs in patients with AIDS with profound T-cell dysfunction.[41] In fact, most cases of PDH now occur in AIDS patients, and most occur in highly endemic areas.[42,43] Immunosuppressive treatment for malignancy and for organ transplantation is also associated with PDH. Newer biologic therapies including TNF-α blockers for rheumatoid arthritis and other autoimmune disorders have added a new pool of immunosuppressed patients at risk for tuberculosis and for histoplasmosis and other T-cell–opportunistic fungal infections.[43a]

In most instances, exposure of an immunosuppressed person to an infectious aerosol is the antecedent event preceding PDH. In the large outbreak in Indianapolis, most patients who were immunocompromised when they developed primary histoplasmosis progressed to PDH.[43] In particular, patients with AIDS nearly always progressed to PDH.[44]

In other cases, the onset of PDH is temporally related to intense immunosuppression, most commonly from progression of AIDS or therapy with high doses of

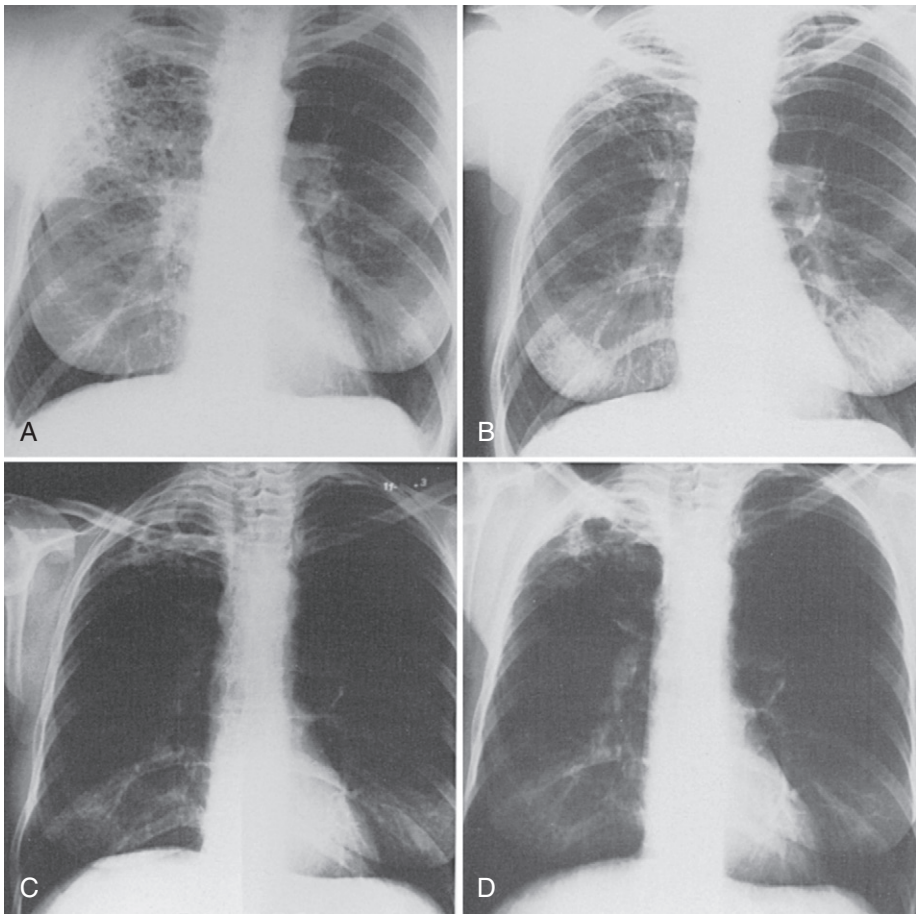

FIGURE 36-4 ■ The evolution of chronic pulmonary histoplasmosis in a smoker. **A,** At the onset of the illness, the chest radiograph shows multiple cavity-like air spaces. **B,** Two and one-half years later, fibrosis has occurred with volume loss of the lobe and retraction of the hilum. **C,** A further 17 months later, the entire right upper lobe appears destroyed. **D,** There are signs of continued activity and a residual cavity at the time of diagnosis. The sputum culture was positive for *Histoplasma capsulatum*.

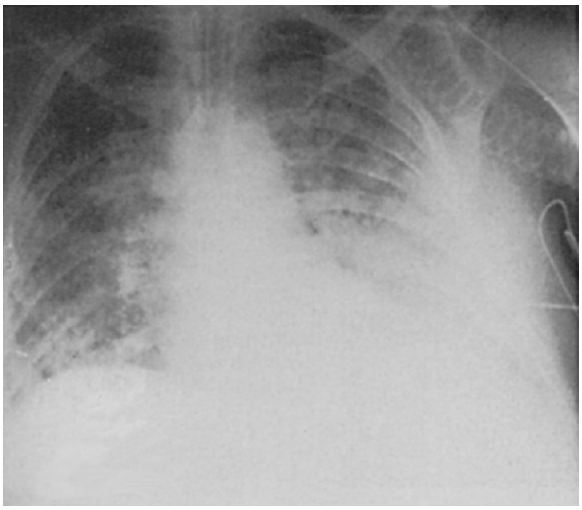

FIGURE 36-5 ■ Admission chest radiograph of a 45-year-old man shows disseminated histoplasmosis. The miliary pattern is clearly seen.

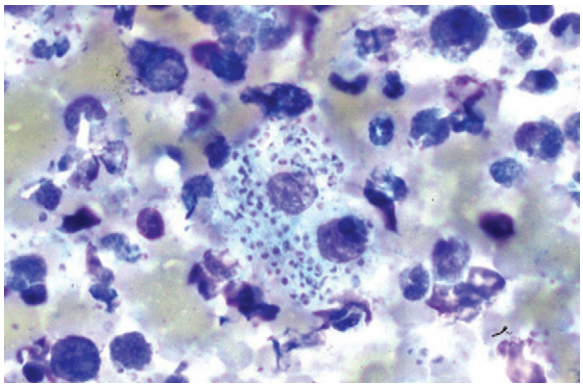

FIGURE 36-6 ■ Photomicrograph of bone marrow biopsy shows abundant small yeast-filling macrophages. There were no well-formed granulomas. (Wright stain; ×450.)

glucocorticoids. In some of these cases, reactivation of dormant histoplasmosis may be the mechanism of infection.[39] Patients with AIDS who develop PDH after long residence in New York City or San Francisco are clear examples of such endogenous reactivation because primary infections are never seen in these cities.

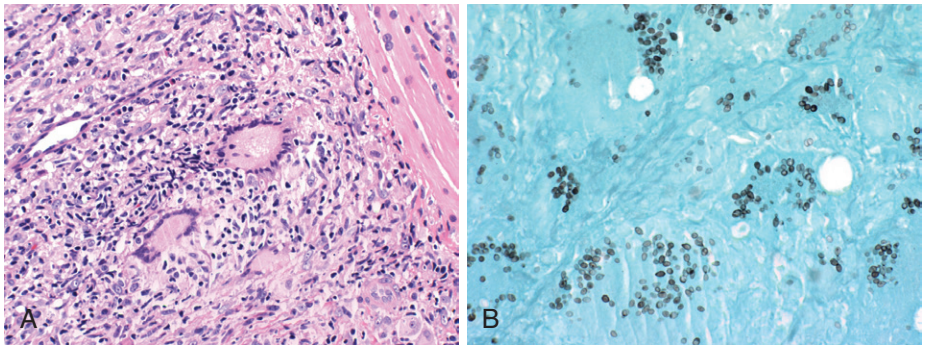

FIGURE 36-7 ■ **A,** Photomicrograph shows a tissue biopsy specimen from a patient with slowly progressing disseminated histoplasmosis. Granulomas are well formed, and no organisms are seen. (Hematoxylin and eosin stain ×450.) **B,** Special stains better demonstrate yeast in tissue sections. (Silver methenamine stain; ×450.)

Some patients with PDH have no major T-cell dysfunction. In fact, when they are tested after recovery from histoplasmosis, T-cell function appears normal. Goodwin and coworkers[5] postulated that these patients have a transient form of T-cell dysfunction, perhaps related to an intercurrent viral infection, which makes them susceptible to PDH. This hypothesis is interesting, but there is little direct evidence to support or reject it.

Some patients with PDH have a smoldering chronic illness. They may have a chronic wasting disease with anorexia, weight loss, and low-grade fever. Mucosal and mucocutaneous junction ulcers may occur in the mouth, oral pharynx, rectum, and glans penis. Adrenal involvement may cause Addison's disease.[45] Biopsy material from involved tissues shows well-formed epithelioid granulomas, and only a diligent search will reveal rare organisms. Demonstration of organisms usually requires special stains (Fig. 36-7). The disease may be systemic or involve only one organ. This more chronic form of PDH generally occurs in patients who are less immunosuppressed than the patients who develop more fulminant PDH.

CNS histoplasmosis is rare and may present as chronic meningitis or intracranial histoplasmoma. Endocarditis can also occur, involving either the aortic or the mitral valves. Vegetations are usually large, and emboli are common. Endocarditis may occur on prosthetic or previously normal valves. Histoplasma involvement of abdominal aortic aneurysms has been reported in a few patients with the chronic form of PDH.[46]

Diagnosis

The "gold standard" of diagnosis is culture of the fungus from biologic material or direct visualization of characteristic 1- to 2-μm yeast within macrophages. Unfortunately, direct examination of sputum is not useful because of the intracellular location within macrophages (uncommon in expectorated sputum) and the small size and nonspecific morphology of the individual yeast forms. (With *B. dermatiditis* and *C. immitis*, discussed later, direct sputum examination is much more important.) Typical histoplasma organisms can often be seen with special stains in other biologic specimens including bone marrow aspirates and tissue biopsies, bronchoalveolar lavage (BAL) fluid, and even in the peripheral blood smear of severely ill patients, most notably those with AIDS.

Mycologic Studies

Unfortunately, sputum cultures are not very useful for diagnosis of acute pulmonary histoplasmosis because the index of suspicion is usually low and the patients seldom have a productive cough. Conversely, patients with chronic cavitary histoplasmosis usually have positive sputum cultures. Specimens obtained from bronchoscopy have a high but poorly defined yield in severe primary histoplasmosis including those with progressive acute respiratory distress syndrome and in PDH in AIDS, when diffuse pulmonary involvement is a common feature.

Bronchoscopy is an important diagnostic tool, especially for PDH. Most studies examining the utility of bronchoscopy for the diagnosis of endemic fungal diseases are retrospective, include all forms of the disease (disseminated or self-limited), and do not distinguish between BAL, washings, cultures, stains, or biopsies. In addition, specific staining procedures are often not described in detail. Recent studies highlight the critical importance of cytologic examination of submitted samples with Papanicolaou staining in addition to the usual preparations (potassium hydroxide [KOH] digestion, periodic acid–Schiff [PAS], and silver stains). Bronchoscopic studies tend to include mainly immunosuppressed patients with diffuse opacities. The most studied population is the AIDS population, which has greatest density of organisms. However, other immunosuppressed groups, including patients receiving intensive cancer chemotherapy, organ transplant recipients, and patients being treated for inflammatory diseases with potent anti-TNF agents, are also at risk.[47]

In highly selected series, the diagnostic yield of bronchoscopy for diagnosis of histoplasmosis in an endemic area is about 60% in patients with radiographic abnormalities and 88% for chronic cavitary histoplasmosis.[48] In an AIDS population in Indianapolis, Indiana, fungal stains performed on BAL fluid provided a rapid diagnosis in

70% of patients; diagnostic yield increased to 89% when culture results (which were not immediately available) were included. In that series, 22% of patients had coinfections or alternative diagnoses that were detected by BAL and would not have been detected if serum histoplasma antigen testing had been the sole diagnostic test.[49] Use of cytologic examination without special fungal staining (silver, PAS) may explain the lower yield of BAL reported in series from nonendemic areas.[50] Although transbronchial biopsy is not mandatory at the time of bronchoscopy and BAL, histopathology does appear to enhance the diagnostic yield.[50] The fungus is difficult to see on standard hematoxylin and eosin stains; special stains (usually a silver stain) are needed. Special stains are particularly important when well-formed granulomas are present because of the paucity of organisms in such cases. This is the "tuberculoid" form of histoplasmosis with paucity of organisms and well-formed granulomas, in contrast to the "lepromatous" form with abundant organisms and little evidence of well-formed granulomas.

In patients with suspected PDH, sampling of the reticuloendothelial system is often effective for diagnosis. Bone marrow biopsy is likely the best and safest method.[40] (Although liver biopsy is also an excellent method to sample the reticuloendothelial system, it is not as safe and is prohibited when there is thrombocytopenia.) In heavily parasitized samples, a direct smear of the bone marrow aspirate, stained with a supravital stain such as Giemsa stain, usually gives a rapid diagnosis. On permanent histologic sections, the fungus is difficult to see on standard slides prepared with hematoxylin and eosin stain. It is best to go directly to special stains, usually one of several modifications of the silver stain. As mentioned, special stains are particularly important when well-formed granulomas are present.

Recently, the role of blood cultures in diagnosis of PDH has expanded. The lysis-centrifugation system increases sensitivity. In AIDS patients with PDH, the density of organisms is higher than in other immunosuppressed patients, and blood cultures are particularly useful, yielding a diagnosis in up to 90% of cases. In fact, in AIDS patients with PDH, typical intracellular organisms can be seen directly on peripheral blood smears (buffy coat preparations) up to 50% of the time. BAL also has a high yield, both by direct smear and by culture in AIDS patients with a high burden of organisms. BAL offers the additional advantage of ready diagnosis of other opportunistic infections that are usually in the differential diagnosis, including *P. jirovecii* pneumonia.

Skin Tests

In highly endemic areas, skin test positivity is practically universal by adulthood. To confound matters, many patients with proven PDH have a negative skin test due either to underlying T-cell deficiency or to the severity of infection. Therefore, a positive skin test never proves current histoplasmosis, and a negative skin test never rules it out. The histoplasmin skin test, however, is valuable as an epidemiologic tool. Skin test conversions are useful in the United States for diagnosing tuberculosis because background skin test positivity is low and because serial skin tests are often performed in individuals with a high chance of acquiring tuberculosis. Neither is true for histoplasmosis. Background positivity is high, and serial studies are almost never performed.

Serologic Studies

Because sputum cultures and skin tests are rarely helpful in the diagnosis of acute histoplasmosis, serologic tests are extremely important.[51] Two standard tests are available for the serodiagnosis of histoplasmosis. The first and most important is the complement fixation (CF) test. The result becomes positive 3 or more weeks after the exposure and remains positive for months or occasionally years in diminishing titer. A fourfold rise in titer or a single determination of 1:32 or higher is suggestive of recent infection. When the clinical picture strongly suggests acute pulmonary histoplasmosis (diffuse nodules 2 weeks after an appropriate exposure, a focal alveolar opacity associated with hilar adenopathy, or isolated unilateral hilar adenopathy), then a titer of 1:8 or higher has strong positive predictive value. Unfortunately, the CF test is negative in about 30% of patients with acute histoplasmosis and in up to 50% of patients with PDH. Patients with chronic pulmonary histoplasmosis frequently have titers of 1:8 or 1:16 that do not rise during the period of observation.

The second test is immunodiffusion testing for precipitating antibodies to the M and H antigens, which produce separate bands (the M band is more common and more important; the H band almost never occurs alone). The test is easy to perform and has more specificity than a low-titer CF test. Regrettably, immunodiffusion fails to identify up to 50% of patients with acute histoplasmosis and usually does not reach maximum positivity for 4 to 6 weeks after exposure.[52]

These serologic tests measure antibodies and are helpful in identifying individual patients with acute histoplasmosis. Their main drawbacks are imperfect sensitivity and lack of timeliness. Several weeks must pass before they become positive. By that time, most patients either have recovered or have required other more invasive methods of diagnosis because of rapidly worsening disease.

Another approach to diagnosis of fungal infections is the use of ultrasensitive assays for fungal antigens. Specificity is very good, but sensitivity is relatively poor in acute histoplasmosis, chronic cavitary histoplasmosis, and even PDH in mildly to moderately immunosuppressed patients. In non-AIDS patients with severe PDH, the sensitivity of urine histoplasma polysaccharide antigen may be about 80%. With severe and especially diffuse pulmonary involvement, the sensitivity of antigen testing on BAL fluid may also be in the 80% range.[53]

The extremely high density of organisms in AIDS patients with PDH makes antigen testing even better in that setting, with almost perfect sensitivity and specificity. In one study, the histoplasma polysaccharide antigen was positive in urine from 70 of 72 patients with

PDH complicating AIDS.[54] Levels of histoplasma polysaccharide antigen in urine and serum also are useful for following the course of treatment and for predicting relapses.[55,56]

Treatment

The overwhelming majority of patients with acute histoplasmosis either are asymptomatic or have rapidly resolving, self-limited disease that requires no treatment. For the rare patient with acute overwhelming pulmonary disease, treatment with amphotericin B is mandatory and may be lifesaving.[57] Treatment with corticosteroids (1–2 mg/kg/day of prednisone in single or divided doses) can be used as adjunctive therapy when there is severe hypoxemia. After clinical improvement, sequential therapy with itraconazole 400 mg/daily is continued for 6 months.

Progressive cavitary upper lobe pulmonary disease can be treated successfully with 400 mg/day of itraconazole.[58] Alternatively, amphotericin B in a total dose of 35 mg/kg may be used over a 12- to 16-week treatment course with excellent results.[59]

Severe cases of PDH in non-AIDS patients are best treated promptly and aggressively with amphotericin B until there is clear clinical improvement. Then the patient is switched to itraconazole (400 mg/day in a single daily dose) to complete a 6-month course of therapy, or 12 months if the patient has moderate immunosuppression such as organ transplantation. Itraconazole can be used from onset for patients with mild to moderate disease.[60] AIDS cases are treated differently from other PDH cases. Relapse is expected if treatment is stopped. All patients require induction therapy to control symptoms and then maintenance therapy. Amphotericin B is used initially for severely ill patients. After clinical response, treatment is changed to itraconazole (400 mg daily for 6 or more months, then 200 mg daily).[61] Lifetime maintenance treatment was recommended in the past but that is changing with more effective antiretroviral therapy. Maintenance therapy can likely be stopped if the immune system recovers to near normal, with CD4 counts above 350. Itraconazole can be used from onset for mild to moderate cases.[62] Other maintenance strategies for those intolerant of itraconazole include weekly amphotericin B infusions or fluconazole at doses of at least 400 mg/day. Ketoconazole therapy is ineffective for maintenance therapy, and fluconazole even at high daily doses (400–800 mg) is less effective than itraconazole.[63]

In a double-blind, randomized trial, liposomal amphotericin B was somewhat more effective than amphotericin B in both time of response and survival, although the differences were not statistically significant.[64] In this study, both forms of amphotericin were used for 14 days before switching to oral itraconazole therapy.

Of the newer antifungal agents, both voriconazole and posaconazole have high activity against histoplasmosis. Voriconazole penetrates better into cerebrospinal fluid. It has been used in CNS disease usually initially in combination with liposomal amphotericin B and then continued as a sequential agent for 12 months. That regimen was first used for treatment failures or relapses but now is often chosen as the first regimen. Posaconazole is very active in animal models and has been used for treatment failures, including CNS disease, in a manner similar to voriconazole. It is unlikely that these agents will ever be studied head to head with itraconazole. The echinocandins are not favorable agents for histoplasmosis.

Amphotericin B, the oral azoles (ketoconazole, fluconazole, itraconazole, and more recently, voriconazole and posaconazole), and the new echinocandins are the current treatment options for most patients with fungal diseases. Treatment is discussed as part of the discussion of each disease, but a brief overview of these agents is presented as background. Recent consensus statements of the Infectious Disease Society of America and the American Thoracic Society discuss treatment issues in greater depth.[65,66]

Amphotericin B

Since its introduction in 1955, the polyene antibiotic amphotericin B has been the mainstay of therapy for most systemic fungal diseases.[67] It is highly effective but has potentially serious side effects. Renal toxicity is most prominent.[68] A dose-dependent reduction of renal function is almost universal. Monitoring renal function at least once a week is mandatory, and reduction of dosage is advisable once the creatinine level reaches 2 mg/dL. Tubular potassium wasting is common, and weekly monitoring of the serum potassium level is advisable to monitor adequacy of potassium supplementation.

Febrile reactions, often with severe chilling, are common. Premedication with 600 mg aspirin and 50 mg diphenhydramine 30 minutes before the start of the infusion and shortening the infusion time to 2 to 3 hours are strategies to reduce the frequency of serious febrile reactions. Pretreatment with intravenous narcotics (meperidine, 50–75 mg) is more effective in preventing amphotericin B reactions, but narcotics should be used only for severe reactions. Usually the reactions, even when initially severe, decrease over the first few weeks of therapy, so narcotic pretreatment can be discontinued.

In stable adult patients, 10 mg amphotericin B can be given on the first day, with daily increments of 10 mg to a dose of 50 mg on the fifth day. If the patient is doing well, 50-mg infusions are given on a Monday-Wednesday-Friday schedule. The package insert recommends a usual dose of 0.5 to 0.7 mg/kg/day, with a maximum daily dose of 1.0 mg/kg. However, to minimize nephrotoxicity, we prefer not to exceed 50 mg as a single daily dose, except in selected patients with invasive aspergillosis. To avoid the problem of diminishing and destroyed peripheral veins, we frequently insert a central venous catheter or a peripherally inserted central catheter. When a patient is critically ill, the early phase of administration of amphotericin B is accelerated. The first infusion contains 20 mg, which is then followed by a further infusion of 30 mg the same day, followed by the daily administration

of 50 mg amphotericin B until the patient is stable. Then the usual Monday-Wednesday-Friday regimen is begun.

The lipid formulations of amphotericin B have less renal toxicity. It is unproved that they have higher efficacy, and their cost is much higher. A review of their safety and efficacy has been published.[69] In a study mentioned previously, amphotericin B was compared with liposomal amphotericin B for initial treatment of PDH complicating AIDS.[64] The observed differences in the two arms were not statistically significant, but liposomal amphotericin B was at least as effective as amphotericin B, with marked reduction in renal toxicity. Infusion-related side effects were slightly but not dramatically reduced. Amphotericin B dosing of 1.0 mg/kg/day or higher almost always causes renal impairment. Diseases requiring amphotericin B dosing at that level, including invasive aspergillosis, should likely be treated with liposomal amphotericin B from onset.

There are differences in the various lipid-based formulations of amphotericin B. In a large study, amphotericin B colloidal dispersion (ABCD) was compared with standard amphotericin B in patients with well-documented aspergillosis. The ABCD also had reduced nephrotoxicity when compared with amphotericin B, but the infusion-related side effects (fever and chilling) with ABCD were more frequent than with the parent compound.[70]

Imidazoles

Ketoconazole, an orally administered imidazole, was the first alternative to amphotericin B for stable patients with mild to moderate cases of histoplasmosis, blastomycosis, and coccidioidomycosis without meningeal involvement.[71] Ketoconazole and the other oral azoles are never indicated for a critically ill patient because they are less potent and have slower onset of positive effect. Ketoconazole is started at 400 mg/day, given once a day before breakfast. If the illness progresses or new lesions appear at the end of 1 month, the daily dose is increased by increments of 200 mg to a total dose of 800 mg/day. There is uncertain added benefit from doses greater than 800 mg/day, although some authorities routinely exceeded that dose, especially in the treatment of coccidioidomycosis.

The main toxicity of ketoconazole is gastrointestinal. Nausea and vomiting are common once the dosage exceeds 400 mg/day. When a higher dose is used, splitting it as equal morning and evening doses frequently allows continued administration of the agent. Gastric acidity is necessary for absorption, and the dosage must be increased to compensate for reduced absorption in achlorhydric patients.[72] Proton pump inhibitors, histamine$_2$ receptor blockers, and even antacids should not be used in patients taking ketoconazole.

Ketoconazole is a potent antitestosterone agent.[73] Decreased libido is common, and aspermia has been noted in some patients. Impotence may force discontinuation. In higher doses, the drug may also block synthesis of cortisol. A single large morning dose has less effect on cortisol secretion than smaller split doses but, as mentioned, may not be tolerated because of nausea and vomiting.

Fluconazole was the second oral azole to become available. The usual dose is 200 to 400 mg/day in a single daily dose. It is well absorbed even without gastric acidity. It has excellent tissue penetration and reaches high levels in cerebrospinal fluid. It is excreted in the urine in high concentrations. For most AIDS patients with cryptococcal meningitis, fluconazole is equally effective compared with standard combined therapy with amphotericin B and 5-flucytosine.[74] Fluconazole is more effective than ketoconazole for candidal esophagitis in patients with AIDS. Fluconazole has also been used with some success for several forms of chronic coccidioidomycosis, including chronic pulmonary infection and meningitis (for primary therapy of mildly symptomatic patients and for long-term maintenance therapy of sicker patients after initial response to amphotericin B). Fluconazole has also become a primary therapy for AIDS patients with disseminated coccidioidomycosis who are stable on presentation, and it is a good maintenance therapy for sicker patients if they improve clinically after an initial course of amphotericin B therapy.

Itraconazole is a potent antifungal agent with a wide range of activity but poor absorption and high protein binding, penetrating poorly into cerebrospinal fluid. The usual dose is 200 to 400 mg/day in a single daily dose. Like ketoconazole, it requires some gastric acidity for maximal absorption. Compared with ketoconazole, it has similar though milder gastrointestinal side effects and a similar but less marked effect on testosterone synthesis. It is the first oral agent with reasonable activity against *Aspergillus* species, and it is useful in solid organ transplant recipients with pulmonary aspergillosis.[75] It is more effective than ketoconazole or fluconazole for treatment of histoplasmosis and blastomycosis.[76]

Itraconazole is very effective for long-term suppression of histoplasmosis in patients with AIDS. Because it is more potent and less toxic than ketoconazole, it has largely replaced that agent for selected cases of histoplasmosis and blastomycosis. It does not replace amphotericin B, which is still necessary for initial treatment of severe infections. Itraconazole has some efficacy for coccidioidomycosis, but is not a major breakthrough for that disease, for which even amphotericin B is marginally effective in some difficult cases. The relative advantages and disadvantages of the various azoles have been reviewed.[77]

V*oriconazole*, a relatively new triazole, combines the potency and wide spectrum of activity of itraconazole and the excellent cerebrospinal fluid and tissue penetration of fluconazole. This agent has excellent bioavailability after oral administration, allowing ready switch from initial intravenous therapy. In adults over 40 kg, a loading dose is recommended for both intravenous therapy (6 mg/kg every 12 hours for two doses) and oral therapy (400 mg by mouth for two doses). After the loading dose, the daily maintenance dose for treatment of aspergillosis is 4 mg/kg every 12 hours. For less serious infections, 3 mg/kg every 12 hours is recommended. For oral use, voriconazole should be taken either 1 hour before or 1

hour after a meal at the dose of 200 mg every 12 hours. For smaller adults, the package insert should be consulted for dosing information.

Rarely, voriconazole can cause severe hepatic injury. The drug should not be used in patients with moderately reduced hepatic function. A common side effect is visual changes, consisting of blurred vision, flashing bright lights, and the appearance of wavy lines. Eye symptoms may occur in as many as half the patients but fortunately resolve upon discontinuing the agent and cause no eye damage.[78]

Another relatively new potent imidazole is posaconazole. Like voriconazole it has wide spectrum of activity, good absorption after oral intake, and good tissue penetration. It has more activity against mucor species than other azoles.

Caspofungin was the first of several echinocandins,[79] a new class of antifungal drugs that inhibits fungal cell wall synthesis by inhibiting 1,3-β-D glucan synthesis. The drug has an excellent safety profile and is well tolerated. It is available only for intravenous administration. Clearance is somewhat reduced in women and in the elderly, but dose adjustment is not necessary. No dosage changes are needed in patients with renal insufficiency, and because it is not removed by hemodialysis, no adjustments are needed in this population either. In the presence of moderate liver disease (Child-Pugh score of 7–9), the dose must be reduced. The standard loading dose is given, but the daily maintenance dose is reduced by about a third. When caspofungin is given with cyclosporin A, caspofungin level is increased by approximately 35%, without any change in cyclosporin A levels. Conversely, when caspofungin is given with tacrolimus, the caspofungin level does not change, but the tacrolimus level is decreased by 20%. More importantly, caspofungin has no pharmacokinetic effect on amphotericin B or itraconazole. The drug is currently approved for the treatment of esophageal and invasive candidiasis and for invasive aspergillosis. Because it has low toxicity and no apparent effect on amphotericin B kinetics, it is being used in combination with liposomal amphotericin B for seriously ill patients with these infections, even in the absence of data from clinical trials.[79] The loading dose of caspofungin is 70 mg, followed by 50 mg daily; in moderate liver disease, the daily dose is 35 mg.

BLASTOMYCOSIS

Blastomycosis is the illness caused by the thermal dimorphic fungus *B. dermatitidis*. The spectrum of disease ranges from the asymptomatic acquisition of delayed, sometimes transient, hypersensitivity to a rapidly progressive and life-threatening respiratory or disseminated illness.

History and Epidemiology

Blastomycosis is the only one of the three common endemic mycoses of North America that was first described on this continent. In 1894, Gilchrist[80] reported the first case in Baltimore, Maryland. He initially thought that the causative agent was a protozoan. This was similar to Darling's later speculation about the cause of histoplasmosis. However, Gilchrist quickly corrected his mistake. With Stokes, he isolated the organism, determined that it was a fungus, and infected a dog with the isolate, successfully fulfilling Koch's postulates.[80,81]

Soon it became apparent that the disease was more common in the central United States than along the eastern seaboard. Although individual cases were reported regularly, there was little increase in knowledge about the disease beyond the description of individual cases. In 1939, Martin and Smith[82] from Duke University reviewed all the available case material and offered an analysis that later proved incorrect. They thought that the purely cutaneous form of the infection was distinct from the pulmonary illness, with a different portal of entry and a different natural history. In 1951, Schwarz and Baum[83] disproved this artificial separation by showing that the cutaneous form of the disease almost always represented distant spread from a pulmonary focus.

The epidemiology of blastomycosis has remained a difficult puzzle. Because of the obvious similarities between histoplasmosis and blastomycosis, investigators attempted to duplicate the kind of experiments that defined the epidemiology of histoplasmosis but with little success. Attempts to isolate *B. dermatitidis* from soil and define its ecologic niche mostly failed. Attempts to develop a sensitive, reproducible, and useful skin test also failed.

Because there is no good skin test, large-scale skin test surveys have not been possible. The exact endemic area for blastomycosis has not been defined with any degree of certainty, but has been deduced only by the location of reported cases.[84] The proposed endemic area includes much of the central, south-central, and southeastern United States, beginning near the Minnesota–North Dakota border and extending eastward and southward. The southeastern limit extends to South Carolina but not to Florida. This area overlaps most of the endemic area of histoplasmosis.[1] However, the northern limit extends much further. Northern Minnesota and northern Wisconsin and also the adjacent Canadian provinces of Ontario and Manitoba are endemic for blastomycosis but are free of histoplasmosis.[85–88]

As mentioned, early attempts to develop a blastomycin skin test failed. Large series of patients with blastomycosis were tested with various skin test antigens, with mixed results. Most patients had a negative blastomycin skin test reaction. Many of the same patients had a positive histoplasmin skin test reaction.[89] These results led to the conclusion that the blastomycin skin test was insensitive and that there was a great deal of cross reactivity between histoplasmin and blastomycin.

An alternative explanation for these results is also possible. Most of the patients who were skin tested in these studies had widely disseminated blastomycosis. Even those with disease limited to the lungs were often severely ill. Under these circumstances, negative blasto-

mycin skin tests would not be surprising. In addition, because virtually all patients were from the endemic area for histoplasmosis, any positive histoplasmin skin test reactions might have reflected previous, unrelated infection with *H. capsulatum*.

Careful investigation of two large point-source outbreaks supports this view. In the 1972 Big Fork, Minnesota, outbreak, 18 of 21 exposed persons had evidence of blastomycosis.[86,90] Big Fork is in northern Minnesota, beyond the endemic area for histoplasmosis. Twelve patients had an abnormal chest radiograph compatible with acute pulmonary blastomycosis. Ten of the 12 had positive blastomycin skin test reactions. An additional 6 patients had a normal chest radiograph but a positive blastomycin skin test. Thus, 16 of the 21 patients at risk had a positive blastomycin skin test reaction. Only 1 of the 21 at-risk individuals had a positive histoplasmin skin test. Surprisingly, when the 16 blastomycin-positive individuals were retested 3 years later, only 5 were still positive.[91] These results suggest that the blastomycin skin test can be quite useful in point-source outbreaks of acute pulmonary blastomycosis, at least when the issue is not confused by high background skin test positivity to histoplasmin. Furthermore, positive blastomycin skin test reactivity might be short-lived (if true, this represents a difference from the other endemic mycoses, for which skin test positivity is more durable).

During the summer of 1984, an even larger point-source outbreak of blastomycosis occurred in Eagle River in northern Wisconsin. Eagle River, like Big Fork, is north of the endemic area for histoplasmosis. A total of 99 individuals were at risk, and 87% of the total demonstrated either a positive blastomycin skin test reaction or a positive lymphocyte transformation to an alkali-soluble and water-soluble *B. dermatitidis* antigen (AWSE), or both. All patients were histoplasmin skin test negative. The investigators recovered the fungus from a beaver lodge, which was the apparent source of the outbreak.[92,93]

When one examines these two outbreaks and other more recent reports, a much clearer picture emerges. Like *H. capsulatum, B. dermatitidis* is a soil-dwelling fungus. Infection occurs by inhalation of airborne spores. Infected individuals develop a positive blastomycin skin test reaction or the in vitro correlate of delayed hypersensitivity. As with histoplasmosis, isolated microfoci of high infectivity exist in a large endemic area. Such foci are likely even more restricted, and it is much harder to culture *B. dermatitidis* from nature. Outbreaks often occur during activities close to recreational waterways[94]; these are most common when soil temperatures have been increasing for several days and when there is rain on the day of exposure. For sporadic cases, residence close to water in a highly endemic area and recent excavation activity are risk factors.[95,96]

Dogs are also susceptible to blastomycosis. Canine blastomycosis is a well-recognized entity in veterinary practice in the endemic areas. The recognition of canine cases in a community should alert physicians that human blastomycosis may be present in their geographic area.[84,97]

Skin test surveys for histoplasmosis and coccidioidomycosis have proved that there are many subclinical and barely clinical infections. Because no skin test surveys for blastomycosis have been possible, most diagnosed patients have had symptomatic infections. Epidemiologic study of two large outbreaks cited suggests that there are subclinical cases of blastomycosis, as does the clinical pattern of patients presenting with distant disease (skin, bone, prostate) without clear history of previous pneumonia. Based on in vitro lymphocyte responses, a study of highly exposed forestry workers also suggests that a sizable minority of such workers, perhaps 30%, have had previous blastomycosis, without a past history of clinically apparent pneumonia.[98] This suggests that there is considerable undiagnosed and self-limited blastomycosis, but that it may not be nearly as large as it is for the other two major endemic mycoses.

Pathogenesis

At ambient temperatures, the fungus grows as an aerial mycelium. When foci of actively growing *Blastomyces* are disturbed, small, 2- to 5-μm, spores become airborne and are infective. These particles may be inhaled by humans or by other mammals disturbing the site. Some spores may escape the nonspecific defenses of the lung and reach the alveoli.

The initial inflammatory response is neutrophilic. As the organism converts to the parasitic yeast form and begins to multiply, large numbers of yeast are seen, surrounded by neutrophils. Then macrophages increase in number. Eventually, as specific cellular immunity develops, there are giant cells and well-formed epithelioid granulomas. Histopathologic examination often shows a mixed pyogenic and granulomatous response, even in chronic cases.[2]

The major mediator of immunity is a specific Th1 T lymphocyte response. Blastomyces yeast produce a specific protein, initially named WI-1, which adheres to the yeast surface and is both an adhesin and a virulence factor. Because of that property, the antigen was renamed the blastomyces adhesion protein or BAD-1. This protein reduces host TNF-α and increases transforming growth factor-β, thus down-regulating the Th1 response[99,100] in addition to promoting adhesion to pulmonary epithelial cells and macrophages. An experimental strain of blastomycosis that does not produce the BAD-1 protein has reduced virulence in animals[101] and may conceivably be a candidate for a live, attenuated vaccine in high-risk groups.

The histopathologic response in cutaneous blastomycosis is striking. The stratified squamous epithelium becomes markedly hyperplastic, with exaggerated downgrowth of the rete pegs. Within these finger-like projections are a number of microabscesses. The same hypertrophic tissue response is seen when the disease involves the oropharynx or the larynx. The histopathologic appearance may superficially resemble carcinoma. The uniformly benign appearance of the individual cells excludes cancer, however, and the characteristic organisms, seen best with special stains, provide a diagnosis.

The initial inflammatory and immune response may confine the infection to the lungs and the hilar lymph nodes. It is likely (but not proved) that self-limited early fungemia does not occur as often as it does in histoplasmosis. However, in some instances, the organism spreads beyond the lung and the hilar nodes. Dissemination is usually to skin, bones, prostate, and meninges but can be seen in any organ.[2,89]

The incubation time for blastomycosis is longer than that for histoplasmosis and more variable. In the Eagle River outbreak, in which time of exposure was short and precisely defined, the median incubation period was 45 days, with a range of 21 to 106 days.[92,93]

Clinical Manifestations

The portal of entry is almost always the lung, except for rare cases of direct inoculation,[102] and the primary illness is a lower respiratory infection. Some patients have an acute illness that resembles bacterial pneumonia, in contrast to acute pulmonary histoplasmosis, which more closely mimics influenza. The onset of symptoms is abrupt, with high fever and chills, followed by cough that rapidly becomes productive of mucopurulent sputum. Pleuritic chest pain may occur.

This acute onset is common in an outbreak setting, but also may be seen in sporadic cases. In fact, blastomycosis must always be considered in the differential diagnosis of severe community-acquired pneumonia, especially if there is disease progression on empirical antibacterial therapy. However, in most sporadic cases, the onset of clinical symptoms is more gradual. The patient presents with a low-grade fever, productive cough, and weight loss.[89,103] Lung cancer and tuberculosis are highest in the differential diagnosis, rather than bacterial pneumonia, depending on the radiographic findings.

Physical examination is sometimes normal usually unremarkable except for fever. Auscultation of the chest in patients who have segmental or lobar opacities may show crackles and focal consolidation; more often, the pulmonary examination is negative. Skin lesions are highly variable in appearance, ranging from subcutaneous nodules and abscesses to papules to ulcers with heaped-up borders mimicking squamous cell cancers. Perhaps the most characteristic lesion has irregular borders and a crusted surface, varying in size from 1 to 10 cm or more (Fig. 36-8). Skin lesions may be single or multiple and may occur in crops of several new lesions daily or every few days if the disease is rapidly disseminating.

Routine laboratory tests are seldom helpful. In cases resembling acute bacterial pneumonia, the white blood cell count is elevated and, frequently, there is a left shift in the granulocyte series.

There is no "characteristic" chest radiographic pattern in blastomycosis.[104] Lesions may vary from single or multiple round densities to segmental or lobar consolidation. Severe pulmonary infections can present with diffuse nodular, interstitial, or even alveolar radiographic changes. The diffuse alveolar opacities can be identical to acute respiratory distress syndrome of diverse cause. Masslike perihilar shadows, especially on the right side, are common and are often misinterpreted as neoplastic. On the lateral chest radiograph, the masslike lesion is usually behind the hilum, in the apical-posterior segment of the lower lobe. Hilar lymph node involvement may occur but is not nearly as common as in histoplasmosis. Cavities may occur during the acute phase of the illness and usually close during successful treatment. Unlike histoplasmosis, calcification due to healed blastomycosis is rare.

FIGURE 36-8 ■ Photograph shows a characteristic large crusted skin lesion above the elbow in a patient with blastomycosis. A punch biopsy of the edge of the lesion revealed characteristic yeast forms on histopathology.

Extrapulmonary spread of the fungus may occur during the acute, symptomatic phase of the illness. In some instances, only the distant lesion (usually skin or bone) is symptomatic. During evaluation, an asymptomatic chest radiographic abnormality is sometimes discovered. Often, however, the pulmonary process has already resolved spontaneously by the time the extrapulmonary focus becomes apparent, and the chest radiograph is normal. These are the patients with the so-called isolated cutaneous form of the disease, which caused so much confusion in the past. Careful history sometimes but not always reveals a preceding self-limited pulmonary illness. Laskey and Sarosi[105] reported patients whose pulmonary blastomycosis was initially symptomatic but resolved spontaneously without being diagnosed. When extrapulmonary blastomycosis occurred (as much as 3 years later), the pulmonary infections were retrospectively proven blastomycotic by review of cytology specimens obtained during the original illnesses.

The skin and the bony skeleton are the most common sites of symptomatic extrapulmonary spread. The prostate gland, meninges, oral pharynx, larynx, and abdominal viscera, including the liver and the adrenal glands, are involved less frequently.[2]

Blastomycosis can present as a progressive infection in patients with T-cell defects, including organ transplant recipients and other patients being treated with glucocorticoids and other immunosuppressive therapy for malignant and nonmalignant disorders.[106] As with histoplasmosis, the disease can often be cured with amphotericin B and/or azoles in patients with intermediate

degrees of immunosuppression. Blastomycosis can also occur in AIDS. Infection is particularly severe, and cure is less likely. Maintenance therapy is required for those patients who do respond to initial treatment. Blastomycosis is much less common in AIDS and other T-cell–deficient conditions than are histoplasmosis and coccidioidomycosis. This is probably because exposure to this fungus while immunosuppressed is less common and perhaps because there is a smaller reservoir of patients with remote healed infection waiting to relapse should T-cell function markedly decline.[107]

Diagnosis

The easiest and most rapid method of diagnosis is examination of expectorated sputum or aspirated pus after 10% KOH digestion.[2] The characteristic large (8- to 20-μm) organism is easily identified. The yeast is single budding, with a broad neck of attachment between the parent and the daughter cells. The wall is thick and is double refractile, and there are multiple nuclei (Fig. 36-9). Other direct fungal stains, including PAS, calcofluor white, and silver stains, are more sensitive. Another sensitive technique for rapid diagnosis of blastomycosis on direct sputum smears is cytologic analysis with the standard Papanicolaou stain. In one study, sputum samples were positive by direct examination in 78% of patients using the Papanicolaou stain compared with only 37% when using a combination of KOH digestion and PAS staining. The direct techniques are probably complementary, and examining multiple sputum samples increases diagnostic yield.[108]

The role of bronchoscopy for diagnosis of pulmonary blastomycosis is not well defined. Bronchoscopy is useful when patients are unable to expectorate adequate sputum, when urgent diagnosis is needed because of rapid pace of the illness, and when the clinical presentation is compatible with malignancy or tuberculosis. In one study, bronchoscopy was diagnostic in 92% of patients when culture results were included in the final analysis; specimens obtained included BAL fluid in 64% and bronchial washings in all.[109] For patients who are acutely ill or have a clinical picture similar to that of acute respiratory distress syndrome, rapid diagnosis is crucial and can be achieved only by direct examination of respiratory secretions or by lung biopsy. If direct sputum smears are negative or not possible, then bronchoscopy should be done urgently, with BAL fluid and bronchial washings sent both for direct fungal stains (some combination of KOH, calcofluor white, silver stain, PAS, and cytology preparation) and for culture.[110] A reasonable combination of direct techniques might include KOH preparation or calcofluor white, a silver stain, and a Papanicolaou stain. The cytology laboratory should be informed whenever there is high clinical suspicion of fungal infection. Fungal organisms can easily be overlooked if the examination is focusing on malignant cells.[111] Cell blocks of concentrated BAL fluid can be done to maximize the yield of the submitted specimens.

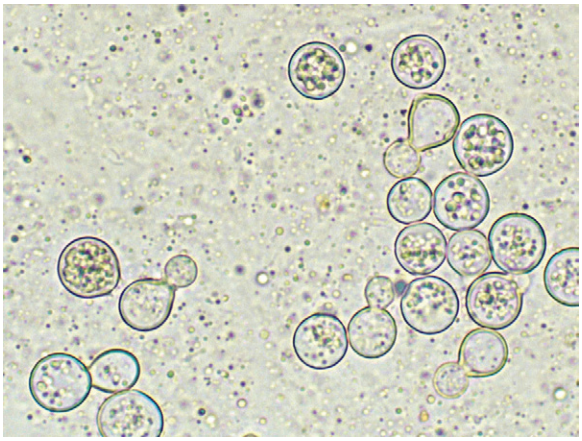

FIGURE 36-9 ■ Micrograph shows *Blastomyces dermatitidis* in fresh sputum after 10% potassium hydroxide digestion. Note the broad neck of attachment, the double refractile cell wall, and the multiple nuclei. (Original magnification ×1000.)

Histopathologic examination of biopsy material is also an excellent way to establish the diagnosis. Standard hematoxylin and eosin stains do not show the fungus, and special stains are required. The PAS stain preserves morphologic detail, but silver stains are more commonly used and likely have better sensitivity. The decision whether or not to perform transbronchial biopsies at the time of initial bronchoscopy will likely depend on contraindications in any given patient that give added risk beyond risk of BAL and on the height of clinical suspicion for malignancy. If infection is much more likely than malignancy, bronchoscopy with BAL can be the initial procedure, reserving transbronchial biopsy for cases with no diagnosis from a safer and easier first procedure. Open lung biopsy may be necessary in selected cases.

Identification of the fungus by culture is not difficult, but it is slower than direct microscopic examination. Growth may occur as early as 5 to 7 days but often takes several weeks. Exoantigen testing can provide positive identification as soon as good growth is established. Formerly, positive identification required conversion of the mycelial culture to the yeast phase of growth, adding 1 or more weeks of delay.

There is no commercially available skin test antigen. Experience during two outbreaks of blastomycosis (described earlier) suggests that skin testing with various antigens may be useful for epidemiologic investigation of outbreaks. In the epidemic in northern Wisconsin, in vitro transformation of antigen-stimulated lymphocytes was an excellent test to identify infected individuals.[112] However, that test is not available for clinical use.

In some cases, the entire clinical picture, including the chest radiograph, suggests cancer rather than infection. Sputum and bronchoscopy specimens are mainly sent for cytologic evaluation, including Papanicolaou stains. Fortunately, the cytology preparations often show the fungus.

Serodiagnosis of blastomycosis remains problematic. The tests (usually immunodiffusion and CF tests to detect antibodies) have lacked sensitivity. Specificity has also been poor due to cross reactions with histoplasmosis, which is a much more common disease. Of course, any

positive test results should focus diagnostic efforts toward proving or disproving blastomycosis. Tests using blastomycin (crude mixture of antigens) and even somewhat purified antigens such as "AWSE (alkali and water soluble extract)" and "antigen A" all have major cross reactivity. It appears that what was described as antigen A was essentially the BAD-1 protein plus a carbohydrate component and that the cross reactivity was largely contained within the carbohydrate portion. It is hoped that better serodiagnostic tests can be developed using specific protein antigens—both tests for host antibodies and tests to identify antigens directly in appropriate biologic specimens. There is one commercially available test for blastomyces antigen in urine and other biologic specimens including cerebrospinal fluid and BAL fluid.[113] It is sensitive in pulmonary and disseminated blastomycosis in selected cases. It is also positive (cross reactions) in more than 95% of selected cases of histoplasmosis. A commercially available histoplasma antigen can also be used diagnostically (in BAL fluid) for suspected blastomycosis cases, because the cross reactivity is so high.[53] It is seldom positive in coccidioidomycosis, other fungal pneumonias, or other pulmonary infections. At present, most cases of blastomycosis are diagnosed in relatively low-tech fashion, by smear, culture, and histopathology on appropriate specimens obtained by astute clinicians. However, major advances in immunodiagnosis may be close.

Treatment

The most severely ill patients with pulmonary blastomycosis require aggressive antifungal treatment, as discussed later. However, there is some controversy as to whether all patients with acute pulmonary blastomycosis require treatment. It is likely that some patients with acute pulmonary blastomycosis would recover without treatment (Fig. 36-10). That was first suggested during the Big Fork, Minnesota, outbreak in 1972. All the patients recovered without specific antifungal therapy.[90] After that experience, 39 carefully selected patients (blastomycosis limited to the lung, acute onset, not severely ill, and already improving when diagnosed) were followed carefully without treatment. All of these patients recovered, and only 1 of the 39 patients followed for up to 20 years had a relapse.[114]

The self-limited nature of some cases of blastomycosis was confirmed during the northern Wisconsin outbreak in the summer of 1984. Klein and associates[92] found 9 "definite" and 39 "probable" cases of acute pulmonary blastomycosis. Of these, 26 were symptomatic and 22 were asymptomatic. Although the 9 patients culturally proved to have the disease were all treated with amphotericin B, the 39 probable patients were not. All probable cases, many with symptoms of pneumonia and abnormal chest radiographs, had complete clinical recovery. Chest radiographs either cleared completely or remained stable. Together these experiences suggest that some highly selected patients with acute pulmonary blastomycosis may safely be followed without treatment.

However, amphotericin B is no longer the only available therapy. There is safe and nontoxic oral therapy with itraconazole. Withholding treatment should be considered only for those patients who present with an acute pneumonia, have relatively mild initial symptoms, and are already improved by the time a specific diagnosis is established—usually by the late return of a positive culture from a respiratory specimen. All patients who are ill at the time of diagnosis should be treated.

Most patients with sporadic pulmonary blastomycosis present with subacute or chronic symptoms (chronic cough, low-grade fever, night sweats, and weight loss) of weeks' to months' duration more closely resembling tuberculosis or lung cancer than acute bacterial pneumonia. All such patients require antifungal therapy to improve their symptoms and prevent progression of disease (Fig. 36-11).

Itraconazole is highly effective for blastomycosis and is the treatment of choice for most patients with pulmonary and nonmeningeal disseminated disease. Oral therapy with 400 mg/day for 6 months successfully treats most patients with mild to moderate pulmonary disease and skin disease. Twelve months' duration of therapy is preferred for bone disease. Amphotericin B to clinical improvement followed by itraconazole in the same manner is preferred for a small minority of severely ill patients, including all patients with diffuse pulmonary involvement and severe gas-exchange abnormalities.

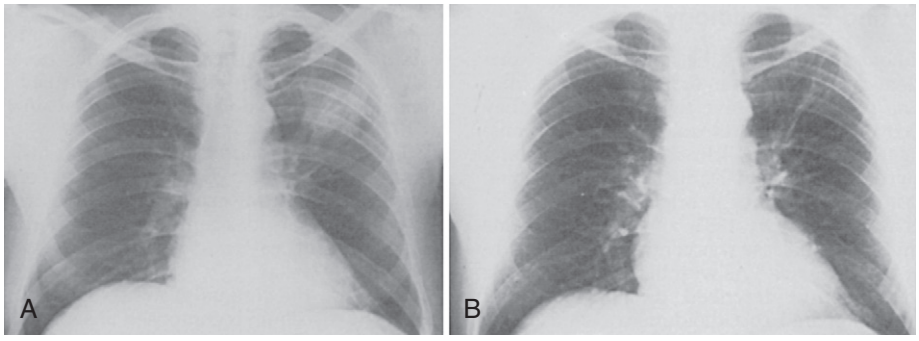

FIGURE 36-10 ■ Chest radiographs show acute self-limited pulmonary blastomycosis. **A,** A chest radiograph taken at the time of diagnosis. Note the left upper zone opacity. **B,** Four months later, the opacity has cleared, leaving a small scar. The patient has remained well for over 4 years.

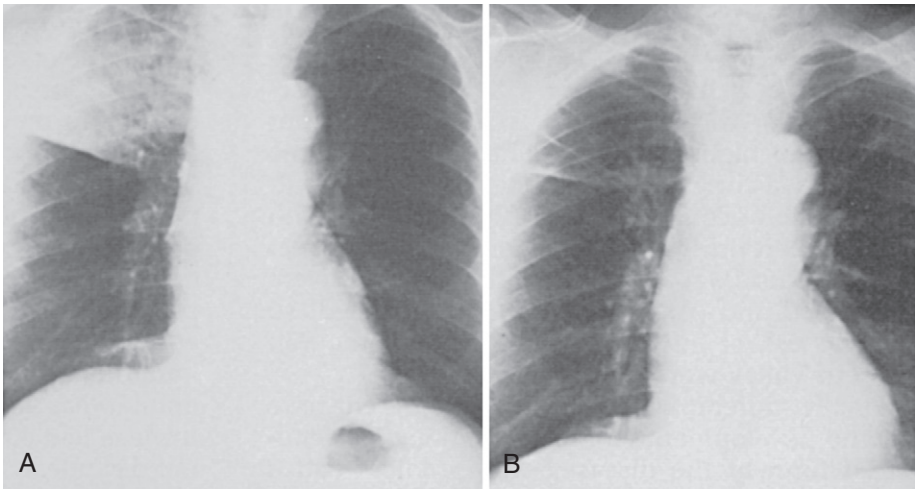

FIGURE 36-11 ■ Chest radiographs show pulmonary blastomycosis successfully treated with ketoconazole. The patient also had a skin lesion. **A,** A chest radiograph taken at the time of diagnosis. Note the right upper lobe alveolar opacity. **B,** After 4 months of ketoconazole treatment, the chest radiograph shows near-complete resolution.

Corticosteroids may have an adjunctive role and may improve gas exchange.[115] Patients with edematous lobar pneumonia (bulging fissures), extremely toxic patients, and patients who are rapidly disseminating should also receive amphotericin B as initial therapy. This general approach is also used for AIDS patients except that lifelong maintenance therapy with itraconazole is needed after induction therapy to prevent relapse (unless immune status returns to nearly normal levels with antiretroviral treatment). Itraconazole is poorly absorbed, although the liquid formulation is somewhat better. The drug has high protein binding and penetrates the CNS poorly.

Meningeal blastomycosis is treated with systemic amphotericin B therapy in standard doses. Liposomal amphotericin B achieves higher brain tissue levels in animals and may be preferred. Fluconazole is overall less potent for blastomycosis than itraconazole but penetrates the CNS much better. High-dose fluconazole (often in combination with liposomal amphotericin B) has been used for CNS blastomycosis.

Because it is better absorbed and has better tissue penetration, voriconazole is theoretically attractive for some forms of blastomycosis, including CNS infections and pulmonary and systemic infections in patients who have poor absorption of itraconazole. There are case reports of use of voriconazole after failure of other regimens, particularly for difficult CNS cases.[113,116,117] Posaconazole has activity against blastomyces in animal models but has not been studied in clinical trials. The echinocandins do not have good activity against blastomyces and, unlike voriconazole, probably should not be used as alternative therapy. Controlled trials comparing itraconazole with newer azoles will likely never be done.

COCCIDIOIDOMYCOSIS

Coccidioidomycosis is the illness caused by the tissue-dimorphic fungus *C. immitis* or *Coccidioides posadasii*. Although most infections are mild and self-limited, the spectrum of illness includes life-threatening pulmonary disease and widely disseminated systemic disease with a high mortality rate. Differences from histoplasmosis and blastomycosis include different endemic area, higher frequency of meningeal infections, and poorer therapeutic response to all antifungal agents, including amphotericin B. Similarities to histoplasmosis and blastomycosis include induction of effective cellular immune responses, ability to mimic typical community acquired pneumonia, and formation of residual nodules, worrisome for malignancy, on radiographic imaging.

History and Epidemiology

Coccidioidomycosis, the first discovered of the endemic mycoses, was identified in Argentina in 1892. The investigators thought they had found a new protozoan infection, a mistake later repeated in the initial descriptions of blastomycosis in 1894 and histoplasmosis in 1906. The fungal origin of coccidioidomycosis was proved by 1905, and it soon became apparent that the disease was common in the southwestern United States.[118] As in histoplasmosis, the early reports described dramatic cases of widely disseminated coccidioidomycosis that were always fatal.

Observations by Dickson[119] and Dickson and Gifford[120] enlarged the recognized clinical spectrum of coccidioidomycosis. They demonstrated that primary infection with *C. immitis* was the cause of several acute self-limited syndromes that had been noticed in the San Joaquin Valley in California. These included a nonspecific febrile illness ("valley fever"), an acute polyarthritis ("desert rheumatism"), and erythema nodosum ("the bumps"). They also demonstrated that the primary pulmonary infection was common, was mostly benign, and usually did not disseminate.[119,120]

When World War II broke out, the San Joaquin Valley was chosen for flight training because of the large

number of clear-sky days and the ample space available to construct airfields and supporting facilities. In a series of elegant studies, the epidemiology of coccidioidomycosis was defined, largely through the efforts of C. E. Smith.[120a–120f] All recruits were skin-tested with coccidioidin on arrival. Those with negative skin tests were susceptible to coccidioidomycosis. Many recruits had skin test conversion from negative to positive, without any symptoms. A minority had symptoms with the primary infection. Most had a self-limited febrile respiratory illness, sometimes with polyarthralgias. Less than 1% of infections progressed to dissemination. Recruits with a positive skin test on arrival were protected and did not become ill. The risk of infection was lowest during the wet and cold winter season and highest during late summer, when the weather was driest. New infections correlated with construction activity and were most frequent with construction during the dry months, when a great deal of dust was raised. As the air bases were completed and construction activity decreased, so did the risk of infection. Finally, black soldiers had a higher risk of dissemination than did white soldiers, even though the incidence of primary disease (as judged by skin test conversion) was the same.[121,122]

The endemic area for coccidioidomycosis in North America is the southwestern United States and the contiguous areas of northern Mexico. In the United States, this includes central and southern California and extends eastward to Arizona, New Mexico, and western Texas. In nature, the fungus grows as an aerial mycelium with septate hyphae. Alternating cells form thick-walled, barrel-shaped structures called *arthroconidia*, with empty cells in between. When a natural site harboring the fungus is disturbed, the mature arthrospores easily detach and become airborne, producing an infective aerosol. Strong winds can carry the arthrospores for long distances. A huge wind storm that blew north from the San Joaquin Valley in 1977 caused a major outbreak of coccidioidomycosis in Sacramento, far north of the usual endemic area.[123] Not surprisingly, occupations and activities with exposure to the soil carry the greatest risk for infection, including construction work, farm labor, and working on archeological digs.[124,125] In a recent study, 29% of patients with community-acquired pneumonia had positive serologic tests for coccidioidomycosis, suggesting this infection is a frequent cause of pneumonia in the endemic areas.[126] The overall frequency of coccidioidomycosis has been increasing since the late 1990s, especially in North America.[127]

Pathogenesis

After being inhaled, some arthrospores evade the nonspecific lung defenses and reach the alveoli, where germination begins. The arthrospores develop into spherules, the tissue phase of the fungus. Spherules are large, round, thick-walled structures that vary in diameter between 10 and 80 µm. Reproduction of the fungus occurs within the spherule (Fig. 36-12). The cytoplasm of the spherule undergoes progressive cleavage, forming numerous endospores within the spherule. Once a spherule matures, it bursts and releases the endospores into the surrounding tissues. Each endospore can become a new spherule and thus repeat the process.

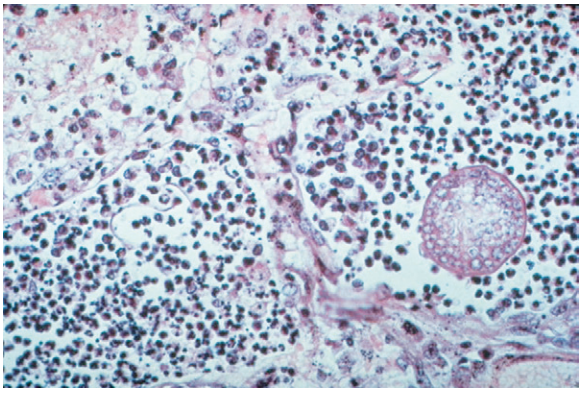

FIGURE 36-12 ■ Photomicrograph shows characteristic giant spherule of coccidioidomycosis in a lung biopsy. (Hematoxylin and eosin stain; original magnification ×450.)

The initial inflammatory response to inhaled arthrospores is neutrophilic. Resident alveolar macrophages also phagocytose the arthrospores and prime specific T lymphocytes, which multiply, recruit more macrophages, and arm the macrophages, engaging specific cell-mediated immunity. Even though many well-formed granulomas are seen, the neutrophilic inflammatory exudate does not disappear. Histopathologically, there is a mixed granulomatous and suppurative reaction with perigranulomatous clusters of B cells and interspersed CD4 T cells.[128] Delayed type hypersensitivity responses to coccidioidin and in vitro T-cell responses to a variety of antigen extracts appear to correlate with long-term immunity.

Clinical Manifestations

Coccidioidal infection can manifest as pulmonary or extrapulmonary disease. Pulmonary coccidioidomycosis makes up 95% of all cases. Most primary infections occur after inhalation and are asymptomatic or relatively mild. The fungus usually remains localized to the lung and hilar lymph nodes. About 60% of individuals with primary pulmonary infection remain totally asymptomatic and can be detected only by skin test conversion. In the remaining 40%, the spectrum of disease ranges from a mild, influenza-like respiratory illness to a severe, life-threatening pneumonia.[129] Dissemination occurs in less than 1% of patients. Hematogenous spread can affect many tissues, including the skin, bones, lymph nodes, visceral organs, and meninges. Meningitis is the most feared clinical syndrome, with a poor prognosis.

Some diagnostic approaches subclassify coccidioidomycosis as "uncomplicated" and "complicated" pulmonary coccidioidomycosis. The latter includes the clinical entities of persistent pneumonia, progressive primary coccidioidomycosis, fibrocavitary coccidioidomycosis, empyema, and acute respiratory distress syndrome.[130] Residual disease with pulmonary nodules, thin-walled cavities, and fibrosis also occurs.

Common symptoms include cough, fever, and pleuritic chest pain. Cough may be nonproductive or may produce small amounts of mucopurulent sputum. Hemoptysis may occur. True rigors are uncommon. Headache, common during the acute phase of the illness, is nonspecific. Severe headache is always worrisome, however, because coccidioidal meningitis often becomes clinically apparent during the early part of the illness. If meningitis is suspected, a lumbar puncture should be performed.

Dermatologic manifestations of coccidioidomycosis include an erythematous macular rash that occurs early during the illness. This finding is frequently misdiagnosed as a drug rash or a heat rash. Erythema nodosum and erythema multiforme are other skin manifestations of primary coccidioidal infection. Together with fever and arthralgias, these skin lesions are part of a variable symptom complex first recognized in the San Joaquin Valley of south-central California and labeled "valley fever."[119,120] The term is now widely applied to symptomatic primary coccidioidal infections irrespective of geographic location. Erythema nodosum, when present, becomes apparent at about the time the coccidioidin skin test turns positive. It is thought to be a good prognostic sign, reflecting hypersensitivity to the fungus. Patients with erythema nodosum characteristically have a severe reaction to coccidioidin skin testing.[131] If skin testing is necessary in these patients, very dilute antigen should be used.

More than 75% of patients with primary coccidioidomycosis have an abnormal chest radiograph. The most common radiographic abnormality is a single area or multiple areas of patchy pneumonitis. The ipsilateral hilar nodes are enlarged in about 25% of patients.[132] Hilar adenopathy may also be seen without recognizable parenchymal disease. Single or multiple pulmonary nodules are also common findings on CT scan, with or without associated pneumonitis. This primary complex usually heals rapidly. In a small fraction of the patients, the parenchymal abnormalities, the hilar abnormalities, or both may persist. The patchy opacities may evolve into spherical coin lesions. They have semisolid centers containing viable organisms. Unlike histoplasmosis, these coin lesions rarely calcify and may mimic malignant pulmonary neoplasms.[133] Unless previous chest radiographs are available to trace the development of these nodules, excision or needle biopsy is the only certain way to exclude a malignancy. In many cases, these nodules are handled clinically much like those of histoplasmosis, with serial imaging to ensure stability. Necrosis in the center of such lesions may produce cavitation. Shelling out of the necrotic material may occur as early as 2 weeks, but characteristically occurs 1 to several months after infection. Most cavities are thin walled and under 4 cm in diameter. Once formed, they may be stable for years. However, many cavities close within 2 years, without specific therapy.

Even though the natural history of coccidioidal cavities is usually benign, several complications may arise. The cavities may become infected with pyogenic organisms, or they may be colonized by *Aspergillus* species, with subsequent formation of a fungus ball. Occasionally, *C. immitis* itself may grow in the mycelial phase in the cavities, producing a coccidioidal fungus ball. Hemoptysis as a late complication is uncommon but can be life-threatening, in contrast to the minimal bleeding that is often seen as the cavity forms. Another complication is rupture of a cavity with development of a pyopneumothorax (Fig. 36-13). This may occur in a patient without previous symptoms. Resection should be considered if cavities are subpleural and progressively enlarging.

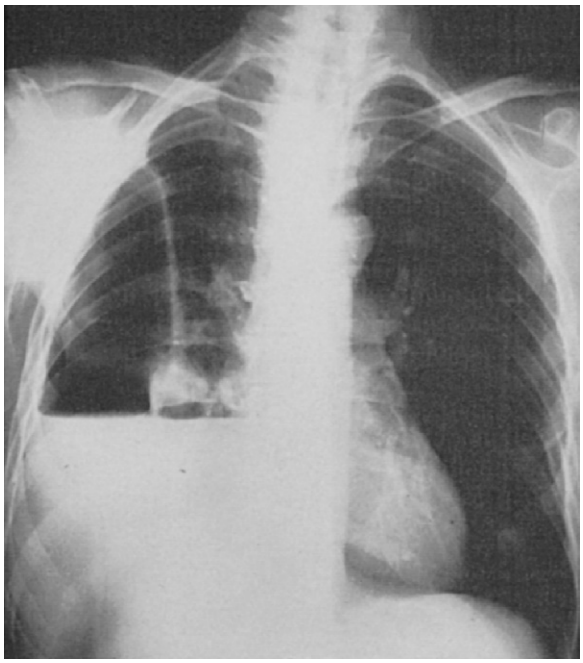

FIGURE 36-13 ■ Chest radiograph shows complications following rupture of a coccidioidomycotic cavity with formation of a bronchopleural fistula with empyema.

Patients receiving corticosteroids, cytotoxic therapy, or immune-modulating therapy such as anti-TNF therapy[134–136] are at risk for severe infection. Patients with persistent pulmonary infection after 6 weeks and those with chronic fibrocavitary pneumonia are at risk for progression and dissemination. Organ transplant recipients and especially patients with AIDS are at high risk for widespread and even fatal disease.[137] The excess risk of coccidioidomycosis in organ transplant recipients in highly endemic areas has led to targeted prophylaxis to prevent reactivation whenever there is a history of coccidioidal infection or positive serologic results on pretransplant screening.[138–141] There are other well-recognized risk factors for dissemination. Race and ethnicity are important. Disseminated coccidioidomycosis is more likely in blacks, Filipinos, and Native Americans than in whites.[121,122] Male gender is also a risk factor, as is diabetes mellitus. The very young and the very old are more likely to have dissemination.[129] There is anecdotal information suggesting that coccidioidomycosis during the third trimester of pregnancy may be a severe illness with rapid dissemination.

Extrapulmonary dissemination from the primary pulmonary focus tends to occur early, usually within a few months after a symptomatic pulmonary infection. However, in some patients, the findings of distant disseminated disease are the first manifestations of coccidioidomycosis, presumably because the preceding pulmonary infection was subclinical and resolved. Dissemination may involve any organ in the body. The skin is one of the most common sites of dissemination[142] and is involved in most patients at some time in the course of the disease. Skin lesions may be single or multiple. Gross appearance is variable, ranging from trivial scaling and induration to large, draining pustules. The clinical course varies from spontaneous healing to rapid ulceration and progression. Subcutaneous abscesses are frequent. They may be the result of sinus tract formation from deep sites of infection, including lymph nodes, bones, and viscera. When such an abscess is incised, thick gelatinous pus is found, laden with spherules.

Involvement of the bones is the next most common manifestation of disseminated coccidioidomycosis, present in up to half of patients.[143] Osteomyelitis may be either the sole evidence of extrapulmonary spread or part of a more widespread dissemination. Vertebral bodies are most commonly involved, followed by tibia, skull, and metatarsal and metacarpal bones, although any bone may be involved. Radiologic studies usually show nonspecific abnormalities. Coccidioidomycotic osteomyelitis of the spine spares the disc space in its early phases, very much like tuberculosis. Paraspinous abscess often accompanies these lesions. Without early and aggressive treatment, there is risk of spinal cord compression. Early bony lesions are frequently asymptomatic. A bone scan for every patient with disseminated coccidioidomycosis is useful to identify such lesions. Diagnosis of coccidioidomycotic joint disease may be difficult because the organism is seldom seen in synovial fluid, and synovial biopsy may be necessary for diagnosis.

Meningitis is the most dreaded complication of coccidioidal dissemination. Between one third and one half of all patients with disseminated disease have meningitis, frequently as the only obvious extrapulmonary site. The onset of meningitis may be subtle, with only mild headache and minimal alteration of mental functions. Involvement of the base of the brain is characteristic. Vasculitis may occur. As the disease progresses, an exudate frequently obstructs the aqueduct of Sylvius and the foramina of the fourth ventricle, producing hydrocephalus.[144] When obstruction occurs, the patient's clinical condition may suddenly worsen, with diminished level of consciousness and the development of papilledema. The cerebrospinal fluid shows characteristics of chronic meningitis: predominantly mononuclear cell pleocytosis, increased protein, and decreased glucose.

When coccidioidomycosis complicates HIV infection, the severity depends on the residual immune competence of the host. With near-normal CD4 lymphocyte counts, coccidioidomycosis is not significantly different from the disease seen in normal hosts. When the CD4 count falls below 200 cells/μL, disseminated disease tends to be severe and rapidly progressive. Patients usually have a high fever, complain of dyspnea, and are hypoxemic; chest radiographs often show diffuse reticulonodular opacities with nodules 5 mm or greater in diameter (Fig. 36-14). These diffuse large nodules are present in less than 1% of non-AIDS patients with disseminated coccidioidomycosis, but in up to 50% of advanced AIDS patients with this condition. Meningeal disease is present in up to 25% of advanced AIDS patients.[145,146]

Diagnosis

Mycologic Studies

Direct examination of sputum and other respiratory specimens (or pus from a nonpulmonary site) may reveal the diagnostic spherules of *Coccidioides*. Direct smears have highest utility in patients who produce copious sputum or have multilobar opacities.[147] Bronchoscopy is often performed in selected cases. In one study, bronchoscopy was diagnostic in 69% of patients, compared

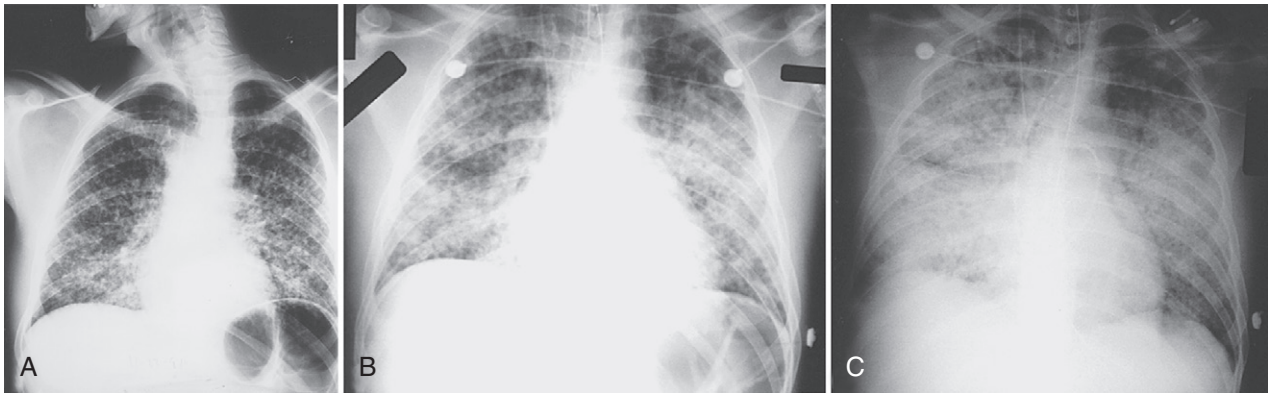

FIGURE 36-14 ■ Serial chest radiographs from a severely immunosuppressed acquired immunodeficiency syndrome patient show disseminated coccidioidomycosis. **A,** Reticulonodular opacities were detected at the time of diagnosis. Treatment with amphotericin B was started on that day. **B,** There was progression over 4 days despite therapy. The patient was then intubated to provide respiratory support. **C,** After further progression over 2 additional days, the patient expired.

with 32% for sputum stains and cultures, when patients with solitary pulmonary nodules on chest radiograph were excluded from analysis.[148] This older study also showed usefulness of a postbronchoscopy sputum examination and equivalent sensitivity for Papanicolaou and silver staining. The airway can be examined at the time of bronchoscopy and may be abnormal, providing clues to the diagnosis.[149]

Bronchoscopy is typically performed in patients who are immunosuppressed and severely ill, especially if they have diffuse opacities on chest radiograph. Multiple infections often coexist, giving additional value to diagnostic bronchoscopy early in the course of illness.[150,151] Bronchial washings and BAL fluid should be sent for cytology, fungal stains, and culture. In a study of an AIDS population in Phoenix, Arizona, the Papanicolaou stain was the most useful direct test (when compared with KOH and calcofluor white) for rapid diagnosis of pulmonary coccidioidomycosis and was even positive in two patients with negative cultures.[152] Histopathologic examination of transbronchial biopsy specimens is extremely helpful. When mature spherules (visible on standard hematoxylin and eosin–stained tissue sections) are seen, the diagnosis is secure. More commonly, only endospores, immature spherules, or spherule fragments are present. Therefore, fungal stains such as a silver stain should always be used in addition to hematoxylin and eosin staining. In one study, transbronchial biopsy yielded a specific tissue diagnosis of coccidioidomycosis in eight of eight patients.[153] Cultural identification of the fungus is not difficult but is hazardous to laboratory personnel. Isolation should be attempted only by experienced laboratories under rigid biohazard protection.

Serologic Studies

Classically, a tube precipitin test for detection of immunoglobulin M (IgM) antibodies is positive in 90% of patients by 1 to 3 weeks (negative only in very mild infections). Because the test usually reverts to negative within 3 months, it is quite specific for recent infection.[3] Currently, an immunodiffusion test for IgM has largely replaced the tube precipitin test. The immunodiffusion test measures the same antibodies, but it is easier to perform. An enzyme immunoassay for IgM is also available and maintains a low false-positive rate, suggesting an isolated positive test should prompt further investigation.[154]

CF antibodies are of the immunoglobulin G (IgG) class and appear later than IgM antibodies. In most symptomatic patients, the CF test is positive by 2 months and remains positive for several months or longer.[155] The test is highly specific but is not sensitive. In the traditional CF test, even titers of 1:2 should raise suspicion of recent exposure and infection. The antigen recognized by IgG antibody (but not by IgM antibody) is known to be a cell wall chitinase. Titers of 1:32 or higher are generally associated with more severe infections, dissemination, and poorer prognosis. A steadily rising titer should raise the suspicion of disseminated coccidioidomycosis and prompt further tests to better define the extent of disease. In addition, titers can be used to follow response to treatment, except in cases of meningitis in which serum antibodies are far less reliable. For suspected meningitis, antibody studies should be done on spinal fluid because they are more sensitive than cerebrospinal fluid cultures. Immunosuppressed individuals may have false-negative serodiagnostic tests. Because immunodiffusion and enzyme immunoassay tests are more widely used than traditional CF, results may not be reported as a dilution or titer. A confirmatory CF test can be considered if it is important to know the actual titer. The enzyme immunoassay has excellent sensitivity and specificity when compared with traditional CF testing.[156]

In 2008, a commercial *antigen* detection assay became available for use on biologic fluids. Although cross reactivity with other endemic mycoses exists and the assay has only modest sensitivity, it provides the more rapid diagnosis in select patients. Although there is great enthusiasm for use of polymerase chain reaction (PCR) on biologic samples, none is yet commercially available.

Skin Tests

Largely through the efforts of C. E. Smith, the role of skin testing in coccidioidomycosis is well defined. There are two skin test antigens: coccidioidin, prepared from the mycelial growth of the fungus, and spherulin, prepared from spherules. Induration is measured at 24 and 48 hours. A positive skin test reaction is 5 mm or more of induration and implies recent or remote infection. Spherulin was initially developed to try to increase sensitivity of skin testing. In epidemiologic studies, it is about 30% more sensitive than coccidioidin.[157] However, for routine clinical evaluation of symptomatic patients, the two skin test antigens are equal.[132] There is less than 10% cross reactivity of both antigens to histoplasmin.[157]

The skin test has been more useful in epidemiologic investigations than in diagnosing individual cases. Up to 50% of patients with disseminated coccidioidomycosis have a negative skin test, and about 10% of patients with coccidioidal pulmonary nodules or cavities have negative tests. Once acquired, the coccidioidin skin test reaction persists for a long time, perhaps even for life in some patients, producing high background levels of reactivity in an endemic area. When the recent skin test status of a given patient is known, conversion from negative to positive does imply recent coccidioidal infection. Currently, no skin test reagent is commercially available in the United States but the coccidioidin skin test may become available again in the near future. The role of skin testing in the contemporary management of this disease is not clear but is likely very limited.

Treatment

Most patients with acute pulmonary coccidioidomycosis require no treatment. Most never come to medical attention because they have minimal or no symptoms. Mildly or even moderately symptomatic patients with primary pulmonary coccidioidomycosis also need no treatment and often are indistinguishable from other

community-acquired pneumonia. Careful clinical and serologic follow-up for 1 to 2 years is necessary to identify illness that either progresses or does not resolve.

Azole therapy is usually the initial regimen of choice. Instances in which amphotericin B deoxycholate or lipid formulations of amphotericin are used include diffuse opacities with hypoxemia, critically ill patients, dissemination to spine and other important sites, and patients failing initial azole therapy. Amphotericin is also used for women in the third trimester of pregnancy. Because dissemination is more likely in immunosuppressed patients, in diabetics, and in certain racial and ethnic groups, it may be prudent to treat patients in high-risk groups during the primary infection, before dissemination takes place. In current practice, many such patients are often given fluconazole for 3 to 6 months; other, less symptomatic, patients with pulmonary coccidioidomycosis receive a shorter duration of therapy. These recommendations are based on expert opinion and observational studies.[158] For persistent pulmonary coccidioidomycosis, including chronic fibrocavitary disease, fluconazole and itraconazole are initial drugs of choice. Amphotericin B can be used for more severe or nonresolving cases.

Disseminated coccidioidomycosis always requires prompt and aggressive treatment. Unfortunately, amphotericin B is not as effective for disseminated coccidioidomycosis as it is for disseminated histoplasmosis or blastomycosis. Currently, mild to moderately ill patients with disseminated disease should be treated with fluconazole or itraconazole first. Amphotericin B preparations should be reserved for severe disease or treatment failure.

Pulmonary nodules caused by coccidioidomycosis usually do not need treatment. Thin-walled cavities are treated only if there are symptoms and positive sputum cultures caused by ongoing growth of fungus within the cavity. Specific antifungal treatment is not needed after uncomplicated surgical resection of nodules or cavities. Treatment of pyopneumothorax from rupture of a subpleural cavity includes chest tube drainage and antifungal therapy (either amphotericin B, fluconazole, or itraconazole). Surgery is indicated for persistent air leak or poor response to antifungal therapy, if the patient is a good surgical candidate.

Ketoconazole was the first therapeutic alternative to amphotericin B for certain patients with mild or moderate nonmeningeal coccidioidomycosis. A daily dose of 400 to 800 mg was used for a minimum of 1 year. Because high-dose ketoconazole has considerable toxicity and limited efficacy, fluconazole and itraconazole are now the azoles of choice for nonmeningeal disseminated coccidioidomycosis. The fluconazole dose should be at least 400 mg/day and 800 mg/day is likely to be better. The itraconazole dose should be 400 to 600 mg/day. Neither is perfect for difficult cases, for which even amphotericin B is often only suppressive. Long-term therapy is often required, extending to years or even indefinitely. Fluconazole has the advantages of better absorption, less gastrointestinal upset, and better penetration of the CNS. One randomized, controlled trial compared oral fluconazole and itraconazole for treatment of nonmeningeal coccidioidomycosis. Soft-tissue dissemination responded best. Overall, itraconazole was somewhat more effective than fluconazole, producing response in 63% of the patients versus 50% response in fluconazole-treated patients ($P = .08$). Among patients with skeletal infections, itraconazole was superior ($P = .05$).[159] Some difficult cases of bone, lymph node, and soft-tissue coccidioidomycosis may be best managed with surgical drainage of the abscesses, a 1000- to 2000-mg course of amphotericin B, and a prolonged course of itraconazole or fluconazole.

As might be expected, the treatment of disseminated coccidioidomycosis in AIDS is particularly difficult. Because of the rapid tempo of the disease, amphotericin B should be considered initially, especially if the patient is severely ill. If the clinical course stabilizes, it is reasonable to switch to fluconazole for long-term suppression. Prognosis is poor. Even with prompt diagnosis and treatment, up to 40% of severely immunosuppressed patients die during the initial hospitalization. Other patients, usually with lesser degrees of immunosuppression, respond well to treatment.[145,146] Select patients with high CD4 counts may be able to stop therapy if infection appears controlled, with close clinical, radiologic, and serologic follow-up. However, if infection is in a vital area, stopping therapy may lead to relapse with serious consequences. Many clinicians continue therapy for years or indefinitely, certainly in patients with AIDS but even in immunocompetent patients with risk factors, as discussed later for meningeal disease.

Meningeal coccidioidomycosis is a major therapeutic challenge. Fluconazole is currently primary therapy for patients with meningitis and as suppressive therapy after initial response. Most patients respond favorably to fluconazole and maintain good clinical function. Dosage is 400 to 800 mg daily or even higher. Therapy should be continued long term, likely indefinitely.[160] Patients may also be treated with intrathecal amphotericin B.[161] Occasionally, severely ill patients are treated with intravenous amphotericin B for initial therapy of the nonmeningeal disease and with fluconazole to control the CNS infection. Amphotericin B is continued to clinical improvement while fluconazole is continued indefinitely. Itraconazole at doses of 400 mg/day or higher has shown benefit in meningeal disease as well.[162] Hydrocephalus, a feared complication of coccidioidal meningitis, requires shunting in almost all cases. CNS vasculitis is sometimes treated with a short course of steroids but there is little evidence to support this.

The potential role of newer antifungals in coccidioidomycosis is uncertain. Posaconazole has shown the most promise in small studies.[163,164] Voriconazole has shown success in case reports.[165] The role of surgery in the management of pulmonary coccidioidomycosis continues to evolve. Pulmonary cavities may be resected when there is a high risk of rupture (large size, subpleural location, size increasing under observation) or when there is major hemoptysis. Extrapulmonary abscesses should be drained or resected whenever possible. Surgery for extrapulmonary foci of infection is often required for optimum control and usually combined with concurrent antifungal therapy.

Although considerable research is aimed at developing a vaccine for coccidiomycosis because it is a common and severe infection in highly endemic areas,[166] there is no immediate prospect for an effective vaccine.

PARACOCCIDIOIDOMYCOSIS

Paracoccidioidomycosis is the illness caused by the thermal dimorphic fungus *Paracoccidioides brasiliensis.* The spectrum of illness ranges from asymptomatic skin test conversion to widespread disseminated disease.

Epidemiology

The fungus is endemic in South America, Central America, and southern Mexico.[167,168] Most cases are from Brazil, Columbia, and Venezuela. Unlike histoplasmosis, it is not found in the Caribbean islands. Although it is undoubtedly a soil organism, it has been difficult to isolate from the soil (similar to *B. dermatitidis*). As with other respiratory mycoses, inhalation of the infective spores is the usual method of infection. Most patients with the disease are male agricultural workers in close daily contact with the soil.

Although 13 patients with paracoccidioidomycosis have been reported in the United States, all previously resided in areas of known endemicity and represent endogenous reactivation of remote infection. The United States is not in the endemic area for this fungus.[169]

Pathogenesis

After inhalation of the infective particles, an area of alveolitis occurs. The initial inflammatory exudate contains predominantly neutrophils. Later, macrophages are recruited, and granuloma formation occurs in immunologically intact patients. Cell-mediated immunity is important to limit the infection.[170] The initial episode of pneumonitis tends to be self-limited and may be common in childhood in highly endemic areas, similar to histoplasmosis. Disseminated infection may result from unchecked progression of a primary infection or from late activation of latent infection. Disseminated infection can be fulminant, as in AIDS with markedly diminished T-cell function, or it may be a smoldering subacute to chronic process. The most common sites of distant spread include skin, mucous membranes, lymph nodes, adrenal glands, liver, and spleen.[171]

Clinical Manifestations

In many patients, the primary infection is mild, self-limited, and never diagnosed.[172] In some cases, there are residual pulmonary nodules. Calcifications are rare. In endemic areas, single nodules surgically removed primarily to rule out lung cancer often prove to be paracoccidiodal granulomas. Many of these patients have no history of any symptomatic pneumonia.

Many patients currently diagnosed with paracoccidioidomycosis have pulmonary symptoms at the time of diagnosis. Up to one third of diagnosed patients have only pulmonary disease[173] and may present with nonspecific symptoms of fever, weight loss, and chronic cough. Chest radiographs are variable, with opacities, nodules, cavities, and sometimes impressive intrathoracic lymphadenopathy (even to the point of mimicking lymphoma). The findings on high-resolution CT often show more extensive lymphadenopathy than suspected from plain films.[174] In immunocompromised patients, paracoccidioidomycosis can present as a severe, rapidly progressive pneumonia. Such patients often have high fever and are acutely ill. As with the other endemic mycoses, particularly severe disease including presentation as respiratory distress syndrome has been reported in patients with AIDS.[175]

The majority of patients currently diagnosed with paracoccidioidomycosis have disseminated disease. Skin, mucocutaneous, and cervical lymph node involvement is often obvious and dramatic and causes most patients to seek medical attention quickly. Patients usually present with lesions on the skin or in the oropharynx. Prominent cervical adenopathy is much more common than in the other endemic mycoses. Some patients have concomitant pulmonary disease. In other cases, the lungs are clear when extrapulmonary spread is recognized. Presumably, initial asymptomatic or minimally symptomatic pulmonary lesions have already healed, and disseminated disease presents months or even years later.

The clinical appearance of the oropharyngeal lesions is somewhat characteristic.[176] Ulcers are infiltrated and show multiple hemorrhagic spots. The oral mucosal lesions commonly extend to adjacent skin. Similarly, lesions involving the rectal mucosa often extend to the perianal skin.

Organs of the reticuloendothelial system are frequently involved. Hepatosplenomegaly is common, and lymph nodes may be involved. Cervical adenopathy commonly accompanies mucosal lesions of the mouth and oral pharynx. Necrosis occurs within the nodes, and draining fistulas may extend from infected nodes to the skin. The adrenal glands are often affected with about half of autopsied cases showing involvement. However, clinically significant hypoadrenalism is uncommon. Other sites of dissemination include the kidneys, the male genital tract, and the meninges.

Diagnosis

Direct examination of tissue or sputum after 10% KOH digestion frequently shows the characteristic "pilot wheel" yeast. The organism is large (6–30 μm in diameter) and shows multiple buds circling the parent cell, each with a narrow neck of attachment. Histopathologic examination of biopsy material is also useful. Although the fungus can be seen on sections stained with hematoxylin and eosin, silver stains increase the diagnostic yield.

The fungus is readily cultured from biologic material. It grows slowly, and a positive identification usually takes 3 to 4 weeks. Specimens cultured at room temperature grow as a mycelium. Specimens cultured at 37°C grow in the yeast form.

A skin test is available for the diagnosis of paracoccidioidomycosis. There is some cross reactivity with histoplasmin. The diagnostic accuracy of the skin test is low. Up to 40% of 60% of patients tested have a negative skin test reaction at the time of diagnosis. Skin test reactivity is low because most patients have widely disseminated disease. It is not certain whether the skin test is useful in diagnosing primary pulmonary paracoccidioidomycosis because the sensitivity of the test and the background positivity in endemic areas are not known.

Serologic tests are very useful.[177,178] The CF test for antibodies against a yeast-derived antigen yields a positive result in 80% of cases. Titers of 1:64 or higher are considered diagnostic. A rising CF titer suggests progressive disease or a relapse following initial treatment. Low titers may persist for years, even after successful treatment. An immunodiffusion test is positive in 95% of cases. Cross reactions are rare, and most patients convert to negative after successful treatment. There is now also a direct test for antigen in urine, cerebrospinal fluid, and bronchoalveolar fluid.[179] It has very high specificity, and as with antigen testing in histoplasmosis, it is quite sensitive with severe infection and less helpful in localized or smoldering infection. It is neither fully standardized as yet nor uniformly available.

Treatment

In the past, long courses (often for several years) of sulfadiazine were used successfully for treatment of paracoccidioidomycosis. Two thirds of the patients had a good clinical response. Amphotericin B was used for patients who did not respond to sulfadiazine and for those who relapsed after treatment was stopped. The usual total dose ranged from 1000 to 1500 mg. After a course of amphotericin B, sulfonamide therapy was resumed and continued long term.

Treatment options have expanded with the availability of oral azoles. Ketoconazole is very effective and now, with itraconazole, is one of two preferred treatments.[167,177] A daily dose of 400 mg of ketoconazole usually produces clinical remission in 6 to 8 weeks. Treatment should be continued for a minimum of 12 months with dose reduced to 200 mg/day after the initial phase of therapy. Itraconazole 200 mg/day for 12 months is also highly effective, curing more than 90% of patients. Amphotericin B is used only for critically ill patients and for patients who fail oral azole therapy. Currently, only a small number of patients meet these criteria. Prolonged therapy is required because relapse occurs frequently after shorter courses of therapy. Patients have to be followed clinically and with serial radiographs for several years after completion of therapy.

CRYPTOCOCCOSIS

Cryptococcosis is most commonly caused by the encapsulated yeast *Cryptococcus neoformans*. Recently, disease caused by the closely related *Cryptococcus gattii* has emerged as an important pathogen even in immunocompetent individuals. The spectrum of disease for *C. neoformans* ranges from asymptomatic pulmonary infection in normal hosts to rapidly fatal meningitis in immunosuppressed individuals.

Epidemiology

C. neoformans has been recognized worldwide. Isolation from nature is easy, usually from pigeon or bird droppings. In nature and in the mammalian host, the fungus exists as a yeast form, with an average diameter of 4 to 8 μm. Its distinctive feature is a thick carbohydrate capsule that may be two to three times larger than the yeast itself. It is thought that in nature the yeast dries and loses much of its capsule, allowing it to be aerosolized and inhaled by humans or other mammals.[180] *C. gattii* appears to be endemic to the Pacific northwest and on Vancouver Island.[181]

Pathogenesis

Although newly acquired infection clearly can cause disease, the main mechanism of disseminated infection is due to reactivation during times of immunosuppression. The portal of entry is the lung. Once in the alveoli, the yeast grows and the large capsule quickly appears. Thin-necked, small buds are seen as the yeast multiplies. Alveolar macrophages are the first line of defense in the alveolus. The *C. neoformans* antiphagocytic protein (App1) inhibits a complement-mediated pathway for attachment and ingestion of yeast cells.[182] The polysaccharide capsule also plays an important part in the pathogenesis of cryptococcal infection. Nonencapsulated organisms are readily ingested and destroyed by neutrophils, whereas encapsulated strains resist phagocytosis and killing. The capsule of *C. neoformans* has been shown to interfere with the maturation of dendritic cells in vitro, resulting in diminished fungicidal interferon-γ and T-cell responses.[183] Sophisticated molecular techniques have recently been employed to define novel cryptococcal capsule, growth, and virulence mutations.[184]

Cell-mediated immunity figures prominently in host defense against cryptococci. Before glucocorticoids and cytotoxic agents were in common use, it was recognized that patients with Hodgkin's disease were unusually susceptible to cryptococcal infection. Many presented with fulminant meningitis. The central role of cell-mediated immunity in cryptococcal disease is emphasized by its frequent association with AIDS. Before AIDS, cryptococcal meningitis was uncommon and about half of the patients had immunosuppression. Today, most serious cryptococcal infections occur in AIDS patients.[185] *C. neoformans* antigens, when presented to CD4 T cells, stimulate the production of interleukin-15 and other cytokines, which then activate CD8 T cells. CD8 T cell through production of granulysin, and other mechanisms, is cytotoxic to the fungi.[186] In AIDS, the hallmark CD4 lymphopenia interrupts this cascade.

In patients receiving anti-TNF therapy, fungal infections are increasingly common.[187] In a mouse model of

cryptococcal infection, administration of anti–TNF-α monoclonal antibody on day 0 had no effect on fungal burden in BAL fluid through day 7. However, interleukin-12 and interferon-γ were not induced at day 7 to the same levels seen in controls. This study suggests that anti-TNF therapy neutralizes the type 1 T helper cell arm of defense, which is necessary to prevent fungal dissemination.[188]

Cryptococcal infection in the lung in normal hosts is eventually limited by a granulomatous inflammatory reaction.[189] It is not known whether early systemic spread of the fungus is a routine event, as it is in histoplasmosis, or occurs only in patients with defective cell-mediated immunity. Patients with severe depression of cell-mediated immunity do not form granulomas, and the organism grows unchecked. Large gelatinous masses of cryptococci are sometimes seen in surgical specimens or at autopsy. The fungus is trophic for the CNS, and cryptococcal meningitis is the most common form of extrapulmonary disease.

Clinical Manifestations

Although the lung is the portal of entry, symptomatic cryptococcal pulmonary disease is uncommon. In 1966, Campbell[190] searched the literature and found only 101 instances of cryptococcal disease restricted to the lung. Although the number of reported cases has increased since then, symptomatic pulmonary cryptococcosis is still relatively uncommon.

Fever, malaise, chest pain, and cough occur frequently in symptomatic patients with cryptococcal pulmonary disease. Many patients have no pulmonary symptoms but have changes on routine chest radiographs obtained during evaluation for symptoms of chronic meningitis. This suggests that asymptomatic pulmonary cryptococcosis may be common.[191]

The chest imaging findings are variable. Lesions may be single or multiple and may mimic those of other pulmonary infections and neoplasms. Pleural effusions may be present. The chest radiograph may suggest primary tuberculosis or acute pulmonary histoplasmosis with a small lesion in the periphery of the lung and associated hilar adenopathy. Immunosuppressed patients tend to have more prominent findings including cavitation, confluence of lesions, masses, and other changes.[192] Neurologic imaging can show abnormalities of brain parenchyma, leptomeningitis, or hydrocephalus.[193]

Even though apparently normal persons occasionally develop cryptococcal disease, the illness is most common in patients with AIDS,[194] those with Hodgkin's disease, organ transplant recipients,[195] and patients receiving corticosteroids and other immune-modulating therapies. Although the natural history of pulmonary cryptococcal infection in normal hosts is spontaneous resolution, it is advisable not to dismiss this pathogen as a routine colonizer, but to treat almost all patients who have positive cultures from respiratory specimens.

Meningitis is the most common clinically significant form of cryptococcosis. Patients may present with a subacute illness, consisting of fever, confusion, and headache, or rarely with an acute, fulminant illness with nuchal rigidity, papilledema, and coma. Cranial nerve palsies are common,[196] and there may be symptoms due to hydrocephalus, such as headache and a depressed level of consciousness.[197]

Diagnosis

C. neoformans and some non-*neoformans* species of cryptococci can be recovered from sputum. Non-*neoformans* species can also be recovered from skin. Isolates from the CNS are usually *C. neoformans* and always indicate cryptococcal meningitis. In tissues, the organism appears as yeast of variable size. The unstained capsule looks like a thick "halo" on sections stained with hematoxylin and eosin. The mucicarmine stain shows a bright red carbohydrate capsule. Silver stains commonly used to identify fungi stain the yeast but not the capsule.

The cerebrospinal fluid in cases of meningitis usually shows modest mononuclear cell pleocytosis. The white blood cell count is usually less than 100 cells/μL. The protein level is variably elevated, and the glucose level is variably reduced. The latex particle agglutination test for measurement of cryptococcal antigen is excellent for testing cerebrospinal fluid.[198,199] It is positive in 95% of patients with cryptococcal meningitis. Measurement of cryptococcal antigen in serum is not very sensitive in non-AIDS patients with cryptococcal meningitis and is sometimes negative even in nonmeningeal disseminated cryptococcal disease.[198] The situation is very different when AIDS is present. Virtually all AIDS patients with cryptococcal meningitis have a positive serum test for cryptococcal antigen in addition to a positive cerebrospinal fluid antigen test. In fact, a negative serum cryptococcal antigen test in an AIDS patient virtually excludes cryptococcal meningitis. Occasional false-positive cryptococcal antigen test results in cerebrospinal fluid or, more commonly, in serum result from high-titer rheumatoid factor.[200]

Risk factors for poor outcome of cryptococcal meningitis despite adequate treatment include AIDS, lymphoreticular malignancy, glucocorticoid therapy, high opening pressure on lumbar puncture, a leukocyte count of less than 20 cells/μL in cerebrospinal fluid, positive India ink smear of cerebrospinal fluid, isolation of the fungus from an extraneural site, and high cryptococcal antigen titer in the cerebrospinal fluid.[198] Other sites of cryptococcal disease include the skin, bones, and prostate. Unless there is a primary chancre with a local bubo, implying direct inoculation, all forms of cutaneous cryptococcosis should be assumed to be manifestations of disseminated disease from a deep focus.[201]

Treatment

There is always uncertainty whether to treat a patient when *C. neoformans* is isolated from the sputum. If the patient is a normal host or has chronic bronchitis and has no symptoms and a normal chest radiograph, then careful observation is an option. However, some advocate a course of fluconazole up to 3 to 6 months given low

treatment toxicity profile. If the fungus is isolated from the sputum of an immunocompetent patient with symptomatic pneumonia, a lumbar puncture is recommended. Although the risk of progression to meningitis is low, it is not zero. Many clinicians now treat all diagnosed cases of isolated cryptococcal pneumonia with fluconazole 200 to 400 mg/day for 6 to 12 months.[202] When an immunocompromised patient has pulmonary disease, even if the cerebrospinal fluid is normal, antifungal treatment is mandatory. Options include fluconazole 400 mg daily or amphotericin B (total dose 1000–2000 mg). Choices of therapy for cryptococcal meningitis in non-AIDS patients include fluconazole 400 mg/day for very mild illness with normal mental status and treatment similar to HIV-infected patients when disease is severe.

Cryptococcal meningitis is fatal approximately 50% of the time even with optimal therapy. Treatment of cryptococcal meningitis in AIDS is very different because the disease relapses when treatment is stopped. First, a remission must be induced. Second, lifetime maintenance must be given to prevent relapse. Current evidence suggests that oral fluconazole is the best long-term maintenance therapy.[203] Severely ill patients with abnormal mental status (somnolence, lethargy, obtundation) may have a higher risk of death during initial induction therapy. For the majority of patients with cryptococcal meningitis, an induction regimen of amphotericin B 0.7 to 1 mg/kg/day in combination with flucytosine 100 mg/kg/day for 2 weeks followed by fluconazole 400 mg/day for a minimum of 10 weeks is the regimen of choice provided clinical improvement occurs. Liposomal amphotericin at a dose of 3 to 5 mg/kg/day is probably most appropriate for those intolerant of amphotericin B.[202,204] Evidence suggests itraconazole can be used instead of fluconazole if needed. Voriconazole and posaconazole have been used sparingly thus far, though in vitro susceptibilities suggest they are likely as effective as fluconazole and itraconazole.

Management of elevated intracranial pressure is also important.[205] Patients with initial pressures greater than 20 to 25 cm H_2O should have enough cerebrospinal fluid removed to reduce the pressure by 50%. Lumbar drains may be needed if pressure is very high or repeated lumbar punctures are not effective. Imaging should be performed prior to lumbar puncture to exclude a space-occupying lesion.[202]

Patients with AIDS who receive antiretroviral therapy may experience a paradoxical worsening of their symptoms due to immune reconstitution inflammatory syndrome.[205] Elevated intracranial pressure and formation of CNS cryptococcoma may become manifest with immune reconstitution during antiretroviral therapy and can be treated with adjunctive corticosteroids.

ASPERGILLOSIS

Aspergillosis is an illness caused by any member of the genus *Aspergillus*. The spectrum of human illness is extensive, ranging from allergic reactions to colonization of preexisting pulmonary cavities to invasion and destruction of lung tissue with pyemic spread to brain, skin, and other organs and rapid death.

Epidemiology

Members of the genus *Aspergillus* are ubiquitous in nature. These saprophytic molds exist wherever organic matter is decomposing. More than 100 species have been identified, but over 95% of human illness is caused by *Aspergillus fumigatus*. Other species that occasionally cause human disease are *A. niger, A. terreus, A. flavus*, and *A. nidulans*. The fungi are not dimorphic; they always grow as a mycelium. On the tips of specialized branching hyphae are spore heads that are characteristic for each species.[206] Owing to the ubiquitous nature of *Aspergillus*, everyone has daily contact with their spores, and total avoidance is virtually impossible.

Because the organism causes disease of such wide clinical diversity, a unitary concept of pathogenesis is not possible. Hypersensitivity pneumonitis caused by inhalation of fungal antigens is beyond the scope of this chapter and is dealt with elsewhere (see Chapter 66). Of the remaining clinical forms, five readily distinguishable types emerge: (1) *Tracheobronchial aspergillosis*, often a localized infection of the anastomosis in lung transplant recipients (see Chapter 95); (2) *allergic bronchopulmonary aspergillosis*, which affects patients with asthma (see Chapter 38) and bronchiectasis (see Chapter 42); (3) *mycetomas*, or fungus balls, in which the fungus colonizes existing pulmonary cavities; (4) *chronic necrotizing pulmonary aspergillosis*, in which the fungus locally invades abnormal lung and adjacent pleura; and (5) *invasive aspergillosis*, which occurs in patients with defects in phagocyte number, function, or both. Although other molds can cause similar entities, *Aspergillus* is the best recognized and most well studied pathogen.

Tracheobronchial Aspergillosis

Tracheobronchial aspergillosis has a spectrum of disease ranging from colonization to destructive tracheobronchitis. Although airway involvement is initially localized, untreated tracheobronchial aspergillosis can lead to dissemination. Tracheobronchial aspergillosis has been described almost exclusively in immunosuppressed individuals including patients with far advanced AIDS with extremely low CD4 counts. Patients who have undergone lung transplantation are at highest risk of infection and complications. Often these patients receive antifungal prophylaxis that can interfere with diagnosis. Tracheobronchial aspergillosis with infection of the anastomotic site, particularly in single-lung transplant recipients, has been associated with poor outcome and decreased survival.[207,208] Because clinical symptoms can mimic (and are often associated with) chronic rejection and because tracheobronchial aspergillosis is often isolated to the airway with normal radiographic studies, bronchoscopy is required for diagnosis. Treatment with nebulized amphotericin B is occasionally used in instances of true colonization. However, treatment regimens usually include systemic therapy, with more exten-

sive tracheobronchial aspergillosis being treated the same as invasive aspergillosis (see later).

Allergic Bronchopulmonary Aspergillosis

Allergic bronchopulmonary aspergillosis was first described in England in 1952.[209] Its frequency is approximately 5% to 10% of chronically steroid-dependent asthmatics.[210] Patients with cystic fibrosis also have a much higher prevalence [211,212] Although an immunologic reaction to aspergillus antigens is the most important factor leading to allergic bronchopulmonary aspergillosis,[213] the intensity of exposure to the fungus may also be important. In a survey from Chicago, almost 80% of the exacerbations occurred during periods of highest mold counts in the environment.[214]

Pathogenesis

A. fumigatus is the most common organism causing this condition; however, other species of *Aspergillus* and other fungi may cause a similar syndrome, prompting a change in terminology to "allergic bronchopulmonary mycosis." Both immunoglobulin E (IgE) and IgG have been implicated in the intense immunologic response to intrabronchial growth of the fungus.[215] More recently, predisposition to allergic bronchopulmonary aspergillosis was linked to specific polymorphisms in Toll-like recognition receptors.[216] T-cell immunity is an important contributor of inflammation and studies suggest a human leukocyte antigen (HLA)–restricted response.[217] The combination of a lymphocyte and specific IgE response causes cytokine and chemokine accumulation, mast cell degranulation, mediator release, and intense local inflammation, eventually leading to fibrosis or bronchiectasis.

Clinical Manifestations

Patients may be asymptomatic, even if abnormalities are present on radiographs. A symptom complex of fleeting pulmonary opacities, eosinophilia, wheezing, fever, and expectoration of brownish plugs is characteristic of allergic bronchopulmonary aspergillosis. Exacerbations mimic bacterial pneumonia, with pulmonary opacities, mucopurulent or bloody sputum, and fever. Other exacerbations of allergic bronchopulmonary mycosis have prominent wheezing and may appear at first to be exacerbations of ordinary asthma.

Radiographic findings include consolidation, segmental and lobar atelectasis, finger-like shadows from mucous impaction, and tram lines of bronchiectasis. The majority of findings are related to mucoid impaction or abnormal bronchi.[218] High-resolution CT scanning frequently demonstrates central bronchiectasis.[219] Pulmonary function testing varies with disease activity, with obstructive defects being common. Patients may have a combined obstructive and restrictive ventilatory defect. It is hoped but not proved that early treatment prevents development of bronchiectasis or slows progression to fibrosis.

Diagnosis

The diagnosis of allergic bronchopulmonary aspergillosis can be challenging and often is made by a combination of clinical, radiographic, and immunologic findings. Diagnostic criteria for allergic bronchopulmonary aspergillosis include (1) asthma, (2) central bronchiectasis, (3) immediate cutaneous reactivity to *Aspergillus* skin test antigen, (4) serum total IgE concentration greater than 1000 ng/mL, and (5) elevated *Aspergillus*-specific IgG or IgE compared with asthma controls. Those without central bronchiectasis can be diagnosed as allergic bronchopulmonary aspergillosis seropositive.[220] Other classic findings include circulating blood eosinophilia of more than 500 eosinophils/μL, sputum or BAL cultures positive for *Aspergillus*, precipitating antibodies against *Aspergillus* antigen, and history of recurrent pulmonary opacities. Unfortunately, most of these clinical criteria lack specificity because asthmatic persons without bronchopulmonary aspergillosis can have similar findings. Histologic findings often show airway inflammation and a component of bronchocentric granulomatosis.

Treatment

Glucocorticoid therapy hastens recovery from acute exacerbations and may prevent permanent residual damage. Although regimens vary, treatment of active allergic bronchopulmonary aspergillosis typically includes prednisone 0.5 mg/kg daily for 2 weeks followed by 0.5 mg/kg on alternate days for 3 to 6 months.[220] Serial IgE levels should be tested monthly and a doubling may herald an exacerbation. Chest radiographs are obtained 2 months after initiation of therapy and whenever there is an increase in symptoms. At the first hint of an exacerbation, the prednisone dosage should be increased. The role of inhaled corticosteroids is unclear, but they are often used during times of asthma exacerbation. In a double-blind, placebo-controlled trial, itraconazole, 200 mg twice daily for 16 weeks, was beneficial as add-on treatment for those requiring prolonged corticosteroid therapy.[221] Corticosteroids plus itraconazole are now a popular initial choice for patients with this condition. The newer azoles (voriconazole and posaconazole) are likely to be efficacious but only limited reports are available. The role of anti-IgE therapy is not clearly defined but may be most useful in children in order to spare the effects of steroids.[222]

Aspergilloma

Aspergillomas are masses of fungal mycelia that grow in preexisting lung cavities (Fig. 36-15). Although these mycetomas or "fungus balls" can be caused by many different fungi, the vast majority are caused by members of the genus *Aspergillus*. The exact incidence of aspergilloma is uncertain. A large, multicenter study in the United Kingdom evaluated 544 patients with healed tuberculous cavities at least 2.5 cm in diameter, and 11% had radiographic evidence of a fungus ball. Three years

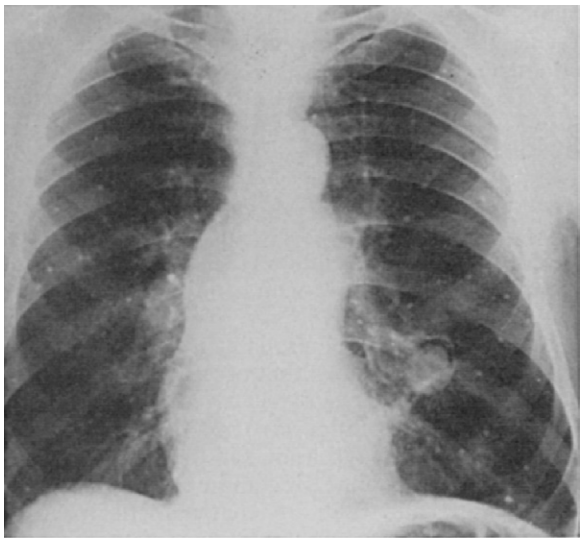

FIGURE 36-15 ■ Chest radiograph shows aspergilloma in an asymptomatic patient. The characteristic air crescent is readily seen. The radiograph also shows the multiple "buckshot" calcification of healed histoplasmosis.

after the original survey, the incidence of aspergillomas had increased to 17%.[223] Patients with residual cavitary disease from tuberculosis, endemic fungal infections, sarcoidosis, bullous emphysema, and fibrotic lung diseases are at risk.

Clinical Manifestations

The natural history of aspergillomas is variable. Most are stable and do not progress under observation. Some increase in size, and a substantial percentage resolve spontaneously. Many fungus balls are asymptomatic and are discovered only during routine radiographic surveillance. Some patients present with hemoptysis, which is the most important clinical feature of this illness. It is estimated that 90% of the patients experience at least one episode of hemoptysis. The magnitude of the hemoptysis ranges from trivial to massive. Hemoptysis has been ascribed to local vascular invasion of the cavity wall by *Aspergillus* organisms, but the source is not always evident. Collateral vessels from the bronchial arteries and from systemic arteries of the chest wall may help supply blood to the inflammatory tissue around the cavity, predisposing to serious bleeding.

Diagnosis

The diagnosis is usually established radiographically. Characteristically, the lung cavities containing the aspergilloma are in the upper lobes (because most residual cavities are due to old tuberculosis and fibrocavitary sarcoidosis) and have thickened walls. The presence of a mobile mass within a cavity is highly suggestive of aspergilloma. The organism can usually be cultured from expectorated sputum. Serologic evaluation is not routinely performed when classic radiographic features are present, but is frequently positive.

Treatment

Aspergillomas usually require no treatment. Although resection of the abnormal lung is curative, many patients have advanced underlying lung disease and cannot tolerate extensive surgery. In one study, 5.7% postoperative mortality was noted.[224] Systemic antifungal therapy for aspergillomas has not been very effective and is not routinely used unless a component of "chronic necrotizing pulmonary aspergillosis" or "chronic cavitary aspergillosis" is also suspected. Patients with aspergillomas who are started on immunosuppressive therapy can have local progression to these semi-invasive forms, necessitating systemic therapy. Bronchial artery embolization under radiographic guidance is often attempted first line to control bleeding in patients with high operative risk.[225] Resection of the lesion will stop the bleeding and cure the patient, if there is adequate pulmonary reserve. Direct (by needle or by percutaneous endobronchial catheter) instillation of amphotericin B or a sclerosing agent into the cavity may also be associated with decreased bleeding and can occasionally be tolerated in patients who are poor candidates for resectional surgery.[226]

Chronic Pulmonary Aspergillosis

Chronic forms of pulmonary aspergillosis requiring systemic antifungal treatment include chronic necrotizing pulmonary aspergillosis and chronic cavitary pulmonary aspergillosis. These entities have been referred to as "semi-invasive aspergillosis" or "complex aspergilloma." They are clearly locally invasive and occur in patients with underlying lung disease.[227,228] Many reported patients with chronic necrotizing pulmonary aspergillosis have had modest degrees of immunosuppression. Chronic cavitary pulmonary aspergillosis is a multicavitary disease that can occur with or without fungus balls and progresses (analogous to chronic cavitary histoplasmosis) over time. This patient population and the allergic bronchopulmonary aspergillosis population may have distinct polymorphisms in Toll-like receptor and surfactant proteins responsible for disease phenotype.[229,230] Most of the symptoms (shortness of breath, cough, sputum production) are due to the underlying lung disease, but slowly advancing tissue destruction from the *Aspergillus* infection worsens the symptoms.

The diagnosis is often suggested by the chest radiograph and CT scan findings, but must be confirmed by culture and sometimes by histopathology. A typical scenario is a patient with chronic obstructive pulmonary disease who develops upper lobe fibrocavitary disease and is initially suspected of having smear-negative tuberculosis. In this setting, repeated cultures that are negative for *Mycobacterium* and *Histoplasma* but are positive for *Aspergillus* cannot be ignored and should prompt therapy for chronic cavitary pulmonary aspergillosis. Chronic cavitary and necrotizing pulmonary aspergillosis frequently respond to oral antifungal therapy with itraconazole or voricoanzole.[228,231] Chronic cavitary forms of the disease often require lifelong suppressive therapy.

Systemic therapy, as is given for invasive aspergillosis, may be needed. Resectional surgery can sometimes be helpful for disease confined to one lobe but is reserved for medically nonresponsive disease because morbidity is high. Pyopneumothorax and aspergillus empyema are known complications.

Invasive Aspergillosis

Myelosuppression is the greatest risk factor for development of invasive pulmonary aspergillosis.[232] Advanced AIDS,[233] organ transplantation, high-dose glucocorticoid therapy, cytotoxic therapy, and treatment with biologics, including anti–TNF antibody therapy[234] are other predisposing factors. Among heart transplant recipients, invasive aspergillosis is the opportunistic infection with the highest attributable mortality. Most cases occur in the first 90 days after transplantation.[235] In one series of lung transplant recipients, 6.2% developed aspergillosis, with invasive pulmonary infection (32% of total infections) and disseminated infection (22% of total infections) predominating. Overall mortality was 52%.[193] Patients with chronic granulomatous disease who have deficient neutrophil oxidative burst are particularly susceptible to *Aspergillus* infection.

Pathogenesis

In vitro studies have shown the critical role of phagocytic cells in host defense against *Aspergillus*. Polymorphonuclear leukocytes are protective against mycelial forms, whereas monocytes are protective against the conidia.[236] Unchecked, the fungus grows into blood vessels, producing multiple areas of hemorrhagic pulmonary infarction distally. Dissemination can then occur. Necrosis and subsequent cavitation can ensue in the distribution of involved blood vessels. Cavitation of these infarcted areas often occurs when the previously suppressed leukocyte count returns toward normal, for example, as a patient with acute leukemia enters remission.[237] Prolonged neutropenia is the most important risk factor for invasive aspergillosis (Fig. 36-16).

Clinical Manifestations

The presentation often mimics that of acute bacterial pneumonia. The typical patient has a hematologic malignancy or has neutropenia due to treatment of malignancy and has been receiving broad-spectrum antibiotics for undiagnosed fever. Nonproductive cough, high fever, and pleuritic chest pain are common features; pleural friction rubs also occur. When dissemination occurs, symptoms at distant sites can predominate.

Diagnosis

Chest imaging is nondiagnostic but certain findings on CT are suggestive of invasive fungal infection. In a recent global comparative aspergillosis study, 94% of patients had one or more nodules and 61% had an associated "halo" sign with an area of lucency surrounding the nodule. Other imaging findings included consolidations (30%), infarct-shaped opacities (27%), cavitary lesions (20%), and air crescent signs (10%). Patients presenting with a halo sign had significantly better responses to treatment than did patients who presented with other imaging findings.[238] The authors concluded that presence of a halo sign in the appropriate clinical setting is sufficient to start antifungal therapy pending final diagnosis. The diagnosis of invasive pulmonary aspergillosis is often difficult and cases are sometimes categorized in the literature as proven, probable, or possible.[239] Sputum cultures may be negative. Even when positive, they are not absolutely diagnostic because the organism frequently colonizes the upper and lower airways. Nevertheless, isolation of *Aspergillus* from sputum of a patient who is at risk is highly suggestive of invasive aspergillosis and should prompt treatment. Cultures may be falsely negative due to antifungal use in prophylactic regimens. Thus, negative cultures do not exclude the diagnosis of invasive aspergillosis. Proof of invasive aspergillosis requires the demonstration of septate hyphae with acute-angle branching in tissue (Fig. 36–17).

The method used to obtain the diagnostic samples depends partly on local circumstances. Transbronchial lung biopsy by fiberoptic bronchoscopy has moderate

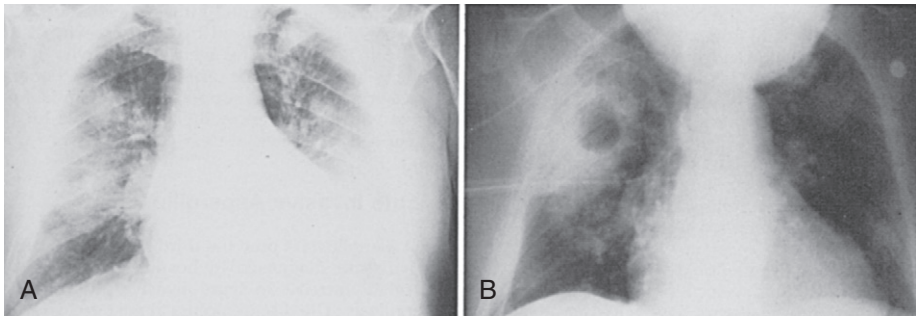

FIGURE 36-16 ■ Chest radiographs show rapidly advancing opacities caused by *Aspergillus fumigatus* in a patient with acute leukemia and fever. **A,** Bilateral nodular densities on day 4 of the fever. **B,** The same densities 2 weeks later. Note the large cavity in the confluent opacity.

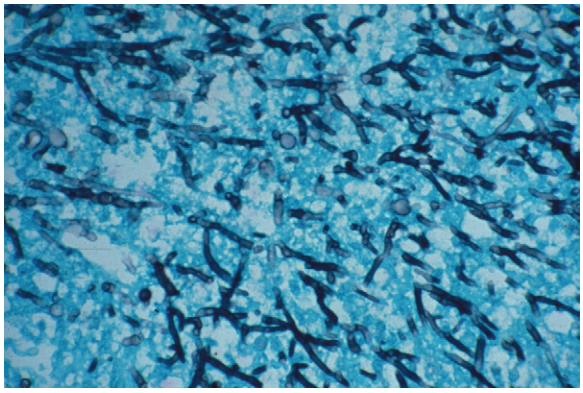

FIGURE 36-17 ■ Micrograph shows typical aspergillus organisms in tissue biopsy (septate, hyphae with finger-like branching at acute angles). (Silver methenamine stain; original magnification ×450.)

sensitivity and is specific when positive. Bronchial washings and BAL have higher (though imperfect) sensitivity and are safer than transbronchial biopsy.[240] Fine-needle aspiration of nodular lesions under CT guidance is often helpful. Some authorities believe that open lung biopsy is the procedure of choice, but it carries risk and is often reserved for situations when definitive diagnosis is elusive and the patient is not improving. Sites of distant spread include skin, brain, kidney, spleen, and other organs. Distant spread to the skin worsens the prognosis but provides a safe, easy site for biopsy to confirm the diagnosis.

Advances in antigen detection assays have significantly enhanced diagnosis of invasive aspergillosis. Studied most in stem cell transplant recipients,[241] galactomannan enzyme immunoassay antigen testing is a noninvasive tool for early diagnosis of aspergillosis in high-risk patients. There are false-positive results in patients receiving intravenous medications manufactured with yeast (i.e., piperacillin/tazobactam, plasmalyte)[242] and cross reactions in patients infected with other fungal pathogens (*Penicillium*, *Histoplasma*). Many studies have been performed in the context of surveillance, with serial testing rather than a single test.[243] Studies are currently ongoing to determine the utility of galactomannan in other patient populations and in biologic fluids including BAL.[244,245] The use of galactomannan testing in the decision to stop or reinstitute therapy is currently investigational. The (1,3)-β-D-glucan assay can detect *Aspergillus* with relatively high sensitivity, but is not specific. PCR-based detection assays are potentially powerful tools in the diagnosis of aspergillosis but, in contrast to antigen detection assays, are not yet standardized or commercially available.

Treatment

Recent guidelines and evidence from controlled trials suggest voriconazole is the treatment of choice for invasive aspergillosis.[246,247] Dosing is 6 mg/kg intravenous loading every 12 hours on day 1, then 4 mg/kg intravenously every 12 hours for the first week, transitioning to 200 mg orally twice daily. Although early reports suggested uniformly poor prognosis for invasive pulmonary aspergillosis, it is now well established that early and aggressive therapy can result in cure of some patients. Better results can be expected when granulocytopenia improves during the course of treatment. Response to therapy requires careful monitoring because many clinical trial end points are reported at 6 to 12 weeks.[248] Weaning of steroids or other immunosuppression is recommended whenever possible. Addition of growth factors (granulocyte-macrophage colony-stimulating factor [GM-CSF] for neutropenia or interferon-γ for chronic granulomatous disease) may be considered on an individual basis.

Amphotericin B is also an effective agent. Many seriously ill immunosuppressed patients have compromised renal function and are receiving potentially nephrotoxic agents such as cyclosporin A. Lipid formulations of amphotericin B permit higher dosing and longer treatment periods, providing the rationale for starting therapy with liposomal amphotericin B from onset of therapy. A recent trial comparing 3 mg/kg/day versus 10 mg/kg/day of liposomal amphotericin B showed equal efficacy but more renal dysfunction with the higher dose in patients being treated for invasive mold infections, primarily aspergillosis.[249] Commonly used dosing for liposomal amphotericin B is 3 to 5 mg/kg/day. Many centers are using combined therapy with voriconazole and liposomal amphotericin B for invasive pulmonary aspergillosis and for disseminated disease with extrapulmonary foci of infection, although clinical trials supporting that approach are not available.

Itraconazole, posaconazole, amphotericin B, if not used in the initial regimen, and echinocandins including caspofungin are alternative treatments for invasive aspergillosis.[250] *A. terreus* is resistant to amphotericin, and treatment with an azole is required.[247] Residual nodules and cavitary lesions can be removed surgically. Surgical removal is especially useful for infection near pericardium or great vessels and in patients who must undergo further episodes of intensive immunosuppression. Precise indications for resection of residual disease are uncertain. An alternative to resection of residual disease is secondary prophylaxis with antifungal therapy to cover all future periods of neutropenia.

ZYGOMYCOSIS

Zygomycosis (also known as mucormycosis or phycomycosis) refers to infection caused by any of several genera of fungi, including *Mucor*, *Rhizopus*, and *Absidia*. The most common manifestations include rhinocerebral zygomycosis in diabetics with ketoacidosis, pulmonary zygomycosis in immunocompromised patients, and local invasion of burned or otherwise denuded skin. These fungi are ubiquitous in nature and, as a rule, are unable to invade normal hosts. They live on decaying organic matter, and everyone has contact with their spores.

Invasion can occur only when normal defenses are altered. Inhibition of polymorphonuclear leukocyte

function by diabetic ketoacidosis,[251] suppression of polymorphonuclear leukocytes and alveolar macrophages by glucocorticoids or cytotoxic agents,[252] and destruction of cutaneous barriers by burns[253] predispose to the usual forms of the disease. Iron overload and treatment with desferoxamine (which acts as siderophore and increases availability of iron to the fungus) also predispose to infection. It is interesting that the incidence of rhinocerebral zygomycosis in diabetics in the United States is declining. One speculation credits wider use of statins, which have in vitro inhibitory activity against mucor species.[254] Conversely, pulmonary zygomycosis in patients with hematologic malignancy seems to be increasing, with reports from cancer centers linking that increase to more widespread use of voriconazole.[255]

The fungus invades blood vessels and causes distal ischemic necrosis.[252] The morphology in tissue is different from aspergillus. The fungus is nonseptate with short stubby side branches at a 90-degree angle. Inflammatory cells are usually polymorphonuclear leukocytes, and granuloma formation is not a feature of the histopathology.

Clinical Manifestations

Rhinocerebral zygomycosis occurs almost exclusively in the setting of diabetic ketoacidosis. High blood glucose levels and low tissue pH favor fungal growth and inhibit polymorphonuclear leukocyte function. Infection usually begins in the nose, with rapid invasion of the palate, sinuses, and orbits and eventual erosion into the cranium. The presence of a black eschar in these areas in a diabetic with ketoacidosis is strongly suggestive of mucormycosis.[251]

Pulmonary zygomycosis is seen almost exclusively in immunocompromised patients, in patients with hematologic malignancy undergoing cytotoxic therapy, and less commonly in organ transplant recipients.[256] The illness begins as an acute pneumonia with fever and cough, followed by signs and symptoms of pulmonary infarction, with pleuritic chest pain and hemoptysis. The chest radiograph usually shows one or multiple wedge-shaped pulmonary opacities extending to the pleura. On CT, the range of findings includes alveolar opacities, masses, nodules, pleural effusions. Reverse halo sign has been reported (central clear area from ischemic area surrounded by a radiographic density), but cavitary lesions with air crescents are much less common than in invasive aspergillosis. There may be systemic spread to multiple other organs, including the skin.[252] The clinical disease is very similar to invasive pulmonary aspergillosis. In one large series, clinical features that favored zygomycosis over aspergillosis included concomitant sinusitis, more than 10 nodules, pleural effusion, and prior treatment with voriconazole.[257]

Diagnosis and Treatment

Because the fungi are ubiquitous in nature, positive cultures must be correlated with the clinical picture. Histopathologic examination of involved tissue that reveals characteristic broad (10–20 μm), nonseptate hyphae, with occasional stubby side branches coming off usually at 90-degree angles is diagnostic. Unlike the hyphae of other fungi, those of mucor and other species may stain better with standard hematoxylin and eosin stains than with silver stains or other special stains usually used for fungal diseases. No serologic test and no skin test are available. Diagnosis often depends on direct identification of characteristic organisms in tissue biopsies. Culture confirmation may be difficult in many cases. Organisms may also be seen directly in sputum and bronchoalveolar fluid samples in patients with pneumonia, sometimes confirmed by culture.

There is no uniformly effective therapy, although amphotericin B has been widely used historically. Best results have been accomplished with the combined use of amphotericin B and aggressive surgical resection. Anecdotal reports describe use of liposomal amphotericin B plus surgical resection (two cases),[258] combination therapy with liposomal amphotericin B and caspofungin,[259] and posaconazole. Posaconazole had surprising efficacy in a salvage study of 91 patients failing or intolerant to standard therapy. There was a clinical response in 60% and 21 had control of their disease.[260] Note that voriconazole and fluconazole have no efficacy. Current approach includes liposomal amphotericin B with posaconazole concomitantly or as a sequential agent after initial response. Surgical resection of localized disease is appropriate for selected patients. Use of an echinocandin as second agent (with liposomal amphotericin B) has also been reported. Further studies may indicate a larger role for posaconazole in initial therapy, especially if an intravenous formulation is developed. Unfortunately, large comparative studies of various regimens are unlikely to be done because of the rarity of disease and the severity of underlying illnesses. The overall mortality and pulmonary zygomycosis in severely immunosuppressed patients remain very high.

CANDIDIASIS

Candidiasis refers to infection caused by members of the genus *Candida*, usually *C. albicans* but occasionally *C. tropicalis* or other species and increasingly the more resistant *C. glabrata*. Systemic candidiasis is a relatively common opportunistic infection, and the lung is frequently involved in widespread hematogenous dissemination. However, primary pulmonary infections in which the mechanism is aspiration of pharyngeal contents are very uncommon.

Candida organisms are ubiquitous in nature and are normal inhabitants of the human mouth and gastrointestinal tract. Thrush in infants and candida vulvovaginitis in young women have long been recognized as common infections in otherwise healthy hosts. Glucocorticoid therapy and broad-spectrum antibiotics also predispose to these conditions. Thrush is also common in persons with HIV infection and serves as a harbinger of progression to full-blown AIDS.[261] When thrush occurs in patients already diagnosed with AIDS, it nearly always

indicates the simultaneous presence of *Candida* esophagitis.[262] Systemic candidiasis is a known complication of neutropenia, parenteral nutrition, and heroin abuse.[263] Different patterns of systemic involvement may be seen with these underlying conditions, but the pulmonary involvement (with multiple hematogenous microabscesses) is usually overshadowed clinically by disease of other organs such as the skin, bones, joints, and eyes.

Pathogenesis

Systemic candidiasis occurs through different portals of entry. The organism may enter the body across injured gastrointestinal mucosa or may cross from the skin into the bloodstream, often aided by an indwelling vascular catheter. Bronchopulmonary candidiasis including pneumonia can result from aspiration from the oropharynx into the lungs but is very uncommon. Most patients with clinically significant candidiasis have not only a portal of entry but impaired host defense mechanisms as well. Normal polymorphonuclear leukocytes are important defenders against *C. albicans*. The role of humoral and cell-mediated immune mechanisms for protection against deep invasion is less clear,[264] although cell-mediated immunity plays a large role in preventing mucosal overgrowth, as seen when AIDS patients get marked mucosal overgrowth, but little tendency to have deep invasion.

Clinical Manifestations

The clinical features of systemic candidiasis depend on the sites of infection, the extent of involvement, and the host immune response. In addition, there is nearly always the confounding presence of underlying disease.

Bronchopulmonary candidiasis can present with cough productive of purulent sputum, dyspnea, and fever. Chest radiographs may show patchy or lobar opacities or be surprisingly normal.[265] The entirely nonspecific manifestations of pulmonary involvement help to explain why pulmonary candidiasis is often not diagnosed until autopsy examination.

Diagnosis

Two factors contribute to the difficulty in diagnosing bronchopulmonary candidiasis during life. First, the presence of *Candida* in cultures or KOH preparations of sputum or even bronchoscopic specimens is virtually impossible to interpret because of frequent oropharyngeal and tracheobronchial colonization, which is nearly universal in patients receiving broad-spectrum antibacterial therapy. Second, there is no satisfactory serologic test despite considerable effort to develop one.[266] The histopathology of *Candida* infection includes yeast that serially buds to form so-called sprout mycelia.

Candidiasis is the only fungal infection in which yeast and pseudohyphae are seen together in tissue sections. Histologic demonstration of tissue invasion is required to prove *Candida* pneumonia.

Treatment

Prevention of systemic candidiasis depends on control of local mucocutaneous sites of infection, control of gastrointestinal overgrowth, and maintenance of healthy barriers (skin and gastrointestinal mucosa) and adequate numbers of functioning phagocytes. Removal of contaminated vascular access lines plus antifungal therapy is usually required to cure *Candida* fungemia. Any positive blood culture is evidence of systemic infection and dictates systemic treatment. Successful treatment of bronchopulmonary and other forms of systemic candidiasis has been reported with several different drug regimens, including amphotericin B (with or without 5-flucytosine), ketoconazole, and fluconazole.

In one study, caspofungin was superior to amphotericin B for treatment of systemic candidiasis. In patients who survived long enough to be evaluable, caspofungin improved the likelihood of eliminating the fungus and had markedly reduced toxicity compared with that of amphotericin B.[267] *C. glabrata* is increasing in frequency, partly due to antibiotic pressure from broad use of fluconazole, to which it is generally resistant. *C. glabrata* is sensitive to caspofungin and other echinocandins.

UNCOMMON PULMONARY FUNGAL INFECTIONS

The number of other fungi that can cause pulmonary disease is increasing, particularly for intensely immunosuppressed patients.

Pulmonary Infections Due to *Scedosporium* (Formerly Pseudallescheriosis, Allescheriosis, Maduromycosis of the Lung)

Human illness caused by *Scedosporium apiospermum* (asexual stage of *Pseudoallescheria boydii*) is uncommon and usually occurs in an altered host.[268,269] The spectrum of illness is similar to that of aspergillosis and includes slowly progressive pulmonary infections in patients with underlying lung disease, intracavitary fungus balls in preexisting cavities,[270] and invasive pulmonary infection.

Epidemiology and Clinical Manifestations

The fungus, a soil saprophyte, is ubiquitous in nature. It may produce a slowly progressive upper lobe cavitary disease, with or without a fungus ball, in minimally abnormal hosts. This illness is similar to chronic necrotizing aspergillosis. In more severely immunocompromised patients, the organism may cause pneumonia with blood vessel invasion and pulmonary infarction, similar to that seen in invasive aspergillosis or pulmonary zygomycosis.

Diagnosis

Cultural recovery of the organism is often hard to interpret because the organism is common in the environment. The histopathologic appearance is identical to that of aspergillosis, with septate hyphae branching at acute angles. Proof of diagnosis usually requires demonstration of aspergillus-like organisms in tissue biopsies or biologic specimens and positive cultures for scedosporum and not for aspergillus.

Treatment

It is important to clearly separate scedosporium infections from aspergillosis in part because amphotericin B is not an effective treatment for scedosporium infections.[271] Voriconazole is probably the treatment of choice and is continued for at least 12 weeks. Miconazole also has activity and was used in the past. There were 24 patients with scedosporium infection included in a large (total of 520 patients) clinical trial of voriconazole for primary and salvage therapy of infections due to aspergillus, scedosporium, and fusarium species.[272] Treatment was successful in 15 of the 24 patients including 6 of 10 with CNS involvement. There are published reports of successful use of voriconazole in small numbers of patients with pulmonary and CNS infections.[273] There likely will not be clinical trials comparing different treatment options because the infection is rare and the patients are difficult to study because of the complexity of the underlying illnesses. This makes it unlikely that there will be a best-treatment strategy that is evidence based.

Pulmonary Sporotrichosis

Even though lymphocutaneous sporotrichosis is far more common than the pulmonary illness, occasional isolated pulmonary disease does occur, probably acquired by inhalation.[274] Recovery of *Sporothrix schenckii* from sputum or bronchoscopic specimens in a compatible clinical setting (chronic radiographic changes, chronic cough, and low-grade fever) is the usual method of diagnosis.

The treatment of sporotrichosis lung disease is not established. Although historically many authorities considered amphotericin B the drug of choice,[275] it was difficult to demonstrate that amphotericin was better than other agents, such as saturated solution of potassium iodide. Ketoconazole has little activity against sporotrichosis.[276] Itraconazole is somewhat more active.[277] Surgical resection of isolated disease, alone or in combination with other treatment, is frequently effective.[278] The disease is rare and its natural history poorly understood, complicating interpretation of treatment results. At present, itraconazole may be a reasonable choice for therapy.

Other Fungi

Many other normally saprophytic fungi can cause pulmonary infection in severely immunocompromised patients. These infections are difficult to diagnose because the causative organisms are frequent contaminants in the laboratory. Proof of infection requires documentation of tissue invasion. These organisms include *Geotrichum*, *Hansenula*, *Penicillium*, *Fusarium*,[279] and many others. These infections occur in the same population of immunosuppressed patients that is susceptible to invasive aspergillosis, but at much lower frequency. Whereas there are many similarities of the mold infections to aspergillosis, there are some differences. For example, fusarium infection has higher frequency of positive blood cultures, higher frequency of peripheral skin lesions, and major resistance to amphotericin B.[273]

Another emerging deep fungal infection is AIDS-related *Penicillium marneffei* (an apparent T-cell opportunist) being reported in AIDS patients in southeastern Asia (see Chapter 80).

KEY POINTS

- Of the endemic mycoses, histoplasmosis, blastomycosis, and coccidioidomycosis are most common in North America and paracoccidioidomycosis is found in South America.
- Histoplasmosis tends to spread to reticuloendothelial organs including lymph nodes, bone marrow, liver, and spleen. Blastomycosis spreads mainly to skin and bones. Coccidioidomycosis spreads to skin and bone, but also to CNS.
- The endemic mycoses and cryptococcosis are T-cell opportunists. They occur in normal hosts and require specific immunity for control of the infection. They exploit T-cell immunodeficiency especially AIDS.
- The endemic mycoses can present as community-acquired pneumonia and must always be considered when a patient has progressive pneumonia despite appropriate antibacterial therapy. Additional diagnostic tests (including bronchoscopy) must be done rather than additional courses of different antibacterial agents largely covering the same pathogens.
- Diagnostic tests include antibody and antigen testing for histoplasmosis and coccidioidomycosis. Organisms causing blastomycosis and coccidioidomycosis have highly

specific morphology (large yeast with single broad-necked bud for blastomycosis and spherule for coccidioidomycosis) that offers specific direct diagnosis in some cases.

- Aspergillus is a ubiquitous soil fungus. Spores can be killed by neutrophils, and the fungus usually cannot invade healthy tissue defended by phagocytes. Aspergillus exploits conditions such as neutropenia, most commonly associated with aggressive treatment of hematologic malignancy and bacterial infections. Of the different forms of disease associated with aspergillus, the invasive form is most lethal.
- For many years, amphotericin B was the major available therapy for deep fungal infections. Now there are other important agents including newer azoles and echinocandins. Treatment is more complex, and guidelines for treatment are regularly updated.

References

1. Goodwin RA Jr, Des Prez RM: State of the art: Histoplasmosis. Am Rev Respir Dis 117:929–956, 1978.
2. Sarosi GA, Davies SF: Blastomycosis. Am Rev Respir Dis 120:911–938, 1979.
3. Drutz DJ, Catanzaro A: Coccidioidomycosis. Part I. Am Rev Respir Dis 117:559–585, 1978.
4. Davies SF, Khan M, Sarosi GA: Disseminated histoplasmosis in immunologically suppressed patients. Occurrence in a nonendemic area. Am J Med 64:94–100, 1978.
5. Goodwin RA Jr, Shapiro JL, Thurman GH, et al: Disseminated histoplasmosis: Clinical and pathologic correlations. Medicine (Baltimore) 59:1–33, 1980.
6. Goodwin RA Jr, Shapiro JL, Thurman GH, et al: The epidemiology of paracoccidoidomycosis. *In* Al-Doory Y (ed): The Epidemiology of Human Mycotic Diseases. Springfield, IL: Charles C. Thomas, 1978, pp 117–141.
7. Schaffner A, Davis CE, Schaffner T, et al: In vitro susceptibility of fungi to killing by neutrophil granulocytes discriminates between primary pathogenicity and opportunism. J Clin Invest 78:511–524, 1986.
8. Darling S: A protozoan general infection producing pseudotubercles in the lungs and focal necrosis in the liver, spleen and lymph nodes. JAMA 46:1283–1285, 1906.
9. daRocha-Lima VH: Beitrag zur Kenntnis der Blastomykosen: Lymphangitis epizootica and histoplasmosis. Zentralbl Bakt 67:233, 1942.
10. Riley WA, Watson CJ: Histoplasmosis of Darling with report of a case originating in Minnesota. Am J Trop Med 6:271–282, 1926.
11. Dodd K, Tompkins EH: Case of histoplasmosis of Darling in an infant. Am J Trop Med 14:127–134, 1934.
12. DeMonbreun WA: The cultivation and cultural characteristics of Darling's *Histoplasma capsulatum*. Am J Trop Med 14:93–126, 1934.
13. Christie A, Peterson J: Pulmonary calcifications in negative reactors to tuberculin. Am J Public Health 35:1131–1147, 1945.
14. Palmer CE: Nontuberculous pulmonary calcification. Am J Public Health 60:513–521, 1945.
15. Emmons CW: Isolation of *Histoplasma capsulatum* from soil. Public Health Rep 64:892–896, 1949.
16. Hammerman KJ, Powell KE, Tosh FE: The incidence of hospitalized cases of systemic mycotic infections. Sabouraudia 12:33–45, 1974.
17. Larsh HW, Hinton A, Cozad GC: Natural reservior of *Histoplasma capsulatum*. Am J Hyg 63:18–27, 1956.
18. Sarosi GA, Parker JD, Tosh FE: Histoplasmosis outbreaks: Their patterns. *In* Balows A (ed): Histoplasmosis: Proceedings of the Second National Conference. Springfield, IL, Charles C. Thomas, 1971, pp 123–128.
19. Wheat LJ, Slama TG, Eitzen HE, et al: A large urban outbreak of histoplasmosis: Clinical features. Ann Intern Med 94:331–337, 1981.
20. Goodwin RA, Loyd JE, Des Prez RM: Histoplasmosis in normal hosts. Medicine (Baltimore) 60:231–266, 1981.
21. Buck BE, Malinin TI, Davis JH: Transmission of histoplasmosis by organ transplantation. N Engl J Med 344:310, 2001.
22. Procknow JJ, Page MI, Loosli CG: Early pathogenesis of experimental histoplasmosis. Arch Pathol 69:413–426, 1960.
23. Zhou P, Miller G, Seder RA: Factors involved in regulating primary and secondary immunity to infection with *Histoplasma capsulatum*: TNF-alpha plays a critical role in maintaining secondary immunity in the absence of IFN-gamma. J Immunol 160:1359–1368, 1998.
24. Allendoerfer R, Biovin GP, Deepe GS Jr: Modulation of immune responses in murine pulmonary histoplasmosis. J Infect Dis 175: 905–914, 1997.
25. Seder RA, Gazzinelli RT: Cytokines are critical in linking the innate and adaptive immune responses to bacterial, fungal, and parasitic infection. Adv Intern Med 44:353–388, 1999.
26. Allendorfer R, Brunner GD, Deepe GS Jr: Complex requirements for nascent and memory immunity in pulmonary histoplasmosis. J Immunol 162:7389–7396, 1999.
27. Allendoerfer R, Deepe GS Jr: Intrapulmonary response to *Histoplasma capsulatum* in gamma interferon knockout mice. Infect Immun 65:2564–2569, 1997.
28. Berry CL: The development of the granuloma of histoplasmosis. J Pathol 97:1–10, 1969.
29. Straub M, Schwarz J: The healed primary complex in histoplasmosis. Am J Clin Pathol 25:727–741, 1955.
30. Feller AE, Furcolow ML, Larsh HW, et al: Outbreak of unusual form of pneumonia at Camp Gruber, Oklahoma, in 1944: Follow-up studies implicating *Histoplasma capsulatum* as the etiologic agent. Am J Med 21:184–192, 1956.
31. D'Alessio DJ, Heeren RH, Hendricks SL, et al: A starling roost as the source of urban epidemic histoplasmosis in an area of low incidence. Am Rev Respir Dis 92:725–731, 1965.
32. Tosh FE, Doto IL, D'Alessio DJ, et al: The second of two epidemics of histoplasmosis resulting from work on the same starling roost. Am Rev Respir Dis 94:406–413, 1966.
33. Medeiros AA, Marty SD, Tosh FE, Chin TD: Erythema nodosum and erythema multiforme as clinical manifestations of histoplasmosis in a community outbreak. N Engl J Med 274:415–420, 1966.
34. Goodwin RA, Nickell JA, Des Prez RM: Mediastinal fibrosis complicating healed primary histoplasmosis and tuberculosis. Medicine (Baltimore) 51:227–246, 1972.
35. Wheat LJ, Stein L, Corya BC, et al: Pericarditis as a manifestation of histoplasmosis during two large urban outbreaks. Medicine (Baltimore) 62:110–119, 1983.
36. A report of ten proven cases of histoplasmosis. U S Public Health Rep 63:299–316, 1948.
37. Goodwin RA Jr, Owens FT, Snell JD, et al: Chronic pulmonary histoplasmosis. Medicine (Baltimore) 55:413–452, 1976.
38. Davies SF, Sarosi GA: Acute cavitary histoplasmosis. Chest 73: 103–105, 1978.
39. Davies SF, Khan M, Sarosi GA: Disseminated histoplasmosis in immunologically suppressed patients. Occurrence in a nonendemic area. Am J Med 64:94–100, 1978.
40. Davies SF, McKenna RW, Sarosi GA: Trephine biopsy of the bone marrow in disseminated histoplasmosis. Am J Med 67:617–622, 1979.

41. Wheat LJ, Slama TG, Zeckel ML: Histoplasmosis in the acquired immune deficiency syndrome. Am J Med 78:203–210, 1985.
42. Johnson PC, Hamill RJ, Sarosi GA: Clinical review: Progressive disseminated histoplasmosis in the AIDS patient. Semin Respir Infect 4:139–146, 1989.
43. Wheat LJ, Slama TG, Norton JA, et al: Risk factors for disseminated or fatal histoplasmosis. Analysis of a large urban outbreak. Ann Intern Med 96:159–163, 1982.
44. Wheat LJ, Connolly-Stringfield PA, Baker RL, et al: Disseminated histoplasmosis in the acquired immune deficiency syndrome: Clinical findings, diagnosis and treatment, and review of the literature. Medicine (Baltimore) 69:361–374, 1990.
45. Sarosi GA, Voth DW, Dahl BA, et al: Disseminated histoplasmosis: Results of long-term follow-up. A Centers for Disease Control Cooperative Mycoses Study. Ann Intern Med 75:511–516, 1971.
46. Hawkins SS, Gregory DW, Alford RH: Progressive disseminated histoplasmosis: Favorable response to ketoconazole. Ann Intern Med 95:446–449, 1981.
47. Wood KL, Hage CA, Knox KS, et al: Histoplasmosis after treatment with anti-tumor necrosis factor-alpha therapy. Am J Respir Crit Care Med 167:1279–1282, 2003.
48. Prechter GC, Prakash UB: Bronchoscopy in the diagnosis of pulmonary histoplasmosis. Chest 95:1033–1036, 1989.
49. Wheat LJ, Connolly-Stringfield P, Williams B, et al: Diagnosis of histoplasmosis in patients with the acquired immunodeficiency syndrome by detection of Histoplasma capsulatum polysaccharide antigen in bronchoalveolar lavage fluid. Am Rev Respir Dis 145:1421–1424, 1992.
50. Salzman SH, Smith RL, Aranda CP: Histoplasmosis in patients at risk for the acquired immunodeficiency syndrome in a nonendemic setting. Chest 93:916–921, 1988.
51. Wheat J, French ML, Kohler RB, et al: The diagnostic laboratory tests for histoplasmosis: Analysis of experience in a large urban outbreak. Ann Intern Med 97:680–685, 1982.
52. Davies SF: Serodiagnosis of histoplasmosis. Semin Respir Infect 1:9–15, 1986.
53. Hage CA, Davis TE, Egan L, et al: Diagnosis of pulmonary histoplasmosis and blastomycosis by detection of antigen in bronchoalveolar lavage fluid using an improved second-generation enzyme-linked immunoassay. Respir Med 101:43–47, 2007.
54. Wheat LJ, Connolly-Stringfield P, Kohler RB, et al: *Histoplasma capsulatum* polysaccharide antigen detection in diagnosis and management of disseminated histoplasmosis in patients with acquired immunodeficiency syndrome. Am J Med 87:396–400, 1989.
55. Wheat LJ, Connolly-Stringfield P, Blair R, et al: Histoplasmosis relapse in patients with AIDS: Detection using *Histoplasma capsulatum* variety *capsulatum* antigen levels. Ann Intern Med 115:936–941, 1991.
56. Wheat LJ, Connolly-Stringfield P, Blair R, et al: Effect of successful treatment with amphotericin B on *Histoplasma capsulatum* variety *capsulatum* polysaccharide antigen levels in patients with AIDS and histoplasmosis. Am J Med 92:153–160, 1992.
57. Naylor BA: Low-dose amphotericin B therapy for acute pulmonary histoplasmosis. Chest 71:404–406, 1977.
58. Dismukes WE, Bradsher RW Jr, Cloud GC, et al: Itraconazole therapy for blastomycosis and histoplasmosis. NIAID Mycoses Study Group. Am J Med 93:489–497, 1992.
59. Parker JD, Sarosi GA, Doto IL, et al: Treatment of chronic pulmonary histoplasmosis. N Engl J Med 283:225–229, 1970.
60. Freifeld AG, Wheat LJ, Kaul DR: Histoplasmosis in solid organ transplant recipients: early diagnosis and treatment. Curr Opin Organ Transplant 14:601–605, 2009.
61. Hecht FM, Wheat J, Korzun AH, et al: Itraconazole maintenance treatment for histoplasmosis in AIDS: A prospective, multicenter trial. J Acquir Immune Defic Syndr Hum Retrovirol 16:100–107, 1997.
62. Wheat J, Hafner R, Korzun AH, et al: Itraconazole treatment of disseminated histoplasmosis in patients with the acquired immunodeficiency syndrome. AIDS Clinical Trial Group. Am J Med 98: 336–342, 1995.
63. Wheat J, MaWhinney S, Hafner R, et al: Treatment of histoplasmosis with fluconazole in patients with acquired immunodeficiency syndrome. National Institute of Allergy and Infectious Diseases Acquired Immunodeficiency Syndrome Clinical Trials Group and Mycoses Study Group. Am J Med 103:223–232, 1997.
64. Johnson PC, Wheat LJ, Cloud GA, et al: Safety and efficacy of liposomal amphotericin B compared with conventional amphotericin B for induction therapy of histoplasmosis in patients with AIDS. Ann Intern Med 137:105–109, 2002.
65. Chapman SW, Dismukes WE, Proia LA, et al: Clinical practice guidelines for the management of blastomycosis: 2008 update by the Infectious Diseases Society of America. Clin Infect Dis 46:1801–1812, 2008.
66. Wheat LJ, Freifeld AG, Kleiman MB, et al: Clinical practice guidelines for the management of patients with histoplasmosis: 2007 update by the Infectious Diseases Society of America. Clin Infect Dis 45:807–825, 2007.
67. Donovick R, Gold W, Pagano JF, Stout HA: Amphotericins A and B, antifungal antibiotics produced by a streptomycete. I. In vitro studies. Antibiot Annu 3:579–586, 1955.
68. Butler WT, Bennett JE, Alling DW, et al: Nephrotoxicity of amphotericin B: Early and late effects in 81 patients. Ann Intern Med 61:175–187, 1964.
69. Herbrecht R, Letscher V, Andres E, Cavalier A: Safety and efficacy of amphotericin B colloidal dispersion. An overview. Chemotherapy 45(Suppl 1):67–76, 1999.
70. Bowden R, Chandrasekar P, White MH, et al: A double-blind, randomized, controlled trial of amphotericin B colloidal dispersion versus amphotericin B for treatment of invasive aspergillosis in immunocompromised patients. Clin Infect Dis 35:359–366, 2002.
71. Dismukes W, Karam G, Bowles C: A multi-center prospective randomized trial of two different dosage regimens of ketoconazole for the treatment of histoplasmosis (abstract). *In* Proceedings of the 23rd Interscience Conference on Antimicrobial Agents and Chemotherapy. Las Vegas, Oct. 24–26, 1983, pp 24–26.
72. Mannisto PT, Mantyla R, Nykanen S, et al: Impairing effect of food on ketoconazole absorption. Antimicrob Agents Chemother 21:730–733, 1982.
73. Pont A, Graybill JR, Craven PC, et al: High-dose ketoconazole therapy and adrenal and testicular function in humans. Arch Intern Med 144:2150–2153, 1984.
74. Saag MS, Powderly WG, Cloud GA, et al: Comparison of amphotericin B with fluconazole in the treatment of acute AIDS-associated cryptococcal meningitis. The NIAID Mycoses Study Group and the AIDS Clinical Trials Group. N Engl J Med 326:83–89, 1992.
75. Denning DW, Tucker RM, Hanson LH, Stevens DA: Treatment of invasive aspergillosis with itraconazole. Am J Med 86:791–800, 1989.
76. Johnson PC, Khardori N, Najjar AF, et al: Progressive disseminated histoplasmosis in patients with acquired immunodeficiency syndrome. Am J Med 85:152–158, 1988.
77. Terrell CL: Antifungal agents. Part II. The azoles. Mayo Clin Proc 74:78–100, 1999.
78. Herbrecht R, Denning DW, Patterson TF, et al: Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. N Engl J Med 347:408–415, 2002.
79. Theuretzbacher U: Pharmacokinetics/pharmacodynamics of echinocandins. Eur J Clin Microbiol Infect Dis 23:805–812, 2004.
80. Gilchrist TC, Stokes WR: Case of pseudolupus vulgaris caused by blastomycosis. J Exp Med 3:53–78, 1898.
81. Protozoan dermatitis. J Cutan Gen Dis 36:1445–1457, 1894.
82. Martin DS, Smith D: Blastomycosis II: A report of thirteen new cases. Am Rev Tuberc 39:488–515, 1939.
83. Schwarz J, Baum GL: Blastomycosis. Am J Clin Pathol 21:999–1029, 1951.
84. Furcolow ML, Chick EW, Busey JF, Menges RW: Prevalence and incidence studies of human and canine blastomycosis. 1. Cases in the United States, 1885–1968. Am Rev Respir Dis 102:60–67, 1970.
85. Kepron MW, Schoemperlen, Hershfield ES, et al: North American blastomycosis in Central Canada. A review of 36 cases. Can Med Assoc J 106:243–246, 1972.
86. Tosh FE, Hammerman KJ, Weeks RJ, Sarosi GA: A common source epidemic of North American blastomycosis. Am Rev Respir Dis 109:525–529, 1974.

87. Morris SK, Brophy J, Richardson SE, et al: Blastomycosis in Ontario, 1994–2003. Emerg Infect Dis 12:274–279, 2006.
88. Parmar MS: Paradise—Not without its plagues: Overwhelming *Blastomycosis pneumonia* after visit to lakeside cottages in Northeastern Ontario. BMC Infect Dis 5:30, 2005.
89. Witorsch P, Utz JP: North American blastomycosis: A study of 40 patients. Medicine (Baltimore) 47:169–200, 1968.
90. Sarosi GA, Hammerman KJ, Tosh FE, Kronenberg RS: Clinical features of acute pulmonary blastomycosis. N Engl J Med 290:540–543, 1974.
91. Sarosi GA, King RA: Apparent diminution of the blastomycin skin test: Follow-up of an epidemic of blastomycosis. Am Rev Respir Dis 116:785–788, 1977.
92. Klein BS, Vergeront JM, Weeks RJ, et al: Isolation of *Blastomyces dermatitidis* in soil associated with a large outbreak of blastomycosis in Wisconsin. N Engl J Med 314:529–534, 1986.
93. Klein BS, Vergeront JM, Davis JP: Epidemiologic aspects of blastomycosis, the enigmatic systemic mycosis. Semin Respir Infect 1:29–39, 1986.
94. Greenberg SB: Serious waterborne and wilderness infections. Crit Care Clin 15:387–414, 1999.
95. Baumgardner DJ, Brockman K: Epidemiology of human blastomycosis in Vilas County, Wisconsin. II: 1991–1996. WMJ 97:44–47, 1998.
96. Reed KD, Meece JK, Archer JR Peterson AT: Ecologic niche modeling of *Blastomyces dermatitidis* in Wisconsin. PLoS ONE 3:e2034, 2008.
97. Sarosi GA, Eckman MR, Davies SF, Laskey WK: Canine blastomycosis as a harbinger of human disease. Ann Intern Med 91:733–735, 1979.
98. Vaaler AK, Bradsher RW, Davies SF: Evidence of subclinical blastomycosis in forestry workers in northern Minnesota and northern Wisconsin. Am J Med 89:470–476, 1990.
99. Wuthrich M, Finkel-Jimenez B, Brandhorst TT, et al: Analysis of non-adhesive pathogenic mechanisms of BAD1 on *Blastomyces dermatitidis*. Med Mycol 44:41–49, 2006.
100. Finkel-Jimenez B, Wuthrich M, Klein BS: BAD1, an essential virulence factor of *Blastomyces dermatitidis*, suppresses host TNF-alpha production through TGF-beta-dependent and -independent mechanisms. J Immunol 168:5746–5755, 2002.
101. Wuthrich M, Filutowicz HI, Klein BS: Mutation of the WI-1 gene yields an attenuated *Blastomyces dermatitidis* strain that induces host resistance. J Clin Invest 106:1381–1389, 2000.
102. Baum GL, Lerner PI: Primary pulmonary blastomycosis: A laboratory-acquired infection. Ann Intern Med 73:263–265, 1970.
103. Abernathy RS: Clinical manifestations of pulmonary blastomycosis. Ann Intern Med 51:707–727, 1959.
104. Laskey W, Sarosi GA: The radiological appearance of pulmonary blastomycosis. Radiology 126:351–357, 1978.
105. Laskey W, Sarosi GA: Endogenous activation in blastomycosis. Ann Intern Med 88:50–52, 1978.
106. Gauthier GM, Safdar N, Klein BS, Andes DR: Blastomycosis in solid organ transplant recipients. Transpl Infect Dis 9:310–317, 2007.
107. Davies S, Sarosi GA: Clinical manifestations and management of blastomycosis in the compromised patient. *In* Warnock DW, Richard MD (eds): Fungal Infection in the Compromised Patient. New York: John Wiley and Sons, 1982, pp 215–229.
108. Trumbull ML, Chesney TM: The cytological diagnosis of pulmonary blastomycosis. JAMA 245:836–838, 1981.
109. Martynowicz MA, Prakash UB: Pulmonary blastomycosis: An appraisal of diagnostic techniques. Chest 121:768–773, 2002.
110. Lemos LB, Guo M, Baliga M: Blastomycosis: Organ involvement and etiologic diagnosis. A review of 123 patients from Mississippi. Ann Diagn Pathol 4:391–406, 2000.
111. Sanders JS, Sarosi GA, Nollet DJ, Thompson JI: Exfoliative cytology in the rapid diagnosis of pulmonary blastomycosis. Chest 72:193–196, 1977.
112. Bradsher RW: Development of specific immunity in patients with pulmonary or extrapulmonary blastomycosis. Am Rev Respir Dis 129:430–434, 1984.
113. Durkin M, Witt J, Lemonte A, et al: Antigen assay with the potential to aid in diagnosis of blastomycosis. J Clin Microbiol 42:4873–4875, 2004.
114. Sarosi GA, Davies SF, Phillips JR: Self-limited blastomycosis: A report of 39 cases. Semin Respir Infect 1:40–44, 1986.
115. Lahm T, Neese S, Thornburg AT, et al: Corticosteroids for blastomycosis-induced ARDS: A report of two patients and review of the literature. Chest 133:1478–1480, 2008.
116. Bakleh M, Aksamit AJ, Tleyjeh IM, Marshall WF: Successful treatment of cerebral blastomycosis with voriconazole. Clin Infect Dis 40:e69–e71, 2005.
117. Borgia SM, Fuller JD, Sarabia A, El Helou P: Cerebral blastomycosis: A case series incorporating voriconazole in the treatment regimen. Med Mycol 44:659–664, 2006.
118. Hirschmann JV: The early history of coccidioidomycosis: 1892–1945. Clin Infect Dis 44:1202–1207, 2007.
119. Dickson EC: Coccidiodomycosis—The preliminary acute infection with fungus coccidiodes. Am Med Assoc 111:1362–1365, 1938.
120. Dickson EC, Gifford MA: Coccidioides infection (coccidioidomycosis) II: The primary type of infection. Arch Intern Med 62:853–871, 1938.
120a. Smith CE, Saito MT, Simons SA: Pattern of 39,500 serologic tests in coccidioidomycosis. J Am Med Assoc 160:546–552, 1956.
120b. Smith CE: Diagnosis of pulmonary coccidioidal infections. Calif Med 75:385–391, 1951.
120c. Smith CE, Saito MT, Beard RR, et al: Serological tests in the diagnosis and prognosis of coccidioidomycosis. Am J Hyg 52:1–21, 1950.
120d. Smith CE: Medical progress: Recent progress in pulmonary mycotic infections. Calif Med 67:179–185, 1947.
120e. Smith CE, Beard RR: Varieties of coccidioidal infection in relation to the epidemiology and control of the diseases. Am J Public Health Nations Health 36:1394–1402, 1946.
120f. Smith CE: Epidemiology of acute coccidioidomycosis with erythema nodosum ("San Joaquin" or "Valley Fever"). Am J Public Health Nations Health 30:600–611, 1940.
121. Forbes WDBA: Coccidioidomycosis: A study of 95 cases of the disseminated type with special reference to the pathogenesis of the disease. Milit Surg 99:653–719, 1946.
122. Crum NF, Lederman ER, Stafford CM, et al: Coccidioidomycosis: A descriptive survey of a reemerging disease. Clinical characteristics and current controversies. Medicine (Baltimore) 83:149–175, 2004.
123. Flynn NM, Hoeprich PD, Kawachi MM, et al: An unusual outbreak of windborne coccidioidomycosis. N Engl J Med 301:358–361, 1979.
124. Werner SB, Pappagianis D, Heindl I, Mickel A: An epidemic of coccidioidomycosis among archeology students in northern California. N Engl J Med 286:507–512, 1972.
125. Petersen LR, Marshall SL, Barton-Dickson C, et al: Coccidioidomycosis among workers at an archeological site, northeastern Utah. Emerg Infect Dis 10:637–642, 2004.
126. Valdivia L, Nix D, Wright M, et al: Coccidioidomycosis as a common cause of community-acquired pneumonia. Emerg Infect Dis 12:958–962, 2006.
127. Sunenshine RH, Anderson S, Erhart L, et al: Public health surveillance for coccidioidomycosis in Arizona. Ann N Y Acad Sci 1111: 96–102, 2007.
128. Ampel NM: The complex immunology of human coccidioidomycosis. Ann N Y Acad Sci 1111:245–258, 2007.
129. Ampel NM: Coccidioidomycosis: a review of recent advances. Clin Chest Med 30:241–251, 2009.
130. Spinello IM, Munoz A, Johnson RH: Pulmonary coccidioidomycosis. Semin Respir Crit Care Med 29:166–173, 2008
131. Smith C, Whiting EG, Baker EE, et al: The use of coccidioidin. Am Rev Tuberc 57:330–360, 1948.
132. Bayer AS: Fungal pneumonias; pulmonary coccidioidal syndromes (Part 1). Primary and progressive primary coccidioidal pneumonias—Diagnostic, therapeutic, and prognostic considerations. Chest 79:575–583, 1981.
133. Bayer AS: Fungal pneumonias: pulmonary coccidioidal syndromes (Part 2). Miliary, nodular, and cavitary pulmonary coccidioidomycosis: Chemotherapeutic and surgical considerations. Chest 79:686–691, 1981.
134. Bergstrom L, Yocum DE, Ampel NM, et al: Increased risk of coccidioidomycosis in patients treated with tumor necrosis factor alpha antagonists. Arthritis Rheum 50:1959–1966, 2004.
135. Mertz LE, Blair JE: Coccidioidomycosis in rheumatology patients: Incidence and potential risk factors. Ann N Y Acad Sci 1111:343–357, 2007.

136. Dweik M, Baethge BA, Duarte AG: Coccidioidomycosis pneumonia in a nonendemic area associated with infliximab. South Med J 100:517–518, 2007.
137. Ampel NM: Coccidioidomycosis in persons infected with HIV-1. Ann N Y Acad Sci 1111:336–342, 2007.
138. Blair JE, Douglas DD, Mulligan DC: Early results of targeted prophylaxis for coccidioidomycosis in patients undergoing orthotopic liver transplantation within an endemic area. Transpl Infect Dis 5:3–8, 2003.
139. Blair JE: Coccidioidomycosis in patients who have undergone transplantation. Ann N Y Acad Sci 1111:365–376, 2007.
140. Blair JE, Kusne S, Carey EJ, Heilman RL: The prevention of recrudescent coccidioidomycosis after solid organ transplantation. Transplantation 83:1182–1187, 2007.
141. Blair JE: Coccidioidal pneumonia, arthritis, and soft-tissue infection after kidney transplantation. Transpl Infect Dis 6:74–76, 2004.
142. Blair JE: State-of-the-art treatment of coccidioidomycosis: Skin and soft-tissue infections. Ann N Y Acad Sci 1111:411–421, 2007.
143. Blair JE: State-of-the-art treatment of coccidioidomycosis skeletal infections. Ann N Y Acad Sci 1111:422–433, 2007.
144. Johnson RH, Einstein HE: Coccidioidal meningitis. Clin Infect Dis 42:103–107, 2006.
145. Bronnimann DA, Adam RD, Galgiani JN, et al: Coccidioidomycosis in the acquired immunodeficiency syndrome. Ann Intern Med 106:372–379, 1987.
146. Fish DG, Ampel NM, Galgiani JN, et al: Coccidioidomycosis during human immunodeficiency virus infection. A review of 77 patients. Medicine (Baltimore) 69:384–391, 1990.
147. Warlick MA, Quan SF, Sobonya RE: Rapid diagnosis of pulmonary coccidioidomycosis. Cytologic v potassium hydroxide preparations. Arch Intern Med 143:723–725, 1983.
148. Wallace JM, Catanzaro A, Moser KM, Harrell JH: Flexible fiberoptic bronchoscopy for diagnosing pulmonary coccidioidomycosis. Am Rev Respir Dis 123:286–290, 1981.
149. Polesky A, Kirsch CM, Snyder LS, et al: Airway coccidioidomycosis—Report of cases and review. Clin Infect Dis 28:1273–1280, 1999.
150. Mahaffey KW, Hippenmeyer CL, Mandel R, Ampel NM: Unrecognized coccidioidomycosis complicating *Pneumocystis carinii* pneumonia in patients infected with the human immunodeficiency virus and treated with corticosteroids. A report of two cases. Arch Intern Med 153:1496–1498, 1993.
151. Sobonya RE, Barbee RA, Wiens J, Trego D: Detection of fungi and other pathogens in immunocompromised patients by bronchoalveolar lavage in an area endemic for coccidioidomycosis. Chest 97:1349–1355, 1990.
152. Sarosi GA, Lawrence JP, Smith DK, et al: Rapid diagnostic evaluation of bronchial washings in patients with suspected coccidioidomycosis. Semin Respir Infect 16:238–241, 2001.
153. DiTomasso JP, Ampel NM, Sobonya RE, Bloom JW: Bronchoscopic diagnosis of pulmonary coccidioidomycosis. Comparison of cytology, culture, and transbronchial biopsy. Diagn Microbiol Infect Dis 18:83–87, 1994.
154. Blair JE, Currier JT: Significance of isolated positive IgM serologic results by enzyme immunoassay for coccidioidomycosis. Mycopathologia 166:77–82, 2008.
155. Smith CE, Saito MT, Beard RR, et al: Serological tests in the diagnosis and prognosis of coccidioidomycosis. Am J Hyg 52:1–21, 1950.
156. Zartarian M, Peterson EM, de la Maza LM: Detection of antibodies to *Coccidioides immitis* by enzyme immunoassay. Am J Clin Pathol 107:148–153, 1997.
157. Levine HB, Restrepon A, Eyck DR, Stevens DA: Spherulin and coccidioidin: Cross-reactions in dermal sensitivity to histoplasmin and paracoccidioidin. Am J Epidemiol 101:512–516, 1975.
158. Galgiani JN, Ampel NM, Blair JE, et al: Coccidioidomycosis. Clin Infect Dis 41:1217–1223, 2005.
159. Galgiani JN, Catanzaro A, Cloud GA, et al: Comparison of oral fluconazole and itraconazole for progressive, nonmeningeal coccidioidomycosis. A randomized, double-blind trial. Mycoses Study Group. Ann Intern Med 133:676–686, 2000.
160. Dewsnup DH, Galgiani JN, Graybill JR, et al: Is it ever safe to stop azole therapy for *Coccidioides immitis* meningitis? Ann Intern Med 124:305–310, 1996.
161. Stevens DA, Shatsky SA: Intrathecal amphotericin in the management of coccidioidal meningitis. Semin Respir Infect 16:263–269, 2001.
162. Tucker RM, Denning DW, Dupont B, Stevens DA: Itraconazole therapy for chronic coccidioidal meningitis. Ann Intern Med 112:108–112, 1990.
163. Catanzaro A, Cloud GA, Stevens DA, et al: Safety, tolerance, and efficacy of posaconazole therapy in patients with nonmeningeal disseminated or chronic pulmonary coccidioidomycosis. Clin Infect Dis 45:562–568, 2007.
164. Anstead GM, Corcoran G, Lewis J, et al: Refractory coccidioidomycosis treated with posaconazole. Clin Infect Dis 40:1770–1776, 2005.
165. Cortez KJ, Walsh TJ, Bennett JE: Successful treatment of coccidioidal meningitis with voriconazole. Clin Infect Dis 36:1619–1622, 2003.
166. Cole GT, Xue JM, Okeke CN, et al: A vaccine against coccidioidomycosis is justified and attainable. Med Mycol 42:189–216, 2004.
167. Restrepo-Moreno A, Greer D: Paracoccidioidomycosis. *In* Disalvo A (ed): Occupational Mycoses. Philadelphia: Williams and Wilkins 1983, pp 43–64.
168. Greer D, Restrepo A: The epidemiology of paracoccidiodomycosis. *In* Al-Doory Y (ed): The Epidemiology of Human Mycotic Diseases. Springfield, IL: Charles C. Thomas, 1975, pp 114–141.
169. Joseph EA, Mare A, Irving WR Jr: Oral South American blastomycosis in the United States of America. Report of a case. Oral Surg Oral Med Oral Pathol 21:732–737, 1966.
170. Robledo MA, Graybill JR, Ahrens J, et al: Host defense against experimental paracoccidioidomycosis. Am Rev Respir Dis 125:563–567, 1982.
171. Londero AT, Ramos CD: Paracoccidioidomycosis. A clinical and mycologic study of forty-one cases observed in Santa Maria, RS, Brazil. Am J Med 52:771–775, 1972.
172. Furtado T: Infection versus disease in South American blastomycosis. Int J Dermatol 14:117–125, 1975.
173. Londero AT, Severo LC: The gamut of progressive pulmonary paracoccidioidomycosis. Mycopathologia 75:65–74, 1981.
174. Funari M, Kavakama J, Shikanai-Yasuda MA, et al: Chronic pulmonary paracoccidioidomycosis (South American blastomycosis): High-resolution CT findings in 41 patients. AJR Am J Roentgenol 173:59–64, 1999.
175. Silva-Vergara ML, Teixeira AC, Curi VG, et al: Paracoccidioidomycosis associated with human immunodeficiency virus infection. Report of 10 cases. Med Mycol 41:259–263, 2003.
176. Restrepo A, Robledo M, Giraldo R, et al: The gamut of paracoccidioidomycosis. Am J Med 61:33–42, 1976.
177. Cuce LC, Wroclawski EL, Sampaio SA: Treatment of paracoccidioidomycosis with ketoconazole. Rev Inst Med Trop Sao Paulo 23:82–85, 1981.
178. de Camargo ZP: Serology of paracoccidioidomycosis. Mycopathologia 165:289–302, 2008.
179. Salina MA, Shikanai-Yasuda MA, Mendes RP, et al: Detection of circulating *Paracoccidioides brasiliensis* antigen in urine of paracoccidioidomycosis patients before and during treatment. J Clin Microbiol 36:1723–1728, 1998.
180. Powell KE, Dahl BA, Weeks RJ, Tosh FE: Airborne *Cryptococcus neoformans*: Particles from pigeon excreta compatible with alveolar deposition. J Infect Dis 125:412–415, 1972.
181. Kidd SE, Hagen F, Tscharke RL, et al: A rare genotype of *Cryptococcus gattii* caused the cryptococcosis outbreak on Vancouver Island (British Columbia, Canada). Proc Natl Acad Sci U S A 101: 17258–17263, 2004.
182. Luberto C, Martinez-Marino B, Taraskiewicz D, et al: Identification of App1 as a regulator of phagocytosis and virulence of *Cryptococcus neoformans*. J Clin Invest 112:1080–1094, 2003.
183. Vecchiarelli A, Pietrella D, Lupo P, et al: The polysaccharide capsule of *Cryptococcus neoformans* interferes with human dendritic cell maturation and activation. J Leukoc Biol 74:370–378, 2003.
184. Liu OW, Chun CD, Chow ED, et al: Systematic genetic analysis of virulence in the human fungal pathogen *Cryptococcus neoformans*. Cell 135:174–188, 2008.

185. Chuck SL, Sande MA: Infections with *Cryptococcus neoformans* in the acquired immunodeficiency syndrome. N Engl J Med 321:794–799, 1989.
186. Ma LL, Spurrell JC, Wang JF, et al: CD8 T cell-mediated killing of *Cryptococcus neoformans* requires granulysin and is dependent on CD4 T cells and IL-15. J Immunol 169:5787–5795, 2002.
187. Hage CA, Wood KL, Winer-Muram HT, et al: Pulmonary cryptococcosis after initiation of anti-tumor necrosis factor-alpha therapy. Chest 124:2395–2397, 2003.
188. Herring AC, Lee J, McDonald RA, et al: Induction of interleukin-12 and gamma interferon requires tumor necrosis factor alpha for protective T1-cell-mediated immunity to pulmonary *Cryptococcus neoformans* infection. Infect Immun 70:2959–2964, 2002.
189. Salyer WR, Salyer DC, Baker RD: Primary complex of *Cryptococcus* and pulmonary lymph nodes. J Infect Dis 130:74–77, 1974.
190. Campbell GD: Primary pulmonary cryptococcosis. Am Rev Respir Dis 94:236–243, 1966.
191. Lewis JL, Rabinovich S: The wide spectrum of cryptococcal infections. Am J Med 53:315–322, 1972.
192. Khoury MB, Godwin JD, Ravin CE, et al: Thoracic cryptococcosis: immunologic competence and radiologic appearance. AJR Am J Roentgenol 142:893–896, 1984.
193. Singh N, Husain S: Aspergillus infections after lung transplantation: Clinical differences in type of transplant and implications for management. J Heart Lung Transplant 22:258–266, 2003.
194. Jarvis JN, Harrison TS: HIV-associated cryptococcal meningitis. AIDS 21:2119–2129, 2007.
195. Singh N, Dromer F, Perfect JR, Lortholary O: Cryptococcosis in solid organ transplant recipients: Current state of the science. Clin Infect Dis 47:1321–1327, 2008.
196. Sarosi GA, Parker JD, Doto IL, Tosh FE: Amphotericin B in cryptococcal meningitis. Long-term results of treatment. Ann Intern Med 71:1079–1087, 1969.
197. Mangham D, Gerding DN, Peterson LR, Sarosi GA: Fungal meningitis manifesting as hydrocephalus. Arch Intern Med 143:728–731, 1983.
198. Diamond RD, Bennett JE: Prognostic factors in cryptococcal meningitis. A study in 111 cases. Ann Intern Med 80:176–181, 1974.
199. Bloomfield N, Gordon MA, Elmendorf DF Jr: Detection of *Cryptococcus neoformans* antigen in body fluids by latex particle agglutination. Proc Soc Exp Biol Med 114:64–67, 1963.
200. Bennett JE, Bailey JW: Control for rheumatoid factor in the latex test for cryptococcosis. Am J Clin Pathol 56:360–365, 1971.
201. Sarosi GA, Silberfarb PM, Tosh FE: Cutaneous cryptococcosis. A sentinel of disseminated disease. Arch Dermatol 104:1–3, 1971.
202. Saag MS, Graybill RJ, Larsen RA, et al: Practice guidelines for the management of cryptococcal disease. Infectious Diseases Society of America. Clin Infect Dis 30:710–718, 2000.
203. Sugar AM, Saunders C: Oral fluconazole as suppressive therapy of disseminated cryptococcosis in patients with acquired immunodeficiency syndrome. Am J Med 85:481–489, 1988.
204. Bicanic T, Wood R, Meintjes G, et al: High-dose amphotericin B with flucytosine for the treatment of cryptococcal meningitis in HIV-infected patients: A randomized trial. Clin Infect Dis 47:123–130, 2008.
205. Lortholary O, Fontanet A, Memain N, et al: Incidence and risk factors of immune reconstitution inflammatory syndrome complicating HIV-associated cryptococcosis in France. AIDS 19:1043–1049, 2005.
206. Al-Doory Y: The mycology of the aspergilli. *In* Al-Doory Y, Wagner G (eds): Aspergillosis. Springfield, IL: Charles C. Thomas, 1985, pp 7–24.
207. Sole A, Morant P, Salavert M, et al: Aspergillus infections in lung transplant recipients: Risk factors and outcome. Clin Microbiol Infect 11:359–365, 2005.
208. Singh N, Husain S: Aspergillus infections after lung transplantation: Clinical differences in type of transplant and implications for management. J Heart Lung Transplant 22:258–266, 2003.
209. Hinson KF, Moon AJ, Plummer NS: Broncho-pulmonary aspergillosis: A review and a report of eight new cases. Thorax 7:317–333, 1952.
210. Henderson AH, English MP, Vecht RJ: Pulmonary aspergillosis. A survey of its occurrence in patients with chronic lung disease and a discussion of the significance of diagnostic tests. Thorax 23:513–518, 1968.
211. Geller DE, Kaplowitz H, Light MJ, Colin AA: Allergic bronchopulmonary aspergillosis in cystic fibrosis: Reported prevalence, regional distribution, and patient characteristics. Scientific Advisory Group, Investigators, and Coordinators of the Epidemiologic Study of Cystic Fibrosis. Chest 116:639–646, 1999.
212. Stevens DA, Moss RB, Kurup VP, et al: Allergic bronchopulmonary aspergillosis in cystic fibrosis—State of the art: Cystic Fibrosis Foundation Consensus Conference. Clin Infect Dis 37(Suppl 3):S225–S264, 2003.
213. Chauhan B, Knutsen A, Hutcheson PS, et al: T cell subsets, epitope mapping, and HLA-restriction in patients with allergic bronchopulmonary aspergillosis. J Clin Invest 97:2324–2331, 1996.
214. Radin RC, Greenberger PA, Patterson R, Ghory A: Mould counts and exacerbations of allergic bronchopulmonary aspergillosis. Clin Allergy 13:271–275, 1983.
215. Rosenberg M, Patterson R, Mintzer R, et al: Clinical and immunologic criteria for the diagnosis of allergic bronchopulmonary aspergillosis. Ann Intern Med 86:405–414, 1977.
216. Carvalho A, Pasqualotto AC, Pitzurra L, et al: Polymorphisms in Toll-like receptor genes and susceptibility to pulmonary aspergillosis. J Infect Dis 197:618–621, 2008.
217. Chauhan B, Knutsen A, Hutcheson PS, et al: T cell subsets, epitope mapping, and HLA-restriction in patients with allergic bronchopulmonary aspergillosis. J Clin Invest 97:2324–2331, 1996.
218. Buckingham SJ, Hansell DM: Aspergillus in the lung: Diverse and coincident forms. Eur Radiol 13:1786–1800, 2003.
219. Ward S, Heyneman L, Lee MJ, et al: Accuracy of CT in the diagnosis of allergic bronchopulmonary aspergillosis in asthmatic patients. AJR Am J Roentgenol 173:937–942, 1999.
220. Greenberger PA: Allergic bronchopulmonary aspergillosis. J Allergy Clin Immunol 110:685–692, 2002.
221. Stevens DA, Schwartz HJ, Lee JY, et al: A randomized trial of itraconazole in allergic bronchopulmonary aspergillosis. N Engl J Med 342:756–762, 2000.
222. Zirbes JM, Milla CE: Steroid-sparing effect of omalizumab for allergic bronchopulmonary aspergillosis and cystic fibrosis. Pediatr Pulmonol 43:607–610, 2008.
223. Aspergilloma and residual tuberculous cavities—The results of a resurvey. Tubercle 51:227–245, 1970.
224. Regnard JF, Icard P, Nicolosi M, et al: Aspergilloma: A series of 89 surgical cases. Ann Thorac Surg 69:898–903, 2000.
225. Kato A, Kudo S, Matsumoto K, et al: Bronchial artery embolization for hemoptysis due to benign diseases: Immediate and long-term results. Cardiovasc Intervent Radiol 23:351–357, 2000.
226. Munk PL, Vellet AD, Rankin RN, et al: Intracavitary aspergilloma: Transthoracic percutaneous injection of amphotericin gelatin solution. Radiology 188:821–823, 1993.
227. Denning DW: Chronic forms of pulmonary aspergillosis. Clin Microbiol Infect 7(Suppl 2):25–31, 2001.
228. Camuset J, Nunes H, Dombret MC, et al: Treatment of chronic pulmonary aspergillosis by voriconazole in nonimmunocompromised patients. Chest 131:1435–1441, 2007.
229. Carvalho A, Pasqualotto AC, Pitzurra L, et al: Polymorphisms in Toll-like receptor genes and susceptibility to pulmonary aspergillosis. J Infect Dis 197:618–621, 2008.
230. Vaid M, Kaur S, Sambatakou H, et al: Distinct alleles of mannose-binding lectin (MBL) and surfactant proteins A (SP-A) in patients with chronic cavitary pulmonary aspergillosis and allergic bronchopulmonary aspergillosis. Clin Chem Lab Med 45:183–186, 2007.
231. Saraceno JL, Phelps DT, Ferro TJ, et al: Chronic necrotizing pulmonary aspergillosis: Approach to management. Chest 112:541–548, 1997.
232. Nivoix Y, Velten M, Letscher-Bru V, et al: Factors associated with overall and attributable mortality in invasive aspergillosis. Clin Infect Dis 47:1176–1184, 2008.
233. Mylonakis E, Barlam TF, Flanigan T, Rich JD: Pulmonary aspergillosis and invasive disease in AIDS: Review of 342 cases. Chest 114:251–262, 1998.

234. Tsiodras S, Samonis G, Boumpas DT, Kontoyiannis DP: Fungal infections complicating tumor necrosis factor alpha blockade therapy. Mayo Clin Proc 83:181–194, 2008.
235. Montoya JG, Chaparro SV, Celis D, et al: Invasive aspergillosis in the setting of cardiac transplantation. Clin Infect Dis 37(Suppl 3):S281–S292, 2003.
236. Schaffner A, Douglas H, Braude A: Selective protection against conidia by mononuclear and against mycelia by polymorphonuclear phagocytes in resistance to *Aspergillus*. Observations on these two lines of defense in vivo and in vitro with human and mouse phagocytes. J Clin Invest 69:617–631, 1982.
237. Albelda SM, Talbot GH, Gerson SL, et al: Pulmonary cavitation and massive hemoptysis in invasive pulmonary aspergillosis. Influence of bone marrow recovery in patients with acute leukemia. Am Rev Respir Dis 131:115–120, 1985.
238. Greene RE, Schlamm HT, Oestmann JW, et al: Imaging findings in acute invasive pulmonary aspergillosis: Clinical significance of the halo sign. Clin Infect Dis 44:373–379, 2007.
239. de Pauw B, Walsh TJ, Donnelly JP, et al: Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. Clin Infect Dis 46:1813–1821, 2008.
240. Levy H, Horak DA, Tegtmeier BR, et al: The value of bronchoalveolar lavage and bronchial washings in the diagnosis of invasive pulmonary aspergillosis. Respir Med 86:243–248, 1992.
241. Maertens J, Verhaegen J, Lagrou K, et al: Screening for circulating galactomannan as a noninvasive diagnostic tool for invasive aspergillosis in prolonged neutropenic patients and stem cell transplantation recipients: A prospective validation. Blood 97: 1604–1610, 2001.
242. Walsh TJ, Shoham S, Petraitiene R, et al: Detection of galactomannan antigenemia in patients receiving piperacillin-tazobactam and correlations between in vitro, in vivo, and clinical properties of the drug-antigen interaction. J Clin Microbiol 42:4744–4748, 2004.
243. Pfeiffer CD, Fine JP, Safdar N: Diagnosis of invasive aspergillosis using a galactomannan assay: A meta-analysis. Clin Infect Dis 42:1417–1427, 2006.
244. Clancy CJ, Jaber RA, Leather HL, et al: Bronchoalveolar lavage galactomannan in diagnosis of invasive pulmonary aspergillosis among solid-organ transplant recipients. J Clin Microbiol 45:1759–1765, 2007.
245. Meersseman W, Lagrou K, Maertens J, et al: Galactomannan in bronchoalveolar lavage fluid: A tool for diagnosing aspergillosis in intensive care unit patients. Am J Respir Crit Care Med 177:27–34, 2008.
246. Herbrecht R, Denning DW, Patterson TF, et al: Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. N Engl J Med 347:408–415, 2002.
247. Walsh TJ, Anaissie EJ, Denning DW, et alF: Treatment of aspergillosis: Clinical practice guidelines of the Infectious Diseases Society of America. Clin Infect Dis 46:327–360, 2008.
248. Segal BH, Herbrecht R, Stevens DA, et al: Defining responses to therapy and study outcomes in clinical trials of invasive fungal diseases: Mycoses Study Group and European Organization for Research and Treatment of Cancer consensus criteria. Clin Infect Dis 47:674–683, 2008.
249. Cornely OA, Maertens J, Bresnik M, et al: Liposomal amphotericin B as initial therapy for invasive mold infection: A randomized trial comparing a high-loading dose regimen with standard dosing (AmBiLoad trial). Clin Infect Dis 44:1289–1297, 2007.
250. Caira PL, Candoni CA, Martino OM, et al: Invasive aspergillosis in patients with acute myeloid leukemia: SEIFEM-2008 registry study. Haematologica 2009, Epub ahead of print.
251. Meyer RD, Armstrong D: Mucormycosis-changing status. CRC Crit Rev Clin Lab Sci 4:421–451, 1973.
252. Meyer RD, Rosen P, Armstrong D: Phycomycosis complicating leukemia and lymphoma. Ann Intern Med 77:871–879, 1972.
253. Gartenberg G, Bottone EJ, Keusch GT, Weitzman I: Hospital-acquired mucormycosis (*Rhizopus rhizopodiformis*) of skin and subcutaneous tissue: Epidemiology, mycology and treatment. N Engl J Med 299:1115–1118, 1978.
254. Kontoyiannis DP: Decrease in the number of reported cases of zygomycosis among patients with diabetes mellitus: A hypothesis. Clin Infect Dis 44:1089–1090, 2007.
255. Kauffman CA, Malani AN: Zygomycosis: An emerging fungal infection with new options for management. Curr Infect Dis Rep 9:435-–440, 2007.
256. Roden MM, Zaoutis TE, Buchanan WL, et al: Epidemiology and outcome of zygomycosis: A review of 929 reported cases. Clin Infect Dis 41:634–653, 2005.
257. Chamilos G, Marom EM, Lewis RE, et al: Predictors of pulmonary zygomycosis versus invasive pulmonary aspergillosis in patients with cancer. Clin Infect Dis 41:60–66, 2005.
258. Kofteridis DP, Karabekios S, Panagiotides JG, et al: Successful treatment of rhinocerebral mucormycosis with liposomal amphotericin B and surgery in two diabetic patients with renal dysfunction. J Chemother 15:282–286, 2003.
259. Voitl P, Scheibenpflug C, Weber T, et al: Combined antifungal treatment of visceral mucormycosis with caspofungin and liposomal amphotericin B. Eur J Clin Microbiol Infect Dis 21:632–634, 2002.
260. van Burik JA, Hare RS, Solomon HF, et al: Posaconazole is effective as salvage therapy in zygomycosis: A retrospective summary of 91 cases. Clin Infect Dis 42:e61–e65, 2006.
261. Murray HW, Hillman JK, Rubin BY, et al: Patients at risk for AIDS-related opportunistic infections. Clinical manifestations and impaired gamma interferon production. N Engl J Med 313:1504–1510, 1985.
262. Tavitian A, Raufman JP, Rosenthal LE: Oral candidiasis as a marker for esophageal candidiasis in the acquired immunodeficiency syndrome. Ann Intern Med 104:54–55, 1986.
263. Dupont B, Drouhet E: Cutaneous, ocular, and osteoarticular candidiasis in heroin addicts: New clinical and therapeutic aspects in 38 patients. J Infect Dis 152:577–591, 1985.
264. Williams DM, Krick JA, Remington JS: Pulmonary infection in the compromised host: Part I. Am Rev Respir Dis 114:359–394, 1976.
265. Binder RE, Faling LJ, Pugatch RD, et al: Chronic necrotizing pulmonary aspergillosis: A discrete clinical entity. Medicine (Baltimore) 61:109–124, 1982.
266. Serodiagnosis of *Candida* infections. Lancet 2:1373–1374, 1986.
267. Mora-Duarte J, Betts R, Rotstein C, et al: Comparison of caspofungin and amphotericin B for invasive candidiasis. N Engl J Med 347:2020–2029, 2002.
268. Arnett JC Jr, Hatch HB Jr: Pulmonary allescheriasis. Report of a case and review of the literature. Arch Intern Med 135:1250–1253, 1975.
269. Winston DJ, Jordan MC, Rhodes J: *Allescheria* boydii infections in the immunosuppressed host. Am J Med 63:830–835, 1977.
270. Jung JY, Salas R, Almond CH, et al: The role of surgery in the management of pulmonary monosporosis. A collective review. J Thorac Cardiovasc Surg 73:139–144, 1977.
271. Lutwick LI, Galgiani JN, Johnson RH, Stevens DA: Visceral fungal infections due to *Petriellidium boydii (Allescheria boydii)*. In vitro drug sensitivity studies. Am J Med 61:632–640, 1976.
272. Pfizer: Package insert VFEND (Voriconazole). New York: Pfizer, Inc., 2006, pp 1–42.
273. Nucci M, Anaissie E: Fusarium infections in immunocompromised patients. Clin Microbiol Rev 20:695–704, 2007.
274. Lynch PJ, Voorhees JJ, Harrell ER: Systemic sporotrichosis. Ann Intern Med 73:23–30, 1970.
275 Parker JD, Sarosi GA, Tosh FE: Treatment of extracutaneous sporotrichosis. Arch Intern Med 125:858–863, 1970.
276. Dismukes WE, Stamm AM, Graybill JR, et al: Treatment of systemic mycoses with ketoconazole: Emphasis on toxicity and clinical response in 52 patients. National Institute of Allergy and Infectious Diseases collaborative antifungal study. Ann Intern Med 98:13–20, 1983.
277. Restrepo A, Robledo J, Gomez I, et al: Itraconazole therapy in lymphangitic and cutaneous sporotrichosis. Arch Dermatol 122:413–417, 1986.
278. Rohatgi PK: Pulmonary sporotrichosis. South Med J 73:1611–1617, 1980.
279. Blazar BR, Hurd DD, Snover DC, et al: Invasive *Fusarium* infections in bone marrow transplant recipients. Am J Med 77:645–651, 1984.

CHAPTER 37

PARASITIC LUNG INFECTIONS

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INTRODUCTION

PROTOZOAL INFECTIONS
Amebiasis
Malaria
Toxoplasmosis

HELMINTHS
Intestinal Nematode Infections
Tissue-Dwelling Nematodes

INTRODUCTION

Parasites are eukaryotic organisms that require or prefer to live within another organism or host. They are divided into two groups: protozoa, or single-celled organisms, and multicellular helminths. Whereas protozoa are often intracellular in humans, helminths are usually extracellular (the exception is *Trichinella*, which encysts within muscle cells).

Many parasites have complex life cycles, with multiple stages, often requiring multiple host species to complete their life cycle. These host species could be another mammal (e.g., pigs and horses for *Trichinella*), an invertebrate host (snails for *Schistosoma* spp.), or an insect vector such as *Anopheline* mosquitoes for malaria. For most parasitic infections, humans are the definitive hosts in which the adult or sexual stage of the parasite, if there is one, resides. For other parasites, humans are the intermediate hosts or an incidental dead-end host and other species are the definitive host (e.g., *Dirofilaria*, *Toxocara*, *Toxoplasma*).

Infection with these organisms is acquired in a number of different ways: some are ingested and are spread person to person or through fecal-oral or fecal-soil-oral transmission (e.g., *Ascaris*). Others require insect vectors for transmission, passing through intermediate species where they complete part of their life cycles. Some organisms can enter from a contaminated environment by penetrating through the skin (e.g., *Strongyloides*, *Schistosoma*).

Except for *Paragonimus*, the lung fluke, few parasites specifically go to the lungs as their final target organ. The majority that affect the lungs migrate through the lung en route to another organ (e.g., *Strongyloides*, *Ascaris*) or infect the lungs as a secondary site (e.g., amebiasis, toxoplasmosis, echinococcosis). In a few infections, lung pathology is primarily due to a systemic cytokine-mediated inflammatory response (e.g., severe malaria) or to a hypersensitivity response to parasite antigen (e.g., tropical pulmonary eosinophilia [TPE] in filarial infection).

Although some of these organisms have worldwide distribution (e.g., *Ascaris*, *Toxoplasma*), most have narrower geographic distribution. Often, endemic areas are in developing countries with limited resources and access to clean water and sanitation. In industrialized countries, these infections are most commonly encountered in immigrants or returning travelers.

Control programs require resources, a well-developed healthcare infrastructure enabling diagnosis and treatment with appropriate medication, and vector control programs with safe insecticides and molluscides, all of which are difficult in resource poor countries.

Once thought exotic, parasitic diseases are becoming increasingly recognized in industrialized countries because of returning travelers, immigration, and mass movement of people. An awareness of the clinical manifestations and management of these diseases is therefore important for both primary care physicians and specialists. This chapter details the most frequently encountered parasites causing pulmonary pathology. A summary is shown in Table 37-1.

PROTOZOAL INFECTIONS

Amebiasis

Entamoeba histolytica, the causative organism of invasive amebiasis, is a ubiquitous protozoan. The infection usually manifests clinically as dysentery or liver abscess. It is estimated that 40 to 50 million cases of amebiasis

TABLE 37-1. Characteristics of the Most Frequently Encountered Parasites Causing Pulmonary Pathology

Parasite and Disease	Principal Clinical Features of Pulmonary Involvement	Geographic Distribution	Radiologic Appearance	Diagnostic Approach	Treatment
PROTOZOA					
Malaria	ARDS	Widely in tropics	Interstitial infiltrates	Blood film	Antimalarial therapy (see text)
Toxoplasmosis	Interstitial pneumonia	In association with 1st-degree immunosuppressive illness and feline exposure	Interstitial infiltrates	Cytology of BAL fluid Serology	Pyrimethamine-sulfadiazine
Amebiasis	Necrotizing abscess, frequently in contiguity with liver	Widely in tropics	Local abscess	Percutaneous aspiration	Metronidazole, tinidazole
NEMATODES					
Ascaris	Loeffler's syndrome	Widely in tropics	Transient infiltrates	Expectant, stool parasitology	Albendazole Mebendazole
Hookworm	Loeffler's syndrome	Widely in tropics	Transient infiltrates	Expectant, stool parasitology	Albendazole Mebendazole
Strongyloides	Loeffler's syndrome Chronic cough Pneumonia in hyperinfecion	Widely in tropical and subtropical areas	Variable	Stool parasitology Serology	Ivermectin
Lymphatic filariasis	Tropical pulmonary eosinophilia	Tropics, particularly south Asia	Interstitial infiltrates	Circulating antigen test, serology, BAL	DEC Doxycycline
Dirofilariasis	Pulmonary nodule	Widely	Nodule	Exclude other causes of lesion, usually by excision	Nil
Trichinosis	Respiratory distress	Zoonosis	Variable	Muscle biopsy	Albendazole
Visceral larva migrans	Eosinophilic pneumonia	Worldwide	Interstitial infiltrates	Serology	Albendazole
CESTODES					
Echinococcosis	Intrapulmonary fluid-filled cyst	Worldwide (particularly in sheep-raising areas)	Intrapulmonary fluid-filled cyst	Serology Surgical resection	Surgical resection Albendazole
TREMATODES					
Paragonamiasis	Cavitating lung lesion	Southeast Asia, South America, Africa	Cavitating lung lesion	Eggs in sputum or stool, serology	Praziquantel Triclabendazole
Schistosomiasis	Pulmonary hypertension	Asia, South America, Africa	Pulmonary hypertension	Eggs in stool, serology	Praziquantel

ARDS, acute respiratory distress syndrome; BAL, bronchoalveolar lavage; DEC, diethylcarbamazine.

occur each year with 40,000 to 100,000 deaths.[1-3] *Entamoebae* infect people of both genders and all ages. It is more common in developing countries with limited access to adequate sanitation. In these countries, from 1% to 21% of people harbor *E. histolytica*.[4] In the United States, most cases occur among immigrants from endemic areas, travelers, and people living along the Mexican border.

Other risk factors for infection include institutionalization, daycare, mental illness, men who have sex with men, and malnutrition. Chronic alcoholism increases the risk of liver disease, and atrial septal defects may increase the risk of pulmonary disease.[5] Although a study from Mexico found an association with human leukocyte antigen (HLA)-DR 3[6] and susceptibility to invasive disease, another study of amebic liver abscess in Vietnam, found no household clustering.[7] Pleuropulmonary amebiasis is a significant complication of amebic liver abscess and, rarely, of hematogenous spread of the infection.

Transmission

The infective form of *E. histolytica* is the cyst, which is 10 to 16 μm in diameter and has four nuclei when mature. Excystation occurs in the small intestine, where the organisms go through cytoplasmic and nuclear

division, resulting in eight motile uninucleated trophozoites (20–40 μm).[2] The trophozoites then migrate into the large intestine, where they can divide by binary fission into either cysts or trophozoites. Both cysts and trophozoites can be passed into the stool. Cysts passed in the fecal stream are responsible for transmission because their protective wall enables them to survive for days to weeks in the environment. Up to 15 million cysts may be excreted daily by individuals with asymptomatic infection. Trophozoites cannot survive outside of the body's environment.

Demonstration of significant molecular differences between morphologically identical but pathogenic and nonpathogenic strains has resulted in the reclassification of the species into two separate species, the nonpathogenic known as *E. dispar* and the pathogenic as *E. histolytica*.[4] These can also be distinguished on the basis of antigenic differences and can be differentiated by both a fecal antigen test and a polymerase chain reaction (PCR) test.[8] It is estimated that up to 90% of organisms in some areas are the nonpathogenic *E. dispar* species.[9] A new noninvasive species, *E. moshkovskii* has been identified in humans.[10,11]

Transmission usually occurs by a fecal-oral route, especially with contaminated water supplies. It can also occur with fecal exposure through sexual contact, especially among men who have sex with men.[12] In this case, the trophozoites can also be infective. However, many homosexual men previously thought to be infected with *E. histolytica* are actually colonized with *E. dispar*.[4,13,14] Other means of transmission include cockroaches. A study of two species of cockroaches outside a school in Taiwan found *E. histolytica* and *E. dispar* cysts on the cuticles and in the intestinal tract in up to 25% of the roaches.[15]

With interruptions in clean water and sanitation, outbreaks can occur. In Tbilisi, Georgia, invasive amebiasis was rare until July 1998 when a breakdown in water treatment occurred. Between then and September, 177 cases of amebiasis were reported, 52 of which were liver abscesses. Based on serology, from 84,000 to 225,000 people may have been affected.[16]

Pathogenesis

E. histolytica trophozoites adhere to mucosa via the galactose and *N*-acetyl-D-galactosamine (Gal/GalNAc)–specific lectin.[5,11] The virulence of *E. histolytica* derives from the parasite's ability to kill and phagocytose host cells.[17] Amebae kill cells by triggering apoptosis. In the intestine, the macroscopic appearance of lesions can resemble inflammatory bowel disease. A wide range of histologic findings has been described. There may be multiple discrete ulcers, areas of mucosal thickening separated by normal colon, diffusely inflamed mucosa, necrosis, and perforation.[5] Unlike other protozoa, tissue invasion is not an obligatory part of the life cycle. In fact, it is a dead end that cannot lead to infection of a new host.

Trophozoites migrate from the intestine to the liver via the portal circulation. When infection becomes established in the liver, it results in areas of hepatic necrosis through obstruction of portal vessels.[18] The average interval between infection and onset of liver abscess is 5 months.[19] Survival within the liver requires substantial changes in the basic aspects of amebic cell metabolism, a process that may involve regulation of heat shock proteins.[19]

A previous amebic liver abscess does not necessarily confer immunity to subsequent infections. Residents in a highly endemic area in Vietnam who had been treated for a liver abscess were actually more likely to get a second amebic infection. Ameba-specific antilectin antibodies do form after invasive disease. Protective immunity in animals can be correlated with the development of an antibody response to a different domain of the same antigen, whereas exacerbation of disease can be linked to the development of antibodies to another domain of the same antigen. Individuals who are colonized with *E. histolytica* but are resistant to invasive disease have a high prevalence of antibodies to the protective epitopes.[20]

Clinical Manifestations

The clinical manifestations of *E. histolytica* infection are protean. Only about 10% of people infected with *E. histolytica* develop disease; others may spontaneously clear asymptomatic infection within a year.[21–23] Intestinal disease can manifest in several different ways: from acute or chronic diarrhea of varied severity to bloody diarrhea (dysentery) and fulminant colitis. Whereas fever rarely occurs with intestinal disease, it is present in most cases of extraintestinal (invasive) disease.[16]

The most common site of extraintestinal infection with *E. histolytica* is the liver, which occurs in 3% to 9% of cases of amebiasis. The most significant complication of hepatic abscess is rupture (in 2%–7%). Abscesses characteristically rupture upward through the diaphragm into the pleural space or the lung parenchyma. An abscess located in the left lobe may rupture into the pericardium, leading to cardiac tamponade with a mortality of 60%. Intraperitoneal rupture can also occur.[18]

Pleuropulmonary Disease

Lung disease occurs in 2% to 7% of those with invasive amebiasis. It is the second most common site of extraintestinal infection after the liver.[5] Owing to the male predominance in amebic liver disease, male gender is associated with lung disease (67% in a series of 501 cases from Mexico).[24] Because most amebic liver abscesses are right-sided, the lower and middle lobes of the right lung are the most affected, but it can affect the left lower lobe or lingula. Right-sided lesions are found in 86% of the cases, left-sided in 13.5%, and bilateral in 1.7%.[5]

Although rare, amebic lung disease can result from inhalation or aspiration.[25] About 14% of lung involvement arises from hematogenous spread from the intestines or liver, but as noted, pulmonary disease most commonly develops by direct extension of a liver abscess through the diaphragm, followed by rupture, either into the pleural space (leading to pleurisy, effusion, or

empyema) or into the lung with development of pulmonary consolidation, lung abscess, or hepatobronchial fistula.[26] Up to 40% of patients with liver abscess develop pulmonary complications. The most common is reactive pleuritis secondary to a contiguous hepatic abscess. These patients may complain of right upper quadrant pain with pleuritic chest pain and may have a pleural rub. Of note, they frequently have normal liver enzymes. The fluid in the pleural space is exudative and sterile. If the abscess extends into the pleural cavity, an amebic empyema can form. Onset of liver abscess can be insidious or acute. It is typically characterized by fever, right upper quadrant and chest pain, and a dry cough. Rupture into the pleural cavity may result in abrupt exacerbation of pain, with rapidly progressive respiratory distress, and shock.[24]

Commonly, the initial pleural irritation of the abscess from below the diaphragm results in pleural scarring, thus preventing extension of the abscess into the pleural space.[27] In this instance, the abscess can extend directly into the lung parenchyma, causing pulmonary consolidation. If invasion into a bronchus occurs, expectoration of blood-stained sputum containing the characteristic anchovy paste–like pus from the amebic abscess may be observed. In a series of more than 2000 patients with amebic liver abscess in South Africa, 146 had thoracic amebiasis; in this series, 47% had hepatobronchial fistula, 29% had pleural effusion and empyema, 14% had lung abscess, and 10% had pulmonary consolidation.[28]

Findings on physical examination in amebic lung disease typically include hepatic enlargement and tenderness, dullness to percussion at the right base with decreased or absent breath sounds, and a pleural rub with occasional crepitation. If the lung disease is chronic, emaciation and clubbing can sometimes be found.

In a series of 75 patients with amebic liver abscess, radiographic abnormalities on chest radiograph were noted in 57% of patients. Presenting symptoms in this group included cough in 16% and chest pain in 19%.[18] Computed tomography (CT) will show the pulmonary lesions and pleural fluid, and loculations. Magnetic resonance imaging (MRI), which is useful in detecting cerebral lesions, is less helpful for identifying lung lesions.[5]

The mortality among patients with amebic lung disease has been reported to range from 5% to 16%.[24,28] Mortality is increased if not diagnosed promptly, which occurs especially in nonendemic areas. Untreated, the mortality of invasive amebiasis[4] and amebic liver abscesses is over 80%.[18]

Diagnosis

Parasitologic examination of stools is frequently negative for the organism (<60%[8]), but antigen tests and PCR diagnosis are more sensitive (>95% and >70%, respectively[8]). A Papanicolaou stain of sputum or bronchoalveolar lavage (BAL) fluid can identify amebas, which appear as 20- to 30-µm oval, cyanophilic erythrophagocytic organisms.[29] In pilot studies of patients with liver abscess, an antigen test demonstrated high sensitivity.[30] Serology is a reliable way of diagnosing invasive amebiasis, especially in patients with extraintestinal disease.[8] Patients infected with *E. histolytica* generally test positive for antiamebic antibodies, whereas those colonized with *E. dispar* do not. The sensitivity of the antibody tests for *E. histolytica* has been reported as 95% for patients with extraintestinal amebiasis, 70% for those with active intestinal infection, and 10% for asymptomatic cyst passers. The specificity is greater than 95%.[31] However, the utility of serology as a diagnostic tool in highly endemic areas is limited because individuals may remain seropositive for years after an infection has been cleared. The prevalence of seropositivity may exceed 25% in some areas. Enzyme assay–based stool antigen detection kits that utilize monoclonal or polyclonal antibodies to identify *E. histolytica* and to differentiate it from *E. dispar* are commercially available.[3,7] PCR techniques are more frequently applied to the diagnosis of amebiasis and are more sensitive and specific than antibody tests.[32] They are of similar sensitivity to antigen-based diagnostic tests.[8]

Hematologic and biochemistry analyses are not usually helpful. Often, in invasive amebiasis, a leukocytosis notably without eosinophilia is observed. Liver function tests with the exception of alkaline phosphatase are often normal.

Radiologic investigation shows elevation of the right hemidiaphragm and hepatomegaly, with pleural effusion in 63% of patients with liver abscess (Fig. 37-1). Basal pulmonary opacities and pleural thickening are often seen. Amebic empyemas rarely are loculated or septated. Ultrasound, CT, and MRI are equally effective at diagnosing amebic liver abscesses, although none is specific. On ultrasound, an amebic abscess appears as a homogenous hypoechoic round or oval lesion.[33] Aspiration of the fluid often reveals odorless pink, red, yellow, or brown "anchovy paste" fluid that may contain trophozoites but is sterile on bacterial culture.[5] It is not unusual for radiographic disease to worsen for a 1- to 2-week period after the start of therapy.[27]

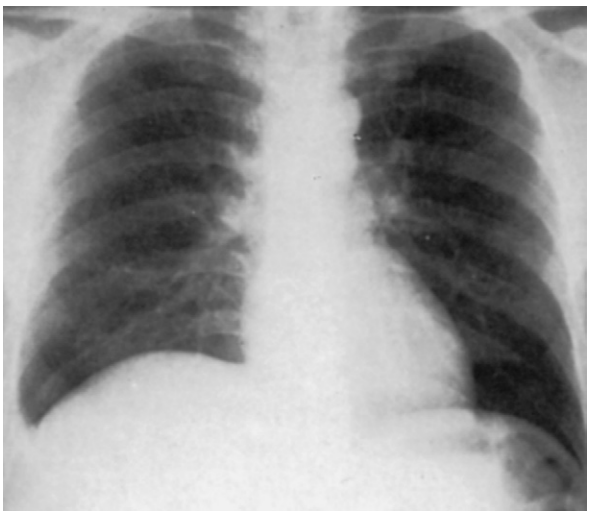

FIGURE 37-1 ■ Chest roentgenogram of a 39-year-old Chinese man with a documented amebic liver abscess shows elevated right hemidiaphragm and a small right pleural effusion.

Treatment

Invasive disease should be treated first with a tissue amebicide, such as metronidazole or tinidazole, followed by a luminal agent to eradicate cysts that are nonsusceptible to these drugs. Metronidazole is given at 500 to 750 mg three times a day orally or intravenously for 10 days. After this, a luminal agent such as paromomycin is given at 25 to 35 mg/kg/day divided in three doses for 7 days or diloxanide furoate, which can be obtained from the Centers for Disease Control and Prevention (CDC) Parasitic Disease Drug Service, is administered at a dose of 500 mg three times daily for 10 days.[10] Noninvasive disease does not require the tissue amebicide.[2] In one small trial, paromomycin was more effective than diloxanide at clearing asymptomatic *E. histolytica* carriage (85% vs. 51%).[2]

Although treatment failures occur and drug resistance can be induced in vitro, resistance has not been documented clinically, but it may be emerging.[34,35] A promising new drug class being investigated is the alkylphosphocholines. One member, miltefosine, has in vivo activity against other protozoa, such as *Leishmania*, and in vitro activity against *Entamoeba*.[34,36] Nitazoxanide and its metabolite tizoxanide have also been shown to be more active than metronidazole against *Entamoeba*. They may also have activity against less susceptible strains.[37] In a group of Mexican children, *E. histolytica/dispar* was found in 10% of children surveyed. After a single course of nitazoxanide, 96% were cured, and this increased to 100% after a second course.[38]

Surgical or noninvasive drainage of amebic abscesses should be reserved for those who have not responded to appropriate medical therapy or for those with abscesses that are at risk of rupture.[10,24] Empyemas should be drained with chest tubes to prevent superinfection and a need for decortication.[24]

Prevention and Control

Prevention of amebiasis depends on improved sanitation, clean water, and safe food in countries where it is prevalent. Efforts to stop transmission include early detection and treatment of infection and disease, health education, and handwashing. *Entamoeba* cysts are resistant to chemical disinfectants including chlorine, but they die if dried, heated, or frozen.[3]

A vaccine that elicits a mucosal response to the parasite may protect against infection and disease and, eventually, help in the eradication of this disease. Several vaccine candidates based on the Gal/GalNAc lectin have demonstrated protective immunity against hepatic amebiasis in animals.[20,39] Bangladeshi children who developed mucosal immunoglobulin A (IgA) antibodies against the lectin had 86% fewer *E. histolytica* infections over a year than those who did not.[40]

Malaria

Malaria is caused by infection with one of four species of the protozoan genus *Plasmodium*: *P. falciparum*, *P. vivax*, *P. ovale*, and *P. malariae*. The life cycles of all four species are very similar, with each having an asexual stage, occurring in the human host, and a sexual stage occurring in the female *Anopheles* mosquito.

Malaria occurs worldwide in tropical and subtropical regions. An estimated 3 million deaths occur due to malaria worldwide, 90% of which occur in Africa, mostly in children.[41] In 2000, there were an estimated 350 to 500 million cases of malaria and more than 1 million deaths, most of them occurring in Africa and Asia-Pacific.[41] Up to 5% of African children born in endemic areas will die from malaria. Malaria represents the third largest cause of infectious disease mortality after human immunodeficiency virus (HIV) and tuberculosis, making it the most lethal parasite of humans.

P. falciparum is responsible for the majority of cases of malaria in Africa, and about half of those in endemic areas outside of sub-Saharan Africa. An estimated 70 to 80 million cases annually are due to *P. vivax*, mostly in South and southeast Asia and South America.[42] *P. malariae* and *P. ovale* are less common. *P. ovale*, found in sub-Saharan Africa and southeast Asia, generally causes the mildest form of malaria with the lowest levels of parasitemia.[43]

Malaria is a major cause of fever and illness in travelers to endemic areas, and it is not uncommon to see imported cases in nonendemic areas; moreover, there can be a delay in onset of symptoms in such travelers owing to the interval between the bite of the infected mosquito and release of parasites from the liver.[44] Although malaria cannot be spread from person to person, a few cases of local transmission of malaria have occurred in the nonendemic regions of the world as well as, very rarely, transfusion-transmitted infection.

Transmission

Infected mosquitoes transmit the malaria sporozoites to a new host during a blood meal. The sporozoites travel through the bloodstream to the liver, where they mature into tissue schizonts within hepatocytes. The hepatocytes rupture, releasing thousands of merozoites that reenter the bloodstream and invade red blood cells. There, merozoites mature within the cells, forming rings, trophozoites, and then schizonts, which rupture the cell, releasing more merozoites. Some of these develop into gametocytes, which when taken up by a mosquito during a blood meal, restart the cycle.

The release of parasites from the liver in *P. vivax* and *P. ovale* infection may be delayed due to the propensity of these species to reside in the liver for a considerable time, the so-called hypnozoite stage. Unless specific "radical cure" is given, infection may relapse with the rupture of another infected hepatocyte.

Pathogenesis

P. falciparum is the most virulent species of malaria because it has the ability to parasitize a greater percentage of red blood cells and to sequester in the capillaries and postcapillary venules in many tissues. When *P.*

falciparum parasites infect red blood cells, they cause morphologic changes, including the formation of "knobs" on the surface of the red cells. These make the infected cells more adherent, allowing them to adhere to vascular endothelium, a process that leads to sequestration and obstruction of the microvasculature with resultant tissue ischemia. Sequestration is aided by decreased deformability of the infected red cells and by rosetting (adherence of infected and uninfected cells in clumps). With red blood cell destruction, parasite antigen release, and ischemia due to this sequestration, inflammatory cytokines may mediate at least some of the end-organ damage seen in severe malaria.[45]

The mechanisms mediating lung injury in malaria are poorly understood. In contrast to the frequently observed pattern in severe *P. falciparum* malaria in which splanchnic and cerebral vascular beds are heavily affected by sequestration, high-level sequestration of parasitized red blood cells is seldom observed in pulmonary capillary beds. Autopsy findings of patients who have died with respiratory distress as a feature of severe malaria have demonstrated swelling of the alveolar septa, with marked interstitial edema.[46,46a]

Clinical Manifestations

Malaria usually presents with periodic fever, chills, headache, and malaise. Splenomegaly and anemia are frequent clinical findings. Most cases of malaria are uncomplicated. Infections with *P. malariae*, *P. ovale*, and *P. vivax* are rarely life-threatening. Falciparum malaria can progress rapidly to a fatal disease, involving multiple organs. The World Health Organization's criteria for severe malaria[47] include coma, severe anemia, pulmonary edema, hypoglycemia, hemodynamic collapse, renal failure, bleeding, recurrent seizures, acidosis, or hemoglobinuria. Hyperparasitemia and jaundice have also been added[48] to criteria for severe malaria. The clinical manifestations of severe malaria vary with age. Severe anemia is more common in infancy and early childhood, whereas cerebral malaria occurs more frequently later in childhood. Adults are more likely to develop renal failure, jaundice, and pulmonary edema. However, severe manifestations may occur at any age group.[49]

Falciparum malaria is especially dangerous during pregnancy, representing a major cause of anemia in the pregnant mother, and low birth weight, prematurity, or miscarriage of the infant[50]; the presence of coexisting HIV infection adds greatly to these hazards.[51] The pathogenesis of malaria in pregnancy is largely explained by the ability of *P. falciparum* to express ligands on the surface of the red cell that facilitate sequestration in the placental vascular bed. The severe manifestations of malaria in pregnancy are more likely to occur in women in their first pregnancy than in the second and third trimester and the immediate postpartum period.[52,53] In a recent case report of a fatal case of *P. vivax* infection attributed to respiratory failure, postmortem findings showed changes typical of the Acute Respiratory Distress Syndrome,[46a] again highlighting the potential of *P. vivax* infection to rarely cause lethal pulmonary complications.

Pulmonary Disease

Pulmonary disease in malaria is most commonly a result of infection with *P. falciparum*; but it is increasingly recognized that *P. vivax* can cause pulmonary edema.[54–57] Recent papers report a high frequency of respiratory distress associated with both *P. falciparum* and *P. vivax* in adults and children in endemic areas.[58,59] *P. ovale* is now also recognized to cause pulmonary edema.[43,60] Infection with *P. malariae* has never been associated with pulmonary edema, but has been reported to cause respiratory symptoms. In addition, there has been one reported case of bronchiolitis obliterans following vivax malaria.[61] An Australian study of acute, uncomplicated malaria showed that 4 of 11 patients with *P. falciparum* and 8 of 15 patients with *P. vivax* infection had a cough at the time of diagnosis of malaria. Moreover, subclinical impairment of lung function (small airway obstruction, reduced diffusion capacity) was observed in these patients, both on admission as well as 12 to 20 days later. These abnormalities ultimately resolved in all patients with the successful treatment of their malaria.[56] These findings have also been shown in patients with both falciparum and vivax malaria in endemic areas.[56,62] In another study of Israeli expatriates living in Cameroon, 18% of cases with uncomplicated malaria had a decrease in peak expiratory flow rate while parasitemic.[63]

The most severe form of lung injury in falciparum malaria is a noncardiogenic pulmonary edema with acute respiratory distress syndrome (ARDS). This occurs in less than 1% of infected patients but is associated with a higher mortality. When this manifestation occurs, it often follows the initial treatment after the parasitemia begins to decrease. Patients often have normal pulmonary capillary wedge pressures, and do not respond as well to diuretics as do patients with cardiogenic pulmonary edema.[64] In adults, the pathophysiology likely entails parasite sequestration in pulmonary microvasculature as well as inflammatory response. The causes of respiratory distress in children are less clear, but include acidosis and concurrent pneumonia. The role of pulmonary parasite sequestration and pulmonary inflammation requires further investigation.

Among 188 individuals with malaria admitted to a French intensive care unit, 93 had severe disease, 43% required mechanical ventilation for pulmonary edema; 11% of these patients died. An increased risk of mortality was associated with nonimmune status, coma, pulmonary edema, shock, and metabolic acidosis.[48]

Diagnosis

The standard diagnostic test for malaria is a Giemsa stain of a thick or thin blood smear to identify parasites. Although negative blood smear makes the diagnosis less likely, if the clinical suspicion of malaria is high, blood smears should be repeated every 12 hours for 48 to 72 hours.

Several antigen detection tests are now available and enable a rapid diagnosis of falciparum malaria. They are

based on detection of one of two parasite-specific proteins, the histidine-rich protein 2 (specific for *P. falciparum*) or parasite-lactate dehydrogenase (for either *P. falciparum* or *P. vivax*). Although only one is approved by the U.S. Food and Drug Administration (FDA), field trials have shown good sensitivity (78%–93%) and specificity (92%–98%) for *P. falciparum*.[65-68] PCR diagnosis of malaria species is used for research purposes, but is not widely available.

Treatment

Uncomplicated malaria caused by *P. vivax*, *ovale*, *or malariae* can be treated with chloroquine for 3 days, as can mild falciparum malaria from the few regions where chloroquine-sensitive *P. falciparum* remains (Central America north of the Panama Canal, North Africa, and the Middle East). Therapy of vivax and ovale malaria requires an additional 2-week course of primaquine to eradicate the liver stage of the parasite. Falciparum malaria is almost universally chloroquine-resistant. A range of drug regimens is suitable for treating mild falciparum malaria, including quinine sulfate (650 mg daily for 3 days) plus tetracycline, mefloquine (750 mg followed by 500 mg 12 hours later).[49] Atovaquone-proguanil (Malarone), 4 tablets daily for 3 days in adults, or artemether-lumefantrine (Coartem, Riamet; 20 mg artemether and 120 mg lumefantrine) administered as six consecutive doses (each of four tablets, i.e., 80 mg of artemether and 480 mg of lumefantrine) at 0 and 8 hours on day 1 and twice daily (~8 hr apart) on the following 2 days.[69,70] The treatment of choice for severe malaria is intravenous artesunate administered in four equal doses of 2.4 mg/kg of body weight, with the first dose given on admission, followed by doses at 12 hours and 24 hours, then once on day 3.[71] The drug is available under an Investigational New Drug (IND) from the CDC, by calling the CDC Malaria Hotline (770-488-7788 or 770-488-7100). If the drug cannot be made rapidly available, the second-line agent, quinidine, should be used (see later). Quinine and its D-enatiometer quinidine are alternatives, administered by intravenous infusion as 20 mg salt/kg on admission, then 10 mg/kg every 8 hours. Infusion rate should not exceed 5 mg salt/kg/hr due to cardiotoxicity and ideally should be administered in a monitored environment owing to potential toxicity.

Despite intensive support, severe malaria has a high fatality rate due to end-organ damage. Close monitoring of fluid balance is appropriate to prevent fluid overload and respiratory distress. Early renal replacement therapy is appropriate. Hypoglycemia should be corrected with glucose infusions, and respiratory symptoms with oxygen and, if necessary, intubation and ventilation. Concomitant bacterial infections should be managed with appropriate antibiotic therapy. Transfusion is often necessary for the anemia. Some experts recommend exchange transfusions in patients with a high level of parasitemia. However, no randomized trials have been done that show clear benefit.[72]

Prevention

Prevention of malaria entails several approaches, including decreasing mosquito contact with bed nets, insect repellants, and protective clothing to decreasing transmission from the mosquito (vector control) and susceptibility of the host (antimalarial prophylaxis). Vector control includes extensive use of insecticides and decreasing mosquito breeding areas. Insecticide-impregnated bed nets are an inexpensive and effective method of preventing transmission.[73] They have been shown to decrease parasitemia and anemia, as well as death in children under 5.[74,75] Other less well studied methods for travelers include insecticide-treated clothing and topical insecticides.[76]

Chemoprophylaxis is frequently indicated in nonimmune travelers to endemic areas. Because most *P. falciparum* is now resistant to chloroquine, alternative agents must be given. Agents most commonly used at this time are mefloquine, doxycycline, and atovaquone-proguanil. Mefloquine is given weekly, starting 1 week before travel, and continuing for 4 weeks afterward. It is generally well tolerated, although a significant percentage of people report bizarre dreams and occasionally hallucinations. It should not be given to anyone with a major psychiatric illness or to those with a seizure disorder or disturbance of cardiac rhythm. Atovaquone-proguanil is approved for prophylaxis as a fixed-dose combination pill that is taken daily. Its advantage over mefloquine is that it need be started only 1 to 2 days before travel and continued for just 1 week after return. However, because it is more expensive than mefloquine, it is generally not cost-effective for trips over 2 to 3 weeks duration. Doxycycline is also an effective daily prophylactic agent. Although it is cheaper than atovaquone-proguanil, it cannot be given to pregnant women or small children.

Although vaccines against malaria are being actively developed, most are still in the preclinical phase or early clinical trials. The malaria vaccine candidate that is the most advanced in development is based on the repetitive sequence of four amino acids in the circumsporozoite antigen on the surface of the sporozoite of *P. falciparum*.[77] This vaccine has been subjected to extensive studies involving human volunteers, the results of which indicated a potential protective efficacy of about 40%.[78,79] In a recently completed phase IIb study undertaken in Africa, the vaccine reduced the risk of malaria infection and clinical disease by 65% and 59%, respectively.[80] A phase 3 clinical trial of this vaccine is ongoing.

Toxoplasmosis

Toxoplasma gondii is an obligate intracellular parasite, with humans being incidental hosts. A zoonosis, it can complete its life cycle only within felines, although a wide range of birds and mammals can serve as intermediate hosts.[81] Prior to the HIV epidemic, it was recognized primarily as a cause of congenital infection and of disease in the immunosuppressed. Since the onset of the

HIV epidemic, it has emerged as a common cause of neurologic disease in patients with the acquired immunodeficiency disease syndrome (AIDS). Up to 50% of the world's population are estimated to be infected with *T. gondii*, with great geographic variation.[82]

Transmission

Toxoplasmosis is most frequently acquired by ingestion of cysts measuring 10 × 12 μm. These are excreted in cat feces and sporulate in the environment, where they can remain viable and infective for months. Environmental exposure can occur without direct exposure to a cat, by eating oocysts contaminating raw vegetables or fruits. An alternate, less common mode of transmission is through ingestion in raw or poorly cooked meat of tissue cysts containing thousands of bradyzoites. Tissue cysts are killed by freezing or by exposure to temperatures greater than 60°C.[83] Toxoplasma infection can also be acquired from organ transplantation or congenitally from mother to fetus.

Pathogenesis

Upon entering a host, *T. gondii* must evade host defenses, but can invade any cell in the body, although brain, lymph nodes, heart, and lung are most common. Tachyzoites bind to receptors on the cell surface and are internalized within a vacuole derived from the host plasma membrane, termed the parasitophorous vacuole. Host defense against *Toxoplasma* requires both a functional innate and an adaptive immune system. Typically, *Toxoplasma* infection triggers macrophages to make interleukin (IL)-12, resulting in secretion of interferon-γ (IFN-γ) by $CD4^+$ T cells and natural killer cells. IFN-γ activates macrophage toxoplasmocidal activity, allowing macrophages and monocytes to kill the parasite through oxygen radical formation.[84] IL-10 secretion triggered by the parasite prevents an overexuberant immune response as well as allows the parasite to evade killing by downregulating the immune response.[85] The vast majority of people quickly contain infection, and bradyzoites are confined within tissue cysts.

In the lung, *T. gondii* infection can cause a necrotizing pneumonia with nodule formation, diffuse alveolar damage, and interstitial pneumonitis. Edema develops at the alveolar-capillary interface, accompanied by lymphocyte infiltration.[82] In a French autopsy study of 80 patients who died with AIDS, 44% of the patients had *T. gondii* in their tissues, 5 of whom had evidence of lung disease. Pathologic findings included foci of coagulative necrosis, disseminated microfocal bronchopneumonia, and florid bronchitis with granulocytic infiltrations. Numerous trophozoites were found within the lesions, especially at the margins.[86]

Clinical Manifestations

The vast majority of immunocompetent people who acquire *T. gondii* remain asymptomatic. Ten percent to 20% of infected people develop a painless lymphadenopathy[87]; in an even smaller percentage, a prolonged mononucleosis-like illness occurs, with generalized lymphadenopathy, fevers, and malaise. Rarely, solid organ involvement occurs.

A more fulminant illness can occur among immunosuppressed individuals, either during primary infection or with reactivation of latent infection. Cerebral toxoplasmosis is the most common clinical manifestation among immunocompromised individuals, with necrotizing encephalitis occurring in up to 10% to 40% of AIDS patients not on chemoprophylaxis for toxoplasmosis. Ocular, cardiac, pulmonary, disseminated toxoplasmosis or septic shock can also occur. Extracerebral *Toxoplasma* infection occurs in 1.5% to 2% of AIDS patients, with pulmonary disease occurring in 0.5% of patients.[88]

Pulmonary Disease

AIDS patients with *Toxoplasma* pneumonia present with cough, dyspnea, and fever. As toxoplasmosis is generally seen only in advanced HIV infection with CD4 counts below 100, the majority of AIDS patients who develop toxoplasma pneumonia already have had previous HIV-associated opportunistic infections. The difficulty of defining the contribution of *T. gondii* infection to pneumonitis in a setting where other pathogens such as cytomegalovirus (CMV) and *P. jirovecii* infection are also present is significant, especially where PCR-based diagnosis is employed without quantitation of the infective burden.[89] Nevertheless, the mortality among patients with *Toxoplasma* pneumonia appears to be higher than among patients with extrapulmonary disease, with a median survival of 150 days after diagnosis.[90]

The majority of pulmonary disease is from reactivation of latent disease, although cases of acute primary disease have been reported.[91] In solid organ transplant patients, this is most commonly due to transplantation of a toxoplasma-seropositive lung or heart into a seronegative recipient, resulting in primary pulmonary disease. There is no evidence that specific isolates of *T. gondii* have a predilection to cause pulmonary disease.[91a] Occasionally, in transplant patients, hematogenous spread of the organism can lead to multiple nodules within the lung.[82]

In bone marrow transplant patients, pulmonary toxoplasmosis occurs in 0.28% to 0.45% of patients. Unlike solid organ transplant patients, most of these patients have reactivation, not primary disease. The major risk factors are pretransplantation seropositivity of the recipient, an allogeneic transplant, and graft versus host disease (GVHD) entailing intensification of immunosuppression.[92] Pulmonary disease generally results from dissemination from another site. Most patients developed symptoms within the first 2 months of bone marrow transplantation, at times despite prophylaxis.[93] In a series of 55 cases of disseminated toxoplasmosis after bone marrow transplantation, only 4 patients survived the infection, a mortality rate of 93%.[94]

T. gondii pneumonia can occur in immunocompetent subjects.[95] Apart from the expected features of pneumonia, myalgia, rash, and abnormal liver function tests were

prominent findings. Testing for *T. gondii*–specific IgM antibodies was a sensitive diagnostic approach, as was cytologic examination of BAL fluid for tachyzoites. Full recovery is usual.

Diagnosis

Although serum lactate dehydrogenase may be extremely elevated in toxoplasma pneumonia, it is neither sensitive nor specific. Serology in the appropriate clinical setting can confirm exposure, but is not sufficiently specific. Microscopic examination of lung lavage fluid is the technique of choice for diagnosis of pulmonary toxoplasmosis. Histologic examination of lung biopsy can also identify the organisms. Tachyzoites can be visualized by Giemsa or eosin-methylene blue stains, whereas the cyst forms can be seen on hematoxylin and eosin or silver staining. Immunohistochemical or indirect immunofluorescence staining is also useful for confirmation of the diagnosis, but is not as sensitive.

A range of radiographic patterns have been reported, including interstitial or alveolar opacities, nodules, or a miliary pattern (Fig. 37-2). Pneumonia may be associated with pleural effusions or pneumothorax. In the French study of HIV patients, chest radiographs were abnormal in 53% of patients and 88% of patients with a positive lavage; the remainder were diagnosed on biopsy or autopsy.[88]

PCR techniques are now being explored for early diagnosis of reactivation of toxoplasmosis in bone marrow transplantation patients. This would enable prophylaxis and treatment of positive patients, without exposing others to the potential toxicity of drugs used for prophylaxis.[96] Although PCR has been used in AIDS patients to detect *T. gondii* in brain,[97] lung lavage fluid,[98] and sputum,[99] this technique is not widely used.

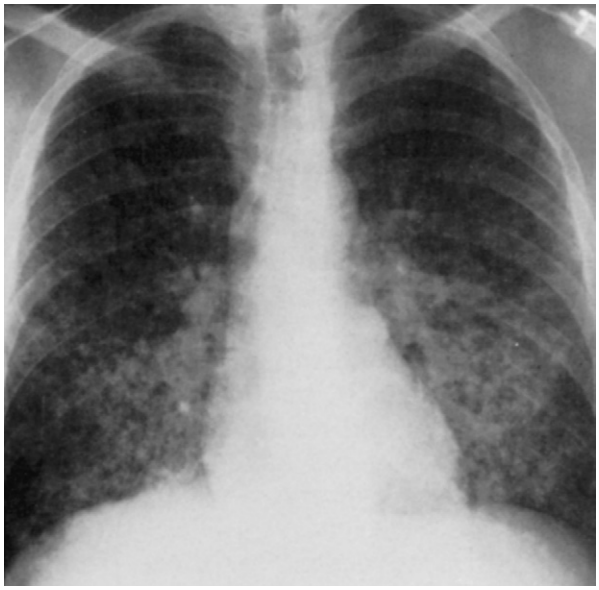

FIGURE 37-2 ■ Chest roentgenogram of a 29-year-old with acquired immunodeficiency syndrome and cerebral and pulmonary toxoplasmosis shows multiple nodular densities throughout both lung fields.

Treatment

Treatment regimens for toxoplasma pneumonia are based on those developed for treatment of cerebral disease. Standard treatment is oral pyrimethamine 50 to 100 mg and folinic acid 10 to 25 mg daily, along with oral sulfadiazine, 1.0 to 1.5 mg every 6 hours. Both drugs act on the parasite's folate pathway. The most common adverse effects are with sulfa drugs, including myelosuppression, rash, hepatotoxicity, and renal impairment. Alternate regimens include pyrimethamine in the just discussed dose, and clindamycin (400–600 mg orally or 600–1200 mg intravenously) every 6 hours. Once an immunosuppressed patient develops toxoplasmosis, lifelong chronic suppressive treatment is necessary unless the immunosuppression can be reversed, for example, by immune reconstitution in HIV infection. Pyrimethamine 25 to 50 mg daily with leucovorin plus sulfadiazine 500 to 1000 mg four times daily is the recommended regimen for suppressive therapy.

Prevention

Prevention of primary infection entails avoiding contact with infected cat feces, washing hands and kitchen utensils that come into contact with raw meat, washing fruits and vegetables well, and cooking all meat thoroughly.

As HIV patients have a significant risk of toxoplasmosis once their CD4 count falls below 200, it is recommended that baseline serology is performed. Trimethoprim-sulfamethoxazole (TMP-SMX), the drug of choice for prophylaxis of *P. jirovecii.* Pneumonia, has additional activity in preventing *T. gondii* infection.[100–102] In sulfa-allergic patients, pyrimethamine or dapsone can also be used. Pyrimethamine-sulfadoxine has also been demonstrated to be effective prophylaxis in *T. gondii*–seropositive bone marrow transplant patients,[103] whereas pyrimethamine given alone has been demonstrated to be effective prophylaxis for heart and heart-lung transplant patients.[104]

HELMINTHS

Intestinal Nematode Infections

Roundworms or nematodes can be classified broadly into those inhabiting the intestine, which are by far the most common, and those infecting deep tissue. Although some of these parasites can be transmitted from human to human, most require some period of maturation in the environment before becoming infectious to the human host. With the exception of *Strongyloides stercoralis*, intestinal nematodes do not multiply within humans; diagnosis is made by finding either eggs or parasites, usually in the stool. It is estimated that there are more than 1 billion cases of ascariasis worldwide. *Strongyloides*, through its autoinfection cycle, can multiply and disseminate widely in an immunocompromised individual (the hyperinfection syndrome).

Although significant pulmonary disease is not a recognized feature of intestinal helminth infections, transient pulmonary symptoms frequently occur during larval migration through the lungs en route to the intestine. Among the intestinal helminths, *Ascaris lumbricoides* (roundworm), *Necator americanus*, or *Ancylostoma duodenale* (hookworm), and *Strongyloides* are the most common helminths whose life cycle entails passage through the lung. The symptoms, typically a transient Loeffler-like syndrome, are characterized by cough, asthma, fever, patchy pulmonary opacities on chest radiographs, and eosinophilia (see Chapter 61).

Ascariasis

A. lumbricoides is the most ubiquitous of the intestinal parasites. Growing to a length of up to 35 cm, it infects more than 1.3 billion people worldwide.[105] Although morbidity and mortality data are difficult to obtain, it is estimated that between 8,000 and 10,000 children die each year from complications of ascariasis, particularly intestinal and biliary obstruction.[106]

Ascariasis is most common in the tropics and subtropics, especially in areas with high rainfall, but its prevalence depends on many factors. It is generally low in developed countries (<1%) and more common in developing countries, ranging from 4% in Mafia Island, Tanzania,[107] to 45% in one study in Vietnam,[108] and 91% in children in northern Pakistan.[109] An estimated 4 million people in the United States are infected.[110] *Ascaris* is still prevalent in the rural areas of the southern United States and is frequently seen in travelers from endemic areas. Some cases may arise from pigs (*Ascaris suum*).[111] Children carry heavier worm burdens than adults, perhaps owing to geophagia or acquired immunity in adults.

Transmission. Humans are the only natural host of *A. lumbricoides*, although the pig species *A. suum* is almost identical except for small differences in morphology and biochemistry. Although individual worms from humans and pigs cannot be differentiated on clinical or morphologic grounds, species-specific genetic markers enable differentiation of host-specific populations.[106,108] The two populations of worms are reproductively isolated.[112] Female worms produce up to 200,000 eggs per day that are shed in the stool. Once in the environment, the embryonated egg matures in moist conditions into a rhabditiform larva within the egg. Infection occurs by ingestion of food or water contaminated with eggs rather than by direct person-to-person contact. Once swallowed, the eggs hatch in the duodenum, where the larvae are released. They burrow through the walls of the intestine and enter the portal circulation, passing through the heart to reach the lungs. In the lungs, they molt twice and then break into the alveoli. They then crawl up the bronchial tree and are swallowed. They then make their way to the small intestine where they mature into adult worms. Eggs are produced after adult worm maturation, a few months after infection. Adult worms feed on intestinal contents and can live for 10 to 24 months in the host. In hyperendemic areas where high worm and egg burdens are prevalent, transmission can even occur by inhaling eggs or swallowing contaminated respiratory secretions.[106,112]

Pathophysiology. The pathophysiology of lung disease due to *Ascaris* is varied. The first effects are attributable to larval migration through pulmonary tissue. The host response to the larva, which results in production of IgE and an eosinophilic inflammatory infiltration, leads to significant pathology. Eosinophils coat the larvae and can envelop them in eosinophilic granulomas. During pulmonary migration, a hypersensitivity reaction can occur, leading to an alveolar serous exudate, with eosinophilic infiltration of the peribronchial tissue and increased mucus production. This can lead to bronchospasm and airway hyperreactivity. On rare occasions, retrograde peristalsis and vomiting can lead to expulsion of fully developed adults from the intestine into the upper airways, leading to upper airway obstruction.[110,113]

On gross examination of ascaris-infected lung tissue, small, consolidated gray patches are seen, especially in the lower lobes. Histologically, interstitial pneumonitis with thickened alveolar walls can be found, as well as bronchiolar infiltration with eosinophils and fibrin. Larvae can occasionally be isolated from airways.[110]

Clinical Manifestations. Most patients with ascariasis are asymptomatic, although nonspecific abdominal symptoms are common. The pulmonary phase occurs while the larvae are passing through the lung. Once they reach the intestine, associated symptoms include nausea, vomiting, vague abdominal pain, and anorexia. The intensity and frequency of symptoms appear to be related to adult worm burden. Complications of ascaris infection are usually associated with ectopic migration of the adult worms into the common bile duct or pancreatic duct resulting in cholangitis, pancreatitis, or liver abscess. Likewise, appendicitis is recognized as is intestinal obstruction in heavy infection leading to perforation with peritonitis.[110]

Heavy worm burdens can cause malnutrition in children, which can lead to stunted growth and neurologic development. Conversely, treatment of intestinal helminths leads to improved growth. Indeed, some studies suggest that deworming may improve learning ability and cognition.[112]

Pulmonary Disease. The classic pulmonary disease in *Ascaris* infection is Loeffler's syndrome, which manifests as transient pulmonary opacities and eosinophilia coinciding with the larval migration through the lungs. Worldwide, ascariasis is the most common cause of transient eosinophilic pulmonary radiographic opacities. In some areas, the pneumonitis occurs at specific times of the year where climatic factors influence transmission.[114]

Symptoms from larval migration through the lungs develop 9 to 12 days after ingestion of the eggs and can last from 2 to 3 weeks. They include a nonproductive cough, burning substernal pain that can be pleuritic, dyspnea, and occasionally mild hemoptysis, crackles, or wheezes.[112] Associated findings include an urticarial rash and low-grade fever. Rarely, an adult worm can

ectopically migrate into the lungs or other viscera and get "lost." For example, adult worms have been found in a tuberculous pyopneumothorax, causing a bronchopleural fistula.[115]

The relationship between helminth infection and asthma and other allergic diseases has led to the postulation of the so-called hygiene hypothesis.[116] Several studies have suggested that intestinal helminth infection decreases the risk of atopy and asthma.[117,118] However, others have found that *Ascaris* and other helminths infections are associated with asthma and that treating the helminths led to better asthma control in asthmatic children.[119–121]

Diagnosis. For the intestinal phase of ascariasis, stool examination for the large, thick-shelled eggs is the most common and reliable diagnostic approach. Because the worms produce so many eggs per day, eggs are relative easy to find in the feces of infected patients. However, because the pulmonary symptoms are due to larval stages, eggs may not be present in the stool during the pulmonary phase if it is the initial infection. Further, ascaris eggs in the stool of a patient with pulmonary symptoms are not necessarily indicative of pulmonary ascariasis, because the patient may not have any larval stages left. Laboratory abnormalities are nonspecific and include blood and sputum eosinophilia that usually appear after the onset of symptoms. The chest radiograph typically shows migratory, transient opacities of varying sizes.

Treatment. Pulmonary ascariasis is a self-limited disease that does not require specific treatment. Thus, anthelmintic treatment probably does not have an effect on larval stages in the lungs.[112] In patients with severe symptoms, corticosteroids can be used to attenuate the inflammatory response. A range of anthelmintics are effective for treatment of ascariasis. Whereas single-dose therapy with albendazole, 400 mg (adults), or mebendazole, 500 mg, dramatically reduces worm burden and egg output, it may not lead to cure.[122] Mebendazole in a dose of 100 mg twice a day for 3 days may be more effective. Alternative treatments are pyrantel pamoate 11 mg/kg (to 1 g maximum) as a single dose or ivermectin (not normally given for the treatment of intestinal helminth infection).[123] Albendazole and mebendazole were both more than 97% effective at eliminating *Ascaris* infection in school children in Zanzibar,[124] although a more recent study showed that albendazole cured infection in only 70% of children in the Philippines.[123] Nitazoxanide, recently approved for use in children in the United States, had a 100% efficacy in curing light to moderate ascariasis in Mexican school children.[38] In patients with intestinal obstruction, piperazine citrate at 75 mg/kg for 2 days narcotizes the worms and helps relieve obstruction prior to treatment with an anthelmintic agent.

Prevention. Transmission of *Ascaris* can be interrupted with improved hygiene, sanitation, cessation of use of human waste as fertilizer, and access to clean water. Education about washing fruits and vegetables and boiling water is also helpful. Mass treatment campaigns of whole populations or targeted to children have been shown to decrease intensity and prevalence of infection and morbidity associated with high worm burdens.[125,126]

Hookworm

Human hookworm disease is caused primarily by either *Ancylostoma duodenale* or *N. americanus*. Together, these two species infect 1.2 billion people and are a major cause of morbidity worldwide.[127] Adult hookworms live in the small intestine and can be identified by the buccal capsule that they use to attach to the small bowel mucosa. The worms feed on blood and tissues from the human host, resulting in iron-deficiency anemia in areas where dietary iron levels are low. Hookworm infection is most common in tropical and subtropical areas. In parts of the world, it is the most common intestinal helminth.

Transmission. Hookworm is generally transmitted by entry of the rhabditiform larvae through the skin, usually of the feet or hands. Once the larvae enter the body, they migrate to the lungs. There, they molt and then crawl up the bronchial tree and are swallowed. In the small intestine, another molt occurs before the worm attaches to the intestinal lumen to feed. Following fertilization, *Necator* begins shedding eggs within 2 months of infection, whereas *Ancylostoma* does so at approximately 38 weeks.[110] Once the eggs are shed in the stool, they hatch, molt into rhabditiform larvae, and crawl to the surface of the soil from which they can infect another host, thus completing the life cycle. Adult worms are small (1 cm long) and cylindrical. Adults can produce up to 7000 eggs/day and can live for up to 8 years.[128]

Pathophysiology. In the lung, migrating larvae may cause alveolar hemorrhage.[110] Bronchoscopy undertaken during the pulmonary migration has revealed airway erythema, with BAL cytology showing a marked eosinophil predominance.[129] The blood loss from the intestine due to hookworm infection can be significant if the burden of infection is heavy. The average daily blood loss is 0.2 mL/adult worm for *Ancylostoma* and 0.03 mL/adult worm for *Necator*.[128] The adult worm changes locations every few hours, leaving behind bleeding, raw mucosa. The consequent anemia can be severe, leading to cardiac decompensation and, rarely, death.

Unlike other helminth infections, hookworm prevalence in communities continues to increase with age, and therefore, the highest prevalence is in older adults and elderly. Protective immunity to hookworm rarely occurs and may require a specific IgE response to hookworm antigens.[127]

Clinical Manifestations. As in ascariasis, the symptoms of hookworm infection depend on the location of the parasite. In the majority of patients, the infection is subclinical. Symptoms are usually related to the burden of infection. Initially, as the parasite enters the skin, a pruritic dermatitis can occur, termed "ground itch." It can be intense in nature, depending on the number of infecting organisms and previous host sensitization. Local pruritus is reported to be more common in *N. americanus* infection than in *A. duodenale* and

generally occurs on the feet where the parasites tend to enter. In an outbreak of hookworm in a cohort of young North Indian men who were heavily infected after playing in a field heavily contaminated with human excrement, the rash lasted for a mean of 6.5 days (but in some continued for up to 30 days). Several days after the pruritus resolved, the pulmonary symptoms started in the majority of patients. These lasted for up to 3 months in this cohort.[130] In five patients experimentally infected with a low numbers of larvae, no appreciable pulmonary symptoms were seen.[129] Transient gastrointestinal symptoms generally follow, manifesting as vague abdominal discomfort, increased flatulence, nausea, vomiting, or severe cramping that can be postprandial in nature. Anemia is the most important consequence of hookworm infection and can cause cognitive and learning problems. Malnutrition and hypoproteinemia can occur from the loss of plasma proteins.[110]

Pulmonary Disease. The migration of the larvae through the lungs may cause a Loeffler syndrome as with ascariasis. Patients may have a mild cough, or the symptoms may be more severe, with associated dyspnea and wheezing. Symptoms generally last about 2 weeks, but in heavy infection, they can last for up to 3 months. The chest radiograph may show transient, migratory opacities, especially in the hilar areas, with spontaneous clearing.[110]

Diagnosis. In intestinal disease, stool examination reveals characteristic hookworm eggs. The diagnosis of pulmonary disease is more difficult, because, as in ascariasis, the pulmonary symptoms occur before patent infection has developed. Definitive diagnosis depends on the isolation of larvae from respiratory secretions or by BAL or from gastric secretions. A history suggestive of exposure, with a characteristic rash followed by pulmonary symptoms several days later, should raise suspicion of hookworm. A retrospective diagnosis can be made if eggs appear in the stool 2 to 3 months later.

Treatment. Anthelmintic drugs are not effective against the larval stages in the lungs, so there is no specific treatment for the pulmonary stage of hookworms. Symptomatic relief of the pulmonary disease associated with hookworm if indicated can be obtained by using bronchodilators or, in rare circumstances, corticosteroids. For intestinal infections, a single dose of albendazole (400 mg) is the recommended therapy for hookworm infection. Mebendazole (100 mg twice daily for 3 days) can also be used. However, both regimens when administered in single dose are less than 100% effective.[122] Community-wide (or targeted mass treatment) campaigns has been shown to decrease the morbidity and cognitive dysfunction associated with intestinal helminths[105] including hookworm. An alternative regimen is pyrantel pamoate 11 mg/kg to a maximum dose of 1 g given as a single dose.

Prevention. Prevention of hookworm infection entails improving sanitation and hygiene. Sewage collection and proper waste disposal and barriers to contaminated areas can decrease transmission. Whereas an effective vaccine for dog hookworm, based on irradiated larvae, was available for a time, indicating that development of a vaccine is possible, the development of a human vaccine appears to be some way off.[127] An intriguing study in Brazil showed that children who had a Bacille Calmette-Guérin (BCG) vaccination scar had a lower prevalence of hookworm infection (by 41%) than those without a BCG scar and intensity of infection even after controlling for possible confounding variables.[131]

Strongyloides

S. stercoralis is rare among intestinal helminths in its ability to complete its life cycle within the human host, which enables a cycle of autoinfection that can persist for decades after initial infection. When host immune surveillance is attenuated by corticosteroids, human T-cell lymphotrophic virus 1 (HTLV-1) infection, malignancy, or certain immunosuppressive drugs, infection can amplify, resulting in disseminated infection leading to a fulminant, overwhelming course with a high mortality rate.[131a] Although epidemiologic estimates are likely to be inaccurate, an estimated 50 to 100 million people are infected worldwide, with between 0.4% to 6% of the population of the southeast United States infected.[132,133] Populations at significantly greater risk for strongyloidiasis include immigrants, travelers from any developing country, veterans who have served in endemic areas, institutionalized persons, and those with achlorhydria.

Transmission. *S. stercoralis* is found throughout the tropical and subtropical world. It is endemic in the southeast United States and in urban centers with large immigrant populations. It is also frequently found in institutionalized populations. Like hookworm, transmission is through contact with soil or water contaminated with feces. Once filariform larvae of the parasite penetrate the skin, they migrate through the venous circulation or lymphatics to the lungs. There, they penetrate the alveolar wall and migrate up the bronchial tree to be swallowed by the host. In the small intestine, larvae molt twice to become adult female worms, which burrow into the wall of the duodenum and jejunum. The parthenogenic female adult parasite begins laying eggs 28 days after infection. These eggs are shed into the lumen of the small bowel and rapidly hatch to become rhabditiform larvae that can either be shed with the feces out into the environment or molt in the bowel into filariform larvae and reinvade the intestinal wall or perianal skin to start the cycle of infection over again. Once in the environment, the rhabditiform larvae can develop either into filariform larvae to await another host to infect or into free-living adult males and females that reproduce sexually. The worms can either continue to exist as free-living organisms or parasitize another person.[134] Human-to-human spread has rarely been reported to occur with sexual contact.

Patients with HTLV-1 infection are more susceptible to infection with *Strongyloides* and to complications of that infection. It has been demonstrated in multiple studies that HTLV-1–positive patients had higher rates of *Strongyloides* infections.[135,136] Also, patients with *Strongyloides* who fail treatment are more likely to have HTLV-1 infection than those who responded to treatment.[137] A

possible explanation for this observation is that HTLV-1 infection skews the immune response toward a Th1 response, with elevation of IFN-γ, and away from a Th2 response characterized by elevation of IL-5 and necessary to control *Strongyloides* infection.[138] Fortunately, this does not seem to be true for HIV-infected individuals, and an increased incidence of disseminated *Strongyloides* has not been seen in areas with high HIV prevalence.[139]

Pathogenesis. The pathology caused by *Strongyloides* infection is largely due to the migration of the worms through tissues and to the immune reaction to them. When the organisms penetrate the skin, a cutaneous eruption can result. Likewise, as the worms migrate through the lungs, a Loeffler-like syndrome can result. If the host immune status is compromised, the autoinfective life cycle can amplify with worms migrating across the intestinal wall, these carrying enteric bacteria with them to multiple sites, resulting in life-threatening sepsis or meningitis.

Extensive alveolar hemorrhage is typically found in patients who succumb to disseminated strongyloidiasis; such hemorrhage is not observed in other organs. In other patients, postmortem histopathologic examination has revealed areas of lung tissue necrosis and neutrophil infiltration with increased congestion. Occasionally, a significant pleural effusion can occur.[140] In most patients with significant pulmonary involvement, larvae and occasionally adult worms and eggs can be identified in BAL fluid or sputum.[141] Other pathologic findings include pulmonary edema and bronchopneumonia. The death of the organisms can cause ARDS.[142] One patient with longstanding obstructive and restrictive lung disease was found on autopsy to have fibrosis of the interlobular septae, within which numerous granulomas were observed with a cellular composition including lymphocytes, plasma cells, histiocytes, giant cells, eosinophils, and neutrophils. In the center of these granulomas, *Strongyloides* larvae were seen.[143]

Clinical Manifestations. Infection with *Strongyloides*, as with other intestinal helminths, is completely asymptomatic in a large proportion of people infected. When symptoms occur, their character depends on the stage of infection and the location of the worms. Upon penetration of the skin by filariform larvae, a characteristic pruritic rash can develop at the site of infection, termed *larva currens*. This can last for up to 3 weeks. This may be followed shortly thereafter by pulmonary symptoms as the worms migrate through the lungs. Abdominal symptoms, characterized by bloating, vague abdominal pain, nausea, and diarrhea, may follow once the parasites reach the intestines. This symptom pattern can recur as autoinfection occurs. Indeed, chronic cough is a recognized feature of occult strongyloidiasis[144] and resolves following curative chemotherapy.[145]

In the hyperinfection syndrome, in addition to symptoms seen in ordinary infections, ileus or intestinal perforation can occur owing to the migration of large numbers of worms across the mucosa and carriage of enteric bacteria into a range of body sites, resulting in pneumonia, sepsis, or meningitis.[134]

Pulmonary Symptoms. In uncomplicated strongyloidiasis, the pulmonary symptoms are predominantly cough, dyspnea, and bronchospasm during the migratory phase, although persistent asthma due to *Strongyloides* infection has also been reported.[146] Patients with chronic lung disease may rarely retain the larvae in the lungs, where they molt into adults and complete their entire life cycle, leading to worsening lung disease, with chronic cough and bronchospasm.[147] In disseminated disease, high worm burdens or the secondary inflammatory response can cause acute respiratory distress or alveolar hemorrhage. Bacterial superinfection of the lungs with enteric pathogens can occur.

In a review of 20 patients in Kentucky admitted with pulmonary *Strongyloides* infection, a recognized risk factor for disseminated disease was present in 18 (90%).[133] These included corticosteroid therapy (65%) and chronic lung disease (45%). Pulmonary symptoms were noted in 95% of the patients, including cough, dyspnea, wheezing, or hemoptysis; 35% had a history of recurrent pneumonia. ARDS developed in 9 (45%) of the patients, 6 of whom subsequently died despite treatment. Gastrointestinal symptoms and eosinophilia were each present in 75% of the patients; 60% of them had secondary bacterial and fungal infection manifesting as pneumonia, lung abscess, or sepsis.

Diagnosis. Making a diagnosis of strongyloidiasis can be challenging. In immunocompetent people, eosinophilia is often present but not universal. In a Spanish study undertaken in a population of farm workers, 26 variables were investigated as predictors of strongyloidiasis.[148] Only eosinophilia was found to be significantly different between *S. stercoralis*–infected and –uninfected workers.[148] However, immunosuppressed individuals often do not have eosinophilia, and eosinopenia is associated with a poor prognosis.[136] The triad of pulmonary disease, gastrointestinal symptoms, and peripheral blood eosinophilia in a person with a history of travel or residence in an endemic area should suggest *Strongyloides* infection. Whereas larvae can often be isolated in stools (eggs are not present), the sensitivity of parasitologic examination of stools is poor, and multiple stools should be examined. Examination of the small bowel fluid by aspirate or string test or tissue by biopsy will often result in identification of larvae or adults. In hyperinfection and dissemination, larvae can be found in other specimens such as sputum, BAL fluid, urine, and cerebrospinal fluid (Fig. 37-3). The organisms can be seen by wet mount or Papanicolaou or Gram stain. Serology is available from CDC and private laboratories. Although the test is highly specific, its sensitivity is less reliable.[149] Concerns that relate to the ability of the test to discriminate between past and present infection likely reflect in part the inability to reliably establish cure. More recent studies in which ivermectin has been used have demonstrated seroreversion.[150] The cross reactivity of the antibody response with other helminth infections is an additional problem.[151]

The migration of larvae through the lungs can cause nodular radiographic changes. The vast majority of patients with pulmonary disease have abnormal chest

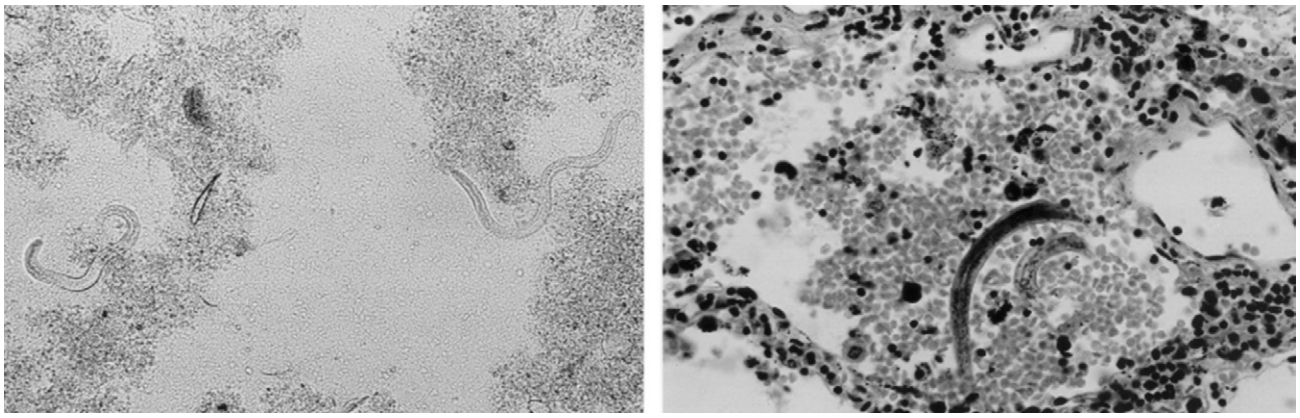

FIGURE 37-3 ■ *Strongyloides stercoralis* larvae identified in sputum (*left*) and in lung specimen taken at autopsy (*right*) in patients with *S. stercoralis* hyperinfection syndrome. (Courtesy of Dr. Franklin A. Neva.)

radiographs. In the Kentucky series,[133] 95% of the patients (18/19) had pulmonary alveolar, interstitial, or both opacities. These progressed to an ARDS pattern in half of the patients. The patient without parenchymal opacities had pulmonary symptoms and bilateral pleural effusions that responded to anthelmintic treatment. Pleural effusions were present in 40% of the patients and lung abscess in 15%.[133]

Treatment. Ivermectin, 200 μg/kg in a single dose and repeated after 1 week if necessary, is the drug of choice for strongyloidiasis. Albendazole, 400 mg daily for 3 days, is a less effective alternative.[145] Patients with disseminated disease or hyperinfection may require treatment for longer periods. There have been case reports of the successful administration of ivermectin per rectum,[152] or the administration of a veterinary preparation of ivermectin by subcutaneous injection,[153] as therapy for patients with ileus or intestinal perforation among whom enteral medications are not tolerated or absorbed. Supportive therapy and treatment of secondary bacterial infection is important. Of note, cyclosporine demonstrates an anti-*Strongyloides* effect,[154] and immunosuppressive therapy with this drug may protect against hyperinfection. It is necessary to treat all patients with strongyloidiasis, even if asymptomatic, because of the risk of later disseminated disease.

Prevention. The prevention of strongyloidiasis entails improving sanitation and hygiene and wearing footwear to prevent skin penetration. To prevent disseminated disease, vigilance in screening and treating asymptomatic and at-risk patients is appropriate. At-risk groups include patients from endemic areas with chronic lung disease, impaired cellular immunity, on corticosteroids, and those with malignancy or HTLV-1 infection. The best approach to identification of patients with occult infection, such as immigrants from endemic areas, has been debated. Screening for peripheral eosinophilia could be an effective approach,[148] but this strategy may miss those most vulnerable to severe disease who often do not have eosinophilia. Others argue that it may be more cost effective to treat all immigrants at risk of intestinal helminth infection with a 5-day course of albendazole without testing them for infection.[155]

Tissue-Dwelling Nematodes

Filarial Infections

Eight species of filarial parasites infect over 150 million people living in tropical and subtropical regions of the world. Adult worms of *Wuchereria bancrofti*, *Brugia malayi*, and *Brugia timori* inhabit lymphatic vessels and produce lymphatic obstruction with resulting elephantiasis and hydrocele. *Loa loa* adult worms reside in the subcutaneous tissues and cause periodic angioedema. Parasitic stages of *Onchocerca volvulus* migrate in the skin and eye and cause dermatitis and inflammation of the cornea, iris, and retina (river blindness). *Mansonella perstans*, *Mansonella streptocerca*, and *Mansonella ozzardi* occur less commonly. The major pulmonary manifestation of these parasites is TPE, seen in infection with *W. bancrofti* and *B. malayi*. Rarely, pulmonary manifestations occur in infections with *L. loa*,[156,157] but none has been documented in onchocerciasis with the exception of a single report in the English language literature of *O. volvulus* microfilaria found in the lungs and other deep tissues of a Zairian man who died of pulmonary edema after treatment of elephantiasis (lymphatic filariasis) with diethylcarbamazine.[158]

Bancroftian filariasis is found throughout tropical and subtropical regions of Africa, Asia, the Pacific Islands, South America, and the Caribbean. Brugian filariasis is more limited in range, being confined to India and East and southeast Asia. *O. volvulus* is endemic in parts of equatorial Africa, Central and South America, and the Arabian Peninsula. *L. loa* is found in central and west Africa.

Transmission. Filariae have five morphologically and physiologically distinct stages—humans are infected by third-stage larvae deposited on the skin by blood-feeding arthropod vectors. For the agents of lymphatic filariasis, the vectors include *Culex*, *Aedes*, *Anopheles*, and *Mansonia*, whereas *L. loa* is transmitted by *Chrysops* (deer flies) and *O. volvulus* by various blackflies of the *Simulium* genus. After infective larvae penetrate the skin, they molt twice and develop into adults over the course of 6 months to 1 year. Adult worms remain viable for 5 to 20 years depending on the filarial species;

first-stage larvae or microfilariae (250–290 μm in length) are released by fertilized female worms and find their way into the circulation in the lymphatic filariasis, to the skin in loiasis, and to the eye in onchocerciasis.

The microfilariae of *W. bancrofti* and *B. malayi* circulate throughout the bloodstream, with a characteristic periodicity that is coincident with the feeding habits of the mosquitoes that transmit them.[159] The other major blood-borne filarial pathogen, *L. loa*, has a diurnal periodicity, with microfilaremia peaking at midday.

Pathology and Pathogenesis. The usual pathology of the lymphatic filariae is lymphatic dysfunction and obstruction that can lead to lymphedema. In advanced disease, severe, deforming swelling (elephantiasis) can occur, including disabling hydrocele in men with *W. bancrofti* infection.[160] The lymphatic pathology is caused by "nests" of adult worms within afferent lymphatics, usually of the scrotum (in males), and in the axilla, breast, or groin (in females). Ultrasonographic studies have demonstrated that lymphatics containing live worms dilate at a rate of 1.2 mm/person/yr.[161]

In TPE, the pathology appears to be related to increased immune responsiveness to the parasite. In contrast to most patients with lymphatic filariasis, patients with TPE almost never have microfilariae present in the peripheral blood. It is hypothesized that as microfilariae enter the blood, they are opsonized and cleared on first pass through the pulmonary circulation. The clearance of microfilariae leads to an inflammatory process that initially results in recruitment of histiocytes and then eosinophils into the lungs, causing an eosinophilic alveolitis. An increased number of pulmonary eosinophils is significantly associated with decreased forced vital capacity.[162] These eosinophils are activated and have a degranulated morphology.[163]

With time, the eosinophil predominance shifts to one dominated by histiocytes and the resultant chronic alveolitis can lead to fibrosis that can progress to irreversible changes.[164,165] Histologic examination of lung biopsy material early in the disease process reveals microfilariae surrounded by histiocytes. Later, degenerating microfilariae can be seen within eosinophilic granulomas (Fig. 37-4).[166] Although other organs, such as liver, spleen, and lymphatics, can be affected, most of the clinical effects in TPE occurs in the lungs.[167]

Clinical Manifestations. The vast majority of people with lymphatic filarial infection remain asymptomatic or have subclinical pathology, especially if they are natives of an endemic area. Of those with symptomatic infection, most have evidence of lymphatic dysfunction (or obstruction), the initial presentation being fever with acute (retrograde) lymphangitis or adenolymphangitis.

The rare syndrome of TPE has a strong geographic bias, and is more likely to occur in south and southeast

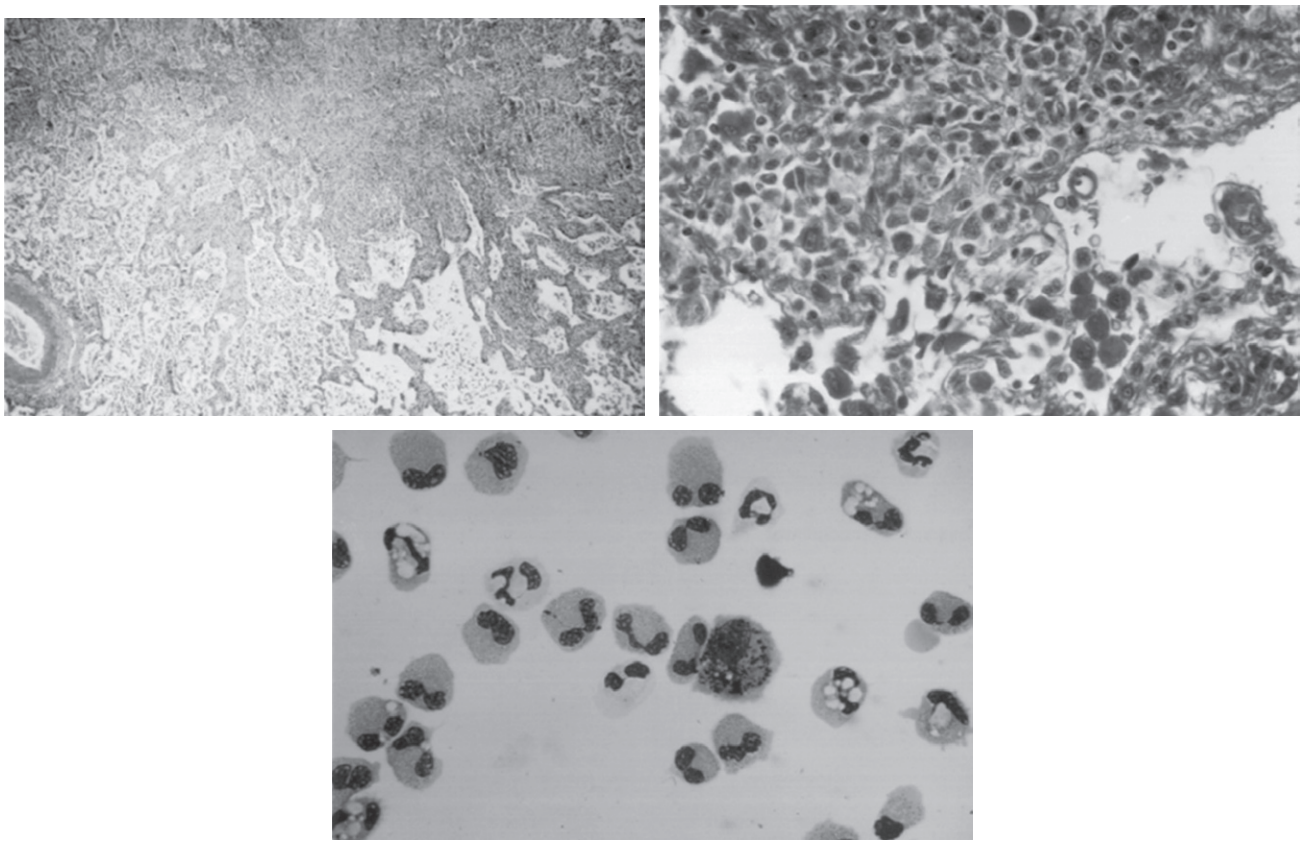

FIGURE 37-4 ■ Pulmonary specimens in tropical pulmonary eosinophilia (TPE). Hematoxylin and eosin–stained section of lung biopsy of patient with proven TPE at low magnification (40×) (*left*) and at higher magnification (160×) (*middle*). *Right,* A Wright-stained specimen from bronchoalveolar lavage from another patient with TPE shows numerous vacuolated and normal bilobed eosinophils.

Asia and Brazil. Males outnumber females by more than 4 to 1,[162,165,168,169] and although people of any age can develop it, it is more likely to occur during the third and fourth decades of life. Although precise incidence figures are not available, it is likely that significantly less than 0.1% of those infected with the lymphatic filarial parasites develop TPE (0.4% of 4282 school children in north India in 1 survey[170]). Whereas naive travelers to an endemic area are more likely to develop symptomatic infection resulting in lymphadenitis and hepatosplenomegaly, with acute lymphedema and eosinophilia,[171] TPE as a manifestation of filarial infection in travelers is rare.

Pulmonary Disease. TPE should be regarded as a systemic syndrome, with the pulmonary component being the most significant. Initially, patients complain of vague systemic symptoms, including low-grade fevers and myalgia. Then, pulmonary symptoms begin, which include cough and wheezing, both of which are worse at night, dyspnea, and occasionally chest pain. These symptoms are often mistaken for asthma, and patients may be incorrectly treated for more common disorders.

In the initial stage, obstructive pulmonary function is characteristic, and later, a restrictive pattern commonly predominates[169] as fibrosis develops.[162,165,172] A decreased diffusion capacity, with hypoxemia occurs in a minority of patients.[168] The pattern of disease progression is variable; symptoms can spontaneously remit and recur, or gradually worsen, with a decrease in the wheezing, but an increase in dyspnea. The condition eventually leads to chronic lung disease with dyspnea and hypoxemia at rest, which in later stages is indistinguishable from any cause of pulmonary fibrosis.[165] Rarely, TPE can present as cor pulmonale.[173]

Of the other common human filarial infections, aberrant migration of *L. loa* microfilariae has been reported to result in lung disease in rare cases.[157,174] A syndrome characterized by loculated eosinophilic pleural effusion has been described.[156]

Diagnosis. The definitive diagnosis of lymphatic filarial infection is made by filtration of peripheral blood to detect microfilariae or by finding adult worms in spermatic cord lymphatics or on biopsy. It is important to draw peripheral blood at a time coincident with the peak frequency of circulating microfilariae from 10 pm to 6 am for nocturnally periodic lymphatic filariae and noon for *L. loa*. A highly sensitive enzyme-linked immunosorbent assay (ELISA) is available to detect an antibody response to lymphatic filarial parasites.[175] This uses crude *B. malayi* adult worm extract as the antigen and is highly sensitive. In addition, a number of antigen tests are available for detection of circulating filarial antigen in bancroftian filariasis,[176] but not brugian filariasis. These include an immunochromatographic card test with greater than 99% specificity and only slightly less sensitivity than the ELISA for the same circulating antigen.

The diagnosis of TPE requires (1) a history of paroxysmal nocturnal dyspnea, (2) radiographic evidence of pulmonary opacities, (3) peripheral blood eosinophilia greater than 3000/μL, (4) elevation of serum IgE levels, (5) high levels of antifilarial antibodies, and (6) a rapid clinical response to antifilarial therapy with diethylcarbamazine . The antifilarial antibody values found in TPE are much higher than those of individuals with active filarial infection with or without microfilaremia. Circulating microfilariae are absent from night blood samples taken from patients with TPE. Examination of BAL of persons with TPE shows an alveolitis with eosinophils constituting more than 50% of the total cells recovered.[163] The eosinophils are activated with a reduction of granules and an increase of vacuoles, indicating the release of eosinophil granule proteins. The differential diagnosis includes other infectious and noninfectious causes of pulmonary disease with eosinophilia, such as other helminth infections, allergic granulomatosis with angiitis (Churg-Strauss), allergic bronchopulmonary aspergillosis, Wegener's granulomatosis, and the idiopathic hypereosinophilic syndrome.

Although chest radiographs of patients with TPE may be normal, the vast majority have small nodular opacities (1–3 mm) in a miliary pattern that can be confused with tuberculosis. Increased bronchovascular markings are often seen (Fig. 37-5).[164,169] Other radiographic patterns include lobar or sublobar consolidation, cavities, or pleural effusions, although these are less common.[177] High-resolution CT provides more detailed information. In a series of 10 patients with TPE, 3 were found on CT to have paratracheal adenopathy and 2 had bronchiectasis.[178] In hypoxic patients, ventilation-perfusion defects and mismatches are often found.[179]

Treatment. The majority of patients with TPE respond quickly to treatment with diethylcarbamazine (6 mg/kg orally daily for 12 days), although a significant

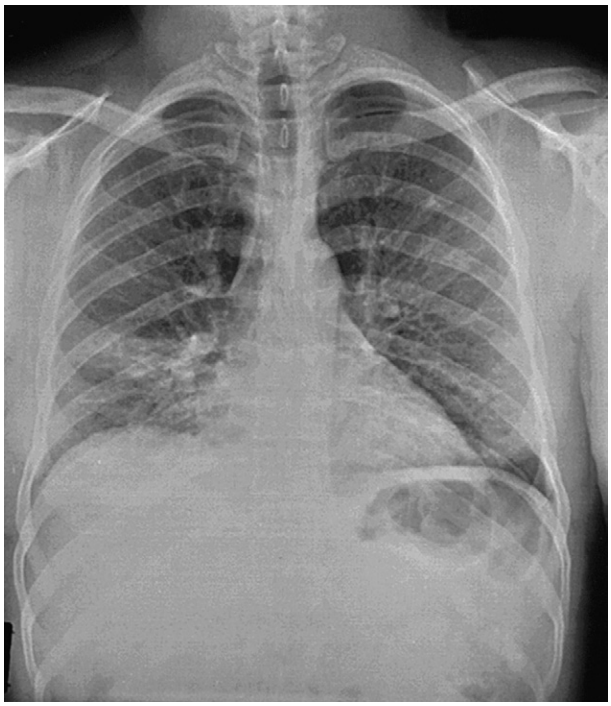

FIGURE 37-5 ■ Chest roentgenogram of a South Indian man with tropical pulmonary eosinophilia shows bilateral diffuse interstitial infiltrates.

percentage (12%–20%) fail to respond or their symptoms recur after treatment. These patients may respond to a course of treatment of longer duration (≤12 mg/kg for 30 days).[180] If, after diethylcarbamazine, patients remain symptomatic, an alternative diagnosis should be excluded. Of note, ivermectin, although effective for treatment of lymphatic filariasis, is not useful for treatment of TPE, probably because it has little effect on adult worms. Data have documented the effectiveness of doxycycline in lymphatic filariasis, through its ability to kill the endosymbiont bacteria *Wolbachia* and thereby lead to permanent damage to adult worms.[181] This indicates that the addition of a 6-week course of doxycycline to diethylcarbamazine is an appropriate, but yet to be proved, supplemental approach to treatment of TPE.

Although symptoms often improve with treatment, and the level of eosinophils and immunoglobulins in BAL fluid quickly decreases,[163] the abnormalities in pulmonary function tests, especially diffusion capacity, do not always return to baseline and can persist for at least 1 month after treatment.[168]

Prevention. Lymphatic filariasis eradication programs based on mass drug administration are ongoing in many of the endemic regions of the world. As these reduce the prevalence of lymphatic filariasis, the incidence of TPE should decrease as well. In the meantime, travelers to endemic areas can take diethylcarbamazine as a prophylactic measure.

Dirofilariasis

Dirofilaria immitis, or the dog heartworm, is an uncommon but well-recognized cause of pulmonary nodules (or "coin lesions") in humans. It is a mosquito-transmitted filarial infection primarily of dogs, with humans being an incidental or dead-end host of this parasite. Whereas most human cases have been reported in the United States, where *Dirofilaria immitis* is found in dogs of all states except Nevada, it has also been reported from many countries including Japan, Brazil, Australia, Italy, and the Netherlands.[182–186] With the increasing use of heartworm prophylaxis for domestic dogs, the incidence of dirofilarial infection in dogs appears to be falling. In the United States, the parasite is concentrated along the Atlantic seaboard and the southeast.

Transmission. The definitive hosts of *D. immitis* (or rarely, *D. repens* in the Old World[184]) are dogs and other carnivores (e.g., cats, wolves, sea lions). Adult worms live within the right ventricle of the animals and release thousands of microfilariae into the bloodstream daily. Mosquitoes of the genera *Anopheles*, *Aedes*, and *Culex* take up the larvae during a blood meal, and the microfilariae develop within the mosquito into infective larvae. When the mosquito bites again, the larvae enter a new host and find their way into the circulatory system where they molt and mature into adults. In humans, the larvae are unable to complete their life cycle and rarely make it through the subcutaneous tissue. If a stray larva is able to enter the circulation, it remains immature despite reaching the heart. Once the larva dies, it is swept into the pulmonary artery, where it embolizes in a distal arteriole.[183]

Pathogenesis. The pathology associated with pulmonary dirofilariasis is related to the infarct caused by the embolization of the parasite and the inflammatory reaction that occurs in response. The infection per se is self-limited.

On pathologic examination, the nodules that are formed are firm, well-circumscribed granulomas, 1 to 3 cm in diameter, grayish-yellow and noncalcified. They have central necrosis with a surrounding wall of fibrous tissue composed of epithelial cells, eosinophils, plasma cells, and lymphocytes, with a few giant cells. Parasite remnants can be found within the granulomas within a pulmonary artery. There may be one or several parasites in one nodule. The surrounding lung tissue and vessels may show evidence of inflammation with surrounding eosinophilic pneumonitis and endarteritis. Although the nodules are commonly subpleural, pleural thickening is present in a minority of cases.[185,186]

Clinical Manifestations and Pulmonary Disease. The majority of patients (54%–59%) with dirofilariasis are asymptomatic.[182,186,187] Nodules are usually incidental findings, most often observed in men in their 50s and 60s. Of those who are symptomatic, the most common symptoms are cough, chest pain, fever, and malaise. Hemoptysis, especially of significant amounts, is extremely uncommon.[186]

Diagnosis. Pulmonary dirofilarial infection usually presents as an incidental finding on a routine chest radiograph obtained for other reasons. The nodules are usually round, solitary (75%),[186] well-circumscribed, and in the periphery of the lower lung fields, most commonly on the right (76%), although they can occur in any lobe. A minority of patients will have multiple nodules, either unilateral or bilateral.[187,188] Pleural effusion can occur, but is rare.[188] CT allows for better definition of nodules, and contrast CT may suggest dirofilariasis if it shows a pulmonary artery entering a density without pleural involvement and speculations.[167]

Unfortunately for such a benign disease, the diagnosis of dirofilariasis is usually not considered or made except by excisional biopsy of the nodule. Because the differential diagnosis includes malignancy, and because people obtaining routine chest radiographs are older adults at higher risk for malignancy, surgery is generally necessary to rule out malignancy. Needle biopsy is usually not successful in making the diagnosis, although in two cases, its successful use in prevention of a more invasive procedure was reported.[189] Finding the parasite embolized within a pulmonary artery establishes the diagnosis. Because the worm can be degenerating, it may be easier to see with silver staining or with specific antibody probes.

Eosinophilia is seen in only a minority of patients (7.5%–10%),[186,187] with the average eosinophil percent only 5%. Serologic tests for *D. immitis*, although available, are not widely used and are rarely clinically useful.

Treatment. No treatment is necessary because there is no active ongoing infection. There is no known complication from this infection.

Prevention. The only ways to prevent this disease in humans are to decrease its prevalence in dogs or to decrease the prevalence of the mosquito vector.

Trichinosis

Trichinosis is a zoonotic infection caused by nematodes belonging to the genus *Trichinella*. *T. spiralis* was the species originally described to be transmitted to humans by domestic pigs. To date, a total of seven species have been reported to infect humans.[190] *Trichinella* spp. are the only nematodes known to occupy an intracellular location in the host and are transmitted only by consumption of contaminated meat. They are found on all continents and climates. The disease is much more common in Europe than in the United States, with 20,000 cases reported in Europe in the 10 years between 1991 and 2000,[190,191] compared with 230 cases reported in the United States in the 5-year interval between 1991 and 1995.[192]

Transmission. *Trichinella* completes its life cycle within a single host. When a person eats undercooked contaminated meat (most often pig, boar, horse, or bear), digestion of the meat in the stomach and intestine releases the encysted larvae. The larvae invade the intestinal wall and live under the columnar epithelium. There, they molt several times to become adults. Fully developed adults form within 5 to 7 days of infection. It is believed that adults only live within a human host for several weeks before they are expelled from the intestine. The adults, however, release larvae that invade the intestinal epithelium and enter the circulation. The larvae travel to muscles, where they invade muscle cells. Once a larva has entered a muscle cell, it molts again into an infective stage and starts to encyst. The infected muscle cell transforms into a "nurse cell," which provides the larva with the nutrients it needs to grow. As time progresses, the larval capsule becomes thicker. In nonhuman mammals, the cycle starts again when another carnivore eats the muscle of the host.

Pathogenesis. The parasite invading the intestinal lumen results in a local influx of eosinophils and mast cells. As the second-generation larvae migrate throughout the body, more eosinophils are recruited into areas where larvae reside, including around the nurse cell. Degeneration of muscle fibers with increased vascularity can be seen. With time, the encysted larvae die within the muscle and calcify.[190,193]

Clinical Manifestations and Pulmonary Disease. The symptoms attributable to trichinosis depend on the infectious burden, the host immune status, and the species of parasite. The incubation period ranges from 6 to 30 days.[190,194,195] As the larvae excyst and invade the intestinal wall, malaise, abdominal pain, fever, nausea, vomiting, and diarrhea, which can be persistent and voluminous, ensue. Although the typical duration of the enteral phase is 2 to 7 days, it can persist for weeks and overlap with the parenteral phase. As the larvae invade muscle cells, more characteristic features develop, which include facial or generalized edema, especially periorbital, remitting fever that lasts for several weeks, myalgia, and muscle weakness. Symptoms can be sufficiently severe to interfere with walking, arms movement, speaking, or breathing. Myocarditis can occur as cardiac muscle cells are infected and can lead to heart failure, arrhythmia, or sudden death. The central nervous system is involved in a minority of patients, with meningoencephalitis the most common manifestation of neurotrichinosis. Although the lungs are rarely directly involved in trichinosis, involvement of the diaphragm and other muscles of respiration can lead to dyspnea and, rarely, respiratory failure.[196,197] Cough and hoarseness can also occur, as can secondary complications such as bronchopneumonia and pulmonary embolism.

Diagnosis. A definitive diagnosis of trichinosis is made by histologic demonstration of larvae in a muscle biopsy. This can be facilitated by enzymatic digestion of the biopsy to locate the larvae. Digestion can only be undertaken once larvae have had time to encyst. Of note, the two *Trichinella* species *T. pseudospiralis* and *T. papuae* do not encyst, and so have to be more carefully isolated. Because of the invasive nature of muscle biopsy, it is not recommended unless the results of other tests are equivocal.[190]

Laboratory tests that are typically abnormal in trichinosis include those associated with muscle damage, an elevated creatinine kinase and lactic dehydrogenase, elevated total white blood cell count and eosinophilia in a majority of patients, and high levels of serum IgE. Serologic identification of *T. spiralis*–specific antibodies is a useful diagnostic test.[198] Molecular methods, including PCR and DNA sequence analysis are useful to speciate the organism if found in muscle and may provide useful epidemiologic information.[199]

Treatment. Controversy exists as to whether treatment alters the course of the infection. In one trial undertaken in Thailand during an outbreak, a faster resolution of symptoms and normalization of laboratory abnormalities was observed among patients who received mebendazole or thiabendazole compared with those treated with placebo.[197] The current recommended treatment for trichinosis is albendazole 400 to 800 mg orally per day (in one or two doses) for 7 to 14 days.[200] However, the optimal duration of treatment has not been reliably established. Because chemotherapy is only effective against larval stages, and only before they have become encysted in the muscle, early administration of treatment is recommended. In patients with significant symptoms secondary to the host reaction, a short course of corticosteroids given concurrently with the anthelmintic drug may be beneficial.

Prevention. The prevention of trichinosis in humans is dependent on its eradication from the food supply. Meat inspection is the first line of defense: meat sold commercially should be inspected prior to release. Such procedures are well established in developed countries, but in countries where oversight of slaughterhouse practices is less robust, infected meat may enter the human food supply.[201] For meat not obtained commercially (e.g., game, wild animals), educating people to freeze it or to adequately cook it (internal temperature of at least

60°C for at least 1 minute) will reduce the incidence of this emerging zoonotic infection.[194]

Visceral Larva Migrans

Visceral larva migrans (or toxocariasis) is a zoonotic infection caused primarily by infection with the dog and cat roundworms (ascarids), *Toxocara canis* and *Toxocara catis*. Other animal species (including other *Toxocara* spp., *Capillaria*, and *A. suum*) may rarely cause the syndrome.[202] An emerging infection in some parts of the world, it is likely an underreported and underrecognized disease owing of the difficulty of diagnosis. Overall seroprevalence in the United States is 2.8%, although this varies by age (6.4% in children), race, socioeconomic status, and region. In some parts of the world, the prevalence is much higher, reaching up to 80% in children in some areas.[203]

Transmission. In their natural hosts, the life cycle of these organisms is like that of *Ascaris* in humans. The adults live in the intestine, where they shed eggs into the stool. The eggs embryonate in moist soil and then are ingested by the next host where they hatch into larvae. The larvae migrate to the lungs via the circulatory system and then molt. The developing larvae travel up the trachea, to the epiglottis, and are swallowed. In the intestine, the larvae molt again into adults. Fertilization of the adult females leads to egg production and recommencement of the cycle.[167] In many species the infection can also be transmitted transplacentally; thus, puppies represent a major sources of eggs.[204] Humans become incidental hosts when they ingest food contaminated with the eggs. Children are at higher risk of ingesting the eggs because they may exhibit pica or geophagia[205] and because they are more likely to eat with soil-contaminated hands. They can also come into contact with infective eggs in contaminated sandboxes or playgrounds.[204] Having had a dog or a cat increases a child's risk of being seropositive for *Toxocara* antibodies, but does not necessary represent infection.[206] When the larvae hatch from the eggs in humans, they penetrate the intestinal mucosa and begin migrating. Because these nematodes are unable to complete their life cycle within humans, larvae can migrate throughout the body for months or years, leading to the clinical features of this infection.[204]

Pathogenesis. The pathology of visceral larva migrans is attributable to hypersensitivity (or inflammatory) responses to the migrating larvae.[204] The damage done and symptoms depend on the organ that is invaded during migration. It is also dependent on the size of the inoculum and the frequency of reinfection.[203]

In experimental animals, within the first 2 weeks of infection, there is an acute inflammatory reaction, with recruitment of eosinophils and neutrophils. One month after infection, an early collagenous capsule covers the larvae and larval tracks. Later, the larvae are encapsulated within eosinophilic granulomas. Larvae typically cannot be identified in most of the granulomas found, suggesting that they have undergone degeneration or else the granuloma has formed around larval antigens.[203] The liver, lungs, central nervous system, and eyes are the organs most commonly affected. In the lungs, *T. canis* induces airway inflammation, increased pulmonary resistance, and decreased compliance**.** Histologically, there is perivascular and peribronchial edema.[167] Protective immunity, if it occurs, is slow to develop,[204] and thus reinfection can occur.[207]

Clinical Manifestations. Most people who are infected with *Toxocara* spp. remain asymptomatic. Symptoms depend on the intensity and frequency of infection, the distribution of larvae in tissues, and the inflammatory response of the host.[203] Two clinical syndromes of infection are well-recognized: visceral larval migrans or ocular larval migrans. The clinical features of visceral larva migrans are related to the organ invaded, most commonly the liver, lung, or other thoracic or abdominal organ. Visceral larva migrans usually affects children younger than 5 years old, although it can affect adults.[208] In a study of children with visceral larva migrans and eosinophilia, 86% had pulmonary symptoms, 80% had fever, and 28% had seizures. On examination, 65% had hepatomegaly; 43% had an abnormal pulmonary examination (wheezes or crackles); 39% were malnourished; and 45% were anemic, although many of these children had concurrent infections with other intestinal helminthes.[202] Rarely, disease can manifest as myocarditis, nephritis, encephalitis, or seizures. Ocular larva migrans usually occurs in older children (average age is 8 yr) and may represent a lower infectious inoculum. In the eye, the granulomatous reaction can impair sight and be confused with retinoblastoma, often necessitating enucleation. Visceral larva migrans and ocular larva migrans rarely occur at the same time or in the same person. So-called covert toxocariasis is thought to be due to long-term subclinical infection. Symptoms are nonspecific. They may include asthma, urticarial rash, arthralgia, adenitis, weakness, dizziness, abdominal pain, anorexia, nausea, vomiting, and sleep and behavioral disturbances.[167,203,204,208]

Pulmonary Symptoms. Between 33% and 86% of people with visceral larva migrans are found to have pulmonary symptoms.[202,203] The most common symptoms are chronic cough, which may be paroxysmal and worse at night, and wheezing. The chest radiograph may be abnormal. Rarely, severe eosinophilic pneumonitis of *Toxocara* has caused respiratory failure.[209,210] Other manifestations include chronic eosinophilic pneumonia that is responsive to albendazole[211] and noncavitating pulmonary nodules with eosinophilia and liver and renal nodules.[212] A Dutch study of children with asthma found a correlation with anti-*Toxocara* antibodies.[206] Seropositive children were also more likely to have an allergic reaction after exposure to animals, and greater allergen-specific IgE, suggesting that *Toxocara* stimulated the production of allergen specific-IgE.[206]

Diagnosis. Diagnosis of human toxocariasis relies on clinical and serodiagnosis. It should be suspected in any child with unexplained fever and eosinophilia, especially if a history of pica and hepatosplenomegaly is also present.[204] Parasitologic diagnosis by detecting *Toxocara* larvae by biopsy is not feasible. In most serodiagnostic tests, excretory-secretory antigens from *T. canis*

second-stage larvae are detected by ELISA.[213,214] Although this test has a reasonable sensitivity (73%) and specificity (92%),[215] cross reactivity with other helminth infections can occur.[214,216–218] Others have reported a higher specificity and sensitivity (92% and 78%, respectively).[203] In areas where the baseline seroprevalence is relatively high, serologic tests may not be as useful.[219]

Patients with visceral larva migrans may have hypergammaglobulinemia, with elevations of total immunoglobulin, IgG, and IgM.[202] Eosinophils and total IgE are greater in seropositive children, regardless of symptoms.[206]

Treatment. Although visceral larva migrans is generally benign, and usually resolves without specific anthelmintic therapy, the recommended treatment is albendazole 10 mg/kg/day in two divided doses for 5 days (for adults, 400 mg twice a day).[204] Corticosteroid therapy may be useful to decrease the inflammatory responses in patients with severe symptoms.

Prevention. Prevention of toxocariasis depends on decreasing exposure to eggs. Covering sandboxes at night, routine deworming of dogs and cats, and decreasing geophagia are all methods to decrease egg shedding and exposure. In some areas, sandboxes have been removed from public playgrounds in order to decrease infection rates.

Pulmonary Capillariasis

The syndrome of pulmonary capillariasis is a very rare event in humans, occurring through zoonotic infection with the nematode parasite *Capillaria aerophila* (synonyms, *Eucoleus aerophilus*, *Thominx aerophilus*).[220,221] It is a nematode that parasitizes the respiratory tree of a variety of carnivorous mammals. Manifestation of accidental infection of humans include cough productive of mucoid or blood-tinged sputum, fever, dyspnea, and eosinophilia. Diagnosis can be made by detecting characteristic eggs in sputum or feces. In a recent case report, the presentation resembled that of bronchial carcinoma.[220] It has been documented in Russia, Ukraine, Morocco, Iran, France, and Serbia.[220] Because a limited number of human infections have been documented, the incubation period is unknown, although some authors believe that it could be similar to the prepatent period in animals (i.e., 25–40 days). Although experience in the treatment of human infection is limited, mebendazole and albendazole have been shown to be effective.[220]

Echinococcosis

Echinococcosis is caused by one of two species of small animal cestodes: *Echinococcus granulosus*, the dog tapeworm, causing cystic hydatid cyst disease, and *E. multilocularis*, the fox tapeworm, causing alveolar hydatid disease. The life cycle requires two hosts for its completion, a canid definitive host and an intermediate host, typically a sheep, goat, kangaroo, or a range of other animals. It has a global distribution, with well-described regions of high prevalence, including in the Mediterranean area, South and Central America, Russia, China, and sub-Saharan Africa.[222,222a] *E. multilocularis*, the fox tapeworm, has a sylvatic life cycle whereby foxes and other carnivores are definitive hosts and the intermediate hosts are rodents and small mammals. Alveolar echinococcosis is endemic in the Northern Hemisphere, particularly at high latitudes in Europe, China, and northern Canada and Alaska. Although *E. granulosus* is more commonly a cause of human disease, *E. multilocularis* is the more pathogenic of the two major species.

Transmission. In the normal life cycle, adult worms live in the intestines of the definitive host and shed millions of eggs with the stool. When an intermediate host ingests an egg, a larva emerges, penetrates the intestinal mucosa, and migrates through the blood or lymphatics to target organs. Larvae usually lodge in the liver or lung (or less commonly, other organs or the body wall), become metacestodes that create vesicles that enlarge over time, eventually forming a mature hydatid cyst. Within the hydatid cyst are multiple brood capsules and protoscolices. When the cyst is ingested by the definitive host, the adult tapeworm develops.[222,223] Humans are incidental intermediate hosts when they ingest eggs from infected dogs through contaminated hands or by consuming contaminated food or water.

Pathology and Pathogenesis. In echinococcosis, the cyst comprises three layers: The inner endocyst is the germinal layer with a nucleated syncytial layer that forms brood capsules and protoscolices. The middle layer, or exocyst, is a carbohydrate-rich acellular hyaline laminated layer that is also parasite-derived and porous to nutrients. The external pericyst is a host-produced fibrous adventitial layer felt to be a by-product of the initial immune response to the cyst. Daughter cysts may form within the larger cyst.[222,223] The interior of an intact cyst contains clear fluid with "hydatid sand": remnants of hooklets, protoscolices, and brood capsules. Cysts expand at a rate of 1 cm per year in the liver, faster (1–5 cm/yr) in the lung.[223,224]

The liver is the organ most commonly affected (in 60% of cases); the lungs are the second most common, affected in 20% to 30% of cases. In pulmonary hydatid disease, the cyst can be anywhere in the lung but has a predilection for the right lobe (54%–63% right vs. 37%–46% left), and for the lower lobes (52%–67.5%) (Fig. 37-6). Children are more likely to have pulmonary disease than adults. Single cysts are most common (72%–83%), with unilateral multiple cysts being found in 10% to 15% of cases and bilateral cysts in 6% to 13%. Among those with pulmonary hydatid disease, the liver may also be involved 10% to 40% of the time.[223,225–229] Cysts can also involve the chest wall as well as the lung parenchyma.[230]

Whereas lesions caused by *E. granulosus* are well circumscribed and defined, *E. multilocularis* lacks the external thick host-derived capsule and proliferates slowly, exhibiting tumor-like behavior, which can invade tissues and metastasize to distant sites. The liver is most commonly affected (97%), but it invades or metastasizes to the lung in about 10% of cases.[231]

With an intact cyst, most of the pathology results from the space-occupying lesion, mechanical compression of nearby structures. Pulmonary tissue surrounding the cyst

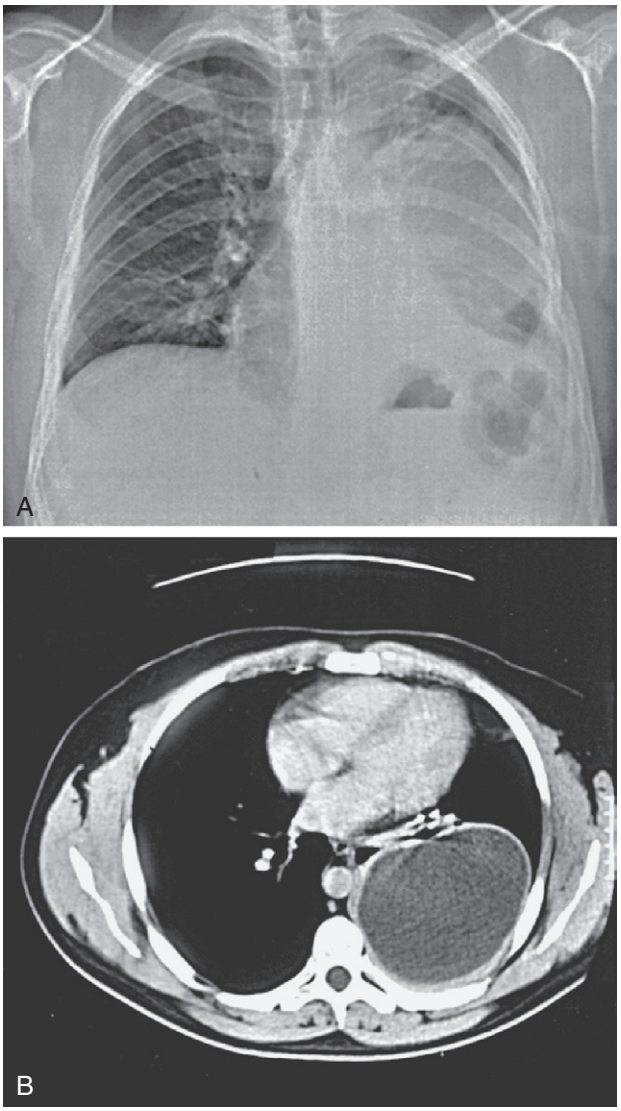

FIGURE 37-6 ■ Chest roentgenogram (**A**) and computed tomography (CT) scan (**B**) of a Peruvian man who had had a left lower lobectomy for hydatid disease and now has a recurrent hydatid cyst in the remaining left lung.

may be normal, be compressed with atelectasis, or have chronic inflammation and fibrosis.[224,225] When a cyst leaks or ruptures, an inflammatory reaction can develop. In its most severe form, it can present as anaphylaxis due to preexisting hypersensitivity to antigens present in cyst contents. If protoscolices are released with cyst rupture, disseminated disease may occur, leading to multiple secondary cysts.

Clinical Manifestations. Infection with *Echinococcus* is generally asymptomatic for months to decades. Cysts are commonly found when compressive symptoms develop, the cyst ruptures, or on routine imaging. For *E. multilocularis*, the latent period is assumed to be at least 5 to 15 years because of the very small numbers of patients younger than 20 years old found to have this form of the disease (2.1% of 559 patients).[231] Symptoms develop through one of one of three pathogenic mechanisms: (1) mechanical pressure or deformation of tissues or nearby vascular structures; (2) rupture or leakage of the cyst; or (3) superinfection. Alveolar echinococcosis causes more severe disease with a greater than 95% mortality among untreated cases within 10 years of diagnosis.[232]

Pulmonary Symptoms. Pulmonary symptoms occur in 67% to 89% of patients with pulmonary cysts. The most commonly reported symptoms are cough, fever, and chest pain.[226,229] Occasionally, hemoptysis can occur, and rarely, bilioptysis, pneumothorax, or pleuritis.[222] With rupture of the cyst into a bronchus, hydatid vomica of cystic contents can occur: clear, salty and peppery fluid with or without hemoptysis. The fluid can be purulent if superinfected. With airway dissemination of the antigenic fluid, respiratory failure or anaphylaxis can occur. One third of diagnosed cases of pulmonary hydatid cyst present following cyst rupture or the development of secondary cyst infection. Cysts can also rupture into pleura; in one study, this occurred in 5% of 400 individuals studied.[225] More rarely, rupture can occur into other mediastinal structures such as the myocardium, which has been reported to occur in 0.5% to 2% of all hydatid cysts.[233] Invasion of the aortic wall causing aortic rupture and pseudoaneurysm formation is very rare and has been described in less than a dozen cases.[234]

Hydatid pulmonary embolism can occur as a result of a hepatic or abdominal cyst rupturing into the hepatic vein, the inferior vena cava, or directly into heart. This event can be acute and fatal or subacute and result in progressive pulmonary hypertension.[235–238]

Diagnosis. The diagnosis of echinococcosis is generally made by clinical history and pathognomic radiologic findings. A history of exposure to dogs, especially in sheep-raising areas, is often, but not always, present for cystic disease. On plain radiograph, if intact, the cyst appears as a homogenous opacity with a well-demarcated margin. In the lung, following bronchial rupture, air can appear in the cyst; with the evacuation of some of the fluid and collapse of the membrane onto the residual fluid, resulting in the well recognized "water lily" sign. With rupture into the pleural cavity, a hydrothorax or a hydropneumothorax can occur.[225] Calcification occurs commonly in hepatic cysts after 5 to 10 years, but it is less common in pulmonary cysts. Alveolar echinococcosis can show radiologic evidence of calcifications within the structure.[223] Ultrasound is the diagnostic modality of choice in abdominal hydatid disease; it is less useful in pulmonary disease. CT better defines cysts than plain chest radiographs, revealing not only their cystic nature but also the density of the fluid within them and their shape. An "inverse crescent sign" appears when air dissects posteriorly separating membranes, without anterior extension; air within the wall of the cyst can create a signet ring appearance.[227]

With MRI, the image depends on whether the cyst is unilocular or multilocular and on the developmental stage of the cyst. In most situations, the capsule is well-defined, with low signal intensity on T2 images (and indistinct in most patients on T1). The daughter cells are, however, better seen on T1-weighted images.

Complicated cysts may not have the characteristic signal of hydatid disease.[239] If a hydatid pulmonary embolism is suspected, the diagnostic techniques of choice are an echocardiogram, a spiral CT, or MRI.[235] Bronchoscopy is not recommended because of the risk of cyst rupture, except if necessary to exclude malignancy.

Serologic tests to evaluate for echinococcosis are available. In a comparison of six different serologic tests (latex agglutination, passive hemagglutination, immunoelectrophoresis, specific IgE, IgM, and IgG ELISA), hydatid antigen-specific IgG was the most sensitive and specific test in pulmonary echinococcosis (83.5% and 99.5%, respectively). The sensitivity of serology increases in patients with multiple cysts, and the test is positive in 96% of patients with both liver and pulmonary cysts.[225,240] Tests based on antigen components of hydatid cyst fluid have not been shown to increase sensitivity or specificity.[241] Serologic tests for alveolar echinococcosis are more sensitive and specific than tests for cystic disease, because they are based on purified species-specific antigens.[222]

Treatment. The recommended treatment for resectable pulmonary hydatid cysts is surgical removal, if possible. Surgery allows for eradication of the parasite, prevention of the complications of rupture, and removal or closure of the cavity. Importantly, medical therapy with adjuvant albendazole therapy should be undertaken before and after surgical resection. It should also be used in the perioperative period to prevent dissemination of viable protoscolices if inadvertent cyst rupture occurs during surgery. Anthelmintic therapy prior to surgery has been shown to decrease the risk of recurrent disease by 3.5 times.[242] The recommended albendazole regimen is 10 to 15 mg/kg/day in two doses at least 4 days prior to surgery and continued for at least 1 month after surgery.[243] In one study, a combination of albendazole and praziquantel (25 mg/kg/day) for 1 month prior to surgical removal of the cysts was more scolicidal than albendazole alone.[244]

Patients who are not operative candidates may benefit from medical therapy; 28% to 45% are reported to be cured and 45% to 51% show improvement after a prolonged course of albendazole, compared with patients not receiving anthelmintic chemotherapy who were reported to show improvement in 15% to 25% with no cure.[245,246] A nonsurgical drainage technique, termed PAIR (puncture, aspiration, injection, and reaspiration), whereby a scolicidal agent typically hypertonic saline is injected into the cavity and then aspirated, has been developed for hepatic cysts. However, PAIR for pulmonary cysts is not recommended.

Treatment of alveolar echinococcosis entails radical surgical excision with wide margins, as would be undertaken for a malignant tumor, if possible. In cases in which complete resection is not possible, prolonged treatment with albendazole, usually for life, is necessary. Because long-term therapy with albendazole can cause significant hematologic toxicity and hepatotoxicity, regular monitoring of blood count and liver function is appropriate.[247] Positron emission tomography may be useful in determining if cysts are metabolically inactive and thus help assess the efficacy of medical treatment.[248] For patients with alveolar echinococcosis that is not responding to albendazole, or where the drug is not tolerated, alternative salvage treatment with nitazoxanide[249] or amphotericin B may be possible.[250]

Prevention. Prevention of hydatid cyst disease involves decreasing the prevalence in the definitive host by deworming dogs, preventing them from eating cysts contaminating intermediate hosts (commonly by preventing farm dogs feeding on offal), and improving hygiene and sanitation in endemic areas. An effective vaccine for dogs has been developed[251] but is not commercially available.

Paragonimiasis

Paragonimiasis is caused by a trematode flatworm of the genus *Paragonimus* and is commonly referred to as the lung fluke. Humans are incidental hosts of this parasite that typically infects other carnivorous animals. Although 43 species of *Paragonimus* are recognized, only 12 have been reported to infect humans of which *P. westermani* is the most prevalent, especially in eastern and southeastern Asia. Paragonimiasis occurs worldwide, the most endemic areas being in Asia, West Africa, and parts of Central and South America.[252] In the United States, most cases are imported and are seen among immigrants and visitors from east and southeast Asian countries where the parasite is endemic.[253] However, infection can be acquired in North America because *P. kellicotti* exists in the midwestern and eastern United States and infects crayfish and a variety of carnivores.[254–256a]

Food preparation practices that lead to ingestion of raw, undercooked, or pickled crabs (crabs soaked in wine, "drunken crabs") or crayfish increase the risk of infection. Infection can also be transmitted by contaminated utensils or raw juice from the infected crustaceans.

Transmission. *Paragonimus* spp. have a complex life cycle involving freshwater snails, crustaceans, and mammals. Humans, when infected, are accidental definitive hosts for the fluke, taking the place of other crustacean-eating mammals. Adult worms live in the definitive host (e.g., canines, felines, otters, boars, skunks) and lay eggs that are shed with feces. In fresh water, the eggs hatch into miracidia that can infect snails. The next life cycle stage, the cerceria, is released from the infected snail; these then infect the next intermediate host, generally crabs or crayfish. Larvae develop within these invertebrates into encysted metacercaria. Humans or other definitive hosts become infected when they ingest infected raw or undercooked crustaceans or infective material contaminating utensils or other food. Once the larvae reach the small intestine, they excyst and penetrate into the peritoneum. They then migrate through the diaphragm and pleura into the lungs. There, worm pairs encyst together near bronchial passages and mature into adult worms that begin egg laying 5 to 6 weeks after infection. When the cysts rupture into a bronchiole, they are expectorated or swallowed and shed with the feces. If they reach fresh water, the cycle starts again. Paratenic animals, carnivores in which the metacercariae do not

develop (e.g., wild boars in Japan), harbor the infection and can serve as vehicles for transmission to humans.[254,257,258]

Pathogenesis. The clinical features of paragonimiasis initially arise through the migration of the worms through the body, causing a hemorrhagic and inflammatory response to the worms and their secreted antigens. As the parasite traverses the pleura, an exudative pleural effusion can form that has an eosinophilic predominance that is likely mediated by IL-5.[259,260] The histologic appearance of lung lesions in the acute phase is that of eosinophilic pneumonitis.[261] Once in the lungs, the parasite encysts and becomes walled off from the immune system. The cyst wall progressively becomes thick and fibrous. Most cysts are connected to, or in communication with, a bronchiole, into which eggs are released. Release of cyst contents or eggs into the lung parenchyma triggers an inflammatory reaction with local bronchopneumonia and granuloma formation. Once the parasite eventually dies, the cyst evolves into a fibrotic scar that may calcify.

Occasionally, the metacercariae can aberrantly migrate to other organs; the central nervous system is the most common extrapulmonary site of disease, and flukes may be present in the central nervous system of 1% to 24% of patients with lung disease.[262] Patients with paragonimiasis typically have high levels of eosinophils in the blood, pleural fluid, and in BAL washings. They also have elevated levels of IL-5 when compared with noninfected persons.[258]

Clinical Features. Paragonimiasis is rarely a serious or fatal infection. Symptoms depend on the location of the worms and their developmental stage. Shortly after infection, patients may complain of diarrhea or abdominal discomfort, although most people are asymptomatic in the initial phase, with symptoms generally commencing 6 to 27 months after infection.[252] Acute symptoms are caused by migration of metacercariae and their encystation. The initial migration of the larvae through the diaphragm and pleura can cause pleuritic chest pain and pneumothoraces. Chronic symptoms are due to the presence of the encysted worms and rupture into the airways. The infection can cause chronic debilitating symptoms that last for years.[263] The clinical manifestations and the amount of extrapulmonary manifestations appear to depend in part on the causative species. A minority of patients have fever, and patients may remain asymptomatic, with the diagnosis made incidentally.[259] Whereas aberrant migration of *Paragonimus* can occur, full maturation into the egg-laying stage cannot occur in tissues other than the lung. Whereas the majority of aberrantly migrating parasites do not cause symptoms, some can cause disease depending on the location. Parasites in the brain can cause headache, dizziness, and visual disturbances. Chronic cerebral paragonimiasis can manifest as seizures, paralysis, or mental impairment.[262] Occasionally, paragonimiasis can manifest with subcutaneous nodules.

Pulmonary Manifestations. Symptoms of paragonimiasis include cough (62%–100% of patients), hemoptysis (61%–95%), and chest pain (38%–94%).[258,263] The hemoptysis is usually rusty or chocolate-colored sputum; hemoptysis with large volumes of fresh blood is unusual. Pleural effusions can form and, if large, can result in dyspnea. Chronic infection is often mistaken for tuberculosis, especially in areas where paragonimiasis is less prevalent. However, in some instances, tuberculosis and paragonimiasis can coexist.[264] The physical examination is usually normal, although crackles may be heard. Rarely, finger clubbing is present.[262]

Diagnosis. A key clue to the diagnosis of paragonimiasis is a history of handling or eating freshwater crabs or crayfish, especially if raw or undercooked. Isolating *Paragonimus* eggs in the sputum or stool makes the diagnosis. Because of the low yield in a single sputum sample, the examination of multiple samples may be necessary to establish the diagnosis. Although the diagnostic yield is greatest from the examination of sputum, parasitologic examination of stool is also useful.[263] The eggs are golden brown and operculated.

Serology, based on an immunoblot assay using crude antigen from whole worm, is available from the CDC. This test is especially useful in patients with ectopic disease in whom eggs are not present in sputum or stool. A skin test using whole worm antigen has been developed but is not generally available. Although less specific than the immunoblot assay, it was reported to be a good screening test in areas where laboratory tests are not readily available.[263] Cytologic and biochemical examination of the pleural fluid reveals an exudate with an eosinophil predominance. It is usually sterile without ova being present. Other laboratory tests are nonspecific. Eosinophilia and an elevated IgE and other inflammatory markers are common.[258]

The radiographic appearance of paragonimiasis may include nodules, pneumothoraces, interstitial opacities, cavities, and ring cysts resembling bronchiectasis (Fig. 37-7).[252,255,261] The chest radiograph can be normal in 10% to 20% of cases.[256] The most common findings are pleural abnormalities. Effusions are seen in 48% to 62% of patients[258,261]; pleural nodules are increasingly recognized on CT scan. Parenchymal consolidation is seen in the majority of patients. Linear streaking is seen in 3% to 41% of chest radiographs of patients with paragonimiasis.[254] These changes can be transient, especially in acute infection when the worms are migrating. The migration tracts of the worms can be seen on CT scan, appearing as linear opacities, whereas cysts can be later seen within parenchymal consolidation, as the inflammation resolves. Ring shadows may represent cysts with attached parasite along the wall.[262] One study in Nigeria of 100 patients noted that most of the lesions are in the midzones, with more in the left lung than in the right.[264]

Treatment. Praziquantel 25 mg/kg/day in three doses for 2 days is now the treatment of choice for paragonimiasis, because it is safer, better tolerated, and more effective than older treatments that included bithionol and niclofolan. A transient increase in eosinophilia immediately after treatment can be seen.[252,254] Three clinical trials, involving a total of 261 subjects in Cameroon and Ecuador, reported the successful treatment of paragonimiasis with triclabendazole.[265,266] The optimal treatment regimen of paragonimiasis with

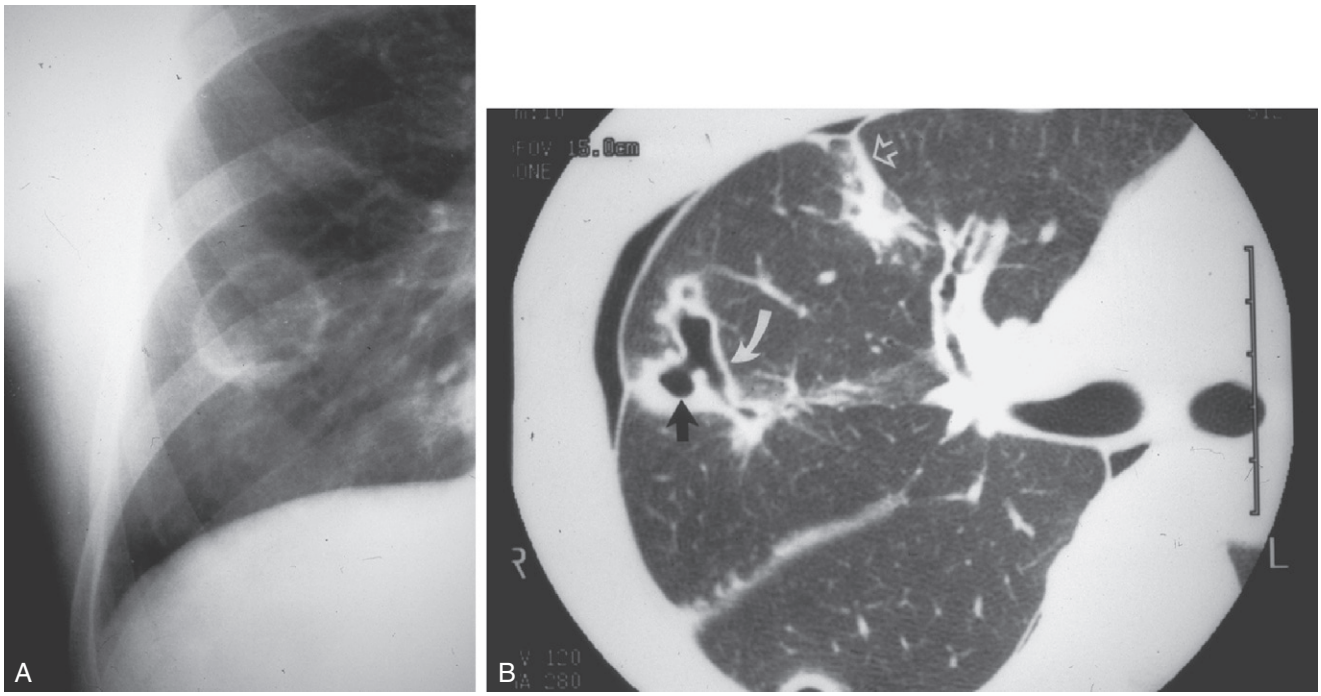

FIGURE 37-7 ■ **A,** Chest roentgenogram of a Korean adult with a large *Paragonimus* cyst in the right lower lung. **B,** CT scan of the chest at the level of the right upper lobe bronchus of a 20-year-old South Korean woman showing an unusually shaped air-filled space (*curved arrow*) and a bandlike opacity abutting the visceral pleura (*open arrow*), indicating worm migration tracks, as well as an air-filled worm cyst (*straight arrow*), a small right-sided pneumothorax, and a second worm cyst in the right lower lobe peripherally (*bottom*). (A and B, From Im J-G, Chang K-H: Paragonimiasis. In Palmer ES, Reeder MM [eds]: The Imaging of Tropical Diseases with Epidemiological, Pathological, and Clinical Correlation, 2nd ed. New York: Springer-Verlag, 2001.)

triclabendazole is 20 mg/kg given in two equal doses. The clinical studies in Ecuador[265,267] demonstrated that triclabendazole is equally effective and well tolerated as praziquantel. Corticosteroids can be used during treatment of cerebral paragonimiasis to decrease the inflammation triggered by the death of parasite. Patients with chronic empyema due to paragonimiasis may also require decortication in addition to anthelmintic treatment.[258]

Prevention. Metacercariae are heat sensitive and are killed by cooking, so the best means of prevention is the thorough cooking of crabs or crayfish before consumption. Handwashing and cleansing of utensils that may have come into contact with raw crustaceans is also an important preventive measure. Irradiation can sterilize the larvae if the consumption of raw crab or crayfish is desired.[254] Given the number of species that can potentially infect humans, it is unlikely that the natural reservoir for this infection will ever become eradicated. Thus, changing food preparation practices is the most feasible means of prevention.

Schistosomiasis

Human schistosomiasis is caused by one of the five species of the trematode (fluke) genus *Schistosoma*. *S. mansoni* is endemic in parts of Africa, the Middle East, South America, and the Caribbean. *S. haematobium* is found in Africa, the Middle East, and in one focus in India, while *S. japonicum* is a zoonosis that is found in China, Indonesia and the Philippines. Less common are *S. intercalatum* (central Africa) and *S. mekongi* (Cambodia and Laos). It is estimated that almost 200 million people in 74 countries are infected with schistosomiasis, with another 650 million at risk for infection. Twenty million people have severe disease.[268–270] Repeated infection is common in endemic areas, with the peak intensity usually occurring in individuals about 15 to 20 years of age.

Transmission. The adult worms reside in abdominal venous plexus in humans (or other definitive mammalian hosts). The favored site for *S. mansoni* is the superior mesenteric veins, for *S. haematobium*, the vesical plexus and veins of the ureters. For *S. japonicum*, the inferior mesenteric veins are preferred. The majority of eggs that are shed pass through the wall of the vessels into the intestinal or bladder lumen, where they are shed in the stool or urine. When eggs reach fresh water, they hatch into swimming miracidia that infect the appropriate snail species (the intermediate host). Within the snail, the parasites multiply over two generations, resulting in the release of many cercariae from a snail infected with one miracidium. Cercariae penetrate the skin of a human host in contaminated fresh water. Once it has penetrated the skin, the tail is lost, and the schistosomulum migrates to the lungs within a week; thence, it goes to the intrahepatic portal veins 2 to 3 weeks later. In the liver, the worms mature into adults and mate. Each pair then migrates to their target venous plexus where they

start producing eggs 1 to 3 months after infection.[269,271] The life span of adult worms is about 5 years, although people have been known to shed eggs for over 30 years after leaving an endemic area.[272]

Pathogenesis.[272a] Acute schistosomiasis otherwise known as Katayama fever, usually occurs in nonimmune persons, with symptoms developing as the worms migrate and mature into adult forms, before eggs are laid. The symptoms are thought to be due to antigen released by the worm: circulating immune complexes are found in the majority of acutely symptomatic patients, but are found only in a minority of chronically infected patients.[273] The level of circulating immune complexes correlates with symptoms and with intensity of infection. With time, the immune response to the parasite is down-modulated, and the symptoms resolve.[271] Lymphocytes from acutely symptomatic patients show high baseline production of tumor necrosis factor-α (TNF-α), IL-6, IL-1, and IFN-γ, suggesting that these proinflammatory cytokines may be responsible for some of the symptoms. In contrast, patients with chronic infection tend to have a predominant production of IL-10, an inhibitory cytokine in response to schistosome egg antigen.[274] In the uncommon circumstance in which lungs are affected during acute disease, eosinophilic pneumonia is the most common finding with a typical eosinophil predominance seen on biopsy or BAL.[275,276]

Once oviposition begins, not all the eggs are excreted from the body. It is the eggs that remain in the tissues that cause most of the chronic disease in schistosomiasis. The host immune system responds to the presence of the egg antigen by forming granulomas around the eggs. The granulomas are characterized by an eosinophilic infiltrate and central necrosis.[277] *S. mansoni* and *S. japonicum* eggs are commonly carried downstream to the liver where the resultant inflammatory response may lead to so-called Symmer's clay pipe stem fibrosis—in which fibrosis develops around the portal vein branches, with intervening normal tissue. As this fibrosis progresses, portal hypertension develops, leading to hepatosplenomegaly.[278]

With the development of significant portal fibrosis and hypertension, portacaval shunts develop, enabling eggs in the mesenteric blood to bypass the liver and lodge instead in pulmonary vessels. As eggs are embolized into the pulmonary vasculature, the local inflammatory response results in a necrotizing vasculitis surrounding the eggs, with eosinophilic infiltration and granuloma formation. Even in vessels that do not contain eggs, a vasculitis can be seen that may be a reaction to circulating antigen. With time, the vessel becomes obstructed and fibrotic, causing an obliterative vasculitis.[279] With the fibrin deposition, focal congestion, endothelial hyperplasia, dilation of the vessels, and a plexiform pattern develop in the vessels, increasing pulmonary resistance and resulting in pulmonary hypertension. Dumbbell-shaped interarterial and perivascular granulomas with local angiogenesis are typically seen on histology.[272] Whereas pulmonary hypertension occurs in 7% to 23% of patients with hepatosplenomegaly due to schistosomiasis, cor pulmonale occurs in less than 5%.[280]

S. mansoni is more commonly a cause of significant chronic pulmonary morbidity than other species. In a study of 78 patients who died of *S. mansoni* infection in Brazil, most had pulmonary findings on autopsy; 45% had only a few scattered granulomas around the remnants of eggs; 9% had many granuloma in alveolar and vascular tissue, but no histologic evidence of pulmonary hypertension.[277] Only 18% had evidence of end-stage lung disease, with diffuse thickening of the intima of the small arteries, edema, and fibrous deposition in the lungs. This group had obstruction of the small arteries with thrombosis and collateral formation; clinical evidence of cor pulmonale was present in 27%.[277]

Clinical Manifestations. The clinical manifestations of schistosomiasis depend on the location and life cycle stage of the parasite. As the cercariae penetrate the skin, a pruritic rash can develop. This "swimmer's itch" can also be caused by nonhuman (usually avian) schistosome species that cannot progress beyond the dermis. With the migration of the schistosomula to the lungs and liver, the acute syndrome known as Katayama fever can develop in a portion of immunologically naive people, usually travelers or immigrants from areas not endemic for *S. japonicum* or *S. mansoni*. This occurs 3 to 8 weeks after infection (average 36 days after exposure). The symptoms of Katayama fever are nonspecific and include fever, accompanied by lethargy, myalgia, chills, and sweats, abdominal pain, and diarrhea. Cough is present in 44% to 80% of people with this syndrome. Clinical examination is generally unremarkable, although a minority has hepato- or splenomegaly, rash, or wheeze.[274,281–283] The hepatomegaly can be tender. The acute disease can be more severe and potentially fatal in *S. japonicum* infection.[274]

Patients with *S. haematobium* infection may develop dysuria or terminal hematuria that first occurs 10 to 12 weeks after infection, once egg laying has begun.[269] Once an infection is established, it can remain subclinical for years, emerging decades later as a consequence of cumulative chronic inflammatory response to the eggs. In *S. mansoni* and *S. japonicum*, the hepatic fibrosis that develops causes hepatomegaly and, ultimately, portal hypertension, resulting in splenomegaly, and varices. Coinfection with hepatitis B or C can accelerate the progression of liver disease. In *S. haematobium* infection, late manifestations of disease include proteinuria, bladder scarring with calcification, and ureteric obstruction, leading to hydronephrosis and obstructive nephropathy. *S. haematobium* infection also increases the risk of squamous cell carcinoma of the bladder.[269]

Pulmonary Symptoms. Respiratory symptoms occur in a significant portion of patients with Katayama fever: 80% of patients in one study had cough, 52% had dyspnea, and 39% had chest pain.[274] In addition to classic Katayama fever, pulmonary symptoms can occur shortly after infection in a proportion of nonimmune people. These symptoms manifest as shortness of breath and a dry cough with occasional urticaria[275] and may present after the acute febrile stage or occur without fever. In such patients, the physical examination is usually normal,

and symptoms and radiographic abnormalities may occur together or independently.[272] Pulmonary function testing in the acute phase is not generally helpful, with a restrictive pattern typically observed. In one study, a decreased forced expiratory volume in 1 second was seen in a majority of patients, whereas a decreased total lung capacity and forced vital capacity were present in a minority; these were reversible with resolution of symptoms. Gas exchange was usually not affected.[284] In another study, reduced maximal voluntary ventilation and vital capacity was observed.[285]

The clinical manifestations of pulmonary hypertension and cor pulmonale due to schistosomiasis are the same as those caused by other etiologies: dyspnea with exertion, fatigue, chest pain, and cough,[272] with typical findings of jugular venous distention, right ventricular heave, and tricuspid and pulmonary regurgitant murmurs.[286] Whereas pulmonary hypertension usually follows portal hypertension in patients with *S. mansoni* infection, people with *S. haematobium* infection can develop pulmonary hypertension in the absence of hepatic fibrosis.

Diagnosis. Acute schistosomiasis is a clinical diagnosis to be suspected in patients with a history of exposure to fresh water in endemic areas, fever, and other characteristic symptoms and eosinophilia and no other cause found. Serology is available through the CDC. Whereas the ELISA test is sensitive and specific, it is not usually positive in acute disease. The average time to seroconversion in two studies was 1.6 months and ranged from 0 to 6 months.[272,281] The development of specific IgM response to somatic antigen (by immunofluorescence) develops earlier, between 26 to 34 days following infection, whereas an IgG to egg antigen becomes positive between 34 and 51 days after infection.[282] Newer specific immunoblot tests can differentiate between infections with different schistosome species and, when used with the ELISA test, can increase sensitivity.[287] The schistosomal ELISA can remain positive for years after treatment, making it less useful in following treatment efficacy or to look for reinfection. Circulating antigen tests enabling detection of current infection have been developed.[287]

Parasitologic diagnosis by identifying eggs in stool or urine is useful in established infection, but is not positive till egg laying begins, usually at least 6 weeks after initial water exposure.[274] Several techniques have been developed to isolate eggs from stool; classically the Kato-Katz thick smear or formalin concentration is used. Quantifying the intensity of infection by the number of eggs per weight or volume of stool or urine is useful.[286] Mean egg counts were found to be significantly associated with the severity of acute symptoms in one study[283] but not in others.[282] In patients who are not shedding eggs, rectal or bladder biopsies can be examined for the presence of eggs.[286]

Eosinophilia and elevated levels of IgE occur in almost all patients with acute schistosomiasis. Mild nonspecific elevation of liver enzymes is often present.[283] In patients with pulmonary symptoms, BAL, although usually not necessary, can reveal eosinophilic alveolitis in the absence of parasites.[276]

On chest radiographs of patients with acute symptoms, nodules with ill-defined borders are seen frequently; on CT, these nodules can have a ground-glass "halo appearance." The radiographic abnormalities may not appear until after treatment has been administered.[275,288] Bronchial thickening and beaded micronodular infiltrates can be seen in patients with interstitial lung disease and is found on CT in a majority of patients with hepatosplenomegaly due to schistosomiasis. The chest radiographic appearance of pulmonary hypertension due to schistosomias does not differ from that of other causes. On CT, vessel thickening is evident.[280] Rarely, a cavitary lesion can mimic tuberculosis.[289]

Treatment. The treatment for infection with *S. mansoni* and *S. haematobium* is praziquantel in a total dose of 40 mg/kg divided into two doses given 12 hours apart, with cure rates of 75% to 100% expected.[286] For *S. japonicum*, a higher total dose of 60 mg/kg given in three doses over 24 hours is required. Taking the drug with cimetidine (an inhibitor of cytochrome P-450) or grapefruit juice can increase drug levels, as can taking the medication with a high-carbohydrate meal.[290,291] Although praziquantel kills the adult worm, it is not active against immature parasites, thus compromising its efficacy in acute disease. In addition, the clinical condition of patients with Katayama fever can occasionally worsen after treatment with praziquantel, perhaps due to release of antigen from dying worms causing increased inflammation.[276,282,292] The acute syndrome is generally self-limited and generally does not require therapy. However, corticosteroid treatment may be used to decrease the inflammatory response to the parasite. Because corticosteroids may decrease the efficacy of praziquantel,[293] it may be prudent to defer praziquantel therapy in acute schistosomiasis until the symptoms have resolved and the worms have matured. Nonviable eggs may be shed for a prolonged period after treatment, so careful examination for viability needs to be done if posttreatment samples are collected to define cure.

Prevention. The prevention of schistosomiasis involves the interruption of the human-snail life cycle. Widespread eradication campaigns are underway in many countries, with mass treatment and application of molluscicides to fresh water to decrease the snail levels. However, because of the large animal reservoirs, this approach may not be effective. Because acute schistosomiasis in developed countries is most commonly seen in returning travelers, pretravel counseling and warnings about freshwater exposure may help decrease the incidence.

Artemether compounds have been shown to be effective in early infection when praziquantel is inactive and have been studied as prophylaxis for schistosomiasis in endemic areas where they seem to have an effect on decreasing the incidence of infection.[294,295] N,N-diethyl-3-methylbenzamide (DEET) and other insecticides have been studied in animal trials and seem to prevent skin penetration by schistosomal cercariae.[296,297] Vaccines are in development,[298] although they have yet to reach large-scale human trials.

KEY POINTS

- Parasites are eukaryotic organisms that live within another organism or host. They may be unicellular protozoa or multicellular helminths. In humans, protozoa usually live intracellularly and helminths usually live extracellularly, except trichinella, which encysts within muscle cells.
- Most parasites have complex life cycles with multiple stages and often multiple host species. Humans may be the definitive or intermediate hosts.
- Infection generally occurs through ingestion, insect vectors, or by penetration through the skin.
- Except for *Paragonimus*, most parasites migrate through the lung en route to another organ or infect the lungs as a secondary site.
- Although the worldwide burden of parasitic infections is enormous, most parasites have ecologic niches; presence in nonendemic areas usually results from travel to endemic areas.
- In most cases, the diagnosis is suspected by identifying an environmental association, compatible symptoms, and eosinophilia. The diagnosis is usually made by detecting antigens or isolating the parasite from the host.

References

1. Petri WA Jr, Haque R, Lyerly D, Vines RR: Estimating the impact of amebiasis on health. Parasitol Today 16:320–321, 2000.
2. Anonymous: WHO/PAHO/UNESCO report. A consultation with experts on amoebiasis. Mexico City, Mexico 28–29 January, 1997. Epidemiol Bull 18:13–14, 1997.
3. Davis A, Pawlowski ZS: Amoebiasis and its control. Bull World Health Organ 63:417–426, 1985.
4. Stanley SL Jr: Amoebiasis. Lancet 361:1025–1034, 2003.
5. Shamsuzzaman SM, Hashiguchi Y: Thoracic amebiasis. Clin Chest Med 23:479–492, 2002.
6. Arellano J, Perez-Rodriguez M, Lopez-Osuna M, et al: Increased frequency of HLA-DR3 and complotype SCO1 in Mexican mestizo children with amoebic abscess of the liver. Parasite Immunol 18:491–498, 1996.
7. Blessmann J, Van Linh P, Nu PA, et al: Epidemiology of amebiasis in a region of high incidence of amebic liver abscess in central Vietnam. Am J Trop Med Hyg 66:578–583, 2002.
8. Tanyuksel M, Petri WA Jr: Laboratory diagnosis of amebiasis. Clin Microbiol Rev 16:713–729, 2003.
9. Amin OM: Seasonal prevalence of intestinal parasites in the United States during 2000. Am J Trop Med Hyg 66:799–803, 2002.
10. Haque R, Huston CD, Hughes M, et al: Amebiasis. N Engl J Med 348:1565–1573, 2003.
11. Ali IK, Hossain MB, Roy S, et al: *Entamoeba moshkovskii* infections in children, Bangladesh. Emerg Infect Dis 9:580–584, 2003.
12. Phillips SC, Mildvan D, Williams DC, et al: Sexual transmission of enteric protozoa and helminths in a venereal disease clinic population. N Engl J Med 305:603–606, 1981.
13. Allason-Jones E, Mindel A, Sargeaunt P, Williams P: *Entamoeba histolytica* is a commensal intestinal parasite in homosexual men. N Engl J Med 315:353–356, 1986.
14. Markell EK, Havens RF, Kuritsubo RA, Wingerd J: Intestinal protozoa in homosexual men of the San Francisco Bay area: Prevalence and correlates of infection. Am J Trop Med Hyg 33:239–245, 1984.
15. Pai HH, Ko YC, Chen ER: Cockroaches (*Periplaneta americana* and *Blattella germanica*) as potential mechanical disseminators of *Entamoeba histolytica*. Acta Trop 87:355–359, 2003.
16. Barwick RS, Uzicanin A, Lareau S, et al: Outbreak of amebiasis in Tbilisi, Republic of Georgia, 1998. Am J Trop Med Hyg 67:623–631, 2002.
17. Huston CD, Boettner DR, Miller-Sims V, Petri WA Jr: Apoptotic killing and phagocytosis of host cells by the parasite *Entamoeba histolytica*. Infect Immun 71:964–972, 2003.
18. Hoffner RJ, Kilaghbian T, Esekogwu VI, Henderson SO: Common presentations of amebic liver abscess. Ann Emerg Med 34:351–355, 1999.
19. Bruchhaus I, Roeder T, Lotter H, et al: Differential gene expression in *Entamoeba histolytica* isolated from amoebic liver abscess. Mol Microbiol 44:1063–1072, 2002.
20. Lotter H, Zhang T, Seydel KB, et al: Identification of an epitope on the *Entamoeba histolytica* 170-kD lectin conferring antibody-mediated protection against invasive amebiasis. J Exp Med 185:1793–1801, 1997.
21. Zaki M, Reddy SG, Jackson TF, et al: Genotyping of *Entamoeba* species in South Africa: Diversity, stability, and transmission patterns within families. J Infect Dis 187:1860–1869, 2003.
22. Gathiram V, Jackson TF: A longitudinal study of asymptomatic carriers of pathogenic zymodemes of *Entamoeba histolytica*. S Afr Med J 72:669–672, 1987.
23. Nanda R, Baveja U, Anand BS: *Entamoeba histolytica* cyst passers: Clinical features and outcome in untreated subjects. Lancet 2:301–303, 1984.
24. Ibarra-Perez C: Thoracic complications of amebic abscess of the liver. Report of 501 cases. Chest 79:672–677, 1981.
25. Afsar S, Choudhri AN, Ali J, Muneer A: Primary pulmonary amoebiasis—An unusual cause of pulmonary consolidation. J Pak Med Assoc 42:245–246, 1992.
26. Le Roux BT: Pleuro-pulmonary amoebiasis. Thorax 24:91–101, 1969.
27. Landay MJ, Setiawan H, Hirsch G, et al: Hepatic and thoracic amaebiasis. AJR Am J Roentgenol 135:449–454, 1980.
28. Adams EB, Macleod IN: Invasive amebiasis II. Amebic liver abscess and its complications. Medicine (Baltimore) 56:325–334, 1977.
29. Walsh TJ, Berkman W, Brown NL, et al: Cytopathologic diagnosis of extracolonic amebiasis. Acta Cytol 27:671–675, 1983.
30. Zengzhu G, Bracha R, Nuchamowitz Y, et al: Analysis by enzyme-linked immunosorbent assay and PCR of human liver abscess aspirates from patients in China for *Entamoeba histolytica*. J Clin Microbiol 37:3034–3036, 1999.
31. Centers for Disease Control and Prevention: National Center for Infectious Diseases DoP. Laboratory Identification of Parasites of Public Health Concern. www.dpd.cdc.gov/dpdx/default.htm (Accessed November 26, 2009).
32. Mirelman D, Nuchamowitz Y, Stolarsky T: Comparison of use of enzyme-linked immunosorbent assay-based kits and PCR amplification of rRNA genes for simultaneous detection of *Entamoeba histolytica* and *E. dispar*. J Clin Microbiol 35:2405–2407, 1997.
33. Petri WA Jr, Singh U: Diagnosis and management of amebiasis. Clin Infect Dis 29:1117–1125, 1999.

34. Seifert K, Duchene M, Wernsdorfer WH, et al: Effects of miltefosine and other alkylphosphocholines on human intestinal parasite *Entamoeba histolytica*. Antimicrob Agents Chemother 45:1505–1510, 2001.
35. Orozco E, Lopez C, Gomez C, et al: Multidrug resistance in the protozoan parasite *Entamoeba histolytica*. Parasitol Int 51:353–359, 2002.
36. Croft SL, Seifert K, Duchene M: Antiprotozoal activities of phospholipid analogues. Mol Biochem Parasitol 126:165–172, 2003.
37. Adagu IS, Nolder D, Warhurst DC, Rossignol JF: In vitro activity of nitazoxanide and related compounds against isolates of *Giardia intestinalis, Entamoeba histolytica* and *Trichomonas vaginalis*. J Antimicrob Chemother 49:103–111, 2002.
38. Diaz E, Mondragon J, Ramirez E, Bernal R: Epidemiology and control of intestinal parasites with nitazoxanide in children in Mexico. Am J Trop Med Hyg 68:384–385, 2003.
39. Kelsall BL, Ravdin JI: Immunization of rats with the 260-kilodalton *Entamoeba histolytica* galactose-inhibitable lectin elicits an intestinal secretory immunoglobulin-A response that has invitro adherence-inhibitory activity. Infect Immun 63:686–689, 1995.
40. Haque R, Duggal P, Ali IM, et al: Innate and acquired resistance to amebiasis in Bangladeshi children. J Infect Dis 186:547–552, 2002.
41. Breman JG, Mills A, Snow RW, et al (eds): Conquering Malaria. Disease Control Priorities in Developing Countries, 2nd ed . New York: Oxford University Press, 2006, pp 413–432.
42. Mendis K, Sina BJ, Marchesini P, Carter R: The neglected burden of *Plasmodium vivax* malaria. Am J Trop Med Hyg 64(1–2 Suppl):97–106, 2001.
43. Lee EY, Maguire JH: Acute pulmonary edema complicating ovale malaria. Clin Infect Dis 29:697–698, 1999.
44. Schwartz E, Parise M, Kozarsky P, Cetron M: Delayed onset of malaria—Implications for chemoprophylaxis in travelers. N Engl J Med 349:1510–1516, 2003.
45. Taylor WR, White NJ: Malaria and the lung. Clin Chest Med 23:457–468, 2002.
46. Duarte MI, Corbett CE, Boulos M, Amato Neto V: Ultrastructure of the lung in falciparum malaria. Am J Trop Med Hyg 34:31–35, 1985.
46a. Valecha N, Pinto RG, Turner GD, et al: Histopathology of fatal respiratory distress caused by Plasmodium vivax malaria. Am J Trop Med Hyg 81:758–762, 2009.
47. Marsh K, Forster D, Waruiru C: Indicators of life-threatening malaria in African children. N Engl J Med 332:1399–1404, 1995.
48. Bruneel F, Hocqueloux L, Alberti C, et al: The clinical spectrum of severe imported falciparum malaria in the intensive care unit: Report of 188 cases in adults. Am J Respir Crit Care Med 167:684–689, 2003.
49. White NJ: The treatment of malaria. N Engl J Med 335:800–806, 1996.
50. Steketee RW, Nahlen BL, Parise ME, Menendez C: The burden of malaria in pregnancy in malaria-endemic areas. Am J Trop Med Hyg 64(1–2 Suppl):28–35, 2001.
51. ter Kuile FO, Parise ME, Verhoeff FH, et al: The burden of co-infection with human immunodeficiency virus type 1 and malaria in pregnant women in sub-Saharan Africa. Am J Trop Med Hyg 71(2 Suppl):41–54, 2004.
52. Shulman CE, Dorman EK: Importance and prevention of malaria in pregnancy. Trans R Soc Trop Med Hyg 97:30–35, 2003.
53. Diagne N, Rogier C, Sokhna CS, et al: Increased susceptibility to malaria during the early postpartum period. N Engl J Med 343:598–603, 2000.
54. Pukrittayakamee S, Chantra A, Vanijanonta S, White NJ: Pulmonary oedema in vivax malaria. Trans R Soc Trop Med Hyg 92:421–422, 1998.
55. Curlin ME, Barat LM, Walsh DK, Granger DL: Noncardiogenic pulmonary edema during vivax malaria. Clin Infect Dis 28:1166–1167, 1999.
56. Anstey NM, Jacups SP, Cain T, et al: Pulmonary manifestations of uncomplicated falciparum and vivax malaria: Cough, small airways obstruction, impaired gas transfer, and increased pulmonary phagocytic activity. J Infect Dis 185:1326–1334, 2002.
57. Tan LK, Yacoub S, Scott S, et al: Acute lung injury and other serious complications of *Plasmodium vivax* malaria. Lancet Infect Dis 8:449–454, 2008.
58. Genton B, D'Acremont V, Rare L, et al: *Plasmodium vivax* and mixed infections are associated with severe malaria in children: A prospective cohort study from Papua New Guinea. PLoS Med 5:e127, 2008.
59. Tjitra E, Anstey NM, Sugiarto P, et al: Multidrug-resistant *Plasmodium vivax* associated with severe and fatal malaria: A prospective study in Papua, Indonesia. PLoS Med 5:e128, 2008.
60. Rojo-Marcos G, Cuadros-González J, Mesa-Latorre JM, et al: Case report: Acute respiratory distress syndrome in a case of *Plasmodium ovale* malaria. Am J Trop Med Hyg 79:391–393, 2008.
61. Yale SH, Adlakha A, Sebo TJ, Ryu JH:. Bronchiolitis obliterans organizing pneumonia caused by *Plasmodium vivax* malaria. Chest 104:1294–1296, 1993.
62. Anstey NM, Handojo T, Pain MC, et al: Lung injury in vivax malaria: Pathophysiological evidence for pulmonary vascular sequestration and posttreatment alveolar-capillary inflammation. J Infect Dis 195:589–596, 2007.
63. Gozal D: The incidence of pulmonary manifestations during *Plasmodium falciparum* malaria in non-immune subjects. Trop Med Parasitol 43:6–8, 1992.
64. Cosgriff TM: Pulmonary edema in falciparum malaria. Slaying the dragon of volume overload. Chest 98:10–12, 1990.
65. Cropley IM, Lockwood DN, Mack D, et al: Rapid diagnosis of Falciparum malaria by using the ParaSight F test in travellers returning to the United Kingdom: Prospective study. BMJ. 321:484–485, 2000.
66. Cooke AH, Chiodini PL, Doherty T, et al: Comparison of a parasite lactate dehydrogenase-based immunochromatographic antigen detection assay (OptiMAL) with microscopy for the detection of malaria parasites in human blood samples. Am J Trop Med Hyg 60:173–176, 1999.
67. Iqbal J, Khalid N, Hira PR: Performance of rapid malaria Pf antigen test for the diagnosis of malaria and false-reactivity with autoantibodies. Adv Exp Med Biol 531:135–148, 2003.
68. Lema OE, Carter JY, Nagelkerke N, et al: Comparison of five methods of malaria detection in the outpatient setting. Am J Trop Med Hyg 60:177–182, 1999.
69. Lalloo DG, Shingadia D, Pasvol G, et al: UK malaria treatment guidelines. J Infect 4:111–121, 2007.
70. Lefevre G, Looareesuwan S, Treeprasertsuk S, et al: A clinical and pharmacokinetic trial of six doses of artemether-lumefantrine for multidrug-resistant *Plasmodium falciparum* malaria in Thailand. Am J Trop Med Hyg 64:247–256, 2001.
71. Rosenthal PJ: Artesunate for the treatment of severe falciparum malaria. N Engl J Med 358:1829–1836, 2008.
72. Fontes CJ, Munhoz S: Severe falciparum malaria with hyperparasitaemia: Management without exchange blood transfusion. Trop Med Int Health 1:820–823, 1996.
73. Whitty CJ, Rowland M, Sanderson F, Mutabingwa TK: Malaria. BMJ 325:1221–1224, 2002.
74. Schellenberg JR, Abdulla S, Nathan R, et al: Effect of large-scale social marketing of insecticide-treated nets on child survival in rural Tanzania. Lancet 357:1241–1247, 2001.
75. Mathanga D, Molyneux ME: Bednets and malaria in Africa. Lancet 357:1219–1220, 2001.
76. Croft A: Extracts from "Clinical Evidence." Malaria: Prevention in travellers. BMJ 321:154–160, 2000.
77. Gordon DM, McGovern TW, Krzych U, et al: Safety, immunogenicity, and efficacy of a recombinantly produced *Plasmodium falciparum* circumsporozoite protein-hepatitis B surface antigen subunit vaccine. J Infect Dis 171:1576–1585, 1995.
78. Kester KE, McKinney DA, Tornieporth N, et al: Efficacy of recombinant circumsporozoite protein vaccine regimens against experimental *Plasmodium falciparum* malaria. J Infect Dis 183:640–647, 2001.
79. Stoute JA, Slaoui M, Heppner DG, et al: A preliminary evaluation of a recombinant circumsporozoite protein vaccine against *Plasmodium falciparum* malaria. N Engl J Med 336:86–91, 1997.
80. Abdulla S, Oberholzer R, Juma O, et al: Safety and immunogenicity of RTS,S/AS02D malaria vaccine in infants. N Engl J Med 359:2533–2544, 2008.

81. Su C, Evans D, Cole RH, et al: Recent expansion of Toxoplasma through enhanced oral transmission. Science 299:414–416, 2003.
82. Campagna AC: Pulmonary toxoplasmosis. Semin Respir Infect 12:98–105, 1997.
83. Mariuz P, Bosler EM, Luft BJ: Toxoplasma pneumonia. Semin Respir Infect 12:40–43, 1997.
84. Suzuki Y, Orellano MA, Schreiber RD: Interferon-gamma: The major mediator of resistance against *Toxoplasma gondii*. Science 240:516–518, 1988.
85. Ortonne N, Ribaud P, Meignin V, et al: Toxoplasmic pneumonitis leading to fatal acute respiratory distress syndrome after engraftment in three bone marrow transplant recipients. Transplantation 72:1838–1840, 2001.
86. Jautzke G, Sell M, Thalmann U, et al: Extracerebral toxoplasmosis in AIDS. Histological and immunohistological findings based on 80 autopsy cases. Pathol Res Pract 189:428–436, 1993.
87. Montoya JG: Laboratory diagnosis of *Toxoplasma gondii* infection and toxoplasmosis. J Infect Dis 185(Suppl 1):S73–S82, 2002.
88. Rabaud C, May T, Amiel C, et al: Extracerebral toxoplasmosis in patients infected with HIV. A French National Survey. Medicine (Baltimore) 73:306–314, 1994.
89. Petersen E, Edvinsson B, Lundgren B, et al: Diagnosis of pulmonary infection with *Toxoplasma gondii* in immunocompromised HIV-positive patients by real-time PCR. Eur J Clin Microbiol Infect Dis 25:401–404, 2006.
90. Rabaud C, May T, Lucet JC, et al: Pulmonary toxoplasmosis in patients infected with human immunodeficiency virus: A French National Survey. Clin Infect Dis 23:1249–1254, 1996.
91. Renold C, Wintsch J, Filthuth I, et al: Pneumonia and respiratory distress syndrome during primary infection with *Toxoplasma gondii*. Clin Infect Dis 21:690–691, 1995.
91a. Ajzenberg D, Yera H, Marty P, et al: Genotype of 88 Toxoplasma gondii isolates associated with toxoplasmosis in immunocompromised patients and correlation with clinical findings. J Infect Dis 199:1155–1167, 2009.
92. Dawis MA, Bottone EJ, Vlachos A, Burroughs MH: Unsuspected *Toxoplasma gondii* empyema in a bone marrow transplant recipient. Clin Infect Dis 34:e37–e39, 2002.
93. Sing A, Leitritz L, Roggenkamp A, et al: Pulmonary toxoplasmosis in bone marrow transplant recipients: Report of two cases and review. Clin Infect Dis 29:429–433, 1999.
94. Chandrasekar PH, Momin F: Disseminated toxoplasmosis in marrow recipients: A report of three cases and a review of the literature. Bone Marrow Transplant Team. Bone Marrow Transplant 19:685–689, 1997.
95. Leal FE, Cavazzana CL, de Andrade HF Jr, et al: *Toxoplasma gondii* pneumonia in immunocompetent subjects: Case report and review. Clin Infect Dis 44:e62–e66, 2007.
96. Bretagne S, Costa JM, Foulet F, et al: Prospective study of toxoplasma reactivation by polymerase chain reaction in allogeneic stem-cell transplant recipients. Transpl Infect Dis 2:127–132, 2000.
97. Holliman RE, Johnson JD, Savva D: Diagnosis of cerebral toxoplasmosis in association with AIDS using the polymerase chain reaction. Scand J Inf Dis 22:243–244, 1990.
98. Lavrard I, Chouaid C, Roux P, et al: Pulmonary toxoplasmosis in HIV-infected patients: Usefulness of polymerase chain reaction and cell culture. Eur Respir J 8:697–700, 1995.
99. Abraham B, Tamby I, Reynes J, Bastien P: Polymerase chain reaction on sputum for the diagnosis of pulmonary toxoplasmosis in AIDS patients. AIDS 14:910–911, 2000.
100. Gallant JE, Moore RD, Chaisson RE: Prophylaxis for opportunistic infections in patients with HIV infection. Ann Intern Med 120:932–944, 1994.
101. Luft BJ, Remington JS: Toxoplasmic encephalitis in AIDS. Clin Infect Dis 15:211–222, 1992.
102. Richards FO Jr, Kovacs JA, Luft BJ: Preventing toxoplasmic encephalitis in persons infected with human immunodeficiency virus. Clin Infect Dis 21(Suppl 1):S49–S56, 1995.
103. Foot AB, Garin YJ, Ribaud P, et al: Prophylaxis of toxoplasmosis infection with pyrimethamine/sulfadoxine (Fansidar) in bone marrow transplant recipients. Bone Marrow Transplant 14:241–245, 1994.
104. Wreghitt TG, Gray JJ, Pavel P, et al:. Efficacy of pyrimethamine for the prevention of donor-acquired *Toxoplasma gondii* infection in heart and heart-lung transplant patients. Transpl Int 5:197–200, 1992.
105. de Silva NR, Brooker S, Hotez PJ, et al: Soil-transmitted helminth infections: Updating the global picture. Trends Parasitol 19:547–551, 2003.
106. Anonymous: Ascariasis. Lancet 1:1336, 1989.
107. Albonico M, Ramsan M, Wright V, et al: Soil-transmitted nematode infections and mebendazole treatment in Mafia Island schoolchildren. Ann Trop Med Parasitol 96:717–726, 2002.
108. Verle P, Kongs A, De NV, et al:. Prevalence of intestinal parasitic infections in northern Vietnam. Trop Med Int Health 8:961–964, 2003.
109. Nishiura H, Imai H, Nakao H, et al: *Ascaris lumbricoides* among children in rural communities in the Northern Area, Pakistan: Prevalence, intensity, and associated socio-cultural and behavioral risk factors. Acta Trop 83:223–231, 2002.
110. Sarinas PS, Chitkara RK: Ascariasis and hookworm. Semin Respir Infect 12:130–137, 1997.
111. Anderson TJ: Ascaris infections in humans from North America: Molecular evidence for cross-infection. Parasitology 110(Pt 2):215–219, 1995.
112. O'Lorcain P, Holland CV: The public health importance of *Ascaris lumbricoides*. Parasitology 121(Suppl):S51–S71, 2000.
113. Salata RA: Intestinal nematodes. *In* Mahmoud AAF (ed): Parasitic Lung Diseases. New York: Marcel Dekker, 1997, pp 89–108.
114. Gelpi AP, Mustafa A: Seasonal pneumonitis with eosinophilia: A study of larval ascariasis in Saudi Arabia. Am J Trop Med Hyg 16:646–647, 1967.
115. Sen MK, Chakrabarti S, Ojha UC, et al: Ectopic ascariasis: An unusual case of pyopneumothorax. Indian J Chest Dis Allied Sci 40:131–133, 1998.
116. Cooper PJ: The potential impact of early exposures to geohelminth infections on the development of atopy. Clin Rev Allergy Immunol 26:5–14, 2004.
117. Cooper PJ, Chico ME, Rodrigues LC, et al: Reduced risk of atopy among school-age children infected with geohelminth parasites in a rural area of the tropics. J Allergy Clin Immunol 111:995–1000, 2003.
118. Dagoye D, Bekele Z, Woldemichael K, et al: Wheezing, allergy, and parasite infection in children in urban and rural Ethiopia. Am J Respir Crit Care Med 167:1369–1373, 2003.
119. Palmer LJ, Celedon JC, Weiss ST, et al: *Ascaris lumbricoides* infection is associated with increased risk of childhood asthma and atopy in rural China. Am J Respir Crit Care Med 165:1489–1493, 2002.
120. Lynch NR, Goldblatt J, Le Souef PN: Parasite infections and the risk of asthma and atopy. Thorax 54:659–660, 1999.
121. Lynch NR, Palenque M, Hagel I, DiPrisco MC: Clinical improvement of asthma after anthelminthic treatment in a tropical situation. Am J Respir Crit Care Med 156:50–54, 1997.
122. Keiser J, Utzinger J: Efficacy of current drugs against soil-transmitted helminth infections: Systematic review and meta-analysis. JAMA 299:1937–1948, 2008.
123. Belizario VY, Amarillo ME, de Leon WU, et al: A comparison of the efficacy of single doses of albendazole, ivermectin, and diethylcarbamazine alone or in combinations against *Ascaris* and *Trichuris* spp. Bull World Health Organ 81:35–42, 2003.
124. Albonico M, Smith PG, Hall A, et al: A randomized controlled trial comparing mebendazole and albendazole against *Ascaris, Trichuris* and hookworm infection. Trans R Soc Trop Med Hyg 88:585–589, 1994.
125. Ranque S, Chippaux JP, Garcia A, Boussinesq M: Follow-up of *Ascaris lumbricoides* and *Trichuris trichiura* infections in children living in a community treated with ivermectin at 3-monthly intervals. Ann Trop Med Parasitol 95:389–393, 2001.
126. Albonico M, Stoltzfus RJ, Savioli L, et al: A controlled evaluation of two school-based anthelminthic chemotherapy regimens on intensity of intestinal helminth infections. Int J Epidemiol 28:591–596, 1999.
127. Hotez PJ, Zhan B, Bethony JM, et al: Progress in the development of a recombinant vaccine for human hookworm disease: The

Human Hookworm Vaccine Initiative. Int J Parasitol 33:1245–1258, 2003.
128. Mahmoud AAF: Intestinal nematodes (roundworms). *In* Mandel GL, Bennett JE, Dolin R (eds): Principles and Practices of Infectious Diseases (4th ed). New York: Churchill Livingstone, 1995, pp 2526–2538.
129. Maxwell C, Hussain R, Nutman TB, et al: The clinical and immunologic responses of normal human volunteers to low dose hookworm (*Necator americanus*) infection. Am J Trop Med Hyg 37:126–134, 1987.
130. Koshy A, Raina V, Sharma MP, et al: An unusual outbreak of hookworm disease in North India. Am J Trop Med Hyg 27(1 Pt 1):42–45, 1978.
131. Barreto ML, Rodrigues LC, Silva RC, et al: Lower hookworm incidence, prevalence, and intensity of infection in children with a Bacillus Calmette-Guérin vaccination scar. J Infect Dis 182:1800–1803, 2000.
131a. Balagopal A, Mills L, Shah A, Subramanian A: Detection and treatment of Strongyloides hyperinfection syndrome following lung transplantation. Transpl Infect Dis 11:149–154, 2009.
132. Kappus KK, Juranek DD, Roberts JM: Results of testing for intestinal parasites by state diagnostic laboratories, United States, 1987. MMWR CDC Surveill Summ 40:25–45, 1991.
133. Woodring JH, Halfhill H, Berger R, et al: Clinical and imaging features of pulmonary strongyloidiasis. South Med J 89:10–18, 1996.
134. Wehner JH, Kirsch CM: Pulmonary manifestations of strongyloidiasis. Semin Respir Infect 12:122–129, 1997.
135. Chieffi PP, Chiattone CS, Feltrim EN, et al: Coinfection by *Strongyloides stercoralis* in blood donors infected with human T-cell leukemia/lymphoma virus type 1 in Sao Paulo City, Brazil. Mem Inst Oswaldo Cruz 95:711–712, 2000.
136. Adedayo AO, Grell GA, Bellot P: Case study: Fatal strongyloidiasis associated with human T-cell lymphotropic virus type 1 infection. Am J Trop Med Hyg 65:650–651, 2001.
137. Terashima A, Alvarez H, Tello R, et al: Treatment failure in intestinal strongyloidiasis: An indicator of HTLV-I infection. Int J Infect Dis 6:28–30, 2002.
138. Porto AF, Neva FA, Bittencourt H, et al: HTLV-1 decreases Th2 type of immune response in patients with strongyloidiasis. Parasite Immunol 23:503–507, 2001.
139. Viney ME, Brown M, Omoding NE, et al: Why does HIV infection not lead to disseminated strongyloidiasis? J Infect Dis 190:2175–2180, 2004.
140. Kinjo T, Tsuhako K, Nakazato I, et al: Extensive intra-alveolar haemorrhage caused by disseminated strongyloidiasis. Int J Parasitol 28:323–330, 1998.
141. Haque AK, Schnadig V, Rubin SA, Smith JH: Pathogenesis of human strongyloidiasis: Autopsy and quantitative parasitological analysis. Mod Pathol 7:276–288, 1994.
142. Upadhyay D, Corbridge T, Jain M, Shah R: Pulmonary hyperinfection syndrome with *Strongyloides stercoralis*. Am J Med 111:167–169, 2001.
143. Lin AL, Kessimian N, Benditt JO: Restrictive pulmonary disease due to interlobular septal fibrosis associated with disseminated infection by *Strongyloides stercoralis*. Am J Respir Crit Care Med 151:205–209, 1995.
144. Nwokolo C, Imohiosen EA: Strongyloidiasis of respiratory tract presenting as "asthma." Br Med J 2:153–154, 1973.
145. Marti H, Haji HJ, Savioli L, et al: A comparative trial of a single-dose ivermectin versus three days of albendazole for treatment of *Strongyloides stercoralis* and other soil-transmitted helminth infections in children. Am J Trop Med Hyg 55:477–481, 1996.
146. Nwokolo C, Imohiosen EAE: Strongyloides of respiratory tract presenting as asthma. Br Med J 2:153–154, 1973.
147. Chu E, Whitlock WL, Dietrich RA: Pulmonary hyperinfection syndrome with *Strongyloides stercoralis*. Chest 97:1475–1477, 1990.
148. Roman-Sanchez P, Pastor-Guzman A, Moreno-Guillen S, et al: High prevalence of *Strongyloides stercoralis* among farm workers on the Mediterranean coast of Spain: Analysis of the predictive factors of infection in developed countries. Am J Trop Med Hyg 69:336–340, 2003.
149. Siddiqui AA, Berk SL: Diagnosis of *Strongyloides stercoralis* infection. Clin Infect Dis 33:1040–1047, 2001.
150. Page WA, Dempsey K, McCarthy JS: Utility of serological follow-up of chronic strongyloidiasis after anthelminthic chemotherapy. Trans R Soc Trop Med Hyg 100:1056–1062, 2006.
151. Gam AA, Neva FA, Krotoski WA: Comparative sensitivity and specificity of ELISA and IHA for serodiagnosis of strongyloidiasis with larval antigens. Am J Trop Med Hyg 37:157–161, 1987.
152. Tarr PE, Miele PS, Peregoy KS, et al: Case report: Rectal adminstration of ivermectin to a patient with *Strongyloides* hyperinfection syndrome. Am J Trop Med Hyg 68:453–455, 2003.
153. Chiodini PL, Reid AJ, Wiselka MJ, et al: Parenteral ivermectin in *Strongyloides* hyperinfection. Lancet 355:43–44, 2000.
154. Schad GA: Cyclosporine may eliminate the threat of overwhelming strongyloidiasis in immunosuppressed patients (letter). J Infect Dis 153:178, 1986.
155. Muennig P, Pallin D, Sell RL, Chan MS: The cost effectiveness of strategies for the treatment of intestinal parasites in immigrants. N Engl J Med 340:773–779, 1999.
156. Klion AD, Eisenstein EM, Smirniotopoulos T, et al: Pulmonary involvement in loiasis. Am Rev Resp Dis 145:961–963, 1992.
157. Hulin C, Rabaud C, May T, et al: [Pulmonary involvement with a favorable course during *Loa loa* filariasis] (French). Bull Soc Pathol Exot 87:248–250, 1994.
158. Meyers WM, Neafie RC, Connor DH: Onchocerciasis: Invasion of deep organs by *Onchocerca volvulus*. Am J Trop Med Hyg 26:650–657, 1977.
159. Scott AL: Lymphatic-dwelling filariae. *In* Nutman TB (ed): Lymphatic Filariasis. London: Imperial College Press, 2000, pp 5–39.
160. Amaral F, Dreyer G, Figueredo-Silva J, et al: Live adult worms detected by ultrasonography in human *Bancroftian filariasis*. Am J Trop Med Hyg 50:753–757, 1994.
161. Dreyer G, Addiss D, Roberts J, Noroes J: Progression of lymphatic vessel dilatation in the presence of living adult *Wuchereria bancrofti*. Trans R Soc Trop Med Hyg 96:157–161, 2002.
162. Sharma SK, Pande JN, Khilnani GC, et al: Immunologic and pulmonary function abnormalities in tropical pulmonary eosinophilia. Indian J Med Res 101:98–102, 1995.
163. Pinkston P, Vijayan VK, Nutman TB, et al: Acute tropical pulmonary eosinophilia. Characterization of the lower respiratory tract inflammation and its response to therapy. J Clin Invest 80:216–225, 1987.
164. Marshall BG, Wilkinson RJ, Davidson RN: Pathogenesis of tropical pulmonary eosinphilia: Parasitic alveolitis and parallels with asthma. Resp Med 92:1–3, 1998.
165. Udwadia FE: Tropical eosinophilia. A correlation of clinical, histopathologic and lung function studies. Dis Chest 52:531–538, 1967.
166. Joshi VV, Udwadia FE, Gadgil RK: Etiology of tropical eosinophilia: A study of lung biopsies and a review of published reports. Am J Trop Med Hyg 18:231–240, 1969.
167. Chitkara RK, Sarinas PS: Dirofilaria, visceral larva migrans, and tropical pulmonary eosinophilia. Semin Respir Infect 12:138–148, 1997.
168. Vijayan VK, Kuppu Rao KV, Sankaran K, et al: Tropical eosinophilia: Clinical and physiological response to diethylcarbamazine. Resp Med 85:17–20, 1991.
169. Ottesen EA, Nutman TB: Tropical pulmonary eosinophilia. Annu Rev Med 43:417–424, 1992.
170. Ray D, Abel R: Pulmonary eosinophilia in children: Report of a school survey in rural Tamil Nadu in India. J Trop Pediatr 40:49–51, 1994.
171. Kumaraswami V: The clinical manifestations of lymphatic filariasis. *In* Nutman TB (ed): Lymphatic Filariasis. London: Imperial College Press, 2000, pp 103–125.
172. Rom WN, Vijayan VK, Cornelium MJ, et al: Persistent lower respiratory tract inflammation associated with interstitial lung disease in patients with tropical pulmonary eosinophilia following conventional treatment with diethylcarbamazine. Am Rev Resp Dis 142:1088–1092, 1990.
173. Quah BS, Anuar AK, Rowani MR, Pennie RA: Cor pulmonale: An unusual presentation of tropical eosinophilia. Ann Trop Pediatr 17:77–81, 1997.

174. Madell SH, Spingarn GL: Unusual thoracic manifestations in filariasis due to *Loa loa*: Results of treatment with hetrazan and naphuride sodium. Am J Med 15:272–280, 1953.
175. Lal RB, Ottesen EA: Enhanced diagnostic specificity in human filariasis by IgG4 antibody assessment. J Infect Dis 158:1034–1037, 1988.
176. Weil GJ, Lammie PJ, Weiss N: The ICT filariasis test: A rapid format antigen test for diagnosis of *Bancroftian filariasis*. Parasitol Today 13:401–404, 1997.
177. Savani DM, Sharma OP: Eosinophilic lung disease in the tropics. Clin Chest Med 23:377–396, ix, 2002.
178. Sandhu M, Mukhopadhyay S, Sharma SK: Tropical pulmonary eosinophilia: A comparative evaluation of plain chest radiography and computed tomography. Australas Radiol 40:32–37, 1996.
179. Ray D, Jayachandran CA: Ventilation-perfusion scintiscanning in tropical pulmonary eosinophilia. Chest 104:497–500, 1993.
180. Ong RKC, Doyle RL: Tropical pulmonary eosinophilia. Chest 113:1673–1679, 1998.
181. Taylor MJ, Makunde WH, McGarry HF, et al: Macrofilaricidal activity after doxycycline treatment of *Wuchereria bancrofti*: A double-blind, randomised placebo-controlled trial. Lancet 365:2116–2121, 2005.
182. Ciferri F: Human pulmonary dirofilariasis in the United States: A critical review. Am J Trop Med Hyg 31:302–308, 1982.
183. Echeverri A, Long RF, Check W, Burnett CM: Pulmonary dirofilariasis. Ann Thorac Surg 67:201–202, 1999.
184. Rena O, Leutner M, Casadio C: Human pulmonary dirofilariasis: Uncommon cause of pulmonary coin-lesion. Eur J Cardiothorac Surg 22:157–159, 2002.
185. Hirano H, Kizaki T, Sashikata T, Matsumura T: Pulmonary dirofilariasis—Clinicopathological study. Kobe J Med Sci 48:79–86, 2002.
186. Milanez de Campos JR, Barbas CS, Filomeno LT, et al: Human pulmonary dirofilariasis: Analysis of 24 cases from Sao Paulo, Brazil. Chest 112:729–733, 1997.
187. Flieder DB, Moran CA: Pulmonary dirofilariasis: A clinicopathologic study of 41 lesions in 39 patients. Hum Pathol 30:251–256, 1999.
188. Yoshino N, Hisayoshi T, Sasaki T, et al: Human pulmonary dirofilariasis in a patient whose clinical condition altered during follow-up. Jpn J Thorac Cardiovasc Surg 51:211–213, 2003.
189. Asimacopoulos PJ, Katras A, Christie B: Pulmonary dirofilariasis. The largest single-hospital experience. Chest 102:851–855, 1992.
190. Bruschi F, Murrell KD: New aspects of human trichinellosis: The impact of new *Trichinella* species. Postgrad Med J 78:15–22, 2002.
191. Murrell KD, Pozio E: Trichinellosis: The zoonosis that won't go quietly. Int J Parasitol 30:1339–1349, 2000.
192. Moorhead A, Grunenwald PE, Dietz VJ, Schantz PM: Trichinellosis in the United States, 1991–1996: Declining but not gone. Am J Trop Med Hyg 60:66–69, 1999.
193. Pozio E, Sacchini D, Sacchi L, et al: Failure of mebendazole in the treatment of humans with *Trichinella spiralis* infection at the stage of encapsulating larvae. Clin Infect Dis 32:638–642, 2001.
194. Schellenberg RS, Tan BJ, Irvine JD, et al: An outbreak of trichinellosis due to consumption of bear meat infected with *Trichinella nativa*, in 2 northern Saskatchewan communities. J Infect Dis 188:835–843, 2003.
195. Ranque S, Faugere B, Pozio E, et al: *Trichinella pseudospiralis* outbreak in France. Emerg Infect Dis 6:543–547, 2000.
196. Compton SJ, Celum CL, Lee C, et al:. Trichinosis with ventilatory failure and persistent myocarditis. Clin Infect Dis 16:500–504, 1993.
197. Watt G, Saisorn S, Jongsakul K, et al: Blinded, placebo-controlled trial of antiparasitic drugs for trichinosis myositis. J Infect Dis 182:371–374, 2000.
198. Noordin R, Smith HV, Mohamad S, et al: Comparison of IgG-ELISA and IgG4-ELISA for Toxocara serodiagnosis. Acta Trop 93:57–62, 2005.
199. Jacobs DE, Zhu X, Gasser RB, Chilton N: PCR-based methods for identification of potentially zoonotic ascaridoid parasites of the dog, fox and cat. Acta Trop 68:191–200, 1997.
200. Dupouy-Camet J, Kociecka W, Bruschi F, et al: Opinion on the diagnosis and treatment of human trichinellosis. Expert Opin Pharmacother 3:1117–1130, 2002.
201. Djordjevic M, Bacic M, Petricevic M, et al: Social, political, and economic factors responsible for the reemergence of trichinellosis in Serbia: A case study. J Parasitol 89:226–231, 2003.
202. Huntley CC, Costas MC, Lyerly A: Visceral larva migrans syndrome: Clinical characteristics and immunologic studies in 51 patients. Pediatrics 36:523–536, 1965.
203. Schantz PM: Toxocara larva migrans now. Am J Trop Med Hyg 41(3 Suppl):21–34, 1989.
204. Despommier D: Toxocariasis: Clinical aspects, epidemiology, medical ecology, and molecular aspects. Clin Microbiol Rev 16:265–272, 2003.
205. Glickman LT, Schantz DM: Epidemiology and pathogenesis of zoonotic toxocariasis. Epidemiol Rev 3:230–250, 1981.
206. Buijs J, Borsboom G, Renting M, et al: Relationship between allergic manifestations and *Toxocara* seropositivity: A cross-sectional study among elementary school children. Eur Respir J 10:1467–1475, 1997.
207. Bass JL, Mehta KA, Glickman LT, et al: Asymptomatic toxocariasis in children. A prospective study and treatment trial. Clin Pediatr (Phila) 26:441–446, 1987.
208. Glickman LT, Magnaval JF, Domanski LM, et al: Visceral larva migrans in French adults: A new disease syndrome? Am J Epidemiol 125:1019–1034, 1987.
209. Bartelink AKM, Kortbeek LM, Huidekoper HJ, et al: Acute respiratory failure due to toxocara infection (letter). Lancet 342:1234, 1993.
210. Roig J, Romeu J, Riera C, et al: Acute eosinophilic pneumonia due to toxocariasis with bronchoalveolar lavage findings. Chest 102:294–296, 1992.
211. Inoue K, Inoue Y, Arai T, et al: Chronic eosinophilic pneumonia due to visceral larva migrans. Intern Med 41:478–482, 2002.
212. Sane AC, Barber BA: Pulmonary nodules due to *Toxocara canis* infection in an immunocompetent adult. South Med J 90:78–79, 1997.
213. de Savigny DH, Voller A, Woodruff AW: Toxocariasis: Serological diagnosis by enzyme immunoassay. J Clin Pathol 32:284–288, 1979.
214. Jacquier P, Gotstein B, Stingelin Y, Eckert J: Immunodiagnosis of toxocarosis in humans: Evaluation of a new enzyme-linked immunosorbent assay kit. J Clin Microbiol 29:1831–1835, 1991.
215. Glickman LT, Schantz PM, Cypess RH: Evaluation of serodiagnostic tests for visceral larva migrans. Am J Trop Med Hyg 27:492–498, 1978.
216. Gillespie SH, Bidwell D, Voller A, et al: Diagnosis of human toxocariasis by antigen capture enzyme linked immunosorbent assay. J Clin Pathol 46:551–554, 1993.
217. Lynch NR, Wilkes LK, Hodgen AN, Turner KJ: Specificity of *Toxocara* ELISA in tropical populations. Parasite Immunol 10:323–337, 1998.
218. Magnaval JF, Fabre R, Maurières P, et al: Application of the western blotting procedure for the immunodiagnosis of human toxocariasis. Parasitol Res 77:697–702, 1991.
219. Wolach B, Sinnreich Z, Uziel Y, et al: Toxocariasis: A diagnostic dilemma. Isr J Med Sci 31:689–692, 1995.
220. Lalosevic D, Lalosevic V, Klem I, et al:. Pulmonary capillariasis miming bronchial carcinoma. Am J Trop Med Hyg 78:14–16, 2008.
221. Aftandelians R, Raafat F, Taffazoli M, Beaver PC: Pulmonary capillariasis in a child in Iran. Am J Trop Med Hyg 26:64–71, 1977.
222. Gottstein B, Reichen J: Hydatid lung disease (echinococcosis/hydatidosis). Clin Chest Med 23:397–408, ix, 2002.
222a. Shehatha J, Alizzi A, Alward M, Konstantinov I: Thoracic hydatid disease; a review of 763 cases. Heart Lung Circ 17:502–504, 2008.
223. Morar R, Feldman C: Pulmonary echinococcosis. Eur Respir J 21:1069–1077, 2003.
224. Baden LR, Elliott DD: Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 4-2003. A 42-year-old woman with cough, fever, and abnormalities on thoracoabdominal computed tomography. N Engl J Med 348:447–455, 2003.

225. Ramos G, Orduna A, Garcia-Yuste M: Hydatid cyst of the lung: Diagnosis and treatment. World J Surg 25:46–57, 2001.
226. Tor M, Atasalihi A, Altuntas N, et al: Review of cases with cystic hydatid lung disease in a tertiary referral hospital located in an endemic region: A 10 years' experience. Respiration 67:539–542, 2000.
227. Koul PA, Koul AN, Wahid A, Mir FA: CT in pulmonary hydatid disease: Unusual appearances. Chest 118:1645–1647, 2000.
228. Burgos L, Baquerizo A, Munoz W, et al: Experience in the surgical treatment of 331 patients with pulmonary hydatidosis. J Thorac Cardiovasc Surg 102:427–430, 1991.
229. Dogan R, Yuksel M, Cetin G, et al: Surgical treatment of hydatid cysts of the lung: Report on 1055 patients. Thorax 44:192–199, 1989.
230. Redington AE, Russell SG, Ladhani S, et al: Pulmonary echinococcosis with chest wall involvement in a patient with no apparent risk factors. J Infect 42:285–288, 2001.
231. Kern P, Bardonnet K, Renner E, et al: European Echinococcosis Registry: Human alveolar echinococcosis, Europe, 1982–2000. Emerg Infect Dis 9:343–349, 2003.
232. Craig P: Echinococcus multilocularis. Curr Opin Infect Dis 16:437–444, 2003.
233. Men S, Yucesoy C, Edguer TR, et al: Intraaortic growth of hydatid cysts causing occlusion of the aorta and of both iliac arteries: Case report. Radiology 213:192–194, 1999.
234. Aydin NB, Celik S, Suzer A, et al: Hydatid cyst in the wall of the ascending aorta. Asian Cardiovasc Thorac Ann 14:153–154, 2006.
235. Lioulias A, Kotoulas C, Kokotsakis J, Konstantinou M: Acute pulmonary embolism due to multiple hydatid cysts. Eur J Cardiothorac Surg 20:197–199, 2001.
236. Franquet T, Plaza V, Llauger J, et al: Hydatid pulmonary embolism from a ruptured mediastinal cyst: High-resolution computed tomography, angiographic, and pathologic findings. J Thorac Imaging 14:138–141, 1999.
237. Rothlin MA: Fatal intraoperative pulmonary embolism from a hepatic hydatid cyst. Am J Gastroenterol 93:2606–2607, 1998.
238. Yague D, Lozano MP, Lample C, et al: Bilateral hydatid cyst of pulmonary arteries: MR and CT findings. Eur Radiol 7:1170–1172, 1998.
239. Singh S, Gibikote SV: Magnetic resonance imaging signal characteristics in hydatid cysts. Australas Radiol 45:128–133, 2001.
240. Zarzosa MP, Orduna Domingo A, Gutierrez P, et al: Evaluation of six serological tests in diagnosis and postoperative control of pulmonary hydatid disease patients. Diagn Microbiol Infect Dis 35:255–262, 1999.
241. Zhang W, Li J, McManus DP: Concepts in immunology and diagnosis of hydatid disease. Clin Microbiol Rev 16:18–36, 2003.
242. El-On J: Benzimidazole treatment of cystic echinococcosis. Acta Trop 85:243–252, 2003.
243. Anonymous: Guidelines for treatment of cystic and alveolar echinococcosis in humans. WHO Informal Working Group on Echinococcosis. Bull World Health Organ 74:231–242, 1996.
244. Cobo F, Yarnoz C, Sesma B, et al: Albendazole plus praziquantel versus albendazole alone as a pre-operative treatment in intra-abdominal hydatidosis caused by *Echinococcus granulosus*. Trop Med Int Health 3:462–466, 1998.
245. Keshmiri M, Baharvahdat H, Fattahi SH, et al: A placebo controlled study of albendazole in the treatment of pulmonary echinococcosis. Eur Respir J 14:503–507, 1999.
246. Keshmiri M, Baharvahdat H, Fattahi SH, et al: Albendazole versus placebo in treatment of echinococcosis. Trans R Soc Trop Med Hyg 95:190–194, 2001.
247. Horton RJ. Albendazole in treatment of human cystic echinococcosis: 12 years of experience. Acta Trop 64:79–93, 1997.
248. Reuter S, Schirrmeister H, Kratzer W, et al: Pericystic metabolic activity in alveolar echinococcosis: Assessment and follow-up by positron emission tomography. Clin Infect Dis 29:1157–1163, 1999.
249. Winning A, Braslins P, McCarthy JS: Nitazoxanide for treatment of refractory bony hydatid disease. Am J Hyg Trop Med 80:176–178, 2009.
250. Reuter S, Buck A, Grebe O, et al: Salvage treatment with amphotericin B in progressive human alveolar echinococcosis. Antimicrob Agents Chemother 47:3586–3591, 2003.
251. Zhang W, McManus DP: Vaccination of dogs against *Echinococcus granulosus*: A means to control hydatid disease? Trends Parasitol 24:419–424, 2008.
252. Meehan AM, Virk A, Swanson K, Poeschla EM: Severe pleuropulmonary paragonimiasis 8 years after emigration from a region of endemicity. Clin Infect Dis 35:87–90, 2002.
253. Yee B, Hsu J-I, Favour CB, Lohne E: Pulmonary paragonimiasis in Southeast Asians living in the Central San Joaquin Valley. West J Med 156:423–425, 1992.
254. Procop GW, Marty AM, Scheck DN, et al: North American paragonimiasis. A case report. Acta Cytol 44:75–80, 2000.
255. Castilla EA, Jessen R, Sheck DN, Procop GW: Cavitary mass lesion and recurrent pneumothoraces due to *Paragonimus kellicotti* infection: North American paragonimiasis. Am J Surg Pathol 27:1157–1160, 2003.
256. DeFrain M, Hooker R: North American paragonimiasis: Case report of a severe clinical infection. Chest 121:1368–1372, 2002.
256a. Lane MA, Barsanti MC, Santos CA, et al: Human paragonimiasis in North America following ingestion of raw crayfish. Clin Infect Dis 49:e55–e61, 2009.
257. Kawane H: Wild boars and pulmonary paragonimiasis. Chest 96:957–958, 1989.
258. Mukae H, Taniguchi H, Matsumoto N, et al: Clinicoradiologic features of pleuropulmonary *Paragonimus westermani* on Kyusyu Island, Japan. Chest 120:514–520, 2001.
259. Kagawa FT: Pulmonary paragonimiasis. Semin Respir Med 12:149–158, 1997.
260. Taniguchi H, Mukae H, Matsumoto N, et al: Elevated IL-5 levels in pleural fluid of patients with paragonimiasis westermani. Clin Exp Immunol 123:94–98, 2001.
261. Johnson RJ, Johnson JR: Paragonimiasis in Indochinese refugees. Roentgenographic findings with clinical correlations. Am Rev Resp Dis 128:534–538, 1983.
262. Im JG, Chang KH, Reeder MM: Current diagnostic imaging of pulmonary and cerebral paragonimiasis, with pathological correlation. Semin Roentgenol 32:301–324, 1997.
263. Singh TS, Mutum SS, Razaque MA: Pulmonary paragonimiasis: Clinical features, diagnosis and treatment of 39 cases in Manipur. Trans R Soc Trop Med Hyg 80:967–971, 1986.
264. Okagwu M, Nwokolo C: Radiological findings in pulmonary paragonimiasis as seen in Nigeria: A review based on one hundred cases. Br J Radiol 46:699–705, 1973.
265. Calvopina M, Guderian RH, Paredes W, et al: Treatment of human pulmonary paragonimiasis with triclabendazole: Clinical tolerance and drug efficacy. Trans R Soc Trop Med Hyg 92:566–569, 1998.
266. Ripert C, Couprie B, Moyou R, eet al: Therapeutic effect of triclabendazole in patients with paragonimiasis in Cameroon: A pilot study. Trans R Soc Trop Med Hyg 86:417, 1992.
267. Calvopina M, Guderian RH, Paredes W, Cooper PJ: Comparison of two single day regimens of triclabendazole for the treatment of human pulmonary paragonimiasis. Trans R Soc Trop Med Hyg 97:451–454, 2003.
268. Engels D, Chitsulo L, Montresor A, Savioli L: The global epidemiological situation of schistosomiasis and new approaches to control and research. Acta Trop 82:139–146, 2002.
269. Ross AG, Bartley PB, Sleigh AC, et al: Schistosomiasis. N Engl J Med 346:1212–1220, 2002.
270. Chitsulo L, Engels D, Montresor A, Savioli L: The global status of schistosomiasis and its control. Acta Trop 77:41–51, 2000.
271. Nash TE, Cheever AW, Ottesen EA, Cook JA: Schistosome infections in humans: Perspectives and recent findings. Ann Intern Med 97:740–754, 1982.
272. Schwartz E: Pulmonary schistosomiasis. Clin Chest Med Jun 23:433–443, 2002.
272a. Gobert GN, Moertel L, Brindley PJ, McManus DP: Developmental gene expression profiles of the human pathogen Schistosoma japonicum. BMC Genomics 10:128, 2009.
273. Lawley TJ, Ottesen EA, Hiatt RA, Gazze LA: Circulating immune complexes in acute schistosomiasis. Clin Exp Immunol 37:221–227, 1979.
274. de Jesus AR, Silva A, Santana LB, et al: Clinical and immunologic evaluation of 31 patients with acute schistosomiasis mansoni. J Infect Dis 185:98–105, 2002.

275. Schwartz E, Rozenman J, Perelman M: Pulmonary manifestations of early schistosome infection among nonimmune travelers. Am J Med 109:718–722, 2000.
276. Davidson BL, el-Kassimi F, Uz-Zaman A, Pillai DK: The "lung shift" in treated schistosomiasis. Bronchoalveolar lavage evidence of eosinophilic pneumonia. Chest 89:455–457, 1986.
277. Andrade ZA, Andrade SG: Pathogenesis of schistosomal pulmonary arteritis. Am J Trop Med Hyg 19:305, 1970.
278. Cheever AW, Andrade ZA: Pathological lesions associated with *Schistosoma mansoni* infection in man. Trans R Soc Trop Med Hyg 19:305, 1967.
279. Chaves E: Necrotizing and healing pulmonary arteritis in schistosomal cor pulmonale: A retrospective study of ten cases. Am J Trop Med Hyg 15:162–167, 1966.
280. Bethlem EP, Schettino GdP, Carvalho C: Pulmonary schistosomiasis. Curr Opin Pulm Med 3:361–365, 1997.
281. Doherty JF, Moody AH, Wright SG: Katayama fever: An acute manifestation of schistosomiasis. BMJ 313:1071–1072, 1996.
282. Visser LG, Polderman AM, Stuiver PC: Outbreak of schistosomiasis among travelers returning from Mali, West Africa. Clin Infect Dis 20:280–285, 1995.
283. Hiatt RA, Sotomayor ZR, Sanchez G, et al: Factors in the pathogenesis of acute schistosomiasis mansoni. J Infect Dis 139:659–666, 1979.
284. Fuleihan FJ, Habaybeh A, Abdallah A, et al: Respiratory function in moderate schistosomal infection. Effect of chemotherapy. Am Rev Respir Dis 100:651–661, 1969.
285. Frayser R, De Alonso AE: Studies of pulmonary function in patients with *Schistosomiasis mansoni*. Am Rev Respir Dis 95:1036–1040, 1967.
286. Morris W, Knauer CM: Cardiopulmonary manifestations of schistosomiasis. Semin Respir Infect 12:159–170, 1997.
287. Al-Sherbiny MM, Osman AM, Hancock K, et al: Application of immunodiagnostic assays: Detection of antibodies and circulating antigens in human schistosomiasis and correlation with clinical findings. Am J Trop Med Hyg 60:960–966, 1999.
288. Waldman AD, Day JH, Shaw P, Bryceson AD: Subacute pulmonary granulomatous schistosomiasis: High resolution CT appearances—Another cause of the halo sign. Br J Radiol 74:1052–1055, 2001.
289. Schaberg T, Rahn W, Racz P, Lode H: Pulmonary schistosomiasis resembling acute pulmonary tuberculosis. Eur Respir J 4:1023–1026, 1991.
290. Castro N, Medina R, Sotelo J, Jung H: Bioavailability of praziquantel increases with concomitant administration of food. Antimicrob Agents Chemother;44:2903–2904, 2000.
291. Castro N, Jung H, Medina R, et al: Interaction between grapefruit juice and praziquantel in humans. Antimicrob Agents Chemother 46:1614–1616, 2002.
292. Cooke GS, Lalvani A, Gleeson FV, Conlon CP: Acute pulmonary schistosomiasis in travelers returning from Lake Malawi, sub-Saharan Africa. Clin Infect Dis 29:836–839, 1999.
293. Vazquez ML, Jung H, Sotelo J: Plasma levels of praziquantel decrease when dexamethasone is given simultaneously. Neurology 37:1561–1562, 1987.
294. N'Goran EK, Utzinger J, Gnaka HN, et al: Randomized, double-blind, placebo-controlled trial of oral artemether for the prevention of patent *Schistosoma haematobium* infections. Am J Trop Med Hyg 68:24–32, 2003.
295. Utzinger J, N'Goran EK, N'Dri A, et al: Oral artemether for prevention of *Schistosoma mansoni* infection: Randomised controlled trial. Lancet 355:1320–1325, 2000.
296. Ramaswamy K, He YX, Salafsky B, Shibuya T: Topical application of DEET for schistosomiasis. Trends Parasitol 19:551–555, 2003.
297. Secor WE, Freeman GL Jr, Wirtz RA: Short report: Prevention of *Schistosoma mansoni* infections in mice by the insect repellents AI3-37220 and N,N-diethyl-3-methylbenzamide. Am J Trop Med Hyg 60:1061–1062, 1999.
298. Tran MH, Pearson MS, Bethony JM, et al: Tetraspanins on the surface of *Schistosoma mansoni* are protective antigens against schistosomiasis. Nat Med 12:835–840, 2006.

CHAPTER 38
ASTHMA

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INTRODUCTION

Asthma is one of the oldest known diseases, but it has only been recognized as a major public health problem since the mid 1970s. The prevalence of asthma has increased dramatically and asthma is now recognized as a major cause of disability, medical expense, and preventable death. Asthma has attracted the full spectrum of biomedical investigation, from studies of the prevalence of asthmatic symptoms in different populations to studies of the effects of substitution of single base pairs in genes in animal models of allergic sensitization of the airways. These studies continue to refine the scientific understanding of asthma and suggest new approaches to diagnosis and treatment. The scope and depth of these studies present significant challenges in reviewing the topic of asthma. This chapter combines the perspectives of the authors with a "snapshot" of the body of knowledge, which is expanding at an explosive pace.

DEFINITION

Although asthma is a clearly recognized clinical entity, agreement on a precise definition of asthma has proved elusive. Asthma has been more often described than defined. The earliest feature described was the labored, rapid breathing typical of asthmatic attacks, because the word "asthma" is derived from the ancient Greek word for "panting." As knowledge about asthma has grown, the features described as characteristic of asthma have expanded. Measurement of maximal expiratory flow led to recognition of reversible airflow obstruction as a characteristic feature; measurement of changes in airflow

after inhalation of chemical or physical irritants led to the definition of bronchial hyperresponsiveness. In addition, studies of bronchial biopsies added a description of characteristic pathologic features. This evolution in the understanding of asthma is summarized in the definition offered in the National Heart, Lung, and Blood Institute's 2007 Update on Asthma Pathophysiology and Treatment Guidelines.[1]

Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role, including mast cells, eosinophils, T lymphocytes, macrophages, neutrophils, and epithelial cells. In susceptible individuals, inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment. The inflammation also causes an associated increase in bronchial hyperresponsiveness to a variety of stimuli.

A feature found even more consistently than eosinophilia in bronchial biopsies from patients with asthma is thickening of the lamina reticularis immediately underneath the subepithelial basement membrane, which is considered a hallmark of airway "remodeling," however this feature has not yet been incorporated into consensus definitions of asthma's features.

The consensus conference "definition" of asthma serves well as a description of the major features of asthma but does not hold up as a precise definition. No feature is unique to asthma, and no feature is universal in patients with the condition. For example, all tests of airway caliber may be normal between attacks, even in patients whose attacks are sudden and severe. Bronchial responsiveness may be normal over most of the year in patients with seasonal asthma, and bronchial hyperresponsiveness is often found in people with allergic rhinitis but without asthma. Even the association between eosinophilic bronchial inflammation and asthma is inconstant. Some patients with recurrent episodes of wheezing and dyspnea associated with reversible airflow obstruction and bronchial hyperresponsiveness have no evidence of eosinophilic inflammation on bronchial biopsies. Other patients have eosinophilic inflammation of the bronchial mucosa and chronic cough responsive to treatment with an inhaled corticosteroid but have neither airflow obstruction nor bronchial hyperresponsiveness. Finally, some patients with severe asthma have a predominance of neutrophils, rather than eosinophils, in their bronchial mucosa.

The lack of firm, universally agreed-upon criteria for defining asthma complicates epidemiologic studies of the prevalence of asthma in different populations and of changes in prevalence in the same population over time, but agreement on "working definitions" of asthma has led to many informative studies.

Logically, studies of the genetic basis of asthma should be the most affected by lack of precise diagnostic criteria, but the approach developed by genetic researchers has refined concepts of the disease. Geneticists recognized that asthma is a complex trait, reflecting variations in many genes and their interactions with the environment, so they examined the genetic determinants of well-defined phenotypes rather than those of clinically defined asthma. This approach has clarified the role of genes as determinants of atopy, bronchial responsiveness, and responsiveness to treatment, such as β-agonists. The recognition of asthma as a complex, multifactorial disorder has led to a greater focus on the individual and the varied disturbances in function that contribute to a more or less common clinical expression. Recent advances in science have not necessarily led to a more precise definition of asthma; rather, these advances have made the need for agreement on a definition seem less urgent.

ASTHMA EPIDEMIOLOGY AND RISK FACTORS

Introduction

The epidemiology of asthma is complex and careful epidemiologic studies are essential to enhancing our understanding of a disease that affects millions of people worldwide. The challenges faced when studying asthma epidemiology begin with the lack of a universally accepted definition for the disease. Asthma was defined by the American Thoracic Society in 1962 as a disease characterized by increased hyperresponsiveness of the bronchi and trachea to various stimuli, involving widespread narrowing of the airways that changes in severity either spontaneously or as a result of therapy.[1a,2] In 1975, the World Health Organization (WHO) described asthma as a chronic condition characterized by recurrent bronchospasm resulting from a tendency to develop reversible narrowing of airway lumina in response to stimuli of a level or intensity not causing such narrowing in normal individuals.[2] The emphasis on bronchoconstriction or bronchospasm as the mechanism of asthma is warranted. However, recent advances in research techniques have shown that asthma is a complicated disease that involves both bronchoconstriction and inflammation.

Epidemiologic studies rely on questionnaire assessments of asthma symptoms, physician diagnosis of asthma, and use of asthma medications. Unfortunately, highly sensitive and specific physiologic tests to diagnose asthma are not available. The methacholine challenge test is highly sensitive but not specific. In 1991, the National Institutes of Health (NIH) and National Heart, Lung, and Blood Institute (NHLBI) described asthma as a chronic inflammatory disorder of the airways in which many cells and cellular elements are involved. The chronic inflammation causes an associated increase in airway hyperresponsiveness that leads to recurrent wheezing, breathlessness, chest tightness, and coughing, particularly at night and in the early morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible, either spontaneously or with treatment. The NIH updated the asthma diagnosis and treatment guidelines in 2007.[3] Current guidelines emphasize the role of inflammation

in asthma and focus on evidence that the patterns and degrees of inflammation are variable, resulting in phenotypic differences that have important influences on response to therapy.

Prevalence of Asthma

The prevalence of asthma has been increasing worldwide over the past several decades.[4] The etiology of this increase in prevalence is unclear but is likely multifactorial. Factors resulting in increased prevalence rates include obesity and exposure to allergens such as house dust mites, mold, and tobacco smoke. Exposure to environmental triggers results in increased bronchial hyperresponsiveness and asthma. Atopy and allergic rhinitis related to exposure to allergens at an early age likely contribute to the increased incidence of asthma.[5] Obesity has also been increasing in prevalence since the mid 1980s.[6] Although the available studies cannot address the direction of causality, they indicate that there are important relationships between environmental and individual factors that warrant further investigation.

In 2006, the National Health Interview Survey (NHIS) estimated that 16.1 million adults (7.3% of the population) and 6.8 million children (9.4% of the population) in the United States had a diagnosis of asthma.[7] The prevalence of asthma in the United States increased from 3.1% in 1980 to 7.7% in 2005. The prevalence of asthma decreases with increasing age. There are important racial differences in the prevalence and morbidity of asthma. In 2005, Puerto Ricans had an asthma prevalence rate 125% higher than non-Hispanic whites and 80% higher than non-Hispanic blacks. Females had a 40% higher prevalence rate than males; however, boys under the age of 18 years old had a higher prevalence than girls.[4]

The International Study of Asthma and Allergies in Childhood (ISAAC) was performed between June 1996 and November 1997.[5] This is the largest study to document the worldwide prevalence of asthma. The study involved 91 centers in 56 countries and over 6000 subjects. The study enrolled two cohorts of subjects: children aged 6 to 7 years old and 13 to 14 years old. The prevalence of asthma varied widely between countries, ranging from 2.1% to 4.4% in Albania, China, Greece, and Indonesia to 29.1% to 32.2% in Australia, New Zealand, and the United Kingdom. Lower prevalence rates were seen in Asia, Northern Africa, Eastern Europe, and Eastern Mediterranean areas (Fig. 38-1). The prevalence rates in the younger cohort ranged from an average of 4.1% in India, Indonesia, Iran, and Malaysia to 32.1% in Australia, Brazil, New Zealand, and Panama. The results of the ISAAC study indicate that atopy, allergic rhinoconjunctivitis, and atopic eczema are highly correlated with the prevalence and symptoms of asthma. Countries with lower rates of atopy had lower prevalence rates of asthma.

The goal of phase II of the ISAAC study was to further investigate the contribution of atopic sensitization to the large international variation in the prevalence of asthma.[8] This was a cross-sectional study of random samples obtained from 8- to 12-year-old children in 30 centers in 22 countries. The countries covered a wide range of environments including both urban and rural areas. The relationship between atopic sensitization and current wheeze was not significant. However, there was a correlation between wheezing and atopy in countries with higher gross national income (typically in the developed world).[9] Asthma prevalence rates are higher in affluent countries, an effect that is attributed to differential environmental exposures in industrialized countries as compared with developing countries, in which more people live in rural than in urban areas.[10]

ISAAC phase III aimed to identify temporal changes in asthma prevalence rates. The prevalence of asthma symptoms increased in Africa, Latin America, and parts of Asia during the observation period, but the overall prevalence of wheezing decreased in English-speaking countries and Western Europe.[11]

The European Community Respiratory Health Survey (ECRHS)[12] was designed to collect data on asthma prevalence, variation in symptoms, risk factors, and treatment patterns in Europe and several centers outside Europe. In 1996, the ECRHS reported a wide variation in the prevalence of asthma symptoms among countries. The lowest prevalence rates occurred in India and Algeria, whereas the highest prevalence rates occurred in the British Isles, New Zealand, Australia, and the United States.[13] The increased prevalence of asthma has been substantiated by several large epidemiologic studies.[14–18]

Death from asthma was previously thought to be very uncommon; however, asthma-related deaths steadily increased in the United States and worldwide between 1980 and the mid-1990s.[19–21] There was a sharp rise in asthma-related deaths in Australia and New Zealand in the early 1980s. This increased risk of death was attributed to overuse of the β-agonist fenoterol.[22] In 1999, a new diagnostic coding system was initiated, which is thought to have caused the apparent decline in death rates between 1998 and 1999. Although recent death rates have been declining, asthma-related morbidity and mortality continue to be a significant problem. Worldwide, approximately 180,000 deaths are attributable to asthma each year, although considerable regional variation exists.[18]

Approximately 4000 deaths/yr in the United States are attributed to asthma.[23] The recent decline in asthma-related deaths is likely related to the increased use of inhaled corticosteroids, improved access to better medical care, and improved recognition and diagnosis of asthma. Disparities exist in asthma-related morbidity and mortality. In the United States, certain populations have a higher burden of asthma-related morbidity and mortality. Deaths from asthma are rare under the age of 18 years. The Morbidity and Mortality Weekly Report (MMWR)[23] reported a plateau in asthma related deaths between 2001 and 2003. In 2003, 4055 asthma deaths occurred, suggesting a rate of 1.4/10,000 persons. Higher death rates were noted in persons older than age 65 years and in women (death rate 2.3/10,000 compared with 1.8/10,000 in men).[23] Females had a 45% higher risk of dying from asthma than males. Puerto Ricans were the

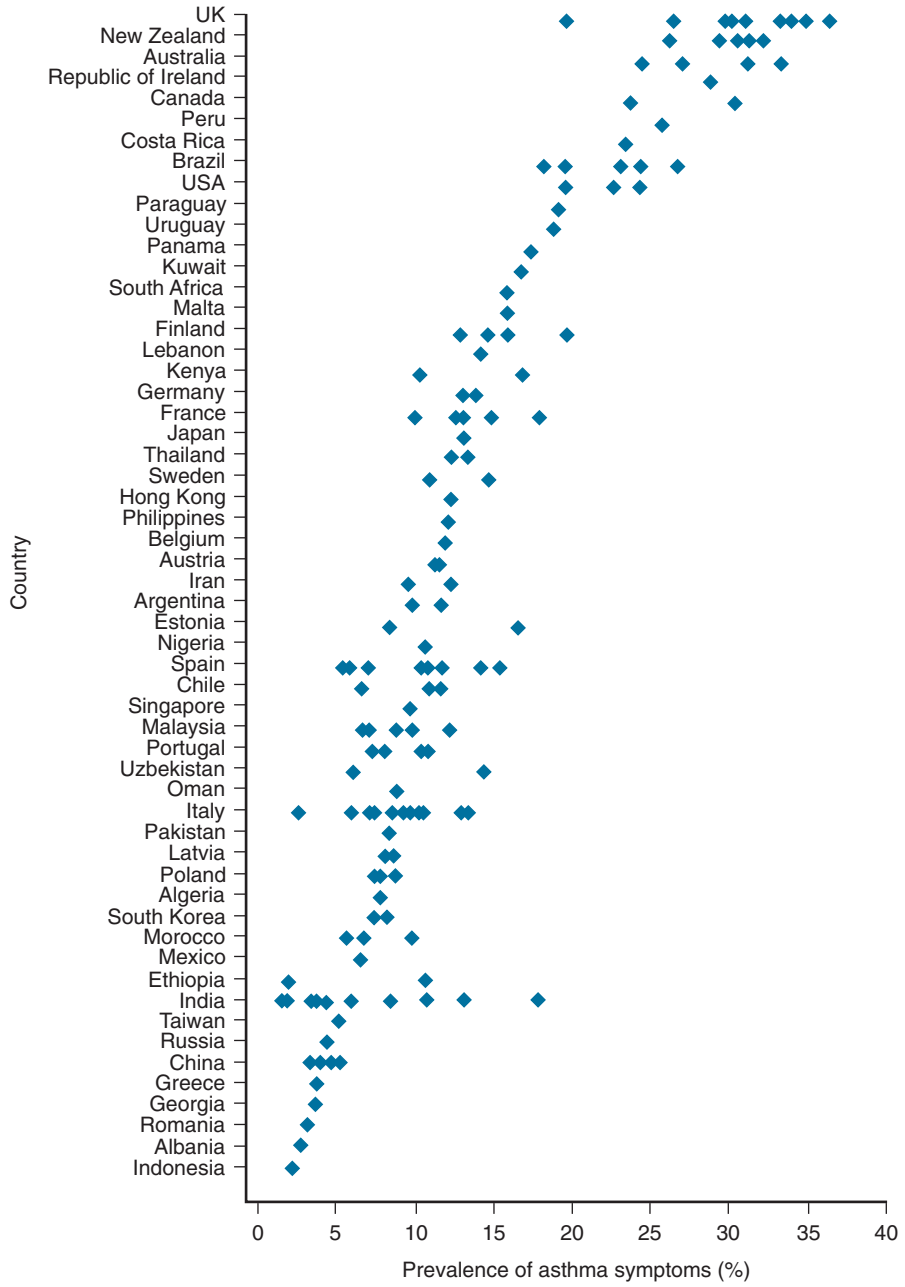


FIGURE 38-1 ■ **Prevalence of asthma symptoms as reported by written questionnaire.** (Redrawn from The International Study of Asthma and Allergies in Childhood [ISAAC] Steering Committee. Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis and atopic eczema. ISAAC. Lancet 351:1225–1232, 1998; with permission.)

most likely to die of asthma, with a death rate 3.6 times higher than non-Hispanic whites. Non-Hispanic blacks had an asthma death rate twice as high as non-Hispanic whites.[24] The disparate rates of death are attributed to variations in severity of disease, socioeconomic factors such as lack of access to quality health care, increased exposure to exacerbating factors in inner city areas, lack of access to medications, and differences in medications prescribed by medical professionals.[20] Health care disparities contribute to the major differences in outcomes in different populations.

Risk Factors

Hygiene Hypothesis

Several large epidemiologic studies have been designed to identify the risk factors that predispose individuals to developing asthma. In 1989, Strachan[25] proposed that exposure to infections early in life results in the development of a predominately T-helper (Th)1-mediated immune response and down-regulation of the Th2-mediated response. The lack of exposure to microbes early in life results in an overactive Th2-mediated response

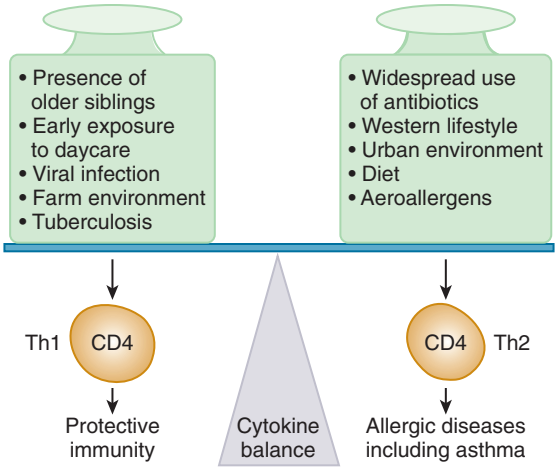


FIGURE 38-2 ■ Determinants of the direction of differentiation of precursor T cells in early life. The concept is that environmental factors in early life can have key influences on the direction of differentiation of precursor T cells. Several factors favor development of a Th1 phenotype, leading to the absence of allergy and asthma.

with increased allergic rhinitis and atopy and an increased risk of developing asthma.[25,26] Modern environments are more likely to be hygienic, with smaller families, increased access to antibiotics, and decreased exposure to bacterial pathogens and microbes, leading to imbalance between the innate and the adaptive immune mechanisms. This maladaptive system increases the risk of developing allergic diseases such as asthma. The presence of a predominantly allergic, Th2-driven milieu results in defective host defense mechanisms that make the host more susceptible to infection (Fig. 38-2).[27] The hygiene hypothesis is supported by data obtained from several subsequent epidemiologic studies involving birth cohorts in the United Kingdom, Europe, and prospective studies worldwide.[28,29] This association appears to be stronger in Europe than in other countries.[10] For instance, the higher incidence of asthma in the inner city is not explained by this hypothesis. Von Mutius[10] concluded that the hygiene hypothesis has led to important discoveries about the etiology of asthma and the interaction between innate and adaptive immune mechanisms, even though it still lacks a unifying etiology. The practical implications of the hygiene hypothesis have not been fully tested.

Infections

The effect of respiratory infections on the incidence of asthma is incompletely understood. Exposure to microbes early in life may be protective against the development of asthma and allergic rhinitis later in life.[25] Respiratory infections, particularly from viral pathogens, are especially common in infancy and childhood. The relationship between infection and the development of atopy and asthma is complex and highly dependent on the type of infection.[30] Exposure to respiratory illness might increase or decrease the incidence of asthma, depending on host factors and the timing, location, and type of microbial exposure.[31,32] Using a birth cohort, Ramsey and coworkers found that having physician-diagnosed croup or having two or more physician-diagnosed ear infections in the first year of life was inversely related to atopy at school age. In contrast, bronchiolitis in the first year of life was associated with increased odds of developing asthma at age 7 years.[30]

Respiratory syncytial virus (RSV) is the most common cause of bronchiolitis and is associated with an increased risk of developing subsequent wheezing or asthma.[31,33–43] Recently, rhinovirus has been recognized as an important risk factor for the development of asthma. Rhinovirus infections are common in childhood and occur in the spring and fall. Rhinovirus is a known cause of bronchiolitis and is the second most common cause of severe bronchiolitis resulting in hospitalizations. Until recently, little was known about the role of moderately severe outpatient lower respiratory tract infections in the development of asthma. Jackson and colleagues[43] performed nasal sinus lavage, culture, and polymerase chain reaction (PCR) for microbial RNA on infants and children with outpatient wheezing illnesses. Viral etiologies were responsible for more than 90% of wheezing illnesses during early childhood. From birth to 3 years of age, wheezing with RSV, rhinovirus, or both resulted in odds ratios of 2.6, 9.8, and 10 for developing asthma by the age of 6 years.[43] Other studies also support the increased risk of developing asthma following rhinovirus infections.[44] Rhinovirus is a very important predictor of asthma if the infection occurs early in life.

Understanding the mechanism by which viruses modify the risk of developing asthma is an area of intense research. In humans, severe viral infections and bronchiolitis result in alterations in both Th1 and Th2 cytokine levels. RSV invades the respiratory epithelium through attachment and fusion proteins. Rhinovirus binds intracellular adhesion molecule (ICAM)-1 and low-density lipoprotein receptors (LDLPRs) on the respiratory epithelium and is internalized with subsequent receptor upregulation. Downstream effects include the induction of inflammatory chemokines and cytokines, including type 1 interferon (IFN), interleukin (IL)-12 and IL-18.[45,46] Additional factors that mediate the effects of acute viral infections in the airways include neuropeptides, growth factors, and leukotrienes.[47,48] The secretion of proinflammatory cytokines causes airway inflammation, whereas growth factors result in airway remodeling, which may eventually increase the risk of wheezing. Although there is substantial knowledge about the mechanisms by which viruses induce acute airway inflammation, little is known about why these changes produce asthma months or years later. Severe respiratory infections may permanently alter the innate immune system, and up-regulation of Th2 cytokines[49] acutely may cause irreversible changes in the airway that lead to increased airway hyperresponsiveness (AHR) and asthma at later times.[48]

Atypical bacterial pathogens are implicated in triggering acute asthma and propagating chronic asthma and airway inflammation.[50] The role of these pathogens in

initiating asthma is poorly defined.[50] Johnston and Martin[50] reported that with few exceptions, the majority of studies support the presence of a relationship between atypical pathogens and chronic stable asthma.[50–55] *Chlamydophila pneumoniae* and *Mycoplasma pneumoniae* are present in the airways of chronic asthmatics and are associated with increased airway inflammation and a more severe asthma phenotype.[56–58] The interaction between pathogens and asthma is not necessarily causative but rather could indicate an increased susceptibility to infections associated with atopy and asthma. Further evidence is required to determine the role of infections in the development of asthma.

Atopy

The incidence of asthma in childhood is strongly and independently associated with hay fever and eczema.[59–61] ISAAC phase I involved 155 centers in 56 countries and focused on the prevalence of asthma, allergic rhinitis, and atopic eczema in two childhood cohorts. This study found wide variations in the prevalence of asthma between countries and in different regions within countries.[5,7] The prevalence rates differed by more than 20-fold between study centers.[5,7,26,60] This variability was likely to be explained by environmental or lifestyle factors.

ISAAC phase II was designed to determine the role of environmental and lifestyle factors on the observed differences in prevalence rates.[8] This study included a smaller cohort of children 9 to 11 years old from 30 study centers in 22 countries and added objective measurements of atopy including skin examination, skin prick tests, bronchial challenge testing, and specific immunoglobulin E (IgE) measurements. Study site selection was based on prevalence rates, and sites with high or low prevalence were included in the second phase of the study.[8] Logistic regression modeling revealed no significant correlation between atopy and wheezing in this cohort of children. Subgroup analysis based on per capita income showed an increase in wheezing associated with atopy and allergy in countries with higher gross national income.[9] The association between maternal or paternal atopy and the occurrence of asthma in children is controversial. Paternal atopy or asthma is not strongly associated with the incidence of asthma in childhood[9]; however, maternal AHR is associated with nonatopic wheezing in children.[62] In contrast, several studies show that a family history of atopy is an important risk factor for atopy in children.[63,64]

The type of allergen and duration of exposure may be important predictors of asthma in childhood and later life. Torrent and associates[65,66] demonstrated that a threshold dose of environmental allergen exposure is required to induce sensitization or asthma, whereas no dose-response relationship existed above this threshold. The determinants of whether one develops allergic rhinitis/atopy, asthma, or both are unclear. The role of early childhood atopy in the development of asthma continues to be an area on ongoing research, and although the data demonstrate a significant link, important questions still remain.

Obesity

The role of obesity in the development of asthma is a new area of investigation. The obesity epidemic has been increasing for the past several decades and there are no signs that the trend will change in the near future. The recent Centers for Disease Control and Prevention (CDC) NHIS survey reported that 30% of adults over the age of 18 years are obese and about 68% of United States adults are either obese or overweight. The incidence of obesity has almost doubled since 1990.[6] The incidence and prevalence of asthma also have increased, and current prevalence data suggest that asthma affects approximately 5% of the U.S. population. Many studies have examined whether the increased prevalence of obesity has resulted in the increasing incidence of asthma. More than 30 cross-sectional and case-control studies of the relationship between obesity and asthma have appeared since the 1990s.[67–71] Almost without exception, these studies report an increased prevalence of asthma in obese and overweight individuals throughout the world. Although such studies do not address the direction of causality, several large epidemiologic studies have found that obese individuals have an increased odds ratio or relative risk of developing asthma (defined as a body mass index [BMI] > 30).[72,73] Obesity is associated with multiple comorbidities, including hypertension, hypercholesterolemia, diabetes mellitus, obstructive sleep apnea, gastroesophageal reflux disease (GERD), and depression.

The biologic basis for the relationship between obesity and asthma has not been established, but several mechanisms have been proposed, including common genetic etiologies, comorbidities, effect of obesity on lung mechanics, and the role of inflammatory mediators secreted by adipose tissue (adipokines). Weiss[74] suggested that obesity and asthma share common etiologies, for example, common effects of fetal programming or common genetics. Obesity may increase the risk of asthma through its effects on other disease processes such as sleep-disordered breathing (SDB) and GERD. The effect of these disease processes on the development of asthma is controversial. In a community-based cohort study of almost 800 children, Sulit and coworkers[75] reported that the association between obesity and asthma was strong even after adjusting for SDB. GERD is associated with increased AHR and wheezing[76–78] as a result of vagal nerve stimulation by acid refluxing into the distal esophagus and microaspiration of acid into the bronchi.[79,80] Treatment of GERD with medications or surgical intervention with Nissen fundoplication improves asthma control and decreases bronchial hyperresponsiveness.[81–85] Whereas GERD and SDB may contribute to the development of bronchial hyperresponsiveness and affect asthma control, these diseases do not entirely account for the association between obesity and asthma.

Recently, there has been interest in the role of adipokines in the development and perpetuation of asthma.[85a]

One link between obesity and asthma may be the effects of adipokines on airway inflammation. Adipose tissue is metabolically active and participates in energy homeostasis. Animal studies of obesity show that adipose tissue secretes biologically active cytokines, including tumor necrosis-α (TNF-α) and IL-6, and adipokines such as leptin, adiponectin, plasminogen activator inhibitor-1 (PAI-1), and resistin.[86] Adiponectin, a potent anti-inflammatory hormone secreted by adipose tissue, is found in low levels in the serum of obese individuals. Adiponectin attenuates allergen-induced airway inflammation and hyperresponsiveness in OVA sensitized and challenged mice.[87] In humans, obesity results in systemic inflammation characterized by elevated serum levels of these adipokines, chemokines, and acute phase proteins.[88] Obesity is associated with increased leptin levels, which may be associated with increased inflammation in the airways of obese asthmatics. Guler and colleagues[89] noted that serum leptin was predictive of asthma in boys, even after adjusting for BMI. Other studies reveal higher leptin levels in asthmatic women as compared with normal women; however, adjusting for serum leptin does not affect the association between BMI and asthma.[90] The relationship between obesity and asthma does not appear to be mediated via leptin in spite the fact that leptin may be an independent predictor of asthma. The effect of obesity on the development of asthma remains incompletely understood, but these early studies are promising and more work in this area is needed.

Genetics

Genetics play a significant role in the development of asthma and allergic diseases and is discussed in greater detail in the "Genetics of Asthma" section. The interplay between genetic predisposition and environmental exposures underlies the development of asthma. Advances in genomics have led to the discovery of several polymorphisms that are important in the development of asthma[91] and the response to therapy. Senthilselvan and associates[92] studied a cohort of 915 nonsmoking students and identified an association between Toll-like receptor 4 (TLR4) polymorphisms and atopy in females. TLR4 polymorphisms reduced the odds of having hay fever by 88%.[92,93] Conversely, Raby and coworkers[94] found no associations between TLR4 polymorphisms and asthma or atopy-related phenotypes. Other polymorphisms of interest in asthma include polymorphisms in IL-4, IL-4 receptor-α, and IL-5 polymorphisms that contribute to susceptibility for bronchial asthma.[95–98] The phenotypic and genetic heterogeneity in asthma poses a challenge to discovering specific genetic mutations that solely increase the risk of asthma.[99]

Tobacco Use and Environmental Exposure

Exposure to environmental tobacco smoke is common and its role in the development of asthma and abnormal lung function in childhood is controversial. There is increasing evidence that both in utero and childhood exposure to tobacco results in detrimental effects on respiratory health. Studies have demonstrated that in utero and early childhood exposure to tobacco leads to an increased risk of abnormal lung function[100,101] and wheezing illnesses in childhood,[102–104] an effect that persists into adulthood.[105] Population-based studies demonstrate that environmental tobacco exposure in childhood also results in an increased risk of asthma.[106,107] These effects of tobacco exposure early in life are thought to be mediated by influences on early immune function, specifically alterations in TLR signaling, which result in an increased susceptibility to microbial infections and a decreased ability to activate regulatory pathways that inhibit allergic responses.[108] The effect of early tobacco exposure on the development of allergic rhinitis and atopy is controversial; however, there is increasing evidence that a strong interaction exists.[109] Gene-environment interactions are important mediators of the effects of in utero exposure on the development of asthma.[110] Polymorphisms of IL-13[111] and β-receptors[102] modify the effect of exposure to tobacco smoke on asthma and wheezing in childhood. Tobacco use is also associated with an increased risk of developing asthma.[112] Polosa and colleagues[113] found that the risk of developing asthma occurs in a dose-response manner in adults with allergic rhinitis. There was an odds ratio of 2.98 (95% confidence interval [CI], 1.81–4.92) of developing asthma in smokers with allergic rhinitis.[113] Environmental smoke exposure in adults results in increased morbidity and poorer asthma control.

Asthma is a complex disease that is the result of the interaction between genetic predisposition, environmental exposures, and responses of the innate and adaptive immune systems. Advances in research have led to the discovery of many possible mechanisms that underlie the development and persistence of asthma. These advances support the conclusion that asthma includes many distinct phenotypes that relate to the underlying pathophysiology and mechanisms of disease. Defining these phenotypes will enhance our ability to tailor therapies and improve outcomes for patients with asthma.

GENETICS OF ASTHMA

Overview

Studies of mono- and dizygotic twins were used initially to estimate the heritability of asthma. These studies showed a higher concordance rate for asthma in monozygotic than in dizygotic twins.[114] Studies showing an increased prevalence of asthma in first-degree relatives[115] lend further support to this hypothesis. Many efforts have been made to study the genetic etiology of asthma in order to better understand its pathogenesis and thereby improve strategies to prevent, diagnose, and treat asthma. Publication of the human genome in 2001 and completion of the International HapMap Project in

2005 produced exponential growth in the field, and over 1 million markers of asthma have been identified. However, asthma is very heterogenous and varies not only in the age of onset, degree of severity, and response to therapy but also in the phenotype, which includes nonspecific AHR, atopy, eosinophilia, and mucus hypersecretion. Moreover, these phenotypes change during life, which further complicates the search to find genetic risk factors for asthma.

Linkage Analysis versus Candidate Gene Approaches

Studies of asthma susceptibility genes have been carried out using two general approaches: linkage analysis and candidate gene association studies. Linkage analysis is a technique used to systematically scan the entire genome of various family members affected by a disease to identify genetic regions associated or "in linkage" with a disease phenotype. Affected family members are hypothesized to share certain alleles located in the identified regions more frequently than would be expected by chance alone. Linkage analysis has been successful in identifying diseases in which the disease penetrance follows simple mendelian genetics but is limited because it has less power than association studies to detect weak genetic effects of loci involved in complex diseases that do not follow mendelian genetics.[116,117] This approach, originally called "reverse genetics," also called positional cloning, does not require a prior hypothesis about which genes cause asthma and has been successful in identifying candidate genes for asthma.[118–121] ADAM 33 was the first gene identified as an asthma susceptibility gene using a positional cloning approach.[120] ADAM 33 belongs to a family of proteins that are membrane-anchored metalloproteases with diverse functions, including the shedding of cell-surface proteins. Increased immunostaining of ADAM33 has been found in the lungs of patients with severe asthma as compared with control subjects or those with mild asthma.[122]

Several studies also have identified linkage between regions of genes and asthma-associated phenotypes, including atopy, AHR, and elevated IgE levels.[123–126] These studies have shown that, although asthma, elevated IgE, and AHR are genetically determined,[127] no single gene controls inheritance of these phenotypes and heritability of the phenotypes is not the same.[128,129]

In contrast to linkage analysis, candidate gene association studies select specific genes based on a biologic theory about their putative role. The gene of interest is chosen because it is believed to influence the expression of a phenotype because of its biologic role or because of its proximity to a region of linkage or association on a specific chromosome. Association studies are thought to be more powerful than linkage studies in detecting alleles that confer modest risk of disease.[116] Furthermore, association studies take advantage of the fact that it is easier to recruit large populations of unrelated individuals than it is to recruit large numbers of family numbers. Furthermore, there is greater statistical power in studying case-control associations than in family-based linkage studies.

To test genes associated with a specific biologic hypothesis, candidate gene studies use case-control or family-based designs. Case-control designs compare allele frequencies between subjects with and without asthma. Case-control designs have been criticized because the recruitment of study populations can create differences in allele frequencies between cases and controls unrelated to disease status and introduce type I error. The family-based design, conversely, avoids issues of population structure and compares the alleles that parents transmit to children with asthma with alleles parents do not transmit. If an allele increases the risk for asthma, it should be more common among the transmitted alleles than the nontransmitted alleles.

More than 100 genes have been associated with asthma phenotypes. However, few reports of associations between asthma and candidate genes have been replicated across studies. In a review of nearly 500 papers on disease association studies, Ober and Hoffjan[130] identified 25 genes that are associated with asthma or atopy in six or more populations and 10 genes that have been associated with asthma or atopy in more than 10 studies (IL-4, IL-13, CD14, adrenergic receptor beta 2 [ADRB2], human leukocyte antigen [HLA]-DRB1, HLA-DQB1, TNF, FCER1B, IL-4Ra, and ADAM 33). These genes in general fall into four broad categories: innate immunity (CD14, HLA-DRB1, HLA-DQB1), Th2 cell signaling (IL-4, IL-13, IL-4Ra), cellular inflammation (TNF, FCEDR1B), and lung development (ADAM 33, ADRB2).

Genome-Wide Association Studies

The completion of the International HapMap Project in 2005 laid the foundation for the next step in investigating genetics in asthma, genome-wide association studies. In genome-wide association studies (GWAS), high-throughput screening of common genetic variations across the genome is used to genotype a single population. This unbiased approach has the potential to identify novel susceptibility genes and pathways not previously identified with asthma. The first GWAS for asthma was published in 2007[131] and revealed an association between a gene on chromosome 17q21 locus and childhood asthma. This finding led to the identification of ORMDL3 as an asthma susceptibility gene. The potential role of this gene in asthma has not yet been defined, and further studies must be performed to determine its effect on susceptibility to asthma. The second GWAS on asthma was reported by Ober and colleagues[132] and showed an association between a promoter variant in the chitinase 3-like 1 gene encoding YKL-40 and asthma, AHR, and decreased lung function. GWAS have also identified the 11p14 locus,[133] 5q23 locus,[134] and chromosome 18[135] as potential regions harboring asthma susceptibility loci that warrant further investigation.

Future Studies

GWAS also have the ability to identify gene-gene interactions and gene-environment interactions. Gene-gene interactions identify whether one gene can modify the effect of another in a biologic pathway. Alone the variant has a modest effect; however, when combined with another genetic variant in the signaling pathway, the variant might amplify the impact on the disease.[97] By analyzing steps in a pathway, discovery of new genes in an unbiased way can occur.

Gene-environment interactions can be used to study the effect that external factors have on influencing phenotypic variance. This approach has shown that the influence of susceptibility genes for common diseases, such as asthma, might not become apparent unless the appropriate exposure to the environmental stimulus occurs. Miller and Ho[136] listed 20 different reports as identifying specific gene-environment interactions with asthma. As an example, linkage of 5q to bronchial hyperresponsiveness was found in asthmatic children exposed to passive smoking, but not in children from non–smoke-exposed families.[137]

The future of GWAS also lies in studying the role of epigenetics in the etiology of asthma and the effect of disease modifiers, such as obesity. Epigenetic modifications are defined as a collection of heritable changes in gene expression that do not directly alter DNA sequences. The most common epigenetic modifications of the human genome are DNA methylation and posttranslational modification of core histone proteins. DNA methylation involves the covalent addition of a methyl group to a cytosine and usually occurs near CpG sites. Methylation of CpG islands can affect gene expression. Posttranslational modification of histones can involve acetylation, methylation, phosphorylation, and ubiquitinylation and can alter transcriptional activity. Both of these epigenetic modifications can be heritable and influence gene expression during growth and development.[138] If environmental exposures such as allergens, antibiotics, air pollution, diet, and tobacco exposure can induce epigenetic regulation in vivo, then epigenetics provides an attractive explanation for environmentally regulated alteration of gene expression. Indeed, evidence from two large prospective clinical studies indicates that prenatal exposure to tobacco smoke is associated with an increased incidence of asthma in young children and adolescents.[139,140] Moreover, data also suggest that exposure to tobacco smoke can increase the risk of asthma across generations.[141] Determining whether genetic or environmentally triggered epigenetic changes occur in the genome will be important in advancing understanding of the pathogenesis of asthma.

The first study to demonstrate genome-wide linkage and association of gene expression traits in tissues other than lymphoblastoid cell lines was published in 2008.[142] Emilsson and associates[142] showed that compared with the 10% correlation found in blood, more than 50% of all gene expression traits in adipose tissue correlated strongly with obesity-related traits. They then used genome-wide linkage and association studies to demonstrate heritability of genetic variations in the two tissues. This approach can be used to determine the effect of disease modifiers on asthma.

GWAS also have the potential to significantly affect medical care in the future by laying the groundwork for personalized medicine. Genetic profiling in subpopulations of asthmatics can be used to determine whether genetic polymorphisms predict response to therapy and adverse effects of therapy. The U.S. Food and Drug Administration (FDA) has approved several genetic tests for cytochrome 2D6 and 2C19 variants as part of its efforts to improve patient safety in the treatment of human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS). Pharmacogenetics is also used in the treatment of childhood leukemia; however, tailored therapies for asthma are still under investigation. To date, the most studied genetic variations in asthma are the β_2-adrenergic receptor polymorphisms. Three loci at amino acid positions 16, 27, and 164 have been found to significantly alter function.[143–145] Genetic association studies and linkage analyses in families have further established the importance of these polymorphisms. Randomized placebo-controlled studies demonstrate that the polymorphism at position 16 may negatively influence response to short acting β_2-agonists.[146] However, the data with regard to the effect of the polymorphism and response to long-acting β-agonists (LABAs) are controversial[147,148] because one small, retrospective study suggested a relationship,[149] whereas two other larger retrospective studies did not.[147,148] Two prospective, genotype-stratified studies are now in progress that should answer this question.

PATHOPHYSIOLOGY OF ASTHMA

Etiology of Asthma

Asthma is a complex inflammatory disease of the airways that involves many different cells (e.g., neutrophils, basophils, eosinophils, mast cells, macrophages, structural cells) and mediators (e.g., cytokines, chemokines, histamine, leukotrienes, reactive oxygen species, and thromboxanes). The concepts about the pathogenesis of asthma have evolved since the mid 1980s, primarily due to new techniques that have linked various asthma phenotypes to genotypic patterns. Based on this work, there is a general consensus that airway inflammation and remodeling are critical components of asthma. Furthermore, environmental exposures throughout life can modulate the expression of asthma susceptibility genes, making asthma a dynamic disease.

Although asthma is multifactorial in origin, inflammation is believed to be the cornerstone of the disease and is thought to result from inappropriate immune responses to a variety of antigens in genetically susceptible individuals. Evidence from patients with asthma and animal models of bronchial hyperreactivity suggests that recruited CD4 lymphocytes orchestrate and implement immune responses and inflammation that contribute to asthma.

Cellular Inflammation and Asthma

CD4 Lymphocytes

Four distinct subsets of CD4 lymphocytes, Th1, Th2, regulatory T cells (T_{Reg}), and T17 cells can differentiate from precursor T cells at the time of antigen presentation and influence cytokine production. The differentiated Th cells are characterized by the specific sets of cytokines they release when stimulated. For many years, it was believed that asthma and other allergic diseases resulted from an imbalance between Th1 and Th2 responses in favor of a Th2 response, promoting an allergic diathesis based on Th2 cell responses. The identification of transcription factors controlling Th1 and Th2 differentiation has provided further support for a predominant role of Th2 cells in the pathogenesis of asthma, because Tbet expression is reduced in the asthmatic lung[150] and GATA 3 is overexpressed.[151,152] However, recent discoveries and an improved understanding of the interaction between Th17 cells and regulatory T cells have shown that the simple Th1/Th2 hypothesis is not sufficient to explain asthma.

Th1 cells drive cell-mediated immune responses and are characterized by the production of IFN-γ, TNF-α, and IL-2 without production of IL-4, IL-5, IL-9, and IL-13. By contrast, Th2 cells mediate humoral responses and are characterized by their secretion of IL-4, IL-5, IL-9, and IL-13 in the absence of IFN-γ and TNF-α. Antigen recognition by naive T cells in the presence of IL-12 favors STAT4 and Tbet activation which promote Th1 cell differentiation. Early IL-4 production favors STAT6 and GATA3 activation, which lead to Th2 cell production. Th17 cells, a newly discovered subset, produce IL-17 and IL-22.[153] These T cells are proinflammatory and have been studied primarily in mice. They express a characteristic transcription factor, retinoic acid orphan nuclear receptor (ROR-γ).[154] In a murine model of allergic asthma, IL-17 was found to be necessary for the induction of allergic asthma. In healthy human subjects with asthma, IL-17 production increases in peripheral blood after allergen challenge. In addition to its proinflammatory role in asthma, Th17 cells also have been detected in other inflammatory autoimmune diseases such as Crohn's disease, rheumatoid arthritis, and multiple sclerosis and have been shown to be important in host defense against bacterial pathogens.[155]

In contrast to Th1, Th2, and Th17 cells, T_{Reg} cells act directly or indirectly to suppress the function of effector T cell responses in allergic asthma. These cells have cytokine profiles that are distinct from Th1 and Th2 cells and appear to control development of autoimmune disease[156] and are able to inhibit development of allergic Th2 responses. Several subsets of T_{Reg} cells have been identified, including natural $CD4^+CD25^+T_{Reg}$ cells, Th3 cells, and inducible type 1 T_{Reg} (TR1) cells.[157] A deficiency in $CD4^+CD25^+T_{Reg}$ cells can result in the development of asthma.[158] These cells originate in the thymus, require expression of the transcription factor FoxP3 for the development of the suppressive function, and do not produce cytokines. Th3 cells produce mainly transforming growth factor-β (TGF-β) and their regulatory function is due to a TGF-β–dependent mechanism. TR1 cells are inducible and secrete high levels of IL-10, IFN-γ, and TGF-β but no IL-4 or IL-2.[159] These cells do not overexpress FoxP3 and appear to be regulated through different pathways.

Epidemiologic studies demonstrate a higher prevalence of asthma in industrialized Western societies than in less technologically advanced societies.[7] These observations are the essence of the "hygiene hypothesis."[160] The hygiene hypothesis proposes that increased hygiene and lack of exposure to environmental antigens, such as animal allergens, may be affecting the immune system by changing the relative balance of the Th1 and Th2 immunologic profile. Early exposures to various triggers that might occur at an increased frequency in a rural setting can tilt the balance to a Th1 dominant response that is protective against the allergic diathesis promoted by Th2 responses. Therefore, in more urban "cleaner" societies where early childhood exposures are less pronounced, a shift toward a Th2 immunologic profile occurs, resulting in a higher incidence of asthma and other allergic diseases.

Eosinophils

Eosinophils are prominent cells in the airways of many patients with asthma. Most asthma phenotypes are associated with increased numbers of eosinophils in blood, bone marrow, and lung, leading to the hypothesis that the eosinophil is a central effector cell in asthma that contributes to ongoing airway inflammation. The secretion of eosinophil peroxidase, leukotrienes, reactive oxygen species/reactive nitrogen species (ROS/RNS) by eosinophils can result in epithelial damage, bronchoconstriction, and mucus hypersecretion. Eosinophils also present antigens and secrete cytokines which can further amplify the Th2 response.[161] Indeed, the number of eosinophils in bronchoalveolar lavage (BAL) and blood correlates with severity of disease in humans with asthma. However, whether the eosinophil is causal in the pathogenesis of asthma or an innocent bystander is still debated. Studies in mice blocking IL-5 either by targeted gene deletion or using anti-IL-5 monoclonal antibodies have produced conflicting results.[162,163] Further studies in humans confirm that pharmacologic inhibition of IL-5 can result in eosinophil depletion, but this does not provide significant improvement in airway function or disease symptoms in asthma.[164] Two published studies[165,166] supported the concept that eosinophils are critical in allergic asthma in mice. In one study, Humbles and coworkers[165] deleted the high-affinity GATA-1 binding site on the GATA-1 promoter, the transcription factor required for differentiation of immature myeloid cells, and found that despite eosinophil depletion, there was no effect on AHR and mucus production. In an entirely different approach, Lee and colleagues[166] used an eosinophil peroxidase promoter to control transgenic expression of diphtheria toxin A chain, to destroy eosinophils, and found that eosinophils were essential for AHR and mucus production. The divergent findings in these two studies are difficult to explain and have been

attributed to background strain variability, controversy about the IL-5 antibody used in the studies, and indirect effects of diphtheria toxin A.[167]

Inflammatory Cytokines and Asthma

Atopic asthmatics have increased expression of Th2 cytokines in airway biopsies and BAL compared with healthy volunteers.[168] Th2 cells regulate allergic inflammation via production of IL-3, IL-4, IL-5, IL-9, IL-10, and IL-13. IL-5 has an essential role in regulating eosinophilic inflammation in asthma and subsequent AHR.[169] IL-9 appears to augment Th2-driven inflammation and be involved in mast cell release, IgE production, and mucus hypersecretion.[170] IL-10 is an anti-inflammatory cytokine and acts to inhibit inflammatory cytokine expression, chemokines, IL-5[171] and granulocyte-macrophage colony-stimulating factor (GM-CSF) production[172] in asthma.

Although all Th2 cytokines contribute to the pathogenesis of asthma, IL-4 and IL-13 are particularly relevant. IL-4 is critical for the synthesis of IgE and is involved in eosinophil recruitment to the airways.[173] Because IL-4 also acts to promote Th2 cell differentiation, it acts at a critical proximal site in the allergic response and is an attractive target for inhibition. This concept is supported by studies in IL-4–deficient mice, which show that IL-4 is essential for the development of allergic symptoms, because allergen-challenged IL-4–deficient mice do not develop an asthma phenotype.[174]

IL-13 has a similar structure to IL-4 and shares a functional receptor, IL-4Rα. A substantial body of evidence supports IL-13 as necessary and sufficient to induce allergic asthma.[175,176] Acute administration of IL-13 to mice recapitulates many of the features of allergic asthma, including AHR, eosinophilia, mucus hypersecretion,[175,176] and subepithelial fibrosis.[177] Genetic evidence in humans further supports a role for IL-13 dysregulation in allergic asthma. Polymorphisms in the promoter region and coding regions of the gene are associated with increased risk of developing asthma.[178,179]

Biochemical Mediators of Asthma

Reactive Oxygen Species

Asthma is characterized by altered airway redox chemistry and increased oxidative stress in the airways.[180] Lung inflammatory cells, including eosinophils, macrophages, and neutrophils, are increased in the asthmatic airway and able to release large quantifies of ROS and RNS.[181] Furthermore, eosinophils, macrophages, and neutrophils isolated from asthmatics produce increased concentrations of ROS compared with normal subjects.[182] Myeloperoxidase and eosinophil peroxidase produced by these granulocytes are increased in BAL and peripheral blood in asthmatics and can produce large amounts of the potent ROS, hydroxyl radical,[182] resulting in epithelial damage and increased AHR in asthmatic individuals. The observation that lung eosinophils in BAL and blood correlate with AHR in asthma provides further support for a proinflammatory role of ROS in asthma. Concurrent with the increased oxidants in asthma, the antioxidant activity in the lower airways is reduced, providing further indirect support for the importance of oxidants in asthma.[183]

Reactive Nitrogen Species

In addition to increased ROS, RNS also may be important in the pathogenesis of asthma. It is well-established that the exhaled breath of asthmatics contains higher concentrations of nitric oxide (NO) than the exhaled breath of normal individuals.[184] NO is produced by nitric oxide synthase (NOS). The three known isoforms of NOS are members of a family of different but related NOS proteins: neuronal NOS (NOS1), immunologic NOS (NOS2), and endothelial NOS (NOS3). NOS1 and NOS3 are constitutively expressed, although they can be regulated.[185] NOS2 was originally described in macrophages and is inducible. All NOS isoforms are expressed in the lung.[186] Whereas NOS1 is found primarily in the neuronal plexus; NOS3 is ubiquitous and expressed in respiratory epithelium, vascular endothelium, and neurons.[187] In contrast, the expression of NOS2 is inducible in respiratory epithelium and macrophages.[187] NO can react with oxygen or ROS to form oxidation products, NO_2^-, NO_3^-, and peroxynitrite,[188] which can induce tissue damage. The concentrations of NO are increased in the exhaled breath of asthmatics, and measurements of expired NO can be used to monitor disease[189] and titrate inhaled corticosteroid therapy.[190] Exhaled NO is a summation of airway NO formation, superoxide anion metabolism, changes in airway pH, and metabolism of S-nitrosoglutathione (GSNO), an endogenous bronchodilator present in the lung. GSNO is deficient in the airways of children with acute asthmatic respiratory failure. Mice deficient in GSNO-reductase (GSNOR), an enzyme that metabolizes GSNO, develop allergic airway inflammation, but do not develop AHR,[191] which suggests that *S*-nitrosothiols may play a critical role in reducing bronchoconstriction in allergic asthma.

Arginase

Recent evidence indicates that arginine metabolism may also contribute to the development of AHR in allergic asthma. Increased arginase activity in allergic asthma was first described in a guinea pig model whereby administration of an arginase inhibitor, *N*-hydroxy-nor-L-arginine (NOHA), reduced AHR and restored NO production.[192] Arginase expression is also increased in BAL cells, inflammatory cells, and airway epithelium obtained from bronchial biopsies of asthmatic subjects.[193] Furthermore, genetic polymorphisms in arginase have been identified, supporting a role for arginase in asthma and atopy in children.[194]

Arachidonic Acid Metabolism

Products of arachidonic acid metabolism are also increased in the exhaled breath of patients with asthma.[195] Cysteinyl leukotrienes and other products of the 5-

lipoxygenase pathway are potent inflammatory mediators implicated in the pathogenesis of asthma. Elevated concentrations of cysteinyl leukotrienes are produced in the airway of asthmatics[196] and have been recovered from the urine of patients with allergen-induced asthma,[197] exercise-induced asthma,[198] and aspirin-induced asthma.[199] Leukotrienes act by binding to receptors on the surface of structural and inflammatory cells. These receptors activate G protein–coupled receptors in the cytoplasm and increase intracellular calcium, resulting in bronchoconstriction and mucus secretion.[200] Inhibitors of the 5-lipoxygenase pathway and cysteinyl leukotriene receptor 1 are used to treat asthmatics who remain symptomatic despite using inhaled corticosteroids.

AIRWAY REMODELING IN ASTHMA

Introduction

Airway remodeling is one of the cardinal pathologic features of chronic asthma and is defined as structural alteration of the airway with characteristic changes in the nature, content, and distribution of airway elements.[201] The degree of remodeling is a function of disease severity over time, because the degree of structural changes on biopsy and imaging studies correlates with the clinical severity of asthma.[202–204] The major pathologic changes include increased deposition of subepithelial collagen, airway smooth muscle (ASM) hyperplasia, proliferation and hyperplasia of goblet cells and submucosal glands, and microvascular changes.[205] These structural changes result in thickening of airway walls and decreased diameter of the airway lumen, which have been observed in pathologic and radiographic studies.[206,207] Ultimately, remodeling contributes to the characteristic physiologic changes of asthma discussed previously, including airflow limitation, AHR, and mucus hypersecretion.

The primary hypothesis about the pathogenesis of airway remodeling is that remodeling is caused by exaggerated airway inflammation in response to environmental stimuli. The experimental support for this hypothesis includes animal data linking allergen-driven Th2 inflammatory responses with extensive airway remodeling in mice.[208,209] For example, overexpression of the Th2 cytokine IL-13 in transgenic mice leads to the characteristic changes of airway remodeling, including increased subepithelial collagen deposition, epithelial hyperplasia, enhanced mucus production, and microvascular changes.[210] Similarly, in an ovalbumin challenge model of allergic asthma, inhibition of leukotriene formation substantially reduced airway remodeling and reduced the expression of Th2 cytokines.[211] Nevertheless, the limited efficacy of anti-inflammatory treatment in preventing remodeling suggests that remodeling may not be entirely due to inflammation. Some evidence suggests that remodeling may occur independently of the recruitment of inflammatory cells.[212] Native airway constituents, including epithelial cells, fibroblasts, and ASM cells, have been shown to produce mediators associated with remodeling in vitro and, to a lesser extent, in vivo.[213,214] The precise relationship between remodeling and inflammation is unclear.

Epithelium

Normal airway epithelium contains ciliated columnar, mucus-secreting goblet, and surfactant-secreting Clara cells that form a highly regulated and impermeable barrier made possible by tight junctions located on the apical surface of the columnar cells.[215,216] The airway epithelium is altered in the airways of mild and severe asthmatics, because epithelial changes have been identified in biopsies of airways of adults and children.[217] Although initial pathologic studies in asthma attributed epithelial abnormalities to bronchoscopy-related injury,[218,219] recent studies have revealed that the airway epithelium is abnormal both in vitro and in vivo. The finding that damaged asthmatic epithelium is associated with up-regulated epidermal growth factor receptors and impaired proliferation suggests a pattern of chronic injury and aberrant repair.[220] This is hypothesized to lead to increased epithelial permeability due to dysfunction of the airway tight junctions[221] and may in part be responsible for the increased susceptibility of asthmatic epithelium to oxidant injury.[222]

A great deal of evidence suggests that the airway epithelium is a central participant in innate and adaptive immune responses.[223] Disruption of the tight junctions allows easy entry of microparticles, allergens, and microbes into the subepithelial space with resultant activation of inflammatory cells, leading to the production of cytokines and chemokines and propagation of inflammation.[215,224] Subsequent production of growth factors is thought to lead to subepithelial fibrosis and airway remodeling. Holgate[225] proposed the concept of the epithelial mesenchymal trophic unit (EMTU) (Fig. 38-3), which is analogous to the "soil" that allows the "seed" of Th2 inflammation to persist. The activated EMTU is hypothesized to propagate Th2 inflammation through interactions with resident airway immune cells via proinflammatory mediators derived from the activated structural cells of the EMTU.[226] The cytokines produced by immune cells are proposed to feed back to the EMTU, contributing to a cycle of persistent chronic inflammation, with propagation of myofibroblasts, proliferation of smooth muscle, and alterations in microvasculature.

Epithelial Basal Lamina

A characteristic feature of asthma in adults and children is the hyalinization and thickening of the basal lamina beneath a normal-appearing epithelial basement membrane.[216] Accompanying this unique change in airway structure is an increased number of myofibroblasts capable of laying down matrix,[227] including increased amounts of type III and V collagens, fibronectin, and tenascin.[228,229] Asthma is not associated with basement membrane thickening but rather subepithelial fibrosis

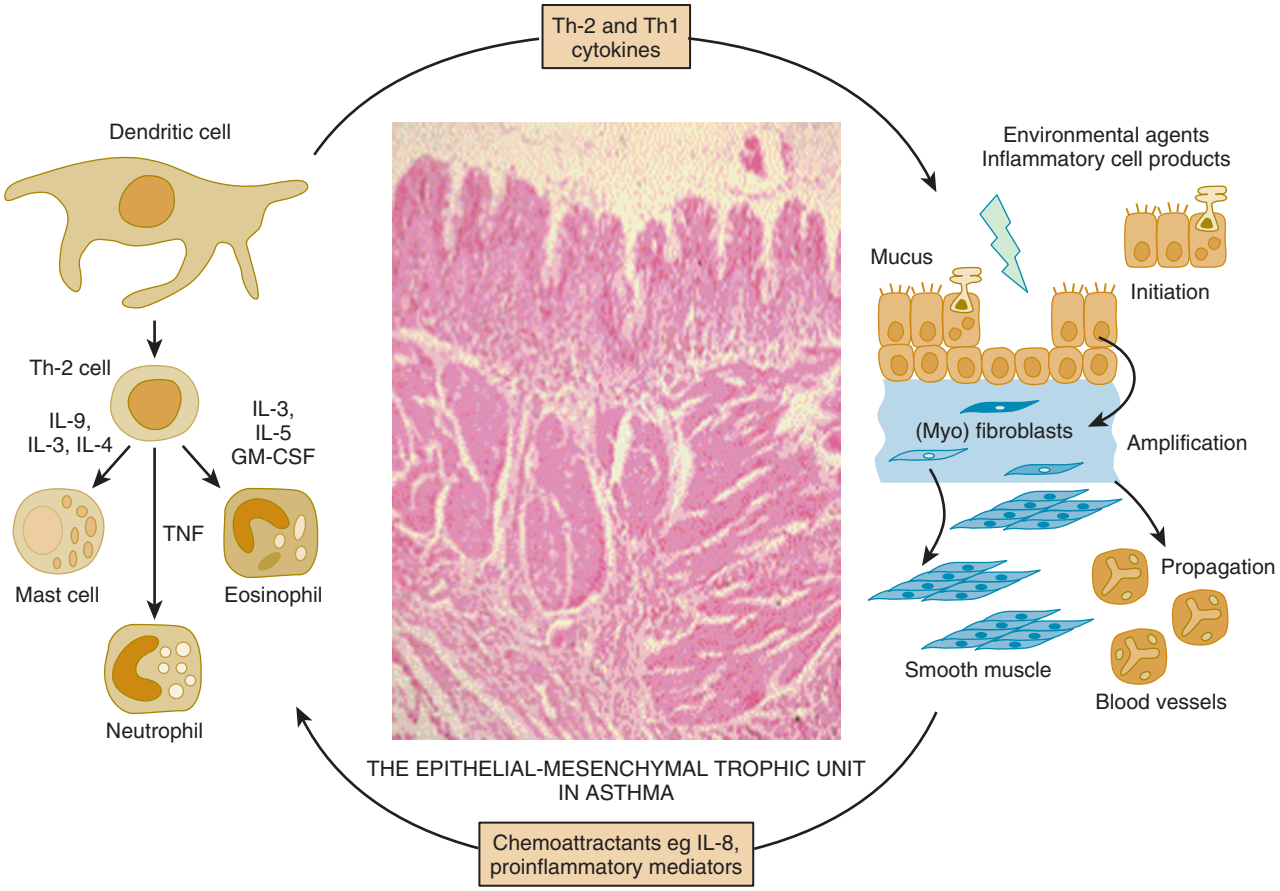


FIGURE 38-3 ■ Schematic representation of the interaction between immune, inflammatory, and structural cells through the epithelial-mesenchymal trophic unit (EMTU) in the pathogenesis of asthma. (Adapted from Holgate ST: The airway epithelium is central to the pathogenesis of asthma. Allergol Int 57:1–10, 2008.)

with deposition of collagen beneath the basement membrane.[230] These changes have been reported in early asthma close to the beginning of the disease, suggesting that the changes in matrix deposition are not the result of chronic inflammation.[216,225,231,232] Both the Tucson Children's Respiratory Study and the Childhood Asthma Management Program demonstrated that reduced lung function can occur early in life and is unabated by conventional therapies.[233,234] The mechanisms involved in remodeling of the basal lamina are unknown. However, murine models of asthma have suggested roles for platelet-derived growth factor (PDGF), TGF-β, and IL-13.[235] TGF-β promotes the differentiation of fibroblasts into myofibroblasts, which form collagen and secrete growth factors.[236] In humans, PDGF has been implicated in airway remodeling by inducing airway fibroblasts to produce collagen and increase matrix formation. The PDGF-BB isoform enhances fibroblast procollagen I formation in subjects with severe asthma as compared to those with mild to moderate asthma.[237,238] Additionally, PDGF and TGF-β have been shown to modulate expression of matrix metalloproteinases and regulation of migratory function of human airway smooth muscle cells.[238a] Further research is required to determine the mechanisms of airway fibrosis and to guide more specific therapy in asthma.

Extracellular Matrix

Extracellular matrix (ECM) is increased in the airway walls of humans with asthma and is seen in experimental models. In ovalbumin challenge models, airway wall collagen, fibronectin, and proteoglycan deposition are increased.[239,240] Loss of elastic fiber content in the small airway adventitial layer has been demonstrated in studies of severe and fatal asthma.[241–243] Airway elastin, the matrix component whose degradation is central to emphysema, is also decreased in biopsy specimens from asthmatic patients.[244–246] These changes appear to be mediated, at least in part, by exposure to Th2 cytokines. For example, IL-5 exposure increases allergen-induced collagen deposition, whereas allergen-challenged IL-5 knockout mice have decreased collagen deposition.[247,248] Mice with a knockout of Tbet, a Th1-specific transcription factor, have profound defects in the production of Th1 cytokines and increased production of Th2 cytokines. As a result, the mice develop a remodeled asthmatic phenotype, with high levels of Th2 cytokines and increased subepithelial collagen deposition. The central role of IL-13 is illustrated by the amelioration of airway remodeling that occurs when IL-13 is neutralized.[249]

TGF-β, derived from eosinophils, macrophages, and other cells, is also strongly implicated in ECM remodeling. Mice treated with anti-TGF-β antibody have decreased ECM deposition,[250] whereas treatment of asthmatics with anti-IL-5 antibody decreases ECM deposition and reduces BAL concentrations of TGF-β.[251] In addition, the gene for TGF-β is up-regulated in allergen-challenged mice[252] and Tbet/IFN-γ–deficient mice have elevated levels of TGF-β.[249]

Changes in the ECM appear to correspond with physiologic changes seen in asthma.[253] Increased submucosal matrix protein deposition, in addition to contributing to luminal narrowing, changes the mechanical properties of the airway wall. Stiffening of the airway wall reduces forces exerted on lung parenchyma, leading to reduced distensibility. There are also data to suggest loss of elastic recoil in asthma, and early data suggest that loss of elastin may play a role.[241,246,254]

Airway Smooth Muscle

Airway smooth muscle (ASM) mass is increased in humans with asthma and experimental animal models. The increased smooth muscle mass in airway walls contributes to airway luminal narrowing by occupying space and increasing the extent of narrowing for each degree of smooth muscle contraction.[255,256] In animal models, increased ASM mass accounts for a significant percentage of AHR[257] and correlates with methacholine sensitivity.[258] In pathologic studies, increased ASM mass in large airways is linked with both severe and fatal asthma.[259,260]

In addition to the effects of increased smooth muscle mass on airway physiology, ASM cells have been shown to play a central role in the molecular events that initiate and propagate airway remodeling. The relationship of smooth muscle to the ECM is complex, with smooth muscle cells elaborating matrix proteins, as well as matrix metalloproteinases (MMPs) and their tissue inhibitors (TIMPs), possibly via signaling between the ECM and cell surface receptors.[261] Proof of this relationship comes from the ability of ASM cells to secrete ECM proteins in response to asthmatic sera, suggesting autocrine regulation of airway remodeling.[262] Furthermore, ASM obtained from asthmatic airways secretes more ECM protein than nonasthmatic ASM and ECM from asthmatics induces a greater degree of cell proliferation.[262]

The relative contributions of smooth muscle hypertrophy versus hyperplasia in increasing smooth muscle mass is not clear. Data from a Norway rat ovalbumin-challenge model shows that increases in ASM mass are associated with increased DNA synthesis, suggesting smooth muscle hyperplasia.[263] More recent human biopsy data demonstrate that muscle mass increases along with the number of nuclei, providing additional support for the role of hyperplasia in smooth muscle remodeling.[264] However, a second ovalbumin-challenge model showed increased muscle mass without a concomitant increase in the number of smooth muscle cell nuclei.[265] Furthermore, human biopsy studies support hypertrophy as the cause of increased smooth muscle mass in asthma, with greater smooth muscle cellular diameter associated with more severe asthma.[259] Taken together, it seems likely that both hypertrophy and hyperplasia contribute to the increased smooth muscle mass characteristically seen in remodeled airways of patients with asthma.

Asthmatic ASM may be phenotypically different from ASM in nonasthmatic airways, with altered proliferative or contractile capacities. Smooth muscle cells exhibit phenotypic plasticity in vitro, with the ability to switch between a hyperproliferative and a hyperfunctional phenotype, depending on culture conditions. This phenomenon could theoretically explain the variable presence of both ASM hyperplasia and hypertrophy in asthma. To date, gene expression studies addressing this possibility are intriguing but inconclusive.[266]

In addition to alterations in quantity and function, asthmatic ASM appears to have an altered anatomic relationship with inflammatory cells. Data demonstrate that smooth airway infiltration by mast cells is an important feature of asthmatic airway remodeling.[267] Notably, this colocalization of mast cells and ASM is present in a cross section of asthma phenotypes and degrees of severity.[268] Several mast cell products have the potential to adversely affect the growth and function of smooth muscle, and their localization in the smooth muscle may facilitate this interaction. For example, the mast cell–derived mediators histamine, prostaglandin D_2, and the cysteinyl leukotrienes are potent constrictors of airway smooth muscle.[269] Human ASM promotes human lung mast cell (HLMC) survival in vitro, induces rapid HLMC proliferation, and enhances constitutive HLMC degranulation, suggesting a smooth muscle–driven allergen-independent mechanism of chronic mast cell activation.[270]

Goblet Cell Hyperplasia and Mucus Hypersecretion

Goblet cell hyperplasia is a hallmark of the pathology of asthma in mild, moderate, and severe disease. Mucin is secreted by goblet cells in the airway epithelium and mucus glands in the submucosal space. Airway mucus is a viscoelastic gel composed of cells, secreted polypeptides, and cellular debris, which forms a thin film lining the airway surface.[271] Under normal circumstances, airway mucus serves a protective function, trapping foreign debris, bacteria, and viruses, then working in concert with the ciliated epithelium to clear captured material. In asthma, excessive production of mucus contributes to airway obstruction. Secreted mucin levels in induced sputum are higher in patients with lower forced expiratory volume in 1 second (FEV_1) values, indicating that mucus hypersecretion plays an important role in airway obstruction in asthma.[272] Accumulation of intraluminal mucus plays a significant role in fatal or near-fatal asthma, and widespread occlusion of airways by mucus is a common finding in autopsy studies of fatal asthma.[273,274] Mucin is the major protein component of these plugs, which is a high-molecular-weight glycoprotein produced by goblet cells in the epithelium and glands in the submucosa.[275,276] Secreted and oligimerized

mucins have an important role in determining the properties of the extracellular mucus layer.

In patients with asthma, the number of mucus-secreting goblet and submucosal cells in the airway is increased compared with that in normal individuals.[277] Although 19 human mucin genes (MUC) have been described, the major secreted mucus proteins include the gene products MUC5AC and MUC5B. MUC5AC is the predominant gel-forming mucin and is disproportionately increased in asthma.[278] In addition to quantitative differences in mucus gene products in asthma, asthmatic mucus may be functionally different. The increased viscosity seen in asthmatic mucus may be accounted for by variations in oligimerization and by incomplete release of mucins from goblet cells.[279] The latter may lead to "tethering" of luminal mucins to the airway epithelium and increased adherence of mucus to airway walls.[280]

The increase in mucus production seen in asthma may be attributed to increased mucin production, increased exocytosis of previously formed mucus from airway cells, or both. The migration of mucus from preformed granules to the apical surface of epithelial cells is dependent on the presence of myristolated alanine-rich C kinase substrate (MARCKS protein), and activation of the MARCKS protein requires phosphorylation by protein kinase C.[281] The strength of this relationship is bolstered by the observation that protein kinase C is up-regulated together with mucin production after stimulation of airway epithelial cells with neutrophil elastase.[282] Binding of mycoplasma to TLR and subsequent expression of Th2 cytokines has also been shown to lead to increased mucus production in a murine model of asthma, possibly mediated by a nuclear factor-κB (NF-κB) binding site on the MUC5AC promoter.[283] However, TLR2 knockout mice have increased mucus production, possibly due to decreased levels of IFN-γ and subsequently increased TGF-β levels.[284]

Microvascular Changes

Bronchial neovascularization is a recognized feature of airway remodeling, with dilated and tortuous mucosal blood vessels present even in mild asthma.[285] Functionally, the airway microvasculature is more permeable, with leakage of plasma proteins into the extravascular space associated with mucosal edema.[286] Mucosal edema results in airway narrowing, which may have a pronounced effect on airway function.[286]

Vascular endothelial growth factor (VEGF) appears to be a key mediator of the pathogenesis of airway vascular abnormalities in asthma. VEGF levels are increased in the asthmatic airway,[287] with levels of VEGF staining corresponding to increasing bronchial vascularity.[288] A number of different stimuli for VEGF expression are present in asthma. Th2 cytokine exposure prompts the release of VEGF from ASM cells,[289,290] as does increased mechanical strain as seen in symptomatic airway obstruction.[291] Transgenic induction of VEGF in murine airway epithelial cells leads to increased pulmonary angiogenesis and increased expression of Th2 cytokines, suggesting the presence of a feedback loop increasing vascular remodeling.[292]

Physiologic Manifestations of Asthma

Airway Hyperresponsiveness

AHR is a characteristic feature of asthma. Hyperresponsiveness can occur in response to a number of nonspecific environmental irritants, pharmacologic agonists, and inflammatory mediators. In the past, the predominant view was that airway inflammation was the mechanism causing AHR. This concept has been criticized, because a number of studies have shown dissociation between AHR and inflammation,[191,293] highlighting the fact that inflammation alone is insufficient as a mechanism of disease. Evidence suggests that a number of inflammatory Th2 cytokines, CD4 cells, and biochemical mediators contribute to the development of AHR in asthma. Exposure to Th2 cytokines in asthmatic airways can increase the isometric constrictor response of ASM by increasing calcium release from intracellular stores.[294,295] In addition to the airway inflammation, factors contributing to mechanical airway obstruction have also been implicated in the pathogenesis of AHR, including epithelial permeability, smooth muscle hypertrophy, mucus hypersecretion, and airway remodeling.

Epithelial Permeability

The airway epithelium is the source of many of the cytokines and inflammatory mediators contributing to airway inflammation and increased AHR in asthma. The airway epithelium serves several different functions within the lung. The airway epithelium is in a unique position, because it is exposed to the environment and is the primary target of viruses and inhaled agents known to cause or exacerbate asthma. In addition to barrier protection and mucociliary clearance of unwanted pathogens, the epithelium can regulate the response of other lung cells involved in the inflammatory and fibrotic response of the lung to external stimuli.

In asthma, there is evidence that airway epithelial barrier function is impaired and epithelial tight junctions are disrupted. These cells show reduced transepithelial resistance indicating epithelial permeability, which is associated with AHR. Confocal microscopy with antibodies directed at adapter proteins (ZO-1) and tight junction proteins (occludin) support the concept that tight junctions are poorly developed in asthmatic epithelium. In addition to disruption of the tight junctions, epithelial desquamation has been described as a pathologic feature in patients with asthma who die from acute respiratory failure.[296] Furthermore, markers of apoptosis indicating programmed cell death have also been noted in airway tissue of subjects with asthma and correlate with disease severity and chronicity.[222]

Smooth Muscle Hypercontractility

Hypercontractility of ASM is believed to be a key determinant of the development of AHR in asthma. It is still unclear whether contractile force is enhanced in the asthmatic airway, where inflammatory mediators accu-

mulate, or whether smooth muscle is abnormal in asthma. Numerous reports have identified increased ASM mass in fatal and nonfatal asthma. The cellular mechanism of increased ASM mass in asthma represents a balance between smooth muscle hypertrophy and proliferation.[297] Benayoun and associates[259] found that patients with mild asthma had larger smooth muscle cell diameter in their airways than control subjects. The increase in ASM mass correlated with asthma severity, suggesting a causal role for smooth muscle hypertrophy in the development of AHR. Conversely, Woodruff and colleagues[264] found that hyperplasia of smooth muscle occurs in mild to moderate asthma without changes in cell size or gene expression.

Excessive shortening of ASM also can result in excessive narrowing of the airways, and several different mechanisms have been proposed. One proposal suggests that exposure to chronic inflammatory mediators in the local asthmatic environment results in chronic shortening of ASM, so that further shortening occurs during activation.[298] A second proposal suggests that the ECM surrounding ASM alters the ASM phenotype by increasing ASM mass and decreasing its secretory properties.[299] A third scenario suggests that abnormal relaxation of ASM occurs in asthma, which can contribute to increased bronchospasm,[300] whereas a fourth scenario suggests that there is a change in the interdependence between the airway wall and the surrounding lung.[300,300a]

Effects of Treatment on Remodeling

Because of the importance of airway remodeling in the pathogenesis of asthma, efforts have been devoted to reversing airway remodeling. One hypothesis is that treatment of the inflammatory component of asthma may lessen airway remodeling. In a murine model of asthma, administration of corticosteroids in combination with allergen avoidance reduced airway fibrosis and smooth muscle mass.[301] In another study comparing a leukotriene antagonist and a corticosteroid in an allergy-driven mouse model of asthma, the leukotriene inhibitor decreased ASM mass and subepithelial collagen deposition, whereas corticosteroids had no effect on remodeling.[302]

An alternative approach is to mechanically reduce smooth muscle mass in order to improve physiologic function. The application of controlled thermal energy via a radiofrequency catheter in order to reduce smooth muscle mass has been shown to reduce methacholine responsiveness in dogs.[303] Early clinical trials in human subjects have shown beneficial effects on asthma symptoms via reduction in smooth muscle mass, with results that were sustained for 1 year.[304]

With an increased understanding of the molecular mechanisms of asthma pathophysiology and airway remodeling, more focused therapeutic strategies can be explored.[304a] In vitro studies of compounds targeting putative mediators involved in remodeling suggest a promising role for novel agents in the treatment of asthma.[253,305,306] Recent studies highlighting novel genes associated with airway remodeling and asthmatic symptoms suggest new therapeutic avenues targeting the underlying pathogenesis of airway remodeling in asthma.[130]

PHYSIOLOGY

Introduction

As understanding of the pathogenesis of asthma improves and strategies for treatment evolve, it is important to recognize that the link between the pathophysiology and the treatment of asthma is functional, involving variable limitation of air flow. These two cardinal manifestations of asthma, variability of symptoms in response to environmental factors and limitation of air flow, are crucial to making the diagnosis of asthma and distinguishing asthma from other obstructive lung diseases.

Physiology of Airflow Limitation

During asthma exacerbations, diffuse narrowing of the airways results in profound physiologic consequences. This narrowing has been thought to occur disproportionately in the small bronchi,[307] although recent studies suggest a prominent role for large and medium airways.[308] As a result, lung function tests are abnormal, with an increase in airway resistance and a decline in maximal expiratory flow. Airway narrowing also prevents the lungs from completely emptying ("air trapping") due to resistance to expiratory flow and to bronchial closure at higher than normal lung volumes. The breath-to-breath variability of asthmatic obstruction and air trapping led to the concept of dynamic hyperinflation.[309] As a result of dynamic hyperinflation, asthmatics breathe at higher total lung volumes, detectable as increased residual volume.[310] Despite elevated total lung volumes, asthmatics typically have reduced tidal ventilation. Decreasing forced vital capacity (FVC) suggests worsening air trapping, whereas worsening of the FEV_1/FVC ratio indicates increasing airway narrowing.[311]

At high lung volumes, flow limitation due to bronchial narrowing is offset by increased circumferential traction on the bronchial airways due to "tethering" of airways to inflated alveoli.[312] This response may be less effective in asthma, because the altered mechanical properties of the ECM in asthmatic airways reduce the mechanical forces opposing ASM contraction.[313] The net effect is that the work of breathing increases significantly, due in part to decreased lung and chest wall compliance at higher thoracic volumes and in part to the greater effort required to overcome the resistance of narrowed airways. The diaphragm and intercostal muscles are overloaded due to thoracic hyperinflation and mechanically disadvantaged due to suboptimal positioning on their length-tension curves.[314] As a result, accessory muscles of respiration, including the abdominal muscles and sternocleidomastoids, are required.[315] A large proportion of the subjective dyspnea associated with asthma exacerbations has been attributed to respiratory muscle fatigue.[316]

The airway obstruction and closure in asthma is nonuniform, with significant regional variability that may not be completely reflected by decreases in peak flow.[317,318] Although pulmonary blood flow is reduced in areas of alveolar hypoventilation, the magnitude of this response in insufficient to offset more than moderate or severe airflow obstruction. Ventilation-perfusion mismatching leads to a widened alveolar-arterial oxygen difference that tracks with increasing asthma severity; the arterial oxygen tension in acute severe asthma typically falls below 70 mm Hg.[319,320] Arterial carbon dioxide tension initially falls as alveolar ventilation increases, because CO_2 elimination is less impaired than O_2 uptake by ventilation-perfusion mismatching.[321] As respiratory muscles fatigue, carbon dioxide tension increases, so that a normal or elevated P_{CO_2} during an asthma exacerbation suggests impending respiratory failure.[322] Worsening of airflow obstruction or any factor that decreases respiratory drive (such as sedation) can drop alveolar ventilation precipitously; the resultant rise in P_{CO_2} further inhibits respiratory drive and muscle performance and hastens respiratory failure.[323]

Pulmonary Function Testing

Even between asthma exacerbations, pulmonary function testing shows characteristic changes reflecting the reduced flow and air trapping of dynamic hyperinflation. Decreased expiratory flow can be easily and reproducibly detected with a peak flowmeter in ambulatory patients, and peak expiratory flow (PEF) measurement is an accepted method to correlate physiologic function with the clinical severity of asthma. However, peak flow measurements are not standardized and cannot be correlated with other measures of lung function.[324] PEF as a percentage of the predicted value is 10% higher than FEV_1 on average, with a great deal of variability between measurements.[325] PEF measurements tend to underestimate less severe obstruction and overestimate more severe obstruction.[326] Currently, the recommended use of PEF measurement is for the daily monitoring of ambulatory patients. In this situation, the values should be compared with an individual patient's baseline measurement obtained when asymptomatic and well-controlled.[327,328] Evaluation of peak flow measurements obtained during a trial of long- versus short-acting β-agonists suggests that individual peak flow is highly variable and that the variability in PEF has a greater predictive value for asthma exacerbations than the absolute PEF measurement.[329,330]

Spirometry

The best and most standardized test of airflow obstruction is the FEV_1. The FEV_1 has the advantage of being an objective, non–patient-reported measurement of lung function. Improvement in FEV_1 of more than 12% and 200 mL after bronchodilator treatment indicates reversible airflow obstruction and is suggestive, but not diagnostic, of asthma.[331] Prebronchodilator FEV_1 is a strong predictor of decline in asthma control whereas postbronchodilator FEV_1 is a marker of future risk.[332,333] However, accurate measurement requires stopping LABAs for at least 12 hours and short-acting bronchodilators for at least 6 hours. Furthermore, because the FEV_1 may be normal or near-normal between asthma flares, it is a poor marker of response to bronchodilators in mild asthma. The absolute value of the FEV_1 is dependent on FVC and also reflects the small airways. Interpretation of FEV_1 therefore requires simultaneous FVC measurement. In asthma, the relative reduction in FEV_1 is typically greater than the reduction in the FVC. As a result, the FEV_1/FVC ratio in asthma is usually less than 70%. A characteristic flow-volume loop is created with scooping of the expiratory loop consistent with airflow limitation (Fig. 38-4). However, in severe asthma, this ratio may actually increase as profound air trapping increases residual volume and reduces the FVC. This reversible restriction due to air trapping has been reported in asthma.[311,334]

The performance of the forced expiratory maneuver requires inhalation to total lung capacity prior to exhalation. In normal patients, the resultant stretch of intrapulmonary airways causes reflex bronchodilation and a shift

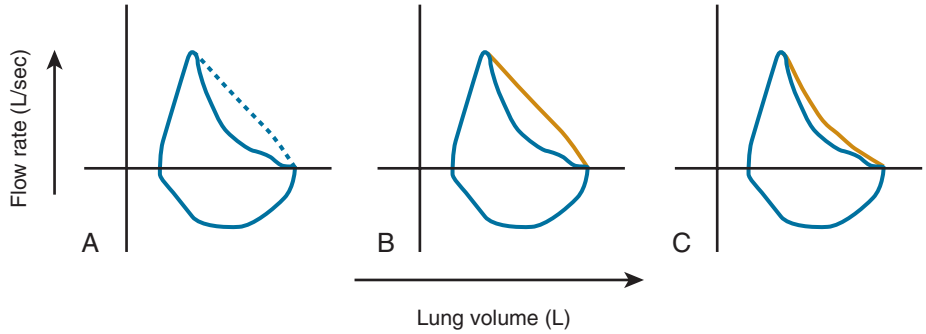


FIGURE 38-4 ■ Flow-volume loops in asthma. **A,** The typical scooped appearance of the flow-volume loop in asthma is shown as the *solid blue line*. The predicted normal flow-volume loop is shown by the *dashed line*. **B,** The scooped appearance of the initial flow-volume loop (*blue line*) may show complete reversal following use of a bronchodilator (*brown line*). **C,** In some cases, the reversal of the scooped appearance following use of a bronchodilator is incomplete (*brown line*). (A-C, Adapted from Sameer KM: Asthma: Diagnosis and management. Med Clin North Am 90:39–60, 2006.)

in the pressure-volume curve. This alteration in lung mechanics is generally attributed to a transient decrease in ASM tone.[335] However, some asthmatics have the opposite response, developing bronchoconstriction during deep inspiration. The mechanism of this "spirometry-induced bronchoconstriction" is unknown, but some evidence suggests that it may be partly due to increased inflammation and remodeling of asthmatic airways.[336]

An alternative method for assessing airflow obstruction is to evaluate midexpiratory flow, measured between 25% and 75% of the FVC ($FEF_{25\%-75\%}$). Obtained at lower lung volumes, reductions in the $FEF_{25\%-75\%}$ may be more sensitive for identifying obstruction in small airways.[337] Studies in patients at high risk for asthma based on atopic symptoms have shown that this index is valuable in predicting AHR.[338] Similarly, in childhood asthmatics who have become asymptomatic, the $FEF_{25\%-75\%}$ is a sensitive marker of residual physiologic abnormalities.[339] The clinical utility of the $FEF_{25\%-75\%}$ is limited by the lack of acceptable standardized values. High numbers of false-positive and false-negative results occur when 80% of predicted $FEF_{25\%-75\%}$ is used for classification.[340]

The limitations of the $FEF_{25\%-75\%}$ are in part due to large variation in the duration of FVC maneuvers. To address this issue, measurement of the forced expiratory volume over the first 6 seconds (FEV_6) has been proposed as an alternative to the FVC. The advantages of this maneuver over the FVC include ease of measurement, a more explicit end-of-test definition, and reduced risk of syncope.[341] Data are available suggesting parameters that may be used for disease classification, although the sensitivity and specificity of the FEV_1/FEV_6 in comparison to the FEV_1/FVC ratio remain controversial.[342,343]

Lung Volumes and Diffusing Capacity

As a result of dynamic hyperinflation and consequent air trapping, residual volume, functional residual capacity, and total lung capacity may be elevated in asthma. Exhaled gas dilution measures only the communicating volume of gas and may underestimate these volumes due to regional heterogeneity in the distribution of ventilation.[344] For this reason, body plethysmography is often considered the method of choice for lung volume evaluation in severe asthma. However, because plethysmography measures the total volume of compressible gas within the thorax and abdomen, the inclusion of intra-abdominal gas may lead to overestimation of total lung capacity, particularly in severely obstructed asthmatics.[345]

Single-breath diffusing capacity is a marker of carbon monoxide gas transfer in the lungs and is reduced in most chronic lung diseases because of altered alveolar capillary surface area and/or maldistribution of inspired gas due to airflow obstruction. In asthma, the diffusing capacity is normal or elevated if airflow obstruction is not severe, and this can be useful in distinguishing asthma from other obstructive lung diseases.[346] Elevated diffusing capacity in asthma has been attributed to improved perfusion of well-ventilated upper lung zones and is associated with large lung volumes. The unexpected finding of an increase in diffusing capacity should raise the possibility of undiagnosed asthma, whereas decreased diffusing capacity in a suspected asthmatic is suggestive of an alternate diagnosis or coexisting condition.[347]

Provocative Challenges and Airway Hyperresponsiveness

AHR to environmental stimuli is a hallmark of asthma. Patients suspected of having asthma despite normal lung function testing usually develop bronchoconstriction in response to a provocative stimulus. Direct stimulation, during which a substance known to induce bronchoconstriction via direct action on smooth muscle is inhaled into the airways, is the most widely used method of assessing bronchial hyperresponsiveness. Nebulized methacholine, delivered in doubling concentrations until FEV_1 falls by more than 20%, is the most commonly used agent. The concentration that causes a 20% fall is labeled the PC_{20} (provocative concentration resulting in 20% fall in the FEV_1) and can be used to measure the degree of AHR. A PC_{20} less than 16 mg/mL is consistent with mild AHR, less than 4 mg/mL is consistent with moderate AHR, and less than 1 mg/mL with severe AHR,[348] with lower PC_{20} levels generally corresponding to more severe asthma.[349] Bronchial hyperresponsiveness also has been associated with increased risk of developing persistent asthma and airway remodeling.[350]

Indirect stimuli, such as cold air exposure, exercise, inhalation of hypertonic saline, mannitol, and adenosine monophosphate, may also induce bronchoconstriction. Rather than working directly on smooth muscle, indirect stimuli cause the release of inflammatory mediators from airway cells that then interact with ASM to induce bronchoconstriction. Although the dose response is more difficult to assess with indirect stimuli, the results have direct applicability to daily asthma symptoms. For example, direct challenge of athletes suspected of having exercise-induced bronchospasm is less likely to uncover bronchospasm than indirect challenge using a surrogate for physical activity.[351] There also may be differences between direct and indirect stimuli in the evaluation of response to treatment, with indirect challenge providing a better idea about response to therapy.[352]

MANAGEMENT OF ASTHMA

Introduction

The inherent complexities in evaluating and treating asthma are evident from studies in the 1970s and 1980s documenting a significant number of asthma deaths that were attributable to failure of clinicians to recognize the clinical severity of asthma, leading to inadequate management. For example, a study of asthma deaths in the West Midland and Mersey regions of England in 1979 led to the conclusion that failure to recognize the

severity of asthma delayed treatment, that routine asthma management was unsatisfactory, and that 86% of the deaths might have been preventable.[353] A similar study in 1988 included the observation that a large number of asthmatics admitted to the hospital for observation were discharged with no escalation in the management of their asthma.[354] This ultimately led the NHLBI to convene the first expert panel to develop guidelines for the diagnosis and treatment of asthma, and the resulting recommendations were published in 1991.[355] Other guidelines soon followed, extending the NHLBI's initial recommendations. Subsequent revisions have provided clinicians with a reliable framework for evidence-based management of patients with asthma. These guidelines emphasize maintaining long-term control of symptoms through attention to environmental and social components of asthma and using treatment regimens tailored to the severity of each patient's symptoms. Crucial components of management include initial evaluation of severity and ongoing assessment of control; appropriate pharmacologic therapy to reverse bronchoconstriction and ameliorate inflammation; identification and control of environmental factors that worsen symptoms or trigger exacerbations; and creation of a partnership between the patient and the health care professional to ensure that therapy is tailored to symptoms.

Assessment

Asthma Control

The assessment of patients with asthma involves five essential features: the current degree of control, based on symptoms, reliever medication use, recent exacerbations, and clinical lung function; and the risk of future adverse outcomes. With this in mind, the NHLBI recently updated guidelines, and the Global Initiative for Asthma (GINA) proposed a parallel scheme for asthma control based on expert opinion[328] (Table 38-1). The NHLBI and GINA categorizations represent categorical interval variables with threshold values. For example, the GINA guidelines accept some daytime symptoms (≤2 times/wk) in the definition of "controlled" asthma, whereas nocturnal symptoms move a patient to the "partially controlled" category. The importance of control indices is underscored by the relationship between poor asthma control and substantial degrees of physical impairment and diminished quality of life, even after taking the baseline severity of asthma into account.[356]

Several different validated instruments exist for assessing asthma, including the Asthma Control Questionnaire, Asthma Control Test, Asthma Therapy Assessment Questionnaire, and Asthma Control Scoring System.[357–360] All are useful because they direct history taking, provide

TABLE 38-1. Classification of Asthma Control in Adults and Children Older than 12 Years of Age

Components of Control		CLASSIFICATION OF ASTHMA CONTROL (YOUTHS ≥ 12 YR OF AGE AND ADULTS)		
		Well-Controlled	**Not-Well-Controlled**	**Very Poorly Controlled**
IMPAIRMENT	Symptoms	≤2 days/wk	>2 days/wk	Throughout the day
	Nighttime awakening	≤2 times/mo	1-3 times/wk	≥4 times/wk
	Interference with normal activity	None	Some limitation	Extremely limited
	Short-acting β-agonist use for symptom control (not prevention of EIB)	≤2 days/wk	>2 days/wk	Several times/day
	FEV_1 or peak flow	>80% predicted/personal best	60%–80% predicted/personal best	<60% predicted/personal best
	Validated questionnaires			
	ATAQ	0	1–2	3–4
	ACQ	≤0.75*	≥1.5	N/A
	ACT	≥20	16–19	≤15
RISK	Exacerbations	0-1/yr	≥2/yr†	
		Consider severity and interval since last exacerbation		
	Progressive loss of lung function	Evaluation requires long-term follow-up care		
	Treatment-related adverse effects	Medication side effects can vary in intensity from none to very troublesome and worrisome. The level of intensity does not correlate to specific levels of control but should be considered in the overall assessment of risk		

*ACQ values of 0.76–1.4 are indeterminate regarding well-controlled asthma.

†(1) The level of control is based on the most severe impairment or risk category. Assess impairment domain by patient's recall of previous 2–4 wk and by spirometry or peak flow measures. Symptom assessement for longer periods should reflect a global assessment, such as inquiring whether the patient's asthma is better or worse since the last visit. (2) At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma control. In general, more frequent and intense exacerbations (e.g., requiring urgent, unscheduled care, hospitalization, or intensive care unit admission) indicate poorer disease control. For treatment purposes, patients who had two or more exacerbations requiring oral systemic corticosteroids in the past year may be considered the same as patients who have not-well-controlled asthma, even in the absence of impairment levels consistent with not-well-controlled asthma.

ACQ, Asthma Control Questionnaire; ACT, Asthma Control Test; ATAQ, Asthma Therapy Assessment Questionnaire; EIB, exercise-induced bronchospasm; FEV_1, forced expiratory volume in 1 second; N/A, not applicable.

Adapted from National Heart, Lung, and Blood Institute as a part of the National Institutes of Health and the U.S. Department of Health and Human Services, 2007.

goals for the management of symptoms, and guide adjustments in treatment.

Lung Function

Lung function testing is an important part of assessing asthma, both for making the initial diagnosis and as a means of evaluating the response to therapy. A recent study from the Genetics in Asthma Network[361] suggested that FEV_1 and FVC are useful components of a standardized scheme for identifying the contribution of genes and environments to disease expression. Further proof of the importance of lung function testing was provided by a recent finding that asthmatic patients with lower FEV_1 values were at significantly higher risk of needing acute care.[362] Although the FEV_1, the FEV_1/FVC ratio, and PEF are useful in the diagnosis and monitoring of asthma, the utility of these measurements in improving the outcome of asthma remains incompletely defined. FEV_1 is an objective measurement of lung function. The prebronchodilator FEV_1 is related to asthma control, whereas postbronchodilator FEV_1 is related to future risk of exacerbations. Accurate measurement requires stopping LABAs for 12 hours and short-acting bronchodilators for 6 hours. Because FEV_1 is often normal or near-normal in mild asthma, FEV_1 may be poorly responsive to bronchodilators in mild asthma.

PEF measurement is a standard method to correlate physiologic function with asthma severity, and has been used as a marker of asthma control in many clinical trials. However, individual peak flow measurements are highly variable and the variability in peak flow has a greater predictive value for future exacerbations than individual PEF measurements themselves.[329,330] The clinical usefulness of peak flow measurements is also limited by patient resistance to home monitoring and difficulty with consistently maintaining peak flow records.

Biomarkers

The presence of sputum eosinophilia provides useful information about the asthma phenotype. Low sputum eosinophil counts predict response to inhaled corticosteroids and decreased risk of exacerbations, whereas elevated sputum eosinophil counts (>10%) put the subject at high risk for future exacerbations.[363,364] A change of 50% in sputum eosinophil counts is considered to be clinically significant, whereas a decline in absolute eosinophil count predicts deterioration when inhaled corticosteroids are withdrawn.[365,366] However, induced sputum eosinophils may be difficult to obtain in clinical practice. Furthermore, the lag between specimen collection and processing may lead to delays in adjusting treatment.

Fractional excretion of nitric oxide (FeNO) has some advantages over counting the number of sputum eosinophils. Measurement of FeNO can be performed rapidly in a primary care setting, requires less technical expertise, and provides real-time objective physiologic data. However, the FeNO in stable, mild asthma after use of inhaled corticosteroids is often in the same range as that in normal, nonasthmatic patients.[367,368] FeNO falls in a dose-dependent manner with steroid use, making FeNO less useful as an ongoing biomarker in patients using steroid therapy.[369,370] A recent trial showed that an FeNO of more than 45 parts/billion excludes well-controlled asthma with a negative predictive value of nearly 90%. High FeNO suggests a severe, steroid-responsive phenotype. A decline in FeNO of more than 40% between visits is a sign of improved control, and low levels of FeNO predicted lower risk of acute exacerbation.[371] Measuring the FeNO during a period of good control can provide a baseline for comparing trends over time when following symptoms and response to treatment. Although the FeNO is a promising biomarker in asthma, the cost/benefit ratio of using FeNO to assess asthma control requires more study.

Treatment

Overview

Pharmacologic therapy for asthma is subdivided into acute, short-term "reliever" medications and chronic "controller" medications. Reliever medications target bronchoconstriction by relaxing ASM. The β-agonists such as inhaled albuterol are the most effective reliever medications. Other reliever medications include methylxanthines (e.g., theophylline) and short-acting anticholinergics such as inhaled ipatropium bromide. The most widely used controller medications are inhaled corticosteroids, which have a localized anti-inflammatory effect. There is overlap in the use and mechanism of action of reliever and controller medications. LABAs, used in conjunction with an inhaled corticosteroid, provide additional control of symptoms. Theophylline, although primarily a bronchodilator, also has a sustained anti-inflammatory effect at low doses, whereas inhaled corticosteroids such as budesonide have been used in the acute treatment of asthma exacerbations.[372,373] The introduction of omalizumab, a specific anti-IgE antibody, provided the first opportunity to treat and control asthma based on specific pathophysiologic characteristics. Tailoring biologic therapy based on pathophysiologic mechanisms in individual patients is an area of active clinical investigation, and additional agents addressing the allergic and nonallergic phenotypes of asthma are under investigation.

Specific Pharmacologic Agents

Current guidelines recommend adjusting therapy in a stepwise fashion to reduce daily symptoms and risk of exacerbations, while minimizing the use of medications.[374,375] The hierarchy of treatment recommendations is based on the available literature about efficacy and safety and provides a prominent role for controller medications at all levels of asthma treatment. In general, the strategy and recommendations in adults and children are similar. However, the increased risk of adverse effects and/or the lack of safety data in pediatric patients for theophylline, omalizumab, and the 5-lipoxygenase inhib-

itor zileuton, lead to their exclusion from current pediatric treatment guidelines.[374]

β_2-Agonists. β_2-Agonists have been used for thousands of years in the form of the ephedrine-containing herbal preparation ma huang.[376] However, it was not until the 1940s, when the nonselective β-agonist isoproterenol was introduced, that β-agonists became the standard of care for treating airway disease. The subsequent development of the β_2-selective agents albuterol and terbutaline, with improved side effect profiles, led to their current role as the cornerstone of asthma therapy.[377]

β_2-Agonist activity is primarily mediated by binding to a specific G-coupled transmembrane receptor found in high abundance on ASM. Receptor binding leads to increased intracellular cyclic adenosine monophosphate (AMP) and relaxation of ASM.[378] Notably, β_2-receptors are also found on other resident airway cells, including airway epithelial cells and circulating immune cells, and binding to these sites may reduce vascular permeability and inflammatory mediator release.[379] One concern raised about the chronic use of β_2-agonists is that of receptor desensitization.[380] As with most signaling receptors, repeated exposure to β_2-agonists can lead to decreased responsiveness of membrane receptors through receptor down-regulation via receptor endocytosis and uncoupling of receptor from downstream transduction pathways. This response appears to be self-limited in ASM.

β_2-Selective agonists are usually administered by aerosol, which maximizes delivery to target tissue (ASM), while minimizing the exposure of nontarget tissues. Both short-acting and long-acting agents are available, and the onset and duration of action are primarily related to lipophilicity.[16] Short-acting agents are used for rescue or emergent treatment, whereas LABAs are used in combination with inhaled corticosteroids for chronic management.

A number of highly selective short-acting β_2-agonists are now available, and all have a rapid onset of action with peak action between 60 and 90 minutes. Because they are inhaled directly into the airways, systemic side effects are minimal, even at high doses. A β_2-agonist preparation containing only the active isomer of albuterol was developed in an attempt to minimize side effects. However, clinical trials have not shown significant differences in outcome or tolerability.[381] Based on current guidelines, these medications should be used to treat symptoms not adequately controlled on a regimen of long-acting agents. Increased frequency of short-acting β_2-agonist use is a sign of inadequate control of symptoms or overreliance on rescue medication. Patients using more than one canister a month or requiring excessive doses of rescue inhalers (defined as >2 doses/wk) should be considered for a step-up in therapy.[374,375]

LABAs have minimal utility for treating acute asthmatic symptoms because of their delayed onset of action. However, in patients with inadequately controlled asthma, they can be added to an inhaled corticosteroid to improve symptoms. Formoterol and salmeterol are the two LABAs available. Formoterol has a shorter onset of action than salmeterol, whereas salmeterol has a longer duration of action. Each has been shown to improve lung function, reduce symptoms, and reduce the frequency of exacerbations.[382]

Adverse events associated with the use of β_2-agonists are primarily due to unwanted activation of β_2-receptors on nonpulmonary tissue. Cardiac stimulation causes tachycardia and arrhythmias, whereas skeletal muscle stimulation causes tremors and hypokalemia. Since the introduction of β-agonists, there has been concern about the clinical implications of receptor desensitization. The short-acting β-agonist fenoterol was implicated in two epidemiologic studies of increased asthma deaths in the 1960s and 1970s[383,384]; later analysis suggested that this might have been due to excessive use, rebound bronchoconstriction due to short duration of action, or tachyphylaxis. After fenoterol was withdrawn, mortality declined,[385] and the safety profile of subsequent short-acting β_2-agonists has been good. Clinical data suggest that "as-needed" versus scheduled short-acting β_2-agonist treatment is associated with improved physiology[386] and fewer, less severe exacerbations.[387]

Adverse events with long-acting β_2-agonists also are of concern, particularly because of their long duration of action. In the Salmeterol Multicenter Asthma Research Trial (SMART),[388] patients were randomized to salmeterol or placebo plus usual care, with approximately 13,000 patients in each arm. There was no significant difference in risk of death in either group, but subgroup analysis identified a small but increased risk of death that was more prominent in African American subjects in the salmeterol arm of the trial. However, the African American patients also had poorer control of symptoms at baseline (with more exacerbations and hospitalizations) and a lower rate of inhaled corticosteroid use than the white patients.[388] Importantly, the use of LABAs with inhaled corticosteroids in the same metered-dose inhaler has been shown to be safe and effective.[389]

Several studies have explored the relationship between polymorphisms in the β_2-receptor and responses to β-agonist therapy. Specifically, the presence of the Arg/Arg mutation at the B16 locus has been associated with lower PEF, FEV_1, symptoms, rescue inhaler use, and increased rate of exacerbations in patients treated with scheduled albuterol as compared with patients who lack the Arg/Arg mutation. All of these symptoms improve when regular albuterol is withdrawn.[146,390,391] Use of LABAs (with and without inhaled corticosteroids) has been shown to worsen physiologic markers of respiratory function in Arg/Arg patients in some studies, although these findings are not consistent.[149,392] Two large randomized trials are currently underway that should shed light on this issue.

Other Bronchodilators. Anticholinergic agents act as bronchodilators via competition with acetylcholine at neuromuscular junctions, thereby blocking transmission of bronchoconstrictor reflexes.[393] The short-acting anticholinergic ipratropium bromide is effective in patients with chronic obstructive pulmonary disease (COPD) but is considered a second-line agent for treating asthma, most likely because cholinergic tone contributes

less to bronchoconstriction in asthma. Although no trials have compared short-acting anticholinergics with short-acting β-agonists, randomized trials studying the addition of anticholinergics to β-agonists do not show any additional benefit in patients with chronic asthma. However, specific asthma phenotypes might be more likely to respond to anticholinergic treatment, including patients with fixed airflow obstruction, advanced age,[394] or longer duration of disease.[395] Furthermore, anticholinergics may be an acceptable alternative for certain subgroups of patients who do not tolerate β-agonist treatment or for patients with the Arg/Arg-16 genotype, although this has not been studied directly.

Tiotropium, a long-acting anticholinergic agent, has been shown to be beneficial for treating the symptoms of COPD. The value of tiotropium in patients with asthma is not clear, but a randomized trial is in progress. Spirometric improvement has been demonstrated in case series of asthmatics who do not have sputum eosinophilia[396] and asthmatics with concomitant COPD.[397] Animal data suggest that tiotropium may have an antiremodeling effect comparable with that of budesonide.[398]

Inhaled Corticosteroids. With recognition of the central role of inflammation in the pathophysiology of asthma, contemporary treatment strategies now emphasize corticosteroids for long-term control of symptoms. Corticosteroids suppress inflammatory responses through a broad influence on signal transduction and gene expression pathways. Corticosteroids bind to a specific cytoplasmic receptor that translocates to the nucleus, where it modulates expression of inflammatory genes through inhibition of histone acetyltransferases and recruitment of histone deacetylases.[399,400] Airway inflammatory cell influx and markers of airway inflammation in asthma are reduced by corticosteroid administration.[401,402]

Systemic corticosteroids have been used in the treatment of asthma since the 1940s and continue to be a cornerstone of the management of acute exacerbations. However, systemically administered corticosteroids are associated with a variety of undesirable side effects. The introduction of inhaled corticosteroids (ICS) in the 1970s ushered in a new era in the treatment of asthma. As with bronchodilators, delivery of drug directly into the lungs through the use of inhaled preparations minimizes systemic toxicity and improves therapeutic benefit.

The use of ICS improves all aspects of asthma control. ICS reduce asthmatic symptoms, improve lung function, decrease airway inflammation, and control AHR.[403,404] A large meta-analysis showed that inhaled corticosteroids reduce asthma exacerbations by 55% as compared with placebo[405] and reduce the risk of hospitalization by 50% as compared with use of as-needed β-agonists alone.[406] Furthermore, risk of death from asthma is reduced in a dose-response manner with the use of ICS.[407] As a result, ICS are considered to be first-line therapy for all patients requiring more than twice-weekly β-agonist use.[375]

The risk of systemic toxicity is diminished but not absent with the use of ICS, particularly at doses less than 400 μg budesonide daily or the equivalent. Data are conflicting about the risk of bone demineralization from ICS; although a small observational study suggested increased risk,[408] a meta-analysis of several randomized controlled trials did not corroborate this finding.[409] The risks of cataract formation[410] and glaucoma[411] are slightly increased, whereas hypothalamic-pituitary axis suppression, gastrointestinal bleeding, and other complications of systemic steroids are not associated with inhaled preparations. The Towards a Revolution in COPD Health (TORCH) trial of the use of inhaled corticosteroids for COPD showed an increased risk of pneumonia, but this has not been demonstrated in patients with asthma.[412] The use of inhaled corticosteroids in the pediatric population has raised concerns about growth suppression. However, available data show only a small and transient decrease in growth trajectory that does not translate into a reduction in adult height.[404,413,414]

Leukotriene Modifiers. Leukotrienes (LTs) are derived from cell membrane arachadonic acid metabolism. LT receptors on ASM and macrophages mediate bronchoconstriction, mucus hypersecretion, and mucosal edema.[415] As a result, the LT pathway is a primary target for the development of novel asthma controller medications. Commercially available leukotriene modifiers (LTMs) work in one of two places in the LT pathway. Zileuton blocks 5-lipoxygenase, the enzyme that converts arachadonic acid to LTA4, which is the first step in LT synthesis. Montelukast, zafirlukast, and pranlukast all inhibit LT receptors, blocking the final step in the LT pathway. All are taken orally as either once-daily or twice-daily doses.

LTMs have a modest bronchodilator effect and may improve asthma symptoms and exacerbation rates.[416] Physiologic benefits have also been seen, with improvements in spirometry and measures of airway inflammation.[417] Whereas the subpopulation of patients with aspirin-sensitive asthma may derive great benefit from LTMs,[418] data also suggest that LTMs are adequate as single agents in mild persistent asthma.[419,420] Although LTMs treat multiple asthma symptoms, they are less efficacious than low-dose ICS. As a result, patients who require ICS for asthma control cannot be safely switched to LTM monotherapy. Therefore, the primary role of LTMs is as an adjunct to ICS, and the addition of LTMs typically leads to a reduction in the corticosteroid dose or an improvement in asthma control.[421,422] Recent data suggest that the substitution of LTMs for ICS in smokers with asthma leads to similar symptomatic benefits, possibly due to impaired therapeutic responses to ICS in this population. However, it is not clear whether this benefit would persist with the addition of LTMs to ICS in patients who smoke cigarettes.[423] Overall, LTMs are less effective than LABAs as adjunctive therapy and do not seem to confer added benefits when added to a regimen that includes an ICS and an LABA.[424,425]

Overall, LTMs are well tolerated. Initial reports suggested a link between LTMs and Churg-Strauss syndrome, but this is now thought more likely to be due to an unmasking of the syndrome by a reduction in corticosteroid dose with the introduction of an LTM.[426] Zileuton is metabolized by the cytochrome P-450 system and has been associated with reports of hepatotoxicity. As a

result, liver function should be monitored during its use. The availability of a sustained-release preparation of zileuton has made it a better option as adjunctive therapy. At present, zileuton is reserved for patients with refractory asthma or who have an asthmatic phenotype suggesting benefit from the use of an LTM.[427]

Phosphodiesterase 4 Inhibitors (Theophylline). Theophylline is a well-established phosphodiesterase inhibitor that has mild anti-inflammatory properties. Because of its narrow therapeutic index, theophylline is not widely used in treating asthma. However, the discovery of additional anti-inflammatory properties, likely mediated by histone deacetylation, has led to a resurgence of interest.[428] Although no longer a first-line therapy, theophylline is currently used in low doses as adjunctive treatment for asthma that is difficult to control with steroids alone.[429] The addition of theophylline to an existing drug regimen for poorly controlled asthma improves markers of control (rescue inhaler use, lung function) to a greater extent than LTMs.[423] Dose-related side effects, such as anorexia, palpitations, dysrhythmias, and seizures, require careful clinical and laboratory monitoring.

Anti-Immunoglobulin E Treatment. The introduction of omalizumab, a monoclonal antibody to IgE, represents a new era of therapy targeted to specific asthma phenotypes. Omalizumab targets the receptor-binding portion of IgE, preventing it from interacting with immune cells to cause degranulation.[430] The addition of omalizumab to ICS in poorly controlled allergic asthmatics is associated with improved asthma control and fewer exacerbations.[431] Omalizumab is generally well tolerated, but rare reports of anaphylaxis have led to recommendations that patients be observed for 2 hours after each of the first three injections to ensure safety.[304] High cost, the requirement for monitoring during treatment, and the need to carefully select patients likely to benefit have limited the use of omalizumab. However, cost analysis suggests that anti-IgE therapy in patients with severe allergic asthma results in a cost-per-quality-adjusted life year that compares favorably with other uses of expensive health care resources.[432]

Nonpharmacologic Treatment

Bronchial thermoplasty is a novel intervention for asthma that is based on the observation that increased ASM mass is a characteristic feature of asthma. During thermoplasty, controlled thermal energy is delivered to the airway wall, resulting in reduction of ASM mass. In patients with moderately severe asthma, thermoplasty been shown to reduce airway responsiveness to an inhaled constrictor and improve lung function.[433] Treatment leads to improvements in symptoms and quality of life and reduction in the use of rescue medication in patients with moderate or severe asthma.[304] However, treatment requires a series of three bronchoscopies, exposing patients to the concomitant procedural risk, and long-term outcome data are lacking. Nevertheless, the specific targeting of ASM in asthma remains an area of investigation.

Additional Management Strategies

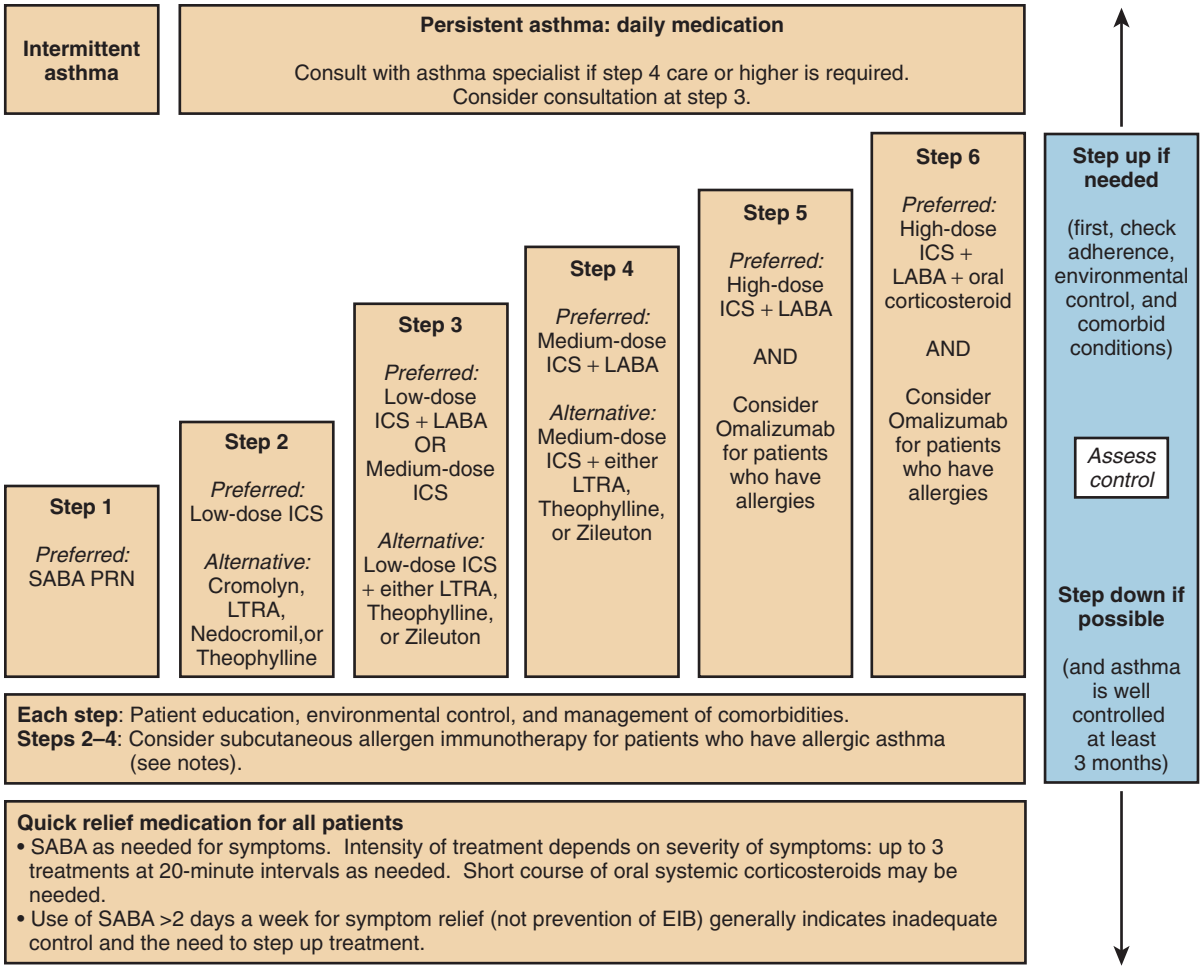
Control of Triggers

Environmental factors have been shown to contribute to the pathogenesis of asthma, including occupational exposures, tobacco smoke, pollutants, respiratory infections, allergen exposures, and comorbid conditions. Cigarette smoking decreases asthma control and reduces the efficacy of corticosteroids. All patients with asthma who smoke cigarettes should be strongly encouraged to quit.[434] Certain comorbid conditions, including GERD and rhinosinusitis, may worsen asthma symptoms and severity. Because treatment of GERD and sinusitis often improves the control of asthma, all difficult-to-treat patients with asthma should be evaluated for these underlying conditions.[435,436]

Reduction of allergen exposure and provision of allergen immunotherapy are common strategies for treating asthma. Allergic asthmatics improve when removed from their domestic environment, but environmental control is often difficult to achieve.[437] The most common allergens include dust mites and cat dander. Whereas avoiding environmental allergens is ideal, most patients do not like the idea of avoiding or giving away their pets. Although overall data are mixed, several studies have shown clinical benefits from dust mite control measures (i.e., impermeable mattress covers, frequent vacuuming, cockroach control).[438,439] For patients with an allergic asthma phenotype, allergen-specific immunotherapy may reduce asthma symptoms and improve bronchial hyperreactivity.[440,441] However, administration must take place under careful conditions owing to the risk of anaphylaxis, and the optimal duration of treatment is not completely clear.

Medication Adjustment Based on Asthma Control

The definition of asthma severity is based on the severity of symptoms at the time of diagnosis. More recent definitions take into account the degree of treatment necessary to maintain control and the frequency of exacerbations. Asthma control, defined as the degree of symptoms present while on appropriate therapy, is more fluid. Depending on the extent of control, a more or less aggressive approach to symptom management may be needed. Recent studies support the importance of focusing on asthma control as a means of reducing exacerbations and morbidity.[441a] Published guidelines provide an up-to-date framework for medication choices when "stepping up" therapy to improve asthma control and "stepping down" therapy when control has been achieved (Fig. 38-5). For patients with mild, intermittent asthma, with symptoms that return to baseline between episodes, as-needed use of a short-acting bronchodilator is usually sufficient to maintain control of symptoms. For patients with chronic asthma (symptoms that occur >2 times/wk, nocturnal symptoms, or symptoms that affect activity), the addition of a controller medication is needed, and an ICS is the initial agent of choice.[404,442,443]



Key: Alphabetical order is used when more than one treatment option is listed within either preferred or alternative therapy. EIB, exercise-induced bronchospasm; ICS, inhaled corticosteroid; LABA, long-acting inhaled beta$_2$-agonist; LTRA, leukotriene receptor antagonist; SABA, inhaled short-acting beta$_2$-agonist.

FIGURE 38-5 ■ Medication recommendations for control of asthma in adults and children older than 12 years of age. (Adapted from the National Heart, Lung, and Blood Institute as a part of the National Institutes of Health and the U.S. Department of Health and Human Services, 2007.)

As mentioned previously, when used properly, ICS ameliorate all asthma symptoms, improve airway physiology, and reduce hospitalizations and asthma mortality. Failure to respond to ICS suggests nonadherence to medications, uncontrolled trigger exposures and/or comorbidities, or a steroid-nonresponsive phenotype. Approximately 30% of asthmatics fall into the last category. These patients typically have less airway inflammation and obtain their maximum response to a low-dose of ICS.[444,445] LTMs are an alternative for patients who do not tolerate ICS and are the preferred agent for patients with concomitant allergic rhinitis.[416,417]

For patients with persistent asthmatic symptoms despite the appropriate use of a controller medication, clinicians have several different options for "stepping-up" therapy. Some guidelines recommend the addition of an LABA to low-dose ICS (often in a combination inhaler) based on a large amount of efficacy data.[446–449] However, because of concerns over the potential side effects of LABAs, the National Asthma Education and Prevention Program (NAEPP) guidelines give the options of increasing the dose of ICS or adding an LABA. This is also the preferred approach for pediatric patients. A third option is the addition of LTMs to low-dose ICS.[422]

If symptoms are still not controlled on one of the regimens just discussed, the next medication added depends on previous medication choices. For patients on increased doses of ICS, the recommended next step is the combination of a moderate- to high-dose ICS with an LABA. However, increasing the ICS dose for a patient already on an ICS/LABA combination is less likely to be effective.[450,451] Other options include the addition of an LTM or sustained-release theophylline to an ICS.[452] If symptoms remain uncontrolled on a full complement of standard medications, options include the addition of systemic corticosteroids or specific anti-IgE therapy for patients with allergic asthma.[431]

Once symptoms are controlled for a protracted period of time, therapy can be stepped down. Strategies for de-

escalation of therapy are determined by a patient's controller regimen. Patients on an ICS alone can be considered for a decrease in dose or dosing interval. Some data suggest that conversion to as-needed combined short-acting β_2-agonists/ICS may be effective with a lower total steroid dose.[453,454] However, an as-needed regimen is not yet part of NHLBI guidelines. Similarly, for patients on a combined ICS/LABA regimen or LTM/ICS regimen, clinicians should focus first on reducing the ICS component.

Management of Acute Asthma

Asthma is a common cause of emergency room visits and hospital admissions. In 2004, asthma accounted for 1.8 million visits to emergency departments, or 64/10,000 people, with 497,000 asthma hospitalizations, or 17/10,000 people.[24] The treatment of acute asthma is based on the cornerstones of chronic asthma therapy but typically requires greater attention to patient monitoring and an escalation in the aggressiveness of asthma care.

Asthma exacerbations are characterized by increased shortness of breath, coughing, and/or chest tightness, and airflow limitation (as measured by decreased peak flow or FEV_1) is a cardinal feature. Increased symptoms typically precede a detectable decrease in air flow,[455] although a subset of patients are at high risk of exacerbations due to poor perception of airflow limitations. In the outpatient setting, increased requirement for rescue inhalers, especially in a patient previously on a stable regimen, suggests an asthma flare.

Patients with asthma exacerbations require prompt evaluation and treatment in order to limit morbidity and mortality. Goals include relief of airflow obstruction and amelioration of respiratory symptoms. Patients with milder symptoms (with peak flow decrease <20%) may be evaluated in an outpatient setting but should be referred to an acute care facility if they fail to respond promptly to aggressive treatment with bronchodilators and systemic glucocorticoids.[374] Conversely, certain patients are at high risk of asthma-related death and should be evaluated in the emergency department as soon as possible when their symptoms worsen. This includes patients with a history of recent exacerbation or previous near-fatal asthma, overutilization of short-acting β_2-agonists or underutilization of ICS, recent oral glucocorticoid use, poor compliance with asthma action plans, or concomitant psychiatric disease.[456]

In the acute care setting, the severity of an asthma exacerbation should be assessed by physical examination, including oximetry and measurement of peak expiratory flow. Use of accessory muscles, ability to complete sentences, and arterial oxygen tension all should be evaluated. Patients require close monitoring during the early stages of treatment, because it may take several hours for symptoms to resolve. Chest radiography is useful if pneumothorax is suspected but does not usually provide clues as to the etiology of an exacerbation. Arterial blood gas measurement typically reflects mild hypoxemia and respiratory alkalosis; the normalization of $PaCO_2$ in the absence of significant symptomatic improvement suggests impending respiratory failure. Anion gap metabolic acidosis may also be present, which is usually due to elevated lactate levels. Patients who fail to respond to albuterol administration within 30 to 60 minutes, with persistent dyspnea and peak flow less than 70% of baseline, require hospital admission.[374]

Key pharmacologic components of treatment include repeated or continuous short-acting bronchodilator administration (via nebulizer or metered-dose inhaler with a spacer) and systemic glucocorticoids.[457] The combination of short-acting β-agonists and ipratropium at the initiation of treatment is associated with physiologic improvements and reduced rate of hospitalization, but the benefits do not persist after hospitalization.[458] Systemic corticosteroids are unequivocally associated with more rapid return to baseline function and are considered the first-line therapy for acute asthma. The initial dosing range for adult hospitalized patients is from 1.5 to 2.0 mg/kg of intravenous methylprednisolone or the equivalent.[459] ICS are typically not used acutely, although some data suggest that the addition of inhaled budesonide to systemic corticosteroids following an emergency department visit leads to improved symptoms and a decreased relapse rate.[460,461] Intravenous magnesium sulfate, usually given as a 2-g bolus, may act as a smooth muscle relaxant and has been shown to reduce hospital admission rates.[462] Supplemental oxygen to keep saturations above 90% helps maintain oxygen delivery to peripheral tissues and minimizes hypoxemic vasoconstriction.

Severe exacerbations of asthma are characterized by persistent reductions in peak expiratory flow of less than 40% predicted with poor response to initial treatment. These patients may demonstrate progressive hypercapnia, fatigue, altered sensorium, and dysrhythmias and are at high risk for respiratory arrest. Low-level noninvasive positive-pressure ventilation without positive end-expiratroy pressure (PEEP) has been shown to reduce the rate of hospitalization and may be considered in alert, cooperative patients who are not in immediate need of intubation.[463] Helium/oxygen mixtures increase flow through the airways and may be a useful adjunct in patients with severe exacerbations that do not respond to initial emergency treatment.[464,465]

Oral intubation and mechanical ventilation are mandatory for patients in respiratory arrest or impending respiratory arrest. Mechanical ventilation in patients with severe asthma exacerbations may be complicated by immediate postintubation worsening of gas exchange and hemodynamic instability due to increased airway and intrathoracic pressures from dynamic lung hyperinflation. Provided that the patient is adequately oxygenated, briefly decreasing the mandatory respiratory rate to allow an extended expiratory phase is often successful. Initial ventilator settings should be focused on minimizing dynamic hyperinflation by using a relatively low minute ventilation (with respiratory rate between 12 and 14/min and tidal volumes in the 6-8 mL/kg range), a high inspiratory flow rate, and minimal to no PEEP.[466] Aggressive sedation should be given to improve comfort and patient-ventilator synchrony. Short-term paralysis may be

necessary in patients for whom ventilator synchrony cannot be achieved with sedation alone. Bronchodilator administration should be continued until airway resistance decreases.

Conclusion: Clinician-Patient Partnership

For chronic asthma, treatment should balance the best symptom control with the lowest possible dosage of medication.[374] Effective management requires that the patients form a partnership with the health care providers in order to ensure an appropriate flow of information, with the patients assuming a major role in the assessment and treatment of their disease. Through collaborative effort, a guided self-management plan can be developed, allowing patients to titrate their own treatment based on changes in symptoms and peak expiratory flow with some degree of independence. The use of such guided self-management reduces asthma morbidity in different patient populations and patient care settings.[467]

Crucial components of self-management plans include education, self-monitoring with symptoms and/or peak flow, regular review, and patient directed self-management using a written action plan. Effective patient education is central to this approach. Better communication by health care providers translates into measurably better outcomes with no additional physician time commitment.[468] Even for patients unable to engage in guided self-management, regular follow-up and medication review is beneficial, because approximately 50% of patients on long-term therapy fail to take medications as directed some of the time.[469]

KEY POINTS

- Asthma is an important cause of disability, death, and economic cost.
- Asthma is increasing in developed countries and appears to be increasing to epidemic proportions in non-Western societies that have adopted features of Western culture.
- On a fundamental level, asthma is a disease of misdirected immunity, with the direction of immune function being influenced by many genes and probably also by airway infections, especially with viruses, but established in the first few years of life. The cells most important in orchestrating this "misdirected" immune response in the airways are dendritic cells and CD4 Th2 lymphocytes.
- The cytokines produced by these lymphocytes, particularly IL-13, alter the function of immunological and structural cells in the airways, either directly through activation of specific receptors on the cells or indirectly through their effects on other cells, such as B lymphocytes, mast cells, eosinophils, and polymorphonuclear leukocytes. Repeated release of these cytokines alters the function and structure of the airways.
- The structural changes, often referred to as "remodeling," are now recognized as potentially irreversible.
- The approach to the diagnosis, assessment, and treatment of asthma has changed in response to the recognition of asthma as a chronic inflammatory disease punctuated by intermittent exacerbations.
- The therapies available are effective in controlling asthma, but their efficacy depends on engaging the patient as a full partner in care.
- Before the most economical and effective approach for preventing asthma can be undertaken, more information is needed about the interplay between individual genotypes and environmental stimuli that are responsible for initiating and perpetuating the disease.
- Until a curative treatment is developed, only the combined use of anti-inflammatory and bronchodilator therapies, coupled with measures to reduce environmental exposures, can reduce the costs of asthma for the individuals affected. Applied widely, these measures can also reduce the consequences and costs for the health care system.

References

1. http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm
1a. Meneely GR, Ball CO, Ferguson JL, et al: Use of computers in measuring body electrolytes by gamma spectrometry. Circ Res 11:539–548, 1962.
2. Tang EW, Wiesch D, Samet J: Epidemiology of asthma and allergic diseases. *In* Adkinson Jr NY, Yunginger JW, Busse WW, et al (eds): Middleton's Allergy: Principles and Practice. St. Louis: Mosby, 2003:1127–1144.
3. NHLBI/WHO Workshop Report: Global Strategy for Asthma Management and Prevention. Publication 02-3659. Bethesda, MD: National Institutes of Health, 2006.
4. Eder W, Ege MJ, von Mutius E: The asthma epidemic. N Engl J Med 355:2226–2235, 2006.
5. Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. The Interna-

tional Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. Lancet 351:1225–1232, 1998.
6. Centers for Disease Control and Prevention: Obesity trends in the United States. Available at http://www.cdc.gov/nccdphp/dnpa/obesity/trend/index/htm
7. http://www.cdc.gov/hchs/fastats/asthma.htm
8. Weiland SK, Bjorksten , Brunekreef B, et al: Phase II of the International Study of Asthma and Allergies in Childhood (ISAAC II): Rationale and methods. Eur Respir J 24:406–412, 2004.
9. Weinmayr G, Weiland SK, Bjorksten B, et al: Atopic sensitization and the international variation of asthma symptom prevalence in children. Am J Respir Crit Care Med 176:565–574. Epub 2007; June 15.
10. Von Mutius E: Worldwide asthma epidemic. Immunol Allergy Clin North Am 22:701–711, 2002.
11. Pearce N, Ait-Khaled N, Beasley R, et al: Worldwide trends in the prevalence of asthma symptoms: Phase III of the International Study of Asthma and Allergies in Childhood (ISAAC). Thorax 62:758–766. Epub 2007;May 15.
12. Burney PG, Luczynska C, Chinn S, et al: The European Community Respiratory Health Survey. Eur Respir J 7:954–960, 1994.
13. Variations in the prevalence of respiratory symptoms, self-reported asthma attacks, and use of asthma medication in the European Community Respiratory Health Survey (ECRHS). Eur Respir J 9:687–695, 1996.
14. Burr ML: Is asthma increasing? J Epidemiol Community Health 41:185–189, 1987.
15. Anderson HR: Is the prevalence of asthma changing? Arch Dis Child 64:172–175, 1989.
16. Anderson HR, Butland BK, Strachan DP: Trends in prevalence and severity of childhood asthma. BMJ 308:1600–1604, 1994.
17. Peat JK, van den Berg RH, Green WF, et al: Changing prevalence of asthma in Australian children. BMJ 308:1591–1596, 1994.
18. Masoli M, Fabian D, Holt S, et al: The global burden of asthma: Executive summary of the GINA Dissemination Committee report. Allergy 59: 469–478, 2004.
19. Anderson HR, Strachan DP: Asthma mortality in England and Wales, 1979–89. Lancet 337:1357, 1991.
20. Braman SS: The global burden of asthma. Chest 130(1 Suppl):4S–12S, 2006.
21. Tual S, Godard P, Piau JP, et al: Asthma-related mortality in France, 1980–2005: Decline since the last decade. Allergy 63: 621–623, 2008.
22. Pearce N, Crane J, Burgess C, et al: Fenoterol and asthma mortality in New Zealand. N Z Med J 103:73–75, 1990.
23. Moorman JE, Rudd RA, Johnson CA: et al: National surveillance for asthma—United States, 1980–2004. MMWR Surveill Summ 56:1–54, 2007.
24. Akinbami L: Asthma prevalence, health care use and mortality: United States, 2003–05. 2008. Available at http://www.cdc.gov/hchs/products/pubs/pubd/hestats/asthma03-05/asthma03-05.htm
25. Strachan DP: Hay fever, hygiene, and household size. BMJ 299:1259–1260, 1989.
26. Strachan D, Sibbald B, Weiland S, et al: Worldwide variations in prevalence of symptoms of allergic rhinoconjunctivitis in children: The International Study of Asthma and Allergies in Childhood (ISAAC). Pediatr Allergy Immunol 8:161–176., 1997.
27. Beisswenger C, Bals R: Interaction of allergic airway inflammation and innate immunity: Hygiene and beyond. J Occup Med Toxicol 3(Suppl 1):S3, 2008.
28. Kiechl-Kohlendorfer U, Horak E, Mueller W, et al: Neonatal characteristics and risk of atopic asthma in schoolchildren: Results from a large prospective birth-cohort study. Acta Paediatr 96: 1606–1610. Epub 2007;September 19.
29. Stelmach I, Smejda K, Jerzynska J, et al: Decreased markers of atopy in children with presumed early exposure to allergens, unhygienic conditions, and infections. Ann Allergy Asthma Immunol 99:170–177, 2007.
30. Ramsey CD, Gold DR, Litonjua AA, et al: Respiratory illnesses in early life and asthma and atopy in childhood. J Allergy Clin Immunol 119:150–156, 2007. Epub 2006;October 23.
31. Stein RT, Sherrill D, Morgan WJ, et al: Respiratory syncytial virus in early life and risk of wheeze and allergy by age 13 years. Lancet 354:541–545, 1999.
32. Illi S, von Mutius E, Lau S, et al: Early childhood infectious diseases and the development of asthma up to school age: A birth cohort study. BMJ 322:390–395, 2001.
33. Rooney JC, Williams HE: The relationship between proved viral bronchiolitis and subsequent wheezing. J Pediatr 79:744–747, 1971.
34. Gurwitz D, Mindorff C, Levison H: Increased incidence of bronchial reactivity in children with a history of bronchiolitis. J Pediatr 98:551–555, 1981.
35. Hall CB, Hall WJ, Gala CL, et al: Long-term prospective study in children after respiratory syncytial virus infection. J Pediatr 105:358–364, 1984.
36. Mok JY, Simpson H: Outcome for acute bronchitis, bronchiolitis, and pneumonia in infancy. Arch Dis Child 59:306–309, 1984.
37. Mok JY, Simpson H: Symptoms, atopy, and bronchial reactivity after lower respiratory infection in infancy. Arch Dis Child 59:299–305, 1984.
38. Wright AL, Taussig LM, Ray CG, et al: The Tucson Children's Respiratory Study. II. Lower respiratory tract illness in the first year of life. Am J Epidemiol 129:1232–1246, 1989.
39. Noble V, Murray M, Webb MS, et al: Respiratory status and allergy nine to 10 years after acute bronchiolitis. Arch Dis Child 76:315–319, 1997.
40. Sigurs N, Bjarnason R, Sigurbergsson F, et al: Respiratory syncytial virus bronchiolitis in infancy is an important risk factor for asthma and allergy at age 7. Am J Respir Crit Care Med 161:1501–1507, 2000.
41. Sigurs N, Gustafsson PM, Bjarnason R, et al: Severe respiratory syncytial virus bronchiolitis in infancy and asthma and allergy at age 13. Am J Respir Crit Care Med 171:137–141, 2005. Epub 2004;October 29.
42. Perez-Yarza EG, Moreno A, Lazaro P, et al: The association between respiratory syncytial virus infection and the development of childhood asthma: A systematic review of the literature. Pediatr Infect Dis J 26:733–739, 2007.
43. Jackson DJ, Gangnon RE, Evans MD, et al: Wheezing rhinovirus illnesses in early life predict asthma development in high-risk children. Am J Respir Crit Care Med 178:667–672. Epub 2008;June 19.
44. Lemanske RF Jr, Jackson DJ, Gangnon RE, et al: Rhinovirus illnesses during infancy predict subsequent childhood wheezing. J Allergy Clin Immunol 116:571–577, 2005.
45. Singh AM, Moore PE, Gern JE, et al: Bronchiolitis to asthma: A review and call for studies of gene-virus interactions in asthma causation. Am J Respir Crit Care Med 175:108–119, 2007. Epub 2006;October 19.
46. Peebles RS Jr, Graham BS: Pathogenesis of respiratory syncytial virus infection in the murine model. Proc Am Thorac Soc 2:110–115, 2005.
47. Dakhama A, Lee YM, Gelfand EW: Virus-induced airway dysfunction: Pathogenesis and biomechanisms. Pediatr Infect Dis J 24(11 Suppl):S159–S169, 2005.
48. Hansbro NG, Horvat JC, Wark PA, et al: Understanding the mechanisms of viral induced asthma: New therapeutic directions. Pharmacol Ther 117:313–353, 2008. Epub 2008;January 29.
49. Johnson TR, Graham BS: Secreted respiratory syncytial virus G glycoprotein induces interleukin-5 (IL-5), IL-13, and eosinophilia by an IL-4–independent mechanism. J Virol 73:8485–8495, 1999.
50. Johnston SL, Martin RJ: *Chlamydophila pneumoniae* and *Mycoplasma pneumoniae*: A role in asthma pathogenesis? Am J Respir Crit Care Med 172:1078–1089, 2005. Epub 2005;June 16.
51. Emre U, Roblin PM, Gelling M, et al: The association of *Chlamydia pneumoniae* infection and reactive airway disease in children. Arch Pediatr Adolesc Med 148:727–732, 1994.
52. Hahn DL, Golubjatnikov R: Asthma and chlamydial infection: A case series. J Fam Pract 38:589–595, 1994.
53. Cook PJ, Davies P, Tunnicliffe W, et al: *Chlamydia pnuemoniae* and asthma. Thorax 53:254–259, 1998.
54. Huittinen T, Hahn D, Anttila T, et al: Host immune response to *Chlamydia pneumoniae* heat shock protein 60 is associated with asthma. Eur Respir J 17:1078–1082, 2001.

55. Sutherland ER, Brandorff JM, Martin RJ: Atypical bacterial pneumonia and asthma risk. J Asthma 41:863–868, 2004.
56. Kraft M, Hamid Q, Cassell GH, et al: *Mycoplasma* and *Chlamydia* cause increased airway inflammation that is responsive to clarithromycin. Am J Respir Crit Care Med 159:A517, 1999.
57. Kraft M, Cassell GH, Pak J, et al. *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* in asthma: Effect of clarithromycin. Chest 121:1782–1788, 2002.
58. Kraft M, Adler KB, Ingram JL, et al: *Mycoplasma pneumoniae* induces airway epithelial cell expression of MUC5AC in asthma. Eur Respir J 31:43–46, 2008.
59. Strachan DP, Butland BK, Anderson HR: Incidence and prognosis of asthma and wheezing illness from early childhood to age 33 in a national British cohort. BMJ 312:1195–1199, 1996.
60. Strachan DP, Harkins LS, Johnston ID, et al: Childhood antecedents of allergic sensitization in young British adults. J Allergy Clin Immunol 99:6–12, 1997.
61. Strachan DP: Family size, infection and atopy: The first decade of the "hygiene hypothesis." Thorax 55(Suppl 1):S2–S10, 2000.
62. Ozdemir C, Ceyhan BB, Yazi D, et al: Non-atopic asthma in children is related to maternal bronchial hyperreactivity. Pediatr Allergy Immunol 19:248–254, 2008.
63. Tariq SM, Matthews SM, Hakim EA, et al: The prevalence of and risk factors for atopy in early childhood: A whole population birth cohort study. J Allergy Clin Immunol 101:587–593, 1998.
64. Porsbjerg C, von Linstow ML, Ulrik CS, et al: Risk factors for onset of asthma: A 12-year prospective follow-up study. Chest 129:309–316, 2006.
65. Torrent M, Sunyer J, Garcia R, et al: Early-life allergen exposure and atopy, asthma, and wheeze up to 6 years of age. Am J Respir Crit Care Med 176:446–453, 2007. Epub 2007;June 15.
66. Celedon JC, Milton DK, Ramsey CD, et al: Exposure to dust mite allergen and endotoxin in early life and asthma and atopy in childhood. J Allergy and Clinical Immunol 120:144–149, 2007.
67. Nystad W, Meyer HE, Nafstad P, et al: Body mass index in relation to adult asthma among 135,000 Norwegian men and women. Am J Epidemiol 160:969–976, 2004.
68. Chen Y, Dales R, Tang M, et al: Obesity may increase the incidence of asthma in women but not in men: Longitudinal observations from the Canadian National Population Health Surveys. Am J Epidemiol 155:191–197, 2002.
69. Bibi H, Shoseyov D, Feigenbaum D, et al: The relationship between asthma and obesity in children: Is it real or a case of over diagnosis? J Asthma 41:403–410, 2004.
70. Rizwan S, Reid J, Kelly Y, et al: Trends in childhood and parental asthma prevalence in Merseyside, 1991–1998. J Public Health (Oxf) 26:337–342, 2004.
71. von Kries R, Hermann M, Grunert VP, et al: Is obesity a risk factor for childhood asthma? Allergy 56:318–322, 2001.
72. Beuther DA, Sutherland ER: Overweight, obesity, and incident asthma: A meta-analysis of prospective epidemiologic studies. Am J Respir Crit Care Med 175:661–666, 2007. Epub 2007;January 18.
73. Shore SA: Obesity and asthma: Possible mechanisms. J Allergy Clin Immunol 121:1087–1093, 2008 [quiz 1094–1095]. Epub 2008;April 11.
74. Weiss ST: Obesity: Insight into the origins of asthma. Nat Immunol 6:537–539, 2005.
75. Sulit LG, Storfer-Isser A, Rosen CL, et al: Associations of obesity, sleep-disordered breathing, and wheezing in children. Am J Respir Crit Care Med 171:659–664, 2005. Epub 2004;December 10.
76. Hancox RJ, Poulton R, Taylor DR, et al: Associations between respiratory symptoms, lung function and gastro-oesophageal reflux symptoms in a population-based birth cohort. Respir Res 7:142, 2006.
77. Bagnato GF, Gulli S, Giacobbe O, et al: Bronchial hyperresponsiveness in subjects with gastroesophageal reflux. Respiration 67:507–509, 2000.
78. Bagnato VJ: Laparoscopic Nissen fundoplication. Surg Laparosc Endosc 2:188–190, 1992.
79. Stein MR: Possible mechanisms of influence of esophageal acid on airway hyperresponsiveness. Am J Med 115(Suppl 3A):55S–59S, 2003.
80. Harding SM: Gastroesophageal reflux, asthma, and mechanisms of interaction. Am J Med 111(Suppl 8A):8S–12S, 2001.
81. Kiljander T, Salomaa ER, Hietanen E, et al: Asthma and gastro-oesophageal reflux: Can the response to anti-reflux therapy be predicted? Respir Med 95:387–392, 2001.
82. Kiljander TO, Salomaa ER, Hietanen EK, et al: Gastroesophageal reflux and bronchial responsiveness: Correlation and the effect of fundoplication. Respiration 69:434–439, 2002.
83. Harding SM: Recent clinical investigations examining the association of asthma and gastroesophageal reflux. Am J Med 115(Suppl 3A):39S–44S, 2003.
84. Harding SM: Gastroesophageal reflux as an asthma trigger: Acid stress. Chest 126:1398–1399, 2004.
85. Harding SM: Gastroesophageal reflux: A potential asthma trigger. Immunol Allergy Clin North Am 25:131–148, 2005.
85a. Dixon AE: Adipokines and asthma. Chest 135:255–256, 2009.
86. Milan G, Granzotto M, Scarda A, et al: Resistin and adiponectin expression in visceral fat of obese rats: Effect of weight loss. Obes Res 10:1095–1103, 2002.
87. Shore SA, Johnston RA: Obesity and asthma. Pharmacol Ther 110:83–102, 2006. Epub 2005;November 17.
88. Straczkowski M, Dzienis-Straczkowska S, Stepien A, et al: Plasma interleukin-8 concentrations are increased in obese subjects and related to fat mass and tumor necrosis factor-alpha system. J Clin Endocrinol Metab 87:4602–4606, 2002.
89. Guler N, Kirerleri E, Ones U, et al: Leptin: Does it have any role in childhood asthma? J Allergy Clin Immunol 114:254–259, 2004.
90. Sood A, Ford ES, Camargo CA Jr: Association between leptin and asthma in adults. Thorax 61:300–305,, 2006. Epub 2006;March 15.
91. Vercelli D: Advances in asthma and allergy genetics in 2007. J Allergy Clin Immunol 122:267–271, 2008. Epub 2008;July 10.
92. Senthilselvan A, Rennie D, Chenard L, et al: Association of polymorphisms of Toll-like receptor 4 with a reduced prevalence of hay fever and atopy. Ann Allergy Asthma Immunol 100:463–468, 2008.
93. Yang IA, Fong KM, Holgate ST, et al: The role of Toll-like receptors and related receptors of the innate immune system in asthma. Curr Opin Allergy Clin Immunol 6:23–28, 2006.
94. Raby BA, Klimecki WT, Laprise C, et al: Polymorphisms in Toll-like receptor 4 are not associated with asthma or atopy-related phenotypes. Am J Respir Crit Care Med 166:1449–1456, 2002.
95. Adjers K, Karjalainen J, Pessi T, et al: Epistatic effect of TLR4 and IL4 genes on the risk of asthma in females. Int Arch Allergy Immunol 138:251–256, 2005. Epub 2005;October 7.
96. Zhang H, Zhang Q, Wang L, et al: Association of IL4R gene polymorphisms with asthma in Chinese populations. Hum Mutat 28:1046, 2007.
97. Howard TD, Koppelman GH, Xu J, et al: Gene-gene interaction in asthma: IL4RA and IL13 in a Dutch population with asthma. Am J Hum Genet 70:230–236, 2002. Epub 2001;November 14.
98. Freidin MB, Kobyakova OS, Ogorodova LM, et al: Association of polymorphisms in the human IL4 and IL5 genes with atopic bronchial asthma and severity of the disease. Comp Funct Genomics 4:346–350, 2003.
99. Denham S, Koppelman GH, Blakey J, et al: Meta-analysis of genome-wide linkage studies of asthma and related traits. Respir Res 9:38, 2008.
100. Wang L, Pinkerton KE: Detrimental effects of tobacco smoke exposure during development on postnatal lung function and asthma. Birth Defects Res C Embryo Today 84:54–60, 2008.
101. Moshammer H, Hoek, G, Luttmann-Gibson H, et al: Parental smoking and lung function in children: An international study. Am J Respir Crit Care Med 173(:1255–1263, 2006. Epub 2006;February 16.
102. Wang C, Salam MT, Islam T, et al: Effects of in utero and childhood tobacco smoke exposure and beta$_2$-adrenergic receptor genotype on childhood asthma and wheezing. Pediatrics 122:e107–e114, 2008. Epub 2008;June 16.
103. Goksor E, Amark M, Alm B, et al: The impact of pre- and post-natal smoke exposure on future asthma and bronchial hyper-responsiveness. Acta Paediatr 96:1030–1035, 2007. Epub 2007;May 10.
104. Raherison C, Penard-Morand C, Moreau D, et al: In utero and childhood exposure to parental tobacco smoke, and allergies in

schoolchildren. Respir Med 101:107–117, 2007. Epub 2006; June 2.
105. Landau LI: Tobacco smoke exposure and tracking of lung function into adult life. Paediatr Respir Rev 9:39–43, 2008 [quiz 43–44]. Epub 2008;February 5.
106. Whu R, Cirilo G, Wong J, et al: Risk factors for pediatric asthma in the South Bronx. J Asthma 44:855–859, 2007.
107. Vork KL, Broadwin RL, Blaisdell RJ: Developing asthma in childhood from exposure to secondhand tobacco smoke: Insights from a meta-regression. Environ Health Perspect 115:1394–1400, 2007.
108. Prescott SL: Effects of early cigarette smoke exposure on early immune development and respiratory disease. Paediatr Respir Rev 9:3–9, 2008 [quiz 10]. Epub 2008;February 5.
109. Guedes HT, Souza LS: Exposure to maternal smoking in the first year of life interferes in breast-feeding protective effect against the onset of respiratory allergy from birth to 5 yr. Pediatr Allergy Immunol 20:30–34, 2009. Epub 2008;January 12.
110. Thomson NC: The role of environmental tobacco smoke in the origins and progression of asthma. Curr Allergy Asthma Rep 7:303–309, 2007.
111. Sadeghnejad A, Karmaus W, Arshad SH, et al: IL13 gene polymorphisms modify the effect of exposure to tobacco smoke on persistent wheeze and asthma in childhood, a longitudinal study. Respir Res 9: 2, 2008.
112. Plaschke PP, Janson C, Norrman E, et al: Onset and remission of allergic rhinitis and asthma and the relationship with atopic sensitization and smoking. Am J Respir Crit Care Med 162:920–924, 2000.
113. Polosa R, Knoke JD, Russo C, et al: Cigarette smoking is associated with a greater risk of incident asthma in allergic rhinitis. J Allergy Clin Immunol 121:1428–1434, 2008. Epub 2008; April 24.
114. Sarafino EP, Goldfedder J: Genetic factors in the presence, severity, and triggers of asthma. Arch Dis Child 73:112–116, 1995.
115. Lefkowitz RJ, Caron MG, Stiles GL: Mechanisms of membrane-receptor regulation. Biochemical, physiological, and clinical insights derived from studies of the adrenergic receptors. N Engl J Med 310:1570–1579, 1984.
116. Risch N, Merikangas K: The future of genetic studies of complex human diseases. Science 273:1516–1517, 1996.
117. Asthma mortality and hospitalization among children and young adults—United States, 1980–1993. MMWR Morb Mortal Wkly Rep 45:350–353, 1996.
118. Laitinen T, Polvi A, Rydman P, et al. Characterization of a common susceptibility locus for asthma-related traits. Science 304:300–304, 2004.
119. Nicolae D, Cox NJ, Lester LA, et al: Fine mapping and positional candidate studies identify HLA-G as an asthma susceptibility gene on chromosome 6p21. Am J Hum Genet 76:349–357, 2005. Epub 2004;December 20.
120. Van Eerdewegh P, Little RD, Dupuis J, et al: Association of the ADAM33 gene with asthma and bronchial hyperresponsiveness. Nature 418:426–430, 2002. Epub 2002;July 10.
121. Zhang M, Su X, Mileykovskaya E, et al: Cardiolipin is not required to maintain mitochondrial DNA stability or cell viability for *Saccharomyces cerevisiae* grown at elevated temperatures. J Biol Chem 278:35204–35210, 2003.
122. Foley SC, Mogas AK, Olivenstein R, et al: Increased expression of ADAM33 and ADAM8 with disease progression in asthma. J Allergy Clin Immunol 119:863–871, 2007. Epub 2007;March 6.
123. Chen Y, Schnell AH, Rennie DC, et al: Segregation analyses of asthma and respiratory allergy: the Humboldt family study. Am J Med Genet 104:23–30, 2001.
124. Holberg CJ, Halonen M, Wright AL, et al: Familial aggregation and segregation analysis of eosinophil levels. Am J Respir Crit Care Med 160:1604–1610, 1999.
125. Sampogna F, Demenais F, Hochez J, et al: Segregation analysis of IgE levels in 335 French families (EGEA) using different strategies to correct for the ascertainment through a correlated trait (asthma). Genet Epidemiol 18:128–142, 2000.
126. Xu J, Levitt RC, Panhuysen CI, et al: Evidence for two unlinked loci regulating total serum IgE levels. Am J Hum Genet 57:425–430, 1995.
127. Bleecker ER, Amelung PJ, Levitt RC, et al: Evidence for linkage of total serum IgE and bronchial hyperresponsiveness to chromosome 5q: A major regulatory locus important in asthma. Clin Exp Allergy 25(Suppl 2):84–88, 1995 [discussion appears 95–96].
128. Koppelman GH, Stine OC, Xu J, et al: Genome-wide search for atopy susceptibility genes in Dutch families with asthma. J Allergy Clin Immunol 109:498–506, 2002.
129. Postma DS, Meyers DA, Jongepier H, et al: Genomewide screen for pulmonary function in 200 families ascertained for asthma. Am J Respir Crit Care Med 172:446–452, 2005. Epub 2005; May 18.
130. Ober C, Hoffjan S: Asthma genetics 2006: The long and winding road to gene discovery. Genes Immun 7:95–100, 2006.
131. Moffatt MF, Kabesch M, Liang L, et al: Genetic variants regulating ORMDL3 expression contribute to the risk of childhood asthma. Nature 448:470–473, 2007. Epub 2007;July 4.
132. Ober C, Tan Z, Sun Y, et al: Effect of variation in CHI3L1 on serum YKL-40 level, risk of asthma, and lung function. N Engl J Med 358:1682–1691, 2008. Epub 2008;April 9.
133. Guilloud-Bataille M, Bouzigon E, Annesi-Maesano I, et al: Evidence for linkage of a new region (11p14) to eczema and allergic diseases. Hum Genet 122:605–614, 2008. Epub 2007;October 18.
134. Choudhry S, Taub M, Mei R, et al: Genome-wide screen for asthma in Puerto Ricans: Evidence for association with 5q23 region. Hum Genet 123:455–468, 2008. Epub 2008;April 10.
135. Hui J, Oka A, James A, et al:. A genome-wide association scan for asthma in a general Australian population. Hum Genet 123:297–306, 2008. Epub 2008;February 6.
136. Miller RL, Ho SM: Environmental epigenetics and asthma: Current concepts and call for studies. Am J Respir Crit Care Med 177:567–573, 2008. Epub 2008;January 10.
137. Meyers DA, Postma DS, Stine OC, et al: Genome screen for asthma and bronchial hyperresponsiveness: Interactions with passive smoke exposure. J Allergy Clin Immunol 115:1169–1175, 2005.
138. Oates NA, van Vliet J, Duffy DL, et al: Increased DNA methylation at the AXIN1 gene in a monozygotic twin from a pair discordant for a caudal duplication anomaly. Am J Hum Genet 79:155–162, 2006. Epub 2006;May 22.
139. Alati R, Al Mamun A, O'Callaghan M, et al: In utero and postnatal maternal smoking and asthma in adolescence. Epidemiology 17:138–144, 2006.
140. Magnusson LL, Olesen AB, Wennborg H, et al: Wheezing, asthma, hayfever, and atopic eczema in childhood following exposure to tobacco smoke in fetal life. Clin Exp Allergy 35:1550–1556, 2005.
141. Li YF, Langholz B, Salam MT, et al: Maternal and grandmaternal smoking patterns are associated with early childhood asthma. Chest 127:1232–1241, 2005.
142. Emilsson V, Thorleifsson G, Zhang B, et al: Genetics of gene expression and its effect on disease. Nature 452:423–428, 2008. Epub 2008;March 16.
143. Israel E: Genetics and the variability of treatment response in asthma. J Allergy Clin Immunol 115(4 Suppl):S532–S538, 2005.
144. Liggett SB: Polymorphisms of the beta$_2$-adrenergic receptor and asthma. Am J Respir Crit Care Med 156:S156–S162, 1997.
145. Reihsaus E, Innis M, MacIntyre N, et al: Mutations in the gene encoding for the beta $_2$-adrenergic receptor in normal and asthmatic subjects. Am J Respir Cell Mol Biol 8:334–339, 1993.
146. Israel E, Drazen JM, Liggett SB, et al: The effect of polymorphisms of the beta(2)-adrenergic receptor on the response to regular use of albuterol in asthma. Am J Respir Crit Care Med 162:75–80, 2000.
147. Bleecker ER, Postma DS, Lawrance RM, et al: Effect of ADRB2 polymorphisms on response to longacting beta2-agonist therapy: A pharmacogenetic analysis of two randomised studies. Lancet 370:2118–2125, 2007.
148. Bleecker ER, Yancey SW, Baitinger LA, et al: Salmeterol response is not affected by beta$_2$-adrenergic receptor genotype in subjects with persistent asthma. J Allergy Clin Immunol 118:809–816, 2006. Epub 2006;August 28.
149. Wechsler ME, Lehman E, Lazarus SC, et al: Beta-Adrenergic receptor polymorphisms and response to salmeterol. Am J Respir Crit Care Med 173:519–526, 2006. Epub 2005;December 1.

150. Finotto S, Neurath MF, Glickman JN, et al: Development of spontaneous airway changes consistent with human asthma in mice lacking T-bet. Science 295:336–338, 2002.
151. Nakamura Y, Christodoulopoulos P, Cameron L, et al: Upregulation of the transcription factor GATA-3 in upper airway mucosa after in vivo and in vitro allergen challenge. J Allergy Clin Immunol 105:1146–1152, 2000.
152. Nakamura Y, Ghaffar O, Olivenstein R, et al: Gene expression of the GATA-3 transcription factor is increased in atopic asthma. J Allergy Clin Immunol 103:215–222, 1999.
153. Harrington LE, Hatton RD, Mangan PR, et al: Interleukin 17-producing $CD4^+$ effector T cells develop via a lineage distinct from the T helper type 1 and 2 lineages. Nat Immunol 6:1123–1132, 2005. Epub 2005;October 2.
154. Ivanov II, McKenzie BS, Zhou L, et al: The orphan nuclear receptor RORgammat directs the differentiation program of proinflammatory IL-17^+ T helper cells. Cell 126:1121–1133, 2006.
155. Steinman: A brief history of T(H)17, the first major revision in the T(H)1/T(H)2 hypothesis of T cell-mediated tissue damage. Nat Med 13:139–145, 2007.
156. Gregori S, Giarratana N, Smiroldo S, et al: Dynamics of pathogenic and suppressor T cells in autoimmune diabetes development. J Immunol 171:4040–4047, 2003.
157. Akdis M, Blaser K, Akdis CA: T regulatory cells in allergy: novel concepts in the pathogenesis, prevention, and treatment of allergic diseases. J Allergy Clin Immunol 116:961–968, 2005 [quiz 969]. Epub 2005;October 10.
158. Lewkowich IP, Herman NS, Schleifer KW, et al: $CD4^+CD25^+$ T cells protect against experimentally induced asthma and alter pulmonary dendritic cell phenotype and function. J Exp Med 202:1549–1561, 2005. Epub 2005;November 28.
159. Levings MK, Sangregorio R, Roncarolo MG: Human cd25(+) cd4(+) t regulatory cells suppress naive and memory T cell proliferation and can be expanded in vitro without loss of function. J Exp Med 193:1295–1302, 2001.
160. Weiss ST: Eat dirt—The hygiene hypothesis and allergic diseases. N Engl J Med 347:930–931, 2002.
161. Leckie MJ, ten Brinke A, Khan J, et al: Effects of an interleukin-5 blocking monoclonal antibody on eosinophils, airway hyperresponsiveness, and the late asthmatic response. Lancet 356: 2144–2148, 2000.
162. Larson KA, Olson EV, Madden BJ, et al: Two highly homologous ribonuclease genes expressed in mouse eosinophils identify a larger subgroup of the mammalian ribonuclease superfamily. Proc Natl Acad Sci U S A 93:12370–12375, 1996.
163. Macias MP, Welch KC, Denzler KL, et al: Identification of a new murine eosinophil major basic protein (mMBP) gene: Cloning and characterization of mMBP-2. J Leukoc Biol 67:567–576, 2000.
164. Horton MA, Larson KA, Lee JJ, et al: Cloning of the murine eosinophil peroxidase gene (mEPO): Characterization of a conserved subgroup of mammalian hematopoietic peroxidases. J Leukoc Biol 60:285–294, 1996.
165. Humbles AA, Lloyd CM, McMillan SJ, et al: A critical role for eosinophils in allergic airways remodeling. Science 305:1776–1779, 2004.
166. Lee JJ, Dimina D, Macias MP, et al: Defining a link with asthma in mice congenitally deficient in eosinophils. Science 305:1773–1776, 2004.
167. Wills-Karp M, Karp CL: Biomedicine. Eosinophils in asthma: remodeling a tangled tale. Science 305:1726–1729, 2004.
168. Robinson DS, Hamid Q, Ying S, et al: Predominant TH2-type bronchoalveolar lavage T-lymphocyte activation in atopic asthma. N Engl J Med 326:298–304, 1992.
169. Greenfeder S, Umland SP, Cuss FM, et al: Th2 cytokines and asthma. The role of interleukin-5 in allergic eosinophilic disease. Respir Res 2:71–79, 2001. Epub 2001;March 8.
170. Longphre M, Li D, Gallup M, et al: Allergen-induced IL-9 directly stimulates mucin transcription in respiratory epithelial cells. J Clin Invest 104:1375–1382, 1999.
171. Schandene L, Alonso-Vega C, Willems F, et al: B7/CD28-dependent IL-5 production by human resting T cells is inhibited by IL-10. J Immunol 152:4368–4374, 1994.
172. Arock M, Zuany-Amorim C, Singer M, et al: Interleukin-10 inhibits cytokine generation from mast cells. Eur J Immunol 26:166–170, 1996.
173. Steinke JW, Borish L:. Th2 cytokines and asthma. Interleukin-4: Its role in the pathogenesis of asthma, and targeting it for asthma treatment with interleukin-4 receptor antagonists. Respir Res 2:66–70, 2001. Epub 2001;February 19.
174. Brusselle G, Kips J, Joos G, et al: Allergen-induced airway inflammation and bronchial responsiveness in wild-type and interleukin-4–deficient mice. Am J Respir Cell Mol Biol 12:254–259, 1995.
175. Wills-Karp M, Luyimbazi J, Xu X, et al: Interleukin-13: Central mediator of allergic asthma. Science 282:2258–2261, 1998.
176. Grunig G, Warnock M, Wakil AE, et al: Requirement for IL-13 independently of IL-4 in experimental asthma. Science 282:2261–2263, 1998.
177. Zhu Z, Homer RJ, Wang Z, et al: Pulmonary expression of interleukin-13 causes inflammation, mucus hypersecretion, subepithelial fibrosis, physiologic abnormalities, and eotaxin production. J Clin Invest 103:779–788, 1999.
178. van der Pouw Kraan TC, van Veen A, Boeije LC, et al: An IL-13 promoter polymorphism associated with increased risk of allergic asthma. Genes Immun 1:61–65, 1999.
179. Arima K, Umeshita-Suyama R, Sakata Y, et al: Upregulation of IL-13 concentration in vivo by the IL13 variant associated with bronchial asthma. J Allergy Clin Immunol 109:980–987, 2002.
180. Bowler RP, Crapo JD: Oxidative stress in allergic respiratory diseases. J Allergy Clin Immunol 110:349–356, 2002.
181. Nakamura H: Thioredoxin and its related molecules: Update 2005. Antioxid Redox Signal 7:823–828, 2005.
182. Bowler RP, Crapo JD: Oxidative stress in airways: Is there a role for extracellular superoxide dismutase? Am J Respir Crit Care Med 166:S38–S43, 2002.
183. De Raeve HR, Thunnissen FB, Kaneko FT, et al: Decreased Cu,Zn-SOD activity in asthmatic airway epithelium: Correction by inhaled corticosteroid in vivo. Am J Physiol 272:L148–L154, 1997.
184. Kharitonov SA, Barnes PJ: Exhaled markers of pulmonary disease. Am J Respir Crit Care Med 163:1693–1722, 2001.
185. Michel T, Feron O: Nitric oxide synthases: Which, where, how, and why? J Clin Invest 100:2146–2152, 1997.
186. Asano K, Chee CB, Gaston B, et al: Constitutive and inducible nitric oxide synthase gene expression, regulation, and activity in human lung epithelial cells. Proc Natl Acad Sci U S A 91:10089–10093, 1994.
187. Nathan C, Xie QW: Nitric oxide synthases: Roles, tolls, and controls. Cell 78:915–918, 1994.
188. Dweik RA, Comhair SA, Gaston B, et al: NO chemical events in the human airway during the immediate and late antigen-induced asthmatic response. Proc Natl Acad Sci U S A 98:2622–2627, 2001. Epub 2001;February 20.
189. Jones SL, Kittelson J, Cowan JO, et al: The predictive value of exhaled nitric oxide measurements in assessing changes in asthma control. Am J Respir Crit Care Med 164:738–743, 2001.
190. Smith AD, Cowan JO, Brassett KP, et al. Use of exhaled nitric oxide measurements to guide treatment in chronic asthma. N Engl J Med 352:2163–2173, 2005. Epub 2005;May 24.
191. Que LG, Liu L, Yan Y, et al: Protection from experimental asthma by an endogenous bronchodilator. Science 308:1618–1621, 2005. Epub 2005;May 26.
192. Meurs H, McKay S, Maarsingh H, et al: Increased arginase activity underlies allergen-induced deficiency of cNOS-derived nitric oxide and airway hyperresponsiveness. Br J Pharmacol 136:391–398, 2002.
193. Zimmermann N, King NE, Laporte J, et al: Dissection of experimental asthma with DNA microarray analysis identifies arginase in asthma pathogenesis. J Clin Invest 111:1863–1874, 2003.
194. Li H, Romieu I, Sienra-Monge JJ, et al: Genetic polymorphisms in arginase I and II and childhood asthma and atopy. J Allergy Clin Immunol 117:119–126, 2006. Epub 2005;November 28.
195. Montuschi P, Barnes PJ: Exhaled leukotrienes and prostaglandins in asthma. J Allergy Clin Immunol 109:615–620, 2002.
196. Samuelsson B, Dahlen S-E, Lindgren JÅ, et al: Leukotrienes and lipoxins: Structures, biosynthesis, and biological effects. Science 237:1171–1176, 1987.

197. Kumlin M, Dahlen B, Bjorck T, et al: Urinary excretion of leukotriene E4 and 11-dehydro-thromboxane B_2 in response to bronchial provocations with allergen, aspirin, leukotriene D_4, and histamine in asthmatics. Am Rev Respir Dis 146:96–103, 1992.
198. Reiss TF, Hill JB, Harman E, et al: Increased urinary excretion of LTE_4 after exercise and attenuation of exercise-induced bronchospasm by montelukast, a cysteinyl leukotriene receptor antagonist. Thorax 52:1030–1035, 1997.
199. Christie PE, Tagari P, Ford-Hutchinson AW, et al: Urinary leukotriene E_4 concentrations increase after aspirin challenge in aspirin-sensitive asthmatic subjects. Am Rev Respir Dis 143:1025–1029, 1991.
200. Kanaoka Y, Boyce JA:. Cysteinyl leukotrienes and their receptors: Cellular distribution and function in immune and inflammatory responses. J Immunol 173:1503–1510, 2004.
201. Bergeron C, Boulet LP: Structural changes in airway diseases: Characteristics, mechanisms, consequences, and pharmacologic modulation. Chest 129:1068–1087, 2006.
202. Boulet LP, Laviolette M, Turcotte H, et al: Bronchial subepithelial fibrosis correlates with airway responsiveness to methacholine. Chest 112:45–52, 1997.
203. Little SA, Sproule MW, Cowan MD, et al: High resolution computed tomographic assessment of airway wall thickness in chronic asthma: Reproducibility and relationship with lung function and severity. Thorax 57:247–253, 2002.
204. Aysola RS, Hoffman EA, Gierada D, et al: Airway remodeling measured by multidetector computed tomography is increased in severe asthma and correlates with pathology. Chest 134:1183–1191, 2008.
205. Davies DE, Wicks J, Powell RM, et al: Airway remodeling in asthma: New insights. J Allergy Clin Immunol 111:215, 2003.
206. Paganin F, Séneterre E., Chanez P, et al: Computed tomography of the lungs in asthma: Influence of disease severity and etiology. Am J Respir Crit Care Med 153:110–114, 1996.
207. Nakano Y, Müller NL, King GG, et al: Quantitative assessment of airway remodeling using high-resolution CT. Chest 122(6 Suppl):271S–S275, 2002.
208. Leigh R, Ellis R, Wattie J, et al: Dysfunction and remodeling of the mouse airway persist after resolution of acute allergen-induced airway inflammation. Am J Respir Cell Mol Biol 27:526–535, 2002.
209. Ramos-Barbon D, Presley JF, Hamid QA, et al: Antigen-specific $CD4^+$ T cells drive airway smooth muscle remodeling in experimental asthma. J Clin Invest 115:1580–1589, 2005.
210. Elias JA, Zheng T, Lee CG, et al: Transgenic modeling of interleukin-13 in the lung. Chest 123(3 Suppl): 339S–S345, 2003.
211. Henderson WR Jr, Tang LO, Chu SJ, et al. A role for cysteinyl leukotrienes in airway remodeling in a mouse asthma model. Am J Respir Crit Care Med 165:108–116, 2002.
212. Kuperman DA, Huang X, Koth LL, et al: Direct effects of interleukin-13 on epithelial cells cause airway hyperreactivity and mucus overproduction in asthma. Nat Med 8:885–889, 2002.
213. Cohn L, Elias JA, Chupp GL: Asthma: Mechanisms of disease persistence and progression. Annu Rev Immunol 22:789–815, 2004.
214. Pepe C, Foley S, Shannon J, et al: Differences in airway remodeling between subjects with severe and moderate asthma. J Allergy Clin Immunol 116:544–549, 2005.
215. Roche WR, Montefort S, Baker J, et al: Cell adhesion molecules and the bronchial epithelium. Am Rev Respir Dis 148:S79–S82, 1993.
216. Holgate ST: Epithelium dysfunction in asthma. J Allergy Clin Immunol 120:1233–1244, 2007 [quiz 1245–1246].
217. Fedorov IA, Wilson SJ, Davies DE, et al: Epithelial stress and structural remodelling in childhood asthma. Thorax 60:389–394, 2005.
218. Ordonez C, Ferrando R, Hyde DM, et al: Epithelial desquamation in asthma: Artifact or pathology? Am J Respir Crit Care Med 162:2324–2329, 2000.
219. Shebani E, Shahana S, Janson C, et al: Attachment of columnar airway epithelial cells in asthma. Tissue Cell 37:145–152, 2005.
220. Kicic A, Sutanto EN, Stevens PT, et al: Intrinsic biochemical and functional differences in bronchial epithelial cells of children with asthma. Am J Respir Crit Care Med 174:1110–1118, 2006.
221. Knight D: Increased permeability of asthmatic epithelial cells to pollutants. Does this mean that they are intrinsically abnormal? Clin Exp Allergy 32:1263–1265, 2002.
222. Bucchieri F, Puddicombe SM, Lordan JL, et al: Asthmatic bronchial epithelium is more susceptible to oxidant-induced apoptosis. Am J Respir Cell Mol Biol 27:179–185, 2002.
223. Schleimer RP, Kato A, Kern R, et al: Epithelium: At the interface of innate and adaptive immune responses. J Allergy Clin Immunol 120:1279–1284, 2007.
224. Hackett TL, Knight DA: The role of epithelial injury and repair in the origins of asthma. Curr Opin Allergy Clin Immunol 7:63–68, 2007.
225. Holgate ST: The airway epithelium is central to the pathogenesis of asthma. Allergol Int 57:1–10, 2008.
226. Phipps S, Benyahia F, Ou T-T, et al: Acute allergen-induced airway remodeling in atopic athma. Am J Respir Cell Mol Biol 31:626–632, 2004.
227. Roche WR, Beasley R, Williams JH, et al: Subepithelial fibrosis in the bronchi of asthmatics. Lancet 1:520–524, 1989.
228. Laitinen A, Altraja A, Kampe M, et al: Tenascin is increased in airway basement membrane of asthmatics and decreased by an inhaled steroid. Am J Respir Crit Care Med 156:951–958, 1997.
229. Karjalainen EM, Lindqvist A, Laitinen LA, et al: Airway inflammation and basement membrane tenascin in newly diagnosed atopic and nonatopic asthma. Respir Med 97:1045–1051, 2003.
230. Slade DJ, Kraft M: Airway remodeling from bench to bedside: Current perspectives. Clin Chest Med 27:71–85, 2006.
231. Payne DN, Rogers AV, Adelroth E, et al: Early thickening of the reticular basement membrane in children with difficult asthma. Am J Respir Crit Care Med 167:78–82, 2003.
232. Saglani S, Malmstrom K, Pelkonen AS, et al: Airway remodeling and inflammation in symptomatic infants with reversible airflow obstruction. Am J Respir Crit Care Med 171:722–727, 2005.
233. Covar RA, Spahn JD, Murphy JR, et al: Progression of asthma measured by lung function in the Childhood Asthma Management Program. Am J Respir Crit Care Med 170:234–241, 2006. Epub 2004;March 17.
234. Martinez FD, Wright AL, Taussig LM, et al: Asthma and wheezing in the first six years of life. The Group Health Medical Associates. N Engl J Med 332:133–138, 1995.
235. Locke NR, Royce SG, Wainewright JS, et al: Comparison of airway remodeling in acute, subacute, and chronic models of allergic airways disease. Am J Respir Cell Mol Biol 36:625–632, 2007.
236. van den Toorn LM, Overbeek SE, de Jongste JC, et al: Airway inflammation is present during clinical remission of atopic asthma. Am J Respir Crit Care Med 164:2107–2113, 2001.
237. Lewis CC, Chu HW, Westcott JY, et al: Increased expression of platelet-derived growth factor receptor-beta in airway fibroblasts of severe asthmatics. Chest 123(3 Suppl):428S–429S, 2003.
238. Lewis CC, Chu HW, Westcott JY, et al: Airway fibroblasts exhibit a synthetic phenotype in severe asthma. J Allergy Clin Immunol 115:534–540, 2005.
238a. Ho I, Fixman ED, Asai K, et al: Platelet-derived growth factor and transforming growth factor-beta modulate the expression of matrix metalloproteinases and migratory function of human airway smooth muscle cells. Clin Exp Allergy 39:1370–1380, 2009.
239. Palmans E, Kips JC, Pauwels RA: Prolonged allergen exposure induces structural airway changes in sensitized rats. Am J Respir Crit Care Med 161:627–635, 2000.
240. Blyth DI, Wharton TF, Pedrick MS, et al: Airway subepithelial fibrosis in a murine model of atopic asthma: Suppression by dexamethasone or anti-interleukin-5 antibody. Am J Respir Cell Mol Biol 23:241–246, 2000.
241. Gelb AF, Licuanan J, Shinar CM, et al: Unsuspected loss of lung elastic recoil in chronic persistent asthma. Chest 121:715–721, 2002.
242. Mauad T, Xavier ACG, Saldiva PHN, et al. Elastosis and fragmentation of fibers of the elastic system in fatal asthma. Am J Respir Crit Care Med 160:968–975, 1999.
243. Mauad T, Silva LFF, Santos MA, et al: Abnormal alveolar attachments with decreased elastic fiber content in distal lung in fatal asthma. Am J Respir Crit Care Med 170:857–862, 2004.

244. Shi W, Bellusci S, Warburton D: Lung development and adult lung diseases. Chest 132:651–656, 2007.
245. Slats AM, Janssen K, van Schadewijk A, et al: Expression of smooth muscle and extracellular matrix proteins in relation to airway function in asthma. J Allergy Clin Immunol 121:1196, 2008.
246. Pham DN, Chu HW, Martin RJ, et al: Increased matrix metalloproteinase-9 with elastolysis in nocturnal asthma. Ann Allergy Asthma Immunol 90:72–78, 2003.
247. Kenyon NJ, Ward RW, McGrew G, et al: TGF-beta$_1$ causes airway fibrosis and increased collagen I and III mRNA in mice. Thorax 58:772–777, 2003.
248. Cho JY, Miller M, Baek KJ, et al: Inhibition of airway remodeling in IL-5–deficient mice. J Clin Invest 113:551–560, 2004.
249. Finotto S, Hausding M, Doganci A, et al. Asthmatic changes in mice lacking T-bet are mediated by IL-13. Int Immunol 17:993–1007, 2005.
250. McMillan SJ, Xanthou G, Lloyd CM: Manipulation of allergen-induced airway remodeling by treatment with anti-TGF-beta antibody: Effect on the Smad signaling pathway. J Immunol 174:5774–5780, 2005.
251. Flood-Page P, Menzies-Gow A, Phipps S, et al: Anti-IL-5 treatment reduces deposition of ECM proteins in the bronchial subepithelial basement membrane of mild atopic asthmatics. J Clin Invest 112:1029–1036, 2003.
252. Kelly MM, Leigh R, Bonniaud P, et al: Epithelial expression of profibrotic mediators in a model of allergen-induced airway remodeling. Am J Respir Cell Mol Biol 32:99–107, 2005.
253. Lee JH, Haselkorn T, Borish L, et al: Risk factors associated with persistent airflow limitation in severe or difficult-to-treat asthma: Insights from the TENOR study. Chest 132:1882–1889, 2007.
254. Kraft M, Cairns CB, Ellison MC, et al: Improvements in distal lung function correlate with asthma symptoms after treatment with oral montelukast. Chest 130:1726–1732, 2006.
255. Armour CL, Black JL, Berend N, et al: The relationship between bronchial hyperresponsiveness to methacholine and airway smooth muscle structure and reactivity. Respir Physiol 58:223–233, 1984.
256. James AL, Pare PD, Hogg JC: The mechanics of airway narrowing in asthma. Am Rev Respir Dis 139:242–246, 1989.
257. Lambert RK, Wiggs BR, Kuwano K, et al: Functional significance of increased airway smooth muscle in asthma and COPD. J Appl Physiol 74:2771–2781, 1993.
258. Sapienza S, Du T, Eidelman DH, et al: Structural changes in the airways of sensitized brown Norway rats after antigen challenge. Am Rev Respir Dis 144:423–427, 1991.
259. Benayoun L, Druilhe A, Dombret MC, et al: Airway structural alterations selectively associated with severe asthma. Am J Respir Crit Care Med 167:1360–1368, 2003.
260. Carroll N, Elliot J, Morton A, et al: The structure of large and small airways in nonfatal and fatal asthma. Am Rev Respir Dis 147:405–410, 1993.
261. Black JL, Burgess JK, Johnson PR: Airway smooth muscle—Its relationship to the extracellular matrix. Respir Physiol Neurobiol 137:339–346, 2003.
262. Johnson PR, Burgess JK, Underwood PA, et al: Extracellular matrix proteins modulate asthmatic airway smooth muscle cell proliferation via an autocrine mechanism. J Allergy Clin Immunol 113:690–696, 2004.
263. Panettieri RA Jr, Murray RK, Eszterhas AJ, et al: Repeated allergen inhalations induce DNA synthesis in airway smooth muscle and epithelial cells in vivo. Am J Physiol 274:L417–L424., 1998.
264. Woodruff PG, Dolganov GM, Ferrando RE, et al: Hyperplasia of smooth muscle in mild to moderate asthma without changes in cell size or gene expression. Am J Respir Crit Care Med 169:1001–1006, 2004.
265. Moir LM, Leung SY, Eynott PR, et al: Repeated allergen inhalation induces phenotypic modulation of smooth muscle in bronchioles of sensitized rats. Am J Physiol Lung Cell Mol Physiol 284:L148–L159, 2003.
266. Woodruff PG: Gene expression in asthmatic airway smooth muscle. Proc Am Thorac Soc 5:113–118, 2008.
267. Brightling CE, Bradding P, Symon FA, et al: Mast-cell infiltration of airway smooth muscle in asthma. N Engl J Med 346:1699–1705, 2002.
268. Berry M, Morgan A, Shaw DE, et al: Pathological features and inhaled corticosteroid response of eosinophilic and non-eosinophilic asthma. Thorax 62:1043–1049, 2007.
269. Page S, Ammit AJ, Black JL, et al: Human mast cell and airway smooth muscle cell interactions: Implications for asthma. Am J Physiol Lung Cell Mol Physiol 281:L1313–L1323, 2001.
270. Hollins F, Kaur D, Yang W. et al: Human airway smooth muscle promotes human lung mast cell survival, proliferation, and constitutive activation: Cooperative roles for CADM1, stem cell factor, and IL-6. J Immunol 181:2772–2780, 2008.
271. Williams OW, Sharafkhaneh A, Kim V, et al: Airway mucus: From production to secretion. Am J Respir Cell Mol Biol 34:527–536, 2006.
272. Fahy JV: Goblet cell and mucin gene abnormalities in asthma. Chest 122(6 Suppl):320S–326S, 2002.
273. Kuyper LM, Pare PD, Hogg JC, et al: Characterization of airway plugging in fatal asthma. Am J Med 115:6–11, 2003.
274. Aikawa T, Shimura S, Sasaki H, et al: Marked goblet cell hyperplasia with mucus accumulation in the airways of patients who died of severe acute asthma attack. Chest 101:916–921, 1992.
275. Sheehan JK, Howard M, Richardson PS, et al: Physical characterization of a low-charge glycoform of the MUC5B mucin comprising the gel-phase of an asthmatic respiratory mucous plug. Biochem J 338:507–513, 1999.
276. Rogers DF, Barnes PJ: Treatment of airway mucus hypersecretion. Ann Med 38:116–125, 2006.
277. Ordonez CL, Khashayar R, Wong HH, et al: Mild and moderate asthma is associated with airway goblet cell hyperplasia and abnormalities in mucin gene expression. Am J Respir Crit Care Med 163:517–523, 2001.
278. Kirkham S, Sheehan JK, Knight D, et al: Heterogeneity of airways mucus: Variations in the amounts and glycoforms of the major oligomeric mucins MUC5AC and MUC5B. Biochem J 361:537–546, 2002.
279. Sheehan JK, Richardson PS, Fung DC, et al: Analysis of respiratory mucus glycoproteins in asthma: A detailed study from a patient who died in status asthmaticus. Am J Respir Cell Mol Biol 13:748–756, 1995.
280. Shimura S, Andoh Y, Haraguchi M, et a: Continuity of airway goblet cells and intraluminal mucus in the airways of patients with bronchial asthma. Eur Respir J 9:1395–1401, 1996.
281. Li Y, Martin LD, Spizz G, et al: MARCKS protein is a key molecule regulating mucin secretion by human airway epithelial cells in vitro. J Biol Chem 276:40982–40990, 2001.
282. Park JA, Crews AL, Lampe WR, et al: Protein kinase C delta regulates airway mucin secretion via phosphorylation of MARCKS protein. Am J Pathol 171:1822–1830, 2007.
283. Chu HW, Balzar S, Seedorf GJ, et al: Transforming growth factor-beta$_2$ induces bronchial epithelial mucin expression in asthma. Am J Pathol 165:1097–1106, 2004.
284. Wu Q, Martin RJ, Rino JG, et al: A deficient TLR2 signaling promotes airway mucin production in *Mycoplasma pneumoniae*–infected allergic mice. Am J Physiol Lung Cell Mol Physiol 292:L1064–L1072, 2007.
285. Li L, Kaplan J: Characterization of two homologous yeast genes that encode mitochondrial iron transporters. J Biol Chem 272:28485–28493, 1997.
286. Kanazawa H, Asai K, Hirata K, et al. Vascular involvement in exercise-induced airway narrowing in patients with bronchial asthma. Chest 122:166–170, 2002.
287. Hoshino M, Nakamura Y, Hamid QA: Gene expression of vascular endothelial growth factor and its receptors and angiogenesis in bronchial asthma. J Allergy Clin Immunol 107:1034–1038, 2001.
288. Chetta A, Zanini A, Foresi A. et al: Vascular endothelial growth factor up-regulation and bronchial wall remodelling in asthma. Clin Exp Allergy 35:1437–1442., 2005.
289. Faffe DS, Flynt L, Bourgeois K, et al: Interleukin-13 and interleukin-4 induce vascular endothelial growth factor release from airway smooth muscle cells: Role of vascular endothelial growth factor genotype. Am J Respir Cell Mol Biol 34:213–218, 2006. Epub 2005;October 6.

290. Simcock DE, Kanabar V, Clarke GW, et al: Induction of angiogenesis by airway smooth muscle from patients with asthma. Am J Respir Crit Care Med 178:460–468, 2008. Epub 2008;June 12.
291. Hasaneen NA, Zucker S, Lin RZ, et al: Angiogenesis is induced by airway smooth muscle strain. Am J Physiol Lung Cell Mol Physiol 293:L1059–L1068, 2007. Epub 2007;August 10.
292. Lee JW, Ovadia B, Azakie A, et al: Increased pulmonary blood flow does not alter surfactant protein gene expression in lambs within the first week of life. Am J Physiol Lung Cell Mol Physiol 286:L1237–L1243, 2004.
293. Crimi E, Spanevello A, Neri M, et al: Dissociation between airway inflammation and airway hyperresponsiveness in allergic asthma. Am J Respir Crit Care Med 157:4–9, 1998.
294. Grunstein MM, Hakonarson H, Leiter J, et al: IL-13–dependent autocrine signaling mediates altered responsiveness of IgE-sensitized airway smooth muscle. Am J Physiol Lung Cell Mol Physiol 282:L520–L528, 2002.
295. Hakonarson H, Herrick DJ, Serrano PG, et al: Autocrine role of interleukin 1beta in altered responsiveness of atopic asthmatic sensitized airway smooth muscle. J Clin Invest 99:117–124, 1997.
296. Hogg JC: Pathology of asthma. J Allergy Clin Immunol 92:1–5, 1993.
297. Ebina M, Takahashi T, Chiba T, et al: Cellular hypertrophy and hyperplasia of airway smooth muscles underlying bronchial asthma. A 3-D morphometric study. Am Rev Respir Dis 148:720–726, 1993.
298. McParland BE, Tait RR, Pare PD, et al: The role of airway smooth muscle during an attack of asthma simulated in vitro. Am J Respir Cell Mol Biol 33:500–504, 2005. Epub 2005;July 29.
299. Hirst SJ, Martin JG, Bonacci JV, et al: Proliferative aspects of airway smooth muscle. J Allergy Clin Immunol 114(2 Suppl):S2–S17, 2004.
300. An SS, Bai TR, Bates JH, et al: Airway smooth muscle dynamics: A common pathway of airway obstruction in asthma. Eur Respir J 29:834–860, 2007.
300a. Blach JL, Roth M: Intrinsic asthma: Is it intrinsic to the smooth muscle? Clin Exp Allergy 39:962–965, 2009.
301. Cho W, Stahelin R: Membrane protein interactions in cell signaling and membrane trafficking. Annu Rev Biophys Biomol Struct 34:119–151, 2005.
302. Henderson WR Jr, Chiang GK, Tien YT, et al: Reversal of allergen-induced airway remodeling by CysLT1 receptor blockade. Am J Respir Crit Care Med 173:718–728, 2006.
303. Danek CJ, Lombard CM, Dungworth DL, et al: Reduction in airway hyperresponsiveness to methacholine by the application of RF energy in dogs. J Appl Physiol 97:1946–1953, 2004.
304. Cox L, Platts-Mills TA, Finegold I, et al: American Academy of Allergy, Asthma & Immunology/American College of Allergy, Asthma and Immunology Joint Task Force Report on omalizumab-associated anaphylaxis. J Allergy Clin Immunol 120:1373–1377, 2007.
304a. Holgate ST: Novel targets of therapy in asthma. Curr Opin Pulm Med 15:63–71, 2009.
305. Ratnovsky A, Mellema M, An SS, et al: Airway smooth muscle proliferation and mechanics: Effects of AMP kinase agonists. Mol Cell Biomech 4:143–157, 2007.
306. Simoes DCM, Vassilakopoulos T, Toumpanakis D, et al: Angiopoietin-1 protects against airway inflammation and hyperreactivity in asthma. Am J Respir Crit Care Med 177:1314–1321, 2008.
307. Kessler GF, Austin JH, Graf PD, et al: Airway constriction in experimental asthma in dogs: Tantalum bronchographic studies. J Appl Physiol 35:703–708, 1973.
308. Brown RH, Pearse DB, Pyrgos G, et al: The structural basis of airways hyperresponsiveness in asthma. J Appl Physiol 101:30–39, 2006.
309. Pellegrino R, Violante B, Nava S, et al: Expiratory airflow limitation and hyperinflation during methacholine-induced bronchoconstriction. J Appl Physiol 75:1720–1727, 1993.
310. Wagers SS, Jaffe EF, Irvin CG: Development structure and physiology in normal and asthmatic lung. *In* Adkinson Jr NY, Yunginger JW, Busse WW, et al (eds): Middleton's Allergy: Principles and Practice. St. Louis: Mosby, 2003.
311. Sorkness RL, Bleecker ER, Busse WW, et al: Lung function in adults with stable but severe asthma: Air trapping and incomplete reversal of obstruction with bronchodilation. J Appl Physiol 104:394–403, 2008.
312. Adler A, Cowley EA, Bates JH, et al: Airway-parenchymal interdependence after airway contraction in rat lung explants. J Appl Physiol 85:231–237, 1998.
313. Bai TR, Knight DA: Structural changes in the airways in asthma: Observations and consequences. Clin Sci 108:463–477, 2005.
314. Martin J, Powell E, Shore S, et al: The role of respiratory muscles in the hyperinflation of bronchial asthma. Am Rev Respir Dis 121:441–447, 1980.
315. McFadden ER Jr, Kiser R, DeGroot WJ: Acute bronchial asthma. Relations between clinical and physiologic manifestations. N Engl J Med 288:221–225, 1973.
316. O'Donnell DE, Bertley JC, Chau LK, et al: Qualitative aspects of exertional breathlessness in chronic airflow limitation: Pathophysiologic mechanisms. Am J Respir Crit Care Med 155:109–115, 1997.
317. Venegas JG, Schroeder T, Harris S, et al: The distribution of ventilation during bronchoconstriction is patchy and bimodal: A PET imaging study. Respir Physiol Neurobiol 148:57–64, 2005.
318. Wagner PD, Hedenstierna G, Rodriguez-Roisin R: Gas exchange, expiratory flow obstruction and the clinical spectrum of asthma. Eur Respir J 9:1278–1282, 1996.
319. Tai E, Read J: Blood-gas tensions in bronchial asthma. Lancet 1:644–646, 1967.
320. Rodriguez-Roisin R, Roca J: Contributions of multiple inert gas elimination technique to pulmonary medicine.3. Bronchial asthma. Thorax 49:1027–1033, 1994.
321. Mcfadden E: Hypoxemia and hypocapnia in asthma. N Engl J Med 278:1068, 1968.
322. Cherniack RM: Physiologic diagnosis and function in asthma. Clin Chest Med 16:567–581, 1995.
323. McFadden ER Jr: Acute severe asthma. Am J Respir Crit Care Med 168:740–759, 2003.
324. Brand PL, Duiverman EJ, Waalkens HJ, et al: Peak flow variation in childhood asthma: Correlation with symptoms, airways obstruction, and hyperresponsiveness during long-term treatment with inhaled corticosteroids. Dutch CNSLD Study Group. Thorax 54:103–107, 1999.
325. Llewellin P, Sawyer G, Lewis S, et al: The relationship between FEV_1 and PEF in the assessment of the severity of airways obstruction. Respirology 7:333–337, 2002.
326. Aggarwal AN, Gupta D, Jindal SK: The relationship between FEV_1 and peak expiratory flow in patients with airways obstruction is poor. Chest 130:1454–1461, 2006.
327. Reddel HK, Marks GB, Jenkins CR: When can personal best peak flow be determined for asthma action plans? Thorax 59:922–924, 2004.
328. Bateman ED, Hurd SS, Barnes PJ, et al: Global strategy for asthma management and prevention: GINA executive summary. Eur Respir J 31:143–178, 2008.
329. Taylor DR, Town GI, Herbison GP, et al: Asthma control during long-term treatment with regular inhaled salbutamol and salmeterol. Thorax 53:744–752, 1998.
330. Frey U, Brodbeck T, Majumdar A, et a: Risk of severe asthma episodes predicted from fluctuation analysis of airway function. Nature 438:667–670, 2005.
331. Pellegrino R, Viegi G, Brusasco V, et al: Interpretative strategies for lung function tests. Eur Respir J 26:948–968, 2005.
332. Nowak RM, Tomlanovich MC, Sarkar DD, et al: Arterial blood gases and pulmonary function testing in acute bronchial asthma. Predicting patient outcomes. JAMA 249:2043–2046, 1983.
333. Fuhlbrigge AL, Weiss ST, Kuntz KM, et al: Forced expiratory volume in 1 second percentage improves the classification of severity among children with asthma. Pediatrics 118:e347–e355, 2006.
334. Moore WC, Bleecker ER, Curran-Everett D, et al: Characterization of the severe asthma phenotype by the National Heart, Lung, and Blood Institute's Severe Asthma Research Program. J Allergy Clin Immunol 119:405, 2007.
335. Burns GP, Gibson GJ: A novel hypothesis to explain the bronchconstrictor effect of deep inspiration in asthma. Thorax 57:116–119, 2002.

336. Lutchen KR, Jensen A, Atileh H, et al: Airway constriction pattern is a central component of asthma severity. The role of deep inspirations. Am J Respir Crit Care Med 164:207–215, 2001.
337. McFadden ER, Linden DA: A reduction in maximum and mid-expiratory flow rate. A spirometric manifestation of small airway disease. Am J Med 52:725–737, 1972.
338. Marseglia GL, Cirillo I, Vizzaccaro A, et al: Role of forced expiratory flow at 25–75% as an early marker of small airways impairment in subjects with allergic rhinitis. Allergy Asthma Proc 28:74–78, 2007.
339. Chiang CH, Hsu K: Residual abnormalities of pulmonary function in asymptomatic young adult asthmatics with childhood-onset asthma. J Asthma 34:15–21, 1997.
340. Hansen JE, Sun XG, Wasserman K: Should forced expiratory volume in six seconds replace forced vital capacity to detect airway obstruction? Eur Respir J 27:1244–1250, 2006.
341. Ferguson GT, Enright PL, Buist AS, et al: Office spirometry for lung health assessment in adults: A consensus statement from the National Lung Health Education Program. Chest 117:1146–1161, 2000.
342. Vandevoorde J, Verbanck S, Schuermans D, et al: Obstructive and restrictive spirometric patterns: fixed cut-offs for FEV_1/FEV_6 and FEV_6. Eur Respir J 27:378–383, 2006.
343. Hansen JE, Sun XG, Wasserman K: Discriminating measures and normal values for expiratory obstruction. Chest 129:369–377, 2006.
344. Punjabi NM, Shade D, Wise RA: Correction of single-breath helium lung volumes in patients with airflow obstruction. Chest 114:907–918, 1998.
345. Brown R, Hoppin FG Jr, Ingram RH Jr, et al: Influence of abdominal gas on the Boyle's law determination of thoracic gas volume. J Appl Physiol 44:469–473, 1978.
346. Saydain G, Beck KC, Decker PA, et al: Clinical significance of elevated diffusing capacity. Chest 125:446–452, 2004.
347. Collard P, Njinou B, Nejadnik B, et al: Single breath diffusing capacity for carbon monoxide in stable asthma. Chest 105:1426–1429, 1994.
348. Guidelines for Methacholine and Exercise Challenge Testing—1999. This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999. Am J Respir Crit Care Med 161:309–329, 2000.
349. Josephs LK, Gregg I, Mullee MA, et al: Nonspecific bronchial reactivity and its relationship to the clinical expression of asthma. A longitudinal study. Am Rev Respir Dis 140:350–357, 1989.
350. Jansen DF, Schouten JP, Vonk JM, et al: Smoking and airway hyperresponsiveness especially in the presence of blood eosinophilia increase the risk to develop respiratory symptoms: A 25-year follow-up study in the general adult population. Am J Respir Crit Care Med 160:259–264, 1999.
351. Holzer K, Brukner P, Douglass J: Evidence-based management of exercise-induced asthma. Curr Sports Med Rep 1:86–92, 2002.
352. Benckhuijsen J, van den Bos JW, van Velzen E, et al: Differences in the effect of allergen avoidance on bronchial hyperresponsiveness as measured by methacholine, adenosine 5′-monophosphate, and exercise in asthmatic children. Pediatr Pulmonol 22:147–153, 1996.
353. Death from asthma in two regions of England. British Thoracic Association. Br Med J (Clin Res Ed) 285:1251–1255, 1982.
354. Bucknall CE, Moran F, Stevenson RD: A retrospective survey of asthma management in hospital. Scott Med J 33:328–330, 1988.
355. Sheffer AL: The National Asthma Education Program attacks asthma. J Allergy Clin Immunol 87:468–469, 1991.
356. Chen H, Gould MK, Blanc PD, et al: Asthma control, severity, and quality of life: Quantifying the effect of uncontrolled disease. J Allergy Clin Immunol 120:396–402, 2007.
357. Juniper EF, O'Byrne PM, Guyatt GH, et al: Development and validation of a questionnaire to measure asthma control. Eur Respir J 14:902–907, 1999.
358. Nathan RA, Sorkness CA, Kosinski M, et al: Development of the asthma control test: A survey for assessing asthma control. J Allergy Clin Immunol 113:59–65, 2004.
359. Vollmer WM, Markson LE, O'Connor E, et al: Association of asthma control with health care utilization and quality of life. Am J Respir Crit Care Med 160:1647–1652, 1999.
360. Boulet LP, Boulet V, Milot J: How should we quantify asthma control? A proposal. Chest 122:2217–2223, 2002.
361. Pillai SG, Tang Y, van den Oord E, et al: Factor analysis in the Genetics of Asthma International Network family study identifies five major quantitative asthma phenotypes. Clin Exp Allergy 38:421–429, 2008.
362. Osborne ML, Pedula KL, O'Hollaren M, et al: Assessing future need for acute care in adult asthmatics: The Profile of Asthma Risk Study: A prospective health maintenance organization-based study. Chest 132:1151–1161, 2007.
363. Bacci E, Cianchetti S, Bartoli M, et al: Low sputum eosinophils predict the lack of response to beclomethasone in symptomatic asthmatic patients. Chest 129:565–572, 2006.
364. Green RH, Brightling CE, McKenna S, et al: Asthma exacerbations and sputum eosinophil counts: A randomised controlled trial. Lancet 360:1715–1721, 2002.
365. Kips J: Managing a variable disease. Pulm Pharmacol Ther 15:485–490, 2002.
366. Deykin A, Lazarus SC, Fahy JV, et al: Sputum eosinophil counts predict asthma control after discontinuation of inhaled corticosteroids. J Allergy Clin Immunol 115:720–727, 2005.
367. Travers J, Marsh S, Aldington S, et al: Reference ranges for exhaled nitric oxide derived from a random community survey of adults. Am J Respir Crit Care Med 176:238–242, 2007.
368. Olin AC, Rosengren A, Thelle DS, et al: Height, age, and atopy are associated with fraction of exhaled nitric oxide in a large adult general population sample. Chest 130:1319–1325, 2006.
369. Kharitonov SA, Yates DH, Barnes PJ: Inhaled glucocorticoids decrease nitric oxide in exhaled air of asthmatic patients. Am J Respir Crit Care Med 153:454–457, 1996.
370. Silkoff PE, McClean P, Spino M, et al: Dose-response relationship and reproducibility of the fall in exhaled nitric oxide after inhaled beclomethasone dipropionate therapy in asthma patients. Chest 119:1322–1328, 2001.
371. Michils A, Baldassarre S, Van Muylem A: Exhaled nitric oxide and asthma control: A longitudinal study in unselected patients. Eur Respir J 31:539–546, 2008.
372. Sun JG, Deng YM, Wu X, et al: Inhibition of phosphodiesterase activity, airway inflammation and hyperresponsiveness by PDE_4 inhibitor and glucocorticoid in a murine model of allergic asthma. Life Sci 79:2077–2085, 2006.
373. Volovitz B: Inhaled budesonide in the management of acute worsenings and exacerbations of asthma: A review of the evidence. Respir Med 101:685, 2007.
374. NHLBI/NIH. (National Institutes of Health, National Asthma Education and Prevention Program, 2007). Managing asthma long term in children 0–4 years of age and 5–11 years of age. Available at http://www.nhlbi.nih.gov/guidelines/asthma/08_Sec4_lt_0-11.pdf
375. GINA Report: Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA), 2007. Available at http://www.ginasthma.com/Guidelineitem.asp?l1=2&l2=1&intId=60. Bethesda, MD: NIH, Publication No. 02-3659.
376. Bielory L, Lupoli K: Herbal interventions in asthma and allergy. J Asthma 36:1–65, 1999.
377. Sears MR, Lotvall J: Past, present and future—$Beta_2$-adrenoceptor agonists in asthma management. Respir Med 99:152–170, 2005.
378. Johnson M: Molecular mechanisms of $[beta]_2$-adrenergic receptor function, response, and regulation. J Allergy Clin Immunol 117: 18, 2006.
379. Zink S, Rosen P, Sackmann B, et al: Regulation of endothelial permeability by beta-adrenoceptor agonists: Contribution of beta 1- and beta 2-adrenoceptors. Biochim Biophys Acta 1178:286–298, 1993.
380. Johnson M: The beta-adrenoceptor. Am J Respir Crit Care Med 158:146S–153S, 1998.
381. Ahrens R, Weinberger M: Levalbuterol and racemic albuterol: Are there therapeutic differences? J Allergy Clin Immunol 108:681–684, 2001.
382. Walters EH, Gibson PG, Lasserson TJ, et al: Long-acting $beta_2$-agonists for chronic asthma in adults and children where background therapy contains varied or no inhaled corticosteroid. Cochrane Database Syst Rev 1:CD001385, 2007.

383. Stolley PD: Asthma mortality. Why the United States was spared an epidemic of deaths due to asthma. Am Rev Respir Dis 105:883–890, 1972.
384. Hancox RJ: Concluding remarks: Can we explain the association of beta-agonists with asthma mortality? A hypothesis. Clin Rev Allergy Immunol 31:279–288, 2006.
385. Pearce N, Beasley R, Crane J, et al: End of the New Zealand asthma mortality epidemic. Lancet 345:41–44, 1995.
386. Drazen JM, Israel E, Boushey HA, et al: Comparison of regularly scheduled with as-needed use of albuterol in mild asthma. Asthma Clinical Research Network. N Engl J Med 335:841–847, 1996.
387. Taylor DR, Sears MR, Herbison GP, et al: Regular inhaled beta agonist in asthma: Effects on exacerbations and lung function. Thorax 48:134–138, 1993.
388. Nelson HS, Weiss ST, Bleecker ER, et al: The Salmeterol Multicenter Asthma Research Trial: A comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. Chest 129:15–26, 2006.
389. Donohue JF: Safety and efficacy of beta agonists. Respir Care 53:618–622, 2008 [discussion appears 623–624].
390. Taylor DR, Drazen JM, Herbison GP, et al: Asthma exacerbations during long term beta agonist use: Influence of beta(2) adrenoceptor polymorphism. Thorax 55:762–767, 2000.
391. Israel E, Chinchilli VM, Ford JG, et al: Use of regularly scheduled albuterol treatment in asthma: Genotype-stratified, randomised, placebo-controlled cross-over trial. Lancet 364:1505–1512, 2004.
392. Bleecker ER, Emmett A, Crater G, et al: Lung function and symptom improvement with fluticasone propionate/salmeterol and ipratropium bromide/albuterol in COPD: Response by beta-agonist reversibility. Pulm Pharmacol Ther 21:682-–688, 2008. Epub 2008;May 1.
393. Beakes DE: The use of anticholinergics in asthma. J Asthma 34:357–368, 1997.
394. Cazzola M, Centanni S, Donner CF: Anticholinergic agents. Pulm Pharmacol Ther 11:381–392, 1998.
395. Partridge MR, Saunders KB: Site of action of ipratropium bromide and clinical and physiological determinants of response in patients with asthma. Thorax 36:530–533, 1981.
396. Iwamoto H, Yokoyama A, Shiota N, et al: Tiotropium bromide is effective for severe asthma with noneosinophilic phenotype. Eur Respir J 31:1379–1380, 2008.
397. Magnussen H, Bugnas B, van Noord J, et al: Improvements with tiotropium in COPD patients with concomitant asthma. Respir Med 102:50–56, 2008.
398. Bos IST, Gosens R, Zuidhof AB, et al: Inhibition of allergen-induced airway remodelling by tiotropium and budesonide: A comparison. Eur Respir J 30:653–661, 2007.
399. Barnes PJ: How corticosteroids control inflammation: Quintiles Prize Lecture 2005. Br J Pharmacol 148:245–254, 2006.
400. Adcock IM, Ito K, Barnes PJ: Glucocorticoids: Effects on gene transcription. Proc Am Thorac Soc 1:247–254, 2004.
401. van Rensen EL, Straathof KC, Veselic-Charvat MA, et al: Effect of inhaled steroids on airway hyperresponsiveness, sputum eosinophils, and exhaled nitric oxide levels in patients with asthma. Thorax 54:403–408, 1999.
402. Olivieri D, Chetta A, Del Donno M, et al: Effect of short-term treatment with low-dose inhaled fluticasone propionate on airway inflammation and remodeling in mild asthma: A placebo-controlled study. Am J Respir Crit Care Med 155:1864–1871, 1997.
403. Juniper EF, Kline PA, Vanzieleghem MA, et al: Effect of long-term treatment with an inhaled corticosteroid (budesonide) on airway hyperresponsiveness and clinical asthma in nonsteroid-dependent asthmatics. Am Rev Respir Dis 142:832–836, 1990.
404. Long-term effects of budesonide or nedocromil in children with asthma. The Childhood Asthma Management Program Research Group. N Engl J Med 343:1054–1063, 2000.
405. Sin DD, Man J, Sharpe H, et al: Pharmacological management to reduce exacerbations in adults with asthma: A systematic review and meta-analysis. JAMA 292:367–376, 2004.
406. Donahue JG, Weiss ST, Livingston JM, et al: Inhaled steroids and the risk of hospitalization for asthma. JAMA 277:887–891, 1997.
407. Suissa S, Ernst P, Benayoun S, et al: Low-dose inhaled corticosteroids and the prevention of death from asthma. N Engl J Med 343:332–336, 2000.
408. Israel E, Banerjee TR, Fitzmaurice GM, et al: Effects of inhaled glucocorticoids on bone density in premenopausal women. N Engl J Med 345:941–947, 2001.
409. Halpern MT, Schmier JK, Van Kerkhove MD, et al: Impact of long-term inhaled corticosteroid therapy on bone mineral density: Results of a meta-analysis. Ann Allergy Asthma Immunol 92:201–207, 2004 [quiz 207–208, 267].
410. Cumming RG, Mitchell P, Leeder SR: Use of inhaled corticosteroids and the risk of cataracts. N Engl J Med 337:8-–14, 1997.
411. Garbe E, LeLorier J, Boivin JF, et al: Inhaled and nasal glucocorticoids and the risks of ocular hypertension or open-angle glaucoma. JAMA 277:722–727, 1997.
412. Calverley PM, Anderson JA, Celli B, et al: Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. N Engl J Med 356:775–789, 2007.
413. Skoner DP, Szefler SJ, Welch M, et al: Longitudinal growth in infants and young children treated with budesonide inhalation suspension for persistent asthma. J Allergy Clin Immunol 105:259–268, 2000.
414. Agertoft L, Pedersen S: Effect of long-term treatment with inhaled budesonide on adult height in children with asthma. N Engl J Med 343:1064–1069, 2000.
415. Henderson WR Jr: The role of leukotrienes in inflammation. Ann Intern Med 121:684–697, 1994.
416. Barnes NC, Miller CJ: Effect of leukotriene receptor antagonist therapy on the risk of asthma exacerbations in patients with mild to moderate asthma: An integrated analysis of zafirlukast trials. Thorax 55:478–483, 2000.
417. Drazen JM, Israel E, O'Byrne PM: Treatment of asthma with drugs modifying the leukotriene pathway. N Engl J Med 340:197–206, 1999.
418. Dahlen B, Nizankowska E, Szczeklik A, et al: Benefits from adding the 5-lipoxygenase inhibitor zileuton to conventional therapy in aspirin-intolerant asthmatics. Am J Respir Crit Care Med 157:1187–1194, 1998.
419. Leff J.A, Busse WW, Pearlman D, et al: Montelukast, a leukotriene-receptor antagonist, for the treatment of mild asthma and exercise-induced bronchoconstriction. N Engl J Med 339:147–152, 1998.
420. Nelson H, Kemp J, Berger W, et al: Efficacy of zileuton controlled-release tablets administered twice daily in the treatment of moderate persistent asthma: A 3-month randomized controlled study. Ann Allergy Asthma Immunol 99:178–184, 2007.
421. Lofdahl CG, Reiss TF, Leff JA, et al:. Randomised, placebo controlled trial of effect of a leukotriene receptor antagonist, montelukast, on tapering inhaled corticosteroids in asthmatic patients. BMJ 319:87–90, 1999.
422. Vaquerizo MJ, Casan P, Castillo J, et al: Effect of montelukast added to inhaled budesonide on control of mild to moderate asthma. Thorax 58:204–210, 2003.
423. Clinical trial of low-dose theophylline and montelukast in patients with poorly controlled asthma. Am J Respir Crit Care Med 175:235–242, 2007. Epub 2006;September 22.
424. Fish JE, Israel E, Murray JJ, et al: Salmeterol powder provides significantly better benefit than montelukast in asthmatic patients receiving concomitant inhaled corticosteroid therapy. Chest 120:423–430, 2001.
425. Deykin A, Wechsler ME, Boushey HA, et al: Combination therapy with a long-acting beta-agonist and a leukotriene antagonist in moderate asthma. Am J Respir Crit Care Med 175:228–234, 2007.
426. Wechsler ME, Finn D, Gunawardena D, et al: Churg-Strauss syndrome in patients receiving montelukast as treatment for asthma. Chest 117:708–713, 2000.
427. Wenzel S, Busse W, Calhoun W, et al: The safety and efficacy of zileuton controlled-release tablets as adjunctive therapy to usual care in the treatment of moderate persistent asthma: A 6-month randomized controlled study. J Asthma 44:305–310, 2007.
428. Barnes PJ: Theophylline: New perspectives for an old drug. Am J Respir Crit Care Med 167:813–818, 2003.
429. Evans DJ, Taylor DA, Zetterstrom O, et al: A comparison of low-dose inhaled budesonide plus theophylline and high-dose inhaled

budesonide for moderate asthma. N Engl J Med 337:1412–1418, 1997.
430. Ayres JG, Higgins B, Chilvers ER, et al: Efficacy and tolerability of anti-immunoglobulin E therapy with omalizumab in patients with poorly controlled (moderate-to-severe) allergic asthma. Allergy 59:701–708, 2004.
431. Humbert M, Beasley R, Ayres J, et al: Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE. Allergy 60:309–316, 2005.
432. Brown R, Turk F, Dale P, et al: Cost-effectiveness of omalizumab in patients with severe persistent allergic asthma. Allergy 62:149–153, 2007.
433. Cox G, Miller JD, McWilliams A, et al: Bronchial thermoplasty for asthma. Am J Respir Crit Care Med 173:965–969, 2006.
434. Chaudhuri R, Livingston E, McMahon AD, et al: Effects of smoking cessation on lung function and airway inflammation in smokers with asthma. Am J Respir Crit Care Med 174:127–133, 2006.
435. Rachelefsky GS, Katz RM, Siegel SC: Chronic sinus disease with associated reactive airway disease in children. Pediatrics 73:526–529, 1984.
436. Patterson PE, Harding SM: Gastroesophageal reflux disorders and asthma. Curr Opin Pulm Med 5:63–67, 1999.
437. Platts-Mills TA, Tovey ER, Mitchell EB, et al: Reduction of bronchial hyperreactivity during prolonged allergen avoidance. Lancet 2:675–678, 1982.
438. Morgan WJ, Crain EF, Gruchalla RS, et al: Results of a home-based environmental intervention among urban children with asthma. N Engl J Med 351:1068–1080, 2004.
439. Gotzsche PC, Johansen HK, Schmidt LM, et al. House dust mite control measures for asthma. Cochrane Database Syst Rev 4:CD001187, 2004.
440. Calamita Z, Saconato H, Pela AB, et al: Efficacy of sublingual immunotherapy in asthma: Systematic review of randomized-clinical trials using the Cochrane Collaboration method. Allergy 61:1162–1172, 2006.
441. Abramson MJ, Puy RM, Weiner JM: Allergen immunotherapy for asthma. Cochrane Database Syst Rev 4:CD001186, 2003.
441a. Haselkorn T, Fish JE, Zeiger RS, et al: Consistently very poorly controlled asthma, as defined by the impairment domain of the Expert Panel Report 3 guidelines, increases risk of future severe asthma exacerbations in the Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) Study. J Allergy Clin Immunol 2009 [Epub ahead of print].
442. Pauwels RA, Pedersen S, Busse WW, et al: Early intervention with budesonide in mild persistent asthma: A randomised, double-blind trial. Lancet 361:1071–1076, 2003.
443. Adams NP, Bestall JB, Malouf R, et al: Inhaled beclomethasone versus placebo for chronic asthma. Cochrane Database Syst Rev 1:CD002738, 2005.
444. Bousquet J, Ben-Joseph R, Messonnier M, et al. A meta-analysis of the dose-response relationship of inhaled corticosteroids in adolescents and adults with mild to moderate persistent asthma. Clin Ther 24:1-–20, 2002.
445. Szefler SJ, Martin RJ, King TS, et al: Significant variability in response to inhaled corticosteroids for persistent asthma. J Allergy Clin Immunol 109:410–418., 2002.
446. Lazarus SC, Boushey HA, Fahy JV, et al: Long-acting beta$_2$-agonist monotherapy vs continued therapy with inhaled corticosteroids in patients with persistent asthma: A randomized controlled trial. JAMA 285:2583–2593, 2001.
447. Lemanske RF Jr, Sorkness CA, Mauger EA, et al: Inhaled corticosteroid reduction and elimination in patients with persistent asthma receiving salmeterol: A randomized controlled trial. JAMA 285:2594–2603, 2001.
448. Greening AP, Ind PW, Northfield M, et al: Added salmeterol versus higher-dose corticosteroid in asthma patients with symptoms on existing inhaled corticosteroid. Allen & Hanburys Limited UK Study Group. Lancet 344:219–224, 1994.
449. Shrewsbury S, Pyke S, Britton M: Meta-analysis of increased dose of inhaled steroid or addition of salmeterol in symptomatic asthma (MIASMA). BMJ 320:1368–1373, 2000.
450. Bateman ED, Boushey HA, Bousquet J, et al: Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma ControL study. Am J Respir Crit Care Med 170:836–844, 2004.
451. Pauwels RA, Lofdahl CG, Postma DS, et al: Effect of inhaled formoterol and budesonide on exacerbations of asthma. Formoterol and Corticosteroids Establishing Therapy (FACET) International Study Group [published erratum appears in N Engl J Med 338:139, 1998]. N Engl J Med 337:1405–1411, 1997.
452. Virchow JC Jr, Prasse A, Naya I, et al: Zafirlukast improves asthma control in patients receiving high-dose inhaled corticosteroids. Am J Respir Crit Care Med 162:578–585, 2000.
453. Peters SP, Anthonisen N, Castro M, et al: Randomized comparison of strategies for reducing treatment in mild persistent asthma. N Engl J Med 356:2027–2039, 2007.
454. Papi A, Canonica GW, Maestrelli P, et al: Rescue use of beclomethasone and albuterol in a single inhaler for mild asthma. N Engl J Med 356:2040–2052, 2007.
455. Chan-Yeung M, Chang JH, Manfreda J, et al: Changes in peak flow, symptom score, and the use of medications during acute exacerbations of asthma. Am J Respir Crit Care Med 154:889–893, 1996.
456. Turner MO, Noertjojo K, Vedal S, et al: Risk factors for near-fatal asthma. A case-control study in hospitalized patients with asthma. Am J Respir Crit Care Med 157:1804–1809, 1998.
457. Beasley R, Miles J, Fishwick D, et al: Management of asthma in the hospital emergency department. Br J Hosp Med 55:253–257, 1996.
458. Rodrigo GJ, Rodrigo C: First-line therapy for adult patients with acute asthma receiving a multiple-dose protocol of ipratropium bromide plus albuterol in the emergency department. Am J Respir Crit Care Med 161:1862–1868, 2000.
459. Manser R, Reid D, Abramson M: Corticosteroids for acute severe asthma in hospitalised patients. Cochrane Database Syst Rev 1:CD001740, 2001.
460. Rowe BH, Bota GW, Fabris L, et al: Inhaled budesonide in addition to oral corticosteroids to prevent asthma relapse following discharge from the emergency department: A randomized controlled trial. JAMA 281:2119–2126, 1999.
461. Edmonds ML, Camargo CA, Saunders LD, et al: Inhaled steroids in acute asthma following emergency department discharge. Cochrane Database Syst Rev 3:CD002316, 2000.
462. Rowe BH, Bretzlaff JA, Bourdon C, et al: Magnesium sulfate for treating exacerbations of acute asthma in the emergency department. Cochrane Database Syst Rev 2:CD001490, 2000.
463. Soroksky A, Stav D, Shpirer I: A pilot prospective, randomized, placebo-controlled trial of bilevel positive airway pressure in acute asthmatic attack. Chest 123:1018–1025, 2003.
464. Ho AMH, Lee A, Karmakar MK, et al. Heliox vs air-oxygen mixtures for the treatment of patients with acute asthma: A systematic overview. Chest 123:882–890, 2003.
465. Rodrigo G, Pollack C, Rodrigo C, et al: Heliox for nonintubated acute asthma patients. Cochrane Database Syst Rev 4:CD002884, 2006.
466. Williams TJ, Tuxen DV, Scheinkestel CD, et al: Risk factors for morbidity in mechanically ventilated patients with acute severe asthma. Am Rev Respir Dis 146:607–615, 1992.
467. Cote J, Cartier A, Robichaud P, et al. Influence on asthma morbidity of asthma education programs based on self-management plans following treatment optimization. Am J Respir Crit Care Med 155:1509–1514, 1997.
468. Clark GJ, Angel N, Kato M, et al: The role of dendritic cells in the innate immune system. Microbes Infect 2:257–272, 2000.
469. Coutts JA, Gibson NA, Paton JY: Measuring compliance with inhaled medication in asthma. Arch Dis Child 67:332–333, 1992.

CHAPTER 39

CHRONIC BRONCHITIS AND EMPHYSEMA

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INTRODUCTION

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a collection of conditions characterized by persistent expiratory airflow limitation. Although the clinical presentation and course of COPD can vary from individual to individual, there is sufficient overlap that it has been practical to group COPD as a single entity defined on the shared parameter of airflow limitation. The current consensus definition of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) centers on the common feature of altered lung function but recognizes both the systemic nature and the heterogeneity of COPD.

COPD is a preventable and treatable disease with some significant extrapulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles and gases.[1]

The heterogeneity of COPD results from several causes. First, COPD can result from several etiologies,

most importantly cigarette smoke. These exposures can affect the lung by several distinct mechanisms, and it is likely that many genes can modulate individual responses, resulting in marked interindividual differences in susceptibility. Importantly, several anatomic lesions can result in the alveolar walls, in the proximal and distal airways, and in the pulmonary and bronchial vasculature that can cause the airflow limitation and contribute to the clinical features. Finally, as noted in the GOLD definition, COPD is commonly, but variably, associated with disease in other organ systems that can contribute to the clinical features in individual patients. Recognition that COPD is heterogeneous clinically and at a pathophysiologic level has led to new initiatives to categorize and define the subsets of COPD and holds the promise of developing treatments that will be more effective for the individual patient.

HISTORICAL BACKGROUND

Obstructive airway disorders have been known since antiquity. Chronic bronchitis was a major cause of death in Europe following industrialization, but was not well studied until recently, perhaps because then, as now, it is more common among those of lower social economic status.[2] In their detailed review of the history of chronic bronchitis, Fletcher and colleagues[2] attribute the first use of the term to Badham in 1808.[3] Although there were clinical and pathologic studies of chronic bronchitis in the 19th century, including those of Laennec,[4] it was probably the severe London smog of December 5–9, 1952, with the marked increase in acute mortality, which led to increased interest in the condition. The pathologic studies of Reid[5] demonstrating increased mucus gland size led to the development of the "Reid Index" and highlighted the anatomic basis for the clinical syndrome.

Emphysema has also been described for centuries.[6] Enlarged respiratory air spaces on the surface of human lungs was illustrated by Ruysch[7] in 1691. Late in the 18th century, Matthew Baillie provided the earliest illustration[8] and a brief description[9] of emphysema. Laennec,[4] using air-dried inflated lung specimens, also described emphysema. Insightfully, he suggested that the peripheral airways were the primary site of obstruction in emphysema and speculated that loss of elastic recoil was a likely contributor to diminished airflow. In the 1950s, Gough and his coworkers,[10] using sections of whole inflation-fixed lungs mounted on paper, described centriacinar emphysema and distinguished it from panacinar emphysema.

The increasing interest in COPD resulted in several "hypotheses" to explain the pathogenesis of airflow obstruction. The concept espoused by Orie and associates from the Netherlands,[11] which came to be known as the "Dutch hypothesis", was that asthma and airway hyperreactivity could eventually lead to fixed airflow limitation. This was often contrasted with the concept that mucus hypersecretion led to airway remodeling and airflow limitation, a concept proposed by British investigators[2] and, hence, termed the "British hypothesis." In addition, the association of homozygous alpha$_1$ protease inhibitor deficiency with emphysema was discovered by Laurell and Eriksson in Sweden.[12] Together with the description of protease-induced emphysema in animal models,[13] this led to the concept of the "protease-antiprotease hypothesis" of emphysema, which could be termed the "Swedish hypothesis," although this term has never been used. Finally, at about the same time, the American pathologist Averill Liebow[14] suggested that deficient maintenance of lung structure, particularly of alveolar capillaries, could lead to emphysema. This concept—that altered repair mechanisms contribute to the development of COPD—has been termed the "American hypothesis."[15]

Current evidence suggests that the mechanisms proposed by all these "hypotheses" contribute to COPD. The multiplicity of nonexclusive mechanisms, which may be simultaneously present in a given individual, has contributed to the difficulty of clinical subclassification of COPD. Defining the precise mechanisms relevant to individual patients is a key goal of current attempts to define COPD subtypes.

Attempts to subclassify COPD are not new. Pathologic studies delineate inflammation and alteration of airway structures (bronchitis) from destruction of the alveolar wall (emphysema). The concept that altered airway anatomy would lead to heterogeneity of airflow distribution within the lung, resulting in ventilation-perfusion imbalance, hypoxemia, and right heart failure, suggested that bronchitis might be associated with a "blue bloater" clinical phenotype. In contrast, the concept was that emphysema would not cause hypoxia, although there would be decreased airflow, resulting in a "pink puffer" phenotype. These entities are not exclusive, however, and most commonly, individual patients have features of both. The relationship of COPD to asthma, which causes variable airflow limitation and may cause fixed airflow limitation in a subset of individuals, has further confounded clinical classification. To provide a conceptual model to integrate these concepts, Snider and coworkers suggested the "Nonproportional Venn Diagram,"[16] which emphasized the independence of these causes of airflow limitation and the heterogeneity of COPD (Fig. 39-1).

CLINICAL FEATURES OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

History

Cough and dyspnea are the most frequent symptoms reported by patients with COPD. Dyspnea is typically present only with exertion until late in the course of the disease. Cough, therefore, may be the presenting symptom. Either symptom should initiate a diagnostic evaluation that includes spirometry. Most often, however, neither symptom causes the patient to seek medical care until advanced disease is present, and both symptoms should be aggressively sought in routine questioning.

Cough may be very troublesome and can compromise quality of life significantly.[17] In many cases, however, the

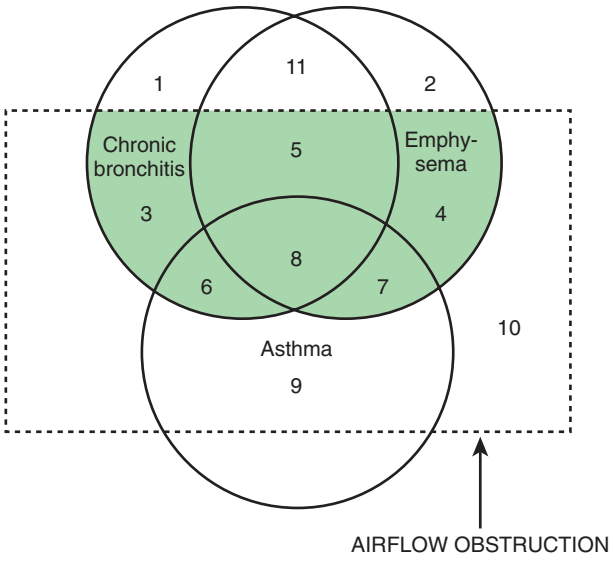

FIGURE 39-1 ■ Schema of subsets of COPD. This non-proportional Venn diagram shows subsets of patients with chronic bronchitis, emphysema, and asthma and their relationship to airflow obstruction (box). The subsets comprising COPD are in green. Subset areas are not proportional to actual relative subset sizes. Asthma is by definition associated with reversible airflow obstruction and those with asthma whose airflow obstruction is completely reversible (subset 9) are not considered to have COPD. Because it is nearly impossible to differentiate patients with asthma with partially reversible airflow obstruction from persons with chronic bronchitis and emphysema who also have partially reversible airflow obstruction, patients with unremitting asthma are classified as having COPD (subsets 6, 7, 8). Chronic bronchitis and emphysema with airflow obstruction are often seen together (subset 5) and some patients may have asthma associated with these two disorders (subset 8). Individuals with asthma exposed to chronic irritation, as from cigarette smoke, may develop chronic productive cough, a feature of chronic bronchitis (subset 6), often called *asthmatic bronchitis*. Persons with chronic bronchitis and/or emphysema without airflow obstruction (subsets 1, 2, and 11) are not classified as having COPD. Patients with airway obstruction due to diseases with known etiology or specific pathology, such as cystic fibrosis or obliterative bronchiolitis (subset 10), are not included in this definition. (From ATS: Standards for the diagnosis and care of patients with COPD. Am J Respir Care Med 152:S77–S121, 1995.)

patient is unaware of cough frequency, and an accurate history may be best obtained from a spouse. A productive cough should not be suppressed and a chronic daily cough is predictive of frequent exacerbations.[18]

Sputum production is insidious in its onset and, in the majority of patients, it is "scanty," defined as less than several tablespoons per day. Sputum production may also relate to smoking status, with current smokers having much more production. The sputum is usually mucoid but becomes purulent during exacerbations. Following smoking cessation, cough and sputum may become transiently more difficult, but symptoms generally improve following smoking cessation.[19]

Hemoptysis complicating chronic bronchitis is the most common cause of hemoptysis in the United States and usually occurs in association with an exacerbation.[20] However, other etiologies of hemoptysis, in particular lung cancer, must be kept in mind in this susceptible population.[21]

Dyspnea, especially with exertion, is usually the presenting symptom and, as the disease progresses, occurs with less and less effort. Dyspnea in COPD patients probably results from dynamic hyperinflation that worsens with increasing respiratory rate (see later). As a result, many patients will avoid dyspnea by avoiding exertion and may become exceedingly sedentary. This may develop insidiously and the patient may have an extremely restricted level of function. As with other chronic diseases, many patients reset their expectations with regard to health, termed "response shift." This frequently results in very few complaints despite patients being very cognizant of their limitations.[17]

Health status, sometimes termed "quality of life," is abnormal in COPD patients. Two instruments have been widely used in research settings, the St. George Respiratory Questionnaire (SGRQ)[22] and the Chronic Respiratory Disease Questionnaire (CRDQ).[23] These measures demonstrate that health status correlates, although poorly, with forced expiratory volume in 1 second (FEV_1) and correlates better with exercise performance,[22] emphasizing the systemic features that can dominate the clinical presentation of COPD. Health status also correlates with survival independently of FEV_1.[24]

Exacerbations, which are characterized by increased cough, sputum, dyspnea, and fatigue, are increasingly frequent as the disease worsens. They generally resolve over a few weeks, but full recovery may take months.[25] Exacerbations may be difficult to distinguish from other acute causes of dypsnea, cough, and/or sputum including pneumonia, congestive heart failure, pulmonary embolism, or pneumothorax without radiologic or laboratory evaluation.

Physical Examination

In many patients with COPD, physical examination reveals little abnormality especially during quiet breathing. Coarse crackles occurring early in inspiration have been associated with obstructive lung disease, although other adventitious sounds may be present. Rhonchi are more prevalent in patients complaining of dyspnea and are usually present during both inspiration and expiration. Wheezing is not a consistent finding and does not relate to the severity of obstruction. The most consistent finding in patients with symptomatic COPD is the prolonged expiratory time, which is best determined by listening over the larynx during a forced expiratory maneuver. Prolongation of the expiratory phase longer than the normal 4 seconds is indicative of significant obstruction. However, the clinical diagnosis of COPD is notoriously poor.[26] Quantification of airflow by spirometry, which is simple and can be done accurately on relatively inexpensive equipment appropriate for the

generalist office,[27] should always be performed when the diagnosis of COPD is considered.[1]

When COPD becomes severe, patients demonstrate more apparent physical signs. These include the barrel-shaped chest, purse-lipped breathing, emaciation, and frequently, inguinal hernias. Patients may be observed sitting forward and leaning on their elbows, or supporting their upper body with extended arms, in a position known as "tripoding." This position stabilizes the shoulder girdle and helps to maximize intrathoracic volume. These are late developments, however, and the diagnosis should be made earlier by spirometry in individuals with relevant histories.

Pulmonary hypertension may develop in patients with COPD and may be worse with exercise.[28] It may be suspected with a loud pulmonary component of the second heart sound and heart sounds may be displaced to the midline due to hyperinflation.

Laboratory Findings

Pulmonary Function Tests

Assessment of lung function (see Chapter 24) is essential to establish a diagnosis and to gauge the severity of COPD. The most important test is spirometry. Measurement of lung volumes and diffusion capacity, which generally requires a specialized laboratory, may also be helpful, particularly in determining whether airflow limitation is due to emphysema or airway disease.

Spirometry. Simple spirometry is the most important test to diagnose and stage COPD. After taking a maximally deep breath, a subject exhales as forcefully as possible, and the volume of air exhaled is measured as a function of time. The FEV_1 is the most important measure. The maximal volume exhaled is the forced vital capacity (FVC). A reduction in FEV_1/FVC ratio is diagnostic of airway obstruction. Because it may take some time for a patient to empty his or her lungs fully, particularly if COPD is present, the forced expiratory volume after 6 seconds, FEV_6, is recommended for use in most office settings.[29] Not only is it easier to perform, but avoiding prolonged exhalation maneuvers reduces the chance of syncope during the test. Because of variability in the FVC (or FEV_6) measure, the FEV_1/FVC ratio can establish a diagnosis of obstruction but is not useful to monitor disease progression.[30] Many other quantitative measures of airflow can be obtained from spirometry, but these usually add little to the FEV_1 and FVC (or FEV_6). Similarly, peak expiratory flow is generally regarded as less useful than the FEV_1. If airflow is abnormal, postbronchodilator testing should be performed. Correction to the normal range suggests a diagnosis of asthma and could exclude COPD. Partial correction, which may vary from day to day in an individual patient,[31] may help to define therapeutic goals.

Lung Volumes. The FVC can be measured spirometrically. Other lung volumes, which include the volume of air remaining in the chest, require specialized testing. The most commonly used method is the body plethysmograph (i.e., "body box") that uses Boyle's law to calculate intrathoracic volumes. In general, the total lung capacity is increased in emphysema because the loss of elastic recoil permits the lungs to expand to a greater maximal volume. The residual volume and the functional residual capacity are also increased. Because the residual volume increases more than the total lung capacity, the vital capacity is decreased. Increases in lung volume with increasing respiratory rate (i.e., dynamic hyperinflation) can be measured but require specialized procedures and are not routinely used in clinical practice. The inspiratory capacity, which is the volume that can be inhaled from end-expiratory lung volume, that is, the volume at which a normal breath starts, has been suggested as a surrogate for the measurement of dynamic hyperinflation. Although it can be readily measured with routine spirometry equipment, standardized procedures for its determination and its use in clinical practice are undefined.

Volume-Pressure Relationship. Compliance of the lungs can be measured with an esophageal balloon. With severe emphysema, compliance of the lungs is increased.[32] Measurement of the volume-pressure curve of the lung is a research procedure not generally used in routine clinical practice.

Diffusing Capacity. The single-breath diffusing capacity is decreased in proportion to the severity of emphysema because of the destruction of the alveoli and the loss of alveolar capillary bed.[32] However, the measurement is not sensitive to low grades of emphysema.[33] It is also reduced in other diseases that destroy the alveolar capillary bed.

Arterial Blood Gases. Arterial blood gases reveal mild or moderate hypoxemia without hypercapnia in the early stages of COPD. In the later stages of the disease, hypoxemia tends to become more severe and may be accompanied by hypercapnia with increased serum bicarbonate levels.[32] Blood gas abnormalities worsen during acute exacerbations and may also worsen during exercise[34] and sleep.[35] Alterations in blood gases largely reflect alteration in ventilation-perfusion relationships. As a result, the relationship between spirometric values, which assess only airflow, and blood gas abnormalities is weak. Hypercapnia is observed with increasing frequency as values of the FEV_1 fall below 1 L. (Acid-base balance is discussed in Chapter 7.)

Imaging

Chest Radiography. Chest radiography can help exclude other pathology in patients with COPD. COPD is a functional diagnosis and, as such, chest radiographs can only suggest this diagnosis. Increased thickness of bronchial walls viewed on end and an increased prominence of lung markings can suggest the diagnosis of chronic bronchitis, but are neither specific nor sensitive. There are two radiographic patterns associated with emphysema, although both are signs of late disease. These are the patterns of pulmonary arterial deficiency and of increased markings. The triad of overinflation, oligemia, and bullae make up the arterial deficiency pattern, which is most often associated with

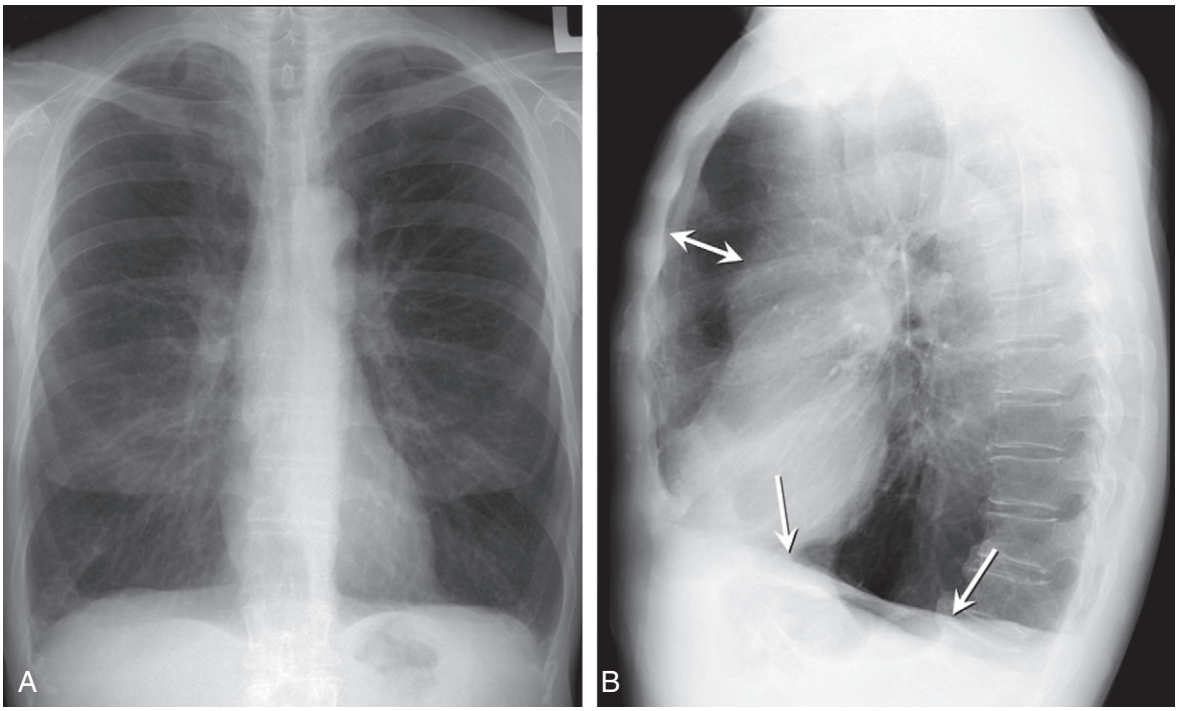

FIGURE 39-2 ■ Frontal (**A**) and lateral (**B**) chest radiograph in a 54-year-old female smoker with centriacinar emphysema. Note the very large lung volumes, with hyperlucency primarily seen in the upper lobes, consistent with a centriacinar emphysema pattern. Flattening of the diaphragms (*arrows*), a prominent retrosternal clear space on the lateral radiograph (*double arrow*), and a small-appearing heart on the frontal radiograph are findings consistent with abnormally increased lung volumes and are typical of advanced emphysema. The upper lobe lucency typical of centriacinar emphysema contrasts with the lower lobe predominant lucency seen in patients with panacinar emphysema (see Fig. 39-13). *See CT scan video of this patient online.* (Courtesy of Michael B. Gotway, MD, Scottsdale Medical Imaging and the Department of Radiology, University of California, San Francisco.)

emphysema, and the increased markings pattern, which resembles the "dirty chest" appearance seen in chronic bronchitis. The best evidence of overinflation is flattening of the diaphragms with a concavity of the superior surface of the diaphragm (Fig. 39-2). Another sign is an increase in the width of the retrosternal air space, but this is less sensitive. Clinical correlation is important when overdistention is present on the chest radiograph because these findings may also be seen with severe asthma. However, this sign resolves in asthma with clinical improvement in airflow limitation.

Computed Tomography. In contrast to conventional radiography, computed tomography (CT) has the resolution needed to delineate and quantify subtle findings in the chest and is therefore much more sensitive, particularly in the diagnosis of emphysema (Fig. 39-3). There are several methods to assess COPD using CT. CT density can be used to quantify emphysema, because loss of density is a characteristic feature. This permits estimates of both severity and extent of disease.[36] Analytic methods have been developed that may also distinguish the pattern of emphysema. The ability to distinguish bullae and to determine the location of disease is essential in determining whether individual patients are candidates for surgical therapy[37] (also see later). Several studies suggest that small airways may also be evaluated.[38]

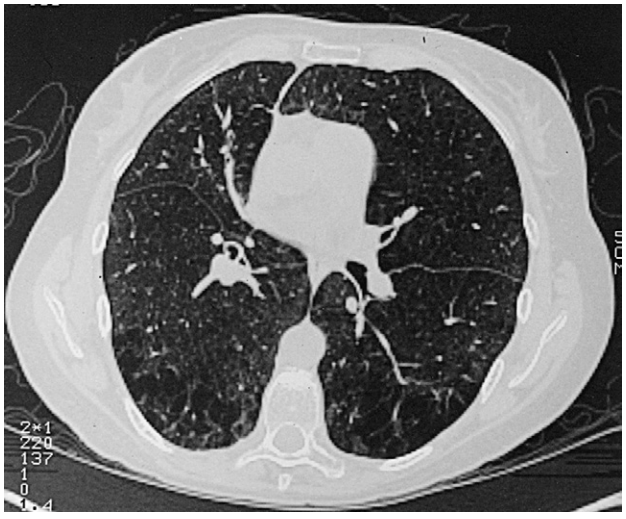

FIGURE 39-3 ■ High-resolution CT scan of the chest of a 65-year-old woman shows enlarged respiratory air spaces posteriorly in both lung fields representing emphysema. The posterior location of the lesions in the upper portions of both lower lobes suggests that the emphysema is centriacinar in type. (Courtesy of Robert Pugatch, MD.)

Laboratory Tests

Biomarkers. Identification of biomarkers, either in peripheral blood or in other body fluids, that reflect specific aspects of COPD is an area of active interest.[39,40] None have yet affected clinical practice.

Erythrocytosis/Anemia. Erythrocytosis may develop in COPD patients. It is generally thought to arise either persistently or intermittently.[41] Anemia may also be a feature of COPD.[42] The presence of a normal hemoglobin should not be used to forgo evaluation of arterial blood gases.

Sputum Examination. In stable bronchitis, sputum is mucoid, and microscopic examination reveals a predominance of macrophages; bacteria are few. During an exacerbation, the sputum often becomes grossly purulent due to an influx of neutrophils. Eosinophils, if present, may indicate a greater likelihood to respond to inhaled glucocorticoid therapy.[43] With an exacerbation, the number of organisms seen on Gram stain usually increases. The pathogens most often cultured from the sputum are *Streptococcus pneumoniae* and *Haemophilus influenzae*. Other oropharyngeal commensal flora such as *Moraxella catarrhalis* can be recovered. Increased numbers of organisms are associated with increased inflammation in stable COPD.[44] Although not always present in exacerbations, increased numbers of bacteria[45] or changes in bacterial strain are associated with exacerbation.[46] Cultures and Gram stains, however, are rarely necessary for institution of antimicrobial therapy unless the patient has sustained an exacerbation during or soon after receiving a course of antibiotic therapy.[47]

COMPLICATIONS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Pneumothorax

Spontaneous pneumothorax in a person with normal lungs produces minor symptoms and disruption of lung function (see Chapter 74). Pneumothorax complicating COPD, however, can precipitate severe dyspnea and acute respiratory failure and may be life threatening. Even a small pneumothorax can cause severe respiratory impairment in COPD patients who have only a marginal pulmonary reserve, and because it is often accompanied by a persistent air leak between the involved lung and the pleural space (bronchopleural fistula), it may be difficult to treat.

Cor Pulmonale

Chronic cor pulmonale is defined as enlargement of the right ventricle (hypertrophy or dilation) due to increased right ventricular afterload from diseases of the lungs or pulmonary circulation (see Chapter 56). Resting mean pulmonary arterial pressures may rise to 30 to 40 mm Hg in patients with advanced COPD as opposed to the normal value of 10 to 18 mm Hg. With exercise, mean pressures may rise as high as 50 to 60 mm Hg or greater. The causes of the pulmonary hypertension in COPD are several.[48,49] Once a common feature in late-stage COPD patients, it is now much less common, perhaps because of the appropriate use of oxygen therapy.

Pathophysiology

Emphysema results in a loss of the pulmonary vascular bed. However, the major cause of increased pulmonary vascular resistance in patients with COPD is vasoconstriction due to alveolar hypoxia. There is subsequent remodeling of the pulmonary vasculature with medial hypertrophy of muscular pulmonary arteries along with the appearance of smooth muscle in normally nonmuscular vessels of the pulmonary circulation. Nocturnal hypoxemia alone, even with noncritical hypoxemia in the awake state, may produce pulmonary hypertension in some patients.[50] Acidemia augments hypoxic vasoconstriction and can play a role in transient rises in pulmonary blood pressure during acute exacerbations of COPD. Increased intrathoracic pressures as a result of airflow limitation with air trapping can also increase pulmonary vascular resistance by compressing pulmonary vessels. Greater viscosity of blood occurring with erythrocytosis secondary to hypoxemia may play a role in the genesis of pulmonary hypertension, although this factor is far less important than hypoxic pulmonary vasoconstriction. Blood volume may be increased in patients with cor pulmonale, in part from impaired sodium and water excretion.[51] This increase in blood volume, along with increases in cardiac output in response to hypoxemia, may contribute to higher mean pulmonary arterial pressure in the presence of a restricted pulmonary vascular bed. Although left ventricular dysfunction is relatively uncommon in patients with cor pulmonale due to COPD, when such dysfunction is present, left ventricular failure and elevated pulmonary venous pressure may also contribute to pulmonary hypertension. In addition, COPD patients are prone to develop chronic pulmonary thromboembolic disease, and embolism should always be considered when the magnitude of pulmonary hypertension is out of proportion to a patient's underlying lung disease and arterial hypoxemia.

The detection of pulmonary hypertension and right ventricular enlargement by noninvasive means can be difficult. The best means is two-dimensional echocardiography, especially with an esophageal transducer, and pulsed Doppler techniques with echocardiography to estimate mean pulmonary arterial pressure.[52–54] Cardiac scintography is rarely required, although cardiac catheterization may be needed to confirm and evaluate pulmonary hypertension.

Successful treatment of cor pulmonale in patients with COPD begins with optimal management of the underlying airflow limitation. Correction of hypoxemia using long-term oxygen therapy is of the greatest importance. Use of pulmonary vasodilators employing a wide range of agents has proved disappointing, with no sustained improvement in hemodynamics or enhanced survival. This remains an active area of research, however, and the availability of newer, more easily administered

agents that may affect vascular remodeling holds promise.

Pneumonia

COPD is generally considered to be an important predisposing condition increasing the risk for pneumonia and for pneumonia of greater severity, although epidemiologic data are limited.[55,56] Pneumonia may also be difficult to distinguish from an acute exacerbation of COPD.[57]

Sleep Abnormalities

A slight decrease in alveolar ventilation with an accompanying modest rise in arterial carbon dioxide pressure (P_{CO_2}) and fall in arterial oxygen pressure (P_{O_2}) is normal during sleep.[58] (Sleep disorders are discussed in detail in Chapter 79.) COPD patients, therefore, may have deterioration in their blood gases at night, even in the absence of sleep apnea. It is not thought appropriate to monitor patients routinely for nocturnal desaturation. However, monitoring nocturnal oximetry could be considered in COPD patients with findings, such as pulmonary hypertension, erythrocytosis or mental status changes, which suggest the presence of intermittent hypoxemia.

Giant Bullae

Bullae occupying one third to one half of one or both hemithoraces may occasionally produce a dramatic chest radiograph. Bullae may become infected and may compromise the function of the remaining lung by filling the chest (Fig. 39-4). There is an increased frequency of carcinoma of the lung with large bullae.[59,60] Tumors may occur in young men with bullae,[60] but occur most frequently in those in the sixth decade of life.[61]

Systemic Manifestations and Comorbidities

It is becoming increasingly clear that COPD is characterized by manifestations outside the lung (Table 39-1). Osteoporosis is also more common in COPD patients and is of clinical significance because it may lead to fractures.[62] Skeletal muscle weakness correlates much better with walking distance in COPD patients than does FEV_1.[63] Walking distance, in turn, is a much better predictor of health status (sometimes termed "quality of life") than is FEV_1.[22] The importance of these features of COPD, which may be independent of airflow limitation, have led to the creation of a multidimensional scoring system, the BODE (body, obstruction, dyspnea, exercise) index (Table 39-2).[64] Interestingly, this index appears to be a much better predictor of mortality than are isolated measures of airflow.

The most common cause of death among COPD patients is coronary artery disease,[65] and reduced lung function has long been recognized as an independent risk factor for cardiac disease.[66] The mechanisms by which COPD increases risk for cardiac disease are not established, but systemic inflammation may play a role in the pathogenesis of atherosclerosis. Hypercoagulability, perhaps due to systemic inflammation, may account for increased risk of deep venous thrombosis and pulmonary embolism in COPD patients. Finally, although controversial, COPD patients may have a higher incidence of depression,[67] which may also result, at least in part, from systemically active inflammatory mediators. These systemic features of COPD are often the major clinical problems faced by patients suffering from this condition.

The mechanisms accounting for the systemic manifestations of COPD are not yet fully defined, but the systemic effects of inflammation have been suggested as the link. Weight loss, for example, may be due, at least in part, to metabolic alterations.[68] Circulating cytokines derived from inflammation in the lung may play a role. Tumor necrosis factor-α (TNF-α), for example, may contribute to the loss of lean body mass and to skeletal muscle dysfunction.[69] Interleukin-6 (IL-6) may account for increased fibrinogen levels and hypercoagulability.[70]

TABLE 39-1. Systemic Manifestations and Comorbidities of COPD

Cardiovascular	Infarction
	Arrhythmia
	Congestive heart failure
	Aortic aneurysm
Hypercoagulability	Stroke
	Pulmonary embolism
	Deep vein thrombosis
	Atrophy
Systemic	Weight loss
	Osteoporosis
	Skin wrinkling
	Anemia
	Fluid retention
	Depression
Lung cancer	

TABLE 39-2. BODE Index for Staging COPD

Parameter	0 Points	1 Point	2 Points	3 Points
Body: BMI	>21	≤21	—	—
Obstruction: FEV_1 (% predicted)	≥65%	50–64%	36–49%	≤35%
Dyspnea: MMRC score	0-1	2	3	4
Exercise: 6-minute walk distance (meters)	≥350	250–349	150–249	≤149

BMI, body mass index; FEV_1, forced expiratory volume in 1 second; MMRC, Modified Medical Research Council.

Adapted from Celli BR, Cote CG, Marin JM, et al: The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. N Engl J Med 350:1005–1012, 2004.

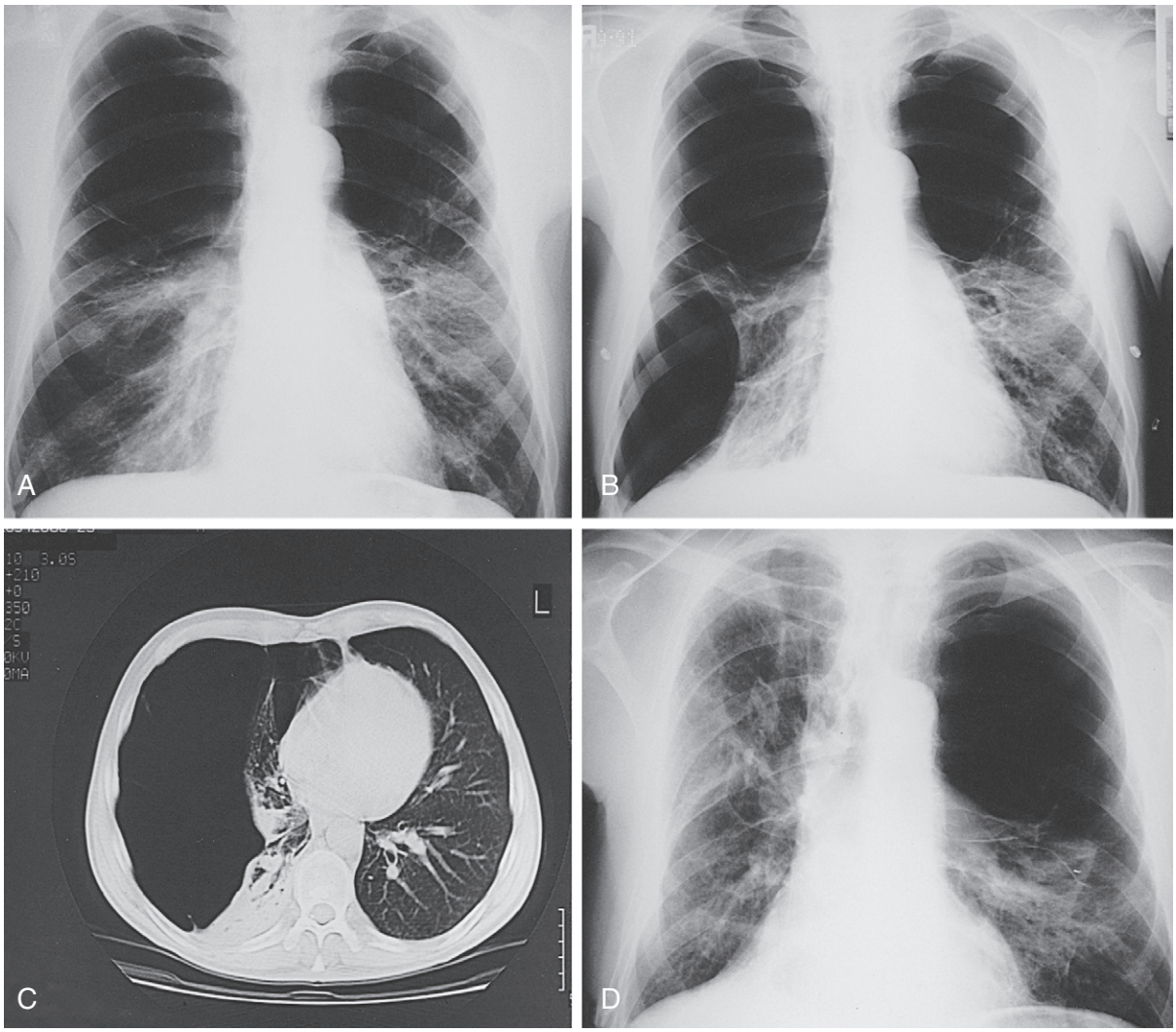

FIGURE 39-4 ■ Radiographs of a 46-year-old man who had smoked an average of 2 packs of cigarettes daily from age 18 years and who presented in the summer of 1991 with dyspnea after walking 20 yards on the level. He was known to have giant bullous lung disease and had had multiple episodes of bronchitis and pneumonia. His serum alpha$_1$-antitrypsin level was normal. Pulmonary function studies revealed an FVC of 2.22 L (44% predicted), FEV_1 1.28 L (34% predicted), FEV_1/FVC 0.58, and diffusing capacity of 9.1 mL/min/mm Hg. Arterial blood gases while breathing air were pH 7.43, P_{CO_2} 38 mm Hg, and P_{O_2} 58 mm Hg. Hematocrit was 51%. Lung perfusion scintiscans showed that virtually all of the perfusion went to the lower half of the left lung. **A,** The chest radiograph of November 14, 1988, reveals giant bullae occupying the upper half of both lung fields with crowding of vascular shadows in the lower lung fields. **B,** In the radiograph of August 9, 1991, an additional giant bulla is seen in the right lower lung field, and a small bulla is noted at the left base. **C,** The CT scan on October 16, 1991 shows atelectasis of the right lower lobe due to compression by giant bullae. The patient stopped smoking. Right thoracotomy with bullectomy was performed on January 14, 1992. **D,** The chest radiograph of February 24, 1992, shows expansion of the right lung with remaining bullae in the left lung. On November 3, 1992, the FVC was 2.81 L, FEV_1 1.80 L, FEV_1/FVC 0.64, and the diffusing capacity was 19.7 mL/min/mm Hg. Arterial blood gases breathing room air were pH 7.43, P_{CO_2} 40 mm Hg, and P_{O_2} 71 mm Hg. The hematocrit was 42%. Dyspnea was markedly diminished, and the patient returned to clerical work.

Renin-angiotensin alterations may contribute to polycythemia.[71] It is likely that cytokines such as granulocyte-macrophage colony-stimulating factor (GM-CSF) can also contribute. These cytokines may alter both net fluid and salt balance, as well as vascular permeability. Thus, edema and fluid status present in COPD are also likely manifestations of systemic disease as well as of hemodynamic abnormalities.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of chronic airflow limitation relates back to the Venn diagram shown in Figure 39-1. The diagnosis of chronic bronchitis is made on the basis of symptoms, that of asthma is made on the basis of near-complete reversibility spontaneously or with bronchodi-

lators, and that of emphysema on the basis of destruction of alveoli best seen on CT scans of the chest. History and physical examination provide an initial database. Spirometry is essential, because it reveals the defining feature of COPD. The chest radiograph may help to exclude other pulmonary disorders. The single-breath diffusing capacity for carbon dioxide (D_{LCO}) may help determine the presence of emphysema although the CT scan is more sensitive. The CT scan can also show the location of emphysema, which is necessary to identify potential surgical candidates, and can reveal other pathologies.

The most difficult clinical problem is to distinguish asthma from COPD. Spirometry with and without bronchodilators is the most useful test. Improvement in lung function is the characteristic feature of asthma. Improvement into the normal range excludes a diagnosis of COPD. Less useful is the methacholine challenge test, which is usually more severely abnormal in asthma than in COPD. Importantly, as indicated in Figure 39-1, asthma and COPD may coexist. In such a case, compromised lung function may partially correct after bronchodilators. If both asthma and COPD are present, therapeutic goals should target both conditions. For this reason, pulmonary function testing should be used to define the presence or absence of both conditions.

Other Conditions

The most common radiographic presentation of emphysema is that of increased lung volume and vascular shadow attenuation and, therefore, of hyperlucency of involved lung compared with nonemphysematous lung. A number of conditions presenting as unilateral or lobar hyperlucency in the chest radiograph are different from emphysema in pathogenesis and natural history.[72] These conditions may need to be differentiated from unilaterally preponderant emphysema (Table 39-3). Hyperlucency in the chest radiograph may also have a chest wall origin, such as from congenital absence of the pectoralis major muscle or absence of the female breast and pectoral muscles after radical mastectomy.

Unilateral Bronchiolitis Obliterans

In 1953, Swyer and James,[73] and in 1954, Macleod,[74] giving much more detail, described patients with unilateral hyperlucent lungs. Subsequent study showed this entity to be due to patchy bronchitis and bronchiolitis obliterans, sometimes with bronchiectasis and generally with respiratory air space enlargement. This condition is best called *unilateral bronchiolitis obliterans with hyperinflation*, but it is referred to by many other terms in the literature, including *Swyer-James* or *Macleod's syndrome*, *unilateral hyperlucent lung*, and *unilateral emphysema*.[75]

Unilateral bronchiolitis obliterans with hyperinflation is quite rare, with a prevalence of 0.01% in 17,450 survey chest radiographs.[72] The condition is usually asymptomatic and is discovered accidentally by chest radiography. Unilateral bronchiolitis obliterans is believed to originate from a destructive bronchitis and bronchiolitis.

TABLE 39-3. Classification of Causes of Unilateral Hyperlucent Lung*

INCREASED RADIOLUCENCY OF CHEST WALL ORIGIN (SPURIOUS)
Congenital absence of pectoralis major muscle
Mastectomy

CONGENITAL ANOMALIES
Absence or hypoplasia of one pulmonary artery
Pulmonary agenesis
Extrapulmonary sequestration

INTRINSIC OBSTRUCTION OF ONE PULMONARY ARTERY
Embolus
Tumor

EXTRINSIC COMPRESSION OF ONE PULMONARY ARTERY
Tumor
Nodes

COMPENSATORY HYPERINFLATION
Atelectasis
Post-lobectomy

INTRINSIC OBSTRUCTION OF MAJOR BRONCHUS
Tumor—benign or malignant
Postinflammatory stricture
Foreign body
Amyloid

EXTRINSIC OBSTRUCTION
Congenital
  Aberrant vessel
  Extrapulmonary sequestration
Tumor
Nodes

CONGENITAL MALFORMATION OF BRONCHUS (DEFECTIVE CARTILAGE OR MUCOSAL FOLD) CAUSING "CONGENITAL EMPHYSEMA"

UNILATERAL ACQUIRED BRONCHITIS AND BRONCHIOLITIS OBLITERANS
Swyer-James-Macleod syndrome

*The list includes examples; all possible conditions are not mentioned.
Modified from Gaensler EA: Unilateral hyperlucent lungs. *In* Simon M, Potchen EJ, LeMay M (eds): Frontiers of Pulmonary Radiology. Orlando, FL: Grune & Stratton, 1969, pp 312–359.

Inhalation of corrosive gases and infections, especially by adenovirus, have been implicated. This usually occurs in childhood, before the full number of alveoli have formed by about age 8, but cases have been documented in adults who were previously normal. Air space enlargement may be due to a reduced number of alveoli (reduced and fixed in number by the insult to the lung during development) which then distend as the thorax grows.

Congenital Hypoplasia

Congenital hypoplasia or absence of a pulmonary artery may also give rise to a small hyperlucent lung[72,75–77]; the amount of hyperlucency varies, depending on the extent

of bronchial artery hyperplasia. Unlike unilateral hyperlucent lung with bronchiolitis obliterans, the affected lung empties at a normal rate.

Atelectasis

Atelectasis of a lobe, especially the left lower lobe, may occasionally lead to impressive hyperlucency of the overdistended upper lobe. The presence of atelectasis and the normal emptying of the overdistended lobe enable easy diagnosis.

Extrinsic compression of a main bronchus by bronchogenic carcinoma with distal air trapping usually presents no diagnostic problem. An intrabronchial neoplasm or postinflammatory stricture of a main bronchus may give trouble in differential diagnosis if hyperlucency of the affected lung results. Emptying of the diseased lung will be delayed and incomplete, with contralateral mediastinal shift on expiration. A localized wheeze may be heard. A CT scan or bronchoscopy is diagnostic.

Congenital Lobar Emphysema

Marked overdistention of a lobe, usually the upper lobe, may give rise to severe respiratory distress in infancy. The condition may also occur later in life and is usually referred to as congenital lobar emphysema. Its cause is unclear. Bronchial cartilage abnormalities and mucosal folds have been identified in some cases.[78] Occasionally, a hyperlucent lung or lobe can be seen as part of bronchial atresia or pulmonary agenesis.[79,80] Both of these conditions are usually manifested in childhood, but bronchial atresia may not become manifest until adulthood. In infancy and childhood, resection is indicated if normal lung tissue is severely compressed resulting in pulmonary insufficiency. Most adults are asymptomatic, and differentiation from unilateral obliterative bronchiolitis may not be possible short of pathologic examination of resected tissue. Such resection is usually not indicated.

EPIDEMIOLOGY

COPD is a major public health problem. Its impact is almost certainly underestimated. It is recognized as the fourth leading cause of death in the United States, accounting for more than 120,000 deaths annually.[81] COPD prevalence and impact have been increasing for several decades, following the epidemic of cigarette smoking in the 20th century, and COPD is projected to be the third leading cause of death by 2020.[82] Mortality may be peaking among men in the United States but, among women, mortality continues to rise and deaths from COPD among women now exceed those among men.[83]

A major goal of the GOLD program is to facilitate the diagnosis and staging of COPD.[1] The key feature necessary to establish the diagnosis of COPD is airflow limitation that is not fully reversible. For diagnosis, a ratio of the FEV_1 to the FVC of less than 0.7 ($FEV_1/FVC < 0.7$) has been used. The FEV_1 can be reliably measured as the disease worsens but, because the FVC may be underestimated, the FEV_1/FVC ratio is only used to establish a diagnosis. The FEV_1, expressed as the percentage of predicted, is used to stage severity.

This classification does not incorporate changes that occur with age. In normals, the FEV_1/FVC ratio may decline with age, resulting in some "overdiagnosis" of mild COPD in the elderly.[84] Because underdiagnosis and undertreatment is a major problem, it was decided to select a simple classification that could be readily used clinically and the ratio was adopted in the GOLD guidelines.

The National Health and Nutrition Examination Survey (NHANES) study, in which lung function was measured in a representative portion of the population, suggests that 24 million people have impaired lung function in the United States.[83] The diagnosis of COPD, however, is extremely inaccurate. It is estimated that 10 million Americans have a diagnosis of COPD. Not only does this reflect tremendous underdiagnosis, but diagnosis in the absence of spirometry is notoriously inaccurate, with more than half of patients misdiagnosed.[26] This inaccuracy of diagnosis is true not only in the United States but also in other population-based studies.[85] This emphasizes the importance of using spirometry to diagnose and stage COPD. Although not recommended for screening of unselected individuals,[86] spirometry should be available in primary care practices to assess those with suggestive symptoms or those at increased risk due to exposures or family history.[86]

The economic impact of COPD in the United States has been estimated to be nearly $40 billion.[87] This includes both direct and indirect costs, and involves a number of assumptions.[88] Nevertheless, these estimates are probably modest. More than half of the direct costs attributable to COPD are attributable to acute exacerbations and are relatively easy to track.[89] COPD patients, however, also have considerably greater total direct healthcare costs than do similarly aged non-COPD patients. The difference in cost is only partially due to direct costs for COPD, indicating that the COPD patient has increased costs for "non-COPD" health problems. This suggests that many of the costs related to COPD may be attributed to associated comorbid conditions.

COPD progresses with age and COPD is more prevalent in elderly populations. In the United States, 15% of the total population aged 55 to 64 will have at least moderate COPD (GOLD stage 2, $FEV_1 < 80\%$ predicted), and this increases to over 25% for those older than 75.[90] There are similar numbers of patients with mild disease (GOLD stage 1, $FEV_1 > 80\%$, FEV_1/FVC ratio < 0.7), although the clinical significance of mild disease in the elderly remains controversial. In two studies designed to determine the prevalence of COPD, standardized spirometric methods were used to estimate the prevalence of COPD in different countries.[91-93] With these spirometric standards, COPD prevalence was found to vary from 2% to 22% (Fig. 39-5).[93] The large variation was only partially explained by variations in age and smoking status, emphasizing the role of other risk factors.

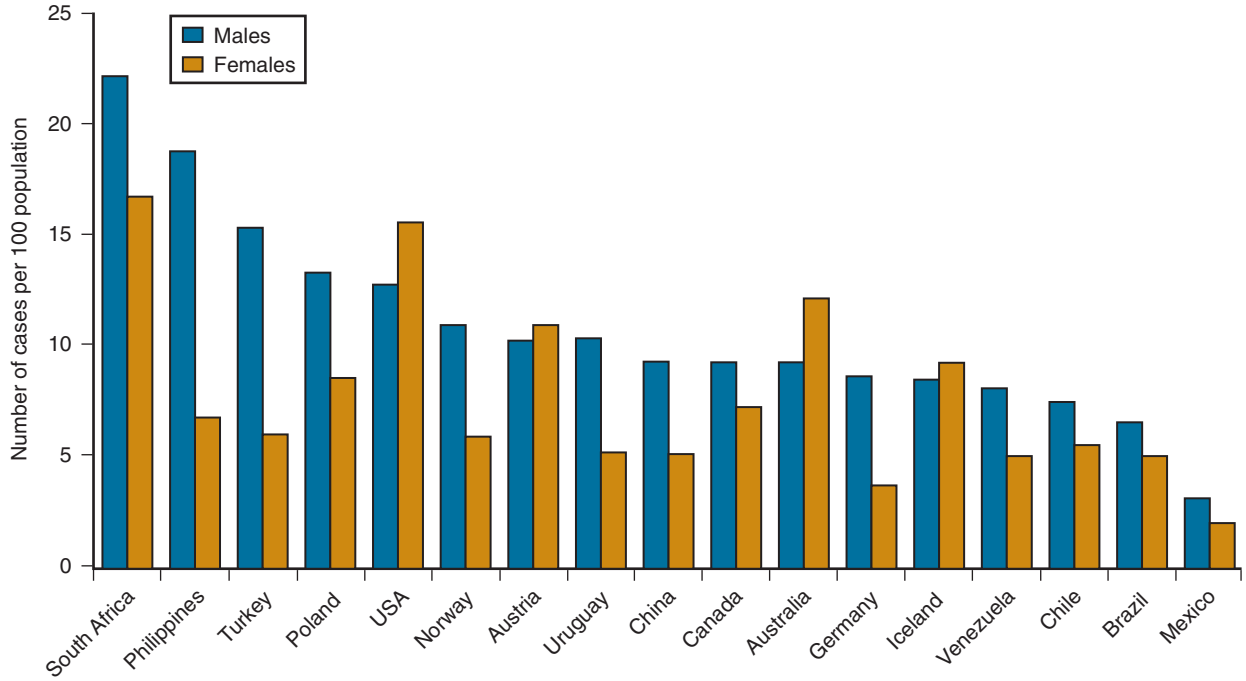

FIGURE 39-5 ■ Prevalence of COPD in different countries. Data were pooled from two multinational epidemiologic studies which used similar methodology. The prevalence of COPD, GOLD stage 2 or higher, is shown on the vertical axis for men (*blue*) and women (*orange*). The sampling sites in the various countries included on the horizontal axis were small and may not be generalizable to the entire population. (Redrawn from Mannino DM, Buist AS: Global burden of COPD: Risk factors, prevalence, and future trends. Lancet 370:765–773, 2007, with permission.)

Risk Factors

Exposure to Toxic Fumes and Gases

Cigarette Smoking. Cigarette smoking is firmly established as the most important risk factor for COPD. Fletcher and colleagues[2] suggested that a minority, perhaps 10% to 15% of smokers, would get clinically significant COPD. This has led to a serious misconception that only 15% of smokers get COPD.[94] In fact, smokers lose lung function in a dose-dependent manner (Fig. 39-6). Thus, the majority of smokers are likely to have reduced lung function, particularly as they age (Fig. 39-7). Even if undiagnosed, this reduced lung function has an adverse prognostic effect. The impact of smoking, therefore, should not be underestimated. Eighty percent of individuals who have COPD and 80% who die from COPD in the United States are smokers.[83] Among these individuals, however, there is variable susceptibility to the effects of cigarette smoke, and other factors also contribute to risk. These other risk factors, which vary greatly among different populations, are estimated to contribute between 27% and 60% of the overall risk for COPD mortality.[93]

Other Exposures

Occupational exposures are also associated with increased risk for accelerated loss of lung function. Whereas the effect of occupational exposures has been stated to be small compared with the effect of cigarette smoking,[95] a recent study attributes nearly 20% of COPD risk to occupational exposures among smokers and more than 30% among nonsmokers.[96] Farming or work in dusty occupations increases the risk of developing chronic bronchitis two- to threefold and, in combination with smoking, the risk increases to sixfold.[97,98] Environmental air pollution, especially due to particulates, may contribute to accelerated decline in lung function,[99] and episodes of increased pollution may contribute to increased mortality.[100] Indoor air pollution, particularly from exposure to smoke generated from the use of biomass fuels, is a major cause of COPD in the developing world.[101] Systemic exposures have also been suggested to play a role. Cadmium is increased in the urine of individuals with COPD[102] and can lead to COPD in animal models. However, because cadmium is present in cigarette smoke, the role of environmental cadmium is not yet defined.

Genetic Susceptibility

COPD most often results from harmful environmental exposures, most importantly, the chronic inhalation of cigarette smoke, in a genetically predisposed individual. Familial aggregation of airflow obstruction has been observed in smokers, suggesting a genetic component. With respect to specific genes, mutations in the serine proteinase inhibitor, alpha$_1$-protease inhibitor (A1PI) (discussed later) represents the only proven genetic abnormality that predisposes to COPD.[12,103] Of note, cigarette smoking markedly accelerates loss of lung function in patients with A1PI deficiency as well.[104]

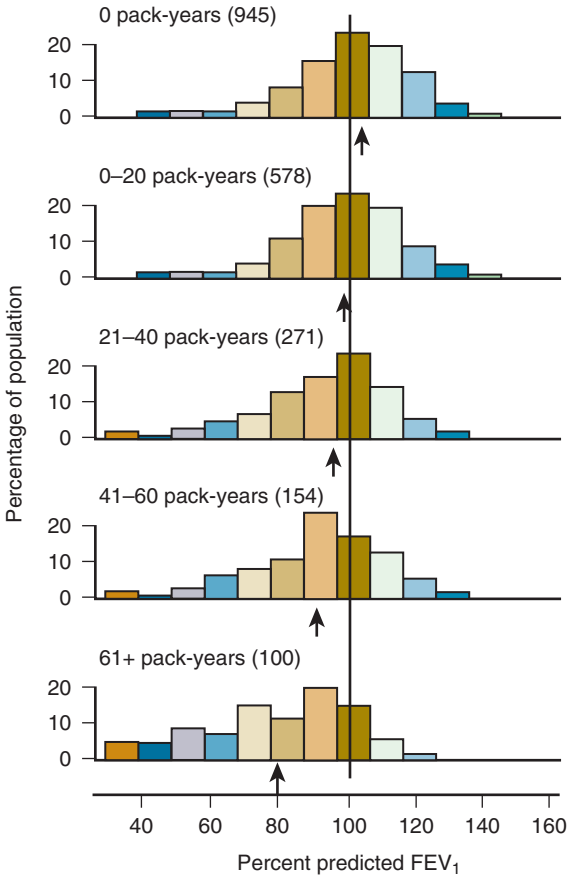

FIGURE 39-6 ■ Distribution of FEV_1 values (as % predicted) in subjects with varying pack-years of smoking. Subjects with "respiratory trouble" before age 16 were excluded. Medians (*arrows*) are shown for each smoking group with numbers of patients in parentheses. (Redrawn from Burrows B, Knudson RJ, Cline MG, Lebowitz MD: Quantitative relationships between cigarette smoking and ventilatory function. Am Rev Respir Dis 115:751–760, 1979.)

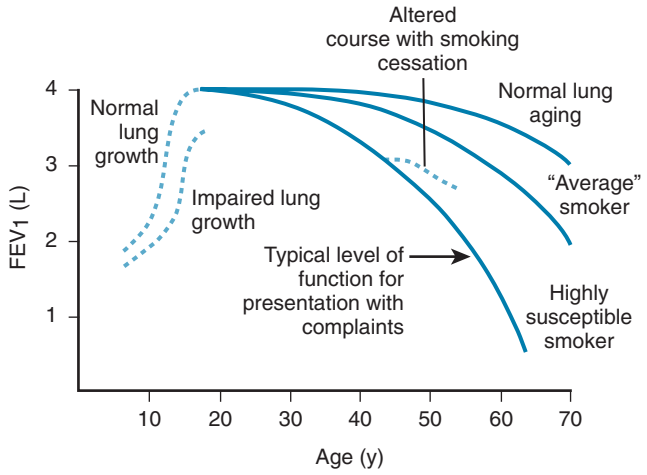

FIGURE 39-7 ■ Natural history of COPD. Lung function increases with growth in childhood and adolescence. Fetal and childhood events can affect lung growth and development, resulting in reduced maximally attained lung function, for convenience shown here as an FEV_1 of 4 liters. Actual predicted values depend on height and gender. After growth is completed, lung function remains constant for some time, the "plateau phase," after which lung function declines at an accelerating rate with age. Smoking reduces the duration of the plateau phase and accelerates the rate of lung function loss. Smoking cessation early in the course of the disease can reduce the rate of lung function loss to that of a nonsmoker. Patients typically present with symptoms when lung function declines below 50% of that in young adulthood but may have limitation much earlier. (See text for details.)

There are probably many other genetic determinants of COPD. Association studies comparing candidate genes in patients with COPD versus control subjects have identified a variety of potential genes. However, these studies are often underpowered and are not adequately controlled. Hence, no gene has been shown unequivocally to be involved in COPD by a candidate gene analysis. Linkage analysis of early-onset COPD families, a more robust method of identifying COPD genes, has identified linkage of airway obstruction to several chromosomal regions.[105] The search is on to narrow these regions to specific genes. The first gene identified by this technique is serpin E2 on chromosome 2.[106] Interestingly, this gene, like A1PI, is a serpin or serine proteinase inhibitor. However, unlike A1PI, serpin E2 is not an elastase inhibitor, suggesting a novel disease pathway. A large genome-wide association study for COPD has recently been launched. This newer technique is complicated but does not require candidate genes to uncover COPD genes throughout the genome.

Early Life Events

Maternal smoking may be a risk factor for the development of COPD, because it has been associated with low birth weight and an increased incidence of respiratory illnesses, including asthma, in children.[107,108] Studies have suggested that both low birth weight and childhood respiratory infections are risk factors for the development of COPD, although these findings are not uniformly reproduced.[108–112] Consistent with the concept that early life events contribute to COPD risk, maximally attained lung function (which is likely related to early lung growth and development) appears related to the risk of development of COPD.[113]

Asthma

As noted previously, the suggestion that asthma can progress to COPD has come to be known as the Dutch hypothesis.[114] Several epidemiologic studies have demonstrated accelerated loss of lung function among asthmatics,[115,116] although it may be that all of the risk is in a subset of asthmatics.[117] Functional changes in both the small airways[118] and the alveolar parenchyma[119] have been reported. Whether airway hyperresponsiveness itself, apart from asthma, is a risk factor remains controversial.[120]

Mucus Hypersecretion

The concept that mucus in the airways could contribute to the development of fixed airflow limitation became known as the "British hypothesis."[2] A classic study of British postal workers was conducted to evaluate this hypothesis, and Fletcher and colleagues[2] concluded that there was no effect of mucus hypersecretion on loss of lung function, after correction for smoking. More recent studies in larger cohorts, however, suggest that mucus hypersecretion does have an effect, though small.[121] Similarly, individuals who experience more frequent acute exacerbations also appear to have a more rapid decline in lung function.[122]

Gender

COPD prevalence shows a gender predominance that is largely related to the demographics of exposure to cigarettes or other inhaled toxins within a population. This accounts for the historically increased prevalence among men. The most recent estimates, however, suggest that COPD is equally prevalent among women in many populations (see Fig. 39-5).[93] Compared to men with COPD, women do appear to have different comorbidities, with a lower prevalence of ischemic heart disease but a higher prevalence of CHF, osteoporosis and diabetes.[123]

Socioeconomic Status

Morbidity and mortality rates have been shown to be inversely related to socioeconomic status, and this relationship has been documented repeatedly in studies over several decades.[93,124,125] A mechanism for this association has not been established. However, it is likely that the relative lack of diagnostic effort and lack of coverage for COPD therapy is, in part, connected to the socioeconomic status of the affected population.

NATURAL HISTORY

Factors that contribute to the natural history of COPD include early life events such as intrauterine lung development and childhood and adolescent lung growth as well as later events such as adult lung exposures. The natural history of COPD, therefore, extends over the entire life span of the individual; in fact, potential effects could precede conception. To date, no longitudinal studies have tracked the entire course of the natural history of COPD. Longitudinal studies have been conducted, but generally for a limited number of years.[126] The classic monograph of Fletcher and colleagues,[2] for example, was a longitudinal study of 8 years. The "natural history" was based on an extrapolation of the collected data. The resulting picture of the natural history of COPD, which is so widely used that a plot of FEV_1 versus age is commonly called a "Fletcher-Peto curve," is also limited by the fact that Fletcher and colleagues did not consider the nonsmoker with COPD. In addition, Fletcher and colleagues were fully aware of the extra-pulmonary features of COPD, but these are not included in the famous curve. Nevertheless, the image of COPD natural history illustrated in the Fletcher-Peto curve helps describe several key clinical issues.

Because COPD develops slowly, the early stages of the illness are often "silent." Exertional dyspnea in COPD patients is believed to result, in large part, from dynamic hyperinflation, which develops with increasing respiratory rate.[127] The COPD patient, therefore, can avoid dyspnea by avoiding tachypnea, which can be achieved by decreasing exercise. As a result, COPD patients become progressively more sedentary. The lack of activity in COPD patients results in severe muscle detraining. Whether skeletal muscle is also abnormal because of the effects of systemic inflammation or systemic vasculopathy is currently debated.[128,129] What is clear is that muscle weakness is a major feature of COPD and often limits exercise more than dyspnea does. This may help explain the observation that health status (sometimes termed "quality of life") is more closely related to exercise performance than to lung function.[130]

Little is known about the natural history of COPD beyond the FEV_1. Several ongoing longitudinal studies, however,[131,132] promise to help define the "Fletcher-Peto curve" by tracking other features of the COPD patient over time. Nevertheless, despite the large gaps in understanding the natural history of COPD, particularly for effects outside the lung and for exposures other than cigarette smoking, a number of important features have been described.

Lung Growth

In the human, the conducting airways are developed by the 16th week of gestation.[133] Gas exchange structures, including respiratory bronchioles and alveoli, develop subsequently. Some alveoli are present at birth, but branching of alveolar wall continues postnatally for several years. Alveolar number does not increase after age 8, and subsequent growth of the lung is due to increase in alveolar size. The airways increase in diameter, but not in number, throughout this later growth process. As a result, maximal lung function is attained in young adulthood. This level of function remains relatively constant for perhaps 10 years and then begins to decline in a slowly accelerating manner.[113] Over 50 years of adult life, a normal individual may lose 1 L of FEV_1, a decline that averages 20 mL/yr, but this decline is not linear and probably accelerates with increasing age.

Cigarette Smoking

Smoking affects this natural history in several ways. First, smoking during the years of lung growth reduces maximally attained lung function.[134] Second, the "plateau phase" is reduced in duration and may be absent.[135] Finally, the rate at which lung function declines is probably increased.[2] Because lung function declines faster with advancing age, this could represent either a shift in the "normal" age-related changes to a younger group or a different pathologic process. As a result of these various

effects, the average smoker loses about 2 L of FEV_1 over 50 years, an average decline of about 40 mL/yr, although there is considerable variation in the rate of lung function decline. How other causative factors affect the natural history of COPD is not defined. Smoking cessation in adulthood can slow the rate of decline among individuals with mild COPD.[136] Whether such benefits can be expected among individuals with more severe disease or in the elderly is unclear,[137] although smoking cessation has many other established benefits.[138]

Decline in lung function, moreover, may not be continuous. Exacerbations, which are characterized by acutely compromised lung function, may not completely resolve and may result in stepwise decrements of lung function.[114] Finally, some individuals may experience a rapid decline in lung function. Starvation, for example, has been reported to cause the accelerated development of emphysema in both animal models and humans.[139]

Individuals who are "rapid decliners" have been observed in prospective studies.[140] Compared to those with a more normal FEV_1, those with a low FEV_1 probably had, and will continue to have, a more rapid rate of decline of FEV_1 and will be more likely to develop COPD, a prediction known as the "horse-racing effect" (analogous to a prediction that, at a given point in the race, the horse in the lead was the fastest, will continue to be the fastest, and is more likely to win)."[141] Interestingly, prospective studies have found that decrease in lung function is more rapid in individuals with less severe COPD.[142,143] Identification of slow and rapid decliners in longitudinal studies such as the Lung Health Study has allowed investigation of biomarkers to distinguish these groups and to define the mechanistic bases for lung function decline.[144,145] Importantly, systemic markers of inflammation have been associated with poorer lung function[146,147] and, in some[148,149] but not all studies,[150] with an increased rate of decline in lung function.

Early Disease

Treatment goals in COPD are largely focused on alleviation of symptoms. Because patients with early disease often have no complaints, the importance of identifying individuals with early disease was not recognized until recently. The 1995 American Thoracic Society (ATS) guidelines, for example, incorrectly suggested that it was not necessary to diagnose such individuals.[151] However, individuals with mild lung function compromise have increased mortality, which is primarily due to acute cardiac events.[65,66] This relationship is true for both smokers and nonsmokers.[152] The link between cardiac events and mild COPD may be systemic inflammation. Identifying a group of individuals with increased cardiac risk, and identifying that they may need treatment to benefit maximally from an exercise training program, has potential clinical benefit.

Advancing Disease

As FEV_1 declines, risk for mortality increases. Cardiac events remain a major cause of death, even when COPD is severe. The relative incidence of death due to respiratory causes, however, increases with increasing severity of lung function compromise. Exacerbations, which increase in frequency as FEV_1 declines, are times at which individuals are at particular risk for death. Mortality is also increased among those who have recovered from an exacerbation. The 2-year mortality rate for patients admitted for acute exacerbation of COPD with CO_2 retention in the SUPPORT (Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments) trial was 49%.[153] In a retrospective study of a large Canadian database, 1-year mortality of 30% to 40% was observed following hospitalization for COPD exacerbation among individuals over the age of 65, although survival may have been influenced by treatment.[154] However, studies from several centers have shown that some patients with severe obstructive airway disease may survive for many years.[155–158] Thus, it is not possible to predict the course of an individual with a high degree of certainty. Decisions relating to level of care and end-of-life issues, therefore, must be individualized and must be based on many factors in addition to lung function.

PATHOLOGY

Airway Disease—Chronic Bronchitis

Bronchi

A number of morphologic changes in the bronchi have been described in chronic bronchitis.[159] The submucosal glands reveal dilated ducts and hypertrophy and hyperplasia of their glandular elements (Fig. 39-8). The traditional way of measuring glandular enlargement is the Reid index or the ratio of glandular to bronchial wall thickness.[5] Goblet cell frequency is also increased. Patchy areas of squamous metaplasia and dysplasia may replace normal ciliated epithelium.[160] The amount of airway smooth muscle is increased.[161,162] The airway wall contains an infiltrate of inflammatory cells in which monocytes and lymphocytes, especially $CD8^+$ T cells, are prominent.[163,164] BALT (bronchus-associated lymphoid tissue) is also present in late GOLD stages.[165] Whether BALT is related to autoimmune phenomena or is a marker of bacterial colonization is not clear. This inflammation contrasts with the $CD4^+$ Th2 cells that are prominent in asthma.

Neutrophils are more frequently found in the airway lumen[166] and in the glands[167] than in the airway wall. Neutrophil numbers increase with exacerbations. Eosinophils may be present, but are much less common than in asthma,[168] although eosinophils may increase during exacerbations.[169]

Bronchioles

The respiratory bronchioles that represent airways less than 2 mm in diameter are the primary sites of physiologic airway obstruction with narrowing[165,170] (Fig. 39-9). The airway remodeling processes are similar to those in the larger airways involving goblet cell metaplasia with

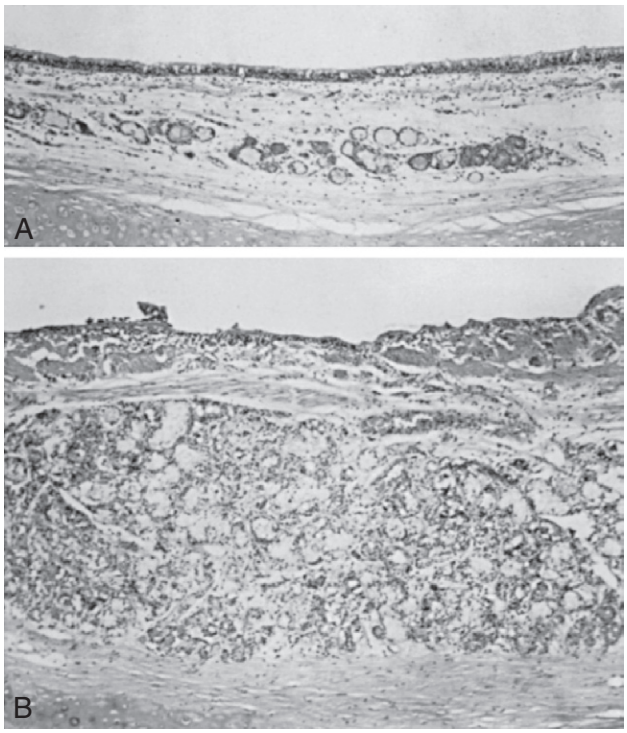

FIGURE 39-8 ■ Photomicrographs show the left main bronchus from a patient without respiratory symptoms (**A**) and from a patient with many years of productive cough and airflow obstruction (**B**). Serous acini (*dark staining*) and mucous acini (*light staining*) constitute the submucosal gland in **A**. The average gland thickness represents about one third the distance between the epithelial basement membrane and the perichondrium. The submucosal gland in **B** is markedly thickened, is made up mostly of mucous acini, and constitutes most of the wall thickness between the epithelial basement membrane and the perichondrium; note also that the epithelium shows desquamation. (From Snider GL [ed]: Clinical Pulmonary Medicine. Boston: Little, Brown, 1981.)

mucus plugging, inflammation, smooth muscle hyperplasia, and fibrosis. Smoking leads to a predominantly mononuclear inflammatory process[170,171] in the small airways and lung parenchyma. Destruction of lung parenchyma may lead to loss of alveolar attachments, predisposing to small airway collapse.[172,173]

Emphysema

Emphysema is characterized by destruction of gas-exchanging air spaces including respiratory bronchioles, alveolar ducts, and alveoli. Cigarette smoking leads to inflammatory cell recruitment, proteolytic injury to the extracellular matrix (ECM), and cell death. Alveolar walls become perforated and later, in the absence of repair, become obliterated with coalescence of small distinct air spaces into abnormal and much larger air spaces.[174]

Pulmonary emphysema, defined as destruction and enlargement of air spaces distal to the terminal bronchiole, may be contrasted with a variety of developmental abnormalities in alveogenesis leading to impaired septation and alveolarization with consequent enlarged air spaces. "Simple air space enlargement," in which there is no destruction or loss of orderly appearance of the lung acinus, also occurs in the contralateral lung following pneumonectomy. Air spaces, particularly alveolar ducts, enlarge with advancing age, resulting in what has been termed "senile emphysema."

Localization of the lesions of mild emphysema in the acinus serves as the basis for classification into several types of emphysema (Table 39-4).[175] The acinus or secondary lung lobule is the unit of lung structure distal to the terminal bronchiole. The acinus is composed of three to five orders of respiratory bronchioles, which have alveoli originating directly from their walls (Fig. 39-10). All of the structures distal to the terminal bronchiole participate in gas exchange and constitute

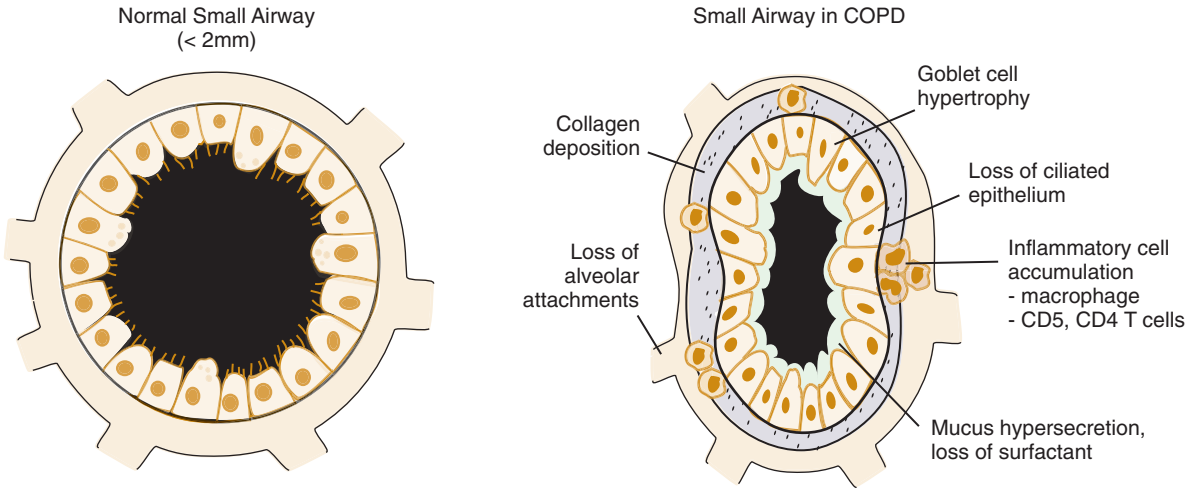

FIGURE 39-9 ■ Small airway obstruction in COPD. In contrast to a normal small airway (*left*), a variety of factors lead to narrowing of the airway lumen in COPD. These changes include mucus hypersecretion, inflammatory cell accumulation, and fibrosis (collagen deposition). Loss of surfactant and loss of alveolar attachments predispose to airway collapse. (Redrawn from Shapiro SD: Evolving concepts in the pathogenesis of chronic obstructive pulmonary disease. Clin Chest Med 21:621–632, 2000.)

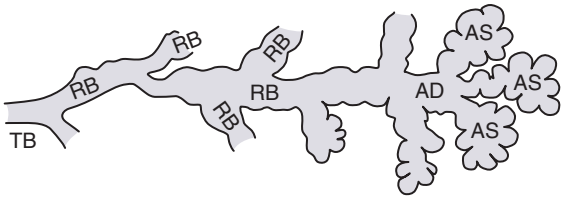

FIGURE 39-10 ■ Normal respiratory air spaces. The terminal bronchiole (TB) leads into several orders of respiratory bronchioles (RB), which in turn open into alveolar ducts (AD) and alveolar sacs (AS). The respiratory air spaces arising from a single terminal bronchiole constitute the secondary lung lobule or acinus. Centriacinar (or centrilobular) emphysema begins in first-order respiratory bronchioles, hence its central localization in the secondary lung lobule. Panacinar (or panlobular) emphysema involves all the respiratory spaces. (Redrawn from Snider GL [ed]: Clinical Pulmonary Medicine. Boston: Little, Brown, 1981.)

TABLE 39-4. Classification of Respiratory Air Space Enlargement

SIMPLE AIR SPACE ENLARGEMENT
Congenital
Congenital lobar overinflation
Down syndrome
Acquired
Secondary to loss of lung volume
EMPHYSEMA
Proximal acinar emphysema
Focal emphysema
Centriacinar emphysema
Panacinar emphysema
Distal acinar emphysema (paraseptal)
Airspace enlargement with pulmonary fibrosis
Bullae
Blebs and cysts

the respiratory tissues of the lungs. The description of subtypes of emphysema based on location and distribution has been useful. In most patients, however, the process within the lung will be heterogeneous.

The most important types of emphysema are centriacinar (or centrilobular) and panacinar (or panlobular). The anatomic patterns of emphysema suggest specific pathogenetic mechanisms. The use of CT scans now allows the clinician to more carefully define the type of emphysema and to quantify it better.[176–180]

Proximal Acinar Emphysema

Proximal acinar *emphysema* refers to those types of emphysema that begin in the respiratory bronchioles.[159,181] Scarring and focal dilation of the bronchioles and of the adjacent alveoli result in the development of an enlarged air space or microbulla in the center of the secondary lung lobule. Air space enlargement spreads peripherally from the centriacinar region. This type of emphysema includes focal emphysema and centriacinar emphysema.

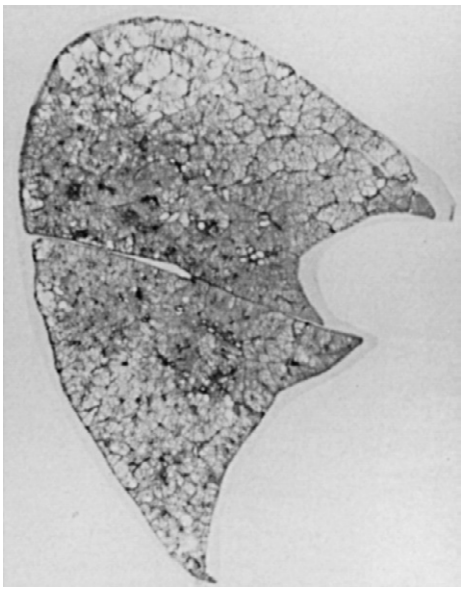

FIGURE 39-11 ■ Centriacinar emphysema is shown. Mounted section of inflation-fixed left lung shows centriacinar emphysema. The disruption of respiratory air spaces is present in the basilar segments of the left lower lobe and lingula but is locally most severe in the apical-posterior segment of the upper lobe and superior segment of lower lobe. (From Snider GL [ed]: Clinical Pulmonary Medicine. Boston: Little, Brown, 1981.)

Focal Emphysema

A form of centriacinar emphysema, occurring in persons who have had heavy exposure to a relatively inert dust such as coal dust,[182] is called *focal emphysema*. Large numbers of pigment-laden macrophages are noted in association with focal emphysema, which is distributed through the lungs.

Centriacinar Emphysema

Centriacinar emphysema is the form of emphysema most frequently associated with prolonged cigarette smoking in persons who have had no unusual dust exposure.[183] This lesion involves the upper and posterior portions of the lungs more than the lower portions (Figs. 39-2 and 39-11).[184,185]

Panacinar Emphysema

The term *panacinar emphysema* refers to dilation of all of the respiratory air spaces of the secondary lung lobule. This form of emphysema may be either focal or diffuse; in the focal form, lesions are more common at the lung bases than at the apices and are often seen in older persons.[165,186] Panacinar emphysema also commonly occurs in the lung bases of smokers in association with centriacinar emphysema in the lung apices. As the disease process becomes more severe, the lesion becomes indistinguishable from centriacinar emphysema.[186,187]

Diffuse panacinar emphysema is the lesion most often associated with A1PI deficiency; the emphysema is

usually more severe at the bases than at the apices. Congenital lobar overinflation or emphysema results in infancy from bronchial atresia, most often in the apicoposterior segmental bronchus of the left upper lobe; available information suggests that the accompanying emphysema is panacinar in type.[79] A group of young (average age about 35 years) intravenous Ritalin (methylphenydate tablet) abusers with severe airflow obstruction and severe panacinar emphysema has been described.[188]

Distal Acinar Emphysema

In contrast to other forms of emphysema that tend to be generalized, *distal acinar emphysema*, which is also known as *paraseptal* or *subpleural emphysema*, is localized along fibrous interlobular septa or beneath the pleura. The remainder of the lung is often spared, so pulmonary function may be normal or nearly so despite the presence of many superficial areas of locally severe emphysema.[79,189] This is the type of emphysema that produces the apical bullae giving rise to simple spontaneous pneumothorax in young persons, as described in Chapter 74.

Air Space Enlargement with Pulmonary Fibrosis

Another type of localized emphysema, *air space enlargement with pulmonary fibrosis*, is commonly seen as an inconsequential lesion adjacent to scars. At times, the air space enlargement may be quite extensive and may be important clinically, arising as a complication of fibrosing diseases such as tuberculosis, silicosis, and sarcoidosis.[159,190] The underlying disease is usually evident radiographically, with extensive linear or nodular shadows evident along with the enlarged air spaces. Air space enlargement with fibrosis is the anatomic lesion underlying emphysema associated with the pulmonary apical cap.[191] Honeycombing or the end-stage of interstitial lung disease is different from air space enlargement with fibrosis. In honeycombing, cystic spaces 0.5 to 2 cm in diameter are located mainly in the periphery of the lung, although they can sometimes be widespread. The spaces have dense fibrous walls and are mostly lined by bronchiolar epithelium.[192] To differentiate air space enlargement due to fibrosis from COPD, definitions of COPD are used to exclude fibrosis. However, this is problematic because scarring, particularly in the small airway subepithelial space, is often a consequence of cigarette smoking and a contributing factor to airflow obstruction in COPD. In addition, collagen accumulates around larger disrupted air spaces. Hence, fibrosis and emphysema might be less distinct than we have previously believed.

Bullae

Bullae are areas of marked focal dilation of respiratory air spaces that may result from coalescence of adjacent areas of emphysema, from locally severe panacinar emphysema, or from a ball-valve effect in the bronchi supplying an emphysematous area.[79,159,183] The bullae may be simple air spaces or may retain the trabeculae of the emphysema that led to them. Most frequently, bullae occur as a part of widespread emphysema. Although locally severe emphysema of any type can give rise to bullae, giant bullae are particularly likely to complicate distal acinar emphysema. In the setting of bullae, the amount of emphysema in adjacent lung without bullae varies. In distal acinar emphysema, the emphysematous changes may be confined to the bullous areas; however, if these bullae become large and compress adjacent lung tissue, they may have important physiologic consequences.

Blebs and Cysts

Blebs are intrapleural collections of air and are, therefore, a form of interstitial emphysema. They may be a complication of interstitial emphysema in the newborn period or a complication of pulmonary barotrauma complicating mechanical ventilation. They may also be a part of the spontaneous pneumomediastinum of adults. Ruptured blebs are a cause of spontaneous pneumothorax.[79,159,183]

Cysts in the lung are air spaces lined by epithelium, which usually have the characteristics of bronchial epithelium.[193,194] They are classically known as intrapulmonary bronchogenic cysts and usually occur near the tracheal bifurcation, but they may be seen more peripherally in the lung parenchyma. Air spaces with fibrous walls, as seen in sarcoidosis and open healed of tuberculous cavities, are sometimes referred to as "cysts." As described previously, they are better referred to as "air space enlargement with fibrosis."

Structure-Function Correlations

The Cause of Airflow Limitation in Chronic Obstructive Pulmonary Disease

The mechanical principles underlying airflow limitation are presented in Chapter 5, and the pulmonary function tests used to evaluate airflow limitation are discussed in Chapter 24. Airflow is not obstructed by bronchial gland enlargement,[195–197] perhaps because the process gives rise to only slight thickening of the mucosa and minimally encroachment of the lumen of the cartilaginous airways. In contrast, airflow is reduced by narrowing of airways due to smooth muscle contraction, narrowing of airways, particularly the small airways, due to peribronchial fibrosis, and destruction of the alveolar wall that results in loss of lung elastic recoil and loss of tethering of small airways, thus permitting small airway collapse during expiration. In a given individual, it may be difficult to distinguish among these mechanisms. Emphysema and bronchiolitis commonly appear together in moderate or severe COPD.

Small airway obstruction has the strongest correlation to airflow obstruction. The internal diameter of respiratory and membranous bronchioles correlates strongly with FEV_1 percent predicted (r = 0.79 and 0.82, respec-

tively).[197,198] The relationship between airflow limitation and bronchiolar pathology persists as airflow limitation and emphysema become moderate in severity, but the strength of the association is less. Airway disease may be a more important determinant of airflow limitation in mild COPD and emphysema more important in severe COPD. This is consistent with autopsy studies that suggest emphysema is the major determinant of airflow limitation.[170,199,200] It also suggests that the various lesions associated with airflow limitation in COPD may have differing natural histories.

Compliance and Lung Volumes in Emphysema

Increased compliance of the lungs was first described in severe emphysema in the 1930's.[201,202] Even in mild emphysema, elastic recoil pressures are consistently decreased.[203] There is increased lung distensibility with an accompanying increase in total lung capacity, functional residual capacity, and residual volume and a decrease in vital capacity. However, the correlations between measures of the whole lung volume-pressure relationship with the pathologic severity of emphysema are relatively weak.[204,205] This may reflect the heterogeneity of emphysema within the lung while the volume-pressure relationship assesses whole-lung function. In addition, the air spaces of centriacinar emphysema may be less compliant than normal lung and much less compliant than the emphysematous lung around them.[204] This may reflect lung destruction that results in maximal expansion of selected areas. These fully expanded regions, paradoxically, are not compliant because they cannot expand further.

Carbon Monoxide Diffusing Capacity

The D_{LCO}—whether measured by the single-breath or steady-state method and whether values are expressed in absolute terms, as percent predicted, as a function of alveolar volume, or as fractional uptake of carbon monoxide—has consistently been a solid functional predictor of the severity of emphysema.[183,190] The correlation coefficients have ranged between 0.60 and 0.87. This relationship probably reflects the loss of internal surface area and of the capillary bed of the lung with emphysema. However, this test is neither a specific nor a sensitive test of mild emphysema. Interestingly, whereas the D_{LCO} increases in normal subjects in the supine or prone position, it fails to increase in COPD patients, possibly due to loss of capillary capacitance or capillary volume.[206]

PATHOGENESIS

Chronic Obstructive Pulmonary Disease

Small Airway Obstruction

Chronic bronchitis refers to symptoms of chronic sputum production. This is mainly a manifestation of large airway disease and is not associated with airflow obstruction. However, small airway obstruction, obstruction of bronchioles less than 2 mm diameter, which is probably caused by similar mechanisms that lead to chronic bronchitis, is a major factor in airflow obstruction in COPD. Our understanding of the pathogenesis of airway disease is much less complete than our understanding of emphysema. This probably relates to the fact that the airways in small animals are less similar to human airways than are the alveoli, hence making small animal modeling of the airway in COPD imperfect.

Whereas cigarette smoke may lead to similar types of injury and inflammation in the airway as in the airspaces, the manifestations are distinct. CT scanning has shown that emphysema and airway abnormalities are fairly independent processes, suggesting distinct pathophysiologic mechanisms, although both lead to airflow obstruction.[179,180] Airway remodeling in patients with COPD leads to physical narrowing of the airway resulting in airway obstruction. As mentioned previously, major remodeling events include goblet cell hyperplasia with excessive mucus production, epithelial dysplasia, smooth muscle hypertrophy, airway fibrosis, and inflammation including BALT in late GOLD stages.

Airway Inflammation

The airways in patients with COPD are characterized by increased numbers of neutrophils, monocytes, and lymphocytes. The numbers of $CD8^+$ T cells and B cells, in particular, grow with increasing severity of COPD.[207] Oxidants and other particulates in cigarette smoke induce epithelial cells and constitutive macrophages to release cytokines and chemokines that activate the innate as well as adaptive immune response. A recent concept is that COPD may in part be an autoimmune disease.[207,208] Infectious agents also activate the immune system during exacerbations.

Goblet Cell Metaplasia

Structural changes, including glandular hyperplasia and increased number of goblet cells, occur in COPD and are responsible for increased mucus production. Neutrophil elastase not only causes elastin destruction in the lung parenchyma but also acts as a potent secretagogue working via cleavage of membrane tethered transforming growth factor-α (TGF-α) that activates the epidermal growth factor receptor (EGFR), leading to expression of the MUC5AC mucin.[209,210] Other factors such as oxidants[211] and matrix metalloproteinases (MMPs)[212] may also induce EGFR-mediated mucus production.

Epithelial Injury, Repair, and Fibrosis

A variety of insults to the airway epithelium may lead to endoplasmic reticulum stress and potentially to cell death.[213] Analogous to skin wound healing, the lung likely can restore epithelial integrity. In the skin, fibroblasts lay down a provisional matrix. Neighboring epithelial cells and perhaps stem cells are rapidly recruited, resulting in cells that proliferate, migrate over the provisional matrix via cell-matrix interactions, and then differentiate. Signals from the epithelium turn off fibroblast

proliferation, resulting in a restored epithelial barrier. This suggests that the repair process involves interactions involving epithelial cells, mediators present within the local milieu, and the local extracellular proteinases and matrix.

Aberrant repair can fail to "turn off" the fibroblast response or lead to epithelial mesenchymal transformation,[214] leading to peribronchial fibrosis that contributes to expiratory airflow limitation.[165,172] In this regard, a general property of fibrotic tissues is contraction. In the skin, this may serve to limit wound size and to maintain structural integrity. In a parenchymal organ, this contraction may lead to tissue distortion. In the airway, this process may be responsible for the airway narrowing that characterizes airflow limitation in mild to moderate COPD. Of note, fibroblasts can contract three-dimensional collagenous matrices, and this process can be modulated by exogenous mediators. Interestingly, epithelial cells can both regulate fibroblast contraction of collagenous matrices[215] and contract the matrices themselves.[216] This suggests that interactions between the epithelium and the mesenchyme in the airway may be important in regulating airway luminal diameter. In asthma models and perhaps also in COPD, abnormal stretch exerted on the epithelium alone may induce release of profibrotic growth factors.[217] MMP-9 produced by activated epithelial cells proteolytically activates TGF-β, further contributing to airway fibrosis.[218]

Exacerbations

Pathogens first encounter innate host defense including mucociliary clearance, the epithelial barrier, constitutive host macrophages, and rapidly accumulating neutrophils. Tobacco smoking impairs macrophage phagocytosis, and airway remodeling interferes with mucociliary clearance, each predisposing to airway colonization and acute infectious bacteria and viruses.[219]

Chronic infections with a variety of pathogens including adenovirus[220] or *Chlamydia*[221] may lead to increased chronic inflammation. A similar role has been suggested for chronic bacterial colonization of the airways. The increased chronic inflammation can potentially predispose both to loss of lung function and to increased risk for acute exacerbation. Finally, acute infections with viruses[222] and bacteria[219] are major causes of acute exacerbations. These exacerbations, moreover, may have adverse effects. Individuals with frequent exacerbations appear to lose lung function at an accelerated rate,[122] and exacerbations result in adverse effects on health status that may persist for months.[25]

Emphysema

The overall scheme (Fig. 39-12) that is emerging for the pathogenesis of emphysema is that cigarette smoke and, less commonly, other toxic particulates lead to inflammation with activation and release of elastases and other matrix-degrading proteinases. Cell death also occurs either as a result of altered ECM attachment or as a direct effect of smoke exposure.[223,224] In the absence of normal cellular and matrix repair, the disrupted air spaces disappear and coalesce, resulting in the air space enlargement that defines emphysema.[225]

Inflammatory Cells

Cigarette smoke leads to recruitment of several inflammatory and immune cell types in the air space.[174,226,227] Neutrophils rapidly accumulate in the lung in response

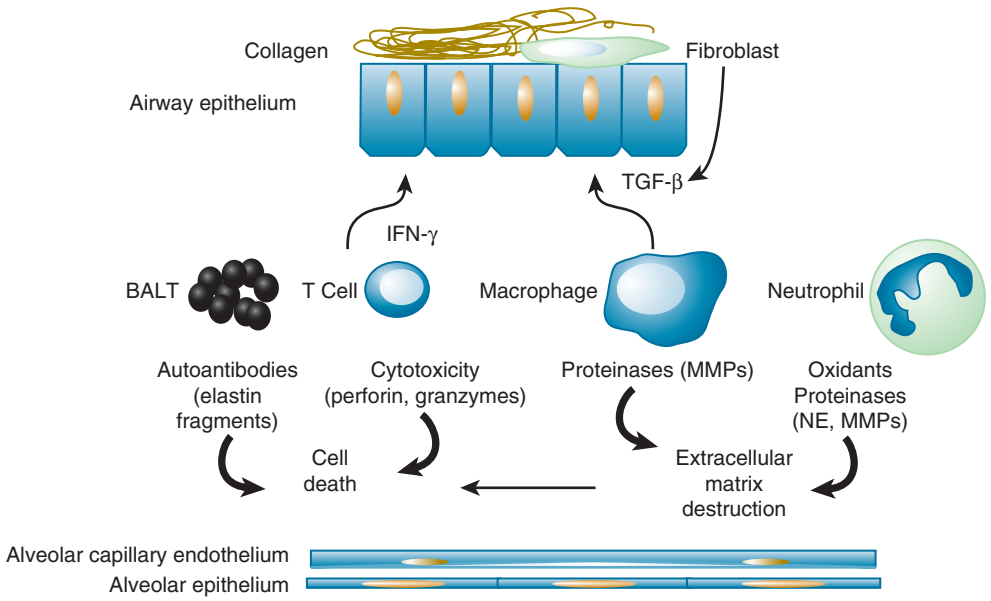

FIGURE 39-12 ■ Alveolar destruction and airway fibrosis in COPD. Loss of an alveolar unit requires destruction of the extracellular matrix by proteinases of macrophage and neutrophil origin, as well as cell death. Proteinases include matrix metalloproteinases (MMPs) and neutrophil elastase (NE). Cell death may occur via oxidant injury, via T-cell cytotoxic products (perforin and granzymes), via autoantibodies produced by bronchus-associated lymphoid tissue (BALT) or via loss of matrix attachment. Fibrosis of airways (and lung parenchyma) is also a feature of COPD. Production of interferon-γ (IFN-γ) by T cells and transforming growth factor-β (TGF-β) by several cell types contributes to accumulation of collagen.

to cigarette smoke. Recruitment occurs via stimulation of epithelial cells and macrophages by cigarette smoke, resulting in release of TNF-α and neutrophil chemokines CXCL1 and CXCL8 (IL-8) operating through the neutrophil receptor CXCR2.[227] Oxidants present in smoke and those generated by the inflammatory cells also promote neutrophilic inflammation.[224,228] Oxidants also play a role in cigarette smoke–induced cell death. Neutrophils contain proteinases that are preformed and stored in granules. Upon neutrophil activation, secondary and tertiary granules containing MMPs, particularly MMP-9, are readily released. Primary or azurophil granules that contain serine proteinases including neutrophil elastase (NE) are not readily released, although a portion of granules translocate to the cell surface upon activation where they are difficult to inhibit.[229] In addition to causing matrix destruction, proteinases from the neutrophil and other cells generate fragments of ECM proteins such as collagen[230] and laminin[231,232] that are also chemotactic for neutrophils, leading to a vicious feedback circle of inflammation and tissue destruction.

COPD is characterized by a gradual, progressive accumulation of macrophages in the lung. Prior to clinical disease, macrophage accumulation is most apparent in respiratory bronchioles, the primary site of centriacinar emphysema.[170] Activation of constitutive macrophages leads to production of both neutrophil chemokine and cytokines, as mentioned previously, as well as production of macrophage chemotactic protein-1 (MCP-1; CCL2), which recruits more monocytes from the peripheral blood, which later differentiate into macrophages.[227] In addition, proteolyzed elastin fragments are chemotactic for macrophages.[233,234] Macrophages have the capacity to produce a variety of MMPs, particularly elastases such as MMP-9 and MMP-12, and thus participate directly in lung destruction. Although macrophage activation promotes inflammation, it should also be recognized that removal of apoptotic cells by macrophages not only limits release of toxic products from dying cells but also results in the production of anti-inflammatory factors and growth factors such as TGF-β and human growth factor (HGF) that may promote tissue repair.[235,236]

Both $CD8^+$ and $CD4^+$ T cells are also increased in airway walls and alveoli of patients with COPD, with $CD8^+$ cells predominant.[164] Airway epithelial cells in smokers with COPD (but not those without COPD) have increased expression of CXCL10 (IP-10), the ligand for CXCR3[237,238] that is expressed on T cells and macrophages. Human studies[238] and animal models[239] show that CXCL10 triggers macrophages, via CXCR3, to produce MMP-12, demonstrating regulation of macrophage proteolysis by $CD8^+$ T cells. Cytotoxic T cells may target epithelial cells and induce cell death, particularly those with (latent) viral infection. Other hematopoietic cells such as dendritic cells, eosinophils, and mast cells have also been observed in COPD, but their roles in the disease process are less well defined.

Recognition of the increased numbers of B cells and lymphoid follicles in the lung has led to the notion of COPD as an autoimmune disease.[207,208] In fact, elastin fragments themselves have been shown to serve as autoantigens.[240] Immunoglobulin G (IgG) autoantibodies with avidity for pulmonary epithelium, and with the potential to mediate cytotoxicity, have also been detected in patients with COPD.[241]

Cigarette smoke both directly and indirectly initiates inflammation, but other factors sustain inflammation later in the disease process in the absence of cigarette smoke. Analysis of end-stage lung tissue obtained from lung volume reduction surgery (LVRS) years after smoking cessation has revealed intense inflammation composed of a variety of cell types.[242] The factors perpetuating inflammation are unknown but could include the presence of pathogens in the airway including colonizing bacteria and latent viral infection with adenovirus.[243,244] Also, as discussed, chemotactic matrix fragments generated by proteinases promote further inflammation.

In summary, multiple inflammatory cell types are present in the lung in response to cigarette smoking and interact to cause COPD. Focus on the innate and adaptive inflammatory-immune network will be required to abrogate inflammation and lung destruction in COPD.

Proteinase-Antiproteinase Hypothesis

Experimental evidence for the role of elastases in emphysema began in 1963 when Laurell and Eriksson[12] reported an association of chronic airflow obstruction and emphysema with deficiency of serum A1PI, the endogenous inhibitor of NE. In 1964, Gross and colleagues[245] intratracheally instilled papain, a plant-derived cysteine proteinase, into experimental animals, resulting in air space enlargement. Together, these observations indicated that emphysema could be induced by proteolytic injury to the lung ECM. These observations formed the basis for the elastase-antielastase hypothesis of emphysema, a concept that persists today.

Elastase-Induced Emphysema. Much of our knowledge of emphysema has come from instillation of elastolytic enzymes into lungs of experimental animals to induce emphysema. Treatment with human NE causes increased air space size and lung volumes,[246–248] but the changes are considerably less severe than those induced by doses of pancreatic elastase with comparable in vitro elastolytic effect. Different susceptibility to these two enzymes may relate to differing accessibility of the enzymes to alveolar elastic tissue,[249] or pancreatic elastase may have a greater ability to activate proteolytic and inflammatory cascades that amplify the initial proteolytic insult.[250]

Emphysema induced by porcine pancreatic elastase (PPE) causes an initial rapid increase in air space size due to direct elastolysis with diminution of lung elastin content at 24 hours followed by rapid restoration of total lung elastin to normal levels.[251] However, the anatomic arrangement of the restored elastic fibers is grossly disordered. The model is also characterized by inflammation with neutrophils and macrophages with subsequent release of endogenous inflammatory mediators including IL-1β and TNF-α with endogenous proteolytic progression of the disease for at least 1 month.[252]

The marked increase in total lung capacity in experimental (and human) emphysema is not likely to arise without disruption of the collagen network of the lungs. There is biochemical evidence of damage and subsequent repair of collagen in experimental elastase-induced emphysema. Elastase-induced emphysema is worse in animals fed diets that prevent lysyl oxidase cross-linking of elastin and collagen.[251] However, not all of the damage is proteolytic. Mechanical forces during breathing are capable of causing failure of the remodeled ECM at loci of stress concentrations and so contribute to the progression of emphysema.[253]

Although elastin is critical to the structural integrity of the lung, and only elastases instilled into the lung cause experimental emphysema, other matrix components such as collagen must also be lost for an alveolar space to enlarge. Thus, a broader concept is the proteinase-antiproteinase hypothesis, which states that the balance between matrix-degrading proteinases and their endogenous inhibitors determines whether the lung is protected or susceptible to proteolytic injury.

Of note, "microenvironmental" localization of proteinases and their inhibitors is an important concept. For example, release of proteinases from a cell in contact with the ECM may block inhibitors from preventing proteolysis.[254] Moreover, proteolytic degradation due to NE released from neutrophil granules takes place by "quantum proteolysis." That is, discrete release of granules results in very high concentrations of their contents at the site of release with decreasing concentrations at increasing distances from the site of release due to diffusion. Inhibition occurs as the concentration decreases with diffusion from the burst.[255] This has significant implications in A1PI deficiency in which inhibitor concentrations are low. Also, when proteinases such as NE and MMP-9 are bound to the surface of the neutrophil, they are resistant to complete inhibition by A1PI[229] and tissue inhibitors of metalloproteinases (TIMPs),[256] respectively. However, synthetic small-molecular-weight inhibitors will fully neutralize cell surface proteolytic activity.

Proteinases and Antiproteinases. There are four classes of proteinases, serine, cysteine, aspartic, and metalloproteinases, that are distinguished by their mechanism of catalysis and endogenous inhibitors.

Serine Proteinases. The serine proteinase NE was first implicated in COPD after the findings that patients deficient in its endogenous inhibitor, A1PI, are at increased risk for emphysema and that instillation of NE caused emphysema in experimental models. NE also plays a role in airway disease. In fact, NE is one of the most potent secretagogues known.[257] In addition, NE is involved in monocyte transvascular migration[258] and, in some instances, mediates neutrophil migration, although probably not simply by creating paths of degraded matrix. Despite intense interest in the development of NE inhibitors over the years, they remain largely untested in terms of their efficacy in COPD.

Mice deficient in NE are protected by two thirds from the development of emphysema in response to cigarette smoke.[258] The role of NE in emphysema is due to a direct effect of NE on elastin as well as to the ability of NE to inactivate TIMPs and mediate monocyte migration into the lung. NE-null mutant mice have also been helpful in defining the major physiologic function of NE, which is one of host defense. NE is a potent bactericidal and fungicidal agent that acts within the neutrophil lysosome.[259,260]

As the name implies, NE is produced mainly by neutrophils, but also to a small degree by monocytes. Two other serine proteinases that are also neutrophil- and monocyte-derived are cathepsin G (CG) and proteinase 3 (PR3). There is some evidence from animal models that PR3, which has some elastolytic capacity, may also be involved in the development of COPD.[261]

Serine proteinases are inhibited by A1PI, as alluded to earlier and discussed in detail later. Inhibition of A1PI ameliorates smoke-induced emphysema in mice.[262] $Alpha_1$-macroglobulin is a large-molecular-weight inhibitor of multiple classes of proteinases that is restricted to the bloodstream. Two smaller-molecular-weight inhibitors include secretory leukoprotease inhibitor (SLPI) and elafin. SLPI is a 12-kDa protein produced by mucus-secreting and epithelial cells in the airway as well as by type 2 pneumocytes. SLPI inhibits NE and CG, but not PR3. Elafin, also produced by airway secretory and epithelial cells, is released as a 12-kDa precursor that is processed to a 6-kDa form that specifically inhibits NE and PR3. These inhibitors are able to inhibit NE bound to substrate, giving them an added dimension that A1PI lacks.

Matrix Metalloproteinases. MMPs represent a family of 24 enzymes that require coordination of zinc at the active site, have overlapping substrate specificity, and are inhibited by TIMPs.[263] Several MMPs degrade elastin and hence are likely to contribute to emphysema including MMP-2, MMP-9 (gelatinase A and B), MMP-7 (matrilysin), and MMP-12 (macrophage elastase). MMP-1, -8, -13 are collagenases, and thus degrade another critical matrix component.

Several MMPs have been associated with human COPD including MMP-1, MMP-9, MT1-MMP, and MMP-12.[264–266] Macrophages have the capacity to produce MMP-1, MMP-3, MMP-7, MMP-9, MMP-12, and MMP-19. MMP-12 has been found in macrophages of smokers[267] and is one of the most highly up-regulated genes both in human smokers and in mouse models of emphysema.[268] MMP-9 has been detected in macrophages of smokers with COPD, to a greater degree than in "healthy" smokers, and has been a prime therapeutic target.[269] MMP-9 and MMP-8 (neutrophil collagenase) are also stored in neutrophil-specific granules. A search for genetic polymorphisms in Caucasians uncovered polymorphisms in the MMP-1 promoter region (the more active promoter had better lung function) and in MMP-12 that together correlated with the rate of lung function decline.[270]

Several animal models have supported roles for MMPs in COPD. Transgenic mice constitutively overexpressing MMP-1 were found to develop air space enlargement.[271] Mice lacking MMP-12 were resistant to long-term cigarette smoke–induced emphysema.[272] Subsequent studies have shown that mice deficient in $\alpha v\beta 6$ develop spontaneous emphysema over time.[273] In the absence of $\alpha v\beta 6$, there is no TGF-β activation. Because TGF-β normally

inhibits MMP-12, αvβ6-deficient mice have 100-fold excess MMP-12 expression over control mice and consequently develop emphysema. Mice that inducibly overexpress IL-13 develop inflammation and expression of MMP-9, MMP-12, and cathepsin S followed by emphysema.[274] This highlights the potential interactions between mediators of asthma and COPD. Of note, mice overexpressing IFN-γ, a Th1 cytokine, also develop cell death, inflammation, and air space enlargement.[274]

Cysteine Proteinases. The cysteine proteinase family includes several highly elastolytic enzymes.[275] Although predominantly intracellular enzymes that work most effectively in an acidic pH, several cysteine proteinases retain significant activity at neutral pH. Moreover, it is possible that cells have the capacity to acidify their immediate extracellular environment.[276] Overall, cathepsins are widely expressed in the lung. Cathepsin L, S, and K are macrophage products. In addition to ECM catalysis, a normal function of cathepsin S is to process antigens in T cells.[277] Cathepsin K is the most potent elastase and collagenase and, hence, might be quite destructive in COPD if present. Cathepsin B is an epithelial cell product that has been shown to have proapoptotic properties.[278]

Cathepsins are inhibited by cystatins, some of which are intracellular whereas others, such as cystatin C, are extracellular. Cystatin C is the most ubiquitous cystatin; it is found in all human tissues and body fluids tested, providing general protection against tissue destruction by intracellular cathepsin enzymes leaking from dying cells. Overall, cathepsins have the potential to contribute to COPD, although they have been less thoroughly studied than other classes of proteinases.

Proteinase Functions in Chronic Obstructive Pulmonary Disease. Cigarette smoke exposure leads to a variety of abnormalities in both the airways and the lung parenchyma that result in the syndrome termed COPD. A variety of proteinases participate in COPD, with their major role being destruction of ECM components, particularly elastin. However, proteinases also regulate inflammation, not only by blazing trails for cells through tissue barriers, but also via both the generation and the degradation of chemokines and cytokines. For example, ADAMs (a disintegrin and metalloproteinase) and select MMPs such as MMP-12 "shed" active TNF-α from the cell surface.[279] Epithelial-derived MMP-7 cleaves IL-8–bound syndecan, generating a chemotactic gradient for neutrophils following bleomycin lung injury.[280] MMPs also limit inflammation via processing of chemokines. For example, MMP-9 was shown to proteolytically process active MCP-3, resulting in maintained chemokine binding to its receptor but without the ability to transmit calcium influx or a chemotactic response.[281]

Within the airways, NE induces mucus secretion, as mentioned previously. This response is mediated by NE-dependent proteolytic activation of EGFR via a TGF-α–dependent mechanism.[209] MMP-9 has been shown to activate TGF-β and mediate airway fibrosis in an animal model of asthma[218] and probably also COPD. Thus, proteinases participate in multiple activities at several anatomic lung sites in the development of COPD.

Cell Death

Alveolar destruction resulting in air space enlargement requires loss of both cells within the alveolar space as well as the ECM components. Traditional theories suggest that the primary event is release of inflammatory cell proteinases resulting in degradation of lung ECM. Because cell viability requires cell-matrix attachment via integrins, loss of matrix disrupts the contact and predisposes to cell death (termed "anoikis"). Experimental models show that noninflammatory cell death can initiate air space enlargement. For example, inhibition of vascular endothelial growth factor receptor (VEGFR) in endothelial cells[223] and epithelial cells[282] of the lung or instillation of active caspase 3 in epithelial cells[283] results in cell death followed by air space enlargement in rodents. Following cell death, presumably, proteinases may be released directly or inflammation initiated that subsequently degrades the ECM. Thus, whereas COPD is characterized by inflammation and proteinase production, these events are not necessarily required for initiation of emphysema in experimental models. Whether these mechanisms play a role in human COPD is unknown; however, it has been shown that increased septal cell apoptosis is associated with reduced lung expression of vascular endothelial growth factor (VEGF) and VEGR receptor-2 in human emphysematous lungs.[284]

Repair

Destruction in emphysema is followed by aberrant repair of alveolar cells and matrix resulting in coalesced and enlarged air spaces with depleted and disordered parenchymal elastic fibers and excessive, abnormally arranged collagen. Whether adult humans can ever reinitiate the process of septation that was responsible for the intricate juxtaposition of matrix, epithelial, and endothelial cells to form functional alveoli during lung development is not clear. It should be noted that, in animal models of COPD, treatment with all-*trans* retinoic acid resulted in limited but significant repair.[285] It has been known for years that following pneumonectomy, there is compensatory lung growth of the remaining lung in humans and animal models.[286,287]

Elastin is the principal component of elastic fibers. Elastic fibers, which possess rubber-like reversible extensibility, come under tension and provide elastic recoil throughout the respiratory cycle. In the lung parenchyma, elastic fibers loop around alveolar ducts, form rings at the mouths of the alveoli, and penetrate as wisps into the alveolar septae where they are concentrated at bends and junctions.

Elastin[288] is secreted as a soluble protein of 60- to 70-kDa called tropoelastin, which is deposited into the extracellular space and aligned on a "scaffold" of microfibrils that consist of fibrillins, microfibril-associated proteins, and latent TGF-β–binding proteins. In the extracellular space, lysyl oxidase modifies lysine residues in tropoelastin monomers, causing them to cross-link and form elastin, a highly insoluble, rubber-like polymer.

The lysine-derived cross-links in elastin are known as desmosines and isodesmosines, which are unique to elastin, and therefore can be used to quantify elastin in tissues and to serve as markers of elastin degradation in body fluids.

Under normal conditions, elastin synthesis in the lung begins in the late neonatal period, peaks during early postnatal development, continues to a much lesser degree through adolescence paralleling lung growth, and stops in adult life.[289] There is evidence that the tropoelastin gene remains transcriptionally active but rapid mRNA degradation prevents expression of the protein.[290] Multiple cell types are responsible for elastin synthesis in the lungs and associated structures. Elastin is resistant to most proteinases and lung elastin normally lasts a human life span, despite virtually absent elastin synthesis in the normal adult lung.[289]

Following elastolytic injury, it is not known whether normal elastic fibers can be properly formed in the lung after the period of growth and development.[291] After an intratracheal injection of elastase into an experimental animal, there is acute depletion of elastin followed by a burst of ECM synthesis so that, over a few weeks, the elastin content of the lungs returns to normal, although the lungs develop emphysema. The newly synthesized elastic fibers appear disorganized, similar to the elastic fibers in human emphysema.[250,251] Less is known about the turnover of other ECM components in human lungs affected by COPD.

Collagen turnover in COPD is complex.[292] Total collagen content in the lung is actually increased in animal models of COPD and humans with COPD.[292] These findings suggest that emphysema is not purely a destructive process but one of aberrant matrix turnover. With loss of an alveolar unit, all local collagen is lost, but this is more than compensated for by excessive collagen deposition around the larger coalesced airspaces. Small airway fibrosis is also prominent in COPD.

Alpha$_1$-Protease Inhibitor Deficiency

Physiologic Role of Alpha$_1$-Protease Inhibitor. A1PI is a serpin or serine proteinase inhibitor that is a prominent protein in the serum. A1PI is also commonly known as alpha$_1$-antitrypsin. The protein is produced mainly in the liver, is found in high concentrations in the bloodstream, and permeates tissues including the lung. A1PI is also an acute phase reactant, with its serum concentration rising during pregnancy, during infections, after severe burns, and in the presence of malignant tumors. Smoking elevates the serum A1PI concentration by about 20%. Serine proteinases whose activities are inhibited by A1PI include pancreatic trypsin, chymotrypsin, NE, and proteases from some microorganisms.[293] However, its main substrate in vivo is believed to be NE.[294]

Genetic Variations. A1PI is a 52-kDa glycoprotein composed of 394 amino acids, and it is coded for by a single gene on chromosome 14. The serum protease inhibitor phenotype (Pi type) is determined by the independent expression of the two parental alleles. The A1PI gene is highly pleomorphic. More than 75 alleles are known, and they have been classified into normal (associated with normal serum levels of normally functioning A1PI), deficient (associated with serum A1PI levels lower than normal), null (associated with undetectable A1PI in the serum), and dysfunctional (A1PI is present in normal amount but does not function normally).[294]

Most variants of A1PI arise because of point mutations that result in a single amino acid substitution. The Z variant results from the substitution of a lysine for a glutamic acid,[295] which changes the charge of the molecule and, therefore, its electrophoretic mobility. The mutant protein can polymerize and the aggregated form can cause cell injury.[296,297] The Z protein is also incompletely glycosylated, which may interfere with the protein's excretion from the liver into body fluids.

The normal M alleles (the alleles are assigned a letter code) are found in about 90% of persons of European descent with normal serum A1PI levels; their phenotype is designated Pi MM. Normal values of serum A1PI are 150 to 350 mg/dL or 20 to 48 μmol. More than 95% of persons in the severely deficient category are homozygous for the Z allele, designated Pi ZZ, and have serum A1PI levels of 2.5 to 7 μmol (mean, 16% normal). Almost all of these persons are whites of northern European descent, because the Z allele is rare in Asians and African Americans. Rarely observed phenotypes that are associated with these low levels of serum A1PI include the following: Pi SZ and persons with nonexpressing alleles; Pi null, found in homozygous form as Pi null-null and found in heterozygous form with a deficient allele as Pi Z null. Persons with phenotype Pi SS have A1PI values ranging from 15 to 33 μmol (mean, 52% of normal). The threshold protective level of 11 μmol (35% of normal) is based on the knowledge that Pi SZ heterozygotes, with serum A1PI values of 8 to 19 μmol (mean, 37% of normal), rarely develop emphysema. Pi MZ heterozygotes have serum A1PI levels that are intermediate between Pi MM normals and Pi ZZ homozygotes (12–35 μmol; mean, 57% of normal). Case-control studies showed increased odds of COPD in Pi MZ individuals, but this finding was not confirmed in cross-sectional studies. Overall, there appears to be a small increase in risk of COPD in all Pi MZ individuals (or a larger risk in a subset of subjects).[298]

Lung Disease in Alpha$_1$-Protease Inhibitor–Deficient Phenotypes. The premature development of severe emphysema is the hallmark of homozygous A1PI deficiency.[299] Symptoms or signs of pulmonary disease rarely develop before age 25 years. The onset of dyspnea occurs at a median age of 40 years in Pi Z smokers and 53 years in nonsmokers.[300] Bronchiectasis has been reported in association with A1PI deficiency.[301] In the 1970s, it was stated that more than half of those with type Pi Z die from pulmonary disease,[299] and this probably remains the case today.

Tobacco smoking and the development of pulmonary disease are strongly associated. Smokers who are type Pi Z have a significantly lower life expectancy than nonsmokers who are type Pi Z. Nonsmokers in the Swedish National Registry did not have reduced life expectancy

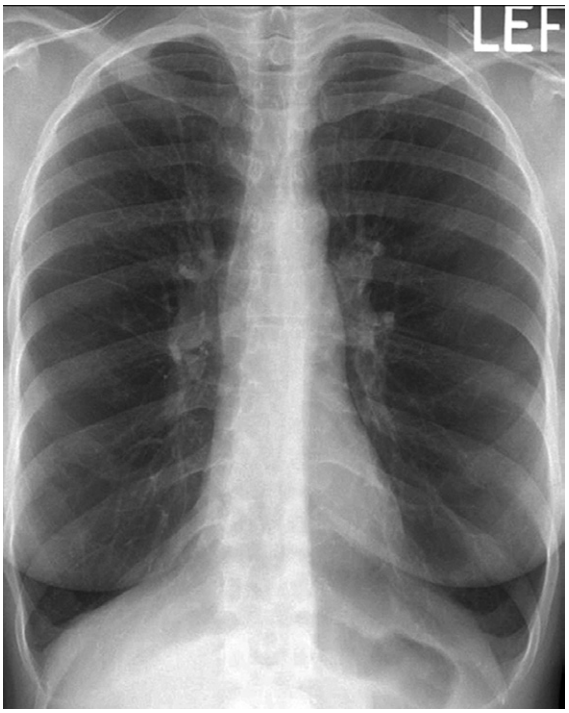

FIGURE 39-13 ■ Frontal chest radiograph in a 51-year-old female with alpha-1-protease inhibitor deficiency presenting for lung transplant evaluation. Note the very large lung volumes with hyperlucency primarily seen in the bases, consistent with panacinar emphysema, as well as flattening of the diaphragms. Contrast the lower lobe lucency in this patient with Figure 39-2, which shows upper lobe hyperlucency in a patient with centriacinar emphysema. *See CT scan video of this patient online.* (Courtesy of Michael B. Gotway, MD, Scottsdale Medical Imaging and the Department of Radiology, University of California, San Francisco.)

compared with the general population, but nearly one half of them died of emphysema.[302] Annual decline of FEV_1 is greater than normal in nonsmokers who are type Pi Z, but it is much greater in smokers who are type Pi Z than in nonsmokers.[303]

Severity of lung disease varies markedly[104,304] and indicates the presence of other modifying factors, which remain to be defined. In addition to cigarette smoking, asthma, recurrent respiratory infections, and unidentified genetic factors have been suggested as possible risk factors for chronic airflow limitation.

Radiographically, Pi Z patients characteristically have more definite evidence of emphysema than seen with garden-variety COPD. The finding of basilar emphysema is not constant in Pi Z patients, but when present, it is strongly suggestive of the diagnosis (Fig. 39-13).[305,306] It is common with advanced disease to see hairline arcuate shadows separating markedly radiolucent areas in the lung bases from the less severely involved upper portions of the lungs.

Liver Disease in Alpha$_1$-Protease Inhibitor–Deficient Phenotypes. Homozygous A1PI deficiency is often associated in infancy with hepatomegaly or hepatosplenomegaly and evidence of cholestasis and elevation of hepatocellular enzymes. Some patients with this abnormality may go on to develop cirrhosis. A1PI deficiency is the most common cause of liver transplantation in children. Because the transplanted liver produces normal A1PI, this effectively cures the disorder.[307] Cirrhosis, often with hepatoma, is second in frequency to emphysema as a cause of death in adults.[308]

Liver disease is a result of the Z form of the mutant protein, which forms aggregates in the endoplasmic reticulum.[309] Normally, this leads to the unfolded protein response and autophagy to remove the aberrant proteins but, in a subset of patients with A1PI deficiency, these responses are lacking,[310] leading to hepatic cell injury and potentially to hepatocellular carcinoma.[311]

Diagnosis of Alpha$_1$-Protease Inhibitor Deficiency. The diagnosis of A1PI deficiency is made by measuring the serum A1PI level, followed by Pi typing for confirmation. A1PI should be excluded in patients with premature onset of chronic bronchitis, emphysema, and dyspnea and in nonsmokers presenting with COPD. A predominance of basilar emphysema should raise the possibility of the genetic defect. Some have advocated testing for all new diagnoses of COPD, citing the high prevalence of undiagnosed A1PI-deficient patients, behavioral change (smoking cessation) opportunities, the economic benefits of avoiding further tests, and uncontrolled trials suggesting benefit from augmentation therapy (see later). Others would argue that augmentation therapy has not yet undergone controlled trials, it is not known whether smokers with a diagnosis of A1PI deficiency would stop smoking, and A1PI testing is an added expense. Moreover, there is concern regarding the adverse psychological consequences of the diagnosis to one who is asymptomatic and, importantly, there is a concern for potential genetic discrimination.

Estimates of the frequency of the Pi ZZ phenotype in North America and Europe range from about 1 in 1600 to 1 in 4000,[312] a prevalence approximating that of cystic fibrosis and suggesting that severe A1PI deficiency is among the most common potentially serious genetic conditions. Of note, rigorous attempts to collect all available cases have garnered 10% of estimated cases at most.[312] This suggests that either most subjects who are type Pi Z are asymptomatic or they are masquerading under other diagnoses such as asthma.

Alpha$_1$-Protease Inhibitor Augmentation Therapy. Augmentation therapy with purified human A1PI for patients with severe A1PI deficiency is based on the concept that a deficient protein is being restored to protective levels.[313] Augmentation therapy was approved in the United States as an orphan indication that showed biochemical efficacy. In the 1980s, the ATS published guidelines for augmentation therapy,[314] suggesting that it should be reserved for patients whose serum concentration of A1PI was less than 11 μmol; it is not indicated for patients with cigarette-smoking–related emphysema who have normal or heterozygous phenotypes. It is also not indicated in patients who have liver disease associated with A1PI deficiency unless they also have lung disease. Subsequently, a randomized trial using CT scan as the end point demonstrated some benefit of

treatment.[315] Randomized, controlled trials using lung function are not yet available, but registry data and small prospective trials suggest benefits of treatment for at least some patients.[316,317]

Persons with normal lung function should be monitored but not treated; augmentation therapy should be considered when lung function is abnormal and especially if serial studies show deterioration. The ATS guidelines[314] make the point that it is inappropriate to define a lower limit of lung function or an upper limit of age for administration of augmentation therapy because it is unethical to withhold treatment that may have benefit even in severe end-stage disease. However, it seems reasonable to weigh carefully the advantages and disadvantages of augmentation therapy and to reach a decision jointly with elderly persons or with those with severe lung function impairment (FEV_1 values < 0.8 L). For severely impaired persons, generally younger than age 50, lung transplantation may be a reasonable consideration.

Research continues to explore the benefits of monthly rather than weekly inhaled augmentation therapy, synthetic elastase inhibitors, and recombinant forms of $alpha_1$-antitrypsin. Nevertheless, costly plasma-derived weekly intravenous therapy remains the mainstay.

TREATMENT

Patients with COPD benefit from treatment.[30] Therapeutic goals include (1) prevention of disease progression; (2) relief of symptoms; (3) improvement in exercise tolerance; (4) improvement in health status; (5) prevention and treatment of exacerbations; (6) prevention and treatment of COPD-related complications; and (7) reduction in mortality. These therapeutic goals may be divided into several components: reduction of risk factors; symptomatic management of stable disease; and prevention and management of exacerbations.

General Approach to Therapy

Several consensus staging systems have been developed to rate the severity of COPD. The GOLD guidelines[30] represent a major change in the strategy of disease management (Fig. 39-14). Earlier guidelines, such as the ATS Statement (1995),[151] described symptomatic management after the patient presented to the healthcare system with specific complaints. Because it is now recognized that most patients lose lung function insidiously for many years prior to diagnosis, earlier and more aggressive diagnosis is warranted. Treatment of previously unidentified individuals can help, not only by preventing progression through controlling risk factors but also by improving symptomatic control. In this context, symptomatic improvement in "asymptomatic" individuals can be achieved if improved physiology is combined with an increased level of activity. To achieve optimum results, pharmacotherapy needs to be combined with rehabilitation (See Chapter 94). In addition, treatment of concurrent morbidity is an important component of a comprehensive treatment plan. Depression is frequent among COPD patients and may be more prevalent than expected based on age and morbidity.[318,319] Although psychiatric dysfunction does not directly compromise exercise performance in COPD patients,[320] even subclinical psychiatric disorders are associated with increased morbidity[321] and may compromise participation in an integrated treatment program. Therefore, current guidelines recommend a proactive program of diagnosis and therapy that includes integrated disease management.[30] A general guide to stepwise introduction of treatment modalities based on disease severity has been suggested. It is likely that treatment intensity will need to escalate with time as severity worsens.

Reduction of Risk Factors

Smoking Cessation

Cigarette smoking is the most important risk factor for the development of COPD, and every effort should be made to help the patient stop smoking (see Chapter 40). Cessation early in the development of COPD can stop the accelerated loss of lung function that characterizes COPD.[322] Cessation later in the course of disease may not be as effective because airway inflammation may persist.[323,324] Nevertheless, cessation at any age reduces overall mortality.[325] Smoking should be regarded as a primary disease.[326] Current recommendations are to provide every smoker with the best chance of achieving a remission at each attempt to quit. This requires both the most aggressive behavioral support program appropriate for the patient as well as pharmacologic support. In addition to nicotine replacement therapy, which is available in several formulations, bupropion, varenicline, and two "off-label" medications are currently supported in guidelines: nortryptiline and clonidine.[326]

Other Risk Factors

It is likely that avoidance of exposures to other noxious dusts and fumes that may occur as a result of environmental or occupational exposures may be of benefit in slowing disease progression, but there are no data to support such an approach and no current guidelines. The association of particulate air pollution with increased acute events including mortality[100,327] suggests that a reduction in such exposures may have benefit even late in the disease.

Influenza vaccination can reduce mortality among elderly patients[328,329] and should be given annually to all COPD patients. Although less data support a benefit of the pneumococcal vaccine, its use is also recommended.[30,330]

Development of New Treatments

A variety of novel therapeutics are being explored to address the complex problems of COPD. These include anti-inflammatory agents directed at blocking inflammatory cell recruitment, activation, and the effect of inflam-

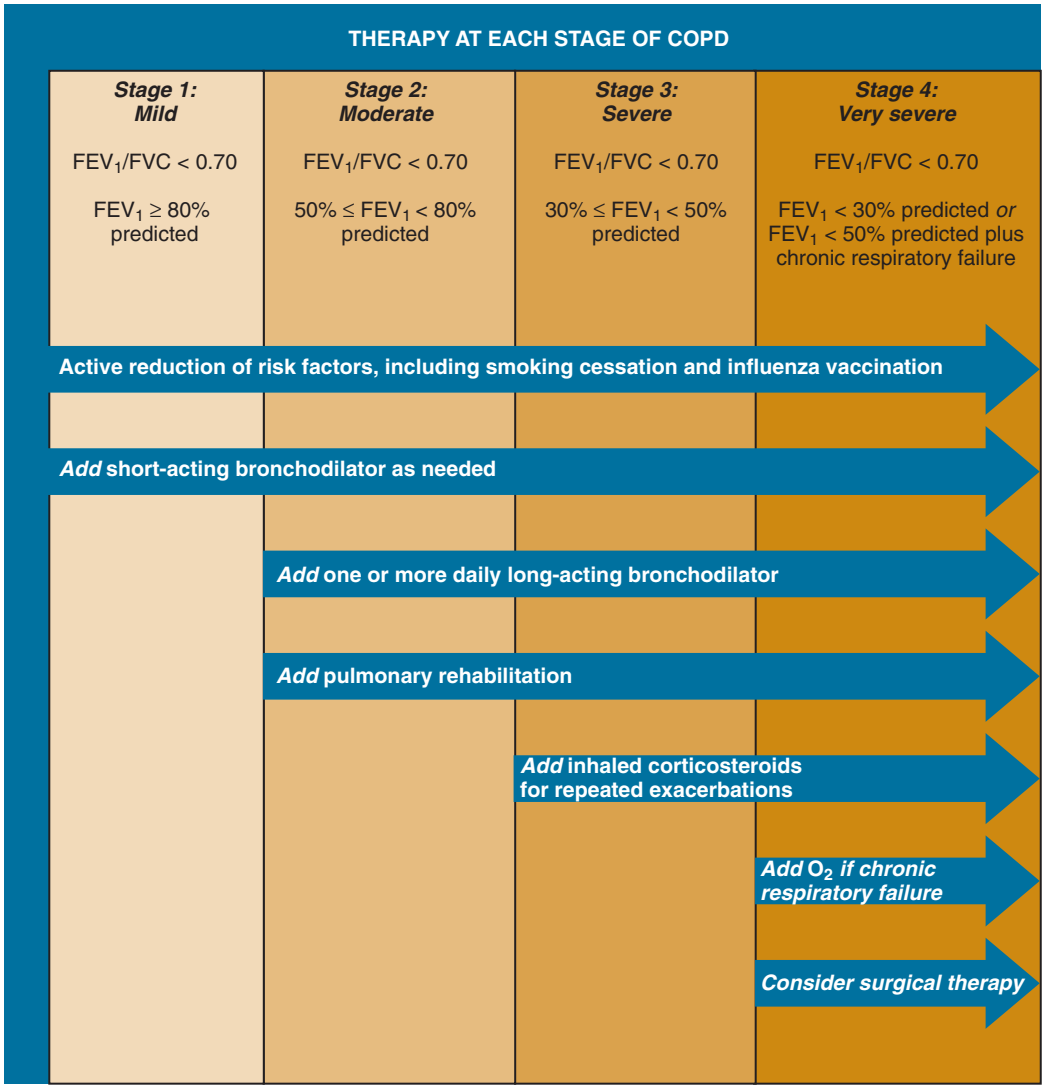

FIGURE 39-14 ■ Step care for COPD patients. The classification and suggested treatments were accessed from the GOLD guidelines. (Redrawn from the Guideline "Global Strategy for Diagnosis, Management, and Prevention of COPD." Updated 12/2009 at http://www.goldcopd.com [accessed 2009].)

matory mediators, as well as treatments that can modify the structural cells of the lung. All studies designed to improve the natural history of COPD face a common problem. Because the disease progresses slowly, a relatively long time is needed to demonstrate a change in the rate of progression.[2] In addition, the changes likely to be observed are small, particularly when compared with the variation in the physiologic measures classically assessed in COPD (e.g., spirometry). As a result, studies of over a thousand subjects for a period of years are needed in order to have adequate statistical power to evaluate changes in the rate of decline of FEV_1.[331] This is a function of the means of assessment and is independent of the intervention. More responsive measures of outcome in COPD are, therefore, urgently needed. A number have been suggested including high-resolution CT, quality of life assessment, and measures of surrogate markers, particularly assessment of inflammation by histology, bronchoalveolar lavage (BAL), induced sputum, markers of elastin turnover, and exhaled air analysis. The hope is that it will be possible to prevent the progression of emphysema in persons who have the beginnings of this disease but are unable to stop smoking.

Pharmacotherapy for Chronic Obstructive Pulmonary Disease

A variety of drugs are frequently prescribed for patients with COPD. The goals of treatment vary and each agent should be assessed in terms of both its efficacy in achieving treatment goals and its associated side effects and risks. The U.S. Food and Drug Adminstration (FDA) recommends five treatment end points be considered for COPD: improvement in airflow obstruction, providing symptom relief, modifying or preventing exacerbations, altering disease progression (including mortality), and modifying lung structure. To date, the primary roles of

pharmacotherapy have been in symptom improvement and in the prevention and treatment of exacerbations.

Symptomatic Therapy

Current symptom-based therapies are primarily directed at reducing airway smooth muscle tone or at reducing inflammation. Because some of the symptoms experienced by COPD patients are due to systemic effects of the disease, treatment directed at extrapulmonary targets may also be of benefit. Finally, effective treatment of the COPD patient requires effective integration of pharmacologic treatment and nonpharmacologic therapy, most importantly pulmonary rehabilitation (see later).

Bronchodilators. In the presence of bronchospasm, as occurs in asthma, bronchodilators can cause marked improvement in airflow. Even normal individuals, however, have some degree of airway smooth muscle tone, and bronchodilators often result in small improvements in airflow that are not clinically meaningful. Some COPD patients have large improvement in airflow following administration of bronchodilators. Most, however, have modest improvements that resemble in magnitude those of normal individuals, which may be due to alterations in resting tone rather than an effect on "bronchospasm." Even these modest improvements, however, may be of benefit for the compromised COPD patient. In addition, improvement in lung volumes, particularly in dynamic hyperinflation, may also occur following bronchodilator treatment. As a result, many patients with COPD will have reduced dyspnea and improved exercise tolerance with bronchodilator therapy, even if improvement in resting spirometry is very modest.[332] Finally, the response of a COPD patient to a bronchodilator can vary from day to day.[333,334] Thus, patients with COPD should always be given a clinical trial of bronchodilators. Both spirometric response and clinical response should be used to gauge effectiveness.

Bronchodilators are often used in COPD both on a chronic basis and also as needed for "rescue."[30] Unlike asthmatic patients who experience dyspnea when acute bronchospasm occurs, patients with COPD most commonly experience dyspnea due to increased respiratory demands, such as occurs with exertion. Rather than treating such episodes with "rescue" medications, it is more appropriate to prevent them, if possible, with maintenance therapy.[335] For such a purpose, long-acting bronchodilators are probably both more convenient and more effective, and their use is recommended. When rescue is needed, a rapidly acting agent is desirable.[30]

β-Agonists. This term refers to the group of medications that bind to the β-adrenergic receptor present on airway smooth muscle, resulting in bronchodilation and improvement in airflow in some patients with COPD. β-Agonists have also been reported to increase ciliary beating frequency and to improve mucus transport[336] and may improve endurance of fatigued respiratory muscles.[337]

Available β-agonists can be divided into "short-acting" and "long-acting" categories. The short-acting agents have a relatively rapid onset of action after inhalation, on the order of 5 to 15 minutes, that persists for 2 to 4 hours. A number of short-acting β-agonist (SABA) compounds are available. The most widely prescribed is albuterol (salbutamol). Recently, the racemer of albuterol has been introduced in hopes of providing equivalent efficacy with fewer side effects (discussed later). The SABAs are available in formulations for inhalation and oral intake. The inhaled route is preferable owing to more favorable ratio of therapeutic effect to undesirable side effects.

Long-acting β-agonists (LABAs) typically have a longer onset of action but produce bronchodilation for up to 12 hours or more. The two agents currently available are formoterol, which has an onset of effect similar to short-acting agents, and salmeterol, which is somewhat slower in onset. Salmeterol has been more extensively studied than formoterol for nonbronchodilator effects.[338] It has been noted to have anti-inflammatory effects, to reduce edema, and to reduce airway epithelial cell injury in model systems.

Mode of Administration. The preferred mode for administering β-agonists is by inhalation using a metered-dose inhaler (MDI) or a dry powder inhaler (DPI). These methods are superior to oral administration in improving FEV_1 and produce fewer side effects.[339] A large number of studies have also convincingly shown that a properly used MDI is as effective as and less expensive than nebulized aqueous solutions of β-agonist for most individuals. The ease of use of DPIs and the lack of necessity for a propellant suggest they will become the standard. However, some patients with COPD may be unable to generate the flow rates needed for effective use of these devices. Nebulizers may be more effective in patients too weak to use an inhaler device, in those with altered mental status,[340] or in those whose inspiratory capacity is too limited to permit effective inhalation[340]; intermittent positive-pressure breathing is not indicated for this purpose.[333]

Treatment Effects.

- Improvement in airflow obstruction. The magnitude of improvement in lung function, as assessed by the FEV_1, in response to inhaled β-agonists is less in COPD than in asthma and, by definition, does not normalize. The proportion of patients who experience a "positive bronchodilator response" as defined by the ATS is 25% to 30% on any given day. More than 50% of patients have a positive response on one or more occasions when tested serially over a 6-month period.[334] Both SABAs and LABAs produce, on average, modest improvements in FEV_1. For salmeterol, reported improvements are 50 to 120 mL, depending on dose in patients who are "poorly reversible," and somewhat higher in those with a greater than 15% improvement in FEV_1 after administration of an SABA.[341]
- Symptom relief. β-Agonists, particularly the LABAs, have been reported to improve symptoms, including those utilizing the St. George's Respiratory Questionnaire (SGRQ). The magnitude of improvement is modest, but significantly better than

placebo. Effects on dyspnea and exercise tolerance are variable, but when a difference was noted, it was in favor of the use of LABAs.[341,342]
- Exacerbation prevention. The LABAs have been reported to reduce exacerbation frequency by 20% to 30%.[341,343]
- Alteration of disease progression. This is usually measured by quantifying the rate of change in FEV_1 over a several-year period. The available data suggest that β-agonists do not change this rate of decline by a clinically meaningful amount.[142]
- Modification of lung structure. There are no human data available to suggest that β-agonists modify lung structure.

Side Effects. Although systemic effects are more common with oral formulations, they may occur with any β-agonist formulation. Tremor, palpitations, anxiety, and insomnia are the most common side effects. Ventricular arrhythmias and hypokalemia may also occur. The heart, in addition to β_1-receptors, also has β_2-receptors, and these probably mediate the cardiac effects of the currently used selective β_2-agonist bronchodilators.[344] Because the systemic side effects are due to drug absorbed from both the lung and that deposited in the pharynx, systemic side effects associated with MDI use may be reduced with a spacer device that reduces oral deposition. DPIs, which generally result in less oral and pharyngeal deposition may be desirable in this situation.

More recently, levalbuterol, the (R)-enantiomer of albuterol, has been marketed based on the observations that it has a shorter half-life than the (S)-enantiomer, is the active constituent that binds to the β-adrenergic receptor and produces bronchodilation. In addition, the (R)-enantiomer may be preferable because the (S)-enantiomer may promote airway inflammation and be associated with some of the systemic side effects. Albuterol is typically available as a racemic mixture of both enantiomers, so levalbuterol was expected to be as efficacious with a more desirable side effect profile. In practice, this is true but the magnitude of the difference in side effects is small and there is some debate as to their clinical relevance.[345] For patients who experience significant tachycardia or tremor while using racemic albuterol, use of levalbuterol may reduce these symptoms.

Owing to reports implicating the LABA salmeterol in an apparent increased rate of death in patients with asthma, there has been concern as to whether this could also be happening in COPD. A recent analysis concluded that this risk is not seen in patients with COPD and that the medications are safe to use.[342]

Many patients with COPD have concurrent cardiac disease and have strong indications for β-blocker therapy. Nonselective β-blockers should be avoided in COPD patients. Use of selective β_1-blockers has been reported to improve survival in patients with cardiac disease and, in meta-analyses, does not adversely affect lung function.[346] Conversely, β-agonist bronchodilators have not been associated with increased cardiac disease in COPD clinical trials that excluded patients with unstable cardiac disease.[347–352] The use of bronchodilators other than β-agonists may be preferred in patients with unstable cardiac disease, if possible, because β-agonists may exacerbate concurrent cardiac disease.[353,354] However, the possibility that other classes of bronchodilators are associated with increased cardiac mortality[355] makes such choices difficult, particularly without an adequate evidence base (see the following section on Anticholinergic Therapy).

Anticholinergics. Anticholinergic bronchodilators have been used in Asia since antiquity and in Western medicine since the early 1800s.[356] Most of these traditional compounds (e.g., atropine) carry a weak ionic charge and thus move easily across the blood-brain barrier; their use is associated with systemic and central nervous system side effects. For use as bronchodilators in COPD, they have been largely replaced by quarternary amines, such as ipratropium and glycopyrrolate, which, having a stronger ionic charge, do not cross the blood-brain barrier and have limited absorption into the circulation. As a result, they have a very high therapeutic ratio (see Chapter 8).

Anticholinergics work as bronchodilators by blocking the action of acetylcholine on M_3 muscarinic receptors, which induce contraction of airway smooth muscle.[357] Tiotropium has a prolonged duration of action because it dissociates from the receptor extremely slowly.[358] When administered chronically, the bronchodilator effect of tiotropium increases with daily dosing and is maximal after 1 week.[359] Because it dissociates from the M_2 receptor faster than from the M_3 receptor, tiotropium demonstrates some receptor selectivity. The clinical significance of M_2-receptor inhibition is undefined. However, M_2 receptors function as feedback inhibitors of acetylcholine release, and these receptors may inhibit bronchoconstriction in COPD patients.[360] M_2 antagonism, therefore, may have untoward effects, and the relative lack of effect of tiotropium on M_2 receptors may be a potential advantage.

Many cells, including airway epithelial cells, express the enzyme choline acetyl transferase,[361] suggesting that non-neuronal cells can produce acetylcholine. In addition, muscarinic receptors are present on many cells in addition to airway smooth muscle cells. In airway smooth muscle cells, acetylcholine stimulates the production of neutrophil chemotactic activity[362] and an anticholinergic could, theoretically, have an anti-inflammatory action. The clinical significance of these findings is unknown.

"Short-acting" agents currently in use include ipratropium and, in some countries, oxitropium which produce bronchodilation in 10 to 15 minutes and last for 4 to 6 hours. The long-acting anticholingergic tiotropium is slower in onset, achieving peak bronchodilator activity after 1 to 2 hours, but has a markedly prolonged duration of action and is used once daily.

Mode of Administration. The preferred mode of administration is by inhalation using an MDI or DPI. Ipratropium is available in several formulations including a nebulized solution. Tiotropium is available only in a DPI. Glycopyrrolate is available as a solution for nebulizer use, although it is not approved by the FDA for this purpose.

Treatment Effects.

- Improvement in airflow obstruction. Anticholinergics produce a modest improvement in FEV_1 of a magnitude similar to that reported for β-agonists.[363,364]
- Symptom relief. Anticholinergics produce modest benefits in symptoms and health-related quality of life (HRQOL) in patients with COPD.[343,363] In clinical trials, tiotropium improves airflow and lung volumes, reduces dyspnea, and improves health status and exercise performance.[359,365-368] The improvement in exercise performance appears to be due to reduction in hyperinflation.[369]
- Exacerbation prevention. Tiotropium and ipratropium in combination with albuterol have been reported to reduce risk of COPD exacerbation. The magnitude of the risk reduction is 20% to 25%.[343,364]
- Alteration of disease progression. A recent prospective trial of tiotropium designed to test the hypothesis that its use would reduce the rate of decline in FEV_1 failed to show a benefit in this measure.[363] There was a trend of decreased mortality in the tiotropium-treated patients that did not reach statistical significance.
- Modification of lung structure. There are no human data available to suggest that anticholinergics modify lung structure.

Side Effects. Local toxicities can occur. For example, if sprayed directly in the eye, anticholinergics can precipitate acute attacks of glaucoma. Some systemic effects can be seen including dry mouth associated with tiotropium and urinary retention.

The report from the Lung Health Study[355] of increased cardiac mortality that did not achieve statistical significance among the subjects randomized to treatment with ipratropium raised concerns about cardiac toxicity related to anticholinergic use. Several subsequent publications have provided additional data related to this issue. Two reports have suggested increased cardiac events in patients using anticholinergic therapy. One is a retrospective database review that found an increased risk of all-cause mortality among a cohort of men prescribed ipratropium for COPD.[370] The second is a meta-analysis of anticholinergic use in COPD, the majority of which was ipratropium, that found an increased risk of cardiovascular death, myocardial infarction, and stroke in patients treated with anticholinergic therapy.[371] These data are in contrast to prospectively collected data in a randomized trial of tiotropium, which showed a significant reduction in the rate of cardiovascular events in patients with tiotropium and did not show any increase in mortality in the tiotropium-treated patients.[363] It is unclear whether these contradictory data reflect differences between tiotropium and ipratropium, the former being more selective for M_1 and M_3 receptors, characteristics of the patient population, confounding by indication, or other factors.

Methylxanthines. Theophylline is the only methylxanthine currently used to treat COPD patients. It has modest bronchodilator activity, but it also has additional effects that may be therapeutic.[372] In this regard, theophylline exerts anti-inflammatory effects,[373] has modest inotropic and diuretic effects, and may augment skeletal muscle strength. Whereas bronchodilator effects are modest,[374,375] subjective responses may be greater than the objective improvements in FEV_1,[376] although several studies have failed to observe such benefits.[377,378] If used, the currently recommended target blood levels are 5 to 10 μg/mL, which often achieve adequate clinical response and provide a greater margin of safety than higher levels. Dose-related adverse effects of theophylline include nausea and vomiting, seizures, and arrhythmias. Its use is also complicated by many drug interactions and, because it is cleared by hepatic metabolism, concurrent morbidity that affects liver function, including congestive heart failure and nonspecific responses to viral infections, can alter theophylline levels.

Combination Therapy with Bronchodilators. It is current practice to begin bronchodilator therapy with a single agent. However, most patients with COPD have modest responses. Combination therapy with a second or third bronchodilator from different classes can result in improved bronchodilator and clinical effect. Data support essentially all possible combinations of bronchodilator classes. Both SABAs and LABAs have been evaluated with both short- and long-acting anticholinergics[379-381] and with theophylline.[374,376] Anticholinergics and theophylline have been evaluated,[382,383] as have all three bronchodilators in combination.[384] Although clinical responses among individual patients may vary, bronchodilator combinations are both rational and encouraged by current guidelines.[30,385] A fixed combination containing the SABA albuterol with the short-acting anticholinergic ipratropium has proved to be widely popular. In clinical trials, its bronchodilator efficacy is superior to that of either agent used alone.[379] Other fixed combinations of inhaled bronchodilators are likely to become available in the future. Their convenience alone is likely to make them popular with patients and physicians.

Choice of Bronchodilators. To date, the use of bronchodilators is for symptom relief and their use is empirical. Any of the bronchodilators may be used, the choice of agent depending on patient and physician preference and on cost.[30,385] For regular use, long-acting agents have advantages of convenience and, probably, efficacy, as discussed previously. When used empirically, it is reasonable to give them a clinical trial in each patient. If little benefit is obtained, it may be reasonable to forgo therapy. However, failure of a patient to respond may be due to several reasons. Poor compliance and ineffective use of the device must be considered. Even if used correctly, however, many patients with COPD may fail to benefit from bronchodilator therapy unless it is integrated into a rehabilitation program (see later and Chapter 94).[386] The reason for this is the severely restricted activity and marked detraining present in many COPD patients. Optimizing physiology of the lung is only one requirement to improve the patient's condition. Even if the patient fails to respond, a repeat clinical trial may be warranted in the future because, with disease progression, responsiveness may increase.

During an acute exacerbation of COPD requiring emergency room treatment, ipratropium appeared to be only equally effective to inhaled β-agonists, with no further benefit from combination therapy,[387,388] and ipratropium did not provide additional improvement when added to an emergency room regimen of inhaled β-agonists and corticosteroids.[388] There is one report, however, that adding ipratropium to β-agonist therapy accelerated the improvement of COPD exacerbations and shortened the duration of emergency room treatment.[389]

Corticosteroids

Inhaled Glucocorticoids. Because inflammation is believed to contribute to the pathogenesis of COPD, it is appealing that anti-inflammatory therapy should alter the disease course. Data supporting this approach, however, are limited.

Treatment Effects.

- Improvement in airflow obstruction. Inhaled glucocorticoids (ICS) cause a modest improvement in airflow. The effect is usually a 50- to 100-mL increase in FEV_1, compared to the 200- to 300-mL benefit achieved with bronchodilators.[390,391] However, glucocorticoids may result in further benefit when added to bronchodilators, and thus, combinations are rational (also see later).[392-394]
- Symptom relief. ICS have been reported to produce modest improvement in symptoms and to slow the deterioration in HRQOL that is seen in untreated COPD. They have not been demonstrated to have a significant effect on exercise capacity.[395]
- Exacerbation prevention. ICS reduce the frequency and severity of exacerbations in COPD.[142,392,393,396] The mechanism for this effect remains to be determined, but it has been observed with both fluticasone and budesonide and, therefore, appears to be a class effect. Current guidelines, therefore, recommend that ICS can be used in patients with COPD experiencing frequent exacerbations,[30] which are more common as FEV_1 declines below 50% predicted. The magnitude of risk reduction is comparable to that seen with LABAs or anticholinergics, approximately 20% to 25%.[343,363]
- Alteration of disease progression. Four large trials evaluated the possibility that inhaled glucocorticoids may affect the rate of decline in FEV_1.[390,391,397,398] None resulted in a statistically significant reduction in the rate at which lung function declines. A number of meta-analyses have been published examining the effect of the regular use of ICS on rate of decline in FEV_1, with the majority concluding that there is no significant effect on this measure.[399-401] With the current evidence base, therefore, ICS are not currently recommended for routine use to prevent lung function decline in COPD.[30,385] Retrospective analyses of several databases have suggested that use of ICS is associated with reduced hospitalization and reduced mortality.[154,402] A prospective trial examining the impact of fluticasone, with or without concomitant salmeterol, reported a reduction in mortality that failed to reach statistical significance ($P = .052$ for combination therapy). In addition to the mortality data, a retrospective analysis of a Veterans Administration pharmacy database demonstrated a reduced incidence in lung cancer among users of ICS.[403]
- Modification of lung structure. There are no currently available data in humans that the use of ICS has any effect on lung structure.

Side Effects. ICS can have adverse effects. Local effects include oral candidiasis (thrush) and dysphonia.[390] Systemic effects include increased bruising[390] and reduced bone density.[398,404] The clinical importance of these effects remains uncertain, however, but appropriate caution and monitoring is essential. In addition, while reducing the frequency of COPD exacerbations, ICS have been associated with an increased incidence of pneumonia.[142]

Selecting Patients for Inhaled Glucocorticoid Therapy. No paradigm exists that effectively predicts which COPD patients benefit from ICS. The 1995 ATS guidelines[16] recommended an oral glucocorticoid challenge but, not only is this inaccurate,[405] the challenge has adverse effects and such an empirical test is no longer recommended.[30] A trial of ICS is more reasonable. Improvements in FEV_1 can occur within weeks, but patients may perceive a symptomatic benefit only after several months.[392,393,406] Because patients with more severe disease, particularly those with FEV_1 less than 50% predicted, are more likely to experience frequent exacerbations, it is this group who have the most to gain from exacerbation prevention. If used for such a goal, however, it is unlikely that the clinician can gauge whether a benefit has occurred in an individual patient because most patients experience only a few exacerbations annually. A reduction of one or two may not be easily recognized. If ICS are started for exacerbation prevention, therapy probably will be continued indefinitely in the absence of side effects.

Combination Glucocorticoid and Long-Acting β-Agonist Inhalers. Potential synergistic interactions between LABAs and ICS have attracted considerable attention, particularly in the treatment of asthma. Fixed combinations of ICS and LABAs have been tested in both asthma and COPD. These trials demonstrate added clinical benefits of the combinations over the individual components.[142,392,393,407] Their use has become popular among patients with COPD. Whether this is due entirely to the convenience of the formulations, to compliance benefits that ensue when an anti-inflammatory drug is added to a bronchodilator, or to synergistic pharmacologic effects is undetermined.

Systemic Glucocorticoids. If at all possible, systemic glucocorticoids should be avoided in the treatment of stable COPD. The regular use of systemic glucocorticoids is associated with increased mortality,[408] although this may be due to the severity of the disease as much as effects of the drug. It is clear, however, that systemic glucocorticoids have major adverse side effects that should be avoided, if possible. A randomized study demonstrated no difference in FEV_1, symptoms, or exacerbation frequency in a cohort of patients on daily glu-

cocorticoids who were randomized to steroid withdrawal in a double-blind, placebo-controlled study design, reinforcing the recommendation to limit parenteral glucocorticoid use to short-term administration for the treatment of exacerbations.[409]

Cromolyn Sodium Nedocromil and Leukotriene Antagonists. There are no data establishing a role for cromolyn, nedocromil, or cysteinyl leukotriene antagonists in treating COPD. Nevertheless, a clinical trial may be undertaken if the patient is properly informed, particularly in patients with evidence of hyperreactive airways.[410]

Thinning and Mobilization of Airway Secretions. Increased mucus production by hypertrophied and hyperplastic airway submucosal glands and goblet cells together with impaired mucociliary clearance and cough are frequent in COPD patients. Cough and sputum production are also the defining features of chronic bronchitis, although airflow limitation can result from other processes. Sputum expectoration in the stable COPD patient may range from only a few milliliters on awakening in the morning to frank bronchorrhea with day-long production of sputum exceeding 100 mL/day.

The most successful means of controlling excessive airway mucous secretion is avoidance of inhaled irritants. Smoking cessation usually reduces sputum expectoration dramatically over several months[19]; the early period of smoking cessation may be associated with more difficult cough and expectoration, especially in the morning. Individuals who complain that their cough worsens upon quitting should be encouraged that this generally resolves. Patients should avoid smoke-filled rooms and stay indoors when air pollution reaches dangerous levels. Air conditioners and electrostatic precipitators can reduce indoor air pollution, but their clinical benefits, if any, are undefined.

A large number of remedies have been proposed and are in use to assist in the control of secretions. None is supported by evidence from rigorous clinical trials.[30] With the lack of evidence, the clinician must individualize patient management. Although, traditionally, patients have been encouraged to drink several glasses of water per day, aggressive hydration in COPD patients has not been shown to improve sputum volume, the physical properties of sputum, or the ease of expectoration.[411] Bland aerosols of water or saline are also of limited value in clearing airway secretions in COPD and such aerosols can precipitate bronchospasm.[412] Some patients expectorate thick secretions more readily after inhaling steam from hot water in a sink.

Mucolytic agents are not recommended for routine use[30] and are not commonly used in the United States, but some agents are widely used elsewhere. *N*-Acetyl cysteine, in particular, is popular in Europe. The agent is an active antioxidant, and this may be its means of action rather than its properties as a mucolytic. Because it can also reverse epithelial metaplasia in an animal model,[413] it continues to attract interest. This agent has been evaluated clinically and was thought to be associated with an improvement in symptoms and in exacerbation frequency.[414] A subsequent prospective, randomized trial failed to show any benefit in patients with COPD, with the possible exception of reducing exacerbations in patients not taking ICS.[415]

Once available in the United States, iodinated glycerol may have had some symptomatic benefits,[416] but has been removed from the marketplace because of toxicity concerns. Saturated solution of potassium iodide (SSKI) may be an alternative. Recombinant human DNAse, currently used for cystic fibrosis, has not proved useful in chronic bronchitis despite initial favorable reports in acute exacerbations of bronchitis.[417]

Expectorants. Therapy with β-agonists and theophylline enhances mucociliary clearance. Bronchorrhea may be controlled by oral corticosteroids[418] and by inhaled indomethacin[419] and atropine.[420] Ipratropium bromide is not used to influence airway mucous production or clearance. The role of oral expectorants in promoting mucous clearance in COPD patients remains controversial; the consensus has been that agents like guaifenesin and glyceryl guaiacolate provide little or no benefit in most patients.[421]

Controlled Coughing. Cough is usually impaired in COPD patients, with frequent uncontrolled coughing inducing fatigue, chest wall pain, and dyspnea. An effective cough is the best means for expelling airway mucus. Controlled cough and the forced expiratory technique, or huffing, have been advocated as safe, useful alternatives.[422] With controlled cough, patients are taught to inspire deeply, hold their breath for a few seconds, and then cough two or three times with their mouth open and without taking another breath. After repeating this sequence several times, patients should rest before beginning the procedure again. Controlled cough is believed to work because the cleansing action of cough in large airways takes place primarily during the first one or two coughs of a cough sequence.[423] The forced expiratory technique consists of one or two forced exhalations without glottic closure, starting at mid lung volume. This is followed by a forced expectoration or a controlled cough at high lung volume to clear mucus from the central airways.

Physical Therapy. It is appropriate to try postural drainage in patients who are major sputum producers (>30 mL/day) and who have difficulty coughing up their secretions. This technique is safe in COPD patients who have negligible changes in lung volumes and arterial oxygen saturation (Sa_{O_2}) after being positioned in up to a 25° head-down tilt for 20 to 30 minutes.[424] An inhaled bronchodilator should be administered 20 to 30 minutes before postural drainage.[425] If difficulty in clearing airway secretions persists, family members can be taught cupped-hand chest wall percussion or the use of an electromechanical percussor. The routine use of postural drainage and chest percussion and vibration in COPD patients is not indicated. Patients who produce only small quantities of sputum, either when stable or during an acute COPD exacerbation, benefit minimally or not at all.[426]

Therapy for Dyspnea

Pharmacologic. Many COPD patients, especially those with severe emphysema, experience intolerable dyspnea,

especially during exertion, which is poorly responsive to standard bronchodilator therapy.

Some patients have been reported to benefit from opioid narcotics, and this can be considered in patients with advanced, not yet terminal, COPD when dyspnea is disabling.[427]

Carotid Body Resection. Of historical interest, bilateral but not unilateral carotid body resection was reported to relieve dyspnea in patients with severe COPD, during both rest and exercise, mainly because of a large fall in respiratory rate, minute ventilation, and therefore, probably dynamic hyperinflation. However, most patients developed worsened hypoxemia and hypercapnia, and death may have been hastened by such surgery.[428]

Long-Term Oxygen Therapy. Two studies, the British Medical Research Council trial[429] evaluating oxygen for 15 hr/day versus no oxygen and the National Institutes of Health (NIH) Nocturnal Oxygen Therapy Trial[430] comparing 12 versus 24 hours of oxygen/day, have firmly established a place for prolonged long-term oxygen therapy in the management of severe COPD. Long-term oxygen therapy extends life in hypoxemic COPD patients; the 24-hour regimen is more beneficial than the 12-hour regimen.[430]

Other benefits of continuous oxygen therapy are a reduction in hematocrit,[430] modest neuropsychological improvement,[431] and some improvement in pulmonary hemodynamics.[432] The dramatic reduction in the prevalence of cor pulmonale has been attributed to routine use of long-term oxygen in hypoxemic COPD patients. Oxygen therapy may also improve dyspnea and the work of breathing by reducing airway resistance[433] and decreasing minute ventilation needs.[434] Home oxygen therapy causes only small increases in arterial P_{CO_2} in patients with hypercapnia[435] and does not result in pulmonary oxygen toxicity.[436] Although patients must be taught the dangers of smoking during oxygen use and some other simple precautions, there is no appreciable increase in fire hazard.[437]

Indications. Long-term oxygen therapy should be prescribed for patients who have a resting arterial P_{O_2} of 55 mm Hg or less while breathing air. For those whose resting arterial P_{O_2} is between 56 and 59 mm Hg, long-term oxygen therapy is indicated if they demonstrate erythrocytosis (hematocrit ≥ 55%) or evidence of cor pulmonale (see Table 39-4). Stable ambulatory patients should meet these criteria after being on an optimal treatment regimen for at least 30 days.[438–440] Patients recovering from a bout of acute respiratory failure may be given ambulatory oxygen treatment even though they have not been observed for sufficiently long periods. They must be reevaluated after approximately 1 month, however, to ascertain that they meet the necessary criteria for long-term oxygen.

Oxygen during Exercise. Patients with an arterial P_{O_2} of 60 mm Hg or higher while breathing room air may develop worsening hypoxemia with exercise. In addition, oxygen therapy has been shown to improve exercise endurance in many studies,[441,442] in part because of greater oxygen transport and improved oxygen utilization by exercising muscles.[443,444] Oxygen has also been found to delay fatigue in exercising ventilatory muscle, as shown by the late appearance of abdominal paradox and a delayed fall in the high-to-low frequency components of the diaphragm electromyogram (a marker of fatigue).[445] Patients participating in exercise training programs benefit from supplemental oxygen, even in the absence of hypoxemia.[446] This has been attributed to a reduced ventilatory rate when breathing oxygen, due to suppression of the carotid body, which results in less dynamic hyperinflation and thus permits a better training effect. However, it makes little sense to perform exercise testing or prescribe oxygen for patients during exercise if they undertake little or no exercise.

Oxygen during Sleep. Patients with COPD typically have a drop in arterial oxygen tension during sleep, particularly those patients with mild resting hypoxemia.[447] This occurs in roughly 50% of patients with daytime resting Sa_{O_2} less than 95%, which represents approximately 5% of the total COPD population.[447] This desaturation is the result of changes in the ventilatory pattern during sleep, particularly during rapid eye movement (REM) sleep, resulting in alveolar hypoventilation, and occurs in the absence of frank sleep apnea.[448] This has prompted concern over the sequelae of recurrent episodes of hypoxemia in this population and has resulted in the recommendation that a clinical trial be performed to determine whether supplemental oxygen produces measurable health benefit.[449] Several smaller studies have failed to show any benefit arising from nocturnal oxygen supplementation in patients with Sa_{O_2} less than 90% for more than 30% of sleep.[450–452] Despite the lack of data supporting its efficacy, many practitioners continue to prescribe supplemental oxygen for patients with nocturnal desaturation.[453]

Modes of Administration

Nasal Cannula. The most frequently used oxygen delivery system at rest is the nasal cannula at a flow rate sufficient to achieve an arterial P_{O_2} of 60 to 75 mm Hg (Sa_{O_2} > 90%). In patients using continuous oxygen, it is common practice to increase the resting oxygen flow rate by 1 L/min during sleep and exercise to prevent falls in arterial P_{O_2} during these periods. For patients who qualify for oxygen only during sleep or exercise, the oxygen flow rate should be set to maintain an Sa_{O_2} of 90% or greater.

Ambulatory Systems. A primary goal of oxygen therapy is to allow all patients to be as active as possible, both in the home and, where appropriate, outside it. Attaining this goal requires prescription of special equipment permitting ambulation. Electrically driven concentrators with a 50-ft length of tubing along with small tanks of compressed oxygen for portable use in a stroller may be used for patients who spend only brief periods outside the home. Nevertheless, concentrators, because of their low equipment and service costs, are often provided to patients who should be using a liquid system. Vendors have been motivated to do this because home oxygen has been reimbursed under a fixed schedule, keyed to the prescribed oxygen flow rate, regardless of the oxygen system used or the needs of the patient.[454]

Liquid oxygen systems with refillable portable units are the most flexible but are also more expensive.[438,454,455] Most recently, several portable concentrators have been introduced, powered by self-contained batteries. Several of these devices are approved for use on commercial airlines, eliminating the need for patients to arrange for supplemental oxygen during airline travel.[456] Battery life and weight remain limitations, but this area of technology is rapidly evolving.

Conserving Devices. Several oxygen-conserving devices are now available that improve the efficiency of oxygen delivery by collecting oxygen flowing during expiration or by providing oxygen flow only during inspiration. These systems result in oxygen savings of 50% or more, thereby prolonging the time of use of ambulatory reservoirs. The types of systems that have gained widest acceptance are a reservoir pendant leading to a two-pronged nasal cannula (Oxymizer; Chad Therapeutics, Inc, Chatsworth, CA) and several demand oxygen delivery systems.[440]

Transtracheal Catheters. Transtracheal catheters are inserted permanently into the trachea. The respiratory dead space is filled with undiluted oxygen flowing from the catheter, thus providing high-concentration oxygen early in inspiration. Several transtracheal catheter systems are available.[457] These systems are invasive and are associated with a wide range of complications including occasional life-threatening tracheal obstruction by mucous balls.[458,459] However, they may correct severe hypoxemia in COPD patients who are refractory to high-flow oxygen by nasal cannula.[460] They can be almost completely concealed by clothing and result in increased compliance by some patients who will not accept the visibility of a nasal cannula.

Commercial Air Travel. The cabins of commercial airliners flying in the stratosphere are pressurized to an altitude between 5000 and 10,000 ft. Accordingly, patients with COPD in these cabins are subject to the added stress of a reduced inspired oxygen partial pressure. The arterial P_{O_2} may fall below 40 mm Hg in some patients with COPD.[461] Fortunately, extensive experience has proved that flying without supplemental oxygen is safe for most subjects with COPD.[462] Hypercapnic COPD patients should employ supplemental oxygen while flying. Normocapnic patients with a sea level arterial P_{O_2} above 68 mm Hg generally have a flight arterial P_{O_2} above 50 mm Hg and do not require supplemental oxygen.[461,463]

In flight desaturation can be measured by a hypoxic challenge,[464] which correlates well within flight saturation.[465] The clinical utility of such testing, however, is uncertain.[1] One hundred percent oxygen at a flow rate of 1 to 3 L/min by nasal cannula should provide a safe arterial P_{O_2}.

To arrange for in-flight oxygen, patients should contact the airline more than 48 hours in advance and be aware that there will be a supplemental charge for oxygen use. The patient's physician may be contacted by the airline for an oxygen prescription as well as for medical clearance to fly.[464] Because some airlines provide only face masks for oxygen delivery, patients should bring their own nasal cannulas. The patient also should know that the airline companies are not responsible for providing oxygen at stopover points or at the final destination.[464] As mentioned previously, several of the recently introduced portable concentrators have been approved by the Federal Aviation Administration (FAA) for use on commercial airliners; participation by carriers is voluntary, so patients should check with the airline on which they plan to travel.[456]

Compact modern respirators can be brought into airplanes by patients, although this usually requires the purchase of an additional seat. However, only gel-cell batteries are approved for air travel. Some airlines provide inverters that convert cabin power to a usable form of electricity for respirators.[466]

Finally, if the patient has major bullous disease, the physician should always warn the patient that ascent to high altitude can precipitate life-threatening pneumothorax. Such a patient should probably not fly.

Pulmonary Rehabilitation

Pulmonary rehabilitation, which attempts to return patients to their highest possible functional capacity, has become an essential component in comprehensive care for patients with severe COPD.[16] (See Chapter 94 for a detailed discussion of rehabilitation.) Numerous studies have confirmed the overall value of a comprehensive rehabilitation program for COPD patients.[467] The benefits are improved independence and quality of life, decreased hospital days, and improved exercise capacity. Lung function, assessed by FEV_1, is not improved. Despite the lack of improvement in airflow, the effects of rehabilitation on health status ("quality of life") are generally much greater than seen with pharmacologic treatments.[468] Whereas all components contribute to patient well-being, exercise training is key.[469]

Exercise conditioning is the single most important aspect of rehabilitation and has been repeatedly shown to improve exercise capacity and endurance in COPD patients, albeit only modestly. Patients should undertake both general exercises and specific muscle training. As with any exercise program, gains in conditioning are lost if the exercise program is stopped. Maintenance of exercise training, therefore, should be a key therapeutic goal in the support of COPD patients. Oxygen during exercise is recommended for patients who both have significant exercise desaturation (<88%) and show improved exercise tolerance while using oxygen.[470] As noted previously, the training benefit of exercise can be optimized if patients are given supplemental oxygen, even in the absence of hypoxemia.[446] It is likely that optimal control of airflow with maximal bronchodilator therapy also improves training. Upper extremity exercises using light weights may improve upper extremity performance and reduce fatigue,[471] perhaps because these muscles participate as accessory muscles of ventilation.[472]

Respiratory muscle training is controversial. The simplest, most reliable method for home use is a pressure-threshold breathing device for endurance training. The

inspiratory pressure needed to achieve training has to be at least 30% of the maximum inspiratory pressure that the patient can generate, and training duration should eventually reach 30 min/day.[473] Such training increases the endurance time that these muscles can tolerate a given load and may improve respiratory muscle strength, diminish dyspnea to the inspired load, and modestly increase walking distance.[474,475] However, up to 50% of patients fail to complete training and, among those who do, the effects abate after several months.[476]

Controlled Breathing

Controlled breathing techniques include pursed-lip breathing and deliberately slow prolonged expiration, which may be coupled with manual upper abdominal compression and the standing bent-forward position, with the outstretched arms and hands supporting the body. The benefits of these methods include control of resting dyspnea, anxiety, and panic attacks.[477] Some patients adopt breathing with pursed lips and the bending-forward posture intuitively during bouts of dyspnea; others adopt them only after instruction. The goal of these methods is to reduce respiratory rate and increase expiratory tidal volume, thereby decreasing air trapping. Pursed-lip breathing may also increase airway pressure and thus prevent dynamic airway collapse[478] and may transiently improve arterial P_{O_2}.[479] The main benefit appears to be a decrease in end-expiratory lung volumes as a result of the prolongation of expiratory time.[480,481] The bending-forward posture improves diaphragmatic function by increasing abdominal pressure, thus placing the diaphragm in a better position for contraction.[482] The overall clinical benefit of these techniques, however, remains to be established.[483]

Nutrition

Patients with advanced COPD and a predominance of emphysema often experience progressive weight loss, with some patients becoming frankly cachectic.[484] Such patients have findings of marked somatic depletion including a significant reduction in triceps skinfold thickness. However, they may show no evidence of protein malnutrition, as indicated by normal serum albumin levels and blood lymphocyte counts. The cause of this excessive weight loss is multifactorial including a 15% to 25% increase in resting energy expenditure,[485,486] perhaps the result of a markedly elevated work of breathing and increases in circulating inflammatory cytokines.[487,488] A higher energy cost of daily activities and a reduced caloric intake relative to need may be other important factors. The main consequence of this excessive weight loss is reduced muscle strength including weakness of both the inspiratory and the expiratory muscles.[489] This depletion has an adverse effect on prognosis[490] and performance.[63]

Improved nutrition can restore respiratory and general muscle strength and endurance, but such improvement is realized only after clear-cut weight gain.[491,492] Unfortunately, this may be difficult to achieve. Use of anabolic androgens can improve muscle strength and may improve body mass,[490,493,494] but there is insufficient evidence to support their routine use either to improve nutrition or facilitate rehabilitation.[30]

Therapy of Respiratory/Ventilatory Failure

Chronic Ventilatory Failure

Intermittent Noninvasive Ventilation. The use of noninvasive mechanical ventilators in an attempt to rest respiratory muscles is based on the concept that, in patients with severe COPD, the respiratory muscles are at the fatigue threshold. Resting the muscles provides time for "recovery" and prevents small increases in respiratory requirements from precipitating fatigue and perhaps acute respiratory failure. A number of small clinical trials have yielded conflicting results. A randomized study comparing 39 patients treated with noninvasive ventilation with 47 untreated patients showed small improvements in P_{CO_2} and in quality of life over 24 months.[495] However, a 12-month study comparing 20 treated and 24 untreated patients failed to show benefits.[496] At present, the routine use of this form of support for COPD patients is not recommended.[30] Whether selected individuals may benefit, as do patients with chest wall deformities and neuromuscular disease, remains to be determined.[497]

Altering Ventilatory Control

Almitrine. Almitrine bismesylate, a peripheral chemoreceptor agonist not currently available in the United States, significantly improves resting room air arterial P_{O_2} in about 80% of stable COPD patients in a dose-dependent fashion; a maximal increase of about 10 to 11 mm Hg is seen after 100 mg of the drug.[498] This increase results mainly from improved ventilation-perfusion relationships because almitrine enhances hypoxic pulmonary vasoconstriction by way of sympathetic efferent pathways.[499] Improvement in arterial blood gases persists during exercise[500] and with sleep.[501] The concern that almitrine might significantly increase pulmonary vascular resistance and pulmonary artery pressures has not been borne out.[502] Its use has been limited because of side effects. However, an intermittent dosing schedule with 100 mg of almitrine daily given for 2 consecutive months followed by a 1-month washout has been suggested to maintain therapeutic efficacy while avoiding complications such as progressive weight loss and peripheral neuropathy.[502] Its routine use in COPD is not recommended.[30]

Analeptic Agents. The benefit of the true analeptic agents in COPD, like acetazolamide, which stimulates respiration by acidifying plasma and cerebrospinal fluid, and medroxyprogesterone acetate, which directly acts on brainstem respiratory neurons, is not established. Acetazolamide does not sustain increased ventilation in most COPD patients with chronic hypercapnia,[503] whereas medroxyprogesterone in a dose of 20 to 40 mg thrice daily may help COPD patients whose resting ventilation is much lower than expected given their lung mechanics. Patients with severe ventilatory limitation

(FEV_1 < 0.5-0.75 L) who are unable to reduce their arterial Pco_2 with voluntary hyperventilation will not respond to this medication.[503] Doxapram has also been used to stimulate ventilation. Clinical benefits are not established for these medications and their use to stimulate ventilation in COPD is not recommended.[30]

Surgical Treatment for Emphysema

Lung Volume Reduction Surgery

Dr. Otto Brantigan pioneered resectional surgery for diffuse emphysema in the late 1950s. A mortality rate of 16% soon caused the procedure to fall out of favor.[504] Advances in technology and in surgical technique resulting from experience with lung transplantation led to a revival of surgical treatments of emphysema. In 1995, Cooper and colleagues presented results of 20 patients who had undergone a resection of between 20% and 30% of each lung via median sternotomy.[505] The improvements in physical measures were remarkable as were functional and quality of life measures. This report generated tremendous interest in the procedure and led eventually to the National Emphysema Treatment Trial (NETT), which attempted to compare surgical and medical treatment in a randomized, controlled study and to evaluate subsets of patients with distinct responses.[506] The first observation made by this study was that individuals with an FEV_1 less than 20% predicted and either homogenous disease or a diffusion capacity of less than 20% predicted were at very high risk for mortality if treated surgically.[507] Cooper and colleagues, however, have reported that selected individuals with heterogenous disease that would be excluded by the NETT criteria may benefit.[508]

In contrast to the group with increased mortality, the NETT study indentified some individuals, specifically those with localized disease and with poor exercise capacity, who experienced a substantial reduction in mortality and improvements in HRQOL and exercise capacity as a result of lung volume reduction surgery (LVRS).[37] In addition, many individuals experienced improvement in lung function, performance, and health status. Although the disease continued to progress, the benefits achieved by surgery persisted for several years following the surgery, confirming earlier trials.[509,510] Although not a goal of the trial, one of the striking observations was the marked benefit of well-designed rehabilitation programs. A large number of questions related to LVRS remain. It is currently available at a limited number of centers and should be considered for patients likely to meet the selection criteria. Much of the current activity in this area centers on attempts to develop less invasive approaches to lung volume reduction, typically performed with a bronchoscopic approach.[511-518]

Lung Transplantation

Transplantation of the lung has proved more difficult than transplantation of other solid organs such as kidney, heart, or liver. It is the only organ in constant communication with the atmosphere, it is prone to infection as well as rejection, and there are special problems related to its preservation before transplantation. Nevertheless, there has been considerable progress in lung transplantation (see Chapter 95). In the years following the initial report by Mal and colleagues,[519] single-lung transplant has become most common procedure of choice when transplantation is performed for emphysema. Single-lung transplantation is an easier operation to perform than double-lung transplantation, cardiac bypass is usually not necessary, and two recipients may receive transplants. More recently, however, data have suggested that bilateral lung transplantation may provide better outcomes and current practice varies from center to center.[520] Available data suggest that lung transplantation offers improved function and HRQOL to patients with advanced COPD, but it is not clear that it offers any survival benefit.[521,522] Worldwide, COPD is the most common reason for lung transplantation, but the number of procedures is limited by the number of available organs. Recent changes in the algorithm for donor organ allocation in the United States are likely to result in a reduction in the proportion of lung transplants done for COPD.[523]

Surgery for Bullous Lung Disease

In the presence of a giant hyperlucent air space in the chest in a patient with compromised lung function, surgical excision may be considered. However, if lung function is not improved by the surgery, the morbidity and mortality of the procedure are high. It is not easy to know when to undertake surgery.

The determinants of the outcome of surgery are the size of the bulla and the impairment of function of the nonbullous lung tissue. Two mechanisms have been invoked for impairment of function by a giant bulla. There may be compression of nonbullous lung by a giant bulla whose internal pressure is high and whose volume does not change during respiration, or there may be impairment of ventilation because of the large amount of space occupied in the thorax by the bulla, with resultant loss of linkage between the chest wall and the nonbullous lung tissue.[20,524] There is little improvement in function after excision when bullae occupy less than one third of the hemithorax and lung function is only minimally impaired. The presence of generalized emphysema is also a predictor of a poor result.

As already noted, surgery in the presence of a low FEV_1, hypercapnia, or cor pulmonale is fraught with danger unless compressed, relatively normal lung can be released by the operation.[525,526] This is best assessed by CT performed, if possible, at both full inspiration and full expiration.[524,527] In general, patients do best who have large bullae occupying at least 30% to 50% of the hemithorax and an FEV_1 of about half the predicted normal value.[20,526] Other physiologic parameters predictive of successful surgery include plethysmographic lung volumes substantially larger than those measured by helium dilution, indicating sequestered gas, and a reasonably well preserved diffusing capacity and normocapnia.[528] The amount of uninvolved lung tissue resected should be kept to a minimum. Follow-up reveals that

resection of giant bullae does not appear to affect the size of other bullae.[526,529]

Acute Exacerbations

The course of COPD is characterized by episodic periods of worsening symptoms, termed *exacerbations*. It has proved difficult to establish a consensus definition of exacerbations, probably because they are heterogeneous and their clinical nature varies with the stage of the disease. The most widely used definitions relate increasing symptoms to increased need to utilize healthcare resources.[530] Although easy to apply, this definition is limited by local variations in health service practice. There are two key approaches to exacerbation management: prevention and acute care.

Prevention

As noted previously, several interventions can reduce exacerbation frequency or severity. ICS have consistently resulted in about a 20% reduction in exacerbation frequency and are recommended in the GOLD guidelines for this purpose.[30] The anticholinergic tiotropium has an effect of similar magnitude.[365,366] Ipratropium may have a modest effect, but conventional doses are not as effective as tiotropium.[366] LABA bronchodilators, used alone, may also reduce exacerbations and salmeterol[348,349] may be more effective than formoterol.[350,352] Influenza vaccination probably reduces the frequency of influenza-associated exacerbations.

Acute Management

As noted previously, acute exacerbations of COPD are events that place patients at increased risk. Comorbidities may complicate the clinical picture. Rib fractures and pneumothorax may occur. Congestive heart failure and pneumonia may be difficult to distinguish from an acute exacerbation because, in severe emphysema, the characteristic radiologic features of these conditions may be masked. Moreover, both conditions may be present with or may complicate an exacerbation. Limited studies suggest deep venous thrombosis and pulmonary embolism are associated with acute exacerbations.[531,532] Exacerbations are associated with acutely worsening health status that may take months to resolve.[25] Interestingly, one prospective study that monitored patient symptoms indicated that nearly half of exacerbations are not reported to healthcare providers.[533] The long-term impact of these exacerbations is not known, but the same study noted that delay in treatment was associated with slower resolution and increased risk of hospitalization for treatment.[533] Mortality is increased, both during the acute exacerbation and in the months following. Tracheal stenosis due to mechanical ventilation can cause deterioration in the postexacerbation period.[534] Current mortality rates of about 10% are reported in hospital, with intensive care unit and non–intensive care unit mortality being similar.[153,535] Mortality of 30% to 40% in the 6 to 12 months following hospitalization for exacerbations with evidence of respiratory failure are also reported,[154,536] but long-term survival is possible, complicating end-of-life decisions. To what extent end-of-life planning affects reported mortality statistics is not known. Based on the currently available evidence, however, aggressive treatment of exacerbations and the associated comorbidities is warranted.

Antibiotics. About one half of acute exacerbations of chronic bronchitis are associated with bacterial infection by pathogens that commonly colonize the respiratory tract: *H. influenzae*, *S. pneumoniae*, and *M. catarrhalis*.[537,538] Infected patients generally have larger numbers of bacteria in their sputum than when they are clinically stable.[537,539] Changes in the strain of bacteria have been associated with increased risk for acute exacerbation.[46] The sputum Gram stain provides semiquantitative information on the number of bacteria in the sputum; the culture provides information only on the identity of the organisms[540] and cannot separate colonization from infection. Clinical criteria alone are sufficient to justify a course of antibiotic for a COPD exacerbation in the ambulatory setting. In general, the more symptoms a patient experiences from the triad of dyspnea, cough, and sputum, and the more purulent the sputum, the more likely antibiotics are to be of benefit.[541,542]

A large number of oral antimicrobial agents have been approved for treating acute COPD exacerbations. Treatment is usually empirical and not based on sputum cultures.[47] Because response is generally good even without treatment,[541] a low-cost antibiotic such as trimethoprim-sulfamethoxasole, ampicillin, or a tetracycline is often used for mild exacerbations in relatively uncompromised patients. A 7- to 10-day course is most often prescribed, although 5 days is probably sufficient. Providing patients with a prescription to fill if needed for an increase in symptoms is commonly accepted practice. As baseline disease and exacerbation severity increase, broader-spectrum antibiotics that will be effective against resistant strains of *H. influenzae* and *S. pneumoniae* become increasingly recommended. If systemic symptoms such as fever are prominent, the patient should be regarded as having pneumonia and treated with broad-spectrum antibiotic coverage as recommended.[543]

For the patient with frequent purulent exacerbations, a treatment approach similar to that used for bronchiectasis with the regular use of prophylactic antibiotics may be beneficial. High-resolution CT of such patients may reveal bronchiectasis not apparent on routine chest radiography.[544]

Glucocorticoids. Systemic glucocorticoids have been demonstrated to reduce recovery time and to reduce treatment failures when used to treat acute exacerbations.[545–547] The dose required is not clear, but 30 to 60 mg of prednisone or equivalent appears to be adequate. The duration of treatment is also not established, but 2 weeks of therapy appears sufficient and, in one study, 8 weeks of therapy had no additional benefit.[546] In one recent study, the combination of an antibiotic (doxycycline) and systemic glucocorticoids was more effective than systemic steroids alone.[548]

Bronchodilators. The bronchodilators discussed previously should be used aggressively during an acute exacerbation. It is general practice to use rapidly acting agents and, for very ill patients, to use nebulizers, because many patients may not be able to generate the flows required to use other devices during an exacerbation. Intravenous aminophylline can improve lung function slightly,[549] but its overall clinical benefits remain controversial.[30] It should be used only with caution and blood theophylline levels should be monitored.

Acute Respiratory Failure

Acute respiratory failure in COPD is defined as the development of an arterial P_{CO_2} above 50 mm Hg or an arterial P_{O_2} below 50 mm Hg in association with recent clinical worsening. Most episodes are caused by a superimposed acute chest illness such as an acute exacerbation, but other causes such as pneumothorax, congestive heart failure, pulmonary embolus and metabolic derangements like hypophosphatemia or hypokalemia should be assessed.[550,551] The goals of treatment are primarily maintenance of adequate oxygenation and secondarily prevention of respiratory acidosis, while preventing secondary complications.

Oxygen. Supplemental oxygen should be given to maintain the P_{O_2} above 60 mm Hg and the Sa_{O_2} above 90%.[30] The concentration of oxygen required will vary with the severity of the exacerbation and the underlying disease. Arterial blood gases should be evaluated 30 minutes after initiating oxygen therapy, both to ensure adequate oxygenation and to assess for CO_2 retention, which cannot be determined by pulse oximetry. Rises in arterial P_{CO_2} may occur because of the suppression of hypoxic peripheral chemoreceptor ventilatory drive, the Haldane effect, in which oxygenated hemoglobin transports less carbon dioxide than deoxygenated hemoglobin, and the worsening of ventilation-perfusion matching in the diseased lungs.[552] The hypoxic ventilatory drive is not usually suppressed until the arterial P_{O_2} increases to 60 mm Hg or higher.

Ventilatory Support. A major advance in the treatment of acute exacerbations of COPD has been the implementation of noninvasive positive-pressure ventilation (see Chapter 92). Not only can intubations be avoided, but mortality for severe COPD exacerbations is also substantially reduced.[30,553,554] Several methods have been described including negative-pressure ventilation,[555] as well as nasal,[556] mouthpiece,[557] and face mask[558] intermittent positive-pressure ventilation. A recent randomized trial testing the benefit of a helium-oxygen mixture for use in noninvasive ventilatory support in COPD exacerbations did not show superiority.[559] It is common practice for this form of ventilatory support to be provided in an intensive care unit setting with specially trained staff. There are several contraindications to its use including respiratory arrest, cardiac instability, high aspiration risk, and inability to fit the device securely. If contraindications are present or if noninvasive ventilation is inadequate, patients may require intubation and mechanical ventilatory support (See Chapters 89 and 92).

KEY POINTS

- COPD is very common and its incidence is rising globally.
- COPD is often associated with and worsens outcome of a variety of other cigarette-related diseases such as heart disease and lung cancer.
- COPD is a complex disease caused by an environmental insult, most often cigarette smoke, on a susceptible genetic background.
- COPD is characterized by airflow obstruction that is not fully reversible. Airflow obstruction may be secondary to narrowing of small airways or emphysema (i.e., destruction of alveoli and ECM with consequent decreased elastic recoil).
- Airway narrowing is a result of excess mucus production, airway fibrosis, inflammation, and hypertrophy of structural cells.
- Emphysema is a result of inflammatory proteinases that degrade ECM, combined with cell death and imperfect repair.
- Oxygen therapy is indicated for patients with resting hypoxemia ($Sa_{O_2} < 88\%$) and/or signs of pulmonary hypertension.
- β-Agonists, anticholinergics, and inhaled corticosteroids have all been shown to improve function, reduce symptoms, and reduce exacerbations.
- Pulmonary rehabilitation is an important and underutilized treatment in patients with moderate to advanced COPD.
- Lung volume reduction surgery and lung transplantation offer significant benefits for highly selected patients with advanced COPD.

References

1. Global Strategy for Diagnosis, Management and Prevention of COPD. 2009. Available at www.goldcopd.com (accessed 2009).
2. Fletcher C, Peto R, Tinker C, Speizer FE (eds): The Natural History of Chronic Bronchitis and Emphysema. New York: Oxford University Press, 1976.
3. Badham C: Observations on the Inflammatory Affections of the Mucous Membrane of the Bronchiae. London: Callow, 1808.
4. Laennec RTH: A treatise on the diseases of the chest and on mediate auscultation. Translated by Forbes J. *In* Desilver, Thomas & Co. Philadelphia: Thomas, 1835, pp 135–163.
5. Reid LM: Measurement of bronchial mucous gland layer. A diagnostic yardstick in chronic bronchitis. Thorax 15:132–141, 1960.
6. Snider GL: Emphysema: The first two centuries—and beyond. A historical overview, with suggestions for future research: Part 2. Am Rev Respir Dis 146:1615–1622, 1992.
7. Ruysch F: Observationem Anatomico-Chirurgicarum. Amsterdam: Henricum Boom, 1691, pp 25–27.
8. Baillie M: A series of engravings, accompanied with explanations which are intended to illustrate the morbid anatomy of some of the most important parts of the human body, divided into 10 fasciculi. In Co. WBa (ed) London: W. Bulmer, 1799.
9. Baillie M: The morbid anatomy of some of the most important parts of the human body. In Fessenden W (ed). Brattleborough: W. Fessenden, 1808, pp 52–53.
10. Gough J: Discussion on the diagnosis of pulmonary emphysema. The pathological diagnosis of emphysema. Proc R Soc Med 45:576–577, 1952.
11. Orie NG, Sluiter HJ, DeVries K, et al: The host factor in bronchitis. In Orie NGM, Sluiter HJ (eds): Bronchitis, An International Symposium. Assen, Netherlands: Springfield, IL: Charles C. Thomas, 1961, pp 43–59.
12. Laurell CB, Eriksson S: The electrophoretic alpha 1-globulin pattern of serum in alpha 1-antitrypsin deficiency. Scand J Clin Lab Invest 15:132–140, 1963.
13. Snider GL, Hayes JA, Franzblau C, et al: Relationship between elastolytic activity and experimental emphysema-inducing properties of papain preparations. Am Rev Respir Dis 110:254–262, 1974.
14. Liebow AA: Pulmonary emphysema with special reference to vascular changes. Am Rev Respir Dis 80:67–93, 1959.
15. Rennard S: Defective repair in COPD: The American hypothesis. In Pauwels RA, Postma DS (eds): Long-Term Intervention in Chronic Obstructive Pulmonary Disease. New York: Marcel Dekker, 2004, pp 165–200.
16. Celli BR, Snider GL, Heffner J, et al: Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 152:S77–S120, 1995.
17. Rennard S, Decramer M, Calverley PM, et al: Impact of COPD in North America and Europe in 2000: Subjects' perspective of confronting COPD International Survey. Eur Respir J 20:799–805, 2002.
18. Seemungal TA, Donaldson GC, Paul EA, et al: Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 157:1418–1422, 1998.
19. Buist AS, Sexton GJ, Nagy JM, Ross BB: The effect of smoking cessation and modification on lung function. Am Rev Respir Dis 114:115–122, 1976.
20. Kinnear WJM, Tattersfield AE: Emphysematous bullae: Surgery is best for large bullae and moderately impaired lung function. Br Med J 300:208–209, 1990.
21. Thompson AB, Teschler H, Rennard SI: Pathogenesis, evaluation, and therapy for massive hemoptysis. Clin Chest Med 13:69–82, 1992.
22. Jones PW, Quirk FH, Baveystock CM: The St George's Respiratory Questionnaire. Respir Med 85(Suppl B):25–31, 1991 [discussion 3–7].
23. Guyatt GH, Berman LB, Townsend M, et al: A measure of quality of life for clinical trials in chronic lung disease. Thorax 42:773–778, 1987.
24. Halpin DM, Peterson S, Larsson TP, Calverley PM: Identifying COPD patients at increased risk of mortality: Predictive value of clinical study baseline data. Respir Med 102:1615–1624, 2008.
25. Spencer S, Jones PW: Time course of recovery of health status following an infective exacerbation of chronic bronchitis. Thorax 58:589–593, 2003.
26. Mannino DM, Gagnon RC, Petty TL, Lydick E: Obstructive lung disease and low lung function in adults in the United States: Data from the National Health and Nutrition Examination Survey, 1988–1994. Arch Intern Med 160:1683–1689, 2000.
27. Petty TL: Simple office spirometry. Clin Chest Med 22:845–859, 2001.
28. Finlay M, Middleton HC, Peake MD, Howard P: Cardiac output, pulmonary hypertension, hypoxaemia and survival in patients with chronic obstructive airways disease. Eur J Respir Dis 64:252–263, 1983.
29. Enright RL, Connett JE, Bailey WC: The FEV_1/FEV_6 predicts lung function decline in adult smokers. Respir Med 96:444–449, 2002.
30. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease. Available at http://www.goldcopd.com/wr.html 2003 (accessed 2003).
31. Anthonisen NR, Wright E: Bronchodilator response in chronic obstructive pulmonary disease. Am Rev Respir Dis 133:814–819, 1986.
32. Bates DV (ed): Respiratory Function in Disease (3rd ed). Philadelphia: WB Saunders; 1989.
33. Symonds G, Rensetti AD, Mitchell MM: The diffusing capacity in pulmonary emphysema. Am Rev Respir Dis 109:391–394, 1974.
34. Belman MJ: Exercise in patients with chronic obstructive pulmonary disease. Thorax 48:936–946, 1993.
35. Mulloy E, McNicholas WT: Ventilation and gas exchange during sleep and exercise in severe COPD. Chest 109:387–394, 1996.
36. Coxson HO, Lam S.: Quantitative assessment of the airway wall using computed tomography and optical coherence tomography. Proc Am Thorac Soc 6:439–443, 2009.
37. Fishman A, Martinez F, Naunheim K, et al: A randomized trial comparing lung-volume-reduction surgery with medical therapy for severe emphysema. N Engl J Med 348:2059–2073, 2003.
38. Kim WJ, Silverman EK, Hoffman E, et al: CT metrics of airway disease and emphysema in severe COPD. Chest 136:396–404, 2009.
39. Pinto-Plata V, Toso J, Lee K, et al: Profiling serum biomarkers in patients with COPD: Associations with clinical parameters. Thorax 62:595–601, 2007.
40. Bon JM, Leader JK, Weissfeld JL, et al: The influence of radiographic phenotype and smoking status on peripheral blood biomarker patterns in chronic obstructive pulmonary disease. PLoS ONE 4:e6865, 2009.
41. Donahoe M, Rogers RM: Laboratory evaluation of the patient with chronic obstructive pulmonary disease. *In* Cherniack NS (ed): Chronic Obstructive Pulmonary Disease. Philadelphia: WB Saunders, 1991, pp 373–386.
42. Cote C, Zilberberg MD, Mody SH, et al: Haemoglobin level and its clinical impact in a cohort of patients with COPD. Eur Respir J 29:923–929, 2007.
43. Brightling CE, McKenna S, Hargadon B, et al: Sputum eosinophilia and the short term response to inhaled mometasone in chronic obstructive pulmonary disease. Thorax 60:193–198, 2005.
44. Hill AT, Campbell EJ, Hill SL, et al: Association between airway bacterial load and markers of airway inflammation in patients with stable chronic bronchitis. Am J Med 109:288–295, 2000.
45. Miravitlles M: Exacerbations of chronic obstructive pulmonary disease: When are bacteria important? Eur Respir J Suppl 36:9s–19s, 2002.
46. Sethi S, Evans N, Grant BJ, Murphy TF: New strains of bacteria and exacerbations of chronic obstructive pulmonary disease. N Engl J Med 347:465–471, 2002.
47. Iyer Parameswaran G, Murphy TF: Chronic obstructive pulmonary disease: role of bacteria and updated guide to antibacterial selection in the older patient. Drugs Aging 26:985–995, 2009.
48. Chaouat A, Naeije R, Weitzenblum E. Pulmonary hypertension in COPD. Eur Respir J 32:1371–1385, 2008.
49. Weitzenblum E, Chaouat A, Canuet M, Kessler R: Pulmonary hypertension in chronic obstructive pulmonary disease and inter-

stitial lung diseases. Semin Respir Crit Care Med 30:458–470, 2009.
50. Fletcher EC, Luckett RA, Miller T, Fletcher JG: Exercise hemodynamics and gas exchange in patients with chronic obstruction pulmonary disease, sleep desaturation, and a daytime Pa_{O_2} above 60 mm Hg. Am Rev Respir Dis 140:1237–1245, 1989.
51. Farber MO, Roberts LR, Weinberger MH, et al: Abnormalities of sodium and H_2O handling in chronic obstructive lung disease. Arch Intern Med 142:1326–1330, 1982.
52. Fisher MR, Forfia PR, Chamera E, et al: Accuracy of Doppler echocardiography in the hemodynamic assessment of pulmonary hypertension. Am J Respir Crit Care Med 179:615–621, 2009.
53. Tramarin R, Torbicki A, Marchandise B, et al: Doppler echocardiographic evaluation of pulmonary artery pressure in chronic obstructive pulmonary disease. A European multicentre study. Working group on noninvasive evaluation of pulmonary artery pressure. European Office of the World Health Organization. Eur Heart J 12:103–111, 1991.
54. Sajkov D, Cowie RJ, Bradley JA, et al: Validation of new pulsed Doppler echocardiographic techniques for assessment of pulmonary hemodynamics [see comments]. Chest 103:1348–1353, 1993.
55. Griffith DE, Mazurek GH: Pneumonia and chronic obstructive lung disease. Infect Dis Clin North Am 5:467–484, 1991.
56. Ewig S, Torres A: Severe community-acquired pneumonia. Clin Chest Med 20:575–587, 1999.
57. Lieberman D, Gelfer Y, Varshavsky R, et al: Pneumonic vs nonpneumonic acute exacerbations of COPD. Chest 122:1264–1270, 2002.
58. Midgren B, Hansson L: Changes in the transcutaneous P_{CO_2} with sleep in normal subjects and in patients with chronic respiratory diseases. Eur J Respir Dis 71:384–387, 1987.
59. Goldstein MJ, Snider GL, Liberson M, et al: Bronchogenic carcinoma and giant bullous disease. Am Rev Respir Dis 97:1062–1070, 1968.
60. Aronberg DJ, Sagel SS, LeFrak S, et al: Lung carcinoma associated with bullous lung disease in young men. AJR Am J Roentgenol 134:249–252, 1980.
61. Tsutsui M, Araki Y, Shirakusa T, et al: Characteristic radiographic features of pulmonary carcinoma associated with large bulla. Ann Thorac Surg 46:679–683, 1988.
62. Dam TT, Harrison S, Fink HA, et al: Bone mineral density and fractures in older men with chronic obstructive pulmonary disease or asthma. Osteoporos Int 9:Oct. 9, 2009 (Epub ahead of print).
63. Schols AM, Mostert R, Soeters PB, Wouters EF: Body composition and exercise performance in patients with chronic obstructive pulmonary disease. Thorax 46:695–699, 1991.
64. Celli BR, Cote CG, Marin JM, et al: The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. N Engl J Med 350:1005–1012, 2004.
65. Mannino DM, Buist AS, Petty TL, et al: Lung function and mortality in the United States: Data from the First National Health and Nutrition Examination Survey follow up study. Thorax 58:388–393, 2003.
66. Ashley F, Kannel WB, Sorlie PD, Masson R: Pulmonary function: Relation to aging, cigarette habit, and mortality. Ann Intern Med 82:739–745, 1975.
67. van den Bemt L, Schermer T, Bor H, et al: The risk for depression comorbidity in patients with COPD. Chest 135:108–114, 2009.
68. Debigare R, Marquis K, Cote CH, et al: Catabolic/anabolic balance and muscle wasting in patients with COPD. Chest 124:83–89, 2003.
69. Wouters EF, Creutzberg EC, Schols AM: Systemic effects in COPD. Chest 121:127S–130S, 2002.
70. Bhowmik A, Seemungal TA, Sapsford RJ, Wedzicha JA: Relation of sputum inflammatory markers to symptoms and lung function changes in COPD exacerbations [see comments]. Thorax 55:114–120, 2000.
71. Vlahakos DV, Kosmas EN, Dimopoulou I, et al: Association between activation of the renin-angiotensin system and secondary erythrocytosis in patients with chronic obstructive pulmonary disease. Am J Med 106:158–164, 1999.
72. Gaensler EA: Unilateral hyperlucent lung. *In* Simon M, Potchen EJ, LeMay M (eds): Frontiers of Pulmonary Radiology. New York: Grune & Stratton, 1969, pp 312–359.
73. Swyer P, James G: A case of unilateral pulmonary emphysema. Thorax 8:133–136, 1953.
74. Macleod WM: Abnormal transradiancy of one lung. Thorax 9:147–153, 1954.
75. Fraser RG, Pare JAP, Pare PS: Diagnosis of diseases of the chest. In Philadelphia: WB Saunders, 1990, pp 2116–2144.
76. Gluck MC, Moser KM: Pulmonary artery agenesis. Diagnosis with ventilation and perfusion scintiphotography. Circulation 41:859–867, 1970.
77. Isawa T, Taplin GV: Unilateral pulmonary artery agenesis, stenosis and hypoplasia. Radiology 99:605–614, 1971.
78. Lincoln JCR, Stark J: Congenital lobar emphysema. Ann Surg 173:55–62, 1971.
79. Reid L: The pathology of emphysema. *In* Chicago: Year Book–Medical, 1967.
80. Thurlbeck WM: Chronic airflow obstruction. *In* Thurlbeck WM (ed): Pathology of the Lung. New York: Thieme Medical, 1988, pp 519–575.
81. Deaths from chronic obstructive pulmonary disease–United States, 2000–2005. MMWR Morb Mortal Wkly Rep 57:1229–1232, 2008.
82. Murray CJ, Lopez AD: Alternative projection of mortality by cause 1990–2020: Global burden of disease study. Lancet 349:1498–1504, 1997.
83. Mannino DM, Homa DM, Akinbami LJ, et al: Chronic obstructive pulmonary disease surveillance—United States, 1971–2000. MMWR Surveill Summ 51:1–16, 2002.
84. Medbo A, Melbye H: Lung function testing in the elderly—Can we still use $FEV_1/FVC < 70\%$ as a criterion of COPD? Respir Med 101:1097–1105, 2007.
85. Schirnhofer L, Lamprecht B, Vollmer WM, et al: COPD prevalence in Salzburg, Austria: Results from the Burden of Obstructive Lung Disease (BOLD) Study. Chest 131:29–36, 2007.
86. Yawn BP: Differential assessment and management of asthma vs chronic obstructive pulmonary disease. Medscape J Med 11:20, 2009.
87. Foster TS, Miller JD, Marton JP, et al: Assessment of the economic burden of COPD in the U.S.: A review and synthesis of the literature. COPD 3:211–218, 2006.
88. Ramsey SD, Sullivan SD: The burden of illness and economic evaluation for COPD. Eur Respir J Suppl 41:29s–35s, 2003.
89. Miller JD, Foster T, Boulanger L, et al: Direct costs of COPD in the U.S.: An analysis of Medical Expenditure Panel Survey (MEPS) data. COPD 2:311–318, 2005.
90. Stockley RA, Mannino D, Barnes PJ: Burden and pathogenesis of chronic obstructive pulmonary disease. Proc Am Thorac Soc 15:524–526, 2009.
91. Menezes AM, Perez-Padilla R, Jardim JR, et al: Chronic obstructive pulmonary disease in five Latin American cities (the PLATINO study): A prevalence study. Lance 366:1875–1881, 2005.
92. Buist AS, McBurnie MA, Vollmer WM, et al: International variation in the prevalence of COPD (the BOLD Study): A population-based prevalence study. Lancet 370:741–750, 2007.
93. Mannino DM, Buist AS: Global burden of COPD: Risk factors, prevalence, and future trends. Lancet 370:765–773, 2007.
94. Rennard SI, Vestbo J: COPD: The dangerous underestimate of 15%. Lancet 367:1216–1219, 2006.
95. Kauffmann F, Drouet D, Lelouch J: Occupational exposure and 12-year spirometric changes among Paris area workers. Br J Industr Med 39:221–232, 1982.
96. Hnizdo E, Sullivan PA, Bang KM, Wagner G: Airflow obstruction attributable to work in industry and occupation among U.S. race/ethnic groups: A study of NHANES III data. Am J Ind Med 46:126–135, 2004.
97. Salvi SS, Barnes PJ: Chronic obstructive pulmonary disease in non-smokers. Lancet 374:733–743, 2009.
98. Melbostad E, Eduard W, Magnus P: Chronic bronchitis in farmers. Scand J Work Environ Health 23:271–280, 1997.

99. Tashkin DP, Clark VA, Coulson AH, et al: The UCLA population studies of chronic obstructive respiratory disease. Am Rev Respir Dis 130:707–715, 1984.
100. Samet JM, Dominici F, Curriero FC, et al: Fine particulate air pollution and mortality in 20 U.S. cities, 1987–1994. N Engl J Med 343:1742–1749, 2000.
101. Lopez AD, Mathers CD, Ezzati M, et al: Global and regional burden of disease and risk factors, 2001: Systematic analysis of population health data. Lancet 367:1747–1757, 2006.
102. Mannino DM, Holguin F, Greves HM, et al: Urinary cadmium levels predict lower lung function in current and former smokers: Data from the Third National Health and Nutrition Examination Survey. Thorax 59:194–198, 2004.
103. Ericksson S: Pulmonary emphysema and alpha-1 antitrypsin deficiency. Acta Med Scand 175:197–205, 1964.
104. Silverman EK, Spira A, Pare PD: Genetics and genomics of chronic obstructive pulmonary disease. Proc Am Thorac Soc 6:539–542, 2009.
105. Wilk JB, Chen TH, Gottlieb DJ, et al: A genome-wide association study of pulmonary function measures in the Framingham Heart Study. PLoS Genet 5:e1000429, 2009.
106. DeMeo D, Mariani T, Lange C, et al: The SERPINE2 gene is associated with chronic obstructive pulmonary disease. Proc Am Thorac Soc 3:502, 2006.
107. Oliveti JF, Kercsmar CM, Redline S: Pre- and perinatal risk factors for asthma in inner city African-American children. Am J Epidemiol 143:570–577, 1996.
108. Shaheen S: The beginnings of chronic airflow obstruction. Br Med Bull 53:58–70, 1997.
109. Marossy AE, Strachan DP, Rudnicka AR, Anderson HR: Childhood chest illness and the rate of decline of adult lung function between ages 35 and 45 years. Am J Respir Crit Care Med 175:355–359, 2007.
110. Shaheen SO, Barker DJ, Shiell AW, et al: The relationship between pneumonia in early childhood and impaired lung function in late adult life. Am J Respir Crit Care Med 149:616–619, 1994.
111. Shaheen SO, Sterne JA, Florey CD: Birth weight, childhood lower respiratory tract infection, and adult lung function. Thorax 53:549–553, 1998.
112. Barker DJP, Godfrey KM, Fall CHD, et al: Relation of birthweight and childhood respiratory infection to adult lung function and death from chronic obstructive airways disease. BMJ 303:671–675, 1991.
113. Weiss ST, Ware JH: Overview of issues in the longitudinal analysis of respiratory data. Am J Respir Crit Care Med 154:S208–S211, 1996.
114. Burrows B: Airways obstructive diseases: Pathogenetic mechanisms and natural histories of the disorders. Med Clin North Am 74:547–560, 1990.
115. Peat JK, Salome CM, Sedgwick CS, et al: A prospective study of bronchial hyperresponsiveness and respiratory symptoms in a population of Australian schoolchildren. Clin Exp Allergy 19:299–306, 1989.
116. Lange P, Parner J, Vestbo J, et al: A 15-year follow-up study of ventilatory function in adults with asthma. N Engl J Med 339:1194–1200, 1998.
117. Ulrik CS, Backer V: Nonreversible airflow obstruction in life-long nonsmokers with moderate to severe asthma. Eur Respir J 14:892–896, 1999.
118. Wagner EM, Liu MC, Weinmann GG, et al: Peripheral lung resistance in normal and asthmatic subjects. Am Rev Respir Dis 141:584–588, 1990.
119. Gelb AF, Zamel N: Unsuspected pseudophysiologic emphysema in chronic persistent asthma. Am J Respir Crit Care Med 162:1778–1782, 2000.
120. Scanlon PD, Connett JE, Waller LA, et al: Smoking cessation and lung function in mild-to-moderate chronic obstructive pulmonary disease. The Lung Health Study. Am J Respir Crit Care Med 161:381–390, 2000.
121. Vestbo J, Prescott E, Lange P: Association of chronic mucus hypersecretion with FEV_1 decline and chronic obstructive pulmonary disease morbidity. Am J Respir Crit Care Med 153:1530–1535, 1996.
122. Donaldson GC, Seemungal TAR, Bhowmik A, Wedzicha JA: Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. Thorax 57:847–852, 2002.
123. Almagro P, Lopez Garcia F, Cabrera F, et al: Comorbidity and gender-related differences in patients hospitalized for COPD. The ECCO study. Respir Med Oct. 29, 2009. (Epub ahead of print)
124. U.S. Surgeon General: The health consequences of smoking: COPD. Publication No. 84-50205. Washington, DC: U.S. Department of Health and Human Resources, 1984.
125. Eisner MD, Blanc PD, Omachi TA, et al: Socioeconomic status, race, and COPD health outcomes. J Epidemiol Community Health 2009. (Epub ahead of print)
126. Rennard SI, Vestbo J: Natural history of chronic obstructive pulmonary disease. Proc Am Thorac Soc 5:878–883, 2008.
127. O'Donnell DE, Revill SM, Webb KA: Dynamic hyperinflation and exercise intolerance in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 164:770–777, 2001.
128. Wagner PD: Skeletal muscles in chronic obstructive pulmonary disease: Deconditioning, or myopathy? Respirology 11:681–686, 2006.
129. Decramer M, Rennard S, Troosters T, et al: COPD as a lung disease with systemic consequences—Clinical impact, mechanisms, and potential for early intervention. COPD 5:235–256, 2008.
130. Jones PW: Issues concerning health-related quality of life in COPD. Chest 107:187S–193S, 1995.
131. Vestbo J, Anderson W, Coxson HO, et al: Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE). Eur Respir J 31:869–873, 2008.
132. Borrell E, Rodriguez M, Toran P, et al: Incidence and risk factors of exacerbations among COPD patients in primary care: APMPOC study. BMC Public Health 9:8, 2009.
133. Ten Have-Opbroek AAW: The development of the lung in mammals: An analysis of concepts and findings. Am J Anat 162:201–219, 1981.
134. Gold DR, Wang X, Wypij D, et al: Effects of cigarette smoking on lung function in adolescent boys and girls. N Engl J Med 335:931–937, 1996.
135. Tager I, Segal M, Speizer F, Weiss S: The natural history of forced expiratory volumes. Am Rev Respir Dis 138:837–849, 1988.
136. Anthonisen NR, Connett JE, Murray RP: Smoking and lung function of Lung Health Study participants after 11 years. Am J Respir Crit Care Med 166:675–679, 2002.
137. Kohansal R, Martinez-Camblor P, Agusti A, et al: The natural history of chronic airflow obstruction revisited: An analysis of the Framingham Offspring Cohort. Am J Respir Crit Care Med 180:3–10, 2009.
138. The health benefits of smoking cessation, DHHS publication (CDC) 90-8416. Rockville, MD: U.S. Government Printing Office, 1990.
139. Stein J, Fenigstein H: Anatomie pathologique de la maladie de famine. In Apfelbaum E (ed): Maladie de famine. Warsaw, Poland: American Joint Distribution Committee, 1946, pp 21–27.
140. Gottlieb DJ, Stone PJ, Sparrow D, et al: Urinary desmosine excretion in smokers with and without rapid decline of lung function. Am J Respir Crit Care Med 154:1290–1295, 1996.
141. Burrows B, Knudson RJ, Camilli AE, et al: The "horse-racing effect" and predicting decline in FEV1 from screening spirometry. Am Rev Respir Dis 135:788–793, 1987.
142. Calverley PM, Anderson JA, Celli B, et al: Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. N Engl J Med 356:775–789, 2007.
143. Tashkin DP, Celli B, Senn S, et al: A 4-year trial of tiotropium in chronic obstructive pulmonary disease. N Engl J Med 359:1543–1554, 2008.
144. He JQ, Burkett K, Connett JE, et al: Interferon gamma polymorphisms and their interaction with smoking are associated with lung function. Hum Genet 119:365–375, 2006.
145. Ogawa E, Ruan J, Connett JE, et al: Transforming growth factor-beta1 polymorphisms, airway responsiveness and lung function decline in smokers. Respir Med 101:938–943, 2007.
146. Sin DD, Man SF: Why are patients with chronic obstructive pulmonary disease at increased risk of cardiovascular diseases? The

potential role of systemic inflammation in chronic obstructive pulmonary disease. Circulation 107:1514–1519, 2003.
147. Kony S, Zureik M, Driss F, et al: Association of bronchial hyperresponsiveness and lung function with C-reactive protein (CRP): A population-based study. Thorax 59:892–896, 2004.
148. Shaaban R, Kony S, Driss F, et al: Change in C-reactive protein levels and FEV_1 decline: A longitudinal population-based study. Respir Med;100:2112–2120, 2006.
149. Jiang R, Burke GL, Enright PL, et al: Inflammatory markers and longitudinal lung function decline in the elderly. Am J Epidemiol 168:602–610, 2008.
150. Fogarty AW, Jones S, Britton JR, et al: Systemic inflammation and decline in lung function in a general population: A prospective study. Thorax 62:515–520, 2007.
151. Celli B, Snider GL, Heffner J, et al: Definitions, epidemiology, pathophysiology, diagnosis, and staging. Am J Resp Crit Care Med 152:S78–S121, 1995.
152. Sin DD, Wu L, Man SF: The relationship between reduced lung function and cardiovascular mortality: A population-based study and a systematic review of the literature. Chest 127:1952–1959, 2005.
153. Connors AF Jr, Dawson NV, Thomas C, et al: Outcomes following acute exacerbation of severe chronic obstructive lung disease. The SUPPORT investigators (Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments). Am J Respir Crit Care Med 154:959–967, 1996.
154. Sin DD, Tu JV: Inhaled corticosteroids and the risk of mortality and readmission in elderly patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 164:580–584, 2001.
155. Anthonisen NR: Prognosis in chronic obstructive pulmonary disease: Results from multicenter clinical trials. Am Rev Respir Dis 133:S95–S99, 1989.
156. Traver GA, Cline MG, Burrows B: Predictions of mortality in COPD: A 15-year follow-up study. Am Rev Respir Dis 119:895–902, 1979.
157. Kanner RE, Renzetti AD Jr, Stanish WM, et al: Predictions of survival in subjects with chronic airflow limitation. Am J Med 174:249–255, 1983.
158. Kanner RE, Renzetti AD Jr: Predictions of spirometric changes and mortality in the obstructive airway disorders. Chest 85:15S–17S, 1984.
159. Thurlbeck WM: Pathology of chronic airflow obstruction. *In* Cherniack NS (ed): Chronic Obstructive Pulmonary Disease. Philadelphia: WB Saunders, 1991, pp 3–20.
160. Auerbach O, Stout AP, Hammond EC, et al: Changes in bronchial epithelium in relation to cigarette smoking and in relation to lung cancer. N Eng J Med 265:253–258, 1961.
161. Hossain S, Heard BE: Hyperplasia of bronchial muscle in chronic bronchitis. J Pathol 101:171–184, 1970.
162. Nagai A, West WW, Thurlbeck WM: The National Institutes of Health Intermittent Positive-Pressure Breathing Trial: Pathology studies II. Correlation between morphologic findings, clinical findings, and evidence of expiratory airflow obstruction. Am Rev Respir Dis 132:946–953, 1985.
163. Saetta M: Activated T-lymphocytes and macrophages in bronchial mucosa of subjects with chronic bronchitis. Am Rev Respir Dis 147:301–306, 1993.
164. Saetta M, Di Stefano A, Turato G, et al: $CD8^+$ T-lymphocytes in peripheral airways of smokers with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 157:822–826, 1998.
165. Hogg JC, Timens W: The pathology of chronic obstructive pulmonary disease. Annu Rev Pathol 4:435–459, 2009.
166. Thompson AB, Daughton D, Robbins RA, et al: Intraluminal airway inflammation in chronic bronchitis: Characterization and correlation with clinical parameters. Am Rev Respir Dis;140:1527–1537, 1989.
167. Saetta M, Turato G, Facchini F, et al: Macrophage and neutrophil infiltration in the bronchial glands of subjects with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 155:A595, 1997.
168. D'Armiento JM, Scharf SM, Roth MD, et al: Eosinophil and T cell markers predict functional decline in COPD patients. Respir Res 10:113, 2009.
169. Zhu J, Qiu YS, Majumdar S, et al: Exacerbations of bronchitis: Bronchial eosinophilia and gene expression for interleukin-4, interleukin-5, and eosinophil chemoattractants. Am J Respir Crit Care Med 164:109–116, 2001.
170. Niewoehner DE, Kleinerman J, Rice DB, Div M: Pathologic changes in the peripheral airways of young cigarette smokers. N Engl J Med 291:755–758, 1974.
171. Shaykhiev R, Krause A, Salit J, et al: Smoking-dependent reprogramming of alveolar macrophage polarization: Implications for the pathogenesis of chronic obstructive pulmonary disesase. J Immunol 183:2867–2883, 2009.
172. Wright JL, Cagle P, Churg A, et al: Disease of the small airways. Am Rev Respir Dis 146:240–262, 1992.
173. Linhartova A, Anderson AE, Foraker AG: Radial traction and bronchiolar obstruction in pulmonary emphysema. Arch Pathol 92:384–391, 1971.
174. Shapiro SD, Ingenito EP: The pathogenesis of chronic obstructive pulmonary disease: Advances in the past 100 years. Am J Respir Cell Mol Biol 32:367–372, 2005.
175. Pipavath SN, Schmidt RA, Takasugi JE, Godwin JD: Chronic obstructive pulmonary diseaes: Radiology – pathology correlation. J Thorac Imaging 24:171–180, 2009.
176. Webb WR, Stein MG, Finkbeiner WE, et al: Normal and diseased isolated lungs: High-resolution CT. Radiology 166:81–87, 1988.
177. Klein JS, Gamsu G, Webb WR: High-resolution CT diagnosis of emphysema in symptomatic patients with normal chest radiographs and isolated low diffusing capacity. Radiology 182:817–821, 1992.
178. Nishino M, Washko GR, Hatabu H: Volumetric expiratory HRCT of the lung: clinical applications. Radiol Clin North Am 48:177–183, 2010.
179. Washko GR, Criner GJ, Mohsenifar Z, et al: Computed tomographic-based quantification of emphysema and correlation to pulmonary function and mechanics. COPD 5:177–186, 2008.
180. Coxson HO, Rogers RM, Whittall KP, et al: A quantification of the lung surface area in emphysema using computed tomography. Am J Respir Crit Care Med 159:851–856, 1999.
181. Leopold JG, Gough J: The centrilobular form of hypertrophic emphysema and its relation to chronic bronchitis. Thorax 12:219–235, 1957.
182. Morgan WKC, Seaton A (eds): Occupational Lung Diseases. Philadelphia: WB Saunders, 1984.
183. Thurlbeck WM (ed): Chronic airflow obstruction in lung disease. In Major Problems in Pathology. Philadelphia: WB Saunders, 1976, p. 456.
184. Thurlbeck WM: The incidence of pulmonary emphysema: With observations on the relative incidence and spatial distribution of various types of emphysema. Am Rev Respir Dis 87:206–215, 1963.
185. Snider GL, Brody JS, Doctor L: Subclinical pulmonary emphysema. Am Rev Respir Dis 85:666–683, 1962.
186. Kim WD, Eidelman DH, Izquierdo JL, et al: Centrilobular and panlobular emphysema in smokers. Two distinct morphologic and functional entities. Am Rev Respir Dis 144:1385–1390, 1991.
187. Thurlbeck WM, Angus GE: A distribution curve for chronic bronchitis. Thorax 19:436–442, 1964.
188. Schmidt RA, Glenny RW: Panlobular emphysema in young intravenous ritalin abusers. Am Rev Respir Dis 143:649–656, 1991.
189. Edge J, Simon G, Reid L: Peri-acinar (paraseptal) emphysema: Its clinical, radiological and physiological features. Br J Dis Chest 60:10–18, 1966.
190. Reid L, Simon G: Unilateral lung transradiancy. Thorax 17:230–239, 1962.
191. Butler C, Kleinerman J: Pathology of chronic obstructive pulmonary disease. Am J Pathol 60:205–216, 1970.
192. Akashi T, Takemura T, Ando N, et al: Histopathologic analysis of 16 autopsy cases of chronic hypersensitivity pneumonitis and comparison with IPF/UIP. Am J Clin Pathol 131:405–415, 2009.
193. Rogers LF, Osmer JC: Bronchogenic cyst: A review of 46 cases. AJR Am J Roentgenol 91:273–283, 1964.
194. Reed JC, Sobonya RE: Morphologic analysis of foregut cysts in the thorax. AJR Am J Roentgenol 120:851–860, 1974.

195. Nagai A, West WW, Paul JL: The National Institutes of Health Intermittent Positive-Pressure Breathing Trial: Pathology studies. Am Rev Respir Dis 132:937–945, 1985.
196. Jamal K, Cooney TP, Fleetham JA, Thurlbeck WM: Chronic bronchitis: Correlation of morphological findings to sputum production and flow rates. Am Rev Respir Dis 129:719–722, 1984.
197. Matsuba K, Takayuki S, Kuwano K: Small airways disease in patients without chronic airflow limitation. Am Rev Respir Dis 136:1105–1111, 1987.
198. Matsuba K, Ikeda T, Nagai A, Thurlbeck WM: The National Institutes of Health Intermittent Positive-Pressure Breathing Trial: Pathology studies. Am Rev Respir Dis 139:1439–1445, 1989.
199. Nagsai A, Yamawaki I, Takizawa T, et al: Alveolar attachments in emphysema of human lungs. Am Rev Respir Dis 144:888–891, 1991.
200. Mitchell RS, Stanford RE, Johnson JM, et al: The morphologic features of the bronchi, bronchioles and alveoli in chronic airway obstruction: A clinicopathologic study. Am Rev Respir Dis 114:137–145, 1976.
201. Christie RV, McIntosh CA: The measurement of the intrapleural pressure in man. J Clin Invest 13:279–294, 1934.
202. Silvers GW, Petty TL: Elastic recoil changes in early emphysema. J Clin Invest 35:490–495, 1980.
203. Petty TL, Silvers W, Stanford RE: Mild emphysema is associated with reduced elastic recoil and increased lung size, but not with airflow limitation. Am Rev Respir Dis 136:867–876, 1980.
204. Hogg JC, Nepszy SJ, Macklem PT: Elastic properties of the centrilobular emphysematous space. J Clin Invest 48:1306–1312, 1969.
205. Clausen JL: The diagnosis of emphysema, chronic bronchitis and asthma. Am Rev Respir Dis 126:405–416, 1990.
206. Terzano C, Conti V, Petroianni A, et al: Effect of postural variations on carbon monoxide diffusing capacity in healthy subjects and patients with chronic obstructive pulmonary disease. Respiration 77:51–57, 2009.
207. Curtis JL, Freeman CM, Hogg JC: The immunopathogenesis of chronic obstructive pulmonary disease: Insights from recent research. Proc Am Thorac Soc 4:512–521, 2007.
208. Taraseviciene-Stewart L, Voelkel NF: Molecular pathogenesis of emphysema. J Clin Invest 118:394–402, 2008.
209. Kohri K, Ueki IF, Nadel JA: Neutrophil elastase induces mucin production by ligand-dependent epidermal growth factor receptor activation. Am J Physiol Lung Cell Mol Physiol 283:L531–L540, 2002.
210. Takeyama K, Dabbagh K, Lee HM, et al: Epidermal growth factor system regulates mucin production in airways. Proc Natl Acad Sci U S A 96:3081–3086, 1999.
211. Takeyama K, Dabbagh K, Jeong Shim J, et al: Oxidative stress causes mucin synthesis via transactivation of epidermal growth factor receptor: role of neutrophils. J Immunol 164:1546–1552, 2000.
212. Deshmukh HS, Case LM, Wesselkamper SC, et al: Metalloproteinases mediate mucin 5AC expression by epidermal growth factor receptor activation. Am J Respir Crit Care Med 171:305–314, 2005.
213. Adair-Kirk TL, Atkinson JJ, Senior RM: Smoke particulates stress lung cells. Nat Med 14:1024–1025, 2008.
214. Kim KK, Kugler MC, Wolters PJ, et al: Alveolar epithelial cell mesenchymal transition develops in vivo during pulmonary fibrosis and is regulated by the extracellular matrix. Proc Natl Acad Sci U S A 103:13180–13185, 2006.
215. Mio T, Adachi Y, Romberger DJ, et al: Human bronchial epithelial cells modulate collagen gel contraction by fibroblasts. Am J Respir Crit Care Med 151:A561, 1995.
216. Liu X, Umino T, Cano M, et al: Human bronchial epithelial cells can contract type I collagen gels. Am J Physiol 274:L58–L65, 1998.
217. Tschumperlin DJ, Dai G, Maly IV, et al: Mechanotransduction through growth-factor shedding into the extracellular space. Nature 429:83–86, 2004.
218. Lee CG, Homer RJ, Zhu Z, et al: Interleukin-13 induces tissue fibrosis by selectively stimulating and activating transforming growth factor beta(1). J Exp Med 194:809–821, 2001.
219. Sethi S, Murphy TF: Infection in the pathogenesis and course of chronic obstructive pulmonary disease. N Engl J Med 359:2355–2365, 2008.
220. Morimoto K, Gosselink J, Kartono A, et al: Adenovirus E1A regulates lung epithelial ICAM expression by interacting with transcriptional regulators at its promotor. Am J Physiol Lung Cell Mol Physiol 296:L361–L371, 2009.
221. Blasi F, Damato S, Cosentini R, et al: *Chlamydia pneumoniae* and chronic bronchitis: Association with severity and bacterial clearance following treatment. Thorax 57:672–676, 2002.
222. De Serres G, Lampron N, La Forge J, et al: Importance of viral and bacterial infections in chronic obstructive pulmonary disease exacerbations. J Clin Virol 46:129–133, 2009.
223. Kasahara Y, Tuder RM, Taraseviciene-Stewart L, et al: Inhibition of VEGF receptors causes lung cell apoptosis and emphysema. J Clin Invest 106:1311–1319, 2000.
224. MacNee W, Tuder RM: New paradigms in the pathogenesis of chronic obstructive pulmonary disease I. Proc Am Thorac Soc 6:527–533, 2009.
225. American Thoracic Society: Chronic bronchitis, asthma and pulmonary emphysema. A statement by the committee on diagnostic standards for nontuberculous respiratory diseases. Am Rev Respir Dis 85:762–768, 1962.
226. Barnes PJ, Shapiro SD, Pauwels RA: Chronic obstructive pulmonary disease: Molecular and cellular mechanisms. Eur Respir J 22:672–688, 2003.
227. Barnes PJ: The cytokine network in asthma and chronic obstructive pulmonary disease. J Clin Invest 118:3546–3556, 2008.
228. Rennard SI: Repair. *In* Calverley PMA, MacNee W, Pride NB, Rennard SI (eds): Chronic Obstructive Pulmonary Disease. London: Arnold, 2003, pp 139–150.
229. Owen CA, Campbell MA, Sannes PL, et al: Cell surface-bound elastase and cathepsin G on human neutrophils: A novel, nonoxidative mechanism by which neutrophils focus and preserve catalytic activity of serine proteinases. J Cell Biol 131:775–789, 1995.
230. Gaggar A, Jackson PL, Noerager BD, et al: A novel proteolytic cascade generates an extracellular matrix-derived chemoattractant in chronic neutrophilic inflammation. J Immunol 180:5662–5669, 2008.
231. Mydel P, Shipley JM, Adair-Kirk TL, et al: Neutrophil elastase cleaves laminin-332 (laminin-5) generating peptides that are chemotactic for neutrophils. J Biol Chem 283:9513–9522, 2008.
232. Adair-Kirk TL, Atkinson JJ, Broekelmann TJ, et al: A site on laminin alpha 5, AQARSAASKVKVSMKF, induces inflammatory cell production of matrix metalloproteinase-9 and chemotaxis. J Immunol 171:398–406, 2003.
233. Senior RM, Griffin GL, Meacham RP: Chemotactic activity of elastin-derived peptides. J Clin Invest 66:859–862, 1980.
234. Houghton AM, Quintero PA, Perkins DL, et al: Elastin fragments drive disease progression in a murine model of emphysema. J Clin Invest 116:753–759, 2006.
235. Henson PM, Vandivier RW, Douglas IS: Cell death, remodeling, and repair in chronic obstructive pulmonary disease? Proc Am Thorac Soc 3:713–717, 2006.
236. Huynh ML, Fadok VA, Henson PM: Phosphatidylserine-dependent ingestion of apoptotic cells promotes TGF-beta1 secretion and the resolution of inflammation. J Clin Invest 109:41–50, 2002.
237. Saetta M, Mariani M, Panina-Bordignon P, et al: Increased expression of the chemokine receptor CXCR3 and its ligand CXCL10 in peripheral airways of smokers with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 165:1404–1409, 2002.
238. Grumelli S, Corry DB, Song LZ, et al: An immune basis for lung parenchymal destruction in chronic obstructive pulmonary disease and emphysema. PLoS Med 1:e8, 2004.
239. Maeno T, Houghton AM, Quintero PA, et al: $CD8^+$ T cells are required for inflammation and destruction in cigarette smoke-induced emphysema in mice. J Immunol 178:8090–8096, 2007.
240. Lee SH, Goswami S, Grudo A, et al: Antielastin autoimmunity in tobacco smoking-induced emphysema. Nat Med 13:567–569, 2007.
241. Feghali-Bostwick CA, Gadgil AS, Otterbein LE, et al: Autoantibodies in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 177:156–163, 2008.

242. Retamales I, Elliott WM, Meshi B, et al: Amplification of inflammation in emphysema and its association with latent adenoviral infection. Am J Respir Crit Care Med 164:469–473, 2001.
243. Hogg JC: Role of latent viral infections in chronic obstructive pulmonary disease and asthma. Am J Respir Crit Care Med 164:S71–S75, 2001.
244. Meshi B, Vitalis TZ, Ionescu D, et al: Emphysematous lung destruction by cigarette smoke. The effects of latent adenoviral infection on the lung inflammatory response. Am J Respir Cell Mol Biol 26:52–57, 2002.
245. Gross P, Babjak M, Tolker E, et al: Enzymatically produced pulmonary emphysema: A preliminary report. J Occup Med 6:481–484, 1964.
246. Janoff A, Sloan B, Weinbaum G, et al: Experimental emphysema induced with purified human neutrophil elastase: Tissue localization of the instilled protease. Am Rev Resp Dis 115:461–478, 1977.
247. Senior RM, Tegner H, Kuhn C, et al: The induction of pulmonary emphysema with human leukocyte elastase. Am Rev Resp Dis 116:469–475, 1977.
248. Snider GL, Lucey EC, Christensen TG, et al: Emphysema and bronchial secretory cell metaplasia induced in hamsters by human neutrophil products. Am Rev Respir Dis 129:155–160, 1984.
249. Lucey EC, Stone PJ, Snider GL: Consequences of proteolytic injury. In Crystal RG (ed): The Lung: Scientific Foundations. New York: Raven, 1991, pp 1789–1801.
250. Karlinsky JB, Fredette J, Davidovits G: The balance of lung connective tissue elements in elastase-induced emphysema. J Lab Clin Med 102:151–162, 1983.
251. Kuhn C, Senior RM: The role of elastases in the development of emphysema. Lung 155:185–197, 1978.
252. Lucey EC, Keane J, Kuang PP, et al: Severity of elastase-induced emphysema is decreased in tumor necrosis factor-alpha and interleukin-1beta receptor-deficient mice. Lab Invest 82:79–85, 2002.
253. Kononov SBK, Sakai H, Cavalcante FS, et al: Roles of mechanical forces and collagen failure in the development of elastase-induced emphysema. Am J Respir Crit Care Med 164:1753–1754, 2001.
254. Owen CA, Campbell EJ: Extracellular proteolysis: New paradigms for an old paradox. J Lab Clin Med 134:341–351, 1999.
255. Campbell EJ, Campbell MA, Boukedes SS, Owen CA: Quantum proteolysis by neutrophils: Implications for pulmonary emphysema in a_1-antitrypsin deficiency. J Clin Invest 104:337–344, 1999.
256. Owen CA, Hu Z, Barrick B, Shapiro SD: Inducible expression of tissue inhibitor of metalloproteinases-resistant matrix metalloproteinase-9 on the cell surface of neutrophils. Am J Respir Cell Mol Biol 29:283–294, 2003.
257. Sommerhoff CP, Nadel JA, Basbaum CB, Caughey GH: Neutrophil elastase and cathepsin G stimulate secretion from cultured bovine airway gland serous cells. J Clin Invest 85:682–689, 1990.
258. Shapiro SD, Goldstein NM, Houghton AM, et al: Neutrophil elastase contributes to cigarette smoke-induced emphysema in mice. Am J Pathol 163:2329–2335, 2003.
259. Belaaouaj A, McCarthy R, Baumann M, et al: Mice lacking neutrophil elastase reveal impaired host defense against gram negative bacterial sepsis. Nat Med 4:615–618, 1998.
260. Tkalcevic J, Novelli M, Phylactides M, et al: Impaired immunity and enhanced resistance to endotoxin in the absence of neutrophil elastase and cathepsin G. Immunity 12:201–210, 2000.
261. Kao R, Wehner NG, Skubitz KM, et al: Proteinase 3: A distinct human polymorphonuclear leukocyte proteinase that produces emphysema in hamsters. J Clin Invest 82:1963–1973, 1988.
262. Churg A, Wang RD, Xie C, Wright JL: Alpha-1-Antitrypsin ameliorates cigarette smoke-induced emphysema in the mouse. Am J Respir Crit Care Med 168:199–207, 2003.
263. Parks WC, Shapiro SD: Matrix metalloproteinases in lung biology. Respir Res 2:10–19, 2001.
264. Imai K, Dalal SS, Chen ES, et al: Human collagenase (matrix metalloproteinase-1) expression in the lungs of patients with emphysema. Am J Respir Crit Care Med 163:786–791, 2001.
265. Russell RE, Culpitt SV, DeMatos C, et al: Release and activity of matrix metalloproteinase-9 and tissue inhibitor of metalloproteinase-1 by alveolar macrophages from patients with chronic obstructive pulmonary disease. Am J Respir Cell Mol Biol 26:602–609, 2002.
266. Molet S, Belleguic C, Lena H, et al: Increase in macrophage elastase (MMP-12) in lungs from patients with chronic obstructive pulmonary disease. Inflamm Res 54:31–36, 2005.
267. Shapiro SD, Kobayashi DK, Ley TJ: Cloning and characterization of a unique elastolytic metalloproteinase produced by human alveolar macrophages. J Biol Chem 268:23824–23829, 1993.
268. Woodruff PG, Koth LL, Yang YH, et al: A distinctive alveolar macrophage activation state induced by cigarette smoking. Am J Respir Crit Care Med 172:1383–1392, 2005.
269. Atkinson JJ, Senior RM: Matrix metalloproteinase-9 in lung remodeling. Am J Respir Cell Mol Biol 28:12–24, 2003.
270. Hunninghake GM, Cho MH, Tesfaigzi Y, et al: MMP-12, lung function, and COPD in high risk populations. N Engl J Med 361:2599–2608, 2009.
271. D'Armiento J, Dalal SS, Okada Y, et al: Collagenase expression in the lungs of transgenic mice causes pulmonary emphysema. Cell 71:955–961, 1992.
272. Hautamaki RD, Kobayashi DK, Senior RM, Shapiro SD: Requirement for macrophage elastase for cigarette smoke-induced emphysema in mice. Science 277:2002–2004, 1997.
273. Morris DG, Huang X, Kaminski N, et al: Loss of integrin alpha(v) beta6-mediated TGF-beta activation causes MMP12-dependent emphysema. Nature 422:169–173, 2003.
274. Wang Z, Zheng T, Zhu Z, et al: Interferon gamma induction of pulmonary emphysema in the adult murine lung. J Exp Med 192:1587–1600, 2000.
275. Chapman H, Munger J, Shi G: The role of thiol proteases in tissue injury and remodeling. Am J Respir Crit Care Med 150:S155–S159, 1994.
276. Punturieri A, Filippov S, Allen E, et al: Regulation of elastinolytic cysteine proteinase activity in normal and cathepsin K-deficient human macrophages. J Exp Med 196:789–799, 2000.
277. Riese RJ, Mitchell RN, Villadangos JA, et al: Cathepsin S activity regulates antigen presentation and immunity. J Clin Invest 101:2351–2363, 1998.
278. Foghsgaard L, Wissing D, Mauch D, et al: Cathepsin B acts as a dominant execution protease in tumor cell apoptosis induced by tumor necrosis factor. J Cell Biol 153:999–1010, 2001.
279. Churg A, Wang RD, Tai H, et al: Macrophage metalloelastase mediates acute cigarette smoke-induced inflammation via tumor necrosis factor-alpha release. Am J Respir Crit Care Med 167:1083–1089, 2003.
280. Li Q, Park PW, Wilson CL, Parks WC: Matrilysin shedding of syndecan-1 regulates chemokine mobilization and transepithelial efflux of neutrophils in acute lung injury. Cell 111:635–646, 2002.
281. McQuibban GA, Gong JH, Tam EM, et al: Inflammation dampened by gelatinase A cleavage of monocyte chemoattractant protein-3. Science 289:1202–1206, 2000.
282. Tang K, Rossiter HB, Wagner PD, Breen EC: Lung-targeted VEGF inactivation leads to an emphysema phenotype in mice. J Appl Physiol 97:1559–1566, 2004 [discussion 1549].
283. Aoshiba K, Yokohori N, Nagai A: Alveolar wall apoptosis causes lung destruction and emphysematous changes. Am J Respir Cell Mol Biol 28:555–562, 2003.
284. Kasahara Y, Tuder RM, Cool CD, et al: Endothelial cell death and decreased expression of vascular endothelial growth factor and vascular endothelial growth factor receptor 2 in emphysema. Am J Respir Crit Care Med 163:737–744, 2001.
285. Massaro G, Massaro D: Retinoic acid treatment abrogates elastase-induced pulmonary emphysema in rats. Nat Med 3:675–677, 1997.
286. Buhain WJ, Brody JS: Compensatory growth of the lung following pneumonectomy. J Appl Physiol 35:898–902, 1973.
287. Nolen-Walston RD, Kim CF, Mazan MR, et al: Cellular kinetics and modeling of bronchioalveolar stem cell response during lung regeneration. Am J Physiol Lung Cell Mol Physiol 294:L1158–L1165, 2008.
288. Wagenseil JE, Mecham RP: New insights into elastic fiber assembly. Birth Defects Res C Embryo Today 81:229–240, 2007.
289. Shapiro SD, Endicott SK, Province MA, et al: Marked longevity of human lung parenchymal elastic fibers deduced from prevalence

of D-aspartate and nuclear weapons-related radiocarbon. J Clin Invest 87:1828–1834, 1991.
290. Swee MH, Parks WC, Pierce RA: Developmental regulation of elastin production. Expression of tropoelastin pre-mRNA persists after down-regulation of steady-state mRNA levels. J Biol Chem 270:14899–14906, 1995.
291. Shifren A, Mecham RP: The stumbling block in lung repair of emphysema: Elastic fiber assembly. Proc Am Thorac Soc 3:428–433, 2006.
292. Wright JL, Churg A: Smoke-induced emphysema in guinea pigs is associated with morphometric evidence of collagen breakdown and repair. Am J Physiol 268:L17–L20, 1995.
293. Travis J: Alpha 1-proteinase inhibitor deficiency. *In* Massaro M (ed): Lung Cell Biology. New York: Marcel Dekker, 1989, pp 1227–1246.
294. Brantly M, Nukiwa T, Crystal RG: Molecular basis of alpha-1-antitrypsin deficiency. Am J Med 84:13–31, 1988.
295. Yoshida L, Lieberman L, Gaidulis L: Molecular abnormality of human alpha-1-antitrypsin variant (piZ) associated with plasma activity deficiency. Proc Natl Acad Sci U S A 73:1324–1330, 1976.
296. Ekeowa UI, Gooptu B, Belorgey D, et al: Alpha-1-antitrypsin deficiency, chronic obstructive pulmonary disease, and the serpinopathies. Clin Sci (Lond) 116:837–850, 2009.
297. Gooptu B, Lomas DA: Polymers and inflammation: Disease mechanisms of the serpinopathies. J Exp Med 205:1529–1534, 2008.
298. Hersh CP, Dahl M, Ly NP, et al: Chronic obstructive pulmonary disease in alpha1-antitrypsin PI MZ heterozygotes: A meta-analysis. Thorax 59:843–849, 2004.
299. Silverman EK, Sandhaus RA: Clinical practice. Alpha-1-antitryspin deficiency. N Engl J Med 360:2749–2757, 2009.
300. Tobin MJ, Cook PJL, Hutchinson DCS: Alpha 1-antitrypsin deficiency: The clinical features and physiological features of pulmonary emphysema in subjects homozygous for Pi type Z. A survey by the British Thoracic Association. Br J Dis Chest 77:14–27, 1983.
301. Jones DK, Godden D, Cavanagh P: Alpha-1-antitrypsin deficiency presenting as bronchiectasis. Br J Dis Chest 79:301–304, 1985.
302. Tanash HA, Nilsson PM, Nilsson JA, Piitulainen E: Clinical course and prognosis of never-smokers with severe alpha-1-antitrypsin deficiency (PiZZ). Thorax 63:1091–1095, 2008.
303. Janus ED, Phillips NT, Carrell RW: Smoking, lung function, and alpha-1-antitrypsin deficiency. Lancet 1:152–154, 1985.
304. Brantly ML, Paul LD, Miller BH: Clinical features and history of the destructive lung disease associated with alpha-1-antitrypsin deficiency of adults with pulmonary symptoms. Am Rev Respir Dis 138:327–336, 1988.
305. Hepper NG, Mulm JR, Sheehan WC: Roentgenographic study of chronic obstructive pulmonary disease by alpha-1-antitrypsin phenotype. Mayo Clin Proc 53:166–172, 1978.
306. Gishen P, Saunders AJS, Tobin MJ: Alpha-1-antitrypsin deficiency: The radiologic features of pulmonary emphysema in subjects of pi type Z and SZ: A survey of the British Thoracic Association. Clin Radiol 33:371–380, 1982.
307. Pratschke J, Steinmuller T, Bechstein WO, et al: Orthotopic liver transplantation for hepatic-associated metabolic disorders. Transplant Proc 31:382–384, 1999.
308. Eriksson RM, Carlson J, Velez R: Risk of cirrhosis and primary liver cancer in alpha-1-antitrypsin deficiency. N Engl J Med 314:736–739, 1986.
309. Lomas DA, Evans DL, Finch JT, Carrell RW: The mechanism of Z alpha 1-antitrypsin accumulation in the liver. Nature 357:605–607, 1992.
310. Hidvegi T, Schmidt BZ, Hale P, Perlmutter DH: Accumulation of mutant alpha1-antitrypsin Z in the endoplasmic reticulum activates caspases-4 and -12, NFkappaB, and BAP31 but not the unfolded protein response. J Biol Chem 280:39002–39015, 2005.
311. Perlmutter DH, Brodsky JL, Balistreri WF, Trapnell BC: Molecular pathogenesis of alpha-1-antitrypsin deficiency-associated liver disease: A meeting review. Hepatology 45:1313–1323, 2007.
312. Hutchison DC: Natural history of alpha-1-protease inhibitor deficiency. Am J Med 84:3–12, 1988.
313. Sandhaus RA: Augmentation therapy in alpha-1-antitryspin deficiency. COPD 6:147–148, 2009.
314. Buist AS, Burrows B, Cohen A, et al: Guidelines for the approach to the individual with severe hereditary alpha-1-antitrypsin deficiency. An official statement of the American Thoracic Society. Am Rev Respir Dis 140:1494–1497, 1989.
315. Dirksen A, Dijkman JH, Madsen F, et al: A randomized clinical trial of alpha(1)-antitrypsin augmentation therapy. Am J Respir Crit Care Med 160:1468–1472, 1999.
316. Wencker M, Fuhrmann B, Banik N, Konietzko N: Longitudinal follow-up of patients with alpha(1)-protease inhibitor deficiency before and during therapy with IV alpha(1)-protease inhibitor. Chest 119:737–744, 2001.
317. Survival and FEV_1 decline in individuals with severe deficiency of alpha1-antitrypsin. The Alpha-1-Antitrypsin Deficiency Registry Study Group. Am J Respir Crit Care Med 158:49–59, 1998.
318. Brenes GA: Anxiety and chronic obstructive pulmonary disease: Prevalence, impact, and treatment. Psychosom Med 65:963–970, 2003.
319. Singer HK, Ruchinskas RA, Riley KC, et al: The psychological impact of end-stage lung disease. Chest 120:1246–1252, 2001.
320. Borak J, Chodosowska E, Matuszewski A, Zielinski J: Emotional status does not alter exercise tolerance in patients with chronic obstructive pulmonary disease. Eur Respir J 12:370–373, 1998.
321. Yohannes AM, Baldwin RC, Connolly MJ: Prevalence of subthreshold depression in elderly patients with chronic obstructive pulmonary disease. Int J Geriatr Psychiatry 18:412–416, 2003.
322. Anthonisen NR, Connett JE, Kiley JP, et al: Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV_1. JAMA 272:1497–1505, 1994.
323. Turato G, Di Stefano A, Maestrelli P, et al: Effect of smoking cessation on airway inflammation in chronic bronchitis. Am J Respir Crit Care Med 152:1262–1267, 1995.
324. Rutgers SR, Postma DS, ten Hacken NH, et al: Ongoing airway inflammation in patients with COPD who do not currently smoke. Thorax 55:12–18, 2000.
325. Department of Health and Human Services: Health benefits of smoking cessation. A report of the Surgeon General. Publication No. (CDC) 90-8416. Washington, DC: Department of Health and Human Services (US), 1990.
326. Treating tobacco use and dependence: 2008 update U.S. Public Health Service Clinical Practice Guideline executive summary. Respir Care 53:1217–1222, 2008.
327. Dominici F, McDermott A, Zeger SL, Samet JM: Airborne particulate matter and mortality: Timescale effects in four US cities. Am J Epidemiol 157:1055–1065, 2003.
328. Nichol KL, Margolis KL, Wuorenma J, Von Sternberg T: The efficacy and cost effectiveness of vaccination against influenza among elderly persons living in the community. N Engl J Med 331:778–784, 1994.
329. Prevention and control of influenza: Recommendations of the Advisory Committee on Immunization Practices (ACIP). Centers for Disease Control and Prevention. MMWR Morb Mortal Wkly Rep 47(RR-6):1-26, 1998.
330. Varkey JB, Varkey AB, Varkey B: Prophylactic vaccinations in chronic obstructive pulmonary disease: current status. Curr Opin Pulm Med 15:90–99, 2009.
331. Anthonisen N, Connett J, Friedman B, et al: Design of a clinical trial to test a treatment of the underlying cause of emphysema. Ann N Y Acad Sci 624:31–34, 1991.
332. O'Donnell DE: Assessment of bronchodilator efficacy in symptomatic COPD: Is spirometry useful? Chest 117:42S–47S, 2000.
333. Interment Positive-Pressure Breathing Therapy Group: Intermittent positive-pressure breathing therapy of chronic obstructive pulmonary disease: A clinical trial. Ann Intern Med 99:612–620, 1983.
334. Calverley PM, Burge PS, Spencer S, et al: Bronchodilator reversibility testing in chronic obstructive pulmonary disease. Thorax 58:659–664, 2003.
335. Rennard SI, Calverley P: Rescue! Therapy and the paradox of the Barcalounger. Eur Respir J 21:916–917, 2003.
336. Santa Cruz R, Landa J, Hirsch J, et al: Tracheal mucous velocity in normal man and patients with obstructive lung disease: Effects of terbutaline. Am Rev Respir Dis 109:458–463, 1974.
337. Nava S, Crotti P, Gurrieri G, et al: Effect of a β2-agonist (Broxaterol) on respiratory muscle strength and endurance in patients

with COPD with irreversible airway obsruction. Chest 101:133–140, 1992.
338. Johnson M, Rennard S: Alternative mechanisms for long-acting beta(2)-adrenergic agonists in COPD. Chest 120:258–270, 2001.
339. Shim CS, Williams MH Jr: Bronchodilator response to oral aminophylline and terbutaline versus aerosol albuterol in patients with chronic obstructive pulmonary disease. Am J Med 75:697–701, 1983.
340. Tenholder MG, Bryson MJ, Waller RF, et al: Can MDIs be used effectively by extubated ICU patients? Am J Med 77:834–838, 1992.
341. Appleton S, Poole P, Smith B, et al: Long-acting beta2-agonists for poorly reversible chronic obstructive pulmonary disease. Cochrane Database Syst Rev 3:CD001104, 2006.
342. Rodrigo GJ, Nannini LJ, Rodriguez-Roisin R: Safety of long-acting beta-agonists in stable COPD: A systematic review. Chest 133:1079–1087, 2008.
343. Sin DD, McAlister FA, Man SF, Anthonisen NR: Contemporary management of chronic obstructive pulmonary disease: Scientific review. JAMA 290:2301–2312, 2003.
344. Xiao RP: Beta-adrenergic signaling in the heart: Dual coupling of the beta2-adrenergic receptor to G(s) and G(i) proteins. Sci STKE 104:RE15, 2001.
345. Donahue JF, Hanania NA, Ciubotaru RL, et al: Comparison of levalbuterols with racemic albuterol in hospitalized patients with acute asthma or COPD: A 2-week, multicenter, randomized, open-label study. Clin Ther 30:989–1002, 2008.
346. Salpeter SR, Ormiston TM, Salpeter EE, et al: Cardioselective beta-blockers for chronic obstructive pulmonary disease: A meta-analysis. Respir Med 97:1094–1101, 2003.
347. Suissa S, Assimes T, Ernst P: Inhaled short acting beta agonist use in COPD and the risk of acute myocardial infarction. Thorax 58:43–46, 2003.
348. Mahler DA, Donohue JF, Barbee RA, et al: Efficacy of salmeterol xinafoate in the treatment of COPD. Chest 115:957–965, 1999.
349. Rennard SI, Anderson W, Zu WR, et al: Use of a long-acting inhaled beta(2)-adrenergic agonist, salmeterol xinafoate, in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 163:1087–1092, 2001.
350. Dahl R, Greefhorst LA, Nowak D, et al: Inhaled formoterol dry powder versus ipratropium bromide in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 164:778–784, 2001.
351. Friedman M, Della Cioppa G, Kottakis J: Formoterol therapy for chronic obstructive pulmonary disease: A review of the literature. Pharmacotherapy 22:1129–1139, 2002.
352. Aalbers R, Ayres J, Backer V, et al: Formoterol in patients with chronic obstructive pulmonary disease: A randomized, controlled, 3-month trial. Eur Respir J 19:936–943, 2002.
353. Cazzola M, Imperatore F, Salzillo A, et al: Cardiac effects of formoterol and salmeterol in patients suffering from COPD with preexisting cardiac arrhythmias and hypoxemia [see comments]. Chest 114:411–415, 1998.
354. Au DH, Curtis JR, Every NR, et al: Association between inhaled beta-agonists and the risk of unstable angina and myocardial infarction. Chest 121:846–851, 2002.
355. Anthonisen NR, Connett JE, Enright PL, Manfreda J: Hospitalizations and mortality in the Lung Health Study. Am J Respir Crit Care Med 166:333–339, 2002.
356. Gross NJ. Ipratropium bromide. N Engl J Med 319:486–494, 1988.
357. Rennard SI: Anticholinergic bronchodilators. *In* Martin RJ, Kraft M (eds): Combination Therapy for Asthma and Chronic Obstructive Pulmonary Disease. New York: Marcel Dekker, 2000, pp 159–180.
358. Hansel TT, Barnes PJ: Tiotropium bromide: A novel once-daily anticholinergic bronchodilator for the treatment of COPD. Drugs Today (Barc) 38:585–600, 2002.
359. Littner MR, Ilowite JS, Tashkin DP, et al: Long-acting bronchodilation with once-daily dosing of tiotropium (Spiriva) in stable chronic obstructive pulmonary disease. Am J Respir Crit Care Med 161:1136–1142, 2000.
360. On LS, Boonyongsunchai P, Webb S, et al: Function of pulmonary neuronal M(2) muscarinic receptors in stable chronic obstructive pulmonary disease. Am J Respir Crit Care Med 163:1320–1325, 2001.
361. Wessler IK, Kirkpatrick CJ: The non-neuronal cholinergic system: An emerging drug target in the airways. Pulm Pharmacol Ther 14:423–434, 2001.
362. Koyama S, Rennard SI, Robbins RA: Acetylcholine stimulates bronchial epithelial cells to release neutrophil and monocyte chemotactic activity. Am J Physiol 262:L466–L471, 1992.
363. Tashkin DP, Celli B, Senn S, et al: A 4-year trial of tiotropium in chronic obstructive pulmonary disease. N Engl J Med 359:1543–1554, 2008.
364. Niewoehner DE, Rice K, Cote C, et al: Prevention of exacerbations of chronic obstructive pulmonary disease with tiotropium, a once-daily inhaled anticholinergic bronchodilator: A randomized trial. Ann Intern Med 143:317–326, 2005.
365. Casaburi R, Mahler DA, Jones PW, et al: A long-term evaluation of once-daily inhaled tiotropium in chronic obstructive pulmonary disease. Eur Respir J 19:217–224, 2002.
366. Vincken W, van Noord JA, Greefhorst AP, et al: Improved health outcomes in patients with COPD during 1 year's treatment with tiotropium. Eur Respir J 19:209–216, 2002.
367. Donohue JF, van Noord JA, Bateman ED, et al: A 6-month, placebo-controlled study comparing lung function and health status changes in COPD patients treated with tiotropium or salmeterol. Chest 122:47–55, 2002.
368. Celli B, ZuWallack R, Wang S, Kesten S: Improvement in resting inspiratory capacity and hyperinflation with tiotropium in COPD patients with increased static lung volumes. Chest 124:1743–1748, 2003.
369. O'Donnell DE, Lam M, Webb KA: Spirometric correlates of improvement in exercise performance after anticholinergic therapy in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 160:542–549, 1999.
370. Lee TA, Pickard AS, Au DH, et al: Risk for death associated with medications for recently diagnosed chronic obstructive pulmonary disease. Ann Intern Med 149:380–390, 2008.
371. Singh S, Loke YK, Furberg CD: Inhaled anticholinergics and risk of major adverse cardiovascular events in patients with chronic obstructive pulmonary disease: A systematic review and meta-analysis. JAMA 300:1439–1450, 2008.
372. Barnes PJ: Theophylline: New perspectives for an old drug. Am J Respir Crit Care Med 167:813–818, 2003.
373. Culpitt SV, de Matos C, Russell RE, et al: Effect of theophylline on induced sputum inflammatory indices and neutrophil chemotaxis in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 165:1371–1376, 2002.
374. ZuWallach RL, Mahler DA, Reilly D, et al: Salmeterol plus theophylline combination therapy in the treatment of COPD. Chest 119:1661–1670, 2001.
375. Rossi A, Kristufek P, Levine BE, et al: Comparison of the efficacy, tolerability, and safety of formoterol dry powder and oral, slow-release theophylline in the treatment of COPD. Chest 121:1058–1069, 2002.
376. Taylor DR, Buick B, Kinney C, et al: The efficacy of orally administered theophylline, inhaled salbutamol, and a combination of the two as chronic therapy in the management of chronic bronchitis with reversible air-flow obstruction. Am Rev Respir Dis 131:747–751, 1985.
377. Alexander MR, Dull WL, Kasik JE: Treatment of chronic obstructive pulmonary disease with orally administered theophylline: A double-blind, controlled study. JAMA 244:2286–2290, 1980.
378. Eaton ML, Green BA, Church TR, et al: Efficacy of theophylline in "irreversible" airflow obstruction. Ann Intern Med 92:758–761, 1980.
379. CIAS Group: In chronic obstructive pulmonary disease, a combination of ipratropium and albuterol is more effective than either agent alone. Chest 105:1411–1419, 1994.
380. van Noord JA, de Munck DR, Bantje TA, et al: Long-term treatment of chronic obstructive pulmonary disease with salmeterol and the additive effect of ipratropium. Eur Respir J 15:878–885, 2000.
381. Cazzola M, Marco FD, Santus P, et al: The pharmacodynamic effects of single inhaled doses of formoterol, tiotropium and their

combination in patients with COPD. Pulm Pharmacol Ther 17:35–39, 2004.
382. Bleecker ER, Britt EJ: Acute bronchodilating effects of ipratropium bromide and theophylline in chronic obstructive pulmonary disease. Am J Med 91:24S–27S, 1991.
383. Bellia V, Foresi A, Bianco S, et al: Efficacy and safety of oxitropium bromide, theophylline and their combination in COPD patients: A double-blind, randomized, multicentre study (BREATH Trial). Respir Med 96:881–889, 2002.
384. Nishimura K, Koyama H, Ikeda A, et al: The additive effect of theophylline on a high-dose combination of inhaled salbutamol and ipratropium bromide in stable COPD. Chest 107:718–723, 1995.
385. ATS/ERS Task Force: Standards for the diagnosis and management of patients with COPD. Version 1.2. New York: ATS; 2004 [updated 2005]. From: http://www.thoracic.org/go/copd
386. Weiner P, Magadle R, Berar-Yanay N, et al: The cumulative effect of long-acting bronchodilators, exercise, and inspiratory muscle training on the perception of dyspnea in patients with advanced COPD. Chest 118:672–678, 2000.
387. Karpel JP, Pesin J, Greenberg D, Gentry E: A comparison of the effects of ipratropium bromide and metaproterenol sulfate in acute exacerbations of COPD. Chest 98:835–839, 1990.
388. Patrick DM, Dales RE, Stark RM, et al: Severe exacerbations of COPD and asthma. Chest 98:295–297, 1990.
389. Shrestha M, O'Brien T, Haddox R, et al: Decreased duration of emergency department treatment of chronic obstructive pulmonary disease exacerbations with the addition of ipratropium bromide to beta-agonist therapy. Ann Emerg Med 20:1206–1209, 1991.
390. Pauwels RA, Lofdahl CG, Laitinen LA, et al: Long-term treatment with inhaled budesonide in persons with mild chronic obstructive pulmonary disease who continue smoking. N Engl J Med 340:1948–1953, 1999.
391. Burge PS, Calverley PM, Jones PW, et al: Randomised, double-blind, placebo-controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: The ISOLDE trial. BMJ 320:1297–1303, 2000.
392. Szafranski W, Cukier A, Ramirez A, et al: Efficacy and safety of budesonide/formoterol in the management of chronic obstructive pulmonary disease. Eur Respir J 21:74–81, 2003.
393. Calverley P, Pauwels R, Vestbo J, et al: Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease: A randomised controlled trial. Lancet 361:449–456, 2003.
394. Mahler DA, Wire P, Horstman D, et al: Effectiveness of fluticasone propionate and salmeterol combination delivered via the diskus device in the treatment of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 166:1084–1091, 2002.
395. Yang IA, Fong KM, Sim EH, et al: Inhaled corticosteroids for stable chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2:CD002991, 2007.
396. Jones PW, Willits LR, Burge PS, Calverley PM: Disease severity and the effect of fluticasone propionate on chronic obstructive pulmonary disease exacerbations. Eur Respir J 21:68–73, 2003.
397. Vestbo J, Sorensen T, Lange P, et al: Long-term effect of inhaled budesonide in mild and moderate chronic obstructive pulmonary disease: A randomised controlled trial. Lancet 353:1819–1823, 1999.
398. Lung Helath Study Research Group: Effect of inhaled triamcinolone on the decline in pulmonary function in chronic obstructive pulmonary disease. N Engl J Med 343:1902–1909, 2000.
399. Highland KB, Strange C, Heffner JE: Long-term effects of inhaled corticosteroids on FEV_1 in patients with chronic obstructive pulmonary disease. A meta-analysis. Ann Intern Med 138:969–973, 2003.
400. Sutherland ER, Allmers H, Ayas NT, et al: Inhaled corticosteroids reduce the progression of airflow limitation in chronic obstructive pulmonary disease: A meta-analysis. Thorax 58:937–941, 2003.
401. Soriano JB, Sin DD, Zhang X, et al: A pooled analysis of FEV_1 decline in COPD patients randomized to inhaled corticosteroids or placebo. Chest 131:682–689, 2007.
402. Soriano JB, Vestbo J, Pride NB, et al: Survival in COPD patients after regular use of fluticasone propionate and salmeterol in general practice. Eur Respir J 20:819–825, 2002.
403. Parimon T, Chien JW, Bryson CL, et al: Inhaled corticosteroids and risk of lung cancer among patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 175:712–719, 2007.
404. Johnell O, Pauwels R, Lofdahl CG, et al: Bone mineral density in patients with chronic obstructive pulmonary disease treated with budesonide Turbuhaler. Eur Respir J 19:1058–1063, 2002.
405. Burge PS, Calverley PM, Jones PW, et al: Prednisolone response in patients with chronic obstructive pulmonary disease: Results from the ISOLDE study. Thorax 58:654–658, 2003.
406. Hanania NA, Darken P, Horstman D, et al: The efficacy and safety of fluticasone propionate (250 microg)/salmeterol (50 microg) combined in the Diskus inhaler for the treatment of COPD. Chest 124:834–843, 2003.
407. Kristufek P, Levine B, Till D, Byrne A: Inhaled formoterol (Foradil®) improves lung function in patients with both reversible and poorly reversible COPD. Am J Respir Crit Care Med 163:A280, 2001.
408. Schols AM, Wesseling G, Kester AD, et al: Dose dependent increased mortality risk in COPD patients treated with oral glucocorticoids. Eur Respir J 17:337–342, 2001.
409. Rice KL, Rubins JB, Lebahn F, et al: Withdrawal of chronic systemic corticosteroids in patients with COPD: A randomized trial. Am J Respir Crit Care Med 162:174–178, 2000.
410. deJong JW, Postma DS, van der Mark TW, Koeter GH: Effects of nedocromil sodium in the treatment of non-allergic subjects with chronic obstructive pulmonary disease. Thorax 49:1022–1024, 1994.
411. Shim C, King M, Williams MH Jr: Lack of effect of hydration on sputum production in chronic bronchitis. Chest 92:679–682, 1987.
412. Sheppard D, Rizk N, Boushey HA, et al: Mechanism of cough and bronchoconstriction induced by distilled water aerosol. Am Rev Respir Dis 127:691–694, 1983.
413. Rogers DF, Jeffery PK: Inhibition by oral *N*-acetylcysteine of cigarette smoke-induced "bronchitis" in the rat. Exp Lung Res 10:267–283, 1986.
414. Babolini G, Blasi A, Cornia G, et al: Long-term oral acetylcysteine in chronic bronchitis: A double-blind controlled study. Eur J Respir Dis 111:93-108, 1980.
415. Decramer M, Rutten-van Molken M, Dekhuijzen PN, et al: Effects of *N*-acetylcysteine on outcomes in chronic obstructive pulmonary disease (Bronchitis Randomized on NAC Cost-Utility Study, BRONCUS): A randomised placebo-controlled trial. Lancet 365:1552–1560, 2005.
416. Petty TL: The National Mucolytic Study. Results of a randomized, double-blind, placebo-controlled study of iodinated glycerol in chronic obstructive bronchitis. Chest 97:75–83, 1990.
417. Fick RB, Ansueto A, Mahutte K: Recombinant DNase mortality reduction in acute exacerbations of chronic bronchitis. Clin Res 42:294A, 1994.
418. Kaliner M, Shelhamer JH, Borson B, et al: Human respiratory mucus. Am Rev Respir Dis 134:612–621, 1986.
419. Tamaoki J, Chiyotani A, Kobayashi K, et al: Effect of indomethacin on bronchorrhea in patient with chronic bronchitis, diffuse panbrochitis, or bronchiectasis. Am Rev Respir Dis 145:548–552, 1992.
420. Wick MM, Ingram RH: Bronchorrhea responsive to aerosolized atropine. JAMA 235:1356, 1976.
421. Hirsch SR, Viernes PF, Kory RC: The expectorant effect of glyceryl guaiacolate in patients with chronic bronchitis. Chest 63:9–14, 1973.
422. Sutton PP, Parker RA, Webber BA, et al: Assessment of the forced expiration technique, postural drainage and directed coughing in chest physiotherapy. Eur J Respir Dis 64:62–68, 1983.
423. Harris RS, Lawson TV: The relative mechanical effectiveness and efficiency of successive voluntary coughs in healthy young adults. Clin Sci 34:569–577, 1968.
424. Marini JJ, Tyler ML, Hudson LD, et al: Influence of head-dependent positions on lung volumes and oxygen saturation in chronic airflow obstruction. Am Rev Respir Dis 129:101–105, 1984.

425. Sutton PP, Gemmell HG, Innes N, et al: Use of nebulized saline and nebulized terbutaline as an adjunct to chest physiotherapy. Thorax 43:57–60, 1988.
426. Faling LJ, Snider GL: Treatment of chronic obstructive pulmonary disease. In Simmons D (ed): Current Pulmonology. St. Louis: Year Book–Medical, 1989, pp 209–263.
427. Rocker G, Horton R, Currow D, et al: Palliation of dyspnoea in advanced COPD: revisiting a role for opioids. Thorax 64:910–915, 2009.
428. Stulbarg MS, Winn WR: Bilateral carotid body resection for the relief of dyspnea in severe chronic obstructive pulmonary disease. Chest 96:1123–1128, 1989.
429. Long-term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. Report of the Medical Research Council Working Party. Lancet 1:681–686, 1981.
430. Kvale PA, Cugell DW, Anthonisen NR, et al: Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease. Ann Intern Med 93:391–398, 1980.
431. Heaton RK, Grant I, McSweeny J, et al: Psychologic effects of continuous and nocturnal oxygen therapy in hypoxemic chronic obstructive pulmonary disease. Arch Intern Med 143:1941–1947, 1983.
432. Timms RM, Khaja FU, Williams GW, et al: Hemodynamic response to oxygen therapy in chronic obstructive pulmonary disease. Arch Intern Med 102:29–36, 1985.
433. Astin TW, Penman RWB: Airways obstruction due to hypoxemia in patients with chronic lung disease. Am Rev Respir Dis 95:567–575, 1967.
434. Couser JI, Make BJ: Transtracheal oxygen decreases inspired minute ventilation. Am Rev Respir Dis 139:627–631, 1989.
435. Goldstein R: Effect of supplemtntal nocturnal oxygen on gas exchange in patients with severe obstructive lung disease. N Engl J Med 310:425–429, 1984.
436. Petty TL, Standford RE, Neff TA: Continuous oxygen therapy in chronic airway obstruction: Observations on possible oxygen toxicity and survival. Ann Intern Med 75:361–367, 1971.
437. Petty TL, Neff TA, Creagh CE, et al: Outpatient oxygen therapy in chronic obstructive pulmonary disease. Arch Intern Med 139:28–32, 1979.
438. Petty TL, Snider GL: Second Oxygen Consensus Conference Report: Further recommendations for prescribing and supplying long-term oxygen therapy. Am Rev Respir Dis 138:745–747, 1988.
439. Petty TL: Home oxygen-a revolution in the care of advanced COPD. Med Clin North Am 74:715–729, 1990.
440. Tiep B: Long-term home oxygen therapy. Clin Chest Med 11:505–521, 1990.
441. Cotes JE, Gilson JC: Effect of oxygen on exercise ability in chronic respiratory insufficiency. Lancet 1:872–876, 1956.
442. Woodcock AA, Gross ER, Gellert AA, et al: Effects of dihydrocodeine, alcohol, and caffeine on breathlessness and exercise tolerance in patients with chronic obstructive lung disease and normal blood gases. N Engl J Med 305:1611–1616, 1981.
443. Vyas MN, Banister EW, Morton JW, et al: Response to exercise in patients with chronic airway obstruction: II. Effects of breathing 40 percent oxygen. Am Rev Respir Dis 103:401–412, 1971.
444. Stanek KA, Nagle FJ, Bisgard GE, et al: Effect of hyperoxia in oxygen consumption in exercising ponies. J Appl Physiol 46:1115–1118, 1979.
445. Bye PTP, Esau SA, Levy RD, et al: Ventilatory muscle function during exercise in air and oxygen in patients with chronic airflow limitation. Am Rev Respir Dis 132:236–240, 1985.
446. Emtner M, Porszasz J, Burns M, et al: Benefits of supplemental oxygen in exercise training in nonhypoxemic chronic obstructive pulmonary disease patients. Am J Respir Crit Care Med 168:1034–1042, 2003.
447. Lewis CA, Ferguson W, Eaton T, et al: Isolated nocturnal desaturation in COPD: Prevalence and impact on quality of life and sleep. Thorax 5:878–883, 2008.
448. Weitzenblum E, Chaouat A: Sleep and chronic obstructive pulmonary disease. Sleep Med Rev 8:281–294, 2004.
449. Croxton TL, Bailey WC: Long-term oxygen treatment in chronic obstructive pulmonary disease: Recommendations for future research: an NHLBI workshop report. Am J Respir Crit Care Med 174:373–378, 2006.
450. Chaouat A, Weitzenblum E, Kessler R, et al: Outcome of COPD patients with mild daytime hypoxaemia with or without sleep-related oxygen desaturation. Eur Respir J 17:848–855, 2001.
451. Chaouat A, Weitzenblum E, Kessler R, et al: A randomized trial of nocturnal oxygen therapy in chronic obstructive pulmonary disease patients. Eur Respir J 14:1002–1008, 1999.
452. Zanchet RC, Viegas CA: Nocturnal desaturation: Predictors and the effect on sleep patterns in patients with chronic obstructive pulmonary disease and concomitant mild daytime hypoxemia. J Bras Pneumol 32:207–212, 2006.
453. Lacasse Y, Series F, Martin S, Maltais F: Nocturnal oxygen therapy in patients with chronic obstructive pulmonary disease: a survey of Canadian respirologists. Can Respir J 14:343–348, 2007.
454. Report C: New problems in supply, reimbursement, and certification of medical necessity for long-term oxygen therapy. Am Rev Respir Dis 142:721–724, 1990.
455. O'Donohue WJ Jr: Prescribing home oxygen therapy: What the primary care physician needs to know. Arch Intern Med 152:746–748, 1992.
456. United States Federal Air Administration: Portable Oxygen Concentrators. *In* US Dept of Transportation, Federal Aviation Administration (ed): Advisory Circular; AC No: 120-95; 2007.
457. Barker AF, Burgher LW, Plummer AL: Oxygen conserving methods for adults. Chest 105:248–252, 1994.
458. Adamo JP, Mehta AC, Stelmach K, et al: The Cleveland Clinic's initial experience with transtracheal oxygen therapy. Respir Care 35:153–160, 1990.
459. Harrow EM, Oldenburg FA, Lingenfelter MS, et al: Respiratory failure and cor pulmonale associated with tracheal mucoid accumulation from SCOOP transtracheal oxygen catheter. Chest 101:580–581, 1992.
460. Christopher KL, Spofford BT, Brannin PK, et al: Transtracheal oxygen therapy for refractory hypoxemia. JAMA 256:494–497, 1986.
461. Schwartz JS, Bencowitz HZ, Moser KM: Air travel hypoxemia with chronic obstructive pulmonary disease. Ann Intern Med 100:473–477, 1984.
462. Dillard TA, Berg BW, Rajagopal KR, et al: Hypoxemia during air travel in patients with chronic obstructive pulmonary disease. Ann Intern Med 111:362–367, 1989.
463. Gong HJ, Tashkin DP, Lee EY, et al: Hypoxia-altitude simulation test. Am Rev Respir Dis 130:980–986, 1984.
464. Gong H Jr: Air travel and patients with pulmonary and allergic conditions. J Allergy Clin Immunol 87:879–885, 1991.
465. Kelly PT, Swanney MP, Seccombe LM, et al: Air travel hypoxemia vs. the hypoxia inhalation test in passengers with COPD. Chest 133:920–926, 2008.
466. Poundstone W: Air travel and supplemental oxygen. Respir Ther 136:79–82, 1983.
467. Saey D, Bernard S, Gagnon P, et al: Pulmonary rehabilitation in chronic obstructive pulmonary disease. Panminerva Med 51:95–114, 2009.
468. Finnerty JP, Keeping I, Bullough I, Jones J: The effectiveness of outpatient pulmonary rehabilitation in chronic lung disease: A randomized controlled trial. Chest 119:1705–1710, 2001.
469. Ries AL, Kaplan RM, Limberg TM, Prewitt LM: Effects of pulmonary rehabilitation of physiologic and psychosocial outcomes in patients with chronic obstructive pulmonary disease. Ann Intern Med 122:823–832, 1995.
470. Americn Thoracic Society: Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease (COPD) and asthma. Am Rev Respir Dis 136:225–244, 1987.
471. Ries A, Ellis B, Hawkins R: Upper extremity exercise training in chronic obstructive pulmonary disease. Chest 93:688–692, 1988.
472. Martinez FJ, Couser JI, Celli BR: Respiratory response to arm elevation in patients with chronic airflow obstruction. Am Rev Respir Dis 143:476–480, 1991.
473. Larson JL, Kim MJ, Sharp JT, et al: Inspiratory muscle training with a pressure threshold breathing device in patients with

chronic obstructive pulmonary disease. Am Rev Respir Dis 138:689–696, 1988.
474. Celli B: Training and the respiratory muscles. *In* Marini JJ, Roussos C (eds): Ventilatory Failure Update in Intensive Care and Emergency Medicine. Berlin: Springer-Verlag, 1991, pp 153–170.
475. Lotters F, van Tol B, Kwakkel G, Gosselink R: Effects of controlled inspiratory muscle training in patients with COPD: A meta-analysis. Eur Respir J 20:570–576, 2002.
476. Weiner P, Magadle R, Beckerman M, et al: Maintenance of inspiratory muscle training in COPD patients: One year follow-up. Eur Respir J 23:61–65, 2004.
477. Carlin BW: Pulmonary rehabilitation: a focus on COPD in primary care. Postgrad Med 121:140–147, 2009.
478. Ingram RH Jr, Schilder DP: Effect of pursed lips expiration on the pulmonary pressure-flow relationship in obstructive lung disease. Am Rev Respir Dis 96:381–388, 1967.
479. Tiep BL, Burns M, Kao D, et al: Pursed lips breathing training using ear oximetry. Chest 90:218–221, 1986.
480. Bianchi R, Gigliotti F, Romagnoli I, et al: Patterns of chest wall kinematics during volitional pursed-lip breathing in COPD at rest. Respir Med 101:1412–1418, 2007.
481. Bianchi R, Gigliotti F, Romagnoli I, et al: Chest wall kinematics and breathlessness during pursed-lip breathing in patients with COPD. Chest 125:459–465, 2004.
482. Sharp JT, Drutz WS, Moisan T, et al: Postural relief of dyspnea in severe chronic obstructive pulmonary disease. Am Rev Respir Dis 122:201–211, 1980.
483. Gosselink R: Controlled breathing and dyspnea in patients with chronic obstructive pulmonary disease (COPD). J Rehabil Res Dev 40:25–33, 2003.
484. Openbrier DR, Irwin MM, Rogers RM, et al: Nutritional status and lung function in patients with emphysema and chronic bronchitis. Chest 83:17–22, 1983.
485. Donahoe M, Rogers RM, Wilson DO, et al: Oxygen consumption of the respiratory muscles in normal and in malnourished patients with chronic obstructive pulmonary disease. Am Rev Respir Dis 140:385–391, 1989.
486. Goldstein S: Nitrogen and energy relationships in malnourished patients with emphysema. Am Rev Respir Dis 138:636–644, 1988.
487. Barnes PJ: The cytokine network in chronic obstructive pulmonary disease. Am J Respir Cell Mol Biol 41:631–638, 2009.
488. Di Francia M, Barbier D, Mege JL, Orehek J: Tumor necrosis factor-alpha levels and weight loss in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 150:1453–1455, 1994.
489. Rochester DF, Esau SA: Malnutrition and the respiratory system. Chest 85:411–415, 1984.
490. Schols AM, Slangen J, Vovovics L, Wouters EF: Weight loss is a reversible factor in the prognosis of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 157:1791–1797, 1998.
491. Wilson D: Nutritional intervention in malnourished patients with emphysema. Am Rev Respir Dis 134:672–677, 1986.
492. Whittaker JS, Ryan CF, Buckley PA, et al: The effects of refeeding on peripheral and respiratory muscle function in malnourished chronic obstructive pulmonary disease patients. Am Rev Respir Dis 142:283–288, 1990.
493. Creutzberg EC, Wouters EF, Mostert R, et al: A role for anabolic steroids in the rehabilitation of patients with COPD? A double-blind, placebo-controlled, randomized trial. Chest 124:1733–1742, 2003.
494. Yeh SS, DeGuzman B, Kramer T: Reversal of COPD-associated weight loss using the anabolic agent oxandrolone. Chest 122:421–428, 2002.
495. Clini E, Sturani C, Rossi A, et al: The Italian multicentre study on noninvasive ventilation in chronic obstructive pulmonary disease patients. Eur Respir J 20:529–538, 2002.
496. Casanova C, Celli BR, Tost L, et al: Long-term controlled trial of nocturnal nasal positive pressure ventilation in patients with severe COPD. Chest 118:1582–1590, 2000.
497. Kolodziej MA, Jensen L, Rowe B, Sin D: Systematic review of noninvasive positive pressure ventilation in severe stable COPD. Eur Respir J 30:293–306, 2007.
498. Bury T, Jeannot JP, Ansquer JC, et al: Dose-response and pharmacokinetic study with almitrine bismesylate after single oral administrations in COPD patients. Eur Respir J 2:49–55, 1989.
499. Romaldini H, Rodriguez-Roisin R, Wagner PD, et al: Enhancement of hypoxic pulmonary vasoconstriction by almitrine in the dog. Am Rev Respir Dis 128:288–293, 1983.
500. Simmonneau G, Meignan M, Denjean A, et al: Cardiopulmonary effects of a single oral dose of almitrine at rest and on exercise in patients with hypoxic chronic airflow obstruction. Chest 89:174–179, 1986.
501. Connaughton JJ, Douglas NJ, Morgan AD, et al: Almitrine improves oxygenation when both awake and asleep in patients with hypoxia and carbon dioxide retention caused by chronic bronchitis and emphysema. Am Rev Respir Dis 132:206–210, 1985.
502. Weitzenblum E, Schrijen F, Apprill M, et al: One year treatment with almitrine improves hypoxaemia but does not increase pulmonary artery pressure in COPD patients. Eur Respir J 4:1215–1222, 1991.
503. Skatruc JB, Dempsey JA: Relative effectiveness of acetazolamide versus medroxyprogesterone acetate in correction of chronic carbon dioxide retention. Am Rev Respir Dis 127:405–412, 1983.
504. Fein AM: Lung volume reduction surgery: Answering the crucial questions. Chest 113:277S–282S, 1998.
505. Barth J, Mollmann HW, Armbruster B, et al: Analysis of shape, particle size distribution and aggregation of the crystals of sodium cromoglycate and nedocromil sodium. Eur J Hosp Parm 3:20–28, 1993.
506. Rationale and design of the National Emphysema Treatment Trial (NETT): A prospective randomized trial of lung volume reduction surgery. J Thorac Cardiovasc Surg 118:518–528, 1999.
507. Patients at high risk of death after lung-volume-reduction surgery. N Engl J Med 345:1075–1083, 2001.
508. Meyers BF, Yusen RD, Guthrie TJ, et al: Results of lung volume reduction surgery in patients meeting a national emphysema treatment trial high-risk criterion. J Thorac Cardiovasc Surg 127:829–835, 2004.
509. Cooper JD, Patterson GA, Sundaresean RS, et al: Results of 150 consecutive bilateral lung volume reduction procedures in patients with severe emphysema. J Thorac Cardiovasc Surg 112:1319–1330, 1996.
510. Brenner M, McKenna RJ, Gelb AF, et al: Rate of FEV change following lung volume reduction surgery. Chest 113:652–659, 1998.
511. Ingenito EP, Wood DE, Utz JP: Bronchoscopic lung volume reduction in severe emphysema. Proc Am Thorac Soc 5:454–460, 2008.
512. Bhattacharyya P, Sarkar D, Nag S, et al: Transbronchial decompression of emphysematous bullae: A new therapeutic approach. Eur Respir J 29:1003–1006, 2007.
513. Reilly J, Washko G, Pinto-Plata V, et al: Biological lung volume reduction: A new bronchoscopic therapy for advanced emphysema. Chest 131:1108–1113, 2007.
514. Snell GI, Hopkins P, Westall G, et al: A feasibility and safety study of bronchoscopic thermal vapor ablation: a novel emphysema therapy. Ann Thorac Surg 88:1993–1998, 2009.
515. Wan IY, Toma TP, Geddes DM, et al: Bronchoscopic lung volume reduction for end-stage emphysema: Report on the first 98 patients. Ann Thorac Surg 88:1993–1998, 2009.
516. Springmeyer SC, Bolliger CT, Waddell TK, et al: Treatment of heterogeneous emphysema using the spiration IBV valves. Thorac Surg Clin 19:247–253, ix–x, 2009.
517. Ingenito EP, Reilly JJ, Mentzer SJ, et al: Bronchoscopic volume reduction: A safe and effective alternative to surgical therapy for emphysema. Am J Respir Crit Care Med 164:295–301, 2001.
518. Venuta F, Rendina EA, Coloni GF: Endoscopic treatment of emphysema with one-way valves. Thorac Surg Clin 19:255–260, 2009.
519. Mal H, Andreassian B, Pamela F, et al: Unilateral lung transplantation in end-stage pulmonary emphysema. Am Rev Respir Dis 140:797–802, 1989.
520. Meyer DM, Bennett LE, Novick RJ, Hosenpud JD: Single vs bilateral, sequential lung transplantation for end-stage emphysema: Influence of recipient age on survival and secondary end-points. J Heart Lung Transplant 20:935–941, 2001.
521. Marulli G, Rea F: Lung transplantation for emphysema. Transplant Proc 40:2006–2009, 2008.

522. Stavem K, Bjortuft O, Borgan O, et al: Lung transplantation in patients with chronic obstructive pulmonary disease in a national cohort is without obvious survival benefit. J Heart Lung Transplant 25:75–84, 2006.
523. Kozower BD, Meyers BF, Smith MA, et al: The impact of the lung allocation score on short-term transplantation outcomes: A multicenter study. J Thorac Cardiovasc Surg 135:166–171, 2008.
524. Morgan MDL, Denison DM: The value of computed tomography for selecting patients with bullous lung disease for surgery. Thorax 41:855–862, 1986.
525. Gaensler EA, Angell DW, Knudson RJ, et al: Surgical management of emphysema. Clin Chest Med 4:443–463, 1983.
526. Nickoladze GD: Functional results of surgery for bullous emphysema. Chest 101:119–122, 1992.
527. Morgan MDL: Computed tomography in the assessment of bullous lung disease. Chest 78:10–25, 1984.
528. Ohta M, Nakahara K, Yasumitsu T, et al: Prediction of postoperative performance status in patients with giant bullae. Chest 101:668–673, 1992.
529. Fitzgerald MX, Keelan PJ, Cugell DW, et al: Long-term results of surgery for bullous emphysema. J Thorac Cardiovasc Surg 68:566–587, 1974.
530. Rodriguez-Roisin R: Toward a consensus definition for COPD exacerbations. Chest 117:398S–401S, 2000.
531. Ambrosetti M, Ageno W, Spanevello A, et al: Prevalence and prevention of venous thromboembolism in patients with acute exacerbations of COPD. Thromb Res 112:203–207, 2003.
532. Erelel M, Cuhadaroglu C, Ece T, Arseven O: The frequency of deep venous thrombosis and pulmonary embolus in acute exacerbation of chronic obstructive pulmonary disease. Respir Med 96:515–518, 2002.
533. Wilkinson TM, Donaldson GC, Hurst JR, et al: Early therapy improves outcomes of exacerbations of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 169:1298–1303, 2004.
534. Gelb AF, Tashkin DP, Epstein JD, et al: Nd-YAG laser surgery for severe tracheal stenosis physiologically and clinically masked by severe diffuse obstructive pulmonary disease. Chest 91:166–170, 1987.
535. Groenewegen KH, Schols AM, Wouters EF: Mortality and mortality-related factors after hospitalization for acute exacerbation of COPD. Chest 124:459–467, 2003.
536. Knaus WA, Harrell FE, Lynn J, et al: Objective estimates of survival for seriously ill hospitalized adults. Ann Intern Med 122:191–203, 1995.
537. Murphy T, Sethi S: Bacterial infection in chronic obstructive pulmonary disease. Am Rev Respir Dis 146:1067–1083, 1992.
538. Fagon JY, Chastre J, Trouillet JL, et al: Characterization of distal bronchial microflora during acute exacerbation of chronic bronchitis. Am Rev Respir Dis 142:1004–1008, 1990.
539. Chodosh S: Treatment of acute exacerbations of chronic bronchitis: State of the art. Am J Med 91(Suppl):87–92, 1991.
540. Murray PR, Washington JA: Microscopic and bacteriologic analysis of expectorated sputum. Mayo Clin Proc 50:339–344, 1975.
541. Anthonisen NR, Manfreda J, Warren CPW, et al: Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. Ann Intern Med 106:196–204, 1987.
542. Sethi S: Infectious exacerbations of chronic bronchitis: Diagnosis and management. J Antimicrob Chemother 43(Suppl A):97–105, 1999.
543. Guidelines for the initial management of adults with community-acquired pneumonia: Diagnosis, assessment of severity and initial antimicrobial therapy. Am Rev Respir Dis 148:1418–1426, 1993.
544. Lee PH, Carr DH, Rubens MB, et al: Accuracy of CT in predicting the cause of bronchiectasis. Clin Radiol 50:839–841, 1995.
545. Albert R, Martin T, Lewis S: Controlled clinical trial of methylprednisolone in patients with chronic bronchitis and acute respiratory insufficiency. Ann Intern Med 92:753–758, 1980.
546. Niewoehner DE, Erbland ML, Deupree RH, et al: Effect of systemic glucocorticoids on exacerbations of chronic obstructive pulmonary disease. N Engl J Med 340:1941–1947, 1999.
547. Thompson WH, Nielson CP, Carvalho P, et al: Controlled trial of oral prednisone in outpatients with acute COPD exacerbation. Am J Respir Crit Care Med 154:407–412, 1996.
548. Daniels JM, Snijders D, de Graaff CS, et al: Antibiotics in addition to systemic corticosteroids for acute exacerbations of COPD. Am J Respir Crit Care Med 18:150–157, 2010.
549. Barbera JA, Reyes A, Roca J, et al: Effect of intravenously administered aminophylline on ventilation/perfusion inequality during recovery from exacerbation of chronic obstructive pulmonary disease. Am Rev Respir Dis 145:1328–1333, 1992.
550. Derenne J, Fleury B, Pariente R: Acute respiratory failure of chronic obstructive pulmonary disease. Am Rev Respir Dis 138:1006–1033, 1988.
551. Schmidt GA, Hall JB: Acute or chronic respiratory failure. Assessment and management of patients with COPD in the emergent setting. JAMA 261:3444–3453, 1989.
552. Dunn WF, Nelson SB, Hubmayr RD: Oxygen-induced hypercarbia in obstructive pulmonary disease. Am Rev Respir Dis 144:526–530, 1991.
553. Kramer N, Meyer TJ, Meharg J, et al: Randomized, prospective trial of noninvasive positive pressure ventilation in acute respiratory failure [see comments]. Am J Respir Crit Care Med 151:1799–1806, 1995.
554. Plant PK, Owen JL, Elliott MW: Non-invasive ventilation in acute exacerbations of chronic obstructive pulmonary disease: Long-term survival and predictors of in-hospital outcome. Thorax 56:708–712, 2001.
555. Gorini M, Ginanni R, Villella G, et al: Non-invasive negative and positive pressure ventilation in treatment of acute or chronic respiratory failure. Intensive Care Med 30:875–881, 2004.
556. Carrey Z, Gottfried SB, Levy RD: Ventilatory muscle support in respiratory failure with nasal positive pressure ventilation. Chest 97:150–158, 1990.
557. Glerant JC, Rose D, Oltean V, et al: Noninvasive ventilation using a mouthpiece in patients with COPD and acute respiratory failure. Respiration 74:632–639, 2007.
558. Brochard L, Isabey D, Piquet J, et al: Reversal of acute exacerbations of chronic obstructive lung disease by inspiratory assistance with a face mask. N Engl J Med 323:1523–1530, 1990.
559. Maggiore SM, Richard JC, Abroug F, et al: A multicenter, randomized trial of noninvasive ventilation with helium-oxygen mixture in exacerbations of chronic obstructive lung disease. Crit Care Med 38:145–155, 2010.

CHAPTER 40

SMOKING HAZARDS AND CESSATION

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INTRODUCTION

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INTRODUCTION

Cigarette smoking remains the leading cause of preventable premature morbidity and mortality in the United States and in many countries around the world. An average of 435,000 people in the United States die prematurely from tobacco-related disease in a year, which includes one of every three cancers and one in five deaths overall.[1] A lifelong smoker has about a one in three chance of dying prematurely from a complication of smoking.[2]

Smoking is particularly relevant to respiratory medicine, as it is by far the major cause of lung cancer and chronic obstructive pulmonary disease (COPD) in developed countries. Smoking is also a substantial causative factor in respiratory infections, including pneumococcal pneumonia, influenza, and tuberculosis.

EPIDEMIOLOGY OF CIGARETTE SMOKING

Currently, about 43.4 million individuals in the United States are cigarette smokers (19.8% of the adult population), including 22.3% of men and 17.4% of women.[3] People who are poor, are less well educated, and/or have unskilled occupations are more likely to smoke. For example, 33.3% of people with 9 to 11 years of education are smokers, compared with 11.4% of those with a college degree A recent study using a serum biomarker of tobacco use found a prevalence of active smoking of 40% and of active, recent, or heavy secondhand smoke exposure of 55% at San Francisco General Hospital, an urban public hospital that treats primarily the uninsured, disadvantaged minorities, and those with psychiatric and substance abuse problems.[4] The global tobacco disease burden has been reviewed by the World Health Organization in *World Health Report 2002*.[5] Smoking prevalence continues to rise in many low and middle income countries. Disease burden was estimated using disability-adjusted life years (DALYs) lost. In 2000, 8.8% of the global total deaths were attributable to tobacco use, a 45% increase from 1990. If the current levels of smoking remain unchanged, the burden from tobacco consumption is estimated to double by 2020. These figures informed the recently negotiated WHO Framework Convention on Tobacco Control,[6] which aims to reduce both demand and supply of tobacco around the world, through educational, political, and legislative means.

TOXICOLOGY OF CIGARETTE SMOKE

Tobacco smoke is an aerosol of droplets (particulates) containing water, nicotine and other alkaloids, and tar. Tobacco smoke contains several thousand different chemicals, many of which may contribute to human

disease.[7] Major toxic chemicals in the particulate phase of tobacco include nicotine, benzo(a)pyrene and other polycyclic hydrocarbons, *N′*-nitrosonornicotine, β-naphthylamine, polonium-210, nickel, cadmium, arsenic, and lead. The gaseous phase contains carbon monoxide, acetaldehyde, acetone, methanol, nitrogen oxides, hydrogen cyanide, acrolein, ammonia, benzene, formaldehyde, nitrosamines, and vinyl chloride. Tobacco smoke may produce illness by way of systemic absorption of toxins and/or cause local pulmonary injury by oxidant chemicals.

SMOKING-RELATED DISEASES

Tobacco use is a major cause of death from cancer, cardiovascular disease, and pulmonary disease (Table 40-1). Smoking is also a major risk factor for osteoporosis, reproductive disorders, and fire-related and trauma-related injuries.

Cancer

Smoking, the largest preventable cause of cancer (Table 40-2), is responsible for about 30% of cancer deaths.[8] Many chemicals in tobacco smoke may contribute to carcinogenesis as tumor initiators, co-carcinogens, tumor promoters, or complete carcinogens.[9] Binding of tobacco smoke carcinogens to DNA is thought to be a crucial step in cancer induction.[10] Cigarette smoking induces specific patterns of p53 gene mutations that are associated with squamous cell carcinomas of the lung, head, and neck.[11] Lung cancer is the leading cause of cancer deaths in the United States and is predominantly attributable to cigarette smoking. The risk of lung and other cancers is proportional to the number of cigarettes smoked per day and even more strongly to the duration of smoking. In current smokers, the levels of DNA adducts (covalently bound carcinogens) in nontumorous lung tissue or blood mononuclear cells are related to cigarette consumption.[12] Of note, however, in former smokers, DNA adduct levels were inversely associated with age of initiation of smoking. This finding suggests that young smokers are more susceptible to DNA damage and persistence of genetic alterations than are those who begin smoking at an older age, which has substantial implications for the need to prevent adolescent smoking.[13]

Workplace exposure to asbestos or α-radiation (the latter in uranium miners) synergistically increases the risk of lung cancer in cigarette smokers.[14] Alcohol use interacts synergistically with tobacco in causing oral, laryngeal, and esophageal cancer.[15] The mechanism of interaction may involve alcohol solubilizing tobacco carcinogens and/or alcohol-related induction of liver or gastrointestinal enzymes that metabolize and activate tobacco carcinogens. Smoking is associated with 15% of leukemia cases in adults and 20% of colorectal cancers.[16,17]

A detailed description of the epidemiology and the pathogenesis of smoking-induced lung cancer is presented elsewhere in this textbook (see Chapters 45 and 46).

TABLE 40-1. Health Hazards of Tobacco Use (Risks Increased by Smoking)

CANCER (SEE TABLE 40-2)

CARDIOVASCULAR DISEASE
- Sudden death
- Acute myocardial infarction
- Unstable angina
- Stroke
- Peripheral arterial occlusive disease (including thromboangiitis obliterans)
- Aortic aneurysm
- Worsening of congestive heart failure

PULMONARY DISEASE
- Lung cancer
- Chronic bronchitis
- Emphysema
- Asthma
- Increased susceptibility to pneumonia and to pulmonary tuberculosis
- Increased susceptibility to desquamative interstitial pneumonitis
- Increased morbidity from viral respiratory infection

GASTROINTESTINAL DISEASE
- Peptic ulcer
- Esophageal reflux

REPRODUCTIVE DISTURBANCES
- Reduced fertility
- Premature birth
- Lower birth weight
- Spontaneous abortion
- Abruptio placentae
- Premature rupture of membranes
- Increased perinatal mortality

ORAL DISEASE (SMOKELESS TOBACCO)
- Oral cancer
- Leukoplakia
- Gingivitis
- Gingival recession
- Tooth staining

OTHER
- Non–insulin-dependent diabetes mellitus
- Earlier menopause
- Osteoporosis
- Cataract
- Tobacco amblyopia (loss of vision)
- Age-related macular degeneration
- Premature skin wrinkling
- Aggravation of hypothyroidism
- Altered drug metabolism or effects

Chronic Pulmonary Disease

More than 80% of chronic obstructive pulmonary disease in the United States is attributable to cigarette smoking. Cigarette smoking also increases the risk of respiratory infection, including pneumonia, and results in greater disability from viral respiratory tract infections.[18,19] Pul-

TABLE 40-2. Cigarette Smoking and Cancer Risk

Cancer Site	Average Relative Risk
Lung	15.0–30.0
Urinary tract	3.0
Oral cavity	4.0–5.0
Oro- and hypopharynx	4.0–5.0*
Esophagus	1.5–5.0*
Larynx	10.0*
Pancreas	2.0–4.0
Nasal cavity, sinuses, nasopharynx	1.5–2.5
Stomach	1.5–2.0
Liver	1.5–2.5
Kidney	1.5–2.0
Uterine cervix	1.5–2.5
Myeloid leukemia	1.5–2.0

*Synergistic interaction with alcohol use.
Adapted from Vineis P, Alavanja M, Buffler P, et al: Tobacco and cancer: Recent epidemiological evidence. J Natl Cancer Inst 96:99–106, 2004; and International Agency for Research on Cancer: Tobacco smoking and Involuntary smoking. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. IARC Scientific Publication 83. Lyon: IARC, 2004.

monary disease from smoking includes the overlapping syndromes of chronic bronchitis (cough and mucus secretion), emphysema, and airway obstruction. The lung pathology produced by cigarette smoking includes loss of cilia, mucus gland hyperplasia, increased number of goblet cells in the central airways, inflammation, goblet cell metaplasia, squamous metaplasia, mucus plugging of small airways, destruction of alveoli, and a reduced number of small arteries. The mechanism of injury is complex and seems to include inflammation as well as direct injury by oxidant chemicals, increased activity of elastase (a protein that breaks down elastin and other connective tissue), and decreased antiprotease activity.[20] A genetic deficiency of α_1-antiprotease activity produces a similar imbalance between pulmonary protease and antiprotease activity and is a risk factor for early and severe smoking-induced pulmonary disease.[21]

In addition to the effects of cigarette smoke-induced injury, the delivery of carbon monoxide from cigarette smoke serves to worsen the level of functioning in smokers who have significant COPD. Carbon monoxide binds to hemoglobin, reduces the capacity of hemoglobin to carry oxygen, and impairs oxygen release. Thus, carbon monoxide exposure produces a functional anemia. Carboxyhemoglobin levels are typically 5% to 10% in smokers, compared with 1% or less in nonsmokers. In a normal person, carbon monoxide from cigarette smoke causes few symptoms, but in patients with pulmonary disease, carbon monoxide has the potential to cause significant impairment. Exposure to carbon monoxide at levels less than that derived from cigarette smoking can reduce exercise tolerance in patients with COPD.

Cigarette smoking may contribute to the development of asthma, although this potential link could be confounded by the increased rate of pulmonary infections observed in smokers. A longitudinal study of 5800 individuals taking part in a British national study suggested that regular smoking was associated with asthma in people between the ages of 17 and 33 (odds ratio [OR] = 4.42).[22] The relationship between asthma and smoking was further studied in more than 14,000 Finnish adults, and the prevalence of asthma was higher among male smokers than among male nonsmokers (risk ratio [RR] = 1.73), although no smoking effect was observed for women.[23] Compared with never smokers and ex-smokers, current smokers demonstrate higher asthma severity scores, more frequent asthma symptoms, and more frequent asthma attacks (OR = 2.39).[24] Silverman and coworkers[25] evaluated 1847 emergency room patients presenting with acute asthma and found that 35% of patients were current smokers. Fifty percent of these smoking asthmatics reported that cigarette use worsened their asthma symptoms.

The link between secondhand smoke and asthma would support the hypothesis that bronchial hyperresponsiveness is worsened by tobacco exposure. A study evaluating infants in their first year of life exposed to smoking mothers demonstrated that they were 2.1 times more likely to develop asthma than children of nonsmoking mothers.[26] Likewise, the Swiss Study on Air Pollution and Lung Disease in Adults suggested that secondhand smoke was associated with an increased risk of asthma (OR = 1.39) or reactive airway disease in nonsmoking adults.[27]

Bronchoalveolar lavage fluid in a small cohort of healthy nonasthmatic smokers documented altered macrophage cytokine release, increased cellularity, and an altered cytokine environment.[28] These abnormalities would further suggest a plausible link between smoking and an increased incidence and severity of a chronic lung inflammatory condition such as asthma.

Cigarette smoking has been associated with multiple non-neoplastic pulmonary disorders other than emphysema and chronic bronchitis. These include respiratory bronchiolitis-associated interstitial lung disease, desquamative interstitial pneumonitis (DIP), Langerhans cell histiocytosis, cryptogenic fibrosing alveolitis, and eosinophilic pneumonia.[29] Ninety percent of patients with pulmonary Langerhans cell histiocytosis are smokers. Respiratory bronchiolitis and DIP have similar histopathologic features and are characterized by the accumulation of pigmented macrophages within the alveoli. Respiratory bronchiolitis ("smoker's bronchiolitis") is most often an asymptomatic finding that can persist after smoking cessation.[30] DIP often affects smokers in their fourth or fifth decade of life and the symptoms are more frequent in smokers.[29] Smoking may also have an association with idiopathic pulmonary fibrosis.[31]

Infection

Cigarette smoking is a major risk factor for respiratory tract and other systemic infections.[32] Both active and passive cigarette smoke exposure increases the risk of infection. The mechanisms by which smoking increases risk are multifactorial and include structural and immunologic alterations. As mentioned previously, cigarette

smoking causes structural changes in the respiratory tract. These changes include peribronchiolar inflammation and fibrosis, increased mucosal permeability, impairment of mucociliary clearance, changes in pathogen adherence, and disruption of the respiratory epithelium. A number of components of cigarette smoke, including acrolein, acetaldehyde, formaldehyde, free radicals produced from chemical reactions within the cigarette smoke, and nitric oxide, may contribute to the observed structural alterations in airway epithelial cells.

Immunologic mechanisms include alterations in cellular and humoral immune system function. These include a decreased level of circulating immunoglobulins, a depression of antibody response to certain antigens, a decrease in $CD4^+$ lymphocyte counts, an increase in $CD8^+$ lymphocyte counts, depressed phagocyte activity, and decreased release of proinflammatory cytokines. Many of the immunologic disturbances in smokers resolve within six weeks after smoking cessation, supporting the idea that smoking cessation is highly effective in a relatively short period of time in the prevention of infection.[32]

Cigarette smoking is associated with an increased risk of bacterial and viral infections (Table 40-3). Cigarette smoking is a substantial risk factor for pneumococcal pneumonia, especially in patients with COPD. Smoking is strongly associated with invasive pneumococcal disease in otherwise healthy adults. A population-based case-control study showed that smoking was the strongest independent risk factor for invasive pneumococcal disease among immunocompetent adults.[18] The OR was 4.1 (95% confidence interval [CI], 2.4–7.3) for active smoking and 2.5 (95% CI, 1.2–5.1) for passive smoke exposure in nonsmokers compared with nonexposed nonsmokers. The attributable risk in this population was 51% for cigarette smoking and 17% for passive smoking, and this effect showed a strong dose response. The risk of pneumococcal disease declined to nonsmoker levels 10 years after cessation. Cigarette smoking has also been shown to be associated with a nearly twofold increased risk of community-acquired pneumonia, with 32% of the risk attributable to cigarette smoking.[33]

Cigarette smoking increases the risk of developing viral infections including the common cold, influenza, and varicella and increases their severity. For example, influenza infections are more severe, with more cough, acute and chronic phlegm production, breathlessness, and wheezing in smokers.[19] Influenza infections produce more work-loss days in smokers than in nonsmokers. Influenza vaccination is effective in preventing the disease in smokers, and smoking should be considered to be a high-priority indication for influenza vaccination. The risk of development of varicella pneumonitis in adults is reported to be substantially greater in smokers than in nonsmokers.[34]

Tuberculosis is perhaps the most important smoking-associated infection. Cigarette smoking is a risk factor for tuberculin skin test reactivity, skin test conversion, and for the development of active tuberculosis. Of note is a recent large case-control study from India examining smoking and tuberculosis in men between 35 and 69 years of age. The tuberculosis prevalence risk ratio was 2.9 (95% CI, 2.6–3.3) for ever smokers compared with never smokers, and the prevalence was higher with a higher level of cigarette consumption.[35] The mortality from tuberculosis among men 25 to 69 years old showed a risk ratio of 4.5 (95% CI, 4.0–5.0) and 4.2 (95% CI, 3.7–4.8) for urban and rural residents, respectively. The authors found that the smoking-attributable proportion of deaths from tuberculosis was 61% greater than the proportion of smoking-attributable deaths from vascular disease or cancer. Thus, it is likely that smoking contributes substantially to the worldwide disease burden of tuberculosis.[36]

Of historical interest is the relationship between tuberculosis and the risk of cigarette smoking in the early 20th century. Prior to that time, chewing tobacco was the preferred type of tobacco. Public fears that users of chewing tobacco who spit in public places might be spreading tuberculosis is one of the factors that led to the increase in cigarette sales in the United States. This is nicely described by Kluger as follows: "Chewing tobacco was no longer merely messy but socially disagreeable in more crowded urban America, and its inevitable byproduct, spitting, was now identified as a spreader of tuberculosis and other contagions and thus an official health menace. The leisurely pipe all at once seemed a remnant of a slower-tempo age, and cigar fumes were newly offensive amid thronged city life. The cigarette, by contrast, could be quickly consumed and easily snuffed out on the job as well as to and from work."[37]

TABLE 40-3. Cigarette Smoking and Infection

	Odds Ratio (95% CI)
Tuberculosis	4.5 (4.0–5.0)
Legionnaire's disease	3.5 (2.1–5.8)
HIV infection	3.4 (1.6–7.5)
Periodontal disease	2.8 (1.9–4.1)
Pneumococcal pneumonia	2.6 (1.9–3.5)
Meningococcal disease	2.4 (0.9–6.6)
Influenza	2.4 (1.5–3.8)
Common cold	1.5 (1.1–1.8)

CI, confidence interval; HIV, human immunodeficiency virus.

Cardiovascular Disease

Although not the focus of this textbook, cardiovascular disease is common in patients with respiratory disease. This relates to the facts that both diseases are common and both increase with age and that smoking is a major risk factor for both respiratory disease and cardiovascular disease.

Cigarette smoking accounts for about 20% of cardiovascular deaths in the United States. Risks are increased for coronary artery disease, sudden death, cerebrovascular disease, and peripheral vascular disease, including aortic aneurysm.[38] Cigarette smoking accelerates atherosclerosis and promotes acute ischemic events. The mechanisms of the effects of cigarette smoking are not fully

elucidated but are believed to include: (1) hemodynamic stress (nicotine increases the heart rate and transiently increases blood pressure); (2) endothelial injury and dysfunction (nitric oxide release and resultant vasodilation are impaired); (3) development of an atherogenic lipid profile (smokers have on average higher low density lipoprotein, more oxidized low-density lipoprotein, and lower high-density lipoprotein cholesterol than nonsmokers do); (4) enhanced coagulability; (5) arrhythmogenesis, and (6) relative hypoxemia because of the effects of carbon monoxide.[39] Carbon monoxide reduces the capacity of hemoglobin to carry oxygen and impairs the release of oxygen from hemoglobin to body tissues, both of which combine to result in a state of relative hypoxemia. As a compensation for the reduced oxygen-carrying capacity, polycythemia can develop in smokers, with hematocrits often 50% or more. The polycythemia and the increased fibrinogen levels that are found in cigarette smokers also increase blood viscosity, which adds to the risk of thrombotic events. Cigarette smoking also induces a chronic inflammatory state, as evidenced by increased neutrophil count and increased levels of fibrinogen and C-reactive protein in the blood of smokers. Chronic inflammation is thought to contribute to atherogenesis.

Cigarette smoking acts synergistically with other cardiac risk factors to increase the risk of ischemic heart disease. Although the risk of cardiovascular disease is roughly proportional to cigarette consumption, the risk persists even at low levels of smoking, that is, at one to two cigarettes per day.[40] Cigarette smoking reduces exercise tolerance in patients with angina pectoris and intermittent claudication. Vasospastic angina is more common and the response to vasodilator medication is impaired in patients who smoke. The number of episodes and total duration of ischemic episodes as assessed by ambulatory electrocardiographic monitoring in patients with coronary heart disease are substantially increased by cigarette smoking.[41] The increase in relative risk of coronary heart disease because of cigarette smoking is greatest in young adults who, in the absence of cigarette smoking, would have a relatively low risk.[38] Women who use oral contraceptives and smoke cigarettes have a synergistically increased risk of both myocardial infarction and stroke. Recent data suggest that implementing smoking bans at the community level has an appreciable impact on lowering hospital admission rates for coronary artery disease.[42]

After acute myocardial infarction, the risk of recurrent myocardial infarction is higher and survival is half over the next 12 years in persistent smokers as compared with quitters.[43] Smoking also interferes with revascularization therapy for acute myocardial infarction. After thrombolysis, the reocclusion rate is fourfold higher in smokers who continue than in those who quit.[44] The risk of reocclusion of a coronary artery after angioplasty or occlusion of a bypass graft is increased in smokers.[45] Cigarette smoking is not a risk factor for hypertension per se but does increase the risk of complications, including the development of nephrosclerosis and progression to malignant hypertension.[46] Cigarette smoking has been shown to be a substantial contributor to morbidity and mortality in patients with left ventricular dysfunction. The mortality benefit of stopping smoking in such patients is equal to or greater than the benefit of therapy with angiotension-converting enzyme inhibitors, β-blockers, or spironolactone.[47]

Wound Healing/Postoperative Complications

Cigarette smoking is associated with adverse postoperative events and delayed wound healing. The mechanisms include cutaneous vasoconstriction (reducing skin blood flow), local thrombosis, and reduced oxygen-carrying capacity, all of which can delay wound healing. Impaired clearance of secretions, altered immune function, altered collagen synthesis, as well as the influence of underlying tobacco-related diseases (e.g., COPD and altered cardiovascular function), also contribute to postoperative complications.

The harmful effects of smoking have been shown by preoperative smoking-cessation studies. Moller and colleagues[48] published the results of a randomized, controlled trial of smokers awaiting elective hip or knee surgery at three hospitals in Copenhagen. They compared 56 patients in a smoking-cessation intervention arm (83% stopped or reduced smoking) versus 62 patients in a usual care arm. The overall complication rate was 18% in the intervention arm and 52% in the controls, a highly significant difference. The greatest differences were seen in wound complication rates (5 vs. 31%) and cardiovascular complications (0 vs. 2%), without a significant difference in length of hospital stay.

The harmful effects of smoking are found for a variety of postoperative complications and procedures. A study of 489 adult patients undergoing ambulatory surgery demonstrated a significantly higher rate of respiratory complications (32.8% in smokers vs. 25.9% in nonsmokers) and wound infections (3.6% in smokers vs. 0.6% in nonsmokers, respectively).[49] Causes of major pulmonary events after pneumonectomy for lung surgery were sought in a retrospective analysis of 261 patients.[50] Patients who continued to smoke within 1 month of operation were determined to be at an increased risk of pulmonary events, which were associated with increased postoperative mortality. Cigarette smoking is associated with an increased risk of hepatic artery thrombosis after liver transplantation, and cessation 2 years before transplantation was associated with a decreased risk.[51] Similar data exist regarding renal transplantation and allograft survival in smokers compared with nonsmokers.[52]

The optimal window for smoking-cessation intervention may be at 8 weeks prior to elective surgery, as suggested by data demonstrating that patients who had stopped smoking at least 2 months preoperatively had nearly maximal reduction in postoperative respiratory complications.[53] Data suggest that short-term (2- to 3-week) cessation or reduction in smoking does not substantially alter postoperative wound complications in patients receiving colorectal surgery.[54]

An important issue related to elective surgery is that patients are often highly motivated to quit smoking just

before elective surgery and can benefit from cessation counseling prior to surgery as well as in the hospital and from medication in the postoperative setting. Specific issues related to smoking cessation are discussed later in this chapter.

Other Complications of Cigarette Smoking

Cigarette smoking increases the risk of duodenal and gastric ulcers, delays the rate of ulcer healing, and increases the risk of relapse after ulcer treatment.[55,56] Smoking is also associated with esophageal reflux symptoms. Smoking produces ulcer disease by increasing acid secretion, reducing pancreatic bicarbonate secretion, impairing the gastric mucosal barrier (related to decreased gastric mucosal blood flow and/or inhibition of prostaglandin synthesis), reducing pyloric sphincter tone, and increasing the risk of *Helicobacter pylori* infection.[57]

Cigarette smoking is an independent risk factor for the development of non–insulin-dependent diabetes mellitus, which is a consequence of development of resistance to the effects of insulin.[58] The effects of nicotine seem to contribute at least in part to insulin resistance, and insulin resistance has been described in users of smokeless tobacco, who are not exposed to tobacco combustion products.

Cigarette smoking is a risk factor for osteoporosis in that it reduces the peak bone mass attained in early adulthood and increases the rate of bone loss in later adulthood. Smoking antagonizes the protective effect of estrogen replacement therapy on the risk of osteoporosis in postmenopausal women.[59]

Cigarette smoking is a major cause of reproductive problems and results in approximately 4600 U.S. infant deaths annually. Growth retardation from cigarette smoking has been termed "fetal tobacco syndrome." Cigarette smoking causes reproductive complications by causing placental ischemia mediated by the hypoxic effects of chronic carbon monoxide exposure, endothelial dysfunction, and the general increase in coagulability produced by oxidant chemicals in cigarette smoke.[60]

Other adverse effects of cigarette smoking include premature facial wrinkling, an increased risk of cataracts, olfactory dysfunction, and fire-related injuries. Damage and injuries from fire contribute significantly to the economic costs of tobacco use. Cigarette smoking is associated with an increased incidence of Graves' hyperthyroidism, and particularly of the ophthalmopathy associated with Graves' disease.[61] Smoking reduces the secretion of thyroid hormone in women with subclinical hypothyroidism and increases the severity of clinical symptoms of hypothyroidism in women with subclinical or overt hypothyroidism, the latter effect reflecting antagonism of thyroid hormone action.[61]

Cigarette smoking also potentially interacts with a variety of drugs by accelerating drug metabolism or by antagonizing their pharmacologic effects (Table 40-4). As an example of the clinical consequences of enzyme

TABLE 40-4. Interaction between Cigarette Smoking and Drugs

Drugs	Interaction (Effects Compared with Nonsmokers)	Significance
Antipyrine Caffeine Chlorpromazine Clozapine Desmethyldiazepam Erlotinib Estradiol Estrone Flecainide Fluvoxamine Haloperidol Imipramine Irinotecan Lidocaine Olanzapine Oxazepam Pentazocine Phenacetin Phenylbutazone Propranolol Tacrine Theophylline	Accelerated metabolism	May require higher doses in smokers, reduced doses after quitting. Reduced toxicity with standard doses (e.g., irinotecan)
Oral contraceptives	Enhanced thrombosis, increased risk of stroke and myocardial infarction	Do not prescribe to smokers, especially if >35 yr old
Cimetidine and other H_2 blockers	Lower rate of ulcer healing, higher ulcer recurrence rates	Consider using mucosal protective agents
Propranolol	Less antihypertensive effect, less antianginal efficacy; more effective in reducing mortality after myocardial infarction[61a]	Consider the use of cardioselective β-blockers
Nifedipine (and probably other calcium blockers)	Less antianginal effect	May require higher doses and/or multiple-drug antianginal therapy
Diazepam, chlordiazepoxide (and possibly other sedative-hypnotics)	Less sedation	Smokers may need higher doses
Chlorpromazine (and possibly other neuroleptics)	Less sedation, possibly reduced efficacy	Smokers may need higher doses
Propoxyphene	Reduced analgesia	Smokers may need higher doses

induction from smoking on response to treatment of lung cancer, accelerated metabolism of erlotinib most likely explains the poorer response of smokers versus nonsmokers with non–small cell lung cancer.[62] Smoking is also associated with a decreased risk of hematologic toxicity from irinotecan, a drug widely used for solid tumors, including lung cancer.[63] Smoking accelerates the metabolism of irinotecan to its active metabolite, SN-38, and further accelerates the glucuronidation of SN-38, explaining the reduced toxicity, but also suggesting that smoking could reduce efficacy.

HEALTH HAZARDS OF SECONDHAND SMOKE

Considerable evidence indicates that exposure to secondhand smoke, also known as environmental tobacco smoke, is harmful to the health of nonsmokers (Table 40-5). The U.S. Environmental Protection Agency (EPA) classifies secondhand smoke as a class A carcinogen, which means that it has been shown to cause cancer in humans.[64] Secondhand smoke consists of sidestream smoke that is generated while the cigarette is smoldering and of mainstream smoke that has been exhaled by the smoker. Of the total combustion product from a cigarette, 75% or more enters the air. The constituents of secondhand smoke are qualitatively similar to those of mainstream smoke. However, some toxins, such as ammonia, formaldehyde, 1,3-butadiene and nitrosamines, are present in much higher concentrations in secondhand smoke than in mainstream smoke.

The EPA has estimated that secondhand smoke is responsible for approximately 3000 lung cancer deaths annually in nonsmokers in the United States, is causally associated with 150,000 to 300,000 cases of lower respiratory tract infection in infants and young children up to 18 months of age, and is causally associated with the aggravation of asthma in 200,000 to 1 million children.[58] More recently, the California EPA found that secondhand smoke exposure is also causally associated with asthma induction and aggravation in adults.[65,66] Exposure to secondhand smoke also adversely effects health outcomes in patients with COPD.[67]

TABLE 40-5. Health Hazards of Secondhand Smoke in Nonsmokers

Children	Adults
Hospitalization for respiratory tract infection in first year of life	Lung cancer
Wheezing	Myocardial infarction
Middle ear effusion	Reduced pulmonary function
Asthma	Irritation of eyes, nasal congestion, headache
Sudden infant death syndrome	Cough

An appreciation of the hazards of secondhand smoke for children is important to the physician because it provides a basis for advising parents to quit smoking, for counseling parents who are unable to quit not to smoke in the home or in family vehicles, and for insisting that child care facilities be smoke-free. Although screening for secondhand smoke exposure among adult patients is not yet part of accepted standard of care, all patients presenting with asthma or COPD should be asked about their secondhand smoke exposure and advised to avoid exposure. The known risks of secondhand smoke exposure provide strong support for smoke-free policies in all public places.

NICOTINE ADDICTION

Tobacco use is motivated primarily by the desire for nicotine. *Drug addiction* is defined as compulsive use of a psychoactive substance, the consequences of which are detrimental to the individual or society. Understanding addiction is useful in providing effective smoking-cessation therapy.[68] Nicotine is absorbed rapidly from tobacco smoke into the pulmonary circulation; it then moves quickly to the brain, where it acts on nicotinic cholinergic receptors to produce its gratifying effects, which occur within 10 to 15 seconds after a puff. Smokeless tobacco is absorbed more slowly and results in less intense acute pharmacologic effects. With long-term use of tobacco, physical dependence develops, associated with an increased number of nicotinic cholinergic receptors in the brain.[69] When tobacco is unavailable, even for only a few hours, withdrawal symptoms often occur, including anxiety, irritability, difficulty concentrating, restlessness, hunger, craving for tobacco, disturbed sleep, and in some people, depression.

Addiction to tobacco is multifactorial, including a desire for the direct pharmacologic actions of nicotine, relief of withdrawal symptoms, and learned associations. Smokers report a variety of reasons for smoking, including pleasure, arousal, enhanced vigilance, improved performance, relief of anxiety or depression, reduced hunger, and control of body weight. Environmental cues—such as a meal, a cup of coffee, talking on the phone, an alcoholic beverage, or friends who smoke—often trigger an urge to smoke. Smoking and depression are strongly linked. Smokers are more likely to have a history of major depression than are nonsmokers. Smokers with a history of depression are also likely to be more highly dependent on nicotine and have a lower likelihood of quitting. When they do quit, depression is more apt to be a prominent withdrawal symptom.

Most tobacco use begins in childhood or adolescence.[70] Risk factors for youth smoking include peer and parental influences; behavioral problems (e.g., poor school performance); personality characteristics such as rebelliousness or risk taking, depression, and anxiety; and genetic influences. The adolescent's desire to appear older and more sophisticated, by emulating older role models, is another strong motivator. Environmental influences such as advertising and smoking in movies also

contribute. Although smoking rates among adults have been declining since the 1970s, initiation rates for youth have remained constant since the mid-1980s. Approaches to preventing tobacco addiction in youth include educational activities in schools, aggressive anti-tobacco media campaigns, taxation of tobacco products, changing the social and environmental norms (restricting indoor smoking, educating parents not to smoke around children), and deglamorizing smoking.

Neurobiologic Mechanisms of Addiction

Nicotine binds stereoselectively to nicotinic cholinergic receptors in the brain, autonomic ganglia, the adrenal medulla, and neuromuscular junctions. Most relevant to nicotine addiction are the neuronal nicotinic cholinergic receptors. These are found throughout the brain, with the greatest number of binding sites in the cortex, thalamus, and interpeduncular nucleus, and substantial binding in the amygdala, septum, brain-stem motor nuclei, and locus coeruleus. The nicotinic cholinergic receptor is a ligand-gated ion channel, composed of five subunits. Most brain nicotinic cholinergic receptors are comprised of α- and β-subunits. Usually, there are two α- and three β-subunits, with the α-subunits responsible for ligand binding and the β-subunits mediating other aspects of receptor function.[71] There is much diversity of nicotinic cholinergic receptors with nine α-subunit isoforms (α_2 through α_{10}) and three β-subunit isoforms (β_2 through β_4) identified in brain tissues. Different nicotinic receptors are found in different parts of the brain and have different chemical conductances for sodium and calcium and different sensitivity to different nicotinic agonists. The different nicotinic receptors are believed to mediate different pharmacologic actions of nicotine, perhaps corresponding to the multiple effects of nicotine experienced by human smokers.[72]

Nicotine receptors appear to be located both on cell bodies and at nerve terminals. All nicotine receptors are permeable to calcium ions. Nicotinic receptor activation works, at least in part, by facilitating the release of neurotransmitters, including acetylcholine, norepinephrine, dopamine, serotonin, β-endorphin, gamma-aminobutyric acid (GABA), and others.[73] Nicotine enhances fast excitatory synaptic transmission, which may contribute to learning and memory.[74,75] Nicotine also releases growth hormone, prolactin, vasopressin, and adrenocorticotropic hormone (ACTH). Behavioral rewards from nicotine and perhaps nicotine addiction as well appear to be linked to dopamine release.[76]

The two main dopamine systems in the brain are the mesocorticolimbic and the nigrostriatal systems. The mesocorticolimbic system includes the ventral tegmental area projecting to the nucleus accumbens, the cortex, and limbic regions. The nigrostriatal system connects the substantia nigra to the dorsal striatum. Nicotine causes an increase in burst firing of ventral tegmental area neurons, resulting in release of dopamine in the nucleus accumbens.[76] Dopamine release is potentiated and sustained by nicotine-mediated release of glutamate.[77] Dopamine release in the outer shell of the nucleus accumbens is characteristic of the effects of many addicting drugs (e.g., heroin, cocaine, alcohol) and is thought to be an important site for drug-mediated reinforcement.[78]

Whereas acute exposure to nicotine produces stimulation of dopaminergic neurons in mesolimbic pathways, chronic exposure to nicotine and other drugs of abuse produces other changes in mesolimbic function. Chronic nicotine exposure results in neuroadaptation or the development of tolerance, and the absence of nicotine results in subnormal release of dopamine and other neurotransmitters. Thus, nicotine withdrawal may result in a state of deficient dopamine responses to novel stimuli in general and to a state of malaise and inability to experience pleasure. This has been termed by Koob and LeMoal as "hedonic dysregulation."[79] Hedonic dysregulation may explain craving, and sensitivity to drug effects may explain why even a single slip might easily result in a return to compulsive drug use.

The release of various neurotransmitters discussed previously results in behavioral arousal, sympathetic neural activation, and a number of other effects that are believed to be rewarding.[80] The release of specific neurotransmitters has been speculatively linked to the reported reinforcing effects of nicotine (Fig. 40-1). For example, enhanced release of dopamine and norepinephrine may be associated with pleasure as well as appetite suppression, the latter of which may contribute to lower body weight. Release of acetylcholine may be associated with improved performance on behavioral tasks and improvement of memory. Release of β-endorphin may be associated with reduction of anxiety and tension.

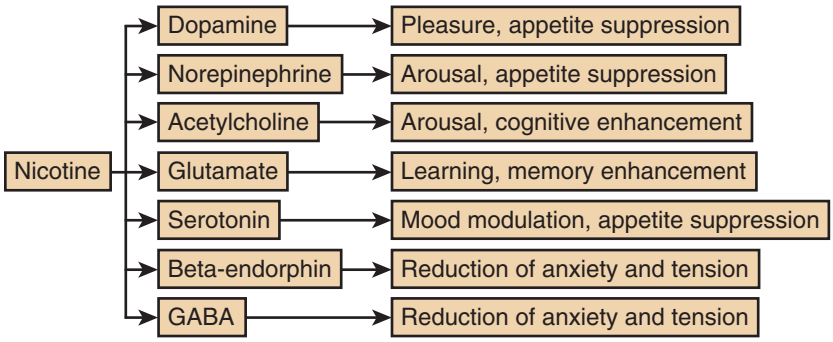

FIGURE 40-1 ■ Neurochemical effects of nicotine.

Although smokers give different explanations for their smoking, most agree that smoking produces arousal, particularly with the first cigarettes of the day, and relaxation, particularly in stressful situations. Consistent with reports of arousal, cigarette smoking or administration of nicotine induces electroencephalographic desynchronization, with an upward shift in the dominant alpha frequency and decreased total alpha and theta power.[81]

Low-Yield Cigarettes

It has been clearly demonstrated that smokers regulate their intake of nicotine. Smokers change the way they puff a cigarette depending on nicotine yield, as determined by a cigarette smoking machine.[82,83] They puff lower-yield cigarettes more frequently or more intensely than higher-yield cigarettes, presumably to obtain more nicotine. Smokers who switch from higher-yield to lower-yield cigarettes consume more nicotine from the lower-yield cigarettes than is predicted by smoking machine tests. Conversely, smokers consume less nicotine than predicted from higher-yield cigarettes. The intake of nicotine, with blood cotinine or nicotine concentrations or urine metabolites used as markers of nicotine intake, has been studied in large groups of people smoking their own chosen brand of cigarettes.[82] In such studies, nicotine intake correlates only weakly with the machine-determined yield. Despite smoking cigarettes with widely differing nicotine yields, smokers demonstrate only small differences in nicotine intake. Correspondingly, the health benefits of switching from higher-yield to lower-yield cigarettes are quite small, if any.[84,85]

The shift over the years from higher- to lower-yield cigarettes may explain the change in the pathology of lung cancer.[86] That is, the percentage of lung cancers that are adenocarcinomas has increased, while the percentage of squamous cell cancers has decreased. The change in tumor type is believed to reflect the higher nitrosamine delivery of lower-yield cigarettes and the increased depth or volume of inhalation of lower-yield cigarettes to compensate for lower level concentrations of nicotine in the smoke.

SMOKING CESSATION

Of cigarette smokers, 70% would like to quit and 46% try to quit each year. Spontaneous quit rates are about 1% per year. Simple physician advice to quit increases the quit rate to 3%. Minimal intervention programs increase quit rates to 5% to 10%, whereas more intensive treatments, including smoking-cessation clinics, can yield quit rates of 25% to 30%.[87]

The main strategies for cessation are behavioral counseling, pharmacologic intervention, or a combination of the two. Many patients try over-the-counter smoking cessation medications prior to discussing smoking with their healthcare providers. The efficacy of over-the-counter medications may be limited by improper use of medications and concomitant untreated issues such as depression, alcoholism, or other factors. Before a therapeutic intervention is attempted, it is important to obtain a history assessing the level of stress, possible exposure to family members or roommates who smoke, or other factors shown to predict relapse.

Guidelines

Evidence-based guidelines for the treatment of tobacco addiction emphasize identifying all tobacco users in a physician's practice and ascertaining each patient's intent with respect to quitting smoking (Fig. 40-2).[88] Identification of tobacco use is facilitated by the implementation of an office-based system so that patients are queried about tobacco use at every visit. Tobacco use

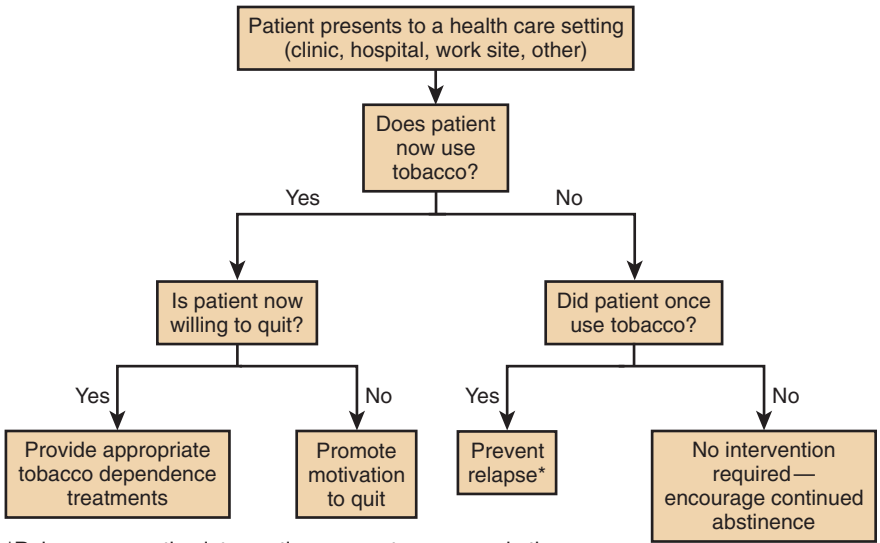

FIGURE 40-2 ■ An algorithm for treating tobacco use.

*Relapse prevention interventions are not necessary in the case of the adult who has not used tobacco for many years.

should be treated as a vital sign by using tobacco status stickers on patients' charts, electronic medical records, or computer reminder systems. The practice of routinely recording a patient's tobacco use status increases the odds ratio for quitting by twofold. Pediatric patients and patients with COPD and asthma should also be asked routinely about their secondhand smoke exposure and counseled to avoid all exposure.

Brief strategies to help a patient quit (the "5 A's") (Table 40-6), which can be implemented in as little as 3 minutes, increase cessation rates significantly. In a meta-analysis of 31 trials, brief physician advice increased quit rates by 70%.[87] Intensive behavioral treatment of tobacco dependence produces higher success rates than brief advice does and is cost-effective. However, these intensive programs are less widely available and may be less acceptable to patients than brief interventions. Nevertheless, clinicians with training in intensive smoking-cessation therapy should be identified as a referral source for smokers who are interested.

The recent Public Health Service guideline[88] recommends that all smokers trying to quit should be offered pharmacotherapy (Table 40-7). In brief, three types of medications have been approved by the U.S. Food and Drug Administration (FDA) for smoking cessation—bupropion, which was originally marketed as an antidepressant drug, nicotine, and varenicline (Table 40-8). Other drugs such as nortriptyline and clonidine have been shown in clinical trials to be effective in aiding smoking cessation but have not been approved by the FDA for this purpose.

Smoking-Cessation Counseling

Counseling smokers about the dangerous effects of tobacco should be routine medical practice and has been

TABLE 40-6. Brief Strategies to Help the Patient Willing to Quit Tobacco Use—The "5 A's"

Strategies for Implementation	Action
Ask—Systematically identify all tobacco users at every visit.	Implement an office-wide system that ensures that, for every patient at every clinic visit, tobacco-use status is queried and documented.
Advise—Strongly urge all tobacco users to quit.	In a clear, strong, and personalized manner, urge every tobacco user to quit.
Assess—Determine willingness to make a quit attempt.	Ask every tobacco user if he or she is willing to make a quit attempt at this time (e.g., within the next 30 days).
Assist—Aid the patient in quitting.	Help the patient with a quit plan.
	Provide practical counseling (problem solving/skills training).
	Provide encouragement and support during treatment.
	Help patient obtain outside social support.
	Recommend the use of approved pharmacotherapy except in special circumstances.
Arrange—Schedule follow-up contact.	Schedule follow-up contact, either in person or via telephone.

Adapted from A clinical practice guideline for treating tobacco use and dependence: 2008 update. A U.S. Public Health Service report. Am J Prev Med 35:158–176, 2008.

TABLE 40-7. General Clinical Guidelines for Prescribing Pharmacotherapy for Smoking Cessation

- In general, all smokers trying to quit smoking should be offered pharmacotherapy.
- There are seven first-line smoking cessation medications—five types of nicotine replacement therapy, sustained-release bupropion, an antagonist of the nicotinic receptor, and varenicline, a partial agonist of the nicotinic receptor. Varenicline or the combination of nicotine patch plus ad libitum short-acting nicotine products appear to be the most effective. However, the choice of first-line therapy should be governed by patient preference, familiarity of the clinician with the medication, contraindications for specific patients, and prior experience of the patient with specific pharmacotherapies.
- Second-line therapies include clonidine and nortriptyline. These should be reserved for individuals with contraindications to/or failure of response to first-line medications.
- Bupropion and nicotine replacement therapies may delay but not prevent weight gain after smoking cessation. It is recommended that patients start or increase physical activity, but strict dieting is discouraged because this appears to increase the likelihood of relapse to smoking. Patients should be reassured that weight gain after quitting is self-limited and poses much less of a risk to health than smoking.
- Transdermal nicotine (patches), nicotine gum, and bupropion appear to be safe for patients with chronic cardiovascular disease. Other medications are likely to be much safer than smoking in the presence of medical disease, but need further evaluation.
- In those with prolonged withdrawal symptoms or in those who cannot resist smoking without medication, long-term therapy with nicotine replacement medication, bupropion, or varenicline appears to be safe and effective therapy.
- Recent research suggests that combining bupropion with nicotine patches or combining nicotine patches with ad libitum use of nicotine gum or nicotine nasal spray increases abstinence rates compared with the rates produced by a single form of therapy.

Adapted from A clinical practice guideline for treating tobacco use and dependence: 2008 update. A U.S. Public Health Service report. Am J Prev Med 35:158–176, 2008.

TABLE 40-8. Suggestions for the Clinical Use of Pharmacotherapies for Smoking Cessation

Pharmacotherapy	Precautions/ Contraindications	Adverse Effects	Dosage	Duration	Availability
FIRST-LINE					
Bupropion hydrocloride, Sustained release	History of seizure History of eating disorders	Insomnia Dry mouth	150 mg every morning for 3 days then 150 mg twice daily (begin treatment 1–2 wk prequit)	7–12 wk maintenance up to 6 mo	Prescription only
Varenicline	Significant kidney disease Patients on dialysis	Nausea Abnormal or vivid strange dreams Depressed mood and other psychiatric symptoms Trouble sleeping	0.5 mg/day for 3 days, 0.5 mg twice/day for 4 days, then 1 mg twice/day (begin treatment 1 wk prequit)	3–6 mo	Prescription only
Nicotine gum	Temperomandibular joint disorder	Mouth soreness Dyspepsia	if 1–24 cigarettes/day; 2 mg gum (≤24 pieces/day) if ≥25 cigarettes/day; 4 mg gum (≤24 pieces/day)	≤12 wk	OTC only
Nicotine inhaler		Local irritation of mouth and throat	6–16 cartridges/day	≤6 mo	Prescription only
Nicotine nasal spray	Chronic nasal disorders, including rhinitis, polyps, and sinusitis	Nasal irritation Throat burning	8–40 doses/day	3–6 mo	Prescription only
Nicotine patch	Skin diseases, such as atopic or eczematous dermatitis	Local skin reaction Insomnia	21 mg/24 hr 14 mg/24 hr 7 mg/24 hr 15 mg/16 hr	4 wk then 2 wk then 2 wk 8 wk	Prescription and OTC
SECOND-LINE					
Clonidine	Rebound hypertension	Dry mouth Drowsiness Dizziness Sedation	0.15–0.75 mg/day	3–10 wk	Prescription only (oral formulation) Prescription only (patch)
Nortriptyline	Risk of arrhythmias	Sedation Dry mouth	75–100 mg/day	12 wk	Prescription only

OTC, over the counter.
Adapted from A clinical practice guideline for treating tobacco use and dependence: 2008 update. A U.S. Public Health Service report. Am J Prev Med 35:158–176, 2008.

shown to be an effective method to improve cessation rates. Based on a review of 188 randomized trials, personal advice and encouragement to stop smoking provided by a physician during a routine office visit resulted in an estimated 2% of all smokers stopping and not relapsing over 1 year.[89] Whereas this percentage seems low, it is both cost-effective and important when considering the large population at risk for disease. Specific patient populations may have better results—8% of pregnant smokers, 21% of healthy men at risk for cardiovascular disease, and 36% of survivors of myocardial infarction will stop smoking when receiving advice and encouragement. This high success rate reflects the patient's inherent motivation once challenged by a condition that has been caused or may be aggravated by cigarette smoking.

Group counseling is less cost-effective than brief advice, but may be necessary for smokers who are having a hard time quitting with less intensive therapy. A review of 16 studies comparing group counseling found increased rates of cessation over that of self-help programs (16 studies; OR 1.97) or no intervention (6 studies; OR 2.19).[87] There is no evidence that group counseling is more effective than a similar intensity of individual counseling.

Telephone counseling is also effective in promoting cessation. In a large randomly controlled trial of 1973 intensively counseled callers versus 1309 controls, tele-

phone counseling through the California Quitline nearly doubled abstinence rates.[90] The 12 month self-reported cessation rates for those who made one or more cessation attempts was 23.3% in the treatment group and 18.4% in the control group. Telephone hot lines for smoking cessation are available at no cost in many states across the United States. Thus, the busiest physician can easily refer patients to a hot line for cessation if personal counseling time is not readily available.

Another approach to smoking-cessation counseling that requires no physician resources and allows smokers to be counseled in their homes is the use of web- and computer-based smoking-cessation programs. A number of clinical trials have been conducted on the effectiveness of these interventions, and a meta-analysis of those trials has been recently published.[91] Both web- and computer-based interventions were found to be effective, with a relative risk for smoking cessation of 1.40 (95% CI, 1.13–1.72) and 1.48 (1.25–1.76), respectively.

In-hospital counseling is found to be effective for patients admitted with cardiovascular disease, but is not well studied in other populations. Molyneux and associates[92] evaluated 274 patients in a randomized, controlled trial and found that nicotine replacement therapy given with brief counseling is more effective than counseling alone or usual care. Counseling alone was not more effective than usual care, and differences between all groups disappeared at 12 months. These findings underscore the value of cessation medications when given with even brief advice. Longer physician counseling time and more office visits translate into higher cessation rates, independent of pharmacotherapy.

Pharmacotherapy of Smoking Cessation

Nicotine Replacement Therapy

Currently, three medications have been approved for smoking cessation: nicotine, bupropion, and varenicline. All types of smoking-cessation medications, if used properly, double smoking-cessation rates compared with placebo treatments.[88] Nicotine replacement medications include 2- and 4-mg nicotine polacrilex gum, transdermal nicotine patches, nicotine nasal spray, the nicotine inhaler, and nicotine lozenges. All seem to have comparable efficacy but, in a randomized study, compliance was greatest for the patch, lower for gum, and very low for the spray and the inhaler.[93] A smoker should be instructed to quit smoking entirely before beginning nicotine replacement therapies. Optimal use of nicotine gum includes instructions to chew slowly, to chew 8 to 10 pieces/day for 20 to 30 minutes each, and to continue long enough for the smoker to learn a lifestyle without cigarettes, usually 3 months or longer. Side effects of nicotine gum are primarily local and can include jaw fatigue, sore mouth and throat, upset stomach, and hiccups.

Several different transdermal nicotine preparations are marketed—three deliver 21 or 22 mg over a 24-hour period, and one delivers 15 mg over a period of 16 hours. Most brands have lower-dose patches for tapering. Patches are applied in the morning and removed either the next morning or at bedtime, depending on the patch. Patches intended for 24-hour use can also be removed at bedtime if the patient is experiencing insomnia or disturbing dreams. Full-dose patches are recommended for most smokers for the first 1 to 3 months, followed by one to two tapering doses for 2 to 4 weeks each. Nicotine nasal spray, one spray into each nostril, delivers about 0.5 mg nicotine systemically and can be used every 30 to 60 minutes. Local irritation of the nose commonly produces burning, sneezing, and watery eyes during initial treatment, but tolerance develops to these effects in 1 to 2 days. The nicotine inhaler actually delivers nicotine to the throat and upper airway, from where it is absorbed similarly to nicotine from gum. It is marketed as a cigarette-like plastic device and can be used ad libitum.

Most recently, nicotine lozenges have been marketed over the counter. The lozenges are available in 2- and 4-mg strengths and are to be placed in the buccal cavity where they are slowly absorbed over 30 minutes.[94] Smokers are instructed to choose their dose according to how long after awakening in the morning they smoked their first cigarette (a measure of the level of dependence). Those who smoke within 30 minutes are advised to use the 4-mg lozenge, whereas those who smoke their first cigarette at 30 or more minutes are advised to use the 2-mg lozenges. Use is recommended every 1 to 2 hours.

Nicotine medications seem to be safe in patients with cardiovascular disease and should be offered to them.[95–98] Although smoking-cessation medications are recommended by the manufacturer for relatively short-term use (generally 3–6 mo), the use of these medications for 6 months or longer is safe and may be helpful in smokers who fear relapse without medications.

Bupropion

Bupropion sustained release, a dopamine-norepinephrine reuptake inhibitor that also has nicotinic cholinergic receptor antagonist activity, was originally marketed and is still widely used as an antidepressant. Bupropion was found to aid smoking cessation independent of whether a smoker was depressed or not.[99] Hurt and coworkers[99] demonstrated that with a 300-mg sustained-release dose, 44% of patients quit at 7 weeks versus 19% of controls. This difference was sustained at 12 months (23% vs. 12%). This study also indicated that when smokers quit, they gain less weight while taking bupropion compared with placebo. An additional randomized, placebo-controlled trial demonstrated that the combination of bupropion with a nicotine patch is safe, and that bupropion alone or in combination was as effective or more effective than the patch alone.[100] Bupropion used for 1 year for relapse prevention was demonstrated to be safe and effective and significantly better at promoting cessation (55%) than placebo (42%) (assessed as *point prevalence abstinence*, or no smoking within seven days of assessment).[101] Given its antidepressant properties, bupropion is a logical choice for depressed

smokers but, as mentioned previously, has clear efficacy in smokers without depression as well.

Bupropion is dosed at 150 mg sustained release per day for 7 days prior to stopping smoking, then at 300 mg (two 150-mg sustained-release doses) per day for the next 6 to 12 weeks. Bupropion in excessive doses can cause seizures and should not be used in an individual with a history of seizures or with eating disorders (bulemia or anorexia).

Varenicline

Varenicline, available by prescription only, is a nicotinic receptor partial agonist that selectively binds to $\alpha4\beta2$ nicotinic cholinergic receptors in the brain.[102] This receptor mediates dopamine release and is thought to be the major receptor involved in nicotine addiction. A partial agonist means that the drug both activates the receptor and blocks the effects of other agonists on the receptor. Varenicline activates the $\alpha4\beta2$ nicotinic cholinergic receptor with a maximal effect about 50% that of nicotine and, at the same time, blocks effects of nicotine from tobacco use on the receptor. As a consequence of the receptor stimulation, nicotine withdrawal symptoms are relieved, and as a consequence of receptor blockade, the rewarding effects of smoking are diminished. The latter effect reduces the desire to smoke and, in the case of a lapse, may prevent continued smoking.

In clinical trials, varenicline treatment for 12 weeks has been shown to be more effective than bupropion sustained-release 300 mg and placebo.[103] Abstinence rates from 9 to 52 weeks were 23%, 15%, and 10% for varenicline, bupropion, and placebo, respectively (assessed as *continuous abstinence*, or the absence of any smoking during the study period). Varenicline has also been shown to be effective in preventing relapse over 6 months.[104]

The major side effects of varenicline are nausea, vomiting, and insomnia. A variety of neuropsychiatric side effects including depression, psychosis, and suicide have been reported anecdotally but were not observed in clinical trials. The causal relationship between varenicline and these neuropsychiatric events has not been established because smoking cessation itself can be associated with mood disturbances, including suicidality. In any case, smokers treated with varenicline should be advised about possible neuropsychiatric effects and monitored for such events during treatment.

Varenicline is initiated in a dose of 0.5 mg/day for 3 days, then 0.5 mg twice daily for 4 days, followed by a maintenance dose of 1 mg twice daily. Lower doses may be used if nausea is a problem at higher doses. Because varenicline is eliminated by the kidneys, dose reductions are required in the presence of severe renal disease. The approved duration of treatment is 3 months, with another 3 months optional for prevention of relapse.

Combination Therapy

Combined medications for smoking cessation can be more effective than individual therapies, particularly when combining long-acting medications such as nicotine patch or bupropion with short-acting nicotine replacement therapy used at times of intense urges or cravings to smoke. Only the combination of bupropion and transdermal nicotine has been approved by the FDA. However, a number of studies have looked at various combinations of medications, and there have been no significant safety issues.[101,105–107] Studies comparing different therapies have found that combinations are two to three times more effective than single medications used alone. A stepwise process that incorporates combination therapies after patients have failed single therapies would be logical and would balance the increased costs associated with additional medications with increased benefit.

Motivating Smokers to Quit

The well-known association between cigarette use and lethal diseases such as lung cancer, myocardial infarction, stroke, and COPD is insufficient to motivate many cigarette smokers to quit. This is due to addiction to nicotine, which includes denial and rationalization (which are a part of all drug addictions). As described previously, many smokers depend on nicotine to cope with stressors encountered in daily life. The perceived stress-reducing effect of nicotine is rapid and readily available. In contrast, quitting for many smokers results in a period of intense dysphoria and dysfunction that can easily be avoided by smoking one more cigarette. A telephone-based survey conducted in 1999[108] found that only 29% of smokers felt that they were at greater risk of myocardial infarction, and only 40% felt they were at greater risk for development of cancer compared with nonsmokers. This clearly indicates denial of risk and may explain why many smokers become motivated to quit only when they develop a medical condition later in life. Becoming a nonsmoker requires a profound change of self-image and a discovery of personal coping skills that may not have been used previously.

The physician's role in the motivation process can be substantial. The message to the smoker must be consistent and inspirational. Patients clearly respond to physician advice, and hopelessness can by allayed by describing the many options available for cessation medication and counseling. Smoking cessation is the most important health initiative many patients will ever undertake and is highly cost-effective for the healthcare system. It is difficult to address smoking in patients when three or four medical issues are being managed in addition to smoking cessation. For this reason, a separate return appointment focused solely on smoking cessation is recommended.

Motivating patients to quit needs to be more than steering them away from disease, but also steering them toward greater self-control, self-expression, independence, and positive role modeling. Exercise during trials of smoking cessation may reduce anxiety, tension, and stress but was not found to be an independent predictor of success in a randomized, controlled trial.[109] Walking on a regular basis is a reasonable initial step and in many cases improves self-esteem and investment in health.

Benefits of Quitting

The benefits of quitting smoking are substantial for smokers of any age. A person who quits smoking before age 50 has half the risk of dying in the next 15 years compared with a continuing smoker.[110] Smoking cessation reduces the risks of developing lung cancer, with the risk falling to half that of a continuing smoker by 10 years and one sixth that of a smoker after 15 years' cessation. Quitting smoking in middle age substantially reduces lung cancer risk, with a 50% reduction in risk if a lifelong smoker quits at age 55 compared with age 75.[111] The risk of acute myocardial infarction falls very rapidly after quitting and approaches nonsmoking levels within 1 year of abstinence. Cigarette smoking produces a progressive loss of airway function over time that is characterized by an accelerated loss of forced expiratory volume in 1 second (FEV_1) with increasing age. Loss of FEV_1 due to cigarette smoking cannot be regained by cessation, but the rate of decline slows after smoking cessation and returns to that of nonsmokers.[112] Women who stop smoking during the first 3 to 4 months of pregnancy reduce the risk of having a low-birth-weight infant to that of a woman who has never smoked.

After quitting, smokers gain an average of 5 to 7 pounds, which is perceived by some smokers as undesirable and as a reason not to quit.[113] Smokers tend to be thinner because nicotine increases energy expenditure and suppresses a compensatory increase in food consumption. After they quit smoking, ex-smokers tend to reach the weight expected had they never smoked. On balance, the benefits of quitting far outweigh the risks associated with weight gain, and patients should be counseled accordingly.

Resources for Physicians

Most hospitals have smoking-cessation services available that will enable referral of smokers if deemed necessary. Most states have toll-free quit lines that can be accessed through a national network at 1-800-QUIT-NOW (1-800-784-8669) and that provide smoking-cessation information and counseling and have been shown to be effective.[90] Internet-based programs such as QuitNet (www.quitnet.com) can provide online chat rooms and can give smokers with access to a computer a sense of community with other smokers in a similar position. If patients do not have their own computer, the public library is a smoke-free environment where they can access computers. The American Lung Association (www.lungusa.org) has significant information and a free online program called "Freedom from Smoking" to which patients can be referred (www.ffsonline.org). The Centers for Disease Control and Prevention has information that can be downloaded for adults, youth, and Spanish-speaking patients (www.cdc.gov/Tobacco/). Patients suspected of having underlying depression, anxiety, or other substance abuse disorders may benefit from psychiatric referral to evaluate these conditions known to reduce the likelihood of smoking cessation.[114]

KEY POINTS

- Cigarette smoking is the most important preventable cause of respiratory disease, including lung cancer and COPD, but also of respiratory infections, including pneumococcal pneumonia, influenza, and tuberculosis, as well as for desquamative interstitial pneumonitis and other forms of interstitial lung disease.
- Smoking is a major risk factor for adverse postoperative events, including respiratory infection, cardiovascular events, and delayed wound healing.
- Tobacco use is motivated primarily by a desire for nicotine, a stimulant that acts on specific cholinergic receptors in the brain and leads to changes in brain chemistry and structure.
- Most smokers want to quit smoking but have difficulty doing so because of nicotine addiction. Both behavioral counseling and pharmacotherapy (nicotine replacement therapy, bupropion, and varenicline) enhance quit rates, and the effects of these interventions are generally additive.
- Office practices should identify all smokers, counsel them to quit, and provide guidance and, if necessary, prescriptions for pharmacotherapy.
- Quitting smoking results in tremendous benefits in reducing risks for respiratory cancer as well as for cardiovascular disease risk and in slowing the progression of COPD. Smoking-cessation therapy is far more cost-effective than almost any other preventive medicine intervention.

References

1. Mokdad AH, Marks JS, Stroup DF, Gerberding JL: Actual causes of death in the United States, 2000. JAMA 291:1238–1245, 2004.
2. Peto R, Lopez AD, Boreham J, et al: Mortality from tobacco in developed countries: Indirect estimation from national vital statistics. Lancet 339:1268–1278, 1992.
3. Cigarette smoking among adults—United States, 2007. MMWR Morb Mortal Wkly Rep 57:1221–1226, 2008.

4. Benowitz NL, Schultz KE, Haller CA, et al: Prevalence of smoking assessed biochemically in an urban public hospital: A rationale for routine cotinine screening. Am J Epidemiol 170:885–891, 2009.
5. World Health Organization (WHO): The World Health Report 2002: Reducing Risks, Extending Healthy Life. Geneva: WHO, 2002.
6. Shibuya K, Ciecierski C, Guindon E, et al: WHO Framework Convention on Tobacco Control: Development of an evidence-based global public health treaty. BMJ 327:154–157, 2003.
7. Hoffmann D, Hoffmann I: The changing cigarette, 1950–1995. J Toxicol Environ Health 50:307–364, 1997.
8. Vineis P, Alavanja M, Buffler P, et al: Tobacco and cancer: Recent epidemiological evidence. J Natl Cancer Inst 96:99–106, 2004.
9. Pfeifer GP, Denissenko MF, Olivier M, et al: Tobacco smoke carcinogens, DNA damage and p53 mutations in smoking-associated cancers. Oncogene 21:7435–7451, 2002.
10. Wiencke JK: DNA adduct burden and tobacco carcinogenesis. Oncogene 21:7376–7391, 2002.
11. Hainaut P, Pfeifer GP: Patterns of p53 G–>T transversions in lung cancers reflect the primary mutagenic signature of DNA-damage by tobacco smoke. Carcinogenesis 22:367–374, 2001.
12. Wiencke JK, Thurston SW, Kelsey KT, et al: Early age at smoking initiation and tobacco carcinogen DNA damage in the lung. J Natl Cancer Inst 91:614–619, 1999.
13. Flanders WD, Lally CA, Zhu BP, et al: Lung cancer mortality in relation to age, duration of smoking, and daily cigarette consumption: Results from Cancer Prevention Study II. Cancer Res 63: 6556–6562, 2003.
14. Department of Health and Human Services PHS: The Health Consequences of Smoking. Cancer and Chronic Lung Disease in the Workplace. A Report of the Surgeon General. Washington, DC: Government Printing Office, 1985.
15. Thun MJ, Henley SJ, Calle EE: Tobacco use and cancer: An epidemiologic perspective for geneticists. Oncogene 21:7307–7325, 2002.
16. Thomas X, Chelghoum Y: Cigarette smoking and acute leukemia. Leuk Lymphoma 45:1103–1109, 2004.
17. Giovannucci E: An updated review of the epidemiological evidence that cigarette smoking increases risk of colorectal cancer. Cancer Epidemiol Biomarkers Prev 10:725–731, 2001.
18. Nuorti JP, Butler JC, Farley MM, et al: Cigarette smoking and invasive pneumococcal disease. Active Bacterial Core Surveillance Team. N Engl J Med 342:681–689, 2000.
19. Kark JD, Lebiush M, Rannon L: Cigarette smoking as a risk factor for epidemic A(H_1N_1) influenza in young men. N Engl J Med 307:1042–1046, 1982.
20. Barnes PJ, Shapiro SD, Pauwels RA: Chronic obstructive pulmonary disease: Molecular and cellular mechanisms. Eur Respir J 22:672–688, 2003.
21. Walter R, Gottlieb DJ, O'Connor GT: Environmental and genetic risk factors and gene-environment interactions in the pathogenesis of chronic obstructive lung disease. Environ Health Perspect 108(Suppl 4):733–742, 2000.
22. Strachan DP, Butland BK, Anderson HR: Incidence and prognosis of asthma and wheezing illness from early childhood to age 33 in a national British cohort. BMJ 312:1195–1199, 1996.
23. Vesterinen E, Kaprio J, Koskenvuo M: Prospective study of asthma in relation to smoking habits among 14,729 adults. Thorax 43:534–539, 1988.
24. Siroux V, Pin I, Oryszczyn MP, et al: Relationships of active smoking to asthma and asthma severity in the EGEA study. Epidemiological study on the Genetics and Environment of Asthma. Eur Respir J 15:470–477, 2000.
25. Silverman RA, Boudreaux ED, Woodruff PG, et al: Cigarette smoking among asthmatic adults presenting to 64 emergency departments. Chest 123:1472–1479, 2003.
26. Weitzman M, Gortmaker S, Walker DK, Sobol A: Maternal smoking and childhood asthma. Pediatrics 85:505–511, 1990.
27. Leuenberger P, Schwartz J, Ackermann-Liebrich U, et al: Passive smoking exposure in adults and chronic respiratory symptoms (SAPALDIA Study). Swiss Study on Air Pollution and Lung Diseases in Adults, SAPALDIA Team. Am J Respir Crit Care Med 150:1222–1228, 1994.
28. McCrea KA, Ensor JE, Nall K, et al: Altered cytokine regulation in the lungs of cigarette smokers. Am J Respir Crit Care Med 150:696–703, 1994.
29. Desai SR, Ryan SM, Colby TV: Smoking-related interstitial lung diseases: Histopathological and imaging perspectives. Clin Radiol 58:259–268, 2003.
30. Fraig M, Shreesha U, Savici D, Katzenstein AL: Respiratory bronchiolitis: A clinicopathologic study in current smokers, ex-smokers, and never-smokers. Am J Surg Pathol 26:647–653, 2002.
31. Baumgartner KB, Samet JM, Stidley CA, et al: Cigarette smoking: a risk factor for idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 155:242–248, 1997.
32. Arcavi L, Benowitz NL: Cigarette smoking and infection. Arch Intern Med 164:2206–2216, 2004.
33. Almirall J, Gonzalez CA, Balanzo X, Bolibar I: Proportion of community-acquired pneumonia cases attributable to tobacco smoking. Chest 116:375–379, 1999.
34. Mohsen AH, McKendrick MW: Risk factors for pneumonia in adults with chickenpox. J Infect Dis 186:1053, 2002 [author reply 1053–1054].
35. Gajalakshmi V, Peto R, Kanaka TS, Jha P: Smoking and mortality from tuberculosis and other diseases in India: Retrospective study of 43000 adult male deaths and 35000 controls. Lancet 362:507–515, 2003.
36. Slama K, Chiang CY, Enarson DA, et al: Tobacco and tuberculosis: A qualitative systematic review and meta-analysis. Int J Tuberc Lung Dis 11:1049–1061, 2007.
37. Kluger R (ed): Ashes to Ashes: America's Hundred-Year Cigarette War, the Public Health, and the Unabashed Triumph of Philip Morris. New York: Alfred A. Knopf, 1996, p 19.
38. Burns DM: Epidemiology of smoking-induced cardiovascular disease. Prog Cardiovasc Dis 46:11–29, 2003.
39. Benowitz NL: Cigarette smoking and cardiovascular disease: Pathophysiology and implications for treatment. Prog Cardiovasc Dis 46:91–111, 2003.
40. Law MR, Wald NJ: Environmental tobacco smoke and ischemic heart disease. Prog Cardiovasc Dis 46:31–38, 2003.
41. Barry J, Mead K, Nabel EG, et al: Effect of smoking on the activity of ischemic heart disease. JAMA 261:398–402, 1989.
42. Khuder SA, Milz S, Jordan T, et al: The impact of a smoking ban on hospital admissions for coronary heart disease. Prev Med 45:3–8, 2007.
43. Mulcahy R: Influence of cigarette smoking on morbidity and mortality after myocardial infarction. Br Med J 49:410–415, 1983.
44. Rivers JT, White HD, Cross DB, et al: Reinfarction after thrombolytic therapy for acute myocardial infarction followed by conservative management: Incidence and effect of smoking. J Am Coll Cardiol 16:340–348, 1990.
45. Galan KM, Deligonul U, Kern MJ, et al: Increased frequency of restenosis in patients continuing to smoke cigarettes after percutaneous transluminal coronary angioplasty. Am J Cardiol 61:260–263, 1988.
46. Isles C, Brown JJ, Cumming AM, et al: Excess smoking in malignant-phase hypertension. Br Med J 1:579–581, 1979.
47. Suskin N, Sheth T, Negassa A, Yusuf S: Relationship of current and past smoking to mortality and morbidity in patients with left ventricular dysfunction. J Am Coll Cardiol 37:1677–1682, 2001.
48. Moller AM, Villebro N, Pedersen T, Tonnesen H: Effect of preoperative smoking intervention on postoperative complications: A randomised clinical trial. Lancet 359:114–117, 2002.
49. Myles PS, Iacono GA, Hunt JO, et al: Risk of respiratory complications and wound infection in patients undergoing ambulatory surgery: Smokers versus nonsmokers. Anesthesiology 97:842–847, 2002.
50. Vaporciyan AA, Merriman KW, Ece F, et al: Incidence of major pulmonary morbidity after pneumonectomy: Association with timing of smoking cessation. Ann Thorac Surg 73:420–425, 2002 [discussion 425–426].
51. Pungpapong S, Manzarbeitia C, Ortiz J, et al: Cigarette smoking is associated with an increased incidence of vascular complications after liver transplantation. Liver Transpl 8:582–587, 2002.
52. Sung RS, Althoen M, Howell TA, et al: Excess risk of renal allograft loss associated with cigarette smoking. Transplantation 71:1752–1757, 2001.

53. Warner MA, Divertie MB, Tinker JH: Preoperative cessation of smoking and pulmonary complications in coronary artery bypass patients. Anesthesiology 60:380–383, 1984.
54. Sorensen LT, Jorgensen T: Short-term pre-operative smoking cessation intervention does not affect postoperative complications in colorectal surgery: A randomized clinical trial. Colorectal Dis 5:347–352, 2003.
55. Rosenstock S, Jorgensen T, Bonnevie O, Andersen L: Risk factors for peptic ulcer disease: A population based prospective cohort study comprising 2416 Danish adults. Gut 52:186–193, 2003.
56. Kato I, Nomura AM, Stemmermann GN, Chyou PH: A prospective study of gastric and duodenal ulcer and its relation to smoking, alcohol, and diet. Am J Epidemiol 135:521–530, 1992.
57. Maity P, Biswas K, Roy S, et al: Smoking and the pathogenesis of gastroduodenal ulcer—Recent mechanistic update. Mol Cell Biochem 253:329–338, 2003.
58. Cho NH, Chan JC, Jang HC, et al: Cigarette smoking is an independent risk factor for type 2 diabetes: a four-year community-based prospective study. Clin Endocrin 71:679–685, 2009.
59. Bjarnason NH, Christiansen C: The influence of thinness and smoking on bone loss and response to hormone replacement therapy in early postmenopausal women. J Clin Endocrinol Metab 85:590–596, 2000.
60. Dempsey DA, Benowitz NL: Risks and benefits of nicotine and other medications to aid smoking cessation in pregnancy. Drug Safety 24:277–322, 2001.
61. Kapoor D, Jones TH: Smoking and hormones in health and endocrine disorders. Eur J Endocrinol 152:491–499, 2005.
61a. Jafri SM, Tilley BC, Peters R, et al: Effects of cigarette smoking and propranolol in survivors of acute myocardial infarction. Am J Cardiol 65:271–276, 1990.
62. Hamilton M, Wolf JL, Rusk J, et al: Effects of smoking on the pharmacokinetics of erlotinib. Clin Cancer Res 12:2166–2171, 2006.
63. van der Bol JM, Mathijssen RH, Loos WJ, et al: Cigarette smoking and irinotecan treatment: Pharmacokinetic interaction and effects on neutropenia. J Clin Oncol 25:2719–2726, 2007.
64. Environmental Protection Agency: Respiratory Health Effects of Passive Smoking: Lung Cancer and Other Disorders. Washington, DC: Office of Research and Development, U.S. Environmental Protection Agency, 1992.
65. California Environmental Protection Agency: Air Resources Board: Proposed Identification of Environmental Tobacco Smoke as a Toxic Air Contaminant. Tobacco Control. CALEPA, 2005.
66. Glantz SA, Parmley WW: Passive smoking and heart disease. Epidemiology, physiology, and biochemistry. Circulation 82:1–12, 1991.
67. Eisner MD, Balmes J, Yelin EH, et al: Directly measured secondhand smoke exposure and COPD health outcomes. BMC Pulm Med 6:12, 2006.
68. Benowitz NL: Pharmacology of nicotine: Addiction, smoking-induced disease, and therapeutics. Annu Rev Pharmacol Toxicol 49:57–71, 2008.
69. Benwell MEM, Balfour DJK, Anderson JM: Evidence that tobacco smoking increases the density of (-)-[^{3}H]nicotine binding sites in human brain. J Neurochem 50:1243–1247, 1988.
70. Institute of Medicine: The nature of nicotine addiction. *In* Lynch BS, Bonnie RJ (eds): Growing Up Tobacco Free—Preventing Nicotine Addiction in Children and Youths. Washington, DC: National Academy Press, 1994, pp 28–68.
71. Picciotto MR, Caldarone BJ, King SL, Zachariou V: Nicotinic receptors in the brain. Links between molecular biology and behavior. Neuropsychopharmacology 22:451–465, 2000.
72. Fattinger K, Verotta D, Benowitz NL: Pharmacodynamics of acute tolerance to multiple nicotinic effects in humans. J Pharmacol Exp Ther 281:1238–1246, 1997.
73. Wonnacott S: Presynaptic nicotinic ACh receptors. Trends Neurosci 20:92–98, 1997.
74. McGehee DS, Heath MJS, Gelber S, et al: Nicotine enhancement of fast excitatory synaptic transmission in CNS by presynaptic receptors. Science 269:1692–1696, 1995.
75. Gray R, Rajan AS, Radcliffe KA, et al: Hippocampal synaptic transmission enhanced by low concentrations of nicotine. Nature 383:713–716, 1996.
76. Corrigall WA, Coen KM, Adamson KL: Self-administered nicotine activates the mesolimbic dopamine system through the ventral tegmental area. Brain Res 653:278–284, 1994.
77. Mansvelder HD, Lodder JC, Sons MS, Kits KS: Dopamine modulates exocytosis independent of Ca(2+) entry in melanotropic cells. J Neurophysiol 87:793–801, 2002.
78. Pontieri FE, Tanda G, Orzi F, DiChiara G: Effects of nicotine on the nucleus accumbens and similarity to those of addictive drugs. Nature 382:255–257, 1996.
79. Koob GF, LeMoal M: Drug abuse: Hedonic homeostatic dysregulation. Science 278:52–58, 1997.
80. Benowitz NL: Clinical pharmacology of nicotine: Implications for understanding, preventing, and treating tobacco addiction. Clin Pharmacol Ther 83:531–541, 2008.
81. Pickworth WB, Herning RI, Henningfield JE: Spontaneous EEG changes during tobacco abstinence and nicotine substitution in human volunteers. J Pharmacol Exp Ther 251:976–982, 1989.
82. Benowitz NL: Compensatory smoking of low yield cigarettes. In Shopland DR, Burns DM, Benowitz NL, Amacher RH (eds): Risks Associated with Smoking Cigarettes with Low Machine-Measured Yields of Tar and Nicotine. NCI Smoking and Tobacco Control Monograph No. 13, NIH Publication No. 02-507. Bethesda, MD: U.S. National Institutes of Health, National Cancer Institute, October, 2001, pp 39–64.
83. Benowitz NL, Jacob P III, Yu L, et al: Reduced tar, nicotine, and carbon monoxide exposure while smoking ultralow- but not low-yield cigarettes. JAMA 256:241–246, 1986.
84. Burns DR, Major JM, Shanks TG, et al: Smoking lower yield cigarettes and disease risks. In Shopland DR, Burns DM, Benowitz NL, Amacher RH (eds): Risks Associated with Smoking Cigarettes with Low Machine-Measured Yields of Tar and Nicotine. NCI Smoking and Tobacco Control Monograph No. 13, NIH Publication No. 02-5074. Bethesda, MD: U.S. National Institutes of Health, National Cancer Institute, October 2001, pp 65–158.
85. Harris JE, Thun MJ, Mondul AM, Calle EE: Cigarette tar yields in relation to mortality from lung cancer in the Cancer Prevention Study II prospective cohort, 1982–8. BMJ 328:72, 2004.
86. Thun MJ, Lally CA, Flannery JT, et al: Cigarette smoking and changes in the histopathology of lung cancer. J Natl Cancer Inst 89:1580–1586, 1997.
87. Lancaster T, Stead L, Silagy C, Sowden A: Effectiveness of interventions to help people stop smoking: Findings from the Cochrane Library. BMJ 321:355–358, 2000.
88. A clinical practice guideline for treating tobacco use and dependence: 2008 update. A U.S. Public Health Service report. Am J Prev Med 35:158–176, 2008.
89. Law M, Tang JL: An analysis of the effectiveness of interventions intended to help people stop smoking. Arch Intern Med 155:1933–1941, 1995.
90. Zhu SH, Anderson CM, Tedeschi GJ, et al: Evidence of real-world effectiveness of a telephone quitline for smokers. N Engl J Med 347:1087–1093, 2002.
91. Myung SK, McDonnell DD, Kazinets G, et al: Effects of Web- and computer-based smoking cessation programs: Meta-analysis of randomized controlled trials. Arch Intern Med 169:929–937, 2009.
92. Molyneux A, Lewis S, Leivers U, et al: Clinical trial comparing nicotine replacement therapy (NRT) plus brief counselling, brief counselling alone, and minimal intervention on smoking cessation in hospital inpatients. Thorax 58:484–488, 2003.
93. Hajek P, West R, Foulds J, et al: Randomized comparative trial of nicotine polacrilex, a transdermal patch, nasal spray, and an inhaler. Arch Intern Med 159:2033–2038, 1999.
94. Shiffman S, Dresler CM, Hajek P, et al: Efficacy of a nicotine lozenge for smoking cessation. Arch Intern Med 162:1267–1276, 2002.
95. Meine TJ, Patel MR, Washam JB, et al: Safety and effectiveness of transdermal nicotine patch in smokers admitted with acute coronary syndromes. Am J Cardiol 95:976–978, 2005.
96. Thomson CC, Rigotti NA: Hospital and clinic-based smoking cessation interventions for smokers with cardiovascular disease. Prog Cardiovasc Dis 45:459–479, 2003.
97. Joseph AM, Fu S: Safety varies for smoking in patients with cardiovascular disease. Prog Cardiovasc Dis 45:429–441, 2003.

98. Miller NH, Smith PM, DeBusk RF, et al: Smoking cessation in hospitalized patients. Results of a randomized trial. Arch Intern Med 157:409–415, 1997.
99. Hurt RD, Sachs DP, Glover ED, et al: A comparison of sustained-release bupropion and placebo for smoking cessation. N Engl J Med 337:1195–1202, 1997.
100. Jorenby DE, Leischow SJ, Nides MA, et al. A controlled trial of sustained-release bupropion, a nicotine patch, or both for smoking cessation. N Engl J Med 340:685–691, 1999.
101. Hays JT, Hurt RD, Rigotti NA, et al: Sustained-release bupropion for pharmacologic relapse prevention after smoking cessation. A randomized, controlled trial. Ann Intern Med 135:423–433, 2001.
102. Coe JW, Brooks PR, Vetelino MG, et al: Varenicline: An alpha-4beta2 nicotinic receptor partial agonist for smoking cessation. J Med Chem 48:3474–3477, 2005.
103. Gonzales D, Rennard SI, Nides M, et al. Varenicline, an alpha-4beta2 nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation: A randomized controlled trial. JAMA 296:47–55, 2006.
104. Tonstad S, Tonnesen P, Hajek P, et al: Effect of maintenance therapy with varenicline on smoking cessation: A randomized controlled trial. JAMA 296:64–71, 2006.
105. Kornitzer M, Boutsen M, Dramaix M, et al: Combined use of nicotine patch and gum in smoking cessation: A placebo-controlled clinical trial. Prev Med 24:41–47, 1995.
106. Puska P, Korhonen HJ, Vartiainen E: Combined use of nicotine patch and gum compared with gum alone in smoking cessation: A clinical trial in North Karelia. Tob Control 4:321, 1995.
107. Blondal T, Gudmundsson LJ, Olafsdottis I, et al: Nicotine nasal spray with nicotine patch for smoking cessation: Randomized trial with six years followup. BMJ 318:285–288, 1999.
108. Ayanian JZ, Cleary PD: Perceived risks of heart disease and cancer among cigarette smokers. JAMA 281:1019–1021, 1999.
109. Ussher M, West R, McEwen A, et al: Efficacy of exercise counselling as an aid for smoking cessation: A randomized controlled trial. Addiction 98:523–532, 2003.
110. Department of Health and Human Services PHS: The Health Benefits of Smoking Cessation. A Report of the Surgeon General. DHHS (CDC) Publication No. 90-8406. Washington DC: Government Printing Office, 1990.
111. Peto R, Darby S, Deo H, et al: Smoking, smoking cessation, and lung cancer in the UK since 1950: Combination of national statistics with two case-control studies. BMJ 321:323–329, 2000.
112. Fletcher C, Peto R: The natural history of chronic airflow obstruction. Br Med J 1:1645–1648, 1977.
113. Williamson DF, Madans J, Anda RF, et al: Smoking cessation and severity of weight gain in a national cohort. N Engl J Med 324:739–745, 1991.
114. Fagerstrom K, Aubin HJ: Management of smoking cessation in patients with psychiatric disorders. Curr Med Res Opin 25:511–518, 2009.

CHAPTER 41

CYSTIC FIBROSIS

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INTRODUCTION

Cystic fibrosis (CF) is a multisystem disorder affecting children and, increasingly, adults.[1] CF is characterized chiefly by chronic airway obstruction and infection and by exocrine pancreatic insufficiency and gastrointestinal tract dysfunction, with consequent effects on nutrition, growth, and maturation. This condition is the most common life-threatening genetic trait in the white population.[2] Numerous mutations of the cystic fibrosis

transmembrane regulator (CFTR) gene are responsible for the CF syndrome and for variation in its severity. The gene encodes the CFTR protein, which is of the membrane protein class. CFTR functions in many tissues as a kinase regulated Cl^- channel. In some tissues, CFTR also regulates the activity of other ion channels. Typically, mutations in CFTR affect both of these functions.

CF is an important medical problem for a number of reasons. It is the major source of severe chronic lung disease in children and has become an important cause of morbidity and mortality from chronic lung disease in young adults. CF is responsible for most cases of exocrine pancreatic insufficiency in childhood and early adulthood and for many cases of nasal polyposis, pansinusitis, rectal prolapse, nonketotic insulin-dependent hyperglycemia, and biliary cirrhosis in these age groups. Therefore, CF enters into the differential diagnosis of many pediatric and young adult patients. Finally, research advances have produced novel pharmacologic therapies to combat the broad range of manifestations and complications.

Central to CF diagnosis and care is a carefully integrated and closely monitored network of approximately 120 referral centers in the United States, sponsored by the Cystic Fibrosis Foundation. The Foundation also supports a smaller number of multidisciplinary research centers aimed at elucidating the molecular pathophysiology and improving the quality of life for patients with CF. Similar care and research centers are found in Canada and many European countries.

HISTORICAL PERSPECTIVES

CF was first described as a distinct clinical entity in the late 1930s. However, numerous references to infants and children with meconium ileus and characteristic pancreatic and lung diseases are sprinkled throughout the literature as early as 1650. Of interest are references in European folklore to the association of salty skin and early demise.[3] Dorothy Andersen,[4] a pathologist at Babies Hospital in New York City, is usually credited with the first comprehensive description of CF in 1938. She coined the term *cystic fibrosis of the pancreas*. In 1945, Farber[5] suggested that CF is a disease of exocrine glands, characterized largely by failure to clear their mucous secretory product. He introduced the term *mucoviscidosis*, which was used for a number of years. Chronic infection of the lungs was recognized early as a major contributing factor, and antibiotics were first used for the treatment of CF in the 1940s. At the same time, an autosomal recessive inheritance pattern for CF was suggested by Andersen and Hodges.[6] In 1953, di Sant'Agnese and colleagues[7] investigated salt depletion in children with CF during a summertime heat wave and concluded that excessive loss of salt occurred via the sweat. Subsequently, they documented that sodium and chloride levels in sweat are elevated in virtually all (>98%) persons with CF. This observation led to a description by Gibson and Cooke[8] of the pilocarpine iontophoresis method for sweat testing, a method that remains the diagnostic standard to this day. By the late 1950s, CF was reported occasionally in older children and young adults. Soon thereafter, comprehensive and aggressive approaches to the care of patients were instituted in many treatment centers, and these approaches have been credited with the survival into adulthood of a steadily increasing number of patients with CF. Since the 1970s, a markedly refined description of the CF syndrome and the many related complications has emerged.

Several more recent observations have resulted in more comprehensive understanding of CF pathogenesis at a molecular level. In the early 1980s, epithelial physiologists described abnormalities of both sodium and chloride transport by CF respiratory epithelia[9] and chloride impermeability of sweat gland ducts from patients with CF.[10] These observations focused attention on a pathogenetic role for abnormal electrolyte and water movement across CF epithelia. From 1985 to 1987, geneticists, using restriction fragment-length polymorphism analysis, located the CFTR gene on the long arm of chromosome 7.[11–14] Shortly thereafter, the CFTR gene was isolated, cloned, and sequenced,[15] and the major mutation of this gene was characterized.[16] Transfer of a wild-type (normal) gene into CF cells corrected the chloride transport defect.[17,18] The product of the CF gene, the CFTR, was studied and found to be both a Cl^- channel[19–21] and a regulator of other channels.[22,23] Studies of the intracellular maturation of CFTR suggested most mutations led to abnormal folding and mislocation of the protein.[24–26] Detailed studies of (1) the structure of CFTR domains[27] and (2) interactions with other proteins during CFTR's maturation process have provided much new information suitable for novel drug design. Knockout of the CFTR gene in transgenic mice has provided an animal model that possesses several physiologic and clinical similarities to human CF.[28–31] These observations provided a detailed understanding of CFTR structure and function and have laid the groundwork for development of more specific therapeutic interventions, including gene therapy.

EPIDEMIOLOGY

CF is recognized in approximately 1:2500[32] and 1:17,000[33] live births in white and black populations, respectively, in the United States. The range of reported incidence figures worldwide varies from 1:569[34] in a confined Ohio Amish population to 1:90,000 in an Asian population of Hawaii.[35]

Generally, mutations of the CF gene are most prevalent in northern and central Europeans and in persons who derive from these areas. An intermediate incidence is likely, although less well documented, in non-European whites. CF is considered rare in American Indians, Asian populations, and black natives of Africa. It has been suggested that the relatively low frequency in populations living in tropical and semitropical geographic locations is related to adverse consequences in the past from excessive salt loss in heterozygotes as well as homozygotes for the CF gene. In white populations, 2%

to 5% are carriers of a CF gene mutation. These people have no clinical stigmas of CF. Although a number of chemical or physiologic alterations have been described in heterozygotes, these alterations can be identified only on a statistical basis.

GENETIC BASIS

CF is an autosomal recessive trait, resulting from mutations at a single gene locus on the long arm of chromosome 7.[32,36] This locus spans approximately 250 kB of DNA, contains at least 27 exons, and codes for a large protein that has several transmembrane domains, two cytoplasmic nucleotide (adenosine triphosphate [ATP])-binding folds (NBFs), and numerous phosphorylation sites contained a cytoplasmic regulatory (R) domain (Fig. 41-1). The primary and secondary structure of the protein product of the CF gene resembles other membrane proteins that act as pumps, for example, the ATP binding cassette (ABC) transporters.[15]

The predominant *CFTR* mutation is a 3 base pair deletion that eliminates the phenylanine of CFTR at position 508, the so-called ΔF508 mutation.[16] This deletion has been detected in 66% of more than 20,000 CF patient chromosomes analyzed worldwide,[2,32,37,38] but its prevalence varies considerably from population to population (Table 41-1). In general, ΔF508 is more prevalent in Northern than Southern European or Middle Eastern populations.[32] More than 1500 other mutations of the CF gene have been reported, but all at a relatively low frequency. The occurrence of known mutations accounts for only 90% of all CF gene abnormalities.[32,38] CFTR mutations include other deletions, missense mutations, nonsense mutations, frameshift mutations, and introduction of new splice sites.[32,38]

Correlations between genotype and phenotype are beginning to emerge. For example, homozygosity for the ΔF508 mutation almost always confers exocrine pancreatic insufficiency.[33] A severe phenotype, including meconium ileus and liver disease, is strongly associated with the presence of two "severe" (i.e., pancreatic exocrine insufficiency) alleles.[39–41] Regions on human chromosomes 4q35, 8p23, 11q25, and 19q13 have been identi-

TABLE 41-1. Frequency of the ΔF508 Mutation

Population	Cystic Fibrosis Chromosomes (%)
North American whites	76
North American Hispanics	46
United Kingdom	74
Spain	49
Italy	43
Ashkenazi Jews	30

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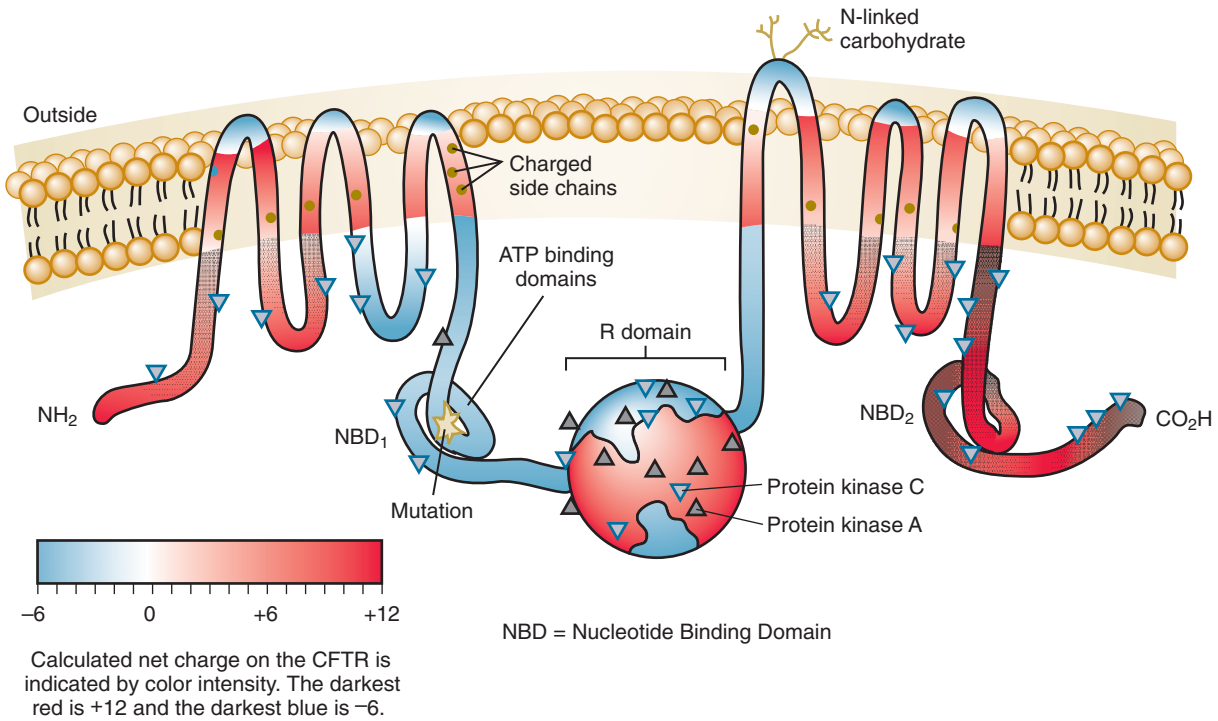

FIGURE 41-1 ■ Proposed structure for the cystic fibrosis transmembrane regulator (CFTR) protein. Two repeat segments each consist of six transmembrane spans followed by a nucleotide-binding domain. The segments are joined by a highly charged region that contains multiple phosphorylation sites, the R domain. Much of the CFTR is intracytoplasmic. Glycosylation occurs on an extracellular loop of the second motif.

fied as modifier loci for meconium ileus.[42,43] Conflicting data exist on whether ΔF508 homozygosity versus other severe alleles is associated with a more severe form of chronic lung disease.[34] Conversely, "mild" mutations with some residual CFTR function and preservation of pancreatic exocrine function have been identified that are associated with normal concentrations of sweat chloride, exocrine pancreatic sufficiency, or both.[44,45] Moreover, variable phenotypes with "mono-organ" disease are also emerging; for example, idiopathic pancreatitis and congenital bilateral absence of the vas deferens are associated with mutations in the CFTR gene.[46–48] In summary, it is now clear that CF is indeed a syndrome, caused by many combinations of mutations at a single gene locus, each of which may confer a slightly different phenotype.[49] The ultimate phenotype of each person with CF is undoubtedly also influenced by genetic background, that is, "modifier genes,"[50–53] as well as postnatal environmental factors.[54]

DNA analysis can now be used to confirm the diagnosis, make prenatal diagnoses, and screen for carrier status in selected cases. For example, probes for 28 of the most common CF mutations in North Carolina provided definitive diagnostic information in less than 90% of persons with CF. Screening for CF carriers using the ΔF508 probe will identify only 50% to 60% of couples at risk of having a CF child.[55]

The high frequency of CF gene mutations in many populations has been ascribed to an unknown heterozygote advantage. Some evidence suggests a reproductive advantage for the carrier state.[56,57] Others have postulated that reduced capacity to generate a secretory diarrhea in response to cholera infection, because of diminished intestinal chloride transport, may have provided an historical survival advantage to heterozygotes.[58–60]

PATHOLOGY

Soon after the original description of the CF syndrome, Farber[5] pointed out the prominent accumulation of mucus in the respiratory and gastrointestinal tracts. Subsequently, mucus stasis has been described in numerous sites, including the conducting airways of the lung,[61] paranasal sinuses, mucus-secreting salivary glands, apocrine sweat glands, small intestine, appendix, pancreas, biliary system, uterine cervix, and wolffian duct structures. However, the eccrine sweat gland, which figures prominently in the pathophysiology of CF, is morphologically normal at all ages. Pathologic changes in the lung, which is the primary site of organ dysfunction, also reflect chronic infection.

Lung Pathology

It is clear that disease of the conducting airways in CF is acquired postnatally. The airways of children with CF who have died within the first days of life display only subtle abnormalities. The earliest macroscopic pathologic lesion is reported to be mucous obstruction of bronchioles.[61] However, the numbers and distribution of mucus-producing goblet cells and the numbers and size of submucosal glands appear to be within normal ranges at birth. A careful morphometric analysis of CF airways early in life demonstrated dilation of submucosal gland acinar and ductal lumens before reaction to chronic infection would be expected.[62] This finding suggests that either hypersecretion or, more likely, failure to clear secretions at an early age accounts for mucus accumulation in bronchial regions, whereas the mucus retention in bronchioles presumably reflects the failure to clear mucus secreted by surface secretory (goblet) cells. Failure to clear secretions from the airway lumens likely initiates infection.

With the progression of lung disease, evidence for bronchiolitis and bronchitis becomes more prominent, the submucosal glands hypertrophy, and goblet cells not only become more numerous but also propagate into the bronchioles. Small airways may be completely obstructed by secretions (Fig. 41-2).[63] Bronchiolectasis and then bronchiectasis are consequences of persistent obstruction-infection cycles. Bronchiectasis had been thought to be manifest in the second decade of life, but now is being detected earlier in life with increased use of computed tomography (CT) scans. Pneumonia, when present, generally assumes a peribronchial pattern.

Detailed pathologic descriptions of lung disease are based on examination of lungs at autopsy or lung transplant and reflect advanced changes.[64–67] Bronchiectatic cysts occupy as much as 50% of the cross-sectional area of the late-stage CF lung.[68] In general, bronchiectasis is more severe in upper than in lower lobes. In addition to dilation of the small airways, bronchioles may be stenotic or even obliterated. The extent of obliterative bronchiolitis appears to be directly correlated with age at death.[65] Autopsied lungs also show extensive overinflation of air spaces. Small amounts of destructive emphysema are seen in many patients, especially those who have lived for 2 or 3 decades.[65] Absence of more extensive alveolar wall destruction can be explained by the confinement of chronic infection to conducting airways. Several patterns of interstitial pneumonia have also been described in autopsied lungs, including usual interstitial pneumonitis, interstitial pneumonitis with organizing pneumonia, and diffuse alveolar damage.[69] Fibrosis is extensive in peribronchiolar and peribronchial regions and may contribute to the restrictive lung function pattern that is superimposed on obstruction in end-stage lung disease.[70] Subpleural cysts often occur on the mediastinal surfaces of the upper lobes and are thought to be related to the frequent occurrence of pneumothorax in patients with advanced lung disease.[71] The bronchial arteries become large and tortuous,[72] contributing to a propensity for hemoptysis in ectatic airways. The pulmonary arteries display varying degrees of change reflecting pulmonary hypertension.

Other Respiratory Tract Pathology

Hypertrophy and hyperplasia of secretory elements, mucus accumulation, and chronic inflammatory changes are also features of the paranasal sinuses and the nasal

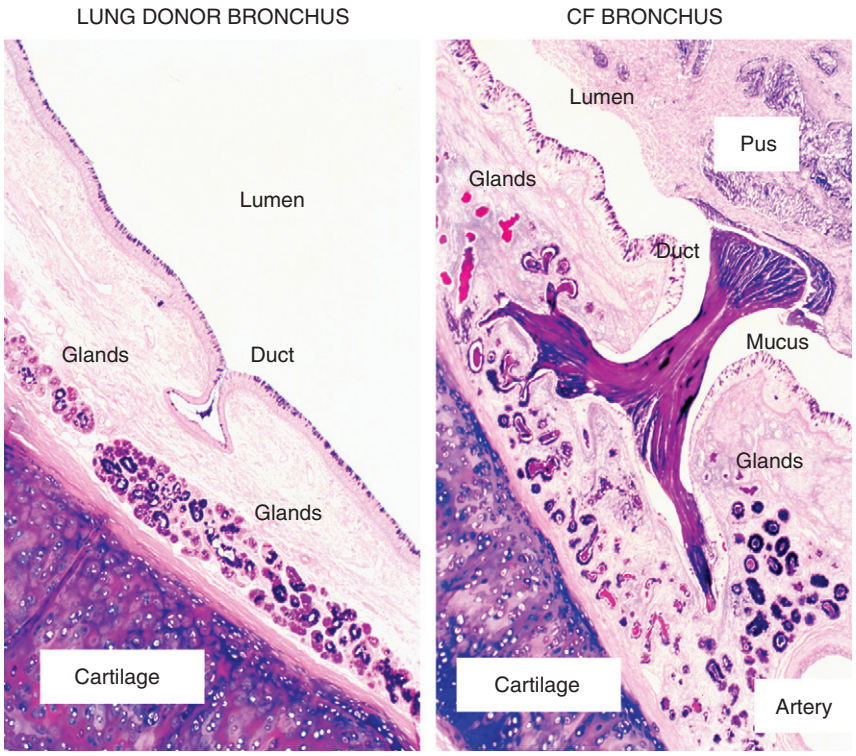

FIGURE 41-2 ■ Large airway pathology. Representative photomicrograph from a lung donor on the left and from an end stage CF lung excised at transplant on the right. In the CF example, note the thinner, less dense appearance of the cartilage, apparent bronchial artery hypertrophy, thickening of the lamina propria with a greater proportion occupied by glands (higher Reid index), a prominent arborized mucus plug in gland ducts, hypertrophic surface epithelium and abundant luminal mucopurulent secretions. Note areas of post-obstructive gland atropy in the end stage CF specimen. (Alcian blue-Periodic acid-Schiffs stain, original magnification ×20.) (Images provided by Dr. Scott H. Randell.)

passages. A common feature of nasal pathology is inflammatory edema of the mucosa with subsequent pedunculation and formation of polyps.[73]

Nonrespiratory Pathologic Features

Most of the nonpulmonary pathology in CF occurs in the gastrointestinal tract and related organs. Striking changes are seen in the exocrine pancreas.[74] Obstruction of ducts by inspissated secretions is an early feature, followed by dilation of secretory ducts and acini and flattening of the epithelium. Loss of acinar cells is widespread, and areas of destruction are replaced by fibrous tissue and fat. Intraluminal calcifications may occur and may be recognized radiographically. Small cysts are common and generally represent dilated ducts. Inflammatory changes are not prominent. The islets of Langerhans are spared until later periods of life. Changes in the islets include disruption by fibrous tissue bands that may provide a barrier between hormone-secreting cells and the vascular spaces.[75] Pathologic changes in the pancreas are used occasionally to make a postmortem diagnosis in atypical or missed cases of CF.

The pancreas is abnormal in almost all patients with CF and is virtually destroyed in approximately 90% of CF patients studied at autopsy. Liver changes are not as frequent or consistent.[76,77] In 25% or more of all autopsies, islands of relatively normal parenchymal cells are divided by fibrotic bands, creating a distinctive multilobular appearance. Microscopically, this focal biliary cirrhosis is characterized by inspissation of secretions within the bile ductules, bile duct proliferation, inflammatory reaction, and a paucity of evidence for bile stasis. Approximately 30% of patients also display fatty infiltration of the liver, which cannot always be ascribed to malnutrition. In approximately 25% of cases, the gallbladder is hypoplastic and contains a gelatinous mucus-like material. Cholelithiasis is an increasingly frequent observation.

Changes in the intestinal tract itself are less prominent.[78] Brunner's glands of the duodenum are hypertrophied, with dilated ducts and acinar lumens filled with mucus. There is little, if any, primary change of the small intestinal tract mucosa. The appendix frequently displays goblet cell hyperplasia of the epithelium and accumulation of secretions within crypts and in the lumen, changes that may be diagnostic of CF. A number of investigators have claimed the ability to diagnose CF by rectal biopsy, based on goblet cell hyperplasia and accumulation of mucus in the crypts.[78a] However, subsequent studies have demonstrated that these findings are not consistent in the rectal mucosa of patients with CF.[79]

Reproductive abnormalities are frequent and characteristic.[80] In a large majority of male patients with CF, the vas deferens, the tail and body of the epididymis, and the seminal vesicles are obliterated by fibrous tissue or are completely absent. Women with CF have mucus-distended uterine cervical glands and plugging of the cervical canal with tenacious mucous secretions. Endocervicitis is a frequent finding.

Non–mucus-secreting glands such as the sweat glands and the parotid salivary glands have a normal gross and histologic appearance. Mucus-secreting salivary glands are usually somewhat enlarged, contain prominent mucus-secreting cells, and display a varied amount of mucus plugging in duct lumens.

PATHOPHYSIOLOGY

Cystic Fibrosis Transmembrane Regulator Protein: Structure, Metabolism, and Function

The CFTR is a single peptide chain that contains 1480 amino acids. The calculated molecular weight is 170 kD, but CFTR migrates in its mature form as an approximately 180-kD glycoprotein due to variable *N*-glycosylation.[32,81] Figure 41-1 demonstrates the domain structure of CFTR, with two repeat motifs, each consisting of six transmembrane-spanning segments followed by a consensus NBF (ATP-binding region). These two segments are linked by a highly charged region, the R (regulatory) domain, that contains multiple phosphorylation sites.[15] The N and C terminii contain important motifs that mediate protein-protein interactions that position CFTR within specialized cellular domains in the apical membrane of epithelia.[82,83] The CFTR structure closely resembles that of a number of other solute transport proteins and places the CF gene product in the ABC super family of proteins.[84] This homology has facilitated the three-dimensional structural modeling of this and other members of the ABC transporter protein family.[27]

CFTR mRNA expression is largely restricted to epithelial cells and is found at moderate levels in human pancreas, salivary glands, sweat glands, intestine, liver (cholangiocytes), and the reproductive tract.[15,81,85] In the lung, CFTR mRNA is expressed in the surface epithelium of the airways and within serous cells of submucosal glands.[86] These sites of CFTR mRNA expression are consistent with locations of tissue dysfunction in patients with CF. Biochemical and immunohistochemical studies describe an apical membrane location for CFTR in predominantly ciliated cells in the lung,[87] although CFTR may also be inserted into the basolateral membrane of sweat ductal epithelia.[88]

Most studies indicate that a central feature of the molecular pathophysiology of CF is that mutated CFTR (e.g., ΔF508) is not normally folded and processed and, hence, does not reach the Golgi or apical plasma membranes (Fig. 41-3).[24,89] The abnormal CFTR ΔF508 trafficking is temperature-sensitive, and some degree of normal processing and delivery of CFTR ΔF508 to the plasma membrane can be detected when temperatures are lowered.[90] Considerable information is emerging on the (1) interactions between different domains of CFTR during folding[27] and (2) the "interactome" of proteins involved in assisting CFTR in this folding process.[91–93]

Most (>80%) of the other identified CFTR mutations also produce a protein that is not normally processed.[94]

Abnormal processing, however, is not characteristic of all CFTR mutations.[94,95] Mutant CFTR may reach the plasma membrane but be refractory to regulatory influences or exhibit conduction abnormalities as a consequence of several types of CFTR gene mutations.[96] The classification of a mutation as one producing a maturational defect versus a regulation/gating defect has become increasingly important, as novel pharmacologic therapies are becoming available that are targeted toward specific CFTR dysfunctions (see later).

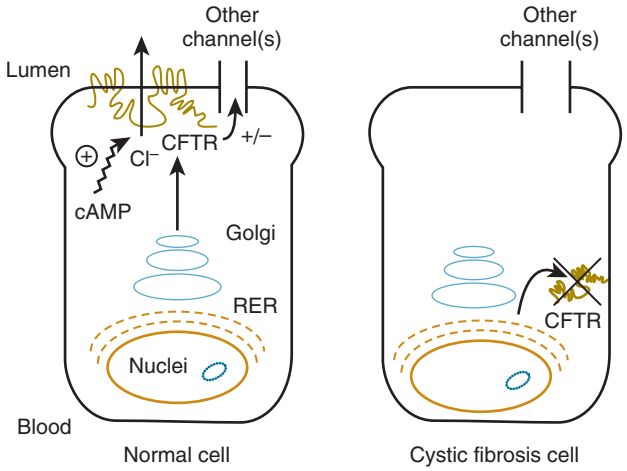

FIGURE 41-3 ■ Schema of biogenesis of CFTR in normal cell (*left*) and ΔF508 CF cell (*right*). In the normal cell, the mature CFTR polypeptide has been synthesized in the rough endoplasmic reticulum (RER), glycosylated in the Golgi, and localized to the apical membrane to function as a cAMP-regulated Cl^- channel and regulator of other channels (e.g., as an inhibitor of the epithelial Na^+ channel). In the CF cell, the ΔF508 CFTR polypeptide has misfolded and been degraded by intracellular proteolytic airways. Hence, it is not positioned in the apical membrane to act as a cAMP-regulated Cl^- channel or to inhibit epithelial Na^+ channel.

The CFTR protein has multiple functions (see Fig. 41-3). It serves as a chloride channel,[20,21] modulates the activity of other plasma membrane channels,[22,23] and perhaps regulates exocytotic and endocytotic events.[97,98] Most of these functions reside at the plasma membrane, although there are unconfirmed data suggesting a role for CFTR in regulating the milieu of intracellular compartments.[99,100] Its chloride channel activity (open probability [P_o]) is regulated through cyclic adenosine monophosphate (cAMP)–dependent kinase, C kinase, and tyrosine kinase pathways.[101–103] Phosphorylation of R-domain serine residues and ATP binding and hydrolysis by the NBFs are necessary and independent steps in the activation of chloride conductance.[104,105]

Abnormal Airway Mucosal Salt and Water Transport

CF is a disease that affects the epithelia lining various organs of the body. Because the native functions of affected epithelia in these organs vary widely, that is, some are salt- but not volume-absorbing (sweat duct), some are volume-absorbing (airways), and others are volume-secreting (pancreas), it is not surprising that the physiologic consequences of mutant CFTR in these epithelia differ widely.

In the lung, airway but not alveolar epithelia are primarily affected. It is not yet clear whether the predominant pathophysiology of CF in the airway occurs in the

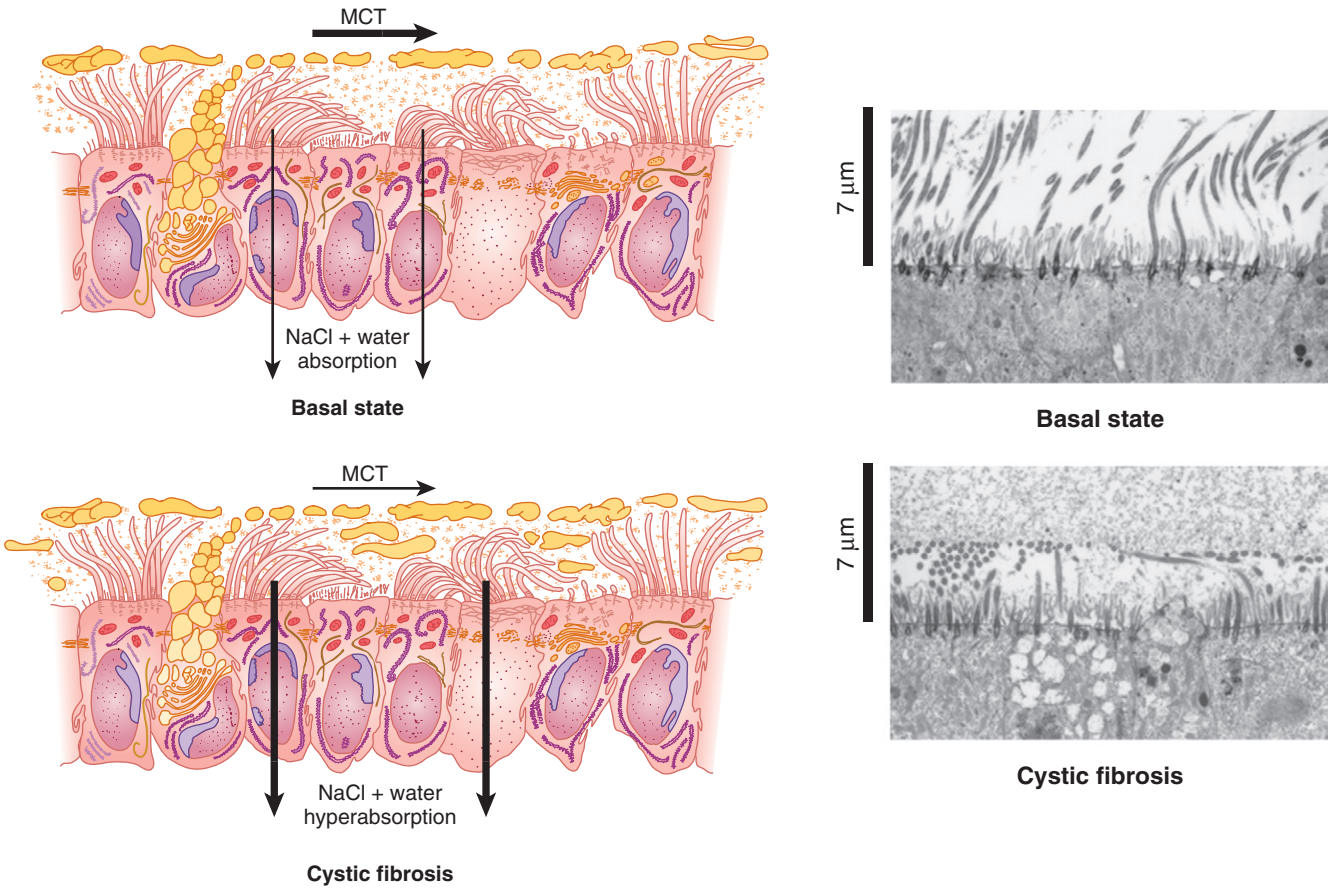

FIGURE 41-4 ■ Schema describing the mucociliary transport (MCT) apparatus in normal and CF airway epithelia. In normal airways (*upper left panel*), the volume and composition of airway surface liquids (granules between cilia) are adjusted so that the extended cilium can transmit energy to the mucous layer that rests on the surface of the periciliary liquid layer. The height (volume) and the composition of this liquid layer are regulated by the superficial epithelial cells. The low-power electron micrograph (*upper right panel*) shows the 7-µm deep periciliary liquid layer on the surface of a cultured normal airway epithelium that exhibits mucus transport.[113] In CF airways (*lower left panel*), hyperabsorption of volume in response to excessive Na^+ transport depletes the height (volume) of the airway surface periciliary layer. It is postulated that this depletion of liquid contributes to slower airway clearance in CF by impacting mucus on cilial shafts and by altering cough clearance properties of mucus. The low-power electron micrograph (*lower right panel*) shows the depleted periciliary layer on the surface of a CF airway epithelial culture that has lost the ability to perform mucus transport.[113] Other composition abnormalities of the periciliary secretory layer also may be important but are as yet unidentified.

superficial epithelium or the glandular elements in the airway wall. The likelihood that the superficial epithelium may be the more important affected epithelium in the lung is suggested by data indicating that the earliest functional manifestation in the CF lung is airflow obstruction in the bronchioles, a region that contains no glands.[106]

A classic premise of CF research has been that abnormalities of chloride and likely sodium transport lead to abnormal regulation of airway surface liquid volume, that is, a depletion of both salt and water (volume) on the CF airway surface (Fig. 41-4). As a result of airway surface liquid volume reduction, mucus concentration and adhesion to cell surfaces occurs, which causes airflow obstruction and ultimately bacterial infection. A second hypothesis linking abnormal sodium and chloride transport to CF pathogenesis focused on differences in salt concentration and activity of antimicrobial factors (e.g., defensins) in CF versus normal airway surface liquid.[107,108] This hypothesis suggested that airway epithelia regulate the ionic concentration, not volume, of airway surface liquid, and sodium chloride concentrations are predicted to be low (<50 mmol/L) in the airway surface liquids of normal individuals and "high" in CF (>100 mmol/L). When salt is low in the airway surface liquid, defensins are active, whereas when salt is high, they are inactive. The result of inactive defensins in CF would be chronic infection. Table 41-2 describes the airway surface liquid composition in normal subjects and CF subjects prior to infection. These data do not support a difference in airway surface liquid sodium chloride composition as central to the initiation of CF lung disease. Further, defensins are found in small quantities in both normal and CF airway surface liquid and are typically bound to mucins.[109]

As discussed in Chapter 8, the role of active ion systems in the pulmonary epithelium can be reviewed on two levels: (1) the requirement of pulmonary epithe-

TABLE 41-2. Composition of Airway Surface Liquid in Normal Subjects and Uninfected Cystic Fibrosis Patients

Region/Phenotype	Study	*N*	Na^+ (mmol/L)	Cl^- (mmol/L)	K^+ (mmol/L)
Normal nose	Knowles et al[163]	8	109 ± 5	126 ± 5	29 ± 3
	Hull et al[446]	10	106 ± 4	115 ± 4	ND
CF nose	Knowles et al[163]	8	110 ± 6	132 ± 5	28 ± 3
	Hull et al[446]	10	116 ± 7	125 ± 4	ND
Normal lower airway	Knowles et al[163]	11	91 ± 7	81 ± 6	17 ± 3
	Hull et al[446]	7	85 ± 10	108 ± 5	ND
CF lower airway	Knowles et al[163]	8	87 ± 4	77 ± 6	21 ± 2
	Hull et al[446]	5	78 ± 16	77 ± 7	ND

ND, not done.

lium to coordinate intrapulmonary surface liquid volume during "axial" (i.e., surface) flow between different pulmonary regions, such as alveolar and airway surfaces, and (2) the requirement to regulate surface liquid volume in local airway microenvironments to mediate efficient mucus transport. Several studies have increased the level of understanding of how airway epithelia normally regulate airway surface liquid volume under a variety of conditions and how CF airway epithelia fail to do so. For example, confocal microscopy studies of well-differentiated human bronchial epithelial cultures that exhibit rotational mucus transport have revealed normal airway epithelia can autoregulate airway surface liquid volume to maintain sufficient hydration of the periciliary layer and mucus layers for efficient mucus transport.[110–112] Further studies with this system revealed that a failure to regulate volume absorption is a feature of CF airway epithelia, which abolishes mucus transport both by depletion of the 7-μm periciliary liquid layer and by concentration of mucins in the mucus layer.[111,113] The depletion of liquid in the periciliary layer is a "severe" lesion, because it is predicted to reduce the lubricant activities of this layer required for both cilial-dependent and cough-dependent mucus clearance. Consistent with this prediction, the evidence that mucociliary and particularly cough clearance are depressed in CF patients in vivo is mounting.[114,115]

Active Ion Transport Properties of Airway Epithelia

Normal airway epithelia exhibit the capacity to actively absorb Na^+ and actively secrete Cl^- ions. Each of these processes is electrogenic, and they are coordinately regulated, in part by soluble mediators in airway surface liquid.[110–112,116] The relative physiologic role of each process varies depending on the volume of liquid on airway surfaces.

A parameter that describes the overall airway transport activity of airway epithelia is the transepithelial electric potential difference. The transepithelial potential difference can be analyzed simply as the product of the active ion transport rate (short-circuit current [I_{sc}]) and the ionic resistance of the epithelium (R_t). A diagnostic hallmark of CF airway epithelia is a raised potential difference. A series of in vivo ion substitution studies,[9] complemented by in vitro isotopic flux studies of excised tissues,[9,117,118] have revealed that the raised potential difference in CF airway epithelia reflects contributions of both increased ion transport (Na^+ absorption) and increased epithelial resistance (due to decreased cellular Cl^- permeability). Indirect evidence from studies measuring the effects of amiloride, a Na^+ channel blocker, in vivo indicates that the elevated Na^+ absorptive rate rather than the defective Cl^- conductance raised the potential difference of the superficial epithelium of CF airways.

Abnormalities of Superficial Epithelial Cl^- Transport

In vivo potential difference,[9] Ussing flux chamber,[117] and microelectrode studies[119–123] all agree that CF airway epithelial cells exhibit an abnormally low apical membrane conductive Cl^- permeability. Studies utilizing double-barreled Cl^--selective microelectrodes indicate that the basolateral membrane Cl^- conductance and Na^+, K^+, $2Cl^-$ cotransport activities of CF cells are not different from those of normal cells.[121,122,124]

The abnormality in the resting apical membrane Cl^- conductance of airway epithelia reflects the absence of tonic CFTR function at this site. Like other affected epithelia, CF airway epithelia do not respond with Cl^- secretion to agents that raise cellular cAMP (e.g., β-agonists or adenosine), whereas normal airway epithelia do, if the apical membrane Na^+ permeability is blocked.[102,118,125–129] This abnormal response in CF airway epithelia does not reflect dysfunction of adenylyl cyclase or cAMP-dependent protein kinase activities. Rather, CF airway epithelial cells fail to secrete Cl^- due to the absence of CFTR in the apical membrane or to intrinsic defects in mutant CFTR.

Unlike normal airway epithelia, CF epithelia also do not respond with Cl^- secretion to activators of other intracellular kinases. For example, studies with the expressed CFTR protein have indicated that the CFTR Cl^- channel is directly regulated by protein kinase C

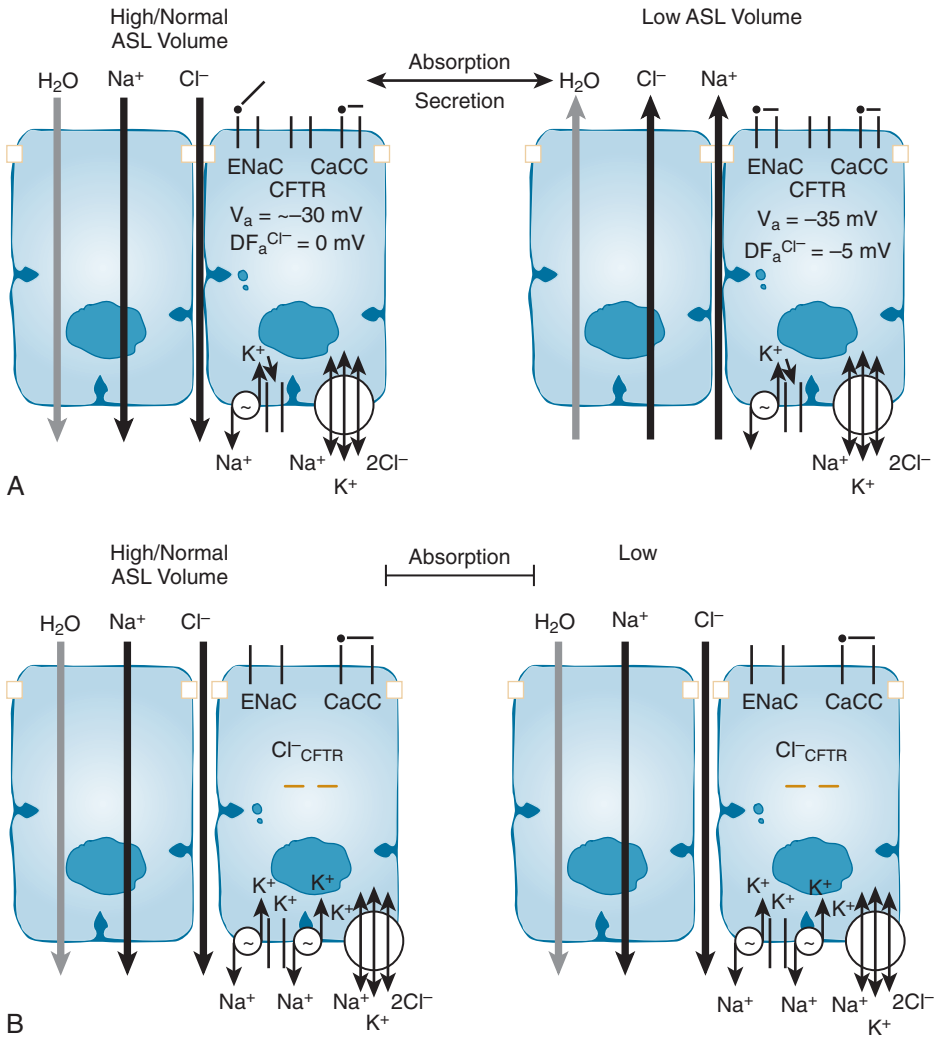

FIGURE 41-5 ■ **A,** Normal human airway epithelia can switch between absorptive and secretory ion transport modes. *Left,* When excess airway surface liquid is present, epithelial Na^+ channel (ENaC)-mediated Na^+ absorption is dominant. Cl^- is projected to be absorbed passively via the paracellular path, reflecting the fact that there is no electrochemical driving force (DF_a^{Cl-}) favoring Cl^- exit from the cell. In contrast, both the negative apical membrane potential (V_a) and low intracellular Na^+ activity (–20 mM) favor Na^+ entry into the cell. Water is absorbed in response to the osmotic gradients generated by combined sodium chloride absorption. *Right,* When airway surface liquid volume is low, the ENaC is inhibited, the apical membrane potential becomes more negative, and a driving force for Cl^- secretion is generated. NaCl and water are secreted. **B,** CF airway epithelia exhibit accelerated airway surface liquid volume absorption under high and normal airway surface liquid volume conditions and cannot switch to a secretory mode during low airway surface liquid volume conditions. *Left,* The routes of raised Na^+, Cl^-, and water absorption and cellular mechanisms for raised Na^+ transport in CF airway epithelia under high or normal airway surface liquid volume conditions. *Right,* The absence of CFTR from the apical membrane eliminates regulation of the ENaC and limits capacity for Cl^- secretion. CaCC, Ca^{2+}-activated Cl^- channel.

phosphorylation.[130] Other studies have shown that CFTR is also regulated by tyrosine kinases and other kinases.[131] The failure of CF airway epithelia to respond to protein kinase C or other kinases reflects absence or dysfunction of the mutated CFTR Cl^- channel itself at the plasma membrane. An area of present research is how CFTR is functionally and physically associated with regulatory kinases and phosphatases in the apical domains of epithelial cells.[132,133]

Recent studies have placed in perspective the function of defective CFTR-mediated Cl^- transport in airway epithelia.[133a–133c] In normal airway epithelia, the maintenance of a normal airway surface liquid volume depends on both the regulation of Na^+ transport rates (see later) and the ability to secrete Cl^- (Fig. 41-5). Specifically, as airway surface liquid layer diminishes to approximately 7 μm, Na^+ absorption is inhibited and CFTR-mediated Cl^- secretion initiated. In CF, the absence of CFTR-dependent Cl^- secretion contributes to the failure to maintain adequate liquid volume on airway surfaces.

CF airway epithelial cells retain the normal capacity to secrete Cl^- in response to elevations in intracellular Ca^{2+}.[134,135] Data derived from studies of cultured monolayers impaled with double-barreled Cl^--selective micro-

electrodes indicate that elevation of intracellular Ca^{2+} with calcium ionophores, such as ionomycin, initiate Cl^- secretion in both CF and normal cells. The Cl^- channel activated by raised Ca^{2+} is molecularly distinct from CFTR, as evidenced by retention of this activity in gene targeted ("CF") mice.[136] This Ca^{2+}-activated Cl^- channel has recently been identified as TMEM16A, a member of an eight transmembrane-spanning family.[137–139] Intense investigations are under way to understand the role of Ca^{2+} regulation of TMEM16A and its relationship to other members of this family.

The observation that Ca^{2+}-regulated Cl^- secretion can be triggered in CF airway epithelia has therapeutic implications. In a search for compounds that interact with receptors on the lumen of airway epithelial cells that regulate intracellular Ca^{2+} levels, it was discovered that the triphosphate nucleotides (ATP, uridine triphosphate [UTP]) were highly effective in initiating Cl^- secretion in CF and normal airway epithelial cells.[140–143] Triphosphate nucleotides increase intracellular Ca^{2+} by interacting with purinoceptors ($P2Y_2$) that via activation of phospholipase C, increase inositol triphosphate (IP_3) levels. In vivo studies found that ATP and UTP were effective Cl^- secretagogues in the nasal mucosa of CF subjects.[142] Indeed, an intriguing finding was that the triphosphate nucleotides were more effective in initiating Cl^- secretion in CF than in normal subjects. These observations have led to the clinical testing of analogues of UTP that, by virtue of being resistant to hydrolysis in CF airways, may have a long duration of action.[144,145]

Abnormalities of Superficial Epithelial Na^+ Transport

Abnormalities in Na^+ transport in CF appear to be confined to epithelia that are involved in volume absorption. Accelerated Na^+ absorption is a feature of the proximal tubule of the kidney,[146,147] jejunum, ileum,[148–150] and airways of CF patients.[118] Interestingly, the mechanisms of Na^+ hyperabsorption may differ in the different affected epithelia. Na^+-coupled solute movements may be the major affected pathways in the intestine, whereas defective regulation of the epithelial Na^+ channel (ENaC) is the major abnormality in the lung.

Studies of freshly excised airway specimens established that the raised potential difference that characterizes CF airway epithelia reflects in part an accelerated basal rate of active Na^+ absorption.[119] These studies also identified a defect in acute regulation of Na^+ transport rates in CF.[119] β-Agonists and other reagents that raise intracellular cAMP paradoxically raise the already accelerated basal rate of Na^+ transport in CF tissues but do not affect Na^+ transport rates in normal tissues.[119]

The principal abnormality in the Na^+ transport path in CF airway epithelia resides in the apical membrane Na^+ conductance.[119] Studies of cultured airway epithelia with double-barreled Na^+ selective microelectrodes show that the apical membrane Na^+ permeability in CF is two- to threefold higher than in normal cells.[151,152] Thus, these studies place a second ion permeability abnormality in the CF apical membrane and strongly suggest that the Na^+ transport abnormality is not secondary to the changes in the electrochemical driving forces for Na^+ entry consequent to absence of an apical membrane Cl^- permeability.

The effects of the CF defect on the regulation of Na^+ transport rates at the single-channel level are still not understood. The available evidence indicates that the fraction of time that the Na^+ channel is capable of conducting ions, the P_o, is approximately threefold greater in CF compared with normal cells.[153–155] This finding suggests that the defect responsible for accelerated Na^+ transport in airway epithelia reflects an absence of the tonic inhibition of epithelial Na^+ channel provided by wild-type CFTR.

A key issue with respect to the Na^+ transport defect relates to its role in pathogenesis of airway infection. As discussed previously, recent laboratory data indicate that both regulation of Na^+ transport rates as a function of the available liquid volume on an airway surface and the capacity to secrete Cl^- are required for airway surface liquid volume homeostasis (see Fig. 41-5). Further, these studies have shown that CF airways fail to normally regulate Na^+ absorption and this defect contributes to abnormally low liquid on CF airway surfaces. For example, in vitro studies of cultured CF bronchial epithelia have shown that in CF, Na^+ hyperabsorption persists despite low airway surface liquid volume and that this defect contributes to periciliary layer depletion and mucus stasis (Fig. 41-6). Further evidence for the role of raised Na^+ absorption in the pathogenesis of CF has emerged from in vivo studies of mice with airway-specific overexpression of ENaC. These mice exhibit raised Na^+ absorption and a lung phenotype that resembles CF (e.g., mucus obstruction, neutrophilic inflammation, and defects in bacterial clearance).[156]

Function of Normal and Cystic Fibrosis Ion Transport under Dynamic Conditions In Vivo

Whereas most standard laboratory assessments of airway epithelial ion transport function are performed under "static" conditions, airway epithelia in vivo are exposed to a variety of respiration-dependent phasic stresses.[157] Studies of airway surface liquid physiology under phasic stress conditions that mimic respiration have revealed key data for understanding airway surface liquid volume homeostasis in vivo. For example, phasic shear stress increases the rate of ATP release from airway epithelia.[111,158–160] The increased rate of ATP release increases airway surface liquid ATP concentrations and, to a lesser extent, adenosine concentrations. In normal airway epithelia, the increased ATP activation of $P2Y_2$ receptors increases inhibition of epithelial Na^+ channel and activation of both CFTR and Ca^{2+}-activated Cl^- channel (TMEM16A), which raise airway surface liquid volume. In CF, shear stress also increases ATP release, which, via ENaC inhibition and Ca^{2+}-activated Cl^- channel activation, increases airway surface liquid sufficiently to

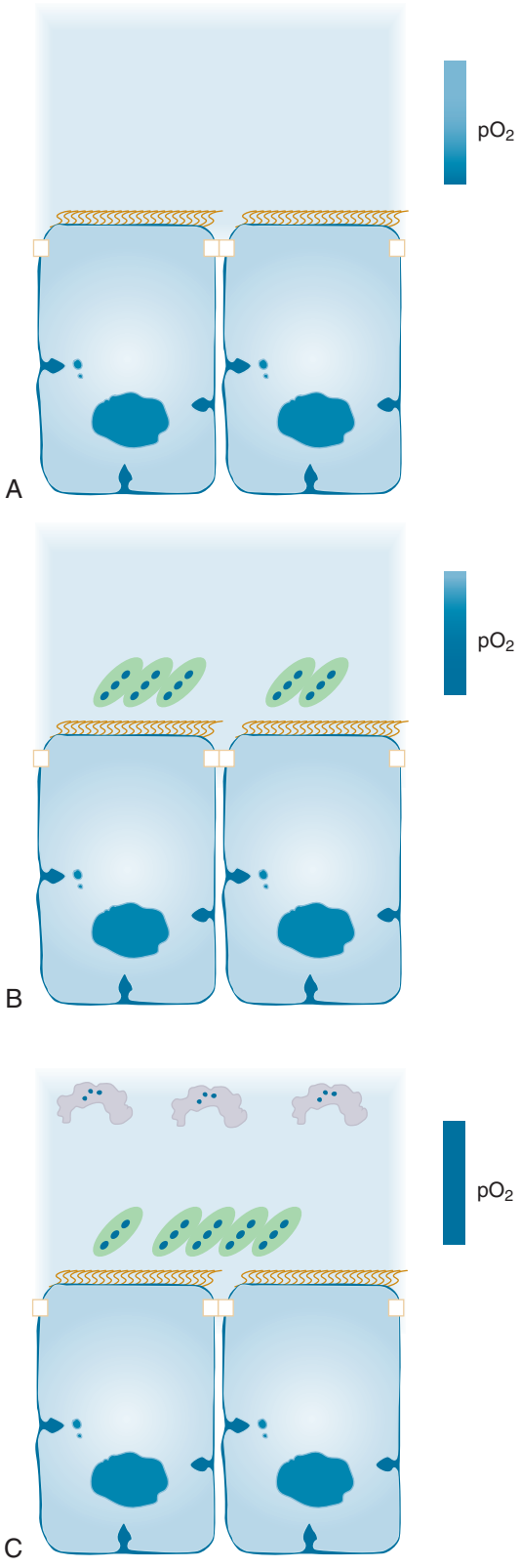

FIGURE 41-6 ■ **A,** Failure of mucus transport, coupled with persistent mucus secretion, with time produces adherent mucus masses or plugs. The raised epithelial oxygen consumption (Q_{O_2}) required to fuel accelerated CF Na^+ absorption generates steep O_2 pressure gradients (*light to dark blue shading in bar*) in thickened mucus masses. **B,** *Pseudomonas aeruginosa* deposited on mucus masses grows and adapts to hypoxic niches within these masses as macrocolonies (biofilms). **C,** The thickened mucus, coupled with macrocolony growth, resists secondary defenses, including neutrophils, setting the stage for chronic infection. The presence of increased macrocolony density and, to a lesser extent, neutrophils renders these mucopurulent masses frankly anaerobic (*blue bar*).

mediate mucus transport.[111,159] This capacity of ATP to partially balance airway surface liquid volume homeostasis under phasic stress conditions in vitro may explain why mucus clearance rates are normal in portions of CF lungs in vivo.[161]

The observation that CF airway epithelia can produce sufficient airway surface liquid with phasic stress to mediate mucus transport raises the question of why CF lungs get infected. Clinical data suggest that CF lung disease is episodic, with intervals of constancy interrupted by acute exacerbations. Further, a substantial fraction of acute exacerbations are triggered by viral infections. Laboratory studies of respiratory syncytial virus (RSV) infection of cultured CF airway epithelia show that RSV can up-regulate extracellular ATPases, under phasic stress conditions. The increased ATPase activity reduces airway liquid ATP concentrations, $P2Y_2$-mediated inhibition of ENaC, and activation of Ca^{2+}-activated Cl^- channel and depletes airway surface liquid volume, which promotes mucus adhesion to airway. The mucostasis associated with viral infection thus could facilitate airway bacterial colonization and growth.

Ion Transport Defects of Glandular Epithelium

In situ hybridization and immunocytochemical studies indicate that lung CFTR is expressed at the highest level in some serous cells in submucosal gland acini and ciliated cells of the ductal epithelium.[87,162]

Unlike the sweat duct, but similar to the parotid duct, nasal glands and ductal epithelium appear to have a similar capacity to secrete volume in CF and normal subjects.[163] However, these studies raised the possibility that submucosal gland ducts could modify the gland secretion to reduce sodium chloride concentrations and make it hypotonic.

In vitro studies indicate that cultured CF bronchial gland acinar cells, unlike the superficial airway epithelium of CF subjects, do not respond to raised intracellular Ca^{2+} with Cl^- secretion, whereas normal glandular cells do.[163a] Thus, the bronchial glands could have a Cl^- transport phenotype that is more similar to gastrointestinal epithelia than the superficial airway epithelium.[150,164,165] Studies of bronchial glands on fresh tissue from lungs removed with transplantation procedures showed that CF airway gland acini, like superficial airway epithelia, do not secrete Cl^- in response to β-agonists, whereas glands from normal subjects do.[164–166] Interestingly, both normal and CF glands secrete Cl^- in response to cholinergic agents, suggesting that Ca^{2+}-regulated Cl^- secretion is preserved. Further, the properties of stimulated CF gland secretions are different from normal, with CF secretions being more viscous and slightly lower pH.[167,168] The relative role of the gland defect in CF airway surface liquid volume depletion is presently unknown, but at a minimum, this deficiency exacerbates the airway surface liquid volume defect generated by the CF superficial epithelium and possibly reduces the secreted load of gland antimicrobial factors onto airway surfaces.

Mucin Macromolecule Secretion in the Cystic Fibrosis Airway

Following Farber's report[5] of mucous obstruction in many exocrine glands, a search was initiated for abnormal macromolecules that might change the physical properties of CF exocrine secretions. Particular emphasis was placed on analysis of mucin glycoproteins, the high-molecular-weight glycoconjugates that are the determinants of the viscoelastic properties of mucus.[169] One of the difficulties in comparing these substances sampled from CF and control airways is that they are susceptible to proteolytic and perhaps other degradative enzymes to which they are exposed in vivo. This problem likely explains the report that CF sputum contains less mucin than normal (i.e., the epitopes used for antibody detection of mucins were selectively degraded in CF mucins).[170] In addition, these glycoproteins display extensive microheterogeneity of carbohydrate constituents and, therefore, are difficult to compare from subject to subject as well as patient group to control group.

Overall, purified mucins from CF patients and control subjects show considerable similarity. Early suggestions that the fucose content of CF glycoproteins was elevated and the sialic acid content decreased appears to reflect the effects of chronic infection and inflammation and not a CF-specific defect.[171] In addition, several investigators have reported that CF mucous glycoproteins from both respiratory and gastrointestinal sources contained increased numbers of sulfated sugars.[172–175] Goblet cells within the bronchial epithelium of patients with CF have an elevated sulfur content,[176] which, if present as sulfate, could reflect increased sulfation of secretory glycoconjugates. However, again, most evidence, including the observation that goblet cells express little or no CFTR, suggests that increased sulfation likely is a reflection of chronic infection rather than a consequence of CFTR mutations.[87,171]

There is also no convincing evidence that CF epithelial cells hypersecrete mucin macromolecules before the onset of airway injury.[177] However, hypersecretion of mucus does occur in response to proteases, oxidative metabolites, and other products of chronic infection and inflammation. This induced hypersecretion, coupled with goblet cell hyperplasia, likely significantly exacerbates the mucus accumulation and obstruction that is initiated by airway liquid volume depletion.[178]

Future research should focus on the behavior of mucins in reduced airway surface liquid volume environments, especially on how mucins are unpackaged from granules and released into a CF-like environment with little water and perhaps more acidic pH.[179] A second key area is to elucidate the nature of the adhesive interactions that occur when a thickened mucus layer comes into contact with cell surface (tethered) mucins in the absence of periciliary layer (see Fig. 41-2). Elucidation of the mechanism of this interaction may lead to therapies to reverse this adhesion and allow clearance of adherent mucus plaques.

Analyses of other macromolecular secretory products from patients with CF have failed to uncover substantial abnormalities. These macromolecules have included α-amylase, ribonuclease, and lysozyme from salivary secretions, and pancreatic enzymes, including chymotrypsin, trypsin, carboxypeptidase, amylase, and lipase.

Pathophysiology of Infection

Failure of the airways to clear mucus normally is likely the primary pathophysiologic event in CF (see Fig. 41-6). Adherent mucus plaques and plugs are the site of the chronic bacterial infection of CF airways.[180] These bacteria are usually found in macrocolonies that appear to represent the biofilm-type of growth characteristic of CF infections. In general, biofilms represent a type of bacterial growth in which bacteria form and become enmeshed in an extensive extracellular matrix. Bacterial cellular physiology may change in this environment and the matrix may provide a barrier to antimicrobial agents and inflammatory cells, thus promoting bacterial persistence. The generation of immobile mucus surfaces thus provides the nidus for the chronic respiratory tract infection that is the major contributor to the loss of lung function and eventual demise of patients with CF.

The chronic infection of the CF lung usually is localized to endobronchial regions and the bacterial species most commonly cultured are *Staphylococcus aureus* and *Pseudomonas aeruginosa*. However, analyses of CF airway secretions with unbiased molecular approaches, including terminal restriction fragment length polymorphism (T-RFLP) and gene chip approaches, suggest a greater diversity of infecting bacteria than heretofore appreciated. Indeed, CF secretions of the typical young adult may contain 12 to 30 distinct bacterial species and many anaerobes.[181–183]

Once established, infection of the CF lung is rarely eradicated. Bacterial infection extending beyond the airways, however, is distinctly uncommon, indicating that local airway, rather than generalized host or pulmonary defense mechanisms, are impaired.

As noted previously, the volume of liquid on CF airway surfaces is severely reduced, which is likely to decrease the function of the periciliary layer and increase the adhesiveness of the mucus layer, leading to a failure of both mucociliary and cough clearance. Mucus stasis, adhesion, and obstruction are likely to be responsible for the lung infections. Mucus clearance reduction is more heterogeneous in the central airways[115] than in the more peripheral airways.[184] Virtually all studies agree that ciliary morphology and beat frequency are normal in CF airway epithelia[185,186] (see Fig. 41-6).

S. aureus and *P. aeruginosa* are infrequent respiratory tract pathogens of children and adults, except in CF. The role played by these organisms in endobronchial infection has prompted suggestions that surface properties of CF airway epithelia are altered in a fashion that promotes their adherence. *S. aureus* does not preferentially adhere to CF airway epithelial cells,[187] and studies of respiratory cell interactions with *P. aeruginosa* also have not demonstrated consistent differences between CF and normal cells.[188,189] In an opposite formulation, studies have suggested that the wild-type CFTR expressed on normal epithelial cells binds *Pseudomonas* and mediates bacterial internalization, which ultimately kills the microorganism. CF cells are reported to fail to perform this function.[190] Although intriguing, there is little pathologic evidence for *Pseudomonas* internalization in normal well-differentiated airway epithelial cells, and this hypothesis does not account for infection in CF patients who express mutant CFTR in the apical membrane (e.g., G551D CFTR).

No difference in bacterial binding to CF versus normal mucins have been detected for *Staphylococcus* or *Pseudomonas*.[187,191,192] Recent biophysical studies suggest that the increase in mucus concentration due to CF airway surface dehydration physically restricts bacterial motility and permeation of *Pseudomonas* quorum-sensing molecules, facilitating biofilm growth.[193]

An important new concept is that the mucus adherent to airway surfaces may be hypoxic or anaerobic (see Fig. 41-6).[192] Prior to infection, the increased O_2 consumption by CF airway epithelia (required to fuel increased Na^+ absorption), coupled with increased diffusion distances for O_2 through mucus plaques, can create relatively hypoxic zones near the epithelial surface. As bacterial densities in CF mucus reach ranges of 10^6 colony-forming units (CFU)/mL, the bacteria consume the remaining O_2 in the environment. Direct measurements of oxygen pressure (P_{O_2}) in vivo with O_2 electrodes have recorded P_{O_2} less than 2 torr in infected CF mucus.[192] This observation has two important consequences.

First, *P. aeruginosa* can adapt to and grow in biofilms in a hypoxic environment, and this environment may exert a subtle pressure that favors *Pseudomonas* acquisition in CF.[194] There are also implications for CF therapy. *P. aeruginosa* sensitivities to antimicrobials change in O_2-depleted versus O_2-rich environments (e.g., macrolides become more effective against *Pseudomonas* in O_2-depleted environments). Thus, clinical testing of *Pseudomonas* isolates for antimicrobial sensitivities may require studies under anaerobic conditions. Because *Pseudomonas* physiology differs under anaerobic than under aerobic conditions,[194] identification of essential genes for anaerobic growth may represent novel therapeutic targets.

Second, the observation that CF mucus may be anaerobic has led to a search for obligate anaerobes in CF airway secretions. Because of the difficulty in culturing many anaerobes, this search has combined specialized culture techniques and molecular approaches for identification and quantitation. Recent reports suggest there may be high concentrations of obligate anaerobes (e.g., *Prevotella* spp., *Veillonella* spp., *Fusobacteria*) in CF secretions.[181] These findings serve to confirm the notion that CF secretions are anaerobic, but the natural history of obligate anaerobe acquisition by the CF patient and their role in pathogenesis (and hence requirement for treatment) are at present unknown.

Once bacterial infection of mucus has occurred, bacteria release products that diffuse to the underlying epithelium and stimulate mucin production[195,196] and

cytokine responses[197] that mediate cell damage. The infection may be worsened after cell damage by bacterial binding to the injured cells.[198]

The immunology of CF has been investigated extensively and little has been found to indicate any deficiency. Although CF subjects tend to have low levels of serum immunoglobulin G (IgG) in the first decade of life, these levels increase dramatically as chronic infection is established.[199] Secretory antibody levels appear to be normal or enhanced.[200] Antibody responses specific for infecting organisms in the respiratory tract are brisk.[201,202] The number of B lymphocytes and plasma cells that differentiate into immunoglobulin-secreting cells are not depressed.[203] T lymphocyte numbers are adequate, and these lymphocytes proliferate in response to nonspecific mitogens.[204] With advancing severity of pulmonary disease, lymphocytes may proliferate less briskly in response to *P. aeruginosa* and other gram-negative organisms.[205] This acquired dysfunction at times can be reversed by intensive antibiotic treatment, but it may contribute to the resistance to antimicrobial therapy in advanced lung disease.

Polymorphonuclear leukocytes and macrophages are plentiful in CF airways and function normally when removed from their usual environment,[206] which suggests that potential phagocytic defects in vivo could reflect infection-induced degradation of opsonins (e.g., IgG and complement) and possibly defective leukocyte migration through thickened, adhesive mucus.[207]

There is an increased inflammatory response in CF.[208,209] Studies from lung lavage fluid from CF neonates indicate that magnitude of the neutrophil response normalized to bacterial counts in lavage fluid is increased in CF as compared with non-CF infants with lung infections.[210] The cytokine interleukin-10 (IL-10), which normally serves to dampen epithelial cell IL-6 and IL-8 responses to luminal bacterial infection, is not produced at normal levels in CF airway epithelia.[211,212] Whether the increased neutrophil influx observed in CF reflects failure to kill bacteria growing in biofilms, failure of an epithelial regulatory mechanism for neutrophil influx, epithelial compensation to a chronic stimulus, or a combination thereof is unknown.

Progressive destruction of airway walls occurs in CF, and proteinases may contribute to this process.[213] Leukocytes and bacteria produce large quantities of elastase that exceed the neutralization capacity of airway antiproteinases. Both leukocyte and bacterial elastases generate C5a nonimmunologically in CF secretions.[214] High levels of this chemotactic factor stimulate further polymorphonuclear leukocyte recruitment, increasing the burden of free elastase in the airway lumen and possibly airway wall. Similarly, a cycle of airway wall destruction may be mediated by polymorphonuclear leukocyte collagen interactions that produce a chemoattractant that reinforces polymorphonuclear migration into airway walls.[215] Ultimately, proteolytic injury to airway walls contributes to their destruction with development of widespread bronchiolectasis and bronchiectasis.[216] The fact that destructive emphysema is not a prominent feature of CF lungs, especially early in the course of lung disease, can be attributed to confinement of infection to endobronchial spaces in mild to moderate lung disease. Other mechanisms of conducting airway tissue injury undoubtedly exist but have not been described in detail.

CLINICAL MANIFESTATIONS

CF presents in many different ways and mimics a number of other clinical entities. Usual presentations include early onset of respiratory tract symptoms, particularly persistent cough and recurrent or refractory chest radiographic changes. Usual gastrointestinal presentations include meconium ileus in approximately 15% of patients and failure to thrive with steatorrhea. A surprising number of people with CF escape detection in the first decade or two of life, often because symptoms are unusual, subtle, or even absent. Patients with "mild" mutations may present in childhood or later in life.[37] A list of unusual presentations is compiled in Table 41-3, and presentations that may be expected at adolescence or early adulthood are highlighted. Recognition of the protean manifestations of CF and a high index of suspicion are required to detect all cases of CF, either in childhood or later in life.

Lower Respiratory Tract Disease

The earliest manifestation of CF lung disease is generally cough. At first, it is intermittent, coinciding with episodes of acute respiratory tract infection and persisting

TABLE 41-3. Unusual Presentations of Cystic Fibrosis*

Respiratory	Bronchiolitis/asthma
	***Pseudomonas aeruginosa* or *Staphylococcus aureus* colonization of the respiratory tract**
	Staphylococcal pneumonia
	Nasal polyposis
	Nontuberculous mycobacterial infection
Gastrointestinal	Meconium plug syndrome
	Rectal prolapse
	Recurrent abdominal pain and/or right lower quadrant mass
	Hypoproteinemic edema
	Prolonged neonatal jaundice
	Biliary cirrhosis with portal hypertension
	Vitamin deficiency states (A, D, E, K)
	Acrodermatitis enteropathica–like eruption with fatty acid and zinc deficiency
	Recurrent pancreatitis
Genitourinary	**Male infertility**
	Female infertility
Other	Hypochloremic, hyponatremic alkalosis
	Mother of a child with cystic fibrosis

*Presentations noted in **boldface** are those that may occur in adolescents or adults with cystic fibrosis.

longer than expected. With time, the cough becomes a daily event. It is often worse at night and especially on arising in the morning. With progression of lung disease, the cough becomes productive and then paroxymal, with associated gagging and emesis. Sputum is usually tenacious, purulent, and often green, reflecting bacterial infection. Hyperinflation of the lungs is noted early in the progression of lung disease. In fact, it is unusual to see CF respiratory tract disease without at least a moderate increase in lung volume. Asthmatic or bronchiolitic-type wheezing is most common during the first 2 years of life but may be encountered at any age. Wheezing may occur with or without evidence of atopy, which is probably not more frequent in patients with CF.[217] Lung sounds are often unremarkable and, often, diminution in the intensity of breath sounds may be the only abnormality noted, correlating with the extent of hyperinflation. Adventitious lung sounds are usually heard first over the upper lobes and often are localized to the right side.

CF patients may have only mild bronchitic symptoms for long periods of time, in some cases for a decade or two, but eventually, these periods of stability are punctuated with exacerbations of symptoms, including increased intensity of cough, tachypnea, shortness of breath, decreased activity and appetite, and weight loss. It has been assumed that these exacerbations are triggered by acute respiratory infections, perhaps of viral or mycoplasmal origin, although studies differ concerning evidence for these infections during periods of increased lung symptoms.[218–223] Environmental factors, including cigarette smoke,[224] also may evoke more respiratory symptoms. Intense antibiotic therapy and assistance with clearance of mucus are usually required to reduce lung symptoms and improve lung function. Exacerbations characteristically occur with increasing frequency. Frank limitation of activity or disability is associated with end-stage lung disease and heralds a sequence of terminal events, including substantial hypoxemia, pulmonary hypertension, cor pulmonale, and death.

Microbiology

The airways of patients with CF are colonized early with bacteria, and once established, infection is rarely, if ever, eradicated. *S. aureus* and *Haemophilus influenzae* are often the first organisms detected.[225] *P. aeruginosa* characteristically is cultured from respiratory secretions months to years later, although this organism is present at diagnosis with increasing frequency. Age at acquisition of *P. aeruginosa* is graphed in Figure 41-7 and is dependent in part on genotype, earlier acquisition occurring in persons homozygous for ΔF508.[34] The possibility of nosocomial acquisition of *P. aeruginosa* has been raised.[226] With progression of lung disease, *P. aeruginosa* is often the only organism recovered from sputum and may be present in several types of colonies, usually with different antibiotic sensitivity patterns. Typically, one of these types is mucoid, due to elaboration of large amounts of alginate. These mucoid organisms are found in microcolonies of pseudomonads embedded and growing in biofilms of alginate.[227] Mucoid properties are thought to inhibit opsonic and nonopsonic phagocytosis, enhance adherence properties, and decrease sensitivity to antibiotics and toxic, reactive intermediates produced by leukocytes.[180,228–230] The recovery of *P. aeruginosa*, particularly the mucoid form, from the lower respiratory tract of a child or young adult with chronic lung symptoms is virtually diagnostic of CF, although it may also occur in patients with primary ciliary dyskinesia.[231]

Recently, other species have been recovered from CF lungs with increasing frequency, including obligate anaerobes.[181] *Burkholderia cepacia* has become prevalent in a few CF care centers and is particularly difficult to treat because it is usually resistant to most antimicrobial drugs. Evidence for patient-to-patient spread is strong and has led to recommendations for stringent infection control measures within CF care settings.[232,233] Colonization has been linked to the rapid demise of a

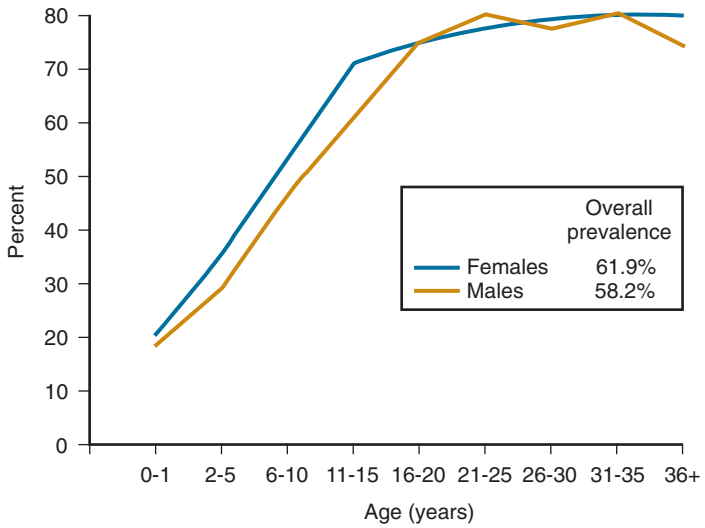

FIGURE 41-7 ■ Prevalence of *P. aeruginosa* infection by age and sex in CF patients enrolled in the U.S. Cystic Fibrosis Foundation Registry, 1991, based on an analysis of 16,417 patients. (Courtesy of Dr. S. FitzSimmons.)

small percentage of patients[234] with what is called the "cepacia syndrome." Molecular analyses have distinguished different genomovars of *B. cepacia*, some of which comprise distinct species.[235-238] Genomovars II (*B. multivorans*) and III (*B. cenocepacia*) have been associated with the cepacia syndrome, and genomovar III includes the highly transmissible strain that may be linked to expression of the cable pilus.[237-239] Occasionally, other gram-negative rods are present in sputum, including mucoid *Escherichia coli*, *Stenotrophomonas maltophilia*, *Alcaligenes xylosoxidans, Klebsiella*, and *Proteus*. Anaerobes have been recovered from CF lung tissue; they may be undetected pathogens and are found in large abscess cavities on rare occasions.[240]

Sputum bacteriology correlates reasonably well with specimens obtained directly from the lower respiratory tract. Oropharyngeal swab cultures that yield *S. aureus* or *P. aeruginosa* are modestly predictive of results from bronchoscopic specimens, but negative pharyngeal cultures do not rule out the presence of these organisms in lower airways.[241] Quantitative bacteriology may be particularly useful for determining the relative contributions of organisms isolated.

A large number of sputum specimens contain yeast and *Aspergillus fumigatus*. Neither organism has been considered a serious pathogen, although the latter causes the symptoms of allergic bronchopulmonary aspergillosis (ABPA) in a small percentage of patients.[242,243] Colonization of lungs with rapidly growing mycobacteria has been documented with increasing frequency. Up to 20% of adult patients in some clinics are colonized by nontuberculous mycobacteria, occasionally prompting treatment with agents directed against these organisms.[244-248] *Mycobacterium tuberculosis* infection has been seen in only very sporadic cases.

Radiology

The earliest radiographic change is usually hyperinflation of the lungs, reflecting obstruction of small airways. The degree of hyperinflation generally increases with age. As bronchitis progresses, peribronchial cuffing becomes increasingly prominent. Mucous impaction in airways may be seen as branching finger-like shadows. Evidence of bronchiectasis, such as enlarged ring shadows and cysts, is common by 5 to 10 years of age. Frequently, peripheral rounded densities are noted during acute exacerbations and may disappear with treatment, leaving residual cysts. Subpleural blebs often become evident during the second decade of life and are most prominent along the mediastinal border. For reasons that remain unexplained, the right upper lobe usually displays the earliest and most severe changes. With advancing disease, the pulmonary artery segments become more prominent. A relatively small and vertical cardiac shadow is typical, but the heart enlarges with onset of cor pulmonale. Hilar adenopathy is rarely prominent. Lobar or segmental atelectasis is uncommon but is most often seen in infants or small children. Chest radiographic scoring systems have been introduced and may be useful for clinical studies and to chart the course of lung injury.[249]

Radiographic improvement with intensive treatment is not readily appreciated because of the fixed nature of airway changes. The most striking improvement often is reduced inflation of the lungs, a change that tends to make the fixed lung markings more prominent.

CT of the chest has not been used routinely for monitoring the course of CF lung changes. The cost is high and resolution for younger patients was initially poor. With the advent of rapid scanning, however, mild bronchiectasis and mucoid impaction can be observed at all ages.[250,251] CT scanning detects these lesions, even when the chest radiograph is nearly normal. The severity of bronchiectasis can be graded in older patients.[252] The indications for CT scanning in place of routine chest radiography are not established. One indication may be the evaluation of a patient considered for lobectomy. Magnetic resonance imaging (MRI) also defines peribronchial thickening, mucoid impaction, and bronchiectasis but has no well-documented advantage over CT scans in these areas of imaging.[253] MRI may be superior for distinguishing hilar adenopathy and prominent pulmonary vessels.[254]

Lung Function

Newborns with CF are thought to have normal lung function. However, within weeks to months, many infants with CF show evidence of increased airway resistance, gas trapping, and diminished flow rates.[255,256] When children reach an age that makes cooperation possible, more complete testing first demonstrates airway obstruction, which presumably occurs in small airways as indicated by reduced maximum midexpiratory flow rates, reduced flows at low lung volumes, and an elevation of the ratio of residual volume to total lung capacity (RV/TLC).[257-259] Other sensitive indicators of lung pathology include an increased alveolar-arterial oxygen gradient, frequency dependence of dynamic compliance, reduced response of flows to a helium-oxygen mixture, elevated slope of phase III of the single-breath nitrogen washout, and an elevated physiologic dead space.[260] Tests that are used most often to follow the course of pulmonary function include spirometry, lung volume measurements, and measures of oxygenation. In general, patients progress from initial reductions in maximum midexpiratory flow rates to reductions in forced expiratory volume in 1 second/forced vital capapcity (FEV_1/FVC) and then to diminished vital capacity and total lung volumes. This progression from peripheral airway obstruction to more generalized obstruction and then to acquisition of a restrictive component is illustrated in Table 41-4.

By the time a diagnosis is made, many children with CF show mild decrements of arterial P_{O_2}. Oxygenation declines slowly throughout life. As a rule, patients who maintain satisfactory oxygenation do well, independent of the extent of the obstructive impairment. When arterial P_{O_2} values dip below 55 mm Hg on a sustained basis, symptomatic pulmonary hypertension should be expected.[261,262] Exaggerated nocturnal desaturation experienced by patients with CF may be a contributing factor to pulmonary hypertension.[263] Hypoxemia gener-

TABLE 41-4. Representative Pulmonary Function Test Results from Three Young Adult Males with Mild (A), Moderate (B), and Severe (C) Lung Disease*

	PATIENT		
Test	**A**	**B**	**C**
FVC	98	72	48
FEV_1	92	46	34
FEV_1/FVC	(0.81)	(0.70)	(0.64)
MMEF	83	15	6
$\dot{V}max50$	91	19	11
$\dot{V}max25$	52	10	5
FRC	162	112	75
RV	189	200	120
TLC	131	105	62
RV/TLC	(0.29)	(0.45)	(0.50)
Pa_{O_2} (room air)	[87]	[74]	[48]

*Values are percent predicted, except those in parentheses, which are simple ratios, and those in brackets, which are millimeters of mercury. Patient A coughs several times a day; the cough is occasionally productive. He shows no restriction of activity. Patient B coughs frequently, expectorates moderately large amounts of mucus, but is able to jog 3 miles daily and is a full-time student in a professional school. Patient C has chronic right heart failure, but is able to work daily as a hair stylist.

FEV_1, forced expiratory volume in 1 second; FRC, functional residual capacity; FVC, forced vital capacity; MMEF, maximal midexpiratory flow; Pa_{O_2}, arterial oxygen pressure; RV, residual volume; TLC, total lung capacity; $\dot{V}max$, maximal consumption.

ally is not accompanied by polycythemia, at least in part due to an expanded plasma volume and in some persons to suppressed erythropoiesis secondary to chronic infection. Elevation of arterial carbon dioxide pressure (P_{CO_2}) generally occurs with FEV_1 volumes less than 30% of those predicted and constitutes an end-stage event for most patients. Less than 50% of patients with FEV_1 less than 30% of predicted, arterial P_{CO_2} greater than 50 mm Hg, or arterial P_{O_2} less than 55 mm live for 24 additional months.[264]

Airway hyperreactivity is a frequent feature of CF lung disease and can be demonstrated by exercise testing, histamine challenge, or response to bronchodilators. Up to 68% of the CF population demonstrates decreased flows after histamine, and flows improve in as many as 40% with aerosolized bronchodilators.[265] In contrast to cross-sectional studies, repeated tests every 1 to 3 months for a year have demonstrated bronchodilator responsiveness at least once in 95% of subjects.[265] Responsiveness is unrelated to the severity of pulmonary disease or indices of atopy, but seems to be more prevalent during winter than during summer months. Responsiveness diminishes with exacerbations of lung disease, but returns as lung function improves over 2 weeks of intensive in-hospital therapy. Several investigators have noted that occasional patients with CF have a paradoxical response to bronchodilators, perhaps due to further loss of tone in bronchiectatic airways. The pathogenesis of bronchial hyperreactivity in CF is unclear.

Exercise tolerance is related to the severity of airway obstruction.[266,267] Most patients with CF maintain adequate oxygen saturation, even with maximal exercise. However, in one study, 12 of 29 patients with an FEV_1 less than 50% of FVC had an arterial oxygen saturation below 90% at peak exercise, compared with no drop for patients with higher FEV_1 values.[268] Persons with CF have higher than expected ventilatory muscle endurance, and this endurance can be further improved with inspiratory muscle training. However, improved inspiratory muscle strength and endurance do not augment exercise performance.[269] Exercise does improve cardiorespiratory fitness, but does not improve standard pulmonary function test results. Varied weight training, however, in one study increased weight and muscle size and in addition reduced RV/TLC by 12%.[270] Another study demonstrated that adults with CF and advanced lung disease improve with exercise, but those with only moderate lung disease decrease end-expiratory lung volumes after graded exercise on a cycle ergometer.[271] Maximum oxygen consumption during exercise appears to be a better predictor of survival than routine pulmonary function testing.[272]

Resting energy expenditure is variably elevated in patients with CF. Although some have claimed that there are genetically determined increases in energy expenditure (e.g., increased ATP hydrolysis) related to certain CFTR mutations,[273] others have found increased work of breathing to be a more plausible explanation.[274]

Upper Respiratory Tract Disease

Virtually all patients with CF have radiographic opacification of the paranasal sinuses[275] and intermittent symptoms of increased upper airway secretions and moderate airflow obstruction.[276] *Nasal polyps* occur in 15% to 20% of patients and are most common toward the end of the first decade and during the second decade of life.[73] Manifestations include severe or complete airflow obstruction, rhinorrhea, and occasionally widening of the bridge of the nose. Despite the presence of radiographic abnormalities, acute or chronic symptoms of *sinusitis* occur in less than 10% of children[277] and approximately 24% of adults.[278,279]

Complications of Respiratory Tract Disease

Lobar and segmental *atelectasis* occurs in about 5% of patients.[280] This complication is most prevalent in the first 5 years of life and thereafter has a diminishing frequency. The right lung is the site of atelectasis in the majority of patients. Many episodes occur in conjunction with an exacerbation of clinical symptoms, but silent atelectasis is common. Occasionally, volume loss is associated with allergic aspergillosis and endobronchial mucous plugs. However, in most instances, a discrete plug is not evident on bronchoscopy.

Pneumothorax is a more frequent complication and is caused by rupture of subpleural blebs. The overall

incidence is about 1%/yr, and increases with age and disease severity, so that about 20% of CF adults will experience at least one pneumothorax.[281] Pneumothorax occurs equally in both sexes and is more frequent in the right chest. A small asymptomatic pneumothorax may be discovered at the time of routine chest radiographic examination. More commonly, patients develop acute onset of shortness of breath, chest pain, or hemoptysis. The incidence of tension pneumothorax is probably higher in patients with CF than in those with less severe or no lung disease, and under these circumstances, the accumulation of pleural air may become a life-threatening event. Simultaneous bilateral pneumothoraces have been described and constitute an urgent situation. Recurrent pneumothoraces are very common.

Hemoptysis is a common event in older CF patients, correlates with clinical and radiologic evidence of bronchiectasis, and is usually due to airway inflammation rather than vigorous activity or trauma to the chest. Blood streaking in the sputum ("minor hemoptysis") is common, whereas massive hemoptysis (>240 mL blood in 24 hr) occurs in approximately 5% of patients.[282] There is a strong correlation between the occurrence of hemoptysis and the exacerbation of lung infection. Any lobe may be involved and localization may be difficult even with emergent bronchoscopy. In the past, the mortality with massive hemoptysis was as high as 10%, but with proper management, it is not much different from the remainder of the CF population.[283]

Allergic bronchopulmonary aspergillosis (ABPA) develops in 1% to 10% of patients at some time in their lives.[284] In one study, more than 50% of patients with CF had precipitating antibodies to *A. fumigatus* in their serum, and this organism can be recovered from the sputum with a similar frequency.[285] New chest radiographic changes, increased cough, respiratory distress, wheezing, and the expectoration of rusty brown plugs of sputum containing many eosinophils suggest this diagnosis. Atelectasis due to plugging of a lobar or segmental bronchus with hyphae-laden mucus may occur. Chronic airway colonization with aspergillus is common, and diagnosis of ABPA requires new clinical findings plus skin hypersensitivity and elevated levels of IgG and IgE antibodies against *A. fumigatus* or other fungi.[242,243]

Pleural effusions and *empyema* are uncommon in patients with CF, but pleuritic symptoms and signs may accompany exacerbations of lung disease. Staphylococcal and pseudomonal empyemas have been described, but respiratory tract infections usually spare the pleural space.[286]

Digital *clubbing* occurs in virtually all patients with CF and is usually present early in the course of symptomatic lung disease. The cause of clubbing is unknown, but its severity generally correlates with the severity of lung disease.[287] *Hypertrophic pulmonary osteoarthropathy* occurs in as many as 15% of older adolescents and adults.[204,288] If radiographic evidence for periostitis is used as the definition, the incidence is 8%. The most common sites are the distal aspects of the tibia, fibula, radius, and ulna. Signs and symptoms include pain, bone tenderness, swelling, and warmth over the involved areas. Effusions in nearby joints may occur. There is often discomfort with ambulation. Hypertrophic pulmonary osteoarthropathy frequently becomes more symptomatic with pulmonary disease exacerbations and tends to subside when control of pulmonary symptoms is achieved. There are rare instances of cutaneous vasculitis due to CF, which causes a self-limited, painless, palpable purpura, typically involving the lower extremities.[288]

Respiratory failure leads to death in greater than 90% of CF patients. *Hypoxemia* often develops during exertion[289] or sleep[290] and progresses over years. Hypercapnia reflects severe airway obstruction and increases with disease severity and acute exacerbations. Hepatic congestion and peripheral edema caused by pulmonary hypertension and cor pulmonale may develop in the last year of life,[291] particularly if hypoxemia is not adequately treated. Occasionally, infections such as RSV or influenza cause acute respiratory failure that is fully reversible.[292]

Gastrointestinal Manifestations

Meconium ileus occurs in at least 15% of newborns with CF and is virtually diagnostic for CF.[78] These infants fail to pass meconium in the first day or two of life, develop abdominal distention, and proceed to bilious emesis. Occasionally, perforation and peritonitis accompanied by shock occurs. Abdominal radiographic images reveal multiple dilated loops of intestine and air-fluid levels. The lower abdomen may take on a granular appearance from accumulated meconium containing small air bubbles. A barium enema demonstrates a small colon, and if contrast material can be refluxed into the ileum, the point of ileal obstruction can be identified. In utero, ileal perforation results in peritoneal and scrotal calcification. Occasionally, obstruction occurs lower in the intestinal tract and causes only delayed passage of meconium. This condition has been termed the *meconium plug syndrome* and is much less specific for CF.[293] Meconium ileus is also a prominent feature of transgenic mice with a disrupted CFTR gene.[28]

Beyond the newborn period, intestinal obstruction may occur for a variety of reasons. About 20% of patients develop obstruction in the terminal ileum associated with voluminous, sticky, incompletely digested intestinal contents as seen with meconium ileus.[39,78,294] With partial obstruction, intermittent abdominal pain may be the only symptom, but complete obstruction is associated with failure to pass stools, abdominal distention, and vomiting. A mobile right lower quadrant mass may be palpable. Obstruction beyond the immediate newborn period is also characteristic of the CF mouse model. Other causes of abdominal pain and obstruction include intussusception, intestinal adhesions from previous abdominal surgery, low-grade appendicitis, which may be associated with partially suppressed antibiotic therapy, and periappendiceal abscess.[295] Nonfilling of the appendix with contrast enema is frequent in patients with CF, even in the absence of appendicitis.[296] Duodenal irritation, caused by failure to buffer gastric acid, may

underlie radiographic changes in this area and recurrent epigastric pain.[297]

Rectal prolapse occurs in nearly 20% of children, but is an infrequent event for adults with CF.[298] In fact, CF is said to be the most common cause of rectal prolapse in the United States. Factors contributing to rectal prolapse include the presence of bulky sticky stools that adhere to rectal mucosa, loss of the perirectal fat that normally supports the rectum, and increased frequency of high intra-abdominal pressure due to paroxysmal coughing. *Pneumatosis coli* has been reported in association with rectal prolapse in an 18-year-old patient with CF.

Pancreatic Disease

Pancreatic exocrine insufficiency is present from birth in the large majority of patients with CF.[299] It has been estimated that only 5% to 10% of patients have significant pancreatic enzyme release. Exocrine pancreatic sufficiency has been associated with several mutations, including 3789 + 10 Kb C to T, R117H, R334W, R347H, R347P, A455E, P574H, and Y563N. Enzyme deficiency results in fat and protein maldigestion, producing a distended abdomen and frequent bulky, greasy, foul-smelling stools. Uncorrected maldigestion results in failure to gain weight and, ultimately, a failure of linear growth. However, poor growth also may be associated with increased expenditure of energy to accomplish the work of breathing, a point that is often overlooked in the assessment of patients who are short or excessively thin.[300] Fat loss in stools may be as high as 50% to 70% of total intake. Nitrogen malabsorption is roughly comparable or perhaps somewhat less severe. In general, carbohydrates are adequately absorbed in CF. Deficient absorption of fat-soluble vitamins occasionally produces symptoms. Symptomatic vitamin A deficiency, initially a prominent part of the CF syndrome, is rare and occurs only in patients who do not take supplementary vitamins or pancreatic enzymes. Increased intracranial pressure, xerophthalmia, and night blindness may result. Vitamin D deficiency, rickets, is rarely seen. However, bone demineralization is common in CF patients.[301-304] Vitamin E deficiency is common in unsupplemented patients but only rarely causes symptoms, including increased red blood cell destruction and neuroaxonal dystrophy.[305] Vitamin K–dependent coagulation factors may also be deficient, resulting in a hemorrhagic diathesis. Although severe hemorrhagic problems occur mostly in young children, associated symptoms such as hemoptysis are occasionally seen in older patients.

It is now recognized that symptoms of pancreatitis are encountered in less than 1% of identified adolescent or adult CF patients and are limited to those who have retained some exocrine pancreatic function.[306] However, recurrent pancreatitis has been reported as associated with mutations in CFTR and is becoming more frequently recognized as a presenting symptom in adults with CF.[47,307,308] Pancreatic calcifications are occasionally seen radiographically but do not seem to correlate with symptomatic pancreatitis.

Hepatobiliary Disease

Focal biliary cirrhosis is characteristic of CF but produces symptoms in less than 5% of CF patients and causes death in about 2%.[40,309] Hepatic abnormalities can present as hepatosplenomegaly or as persistent elevation of hepatic enzymes (particularly alkaline phosphatase). Rarely, patients present with esophageal varices and hemorrhage due to portal hypertension. Fatty liver is more common and may improve with adequate nutrition. Gallbladder disease is common in adults with CF. Ten percent to 30% of patients have dysfunctional gallbladders[310] or gallstones.[311] Common bile duct stenosis secondary to CF is rare.[312]

Genitourinary Tract Abnormalities

More than 99% of male patients with CF have obstructive azoospermia due to obstruction of the vas deferens.[48] Relatively high incidences of inguinal hernia and hydrocele also have been noted. Failure of reproductive function does not become an issue until well into the second decade of life. Semen analysis may be required to identify the 1% of male CF patients who are fertile. The volume of ejaculate is usually one third to one half of normal. There usually is complete absence of spermatozoa, and a number of chemical abnormalities of semen that reflect absence of secretions from the seminal vesicles can be demonstrated.[313]

Female infertility in CF may be as high as 20%.[313] Some women with CF are anovulatory because of chronic lung disease and malnutrition. Another obstacle to conception may be the presence of thick tenacious cervical mucus, which is difficult to dislodge from the os. This mucus is dehydrated and has abnormal electrolyte concentrations, preventing the usual ferning at midcycle and perhaps impeding normal sperm migration.[314] Endocervicitis is commonly noted.

More than 600 pregnancies in CF females have been reported. A longitudinal study of 325 pregnant women with CF demonstrated 258 live births (79%) and 67 therapeutic abortions.[315] Compared with 1142 age- and severity-matched controls, pregnancy in a woman with CF did not have an independent negative effect on pulmonary status or mortality over 2 years.[316] However, it is essential that CF females consider their own health and expected life span in the context of family planning. Women with CF can breast feed successfully.[317]

Sweat Gland Dysfunction

Sweat chloride is elevated in most CF patients due to abnormal sodium chloride reabsorption in the sweat ducts.[318] Excessive loss of salt in the sweat predisposes young children to depletion episodes, especially at times when there is additional salt loss due to vomiting or diarrhea. These children present with lethargy, anorexia, and hypochloremic alkalosis, a presentation that is more common in warm arid zones. Such hypochloremic alkalosis is rare in older children and adults.[319]

TABLE 41-5. Criteria for the Diagnosis of Cystic Fibrosis

PHENOTYPIC CLINICAL FEATURES
Chronic sinopulmonary disease
Chronic cough and sputum production
Persistent infection with characteristic pathogens (*Staphylococcus aureus* and *Pseudomonas aeruginosa*)
Airflow obstruction
Chronic chest radiographic abnormalities
Sinus disease; nasal polyps
Gastrointestinal and nutritional abnormalities
Pancreatic exocrine insufficiency; recurrent pancreatitis
Meconium ileus; DIOS
Obstructive azoospermia in males
LABORATORY EVIDENCE OF CFTR DYSFUNCTION
Elevated sweat Cl^-
Mutation in the CF gene on both alleles
Characteristic bioelectric abnormalities (potential difference) in nasal epithelium in vivo

CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; DIOS, distal intestinal obstruction syndrome.
Adapted from Farrell PM, Rosenstein BJ, White TB, et al: Guidelines for diagnosis of cystic fibrosis in newborns through older adults: Cystic Fibrosis Foundation consensus report. J Pediatr 153:S4–S14, 2008.

TABLE 41-6. Conditions Other Than Cystic Fibrosis Associated with Elevated Sweat Chloride Levels

Adrenal insufficiency
Anorexia nervosa
Atopic dermatitis
Pseudohypoaldosteronism
Hypothyroidism
Hypoparathyroidism
Nephrogenic diabetes insipidus
Ectodermal dysplasia
Glycogen storage disease (type I)
Mucopolysaccharidosis
Fucosidosis
Malnutrition
Mauriac's syndrome
Familial cholestasis syndrome
Prostaglandin E_1 administration
Hypogammaglobulinemia

DIAGNOSIS

The diagnosis of CF is based on carefully defined clinical criteria and laboratory evidence of CFTR dysfunction, including abnormal sweat Cl^- levels.[318,320] Accepted diagnostic criteria are listed in Table 41-5. Any one of these clinical features, if accompanied by a sweat chloride level greater than 60 mEq/L, is sufficient to make the diagnosis. Characteristic nasal epithelial bioelectric abnormalities can also serve as laboratory evidence of CFTR dysfunction and be used to diagnose CF, when phenotypic clinical features are present.[318,321] Many diagnoses are verified by identifying a mutation in CFTR on both alleles. At this time, however, a substantial number of patients have unidentified mutations. A few persons with sweat chloride values persistently in the diagnostic range but without clinical features of CF or a family history have been identified. As long as they remain symptom-free and mutations of both CFTR genes are not identified, the diagnosis of CF cannot be made. Other clinical entities may be accompanied by elevated sweat chloride concentrations; these are listed in Table 41-6. None of these disorders are easily confused with CF. It is now recognized that a small percentage of persons with CF have sweat values in an intermediate (40–60 mEq/L) or even normal range.[37,322,323]

For the 1% to 2% of patients with compatible clinical features of CF but normal sweat chloride levels, several approaches to the diagnosis are available. Clinical criteria for making the diagnosis of CF in the presence of a normal sweat chloride value were proposed prior to modern diagnostic options.[322] The discovery that bioelectric potential differences across respiratory epithelia are abnormal in patients with CF[9,117,321] offers a more quantitative diagnostic test that has been useful in the evaluation of atypical patients. Also, DNA analysis techniques are now available for detection of CF gene mutations, particularly in clinical variants. For example, a single mutation of the CFTR gene, 3789 + 10 Kb C to T, is associated with many of the suspected patients with CF whose sweat chloride values are in the normal range.[37,44]

Although DNA analysis is becoming a standard of care in CF, the sweat test remains the diagnostic standard. Only one method is recognized by the Cystic Fibrosis Foundation as adequate for the definitive diagnosis of CF. This test involves collection of sweat by pilocarpine iontophoresis, coupled with chemical determination of the chloride concentration.[324,325] The procedure must be carried out in a meticulous fashion to avoid errors that frequently contribute to misleading values. As many as 40% of patients referred to CF centers have been inaccurately diagnosed elsewhere because of false-positive or false-negative sweat test results. In addition to frequent laboratory errors, faulty values can be obtained if the sweat rate is not sufficiently high. At least 50 mg of sweat must be collected in a 30-minute period. Potential pitfalls in interpretation include the presence of hypoproteinemic edema, failure to consider age-related effects, and concurrent administration of corticosteroids. Although using a threshold of 60 mEq/L of chloride in sweat appears to discriminate nearly all adults with CF from those with other lung conditions,[326] normal values of sweat chloride do increase with age, and some investigators insist on documentation of sweat chloride levels in excess of 70 mEq/L for the diagnosis of CF in adults.

Newborn screening for CF is now carried out on all infants in 49 states.[327–329] The test used is an assay of immunoreactive trypsin in dried blood spots collected

on filter paper in the first several days of life. Experience thus far suggests that most newborns with CF may be identified with this test.[330,331] This test has an acceptable rate of false-positive results. Follow-up testing is performed by sweat Cl^- and/or *CFTR* genotyping.[332] Studies of newborns with CF discovered by screening have detected nutritional deficits and infectious/inflammatory lung disease, which suggests that early identification and treatment may be useful to protect against loss of lung function.[333–339] In addition, pharmacologic and gene transfer therapies currently at an experimental stage are theoretically most effective early in life and, if their efficacy is documented, newborn screening will play an important role.

Antenatal diagnosis can now be carried out, especially when the genotype of parents is established. For more than a decade, genetic testing for CF has been offered to couples currently planning a pregnancy,[340] which has necessitated the development of counseling programs.[341,342]

TREATMENT

The primary objectives of CF treatment are to control infection, promote mucus clearance, and improve nutrition.[343] In addition, experience has repeatedly demonstrated that attention to preventive aspects of lung care and psychosocial factors is important. An important concept has emerged from both pathologic and functional (mucus clearance) studies, that is, CF lung disease is heterogeneous.[344] This observation suggests that specific therapies (e.g., CFTR correctors or potentiators or rehydrating agents) may be able to prevent the spread of chronic bacterial infection throughout the CF lung and, hence, truly "arrest" disease progression.

Ambulatory Care

At diagnosis, most patients are introduced to a care program including postural drainage with chest percussion, administration of antibiotics as indicated, and a nutritional regimen including pancreatic enzymes and fat-soluble vitamins. Other therapeutic modalities are prescribed as indicated.

Physical Measures to Promote Airway Clearance

The use of postural drainage with chest percussion to clear mucus is based on the concept that cough clears mucus from large airways but chest vibrations are necessary to move secretions from the small airways where expiratory flow rates are low. The most compelling argument for the use of this therapeutic modality comes from a study of older children with mild to moderate airflow limitation.[345] When patients were receiving chest physical therapy on a regular basis, the only immediate effect documented was an increase in peak expiratory flow rate 30 minutes after therapy. However, after 3 weeks without chest physical therapy, both FVC and flow rates were significantly reduced. The diminution in lung function could be reversed with renewal of regular chest physical therapy. A meta-analysis of 35 studies concluded that standard chest physical therapy increases sputum production and improves FEV_1.[346] Most care centers prescribe this therapy one to four times a day, depending on the severity of illness. A variety of mechanical percussors are available to assist, especially for those patients who do their own therapy. Several studies in the literature suggest that repeated forced expiratory maneuvers,[347] use of positive expiratory pressure,[348] and vigorous exercise[349–351] may substitute for chest physical therapy. The advisability of chest physical therapy for patients who have minimal cough and no apparent sputum production is open to question. Study results are not available to answer this question. Theoretically, chest physical therapy might prevent or delay inspissation of mucus in small airways, which is the earliest lesion. In addition, caregivers have found that many patients who do not receive chest physical therapy on a regular basis are unlikely to initiate this therapy when pulmonary exacerbations arise.

Inhaled Hypertonic Saline for Airway Clearance

Inhaled hypertonic saline (HS) osmotically draws water onto airway surfaces. Indeed, because of the limitation with respect to Cl^- permeability of CF airway epithelia, inhaled salt may remain on CF airway surfaces longer, and hence be osmotically more active, than on normal airway surfaces.[344] Recent data suggest that the rehydrating effect of inhaled HS (7%, four times daily) produces short term (2-wk) effects that restore mucus clearance and improve lung function and quality of life.[161] Further, data from Australia, also using 7% inhaled HS and an identical delivery device (Pari-LC Star), indicated that twice-daily inhalation of HS produced a durable increase in lung function, a substantial reduction in acute exacerbations, a reduction in newly acquired bacterial pathogens, a reduction in days lost from school/work, and an improvement in quality of life.[352] Many centers now consider inhaled HS (7%, twice daily) as a standard of care. However, more data are needed with respect to effectiveness of the wide variety of regimens currently in use (e.g., role of nebulizer type, strength of HS, number of administrations/day).

Aerosolized rhDNase

The lysis of viscous DNA with the recombinant enzyme DNase offers benefit to some patients with purulent airway secretions.[353] When taken once daily, aerosolized DNase reduced relative risk of respiratory exacerbations by 28% and improved FEV_1 approximately 6% above baseline over 6 months. Not all patients had objective improvement in lung function, but symptomatic benefit occurred in many of treated patients without improved lung function. Daily inhalation slows the usual decline

in lung function and decreases the frequency of exacerbations.[354]

Novel Airway Surface Rehydrating Agents

A number of novel agents are being developed to treat CF airways dehydration. For example, as an alternative osmotic agent, inhaled mannitol ("Bronchitol") is being developed as a dry powder inhalation and is currently in phase III clinical testing. There are also novel small molecules in development designed to redirect CF ion transport from absorptive to secretory modes. An extracellular ATPase resistant analogue of UTP, INS37217, is currently completing phase III testing.[145] Like endogenous ATP, INS37217 slows Na^+ absorption and activates Ca^{2+}-activated Cl^- channel-mediated Cl^- secretion in CF airways to rehydrate surfaces. In parallel, long-acting, potent, and safer amiloride derivatives (e.g., GS9411) are being developed for inhalation in an HS vehicle to greatly amplify the hydrating effect of HS. The GS9411/HS combination is currently in phase I testing.

Antibiotics

Lung infection is the major source of morbidity and mortality in CF. Therefore, antibiotics are the mainstay of therapy designed to control progression of disease. In general, antibiotic therapy should be predicated on the presence of symptoms and guided by the identification of organisms from the lower respiratory tract. There is evidence that early and vigorous use of antibiotics produces better results than delaying the administration of antibiotics until symptoms are well developed or advanced.[355] Similarly, *P. aeruginosa* infection has been treated by regularly scheduled courses of intravenous antibiotics.[356] Data justifying these approaches are lacking.

Another principle of antimicrobial therapy in CF is that dosages need to be higher than for non–CF-related chest infections. Both total body clearance and volume of distribution are considerably greater for CF than for other patients.[357] In addition, large doses are needed to achieve therapeutic levels in the infected and mucus- or pus-filled endobronchial space. Sputum levels achieved are highly varied but usually are less than half of the levels measured in serum.[358] Experience also has led many caregivers of CF patients to use longer than usual courses of antibiotics, continuing for at least 2 weeks and, frequently, 3 or 4 weeks.

The choice of antibiotics optimally should be based on the results of sputum culture and sensitivity testing. For patients with nonproductive cough, specimens are best obtained by harvesting secretions with a throat swab placed just above the glottis during repetitive coughing. Nasopharyngeal cultures are not useful as a guide for selection of antibiotics. If *S. aureus* is present or expected, the choice may include a semisynthetic penicillin, a combination of ampicillin and clavulanic acid, a cephalosporin, or clindamycin. Suggested drugs and doses are given in Table 41-7. *Haemophilus* infections are best treated with ampicillin, trimethoprim-sulfamethoxazole, cefuroxime, or cefaclor. In the majority of cases, these antibiotics will eradicate *S. aureus* and *H. influenzae* from the airways on a temporary basis. In older children and adults, tetracyclines may provide useful empirical therapy. Ciprofloxacin appears to control symptoms and reduces numbers of *Pseudomonas* organisms in CF airways, but its usefulness is limited by rapid emergence of resistant organisms.[359]

Because of limited options for treatment of *Pseudomonas* with oral antibiotics, parenteral preparations of aminoglycosides or other antibiotics have been delivered to the lower respiratory tract by aerosol.[360,361] Some studies show clear short-term benefit of aerosolized tobramycin (300 mg in nebulizer) taken twice daily.[362] This treatment, taken in alternate months for three cycles, improved lung function, decreased bacterial burden, and decreased relative risk for hospitalization. The rate of acquired tobramycin resistance was approximately 7% over 24 weeks in the treated group.

Macrolides

Long-term macrolide antibiotics effectively treat diffuse panbronchiolitis and have been tested in CF. Randomized, controlled clinical trials in CF children in the United Kingdom,[363] in adults who were chronically infected with *P. aeruginosa* in Australia,[364] and in chronically *P. aeruginosa*–infected children and adults in the United States[365] demonstrated clinical improvement (better pulmonary function and fewer pulmonary exacerbations) with azithromycin. A sputum acid-fast bacilli (AFB) smear and culture should be obtained prior to initiating chronic macrolide therapy because of the risk that undiagnosed nontuberculous mycobacterial infection could develop macrolide resistance. For patients on chronic macrolide therapy, an AFB smear and culture should be obtained every 6 months.

Bronchodilators

As detailed in the "Clinical manifestations" section, many patients demonstrate bronchial lability, prompting frequent use of bronchodilators,[260] particularly β-adrenoceptor agonists. Although their immediate effectiveness can be documented in the pulmonary function laboratory, overall improvement or long-term benefit has not been established. Indications for the use of bronchodilators include troublesome wheezing and a documented improvement in pulmonary function (e.g., at least a 15% improvement of FEV_1). β-Agonists can be nebulized, administered by metered-dose inhalers, or given orally. Caution should be exercised concerning long-term therapy with these agents because animal studies show that administration of large amounts of β-adrenoceptor agonists cause submucosal gland hypertrophy and presumably a hypersecretory state.[366] Theophylline preparations also may be effective in selected

TABLE 41-7. Antimicrobial Agents Used to Treat Cystic Fibrosis Lung Infection

Route	Organism	Agent	DOSE		Doses/day
			Pediatric (mg/kg/day)	Adult (g/day)	
Oral	*S. aureus*	Dicloxacillin	50–100	2–4	4
		Cefaclor	40	0.75–1.5	3
		Clindamycin	15–25	0.6–1.2	4
		Erythromycin	50	2	4
		Amoxicillin/clavulanate	40	1.5	3
		Azithromycin	—	0.5 day 1, then 0.25 daily for 2–5 days	1
		Linezolid	30	0.6	2–3
	H. influenzae	Amoxicillin	40–60	1.5	3
		Trimethoprim-sulfamethoxazole	20*	0.32–0.64*	2–4
	P. aeruginosa	Ciprofloxacin	—	1.5–2.25	3
		Ofloxacin	—	0.8–1.2	2–3
	Empirical	Tetracycline	50–100	2	3–4
Intravenous	*S. aureus*	Oxacillin	150–200	†	4
		Vancomycin	40	2	2–4
		Linezolid	30	0.6	2–3
	P. aeruginosa	Gentamicin or tobramycin	8–20	†	2–3
		Amikacin	15–30	†	2–3
		Carbenicillin or Ticarcillin	250–500	†	4–6
		Piperacillin, Mezlocillin, or Azlocillin	250–450	†	4–6
		Ticarcillin/clavulanate	250–450	†	4–6
		Imipenem/cilastatin or Meropenem	45–90	4	3–4
	P. aeruginosa and *B. cepacia*	Ceftazidime or Cefepime	150	4–6	3
Aerosol	*P. aeruginosa*	Gentamicin	40–600‡	80–600‡	2–4
		Tobramycin	40–600‡	80–600‡	2–4

*Quantity of trimethoprim.
†Usually dosed by mg/kg/day as with children.
‡Total dose in milligrams.

cases. However, CF patients seem to be less tolerant of theophylline because of frequent gastrointestinal irritation.[367] Ipratropium bromide is at least as effective as β-agonists in CF,[368–370] although distal intestinal obstruction syndrome has been reported coincident with use of this agent.[371] Cromolyn sodium has also been used; a single study failed to demonstrate efficacy.[372]

Corticosteroids

An initial double-blind controlled study of alternate-day oral corticosteroid administration demonstrated better maintenance of pulmonary function and fewer exacerbations of lung disease requiring hospitalization over a 4-year period.[373] A recent Cochrane review of 13 trials of inhaled corticosteroids in patients with cystic fibrosis concluded that there was insufficient evidence to document efficacy and some evidence that they may suppress growth.[373a] Widespread use of oral or inhaled corticosteroids cannot be advocated. They may be used for specific indications such as ABPA.

Anti-inflammatory Therapy with Ibuprofen

A study of high-dose ibuprofen over 4 years indicated that CF patients younger than age 13 years with mild lung disease have remarkable slowing of decline of lung function (eightfold) as compared with placebo control subjects.[374] No effect was documented in patients older than 13 years, even among patients with mildest lung disease. There were few side effects, but most of the patients were taking antacids or H_2-receptor blockers.

Other Respiratory Therapies

Mucolytics, expectorants, and cough suppressants have been used for relief of chest symptoms. In general, cough is an important mucus clearance mechanism for patients with CF and should not be suppressed. Expectorants, which assist in the elimination of airway secretions

during cough, probably do not achieve that objective. Rather than being helpful, long-term administration of iodides to patients with CF has been associated with a high incidence of goiter and hypothyroidism.[375] Mucolytics such as *N*-acetylcysteine are injurious to respiratory epithelium and promote bronchitis when used regularly. Therefore, aerosol inhalation of this substance should be used selectively and only for short periods. Another experimental approach, delivery of elastase inhibitors to airways by aerosol, is the subject of ongoing clinical trials.

Exercise is generally considered beneficial for patients with CF and should be encouraged for all but those with the most severe lung disease and hypoxemia.[376] A 12-week exercise program consisting of three 1-hour sessions a week, during which jogging was used to produce a heart rate averaging 70% to 85% of peak heart rate, has been shown to increase exercise tolerance and cardiorespiratory fitness, probably by increasing respiratory muscle endurance.[270] However, this program did not improve pulmonary function. Most caregivers of patients with CF believe that regular, vigorous exercise promotes a positive self-concept and increases the perception of wellness. In addition to cardiopulmonary conditioning exercises, isometric exercises such as weight lifting may build abdominal and upper body muscle strength and in this way promote deep breathing and effective coughing.

Systemic Agents Designed to Restore Cystic Fibrosis Transmembrane Regulator Function

Two classes of small molecule therapeutics are under development for treatment of CFTR mutant protein. The first class is aimed to improve the maturation of misfolded mutant CFTR (e.g., ΔF508 CFTR). If these drugs are successful, they would have the capacity to move mutant CFTR to the plasma membrane, where residual Cl^- function appears to be adequate to provide therapeutic benefit.[377] A first such compound, VX809, is in phase I testing.

The second class is aimed at mutant CFTRs that have normally folded, and are targeted to the apical membrane, but function poorly. Molecules such as VX770 have been shown to activate, that is, improve the gating, of such mutant CFTR (e.g., G551D). VX770 is currently in phase II clinical testing. Preliminary results suggest benefits on sweat chloride levels, nasal potential difference, and exacerbation frequency.

Gene Transfer Technology

It is technically possible using genetically engineered viral vectors to transfer the wild-type CFTR gene to respiratory epithelial cells in vitro, where it can be expressed at least for days to weeks.[378] Currently, work is ongoing at the laboratory level on adeno-associated virus–, lentiviral-, and paramyxoviral-based vectors for this purpose. When warranted, translation into human studies should be rapid, based on previous experience with preclinical models and human trials.[379,380]

Nutrition

Approximately 90% of patients with CF require mealtime pancreatic enzymes, packaged as granules that are coated with acid-resistant material to promote delivery to the small intestine. Capsules containing 4000 to 24,000 units of lipase are available. Numbers of capsules taken should be adjusted based on weight gain, presence or absence of abdominal cramping, and the character of stools. Dosage should be limited to current guidelines (~2500 lipase units/kg/meal), because a large total daily dose of enzymes has been associated with fibrosing colonopathy.[381–384] Vitamins A and D are supplied by a daily multiple vitamin preparation. Vitamin E, 100 to 200 units daily, is recommended because serum levels are generally low in unsupplemented patients. Vitamin K is given sporadically to treat bleeding complications or to correct prolonged prothrombin times. Other vitamins and trace minerals may be deficient and require supplementation on a selective basis.[300]

Many patients with CF have a higher than normal caloric need because of the increased work of breathing. In general, patients should be encouraged to eat a balanced diet, including at least a moderate amount of fat. When the anorexia of chronic infection supervenes, failure to gain weight or weight loss occurs. Further encouragement to eat high-calorie foods may be helpful. Supplementation with elemental dietary preparations by mouth is unlikely to be sustained over an extended period of time. Some CF care centers administer supplementary elemental feedings nocturnally by nasogastric tube or by percutaneous duodenostomy.[300,385] Although short-term benefits such as increased weight gain can be achieved, long-term beneficial effects on pulmonary function have not been established.

Patients with CF who retain exocrine pancreatic function and maintain good nutrition experience a slower rate of decline of pulmonary function than those with pancreatic dysfunction.[386] This observation has been used as a rationale for emphasizing nutritional interventions. Although this approach may have merit, it is generally more efficacious to maintain good nutrition by preventing progression of lung disease than to maintain good lung function by emphasizing nutritional therapy.

Psychosocial Factors

As with any chronic disease, compliance with therapy and ability to function fully are highly dependent on the patient's attitude. Therefore, approaches that promote a positive self-concept and foster the ability of patients to take control of their medical management, and enable them to participate fully in life events, are likely to promote well-being and perhaps longevity. Medical care that provides continuity and fosters trust may pay large dividends. Personnel who specifically provide psychosocial support are important contributors to CF care teams.[387]

Immunization for Lung Pathogens

Rubeola, pertussis, and influenza infections are particularly injurious to CF lungs and may trigger a downward spiral of lung function. Adequate immunization early in life for pertussis and measles is mandatory. Patients of all ages should be immunized for influenza virus on a yearly basis and the early treatment of influenza A infections may prevent adverse consequences. Other routine vaccines should be administered as for the general population. There is no evidence that administration of pneumococcal vaccine is useful.

Hospital Therapy

Indications for hospitalization and intensive pulmonary therapy include increased cough or wheezing, respiratory distress with decreased activity, weight loss, sustained downward trend in pulmonary function, increasing hypoxemia, or a major pulmonary complication. Hospitalization allows easy administration of intravenous antimicrobial agents to control *Pseudomonas* infections and intensification of all therapies including physical maneuvers to clear airway secretions.

Antibiotics for intravenous administration should be selected on the basis of respiratory tract cultures and susceptibility studies. Two-drug treatment of *Pseudomonas* infection is the rule. A third antibiotic may be added as necessary for control of *S. aureus* or other organisms. Drugs and dosages currently used for intravenous therapy are listed in Table 41-7. A clinical response is often not seen for 4 to 7 days after initiation of therapy. In general, a 2-week course provides good improvement in pulmonary function[388,389] and more sustained benefit than shorter courses. With refractory infection, treatment for 3 weeks or more is not unusual. Some advocate intensive therapy until pulmonary function has returned to a previous baseline or until improvement has reached a plateau. Prolonged courses of antibiotic therapy should include periodic monitoring of respiratory tract organisms and their antibiotic sensitivities, because shifts in either are common.

Aminoglycosides have been the mainstay of anti-*Pseudomonas* therapy for many years. A major advantage is ability to monitor and adjust blood levels. For gentamicin or tobramycin, two to three times a day dosage and achievement of peaks in the range of 10 to 12 μg/mL and troughs less than 2 μg/mL seem to be optimal. Patients should be monitored during aminoglycoside therapy for nephrotoxicity and ototoxicity. An aminoglycoside is usually paired with one of the penicillin derivatives or with ceftazidime.

Patients with CF, particularly those who are in school or holding full-time jobs, may opt to administer intravenous antibiotics at home for all or a portion of the treatment course. This seems to work well in selected cases and may be as effective as hospital treatment.[390,391] For patients requiring frequent courses or long-term home antibiotic therapy, central intravenous catheters have been surgically placed and used for prolonged periods.

One study suggested that the infusion of 500 mg/kg of intravenous immunoglobulin during a course of intravenous antibiotics enhances the pulmonary function response[392]; further studies are needed to confirm these observations.

Interest in bronchial lavage as a therapeutic modality has been tempered by the realization that long-term benefits are unlikely to accrue from this approach and that acute deterioration of lung function is a possible outcome.[393] In fact, there is no evidence that bronchoscopy and lavage, whether it be whole lung, lobar, or segmental, is superior to intensive antibiotic therapy and chest percussion.

Treatment of Lung Complications

Hypercapnic and hypoxemic *respiratory failure* in CF are primarily due to progressive obstructive airway disease with alveolar hypoventilation and ventilation-perfusion mismatching. Treatment of airway infection and inflammation with antibiotics and the airway clearance measures summarized previously is essential. Low-flow oxygen is effective at relieving nocturnal, exertional, and resting hypoxemia and does not usually cause significant hypercapnia.[394] The use of supplemental oxygen in children has been discouraged[395] because nocturnal oxygen did not improve survival or prevent the development of cor pulmonale in one controlled trial.[396] A larger study demonstrated that the development of pulmonary hypertension in adults with CF is strongly correlated with hypoxemia and is associated with increased mortality.[397] Therefore, supplemental oxygen in accordance with the guidelines established for chronic obstructive pulmonary disease[398] is recommended.[399] Diuretics, inotropic agents, and theophylline produce few benefits and are rarely used. Cor pulmonale is a late complication of airway obstruction, and no treatment options beyond those for the primary disease processes are effective.

Ventilatory assistance is effective in CF patients with acute respiratory failure caused by reversible insults[292] but produces few long-term benefits in patients with respiratory failure due to irreversible lung damage caused by CF bronchiectasis.[400] Assisted ventilation using nasal or face masks[401] or endotracheal tubes[402,403] can effectively treat patients awaiting lung transplantation. The airway disease generally progresses, however, and long-term ventilatory support is rarely feasible.

Atelectasis is best treated by vigorous standard therapy, including airway clearance and antibiotics. Corticosteroids may be helpful in the presence of reactive airways or severe airway inflammation. There is no evidence that bronchoscopy and lavage are effective in expanding collapsed segments of lobes.[280] *ABPA* responds to standard doses of systemic corticosteroids.[404] Inhaled steroids[405] and the oral antifungal agent itraconazole[406] may prove to be useful.

Pneumothorax can be observed for spontaneous resolution if small and minimally symptomatic. A pneumothorax more than 20% of the hemithorax volume, compromising ventilation or causing hypotension,

requires tube drainage.[262] Recurrences are very common and may require thoracoscopic talc poudrage or surgical pleural abrasion.[286]

Hemoptysis requires treatment of airway infection and supplemental vitamin K if the prothrombin time is prolonged due to inadequate absorption. Massive hemoptysis may resolve with such conservative therapy and modest cough suppression for 1 to 2 days,[282] but bronchial artery embolization[283,407] provides more definitive control, which usually persists for more than 6 months.

Treatment of Gastrointestinal Complications

Meconium ileus can be relieved in a number of cases with enemas using meglumine diatrizoate (Gastrografin) or other contrast materials, which are refluxed into the terminal ileum under fluoroscopy. If this fails, or if there is evidence of perforation, surgical intervention is required. *Distal intestinal obstruction syndrome* also can be relieved with contrast enemas that reach the terminal ileum. However, this approach has been largely supplanted by intestinal "flushes" with a balanced salt solution; 1 to 2 L rapidly instilled into the stomach is usually effective. Occasionally, surgical intervention is necessary. *Rectal prolapse* usually can be reduced voluntarily by older patients, using abdominal, perineal, and gluteal muscles, but in small children, rectal prolapse must be reduced manually by continuous gentle pressure with the patient in the knee-chest position[298]; sedation may be helpful. Adequate pancreatic enzyme therapy, decreased fat in the diet, and control of pulmonary infection usually prevent recurrences. A few patients may require surgical stabilization of the rectum.

Cirrhosis is generally focal and usually does not require specific therapy. Localization of CFTR to bile ductule cells suggests that abnormal bile secretion may be germane to CF liver disease. Ursodeoxycholic acid (URSO) is effective treatment for primary biliary cirrhosis.[408] Early trials of URSO in CF patients showed improved liver function tests, but the long-term effect on liver function is not known.[409,410] The thresholds for initiating therapy and clinical outcomes are under investigation. Bleeding esophageal varices that complicate cirrhosis often can be managed with banding or sclerotherapy. In the past, significant bleeding has been treated successfully with portal-systemic shunting.[411] Splenorenal anastomoses have been most effective, and hepatic encephalopathy has not been a problem. The transjugular intrahepatic portasystemic shunt procedure[412,413] can relieve portal hypertension and reduce bleeding episodes. Liver failure and ascites are treated as in other patients. Liver transplantation has been successfully performed, with a 2-year survival exceeding 50%.[414,415] Pancreatitis, when it occurs in adolescents or young adults with CF, is treated with standard measures.

Hyperglycemia as a complication of CF can occur at any age, but it is generally a problem of the second and third decades of life.[301] Ketoacidosis is rarely encountered. When blood glucose levels are only intermittently elevated and glycosuria is not present, no treatment is necessary. With the advent of sustained glycosuria, insulin treatment should be instituted. Oral hypoglycemic agents, considered ineffective in the past, may be helpful in selected patients.[416] The development of significant hyperglycemia may not change longevity.[417,418] However, vascular disease affecting the retina and kidneys has been documented in CF patients who have had prolonged hyperglycemia.[419,420] Therefore, careful control of blood sugar levels is desirable. Intensive screening and management regimens have been recommended.[421]

Surgical Therapy

Nasal polypectomy to relieve obstruction is the most common surgical procedure in CF, and most patients get symptomatic improvement.[422] Recurrence of polyps is common,[423] but the incidence of polyposis usually wanes after the second decade. Gallstones are common and symptomatic disease may require elective cholecystectomy in as many as 5% of CF adults.[424] Lobectomy is occasionally indicated for massive hemoptysis that is refractory to bronchial artery embolization. Partial lung resection has been advocated for apparently localized disease and recurrent severe exacerbations.[425] However, the generalized lung disease continues to progress; the limited probability of long-term benefits dictates caution in patient selection.

Transplantation

Lung transplantation has become an accepted therapy for respiratory failure secondary to CF.[426] Heart-lung transplant has been largely replaced by sequential double-lung transplant because of limited organ availability. Patients should be referred when their prognosis is about equal to the waiting time for donor lungs, currently about 2 years after acceptance as a lung transplant candidate. In 2005 in the United States, the allocation of donor lungs was changed to a system that incorporates waiting list and posttransplant survival probabilities based on underlying disease, pulmonary function, and other factors.[427] More than 2300 lung transplants have been performed for CF around the world. The transplanted lungs remain free of CF, but are subject to secondary infection, acute rejection, and chronic rejection (bronchiolitis obliterans syndrome). The 5-year survival is 48%, as good as that of lung transplant recipients with other causes of lung disease. Living lobar transplantation is an effective alternative to conventional cadaveric lung transplants.[428] The lobe donors must have sufficiently large lungs so that their lower lobe will fill the recipient's hemithorax. Survival appears to be similar to that following conventional lung transplantation.

Course of the Disease and Prognosis

CF runs a highly varied course, ranging from death due to complications of meconium ileus in the first days of

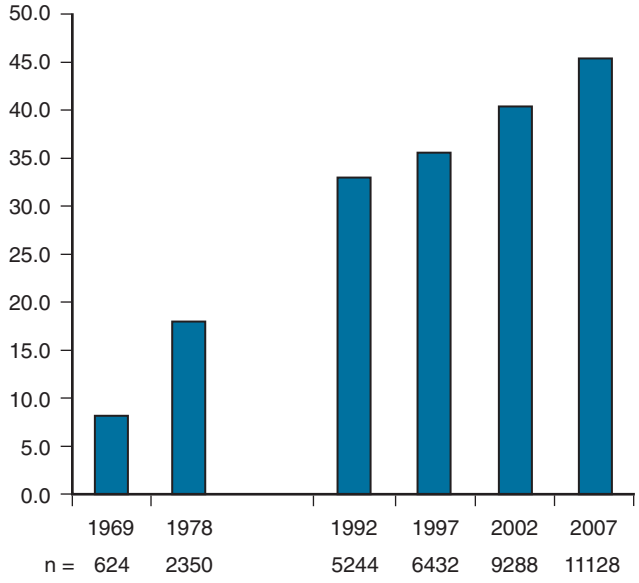

FIGURE 41-8 ■ Percent of CF patients aged 18 or older as shown for 1969 to 2007. (Data from the Patient Registry, Cystic Fibrosis Foundation, Bethesda, MD, courtesy of Dr. S. FitzSimmons.)

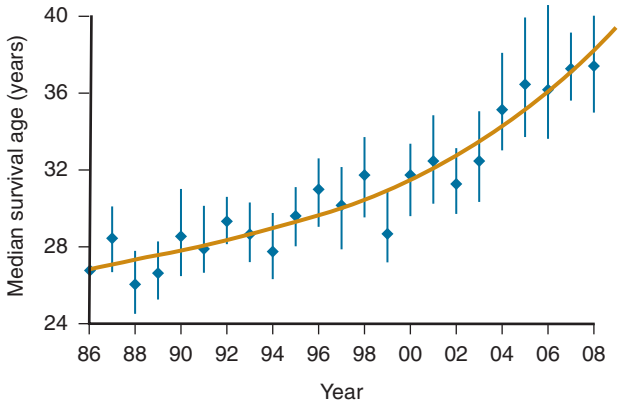

FIGURE 41-9 ■ Median predicted survival age for CF patients in US Cystic Fibrosis centers dating from 1986. (Data from the Patient Registry, Cystic Fibrosis Foundation, Bethesda, MD.)

life or death from severe respiratory tract problems within the first months of life to essentially asymptomatic existence for 10 to 20 years[429] and protracted survival. A few patients with CF do live into the sixth and seventh decades of life.[294] More than 11,100 (45%) of the patients in the U.S. CF registry are 18 years of age or older.[430] The changing age distribution is demonstrated in Figure 41-8.

At most care centers, patients with CF are monitored by general clinical assessment, which often involves the use of a scoring system,[431,432] periodic monitoring of respiratory tract pathogens, periodic chest radiographs, serial pulmonary function testing, and ongoing nutritional assessment. Initial intensive treatment is usually followed by improvement in pulmonary function tests as well as substantial improvement of weight-to-height ratios and accelerated linear growth in children. After initial improvement or stabilization, there is often an extended period of stable lung function that may last 5, 10, or even 15 years. Progressive dysfunction inevitably supervenes. Longitudinal patterns of pulmonary function in older individuals with CF are highly variable.[433,434]

The most recent statistics from the Cystic Fibrosis Foundation indicate that 50% of patients can now be expected to survive beyond age 37 years. These data were generated from all patients under care in Cystic Fibrosis Foundation–sponsored centers in 2007 (Fig. 41-9). Analyses of survival curves over the years have suggested that longevity has increased steadily to the present time. Some of the improvement in survival may have resulted from the diagnosis of milder forms of the disease. However, there is considerable opinion that improved symptomatic therapy has also contributed to better survival.

Multiple factors determine the prognosis for individuals with CF.[432] Data from all U.S. CF centers suggest that survival is better for patients living in northern climates than those living in the South. On average, male patients live 3 years longer than do female patients. The reason for this gender difference is not known, but there is no significant survival difference for CF patients born after 1990.[432] Blacks who survive the first several years of life may have a better prognosis than whites. Age at diagnosis has not emerged as a clear determinant of survival. However, a study of sibling pairs suggests that the younger sibling who is diagnosed before 1 year of age, before the onset of symptoms, usually has better pulmonary function at 7 years of age than does the older sibling diagnosed at an older age because of symptoms.[434]

Several studies suggest that the clinical features present when the patient is first seen make a difference. Patients who initially have only steatorrhea and failure to thrive generally improve remarkably after institution of therapy and do well for extended periods of time.[435] Conversely, patients who have respiratory tract symptoms when first seen usually continue to have respiratory tract problems and have a less favorable prognosis.[436] When the entire CF population is considered, those patients who retain pancreatic exocrine function display a slower progression of pulmonary disease.[33,437] Meconium ileus does not influence longevity if the patient survives the first months of life. Initial claims that CF patients with allergies have improved survival cannot be substantiated. There are many indicators of poor prognosis once airway disease has been established, including colonization with *P. aeruginosa* or *B. cepacia* and occurrence of pulmonary complications such as pneumothorax and massive hemoptysis.[438] Onset of insulin-dependent hyperglycemia is associated with worse lung function, poorer nutrition, and decreased survival compared with those in nondiabetic CF patients.[421,439]

Little is known about the influence of medical care on longevity. Several studies suggest that patients followed at established care centers have a greater median survival than those who receive care in nonspecialized settings.[440] In addition, evidence suggests that center-to-center variation in survival of patients is directly related to the intensity of care rendered in each center, including

frequency of monitoring, antibiotic use, and hospitalization for treatment of pulmonary exacerbations.[355] The U.S. Cystic Fibrosis Foundation now reports center-specific outcomes data on the internet (www.cff.org). It has sponsored a series of quality improvement initiatives to improve care processes and outcomes.[441] This work has already produced pulmonary, nutrition, and survival benefits, and led to the Cystic Fibrosis Foundation's receipt of a 2009 Health Quality Award from the National Committee for Quality Assurance (NCQA).

Finally, psychosocial factors undoubtedly play a prominent role in outcome, although this is difficult to document.[442–444] The role of a supportive family is crucial. Suicide is uncommon. However, it is widely recognized that a substantial number of adolescent and adult patients do not comply fully with therapy regimens because of denial, unresolved dependence-independence issues, and depression. Clearly, attitude and the ability to cope with a fatal illness during maturation and early adulthood do influence outcome.

Even though faced with a life-threatening illness and burdened with staggering demands on time, energy, and financial resources to comply with therapy, most adolescents and young adults cope admirably and are able to achieve a satisfactory quality of life. Successful relationships,[445] advanced education, and a full-time occupation are frequently achieved (Table 41-8), indicating that independent lifestyles and full participation in life events are attainable goals for many patients.

TABLE 41-8. Educational and Employment Records of Adults with Cystic Fibrosis

CF 2009.	
Education & Employment	
Data from CFF Patient Registry 2007	
Records of CF Adults (≥18 years) seen in CF Care Centers in 2007 (N = 11,128)	
Highest Education Level	
College graduate	31%
Some college	33%
High school diploma	27%
Less than high school	9%
Current Employment	
Retired	1%
Full-time	37%
Part-time	11%
Student	25%
Homemaker	4%
Unemployed	8%
Disabled	14%

KEY POINTS

- CF is a prevalent autosomal-recessive disease caused by a mutation in a gene encoding for CFTR, an integral membrane protein that regulates a chloride channel and other ion channels in epithelial cells.
- The CFTR defect results in alterations of electrolyte content, intraluminal volume, and diminished clearance of exocrine secretions.
- Lung pathophysiology results from airway obstruction by accumulated mucus and secondary bacterial infection.
- Diagnosis is made by identification of the typical pulmonary or pancreatic manifestations, family history, and documentation of elevated chloride concentrations in sweat or genetic testing.
- Treatment encompasses control of mucus retention and chronic infection in the lungs, replacement of pancreatic enzymes, and nutritional therapy.
- Close monitoring, vigorous attempts to reverse deterioration of lung function and nutritional deficits, and psychosocial support are beneficial.
- The outcome is highly variable, but longevity and quality of life have increased steadily. The median survival now exceeds 31 years.
- New approaches to therapy, including lung transplantation, pharmacologic interventions targeted to epithelial cell pathophysiology, and gene transfer to airway epithelium, offer hope for further advances.

References

1. Davis PB, Drumm M, Konstan MW: Cystic fibrosis. Am J Respir Crit Care Med 154:1229–1256, 1996.
2. Cutting GR, Accurso F, Ramsey BW, Welsh MJ: Cystic fibrosis. *In* Valle D, Beaudet AL, Vogelstein BS, et al (eds): Metabolic and Molecular Bases of Inherited Disease. New York: McGraw-Hill Health Professions Division, 2009.
3. Taussig LM (ed): Cystic Fibrosis. New York: Thieme-Stratton, 1984.
4. Andersen DH: Cystic fibrosis of the pancreas and its relation to celiac disease. A clinical and pathologic study. Am J Dis Child 56:344–399, 1938.
5. Farber S: Some organic digestive disturbances in early life. J Mich Med Sci 44:587–594, 1945.
6. Andersen DH, Hodges RG: Celiac syndrome. V. Genetics of cystic fibrosis of the pancreas with a consideration of etiology. Am J Dis Child 72:62–80, 1946.
7. di Sant'Agnese PA, Darling RC, Perera GA, Shea E: Abnormal electrolyte composition of sweat in cystic fibrosis of the pancreas. Pediatrics 12:549–563, 1953.
8. Gibson LE, Cooke RE: A test for concentration of electrolytes in sweat in cystic fibrosis of the pancreas utilizing pilocarpine by iontophoresis. Pediatrics 23:545–549, 1959.
9. Knowles M, Gatzy J, Boucher R: Increased bioelectric potential difference across respiratory epithelia in cystic fibrosis. N Engl J Med 305:1489–1495, 1981.
10. Quinton PM, Bijman J: Higher bioelectric potentials due to decreased chloride absorption in the sweat glands of patients with cystic fibrosis. N Engl J Med 308:1185–1189, 1983.
11. Tsui LC, Buchwald M, Barker D, et al: Cystic fibrosis locus defined by a genetically linked polymorphic DNA marker. Science 230:1054–1057, 1985.
12. Zengerling S, Tsui LC, Grzeschik KH, et al: Mapping of DNA markers linked to the cystic fibrosis locus on the long arm of chromosome 7. Am J Hum Genet 40:228–236, 1987.
13. White R, Woodward S, Leppert M, et al: A closely linked genetic marker for cystic fibrosis. Nature 318:382–384, 1985.
14. Wainwright BJ, Scambler PJ, Schmidtke J, et al: Localization of cystic fibrosis locus to human chromosome 7cen-q22. Nature 318:384–385, 1985.
15. Riordan JR, Rommens JM, Kerem B-T, et al: Identification of the cystic fibrosis gene: Cloning and characterization of complementary DNA. Science 245:1066–1073, 1989.
16. Kerem B, Rommens JM, Buchanan JA, et al: Identification of the cystic fibrosis gene: Genetic analysis. Science 245:1073–1080, 1989.
17. Drumm ML, Pope HA, Cliff WH, et al: Correction of the cystic fibrosis defect in vitro by retrovirus-mediated gene transfer. Cell 62:1227–1233, 1990.
18. Rich DP, Anderson MP, Gregory RJ, et al: Expression of cystic fibrosis transmembrane conductance regulator corrects defective chloride channel regulation in cystic fibrosis airway epithelial cells. Nature 347:358–363, 1990.
19. Anderson MP, Rich DP, Gregory RJ, et al: Generation of cAMP-activated chloride currents by expression of CFTR. Science 251:679–682, 1991.
20. Anderson MP, Gregory RJ, Thompson S, et al: Demonstration that CFTR is a chloride channel by alteration of its anion selectivity. Science 253:202–205, 1991.
21. Bear CE, Li C, Kartner N, et al: Purification and functional reconstitution of the cystic fibrosis transmembrane conductance regulator (CFTR). Cell 68:809–818, 1992.
22. Egan M, Flotte T, Afione S, et al: Defective regulation of outwardly rectifying Cl^- channels by protein kinase A corrected by insertion of CFTR. Nature 358:581–584, 1992.
23. Stutts MJ, Canessa CM, Olsen JC, et al: CFTR as a cAMP-dependent regulator of sodium channels. Science 269:847–850, 1995.
24. Cheng SH, Gregory RJ, Marshall J, et al: Defective intracellular transport and processing of CFTR is the molecular basis of most cystic fibrosis. Cell 63:827–834, 1990.
25. Jensen TJ, Loo MA, Pind S, et al: Multiple proteolytic systems, including the proteasome, contribute to CFTR processing. Cell 83:129–135, 1995.
26. Gunderson KL, Kopito RR: Conformational states of CFTR associated with channel gating: The role of ATP binding and hydrolysis. Cell 82:231–239, 1995.
27. Serohijos AW, Hegedus T, Aleksandrov AA, et al: Phenylalanine-508 mediates a cytoplasmic-membrane domain contact in the CFTR 3D structure crucial to assembly and channel function. Proc Natl Acad Sci U S A 105:3256–3261, 2008.
28. Snouwaert JN, Brigman KK, Latour AM, et al: An animal model for cystic fibrosis made by gene targeting. Science 257:1083–1088, 1992.
29. Clarke LL, Grubb BR, Gabriel SE, et al: Defective epithelial chloride transport in a gene targeted mouse model of cystic fibrosis. Science 257:1125–1128, 1992.
30. Dorin JR, Dickinson P, Alton EWFW, et al: Cystic fibrosis in the mouse by targeted insertional mutagenesis. Nature 359:211–215, 1992.
31. Grubb BR, Boucher RC: Pathophysiology of gene-targeted mouse models for cystic fibrosis. Physiol Rev 79:S193–S214, 1999.
32. Tsui L-C, Buchwald M: Biochemical and molecular genetics of cystic fibrosis. Adv Hum Genet 20:153–266, 1991.
33. Kerem E, Corey M, Kerem B-S, et al: The relation between genotype and phenotype in cystic fibrosis: Analysis of the most common mutation (DF_{508}). N Engl J Med 323:1517–1522, 1990.
34. Liechti-Gallati S, Bonsall I, Malik N, et al: Genotype/phenotype association in cystic fibrosis: Analyses of the delta F508, R553X, and 3905insT mutations. Pediatr Res 32:175–178, 1992.
35. Cystic Fibrosis Foundation Patient Registry. 2002 Annual Data Report. Bethesda, MD, 2003.
36. Zielenski J, Tsui LC: Cystic fibrosis: Genotypic and phenotypic variations. Annu Rev Genet 29:777–807, 1995.
37. Knowles MR, Friedman KJ, Silverman L. Genetics, diagnosis, and clinical phenotype. *In* Yankaskas JR, Knowles MR (eds): Cystic Fibrosis in Adults. Philadelphia: Lippincott-Raven, 1999, pp 27–42.
38. Castellani C, Cuppens H, Macek M Jr, et al: Consensus on the use and interpretation of cystic fibrosis mutation analysis in clinical practice. J Cyst Fibros 7:179–196, 2008.
39. Gaskin KJ: Intestines. *In* Yankaskas JR, Knowles MR (eds): Cystic Fibrosis in Adults. Philadelphia: Lippincott-Raven, 1999, pp 325–342.
40. Colombo C, Crosignani A, Melzi ML, et al: Hepatobiliary system. *In* Cystic Fibrosis in Adults. Philadelphia: Lippincott-Raven, 1999, pp 309–324.
41. Duthie A, Doherty DG, Williams C, et al: Genotype analysis for delta F508, G551D and R553X mutations in children and young adults with cystic fibrosis with and without chronic liver disease. Hepatology 15:660–664, 1992.
42. Zielenski J, Corey M, Rozmahel R, et al: Detection of a cystic fibrosis modifier locus for meconium ileus on human chromosome 19q13. Nat Genet 22:128–129, 1999.
43. Blackman SM, Deering-Brose R, McWilliams R, et al, and and the CF Twin and Sibling Study: Relative contribution of genetic and nongenetic modifiers to intestinal obstruction in cystic fibrosis. Gastroenterology 131:1030–1039, 2006.
44. Highsmith WE, Burch LH, Zhou Z, et al: A novel mutation in the cystic fibrosis gene in patients with pulmonary disease but normal sweat chloride concentrations. N Engl J Med 331:974–980, 1994.
45. Strong TV, Smit LS, Turpin SV, et al: Cystic fibrosis gene mutation in two sisters with mild disease and normal sweat electrolyte levels. N Engl J Med 325:1630–1634, 1991.
46. Noone PG, Knowles MR: "CFTR-opathies": Disease phenotypes associated with cystic fibrosis transmembrane regulator gene mutations. Respir Res 2:328–332, 2001.
47. Cohn JA, Friedman KJ, Noone PG, et al: Relation between mutations of the cystic fibrosis gene and idiopathic pancreatitis. N Engl J Med 339:653–658, 1998.
48. Wilschanski M, Corey M, Durie P, et al: Diversity of reproductive tract abnormalities in men with cystic fibrosis. JAMA 276:607–608, 1996.
49. Knowles MR, Durie PR: What is cystic fibrosis? N Engl J Med 347:439–442, 2002.

50. Merlo CA, Boyle MP: Modifier genes in cystic fibrosis lung disease. J Lab Clin Med 141:237–241, 2003.
51. Drumm ML, Konstan MW, Schluchter MD, et al, for the Gene Modifier Study Group: Gene modifiers of lung disease in cystic fibrosis. N Engl J Med 353:1443–1453, 2005.
52. Bremer LA, Blackman SM, Vanscoy LL, et al: Interaction between a novel TGFβ1 haplotype and CFTR genotype is associated with improved lung function in cystic fibrosis. Hum Mol Genet 17:2228–2237, 2008.
53. Vanscoy LL, Blackman SM, Collaco JM, et al: Heritability of lung disease severity in cystic fibrosis. Am J Respir Crit Care Med 175:1036–1043, 2007.
54. Collaco JM, Vanscoy L, Bremer L, et al:. Interactions between secondhand smoke and genes that affect cystic fibrosis lung disease. JAMA 299:417–424, 2008.
55. Wilfond BS, Fost N: The cystic fibrosis gene: Medical and social implications for heterozygote detection. JAMA 263:2777–2783, 1990.
56. Danks DM, Allan J, Anderson CM. A genetic study of fibrocystic disease of the pancreas. Ann Hum Genet 28:323–356, 1965.
57. Ten Kate LP: A method for analysing fertility of heterozygotes for autosomal recessive disorders, with special reference to cystic fibrosis, Tay-Sachs disease and phenylketonuria. Ann Hum Genet 40:287–297, 1977.
58. Romeo G, Devoto M, alietta LJV: Why is the cystic fibrosis gene so frequent? Hum Genet 84:1–5, 1989.
59. Boat TF, Dearborn DG: Etiology and pathogenesis. *In* Taussig LM (ed): Cystic Fibrosis. New York: Thieme-Stratton, 1984, pp 25–84.
60. Gabriel SE, Brigman KN, Koller BH, et al: Cystic fibrosis heterozygote resistance to cholera toxin in the cystic fibrosis mouse model. Science 266:107–109, 1994.
61. Zuelzer WW, Newton WA Jr: The pathogenesis of fibrocystic disease of the pancreas. A study of 36 cases with special reference to the pulmonary lesions. Pediatrics 4:53–69, 1949.
62. Sturgess J, Imrie J: Quantitative evaluation of the development of tracheal submucosal glands in infants with cystic fibrosis and control infants. Am J Pathol 106:303–311, 1982.
63. Baker D, Kupke KG, Ingram P, et al: Microprobe analysis in human pathology. Scanning Electron Microsc 1985:659–680, 1985.
64. Tomashefski JF Jr, Bruce M, Goldberg HI, Dearborn DG: Regional distribution of macroscopic lung disease in cystic fibrosis. Am Rev Respir Dis 133:535–540, 1986.
65. Sobonya RE, Taussig LM: Quantitative aspects of lung pathology in cystic fibrosis. Am Rev Respir Dis 134:290–295, 1986.
66. Ogrinc G, Kampalath B, Tomashefski JF Jr: Destruction and loss of bronchial cartilage in cystic fibrosis. Hum Pathol 29:65–73, 1998.
67. Hamutcu R, Rowland JM, Horn MV, et al: Clinical findings and lung pathology in children with cystic fibrosis. Am J Respir Crit Care Med 165:1172–1175, 2002.
68. Tomashefski JF Jr, Dahms BB, Abramowsky CR: The pathology of cystic fibrosis. *In* Davis PB (ed): Cystic Fibrosis (Vol 1). New York: Marcel Dekker, 1993, pp 435–489.
69. Tomashefski JF Jr, Konstan MW, Bruce M. The pathology of interstitial pneumonia in cystic fibrosis. Am Rev Respir Dis 133:A365, 1986.
70. Tomashefski JF Jr, Bruce M, Stern RC, et al: Pulmonary air cysts in cystic fibrosis: Relation of pathologic features to radiologic findings and history of pneumothorax. Hum Pathol 16:253–261, 1985.
71. Boat TF, di Sant'Agnese PA, Warwick WJ, Handwerger SA: Pneumothorax in cystic fibrosis. JAMA 209:1498–1504, 1969.
72. Mack JF, Moss AF, Harper WW, O'Loughlin BJ: The bronchial arteries in cystic fibrosis. JAMA 209:1498–1504, 1965.
73. Stern RC, Boat TF, Wood RE, et al: Treatment and prognosis of nasal polyps in cystic fibrosis. Am J Dis Child 136:1067–1070, 1982.
74. di Sant'Agnese PA, Hubbard VS: The pancreas. *In* Taussig LM (ed): Cystic Fibrosis. New York: Thieme-Stratton, 1984, pp 230–295.
75. Handwerger S, Roth J, Gorden P, et al: Glucose intolerance in cystic fibrosis. N Engl J Med 281:451–461, 1969.
76. Moyer K, Balistreri W: Hepatobiliary disease in patients with cystic fibrosis. Curr Opin Gastroenterol 25:272–278, 2009.
77. Feranchak AP: Hepatobiliary complications of cystic fibrosis. Curr Gastroenterol Rep 6:231–239, 2004.
78. di Sant'Agnese PA, Hubbard VS: The gastrointestinal tract. *In* Taussig LM (ed): Cystic Fibrosis. New York: Thieme-Stratton, 1984, pp 212–229.

78a. Parkins RA, Eidelman S, Rubin CE, et al: The diagnosis of cystic fibrosis by rectal section biopsy. Lancet 2:851–856, 1963.

79. Neutra MR, Trier JS: Rectal mucosa in cystic fibrosis. Morphological features before and after short-term organ culture. Gastroenterology 75:701–710, 1978.
80. Brugman SM, Taussig LM: The reproductive system. *In* Taussig LM (ed): Cystic Fibrosis. New York: Thieme-Stratton, 1984, pp 323–337.
81. Gregory RJ, Cheng SH, Rich DP, et al: Expression and characterization of the cystic fibrosis transmembrane conductance regulator. Nature 347:382–386, 1990.
82. Guggino WB, Stanton BA: New insights into cystic fibrosis: Molecular switches that regulate CFTR. Nat Rev Mol Cell Biol 7:426–436, 2006.
83. Short DB, Trotter KW, Reczek D, et al: An apical PDZ protein anchors the cystic fibrosis transmembrane conductance regulator to the cytoskeleton. J Biol Chem 273:19797–19801, 1998.
84. Hyde SC, Emsley P, Hartshorn MJ, et al: Structural model of ATP-binding proteins associated with cystic fibrosis, multidrug resistance and bacterial transport. Nature 346:362–365, 1990.
85. Feranchak AP, Sokol RJ: Cholangiocyte biology and cystic fibrosis liver disease. Semin Liver Dis 21:471–488, 2001.
86. Engelhardt JF, Yankaskas JR, Ernst SA, et al: Submucosal glands are the predominant site of CFTR expression in human bronchus. Nat Genet 2:240–247, 1992.
87. Kreda SM, Mall M, Mengos A, et al: Characterization of wild-type and ΔF508 cystic fibrosis transmembrane regulator in human respiratory epithelia. Mol Biol Cell 16:2154–2167, 2005.
88. Reddy MM, Quinton PM: Intracellular potentials of microperfused human sweat duct cells. Pfluegers Arch 410:471–475, 1987.
89. Riordan JR: Cystic fibrosis as a disease of misprocessing of the cystic fibrosis transmembrane conductance regulator glycoprotein. Am J Hum Genet 64:1499–1504, 1999.
90. Denning GM, Anderson MP, Amara JF, et al: Processing of mutant cystic fibrosis transmembrane conductance regulator is temperature-sensitive. Nature 358:761–764, 1992.
91. Wang X, Venable J, LaPointe P, et al: Hsp90 cochaperone Aha1 downregulation rescues misfolding of CFTR in cystic fibrosis. Cell 127:803–815, 2006.
92. Younger JM, Chen L, Ren HY, et al: Sequential quality-control checkpoints triage misfolded cystic fibrosis transmembrane conductance regulator. Cell 126:571–582, 2006.
93. Pissarra LS, Farinha CM, Xu Z, et al: Solubilizing mutations used to crystallize one CFTR domain attenuate the trafficking and channel defects caused by the major cystic fibrosis mutation. Chem Biol 15:62–69, 2008.
94. Gregory RJ, Rich DP, Cheng SH, et al: Maturation and function of cystic fibrosis transmembrane conductance regulator variants bearing mutations in putative nucleotide-binding domains 1 and 2. Mol Cell Biol 11:3886–3893, 1991.
95. Anderson MP, Welsh MJ: Regulation by ATP and ADP of CFTR chloride channels that contain mutant nucleotide-binding domains. Science 257:1701–1704, 1992.
96. Drumm M: What happens to Delta F508 in vivo? J Clin Invest 103:1369–1370, 1999.
97. Bradbury NA, Jilling T, Berta G, et al: Regulation of plasma membrane recycling by CFTR. Science 256:530–532, 1992.
98. Bradbury NA, Cohn JA, Venglarik CJ, Bridges RJ: Biochemical and biophysical identification of cystic fibrosis transmembrane conductance regulator chloride channels as components of endocytic clathrin-coated vesicles. J Biol Chem 269:8296–8302, 1994.
99. Teichgraber V, Ulrich M, Endlich N, et al: Ceramide accumulation mediates inflammation, cell death and infection susceptibility in cystic fibrosis. Nat Med 14:382–391, 2008.
100. Haggie PM, Verkman AS: Defective organellar acidification as a cause of cystic fibrosis lung disease: Reexamination of a recurring

hypothesis. Am J Physiol Lung Cell Mol Physiol 296:L859–L867, 2009.
101. Berger HA, Anderson MP, Gregory RJ, et al: Identification and regulation of the cystic fibrosis transmembrane conductance regulator–generated chloride channel. J Clin Invest 88:1422–1431, 1991.
102. Hwang T-C, Lu L, Zeitlin PL, et al: Cl^- channels in CF: Lack of activation by protein kinase C and cAMP-dependent protein kinase. Science 244:1351–1356, 1989.
103. Fischer H, Machen TE: CFTR displays voltage dependence and two gating modes during stimulation. J Gen Physiol 104:541–566, 1994.
104. Anderson MP, Berger HA, Rich DP, et al: Nucleoside triphosphates are required to open the CFTR chloride channel. Cell 67:775–784, 1991.
105. Cheng SH, Rich DP, Marshall J, et al: Phosphorylation of the R domain by cAMP-dependent protein kinase regulates the CFTR chloride channel. Cell 66:1027–1036, 1991.
106. Davis PB (ed): Pathophysiology of the lung disease in cystic fibrosis. *In* Lung Biology in Health and Disease. Vol 64: Cystic Fibrosis. New York: Marcel Dekker, 1993, pp 193–218.
107. Smith JJ, Travis SM, Greenberg EP, Welsh MJ: Cystic fibrosis airway epithelia fail to kill bacteria because of abnormal airway surface fluid. Cell 85:229–236, 1996.
108. Zabner J, Smith JJ, Karp PH, et al: Loss of CFTR chloride channels alters salt absorption by cystic fibrosis airway epithelia in vitro. Mol Cell 2:397–403, 1998.
109. Ganz T: Antimicrobial polypeptides in host defense of the respiratory tract. J Clin Invest 109:693–697, 2002.
110. Tarran R, Grubb BR, Gatzy JT, et al: The relative roles of passive surface forces and active ion transport in the modulation of airway surface liquid volume and composition. J Gen Physiol 118:223–236, 2001.
111. Tarran R, Button B, Picher M, et al: Normal and cystic fibrosis airway surface liquid homeostasis: The effects of phasic shear stress and viral infections. J Biol Chem 280:35751–35759, 2005.
112. Myerburg MM, Butterworth MB, McKenna EE, et al: Airway surface liquid volume regulates ENaC by altering the serine protease-protease inhibitor balance: A mechanism for sodium hyperabsorption in cystic fibrosis. J Biol Chem 281:27942–27949, 2006.
113. Matsui H, Grubb BR, Tarran R, et al: Evidence for periciliary liquid layer depletion, not abnormal ion composition, in the pathogenesis of cystic fibrosis airways disease. Cell 95:1005–1015, 1998.
114. Kohler D, App E, Schmitz-Schumann M, et al: Inhalation of amiloride improves the mucociliary and the cough clearance in patients with cystic fibroses. Eur J Respir Dis 69(Suppl146):319–326, 1986.
115. Regnis JA, Robinson M, Bailey DL, et al: Mucociliary clearance in patients with cystic fibrosis and in normal subjects. Am J Respir Crit Care Med 150:66–71, 1994.
116. Lazarowski ER, Tarran R, Grubb BR, et al: Nucleotide release provides a mechanism for airway surface liquid homeostasis. J Biol Chem 279:36855–36864, 2004.
117. Knowles M, Gatzy J, Boucher R: Relative ion permeability of normal and cystic fibrosis nasal epithelium. J Clin Invest 71:1410–1417, 1983.
118. Knowles MR, Stutts MJ, Spock A, et al: Abnormal ion permeation through cystic fibrosis respiratory epithelium. Science 221:1067–1070, 1983.
119. Boucher RC, Stutts MJ, Knowles MR, et al: Na^+ transport in cystic fibrosis respiratory epithelia. Abnormal basal rate and response to adenylate cyclase activation. J Clin Invest 78:1245–1252, 1986.
120. Cotton CU, Stutts MJ, Knowles MR, et al: Abnormal apical cell membrane in cystic fibrosis respiratory epithelium. An in vitro electrophysiologic analysis. J Clin Invest 79:80–85, 1987.
121. Widdicombe JH, Welsh MJ, Finkbeiner WE: Cystic fibrosis decreases the apical membrane chloride permeability of monolayers cultured from cells of tracheal epithelium. Proc Natl Acad Sci U S A 82:6167–6171, 1985.
122. Willumsen NJ, Boucher RC: Shunt resistance and ion permeabilities in normal and cystic fibrosis airway epithelium. Am J Physiol 256:C1054–C1063, 1989.
123. Willumsen NJ, Davis CW, Boucher RC: Intracellular Cl^- activity and cellular Cl^- pathways in cultured human airway epithelium. Am J Physiol 256:C1033–C1044, 1989.
124. Willumsen NJ, Davis CW, Boucher RC: Cellular Cl^- transport in cultured cystic fibrosis airway epithelium. Am J Physiol 256:C1045–C1053, 1989.
125. Frizzell RA, Rechkemmer G, Shoemaker RL: Altered regulation of airway epithelial cell chloride channels in cystic fibrosis. Science 233:558–560, 1986.
126. Welsh MJ: Abnormal regulation of ion channels in cystic fibrosis epithelia. FASEB J 4:2718–2725, 1990.
127. Welsh MJ, Liedtke CM: Chloride and potassium channels in cystic fibrosis airway epithelia. Nature 322:467–470, 1986.
128. Boucher RC, Cheng EHC, Paradiso AM, et al: Chloride secretory response of cystic fibrosis human airway epithelia: Preservation of calcium but not protein kinase C– and A–dependent mechanisms. J Clin Invest 84:1424–1431, 1989.
129. Rollins BM, Burn M, Coakley RD, et al: A2B adenosine receptors regulate the mucus clearance component of the lungs' innate defense system. Am J Respir Cell Mol Biol 9:190–197, 2008.
130. Tabcharani JA, Chang XB, Riordan JR, Hanrahan JW. Phosphorylation-regulated Cl^- channel in CHO cells stably expressing the cystic fibrosis gene. Nature 352:628–631, 1991.
131. Faria D, Schreiber R, Kunzelmann K: CFTR is activated through stimulation of purinergic P2Y(2) receptors. Pflugers Arch 457:1373–1380, 2008.
132. Luo J, Pato MD, Riordan JR, Hanrahan JW: Differential regulation of single CFTR channels by PP2C, PP2A, and other phosphatases. Am J Physiol 274:C1397–C1410, 1998.
133. Berger HA, Travis SM, Welsh MJ: Regulation of the cystic fibrosis transmembrane conductance regulator Cl^- channel by specific protein kinases and protein phosphatases. J Biol Chem 268:2037–2047, 1993.
133a. Tarran R, Button B, Picher M, et al: Normal and cystic fibrosis airway surface liquid homeostasis. The effects of phasic shear stress and viral infections. J Biol Chem 280:35751–35759, 2005.
133b. Tarran R, Trout L, Donaldson SH, Boucher RC: Soluble mediators, not cilia, determine airway surface liquid volume in normal and cystic fibrosis superficial airway epithelia. J Gen Physiol 127:591–604, 2006.
133c. Myerburg MM, Butterworth MB, McKenna EE, et al: Airway surface liquid volume regulates ENaC by altering the serine protease-protease inhibitor balance: a mechanism for sodium hyperabsorption in cystic fibrosis. J Biol Chem 281:27942–27949, 2006.
134. Willumsen NJ, Boucher RC: Activation of an apical Cl^- conductance by Ca^{2+} ionophores in cystic fibrosis airway epithelia. Am J Physiol 256:C226–C233, 1989.
135. Wagner JA, McDonald TV, Nghiem PT, et al: Antisense oligodeoxynucleotides to the cystic fibrosis transmembrane conductance regulator inhibit cAMP-activated but not calcium-activated chloride currents. Proc Natl Acad Sci U S A 89:6785–6789, 1992.
136. Clarke LL, Grubb BR, Yankaskas JR, et al: Relationship of a non–CFTR-mediated chloride conductance to organ-level disease in *cftr*(–/–) mice. Proc Natl Acad Sci U S A 91:479–483, 1994.
137. Schroeder BC, Cheng T, Jan YN, Jan LY: Expression cloning of TMEM16A as a calcium-activated chloride channel subunit. Cell 134:1019–1029, 2008.
138. Yang YD, Cho H, Koo JY, et al: TMEM16A confers receptor-activated calcium-dependent chloride conductance. Nature 455:1210–1215, 2008.
139. Caputo A, Caci E, Ferrera L, et al: TMEM16A, a membrane protein associated with calcium-dependent chloride channel activity. Science 322:590–594, 2008.
140. Brown HA, Lazarowski ER, Boucher RC, Harden TK. Evidence that UTP and ATP regulate phospholipase C through a common extracellular 5′-nucleotide receptor in human airway epithelial cells. Mol Pharmacol 40:648–655, 1991.
141. Mason SJ, Paradiso AM, Boucher RC: Regulation of transepithelial ion transport and intracellular calcium by extracellular adenosine triphosphate in human normal and cystic fibrosis airway epithelium. Br J Pharmacol 103:1649–1656, 1991.
142. Knowles MR, Clarke LL, Boucher RC: Activation by extracellular nucleotides of chloride secretion in the airway epithelia of patients with cystic fibrosis. N Engl J Med 325:533–538, 1991.

143. Clarke LL, Boucher RC: Chloride secretory response to extracellular ATP in normal and cystic fibrosis nasal epithelia. Am J Physiol 263:C348–C356, 1992.
144. Noone PG, Hamblett N, Accurso F, et al, and The Cystic Fibrosis Therapeutics Development Research Group: Safety of aerosolized INS 365 in patients with mild to moderate cystic fibrosis: Results of a phase I multi-center study. Pediatr Pulmonol 32:122–128, 2001.
145. Kellerman D, Rossi Mospan A, Engels J, et al: Denufosol: a review of studies with inhaled P2Y(2) agonists that led to Phase 3. Pulm Phamacol Ther 21:600–607, 2008.
146. Robson AM, Tateishi S, Ingelfinger JR, et al: Renal function in cystic fibrosis. J Pediatr 79:42–50, 1971.
147. Stenvinkel P, Hjelte L, Alvan G, et al: Decreased renal clearance of sodium in cystic fibrosis. Acta Paediatr Scand 80:194–198, 1991.
148. O'Loughlin EV, Hunt DM, Gaskin KJ, et al: Abnormal epithelial transport in cystic fibrosis jejunum. Am J Physiol 260:G758–G763, 1991.
149. Baxter P, Goldhill J, Hardcastle J, et al: Enhanced intestinal glucose and alanine transport in cystic fibrosis. Gut 31:817–820, 1990.
150. Berschneider HM, Knowles MR, Azizkhan RG, et al: Altered intestinal chloride transport in cystic fibrosis. FASEB J 2:2625–2629, 1988.
151. Willumsen NJ, Boucher RC: Sodium transport and intracellular sodium activity in cultured human nasal epithelium. Am J Physiol 261:C319–C331, 1991.
152. Willumsen NJ, Boucher RC: Transcellular sodium transport in cultured cystic fibrosis human nasal epithelium. Am J Physiol 261:C332–C341, 1991.
153. Chinet T, Fullton J, Yankaskas J, et al: Characterization of sodium channels in the apical membrane of nasal epithelial cells. Am Rev Respir Dis 141:A164, 1990.
154. Chinet T, Fullton J, Boucher R, Stutts J:. Sodium channels in the apical membrane of normal and CF nasal epithelial cells. Pediatr Pulmonol Suppl 5:209, 1990.
155. Chinet T, Fullton J, Yankaskas J, et al: Characteristics of cation channels in cell-attached patches of normal and CF nasal epithelial cells. Am Rev Respir Dis 143:A148, 1991.
156. Mall M: Overexpression of ENaC in mouse airways: A novel animal model for chronic bronchitis and cystic fibrosis lung disease. Pediatr Pulmonol Suppl 25:121, 2003.
157. Tarran R, Button B, Boucher RC: Regulation of normal and cystic fibrosis airway surface liquid volume by phasic shear stress. Annu Rev Physiol 68:543–561, 2005.
158. Grygorczyk R, Hanrahan JW: CFTR-independent ATP release from epithelial cells triggered by mechanical stimuli. Am J Physiol 272:C1058–C1066, 1997.
159. Button B, Picher M, Boucher RC: Differential effects of cyclic and constant stress on ATP release and mucociliary transport by human airway epithelia. J Physiol (Lond) 580:577–592, 2007.
160. Guyot A, Hanrahan JW: ATP release from human airway epithelial cells studied using a capillary cell culture system. J Physiol (Lond) 545:199–206, 2002.
161. Donaldson SH, Bennett WD, Zeman KL, et al: Mucus clearance and lung function in cystic fibrosis with hypertonic saline. N Engl J Med 354:241–250, 2006.
162. Engelhardt JF, Stratford-Perricaudet LD, Yang Y, et al: Direct transfer of recombinant genes into human bronchial epithelia of xenografts with E1 deleted adenoviruses. Nat Genet 4:27–34, 1993.
163. Knowles MR, Robinson JM, Wood RE, et al: Ion composition of airway surface liquid of patients with cystic fibrosis as compared to normal and disease-control subjects. J Clin Invest 100:2588–2595, 1997.
163a. Jiang C, Finkbeiner WE, Widdicombe JH, Miller SS: Fluid transport across cultures of human tracheal glands is altered in cystic fibrosis. J Physiol 501:637–647, 1997.
164. Yamaya M, Finkbeiner WE, Widdicombe JH: Ion transport by cultures of human tracheobronchial submucosal glands. Am J Physiol 261:L485–L490, 1991.
165. Yamaya M, Finkbeiner WE, Widdicombe JH: Altered ion transport by tracheal glands in cystic fibrosis. Am J Physiol 261:L491–L494, 1991.
166. Joo NS, Irokawa T, Wu JV, et al: Absent secretion to vasoactive intestinal peptide in cystic fibrosis airway glands. J Biol Chem 277:50710–50715, 2002.
167. Jayaraman S, Joo NS, Reitz B, et al: Submucosal gland secretions in airways from cystic fibrosis patients have normal [Na^+] and pH but elevated viscosity. Proc Natl Acad Sci U S A 98:8119–8123, 2001.
168. Song Y, Salinas D, Nielson DW, Verkman AS. Hyperacidity of secreted fluid from submucosal glands in early cystic fibrosis. Am J Physiol Cell Physiol 290:C741–C749, 2006.
169. Boat TF, Cheng PW: Biochemistry of airway mucus secretions. Fed Proc 39:3067–3074, 1980.
170. Henke MO, Renner A, Huber RM, et al: MUC5AC and MUC5B mucins are decreased in cystic fibrosis airway secretions. Am J Respir Cell Mol Biol 31:86–91, 2004.
171. Davril M, Degroote S, Humbert P, et al: The sialylation of bronchial mucins secreted by patients suffering from cystic fibrosis or from chronic bronchitis is related to the severity of airway infection. Glycobiology 9:311–321, 1999.
172. Wesley A, Forstner J, Qureshi R, et al: Human intestinal mucin in cystic fibrosis. Pediatr Res 17:65–69, 1983.
173. Cheng P-W, Boat TF, Cranfill K, et al: Increased sulfation of glycoconjugates by cultured nasal epithelial cells from patients with cystic fibrosis. J Clin Invest 84:68–72, 1989.
174. Frates RC Jr, Kaizu TT, Last JA: Mucus glycoproteins secreted by respiratory epithelial tissue from cystic fibrosis patients. Pediatr Res 17:30–34, 1983.
175. Zhang Y, Jiang Q, Dudus L, et al: Vector-specific complementation profiles of two independent primary defects in cystic fibrosis airways. Hum Gene Ther 9:635–648, 1998.
176. Roomans GM, von Euler AM, Muller RM, Gilljam H: X-ray microanalysis of goblet cells in bronchial epithelium of patients with cystic fibrosis. J Submicrosc Cytol 18:613–615, 1986.
177. Holmen JM, Karlsson NG, Abdullah LH, et al: Mucins and their O-glycans from human bronchial epithelial cell cultures. Am J Physiol 287:L824–L834, 2004.
178. Leigh MW, Boat TF: Airway secretions. *In* Chernick V, Mellins RB (eds): Basic Mechanisms of Pediatric Respiratory Disease: Cellular and Integrative. Philadelphia: BC Decker, 1991, pp 328–345.
179. Quinton PM: Cystic fibrosis: Impaired bicarbonate secretion and mucoviscidosis. Lancet 372:415–417, 2008.
180. Lam J, Chan R, Lam K, Costerton JW: Production of mucoid microcolonies by *Pseudomonas aeruginosa* within infected lungs in cystic fibrosis. Infect Immun 28:546–556, 1980.
181. Tunney MM, Field TR, Moriarty TF, et al: Detection of anaerobic bacteria in high numbers in sputum from patients with cystic fibrosis. Am J Respir Crit Care Med 177:995–1001. 2008.
182. Rogers GB, Carroll MP, Serisier DJ, et al: Bacterial activity in cystic fibrosis lung infections. Respir Res 6:49–60, 2005.
183. Rogers GB, Hart CA, Mason JR, et al: Bacterial diversity in cases of lung infection in cystic fibrosis patients: 16S ribosomal DNA (rDNA) length heterogeneity PCR and 16S rDNA terminal restriction fragment length polymorphism profiling. J Clin Microbiol 41:3548–3558, 2003.
184. Bennett WD, Olivier KN, Zeman KL, et al: Effect of uridine 5′-triphosphate plus amiloride on mucociliary clearance in adult cystic fibrosis. Am J Respir Crit Care Med 153:1796–1801, 1996.
185. Katz SM, Holsclaw DS Jr: Ultrastructural features of respiratory cilia in cystic fibrosis. Am J Clin Pathol 73:682–685, 1980.
186. Rutland J, Cole PJ: Nasal mucociliary clearance and ciliary beat frequency in cystic fibrosis compared with sinusitis and bronchiectasis. Thorax 36:654–658, 1981.
187. Ulrich M, Herbert S, Berger J, et al: Localization of *Staphylococcus aureus* in infected airways of patients with cystic fibrosis and in a cell culture model of *S. aureus* adherence. Am J Respir Cell Mol Biol 19:83–91, 1998.
188. Saiman L, Cacalano G, Gruenert D, Prince A: Comparison of adherence of *Pseudomonas aeruginosa* to respiratory epithelial cells from cystic fibrosis patients and healthy subjects. Infect Immun 60:2808–2814, 1992.
189. Plotkowski MC, Chevillard M, Pierrot D, et al: Epithelial respiratory cells from cystic fibrosis patients do not possess specific *Pseudomonas aeruginosa*-adhesive properties. J Med Microbiol 36:104–111, 1992.

190. Pier GB, Grout M, Zaidi TS, et al: Role of mutant CFTR in hypersusceptibility of cystic fibrosis patients to lung infections. Science 271:64–67, 1996.
191. Baltimore RS, Christie CD, Smith GJ: Immunohistopathologic localization of *Pseudomonas aeruginosa* in lungs from patients with cystic fibrosis. Implications for the pathogenesis of progressive lung deterioration. Am Rev Respir Dis 140:1650–1661, 1989.
192. Worlitzsch D, Tarran R, Ulrich M, et al: Effects of reduced mucus oxygen concentration in airway *Pseudomonas* infections of cystic fibrosis patients. J Clin Invest 109:317–325, 2002.
193. Matsui H, Wagner VE, Hill DB, et al: A physical linkage between CF airway surface dehydration and *P. aeruginosa* biofilms. Proc Natl Acad Sci U S A 103:18131–18136, 2006.
194. Yoon SS, Hennigan RF, Hilliard GM, et al: *Pseudomonas aeruginosa* anaerobic respiration in biofilms: relationships to cystic fibrosis pathogenesis. Dev Cell 3:593–603, 2002.
195. Li JD, Dohrman AF, Gallup M, et al: Transcriptional activation of mucin by *Pseudomonas aeruginosa* lipopolysaccharide in the pathogenesis of cystic fibrosis lung disease. Proc Natl Acad Sci U S A 94:967–972, 1997.
196. Dohrman A, Miyata S, Gallup M, et al: Mucin gene (MUC 2 and MUC 5AC) upregulation by gram-positive and gram negative bacteria. Biochim Biophys Acta 1406:251–259, 1998.
197. DiMango E, Zar HJ, Bryan R, Prince A: Diverse *Pseudomonas aeruginosa* gene products stimulate respiratory epithelial cells to produce interleukin-8. J Clin Invest 96:2204–2210, 1995.
198. Plotkowski MC, Zahm JM, Tournier JM, Puchelle E: *Pseudomonas aeruginosa* adhesion to normal and injured respiratory mucosa. Mem Inst Oswaldo Cruz 87(Suppl. V):61–68, 1992.
199. Matthews WJ Jr, Williams M, Oliphint B, et al: Hypogammaglobulinemia in patients with cystic fibrosis. N Engl J Med 302:245–249, 1980.
200. Gugler E, Pallavicini JC, Swedlow H, et al: Immunological studies of submaxillary saliva from patients with cystic fibrosis and from normal children. J Pediatr 73:548–559, 1968.
201. Doring G, Obernesser HJ, Botzenhart K, et al: Proteases of *Pseudomonas aeruginosa* in patients with cystic fibrosis. J Infect Dis 147:744–750, 1983.
202. Baltimore RS, Fick RB Jr, Fino L: Antibody to multiple mucoid strains of *Pseudomonas aeruginosa* in patients with cystic fibrosis, measured by an enzyme-linked immunosorbent assay. Pediatr Res 20:1085–1090, 1986.
203. Sorensen RU, Ruuskanen O, Miller K, Stern RC: B-Lymphocyte function in cystic fibrosis. Eur J Respir Dis 64:524–533, 1983.
204. Sorensen RU, Stern RC, Polmar SH. Cellular immunity to bacteria: impairment of in vitro lymphocyte responses to *Pseudomonas aeruginosa* in cystic fibrosis patients. Infect Immun 18:735–740, 1977.
205. Sorensen RU, Stern RC, Chase P, Polmar SH: Defective cellular immunity to gram-negative bacteria in cystic fibrosis patients. Infect Immun 23:398–402, 1979.
206. Thomassen MJ, Demko CA, Wood RE, et al: Ultrastructure and function of alveolar macrophages from cystic fibrosis patients. Pediatr Res 14:715–721, 1980.
207. Matsui H: Behavior of neutrophils and *Pseudomonas* in thick airway mucus. Pediatr Pulmonol Suppl 25:154–155, 2003.
208. Konstan MW, Berger M: Current understanding of the inflammatory process in cystic fibrosis: Onset and etiology. Pediatr Pulmonol 24:137–142, 1997.
209. Becker MN, Sauer MS, Muhlebach MS, et al: Cytokine secretion by cystic fibrosis airway epithelial cells. Am J Respir Crit Care Med 169:645–653, 2004.
210. Noah TL, Black HR, Cheng P-W, et al: Nasal and bronchoalveolar lavage fluid cytokines in early cystic fibrosis. J Infect Dis 175:638–647, 1997.
211. Bonfield TL, Konstan MW, Burfeind P, et al: Normal bronchial epithelial cells constitutively produce the anti-inflammatory cytokine interleukin-10, which is downregulated in cystic fibrosis. Am J Respir Cell Mol Biol 13:257–261, 1995.
212. Bonfield TL, Panuska JR, Konstan MW, et al: Inflammatory cytokines in cystic fibrosis lungs. Am J Respir Crit Care Med 152:2111–2118, 1995.
213. Birrer P, McElvaney NG, Rudeberg A, et al: Protease-antiprotease imbalance in the lungs of children with cystic fibrosis. Am J Respir Crit Care Med 150:207–213, 1994.
214. Fick RB Jr, Robbins RA, Squier SU, et al: Complement activation in cystic fibrosis respiratory fluids: In vivo and in vitro generation of C5a and chemotactic activity. Pediatr Res 20:1258–1268, 1986.
215. Rowe SM, Jackson PL, Liu G, et al: Potential role of high-mobility group box 1 in cystic fibrosis airway disease. Am J Respir Crit Care Med 178:822–831, 2008.
216. Bruce MC, Poncz L, Klinger JD, et al: Biochemical and pathologic evidence for proteolytic destruction of lung connective tissue in cystic fibrosis. Am Rev Respir Dis 132:529–535, 1985.
217. Davis PB: Clinical pathophysiology and manifestations of lung disease. *In* Yankaskas JR, Knowles MR (eds): Cystic Fibrosis in Adults. Philadelphia: Lippincott-Raven, 1999, pp 45–67.
218. Wang EEL, Prober CG, Manson B, et al: Association of respiratory viral infections with pulmonary deterioration in patients with cystic fibrosis. N Engl J Med 311:1653–1658, 1984.
219. Petersen NT, Hoiby N, Mordhorst CH, et al: Respiratory infections in cystic fibrosis patients caused by virus, *Chlamydia* and *Mycoplasma*—Possible synergism with *Pseudomonas aeruginosa*. Acta Paediatr Scand 70:623–628, 1981.
220. Conway SP, Simmonds EJ, Littlewood JM: Acute severe deterioration in cystic fibrosis associated with influenza A virus infection. Thorax 47:112–114, 1992.
221. Winnie GB, Cowan RG: Association of Epstein-Barr virus infection and pulmonary exacerbations in patients with cystic fibrosis. Pediatr Infect Dis 11:722–726, 1992.
222. Abman SH, Ogle JW, Butler-Simon N, et al: Role of respiratory syncytial virus in early hospitalizations for respiratory distress of young infants with cystic fibrosis. J Pediatr 113:826–830, 1988.
223. Ramsey BW, Gore EJ, Smith AL, et al: The effect of respiratory viral infections on patients with cystic fibrosis. Am J Dis Child 143:662–668, 1989.
224. Campbell PW 3d, Parker RA, Roberts BT, et al: Association of poor clinical status and heavy exposure to tobacco smoke in patients with cystic fibrosis who are homozygous for the F508 deletion. J Pediatr 120:261–264, 1992.
225. Gilligan PH: Microbiology of cystic fibrosis lung disease. *In* Yankaskas JR, Knowles MR (eds): Cystic Fibrosis in Adults. Philadelphia: Lippincott-Raven 1999, pp 93–114.
226. Tummler B, Koopmann U, Grothues D, et al:. Nosocomial acquisition of *Pseudomonas aeruginosa* by cystic fibrosis patients. J Clin Microbiol 29:1265–1267, 1991.
227. Costerton JW, Stewart PS, Greenberg EP. Bacterial biofilms: A common cause of persistent infections. Science 284:1318–1322, 1999.
228. May TB, Shinabarger D, Maharaj R, et al: Alginate synthesis by *Pseudomonas aeruginosa*: A key pathogenic factor in chronic pulmonary infections of cystic fibrosis patients. Clin Microbiol Rev 4:191–206, 1991.
229. Blackwood LL, Pennington JE: Influence of mucoid coating on clearance of *Pseudomonas aeruginosa* from lungs. Infect Immun 32:443–448, 1981.
230. May TB, Chakrabarty AM: *Pseudomonas aeruginosa*: genes and enzymes of alginate synthesis. Trends Microbiol 2:151–157, 1994.
231. Noone PG, Leigh MW, Sannuti A, et al: Primary ciliary dyskinesia: Diagnostic and phenotypic features. Am J Respir Crit Care Med 169:459–467, 2004.
232. LiPuma JJ, Dasen SE, Nielson DW, et al: Person-to-person transmission of *Pseudomonas cepacia* between patients with cystic fibrosis. Lancet 336:1094–1096, 1990.
233. Saiman L, Siegel J: Infection control recommendations for patients with cystic fibrosis: Microbiology, important pathogens, and infection control practices to prevent patient-to-patient transmission. Infect Control Hosp Epidemiol 24:S6–S52, 2003.
234. Isles A, MacLusky I, Corey M, et al: *Pseudomonas cepacia* infection in cystic fibrosis: An emerging problem. J Pediatr 104:206–210, 1984.
235. Fisher MC, LiPuma JJ, Dasen SE, et al: Source of *Pseudomonas cepacia*: Ribotyping of isolates from patients and from the environment. J Pediatr 123:745–747, 1993.

236. Steinbach S, Sun L, Jiang RZ, et al: Transmissibility of *Pseudomonas cepacia* in clinic patients and lung-transplant recipients with cystic fibrosis. N Engl J Med 331:981–987, 1994.
237. Sun L, Jiang RZ, Steinbach S, et al: The emergence of a highly transmissible lineage of *cbl*$^+$ *Pseudomonas (Burkholderia) cepacia* causing CF centre epidemics in North America and Britain. Nat Med 1:661–666, 1995.
238. Vermis K, Coenye T, Mahenthiralingam E, et al: Evaluation of species-specific *recA*-based PCR tests for genomovar level identification within the *Burkholderia cepacia* complex. J Med Microbiol 51:937–940, 2002.
239. Goldstein R, Sun L, Jiang RZ, et al: Structurally variant classes of pilus appendage fibers coexpressed from *Burkholderia (Pseudomonas) cepacia*. J Bacteriol 177:1039–1052, 1995.
240. Lester LA, Egge A, Hubbard VS, di Sant'Agnese PA: Aspiration and lung abscess in cystic fibrosis. Am Rev Respir Dis 127:786–787, 1983.
241. Ramsey BW, Wentz KR, Smith AL, et al: Predictive value of oropharyngeal cultures for identifying lower airway bacteria in cystic fibrosis patients. Am Rev Respir Dis 144:331–337, 1991.
242. Hutcheson PS, Rejent AJ, Slavin RG: Variability in parameters of allergic bronchopulmonary aspergillosis in patients with cystic fibrosis. J Allergy Clin Immunol 88:390–394, 1991.
243. Stevens DA, Moss RB, Kurup VP, et al, and Participants in the Cystic Fibrosis Foundation Consensus Conference: Allergic bronchopulmonary aspergillosis in cystic fibrosis—sState of the art: Cystic Fibrosis Foundation Consensus Conference. Clin Infect Dis 37(Suppl 3):S225–S264, 2003.
244. Kilby JM, Gilligan PH, Yankaskas JR, et al: Nontuberculous mycobacteria in adult patients with cystic fibrosis. Chest 102:70–75, 1992.
245. Aitken ML, Burke W, McDonald G, et al: Nontuberculous mycobacterial disease in adult cystic fibrosis patients. Chest 103:1096–1099, 1993.
246. Olivier KN, Weber DJ, Wallace RJ Jr, et al: Nontuberculous mycobacteria in cystic fibrosis: I. Multicenter prevalence study of a potential pathogen in a susceptible population. Am J Respir Crit Care Med 167:835–840, 2003.
247. Olivier KN, Weber DJ, Lee JH, et al, and Nontuberculous Mycobacteria in Cystic Fibrosis Study Group: Nontuberculous Mycobacteria: II. Nested cohort study of impact on cystic fibrosis lung disease. Am J Respir Crit Care Med 167:835–840, 2003.
248. Olivier KN, Yankaskas JR, Knowles MR. Nontuberculous mycobacterial pulmonary disease in cystic fibrosis. Semin Respir Infect 11:272–284, 1996.
249. Brasfield D, Hicks G, Soong S, Tiller R: The chest roentgenogram in cystic fibrosis: A new scoring system. Pediatrics 63:24–29, 1979.
250. Nathanson I, Conboy K, Murphy S, et al: Ultrafast computerized tomography of the chest in cystic fibrosis: A new scoring system. Pediatr Pulmonol 11:81–86, 1991.
251. Robinson TE, Leung AN, Northway WH, et al: Composite spirometric-computed tomography outcome measure in early cystic fibrosis lung disease. Am J Respir Crit Care Med 168:588–593, 2003.
252. Bhalla M, Turcios N, Aponte V, et al: Cystic fibrosis: scoring system with thin-section CT. Radiology 179:783–788, 1991.
253. Kinsella D, Hamilton A, Goddard P, et al: The role of magnetic resonance imaging in cystic fibrosis. Clin Radiol 44:23–26, 1991.
254. Fiel SB, Friedman AC, Caroline DF, et al: Magnetic resonance imaging in young adults with cystic fibrosis. Chest 91:181–184, 1987.
255. Davis SD, Brody AS, Emond MJ, et al: Endpoints for clinical trials in young children with cystic fibrosis. Proc Am Thorac Soc 4:418–430, 2007.
256. Harrison AN, Regelmann WE, Zirbes JM, Milla CE: Longitudinal assessment of lung function from infancy to childhood in patients with cystic fibrosis. Pediatr Pulmonol 44:330–339, 2009.
257. Levison H, Godfrey S: Pulmonary aspects of cystic fibrosis. *In* Mangos JA, Talamo RC (eds): Cystic Fibrosis: Projections into the Future. New York: Stratton Intercontinental Book Corporation, 1976, pp 3–24.
258. Hanrahan JP, Brown RW, Carey VJ, et al: Passive respiratory mechanics in healthy infants. Effects of growth, gender, and smoking. Am J Respir Crit Care Med 154:670–680, 1996.
259. Feher A, Castile R, Kisling J, et al: Flow limitation in normal infants: A new method for forced expiratory maneuvers from raised lung volumes. J Appl Physiol 80:2019–2025, 1996.
260. Taussig LM, Landau LI, Marks MI: Respiratory system. *In* Taussig LM (ed): Cystic Fibrosis (Vol 1). New York: Thieme-Stratton, 1984, pp 115–174.
261. Siassi B, Moss AJ, Dooley RR: Clinical recognition of cor pulmonale in cystic fibrosis. J Pediatr 78:794–805, 1971.
262. Yankaskas JR, Egan TM, Mauro MA: Major complications. *In* Yankaskas JR, Knowles MR (eds): Cystic Fibrosis in Adults. Philadelphia: Lippincott-Raven, 1999, pp 175–193.
263. Francis PW, Muller NL, Gurwitz D, et al: Hemoglobin desaturation: Its occurrence during sleep in patients with cystic fibrosis. Am J Dis Child 134:734–740, 1980.
264. Boat T: Comparison of lung function and survival patterns between cystic fibrosis and emphysema or chronic bronchitis patients. *In* Sturgess JM (ed): Perspectives in Cystic Fibrosis. Mississanga, Ontario: Imperial Press, 1980, pp 236–245.
265. Hordvik NL, Koenig P, Morris D, et al: A longitudinal study of bronchodilator responsiveness in cystic fibrosis. Am Rev Respir Dis 131:889–893, 1985.
266. Godfrey S, Mearns M: Pulmonary function and response to exercise in cystic fibrosis. Arch Dis Child 46:144–152, 1971.
267. Lands LC, Coates AL: Cardiopulmonary and skeletal muscle function and their effects on exercise limitation. *In* Yankaskas JR, Knowles MR (eds): Cystic Fibrosis in Adults. Philadelphia: Lippincott-Raven, 1999, pp 365–382.
268. Henke KG, Orenstein DM: Oxygen saturation during exercise in cystic fibrosis. Am Rev Respir Dis 129:708–711, 1984.
269. Asher MI, Pardy RL, Coates AL, et al:. The effects of inspiratory muscle training in patients with cystic fibrosis. Am Rev Respir Dis 126:855–859, 1982.
270. Orenstein DM, Franklin BA, Doershuk CF, et al: Exercise conditioning and cardiopulmonary fitness in cystic fibrosis. Chest 80:392–398, 1981.
271. Regnis JA, Alison JA, Henke KG, et al: Changes in end-expiratory lung volume during exercise in cystic fibrosis relate to severity of lung disease. Am Rev Respir Dis 144:507–512, 1991.
272. Nixon PA, Orenstein DM, Kelsey SF, Doershuk CF: The prognostic value of exercise testing in patients with cystic fibrosis. N Engl J Med 327:1785–1788, 1992.
273. O'Rawe A, McIntosh I, Dodge JA, et al: Increased energy expenditure in cystic fibrosis is associated with specific mutations. Clin Sci 82:71–76, 1992.
274. Davies PSW, Bronstein MN: Energy expenditures of infants with cystic fibrosis. Pediatr Pulmonol Suppl 8:175–176, 1992.
275. Gharib R, Allen RP, Joos HA, Bravo LR: Paranasal sinuses in cystic fibrosis: Incidence of Roentgen abnormalities. Am J Dis Child 108:499–502, 1964.
276. Stern RC, Jones K: Nasal and sinus disease. *In* Cystic Fibrosis in Adults. Philadelphia: Lippincott-Raven, 1999, pp 221–231.
277. Cepero R, Smith RJH, Catlin FI, et al: Cystic fibrosis—An otolaryngologic perspective. Otolaryngol Head Neck Surg 97:356–360, 1987.
278. Shwachman H, Kowalski M, Shaw K-T: Cystic fibrosis: A new outlook. Seventy patients above 25 years of age. Medicine (Baltimore) 56:129–149, 1977.
279. Jaffe BF, Strome M, Khaw K-T, Shwachman H: Nasal polypectomy and sinus surgery for cystic fibrosis—A 10-year review. Otolaryngol Clin North Am 10:81–90, 1977.
280. Stern RC, Boat TF, Orenstein DM, et al: Treatment and prognosis of lobar and segmental atelectasis in cystic fibrosis. Am Rev Respir Dis 118:821–826, 1978.
281. Spector ML, Stern RC: Pneumothorax in cystic fibrosis: A 26-year experience. Ann Thorac Surg 47:204–207, 1989.
282. Stern RC, Wood RE, Boat TF, et al: Treatment and prognosis of massive hemoptysis in cystic fibrosis. Am Rev Respir Dis 117:825–828, 1978.
283. Brinson GM, Noone PG, Mauro MA, et al: Bronchial artery embolization for the treatment of hemoptysis in patients with cystic fibrosis. Am J Respir Crit Care Med 157:1951–1958, 1998.

284. Becker JW, Burke W, McDonald G, et al: Prevalence of allergic bronchopulmonary aspergillosis and atopy in adult patients with cystic fibrosis. Chest 109:1536–1540, 1996.
285. Schonheyder H, Jensen T, Hoiby N, et al:. Frequency of *Aspergillus fumigatus* isolates and antibodies to *Aspergillus* antigens in cystic fibrosis. Acta Pathol Microbiol Scand 93:105–112, 1985.
286. Egan TM: Thoracic surgery for patients with cystic fibrosis. *In* Orenstein DM, Stern RC (eds): Treatment of the Hospitalized Patient with Cystic Fibrosis. New York: Marcel Dekker, 1998, pp 231–247.
287. Lemen RJ, Gates AJ, Mathe AA, et al: Relationships among digital clubbing, disease severity, and serum prostaglandings F2alpha and E concentrations in cystic fibrosis patients. Am Rev Respir Dis 117:639–646, 1978.
288. Noone PG, Bresnihan B: Rheumatic disease in cystic fibrosis. *In* Yankaskas JR, Knowles MR (eds): Cystic Fibrosis in Adults. Philadelphia: Lippincott-Raven, 1999, pp 439–447.
289. Nixon PA, Orenstein DM, Curtis SE, Ross EA: Oxygen supplementation during exercise in cystic fibrosis. Am Rev Respir Dis 142:807–811, 1990.
290. Tepper RS, Skatrud JB, Dempsey JA: Ventilation and oxygenation changes during sleep in cystic fibrosis. Chest 84:388–393, 1983.
291. Stern RC, Borkat G, Hirschfeld SS, et al: Heart failure in cystic fibrosis. Treatment and prognosis of cor pulmonale with failure of the right side of the heart. Am J Dis Child 134:267–272, 1980.
292. Garland JS, Chan YM, Kelly KJ, Rice TB: Outcome of infants with cystic fibrosis requiring mechanical ventilation for respiratory failure. Chest 96:136–138, 1989.
293. Rosenstein BJ, Langbaum TS: Incidence of meconium abnormalities in newborn infants with cystic fibrosis. Am J Dis Child 134:72–73, 1980.
294. di Sant'Agnese PA, Davis PB: Cystic fibrosis in adults. 75 cases and a review of 232 cases in the literature. Am J Med 66:121–132, 1979.
295. McCarthy VP, Mischler EH, Hubbard VS, et al: Appendiceal abscess in cystic fibrosis. A diagnostic challenge. Gastroenterology 86:564–568, 1984.
296. Fletcher BD, Abramowsky CR: Contrast enemas in cystic fibrosis: Implications of appendiceal nonfilling. AJR Am J Roentgenol 137:323–326, 1981.
297. Taussig LM, Saldino RM, di Sant'Agnese PA: Radiographic abnormalities of the duodenum and small bowel in cystic fibrosis of the pancreas (mucoviscidosis). Radiology 106:369–376, 1973.
298. Stern RC, Izant RJ Jr, Boat TF, et al: Treatment and prognosis of rectal prolapse in cystic fibrosis. Gastroenterology 82:707–710, 1982.
299. Durie PR, Forstner GG: The exocrine pancreas. *In* Yankaskas JR, Knowles MR (eds): Cystic Fibrosis in Adults. Philadelphia: Lippincott-Raven, 1999, pp 261–287.
300. Kalnins D, Stewart C, Tullis E, Pencharz PB: Nutrition. *In* Yankaskas JR, Knowles MR (eds): Cystic Fibrosis in Adults. Philadelphia: Lippincott-Raven, 1999, pp 289–307.
301. Robbins MK, Ontjes DA: Endocrine and renal disorders in cystic fibrosis. *In* Yankaskas JR, Knowles MR (eds): Cystic Fibrosis in Adults. Philadelphia: Lippincott-Raven, 1999, pp 383–418.
302. Henderson RC, Madsen CD: Bone density in children and adolescents with cystic fibrosis. J Pediatr 128:28–34, 1996.
303. Salamoni F, Roulet M, Gudinchet F, et al:. Bone mineral content in cystic fibrosis patients: Correlation with fat-free mass. Arch Dis Child 74:314–318, 1996.
304. Aris RM, Neuringer IP, Weiner MA, et al: Severe osteoporosis before and after lung transplantation. Chest 109:1176–1183, 1996.
305. Aris RM, Merkel PA, Bachrach LK, et al: Guide to bone health and disease in cystic fibrosis. J Clin Endocrinol Metab 90:1888–1896, 2005.
306. Shwachman H, Lebenthal E, Khaw KT. Recurrent acute pancreatitis in patients with cystic fibrosis with normal pancreatic enzymes. Pediatrics 55:86–95, 1975.
307. Sharer N, Schwarz M, Malone G, et al: Mutations of the cystic fibrosis gene in patients with chronic pancreatitis. N Engl J Med 339:645–652, 1998.
308. Noone PG, Zhou Z, Silverman LM, et al: Cystic fibrosis gene mutations and pancreatitis risk: Relation to epithelial ion transport and trypsin inhibitor gene mutations. Gastroenterology 121:1310–1319, 2001.
309. Sokol RJ, Durie PR: Recommendations for management of liver and biliary tract disease in cystic fibrosis. Cystic Fibrosis Foundation Hepatobiliary Disease Consensus Group. J Pediatr Gastroenterol Nutr 28:S1–S13, 1999.
310. Jebbink MC, Heijerman HG, Masclee AA, Lamers CB: Gallbladder disease in cystic fibrosis. Neth J Med 41:123–126, 1992.
311. Nagel RA, Westaby D, Javaid A, et al: Liver disease and bile duct abnormalities in adults with cystic fibrosis. Lancet 2:1422–1425, 1989.
312. O'Brien S, Keogan M, Casey M, et al: Biliary complications of cystic fibrosis. Gut 33:387–391, 1992.
313. Flume PA, Yankaskas JR: Reproductive issues. *In* Cystic Fibrosis in Adults. Philadelphia: Lippincott-Raven, 1999, pp 449–464.
314. Kopito LE, Kosasky HJ, Shwachman H: Water and electrolytes in human cervical mucus from patients with cystic fibrosis. Fertil Steril 24:512–516, 1973.
315. FitzSimmons SC, Fitzpatrick S, Thompson B, et al: A longitudinal study of the effects of pregnancy on 325 women with cystic fibrosis. Pediatr Pulmonol Suppl 13:99–101, 1996.
316. Goss CH, Rubenfeld GD, Otto K, Aitken ML: The effect of pregnancy on survival in women with cystic fibrosis. Chest 124:1460–1468, 2003.
317. Michel SH, Mueller DH: Impact of lactation on women with cystic fibrosis and their infants: A review of five cases. J Am Diet Assoc 94:159–165, 1994.
318. Rosenstein BJ, Cutting GR: The diagnosis of cystic fibrosis: A consensus statement. Cystic Fibrosis Foundation Consensus Panel. J Pediatr 132:589–595, 1998.
319. Nussbaum E, Boat TF, Wood RE, Doershuk CF: Cystic fibrosis with acute hypoelectrolytemia and metabolic alkalosis in infancy. Am J Dis Child 133:965–966, 1979.
320. Stern RC: The diagnosis of cystic fibrosis. N Engl J Med 336:487–491, 1997.
321. Knowles MR, Paradiso AM, Boucher RC: In vivo nasal potential difference: Techniques and protocols for assessing efficacy of gene transfer in cystic fibrosis. Hum Gene Ther 6:447–457, 1995.
322. Stern RC, Boat TF, Doershuk CF: Obstructive azoospermia as a diagnostic criterion for the cystic fibrosis syndrome. Lancet i:1401–1404, 1982.
323. Stern RC, Boat TF, Abramowsky CR, et al: Intermediate-range sweat chloride concentration and *Pseudomonas* bronchitis: A cystic fibrosis variant with preservation of exocrine pancreatic function. JAMA 239:2676–2680, 1978.
324. Sweat testing: Sample Collection and Quantitative Analysis; Approved Guideline. National Committee for Clinical Laboratory Standards [Document C34-A]. Wayne, PA: NCCLS, 1994.
325. LeGrys VA: Sweat testing for the diagnosis of cystic fibrosis: practical considerations. J Pediatr 129:892–897, 1996.
326. Davis PB, Del Rio S, Muntz JA, Dieckman L: Sweat chloride concentration in adults with pulmonary diseases. Am Rev Respir Dis 128:34–37, 1983.
327. Grosse SD, Boyle CA, Botkin JR, et al: Newborn screening for cystic fibrosis: Evaluation of benefits and risks and recommendations for state newborn screening programs. MMWR Recomm Rep 53:1–36, 2004.
328. Kleven DT, McCudden CR, Willis MS: Cystic fibrosis: Newborn screening in America. MLO Med Lab Obs 40:16–17, 2008.
329. Southern KW, Merelle MM, Dankert-Roelse JE, Nagelkerke AD: Newborn screening for cystic fibrosis. Cochrane Database Syst Rev 1:CD001402, 2009.
330. Rock MJ, Mischler EH, Farrell PM, et al: Newborn screening for cystic fibrosis is complicated by age-related decline in immunoreactive trypsinogen levels. Pediatrics 85:1001–1007, 1990.
331. Kloosterboer M, Hoffman G, Rock M, et al: Clarification of laboratory and clinical variables that influence cystic fibrosis newborn screening with initial analysis of immunoreactive trypsinogen. Pediatrics 123:e338–e346, 2009.
332. Farrell PM, Rosenstein BJ, White TB: Guidelines for diagnosis of cystic fibrosis in newborns through older adults: Cystic Fibrosis Foundation consensus report. J Pediatr 153:S4–S14, 2008.

333. Reardon MC, Hammond KB, Accurso FJ, et al: Nutritional deficits exist before 2 months of age in some infants with cystic fibrosis identified by screening test. J Pediatr 105:271–274, 1984.
334. Ramsey BW, Farrell PM, Pencharz P: Nutritional assessment and management in cystic fibrosis: A consensus report. The Consensus Committee. Am J Clin Nutr 55:108–116, 1992.
335. Farrell PM, Kosorok MR, Laxova A, et al: Nutritional benefits of neonatal screening for cystic fibrosis. Wisconsin Cystic Fibrosis Neonatal Screening Study Group. N Engl J Med 337:963–969, 1997.
336. Waters DL, Wilcken B, Irwig L, et al: Clinical outcomes of newborn screening for cystic fibrosis. Arch Dis Child Fetal Neonatal Ed 80:F1–F7, 1999.
337. Neville LA, Ranganathan SC: Vitamin D in infants with cystic fibrosis diagnosed by newborn screening. J Paediatr Child Health 45:36–41, 2009.
338. Sly PD, Brennan S, Gangell C, et al: Lung disease at diagnosis in infants with cystic fibrosis detected by newborn screenin. Am J Respir Crit Care Med 180:146–152, 2009. Epub 2009; April 16.
339. Farrell PM, Kosorok MR, Rock MJ, et al: Early diagnosis of cystic fibrosis through neonatal screening prevents severe malnutrition and improves long-term growth. Wisconsin Cystic Fibrosis Neonatal Screening Study Group. Pediatrics 107:1–13, 2001.
340. Genetic Testing for Cystic Fibrosis. Apr 14–16. NIH Consensus Statement Online;15:1–20, 1997. www.nlm.nih.gov/archive/20040830/pubs/cbm/cystic_fibrosis.html
341. Mennuti MT: Genetic screening in reproductive health care. Clin Obstet Gynecol 51:3–23, 2008.
342. Kaufman DJ, Katsanis SH, Javitt GH, et al:. Carrier screening for cystic fibrosis in US genetic testing laboratories: A survey of laboratory directors. Clin Genet 74:367–373, 2008.
343. Yankaskas JR, Marshall BC, Sufian B, et al: Cystic fibrosis adult care—Consensus Conference Report. Chest 125:S1–S39, 2004.
344. Boucher RC: Airway surface dehydration in cystic fibrosis: Pathogenesis and therapy. Annu Rev Med 58:157–170, 2007.
345. Desmond KJ, Schwenk WF, Thomas E, et al: Immediate and long-term effects of chest physiotherapy in patients with cystic fibrosis. J Pediatr 103:538–542, 1983.
346. Thomas J, Cook DJ, Brooks D: Chest physical therapy management of patients with cystic fibrosis. A meta-analysis. Am J Respir Crit Care Med 151:846–850, 1995.
347. Mortensen J, Falk M, Groth S, Jensen C: The effects of postural drainage and positive expiratory pressure physiotherapy on tracheobronchial clearance in cystic fibrosis. Chest 100:1350–1357, 1991.
348. Oberwaldner B, Evans JC, Zach MS: Forced expirations agains a variable resistance: A new chest physiotherapy method in cystic fibrosis. Pediatr Pulmonol 2:358–367, 1986.
349. Blomquist M, Freyschuss U, Wiman L-G, Strandvik B: Physical activity and self treatment in cystic fibrosis. Arch Dis Child 61:362–367, 1986.
350. Schneiderman-Walker J, Pollock SL, Corey M, et al: A randomized controlled trial of a 3-year home exercise program in cystic fibrosis. J Pediatr 136:304–310, 2000.
351. Baldwin DR, Hill AL, Peckham DG, Knox AJ: Effect of addition of exercise to chest physiotherapy on sputum expectoration and lung function in adults with cystic fibrosis. Respir Med 88:49–53, 1994.
352. Elkins MR, Robinson M, Rose BR, et al, for the National Hypertonic Saline in Cystic Fibrosis (NHSCF) Study Group. A controlled trial of long-term inhaled hypertonic saline in patients with cystic fibrosis. N Engl J Med 354:229–240, 2006.
353. Fuchs HJ, Borowitz DS, Christiansen DH, et al: Effect of aerosolized recombinant human DNase on exacerbations of respiratory symptoms and on pulmonary function in patients with cystic fibrosis. The Pulmozyme Study Group. N Engl J Med 331:637–642, 1994.
354. Pressler T: Review of recombinant human deoxyribonuclease (rhDNase) in the management of patients with cystic fibrosis. Biologics 2:611–617, 2008.
355. Wood RE: Determinants of survival in cystic fibrosis. Cystic Fibrosis Club Abstracts 26:69, 1985.
356. Pedersen SS, Jensen T, Hoiby N, et al: Management of *Pseudomonas aeruginosa* lung infection in Danish cystic fibrosis patients. Acta Paediatr Scand 76:955–961, 1987.
357. Smith A, Cohen M, Ramsey B: Pharmacotherapy. *In* Yankaskas JR, Knowles MR (eds): Cystic Fibrosis in Adults. Philadelphia: Lippincott-Raven, 1999, pp 345–364.
358. Mendelman PM, Smith AL, Levy J, et al: Aminoglycoside penetration, inactivation, and efficacy in cystic fibrosis sputum. Am Rev Respir Dis 132:761–765, 1985.
359. LeBel M, Bergeron MG, Vallee F, et al: Pharmacokinetics and pharmacodynamics of ciprofloxacin in cystic fibrosis patients. Antimicrob Agents Chemother 30:260–266, 1986.
360. Hodson ME, Penketh ARL, Batten JC: Aerosol carbenicillin and gentamicin treatment of *Pseudomonas aeruginosa* infection in patients with cystic fibrosis. Lancet ii:1137–1139, 1981.
361. Wall MA, Terry AB, Eisenberg J, et al: Inhaled antibiotics in cystic fibrosis. Lancet i:1325, 1983.
362. Ramsey BW, Pepe MS, Quan JM, et al: Intermittent administration of inhaled tobramycin in patients with cystic fibrosis. The Cystic Fibrosis Inhaled Tobramycin Study Group. N Engl J Med 340:23–30, 1999.
363. Equi A, Balfour-Lynn IM, Bush A, Rosenthal M: Long-term azithromycin in children with cystic fibrosis: A randomised, placebo-controlled crossover trial. Lancet 360:978–984, 2002.
364. Wolter J, Seeney S, Bell S, et al: Effect of long-term treatment with azithromycin on disease parameters in cystic fibrosis: A randomised trial. Thorax 57:212–216, 2002.
365. Saiman L, Marshall BC, Mayer-Hamblett N, et al: Azithromycin in patients with cystic fibrosis chronically infected with *Pseudomonas aeruginosa*: A randomized controlled trial. JAMA 290:1749–1756, 2003.
366. Sturgess J, Reid L: The effect of isoprenaline and pilocarpine on (a) bronchial mucus-secreting tissue and (b) pancreas, salivary glands, heart, thymus, liver and spleen. Br J Exp Pathol 54:388–403, 1973.
367. Shapiro GG, Bamman J, Kanerek P, Bierman CW. The paradoxical effect of adrenergic and methylxanthine drugs in cystic fibrosis. Pediatrics 58:740–743, 1976.
368. Avital A, Sanchez I, Chernick V: Efficacy of salbutamol and ipratropium bromide in decreasing bronchial hyperreactivity in children with cystic fibrosis. Pediatr Pulmonol 13:34–37, 1992.
369. Sanchez I, Holbrow J, Chernick V: Acute bronchodilator response to a combination of beta-adrenergic and anticholinergic agents in patients with cystic fibrosis. J Pediatr 120:486–488, 1992.
370. Weintraub SJ, Eschenbacher WL: The inhaled bronchodilators ipratropium bromide and metaproterenol in adults with CF. Chest 95:861–864, 1989.
371. Mulherin D, FitzGerald MX: Meconium ileus equivalent in association with nebulized ipratropium bromide in cystic fibrosis. Lancet i:552, 1990.
372. Sivan Y, Arce P, Eigen H, et al: A double-blind, randomized study of sodium cromoglycate versus placebo in patients with cystic fibrosis and bronchial hyperreactivity. J Allergy Clin Immunol 85:649–654, 1990.
373. Auerbach HS, Williams M, Kirkpatrick JA, Colten HR: Alternate-day prednisone reduces morbidity and improves pulmonary function in cystic fibrosis. Lancet ii:686–688, 1985.
373a. Balfour-Lynn IM, Welch K: Inhaled corticosteroids for cystic fibrosis. Cochrane Database Syst Rev 21(1):CD001915, 2009.
374. Konstan MW, Byard PJ, Hoppel CL, Davis PB: Effect of high-dose ibuprofen in patients with cystic fibrosis. N Engl J Med 332:848–854, 1995.
375. Dolan TF Jr, Gibson LE: Complications of iodide therapy in patients with cystic fibrosis. J Pediatr 79:684–687, 1971.
376. Sims DE, Westfall JA, Kiorpes AL, Horne MM: Preservation of tracheal mucus by nonaqueous fixative. Biotech Histochem 66:173–180, 1991.
377. Van Goor F, Straley KS, Cao D, et al: Rescue of DeltaF508-CFTR trafficking and gating in human cystic fibrosis airway primary cultures by small molecules. Am J Physiol 290:L1117–L1130, 2006.
378. Johnson LG, Knowles MR: New therapeutic strategies for cystic fibrosis lung disease. *In* Yankaskas JR, Knowles MR (eds): Cystic

Fibrosis in Adults. Philadelphia: Lippincott-Raven, 1999, pp 233–258.
379. Grubb BR, Pickles RJ, Ye H, et al: Inefficient gene transfer by adenovirus vector to cystic fibrosis airway epithelia of mice and humans. Nature 371:802–806, 1994.
380. Knowles MR, Hohneker KW, Zhou Z, et al:. A controlled study of adenoviral vector–mediated gene transfer in the nasal epithelium of patients with cystic fibrosis. N Engl J Med 333:823–831, 1995.
381. Smyth RL, van Velzen D, Smyth AR, et al:. Strictures of ascending colon in cystic fibrosis and high strength pancreatic enzymes. Lancet 343:85–86, 1994.
382. Borowitz DS, Grand RJ, Durie PR: Use of pancreatic enzyme supplements for patients with cystic fibrosis in the context of fibrosing colonopathy. Consensus Committee. J Pediatr 127:681–684, 1995.
383. Smyth RL, Ashby D, O'Hea U, et al: Fibrosing colonopathy in cystic fibrosis: Results of a case-control study. Lancet 346:1247–1251, 1995.
384. FitzSimmons SC, Burkhart GA, Borowitz D, et al: High-dose pancreatic-enzyme supplements and fibrosing colonopathy in children with cystic fibrosis. N Engl J Med 336:1283–1289, 1997.
385. Bertrand JM, Morin CL, Lasalle R, et al: Short-term clinical, nutritional, and functional effects of continuous elemental enteral alimentation in children with cystic fibrosis. J Pediatr 104:41–47, 1984.
386. Gaskin K, Gurevit D, Durie P, et al: Improved respiratory prognosis in patients with cystic fibrosis with normal fat absorption. J Pediatr 100:857–862, 1982.
387. Orenstein DM: Cystic Fibrosis. A Guide for Patient and Family. Philadelphia: Lippincott Raven, 2004.
388. Redding GJ, Restuccia R, Cotton EK, Brooks JG: Serial changes in pulmonary functions in children hospitalized with cystic fibrosis. Am Rev Respir Dis 126:31–36, 1982.
389. Regelmann WE, Elliott GR, Warwick WJ, Clawson CC: Reduction of sputum *Pseudomonas aeruginosa* density by antibiotics improves lung function in cystic fibrosis more than do bronchodilators and chest physiotherapy alone. Am Rev Respir Dis 141:914–921, 1990.
390. Donati MA, Guenette G, Auerbach H: Prospective controlled study of home and hospital therapy of cystic fibrosis pulmonary disease. J Pediatr 111:28–33, 1987.
391. Pond MN, Newport M, Joanes D, Conway SP: Home versus hopsital intravenous antibiotic therapy in the treatment of young adults with cystic fibrosis. Eur Respir J 7:1640–1644, 1994.
392. Winnie GB, Cowan RG, Wade NA: Intravenous immune globulin treatment of pulmonary exacerbations in cystic fibrosis. J Pediatr 114:309–314, 1989.
393. Braunstein MS, Fleet WF: Failure of bronchopulmonary lavage in cystic fibrosis. Chest 66:96–99, 1974.
394. Spier S, Rivlin J, Hughes D, Levison H: The effect of oxygen on sleep, blood gases, and ventilation in cystic fibrosis. Am Rev Respir Dis 129:712–718, 1984.
395. Coates AL: Oxygen therapy, exercise, and cystic fibrosis. Chest 101:2–4, 1992.
396. Zinman R, Corey M, Coates AL, et al:. Nocturnal home oxygen in the treatment of hypoxemic cystic fibrosis patients. J Pediatr 114:368–377, 1989.
397. Fraser KL, Tullis DE, Sasson Z, et al: Pulmonary hypertension and cardiac function in adult cystic fibrosis: Role of hypoxemia. Chest 115:1321–1328, 1999.
398. Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: A clinical trial. Nocturnal Oxygen Therapy Trial Group. Ann Intern Med 93:391–398, 1980.
399. Schidlow DV, Taussig LM, Knowles MR: Cystic Fibrosis Foundation Consensus Conference Report on pulmonary complications of cystic fibrosis. Pediatr Pulmonol 15:187–198, 1993.
400. Davis PB, di Sant'Agnese PA: Assisted ventilation for patients with cystic fibrosis. JAMA 239:1851–1854, 1978.
401. Hodson ME, Madden BP, Steven MH, et al: Non-invasive mechanical ventilation for cystic fibrosis patients—A potential bridge to transplantation. Eur Respir J 4:524–527, 1991.
402. Flume PA, Egan TM, Westerman JH, et al: Lung transplantation for mechanically ventilated patients. J Heart Lung Transplant 13:15–21, 1994.
403. Sood N, Paradowski LJ, Yankaskas JR: Outcomes of intensive care unit care in adults with cystic fibrosis. Am J Respir Crit Care Med 163:335–338, 2001.
404. Knutsen AP, Slavin RG: Allergic bronchopulmonary mycosis complicating cystic fibrosis. Semin Respir Infect 7:179–192, 1992.
405. Imbeault B, Cormier Y: Usefulness of inhaled high-dose corticosteroids in allergic bronchopulmonary aspergillosis. Chest 103:1614–1617, 1993.
406. Mannes GP, van der Heide S, van Aalderen WM, Gerritsen J: Itraconazole and allergic bronchopulmonary aspergillosis in twin brothers with cystic fibrosis. Lancet 341:492, 1993.
407. Fellows KE, Khaw KT, Schuster S, Shwachman H: Bronchial artery embolization in cystic fibrosis: Technique and long-term results. J Pediatr 95:959–963, 1979.
408. Hofmann AF, Popper H: Ursodeoxycholic acid for primary biliary cirrhosis. Lancet ii:398–399, 1987.
409. Galabert C, Montet JC, Lengrand D, et al: Effects of ursodeoxycholic acid on liver function in patients with cystic fibrosis and chronic cholestasis. J Pediatr 121:138–141, 1992.
410. Colombo C, Battezzati PM, Podda M, et al: Ursodeoxycholic acid for liver disease associated with cystic fibrosis: A double-blind multicenter trial. The Italian Group for the Study of Ursodeoxycholic Acid in Cystic Fibrosis. Hepatology 23:1484–1490, 1996.
411. Stern RC, Stevens DP, Boat TF, et al: Symptomatic hepatic disease in cystic fibrosis: Incidence, course, and outcome of portal systemic shunting. Gastroenterology 70:645–649, 1976.
412. Rossle M, Haag K, Ochs A, et al: The transjugular intrahepatic portosystemic stent-shunt procedure for variceal bleeding. N Engl J Med 330:165–171, 1994.
413. Berger KJ, Schreiber RA, Tchervenkov J, et al: Decompression of portal hypertension in a child with cystic fibrosis after transjugular intrahepatic portosystemic shunt placement. J Pediatr Gastroenterol Nutr 19:322–325, 1994.
414. Mieles LA, Orenstein D, Teperman L, et al: Liver transplantation in cystic fibrosis. Lancet i:1073, 1989.
415. Noble-Jamieson G, Barnes N, Jamieson N, et al: Liver transplantation for hepatic cirrhosis in cystic fibrosis. J R Soc MedSuppl 27:31–37, 1996.
416. Rosenbloom AL: Diabetes mellitus in cystic fibrosis. Pediatr Pulmonol Suppl 6:209–210, 1991.
417. Rodman HM, Doershuk CF, Roland JM: The interaction of 2 diseases: Diabetes mellitus and cystic fibrosis. Medicine (Baltimore) 65:389–397, 1986.
418. Finkelstein SM, Wielinski CL, Elliot GR, et al: Diabetes mellitus associated with cystic fibrosis. J Pediatr 112:373–377, 1988.
419. Lass JH, Spurney RV, Dutt RM, et al: A morphologic and fluorophotometric analysis of the corneal endothelium in type I diabetes mellitus and cystic fibrosis. Am J Ophthalmol 100:783–788, 1985.
420. Allen JL: Progressive nephropathy in a patient with cystic fibrosis and diabetes. N Engl J Med 315:764, 1986.
421. O'Riordan SM, Robinson PD, Donaghue KC, Moran A: Management of cystic fibrosis-related diabetes. Pediatr Diabetes 9:338–344, 2008.
422. Duplechain JK, White JA, Miller RH: Pediatric sinusitis. The role of endoscopic sinus surgery in cystic fibrosis and other forms of sinonasal disease. Arch Otolaryngol Head Neck Surg 117:422–426, 1991.
423. Cuyler JP: Follow-up of endoscopic sinus surgery on children with cystic fibrosis. Arch Otolaryngol Head Neck Surg 118:505–506, 1992.
424. Stern RC, Rothstein FC, Doershuk CF: Treatment and prognosis of symptomatic gallbladder disease in patients with cystic fibrosis. J Pediatr Gastroenterol Nutr 5:35–40, 1986.
425. Smith MB, Hardin WD Jr, Dressel DA, et al: Predicting outcome following pulmonary resection in cystic fibrosis patients. J Pediatr Surg 26:655–659, 1991.
426. Yankaskas JR, Mallory GB Jr: Lung transplantation in cystic fibrosis: Consensus Conference Statement. Chest 113:217–226, 1998.
427. Egan TM, Murray S, Bustami RT, et al: Development of the new lung allocation system in the United States. Am J Transplant 6:1212–1227, 2006.

428. Barr ML, Schenkel FA, Cohen RG, et al: Recipient and donor outcomes in living related and unrelated lobar transplantation. Transplant Proc 30:2261–2263, 1998.
429. Stern RC, Boat TF, Doershuk CF, et al: Cystic fibrosis diagnosed after age 13. Twenty-five teenage and adult patients including three asymptomatic men. Ann Intern Med 87:188–191, 1977.
430. Cystic Fibrosis Foundation Patient Registry. 2008 Annual Data Report. Bethesda, MD, 2009.
431. Shwachman H, Kulczycki LL: Long-term study of one hundred five patients with cystic fibrosis. Study made over a five- to fourteen-year period. J Dis Child 96:6–15, 1958.
432. Cystic Fibrosis Foundation Patient Registry. 2006 Annual Data Report to the Center Directors. Bethesda, MD, 2007.
433. Taussig LM, Kattwinkel J, Friedewald WT, di Sant'Agnese PA: A new prognostic score and clinical evaluation system for cystic fibrosis. J Pediatr 82:380–390, 1973.
434. Fink RJ, Doershuk CF, Tucker AS, et al: Pulmonary function and morbidity in 40 adult patients with cystic fibrosis. Chest 74:643–647, 1978.
435. Corey M, Levison H, Crozier D. Five- to seven-year course of pulmonary function in cystic fibrosis. Am Rev Respir Dis 114:1085–1092, 1976.
436. Katz JN, Horwitz RI, Dolan TF, Shapiro ED: Clinical features as predictors of functional status in children with cystic fibrosis. J Pediatr 108:352–358, 1986.
437. Hamosh A, Corey M: Correlation between genotype and phenotype in patients with cystic fibrosis. The Cystic Fibrosis Genotype-Phenotype Consortium. N Engl J Med 329:1308–1313, 1993.
438. Knoke JD, Stern RC, Doershuk CF, et al: Cystic fibrosis: The prognosis for five-year survival. Pediatr Res 12:676–679, 1978.
439. Koch C, Rainisio M, Madessani U, et al: Presence of cystic fibrosis-related diabetes mellitus is tightly linked to poor lung function in patients with cystic fibrosis: Data from the European Epidemiologic Registry of Cystic Fibrosis. Pediatr Pulmonol 32:343–350, 2001.
440. Hill DJ, Martin AJ, Davidson GP, Smith GS: Survival of cystic fibrosis patients in South Australia. Evidence that cystic fibrosis centre care leads to better survival. Med J Aust 143:230–232, 1985.
441. Quinton HB, O'Connor GT: Current issues in quality improvement in cystic fibrosis. Clin Chest Med 28:459–472, 2007.
442. Denning CR, Gluckson MM: Psychosocial aspects of cystic fibrosis. *In* Taussig LM (ed): Cystic Fibrosis. New York: Thieme-Stratton, 1984, pp 461–492.
443. Lewiston NJ: Psychosocial impact of cystic fibrosis. Semin Respir Med 6:321–332, 1985.
444. Yankaskas JR, Fernald GW: Adult social issues. *In* Cystic Fibrosis in Adults. Philadelphia: Lippincott-Raven, 1999, pp 465–476.
445. Levine SB, Stern RC: Sexual function in cystic fibrosis. Relationship to overall health status and pulmonary disease severity in 30 married patients. Chest 81:422–428, 1982.
446. Hull J, Skinner W, Robertson C, Phelan P: Elemental content of airway surface liquid from infants with cystic fibrosis. Am J Respir Crit Care Med 157:10–14, 1998.

CHAPTER 42

BRONCHIECTASIS

Michael D. Iseman, MD • Edward D. Chan, MD

INTRODUCTION

CLASSIFICATION

EPIDEMIOLOGY

PATHOGENESIS

"VICIOUS CIRCLE" AND MICROBIOLOGY

BIOFILMS

ASSOCIATED DISORDERS AND PREDISPOSITIONS
Lung Injury Due to Acute Infection
Cystic Fibrosis
Disorders of Immunity
Alpha$_1$-Antitrypsin Anomalies
Ciliated Epithelium
Bronchial Cartilage
Connective Tissue
Congenital and Developmental Anomalies
Idiopathic Inflammatory Disorders
Aspiration/Inhalation Accidents
Postobstructive Disorders
Allergic Bronchopulmonary Aspergillosis
Miscellaneous

DIAGNOSIS

MANAGEMENT
Airway Hygiene and Hyperosmotic Agents
Antimicrobial Therapy
Anti-inflammatory Therapy
Surgery
Miscellaneous

INTRODUCTION

The condition of bronchiectasis (BXSIS) is defined by dilation, or ectasia, of the airways or bronchos. The primary clinical manifestations of BXSIS are recurrent, chronic, or refractory infections. Other significant sequelae include hemoptysis, chronic airflow obstruction, and progressive impairment of breathing. In the preantibiotic era, secondary amyloidosis and embolic brain abscesses were reported as consequences of chronic suppuration in the lungs; such complications are extremely rare now in industrialized nations.

There are many and varied pathways that lead to the development of BXSIS (Table 42-1). Broadly, BXSIS may develop due to an incidental event or episode that does not reflect the patient's intrinsic host defenses. Examples might include a necrotizing pneumonia following aspiration or chronic infection distal to an obstructing bronchial adenoma. Often, however, BXSIS evolves due to conditions that are inherent to the patient's basic genetic constitution. The most common and dramatic example of this is cystic fibrosis (CF). The distinction between these two models is an important element of prognosis and management.

A central issue in understanding the pathogenesis of BXSIS is whether infection is truly the proximate cause of BXSIS or patients develop infections due to an underlying predisposing condition. For example, it has been a commonly held adage that many cases of BXSIS in adults are due to childhood bouts of pertussis or measles.[1] Although this is undoubtedly true in some instances, one might be skeptical of this simple construct, asking why formerly common childhood illnesses resulted in BXSIS in only a small proportion of the patients. The question that should be addressed more thoroughly is whether the individuals were particularly vulnerable to complications; for example, did the pertussis or measles result in excessive damage due to innate susceptibility of the hosts?

CLASSIFICATION

Although there is considerable overlap and coexistence among the various forms of BXSIS, the radiographic patterns and distribution may provide clues to diagnosis, management, and prognosis.[2] Thus, characterizing the morphologic features and distribution of BXSIS is a useful

TABLE 42-1. Conditions Associated with Bronchiectasis

POSTINFECTIOUS CONDITIONS
Childhood lower respiratory tract infections
Granulomatous infections
Necrotizing pneumonias in adults
Other respiratory infections

PRIMARY IMMUNE DISORDERS
Humoral defects
Cellular and/or mixed disorders
Neutrophil dysfunction
Other

CYSTIC FIBROSIS
Classic CF
Variants of CF
Young's syndrome

ALPHA$_1$-ANTITRYPSIN SYSTEM
Deficiencies
Anomalies

HERITABLE STRUCTURAL ABNORMALITIES
Ciliated epithelium
Cartilage
Connective tissue
Sequestration, agenesis, hypoplasia
Dwarfism

IDIOPATHIC INFLAMMATORY DISORDERS
Sarcoidosis
Rheumatoid arthritis
Ankylosing spondylitis
Systemic lupus erythematosus
Sjögren's syndrome
Inflammatory bowel disease
Relapsing polychondritis

INHALATION AND OBSTRUCTION
Gastroesophageal reflux/aspiration pneumonia
Toxic inhalation/thermal injury
Postobstruction accident
Foreign body
Tumors, benign and malignant
Extrinsic airway compression
Allergic bronchopulmonary aspergillosis/mycosis

MISCELLANEOUS
HIV infection/AIDS
Yellow-nail syndrome
Radiation injury

AIDS, acquired immunodeficiency syndrome; CF, cystic fibrosis; HIV, human immunodeficiency virus.

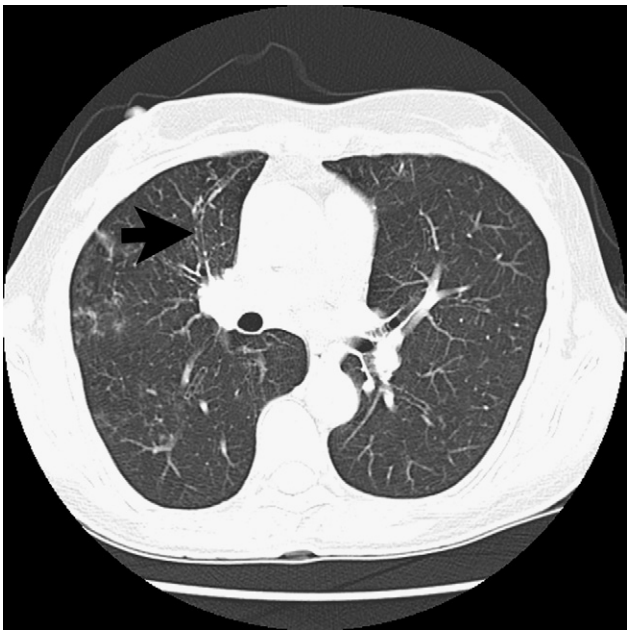

FIGURE 42-1 ■ Cylindrical bronchiectasis (BXSIS). In the anterior segment of the right upper lobe is an extended nontapering airway with moderately thickened and generally regular walls (*arrow*). The patient is a 50-year-old white woman with a slender body habitus and subtle scoliosis but no other identified risk factors for BXSIS. In addition, she had severe varicoid and "honeycomb" BXSIS involving her right middle lobe (see Figs. 42-2 and 42-4).

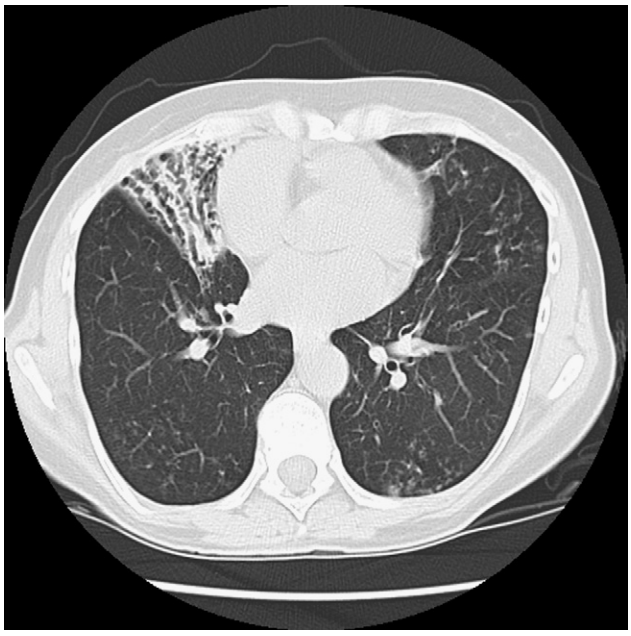

FIGURE 42-2 ■ Varicoid BXSIS. The right middle lobe of this 50-year-old woman is involved with severe atelectasis and dense, side-by-side varicoid BXSIS involving the conducting airways. Distal to this pattern are dramatic honeycomb changes of the terminal air spaces (see Fig. 42-4).

discipline. In this era, BXSIS is primarily identified and described by computed tomography (CT; see later).

Cylindrical BXSIS is described as failure of the involved airways to taper progressively in their distal course. Usually, in this condition, the bronchial walls are smooth or regular (Fig. 42-1). Varicoid BXSIS is an allusion to varicose veins and is marked by irregular dilation, narrowing, and outpouching of the airways (Fig. 42-2). Saccular BXSIS includes focal or cystic distortion of the distal airways; it may be isolated (Fig. 42-3) or may form confluent "honeycomb" patterns (Fig. 42-4).

A traditional clinical distinction within BXSIS has been "wet" versus "dry." Historically, it was observed that some patients with BXSIS had continuous or frequent

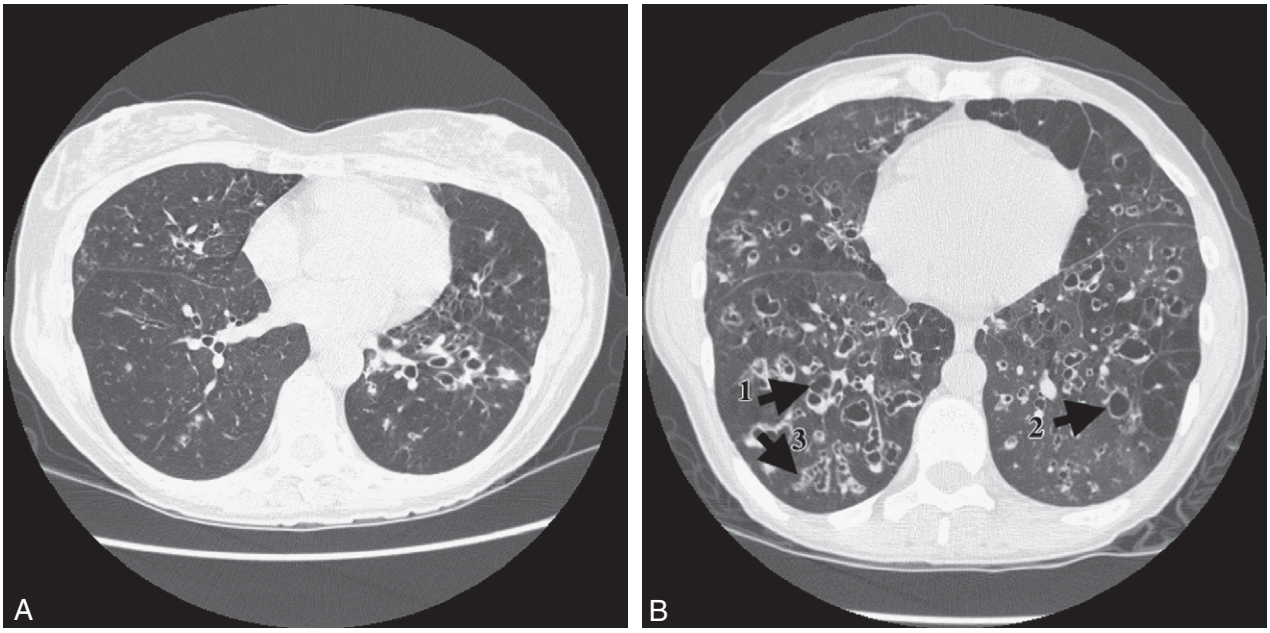

FIGURE 42-3 ■ **A,** Saccular BXSIS. In the left lower lobe of this 52-year-old white woman, there is a clustering of thin-walled dilated airways. Medial to this cluster is a classic "signet ring" consisting of a dilated, thin-walled airway with an accompanying smaller pulmonary artery. **B,** Saccular, cylindrical, and varicoid BXSIS. This 55-year-old woman is alpha$_1$-antitrypsin–deficient with a Pi ZZ phenotype. She has moderately severe chronic obstructive pulmonary disease (COPD) but also suffers advanced BXSIS. In addition to cystic rarefaction of her lung parenchyma, she has features of saccular (*arrow 1*), cylindrical (*arrow 2*), and varicoid (*arrow 3*) BXSIS.

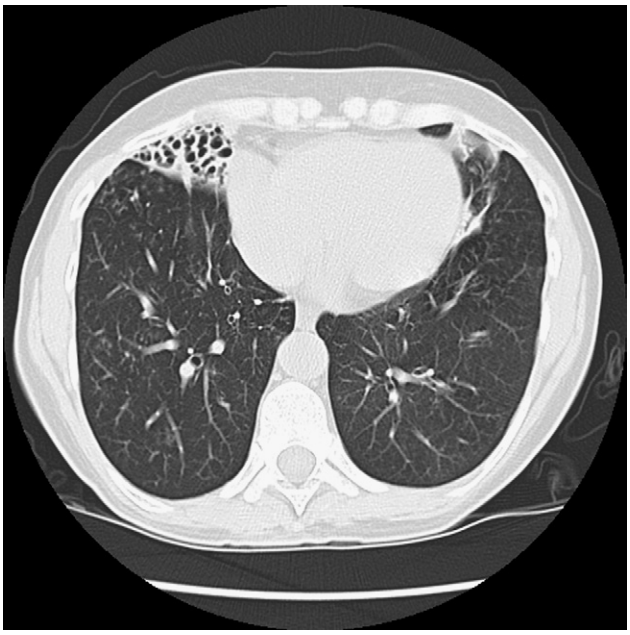

FIGURE 42-4 ■ Honeycomb BXSIS. The inferomedial aspect of the right middle lobe is involved with a coarse cystic process that resembles a honeycomb. Similar changes are often seen in the inferior segment of the lingula. In many cases, such findings are associated with nontuberculous mycobacterial infection; however, in this case, the patient was infected only with gram-negative bacilli including *Pseudomonas aeruginosa* and *Alcaligenes xylosoxidans*.

productive cough that typically yielded copious, often purulent secretions—hence "wet." Others who carried the diagnosis of BXSIS rarely experienced cough, and if they did so, rarely was their cough productive—hence "dry." Independent of etiology, the most frequent patterns associated with wet or dry BXSIS are anatomic localizations. BXSIS involving dependent zones (lower lobes, the right middle lobe, or the lingular segment of the left upper lobe) tends to entail frequent or chronic infections and to be "wet" in nature. By contrast, chronic BXSIS isolated to the upper lobes is less commonly involved with infection and to be "dry" in terms of sputum production. Presumably, this is related in large measure to gravity-driven drainage of the upper zones in contrast to pooling of secretions in the dependent regions.

EPIDEMIOLOGY

There are no systematic data on the incidence or prevalence of BXSIS. Historically, it has been thought that as antibiotics and vaccines were introduced in the 20th century, there has been a declining rate of BXSIS.[3,4] The presumed mechanism was that these modalities lessened the frequency, severity, and duration of lower respiratory tract infections that might result in BXSIS. In this regard, it is suggested that BXSIS remains relatively more common in regions where prompt and effective medical care is not available.[5] However, it should be stressed that there are no careful quantitative studies documenting these trends.

In the United States, there appear to be increasing numbers of BXSIS cases associated with environmental or nontuberculous mycobacteria (NTM).[6,7] Based on serial observations in a cohort now numbering approximately 2000, our group believes that in the majority of cases, the mycobacterial infections both initiate and "drive" the evolution of BXSIS. Of interest, this disorder seems disproportionately to involve women, predominantly slender white women.[8,9] It is not possible to determine whether this is an accurate picture or an artifact of increased awareness and improved diagnostic techniques.

PATHOGENESIS

Various mechanisms operate to produce permanent, pathologic dilation and damage of the airways. In simplest terms, they may be thought of in terms of traction, pulsion, and weakened tensile strength of the airways. In most cases, the pathogenesis becomes inextricably linked with and propelled by the destructive effects of chronic infection.

In normal lungs, airways are held patent by a combination of negative intrapleural pressure (which maintains the lungs in an inflated state) and the cartilaginous rings of the trachea and the large and medium airways. The distending forces of the negative intrapleural pressure are transmitted to the airways by a diffuse system of interstitial tethering. As the lung undergoes fibrotic changes consequent to disorders such as sarcoidosis, interstitial lung disorders, or infections such as tuberculosis, local retractile forces result in fixed dilation of the airways, or "traction" BXSIS.

The prototypic "pulsion" BXSIS occurs with allergic bronchopulmonary aspergillosis (ABPA). In ABPA, there are intense, immunologically mediated reactions to inhaled *Aspergillus* that has lodged in the airways. The proliferating fungi form large mucoid conglomerates that fill and distend the central airways. It is probable that this airway dilation is potentiated by focal damage mediated by inflammatory products that weaken the bronchi.

Weakness of the airways contributing to the development of BXSIS may take many forms. Classic postinfectious BXSIS presumably is mediated in part by chronic damage to the walls of the airways, resulting in secondary loss of structural integrity.[10,11] This is coupled with scarring and loss of volume of the local lung units, leading to regional increases in retractile forces. Examples of primary weakness of the airways contributing to BXSIS includes Mounier-Kuhn syndrome (congenital tracheobronchiomegaly), Williams-Campbell syndrome (absence of cartilaginous rings in the segmental and subsegmental generations of bronchi), Marfan syndrome, or relapsing polychondritis. A case is made later that the apparent propensity of slender women for BXSIS may be based in part on mechanisms analogous to Marfan syndrome.

One particular component of the posited role of "weakened airways" in the pathogenesis of BXSIS that has not received adequate attention is the potential impact of airway collapsibility on the effectiveness of the cough mechanism. Coughing is an essential, primary element of lung defense. An effective cough sends columns of air rushing upward through the bronchial tree at peak speeds measured in the range of 600 mph.[12] To generate these high flow rates, the cartilaginous rings must have the structural integrity to remain patent while the posterior membranous element invaginates into the lumen of the airway to lessen the cross-sectional diameter of the airway and accelerate airflow. While performing bronchoscopy on patients with BXSIS, it is common to observe extraordinary collapsibility of the airways, virtually obstructing the bronchi. It seems likely that such amplified airway compressibility impedes the air-driven propulsion of secretions out of the bronchial tree and helps propagate the chronic or recurring infections that mark most cases of BXSIS.

"VICIOUS CYCLE" AND MICROBIOLOGY

The other major element in the pathogenesis of BXSIS is the destructive effect of chronic airway infections, the vicious cycle theory as described by Cole.[13] Briefly, it is reasoned that once airways are "damaged," they become vulnerable to chronic colonization, which merges into an inflammatory condition; this results in further injury and lessened capacity to resist infection. Analysis of cellular and noncellular constituents in the bronchiectatic airways typically demonstrates intense infiltration by neutrophils as well as mononuclear cells and lymphocytes.[14]

Although there is a burgeoning literature on mechanisms of inflammation and airway damage, the relevance of these findings to the diagnosis and clinical management is not currently apparent and is not addressed in detail in this chapter.

It is apparent that simple colonization and infection of the airways are not sufficient to produce true BXSIS. Sputum from patients with smoking-related chronic bronchitis typically yields organisms such as *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis*, a microbial spectrum similar to that seen with BXSIS.[15] In addition, there is heavy cellular traffic and the presence of a variety of inflammatory mediators. However, significant BXSIS does not appear commonly among patients with simple chronic bronchitis. Hence, it is probable that systemic conditions or focal disturbances as noted later are required for the development of classic BXSIS. Notably, however, the appearance in respiratory secretions of *Pseudomonas aeruginosa* on a chronic or recurring basis does pose the risk of deleterious effects on ciliary function and other host defenses.[16] Pseudomonal infections may be of particular importance due to their role in the formation of biofilms (see later). Two reports note worsened lung function[16] and quality of life[17] among BXSIS patients who become infected with *P. aeruginosa*. In a longitudinal study of the microbiology of 89 patients with BXSIS over a 5-year period, 47% were colonized with *H. influenzae*, 12% with *P. aerugi-*

nosa, and 21% had no identifiable pathogen. After 5 years, there was a slight increase in the number of those colonized with *P. aeruginosa*. As expected, those with the mildest disease had no pathogen whereas those with the worst disease were colonized with *P. aeruginosa*.[18]

As previously noted, NTM can colonize bronchiectatic airways as well as cause BXSIS. Based on two recent studies from the United Kingdom, the prevalence of NTM isolated from a heterogeneous group of bronchiectatic patients was approximately 2% to 10%.[19] Furthermore, bronchiectatic patients with NTM infections also have a greater likelihood of having concomitant *Aspergillus* lung disease.[20]

BIOFILMS

Costerton in 1984[21] hypothesized that *P. aeruginosa* in human infections "attaches to solid or tissue surfaces and grows predominantly in biofilms that release mobile swarmer cells into the surrounding fluid phase. These natural and pathogenic biofilms are covered by an exopolysaccharide matrix (glycocalyx) that serves as a barrier against hostile environmental factors such as host defense mechanisms and antibiotics."[21] Since this discovery, there has been clear evidence for the clinical significance of biofilms in promoting chronic infection in the airways of CF patients[22] as well as a variety of other infections.[23] *P. aeruginosa*, among its various attributes, enjoys cilia-driven motility, which appears critical in the aggregation phase of early biofilm formation.[24] Once biofilm formation has commenced, features of growth and gene activation that release virulence factors are influenced by "quorum sensing." Owing to a combination of physicochemical factors that deny access to the microbes by host defense cells and/or antibiotics, infection may persist despite aggressive treatment. In vitro testing indicates that bacteria embedded in biofilms can survive despite exposure to concentrations of antimicrobials that exceed the minimal inhibitory concentration in a suspension culture by 1000-fold.[25] We may anticipate that future understanding and optimal management of patients with chronic BXSIS will entail interventions to modify or interfere with biofilms.[24]

ASSOCIATED DISORDERS AND PREDISPOSITIONS

Lung Injury Due to Acute Infection

In the traditional model of lung injury due to acute infection, patients are deemed to have normal airways and lungs until they experience a specific lower respiratory tract infection that results in irreversible damage to their airways. In the modern era in industrialized nations, most episodes of lower respiratory tract infection—adequately treated—resolve without residual damage eventuating in BXSIS. However, among the older generations who were not protected by readily available antibiotics and vaccines, there are individuals who offer a convincing story of recurring, localized infections following a discrete episode of "pneumonia" in their childhood or early adult years that presumably produced irreversible damage leading to BXSIS.[1]

Specific traditional pathogens to which BXSIS has been ascribed include *Bordetella pertussis*, mucoid strains of *S. pneumoniae*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, adenoviruses, rubeola (measles), and influenza. Chronic granulomatous pathogens commonly related to BXSIS include *Mycobacterium tuberculosis*, *Histoplasma capsulatum*, and NTM such as *Mycobacterium avium* complex (MAC). In addition, mixed infection, including anaerobic mouth flora related to aspiration, may result in extensive damage to the parenchyma ("lung abscesses") with subsequent BXSIS.

Cystic Fibrosis

CF and CF variants are arguably the most common causes of BXSIS in the United States and other industrialized nations of the Western Hemisphere today. Being the most common autosomal recessive disorder among whites (1 in 2000–2500 live births),[26] CF is increasingly prevalent as improved therapies allow those who are afflicted to live longer. At present, there are approximately 30,000 CF patients in the United States with 40% to 45% of them estimated to be over 18 years old or roughly 12,000 to 14,000 adults with CF. In the next decade, it is predicted that about 50% of all CF patients will be adults.[27] The specific manifestations, severity, and rapidity of progression of CF vary highly according to the genotype and other modifying factors. However, the majority of those with childhood-onset CF who survive into their adolescence or early adult years have manifest BXSIS. (See Chapter 41 for details.)

In addition to these "typical" cases in which CF is recognized early in life, among a large series of adult patients seen at the National Jewish Health (NJH) in Denver with BXSIS associated with NTM, 117 of 865 (13.5%) were found to have one or more abnormal alleles of their cystic fibrosis transmembrane regulator (CFTR) gene,[28] well in excess of the anticipated carrier rate of 6% in the general population. In 19 of the NJH patients (2.1% overall), there were two abnormal alleles, and 98 (11.4%) had only one mutation. Of note, the mean age of these patients was 61 years. The clinical importance of these heterozygous mutations may be disputed; however, patients in this cohort had a high frequency of chronic airflow obstruction, sinusitis, difficulties with conception, and coinfection with pathogens typical of CF, including mucoid strains of *P. aeruginosa*—all features compatible with clinical CF. Among another series of patients with BXSIS and/or NTM lung disease, 24 of 50 (48%) had one or more CFTR mutations.[29] Similarly, among a cohort of 63 patients with NTM lung disease studied at the National Institutes of Health (NIH), 36% had mutations in the CFTR gene.[30] Consistent with the assertion that these heterozygous mutations are clinically relevant is a series of 30 patients with clinical features of CF who were reported to have normal CFTR alleles on comprehensive gene sequencing.[31] The authors

concluded that the modifying factors outside the CFTR genome could result in a clinical condition consistent with CF. It is our contention that heterozygous anomalies in the CF gene acts as a predisposing factor for BXSIS.

Based on contemporary understanding of the complex and diverse features of CF, there appear to be two groups in whom BXSIS occurs. The first and obvious group includes those with classic infancy/childhood-onset disease in whom clinical and laboratory data readily confirm the diagnosis of CF. The other group involves those with less severe disease that manifests later in life and for whom diagnostic testing is ambiguous.[32] Sweat chloride testing may or may not be abnormal, and genotyping may demonstrate heterozygous or even normal CFTR alleles. We might include under this rubric persons carrying the label of Young's syndrome (males with BXSIS, sinusitis, and obstructive azoospermia) and males with congenital bilateral absence of the vas deferens,[33] who have not been consistently regarded as having variant CF.

There are a wide variety of genetic factors lying outside the CFTR region that influence the clinical phenotypes of the patients.[34] (See Chapter 41 for additional discussion.)

Disorders of Immunity

Immunologic deficiencies are also associated with the development of BXSIS. Primary diseases that result in immunodeficiency may devolve from mutations that impair B or T lymphocytes and cause abnormal humoral immunity, cellular immunity, or both. Less frequent anomalies may involve natural killer (NK) lymphocytes, neutrophils, or complement proteins. Some specific immune disorders are noted later.

Common variable immunodeficiency (CVID), or acquired hypogammaglobulinemia, is the most frequent syndrome recognized in this group of diseases. Clinically, it is seen equally among males and females, distinguishing it from X-linked agammaglobulinemia (Bruton's disease), which exclusively involves young males. It may occur throughout all age groups, although it is most commonly recognized in early childhood. Although there are normal numbers of circulating B lymphocytes, they fail to differentiate into antibody-producing cells. This results in particular vulnerability to infections with encapsulated bacteria such as *S. pneumoniae*, *H. influenzae*, *S. aureus*, and *P. aeruginosa*. Recurring infections of the airways with these and other organisms frequently result in BXSIS.[35] The diagnosis is established by demonstrating low levels of gamma globulin and failure to produce appropriate antibody responses following vaccination. A variant of the hypogammaglobulinemic disorders is selective deficiency of subclasses of immunoglobulin G (IgG), notably IgG_2 and IgG_4.[36] Because repletion with gamma globulin is so useful in controlling the recurrent infections, pursuit of the diagnosis of deficient antibody production (CVID or Bruton's disease) is strongly indicated. By contrast, selective deficiency of secretory IgA, another cause of recurrent respiratory infections, cannot be controlled by repletion.[37]

Other, less common primary immune disorders that may result in recurrent or refractory respiratory infections leading to bronchiectasis include hyper-IgM or hyper-IgE (Job's) syndrome and thymic hypoplasia resulting in abnormal cellular immunity (DiGeorge syndrome). There are two forms of the hyper-IgE syndrome: an autosomal dominant form caused by mutations in the signal transducer and activator of transcription 3 (STAT-3) gene, resulting in STAT-3 deficiency, and an autosomal recessive form, for which the precise genetic cause is not known.[38] The susceptibility of such individuals with dominant hyper-IgE syndrome to pyogenic bacteria and NTM organisms may be due to impaired production of cytokines secreted by type 1 helper T cells such as interferon-γ, tumor necrosis factor-α, and interleukin-17 (IL-17), cytokines known to be important in controlling such infections.[39] Genetic anomalies that may result in combined humoral and cellular impairment include severe combined immunodeficiency syndrome (SCIDS), "bare lymphocyte" syndrome, Wiskott-Aldrich (an X-linked recessive illness associated with small platelets and eczema), cartilage-hair hypoplasia (associated with short-limbed dwarfism), ataxia-telangiectasia syndrome, and a variety of other rare disorders.

Alpha$_1$-Antitrypsin Anomalies

Various phenotypic abnormalities of alpha$_1$-antitrypsin (AAT) appeared prominently in a recent series of patients seen at the NJH with BXSIS associated with NTM.[40] Previously, there have been reports of the relationship between AAT deficiency and BXSIS.[41,42] However, in the great majority of cases in the NJH series, the patients were not deficient in AAT but had heterozygous phenotypes (mainly MS; to a lesser extent MZ) with normal AAT levels. The prevalence of AAT anomalies in the overall cohort of NJH patients with various NTM infections was 17%[40]; even more striking was the 27% prevalence of AAT anomalies in the patients with rapidly growing mycobacterial disease.[43] Based on various surveys, AAT anomalies would be anticipated in roughly 8% to 9% of the U.S. population.[44] However, the role of heterozygous anomalies of the AAT system in the pathogenesis of lung disease is controversial.[45] The majority of the NJH patients did not have significant chronic obstructive lung dysfunction or grossly visible emphysema on CT scanning. Hence, we postulate that the AAT anomalies render the patients more vulnerable to respiratory tract infections. Inferential evidence in support of this hypothesis includes an informal survey done among emphysema patients being repleted with Prolastin[46]; 74 of the 89 responding patients described a perceptible benefit, and 56 of the 74 identified a reduction in the frequency of infectious exacerbations of their chronic obstructive pulmonary disease. Possibly relevant to the development of BXSIS is the observation that AAT is produced in airway epithelium (as well as the liver) and "Z" AAT may polymerize in the lung and act as a chemoattractant.[47] Direct evidence in support of the effect of AAT on infection includes evidence that aerosolized Prolastin suppresses *P. aeruginosa* lung infection in an

animal model[48] and the observation by Shapiro and colleagues[49] of the inhibitory effects of AAT on replication of the human immunodeficiency virus (HIV) in whole blood. Further support for a role of AAT in direct resistance to infection is the observation in an African population that two polymorphic variants of the AAT haplotype were associated with significantly greater risks of HIV infection when compared with the other nine haplotypes common in sub-Saharan African populations.[50] Chan and coworkers[43] showed that AAT inhibits phagocytosis of *Mycobacterium abscessus* by human macrophages, partially denying the mycobacteria their preferred intracellular milieu. It should be noted that a group from France studied AAT alleles in a large cohort of BXSIS patients and reached a different conclusion.[51] They found the following phenotypes in their patients: MS 11.9%, MZ 3.5%, SS 1.5%, SZ 0.5%, ZZ 0.5%. In this study, the distribution of these phenotypes was not significantly different in their controls, and they inferred that AAT anomalies did not contribute to the risk for BXSIS. In a study of 74 patients with severe AAT deficiency (PiZ phenotype), 70 had bronchiectatic changes on CT scan.[52]

Ciliated Epithelium

Congenital structural and functional disturbances of the ciliated epithelial cells are seen in association with BXSIS as well as with frequent and severe upper respiratory tract problems.[52a,52b] These disorders appear to be an autosomal recessive process, with an estimated frequency between 1 in 12,500 to 1 in 40,000.[53] Primary ciliary dyskinesia (PCD) embraces a heterogeneous group of ultrastructural deficits involving the axoneme or central functional element of the cilia.[54] The normal axoneme is composed of nine paired or doublet microtubules arrayed peripherally around two central, single microtubules; attached to the peripheral doublet microtubules are outer and inner dynein arms as well as radial spokes (Fig. 42-5). The direction in which the cilia beat is determined by the orientation of the two central microtubules. In a local sheet of bronchial ciliated epithelium, the axes of the central microtubules are arrayed within a fairly narrow range, typically deviating 25 degrees or less from each other along the long axis of the airway. A variety of abnormalities have been described, including the complete or partial absence of

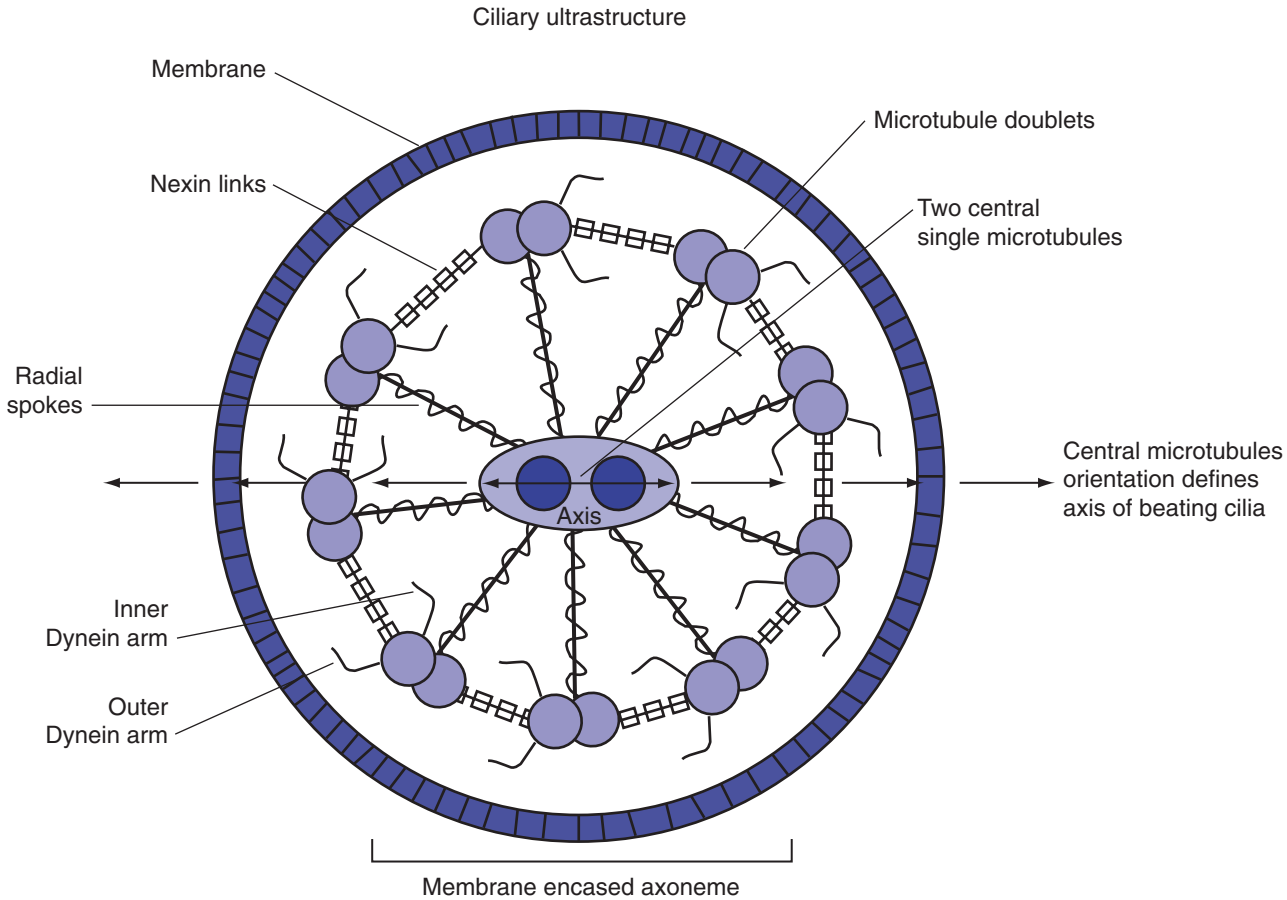

FIGURE 42-5 ■ Ultrastructure of the cilia. The structure and function of cilia are elegant and complex. Each ciliated epithelial cell possesses approximately 200 cilia. The direction of ciliary beating is determined by the orientation of the inner pairs of microtubules. Dysfunction of the ciliary apparatus may involve a variety of structural abnormalities in the cilia or disorganization of the ciliary axes. The cilia beat in a relatively fluidic periciliary medium; above that, adherent by a thin physicochemical junction, is a gelatinous layer of mucus.

outer or inner dynein arms, a lack of radial spokes, disordered microtubule arrangements, ciliary disorientation, and other rare disturbances. Functionally, these disturbances result in reduced or disorganized beating of the ciliated epithelial cells or, in some cases, gross immotility. There may also be inversion of the normal anatomic locations for the organs of the thorax and abdomen, situs inversus universalis or partialis; PCD with situs inversus universalis is known eponymically as Kartagener's syndrome. In the absence of normal ciliary activity, organ orientation appears random, resulting in situs inversus in roughly half of the cases. Evidence in support of this theory includes discordant organ orientation in monozygotic twins with disordered ciliary motility.[55]

The ineffectual beating of the ciliated cells results in stagnation and accumulation of mucus, which classically is associated with early-onset refractory or recurrent infections of the airways including otitis media, mastoiditis, sinusitis, and bronchitis. BXSIS is a common sequelae of PCD, typically involving the dependent zones including the lower lobes, right middle lobe, and/or the lingular segment of the left upper lobe (Fig. 42-6). The defect also involves the flagella of the spermatozoa, resulting usually, although not universally, in male infertility.

Diagnosing PCD is often problematic.[56] Consideration should be given in the setting of early-onset upper and lower respiratory infections (see earlier). Male infertility, although suggestive, is more likely due to Young's syndrome in a North American population. A suggestive feature on high-resolution CT is predominant BXSIS in the lower lobes, with or without right middle lobe or lingular involvement and sparing of the upper lobes (unpublished data). Diffuse, softly marginated flocculent centrilobular opacities in the lower lobes is typical of PCD, reflecting chronic bronchiolitis. Electron microscopic analysis of the ultrastructure of the cilia or clearly documented ciliary dysfunction via high-speed video microscopy are the "gold standard" for diagnosis. However, such testing is complicated by the following factors: (1) chronic infection may denude the airways of ciliated epithelium and (2) chronic infection may damage cilia, resulting in nondiagnostic findings. One report demonstrated that computer-assisted analysis can increase the diagnostic yield significantly over conventional transmission electron microscopy for inner dynein arm disturbances.[57] Direct measurements of ciliary beat frequency or coordination is available only in selected research centers. Among males, dysmotile or immotile spermatozoa may be demonstrated, and ultrastructural analysis of the sperm flagella may confirm the diagnosis. The "saccharine test" has also been employed as an inferential test of ciliary dysfunction. The primary utility of the saccharine test is to exclude PCD by a normal value. An abnormal saccharine test is consistent with, but not diagnostic of, PCD, as individuals with other disorders that result in chronic rhinosinusitis may have denuded their ciliated epithelium or have inflammatory factors that impair ciliary beating. Thus, the test should not be done within a month of an upper respiratory infection.

The latest test for the diagnosis of PCD is nasal nitric oxide (NO) levels.[56] In a large cohort with proven PCD, nasal NO levels were significantly lower than in normals or subjects with CF. Of interest, parents of PCD patients had lower than normal nasal NO levels, intermediate between controls and patients, despite the absence of clinical disease.

Patients with PCD, sinusitis, and BXSIS also have a marked tendency toward colonization and infection with *H. influenzae*.[56] The mechanism(s) for this predilection is unknown. Defective adaptive immunity is a plausible candidate.[34]

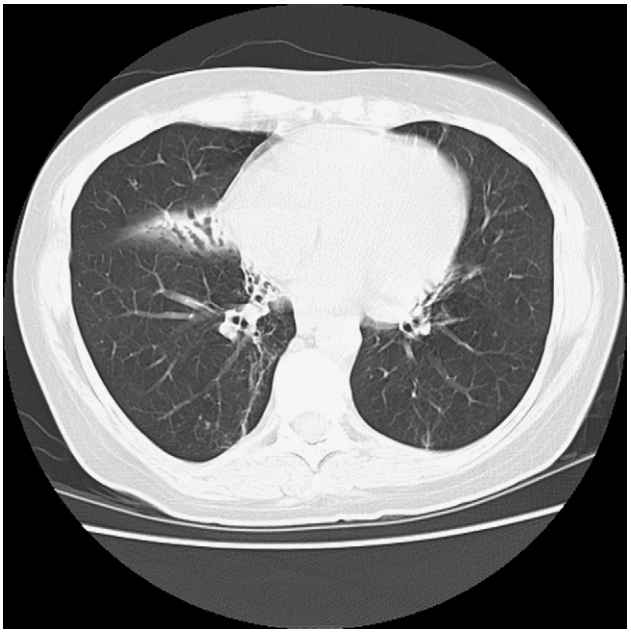

FIGURE 42-6 ■ Dependent-zone BXSIS in primary ciliary dyskinesia (PCD). This 35-year-old white woman has classic PCD. She has atelectasis and saccular BXSIS involving the right middle lobe, the medial basilar segment of the right lower lobe, and the anteromedial aspects of her left lower lobe. She has previously been treated for *Mycobacterium avium* complex (MAC) and now has refractory infections with *P. aeruginosa*.

Bronchial Cartilage

Cartilaginous "C-rings" are present throughout the entire trachea as well as the large and medium-sized airways, typically down to the fourth through sixth generations of the ramifying bronchi. The primary functional role of these structures is to maintain airway patency during expiration including cough. There are two well-described heritable syndromes that involve these cartilaginous structures.

Mounier-Kuhn syndrome, or congenital tracheobronchomegaly, is a rare disorder associated with gross enlargement or dilation of the C-rings in the trachea and segmental bronchi[58] (Fig. 42-7). The underlying defect is atrophy and even absence of elastic fibers and smooth muscle tissues of the large airways.[59] In addition, primary or secondary atrophy of the connective tissue between the rings may result in outpouchings or diverticula, potentially serving as reservoirs for recurrent infections. Distal to the involved airways, bronchial structures gen-

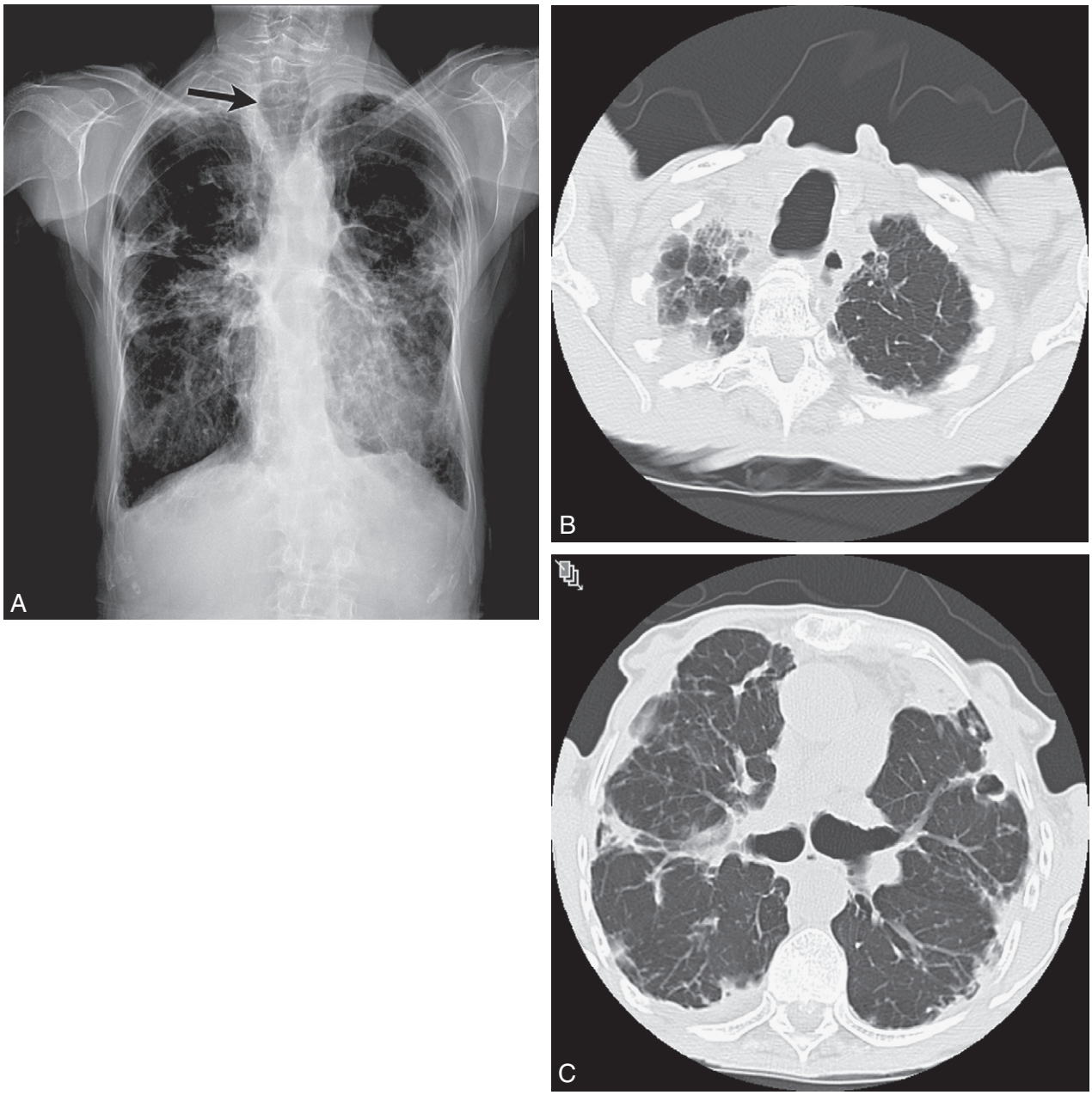

FIGURE 42-7 ■ Congenital tracheobronchomegaly (Mounier-Kuhn syndrome) with BXSIS. This 73-year-old woman has had recurring respiratory infections throughout her adult life, most recently associated with *Mycobacterium avium* complex. **A,** On the posteroanterior view, a massively dilated trachea (*arrow*) is seen. **B,** The dilated trachea with prominent cartilaginous rings is confirmed on a computed tomography (CT) scan. **C,** Not only is the trachea enlarged, but the main-stem bronchi are dilated.

erally appear normal. Clinically, Mounier-Kuhn patients may present in their early years or as late as the fourth decade with recurring lower respiratory infections. In advanced stages, airway collapsibility may result in severe airflow obstruction. The diagnosis is readily made by finding extraordinary dilation of the trachea and central bronchi on CT scans, with airway dimensions 3 standard deviations greater than normal. Special considerations in management include positive end-expiratory pressure support and silicone or metallic stenting. Lung transplantation is an option, although unique issues associated with Mounier-Kuhn syndrome include recurrent infections when tracheal diverticula are present and difficulty with bronchial anastomosis due to discrepancy in the airway diameters between the donor and the recipient lungs.

Williams-Campbell syndrome, or congenital bronchial cartilage deficiency syndrome, is another rare disorder that tends to present early in life with recurring infection and BXSIS.[60] The absence of cartilage from lobar through the first few generations of segmental airways is the typical finding in Williams-Campbell syndrome, although main-stem bronchi may be affected as well. Characteristic findings on CT scan include more extensive periph-

FIGURE 42-8 ■ Williams-Campbell syndrome. This 50-year-old man had a lifelong history of recurring respiratory infections and productive cough. The airways are massively dilated with collections of respiratory secretions pooling in some of the cystic spaces. Notable are the normal dimensions of the main-stem bronchi.

eral BXSIS than would be anticipated by the clinical history and more proximal extension of BXSIS than usual (Fig. 42-8). Inspiratory ballooning and expiratory collapse of the airways on chest CT scan is characteristic of Williams-Campbell syndrome.[61] The degree of peripheral airway distortion suggests that this disorder entails more than simply the absence of proximal cartilage. Patients with Williams-Campbell syndrome are particularly predisposed to proximal bronchomalacia after transplantation due to the combined effects of cartilage deficiency in the main-stem bronchi plus decreased blood supply to the proximal airways due to loss of collateral circulation of the transplanted lung.[62]

Connective Tissue

Among the various formally described heritable disorders of the connective tissues, BXSIS and other structural abnormalities including extensive cystic degeneration of the lungs have been noted most extensively in those with Marfan syndrome.[63,64] In addition to airway and parenchymal abnormalities, persons with Marfan syndrome have various other anomalies, including pectus excavatum, pectus carinatum, scoliosis, straight-back syndrome, and mitral valve prolapse. Two of these conditions, scoliosis and mitral valve prolapse, are found often in patients with two other connective tissue disorders, Ehlers-Danlos syndrome and cutis laxis.

This constellation of findings is mindful of the prototypic female patients we and others are seeing with BXSIS, most commonly in association with NTM. Based on analogy to these heritable disorders, we believe that there may be subtle anomalies or polymorphic variants of connective tissue that predispose to their BXSIS. Phenotypic findings among these patients that are mindful of these connective tissue disorders are various combinations of scoliosis, straight-back syndrome, pectus excavatum or unusually narrowed anteroposterior chest diameter, pectus carinatum, and/or mitral valve prolapse. Among a series of 63 patients reported from the NIH with NTM lung disease, predominantly manifested by BXSIS, careful morphometric studies were performed.[30] Compared with the women in the National Health and Nutrition Examination Survey (NHANES) database, patients with NTM lung disease were found to be significantly taller and more slender. In addition, pectus excavatum, scoliosis, and mitral valve prolapse were found in excess of expected rates. However, the patients did not have dolichostenomelia (a long, narrow frame), hyperdistensible joints, arachnodactyly, or overt aortic root involvement to suggest classic Marfan syndrome.[30] Neither do they have the cutaneous or joint abnormalities typical of Ehlers-Danlos syndrome. Our supposition is that the fundamental "defect" having to do with a propensity for BXSIS is "weakness" of the connective tissue of the bronchial tree. Notable among our patients, as well as other series of females with BXSIS associated with environmental mycobacteria, is bronchiectatic involvement of the right middle lobe and lingular segment of the left upper lobe. Our hypothesis does not identify the "prime factor" in the pathogenesis of the BXSIS: do the airways dilate in response to the high intra-airway pressures generated during coughing that is incidental throughout life, or is there an underlying structural or functional defect that increases the risks for infections that set in motion the coughing and inflammation that lead to BXSIS?

Could slenderness itself—independent of malnutrition or any underlying illness—predispose individuals to mycobacterial infections? One intriguing hypothesis for the increased susceptibility to mycobacterial infections in thin individuals is due to a relative deficiency of leptin, which is normally produced by fat cells. Experimental corroboration for the leptin hypothesis comes from studies showing that leptin-deficient (ob/ob) mice are more susceptible to *M. tuberculosis* and *M. abscessus* lung infections.[65]

In view of the preponderance of females in recent series with BXSIS associated with MAC, two theories have been proposed. "Lady Windermere's syndrome," named after a character in a novel by Oscar Wilde, posits that women—in the effort to be demure or elegant—voluntarily suppress their cough, leading to accumulation of secretions and chronic infections.[66] However, it has been our observation that these patients cough frequently.[67,68] Rather than voluntary suppression, it seems more plausible that their coughing may be ineffectual due to airway collapsibility, which interrupts movement of secretions out of the bronchial tree.

An alternative proposition came from Japan where they, too, have noted a particular female vulnerability to BXSIS with MAC, largely among elderly, postmenopausal women.[69] Tsuyuguchi and associates[69] demonstrated that among female mice, oophorectomy led to higher mycobacterial loads in the lungs and spleen following intravenous challenge with MAC. Furthermore, estrogen

repletion normalized the bacillary burden, and ex vivo macrophages supplemented by estrogens were more competent at limiting mycobacterial growth.

However, neither the putative relationship to connective tissue disorders nor the alleged role of estrogen deficiency can explain the striking disparity of females in recent reports of MAC-related BXSIS. In these series, 80% to 95% of patients described have been women.[6–8] Certainly, this might reflect referral or reporting bias. Furthermore, we cannot exclude the possibility of sex-associated effects on connective tissue strength/integrity or cellular immunity.

An additional remarkable element of the reported cases of MAC-associated BXSIS is the strong preponderance of whites. White females constitute 80% to 95% in recent series, including those compiled in communities/areas with large African American, Hispanic, or other minority populations.[6–8] Again, given the potential for referral, reporting, or ascertainment biases, we cannot be sure of the validity of these observations. However, among the specialists with whom we correspond, this is a strongly held perception. The relatively higher prevalences of CF and AAT anomalies in European-derived populations may partially, but not wholly, explain this apparent imbalance.

Congenital and Developmental Anomalies

Conditions such as sequestration, agenesis, hypoplasia, and atresia may result directly in BXSIS or may predispose to infections that eventuate in this condition. Sequestrations presumably develop due to accessory primordial lung buds, which may be invested within normal lung tissue (intralobar) or external to the normal lungs (extralobar). Sequestrations may or may not connect with the bronchial tree and often derive their blood supply directly from the aorta. Clinically, they most commonly present with recurrent and/or chronic lower respiratory tract infections beginning in the second or third decade of life. Radiographically, they usually appear as irregular, peculiar densities abutting the diaphragm in the posterior basal regions. Unilateral hyperlucent lung (Swyer-James-MacLeod syndrome) is characterized by unilateral bronchiolitis leading to hyperinflation. In some cases, BXSIS is present. The etiology(ies) and pathogenesis of this rare disorder are uncertain but may involve developmental or acquired disturbances of the bronchial tree.

Idiopathic Inflammatory Disorders

There are a wide array of conditions associated with BXSIS that might be included under the rubric of idiopathic inflammatory disorders. They are all systemic illnesses that variably involve the lungs and, in such cases, may or may not result in BXSIS.

Sarcoidosis is by far the most common of these disorders. (See Chapter 59 for a comprehensive review.) Broadly, sarcoidosis may involve the airways by several fundamental mechanisms: diffuse parenchymal scarring resulting in traction and airway distortion, endobronchial granulomatous inflammation including stricture with poststenotic infection, or compression secondary to hypertrophic peribronchial lymphadenopathy.[70]

Rheumatoid arthritis (RA) may entail a variety of pulmonary manifestations. In two early series, BXSIS was seen in 3.2%[71] and 5.2%[72] of referral populations of RA patients. More recently, BXSIS has been described in considerably higher percentages of RA patients undergoing high-resolution CT scanning: 20% to 35%[73]; surely, these studies were skewed by selecting patients with respiratory problems to undergo CT scanning. However, BXSIS was seen in 8% of RA patients without respiratory symptoms.[74] Notably, the majority of the patients in the previously discussed series did not have RA-associated interstitial fibrosis as a presumed cause of the BXSIS. Potential causal mechanisms include increased propensity for infections, either intrinsic to RA or secondary to steroid or cytotoxic therapy. Sjögren's syndrome in association with RA has also been proposed as a risk factor, but the evidence is inconsistent.[73] Clinically, it should be noted that the presence of BXSIS in RA patients was associated with an unfavorable prognosis in one series.[75]

Ankylosing spondylitis has been classically associated with upper lung zone fibrocystic degeneration and ankylotic fusion of the junctions of the ribs and vertebrae, resulting in restricted ventilation. However, in a large series from the Mayo Clinic, pulmonary involvement was described in only 1.2% of the patients.[76] BXSIS independent of apical fibrocystic disease has been seen in a small series from the United Kingdom.[77] Ankylosing spondylitis was reported in association with MAC in an early series from the NJH.[78]

Systemic lupus erythematosus (SLE) may involve an assortment of pulmonary complications, including those intrinsic to SLE and others related iatrogenically (see Chapter 58). BXSIS, as such, was described in 21% of SLE patients studied with high-resolution CT in one series[79]; factors related to BXSIS were not well studied. As with RA, the presence of Sjögren's syndrome may be a comorbid element.

Sjögren's syndrome (SS), keratoconjunctivitis sicca and xerostomia (dry eyes and mouth), may exist in the primary form or in association with other collagen vascular diseases such as RA or SLE. Pulmonary complications of SS include lymphocytic interstitial pneumonia, lymphoma or pseudolymphoma, and/or pulmonary hypertension (see Chapter 58). BXSIS has also been noted.[80–82] It is reasoned that lymphocytic inflammation results in impaired function of mucous glands, in turn resulting in decreased volumes and increased viscosity of mucus. This leads to airway obstruction, poor clearance, and chronic infection. There have not been large surveys employing the CT lung scan in SS patients to quantify the risk for BXSIS. However, we have recently seen several elderly female patients with primary SS in whom BXSIS was prominently involved.

Inflammatory bowel disease (IBD) has been related directly to BXSIS.[83] IBD-associated BXSIS appears to be more common with ulcerative colitis than Crohn's disease.[84] In the majority of cases, the IBD antedates the lung manifestations, but in some cases, the pulmonary

symptoms may herald the IBD. Proposed pathogenic relationships include a cryptogenic infection that incites both airway and intestinal inflammation, common epithelial targets of autoimmunity, or sensitizing agents that are inhaled and/or ingested.

Relapsing polychondritis (RP) is identified essentially as progressive inflammation, weakness, and deformity of cartilaginous structures including the ears, nose, larynx, and tracheobronchial tree, typically associated with nonerosive polyarthritis. In addition, there may be inflammatory and/or functional disturbances of the eyes or the auditory/vestibular components of the ears. Respiratory involvement is a common clinical element of RP and a major cause of mortality. BXSIS in such patients may be due to primary bronchial damage and/or recurrent infection.[85]

Aspiration/Inhalation Accidents

Spillage of foreign matter into the airways may result in BXSIS. There are two fairly distinct scenarios in which such matter might be aspirated into the lungs and cause sufficient damage to result in chronic deformity of the airways. One is the direct spillage of secretions from the oropharynx, infamous for a plethora of microorganisms including microaerophilic and anaerobic bacteria which can produce necrotizing pneumonia. The other is introduction of materials refluxed from the esophagus and/or stomach, which, in addition to the microorganisms noted earlier, contain food particles, hydrochloric acid, biliary or pancreatic secretions, and microbes indigenous to the gut including *Helicobacter pylori*.[86]

Laryngeal protective functions are imperfect, and "microaspiration" occurs frequently. Thus, we might presume that aspiration leading to lower respiratory tract infections involves greater than usual volumes and/or more noxious contents. Also, it is reasonable to posit that once the airways have been damaged, a lesser inoculum can have more substantial clinical effects, a variant of the "vicious circle" theory.

Many factors influence the likelihood/frequency of aspiration. They include (1) depressed sensorium (trauma, alcohol or drug abuse, postictal, general anesthesia); (2) altered brain-stem function (post–cerebrovascular accident, postpolio, primary neurologic diseases such as multiple sclerosis, amyotrophic lateral sclerosis, or syringomyelia); (3) altered laryngeal structure/function (postsurgery, postirradiation); (4) esophageal disorders (dysmotility, obstruction by tumors or strictures, muscular dystrophy, achalasia, tracheoesophageal fistulas, or lower esophageal sphincter (LES) incompetence); and (5) gastric dysfunction (dysmotility or outlet obstruction).

Although all of these elements may contribute to the risk of infection (and BXSIS), it seems likely that gastroesophageal reflux (GER) is the most common factor. Among a cohort of BXSIS patients noted previously from the NIH, approximately three fourths of them had demonstrated abnormalities of esophageal morphology (dilation and thickening), function (dysmotility), anatomy (hiatal herniation), or competence (overt reflux).[87] Indeed, the frequency of esophageal disturbances was so high that one might question whether the esophageal findings were the cause of recurring infections/BXSIS or, in some cases, an effect. In the latter regard, it is important to note that among series of patients with chronic asthma and idiopathic pulmonary fibrosis, the incidence of demonstrated esophageal dysfunction ranged from 80% to 95%.[88,89] It is plausible that labored breathing with wide disparities between intra-abdominal and intrathoracic pressure and/or chronic coughing, which stresses and dilates the diaphragmatic ring, might disrupt the LES and subject the esophagus to distending forces.[90] An additional factor that could contribute to GER is the medications employed for these pulmonary disorders, including anticholinergics, β-agonists, theophylline, and corticosteroids, all of which impair LES function,[91] and broad-spectrum antibiotics which alter gastroesophageal flora.

In any case, clinicians should be alert to the potential of GER/aspiration as a primary or contributing role in the development of BXSIS. For those suspected of disordered deglutition, tailored hypopharyngography employing contrast materials of varying consistency may identify unsuspected aspiration. It is important to note that some patients spill contrast material into their trachea without any awareness or coughing. Such studies may be performed with a speech therapist, who can also aid patients with safer techniques for eating, drinking, and swallowing.

Impaired esophageal motility may be suggested on CT scans of the lungs in which the esophagus is grossly dilated, there is excessive air present along the course of the esophagus, or the walls of the esophagus are thickened. Impaired motility may often be demonstrated on a simple barium swallow. The extent of impaired contractility may be measured by esophageal manometry; this is critical if reconstitution of the LES is contemplated. Demonstrating actual reflux may be problematic. If gross reflux is demonstrated on a routine study, it is sufficient for a presumptive diagnosis. However, if symptoms or other clinical features suggest GER and the upper gastrointestinal series is negative, a 18- to 24-hour pH probe with or without measurement of impedence may both identify and quantify reflux episodes.[88] Recent studies have documented that nonacid reflux may result in chronic cough and even lung injury.[92] Among the implications of these findings is that acid-inhibition measures may not be sufficient to protect the airways. For individuals with evidence of recurrent aspiration, elevation of the head of the bed should be done routinely.

Toxic inhalation or thermal injury may also be associated with BXSIS. Acute and chronic inflammation of the tracheobronchial tree, bronchiolitis, bronchiolitis obliterans, and diffuse alveolar damage may occur after exposure to toxic metal fumes (e.g., aluminum, cadmium, chromium, nickel) or toxic gases (e.g., ammonia, chlorine, phosgene, sulfur dioxide) (see Chapter 68). In severe cases, BXSIS may ensue due to either infectious complications of the exposure, denuding of the ciliated epithelium, or progressive fibrosis. Similarly, chronic airway damage and BXSIS may evolve following thermal or smoke injury.

Postobstructive Disorders

Foreign bodies may be aspirated into the airways in association with infants and children putting foreign objects in their mouths, choking events while eating, trauma, or loss of consciousness including seizures. In some cases, the obstructing object may be radiopaque (teeth, bone, or metal objects), but in most instances, the obstructing material (e.g., peanuts, vegetables) is not discernible by radiographic study. Tumors, benign or malignant, may also result in airway obstruction, poor drainage, recurrent/chronic infection, and BXSIS. The more common tumor types include bronchogenic carcinomas (particularly the squamous cell variety), bronchial adenomas, and papillomas. Extrinsic airway compression due most often to hypertrophic lymphadenitis from granulomatous diseases such as sarcoidosis or infections such as tuberculosis or histoplasmosis may severely narrow or even occlude large airways. In patients with "focal" BXSIS (particularly those with disease limited to only one region, one segment, one lobe, or even one lung), bronchoscopic examination to exclude an obstructing lesion should be performed early if other causes are not evident.

Allergic Bronchopulmonary Aspergillosis

In acute or subacute bronchopulmonary aspergillosis (or other mycoses), ABPA/M, patients develop mucoid plugs in the medium-sized bronchi. The inflammation and distention typically results in thin-walled BXSIS of the central and mid-lung airways (Fig. 42-9). Although ABPA/M typically occurs in the setting of recurrent/refractory (steroid-dependent) asthma, clinicians should be aware that these episodes may also include fever, malaise, pleuritic chest pain, and cough productive of purulent secretions. Such episodes may be confused with pneumonia, acute bronchitis, and/or exacerbations of simple BXSIS, especially if the asthmatic component is absent or minimal. The picture may be particularly obscure if the ABPA/M occurs in individuals with CF, a disorder in which ABPA/M is relatively more common. Features mindful of ABPA/M include characteristic findings on CT scanning, eosinophilia, elevated IgE levels, and dramatic responses to corticosteroids.

The other pathway to BXSIS occurs in the setting of long-standing, inadequately controlled ABPA/M. In such cases, extensive fibrosis and airway distortion may evolve due to uncontrolled inflammation (Fig. 42-10). In these cases, the patients may acquire secondary airway pathogens including *P. aeruginosa* or other gram-negative bacilli as well as NTM. In these "burned-out" cases, the patients may not demonstrate asthma, eosinophilia, or elevated levels of IgE.

Miscellaneous

There are numerous other causes of BXSIS including such diverse entities as HIV infection/acquired immunodeficiency syndrome (AIDS), yellow-nail syndrome, or radiotherapy injury.

Among persons with AIDS, BXSIS has been identified in a significant proportion of those undergoing CT scans, including children.[93,94] Obviously, this is skewed by the selection of those with respiratory problems for scanning. Presumably, the pathogenesis of the BXSIS involves

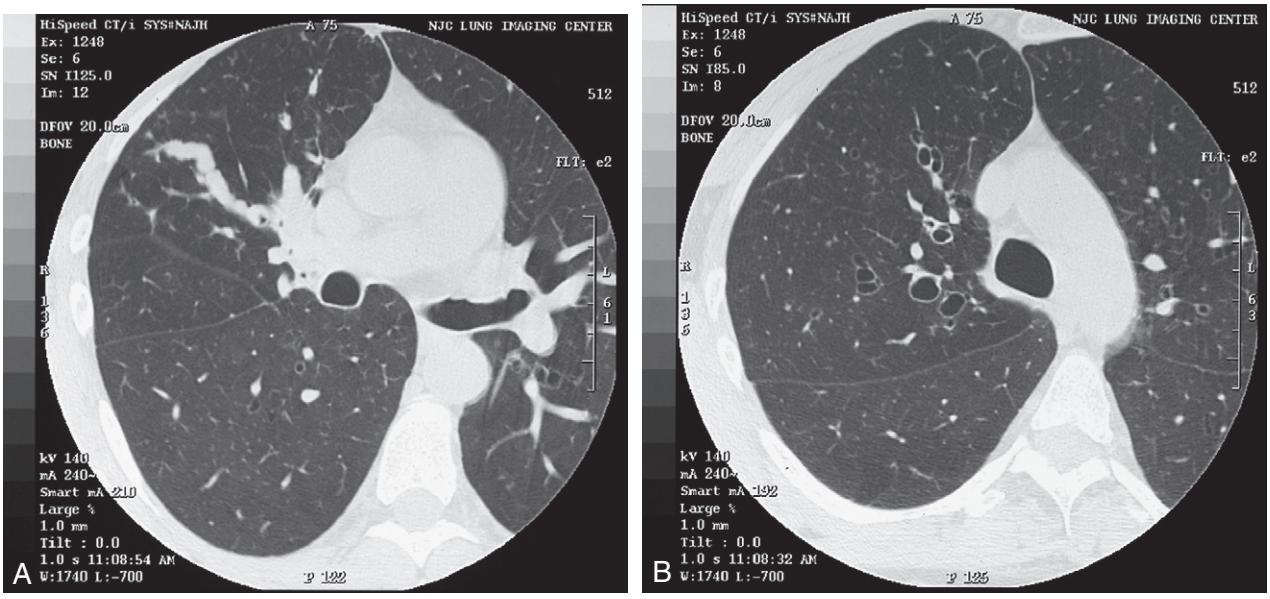

FIGURE 42-9 ■ Allergic bronchopulmonary aspergillosis with mucus-plugging and thin-walled BXSIS. This 44-year-old woman with steroid-dependent asthma reported coughing up gray-green mucus plugs. She had immunoglobulin E (IgE) levels over 1000 IU/mL, 10% to 15% eosinophilia, and precipitins to *Aspergillus fumigatus*. **A,** A classic serpentine mucus plug in the anterior segment of the right upper lobe. **B,** A more cephalad axial CT image of the same patient, showing central thin-walled BXSIS, presumably residual to the more distal mucus plugging.

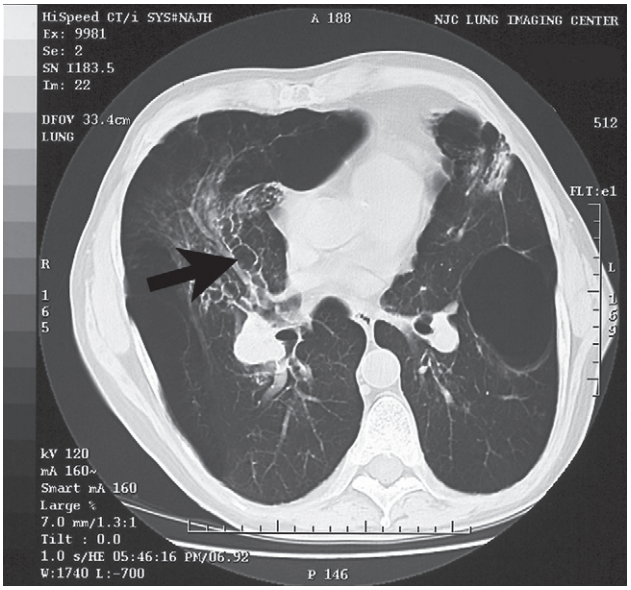

FIGURE 42-10 ■ Late fibrocystic damage from allergic bronchopulmonary aspergillosis (ABPA). The patient is a 70-year-old man with a 30-year history of poorly managed ABPA. CT scan shows residual central thin-walled BXSIS (*arrow*) in addition to fibrotic and cystic damage.

FIGURE 42-11 ■ BXSIS in a field of therapeutic x-irradiation. This 68-year-old woman had been diagnosed with a non–small cell carcinoma of the lung. She received radiotherapy to the right hilar region approximately 18 months previously. Her CT scan shows dense fibrosis and BXSIS in the radiation field. Inferior to this process she had a necrotic, cavitary process associated with *Mycobacterium avium* complex infection.

severe, chronic, and recurrent infections with a variety of opportunistic pathogens. An additional element that has not been fully addressed is the potential impact of oxidative damage associated with infection or other stressors on the AAT system.[95,96] Impairment of AAT function may contribute to the accelerated lung damage, including BXSIS, in persons with AIDS.[97,98]

Yellow-nail syndrome is an uncommon disorder marked by the triad of yellow, thick, dystrophic nails; chronic lymphedema of the face, hands, and lower extremities; and pleural effusions.[99] Females are more often involved than males; the median age of onset is 40 years, with cases ranging from infancy to the seventh decade. The most prominent pulmonary finding is bilateral exudative pleural effusions.[100] Recurrent sinusitis and lower respiratory tract infections are common.[101] BXSIS presumably evolves due to chronic infection. Contributing factors may entail abnormal lymphatic structure, increased vascular permeability, deficient immunoglobulin production, and/or ciliary dysfunction.

Radiation therapy (XRT), typically delivered for carcinoma of the breast or mediastinal tumors including lymphomas, may result in profound damage to the central airways. This reaction is not part of the postirradiation bronchiolitis obliterans syndrome but a distinctive condition marked by focal damage to the cartilage and mucosa of the airways leading to patulous distention and irregularities of the major bronchi in the field of irradiation. In our experience, BXSIS secondary to XRT given for neoplasms has become less common in the recent era when the control of dosage and field has become more refined. In some cases, this condition may be recognized by lung parenchymal scarring in the field of irradiation (Fig. 42-11).

DIAGNOSIS

In the great majority of cases, BXSIS is recognized in the context of chronic or recurring lower respiratory tract infections (deemed to be "bronchitis" or "pneumonia") over many months or years. Some BXSIS patients in whom wheezing is a prominent element may have been identified and treated as "asthmatics" for many years. Occasionally, patients come to attention following an episode of hemoptysis. Less frequently, BXSIS is identified on CT scans done for other considerations.

Although the plain chest radiograph can suggest BXSIS with "tram tracks" (Fig. 42-12) or multiple ring shadows (Fig. 42-13), CT scanning is the current diagnostic study of choice. The finding on the plain lateral chest radiographs of atelectasis of the right middle lobe and/or lingula (Fig. 42-14) is highly suggestive of coexisting BXSIS and should be followed by CT scanning in patients with persistent abnormalities and chronic symptoms.

Once BXSIS has been identified on CT scan, what studies should be performed to help direct management and classify the disease? Certainly, a careful family history may be useful in identifying genetic risk factors; however, the family pattern is rarely specific for a particular disorder unless there is a clear story for CF.

Past medical history and review of systems should focus on the various disorders noted in Table 42-1 and delineated earlier in the discussion of associated disorders and predispositions.

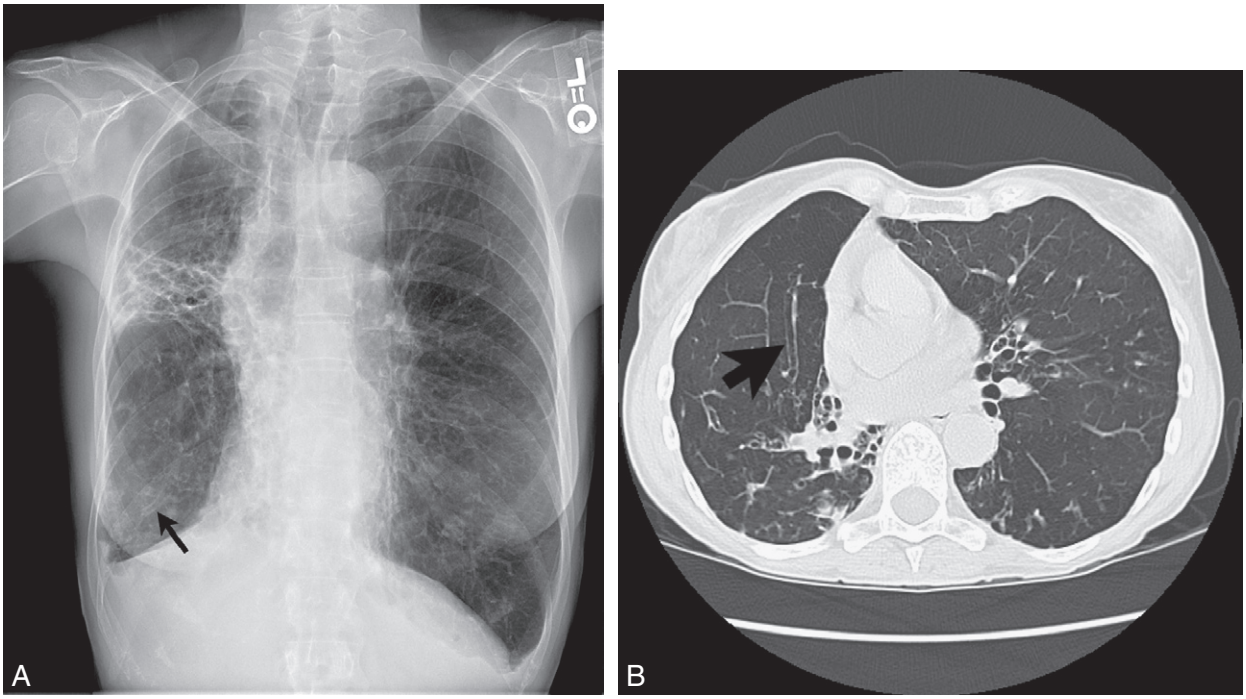

FIGURE 42-12 ■ "Tram tracks" on the routine chest radiograph in BXSIS. **A,** In the right lower lobe are parallel, nontapering shadows, "tram tracks" (*arrow*), representing BXSIS. **B,** The airway is seen as cylindrical BXSIS (*arrow*).

Laboratory testing may variously include the studies noted in Table 42-2. These tests need not all be performed on initial assessment but may be done sequentially, with the more probable disorders being checked initially.

MANAGEMENT

The care of patients with BXSIS typically involves many layers, which may be partitioned into five broad components: airway hygiene, antimicrobial treatment, anti-inflammatory therapy, surgery, and miscellaneous. These modalities are delineated in Table 42-3. Although most patients with BXSIS require various elements of each of these components to enjoy optimal health, there is not a standard formula for treating this disorder. The great majority of recurrently or chronically symptomatic patients benefit from a regular mucus-clearing regimen and periodic antibiotic therapy. For most patients, a pragmatic or "trial-and-error" approach is required to determine individual needs, preferences, and tolerances.

It is important to note that most elements described in this section have not been proved to be efficacious by randomized, controlled clinical trials. Thus, meta-analyses (such as the Cochrane Database of Systematic Reviews) generally cannot confirm the benefits or dysutility of such approaches.[102–109] Perhaps because BXSIS is such a complex mix of varying conditions and/or has been an underappreciated "orphan" disease, a paucity of systematic research has been directed at this very troublesome disorder.

Airway Hygiene and Hyperosmotic Agents

Airway hygiene consists of nonantibiotic therapies directed toward mobilizing and eliminating inflammatory secretions from the tracheobronchial tree and from the paranasal sinuses. Also included under this rubric are steps to prevent/limit aspiration of oropharyngeal or gastroesophageal contents into the airways.

Hypertonic saline, 7% twice or four times daily, has been shown to accelerate mucus clearance, decrease exacerbations, and improve lung function in CF patients.[110] However, its role in non-CF BXSIS remains to be seen. Inhaled dry powder mannitol appears promising in airway clearance in bronchiectatic patients,[111] although more definitive studies are needed.

Antimicrobial Therapy

Antimicrobial therapy historically has been the centerpiece of BXSIS care. However, there is no clear consensus on the major questions in this area including whether treatment should be given on a routine, periodic schedule ("rotating") or an as-needed basis for clinical exacerbations. In a meta-analysis that studied the use of prolonged oral antibiotics for purulent BXSIS, sputum volume/purulence was shown to decrease, but there were no significant beneficial effects in regards to rates of exacerbations, lung function, or death.[112] As well, there are limited data on the preferability of empirical selection of an antimicrobial agent or treatment guided by species identification and in vitro susceptibility testing.

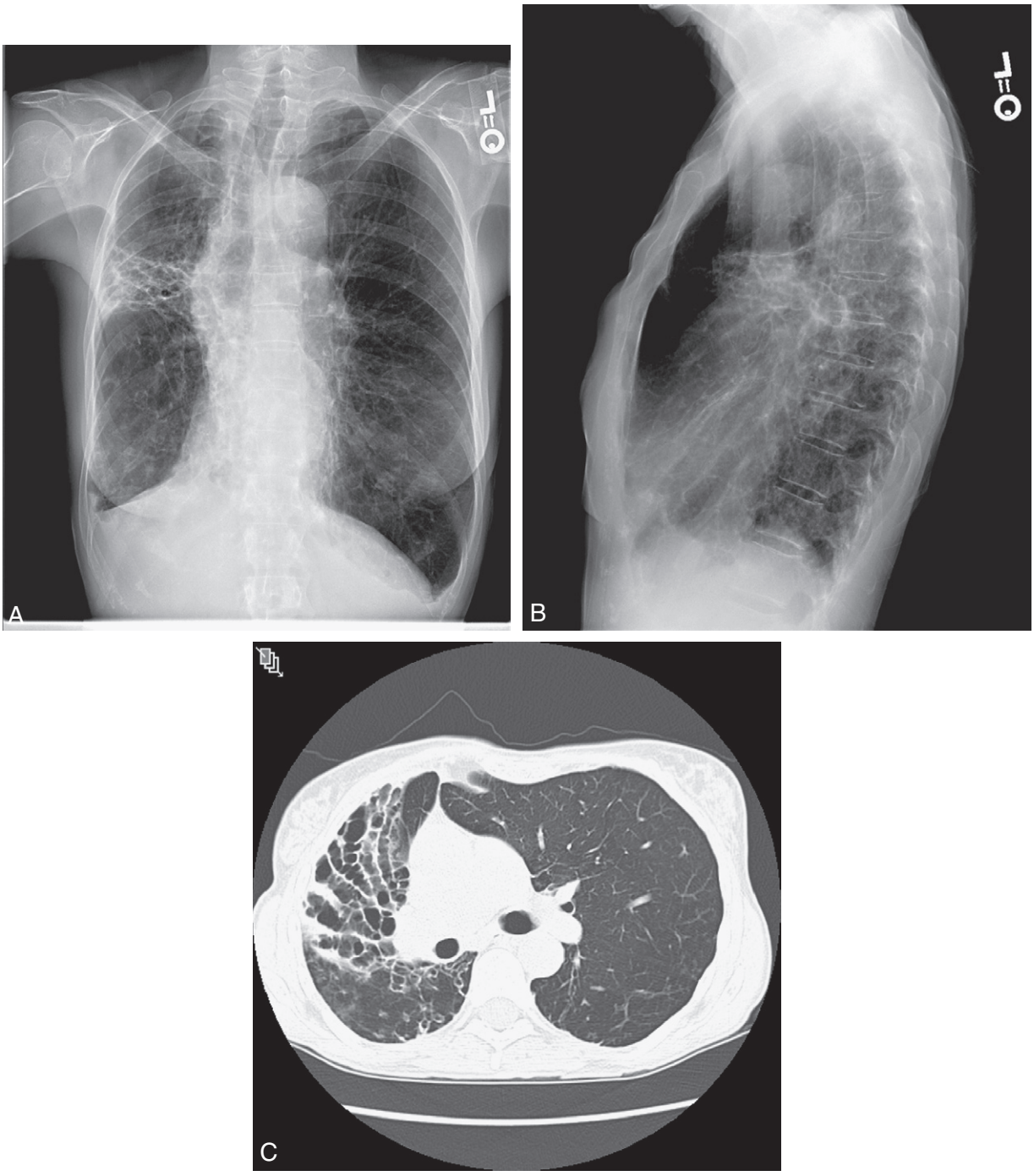

FIGURE 42-13 ■ Multiple ring shadows on the plain chest radiograph in BXSIS. **A,** On the posteroanterior view, thin-walled cystic shadowing is seen in the right mid-lung field. The trachea and mediastinum are shifted to the right, indicating extensive volume loss. **B,** The lateral view confirms the presence of multiple ring shadows in the mid-zone. **C,** CT scan of this 65-year-old white woman indicates severe varicoid BXSIS involving her entire right middle lobe and the anterior segment of the right upper lobe.

Aerosolized antibiotics also appear promising in treating or preventing exacerbations. In patients with CF, inhaled tobramycin twice daily given in alternating months decreased the frequency of exacerbations due to *P. aeruginosa*.[113] Even in patients without CF, inhaled tobramycin was found to be efficacious.[114]

Anti-inflammatory Therapy

The obvious rationale for using the anti-inflammatory agents in BXSIS is that they may reduce the inflammatory cascade, with the goals not only of reducing symptoms but also to limit the progression of disease and decline in lung function. Anti-inflammatory agents that have been examined in BXSIS include the nonsteroidal anti-

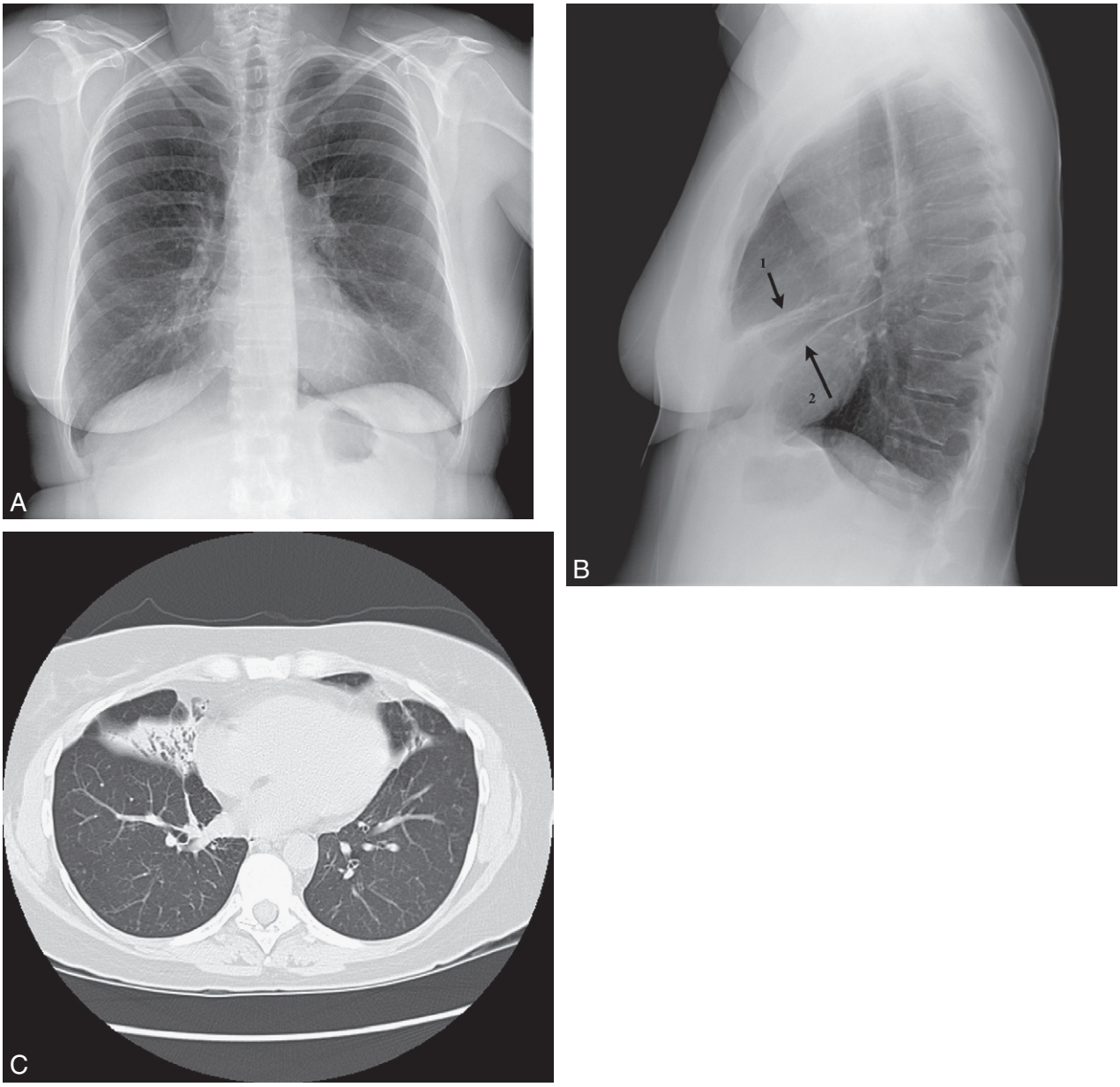

FIGURE 42-14 ■ Atelectasis and BXSIS involving the right middle lobe and lingula on plain chest radiographs and a CT scan. This 60-year-old woman has had recurring "pneumonia" throughout life. **A,** Posteroanterior view shows subtle effacement of the right heart border and cardiophrenic sulcus as well as a hazy opacity at the left heart border. **B,** On the lateral view, there are two oblique densities representing the atelectatic right middle lobe (*arrow 1*) and lingula (*arrow 2*). **C,** CT scan demonstrates BXSIS and atelectasis of the right middle lobe and inferior segment of the lingula.

inflammatory drugs (NSAIDs), inhaled corticosteroids, and intermittent macrolides to exploit their anti-inflammatory and other nonmicrobicidal activities.[114a]

NSAIDs

Because prostaglandins may play a role in augmenting airway secretions, the NSAIDs—by blocking the cyclooxygenase pathway—have been studied in BXSIS. In a double-blind, placebo-controlled study in patients with bronchorrhea due to chronic bronchitis, diffuse panbronchiolitis, and bronchiectasis, inhaled indomethacin significantly decreased the amount of sputum by half as well as the perceived dyspnea.[115] Another mechanism by which indomethacin may help in BXSIS is via inhibition of neutrophil chemotaxis and neutrophil degradation of fibronectin, thereby decreasing airway inflammation and purulence.[116]

In a comprehensive Cochrane Database review of randomized trials of NSAIDs in CF patients, high-dose ibuprofen has been shown to slow the progression of lung disease, especially in children.[117] In contrast, there have been no randomized, controlled trials on the use of NSAIDs in bronchiectatic patients without CF.[118]

TABLE 42-2. Diagnostic Studies for the Classification and Management of Patients with Bronchiectasis

Test	Comments
ROUTINE, UNIVERSAL STUDIES	
Computed tomography lung scan (CTLS)	If bronchiectasis (BXSIS) is suspected, CTLS is the definitive test. Thin-section, high-resolution images may help detect subtle airway dilation before bronchial walls are grossly thickened. Contrast is generally not helpful and may, in fact, compromise the overall resolution of the study. CTLS may also identify esophageal abnormalities.
Pulmonary function tests (PFTs)	For patients with significant BXSIS, comprehensive PFTs, including spirometry, bronchodilator responsiveness, lung volumes, and diffusion capacity, are important studies that aid in management and prognosis. PFTs may also provide useful hints regarding predisposing conditions.
Complete blood count	Anemia may reflect effects of chronic infection or blood loss (consider inflammatory bowel disorders). Leukocytosis may mark severity of infection. Eosinophilia may suggest ABPA/M.
ESR, C-reactive protein	Nonspecific markers of inflammation; very high levels may suggest underlying connective tissue disease or vasculitis.
Routine sputum culture	Antibiotic therapy in BXSIS should generally be directed against specific pathogens and guided by in vitro susceptibility. The presence of mucoid strains of *Pseudomonas aeruginosa* and *Staphylococcus aureus* may raise suspicions for CF. *Stenotrophomonas maltophilia*, *Alcaligenes xylosoxidans*, and *Burkholderia cepacia* are gram-negative bacilli that may prove problematic pathogens in patients with long-standing BXSIS. Isolation of *B. cepacia* and *Helicobacter pylori* require special laboratory techniques.
Mycobacterial sputum culture	Environmental mycobacteria such as *Mycobacterium avium* complex, *M. chelonae*, and *M. abscessus* appear to be increasingly common in contemporary BXSIS. May be commensal but often are pathogenic.
Fungal sputum culture	Especially in patients with an asthmatic component, the presence of *Aspergillus* species (or other molds including Pseudallescheria or penicillium) may suggest etiology.
CT scan of sinuses	Many BXSIS patients also suffer chronic rhinosinusitis. The presence of extensive sinus involvement suggests possible CF, immunoglobulin deficiencies, or ciliary disorders. Also, optimal management often entails aggressive sinus care.
SPECIFIC, DIRECTED STUDIES	
Sweat chloride, CF genotyping, and nasal potential differences	For BXSIS patients with bilateral disease, sinusitis, and no other identified risk factor, mild variants of CF appear to be relatively common (see text and Chapter 41). Sweat chloride is regarded as the primary screening test for CF, but a considerable portion of adults with CF have borderline or normal results. Nasal potential difference may be useful for identifying CF in equivocal cases (see Chapter 41).
$Alpha_1$-antitrypsin (AAT) levels and phenotype	AAT anomalies appear to be a substantial risk factor for BXSIS, especially with white females. Abnormal proteinase inhibitor (Pi) phenotypes, even heterozygous patterns such as MS, appear to confer risk even with normal levels of AAT (see text). Repletion of AAT may enhance resistance to lower respiratory tract infections.
Immunoglobulin (Ig) levels	Deficiencies of IgG or IgA may promote BXSIS; IgG subclass deficiencies may also be a factor. Elevated levels of IgE may suggest ABPA/M or Job's syndrome. Hyper-IgM may be associated, as well, with chronic infections.
Ciliary morphology or function	For individuals with suggestive stories (see text), a nasal ciliated epithelium biopsy with transmission electron microscopy may identify primary ciliary dyskinesia. Other studies including ex vivo ciliary activity, the saccharine test, or spermatozoa analysis may aid in this diagnosis (see text).
Nasal nitric oxide (NNO) levels	Patients with documented PCD have significantly lower levels of NNO than normals or patients with CF.[56] Although not universally available, such testing may prove highly useful in identifying PCD. Paradoxically, exhaled NO levels have been elevated in BXSIS of diverse etiologies[125] except CF.
Barium swallow (BaS)	The BaS may detect disturbed deglutition, esophageal diverticula, obstructing lesions (tumors or strictures), hypomotility, achalasia, hiatal hernias, or lower esophageal sphincter (LES) incompetence with reflux. Note that the absence of reflux on a BaS does not exclude this problem (see pH probe).
pH probe	For patients suspected of gastroesophageal reflux, an 18- to 24-hour study with a transnasal pH probe may identify, quantitate, and characterize reflux. Obviously, medications that inhibit acid production must be stopped before such tests.
Esophageal manometry	For patients being considered for surgical repair of the LES, manometry should be performed to determine that the esophagus generates sufficient pressure to propel food and liquids through the tightened sphincter.
Tailored hypopharyngography (TH)	TH is useful in detecting abnormalities of the initial phase of swallowing, deglutition. Persons particularly prone to problems include those with prior strokes, Parkinson's disease, bulbar disorders including postpolio syndrome, and those with prior laryngeal or pharyngeal surgery. Note that some patients have gross aspiration without clinical manifestations (choking, coughing); this may occur in individuals with none of the above risk factors.
LESS COMMON, EXOTIC STUDIES	
Collagen vascular disease (CVD) serologies	Various CVDs may contribute to the risk for BXSIS, including RA, ankylosing spondylitis, and systemic lupus erythematosus. Thus, for patients with compatible histories or physical findings, assays for rheumatoid factor, HLA-B27, and ANA may provide insight into predisposing conditions. CVD serologies may also suggest the diagnosis of Sjögren syndrome, particularly SSA/Ro and/or SSB/La.
Schirmer's test	For patients with histories suggestive of "sicca syndrome" (dry eyes, dry mouth, oral ulcers), a positive Schirmer test may indicate the presence of either primary or secondary (associated with a CVD) Sjögren's syndrome.

ABPA/M, allergic bronchopulmonary aspergillosis/other mycoses; ANA, antinuclear antibody; CF, cystic fibrosis; ESR, erythrocyte sedimentation rate; HLA, human leukocyte antigen; PCD, primary ciliary dyskinesia; RA, rheumatoid arthritis.

TABLE 42-3. Elements for Management of Patients with Bronchiectasis

Procedure	Comments
AIRWAY HYGIENE	
Tracheobronchial Clearance Techniques	
Mechanical "valve" devices (Flutter, Pep, Acapella, and others)	A variety of these devices exist that are designed to transmit agitating forces to the airways to physically loosen and help propel tenacious secretions out of the bronchial passages. By retarding expiratory flow, they may also stent the airways open. For optimal results, respiratory therapists should assess individual patients' needs and abilities and train them in proper usage.
Postural drainage and chest physiotherapy	For patients with dependent-zone bronchiectasis (BXSIS), positioning in the prone head-down, Trendelenburg, and/or lateral decubitus postures may promote local drainage. This might be optimized by pretreatment with mucus-mobilizing methods (see later) and clapping or vibrating techniques while in these postures.
Therapeutic vest	The pneumatically powered jacket produces high-energy vibrating forces throughout the entire thorax. Of proven utility in CF,[126] the vest may also be useful with BXSIS of other etiologies.
Mucus-Mobilizing Methods	
Inhaled β-agonists (IBAs) and/or anticholinergic bronchodilators (ACBs)	IBAs may accelerate ciliary beat frequency as well as relieve the bronchospasm present in some BXSIS patients. Although the parasympathomimetic ACBs pose a theoretical risk for "drying" secretions, some BXSIS patients tolerate them and enjoy modest benefits not provided by IBAs.[127,128]
Hypertonic saline or mannitol inhalation	Nebulizing hypertonic solutions including saline or mannitol into the airways appears to aid patients in the clearance of tenacious secretions.[129] Hypertonic saline is considerably less expensive than dornase alfa (see later). Mannitol has not yet been approved for use in the United States.
Dornase alfa (Pulmozyme)	This product hydrolyzes neutrophil DNA, which contributes to the viscosity of inflammatory secretions. Of proven utility in CF patients,[130,131] it was not beneficial in BXSIS of differing etiology in one trial.[132] Extended administration in CF patients has been shown to reduce neutrophilic inflammation of the airways.[133] However, we have found it useful in some patients with diagnoses other than CF. It is quite expensive and should be used judiciously.
N-Acetylcysteine (Mucomyst)	Also used primarily in CF patients, it has been generally supplanted by dornase alfa.[126] Its side effects include airway irritation when used in high concentrations. Given orally in Europe, this approach has not been proved efficacious, nor is it approved in the United States.
Anti-inflammatory Airway Management	
Systemic steroids	Mucosal edema and the production of inflammatory secretions may be partially alleviated by corticosteroids. Randomized, controlled trials in young patients with CF have shown improvements in clinical and physiologic parameters with extended courses of alternate-day steroids[134,135] (see Chapter 41 for details). However, there were significant adverse effects, particularly on growth rates in males.[136] Given these and other deleterious effects of long-term systemic steroids, such treatment arguably should be reserved for refractory cases.
Inhaled steroids (ISs)	To avoid some of the complications of systemic steroids, inhaled treatment is a logical approach.[137] Modest evidence of efficacy has been shown in some but not all trials with CF.[119] ISs may also improve the airway hyperreactivity common among BXSIS patients.
Macrolide antibiotics (MLAs)	In addition to their antimicrobial effects, MLAs have demonstrated host defense–modifying activities that include anti-inflammatory effects.[86,140] Azithromycin, an azolide, given over many months has resulted in clinical and physiologic improvement among CF patients infected with *Pseudomonas aeruginosa*.[141–143] These effects must be balanced against the considerable expense and potential for producing drug resistance among bacterial and mycobacterial pathogens common to BXSIS. (Patients should be screened for mycobacterial infections before use.)
Nonsteroidal anti-inflammatory drugs (NSAIDs)	Among young CF patients, long-term administration of ibuprofen has shown some benefits.[144] However, these results may not be generalized, and NSAID therapy should be approached cautiously given the potential side effects and their expense.
Anti-aspiration Measures	
Anti-GER management	Teaching patients to alter their dietary practices (reduced food and liquid intake in the evening), elevated the head of the bed, or most drastically, surgical revision of the LES or hiatal hernia may lessen the risk of recurrent airway soilage.
Improved deglutition	For patients who aspirate on swallowing, changing the consistency of foods or employing maneuvers such as the "chin tuck" may lessen the risk of airway soilage.
Reducing gastric acid	Although lowering gastric acidity with proton-pump inhibitors or H_2-blockers may diminish the symptoms of reflux, it is illogical to think that it should protect against aspiration. Theoretically, lowered acidity of the aspirated matter might result in reduced damage to the lungs; however, it should not be regarded as a lung-protective intervention.
ANTIMICROBIAL THERAPY	
Episodic, targeted antibiotics	Rather than administering "rotating" or "empirical" agents, this approach involves sampling respiratory secretions during clinical exacerbations and employing antimicrobials on the basis of species identification and in vitro susceptibility. Although logically an attractive option, it entails inevitable delays in treatment and may be confounded by the presence of multiple, potential pathogens.

Continued

TABLE 42-3. Elements for Management of Patients with Bronchiectasis—cont'd

Procedure	Comments
Rotating antibiotic therapy	A popular practice, clinicians might treat BXSIS patients with a 1 wk/mo cycle of arbitrarily selected antimicrobials such as, for example, amoxicillin, a fluoroquinolone, and a macrolide. There is some evidence of utility for long-term antibiotic therapy[145]; however, the potential for selecting for drug-resistant strains is a consideration. Imperfect evidence reported in a recent analysis suggests that patients with chronic *P. aeruginosa* infection do better with targeted therapy.[146]
Initial empirical followed by targeted antibiotics	This approach offers the advantage of prompt treatment for an exacerbation, followed by a more narrowly focused regimen based on the results of the initial sputum cultures. To be representative, sputum sampling should be done before initiating empirical antimicrobial therapy.
Role of inhaled antibiotics	The model of inhaled tobramycin in controlling pseudomonal infections in CF patients[147,148] (see Chapter 41) is an attractive model for non-CF BXSIS as well.[149] Certainly, for those patients with chronic or recurrent gram-negative bacillary infections, this approach might be considered. However, our early experience suggests less favorable tolerance of tobramycin in elderly subjects.
Therapy for exotic pathogens	Patients may either acquire secondary infections of preexisting BXSIS or primarily develop BXSIS due to exotic microbes such as environmental mycobacteria or fungi. In such cases, specific therapy may be indicated.
SURGERY	
Resectional surgery	There are no systematic studies of surgical interventions in BXSIS. However, anecdotal observations suggest that extirpation of severely damaged lobes may confer considerable benefit. Disease limited to the right middle lobe or lingula may be particularly amenable.[150–152] Whether such resections should be done through the lateral thoracotomy or VATS approach is unresolved, although our group strongly prefers the former.
Transplantation	For younger patients with BXSIS-associated respiratory insufficiency, the question of transplantation may arise. Based on the model of CF, it is a plausible consideration.
MISCELLANEOUS	
Vaccination vs. *Streptococcus pneumoniae*	Although not specifically proved in BXSIS, this vaccine seems an obvious adjunct.
Vaccination vs. influenza	In addition to vaccination, BXSIS patients should be considered for antiviral therapy if they develop clinical influenza.
Smoking cessation	A priority for all pulmonary patients.
Alpha$_1$-antitrypsin (AAT) repletion	Among COPD patients receiving AAT repletion, there was a perception of reduced frequency of infectious exacerbations (see text). For BXSIS associated with AAT anomalies, repletion might confer protection against recurrent infections.
Oxygen	Patients with BXSIS, especially extensive lower lobe disease, may become hypoxic with exertion or with sleep. Early detection and O_2 supplementation may improve exercise tolerance and physical conditioning. Nocturnal O_2 may lessen pulmonary hypertension and delay the appearance of cor pulmonale.
Methylxanthines (Mx)	Oral Mx (theophylline) theoretically might augment bronchodilation, enhance mucus clearance, and enhance diaphragmatic contractility. However, the side effects, variable pharmacokinetics including interactions with macrolide antibiotics, and GER-promoting effects make Mx a problematic element in most BXSIS patients.
Cromolyn, nedocromil, or leukotriene modifiers	Although these various asthma medications may have some theoretical roles in BXSIS, there have been no studies demonstrating efficacy.

CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease; GER, gastroesophageal reflux; VATS, video-assisted thoracoscopic surgery.

Inhaled Corticosteroids

A review of clinical trials have shown that the use of inhaled corticosteroids in CF did not cause improvement.[119]

Intermittent Macrolide Therapy

Independent of their antimicrobial properties, macrolide antibiotics hold great promise in inhibiting disease activity in BXSIS due to their nonantimicrobial immunomodulatory effects.[120] Intermittent macrolide therapy may help in BXSIS via different mechanisms including decreasing chloride diffusion potential gradient across the airway mucosa (resulting in decreased sputum volume), reducing airway levels of the neutrophil chemotactic factor IL-8, inhibiting both neutrophil and *Pseudomonas* migration, suppressing *Pseudomonas* quorum sensing, and disrupting the established biofilm layer.[121] Clarithromycin but not amoxacillin or cefaclor was shown to significantly reduce sputum production in patients with chronic bronchitis or BXSIS. In a study of a small number of patients with BXSIS[122] randomized to standard care for 6 months followed by the addition of azithromycin given at a dose of 500 mg twice weekly for 6 months or vice versa, azithromycin significantly decreased the incidence of exacerbations and sputum volume compared with standard care.[123] Similar beneficial effects plus improvement in lung function have been shown in various trials using intermittent azithromycin therapy in CF patients chronically infected with *P. aeruginosa* but also in younger CF patients before they have been colonized with *P. aeruginosa*.[124]

Surgery

Surgery remains a controversial issue in the management of BXSIS. No formal systematic studies of the indications and efficacy of resectional surgery have been conducted among patients with BXSIS. Traditional indications for resectional surgery have included chronic disabling infection, recurrent infections of intolerable frequency, or irreversible lung damage distal to a foreign body or benign tumor. Life-threatening hemoptysis may also provoke consideration of surgery, although therapeutic bronchial artery embolization may be the initial treatment of choice. A historical adage has been that surgery does not cure BXSIS. If true, it is likely due to our evolving understanding that most cases of BXSIS are due to innate risk factors that predispose to recurrence. However, surgery is still an appropriate palliative measure in selected cases.

Miscellaneous

Additional measures, such as vaccination against pneumococcal disease or influenza and smoking cessation, are appropriate for all patients. Intuitively, these measures seem particularly important for those with BXSIS; however, no systematic information is available to confirm their usefulness. On the other hand, early recognition of exercise and sleep-related hypoxia has substantially demonstrated benefits in regard to morbidity and mortality.

KEY POINTS

- BXSIS is defined by the presence of permanent dilation of the medium to large bronchi. The main clinical significance of BXSIS is recurrent airway infections by bacterial and fungal organisms resulting in chronic cough, sputum, weight loss, and respiratory compromise.
- Most BXSIS occurs owing to a combination of host susceptibility factors—which may be overt or covert—and the recurrent infections and the largely neutrophilic inflammatory response that perpetuate the airway injury.
- Localized BXSIS is most often due to suboptimally treated bacterial infections. BXSIS due to nontuberculous mycobacteria is increasingly recognized: the two predominant phenotypic presentations are elderly men with upper lobe fibrocavitary disease in a background of emphysema, and postmenopausal women with lingular and right middle lobe BXSIS and nodules.
- BXSIS that is more diffuse is generally due to an underlying host disorder such as cystic fibrosis, primary ciliary dyskinesia, disorders of cartilage as seen with the Mounier-Kuhn and Williams-Campbell syndromes, common variable immune deficiency, and allergic bronchopulmonary aspergillosis.
- BXSIS has also been associated with extrapulmonary disorders such as ulcerative colitis and collagen vascular diseases. Severe fibrotic lung diseases from any cause may also result in a form of BXSIS known as traction BXSIS.
- The linchpins in the management of BXSIS are the timely institution of antimicrobials to treat the culprit pathogens isolated and diligent airway clearance measures to improve symptoms and to decrease the frequency of such infections. Surgical lung resection should also be considered for patients with severe localized disease that are recalcitrant to medical treatment.
- Anti-inflammatory agents such as the NSAIDs and the low-dose intermittent macrolides are promising in helping to alleviate symptoms and reduce the rate of disease progression, but recommendations for their use remain to be defined.

References

1. Pasteur MC, Helliwell SM, Houghton SJ, et al: An investigation into causative factors in patients with bronchiectasis. Am J Respir Crit Care Med 162:1277–1284, 2000.
2. Reiff DB, Wells AU, Carr DH, et al: CT findings in bronchiectasis: Limited value in distinguishing between idiopathic and specific types. AJR Am J Roentgenol 165:261–267, 1995.
3. Trucksis M, Swartz MN: Bronchiectasis: A current view. Curr Clin Top Infect Dis 11:170–205, 1991.
4. Barker AL, Bardana EJ: Bronchiectasis: Update of an orphan disease. Am Rev Respir Dis 137:969–978, 1988.
5. Singleton R, Morris A, Redding G, et al: Bronchiectasis in Alaska native children: Causes and clinical courses. Pediatr Pulmonol 29:182–187, 2000.
6. Kennedy TP, Weber DJ: Nontuberculous mycobacteria: An underappreciated cause of geriatric lung disease. Am J Respir Crit Care Med 149:1654–1658, 1994.
7. Prince DS, Peterson DD, Steiner RM, et al: Infection with *Mycobacterium avium* complex in patients without predisposing conditions. N Engl J Med 321:863–868, 1989.
8. Iseman MD, Buschman DL, Ackerson LM: Pectus excavatum and scoliosis: Thoracic anomalies associated with pulmonary disease due to *M. avium* complex. Am Rev Respir Dis 144:914–916, 1991.

9. Wallace RJ Jr: *Mycobacterium avium* complex lung disease and women: Now an equal opportunity disease. Chest 105:6–7, 1994.
10. Westcott JL, Cole SR: Traction bronchiectasis in end-stage pulmonary fibrosis. Radiology 161:665–669, 1986.
11. Shum DKY, Chan SCH, Ip MSM: Neutrophil-mediated degradation of lung proteoglycans: Stimulation by tumor necrosis factor-alpha in sputum of patients with bronchiectasis. Am J Respir Crit Care Med 162:1925–1931, 2000.
12. Comroe JH Jr (ed): Special acts involving breathing. *In* Physiology of Respiration: An Introductory Text (2nd ed). Chicago: Year Book, 1974, pp 229–233.
13. Cole PJ: A new look at the pathogenesis, management of persistent bronchial sepsis: A "vicious circle" hypothesis and its logical therapeutic connotations. In Davies RJ (ed): Strategies for the Management of Chronic Bronchial Sepsis. Oxford: Medicine Publishing Foundation, 1984, pp 1–20.
14. Gaga M, Bentley AM, Humbert M, et al: Increases in CD4 T lymphocytes, macrophages, neutrophils and interleukin 8 positive cells in the airways of patients with bronchiectasis. Thorax 53:685–691, 1998.
15. Tager I, Speizer FE: Role of infection in chronic bronchitis. N Engl J Med 292:563–571, 1975.
16. Evans SA, Turner SM, Bosch BJ, et al: Lung function in bronchiectasis: The influence of *Pseudomonas aeruginosa*. Eur Respir J 9:1001–1004, 1996.
17. Wilson CB, Jones PW, O'Leary CJ, et al: Effect of sputum bacteriology on the quality of life of patients with bronchiectasis. Eur Respir J 10:1754–1760, 1997.
18. King PT, Holdsworth SR, Freezer NJ, et al: Microbiologic follow-up study in adult bronchiectasis. Respir Med 101:1633–1638, 2007.
19. Fowler SJ, French J, Screaton NJ, et al: Nontuberculous mycobacteria in bronchiectasis: Prevalence and patient characteristics. Eur Respir J 28:1204–1210, 2006.
20. Kunst H, Wickremasinghe M, Wells A, Wilson R: Nontuberculous mycobacterial disease and *Aspergillus*-related lung disease in bronchiectasis. Eur Respir J 28:352–357, 2006.
21. Costerton JW: The etiology and persistence of cryptic bacterial infections: A hypothesis. Rev Infect Dis 6:S608–S616, 1984.
22. Singh PK, Schaefer AL, Parsek MR, et al: Quorum-sensing signals indicate that cystic fibrosis lungs are infected with bacterial biofilms. Nature 407:762–764, 2000.
23. Costerton JW, Stewart PS, Greenberg EP: Bacterial biofilms: A common cause of persistent infections. Science 284:1318–1320, 1999.
24. Stewart PS, Costerton JW: Antibiotic resistance of bacteria in biofilms. Lancet 358:135–138, 2001.
25. Ceri H, Olson ME, Stremick C, et al: The Calgary biofilm device: New technology for rapid determination of antibiotic susceptibilities of bacterial biofilms. J Clin Microbiol 37:1771–1776, 1999.
26. National Institutes of Health Consensus Development Conference: Genetic testing for cystic fibrosis. Arch Intern Med 159: 1529–1539, 1999.
27. Boyle MP: Adult cystic fibrosis. JAMA 298:1787–1793, 2007.
28. DeGroote MA, Huitt G, Fulton K, et al: Retrospective analysis of aspiration risk and genetic predisposition in bronchiectasis patients with and without non-tuberculous mycobacteria infection. Am J Respir Crit Care Med 163:A763, 2001.
29. Ziedalski TM, Kao PN, Henig NR, et al: Prospective analysis of cystic fibrosis transmembrane regulator mutations in adults with bronchiectasis or pulmonary nontuberculous mycobacterial infection. Chest 130:995–1002, 2006.
30. Kim RD, Greenberg DE, Ehrmantraut ME, et al: Pulmonary nontuberculous mycobacterial disease: Prospective study of a distinct preexisting syndrome. Am J Respir Crit Care Med 178:1066–1074, 2008.
31. Groman JD, Meyer ME, Wilmott RW, et al: Variant of cystic fibrosis phenotypes in the absence of CFTR mutations. N Engl J Med 347:401–407, 2002.
32. Kerem E, Corey M, Kerem BS, et al: The relation between genotype and phenotype in cystic fibrosis—Analysis of the most common mutation (delta F508). N Engl J Med 323:1517–1522, 1990.
33. Gilljam M, Moltyaner Y, Downey GP: Airway inflammation and infection in congenital bilateral absence of the vas deferens. Am J Respir Crit Care Med 169:174–179, 2004.
34. Accurso FJ, Sontag MK: Seeking modifier genes in cystic fibrosis. Am J Respir Crit Care Med 167:289–293, 2003.
35. Cunningham-Rundles C, Bodian C: Common variable immunodeficiency: Clinical and immunological features of 248 patients. Clin Immunol 92:34–48, 1999.
36. Hill SL, Mitchell JL, Burnett D, et al: IgG subclasses in the serum and sputum from patients with bronchiectasis. Thorax 53:463–468, 1998.
37. Chipps BE, Talamo RC, Winkelstein JA: IgA deficiency, recurrent pneumonias, and bronchiectasis: Clinical conference in pulmonary disease from the Department of Pediatrics, the Johns Hopkins University School of Medicine. Chest 73:519–526, 1978.
38. Freeman AF, Holland SM: The hyper-IgE syndromes. Immunol Allergy Clin North Am 28:277–291, 2008.
39. Holland SM, DeLeo FR, Elloumi HZ, et al: STAT3 mutations in the hyper-IgE syndrome. N Engl J Med 357:1608–1619, 2007.
40. Chan ED, Feldman NE, Chmura K: Do mutations of the alpha-1-antitrypsin gene predispose to non-tuberculous mycobacterial infection? Am J Respir Crit Care Med 169:A132, 2004.
41. Shin MS, Ho K-J: Bronchiectasis in patients with alpha-1-antitrypsin deficiency: A rare occurrence? Chest 104:1384–1386, 1993.
42. Tomashefski JF Jr, Crystal RG, Wiedemann HP, et al and the Alpha 1-Antitrypsin Deficiency Registry Study Group: The bronchopulmonary pathology of alpha-1 antitrypsin (AAT) deficiency: Findings of the death review committee of the national registry for individuals with severe deficiency of alpha-1 antitrypsin. Hum Pathol 35:1452–1461, 2004.
43. Chan ED, Kaminska AM, Gill W, et al: Alpha-1-antitrypsin (AAT) anomalies are associated with lung disease due to rapidly growing mycobacteria and AAT inhibits *Mycobacterium abscessus* infection of macrophages. Scand J Infect Dis 39:690–696, 2007.
44. De Serres FJ: Worldwide racial and ethnic distribution of alpha-1-antitrypsin deficiency: Summary of an analysis of published genetic epidemiologic surveys. Chest 122:1818–1829, 2002.
45. Dahl M, Tybjaerg-Hansen A, Lange P, et al: Change in lung function and morbidity from chronic obstructive pulmonary disease in alpha-1-antitrypsin MZ heterozygotes: A longitudinal study of the general population. Ann Intern Med 136:270–279, 2002.
46. Lieberman J: Augmentation therapy reduces frequency of lung infections in antitrypsin deficiency: A new hypothesis with supporting data. Chest 118:1480–1485, 2000.
47. Mulgrew AT, Taggart CC, Lawless MW, et al: Z alpha1-antitrypsin polymerizes in the lung and acts as a neutrophil chemoattractant. Chest 125:1952–1957, 2004.
48. Cantin AM, Woods DE: Aerosolized prolastin suppresses bacterial proliferation in a model of chronic *Pseudomonas aeruginosa* lung infection. Am J Respir Crit Care Med 160:1130–1135, 1999.
49. Shapiro L, Pott GB, Ralston AH: Alpha-1-antitrypsin inhibits human immunodeficiency virus type 1. FASEB J 15:115–122, 2001.
50. Hayes VM, Gardiner-Garden M: Are polymorphic markers within the alpha-1-antitrypsin gene associated with risk of human immunodeficiency virus disease? J Infect Dis 188:1205–1208, 2003.
51. Cuvelier A, Muir J-F, Hellot M-F, et al: Distribution of alpha-1-antitrypsin alleles in patients with bronchiectasis. Chest 117:415–419, 2000.
52. Parr DG, Guest PG, Reynolds JH, et al: Prevalence and impact of bronchiectasis in alpha1-antitrypsin deficiency. Am J Respir Crit Care Med 176:1215–1221, 2007.

52a. Amirav I, Cohen-Cymberknoh M, Shoseyov D, Kerem E. Primary ciliary dyskinesia: prospects for new therapies, building on the experience in cystic fibrosis. Paediatr Respir Rev 10:58–62, 2009.

52b. Leigh MW, Zariwala MA, Knowles MR. Primary ciliary dyskinesia: improving the diagnostic approach. Curr Opin Pediatr 21:320–325, 2009.

53. Lillington GA: Dyskinetic cilia and Kartagener's syndrome: Bronchiectasis with a twist. Clin Rev Allergy Immunol 21:65–69, 2001.
54. Geremek M, Witt M: Primary ciliary dyskinesia: Genes, candidate genes and chromosomal regions. J Appl Genet 45:347–361, 2004.

55. Noone PG, Bali D, Carson JL, et al: Discordant organ laterality in monozygotic twins with primary ciliary dyskinesia. Am J Med 82:155–160, 1999.
56. Noone PG, Leigh MW, Annuti A: Primary ciliary dyskinesia: Diagnostic and phenotypic features. Am J Respir Crit Care Med 169:459–467, 2004.
57. Escudier E, Couprie M, Duriez B, et al: Computer-assisted analysis helps detect inner dynein arm abnormalities. Am J Respir Crit Care Med 166:1257–1262, 2002.
58. Woodring JH, Howard RSI, Rehm SR: Congenital tracheobronchomegaly (Mounier-Kuhn syndrome): A report of 10 cases and review of the literature. J Thorac Imaging 6:1–10, 1991.
59. Abdallah EG, Ashton RW: Mounier-Kuhn syndrome: Overcoming a lack of recognition. South Med J 101:14–15, 2008.
60. Jones VF, Eid NS, Franco SM, et al: Familial congenital bronchiectasis: Williams-Campbell syndrome. Pediatr Pulmonol 16:263–267, 1993.
61. George J, Jain R, Tariq SM: CT bronchoscopy in the diagnosis of Williams-Campbell syndrome. Respirology 11:117–119, 2006.
62. Palmer SM Jr, Layish DT, Kussin PS, et al: Lung transplantation for Williams-Campbell syndrome. Chest 113:534–537, 1998.
63. Foster ME, Foster DR: Bronchiectasis and Marfan's syndrome. Postgrad Med J 56:718–719, 1980.
64. Wood JR, Bellamy D, Child AH, et al: Pulmonary disease in patients with Marfan syndrome. Thorax 39:780–784, 1984.
65. Ordway D, Henao-Tamayo M, Smith E, et al: Animal model of *Mycobacterium abscessus* lung infection. J Leukoc Biol 83:1502–1511, 2008.
66. Reich JM, Johnson NR: *Mycobacterium avium* complex pulmonary disease presenting as isolated lingular or middle lobe pattern: The Lady Windermere syndrome. Chest 101:1605–1609, 1992.
67. Iseman MD: That's no lady (letter). Chest 109:1411, 1996.
68. Iseman MD: That's no lady, revisited (letter). Chest 111:255, 1997.
69. Tsuyuguchi K, Suzuki K, Matsumoto H, et al: Effect of oestrogen on *Mycobacterium avium* complex pulmonary infection in mice. Clin Exp Immunol 123:428–434, 2001.
70. Olsson T, Bjornstad-Pettersen H, Stjernberg N: Bronchostenosis due to sarcoidosis: A cause of atelectasis and airway obstruction simulating pulmonary neoplasm and chronic obstructive pulmonary disease. Chest 75:663–666, 1979.
71. Walker WC: Pulmonary infections and rheumatoid arthritis. Q J Med 142:239–250, 1967.
72. Solanki T, Neville E: Bronchiectasis and rheumatoid disease: Is there an association? Br J Rheumatol 31:691–693, 1992.
73. Perez T, Remy-Jardin M, Cortet B: Airways involvement in rheumatoid arthritis. Am J Respir Crit Care Med 157:1658–1665, 1998.
74. Remy-Jardin M, Remy J, Cortet B, et al: Lung changes in rheumatoid arthritis. Radiology 193:375–382, 1994.
75. Swinson DR, Symmons D, Suresh U, et al: Decreased survival in patients with co-existent rheumatoid arthritis and bronchiectasis. Br J Rheumatol 36:689–691, 1997.
76. Rosenow CE, Strimlan CV, Muhm JR, et al: Pleuropulmonary manifestations of ankylosing spondylitis. Mayo Clin Proc 52:641–649, 1977.
77. Casserly IP, Fenlon HM, Breatnach E, et al: Lung findings on high-resolution computed tomography in idiopathic ankylosing spondylitis: Correlation with clinical findings, pulmonary function testing and plain radiography. Br J Rheumatol 36:677–682, 1997.
78. Davidson PT, Khankjo V, Goble M, et al: Treatment of disease due to *Mycobacterium intracellulare*. Rev Infect Dis 3:1052–1059, 1981.
79. Fenlon HM, Doran M, Sant SM, et al: High-resolution chest CT in systemic lupus erythematosus. AJR Am J Roentgenol 166:301–307, 1996.
80. Constantopoulos SH, Padadimitriou CS, Moutsopoulos HM: Respiratory manifestations in primary Sjögren's syndrome: A clinical, functional, and histologic study. Chest 88:226–229, 1985.
81. Robinson DA, Meyer CF: Primary Sjögren's syndrome associated with recurrent sinopulmonary infections and bronchiectasis. J Allergy Clin Immunol 94:263–264, 1994.
82. Vitali C, Tavoni A, Viegi G, et al: Lung involvement in Sjögren's syndrome: A comparison between patients with primary and with secondary syndrome. Ann Rheum Dis 44:455–461, 1985.
83. Camus P, Colby TV: The lung in inflammatory bowel disease. Eur Respir J 15:5–10, 2000.
84. Sharma S, Eschun G. What are the pulmonary manifestations of inflammatory bowel disease? J Respir Dis 28:227–234, 2007.
85. Tillie-Leblond I, Wallaert B, Leblond D, et al: Respiratory involvement in relapsing polychondritis: Clinical, functional, endoscopic, and radiographic evaluations. Medicine (Baltimore) 77:168–176, 1998.
86. Tsang KW, Lam WK, Kwok E, et al: H*elicobacter pylori* and upper gastrointestinal symptoms in bronchiectasis. Eur Respir J 14:1345–1350, 1999.
87. De Groote MA, Huitt G, Fulton K, et al: Retrospective analysis of aspiration risk and genetic predisposition in bronchiectasis patients with and without non-tuberculous mycobacteria infection. Am J Respir Crit Care Med 163:A763, 2003.
88. Harding SM: Recent clinical investigations examining the association of asthma and gastroesophageal reflux. Am J Med 115: 39S–44S, 2003.
89. Raghu G: The role of gastroesophageal reflux in idiopathic pulmonary fibrosis. Am J Med 115:60S–64S, 2003.
90. Zerbib F, Guisset O, Lamouliatte H, et al: Effects of bronchial obstruction on lower esophageal sphincter motility and gastroesophageal reflux in patients with asthma. Am J Respir Crit Care Med 166:1206–1211, 2002.
91. Lagergren J, Bergstrom R, Adami H-O, et al: Association between medications that relax the lower esophageal sphincter and risk for esophageal adenocarcinoma. Ann Intern Med 133:165–175, 2000.
92. Halsey KD, Wald A, Meyer KC, et al: Non-acidic supraesophageal reflux associated with diffuse alveolar damage and allograft dysfunction after lung transplantation: A case report. J Heart Lung Transplant 27:564–567, 2008.
93. McGuinness G, Naidich DP, Garay SM, et al: AIDS associated bronchiectasis: CT features. J Comput Assist Tomogr 17:260–266, 1993.
94. Verghese A, al-Samman M, Nabhan D, et al: Bacterial bronchitis and bronchiectasis in human immunodeficiency virus infection. Arch Intern Med 154:2086–2091, 1994.
95. Lee WL, Downey GP: Leukocyte elastase: Physiological functions and role in acute lung injury. Am J Respir Crit Care Med 164:896–904, 2001.
96. Meyer KC, Nunley DR, Dauber JH, et al: Neutrophils, unopposed neutrophil elastase, and alpha-1-antiprotease defenses following human lung transplantation. Am J Respir Crit Care Med 164:97–102, 2001.
97. Diaz PT, King MA, Pacht ER, et al: Increased susceptibility to pulmonary emphysema among HIV-seropositive smokers. Ann Intern Med 132:369–372, 2000.
98. Bard M, Couderc L-J, Saimot AG, et al: Accelerated obstructive pulmonary disease in HIV infected patients with bronchiectasis. Eur Respir J 11:771–775, 1998.
99. Cordasco E: Clinical features of the yellow nail syndrome. Cleve Clin J Med 57:472–476, 1990.
100. Brofman JD, Hall JB, Scott W, et al: Yellow nails, lymphedema and pleural effusion: Treatment of chronic pleural effusion with pleuroperitoneal shunting. Chest 97:743–745, 1990.
101. Varney VA, Cumberworth V, Sudderick R, et al: Rhinitis, sinusitis and the yellow nail syndrome: A review of symptoms and response to treatment in 17 patients. Clin Otolaryngol 19:237–240, 1994.
102. Corless JA, Warburton CJ: Leukotriene receptor antagonists for non-cystic fibrosis bronchiectasis (Cochrane Review). *In* The Cochrane Library. Oxford: Update Software, 2002.
103. Lasserson T, Holt K, Evans DJ, et al: Anticholinergic therapy for bronchiectasis (Cochrane Review). In The Cochrane Library. Oxford: Update Software, 2002.
104. Crockett AJ, Cranston JM, Latimer KM, et al: Mucolytics for bronchiectasis (Cochrane Review). In The Cochrane Library. Oxford: Update Software, 2002.
105. Corless JA, Warburton CJ: Surgery vs. non-surgical treatment for bronchiectasis (Cochrane Review). *In* The Cochrane Library. Oxford: Update Software, 2002.

106. Steele K, Lasserson JA, Greenstone M: Oral methyl-xanthines for bronchiectasis (Cochrane Review). *In* The Cochrane Library. Oxford: Update Software, 2002.
107. Lasserson T, Holt K, Greenstone M: Oral steroids for bronchiectasis (stable and acute exacerbations) (Cochrane Review). *In* The Cochrane Library. Oxford: Update Software, 2002.
108. Sheikh A, Nolan D, Greenstone M: Long-acting beta-2-agonists for bronchiectasis (Cochrane Review). *In* The Cochrane Library. Oxford: Update Software, 2002.
109. Bradley J, Moran F, Greenstone M: Physical training for bronchiectasis (Cochrane Review). *In* The Cochrane Library. Oxford: Update Software, 2002.
110. Elkins MR, Robinson M, Rose BR, et al: A controlled trial of long-term inhaled hypertonic saline in patients with cystic fibrosis. N Engl J Med 354:229–240, 2006.
111. Wills P, Greenstone M: Inhaled hyperosmolar agents for bronchiectasis. Cochrane Database Syst Rev 2:CD002996, 2006.
112. Evans DJ, Bara AI, Greenstone M: Prolonged antibiotic for purulent bronchiectasis. Cochrane Database Syst Rev 4:CD001392, 2003.
113. Ramsey BW, Pepe MS, Quan JM, et al: Intermittent administration of inhaled tobramycin in patients with cystic fibrosis. Cystic Fibrosis Inhaled Tobramycin Study Group. N Engl J Med 340:23–30, 1999.
114. Barker AF, Couch L, Fiel SB, et al: Tobramycin solution for inhalation reduces sputum P*seudomonas aeruginosa* density in bronchiectasis. Am J Respir Crit Care Med 162:481–485, 2000.
114a. Ilowite J, Spiegler P, Kessler H. Pharmacological treatment options for bronchiectasis: focus on antimicrobial and anti-inflammatory agents. Drugs 69:407–419, 2009.
115. Tamaoki J, Chiyotani A, Kobayashi K, et al: Effect of indomethacin in bronchorrhea in patients with chronic bronchitis, diffuse panbronchiolitis, or bronchiectasis. Am Rev Respir Dis 145:548–552, 1992.
116. Llewellyn-Jones CG, Johnson MM, Mitchell JL, et al: In vivo study of indomethacin in bronchiectasis: Effect on neutrophil function and lung secretion. Eur Respir J 8:1479–1487, 1995.
117. Lands LC, Stanojevic S: Oral non-steroidal anti-inflammatory drug therapy for cystic fibrosis (review). Cochrane Database Syst Rev 2:CD001505, 2007.
118. Kapur N, Chang AB: Oral non steroid anti-inflammatories for children and adults with bronchiectasis (review). Cochrane Database Syst Rev 4:CD006427, 2007.
119. Ross KR, Chmiel JF, Konstan MW: The role of inhaled corticosteroids in the management of cystic fibrosis. Paediatr Drug 11:101–113, 2009.
120. Ilowite J, Spiegler P, Chawla S: Bronchiectasis: New findings in the pathogenesis and treatment of this disease. Curr Opin Infect Dis 21:163–167, 2008.
121. Yalcon E, Kiper N, Ozcelik U, et al: Effects of clarithromycin on inflammatory parameters and clinical conditions in children with bronchiectasis. J Clin Pharm Ther 31:49–55, 2006.
122. Tagaya E, Tamaoki J, Kondo M, Nagai A: Effect of a short course of clarithromycin therapy on sputum production in patients with chronic airway hypersecretion. Chest 122:213–218, 2002.
123. Cymbala AA, Edmonds LC, Bauer MA, et al: The disease-modifying effects of twice-weekly oral azithromycin in patients with bronchiectasis. Treat Respir Med 4:117–122, 2005.
124. Equi A, Balfour-Lynn IM, Bush A, et al: Long term azithromycin in children with cystic fibrosis: A randomised, placebo-controlled crossover trial. Lancet 360:978–984, 2002.
125. Kharitonov SA, Wells AU, O'Connor BJ, et al: Elevated levels of exhaled nitric oxide in bronchiectasis. Am J Respir Crit Care Med 151:1889–1893, 1995.
126. Langenderfer B: Alternatives to percussion and postural drainage. A review of mucus clearance therapies: Percussion and postural drainage, autogenic drainage, positive expiratory pressure, flutter valve, intrapulmonary percussive ventilation, and high-frequency chest compression with the ThAIRapy Vest. J Cardiopulm Rehabil 18:283–289, 1998.
127. Weintraub SJ, Eschenbacher WL: The inhaled bronchodilators ipratropium bromide and metaproterenol in adults with CF. Chest 95:861–864, 1989.
128. Sanchez I, Holbrown J, Chernick V: Acute bronchodilator response to a combination of beta-adrenergic and anticholinergic agents in patients with cystic fibrosis. J Pediatr 120:486–488, 1992.
129. Daviskas E, Robinson M, Anderson SD, et al: Osmotic stimuli increase clearance of mucus in patients with mucociliary dysfunction. J Aerosol Med 15:331–341, 2002.
130. Shak S, Capon DJ, Hellmiss R: Recombinant human DNase I reduces the viscosity of cystic fibrosis sputum. Proc Natl Acad Sci U S A 87:9188–9192, 1990.
131. Fuchs HJ, Borowitz DS, Christiansen DH: Effect of aerosolized recombinant human DNase on exacerbations of respiratory symptoms and on pulmonary function in patients with cystic fibrosis: The Pulmozyme Study Group. N Engl J Med 331:637–642, 1994.
132. O'Donnell AE, Barker AF, Ilowite JS, et al: Treatment of idiopathic bronchiectasis with aerosolized recombinant human DNase I. Chest 113:1329–1334, 1998.
133. Paul K, Rietschel E, Ballmann M, et al: Effect of treatment with dornase alpha on airway inflammation in patients with cystic fibrosis. Am J Respir Crit Care Med 169:719–725, 2004.
134. Rosenstein BJ, Eigen H: Risks of alternate-day prednisone in patients with cystic fibrosis. Pediatrics 87:245–246, 1991.
135. Eigen H, Rosenstein BJ, FitzSimmons SC: A multicenter study of alternate-day prednisone therapy in patients with cystic fibrosis: Cystic Fibrosis Foundation Prednisone Trial Group. J Pediatr 126:515–523, 1995.
136. Lai HC, FitzSimmons SC, Allen DB: Risk of persistent growth impairment after alternate-day prednisone treatment in children with cystic fibrosis. N Engl J Med 342:851–859, 2000.
137. Tsang KW, Ho PI, Chan KN, et al: A pilot study of low-dose erythromycin in bronchiectasis. Eur Respir J 13:361–364, 1999.
138. Van Haren EH, Lammers JWJ, Festen J: The effects of the inhaled corticosteroid budesonide on lung function and bronchial hyperresponsiveness in adult patients with cystic fibrosis. Respir Med 89:209–214, 1995.
139. Nikolaizik WH, Schoni MH: Pilot study to assess the effect of inhaled corticosteroids on lung function in patients with cystic fibrosis. J Pediatr 128:271–274, 1996.
140. Garey KW, Alwani A, Danziger LH, et al: Tissue reparative effects of macrolide antibiotics in chronic inflammatory sinopulmonary disease. Chest 123:261–265, 2003.
141. Equi A, Balfour-Lynn IM, Bush A: Long term azithromycin in children with cystic fibrosis: A randomized, placebo-controlled crossover trial. Lancet 360:978–984, 2002.
142. Wolter J, Seeney S, Bell S: Effect of long-term treatment with azithromycin on disease parameters in cystic fibrosis: A randomised trial. Thorax 57:212–216, 2002.
143. Saiman L, Marshall BC, Mayer-Hamblett N: A multicenter, randomized, placebo controlled, double-blind trial of azithromycin in patients with cystic fibrosis chronically infected with P*seudomonas aeruginosa*. JAMA 290:1749–1956, 2003.
144. Konstan MW, Byard PJ, Hoppel CL: Effect of high-dose ibuprofen in patients with cystic fibrosis. N Engl J Med 332:848–854, 1995.
145. Evans DJ, Bara A, Greenstone M: Prolonged antibiotics for bronchiectasis. Thorax 56:52, 2001.
146. Evans DJ, Greenstone M: Long-term antibiotics in the management of non-CF bronchiectasis—Do they improve outcome? Respir Med 97:851–858, 2003.
147. Gibson RL, Emerson J, McNamara S, et al: Significant microbiological effect of inhaled tobramycin in young children with cystic fibrosis. Am J Respir Crit Care Med 167:841–849, 2003.
148. Moss RB: Administration of aerosolized antibiotics in cystic fibrosis patients. Chest 120:107S–113S, 2001.
149. Barker AF, Couch L, Fiel SB, et al: Tobramycin solution for inhalation reduces sputum P*seudomonas aeruginosa* density in bronchiectasis. Am J Respir Crit Care Med 162:481–485, 2000.
150. Dogan R, Alp M, Kaya S, et al: Surgical treatment of bronchiectasis: A collective review of 487 cases. Thorac Cardiovasc Surg 37:183–186, 1989.
151. Pomerantz M, Denton JR, Huitt GA, et al: Resection of the right middle lobe and lingula for mycobacterial infection. Ann Thorac Surg 62:990–993, 1996.
152. Ayed AK: Resection of the right middle lobe and lingula in children for middle lobe/lingula syndrome. Chest 125:38–42, 2004.

CHAPTER 43

DISORDERS OF THE UPPER AIRWAYS

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INTRODUCTION

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Structure and Function
Allergic and Nonallergic Rhinitis

THE PARANASAL SINUSES
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THE PHARYNX AND HYPOPHARYNX
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INTRODUCTION

The upper airways—anatomically complicated structures that extend from the airway openings at the nares and lips to the trachea—serve numerous physiologic functions. Their respiratory function includes filtering, conditioning, and conveying air to the lungs. The nasal airway also supports the sense of olfaction; the oral airway, pharynx, and larynx also support deglutition, phonation, and coughing. These processes have been studied extensively. This chapter focuses on the role of the upper airways in breathing and on disorders that affect this function. We also discuss some of the air-conditioning functions of the nasal mucosa because they have a direct impact on the health of the lower airways.

The term *upper airways* includes several anatomically distinct regions (Figs. 43-1 and 43-2). The nose constitutes the upper segment, followed by the nasopharyngeal and oropharyngeal airways, which extend from the nasal choanae and oral cavity to the supraglottic space. The paranasal sinuses drain into the nasal cavities and are attached to the lateral, posterior, and superior aspects of the nose. The larynx divides the upper and lower airways, although some place it in the thoracic inlet.

The major function of the upper airway is to control and coordinate the passage of air, liquids, and food to the appropriate site. This function requires exquisite neural control of numerous muscle groups. The actions of pharyngeal sphincters and glottic adductors enable complete occlusion of the airways at specific sites during deglutition. The action of dilators of several airway segments and the transition from solely nasal to oronasal breathing enable augmentation of airflow during exercise.[1-6] Narrowing and indeed occlusion of the upper airways can result from structural bony or soft tissue abnormalities (either intrinsic or extrinsic to the airway lumen or due to dysregulation of normal physiologic function). Following simple principles of airflow dynamics,[7-10] narrowing in certain parts of the upper airway can result from dynamic collapse of these segments when resistance to flow requires greater inspiratory efforts and hence greater drops in upper airway intraluminal pressure relative to ambient atmospheric pressure. Understanding of the structural and functional characteristics of the upper airway allows one to appreciate its vital and essential connection to the functions of the lower respiratory tract.

THE NOSE

Structure and Function

Air enters the nose through the nasal vestibule, an approximately 1-cm channel in the cartilaginous portion of the nose. At the end of the vestibule lies the nasal valve, the narrowest area of the passages (see Fig. 43-1). Thereafter, the nasal passages become convoluted by the folds of the turbinates. The passage of the nasal vestibule is narrow, and the linear velocity of inhaled air becomes quite high.[11,12] The combination of high linear velocities and the transition from upward to horizontal flow that occurs just beyond the nasal valve favors the deposition of most airborne particles in the anterior nose. Air velocities are lower in the main nasal passages (beyond the

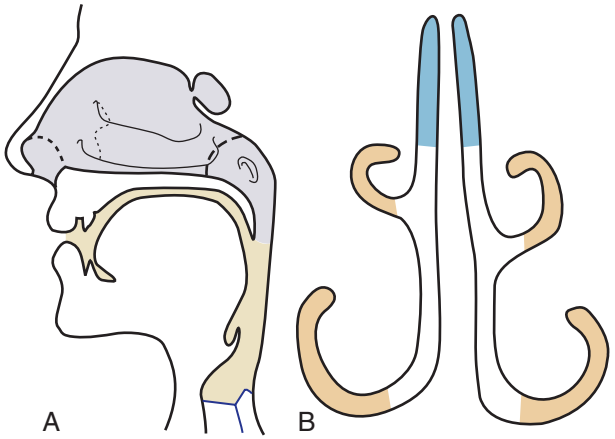


FIGURE 43-1 ■ Upper airways and nasal segments. **A,** Nasal (*gray stripes*) and oropharyngeal (*gold shading*) airways are shown with the nasal septum omitted. The *dashed line on the left* marks the beginning of the nasal valve; the *dotted line* marks the approximate beginning of the ciliated mucosa; the *dashed line on the right* marks the termination of the nasal septum. Note the key position of the soft palate for control of the division between oral and nasal paths for airflow. **B,** This section through the main nasal passage shows the septum and folds of the turbinates. The *blue colored areas* are the olfactory region, through which little inspiratory airflow passes. The *gold colored* areas are meatal spaces, through which there is little airflow. The *clear space* is a region of major inspiratory airflow. (Redrawn from Proctor DF, Anderson I [eds]: The Nose: Upper Airway Physiology and the Atmospheric Environment. Amsterdam: Elsevier Biomedical, 1982.)

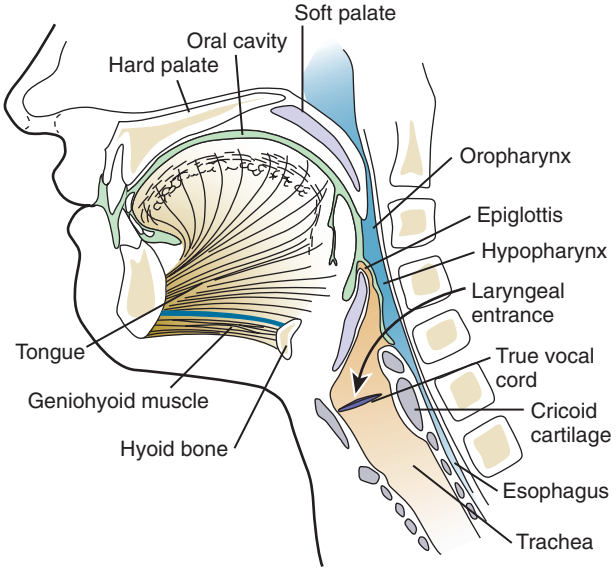


FIGURE 43-2 ■ The major structures that make up the oropharyngeal and laryngeal airway. (Redrawn from Wiegand L, Zwillich CW: Pathogenesis of obstructive sleep apnea: Role of the pharynx. Semin Respir Med 9:540–546, 1988.)

valve) where the cross-sectional area is greater. This reduction in air velocity allows prolonged contact of inspired air with the nasal mucosa, enabling the nose to modify the temperature and water vapor content[13,14] and to remove airborne pathogens and pollutants.[15,16]

Neuromuscular regulation of the skeletal muscles that overlie the cartilaginous portion of the nose (Table 43-1) plays a major role in the control of nasal vestibule patency. Contraction of the transverse part of the alae nasi narrows this segment, whereas activation of the alar part of this muscle and of the depressor septi widens it.[3] When the ventilatory drive is elevated, the pressure difference from the nasal inlet to the pharynx increases as inspiratory effort increases. To avoid collapse of the alar cartilages and limitation of flow during inspiration, a rise in dilator activity at the nasal vestibule is thought to decrease both the resistance and the collapsibility of this nasal segment.[1,8,17] Obstruction in the nasal cavity (which results primarily from vascular engorgement) leads to increases in the resistance downstream to the site of inspiratory airflow limitation in the nasal vestibule.[18] These increases in downstream resistance reduce nasal airflow and increase the driving pressure required to reach maximal flow. Mouth breathing remains the only effective strategy to increase inspiratory flow when elevated nasal resistance occurs.

The specialized functions of the nose are of great importance to the lower airways.[19] A classic example derives from the strong protective effect that nasal breathing has on exercise-induced asthma.[20,21] Nasal functions are attributable to particular anatomic features of the nasal mucosa and are facilitated by the previously described airflow patterns. The nasal mucosa has several key features including numerous submucosal glands and goblet cells in the respiratory epithelium,[22] a dense subepithelial network of fenestrated capillaries,[23] a vascular network of capacitance vessels (venous sinusoids)[24] that rapidly pool blood and engorge mucosal tissue,[25] and an abundance of sensory nerve endings that interdigitate between epithelial cells and act as nonspecialized nociceptors.[26] Production of mucus by seromucous glands and goblet cells provides the trapping material for particles entering the airways with inhaled air. The contents of nasal secretions, which include immunoglobulins (particularly secretory IgA), antibacterial chemicals (lysozyme, lactoferrin), or even antioxidants (uric acid), offer innate and specific immune functions and chemical protection for the lower airways.[27,28] The nasal and particularly the paranasal sinus epithelium are rich in inducible nitric oxide synthase, which confers the ability to produce nitric oxide,[29,30] a substance with antibacterial, antiviral, and smooth muscle–relaxant properties. Rapid passage of blood through the subepithelial capillaries acts as a heat exchanger with tremendous capacity for warming inhaled air. By engorging the tissue, capacitance vessels increase the contact surface with inhaled air and facilitate heat and water exchange. The fenestrae of the subepithelial capillaries are thought to be important in allowing rapid water transportation from the intravascular space to the epithelial layer. Water moves passively through the intraepithelial junctions and effectively humidifies inhaled air. Finally, the nociceptors of the nasal mucosa generate several central reflexes, such as the sneezing reflex, as well as nasonasal reflexes through which the glandular apparatus and the vasculature are activated. Neural reflexes act in concordance to protect the airways.

TABLE 43-1. Muscles Surrounding the Upper Airways

Region	Stabilizing or Widening	May Widen or Narrow	Narrowing or Closing
Nose	Dilator naris	Vascular smooth muscle	Compressor naris
	Alae nasi		
Nasopharynx		Tensor veli palatini	Levator veli palatini
			Palatopharyngeus
Mouth and pharynx	Lateral pterygoid	Salpingopharyngeus	Medial pterygoid
	Genioglossus	Muscles of the lips	Pharyngeal constrictors
	Digastric	Masseter	Pterygopharyngeus
	Mylohyoid	Glossopalatinus	Buccopharyngeus
	Geniohyoid	Omohyoid	Stylopharyngeus
	Stylohyoid	Thyrohyoid	Mylopharyngeus
		Sternohyoid	Glossopharyngeus
		Sternothyroid	Chondropharyngeus
			Ceratopharyngeus
			Thyropharyngeus
			Cricopharyngeus
			Styloglossus
			Hyoglossus
Larynx	Cricoarytenoid posterior	Cricothyroid	Aryepiglottic
			Interarytenoid
			Cricoarytenoid lateralis
			Thyroarytenoid
Trachea			Smooth muscle

Allergic and Nonallergic Rhinitis

Nasal symptoms—sneezing, rhinorrhea, congestion, posterior nasal drainage—are familiar manifestations of the common cold, but they represent the basic repertoire of physiologic responses of the nose to a variety of allergic and nonallergic stimuli. In many circumstances of nonallergic rhinitis, the underlying etiology is nonspecific or not known.

Classification and Epidemiology

Allergic rhinitis is classified into episodic, seasonal, and perennial on the basis of the duration of symptoms. Most recently, a classification into intermittent and persistent rhinitis has been proposed.[31] Most patients with nonallergic rhinitis belong to an "unknown etiology" group. This group can be further classified into three conditions: nonallergic hyperplastic (inflammatory) rhinosinusitis; nonallergic, noninflammatory rhinopathy (also referred to as "vasomotor rhinitis"); and nonallergic rhinitis with eosinophilia syndrome (NARES).[32] Other classifications have also been proposed.[33]

Approximately 30% of the population in industrialized countries reports episodic, seasonal, or chronic symptoms of rhinitis in the absence of an upper respiratory infection.[34] An early estimate of the prevalence of allergic rhinitis in the United States of approximately 20%, from the National Health and Nutrition Examination Survey (NHANES) II,[35] has recently been corroborated, which means that about 60 millions Americans are affected.[36] Because of such a high prevalence and because of the many comorbidities from the respiratory tract (sinus disease, otitis media, lower respiratory involvement), the economic burden of allergic rhinitis is high. Previous estimates of the direct costs in the $1–$3 billion range[37,38] rise to $2–$5 billion when indirect costs are included, but additional information is needed to provide a better picture of the current economic burden.[39]

Pathophysiology

Allergic Rhinitis. Allergic rhinitis, very much like allergic asthma, is characterized by mucosal inflammation and hyperresponsiveness.[40] As in asthma, the allergens responsible are inhaled (aeroallergens). Outdoor allergens, such as plant pollens (especially from ragweed, grasses, and weeds) and molds (e.g., *Alternaria*), typically cause seasonal rhinitis, whereas indoor allergens such as house dust mite, cockroach, and pet danders cause perennial symptoms. In subtropical and tropical climates, where seasons are less distinct, the differentiation between seasonal and perennial patterns of disease is of less value.

As in allergic asthma, a basic cellular event is the interaction of antigen (allergen) with the Fab portion of specific IgE antibody molecules anchored on the surface of two types of cell, the mast cell (a stationary tissue cell) and the basophil (a peripheral blood leukocyte). The interaction between antigen and IgE bridges two nearby IgE molecules, leading to activation of the second-messenger pathways that cause the release of preformed inflammatory mediators, such as histamine and tryptase, and the de novo synthesis and release of others, such as

prostaglandin D_2 and sulfidopeptide leukotrienes. These substances cause acute symptoms including intense local pruritus, sneezing, rhinorrhea, and nasal congestion with airflow limitation. Lacrimation is also part of this constellation. In this acute aspect of the clinical manifestation of allergic rhinitis, histamine is probably the most important mediator because it is the only one to generate the entire spectrum of rhinitic symptoms. In the human nasal mucosa, histamine is the most important chemical mediator of allergic rhinitis.[41] Stimulation of H1, H2 and H3 receptors all play a role in generating the full constellation of histamine-induced symptoms.[42] The cysLT1 and cysLT2 leukotriene receptors are also found in the nasal mucosal blood vessels, and sulfidopeptide leukotrienes are known to increase resistance to airflow.[43]

As in the lower airways, exposure of the nasal mucosa to allergen results not only in an acute (early) reaction but also in a late reaction, which is marked by recrudescence of symptoms, especially nasal congestion, a second wave of inflammatory mediator release, and an increase in the numbers of eosinophils, basophils, mononuclear cells, and neutrophils in nasal secretions.[37,44] Although the late-phase reaction has been studied as a laboratory phenomenon, it is thought to be important in the natural history of allergic rhinitis; the most effective treatment modalities, corticosteroids and immunotherapy, strongly suppress this reaction. In general, late reactions occur in the natural setting after exposure to high levels of allergen.

Mucosal biopsies performed 24 hours after nasal provocation demonstrate an inflammatory infiltrate that is mostly lymphocytic, with eosinophils, basophils, and neutrophils found in increased numbers.[45] As in asthma, immunohistochemical staining and in situ hybridization studies reveal that most of the tissue lymphocytes are $CD4^+$ (helper) T cells, primarily of the T-helper type 2–like subclass. This histologic picture is similar to that seen in chronic allergic rhinitis.[46,47] The exact role of the inflammatory infiltrate in the clinical presentation of the disease has not been elucidated. Among the most important consequences of the activation of leukocytes is the production of cytokines and chemokines (chemokines are also produced by resident epithelial and endothelial cells). These substances are thought to orchestrate the perpetuation of inflammation. Certain cytokines, including interleukin-4 (IL-4) and IL-13, intensify the immune/allergic response, whereas others (e.g., IL-5) activate eosinophils, and others (e.g., histamine-releasing factors) can activate inflammatory cells in the absence of direct allergen stimulation.[48]

Two additional phenomena contribute to the clinical presentation of allergic rhinitis. Priming of the nasal mucosa to allergens was described in the 1960s by Connell,[49] who detailed the observation that, with increasing exposure to allergens, the symptoms are progressively accentuated. This explains why, at the beginning of the pollen season, despite the fact that pollen counts rapidly increase, disease severity remains relatively mild. At the end of the season, despite very low pollen counts, patients with allergic rhinitis remain quite symptomatic. The presence of nonspecific nasal hyperresponsiveness explains the clinical observation that a large number of patients with allergic rhinitis specify not only allergens (e.g., pollen, pets) but also various irritants (e.g., strong perfumes; smoke; cold, dry air) as triggers of their nasal symptoms. Both priming to allergen and nasal hyperresponsiveness can be induced in the laboratory setting with allergen provocation. Allergen-induced increased responsiveness to histamine is thought to reflect primarily hyperresponsiveness of the sensorineural apparatus. Neural hyperresponsiveness has been experimentally demonstrated in natural allergic rhinitis whether seasonal or perennial in nature.[50]

Nonallergic Rhinitis. The pathophysiology of the most common nonallergic rhinitis syndromes is obscure. The histologic features of hyperplastic nonallergic rhinosinusitis are similar to those of its allergic counterpart and are characterized by thickened nasal and paranasal sinus mucosa and excessive mucosal inflammation, as discussed later. The cytokine pattern in the inflamed tissues is somewhat different for allergic and nonallergic disease,[51] but similarities exceed the differences. Hence, it is questionable whether the differences are of clinical significance. Also unknown is the etiology of NARES, but the clinical presentation of this syndrome resembles that of allergic rhinitis.[52] It is possible that an as yet unknown allergen is responsible for this illness or that in these patients, allergic sensitization is limited to the local milieu of the nose. In support of the latter hypothesis, investigators in Newcastle, United Kingdom, have produced data indicating that some patients with inflammatory rhinitis and negative skin tests or no serum-specific IgE against common allergens may develop increased nasal airway resistance after intranasal challenges with house dust mite extract.[53] In nonallergic, noninflammatory rhinopathy (vasomotor rhinitis), not only is nasal mucosal inflammation absent but the few functional abnormalities that have been described appear to be limited to the domain of the autonomic nervous system.[54,55] Many studies indicate that patients with this syndrome benefit from treatment with repetitive nasal applications of capsaicin, which results in defunctionalization or down-regulation of mucosal nociceptors.[56,57] It is possible, therefore, that nonallergic, noninflammatory rhinopathy represents a state of sensorineural imbalance.[58] The etiology, however, remains unknown.

More recently, investigators have shown that laryngopharyngeal reflux is associated with increased nasal symptoms, although the mechanism remains incompletely understood.[59]

Management

Allergic Rhinitis. The management of allergic rhinitis is summarized in Figure 43-3. Management involves environmental control aiming at allergen avoidance, pharmacotherapy, and immunotherapy. Because the offending allergens are the same, environmental control for allergic rhinitis is identical to that recommended for the management of allergic asthma. Perhaps, compared with asthma, pollen avoidance may be more beneficial for allergic rhinitis because the size of pollen particles makes them more likely to deposit in the nasal mucosa. Conversely,

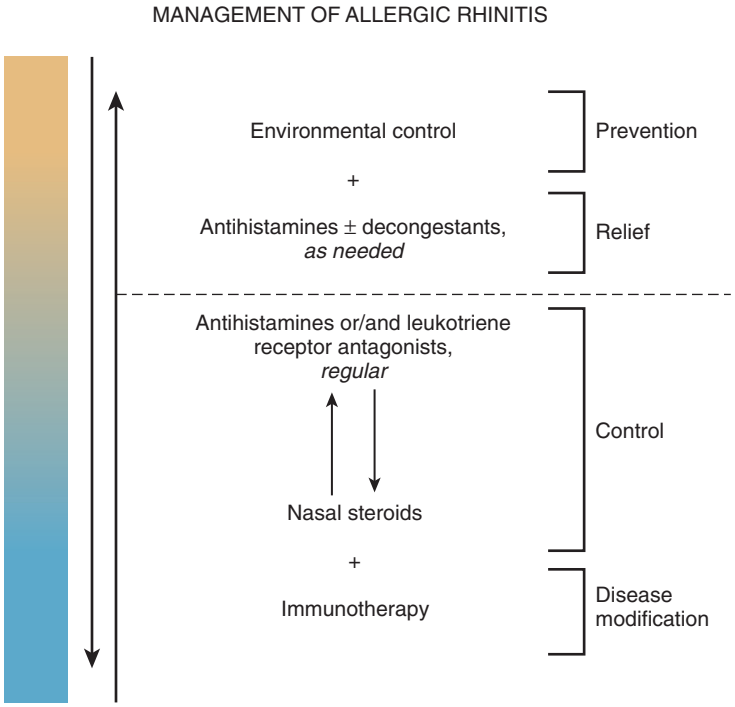


FIGURE 43-3 ■ The management of allergic rhinitis should be based on the severity (*indicated by the increasing darkness of the vertical column*) and the clinical characteristics of the presentation (known environmental exposures, intermittent versus persistent symptoms, predominance of particular symptoms such as sneezing or nasal congestion). In addition, management should be adjusted upward or downward with the goal of optimal control with minimal treatment.

in patients with perennial allergic rhinitis, especially those lacking any evidence of seasonal, pollen-related exacerbations, indoor allergen exposure needs to be targeted as for patients with asthma. A large study has questioned the effectiveness of dust mite control using impermeable bedding covers,[60] but this form of management needs to be evaluated in the context of a more multifaceted strategy involving additional control methods and targeting additional allergens and irritants.

The pharmacologic agents used to treat allergic rhinitis can be separated into two categories: those conferring rapid symptom relief (antihistamines, decongestants, ipratropium bromide) and those controlling the disease on a chronic basis (antihistamines as well as leukotriene receptor antagonists, nasal cromolyn, and nasal glucocorticosteroids). Finally, allergen immunotherapy (allergen vaccines) is widely used as a disease modification strategy.

Antihistamines. Antihistamines are H_1-receptor antagonists.[61] They are effective in reducing pruritus, sneezing, tearing, and rhinorrhea but nasal congestion less so. They can be used on an as-needed basis, although with seasonal disease, they have a better effect if taken either before symptoms develop or continuously. The use of the older compounds (first-generation, or classic, antihistamines) has been limited because of their significant side effects, primarily sedation and systemic anticholinergic activity.[62] Newer agents, first introduced in the early 1980s, are essentially devoid of such adverse effects and can be used with great ease. Also, the newer antihistamines have longer half-lives and active metabolites, which prolong their action. This allows them to be taken once or twice daily, thereby enhancing patient compliance. Currently, four of these agents, cetirizine, desloratadine, fexofenadine, and loratadine, are available in the United States. Additional agents, mizolastine, ebastine, and levocetirizine, are available in many other countries. Azelastine and olopatadine are available in the United States as a nasal spray for topical application. A recent review of the literature supports the current recommendation for nasal antihistamines as first-line treatment for allergic rhinitis.[62a]

Decongestants. Because antihistamines do not have strong clinical potency against nasal congestion, oral and topical decongestants can be used in combination with antihistamines or as single agents.[63] These are α-adrenergic agonists (i.e., vasoconstrictors). The orally available agent pseudephedrine is less potent than the topical ones (oxymetazoline, xylometazoline, phenylephrine) and can cause significant systemic sympathomimetic side effects, including mucosal dryness, insomnia, tachycardia, nervousness, and increased blood pressure. Topical agents are quite potent, but they induce receptor down-regulation and pharmacologic tolerance, which results in a continuously increasing need for dosing and in rebound nasal congestion after discontinuation (rhinitis medicamentosa). Such agents should not be used for more than 4 or 5 consecutive days at a time.

Ipratropium Bromide. Ipratropium bromide, being an antagonist of acetylcholine on muscarinic receptors, can reduce the stimulation of the submucosal nasal glands by cholinergic neural pathways.[64] It is recommended when there is excessive rhinorrhea. This agent has no effects on the other symptoms of allergic rhinitis; therefore, rarely is it sufficient as a single agent to control the disease.

Leukotriene Receptor Antagonists. Montelukast, one of the two leukotriene receptor antagonists currently marketed in the United States, also has approval for the treatment of seasonal allergic rhinitis. Its efficacy

is comparable with that of oral antihistamines,[65] and the spectrum of symptoms it affects is similar. Leukotriene receptor antagonists possess some anti-inflammatory effects. However, antihistamines have a more rapid onset of action and can therefore be used on an "as-needed" basis. Because of the complementarity of histamine and the sulfidopeptide leukotrienes in the pathophysiology of allergic reactions, significant interest has been generated over the efficacy of antihistamine-antileukotriene combinations in allergic rhinitis.[66] Some studies indicate that this combination is as efficacious as nasal glucorticosteroids, whereas others report stronger therapeutic efficacy of steroids.[66a]

Nasal Glucocorticosteroids and Cromolyn. The strategic positioning of nasal glucocorticosteroids and cromolyn in allergic rhinitis is very similar to that in asthma, as are their relative effectiveness and safety profiles. In moderate to severe rhinitis, topical glucocorticosteroids constitute the mainstay of treatment,[67,68] alleviating all symptoms and reducing inflammation and nasal hyperresponsiveness. Continuous use, as opposed to "as needed," results in more effective symptom control. The safety profile is excellent, with the most common side effects being local irritation, dryness, epistaxis, and headaches. In contrast to inhaled steroids, which rather frequently result in oropharyngeal candidiasis, this adverse event is extremely rare with nasal agents. Several studies involving mucosal biopsies have assured us that nasal steroids do not induce mucosal atrophy.[69] There is some systemic bioavailability of these agents, which is associated with some metabolic effects.[70,71] These effects, however, are of far less concern than those of systemically administered glucocorticosteroids. The anti-inflammatory effects of disodium cromoglycate are less than those of nasal steroids and are somewhat limited to mast cell stabilization, although even this property has been questioned. Cromolyn is very well tolerated and can be efficacious in allergic rhinitis so long as it is used on a four times a day or more basis. This results in limited patient acceptability.

Allergen Vaccines (Immunotherapy). The role of immunotherapy in allergic rhinitis is very well established.[72–74] This treatment, during which increasing doses of allergenic extracts are progressively administered subcutaneously once or twice per week until a maintenance dose is reached, alters various aspects of the immune response to allergens, leading to inhibition of many elements of the allergic reaction. Most importantly, it is the only treatment for allergic conditions that can modify the natural history of the disease. For example, some studies suggest that immunotherapy can inhibit the progression of allergic rhinitis to asthma.[75] The indications for immunotherapy include the presence of moderate to severe disease and the lack of effectiveness of conventional medical therapy, intolerance to such therapy, or unavoidable allergen exposure.[76] There are no definitive data determining the optimal duration of treatment, but most specialists recommend 3 to 5 years. The allergens used in immunotherapy are identified on the basis of a thorough diagnostic evaluation with either allergen skin tests or determining the levels of allergen-specific IgE antibodies in the patient's serum. This evaluation has to be complemented by a meticulous exposure history and an assessment of the seasonality of the nasal symptoms so the allergens that are *clinically* relevant are identified. Similar rules apply to the decision regarding the doses of the allergenic extracts to be used. Allergen immunotherapy is a safe form of treatment. Systemic anaphylactic reactions are infrequent and, most of the time, mild and easily manageable. Although very rare, anaphylactic shock can occur, and deaths from immunotherapy have been reported. Therefore, health care providers who administer this treatment should be well trained in the management of anaphylaxis.

Nonallergic Rhinitis. Because of the lack of understanding of the pathophysiology of nonallergic rhinitis syndromes, management of these conditions has not been optimized. In all of these syndromes, symptomatic treatment with antihistamines, decongestants, and ipratropium bromide may provide help so long as the clinical presentation involves sneezing/pruritus, nasal congestion/pressure, and excessive rhinorrhea, respectively. In hyperplastic rhinosinusitis and in NARES, nasal glucocorticosteroid treatment is indicated. The latter syndrome is highly responsive to nasal steroids, whereas a significant number of patients with hyperplastic inflammatory disease do not obtain adequate relief from these agents. Nasal steroids are not indicated in nonallergic, noninflammatory rhinopathy, and symptomatic treatment should be pursued. As mentioned earlier, inactivation of nasal nociceptors with the use of repetitive applications of capsaicin in the nasal mucosa has been suggested for patients with this syndrome.[56,57,77] However, capsaicin therapy has not been approved by regulatory authorities.

THE PARANASAL SINUSES

The paranasal sinuses are four pairs of cavities that are named after the skull bones in which they are located: frontal, ethmoid (anterior and posterior), maxillary, and sphenoid. All sinuses contain air and are lined by a thin layer of respiratory mucosa composed of ciliated, pseudostratified columnar epithelial cells with goblet mucous cells interspersed among the columnar cells.

Structure and Function

The frontal sinuses grow slowly after birth and are barely visible at 1 year of age. After the fourth year, the frontal sinuses begin to enlarge and can usually be demonstrated radiographically in children over 6 years of age. The ostium of these sinuses is located directly posterior to the anterior attachment of the middle nasal turbinate to the lateral nasal wall.

The ethmoid sinuses consist of several air cells, which are present at birth and reach their adult size by age 12. They form a pyramid with the base located posteriorly. The lateral wall of the ethmoid sinuses is the lamina papyracea, which also serves as the paper-thin medial wall of the orbit. The superior boundary separates the ethmoids from the anterior cranial fossa and is composed

by the cribriform plate and the fovea ethmoidalis. The posterior boundary is the anterior wall of the sphenoid sinus. The ethmoidal air cells are divided into an anterior group, which drain into the middle meatus, and a posterior group, which drain into the superior meatus (located inferior to the superior turbinate).

The size of each maxillary sinus is estimated to be 6 to 8 mL at birth, and growth continues into puberty. By adulthood, the maxillary sinus has a capacity of around 15 mL. Its anterior wall is the facial surface of the maxilla, and the posterior wall corresponds to the infratemporal surface of the maxilla. Its roof is the inferior orbital floor and is about twice as wide as its floor. The medial wall of the sinus forms part of the lateral nasal wall and carries the ostium of the sinus, which is located in the infundibulum of the middle meatus. Accessory ostia are present in 25% to 30% of individuals.

At birth, the size of the two sphenoid sinuses is small. By the late teens, most of the sinuses are fully developed. The sphenoid sinuses are frequently asymmetrical. The optic nerve, internal carotid artery, nerve of the pterygoid canal, maxillary nerve, and sphenopalatine ganglion may all appear as impressions indenting the walls of the sphenoid sinuses. The sphenoid sinus drains into the sphenoethmoid recess above the superior turbinate.

Blood is supplied to the paranasal sinuses by the ophthalmic artery (frontals), the maxillary artery (maxillary sinuses), and branches from the internal and external carotids. For several paranasal sinuses, venous blood drains into the cavernous sinus, which is the reason why, in rare cases of sinusitis (particularly in the ethmoids), cavernous sinus thrombosis can occur. Sensory innervation is supplied by the trigeminal nerve. The maxillary sinuses also receive parasympathetic innervation via the preganglionic vidian nerve, which synapses at the sphenopalatine ganglion.

There are many theories as to the function of the paranasal sinuses including imparting additional voice resonance, humidifying and warming inspired air, secreting mucus to keep the nose moist, and providing thermal insulation for the brain. It is also believed that the paranasal sinuses form a collapsible framework to help protect the brain from frontal blunt trauma.

Paranasal Sinus Disease

The most common disease afflicting the paranasal sinuses is sinusitis (i.e., infection/inflammation of the lining mucous membranes and possibly the underlying bone). Sinusitis is often accompanied by rhinitis, thus the term *rhinosinusitis*. Rhinosinusitis ranges from a self-limited acute bacterial infection, most often following a viral upper respiratory infection, to a chronic inflammatory disease. Less common disease entities involving the paranasal sinuses are benign and malignant tumors.

Epidemiology

Recent analysis of the disease burden posed by sinusitis revealed that it was an important cause of emergency room visits and that its health care costs exceeded those of ulcer disease, acute asthma and hay fever.[78] Acute bacterial rhinosinusitis is estimated to complicate up to 2.0% of viral upper respiratory tract infections.[79] This translates into more than 20 million cases of acute bacterial rhinosinusitis in the United States annually. Chronic rhinosinusitis is also very common, with one conservative estimate suggesting that it results in 18 to 22 million U.S. physician office visits annually.[80] The impact on health care expenditure is therefore considerable. Ray and colleagues[81] estimated the 1996 total direct and attributable health care expenditures for the treatment of sinusitis to be $5.8 billion. Several studies have shown that patients with chronic rhinosinusitis have significantly worse overall quality of life compared with the U.S. general population and to patients with various other chronic diseases such as sciatica/back pain, chronic obstructive pulmonary disease (COPD), and angina.

Definitions and Diagnosis

The diagnosis of rhinosinusitis is difficult to make because other nasal diseases, such as allergic rhinitis and viral upper respiratory tract infections, can present with similar clinical symptoms. Yet, misdiagnosing rhinosinusitis leads to erroneous management and might result in prescribing antibiotics that may not be necessary. Most experts agree with the division of rhinosinusitis into acute, acute recurrent, and chronic rhinosinusitis categories based on the duration of illness. Acute rhinosinusitis has an acute onset of symptoms that lasts up to 4 weeks but completely resolves within that timeframe. When symptoms of a viral upper respiratory tract infection last longer than 10 days, worsen after 5 days, or are disproportionate to symptoms seen with a typical upper respiratory tract infection, the diagnosis of acute bacterial rhinosinusitis should be considered. Recurrent acute rhinosinusitis is defined as four or more episodes of acute bacterial rhinosinusitis each year with complete resolution of symptoms between episodes. Last, patients who are symptomatic beyond 12 weeks of medical therapy have chronic rhinosinusitis. Computed tomography (CT) changes 4 weeks or more after an appropriate medical treatment regimen for a single acute episode of acute bacterial rhinosinusitis are also indicative of chronic rhinosinusitis.

An attempt to establish symptom-based definitions for rhinosinusitis was made by the American Academy of Otolaryngology–Head and Neck Surgery in 1997.[82] They divided symptoms that could be associated with rhinosinusitis into major and minor (Table 43-2). However, additional physical findings are now required before the diagnosis can be made. For example, purulent drainage, polyps, and polypoid changes are sufficient to make the diagnosis of chronic rhinosinusitis if the 12-week-duration criterion is met. Mucosal abnormalities of the middle meatus (the narrow passage lateral to the middle turbinate where most sinuses drain) or ethmoidal bulla are also concrete signs of inflammation but usually cannot be confirmed by anterior rhinoscopy, so nasal endoscopy is recommended.

In general, the diagnosis of both acute bacterial and chronic rhinosinusitis is made on the basis of clinical criteria (duration and physical examination). Imaging is helpful in some cases. CT is the preferred radiologic diagnostic examination for visualizing the paranasal sinuses. In acute sinusitis, air-fluid levels are not infrequent, but their absence does not rule out the diagnosis (Fig. 43-4). Unless a compelling diagnostic or treatment dilemma exists, imaging should be performed to rule out residual chronic rhinosinusitis after maximal medical treatment. Plain sinus radiographs lack appropriate sensitivity and specificity and are not recommended as a routine procedure in the diagnosis of rhinosinusitis unless no CT option exists.

In chronic rhinosinusitis, other diagnostic tests may be indicated, such as skin testing or in vitro testing to assess the presence of concomitant allergic rhinitis, immunoglobulin quantitation to rule out immune deficiencies, sweat chloride testing to rule out cystic fibrosis, and nasal biopsy with electron microscopy to rule out immotile cilia syndrome. These procedures may help in the differential diagnosis, which is outlined in Table 43-3.

Allergic fungal rhinosinusitis is a distinctive form of chronic rhinosinusitis. This is usually characterized by nasal polyposis, inspissated greenish secretions with concretions showing a large number of eosinophils (allergic mucin), positive fungal identification by histology or culture, and characteristic CT and magnetic resonance imaging findings.[83] The most commonly isolated fungi are *Bipolaris* and *Aspergillus* species.

TABLE 43-2. Factors Associated with the Diagnosis of Rhinosinusitis

MAJOR FACTORS
Facial pain/pressure*
Nasal obstruction/blockage
Nasal discharge/purulence/discolored postnasal drainage
Hyposmia/anosmia
Purulence in nasal cavity on examination
Fever (acute rhinosinusitis only)
MINOR FACTORS
Headache
Fever (all nonacute)
Halitosis
Fatigue
Dental pain
Cough
Ear pain/pressure/fullness

*Facial pain/pressure alone does not constitute a suggestive history for rhinosinusitis in the absence of another major nasal symptom or sign.
From Lanza DC, Kennedy DW: Adult rhinosinusitis defined. Otolaryngol Head Neck Surg 117:S1–S7, 1997.

Pathophysiology

Acute Rhinosinusitis. Viral rhinosinusitis commonly occurs during a viral upper respiratory tract infection. A study reported by Gwaltney and coworkers in 1994[84] showed that approximately 60% of subjects with a viral upper respiratory tract infection had abnormalities in the ethmoid and maxillary sinuses on CT. These, however, resolve spontaneously with time. Acute bacterial sinusitis occurs mostly as a consequence of viral rhinosinusitis. The most common organisms cultured in cases of acute bacterial rhinosinusitis are listed in Table 43-4.

Chronic Rhinosinusitis. The role of bacteria in chronic rhinosinusitis is less well established. A variety of organisms have been cultured from the paranasal sinuses including α-hemolytic *Streptococcus*, *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and anaerobes. The relationship between these organisms and clinical disease is not definitive and is confounded by the fact that most of these organisms are cultured at the time of surgery after prolonged antibiotic treatment, thus possibly representing colonization.

There is increasing evidence that chronic rhinosinusitis is an inflammatory mucosal disease with the characteristics of inflammation being very similar to those of

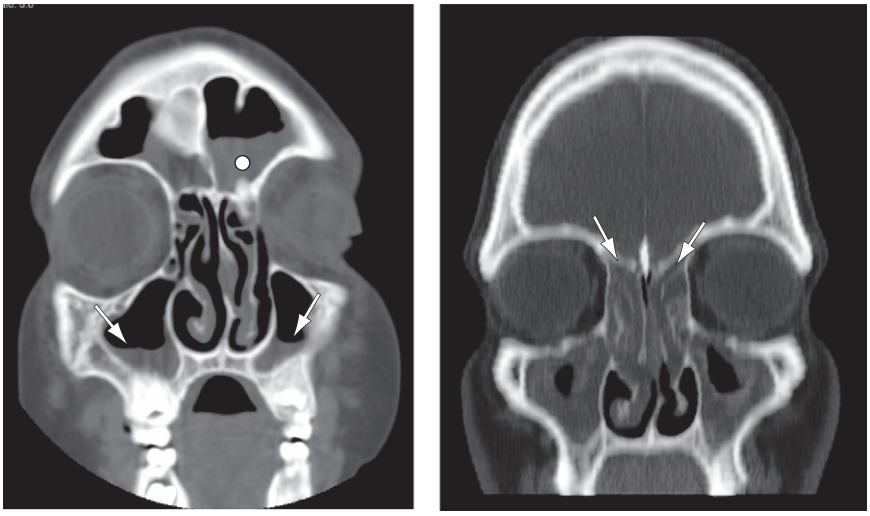


FIGURE 43-4 ■ Paranasal sinus computed tomography. *Left,* An image from a patient with acute rhinosinusitis with air-fluid levels in both maxillary sinuses (*arrows*) and the left frontal sinus (*dot*). *Right,* A scan from a patient with chronic rhinosinusitis and intranasal polyposis. Note the almost complete opacification of both ethmoid (*arrows*) and maxillary sinuses.

TABLE 43-3. Differential Diagnosis of Rhinosinusitis

ALLERGIC RHINITIS
Seasonal
Perennial
Combined seasonal and perennial
Allergic fungal rhinosinusitis

NONALLERGIC RHINITIS
Nonallergic, noninflammatory idiopathic rhinopathy (vasomotor rhinitis)
Nonallergic rhinitis with eosinophilia syndrome (NARES)
Cold dry air–induced rhinitis
Gustatory rhinitis

INFECTIOUS RHINOSINUSITIS
Bacterial
Viral
Fungal
Granulomatous

DRUG-INDUCED RHINITIS
Oral contraceptives
Various antihypertensives and ocular β-blockers
Topical decongestants (rhinitis medicamentosa)
Phosphodiesterase-5 antagonists

MECHANICAL CAUSES OF RHINOSINUSITIS
Septal deviation
Nasal foreign body
Choanal atresia or stenosis
Adenoid hypertrophy
Encephalocele
Glioma
Dermoid

INNATE AND ACQUIRED IMMUNITY DISORDERS
Congenital or acquired immunodeficiencies
Cystic fibrosis
Immotile cilia syndrome

SYSTEMIC INFLAMMATORY DISORDERS
Sarcoidosis
Wegener's granulomatosis
Vasculitis

NEOPLASTIC CAUSES
Benign: polyps, nasopharyngeal angiofibroma, inverting papilloma
Malignant: adenocarcinoma, squamous cell carcinoma, aesthesioneuroblastoma, lymphoma, rhabdomyosarcoma

TABLE 43-4. Microbiology of Acute Rhinosinusitis in Adults

Organism	Range of Prevalence (%)
Streptococcus pneumoniae	20–43
Haemophilus influenzae	22–35
Streptococcus spp.	3–9
Anaerobes	0–9
Moraxella catarrhalis	2–10
Staphylococcus aureus	0–8
Other	4

asthma. Eosinophilic infiltration of the diseased mucosa has been found to be a characteristic feature.[85,86] Driscoll and associates[87] showed an increase in the number of $CD4^+$ T lymphocytes in the sinus tissue of children with chronic rhinosinusitis when compared with adult sphenoid tissue obtained at the time of transsphenoidal hypophysectomy, regardless of allergic status. Two studies by Hamilos and colleagues[51,86] demonstrated a preponderance of proinflammatory cytokines such as IL-3 and granulocyte-macrophage colony-stimulating factor (GM-CSF) in the tissues of patients with chronic rhinosinusitis with significantly higher levels of the Th2 cytokines IL-4 and IL-5 in patients with chronic rhinosinusitis and allergic rhinitis.

The causes leading to the development of chronic inflammation in the paranasal sinuses are unknown. The possibility of anatomic abnormalities leading to obstruction should be considered, although it would be difficult to explain the simultaneous involvement of several paranasal sinus cavities. In most patients with chronic rhinosinusitis, a generalized airway inflammatory disease is present, and the links between rhinitis, sinusitis, and asthma have been very well established.[88] Allergy to inhalants could potentially explain this inflammatory disease, but no more than 50% of patients with chronic rhinosinusitis cases are atopic.[89] Allergic fungal sinusitis appears to represent a distinct subgroup of chronic rhinosinusitis of atopic etiology. It is thought that its pathophysiology is similar to that of allergic bronchopulmonary aspergillosis (ABPA), but definitive evidence is missing. It has been proposed that, perhaps, chronic rhinosinusitis results from an abnormal host response to naturally colonizing fungus, not necessarily of allergic nature. This hypothesis is currently being tested with the use of nebulized antifungal agents.[90] More recently, investigators have demonstrated that many patients with chronic rhinosinusitis have evidence of significant laryngopharyngeal reflux.[59,91–93] This is particularly evident when one assesses reflux events as evidence of pH excursions less than 5 rather than less than 4.

Immune deficiencies, immotile cilia syndromes, and cystic fibrosis produce generalized airway inflammation with a strong chronic rhinosinusitis component, suggesting that some yet unidentified functional abnormality of the respiratory mucosa, possibly related to the innate immunity, may constitute the predisposing factor for the majority of cases that remain unexplained.

Management

Antimicrobial Therapy.

Acute Rhinosinusitis. When bacterial rhinosinusitis is suspected, it should be treated with a first-line antibiotic, such as amoxicillin, along with an intranasal decongestant, the purpose of which is to decrease nasal edema and facilitate sinus drainage.[94] In areas where resistance is high, if a patient has had an antibiotic within the past 2 months or fails the first-line antibiotic (no improvement within 72 hr), a second-line antibiotic should be given,

such as amoxicillin-clavulanate, high-dose amoxicillin-clavulanate, cefpodoxime, cefuroxime, or a quinolone (levofloxacin, gatifloxacin, or moxifloxacin). Clindamycin is very effective if resistant *S. pneumoniae* is suspected, but it does not provide appropriate coverage against *H. influenzae* or *M. catarrhalis*. Antibiotic therapy should continue for 5 to 7 days after the patient's symptoms resolve, resulting in a typical treatment duration of 10 to 14 days. It is to be kept in mind that some studies show no significant difference in symptom resolution in uncomplicated acute rhinosinusitis when placebo and various antibiotics are compared.[95,96] Thus, many cases of uncomplicated acute disease are probably self-limited and may not need antibiotic treatment. These decisions should be individualized on the basis of the general clinical picture of the patient. For example, patients who are quite ill and present with such symptoms as fever, severe headaches, or eye swelling should be treated aggressively to avoid potential complications, which include subperiosteal orbital abscess or even brain abscess.

Chronic Rhinosinusitis. Despite the doubts as to the role of bacterial infection, antibiotics remain the primary therapy for chronic rhinosinusitis. The choice of antibiotic is essentially the same as for acute rhinosinusitis, except that amoxicillin is not the first choice. If an anaerobe or resistant *S. pneumoniae* is suspected, clindamycin is a reasonable option. In patients in whom a course of empirical therapy fails, there might be an advantage in obtaining a culture to be able to better direct antimicrobial therapy. Although maxillary sinus puncture is the best way to obtain a culture, it is invasive and uncomfortable to the patient. An endoscopically directed middle meatal culture has been shown to correlate reasonably well with cultures of the sinus cavities and is a less invasive alternative.[97] Antibiotic nebulization has been used to treat exacerbations of rhinosinusitis in patients who have had prior surgery, but no controlled studies are available.[98] In unoperated patients, penetration of nebulized antibiotics into the sinus cavities has not been shown.

Adjuvant Therapy. Besides antibiotics, multiple other therapies have been used in the treatment of sinus disease. They include saline irrigations or steam inhalations, topical and systemic decongestants, topical and systemic steroids, and mucoevacuants.

Nasal Saline. The rationale behind the use of saline for the treatment of rhinosinusitis is based on its potential beneficial effects on mucociliary clearance, as well as on the moisturizing effect, which reduces crusting of nasal secretions. Several reports suggest a beneficial effect of variously administered saline preparations (nose drops, nose sprays, nebulization, irrigation) at different concentrations (isotonic, hypertonic) to control symptoms of rhinosinusitis.[9,99]

Uren and coworkers[100] have demonstrated the efficacy of mupirocin in the treatment of chronic rhinosinusitis after surgery with evidence of nasoendoscopically directed *S. aureus*.

Decongestants. Both systemic and topical decongestants are used as adjuncts to antibiotics in the treatment of acute and chronic sinusitis. The rationale behind their use is based on their possible role in improving ostial patency and reducing turbinate swelling and congestion. Controlled studies are lacking to support the clinical efficacy of either systemic or topical decongestants in the treatment of rhinosinusitis. Because of their superior potency compared with systemic agents, topical decongestants may be more useful. As mentioned in the management of rhinitis section, the use of topical decongestants in conjunction with antibiotics for acute rhinosinusitis should be limited to a few days during the acute period.

Mucolytics. High viscosity of mucus is thought to contribute to the pathophysiology of chronic rhinosinusitis. Therefore, expectorants, mucolytics, and mucoregulatory agents are commonly used. Guaifenesin is such an agent. Except for one study showing a reduction in nasal congestion and thinning of postnasal drainage in human immunodeficiency virus (HIV)–positive patients with rhinosinusitis,[101] no controlled studies have demonstrated the efficacy of guaifenesin in the treatment of either acute or chronic rhinosinusitis.

Intranasal Glucocorticosteroids. Several studies treating patients with acute rhinosinusitis or exacerbations of chronic rhinosinusitis with oral antibiotics with or without intranasal corticosteroids have suggested that intranasal corticosteroids are useful adjunctive agents.[102,103] It is not clear, however, whether the use of intranasal steroids reduces the recurrence of acute rhinosinusitis. The speculated mechanism of action of these agents is a reduction in inflammation and a decrease in mucosal edema, facilitating paranasal sinus drainage and accelerating resolution.

The evidence supporting the efficacy of intranasal corticosteroids in the treatment of chronic rhinosinusitis is less convincing than that for acute disease, and both positive and negative results have been reported.[104,105] However, it seems very reasonable to use these agents in subjects with allergic rhinitis, in whom the data on nasal symptoms are convincing.

Sachanandani and associates[106] showed the efficacy and safety of intranasal sinus rinse irrigation using budesonide respules in the treatment of chronic rhinosinusitis.

Systemic Corticosteroids. The use of systemic steroids has not been well studied in rhinosinusitis. Clinical experience, however, suggests that these agents are beneficial. Also, beneficial effects are often seen in the medical treatment of nasal polyps, which are strongly associated with chronic rhinosinusitis. However, continuous treatment with systemic steroids is not advocated. Oral steroids should be utilized in the form of short courses during acute exacerbations or prior to obtaining a CT scan to evaluate residual disease after maximal medical treatment.

Anti-Immunoglobulin E Therapy. Several studies have now shown that omalizumab, a monoclonal antibody that binds human IgE and prevents binding to mast cells and basophils, is efficacious in the treatment of allergic rhinosinusitis,[107] as shown by the example of a patient with persistent and refractory asthma, nasal polyposis and chronic rhinosinusitis who made a striking improvement after treatment with omalizumab.[108]

Surgery. When patients fail maximal medical treatment and have evidence of residual disease in the paranasal sinuses on CT scan, referral for consideration of surgical drainage is appropriate. Surgery might also provide relief to patients with recurrent acute disease who have obstructing anatomic abnormalities such as severe septal deviation, Haller cells (air cells that compromise drainage of the maxillary sinuses), or concha bullosa (a pneumatized middle turbinate that can obstruct the middle meatal drainage path). This is usually performed using functional endoscopic sinus surgery, which can fix the previously discussed abnormalities, can widen sinus drainage sites, and can remove obstructive polyps and hypertrophied mucosa. Symptoms and quality of life scores significantly improve in more than 75% of adults and children who undergo surgery for chronic rhinosinusitis.[109] However, endoscopic sinus surgery, as well as other forms of more aggressive surgery, does not, in most cases, offer a cure for the disease; and recurrence is not uncommon.[110]

THE PHARYNX AND HYPOPHARYNX

Structure and Function

The pharyngeal airway travels from the back of the nasal passages to the supraglottic space (see Fig. 43-2). The nasopharyngeal segment ends at the rim of the soft palate, and the oropharyngeal/hypopharyngeal segments extend beyond this point to the aryepiglottic folds. Several bony structures surround the pharyngeal airway (i.e., the cervical vertebrae, mandible, and hyoid bone). The size and physiologic functions are controlled by the activity of the tongue, the intrinsic muscles in the pharyngeal wall, and the inframandibular and cervical strap muscles.

The nasopharyngeal segment adapts to high inspiratory and expiratory flows, such as during exercise, by changes in palatal and tongue position. The soft tissues and muscles of the oropharynx (see Table 43-1) permit a wide range of changes in its conformation and mechanical properties. Liquids and solids are actively propelled into the esophagus by constriction of extrinsic muscles surrounding the oropharynx, whereas air flows passively through this segment as the genioglossus and strap muscles are activated to maintain airway patency during inspiration. The activity of these muscles can be augmented by several factors, including airflow obstruction, chemical stimuli, pressure, and air flow in the upper airways.[111]

Clinical Disorders

Disorders of concern are listed in Table 43-5. Obstructive sleep apnea is covered in detail in Chapter 79. Obstruction of the extrathoracic airway should be considered when (1) patients present with obvious symptoms and signs of stridor or upper airway compromise; (2) there is chronic cough or sore throat; (3) obstructive airways disease has been suspected and/or diagnosed in the absence of definitive findings consistent with asthma or COPD; or (4) these conditions are present but demonstrate pronounced worsening not controlled with standard medication.

TABLE 43-5. Causes of Pharyngeal Obstruction

Malignant or benign tumors (e.g., papillomas, polyps)
Infection (e.g., croup, epiglottitis, tonsillar abscess)
Edema or hypertrophy (e.g., angioneurotic edema, anaphylactic reactions, postradiation therapy, obstructive sleep apnea)
Trauma (e.g., cricoid fracture, cervical subluxation, precervical hematoma)
Burn injury
Extrinsic compression (e.g., goiter or pregnancy-related thyroid enlargement)
Foreign body
Congenital web (infants)
Sarcoidosis and other granulomatous diseases
Amyloid

Foreign bodies and congenital webs are the most common abnormalities in infants and toddlers, whereas in the older population, tumors (both benign and malignant) and pharyngeal manifestations of systemic diseases such as sarcoidosis or collagen vascular diseases are of greatest concern.

Acute obstruction is commonly caused by infections such as of the supraglottitis. This is commonly due to *S. aureus* and *Streptococcus* species. Adult croup is often viral in etiology rather than bacterial. Retropharyngeal abscesses as well as dental, sublingual, submandibular, and other oral cavity infections are commonly due to *Streptococcus* or oral anaerobic species.

Causes of gradually developing pharyngeal obstruction include pharyngeal stenosis due to prior injury or inflammation and gross enlargement of the tonsils. Children in particular may have tonsil or lingual enlargement due to chronic infections. A combination of enlarged tonsils and adenoids in childhood may result in severe airflow obstruction, particularly during sleep, with pulmonary edema or chronic alveolar hypoventilation, hypoxemia, and cor pulmonale. Fortunately, this syndrome rapidly reverses after tonsillectomy and adenoidectomy.

THE LARYNX

Structure and Function

The larynx, the enlarged upper end of the trachea below the base of the tongue, consists of nine cartilages bound together by an elastic membrane and moved by a series of muscles (Fig. 43-5). The cavity of the larynx contains two sets of folds (also referred to as "cords"): the false vocal folds and the true vocal folds. The slitlike opening to the trachea is called the *glottis*. The larynx has three major physiologic functions: maintenance of a patent

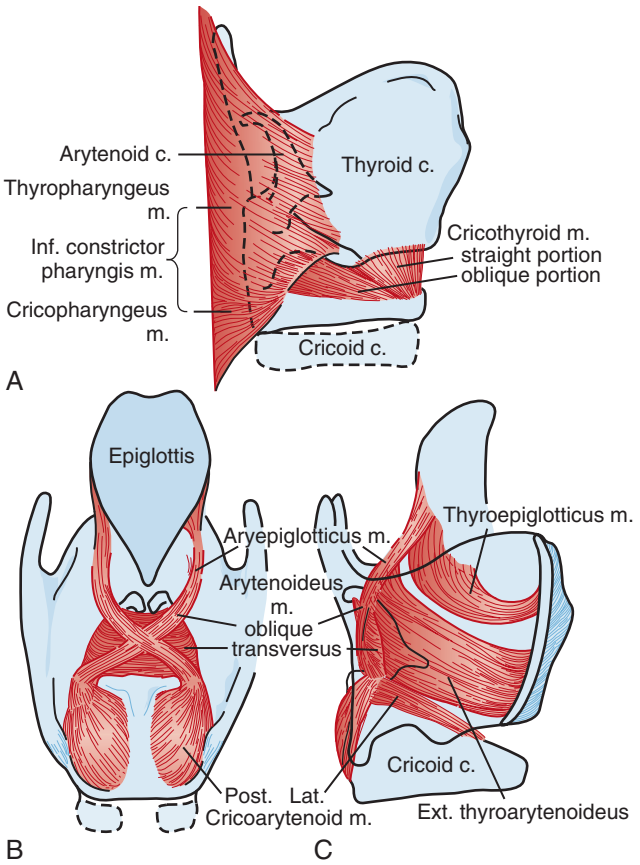


FIGURE 43-5 ■ Muscles of the larynx are shown from the right (**A**), from behind (**B**), and with the right side of the thyroid cartilage cut away (**C**). Note in **A** that the cricothyroid muscle can act to draw the thyroid cartilage toward the cricoid and can draw the thyroid cartilage forward on the sliding cricothyroid joint. (Redrawn from Proctor DF: Physiology of the upper airway. In Fenn WO, Rahn H [eds]: Handbook of Physiology. Washington, DC: American Physiological Society, 1964.)

airway, protection of the airway, and phonation. The laryngeal musculature is involved in the coordination of many important functions, including breathing, swallowing, coughing, phonating, and vomiting. The thyroid and cricoid cartilages provide the major skeletal support. During inspiration, the cross-sectional area between the vocal folds widens and is augmented during deep inspiration.[103] In contrast, the glottis narrows during expiration and may retard expiratory air flow. The movement of glottic structures is controlled by a number of muscles intrinsic to the larynx (Fig. 43-6; see also Table 43-1 and Fig. 43-5).

The caliber of the glottis orifice responds to changes in airflow pressure, temperature, and laryngeal position. In addition, irritant stimuli are capable of stimulating the cough and glottic closure reflexes that are central to protecting the lungs from exogenous noxious agents. The afferent pathway of the glottic closure reflex starts with sensory nerve endings/receptors in the larynx, trachea, and larger airways. The internal branch of the superior laryngeal nerve supplies the supraglottic larynx (epiglottis, aryepiglottic folds, false cords, superior surface of the laryngeal ventricle). The recurrent laryngeal nerve supplies sensory afferents for the glottic and subglottic structures (vocal cords, inferior surface of the laryngeal ventricle, trachea). Nerve impulses are transmitted through the vagus nerve to the nodose (inferior) ganglion and then to the fasciculus solitarius and the nucleus solitarius in the medulla. Major projections then go to the reticular formation, an area in the midbrain important for control of respiration.

The efferent (motor) fibers start in the somatosensory gyrus and pass through the internal capsule, where they partially decussate before joining the somatic motor nucleus (nucleus ambiguous) in the medulla. The nucleus ambiguus receives bilateral cortical input, and the vocal folds function simultaneously. The nucleus ambiguus is

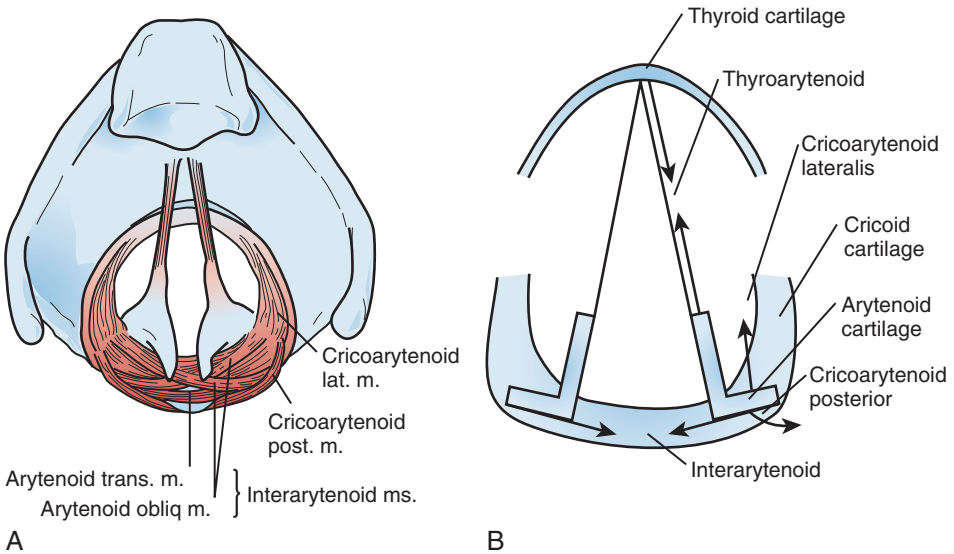


FIGURE 43-6 ■ The muscles involved in opening and closing the glottis. **A,** The cricothyroid muscle is omitted. **B,** The action of these muscles is diagrammed. (B, Redrawn from Proctor DF: Physiology of the upper airway. *In* Fenn WO, Rahn H [eds]: Handbook of Physiology. Washington, DC: American Physiological Society, 1964.)

responsible for the motor innervation of the glossopharyngeal, vagus, and spinal accessory nerves. Important branches of the vagus include the superior laryngeal nerve, which supplies motor innervation to the cricothyroid muscle, and the recurrent laryngeal nerve, which supplies the rest of the motor innervation to the larynx.

The cough and laryngeal closure reflexes are important for protecting the airway during deglutition but also in response to potentially noxious inhaled stimuli. Contraction of the glottic and supraglottic sphincters leads the vocal folds, false folds, and arytenoid cartilages to merge medially and occlude the airway. During swallowing, the larynx elevates under the base of the tongue and pushes the epiglottis out over the airway to act as a shield or roof. The rise in subglottic pressure against a closed glottis is important for the cough reflex but also provides a form of auto-positive end-expiratory pressure (PEEP) by increasing the intra-alveolar pressure. This has been used to advantage by severe asthmatics and those with emphysema to prevent or reduce airway collapse during expiration and thus promote better emptying. This mid to late expiratory closure as a means of creating auto-PEEP should not be regarded as dysfunctional or maladaptive.

Clinical Disorders

Table 43-6 lists acute and chronic causes of laryngeal obstruction. These are frequently associated with problems in the swallowing and phonation functions of the larynx. Acute causes are foreign bodies, accidents (direct, indirect, iatrogenic and noniatrogenic trauma, burns), infectious processes, and angioedema. Slowly developing obstruction has a wider spectrum of etiologies, including tumors and surrounding tissue enlargement, rheumatologic diseases affecting structural aspects of the larynx, and neurologic diseases.

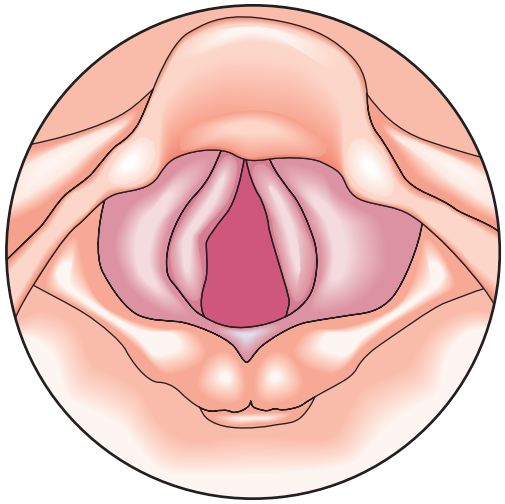
Neuromuscular mechanisms appear to play an important role in the modulation of patency in laryngeal disorders. Laryngeal airway obstruction can result from either decreases in abductor activity or increases in adductor activity (see Table 43-1). Decreased abductor activity accounts for the occurrence of inspiratory airflow obstruction in patients with unilateral and bilateral vocal cord paralysis, most often caused by damage to recurrent laryngeal nerves. When both recurrent laryngeal nerves are injured, the vocal cords move toward the midline (resulting from the action of the still-active cricothyroid muscles). This may go unrecognized because hoarseness may be only slight, and the narrowed airway may still permit limited physical activity for years. Gradually, glottic airflow obstruction increases, and the diagnosis may be made 10 to 20 years later, at which point, surgical intervention is necessary. A past history of a thyroidectomy is frequently elicited in these cases. Unilateral vocal cord paralysis[112] is diagnosed more frequently because for unknown reasons a patient with such a disorder is prone to aspiration and severe laryngospasm during sleep. In a significant percentage of patients, a search for the cause of this condition fails to uncover a specific etiology. The possibility of cervical or mediastinal malignancy or of aortic aneurysm encroaching on one recurrent laryngeal nerve (usually the left) must be considered.[113]

TABLE 43-6. Disorders Associated with Laryngeal Obstruction

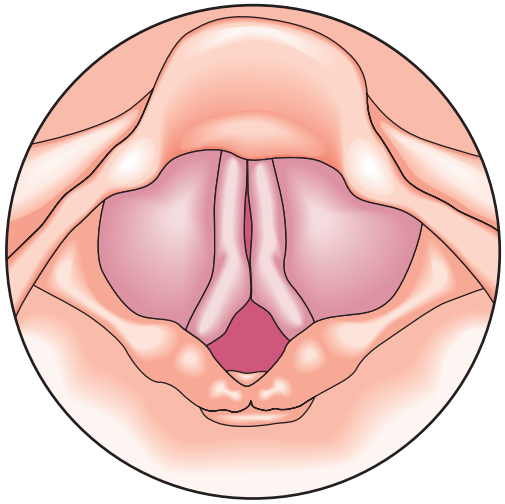
MAY BE ASSOCIATED WITH ACUTE ONSET OF OBSTRUCTION
Foreign bodies
Anesthesia and other states of unconsciousness
Intubation injury
Angioneurotic edema (idiopathic, anaphylactic, C_1-esterase deficiency)
Burn injury
Laryngeal or tracheal trauma
Croup
Epiglottitis
Infections involving surrounding structures
Deep neck infections
Ludwig's angina
Peritonsillar abscess
Retropharyngeal abscess
Malfunction of muscles stabilizing the airways
Syphilitic gumma, tabes dorsalis
USUALLY SLOWLY DEVELOPING OBSTRUCTION
Arthritis cricoarytenoid joint
Enlarged tonsils and adenoids
Esophageal foreign body
Histiocytoma
Laryngeal carcinoma, papilloma, cartilaginous tumors, angioma, cystic hygroma, congenital malformations, polyp, granuloma
Malignant metastases to cervical glands
Neurologic disease
Relapsing polychondritis
Thyroid tumors, malignant and benign
Tracheal cyst, stenosis from cylindroma, tracheomalacia
Vocal cord paralysis

Laryngospasm and Vocal Cord Dysfunction

Disorders in which increases in vocal cord adductor muscle activity lead to laryngeal airflow obstruction include laryngospasm and paradoxical vocal fold adduction or vocal cord dysfunction (VCD). VCD was originally described as paradoxical closure of the vocal folds during inspiration with a characteristic small posterior chink aperture through which patients moved air (Fig. 43-7).[114,115] The etiology and pathophysiology of laryngospasm remain poorly understood. Intubation, certain anesthetics, gastroesophageal reflux disease, and various other etiologies have been implicated.[116–125] As for VCD, it has historically been considered a functional or conversion disorder with terms applied such as "factitious asthma," Munchausen's stridor, or "hysterical asthma." More recently, there has been appreciation for the fact that there can be respiratory symptoms caused by paradoxical adduction of the vocal folds during inspiration and expiration with or without evidence of the posterior



A Normal vocal cords at mid-inspiration



B Vocal cord dysfunction with posterior chinking

FIGURE 43-7 ■ The appearance of the vocal cords during inspiration in a healthy subject (A) and during inspiration in a patient with vocal cord dysfunction (B) show adduction of the vocal cords with the characteristic posterior "chink" opening. (Redrawn from Perkner J, Fennelly K, Balkissoon R, et al: Irritant associated vocal cord dysfunction. J Occup Environ Med 40:136–143, 1998. ©American College of Occupational and Environmental Medicine.)

chink.[126] Morrison and associates[127] have recently introduced the term "irritable larynx syndrome" to encompass individuals with episodic laryngeal dysfunction triggered by irritant exposures with variable clinical manifestations including VCD, cough, muscle tension dysphonia, and globus sensation. Hence, compared with VCD, *irritable larynx syndrome* and *laryngeal dysfunction* are terms that are somewhat more inclusive or descriptive of the phenomenon of upper airway compromise masquerading as asthma. Furthermore, there is a greater appreciation that factors other than psychological problems, such as gastroesophageal reflux and, more specifically, laryngopharyngeal reflux,[127] posterior nasal drainage,[128] neurologic dystonias,[126] or intense irritant exposures,[129] can lead to laryngeal hyperresponsiveness. One may hypothesize that this is simply an accentuation of the normal physiologic reflex known as the glottic closure reflex. One study demonstrated that it was possible to lower the threshold for capsaicin stimulation of laryngeal nociceptor C fibers by pretreatment with halothane anesthetic.[130] Ayres and Gabbott[131] suggested that irritant/inflammatory insults to the region lead to an altered autonomic balance that is perpetuated by repeated local stimuli. Clinically, VCD remains an underrecognized disorder in many cases. Many patients are misdiagnosed as asthmatics for years and develop iatrogenic complications related to steroid therapy, which does not provide significant benefit. This adds to the psychological dimensions of this problem.

Clinical Presentation of Laryngeal Obstruction

The clinical presentation of laryngeal disorders is often ambiguous because breathing difficulties frequently masquerade as swallowing or voice disorders. Conversely, swallowing difficulties that result in failure to clear food particles from the throat may interfere with breathing. Laryngeal obstruction may be noted by the complaint of shortened phrasing and excessively effortful speaking, singing, or both. Conversely, laryngeal complaints often reflect disorders of the pharynx or esophagus such as gastroesophageal reflux disease.[132] Aside from patients being obviously dyspneic, the signs and symptoms of laryngeal obstruction vary according to the cause of the obstruction.

Acute obstruction due to foreign bodies, trauma, or anaphylactic reactions is associated with abrupt onset of throat constriction, panic, and inability to phonate. Cough may be muted or not possible if a foreign body is firmly lodged in the upper trachea such that passage of air is virtually impossible. Salivation may occur. Patients may grab at their throat to identify the point of blockage. Vital signs may show tachycardia and elevated blood pressure or the converse, depending on the degree of hypoxia and/or hypercarbia. Their level of consciousness is affected by the same factors. If the obstruction is almost complete, there may be virtually no audible breath sounds; whereas if the obstruction is partial, laryngeal wheezes (that transmit to the chest and may be mistaken as lower airway wheezing) are best heard directly over the trachea.

Slow-onset laryngeal obstruction may be associated with progressive dyspnea first noted only with exertional activity. Patients may also complain of a chronic dry cough, hemoptysis (rare), sore throat, and/or voice changes. In certain circumstances, patients with space-occupying lesions may also report orthopnea or shortness of breath in relation to positional changes of the neck and consequent compression of the upper airway. There may also be visible evidence of a neck mass such as an obvious goiter or more subtle signs such as asymmetry, bulge, or displacement of the trachea. Individuals with cerebral vascular accidents or central nervous system neoplasms may demonstrate facial asymmetry or cranial nerve deficits.

Evaluation of these patients involves physical examination and various ancillary tests to confirm paradoxical closure of vocal cords and to rule out other disorders or contributory factors. Physical examination may be relatively unremarkable except for direct detection of laryngeal wheezing or stigmata of posterior nasal drainage or gastroesophageal reflux (epigastric tenderness). Skin, neurologic, and musculoskeletal examination is helpful to identify lesions that may explain symptoms as well as signs of rheumatologic or collagen vascular diseases.

Spirometry often provides compelling evidence that an upper airway obstructive process is operative. These patients demonstrate a pattern of extrathoracic airway obstruction on flow-volume loops (truncated inspiratory loop) obtained during an attack (Fig. 43-8). It should be emphasized that these patients may demonstrate flattening in the early segment of the expiratory loop as well. Vlahakis and colleagues[126] reported evidence of an inspiratory flow plateau on the open shutter loop during body plethysmography of a patient with laryngoscopy-confirmed VCD. The utility of this noninvasive measurement requires validation. Radiographic studies are generally not helpful in establishing the diagnosis of VCD but do help to rule out space-occupying lesions that may be due to neoplasm, infection, or chronic inflammatory disease.

Although spirometry can be an extraordinarily useful screening tool for VCD, particularly when the patient is symptomatic, direct visualization of the upper airway is the "gold standard" for making a definitive diagnosis and assessing the nature and severity of the cause of obstruction. Flexible fiberoptic rhinolaryngoscopy is most often sufficient for the evaluation. In the case of an emergent problem involving the upper and possibly the tracheal airway, rigid bronchoscopy may be needed to secure a patent airway. This requires general anesthesia and performance by experienced personnel.

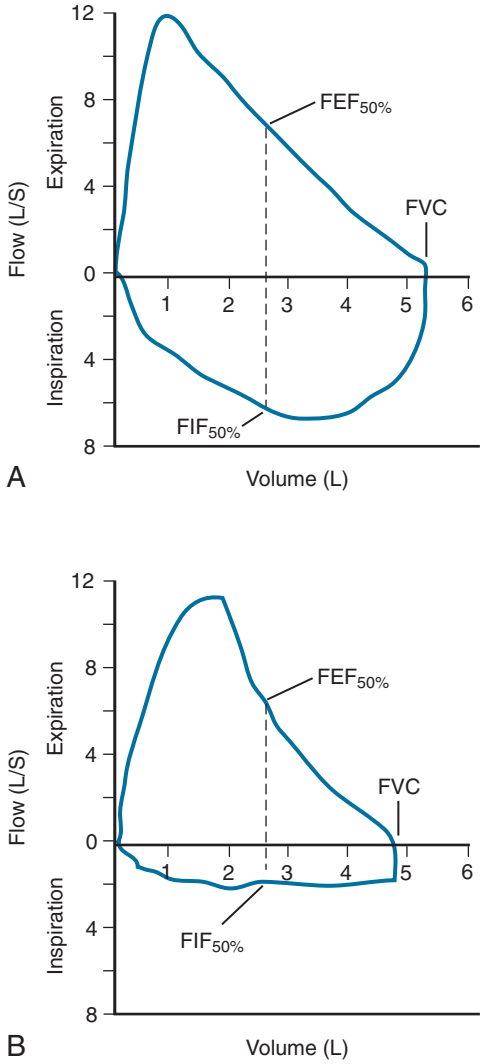


FIGURE 43-8 ■ A, Normal flow volume loop. B, Extrathoracic airflow obstruction with truncation of the inspiratory loop. This is consistent with symptomatic vocal cord dysfunction but may be seen in other laryngeal diseases. FEF_{50}, forced expiratory flow at 50% FVC; FIF_{50}, forced inspiratory flow at 50% FVC; FVC, forced vital capacity. (Redrawn from Perkner J, Fennelly K, Balkissoon R, et al: Irritant associated vocal cord dysfunction. J Occup Environ Med 40:136–143, 1998. ©American College of Occupational and Environmental Medicine.)

Management of Laryngeal Obstruction

Treatment of obstruction of the laryngeal airway is dependent on the etiology. In cases of emergent airway compromise, the key objectives are establishing adequate oxygenation and gas exchange. Ideally, patients are mildly sedated and kept awake if possible. The use of paralytic agents should be avoided, particularly if it is difficult to intubate the patient. The physician should be alerted to evaluate these patients by laryngoscopy during and soon after intubation. In cases in which associated severe tracheal obstruction (e.g., burns, trauma, invasive tumors) is present, one can consider the use of an open ventilating rigid bronchoscope that allows for a secure airway during visualization and ensures adequate oxygenation. Insertion of a rigid bronchoscope also serves the purpose of dilating an acutely narrowing airway. Once the airway is secured, a detailed examination of the upper airway and the tracheobronchial tree can be performed. In cases of massive trauma, patients are intubated for general support; and laryngeal obstruction due to fractures of the laryngeal cartilages, arytenoid cartilage dislocation, hematoma formation, and bilateral vocal cord paralysis can be overlooked or missed and appreciated only after the patient is extubated.

Upper airway obstruction due to laryngeal dysfunction requires the identification of contributing factors (medications, underlying medical problems such as gastroesophageal reflux disease and postnasal drip, psychological factors) and their optimal treatment.[133] Understanding the complex nature of the pathophysiology of VCD and laryngeal dysfunction underscores the need for a multidisciplinary approach.[134]

Speech and language pathologists/therapists specifically trained to address laryngeal dysfunction and to provide instruction in techniques of throat relaxation,

cough suppression, and throat-clearing suppression play a central role in the management and follow-up of VCD.[135] Speech therapists may also be helpful in performing controlled irritant challenges in which individuals are serially exposed to increasing concentrations of a provocative agent and are coached by the therapist during these exposures on how to control their laryngeal response or how to abort an acute attack.

Psychosocial assessment and treatment is key in managing these patients because there is generally some degree (though highly variable) of psychological overlay, either preexisting or as a consequence of developing VCD. Input from psychologists and/or psychiatrists regarding evidence of conversion, panic, anxiety, affective personality, or posttraumatic stress disorder is helpful. In addition, patient education and reassurance are extremely important in managing these patients. Follow-up with supportive counseling and teaching relaxation and/or biofeedback techniques may also be beneficial. Clinicians should discontinue unnecessary medications such as bronchodilators and steroids if coexistent asthma has been ruled out. Treatment for associated gastroesophageal reflux disease and/or rhinosinusitis may reduce symptoms.

Acute severe episodes of laryngeal dysfunction may generally be controlled and managed with sedation and/or heliox (80% helium/20% oxygen).[136] More recent studies have suggested that a simple device that creates resistance during the inspiratory phase can relieve VCD attacks.[137] Topical lidocaine applied to the larynx may also be useful during acute episodes in select patients. In severe cases, superior laryngeal blocks with *Clostridium botulinum* toxin have been attempted with variable success.[138] This treatment has been more successful for muscle tension dysphonia than for VCD.[139] Tracheotomy has been used for some patients with severe VCD refractory to conventional therapy, but it is rarely (if ever) indicated.

KEY POINTS

- As the conduit and indeed the gateway for air destined for the lungs, the upper airway plays a critical role in filtering and conditioning inspired air before it passes to the lower airways.
- Olfaction, allergic responses, nonallergic inflammation, and accentuated laryngeal closure reflexes serve as warning signals and barriers to the entry of noxious or potentially harmful inhalants from reaching the lungs.
- Clinicians who have an appreciation of the important role of the upper airway are better equipped to manage their patients with lower airway disease.

References

1. Strohl KP, et al: Activation of upper airway muscles before onset of inspiration in normal humans. J Appl Physiol 49: 638–642, 1980.
2. Green JH, Neil E: The respiratory function of the laryngeal muscles. J Physiol 129:134–141, 1955.
3. Mann DG, et al: Dilator naris muscle. Ann Otol Rhinol Laryngol 86:362–370, 1977.
4. Brouillette RT, Thach BT: Control of genioglossus muscle inspiratory activity. J Appl Physiol 49:801–808, 1980.
5. Weiner D, et al: Effect of chemical stimuli on nerves supplying upper airway muscles. J Appl Physiol 52:530–536, 1982.
6. Cole P, et al: Dynamic components of nasal resistance. Am Rev Respir Dis 132:1229–1232, 1985.
7. Permutt S, Riley RL: Hemodynamics of collapsible vessels with tone: The vascular waterfall. J Appl Physiol 18:924–932, 1963.
8. Bridger GP, Proctor DF: Maximum nasal inspiratory flow and nasal resistance. Ann Otol Rhinol Laryngol 79:481–488, 1970.
9. Smith PL, et al: Upper airway pressure-flow relationships in obstructive sleep apnea. J Appl Physiol 64:789–795, 1988.
10. Schwartz AR, et al: Effect of positive nasal pressure on upper airway pressure-flow relationships. J Appl Physiol 66:1626–1634, 1989.
11. Haight JS, Cole P: The site and function of the nasal valve. Laryngoscope 93:49–55, 1983.
12. Swift D: Access of air to the respiratory tract. *In* Proctor DF (ed): Respiratory Defense Mechanisms (Part I). Marcel Dekker, New York: 1977.
13. Cole P: Modification of inspired air. *In* Proctor D, Anderson I (eds): The Nose, Upper Airway Physiology and the Atmospheric Environment. Amsterdam: Elsevier Biomedical, 1982, pp 351–376.
14. Cole P: Upper respiratory airflow. *In* Proctor D, Anderson I (eds): The Nose, Upper Airway Physiology and the Atmospheric Environment. Amsterdam: Elsevier Biomedical, 1982, pp 163–190.
15. Bau SK, et al: The measurement of fluid deposition in humans following mist tent therapy. Pediatrics 48:605–612, 1971.
16. Proctor D, Andersen I: The fate and effects of inhaled materials. *In* Proctor D, Andersen I (eds): The Nose, Upper Airway Physiology and the Atmospheric Environment. Amsterdam: Elsevier Biomedical, 1982, pp 423–456.
17. Strohl KP, O'Cain CF, Slutsky AS: Alae nasi activation and nasal resistance in healthy subjects. J Appl Physiol 52:1432–1437, 1982.
18. van Lunteren E, et al: Nasal and laryngeal reflex responses to negative upper airway pressure. J Appl Physiol 56:746–752, 1984.
19. Togias A: The impact of nasal function and dysfunction on the lower airway. *In* Upper and Lower Respiratory Disease. J Corren, A. Toqias, J. Bousquet (eds). Marcel Dekker; 1st ed. 2003, pp 53–86.
20. Shturman-Ellstein R, et al: The beneficial effect of nasal breathing on exercise-induced bronchoconstriction. Am Rev Respir Dis 118:65–73, 1978.
21. Griffin MP, McFadden ER Jr, Ingram RH Jr: Airway cooling in asthmatic and nonasthmatic subjects during nasal and oral breathing. J Allergy Clin Immunol 69:354–359, 1982.
22. Tos M: Goblet cells and glands in the nose and paranasal sinuses. In Proctor D, Anderson I (eds): The Nose, Upper Airway Physiology and the Atmospheric Environment. Amsterdam: Elsevier Biomedical, 1982, pp 99–144.

23. Watanabe K, Watanabe I: The ultrastructural characteristics of the capillary walls in human nasal mucosa. Rhinology 18:183–195, 1980.
24. Burnham H: An anatomical investigation of blood vessels of the lateral nasal wall and their relation to turbinates and sinuses. J Laryngol Otol 50:569–593, 1935.
25. Cauna N: The fine structure of the arteriovenous anastomosis and its nerve supply in the human nasal respiratory mucosa. Anat Rec 168:9–21, 1970.
26. Cauna N, Hinderer KH, Wentges RT: Sensory receptor organs of the human nasal respiratory mucosa. Am J Anat 124:187–209, 1969.
27. Shelhamer J, Marom Z, Kaliner M: The constituents of nasal secretion. Ear Nose Throat J 63:30, 32–33, 1984.
28. Raphael GD, Baraniuk JN, Kaliner MA: How and why the nose runs. J Allergy Clin Immunol 87:457–467, 1991.
29. Lundberg JO, et al: High nitric oxide production in human paranasal sinuses. Nat Med 1:370–373, 1995.
30. Rouby JJ: The nose, nitric oxide, and paranasal sinuses: The outpost of pulmonary antiinfectious defenses? Am J Respir Crit Care Med 168:265–266, 2003.
31. Bousquet J, Van Cauwenberge P, Khaltaev N: Allergic rhinitis and its impact on asthma. J Allergy Clin Immunol 108(5 Suppl):S147–S334, 2001.
32. Togias A: Non-allergic rhinitis. *In* Clinical Aspects. 1993, pp 159–166.
33. Settipane RA, Lieberman P: Update on nonallergic rhinitis. Ann Allergy Asthma Immunol 86:494–507, 2001 [quiz 507–508].
34. Sibbald B, Rink E: Epidemiology of seasonal and perennial rhinitis: Clinical presentation and medical history. Thorax 46:895–901, 1991.
35. Turkeltaub PC, Gergen PJ: Prevalence of upper and lower respiratory conditions in the US population by social and environmental factors: Data from the second National Health and Nutrition Examination Survey, 1976 to 1980 (NHANES II). Ann Allergy 67:147–154, 1991.
36. Meltzer EO, Blaiss MS, Derebery MJ, et al: Burden of allergic rhinitis: results from the Pediatric Allergies in America survey. J Allergy Clin Immunol 124(3 Suppl):S43–S70, 2009.
37. Malone DC, et al: A cost of illness study of allergic rhinitis in the United States. J Allergy Clin Immunol 99:22–27, 1997.
38. Meltzer EO: The prevalence and medical and economic impact of allergic rhinitis in the United States. J Allergy Clin Immunol 99:S805–S828, 1997.
39. Reed SD, Lee TA, McCory DC: The economic burden of allergic rhinitis: a critical evaluation of the literature. Pharmacoeconomics 22:345–361, 2004.
40. Gelfand EW: Inflammatory mediators in allergic rhinitis. J Allergy Clin Immunol 114(5 Suppl):S135–S138, 2004.
41. Suzuki S, Takeuchi K, Majima Y: Localization and function of histamine H3 receptor in the nasal mucosa. Clin Exp Allergy 38:1476–1482, 2008.
42. Taylor-Clark TE: Insights into the mechanisms of histamine-induced inflammation in the nasal mucosa. Pulm Pharmacol Ther 21:455–460, 2008.
43. Shirasaki H, et al: Expression and localization of the cysteinyl leukotriene 1 receptor in human nasal mucosa. Clin Exp Allergy 32:1007–1012, 2002.
44. Naclerio RM, et al: Inflammatory mediators in late antigen-induced rhinitis. N Engl J Med 313:65–70, 1985.
45. Varney VA, et al: Immunohistology of the nasal mucosa following allergen-induced rhinitis. Identification of activated T lymphocytes, eosinophils, and neutrophils. Am Rev Respir Dis 146:170–176, 1992.
46. Igarashi Y, et al: Quantitation of inflammatory cells in the nasal mucosa of patients with allergic rhinitis and normal subjects. J Allergy Clin Immunol 95:716–725, 1995.
47. Lim MC, Taylor RM, Naclerio RM: The histology of allergic rhinitis and its comparison to cellular changes in nasal lavage. Am J Respir Crit Care Med 151:136–144, 1995.
48. MacDonald SM: Human recombinant histamine-releasing factor. Int Arch Allergy Immunol 113:187–189, 1997.
49. Connell JT: Quantitative intranasal pollen challenges. 3. The priming effect in allergic rhinitis. J Allergy 43:33–44, 1969.
50. Sanico AM, et al: Neural hyperresponsiveness and nerve growth factor in allergic rhinitis. Int Arch Allergy Immunol 118:154–158, 1999.
51. Hamilos DL, et al: Evidence for distinct cytokine expression in allergic versus nonallergic chronic sinusitis. J Allergy Clin Immunol 96:537–544, 1995.
52. Jacobs RL, Freedman PM, Boswell RN: Nonallergic rhinitis with eosinophilia (NARES syndrome). Clinical and immunologic presentation. J Allergy Clin Immunol 67:253–262, 1981.
53. Carney AS, et al: Atypical nasal challenges in patients with idiopathic rhinitis: More evidence for the existence of allergy in the absence of atopy? Clin Exp Allergy 32:1436–1440, 2002.
54. Cook JA, Hamilton JW, Jones AS: The diving reflex in non-eosinophilic non-allergic rhinitis. Clin Otolaryngol Allied Sci 21:226–227, 1996.
55. Wilde AD, Cook JA, Jones AS: The nasal response to isometric exercise in non-eosinophilic intrinsic rhinitis. Clin Otolaryngol Allied Sci 21:84–86, 1996.
56. Lacroix JS, et al: Improvement of symptoms of non-allergic chronic rhinitis by local treatment with capsaicin. Clin Exp Allergy 21:595–600, 1991.
57. Blom HM, et al: Intranasal capsaicin is efficacious in non-allergic, non-infectious perennial rhinitis. A placebo-controlled study. Clin Exp Allergy 27:796–801, 1997.
58. Baraniuk JN, et al: Neuropathology in rhinosinusitis. Am J Respir Crit Care Med 171:5–11, 2005.
59. Wise SK, Wise JC, DelGaudio JM: Association of nasopharyngeal and laryngopharyngeal reflux with postnasal drip symptomatology in patients with and without rhinosinusitis. Am J Rhinol 20:283–289, 2006.
60. Terreehorst I, et al: Evaluation of impermeable covers for bedding in patients with allergic rhinitis. N Engl J Med 349:237–246, 2003.
61. Simons FE: H_1-Antihistamines: More relevant than ever in the treatment of allergic disorders. J Allergy Clin Immunol 112(4 Suppl):S42–S52, 2003.
62. Verster JC, Volkerts ER: Antihistamines and driving ability: Evidence from on-the-road driving studies during normal traffic. Ann Allergy Asthma Immunol 92:294–303, 2004 [quiz 303–305, 355].

62a. Kaliner MA: Azelastine and olopatadine in the treatment of allergic rhinitis. Ann Allergy Immunol 103:373–380, 2009.

63. Anggard A, Malm L: Orally administered decongestant drugs in disorders of the upper respiratory passages: A survey of clinical results. Clin Otolaryngol Allied Sci 9:43–49, 1984.
64. Kaiser HB, et al: Long-term treatment of perennial allergic rhinitis with ipratropium bromide nasal spray 0.06%. J Allergy Clin Immunol 95:1128–1132, 1995.
65. Wilson AM, O'Byrne PM, Parameswaran K: Leukotriene receptor antagonists for allergic rhinitis: A systematic review and meta-analysis. Am J Med 116:338–344, 2004.
66. Perry TT, et al: Protective effect of montelukast on lower and upper respiratory tract responses to short-term cat allergen exposure. Ann Allergy Asthma Immunol 93:431–438, 2004.

66a. Malice MP, Dass SB, Reiss TF: Clinical studies of combination montelukast and loratadine in patients with seasonal allergic rhinitis. J Asthma 46:878–883, 2009.

67. Naclerio RM: Allergic rhinitis. N Engl J Med 325:860–869, 1991.
68. Waddell AN, et al: Intranasal steroid sprays in the treatment of rhinitis: Is one better than another? J Laryngol Otol 117:843–845, 2003.
69. Baroody FM, et al: Absence of nasal mucosal atrophy with fluticasone aqueous nasal spray. Arch Otolaryngol Head Neck Surg 127:193–199, 2001.
70. Knutsson U, et al: Effects of intranasal glucocorticoids on endogenous glucocorticoid peripheral and central function. J Endocrinol 144:301–310, 1995.
71. Wilson AM, et al: Effects of intranasal corticosteroids on adrenal, bone, and blood markers of systemic activity in allergic rhinitis. J Allergy Clin Immunol 102:598–604, 1998.
72. Iliopoulos O, et al: Effects of immunotherapy on the early, late, and rechallenge nasal reaction to provocation with allergen: Changes in inflammatory mediators and cells. J Allergy Clin Immunol 87:855–866, 1991.

73. Bousquet J, Lockey R, Malling HJ: Allergen immunotherapy: Therapeutic vaccines for allergic diseases. A WHO position paper. J Allergy Clin Immunol 102:558–562, 1998.
74. Durham SR, et al: Long-term clinical efficacy of grass-pollen immunotherapy. N Engl J Med 341:468–475, 1999.
75. Moller C, et al: Pollen immunotherapy reduces the development of asthma in children with seasonal rhinoconjunctivitis (the PAT-study). J Allergy Clin Immunol 109:251–256, 2002.
76. Malling HJ: Indications and contraindications for allergen-specific immunotherapy. Allergy Clin Immunol Int 10:76–80, 1998.
77. Van Rijswijk JB: Intranasal capsacin reduces nasal hyperreactivity in idiopathic rhinitis: A double-blinded randomized application regimen study. Allergy 58:754–761, 2003.
78. Bhattacharyya N: Contemporary assessment of the disease burden of sinusitis. Am J Rhinol Allergy 23:392–395, 2009.
79. Sokol W: Epidemiology of sinusitis in the primary care setting: Results from the 1999–2000 respiratory surveillance program. Am J Med 111(Suppl 9A):19S–24S, 2001.
80. Benninger MS, Sedory Holzer SE, Lau J: Diagnosis and treatment of uncomplicated acute bacterial rhinosinusitis: Summary of the Agency for Health Care Policy and Research evidence-based report. Otolaryngol Head Neck Surg 122:1–7, 2000.
81. Ray NF, et al: Healthcare expenditures for sinusitis in 1996: Contributions of asthma, rhinitis, and other airway disorders. J Allergy Clin Immunol 103:408–414, 1999.
82. Lanza DC, Kennedy DW: Adult rhinosinusitis defined. Otolaryngol Head Neck Surg 117:S1–S7, 1997.
83. Bent JP 3rd, Kuhn FA: Diagnosis of allergic fungal sinusitis. Otolaryngol Head Neck Surg 111:580–588, 1994.
84. Gwaltney JM Jr, et al: Computed tomographic study of the common cold. N Engl J Med 330:25–30, 1994.
85. Baroody FM, et al: Eosinophilia in chronic childhood sinusitis. Arch Otolaryngol Head Neck Surg 121:1396–1402, 1995.
86. Hamilos DL, et al: Chronic hyperplastic sinusitis: Association of tissue eosinophilia with mRNA expression of granulocyte-macrophage colony-stimulating factor and interleukin-3. J Allergy Clin Immunol 92:39–48, 1993.
87. Driscoll PV, Naclerio RM, Baroody FM: $CD4^+$ lymphocytes are increased in the sinus mucosa of children with chronic sinusitis. Arch Otolaryngol Head Neck Surg 122:1071–1076, 1996.
88. Togias A: Rhinitis and asthma: Evidence for respiratory system integration. J Allergy Clin Immunol 111:1171–1183 2003 [quiz 1184].
89. Benninger MS: Rhinitis, sinusitis, and their relationships to allergies. Am Jf Rhinol 6:37–43, 1992.
90. Ponikau JU, et al: Intranasal antifungal treatment in 51 patients with chronic rhinosinusitis. J Allergy Clin Immunol 110:862–866, 2002.
91. Wise SK, Wise JC, DelGaudio JM: Gastroesophageal reflux and laryngopharyngeal reflux in patients with sleep-disordered breathing. Otolaryngol Head Neck Surg 135:253–257, 2006.
92. DelGaudio JM, Waring JP: Empiric esomeprazole in the treatment of laryngopharyngeal reflux. Laryngoscope 113:598–601, 2003.
93. Berger WE, Schonfeld JE: Nonallergic rhinitis in children. Clin Allergy Immunol 19:197–207, 2007.
94. Brooks I, et al: Medical management of acute bacterial sinusitis. Recommendations of a clinical advisory committee on pediatric and adult sinusitis. Ann Otol Rhinol Laryngol Suppl 182:2–20, 2000.
95. Varonen H, et al: Treatment of acute rhinosinusitis diagnosed by clinical criteria or ultrasound in primary care. A placebo-controlled randomised trial. Scand J Prim Health Care 21:121–126, 2003.
96. van Buchem FL, et al: Primary-care–based randomised placebo-controlled trial of antibiotic treatment in acute maxillary sinusitis. Lancet 349:683–687, 1997.
97. Ozcan M, et al: Correlation of middle meatus and ethmoid sinus microbiology in patients with chronic sinusitis. Rhinology 40:24–27, 2002.
98. Vaughan WC, Carvalho G: Use of nebulized antibiotics for acute infections in chronic sinusitis. Otolaryngol Head Neck Surg 127:558–568, 2002.
99. Wormald PJ, et al: A comparative study of three methods of nasal irrigation. Laryngoscope 114:2224–2227, 2004.
100. Uren B, Psaltis A, Wormald PJ: Nasal lavage with mupirocin for the treatment of surgically recalcitrant chronic rhinosinusitis. Laryngoscope 118:1677–1680, 2008.
101. Wawrose SF, Tami TA, Amoils CP: The role of guaifenesin in the treatment of sinonasal disease in patients infected with the human immunodeficiency virus (HIV). Laryngoscope 102:1225–1228, 1992.
102. Dolor RJ, et al: Comparison of cefuroxime with or without intranasal fluticasone for the treatment of rhinosinusitis. The CAFFS Trial: A randomized controlled trial. JAMA 286:3097–3105, 2001.
103. Meltzer EO, et al: Intranasal flunisolide spray as an adjunct to oral antibiotic therapy for sinusitis. J Allergy Clin Immunol 92:812–823, 1993.
104. Parikh A, et al: Topical corticosteroids in chronic rhinosinusitis: A randomized, double-blind, placebo-controlled trial using fluticasone propionate aqueous nasal spray. Rhinology 39:75–79, 2001.
105. Lavigne F, et al: Intrasinus administration of topical budesonide to allergic patients with chronic rhinosinusitis following surgery. Laryngoscope 112:858–864, 2002.
106. Sachanandani NS, et al: The effect of nasally administered budesonide respules on adrenal cortex function in patients with chronic rhinosinusitis. Arch Otolaryngol Head Neck Surg 135:303–307, 2009.
107. Casale TB, Stokes J: Anti-IgE therapy: Clinical utility beyond asthma. J Allergy Clin Immunol 123:770–771, e1, 2009.
108. Grundmann SA, Hemfort PB, Luger TA, Brehler R: AntiIgE (omalizumab): a new therapeutic approach for chronic rhinosinusitis. J Allergy Clin Immunol 121:257–258, 2008.
109. Damm M, et al: Impact of functional endoscopic sinus surgery on symptoms and quality of life in chronic rhinosinusitis. Laryngoscope 112:310–315, 2002.
110. Senior BA, et al: Long-term results of functional endoscopic sinus surgery. Laryngoscope 108:151–157, 1998.
111. Widdicombe JG: Reflexes from the upper respiratory tract. *In* Fishman AP, Cherniack NS, Widdicombe JG (eds): Handbook of Physiology: The Respiratory System. Vol II: Control of Breathing (Part I). Bethesda, MD: American Physiological Society, 1988, pp 363–394.
112. Clerf LH: Unilateral vocal cord paralysis. J Am Med Assoc 151:900–903, 1953.
113. Parnell FW, Brandenburg JH: Vocal cord paralysis. A review of 100 cases. Laryngoscope 80:1036–1045, 1970.
114. Newman K, Dubester S: Vocal cord dysfunction: Masquerader of asthma. Sem Respir Crit Care Med 15:162–167, 1994.
115. Christopher KL, et al: Vocal-cord dysfunction presenting as asthma. N Engl J Med 308:1566–1570, 1983.
116. Backus WW, et al: Postextubation laryngeal spasm in an unanesthetized patient with Parkinson's disease. J Clin Anesth 3:314–316, 1991.
117. Cohen HA, et al: Nocturnal acute laryngospasm in children: A possible epileptic phenomenon. J Child Neurol 15:202–204, 2000.
118. Cohen JT, et al: Clinical manifestations of laryngopharyngeal reflux. Ear Nose Throat J 81(9 Suppl 2):19–23, 2002.
119. Johnstone RE: Laryngospasm treatment—An explanation. Anesthesiology 91:581–582, 1999.
120. Liistro G, et al: Exercise-induced laryngospasm of emotional origin. Pediatr Pulmonol 8:58–60, 1990.
121. Mortero RF, et al: Severe laryngospasm at tracheal extubation in a patient with superior laryngeal nerve injury. Anesth Analg 92:271–272, 2001.
122. Mutlu GM, et al: Laryngospasm and paradoxical bronchoconstriction after repeated doses of beta 2-agonists containing edetate disodium. Mayo Clin Proc 75:285–287, 2000.
123. van den Bergh AA, Rozario CJ, Savva D: Fentanyl-induced laryngospasm? Anaesthesia 51:804, 1996.
124. White SM: Cannabis abuse and laryngospasm. Anaesthesia 57:622–623, 2002.
125. Warner DO: Intramuscular succinylcholine and laryngospasm. Anesthesiology 95:1039–1040, 2001.
126. Vlahakis NE, et al: Diagnosis of vocal cord dysfunction: The utility of spirometry and plethysmography. Chest 122:2246–2249, 2002.

127. Morrison M, Rammage L, Emami A: The irritable larynx syndrome. J Voice 13:447–455, 1999.
128. Bucca C, et al: Are asthma-like symptoms due to bronchial or extrathoracic airway dysfunction? Lancet 346:791–795, 1995.
129. Perkner JJ, et al: Irritant-associated vocal cord dysfunction. J Occup Environ Med 40:136–143, 1998.
130. Mutoh T, Tsubone H: Hypersensitivity of laryngeal C-fibers induced by volatile anesthetics in young guinea pigs. Am J Respir Crit Care Med 167:557–562, 2003.
131. Ayres JG, Gabbott PL: Vocal cord dysfunction and laryngeal hyperresponsiveness: A function of altered autonomic balance? Thorax 57:284–285, 2002.
132. Vaezi MF: Gastroesophageal reflux disease and the larynx. J Clin Gastroenterol 36:198–203, 2003.
133. Patel NJ, et al: Concurrent laryngeal abnormalities in patients with paradoxical vocal fold dysfunction. Otolaryngol Head Neck Surg 130:686–689, 2004.
134. Andrianopoulos MV, Gallivan GJ, Gallivan KH: PVCM, PVCD, EPL, and irritable larynx syndrome: What are we talking about and how do we treat it? J Voice 14:607–618, 2000.
135. Murry T, Tabaee A, Aviv JE: Respiratory retraining of refractory cough and laryngopharyngeal reflux in patients with paradoxical vocal fold movement disorder. Laryngoscope 114:1341–1345, 2004.
136. Reisner C, Borish L: Heliox therapy for acute vocal cord dysfunction (letter). Chest 108:1477, 1995.
137. Archer GJ, et al: Inspiratory vocal cord dysfunction, a new approach in treatment. Eur Respir J 15:617–618, 2000.
138. Altman KW, et al: Paradoxical vocal fold motion: Presentation and treatment. J Voice 14:99–103, 2000.
139. Bielamowicz S, Ludlow CL: Effects of botulinum toxin on pathophysiology in spasmodic dysphonia. Ann Otol Rhinol Laryngol 109:194–203, 2000.

CHAPTER 44

DISORDERS OF THE INTRATHORACIC AIRWAYS

Stephen C. Lazarus, MD

INTRODUCTION

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LOCALIZED DISORDERS

Neoplasms
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INTRODUCTION

Previous chapters in this section have described the major diseases that affect primarily intrathoracic airways: asthma, bronchitis, cystic fibrosis, and bronchiectasis. There are, in addition, a number of less common entities that involve these airways. Bronchiolitis, bronchiolitis obliterans, and bronchopulmonary dysplasia are diseases of the peripheral airways. In addition, mucus plugging of small airways can occur acutely or chronically in association with a number of diseases. Because of the large cross-sectional area of these peripheral airways, early diagnosis may be difficult. However, the widespread involvement of small bronchi and bronchioles may have major physiologic consequences. Increasing awareness of these diseases has led to an increased frequency of diagnosis. In contrast to these generalized diseases of the peripheral airways, there are also a number of conditions whose effects are localized to more central airways. In this chapter, both the local and the diffuse processes involving intrathoracic airways are discussed. In addition, the use of tracheobronchial stents to treat proximal airway obstruction is described.

DISORDERS WITH DIFFUSE INVOLVEMENT

Anatomic and Physiologic Features

Intrapulmonary airways can be subclassified as bronchi, bronchioles, and gas exchange ducts (see Chapter 1). Although all the conducting airways contain smooth muscle, there are important differences that distinguish bronchi from bronchioles. *Bronchi* contain cartilage, submucosal glands, ciliated epithelial cells, and goblet

cells. Bronchial smooth muscle is innervated by muscarinic output carried in the vagus nerves. Nerve endings responsible for cough ("cough receptors") are found in the large bronchi, mostly at bifurcations. Because of their limited total cross-sectional area, the bronchi are responsible for most of the resistance to airflow in the lung.[1]

In contrast to bronchi, *bronchioles* normally do not contain cartilage, glands, or goblet cells. In many chronic diseases of the airways (e.g., chronic bronchitis, asthma, cystic fibrosis), increased numbers of goblet cells are found in peripheral airways, and they are thought to play significant roles in the pathophysiology of these diseases.[2] Cilia are more sparse in bronchioles than in bronchi, and bronchiolar smooth muscle is not under vagal control. Repeated branching creates a large number of bronchioles arranged in parallel. This results in a large total cross-sectional area, such that bronchioles normally contribute little to total airflow resistance. However, when disease affects large numbers of these peripheral airways, the impact on airway resistance is significant.

Because the walls of the airways are not rigid, their dimensions change with lung volume. The bronchioles are located in the connective tissue structure of the lung, and their walls are relatively thin.[3] Although the contribution of bronchioles to total airflow resistance is small at normal and high lung volumes, they narrow markedly at low lung volumes, and their contribution to resistance increases as residual volume is approached. This increased narrowing explains why normal peripheral bronchioles may close at low lung volumes.[4]

Narrowing of peripheral airways may have profound effects on lung function. For example, local peripheral airway narrowing may decrease ventilation to a diseased area, leading to hypoxemia, but this narrowing may not produce wheezing or striking increases in the total work of breathing. For these reasons, pathologic narrowing of peripheral airways is difficult to detect, and these airways may be considered a "silent zone" of the lung. Despite much effort to design tests to identify obstruction in peripheral airways, no method has been entirely successful (see Chapter 24).

Epidemiology

The frequency of disorders of the peripheral airways is unknown because of the difficulty of localizing abnormalities to these sites. Moreover, because of the continuity between bronchi and bronchioles, it is doubtful whether pure bronchitis or bronchiolitis ever exists. Indeed, some authors prefer to avoid making an anatomic distinction about the site of inflammation and collectively refer to these peripheral airways (<2 mm in diameter) as "small airways."[5] Processes that obstruct small airways may result in severe functional disability.

Bronchiolitis

Bronchiolitis, a cellular and mesenchymal reaction involving bronchioles, is relatively uncommon in adults. Although bronchiolitis may occur in response to various stimuli, identification may be delayed because of the difficulty in detecting this narrowing. Bronchiolitis has been reported after administration of busulfan, gold, or penicillamine.[6] A generalized inflammatory response of the peripheral airways may follow inhalation of a corrosive gas that penetrates deeply into the lungs. Because they are highly soluble, irritants such as sulfur dioxide and ammonia dissolve in the lining fluid of the upper airways, causing damage primarily there. Less soluble gases such as nitrogen dioxide and phosgene pass into peripheral airways where they cause inflammatory changes in bronchioles and alveoli.[7,8] Such toxic fume exposures are a significant industrial and environmental hazard. "Nitrous fumes," for example, may be found in silo gas, jet and missile fuel, metal pickling fumes, and certain fires. Other fumes, such as those associated with food flavoring, have been implicated in the pathogenesis of bronchiolitis.[9,10] (This subject is discussed more fully in Chapter 68.)

After exposure to toxic fumes, three clinical patterns may develop (Fig. 44-1).[7,8] Acutely, patients may develop cough, dyspnea, cyanosis, hemoptysis, hypoxemia, and loss of consciousness. These symptoms and signs may disappear within hours, or they may persist for weeks before they eventually resolve. In patients exposed to higher concentrations, pulmonary edema and severe acute respiratory distress syndrome may develop immediately or following a latent period of 3 to 30 hours. Although most patients recover, death may occur. Finally, some patients develop irreversible airflow obstruction (bronchiolitis obliterans) 2 to 8 weeks after the initial exposure. Typically, this occurs after recovery

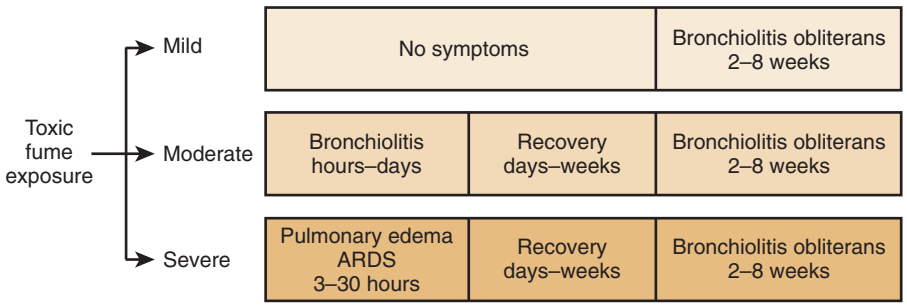

FIGURE 44-1 ■ The severity of bronchiolitis following inhalation of toxic fumes depends in part on the magnitude of the exposure. Most patients will recover from the acute event, although some will develop bronchiolitis obliterans 2–8 wk after the initial insult. ARDS, acute respiratory distress syndrome.

from the acute symptoms of exposure or in patients who had no initial illness; it is characterized by the gradual onset of dyspnea and a nonproductive cough.[7,11] Patients who develop bronchiolitis obliterans after toxic fume inhalation commonly experience progressive deterioration, often leading to death from respiratory failure.

In contrast to adults, in whom it is considered rare, infectious bronchiolitis is a common lower respiratory tract illness in infants and young children. The cause most commonly is a virus, especially respiratory syncytial virus (RSV).[12] In older children and in adults, bronchiolitis has been associated with *Mycoplasma pneumoniae*, *Legionella pneumophilia*, and several viruses including adenovirus, influenza, and parainfluenza.[13–15]

Bronchiolitis in children typically begins as an acute virus-like illness. Within several days, cough, dyspnea, and fever develop. Although wheezing, chest wall retractions, and cyanosis may be seen, respiratory failure is uncommon. Peribronchiolar inflammation with epithelial necrosis and sloughing, when severe, causes airflow obstruction in the peripheral airways of infants, with resulting hyperinflation and severe gas exchange abnormalities.[16] Roentgenograms generally show overinflation of the lungs, and sometimes, nodular shadows appear with areas of focal atelectasis and pneumonia.[15,17,18] Bronchiolitis is usually self-limited, and complete recovery usually occurs within days to weeks. Symptomatic treatment with supplementary oxygen and hydration is usually all that is necessary. Bronchiolitis in infancy has been associated with an increased risk of subsequent wheezing and bronchial hyperreactivity,[19] and non-RSV (e.g., rhinovirus) bronchiolitis may be especially likely to result in wheezing over the next 3 years.[20] However, a direct link to chronic obstructive pulmonary disease has not been shown. Occasionally, bronchiolitis obliterans, bronchiolectasis, and localized emphysema develop as sequelae to bronchiolitis.[12] No role has been proved for bronchodilators, antibiotics, or corticosteroids, although the latter are often used empirically in progressive disease in an attempt to reduce the severity of obliterative bronchiolitis. Elevated levels of cysteinyl leukotrienes have been reported in viral infections,[21,22] and leukotriene modifiers have been shown to reduce respiratory symptoms and wheezing after RSV bronchiolitis in some,[23,24] but not all,[25] studies.

Because of their anatomic features, diseases of peripheral airways are difficult to detect and to differentiate from diseases of large airways. In individual patients, the cause of acute bronchiolitis is often not established, and the disease in patients with progressive bronchiolitis obliterans is frequently classified as "idiopathic." Lung biopsy should be considered in those with chronic progressive disease, and this may require a surgical rather than a transbronchial approach.

Bronchiolitis Obliterans (Obliterative Bronchiolitis)

The term *bronchiolitis obliterans* is commonly used to describe a number of unrelated conditions whose common end point is functional obstruction of bronchioles. Bronchiolitis obliterans was first described by Reynaud in 1835. In 1901, Lange described two young adults who died of rapidly progressive respiratory failure. At autopsy, their lungs revealed fibrous scarring of small airways with polypoid foci of exudate extending into the lumens. Since that time, bronchiolitis obliterans has been described after inhalation of toxic fumes, as a consequence of respiratory infections, in association with connective tissue disorders, and after bone marrow or heart-lung transplantation (Table 44-1). It appears that any damage to the bronchiolar epithelium may lead to excessive proliferation of granulation tissue during the repair phase. The reason this occurs in only a percentage of patients is unknown, but it probably reflects both differences in the magnitude of the provocative stimulus and abnormalities in the responses of host tissue. Bronchiolitis obliterans is classified clinically based upon etiology (see Table 44-1)[26] and histopathologically based on tissue morphology.[27]

TABLE 44-1. Conditions Associated with Bronchiolitis Obliterans

Toxic fume inhalation
Mineral dust exposure
Infection (viral, *Mycoplasma, Legionella*)
Bone marrow transplantation
Lung and heart-lung transplantation
Rheumatoid arthritis
Penicillamine
Systemic lupus erythematosus
Dermatomyositis, polymyositis
Hypersensitivity pneumonitis

Bronchiolitis obliterans characteristically presents with the insidious onset of a nonproductive cough and dyspnea 2 to 8 weeks after an acute respiratory illness or toxic exposure. Physical examination is typically unremarkable but may reveal diffuse expiratory wheezing. Similarly, routine laboratory studies are not helpful. The roentgenographic pattern of bronchiolitis obliterans is variable, and plain chest radiographs are rarely diagnostic. High-resolution computed tomography (HRCT) may show bronchial wall thickening, centrilobular nodules, or diffuse ground-glass opacification, or may on occasion be normal. In some patients, narrowing of small bronchi and bronchioles may result in marked hyperinflation of the distal lung, which is apparent on HRCT as "mosaic perfusion."[18,28] This postobstructive hyperinflation with associated roentgenographic hyperlucency may be generalized or confined to one lung. The unilateral hyperlucent lung syndrome was first described in children by Swyer and James,[29] and a year later, the same abnormality was reported in adults.[30] Currently, it is believed that these forms of hyperinflation with hyperlucency are postobstructive complications of bronchiolitis obliterans.

There are two distinct forms of bronchiolitis obliterans.[27,31,32] "Classic bronchiolitis obliterans," as described

TABLE 44-2. Classification, Prognosis, and Therapy of Bronchiolitis Obliterans

Type	Organizing Pneumonia	Prognosis	Therapy
Toxic fume exposure	Rare	Poor-good	Steroids
Postinfectious	±	Fair-good	Steroids
Connective tissue disease	±	Poor-good	Steroids
Localized	Yes	Good	Resection
Idiopathic	Yes	Fair-good	Steroids

Reproduced with permission from Epler GR, Colby TV: The spectrum of bronchiolitis obliterans. Chest 83:161–162, 1983.

by Lange and currently referred to as *proliferative bronchiolitis*, is characterized by intraluminal polyps of organizing connective tissue. This cellular process with proliferation of fibroblasts is the more common form of bronchiolitis. *Constrictive bronchiolitis*, in contrast, is characterized by partial or complete obstruction of bronchiolar lumens that results from chronic bronchiolar inflammation, concentric submucosal or adventitial scarring, and smooth muscle hypertrophy.[27,31,33] Constrictive bronchiolitis is most commonly seen after inhalation injury. These two forms show little clinical or histopathologic overlap. Histologically, pure bronchiolitis obliterans is rare. When present, there is obliteration of bronchiolar lumens without spread of fibrosis to air spaces or interstitium. Extension of the exudate and granulation tissue into alveoli is referred to as "organizing pneumonia," and the entire process is then known as *bronchiolitis obliterans with organizing pneumonia* (BOOP). Epler and Colby[26] suggested the classification shown in Table 44-2 to describe the histologic effects, prognosis, and response to therapy of different clinical patterns of bronchiolitis obliterans.

Bronchiolitis Obliterans and Connective Tissue Diseases

Bronchiolitis obliterans may occur as an uncommon manifestation of connective tissue or collagen vascular diseases. It has been reported in association with rheumatoid arthritis, where it primarily affects women with long-standing, seropositive rheumatoid arthritis in their fifth or sixth decade of life.[34] The onset and progression of dyspnea and nonproductive cough are rapid, as is the rate of progression of airflow obstruction. The chest roentgenogram usually shows no abnormalities. Unfortunately, no consistent response to corticosteroids has been documented, and the prognosis for these patients generally is poor,[35] although a subset of patients may have a more insidious course.[36] Penicillamine, used to treat rheumatoid arthritis, has been implicated as a potential cause of bronchiolitis obliterans, but confirmation of an etiologic relationship is lacking. Bronchiolitis obliterans has also been reported in systemic lupus erythematosus,[37] polymyositis, and dermatomyositis,[38] and in scleroderma where reflux and chronic microaspiration may play an important role.[39]

Bronchiolitis Obliterans after Bone Marrow Transplantation

Chronic graft-versus-host disease (GVHD) occurs in approximately one third of long-term survivors of allogeneic bone marrow transplantation. Bronchiolitis obliterans occurs in approximately 10% of bone marrow transplant patients who develop chronic GVHD. It is rare after autologous bone marrow transplantation because chronic GVHD does not occur in this setting. Bronchiolitis obliterans is preceded, 2 to 3 months after transplantation, by typical findings of GVHD: mucositis, esophagitis, and skin rash. Four to 6 months later, the patients develop dry, nonproductive cough, and exertional dyspnea that may be severe and rapidly progressive. The physical examination reveals scattered wheezing, and bibasilar crackles are often present. Hypoxemia is common. Of note, the chest roentgenogram usually shows no abnormalities or demonstrates hyperinflation.

Various mechanisms have been proposed to explain bronchiolitis obliterans after bone marrow transplantation.[40] Chronic GVHD and prior methotrexate therapy appear to be risk factors for the development of airflow obstruction.[41] The GVHD may damage small airways directly. Lung epithelial cells can express Ia (class II major histocompatibility complex [MHC]) antigens that may activate T cells from the donor, thus making the airways a target for immunologically mediated injury.[41] Methotrexate, which alone does not cause bronchiolitis obliterans, may act as a "priming" agent in the presence of GVHD, perhaps by inducing antigen expression in the lung. Finally, bronchiolitis obliterans may result from viral infection, and the increased immunosuppression given to treat GVHD may increase the risk of such opportunistic infections. A 25% to 30% incidence of viral infection has been reported in patients with bronchiolitis obliterans after bone marrow transplantation.[42]

Bronchiolitis Obliterans after Lung or Heart-Lung Transplantation

Bronchiolitis obliterans is the major cause of morbidity and mortality of long-term survivors of heart-lung transplantation, developing in 30% to 50% of transplant recipients (see Chapter 81). Although various factors have been suggested as causes of bronchiolitis obliterans after

heart-lung transplantation, including infections, altered mucociliary clearance, altered blood flow secondary to bronchial artery ligation, reaction to immunosuppressive drugs, and loss of the cough reflex with recurrent aspiration, it appears that these entities may act mainly as "cofactors" and that the primary pathogenetic event is chronic transplant rejection.[43,44] By multivariate analysis, human leukocyte antigen (HLA)-A locus mismatch stands out as a significant independent predictor of bronchiolitis obliterans.[45,46] Other factors associated with the development of bronchiolitis obliterans include three or more episodes of acute rejection,[47] primary graft dysfunction (i.e., ischemia-reperfusion injury),[48,49] gastroesophageal reflux disease,[50] and single-lung transplant.[51]

Bronchiolitis obliterans may present several months to several years after lung or heart-lung transplantation. Clinical features include productive cough, dyspnea during exertion, progressive shortness of breath, and irreversible airflow obstruction with moderate reduction of the diffusing capacity. Arterial hypoxemia and hypocapnia are almost always present.

Because bronchoscopy with bronchoalveolar lavage (BAL) and transbronchial biopsy are often used as surveillance for rejection after lung transplantation, this model has provided much information on the immunologic processes involved in the development of bronchiolitis obliterans. Enhanced expression of class II MHC antigens has been found in the epithelium of bronchioles and alveoli of patients with bronchiolitis obliterans after heart-lung transplantation.[52–54] T lymphocytes from the recipient may recognize these donor class II MHC antigens as foreign, resulting in a cascade of lymphocyte activation, proliferation, and differentiation.[55] This concept is supported further by the demonstration of activated T lymphocytes in the cellular infiltrates. Functional testing of BAL cells has been used to monitor patients for the development of bronchiolitis obliterans. Donor-specific activity (primed lymphocyte test, cell-mediated lympholysis) of cells removed from transplanted lung is strongly associated with bronchiolitis obliterans, and alloreactivity of BAL cells may be a significant risk factor for the subsequent development of bronchiolitis obliterans in clinically quiescent patients.[56,57] During rejection, there is marked lymphocytic infiltration of the transplanted organ, and infiltrating cells demonstrate $CD4^+$ and $CD8^+$ phenotypes.[58] A predominant $CD4^+$ cell population, mediating donor-specific class II antigen–directed reactivity, is associated with graft rejection; a predominant $CD8^+$ cell population, mediating donor-specific class I antigen–directed reactivity, is associated with bronchiolitis obliterans.[59] In addition, lung transplant patients with bronchiolitis obliterans have an oligoclonal expansion of $CD4^+$ T cells in peripheral blood.[60] Although the severity of the lymphocytic bronchitis identified on transbronchial biopsies has been identified as a significant risk factor for the development of bronchiolitis obliterans syndrome,[61] this syndrome has also been linked to down-regulation of CD28 on $CD4^+$ T cells.[62]

The role of cofactors such as *Pneumocystis jirovecii* infection or cytomegalovirus (CMV) pneumonia in the initiation of lung allograft rejection and development of bronchiolitis obliterans remains unclear. *Pneumocystis* infection is associated with an increased number and alloreactivity of BAL cells and a higher incidence of chronic rejection leading to bronchiolitis obliterans.[63] It has been suggested that activated T cells, on presentation of antigen by macrophages, proliferate and produce cytokines such as interleukin-2 (IL-2) that lead to an expansion of the number of alloreactive T cells.[63] Similarly, CMV infection may stimulate the release of cytokines such as interferon-γ (IFN-γ), which may lead to the increased expression of MHC antigens on epithelial and endothelial cells.[64–66] Alternatively, CMV may directly stimulate the up-regulation of MHC antigen expression on target cells. Finally, Fujinami and associates[67] described a region of amino acid sequence homology between the immediate-early region of human CMV and the HLA-DR β chain. By "mimicking" the molecular structure of HLAs in the lung, CMV might induce a response directed against the graft (Fig. 44-2). Prophylaxis against CMV with ganciclovir or valganciclovir has been reported to decrease the incidence of bronchiolitis obliterans syndrome.[68]

Bronchiolitis Obliterans with Organizing Pneumonia (Cryptogenic Organizing Pneumonitis)

In 1985, Epler and colleagues[69] described 50 patients whose lung biopsy specimens showed patchy organizing pneumonia in association with bronchiolitis obliterans. They proposed that BOOP was a distinct component of the spectrum of infiltrative lung diseases. Clinically, most patients had a history suggesting a slowly resolving pneumonia spanning weeks or months. The most common symptom on presentation was a persistent, nonproductive cough, and approximately one third of patients reported a flulike illness with fever, sore throat, and malaise. Dyspnea was a prominent feature in half the patients. On physical examination, crackles were present in 68% of patients, and wheezes were rarely present.

Epler and colleagues[69] described an unusual radiographic pattern of bilateral patchy ground-glass densities in 81% of their patients. Other radiographic patterns of BOOP include a miliary nodular pattern resembling miliary tuberculosis, bilateral symmetrical lower lobe interstitial infiltrates, and on rare occasions, a normal chest roentgenogram.[70]

The physiologic abnormalities of BOOP are variable.[35,69] In patients who are symptomatic, arterial hypoxemia is nearly always present. Pulmonary function tests demonstrate a restrictive pattern, with reduction in diffusing capacity in 72% of patients. Airflow obstruction is uncommon in patients who are not smokers.

The histologic pattern identified as BOOP is not specific for a single cause, but rather can occur in association with a large number of pulmonary conditions (Table 44-3). The idiopathic form of BOOP also is known as cryptogenic organizing pneumonitis (COP), and this nomenclature has been recommended by an

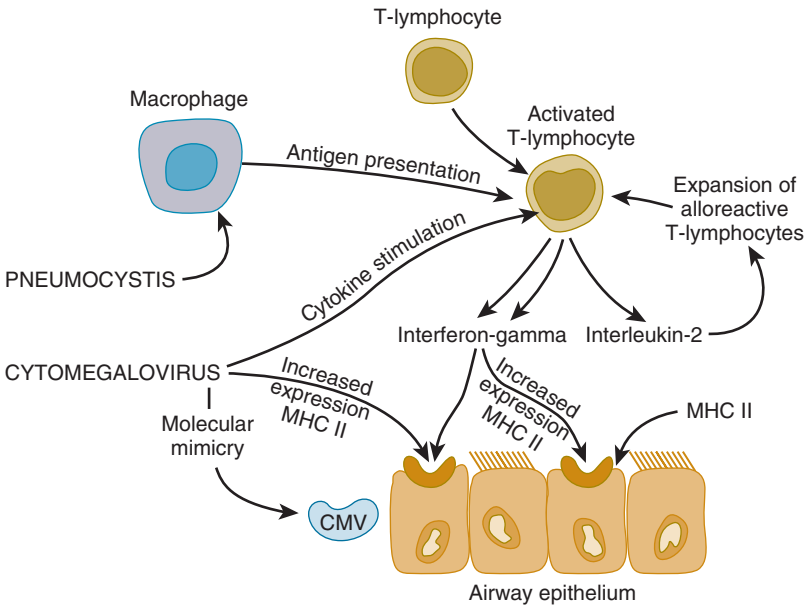

FIGURE 44-2 ■ Schematic diagram shows the potential interactions between infectious and immunologic stimuli that lead to bronchiolitis obliterans following transplantation of lung. Pneumocystis and cytomegalovirus (CMV) may act as "cofactors" to increase numbers of alloreactive T cells and increase expression of class II major histocompatibility complex (MHC) antigens on airway cells.

TABLE 44-3. Etiology of Bronchiolitis Obliterans with Organizing Pneumonia

Infection
Acute respiratory distress syndrome
Bone marrow transplantation
Lung and heart-lung transplantation
Collagen vascular disease
Hypersensitivity pneumonitis
Toxic fume inhalation
Aspiration pneumonitis
Idiopathic

international committee.[71] These patients have a lymphocytic alveolitis with elevated levels of IFN-γ, IL-12, and IL-18,[72] intraluminal fibrosis that appears to be dependent on IFN-γ,[73] and neovascularization associated with increased levels of vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF).[74] Cordier and coworkers[75] described three different clinical profiles. The first group had patchy migratory pneumonic foci. All of these patients recovered completely with corticosteroid therapy but relapsed when therapy was stopped rapidly. In a second group with diffuse interstitial lung disease, approximately half of the patients responded to corticosteroids. A third group had solitary foci of pneumonia that were resected because of concern over carcinoma. These patients recovered without relapse. Other studies have reported similar success with corticosteroid therapy, with an overall response rate of 60% to 70%, and similar rates of recurrence associated with early cessation of corticosteroid therapy.[69,76] Because most patients with BOOP demonstrate complete clinical and physiologic recovery after therapy with corticosteroids, the diagnosis must be confirmed. Usually, this requires an open-lung biopsy to distinguish BOOP from irreversible interstitial lung disease. BOOP should be considered whenever "community-acquired pneumonia" fails to respond to appropriate therapy.

Treatment of Bronchiolitis Obliterans and Bronchiolitis Obliterans with Organizing Pneumonia

Early recognition and therapy of bronchiolitis obliterans is important because treatment is often ineffective when the disease has reached the late, fibrotic stage. Although there is little evidence that smooth muscle contraction plays a significant role, β-adrenergic agonists are usually given in an attempt to provide symptomatic relief. Corticosteroids play an important role and, if administered early, may significantly alter the disease process. This is especially true of bronchiolitis obliterans after exposure to toxic fumes.[8,77,78] Once instituted, corticosteroid therapy should be continued for at least 2 to 3 months, then reduced slowly, to minimize the likelihood of relapse.[75-79] In some patients, it may be necessary to continue low-dose or alternate-day corticosteroid therapy for months or years.

In bronchiolitis obliterans after bone marrow transplantation, the response to therapy has been poor. Generally, by the time severe airflow obstruction has been established, there is minimal if any therapeutic response. Bronchodilators and corticosteroids have not improved airflow in most cases, and the use of immunosuppressive agents to treat chronic GVHD, although occasionally effective,[80,81] has not consistently changed the course of bronchiolitis obliterans.[35] Macrolide antibiotics are sometimes used empirically, but there is little evidence to support this practice.[82] Better prophylaxis against GVHD

and viral infection may reduce the incidence of bronchiolitis obliterans after bone marrow transplantation.

Bronchiolitis obliterans after lung or heart-lung transplantation has been treated by augmenting immunosuppression with high-dose corticosteroids, azathioprine, antithymocyte globulin (ATG), OKT3 monoclonal antibody, tacrolimus (FK506), mycophenolate mofetil, or all of them; the responses have varied. Chronic use of azithromycin has been reported to improve lung function in patients with bronchiolitis obliterans after lung transplantation.[83,84] Patients with prominent BAL neutrophilia are more likely to respond to azithromycin; those who had a rapid pretreatment decline in lung function are not.[85] One study suggests that statin use is associated with decreased rejection and bronchiolitis obliterans after lung transplantation, perhaps by inhibiting expression of MHC class II molecules or by a variety of other antiinflammatory and immunomodulatory effects that have been ascribed to these agents.[86] Furthermore, extracorporeal photophoresis appears to decrease the rate of decline in forced expiratory volume in 1 second (FEV_1) in established bronchiolitis obliterans.[87] If bronchiolitis obliterans is detected early and therapy is initiated immediately, the likelihood of reversal is enhanced.[88] Therapy begun late in the clinical course may stabilize the process or have no effect, although assessing this is difficult because the rate of progression of bronchiolitis obliterans tends to slow spontaneously with time. For patients with progressive bronchiolitis obliterans, retransplantation is an option. In patients who undergo a second lung transplant, the rates of recurrent bronchiolitis obliterans and survival appear to be similar to those of the first transplant.[89,90] The best therapy for bronchiolitis obliterans is primary prevention. Rigorous surveillance for evidence of asymptomatic rejection makes it feasible to prevent the chronic rejection that is thought to lead to bronchiolitis obliterans.

BOOP represents a special situation. Corticosteroid therapy is effective in most cases, and clinical improvement is often dramatic, sometimes occurring within 1 to 2 days of starting therapy.[69,91] In Epler and colleagues' original study,[69] there was complete clinical and physiologic recovery in 65% of patients. Because this lesion is so "steroid-responsive," the diagnosis should be established early so therapy can be initiated before irreversible changes in lung function occur. Corticosteroids should be continued for 1 to 2 months, then tapered slowly (e.g., over 4–6 wk) to prevent relapse. In patients who are not responsive to, or not tolerant of, corticosteroids, cyclophosphamide has been effective.[92,93]

Respiratory Bronchiolitis

Respiratory bronchiolitis (RB) is characterized by the accumulation of pigmented alveolar macrophages in respiratory bronchioles and in the adjacent air spaces. It is a distinct pathologic entity commonly found in cigarette smokers and in patients with mineral dust exposure.[94–96] Previously considered an incidental finding at autopsy, RB currently is thought to be a possible precursor to chronic lung disease in heavy smokers.[94,97] Clinically, RB is often identified radiographically and rarely produces symptoms or physiologic abnormalities. However, in some patients, RB is associated with diffuse pulmonary infiltrates in a disease that resembles idiopathic pulmonary fibrosis. This entity is known as *respiratory bronchiolitis–associated interstitial lung disease* (RB-ILD).[96,98–100] Patients present with subacute cough, dyspnea, and crackles, with diffuse interstitial infiltrates or reticulonodular opacities on chest roentgenogram and pulmonary function tests showing restrictive lung disease with decreased diffusing capacity. HRCT may be useful in differentiating respiratory bronchiolitis from interstitial lung disease, manifesting diffuse or patchy ground-glass densities or fine nodules in the former and peripheral reticular opacities and honeycombing in the latter.[100,101] The duration of symptoms is considerably longer than for BOOP, with patients with RB reporting an average of 37 months of symptoms.[97] Smoking cessation leads to resolution or stabilization of disease in about 30% of patients[102]; some patients develop progressive interstitial fibrosis. Improvement with corticosteroid treatment has been described, but this has not been studied prospectively.[96,98,99]

Panbronchiolitis

Diffuse panbronchiolitis is an obscure inflammatory disease of the respiratory bronchioles and surrounding alveoli. Described originally in Japan, where more than 1000 cases have been identified,[103] it also has been reported in non-Japanese Asians,[104] and in whites in the United States.[105]

Most individuals with diffuse panbronchiolitis are male[103] nonsmokers and almost all have chronic sinusitis. The usual presenting symptoms are cough, dyspnea, and sputum production. The chest radiograph and HRCT are characteristic, showing diffuse small centrilobular nodular opacities and hyperinflation.[101,106] Pulmonary function tests typically reveal progressive airflow obstruction or a mixed obstructive-restrictive pattern, with reduced diffusing capacity of carbon dioxide ($D_{L_{CO}}$).[105] Diffuse panbronchiolitis is associated with recurrent respiratory infections; *Pseudomonas* infection is common late in the disease.[105,107] If untreated, diffuse panbronchiolitis leads to bronchiectasis, respiratory failure, and death. Although the etiology of diffuse panbronchiolitis remains obscure, both genetic and environmental factors are believed to be important.[108–110] HLA-Bw54 is associated with a 13.3-fold increase in risk for diffuse panbronchiolitis.[109] Polymorphisms of the genes for IL-8[110] and MUC5B[111] have been associated with diffuse panbronchiolitis. Airway neutrophilia is a common feature, and chronic treatment with macrolide antibiotics has been shown to be beneficial[112–114] possibly by reducing levels of the neutrophil chemoattractant IL-8.[115,116]

Follicular Bronchiolitis

Follicular bronchiolitis (lymphoid hyperplasia) is characterized by peribronchiolar hyperplastic lymphoid follicles with germinal centers.[117] It has been described with

primary pulmonary lymphoid hyperplasia[118] or as a secondary event in patients with bronchiectasis, collagen vascular diseases (especially rheumatoid arthritis and Sjögren's syndrome), or other infections.[117,119,120] Most patients complain of slowly progressive exertional dyspnea, and centrilobular nodules and ground-glass opacities are seen on HRCT.[118] The natural history of this condition is unknown, and treatment is usually directed at the underlying disease.

Bronchopulmonary Dysplasia

Bronchopulmonary dysplasia (BPD) refers to a common, long-term respiratory complication of premature birth. However, as management of prematurity has evolved, so have the histopathologic and clinical descriptions of the disease. BPD was described initially in newborn babies with the infant respiratory distress syndrome (hyaline membrane disease) after prolonged treatment with high concentrations of inspired oxygen and positive-pressure ventilation.[121] Because these two therapeutic modalities are linked so closely in practice, it has not been possible to separate the pathogenetic contributions of each. In all likelihood, both oxygen and positive-pressure play a role. Characteristic histologic features are unusual abnormalities of the bronchioles, including marked metaplasia, obliteration, and cystic changes.[122] The disorder also has been described in adults after acute respiratory distress syndrome.[123] It is possible that this complication occurs more frequently in adults than currently is recognized. The pathologic findings may be misdiagnosed easily as "honeycombing," a nonspecific consequence of many different fibrosing disorders.

The use of antenatal corticosteroids, exogenous surfactant, and improved ventilatory support have resulted in improved survival of more immature infants, and an evolution of what continues to be called "bronchopulmonary dysplasia."[124,125] The "new" BPD is clinically milder and probably reflects developmental arrest in an immature lung rather than barotrauma and oxygen toxicity.[125,126] Histopathology reveals enlarged air spaces with simplified alveolar and alveolar-capillary development. Unlike the original disease, airway abnormalities are uncommon.[125]

LOCALIZED DISORDERS

Many of the specific causes of localized abnormalities of bronchi also underlie abnormalities of the upper airways. Examples are neoplasms, extrinsic compression, granulomatous disease, malacic lesions, and trauma. However, the manifestations, diagnosis, and therapy of localized bronchial disorders are substantially different from similar disorders in the larynx or trachea.

Neoplasms

Because lung cancers are common, any endobronchial mass must be evaluated carefully for possible malignancy. All histopathologic types of primary lung cancer may protrude into a bronchus and narrow or occlude it. Malignant endobronchial tumors often have an irregular, rather than smooth, surface on bronchoscopic examination. Primary malignant tumors of the lung are described in detail in Chapter 47.

Of patients with extrapulmonary malignancies metastatic to the lung, approximately 5% have predominantly endobronchial metastases.[127] The most common primary malignancies are renal cell, colonic, rectal, cervical, and breast carcinomas and malignant melanomas.[128] In most instances, the manifestations of the primary tumor are apparent before the endobronchial metastasis is discovered.[127] Metastatic malignancies of the lung are discussed in detail in Chapter 49.

In patients with lymphomas or leukemia, malignant infiltrations of the bronchial mucosa occur rarely. In Hodgkin's disease or non-Hodgkin's lymphoma, the endobronchial malignant cells may originate in bronchus-associated lymphoid tissue, may invade the bronchial mucosa by direct extension from hilar or peribronchial lymph nodes, or may seed the bronchial mucosa via lymphatic or blood vessels.[129] Leukemic infiltration of bronchial mucosa occurs as a rare, late manifestation of chronic lymphocytic leukemia.[130]

Involvement of the lung occurs in one third to one half of patients with the acquired immunodeficiency syndrome (AIDS) and Kaposi's sarcoma (see Chapter 80). Endobronchial lesions occur frequently, but they rarely cause airway obstruction or hemoptysis. The lesions are usually multiple, bright red or violaceous, and flat when visualized through the bronchoscope. The diagnosis of endobronchial Kaposi's sarcoma is established when a patient with AIDS has widespread extrapulmonary Kaposi's sarcoma and characteristic-appearing endobronchial lesions. Biopsy of the endobronchial lesions is seldom necessary and may be hazardous because of excessive bleeding.[131]

Benign lung tumors frequently originate from cells in the airways, including nerves (schwannomas, neurofibromas, neurolemmomas), smooth muscle (leiomyomas), cartilage (chondromas), blood vessels (hemangiomas), fat cells (lipomas), glands (cystoadenomas, oxyphilic adenomas), and epithelium (papillomas). These tumors often narrow or obstruct bronchi. By bronchoscopic examination, the tumors often are smooth, round, and well localized. Benign tumors of the lung are described in detail in Chapter 50.

Bronchial Compression

When peribronchial lymph nodes are enlarged by carcinoma, lymphoma, or granulomatous infection, narrowing of adjacent bronchi may occur. Although sarcoidosis frequently results in enlarged hilar and mediastinal lymph nodes, bronchial narrowing from compression by lymph nodes in sarcoidosis is rare. In infants with congenital heart defects such as tetralogy of Fallot and transposition of the great vessels with ventricular septal defect, bronchial compression by dilated pulmonary arteries is an occasional complication.

Mediastinal Fibrosis (Fibrosing Mediastinitis)

In patients with pulmonary histoplasmosis or tuberculosis, an interesting and rare complication is mediastinal fibrosis.[132] In such patients, it appears that fungal or bacterial antigens from granulomatous foci in mediastinal lymph nodes stimulate fibrogenesis in surrounding tissue, perhaps because of unusual sensitivity to the antigens.[132] The fibrosis may result in narrowing or occlusion of vital mediastinal structures, and the structures affected depend on the specific lymph nodes involved by the original infection. Mediastinal fibrosis originating from subcarinal or hilar lymph nodes may result in occlusion of main-stem bronchi, pulmonary blood vessels, or the esophagus. Mediastinal fibrosis originating from right paratracheal lymph nodes commonly produces obstruction of the superior vena cava and azygos veins.[132] CT and magnetic resonance imaging (MRI) are useful to diagnose and follow this condition.[133]

Foreign Bodies

Accidental inhalation of foreign bodies is a major cause of death in children, resulting in approximately 2000 deaths annually in the United States. The foreign bodies, which may be seeds, nuts, nails, or a variety of other objects, most frequently lodge in the right main-stem bronchus. Children with aspirated foreign bodies may present with immediate cyanosis, cough, and wheezing or with the delayed onset of pneumonia or bronchiectasis. Suspected aspiration of a foreign body is an indication for immediate bronchoscopic examination of the airways. In the presence of asphyxia, rigid bronchoscopy is appropriate. In most other situations, foreign bodies can be extracted with the flexible bronchoscope, but personnel and equipment for rigid bronchoscopy should be available.

Granulomatous Inflammation

In patients with pulmonary tuberculosis, spillage of infected material into the middle and lower lobes occasionally causes localized endobronchial infection. Endobronchial tuberculosis may present with hemoptysis, bronchorrhea, or localized bronchial obstruction, causing lobar collapse and persistent postobstructive pneumonitis. These findings may develop during active pulmonary infection by tuberculosis or many years after its treatment. The diagnosis is established most readily by fiberoptic bronchoscopy.[134] The typical finding is the presence of localized endobronchial gelatinous granulation tissue. The mucosa may be nodular, red, and ulcerated, and often the diagnosis of bronchogenic neoplasm is suggested until pathologic examination of biopsy material has been carried out.

In patients with pulmonary sarcoidosis, localized endobronchial granulomatous inflammation rarely may lead to stenosis of bronchi.[135] Pulmonary function tests often show airway obstruction, but the common causes of the obstruction are the structural distortion of bronchi and bronchioles that accompanies pulmonary fibrosis,[136] nonspecific bronchial hyperreactivity,[137] or laryngeal sarcoidosis.[138] Only rarely is bronchostenosis present.

Bronchocentric granulomatosis is an uncommon inflammatory lesion defined morphologically by the presence of necrotizing granulomas surrounding bronchi.[139] The entity occurs most commonly in asthmatic patients with allergic bronchopulmonary aspergillosis, and considerable evidence suggests that the granulomatous bronchitis is an immunologic response to endobronchial fungi. Narrowing or obliteration of bronchi may occur because of the inflammatory reaction itself or because of associated mucoid impaction.[139]

Broncholithiasis

Broncholithiasis is defined as the presence of a calcified fragment of tissue within a bronchus.[140] Any disorder that leads to calcification of lung tissue or of lymph nodes may result in broncholithiasis. Most often this occurs when hilar or peribronchial lymph nodes become calcified as a result of granulomatous infections such as histoplasmosis or tuberculosis or, less commonly, from actinomycosis, coccidioidomycosis, cryptococcosis, or silicosis.[140] Necrotizing pneumonias and bronchiectasis may lead to calcification of bronchial cartilage, which can fragment to produce broncholiths. Occasionally, retained foreign bodies may become calcified. Clinical manifestations of broncholithiasis occur when calcified stones erode or break loose into the airways (see later). These stones are composed of 85% to 90% calcium phosphate and 10% to 15% calcium carbonate and, thus, closely resemble the composition of bone.

Amyloidosis

Amyloidosis is defined on the basis of the extracellular deposition of the fibrous protein amyloid. In both the primary and the secondary forms of the disease, these deposits can occur endobronchially, producing obstruction or incidental findings at the time of bronchoscopy.[141] As many as 30% of patients with primary amyloidosis are symptomatic. Pulmonary involvement is usually associated with amyloid of the light (AL) chain variety.[142] The definitive diagnosis of endobronchial amyloidosis requires biopsy and demonstration of amyloid deposits, as defined by their green birefringence when viewed with polarized light after staining with Congo red.[141] Endobronchial amyloid has been treated successfully with neodymium:yttrium-aluminum-garnet (Nd:YAG) laser therapy.[143]

Bronchomalacia

Softening of the bronchial walls may contribute to narrowing of the airways during exhalation in emphysema. Less commonly, bronchomalacia may be found in infants because of inadequate development of bronchial cartilage. These infants generally present with dyspnea, atelectasis, or recurrent pneumonias.

Traumatic Injury

Tears or complete ruptures of main-stem bronchi or the bronchus intermedius are occasional complications of blunt trauma to the chest. The diagnosis should be suspected in any posttraumatic patient with new onset of cough, respiratory distress, subcutaneous and mediastinal emphysema, or pneumothorax. The associated presence of hemoptysis or hemothorax indicates bronchial vascular damage. Occasionally, the development of manifestations of bronchial tears may be delayed days or weeks after the traumatic injury.

Clinical Features

Patients with localized endobronchial lesions generally present with symptomatic, physical, or radiographic manifestations of the lesion itself or of underlying conditions (e.g., malignancy, infection, AIDS, or sarcoidosis). Only the manifestations of the lesions themselves are described in this section.

The most common symptoms of localized endobronchial disease are cough, hemoptysis, wheeze, dyspnea, and fever and chills secondary to postobstructive pneumonia. If an endobronchial lesion only partially obstructs a bronchus, patients may show manifestations of chronic pulmonary infections, such as lung abscess (see Chapter 32) or bronchiectasis (see Chapter 42). A history of recurrent pneumonias in the same segment or lobe of the lung should prompt a careful evaluation for partial bronchial obstruction by an endobronchial lesion. Similarly, for any edentulous elderly patient with a history of a severe anaerobic pulmonary infection, endobronchial obstruction should be considered.

Symptoms of broncholithiasis include cough, hemoptysis, fever associated with purulent sputum, and expectoration of stones. Often, the cough in broncholithiasis is productive of a mixture of gritty, sandy particles and purulent or bloody sputum.

The physical examination in patients with localized endobronchial lesions may reveal fever and tachypnea. When a bronchus is narrowed but not completely obstructed, examination of the chest may reveal a unilateral palpable rhonchus, a prolonged forced inspiratory time on the affected side (the inspiratory "bagpipe" sign),[144] and a localized wheeze during a forced expiratory maneuver. Once the obstruction is complete, there is a loss of breath sounds and vocal fremitus during auscultation over the portion of the lung distal to the obstruction.

In patients with localized endobronchial disease, the chest roentgenogram may show no abnormality. Radiographically apparent lung collapse depends on the completeness of the obstruction and on the extent to which collateral ventilation from adjacent lung is present. In infants, the pores of Kohn, through which collateral ventilation normally occurs, are poorly developed. Hence, the likelihood of complete collapse from localized bronchial disease is great in this age group. Other findings on the plain chest roentgenogram include mediastinal adenopathy with or without calcification, lung abscess, bronchiectasis, or pneumonia. The presence of air bronchograms in a consolidated region of the lung suggests that the bronchus supplying that region is at least partially patent.

Middle lobe syndrome refers to chronic or recurrent radiographic evidence of collapse of the right middle lobe. Originally, it was postulated that the cause was tuberculous adenitis of lymph nodes in the right middle lobe causing bronchial compression.[145] By bronchoscopic examination, however, most of these patients have completely normal right middle lobe bronchi. Therefore, in most instances, the collapse relates to the normal, relatively long length and narrow caliber of the right middle lobe bronchus or to the relatively ineffective collateral ventilation normally present in this lobe.

Diagnosis

In patients with only partial obstruction of a bronchus, comparing roentgenograms obtained at full inspiration with those obtained at full expiration may assist in establishing the diagnosis. Upon inspiration, the negative intrathoracic pressure distends the partially obstructed bronchus, and air enters the distal lung. Upon expiration, the obstruction becomes complete, and air is trapped behind it. The result is a mediastinal shift away from the affected side on expiration. CT scans may identify hyperinflation, compressing lymph nodes, or calcifications in patients with broncholithiasis, or subtle endobronchial abnormalities.[146]

The definitive procedure for diagnosing localized bronchial abnormalities is direct examination of the bronchi via fiberoptic bronchoscopy. In general, any visualized abnormality should be biopsied, and the biopsied materials submitted for histologic examination as well as for culture. If the lesion is friable and bleeds easily during its examination and manipulation, rigid bronchoscopy may be required.

Routine pulmonary function tests in general do not distinguish between localized and widespread bronchial obstruction. In patients with bronchial compression or mediastinal fibrosis, skin tests for histoplasmosis or tuberculosis may be positive.[132] In bronchocentric granulomatosis, peripheral blood eosinophilia and serum precipitins for *Aspergillus* may be present.[139] In endobronchial amyloidosis, immunoelectrophoretic analysis of blood or urine shows evidence of monoclonal gammopathy in 90% of cases.[147]

Treatment

The appropriate therapy for localized lesions of the bronchi depends on the specific underlying cause. Treatment of bronchial neoplasms is described in Chapter 47. In some patients with inoperable, obstructive neoplasms of the trachea, main-stem bronchi, or bronchus intermedius, the use of the Nd:YAG laser, electrocautery, or argon plasma coagulation can provide immediate relief; the therapeutic effects of cryotherapy, brachytherapy, and photodynamic therapy are slower in onset. Bron-

chial obstruction from extrinsic compression or endobronchial granulomatous inflammation may be relieved by medical treatment of the underlying condition (e.g., lymphoma, tuberculosis), but irreversible fibrotic narrowing often requires surgical resection or stenting. There are reports that airway and vascular obstruction due to fibrosing mediastinitis may improve with corticosteroids or with stenting, but prospective trials are lacking. Foreign bodies usually can be removed with specialized wire claws or baskets inserted through a bronchoscope. When they are lodged in central airways, removal of foreign bodies is performed most effectively via a rigid bronchoscope. Broncholithiasis is often self-limited, requiring no further evaluation or treatment. However, if hemoptysis, persistent cough, atelectasis, or infection is present, bronchoscopic visualization is indicated. Stones sometimes can be removed bronchoscopically, and antibiotics should be administered to treat postobstructive infections. Occasionally, surgical intervention is required to manage persistent or recurrent broncholithiasis.[140] In infants with bronchomalacia, effective treatment may require long-term ventilation of the lungs until normal cartilage is formed, which usually occurs by 6 months to 2 years of age. Patients with suspected traumatic bronchial injury should undergo immediate endotracheal intubation and fiberoptic bronchoscopy followed by thoracotomy.

Tracheobronchial Stents

Although prostheses have been utilized to relieve tracheal and bronchial obstruction for many years,[148] recent technical advances have made the procedure easier and more effective. More than 20 types of tracheobronchial stents are now available, in metal, mesh, or silicone rubber; insertion usually can be accomplished by fiberoptic bronchoscopy without general anesthesia. Stents have been used effectively to relieve airway obstruction caused by malignancy, postinflammatory stenosis, and tracheobronchomalacia and to occlude tracheoesophageal fistulas. The success rate is as high as 80% to 90% in selected patients.[149] Fenestrated or mesh stents are more effective for benign lesions than for neoplasms, which tend to grow through the metal mesh. Careful patient selection, choice of the correct stent, and an experienced bronchoscopist are important determinants of success. Virtual bronchoscopy using CT is often useful in planning stent placement.

KEY POINTS

- Because of the large cross-sectional area of the peripheral airways, symptoms and physiologic changes occur late and conditions affecting these airways, including bronchiolitis and mucus plugging, can be difficult to diagnose.
- For bronchiolitis obliterans and especially bronchiolitis obliterans with organizing pneumonia, early diagnosis and treatment can impact prognosis.
- Chronic graft versus host disease is the major risk factor for bronchiolitis obliterans after bone marrow transplantation.
- Bronchiolitis obliterans after lung transplantation reflects chronic graft rejection; infections, gastroesophageal reflux, immunosuppressive drugs, and primary graft dysfunction act as cofactors.
- Diffuse panbronchiolitis responds to treatment with macrolide antibiotics.
- Endotracheal and endobronchial stents are effective for treating obstruction caused by tumors, postinflammatory stenosis, and tracheobronchomalacia.

References

1. Macklem PT, Mead J: Resistance of central and peripheral airways measured by a retrograde catheter. J Appl Physiol 22:395–401, 1967.
2. Aikawa T, Shimura S, Sasaki H, et al: Marked goblet cell hyperplasia with mucus accumulation in the airways of patients who died of severe acute asthma attack. Chest 101:916–921, 1992.
3. Klingele TG, Staub NC: Terminal bronchiole diameter changes with volume in isolated, air-filled lobes of cat lung. J Appl Physiol 30:224–227, 1971.
4. Hughes JMB, Rosenzweig DY, Kivist PB: Site of airway closure in excised dog lungs: Histologic demonstration. J Appl Physiol 29:340–344, 1970.
5. Macklem PT, Thurlbeck WM, Fraser RG: Chronic obstructive disease of small airways. Ann Intern Med 74:167–177, 1971.
6. Ben-Noun L: Drug-Induced respiratory disorders: Iincidence, prevention and management. Drug Saf 23:143–164, 2000.
7. Milne JEH: Nitrogen dioxide inhalation and bronchiolitis obliterans. J Occup Med 11:538–547, 1969.
8. Horvath EP, doPico GA, Barbee RA, et al: Nitrogen dioxide–induced pulmonary disease. J Occup Med 20:103–110, 1978.
9. Hendrick DJ: "Popcorn worker's lung" in Britain in a man making potato crisp flavouring. Thorax 63:267–268, 2008.
10. van Rooy FG, Smit LA, Houba R, et al: A cross-sectional study of lung function and respiratory symptoms among chemical workers producing diacetyl for food flavorings. Occup Environ Med 66:105–110, 2009.
11. Fleming GM, Chester EH, Montenegro HD: Dysfunction of small airways following pulmonary injury due to nitrogen dioxide. Chest 75:720–721, 1979.
12. Chang AB, Masel JP, Masters B: Post-infectious bronchiolitis obliterans: Clinical, radiological and pulmonary function sequelae. Pediatr Radiol 28:23–29, 1998.

13. Sato P, Madtes DK, Thorning D, et al: Bronchiolitis obliterans caused by *Legionella pneumophilia*. Chest 87:840–842, 1985.
14. Coultas DB, Samet JM, Butler C: Bronchiolitis obliterans due to *Mycoplasma pneumoniae*. West J Med 144:471–474, 1986.
15. Hall CB: Respiratory syncytial virus and parainfluenza virus. N Engl J Med 344:1917–1928, 2001.
16. Simpson H, Matthew DJ, Habel AH, et al: Acute respiratory failure in bronchiolitis and pneumonia in infancy. Br Med J 2:632–636, 1974.
17. McLoud TC: Chest radiographic findings of the healthy and diseased bronchioles. *In* Epler GR (ed):. Diseases of the Bronchioles. New York: Raven, 1994, pp 27–41.
18. Franquet T, Stern EJ: Bronchiolar inflammatory diseases: High-resolution CT findings with histologic correlation. Eur Radiol 9:1290–1303, 1999.
19. Kattan M: Epidemiologic evidence of increased airway reactivity in children with a history of bronchiolitis. J Pediatr 135:8–13, 1999.
20. Valkonen H, Waris M, Ruohola A, et al: Recurrent wheezing after respiratory syncytial virus or non-respiratory syncytial virus bronchiolitis in infancy: A 3-year follow-up. Allergy 64:1359–1365, 2009.
21. Volovitz B, Welliver RC, De Castro G, et al: The release of leukotrienes in the respiratory tract during infection with respiratory syncytial virus: Role in obstructive airway disease. Pediatr Res 24:504–507, 1988.
22. van Schaik SM, Tristram DA, Nagpal IS, et al: Increased production of IFN-gamma and cysteinyl leukotrienes in virus-induced wheezing. J Allergy Clin Immunol 103:630–636, 1999.
23. Bisgaard H: A randomized trial of montelukast in respiratory syncytial virus postbronchiolitis. Am J Respir Crit Care Med 167:379–383, 2003.
24. Fitzgerald DA, Mellis CM: Leukotriene receptor antagonists in virus-induced wheezing: Evidence to date. Treat Respir Med 5:407–417, 2006.
25. Amirav I, Luder AS, Kruger N, et al: A double-blind, placebo-controlled, randomized trial of montelukast for acute bronchiolitis. Pediatrics 122:1249–1255, 2008.
26. Epler GR, Colby TV: The spectrum of bronchiolitis obliterans. Chest 83:161–162, 1983.
27. Meyers JL, Colby TV: Pathologic manifestations of bronchiolitis, constrictive bronchiolitis, cryptogenic organizing pneumonia, and diffuse panbronchiolitis. Clin Chest Med 14:611–621, 1993.
28. Jensen SP, Lynch DA, Brown KK, et al: High-resolution CT features of severe asthma and bronchiolitis obliterans. Clin Radiol 57:1078–1085, 2002.
29. Swyer P, James G: Case of unilateral pulmonary emphysema. Thorax 8:133–136, 1953.
30. Macleod WM: Abnormal translucency of one lung. Thorax 9:147–153, 1954.
31. Gosink BB, Friedman PJ, Liebow AA: Bronchiolitis obliterans. Roentgenologic-pathologic correlation. AJR Am J Roentgenol 117:816–832, 1973.
32. Wright JL, Cagle P, Churg A, et al: Diseases of the small airways. Am Rev Respir Dis 146:240–262, 1992.
33. Markopoulo KD, Cool CD, Elliott TL, et al: Obliterative bronchiolitis: Varying presentations and clinicopathological correlation. Eur Respir J 29:20–30, 2002.
34. Wells AU, du bois RM: Bronchiolitis in association with connective tissue disorders. Clin Chest Med 14:655–666, 1993.
35. King TE: Bronchiolitis obliterans. Lung 167:69–93, 1989.
36. Perez T, Remy-Jardin M, Cortet B: Airways involvement in rheumatoid arthritis. Am J Respir Crit Care Med 157:1658–1665, 1998.
37. Kinney WW, Angelillo VA: Bronchiolitis in systemic lupus erythematosis. Chest 82:646–649, 1982.
38. Kim EA, Lee KS, Johkoh T, et al: Interstitial lung diseases associated with collagen vascular diseases: Radiologic and histopathologic findings. Radiographics 22:S151–S165, 2002.
39. Sweet MP, Patti MG, Hoopes C, et al: Gastro-esophageal reflux and aspiration in patients with advanced lung disease. Thorax 64:167–173, 2009.
40. Crawford SW, Clark JG: Bronchiolitis associated with bone marrow transplantation. Clin Chest Med 14:741–749, 1993.
41. Clark JG, Schwartz DA, Flournoy N, et al: Risk factors for airflow obstruction in recipients of bone marrow transplants. Ann Intern Med 107:648–656, 1987.
42. Shields AF, Hackman RC, Fife KH, et al: Adenovirus infections in patients undergoing bone-marrow transplantation. N Engl J Med 312:529–533, 1985.
43. Belperio JA, Keane MP, Burdick MD, et al: Critical role for CXCR3 chemokine biology in the pathogenesis of bronchiolitis obliterans syndrome. J Immunol 169:1037–1049, 2002.
44. Reynaud-Gaubert M, Marin V, Thirion X, et al: Upregulation of chemokines in bronchoalveolar lavage fluid as a predictive marker of post-transplant airway obliteration. J Heart Lung Transplant 21:721–730, 2002.
45. Sundaresan S, Mohanakumar T, Smith MA, et al: HLA-A locus mismatches and developoment of antibodies to HLA after lung transplantation correlate with the development of bronchiolitis obliterans syndrome. Transplantation 65:648–653, 1998.
46. Girnita AL, McCurry KR, Iacono AT, et al: HLA-specific antibodies are associated with high-grade and persistent-recurrent lung allograft acute rejection. J Heart Lung Transplant 23:1135–1141, 2004.
47. Bando K, Paradis IL, Similo S, et al: Obliterative bronchiolitis after lung and heart-lung transplantation. An analysis of risk factors and management. J Thorac Cardiovasc Surg 110:4–13, 1995.
48. Bharat A, Kuo E, Steward N, et al: Immunological link between primary graft dysfunction and chronic lung allograft rejection. Ann Thorac Surg 86:189–195, 2008.
49. Huang HJ, Yusen RD, Meyers BF, et al: Late primary graft dysfunction after lung transplantation and bronchiolitis obliterans syndrome. Am J Transplant 8:2454–2462, 2008.
50. Cantu E, Appel JZ, Hartwig MG, et al: Early fundoplication prevents chronic allograft dysfunction in patients with gastroesophageal reflux disease. Ann Thorac Surg 78:1142–1151, 2004.
51. Hadjiliadis D, Chaparro C, Gutierrez C, et al: Impact of lung transplant operation on bronchiolitis obliterans syndrome in patients with chronic obstructive pulmonary disease. Am J Transplant 6:183–189, 2006.
52. Taylor PM, Rose ML, Yacoub MH: Expression of MHC antigens in normal human lungs and transplanted lungs with obliterative bronchiolitis. Transplantation 48:506–510, 1989.
53. Yousem SA, Curley JM, Dauber J, et al: HLA-class II antigen expression in human heart-lung allografts. Transplantation 49:991–995, 1990.
54. Romaniuk A, Prop J, Petersen AH, et al: Expression of class II major histocompatibility complex antigens by bronchial epithelium in rat lung allografts. Transplantation 44:209–214, 1987.
55. Lawrence EC, Holland VA, Young JB, et al: Dynamic changes in soluble interleukin-2 receptor levels after lung or heart-lung transplantation. Am Rev Respir Dis 140:789–796, 1989.
56. Rabinowich H, Zeevi A, Paradis IL, et al: Proliferative responses of bronchoalveolar lavage lymphocytes from heart-lung transplant patients. Transplantation 49:115–121, 1990.
57. Jaramillo A, Smith MA, Phelan D, et al: Development of ELISA-detected anti-HLA antibodies precedes the development of bronchiolitis obliterans syndrome and correlates with progressive decline in pulmonary function after lung transplantation. Transplantation 67:1155–1161, 1999.
58. Marck K, Prop J, Wildevuur C, et al: Lung transplantation in the rat: Histopathology of left lung iso- and allografts. Heart Transplant 4:263–265, 1985.
59. Reinsmoen NL, Bolman RM, Savik K, et al: Differentiation of class I– and class II–directed donor-specific alloreactivity in bronchoalveolar lavage lymphocytes from lung transplant recipients. Transplantation 53:181–189, 1992.
60. Duncan SR, Leonard C, Theodore J, et al: Oligoclonal CD4(+) T cell expansions in lung transplant recipients with obliterative bronchiolitis. Am J Respir Crit Care Med 165:1439–1444, 2002.
61. Glanville AR, Aboyoun CL, Havryk A, et al: Severity of lymphocytic bronchiolitis predicts long-term outcome after lung transplantation. Am J Respir Crit Care Med 177:1033–1040, 2008.
62. Studer SM, George MP, Zhu X, et al: CD28 down-regulation on CD4 T cells is a marker for graft dysfunction in lung transplant recipients. Am J Respir Crit Care Med 178:765–773, 2008.

63. Zeevi A, Fung JJ, Paradis IL: Bronchoalveolar macrophage lymphocyte reactivity in heart-lung transplant recipients. Transplant Proc 19:2537–2540, 1987.
64. Steinhoff G, Wonigeit K, Pichlmayr R: Analysis of sequential changes in major histocompatibility complex expression in human liver grafts after transplantation. Transplantation 45:394–401, 1988.
65. Grattan MT, Moreno-Cabral CE, Starnes VA, et al: Cytomegalovirus infection is associated with cardiac allograft rejection and atherosclerosis. JAMA 261:3561–3566, 1989.
66. Ross DJ, Moudgil A, Bagga A, et al: Lung allograft dysfunction correlates with gamma-interferon gene expression in bronchoalveolar lavage. J Heart Lung Transplant 18:627–636, 1999.
67. Fujinami RS, Nelson JA, Walker L, et al: Sequence homology and immunologic cross-reactivity of human cytomegalovirus with HLA-DR β chain: A means for graft rejection and immunosuppression. J Virol 62:100–105, 1988.
68. Chmiel C, Speich R, Hofer M, et al: Ganciclovir/valganciclovir prophylaxis decreases cytomegalovirus-related events and bronchiolitis obliterans syndrome after lung transplantation. Clin Infect Dis 46:831–839, 2008.
69. Epler GR, Colby TV, McLoud TC, et al: Bronchiolitis obliterans organizing pneumonia. N Engl J Med 312:152–158, 1985.
70. Müller NL, Staples CA, Miller RR: Bronchiolitis obliterans organizing pneumonia: CT features in 14 patients. AJR Am J Roentgenol 154:983–987, 1990.
71. American Thoracic Society/European Respiratory Society: American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med 165:277–304, 2002.
72. Forlani S, Ratta L, Bulgheroni A, et al: Cytokine profile of bronchoalveolar lavage in BOOP and UIP. Sarcoidosis Vasc Diffuse Lung Dis 19:47–53, 2002.
73. Majeski EI, Harley RA, Bellum SC, et al: Differential role for T cells in the development of fibrotic lesions associated with reovirus 1/L–induced bronchiolitis obliterans organizing pneumonia versus acute respiratory distress syndrome. Am J Respir Cell Mol Biol 28:208–217, 2003.
74. Lappi-Blanco E, Soini Y, Kinnula V, et al: VEGF and bFGF are highly expressed in intraluminal fibromyxoid lesions in bronchiolitis obliterans organizing pneumonia. J Pathol 196:220–227, 2002.
75. Cordier J-F, Loire R, Brune J: Idiopathic bronchiolitis obliterans organizing pneumonia. Definition of characteristic clinical profiles in a series of 16 patients. Chest 96:999–1004, 1989.
76. Davison AG, Heard BE, McAllister WAC, et al: Cryptogenic organizing pneumonitis. Q J Med 52:382–394, 1983.
77. Tse RL, Bockman AA: Nitrogen dioxide toxicity. Reports of four cases in firemen. JAMA 212:1342–1344, 1970.
78. Jones GR, Proudfoot AT, Hall JI: Pulmonary effects of acute exposure to nitrous fumes. Thorax 28:61–65, 1973.
79. Epler GR, Snider GL, Gaensler EA, et al: Bronchiolitis and bronchitis in connective tissue disease. A possible relationship to the use of penicillamine. JAMA 242:528–532, 1979.
80. Wyatt SE, Nunn P, Hows JM, et al: Airways obstruction associated with graft versus host disease after bone marrow transplantation. Exp Hematol 12:17–18, 1984.
81. Ralph DD, Springmeyer SC, Sullivan KM, et al: Rapidly progressive air-flow obstruction in marrow transplant recipients: Possible association between obliterative bronchiolitis and chronic graft-versus-host disease. Am Rev Respir Dis 129:641–644, 1984.
82. Maimon N, Lipton JH, Chan CK, et al: Macrolides in the treatment of bronchiolitis obliterans in allograft recipients. Bone Marrow Transplant 44:69–73, 2009.
83. Gerhardt SG, McDyer JF, Girgis RE, et al: Maintenance azithromycin therapy for bronchiolitis obliterans syndrome: Results of a pilot study. Am J Respir Crit Care Med 168:121–125, 2003.
84. Verleden GM, Dupont LJ: Azithromycin therapy for patients with bronchiolitis obliterans syndrome after lung transplantation. Transplantation 77:1465–1467, 2004.
85. Gottlieb J, Szangolies J, Koehnlein T, et al: Long-term azithromycin for bronchiolitis obliterans syndrome after lung transplantation. Transplantation 85:36–41, 2008.
86. Johnson BA, Iocono AT, Zeevi A, et al: Statin use is associated with improved function and survival of lung allografts. Am J Respir Crit Care Med 167:1271–1278, 2003.
87. Benden C, Speich R, Hofbauer GF, et al: Extracorporeal photophoresis after lung transplantation: A 10-year single-center experience. Transplantation 86:1625–1627, 2008.
88. Allen WE, Burke CM, McGregor CGA, et al: Steroid-responsive bronchiolitis after human heart-lung transplantation. J Thorac Cardiovasc Surg 92:449–451, 1986.
89. Kawut SM, Lederer DJ, Keshavjee S, et al: Outcomes after lung retransplantation in the modern era. Am J Respir Crit Care Med 177:114–120, 2008.
90. Aigner C, Jaksch P, Taghavi S, et al: Pulmonary retransplantation: Is it worth the effort? A long-term analysis of 46 cases. J Heart Lung Transplant 27:60–65, 2008.
91. Guerry-Force ML, Müller NL, Wright JL, et al: A comparison of bronchiolitis obliterans with organizing pneumonia, usual interstitial pneumonia, and small airways disease. Am Rev Respir Dis 135:705–712, 1987.
92. Lazor R, Vandevenne A, Pelletier A, et al: Cryptogenic organizing pneumonia. Characteristics of relapses in a series of 48 patients. Am J Respir Crit Care Med 162:571–577, 2000.
93. Purcell IF, Bourke SJ, Marshall SM: Cyclophosphamide in severe steroid-resistant bronchiolitis obliterans organizing pneumonia. Respir Med 91:175–177, 1997.
94. Niewoehner DE, Kleinerman J, Rice DB: Pathologic changes in the peripheral airways of young cigarette smokers. N Engl J Med 291:755–758, 1974.
95. Churg A, Wright JL: Small airway disease in mineral dust exposure. Pathol Annu 18:233–251, 1983.
96. Moon J, du Bois RM, Colby TV, et al: Clinical significance of respiratory bronchiolitis on open lung biopsy and its relationship to smoking related interstitial lung disease. Thorax 54:1009–1014, 1999.
97. Bogin RM, Niccoli SA, Waldron JA, et al: Respiratory bronchiolitis: Clinical presentation and bronchoalveolar lavage findings. Chest 94:21S, 1988.
98. Yousem SA, Colby TV, Gaensler EA: Respiratory bronchiolitis–associated interstitial lung disease and its relationship to desquamative interstitial pneumonia. Mayo Clin Proc 64:1373–1380, 1989.
99. Ryu JH, Colby TV, Hartman TE, et al: Smoking-related interstitial lung diseases: Concise review. Eur Respir J 17:122–132, 2001.
100. Park JS, Brown KK, Tuder RM, et al: Respiratory bronchiolitis–associated interstitial lung disease: Radiologic features with clinical and pathologic correlation. J Comput Assist Tomogr 26:13–20, 2002.
101. Lynch DA: Imaging of small airways diseases. Clin Chest Med 14:623–634, 1993.
102. Portnoy J, Veraldi KL, Schwarz MI, et al: Respiratory bronchiolitis–interstitial lung disease: Long-term outcome. Chest 131:664–671, 2007.
103. Izumi T: A nation-wide survey of diffuse panbronchiolitis in Japan. *In* Grassi C, Rizzato G, Pozzi E (eds): Sarcoidosis and Other Granulomatous Disorders. New York: Elsevier Science, 1988, pp 753–757.
104. Tsang KWT, Ooi CGC, Ip MSM, et al: Clinical profiles of Chinese patients with diffuse panbronchiolitis. Thorax 53:274–280, 1998.
105. Fitzgerald JE, King TE, Lynch DA, et al: Diffuse panbronchiolitis in the United States. Am J Respir Crit Care Med 154:497–503, 1996.
106. Nishimura K, Kitaichi M, Izumi T, et al: Diffuse panbronchiolitis: High resolution CT and pathologic findings. Radiology 184:779–785, 1992.
107. Sugiyama Y: Diffuse panbronchiolitis. Clin Chest Med 14:765–772, 1993.
108. Suzuki M, Usui K, Tamura N, et al: Familial cases of diffuse panbronchiolitis. Jpn J Thorac Dis 19:645–651, 1981.
109. Sugiyama Y, Kudoh S, Maeda H, et al: Analysis of HLA antigens in patients with diffuse panbronchiolitis. Am Rev Respir Dis 141:1459–1462, 1990.
110. Emi M, Keicho N, Tokunaga K, et al: Association of diffuse panbronchiolitis with microsatellite polymorphism of the human interleukin 8 (IL-8) gene. J Hum Genet 44:169–172, 1999.

111. Kamio K, Matsushita I, Hijikata M, et al: Promoter analysis and aberrant expression of the MUC5B gene in diffuse panbronchiolitis. Am J Respir Crit Care Med 171:949–957, 2005.
112. Schultz MJ: Macrolide activities beyond their antimicrobial effects: Macrolides in diffuse panbronchiolitis and cystic fibrosis. J Antimicrob Chemother 54:21–28, 2004.
113. Nagai H, Shishido H, Yoneda R, et al: Long-term low-dose administration of erythromycin to patients with diffuse panbronchiolitis. Respiration 58:145–149, 1991.
114. Kudoh S, Azuma A, Yamamoto M, et al: Improvement of survival in patients with diffuse panbronchiolitis treated with low-dose erythromycin. Am J Respir Crit Care Med 157:1829–1832, 1998.
115. Black PN: Anti-inflammatory effects of macrolide antibiotics. Eur Respir J 10:971–972, 1997.
116. Nakamura H, Fujishima S, Inoue T, et al: Clinical and immunoregulatory effects of roxithromycin therapy for chronic respiratory tract infection. Eur Respir J 13:1371–1379, 1999.
117. Yousem SA, Colby TV, Carrington CB: Follicular bronchitis/bronchiolitis. Hum Pathol 16:700–706, 1985.
118. Howling SJ, Hansell DM, Wells AU, et al: Follicular bronchiolitis: Thin-section CT and histologic findings. Radiology 21:637–642, 1999.
119. Hayakawa H, Sato A, Imokawa S, et al: Bronchiolar disease in rheumatoid arthritis. Am J Respir Crit Care Med 154:1531–1536, 1996.
120. Masuda T, Ishikawa Y, Akasaka Y, et al.: Follicular bronchiolitis associated with *Legionella pneumophila* infection. Pediatr Pathol Mol Med 21:41–47, 2002
121. Northway WH, Rosen RC, Porter DY: Pulmonary disease following respiratory therapy of hyaline-membrane disease. N Engl J Med 276:357–368, 1967.
122. Edwards DK, Dyer WM, Northway WH: Twelve years' experience with bronchopulmonary dysplasia. Pediatrics 59:839–846, 1977.
123. Churg A, Golden J, Fligiel S, et al: Bronchopulmonary dysplasia in the adult. Am Rev Respir Dis 127:117–120, 1983.
124. Bancalari E, Claure N, Sosenko IRS: Bronchopulmonary dysplasia: Changes in pathogenesis, epidemiology, and definition. Semin Neonatol 8:63–71, 2003.
125. Coalson JJ: Pathology of new bronchopulmonary dysplasia. Semin Neonatol 8:73–81, 2003.
126. Jobe AH, Bancalari E: Bronchopulmonary dysplasia. NICHD-NHLBI-ORD Workshop. Am J Respir Cell Mol Biol 163:1723–1729, 2001.
127. Braman SS, Whitcomb ME: Endobronchial metastasis. Arch Intern Med 135:543–547, 1975.
128. Sorensen JB: Endobronchial metastases from extrapulmonary solid tumors. Acta Oncol 43:73–79, 2004.
129. Rose RM, Grigas D, Strattemeir E, et al: Endobronchial involvement with non-Hodgkin's lymphoma. A clinical-radiologic analysis. Cancer 57:1750–1755, 1986.
130. Chernoff A, Rymuza J, Lippman ML: Endobronchial lymphocytic infiltration. Unusual manifestation of chronic lymphocytic leukemia. Am J Med 77:755–759, 1984.
131. Pitchenik AE, Fischl MA, Saldano MJ: Kaposi's sarcoma of the tracheobronchial tree: Clinical, bronchoscopic, and pathologic features. Chest 87:122–124, 1985.
132. Goodwin RA, Nickell JA, Des Prez RM: Mediastinal fibrosis complicating healed primary histoplasmosis and tuberculosis. Medicine (Baltimore) 51:227–246, 1972.
133. Rossi SE, McAdams HP, Rosado-de-Christenson ML, et al: Fibrosing mediastinitis. Radiographics 21:737–757, 2001.
134. Kim YH, Kim HT, Lee KS, et al: Serial fiberoptic bronchoscopic observations of endobronchial tuberculosis before and early after anti-tuberculosis chemotherapy. Chest 103:673–677, 1993.
135. Westcott JL, Noehren TH: Bronchial stenosis in chronic sarcoidosis. Chest 63:893–897, 1973.
136. Miller A, Tierstein AS, Jackler I, et al: Airway function in chronic pulmonary sarcoidosis with fibrosis. Am Rev Respir Dis 109:179–189, 1974.
137. Dines DE, Stubbs SE, McDougall JC: Obstructive disease of the airways associated with stage I sarcoidosis. May Clin Proc 53:788–891, 1978.
138. James DG, Jones WW: Intrathoracic and upper respiratory tract. *In* Smith L (ed): Sarcoidosis and other granulomatous disorders. Philadelphia: WB Saunders, 1985, pp 58–59.
139. Katzenstein A, Liebow AA: State of the art: Bronchocentric granulomatosis, mucoid impaction, and hypersensitivity reactions to fungi. Am Rev Respir Dis 111:497–537, 1975.
140. Dixon GF, Donnerberg RL, Schonfeld SA, et al: Clinical commentary: Advances in the diagnosis and treatment of broncholithiasis. Am Rev Respir Dis 129:1023–1030, 1984.
141. Cordier JF, Loire R, Brune J: Amyloidosis of the lower respiratory tract. Clinical and pathologic features in 21 patients. Chest 90:827–831, 1986.
142. Hui AN, Koss MN, Hochholzer L, et al: Amyloidosis presenting in the lower respiratory tract. Clinicopathologic, radiologic, immunohistochemical, and histochemical studies on 48 cases. Arch Pathol Lab Med 110:212–218, 1986.
143. Madden BP, Lee M, Paruchuru P: Successful treatment of endobronchial amyloidosis using Nd:YAG laser therapy as an alternative to lobectomy. Monaldi Arch Chest Dis 56:27–29, 2001.
144. Rabin CB: New or neglected signs in the diagnosis of chest diseases. *In* Fishman AP (ed): Pulmonary Diseases and Disorders. New York: McGraw-Hill, 1980, pp 92–102.
145. Lindskog GE, Spear HC: Middle-lobe syndrome. N Engl J Med 253:489–495, 1955.
146. Arakawa H, Webb WR: Air trapping on expiratory high-resolution CT scans in the absence of inspiratory scan abnormalities: Correlation with pulmonary function tests and differential diagnosis. AJR Am J Roentgenol 170:1349–1353, 1998.
147. Glenner GG: Amyloid deposits and amyloidosis. N Engl J Med 302:1283–1292, 1980.
148. Harkins WB: An endotracheal metallic prosthesis in the treatment of stenosis of the trachea. Ann Otol Rhinol Laryngol 61:932–935, 1952.
149. Wood DE: Airway stenting. Chest Surg Clin North Am 11:841–860, 2001.

CHAPTER 45

BIOLOGY OF NON–SMALL CELL LUNG CANCER

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INTRODUCTION

Lung cancer is the number-one cause of cancer-related death in the Western world. Lung cancer remains the leading cause of cancer mortality for both men and women in the United States.[1] Its incidence is highly correlated with cigarette smoking, and about 10% of long-term smokers will eventually be diagnosed with lung cancer. Among the 10% of patients who develop lung cancer without a smoking history, potential environmental or inherited causes of lung cancer are unclear. As large as the clinical challenges patients and physicians face in managing this disease, equally enormous are the challenges in detailing the complex molecular pathogenesis of lung cancer. Major progress has been made, however, and we are beginning to see this knowledge translated into the clinic. In this chapter, we summarize our understanding of how lung epithelial cell injury leads to signaling pathway activation that triggers the uncontrolled proliferation, resistance to apoptosis, metastasis, and escape from immune surveillance seen in lung cancer. Whereas all subtypes of non–small cell lung cancer (NSCLC) have historically been treated the same, stage-for-stage, recent technological advances have allowed a better understanding of the molecular classification of the disease and provided hypotheses for molecular early detection and targeted therapeutic strategies.

The pathogenesis of lung cancer involves the accumulation of multiple molecular abnormalities over a long period of time.[2] Heritable alterations can happen at the level of gene expression through abnormal microRNA expression or methylation, DNA sequence changes, DNA segment amplification, deletion, or whole chromosome gains or losses. These lesions allow cells to escape the normal regulation of cell division, apoptosis, and invasion and/or alter its interaction with the host. The historical focus of much of this research has been to identify and study the role of specific genetic abnormalities in tumor cells related to chromosomal abnormalities, inactivation of specific tumor suppressor genes, the activation of specific oncogenes, the expression of hormone receptors and growth factor production associated with the development of cancer. More recently, the contribution of stromal interactions, angiogenesis, apoptosis, and epigenetic phenomena such as posttransla-

tional modification of critical genes has been the subject of intense research. The completion of the first draft of the human genome sequence[3] and the availability of high-throughput technologies (e.g., microarrays) have also prompted investigators to propose studies to discover molecular alterations of individual tumors with incredible sensitivity and unprecedented scope. Common molecular abnormalities in both pre- and invasive lung cancers are being integrated and hold the promise for potential utility in prevention, early detection, and therapy.

PREDISPOSITION TO LUNG CANCER

Smoking

Tobacco use continues to be a major cause of cancer in the developed world. Tobacco control efforts are leading to a decrease in cancer mortality in some areas of the world, but globally there are still over 1 billion smokers.[4] Over 85% of all lung cancers are attributable to cigarette smoking; however, only a fraction of long-term cigarette smokers develop lung cancer, suggesting a role for variable inherited genetic susceptibility in lung tumorigenesis.

Lung cancer also develops through a multistage process in a background of increasing genomic instability.[5] For example, cytogenetic alterations arise throughout the airways with monoclonal and trisomic clonal patches observed.[6] These changes develop diffusely in the airway following the distribution of cigarette smoke exposure and confirm the "field cancerization" hypothesis.[7] Therefore, elucidating the molecular determinants responsible for the development of lung cancer and identifying intermediate biomarkers associated with malignant progression remain important questions. Cigarette smoking clearly contributes to the accumulation of genetic alterations in lung cancer.[8–10] Tobacco is rich in pulmonary carcinogens and causes many genetic changes by inducing DNA mutation.[11,12] Tobacco-specific nitrosamines also induce DNA methylation.[13] Levels of DNA adducts such as methylated DNA can, in fact, be used as an index of human tobacco exposure. Tobacco also causes methylation of tumor suppressor genes.[14,15] Cigarette smoke has also been shown to induce demethylation of the proto-oncogene synuclein-gamma in lung cancer.[16] Therefore, cigarette smoke could lead to specific patterns of chromatin structure alterations that may promote cancer development. In the future, specific epigenetic alterations induced by cigarette smoking may be useful as markers of lung cancer development.

Chronic exposure to carcinogens initiates a process characterized by genetic abnormalities, phenotypic changes, and overgrowth of clones of genetically altered epithelial cells throughout the lungs.[17] Genomic alterations may form a pattern referred to as a "genomic signature." The signatures found in NSCLC may contain information about their induction by cigarette smoke[18] and may reflect the pathways to cancer development or represent the product of competitive selection of clones.

Genetic Susceptibility and Familial Predisposition

In epidemiologic studies, smoking confers an approximately 14-fold increased risk for lung cancer, and after controlling for tobacco use, a family history of lung cancer accounts for an approximately 2.5-fold increased risk. Here we address susceptibility as it relates to genetic predisposition and familial predisposition separately.

Rare autosomal dominant genes found by segregation analyses may explain susceptibility to early-onset lung cancer, but these results explain a minority of lung cancer cases, including those with a strong family history. Therefore, more common genetic variants or polymorphisms are likely to affect lung cancer risk. Inherited differences in DNA repair capacity in response to tobacco-mediated damage have been incriminated as underlying some of this predisposition. When lymphocytes from lung cancer patients and age-matched controls are exposed to bleomycin, the lymphocytes from lung cancer cases develop more chromatid breaks than the control lymphocytes.[19] A similar assay has been developed using benzo[alpha]pyrene diol-epoxide (BPDE), a reactive substrate that is derived by in vitro processes from benzo[alpha]pyrene, a major carcinogen in tobacco smoke.[20] These results suggest that the DNA repair capacity influences risk for lung cancer. Telomere length has also been inversely associated with lung cancer risk.[21]

In three lung cancer genome-wide association studies (GWAS), polymorphic differences in chromosome 15q25 have been associated with the risk of developing lung cancer.[22–24] Single nucleotide polymorphisms (SNPs), mapped to a region of strong linkage disequilibrium within 15q25.1, contain nicotinic acetylcholine receptor subunit genes. The genetic variants were associated both with nicotine dependence as well as with certain lung cancer phenotypes, including lung cancer developing in younger patients and in patients with lower amounts of smoking; the variants were not associated with lung cancer in nonsmokers or with other smoking-related cancers like renal or bladder.[25] Thus, these genetic variants appear to increase risk both for smoking and for smoking-related lung cancer. Since then, subsequent analyses identified additional variants that influence lung cancer risk,[26] which will require further investigation in a larger sample size. The relative impact of the nicotinic acetylcholine receptor gene variants on the propensity to smoke or on the response to the direct carcinogenic effects of smoke is undergoing validation in large numbers of smokers and nonsmokers.

Familial risks of lung cancer provide another route for uncovering susceptibility genes. In one genome-wide linkage analysis, a genomic locus on chromosome 6q23-25 has now been associated with a familial risk of lung cancer.[27] To date, no tumor suppressor genes inactivated by mutation have been identified in this locus, although the frequent inactivation of multiple candidate tumor suppressor genes within chromosome 6q likely contributes to development of sporadic lung cancer.[28]

Finally, a genome-wide association analysis was conducted to investigate associations between SNPs and the risk of lung cancer in 194 patients with familial lung cancer and 219 cancer-free control subjects.[29] A strong association was found between common sequence variants at 15q24-25.1 and lung cancer. The risk of lung cancer was more than fivefold higher among those subjects who had both a family history of lung cancer and two copies of high-risk alleles in the 15q24-25.1 locus as compared with control subjects.[29] Thus, studies into sporadic and familial cancer risk may identify some of the same genetic predispositions, such as 15q24-25.1, but have the potential to identify novel genetic predispositions.

EARLY EVENTS IN LUNG TUMORIGENESIS

Mucosal Response to Injury, the Emergence of Critical Mutations

Since the late 1970s, somatic mutations have been identified and associated with the development of cancer. These mutations, involving those of tumor suppressor genes or oncogenes, may or may not be critical events in the formation of the cancer. Epidemiologic data support the hypothesis that clones of cells accumulate several key mutations during oncogenesis. Proposed by Loeb,[30] the model of the mutator phenotype, a phenotype in which mutations develop faster than in normal cells, suggests that this propensity for rapid mutation may be required for multistage carcinogenesis and may be acquired by cells early on. This phenotype may also be hereditary.

DNA mutations may arise from a failure to repair DNA damage. In addition to damage and mutations due to environmental carcinogens, spontaneous errors of replication attributed to DNA polymerase occur at a rate of 1/10,000 to 1/100,000 base pairs. These intrinsic mutations may also be an important component underlying genomic instability and eventually tumor development. A recent analysis of 623 genes in 188 lung adenocarcinomas revealed over 1000 somatic mutations, and those in 26 different genes were found to be mutated at significant frequencies.[31] Many of these mutated genes fall into a handful of common signaling pathways. We briefly comment on a few examples of these commonly acquired mutations in *K-ras*, p53, p16, BRaf, and epidermal growth factor receptor (EGFR).

K-ras mutations are the most common mutations found in lung cancer. The mutations are found in 30% of adenocarcinomas of the lung[32] but much less frequently in other subtypes. Mutations in *K-ras* lead to activation of several pathways. Ras proteins activate the RAF/MEK/ERK pathway, which mediates cell growth and cell cycle entry by phosphorylation of transcription factors (such as c-FOS, ELK1, and MYC); phosphorylation of the RSK (ribosomal protein S6 kinase) and MNK (mitogen-activated protein kinase [MAPK]–interacting serine/threonine kinase) family of kinases; and the phosphatidylinositol-3-kinase (PI3K)/protein kinase B (AKT) pathway, which controls cell survival, cell growth, and metabolism.[33] Mutant *K-ras* (most frequently, codon 12 G-T transversions) can transform airway epithelial cells[34] by activating the extracellular signal-regulated kinase (ERK)–MAPK pathway. Because the *K-ras* mutation is found early in alveolar atypical hyperplasia, a presumed precursor lesion to adenocarcinomas, *K-ras* mutation may be an important step in the genesis of this subtype of lung cancer. The fact that mutant ras transgenic mice develop adenocarcinomas of the lung supports this hypothesis.

p53 is a prototype tumor suppressor gene that is the most common genetic lesion in human cancers[35] and is thus well suited for analysis of the mutational spectrum in human cancers. p53 is a potent regulator of cell growth and DNA damage responses and directly regulates the cell cycle via induction of p21. Mutations of p53 are most commonly seen in squamous carcinoma and small cell carcinoma of the lung. Mutations predominantly representing G to T transversions consistent with causation by bulky DNA adducts such as the polycyclic hydrocarbons are frequently found in the lungs of smokers.[8] When mutated, p53 can function as an oncogene. Mutated p53 exhibits a prolonged half-life, and the protein can be found to be overexpressed in about 50% of lung cancers by immunohistochemistry.[36] Although not consistently associated with prognostic significance, there is little doubt that p53 mutations play a key role in tumor development by dysregulation of cell cycle control and apoptosis.

p16, a cyclin-dependent kinase inhibitor, functions as a tumor suppressor gene and critical member of the retinoblastoma (Rb) cell cycle control pathway. It is inactivated in over 40% of NSCLCs. Previous studies have demonstrated that point mutations, deletion or loss of heterozygosity on 9p21, or hypermethylation of the gene provides alternate mechanisms of inactivation in 30% to 50% of NSCLCs. In smokers, the loss of p16 appears to be from different mechanisms than in nonsmokers. In tumors arising in smokers, p16 was lost due to point mutations or homozygous deletions, whereas in tumors from nonsmokers, p16 was lost via promoter hypermethylation.[37] The relationship between the loss of p16 and tobacco points to p16 as another genetic target of cigarette smoke in the pathogenesis of lung cancer.

BRAF is a serine/threonine kinase that belongs to the RAS/RAF/MEK/ERK/MAPK pathway, and is important for transducing mitogenic signals from the cell surface. BRAF mutations were found in thyroid, colorectal, and lung cancer as well as in a majority of malignant melanomas.[38] The percentage of BRAF-mutant lung cancers appears to be less than 5% and to be limited to lung adenocarcinomas.[39] This observation has led to drug discovery programs dedicated to specific targeting of BRAF-dependent tumors. Trials investigating the efficacy of these agents are ongoing in several tumor types.[40] Whether BRAF-mutant lung cancer can be successfully treated with inhibitors targeting downstream pathway members of BRAF remains to be established.

PIK3CA, the gene encoding the catalytic subunit of the class-1a phosphoinositide-(3,4,5)-kinase, is an important component of the AKT antiapoptotic pathway. Mutations in this gene have been found in a large fraction of epithelial cancers.[41] Although the most frequently mutated oncogene in breast cancer, PIK3CA, was found to be mutated in less than 5% of lung cancers. In several functional analyses, these mutations were found to be oncogenic by their ability to activate the AKT survival pathway.[42] Most recently, preclinical studies involving new generation PI3K-kinase inhibitors suggest that tumors carrying these mutations might be exquisitely sensitive to pathway inhibition.[43]

The receptor tyrosine kinase EGFR is mutated in approximately 10% of white and 40% of East Asian patients with NSCLC,[44–46] leading to constitutive activation of this growth factor receptor. These mutations are more common in patients who have never smoked, whose tumors are of lung adenocarcinoma histology, and who are of East Asian ethnicity. Exon resequencing in responders to the tyrosine kinase inhibitors, gefitinib or erlotinib, revealed that most of them had deletion mutations in exon 19 or point mutations in exon 21 of the EGFR kinase domain, but patients not responding to these drugs only rarely had these mutations.[47] Targeting inhibition to this mutant EGFR appeared to be an additional example of successful therapeutic targeting of oncogenically activated tyrosine kinases. Even though dramatic responses are frequently seen in patients with the common EGFR mutations, most patients initially responding to EGFR inhibitors will eventually relapse. These relapses may be explained by additional mutations in EGFR or activation of other growth pathways. In certain cases, resistance has been found to be due to an activating mutation of EGFR at a second site. This mutation, T790M, is analogous to the T315I mutation of the murine leukemia viral oncogene homolog (ABL) that causes acquired resistance in chronic myelogenous leukemia (CML) patients who had initially responded to imatinib.[48,49] An additional mechanism of acquired resistance is the de novo amplification of the MET receptor tyrosine kinase gene.[50] Understanding the sources of acquired resistance may reveal strategies for prevention of resistance.

Because only a minority of lung cancer patients will respond to anti-EGFR therapy, investigators have sought biomarkers of response to EGFR-directed therapy. Mutations in the *K-ras* oncogene constitute a negative predictive marker of response to EGFR-directed therapy.[51] In addition, *K-ras* mutations, male gender, absence of bronchoalveolar carcinoma (BAC) feature, advanced stage, and smoking history were found to be poor prognostic factors for overall survival, whereas EGFR mutation and amplification were not.[52] It is possible that the presence and type of EGFR mutations will indicate which patients will respond to therapy with EGFR inhibitors. Trials selecting patients either on the basis of the EGFR mutations or on clinical characteristics of EGFR mutations (Asian ethnicity, never smokers, adenocarcinoma) have yielded response rates to EGFR inhibition therapy exceeding 70% and led to median overall survival exceeding 20 months.[53–55] However, as mentioned, EGFR mutations are highly prognostic for improved survival independent of therapy and, thus, their use for the selection of therapy is controversial, especially in Western populations.[56] However, there is an increasing sentiment that EGFR (and *K-ras*) mutation testing should become part of the standard pathologic analysis of lung adenocarcinomas.

The efforts to characterize the genomes of major human cancer types[57,58] have revealed that, beyond known cancer-related genes, many additional genes are mutated in individual cancers. However, most of these mutations are found in only a single tumor, suggesting that each tumor contains an individual set of mutations contributing to tumorigenesis. Ding and coworkers[31] found between 0 and 40 mutations in individual lung adenocarcinomas, with an average of 24.3 for those with a mutant PRKDC gene (involved in DNA repair) and 4.7 for those without this mutation. The average number of mutations for different tumors range from 48 in pancreatic cancer to 101 in breast cancer.[59] Interestingly, both of these numbers are higher than that for lung cancer. Ultimately, functional cell biology experiments will be required to establish the individual contributions of these mutations to oncogenic transformation.

Mutagens

Cigarette smoking may account for 85% of lung cancers. Approximately 1 in 10 life-smokers will develop lung cancer, suggesting individual differences in susceptibility,[60,61] Environmental carcinogenesis resulting from tobacco smoke exposure is a complex process that can involve activation of procarcinogens that lead to DNA adduct formation and subsequent failure of DNA repair, which should normally remove these adducts. Studies comparing DNA repair capacity among newly diagnosed lung cancer patients and age-matched controls indicate significant differences between the two groups.[62]

The majority of lung cancers are now diagnosed among ex-smokers.[63] This suggests that the accumulation of molecular damage during cigarette exposure initiates a cascade of events that will lead to cancer even decades after smoking cessation. Risk factors for lung cancer include smoking, including total consumption, age of initiation, and years of smoking; occupational and environmental exposure (asbestos, uranium, radiation), diet (vitamin A, vitamin E, cholesterol), and host (familial aggregation) and genetic factors. Some of the components of cigarette smoke implicated in lung cancer are now recognized. Cigarette smoke is a complex mixture and includes substances that are responsible for DNA adduct formation such as polycyclic aromatic hydrocarbons (PAHs), aromatic amines, and tobacco-specific nitrosamines (NKKs). These form DNA adducts that may escape normal adduct repair mechanisms and result in heritable alterations in DNA sequence. The conversion of G-C base pairs to T-A leads to activation of the *K-ras* oncogene and inactivation of the p53 tumor suppressor gene.[12] The activated form of benzopyrene (BaP) is the diol epoxide BPDE that can cause DNA adducts, leading to point mutations and single-strand chromatid breaks.[64] A major concern is that people who start smoking at

young ages seem to be have greater amounts of permanent DNA alterations than smokers who start smoking later.[9]

The Field Cancerization Effect

Whereas lung cancer may originate from only one or a few airway epithelial cells, it is clear that exposure of the whole airway mucosa to tobacco smoke could cause the entire bronchial tree to be at increased risk of developing lung cancer, leading to the concept of field cancerization (Fig. 45-1). Field cancerization was first proposed in the 1950s[7] and its molecular correlates later confirmed in the airways of human smokers.[65] Field cancerization is also demonstrated by the elevated Ki-67 labeling index in the airways of smokers at more than one site.[66] In addition, evidence has been found in a single smoker with diffuse dysplasia that a single identical point mutation of p53 could be found diffusely in both lungs, but not in the blood or other solid organs, suggesting that a single progenitor bronchial epithelial clone populated the bronchial mucosa. Although the risk of developing lung cancer increases with the presence of such preinvasive lesions, clearly the entire at-risk epithelium does not undergo malignant transformation, and no one has identified the molecular determinants of preinvasive lesions that may predict irreversible progression to lung cancer. Thus, if one considers the total number of bronchial epithelial cells and the proliferation rate of patches of clonal abnormalities, cancer remains a rare event.[67]

The concept of field cancerization has implications for approaching diagnosis, prevention, and treatment of lung cancer. For example, diagnostic information may be contained even in the normal-appearing airway epithelium; in patients with and without lung cancer, changes in the airway field have been found to correlate with the presence of lung cancer elsewhere in the airways or with an elevated risk of transformation.[68,69] Similarly, prevention efforts should be directed to the entire epithelium, which can then also provide biomarkers for effective prevention. Finally, the field cancerization concept has major implications for therapy because one should consider treating the entire field as opposed to limiting treatment efforts to preinvasive lesions that may never develop into lung cancer.[70]

Genomic Instability

Lung cancer develops along a multistage process in a setting of increasing genomic instability. Genomic instability is universally found during accumulation of these genetic abnormalities.[5,30] Genome instability is a fundamental characteristic of cancer initiation and progression. However, our understanding of the onset of instability, the rate of instability, and the mechanisms

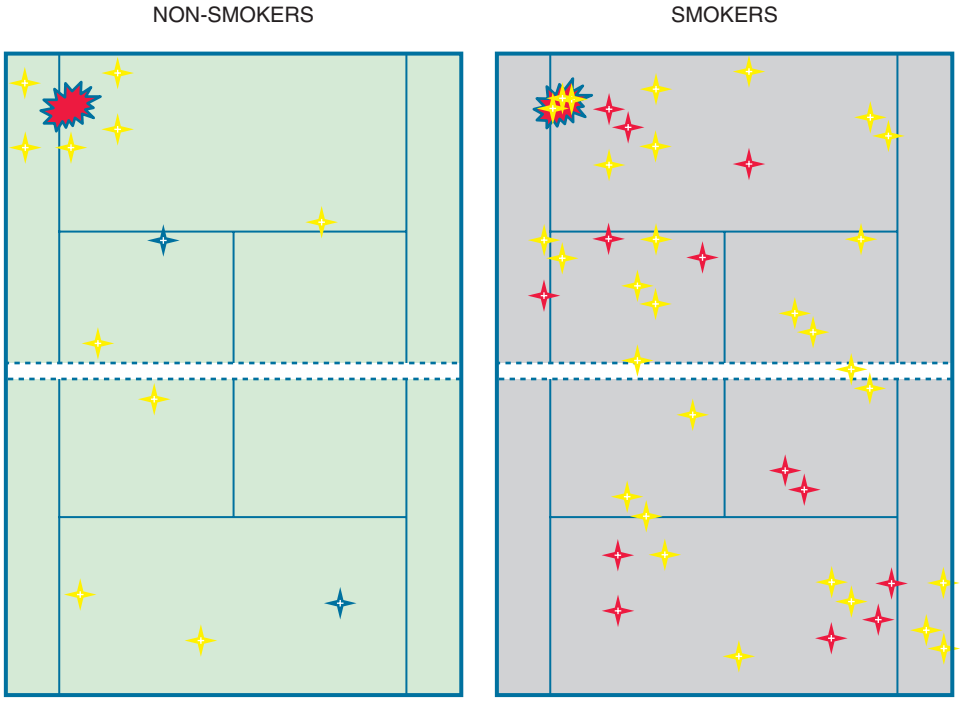

FIGURE 45-1 ■ The different fields of injury in nonsmokers and smokers. The association of lung tumors and genetic mutations differs between nonsmokers and smokers. In this figure, the lung epithelial surface area is displayed as if it were a tennis court, known to be of roughly comparable size. The tumors (*red ovals*) and associated genetic alterations (*red and yellow stars*) are shown as representative for nonsmokers and for smokers. In nonsmokers, lung tumors develop different chromosomal abnormalities (chromosomal segregation and chromatin epigenetic alterations), have a lower number of abnormally expressed genes, and demonstrate a lower mutation rate than that seen in smokers. Other differences, in cancer stem cells or in the inflammatory response to environmental exposures, may also exist between the two groups.

leading to instability is far from complete. We do know that, from initiation to promotion and to the development of an invasive phenotype, a series of molecular changes contribute to a molecular instability that puts the airway epithelium of some smokers at greater risk for lung cancer.

Two main theories of the genomic changes underlying lung tumorigenesis have emerged: the stochastic (random) and the gene-centric (nonrandom) theories. The *stochastic theory* argues that lung cancer arises by genomic aberrations that are stochastic or random in nature.[71] Indeed, in many tumor types, there are relatively few cancer-specific mutations whereas there can be a high degree of subchromosomal aberrations.[72–74] Some of these low-level aberrations have been called noise but may reflect the underlying instability. Nonclonal chromosomal alterations (NCCAs) such as defective mitotic figures, chromosomal fragmentation, or nonrecurrent genomic alterations indicate a dynamic process leading to instability.[71] NCCAs may provide a survival advantage whereas clonal chromosomal alterations at a later stage of progression may confer a growth advantage.

In contrast, the *gene-centric theory* argues that sequential accumulation of epigenetic and genetic aberrations is important for lung cancer development.[75] This gene-centric theory is particularly appealing to explain clonal alterations in genes implicated in tumor cell growth and survival that represent possible targets for the management of cancer.[76] These alterations include single nucleotide point mutations, changes in chromosome copy number (aneuploidy),[6,77] and specific genomic amplifications or deletions.[78–80] These genetic changes are implicated in the pathogenesis of tumor development in part through the activation of oncogenes and inactivation of tumor suppressor genes and are considered the hallmark of cancer.[81] Some genomic signatures seem to persist after tumor development and throughout their progression and their histologic differentiation. The fact that smoking history leads to specific genomic alterations across different tumors also suggests a specific pathogenesis with genomic alteration resulting from a series of dysregulations in DNA repair mechanisms and chromosomal segregation.

The two theories are not necessarily mutually exclusive and both random and nonrandom changes may be important. The progressive accumulation of mutations, loss of apoptotic control and regulation of cell proliferation, and the appearance of an abnormal number of chromosomes (aneuploidy) are associated with worsening dysplasia phenotypes and may reflect underlying dysregulation of mechanisms controlling genomic fidelity. In some lung tumors, mismatch repair deficiency leads to microsatellite instability at the nucleotide sequence level whereas, in other tumors, aneuploidy is the dominant feature.[82] Specific defects in DNA repair may also be present. Polymorphisms in DNA repair genes XPD (codon 312 Asp/Asp vs. Asp/Asn) are associated with impaired efficiency of DNA repair and apoptotic function in lung cancer.[83] Measures of genomic instability parallel rates of loss of heterozygosity[84] and accumulation of other genomic abnormalities.[82] In the airways, progressively more severe and more frequent abnormalities are seen in preinvasive lesions. The progressive accumulation of genomic abnormalities associated with clonal growth among populations of tumor cells is well described. Recent reports use array comparative genomic hybridization (aCGH) to assess genomic instability; in these reports, in addition to numerical chromosome changes, smaller aberrations are found at specific chromosome loci.[85] Clearly, genomic instability itself drives malignant progression and this instability may itself be a target for prevention or therapy of lung cancer.

Role of Inflammation in Lung Tumorigenesis

The tumor cell signaling pathways that trigger the uncontrolled proliferation, resistance to apoptosis, metastasis, and escape from immune surveillance are partially understood. In contrast, how inflammation and its control may participate in lung tumorigenesis remains more poorly understood.

The reason why some smokers develop chronic obstructive pulmonary disease (COPD), some develop lung cancer, and some develop both diseases remains unclear.[86] Cigarette smoke contains high concentrations of oxidants and free radicals (ROS) together with thousands of particles. Local antioxidant and metabolizing enzymes inactivate many toxic species. Nuclear factor-κB (NF-κB) activation and subsequent transactivation of inflammation-related genes appear to play a central role in both COPD and cancer.[87,88] How some smokers remain free of disease while others develop COPD or cancer may be determined by the activation of genes in response to cigarette smoke.[89] Following exposure to the same toxic smoke, individuals appear to progress toward disease along different paths. In those who develop lung cancer, genomic instability develops that causes further chromosomal abnormalities resulting in clonal expansion of cells that have a growth advantage, whereas in those who develop COPD, an intense immune response and further inflammation predominate. The process by which these events diverge is unclear. More likely, heritable genetic polymorphisms that influence susceptibility to DNA or connective tissue damage, efficiency of DNA or connective tissue repair, the intensity of immune responses to constituents of tobacco smoke, intrinsic or acquired genomic instability, or the induction of factors that suppress immune surveillance likely determine the disease pathway taken.

Toll-like receptors (TLRs), which recognize a variety of pathogen-associated molecular patterns, are centrally involved in the initiation of the innate and adaptive immune responses. However, recent evidence shows that functional TLRs are also expressed on a wide variety of tumors, suggesting that TLRs may play important roles in tumor biology, and are being evaluated as therapeutic targets. Activation of tumor cell TLRs not only promotes tumor cell proliferation and resistance to apoptosis but also enhances tumor cell invasion and metastasis by reg-

ulating metalloproteinases and integrins. Moreover, the activation of TLR signaling in tumor cells induces the synthesis of proinflammatory factors and immunosuppressive molecules, which enhances the resistance of tumor cells to cytotoxic lymphocyte attack and leads to immune evasion. Thus, the neoplastic process may usurp TLR signaling pathways to advance cancer progression, which suggests that targeting tumor TLR signaling pathways may open novel therapeutic avenues.

Role of Viruses in Lung Tumorigenesis

Viruses can cause lung cancer in animal models; such viruses, including SV40 large T antigen and polyomavirus (PyV) large and middle T antigens, frequently cause lung cancer in transgenic models. No common respiratory viruses have been conclusively incriminated in the development of human lung cancer, but several have been implicated. Human papillomavirus (HPV), for example, has been associated with lung cancer and, in particular, lung cancer arising in women.[90] Simian virus 40 has been incriminated in the development of mesothelioma[91]; Epstein-Barr virus (EBV) has been suspected to be involved in the development of papillomas, mesotheliomas, and lymphomas of the lung. Some have proposed that the Jaagsiekte sheep retrovirus or a variant may cause BAC in humans as it does in sheep. However, many polymerase chain reaction (PCR)–based assays have attempted to correlate bronchogenic carcinomas with respiratory viruses without success. Recent advances in proteomics may be useful in studying the role of viral infection in airway epithelial cell transformation. The proteomic analysis of tumors may allow the identification of peptide sequences specific to pathogens otherwise unknown in tumorigenesis.

In recent reports, infectious agents associated with diseased human tissues have been discovered by high-throughput sequencing technologies.[92] However, identification of a nucleic acid sequence in a sample does not necessarily implicate an organism in a disease. There may be contamination of tissues, the fragments of nucleic acid do not necessarily mean that the organism itself is present, and viruses (e.g., human herpesvirus and human papillomavirus) may be present and either part of a subclinical infection unrelated to the disease or latent in human tissue but not actively causing the illness.

OTHER MOLECULAR ALTERATIONS DRIVING THE TUMOR PHENOTYPE

Chromosomal Changes

Cancer cells are characterized not only by mutations but also by a series of other chromosomal aberrations including deletions and amplifications.[93–95] Although chromosomal aberrations have been linked to most tumors and are a characteristic of cancer,[81] chromosomal aberrations are recognized as increasingly complicated.[6,96] Many of the observed alterations have been considered consequences instead of causes of lung cancer development. However, there are chromosomal regions with frequent losses found in regions coding for essential tumor suppressor genes and DNA repair genes that may be involved in the pathogenesis of several tumor types.[97]

Genetic alterations in NSCLC have been measured by array comparative genomic hybridization.[79,80,98] Specific areas of amplification and deletion can distinguish squamous from adenocarcinoma of the lung and other subtypes. Among many areas of genomic abnormality, amplification of chromosomal region 3q26-3q29 was the most prevalent abnormality in squamous carcinoma of the lung. These studies confirm and refine previously documented copy number alterations in lung cancer using CGH analysis[78,99] and show particularly common amplified regions on chromosomal arms 1q, 3q, 5p, 8q, 11q, 12p, 17q, and 20q.

Chromosomal abnormalities may have a role in classifying tumors. Attempts have been made to look comprehensively at the genome to identify tumors with common groups of genetic features that might provide biologic or clinical guidance beyond traditional classification by light microscopy. SNP arrays have been developed that are able to analyze loss or gain of genetic material at very high resolution,[80] and cancer genome resequencing efforts are likely to uncover common mutations.[100] From genomic analyses, relatively small differences have been observed between squamous and adenocarcinoma of the lung. The most prevalent differences were described on chromosome 3q and include the p63 gene.[98,101,102] Accumulation of specific chromosomal abnormalities has been correlated with clinical and pathologic data in NSCLC. Chromosomal abnormalities have been correlated with clinical outcome for a variety of cancers,[95] but often, the genes responsible for the observed biology are very difficult to define and are only partly understood.

Chromosomal abnormalities may underlie the progression of cancer. The most common early genetic alterations in NSCLC involve loss of genomic regions of chromosomes 3p and 9p, deletions of the chromosomal arm on 5p, and mutations of p53 and *K-ras*.[103] Loss of chromosomal regions on chromosomes 3p and 9p have been recognized as early events and identified in preinvasive lesions and in the normal-appearing epithelium of smokers.[104,105] In contrast, p53 and *K-ras* mutations have been seen primarily in later stages of preneoplasia or frank invasive lesions.[103] Amplification of large regions on the q arm of chromosome 3 has been characterized in invasive carcinomas[78,79,99,106] and only recently in preinvasive lesions.[101]

Patterns of chromosomal change may be specific to cigarette smoke. In fact, lessons have been learned from the molecular analysis of lung cancers from patients with and without a history of smoking. For example, loss of heterozygosity (LOH), the loss of a chromosome containing a wild-type gene when the gene on the other allele was previously mutated, at chromosome 3p14 was evaluated in smokers and ex-smokers. LOH at this site was found to be more frequent in current smokers (22/25 cases) than in former smokers (5/11 cases), and the high frequency in smokers correlated with a high metaplasia

index.[104,105] This implies that not only are these chromosomal changes frequent in normal-appearing bronchial epithelia but also that cells with these changes may regress after smoking cessation and be replaced by cells without this damage. Patterns of lung cancer alleleic loss have been investigated in detail and new regions of allelic loss have been identified using high-throughput technologies.[84] Interestingly, chromosome losses such as LOH and chromosomal gains are more prevalent at all sites in cancers from smokers than from nonsmokers, indicating a greater chromosomal instability in the cancers from smokers.[10] aCGH has been used to discover specific patterns of genomic alterations found in NSCLC that might be related to smoking history. Smoking-related genomic signatures were identified in NSCLCs and could be predicted with an overall 88% accuracy[18] (Fig. 45-2). Lung tumors arising from current smokers had the greatest number of copy number alterations. The genomic regions most significantly associated with smoking were located within 32 regions and functionally associated with genes controlling the M phase of the cell cycle, the segregation of chromosomes, and the methylation of DNA. Understanding chromosomal abnormalities specific to cigarette smoke exposure may point to the etiology of smoking-induced lung cancer.

Specific translocation is another chromosomal abnormality, but it is much less commonly observed in lung cancer than in hematologic or mesodermal tumors.[107,108] Chromosomal translocations modify gene function through the deregulated expression of cellular proto-oncogenes without altering the structure of the protein product or by generating and expressing a chimeric protein with growth-promoting activities. Unbalanced translocations are also responsible for a large number of LOHs, which is a genetic event known to cause inactivation of tumor suppressor genes.[109] Dang and colleagues[110] identified a chromosome 19-15 balanced translocation associated with overexpression of Notch-3. The authors developed a transgenic mouse model overexpressing Notch-3 causing neonatal mortality with a phenotype suggestive of alveolar cell hyperplasia. These data suggest that Notch-3 overexpression prevents epithelial differentiation and this may play a significant role in promoting oncogenesis in a subset of lung cancers.[111]

Epigenetic Alterations of Gene Expression in Lung Cancer

DNA Adducts

One marker for significant carcinogen exposure is the level of DNA adducts in normal cells. DNA adducts are covalent modifications of the DNA that result from exposure to specific carcinogens. In addition to being markers of carcinogen exposure, it is possible that these adducts may directly alter regulation of transcription of tumor suppressors or oncogenes.[112] The distribution of BPDE adducts along exons of the p53 gene in BPDE-treated HeLa cells and bronchial epithelial cells has been mapped at nucleotide resolution.[8] Cigarette smokers have higher adduct levels than nonsmokers. Because DNA adduct levels in tumor tissue and in blood lymphocytes have been associated with lung cancer[113] and because these levels correlate with daily or lifetime cigarette consumption and do not reverse after smoking cessation,[114] DNA adducts have been proposed as potential biomarkers of risk for lung cancer.

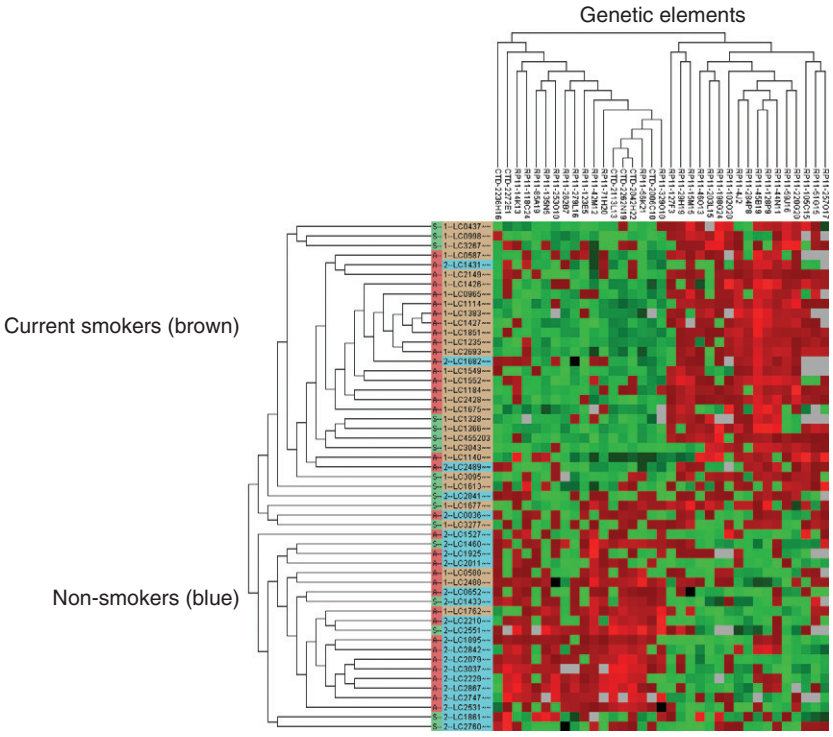

FIGURE 45-2 ■ Smoking-related genomic signatures in non–small cell lung cancer. The genomic signature of lung cancers differs between nonsmokers (N = 23) and smokers (N = 30) and smoking history leaves a specific genomic signature in the DNA of lung tumors. On the y-axis, the current-smokers group is shown in *brown* and the never-smokers or long-term quitters in *blue*. (From Massion PP, Zou Y, Chen H, et al: Smoking-related genomic signatures in non–small cell lung cancer. Am J Respir Crit Care Med 178:1164–1172, 2008.)

In an attempt to identify risk factors associated with the level of DNA adduct accumulation, Wiencke and associates[9] studied DNA adducts in current and former smokers and found that, for current smokers, the most important variable in determining the level of DNA adducts was the number of cigarettes smoked per day. In contrast, they found that for ex-smokers, the most important variable was age at initiation.[9] Mechanisms responsible for the relationship between DNA adduct levels and age of initiation are unknown and the relative contribution of decreased adduct removal by DNA repair or cell turnover or increased adduct formation at younger ages is yet to be determined. Prospective studies are needed to follow current and ex-smokers over time to determine the value of adduct levels in risk assessment.

DNA adducts have been associated with smoking status and with risk of lung cancer. In a matched case-control study nested within the prospective Physicians' Health Study, there was an increased level of DNA adducts in active smokers who later developed lung cancer as compared with smokers who did not develop lung cancer.[115] The level of adducts has also found to be more prevalent among female than male smokers. Women smokers may be at higher risk of developing lung cancer for a given tobacco exposure and women also seem to accumulate aromatic/hydrophobic DNA adducts at a faster rate than men.[116]

DNA Methylation

In contrast to genetic mutations that require two hits to inhibit both alleles, aberrant methylation is a dynamic process over multiple division cycles and may cause increasing degrees of gene function loss by increasing the density of methylation on promoter regions. "CpG islands" the targets of DNA methyltransferase, are associated with the transcription start sites in almost half of human genes.[117] Dense methylation of cytosines within CpG islands can cause heritable gene silencing.[118] Genomic DNA hypomethylation, leading to genomic instability, as well as promoter hypermethylation, leading to inactivation of tumor suppressor genes, have been shown to be common events in human cancers.[119] Gain of methylation in normally unmethylated CpG islands surrounding gene transcription start sites is an increasingly recognized and important means by which gene expression is altered in tumors.[120] The genes affected include over half of the tumor suppressor genes that are known to cause familial cancers. Aberrant methylation can begin early in tumor progression and cause loss of cell cycle control (e.g., p16),[121] loss of mismatch repair function (e.g., MLH1) and loss of cell-cell interaction (e.g., E-cadherin). The exact mechanism by which hypermethylation may cause tumor progression is still unknown. In fact, there is still debate about whether methylation is a result or a cause of gene function loss.[122]

Promoter region hypermethylation has also been proposed as an excellent tumor marker. In lung cancer, methylated loci were found in both tumor and sputum DNA and have been detected in the sputum for up to 3 years before the diagnosis of cancer.[123] Recently, methylation of the promoter region of four genes (TP16, CDH13, RASSFIA, and APC) in patients with stage I NSCLC was shown to be associated with early recurrence.[124]

Histone Acetylation

The association of DNA methylation and histone deacetylation may cause silencing of hypermethylated genes in tumors. During transcription, chromatin unfolds and allows ribosomal access to the DNA. Acetylation of histone tails on the nucleosome is associated with chromatin unfolding and increased regional transcriptional activity. Histone deacetylases (HDACs) modulate chromatin structure by regulating acetylation of core histone proteins. Deacetylation of histones is thus associated with compacting the DNA and repressing transcription. In lung cancer cell lines, for example, deacetylation of histone 3 correlated with refractoriness to retinoic acid, a phenomenon related to RARbeta promoter methylation in a subset of cell lines.[125] Inhibitors of HDACs have already shown to decrease the level of a series of oncoproteins[126] suggesting a potential role as antitumor therapeutic agents.

Expression Arrays

RNA expression patterns may be more relevant than either DNA copy number or epigenetic DNA changes because DNA affects cellular behavior ultimately via proteins translated from the RNA. The microarray technology developed in the mid-1990s offers the hope that a genetic fingerprint of these tumors can be developed associated with clinical features. Beyond the need for better classification of lung cancers, this technical revolution opens a window of understanding to the world of tumor behavior (disease progression, recurrence, response to therapy) as well as to the mechanisms of tumor development. Tumor expression profiles are also influenced by the surrounding nonmalignant cells. The combination of tumor and cell line profiling allows for the study of the regulatory role of both entities.[127]

Expression array data have provided new ways to distinguish and classify tumors. For example, efforts to classify lung cancers based on microarray analysis have revealed subclasses of adenocarcinomas. Selected genes allow the discrimination between primary lung cancer and metastasis of extrapulmonary sites.[128] Studies of expression profiles of adenocarcinomas of the lung using commercially available gene chips[128] or custom arrays[129,130] identified different classes of tumors with some overlap. Four classes of adenocarcinomas were found to have specific prognoses and molecular signatures. These were characterized respectively by their (1) expression of cell cycle or proliferation genes, (2) expression of neuroendocrine markers, (3) expression of markers of alveolar origin, and (4) expression of ornithine decarboxylase or glutathione S-transferase.[128] The neuroendocrine subclass was found to have a clinical outcome significantly worse than the others. These

subclass differences may suggest possible new therapies targeted to these subsets and explain why tumors that superficially seem similar may respond to therapy quite differently. For example, when used to study neuroendocrine tumors, cDNA microarrays found poor correlations between genes expressed in carcinoid and small cell lung cancer (SCLC),[131] tumors that may be morphologically similar but that behave very different clinically.

In sum, since the late 1990s, we have learned that the somatic molecular alterations in cancers yield signatures that can be used for subclassification[128,130] or for predicting patient survival[130,132] risk of recurrence,[133] and response to therapy.[128,134] However, these signatures have not always withstood independent validation.[135]

RNA Regulation by miRNA

Micro-RNA (miRNA) regulates gene transcription and translation.[136,137] In a study analyzing 104 pairs of NSCLC and corresponding normal lung tissues, an expression profile of 43 miRNAs discriminated lung cancers from noncancerous lung tissues.[138] Six miRNAs (hsa-mir-205, hsa-mir-99b, hsa-mir-203, hsa-mir-202, hsa-mir-102, and hsa-mir-204-prec) were differentially expressed in adenocarcinomas when compared with squamous cell carcinomas. Furthermore, high hsa-mir-155 and low hsa-let-7a-2 expression correlated with poor survival in lung adenocarcinomas. In another study of 143 surgically resected NSCLCs, low let-7 expression was also significantly associated with shorter survival whereas overexpression of let-7 in A549 lung adenocarcinoma cell line inhibited lung cancer cell growth in vitro.[139]

Differentially expressed miRNA genes in NSCLC are frequently located in fragile sites of chromosomes highly prone to mutation and/or chromosomal regions with frequent copy number alterations, suggesting that differences in miRNA expression may be induced by genomic alterations. Because greater than 50% of miRNAs are present at cancer-related chromosomal regions, miRNAs are also suspected to play a role as oncogenes or tumor suppressor genes. miRNA expression profiles represent potential markers for lung cancer diagnosis, classification, and prognosis. Methodologic issues related to the reproducibility of the analytical platforms should be resolved soon.

Proteomic Alterations

Changes in DNA and in RNA may not be reflected in changes in protein expression. In fact, recent advances in protein profiling have suggested a poor correlation between gene expression and protein expression. It is now well established that protein activity is often highly regulated by posttranslational modifications such as proteolysis and phosphorylation. Neither protein expression levels nor posttranslational modification can be assessed by genomic or cDNA microarray technologies, prompting interest in evaluation of protein expression, commonly referred to as "proteomics."

Lung cancer has been studied by several proteomic methods including two-dimensional gel electrophoresis, mass spectrometry, and immunohistochemistry to identify biomarkers in tumors[140–142] or in body fluids such as bronchoalveolar lavage (BAL)[143] of patients with or without cancer. Matrix-assisted laser desorption ionization (MALDI) profiling is rapid, high throughput, but detects only the most abundant proteins of relatively low molecular weight and does not enable direct identification when applied to complex proteomes. Two dimensional gel-based analysis suffers problems of interlaboratory reproducibility and throughput. Mass spectrometry has an even lower throughput, but yields confident identification of large numbers of proteins from every cellular compartment.

High-Throughput Profiling Techniques

Matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF MS) is capable of very high throughput in which a sample can be analyzed in seconds and with a higher tolerance for salts, buffers, and other biologic contaminants. Because of these qualities, MALDI MS has been utilized to study proteins/peptides in serum,[144–146] urine,[147] tissue extracts,[148,149] whole cells,[150] and laser-captured microdissected cells.[151] These profiling experiments have been applied to a series of biologic specimens. In one MALDI MS study from our group,[152] hierarchical clustering of data from lung cancers and normal tissues allowed the identification of patterns distinguishing between tumor and normal as well as histologic subgroups.

In general, however, because of a lack of reproducibility between platforms and institutions, proteomic profiling has not yet made a significant impact in clinical medicine. This is in contrast with greater success in the translation of genomic signatures to the clinic.[153,154] Proteomic profiling in biologic fluids or tissue samples is not without challenges. The complexity of the sample composition and the predominance of few abundant proteins in the sample that can mask lower abundant proteins currently limit the utility of this approach.

Molecular Networks, Pathway Analyses

To determine the most informative molecular targets from high-throughput assays, increasingly sophisticated analytic tools are being developed. These analytic tools help define biologic processes, cellular components, or molecular pathways as well as provide gene ontology information about genes of interest; such analytic tools include WebGestalt,[155] Pathway Studio, and Ingenuity. The Kyoto Encyclopedia of Genes and Genomes (KEGG) is a knowledge base for systematic analysis of gene functions in terms of the networks of genes and molecules.[156] Because most pathway and network analysis tools are gene-centric, for tandem mass spectrometry proteomic analyses, a software package called IDPicker has been developed to identify indiscernible protein groups defined by short tryptic peptide sequences. Tools for combining and integrating this multidimensional information at various levels are urgently needed.

TRANSLATING LUNG CANCER BIOLOGY TO THE CLINIC

Biomarkers

Biomarkers are measurable products of tumors that can assist in the diagnosis (identification of cases), prognosis (correlation with outcome independent of interventions), or prediction (associated with outcome after a specific intervention). It is clear that lung cancer outcomes could be improved by high-quality biomarkers addressing each of these categories (Fig. 45-3). Unfortunately, very few candidates have been identified, and even fewer have been validated.

Biomarkers are needed to identify patients at high risk for lung cancer and to identify surrogate end points for response to chemoprevention strategies. The discovery of biomarkers for lung cancer is hampered by the slow onset of lung cancer and the lack of screening tests to identify early disease. The assumption underlying the concept of biomarkers is that certain molecular characteristics of the lesions are highly correlated with specific clinically relevant biologic states. These characteristics include changes in expression levels of genes and proteins and their posttranslational modifications. Detection of cancers at early stages maximizes survival, and identification of blood-borne markers would lead to minimally invasive tests. The best biomarkers are those that are reproducibly measured, that are related to the disease process, and that trigger a clinical decision resulting in improved clinical outcomes (Table 45-1). Despite an intense search for such biomarkers, there are none currently validated for the early diagnosis of lung cancer.[157,158]

Early detection of lung cancer could be aided by biomarkers that are based on the earliest known molecular abnormalities found in lung cancer. Sputum sample analysis for DNA methylation or chromosomal abnormalities by fluorescence in situ hybridization (FISH) may represent approaches suitable for early detection. The analysis of sputum, bronchial biopsies of preinvasive lesions using new detection methods such as fluorescence bronchoscopy,[159] as well as exhaled breath condensate for tumor metabolites may be shown to be efficient ways of assessing high-risk individuals. Early detection by low-dose computed tomography scanning is being evaluated prospectively with the National Lung Cancer Screening Trial in 50,000 smokers. The addition

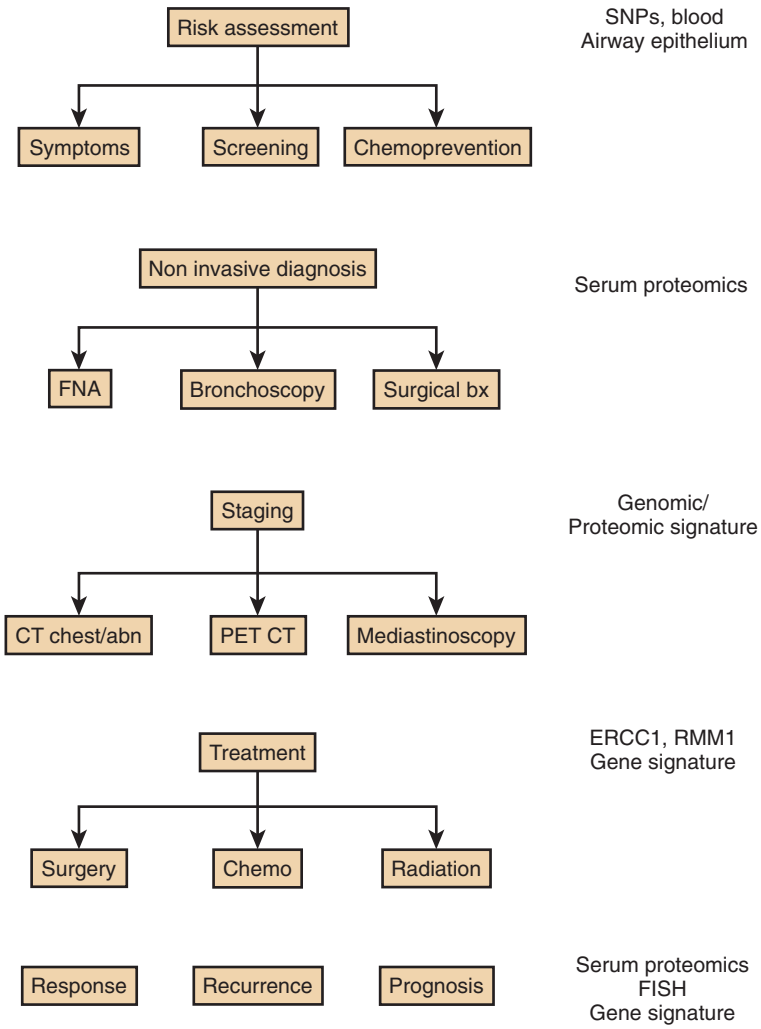

FIGURE 45-3 ■ Future applications envisioned for biomarker-driven personalized management of lung cancer. At each step in the course of the management of lung cancer, important clinical decisions are made. Biomarkers of risk, diagnosis, prognosis, and response to therapy are becoming available and are likely to drive a personalized approach to lung cancer. Examples of such candidate biomarkers are provided in the figure at points in the decision tree where they may affect decision making in the near future.

TABLE 45-1. Characteristics of a Successful Diagnostic Biomarker

Measurable, robust, reproducible, and biologically relevant.
Of proven clinical value *and* triggers a clinical decision.
Clinical community adopts its use and takes advantage of the benefits it affords.
Competitive in terms of cost and insurance reimbursement.

of molecular studies may significantly increase the sensitivity and specificity of this new strategy for early detection.

Prognostic and predictive information may also be provided by biomarkers. Expression array signatures and serum proteomic assays have been discussed previously. Polymorphisms or expression of DNA repair genes (such as ERCC and RRM) have been associated with response to chemotherapy.[160] EGFR gene mutations and copy number alterations are associated with response to EGFR tyrosine kinase inhibitors, and cyclooxygenase-2 (COX-2) expression and urinary prostaglandins have been associated with benefit from COX inhibitors.[161,162] All of these are currently being prospectively tested. For tissue-based predictive and prognostic biomarkers, technical procedures such as tissue processing, use of antibody reagents, and data interpretation need to be developed and standardized. The number of potential cancer-related genes is rapidly growing. Once identified, genes and proteins may be tested in large populations of patients by immunohistochemical or cytogenetic techniques on tissue microarrays.[163] This high-throughput method allows the screening of hundreds of lung cancer samples on a single glass slide and will allow retrospective analysis of material stored with associated clinical outcome. The arrays typically comprise core biopsies 0.6 mm in diameter of different tumors and uninvolved lung from the same individuals retrieved from the pathology archives of various institutions.[164] A firmer understanding of the relationship of relevant protein and genetic markers to clinical and pathologic status could lead to more accurate estimates of the anatomic extent of disease, the risk of recurrence, and the most effective intervention.

Molecular Therapeutics

Many current therapeutic approaches to cancer have been developed to reduce undesirable expression of gene products or otherwise inhibit abnormal protein function: (1) small molecule inhibition of receptor tyrosine kinases, (2) specific antibody approaches (e.g., anti-HER2 or anti-vascular endothelial growth factor [VEGF]), (3) inhibition of p21(ras) farnesylation either by inhibition of farnesyl transferase or by synthesis inhibition of farnesyl moieties, and (4) gene therapy with adenovirus-p53, gene-specific ribozymes, which are able to break down specific RNA sequences, or with antisense oligonucleotides (Table 45-2).

TABLE 45-2. Molecular Targets in Lung Cancer

Characteristics of Cancer	Possible Molecular Targets
Self-sufficient cell growth	EGFR, PI3K, PDGF-R, MAPK
Insensitivity to anti-growth	SMADs, pRb, cyclin-dependent kinases, MYC
Limitless replicative potential	p53, Rb, hTERT, EML4-ALK
Evading apoptosis	*K-ras*, p53, BCL-2, caspases, FAS, TNFR, DR5, IGF/PI3K/AKT, mTOR, *PTEN*, MET, NF-κB
Sustained angiogenesis	VEGF, TGF-β, αvβ3, thrombospondin-1, HIF1α

AKT, protein kinase B; EGFR, epidermal growth factor receptor; EML4-ALK, echinoderm microtubule associated protein like 4-anaplastic lymphomakinase; HIF1α, hypoxia inducible factor 1 alpha; IGF, insulin-like growth factor; MAPK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor-κB; PDGF-R, platelet-derived growth factor receptor; PI3K, phosphatidylinositol-3-kinase; pRb, retinoblastoma protein; *PTEN*, phosphatase and tensin homologue gene; TGF-β, transforming growth factor-β; VEGF, vascular endothelial growth factor.

EGFR Antagonists

One of the most prominent successful molecular therapeutic targets in lung cancer is the EGFR, as described earlier. Interruption of this autocrine pathway with receptor antibodies (extracellular domain of the protein) or tyrosine kinase inhibitors (competition with the kinase adenosine triphosphate [ATP] binding site) can cause tumor regression. Geftinib and erlotinib are potent and specific inhibitors of the tyrosine kinase moiety of EGFR. In clinical trials,[165,166] response rates in heavily pretreated patients with NSCLC varied between 10% and 18%, which may seem low, but it is actually far higher than any standard chemotherapy and represents a major benefit for these low-toxicity oral agents (Fig. 45-4). For patients with activating EGFR mutations in exons 19 or 21, the response rates are as high as 70% to 80%. Studies are proposed to investigate the value of EGFR inhibition with multitargeted inhibitors such as vandetanib (epidermal growth factor [EGF] and VEGF), in combination with chemotherapy or other targeted agents, in earlier stage NSCLC and in lung cancer chemoprevention. Such chemoprevention trials with molecular and morphologic (preinvasive lesions) surrogate end points may suggest reversibility of lesions. However, the rate of spontaneous regression of these preinvasive lesions is, as yet, poorly characterized.

VEGF

Another success story for targeted therapeutics in lung cancer has been the inhibition of the VEGF axis. The addition of bevacizumab, a monoclonal antibody that binds VEGF and inhibits its function, to carboplatin plus paclitaxel prolonged survival in patients with stage IIIB and IV lung cancer.[167] Bevacizumab is now being tested in combination with chemotherapy in the adjuvant treatment of resected lung cancer. In a European trial (AVAIL,

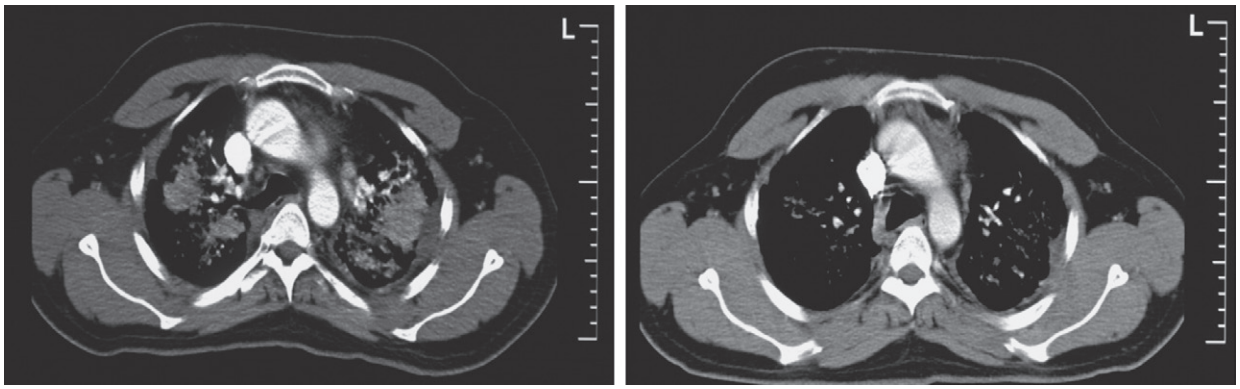

FIGURE 45-4 ■ A response to anti-epidermal growth factor receptor (EGFR)–targeted therapy. Chest computed tomography (CT) scan of a woman with chemotherapy-refractory bronchoalveolar carcinoma shows a dramatic response to gefitinib after 2 months of treatment. This woman was a nonsmoker of Asian ethnicity, a group with a higher frequency of activating EGFR mutations and more frequent responses to EGFR inhibition.

Avastin in Lung Cancer), the combination of bevacizumab with cisplatin plus gemcitabine prolonged progression-free survival, although the duration of follow-up was not sufficient to determine an overall survival benefit.[167a] Tyrosine kinase inhibitors to block the VEGF receptor are also being tested, but have not shown a survival advantage in phase III trials to date.[167b]

p53

Although p53 is a frequently mutated gene in lung cancer, efforts to target this abnormality have not been very successful to date. Several phase I studies have evaluated the safety, biologic effect, and different routes of administration of adenoviral-mediated p53 gene therapy in various tumor types. These studies indicate that introduction of wild-type p53 into tumor cells represents a potentially valuable tool for the therapy of many types of human cancers[168] mainly by causing cell cycle arrest or apoptosis. When injected intratumorally, wt-p53 can be expressed in patients with p53 mutations and 3 of 7 patients showed regression of tumor size.[169] Using the wild-type p53 recombinant adenovirus, the same group of investigators showed in a phase I trial that 16 of 25 patients had stabilization of disease and 2 had partial remissions.[170] One of the major limitations of the intratumoral approach is the inefficient delivery of genes within the tumor mass.

Viruses have been used to facilitate gene entry in vitro into cells (adenovirus-mediated gene transfer) or in vivo into human lung cancer (wild-type p53 delivered by retrovirus)[171] and demonstrated to be administered by bronchoscopy via BAL with repeated dosing.[172] Stabilization of disease and symptomatic improvement may warrant further studies of Ad-p53 or other adenoviruses administered by BAL in patients with BAC.

K-ras: Farnesyl Transferase Inhibitors

K-ras–mutant tumors have so far been refractory to therapeutic targeting. Development of retroviral vectors containing antisense *K-ras* constructs or inhibitors of ras function may reduce proliferation or tumorigenicity. The ras protein is activated by several steps including one critical step in which the activity of farnesyltransferase is necessary to anchor ras to the cell membrane.[173] At the cell membrane, ras relays growth regulatory signals from receptor tyrosine kinases to various pathways of cell signal transduction. Unfortunately, there are some potential barriers to therapeutic blockade of ras. The currently available inhibitors work best with activated *H-ras*, a mutation that is rare in lung cancer compared with the more common *K-ras* activation. Also, the activity of the ras genes does not correlate with antitumor activity. Nonetheless, several farnesyltransferase inhibitors are currently being tested in the clinic, including the inhibitor R115777-Zarnestra, which is being tested in a secondary chemoprevention trial. This trial is essentially based on the efficacy of a similar ras inhibitor on established lung adenomas (considered to be premalignant lesions of the lung) from A/J mice exposed to 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone, a tobacco-related carcinogen.[174]

COX-2 Inhibition

COX-2 is an inducible enzyme that catalyzes the production of prostanoids. COX-2 can activate carcinogens in tobacco smoke,[175] and because it correlates with VEGF levels, COX-2 may play a role in angiogenesis. In addition, COX-2 activity may have a role in inhibiting apoptosis and modulating immune responses.[176] While nonsteroidal anti-inflammatory drugs have been shown to reduce the risk of colorectal cancer, no such evidence yet exists in lung cancer. COX-2 overexpression may be a marker of poor prognosis in early stage NSCLC.[177] Certain COX-2 single nucleotide polymorphisms may also correlate with lymph node metastases or with high tumor stage.[178] COX-2 inhibitors are being evaluated in combination therapy for chemoprevention and therapy for lung cancer.

KEY POINTS

- Patients with lung cancer have only a 15% 5-year survival rate and, even though there is a readily identifiable high-risk population of smokers and ex-smokers, there are no generally accepted screening, early detection, or chemoprevention strategies shown to reduce mortality.
- Lung cancer in smokers is preceded by an accumulation of genetic, epigenetic, and posttranslational abnormalities in the entire bronchial epithelium, showing the validity of the field cancerization concept.
- Lung cancer in never-smokers is less well understood. Nonetheless, the risk for either type of cancer (among smokers or nonsmokers) appears to have a hereditary predisposition, as seen, for example, with genetic alterations in the nicotinic acetylcholine receptors.
- Sequencing of hundreds of candidate genes in adenocarcinomas has shown that there are between 0 and 40 lesions in individual lung tumors and that many fall into a handful of previously defined pathways.
- The most common genes altered in lung cancer are *p53* and *K-ras,* for which effective targeted therapies do not yet exist.
- For some genetic lesions, particularly those now seen in EGFR, targeted therapies exist and striking clinical effectiveness can be observed.
- Targeted therapy to inhibit the VEGF angiogenic pathway has shown significant clinical effectiveness when combined with carboplatin plus paclitaxel in adenocarcinoma.

References

1. Jemal A, Siegel R, Ward E, et al: Cancer statistics, 2008. CA Cancer J Clin 58:71–96, 2008.
2. Knudson AG Jr: Genetics of human cancer. Genetics 79(Suppl):305–316, 1975.
3. Venter JC, Adams MD, Myers EW, et al: The sequence of the human genome. Science 291:1304–1351, 2001.
4. Hecht SS: Progress and challenges in selected areas of tobacco carcinogenesis. Chem Res Toxicol 21:160–171, 2008.
5. Hittelman WN: Genetic instability in epithelial tissues at risk for cancer. Ann N Y Acad Sci 952:1–12, 2001.
6. Varella-Garcia M, Chen L, Powell RL, et al: Spectral karyotyping detects chromosome damage in bronchial cells of smokers and patients with cancer. Am J Respir Crit Care Med 176:505–512, 2007.
7. Slaughter D, Southwick H, Smejkal W: Field cancerization in oral stratified squamous epithelium: Clinical implications of multicentric origin. Cancer 6:963–968, 1953.
8. Denissenko MF, Pao A, Tang M, Pfeifer GP: Preferential formation of benzo[a]pyrene adducts at lung cancer mutational hotspots in p53. Science 274:430–432, 1996.
9. Wiencke JK, Thurston SW, Kelsey KT, et al: Early age at smoking initiation and tobacco carcinogen DNA damage in the lung. J Natl Cancer Inst 91:614–619, 1999.
10. Sanchez-Cespedes M, Ahrendt SA, Piantadosi S, et al: Chromosomal alterations in lung adenocarcinoma from smokers and nonsmokers. Cancer Res 61:1309–1313, 2001.
11. Franklin WA, Gazdar AF, Haney J, et al: Widely dispersed p53 mutation in respiratory epithelium. A novel mechanism for field carcinogenesis. J Clin Invest 100:2133–2137, 1997.
12. Hecht SS: Tobacco smoke carcinogens and lung cancer. J Natl Cancer Inst 91:1194–1210, 1999.
13. Castonguay A, Foiles PG, Trushin N, Hecht SS: Study of DNA methylation by tobacco-specific *N*-nitrosamines. Environ Health Perspect 62:197–202, 1985.
14. Belinsky SA, Klinge DM, Stidley CA, et al: Inhibition of DNA methylation and histone deacetylation prevents murine lung cancer. Cancer Res 63:7089–7093, 2003.
15. Fujiwara K, Fujimoto N, Tabata M, et al: Identification of epigenetic aberrant promoter methylation in serum DNA is useful for early detection of lung cancer. Clin Cancer Res 11:1219–1225, 2005.
16. Liu H, Zhou Y, Boggs SE, et al: Cigarette smoke induces demethylation of prometastatic oncogene synuclein-gamma in lung cancer cells by downregulation of DNMT3B. Oncogene 26:5900–5910, 2007.
17. Auerbach O, Stout AP, Hammond EC, Garfinkel L: Changes in bronchial epithelium in reaction to cigraette smoking and in relation to lung cancer. N Engl J Med 265:253–267, 1961.
18. Massion PP, Zou Y, Chen H, et al: Smoking-related genomic signatures in non–small cell lung cancer. Am J Respir Crit Care Med 178:1164–1172, 2008.
19. Spitz MR, Wei Q, Dong Q, et al: Genetic susceptibility to lung cancer: The role of DNA damage and repair. Cancer Epidemiol Biomarkers Prev 12:689–698, 2003.
20. Li D, Firozi PF, Chang P, et al: In vitro BPDE-induced DNA adducts in peripheral lymphocytes as a risk factor for squamous cell carcinoma of the head and neck. Int J Cancer 93:436–440, 2001.
21. Wu X, Amos CI, Zhu Y, et al: Telomere dysfunction: A potential cancer predisposition factor. J Natl Cancer Inst 95:1211–1218, 2003.
22. Amos CI, Wu X, Broderick P, et al: Genome-wide association scan of tag SNPS identifies a susceptibility locus for lung cancer at 15q25.1. Nat Genet 40:616–622, 2008.
23. Hung RJ, McKay JD, Gaborieau V, et al: A susceptibility locus for lung cancer maps to nicotinic acetylcholine receptor subunit genes on 15q25. Nature 452:633–637, 2008.
24. Thorgeirsson TE, Geller F, Sulem P, et al: A variant associated with nicotine dependence, lung cancer and peripheral arterial disease. Nature 452:638–642, 2008.
25. Spitz MR, Amos CI, Dong Q, et al: The CHRNA5-A3 region on chromosome 15q24-25.1 is a risk factor both for nicotine dependence and for lung cancer. J Natl Cancer Inst 100:1552–1556, 2008.
26. Wang Y, Broderick P, Webb E, et al: Common 5p15.33 and 6p21.33 variants influence lung cancer risk. Nat Genet 40:1407–1409, 2008.
27. Bailey-Wilson JE, Amos CI, Pinney SM, et al: A major lung cancer susceptibility locus maps to chromosome 6q23-25. Am J Hum Genet 75:460–474, 2004.

28. Tessema M, Willink R, Do K, et al: Promoter methylation of genes in and around the candidate lung cancer susceptibility locus 6q23-25. Cancer Res 68:1707–1714, 2008.
29. Liu P, Vikis HG, Wang D, et al: Familial aggregation of common sequence variants on 15q24-25.1 in lung cancer. J Natl Cancer Inst 100:1326–1330, 2008.
30. Loeb LA: Mutator phenotype may be required for multistage carcinogenesis. Cancer Res 51:3075–3079, 1991.
31. Ding L, Getz G, Wheeler DA, et al: Somatic mutations affect key pathways in lung adenocarcinoma. Nature 455:1069–1075, 2008.
32. Westra WH, Slebos RJ, Offerhaus GJ, et al: K-ras oncogene activation in lung adenocarcinomas from former smokers. Evidence that K-RAS mutations are an early and irreversible event in the development of adenocarcinoma of the lung. Cancer 72:432–438, 1993.
33. Konstantinopoulos PA, Karamouzis MV, Papavassiliou AG: Post-translational modifications and regulation of the ras superfamily of GTPases as anticancer targets. Nat Rev Drug Discov 6:541–555, 2007.
34. Lacal JC, Srivastava SK, Anderson PS, Aaronson SA: Ras p21 proteins with high or low GTPase activity can efficiently transform NIH/3T3 cells. Cell 44:609–617, 1986.
35. Harris CC: 1995 Deichmann lecture—p53 tumor suppressor gene: At the crossroads of molecular carcinogenesis, molecular epidemiology and cancer risk assessment. Toxicol Lett 82–83:1–7, 1995.
36. Carbone DP, Mitsudomi T, Chiba I, et al: P53 immunostaining positivity is associated with reduced survival and is imperfectly correlated with gene mutations in resected non–small cell lung cancer. A preliminary report of LCSG 871. Chest 106:377S–381S, 1994.
37. Sanchez-Cespedes M, Decker PA, Doffek KM, et al: Increased loss of chromosome 9p21 but not p16 inactivation in primary non-small cell lung cancer from smokers. Cancer Res 61:2092–2096, 2001.
38. Davies H, Bignell GR, Cox C, et al: Mutations of the BRAF gene in human cancer. Nature 417:949–954, 2002.
39. Naoki K, Chen TH, Richards WG, et al: Missense mutations of the BRAF gene in human lung adenocarcinoma. Cancer Res 62:7001–7003, 2002.
40. Adjei AA, Cohen RB, Franklin W, et al: Phase I pharmacokinetic and pharmacodynamic study of the oral, small-molecule mitogen-activated protein kinase kinase 1/2 inhibitor AZD6244 (ARRY-142886) in patients with advanced cancers. J Clin Oncol 26:2139–2146, 2008.
41. Samuels Y, Wang Z, Bardelli A, et al: High frequency of mutations of the PIK3CA gene in human cancers. Science 304:554, 2004.
42. Kang S, Bader AG, Vogt PK: Phosphatidylinositol 3-kinase mutations identified in human cancer are oncogenic. Proc Natl Acad Sci U S A 102:802–807, 2005.
43. Serra V, Markman B, Scaltriti M, et al: NVP-BEZ235, a dual PI3K/MTOR inhibitor, prevents PI3K signaling and inhibits the growth of cancer cells with activating PI3K mutations. Cancer Res 68:8022–8030, 2008.
44. Lynch TJ, Bell DW, Sordella R, et al: Activating mutations in the epidermal growth factor receptor underlying responsiveness of non–small-cell lung cancer to gefitinib. N Engl J Med 350:2129–2139, 2004.
45. Paez JG, Janne PA, Lee JC, et al: EGFR mutations in lung cancer: Correlation with clinical response to gefitinib therapy. Science 304:1497–1500, 2004.
46. Pao W, Miller V, Zakowski M, et al: EGF receptor gene mutations are common in lung cancers from "Never smokers" and are associated with sensitivity of tumors to gefitinib and erlotinib. Proc Natl Acad Sci U S A 101:13306–13311, 2004.
47. Zhu JQ, Zhong WZ, Zhang GC, et al: Better survival with EGFR exon 19 than exon 21 mutations in gefitinib-treated non–small cell lung cancer patients is due to differential inhibition of downstream signals. Cancer Lett 265:307–317, 2008.
48. Carter TA, Wodicka LM, Shah NP, et al: Inhibition of drug-resistant mutants of ABL, KIT, and EGF receptor kinases. Proc Natl Acad Sci U S A 102:11011–11016, 2005.
49. Pao W, Miller VA, Politi KA, et al: Acquired resistance of lung adenocarcinomas to gefitinib or erlotinib is associated with a second mutation in the EGFR kinase domain. PLoS Med 2:e73, 2005.
50. Engelman JA, Zejnullahu K, Mitsudomi T, et al: MET amplification leads to gefitinib resistance in lung cancer by activating ERBB3 signaling. Science 316:1039–1043, 2007.
51. Massarelli E, Varella-Garcia M, Tang X, et al: Kras mutation is an important predictor of resistance to therapy with epidermal growth factor receptor tyrosine kinase inhibitors in non-small-cell lung cancer. Clin Cancer Res 13:2890–2896, 2007.
52. Kim YT, Kim TY, Lee DS, et al: Molecular changes of epidermal growth factor receptor (EGFR) and Kras and their impact on the clinical outcomes in surgically resected adenocarcinoma of the lung. Lung Cancer 59:111–118, 2008.
53. Cappuzzo F, Ligorio C, Janne PA, et al: Prospective study of gefitinib in epidermal growth factor receptor fluorescence in situ hybridization-positive/phospho-AKT-positive or never smoker patients with advanced non–small-cell lung cancer: The Oncobell trial. J Clin Oncol 25:2248–2255, 2007.
54. Sequist LV, Martins RG, Spigel D, et al: First-line gefitinib in patients with advanced non–small-cell lung cancer harboring somatic EGFR mutations. J Clin Oncol 26:2442–2449, 2008.
55. Yamamoto H, Toyooka S, Mitsudomi T: Impact of EGFR mutation analysis in non–small cell lung cancer. Lung Cancer 63:315–321, 2009.
56. Eberhard DA, Johnson BE, Amler LC, et al: Mutations in the epidermal growth factor receptor and in Kras are predictive and prognostic indicators in patients with non–small-cell lung cancer treated with chemotherapy alone and in combination with erlotinib. J Clin Oncol 23:5900–5909, 2005.
57. Campbell PJ, Stephens PJ, Pleasance ED, et al: Identification of somatically acquired rearrangements in cancer using genome-wide massively parallel paired-end sequencing. Nat Genet 40: 722–729, 2008.
58. Wood LD, Parsons DW, Jones S, et al: The genomic landscapes of human breast and colorectal cancers. Science 318:1108–1113, 2007.
59. Jones S, Zhang X, Parsons DW, et al. Core signaling pathways in human pancreatic cancers revealed by global genomic analyses. Science 321:1801–1806, 2008.
60. Peto R, Darby S, Deo H, et al: Smoking, smoking cessation, and lung cancer in the UK since 1950: Combination of national statistics with two case-control studies. BMJ 321:323–329, 2000.
61. DeMarini DM: Genotoxicity of tobacco smoke and tobacco smoke condensate: A review. Mutat Res 567:447–474, 2004.
62. Qiao Y, Spitz MR, Guo Z, et al: Rapid assessment of repair of ultraviolet DNA damage with a modified host-cell reactivation assay using a luciferase reporter gene and correlation with polymorphisms of DNA repair genes in normal human lymphocytes. Mutat Res 509:165–174, 2002.
63. Burns DM: Primary prevention, smoking, and smoking cessation: Implications for future trends in lung cancer prevention. Cancer 89:2506–2509, 2000.
64. Wei Q, Gu J, Cheng L, et al: Benzo(a)pyrene diol epoxide-induced chromosomal aberrations and risk of lung cancer. Cancer Res 56:3975–3979, 1996.
65. Hittelman WN, Voravud N, Shin DM, et al: Early genetic changes during upper aerodigestive tract tumorigenesis. J Cell Biochem Suppl 17F:233–236, 1993.
66. Lee JJ, Liu D, Lee JS, et al: Long-term impact of smoking on lung epithelial proliferation in current and former smokers. J Natl Cancer Inst 93:1081–1088, 2001.
67. Wistuba II, Behrens C, Milchgrub S, et al: Sequential molecular abnormalities are involved in the multistage development of squamous cell lung carcinoma. Oncogene 18:643–650, 1999.
68. Spira A, Beane J, Shah V, et al: Effects of cigarette smoke on the human airway epithelial cell transcriptome. Proc Natl Acad Sci U S A 101:10143–10148, 2004.
69. Spira A, Beane JE, Shah V, et al: Airway epithelial gene expression in the diagnostic evaluation of smokers with suspect lung cancer. Nat Med 13:361–366, 2007.
70. Breuer RH, Pasic A, Smit EF, et al: The natural course of preneoplastic lesions in bronchial epithelium. Clin Cancer Res 11:537–543, 2005.

71. Ye CJ, Liu G, Bremer SW, Heng HH: The dynamics of cancer chromosomes and genomes. Cytogenet Genome Res 118:237–246, 2007.
72. Garnis C, Buys TP, Lam WL: Genetic alteration and gene expression modulation during cancer progression. Mol Cancer 3:9, 2004.
73. Thomas RK, Weir B, Meyerson M: Genomic approaches to lung cancer. Clin Cancer Res 12:4384s–4391s, 2006.
74. Ma PC, Zhang X, Wang ZJ: High-throughput mutational analysis of the human cancer genome. Pharmacogenomics 7:597–612, 2006.
75. Minna JD, Roth JA, Gazdar AF: Focus on lung cancer. Cancer Cell 1:49–52, 2002.
76. Albertson DG: Gene amplification in cancer. Trends Genet 22:447–455, 2006.
77. Testa JR, Siegfried JM, Liu Z, et al: Cytogenetic analysis of 63 non–small cell lung carcinomas: Recurrent chromosome alterations amid frequent and widespread genomic upheaval. Genes Chromosomes Cancer 11:178–194, 1994.
78. Balsara BR, Sonoda G, du Manoir S, et al: Comparative genomic hybridization analysis detects frequent, often high-level, overrepresentation of DNA sequences at 3q, 5p, 7p, and 8q in human non–small cell lung carcinomas. Cancer Res 57:2116–2120, 1997.
79. Massion PP, Kuo WL, Stokoe D, et al: Genomic copy number analysis of non–small cell lung cancer using array comparative genomic hybridization: Implications of the phosphatidylinositol 3-kinase pathway. Cancer Res 62:3636–3640, 2002.
80. Zhao X, Weir BA, LaFramboise T, et al: Homozygous deletions and chromosome amplifications in human lung carcinomas revealed by single nucleotide polymorphism array analysis. Cancer Res 65:5561–5570, 2005.
81. Albertson DG, Collins C, McCormick F, Gray JW: Chromosome aberrations in solid tumors. Nat Genet 34:369–376, 2003.
82. Lengauer C, Kinzler KW, Vogelstein B: Genetic instability in colorectal cancers. Nature 386:623–627, 1997.
83. Spitz MR, Wu X, Wang Y, et al: Modulation of nucleotide excision repair capacity by xpd polymorphisms in lung cancer patients. Cancer Res 61:1354–1357, 2001.
84. Girard L, Zochbauer-Muller S, Virmani AK, et al: Genome-wide allelotyping of lung cancer identifies new regions of allelic loss, differences between small cell lung cancer and non–small cell lung cancer, and loci clustering. Cancer Res 60:4894–4906, 2000.
85. Ferreira BI, Alonso J, Carrillo J, et al: Array CGH and gene-expression profiling reveals distinct genomic instability patterns associated with DNA repair and cell-cycle checkpoint pathways in Ewing's sarcoma. Oncogene 27:2084–2090, 2008.
86. Brody JS, Spira A: State of the art. Chronic obstructive pulmonary disease, inflammation, and lung cancer. Proc Am Thorac Soc 3:535–537, 2006.
87. Komarova EA, Krivokrysenko V, Wang K, et al: P53 is a suppressor of inflammatory response in mice. FASEB J 19:1030–1032, 2005.
88. Stathopoulos GT, Sherrill TP, Cheng DS, et al: Epithelial NF-KAPPAB activation promotes urethane-induced lung carcinogenesis. Proc Natl Acad Sci U S A 104:18514–18519, 2007.
89. Hackett NR, Heguy A, Harvey BG, et al: Variability of antioxidant-related gene expression in the airway epithelium of cigarette smokers. Am J Respir Cell Mol Biol 29:331–343, 2003.
90. Cheng YW, Chiou HL, Sheu GT, et al: The association of human papillomavirus 16/18 infection with lung cancer among nonsmoking Taiwanese women. Cancer Res 61:2799–2803, 2001.
91. Testa JR, Carbone M, Hirvonen A, et al: A multi-institutional study confirms the presence and expression of simian virus 40 in human malignant mesotheliomas. Cancer Res 58:4505–4509, 1998.
92. Feng H, Shuda M, Chang Y, Moore PS: Clonal integration of a polyomavirus in human Merkel cell carcinoma. Science 319:1096–1100, 2008.
93. Mitelman F, Mertens F, Johansson B: A breakpoint map of recurrent chromosomal rearrangements in human neoplasia. Nat Genet 15:417–474, 1997.
94. Testa JR, Liu Z, Feder M, et al: Advances in the analysis of chromosome alterations in human lung carcinomas. Cancer Genet Cytogenet 95:20–32, 1997.
95. Gray JW, Collins C: Genome changes and gene expression in human solid tumors. Carcinogenesis 21:443–452, 2000.
96. Ried T, Liyanage M, du Manoir S, et al: Tumor cytogenetics revisited: Comparative genomic hybridization and spectral karyotyping. J Mol Med 75:801–814, 1997.
97. Knuutila S, Aalto Y, Autio K, et al: DNA copy number losses in human neoplasms. Am J Pathol 155:683–694, 1999.
98. Tonon G, Wong KK, Maulik G, et al: High-resolution genomic profiles of human lung cancer. Proc Natl Acad Sci U S A 102:9625–9630, 2005.
99. Petersen I, Bujard M, Petersen S, et al: Patterns of chromosomal imbalances in adenocarcinoma and squamous cell carcinoma of the lung. Cancer Res 57:2331–2335, 1997.
100. Jones PA, Baylin SB: The fundamental role of epigenetic events in cancer. Nat Rev Genet 3:415–428, 2002.
101. Massion PP, Taflan PM, Jamshedur Rahman SM, et al: Significance of p63 amplification and overexpression in lung cancer development and prognosis. Cancer Res 63:7113–7121, 2003.
102. Garnis C, Lockwood WW, Vucic E, et al: High resolution analysis of non–small cell lung cancer cell lines by whole genome tiling path array CGH. Int J Cancer 118:1556–1564, 2006.
103. Thiberville L, Payne P, Vielkinds J, et al: Evidence of cumulative gene losses with progression of premalignant epithelial lesions to carcinoma of the bronchus. Cancer Res 55:5133–5139, 1995.
104. Mao L, Lee JS, Kurie JM, et al: Clonal genetic alterations in the lungs of current and former smokers. J Natl Cancer Inst 89:857–862, 1997.
105. Wistuba II, Lam S, Behrens C, et al: Molecular damage in the bronchial epithelium of current and former smokers. J Natl Cancer Inst 89:1366–1373, 1997.
106. Qian J, Massion PP: Role of chromosome 3q amplification in lung cancer. J Thorac Oncol 3:212–215, 2008.
107. Zhou JY, Taguchi T, Siegfried JM, et al: Characterization of 9q;15q whole-arm translocation derivatives in non–small cell lung carcinomas by fluorescence in situ hybridization. Cancer Genet Cytogenet 69:1–6, 1993.
108. Rabbitts TH: Chromosomal translocations in human cancer. Nature 372:143–149, 1994.
109. Ogiwara H, Kohno T, Nakanishi H, et al: Unbalanced translocation, a major chromosome alteration causing loss of heterozygosity in human lung cancer. Oncogene 27:4788–4797, 2008.
110. Dang TP, Gazdar AF, Virmani AK, et al: Chromosome 19 translocation, overexpression of NOTCH3, and human lung cancer. J Natl Cancer Inst 92:1355–1357, 2000.
111. Dang TP, Eichenberger S, Gonzalez A, et al: Constitutive activation of NOTCH3 inhibits terminal epithelial differentiation in lungs of transgenic mice. Oncogene 22:1988–1997, 2003.
112. Wiencke JK: DNA adduct burden and tobacco carcinogenesis. Oncogene 21:7376-7391, 2002.
113. Cheng YW, Chen CY, Lin P, et al: DNA adduct level in lung tissue may act as a risk biomarker of lung cancer. Eur J Cancer 36:1381–1388, 2000.
114. Phillips DH, Hewer A, Martin CN, et al: Correlation of DNA adduct levels in human lung with cigarette smoking. Nature 336:790–792, 1988.
115. Tang D, Phillips DH, Stampfer M, et al: Association between carcinogen-DNA adducts in white blood cells and lung cancer risk in the Physicians' Health Study. Cancer Res 61:6708–6712, 2001.
116. Mollerup S, Ryberg D, Hewer A, et al: Sex differences in lung cyp1a1 expression and DNA adduct levels among lung cancer patients. Cancer Res 59:3317–3320, 1999.
117. Antequera F, Bird A: Number of CPG islands and genes in human and mouse. Proc Natl Acad Sci U S A 90:11995–11999, 1993.
118. Jones PA, Laird PW: Cancer epigenetics comes of age. Nat Genet 21:163–167, 1999.
119. Esteller M, Fraga MF, Paz MF, et al: Cancer epigenetics and methylation. Science 297:1807–1808, 2002 [discussion 1807–1808].
120. Burbee DG, Forgacs E, Zochbauer-Muller S, et al: Epigenetic inactivation of RASSF1A in lung and breast cancers and malignant phenotype suppression. J Natl Cancer Inst 93:691–699, 2001.

121. Belinsky SA, Nikula KJ, Palmisano WA, et al: Aberrant methylation of p16(INK4A) is an early event in lung cancer and a potential biomarker for early diagnosis. Proc Natl Acad Sci U S A 95:11891–11896, 1998.
122. Baylin S, Bestor TH: Altered methylation patterns in cancer cell genomes: Cause or consequence? Cancer Cell 1:299–305, 2002.
123. Palmisano WA, Divine KK, Saccomanno G, et al: Predicting lung cancer by detecting aberrant promoter methylation in sputum. Cancer Res 60:5954–5958, 2000.
124. Brock MV, Hooker CM, Ota-Machida E, et al: DNA methylation markers and early recurrence in stage I lung cancer. N Engl J Med 358:1118–1128, 2008.
125. Suh YA, Lee HY, Virmani A, et al: Loss of retinoic acid receptor beta gene expression is linked to aberrant HISTONE H3 acetylation in lung cancer cell lines. Cancer Res 62:3945–3949, 2002.
126. Yu X, Guo ZS, Marcu MG, et al: Modulation of p53, ERBB1, ERBB2, and RAF-1 expression in lung cancer cells by depsipeptide FR901228. J Natl Cancer Inst 94:504–513, 2002.
127. Virtanen C, Ishikawa Y, Honjoh D, et al: Integrated classification of lung tumors and cell lines by expression profiling. Proc Natl Acad Sci U S A 99:12357–12362, 2002.
128. Bhattacharjee A, Richards WG, Staunton J, et al: Classification of human lung carcinomas by mRNA expression profiling reveals distinct adenocarcinoma subclasses. Proc Natl Acad Sci U S A 98:13790–13795, 2001.
129. Garber ME, Troyanskaya OG, Schluens K, et al: Diversity of gene expression in adenocarcinoma of the lung. Proc Natl Acad Sci U S A 98:13784–13789, 2001.
130. Beer DG, Kardia SL, Huang CC, et al: Gene-expression profiles predict survival of patients with lung adenocarcinoma. Nat Med 8:816–824, 2002.
131. Anbazhagan R, Tihan T, Bornman DM, et al: Classification of small cell lung cancer and pulmonary carcinoid by gene expression profiles. Cancer Res 59:5119–5122, 1999.
132. Lu Y, Lemon W, Liu PY, et al: A gene expression signature predicts survival of patients with stage I non-small cell lung cancer. PLoS Med 3:e467, 2006.
133. Xi L, Lyons-Weiler J, Coello MC, et al: Prediction of lymph node metastasis by analysis of gene expression profiles in primary lung adenocarcinomas. Clin Cancer Res 11:4128–4135, 2005.
134. Potti A, Mukherjee S, Petersen R, et al: A genomic strategy to refine prognosis in early-stage non–small-cell lung cancer. N Engl J Med 355:570–580, 2006.
135. Shedden K, Taylor JM, Enkemann SA, et al: Gene expression-based survival prediction in lung adenocarcinoma: A multi-site, blinded validation study. Nat Med 14:822–827, 2008.
136. Baek D, Villen J, Shin C, et al: The impact of micro-RNAs on protein output. Nature 455:64–71, 2008.
137. Selbach M, Schwanhausser B, Thierfelder N, et al: Widespread changes in protein synthesis induced by micro-RNAs. Nature 455:58–63, 2008.
138. Yanaihara N, Caplen N, Bowman E, et al: Unique micro-RNA molecular profiles in lung cancer diagnosis and prognosis. Cancer Cell 9:189–198, 2006.
139. Takamizawa J, Konishi H, Yanagisawa K, et al: Reduced expression of the LET-7 micro-RNAs in human lung cancers in association with shortened postoperative survival. Cancer Res 64:3753–3756, 2004.
140. Brichory F, Beer D, Le Naour F, et al: Proteomics-based identification of protein gene product 9.5 as a tumor antigen that induces a humoral immune response in lung cancer. Cancer Res 61:7908–7912, 2001.
141. Celis JE, Celis P, Ostergaard M, et al: Proteomics and immunohistochemistry define some of the steps involved in the squamous differentiation of the bladder transitional epithelium: A novel strategy for identifying metaplastic lesions. Cancer Res 59:3003–3009, 1999.
142. Chaurand P, Stoeckli M, Caprioli RM: Direct profiling of proteins in biological tissue sections by MALDI mass spectrometry. Anal Chem 71:5263–5270, 1999.
143. Noel-Georis I, Bernard A, Falmagne P, Wattiez R: Database of bronchoalveolar lavage fluid proteins. J Chromatogr B Analyt Technol Biomed Life Sci 771:221–236, 2002.
144. Sidransky D, Irizarry R, Califano JA, et al: Serum protein MALDI profiling to distinguish upper aerodigestive tract cancer patients from control subjects. J Natl Cancer Inst 95:1711–1717, 2003.
145. Villanueva J, Philip J, Entenberg D, et al: Serum peptide profiling by magnetic particle-assisted, automated sample processing and MALDI-TOF mass spectrometry. Anal Chem 76:1560–1570, 2004.
146. Yildiz PB, Shyr Y, Rahman JS, et al: Diagnostic accuracy of MALDI mass spectrometric analysis of unfractionated serum in lung cancer. J Thorac Oncol 2:893–901, 2007.
147. M'Koma AE, Blum DL, Norris JL, et al: Detection of pre-neoplastic and neoplastic prostate disease by MALDI profiling of urine. Biochem Biophys Res Commun 353:829–834, 2007.
148. Rahman SM, Shyr Y, Yildiz PB, et al: Proteomic patterns of pre-invasive bronchial lesions. Am J Respir Crit Care Med 172:1556–1562, 2005.
149. Yanagisawa K, Xu BJ, Carbone DP, Caprioli RM: Molecular fingerprinting in human lung cancer. Clin Lung Cancer 5:113–118, 2003.
150. Amann JM, Chaurand P, Gonzalez A, et al: Selective profiling of proteins in lung cancer cells from fine-needle aspirates by matrix-assisted laser desorption ionization time-of-flight mass spectrometry. Clin Cancer Res 12:5142–5150, 2006.
151. Xu BJ, Caprioli RM, Sanders ME, Jensen RA: Direct analysis of laser capture microdissected cells by MALDI mass spectrometry. J Am Soc Mass Spectrom 13:1292–1297, 2002.
152. Yanagisawa K, Shyr Y, Xu BJ, et al: Proteomic patterns of tumour subsets in non–small-cell lung cancer. Lancet 362:433–439, 2003.
153. Paik S, Shak S, Tang G, et al: A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. N Engl J Med 351:2817–2826, 2004.
154. van de Vijver MJ, He YD, van't Veer LJ, et al: A gene-expression signature as a predictor of survival in breast cancer. N Engl J Med 347:1999–2009, 2002.
155. Zhang B, Kirov S, Snoddy J: Webgestalt: An integrated system for exploring gene sets in various biological contexts. Nucleic Acids Res 33:W741–W748, 2005.
156. Ermolaeva O, Rastogi M, Pruitt KD, et al: Data management and analysis for gene expression arrays. Nat Genet 20:19–23, 1998.
157. Ludwig JA, Weinstein JN: Biomarkers in cancer staging, prognosis and treatment selection. Nat Rev Cancer 5:845–856, 2005.
158. Sullivan Pepe M, Etzioni R, Feng Z, et al: Phases of biomarker development for early detection of cancer. J Natl Cancer Inst 93:1054–1061, 2001.
159. Lam S, Kennedy T, Unger M, et al: Localization of bronchial intraepithelial neoplastic lesions by fluorescence bronchoscopy. Chest 113:696–702, 1998.
160. Zheng Z, Chen T, Li X, et al: DNA synthesis and repair genes rrm1 and ercc1 in lung cancer. N Engl J Med 356:800–808, 2007.
161. Edelman MJ, Watson D, Wang X, et al: Eicosanoid modulation in advanced lung cancer: Cyclooxygenase-2 expression is a positive predictive factor for celecoxib + chemotherapy—Cancer and Leukemia Group B Trial 30203. J Clin Oncol 26:848–855, 2008.
162. Csiki I, Morrow JD, Sandler A, et al: Targeting cyclooxygenase-2 in recurrent non–small cell lung cancer: A phase II trial of celecoxib and docetaxel. Clin Cancer Res 11:6634–6640, 2005.
163. Kononen J, Bubendorf L, Kallioniemi A, et al: Tissue microarrays for high-throughput molecular profiling of tumor specimens [see comments]. Nat Med 4:844–847, 1998.
164. Ocak S, Sos ML, Thomas RK, Massion PP: High-throughput molecular analysis in lung cancer: insights into biology and potential clinical applications. Eur Respir J 34:489–506, 2009.
165. Baselga J: The EGFR as a target for anticancer therapy—Focus on cetuximab. Eur J Cancer 37(Suppl 4):S16–S22, 2001.
166. Herbst RS: Dose-comparative monotherapy trials of zd1839 in previously treated non–small cell lung cancer patients. Semin Oncol 30:30–38, 2003.
167. Sandler A, Gray R, Perry MC, et al: Paclitaxel-carboplatin alone or with bevacizumab for non–small-cell lung cancer. N Engl J Med 355:2542–2550, 2006.
167a. Reck M, von Pawel J, Zatloukal P, et al: Phase III trial of cisplatin plus gemcitabine with either placebo or bevacizumab as first-line therapy for nonsquamous non-small-cell lung cancer: AVAIL. J Clin Oncol 27:1227–1234, 2009.

167b. Amir E, Mandoky L, Blackhall F, et al: Antivascular agents for non-small-cell lung cancer: current status and future directions. Expert Opin Investig Drugs 18:1667–1686, 2009.
168. Swisher SG, Roth JA, Komaki R, et al: Induction of p53-regulated genes and tumor regression in lung cancer patients after intratumoral delivery of adenoviral p53 (ingn 201) and radiation therapy. Clin Cancer Res 9:93–101, 2003.
169. Roth JA, Nguyen D, Lawrence DD, et al: Retrovirus-mediated wild-type p53 gene transfer to tumors of patients with lung cancer. Nat Med 2:985–991, 1996.
170. Swisher SG, Roth JA, Nemunaitis J, et al: Adenovirus-mediated p53 gene transfer in advanced non–small-cell lung cancer. J Natl Cancer Inst 91:763–771, 1999.
171. Carbone DP, Minna JD: In vivo gene therapy of human lung cancer using wild-type p53 delivered by retrovirus (editorial; comment). J Natl Cancer Inst 86:1437–1438, 1994.
172. Keedy V, Wang W, Schiller J, et al: Phase I study of adenovirus p53 administered by bronchoalveolar lavage in patients with bronchioloalveolar cell lung carcinoma: ECOG 6597. J Clin Oncol 26:4166–4171, 2008.
173. Adjei AA: Blocking oncogenic RAS signaling for cancer therapy. J Natl Cancer Inst 93:1062–1074, 2001.
174. Lantry LE, Zhang Z, Yao R, et al: Effect of farnesyltransferase inhibitor FTI-276 on established lung adenomas from A/J mice induced by 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone. Carcinogenesis 21:113–116, 2000.
175. Wiese FW, Thompson PA, Kadlubar FF: Carcinogen substrate specificity of human COX-1 and COX-2. Carcinogenesis 22:5–10, 2001.
176. Dannenberg AJ, Altorki NK, Boyle JO, et al: Inhibition of cyclooxygenase-2: An approach to preventing cancer of the upper aerodigestive tract. Ann N Y Acad Sci 952:109–115, 2001.
177. Achiwa H, Yatabe Y, Hida T, et al: Prognostic significance of elevated cyclooxygenase 2 expression in primary, resected lung adenocarcinomas. Clin Cancer Res 5:1001–1005, 1999.
178. Grimminger PP, Stohlmacher J, Vallbohmer D, et al: Prognostic significance and clinicopathological associations of COX-2 SNP in patients with nonsmall cell lung cancer. J Oncol 2009 [Epub ahead of print].

CHAPTER 46

EPIDEMIOLOGY OF LUNG CANCER

Anthony J. Alberg, PhD, MPH • Jonathan M. Samet, MD, MS

INTRODUCTION

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INTRODUCTION

Remarkably, at the start of the 20th century, lung cancer was considered a rare disease. However, its epidemic rise across the first decades of that century was soon identified as clinicians began to provide care for increasing numbers of patients with lung cancer and routine vital statistics documented rising mortality. Although tobacco had been widely used throughout the world for centuries, the present pandemic of lung cancer followed the introduction of manufactured cigarettes with addictive properties, which resulted in a new pattern of sustained exposure of the lung to inhaled carcinogens.[1] Epidemiologic research linked smoking to lung cancer in investigations reported from the 1950s forward.[2] Whereas its predominant cause—tobacco smoking—is now well-known, there are other causes of lung cancer as well, some acting in concert with smoking to increase risk synergistically.

This chapter provides a summary of the epidemiologic evidence on lung cancer. It is based primarily on summaries of the evidence prepared by expert committees, and it includes findings of representative and particularly informative studies. Syntheses have been periodically carried out by expert review groups, dating back to reports such as the 1962 report of the Royal College of Physicians[3] and the landmark 1964 Report of the U.S. Surgeon General.[4] The most recent reports include those prepared by the International Agency for Research on Cancer (IARC) in 2004[5] and the 2004 and 2006 reports of the Surgeon General on active and passive smoking, respectively.[6,7]

PATTERNS OF OCCURRENCE

Temporal Trends

Because of the high case-fatality rate of lung cancer, incidence and mortality rates are nearly equivalent, and consequently, routinely collected vital statistics provide a long record of the occurrence of lung cancer. We are at present amidst an epidemic of lung cancer that dates to the mid-20th century (Fig. 46-1).[8,9] The epidemic among women followed that among men, with a sharp rise in rates from the 1960s to the present, making lung cancer the most frequent cause of female cancer mortality in the United States.[10] The epidemic among women not only arose later but also will not peak as high as among men because smoking prevalence crested at substantially lower levels among women than among men.[11–13]

Trends of age-specific lung cancer mortality rates in the United States show differing epidemic patterns in men than in women (Fig. 46-2).[12,14–17] In the older age groups, the rates continue to increase in both sexes, but the rates of increase are decelerating more in men than in women. The rates of lung cancer are now decreasing

in the younger age groups, more for men but also becoming evident in women.[12]

Notable shifts have taken place in the incidence rates of lung cancer by histologic type.[18] After steadily increasing in incidence during the period 1973 to 1987, adenocarcinoma supplanted squamous cell carcinoma as the most frequent form of lung cancer (Table 46-1).[18,19]

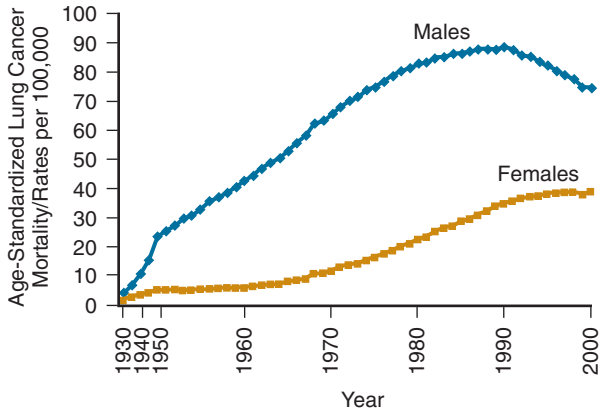

FIGURE 46-1 ■ **Age-standardized lung cancer mortality rates, United States: 1930–2000, age-standardized to 2000 U.S. population.** (Data from Wingo PA, Cardinez CJ, Landis SH, et al: Long-term trends in cancer mortality in the United States, 1930–1998. Cancer 97:3133–3275, 2003; and National Cancer Institute and National Center for Health Statistics: Surveillance, epidemiology, and end results [SEER] Program. SEER Stat Database: Mortality 2003. http://seer.cancer.gov/)

Race and Ethnicity

In the United States, whereas lung cancer incidence rates are similar among African American women and white women, rates are about 40% higher among African American men than among white men.[20] A marked reduction in cigarette smoking among African American youths[21] forecasts a possible reversal of this trend. In addition, lung cancer mortality rates among African Americans and non-Hispanic whites are significantly higher than rates among Hispanics, Native Americans, and Asians/Pacific Islanders.[22,23] However, racial differences in historical patterns of cigarette smoking do not fully explain the racial disparities in lung cancer incidence and mortality rates.[24] The high rates in African Americans may be partially due to greater susceptibility of African American smokers to smoking-induced lung carcinogenesis.[25] The higher mortality rates of lung cancer in African Americans compared with white Americans reflect not only their higher incidence rate but also the poorer survival from lung cancer among African Americans compared with white Americans. The 5-year relative survival rate was 13% lower in African Americans than in white Americans during the period 1995 to 2001.[20] This racial gap persisted within each stage at diagnosis category.[20]

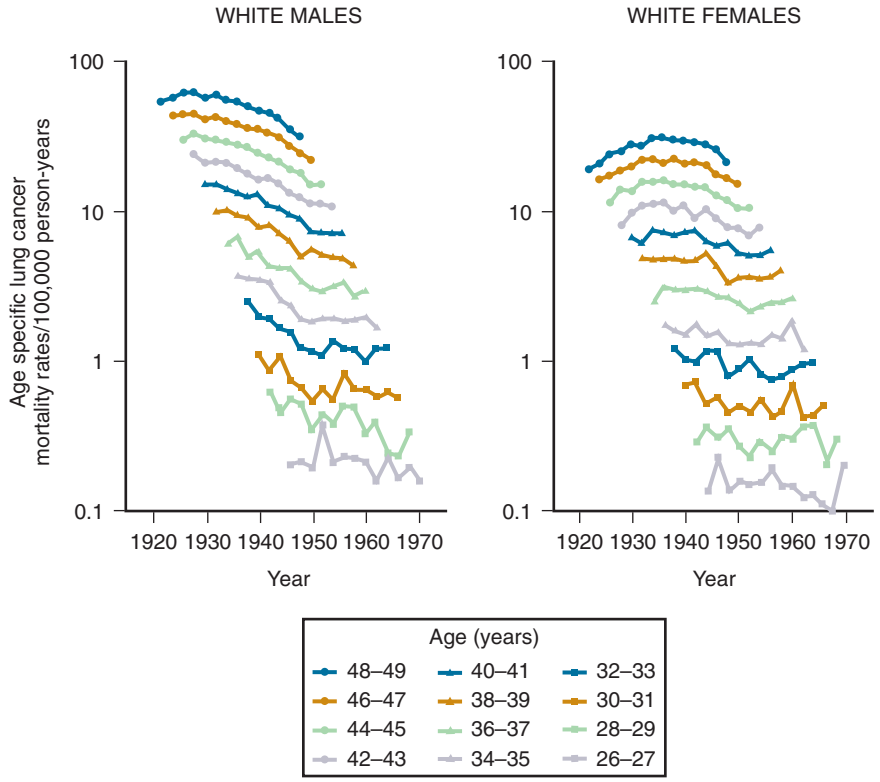

FIGURE 46-2 ■ **U.S. age-specific lung cancer mortality rates (white males and white females) by 2-year age intervals from 26–27 years of age through 48–49 years of age, plotted against birth cohort.** (Data from Jemal A, Chu KC, Tarone RE: Recent trends in lung cancer mortality in the United States. J Natl Cancer Inst 93:277–283, 2001; McKay FW, Hanson MR, Miller RW: Cancer mortality in the United States: 1950–1977. Natl Cancer Inst Monogr 59:1–475, 1982; Ries LAG, Miller BA, Hankey BF, et al: Cancer Statistics Review. Bethesda, MD: U.S. Government Printing Office, 1995, pp 1973–1991; Horm JW, Cicero JB: SEER Program: Cancer Incidence and Mortality in the United States. Washington, DC: U.S. Government Printing Office, 1984, pp 1973–1981; and National Cancer Institute: National Cancer Institute SEER Website. Surveillance, Epidemiology, and End Results [SEER] Program. 2001. http://seer.cancer.gov/)

TABLE 46-1. Age-Adjusted Incidence Rate (Per 100,000) of Lung Cancer by Histologic Subtype and Time Period, SEER 1973–1977, 1978–1982, 1983–1987, and 1990–2000

Group	Subtype	1973–1977*	1978–1982*	1983–1987*	1990–2000†
Total		39.5	46.8	51.4	66.9
	Squamous cell carcinoma	13.4	15.1	15.3	14.4
	Adenocarcinoma	10.5	14.2	16.7	22.1
	Small cell	5.9	8.2	9.4	9.8
	Large cell	0.0	3.9	4.9	NA
White males					
	Squamous cell carcinoma	24.3	26.8	25.5	22.3
	Adenocarcinoma	14.5	19.0	21.3	26.3
	Small cell	9.5	12.5	13.1	12.2
	Large cell	0.0	5.9	7.2	NA
White females					
	Squamous cell carcinoma	4.0	5.5	6.6	8.2
	Adenocarcinoma	6.9	10.2	12.9	19.1
	Small cell	3.4	5.5	7.1	8.9
	Large cell	0.0	2.2	3.1	NA
African American males					
	Squamous cell carcinoma	43.9	46.3	48.5	39.7
	Adenocarcinoma	18.1	27.4	32.5	36.2
	Small cell	9.5	13.3	14.0	12.7
	Large cell	0.0	8.0	10.8	NA
African American females					
	Squamous cell carcinoma	5.6	6.8	9.5	11.4
	Adenocarcinoma	6.8	10.8	13.3	18.9
	Small cell	3.6	3.9	6.0	7.2
	Large cell	0.0	2.0	3.0	NA

*Data from Travis WD, Travis LB, Devesa SS: Lung cancer. Cancer 75:191–202, 1995.
†Calculated from Can Ques and SEER* Stat; http://seer.cancer.gov[19].
NA, not available; SEER, surveillance, epidemiology, and end results.

Geographic Patterns

Lung cancer is the most commonly diagnosed cancer worldwide,[25,26] but its geographic distribution shows marked regional variation[27]: age-standardized incidence rates vary over a wide range, over fourfold among men and fivefold among women (Fig. 46-3).[28] This marked variation in rates cannot be explained on the basis of diagnostic practices and data quality alone. Lung cancer tends to be most common in developed countries, particularly in North America and Europe, and less common in developing countries, particularly in Africa and South America.[29] However, the lung cancer epidemic is on the rise in the developing world.[30]

Substantial geographic variation in lung cancer mortality rates has also been observed within countries, providing clues about determinants of lung cancer. In the past, rates tended to be highest in urban areas, which led to conjecture that air pollution might be a cause of the lung cancer epidemic.[31] High rates in coastal areas in the United States over the period 1950 to 1969 were linked to asbestos exposure in shipyards.[32] Now, lung cancer mortality rates among white males are highest in the South and lower in the Northeast, likely reflecting patterns of cigarette smoking.[33]

Lung Cancer Occurrence by Histologic Type

Lung cancer manifests itself in multiple histologic types as classified by conventional light microscopy. The four major types include squamous cell carcinoma, adenocarcinoma, large cell carcinoma, and small cell undifferentiated carcinoma; together these four types of lung cancer account for over 90% of lung cancer cases in the United States.[34] These primary bronchogenic carcinomas are composed of a family of epithelial tumors that represent a subset of a larger collection of lung and pleural tumors classified most recently by the World Health Organization (WHO) in 2004.[35] The latest consensus classification,[36] written by the International Association for the Study of Lung Cancer (IASLC) pathology panel, was adopted by the WHO in 1994 to provide consistent criteria for research studies.

Few linkages have been made between particular etiologic agents and the development of a particular histologic type of lung cancer. Cigarette smoking increases risk for all major histologic types.[37-39] The dose-response relationship of increased lung cancer risk according to number of cigarettes smoked varies across the types, being steepest for small cell undifferentiated

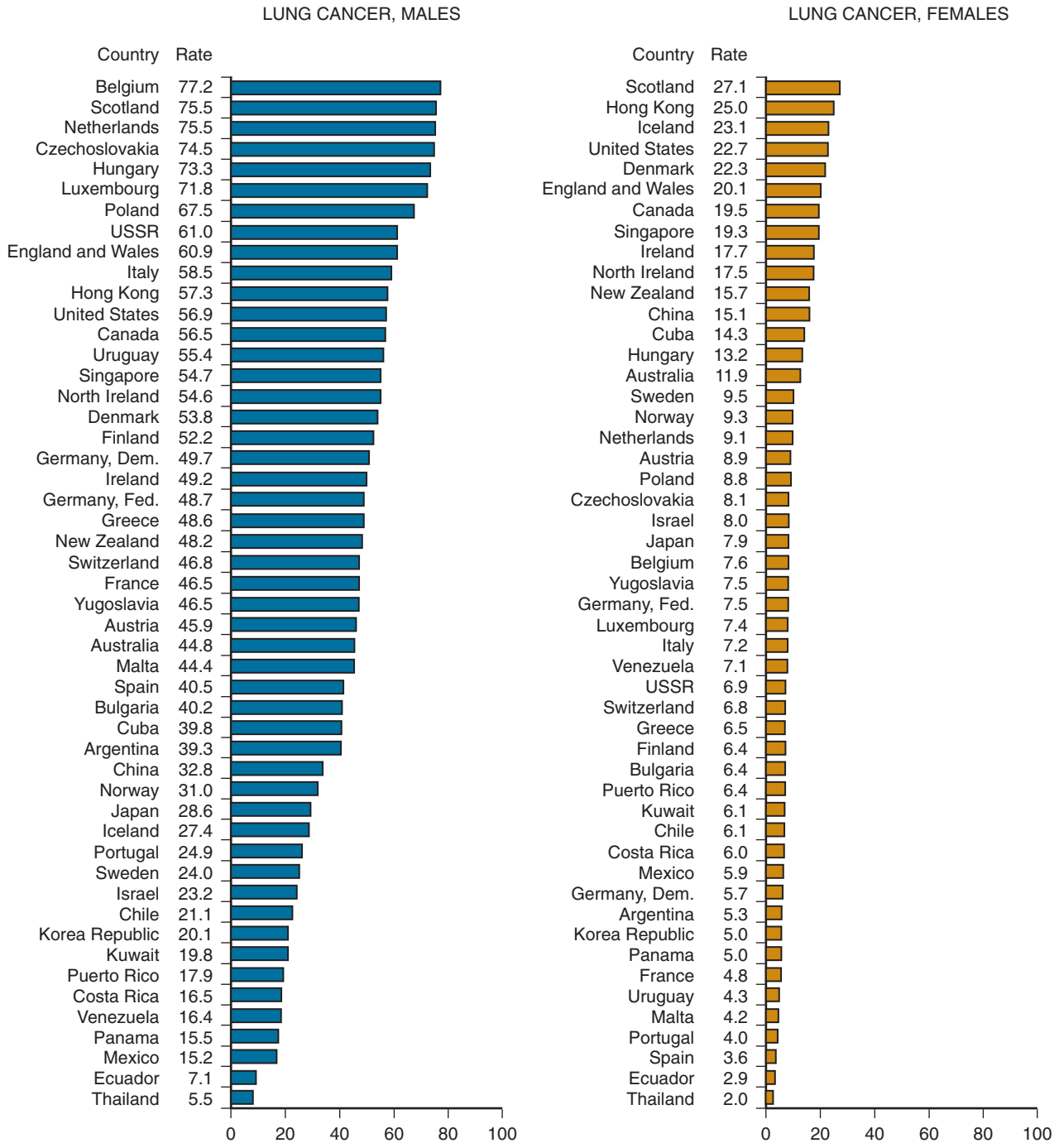

FIGURE 46-3 ■ 1986–1988 Age-adjusted death rates per 100,000 population, male and female. (Data from National Cancer Institute [NCI], Cancer Statistics Branch, and Division of Cancer Prevention and Control: Cancer Rates and Risks. Bethesda, MD: National Institutes of Health, 1996.)

carcinoma.[37-39] A few occupational exposures, such as chloromethyl ethers and radon, have been linked to small cell lung cancer.[34,40]

Since the 1960s, the most commonly diagnosed histologic type of lung cancer has shifted from squamous cell carcinoma to adenocarcinoma. Changing patterns of diagnosis and classification of lung cancers over time could have led to these changes, but most observers have set aside an artifactual change.[34,41,42] For example, even though diagnostic methods have improved, Thun and coworkers[43] analyzed data from the Connecticut Tumor Registry and showed that the rise in adenocarcinoma antedated these diagnostic innovations.

In the United States, during the initial decades of the smoking-caused epidemic of lung cancer, the most frequent type of lung cancer was squamous cell carcinoma, followed by small cell carcinoma. In the 1970s, a shift toward a predominance of adenocarcinoma was

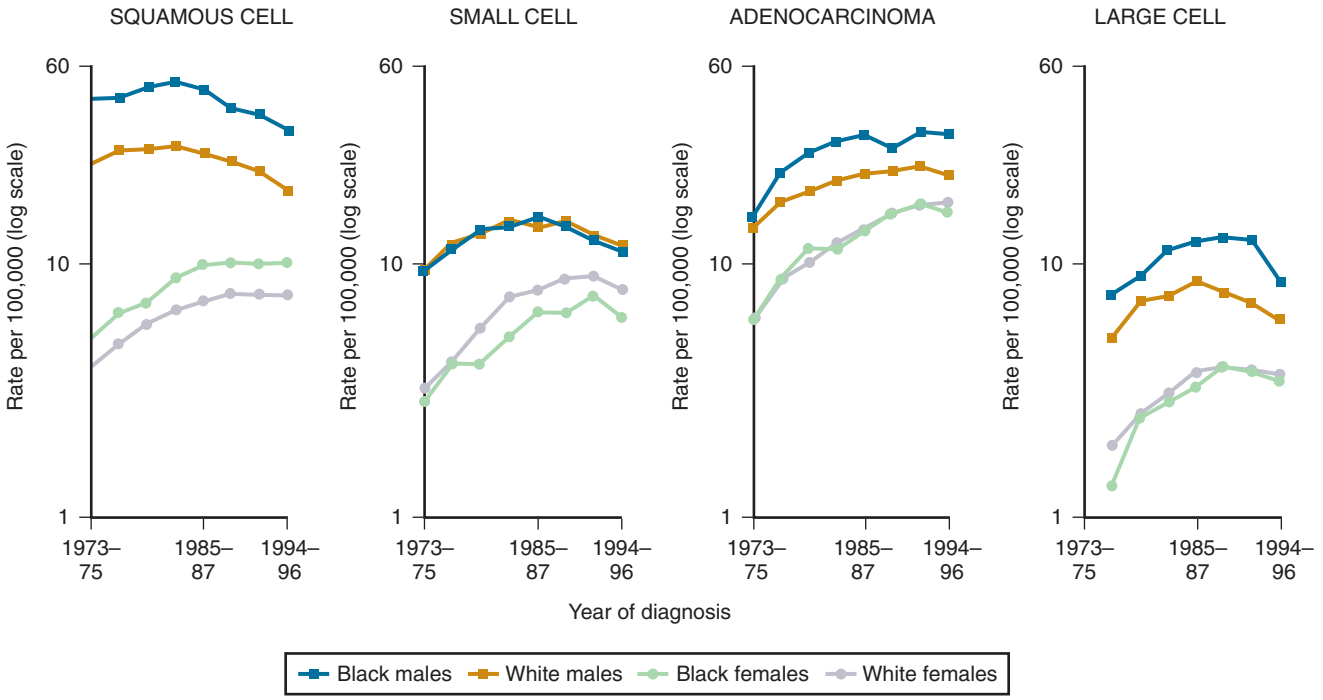

FIGURE 46-4 ■ Cancer of the lung and bronchus: surveillance, epidemiology, and end results (SEER) incidence rates, by histologic type, sex, race, and ethnicity, all ages, 1973–1996. (Data from Wingo PA, Ries LA, Giovino GA, et al: Annual report to the nation on the status of cancer, 1973–1996, with a special section on lung cancer and tobacco smoking. J Natl Cancer Inst 91:675–690, 1999.)

noted,[34,42,44] and with the persistence of this trend, adenocarcinoma is now the most common histologic type.[11,18] In U.S. men, the shift to adenocarcinoma developed in part because, whereas lung cancer incidence and mortality rates began to decline during the 1990s, the decline in lung cancer rates was more rapid for squamous cell and small cell carcinomas than for adenocarcinoma, which is just beginning to show a lower incidence rate (Fig. 46-4).[11] In U.S. women, the increase in lung cancer incidence rates was more pronounced for adenocarcinoma than any other cell type, perhaps because lung cancer rates increased most rapidly among U.S. women during the time period of changing histology.

Similar trends have been noted throughout the globe. Worldwide, adenocarcinoma tends to be the most common cell type seen in female lung cancer patients, accounting for approximately one third of all diagnoses in most regions.[45] In males, squamous cell carcinoma is still the most common cell type in some geographic regions where the lung cancer epidemic has peaked, but trends indicate that the overall percentage of this cell type has fallen over time to 40% or less.

Hypotheses concerning the shift from squamous cell carcinoma to adenocarcinoma have focused on the potential role of changes in the characteristics of cigarettes and consequent changes in the doses and types of carcinogens inhaled.[6,46,47] Puff volume has likely increased over recent decades with the possibility that patterns of deposition in the lung have changed.[46] Nitrate levels in tobacco smoke have also increased due to the rise in the proportion of air-cured tobacco used in manufacturing the blended U.S. cigarette,[46] and the resulting increased production of nitrogen oxides contributes to increased formation of tobacco-specific nitrosamines. An increase in dose of the potent tobacco-specific nitrosamine, NNK, has been postulated as one factor leading to the increase in adenocarcinoma.[48]

When the risks for lung cancers of the different histologic types were compared between participants in the American Cancer Society's Cancer Prevention Study (CPS) I and CPS II, the relative risk associating cigarette smoking with adenocarcinoma of the lung increased markedly in both men and women during the approximately 20-year period between the two studies.[43] These results suggest that the trend of increasing rates of adenocarcinoma is primarily due to changes in cigarette smoking behavior and features of cigarettes.[43]

THE ETIOLOGY OF LUNG CANCER: OVERVIEW

Although the causes of lung cancer are almost exclusively environmental, there is likely substantial individual variation in susceptibility to respiratory carcinogens. For example, only a minority of smokers develop lung cancer. The risk of the disease can be conceptualized as the consequence of the interrelationship between (1) exposure to etiologic (or protective) agents and (2) individual susceptibility to these agents. Given lung cancer's multifactorial etiology, synergistic interactions among risk factors have substantial consequences for lung cancer risk. These interactions have typically been

considered on an agent-by-agent basis, as for example, in studies of the synergistic effect of cigarette smoking on the lung cancer risk from asbestos exposure.[5] Our emerging understanding of cancer genetics indicates the additional relevance of gene-environment interactions.

Given the many risk factors that have been identified for lung cancer, a practical question is the relative contribution of these factors to the overall burden of lung cancer. In the United States, active smoking is estimated to be responsible for about 85% of lung cancer[6]; occupational exposures to carcinogens account for approximately 5% to 10%; radon causes 15% of lung cancer,[40] and outdoor air pollution perhaps 1% to 2%.[49] These known causes may not account for the development of lung cancer in never smokers, an important group for which further epidemiologic research in needed.[49a] The contribution of nutritional factors remains to be determined, but dietary factors have been hypothesized to account for approximately 20% (range, 10%–30%) of the lung cancer burden.[50] Because these attributable risk estimates include joint contributions of risk factors, for example, smoking and occupation, the total percentage can exceed 100%.

ENVIRONMENTAL AND OCCUPATIONAL AGENTS

Smoking

Overview

Cigarette smoking is by far the leading cause of lung cancer, accounting for approximately 80% to 90% of lung cancer cases in the United States[6] and in other countries where cigarette smoking is common.[40] Compared with never smokers, smokers have about a 20-fold increase in lung cancer risk, far higher than the risks for diseases associated with other environmental agents. Cigar and pipe smoking are also established causes of lung cancer.[51] In general, trends of lung cancer occurrence closely reflect patterns of smoking, but rates of occurrence lag smoking rates by about 20 years. According to the Centers for Disease Control and Prevention, in the United States, 156,900 men and women die from smoking-related lung cancer each year.[52] Worldwide, 5.4 million die each year from smoking-related lung cancer.[53]

Quantitative Risks

The risk of lung cancer among cigarette smokers increases with the duration of smoking and the number of cigarettes smoked per day (Table 46-2).[41] In one widely cited analysis, Doll and Peto[54] proposed a quantitative model for lung cancer risk based on data from the cohort study of British physicians. This model predicted a stronger effect from the duration of smoking than from the amount smoked per day. Thus, a tripling of the number of cigarettes smoked per day was estimated to triple the risk whereas a tripling of duration of smoking was estimated to increase the risk 100-fold.[55] These quantitative dimensions of the dose-response relationship between smoking and lung cancer have implications concerning the now widespread smoking among youths. Those starting at younger ages have a greater likelihood of becoming a heavier smoker and remaining a smoker.[56] The exponential effect of duration of smoking on lung cancer risk markedly increases the lifetime risk for those who become regular smokers in childhood.

Smoking Cessation

Cigarette smokers of any age can benefit from quitting smoking. Among those who quit smoking, the likelihood of developing lung cancer decreases when compared with those who continue to smoke[6,57,58] (Table 46-3). As the period of abstinence from smoking cigarettes increases, the risk of lung cancer decreases[57,58] (see Table 46-3). However, even for periods of abstinence of over 40 years, the risk of lung cancer for former smokers remains elevated compared with that for never smokers (see Table 46-3). The benefits derived from smoking cessation also depend on the prior duration of smoking: for a given period of abstinence, the risk decreases with a decrease in the duration of previous smoking.[58]

The Changing Cigarette

The composition and design of cigarettes has changed considerably since the 1950s. The marketplace has shifted from mainly unfiltered cigarettes to predominantly filtered cigarettes and to products that are labeled "light" or "mild." In the mid-1960s, ventilation holes were added to the filter, which dilute the smoke with

TABLE 46-2. Age-Specific Lung Cancer Mortality Rates (Per 100,000) among Men and Women 60 to 69 Years of Age with Comparable Smoking Levels in the American Cancer Society's Cancer Prevention Study II (CPS-II)

		SMOKED 20 CIGARETTES PER DAY FOR		SMOKED 40 CIGARETTES PER DAY FOR	
Group	Never Smokers	30 Years	40 Years	30 Years	40 Years
Men	11.9	224.3	486.8	572.8	606.6
Women	9.8	200.8	264.4	257.7	552.8

From Thun MJ, Day-Lally CA, Myers DG, et al: Trends in tobacco smoking and mortality from cigarette use in Cancer Prevention Studies I (1959–1965) and II (1982–1988). *In* Burns DM, Garfinkel L, Samet JM (eds): Changes in Cigarette-Related Disease Risks and Their Implication for Prevention and Control. Bethesda, MD: U.S. Government Printing Office, 1997, pp 305–382.

TABLE 46-3. Risk of Lung Cancer among Ex-Smokers Relative to Never Smokers According to Length of Time Since Smoking Cessation and Number of Cigarettes Formerly Smoked among a Cohort of U.S. Veterans

	CIGARETTES SMOKED PER DAY				
Years Since Smoked	**1–9**	**10–20**	**21–39**	**40**	**Total**
<5	7.6*	12.5	20.6	26.9	16.1
5–9	3.6	5.1	11.5	13.6	7.8
10–19	2.2	4.3	6.8	7.8	5.1
20–29	1.7	3.3	3.4	5.9	3.3
30–39	0.5	2.1	2.8	4.5	2.0
≥40	1.1	1.6	1.8	2.3	1.5

*Relative risk compared with referent category of never smokers (=1.0).
Adapted from Hrubec Z, McLaughlin JK: Former cigarette smoking and mortality among U.S. veterans: A 26-year follow-up, 1954–1980. *In* Burns DM, Garfinkel L, Samet JM (eds): Changes in Cigarette-Related Disease Risks and Their Implication for Prevention and Control. Bethesda, MD: U.S. Government Printing Office, 1997, pp 501–530.

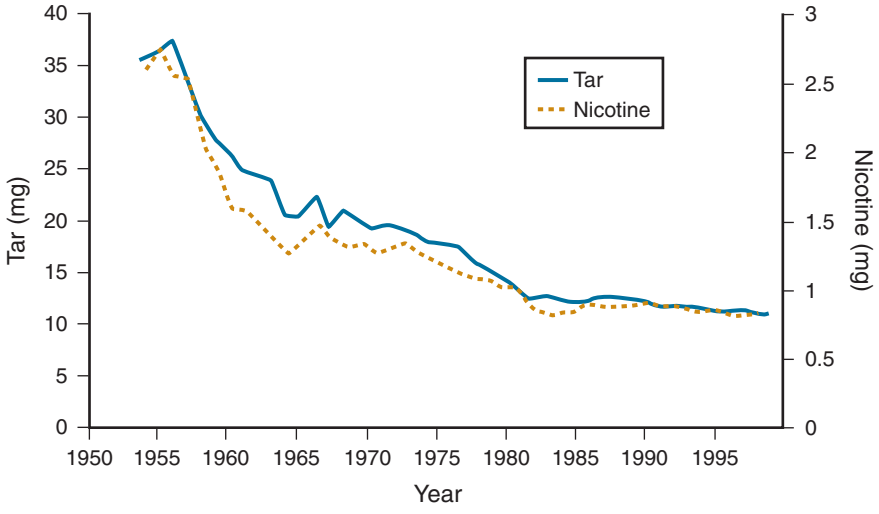

FIGURE 46-5 ■ Tar and nicotine values for U.S. cigarettes as measured using the Federal Trade Commission (FTC) method 1954–1998 and weighted by actual sales to determine the content of tar and nicotine for an average cigarette smoked by the population. (Data from Burns DM, Benowitz NL: Public health implications of changes in cigarette design and marketing. In Burns DM [ed]: Risks Associated with Smoking Cigarettes with Low Machine-Measured Yields of Tar and Nicotine. Bethesda, MD: U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute, 2001, pp 1–12.)

air drawn through them. However, whereas these holes effectively decrease the tar measured by the testing machines, smokers can readily block the holes with their fingers, thereby increasing their tar inhalation and exposure to carcinogens. Reconstituted tobacco, essentially reprocessed tobacco leaf wastes, has been used increasingly since the 1960s, and there have been changes to the cigarette paper and additives.[59] These changes in design and content may also have affected carcinogenicity.

A shift toward lowered levels of "tar" and nicotine yields has thus been defined by measurements using a smoking machine according to a standard protocol of the Federal Trade Commission (FTC) (Fig. 46-5).[60] However, the protocol in use is no longer representative of typical smoking patterns.[61] Studies using biomarkers of exposure to tobacco smoke components show little relationship of these levels with levels expected from calculations using the tar or nicotine yield as measured by the FTC's protocol.[47,61,62] The lack of association of tar and nicotine yields with biomarker levels partially reflects compensatory changes in smoking patterns for those switching from higher- to lower-yield products. The compensation includes blocking of the ventilation holes as mentioned previously but also more frequent and deeper puffs and an increase in the number of cigarettes smoked.[61] In a study of smokers in four countries (Brazil, China, Mexico, and Poland), Blackford and associates[62] examined salivary cotinine level in relationship to number of cigarettes smoked per day. The curves describing the increase in cotinine level with number of cigarettes smoked were comparable for smokers of regular and "light" cigarettes. In other words, in each country, the use of "light" cigarettes did not decrease the nicotine intake per cigarette.

If the FTC test protocol was indeed predictive of carcinogen doses delivered to the lung, one would have expected a gradual reduction in smokers' exposures to carcinogens.[63] However, questions remain as to whether the FTC test method is informative with regard to the risks of lung cancer risk or of other smoking-caused diseases.[61] The early studies showed somewhat reduced risk in those switching from nonfilter to filter cigarettes, but subsequent studies showed that declining tar yields,

as measured by a machine, were not followed by lower lung cancer risk.[6]

Useful insights about whether risks have changed have been gained by comparing the risks in the two studies of the American Cancer Society, CPS I (1960–1972) and CPS II (1980–1986).[64,65] If the risk for lung cancer associated with smoking were decreasing over time, the expectation would be that risks for smokers would be less in CPS II than in CPS I. In fact, the opposite was observed; lung cancer mortality increased in male and female smokers in CPS II compared with their male and female counterparts in CPS I.[41] In a separate analysis with similar findings, Doll and colleagues[66] compared the risks of death from lung cancer and other causes during the first and second 20 years of the 40-year follow-up of the British physician cohort. Even though products smoked should have had a substantially lower tar and nicotine yield over time, lung cancer mortality actually increased among smokers in the second 20 years; for the first 20 years (1951–1971), the annual lung cancer mortality rate among current smokers was 264 per 100,000 and, for the second 20 years (1971–1991), it was 314 per 100,000. In the 50-year follow-up,[67] the excess mortality associated with cigarette smoking was less for men born in the 19th century and was greatest for men born in the 1920s, who would have had the lengthiest exposure to the more recent, lower machine-measured yield products.

Several expert panels have reviewed the findings. The Institute of Medicine[68] carried out a comprehensive review on various harm reduction strategies for reducing the disease burden caused by smoking, including lower-yield cigarettes. The Institute of Medicine report concluded that smoking lower yield products has not been shown to benefit the health of smokers.[68] The National Cancer Institute's *Monograph 13: Risks Associated with Smoking Cigarettes with Low Machine-Measured Yields of Tar and Nicotine*[61] concluded that changes in cigarette design and manufacturing over the last 50 years have not benefited public health. Most recently, a Working Group convened by the IARC of the WHO also reached a similar conclusion,[5] as did the 2004 Report of the U.S. Surgeon General.[6]

Passive Smoking

Passive smokers inhale a complex mixture of smoke now widely referred to as environmental tobacco smoke or secondhand smoke. Passive smoking was first considered as a possible risk factor for lung cancer in 1981 when two studies were published that described increased lung cancer risk among never-smoking women who were married to smokers.[69,70] Additional evidence rapidly accrued so that by 1986, two reports, one from the National Research Council[71] and the 1986 Surgeon General's Report,[72] both concluded that passive smoking causally increased risk for lung cancer. Estimates indicate that passive smoking accounts for about 3400 lung cancer deaths per year in the United States.[73]

Since these conclusions were reached, numerous studies have been carried out to characterize further the association of passive smoking with lung cancer, while taking into account some of the limitations of earlier studies, particularly small sample sizes, exposure misclassification, and omission of some potential confounding factors.[74,75] Various panels since 1986 have also concluded that passive smoking increases lung cancer risk, including most recently the IARC,[5] the California Environmental Protection Agency,[73] and once again, the U.S. Surgeon General.[7]

Passive smoking is more weakly associated with lung cancer than is active smoking, as expected given the lower doses of carcinogens received by the nonsmoker compared with the smoker. Marriage to a smoker is associated with about a 20% increase in risk[76] and exposure in the workplace is associated with between a 24% increase in risk up to a twofold increase at the highest levels of exposure.[77] In general, the estimates indicate increased risk associated with exposure, although they are imprecise owing to a small number of cases.[77]

Diet

The possible role of diet in modifying the risk of lung cancer has been the focus of intensive investigation, driven initially by the rationale that specific micronutrients might have anticarcinogenic activity. The most thoroughly investigated dietary factors are also those that at present appear to have the greatest implications for prevention: fruits, vegetables, and specific antioxidant micronutrients that are commonly found in fruits and vegetables.

The results of case-control and prospective cohort studies have tended to show that individuals with high dietary intake of fruits or vegetables have a lower risk of lung cancer than those with low fruit or vegetable intake.[78] To understand better the basis of this protective association, fruits and vegetables have been grouped into classes and also examined individually in relation to lung cancer risk. For example, tomatoes[78] and cruciferous vegetables[78,79] have been associated with a reduced risk of lung cancer in a number of studies. These food-based analyses can help to clarify whether protection arises from the complex mixture that composes fruits and vegetables or from specific biochemical constituents present in particular fruits and vegetables.

Fruits and vegetables are the major dietary source of antioxidant micronutrients. Much of the research on diet and lung cancer has been motivated by the hypothesis that diets high in antioxidant micronutrients may protect against oxidative DNA damage and thereby protect against cancer. For example, this was one of the hypothesized roles for β-carotene,[80] the focus of now-controversial clinical trials. Two different strategies are used to evaluate the relationship of micronutrients to lung cancer risk in observational epidemiologic studies: (1) estimating micronutrient intake from food-frequency questionnaires and (2) measuring serum concentrations of micronutrients. Prospective studies of both dietary intake[81] and prediagnostic blood concentrations[81] suggest that carotenoids are inversely associated with lung cancer risk.

The protective association predicted between β-carotene and lung cancer on the basis of these observational epidemiologic studies was not confirmed in three randomized, double-blind, placebo-controlled chemoprevention trials.[82–84] In fact, two of these studies with participants at high risk for lung cancer (heavy smokers and asbestos-exposed workers) were stopped early because significantly increased risk of lung cancer was observed in the β-carotene group compared with the placebo group.[83,84]

The results of the randomized chemoprevention trials stand in sharp contrast to the considerable observational epidemiologic evidence favoring a protective association. Among the potential explanations for the contradictory findings are that the randomized trials used relatively high doses of β-carotene and that the observational epidemiologic studies may have been flawed by uncontrolled confounding or selection bias.[81] Because of the powerful role of smoking as a cause of lung cancer, disentangling the effects of other lifestyle-related factors, such as diet, from the effect of smoking may be particularly difficult. Further complicating the assessment of protection by dietary factors is the narrow range of likely effects, much smaller than the effect of smoking, and the unavoidable problem of measurement error, that is, the inevitable inaccuracy in estimating usual dietary consumption of particular foods or groups of foods.

Studies of fruits, vegetables, and micronutrients have been the centerpiece of studies of diet and lung cancer, but other factors have also been investigated. For example, the results of a meta-analysis showed alcohol drinking in the highest consumption categories was associated with increased risk of lung cancer.[85] In addition, anthropometric measures have been studied, indicating a tendency for persons with lower body mass index to have increased lung cancer risk relative to heavier persons.[78] However, both alcohol drinking and low body mass index may be difficult to separate from the concomitant effects of smoking. At present, when considering the possible relationships between lung cancer and factors such as alcohol drinking and lower body mass index, residual confounding by cigarette smoking cannot be dismissed as a possible explanation.

Environmental Exposures

Occupational Exposures

Lung cancer has been found to be associated causally with many workplace exposures. Occupational exposures have been estimated by case-control studies to account for 9% to 15% of lung cancer cases.[86] Cigarette smoking also potentiates the effect of some of the known occupational lung carcinogens.[5]

Asbestos

Asbestos, a well-established occupational carcinogen, refers to several forms of fibrous, naturally occurring silicate minerals.[87] The epidemiologic evidence dates to the 1950s, although clinical case series had previously led to the hypothesis that asbestos causes lung cancer. In a retrospective cohort study published in 1955, Doll observed that asbestos textile workers at a factory in the United Kingdom had a 10-fold elevation in lung cancer risk and that the risk was most heavily concentrated during the timeframe before regulations were implemented to limit asbestos dust in factories.[88] A 7-fold excess of lung cancer was subsequently observed among insulation workers in the United States.[89,90] The peak incidence occurred 30 to 35 years after the initial exposure to asbestos.[91] The risk of lung cancer has been noted to increase with increased exposure to asbestos[92] and to be associated with each of the principal commercial forms of asbestos.[93] Whether asbestos acts directly as a carcinogen or indirectly as, for example, by causing chronic inflammation that eventually leads to cancer remains controversial.[94–96] For asbestos, two competing hypotheses have been posed: (1) that asbestos-caused lung cancer occurs as a consequence of asbestosis or (2) that lung cancer risk is dependent on the cumulative dose of asbestos, regardless of the presence of asbestosis, which may be serving as a marker of asbestos dose. The relevant mechanistic and epidemiologic evidence has gaps and the issue has been made even more controversial because of the implications for compensation of lung cancer in asbestos-exposed workers who have smoked.

Asbestos and cigarette smoking are both independent causes of lung cancer, but in combination, they act synergistically to increase the risk of lung cancer. Uncertainty remains as to the precise quantitative characterization of this synergy, reflecting limitations of the available data[5] and lack of understanding of the underlying mechanisms.[97] Nonetheless, the risk of the combined exposure is much higher than would be expected if one merely added the risks together, showing a strong interaction between the two. In fact, the risks are approximately multiplicative. A person who smokes and has been exposed to asbestos has a greater than 50-fold elevated risk of lung cancer compared to a non-smoker with no asbestos exposure, and a much higher risk than a person exposed to cigarette smoke alone (relative risk, 10.9) or exposed to asbestos alone (relative risk, 5.2) (Table 46-4).[98]

Radiation

Epidemiologic studies of populations exposed to high doses of radiation show that lung cancer is causally associated with exposure to ionizing radiation. Two types of radiation, classified by rate of energy transfer to the tissue, are relevant to lung cancer: high–linear energy transfer (LET) radiation (e.g., neutrons and radon) and low-LET radiation (e.g., x-rays and gamma rays). High-LET radiation produces ionization of relatively higher density in tissues than low-LET radiation, so in equivalent doses, more biologic damage is produced by high-LET than low-LET radiation.[99] For both types of radiation, the epidemiologic evidence comes primarily from cohorts exposed at levels substantially greater than those experienced by the general population. Risk assessment methods are then used to estimate risks to the general population.

TABLE 46-4. The Relationship between Cigarette Smoking and Asbestos Exposure on the Risk of Lung Cancer Mortality

	MORTALITY RATES ASBESTOS-EXPOSED		DIFFERENCE IN RATES ASBESTOS-EXPOSED		RATIO OF RATES ASBESTOS-EXPOSED	
Smoking	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**
No	11.3*	58.4	*0*	*47.1*	*1.0*	*5.2*
Yes	122.6	601.6	*111.3*	*590.3*†	*10.9*	*53.2*‡

*Mortality rate per 100,000.
†Difference in rates compared to no smoking/no asbestos exposure; if there were no interaction of asbestos and smoking, the expected rate of lung cancer in those exposed to both would be the sum of each alone (47.1 + 111.3 = 158.2). The actual value of 590.3 greatly exceeds 158.1 providing evidence of strong interaction between smoking and asbestos.
‡Ratio of rates compared to no smoking/no asbestos exposure; the expected value if risks were multiplicative would be the multiple of the rates, 5.2 × 10.9 = 56.1, close to the actual value of 53.2.
Adapted from Hammond EC, Selikoff IJ, Seidman H: Asbestos exposure, cigarette smoking and death rates. Ann N Y Acad Sci 330:473–490, 1979.

High-LET Radiation: Radon. Radon is an inert gas produced naturally from radium in the decay series of uranium. Two of the radon decay products emit alpha particles that can, consequent to high energy and mass, cause damage to the DNA of cells of the respiratory epithelium. Epidemiologic studies of underground miners of uranium and other ores have established exposure to radon daughters as a cause of lung cancer.[40,100] In the underground miners exposed to radon in past centuries, very high lung cancer risks were observed; in the miners in more contemporary workplaces, the observed risks have been much less as exposure concentrations have been better controlled, but still show clear evidence of existing cancer risk.[40] Cigarette smoking and radon decay products synergistically influence lung cancer risk, for example, in a manner that is greater than simply adding the risks of each together.[40]

Radon is of broader societal interest because it is a ubiquitous air pollutant that enters buildings from the underlying soil. On average, indoor exposures to radon for the general population are much less than for occupational groups such as uranium miners; nonetheless, homes have been identified with concentrations as high as in underground uranium mines. Exposure to radon in indoor air is also assumed to cause lung cancer, but the magnitude of the risk is more uncertain because of the assumptions made to estimate the risk, particularly the extrapolation of findings from uranium miners to the generally lower exposures indoors. Concern about radon arises in part from biologic evidence that a single hit to a cell by an alpha particle may cause permanent cellular change, an assumption leading to a non-threshold dose-response relationship.[40] In addition, pooled analyses of case-control studies in the general population show increased risk in association with indoor radon.[101,102]

The assumptions made by the Environmental Protection Agency and the Biological Effects of Ionizing Radiation (BEIR) VI Committee of the National Research Council have led to estimates that approximately 15,000 to 20,000 lung cancer deaths per year in the United States are caused by radon.[103] In the United States, the Environmental Protection Agency has called for testing of all residences and mitigation of those exceeding a guideline value.

Low-LET Radiation: X-Rays and Gamma-Rays. Epidemiologic data relating low-LET radiation to lung cancer stem from three principal populations[104]: the atomic bomb survivors in Japan, patients with diseases such as ankylosing spondylitis or tuberculosis who received multiple radiation treatments, and occupational groups in professions exposed to radiation. The single, high-dose exposure of the atomic bomb survivors was associated with significant lung cancer risk.[105] Regardless of age at the time of the blast, the excess of lung cancer occurred when the survivors reached the older ages when cancer usually occurs.[106] Quantitative risk models are available that describe how risk rises with radiation dose.[104]

Air Pollution

During a typical day, the average adult inhales about 10,000 L of air.[107] Consequently, even the carcinogens present in the air at low concentrations are of concern as a risk factor for lung cancer. Extrapolation of the risks associated with occupational exposures to the lower concentration of carcinogens in polluted ambient air suggests that a small proportion of lung cancer cases could be due to air pollution.[108]

Atmospheric Air Pollution

Carcinogens generated by the combustion of fossil fuels include polycyclic aromatic hydrocarbons and metals such as arsenic, nickel, and chromium (see Cohen and Samet[109] for a recent review). Because these carcinogens are widespread in outdoor air pollution and a large number of urban dwellers are exposed, even a small effect could be of public importance. Descriptive evidence, showing higher lung cancer rates in polluted urban areas, is consistent with a role for air pollution in causing lung cancer.[110] Biomarkers of exposure were addressed in a 2005 review by Vineis and Husgafvel-Pursiainen.[111]

Air pollution has been assessed as a risk factor for lung cancer in epidemiologic studies of both case-control and cohort design.[49,112] The evidence from case-control studies, which are limited in their exposure assessment, has been mixed.[109] Prospective cohort studies[113–115] that

partially address the weaknesses of earlier studies add evidence that air pollution is weakly associated with lung cancer risk. By prospectively studying air pollution levels in relation to risk of lung cancer and by controlling for possible confounders such as age, smoking, and socioeconomic status at the individual level, these newer studies surmount some shortcomings of previous research.[116] In a study of six U.S. cities, the adjusted risk of lung cancer mortality in the city with the highest fine particulate concentration was 1.4 times (95% confidence interval [CI] = 0.8–2.4) higher than in the least polluted city.[117] Using data from the American Cancer Society's Cancer Prevention Study II, for 1982 to 1989, Pope and colleagues[118] observed that, compared with the least polluted areas, residence in areas with high sulfate concentrations was associated with an increased risk of lung cancer (adjusted relative risk = 1.4; 95% CI = 1.1–1.7) after adjustment for occupational exposures and the factors mentioned previously. However, unlike in the Six-Cities study, fine particulate concentration was not associated with lung cancer risk.[118] In a subsequent updating of this report, follow-up was extended to 1998.[115] In this report, the risk of lung cancer associated with a 10 $\mu g/m^3$ increase in fine particles was estimated as 14%. In a study in the Netherlands, traffic exposure variables were weakly associated with lung cancer risk.[113]

Another research approach to evaluate the risk of air pollution has been to investigate populations residing around point sources of pollution, such as factories and smelters.[119,120] Proximity of residence to the pollution source can be used as a proxy for exposure. Areas surrounding nonferrous smelters—which emit arsenic—have been of particular interest, but other industries have also been investigated.

In sum, Doll and Peto,[108] in their 1981 review of the causes of cancer, estimated that perhaps 1% to 2% of lung cancer was related to air pollution. Even in light of recent findings, this remains a reasonable estimate.[110]

Indoor Air Pollution

Indoor air quality has large potential health implications because people spend substantial amounts of time indoors. Indoor air pollution arises from pollutants that enter from the outside as well as those that originate indoors from tobacco smoking, building materials, soil gases, household products, and combustion from heating and cooking.[121] In the more developed countries, two of the most important indoor pollutants that influence lung cancer risk in never smokers are passive smoking[72] and radon.[100] Asbestos exposure may pose a risk to building occupants, but it is estimated to be minimal.[87] In the developing world, the major source of indoor air contamination results from the use of unprocessed solid fuels, notably coal, for cooking and space heating.[122] Mumford and coworkers[123] inferred that smoky coal was a major determinant of the geographic distribution of lung cancer in Xuan Wei, China, a finding corroborated by an animal model.[124] With a subsequent change in fuel source, lung cancer rates were found to decline in this region.[125] Some case-control studies conducted elsewhere in mainland China[126,127] and Taiwan[128] also implicated coal use as a risk factor for lung cancer. A recent risk assessment projected solid fuel use and smoking as preventable causes of most lung cancer cases in China.[129]

HOST FACTORS

Overview

The long-standing interest in genetic susceptibility to lung cancer has recently intensified. Environmental agents, even cigarette smoking, cause lung cancer in only a minority of exposed persons, leading to the hypothesis that susceptibility is inherently determined. Studies showing that a family history of lung cancer predicts increased risk further support a genetic basis for lung cancer susceptibility. This long-postulated hypothesis is now being actively addressed using the approach of molecular epidemiology. Full coverage of this topic is beyond the scope of this chapter; aspects of genetic susceptibility have been reviewed[130] (see also Chapter 45).

In case-control studies, a family history of lung cancer has been shown to be associated with an increased risk of lung cancer; of importance, most of the studies controlled for smoking, which is known to aggregate in families (Table 46-5).[131–143] In a large study in Louisiana, segregation analysis suggested that lung cancer inheritance was consistent with a mendelian codominant autosomal gene determining early onset of disease.[144] Conversely, the largest study of lung cancer in twins reported to date did not provide evidence indicating a genetic basis for susceptibility.[145]

In a genetic epidemiology study of lung cancer in nonsmokers in Detroit, Schwartz, Yang, and colleagues[142,146] explored familial risk for lung cancer. In nonsmokers, Schwartz and associates[142] found an association between risk and a history of lung cancer in a first-degree relative (odds ratio [OR} =1.4; 95% CI 0.8–2.5). The association was much stronger in those aged 40 to 59 years at diagnosis than in older persons, suggesting that genetic factors may be more important at younger ages. This general finding was confirmed by a subsequent, complex segregation analysis of the same data.[146]

Research Findings on the Genetic Basis of Lung Cancer

With application of the new and powerful tools of modern molecular biology, research findings are now characterizing the changes in cells that are caused by exposure to tobacco smoke and providing a framework for understanding the genetic and epigenetic basis of lung cancer risk. A rapidly expanding literature, based both in the laboratory and in the observational approach often referred to as "molecular epidemiology," addresses dosimetry and metabolism of tobacco carcinogens at the cellular and molecular levels, genetic determinants of susceptibility, and patterns of genetic changes in the tissues of smokers and in the cancers that the tissues develop.[48,130,147]

The understanding of the epigenetic changes that may be involved in the causal pathway to lung cancer is

TABLE 46-5. A Summary of Selected Case-Control Studies of Lung Cancer among Persons with a Family History of Lung Cancer Compared with Those with No Family History of Lung Cancer

First Author	Year	Location	Odds Ratio*	Comment
Tokuhata[132]	1963	Buffalo, NY	2.4 (1.1, 5.2)	Adjusted for cigarette smoking, age, sex, generation
Tokuhata[133]	1964	Baltimore	2.6 (1.4, 5.4)	Adjusted for age, sex, generation
Ooi[134]	1986	Ten Louisiana parishes	2.7 (1.7, 4.2)	Adjusted for smoking, sex
Samet[135]	1986	New Mexico	5.3 (2.2, 12.8) [parental]	Adjusted for cigarette smoking, age, sex, ethnicity
Gao[131]	1987	Shanghai, PRC	1.1 (0.6, 2.3) [parental] 3.0 (0.7, 12.5) [sibling]	Adjusted for smoking, age
Tsugane[136]	1987	Tokyo	1.0 (0.3, 3.9)	Smoking and occupational exposure Data collected, but not adjusted for
Horwitz[137]	1988	New Haven, CT	2.3 (0.6, 9.7)	Adjusted for smoking
McDuffie[138]	1991	Saskatchewan, Canada	2.0 (1.2, 3.4)	Smoking and occupational exposure Data collected, but not adjusted for
Osann[139]	1991	Northern California	1.9 (0.7, 5.6)	Adjusted for cigarette smoking education, matched on age and race
Shaw[140]	1991	Gulf Coast of Texas	1.7 (1.2, 2.4) [1 1st-degree relative with cancer] 2.8 (1.2, 6.6) [2 1st-degree relatives with cancer]	Adjusted for cigarette smoking, passive smoking, and number of first-degree relatives
Filho[141]	1995	Sao Paulo, Brazil	3.2 (1.0, 11.1)	Smoking and occupational exposure Data collected, but not adjusted for
Schwartz[142]	1996	Detroit, MI	6.1 (1.1, 33.4)	Adjusted for smoking, occupational and medical history of each family member
Wu[143]	1996	United States, multisite	1.29 (0.9, 1.9)	Adjusted for secondhand smoke exposure

*Referent category of persons with no family history of lung cancer = 1.0.

advancing rapidly. For example, there is increasing evidence that methylation of cytosine in the DNA, leading to hypermethylation of promoter regions, is frequent in most types of cancers, including lung cancer.[148] Promoter regions of many human genes have loci rich in CpG dinucleotides, regions referred as CpG islands.[148,149] Hypermethylation of the CpG islands can be detected by polymerase chain reaction methods. Cells with abnormal methylation of genes have been detected in sputum of subjects before their diagnosis of lung cancer, suggesting that hypermethylation could be a useful marker for early detection.[150,151]

In a general formulation of determinants of cancer risk, the risk depends on carcinogen exposure as well as the factors that determine host susceptibility, including genetic predisposition.[152] Central to the molecular epidemiology approach are biomarkers, measures of indicators of exposure and dose, susceptibility, and response in biologic materials, including tissue samples, blood, urine, and saliva.[153] As research evolves within this paradigm, a more complete biologic understanding of the specific events underlying the multistage model, originally proposed on a conceptual basis, can be anticipated.

This framework indicates multiple points where genetically determined host characteristics might be important: carcinogen metabolism and activation, DNA repair, and cell cycle control/apoptotic response. There is a rapidly expanding literature on the molecular and cellular basis of lung cancer.[130] The evidence has expanded and deepened our understanding of how smoking injures cells and causes cancer and indicates potential approaches to identifying high-risk individuals and molecular screening.

Studies to investigate genotypic variation in relation to lung cancer risk have evolved rapidly since the 1980s. Initially, the research paradigm relied on identifying and studying candidate genes with functional polymorphisms hypothesized to be directly related to lung carcinogenesis, such as carcinogen detoxification or DNA repair. The sequencing of the human genome and the development of high-throughput assays that enable increasingly larger number of single nucleotide polymorphisms (SNPs) to be measured in larger studies has led to the new paradigm of genome-wide association studies (GWAS). In contrast to the candidate gene approach, which is based on deduction, the GWAS approach is inherently inductive. GWAS studies entail measuring as many tagging SNPs as possible; currently hundreds of thousands to more than a million, to determine which regions of the genome are associated with lung cancer risk. Because of the exploratory nature of the GWAS approach, these studies are usually specifically designed to guard against false-positive findings.

Of primary interest in studies using the candidate gene approach have been genes that encode for enzymes in carcinogen metabolism and DNA repair pathways and that are polymorphic in humans. A few selected examples are described later. The metabolism of toxic agents, including carcinogens, generally proceeds through two phases.[154] In phase 1, unreactive nonpolar compounds

are converted, usually by oxidative reactions, to highly reactive intermediates. These intermediates are then able to form complexes with conjugating molecules in phase 2 conjugation reactions, which are usually less reactive and more easily excreted. However, the intermediate metabolite may react with other cellular components, such as DNA, before conjugation occurs. This binding to DNA may be the first step in the initiation of the carcinogenic process.[154]

Many carcinogenic compounds in tobacco smoke, for example, polycyclic aromatic hydrocarbons, undergo metabolic activation by phase I enzymes of the cytochrome p-450 system to form reactive intermediates that bind to DNA and cause genetic injury. For example, for *CYP1A1*, the current evidence suggests that two specific polymorphisms, in MspI[155] and in exon 7,[156] are associated with increased lung cancer risk.

Glutathione *S*-transferase is a phase II enzyme that detoxifies reactive metabolites of polycyclic aromatic hydrocarbons. The results of a meta-analysis indicated that those with the *GSTM1* null–versus–present genotype had slightly higher risk of lung cancer, but a pooled analysis of data from 21 case-control studies did not indicate that this susceptibility was stronger among cigarette smokers than among nonsmokers.[157] Another pathway where genetic variation has been of hypothesized importance in determining susceptibility to lung cancer is DNA repair.[158,159] One of the most extensively studied DNA repair genes to date is the nucleotide excision repair gene *XPD*.[160,161] The evidence has not yet revealed a consistent pattern of associations for any specific polymorphism. These are examples where the candidate gene approach has not yielded clear-cut associations with lung cancer risk.

GWAS are now being reported, with encouraging results. The results of four separate studies, all published in 2008, have been remarkably consistent in identifying a region on the long arm of chromosome 15 (15q24-25.1).[162–165] For example, those with at least one variant allele of a specific SNP in this region (rs8034191), present in approximately one third of the study population, were at 1.3 times greater risk of lung cancer than those with the wild-type allele.[163–165] Now that this genomic region is identified, identifying the specific genetic variants that are directly responsible for determining lung cancer risk within this region is a major priority.

Presence of Human Immunodeficiency Virus

As human immunodeficiency virus (HIV)–positive patients maintain their immune function with highly active antiretroviral therapy (HAART) and live longer, evidence has emerged to indicate that HIV-positive individuals have an increased risk of lung cancer, especially non–small cell lung cancer (NSCLC).[166,167] In the HAART era, a greater than twofold increase in lung cancer risk has been observed among HIV-positive men and women.[167,168] In addition, HIV-positive individuals are diagnosed with lung cancer at a median age of 45 years or younger,[167,168] younger than the norm.

Some aspects of the occurrence of lung cancer in HIV-positive patients are similar to patterns seen in the general population. This includes a predominance of NSCLC,[169,170] with adenocarcinoma and squamous cell carcinoma as the two most common cell types.[167,169,171] In addition, the increased risk of lung cancer in HIV-positive patients applies to both men and women, so the fact that the preponderance of HIV-positive patients with lung cancer are males[169] may reflect the higher prevalence of HIV infection in men than in women.

There are several hypotheses as to the basis for the excess lung cancer risk in HIV-positive individuals. The elevated lung cancer risk may simply be due to a higher prevalence of cigarette smoking in HIV-positive individuals.[169,172] Alternatively, HIV may itself contribute to lung carcinogenesis.[172a] If so, potential explanations for the increased lung cancer risk could include (1) HIV acting as a viral carcinogen, (2) defective immune surveillance, and (3) recurrent opportunistic infections and parenchymal lung inflammation leading to inflammatory foci and scar carcinomas.

Presence of Acquired Lung Disease

In addition to hereditary factors, increased susceptibility to lung cancer may result from underlying lung disease. Such acquired lung diseases assume two major forms: (1) those that obstruct airflow, such as chronic obstructive pulmonary disease (COPD) and (2) fibrotic disorders that restrict lung capacity, such as pneumoconiosis.[173]

A substantial body of evidence suggests that COPD or impaired lung function is associated with the occurrence of lung cancer.[174] However, because cigarette smoking is the principal cause of both COPD[175] and lung cancer, statistical adjustment procedures that "remove" the effect of cigarette smoking may not be well-founded. For example, the presence of COPD may indicate that the affected individual has received a greater dose of tobacco carcinogens than the typical unaffected individual. Alternatively, cigarette smoke may induce an inflammation that can contribute both to COPD and to lung cancer.[174a] Regardless of mechanism, the presence of COPD is a clinically useful risk indicator.

Clarifying the possible relationship between pneumoconioses and lung cancer poses particularly vexing challenges. Even for asbestos exposure, which is clearly established as a potent cause of lung cancer,[93] whether lung cancer results from asbestos per se or from asbestosis remains unresolved (see earlier). For other mineral fibers, the evidence is even more uncertain.[176] For example, determining whether silica exposure or silicosis mediates the increased lung cancer risk in silica-exposed persons has proved difficult.[177,178] The presence of silicosis is associated with an increased risk of lung cancer.[179] Understanding the basis of this association will entail isolating the independent effects of silica exposure and lung fibrosis while controlling for exposure to smoking and other lung carcinogens.[176]

Such differences in the pattern of associations between pneumoconioses and lung cancer emphasize that "fibrosis" is not a homogeneous exposure, but one dependent

upon the properties of the specific mineral fiber or other environmental agent. Properties of the agent, such as its size, shape, and durability, and the effects of other exposures such as cigarette smoking are important considerations in assessing its potential harmfulness.[180]

Gender

The hypothesis has been advanced that females may have a greater risk of lung cancer than males at the same level of smoking.[181,182] There are several methodologic issues that have clouded the interpretation of the data on this issue,[183] but the results of studies that have compared the relative risk estimates for men and women for a specific degree of smoking history demonstrate very similar risks.[41,184]

FUTURE DIRECTIONS

In developing lung cancer prevention strategies, certain groups warrant particular attention. Steps need to be taken toward the goal of reducing the very high lung cancer incidence rates in African American men.[185] Lung cancer is also a major women's health issue. Owing to historical cigarette smoking patterns, the epidemic of lung cancer started later in women than in men, but in contrast to the situation in men, lung cancer incidence rates in women are still increasing.[186] Though lung cancer remains a critical public health problem, the decrease in the overall lung cancer burden that is presently occurring in the United States, as in much of the developed world, reflects the successes of preventive strategies. A critical global priority is to prevent the uptake of cigarette smoking in developing countries where smoking prevalence is still low.

A consideration of the epidemiology of lung cancer consistently reinforces one major theme: the pandemic of lung cancer is a consequence of the tragic and widespread addiction to cigarettes throughout the world. Curtailing the pandemic of lung cancer will require preventing youths from starting to smoke cigarettes and effectively promoting smoking cessation among addicted smokers.

KEY POINTS

- In the United States, lung cancer remains the leading cause of cancer death in both men and women.
- The predominant cause of lung cancer is exposure to tobacco smoke, with active smoking causing most cases but passive smoking also contributing to the lung cancer burden.
- The reductions in smoking prevalence in men that occurred in the late 1960s through the 1980s will continue to drive lung cancer mortality rates downward in men during the first portion of this century, but rates in women have not yet begun to decrease.
- Fortunately, exposures to major occupational respiratory carcinogens have largely been controlled, but the population is still exposed to environmental causes of lung cancer, including radon, the second leading cause of lung cancer death.

References

1. U.S. Department of Health and Human Services (USDHHS): Reducing the Health Consequences of Smoking. 25 Years of Progress. A Report of the Surgeon General. Washington, DC: U.S. Government Printing Office, 1989.
2. White C: Research on smoking and lung cancer: A landmark in the history of chronic disease epidemiology. Yale J Biol Med 63:29–46, 1990.
3. Royal College of Physicians of London: Smoking and Health. Summary of a Report of the Royal College of Physicians of London on Smoking in Relation to Cancer of the Lung and Other Diseases. London: Pitman Medical, 1962, pp S2–S70.
4. U.S. Department of Health Education and Welfare (DHEW): Smoking and Health. Report of the Advisory Committee to the Surgeon General. DHEW Publication No. [PHS] 1103. Washington, DC: U.S. Government Printing Office, 1964.
5. International Agency for Research on Cancer (IARC): Tobacco Smoke and Involuntary Smoking. IARC Monograph 83. Lyon, France: International Agency for Research on Cancer, 2004.
6. U.S. Department of Health and Human Services (USDHHS): The Health Effects of Active Smoking: A Report of the Surgeon General. Washington, DC: U.S. Government Printing Office, 2004.
7. U.S. Department of Health and Human Services (USDHHS): The Health Effects of Involuntary Exposure to Tobacco Smoke. Rockville, MD: Centers for Disease Control and Prevention (CDC), 2006.
8. Wingo PA, Cardinez CJ, Landis SH, et al: Long-term trends in cancer mortality in the United States, 1930–1998. Cancer 97:3133–3275, 2003.
9. National Cancer Institute and National Center for Health Statistics: Surveillance, epidemiology, and end results (SEER) program. SEER Stat Database: Mortality 2003. http://seer.cancer.gov/
10. American Cancer Society: Cancer Facts & Figures 2008. Atlanta: American Cancer Society, 2008.
11. Wingo PA, Ries LA, Giovino GA, et al: Annual report to the nation on the status of cancer, 1973–1996, with a special section on lung cancer and tobacco smoking. J Natl Cancer Inst 91:675–690, 1999.
12. Jemal A, Chu KC, Tarone RE: Recent trends in lung cancer mortality in the United States. J Natl Cancer Inst 93:277–283, 2001.
13. Shopland DR: Effect of smoking on the incidence and mortality of lung cancer. *In* Johnson BE, Johnson DH (eds): Lung Cancer. New York: John Wiley & Sons, 1995, pp 1–14.
14. McKay FW, Hanson MR, Miller RW: Cancer mortality in the United States: 1950–1977. Natl Cancer Inst Monogr 59:1–475, 1982.

15. Ries LAG, Miller BA, Hankey BF, et al: Cancer Statistics Review. Bethesda, MD: U.S. Government Printing Office, 1995, pp 1973–1991.
16. Horm JW, Cicero JB, SEER Program: Cancer Incidence and Mortality in the United States. Washington, DC: U.S. Government Printing Office, 1984, pp 1973–1981.
17. National Cancer Institute: National Cancer Institute SEER Website. Surveillance, Epidemiology, and End Results (SEER) Program. 2001. http://seer.cancer.gov/
18. Travis WD, Travis LB, Devesa SS: Lung cancer. Cancer 75:191–202, 1995.
19. Stewart SL, Cardinez CJ, Richardson LC, et al: Surveillance for cancers associated with tobacco use—United States, 1999–2004. MMWR Surveill Summ 57:1–33, 2008.
20. American Cancer Society: Cancer Facts & Figures for African Americans 2007–2008. Atlanta: American Cancer Society, 2007.
21. U.S. Department of Health and Human Services (USDHHS), Public Health Service, Centers for Disease Control and Prevention (CDC), National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health: Preventing Tobacco Use Among Young People: A report of the Surgeon General. Washington, DC: U.S. Government Printing Office, 1994.
22. American Cancer Society: Cancer Facts & Figures for Hispanics/Latinos 2006–2008. Atlanta: American Cancer Society, 2006.
23. McCracken M, Olsen M, Chen MS Jr, et al: Cancer incidence, mortality, and associated risk factors among Asian Americans of Chinese, Filipino, Vietnamese, Korean, and Japanese ethnicities. CA Cancer J Clin 57:190–205, 2007.
24. Pinsky PF: Racial and ethnic differences in lung cancer incidence: How much is explained by differences in smoking patterns? (United States). Cancer Causes Control 17:1017–1024, 2006.
25. Haiman CA, Stram DO, Wilkens LR, et al: Ethnic and racial differences in the smoking-related risk of lung cancer. N Engl J Med 354:333–342, 2006.
26. Coleman MP, Esteve J, Damiecki P, et al: Trends in Cancer Incidence and Mortality. Lyon, France: International Agency for Research on Cancer, 1993.
27. Gilliland FD, Samet JM: Lung cancer. Cancer Surv 19–20:175–195, 1994.
28. National Cancer Institute (NCI), Cancer Statistics Branch, and Division of Cancer Prevention and Control: Cancer rates and risks. Bethesda, MD: National Institutes of Health, 1996.
29. Parkin DM, Pisani P, Lopez AD, Masuyer E: At least one in seven cases of cancer is caused by smoking. Global estimates for 1985. Int J Cancer 59:494–504, 1994.
30. Boffetta P, Parkin DM: Cancer in developing countries. CA Cancer J Clin 44:81–90, 1994.
31. Stocks P, Campbell JM: Lung cancer death rates among non-smokers and pipe and cigarette smokers: An evaluation in relation to air pollution by benzpyrene and other substances. Br Med J 2:923–929, 1955.
32. Blot WJ, Fraumeni JF: Cancer Among Shipyard Workers Banbury Report 9. Quantification of Occupational Cancer. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory, 1981.
33. U.S. Cancer Statistics Working Group: United States Cancer Statistics: 2004 Incidence and Mortality. Atlanta: U.S. Department of Health and Human Services, Centers for Diseases Control and Prevention (CDC) and National Cancer Institute, 2007.
34. Churg A: Lung cancer cell type and asbestos exposure. In Samet JM (ed): Epidemiology of Lung Cancer. New York: Marcel Dekker, 1994, pp 413–436.
35. Parkin M, Samet J, Tyczynski JE, et al: Lung cancer epidemiology and etiology. *In* Travis W, Brambilla E, Müller-Hermelink H, Harris CC (eds): World Health Organization Classification of Tumours, International Agency for Research on Cancer, Pathology and Genetics of Tumours of the Lung, Pleura, Thymus and Heart. Lyon, France: International Agency for Research on Cancer, 2004, pp 12–15.
36. Brambilla E, Travis WD, Colby TV, et al: The new World Health Organization classification of lung tumours. Eur Respir J 18:1059–1068, 2001.
37. Wu-Williams AH, Samet JM: Lung cancer and cigarette smoking. *In* Samet JM (ed): Epidemiology of Lung Cancer. New York: Marcel Dekker, 1994, pp 71–108.
38. Wynder EL, Covey LS: Epidemiologic patterns in lung cancer by histologic type. Eur J Cancer Clin Oncol 23:1491–1496, 1987.
39. Wynder EL, Muscat JE: The changing epidemiology of smoking and lung cancer histology. Environ Health Perspect 103(Suppl 8):143–148, 1995.
40. National Research Council (NRC), Committee on Health Risks of Exposure to Radon, Board on Radiation Effects Research, and Commission on Life Sciences: Health Effects of Exposure to Radon (BEIR VI). Washington, DC: National Academy Press, 1999.
41. Thun MJ, Day-Lally CA, Myers DG, et al: Trends in tobacco smoking and mortality from cigarette use in Cancer Prevention Studies I (1959–1965) and II (1982–1988). *In* Burns DM, Garfinkel L, Samet JM (eds): Changes in Cigarette Related Disease Risks and Their Implication for Prevention and Control. Bethesda, MD: U.S. Government Printing Office, 1997, pp 305–382.
42. Charloux A, Quoix E, Wolkove N, et al: The increasing incidence of lung adenocarcinoma: Reality or artefact? A review of the epidemiology of lung adenocarcinoma. Int J Epidemiol 26:14–23, 1997.
43. Thun MJ, Lally CA, Flannery JT, et al: Cigarette smoking and changes in the histopathology of lung cancer. J Natl Cancer Inst 89:1580–1586, 1997.
44. Vincent RG, Pickren JW, Lane WW, et al: The changing histopathology of lung cancer: A review of 1682 cases. Cancer 39:1647–1655, 1977.
45. Janssen-Heijnen ML, Coebergh JW: Trends in incidence and prognosis of the histological subtypes of lung cancer in North America, Australia, New Zealand and Europe. Lung Cancer 31:123–137, 2001.
46. Hoffmann D, Hoffmann I: The changing cigarette, 1950–1995. J Toxicol Environ Health 50:307–364, 1997.
47. National Cancer Institute (NCI): The FTC Cigarette Test Method for Determining Tar, Nicotine, and Carbon Monoxide Yields of U.S. Cigarettes. Monograph 7. Bethesda, MD: National Institutes of Health, 1996.
48. Hecht SS, Samet JM: Cigarette smoking. *In* Rom WM (ed): Environmental and Occupational Medicine (4th ed). Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins, 2007, pp 1521–1551.
49. Samet JM, Cohen AJ: Air pollution and lung cancer. *In* Holgate ST, Samet JM, Koren HS, Maynard RL (eds): Air Pollution and Health. San Diego: Academic Press, 1999, pp 841–864.
49a. Samet JM, Avila-Tang E, Boffetta P, et al: Lung cancer in never smokers: clinical epidemiology and environmental risk factors. Clin Cancer Res 15:5626–5645, 2009.
50. Willett WC: Diet, nutrition, and avoidable cancer. Environ Health Perspect 103(Suppl 8):165–170, 1995.
51. National Institutes of Health (NIH) and National Cancer Institute: Smoking and Cigars: Health Effects and Trends. Tobacco Control Monograph 9. NIH Publication No. 98-4302 Bethesda, MD: U.S. Department of Health and Human Services, 1998.
52. Smoking-attributable mortality, years of potential life lost, and productivity losses—United States, 2000–2004. MMWR Morb Mortal Wkly Rep;57:1226–1228, 2008.
53. World Health Organization: WHO Report on the Global Tobacco Epidemic, 2008: The MPOWER Package. Geneva: World Health Organization, 2008.
54. Doll R, Peto R: Cigarette smoking and bronchial carcinoma: Dose and time relationships among regular smokers and lifelong non-smokers. J Epidemiol Community Health 32:303–313, 1978.
55. Peto R: Influence of dose and duration of smoking on lung cancer rates. *In* Zaridze D, Peto R (eds): Tobacco: A Major International Health Hazard. Proceedings of an International Meeting. Moscow, 4–6 June 1985. IARC Sci Publ no. 74. Lyon, France: World Health Organization, International Agency for Research on Cancer, 1986, pp 23–33.
56. U.S. Department of Health and Human Services (USDHHS): Smoking and Health: A National Status Report. Washington, DC: U.S. Government Printing Office, 1987.
57. U.S. Department of Health and Human Services (USDHHS): The Health Benefits of Smoking Cessation. A Report of the Surgeon General. DHHS Publication Number 90-8416. Washington, DC: U.S. Government Printing Office, 1990.

58. Hrubec Z, McLaughlin JK: Former cigarette smoking and mortality among U.S. veterans: A 26-year follow-up, 1954–1980. *In* Burns DM, Garfinkel L, Samet JM (eds): Changes in Cigarette-Related Disease Risks and Their Implication for Prevention and Control. Bethesda, MD: U.S. Government Printing Office, 1997, pp 501–530.
59. Hoffmann D, Hoffmann I, El-Bayoumy K: The less harmful cigarette: A controversial issue. A tribute to Ernst L. Wynder. Chem Res Toxicol 14:767–790, 2001.
60. Burns DM, Benowitz NL: Public health implications of changes in cigarette design and marketing. *In* Burns DM (ed): Risks Associated with Smoking Cigarettes with Low Machine-Measured Yields of Tar and Nicotine. Bethesda, MD: U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute, 2001, pp 1–12.
61. U.S. Department of Health and Human Services (USDHHS), National Cancer Institute: Risks Associated with Smoking Cigarettes with Low Machine-Measured Yields of Tar and Nicotine. Bethesda, MD: National Institutes of Health, 2001.
62. Blackford AL, Yang G, Hernandez-Avila M, et al: Cotinine concentration in smokers from different countries: Relationship with amount smoked and cigarette type. Cancer Epidemiol Biomarkers Prev 15:1799–1804, 2006.
63. U.S. Department of Health and Human Services (USDHHS): The Health Consequences of Smoking—The Changing Cigarette. A Report of the Surgeon General. Washington, DC: U.S. Government Printing Office, 1981.
64. Burns DM, Garfinkel L, Samet JM: Changes in Cigarette-Related Disease Risks and Their Implication for Prevention and Control. US Department of Health and Human Services (USDHHS), Public Health Service, and National Cancer Institute (NCI). Smoking and Tobacco Control Monograph. NIH Publication No. 97-4213. Bethesda, MD: U.S. Government Printing Office, 1997.
65. Thun MJ, Day-Lally CA, Calle EE, et al: Excess mortality among cigarette smokers: Changes in a 20-year interval. Am J Public Health 85:1223–1230, 1995.
66. Doll R, Peto R, Wheatley K, et al: Mortality in relation to smoking: 40 years' observations on male British doctors. BMJ 309:901–911, 1994.
67. Doll R, Peto R, Boreham J, Sutherland I: Mortality in relation to smoking: 50 years' observations on male British doctors. BMJ 328:1519, 2004.
68. Stratton K, Shetty P, Wallace R, Bondurant S: Clearing the Smoke: Assessing the Science Base for Tobacco Harm Reduction. Washington, DC: National Academy Press, 2001.
69. Hirayama T: Non-smoking wives of heavy smokers have a higher risk of lung cancer: A study from Japan. Br Med J 282:183–185, 1981.
70. Trichopoulos D, Kalandidi A, Sparros L, MacMahon B: Lung cancer and passive smoking. Int J Cancer 27:1–4, 1981.
71. National Research Council (NRC) and Committee on Passive Smoking: Environmental Tobacco Smoke: Measuring Exposures and Assessing Health Effects. Washington, DC: National Academy Press, 1986.
72. U.S. Department of Health and Human Services (USDHHS): The Health Consequences of Involuntary Smoking: A Report of the Surgeon General. DHHS Publication No. (CDC) 87-8398. Washington, DC: U.S. Government Printing Office, 1986.
73. California Environmental Protection Agency (Cal EPA) and Air Resources Board: Proposed Identification of Environmental Tobacco Smoke as a Toxic Air Contaminant. Sacramento, CA: California Environmental Protection Agency, 2005.
74. Fontham ET, Correa P, Reynolds P, et al: Environmental tobacco smoke and lung cancer in nonsmoking women. A multicenter study. JAMA 271:1752–1759, 1994.
75. Boffetta P, Agudo A, Ahrens W, et al: Multicenter case-control study of exposure to environmental tobacco smoke and lung cancer in Europe. J Natl Cancer Inst;90:1440–1450, 1998.
76. Hackshaw A: Passive smoking: Paper does not diminish conclusion of previous reports. BMJ 327:501–502, 2003.
77. Stayner L, Bena J, Sasco AJ, et al: Lung cancer risk and workplace exposure to environmental tobacco smoke. Am J Public Health 97:545–551, 2007.
78. World Cancer Research Fund and American Institute for Cancer Research: Food, Nutrition, Physical Activity, and the Prevention of Cancer: A Global Perspective. Washington, DC: American Institute for Cancer Research, 2007.
79. Lam TK, Gallicchio L, Lindsley K, et al: Cruciferous vegetable consumption and lung cancer risk: A systematic review. Cancer Epidemiol Biomarkers Prev 18:184–195, 2009.
80. Peto R, Doll R, Buckley JD, Sporn MB: Can dietary beta-carotene materially reduce human cancer rates? Nature 290:201–208, 1981.
81. Gallicchio L, Boyd K, Matanoski G, et al: Carotenoids and the risk of developing lung cancer: A systematic review. Am J Clin Nutr 88:372–383, 2008.
82. Cook NR, Le IM, Manson JE, et al: Effects of beta-carotene supplementation on cancer incidence by baseline characteristics in the Physicians' Health Study (United States). Cancer Causes Control 11:617–626, 2000.
83. Virtamo J, Pietinen P, Huttunen JK, et al: Incidence of cancer and mortality following alpha-tocopherol and beta-carotene supplementation: A postintervention follow-up. JAMA 290:476–485, 2003.
84. Goodman GE, Thornquist MD, Balmes J, et al: The Beta-Carotene and Retinol Efficacy Trial: Incidence of lung cancer and cardiovascular disease mortality during 6-year follow-up after stopping beta-carotene and retinol supplements. J Natl Cancer Inst 96:1743–1750, 2004.
85. Korte JE, Brennan P, Henley SJ, Boffetta P: Dose-specific meta-analysis and sensitivity analysis of the relation between alcohol consumption and lung cancer risk. Am J Epidemiol 155:496–506, 2002.
86. Siemiatycki J (ed): Risk Factors for Cancer in the Workplace. Boston: CRC Press, 1991.
87. Health Effects Institute, Asbestos Research Committee, and Literature Review Panel: Asbestos in Public and Commercial Buildings: A Literature Review and a Synthesis of Current Knowledge. Cambridge, MA: Health Effects Institute, 1991.
88. Doll R: Mortality from lung cancer in asbestos workers 1955. Br J Ind Med 50:485–490, 1993.
89. Selikoff IJ, Churg J, Hammond EC: Asbestos exposure and neoplasia. JAMA 188:22–26, 1964.
90. Selikoff IJ, Hammond EC, Seidman H: Mortality experience of insulation workers in the United States and Canada, 1943–1976. Ann N Y Acad Sci 330:91–116, 1979.
91. Selikoff IJ, Hammond EC, Seidman H: Latency of asbestos disease among insulation workers in the United States and Canada. Cancer 46:2736–2740, 1980.
92. Newhouse ML, Berry G: Patterns of mortality in asbestos factory workers in London. Ann N Y Acad Sci 330:53–60, 1979.
93. Lemen RA, Dement JM, Wagoner JK: Epidemiology of asbestos-related diseases. Environ Health Perspect 34:1–11, 1980.
94. Samet JM: Does idiopathic pulmonary fibrosis increase lung cancer risk? Am J Respir Crit Care Med 161:1–2, 2000.
95. Daniels CE, Jett JR: Does interstitial lung disease predispose to lung cancer? Curr Opin Pulm Med 11:431–437, 2005.
96. Henderson DW, Rodelsperger K, Woitowitz HJ, Leigh J: After Helsinki: A multidisciplinary review of the relationship between asbestos exposure and lung cancer, with emphasis on studies published during 1997–2004. Pathology 36:517–550, 2004.
97. Nelson HH, Kelsey K: The molecular epidemiology of asbestos and tobacco in lung cancer. Oncogene 21:7284–7288, 2002.
98. Hammond EC, Selikoff IJ, Seidman H: Asbestos exposure, cigarette smoking and death rates. Ann N Y Acad Sci 330:473–490, 1979.
99. Hendee WR: Estimation of radiation risks. BEIR V and its significance for medicine. JAMA 268:620–624, 1992.
100. National Research Council (NRC) and Committee on the Biological Effects of Ionizing Radiation: Health Risks of Radon and Other Internally Deposited Alpha-Emitters: BEIR IV. Washington, DC: National Academy Press, 1988.
101. Krewski D, Lubin JH, Zielinski JM, et al: A combined analysis of North American case-control studies of residential radon and lung cancer. J Toxicol Environ Health A 69:533–597, 2006.
102. Darby S, Hill D, Deo H, et al: Residential radon and lung cancer—Detailed results of a collaborative analysis of individual data on

7148 persons with lung cancer and 14,208 persons without lung cancer from 13 epidemiologic studies in Europe. Scand J Work Environ Health 32(Suppl 1):1–83, 2006.
103. Pawel DJ, Puskin JS: The U.S. Environmental Protection Agency's assessment of risks from indoor radon. Health Phys 87:68–74, 2004.
104. National Research Council (NRC) and Committee to Assess Health Risks from Exposure to Low Levels of Ionizing Radiation: BEIR VII Phase 2. Washington, DC: National Academy of Sciences, 2005.
105. Shimizu Y, Schull WJ, Kato H: Cancer risk among atomic bomb survivors. The RERF Life Span Study. Radiation Effects Research Foundation. JAMA 264:601–604, 1990.
106. Preston DL, Ron E, Tokuoka S, et al: Solid cancer incidence in atomic bomb survivors: 1958–1998. Radiat Res 168:1–64, 2007.
107. National Research Council (NRC), Commission on Life Sciences, Board on Toxicology and Environmental Health Hazards, and Committee on the Epidemiology of Air Pollutants: Epidemiology and Air Pollution. Washington, DC: National Academy Press, 1985, pp 1–224.
108. Doll R, Peto R: The causes of cancer: Quantitative estimates of avoidable risks of cancer in the United States today. J Natl Cancer Inst 66:1191–1308, 1981.
109. Cohen AJ, Samet JM: Air pollution and cancer. *In* Schottenfeld D, Fraumeni JF (eds) L Cancer Epidemiology and Prevention (3rd ed). New York: Oxford University Press, 2006, pp 355–381.
110. Cohen AJ, Ross Anderson H, Ostro B, et al: The global burden of disease due to outdoor air pollution. J Toxicol Environ Health A 68:1301–1307, 2005.
111. Vineis P, Husgafvel-Pursiainen K: Air pollution and cancer: Biomarker studies in human populations. Carcinogenesis 26: 1846–1855, 2005.
112. Speizer FE, Samet JM: Air pollution and lung cancer. *In* Samet JM (ed): Epidemiology of Lung Cancer. New York: Marcel Dekker, 1994, pp 131–150.
113. Beelen R, Hoek G, van den Brandt PA, et al: Long-term exposure to traffic-related air pollution and lung cancer risk. Epidemiology 19:702–710, 2008.
114. Laden F, Schwartz J, Speizer FE, Dockery DW: Reduction in fine particulate air pollution and mortality: Extended follow-up of the Harvard Six Cities study. Am J Respir Crit Care Med 173:667–672, 2006.
115. Pope CA 3rd, Burnett RT, Thun MJ, et al: Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution. JAMA 287:1132–1141, 2002.
116. Speizer FE: Assessment of the epidemiological data relating lung cancer to air pollution. Environ Health Perspect 47:33–42, 1983.
117. Dockery DW, Pope CA 3rd, Xu X, et al: An association between air pollution and mortality in six U.S. cities. N Engl J Med 329:1753–1759, 1993.
118. Pope CA 3rd, Thun MJ, Namboodiri MM, et al:. Particulate air pollution as a predictor of mortality in a prospective study of U.S. adults. Am J Respir Crit Care Med 151(3 Pt 1):669–674, 1995.
119. Katsouyanni K, Pershagen G: Ambient air pollution exposure and cancer. Cancer Causes Control 8:284–291, 1997.
120. Boffetta P, Nyberg F:. Contribution of environmental factors to cancer risk. Br Med Bull 68:71–94, 2003.
121. Spengler JD: Sources and concentrations of indoor air pollution. In Samet JM, Spengler JD (eds): Indoor Air Pollution. A Health Perspective. Baltimore: Johns Hopkins University Press, 1991, pp 33–67.
122. International Agency for Research on Cancer (IARC): Household Use of Solid Fuels and High-Temperature Frying. IARC monographs on the evaluation of carcinogenic risks to humans, Vol. 95. Lyon, France: International Agency for Research on Cancer, 2008.
123. Mumford JL, He XZ, Chapman RS, et al: Lung cancer and indoor air pollution in Xuan Wei, China. Science 235:217–220, 1987.
124. Mumford JL, Helmes CT, Lee XM, et al: Mouse skin tumorigenicity studies of indoor coal and wood combustion emissions from homes of residents in Xuan Wei, China, with high lung cancer mortality. Carcinogenesis 11:397–403, 1990.
125. Lan Q, Chapman RS, Schreinemachers DM, et al: Household stove improvement and risk of lung cancer in Xuanwei, China. J Natl Cancer Inst 94:826–835, 2002.
126. Xu ZY, Blot WJ, Xiao HP, et al:. Smoking, air pollution, and the high rates of lung cancer in Shenyang, China. J Natl Cancer Inst 81:1800–1806, 1989.
127. Wu-Williams AH, Dai XD, Blot W, et al: Lung cancer among women in north-east China. Br J Cancer 62:982–987, 1990.
128. Ger LP, Hsu WL, Chen KT, Chen CJ: Risk factors of lung cancer by histological category in Taiwan. Anticancer Res 13:1491–1500, 1993.
129. Lin HH, Murray M, Cohen T, et al: Effects of smoking and solid-fuel use on COPD, lung cancer, and tuberculosis in China: A time-based, multiple risk factor, modelling study. Lancet 372: 1473–1483, 2008.
130. Herbst RS, Heymach JV, Lippman SM: Lung cancer. N Engl J Med 359:1367–1380, 2008.
131. Gao YT, Blot WJ, Zheng W, et al:. Lung cancer among Chinese women. Int J Cancer 40:604–609, 1987.
132. Tokuhata GK, Lilienfeld AM: Familial aggregation of lung cancer among hospital patients. Public Health Rep 78:277–283, 1963.
133. Tokuhata GK: Familial factors in human lung cancer and smoking. Am J Public Health Nations Health 54:24–32, 1964.
134. Ooi WL, Elston RC, Chen VW, et al: Increased familial risk for lung cancer. J Natl Cancer Inst 76:217–222, 1986.
135. Samet JM, Humble CG, Pathak DR: Personal and family history of respiratory disease and lung cancer risk. Am Rev Respir Dis 134:466–470, 1986.
136. Tsugane S, Watanabe S, Sugimura H, et al: Smoking, occupation and family history in lung cancer patients under fifty years of age. Jpn J Clin Oncol 17:309–317, 1987.
137. Horwitz RI, Smaldone LF, Viscoli CM: An ecogenetic hypothesis for lung cancer in women. Arch Intern Med 148:2609–2612, 1988.
138. McDuffie HH: Clustering of cancer in families of patients with primary lung cancer. J Clin Epidemiol 44:69–76, 1991.
139. Osann KE: Lung cancer in women: The importance of smoking, family history of cancer, and medical history of respiratory disease. Cancer Res 51:4893–4897, 1991.
140. Shaw GL, Falk RT, Pickle LW, et al: Lung cancer risk associated with cancer in relatives. J Clin Epidemiol 44:429–437, 1991.
141. Filho YW, Magaldi C, Nakao N, Moncau JEC: Industrial work and lung cancer (Spanish). Rev Saude Publica 166–176, 1995.
142. Schwartz AG, Yang P, Swanson GM: Familial risk of lung cancer among nonsmokers and their relatives. Am J Epidemiol 144:554–562, 1996.
143. Wu AH, Fontham ET, Reynolds P, et al: Family history of cancer and risk of lung cancer among lifetime nonsmoking women in the United States. Am J Epidemiol 143:535–542, 1996.
144. Sellers TA, Bailey-Wilson JE, Elston RC, et al: Evidence for mendelian inheritance in the pathogenesis of lung cancer. J Natl Cancer Inst 82:1272–1279, 1990.
145. Braun MM, Caporaso NE, Page WF, Hoover RN: Genetic component of lung cancer: Cohort study of twins. Lancet 344:440–443, 1994.
146. Yang P, Schwartz AG, McAllister AE, et al: Lung cancer risk in families of nonsmoking probands: Heterogeneity by age at diagnosis. Genet Epidemiol 17:253–273, 1999.
147. Vineis P, Caporaso N: Tobacco and cancer: Epidemiology and the laboratory. Environ Health Perspect 103:156–160, 1995.
148. Jones PA, Baylin SB: The fundamental role of epigenetic events in cancer. Nat Rev Genet 3:415–428, 2002.
149. Herman JG, Baylin SB: Gene silencing in cancer in association with promoter hypermethylation. N Engl J Med 349:2042–2054, 2003.
150. Belinsky SA, Nikula KJ, Palmisano WA, et al: Aberrant methylation of p16(INK4a) is an early event in lung cancer and a potential biomarker for early diagnosis. Proc Natl Acad Sci U S A 95:11891–11896, 1998.
151. Palmisano WA, Divine KK, Saccomanno G, et al: Predicting lung cancer by detecting aberrant promoter methylation in sputum. Cancer Res 60:5954–5958, 2000.

152. Hussain SP, Harris CC: Molecular epidemiology of human cancer: Contribution of mutation spectra studies of tumor suppressor genes. Cancer Res 58:4023–4037, 1998.
153. International Agency for Research on Cancer (IARC): IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans: Tobacco Smoking. [Monograph 38]. Lyon, France: World Health Organization, IARC, 1986.
154. Garte S, Zocchetti C, Taioli E: Gene-environment interactions in the application of biomarkers of cancer susceptibility in epidemiology. IARC Sci Publ 142:251–264, 1997.
155. Vineis P, Veglia F, Benhamou S: CYP1A1 T3801 C polymorphism and lung cancer: A pooled analysis of 2451 cases and 3358 controls. Int J Cancer 104:650–657, 2003.
156. Le Marchand L, Guo C, Benhamou S, et al: Pooled analysis of the CYP1A1 exon 7 polymorphism and lung cancer (United States). Cancer Causes Control 14:339–346, 2003.
157. Benhamou S, Lee WJ, Alexandrie AK, et al: Meta- and pooled analyses of the effects of glutathione S-transferase M1 polymorphisms and smoking on lung cancer risk. Carcinogenesis 23: 1343–1350, 2002.
158. Berwick M, Vineis P: Markers of DNA repair and susceptibility to cancer in humans: An epidemiologic review. J Natl Cancer Inst 92:874–897, 2000.
159. Goode EL, Ulrich CM, Potter JD: Polymorphisms in DNA repair genes and associations with cancer risk. Cancer Epidemiol Biomarkers Prev 11:1513–1530, 2002.
160. Gao WM, Romkes M, Day RD, et al: Association of the DNA repair gene XPD Asp312Asn polymorphism with p53 gene mutations in tobacco-related non–small cell lung cancer. Carcinogenesis 24:1671–1676, 2003.
161. Liang G, Xing D, Miao X, et al: Sequence variations in the DNA repair gene XPD and risk of lung cancer in a Chinese population. Int J Cancer 105:669–673, 2003.
162. Thorgeirsson TE, Geller F, Sulem P, et al: A variant associated with nicotine dependence, lung cancer and peripheral arterial disease. Nature 452:638–642, 2008.
163. Hung RJ, McKay JD, Gaborieau V, et al: A susceptibility locus for lung cancer maps to nicotinic acetylcholine receptor subunit genes on 15q25. Nature 452:633–637, 2008.
164. Amos CI, Wu X, Broderick P, et al: Genome-wide association scan of tag SNPs identifies a susceptibility locus for lung cancer at 15q25.1. Nat Genet 40:616–622, 2008.
165. Liu P, Vikis HG, Wang D, et al: Familial aggregation of common sequence variants on 15q24-25.1 in lung cancer. J Natl Cancer Inst 100:1326–1330, 2008.
166. Kirk GD, Merlo C, O'Driscoll P, et al: HIV infection is associated with an increased risk for lung cancer, independent of smoking. Clin Infect Dis 45:103–110, 2007.
167. Powles T, Thirwell C, Newsom-Davis T, et al: Does HIV adversely influence the outcome in advanced non–small-cell lung cancer in the era of HAART? Br J Cancer 89:457–459, 2003.
168. Bower M, Powles T, Nelson M, et al: HIV-related lung cancer in the era of highly active antiretroviral therapy. AIDS 17:371–375, 2003.
169. Spina M, Sandri S, Serraino D, et al:. Therapy of non–small-cell lung cancer (NSCLC) in patients with HIV infection. GICAT. Cooperative Group on AIDS and Tumors. Ann Oncol 10(Suppl 5):S87–390, 1999.
170. Vyzula R, Remick SC: Lung cancer in patients with HIV-infection. Lung Cancer 15:325–339, 1996.
171. Tirelli U, Spina M, Sandri S, et al: Lung carcinoma in 36 patients with human immunodeficiency virus infection. The Italian Cooperative Group on AIDS and Tumors. Cancer 88:563–569, 2000.
172. Parker MS, Leveno DM, Campbell TJ, et al: AIDS-related bronchogenic carcinoma: Fact or fiction? Chest 113:154–161, 1998.
172a. Shiels MS, Cole SR, Kirk GD, Poole C: A meta-analysis of the incidence of non-AIDS cancers in HIV-infected individuals. J Acquir Immune Defic Syndr Sept 17 (Epub ahead of print) 2009.
173. Cotran RS, Kumar V, Robbins SL (eds): Robbins Pathologic Basis of Disease (5th ed). Philadelphia: WB Saunders, 1994.
174. Sin DD, Man SF: Impact of cancers and cardiovascular diseases in chronic obstructive pulmonary disease. Curr Opin Pulm Med 14:115–121, 2008.
174a. Koshiol J, Rotunno M, Consonni D, et al: Chronic obstructive pulmonary disease and altered risk of lung cancer in a population-based case-control study. PLoS ONE 4:e7380, 2009.
175. U.S. Department of Health and Human Services (USDHHS): The Health Consequences of Smoking—Chronic Obstructive Lung Disease. A Report of the Surgeon General. Washington, DC: U.S. Government Printing Office, 1984.
176. Boffetta P: Human cancer from environmental pollutants: The epidemiological evidence. Mutat Res 608:157–162, 2006.
177. Ng TP: Silica and lung cancer: A continuing controversy. Ann Acad Med Singapore 23:752–755, 1994.
178. Pairon JC, Brochard P, Jaurand MC, Bignon J: Silica and lung cancer: A controversial issue. Eur Respir J 4:730–744, 1991.
179. Smith AH, Lopipero PA, Barroga VR: Meta-analysis of studies of lung cancer among silicotics. Epidemiology 6:617–624, 1995.
180. Barrett JC, Lamb PW, Wiseman RW: Multiple mechanisms for the carcinogenic effects of asbestos and other mineral fibers. Environ Health Perspect 81:81–89, 1989.
181. Henschke CI, Miettinen OS: Women's susceptibility to tobacco carcinogens. Lung Cancer 43:1–5, 2004.
182. Bain C, Feskanich D, Speizer FE, et al: Lung cancer rates in men and women with comparable histories of smoking. J Natl Cancer Inst 96:826–834, 2004.
183. Perneger TV: Sex, smoking, and cancer: A reappraisal. J Natl Cancer Inst 93:1600–1602, 2001.
184. Kreuzer M, Boffetta P, Whitley E, et al: Gender differences in lung cancer risk by smoking: A multicentre case-control study in Germany and Italy. Br J Cancer 82:227–233, 2000.
185. U.S. Department of Health and Human Services (USDHHS): Tobacco use among U.S. racial/ethnic minority groups: African Americans, American Indians and Alaska Natives, Asian Americans and Pacific Islanders, Hispanics. A Report of the Surgeon General. Washington, DC: USDHHS, 1998.
186. Ernster VL: Impact of tobacco on women's health. *In* Samet JM, Yoon S-Y (eds): Women and the Tobacco Epidemic: Challenges for the 21st Century. Geneva: World Health Organization, 2001, pp 1–16.

CHAPTER 47

CLINICAL ASPECTS OF LUNG CANCER

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INTRODUCTION

Lung cancer is the most common cause of cancer deaths worldwide. In the United States, lung cancer accounted for an estimated 215,000 cases of cancer and 161,840 cancer deaths in 2008. Although Chapter 46 is dedicated to the epidemiology of lung cancer, some of the information found therein is worth repeating. For example, added together, the number of cancer deaths from breast, colon, and prostate cancer each year would not equal the number of cancer deaths related or due to lung cancer. A common misconception among the general public is that breast cancer accounts for more cancer deaths in women. However, lung cancer will account for 25% of cancer-related deaths among women in the United States. A total of 71,000 women were expected to die from this disease in 2008. Particularly alarming is the fact that young women are the fastest-rising demographic of new cigarette smokers in the United States. Many have clearly made the association between weight control and cigarette smoking. This will have effects on the prevalence of lung cancer in the decades to come.

One of the more disturbing trends in lung cancer is the explosion in rates of lung cancer in countries of the developing world. In 1985, it was estimated that there were 921,000 lung cancer deaths worldwide—an increase of 17% from 1980.[1] The International Agency for Research on Cancer in France found that the rates of lung cancer in Africa in the early 1990s were similar to those in the United States in the 1930s, at about

5/100,000. By 1999, the rate of lung cancer in males of developing countries was 14/100,000 and on the rise, compared with a rate of 71/100,000 in developed countries, which continues to decline. These rates may actually be underestimates of the true rates of lung cancer, because many cases may go undiagnosed or underreported in areas where health care is not readily available.[1] An example of how serious this problem has become is found in China, where it is estimated that nearly 800,000 Chinese men died of lung cancer in 1998.[1] At present, Chinese men smoke an average of 11 cigarettes/day, which is equivalent to the highest average rates of smoking ever seen among males in the United States. In fact, the consumption of cigarettes in China alone may surpass that of all developed countries combined.[1,2] Overall, 66.9% of Chinese men smoke. In view of such statistics, it is imperative that the medical community devotes much of its educational efforts and resources toward the elimination of cigarette smoking worldwide, which would nearly eliminate the development of lung cancer.

This chapter reviews the current strategies for the diagnosis, introduces the new staging system, and describes the current treatment of lung cancer. As much as possible, evidence-based review of the best currently available literature has been included. An extended section on computed tomography (CT) screening for lung cancer is presented because the question of whether or not to screen for lung cancer on a routine basis will be one that pulmonologists will face for years to come. The role of the pulmonologist is described for every aspect of lung cancer care, from diagnosis to staging to caring for the complications of the disease itself and the complications of cancer treatment.

SCREENING FOR LUNG CANCER

The current position of the American Cancer Society and the U.S. Preventive Services Task Force is that there is no role for screening for lung cancer, even in high-risk individuals.[3] This position is based on the results of five randomized, controlled trials that suggest that neither chest radiography nor sputum cytology satisfies the primary criterion of a beneficial screening test: reduction in lung cancer mortality.[4–6] There continues to be ongoing debate about the interpretation of these studies. One deficiency is that most of these studies did not include a "no screening" arm. Others have argued that the sample size of the studies was inadequate. The Mayo Lung Project and the Czechoslovakian studies were powered to detect a 50% reduction in lung cancer mortality in the screened group and could have missed detecting a 20% to 30% reduction.[4,7] An ongoing trial sponsored by the National Cancer Institute (Prostate, Lung, Colorectal, and Ovarian Trial) is a randomized trial of chest radiography versus no screen in a low-risk population of both genders. It is powered to detect a 10% reduction in mortality due to lung cancer. Accrual to this study has been completed, but the final results will not be available for several years.

CT has been shown to be much more sensitive for detecting pulmonary nodules than the standard chest radiograph. As of 2003, there have been at least six reports of single-arm screening trials utilizing low-dose spiral computed tomography (LD-CT), defined as a single breath-hold scan that exposes the patient to five to six times less radiation dose than a standard CT scan, with or without sputum cytology.[4,8–13] These trials have consistently shown that spiral CT detects more lung cancers than chest radiography. The study by Sone and colleagues[11] from Japan detected 44 lung cancers with spiral CT, only 11 of which were visible by chest radiography. Similarly, the New York study detected 27 lung cancers with CT, only 7 of which were visible on chest radiograph.[9] The LD-CT studies have consistently shown a high prevalence of noncalcified nodules. In general, it appears that the thinner the CT slices, the more noncalcified nodules are detected. A study from Germany with 5-mm slices detected at least one noncalcified nodule in 43% of 817 participants screened,[8] and a report from Mayo Clinic investigators observed noncalcified nodules in 51% of individuals with 5-mm slices and 3.75-mm reconstruction intervals.[13] The number of noncalcified nodules detected is increasing as centers begin to use 8- and 16-multislice detector scanners and decreasing slice thickness. In the Mayo Clinic trial, only 1.7% of the noncalcified nodules were subsequently shown to be malignant. However, once found, all noncalcified nodules must be followed up with CT at some interval (at least yearly), which adds to the cost of screening. Studies are under way to try to determine the optimum follow-up and evaluation algorithm, although the best algorithm to date appears to be that set forth by the Fleischner Society.[14]

Recently, a large multicenter, multinational, nonrandomized trial named the International Early Lung Cancer Action Program (I-ELCAP) was reported.[15] The I-ELCAP screened 31,567 subjects using LD-CT. Lung cancer was identified in 484 patients, with 412 having stage I disease. The estimated 10-year survival was 80% for all patients regardless of stage and treatment, and 88% for stage I cancer. This study confirmed earlier observations that lung cancers detected by CT screening are very early stage and highly treatable.

Although this study provides a basis for optimism, it is insufficient to confirm the effectiveness of LD-CT screening for lung cancer. Welch and coworkers[16] nicely summarize the key elements missing from this trial. First is the lack of a control group, which would allow one to understand what would happen to a similar group of subjects in the absence of screening. Second is the absence of an unbiased outcome measure, which would control for the confounding features of *lead-time bias*, *length-time bias*, and *overdiagnosis* that can lead to an apparent increase in survival without actually changing the overall mortality of those with lung cancer. *Lead-time bias* is the detection of tumors earlier in their course; *length-time bias* is the greater detection of less aggressive, slower-growing tumors than more aggressive, faster-growing tumors; and *overdiagnosis* is the detection of tumors that would otherwise

never cause symptoms or death. Third, the study does not take into account what is already known about lung cancer screening, particularly the evidence for overdiagnosis bias arising in single-arm studies from Japan.[17] Finally, although the I-ELCAP accentuates the positives of screening, it does not account for potential harm; particularly the unnecessary workup or therapy for benign disease.[17a]

In contrast to the optimistic findings published by the I-ELCAP investigators, Bach and associates[18] examined three single-arm studies conducted in Milan, Rochester, and Florida that screened 3246 high-risk subjects with annual CT scans with a median follow-up of 3.9 years. The frequency of observed new lung cancer cases, lung cancer resections, advanced lung cancer cases, and deaths from lung cancer was compared with the expected number of cases based on two validated models. There were 144 individuals diagnosed with lung cancer compared with 44.5 expected cases (relative risk [RR], 3.2; 95% confidence interval [CI], 2.7–3.8; $P < .001$). The rate of lung cancer resection was 10-fold higher, 109 resected compared with 10.9 expected cases that were predicted for that cohort (RR, 10.0; 95% CI, 8.2–11.9; $P < .001$). The survivorship of those stage I patients resected was similar to that seen by the I-ELCAP investigators There were 42 cases of advanced lung cancer compared with 33.4 expected cases, and 38 deaths, which is what was predicted for that cohort (RR, 1.0; 95% CI, 0.7–1.3; $P = .90$). This study showed that screening with LD-CT may increase the rate of lung cancer detected and resected, but may not reduce the risk of advanced lung cancer or overall mortality from lung cancer. Screening for lung cancer can be shown to be of benefit only when it is found to decrease the overall mortality from the disease.

The LD-CT trials have consistently detected non–small cell lung cancer (NSCLC) as stage IA in 60% to 90% of cases, and early survival data from Japan suggest a major improvement in 5-year survival.[10] However, it is not possible to determine if this is due to lead-time bias, length-time bias, or overdiagnosis.[19] None of the trials reported to date has had a control arm for comparison and, without the comparison group, screening with LD-CT has not yet been shown to reduce lung cancer mortality. A reduction in lung cancer mortality is the primary end point of the National Lung Cancer Screening Trial (NLST). This trial has randomized 50,000 high-risk participants to screening with LD-CT or chest radiography. Subjects were screened yearly for 3 years and are currently in follow-up for 5 years. The trial is powered to detect a 20% reduction in lung cancer mortality. The NLST completed accrual in early 2004, but final results may not be available until 2010. Until the result of the NLST is known, the American College of Chest Physician guidelines recommend that individuals should be screened with LD-CT only in the context of well-designed clinical trials. The guideline recommends against the use of single LD-CT or serial LD-CT to screen for lung cancer in individuals without symptoms or a history of cancer.[20]

PRESENTATION

Unfortunately, the symptoms of lung cancer can be nonspecific, thereby delaying the diagnoses for patients who present with this disease and leading to an advanced stage at the time of diagnosis. Approximately 40% of patients in a screened population and 98% of patients in a hospitalized population will present with symptoms.[7,21] Table 47-1 displays some of the common symptoms associated with the presentation of lung cancer. Most are nonspecific; however, some clues can be gained from the history, thus raising the clinician's suspicion that lung cancer is present. Although many smokers cough, lung cancer patients usually admit to a change in the character of their cough. The cough can increase in frequency or strength or may not be relieved with local measures. Chest pain can be present in 25% to 50% of patients at the time of presentation for evaluation for lung cancer.[21,22] The pain is generally dull in nature, tends to be persistent, remains in the same location, and is not relieved with local measures. Chest pain is usually related to involvement of the pleura but can be related to extension into the mediastinum or chest wall. Chest pain in and of itself does not preclude the patient from consideration for surgery with curative intent. Dyspnea is frequently a complaint of patients who present with bronchogenic carcinoma, occurring in half of all new patients at presentation.[21] A partial list of the reasons for dyspnea related to lung cancer includes pulmonary embolism, superior vena cava syndrome, deconditioning, reactive airway disease, endobronchial obstruction with tumor, prior obstructive pneumonia, hemoptysis, hemorrhage, malignant pleural effusion, and extrinsic compression of the airway by tumor.

Hemoptysis in a smoker should always raise the suspicion of lung cancer. Hemoptysis can present as blood streaking of the sputum and can be noted over a lengthy period of time before presentation to the physician's office because it is attributed to smoking-related bronchitis. The clinician should not be led astray, even if the chest radiograph is normal, because up to 5% of those patients with a smoking history and a normal radiograph

TABLE 47-1. Presenting Symptoms with Bronchogenic Carcinoma

Symptoms	Patients (%)
Cough	45–75
Weight loss	8–68
Dyspnea	37–58
Hemoptysis	27–57
Chest pain	27–49
Hoarseness	2–18

From Midthun DE, Jett JR: Clinical presentation of lung cancer. *In* Pass HI, Mitchell JB, Johnson DH, et al (eds): Lung Cancer: Principles and Practice. Philadelphia: Lippincott-Raven, 1996, p 422.

can harbor lung cancer.[23] Because of the vascular nature of lung cancer, patients can also present with massive hemoptysis. Weight loss, a nonspecific symptom, in the right clinical setting should raise the suspicion of both lung cancer and metastatic disease. Weight loss alone has been correlated with an advanced presentation and poor outcome from lung cancer.

In summary, patients with lung cancer can present asymptomatically or with relatively nonspecific symptoms of underlying pulmonary disease. There are often clues in the history that should alert the clinician that lung cancer is a possibility and further investigation is warranted.

LUNG CANCER STAGING

Perhaps the most critical role of the pulmonologist in the management of lung cancer is in the diagnostic and staging evaluation of the patient. Accurately staging patients with newly diagnosed lung cancer is critical because staging dictates the patient's treatment options and predicts survival. It is intuitive that early-stage disease has a much better survival than late-stage disease. What may not be so obvious is that simple staging procedures are available to the diagnostician that can help stage patients accurately. The treatment options for lung cancer have now evolved so that treatment for patients in different stages is vastly different. In general, early-stage lung cancer (stage I) is treated with surgery alone. Stage II lung cancer is treated with surgery followed by adjuvant chemotherapy. Locally advanced lung cancer (stage IIIA and B) is treated with a combination of chemotherapy and radiotherapy, and stage IV (metastatic disease) is treated with chemotherapy alone. However, there are important exceptions to these general rules that are discussed later in this chapter.

The staging of NSCLC using the tumor-node-metastasis (TNM) classification underwent revision in 1997 and has recently undergone a major revision.[24,25] The new staging system is remarkable in that it is based on over 100,000 cases of lung cancer from 23 institutions, 12 countries, and 3 continents. The data are robust, internally validated, and externally validated against the Surveillance Epidemiology and End Results (SEER) cancer registry.[25] Tables 47-2 and 47-3 show the revised TNM descriptors and stage groupings.

There are several important changes adopted in the new staging system. The main modifications are in the T and M classification; the N status will remain the same. Within the T classification, tumor size was found to be an important prognosticator and the T factor was subdivided based upon five different size criteria. Because survivorship was better than previously thought, a primary tumor with satellite nodules in the same lobe was reclassified from T4 to T3 and a tumor with additional nodules in a different lobe of the ipsilateral lung was moved from an M1 designation to T4. This change in classification and stage will allow more patients to be considered for surgery. Malignant pleural effusion was reclassified from T4 (or stage IIIB) disease to M1 disease because the survival of patients in this group was found to resemble metastatic disease more than locally advanced disease. Another significant change is that the M status is now split into M1a (metastatic disease confined to the chest) and M1b (extrathoracic metastatic disease) because survival was found to be better in those patients with metastatic disease confined to the thorax compared with those with extrathoracic metastases.

Whereas the TNM staging system is applied to NSCLC, a more simplified version is employed for patients with small cell lung cancer. In this classification, patients are classified as having limited or extensive disease. Limited disease (LD) is disease limited to one hemithorax, although it can include supraclavicular and mediastinal lymphadenopathy; extensive disease (ED) is any disease outside of the hemithorax. The implication in this classification is that LD is treated with chemotherapy and radiotherapy and ED is treated with chemotherapy alone.[26] Malignant pleural effusion can technically be categorized as LD in the staging classification for small cell lung cancer if the patient otherwise meets criteria. However, for all intents and purposes, patients with malignant pleural effusions and small cell lung cancer have the same characteristics as those with ED, and the large cooperative group trials have treated them as such.

Some important nuances to staging are described in detail later in this chapter. However, there are certain tenets of staging that must be emphasized. Prior to classifying a patient within a certain stage, the clinician should make every effort to verify any noninvasive radiologic findings with tissue confirmation of malignancy. This is particularly important in cases in which surgical resection would be precluded based on noninvasive radiologic tests. Thus, a patient who would otherwise be resectable except for a single abnormality suspicious for metastasis should have tissue confirmation of that abnormality prior to being deemed unresectable. As is pointed out later in this chapter, no noninvasive radiologic study is infallible. In studies of the mediastinum, false-positive findings range from 12% in positron emission tomography (PET) scans to 20% in CT scans with lower false-positive findings using integrated PET-CT, at the cost of lower sensitivity.[27,28] Therefore, reliance on the scan alone to predict malignancy is simply not sufficient.

Staging can be accomplished by a number of noninvasive and invasive studies. The choice of the most appropriate study rests with the clinician and is based upon how the patient presents. Some patients—for example, those with isolated solitary pulmonary nodules—may be referred for immediate surgical resection as both a diagnostic and a therapeutic maneuver. Others, such as those with extremely poor performance status or those suspected of widely metastatic disease, may undergo no testing at all. The next sections present a discussion of the attributes of each of the staging options available. For ease of understanding, they are divided into noninvasive and invasive techniques.

TABLE 47-2. Tumor-Node-Metastasis (TNM) Descriptors in the Revised 7th Edition of the TNM Classification of Lung Cancer

T (PRIMARY TUMOR)	
TX	Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor ≤3 cm in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus)[a]
T1a	Tumor ≤2 cm in greatest dimension
T1b	Tumor >2 cm but ≤3 cm in greatest dimension
T2	Tumor >3 cm but ≤7 cm or tumor with any of the following features (T2 tumors with these features are classified T2a if ≤5 cm)
	Involves main bronchus, ≥2 cm distal to the carina
	Invades visceral pleura
	Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung
T2a	Tumor >3 cm but ≤5 cm in greatest dimension
T2b	Tumor >5 cm but ≤7 cm in greatest dimension
T3	Tumor >7 cm or one that directly invades any of the following: chest wall (including superior sulcus tumors), diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium; or tumor in the main bronchus <2 cm distal to the carina[a] but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung or separate tumor nodule(s) in the same lobe
T4	Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina; separate tumor nodule(s) in a different ipsilateral lobe
N (REGIONAL LYMPH NODES)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)
M (DISTANT METASTASIS)	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
M1a	Separate tumor nodule(s) in a contralateral lobe; tumor with pleural nodules or malignant pleural (or pericardial) effusion[b]
M1b	Distant metastasis

[a]The uncommon superficial spreading tumor of any size with its invasive component limited to the bronchial wall, which may extend proximally to the main bronchus, is also classified at T1.

[b]Most pleural (and pericardial) effusions with lung cancer are due to tumor. In a few patients, however, multiple cytopathologic examinations of pleural (pericardial) fluid are negative for tumor, and the fluid is nonbloody and is not an exudate. Where these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging element and the patient should be classified as T1, T2, T3, or T4.

From Goldstraw P, Crowley J, Chansky K, et al: The IASLC Lung Cancer Staging Project. J Thorac Oncol 2:709, 2007.

NONINVASIVE STAGING TECHNIQUES

Chest Radiography

The majority of lung cancers are detected initially by plain chest radiograph. In certain situations, the plain film may be sufficient to detect spread to the mediastinum. For example, the presence of bulky lymphadenopathy in the superior or contralateral mediastinal areas may be considered adequate evidence of metastatic disease to preclude further imaging evaluation of the chest. This may be particularly true if the patient is too ill or unwilling to undergo treatment of any kind. Still, most patients should undergo CT scan of the chest unless they are so debilitated that no further evaluation or treatment is planned. The chest radiograph is simply too insensitive a measure of mediastinal lymph node involvement with lung cancer, and thus, further noninvasive or invasive assessment is usually necessary.

Computed Tomography of the Chest

The vast majority of patients who present with lung cancer will undergo CT scanning of the chest. CT is helpful in defining the size, location, and characteristics of the primary mass (e.g., smooth-bordered, spiculated, calcified), the presence or absence of lymphadenopathy and, if performed through the adrenal glands, the presence of abnormalities in the liver and adrenal glands. The bony structures of the thoracic cavity can also be evaluated by chest CT.

TABLE 47-3. Stage Groupings in the Revised 7th Edition of the TNM Classification of Lung Cancer

Sixth Edition T/M Descriptor	Proposed T/M	N0	N1	N2	N3
T1 (≤2 cm)	T1a	IA	IIA	IIIA	IIIB
T1 (>2–3 cm)	T1b	IA	IIA	IIIA	IIIB
T2 (>3–5 cm)	T2a	IB	**IIA**	IIIA	IIIB
T2 (>5–7 cm)	T2b	**IIA**	IIB	IIIA	IIIB
T2 (>7 cm)	T3	**IIB**	**IIIA**	IIIA	IIIB
T3 (invasion)		IIB	IIIA	IIIA	IIIB
T4 (same lobe nodules)		**IIB**	**IIIA**	**IIIA**	IIIB
T4 (extension)	T4	**IIIA**	**IIIA**	IIIB	IIIB
M1 (ipsilateral lung)		**IIIA**	**IIIA**	**IIIB**	**IIIB**
T4 (pleural effusion)	M1a	**IV**	**IV**	**IV**	**IV**
M1 (contralateral lung)		IV	IV	IV	IV
M1 (distant)	M1b	IV	IV	IV	IV

Cells in **bold** indicate a change from the sixth edition for a particular TNM category.
From Goldstraw P, Crowley J, Chansky K, et al: The IASLC Lung Cancer Staging Project. J Thorac Oncol 2:709, 2007.

CT of the chest is the most widely available and commonly used noninvasive modality for evaluation of the mediastinum in lung cancer. Numerous studies of CT have been performed comparing clinical staging by CT with the "gold standards" of mediastinoscopy or surgery. The results demonstrated that regardless of the lymph node size used as a threshold for defining malignant adenopathy, CT findings in isolation could not be considered as conclusive evidence that lymph nodes were malignant. In other words, in all studies, there are meaningful numbers of false positives detected by CT scan. The vast majority of reports evaluating the accuracy of CT scanning for mediastinal lymph node staging have employed the administration of intravenous contrast material. Although contrast is not absolutely necessary in performing chest CT for this indication, it is useful in helping to distinguish vascular structures from lymph nodes as well as in delineating mediastinal invasion by centrally located tumors. The most widely accepted criterion for an abnormal lymph node is a short-axis lymph node diameter of 1 cm or greater on CT.

The American College of Chest Physicians (ACCP) compiled the studies assessing the performance characteristics of CT scan for staging the mediastinum in a meta-analytic format.[28] Thirty-five studies were identified, comprising 5111 evaluable patients. The pooled sensitivity of CT scanning for staging the mediastinum was 51% (95% CI, 47%–54%) and the pooled specificity was 86% (95% CI, 84%–88%). The corresponding positive and negative likelihood ratios were 3.4 and 0.6, respectively, confirming that CT scanning has a limited ability either to rule in or to exclude mediastinal metastasis.[28] However, because CT usually guides the selection of nodes for biopsy by mediastinoscopy or needle aspiration, it remains an important diagnostic tool in lung cancer. Accurate noninvasive node staging is essential because the choice of individual nodes for sampling by minimally invasive techniques, including transbronchial, transthoracic, or transesophageal needle aspiration, will be directed by the findings of the CT scan. The limitation of CT-based mediastinal lymph node evaluation is evident in the fact that 5% to 15% of patients with clinical T1N0 lesions will be found to have positive lymph node involvement by surgical lymph node sampling.[29] Perhaps the most important message in evaluating the accuracy of CT scanning is that approximately 40% of all nodes deemed malignant by CT criteria are actually benign, depending on the patient population.[30] Specificity can be affected by clinical factors such as the presence of obstructive pneumonitis.[30] There is no node size that can reliably determine stage and operability. In cases in which the CT criteria for identification of a metastatic node are met, the clinician must still prove beyond reasonable doubt by biopsy or resection that the node is indeed malignant. Given the limitations of the imperfect sensitivity and specificity of CT, it is usually inappropriate to rely solely on the CT scan to determine mediastinal lymph node status. Nonetheless, CT continues to play an important and necessary role in the evaluation of patients with lung cancer and is recommended as part of the evaluation of patients who present with newly diagnosed or suspected lung cancer.[28]

CT can also be helpful in the evaluation of pleural effusion in patients with lung cancer. The CT scan can indicate the presence or absence of fluid, the contour of the pleural space, and whether or not nodules or masses are present on the pleural surface. However, the clinician should interpret these findings with caution because pleural disease can predate cancer and the presence of pleural effusion does not guarantee that the cytology will be positive. This is an important staging issue because the finding of malignant pleural effusion in NSCLC is now considered as evidence of metastatic disease or stage IV. If the pleural fluid has benign cytology (e.g., fluid from obstructive pneumonia), then the patient may still be considered for surgical resection. To resolve this issue, recommendations have been made to perform thoracentesis with cytology on two separate occasions, followed by thoracoscopy to evaluate the pleural surface directly. If the patient remains cytology-negative, then the stage and treatment offered should reflect the lower stage. CT is often inaccurate in differentiating direct tumor invasion of the visceral pleura (T2) from that of the parietal pleura or chest wall (T3). Thoracoscopy can be helpful in differentiating the extent of the primary tumor involvement into or through the pleural but, at times, open thoracotomy is needed to sort out this issue. (For a further discussion of these issues, see Chapters 23 and 75.)

Positron Emission Tomography

Perhaps the single most notable addition to the staging armamentarium for the evaluation of lung cancer is PET. With the image created by the biologic activity of neoplastic cells, PET is a metabolic imaging technique based on the function of a tissue rather than on its anatomy. Lung cancer cells demonstrate increased cellular uptake

of glucose and a higher rate of glycolysis when compared with normal cells.[31] The radiolabeled glucose analogue [^{18}F]fluoro-2-deoxy-D-glucose (FDG) undergoes the same cellular uptake as glucose but, after phosphorylation, is not further metabolized and becomes trapped in cells.[32] Accumulation of the isotope can then be identified using a PET detector. Specific criteria for an abnormal PET scan are either a standard uptake value of greater than 2.5 or uptake in the lesion that is greater than the background activity of the mediastinum. It has proved useful in differentiating neoplastic from normal tissues. In two well-performed studies that evaluated the use of PET in the preoperative setting for lung cancer,[33,34] nearly 20% of patients were staged differently after evaluation by PET scan. However, the technique is not infallible because certain non-neoplastic processes, including granulomatous and other inflammatory diseases as well as infections, may also demonstrate positive PET imaging. Furthermore, size limitations are also an issue, with the lower limit of resolution of the study being approximately 7 to 8 mm depending on the intensity of uptake of the isotope in the abnormal cells.[33] One should not rely on a negative PET finding for lesions less than 1 cm on CT scan.

A burgeoning number of studies in the last several years have reported on the utility of FDG-PET scanning in the assessment of the mediastinum in patients with lung cancer. Increasing availability of the technology now allows PET to be used widely as a diagnostic tool. It should be remembered that PET is primarily a metabolic examination and has limited anatomic resolution. It is possible for PET to identify lymph node stations but not individual lymph nodes. CT scanning provides much more anatomic detail but lacks the functional information provided by PET. The second edition of the ACCP guidelines on lung cancer revealed that with more widespread use of this technology, the test characteristics of PET have become slightly less favorable.[28] In 2865 evaluable patients, the pooled estimates of sensitivity and specificity for identifying mediastinal metastasis were 74% (95% CI, 69%–79%) and 85% (95% CI, 82%–88%), respectively. Corresponding positive and negative likelihood ratios for mediastinal staging with PET scanning were 4.9 and 0.3, respectively. These findings demonstrate that PET scanning is more accurate than CT scanning for staging of the mediastinum in patients with lung cancer, though PET is far from perfect. This imaging technique will almost certainly assume an increasingly important role in the evaluation of patients with lung cancer. However, like CT scanning, PET can be wrong. Whereas a negative mediastinal PET may obviate the need for mediastinoscopy prior to thoracotomy in certain situations, a positive mediastinal PET should not negate further evaluation or the possibility of resection. In the latter case, lymph node sampling should still be pursued because the possibility of a false-positive PET scan cannot be ignored.

Where PET is available, a PET scan should be obtained during the staging evaluation for lung cancer.[20] Newer technology includes CT/PET fusion, a single machine that incorporates CT and PET during the same scan. This allows the clinician to obtain anatomic (CT) and functional (PET) images simultaneously. Early work suggests improvement in the number of patients correctly staged with this modality over CT or PET alone.[35,36] The future of PET in lung cancer may also include its use to evaluate response to treatment.

Magnetic Resonance Imaging

There are very few circumstances in which magnetic resonance imaging (MRI) is a useful tool in staging lung cancer. However, MRI can be useful in evaluating superior sulcus tumors, especially for possible invasion of the brachial plexus, and for evaluating vertebral invasion.

The Search for Metastatic Disease

The purpose of extrathoracic scanning in NSCLC is usually to detect metastatic disease at common metastatic sites, such as the adrenal glands, liver, brain, and skeletal system, thereby sparing the patient fruitless surgical intervention.[37] CT of the chest, CT or MRI with contrast of the brain, and ^{99m}Tc nuclear imaging of the skeletal system are the staging studies of choice when the clinician needs to evaluate for metastatic disease. More recently, the use of whole-body PET scans for extrathoracic staging has been introduced, and the initial studies suggest that PET can disclose non–central nervous system metastatic disease not detected by standard methods in 10% to 20% of cases.[33,34,38-40] PET appears to be at least as sensitive as isotope bone scans for detecting metastases and has fewer false-positive results.

The initial clinical evaluation may reveal abnormalities, such as abnormal symptoms, physical findings, and routine blood tests, that then lead to an expanded clinical evaluation (Table 47-4).[37] With abnormalities on these clinical evaluations, scans will be abnormal in

TABLE 47-4. Expanded Clinical Evaluation

SYMPTOMS ELICITED IN HISTORY
Constitutional—weight loss >10 lb
Musculoskeletal—focal skeletal pain
Neurologic—headaches, syncope, seizures, extremity weakness, recent change in mental status
SIGNS FOUND ON PHYSICAL EXAMINATION
Lymphadenopathy (>1 cm)
Hoarseness, superior vena cava syndrome
Bone tenderness
Hepatomegaly (>13-cm span)
Focal neurologic signs, papilledema
Soft tissue mass
ROUTINE LABORATORY TESTS
Hematocrit <40% in males
Hematocrit <35% in females
Elevated alkaline phosphatase, GGT, AST, calcium

AST, aspartate aminotransferase; GGT, gamma-glutamyl transpeptidase.

around 50% of cases. Conversely, in the absence of all clinical abnormalities, the scan yield is much lower, giving rise to the recommendation that scans be omitted in this setting.[28,37] Advanced thoracic lesions and mediastinal lymphadenopathy are important variables because more scan abnormalities are associated with advanced thoracic lesions.[37,41] This is particularly true for N2 disease, in which asymptomatic metastases have been documented at a higher rate than would have been expected.[41] Although several studies have documented a higher incidence of brain metastases in patients with adenocarcinomas than in those with squamous cell cancers,[42,43] the largest single series of patients with stage I and II lung cancer found no difference.[44]

Several important caveats must be considered in the search for metastatic disease. First and foremost, there is the problem of false-positive scans. Adrenal adenomas (present in 2%–9% of the general population), hepatic cysts, degenerative joint disease, old fractures, and a variety of nonmetastatic space-occupying brain lesions are present in the general population. When clinically indicated, additional imaging studies, biopsies, or both are performed to establish the diagnosis; however, complications and costs resulting from such subsequent investigations have received little attention.[45] There is also the problem of false-negative scans, scans that fail to detect actual metastases. For example, in a CT study of the adrenal glands, Pagani[46] found metastatic NSCLC by percutaneous biopsy in 12% of radiologically normal adrenal glands. An additional problem is that the studies in this area often fail to specify exactly which elements make up the prescan clinical evaluation or they use differing clinical indicators. For example, organ-specific findings such as headache and non–organ-specific complaints such as weight loss are both important.[47,48] In addition, in many studies, abnormal findings on scans have not been pursued with biopsies to prove metastatic disease. Finally, there are few prospective randomized trials and outcome studies to guide appropriate use and interpretation of extrathoracic scanning. One retrospective study showed that scanning asymptomatic patients with early NSCLC did not help predict recurrences postoperatively or improve survival.[49] The only prospective randomized trial showed no statistical difference in recurrence rates or survival in a group randomized to bone scintigraphy and CT of the head, liver, and adrenals, compared with the group assigned to CT of the chest and mediastinoscopy, followed by thoracotomy when appropriate.[50] It is hoped that careful studies in this area will improve the workup of patients with lung cancer.

Adrenal and Hepatic Imaging

It is relatively common to encounter adrenal masses on routine CT scan, but many of these lesions are probably unrelated to the malignant process. A unilateral adrenal mass in a patient with NSCLC is more likely to be a metastasis than a benign lesion according to some[51,52] but not other[53,54] studies. In the presence of clinical T1N0 NSCLC, adenomas predominate,[55,56] whereas adrenal metastases are frequently associated with large intrathoracic tumors or other extrathoracic metastases.[52,57] Many studies suggest that the size of a unilateral adrenal abnormality on CT is an important predictor of metastatic spread, but this is not a universal finding.[58] Lesions larger than 3 cm are more likely to signify metastases, but benign disease is still possible.

For adrenal masses, CT, MRI, percutaneous biopsy, and even adrenalectomy can be used to help delineate benign from malignant disease. Well-defined, low-attenuation (fatty) lesions with a smooth rim on unenhanced CT are more likely to be benign adenomas,[59–61] but the CT appearance of many lesions is insufficiently distinctive.[61] Follow-up scanning with repeat CT, serial ultrasonography, MRI (especially with chemical shift and dynamic gadolinium-enhanced techniques[62]), or 6-β-iodo-^{131}I-methyl-norcholesterol scanning[63] can sometimes help with the critical distinction between metastatic disease and adenoma. Percutaneous adrenal biopsy is a relatively safe and effective means of achieving a definitive diagnosis in doubtful cases and is especially important when the histology of the adrenal mass will dictate subsequent management.[64,65] However, this procedure may be nondiagnostic or infeasible due to anatomic constraints. When insufficient material results from a biopsy, repeat aspiration or even adrenalectomy should be considered.[58,61]

Most liver lesions are benign cysts and hemangiomas, but contrast CT (or ultrasound) is often required to establish a likely diagnosis.[29] Percutaneous biopsy can be performed when diagnostic certainty is required. One meta-analysis that specifically reviewed hepatic studies derived a pooled yield of 3% for liver metastases in asymptomatic patients with NSCLC.[45]

Brain Imaging

In most studies, the yield of CT/MRI scanning of the brain in NSCLC patients with negative clinical examinations is 0% to 10%,[37,66–71] possibly rendering the test cost-ineffective.[72] The negative predictive value of the clinical evaluation in this setting is 95% (range, 91%–96%).

An association of positive findings between brain metastases and N2 disease in the chest and adenocarcinoma has been described.[42,68,70] The false-negative rate, wherein patients return with brain metastases within 12 months of the original scan, is reported to be 3%.[70] False-positive scans can be a problem in up to 11% of cases due to brain abscesses, gliomas, and other lesions[73]; therefore, biopsy may be essential in cases in which management is critically dependent on the histology of the brain lesion.

MRI is more sensitive than CT of the brain and picks up more lesions and smaller lesions,[74] but in some studies, this has not translated into a clinically meaningful difference in terms of survival.[75] Although studies show that MRI can identify additional lesions in individual patients with metastases, there are no studies that show that MRI is better than CT in its ability to identify additional patients with metastases from lung cancer. Therefore, CT is an acceptable modality for evaluating

patients for metastatic disease. However, MRI remains the preferential modality at many centers.

Bone Imaging

False-positive scan abnormalities in radionuclide bone scintigraphy are common concerns because of the frequency of degenerative and traumatic skeletal damage and the difficulty in obtaining a definitive diagnosis via follow-up imaging or biopsy. The negative predictive value in this setting is 90% for radionuclide bone imaging with a negative clinical assessment. PET has a higher specificity for bony metastases.[28]

Summary

The noninvasive clinical staging of lung cancer relies on the clinical evaluation and a number of readily available staging studies. The clinician must be wary of abnormal scans that may falsely suggest metastatic disease to the mediastinum and distant sites. Tissue confirmation by whatever means necessary is the rule rather than the exception prior to deciding on correct stage and the most appropriate treatment. The search for metastatic disease is not necessary if the patient has a normal clinical evaluation. If the patient has clinical findings indicative of metastatic disease, further evaluation is necessary because nearly 50% of the time the patient will have metastases.[28]

INVASIVE DIAGNOSTIC AND STAGING TECHNIQUES

There are a myriad of methods that can be utilized to diagnose and stage patients with lung cancer. In certain circumstances, this is accomplished with a single test. For example, a positive percutaneous biopsy of the adrenal gland performed as a first test in a patient with a lung mass will provide both a diagnosis and a stage (stage IV) simultaneously. Every effort should be made to utilize the least invasive, most accurate procedure to expedite the patient's treatment, to minimize patient discomfort and inconvenience, and to ensure that the most appropriate treatment is rendered.

Sputum Cytology

Sputum cytology is the least invasive method for obtaining a diagnosis of lung cancer. Its accuracy depends on the expertise of the health care team in obtaining the sample (three samples are required), the preservation technique, and the size and location of the lesion. Central lesions are more likely to yield positive cytologic results than are peripheral lesions.[76] Sputum cytology should be obtained in all patients with central lesions who are at risk for more invasive biopsy techniques. In addition, patients with hemoptysis with or without a mass on chest radiographs should have sputum cytology obtained. The sensitivity and specificity of sputum cytology are 66% and 99%, respectively.[76]

Transthoracic Needle Aspiration

Transthoracic needle aspiration (TTNA), usually under CT or fluoroscopic guidance, is an expedient and relatively safe way to diagnose the primary tumor mass and establish a diagnosis of lung cancer. As a general rule, if a lesion is less than 3 cm in size and lateral to the midclavicular line, bronchoscopy would not be the diagnostic procedure of choice. TTNA should be considered under such circumstances if tissue diagnosis is necessary. One important point about TTNA or other nonsurgical biopsy techniques for peripheral pulmonary lesions is that they afford no preoperative benefit because they do not eliminate the need for surgery in most cases.[77] In the circumstance of a patient presenting with a solitary pulmonary nodule suspicious for malignancy (e.g., noncalcified, upper lobe, spiculated lesion in a long-term smoker), the diagnosis, stage, and therapy can be accomplished simultaneously with a thoracotomy and surgical resection. Thus, TTNA may be essential only in certain situations: patients who are poor surgical candidates but who require tissue diagnosis prior to treatment, patients in whom a noncancerous lesion is strongly suspected, patients who request that a diagnosis of cancer be confirmed prior to considering surgery, and patients with high likelihood of metastatic disease. The sensitivity and specificity of TTNA are 90% and 97%, respectively.[76]

One drawback of TTNA is the risk of pneumothorax. Several investigations have reported a 22% to 45% risk of pneumothorax for CT-guided TTNA.[78–80] Although pneumothorax may lead to hemodynamic compromise without therapeutic tube thoracostomy, in most cases of pneumothorax secondary to TTNA, treatment is not required.[81] The primary factors shown to increase the risk or incidence of pneumothorax are the presence of emphysema, a smaller lesion size, and a greater depth of needle penetration from the pleural surface to the edge of the lesion.

Fiberoptic Bronchoscopy

More than 50% of patients with advanced-stage lung cancer will have involvement of the central airways either by bulky endobronchial disease, extension into the airways, or extrinsic compression of the airways by the tumor or by lymphadenopathy.[82] Patients with known or suspected lung cancer may have symptoms due to endobronchial involvement that require airway inspection with bronchoscopy: shortness of breath, unilateral wheezing, hemoptysis, and cough. Endobronchial lesions can be visualized easily and biopsied through a flexible bronchoscope. The yield with three or more biopsies should approach 100% for centrally located lesions.[83,84] Data from 4507 patients revealed that central endobronchial biopsies provide the highest sensitivity (74%), followed by brushings brushing (61%) and washings (47%).[76] The combination provides a diagnosis in 88% of cases.[76] Studies on the sensitivity of needle aspiration of centrally located endobronchial lesions are difficult to interpret. These studies have varied dramatically in terms of sample size and technique used. Because

endobronchial biopsies or brushings provide a diagnosis in most cases, endobronchial needle aspiration is rarely performed. However, the diagnosis is likely to be made in a bit more than half the cases using needle aspiration.[76]

Submucosal and Peribronchial Lesions

When lung cancer presents with submucosal infiltration or extrinsic compression from peribronchial disease, endobronchial forceps biopsy has a lower yield (55%) than transbronchial needle aspiration (TBNA) (71%).[85] In these situations, normal mucosal markings are often obscured and the surface is replaced with bronchial collateral vessels and firmer surface tissue, which may have to be penetrated to reach malignant cells. In addition, peribronchial tumor may be inaccessible to biopsy forceps. TBNA can be more effective if the lesion is close enough to the tracheobronchial tree to be encountered with a 1.3- to 1.5-cm-long needle. Of note, in cases like this in which sampling error may be high, diagnostic yields may be improved by combining different methods.

Bronchoscopy for Staging Lung Cancer

Initially, the role of bronchoscopy in staging lung cancer was limited to the determination of T (tumor) status. Now, bronchoscopy has a crucial role in determining the presence of metastatic deposits of tumor in mediastinal lymph nodes, thus contributing to an accurate and a minimally invasive staging method for lung cancer.

The use of TBNA in staging lung cancer has been reported to be both sensitive and specific in diagnosing spread of cancer to lymph nodes.[86–88] The overall sensitivity of TBNA for NSCLC is 78%, and the specificity is 99%.[89] The standard method of performing TBNA starts with a CT scan of the chest to guide needle aspirations toward the most involved group of lymph nodes. Lesions localized by a CT scan can be accessed with bronchoscopy by measuring the number of CT slices above or below the carina (or other airway landmarks) and placing the needle the required distance above or below the landmark corresponding to that number of CT slices. When performing TBNA, the question invariably arises about the number of negative passes to perform before stopping. For various reasons, such as patient comfort and safety, need for sedation, and time spent by medical staff, it is imperative to manage the time for bronchoscopy. It has been shown that a plateau in yield for malignancy is achieved after seven passes with the needle through a lymph node.[90] The importance of having a qualified and experienced cytopathologist on site cannot be overemphasized. Thorough interpretation by such individuals who are available for rapid on-site evaluation has been shown to enhance yield from TBNA.[91] With the assistance of these individuals, the adequacy of sampling can be rigorously assessed. All samples should contain a preponderance of lymphocytes to define true nodal sampling. Specimens without lymphocytes should be deemed unsatisfactory, and the presence of respiratory epithelium should raise concerns about contamination.

TBNA allows for minimally invasive sampling of the mediastinum and hilar lymph nodes and potentially avoids more invasive procedures such as mediastinoscopy, mediastinotomy, and open thoracotomy. There is no doubt that the combined use of TBNA and CT scan can improve not only the diagnostic but also the staging evaluation of lung cancer. However, thus far, there has been wide variability in training and in usage of this helpful procedure. It is also operator-dependent, with certain techniques allowing for higher yields. For an in-depth discussion of bronchoscopy, see Chapter 22.

Endoscopic Ultrasound

Endoscopic ultrasound (EUS) is another modality that has significantly impacted lung cancer staging, primarily due to its superior ability to sample the posterior mediastinum through the esophageal wall. Currently, EUS with fine-needle aspiration is performed using real-time ultrasound. In pooled analysis of more than 1000 patients with lung cancer and mediastinal adenopathy, EUS has a sensitivity and specificity of 84% and 99.5%, respectively.[89] In patients with lung cancer who have no adenopathy seen on CT scan, EUS has been shown to sample nodes as small as 3 mm in diameter. This is useful given the high incidence of metastasis found in normal-sized lymph nodes in lung cancer.[92] Based on surgical studies, it may be possible to predict the location of mediastinal lymph node metastases at certain levels based on the location of the tumor. This relationship may influence the use of EUS in certain patients without adenopathy on chest CT scan. Lymphatic pathways favor spread to aortopulmonary window nodes from left upper lobe tumors and to subcarinal nodes from left and right lower lobe lesions.[93] EUS has been studied in patients with known lung cancer without enlarged mediastinal lymph nodes on CT, and it has detected mediastinal involvement (stage III or IV disease) in up to 42% of cases.[94]

In addition, EUS has the advantage of being able to stage lung cancer from locations outside the mediastinum. The left lobe of the liver, a substantial part of the right lobe of the liver, and the left (but not the right) adrenal gland can be identified and sampled in 97% of patients.[95] In addition, left pleural effusions can be visualized and sampled during an EUS procedure. EUS is increasingly being combined with endobronchial ultrasound (EBUS) for minimally invasive staging of lung cancer (see below).

Endobronchial Ultrasound

Perhaps the greatest addition in the armamentarium for staging lung cancer is endobronchial ultrasound with fine-needle aspiration (EBUS-TBNA). EBUS-TBNA is indicated for the assessment of mediastinal and hilar lymph nodes and diagnosis of lung and mediastinal tumors. It can be used to sample the highest mediastinal (station 1), the upper paratracheal (station 2R, 2L), the lower paratracheal (station 4R, 4L), the subcarinal (station 7), as well as the hilar (station 10), and the interlobar (station 11) lymph nodes (Fig. 47-1A). The para-aortic (station

6), aortopulmonary window or subaortic (station 5), paraesophageal (station 8), and pulmonary ligament (station 9) lymph node stations are usually not accessible by this technique (see Fig. 47-1B). Pooled analysis of nearly 1000 patients shows that EBUS-TBNA has a sensitivity and specificity of 90% and 100%, respectively.[89] Should a patient present with a lung mass and mediastinal lymphadenopathy in the lymph node stations described earlier, EBUS-TBNA should be considered as a test of first choice because this modality can provide a diagnosis and stage simultaneously. The combination of EUS and EBUS has shown better yield than either technique alone and may provide near-complete access to the mediastinum for staging,[95a] even in the radiologically normal mediastinum.[95b] For a further discussion of EBUS, see Chapter 20.

Mediastinoscopy

Mediastinoscopy remains the gold standard for invasively staging the mediastinum in patients with known or suspected lung cancer. If there is mediastinal adenopathy on CT, often a surgical mediastinal procedure is performed prior to thoracotomy. Mediastinoscopy is most often used to sample nodes of the paratracheal (station 4), and anterior subcarinal (station 7) region (see Fig. 47-1A). The subcarinal area is more difficult to sample and thus has a lower yield. An extended cervical mediastinoscopy can be carried out to reach aortopulmonary and para-aortic lymph nodes (stations 5 and 6) by using the same cervical incision as mediastinoscopy but dissecting into a different fascial plane. Alternatively, an anterior mediastinotomy (the so-called Chamberlain procedure) may be needed to sample lymph nodes in these aortopulmonary and para-aortic locations (stations 5 and 6) (see Fig. 47-1B). Overall, mediastinoscopy has a reported sensitivity of 78%, with a specificity of 100%.[89] Mediastinoscopy may also be able to differentiate between stage IIIA and IIIB mediastinal involvement. As more is learned about lung cancer treatment, this will be important for prognosis and for potential therapy. As with any surgical procedure, mediastinoscopy has risks and limitations. It requires general anesthesia, with a morbidity of 2% and a mortality of 0.08%.[89]

TREATMENT OF LUNG CANCER

The overall 5-year survival for patients diagnosed with lung cancer is a dismal 14%.[96] This figure has not changed

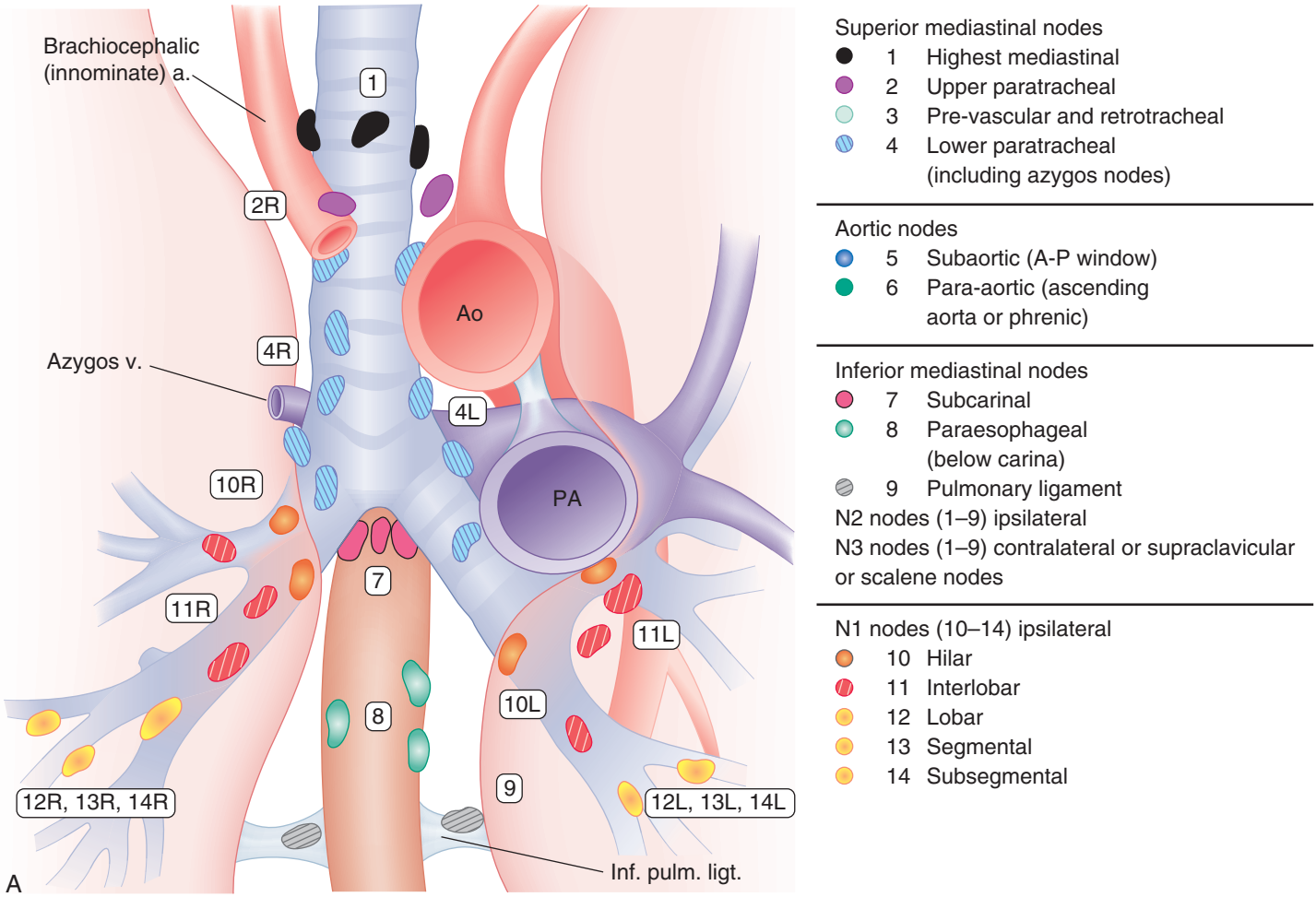
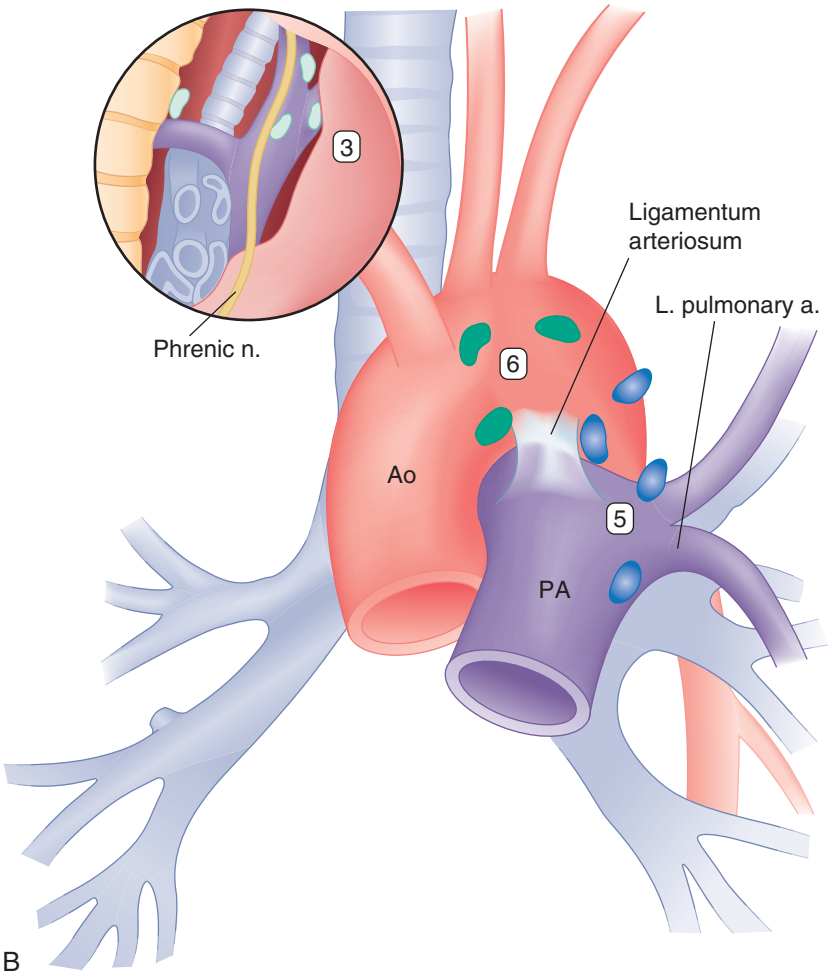


FIGURE 47-1 ■ (A and B) Mediastinal lymph node maps. a, artery; Ao, aorta; A-P, aortic-pulmonary; PA, pulmonary artery; v, vein. (Redrawn from Mountain CR, Dresler CM: Regional lymph node classification for lung cancer staging. Chest 111:1719, 1997.)



Superior mediastinal nodes
- 1 Highest mediastinal
- 2 Upper paratracheal
- 3 Pre-vascular and retrotracheal
- 4 Lower paratracheal (including azygos nodes)

Aortic nodes
- 5 Subaortic (A-P window)
- 6 Para-aortic (ascending aorta or phrenic)

Inferior mediastinal nodes
- 7 Subcarinal
- 8 Paraesophageal (below carina)
- 9 Pulmonary ligament

N2 nodes (1–9) ipsilateral
N3 nodes (1–9) contralateral or supraclavicular or scalene nodes

N1 nodes (10–14) ipsilateral
- 10 Hilar
- 11 Interlobar
- 12 Lobar
- 13 Segmental
- 14 Subsegmental

FIGURE 47-1 ■ cont'd.

substantially since the 1980s. The survival curves vary by stage, with earlier-stage lung cancer patients enjoying a much better survival than do patients with later-stage disease. Treatment is based on the stage of the disease and the patients' performance status at the time therapy is initiated. In general, early-stage disease is surgically managed, locally advanced disease is managed with chemotherapy and radiotherapy, and advanced disease is managed with chemotherapy with supportive care or supportive care alone. This paradigm has begun to shift toward multimodality therapy (surgery, chemotherapy, and radiotherapy).[97-100] This raises the issue of how best to manage patients with newly diagnosed lung cancer through their diagnosis, staging, and therapy. The ACCP guidelines on lung cancer recommend the use of a multidisciplinary lung cancer setting wherein patients can be evaluated by the major disciplines involved in the care of these patients, namely the pulmonologist, the thoracic surgeon, and the medical and radiation oncologists.[101] At the very least, a "tumor board" that includes the aforementioned specialties, with the addition of chest radiology, pathology, nursing, and social work, should review all new cases to ensure that patients receive optimal treatment and are considered for enrollment in clinical trials.

Prognostic Factors for Lung Cancer

Based on an analysis of large databases in inoperable lung cancer patients, the strongest predictors of survival are good performance score (Karnofsky scale), lower extent of disease (stage), age, and absence of weight loss.[102-104] Some reports have shown female gender to be a predictor of better survival, but this varies between studies. Performance score and the presence or absence of symptoms are predictors of outcome even with resectable early-stage disease.[105-107] For example, in stage I NSCLC patients undergoing curative resection, those who were symptomatic at presentation had a worse survival than those who were asymptomatic.[106] Although individual reports have noted superior survival for patients with one cell type of NSCLC versus another, the general consensus in the literature is that histologic subtypes of NSCLC are not a major predictor of survival.[105,106,108] Absence of smoking or smoking cessation has been associated with improved survival. The maximal standard uptake value of the primary tumor on PET scanning has been inversely correlated with survival.[109]

In more recent years, there have been numerous reports that various molecular markers are associated with outcome. Some of the best known markers include

K-Ras, epithelial growth factor receptor (EFGR), p53, p16, and Bcl-2. However, in many instances, the results are conflicting about the prognostic significance of these individual molecular markers,[110–112] perhaps due to the types of cases under review and to individual laboratory variations in techniques for measuring these molecular markers. In a meta-analysis, K-Ras mutations were associated with poorer survival, especially in adenocarcinoma where the hazard ratio was 1.59 (95% CI 1.26–2.02).[113] Whereas testing the genetic profile of resected tumors is not yet standard practice, this is likely to change rapidly; indeed, the testing of K-Ras and EGFR mutations is already standard in some centers (see Chapter 45).

Non–Small Cell Lung Cancer Treatment by Stage

This section presents a discussion of the treatment of NSCLC by stage and cell type, followed by a discussion of the treatment of small cell lung cancer (SCLC). Table 47-5 presents an overview of treatment strategies for NSCLC based on stage.

Stage I

In the new staging system for NSCLC, stage I NSCLC is broken down into stage IA (tumors ≤ 2 cm [T1a] and tumors between 2 and 3 cm [T1b]) and stage IB (tumors between 3 and 5 cm [T2a]). All stage I tumors are completely surrounded by lung parenchyma in the parenchyma, greater than 2 cm away from the carina and not invading the chest wall or parietal pleura (Fig. 47-2). Stage I lung cancer does not include patients who have malignant lymph node disease or patients with metastatic disease. Thus, the TNM classification is either T1aN0M0, T1bN0M0 (stage IA) or T2aN0M0 (stage IB). The differences between the two are the size of the primary tumor and the survival after surgical resection. Although stage I disease offers the best chance for long-term survival, the sad fact is that only 15% of all lung cancers present with stage I disease.[114,115]

The current treatment for stage I lung cancer is surgery alone. The surgical procedure of choice is a lobectomy or pneumonectomy with mediastinal lymph node sampling. It should be recognized that the patient must be a reasonable surgical candidate. The 5-year survival for surgically resected stage IA lung cancer is 73%, whereas the survival for stage IB lung cancer is 58%.[25] Local postoperative radiation for stage I and II lung cancer, after either complete or incomplete resection of the tumor, has not been found to be of any benefit.[114] Postoperative adjuvant chemotherapy has not been shown to improve survival for those with resected stage I disease.[116] A further discussion of postoperative adjuvant therapy is presented later (see "Stage IIIA").

Some patients are surgically resectable but medically inoperable, usually because the patient does not have the pulmonary reserve to tolerate a lobectomy. These patients, particularly those with T1 tumors, may be able to tolerate a wedge resection or segmentectomy of their tumor as opposed to a lobectomy or pneumonectomy. In such cases, the local recurrence rate is higher than that of a complete resection, but the overall 5-year mortality is no different.[117] Still, whenever possible, a complete anatomic resection is preferred over a minimal resection. For discussion of radiofrequency ablation and other non-surgical treatments, see Chapters 22 and 49.

Patients who are "close calls" for surgery should be thoroughly evaluated by both a pulmonologist and a

TABLE 47-5. Summary of Current Treatment Strategies for Non–Small Cell Lung Cancer

Stage	Surgery	Chemotherapy	Combined Radiotherapy	Chemoradiotherapy	Comments
I and II	1st line	Adjuvant—stage IIA, IIB	2nd line	No	Survival improvement with adjuvant therapy (= 5%) Radiotherapy for inoperable patients
IIB (T3N0M0) Pancoast	1st line	No	No	1st line—neoadjuvant	Neoadjuvant chemoradiotherapy improves survival in this subset of stage IIB
IIIA	1st line	Adjuvant treatment—in totally resected IIIA	Controversial	1st line	Combined chemoradiotherapy followed by surgery is feasible, but more data are needed to recommend routinely
IIIB (T4N0-1M0) Resectable	1st line	No	No	± Neoadjuvant—1st line	Neoadjuvant chemoradiotherapy followed by surgery may be considered in carefully selected patients
IIIB Unresectable	No	No	No	1st line	Treatment similar to unresectable stage IIIA
IV	No	1st line	No	No	Radiotherapy is used for palliation only

Bevacizumab is approved as an adjunct to chemotherapy in the first-line setting in patients with nonsquamous histology and no other contraindications.
The EGFR inhibitors are indicated as frontline treatment for those with advanced NSCLC and documented EGFR mutations but, as of this printing, are FDA-approved only as second and third line therapy.
EGFR, epidermal growth factor receptor; FDA, U.S. Food and Drug Administration; NSCLC, non-small cell lung cancer.

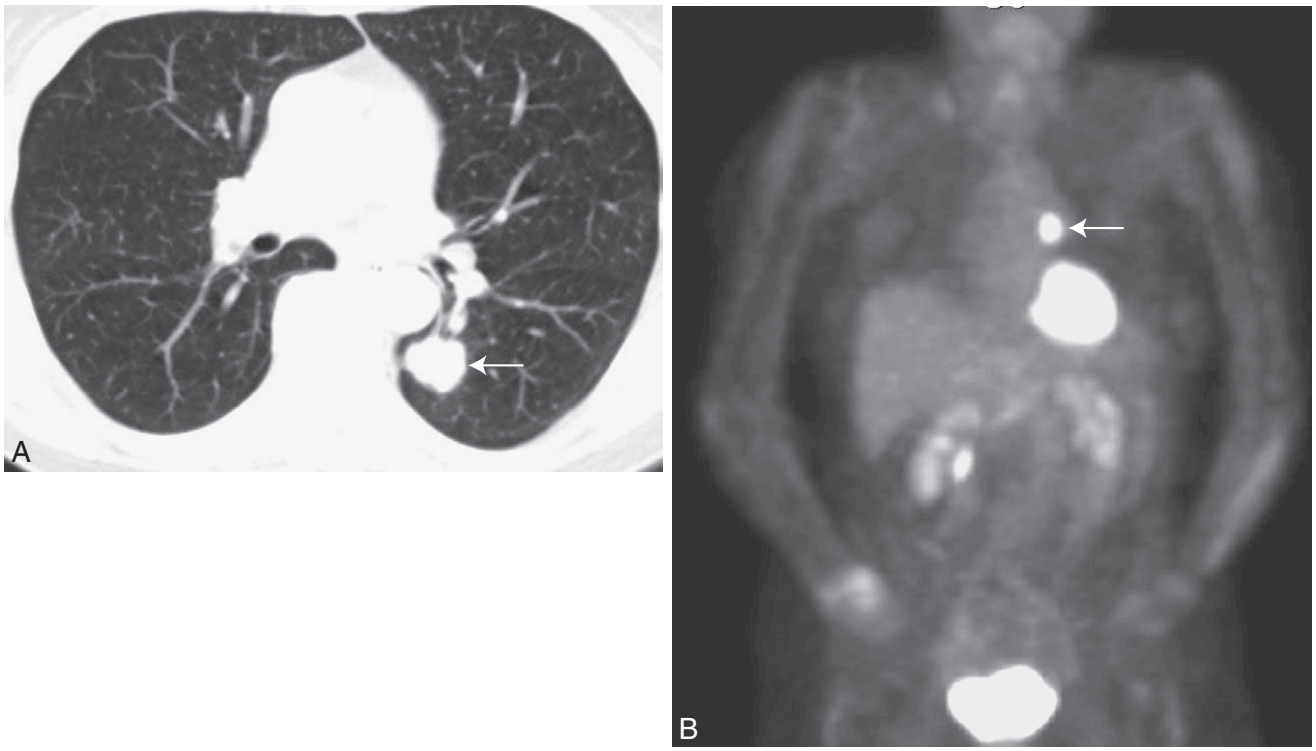


FIGURE 47-2 ■ Computed tomography (CT; **A**) and positron emission tomography (PET; **B**) scans of a patient with T1N0M0 tumor (*arrows*).

thoracic surgeon prior to making a decision on operability. As previously stated, there is a difference between a patient who is resectable and a patient who is operable. Chapter 26 is devoted to the preoperative evaluation of patients with lung disease, but a brief review is warranted here. Patients with a postoperative percent predicted forced expiratory volume in 1 second (FEV_1) or diffusion capacity less than 40% will have a higher morbidity and mortality following lung cancer surgery. Patients with borderline values preoperatively should be referred for a differential ventilation-perfusion scan for a better prediction of postoperative function. Where there is still a question, a cardiopulmonary exercise test can be obtained. Compared with those with an oxygen consumption of greater than 20 mL/kg/min, patients with an oxygen consumption between 11 and 19 mL/kg/min have a higher morbidity but no greater mortality and those with an oxygen consumption less than 10 mL/kg/min have both a higher predicted morbidity and mortality.[118]

For patients who either refuse surgery or are deemed medically unfit for surgery, primary radiotherapy for cure can be considered. This approach was evaluated in a meta-analysis of 1 randomized and 35 nonrandomized trials.[119] The studies were heterogeneous, and the 5-year cancer-specific survival ranged between 13% and 39%. The authors concluded that, even in patients with severe emphysema, radiation therapy can be tolerated if careful planning with three-dimensional conformal techniques is undertaken to minimize the radiation dose to the remaining noncancerous lung. We would recommend referral to a radiotherapist for patients who are medically inoperable for consideration of "curative" radiation therapy.

Stage II

In the new staging system, stage II NSCLC lung cancer remains divided into stage IIA and stage IIB. Stage IIA is defined as a T1aN1M0, T1bN1M0, or T2aN1M0 disease and stage IIB includes T2bN1M0 and T3N0M0. The 5-year survivals for stage IIA and IIB are 46% and 36%, respectively.

Stage IIA lung cancer is quite uncommon, representing between 1% and 5% of patients treated in several surgical series.[120–125] Stage IIB cancer may represent up to 15% of surgically resected cases.[116,120,122,125] For stage IIA and IIB cancer, surgical therapy is the treatment of choice. There is no benefit to postoperative radiotherapy. The value of adjuvant chemotherapy after surgery is discussed later (see "Stage IIIA") but, in short, adjuvant chemotherapy is recommended for all patients with resected stage II disease. With chest wall invasion (T3N0M0), an en bloc resection of the tumor and chest wall is the treatment of choice. A specific discussion of the evaluation and treatment of Pancoast's tumor is discussed later in the chapter.

The outcome of lung cancer surgery is improved when the surgery is performed at hospitals with a higher volume of procedures.[121] It is also important that the surgery be performed by a thoracic surgeon; when lobectomy is performed by a thoracic surgeon compared to a general surgeon, mortality is nearly halved.[126]

Stage IIIA

Stage IIIA NSCLC represents a heterogeneous group of patients with N2 disease and includes T3N1 patients (Fig. 47-3). In addition, within the new staging system, patients with T4N0-1 have been downstaged to IIIA from their previous classification.[25]

For carefully selected T4N0-1M0 patients, surgery may be indicated with or without neoadjuvant chemotherapy or neoadjuvant chemoradiotherapy (superior sulcus tumors). Individuals with T4N0-1 disease due to main carinal involvement have been treated with carinal resection with or without pulmonary resection. Carinal resection carries an operative mortality of 10% to 15% and 5-year survival of approximately 20% in carefully selected series. Patients who are T4N0 due solely to tumor nodules within the ipsilateral nonprimary lobe have a 5-year survival of around 20% with surgery alone.[127]

There is substantial debate over what constitutes resectable IIIA (N2) disease. All agree that T3N1 patients are best treated with surgical resection. At surgery, when a complete resection of the lymph nodes and the primary tumor is possible, some patients are found to have occult N2 metastasis. If so, these patients are best served by resecting all known disease. It is more unclear how best to treat patients when N2 (single or multiple station) metastases are documented prior to thoracotomy. Two small randomized prospective trials have compared surgery alone with preoperative (neoadjuvant) chemotherapy followed by surgery.[98,100] Both trials observed superior survival in those who received preoperative

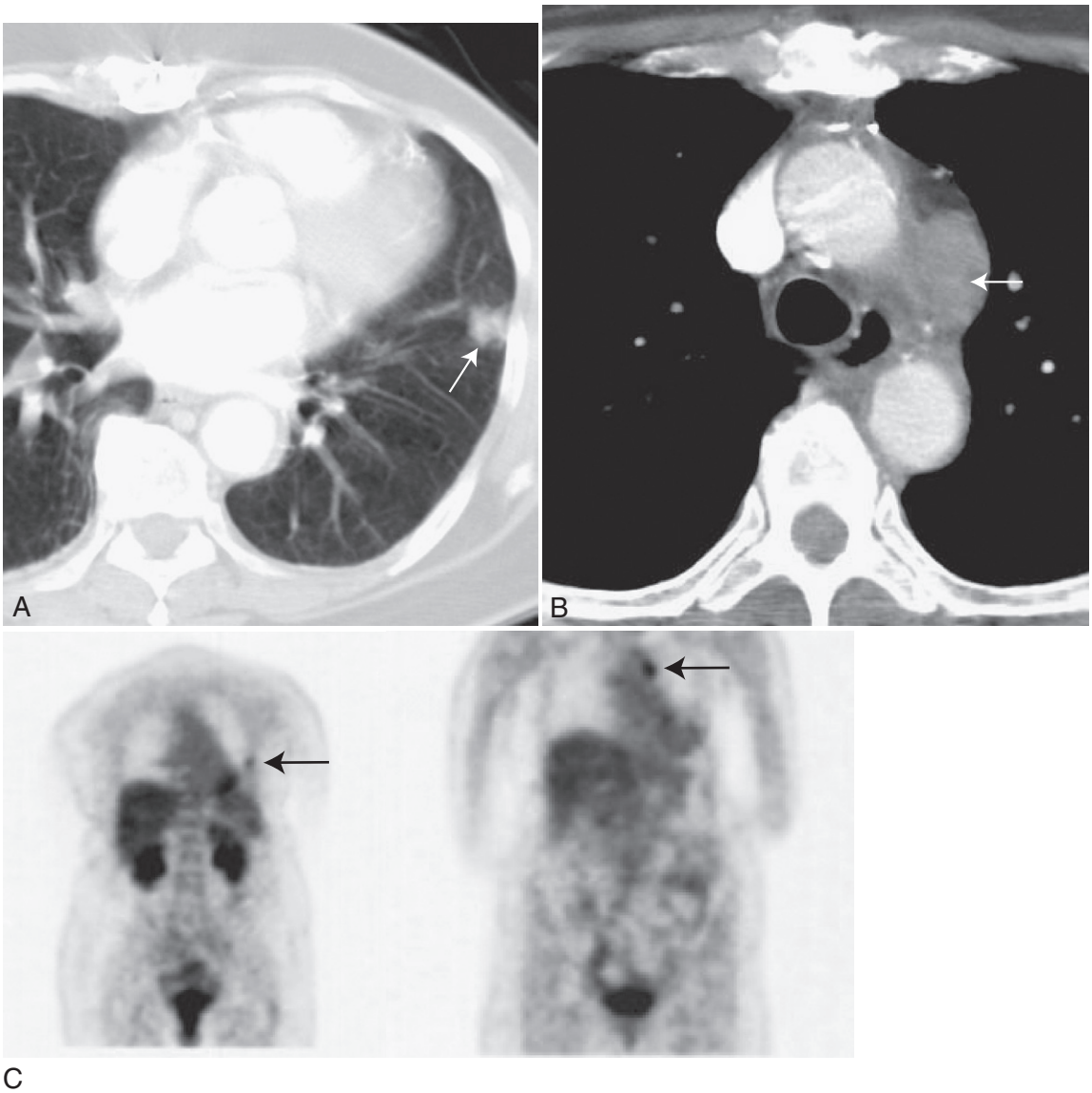


FIGURE 47-3 ■ **A,** CT scan depicts a primary tumor mass invading the chest wall for a stage IIIA non–small cell lung cancer (NSCLC; T3N1) (*arrow*). **B,** CT scan depicts enlarged aortopulmonary lymph node (*arrow*). **C,** PET scan with uptake in primary tumor (*left image, arrow*) and lymph node (*right image, arrow*).

chemotherapy. Investigators have reported the preliminary results of a prospective trial that randomized patients with IIIA (N2) disease to chemoradiotherapy alone versus chemoradiotherapy followed by surgery.[128] There was no difference in the median survival time (23.6 vs. 22.2 mo) or the 5-year survival (27% vs. 20%, respectively; $P = 0.24$). However, the final manuscript on this study has yet to be published. A compilation of several other randomized trials of neoadjuvant chemotherapy followed by surgery versus chemoradiotherapy have found similar results. In the second iteration of the ACCP evidence-based guidelines, a review of all relevant studies on neoadjuvant therapy in stage IIIA lung cancer concluded that there was no benefit to a neoadjuvant chemotherapy/surgical approach. Their final recommendation is that in patients with NSCLC with N2 disease identified preoperatively (IIIA), induction therapy followed by surgery is not recommended except as part of a clinical trial.[129] In summary, the evidence for treatment of stage IIIA disease does not currently support the use of neoadjuvant chemotherapy followed by surgery. The standard of care for patients with stage IIIA lung cancer is combined chemoradiotherapy.

Postoperative (adjuvant) treatment of resected stage IIIA NSCLC is now recommended. The International Adjuvant Lung Trial randomized patients with completely resected stage I, II, and IIIA NSCLC to observation or to three or four cycles of adjuvant cisplatin-based chemotherapy.[130] Approximately 39% of all patients in the trial had stage IIIA disease. Overall, there was an absolute 4% improvement in 5-year survival (44% vs. 40%) in participants receiving adjuvant chemotherapy. National Cancer Institute (NCI) Canada investigators demonstrated a 15% improvement in 5-year survival (69% vs. 54%) with four cycles of vinorelbine and cisplatin adjuvant chemotherapy in patients with resected stage IB and II NSCLC.[131] Similarly, French investigators in the Adjuvant Navelbine International Trialist Association (ANITA) study observed an 8.6% survival advantage with adjuvant therapy in resected stage IB-IIIA NSCLC.[132] A recent pooled analysis (Lung Adjuvant Cisplatin Evaluation [LACE]) of adjuvant chemotherapy trials concluded that adjuvant cisplatin-based chemotherapy resulted in a reduction in the hazard ratio of death of 0.89 and a corresponding 5-year survival benefit of 5.4%.[133] This survival benefit was observed in stage II and IIIA but not in patients with stage IB disease.[133] Adjuvant chemotherapy in completely resected stage II and IIIA NSCLC is now the standard of care. Although adjuvant radiotherapy in the fully resected stage IIIA NSCLC patient has not been shown to improve survival, radiotherapy has been shown to reduce local recurrences and should be considered in selected patients.[128] Several nonrandomized trials have suggested that adjuvant radiotherapy may benefit patients with resected N2 disease; currently, prospective studies are trying to answer this question.[134]

Those individuals with bulky (>2 cm in diameter) or multistation N2 nodal metastasis make up a less favorable subset of stage IIIA disease and are not generally considered to be operable. In the past, these patients were treated with thoracic radiotherapy alone, but their 5-year survival was only 3% to 5%. A multitude of trials have evaluated combination chemotherapy and thoracic radiotherapy versus thoracic radiotherapy alone. Three meta-analyses of these trials have all concluded that cisplatin-based chemotherapy combined with radiotherapy results in survival benefit over radiotherapy alone.[135–137] Anticipated 5-year survival with combined-modality therapy is 15% to 20%. Two multicenter trials have concluded that concurrent chemoradiotherapy is superior to sequential therapy with chemotherapy followed by thoracic radiotherapy.[138,139] Concurrent therapy is recommended for those individuals with good performance scores (0 or 1) and less than 10% weight loss. Concurrent therapy is associated with a higher rate of severe esophagitis than is sequential therapy.

Stage IIIB

Stage IIIB is also a heterogeneous group and includes T4N2M0 and any T N3M0 patients. There are no phase III randomized trials to date that demonstrate that neoadjuvant chemoradiotherapy followed by surgery for stage IIIB disease results in prolonged survival compared with chemoradiotherapy alone.[140]

Patients with unresectable stage IIIB NSCLC are treated the same as those with unresectable IIIA disease. The median survival time is generally 15 to 18 months, with a 5-year survival of 10% to 20%. The randomized trials of chemoradiotherapy versus radiotherapy alone included both stage IIIA and IIIB disease participants. Combination chemotherapy with a cisplatin-based regimen and thoracic radiotherapy results in better survival than radiotherapy alone.[135–137] Trials have evaluated multiple daily fractions of thoracic radiotherapy, but there are no convincing data that hyperfractionated thoracic radiotherapy (the same total dose of radiation therapy split into two treatments in the same day) is superior to standard once-daily treatment. For stage IIIA or IIIB patients with a performance score of 0 or 1 and minimal weight loss, concurrent chemoradiotherapy is recommended.[140] Concurrent therapy appears to be associated with improved survival versus sequential therapy.[138,139]

Stage IV

Malignant pleural or pericardial effusions are now classified as stage IV disease. There are virtually no 5-year survivors with stage IV NSCLC. The goal of therapy is to try to control the disease and palliate symptoms. Major response rates with current chemotherapy regimens are 10% to 30%. Patients who respond to chemotherapy may gain an additional 3 to 9 months of life on average but eventually relapse and die of their disease. In previous trials in the 1970s and 1980s, patients were randomized to best supportive care or systemic chemotherapy. A meta-analysis evaluated eight of these randomized trials, including over 700 patients.[135] Each of these trials used a cisplatin-based chemotherapy versus supportive care. With best supportive care, the median survival time was 4 months and the 1-year survival was 15%; with chemo-

therapy, there was an increase in the median survival of 1.5 months and an increase in 1-year survival of 10%. In the 1990s, a number of new chemotherapy agents were introduced, including paclitaxel, docetaxel, irinotecan, vinorelbine, and gemcitabine. Phase III trials have incorporated these newer agents in combination with cisplatin or carboplatin.[141]

Trials comparing single-agent chemotherapy to a chemotherapy doublet containing a platinum compound have shown that the chemotherapy doublet is superior. Treatment with three drugs has not been shown to be superior to that with two drugs. Large randomized trials have tried to identify the optimum chemotherapy doublet.[142–144] The results were uniformly similar, with response rates of 20% to 30% and median survival times of 7 to 9 months. No one platinum doublet has been shown to be superior. The chemotherapy combinations did have different toxicity profiles.

Since the 1990s, there has been increasing interest in novel targeted therapies for lung cancer. Two main targets of interest are the vascular endothelial growth factor (VEGF) receptor and the EGFR. Bevacizumab is a monoclonal antibody against VEGR. Sandler and coworkers[145] conducted a randomized trial with paclitaxel and carboplatin with or without bevacizumab. The novel agent resulted in superior survival with a median survival time of 12.3 versus 10.3 months and a hazard ratio for death of 0.79; $P = .003$. A large randomized trial in Europe was conducted with gemcitabine and cisplatin with or without bevacizumab.[146] This trial has also shown a small but significant improvement in progression-free survival (6.7 and 6.5 months with low- and high-dose bevacizumab vs 6.1 months with placebo).[146] A large number of antiangiogenesis drugs are currently under evaluation for their activity against lung cancer. This class of agents has been associated with an increased of bleeding, hypertension, and nephrotoxicity.

In 2004, investigators identified activating mutations in the tyrosine kinase domain of EGFR that predicted response to the novel tyrosine kinase inhibitors (TKIs) in selected patients with NSCLC.[147,148] Multiple studies have demonstrated that the phenotypes most associated with response to the EGFR TKIs, gefitinib and erlotinib, are adenocarcinoma, never-smokers, female, and East Asian descent. Subsequent reports have shown that these are the groups most likely to harbor the activating EGFR mutations. Emerging data have demonstrated that K-Ras and EGFR mutations are almost always mutually exclusive and that patients with K-Ras mutations do not respond to EGFR-TKIs.[149] Erlotinib has been shown in a phase III trial in previously treated patients with NSCLC to result in superior survival versus placebo (6.7 vs. 4.7 mo).[150] On this basis, erlotinib was approved by the U.S. Food and Drug Administration (FDA) for second-line treatment. A phase III trial of gefitinib in second-line therapy failed to show a significant improvement in survival and approval for second-line therapy was withdrawn by the FDA in North America.[151] Gefitinib is still used in East Asian countries because of its significantly higher activity in East Asians than in North Americans and Europeans. Phase II trials have documented the activity of both gefitinib and erlotinib in patients with untreated NSCLC and phase III trials with these agents versus standard cisplatin doublet chemotherapy as initial treatment are under way.[152,153] A phase III trial in East Asia randomized patients with untreated stage IV disease to gefitinib- or platinum-based chemotherapy. Gefitinib resulted in superior survival overall (24.9% 12-month progression-free survival with gefitinib vs. 6.7% with carboplatin-paclitaxel). Of the 609 patients, 261 (43%) had EGFR mutations. This subgroup responded significantly better to gefitinib than to chemotherapy. The subgroup negative for mutations responded better to the chemotherapy.[154] The current role for anti-EGF therapy is evolving rapidly and represents an exciting development for targeting treatment for subsets of patients with lung cancer.

The ACCP guidelines recommend that patients with good performance scores (0 or 1) should be considered for platinum-based chemotherapy based on the survival advantage over best supportive care.[155] The duration of first-line therapy should be brief, consisting of four cycles of treatment, or fewer if there are signs of progression. In addition, patients with good performance scores who develop progressive disease should be offered second-line chemotherapy. Single-agent docetaxel, pemetrexed, and erlotinib have all been shown to prolong survival when used in a second-line setting and have been approved by the FDA for this indication.

Small Cell Lung Cancer

SCLC accounts for 15% to 20% of all lung cancers. This cell type has the strongest association with cigarette smoking and is rarely observed in a never-smoker. It is the cell type most commonly associated with paraneoplastic syndromes such as the syndrome of inappropriate (excessive) antidiuretic hormone secretion (SIADH), ectopic corticotropin secretion, Lambert-Eaton myasthenic syndrome (LEMS), and sensory neuropathy.

SCLC usually presents as a centrally located mass in the hilum on chest radiograph and may be associated with obstructive pneumonia. In 5% or fewer cases, SCLC may present as a solitary pulmonary nodule/mass. SCLC is generally staged according to the old Veterans Administration Staging System, rather than the American Joint Committee on Cancer Staging System previously outlined, and classified as limited (LD) or extensive (ED) stage. LD-stage disease is confined to one hemithorax, the mediastinum, and the ipsilateral supraclavicular lymph nodes. It is a disease that can be safely encompassed within one radiation portal without irradiating too much normal lung. ED stage is any disease spread beyond these sites. Malignant pleural effusion or disease extending to the contralateral supraclavicular or hilar lymph nodes is generally considered to be ED. After establishing the histologic diagnosis of SCLC, patients are usually staged with MRI of the brain, CT of the chest (through the adrenal glands), and bone scan or PET scan. In the unusual case of SCLC that presents as a peripheral nodule, the treatment of choice is surgical resection followed by adjuvant chemotherapy and possibly sequential thoracic radiotherapy. Careful preoperative staging should be performed in these individuals to rule

out metastatic disease. Preresection mediastinoscopy should also be performed. If there are mediastinal node metastases, then surgery should be abandoned, and the patient treated with concurrent chemoradiotherapy as outlined later. Five-year survival for peripheral SCLC that is treated with surgery and adjuvant therapy is approximately 30% to 40%.

Approximately one third of patients have LD at diagnosis. LD-SCLC has a response rate of 70% to 80% with standard chemotherapy and thoracic radiotherapy, and a complete clinical response of 50% to 60%. In a meta-analysis of trials with chemotherapy alone versus combined chemotherapy and thoracic radiotherapy, survival was significantly better with combined-modality therapy. Chemotherapy usually consists of a platinum-based regimen. The two most commonly used regimens are etoposide and cisplatin or etoposide and carboplatin. Chemotherapy beyond four to six cycles has not been shown to prolong survival.

The best approach to radiotherapy for LD-SCLC is under evaluation. Two cooperative group trials randomized patients to once-daily versus twice-daily thoracic radiotherapy with concomitant chemotherapy.[156–158] The long-term follow-up of the patients enrolled in the Eastern Cooperative Oncology Group/Radiation Therapy Oncology Group (ECOG/RTOG) trial demonstrated a superior survival at 5 years with the twice-daily radiotherapy (26% vs. 16%).[158] All patients received four cycles of etoposide and cisplatin (two cycles concurrent with radiotherapy) and thoracic radiotherapy began on day 1 with chemotherapy. However, the North Central Cancer Treatment Group trial did not demonstrate any difference in survival with twice-daily radiotherapy versus once-daily therapy.[156,157] All patients received identical chemotherapy with six cycles of etoposide and cisplatin. Radiotherapy began with cycle 4 of chemotherapy. Both trials demonstrated that the median survival time for LD-SCLC is now 18 to 20 months when patients are treated with concurrent chemoradiotherapy, and 20% to 25% of patients will be alive at 5 years. It is unclear if twice-daily thoracic radiotherapy is superior to standard once-daily radiotherapy. Local recurrence is still a problem in over 50% of individuals with radiotherapy doses less than 50 Gy. Current trials are exploring higher doses of thoracic radiotherapy in SCLC. It is generally agreed that concurrent thoracic radiotherapy should begin early, with the first or second cycle of chemotherapy.

ED-SCLC is treated with the same platinum-based chemotherapy doublets and has a response rate of 60% to 80%, with only 20% achieving a clinical complete remission. The median survival time for ED-SCLC is 8 to 9 months, with 10% of patients or fewer alive at 2 years.[159,160] There are virtually no 5-year survivors with ED-SCLC. Many trials have evaluated alternating non–cross-resistant chemotherapy, maintenance chemotherapy (after the initial four to six cycles), and dose-intensity chemotherapy, but none of these approaches has been shown to increase survival. The standard approach to therapy of ED-SCLC is to treat with a platinum-based regimen for four to six cycles and then to observe until the patient's disease progresses, and then offer second-line chemotherapy.[156,158–160] A study from Japan compared irinotecan and cisplatin versus etoposide and cisplatin in ED-SCLC.[160a] The response rate (89% vs. 67%) and survival (median survival time, 12.8 vs. 9.4 mo) were superior with the irinotecan and cisplatin regimen (2-year survival, 19.5% vs. 5.2%). This study was small, with fewer than 100 patients in each arm, and the trial was closed early by the data safety monitoring committee. Subsequently, the Southwestern Oncology Group (SWOG) completed a much larger trial and was unable to observe any difference in survival with the irinotecan and cisplatin regimen (median survival time, 9.9 vs. 9.1 mo).[160b] This regimen was associated with more grade 3 diarrhea, but the etoposide and cisplatin regimen had significantly more hematologic toxicity. Several trials have evaluated a number of the novel agents but, to date, none have shown improved response or survival when added to standard treatment of small cell lung cancer.

Prophylactic cranial irradiation (PCI) is an area of controversy. If a patient with SCLC achieves a complete remission, then there is a 50% chance of development of cranial metastasis within the next 2 years. A meta-analysis of seven randomized trials of PCI versus no PCI for patients in complete remission reported an observed beneficial effect after PCI, with a 5.4% increase in absolute survival (20.7% vs. 15.3%) at 3 years.[161] The major questions raised by the meta-analysis concern the optimal dose of PCI and the neuropsychological sequelae of PCI. Most oncologists recommend PCI in patients who achieve a complete remission with initial therapy.

When patients relapse after initial therapy, the median survival is 3 to 4 months. There are no cures with second-line therapy. If a patient has been off treatment for 6 months or greater, then it is reasonable to use the same agents that he or she received initially. If initial therapy did not include a platinum agent, then second-line therapy should be with a platinum-containing doublet. Currently, the only drug approved for second-line treatment of SCLC by the FDA is single-agent topotecan.[162] Other single agents such as paclitaxel, irinotecan, and epirubicin are active but are not yet approved by the FDA for second-line treatment of SCLC. Epirubicin is commercially available and approved for second-line treatment in Japan. Finally, although there have been promising leads, no targeted therapy has yet been approved for SCLC.[163]

PALLIATIVE CARE

Although much of this chapter is devoted to efforts to cure lung cancer, most patients will eventually succumb to their disease. Although pulmonologists are adept at providing supportive care in the intensive care unit (see Chapter 93), caring for the ambulatory dying patient with lung cancer requires special consideration. There is a vast literature on ambulatory pain management, the use of interventional pulmonary techniques such as tumor ablation and stent placement to relieve malignant airway obstruction, and the use of hospice to provide end-of-life care in the home setting. With the tools now available to physicians, patients need not suffer

debilitating cough, nausea, dyspnea, or pain. Pulmonologists are encouraged to provide "aggressive palliation" with the same conviction that they provide treatments for critically ill patients in the intensive care unit.[164,165]

SPECIAL CONSIDERATIONS IN LUNG CANCER

Superior Sulcus Tumors and Pancoast's Syndrome

Pancoast's syndrome is a constellation of symptoms and signs that include shoulder and arm pain along the distribution of the eighth cranial nerve trunk and first and second thoracic nerve trunks, Horner's syndrome, and weakness and atrophy of the hand.[166–168] The underlying cause is usually local extension of an apical lung tumor located in the superior pulmonary sulcus (Pancoast's tumor). The most common cause of this symptom complex is NSCLC; however, SCLC and a number of other types of tumors and infections may rarely present in this manner.[166] The most common initial symptom is shoulder pain, which is produced by tumor involvement of the parietal pleura, brachial plexus, vertebral bodies, and first, second, and third ribs. The pain may radiate along the upper back or shoulder into the axilla and along the distribution of the ulnar nerve. Patients are commonly treated for arthritis or bursitis of the shoulder for months before the correct diagnosis is determined. Horner's syndrome consists of ptosis, myosis, and anhydrosis and is caused by the invasion of the paravertebral sympathetic chain and the inferior cervical (stellate) ganglion.[166] Pancoast's syndrome is present in approximately one third of patients with superior sulcus tumors reported in the literature. The intrinsic muscles of the hands may become weak and atrophied as the tumor progresses. With further extension through the intervertebral foramina, spinal compression and paraplegia may develop.

The chest radiograph may show an apical tumor, although, in some cases, a tumor can be identified only on a CT scan of the chest. If the diagnosis is suspected, but the chest radiograph is negative, then a CT chest scan should be obtained (Fig. 47-4). CT also provides additional information about the extent of the tumor and is especially helpful in identifying other pulmonary nodules and mediastinal adenopathy. MRI of the chest is considered to be superior for evaluating patients with superior sulcus tumors because of better assessment of invasion through the pleura and subpleural fat, better evaluation of plexus involvement, and better definition of subclavian vessel involvement.[169] Magnetic resonance angiography may give the best assessment of vascular invasion of the subclavian vessels. Flexible fiberoptic bronchoscopy is frequently the first diagnostic test for apical tumors and has a diagnostic yield of approximately 50%.[170] TTNA has a very high diagnostic yield (>90%) even if the bronchoscopy is nondiagnostic.[171] Superior sulcus tumors are usually staged as T3N0M0 (stage IIB) or higher depending on size of the tumor (T3 or T4) and extent of lymph node involvement. In a large series from M. D. Anderson, 25% of patients were stage IIB, 22% were IIIA, and 53% were stage IIIB (T4 or N3).[172] Obviously, some patients are stage IV at diagnosis, but they were excluded from that report. It is estimated that one third to one half of all superior sulcus tumors have identifiable distant metastasis at diagnosis. In addition to the stage of disease and performance score, other important poor prognostic factors include weight loss and vertebral body or supraclavicular involvement. The presence of N1 or N2 nodal involvement and incomplete resections have a worse prognosis.[172,173] In patients treated for localized disease (stage IIB or IIIB), the brain is the most common site of relapse.[174] In the past, the most common treatment for localized superior sulcus tumors due to NSCLC was preoperative radiotherapy of 30 to 50 Gy followed by resection. This resulted in a 5-year survival of 25% to 35%. The current standard of practice is to perform neoadjuvant chemoradiotherapy followed by resection. This is based on results of the North America Intergroup Trial in which patients with a negative mediastinoscopy were treated with two cycles of etoposide and cisplatin chemotherapy and concurrent thoracic radiotherapy (45 Gy in 5 wk). In the resected specimen, a pathologic complete response or minimal microscopic disease was identified in 66% of patients. The overall survival at 5 years was 44% and, for those with a complete resection, 54%.[174] In a phase II trial in Japan, chemotherapy with mitomycin, vindesine, and cisplatin with concurrent thoracic radiotherapy led to a 5-year survival of 56%.[175] Although the optimal regimen of treatment has not been proved, a reasonable choice is that utilized in the U.S. Intergroup Trial study described above.

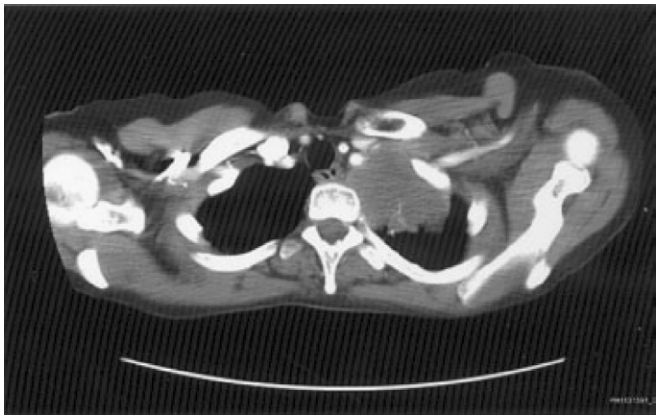


FIGURE 47-4 ■ CT scan of patient with a Pancoast tumor.

Superior Vena Cava Syndrome

The blockage of blood flow in the superior vena cava (SVC) results in SVC syndrome.[176] Bronchogenic carcinoma accounts for the vast majority of these cases in older adults.[177,178] In teenagers and young adults, SVC syndrome is usually due to non-Hodgkin's lymphoma. Patients complain of dyspnea and a sensation of fullness in the head and/or light-headedness when bending over.

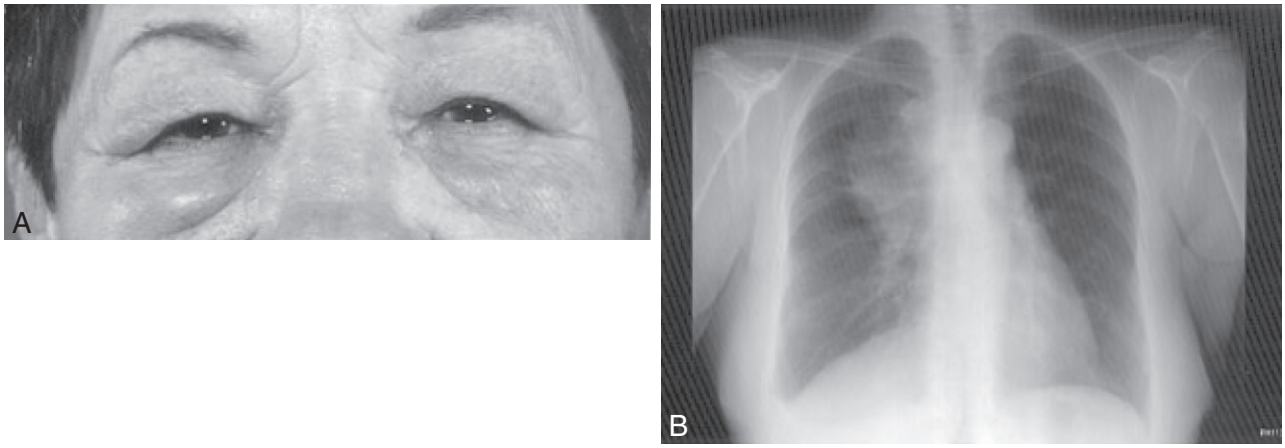


FIGURE 47-5 ■ **A,** Facial swelling in a patient with superior vena cava (SVC) syndrome. **B,** Chest radiograph depicts right hilar mass in patient with SVC syndrome.

They may also note facial swelling. Cough, pain, and dysphagia are less frequent symptoms. Physical examination findings included dilated neck veins, a prominent venous pattern on the chest, facial edema, and a plethoric appearance (Fig. 47-5A). The chest radiograph typically shows widening of the mediastinum or a right hilar mass (see Fig. 47-5B). Occasionally, it may be normal. Dilated veins on the anterior chest wall and compression of the SVC may be demonstrated with a contrast-enhanced CT scan. SVC syndrome is not generally a medical emergency, and patients should not be treated without a tissue diagnosis. Bronchoscopy or mediastinoscopy can be safely performed in the setting of SVC syndrome.[179] SVC syndrome due to SCLC is best treated with chemotherapy. Generally, after treatment, symptoms will start to resolve in 5 to 7 days because SCLC is chemosensitive.[180] NSCLC is best treated with concurrent chemoradiotherapy (see earlier discussion of treatment of stage IIIA/IIIB NSCLC). For immediate relief of SVC obstruction, vascular stenting should be strongly considered. A Cochrane meta-analysis reported that SVC stents relieved obstruction in 95% of cases.[180] Stenting has been associated with a complication rate of 3% to 7%.

PARANEOPLASTIC SYNDROMES

Hormonal, neurologic, hematologic, or other remote effects of cancer not related to the direct invasion, obstruction, or metastatic effects of tumor are generally termed *paraneoplastic syndromes*. Paraneoplastic syndromes related to bronchogenic carcinoma occur in 10% to 20% of patients (Table 47-6).

Musculoskeletal Effects

Clubbing of the digits may be a manifestation of lung cancer or other diseases. Clubbing may involve the fingers and toes and consists of selective enlargement of the connective tissue in the terminal phalanges. Physical findings include loss of the angle between the base of the nail bed and the cuticle, rounded nails, and enlarged fingertips. Clubbing is an isolated finding and is usually asymptomatic. Nonmalignant causes of clubbing include pulmonary fibrosis, congenital heart disease, and bronchiectasis. Hypertrophic pulmonary osteoarthropathy (HPO) is an uncommon process associated with lung cancer. HPO is characterized by painful arthropathy that usually involves the ankles, knees, wrists, and elbows and is most often symmetrical. The pain and arthropathy are caused by proliferative periostitis that involves the long bones but may also affect metacarpal, metatarsal, and phalangeal bones. Patients may have clubbing of fingers and toes in addition to the painful arthralgias. The pathogenesis of HPO is uncertain, but it may arise from a humoral agent. For patients who smoke and have a new onset of arthralgias, HPO must be considered. A radiograph of the long bones (i.e., tibia and fibula) usually shows characteristic periosteal new bone formation. An isotope bone scan typically demonstrates diffuse uptake by the long bones. Large cell and adenocarcinoma are the most common histologic types associated with HPO. The symptoms of HPO may resolve after thoracotomy, whether the primary cancer is resected or not. For inoperable patients, treatment is with nonsteroidal anti-inflammatory agents. Recently, case reports have observed resolution or marked improvement of symptoms with bisphosphonate treatment.[181]

Although still a topic of debate, population-based studies from Scandinavia suggest a frequency of malignancy of 15% to 25% in patients with dermatomyositis-polymyositis.[182] The highest risk of malignancy is in the first 2 years after the diagnosis of dermatomyositis-polymyositis. A reasonable approach to cancer surveillance in these patients is a careful history and physical examination, chest radiograph, basic laboratory tests, and age-appropriate cancer screening examinations. Other tests should be based on abnormalities detected during the basic evaluation.

Hematologic Effects

Anemia frequently occurs in patients who have lung cancer and may be caused by iron deficiency, chronic

TABLE 47-6. Paraneoplastic Syndromes Associated with Bronchogenic Carcinoma

System	Paraneoplastic Syndrome
Musculoskeletal	Clubbing
	Hypertrophic osteoarthropathy
	Polymyositis
	Osteomalacia
	Myopathy
Cutaneous	Dermatomyositis
	Acanthosis nigricans
	Pruritus
	Erythema multiforme
	Hyperpigmentation
	Urticaria
	Scleroderma
Endocrinologic	Cushing's syndrome
	Syndrome of inappropriate secretion of antidiuretic hormone
	Hypercalcemia
	Carcinoid syndrome
	Hyperglycemia/hypoglycemia
	Gynecomastia
	Galactorrhea
	Growth hormone excess
	Calcitonin secretion
	Thyroid-stimulating hormone
Neurologic	Lambert-Eaton myasthenic syndrome
	Peripheral neuropathy
	Encephalopathy
	Myelopathy
	Cerebellar degeneration
	Psychosis
	Dementia
Vascular/hematologic	Thrombophlebitis
	Arterial thrombosis
	Nonbacterial thrombotic endocarditis
	Thrombocytosis
	Polycythemia
	Hemolytic anemia
	Red cell aplasia
	Dysproteinemia
	Leukemoid reaction
	Eosinophilia
	Thrombocytopenic purpura
Miscellaneous	Cachexia
	Hyperuricemia
	Nephrotic syndrome

disease, or bone marrow infiltration. Eosinophilia is more commonly associated with Hodgkin's disease but may occur in patients who have lung cancer. Production of various cytokines by neoplastic cells may result in eosinophilia, leukocytosis, or thrombocytosis, of which thrombocytosis is by far the most common. The association of deep venous thrombosis and malignancy was described by Trousseau over a century ago, and lung cancer is the most common malignancy associated with Trousseau's syndrome. The causes of the hypercoagulable state remain poorly understood. One large study documented clinically significant association of idiopathic thrombosis and the subsequent development of overt cancer; however, other investigators concluded that the literature does not enable firm recommendations about whether to screen for a malignant neoplasm in patients who have unexplained venous thromboembolism.[183] Thromboembolism in the patient who has malignancy is often refractory to warfarin treatment. Treatment with low-molecular-weight heparin (LMWH) on a chronic basis may be effective. In a randomized trial, patients with cancer and deep vein thrombosis, pulmonary embolism, or both were randomized to receive LMWH (dalteparin) subcutaneously once daily or oral warfarin daily for 6 months.[184] At 6 months, the probability of recurrent thromboembolism was 9% with dalteparin treatment and 17% with warfarin, a difference that was highly significant. The risks of major bleeding or any bleeding were not different in the two groups. The other advantage of LMWH is that it is unnecessary to monitor the anticoagulant effect, except in some patients with renal insufficiency. A recent Cochrane analysis concluded that, for long-term treatment in patients with cancer, LMWH reduced venous thromboembolism events, but not death, as compared with vitamin K antagonists. There was no significant difference in the risk of bleeding.[185]

Hypercalcemia

Hypercalcemia in association with malignancy may arise from a bony metastasis or, less commonly, from secretion by the tumor of a parathyroid hormone–related protein (PTHrP) or other bone-resorbing cytokine. The most common cancers to cause hypercalcemia are those of the kidney, lung, breast, head, and neck and myeloma and lymphoma. In one study of 690 consecutive lung cancers, 2.5% of cases had tumor-induced hypercalcemia.[186] Squamous cell histology is the most common cell type associated with hypercalcemia, and generally patients have advanced disease (stage III or IV) and are unresectable. Symptoms of hypercalcemia include anorexia, nausea, vomiting, constipation, lethargy, polyuria, polydipsia, and dehydration. Confusion and coma are late manifestations, as are renal failure and nephrocalcinosis. Cardiovascular effects include shortened QT interval, broad T wave, heart block, ventricular arrhythmia, and asystole. Individual patients may manifest any combination of these signs and symptoms in various degrees.

Hypercalcemia of malignancy that is not caused by bony metastases results from accelerated bone resorption, decreased bone deposition, or increased renal tubular reabsorption of calcium. Accelerated bone resorption is caused by activation of osteoclasts by cytokines or PTHrP in most cases. Serum parathyroid hormone levels are usually normal or low, but an elevated level of PTHrP can be detected in the serum in approximately one half of these patients.[186] Cytokines or PTHrP are secreted autonomously by the tumor. Not only does PTHrP cause renal calcium reabsorption, but

also it interferes with renal mechanisms for reabsorption of sodium and water, with resultant polyuria. Polyuria and vomiting result in dehydration; decreases in glomerular filtration further aggravate the hypercalcemia.

Mild elevation of serum calcium may not require treatment, so the decision is based on the patient's symptoms. For patients who have widely metastatic and incurable malignancy, it may be most appropriate to give supportive care only and not treat the hypercalcemia. The average life expectancy in this situation is 30 to 45 days, even with aggressive treatment.[187] Most patients who have a serum calcium of 12 to 13 mg/dL or higher are treated.

The four basic goals of treatment are to (1) correct dehydration; (2) increase renal excretion of calcium; (3) inhibit bone resorption; and (4) treat the underlying malignancy. Because of the polyuria, patients with hypercalcemia are volume contracted. Initial treatment is with intravenous normal saline, using 3 to 6 L/24 hr as tolerated, with careful attention to volume status. Previously, a loop diuretic such as furosemide or ethacrynic acid was added to maximize calcium excretion but has become less common due to the efficacy of the bisphosphonates in inhibiting bone resorption. Thiazide diuretics are not used because they increase calcium reabsorption in the distal tubule. Fluids and diuretics generally result in only a mild decrease of the calcium; additional treatment is needed to inhibit the accelerated bone resorption. The bisphosphonates have a high affinity for bone and inhibit osteoclast activity. Zoledronate, a newer bisphosphonate, is the most effective; the usual dose is 4 mg given intravenously over 15 minutes.[188] Normal calcium levels are achieved within 4 to 10 days in 85% of patients and last a median of 30 to 40 days. Adverse effects are generally mild and transient and include fever, hypophosphatemia, asymptomatic hypocalcemia and, occasionally, renal failure. Calcitonin inhibits bone resorption, increases renal calcium excretion, and has a rapid onset of action, but the duration of action is short-lived. Calcitonin is a relatively weak agent and, when used alone, does not usually normalize the serum calcium of patients who have marked hypercalcemia. Use of calcitonin is appropriate when the calcium is greater than 14 mg/dL or needs to be lowered urgently (onset of action is 4–6 hr) while waiting for the more effective but slower-acting agents to take effect or when relief of bony pain is desired. The effects of calcitonin and bisphosphonates are additive. Tachyphylaxis may occur to calcitonin after 48 hours. Other agents such as gallium nitrate or plicamycin have been used to treat hypercalcemia but have not generally been adopted as first-line therapies because of inconvenience of administration schedules or associated toxicities.

Syndrome of Inappropriate Antidiuretic Hormone Secretion

Causes of hyponatremia include tumors, pulmonary infections, central nervous system disorders, and drugs. Although only 10% of patients with SCLC exhibit SIADH, SCLC accounts for approximately 75% of cases of SIADH. Antidiuretic hormone (vasopressin) is secreted in the anterior hypothalamus and exerts its action on the renal collecting ducts by enhancing the flow of water from the lumen into the medullary interstitium, thereby concentrating the urine. The criteria for the diagnosis of SIADH include (1) hyponatremia associated with serum hypoosmolality (<275 mOsm/kg), (2) inappropriately elevated urine osmolality (>200 mOsm/kg) relative to serum osmolality; (3) elevated urine sodium (>20 mEq/L); (4) clinical euvolemia without edema; and (5) normal renal, adrenal, and thyroid function. The serum uric acid is usually low, and the urine osmolality–to–serum osmolality ratio is frequently greater than 2. The severity of symptoms is related to the degree of hyponatremia and the rapidity of the fall in serum sodium. In one large series of SIADH patients, only 27% had signs or symptoms of hyponatremia despite a median sodium of 117 mEq/L (range, 101–129 mEq/L). Symptoms of hyponatremia include anorexia, nausea, and vomiting. With a rapid onset of hyponatremia, symptoms caused by cerebral edema may include irritability, restlessness, personality changes, confusion, coma, seizures, and respiratory arrest. In minimally symptomatic or asymptomatic patients, fluid restriction of 500 to 1000 mL/24 hr is the initial treatment of choice. Conivaptan is an intravenous vasopressin receptor antagonist that has been shown to be useful in correcting hyponatremia but its use is limited to the hospital. Oral vasopressin receptor antagonists are under evaluation but not yet available.[189,190]

If further treatment is needed, oral demeclocycline (900–1200 mg/day) can be considered. Demeclocycline induces a nephrogenic diabetes insipidus and blocks the action of antidiuretic hormone on the renal tubule, thereby increasing water excretion. The onset of action varies from a few hours to a few weeks, so this drug is not recommended for acute emergency treatment. Demeclocycline has potential kidney toxicity. In patients who have more severe or life-threatening symptoms (serum sodium <115 mEq/L), treatment consists of intravenous saline, supplemental potassium, and diuresis with loop diuretics such as furosemide or ethacrynic acid. With severe confusion, convulsions, or coma, it may be appropriate to treat with 300 mL of 3% saline given over 3 to 4 hours in combination with a loop diuretic (saline without a diuretic will not increase the sodium concentration). Rapid correction of the sodium may have life-threatening consequences, and caution is advised.[191] The rate of correction of the sodium is best limited to a maximum of 20 mEq/L/day, until a level of 120 to 130 mEq/L is reached. Faster correction has been associated with the development of central pontine myelinolysis, which may result in quadriplegia, cranial nerve abnormalities that manifest as pseudobulbar palsy, alteration in mental status, and subsequent death. Accordingly, in the course of treating hyponatremia, the serum sodium must be monitored frequently to ensure that correction is not too rapid. For patients with SIADH due to SCLC, treatment with chemotherapy should be initiated as soon as possible and is likely to result in

improvement in the hyponatremia within a few weeks. After an initial response to chemotherapy, SIADH may recur when the tumor relapses.

Ectopic Corticotropin Syndrome

Ectopic production of corticotropin or corticotropin-releasing hormone with associated Cushing's syndrome has been identified in patients who have SCLC, carcinoid tumor (lung, thymus, or pancreas), and neurocrest tumors such as pheochromocytoma, neuroblastoma, and medullary carcinoma of the thyroid.[192] Of those with ectopic corticotropin secretion, SCLC accounts for 75% of cases, although only 1% to 2% of patients with SCLC develop Cushing's syndrome. Cushing's syndrome is seldom caused by NSCLC.

Classic features of Cushing's syndrome include truncal obesity, striae, rounded (moon) facies, dorsocervical fat pad (buffalo hump), myopathy and weakness, osteoporosis, diabetes mellitus, hypertension, and personality changes. However, the rapid growth of SCLC means that patients are more likely to present with edema, hypertension, and muscular weakness than with the classic features of Cushing's syndrome. Hypokalemic alkalosis and hyperglycemia are usually present. Patients with SCLC and Cushing's syndrome appear to have shortened survival compared to those without the syndrome, perhaps because of more frequent opportunistic infections. The best screen for Cushing's syndrome is the 24-hour urine free cortisol measurement. Elevation of cortisol production, lack of suppression with high-dose dexamethasone, and plasma corticotropin levels greater than 200 pg/mL (40 pmol/L) are highly suggestive of ectopic corticotropin as the cause of Cushing's syndrome in the absence of a pituitary adenoma. The plasma level of corticotropin is elevated in many, but not all, patients. Treatment of Cushing's syndrome due to ectopic corticotropin has included adrenal enzyme inhibitors such as metyrapone, aminoglutethimide, and ketoconazole, given alone or in combination. Ketoconazole given orally at a dosage of 400 to 1200 mg/day or metyrapone 250 to 750 mg three times per day may control hypercortisolism within a few days to weeks, but the response is variable.[193] Dose adjustments are based on achieving normal urinary free cortisol levels or morning plasma cortisols of 7 to 11 μg/mL. Symptomatic hypoadrenalism may result from treatment, and some authorities recommend a replacement dose of glucocorticoid when an enzyme inhibitor is started. When Cushing's syndrome arises from SCLC, it is advisable to proceed with appropriate chemotherapy and carefully watch for superimposed infections, as is necessary for any patient who is receiving high-dose corticosteroids. Cushing's syndrome related to a bronchial carcinoid or thymic carcinoid is best treated by surgical resection of the tumor.

Neurologic Effects

The paraneoplastic neurologic syndromes associated with lung cancer, mostly small cell type, are quite variable. They include LEMS, subacute sensory neuropathy, encephalomyelopathy, cerebellar degeneration, autonomic neuropathy, retinal degeneration, and opsoclonus.[194] The frequency of any of these neurologic syndromes in SCLC is approximately 5%, and neurologic symptoms may precede the diagnosis by months to years.[195,196] Most patients who have SCLC and an associated paraneoplastic syndrome have LD-SCLC that may or may not be obvious on initial evaluation. Careful radiographic evaluation of the lungs and mediastinum is indicated in a smoker who has a suspected paraneoplastic neurologic syndrome. In this setting, even subtle abnormalities of the mediastinum require a biopsy. A PET scan may help identify an occult lesion and facilitate biopsy confirmation of the diagnosis.[197,198] Many reports have suggested that patients with paraneoplastic neurologic syndromes have a better prognosis than those without the paraneoplastic syndromes with similar stage and histology.

These paraneoplastic neurologic syndromes are thought to be immune-mediated, based on the identification of a number of antibodies in the serum that react with both the nervous system and the underlying cancer.[194] However, not all patients with paraneoplastic syndromes have identifiable antibodies in their serum. The literature is confusing because of different names employed by various investigators. The anti-Hu antibody is the same as antineuronal nuclear antibody type 1 (ANNA-1), and the anti-Ri antibody is identical to ANNA-2. Both of these antibodies, but predominantly ANNA-1, have been associated with SCLC. ANNA-1 binds to the nuclei of all neurons in the central and peripheral nervous system, including the sensory and autonomic ganglia, the myenteric plexus, and cells of the adrenal medulla. Such antibodies should not be confused with the anti–Purkinje cell antibody (anti-Yo), which is characteristically found in patients who have subacute cerebellar degeneration as a manifestation of gynecologic malignancy or breast cancer. The CRMP-5 antibody, also known as anti–CV-2, has been associated with SCLC and thymomas.[194]

In a review of 162 sequential patients who had elevated ANNA-1 (anti-Hu), 142 (88%) were proved to have cancer, 132 of whom had SCLC.[196] In 97% of these cases, the diagnosis of SCLC followed the onset of the associated neurologic syndrome, usually by less than 6 months but, in 20%, the period was greater than 6 months. Of special note is that 90% of cases had disease limited to the lung or to the lung and mediastinum (LD-SCLC). In a report from Europe, 144 patients out of 200 with anti-Hu antibodies had a tumor in the chest.[195] Of these, 111 were proved to be SCLC. In one large series, ANNA-1 antibodies were identified in 16% of all patients with SCLC. These antibodies were associated with limited-stage disease, complete response to therapy, and longer survival compared with patients who had SCLC and no ANNA-1 antibody. These neurologic syndromes seldom improve with treatment, so the goal is to prevent progression by starting treatment of the underlying tumor as soon as possible.

Less common manifestations of neurologic paraneoplastic syndromes are orthostatic hypotension and

intestinal dysmotility. The gastrointestinal symptoms may present as nausea, vomiting, abdominal discomfort, or altered bowel habits suggestive of intestinal pseudo-obstruction. Many of these patients present with gastrointestinal symptoms and significant weight loss prior to the diagnosis of SCLC.

Proximal muscle weakness, hyporeflexia, and autonomic dysfunction characterize LEMS.[199,200] Cranial nerve involvement may be present and does not differentiate LEMS from myasthenia gravis. LEMS has been strongly associated with antibodies directed against P/Q-type presynaptic voltage-gated calcium channels (anti-VGCC antibodies) of peripheral cholinergic nerve terminals. These anti-VGCC antibodies, identified in over 90% of patients with LEMS, block the normal release of acetylcholine at the neuromuscular junction. In contrast, myasthenia gravis is associated with anti–acetylcholine receptor antibodies, which are present in approximately 90% of myasthenic patients. Malignancy is present in approximately one half of patients who have LEMS, and SCLC is by far the most common malignancy. In a recent study of 63 patients with SCLC examined prospectively, only 3% had clinical and electrophysiologic signs of LEMS, 8% had elevated anti-VGCC antibodies and 26% had other neurologic symptoms unrelated to LEMS.[199a] The diagnosis of LEMS is based on characteristic electromyographic findings that show a small amplitude of the resting compound muscle action potential and facilitation with rapid, repetitive, supramaximal nerve stimulation or after brief exercise of the muscle. A single-fiber electromyogram is optimal for making the diagnosis. LEMS is the predominant paraneoplastic neurologic syndrome that may improve with successful treatment of the associated lung cancer. The use of acetylcholinesterase inhibitors is of limited benefit in LEMS.[201] Diaminopyridine enhances the release of acetylcholine and has been used with sustained improvement over months in the majority of patients with LEMS either with or without cancer.[202]

KEY POINTS

- Lung cancer currently claims more lives than breast, colon, and prostate cancer combined and is the number-one cancer killer of both men and women in the United States.
- A new staging system, based on survival data from a large, international population with lung cancer, has changed the tumor (T) and metastasis (M) but not the nodal (N) classifications. The revised classifications and stages should predict survival and guide therapy more closely than the former TMN system.
- Routine screening for lung cancer is not recommended at this time. In the near future, prospective, randomized, controlled studies that avoid lead-time bias, length-time bias, and overdiagnosis bias will help determine whether routine screening actually reduces the mortality from lung cancer.
- In general, for NSCLC, early lung cancer (stage I) is treated with surgery alone, stage II lung cancer is treated with surgery followed by adjuvant chemotherapy, locally advanced lung cancer (stage IIIA and B) is treated with a combination of chemotherapy and radiotherapy, and metastatic disease (stage IV) is treated with chemotherapy alone.
- For SCLC, localized disease (disease within one hemithorax that can be encompassed in a radiation port) is treated by chemoradiotherapy; extensive disease is treated with chemotherapy alone.
- A certain subgroup of lung cancer patients has been recognized to exhibit an activating mutation of the tyrosine kinase domain of the epidermal growth factor receptor. This subgroup, mostly female, never smokers of East Asian descent with adenocarcinoma, may respond to blockade of this receptor by the EGFR TKIs gefitinib and erlotinib. This exciting development is the first example of therapy targeted to a molecular abnormality in lung cancer and illustrates the hope for the future of targeted therapy in this disease.

References

1. Liu BQ, Peto R, Chen ZM, et al: Retrospective proportional mortality study of one million deaths. BMJ 317:1411–1422, 1998.
2. Yang G, Fan L, Tan J, et al: Smoking in China: Findings of the 1996 National Prevalence Survey. JAMA 282:1247–1253, 1999.
3. Smith RA, Cokkinides V, Eyre HJ: American Cancer Society Guidelines of Early Detection of Cancer. CA Cancer J Clin 53:27–43, 2003.
4. Bach PB, Kelly MJ, Tate RC, McCory DC: Screening for lung cancer: A review of the literature. Chest 123:72S–82S, 2003.
5. Fontana RS, Sanderson DR, Woolner LB, et al: Lung cancer screening. The Mayo Program. J Occup Med 28:746–750, 1986.
6. Marcus PM, Bergstralh E, Fagerstrom RM, et al: Lung cancer mortality in Mayo Lung Project: Impact of extended follow-up. J Natl Cancer Inst 92:1308–1316, 2000.
7. Fontana RS, Sanderson DR, Taylor WF, et al: Early lung cancer detection: Results of the initial (prevalence) radiologic and cytologic screening in the Mayo Clinic Study. Am Rev Respir Dis 130:561–565, 1984.
8. Diederich S, Wormanns D, Semik M, et al: Screening for early lung cancer with low-dose spiral CT: prevalence in 817 asymptomatic smokers. Radiology 222:773–781, 2002.

9. Henschke CI, McCauley DI, Yankelevitz DF, et al: Early lung cancer detection project: Overall design and findings from baseline screening. Lancet 354:99–105, 1999.
10. Sobue T, Moriyama N, Kaneko M, et al: Screening for lung cancer with low-dose helical computed tomography: Anti–lung cancer association project. J Clin Oncol 20:911–920, 2002.
11. Sone S, Li F, Yang Z, et al: Characteristics of small lung concerns invisible on conventional chest radiography and detected by population-based screening using spiral CT. Br J Radiol 73:137–145, 2000.
12. Swensen SJ, Jett JR, Hartman TE, et al: Lung cancer screening with CT: Mayo Clinic experience. Radiology 226:756–761, 2003.
13. Swensen SJ, Jett JR, Sloan JA, et al: Screening for lung cancer with low-dose spiral computed tomography. Am J Respir Crit Care Med 165:508–513, 2002.
14. MacMahon H, Austin JHM, Gamsu G, et al: Guidelines for management of small pulmonary nodules detected on CT scans: A statement from the Fleischner Society. Radiology 237:395–400, 2005.
15. Henschke CI, Yankelevitz DF, Libby DM, et al: Survival of patients with stage I lung cancer detected on CT screening. N Engl J Med 355:1763–1771, 2006.
16. Welch HG, Woloshin S, Schwartz LM, et al: Overstating the evidence for lung cancer screening: The International Early Lung Cancer Action Program (I-ELCAP) Study Arch Intern Med 167:2289–2295, 2007.
17. Sone S, Li F, Yang ZG, et al: Results of three-year mass screening programme for lung cancer using mobile low-dose spiral computed tomography scanner. Br J Cancer 84:25–32, 2001.
17a. Smith-Bindman R, Lipson J, Marcus R, et al: Radiation dose associated with common computed tomography examinations and the associated lifetime attributable risk of cancer. Arch Intern Med 169:2078–2086, 2009.
18. Bach PB, Jett JR, Pastorino U, et al: Computed tomography screening and lung cancer outcomes. JAMA 297:953–961, 2007.
19. Welch H: Finding and redefining disease. Effective Clin Pract 2:96–98, 1999.
20. Bach PB, Silvestri GA, Hanger M, Jett JR: Screening for lung cancer: ACCP evidence-based clinical practice guidelines (2nd ed). Chest 132(3 Suppl):69S–77S, 2007.
21. Chute CG, Greenberg ER, Baron J, et al: Presenting conditions of 1539 population-based lung cancer patients by cell type and stage in New Hampshire and Vermont. Cancer 56:2107, 1985.
22. Hyde L, Hyde CI: Clinical manifestations of lung cancer. Chest 65:299, 1974.
23. Colice GL: Detecting lung cancer as a cause of hemoptysis in a patient with a normal radiograph. Chest 111:877–884, 1997.
24. Mountain CF: Revisions in the International System for Staging Lung Cancer. Chest 111:1710–1717, 1997.
25. Goldstraw P, Crowley J, Chansky K, et al: The IASLC Lung Cancer Staging Project: Proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM classification of malignant tumours. J Thorac Oncol 2:706–714, 2007.
26. Darling GE: Staging of the patient with small cell lung cancer. Chest Surg Clin North Am 7:81–94, 1997.
27. Perigaud C, Bridji B, Roussel JC, et al: Prospective preoperative mediastinal lymph node staging by integrated PET-CT in patients with non-small-cell lung cancer. Eur J Cardiothorac Surg 36:731–736, 2009.
28. Silvestri GA, Gould MK, Margolis ML, et a: Noninvasive staging of non-small cell lung cancer: ACCP Evidenced-Based Clinical Practice Guidelines (2nd ed). Chest 132(3 Suppl):178S–201S, 2007.
29. American Thoracic Society, European Respiratory Society: Pretreatment evaluation of non-small cell lung cancer. Am J Respir Crit Care Med 156:320–332, 1997.
30. McLoud TC, Bourgouin PM, Greenberg RW, et al: Bronchogenic carcinoma: Analysis of staging in the mediastinum with CT by correlative lymph node mapping and sampling. Radiology 182:319–323, 1992.
31. Nolop KB, Rhodes CG, Brudin LH, et al: Glucose utilization in vivo by human pulmonary neoplasms. Cancer 60:2682–2689, 1987.
32. Wahl R, Hitchins GD, Buchsbaum D, et al: ^{18}F-2 deoxy-2-fluoro-D-glucose uptake into human tumor xenografts: Feasibility studies for cancer imaging with positron-emission tomography. Cancer 67:1544–1550, 1991.
33. Pieterman RM, van Putten JW, Meuzelaar JJ, et al: Preoperative staging of non–small cell lung cancer with positron-emission tomography. N Engl J Med 343:254–261, 2000.
34. vanTinteren H, Hoekstra OS, Smit EF, et al: Effectiveness of positron emission tomography in the preoperative assessment of patients with suspected non–small cell lung cancer: the PLUS Multicentre Randomised Trial. Lancet 359:1388–1393, 2002.
35. Hany TF, Steinert HC, Goerres GW, et al: PET diagnostic accuracy: Improvement with in-line PET-CT system: Initial results. Radiology 225:575–581, 2002.
36. Antoch G, Stattaus J, Nemat AT, et al: Non–small cell lung cancer: Dual modality PET/CT in preoperative staging. Radiology 229:526–533, 2003.
37. Silvestri GA, Littenberg B, Colice GL: The clinical evaluation for detecting metastatic lung cancer: A meta-analysis. Am J Respir Crit Care Med 152:225–230, 1995.
38. MacManus MP, Hicks RJ, Matthews JP, et al: High rate of unsuspected distant metastases by PET in apparent stage III non–small-cell lung cancer: Iimplications for radical radiation therapy. Int J Radiat Oncology Biol Phys 50:287–293, 2001.
39. Saunders CA, Dussek JE, O'Doherty MJ, Maisey MN: Evaluation of fluorine-18-fluorodeoxyglucose whole body positron emission tomography imaging in the staging of lung cancer. Ann Thorac Surg 67:790–797, 1999.
40. Weder W, Schmid RA, Bruchhaus H, et al: Detection of extrathoracic metastases by positron emission tomography in lung cancer. Ann Thorac Surg 66:886–893, 1998.
41. Grant D, Edwards D, Goldstraw P: Computed tomography of the brain, chest, and abdomen in the preoperative assessment of non–small cell lung cancer. Thorax 43:883–886, 1988.
42. Tarver RD, Richmond BD, Klatte EC: Cerebral metastases from lung carcinoma: Neurological and CT correlation work in progress. Radiology 153:689–692, 1984.
43. Salvatierra A, Baamonde C, Llamas JM, et al: Extrathoracic staging of bronchogenic carcinoma. Chest 97:1052–1058, 1990.
44. Tanaka K, Kubota K, Kodama T, et al: Extrathoracic staging is not necessary for non–small cell lung cancer with clinical stage T1-2 N0. Ann Thorac Surg 68:1039–1042, 1999.
45. Hillers TK, Sauve MD, Guyatt GH: Analysis of published studies on the detection of extrathoracic metastases in patients presumed to have operable non–small cell lung cancer. Thorax 49:14–19, 1994.
46. Pagani J: Non–small cell lung carcinoma adrenal metastases—Computed tomography and percutaneous needle biopsy in their diagnosis. Cancer 53:1058–1060, 1984.
47. Hooper RG, Tenholder MF, Underwood, et al: Computed tomographic scanning in initial staging of bronchogenic carcinoma. Chest 85:774–777, 1984.
48. Quinn DL, Ostrow LB, Porter DK, et al: Staging of non–small cell bronchogenic carcinoma—Relationship of the clinical evaluation to organ scans. Chest 89:270–275, 1986.
49. Ichinose Y, Hara N, Ohta M, et al: Preoperative examination to detect distant metastases is not advocated for asymptomatic patients with stages I and II non–small cell lung cancer—Preoperative examination for lung cancer. Chest 96:1104–1109, 1989.
50. Canadian Lung Oncology Group: Investigating extrathoracic metastatic disease in patients with apparently operable lung cancer. Ann Thorac Surg 71:425–433, 2001.
51. Goerg C, Schwerk WB, Wolf M, Havemann K: Adrenal masses in lung cancer: Sonographic diagnosis and follow-up. Eur J Cancer 28A:1400–1403, 1992.
52. Silvestri GA, Lenz JE, Harper SN, et al: The relationship of clinical findings to CT scan evidence of adrenal gland metastases in the staging of bronchogenic carcinoma. Chest 102:1748–1751, 1992.
53. Oliver TW, Bernardino ME, Miller JI, et al: Isolated adrenal masses in non-small cell bronchogenic carcinoma. Radiology 153:217–218, 1984.
54. Bury T, Dowlati A, Paulus P, et al: Whole-body ^{18}FDG positron emission tomography in the staging of non–small cell lung cancer. Eur Respir J 10:2529–2534, 1997.
55. Pearlberg JL, Sandler MA, Beute GH, et al: T1N0M0 bronchogenic carcinoma: Assessment by CT. Radiology 157:187–190, 1985.

56. Heavey LR, Glazer GM, Gross BH, et al: The role of CT in staging radiographic T1N0M0 lung cancer. AJR Am J Roentgenol 146:285–290, 1986.
57. Eggesbo HB, Hansen G: Clinical impact of adrenal expansive lesions in bronchial carcinoma. Acta Radiol 37:343–347, 1996.
58. Ettinghausen SE, Burt ME: Prospective evaluation of unilateral adrenal masses in patients with operable non–small cell lung cancer. J Clin Oncol 9:1462–1466, 1991.
59. Porte HL, Ernst OJ, Delebecq T, et al: Is computed tomography guided biopsy still necessary for the diagnosis of adrenal masses in patients with resectable non–small cell lung cancer. Eur J Cardiothorac Surg 15:597–601, 1999.
60. Macari M, Rofsky NM, Naidich DP, et al: Non–small cell lung carcinoma: Usefulness of unenhanced helical CT of the adrenal glands in an unmonitored environment. Radiology 209:807–881, 1998.
61. Gillams A, Roberts CM, Shaw P, et al: The value of CT scanning and percutaneous fine needle aspiration of adrenal masses in biopsy-proven lung cancer. Clin Radiol 46:18–22, 1992.
62. Heinz-Peer G, Honigschnabi S, Schneider B, et al: Characterization of adrenal masses using MR imaging with histopathologic correlation. AJR Am J Roentgenol 173:15–22, 1999.
63. Gross MD, Shapiro B, Bouffard JA, et al: Distinguishing benign from malignant euadrenal masses. Ann Intern Med 109:613–618, 1988.
64. Nielson ME, Heaston DK, Dunnick NR, et al: Preoperative CT evaluation of adrenal glands in non–small cell bronchogenic carcinoma. AJR Am J Roentgenol 139:317–320, 1982.
65. Chapman GS, Kumar D, Redmond J, et al: Upper abdominal computerized tomography scanning in staging non–small cell lung carcinoma. Cancer 54:1541–1543, 1984.
66. Butler AR, Leo JS, Lin JP, et al: The value of routine cranial computed tomography in neurologically intact patients with primary carcinoma of the lung. Radiology 131:339–401, 1979.
67. Cole FH, Thomas JE, Wilcox AB, et al: Cerebral imaging in the asymptomatic preoperative bronchogenic carcinoma patient: Is it worthwhile? Ann Thorac Surg 57:838–840, 1994.
68. Ferrigno D, Buccheri G: Cranial computed tomography as a part of the initial staging procedures for patients with non–small cell lung cancer. Chest 106:1025–1029, 1994.
69. Jacobs L, Kinkel WR, Vincent RG: "Silent" brain metastasis from lung carcinoma determined by computerized tomography. Arch Neurol 77:690–693, 1977.
70. Kormas P, Bradshaw JR, Jeyasingham K: Preoperative computed tomography of the brain in non–small cell bronchogenic carcinoma. Thorax 47:106–108, 1992.
71. Mintz BJ, Turhim S, Alexander S, et al: Intracranial metastases in the initial staging of bronchogenic carcinoma. Chest 86:850–853, 1984.
72. Colice GL, Birkmeyer JD, Black WC, et al: Cost-effectiveness of head CT in patients with lung cancer without clinical evidence of metastases. Chest 108:1264–1271, 1995.
73. Patchell RA, Tibbs PA, Walsh JW, et al: A randomized trial of surgery in the treatment of single metastases to the brain. N Engl J Med 322:494–500, 1990.
74. Davis PC, Hudgins PA, Peterman SB, et al: Diagnosis of cerebral metastases: Double-dose delayed CT vs contrast-enchanced MR imaging. AJR Am J Roentgenol 156:1039–1046, 1991.
75. Yokio K, Kamiya N, Matsuguma H, et al: Detection of brain metastasis in potentially operble non–small cell lung cancer—A comparison of CT and MRI. Chest 115:714–719, 1999.
76. Rivera MP, Mehta AC: Initial diagnosis of lung cancer: ACCP Evidence-Based Clinical Practice Guidelines (2nd ed). Chest 132(3 Suppl):131S–148S, 2007.
77. Torringer KG, Kern JD: The utility of fiberoptic bronchoscopy in the evaluation of solitary pulmonary nodules. Chest 104:1021–1024, 1993.
78. Kazerooni EA, Lim FT, Mikhail A, Martinez FJ: Risk of pneumothorax in CT-guided transthoracic needle aspiration biopsy of the lung. Radiology 198:371–375, 1996.
79. Li H, Boiselle PM, Shepard JO: Diagnostic accuracy and safety of CT-guided percutaneous needle aspiration biopsy of the lung: Comparison of small and large pulmonary nodules. AJR Am J Roentgenol 167:105–109, 1996.
80. VanSonnenberg E, Casola G, Ho M, et al: Difficult thoracic lesions: CT-guided biopsy experience in 150 cases. Radiology 167:457–461, 1988.
81. Ost D, Fein AM, Feinsilver SH: The solitary pulmonary nodule. N Engl J Med 348:2535–2542, 2003.
82. Simoff MJ: Endobronchial management of advanced lung cancer. Cancer Control 8:337, 2001.
83. Popovich J, Kvale PA, Eichenhorn MS, et al: Diagnostic accuracy of multiple biopsies from flexible bronchoscopy. A comparison of central versus peripheral carcinoma. Am Rev Respir Dis 125:521–523, 1982.
84. Shure D, Astarita RW: Bronchogenic carcinoma presenting as an endobronchial mass. Chest 83:865–867, 1983.
85. Schreiber G, McCrory DC: Performance characteristics of different modalities for diagnosis of suspected lung cancer. Chest 123(1 Suppl):115S–128S, 2003.
86. Schenk DA, Bower JH, Bryan CL, et al: Transbronchial needle aspiration staging of bronchogenic carcinoma. Am Rev Respir Dis 134:146–148, 1986.
87. Shure D, Fedullo PF: The role of transcarinal needle aspiration in the staging of bronchogenic carcinoma. Chest 86:693–696, 1984.
88. Wang KP, Brower R, Happonik EF, et al: Flexible transbronchial needle aspiration for staging of bronchogenic carcinoma. Chest 84:671–676, 1983.
89. Detterbeck FC, Jantz MA, Wallace M, et al: Invasive mediastinal staging of lung cancer: ACCP Evidence-Based Clinical Practice Guidelines (2nd ed). Chest 132(3 Suppl):202S–220S, 2007.
90. Chin R, McCain TW, Lucia MA, Cappellari JO: Transbronchial needle aspiration in diagnosing and staging lung cancer. Am J Respir Crit Care Med 166:377–381, 2002.
91. Davenport R: Rapid on-site evaluation of transbronchial aspirates. Chest 98:59–61, 1990.
92. Arita T, Kuramitsu T, Kawamura M, et al: Bronchogenic carcinoma: Incidence of metastasis to normal sized lymph nodes. Thorax 50:1267–1269, 1995.
93. Asamura H, Nakayama H, Kondo H, et a: Lobe specific extent of systematic lymph node dissection for non–small cell lung carcinomas according to a retrospective study of metastasis and prognosis. J Thorac Cardiovasc Surg 117:1102–1111, 1999.
94. Wallace MB, Silvestri GA, Sahai AV, et al: Endoscopic ultrasound-guided fine needle aspiration for staging patients with carcinoma of the lung. Ann Thorac Surg 72:1861–1867, 2001.
95. Chang K, Erickson R, Nguyen P: Endoscopic ultrasound (EUS) and EUS-guided fine-needle aspiration of the left adrenal gland. Gastrointest Endosc 44:568–572, 1996.
95a. Wallace MB, Pascual JMS, Raimondo M, et al: Minimally invasive endoscopic staging of suspected lung cancer. JAMA 299:540–546, 2008.
95b. Szlubowski A, Zielinski M, Soja J, et al: A combined approach of endobronchial and endoscopic ultrasound-guided needle aspiration in the radiologically normal mediastinum in non-small-cell lung cancer staging—a prospective trial. Eur J Cardiothorac Surg 2009, Epub ahead of print.
96. American Cancer Society (ACS): Cancer Facts and Figures. Atlanta: American Cancer Society. 1999.
97. Rosell R, Gomez-Codina J, Camps C, et al: Preresectional chemotherapy in stage IIIA non–small cell lung cancer: A 7-year assessment of a randomized controlled trial. Lung Cancer 26:7–14, 1999.
98. Rosell R, Gomez-Codina J, Camps C, et a: A randomized trial comparing preoperative chemotherapy plus surgery with surgery alone in patients with non–small cell cell lung cancer. N Engl J Med 330:153–158, 1994.
99. Roth JA, Atkinson EN, Fossella F, et al: Long-term follow-up of patients enrolled in a randomized trial comparing perioperative chemotherapy and surgery with surgery alone in resectable stage IIIA non–small cell lung cancer. Lung Cancer 21:1–6, 1998.
100. Roth JA, Fossella F, Komaki R, et al: A randomized trial comparing perioperative chemotherapy and surgery with surgery alone in resectable stage IIIA non–small cell cell lung cancer. J Natl Cancer Inst 86:673–680, 1994.
101. Alberts M, Bepler G, Hazelton T, et al: Practice organization. Chest 123:332–337s, 2003.

102. Pater JL, Loeb M: Non-anatomic prognostic factors in carcinoma of the lung: A multivariate analysis. Cancer 50:326, 1982.
103. Sculier J, Chansky K, Crowley J, et al: The impact of additional prognostic factors on survival and their relationship with the anatomical extent of disease expressed by the 6th edition of the TNM classification of malignant tumors and the proposals for the 7th edition. J Thorac Oncol 3:457–466, 2008.
104. Stanley KE: Prognostic factor for survival in patients with inoperable lung cancer. J Natl Cancer Inst 65:25, 1980.
105. Gail MH, Eagan RT, Feld R, et al: Prognostic factors in patients with resected stage I NSCLC: A report from the Lung Cancer Study Group. Cancer 54:1802–1813, 1984.
106. Harpole DH Jr, Herndon JE 2nd, Young WG Jr, et al: Stage I non–small cell lung cancer: A multivariate analysis of treatment methods and patterns of recurrence. Cancer 76:787–796, 1995.
107. Sorensen JB, Badsberg JH: Prognostic factors in resected stage I and II adencarcinoma of the lung. J Thorac Cardiovasc Surg 99:218, 1990.
108. Pairolero P, Williams D, Bergstralh E, et al: Postsurgical stage I bronchogenic carcinoma: Morbid implications of recurrent disease. Ann Thorac Surg 38:331, 1984.
109. Berghmans T, Dusart M, Paesmans M, et al: Primary tumor standardized uptake value (SUVmax) measured on fluorodeoxyglucose positron emission tomography (FDG-PET) is of prognostic value for survival in non–small cell lung cancer (NSCLC): A systematic review and meta-analysis (MA) by the European Lung Cancer Working Party for the IASLC Lung Cancer Staging Project. J Thorac Oncol 3:6–12, 2008.
110. Ahrendt SA, Hu Y, Buta M, et al: p53 mutations and survival in stage I non–small cell lung cancer: Results of a prospective study. J Natl Cancer Inst 95:961–970, 2003.
111. Graziano SL, Gamble GP, Newman NB, et al: Prognostic significance of K-ras codon 12 mutations in patients with resected stage I and II non–small cell lung cancer. J Clin Oncol 17:668–675, 1999.
112. Schiller JH, Adak S, Feins RH, et al: Lack of prognostic significance of p53 and K-ras mutations in primary resected non-small cell lung cancer on E4592. J Clin Oncol 19:448–457, 2001.
113. Mascaux C, Iannino N, Martin B, et al: The role of RAS oncogene in survival of patients with lung cancer: A systematic review of the literature with meta-analysis. Br J Cancer 92:131–139, 2005.
114. PORT Meta-analysis Trialists Group: Post operative radiotherapy in non–small cell cell lung cancer: Aystemic review and meta-analysis of individual patient data from nine radomized controlled trials. Lancet 352:257–263, 1998.
115. Ries LG, Kosary CL, Hankey BF, et al: SEER cancer statistics review 1973–1994: Tables and graphs. NIH Publication No. 97-2789. Bethesda, MD: National Cancer Institute, 1997.
116. Scott WJ, Howington J, Feigenberg S, et al: Treatment of non–small cell lung cancer stage I and stage II: ACCP Evidence-Based Clinical Practice Guidelines (2nd ed). Chest 132(3 Suppl):234S–242S, 2007.
117. Ginsburg RJ, Rubinstein LV: A randomized comparative trial of lobectomy vs limited resection for patients T1NO non–small cell lung cancer. Lung Cancer 7:83–88, 1995.
118. Colice GL, Shafazand S, Griffin JP, et al: Physiologic evaluation of the patient with lung cancer being considered for resectional surgery: ACCP Evidenced-Based Clinical Practice Guidelines (2nd ed). Chest 132(3 Suppl):161S–177S, 2007.
119. Rowell NP, Williams CJ: Radical radiotherapy for stage I/II non–small cell lung cancer inpatients not sufficiently fit for or declining surgery (medically inoperable): A systematic review. Thorax 56:628–638, 2001.
120. Adebonojo S, Bowser A, Moritz D, et al: Impact of revised stage classification of lung cancer on survival: A military experience. Chest 115:1507–1513, 1999.
121. Bach PB, Cramer L, Schrag D, et al: The influence of hospital volume on survival after resection for lung cancer. N Engl J Med 345:181–188, 2001.
122. Inoue K, Sato M, Fujimura S, et al:. Prognostic assessement of 1310 patients with non–small cell lung cancer who underwent complete resection from 1980–1993. J Thoric Cardiovasc Surg 116:407–411, 1998.
123. Jassem J, Skokowski J, Dziadziuszko R, et al: Results of surgical treatment of non–small cell lung cancer: Validation of the new postoperative pathologic TNM classification. J Thorac Cardiovasc Surg 119:1141–1146, 2000.
124. Scott WJ, Howington J, Movsas B: Treatment of stage II non–small cell lung cancer. Chest 123:188s–201s, 2003.
125. van Rens MT, de la Riviere AB, Elbers HR, van Den Bosch JM: Prognostic assessment of 2,361 patients who underwent pulmonary resection for non–small cell lung cancer, stage I, II, and III A. Chest 117:374–379, 2000.
126. Silvestri GA, Handy J, Lackland D, et al: Specialists achieve better outcomes than generalists for lung cancer surgery. Chest 114:675–680, 1998.
127. Rami-Porta R, Ball D, Crowley J, et al. The IASLC Lung Cancer Staging Project: Proposals for the revision of the T descriptors in the forthcoming (seventh) edition of the TNM classification for lung cancer. J Thorac Oncol 2:593–602, 2007.
128. Robinson LA, Wagner H Jr, Ruckdeschel JC: Treatment of stage IIIa non–small cell lung cancer. Chest 123:202S–220S, 2003.
129. Robinson LA, Ruckdeschel JC, Wagner H, Stevens CW: Treatment of non–small cell lung cancer-stage IIIA: ACCP Evidence-Based Clinical Practice Guidelines (2nd ed). Chest 132:2435S–2655S, 2007.
130. IALT Collaborative Group: Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer. N Engl J Med 350:351–360, 2004.
131. Winton T, Livingston R, Johnson D, et al: Vinorelbine plus cisplatin vs. observation in resectd non–small-cell lung cancer. N Engl J Med 352:2589–2597, 2005.
132. Douillard J, Rossell R, Carpagnano F, et al: Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB-IIIA non–small-cell lung cancer (Adjuvant Navelbine International Trialist Association (ANITA): A randomized controlled trial. Lancet Oncol 7:719–727, 2006.
133. Pignon J, Tribodet H, Scagliotti G, et al: Lung adjuvant cisplatin evaluation: A pooled analysis by the LACE collaborative group. J Clin Oncol 26:3552–3559, 2008.
134. Lally B, Zelterman D, Colasanto J, et al: Postoperative radiotherapy for stage II or III non–small-cell lung cancer using the surveillance, epidemiology, and end results database. J Clin Oncol 24:2998–3006, 2006.
135. Non–small Cell Lung Cancer Collaborative Group: Chemotherapy in non–small cell lung cancer: A meta-analysis using updated data on individual patients from 52 randomised clinical trials. BMJ 311:899–909, 1995.
136. Pritchard RS, Anthony SP: Chemotherapy plus radiotherapy compared with radiotherapy alone in the treatment of locally advanced, unresectable, non–small cell lung cancer: A meta-analysis. Ann Intern Med 125:723–729, 1996.
137. Marino P, Preatoni A, Cantoni A: Randomized trials of radiotherapy alone vs combined chemotherapy and radiotherapy in stages IIIA and IIIB non–small cell lung cancer. Cancer 76:593–601, 1995.
138. Curran WJ, Scott CB, Langer CJ, et al: Long-term benefit is observed in phase II comparison of sequential vs concurrent chemoradiation for patients with unresectable stage III NSCLC: RTOG 9410. Proc Am Soc Clin Oncol 22:621, 2003.
139. Furuse K, Fukuoka M, Kawahara M, et al. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine, and cisplatin in unresectable stage III non–small cell lung cancer. J Clin Oncol 17:2692–2699, 1999.
140. Jett J, Schild S, Keith R, Kesler K: Treatment of non–small cell lung cancer, stage IIIB. Chest 132:266S–276S, 2007.
141. Molina J, Adjei A, Jett J: Advances in chemotherapy of non–small cell lung cancer. Chest 130:1211–1219, 2006.
142. Kelly K, Crowley J, Bunn PA Jr, et al: Randomized phase III trial of paclitaxel plus carboplatin versus vinorelbine plus cisplatin in the treatment of patients with advanced non–small cell lung cancer: A Southwest Oncology Group trial. J Clin Oncol 19:3210–3218, 2001.
143. Scagliotti GV, DeMarinis F, Rinald M, et al: Phase III randomized trial comparing three platinum-based doublets in advanced non–small cell lung cancer. J Clin Oncol 20:4285–4291, 2002.

144. Schiller JH, Harrington D, Belani CP, et al: Comparison of four chemotherapy regimens for advanced non–small cell lung cancer. N Engl J Med 346:92–98, 2002.
145. Sandler A, Gray R, Perry M, et al: Paclitaxel-carboplatin alone or with bevacizumab for non–small-cell lung cancer. N Engl J Med 355:2542–2550, 2006.
146. Reck M, von Pawel J, Zatloukal P, et al: Phase III trial of cisplatin plus gemcitabine with either placebo or bevacizumab as first-line therapy for nonsquamous non-small-cell lung cancer: AVAil. J Clin Oncol 27:1227–1234, 2009.
147. Lynch T, Bell D, Sordella R, et al: Activating mutations in the epidermal growth factor receptor underlying responsiveness of non–small-cell lung cancer to gefitinib. N Engl J Med 350:2129–2139, 2004.
148. Paez J, Janne P, Lee J, et al: EGFR mutations in lung cancer; correlation with clinical response to gefitinib therapy. Science 304:1497–1500, 2004.
149. Marks J, Broderick S, Zhou Q, et al: Prognostic and therapeutic implications of EGFR and KRAS mutations in resected lung adenocarcinoma. J Thorac Oncol 3:111–116, 2008.
150. Shepherd F, Pereira J, Ciuleanu T, et al: Erlotinib in previously treated non–small-cell lung cancer. N Engl J Med 353:123–132, 2005.
151. Thatcher N, Chang A, Parikh P, et al: Gefitinib plus best supportive care in previously treated patients with refractory advanced non–small-cell lung cancer: Results from a randomized, placebo-controlled, multicentre study (Iressa Survival Evaluation in Lung Cancer). Lancet 366:1527–1537, 2005.
152. West H, Franklin W, McCoy J: Gefitinib therapy in advanced bronchioalveolar carcinoma: Southwest Oncology Group study of SO126. J Clin Oncol 24:1807–1813, 2006.
153. Giaccone G, Ruiz M, Le Chevalier T, et al: Erlotinib for frontline treatment of advanced non–small cell lung cancer: A phase II study. Clin Cancer Res 12:6049, 2006.
154. Mok T, Wu Y-L, Thongprasert S, et al: Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med 361:947–957, 2009.
155. Socinski M, Crowell R, Hensing T, et al:. Treatment of non–small cell lung cancer, stage IV. Chest 132:277S–289S, 2007.
156. Bonner JA, Sloan JA, Shanahan TG, et al: Phase III comparison of twice-daily split course irradiation versus once-daily irradiation for patients with limited stage small cell lung carcinoma. J Clin Oncol 17:2681–2691, 1999.
157. Schild SE, Bonner JA, Shanahan TG, et al: Long-term results of a phase III trial comparing once-daily radiotherapy with twice-daily radiotherapy in limited-stage small-cell lung cancer. Int J Radiat Oncol Biol Phys 59:943–951, 2004.
158. Turrisi AT III, Kim K, Blum R, et al: Twice-daily compared with once-daily thoracic radiotherapy in limited small cell lung cancer treated concurrently with cisplatin and etoposide. N Engl J Med 340:265–271, 1999.
159. Fukuoka M, Furuse K, Saijo N, et al: Randomized trial of cyclophosphamide, doxorubicin, and vincristine versus cisplatin and etoposide versus alternation of these regimens in small cell lung cancer. J Natl Cancer Inst 83:855–861, 1991.
160. Roth BJ, Johnson DH, Einhorn LH, et al: Randomized study of cyclophosphamide, doxorubicin, and vincristine versus etoposide and cisplatin versus alternation of these two regimens in extensive small cell lung cancer: a phase III trial of the Southeastern Cancer Study Group. J Clin Oncol 10:282–291, 1992.
160a. Noda K, Nishiwaki Y, Kawahara M, et al: Irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive small-cell lung cancer. N Engl J Med 346:85–91, 2002.
160b. Lara PN, Natale R, Crowley J, et al: Phase III trial of irinotecan/cisplatin compared with etoposide/cisplatin in extensive-stage small-cell lung cancer. J Clin Oncol 27:2530–2535, 2009.
161. Auperin A, Arriagada R, Pignon JP, et al: Prophylactic cranial irradiation for patients with small cell lung cancer in complete remission. Prophylactic Cranial Irradiation Overview Collaborative Group. N Engl J Med 341:476–484, 1999.
162. von Pawel J, Shciller J, Sheperd FA, et al: Topotecan versus cyclophosphamide, doxorubicin, and vincristine for the treatment of recurrent small cell lung cancer. J Clin Oncol 17:658–667, 1999.
163. Rossi A, Maione P, Palazzolo G, et al: New targeted therapies and small-cell lung cancer. Clin Lung Cancer 9:271–279, 2008.
164. Kvale PA, Selecky PA, Prakash UB: Palliative care in lung cancer: ACCP Evidence-Based Clinical Practice Guidelines (2nd ed). Chest 132(3 Suppl):368S–403S, 2007.
165. Silvestri GA, Sherman C, Leong SS, et al: Caring for the dying patient with lung cancer. Chest 122:1028–1036, 2002.
166. Arcasoy SM, Jett JR: Superior pulmonary sulcus tumors and Pancoast's syndrome. N Engl J Med 337:1370–1376, 1997.
167. Pancoast HK: Importance of careful roentgen-ray investigations of apical chest tumors. JAMA 83:1407–1411, 1924.
168. Pancoast HK: Superior pulmonary sulcus tumor: Tumor characterized by pain, Horner's syndrome, destruction of bone and atrophy of hand muscles. JAMA 99:1391–1396, 1932.
169. Heelan RT, Demas BE, Caravelli JF, et al: Superior sulcus tumors: CT and MR imaging. Radiology 170:637–641, 1989.
170. Maxfield RA, Aranda CP: The role of fiberoptic bronchoscopy and transbronchial biopsy in the diagnosis of Pancoast's tumor. N Y State J Med 87:326–329, 1987.
171. Walls WJ, Thornburg JR, Naylor B: Pulmonary needle aspiration biopsy in the diagnosis of Pancoast tumors. Radiology 111:99–102, 1974.
172. Komaki R, Roth JA, Walsh GL, et al: Outcome predictors for 143 patients with superior sulcus tumors treated by multidisciplinary approach at the Universtiy of Texas MD Anderson Cancer Center. Int J Radiat Oncol Biol Phys 48:347–354, 2000.
173. Rusch V, Parekh K, Leon L: Factors determining outcome after surgical resection of T3 and T4 lung cancers of the superior sulcus. J Thoric Cardiovasc Surg 119:1147–1153, 2000.
174. Rusch V, Giroux D, Kraut M, et al: Induction chemoradiation and surgical resection for superior sulcus non–small-cell lung carcniomas: Long-term results of Southwest Oncology Group trial 0416 (intergroup trial 0160). J Clin Oncol 25:313–318, 2007.
175. Kunitoh H, Kato H, Tsuboi M, et al: Phase II trial of preoperative chemoradiotherapy followed by surgical resection of patients with superior sulcus non–small-cell lung cancers: Report of Japan Clinical Oncology Group trial 9806. J Clin Oncol 26:644–649, 2008.
176. Wilson L, Detterbeck F, Yahalom J, et al: Superior vena cava syndrome with malignant causes. N Engl J Med 356:1862–1869, 2007.
177. Bell DR, Woods RL, Levi JA: Superior vena cava obstruction: A ten-year experience. Med J Aust 146:566–568, 1986.
178. Escalante CP: Causes and management of superior vena cava syndrome. Oncology 7:61, 1993.
179. Mineo TC, Ambrogi V, Nofroni I, Pistolese C: Mediastinoscopy in superior vena cava syndrome: Analysis of 80 consecutive patients. Ann Thorac Surg 68:223, 1999.
180. Rowell NP, Gleeson F: Steroids, radiotherapy, chemotherapy and stents for superior vena cava obstruction in carcinoma of the bronchus. Cochrane Database Syst Rev 4:CD001316, 2001.
181. Mauricio O, Francis L, Athar U, et al: Hypertrophic osteoarthropathy masquerading as lower extremity cellulitis and responding to bisphosphonates. J Thorac Oncol 4:260–262, 2009.
182. Sigurgeirsson B, Lindelof B, Edhag O, Allander E: Risk of cancer in patients with dermatomyositis or polymyosistis. N Engl J Med 326:363–367, 1992.
183. Cornuz J, Pearson SD, Creager MA, et al: Importance of findings on the initial evaluation for cancer in patients with symptomatic idiopathic deep venous thrombosis. Ann Intern Med 125:785–793, 1996.
184. Lee AYY, Levine MN, Baker RI, et a: Low molecular weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. N Engl J Med 349:146–153, 2003.
185. Aki EA, Barba M, Rohilla S, et al: Anticoagulation for the long term treatment of venous thromboembolism in patients with cancer. Cochrane Database Syst Rev 2:CD006650, 2008.
186. Takai E, Yano T, Iguchi H, et a: Tumor induced hypercalcemia and parathyroid hormone related protein in lung carcinoma. Cancer 78:1384–1387, 1996.
187. Ralston SH, Gallacher SJ, Patel U, et al: Cancer associated hypercalcemia: Morbidity and mortality. Ann Intern Med 112:499–504, 1990.

188. Major P, Lortholarhy A, Hon J, et al: Zolendronic acid is superior to pamindronate in the treatment of hypercalcemia of malignancy: A pooled analysis of two randomized controlled trials. J Clin Oncol 19:558–567, 2001.
189. Zeltser D, Rosansky S, van Rensburg H, et al: Assessment of the efficacy and safety of conivaptan in euvolemic and hypervolemic hyponatremia. Am J Nephrol 27:447, 2007.
190. Schrier R, Gross P, Gheorghiade M, et al: Tolvaptan, a selective oral vasopressin V2-receptor antagonist, for hyponatremia. N Engl J Med 355:2099–2112, 2006.
191. Ayus JC, Krothapalli RK, Arieff AI: Treatment of symptomatic hyponatremia and its relation to brain damage: A prospective study. N Engl J Med 317:1190–1195, 1987.
192. Orth DN: Cushing's syndrome. N Engl J Med 392:791–803, 1995.
193. Winquist E, Laskey J, Crump M, et al: Ketoconazole in the management of paraneoplastic Cushing's syndrome secondary to ectopic adrenocorticotropin production. J Clin Oncol 13:157–164, 1995.
194. Darnell RB, Posner JB: Paraneoplastic syndromes involving the nervous system. N Engl J Med 349:1543–1554, 2003.
195. Graus F, Keime Guibert F, Rene R, et al: Anti–Hu-associated paraneoplastic encephalomyelitis: Analysis of 200 patients. Brain 124:1138–1148, 2001.
196. Lucchinetti CF, Kimmel DW, Lennon VA: Paraneoplastic and oncological profiles of patients seropositive for type 1 anti-neuronal nuclear autoantibodies. Neurology 50:652–657, 1998.
197. Patel R, Subramaniam R, Mandrekar J, et al: Occult malignancy in patients with suspected paraneoplastic neurologic syndrome: Value of positron emission tomography in diagnosis. Mayo Clin Proc 83:917–922, 2008.
198. Vedeler C, Antoine J, Giometto B, et al: Management of paraneoplastic neurological syndromes: Report of an EFNS Task Force. Eur J Neurol 13:682–690, 2006.
199. Carpentier AF, Delattre JY: The Lambert-Eaton myasthenic syndrome. Clin Rev Allergy Immunol 20:155–158, 2001.
199a. Payne M, Bradbury P, Lang B, et al: Prospective study into the incidence of Lambert Eaton myasthenic syndrome in small cell lung cancer. J Thorac Oncol 5:34–38, 2010.
200. Lennon VA, Kryzer TJ, Griesmann GE, et a: Calcium channel antibodies in the Lambert-Eaton syndrome and other paraneoplastic syndromes. N Engl J Med 332:1467–1474, 1995.
201. Skeie G, Apostolski S, Evoli A, et al: Guidelines for the treatment of autoimmune neuromuscular transmission disorders. Eur J Nephrol 13:691–699, 2006.
202. Sanders DB, Massey JM, Sanders LL, Edwards LJ: A randomized trial of 3,4 dyaminopyridine in Lambert-Eaton myasthenic syndrome. Neurology 54:603–607, 2000.

CHAPTER 48

LYMPHOMA, LYMPHOPROLIFERATIVE DISEASES, AND OTHER PRIMARY MALIGNANT TUMORS

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INTRODUCTION

CHARACTERIZATION OF RARE LUNG TUMORS

PRIMARY PULMONARY LYMPHOMA AND OTHER LYMPHOPROLIFERATIVE DISEASES
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General Therapeutic Management

INTRODUCTION

Rare lung tumors are defined as lung tumors with low prevalence and unusual histology. Overall, these tumors account for less than 1% of all primary lung tumors, whereas they correspond to more than 100 different histologic, clinical, radiologic, and prognostic entities. Some rare lung tumors are specific to the lung, whereas others represent tumors more frequently found in other organs that only rarely occur in the lungs. It is estimated that about 60% of rare primary pulmonary tumors correspond to benign and low-grade lesions and 40% are malignant.

The rare tumors are characterized by their low incidence, but also by poor clinical and imaging descriptions, by the low number of experienced specialists for each tumor subtype, and by the absence of specific therapeutic data. Recognition of rare lung tumors relies on characteristic clinical and radiologic signs, on a modified diagnostic and imaging strategy, and on the determination of their primary or secondary nature.

Because an exhaustive review is outside the scope of this chapter, we discuss selected lesions of special interest because of their relatively high incidence or because they illustrate specific issues regarding the overall diagnostic and therapeutic management of rare malignant primary pulmonary tumors.

CHARACTERIZATION OF RARE LUNG TUMORS

Although accounting for less than 1% of lung malignancies, rare lung tumors correspond to a large array of

histopathologic, clinical, radiologic entities.[1–4] Prevalence may also range from merely uncommon lesions, such as carcinoids, which account for 0.15% of primary lung tumors, to extremely unusual tumors, such as primary pulmonary melanoma, with fewer than 50 reported cases.[5,6] Overall, the most frequent rare malignant primary lung tumors are, in decreasing order of frequency: carcinoid, mucosa-associated lymphoid tissue (MALT) lymphoma, and pneumoblastoma.[1,7]

Most rare lung tumors develop from orthotopic tissues, constitutive of the normal lung parenchyma, and from hematopoietic tissues[1,2] whereas tumors derived from ectopic tissues, including melanoma and meningioma, are more uncommon.[8] Some rare tumor subtypes, such as lymphomatoid granulomatosis, arise specifically within the lung, whereas others, such as blastomas and perivascular epithelioid cell tumors, arise in many different tissues of the body including the lung and are infrequent wherever they are located. Furthermore, some primary tumors that are uncommon within the lung may be frequent in other locations, including lymph node lymphomas and soft tissue sarcomas, which present with specific histopathologic differentiation when originating in the lung, such as MALT lymphoma and angiosarcoma, respectively.[1]

Knowledge regarding these tumors is mainly based upon case reports or small retrospective series, most of which are out of date. Moreover, the interpretation of early series may be hampered by the evolution of concepts in histopathologic classifications; for example, some tumor subtypes such as large cell neuroendocrine, basaloid, and sarcomatoid carcinomas were added to the 1999 and 2004 World Health Organization (WHO) classifications.[7]

From a clinical point of view, the hallmarks of rare lung tumors may be, more than their actual low frequency, the absence of comprehensive clinical data, the low number of specialized groups for the care of each tumor subtype, and the lack of specific therapeutic recommendations. More than 90% of rare lung tumor observations are published as case reports or small series including fewer than five patients.[7] Currently, only carcinoids and large cell neuroendocrine carcinoma, as the most frequent of the rare tumor subtypes, have been characterized regarding their clinical, therapeutic, and prognostic features in large retrospective and prospective studies.[9–11]

Patients with rare lung tumors, as many patients with cancer, tend to go through several stages of grief, including depression, uncertainty, hope, disappointment and, in most cases, physical degradation and social isolation. The rarity of the tumor may also enhance these feelings, owing to the relative lack of information and the increased feeling of isolation, the geographic disparity in access to specific care, the longer duration of the pretherapeutic workup, the involvement of multiple specialists, a feeling of injustice especially in young and never-smoking patients, and the complex management undertaken in a state of uncertainty.[12] As a result, patients with rare lung tumors may not receive equal care and some may feel as "orphans," being incompletely integrated in the process of care of patients with the more frequent bronchogenic carcinoma.

PRIMARY PULMONARY LYMPHOMA AND OTHER LYMPHOPROLIFERATIVE DISEASES

Primary pulmonary lymphoma is defined as a lymphoma affecting one or both lungs, without evidence of extrapulmonary involvement or bone marrow disease at the time of diagnosis and during the subsequent 3 months.[13] For clinicians, pulmonary lymphomas associated with small-size satellite mediastinal and/or systemic nodes are also regarded as originating from the lung.[13–16] Even including these tumors, primary pulmonary lymphomas are rare, representing 0.4% of all lymphomas.[15,17] The most frequent subtypes are MALT-type lymphoma and lymphomatoid granulomatosis. Other subtypes are found only in immunocompromised patients.

Mucosa-Associated Lymphoid Tissue Lymphoma

Pulmonary MALT lymphoma is referred to as nodal marginal-zone B-cell lymphoma, with similar cytopathologic features to other MALT lymphomas, especially gastric lymphoma.[18] These low-grade lymphomas account for 70% to 90% of primary pulmonary lymphomas. At pathologic examination, MALT lymphoma appears as a diffuse infiltrate of small monomorphic lymphoid cells, with a typical lymphangitic growth pattern spreading along the bronchovascular bundles and interlobular septa, and forming solid nodules that fill the alveolar spaces and obliterate the normal lung architecture (Fig. 48-1C and D). Immunohistochemistry forms the basis of the subtype classification, with the expression of the pan-B-markers CD20 and CD79 and the absence of staining for CD5 and CD10.[19] The proliferation is monotypic, with surface and/or cytoplasmic expression of immunoglobulin M (IgM) and, less frequently, IgG and IgA (see Fig. 48-1E and F). Light chain restriction can be detected in the plasmacytic component using flow cytometry. MALT lymphomas are associated with unique chromosomal translocations, such as the t(11;18)(q21,q21) resulting in a fusion of the *API2* and *MALT1* genes, the t(1;14)(p22;q32) involving the *BCL10* and *IgH* genes—which is overall much less frequent, more specific to lung locations, and never found in high-grade lymphoma—and the t(14;18)(q32;q21) involving the *IgH* and *MALT1* genes.[20] The precise mechanisms leading to the development of these translocations remain unknown but they all appear to result in an inhibition of apoptosis and a survival advantage to the cells.[20] In cases with the t(1;14)(*BCL10/IgH*) translocation, immunohistochemistry on paraffin-embedded tissues can detect the strong nuclear overexpression of BCL10, thought to have prosurvival functions. The diagnosis often requires a surgical lung biopsy, as cytologic examination of bronchoalveolar lavage or fine-needle biopsy may show the CD20-positive B-cell infiltration but fail to exclude differential diag-

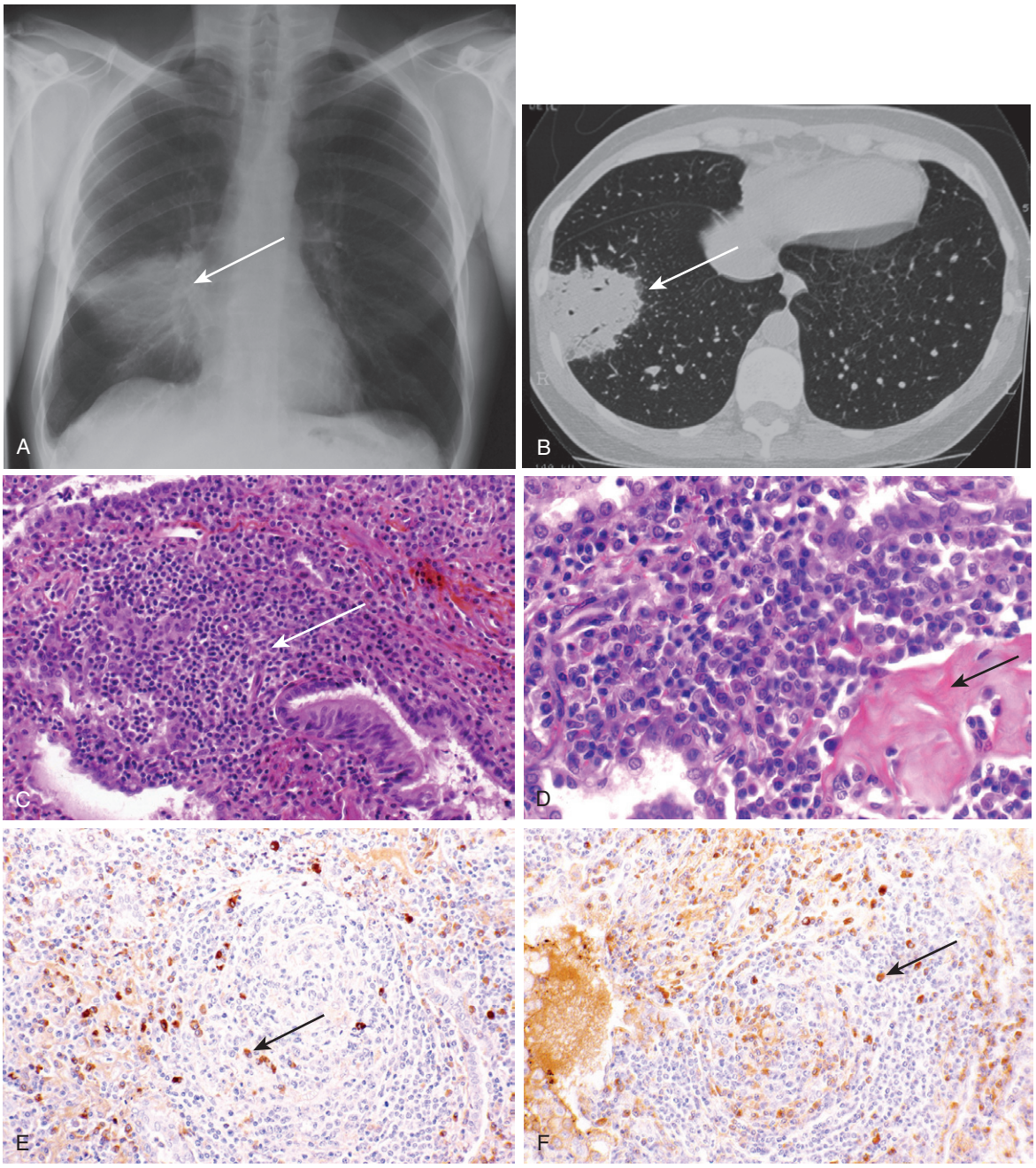

FIGURE 48-1 ■ Primary pulmonary mucosa-associated lymphoid tissue (MALT) lymphoma. Chest radiography (**A**) and computed tomography (CT) scan (**B**) show persistent alveolar opacities in the right lower lobe, despite prolonged antibiotic therapy. Pathologic examination of surgical biopsy showed: **C,** proliferation of small-size lymphoid cells infiltrating the bronchial wall. Note a bronchial epithelium encased in destructive lymphoid proliferation (*arrow*); **D,** at high magnification, lymphoplasmacytic-like cells of the marginal zone lymphoma associated with amyloid deposit (*arrow*); **E,** with immunoglobulin (Ig) lambda light chain immunostaining, a predominance of lambda chain plasma cells (lambda chain restriction) (*arrow*); and **F,** with Ig mu heavy chain immunostaining, a predominance of IgM type in plasmacytic and plasma cells (*arrow*).

noses, such as reactional lymphoid proliferation, follicular bronchiolitis, or lymphoid interstitial pneumonia.[14,18,19] Amplification of the *IgH* gene from paraffin-embedded or cytologic samples with polymerase chain reaction (PCR)–based assays, was demonstrated to be a reliable method to detect monoclonality in more than 60% of MALT lymphomas.[21]

Contrary to extrapulmonary MALT lymphomas, for which a strong relationship has been established with chronic bacterial inflammation related to *Helicobacter pylori* in the stomach and to *Chlamydia psittacci* in the ocular adnexae, no chronic infectious condition has been associated with pulmonary MALT lymphoma, although concurrent evolution with chronic hepatitis C

has been described. However, MALT is absent in the normal bronchial tree and is thought to develop only after long-term inflammation, secondary to smoking or to an autoimmune condition.

MALT lymphoma has mainly been observed in patients older than 45 years, with a slight male predominance, but may also arise in younger patients with underlying immunosuppression, especially related to human immunodeficiency virus (HIV) infection, or with inflammatory conditions such as Sjögren's disease or rheumatoid arthritis, or in association with Epstein-Barr virus (EBV) infection.[14–17,22–24] Less than 50% of patients are symptomatic, with nonspecific symptoms including cough, dyspnea, and chest pain.[14–17] Unlike the situation with other lymphomas, systemic signs such as fever, swelling, and weight loss are uncommon. Association with IgM or IgG blood monoclonal gammopathy is observed in 30% of cases. MALT lymphoma exhibits three imaging patterns at chest radiography and computed tomography (CT) scan: (1) the most frequent and suggestive is the "pneumonia-like" alveolar consolidation with an air bronchogram, typically localized in the middle lobe (see Fig. 48-1A and B); (2) the "tumor-like" aspect with a solitary well-circumscribed nodular opacity (30% of cases) and possible central air bronchogram; and (3) the "infiltrative" pattern with diffuse poorly defined ground-glass opacities, assumed to represent early-stage disease before tumor cells invade alveolar spaces.[14–17,25] The combination of a nodular opacity with peripheral peribronchovascular ground-glass attenuation halo is frequent. Pleural effusion is unusual.

About a third of MALT lymphomas are multifocal at the time of diagnosis, a presentation that may hamper the determination of the primary site.[26] Pulmonary MALT lymphomas are associated with tumor locations in the gastric mucosa in 10% to 20% of patients and in the bone marrow in 15% to 20% of patients. Gastroscopy and bone marrow biopsy are then frequently performed as a pretreatment workup. ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) scan may not be sensitive enough in MALT lymphoma to exclude extrathoracic disease. The Ann Arbor staging system, although not designed for extranodal lymphoma, may be applied in pulmonary MALT lymphoma, which would be staged as IE (one site, extranodal) in case of lung unilateral or bilateral involvement, and IIE (two sites, both above the diaphragm, extranodal) in case of hilar or mediastinal lymph nodes.

Therapeutic options are based on the degree of tumor extension. Surgical resection ensures both the diagnosis and the treatment of nodular lesions. In asymptomatic patients, a watch-and-wait attitude may be preferred to aggressive treatment. More advanced MALT lymphoma requires more aggressive management, and several options have been described, from resection to radiotherapy, or single-agent chemotherapy with chlorambucil, fludarabine, or rituximab. Rituximab, an anti-CD20 antibody, is particularly effective and well-tolerated and may represent an alternative to chemotherapy, especially in the case of t(11;18) translocation.[27] Current data favor systemic treatments in MALT lymphomas, considering that these tumors may represent the early-stage manifestation of a systemic disorder of mucosal immunity.[15,17] Furthermore, the fact that surgical resection has not been shown to improve prognosis in some series is an additional argument against local treatments.[15] Prognosis of MALT lymphomas is excellent, with an indolent and localized prolonged course. Historical series reported 5-year survival rates higher than 80%, and the more recent availability of rituximab may even improve these results.[14] Local and systemic recurrences develop in about 50%, but are usually controllable with chemotherapy. Evolution to high-grade B-cell lymphoma occurs in less than 5% of cases. Young age is the most significant favorable prognostic factor.

Lymphomatoid Granulomatosis

Lymphomatoid granulomatosis, also called "angiocentric lymphoma," is a malignant B-cell angiocentric and angiodestructive lymphoproliferative disorder. Long considered an inflammatory granulomatous disease owing to its radioclinical presentation similar to other granulomatoses such as Wegener's disease, lymphomatoid granulomatosis is now recognized as a lymphoid malignancy. The lung is the most frequent location, but the disease may also involve the brain, the skin, and the liver.[28–30]

Lymphomatoid granulomatosis forms multiple and confluent nodules composed of an atypical, angiocentric, and polymorphous lymphoid infiltration involving the vascular walls, from the subendothelium to the adventitial zones, with focal lumen obliteration. By immunohistochemistry, these lymphoid cells are characterized mostly as $CD4^+$ T-lymphocytes, with scattered atypical cells of B-phenotype.[28] Large B-cells are infected by EBV in 65% of cases, a fact that correlates with the grade of the lesion. Pulmonary biopsy is required in most cases to exclude Wegener's granulomatosis, which is a polyclonal proliferation of inflammatory cells associated with necrotizing vasculitis.

Lymphomatoid granulomatosis occurs in middle-aged patients, from 40 to 50 years old, with a male predominance.[29,30] Nearly all patients present with respiratory and systemic symptoms, consisting of cough, dyspnea, hemoptysis, chest pain, fever, and weight loss. Peripheral and mediastinal lymphadenopathy is absent. Prolonged immunosuppression is a frequent underlying condition. The typical radiologic presentation consists of multiple smooth bilateral nodules, exhibiting a peribronchovascular pattern, ranging from 2 to 10 cm, and mainly localized in the lower lobes, mimicking multiple metastases.[1,13,29] As in Wegener's granulomatosis, convergent nodules may migrate and form cavitated pseudotumoral masses.

Chemotherapy based on high-dose steroids with cyclophosphamide is the most frequently reported treatment of lymphomatoid granulomatosis. The additional use of rituximab may increase the efficacy of these cytotoxic agents.[31] The overall prognosis is grim, with a 5-year survival of 30% to 40%, owing to progression to nodal diffuse aggressive lymphoma in 20% to 50% of patients. As in lymphoma, the main prognostic factors are age, extension of the lesions, and response to first-

line chemotherapy.[32] Lymphomatoid granulomatosis is increasingly considered a low-grade or early-stage lymphoma, and a histopathologic grading system has been developed, based on the degree of cellular atypia and necrosis, to predict the risk of evolution to high-grade lymphoma and to select patients for early aggressive treatment.[32]

Other Lymphomas and Lymphoproliferative Diseases

Other primary pulmonary malignant lymphoproliferative diseases are very rare and include high-grade diffuse large B-cell lymphoma, intravascular large cell lymphoma, Hodgkin's lymphoma, and plasmacytoma.

Primary pulmonary diffuse large B-cell lymphoma is likely underrecognized owing to its rapid spread to mediastinal nodes and other extrathoracic sites, which may hide its pulmonary origin.[22,33] Histologically, it shows characteristics similar to those of diffuse large B-cell lymphomas at other sites, with diffuse infiltration of large blastic lymphoid cells, expressing pan-B antigens (CD20 and CD79a). Primary pulmonary high-grade B-cell lymphomas typically develop in immunocompetent patients in their sixth to seventh decade. In younger patients, large B-cell lymphoma may be caused by latent EBV infection, which may develop following drug-induced immunosuppression, as from methotrexate or antilymphocyte antibodies in transplant recipients,[34] or following HIV-related immunosuppression. In patients with HIV infection, the availability of highly active antiretroviral therapy led to the near disappearance of primary pulmonary high-grade lymphomas, which are now less frequent than MALT lymphomas in these patients.[13,22] Patients often present with marked respiratory and systemic symptoms. Radiologic studies usually show multiple well-defined rounded solid masses of various sizes, more frequently in the subpleural areas of the lower lobes.[24] Chemotherapy is based on the same multiagent regimens as those used in high-grade nodal lymphomas, including adriamycin, prednisone, and rituximab.[13,22] The overall prognosis is much worse than for MALT lymphoma, with a 5-year survival lower than 20%.

Intravascular large cell lymphoma is a variant of non-Hodgkin's lymphoma, in which neoplastic lymphoid cells proliferate within the lumen of small and intermediate-sized blood vessels, resulting in thrombotic and ischemic complications.[35] Clinical manifestations are multiple, but lymphadenopathy is usually absent. Pulmonary imaging features include bilateral ground-glass opacities and/or sometimes migratory atelectatic shadows.[35] Treatment with conventional combination chemotherapy with or without rituximab leads to remission with prolonged survival.[13,35]

Primary pulmonary Hodgkin's lymphoma has been reported exclusively in old studies, and might actually correspond to nodal Hodgkin's disease with secondary pulmonary involvement.[36] At chest radiography, it is described as a solitary mass with cystic and heterogeneous features, typically involving the upper lobes, or as a multinodular disease. Diagnosis is based on the recognition of characteristic Reed-Sternberg cells at pathologic examination. The overall outcome is poorer than in nodal Hodgkin's lymphoma.

Primary pulmonary plasmacytoma is a solitary lesion exclusively composed of atypical monoclonal plasmocytes, possibly associated with amyloid deposition, without evidence of extrapulmonary myelomatous disease.[13,37,38] Again, the apparent decrease of the incidence of primary pulmonary plasmacytoma may be related to the increased sensitivity of biologic and imaging studies for the detection of primary extrapulmonary disease. Moreover, about one third of patients operated upon for pulmonary plasmacytoma were reported to present with multiple myeloma in following years.[37,38] Surgical resection is, however, recommended for solitary tumors, with a 5-year survival of 60%.[38]

Amyloidosis

Amyloidosis is characterized histopathologically by tissue infiltration with fibrillar protein with a β-sheet structural conformation, specifically stained by Congo red dye with a yellow-green birefringence under polarized light.[39] Amyloidosis has a highly variable presentation and may manifest in the lung as either parenchymal nodules or masses.[40] Pulmonary amyloidosis may be localized to the lung or be associated with systemic amyloidosis.

Pulmonary nodules usually consist of AL ("amyloid light chain") amyloid, which is the most common subtype of amyloidosis deposition.[40] AL amyloidosis is primary in more than 80% of cases and associated with inflammatory or lymphoproliferative disease in 20% of cases. AL amyloidosis develops as a result of the abnormal production of light immunoglobulin chains, often of lambda isotype. AL amyloidosis may be either systemic (e.g., in myeloma) or localized (as in primary pulmonary lymphoma), with mild pulmonary interstitial (especially vascular) involvement that is usually asymptomatic.[41] Serum and/or urinary monoclonal gammopathy is frequent.[42]

Pulmonary nodular amyloidosis has been observed in patients in their seventh decade, without gender predominance. Patients are usually asymptomatic. Association with Sjögren's syndrome has been reported.[43] Radiologically, pulmonary nodules are rounded and sharply delimited. Most nodules are peripheral. The nodules may range from 5 mm to more than 15 cm, may be solitary or multiple, and may be calcified. Nodules have shown increased activity on PET and may thus mimic bronchogenic carcinoma.[44] Fine-needle biopsy may provide a pathologic diagnosis.[45] Pulmonary amyloid nodules may remain stable for years,[46] and surgical resection is proposed only in case of threatening symptoms. Recurrence is frequent after surgery.[47]

Nonamyloidotic Monoclonal Immunoglobulin Deposition Disease

Nonamyloidotic monoclonal immunoglobulin deposition disease (NAMIDD) is rarer than amyloidosis and presents with deposits that are not stained by Congo red dye and do not demonstrate birefringence under

polarized light.[48] These deposits most usually consist of light chains, frequently kappa, or more rarely of single heavy chains or of mixed light and heavy chains.[48] The lung is a very rare location.[49–51] Pulmonary NAMIDD most frequently presents as multiple parenchymal nodules or less frequently, as multiple cysts; deposition is usually limited to the lung without systemic involvement. Approximately half of the cases are associated with hematologic malignancies. Treatment of any underlying hematologic disease usually leads to regression of the monoclonal peak but has little effect on existing deposits. Pulmonary NAMIDD may benefit from lung transplantation in cases of severe respiratory failure and in the absence of an underlying hematologic disorder.[50]

CARCINOIDS AND OTHER NEUROENDOCRINE TUMORS

Primary lung neuroendocrine tumors share common histopathologic features and correspond to four different clinical and prognostic entities: low-grade typical carcinoids, intermediate-grade atypical carcinoids, and high-grade large and small cell neuroendocrine carcinomas.[52] The small cell lung carcinomas are quite common, accounting for 15% to 20% of all primary lung malignancies. On the contrary, carcinoids and large cell neuroendocrine carcinomas account for 0.5% to 2% of lung tumors and are thus considered the most frequent lesions among the rare lung tumors.

Pathologic Classification

Neuroendocrine tumors share varying degrees of neuroendocrine morphologic features, including organoid nesting, the palisading and trabecular pattern, and "rosette-like" structures. Classification is mainly based on the mitotic index and the amount of necrosis.[52] Typical carcinoids exhibit neuroendocrine features, with a mitotic index less than 2 mitoses per 10 high-power fields (2 mm^2), and the absence of necrosis in a tumor that is more than 5 mm in diameter. Atypical carcinoids exhibit a mitotic index ranging from 2 to 10, or areas of focal necrosis (Fig. 48-2C). Peripheral carcinoids may also often be associated with small (≤5 mm) neuroendocrine "tumorlets" and/or with diffuse hyperplasia of pulmonary neuroendocrine cells.[53] These lesions may correspond to early-stage in situ carcinoid proliferation.

Large cell neuroendocrine carcinomas exhibit a mitotic index higher than 10 (actually ranging from 70–80 in most cases), and extensive necrosis. Unlike small cell carcinoma, large cell carcinomas have large tumor cells, with moderate to abundant cytoplasm and, frequently, prominent nucleoli. Immunohistochemically, the expression of at least one neuroendocrine marker, including chromogranin, synaptophysin, or N-CAM (CD56), confirms the diagnosis. The pathologic classification also distinguishes large cell neuroendocrine carcinoma from non–small cell lung cancer (NSCLC) "with neuroendocrine differentiation," a pattern without specific prognostic or therapeutic implications.[54]

Carcinoid Tumors

Excluding small cell lung cancer, more than 80% of lung neuroendocrine tumors are carcinoids.[11] Carcinoids arise mostly in never smokers (60%-80% of cases).[5,11] Carcinoids develop in the proximal airways in 60% to 70% of cases and may produce chronic cough, hemoptysis, and signs of bronchial obstruction. Peripheral carcinoids are asymptomatic, unless they are associated with diffuse hyperplasia of pulmonary neuroendocrine cells that produces bronchiolar obstruction in 50% of cases[55] and possible airflow obstruction. Unlike carcinoids in extrathoracic locations, lung carcinoids are small size lesions only rarely associated with liver metastases and do not generally produce the carcinoid syndrome (<2% of cases).[5,11] CT scan shows a peripheral or proximal well-circumscribed solitary nodular lesion in 90% of cases.[55] Carcinoid tumors may present as "iceberg-like" lesions, with a small amount of endobronchial growth and a prominent parenchymal mass (see Fig. 48-2A and B). In some cases, lobar or segmental atelectasis may constitute the sole manifestation of endobronchial small-size

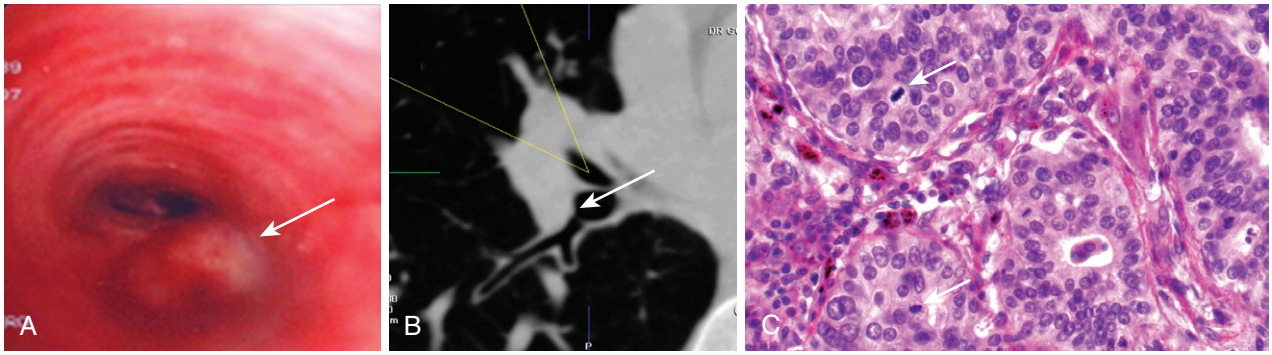

FIGURE 48-2 ■ Atypical carcinoid in a 17-year-old patient, presenting with recurrent infectious pneumonia. **A,** Endobronchial appearance of carcinoid (*arrow*), with a partial stenosis of the right main bronchus. **B,** At CT scan, an "iceberg-like" growth in the lung parenchyma (*arrow* showing small endobronchial aspect overlying larger parenchymal mass). **C,** Histopathologic aspect: endocrinoid growth pattern of uniform polygonal cells shows nestings, palisading, and rosettes. Two mitoses (*arrows*) are present in the field, characterizing this as an atypical carcinoid.

lesions. Peripheral calcifications may be observed in up to 30% of cases.[55] Their hypervascularity can distinguish carcinoids from mucous plugging. Regional lymph node invasion is more frequent in atypical carcinoids (40% to 50% of cases vs. 10% to 15% of typical carcinoids), and the tumor-node-metastasis (TNM) classification, although designed for carcinomas, has been used to stage carcinoids.[5,11,55] Although hypervascularized, carcinoids generally exhibit a low to moderate activity on PET scan.[56] Imaging for somatostatin receptors using ^{111}Indium-labeled octreotide has shown great promise and may increase the sensitivity for diagnosis, staging, and follow-up for recurrence.[57] The risk of hemorrhage following endobronchial biopsy is less than 1%.[11,55,57]

Surgery is the standard treatment for stage I-II and most stage III carcinoids, which account for 75% and 15% of cases, respectively. Typical carcinoids, with a low local recurrence rate, can be treated with limited resection with segmentectomy and regional lymph node dissection; this local approach is associated with local control and survival rates identical to that following extensive procedures.[10] Endobronchial techniques, such as cryotherapy, have also been reported as an alternative approach for typical carcinoid but fail to ensure accurate counting of the mitotic index and, therefore, the confirmation of the subtype.[58] Atypical carcinoids, which have a higher local recurrence rate, require lobectomy and mediastinal lymph node dissection.[10,59] Lung carcinoids metastasize in less than 10% of cases. In those cases, cisplatin-based chemotherapy is ineffective, whereas local treatment of metastases may lead to prolonged remission. In sum, the most significant prognostic factor is the histopathologic subtype, because 5-year survival rates of typical and atypical carcinoids are 87% to 98% and 56% to 73%, respectively.[5,11]

Large Cell Neuroendocrine Carcinoma

The incidence of large cell neuroendocrine carcinoma has long been underestimated, probably because these tumors are often misdiagnosed as large cell undifferentiated carcinoma either on cytology or on tissue sections in the absence of immunostaining for neuroendocrine markers.[5,60]

Large cell neuroendocrine carcinomas are strongly associated with tobacco smoking (90% of cases).[60,61] Clinical and radiologic features are similar to those of other bronchogenic carcinomas, and in most reported series, treatment follows recommendations for NSCLC, including resection in stage I-II tumors.[62,63] Efficacy of chemotherapy is, however, significantly better, with up to 75% of response to the cisplatin-etoposide combination in a neoadjuvant (presurgical) setting.[64,65] Several studies, including one prospective trial, showed a reduced metastatic recurrence rate and increased survival in patients receiving adjuvant chemotherapy even in early-stage tumors.[9,60,62,64] Overall survival is better than in small cell carcinoma, with stage the most significant prognostic factor, with 5-year survival of 52% to 88%, 20% to 45%, and 0% to 15% in stages I-II, III, and IV, respectively.[60–64]

RARE MALIGNANT PRIMARY PULMONARY EPITHELIAL TUMORS

Mucoepidermoid Carcinoma

Primary pulmonary salivary gland type tumors include mucoepidermoid carcinoma, adenoid cystic carcinoma, and epithelial-myoepithelial carcinoma. Mucoepidermoid carcinoma is the most frequent variant. It is a mixed malignant tumor characterized by the presence of squamous cells, goblet mucin-secreting cells, and cells of intermediate type (Fig. 48-3C and D).[65] Identification of these three cellular subtypes in cytologic examination is pathognomonic.[65,66] Tumors are classified as low-, intermediate-, and high-grade lesions, depending on the mitotic index, the degree of cellular atypia, and the degree of necrosis. High-grade tumors contain predominantly squamous and intermediate cells and tend to infiltrate the lung parenchyma.

Mucoepidermoid carcinoma in adults mostly develops between the third and the fourth decades, with an equal sex distribution.[66–69] High-grade tumors (30% of cases) are usually diagnosed in older patients. Mucoepidermoid carcinoma is often associated with tobacco smoking. Symptoms, including dyspnea, cough, and hemoptysis, are related to the level of bronchial obstruction. Metastases are found at time of diagnosis in 20% of cases, mainly in the liver, the bone, and the subcutaneous tissues (see Fig. 48-3B). In the lung, mucoepidermoid carcinoma often presents as a well-circumscribed homogeneous, lobulated homogenous mass, often with cystic and/or calcification features (see Fig. 48-3A).[70] The lesion is solitary in 40% to 70% of cases. Hilar involvement is found only for high-grade lesions. There is increased uptake on PET scanning.[70,71] Proximal mucoepidermoid tumors can be diagnosed using endobronchial biopsy.[67]

Treatment is the same as for NSCLC with, when feasible, extensive surgical resection including mediastinal lymph node dissection.[66–69] High-grade lesions have often been reported to receive postoperative radiotherapy and chemotherapy, without clear benefit. Chemotherapy of metastatic tumors in most cases is based on cisplatin and/or 5-fluorouracil. As in NSCLC, a small number of patients with mucoepidermoid carcinoma may benefit from specific epidermal growth factor inhibitors.[72] Prognosis is correlated to the grade of the lesion, the existence of nodal involvement, and the success of the initial surgical resection. Low-grade mucoepidermoid tumors mostly occur in children and young adults, usually do not present with hilar involvement, and have a 5-year survival ranging from 70% to 80%. High-grade tumors have a substantially worse prognosis, with a 5-year survival of only 30% to 45%.

Pneumoblastoma

Pulmonary blastoma is a biphasic tumor that is classified among the sarcomatoid carcinomas in the current WHO classification. This tumor contains both an epithelial well-differentiated component, showing tubular

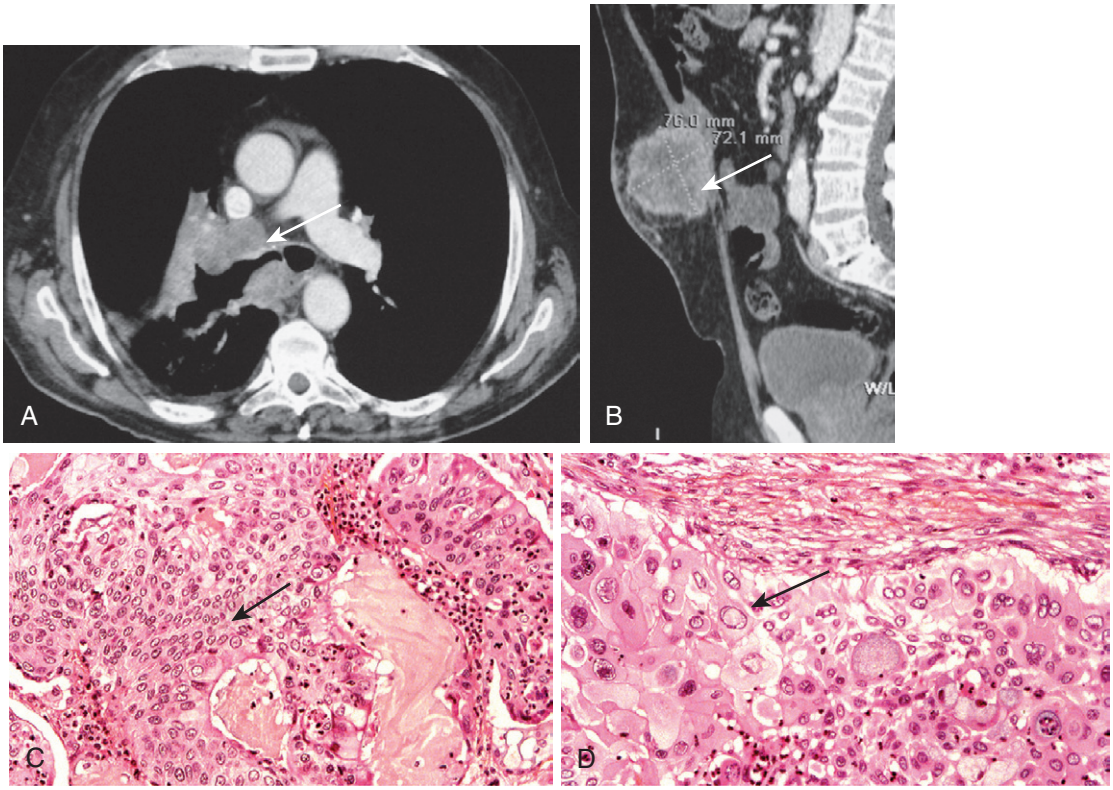

FIGURE 48-3 ■ Primary pulmonary mucoepidermoid carcinoma. **A,** The tumor is located in the right upper lobe and is invading the mediastinum (*arrow*). Radiologic features are identical to those of non–small cell lung cancer (NSCLC). **B,** A metastatic mass is discovered on clinical examination of the abdomen. Magnetic resonance imaging (MRI) confirms the location in the anterior abdominal wall (*arrow*). **C** and **D,** Histopathologic features: a mixture of squamoid (**C**) and mucin-secreting (**D**) cells (see *arrows*).

architecture resembling the normal fetal lung, and a mesenchymal undifferentiated stroma defining the "blastema-like" configuration.[73] Pulmonary pneumoblastoma arises in adults and has to be distinguished from "pleuropulmonary blastoma," a tumor of early childhood related to other embryonic neoplasms, such as nephroblastoma and neuroblastoma.

Pulmonary pneumoblastoma arises in patients from 30 to 45 years old, with a marked female predominance (70% of cases), and frequent association with tobacco smoking.[74–76] CT scan shows a solitary well-circumscribed homogeneous mass,[77] often with cystic and necrotic features. PET scans show increased uptake. In many cases, the tumor is initially thought to be a bronchogenic carcinoma, and complete surgical resection with mediastinal lymph node dissection ensures both the initial diagnosis and the therapy.[74,76,78,79] Adjuvant treatment, mostly consisting of radiotherapy, has been reported in a few cases following incomplete resection or in patients with N2 mediastinal involvement.[76,79–82] In unresectable tumors, chemotherapy is based on protocols used for sarcomas, including doxorubicin and ifosfamide. In most recent reports, survival is better than in NSCLC, especially in completely resected cases.[74]

Sarcomatoid Carcinomas (Other Than Pneumoblastoma)

Sarcomatoid carcinomas are a group of poorly differentiated non–small cell carcinomas that contain a sarcomatous component. In addition to pneumoblastoma, four subtypes are recognized: (1) pleomorphic carcinoma, which corresponds either to the combination of adenocarcinoma, squamous cell carcinoma, or large cell carcinoma with spindle or giant cells or to a carcinoma consisting only of spindle and giant cells[83,84]; (2) spindle cell carcinoma, which is exclusively made of fascicular cells; (3) giant cell carcinoma, composed of highly pleomorphic mono- or multinucleated cells[84]; and (4) carcinosarcoma, containing a mixture of carcinoma (frequently of epidermoid subtype) and poorly differentiated fibromatous sarcoma.[85]

Sarcomatoid carcinoma has been defined in the 1999 WHO classification. These tumors represent from 0.3% to 1.3% of lung tumors, and their specific clinical and radiologic features are rarely reported. Moreover, small biopsies usually do not disclose both the epithelial and the sarcomatous components of the tumor, which is then misdiagnosed as an NSCLC in more than 60% of

cases.[1] Clinical features are similar to other non–small cell carcinomas. Sarcomatoid carcinomas develop mostly in men, with a mean age of 65 years at diagnosis.[83–86] Tobacco smoking is described in more than 80% of cases. Radiologic studies usually show a solitary voluminous peripheral heterogenous mass, invading the chest wall in 60% of cases.[87,88] Vascular invasion is observed in 20% of cases. PET scans show increased uptake.

Sarcomatoid carcinomas are often treated as other non–small cell carcinomas. Alternatively, chemotherapy has been reported to follow soft tissue sarcoma regimens.[89] Response to epidermal growth factor receptor (EGFR)–targeted therapies is infrequent, which may be related to frequent *K-ras* mutations in the epithelial component.[90]

Contrary to pneumoblastomas, the other sarcomatoid carcinomas have been considered as highly aggressive tumors with early metastastic spread, especially in unusual sites such as the esophagus, the peritoneum, the kidney, and the subcutaneous tissues. Median overall survival ranges from 6 to 20 months.[83–86,88] The main favorable prognostic factors include tumor size, stage, and the absence of mediastinal involvement.[83–86,88–90]

PRIMARY PULMONARY SARCOMAS

Primary pulmonary sarcomas account for 20% of all primary rare lung malignancies and comprise parenchymal lung sarcomas, pulmonary artery sarcomas, and small vessel sarcomas.[1,2]

Parenchymal Sarcomas

Primary lung parenchymal sarcomas show identical pathologic subtypes to those of their soft tissue counterparts, with a wide spectrum of differentiation from low- to high-grade. Leiomyosarcoma is the most frequent primary lung sarcoma[91–93] and presents with fascicles of spindle cells at right angles and/or an epithelioid growth pattern with marked hypercellularity and polymorphism. Tumor cells have irregular nuclear chromatin and prominent nucleoli. Immunohistochemistry shows a high level of muscular actin, vimentin, and h-caldesmon, an actin-binding protein. Synovial sarcoma is the second most frequent subtype and presents with a prevalent monophasic growth pattern consisting of interweaving fascicles of densely packed spindle cells. As in their soft tissue location, the chromosomal translocation t(X;18)(p11.2;q11.2) is pathognomonic of the diagnosis[94] and results in the fusion of two genes, *SYT-SSX1* and *SYT-SSX2*. Other subtypes include pleomorphic sarcoma, made of atypical spindle cells showing a "cartwheel" or so-called storiform or radiating pattern, with elongated nuclei and giant cells with multiple and bizarre nuclei and prominent nucleoli, as well as osteosarcoma and chondrosarcoma. Because most mesenchymal malignant tumors have a benign counterpart, pathologic examination must, first, evaluate the grade of the lesion, according to the three-grade system of the French Federation of Cancer Centers Sarcoma Group (FFCCSG),[95] and second, rule out some epithelial tumors with sarcomatoid differentiation, such as pneumoblastoma, or myofibroblastic tumors.[1,7] Differential diagnosis also includes "benign" metastases from uterus (metastasizing leiomyoma) or bone (giant cell tumor).

Compared with their soft tissue counterparts, primary pulmonary sarcomas present in older patients, mainly from the sixth to eighth decade.[91–93,96–99] Clinical symptoms are nonspecific and usually consist of cough, dyspnea, and hemoptysis, depending on the size and the location of the lesions. The incidence of radiation-induced sarcomas has decreased because cobalt-based radiotherapy has been abandoned.[100] Contrary to metastatic sarcoma, primary pulmonary sarcoma presents as a solitary lesion, with heterogeneous cystic, necrotic, or hemorrhagic features but well-defined circumference. Size ranges from 4 to 25 cm (Fig. 48-4A). PET scanning shows increased uptake (see Fig. 48-4B).[101] Tumor progression is mainly local, and mediastinal lymph node invasion and systemic metastases are rare at the time of diagnosis (<2%).[92,93,96]

Surgery is then the most effective treatment, and complete resection is obtained in 80% of cases.[91–93,96–99] Adjuvant chemotherapy, which is recommended for soft tissue sarcoma, has never been evaluated specifically for primary pulmonary sarcoma.[102] Strategies developed in soft tissue sarcoma may not be applicable to primary lung sarcomas: for example, neoadjuvant chemotherapy is commonly used in soft tissue locations but has been disappointing in primary lung tumors.[93,96] In case of unresectable lesions, chemoradiation may be the best therapeutic strategy. As in soft tissue sarcoma, imatinib mesylate is not efficient, despite focal expression of its target CD117/Kit.[103] Prognosis mainly depends on the completeness of initial surgical resection, which, when combined with the grade of the lesion, is the best predictive factor of recurrence-free and overall survival. Overall 5-year survival varies from 40% to 50%[91–93,96–99] and may be better for leiomyosarcomas.[104]

Vascular Sarcomas

Primary pulmonary vascular sarcomas include pulmonary artery sarcomas and small vessel sarcoma, corresponding to epithelioid hemangioendothelioma (EHE), and its high-grade counterpart, angiosarcoma.[105]

Pulmonary artery sarcoma presents as an endoluminal polypoid or nodular mass, which spreads along the intima of the pulmonary artery. Histologic features consist of an undifferentiated spindle cell proliferation, with marked cellular pleomorphism and high mitotic index.[105] Leiomyosarcoma is the most frequent subtype (60% of cases).[105,106] Pulmonary artery sarcomas mainly develop in patients in their fifth to sixth decade.[107,108] Symptoms may mimic pulmonary embolism, with dyspnea, chest pain, cough, and hemoptysis.[107,108] Failure of anticoagulants in this setting, as well as the presence of symptoms of weight loss and fever (arising in 40% of cases), may also suggest the diagnosis. Radiographic findings also help to differentiate between pulmonary artery sarcoma and pulmonary embolism: CT scanning

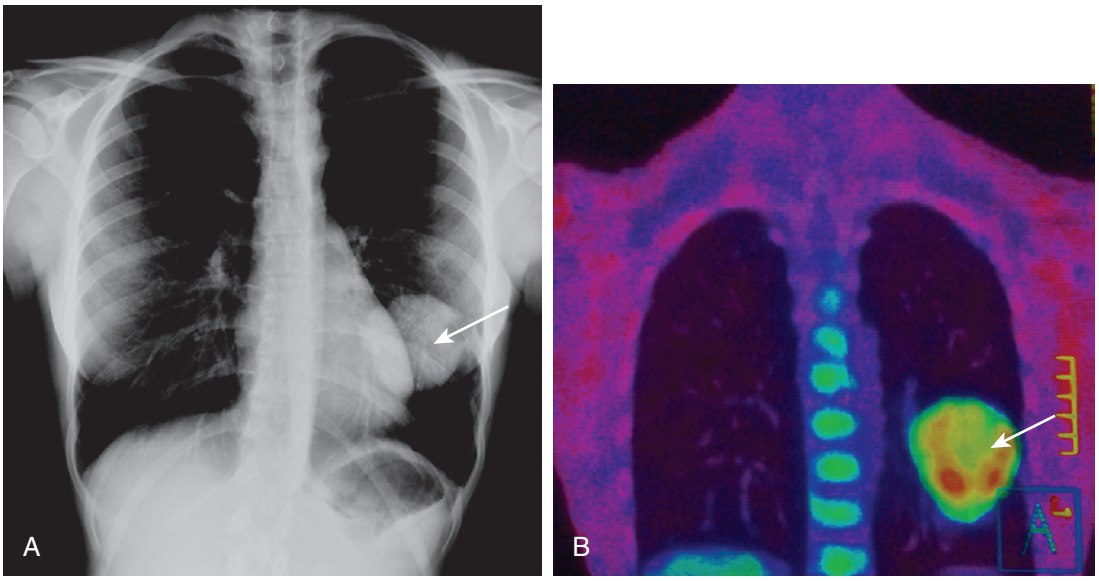

FIGURE 48-4 ■ Primary pulmonary leiomyosarcoma. Chest radiography shows a large well-circumscribed homogeneous mass in the left lung (**A,** *arrow*), which is hypermetabolic at ^{18}F-fluorodeoxyglucose positron emission tomography (PET) scan (**B,** *arrow*).

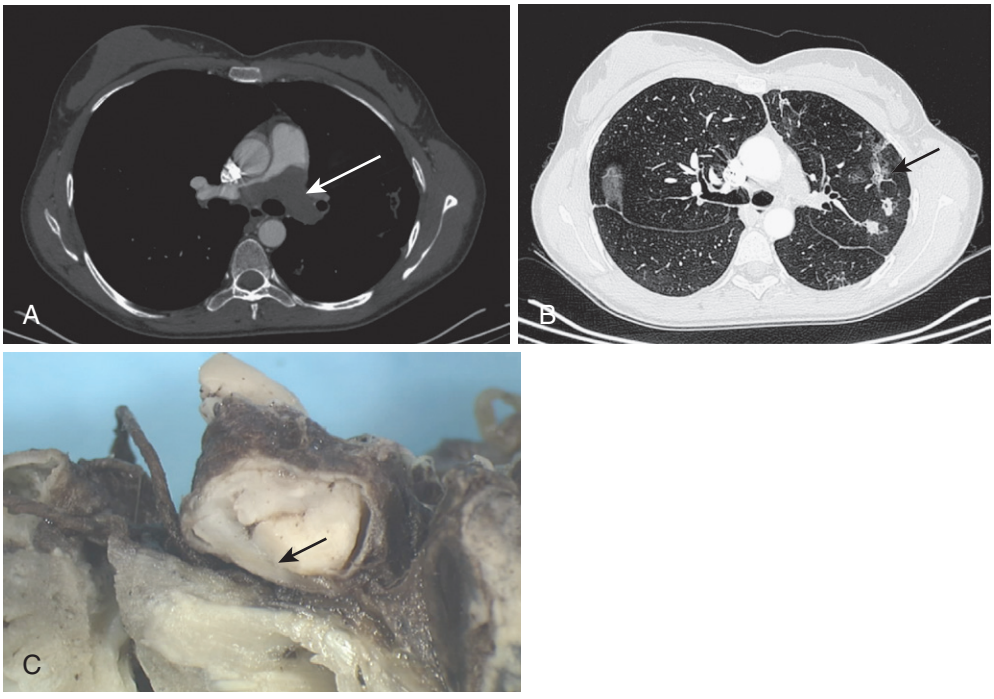

FIGURE 48-5 ■ Pulmonary artery sarcoma. CT scan discloses a mass filling the pulmonary artery lumen (*arrow*) (**A**), associated with peripheral irregular alveolar opacities (*arrow*) (**B**), without pleural contact. **C,** Specimen at pneumonectomy shows the infiltration of the pulmonary artery wall by the tumor (*arrow*).

may show a polypoid filling defect in the pulmonary artery but, contrary to thromboembolic disease, sarcoma forms a contiguously soft, smooth, tapering tissue, with possible extravascular nodular spread in the parenchyma (40% of cases), and localized ground-glass opacities (Fig. 48-5A and B).[108] Sarcoma also presents with a heterogeneous appearance including areas of necrosis and hemorrhage, and with intense hyperactivity on PET scanning.[109] Magnetic resonance imaging (MRI) shows T1-weighted heterogenous enhancement, T2-weighted peripheral enhancement, and increased uptake of gadolinium, signs which are not found in emboli.[109]

Surgery is the only potentially curative treatment and, even if performed in an emergency setting in case of acute right-sided heart failure, allows resectability in 60% to 75% of cases[88–90,92] (see Fig. 48-5C). Alternatively, heart and lung transplantation may be an alternative option for unresectable tumors. A slight improvement of overall

survival has also been reported following adjuvant chemotherapy and/or radiotherapy. Contrary to soft tissue sarcoma, prognosis is mainly related to tumor location, because half of the patients die as a result of the progressive obstruction of the pulmonary trunk.[110] Reoperation is feasible in 30% of cases. However, in recent series, overall median survival is as low as 6 to 12 months.[110]

EHE is a low- to intermediate-grade mixed epithelioid, endothelial, and vascular tumor.[111,112] Lung is the most frequent extrahepatic location (10% of cases), as EHE can also arise from the liver (63% of cases), the bone (8% of cases), and the skin (6% of cases).[113] EHE was initially considered an intravascular and intra-alveolar extension of bronchoalveolar carcinoma, and thus was called "intravascular bronchoalveolar tumor."[111,112] Now, however, it is clearly identified as a mesenchymal tumor, corresponding to low-grade angiosarcoma. EHE is characterized by polypoid nodules, with a central sclerotic paucicellular zone, growing into the alveolar spaces with an angiocentric distribution. Lymphangitic spread may mimic metastatic carcinoma. A recently identified translocation t(1;3)(p36.3;q25) involving the PAX7 gene may be helpful to make the diagnosis.[114]

Clinically, 80% of cases of EHE occur in white females.[113,115] Median age is higher than for other locations and ranges from 35 to 50 years.[115] The tumor is asymptomatic in 50% of cases; when present, symptoms are nonspecific and include pleuritic chest pain, nonproductive cough, dyspnea, and hemoptysis. Physical examination may reveal inspiratory crackles in 30% of cases. By CT imaging, EHE appears either with bilateral slow-growing perivascular multiple nodules, usually located adjacent to small vessels or bronchi, or with predominant infiltrative ground-glass opacities with a micronodular pattern, mimicking carcinomatous lymphangitis. EHE nodules usually range from 3 to 50 mm, and their number varies from 10 to 20 lesions.[113,115] Nodules show increased uptake with PET scanning.[116]

Although there are a few reports of spontaneous remission, the complete resection of all pulmonary nodules is the only curative treatment of EHE.[117,118] Incomplete lung resection, such as by segmentectomy and wedge resection, is associated with a short disease-free interval and poor outcome. Surgery remains effective even in cases of localized recurrence. In contrast, EHE is generally insensitive to chemotherapy or radiotherapy.[118] In most cases, EHE is a slow-growing tumor that rarely metastasizes and is associated with a median survival of 5 to 6 years. Endobronchial spread, pleural effusion, and extended endovascular disease have been identified as unfavorable prognostic factors.[117]

High-grade primary pulmonary vascular sarcomas include epithelioid angiosarcoma and Kaposi's sarcoma. No direct transformation from EHE to angiosarcoma has been so far reported. Clinical features of angiosarcoma are similar to EHE, but massive hemoptysis is more frequent. Radiologic features of angiosarcoma include multiple nodules with a typical surrounding halo of ground-glass attenuation, with a specific "cauliflower-like" appearance on T2-weighted MRI.[119] Management of angiosarcoma is not established: surgical resection is rarely possible owing to local and regional invasion; radiotherapy and chemotherapy are poorly effective, as seen in other localizations of angiosarcoma.

LESSONS LEARNED FOR THE MANAGEMENT OF RARE PRIMARY PULMONARY TUMORS

Specific Radioclinical Presentation

As discussed previously, some clinical and radiologic features, although infrequent, strongly suggest the diagnosis of rare lung tumors, such as the endobronchial "iceberg-like" aspect in carcinoids and mucoepidermoid carcinoma, air bronchograms in MALT lymphoma, or a peripheral "halo" in vascular sarcoma. The absence of tobacco-smoking history, especially in men, is more frequently seen for rare lung tumors than for bronchogenic carcinoma (60% vs. 15%, respectively),[1] as well as a young age at diagnosis, because more than 50% of rare lung tumors occur before the fourth decade. Finally, some rare malignant tumors such as pulmonary sarcoma and MALT lymphoma may also mimic benign lesions, such as pulmonary embolism and recurrent pneumonia, respectively.

Specific Diagnostic Strategy

In addition to the general oncologic workup, which is similar to NSCLC, some rare lung tumors also require specific diagnostic or staging investigations: MRI for vascular sarcomas, bone marrow biopsy for lymphoproliferative disorders, technetium-99m scintigraphy for osteosarcomas, and perhaps ^{111}Indium-octreotide scintigraphy for carcinoid. Preoperative biopsies and intraoperative frozen sections may not be sufficiently representative of the tumor to ensure accurate histopathologic diagnosis, especially in biphasic or composite tumors, for which small-size samples may identify only one cellular component. Rare primary lung tumors that are metastatic at time of diagnosis are usually not resected and may then be misdiagnosed as bronchogenic carcinoma. Sophisticated pathologic studies, including flow cytometry and molecular and cytogenetic analysis, may have a critical role both in diagnosis and in the evaluation of tumor grade.

In many cases, initial surgical resection provides the correct diagnosis and the first step of the therapy of rare lung tumors, even though they are originally considered to be bronchogenic carcinoma. However, preoperative diagnosis remains important for specific subtypes, such as lymphoma, for which extensive resection is ineffective, and for sarcoma, which does not spread to the mediastinal lymph nodes and thus does not require nodal resection.

Distinguishing Primary Tumors from Metastases

In making the diagnosis of a rare primary lung tumor, one must also consider the fact that most lung tumors with

unusual histology represent metastases from extrapulmonary tumors. The main criteria favoring metastases include a prior history of extrathoracic tumor and the finding of multiple pulmonary lesions. PET scanning may also be helpful, assuming that the metabolic features of each rare tumor subtype are sufficiently well-described.[101,120] The primary pulmonary nature of some rare tumors may actually be difficult to establish, either because of early systemic spread, as for EHE which presents with synchronous pulmonary and hepatic lesion in 20% of cases, or because of an ectopic origin, as for melanoma or Hodgkin's disease for which a primary pulmonary origin is highly controversial.

General Therapeutic Management

Finally, three main clinical scenarios may arise in the course of evaluation of patients with rare lung tumors:

1. Surgical resection of a tumor assumed to be NSCLC was complete, and pathologic examination disclosed an unusual histopathologic subtype, such as carcinoid. In this case, no adjuvant therapy is recommended.
2. Specific clinical and radiologic signs led to recognition of a rare tumor, such as lymphoma or pulmonary artery sarcoma, followed by specific diagnostic and therapeutic management.
3. Surgery of a pulmonary mass initially thought to be NSCLC led to recognition of a rare tumor subtype, and therapeutic and prognostic implications are unknown. In those cases, decision of adjuvant treatment is based either on a NSCLC standard of care (e.g., to use radiotherapy in case of incomplete surgical resection) or on therapeutic strategies established for similar tumor subtype in other locations (as it is done for lymphoma and sarcoma).

In the absence of evidence-based recommendations, expert consensus is mandatory for selection of a specific therapeutic strategy. Also, these issues emphasize the need for multicenter collaboration to generate cohorts and to launch observational studies and clinical trials of rare lung tumors.[121]

KEY POINTS

- Rare lung tumors are mainly defined as uncommon lung tumors with unusual histology.
- Diagnosis of rare lung tumors is based on the recognition of specific clinical and radiologic signs, when present, and on the determination of their primary as opposed to metastatic nature.
- The most frequent rare malignant primary lung tumors are carcinoids, mucosa-associated lymphoid tissue lymphoma, and pneumoblastoma.
- Understanding the molecular features of some rare tumors may lead to improved diagnostic techniques (e.g., detection of specific chromosomal translocations in MALT lymphoma or of somatostatin receptors in carcinoid). Moreover, the identification of genes and pathways involved in the carcinogenesis of rare tumors may guide the use of specific targeted therapies.
- Specific therapeutic recommendations are available for carcinoids and large cell neuroendocrine carcinoma. In other cases, expert consensus is mandatory to plan specific therapeutic strategies.

References

1. Girard N, Barbareschi M, Cordier JF, Murer B: What is a rare tumor, and how to deal with it clinically? Eur Respir Monogr 39:85–133, 2007.
2. Miller DL: Rare pulmonary neoplasms. Semin Respir Crit Care Med 18:405–415, 1997.
3. Sekine I, Kodama T, Yokose T, et al: Rare pulmonary tumors—A review of 32 cases. Oncology 55:431–434, 1998.
4. Miller DL, Allen MS: Rare pulmonary neoplasms. Mayo Clin Proc 68:492–498, 1993.
5. Travis WD, Rush W, Flieder DB, et al: Survival analysis of 200 pulmonary neuroendocrine tumors with clarification of criteria for atypical carcinoid and its separation from typical carcinoid. Am J Surg Pathol 22:934–944, 1998.
6. Ost D, Joseph C, Sogoloff H, Menezes G: Primary pulmonary melanoma: Case report and literature review. Mayo Clin Proc 74:62–66, 1999.
7. WHO histological classification of tumours of the lung. *In* Travis WB, Brambilla A, Muller-Hermelinck HK, Harris CC (eds): World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of the Lung, Pleura, Thymus and Heart. Lyon, France: IARC Press, 2004, p 10.
8. Marchevsky AM: Lung tumors derived from ectopic tissues. Semin Diagn Pathol 12:172–184, 1995.
9. Iyoda A, Hiroshima K, Moriya Y, et al: Prospective study of adjuvant chemotherapy for pulmonary large cell neuroendocrine carcinoma. Ann Thorac Surg 82:1802–1807, 2006.
10. Terzi A, Lonardoni A, Falezza G, et al: Sleeve lobectomy for non-small cell lung cancer and carcinoids: Results in 160 cases. Eur J Cardiothorac Surg 21:888–893, 2002.
11. Fink G, Krelbaum T, Yellin A, et al: Pulmonary carcinoid: Presentation, diagnosis, and outcome in 142 cases in Israel and review of 640 cases from the literature. Chest 119:1647–1651, 2001.
12. Cordier JF: Orphan lung diseases: From curiosity to concern. Bull Acad Natl Med 188:755–763, 2004.
13. Cadranel J, Wislez M, Antoine M: Primary pulmonary lymphoma. Eur Respir J 20:750–762, 2002.
14. Cordier JF, Chailleux E, Lauque D, et al: Primary pulmonary lymphomas. A clinical study of 70 cases in nonimmunocompromised patients. Chest 103:201–208, 1993.

15. Kurtin PJ, Myers JL, Adlakha H, et al: Pathologic and clinical features of primary pulmonary extranodal marginal zone B-cell lymphoma of MALT type. Am J Surg Pathol 25:997–1008, 2001.
16. Graham BB, Mathisen DJ, Mark EJ, Takvorian RW: Primary pulmonary lymphoma. Ann Thorac Surg 80:1248–1253, 2005.
17. Ferraro P, Trastek VF, Adlakha H, et al: Primary non-Hodgkin's lymphoma of the lung. Ann Thorac Surg 69:993–997, 2000.
18. Nicholson AG, Harris NL: Marginal zone diffuse B-cell lymphoma of the mucosa-associated lymphoid tissue (MALT) type. In Travis WB, Brambilla A, Muller-Hermelinck HK, Harris CC (eds): World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of the Lung, Pleura, Thymus and Heart. Lyon, France: IARC Press, 2004, pp 88–90.
19. Begueret H, Vergier B, Parrens M, et al: Primary lung small B-cell lymphoma versus lymphoid hyperplasia: Evaluation of diagnostic criteria in 26 cases. Am J Surg Pathol 26:76–81, 2002.
20. Cohen SM, Petryk M, Varma M, et al: Non-Hodgkin's lymphoma of mucosa-associated lymphoid tissue. Oncologist 11:1100–1117, 2006.
21. Zompi S, Couderc LJ, Cadranel J, et al: Clonality analysis of alveolar B lymphocytes contributes to the diagnostic strategy in clinical suspicion of pulmonary lymphoma. Blood 103:3208–3215, 2004.
22. Ray P, Antoine M, Mary-Krause M, et al: AIDS-related primary pulmonary lymphoma. Am J Respir Crit Care Med 158:1221–1229, 1998.
23. Cortot AB, Cottin V, Issartel B, et al: [Pulmonary MALT lymphoma revealing AIDS] (French). Rev Mal Respir 23:353–357, 2006.
24. Bazot M, Cadranel J, Benayoun S, et al: Primary pulmonary AIDS-related lymphoma: Radiographic and CT findings. Chest 116:1282–1286, 1999.
25. Thieblemont C, Berger F, Dumontet C, et al: Mucosa-associated lymphoid tissue lymphoma is a disseminated disease in one third of 158 patients analyzed. Blood 95:802–806, 2000.
26. Wislez M, Cadranel J, Antoine M, et al: Lymphoma of pulmonary mucosa-associated lymphoid tissue: CT scan findings and pathological correlations. Eur Respir J 14:423–429, 1999.
27. Lévy M, Copie-Bergman C, Gameiro C, et al: Prognostic value of translocation t(11;18) in tumoral response of low-grade gastric lymphoma of mucosa-associated lymphoid tissue type to oral chemotherapy. J Clin Oncol 23:5061–5066, 2005.
28. Koss MN, Harris NL: Lymphomatoid granulomatosis. *In* Travis WB, Brambilla A, Muller-Hermelinck HK, Harris CC (eds): World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of the Lung, Pleura, Thymus and Heart. Lyon, France: IARC Press, 2004, pp 92–94.
29. Taniere P, Thivolet-Bejui F, Vitrey D, et al: Lymphomatoid granulomatosis—A report on four cases: Evidence for B phenotype of the tumoral cells. Eur Respir J 12:102–106, 1998.
30. Pisani RJ, DeRemee RA: Clinical implications of the histopathologic diagnosis of pulmonary lymphomatoid granulomatosis. Mayo Clin Proc 65:151–163, 1990.
31. Robak T, Kordek R, Urbanska-Rys H, et al: High activity of rituximab combined with cladribine and cyclophosphamide in a patient with pulmonary lymphomatoid granulomatosis and bone marrow involvement. Leuk Lymphoma 47:1667–1669, 2006.
32. Guinee DG Jr, Perkins SL, Travis WD, et al: Proliferation and cellular phenotype in lymphomatoid granulomatosis: Implications of a higher proliferation index in B cells. Am J Surg Pathol 22:1093–1100, 1998.
33. Nicholson AG, Harris NL: Primary pulmonary diffuse large B-cell lymphoma. In Travis WB, Brambilla A, Muller-Hermelinck HK, Harris CC (eds): World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of the Lung, Pleura, Thymus and Heart. Lyon, France: IARC Press, 2004, p 91.
34. De Giacomo T, Venuta F, Anile M, et al: Non-Hodgkin's lymphoma, presenting as an isolated endobronchial mass after bilateral lung transplantation: a case report. Transplant Proc 39:3541–3544, 2007.
35. Goh SG, Chuah KL, Tan PH: Intravascular lymphomatosis of the lung and liver following eyelid lymphoma in a Chinese man and review of primary pulmonary intravascular lymphomatosis. Pathology 34:82–85, 2002.
36. Radin AI: Primary pulmonary Hodgkin's disease. Cancer 65:550–563, 1990.
37. Joseph G, Pandit M, Korfhage L: Primary pulmonary plasmacytoma. Cancer 71:721–724, 1993.
38. Koss MN, Moran CA, Frizzera G: Pulmonary plasmocytomas: A clinicopathologic and immunohistochemical study of five cases. Ann Diagn Pathol 2:1–11, 1998.
39. Westermark P, Benson MD, Buxbaum JN, et al: Amyloid: Toward terminology clarification. Report from the Nomenclature Committee of the International Society of Amyloidosis. Amyloid 12: 1–4, 2005.
40. Cordier JF, Loire R, Brune J: Amyloidosis of the lower respiratory tract. Clinical and pathologic features in a series of 21 patients. Chest. 90:827–831, 1986.
41. Cordier JF: Pulmonary amyloidosis in hematological disorders. Semin Respir Crit Care Med 26:502–513, 2005.
42. Gertz MA, Kyle RA: Amyloidosis with IgM monoclonal gammopathies. Semin Oncol 30:325–328, 2003.
43. Kobayashi H, Mastuoka R, Kitamura S, et al: Sjögren's syndrome with multiple bullae and pulmonary nodular amyloidosis. Chest 94:438–440, 1988.
44. Pusztaszeri M, Kamel EM, Artemisia S, et al: Nodular pseudotumoral pulmonary amyloidosis mimicking pulmonary carcinoma. Thorax 60:440, 2005.
45. Bierny JP: Multinodular primary amyloidosis of the lung: Diagnosis by needle biopsy. AJR Am J Roentgenol 131:1082–1083, 1978.
46. Suzuki H, Matsui K, Hirashima T, et al: Three cases of the nodular pulmonary amyloidosis with a long-term observation. Int Med 45:283–286, 2006.
47. Dyke PC, Demaray MJ, Delavan JW, Rasmussen RA: Pulmonary amyloidoma. Am J Clin Pathol 61:301–305, 1974.
48. Buxbaum J, Gallo G: Nonamyloidotic monoclonal immunoglobulin deposition disease. Light-chain, heavy-chain, and light- and heavy-chain deposition diseases. Hematol Oncol Clin North Am 13:1235–1248, 1999.
49. Girard N, Vasiljevic A, Cottin V, et al: Respiratory failure with diffuse bronchiectases and cryoglobulinaemia. Eur Respir J 31: 1374–1378, 2008.
50. Colombat M, Stern M, Groussard O, et al: Pulmonary cystic disorder related to light chain deposition disease. Am J Respir Crit Care Med 173:777–780, 2006.
51. Bhargava P, Rushin JM, Rusnock EJ, et al: Pulmonary light chain deposition disease: Report of five cases and review of the literature. Am J Surg Pathol 31:267–276, 2007.
52. Travis WD: The concept of pulmonary neuroendocrine tumors. *In* Travis WB, Brambilla A, Muller-Hermelinck HK, Harris CC (eds): World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of the Lung, Pleura, Thymus and Heart. Lyon, France: IARC Press, 2004, pp 19–20.
53. Davies SJ, Gosney JR, Hansell DM, et al: Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia: An under-recognised spectrum of disease. Thorax 62:248–252, 2007.
54. Ionescu DN, Treaba D, Gilks CB, et al: Nonsmall cell lung carcinoma with neuroendocrine differentiation—An entity of no clinical or prognostic significance. Am J Surg Pathol 31:26–32, 2007.
55. Chong S, Lee KS, Chung MJ, et al: Neuroendocrine tumors of the lung: Clinical, pathologic, and imaging findings. Radiographics 26:41–57, 2006.
56. Erasmus JJ, McAdams HP, Patz EF Jr, et al: Evaluation of primary pulmonary carcinoid tumors using FDG PET. AJR Am J Roentgenol 170:1369–1373, 1998.
57. Musi M, Carbone RG, Bertocchi C, et al: Bronchial carcinoid tumours: A study on clinicopathological features and role of octreotide scintigraphy. Lung Cancer 22:97–102, 1998.
58. Bertoletti L, Elleuch R, Kaczmarek D, et al: Bronchoscopic cryotherapy treatment of isolated endoluminal typical carcinoid tumor. Chest 130:1405–1411, 2006.
59. Marty-Ané CH, Costes V, Pujol JL, et al: Carcinoid tumors of the lung: Do atypical features require aggressive management? Ann Thorac Surg 59:78–83, 1995.
60. Veronesi G, Morandi U, Alloisio M, et al: Large cell neuroendocrine carcinoma of the lung: A retrospective analysis of 144 surgical cases. Lung Cancer 53:111–115, 2006.

61. Takei H, Asamura H, Maeshima A, et al: Large cell neuroendocrine carcinoma of the lung: A clinicopathologic study of eighty-seven cases. J Thorac Cardiovasc Surg 124:285–292, 2002.
62. Zacharias J, Nicholson AG, Ladas GP, Goldstraw P: Large cell neuroendocrine carcinoma and large cell carcinomas with neuroendocrine morphology of the lung: Prognosis after complete resection and systematic nodal dissection. Ann Thorac Surg 75: 348–352, 2003.
63. Rossi G, Valli R, Bertolini F, et al: Role of chemotherapy and the receptor tyrosine kinases KIT, PDGFRalpha, PDGFRbeta, and Met in large-cell neuroendocrine carcinoma of the lung. J Clin Oncol 23:8774–8785, 2005.
64. Iyoda A, Hiroshima K, Moriya Y, et al: Prognostic impact of large cell neuroendocrine histology in patients with pathologic stage Ia pulmonary non–small cell carcinoma. J Thorac Cardiovasc Surg 132:312–315, 2006.
65. Yousem SA, Nicholson AG: Mucoepidermoid carcinoma. *In* Travis WB, Brambilla A, Muller-Hermelinck HK, Harris CC (eds): World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of the Lung, Pleura, Thymus and Heart. Lyon, France: IARC Press, 2004, pp 63–64.
66. Yousem SA, Hochholzer L: Mucoepidermoid tumors of the lung. Cancer 60:1346–1352, 1987.
67. Vadasz P, Egervary M: Mucoepidermoid bronchial tumors: A review of 34 operated cases. Eur J Cardiothorac Surg 17:566–569, 2000.
68. Kim TS, Lee KS, Han J, et al: Mucoepidermoid carcinoma of the tracheobronchial tree: Radiographic and CT findings in 12 patients. Radiology 212:643–648, 1999.
69. El Mezni F, Ben Salha I, Ismaïl O, et al: Mucoepidermoid carcinoma of the lung. A series of 10 cases. Rev Pneumol Clin 61:78–82, 2005.
70. Ishizumi T, Tateishi U, Watanabe SI, Matsuno Y: Mucoepidermoid carcinoma of the lung: High-resolution CT and histopathologic findings in five cases. Lung Cancer 60:125–131, 2008.
71. Shim SS, Lee KS, Kim BT, et al: Focal parenchymal lung lesions showing a potential of false-positive and false-negative interpretation on integrated PET/CT. AJR Am J Roentgenol 186:639–648, 2006.
72. Han SW, Kim HP, Jeon YK, et al: Mucoepidermoid carcinoma of lung: Potential target of EGFR-directed treatment. Available at Lung Cancer doi:10.1016/j.lungcan.2007.11.014, 2008.
73. Corrin B, Wick MR, Chang YL, et al: Sarcomatoid carcinoma. *In* Travis WB, Brambilla A, Muller-Hermelinck HK, Harris CC (eds): World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of the Lung, Pleura, Thymus and Heart. Lyon, France: IARC Press, 2004, pp 53–58.
74. Larsen H, Sorensen JB: Pulmonary blastoma: A review with special emphasis on prognosis and treatment. Cancer Treat Rev 22:145–160, 1996.
75. Force S, Patterson GA: Clinical-pathologic conference in general thoracic surgery: Pulmonary blastoma. J Thorac Cardiovasc Surg 126:1247–1250, 2003.
76. LeMense GP, Reed CE, Silvestri GA: Pulmonary blastoma: a rare lung malignancy. Lung Cancer 15:233–237, 1996.
77. Lee HJ, Goo JM, Kim KW, et al: Pulmonary blastoma: Radiologic findings in five patients. Clin Imaging 28:113–118, 2004.
78. Francis D, Jacobsen M: Pulmonary blastoma. Curr Top Pathol 73:265–294, 1983.
79. Chaugle H, Sivardeen KA, Benbow EW, Keenan DJ: Pulmonary blastoma. Eur J Cardiothorac Surg 13:615–616, 1998.
80. Asimakopoulos G, Krausz T, Smith PL: Radical resection of a pulmonary blastoma involving the mediastinum. Thorac Cardiovasc Surg 47:197–199, 1999.
81. Hill DA, Sadeghi S, Schultz MZ, et al: Pleuropulmonary blastoma in an adult: An initial case report. Cancer 85:2368–2374, 1999.
82. Cutler CS, Michel RP, Yassa M, Langleben A: Pulmonary blastoma: Case report of a patient with a 7-year remission and review of chemotherapy experience in the world literature. Cancer 82: 462–467, 1998.
83. Fishback NF, Travis WD, Moran CA, et al: Pleomorphic (spindle/giant cell) carcinoma of the lung. A clinicopathologic correlation of 78 cases. Cancer 73:2936–2945, 1994.
84. Rossi G, Cavazza A, Sturm N, et al: Pulmonary carcinomas with pleomorphic, sarcomatoid, or sarcomatous elements: A clinicopathologic and immunohistochemical study of 75 cases. Am J Surg Pathol 27:311–324, 2003.
85. Ginsberg SS, Buzaid AC, Stern H, Carter D: Giant cell carcinoma of the lung. Cancer 70:606–610, 1992.
86. Koss MN, Hochholzer L, Frommelt RA: Carcinosarcomas of the lung: A clinicopathologic study of 66 patients. Am J Surg Pathol 23:1514–1526, 1999.
87. Kim TH, Kim SJ, Ryu YH, et al: Pleomorphic carcinoma of lung: Comparison of CT features and pathologic findings. Radiology 232:554–559, 2004.
88. Kim TS, Han J, Lee KS, et al: CT findings of surgically resected pleomorphic carcinoma of the lung in 30 patients. AJR Am J Roentgenol 185:120–125, 2005.
89. Martin LW, Correa AM, Ordonez NG, et al: Sarcomatoid carcinoma of the lung: A predictor of poor prognosis. Ann Thorac Surg 84:973–981, 2007.
90. Pelosi G, Scarpa A, Manzotti M, et al: K-ras gene mutational analysis supports a monoclonal origin of biphasic pleomorphic carcinoma of the lung. Mod Pathol 17:538–546, 2004.
91. Etienne-Mastroianni B, Falchero L, Chalabreysse L, et al: Primary sarcomas of the lung: A clinicopathologic study of 12 cases. Lung Cancer 38:283–289, 2002.
92. Régnard JF, Icard P, Guibert L, et al: Prognostic factors and results after surgical treatment of primary sarcomas of the lung. Ann Thorac Surg 68:227–231, 1999.
93. Penel N, Lartigau E, Fournier C, et al: Sarcomes des tissus mous thoraciques de l'adulte: Étude rétrospective de 40 cas. Ann Chir 128:237–245, 2003.
94. Pelmus M, Guillou L, Hostein I, et al: Monophasic fibrous and poorly differentiated synovial sarcoma: Immunohistochemical reassessment of 60 t(X;18)(SYT-SSX)–positive cases. Am J Surg Pathol 26:1434–1440, 2002.
95. Coindre JM, Trojani M, Contesso G, et al: Reproducibility of a histopathologic grading system for adult soft tissue sarcoma. Cancer 58:306–309, 1986.
96. Porte HL, Metois DG, Leroy X, et al: Surgical treatment of primary sarcoma of the lung. Eur J Cardiothorac Surg 18:136–142, 2000.
97. Janssen JP, Mulder JJ, Wagenaar SS, et al: Primary sarcoma of the lung: A clinical study with long-term follow-up. Ann Thorac Surg 58:1151–1155, 1994.
98. Keel SB, Bacha E, Mark EJ, et al: Primary pulmonary sarcoma: A clinicopathologic study of 26 cases. Mod Pathol 12:1124–1131, 1999.
99. Conte B, Leitner J: Leiomyosarcoma of the lung. J Thorac Cardiovasc Surg 105:1119–1120, 1993.
100. Stinchcombe TE, Walters R, Khandani AH, Socinski MA: Radiation-induced sarcoma after high-dose thoracic radiation therapy in non–small-cell lung cancer. J Clin Oncol 25:1621–1623, 2007.
101. Jadvar H, Fischman AJ: Evaluation of rare tumors with (F-18) fluorodeoxyglucose positron emission tomography. Clin Positron Imaging 2:153–158, 1999.
102. Sarcoma Meta-analysis Collaboration (SMAC): Adjuvant chemotherapy for localised resectable soft tissue sarcoma in adults. Cochrane Database Syst Rev 4:CD001419, 2000.
103. Boroumand N, Raja V, Jones DV, Haque AK: SYT-SSX2 variant of primary pulmonary synovial sarcoma with focal expression of CD117 (c-Kit) protein and a poor clinical outcome. Arch Pathol Lab Med 127:e201–e204, 2003.
104. Moran CA, Suster S, Abbondanzo SL, Koss MN: Primary leiomyosarcomas of the lung: A clinicopathologic and immunohistochemical study of 18 cases. Mod Pathol 10:121–128, 1997.
105. Yi JE, Tazelaar HD, Burke A, Manabe T: Pulmonary artery sarcoma. *In* Travis WB, Brambilla A, Muller-Hermelinck HK, Harris CC (eds): World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of the Lung, Pleura, Thymus and Heart. Lyon, France: IARC Press, 2004, pp 109–110.
106. Devouassoux M, Thivolet Béjui F, Tabone E, et al: Sarcoma of the pulmonary artery. Rev Mal Respir 15:295–299, 1998.
107. Parish JM, Rosenow EC 3rd, Swensen SJ, Crotty TB: Pulmonary artery sarcoma. Clinical features. Chest 110:1480–1488, 1996.

108. Yi CA, Lee KS, Choe YH, et al: Computed tomography in pulmonary artery sarcoma: Distinguishing features from pulmonary embolic disease. J Comput Assist Tomogr 28:34–39, 2004.
109. Thurer RL, Thorsen A, Parker JA, Karp DD: FDG imaging of a pulmonary artery sarcoma. Ann Thorac Surg 70:1414–1415, 2000.
110. Kim HK, Choi YS, Kim K, et al: Surgical treatment for pulmonary artery sarcoma. Eur J Cardiothorac Surg 33:712–716, 2008.
111. Travis WD, Tazelaar HD, Miettinen M: Epithelioid hemangioendothelioma/angiosarcoma. *In* Travis WB, Brambilla A, Muller-Hermelinck HK, Harris CC (eds): World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of the Lung, Pleura, Thymus and Heart. Lyon, France: IARC Press, 2004, pp 97–98.
112. Dail DH, Liebow AA, Gmelich JT, et al: Intravascular, bronchiolar, and alveolar tumor of the lung (IVBAT). An analysis of twenty cases of a peculiar sclerosing endothelial tumor. Cancer 51:452–464, 1983.
113. Mehrabi A, Kashfi A, Fonouni H, et al: Primary malignant hepatic epithelioid hemangioendothelioma: A comprehensive review of the literature with emphasis on the surgical therapy. Cancer 107:2108–2121, 2006.
114. Boudousquie AC, Lawce HJ, Sherman R, et al: Complex translocation (7;22) identified in an epithelioid hemangioendothelioma. Cancer Genet Cytogenet 92:116–121, 1996.
115. Kitaichi M, Nagai S, Nishimura K, et al: Pulmonary epithelioid haemangioendothelioma in 21 patients, including three with partial spontaneous regression. Eur Respir J 12:89–96, 1998.
116. Fagen K, Silverman ED, Cole RL: Detection of a pulmonary epithelioid hemangioendothelioma by FDG PET scan. Clin Nucl Med 29:75–79, 2004.
117. Bagan P, Hassan M, Le Pimpec Barthes F, et al: Prognostic factors and surgical indications of pulmonary epithelioid hemangioendothelioma: A review of the literature. Ann Thorac Surg 82:2010–2013, 2006.
118. Pinet C, Magnan A, Garbe L, et al: Aggressive form of pleural epithelioid haemangioendothelioma: Complete response after chemotherapy. Eur Respir J 14:237–238, 1999.
119. Atasoy C, Fitoz S, Yiğit H, et al: Radiographic, CT, and MRI findings in primary pulmonary angiosarcoma. Clin Imaging 25:337–340, 2001.
120. Poeppel TD, Krause BJ, Heusner TA, et al: PET/CT for the staging and follow-up of patients with malignancies. Eur J Radiology 70:382–392, 2009.
121. Girard N, Triby-Moreau C, Benabidallah S, et al: Pulmonary artery sarcoma, a paradigm of orphan thoracic oncology. Presse Med 38:1167–1170, 2009.

CHAPTER 49

METASTATIC MALIGNANT TUMORS

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INTRODUCTION

The lung is a common site for metastasis of malignant tumors from other organs. Logic would suggest that the lung is a preferred site because it receives the entire right ventricular cardiac output, and therefore, is the natural destination for malignant cells that gain access to the venous circulation.[1] Indeed, this likely does play a role in the eventual seeding of the lungs when cancers metastasize via the hematogenous route. However, as the understanding of the metastatic process becomes more sophisticated, it is clear that specific properties of the primary tumor and the microenvironment of the tissue of origin and of the lung all play a significant role in directing the process of metastasis to the lung. This notion is not new; Paget[2] initially proposed what became known as the "seed and soil" hypothesis in 1889 based upon his observations of the nonrandom nature of breast cancer metastasis. As a result of advances in science, we can now understand this paradigm on a molecular level.[3] This chapter reviews the epidemiology of lung metastasis, advances in our knowledge of the pathophysiology of metastasis, approaches to help distinguish metastasis from primary lung cancer, advances in diagnostic methods, and a variety of treatment options that vary from palliation to curative surgery.

Epidemiology

Estimates of the incidence of lung metastasis among patients with cancer vary from 20% to 40%.[1,4] The precise incidence of metastasis to the lung from all tumors is difficult to determine from published reports because most series focus on a single tumor type as the origin of lung metastases. The reported incidence also varies depending on the duration and the means used for detection and for follow-up. Published reports on the incidence of lung metastasis in patients with cancer have employed different approaches: surveillance of those with respiratory symptoms, routine surveillance with chest radiographs or with computed tomography (CT) scans, or autopsy data. The reported incidence of lung metastasis increases with each of these means of ascertainment, respectively. Whereas the proportion of cancers reported to metastasize to the lung varies, the lung is always among the most commonly reported sites of metastasis of solid tumors.[4]

Clinical History

Lung nodules arising in the context of an extrapulmonary neoplasm can be either *synchronous* (discovered at the same time as the primary tumor) or *metachronous* (discovered at some period after the initial solid tumor, either incidentally in the course of follow up of a prior

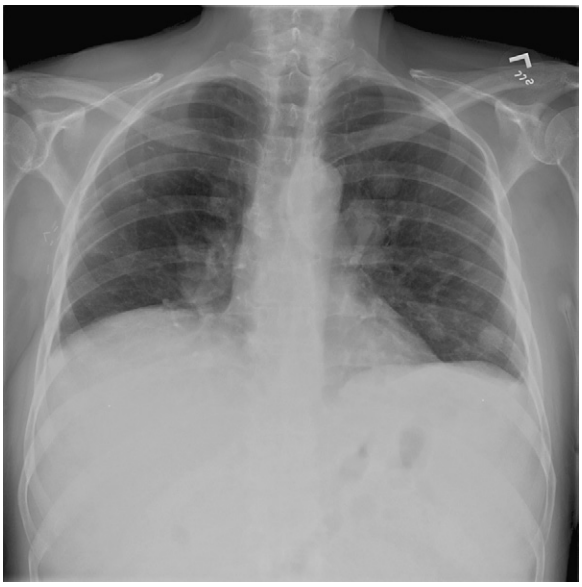

FIGURE 49-1 ■ Plain chest radiograph of a 76-year-old man with a prior history of melanoma who presented only with fatigue and dry cough. Multiple large bilateral lung nodules and masses were present that proved to be metastases.

malignancy or in the context of new pulmonary symptoms). Because of the large degree of reserve pulmonary function in most individuals, hematogenous metastases to the lungs rarely produce symptoms, and even patients with a large metastatic tumor burden can present with minimal or no pulmonary symptoms (Fig. 49-1). Nonspecific symptoms of cough, dyspnea, chest pain or chest discomfort can result from a very large tumor burden, extensive lymphatic infiltration, or the presence of a large pleural effusion. The first clue to the presence of lung metastasis comes most commonly from surveillance radiographs in patients with known prior cancer, in which the most common presentation is multiple nodules in the lower lobe. Occasionally, an incidental solitary pulmonary nodule is the first sign of metastatic cancer from a distant organ, making the distinction of metastasis from that of a primary lung tumor challenging. The physical examination is unlikely to disclose evidence of lung metastasis but, in the context of a solitary pulmonary nodule, the examination should include a search for malignancy elsewhere in the body (e.g., breast or abdominal masses or enlarged lymph nodes). Rarely, a metastasis can affect the airway producing localized wheezing, which an astute clinician discovers on auscultation. Malignant pleural fluid accumulation produces the physical findings of reduced breath sounds, a dull percussion note, and decreased tactile fremitus. These findings should prompt evaluation for a pleural effusion with decubitus chest radiographs and, if needed, thoracentesis with or without ultrasound guidance. Management of malignant pleural effusions is discussed in Chapters 73 and 75.

MECHANISM OF METASTASIS TO THE LUNG

When one considers that the lung receives the entire cardiac output, it is perhaps surprising that lung metastases are not even more common among patients with cancer. However, research has shown that the majority of cancer cells that gain access to the circulation never result in a clinically overt metastatic focus,[5,6] suggesting that mere access to the lung is not sufficient. Additional mechanisms must, therefore, account for the propensity of certain tumors to seed distant organs preferentially in a clinically detectable fashion. Following are examples of recent advances that help clarify our understanding of the molecular and cellular biology of organ-specific metastasis.

Chemokines are a group of small cytokines originally discovered as mediators of leukocyte trafficking. Research now shows that chemokines mediate several important pathologic aspects of tumor biology, including angiogenesis, cell proliferation, invasion, and metastasis.[7] The pattern of constitutive expression of chemokine receptors on cancer cells combined with expression of the corresponding chemokine ligands in various organs may be responsible for the organ-specific pattern of metastasis of a variety of solid tumor types, including breast, prostate, and lung cancer.[8-10] In an important study, the chemokine receptors CXCR4 and CCR7 were found to be highly expressed in human breast cancer cell lines, in primary breast tumor samples, and in their metastases whereas the corresponding ligands CXCL12 and CCL21 were constitutively expressed in organs to which these tumors commonly metastasize (lung, brain, bone, and lymph nodes).[10] In the breast cancer cell lines, signaling through the receptors CXCR4 or CCR7 was shown to promote in vitro migration and invasion. Most interestingly, antibodies or small molecule antagonists directed against CXCR4 significantly impaired metastasis of breast cancer cells to the regional lymph nodes and lung *in vivo*. In another study, malignant melanoma, which has a metastatic pattern similar to that of breast cancer but also has a high incidence of skin metastases, showed high expression of the chemokine receptor CCR10 in addition to CXCR4 and CCR7. The ligand for CCR10 (cutaneous T-cell attracting chemokine, or CTACK/CCL27) is highly expressed in normal dermis, which may explain the frequent metastatic spread of melanoma to the skin.[11] In a study of lung cancer metastasis, cells from metastases were found to be enriched for the expression of CXCR4 compared with cells from the primary tumors, suggesting that CXCR4-expressing cells enjoyed an advantage in the metastatic niche.[9] Chemokine receptors on cancer cells in concert with tissue-specific expression of their chemokine ligands appear to have a critical role in determining the metastatic destination of circulating tumor cells.

Recent insight into another mechanism by which cancer cells target the lung comes from elegant studies showing that transforming growth factor-β (TGF-β), a cytokine present in the local breast tumor microenviron-

ment, primes breast cancer cells for lung-specific metastasis by up-regulation of the gene angiopoietin-like 4 (*ANGPTL4*).[12] TGF-β induction of *ANGPTL4* in breast cancer cells enhanced their subsequent retention in the lungs but not in bone. The tumor cell–derived protein, Angptl4, disrupted the pulmonary microvascular cell-cell junctions, increasing the permeability of lung capillaries and facilitating the passage of tumor cells into the lung parenchyma. In contrast, in the bone marrow sinusoids that are normally more leaky microvascular beds, this mechanism did not confer an advantage.[12] Such advances in the knowledge of molecular mechanisms that promote or facilitate organ-specific metastasis should lead to new treatments to prevent, reduce, or treat established lung metastasis and could have a significant impact on cancer mortality.

DIAGNOSIS

Differential Diagnosis

Given the range of diagnostic and therapeutic options in cases of known or suspected lung metastasis, patient care is optimal when delivered within the context of a multidisciplinary team. A pulmonologist deciding whether to biopsy a lung nodule in a patient with a prior history of cancer should speak to the oncologist and/or the surgeon to know whether metastatic cancer would have therapeutic options or whether the results of a biopsy would alter those options. If a patient with suspected metastasis is otherwise a surgical candidate, a preoperative tissue diagnosis may not change the ultimate management, as is discussed later. Conversely, surgeons may prefer a preoperative tissue diagnosis to improve their discussion of risks, benefits, and alternatives with the patient. For these and other reasons, the management of these patients is best served when clinicians can communicate patient-specific concerns to one another. Multidisciplinary conferences and shared clinical space can facilitate these important discussions.

The patient with a prior history of cancer and suspicion of a lung metastasis should be managed with knowledge of several interacting factors: the type of prior cancer, its natural history, its propensity to cause lung metastasis, its sensitivity to chemotherapy or radiation therapy, and the number and location of lung nodules. A decision to biopsy should take into account the likelihood of an alternative diagnosis and whether the results of the biopsy will change the management options.

The diagnostic possibilities for a single lung nodule or multiple nodules in the patient with a history of cancer vary with the type of prior cancer. For example, the implications of finding a cavitary nodule in a patient with prior leukemia after a bone marrow transplant are quite different from those of finding a cavitary nodule in an individual with prior head and neck cancer. In general, the differential diagnosis of a lung nodule in a patient with prior cancer includes the same diagnoses found in the general population, with the noted exception that metastatic disease must be considered as well. Both primary malignant and benign causes, including infectious and noninfectious etiologies, should be considered (Table 49-1).

TABLE 49-1. Differential Diagnosis of Single or Multiple Pulmonary Nodules in Patients with a Prior History of Cancer

MALIGNANT
Metastasis
Primary lung cancer
BENIGN
Infectious
Fungal granuloma
Mycobacterial granuloma
Nocardia
Septic emboli
Noninfectious
Rheumatoid nodules
Hamartoma
Typical carcinoid
Sarcoidosis
Vasculitic lesions (Wegener's granulomatosis)

Distinguishing Metastases from Primary Lung Tumors

When a nodule or nodules are discovered in a patient with a prior history of cancer, it is important to distinguish lung metastasis from a primary lung cancer because the treatment can be very different. Clues such as the type of prior cancer, radiologic characteristics of the nodule, and the pathologic appearance of subsequent biopsy material can be used to guide treatment decisions. Multiple pulmonary nodules with smooth borders located in the lower (dependent) lobes are most likely to be metastatic, based on clinical grounds alone. When a single nodule is the only evidence of metastasis, recognizing it as metastatic can be more difficult. In some instances, the type of prior cancer can provide a clue to the likelihood of a metastasis versus a primary lung cancer. In a retrospective study of patients with single pulmonary nodules and a prior history of cancer, multiple factors were examined as possible predictors for metastasis including the histologic characteristics of the original extrapulmonary neoplasm, patient age, and smoking history.[13] Of 161 patients with solitary pulmonary nodules, 81 (50%) were determined to have a primary lung cancer; this outcome was more common in patients with a prior history of cancer of the head and neck, bladder, breast, cervix, bile ducts, esophagus, ovary, prostate, or stomach. Fifty patients (31%) were determined to have metastasis, a finding more common in patients with salivary, thyroid, and adrenal tumors, melanoma, and sarcoma. Primary lung cancer or metastases were equally likely in patients with prior cancer of the colon, kidney, or uterus. In those with prior

lymphoma or leukemia, there was a high proportion of patients with a benign diagnosis (6 of 14), perhaps reflecting the predilection of these patients for granulomatous infections.[13] In total, 30 of 161 patients (19%) had nodules of a benign nature. The large percentage of benign diagnoses in this study by Quint and coworkers[13] (1994–1999) contrasts with a larger but much earlier study by Cahan and colleagues[14] (1940–1975) in which only 11 of 800 patients (1.3%) proved to have a benign diagnosis. The higher incidence of benign disease in the later study may be explained by two factors: the greater use of CT scanning and thus the higher rate of detection of nodules in the later study and the fact that the earlier study was a surgical series in which patients with a high pretest probability of benign disease may have been excluded. A consistent finding in these two studies representing nearly 40 total years from two large centers was the high proportion of patients with head and neck squamous or esophageal cancers who subsequently developed a *primary* lung cancer. Of course, common risk factors exist for patients with these types of cancer, and the presence of a smoking history increases the likelihood that a solitary lung nodule in someone with a prior nonpulmonary neoplasm will prove to be a lung cancer. By understanding the data in these and other studies, clinicians can more accurately estimate the likelihood that a pulmonary nodule is metastatic, primary, or benign.

Pathology

When biopsy tissue from the prior cancer and the lung nodule are both available, the pathologist's evaluation of the metastatic nodule begins with a knowledge of the prior cancer, its stage and grade (if applicable), and the pretest likelihood of lung metastasis from a tumor with such characteristics. The gross and microscopic pattern of the possible metastasis may be sufficiently similar to the original primary tumor that the diagnosis is rendered easily. Owing to overlapping histologic features, however, it may be impossible for pathologists to distinguish primary from metastatic carcinoma.[15] In many situations, the appearance of an adenocarcinoma is not sufficiently distinctive to permit a differentiation between metastasis and primary lung cancer, and immunohistochemical stains are used to help guide the diagnosis (Table 49-2). Lung adenocarcinoma can be identified by specific immunohistochemical markers including cytokeratin-7, thyroid transcription factor-1 (TTF-1), and the surfactant proteins A and B (SP-A, SP-B).[15] For example, cytokeratin-7 can be useful for distinguishing adenocarcinoma of the lung from colon cancer metastasis, with cytokeratin-7 favoring lung, and cytokeratin-20 favoring a colon primary.[15] TTF-1, a nuclear transcription protein expressed in embryonic and adult epithelial cells of the lung and thyroid,[16] is detected in 75% of lung adenocarcinomas but rarely detected in other adenocarcinomas that commonly metastasize to the lungs, except for thyroid cancer.[16] Markers specific for other tumors can also be used to identify lesions as metastatic; for example, breast cancers that metastasize to the lung can maintain their original pattern of staining for estrogen receptor or Her-2/Neu and staining of the lung nodule can identify it as a metastasis. Thus, in instances in which the primary tumor stains for specific markers, these stains can be useful for identifying a lesion as a metastasis.

TABLE 49-2. Immunohistochemical Stains Useful for Distinguishing Lung Cancer from Metastatic Cancer from a Nonpulmonary Origin

Cancer	Positive Markers	Negative Markers
Lung	CK7, TTF-1, SP-A, SP-B	CK20
Colon	CK20	TTF-1
Breast	ER, PR, Her2/Neu	TTF-1
Prostate	PSA, prostatic acid phosphatase	TTF-1
Melanoma	HMB45, S100, tyrosine hydroxylase	Cytokeratin
Thyroid	TTF-1, thyroglobulin	
Germ cell	Alpha-fetoprotein	

CK, cytokeratin; ER, estrogen receptor; PR, progesterone receptor; PSA, prostate specific antigen; SP, surfactant protein; TTF, thyroid transcription factor.

Molecular Classification

With the advent of gene expression arrays and, in the future, proteomic classification of tumors, molecular classification is an emerging tool to assist in determining whether a lung nodule is primary or metastatic. Giordano and colleagues[17] attempted to develop a molecular classification scheme to discriminate adenocarcinomas of the lung, colon, and ovary. They identified three groups of 20 differentially expressed genes that correctly identified the origins of all but 2 of 154 tumors.[17] Other groups of investigators have proposed classifiers for a broader representation of tumors in an effort to identify the primary tissue of origin of carcinomas of unknown primary. Tothill and associates[18] developed and validated a gene array-based classifier on a training set of 229 samples of known origin. This gene classifier was then able to assign a "tissue of origin" in 9 of 11 cases of carcinoma of unknown primary.[18] The two tumors that the gene classifier failed to classify were actually not adenocarcinoma, but squamous carcinomas. Subsequent review of the clinical course of the patients supported the assessment of the gene classifier.[18] Another study attempted to generate a gene expression-based classifier to distinguish metastases of head and neck squamous carcinoma from primary lung squamous carcinoma, a clinically difficult task because of both the histologic similarity and the shared risks for these squamous cancers. This study identified 10 genes whose expression was able to discriminate between tumors of lung and upper aerodigestive origin with high accuracy in both training and validation samples.[19] Certainly, molecular techniques will provide new ways of classifying tumors and, in so doing, improve the ability to identify

the origin of a lung nodule. When the prior tissue is available for comparison, molecular testing may also assist identification of the new nodule as either a metastasis related to the prior cancer or a new and different cancer.

Options for Obtaining a Tissue Diagnosis

A biopsy may not be necessary when a patient with a history of prior cancer presents with nodules with highly typical characteristics: (1) history of a cancer likely to metastasize to the lungs with (2) multiple, (3) new (or growing), (4) lower lobe pulmonary nodules with (5) smooth borders. A less common situation in which biopsy *may* be unnecessary is the patient whose prior cancer is associated with measurable serum markers (CA19-9, CA125, carcinoembryonic antigen [CEA], alpha-fetoprotein, β-human chorionic gonadotropin, CYFRA21-1). In such a patient, the presence of a rising level of tumor-associated markers may confirm the diagnosis of metastatic disease and preclude the need for a biopsy. However, for most tumors other than those of germ cell origin, these epithelial markers are not sufficiently specific and a biopsy is warranted to guide therapy. In all cases, before performing a lung biopsy, it is important to search for evidence of metastasis to other sites where a less invasive biopsy may yield the diagnosis. This should begin with a thorough physical examination directed to finding any enlarged lymph nodes, skeletal tenderness, or hepatomegaly that would guide the next imaging study or tissue sampling.

Tissue sampling in older series is generally derived from surgical material, and indeed surgical resection remains the "gold standard" owing to the quantity of material available for gross and microscopic examination, as well as special immunochemical stains or molecular analyses.[14] In addition, surgery may be the appropriate definitive therapy for patients with lung metastases from solid tumors. However, there are now multiple options other than surgery, each with strengths and drawbacks that can be weighed to develop an approach that allows a clinician to determine the best balance between certainty, risk, and cost. The diagnostic options including fiberoptic bronchoscopy, percutaneous CT-guided biopsy, and surgical resection are discussed later, with each successive option associated with increased accuracy (sensitivity and negative predictive value) but also with increased risk and cost.

Bronchoscopy

Fiberoptic bronchoscopy is particularly useful for accessing centrally located lesions and mediastinal lymph nodes. Transbronchial needle aspiration of enlarged mediastinal lymph nodes is safe and has a reasonable diagnostic accuracy in cases of malignant mediastinal lymph node metastasis (see Chapter 22). The addition of real-time linear probe endobronchial ultrasound increases sensitivity and permits the biopsy of much smaller lymph nodes in both the mediastinum and the hilar lymph node stations (see Chapter 20). The accuracy of bronchoscopy for lung parenchymal lesions declines rapidly as the distance from the main-stem bronchi increases, so that traditional transbronchial sampling techniques have less than 20% sensitivity for peripheral lung nodules.[20] More recently, a newer technique employing three-dimensional CT reconstruction combined with electromagnetic navigation of an extended working channel has allowed biopsy of small peripheral lung nodules with significantly greater accuracy. Experienced users of this newer approach report a 69% to 80% sensitivity for the diagnosis of small peripheral lung nodules (as small as 7 mm, ranging up to 8 cm, with an average size < 2 cm).[21,22] Combining this technique with real-time imaging using a radial probe ultrasound catheter to confirm the location suggested by virtual images further increased the accuracy of transbronchial biopsy to 88% in one series[23] (Fig. 49-2). Using bronchoscopy, multiple samples can be taken from one area or from multiple different nodules in a single procedure without an appreciable increase in the risk for pneumothorax. Given the low risk of pneumothorax (1%-5%) and major bleeding, the chief risk of the bronchoscopic biopsy, even when combined with electromagnetic navigation and real-time radial-probe ultrasound, is that of a false-negative biopsy.

CT-Guided Biopsy

Clinicians' experience in CT-guided biopsy is becoming widespread and, as experience has increased, the accuracy of this biopsy technique has improved significantly.[24] This approach has greater sensitivity than bronchoscopy, particularly for peripheral lesions. The sensitivity of CT-guided biopsy of lung nodules varies with the size of the lesion, with a 65% to 75% accuracy for smaller lesions (<1 cm diameter), and a greater than 95% sensitivity for lesions larger than 1.5 cm in diameter.[24,25] Larger size of the nodule and a more peripheral location are factors associated with greater diagnostic accuracy.[26] Core biopsies, in addition to or instead of cytologic material, can be obtained with larger 19-gauge needles. The major risk of CT-guided transthoracic needle biopsy is pneumothorax, with up to 35% of patients developing pneumothorax, and 10% to 15% requiring tube thoracostomy or catheter drainage.[27] The risk of pneumothorax appears to increase with the length of the needle tract, as well as the presence of obstructive lung disease.[26] In one large retrospective series,[27] severe complications of CT-guided biopsy were quite rare; of 6881 cases, 74 patients were reported with severe complications including 6 patients with air embolism, 10 with tension pneumothorax, 6 with severe pulmonary hemorrhage, 9 with hemothorax, and 6 with seeding of the needle tract. Eight deaths were reported. In general, CT-guided biopsies are safe and accurate, especially for peripheral lesions.

Surgery

Resection of a nodule provides the greatest sensitivity in determining the nature of the lesion(s) and makes it possible to diagnose and occasionally to treat the lesions

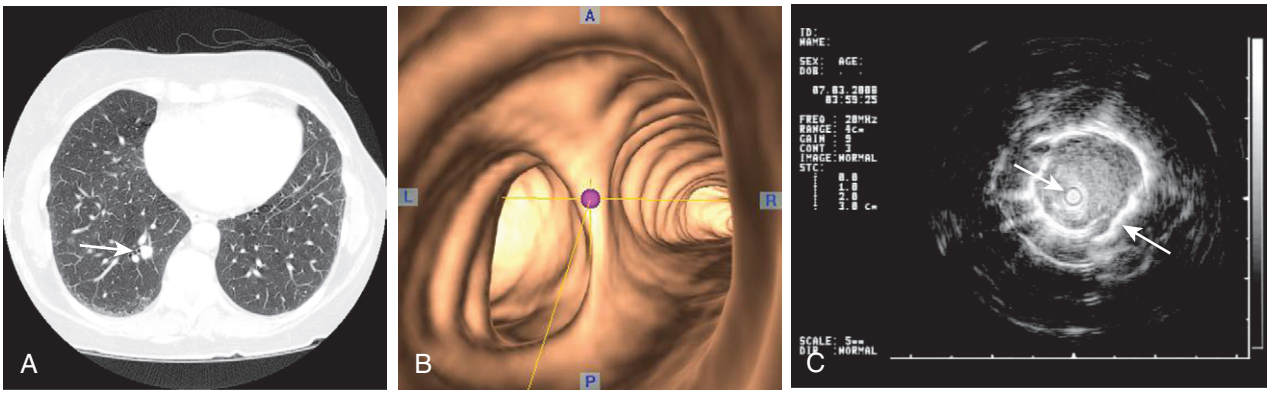

FIGURE 49-2 ■ **A,** Computed tomography (CT) scan of a 53-year-old woman with a newly discovered right lower lobe nodule (*arrow*) 12 years after lumpectomy and adjuvant chemotherapy and radiation for breast cancer. **B,** Virtual bronchoscopic image generated with software for electromagnetic navigation. Fiducial registration points using recognizable airway landmarks are created (*purple dot*) and the nodule is located with planning software. The fiducial points are then registered (touched) during the procedure using a steerable probe, the location of which is sensed within a field generated by the location processor under the patient's thorax, a process that matches the patient's anatomy with the virtual CT images. The navigation of an extended working channel is guided by the virtual CT image during the procedure using the steerable probe. **C,** Real-time radial probe ultrasound image of the nodule, obtained by passing the ultrasound probe through the extended working channel. The probe is seen at the center of the photograph (*upper left arrow*), and the edge of the nodule is indicated by the echogenic border between the solid nodule and the air-filled lung surrounding it (*lower right arrow*). This image is used to confirm the location of the extended working channel within the nodule. The probe is removed, and biopsy tools are then passed through the extended working channel to sample tissue. Transbronchial biopsy in this patient confirmed a diagnosis of metastatic breast cancer.

definitively in a single procedure. The selection of patients in whom nodule resection is appropriate is a matter of controversy. There are few, if any, randomized studies comparing surgical and nonsurgical treatment of lung metastasis and the data from reported series on surgical treatment of lung metastases suffer from a lack of uniformity in selection criteria. The sensitivity of surgery for diagnosis is likely close to 100% given that it is the accepted gold standard for tissue diagnosis of lung lesions. However, very small lung lesions can be difficult for the surgeon to palpate and may be missed. The risks of surgery for diagnosis include those for general anesthesia in addition to the risks associated with lung resection. Thoracoscopic surgery is also discussed later as a treatment and may be the preferred option when surgery is required for diagnosis.

TREATMENT OF LUNG METASTASES

Multimodality Therapy of Systemic Disease

Treatment for lung metastasis is largely dictated by the tissue of origin (Fig. 49-3). In cases of curable cancers, patients with lung metastases should be treated aggressively with multimodal therapy appropriate for the original tumor. Germ cell tumors, neuroblastoma, gestational trophoblastic tumors, lymphoma, and osteosarcoma are included in this category. In certain cases, residual nodules persist following chemotherapy and can then be resected. In patients with nonseminomatous germ cell tumors, resection of residual nodules or masses after systemic chemotherapy is an aggressive but appropriate approach. In cases of testicular cancer, such residual masses after chemotherapy remain in approximately 40% of patients who have advanced disease and negative serum tumor markers at the conclusion of treatment.[28,29] When resected, approximately half of these masses contain only necrotic tissue, a further 25% show a mature teratoma, and the rest contain residual carcinoma. Long-term follow-up studies after chemotherapy suggest that most patients (90%) with metastases from testicular cancer found to have mature teratoma on resection and even 50% of those with residual carcinoma are cured by "adjuvant" surgery.[28,29] In other tumors, treatment options are mainly nonsurgical. For patients with lymphoma, for example, in whom treatment alternatives are more numerous and systemic therapy is necessary, biopsy rather than excision is more appropriate. These varied treatment options highlight the importance of undertaking the care of these patients with multidisciplinary input.

Palliative Care

Unfortunately, most adult patients with pulmonary metastases from solid tumors have incurable disease, and palliative therapy is often necessary. For selected cancers, palliative treatment may include radiotherapy, chemotherapy, hormonal, or biologic/targeted therapies. Agents chosen for palliative therapy should balance acceptable levels of toxicity with the expected degree of tumor response and symptom control. Radiation therapy for patients with radiosensitive tumors can provide rapid and effective symptom relief. For patients

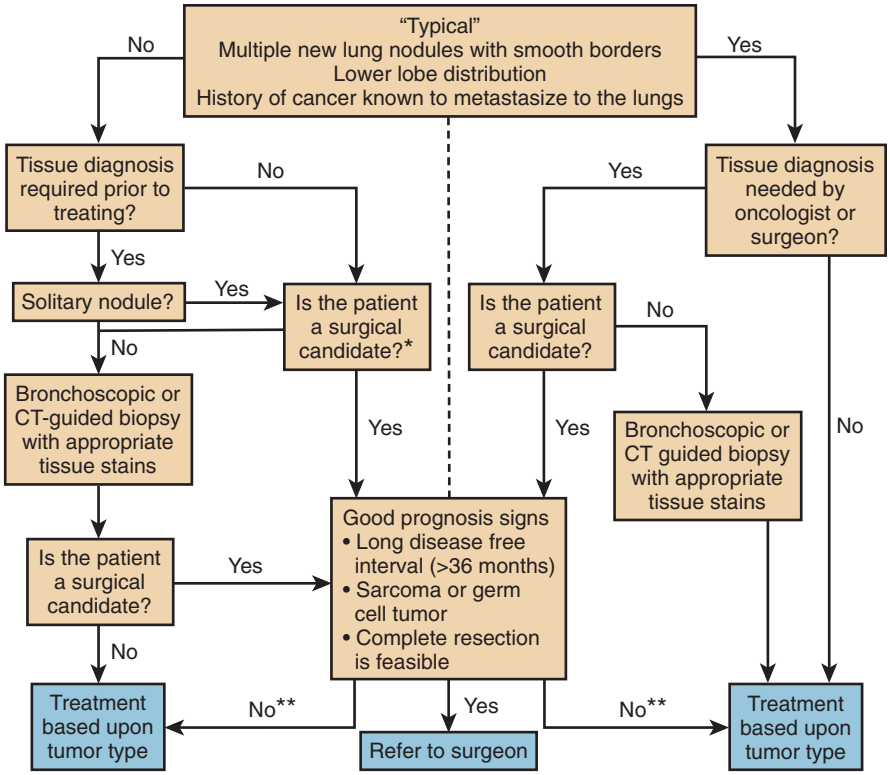

FIGURE 49-3 ■ Suggested management algorithm for patients with known prior cancer and new lung nodule(s). A suggested management algorithm taking into account the typical or atypical appearance of a lung nodule(s) in a patient with prior known cancer, the utility of a tissue diagnosis to the treating physicians, the physiologic fitness of the patient for surgery, and the known prognostic indicators for a favorable outcome after metastasectomy. Each patient should be managed individually, within the context of the skills and experience of local providers with the varied diagnostic and therapeutic options. *Patients at high risk for primary lung cancer should be managed with this possibility in mind, including diagnostic lobectomy when appropriate. **These are suggested criteria for surgical resection of lung metastases, and multidisciplinary teams should make this decision. Radiofrequency ablation (RFA) may be an excellent choice for these patients as well.

with endobronchial obstruction, endobronchial tumor ablation using brachytherapy, laser, or cryoprobes can be very effective for palliation (see Chapter 22). These approaches require specialized training, and referral to a center with experience in such techniques is advisable. Because most centers may specialize only in one, or at most two, of these interventional methods, direct comparisons of the efficacy and safety of palliative interventions for malignant airway obstruction have not been reported. Opiates and oxygen therapy may relieve symptoms of end-stage dyspnea. Social, emotional, and physical rehabilitation support as well as hospice services have important roles in the care of such patients.

Radiofrequency Ablation of Metastases

Thermal ablation is a minimally invasive therapy that can be used for local cure or control of either primary or metastatic lung tumors. Radiofrequency ablation (RFA) which uses radiofrequency energy to generate frictional heating and cell death, is the most commonly performed thermal ablation procedure used to treat lung tumors. Although the role of RFA is not as clearly defined as other options, studies supporting use of this procedure for lung metastases are mounting and the role for RFA in treating lung metastasis is emerging. Although RFA is more commonly performed to treat hepatic and renal tumors, it may be well suited to the lung owing to its ability to concentrate thermal energy focally within tumor tissue with little or no energy spreading to the adjacent aerated normal lung parenchyma.[30]

Smaller tumors, 3 cm or less in diameter, may be more effectively treated with RFA than larger tumors.[31,32] Peripheral tumors surrounded by lung parenchyma and away from hilar structures can be safely treated with RFA.[33,34] Even tumors contiguous with certain vital structures, such as the thoracic aorta and pulmonary vessels, may be safely treated, according to recent reports,[35] because the cooling effect of constant blood flow in large vessels may protect them from tissue damage. Multiple lesions in the same hemithorax can be treated at one sitting by experienced providers, but because of the risk of pneumothorax (as high as 50% in one series[36]), bilateral lesions should not be treated during the same procedure.

Surgical Resection of Metastases

Surgical resection of pulmonary metastases may be the appropriate choice in certain situations. As resection has become more common, factors associated with good outcome have been identified. In general, a complete resection of all metastases is vital to improved survival. Incomplete resection is associated with dismal survival rates that do not differ from those with no treatment at all. Another important good prognostic factor in numerous large series is a long disease-free interval (DFI) between the initial diagnosis of cancer and the discovery of lung metastasis.[37-39] For example, 5-year survival was 33% when the DFI was 0 to 11 months compared with 45% when the DFI was more than 36 months.[40,41] The number of pulmonary metastases was previously

believed to be a prognostic factor, but this has not been a consistent finding. More prognostic factors must be identified to improve selection of patients for metastasectomy. Suggested selection criteria for pulmonary metastasectomy, taken from various large series,[39,42] are shown in Table 49-3. Selection of patients for pulmonary metastasectomy according to these criteria provides the best survival.[39]

In 1991, the International Registry of Lung Metastases (IRLM; comprising over 5000 cases) was established to record and report upon the long-term results of pulmonary metastasectomy for various primary malignancies.[42] According to the registry, long-term success of pulmonary metastasectomy varies according to the primary malignancy. Cancers that metastasize exclusively to the lungs have more favorable outcomes from pulmonary metastasectomy than cancers that metastasize more widely. Malignancies with the greatest long-term survival after pulmonary metastasectomy include osteogenic and soft tissue sarcoma, colorectal cancer, uterine/cervical tumors, head and neck cancer, breast cancer, testicular tumors, renal cell tumors, and melanoma (Table 49-4). Patients undergoing lung metastasectomy for osteosarcoma have some of the best results, but success is not limited to this type of metastasis.[42]

Surgical resection of pulmonary metastases requires careful planning and preparation. As with any lung resection, the number, location, and size of the lesion(s), pulmonary function, and the general condition of the patient must be considered, as must any evidence for local invasion or the prospects for response to systemic therapy. CT has the greatest sensitivity and accuracy for localizing pulmonary nodules for resection. Small nodules can be localized using image-guided wires, dyes, and coils as well as ultrasound and radiation probes. An emerging strategy is the use of electromagnetic guidance navigation followed by dye marking to assist in localizing small peripheral lung nodules prior to thoracoscopic resection[43] (Fig. 49-4). In tumors that can be detected with fluorodeoxyglucose–positron emission

TABLE 49-3. Criteria for Pulmonary Metastasectomy[39]

ABSOLUTE CRITERIA

1. The patient is a good candidate for surgery.
2. The primary tumor is controlled.
3. No extrapulmonary metastases exist or, if present, they must be controllable by surgery or another treatment.
4. Pulmonary metastases are completely resectable.

RELATIVE CRITERIA

1. Pulmonary metastases are symptomatic (e.g., causing pneumothorax, hemoptysis).
2. Surgery is necessary to differentiate metastasis from primary lung cancer.

TABLE 49-4. Tumor-Specific 5-Year Survival Rates following Pulmonary Metastasectomy

Primary Malignancy	5-Year Survival (%)
Soft tissue sarcoma[51–53]	20–35
Osteosarcoma[54]	25–50
Melanoma[55,56]	5–33
Colorectal[57,58]	13–40
Testis (germ cell)[28,59]	50–80
Renal[60,61]	15–20
Breast[38,62,63]	25–50
Head and neck[64,65]	26–30

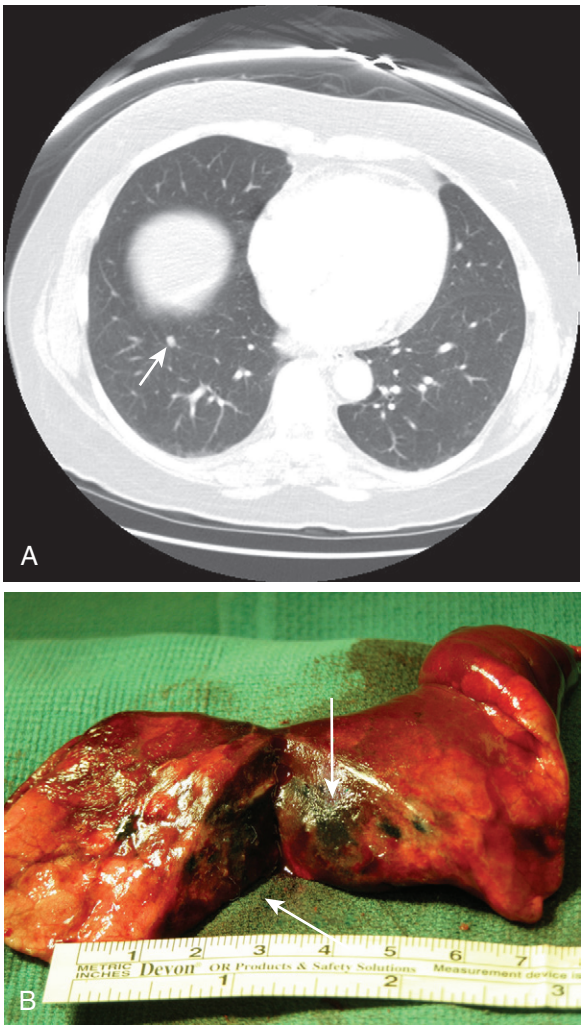

FIGURE 49-4 ■ **A,** Right lower lobe lung nodule (*arrow*) that appeared, then increased on follow-up serial CT scans in a 53-year-old woman with a history of rectal cancer. The nodule was localized using electromagnetic navigation, and the overlying pleura was tattooed with indigo carmine dye. She was then taken to the operating room where she underwent a thoracoscopic wedge resection of the tattooed pleura and underlying parenchyma. **B,** Gross specimen resected by the surgeon after thoracoscopic visualization of the ink on the diaphragmatic surface of the pleura (*lower arrow*) and the intraparenchymal nodule (*upper arrow*), found on pathologic examination to be a metastatic colorectal adenocarcinoma.

tomography (FDG-PET) scanning, it should be performed prior to pulmonary metastasectomy to exclude the presence of synchronous extrathoracic metastasis that would negate the benefit of lung resection. FDG-PET uptake or lymph node enlargement seen on CT can also suggest less invasive biopsy techniques such as mediastinoscopy, transthoracic needle biopsy, and transbronchial needle biopsy (with or without endobronchial ultrasound). With the exception of certain germ cell tumors and perhaps sarcomas,[43a] finding synchronous metastasis outside the lung would be a contraindication to pulmonary metastasectomy.

Thoracotomy has been the most frequently utilized approach for unilateral metastasectomy, primarily because it enables the surgeon to palpate the lung for lesions. Thoracoscopic pulmonary metastasectomy has been criticized based upon its limited ability to permit palpation of the lungs to identify unknown metastases. However, as the resolution of CT scanning improves, especially with multidetector scanners, the likelihood of pulmonary nodules that can be palpated but not visualized on CT scan decreases dramatically, thus improving the relative utility of a thoracoscopic approach for metastasectomy. In addition, instruments and techniques have evolved to allow enhanced visualization and even thoracoscopic palpation of lung parenchyma. Compared with thoracotomy, thoracoscopic metastasectomy has several advantages including smaller incisions, less pain, earlier recovery, and fewer postoperative adhesions. The latter is especially important because repeat pulmonary metastasectomy may be indicated based on the same criteria as the initial metastasectomy.[41,42] Indeed, more than 50% of patients who undergo complete pulmonary metastasectomy will develop recurrence. The probability of relapse is higher for sarcoma and melanoma than for epithelial or germ cell tumors. In the International Registry, repeat metastasectomy yielded 44% survival at 5 years and 29% at 10 years,[42] which is comparable with the results after initial metastasectomy. Thus, thoracotomy or thoracoscopy may be selected based on several criteria, including the surgeon's experience, and the possible need for repeat metastasectomy.[44]

Prior to any resection, all lung lesions should be identified in order to plan a resection that minimizes the loss of lung parenchyma. The extent of pulmonary resection is an important consideration. Registry data reveal that metastasectomy was achieved by wedge resections in 67%, segmentectomy in 9%, and lobectomy or bilobectomy in 21%.[42] Lymph node dissection is not encouraged owing to the low incidence of nodal involvement with pulmonary metastasis, associated morbidity, and the poor survival of patients with nodal metastasis regardless of resection. Pneumonectomy or extended resection was rarely used (3%) and should be reserved for special circumstances with acceptable surgical risk and reasonable likelihood of long-term survival.[42]

The morbidity and mortality for pulmonary metastasectomy should be very low. Most series report less than 2% mortality and 10% morbidity.[42] The most common complications are persistent air leak and infection. Preoperative chemotherapy or radiation may increase the risk of respiratory failure after metastasectomy when high fractional concentrations of oxygen are used perioperatively.[29] Anesthesiologists should be alerted to a history of chest irradiation or chemotherapy (particularly with bleomycin used for germ cell tumors) and use the lowest possible fractions of inspired oxygen possible for these patients. With appropriate patient selection, the survival following pulmonary metastasectomy can be quite good. The decision to operate should be influenced less by the type of prior cancer than on the eligibility criteria described in Table 49-3.

Most reports regarding the effectiveness of pulmonary metastasectomy have been retrospective. These nonrandomized and uncontrolled series introduce selection and lead-time bias that must be kept in mind when considering treatment options. Reported survival rates of 30% to 40% at 5 years are encouraging, but the selection criteria used for surgical resection, as well as the nonrandomized nature of these studies, must be taken into consideration. Additional studies are needed to define candidates that will receive maximum benefit from pulmonary metastasectomy.

SPECIAL CASES

Airway Metastasis

Although rare, large airway involvement with endobronchial metastasis can produce very distressing symptoms of dyspnea and/or hemoptysis. Awareness of the clinical scenario along with available diagnostic and management strategies can be very helpful in palliating these patients. Reported series of patients with endobronchial metastasis are generally small but uniformly emphasize the utility of fiberoptic bronchoscopy for diagnosis as well as for symptom control and palliation. Other than lung cancer, tumors that metastasize to the bronchi include colon, breast, renal cell carcinoma, melanoma, and many others.[45–47] Breast and colon cancers predominate in reported case series of endobronchial metastases, perhaps because they are more prevalent in the population of cancer patients in general. It should be noted that colon cancer can metastasize to the bronchi without involvement of the liver.[46] Radiation can be used for palliation in patients with malignant airway obstruction and radiosensitive tumors. Mechanical means including stents and endobronchial ablative methods (laser, cryoprobe, argon plasma coagulation, or physical débridement) can be used for tumors that are relatively radioresistant (see Chapter 22).

Vascular Embolic Metastasis

A rare but dramatic presentation of lung metastasis is tumor embolism. When clinically evident, the symptoms are those of "subacute cor pulmonale" with dyspnea, edema, elevated jugular venous pressure, and auscultatory evidence of pulmonary hypertension and right ventricular failure. Premortem diagnosis is difficult unless clinical suspicion is high. Tumor emboli have been

reported as the initial presentation of extrapulmonary cancer or as a postmortem finding in those with no premortem respiratory symptoms.[48] In a series of 214 autopsies, 89 had evidence of tumor emboli, and only 50 of these had clinical records indicating the presence of respiratory symptoms prior to death.[49] Tumors arising from the breast, liver, and pancreas accounted for more than 50% of the cases, but many tumor types were represented among this series.[48] When tumor embolism is suspected, cytologic examination of pulmonary capillary blood obtained via a wedged pulmonary arterial catheter is a possible diagnostic method.[50]

KEY POINTS

- Lung metastases are common and arise from most types of solid tumors.
- A pulmonary nodule in a patient with prior cancer can be a metastasis or a primary lung cancer; the likelihood of metastasis will vary with the original type of cancer and lung cancer risk factors.
- When clinical and/or histologic evaluation cannot distinguish primary lung cancer from metastasis, immunohistochemistry for tumor-specific markers can be useful. Future options will likely include molecular phenotyping.
- The choice of diagnostic method will be determined by the patient's clinical status, the natural history of the prior cancer, the availability of specialized diagnostic methods, and the need, or lack thereof, for a diagnosis prior to offering therapy.
- Radiofrequency ablation is a potential therapeutic option for local control when the patient is not a surgical candidate.
- Surgery for both diagnosis and treatment is appropriate for selected patients. The most important predictor of successful treatment is the ability to achieve complete metastasectomy of all visible and palpable lung nodules.

References

1. Herold CJ, Banker AA, Fleischman D: Lung metastases. Cancer Imaging 3:126–128, 2003.
2. Paget S: The distribution of secondary growths in cancer of the breast. Lancet 133:571–573, 1889.
3. Minn AJ, Gupta GP, Siegel PM, et al: Genes that mediate breast cancer metastasis to lung. Nature 436:518–524, 2005.
4. Abrams HL, Spiro R, Goldstein N: Metastases in carcinoma. Analysis of 1000 autopsied cases. Cancer 3:74–85, 1950.
5. Marth C, Kisic J, Kærn J, et al: Circulating tumor cells in the peripheral blood and bone marrow of patients with ovarian carcinoma do not predict prognosis. Cancer 94:707–712, 2002.
6. Schmidt-Kittler O, Ragg T, Daskalakis A, et al: From latent disseminated cells to overt metastasis: Genetic analysis of systemic breast cancer progression. Proc Natl Acad Sci U S A 100:7737–7742, 2003.
7. Zlotnik A: Chemokines and cancer. Int J Cancer 119:2026–2029, 2006.
8. Arya M, Patel HR, McGurk C, et al: The importance of the CXCL12-CXCR4 chemokine ligand-receptor interaction in prostate cancer metastasis. J Exp Ther Oncol 4:291–303, 2004.
9. Phillips RJ, Burdick MD, Lutz M, et al: The stromal derived factor-1/CXCL12-CXC chemokine receptor 4 biological axis in non–small cell lung cancer metastases. Am J Respir Crit Care Med 167:1676–1686, 2003.
10. Muller A, Homey B, Soto H, et al: Involvement of chemokine receptors in breast cancer metastasis. Nature 410:50–56, 2001.
11. Morales J, Homey B, Vicari AP, et al: CTACK, a skin-associated chemokine that preferentially attracts skin-homing memory T cells. Proc Natl Acad Sci U S A 96:14470–14475, 1999.
12. Padua D, Zhang XH, Wang Q, et al: TGFbeta primes breast tumors for lung metastasis seeding through angiopoietin-like 4. Cell 133:66–77, 2008.
13. Quint LE, Park CH, Iannettoni MD: Solitary pulmonary nodules in patients with extrapulmonary neoplasms. Radiology 217:257–261, 2000.
14. Cahan WG, Shah JP, Castro EB: Benign solitary lung lesions in patients with cancer. Ann Surg 187:241–244, 1978.
15. Cagle P: Differential diagnosis between primary and metastatic carcinomas. *In* Brambilla C, Brambilla E (eds): Lung Tumors: Fundamental Biology and Clinical Management. New York: Marcel-Dekker, 1999, pp 127–137.
16. Lazzaro D, Price M, de Felice M, et al: The transcription factor TTF-1 is expressed at the onset of thyroid and lung morphogenesis and in restricted regions of the foetal brain. Development 113:1093–1104, 1991.
17. Giordano TJ, Shedden KA, Schwartz DR, et al: Organ-specific molecular classification of primary lung, colon, and ovarian adenocarcinomas using gene expression profiles. Am J Pathol 159:1231–1238, 2001.
18. Tothill RW, Kowalczyk A, Rischin D, et al: An expression-based site of origin diagnostic method designed for clinical application to cancer of unknown origin. Cancer Res 65:4031–4040, 2005.
19. Vachani A, Nebozhyn M, Singhal S, et al: A 10-gene classifier for distinguishing head and neck squamous cell carcinoma and lung squamous cell carcinoma. Clin Cancer Res 13:2905–2915, 2007.
20. Baaklini WA, Reinoso MA, Gorin AB, et al: Diagnostic yield of fiberoptic bronchoscopy in evaluating solitary pulmonary nodules. Chest 117:1049–1054, 2000.
21. Gildea TR, Mazzone PJ, Karnak D, et al: Electromagnetic navigation diagnostic bronchoscopy: A prospective study. Am J Respir Crit Care Med 174:982–989, 2006.
22. Schwarz Y, Mehta AC, Ernst A, et al: Electromagnetic navigation during flexible bronchoscopy. Respiration 70:516–522, 2003.
23. Eberhardt R, Anantham D, Ernst A, et al: Multimodality bronchoscopic diagnosis of peripheral lung lesions: A randomized controlled trial. Am J Respir Crit Care Med 176:36–41, 2007.
24. Li H, Boiselle PM, Shepard JO, et al: Diagnostic accuracy and safety of CT-guided percutaneous needle aspiration biopsy of the lung: Comparison of small and large pulmonary nodules. AJR Am J Roentgenol 167:105–109, 1996.

25. Ng YL, Patsios D, Roberts H, et al: CT-guided percutaneous fine-needle aspiration biopsy of pulmonary nodules measuring 10 mm or less. Clin Radiol 63:272–277, 2008.
26. Ohno Y, Hatabu H, Takenaka D, et al: CT-guided transthoracic needle aspiration biopsy of small (< or =20 mm) solitary pulmonary nodules. AJR Am J Roentgenol 180:1665–1669, 2003.
27. Tomiyama N, Yasuhara Y, Nakajima Y, et al: CT-guided needle biopsy of lung lesions: A survey of severe complication based on 9783 biopsies in Japan. Eur J Radiol 59:60–64, 2006.
28. Xiao H, Liu D, Bajorin DF, et al: Medical and surgical management of pulmonary metastases from germ cell tumors. Chest Surg Clin North Am 8:131–143, 1998.
29. Jansen RL, Sylvester R, Sleyfer DT, et al: Long-term follow-up of non-seminomatous testicular cancer patients with mature teratoma or carcinoma at postchemotherapy surgery. EORTC Genitourinary Tract Cancer Cooperative Group (EORTC GU Group). Eur J Cancer 27:695–698, 1991.
30. Ahmed M, Liu Z, Afzal KS, et al: Radiofrequency ablation: Effect of surrounding tissue composition on coagulation necrosis in a canine tumor model. Radiology 230:761–767, 2004.
31. Yasui K, Kanazawa S, Sano Y, et al: Thoracic tumors treated with CT-guided radiofrequency ablation: Iinitial experience. Radiology 231:850–857, 2004.
32. Yamakado K, Inoue Y, Takao M, et al: Long-term results of radiofrequency ablation in colorectal lung metastases: Single center experience. Oncol Rep 22:885–891, 2009.
33. Soga N, Yamakado K, Gohara H, et al: Percutaneous radiofrequency ablation for unresectable pulmonary metastases from renal cell carcinoma. BJU Int 104:790–794, 2009.
34. Thanos L, Mylona S, Pomoni M, et al: Percutaneous radiofrequency thermal ablation of primary and metastatic lung tumors. Eur J Cardiothorac Surg 30:797–800, 2006.
35. Sano Y, Kanazawa S, Gobara H, et al: Feasibility of percutaneous radiofrequency ablation for intrathoracic malignancies: A large single-center experience. Cancer 109:1397–1405, 2007.
36. Steinke K, King J, Glenn D, et al: Radiologic appearance and complications of percutaneous computed tomography-guided radiofrequency-ablated pulmonary metastases from colorectal carcinoma. J Comput Assist Tomogr 27:750–757, 2003.
37. Robert JH, Ambrogi V, Mermillod B, et al: Factors influencing long-term survival after lung metastasectomy. Ann Thorac Surg 63:777–784, 1997.
38. Lanza LA, Natarajan G, Roth JA, et al: Long-term survival after resection of pulmonary metastases from carcinoma of the breast. Ann Thorac Surg 54:244–247, 1992 [discussion 248].
39. Kondo H, Okumura T, Ohde Y, et al: Surgical treatment for metastatic malignancies. Pulmonary metastasis: Indications and outcomes. Int J Clin Oncol 10:81–85, 2005.
40. Livartowski A, Chapelier A, Beuzedoc P, et al: Surgery of lung metastases of breast cancer: Analysis of 40 cases. Bull Cancer 85:800, 1998.
41. van Geel AN, Pastorino U, Jauch KW, et al: Surgical treatment of lung metastases: The European Organization for Research and Treatment of Cancer-Soft Tissue and Bone Sarcoma Group study of 255 patients. Cancer 77:675–682, 1996.
42. Pastorino U, Buyse M, Friedel G, et al: Long-term results of lung metastasectomy: Prognostic analyses based on 5206 cases. J Thorac Cardiovasc Surg 113:37–49,1997.
43. Krimsky W, Sethi S, Cicenia JC: Tattooing of pulmonary nodules for localization prior to VATS. Chest 132:425A, 2007.
43a. Blackmon SH, Shah N, Roth JA, et al: Resection of pulmonary and extrapulmonary sarcomatous metastases is associated with long-term survival. Ann Thorac Surg 88:877–884, 2009.
44. Ketchedjian A, Daly B, Luketich J, et al: Minimally invasive techniques for managing pulmonary metastases: Video-assisted thoracic surgery and radiofrequency ablation. Thorac Surg Clin 16:157–165, 2006.
45. Salud A, Porcel JM, Rovirosa A, et al: Endobronchial metastatic disease: Analysis of 32 cases. J Surg Oncol 62:249–252, 1996.
46. Bar-Gil Shitrit A, Shitrit D, Bakal I, et al: Endobronchial metastases from colon cancer without liver metastases: Report of eight cases. Dis Colon Rectum 50:1087–1089, 2007.
47. Katsimbri PP, Bamias AT, Froudarakis ME, et al: Endobronchial metastases secondary to solid tumors: Report of eight cases and review of the literature. Lung Cancer 28:163–170, 2000.
48. Soares FA, Landell GA, de Oliveira JA: Clinical aspects of tumour involvement of the pulmonary vessels. Acta Oncol 31:519–523, 1992.
49. Soares FA, Landell GA, de Oliveira JA: Pulmonary tumor embolism to alveolar septal capillaries. An unusual cause of sudden cor pulmonale. Arch Pathol Lab Med 116:187–188, 1992.
50. Abati A, Landucci D, Danner RL, et al: Diagnosis of pulmonary microvascular metastases by cytologic evaluation of pulmonary artery catheter-derived blood specimens. Hum Pathol 25:257–262, 1994.
51. Anraku M, Yokoi K, Nakagawa K, et al: Pulmonary metastases from uterine malignancies: Results of surgical resection in 133 patients. J Thorac Cardiovasc Surg 127:1107–1112, 2004.
52. Lanza LA, Miser JS, Pass HI, et al: The role of resection in the treatment of pulmonary metastases from Ewing's sarcoma. J Thorac Cardiovasc Surg 94:181–187, 1987.
53. Pfannschmidt J, Klode J, Muley T, et al: Pulmonary metastasectomy in patients with soft tissue sarcomas: Experiences in 50 patients. Thorac Cardiovasc Surg 54:489–492, 2006.
54. Wu PK, Chen WM, Chen CF, et al: Primary osteogenic sarcoma with pulmonary metastasis: clinical results and prognostic factors in 91 patients. Jpn J Clin Oncol 39:514–522, 2009.
55. Andrews S, Robinson L, Cantor A, et al: Survival after surgical resection of isolated pulmonary metastases from malignant melanoma. Cancer Control 13:218–223, 2006.
56. Petersen RP, Hanish SI, Haney JC, et al: Improved survival with pulmonary metastasectomy: An analysis of 1720 patients with pulmonary metastatic melanoma. J Thorac Cardiovasc Surg 133:104–110, 2007.
57. Headrick JR, Miller DL, Nagorney DM, et al: Surgical treatment of hepatic and pulmonary metastases from colon cancer. Ann Thorac Surg 71:975–979, 2001 [discussion 979–980].
58. Saito Y, Omiya H, Kohno K, et al: Pulmonary metastasectomy for 165 patients with colorectal carcinoma: A prognostic assessment. J Thorac Cardiovasc Surg 124:1007–1013, 2002.
59. Pfannschmidt J, Zabeck H, Muley T, et al: Pulmonary metastasectomy following chemotherapy in patients with testicular tumors: Experience in 52 patients. Thorac Cardiovasc Surg 54:484–488, 2006.
60. Murthy SC, Kim K, Rice TW, et al: Can we predict long-term survival after pulmonary metastasectomy for renal cell carcinoma? Ann Thorac Surg 79:996–1003, 2005.
61. Pfannschmidt J, Klode J, Muley T, et al: Nodal involvement at the time of pulmonary metastasectomy: Experiences in 245 patients. Ann Thorac Surg 81:448–454, 2006.
62. Friedel G, Linder A, Toomes H: The significance of prognostic factors for the resection of pulmonary metastases of breast cancer. Thorac Cardiovasc Surg 42:71–75, 1994.
63. Simpson R, Kennedy C, Carmalt H, et al: Pulmonary resection for metastatic breast cancer. Aust N Z J Surg 67:717–719, 1997.
64. Liu D, Labow DM, Dang N, et al: Pulmonary metastasectomy for head and neck cancers. Ann Surg Oncol 6:572–578, 1999.
65. Shiono S, Kawamura M, Sato T, et al: Pulmonary metastasectomy for pulmonary metastases of head and neck squamous cell carcinomas. Ann Thorac Surg 88:856–860, 2009.

CHAPTER 50

BENIGN LUNG TUMORS

Jeffrey L. Myers, MD • Thomas J. Giordano, MD, PhD

INTRODUCTION
Clinical Manifestations
BENIGN EPITHELIAL TUMORS
Papillomas and Adenomas
Micronodular Pneumocyte Hyperplasia
Sclerosing Hemangioma
BENIGN NONEPITHELIAL TUMORS
Hamartoma and Related Lesions
Inflammatory Myofiboblastic Tumor
Solitary Fibrous Tumor
Meningothelial-like Nodules and Intrapulmonary Meningioma
Miscellaneous

INTRODUCTION

Benign lung tumors are uncommon, accounting for fewer than 5% of resected lung neoplasms. Whereas many are rare, other benign lung tumors occur with sufficient frequency to pose periodic diagnostic challenges for primary care providers, pulmonologists, radiologists, surgeons, and pathologists alike. In this chapter we briefly review the clinical and pathological features of benign lung neoplasms. We have included neither nonneoplastic conditions that may mimic tumors on imaging studies (e.g., organizing pneumonia) nor certain low-grade but fully malignant neoplasms, such as carcinoid tumors.

Clinical Manifestations

Most benign lung tumors present as asymptomatic solitary pulmonary nodules typically discovered on chest radiographs or computed tomography (CT) scans performed for other purposes. A minority cause symptoms due to airway obstruction, bleeding, or compression of other structures. A preoperative diagnosis may be possible based on a combination of imaging studies and either endoscopic or percutaneous needle biopsies, but most are recognized only after surgical resection of a lesion in which the possibility of malignancy could not be categorically excluded.[1,2]

A decision to proceed with surgical resection in a patient with an unexplained solitary pulmonary nodule is complex and predicated on analysis of various risk factors. Given the risk of malignancy in lung nodules, establishing a diagnosis and surgical removal should be emphasized. Watchful waiting may occasionally be appropriate but only in highly selected patients in whom the risk of malignancy is low, the risk of surgery is high, or patient preference is to not have surgery (Fig. 50-1).[3] Recent data suggest that nodules 4 to 5 mm or less in size may be safely managed by deferring repeat CT scans for 12 months.[4-6] Others have advocated for a surgical approach in the absence of contraindications or other mitigating clinical circumstances.[7]

BENIGN EPITHELIAL LESIONS

Papillomas and Adenomas

Solitary Papillomas

Papilloma refers to exophytic endobronchial lesions with a papillary architecture (Fig. 50-2). Most solitary papillomas occur in central large airways; rarely, they arise in smaller bronchioles and present as peripheral nodules.[8] Flieder and associates[9] divided lung papillomas into three categories based on the lining epithelium: squamous cell, glandular, and mixed types. Squamous lesions account for nearly 70% of reported cases, occur more frequently in men, and are more often associated with cigarette smoking and human papillomavirus (HPV) infection. Associated foci of squamous cell carcinoma in situ are rare, with only a single well-documented example of invasive carcinoma developing in a patient without respiratory papillomatosis (see later).[10] Most patients with papillomas do well regardless of histologic type. Local recurrences are rare and limited to patients who undergo only biopsy or subtotal bronchoscopic removal. Surgical resection is curative. The differential diagnosis includes rare endobronchial papillary variants

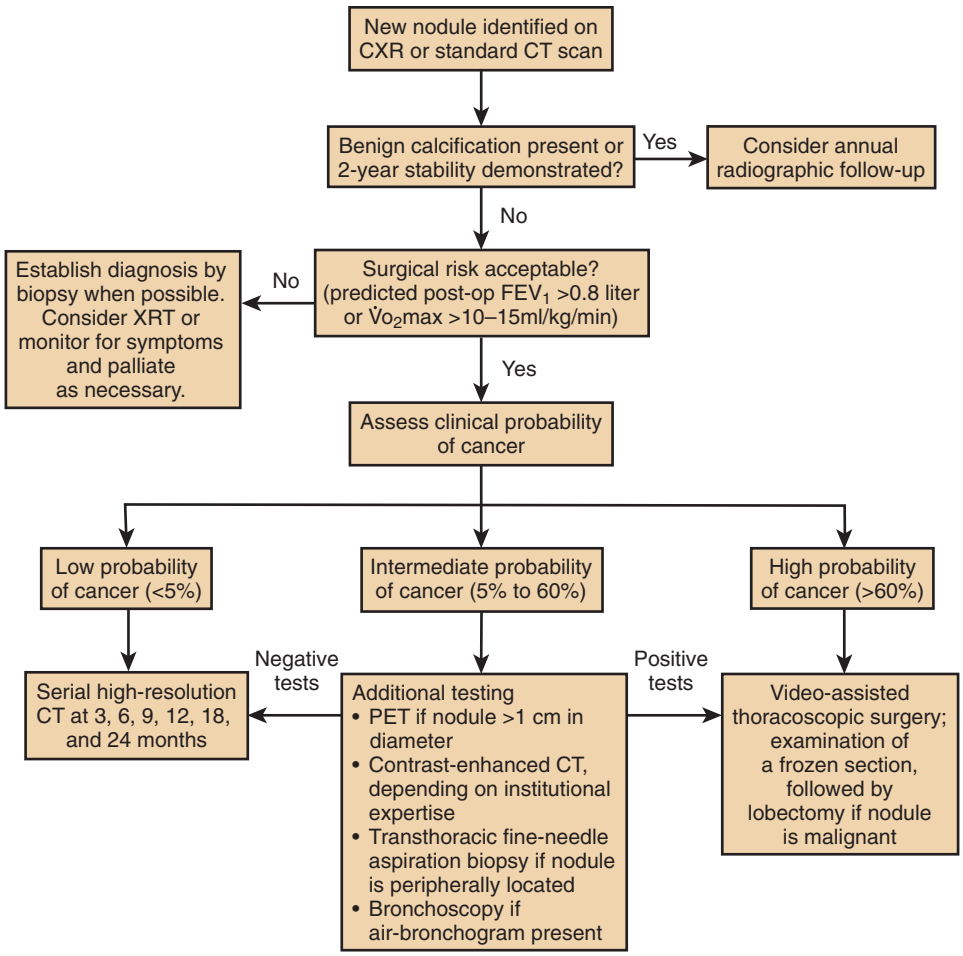

FIGURE 50-1 ■ Management algorithm for patients with solitary pulmonary nodules. CT, computed tomography; CXR, chest radiograph; PET, positron emission tomography; $\dot{V}o_2max$, maximal oxygen consumption; XRT, radiation therapy. (Adapted from Ost D, Fein AM, Feinsilver SH: Clinical practice: The solitary pulmonary nodule. N Engl J Med 348:2535–2542, 2003.)

of squamous cell or adenocarcinoma, a distinction that depends on recognition of cytologic atypia and stromal invasion.

Recurrent Respiratory Papillomatosis

Recurrent respiratory papillomatosis, also termed *juvenile laryngeal* or *laryngotracheal papillomatosis*, is a form of HPV-mediated papillomatosis that presents in early childhood.[11] Presenting symptoms include hoarseness, change or loss of voice, cough, respiratory distress, and stridor. HPV types 11 and 6 have been most commonly implicated and are perinatally acquired from mothers with genital infection.[11] Surgical excision or laser ablation are the mainstays of therapy for patients with symptomatic disease.[11] Recurrences are the rule and often necessitate multiple procedures. Squamous cell carcinoma is an infrequent complication but can affect either the upper or the lower respiratory tracts.[12,13]

Lung involvement occurs in about 3% of patients with juvenile-onset recurrent respiratory papillomatosis (RRP).[14,15] HPV-11 is especially prevalent in patients who develop peripheral lung disease, accounting for nearly 90% in whom testing was performed.[14] The latent period between diagnosis of RRP and recognition of lung involvement is variable but usually on the order of 8 to 10 years.[14] Lung disease presents as multiple asymptomatic nodules that may be cystic or solid (Figs. 50-3 and 50-4).[14–16] Symptomatic patients present with cough and various combinations of hemoptysis, dyspnea, fever, and chest pain. The histopathologic findings are unique, demonstrating tufts of benign squamous papillomas emanating from distal bronchioles with polypoid extensions into adjacent alveolar spaces (Fig. 50-5). The involved bronchioles are often ecstatic, thus mimicking the appearance of cavitation on imaging studies.

Lower respiratory tract disease in patients with RRP is often associated with an aggressive course. There is currently no effective medical therapy. Interferon and cidofovir, an antiviral agent, show inconsistent results and the latter has been implicated as potentially oncogenic.[14] Nearly two thirds of reported patients have died of disease, many from squamous cell carcinoma.[15] About 15% of patients with lower respiratory tract disease develop squamous cell carcinoma of the lung, with an average age at carcinoma diagnosis of 23 years.[14] No risk

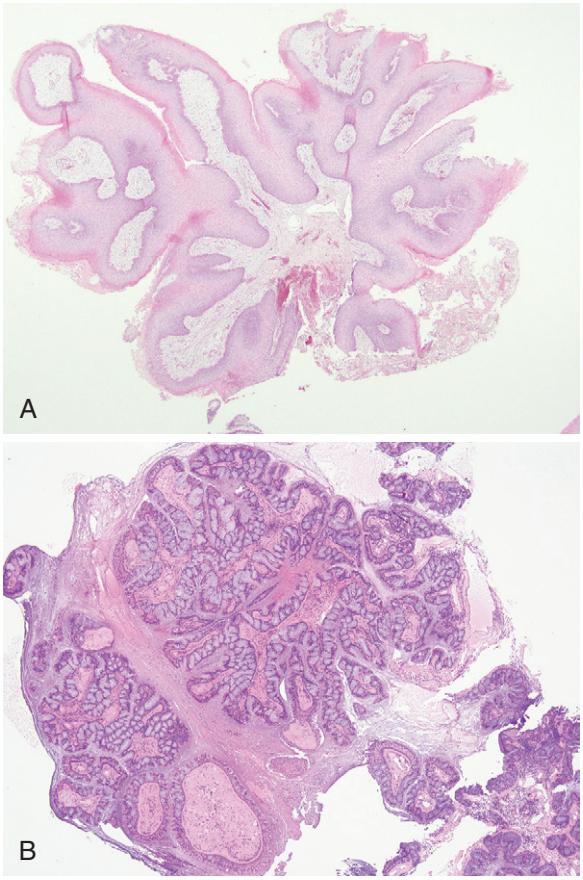

FIGURE 50-2 ■ Low-magnification photomicrographs illustrate two different solitary endobronchial papillomas from adults. **A,** Squamous papilloma showing papillary architecture with central connective tissue stalk covered by benign squamous epithelium with associated keratinous debris (original magnification ×20; hematoxylin and eosin stain). **B,** Glandular papilloma lined by benign mucinous columnar cells with abundant extracellular mucous (original magnification ×40; hematoxylin and eosin stain).

FIGURE 50-3 ■ Computed tomography (CT) scan from patient with recurrent respiratory papillomatosis involving her right lung. There are multiple nodules and opacities, the largest measuring 3 cm in greatest dimension. Some of the nodules appear cavitated. (CT image courtesy of Dr. Jay Ryu, Professor of Medicine, Mayo Medical School.)

FIGURE 50-4 ■ Gross photograph of excised left lower lobe from a 19-year-old with multiple recurrences of respiratory papillomatosis as described by Kerley and coworkers.[16] He had extensive papillomatosis involving his central airways and a large cystic cavity containing innumerable papillomas replacing much of his left lower lobe.

factors clearly identify those patients likely to develop lung carcinoma.

Adenomas

Historically, the term *adenoma* was applied to a pathologically heterogeneous group of low-grade endobronchial malignancies that included carcinoid tumors and carcinomas homologous to those arising from salivary glands (i.e., adenoid cystic and mucoepidermoid carcinomas).[17-19] Today, the term is restricted to a group of benign neoplasms with variable clinical presentations and histologic appearances.

Endobronchial adenomas include two entities analogous to salivary gland counterparts. *Mucous gland adenomas* are rare, presenting as potentially obstructing, sessile, endobronchial masses occurring at the level of lobar or segmental bronchi.[20-22] Average age at diagnosis is 52 to 54 years but with a broad age range that extends to childhood. Most patients are symptomatic at the time of diagnosis. The most frequent complaints are cough, shortness of breath, and wheezing, a combination of findings that can be misconstrued as asthma.[22] Some patients are symptomatic for years before the diagnosis is made. Chest radiographs may be normal but more commonly show a solitary pulmonary nodule and/or postobstructive atelectasis or consolidation.[21] CT scans show discrete nodules that may be accompanied by an air-meniscus sign attesting to an endobronchial location.[21] Histologically, mucous gland adenomas are variably solid and cystic and composed of cytologically bland columnar mucinous cells (Fig. 50-6). Surgical resection is often required for diagnosis and is curative.

Pleomorphic adenomas, also termed *benign mixed tumors*, are biphasic neoplasms composed of stromal and epithelial elements. They usually arise in major salivary glands, with fewer than 20 well-documented

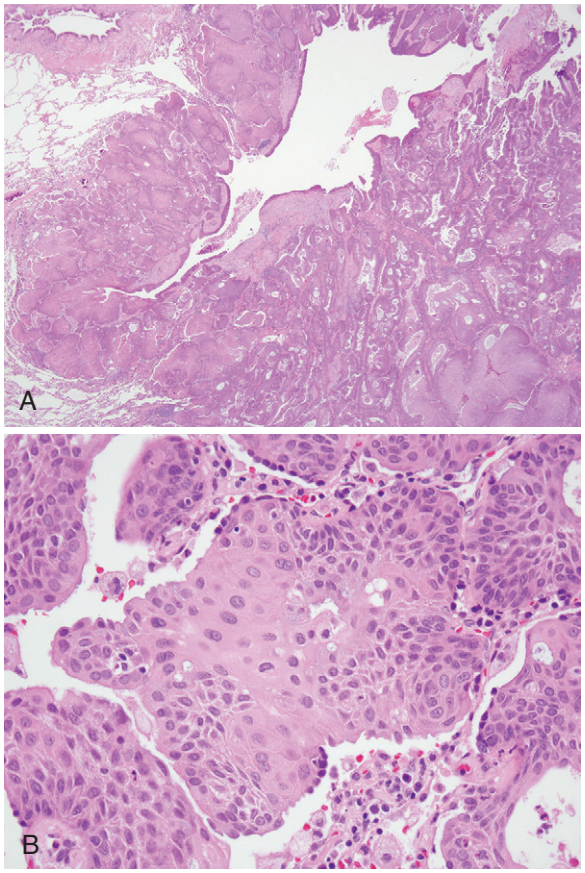

FIGURE 50-5 ■ Photomicrographs illustrate lung involvement in 40-year-old woman first diagnosed with recurrent respiratory papillomatosis at the age of 2 years. She underwent multiple resections of lung nodules starting in her second decade of life. **A,** Low-magnification photomicrograph illustrates multiple benign papillomas streaming from an ectatic bronchiole with a centrally dilated lumen (original magnification ×20; hematoxylin and eosin stain). **B,** High-magnification photomicrograph illustrates cytologically bland, benign appearance of the lung papillomas (original magnification ×400; hematoxylin and eosin stain).

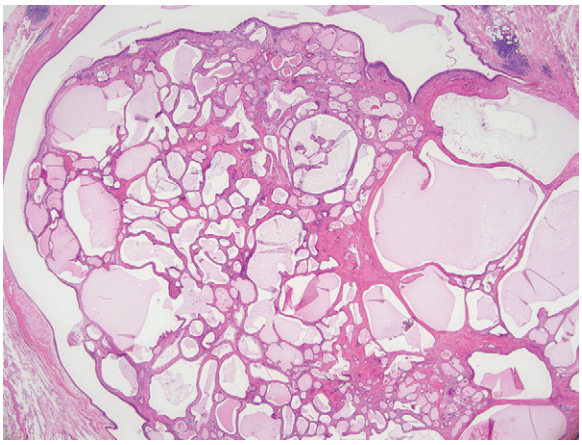

FIGURE 50-6 ■ Low-magnification photomicrograph shows an endobronchial mucous gland adenoma (original magnification ×20; hematoxylin and eosin stain). The smooth surface is covered by ciliated respiratory epithelium whereas the core comprises predominantly cystic spaces lined by variably attenuated columnar mucinous cells.

examples of primary lung tumors.[23-34] Primary pulmonary pleomorphic adenomas have been reported more commonly in women than men by a ratio of 2 : 1 with an average age at diagnosis of about 51 years. Cough is the most frequent presenting complaint and is sometimes associated with postobstructive pneumonia. A third of patients are asymptomatic at the time a solitary pulmonary nodule is discovered. Eighty percent occur within the larger central airways as polypoid exophytic tumors. Chest radiographs and CT scans show a solitary, well-circumscribed solid mass without distinctive features. Positron emission tomography (PET) in a single patient showed high ^{18}F-fluorodeoxyglucose (FDG) avidity.[27] Complete surgical resection with tumor-free margins is curative. As is true for their salivary gland counterparts, rare cases have been associated with malignant transformation usually taking the form of a carcinoma arising from a preexisting benign pleomorphic adenoma (carcinoma ex pleomorphic adenoma).[28] Primary pleomorphic adenoma must be distinguished from so-called *benign metastasizing pleomorphic adenoma*, a term that refers to rare patients in whom histologically benign salivary gland tumors inexplicably metastasize to various sites including lung.[35,36]

Adenomas involving peripheral lung parenchyma are rare. *Alveolar adenoma* is the most common variant with just under 30 reported examples.[37-41] Average age at diagnosis is between 50 and 55 years. Nearly all patients are asymptomatic at the time of diagnosis. Radiologically, alveolar adenomas present as well-circumscribed peripheral nodules averaging just over 2 cm in greatest dimension. Magnetic resonance imaging (MRI) may show a cystic space with central fluid and thin-rim enhancement.[38] Pathologically, alveolar adenomas are partially cystic nodules in which connective tissue septa are lined by cytologically bland epithelial cells (Fig. 50-7). The epithelial cells are derived from pneumocytes whereas the stromal cells are undifferentiated fibroblasts. Cytogenetic studies performed in a single case demonstrated a clonal translocation, supporting the conclusion that these are benign neoplasms.[42]

Papillary adenomas have been described in fewer than 10 patients.[43-46] Men and women are affected equally with an average age at diagnosis of 45 years (range 25–60 years). All patients in whom the lesion was discovered during life underwent surgical resection for an asymptomatic solitary peripheral nodule and remained free of disease at follow-up. Histologically, papillary adenomas are circumscribed lesions composed of connective tissue fronds lined by bland type 2 pneumocytes (Fig. 50-8).

Mucinous cystadenoma is a rare lung neoplasm that overlaps with unequivocally malignant mucinous adenocarcinomas.[47-52] Gao and Urbanski[48] proposed separating them into three histologically defined categories: mucinous cystadenoma, mucinous cystic tumor with atypia, and mucinous cystadenocarcinoma. Histologically

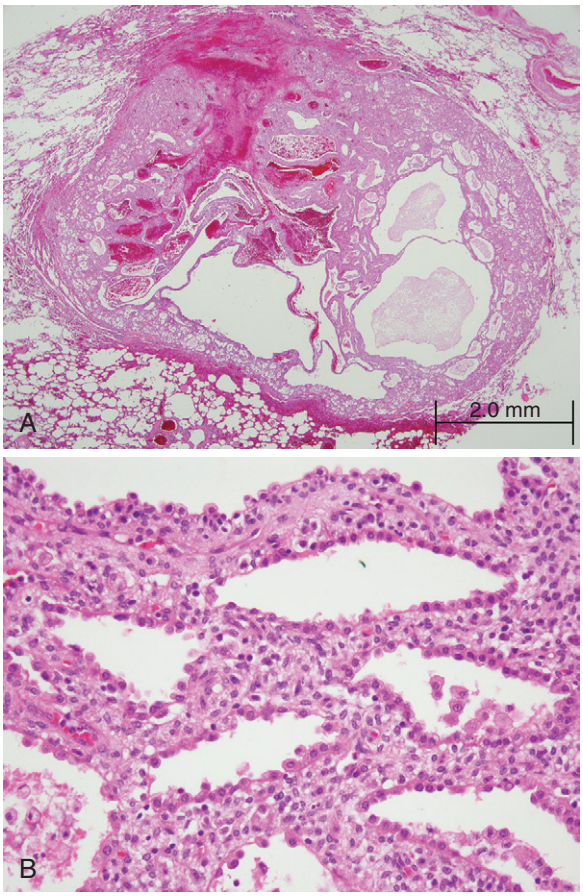

FIGURE 50-7 ■ Alveolar adenoma. **A,** Low-magnification photomicrograph shows a well-demarcated partially cystic mass in peripheral lung biopsy (original magnification ×20; hematoxylin and eosin stain). **B,** Higher-magnification photomicrograph illustrates connective tissue septa lined by bland pneumocytes (original magnification ×400; hematoxylin and eosin stain).

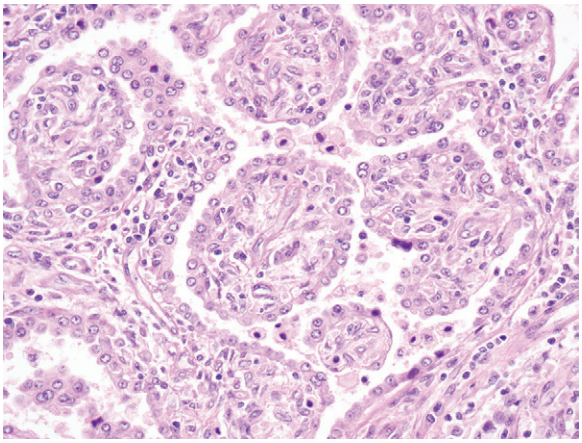

FIGURE 50-8 ■ Papillary adenoma. High-magnification photomicrograph of a solitary peripheral lung nodule shows papillary connective tissue cores lined by bland cuboidal pneumocytes (original magnification ×400; hematoxylin and eosin stain).

benign tumors without atypia accounted for only 13% of reported patients, further emphasizing that this is an extremely rare neoplasm. Patients typically present with slowly growing, well-demarcated, peripheral lung masses that may or may not appear cystic.[50–53] All patients with histologically benign cystadenomas have remained free of disease after surgical resection.

Micronodular Pneumocyte Hyperplasia

Micronodular pneumocyte hyperplasia is an unusual proliferation of alveolar epithelium seen almost exclusively in patients with underlying tuberous sclerosis complex and/or lymphangioleiomyomatosis.[54–58] Over 85% of reported patients were women. Radiologic findings are characterized by scattered nodules that are occasionally numerous and distributed in a miliary fashion, with or without the associated cystic changes typical of lymphangioleiomyomatosis.[55,57] The radiologic abnormalities correspond to ill-defined pale peripheral nodules occurring either in isolation or in the setting of lymphangioleiomyomatosis (Figs. 50-9 and 50-10). Histologically, micronodular pneumocyte hyperplasia demonstrates circumscribed proliferations of bland pneumocytes cytologically identical to those seen in

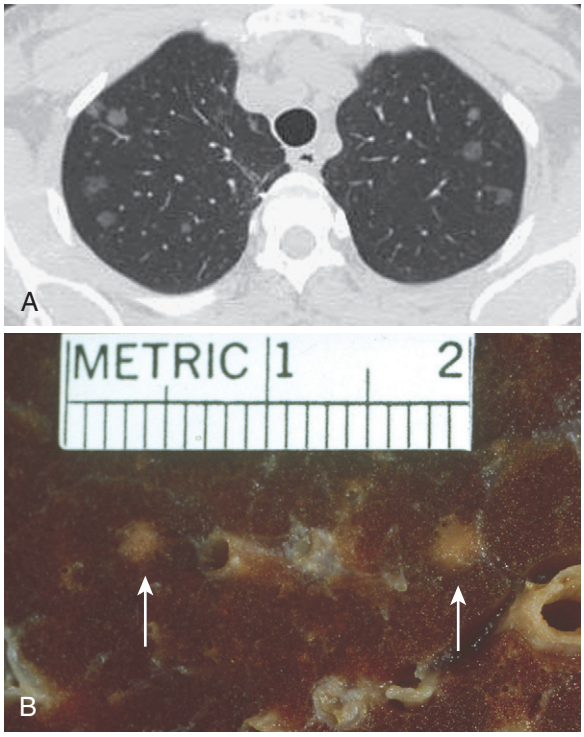

FIGURE 50-9 ■ Micronodular pneumocyte hyperplasia (MNPH) in tuberous sclerosis complex (TSC) without lymphangioleiomyomatosis (LAM). **A,** CT scan from 41-year-old woman with TSC and MNPH shows multiple bilateral nodules characterized by "ground-glass" attenuation. **B,** Photograph of autopsy lung specimen from another patient with TSC and MNPH (*arrows*). (**A,** CT image courtesy of Dr. Jay Ryu, Professor of Medicine, Mayo Medical School.)

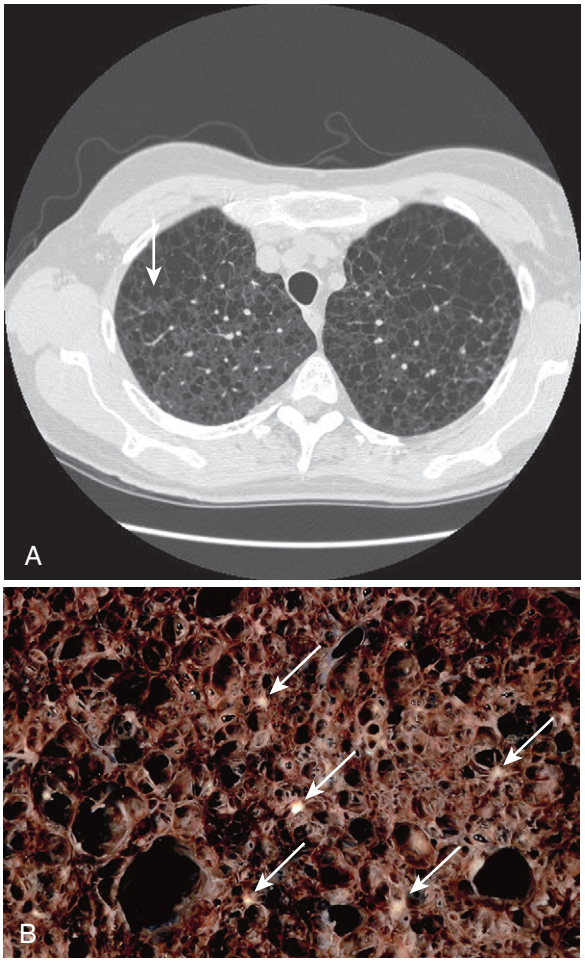

FIGURE 50-10 ■ MNPH associated with LAM. **A,** CT scan from a 55-year-old woman with TSC and LAM and a right lung nodule (*arrow*) attributed to MNPH. **B,** Photograph of a surgical lung specimen shows a combination of LAM and MNPH (*arrows*). (**A,** CT image courtesy of Dr. Jay Ryu, Professor of Medicine, Mayo Medical School.)

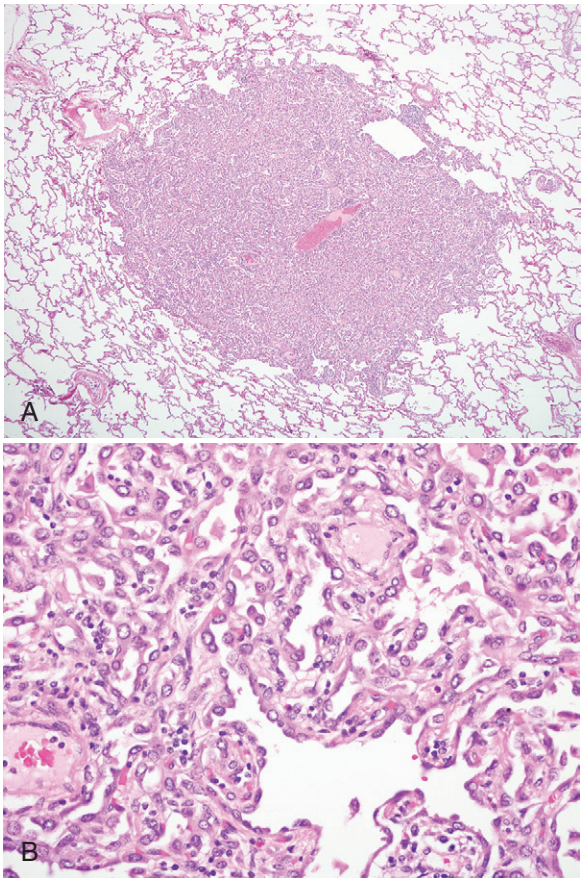

FIGURE 50-11 ■ Histologic features of MNPH in the TSC patient also illustrated in Figure 50-9B. **A,** Low-magnification photomicrograph shows a well-circumscribed nodule (original magnification ×20; hematoxylin and eosin stain). **B,** High-magnification photomicrograph shows cytologically bland pneumocytes distributed along alveolar septa (original magnification ×400; hematoxylin and eosin stain).

papillary adenomas, differing in that they are distributed along intact alveolar septa rather than papillae (Fig. 50-11).

Sclerosing Hemangioma

Sclerosing hemangiomas (SHs) are benign lung neoplasms derived from incompletely differentiated respiratory epithelium. SHs occur more frequently in women than men by a ratio of 7 : 1.[59-67] Mean age at diagnosis is the fifth decade of life, although they have been reported in a wide age range including children. Over three fourths of patients are asymptomatic at the time they are discovered to have a solitary pulmonary nodule. CT scans show well-circumscribed round or oval subpleural nodules with smooth margins and inhomogeneous enhancement.[68,69] Associated calcifications are present in about a third. Dynamic CT studies show strong, rapid enhancement that rivals the imaging characteristic of malignancies.[70] PET scanning has been reported in only one patient and was characterized by intermediate FDG avidity.[71] Multiple lesions occur in about 2% of patients. Deposits in regional lymph nodes are rare and have no impact on the fundamentally benign behavior of these lesions.[72-74]

SHs are usually well-circumscribed subpleural nodules averaging 2 to 3 cm in diameter (Fig. 50-12). The histologic hallmark is a heterogeneous appearance resulting from both a mixture of cell types and highly variable growth patterns. Two populations of epithelial cells are a characteristic feature: (1) surface cuboidal cells derived from pneumocytes or Clara cells and (2) pale interstitial round cells with an incompletely differentiated respiratory epithelial phenotype.[63,75-77] Molecular studies using a variety of techniques suggest that both populations of cells are neoplastic, an observation that fits with descriptions of both components in nodal deposits.[73,78,79] The cells are arranged in various growth patterns that include a focally conspicuous sclerotic stroma that is often calcified (Fig. 50-13). Pseudovascular blood-filled spaces

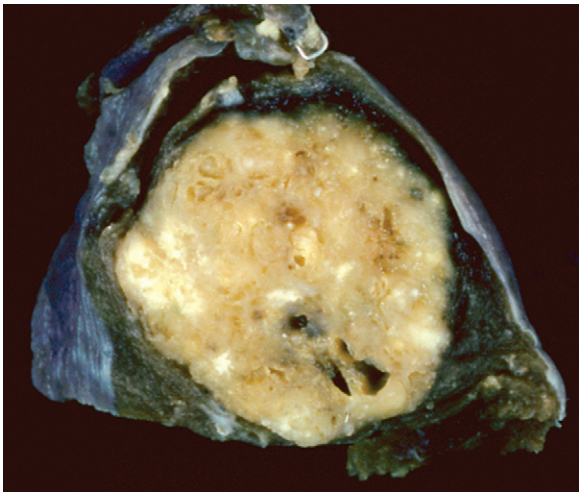

FIGURE 50-12 ■ Photograph of resected sclerosing hemangioma (SH). The lobulated nodule is well circumscribed and situated near the visceral pleura. The cut surface betrays the fundamentally heterogeneous nature of these neoplasms, showing a variegated pattern of pale brown and white with both solid and spongy areas.

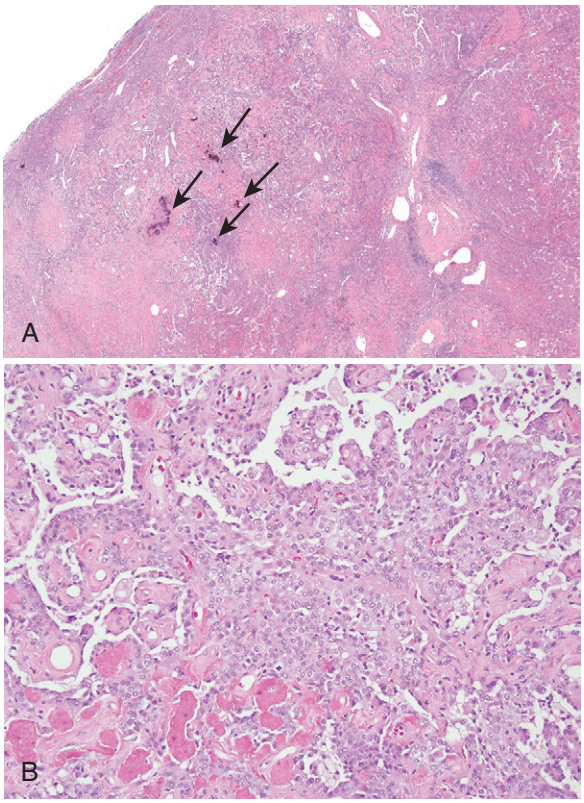

FIGURE 50-13 ■ SH. **A,** Low-magnification photomicrograph shows the classic features of SH in which sclerotic zones with dense collagen deposition and focal calcifications (*arrows*) alternate with variably cellular regions (original magnification ×2; hematoxylin and eosin stain). **B,** Higher-magnification photomicrograph shows solid and papillary growth patterns. The central area is solid and composed of the pale-staining round cells demonstrating a phenotype consistent with incompletely differentiated respiratory epithelium (original magnification ×400; hematoxylin and eosin stain).

occur in some cases and account for the term *hemangioma*, in this case a misnomer.

Molecular studies of these tumors have demonstrated acquired genetic alterations at the *p16* and *RB* genes that resemble those found in early-stage adenocarcinomas, supporting an origin from respiratory epithelial cells and suggesting similarities between the molecular pathogenesis of SHs and bronchoalvealor adenocarcinoma.[80] However, a more recent molecular analysis of SHs failed to identify alterations in some genes (*EGFR*, *HERS*, and *K-ras*) that are commonly mutated in bronchoalvealor adenocarcinoma, thereby raising doubts about a common link.[79] Genome-wide approaches will likely be necessary to resolve this controversy.

BENIGN NONEPITHELIAL LESIONS

Hamartoma and Related Lesions

Pulmonary hamartomas are the most common benign neoplasm in adults who undergo surgical resection but are present in less than 0.5% of consecutively autopsied patients.[2,81,82] The term *hamartoma* implies that these are tumor-like malformations rather than true neoplasms, but recent studies show consistent and characteristic genetic abnormalities indicating that hamartomas are clonal neoplasms.

Pulmonary hamartomas are discovered in men more often than in women by a ratio of 2:1 with an average age at diagnosis in the sixth or seventh decade of life.[83,84] Most patients present with asymptomatic solitary lung nodules with no lobar predilection. Multiple nodules are present in 2% or less of patients.[83,85] About 10% of hamartomas are endobronchial in location and are more likely to be associated with cough. CT scans show a characteristic combination of calcifications and/or fat in two thirds of patients (Fig. 50-14).[86] Resection is nearly always curative with rare reports of recurrence or malignant transformation.[87,88]

Pulmonary hamartomas usually occur as well-circumscribed nodules, averaging 1.5 to 2.0 cm in diameter. A variegated cut surface reflects an admixture of stromal elements (Fig. 50-15). Mature hyaline cartilage is an almost universal component and is typically intermingled with mature fat, fibromyxoid tissue, and rare smooth muscle cells (Fig. 50-16). Any of the stromal components can predominate, however, resulting in a histologic spectrum of neoplasms that includes *leiomyomas* and *lipomas*.[89–91] Entrapped non-neoplastic respiratory epithelium often results in a characteristically biphasic appearance, a phenomenon that contributes to relatively high rates of false-positive diagnoses in fine-needle aspiration biopsies.[92]

Pulmonary hamartomas, like other benign mesenchymal tumors such as lipoma and leiomyomas, frequently contain chromosomal rearrangements of genes encoding nonhistone chromosomal high-mobility group family of proteins (HMGA family) with AT-hook DNA-binding motifs.[93–96] These proteins play a broad role in growth, differentiation, proliferation, and death of mesenchymal

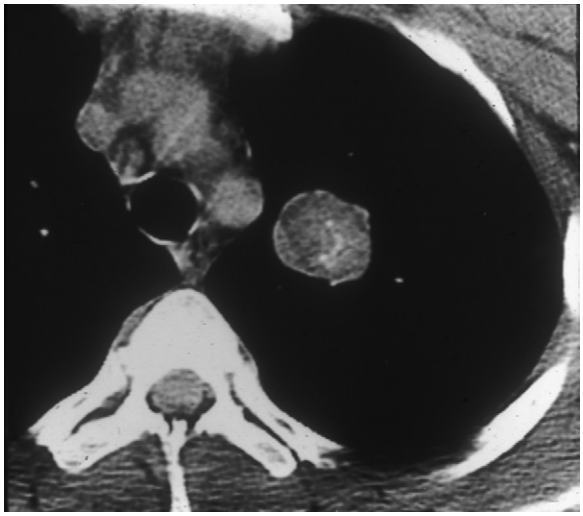

FIGURE 50-14 ■ CT scan of a proven hamartoma shows a well-marginated nodule in which there is evidence of intratumoral fat and calcification. This combination is characteristic but occurs in only about a fourth of cases.

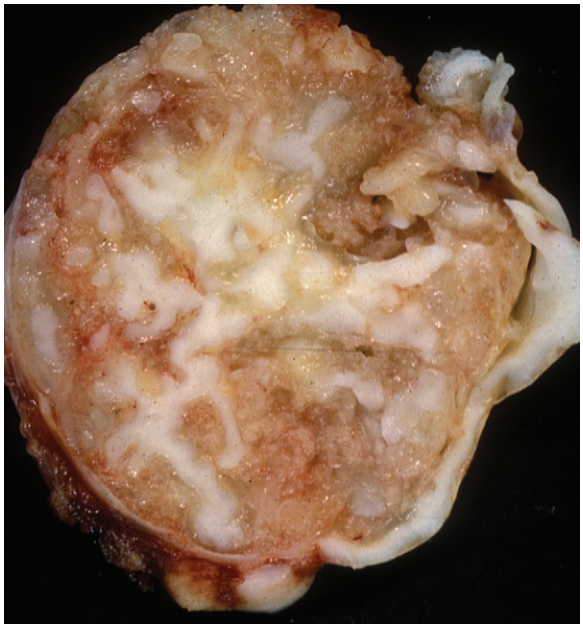

FIGURE 50-15 ■ Photograph of resected hamartoma. The cut surface of this well-circumscribed nodule shows glistening irregularly shaped cartilaginous islands alternating with pale yellow adipose tissue.

cells through a mechanism that involves regulation of transcription via modification of DNA conformation.[97] Two main cytogenetic regions containing abnormalities have been defined in pulmonary hamartoma: 6p21 and 12q14-15. The *HMGA1* (also known as *HMGIY*) gene maps to 6p21.3, whereas *HMGA2* (also known as *HMGIC)* maps to 12q14-15. Their dual role as regulators of adipogenesis and mesenchymal differentiation and gene expression is provocative, although additional

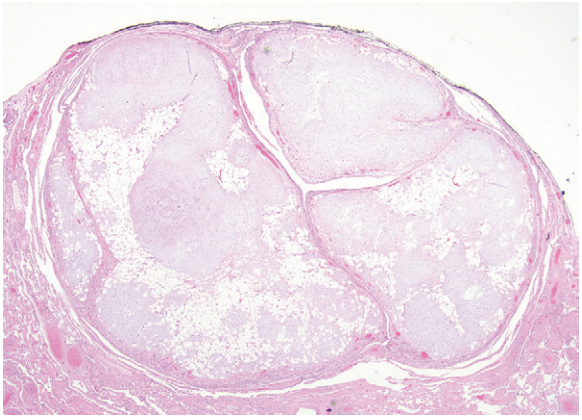

FIGURE 50-16 ■ Low-magnification photograph of a typical pulmonary hamartoma in which cartilaginous islands are interspersed with adipose tissue resulting in a lobulated appearance (original magnification ×20; hematoxylin and eosin stain).

work needs to be done to fully elucidate the role of *HMGA* fusion genes in pulmonary hamartoma.

Pulmonary chondroma, a related cartilaginous lung tumor, constitutes one component of the triad (i.e., pulmonary chondroma, paraganglioma, and gastric stromal tumors) described by Carney and colleagues in 1977.[98] Pulmonary chondromas occur in about three fourths of patients and are multiple in half.[85,99] Chondromas are distinct in being purely cartilaginous without the other stromal and epithelial elements characteristic of hamartoma.[85]

Inflammatory Myofibroblastic Tumor

Inflammatory myofibroblastic tumors (IMTs) of the lung comprise a spectrum of lesions ranging from benign spindle cell tumors to frankly malignant sarcomas. Pulmonary IMTs, also termed *plasma cell granulomas* by Liebow,[100] are defined in the World Health Organization (WHO) classification of lung tumors as "a subgroup of the broad category of 'inflammatory pseudotumours.'"[101] The staggering profusion of synonyms that have been applied to these unusual tumors, which also occur in multiple extrapulmonary sites, reflects the controversy and confusion regarding their pathogenesis and histogenesis.

IMTs of the lung can occur in any age group but tend to affect children and young adults; over half of patients are less than 40 years of age at the time of diagnosis.[100–107] Most patients present with asymptomatic peripheral lung nodules. Endobronchial tumors account for around 15% of patients and are more likely to be accompanied by symptoms of cough and/or hemoptysis. Chest radiographs typically show a well-circumscribed mass ranging in size from 0.8 cm to 36 cm (Fig. 50-17), the majority measuring between 1 and 6 cm in greatest dimension.[100,104,106,108–110] Most primary pulmonary IMTs are cured with complete surgical resection.[102,106,109] Incomplete resection is associated with substantial risk of recurrence and, rarely, locally aggressive behavior and death.[103,110] Cyclooxygenase-2 (COX-2) inhibitors may

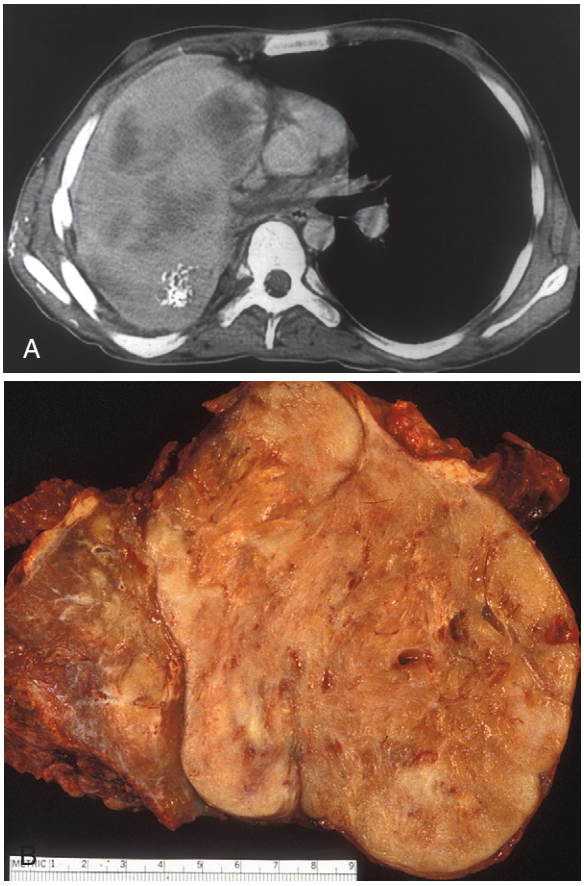

FIGURE 50-17 ■ Large inflammatory myofibroblastic tumor (IMT) occurring in 21-year-old man in whom an intrathoracic mass was first detected at the age of 10. **A,** CT scan shows a large mass filling the right hemithorax with heterogeneous attenuation and calcification. **B,** Photograph of right pneumonectomy specimen shows a large mass that despite its size, was well circumscribed without invasion beyond lung parenchyma.

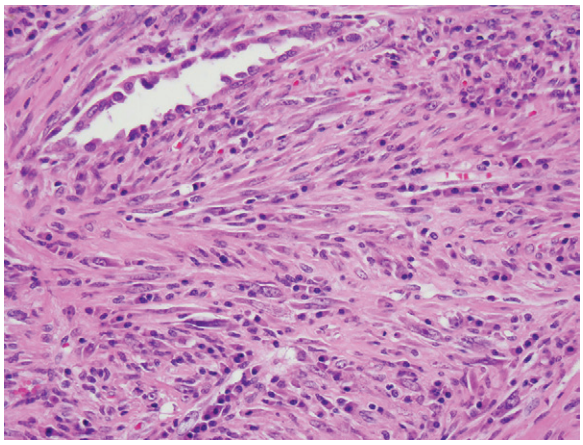

FIGURE 50-18 ■ High-magnification photomicrograph from the IMT illustrated in Figure 50-17. Neoplastic spindle cells are associated with a prominent infiltrate of plasma cells. Nonneoplastic respiratory epithelium (*upper left*) is surrounded by neoplastic spindle cells resulting in a biphasic appearance, a common phenomenon in benign or low-grade nonepithelial tumors (original magnification ×400; hematoxylin and eosin stain).

have therapeutic value in large unresectable tumors, a treatment strategy for which only limited anecdotal evidence is available.[111-113]

The long list of competing terms for IMTs attests to their histologic diversity. The most consistent histologic finding is a combination of neoplastic spindle cells and a variably dense infiltrate of polyclonal plasma cells (Fig. 50-18). Immunohistochemical and ultrastructural studies show that the spindle cells have features of myofibroblasts, including expression of smooth muscle–associated proteins. ALK1 protein expression occurs in somewhere between a third and a half of lung tumors, is more frequent in young patients,[103,114-116] and reflects the observation that the *ALK* gene is fused to a variety of constitutively activated genes via balanced translocations (see later).[117,118] Absence of ALK expression may be associated with a greater risk for aggressive behavior.[103]

IMTs are low-grade neoplasms rather than non-neoplastic inflammatory lesions. Various techniques have identified a range of genetic abnormalities consistent with their neoplastic nature.[115,117-121] The most consistent molecular alteration is a balanced translocation of the *ALK* gene locus (2p23), which encodes a tyrosine kinase receptor. Fusion of a silent gene (*ALK*) with one of several constitutively expressed genes (e.g., *TPM3, TPM4, CLTC*) results in aberrant expression of the silent gene that then typically functions as an oncogene, thus contributing to tumorigenesis. A similar role for *ALK* gene fusions is observed in anaplastic large cell lymphomas. The role of HPV-8 in the pathogenesis of IMTs is controversial and uncertain.[107]

Solitary Fibrous Tumor

Solitary fibrous tumors (SFTs), formerly referred to as *localized fibrous mesotheliomas*, are mesenchymal neoplasms that frequently arise from visceral or parietal pleura. SFTs are not unique to the pleura, however, and have been described as intraparenchymal lung tumors (intrapulmonary solitary fibrous tumors), in the mediastinum, and in numerous extrathoracic sites.[122-126]

Pleural and intrapulmonary solitary fibrous tumors affect men and women equally.[127-132] Mean age at diagnosis is the sixth decade of life. Just over half of patients are symptomatic with presenting complaints that include chest pain (25%), shortness of breath (15%), and/or cough (12%).[128,129,131-133] Clubbing is present in about 2% of patients. A paraneoplastic syndrome of hypoglycemia is rare and results from tumor production of insulin-like growth factor.[30,134-137] Imaging studies show large intrathoracic masses with an average maximum diameter of between 8.5 and 10.5 cm.[128,129,132,133,138] CT scans show a lobulated and sharply marginated mass with a broad base abutting the chest wall, frequently associated with compression of surrounding structures (Fig. 50-19).[138,139] Heterogeneous attenuation and heterogeneous enhancement are characteristic.[138] Calcifications are rare. Most pleural and intrapulmonary solitary fibrous tumors

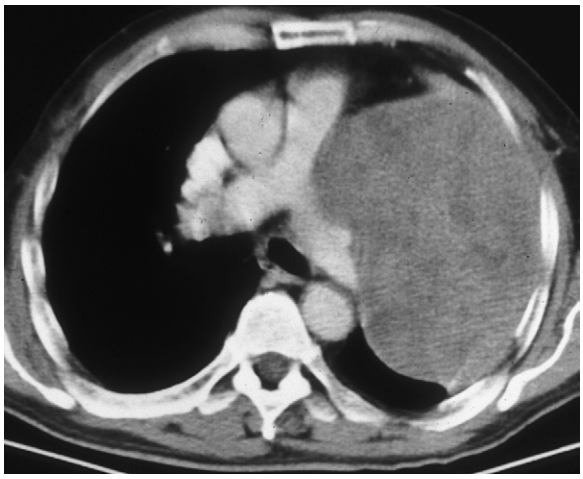

FIGURE 50-19 ■ CT scan shows a large benign solitary fibrous tumor (SFT) arising from the visceral pleura with nearly complete atelectasis of the left lung. Together, SFT and IMT are the most likely diagnoses in patients who present with large benign intrathoracic tumors.

behave as benign neoplasms. Patients with histologically benign tumors are cured with complete surgical excision. A more aggressive course is seen in just over 10% of patients and is limited to those who either undergo incomplete surgical excision or have histologically malignant tumors (malignant SFTs).[127-129,131-133,140]

SFTs are three times more likely to arise from visceral than parietal pleura. Those arising from visceral pleura are frequently pedunculated and attached to the lung surface by a connective tissue pedicle (Fig. 50-20). Occasional examples arise within the fissures, resulting in a radiologic appearance difficult to separate from an intrapulmonary tumor (see Fig. 50-20). Parietal pleural lesions are more commonly sessile with a broad base of attachment to chest wall, diaphragm, or mediastinum. Histologically, SFTs are variably cellular spindle cell neoplasms with a collagenous stroma. Malignant variants are larger, more likely to have an invasive growth pattern, and more cellular with associated cytologic atypia, increased mitotic rates, and necrosis.[128]

Meningothelial-like Nodules and Intrapulmonary Meningioma

Pulmonary *meningothelial-like nodules*, termed *chemodectomas* historically, have been described in as many as 4.9% of autopsies but are seen more commonly as incidental findings in surgical specimens, occurring in 13.8% and 48% of surgical lung biopsies and lobectomies from adults, respectively.[141-145] Meningothelial-like nodules are more common in women and occur with greater frequency in patients with chronic lung diseases, including chronic interstitial pneumonias and thromboembolic disease.[143] A rare syndrome of multiple, bilateral meningothelial-like nodules (diffuse pulmonary meningotheliomatosis) has been described in women who present in the sixth to eighth decade of life with

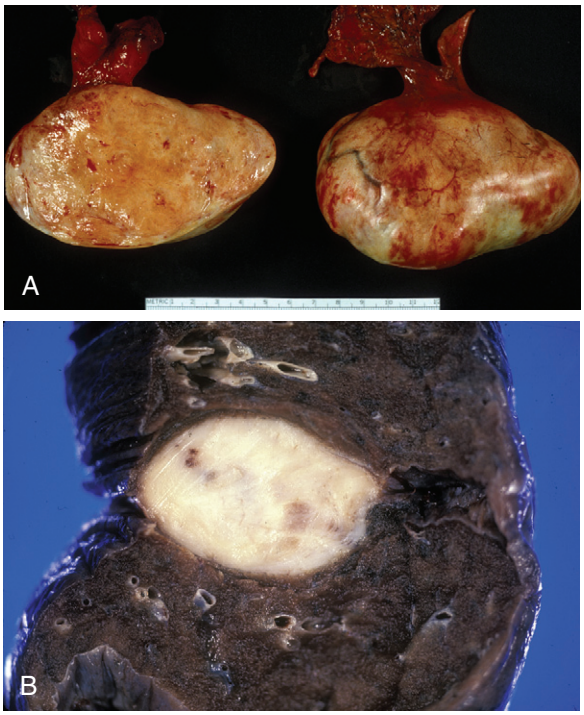

FIGURE 50-20 ■ Photograph of a resected SFT arising from the visceral pleura. **A,** As demonstrated in this example, most visceral pleural SFTs are attached to the lung by a pedicle and are characterized by a smooth glistening surface (*right*) and an encapsulated homogeneous cut surface without necrosis (*left*). **B,** Less commonly, SFT arises within the fissures as illustrated in this bilobectomy specimen.

multiple nodules on CT scan.[146,147] Half complain of dyspnea or cough at presentation. Microscopically, meningothelial-like nodules are composed of nests of epithelioid cells that are histologically and immunophenotypically indistinguishable from meningothelial cells of the central nervous system (Fig. 50-21). Despite this unexplained phenotypic overlap, molecular studies demonstrate significant differences between meningothelial-like nodules and conventional central nervous system meningiomas.[146]

Primary *intrapulmonary meningiomas* are rare solitary lesions that are unrelated to meningothelial-like nodules.[148-150] Men and women are affected equally and present at an average age of 56 years with asymptomatic solitary nodules averaging 3.0 cm (standard deviation ± 2.2 cm) in greatest dimension. Patients with multiple lesions should be presumed to have metastatic disease from a central nervous system primary until proved otherwise.[151] Complete surgical resection is curative in patients with histologically benign meningiomas.

Miscellaneous

Granular cell tumors, referred to in older literature as *granular cell myoblastomas*, are uncommon primary lung neoplasms that typically present as pedunculated or sessile endobronchial tumors (Fig. 50-22).[152,153] Lesions

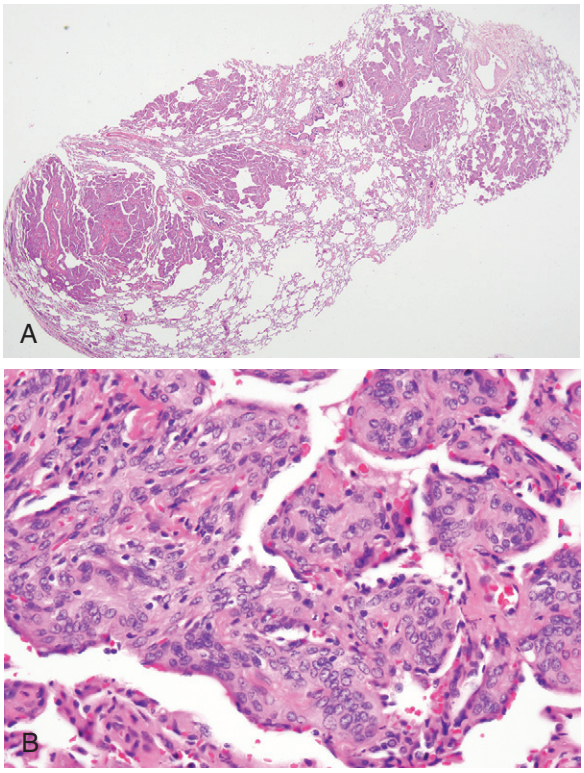

FIGURE 50-21 ■ Multiple meningothelial-like nodules (diffuse pulmonary meningotheliomatosis) in surgical lung biopsy from 56-year-old woman who presented with dyspnea. **A,** At low magnification, multiple nodules are randomly distributed throughout the biopsy (original magnification ×20; hematoxylin and eosin stain). **B,** At higher magnification, the nodules comprise bland meningothelial cells arranged in poorly formed nests and expanding the interstitium (original magnification ×400; hematoxylin and eosin stain).

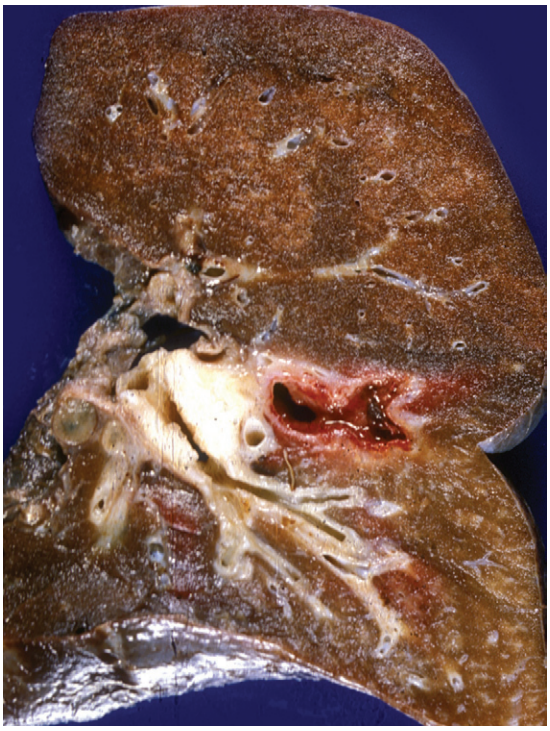

FIGURE 50-22 ■ Photograph demonstrates the cut surface of pneumonectomy specimen in which a granular cell tumor partially obstructs the lower lobe bronchus.

are multiple in a fourth of patients. Symptoms are reported in half and result from airway obstruction. Peripheral lung nodules are rare. Pulmonary granular cell tumors are benign and can usually be managed with conservative excision.

Clear cell ("sugar") tumors are rare primary lung tumors that invariably present as asymptomatic solitary lung nodules.[154] Histologic, ultrastructural, and immunophenotypic features are indistinguishable from PEComas and renal angiomyolipomas, a family of neoplasms derived from perivascular epithelioid cells (PECs) and related to mutations of the tuberous sclerosis complex genes that affect regulation of the mTOR pathway.[155,156]

KEY POINTS

- Benign lung tumors are uncommon but frequently pose challenges in diagnosis and management.
- Benign lung tumors are pathologically diverse, comprising a range of epithelial and nonepithelial neoplasms.
- Benign lung tumors present most commonly as asymptomatic solitary peripheral nodules and less commonly as symptomatic endobronchial lesions.
- Some benign lung tumors may become large enough to cause symptoms by compression or displacement of intrathoracic structures.
- Surgical resection is frequently required for diagnosis of benign lung tumors and is usually curative.

References

1. Smith MA, Battafarano RJ, Meyers BF, et al: Prevalence of benign disease in patients undergoing resection for suspected lung cancer. Ann Thorac Surg 81:1824–1828, 2006.
2. Otani Y, Yoshida I, Kawashima O, et al: Benign tumors of the lung: A 20-year surgical experience. Surg Today 27:310–312, 1997.
3. Ost D, Fein AM, Feinsilver SH: Clinical practice. The solitary pulmonary nodule. N Engl J Med 348:2535–2542, 2003.
4. Henschke CI, Yankelevitz DF, Naidich DP, et al: CT screening for lung cancer: Suspiciousness of nodules according to size on baseline scans. Radiology 231:164–168, 2004.
5. Jin SM, Choi SH, Yoo CG, et al: Small solid noncalcified pulmonary nodules detected by screening chest computed tomography. Respir Med 101:1880–1884, 2007.
6. Piyavisetpat N, Aquino SL, Hahn PF, et al: Small incidental pulmonary nodules: How useful is short-term interval CT follow-up? J Thorac Imaging 20:5–9, 2005.
7. Tan BB, Flaherty KR, Kazerooni EA, Iannettoni MD, American College of Chest Physicians: The solitary pulmonary nodule. Chest 123(1 Suppl):89S–96S, 2003.
8. Aida S, Ohara I, Shimazaki H, et al: Solitary peripheral ciliated glandular papillomas of the lung. A report of 3 cases. Am J Surg Pathol 32:1489–1494, 2008.
9. Flieder DB, Koss MN, Nicholson A, et al: Solitary pulmonary papillomas in adults: A clinicopathologic and in situ hybridization study of 14 cases combined with 27 cases in the literature. Am J Surg Pathol 22:1328–1342, 1998.
10. Xu H, Lu DW, El-Mofty SK, Wang HL: Metachronous squamous cell carcinomas evolving from independent oropharyngeal and pulmonary squamous papillomas: Association with human papillomavirus 11 and lack of aberrant p53, Rb, and p16 protein expression. Hum Pathol 35:1419–1422, 2004.
11. Green GE, Bauman NM, Smith RJ: Pathogenesis and treatment of juvenile onset recurrent respiratory papillomatosis. Otolaryngol Clin North Am 33:187–207, 2000.
12. Cook JR, Hill DA, Humphrey PA, et al: Squamous cell carcinoma arising in recurrent respiratory papillomatosis with pulmonary involvement: emerging common pattern of clinical features and human papillomavirus serotype association. Mod Pathol 13:914–918, 2000.
13. Lele SM, Pou AM, Ventura K, et al: Molecular events in the progression of recurrent respiratory papillomatosis to carcinoma. Arch Pathol Lab Med 126:1184–1188, 2002.
14. Gelinas JF, Manoukian J, Cote A: Lung involvement in juvenile onset recurrent respiratory papillomatosis: A systematic review of the literature. Int J Pediatr Otorhinolaryngol 72:433–452, 2008.
15. Harada H, Miura K, Tsutsui Y, et al: Solitary squamous cell papilloma of the lung in a 40-year-old woman with recurrent laryngeal papillomatosis. Pathol Int 50:431–439, 2000.
16. Kerley SW, Buchon-Zalles C, Moran J, Fishback JL: Chronic cavitary respiratory papillomatosis. Arch Pathol Lab Med 113:1166–1169, 1989.
17. Attar S, Miller JE, Hankins J, et al: Bronchial adenoma: A review of 51 patients. Ann Thorac Surg 40:126–132, 1985.
18. Rozenman J, Pausner R, Lieberman Y, Gamsu G: Bronchial adenoma. Chest 92:145–147, 1987.
19. Markel S, Abell M, Haight C, French A: Neoplasms of bronchus commonly designated as adenomas. Cancer 17:590–608, 1964.
20. England DM, Hochholzer L: Truly benign "bronchial adenoma": Report of 10 cases of mucous gland adenoma with immunohistochemical and ultrastructural findings. Am J Surg Pathol 19:887–899, 1995.
21. Kwon JW, Goo JM, Seo JB, et al: Mucous gland adenoma of the bronchus: CT findings in two patients. J Comp Assist Tomogr 23:758–760, 1999.
22. Milenkovic B, Stojsic J, Mandaric D, Stevic R: Mucous gland adenoma simulating bronchial asthma: Case report and literature review. J Asthma 44:789–793, 2007.
23. Ang KL, Dhannapuneni VR, Morgan WE, Soomro IN: Primary pulmonary pleomorphic adenoma. An immunohistochemical study and review of the literature. Arch Pathol Lab Med 127:621–622, 2003.
24. Davis PW, Briggs JC, Seal RM, Storring FK: Benign and malignant mixed tumours of the lung. Thorax 27:657–673, 1972.
25. Fitchett J, Luckraz H, Gibbs AR, O'Keefe P: A rare case of primary pleomorphic adenoma in main bronchus. Ann Thorac Surg 86:1025–1026, 2008.
26. Hara M, Sato Y, Kitase M, et al: CT and MR findings of a pleomorphic adenoma in the peripheral lung. Radiat Med 19:111–114, 2001.
27. Huang Y-Y, You D-L, Tsou M-H, et al: Primary pulmonary pleomorphic adenoma with high uptake of FDG. Eur J Radiol Extra 62:73–76, 2007.
28. Moran CA, Suster S, Askin FB, Koss MN: Benign and malignant salivary gland-type mixed tumors of the lung. Clinicopathologic and immunohistochemical study of eight cases. Cancer 73:2481–2490, 1994.
29. Payne WS, Schier J, Woolner LB: Mixed tumors of the bronchus (salivary gland type). J Thorac Cardiovasc Surg 49:663–668, 1965.
30. Sakamoto H, Uda H, Tanaka T, et al: Pleomorphic adenoma in the periphery of the lung. Report of a case and review of the literature. Arch Pathol Lab Med 115:393–396, 1991.
31. Spencer H: Bronchial mucous gland tumours. Virchows Arch A Pathol Anat Histol 383:101–115, 1979.
32. Sweeney EC, McDermott M: Pleomorphic adenoma of the bronchus. J Clin Pathol 49:87–89, 1996.
33. Tanigaki T, Shoyama Y, Iwasaki M, et al: Pleomorphic adenoma in the lung. Monaldi Arch Chest Dis 57:30–32, 2002.
34. Wright ES, Pike E, Couves CM: Unusual tumours of the lung. J Surg Oncol 24:23–29, 1983.
35. Wenig BM, Hitchcock CL, Ellis GL, Gnepp DR: Metastasizing mixed tumor of salivary glands. A clinicopathologic and flow cytometric analysis. Am J Surg Pathol 16:845–858, 1992.
36. Yoshizaki T, Kinsen H, Minato H, et al: Metastasizing mixed tumour of the parotid gland presenting as multiple lung metastases. J Laryngol Otol 118:724–726, 2004.
37. Burke LM, Rush WI, Khoor A, et al: Alveolar adenoma: A histochemical, immunohistochemical, and ultrastructural analysis of 17 cases. Hum Pathol 30:158–167, 1999.
38. Fujimoto K, Muller NL, Sadohara J, et al: Alveolar adenoma of the lung: Computed tomography and magnetic resonance imaging findings. J Thorac Imaging 17:163–166, 2002.
39. Halldorsson A, Dissanaike S, Kaye KS: Alveolar adenoma of the lung: A clinicopathological description of a case of this very unusual tumour. J Clin Pathol 58:1211–1214, 2005.
40. Sak SD, Koseoglu RD, Demirag F, et al: Alveolar adenoma of the lung. Immunohistochemical and flow cytometric characteristics of two new cases and a review of the literature. APMIS 115:1443–1449, 2007.
41. Yousem SA, Hochholzer L: Alveolar adenoma. Hum Pathol 17:1066–1071, 1986.
42. Roque L, Oliveira P, Martins C, et al: A nonbalanced translocation (10; 16) demonstrated by FISH analysis in a case of alveolar adenoma of the lung. Cancer Genet Cytogenet 89:34–37, 1996.
43. Fine G, Chang CH: Adenoma of type 2 pneumocytes with oncocytic features. Arch Pathol Lab Med 115:797–801, 1991.
44. Hegg CA, Flint A, Singh G: Papillary adenoma of the lung. Am J Clin Pathol 97:393–397, 1992.
45. Minami Y, Morishita Y, Yamamoto T, et al: Cytologic characteristics of pulmonary papillary adenoma. A case report. Acta Cytol 48:243–248, 2004.
46. Noguchi M, Kodama T, Shimosato Y, et al: Papillary adenoma of type 2 pneumocytes. Am J Surg Pathol 10:134–139, 1986.
47. Dixon AY, Moran JF, Wesselius LJ, McGregor DH: Pulmonary mucinous cystic tumor. Case report with review of the literature. Am J Surg Pathol 17:722–728, 1993.
48. Gao ZH, Urbanski SJ: The spectrum of pulmonary mucinous cystic neoplasia: A clinicopathologic and immunohistochemical study of ten cases and review of literature. Am J Clin Pathol 124:62–70, 2005.
49. Graeme-Cook F, Mark EJ: Pulmonary mucinous cystic tumors of borderline malignancy. Hum Pathol 22:185–190, 1991.
50. Igai H, Okumura N, Ohata K, et al: Pediculate mucinous cystadenoma difficult to differentiate from pleural tumor. Ann Thorac Surg 85:1807–1809, 2008.

51. Kragel PJ, Devaney KO, Meth BM, et al: Mucinous cystadenoma of the lung. A report of two cases with immunohistochemical and ultrastructural analysis. Arch Pathol Lab Med 114:1053–1056, 1990.
52. Roux FJ, Lantuejoul S, Brambilla E, Brambilla C: Mucinous cystadenoma of the lung. Cancer 76:1540–1544, 1995.
53. Guimaraes AR, Wain JC, Mark EJ, Wittram C: Mucinous cystadenoma of the lung. AJR Am J Roentgenol 183:282, 2004.
54. Aubry MC, Myers JL, Ryu JH, et al: Pulmonary lymphangioleiomyomatosis in a man. Am J Respir Crit Care Med 162:749–752, 2000.
55. Franz DN, Brody A, Meyer C, et al: Mutational and radiographic analysis of pulmonary disease consistent with lymphangioleiomyomatosis and micronodular pneumocyte hyperplasia in women with tuberous sclerosis. Am J Respir Crit Care Med 164: 661–668, 2001.
56. Kobashi Y, Yoshida K, Miyashita N, et al: Multifocal micronodular pneumocyte hyperplasia in a man with tuberous sclerosis. Intern Med 44:462–466, 2005.
57. Kobayashi T, Satoh K, Ohkawa M: Multifocal micronodular pneumocyte hyperplasia associated with tuberous sclerosis. Acta Radiol 46:37–40, 2005.
58. Muir TE, Leslie KO, Popper H, et al: Micronodular pneumocyte hyperplasia. Am J Surg Pathol 22:465–472, 1998.
59. Devouassoux-Shisheboran M, Hayashi T, Linnoila RI, et al: A clinicopathologic study of 100 cases of pulmonary sclerosing hemangioma with immunohistochemical studies: TTF-1 is expressed in both round and surface cells, suggesting an origin from primitive respiratory epithelium. Am J Surg Pathol 24:906–916, 2000.
60. Iyoda A, Hiroshima K, Shiba M, et al: Clinicopathological analysis of pulmonary sclerosing hemangioma. Ann Thorac Surg 78:1928–1931, 2004.
61. Katzenstein AL, Gmelich JT, Carrington CB: Sclerosing hemangioma of the lung: A clinicopathologic study of 51 cases. Am J Surg Pathol 4:343–356, 1980.
62. Spencer H, Nambu S: Sclerosing haemangiomas of the lung. Histopathology 10:477–487, 1986.
63. Chan AC, Chan JK: Pulmonary sclerosing hemangioma consistently expresses thyroid transcription factor-1 (TTF-1). A new clue to its histogenesis. Am J Surg Pathol 24:1531, 2000.
64. Leong AS, Chan KW, Seneviratne HS: A morphological and immunohistochemical study of 25 cases of so-called sclerosing haemangioma of the lung. Histopathology 27:121–128, 1995.
65. Nagata N, Dairaku M, Ishida T, et al: Sclerosing hemangioma of the lung. Immunohistochemical characterization of its origin as related to surfactant apoprotein. Cancer 55:116–123, 1985.
66. Sugio K, Yokoyama H, Kaneko S, et al: Sclerosing hemangioma of the lung: Radiographic and pathological study. Ann Thorac Surg 53:295–300, 1992.
67. Wu CT, Chang YL, Lee YC: Expression of the estrogen receptor beta in 37 surgically treated pulmonary sclerosing hemangiomas in comparison with non–small cell lung carcinomas. Hum Pathol 36:1108–1112, 2005.
68. Cheung YC, Ng SH, Chang JW, et al: Histopathological and CT features of pulmonary sclerosing haemangiomas. Clin Radiol 58:630–635, 2003.
69. Im JG, Kim WH, Han MC, et al: Sclerosing hemangiomas of the lung and interlobar fissures: CT findings. J Comput Assist Tomogr 18:34–38, 1994.
70. Chung MJ, Lee KS, Han J, et al: Pulmonary sclerosing hemangioma presenting as solitary pulmonary nodule: Dynamic CT findings and histopathologic comparisons. AJR Am J Roentgenol 187:430–437, 2006.
71. Hara M, Iida A, Tohyama J, et al: FDG-PET findings in sclerosing hemangioma of the lung: A case report. Radiat Med 19:215–218, 2001.
72. Chan NG, Melega DE, Inculet RI, Shepherd JG: Pulmonary sclerosing hemangioma with lymph node metastases. Can Respir J 10:391–392, 2003.
73. Miyagawa-Hayashino A, Tazelaar HD, Langel DJ, Colby TV: Pulmonary sclerosing hemangioma with lymph node metastases: Report of 4 cases. Arch Pathol Lab Med 127:321–325, 2003.
74. Yano M, Yamakawa Y, Kiriyama M, et al: Sclerosing hemangioma with metastases to multiple nodal stations. Ann Thorac Surg 73:981–983, 2002.
75. Illei PB, Rosai J, Klimstra DS: Expression of thyroid transcription factor-1 and other markers in sclerosing hemangioma of the lung. Arch Pathol Lab Med 125:1335–1339, 2001.
76. Yousem SA, Wick MR, Singh G, et al: So-called sclerosing hemangiomas of lung. An immunohistochemical study supporting a respiratory epithelial origin. Am J Surg Pathol 12:582–590, 1988.
77. Satoh Y, Tsuchiya E, Weng SY, et al: Pulmonary sclerosing hemangioma of the lung. A type II pneumocytoma by immunohistochemical and immunoelectron microscopic studies. Cancer 64:1310–1317, 1989.
78. Niho S, Suzuki K, Yokose T, et al: Monoclonality of both pale cells and cuboidal cells of sclerosing hemangioma of the lung. Am J Pathol 152:1065–1069, 1998.
79. Sartori G, Bettelli S, Schirosi L, et al: Microsatellite and EGFR, HER2 and K-RAS analyses in sclerosing hemangioma of the lung. Am J Surg Pathol 31:1512–1520, 2007.
80. Dacic S, Sasatomi E, Swalsky PA, et al: Loss of heterozygosity patterns of sclerosing hemangioma of the lung and bronchioloalveolar carcinoma indicate a similar molecular pathogenesis. Arch Pathol Lab Med 128:880–884, 2004.
81. Arrigoni MG, Woolner LB, Bernatz PE, et al: Benign tumors of the lung. A ten-year surgical experience. J Thorac Cardiovasc Surg 60:589–599, 1970.
82. Murray J, Kielkowski D, Leiman G: The prevalence and age distribution of peripheral pulmonary hamartomas in adult males. An autopsy-based study. S Afr Med J 79:247–249, 1991.
83. Gjevre JA, Myers JL, Prakash UB: Pulmonary hamartomas. Mayo Clin Proc 71:14–20, 1996.
84. Hansen CP, Holtveg H, Francis D, et al: Pulmonary hamartoma. J Thorac Cardiovasc Surg 104:674–678, 1992.
85. Rodriguez FJ, Aubry MC, Tazelaar HD, et al: Pulmonary chondroma: A tumor associated with Carney triad and different from pulmonary hamartoma. Am J Surg Pathol 31:1844–1853, 2007.
86. Siegelman SS, Khouri NF, Scott WW Jr, et al: Pulmonary hamartoma: CT findings. Radiology 160:313–317, 1986.
87. Poulsen JT, Jacobsen M, Francis D: Probable malignant transformation of a pulmonary hamartoma. Thorax 34:557–558, 1979.
88. Trahan S, Erickson-Johnson MR, Rodriguez F, et al: Formation of the 12q14-q15 amplicon precedes the development of a well-differentiated liposarcoma arising from a nonchondroid pulmonary hamartoma. Am J Surg Pathol 30:1326–1329, 2006.
89. Naresh KN, Pai SA, Vyas JJ, Soman CS: Leiomyoma of the bronchus: A case report. Histopathology 22:288–289, 1993.
90. Moran CA, Suster S, Koss MN: Endobronchial lipomas: A clinicopathologic study of four cases. Mod Pathol 7:212–214, 1994.
91. Wood J, Henderson RG: Peripheral intrapulmonary lipoma: A rare lung neoplasm. Br J Radiol 77:60–62, 2004.
92. Hughes JH, Young NA, Wilbur DC, et al, Cytopathology Resource Committee College of American Pathologists: Fine-needle aspiration of pulmonary hamartoma: A common source of false-positive diagnoses in the College of American Pathologists Interlaboratory Comparison Program in Nongynecologic Cytology. Arch Pathol Lab Med 129:19–22, 2005.
93. Hess JL: Chromosomal translocations in benign tumors: The HMGI proteins. Am J Clin Pathol 109:251–261, 1998.
94. Kazmierczak B, Dal Cin P, Wanschura S, et al: HMGIY is the target of 6p21.3 rearrangements in various benign mesenchymal tumors. Genes Chromosomes Cancer 23:279–285, 1998.
95. Kazmierczak B, Meyer-Bolte K, Tran KH, et al: A high frequency of tumors with rearrangements of genes of the HMGI(Y) family in a series of 191 pulmonary chondroid hamartomas. Genes Chromosomes Cancer 26:125–133, 1999.
96. Kazmierczak B, Wanschura S, Rommel B, et al: Ten pulmonary chondroid hamartomas with chromosome 6p21 breakpoints within the HMG-I(Y) gene or its immediate surroundings. J Natl Cancer Inst 88:1234–1236, 1996.
97. Cleynen I, Van de Ven WJ: The HMGA proteins: A myriad of functions (review). Int J Oncol 32:289–305, 2008.
98. Carney JA, Sheps SG, Go VL, Gordon H: The triad of gastric leiomyosarcoma, functioning extra-adrenal paraganglioma and pulmonary chondroma. N Engl J Med 296:1517–1518, 1977.

99. Carney JA: Gastric stromal sarcoma, pulmonary chondroma, and extra-adrenal paraganglioma (Carney triad): natural history, adrenocortical component, and possible familial occurrence. Mayo Clin Proc 74:543–552, 1999.
100. Bahadori M, Liebow AA: Plasma cell granulomas of the lung. Cancer 31:191–208, 1973.
101. Yousem SA, Tazelaar HD, Manabe T, Dehner L: Inflammatory myofibroblastic tumor. *In* Travis WD, Brambilla E, Muller-Hemerlink H, Harris C (eds): Pathology and Genetics of Tumours of the Lung, Pleura, Thymus and Heart. Lyon, France: IARC Press; 2004, pp 105–106.
102. Cerfolio RJ, Allen MS, Nascimento AG, et al: Inflammatory pseudotumors of the lung. Ann Thorac Surg 67:933–936, 1999.
103. Coffin CM, Hornick JL, Fletcher CD: Inflammatory myofibroblastic tumor: Comparison of clinicopathologic, histologic, and immunohistochemical features including ALK expression in atypical and aggressive cases. Am J Surg Pathol 31:509–520, 2007.
104. Spencer H: The pulmonary plasma cell/histiocytoma complex. Histopathology 8:903–916, 1984.
105. Yousem SA, Shaw H, Cieply K: Involvement of 2p23 in pulmonary inflammatory pseudotumors. Hum Pathol 32:428–433, 2001.
106. Sakurai H, Hasegawa T, Watanabe S, et al: Inflammatory myofibroblastic tumor of the lung. Eur J Cardiothorac Surg 25:155–159, 2004.
107. Tavora F, Shilo K, Ozbudak IH, et al: Absence of human herpesvirus-8 in pulmonary inflammatory myofibroblastic tumor: Immunohistochemical and molecular analysis of 20 cases. Mod Pathol 20:995–999, 2007.
108. Ishida T, Oka T, Nishino T, et al: Inflammatory pseudotumor of the lung in adults: Radiographic and clinicopathological analysis. Ann Thorac Surg 48:90–95, 1989.
109. Lee HJ, Kim JS, Choi YS, et al: Treatment of inflammatory myofibroblastic tumor of the chest: The extent of resection. Ann Thorac Surg 84:221–224, 2007.
110. Melloni G, Carretta A, Ciriaco P, et al: Inflammatory pseudotumor of the lung in adults. Ann Thorac Surg 79:426–432, 2005.
111. Applebaum H, Kieran MW, Cripe TP, et al: The rationale for nonsteroidal anti-inflammatory drug therapy for inflammatory myofibroblastic tumors: A Children's Oncology Group study. J Pediatr Surg 40:999–1003, 2005.
112. Chan PW, Omar KZ, Ramanujam TM: Successful treatment of unresectable inflammatory pseudotumor of the lung with COX-2 inhibitor. Pediatr Pulmonol 36:167–169, 2003.
113. Su W, Ko A, O'Connell T, Applebaum H: Treatment of pseudotumors with nonsteroidal antiinflammatory drugs. J Pediatr Surg 35:1635–1637, 2000.
114. Chan JK, Cheuk W, Shimizu M: Anaplastic lymphoma kinase expression in inflammatory pseudotumors. Am J Surg Pathol 25:761–768, 2001.
115. Coffin CM, Patel A, Perkins S, et al: ALK1 and p80 expression and chromosomal rearrangements involving 2p23 in inflammatory myofibroblastic tumor. Mod Pathol 14:569–576, 2001.
116. Cook JR, Dehner LP, Collins MH, et al: Anaplastic lymphoma kinase (ALK) expression in the inflammatory myofibroblastic tumor: A comparative immunohistochemical study. Am J Surg Pathol 25:1364–1371, 2001.
117. Bridge JA, Kanamori M, Ma Z, et al: Fusion of the ALK gene to the clathrin heavy chain gene, CLTC, in inflammatory myofibroblastic tumor. Am J Pathol 159:411–415, 2001.
118. Lawrence B, Perez-Atayde A, Hibbard MK, et al: TPM3-ALK and TPM4-ALK oncogenes in inflammatory myofibroblastic tumors. Am J Pathol 157:377–384, 2000.
119. Cole B, Zhou H, McAllister N, et al: Inflammatory myofibroblastic tumor with thrombocytosis and a unique chromosomal translocation with ALK rearrangement. Arch Pathol Lab Med 130:1042–1045, 2006.
120. Ma Z, Hill DA, Collins MH, et al: Fusion of ALK to the Ran-binding protein 2 (RANBP2) gene in inflammatory myofibroblastic tumor. Genes Chromosomes Cancer 37:98–105, 2003.
121. Snyder CS, Dell'Aquila M, Haghighi P, et al: Clonal changes in inflammatory pseudotumor of the lung: A case report. Cancer 76:1545–1549, 1995.
122. Yousem SA, Flynn SD: Intrapulmonary localized fibrous tumor. Intraparenchymal so-called localized fibrous mesothelioma. Am J Clin Pathol 89:365–369, 1988.
123. Brunnemann RB, Ro JY, Ordonez NG, et al: Extrapleural solitary fibrous tumor: A clinicopathologic study of 24 cases. Mod Pathol 12:1034–1042, 1999.
124. Chan JK: Solitary fibrous tumour—Everywhere, and a diagnosis in vogue. Histopathology 31:568–576, 1997.
125. Goodlad JR, Fletcher CD: Solitary fibrous tumour arising at unusual sites: Analysis of a series. Histopathology 19:515–522, 1991.
126. Witkin GB, Rosai J: Solitary fibrous tumor of the mediastinum. A report of 14 cases. Am J Surg Pathol 13:547–557, 1989.
127. Briselli M, Mark EJ, Dickersin GR: Solitary fibrous tumors of the pleura: Eight new cases and review of 360 cases in the literature. Cancer 47:2678–2689, 1981.
128. England DM, Hochholzer L, McCarthy MJ: Localized benign and malignant fibrous tumors of the pleura. A clinicopathologic review of 223 cases. Am J Surg Pathol 13:640–658, 1989.
129. Magdeleinat P, Alifano M, Petino A, et al: Solitary fibrous tumors of the pleura: Clinical characteristics, surgical treatment and outcome. Eur J Cardiothoracic Surg 21:1087–1093, 2002.
130. Okike N, Bernatz PE, Woolner LB: Localized mesothelioma of the pleura: Benign and malignant variants. J Thorac Cardiovasc Surg 75:363–372, 1978.
131. Schirosi L, Lantuejoul S, Cavazza A, et al: Pleuro-pulmonary solitary fibrous tumors: A clinicopathologic, immunohistochemical, and molecular study of 88 cases confirming the prognostic value of the de Perrot staging system and p53 expression, and evaluating the role of c-kit, BRAF, PDGFRs (alpha/beta), c-met, and EGFR. Am J Surg Pathol 32:1627–1642, 2008.
132. Sung SH, Chang JW, Kim J, et al: Solitary fibrous tumors of the pleura: Surgical outcome and clinical course. Ann Thorac Surg 79:303–307, 2005.
133. Kohler M, Clarenbach CF, Kestenholz P, et al: Diagnosis, treatment and long-term outcome of solitary fibrous tumours of the pleura. Eur J Cardiothorac Surg 32:403–408, 2007.
134. Balduyck B, Lauwers P, Govaert K, et al: Solitary fibrous tumor of the pleura with associated hypoglycemia: Doege-Potter syndrome: A case report. J Thorac Oncol 1:588–590, 2006.
135. Fukasawa Y, Takada A, Tateno M, et al: Solitary fibrous tumor of the pleura causing recurrent hypoglycemia by secretion of insulin-like growth factor II. Pathol Int 48:47–52, 1998.
136. Kim JH, Kim JO, Kim SY, et al: Two cases of large solitary fibrous tumors of the pleura associated with fasting hypoglycemia. Eur Radiol 11:819–824, 2001.
137. Kishi K, Homma S, Tanimura S, et al: Hypoglycemia induced by secretion of high molecular weight insulin-like growth factor-II from a malignant solitary fibrous tumor of the pleura. Intern Med 40:341–344, 2001.
138. Cardinale L, Allasia M, Ardissone F, et al: CT features of solitary fibrous tumour of the pleura: Experience in 26 patients. Radiol Med 111:640–650, 2006.
139. Ferretti GR, Chiles C, Choplin RH, Coulomb M: Localized benign fibrous tumors of the pleura. AJR Am J Roentgenol 169:683–686, 1997.
140. de Perrot M, Fischer S, Brundler MA, et al: Solitary fibrous tumors of the pleura. Ann Thorac Surg 74:285–293, 2002.
141. Churg AM, Warnock ML: So-called "minute pulmonary chemodectoma": A tumor not related to paragangliomas. Cancer 37:1759–1769, 1976.
142. Gaffey MJ, Mills SE, Askin FB: Minute pulmonary meningothelial-like nodules. A clinicopathologic study of so-called minute pulmonary chemodectoma. Am J Surg Pathol 12:167, 1988.
143. Mukhopadhyay S, El-Zammar OA, Katzenstein AL: Pulmonary meningothelial-like nodules: New insights into a common but poorly understood entity. Am J Surg Pathol 33:487–495, 2009.
144. Pelosi G, Maffini F, Decarli N, Viale G: Progesterone receptor immunoreactivity in minute meningothelioid nodules of the lung. Virchows Arch 440:543–546, 2002.
145. Spain DM: Intrapulmonary chemodectomas in subjects with organizing pulmonary thromboemboli. Am Rev Respir Dis 96:1158–1164, 1967.

146. Ionescu DN, Sasatomi E, Aldeeb D, et al: Pulmonary meningothelial-like nodules: A genotypic comparison with meningiomas. Am J Surg Pathol 28:207–214, 2004.
147. Suster S, Moran CA: Diffuse pulmonary meningotheliomatosis. Am J Surg Pathol 31:624–631, 2007.
148. Cesario A, Galetta D, Margaritora S, Granone P: Unsuspected primary pulmonary meningioma. Eur J Cardiothoracic Surg 21:553–555, 2002.
149. Meirelles GS, Ravizzini G, Moreira AL, Akhurst T: Primary pulmonary meningioma manifesting as a solitary pulmonary nodule with a false-positive PET scan. J Thorac Imaging 21:225–227, 2006.
150. Rowsell C, Sirbovan J, Rosenblum MK, Perez-Ordonez B: Primary chordoid meningioma of lung. Virchows Arch 446:333–337, 2005.
151. Adlakha A, Rao K, Adlakha H, et al: Meningioma metastatic to the lung. Mayo Clin Proc 74:1129–1133, 1999.
152. Deavers M, Guinee D, Koss MN, Travis WD: Granular cell tumors of the lung. Clinicopathologic study of 20 cases. Am J Surg Pathol 19:627–635, 1995.
153. Thomas de Montpreville V, Dulmet EM: Granular cell tumours of the lower respiratory tract. Histopathology 27:257–262, 1995.
154. Gaffey MJ, Mills SE, Askin FB, et al: Clear cell tumor of the lung. A clinicopathologic, immunohistochemical, and ultrastructural study of eight cases [see comment]. Am J Surg Pathol 14:248–259, 1990.
155. Bonetti F, Pea M, Martignoni G, et al: Clear cell ("sugar") tumor of the lung is a lesion strictly related to angiomyolipoma—The concept of a family of lesions characterized by the presence of the perivascular epithelioid cells (PEC). Pathology 26:230–236, 1994.
156. Martignoni G, Pea M, Reghellin D, et al: PEComas: The past, the present and the future. Virchows Arch 452:119–132, 2008.

CHAPTER 51

PULMONARY THROMBOEMBOLISM

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INTRODUCTION

The one generalization about venous thromboembolism (VTE) that is free from controversy is that many aspects of this disorder remain controversial. There are multiple reasons why VTE continues to engender lively debate. Perhaps the major reason, notwithstanding the substantial advances that have been made since the late 1990s, is that a number of fundamental questions continue to exist regarding the pathogenesis, clinical presentation, diagnosis, and therapy of the disease.

VTE represents a potentially fatal disease process with a clinical presentation that is often silent or nonspecific and for which a wide range of diagnostic techniques is

available, many with technical and interpretive limitations. Although estimates vary widely, the best available information suggests that at least 5 million episodes of venous thrombosis occur annually in the United States.[1] The overall average age- and sex-adjusted annual incidence of acute pulmonary embolism (PE) is approximately 70/100,000, based on discharge diagnosis (*International Classification of Diseases*, 9th Revision [ICD-9]) codes.[2] Extrapolating the rates on U.S. census data, the annual rate of diagnosed PE has been estimated to be 237,000 cases.[3] These data, of course, represent only those patients in whom the diagnosis of acute PE was correctly made. Autopsy series suggest that the true number of deaths from acute PE (including those patients that died without the diagnosis ever being made) is at least threefold higher.[4–7] For this reason, the most current evidence-based estimation is that the majority of PE–related deaths can be attributed to PE that was undiagnosed (and therefore untreated) during life.

As many as 10% of those patients who suffer embolism may die from their disease.[8] The overwhelming majority of these deaths do not appear to arise from therapeutic failure. With the exception of patients who initially present with hemodynamic impairment, in whom mortality rates approach 20% to 30%, embolic recurrence is rare and death is uncommon once the diagnosis of embolism is confirmed and appropriate therapy initiated.[9] The majority of deaths related to embolism appear to arise from a failure to prevent the disease in patients at risk of it and from a failure to make the diagnosis in those afflicted.[8] The incidence of fatal PE appears to have declined over the past several decades.[10,11] For example, the Centers for Disease Control and Prevention Compressed Mortality File (CMF) for 1978 to 1998 reported that an average of 9685 deaths/year were attributed by clinicians to acute PE.[12] A significant, but incomplete improvement was reported in the current (1999–2005) CMF, in which acute PE was deemed by clinicians to be responsible for an average of 8532 deaths/year.[13] However, these statistics do not account for fatal PE that had been undiagnosed clinically, as described previously. Mortality from acute PE remains a substantial public health care problem as a result of the demographics of an aging population and the ability of modern medicine to treat patients with chronic disease.[14]

Contributing to the debate surrounding VTE is the involvement of a wide range of medical disciplines in its prevention, diagnosis, and management. Thrombosis is not a discrete subspecialty. The problem of VTE involves pulmonologists, cardiologists, hematologists, internists, specialists in vascular disease, radiologists, a range of surgical subspecialists, obstetricians, and others. Because specific prophylactic, diagnostic, and therapeutic strategies within one discipline may not necessarily be applicable to another, a perception of coherence in the clinical approach to this disease process often appears to be lacking.

During the past decade, many of the long-standing controversies surrounding the natural history, diagnosis, and therapy of VTE have been partially or completely reconciled, resulting in substantial changes in the diagnostic and therapeutic approach to the disease. The persistence of a number of unresolved issues, and the emergence of still others, should not be a cause for clinical cynicism. In the approach to the patient with suspected VTE, an understanding of what is unknown can prove invaluable to the decision-making process.

PATHOGENESIS AND RISK FACTORS

The triad of venous stasis, alterations in coagulation, and vascular injury identified by Virchow in 1856 as primary factors in the pathogenesis of VTE has been supported by a considerable amount of clinical and experimental evidence. Over the past several decades, severe abnormalities of the coagulation and fibrinolytic system, including isolated deficiencies of antithrombin III, protein C, protein S, and plasminogen as well as the presence of a lupus anticoagulant, had been described and their high association with first-time and recurrent VTE confirmed (Table 51-1).[15,16] In addition, there has been increasing recognition of less severe, but more common inherited "thrombophilic" conditions that are capable of shifting the hemostatic balance toward thrombosis and mildly increasing the risk of venous thromboembolic events.

The most common of the inherited thrombophilic conditions, first described in 1993 by Dahlback and designated *factor V Leiden mutation*, is the consequence of a single point mutation on the factor V gene (adenine for guanine) resulting in activated factor V (factor Va) with diminished sensitivity to the natural anticoagulant effect of activated protein C.[17] Approximately 5% of whites in Europe and North America are heterozygous for this genetic defect; lower rates of carrier frequency have been reported among Native American, African, and Asian populations.[18,19] Although initially detected in as many as 60% of *selected* patients with VTE, subsequent studies have detected the mutation in 10% to 20% of unselected patients.[20] The heterozygous state carries a 5- to 10-fold increase in lifetime risk for VTE.[21,22] Whereas the relative risk among patients homozygous for this mutation has been estimated to be as high as 80-fold, the estimates are based on a very small number of patients and may be somewhat imprecise.[21,22] Factor V Leiden mutation appears to be an important risk factor for VTE during pregnancy, in the postpartum period, and during oral contraceptive use.[23,23a] Compared with women who do not use oral contraceptives and are not carriers of the factor V mutation, the risk of thrombosis among those with both risk factors is increased approximately 30-fold.[24] In view of the prevalence of thrombophilia and the low prevalence of VTE in nonusers of combined oral contraceptives, the absolute risk remains low. Because the absolute increase in VTE is modest, selective thrombophilia screening based on previous personal or family history of VTE is more cost-effective than universal screening.

A sequence variation in the prothrombin gene (G20210A) was described in 1996 and is estimated to

TABLE 51-1. Thromboembolic Risk Factors

HEREDITARY THROMBOPHILIAS
Protein C deficiency
Protein S deficiency
Antithrombin III deficiency
Factor V Leiden mutation
Prothrombin 20210 G → A variation
Hyperhomocysteinemia
Dysfibrinogenemia
Familial plasminogen deficiency
ACQUIRED SURGICAL PREDISPOSITIONS
Major thoracic, abdominal, or neurosurgical procedures requiring general anesthesia and lasting >30 min
Hip arthroplasty
Knee arthroplasty
Knee arthroscopy
Hip fracture
Major trauma
Open prostatectomy
Spinal cord injury
ACQUIRED MEDICAL PREDISPOSITIONS
Prior venous thromboembolism
Advanced age (>60 yr)
Malignancy
Congestive heart failure
Cerebrovascular accident
Nephrotic syndrome
Estrogen therapy
Pregnancy and the postpartum period
Obesity
Prolonged immobilization
Antiphospholipid antibody syndrome
Lupus anticoagulant
Inflammatory bowel disease
Paroxysmal nocturnal hemoglobinuria
Behçet's syndrome

occur in approximately 2% to 4% of the population.[25] This mutation results in an overproduction of prothrombin, which is otherwise normal. It is associated with a three- to fourfold increased risk of lower extremity venous thrombosis.[25,26]

Hyperhomocyst(e)inemia has also been identified as a potential independent predisposition to VTE. Elevation of plasma homocysteine levels may be the result of genetic abnormalities, nutritional deficiencies of vitamins (B_6, B_{12}, folate), clinical disorders (renal insufficiency, hypothyroidism, inflammatory bowel disease), or a combination of the three. Although retrospective, case-control studies demonstrate an association between hyperhomocyst(e)inemia and VTE, the results of prospective studies have not been uniform.[27,28]

The three "common genetic thrombophilias" (factor V Leiden, prothrombin G20210A, and hyperhomocyst(e)inemia) appear to act as independent risk factors for increasing both the initial and the recurrent thrombosis risk.[29,30] Thus, the relative risk for patients with multiple thrombophilic conditions is higher than for patients with only one of them.

The identification of these risk factors, and the likelihood that others exist, raises the possibility that screening to determine relative thromboembolic risk may be feasible in the future. However, a consensus for such an approach does not exist at the present time. Despite its prevalence in the general population, screening for factor V Leiden mutation is not advised because most patients with this abnormality will never suffer a thromboembolic event. Furthermore, the absence of this abnormality should not influence the decision to provide prophylaxis to patients at clinical risk. In addition, recurrence of VTE is no more common in VTE patients with factor V Leiden[31] or the prothrombin G20210A gene[32] than in VTE patients without these mutations, and there is no evidence that prolonged anticoagulation would be more beneficial for VTE patients with either mutation than it would be in patients without them.

Patients with spontaneous ("unprovoked") VTE who also have *both* factor V Leiden and the prothrombin G20210A gene[32] appear to be at somewhat higher risk for recurrence than similar patients without those mutations. This observation does not establish a risk-benefit relationship for prolonged anticoagulation in patients with the combination of thrombophilic mutations, which remains unknown.

For all the reasons stated previously, the benefits of screening for the common thrombophilias is controversial. Patient groups in which screening is likely to yield positive results include those with a history of recurrent VTE or with a confirmed family history of thromboembolism, a first episode of thromboembolism at an early age, spontaneous venous thrombosis, thromboses in unusual anatomic sites, arterial thrombosis, and thromboembolism associated with pregnancy or estrogen use. Whether screening should be performed prior to the initiation of oral contraceptive agents remains a matter of debate.[33,34] The relative risk of VTE is increased approximately fourfold in users of oral contraceptives, although the increase in absolute risk is modest.[24,35] A policy of routine screening would deny effective contraception to a substantial number of women while preventing only a small number of PEs.

In most patients, even those with an identified thrombophilic state, some clinical condition associated with venous stasis, intimal injury, or both serves as the basis for the thromboembolic event.[36] Several trials have also confirmed that the risk of VTE in hospitalized patients is not limited to patients undergoing surgical procedures. Thromboembolic risk in patients admitted with a wide range of acute medical problems is comparable with that seen in surgical patients.[37–39]

Major risk factors include pelvic or lower extremity fractures, hip and knee surgery, a past history of VTE, acute paralytic stroke or spinal injury, major traumatic injury, open prostatectomy, and abdominal or pelvic surgery for malignant disease. Other factors that enhance risk include prolonged general anesthesia, advancing age, cardiac disease, pregnancy, the postpartum period, the use of estrogen-containing compounds, malignancy,

the presence of a lupus anticoagulant or antiphospholipid antibody, and prolonged immobilization.[40] It is important to recognize that these risk factors may be multiplicative.[36] Thromboembolic risk in an otherwise healthy 45-year-old individual undergoing an elective cholecystectomy is considerably less than the risk experienced by an obese 75-year-old with a history of prior VTE undergoing the same procedure. Similarly, the patient with hip fracture or hip replacement has, by virtue of that condition alone, a 60% to 70% risk of deep venous thrombosis (DVT) and a 2% to 4% risk of experiencing a fatal thromboembolic event in the absence of preventive measures. Add other risk factors, and the incidence of DVT—and the likelihood of a fatal complication—will be even higher. These considerations allow the development of a reasonable "risk profile" in an individual patient, a profile that should influence the use and intensity of prophylactic intervention.[36]

NATURAL HISTORY: DEEP VENOUS THROMBOSIS

Venous thrombi appear to originate either in the vicinity of a venous valve cusp, where eddy currents arise, or at the site of intimal injury.[41] Platelet aggregation and release of mediators initiate the sequence. With local accumulation of such factors, the coagulation cascade is activated and thrombus develops, composed primarily of fibrin and erythrocytes. As thrombus extension occurs, local fibrinolytic activity is enhanced. Thus, thrombus behavior becomes a dynamic process that may result in complete dissolution, partial resolution resulting in a variable degree of intimal narrowing and valvular damage, progressive proximal extension, or embolization. In more than half of patients, some degree of permanent venous wall scarring occurs, which is visible on ultrasound.[42] If the venous wall scarring causes severe obstruction, collateral veins develop.

Extensive autopsy and clinical studies have established that some 90% of PEs that elicit clinical attention arise from venous thrombosis in the deep veins of the lower extremities.[43] Venous thrombi capable of embolization can arise from other sites. Primary iliac or proximal femoral thrombi may develop in patients undergoing surgery involving the hip, and pelvic vein thrombosis can occur in patients undergoing pelvic or prostatic surgery. Axillosubclavian vein thrombosis may be spontaneous, resulting from congenital abnormalities of the thoracic outlet, or may be related to indwelling central venous catheters, pulmonary artery catheters, or transvenous pacing wires.[44,44a] In patients with dilated right heart chambers or pulmonary arteries, thrombi can form at those sites and embolize distally into the branches of the pulmonary artery.

The likelihood of embolism is influenced by the location of thrombi in the veins of the lower extremity. Although the majority of thrombi originate in the veins of the calf, it has been clearly demonstrated that thrombi that remain limited to the calf veins rarely result in PE.[45] However, approximately 25% of symptomatic, isolated calf thrombi when left untreated will extend to involve the proximal veins (popliteal, superficial femoral, and common femoral veins, or even more proximally).[46] Proximal extension poses a risk of embolization that approaches 50%.[47,48]

This natural history of DVT has several important diagnostic and therapeutic implications. First, because the vast majority of emboli arise from thrombi in the veins in the lower extremity, diagnostic approaches to DVT can be focused upon techniques that detect lower extremity DVT. Second, techniques that detect above-knee thrombi are of particular value whether or not they can detect calf-limited thrombi. Finally, although it is true that calf-limited thrombi rarely embolize, many have incorrectly concluded from this information that *symptomatic*, calf-limited DVT represents a clinically irrelevant condition. It must be emphasized that proximal extension of calf-limited thrombi may occur. Furthermore, symptomatic calf vein thrombosis appears to be subject to recurrence, albeit at a lower risk than proximal vein thrombosis.[49]

Although most above-knee thrombi represent extensions from calf thrombi, some do arise in the larger, proximal veins de novo. This occurrence appears to be restricted principally to patients with hip fracture or replacement, pelvic surgery (including prostatic resection), and other high inguinal pelvic trauma.

At any time during this process, a portion or all of the thrombus can detach as an embolus. This risk is highest early in thrombus development before significant fibrinolysis or organization occurs. Beyond this acute phase, the long-term outlook is influenced principally by the extent of residual venous obstruction and valvular damage. If significant obstruction or valvular damage persists, downstream stasis will be present, leading to a risk of recurrent DVT and development of the postphlebitic syndrome.[50,51]

NATURAL HISTORY: PULMONARY EMBOLISM

PE is not an isolated disease; it is generally a complication of venous thrombosis. Nonetheless, once it occurs, embolism can induce a series of pulmonary and cardiac effects.[52]

PE causes a number of consequences to gas exchange and other pulmonary functions. Regional obstruction to pulmonary blood flow, and diversion of the flow to unobstructed portions of the lung, may alter the ventilation-perfusion balance in both the obstructed and the unobstructed regions, resulting in hypoxemia.[53,54] If regional pulmonary vascular obstruction is total, alveolar dead space is created.[55] If a region's blood flow is severely obstructed, bronchoconstriction may occur in the lung distal to the area of obstruction as the result of alveolar hypocapnia.[56] This is probably uncommon in patients because they are free to inhale carbon dioxide–rich dead-space air into the associated lung regions and because obstruction is rarely total. Hyperventilation almost always occurs, the mechanism for which remains

uncertain. Arterial hypoxemia may be worsened when acute increases in right ventricular afterload lower the cardiac output enough to widen the arteriovenous oxygen difference and decrease the saturation of mixed venous gas.[57] This lowering of the mixed venous oxygen content magnifies the effects of the normal venous admixture, thereby lowering the arterial oxygen pressure (P_{O_2}). Another potential mechanism for hypoxemia in patients with massive PE is right-to-left shunt, on either an intrapulmonary or an intracardiac basis.[58] With embolic occlusion sufficient to increase pulmonary artery pressure, hypoxic vasoconstrictive mechanisms can be overcome and perfusion to poorly ventilated or nonventilated lung regions may occur. On occasion, embolic events massive enough to increase right atrial pressure may result in intracardiac right-to-left shunting through a patent foramen ovale. The final mechanism for hypoxemia relates to the loss of pulmonary surfactant.[59] Loss of surfactant does not occur immediately. It requires approximately 24 hours of total occlusion and lack of blood flow to develop. At that time or later, surfactant becomes depleted in the obstructed alveolar zones, resulting in atelectasis and edema. If partial thrombus resolution and reperfusion to this atelectatic region develop, hypoxemia can result.

One uncommon local consequence of PE is pulmonary infarction. Infarction is uncommon because the pulmonary parenchyma has three potential sources of oxygen: the pulmonary arteries, the bronchial arteries, and the airways.[60] In patients with no coexisting cardiopulmonary disease, large infarctions (such as those visible by chest radiography) are rare.[61,62] However, autopsy series suggest that infarctions of smaller pulmonary arteries are more common.[63,64] Infarction occurs in approximately 20% to 33% of patients with significant cardiac or pulmonary disease that compromises either bronchial arterial flow or airway patency. In patients with left ventricular failure, increased pulmonary venous pressure may decrease bronchial flow and infarction may result.[65]

The cardiac and hemodynamic effects of embolism are related to three factors: the degree of reduction of the cross-sectional area of the pulmonary vascular bed, the preexisting status of the cardiopulmonary system, and the physiologic consequences of both hypoxic and neurohumorally mediated vasoconstriction.[66–71] Mechanical obstruction of the pulmonary vascular bed by embolism is accompanied by release of vasoconstrictive substances such as thromboxane A_2 and serotonin.[72] The combination acutely increases the workload on the right ventricle, a chamber ill equipped to deal with high-pressure load. In patients without preexisting cardiopulmonary disease, obstruction of less than 20% of the pulmonary vascular bed results in a number of compensatory events that minimize adverse hemodynamic consequences. Recruitment and distention of pulmonary vessels occur, resulting in a normal or near-normal pulmonary artery pressure and pulmonary vascular resistance; cardiac output is maintained by increases in the right ventricular stroke volume and increases in the heart rate. As the degree of pulmonary vascular obstruction exceeds 30% to 40%, increases in pulmonary artery pressure and modest increases in right atrial pressure occur. The Frank-Starling mechanism maintains right ventricular stroke work and cardiac output. When the degree of pulmonary artery obstruction exceeds 50% to 60%, compensatory mechanisms are overcome, cardiac output begins to fall, and right atrial pressure increases dramatically. With acute obstruction beyond this amount, the right heart dilates, right ventricular wall tension increases, right ventricular ischemia may develop, the cardiac output falls, and systemic hypotension develops. In patients without prior cardiopulmonary disease, the maximal mean pulmonary artery pressure capable of being generated by the right ventricle appears to be 40 mm Hg (representing a pulmonary artery systolic pressure of ~70 mm Hg). The correlation between the extent of pulmonary vascular obstruction and the pulmonary vascular resistance appears to be hyperbolic, reflecting at its lower end the expansible nature of the pulmonary vascular bed and at its upper the precipitous decline in cardiac output that may occur as the right ventricle fails.[73]

The hemodynamic response to acute PE in patients with preexisting cardiopulmonary disease may be considerably different.[71] Unlike patients without prior cardiopulmonary disease, in whom there is a general relationship between the degree of pulmonary vascular obstruction and the level of the pulmonary artery pressure, patients with prior cardiopulmonary disease demonstrate degrees of pulmonary hypertension that are disproportionate to the degree of pulmonary vascular obstruction. As a result, severe pulmonary hypertension may develop in response to a relatively small reduction in pulmonary artery cross-sectional area. Thus, evidence of right ventricular hypertrophy (rather than right ventricular dilation) associated with a mean pulmonary artery pressure in excess of 40 mm Hg (pulmonary artery systolic pressure in excess of ~70 mm Hg) in a patient suspected of embolism should suggest an element of chronic pulmonary hypertension resulting from a potentially diverse group of etiologic possibilities (e.g., chronic thromboembolic pulmonary hypertension, left ventricular failure, valvular disease, right-to-left cardiac shunts).

Beyond the acute embolic event, the behavior of emboli parallels that previously described for venous thrombi; that is, they undergo resolution by fibrinolysis, by organization and recanalization, or both. Although there is a great deal of interpatient variability, resolution of PEs typically is substantial during the first week, somewhat more gradual for the next 4 to 8 weeks, and then very slow thereafter.[55,74–79] (The most rapid resolution of a large embolus that has been documented is 51 hr.[80]) The term *resolution* is used here because it is uncertain, in humans, to what degree lysis (versus organization) participates in embolic resolution. Most sequential data regarding resolution in humans are based on perfusion scan, not angiographic data. However, these data suggest that residual anatomic defects are common following embolism and, contrary to prior opinion, that complete restoration of pulmonary blood flow represents the exception rather than the rule.[55,74–79] In terms of hemo-

dynamic resolution, it would appear that a stable pulmonary artery pressure is reached within 6 weeks.[81] How often anatomic and mild hemodynamic residuals persist is not known. What is known is that residual obstruction sufficient to cause pulmonary hypertension is rare. The clinical course and management of this small group of patients are dealt with later in this chapter.

CLINICAL PRESENTATION

The most common symptoms and physical findings of venous thrombosis include swelling, pain, erythema, and warmth. "Classic" findings such as *Homan's sign* (calf pain with flexion of the knee and dorsiflexion of the ankle), *Moses' sign* (pain with calf compression against the tibia), or a palpable cord occur infrequently and are nonspecific.

Multiple investigations have established that the clinical diagnosis of venous thrombosis is imprecise.[43,82–84a] In patients with clinical signs and symptoms suggestive of venous thrombosis, 60% to 80% will not have the diagnosis established by objective testing. Furthermore, and even more disquieting, the majority of high-risk patients who are monitored and who develop DVT will not have signs or symptoms suggesting that diagnosis.[85] Algorithmic clinical models incorporating risk factors, symptoms, and physical signs have been demonstrated to have the ability to stratify *symptomatic* patients into risk categories, although not to a level in which clinical diagnosis, in the absence of objective testing, can be relied on exclusively to either confirm or exclude the diagnosis.[84,86] The differential diagnosis of DVT is extensive and includes cellulitis, arthritis, muscular injury or tear, neuropathy, arterial insufficiency, lymphedema, ruptured Baker's cyst, superficial thrombophlebitis, and chronic venous insufficiency.

Similarly, the diagnosis of PE cannot be confirmed or excluded solely on clinical grounds.[87–89] However, recognition of the clinical signs and symptoms associated with embolism is valuable because clinical findings and clinical suspicion represent an essential first step in the diagnostic pathway. Although a somewhat arbitrary classification because presenting symptoms and signs of embolism frequently overlap, the presentation of PE can be categorized into one of three clinical syndromes: (1) isolated dyspnea; (2) pleuritic pain or hemoptysis; and (3) circulatory collapse.[90] Among patients without prior cardiopulmonary disease in the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study, the syndrome of pleuritic pain or hemoptysis was the most common mode of presentation, occurring in approximately 60% of patients; isolated dyspnea occurred in approximately 25%, and circulatory collapse occurred in 10%.

The most common presenting symptom of acute embolism is the sudden onset of dyspnea.[89–91] In various studies, this has occurred in the majority of patients. However, it must be emphasized that in the PIOPED study,[91] dyspnea was not present in 27% of patients ultimately proven to have embolism. Pleuritic chest pain was present in 66% of patients, whereas hemoptysis (15%) was uncommon. Other symptoms occurring in less than 50% of patients included cough (37%), leg swelling (28%), and leg pain (26%). A sense of impending doom also is reported, particularly with massive embolism. Angina also can occur with massive embolism, representing, in this circumstance, right ventricular ischemia. Syncope also may be a presenting complaint in major embolic occlusion.

The most common physical finding is unexplained tachypnea (respiratory rate > 20/min). In the PIOPED study,[91] however, tachypnea was not present in approximately 30% of patients with embolism. Clinical findings noted less frequently include crackles (55%), tachycardia (30%), and an increased pulmonic component of the second heart sound (S_2; 23%). Fever may develop some hours after the event and often reaches but rarely exceeds 38.3°C. As noted previously, hemoptysis may be observed; it usually is quite modest in extent, although it persists for some days. Brisk hemoptysis is rare and almost never the initial finding. With massive embolism, there may be evidence of right ventricular overload or failure, such as a right ventricular tap along the left sternal border and an accentuated pulmonary valve closure sound. If right ventricular failure occurs, there may be narrowed or fixed splitting of S_2, an S_3, and/or an S_4, distended neck veins, and cyanosis. Careful examination of the legs may elicit evidence suggesting venous thrombosis. In the PIOPED study,[91] clinically apparent venous thrombosis was found in only 15% of patients.

Obviously, these symptoms and signs are nonspecific. In the PIOPED study,[90,91] none of the presenting symptoms was capable of discriminating between those patients with positive angiograms and those in whom the angiographic findings were negative. Also, in terms of presenting signs, only the presence of crackles, an S_4, and an increased pulmonic component of S_2 could differentiate between those with positive and negative angiograms.[90,91] Furthermore, in patients with underlying cardiopulmonary disease, the presenting symptoms and signs frequently may be obscured by elements of the underlying illness.[88] It is also important to recognize that the clinical presentation of embolism has been characterized in trials composed of symptomatic patients. Prospective studies of high-risk patients have established that asymptomatic emboli occur in some 40% or more of patients with proximal DVT.[47,87,92] It is likely that the frequency and severity of symptoms are influenced by the extent of embolic occlusion and the prior cardiopulmonary status of the patient. Small- or moderate-sized emboli may induce few or no symptoms in an otherwise normal individual. In patients with preexisting cardiopulmonary disease, symptoms are more common and severe.[92a]

Owing to the nonspecific presentation of PE, the differential diagnosis is varied and extensive, especially in hospitalized patients with coexisting cardiac or pulmonary disease. Common considerations include congestive heart failure, exacerbation of chronic lung disease, postoperative atelectasis, and viral pleurisy. Emboli presenting with fever, dyspnea, and chest radiographic abnormalities easily can be confused with a bacterial

pneumonia. The presence of fever and leukocytosis (rarely >15,000/μL) are uncommon but well-described accompaniments of VTE.[93,94]

These precautionary statements regarding clinical diagnosis are not meant to suggest that the clinical presentation of venous thrombosis or PE cannot be used as a basis for clinical decision making. However, they are meant as a reminder that the clinical presentation of VTE may often be atypical or subtle and should serve only to generate a suspicion of that diagnosis. A reliance on signs and symptoms that are considered "classic" prior to making the decision to proceed to confirmatory testing may lead to underdiagnosis and unnecessary mortality.

DIAGNOSIS OF VENOUS THROMBOSIS

The proper diagnostic approach to VTE must take into account the central fact that venous thrombosis and PE are manifestations of the same disease process: venous thrombosis representing the source of PE, and PE representing a complication of venous thrombosis.

Contrast Venography

In validating any test, there must be a "gold standard." In the case of lower extremity venous thrombosis, that standard is contrast venography (Fig. 51-1). In investigative contexts, it is a good gold standard (as indicated later, however, that often is not the case in clinical contexts). The venogram is performed according to a specific protocol described by Rabinov and Paulin in 1972.[95]

FIGURE 51-1 ■ Contrast venogram discloses a large filling defect (*arrows*) due to thrombus in the popliteal and distal superficial femoral veins. Such thrombi pose substantial embolic risk.

The most reliable criterion for the diagnosis of venous thrombosis is a constant intraluminal filling defect evident in two or more views. Other criteria such as nonvisualization of deep veins, venous collaterals, or nonconstant filling defects are less reliable. Under circumstances in which the proper protocol and interpretative criteria are utilized, contrast venography has high sensitivity and specificity. However, the study is not without shortcomings. As those who have seen many venograms recognize, the study is not easy to interpret, especially in patients with a prior history of venous thrombosis. Venous cannulation may often be difficult, especially in the presence of edema; expert interpretation is essential for accurate diagnosis; injection of contrast material with its associated allergic and nephropathic risks is necessary; venous thrombosis may be induced by the procedure itself; and the cost, invasive nature, and discomfort of the study make sequential studies impractical.

Owing to these limitations, a number of noninvasive studies capable of being performed on a sequential basis were introduced into clinical practice. At the present time, the two most commonly validated noninvasive techniques are duplex ultrasonography and impedance plethysmography (IPG). Magnetic resonance imaging (MRI) and computed tomography (CT) have proved capable of detecting thrombi, but their widespread utilization has been limited by cost, limited access, and in the case of CT, the need for contrast administration.

Duplex Ultrasonography

Since the late 1990s, duplex ultrasonography, which refers to the combination of Doppler venous flow detection and real-time B-mode imaging, has assumed a central role in the noninvasive diagnosis of symptomatic lower extremity DVT.[96] A number of criteria are used to diagnose venous thrombosis, the most reliable of which is noncompressibility of a venous segment (Fig. 51-2). Secondary, less reliable criteria include the presence of echogenic material within the venous lumen, venous distention, and loss of phasicity, response to Valsalva's maneuver, and augmentation of spontaneous flow. The absence of an echogenic luminal mass cannot be considered useful in excluding the diagnosis of venous thrombosis because acute thrombus may not demonstrate echogenicity. Multiple studies since the late 1990s have demonstrated sensitivities and specificities exceeding 95% in *symptomatic* patients with proximal venous thrombosis. Although simplified compression examinations limited to the symptomatic leg or to the common femoral and popliteal veins (rather than the entire lower extremity venous system) have been suggested, the time saved with such approaches is limited, and a number of isolated superficial femoral vein or calf-limited thrombi may be overlooked.[97–99] Asymptomatic thrombi in the contralateral leg can be detected in approximately 5% to 10% of patients presenting with symptomatic acute venous thrombosis.[100] Although the detection of asymptomatic, contralateral thrombi has little impact on the immediate management of the patient, it may have long-

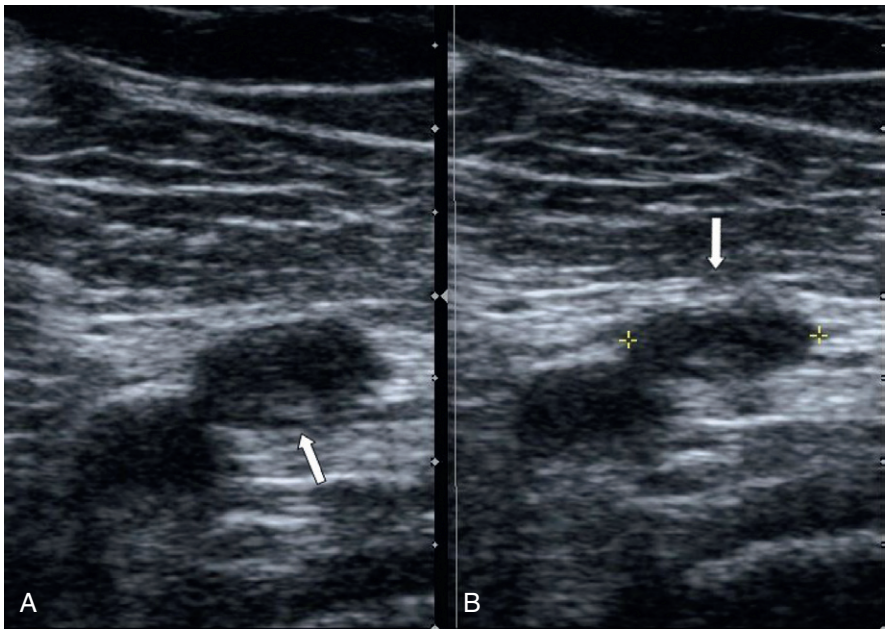

FIGURE 51-2 ■ Duplex ultrasonography demonstrates a noncompressible distal superficial femoral vein containing an echogenic mass (*arrow*), consistent with venous thrombosis.

term consequences when recurrence is suspected. A more prudent approach appears to be a complete examination extending from the inguinal ligament to the popliteal vein and examination of the contralateral extremity if thrombus is detected in the symptomatic leg.

Duplex ultrasonography is less accurate in the detection of symptomatic calf-limited thrombi (sensitivity ~70%) and in asymptomatic proximal vein thrombi (sensitivity ~50%), thereby limiting its utility as a screening study in high-risk populations.[101] When ultrasonography is negative in patients with suspected venous thrombosis, a strategy of serial testing has proved to be effective in detecting proximal extension.[102]

Impedance Plethysmography

IPG, an indirect technique that measures the rate of venous outflow, has been well standardized and carefully validated against contrast venography.[103] False-positive studies may result from conditions that diminish arterial inflow (congestive heart failure, shock, peripheral arterial disease) or that impede venous return (right ventricular failure, obstructive lung disease), thereby lowering the specificity of the technique. Early studies reported sensitivities of approximately 90% in symptomatic patients with proximal venous thrombosis.[103] Calf thrombi are detected in approximately 25%, a figure that reflects the lesser degree of venous obstruction in most (though not all) calf thrombi.

Clinical studies of IPG accuracy have raised questions regarding the ability of IPG to detect even symptomatic proximal vein thrombosis. Reported sensitivities in these studies have been in the range of 65% to 75%.[104,105] The low sensitivity of IPG in these studies may result from its use in patients with less severe symptoms because these patients are more likely to have small, nonocclusive, or distal thrombi that IPG cannot readily detect. Supporting this premise is the fact that IPG sensitivity returns to 85% to 90% when more extensive thrombi and those that have extended into the distal superficial femoral vein are evaluated. These data support the current recommendation that a single negative IPG study should not be used to exclude venous thrombosis in a symptomatic patient. However, a strategy of serial IPG testing has been demonstrated to be useful in detecting proximal extension.[102,106] Although this strategy has proved effective, confirmatory testing with duplex ultrasonography or venography may be necessary when IPG results conflict with clinical impression, especially in patients with limited cardiopulmonary reserve, in whom embolism would be tolerated poorly.[86]

The detection of possible recurrent venous thrombosis represents a diagnostic challenge for which IPG may play a role.[107] The resolution rate for IPG-documented venous thrombosis at 6 months has been found to be 85% and at 12 months to be 95%. Therefore, reversion of IPG results from normal to abnormal in a symptomatic patient with suspected recurrent venous thrombosis provides strong evidence that recurrence has occurred. However, the utility of such an approach mandates that follow-up IPG be performed and that IPG normalization has been documented in an individual patient.

Magnetic Resonance Imaging

MRI techniques for detecting venous thrombosis include spin-echo magnetic resonance, gradient-recalled-echo magnetic resonance, and magnetic resonance venography. Preliminary reports suggest that MRI is at least as sensitive and specific as duplex ultrasonography.[108,109] A potential advantage of MRI is that the entire length of the venous system, including the pelvic veins, can be evaluated. Disadvantages associated with MRI include cost and limited access as well as the expertise required to properly perform and interpret the studies.

Computed Tomography

The role of CT as a stand-alone test for venous thrombosis is limited. The sensitive and specificity of CT venography are comparable with those of ultrasonography but mandate contrast injection with its associated risks and radiation exposure. Potential advantages of CT venography include the ability to visualize the pelvic veins and vena cava. A diagnostic approach combining CT venography with computed tomography pulmonary angiography (CT-PA) may have a role in patients undergoing evaluation for PE (see later).[110,111]

Hemostaseologic Assays

The development of a rapid and accurate blood test capable of diagnosing VTE has held special appeal and has been the subject of considerable investigative interest. A number of different serologic markers have been investigated, including D-dimer, fibrin monomer, prothrombin fragment, thrombin–antithrombin III complex, fibrinopeptide B, and fibronectin. Of these, D-dimer, alone and in combination with other noninvasive studies, has been subject to the most rigorous clinical evaluation.[112,113] D-Dimer testing has proved to be highly sensitive but not specific; that is, elevated levels are present in nearly all patients with thromboembolism but also occur in a wide range of circumstances, including advancing age, pregnancy, trauma, infections, the postoperative period, inflammatory states, and malignancy. Therefore, the role of D-dimer testing is limited to one of thromboembolic exclusion. Multiple assays have been developed with sensitivities that range from 80% to almost 100%.[112,113,113a] Highly sensitive assays such as the enzyme-linked immunosorbent assay are capable of excluding thromboembolism but are associated with such a high frequency of false-positive results that their clinical utility is limited. Less sensitive assays (e.g., latex agglutination, red cell agglutination) lack the ability to exclude thromboembolism in isolation but have been used successfully in combination with either a clinical probability estimate or a noninvasive diagnostic study. Although potentially of substantial value in diagnostic pathways, the burgeoning selection of available assays, variations in sensitivity and specificity related to the type of assay, a range of discriminate values for positivity, and lack of standardization have limited generalized application of the technique due to uncertainty among clinicians regarding the predictive value of the test they are utilizing. D-Dimer testing has been utilized successfully as part of a number of different diagnostic strategies, and negative results of standardized, highly sensitive assays have proved capable of safely excluding venous thrombosis in outpatients presenting with a low or intermediate clinical likelihood of the disease.[114,115]

Clinical Prediction Rules

A major advance in the diagnostic approach to both venous thrombosis and PE has been a transition from a technique-oriented approach to one that utilizes bayesian analysis. In this strategy, the pretest probability of the disease, calculated independently of a particular test result either through empirical means or through a standardized prediction rule, is evaluated in combination with a test's likelihood ratio (derived from the sensitivity and specificity of that test) to create a posttest probability of the disease. This posttest probability can then be utilized as a basis for clinical judgment, either excluding the disease with a certain level of probability, confirming the disease with a certain level of probability, or supporting the need for additional diagnostic testing. This approach to diagnosis has proved especially useful in an era of noninvasive testing in which results are often presented as probabilities rather than as discrete answers.

Several clinical prediction rules for venous thrombosis have been developed and validated.[116] The Wells rule, initially described in 1995 and revised in 1997 to include nine clinical features, proved capable of stratifying patients with suspected venous thrombosis into three probability categories—low, moderate, and high—in which the incidence of venous thrombosis approximates 3%, 17%, and 75%, respectively.[117] By utilizing this prediction rule in combination with lower extremity ultrasonography, the diagnosis of venous thrombosis can be safely excluded in patients with a low clinical likelihood of venous thrombosis in combination with a negative lower extremity ultrasound and confirmed in patients with a high clinical probability and a positive lower extremity ultrasound. Such an approach dramatically reduces the need for contrast venography or serial lower extremity ultrasound studies.

The Wells prediction rule was subsequently revised in 2003 to include 10 clinical characteristics capable of stratifying outpatients into "clinically likely" and "clinically unlikely" categories (Table 51-2). For outpatients falling into the clinically unlikely category, DVT was reliably excluded when the result of a sensitive D-dimer assay was negative, thereby limiting the need for ultrasound evaluation.[115] The ability to exclude venous thrombosis in outpatients using a clinical prediction rule and negative results of a D-dimer assay has been confirmed in other studies.[118] It should be emphasized that clinical prediction rules constructed and validated in outpatients should be viewed critically before they are applied to an inpatient population.

DIAGNOSIS OF PULMONARY EMBOLISM

There are certain parallels between the approaches to the diagnosis of PE and DVT. Perhaps the most important parallels are that clinical evidence in isolation, although capable of raising the suspicion of the disease, cannot be relied upon to confirm or exclude the diagnosis and that the use of clinical prediction rules in combination with noninvasive testing can substantially decrease the need for invasive diagnostic testing.

Standard Laboratory Evaluation

Routine laboratory studies cannot make the diagnosis of PE. Although none has the discriminatory power to confirm the diagnosis of embolism, they do provide valuable adjunctive information and support for therapeutic interventions and may confirm the presence of an alternative diagnosis.

TABLE 51-2. Wells Clinical Model for Predicting the Pretest Probability of Deep Venous Thrombosis

Clinical Characteristic	Score
Active cancer (patient receiving treatment for cancer within the previous 6 mo or currently receiving palliative treatment)	1
Paralysis, paresis, or recent plaster immobilization of the lower extremities	1
Recently bedridden for 3 days or more, or major surgery within the previous 12 wk requiring general or regional anesthesia	1
Localized tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling at least 3 cm larger than that on the asymptomatic side (measured 10 cm below the tibial tuberosity)	1
Pitting edema confined to the symptomatic leg	1
Collateral superficial veins (nonvaricose)	1
Previously documented deep venous thrombosis	1
Alternate diagnosis at least as likely as deep venous thrombosis	−2

Score	Clinical Assessment Probability
<2 points	Unlikely
≥2 points	Likely

From Wells PS, Anderson DR, Rodger M, et al: Evaluation of D-dimer in the diagnosis of suspected deep vein thrombosis. N Engl J Med 349:1227–1235, 2003.

The majority of patients with PE have abnormal chest radiographs.[119] However, these abnormalities are usually subtle, nonspecific, and therefore nondiagnostic (Fig. 51-3). In the PIOPED study,[91] the most common radiographic abnormalities were atelectasis and pulmonary opacities. There is some confusion about the diagnostic configuration of radiographic abnormalities due to embolism. Although usually abutting a pleural surface, the opacities can be of any shape, not necessarily wedge-shaped. Although pleural effusions occur in almost half of the patients, the majority of effusions are small and involve only blunting of the costophrenic angle.[89] Findings once considered specific for embolism, such as the *Westermark sign* (focal areas of avascularity), the *Hampton hump* (pleural-based, wedge-shaped density), and the *Fleischner sign* (prominence of the central pulmonary artery), have not proved to have discriminatory value. In a patient with hypoxemia or pulmonary complaints, a normal chest radiograph may be quite useful in raising the index of suspicion of embolism and in excluding confounding diagnostic options. The major roles of chest radiography in suspected PE, therefore, are to exclude competing diagnoses and, if ventilation-perfusion (V/Q) scanning is anticipated, to evaluate the pulmonary parenchyma.

Likewise, electrocardiographic findings in PE, although occurring frequently, are diverse and nonspecific.[120] The most common abnormalities include nonspecific tachycardia, T wave inversion, and abnormalities of the ST segment. With more extensive occlusion, the electrocardiogram may reveal the more "classic" findings of right heart strain, including an "$S_1Q_3T_3$" pattern, a pseudoinfarction pattern (Qr in V_1), a complete or incomplete right bundle-branch block, or right axis deviation.[120,121] Rhythm disturbances other than sinus tachycardia are uncommon and usually confined to patients with underlying cardiac disease.[120]

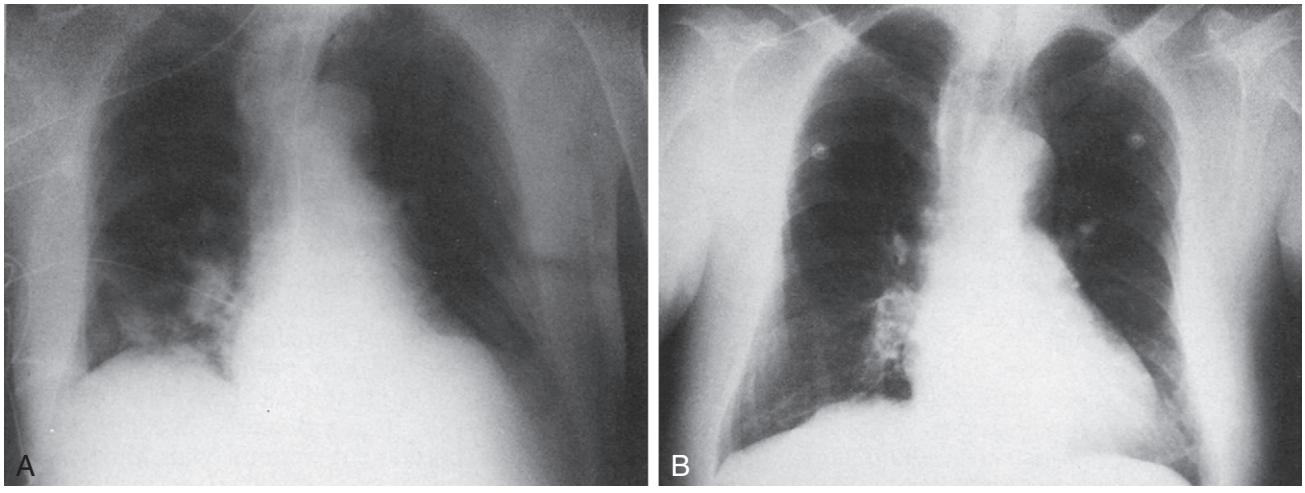

FIGURE 51-3 ■ Chest radiographs in a patient with pulmonary embolism. **A,** Opacities caused by atelectasis with edema in the right lower lobe and in the retrocardiac area in a patient with angiographically confirmed pulmonary embolus. **B,** Two weeks later, the opacities have cleared.

Arterial blood gas analysis is helpful, although not definitive.[122] Arterial hypoxemia may be present, and the more massive the obstruction, the more severe the hypoxemia is likely to be. However, many other conditions also cause hypoxemia, and embolism often does not cause hypoxemia or even a widening of the alveolar-arterial P_{O_2} difference. Hypocapnia usually is present with embolism; hypercapnia, conversely, is rare. Hypercapnia appears with embolism only in patients with marked antecedent ventilatory limitation or when such limitation has been imposed because the patient is on controlled mechanical ventilation when embolism occurs.

Echocardiography

Echocardiography may serve a valuable role in the diagnostic approach to PE. Under appropriate clinical circumstances, the detection of unexplained right ventricular volume or pressure overload might suggest the possibility of embolism and lead to confirmatory testing. A distinct echocardiographic pattern involving akinesia of the mid-free right ventricular wall with apical sparing has been described.[123,124] Properly performed *transesophageal* echocardiography has demonstrated excellent specificity for the detection of proximal emboli that involve the pulmonary trunk and the right and left main pulmonary arteries.[125] Transesophageal echocardiography also has proved valuable in the evaluation of competing diagnostic possibilities such as right ventricular infarction, endocarditis, pericardial tamponade, and aortic dissection in patients with unexplained shock and evidence of elevated central venous pressure. The overall sensitivity of *transthoracic* echocardiography in PE approximates 50%.[126] Therefore, it cannot be considered a primary diagnostic technique. Consideration can be given to its use in that subset of patients with suspected massive PE who are too ill for transportation or who have an absolute contraindication to the administration of a contrast agent.

More recently, echocardiography has been investigated along with other techniques as a means of stratifying risk in patients with embolism.[127] Short-term mortality risk in PE is strongly related to the presence of systemic hypotension at the time of diagnosis. However, systemic hypotension represents a late and potentially fatal manifestation of right ventricular dysfunction. For this reason, transthoracic echocardiography[127] and biochemical markers such as serum troponin[128] or serum brain natriuretic hormone[129] levels have been investigated as a means of evaluating right ventricular function in patients with embolism. Preliminary studies have suggested that these techniques are capable of identifying patients with a good prognosis and may identify a subset of patients who are at risk for adverse events, including death. However, it has not been conclusively established that the potential risks of a more aggressive therapeutic approach in all such patients in the latter group, the majority of whom have a satisfactory outcome when treated with conventional therapy alone, justifies the potential benefit.[130]

Ventilation-Perfusion Scanning

Despite limitations, V/Q lung scanning is a valuable step in the diagnosis of PE if it is interpreted appropriately.[91,131] First, a negative study rules out the diagnosis of PE with the same degree of certainty as a negative pulmonary angiogram (Fig. 51-4) and with a higher degree of certainty than is achieved by a negative CT scan.

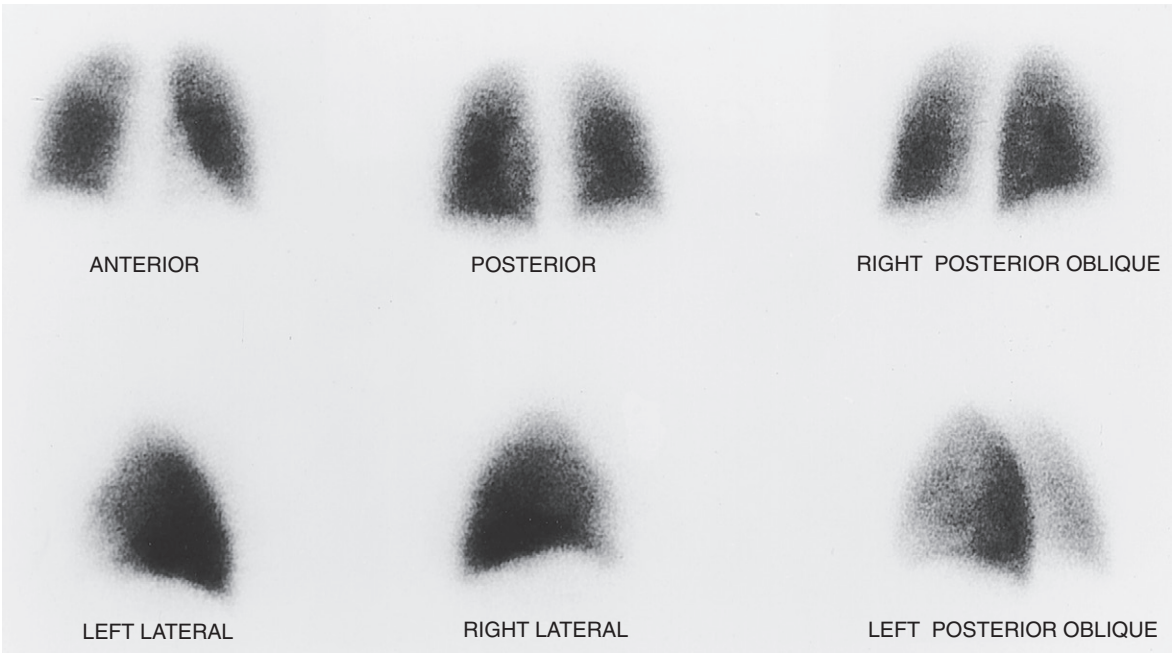

FIGURE 51-4 ■ Normal six-view lung perfusion scan. This finding is capable of excluding the diagnosis of embolism.

The results of clinical trials have been consistent in demonstrating that normal perfusion scans essentially rule out the presence of PE. This conclusion is illustrated by the results of two large prospective clinical trials comparing perfusion scanning to pulmonary angiography, the PIOPED trial[91] (performed in the United States) and the Prospective Investigative Study of Acute Pulmonary Embolism Diagnosis (PISA-PED) trial[132] (performed in Europe). In both trials, normal pulmonary perfusion scanning was a highly sensitive method for ruling out the presence of PE. The value of a normal perfusion scan was not diminished even in a subset of patients who had a high pretest probability for PE[91] or were critically ill.[133]

The significance of a normal perfusion scan disclosed by the PIOPED and PISA-PED trials is consistent with all published longitudinal studies of patients suspected of having PE, but with normal perfusion scans.[134–136] A meta-analysis of diagnostic studies for PE calculated the incidence of PE following a normal perfusion scan to be 0.3%.[137] A subsequent case series of consecutive patients followed clinically after objective testing for PE disclosed no PEs in 188 patients who had normal perfusion scans.[138] These data support the clinical guidelines of the American Thoracic Society,[139] the British Thoracic Society,[140] the American Heart Association,[141] and the European Society of Cardiology,[142] all of which recommend that a normal perfusion scan be accepted as reliably ruling out PE, with the same validity as a pulmonary angiogram.

Second, the PIOPED study[91] demonstrated that a "high-probability" study (one characterized by multiple, segmental-sized, mismatched defects) is associated with embolism in approximately 87% of patients; when coupled with a high clinical probability of embolism, the positive predictive value increased to 96% (Fig. 51-5).

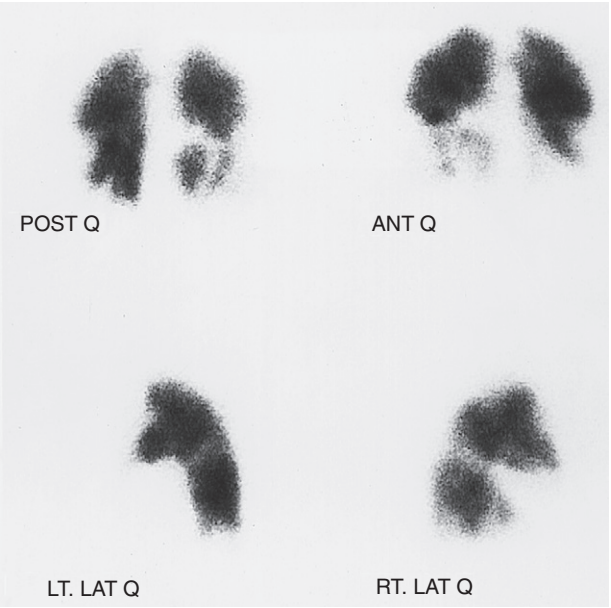

FIGURE 51-5 ■ Lung perfusion (Q) scan shows major segmental and lobar defects bilaterally. Ventilation scan and chest radiograph were normal. This pattern is strongly associated with the presence of embolism.

However, the PIOPED data also provided several pieces of disquieting information: (1) the overwhelming majority of patients with suspected embolism did not have scan findings that fell into a high-probability or normal category, the only categories that can be considered definitive; (2) the majority of patients with embolism did not have a high-probability scan finding; (3) the overwhelming majority of patients without embolism did not have a normal scan; and (4) a substantial and clinically significant percentage of patients with scan findings interpreted as intermediate probability (33%) and low probability (16%) were subsequently demonstrated to have angiographic evidence of embolism.[91] It is essential that clinicians recognize that the concept of a low-probability scan is misleading and potentially dangerous because of the frequency of PE in patients exhibiting this scan pattern.[143]

In order to improve perfusion scan specificity, traditional interpretive criteria, including the PIOPED criteria, rely on the number and size of the perfusion defects as well as on the results of a concurrent ventilation image. The intended basis for doing so is to differentiate pulmonary vascular obstruction ("mismatched" defects) from primary parenchymal disorders that result in compensatory pulmonary vasoconstriction ("matched" defects). The PISA-PED investigators[144] utilized a fundamentally different interpretive scheme that relied on the shape of the perfusion defects regardless of their number or size or their association with ventilation findings. The results of this study suggest that embolism can be diagnosed accurately and the need for angiography limited by perfusion results combined with an assessment of clinical likelihood in the absence of ventilation imaging. An analysis of a subset of patients from the PIOPED study came to a similar conclusion.[145]

The diagnostic approach to PE in patients with underlying chronic obstructive pulmonary disease (COPD) remains especially problematic because the presentation of PE in this population may closely mimic an exacerbation of their underlying disease. Unfortunately, the value of V/Q scanning in this population is even more limited than that in the general population in that an even higher proportion of scans fall into an indeterminate category.[146] However, among the more than half of COPD patients who had high-probability, normal or near-normal scans, both the positive predictive value and the negative predictive value were equivalent to that in the general population.

Spiral (Helical) Computed Tomography

CT has represented a major advance in PE diagnosis. Unlike V/Q scanning, it provides the ability to directly visualize emboli as well as to detect parenchymal abnormalities that may support the diagnosis of embolism or provide an alternative basis for the patient's complaints (Fig. 51-6). The reported sensitivity of helical CT scanning for embolism has ranged from 57% to 100%, with a specificity ranging from 78% to 100%.[147] Factors responsible for this wide divergence relate to the proximal extent of vascular obstruction that can be detected and,

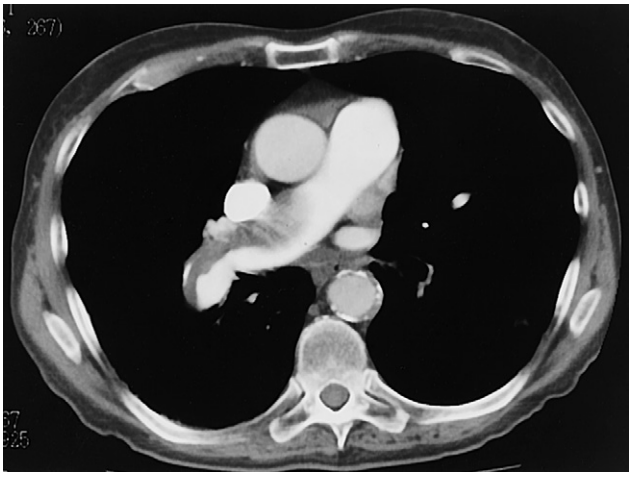

FIGURE 51-6 ■ Chest computed tomography scan demonstrates extensive embolization involving the right main, upper lobe, and lower lobe pulmonary arteries.

in part, to advances in CT technology that allow higher resolution, dramatically faster scanning times, more peripheral visualization, and less motion artifact than that provided by earlier generation scanners. Sensitivity and specificity of CT scanning for emboli involving the main and lobar pulmonary arteries exceeds 95%. Vascular involvement confined to segmental or subsegmental pulmonary vessels is associated with a decline in both sensitivity and specificity. In one series, the sensitivity of CT scanning for subsegmental arteries reported by two readers ranged between 71% and 84% even after nonevaluable scans were excluded.[148] Isolated involvement of the subsegmental pulmonary arteries is not unusual and in various series has been demonstrated to occur in up to 30% of patients.[149,150] These findings suggest that filling defects consistent with embolism involving the main or lobar pulmonary arteries can be considered diagnostic of embolism. Defects involving the segmental and subsegmental arteries can be considered suggestive of embolism but should be supported by additional objective data. The absence of detectable filling defects reduces the likelihood of embolism but appears incapable of excluding the possibility with the same degree of certainty as a negative V/Q scan.

Although CT-PA scanning has increased the number of cases of acute PE that are diagnosed,[151] it has inherent limitations. The technique requires infusion of intravascular iodinated contrast agents and the most common serious complications of testing arise from their use. During CT scanning, the peripherally infused dye fills the lumen of the pulmonary arteries, hopefully at the exact time that the chest is imaged. Emboli are detected as focal defects in pulmonary artery filling. When performed and interpreted expertly, CT-PA scans are capable of identifying emboli in the segmental or larger pulmonary arteries (as does V/Q scanning[152,153]). However, certain areas, such as the hila, are prone to false positives. Reading emboli in these areas should be done with special care. Perhaps more importantly, CT scans have a particular weakness in imaging emboli in subsegmental pulmonary arteries. The smaller clots account for about 20% to 30% of PEs[149,154] and represent the very cases in which V/Q scans are the most limited.[91]

The National Institutes of Health (NIH)–funded "Prospective Investigation of Pulmonary Embolism Diagnosis—2" (PIOPED-2) study highlighted the strengths and limitations of CT-PA.[111] Prior to enrolling the study population of 1090 patients, the investigators excluded 1350 patients because their abnormal creatinine levels reflected some degree of renal dysfunction, which would have increased the risk involved with the administration of contrast dye. An additional 272 patients were excluded because of a history of contrast dye allergy. During the performance of the trial, 6% of the scans were excluded because the images were of poor quality. Even after the inconclusive scans were disregarded, the sensitivity of the thoracic CT scans was only 83%.

The PIOPED-2 investigators also excluded another 976 patients from the study because they had history of long-term anticoagulation therapy. This highlights another weakness of CT-PA in that luminal filling defects remain long after an acute pulmonary embolic event, so the test cannot differentiate between chronic and acute VTE. This is clinically relevant because the rate of recurrence is about 7% during the half-year after an acute PE and about 3%/yr for the subsequent 5 years.[155]

Finally, CT-PA can expose patients to clinically significant doses of radiation.[156,157] Current clinical protocols deliver a radiation dose to the female breast ranging from 4 to 6 cGy per scan.[157] This dose is especially concerning because most CT-PA evaluations are negative, even when the criteria for scanning are rigorously followed.[111,131] In addition, because PE has a relatively high rate of recurrence, patients are commonly reimaged after their first occurrence. Younger women, who have a known elevated incidence of PE, are particularly at risk from radiation damage to breast and lungs.

From a clinical (outcomes-based) perspective, CT scanning and V/Q scanning have many similarities, and either can be used to exclude clinically significant PE in stable patients under many circumstances. Outcome studies have demonstrated that withholding anticoagulant therapy in patients with a negative CT scan coupled with a negative lower extremity ultrasound study appears to be a safe strategy except in those patients who present with a high clinical likelihood of embolism.[158,159] Similarly, withholding anticoagulation from patients with "non–high-probability" findings on V/Q scan coupled with negative lower extremity studies is safe, except in those with inadequate cardiopulmonary reserve.[160,161] A recent randomized, controlled trial comparing CT and V/Q for the management of suspected PE found the two studies to be comparable for excluding clinically significant PE.[131] Specifically, the study disclosed no difference in outcome among patients in whom anticoagulation was withheld based on the combination of a negative CT and negative leg studies compared with patients in whom anticoagulation was withheld based on the combination of a "non–high-probability" V/Q scan and negative leg studies or on a negative V/Q scan (without the need for leg studies). However, it should be emphasized

that the outcome studies were done on relatively stable patients. Those with instability or poor cardiopulmonary reserve may required a higher degree of diagnostic certainty in order to safely rule out PE.[161]

Lower Extremity Venous Evaluation

Because the majority of PEs arise from the deep veins of the lower extremities, the detection of lower extremity proximal vein thrombosis in a patient suspected of embolism, although not confirming that embolism has occurred, is strongly suggestive of that diagnosis and has an equivalent therapeutic implication. Positive ultrasound findings without symptoms or signs referable to the lower extremities should be interpreted judiciously, especially in patients with low pretest probability of PE, because even a highly specific test can yield false-positive results in some circumstances.[162] Lower extremity ultrasonography has a very low yield in patients without leg symptoms or risk factors strongly suggestive of thromboembolism.[163,164] Conversely, it is typically positive in only about 10% to 20% of patients with suspected embolism and in 50% of patients with proven embolism.[165] Therefore, a negative ultrasound finding cannot exclude the diagnosis. CT venography as an adjunct to helical CT scanning appears to be capable of detecting femoropopliteal thrombosis with the same accuracy as duplex ultrasonography while also detecting pelvic and abdominal thrombosis.[110,111] However, the combined CT technique is technically complicated[111] and significantly increases the amount of pelvic radiation exposure to the patient.[156,157,166]

D-Dimer Testing

The utility of D-dimer testing in PE diagnostic pathways is limited by the same shortfalls as those encountered in venous thrombosis pathways: that is, a low specificity that makes it most useful as an exclusionary technique in outpatients and a lack of standardization. However, studies have demonstrated that a normal D-dimer result can safely exclude embolism in patients with a low clinical probability of disease.[167–169] Although preliminary data suggest that a highly sensitive assay is capable of excluding embolism at all levels of clinical probability, these results require confirmation.[169]

Pulmonary Angiography

The studies reviewed to date are capable of excluding or confirming the diagnosis of embolism in the majority of patients with suspected embolism. Angiography should be considered in patients in whom the diagnosis has not been confirmed or excluded using noninvasive techniques and when it is considered unsafe to withhold anticoagulation; when cardiopulmonary instability is present; and when the results of diagnostic testing are at such odds with the clinical impression as to warrant the risk of the procedure. Like contrast venography, however, pulmonary angiography has a number of limitations as a gold standard. First, the procedure is invasive and not without risk, especially in patients with acute right ventricular failure. However, experience has demonstrated that the perception of risk associated with angiography outweighs the actual risk.[170,171] Pulmonary angiography can be performed quite safely if certain safeguards are observed and experienced personnel are involved.

Even though the risk of angiography should be nominal, the procedure has other limitations. One is accessibility: Angiography must be performed in a special facility to which the patient must be transported. In some institutions, the logistical problems involved are modest; in others, they are substantial. The other limitation is interpretation. The interpretation of pulmonary angiograms is heavily influenced by three factors: the location of the thromboembolic obstruction, the quality of the images, and the experience of the interpreters. Only two angiographic findings are diagnostic of acute embolism: the filling defect and abrupt cutoff of a vessel (Fig. 51-7). Technical adequacy of the angiogram is critical to accurate identification of both. Flow artifacts can falsely suggest a filling defect. It is essential that good vessel opacification be obtained and that the filling defects be identified as real on a sequence of images.

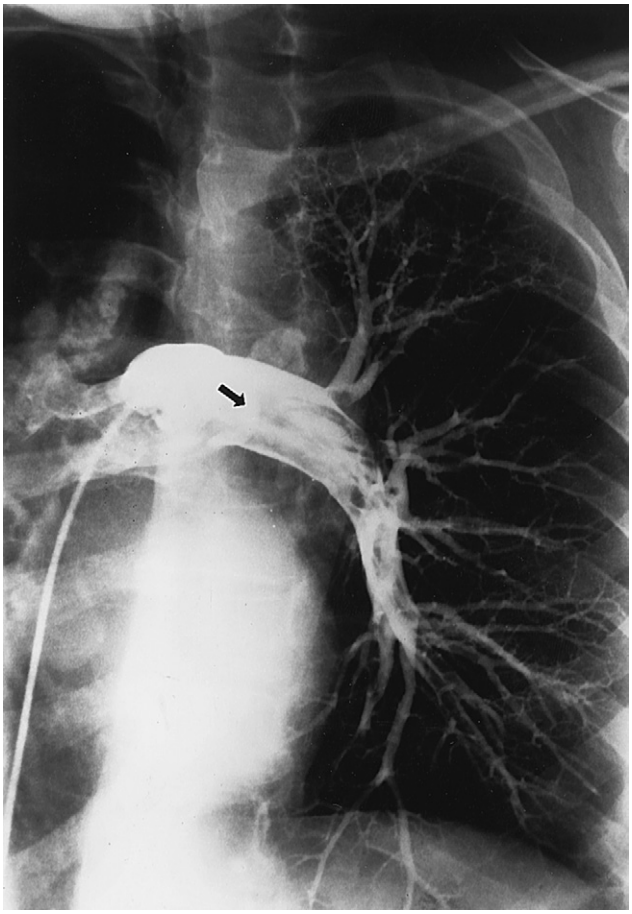

FIGURE 51-7 ■ Left-sided pulmonary angiogram shows extensive filling defects within the left pulmonary artery (*arrow*) and the upper lobe, lingula, and lower lobe arteries, consistent with the diagnosis of pulmonary embolism.

Although concern about risk should not deter pulmonary angiography, there are noteworthy limitations on its performance and value. Still, it is a rather odd commentary on medical thinking that few would advise against performance of a coronary angiogram in a patient with coronary thrombosis or ischemia because of risk, yet the question of risk often deters pulmonary angiography in a patient in whom embolism is suspected. Given that the case-fatality rate of undiagnosed and untreated embolism exceeds that of myocardial infarction, it is not clear why this disparity exists; and it should not exist, given equal competence in the performance and interpretation of these two procedures.

Clinical Prediction Rules

A major advance in the diagnostic approach to embolism, as it has been in the diagnostic approach to venous thrombosis, has been the development of clinical prediction rules. A number of standardized prediction rules have been evaluated and published that range widely in their complexity. Simple, standardized prediction rules (Table 51-3) involve information that can be easily acquired even in an outpatient setting or the emergency room.[167,172] Complicated prediction rules involve an increased number of clinical variables and require expert interpretation of radiographic and electrocardiographic data.[173,174] Although probability assessments, whether empirical or standardized, are incapable of confirming or excluding the presence of PE with a clinically acceptable degree of certainty, they have proved capable of stratifying patients into categories of likelihood. By combining this derived clinical probability with the results of a noninvasive diagnostic technique, diagnostic accuracy in terms of both the confirmation and the exclusion of embolism can be increased well beyond that achieved by the use of either clinical probability or the noninvasive diagnostic technique alone and can substantially limit the number of patients who require pulmonary angiography.

TABLE 51-3. Wells Clinical Model for Predicting the Pretest Probability of Pulmonary Embolism

Variable	Points Assigned
Clinical signs and symptoms of deep venous thrombosis	3.0
An alternative diagnosis is less likely than pulmonary embolism	3.0
Heart rate > 100 beats/min	1.5
Immobilization or surgery in the previous 4 wk	1.5
Previous deep venous thrombosis or pulmonary embolism	1.5
Hemoptysis	1.0
Malignancy (on treatment, treated in the last 6 mo, or palliative)	1.0

Score	Clinical Assessment Probability
<2 points	Low probability
2–6 points	Intermediate probability
>6 points	High probability

From Kearon C: Diagnosis of pulmonary embolism. CMAJ 168:183–194, 2003.

In summary, an almost bewildering array of diagnostic techniques is available for patients with suspected VTE. What the clinician at the bedside must understand and accept is that multiple approaches are possible and that a stepwise diagnostic strategy, rather than any single diagnostic technique, may be necessary to confirm or exclude the diagnosis (Fig. 51-8). Furthermore, the clinician must understand that these steps are essential and potentially lifesaving. Withholding anticoagulation in a patient who has suffered an embolic event places that patient at risk for recurrent, potentially lethal events; instituting empirical anticoagulant therapy in a patient who has not suffered an embolic event will involve unnecessary hospitalization and therapy, places the patient at risk for hemorrhagic complications, and establishes a "preexisting" condition that may adversely affect future health care costs. Finally, the clinician must understand that the use of a clinical prediction rule derived from an outpatient population might have a very different predictive value when applied to an inpatient, less healthy population.

Many strategies to confirm or exclude the diagnosis of PE have been investigated. Because the initiating point for the diagnostic pathway begins with clinical suspicion, the following discussion centers about that approach. Also, given substantial variations in practice that currently exist, strategies that incorporate V/Q scanning or helical CT as the initial objective diagnostic technique are considered.

In patients in whom the clinical suspicion of embolism is considered high (>70% likelihood), a positive helical CT scan or a high-probability V/Q scan result would be considered diagnostic of embolism with greater than 95% certainty, whereas a negative perfusion scan would exclude the diagnosis. In all other patients (non–high-probability V/Q scan or negative CT scan), lower extremity evaluation may be undertaken. A positive study would confirm the diagnosis. In the remaining patients, several strategies are possible. Serial lower extremity evaluations could be performed. Although not confirming the absence of embolism, negative results would suggest that the likelihood of recurrence is small. Alternatively, pulmonary angiography could be performed. This latter approach is especially applicable to unstable patients with preexisting cardiopulmonary disease, in whom the consequences of recurrence could be catastrophic.

The predictive value of CT varies substantially when clinical assessment is taken into account, with the major variance occurring when there is discordance between the clinical assessment and the CT finding. Both the positive predictive value in patients with a low clinical probability and the negative predictive value in those with a high clinical probability are in the range of 60%. For patients in whom the diagnosis remains uncertain,

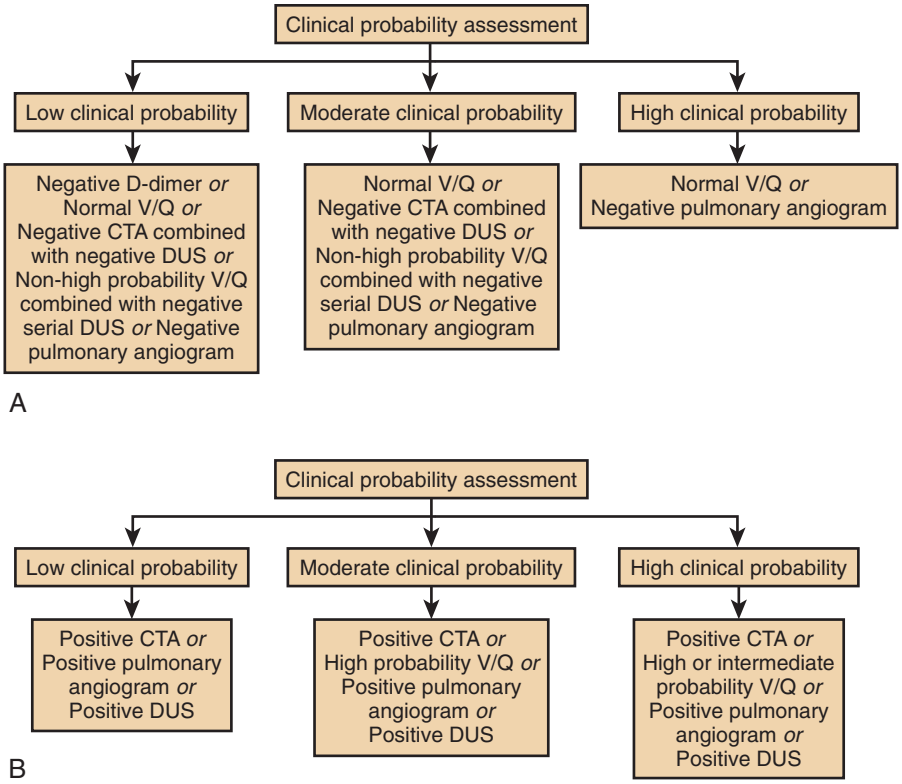

FIGURE 51-8 ■ Diagnostic strategies capable of excluding (**A**) and confirming (**B**) the diagnosis of pulmonary embolism. CTA, spiral computed tomographic angiography; DUS, Doppler ultrasound; V/Q, ventilation-perfusion scan.

lower extremity evaluation may be undertaken. A positive study would confirm the diagnosis. For those in whom CT scanning represented the initial diagnostic procedure, outcome data have demonstrated that withholding anticoagulant therapy is safe when the clinical probability of embolism is considered low and results of CT scanning and lower extremity ultrasonography are negative. For those in whom V/Q scanning represented the initial diagnostic procedure, a low- or intermediate-probability scan result in combination with a negative lower extremity ultrasound study is sufficient to withhold anticoagulation; a high-probability scan result should be followed by additional diagnostic testing (pulmonary angiography, CT, or sequential lower extremity testing). The utility of D-dimer determinations in hospitalized patients is limited by a lack of specificity. However, a negative D-dimer result has been proved capable of safely excluding embolism in outpatients with a low probability of embolism.

In patients in whom the clinical suspicion of embolism is considered moderate (~10%–70% likelihood), a high-probability V/Q scan or a positive helical CT scan would be considered diagnostic of embolism, whereas a negative perfusion scan would exclude the diagnosis. In the remaining patients, lower extremity evaluation should be undertaken. For those in whom CT scanning represented the initial diagnostic procedure, outcome data have demonstrated that withholding anticoagulant therapy is safe when the clinical probability of embolism is considered moderate and results of CT scanning and lower extremity ultrasonography are negative. In some cases in which V/Q scanning represented the initial diagnostic procedure, a non–high-probability scan should be followed by additional diagnostic testing.

Special circumstances do exist that may guide the diagnostic approach. In the setting of severe, preexisting pulmonary parenchymal or airway disease, V/Q scanning is of limited utility given the high likelihood that the scan result will be nondiagnostic. Although the positive predictive value of a high-probability scan and the negative predictive value of a normal or near-normal scan in patients with underlying lung disease are similar to that in the general population, the proportion of patients whose scans fall into a nondiagnostic category is increased substantially.[146] Under this circumstance, an approach utilizing helical CT scanning as the initial objective diagnostic study would be appropriate. The amount of contrast required for CT scanning (100–150 mL) poses a substantial risk of radiocontrast-induced nephropathy for patients with preexisting renal insufficiency, especially when it is associated with diabetes mellitus.[175] In such patients, a strategy utilizing duplex ultrasonography and V/Q scanning would appear prudent, followed by selective conventional pulmonary angiography should the noninvasive techniques not yield a definitive diagnosis. VTE is a leading cause of maternal mortality[176]; however, given the potential risk of radiation exposure to the fetus,[166] a diagnostic approach that limits that exposure is warranted. Therefore, duplex ultrasonography is an appropriate initial diagnostic approach. If ultrasonography is negative, the diagnostic evaluation should proceed as previously described based

on the clinical assessment probability and using V/Q scanning as the next diagnostic technique. Helical CT scanning has not been recommended as a diagnostic choice owing to the risk of fetal radiation exposure, although some data would suggest that fetal radiation exposure with CT scanning is comparable or even lower than with V/Q scanning.[157,177]

PREVENTION OF VENOUS THROMBOEMBOLISM

One of the most striking changes in the field of VTE since the late 1980s has been an emphasis on prevention. This emphasis is totally appropriate and, indeed, should be the cornerstone of modern management. It is clear that if the goal is to prevent PE, the only effective approach is to prevent DVT. The basic information and tools required for developing a prophylactic strategy are now available.

To develop such a strategy, three fundamentals must be in place: (1) the population at risk must be identified; (2) the duration of the increased thromboembolic risk must be ascertained; and (3) effective, low-risk prophylactic options must be available. Populations at risk of DVT, and therefore of PE, have been identified; and such risk can, to a considerable extent, be quantified as high, moderate, or low. Furthermore, a variety of effective and safe prophylactic approaches are available. It should be emphasized that the trend toward earlier hospital discharge has been accompanied by an increased incidence of postdischarge VTE. Thromboembolic risk does not necessarily end at the time of hospital discharge or transfer to a lower level of care.[178] In patients with an ongoing predisposition to thrombosis at the time of discharge from an acute inpatient setting, prophylaxis should be continued until the risk for VTE has resolved.

The objective of the prophylactic strategy is to identify the degree of thromboembolic risk in the individual patient and to match the intensity of prophylaxis to that degree of risk. Although a variety of prophylactic approaches have been investigated and utilized, four approaches have proved effective: low-dose unfractionated heparin, low-molecular-weight heparin (LMWH), intermittent pneumatic compression devices, and warfarin.

Low-Dose Unfractionated Heparin

Low-dose heparin has been widely studied as a prophylactic modality. Heparin, given subcutaneously in a dose of 5000 units every 8 or 12 hours, is begun as soon as the risk of DVT is evident and is continued until that risk has abated. This regimen has been shown to be effective in reducing the incidence of DVT, PE, and fatal PE in patients at low to moderate risk, such as those undergoing surgical procedures requiring general anesthesia for 30 minutes or longer and with medical conditions requiring bed rest for several days.[179] However, this form of prophylaxis has not been optimally effective in patients whose thromboembolic risk is higher, such as those with hip fracture or hip replacement, those undergoing prostate surgery, and patients suffering major traumatic injuries.[180] Furthermore, although the bleeding risk of low-dose heparin is nominal in most patients, there are groups of patients in whom heparin administration is contraindicated, for example, those with active bleeding, hemorrhagic diathesis, and hemorrhagic stroke and those undergoing neurologic surgery. Patients to be placed on prophylactic heparin should be screened with an initial platelet count, partial thromboplastin time, and prothrombin time. During therapy, however, monitoring of coagulation tests is not useful, because such tests do not reflect the safety or efficacy of the regimen. Monitoring of platelet counts on at least a weekly basis would appear to be a prudent option.

Low-Molecular-Weight Heparin

LMWH preparations represent another prophylactic option. In trials that have been performed comparing the prophylactic efficacy of LMWH with unfractionated heparin in general surgical and medical populations, LMWH has not proved superior to unfractionated heparin, although a trend toward increasing bleeding complications associated with unfractionated heparin may exist.[181] However, this may simply represent a dose effect. LMWH preparations appear more effective than unfractionated heparin as prophylactic agents in several high-risk groups: patients undergoing hip or knee replacement, patients with spinal cord injury, patients with ischemic strokes, and patients with multiple trauma.[180,181]

Pneumatic Compression Devices

Another extensively evaluated and effective prophylactic approach in low- to moderate-risk patients is the use of mechanical leg compressive devices.[180] These devices periodically (e.g., once or twice per minute) compress the leg by an air-inflatable bladder. A variety of devices are available: thigh-length systems that provide both thigh and calf compression, calf-compressive devices, single-pulse systems, and sequential compression systems. A variety of questions remain unanswered about pneumatic compression devices. For example, it is not known whether the various compressive devices differ in efficacy. It is also unknown whether efficacy depends on strict (24/7) compliance with this intervention during the period of increased thromboembolic risk.[182,183] In addition, it is unclear whether pneumatic compression devices are as effective as unfractionated heparin in general medical, surgical, gynecologic, and urologic patients, and their use is indicated in patients in whom pharmacologic methods of prophylaxis are contraindicated.

Sodium Warfarin

Warfarin and other "prothrombinopenic" drugs, started like heparin at the onset of high risk (e.g., preoperatively), also have been shown to be effective and safe.[180]

Unfortunately, use of "prothrombinopenic" agents has not gained wide favor as a prophylactic approach. The use of warfarin requires careful monitoring, and there is a perception among physicians that the bleeding risk associated with its use is greater than that reported in the literature. In patients undergoing hip replacement, warfarin has proved effective and has achieved general acceptance. Two regimens are widely used: small doses (1 to 2 mg) given daily for several days before surgery, with dose escalation to therapeutic range, or initiation after surgery.[184] LMWH preparations appear superior to warfarin, albeit at higher bleeding risk, in patients undergoing knee or hip replacement, with efficacy related, in part, to timing of administration.[185] It also has become evident that increased thromboembolic risk in patients undergoing hip or knee replacement can extend for 4 to 6 weeks after hospital discharge.[186] A strategy of extended prophylaxis may be appropriate.[187]

Miscellaneous Agents

Fondaparinux, a synthetic pentasaccharide that selectively inhibits activated factor X (factor Xa), has been demonstrated in several trials to be effective in the prevention of VTE in patients undergoing lower extremity orthopedic surgery.[180,188,189]

There is one option available to prevent PE in patients at high risk who cannot be provided pharmacologic or mechanical prophylaxis. Patients with extensive trauma often fall into this category, particularly those with pelvic or lower extremity fractures and internal or intracranial bleeding. In this group, prophylactic placement of an inferior vena cava filter in selected patients provides protection against otherwise nonpreventable emboli.[190]

In summary, given the effective options available, few patients at risk for venous thrombosis cannot be protected. However, despite this awareness, surveys have demonstrated that prophylaxis is underused in populations at risk.[191,192] A number of different rationales have been proposed to account for this lack of compliance. The overstated perception of bleeding complications associated with pharmacologic methods of prophylaxis appears to remain a deterrent. Furthermore, fatal PE is uncommon in any individual physician's experience, thereby diminishing the perception of risk. Finally, the issue of prophylaxis is often subordinated to the compelling demands of the patient's admitting diagnosis and therapy. Whatever the reason, increased use of prophylaxis must occur if a substantial impact is to be made on the considerable and often unnecessary morbidity and mortality associated with PE. Not only must prophylaxis be applied, it must be applied in a manner proportionate to the patient's risk of thromboembolism.

MANAGEMENT OF VENOUS THROMBOEMBOLISM

The basic approaches to management are defined chiefly by what is known, as already described, about the pathogenesis, pathophysiology, and natural history of venous thrombosis and PE.

Heparin

Heparin, both unfractionated and low molecular weight, remains the mainstay of therapy for venous thrombosis and for PE not associated with hemodynamic compromise.[193] With a strong suspicion of embolism based on clinical findings and laboratory tests, heparin therapy should be instituted immediately, without awaiting diagnostic confirmation, unless anticoagulation places the patient at significant risk.

Data suggest that physician practices in the administration of unfractionated heparin often result in levels of anticoagulation that fall below those currently recommended in the literature.[194] To overcome these problems, standardized protocols for heparin administration and monitoring have been recommended. A number of different intravenous heparin dosing schemes have been published, all of which have demonstrated the potential to reach a therapeutic threshold more rapidly than a nonstandardized approach.[195] The most widely utilized of these is a weight-based system that includes an 80 unit/kg intravenous bolus of heparin followed by an 18 unit/kg/hr infusion.[196] Whatever regimen is used, an activated partial thromboplastin time (aPTT) is generally obtained 6 hours after the bolus dose, 6 hours after each prescribed dose adjustment, and then on a daily basis for the duration of therapy. Because maintenance of the aPTT within a rigidly defined range does not appear to increase the efficacy or safety of the drug, frequent dosage adjustments are not necessary once the dose has been stabilized within a therapeutic range. This therapeutic range of aPTT, which corresponds to heparin levels of 0.2 to 0.4 unit/mL by protamine sulfate titration or 0.3 to 0.7 unit/mL by anti–factor Xa assay, may vary substantially depending on the sensitivity of the reagent utilized and among coagulometers.[197] Given the variance in aPTT values possible with different analyzers and reagents, individual institutional validation should be performed to define a therapeutic aPTT value. It also should be recognized that heparin requirements tend to decrease during the course of therapy, resulting in an increase in the level of the aPTT. For patients with heparin resistance (defined as the need for >40,000 units/day), monitoring heparin with an anti–factor Xa assay appears safe and effective and results in less escalation of the heparin dose than monitoring with the aPTT.[198]

Supporting the importance of using adequate heparin doses are data that suggest *supratherapeutic* aPTT values are not associated with an increased risk of clinically important bleeding complications.[199] There is no direct evidence that the absolute dose of heparin or the level of the aPTT can predict the likelihood of bleeding. Instead, bleeding during heparin therapy appears to be related to the presence of concurrent illness such as renal disease, a history of heavy alcohol consumption, aspirin use, and prior surgical procedures or peptic ulcer disease. Failure to treat patients early with sufficient doses appears to have long-term as well as short-term

implications for thromboembolic recurrence. It is somewhat controversial, however, whether the aPTT level itself, independent of the heparin dose, is associated with higher recurrence rates[200] or whether it is strictly a matter of insufficient dosing itself.[201]

Subcutaneous LMWHs are widely used for the treatment of VTE because of their high bioavailability and longer half-life, which allows the strategy of weight-adjusted dosing once or twice daily, without the need for adjustment by aPTT monitoring.[193,202] However, it has been recently established that the same strategy may also be applicable to subcutaneous (unfractionated) heparin as well, administered in high doses. An approach utilizing a fixed dose of subcutaneous unfractionated heparin, administered as an initial dose of 333 U/kg followed by a dose of 250 U/kg every 12 hours, has been demonstrated to be as safe and effective as LMWH in patients presenting with venous thrombosis and PE.[203] Clinicians must recognize that the administration of LMWH may not be preferable under certain clinical circumstances. Standardized dosing is problematic in patients at the extremes of body weight; owing to renal clearance of the drug, dose adjustments and monitoring with anti–factor Xa levels are necessary in patients with renal insufficiency; the anticoagulant effect of the drug cannot be monitored easily; populations exist (e.g., patients at high bleeding risk) in which a longer drug half-life is not a desirable effect; the ability of protamine sulfate to reverse the anticoagulant effect remains uncertain; and drug costs are substantially higher than with unfractionated heparin.

Clinical trials have demonstrated that the safety and efficacy of LMWH preparations are comparable with those of unfractionated heparin in patients with venous thrombosis.[204] Trials have also demonstrated that most patients with acute venous thrombosis can be treated safely on an outpatient basis with LMWH and that outpatient therapy can reduce total medical expenditure.[205] However, not all patients with venous thrombosis can or should be treated in an outpatient setting. Approximately 50% of patients are ineligible for outpatient therapy owing to such factors as major bleeding risk, compliance problems, renal failure, significant comorbid disease, inadequate cardiopulmonary reserve, and inaccessibility for follow-up. Furthermore, embolism can occur during the early aspects of therapy in patients treated with both unfractionated and LMWH preparations. Although this circumstance would not be diminished in an inpatient setting, the potential consequences of recurrence, especially in patients with preexisting cardiopulmonary disease, might be more promptly detected and managed in this setting. Outpatient therapy would be most feasible in patients with submassive embolism, preserved right ventricular function, and a low risk of bleeding. The definitive answer to this question will likely parallel investigations evaluating the role of risk stratification approaches in PE. Even in patients who require initial inpatient management, however, the duration of hospitalization can be decreased considerably by a quick transition to outpatient therapy.

In terms of duration of heparin therapy, studies have shown that utilizing a 5-day course of therapy in patients with proximal venous thrombosis is associated with a recurrence rate identical to that of a 10-day course.[206] This assumes, of course, that warfarin is started early and is in a therapeutic range for 2 consecutive days before heparin is discontinued, a target often difficult to achieve. It is likely that a short course of heparin therapy would be similarly effective in patients with uncomplicated PE. However, a longer course of therapy is advisable in patients with major PE or extensive iliofemoral venous thrombosis.

The major complications of unfractionated heparin and LMWH are bleeding and the development of thrombocytopenia.[207] There are no predisposing factors to heparin-associated thrombocytopenia other than a history of a previous exposure, and it appears to occur with the same frequency with either (unfractionated) heparin or LMWH.[208] Two types of thrombocytopenia are associated with heparin administration: an early-onset (1–5 days), non–immune-mediated reduction in platelet count (type I) believed to be secondary to a direct agglutinating effect of heparin on platelets; and a late-onset (≥4 days), immune-mediated thrombocytopenia (type II) that may be associated with venous and arterial thrombosis. Immune-mediated thrombocytopenia can occur within a day of initiating therapy in patients who have been exposed to the drug within the prior 100 days.[209] The incidence of thrombosis with heparin-associated thrombocytopenia appears to be low, but when it occurs, it is associated with considerable morbidity and mortality. Therefore, heparin should be immediately withdrawn if this diagnosis is suspected. If heparin-associated thrombocytopenia type II is confirmed by either a functional assay or an immunoassay, withdrawal of heparin alone may be associated with an adverse outcome.[210] A number of options exist, including the use of direct thrombin inhibitors (lepirudin or argatroban), which do not react with heparin antibodies, or danaparoid, which appears to have a low rate of in vivo cross reactivity with heparin.[211,212] Cross reactivity between unfractionated heparin and LMWH is relatively common, and these drugs should be avoided.[213]

Inferior Vena Cava Filters

Scientific evidence supporting the use of inferior vena cava filters (Fig. 51-9) is limited.[214,215] Established indications for filter placement in the therapy of VTE include (1) protection against PE in patients with acute VTE in whom conventional anticoagulation is contraindicated (recent surgery, hemorrhagic cerebrovascular accident, active bleeding, heparin-associated thrombocytopenia, etc.); (2) protection against PE in patients with acute VTE in whom conventional anticoagulation has proved ineffective; and, (3) protection of an already compromised pulmonary vascular bed from further thromboembolic risk (massive PE, chronic thromboembolic pulmonary hypertension).

Mortality from filter placement appears to be quite low regardless of what filter is used.[214] Nonfatal compli-

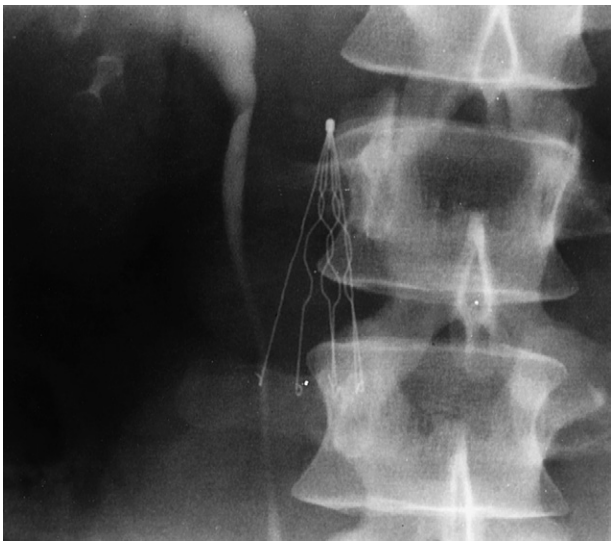

FIGURE 51-9 ■ Inferior vena cava filter in place below the renal veins.

cations of inferior vena cava filters that occur with increased frequency include (1) complications relating to the insertion process; (2) venous thrombosis at the site of insertion; (3) filter migration; (4) filter erosion through the inferior vena cava wall; and (5) inferior vena cava obstruction. The majority of clinically important complications appear to involve venous thrombosis at the insertion site and inferior vena cava obstruction.[215]

Filter placement should not be considered as primary therapy for VTE unless an absolute contraindication to anticoagulation exists. Although protecting the pulmonary vascular bed, filter placement does not inhibit the extension of existing venous thrombi or diminish the systemic prothrombotic state. Small thrombi can pass through patent filters or through collaterals around obstructed filters; furthermore, thrombus extension can occur through the filter itself. One study demonstrated that placement of a vena cava filter was capable of diminishing the incidence of early occurrence of PE.[215] The benefit was somewhat offset by an increased risk of recurrent DVT within 2 years, although an 8-year follow-up did not disclose an increased risk of recurrence or postphlebitic syndrome.[216] The development of retrievable filters suggests that the intervention will no longer be irreversible, although extensive randomized clinical trials have not yet been performed to establish the safety and efficacy of this strategy.[217] Given these considerations, long-term anticoagulation should be utilized following filter placement if no contraindications exist or as soon as any existing bleeding risk resolves.

MASSIVE PULMONARY EMBOLISM

The significant mortality associated with massive PE justifies a separate consideration of the diagnostic and therapeutic approach to this problem.[218] The definition of massive PE should be based on hemodynamic considerations rather than purely anatomic ones. This impression is supported by mortality statistics from the urokinase trials and others.[219–221] Although anatomically massive emboli have a greater likelihood of being associated with hemodynamic compromise, not all anatomically massive emboli lead to hemodynamic compromise. Irrespective of the degree of vascular obstruction, patients with PE who present with shock have a mortality rate, regardless of the type of intervention, that approaches 30%.

The therapeutic approach to the patient with hemodynamically massive PE should be designed to counteract the adverse physiologic consequence of pulmonary vascular obstruction whether or not that obstruction is anatomically massive. Basic care of a critically ill patient should not be overlooked while specific diagnostic and therapeutic considerations are being implemented. Oxygen should be administered to alleviate the hypoxic pulmonary vasoconstriction, which might be contributing to the pulmonary hypertension. Intubation and mechanical ventilatory support might be required to improve oxygenation and decrease metabolic demands. Although volume resuscitation has been advised, excessive preload may further distend the right ventricle and increase right ventricular wall tension, resulting in decreased coronary perfusion and right ventricular ischemia. The judicious use of inotropic support can also prove useful in increasing blood pressure, preserving right coronary artery perfusion, and supporting right ventricular function.[222] Although there is a tendency to utilize central hemodynamic monitoring in critically ill hypotensive patients, this intervention should be considered carefully in the patient with massive PE. A femoral approach poses the risk of dislodging residual ileofemoral thrombus, and balloon flotation poses the risk of dislodging embolic material that might be trapped within the right atrial or ventricular cavities.

Although the central goal of therapy in massive PE should be to relieve pulmonary vascular obstruction, the severely compromised nature of the pulmonary vascular bed makes prevention of recurrence an important secondary consideration. Therefore, assuming the requisite expertise in filter placement is available and that placement of a filter will not interfere with the primary management of the patient, placement of a filter should be considered in all patients with hemodynamically massive embolism.

Thrombolytic Therapy

The use of thrombolytic agents in acute PE remains controversial.[223,224] Although thrombolytic therapy does appear to accelerate the rate of thrombolysis, there is no convincing evidence to suggest that it decreases mortality, increases the ultimate extent of resolution when measured at 7 days, reduces thromboembolic recurrence rates, improves symptomatic outcome, or decreases the incidence of thromboembolic pulmonary hypertension.[225–227] The one issue about which there can be little controversy is that the use of thrombolytic agents is associated with a substantially increased risk of bleeding, including intracranial hemorrhage. Intracranial hemor-

rhage has occurred in 0.5% to 2% of patients treated with thrombolytic agents in trials evaluating the use of these agents in both PE and myocardial infarction.[226,228]

Based on these data, and assuming there is no contraindication to its use, the role of thrombolytic therapy in PE should be limited to those circumstances in which an accelerated rate of thrombolysis may be considered lifesaving, that is, in patients with PE who present with hemodynamic compromise or who develop hemodynamic compromise during conventional therapy with heparin. In patients with embolism associated with intracavitary right atrial or ventricular thrombi, thrombolytics may be a reasonable consideration, although direct, surgical removal should also be considered.[229,230] At the present time, the finding of right ventricular dysfunction on echocardiography in the absence of hemodynamic instability should not serve as a justification for thrombolytic therapy.[130,223] Approximately one third of patients with PE will have echocardiographic evidence of right ventricular dysfunction.[231] Until criteria have been established that identify a subset of patients with right ventricular dysfunction who are at risk for an adverse outcome and benefit from thrombolytic therapy, there is little basis for exposing all such patients to the considerable risk of hemorrhagic complications associated with this intervention. This is especially true given the recent advances that have occurred in heparin administration strategies.

Pulmonary Embolectomy

The role of pulmonary embolectomy in acute hemodynamically massive PE also remains controversial.[232–235] Patients with anatomically massive or submassive emboli who are hemodynamically compromised, who have not had a cardiac arrest, and who do not have an absolute contraindication to thrombolytic therapy should be managed initially with aggressive medical therapy, including thrombolytic therapy plus heparin. Patients in whom acute embolectomy might be considered are those with hemodynamically massive PE who have an absolute contraindication to anticoagulant or thrombolytic therapy, those who have suffered a cardiopulmonary arrest (although the mortality associated with embolectomy in those who have is far higher than those who have not), and those in whom aggressive medical therapy, including the use of thrombolytics, has proved ineffective.

The concept of relieving the pulmonary vascular obstruction and decreasing right ventricular afterload with a percutaneous device has been appealing. Several such devices designed to extract or fragment thrombi have been reported. Their role in massive PE remains investigative.[236]

POSTEMBOLIC PROPHYLAXIS

The duration of outpatient anticoagulation for patients with PE remains a subject of controversy.[49,237–240] Much of the difficulty in making definitive recommendations regarding the duration of outpatient anticoagulation results from the diverse population that is affected by the disease process. The decision to continue or withdraw therapy should be made on an individual basis and take into account factors such as the nature of the initial thromboembolic event (spontaneous or associated with a defined clinical circumstance), the type of initial event (venous thrombosis or PE), the presence of an ongoing predisposition (either clinical or hereditary), and possibly the persistence of residual venous thrombosis as determined by ultrasonography or persistently high D-dimer levels in the blood.[49,51,237–241]

Patients with a clearly defined initial predisposition, whose initial thromboembolic risk factors have resolved and whose V/Q scan and noninvasive lower extremity test results have normalized, can likely be managed with a 3-month course of anticoagulation.[240] Patients without a clearly defined initial predisposition to thromboembolism and those with persistent V/Q scan defects or abnormal lower extremity test results probably should be treated for 6 months or more.[193,237,238] Finally, certain patients should be treated with an indefinite period of anticoagulation even though such a strategy is associated with an increased risk of hemorrhagic complications. Clinical circumstances in which indefinite periods of anticoagulation should be considered include a history of more than one episode of idiopathic venous thrombosis or PE; the presence of certain irreversible acquired or hereditary risk factors for VTE (active cancer, immobilization, antiphospholipid antibody syndrome); the presence of extensive residual venous thrombosis or the postthrombotic syndrome; and the presence of extensive residual V/Q scan or CT scan defects or pulmonary hypertension. Although the presence of the heterozygous factor V Leiden mutation or the prothrombin gene mutation individually does not appear to increase recurrence risk, the presence of homozygous factor V Leiden mutation or the heterozygous factor V Leiden mutation in combination with the prothrombin gene mutation does appear to be associated with an increased recurrence risk.[30]

A standard for repeating noninvasive testing of either the lungs or the deep veins of the lower extremities at the anticipated time of anticoagulant discontinuation does not exist. Although the cost implications would be substantial, such an approach would be beneficial in establishing a new baseline study that could be used for comparison in the event thromboembolic recurrence was suspected and in identifying patients with pulmonary vascular obstruction of sufficient extent to place them at risk for the development of chronic thromboembolic pulmonary hypertension.

Regarding postembolic anticoagulant "intensity," the recommended therapeutic range for the International Normalized Ratio (INR) of prothrombin time in the majority of patients with VTE is 2.0 to 3.0. It is controversial whether patients with the antiphospholipid syndrome should be an exception to this rule, because a retrospective analysis suggested that an INR of 3.0 to 4.0 was considered more effective in reducing recurrence rates than an INR less than 3.0.[242] However, a subsequent randomized treatment trial of patients with the antiphospholipid syndrome showed the standard

INR target of 2.0 to 3.0 to be just as effective as the higher target range.[243] In patients with a lupus anticoagulant, in whom the baseline INR may be elevated, the INR may not reliably reflect the level of anticoagulation. In these patients, the use of tests that are insensitive to the lupus anticoagulant, such as the prothrombin-proconvertin time or chromogenic factor X assay, has been recommended.[244]

Trials evaluating the effectiveness of low-intensity anticoagulation (maintaining the INR in a range of 1.5–2.0) following a standard 3- to 6-month period of anticoagulation have demonstrated that such an approach is superior to placebo but is less effective than standard therapy, without an appreciable reduction in bleeding complications.[245,246]

CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION

After a PE, thrombotic material in the pulmonary arteries either resolves by fibrinolysis or is remodeled into organized scars. The extent to which remodeling occurs, and the severity of the resulting vascular obstruction, varies among patients. In some, lung perfusion is rapidly restored,[80] although the resolution in the first week is typically incomplete. Recovery continues at a slower pace for the next 1 to 2 months,[247,248] during which clot remodeling may be occurring. Residual defects persist commonly beyond this period, suggesting that the clots have been remodeled into permanent vascular scar.[55,74–79,249] In a very small percentage of patients, estimated to represent about 1% of the 450,000 patients who survive a pulmonary embolic event each year in the United States, such resolution does not occur and the residual obstruction is of sufficient extent to cause persistent pulmonary hypertension.[250]

Most patients who present with chronic thromboembolic pulmonary hypertension were previously diagnosed with acute pulmonary emboli or DVT, but their presentations (e.g., clot burden, clinical stability) appear indistinguishable from patients who resolve their acute clots.[250] A prospective study of patients presenting with PE disclosed that in addition to the size of the initial PE, factors such as recurrent PE, idiopathic PE, and PE at a young age were associated with a higher risk for chronic thromboembolic pulmonary hypertension.[251] Other clinical factors associated with chronic thromboembolic pulmonary hypertension are right heart strain (e.g., pulmonary artery pressures < 50 mm Hg) during the acute PE,[81,251] advanced age,[251] previous splenectomy,[252,253] the presence of a ventriculoatrial shunt for the treatment of hydrocephalus,[252,253] and a variety of chronic inflammatory disorders (e.g., osteomyelitis, inflammatory bowel disease).[252,253] A number of laboratory findings have been associated with chronic thromboembolic pulmonary hypertension, the most prominent of which is the lupus anticoagulant.[254] In addition, elevated plasma levels of factor VIII,[255] lipoprotein (a),[256] and even non-O blood groups[257] have had at least a statistical association with chronic thromboembolic pulmonary hypertension after an acute PE.

Despite the associations mentioned previously, the reasons thromboembolic pulmonary hypertension develops are not clear; that is, it is not evident why this minority of patients fail to resolve their emboli. It has been found that in approximately half of the patients, the initial diagnosis of pulmonary thromboembolism was not made and, therefore, no treatment was given.[258] Despite extensive investigation, the only identifiable thrombotic predisposition has been the presence of a lupus anticoagulant or antiphospholipid antibody syndrome in approximately 10% to 50% of patients.[254,259] The prevalence of other thrombophilic tendencies, such as antithrombin III, protein C, and protein S deficiency, does not appear to be higher than that encountered in the normal population. Preliminary evidence also suggests that the factor V Leiden mutation is no more common in patients with chronic thromboembolic pulmonary hypertension than in the general population; moreover, no consistent defect in fibrinolytic activity has been identified.

The diagnosis of thromboembolic pulmonary hypertension is usually not made until the degree of pulmonary hypertension is advanced. As a result, the exact hemodynamic evolution of the disease has not been fully established.[260] The extent of pulmonary vascular obstruction appears to be a major determinant of disease initiation, with involvement of greater than 40% of the pulmonary vascular bed present in the majority of patients. Hemodynamic progression in certain patients may involve thromboembolic recurrence or in situ pulmonary artery thrombosis. However, hemodynamic progression in many patients appears to involve the development of a hypertensive pulmonary arteriopathy, similar to that encountered in other causes of secondary pulmonary hypertension.[261] This supposition is supported by several lines of evidence: a poor correlation between the extent of central anatomic obstruction and the degree of pulmonary hypertension; documented hemodynamic progression in the absence of recurrent embolic events or evidence of in situ pulmonary artery thrombosis; and histopathology demonstrating arteriopathic changes in the resistance vessels of both the involved and the uninvolved pulmonary vascular system.

Survival without intervention is poor and proportional to the degree of pulmonary hypertension at the time of diagnosis. In one study, the 5-year survival rate was 30% when the mean pulmonary artery pressure exceeded 40 mm Hg and 10% when it exceeded 50 mm Hg.[262] In another study, a mean pulmonary artery pressure above 30 mm Hg appeared to serve as a threshold value portending a poor prognosis.[263]

Diagnosis

Perhaps the most important aspect of dealing with this patient group is the proper approach to its recognition. Progressive dyspnea is a complaint common to all patients with chronic thromboembolic pulmonary hypertension. Later in the course of the disease, exertional chest pain, near-syncope or syncope, or lower extremity edema may develop.

Although a history of documented thromboembolism may not be present, many patients can provide a history consistent with an acute embolic event. They may describe an episode of "pleurisy," lower extremity "muscle strain," or prolonged, atypical "pneumonia," or they may describe a hospitalization or surgical procedure from which they never fully recovered. That an episode of VTE was not diagnosed, or was misdiagnosed, is not surprising given recent data confirming the frequency with which venous thrombosis and PE are overlooked in the population at large.[264]

Diagnostic delay, particularly in the absence of an acute history of VTE, occurs commonly. Progressive dyspnea and exercise intolerance are often attributed to coronary artery disease, cardiomyopathy, interstitial lung disease, asthma, deconditioning, or psychogenic dyspnea. Therefore, an abnormality of the pulmonary vascular bed should be considered in any patient with dyspnea in whom a definitive etiology cannot be defined. Later in the course of the disease, exertional chest pain, presyncope, or syncope may occur due to the presence of severe pulmonary hypertension and the inability of a compromised right ventricle to meet cardiac output demands.

Physical examination findings may be subtle early in the course of the illness, thereby contributing to this diagnostic delay. Prior to the development of significant right ventricular hypertrophy or overt right ventricular failure, physical examination abnormalities may be limited to a narrowing of S_2 or to a subtle accentuation of its pulmonic component. Late in the course of the disease, obvious findings such as a right ventricular heave, jugular venous distention, prominent *a*- and *v*-wave venous pulsations, fixed splitting of S_2, a right ventricular S^3, murmurs of tricuspid regurgitation or pulmonic insufficiency, hepatomegaly, and ascites may develop. Peripheral edema, a result of chronic lower extremity venous outflow obstruction or right ventricular failure, may be present.

A unique physical finding in certain patients with chronic thromboembolic disease is the presence of flow murmurs over the lung fields.[265] These subtle bruits, which appear to originate from turbulent flow through partially obstructed or recanalized thrombi, are high pitched and blowing in quality, heard over the lung fields rather than the precordium, accentuated during inspiration, and frequently heard only during periods of breath-holding. Their importance arises in not having been described in primary pulmonary hypertension, which represents the most common competing diagnostic possibility.

The intent of the diagnostic evaluation is to establish the presence and degree of pulmonary hypertension, to define its etiology, and if major vessel thromboembolic disease is present, to determine whether it is accessible to surgical intervention. Findings on standard laboratory tests are nonspecific, depending on the point in the natural history of the disease at which they are obtained, and reflective of the hemodynamic and gas-exchange consequences of the thromboembolic obstruction and the accompanying cardiac dysfunction.

Chest radiography, although often normal, may demonstrate findings that suggest the diagnosis.[266] Enlargement of both main pulmonary arteries or asymmetry in the size of the central pulmonary arteries may be present (Fig. 51-10). Areas of hypoperfusion or hyperperfusion

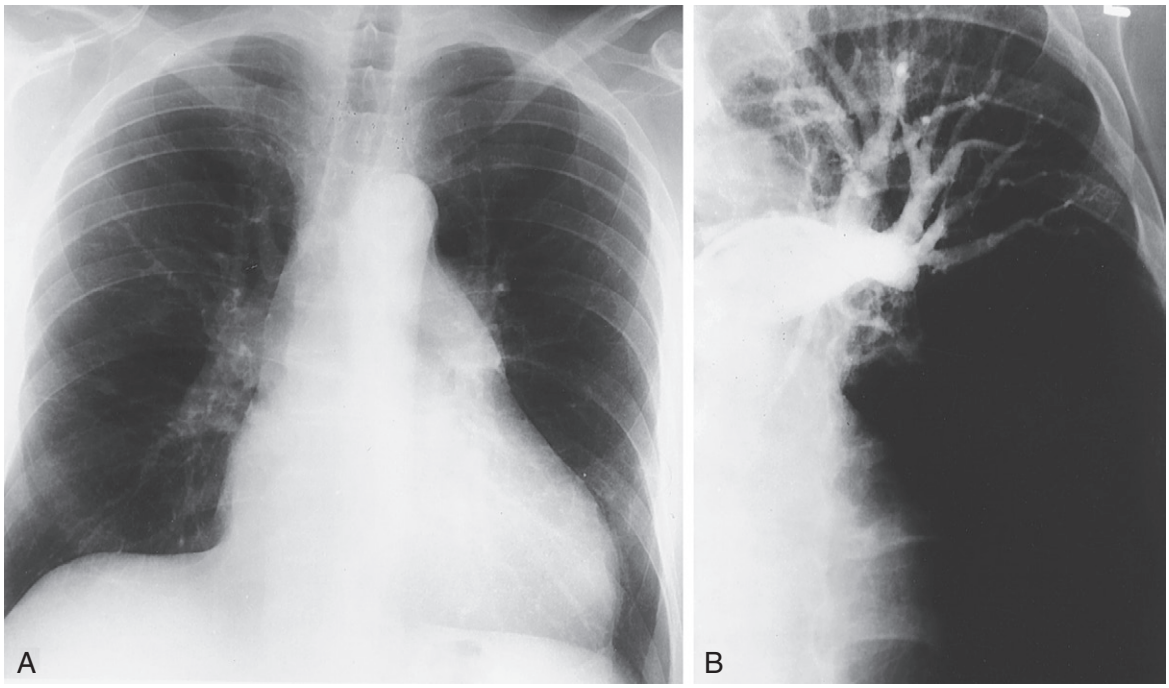

FIGURE 51-10 ■ Chest radiograph in a patient with chronic thromboembolic pulmonary hypertension. **A,** Note asymmetry of central pulmonary arteries, absence of descending left pulmonary artery, left lower lobe oligemia, and peripheral density representing prior infarct. **B,** Angiogram in the same patient demonstrates complete proximal occlusion of the descending left pulmonary artery.

may be present. There also may be evidence of old pleural disease, unilaterally or bilaterally. The cardiac silhouette may reflect obvious right atrial or right ventricular enlargement; more often, right ventricular hypertrophy and enlargement are suggested only on the lateral image by encroachment on the normally empty retrosternal space.

Early in the course of the disease, electrocardiographic findings may be normal. Later in the course, electrocardiography demonstrates evidence of right ventricular hypertrophy. Pulmonary function testing, performed to evaluate the patient's dyspnea, is often within normal limits. The majority of patients have a reduction in the single-breath diffusing capacity for carbon monoxide; however, a normal value does not exclude the diagnosis. Approximately 20% of patients demonstrate a mild to moderate restrictive defect due in part to the presence of infarct-related parenchymal scars.[267] However, the degree of spirometric defect is almost always disproportionate to the patient's gas-exchange abnormalities, symptomatic complaints, and degree of pulmonary hypertension.

In terms of gas-exchange findings, the arterial P_{O_2} may be within normal limits. However, the alveolar-arterial P_{O_2} difference is typically widened, and the majority of patients have a decline in the arterial P_{O_2} with exercise. Dead-space ventilation is often increased at rest and worsens with exercise. Minute ventilation is typically elevated as a result of this increased dead-space ventilation.[268]

Echocardiography commonly provides the initial objective evidence that pulmonary hypertension is present. Once the diagnosis of pulmonary hypertension has been established, determination of whether it originates from abnormalities of the small, resistance vessels or from central, chronic thromboembolic obstruction is essential. V/Q lung scanning appears to provide an excellent, noninvasive means of distinguishing between potentially operable major vessel thromboembolic pulmonary hypertension and small vessel pulmonary hypertension.[269] In chronic thromboembolic disease, at least one (and, more commonly, several) segmental or larger mismatched V/Q defects are present. In primary pulmonary hypertension, perfusion scans either are normal or exhibit a "mottled" appearance characterized by subsegmental defects. Other disorders leading to pulmonary hypertension may be associated with segmental defects on perfusion scan, including pulmonary veno-occlusive disease, pulmonary artery sarcoma, fibrosing mediastinitis, and large vessel vasculitides.[270]

It is important to recognize that the V/Q often understates the actual extent of central pulmonary vascular obstruction.[271] Channels through central obstructing lesions or partial flow around them, a result of the often complex patterns of recanalization and organization that occur following an embolic event, allow the radioisotopic agent to reach the periphery of the lung. Depending on the distribution of flow, these areas may appear normal or as relatively hypoperfused "gray zones." Therefore, V/Q scanning, although capable of suggesting the potential presence of chronic thromboembolic obstruction, is incapable of determining the magnitude, location, or proximal extent of the disease, information critical to the question of surgical accessibility.

The role of CT scanning in the evaluation of patients with chronic thromboembolic disease remains incompletely defined. A variety of CT abnormalities have been described: chronic thromboembolic material located in an eccentric position within the central pulmonary arteries, right ventricular enlargement, dilated central pulmonary arteries, bronchial artery collateral flow, parenchymal abnormalities consistent with prior infarcts, and mosaic attenuation of the pulmonary parenchyma.[272] However, the absence of these findings does not preclude the possibility of surgically accessible chronic thromboembolic disease. Furthermore, the presence of central thrombus has been described in primary pulmonary hypertension and other chronic pulmonary disorders.[273] CT scanning is also incapable of providing essential hemodynamic data. CT is particularly useful in the evaluation of the main pulmonary arteries and of unilateral or predominantly unilateral pulmonary vascular obstruction as determined by V/Q scanning.[272] Under these circumstances, the probability of other diagnostic possibilities such as pulmonary artery sarcoma, vasculitis, malignancy, and mediastinal fibrosis is increased. CT also has a role, along with physiologic testing, in helping to evaluate the status of the pulmonary parenchyma in patients with coexisting obstructive or restrictive lung disease.

Right-heart catheterization and pulmonary angiography are essential to designate the degree of pulmonary hypertension, to exclude competing diagnoses, and to define the surgical accessibility of the obstructing thrombotic lesions. If hemodynamic measurements at rest demonstrate only modest degrees of pulmonary hypertension, measurements should be obtained following a short period of exercise. In patients with chronic thromboembolic obstruction sufficient to abolish normal compensatory mechanisms, exercise-related increases in cardiac output will be accompanied by an almost linear elevation in pulmonary artery pressure.

The angiographic findings in chronic thromboembolic disease bear little resemblance to the sharply defined, intraluminal defects diagnostic of acute embolism.[274] Five distinct angiographic patterns have been described that correlate with the finding of organized thromboembolic material at the time of thromboendarterectomy (Fig. 51-11): (1) pouch defects; (2) pulmonary artery webs or bands; (3) intimal irregularities; (4) abrupt narrowing of the major pulmonary arteries; and (5) obstruction of lobar or segmental vessels at their point of origin, with complete absence of blood flow to pulmonary segments normally perfused by those vessels.

In certain patients, pulmonary angioscopy has proved valuable in confirming the presence of chronic thromboembolic obstruction and in determining whether it is accessible to surgical intervention.[275] The pulmonary angioscope is a fiberoptic device that allows visualization of the pulmonary arteries to the segmental level. The normal pulmonary artery has a round or oval contour with a smooth, pale, glistening appearance to the intima

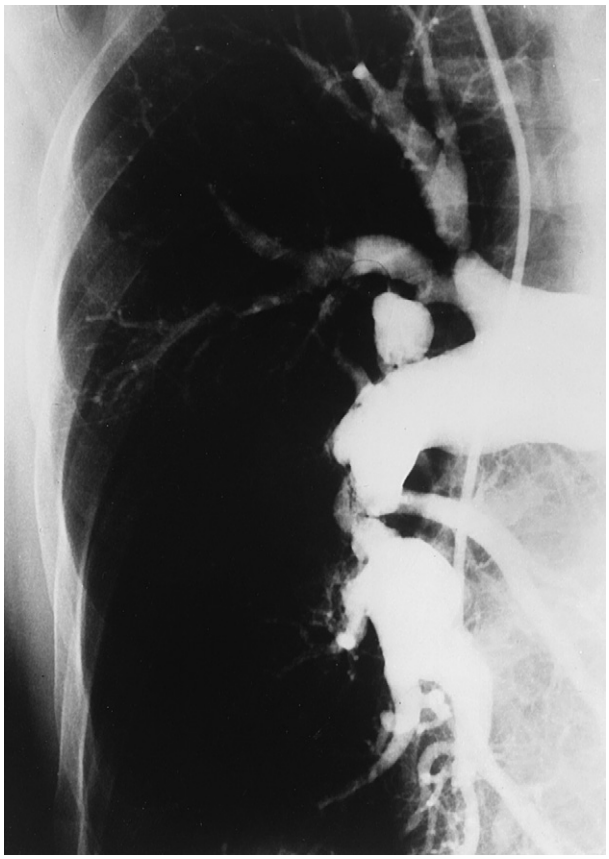

FIGURE 51-11 ■ Right-sided pulmonary angiogram in a patient with chronic thromboembolic pulmonary hypertension. Many of the classic angiographic findings associated with this disease are present, including pouch defects, intimal irregularity, pulmonary artery webs with poststenotic dilation, and complete obstruction to flow of the right middle lobe and several lower lobe segmental arteries.

and bright red blood filling the lumen (Fig. 51-12). The features of organized chronic emboli consist of roughening or pitting of the intimal surface, bands and webs across the lumen, pitted masses of chronic embolic material within the lumen, and partial recanalization.

Although pulmonary angiography/angioscopy usually completes the diagnostic sequence and confirms surgical accessibility, adjunctive studies may be necessary to exclude competing diagnoses. CT of the chest can be useful in determining whether a mediastinal process (e.g., fibrosing mediastinitis, malignancy) is responsible for the angiographic findings and, in selected cases, in defining the extent and accessibility of the obstructing thrombi. Arch aortography can be useful if an arteritis is being considered.[276]

The major conditions from which thromboembolic pulmonary hypertension must be distinguished include primary pulmonary hypertension and other forms of secondary pulmonary hypertension such as fibrosing mediastinitis with pulmonary arterial or venous obstruction, pulmonary hypertension associated with congenital atrial or ventricular septal defects, congenital pulmonary artery branch stenoses, pulmonary artery agenesis, tumors arising in or obstructing the central pulmonary arteries, and Takayasu's arteritis. The standard diagnostic approaches previously discussed, preferably performed at a center experienced in the management of pulmonary hypertension, are capable of excluding the majority of these competing diagnoses.

Treatment

For patients suffering from chronic thromboembolic pulmonary hypertension, the decision to proceed to pulmonary thromboendarterectomy is based on both objective and subjective factors, which are carefully defined during the preoperative evaluation.[277]

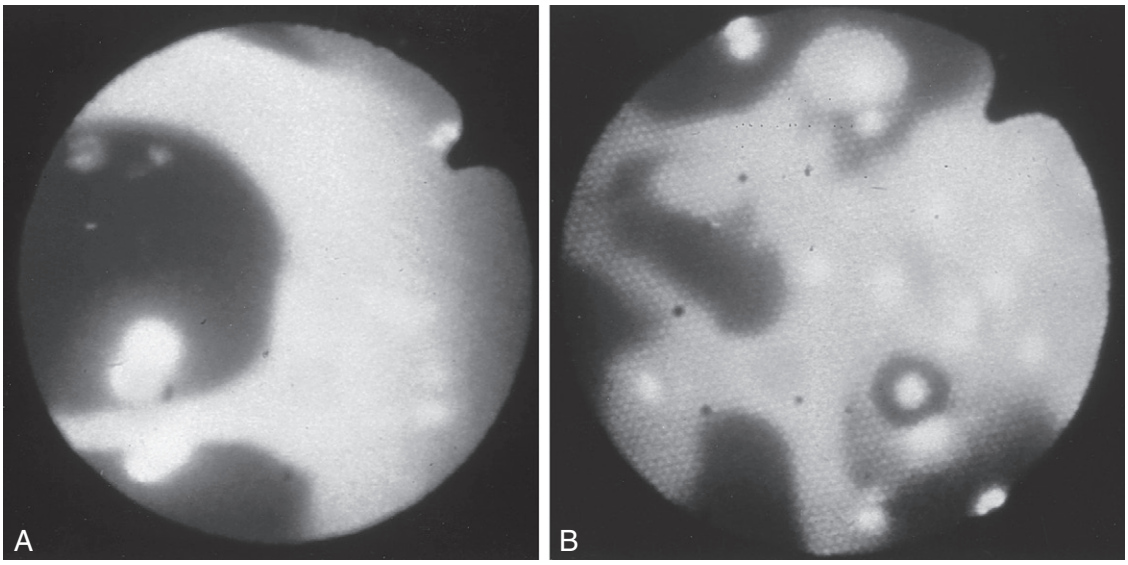

FIGURE 51-12 ■ Pulmonary angioscopy. **A,** Angioscopic appearance of normal pulmonary artery. **B,** Angioscopic appearance of chronic thromboembolic pulmonary artery obstruction demonstrates multiple, recanalized channels.

TABLE 51-4. Published Results for Pulmonary Thromboendarterectomy Since 1999

Year	Study	Location	Patients (*N*)	Preoperative PVR	Postoperative PVR	Mortality (%)
2000	Mares et al[282]	Austria	33	1478 ± 107*	975 ± 93*	9.1
2000	Mares et al[282]	Austria	14	1334 ± 135*	759 ± 99*	21.4
2000	Rubens et al[283]	Canada	21	765 ± 372	208 ± 92	4.8
2000	D'Armini et al[284]	Italy	33	1056 ± 344	196 ± 39†	9.1
2001	Tschol et al[285]	Germany	69	988 ± 554	324 ± 188	10.1
2001	Masuda and Nakajima[217a]	Japan	50	869 ± 299‡	344 ± 174‡	18
2003	Hagl et al[286]	Germany	30	873 ± 248	290 ± 117	10
2003	Jamieson et al[278]	San Diego	500	893 ± 444	285 ± 214	4.4

*Results expressed as pulmonary vascular resistance *index*.
†Data in 23 patients at 3-mo follow-up.
‡34 patients by sternotomy, 16 patients by thoracotomy.
PVR, pulmonary vascular resistance in dyne-sec·cm^{-5}.

Pulmonary thromboendarterectomy is considered in symptomatic patients with hemodynamic or ventilatory impairment at rest or with exercise. The mean pulmonary vascular resistance in patients undergoing surgery (Table 51-4) is typically 800 to 1000 dyne-sec·cm^{-5}, with a range of 300 to 2000 dyne-sec·cm^{-5}.[260] Patients in the lower range of pulmonary hemodynamic impairment include those with involvement limited to one main pulmonary artery, those with vigorous lifestyle expectations in whom high dead-space and minute ventilatory demands are disabling, and those who live at altitude. Thromboendarterectomy is also considered in patients with normal or near-normal pulmonary hemodynamics at rest who develop significant levels of pulmonary hypertension with exercise. If surgery is deferred in patients with this hemodynamic profile, careful monitoring is recommended to detect whether progression of the pulmonary hypertension is occurring.

The location and extent of the proximal thromboembolic obstruction is the most critical determinant of operability. Occluding thrombi must involve the main, lobar, or proximal segmental arteries. Those that originate more distally are not amenable to thromboendarterectomy with current surgical techniques. In terms of extent, the anatomic and hemodynamic findings must be interpreted in concert. An acceptable postoperative hemodynamic outcome requires that the preoperative hemodynamic impairment be consistent with the magnitude of surgically accessible thromboembolic material determined by angiography or angioscopy. This determination is critical. If the major component of the preoperative hemodynamic impairment derives from surgically inaccessible disease or from the resistance conferred by a secondary, small vessel arteriopathy, residual pulmonary hypertension will be present postoperatively. Depending on the extent of the postoperative pulmonary hypertension, this outcome may be associated with adverse short-term and long-term consequences.

The only absolute contraindication to thromboendarterectomy is the presence of severe underlying lung disease, either obstructive or restrictive. Thromboendarterectomy in this population can improve the hemodynamic profile but may have little effect on the ventilatory impairment. Advanced age, severe right ventricular failure, and the presence of collateral disease influence risk assessment but do not represent absolute contraindications to the procedure if the anticipated relief of the pulmonary hypertension will improve both the quality and the duration of life. Patients as young as 16 and as old as 84 years, as well as those with complex comorbid conditions, have successfully undergone the procedure.

Prior to surgery, several other essential issues must be considered. It is important that the patient be protected against embolic recurrence, both over the long term and during the high-risk perioperative period. Therefore, an inferior vena cava filter should be placed prior to surgery unless an obvious nonleg or nonpelvic source of embolism is present. For those at risk of coronary artery disease, coronary angiography is routinely performed prior to surgery, usually at the time of the right heart catheterization and pulmonary angiography. Coronary artery bypass grafting, if necessary, can be performed safely at the time of the thromboendarterectomy.[277]

Sternotomy with cardiopulmonary bypass and periods of circulatory arrest represents the procedure of choice. This approach allows access to both pulmonary arteries and ensures more complete removal of the chronically obstructing material.[278] A sternotomy approach also provides adequate exposure for additional procedures that need to be performed. In a review of 1190 patients undergoing thromboendarterectomy, 90 patients (7.6%) required such a combined procedure exclusive of solitary closure of a patent foramen ovale, which is performed in approximately 30% of thromboendarterectomy procedures.[277] The use of cardiopulmonary bypass allows periods of complete circulatory arrest, which provides a bloodless operative field essential for meticulous lobar and segmental dissections.

Thromboendarterectomy bears little resemblance to acute pulmonary embolectomy. The neointima in chronic thromboembolic disease is deceptive and is often not easily recognizable as chronic thrombus. The procedure is a true endarterectomy that requires careful

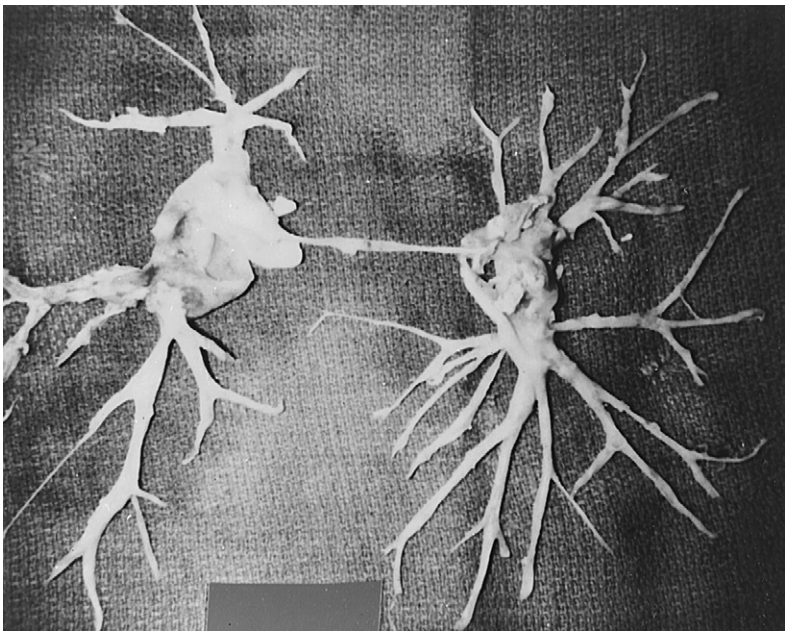

FIGURE 51-13 ■ Specimen obtained at the time of pulmonary thromboendarterectomy. In addition to central thromboembolic obstruction, note multiple segmental extensions. Failure to adequately remove these distal extensions will result in an inadequate hemodynamic outcome.

dissection of chronic endothelialized material from the native intima to restore pulmonary arterial patency. Considerable experience is required by the surgical team to identify the correct operative plane and to remove the segmental-level extensions of the more proximal obstruction (Fig. 51-13). Failure to do so results in an inadequate hemodynamic outcome.

During the development of and early experience with this procedure, mortality was related to many causes. At the present time, the major causes of death have been related to reperfusion pulmonary edema and to residual postoperative pulmonary hypertension and right ventricular failure in patients in whom pulmonary thromboendarterectomy failed to achieve substantial improvement in pulmonary hemodynamics.[278]

Although an immediate improvement in pulmonary hemodynamics occurs, the postoperative course can be complex. In addition to complications common to other forms of cardiac surgery (arrhythmias, atelectasis, wound infection, pericardial effusions, delirium), patients undergoing pulmonary thromboendarterectomy often experience two unique complications capable of significantly impairing gas exchange: reperfusion pulmonary edema and pulmonary artery "steal."[279,280]

Pulmonary artery steal (Fig. 51-14) represents a postoperative redistribution of pulmonary arterial blood flow away from previously well-perfused segments and into the newly endarterectomized segments. Long-term follow-up has demonstrated that pulmonary vascular steal resolves in the majority of patients.[281] Reperfusion pulmonary edema appears to represent a form of high-permeability lung injury that is limited to those areas of lung from which proximal thromboembolic obstructions have been removed (Fig. 51-15). It may appear up to 72 hours after surgery and is highly variable in severity, ranging from a mild form of edema resulting in postoperative hypoxemia to an acute, hemorrhagic, and fatal complication. When associated with pulmonary artery steal, reperfusion pulmonary edema can represent a significant challenge in terms of postoperative gas exchange. Pulmonary blood flow is directed toward edematous, noncompliant areas of lung that contribute poorly to gas exchange. Management of reperfusion edema, as with other forms of acute lung injury, is supportive until resolution occurs.

Although exact figures are not available, approximately 2500 thromboendarterectomy procedures have been performed worldwide. In reported series of patients undergoing thromboendarterectomy since 1999 (see Table 51-4), in-hospital mortality rates have ranged between 4.4% and 21.4%.[278,282–286] The specific factors affecting perioperative mortality have not been completely defined. Several studies have suggested that New York Heart Association functional class IV status, age older than 70 years, the severity of preoperative pulmonary vascular resistance, the presence of right ventricular failure as manifested by high right atrial pressures, details of the postoperative management, and perhaps the duration of pulmonary hypertension may adversely influence outcome. It is also reasonable to suggest that there may exist a strong relationship between volume of procedures performed and outcome, as has been demonstrated with other high-risk surgical procedures.[287] In the case of thromboendarterectomy, this may be related to consistency of patient evaluation, surgical experience, uniform delivery of postoperative care, and the presence of dedicated resources for dealing with postoperative complications. Should this prove to be the case, strong consideration could be given to performing the procedure at a limited number of referral centers.

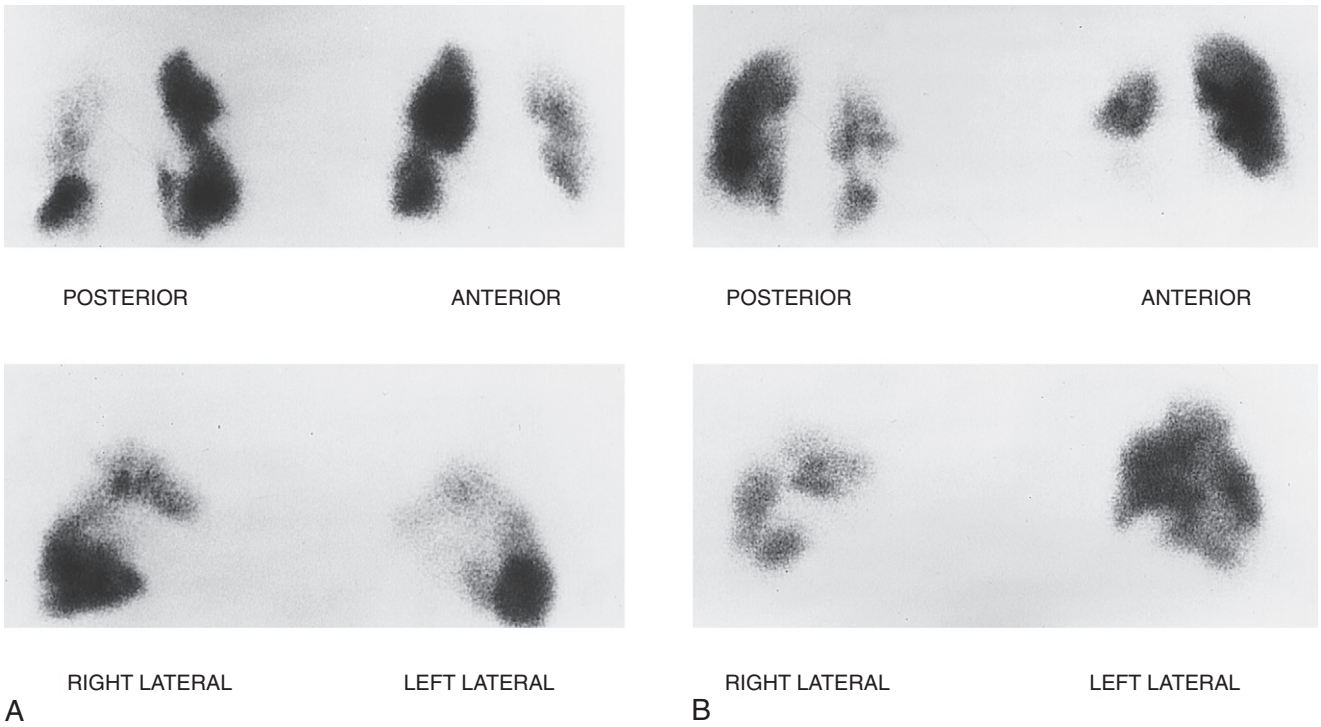

FIGURE 51-14 ■ Perfusion scans show pulmonary artery steal. **A,** Preoperative perfusion scan demonstrates minimal flow to the left lung. **B,** Perfusion scan obtained in the early postoperative period demonstrates dramatic reversal of flow with vascular "steal" from right lung. Equilibration and normalization of flow over time is the rule.

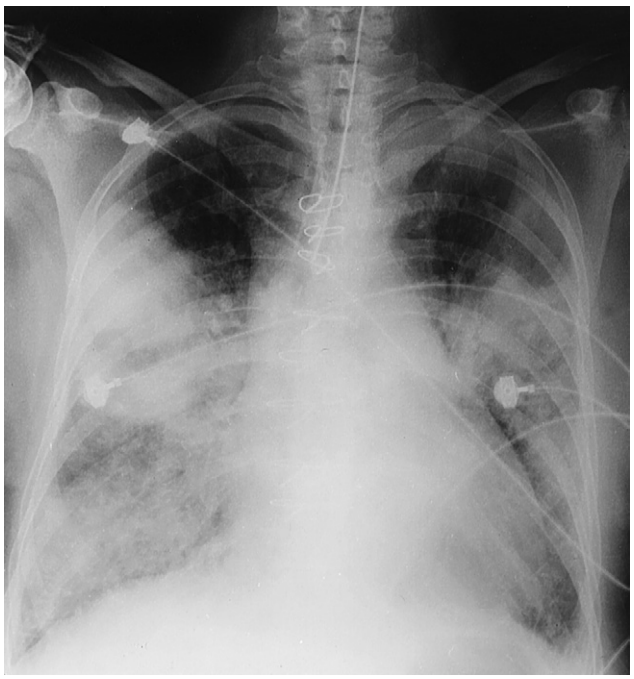

FIGURE 51-15 ■ Chest radiograph shows postoperative reperfusion pulmonary edema. Only the upper lobes, from which no thromboembolic material was dissected, are spared.

Given what is known about the natural history of the disease and the progressive nature of the pulmonary hypertension associated with it, these findings suggest that early referral is preferable to late unless the possibility of a recent embolic event exists. Under this circumstance, a period of 6 to 8 weeks of conventional therapy is recommended to allow optimum thrombus resolution. Beyond this period of time, further improvement in the level of pulmonary hypertension cannot be achieved with medical therapy alone.[81]

Among survivors of thromboendarterectomy, restoration of pulmonary artery patency results in an immediate and dramatic hemodynamic improvement (Fig. 51-16). In published series, the mean reduction in pulmonary vascular resistance has approximated 70%, and a pulmonary vascular resistance in the range of 200 to 350 dyne-sec·cm^{-5} can be achieved (see Table 51-4). The long-term hemodynamic and symptomatic outcomes have been equally dramatic. Many patients are restored to normal activity, the majority return to class I functional status, and essentially all have improved at least one grade in the classification of cardiac disability.[288–290] Approximately 10% to 15% of patients undergoing thromboendarterectomy will have residual levels of pulmonary hypertension following the procedure that have been associated with a negative long-term outcome. One therapeutic option for patients who have undergone thromboendarterectomy with an inadequate hemodynamic outcome and for those not deemed candidates for thromboendarterectomy is lung transplantation. Preliminary

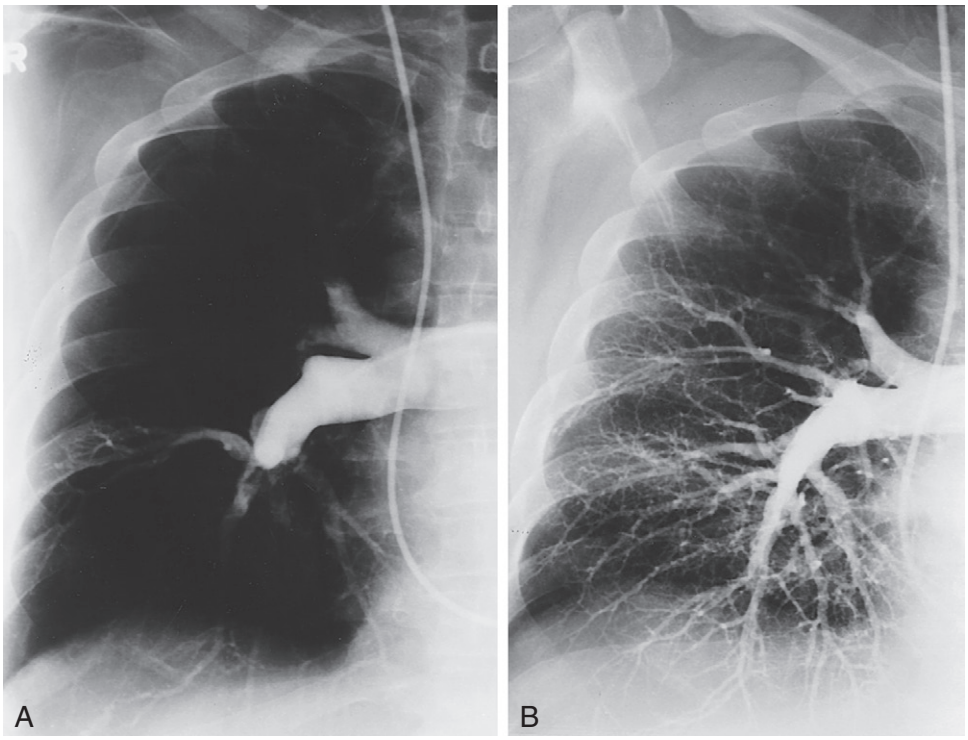

FIGURE 51-16 ■ **A,** Preoperative pulmonary angiogram shows thromboembolic obstruction involving the right upper, middle, and lower lobe arteries. **B,** Postoperative angiogram shows normalization of flow. This angiographic improvement was accompanied by a corresponding hemodynamic improvement.

results suggest that patients who are not considered candidates for thromboendarterectomy and those with residual pulmonary hypertension following the procedure may benefit from medical therapy including prostanoids, endothelin receptor antagonists, and phosphodiesterase inhibitors.[291-294] Epoprostenol has been used preoperatively in patients with chronic thromboembolic pulmonary hypertension associated with severe hemodynamic impairment and has been demonstrated to improve the hemodynamic profile.[295] Whether such an approach improves outcome or decreases the incidence and severity of postoperative complications has not been determined.

OTHER FORMS OF EMBOLISM

Because the lungs receive all of the blood flow returned from the venous system, the pulmonary vascular bed serves as a "sieve" for all particulates entering the venous blood and is the first vascular bed to be exposed to any toxic substance injected intravenously. As a result of its strategic position, the pulmonary vascular bed is therefore exposed to a wide variety of potentially obstructing and injurious agents.

Schistosomiasis

Among such agents, the most common on a worldwide basis, although not within the United States, is schistosomiasis.[296] This parasitic disorder may cause pulmonary hypertension by three mechanisms: anatomic obstruction by the organism itself, an intense inflammatory vasculitic response to the components of the organism, and the development of portopulmonary hypertension. In endemic areas, schistosomal disease is the most common cause of cor pulmonale. Limited data suggest that cardiopulmonary schistosomiasis is seen most often in *Schistosoma mansoni* infection. This form of cor pulmonale does not occur in the absence of concomitant schistosomal liver disease because the liver is always involved, usually quite extensively, before pulmonary involvement occurs. The premortem diagnosis of cardiopulmonary schistosomiasis depends on serology and the detection of schistosomal ova in stool or urine along with evidence of hepatic fibrosis and pulmonary hypertension. Treatment with praziquantel can effectively eradicate schistosomal infections with minimal toxicity. However, cardiopulmonary manifestations are not likely to be reversible given the chronic fibrotic changes that have already occurred (see Chapter 37).

Air Embolism

An increasingly common form of nonthrombotic embolism in the United States is air embolism.[297] The increasing frequency of the problem reflects the wide variety of invasive surgical and medical procedures now available, the broad use of indwelling central venous catheters, the use of positive-pressure ventilation with high levels of positive end-expiratory pressure, and the frequency of thoracic and other forms of trauma. The

simple inadvertent transection or disconnection of a large-bore intravenous catheter, particularly in the jugular or subclavian vein, can result in ingress of substantial quantities of air. Air bubbles enter the pulmonary vascular bed and, from there, are diffusely distributed throughout the body either by way of an intracardiac shunt or, more likely, through microvascular pulmonary shunts.

Physiologic consequences of pulmonary air embolism include an abrupt rise in pulmonary artery pressure. Noncardiogenic pulmonary edema may develop, lung compliance falls, and hypoxemia ensues. The symptoms of air embolism are variable and nonspecific and may include alterations in sensorium, chest pain, dyspnea, or a sense of impending doom. These and other consequences appear to be due to two phenomena: actual lodgment of the bubbles in capillary beds, which interferes with nutrient supply to the affected organs; and the formation of platelet-fibrin aggregates, creating diffuse microthrombi.[298] Thrombocytopenia may be seen as a consequence of this latter event. The most serious consequences result from cerebral or coronary artery air embolism, the severity of the consequences depending upon the volume of air that gains access to the venous circulation.[297]

The best approaches to air embolism are prevention and early detection. Treatment consists of measures designed to restore blood flow and to promote reabsorption of the intravascular air. Measures designed to restore flow include patient positioning (Trendelenburg position with the left side down), removal of air through central venous catheters or direct needle aspiration, and closed-chest cardiac massage. Measures designed to increase absorption include the use of 100% oxygen and the institution of hyperbaric oxygen therapy as early as possible.[299,300] Utilizing such aggressive measures, mortality from air embolism has been dramatically reduced.

Fat Embolism

Another reasonably frequent and dramatic form of nonthrombotic embolism is fat embolism.[301] A rather characteristic syndrome follows entry of neutral fat into the vascular system, consisting of the onset of dyspnea, petechiae, and mental confusion. There is a variable lag time of 24 to 48 hours in the onset of the syndrome following the inciting event.

By far the most common inciting event is traumatic fracture of marrow-containing long bones; the incidence of fat embolism rises with the number of fractures. However, orthopedic procedures and trauma to other fat-laden tissues (e.g., fatty liver) occasionally is followed by the same syndrome.

The reasons for the variability in incidence of the syndrome after apparently comparable injuries are not clear. Perhaps variations in incidence and severity relate to the amount of fat released. The pathophysiologic consequences appear to derive from two events: (1) actual vascular obstruction by neutral particles of fat and (2) the injurious effects of free fatty acids released by the action of lipases on the neutral fat.[302] The latter effect is probably the more important, causing a diffuse vasculitis with leakage from cerebral, pulmonary, and other vascular beds.[303]

The diagnosis of fat embolism syndrome is a clinical one suggested by the onset of dyspnea, neurologic abnormalities, petechiae, and fever in the proper clinical context.[304] Petechiae, typically distributed over the head, neck, anterior chest, and axillae, are present in only 20% to 50% of cases.[305] Therefore, their absence should not preclude consideration of the disease. No laboratory test is diagnostic of the syndrome.

Although a variety of treatments have been suggested (e.g., intravenous ethanol, albumin, dextran, heparin), none has proved effective. The role of corticosteroid therapy to prevent the onset of fat embolism syndrome after an inciting event remains controversial. Supportive treatment, including mechanical ventilatory support when necessary, is the primary approach, and survival is now the rule with meticulous supportive care.

Amniotic Fluid Embolism

Another special form of embolism is amniotic fluid embolism, a rare but unpredictable and catastrophic complication of pregnancy that represents the third leading cause of maternal mortality.[306,306a] This disorder occurs during or after delivery when amniotic fluid gains access to uterine venous channels and, thereby, to the pulmonary and general circulations. The delivery may be either spontaneous or by cesarean section; there are case reports of amniotic fluid emboli occurring during therapeutic abortion. Unexpectedly and suddenly, severe respiratory distress, cyanosis, hypotension, and often, cardiovascular collapse occur. Although obstruction of the pulmonary vascular bed may exist, the major hemodynamic impairment appears to be related to left ventricular dysfunction.[307] Most cases develop during labor, but delayed onset of symptoms up to 48 hours after delivery has been reported.[308] Advanced maternal age, multiparity, premature placental separation, fetal death, and meconium staining of amniotic fluid are associated with increased risk of amniotic fluid embolism.

Amniotic fluid contains particulate materials that can cause pulmonary vascular obstruction, but the major pathogenetic mechanism of the syndrome remains uncertain. Amniotic fluid does have thromboplastic activity that leads to extensive fibrin deposition in the lung vasculature and, occasionally, in other organs. As a consequence of fibrin deposition, a severe consumptive coagulopathy develops, including marked hypofibrinogenemia and thrombocytopenia. Following the acute event, an enhanced fibrinolytic state often occurs.[305,309]

The diagnosis of amniotic fluid embolism is based on a compatible clinical picture, often enhanced by finding amniotic fluid components in the pulmonary circulation. The presence of squamous cells in pulmonary arterial blood, once considered pathognomonic, has proved to be a nonspecific finding.[306]

Although various forms of therapy have been suggested (e.g., antifibrinolytic agents such as aminocaproic acid, cryoprecipitate), the best approach is supportive.

Even in the setting of aggressive supportive measures, however, maternal mortality is in the range of 60% to 80%, with many survivors suffering from long-term neurologic disability.

Septic Embolism

Septic embolism is another special disorder that, unfortunately, is also increasing in frequency owing to widespread injection drug abuse and the expanding use of indwelling intravenous catheters. Previously, septic embolism was almost exclusively a complication of septic pelvic thrombophlebitis secondary to both septic abortion and postpuerperal uterine infection. Those conditions still occur, but injection drug abuse is now by far the more common cause.[310] An increasingly common cause is iatrogenic: infections secondary to indwelling catheters inserted for a variety of diagnostic or therapeutic purposes.[311]

Microscopically, septic phlebitis consists of purulent material admixed with fibrin thrombus. Embolization from such material does occur and can result in obstruction of small pulmonary vessels, but the major consequence is pulmonary infection. Characteristically, the chest radiograph displays scattered pulmonary opacities that undergo cavitation. An increasing number of such opacities develop over periods of hours to a few days. Symptoms and signs include a septic temperature course, dyspnea, cough, pleuritic chest pain, and hemoptysis. Initial treatment consists of appropriate antimicrobial drugs. If an indwelling catheter is the source of the infection, it should be removed. If there is not a prompt response to this regimen, surgical isolation of the septic vein, if present, should be considered. The role of systemic anticoagulation remains uncertain. Endocarditis may complicate septic phlebitis, or mimic it, particularly in drug addicts.

Other Emboli

Because of its sieve function, the lung may also be embolized on occasion by a wide variety of other materials. Cancer cells, of course, often find their way into and adhere to the pulmonary vessels; on occasion, tumor emboli (admixtures of thrombus with cells) can occur and mimic bland embolization. Trophoblastic tissue can escape the uterus and lodge in the pulmonary circulation during evacuation of a molar pregnancy or during hysterectomy for an invasive mole. After head trauma, brain tissue has been found in the lungs; the same is true of liver cells following abdominal trauma and of bone marrow after cardiopulmonary resuscitation.

Finally, in this era of injection drug abuse, noninfectious vasculitic-thrombotic complications are being seen with increasing frequency. Particulate and irritant drug carriers (e.g., talc), and occasionally, the drugs themselves, may cause vascular inflammation and secondary thrombosis.[312] More commonly, uptake of the talc into the pulmonary interstitium results in fibrosis and advanced emphysema.[313,314]

KEY POINTS

- PE from DVT is an extremely important cause of morbidity and mortality.
- A major reduction of this morbidity and mortality will occur only through the widespread use of prophylactic measures in populations at risk and through a heightened clinical suspicion and awareness of the often subtle and nonspecific presentation of the disease.
- Appropriate use of anticoagulants decreases the risk of further thrombosis and recurrent embolism.
- Remaining uncertainties regarding the role of CT scanning in the diagnosis of PE, D-dimer testing in the exclusion of VTE, risk stratification in patients with confirmed embolism, and populations in whom outpatient management is feasible should be resolved.
- Physicians should be aware of these advances and begin to apply the new knowledge about the pathogenesis, natural history, diagnosis, and treatment of PE and, especially, of its antecedent, DVT.

References

1. White RH: The epidemiology of venous thromboembolism. Circulation 107(23 Suppl 1):I4–I8, 2003.
2. Silverstein MD, Heit JA, Mohr DN, et al: Trends in the incidence of deep vein thrombosis and pulmonary embolism: A 25-year population-based study. Arch Intern Med 158:585–593, 1998.
3. Heit JA, Cohen AT, Anderson FA Jr, on Behalf of the VTEIAG: Estimated annual number of incident and recurrent, non-fatal and fatal venous thromboembolism (VTE) events in the US. Am Soc Hematol Annual Meeting Abstracts 106:910, 2005.
4. Rubinstein I, Murray D, Hoffstein V: Fatal pulmonary emboli in hospitalized patients. An autopsy study. Arch Intern Med 148:1425–1426, 1988.
5. Morgenthaler TI, Ryu JH: Clinical characteristics of fatal pulmonary embolism in a referral hospital. Mayo Clin Proc 70:417–424, 1995.
6. Karwinski B, Svendsen E: Comparison of clinical and postmortem diagnosis of pulmonary embolism. J Clin Pathol 42:135–139, 1989.
7. Stein PD, Henry JW: Prevalence of acute pulmonary embolism among patients in a general hospital and at autopsy. Chest 108:978–981, 1995.

8. Dalen JE, Alpert JS: Natural history of pulmonary embolism. Prog Cardiovasc Dis 17:259–270, 1975.
9. Douketis JD, Kearon C, Bates S, et al: Risk of fatal pulmonary embolism in patients with treated venous thromboembolism. JAMA 279:458–462, 1998.
10. Lilienfeld DE: Decreasing mortality from pulmonary embolism in the United States, 1979–1996. Int J Epidemiol 29:465–469, 2000.
11. Horlander KT, Mannino DM, Leeper KV: Pulmonary embolism mortality in the United States, 1979–1998: An analysis using multiple-cause mortality data. Arch Intern Med 163:1711–1717, 2003.
12. Centers for Disease Control and Prevention, National Center for Health Statistics: Compressed Mortality File 1979–1998. CDC WONDER On-line Database, compiled from Compressed Mortality File CMF 1968–1988, Series 20, No. 2A, 2000 and CMF 1989–1998, Series 20, No. 2E, 2003. Available at http://wonder.cdc.gov/cmf-icd9.html (accessed June 2, 2008 1:01:17 AM).
13. Centers for Disease Control and Prevention, National Center for Health Statistics: Compressed Mortality File 1999–2005. CDC WONDER On-line Database, compiled from Compressed Mortality File 1999–2005, Series 20, No. 2K, 2008. Available at http://wonder.cdc.gov/cmf-icd10.html (accessed June 2, 2008 12:44:49 AM).
14. Rosamond W, Flegal K, Furie K, et al: Heart disease and stroke statistics—2008 update: A report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 117:e25–e146, 2008.
15. Macik BG, Ortel TL: Clinical and laboratory evaluation of the hypercoagulable states. Clin Chest Med 16:375–387, 1995.
16. Crowther MA, Kelton JG: Congenital thrombophilic states associated with venous thrombosis: A qualitative overview and proposed classification system. Ann Intern Med 138:128–134, 2003.
17. Dahlback B, Carlsson M, Svensson PJ: Familial thrombophilia due to a previously unrecognized mechanism characterized by poor anticoagulant response to activated protein C: Prediction of a cofactor to activated protein C. Proc Natl Acad Sci U S A 90:1004–1008, 1993.
18. Ridker PM, Miletich JP, Hennekens CH, Buring JE: Ethnic distribution of factor V Leiden in 4047 men and women. Implications for venous thromboembolism screening. JAMA 277:1305–1307, 1997.
19. De Stefano V, Chiusolo P, Paciaroni K, Leone G: Epidemiology of factor V Leiden: Clinical implications. Semin Thromb Hemost 24:367–379, 1998.
20. Ridker PM, Hennekens CH, Lindpaintner K, et al: Mutation in the gene coding for coagulation factor V and the risk of myocardial infarction, stroke, and venous thrombosis in apparently healthy men. N Engl J Med 332:912–917, 1995.
21. Koster T, Rosendaal FR, de Ronde H, et al: Venous thrombosis due to poor anticoagulant response to activated protein C: Leiden Thrombophilia Study. Lancet 342:1503–1506, 1993.
22. Rosendaal FR, Koster T, Vandenbroucke JP, Reitsma PH: High risk of thrombosis in patients homozygous for factor V Leiden (activated protein C resistance). Blood 85:1504–1508, 1995.
23. Walker ID: Thrombophilia in pregnancy. J Clin Pathol 53:573–580, 2000.
23a. Marik PE, Plante LA: Venous thromboembolic disease and pregnancy. N Engl J Med 359:2025–2033, 2008.
24. Vandenbroucke JP, Koster T, Briet E, et al: Increased risk of venous thrombosis in oral-contraceptive users who are carriers of factor V Leiden mutation. Lancet 344:1453–1457, 1994.
25. Poort SR, Rosendaal FR, Reitsma PH, Bertina RM: A common genetic variation in the 3′-untranslated region of the prothrombin gene is associated with elevated plasma prothrombin levels and an increase in venous thrombosis. Blood 88:3698–3703, 1996.
26. Hillarp A, Zoller B, Svensson PJ, Dahlback B: The 20210 A allele of the prothrombin gene is a common risk factor among Swedish outpatients with verified deep venous thrombosis. Thromb Haemost 78:990–992, 1997.
27. Ray JG: Meta-analysis of hyperhomocysteinemia as a risk factor for venous thromboembolic disease. Arch Intern Med 158:2101–2106, 1998.
28. Key NS, McGlennen RC: Hyperhomocyst(e)inemia and thrombophilia. Arch Pathol Lab Med 126:1367–1375, 2002.
29. Salomon O, Steinberg DM, Zivelin A, et al: Single and combined prothrombotic factors in patients with idiopathic venous thromboembolism: Prevalence and risk assessment. Arterioscler Thromb Vasc Biol 19:511–518, 1999.
30. De Stefano V, Martinelli I, Mannucci PM, et al: The risk of recurrent deep venous thrombosis among heterozygous carriers of both factor V Leiden and the G20210A prothrombin mutation. N Engl J Med 341:801–806, 1999.
31. Eichinger S, Pabinger I, Stumpflen A, et al: The risk of recurrent venous thromboembolism in patients with and without factor V Leiden. Thromb Haemost 77:624–628, 1997.
32. De Stefano V, Martinelli I, Mannucci PM, et al: The risk of recurrent venous thromboembolism among heterozygous carriers of the G20210A prothrombin gene mutation. Br J Haematol 113:630–635, 2001.
33. Walker ID: Factor V Leiden: Should all women be screened prior to commencing the contraceptive pill? Blood Rev 13:8–13, 1999.
34. Seligsohn U, Lubetsky A: Genetic susceptibility to venous thrombosis. N Engl J Med 344:1222–1231, 2001.
35. Spannagl M, Heinemann LA, Schramm W: Are factor V Leiden carriers who use oral contraceptives at extreme risk for venous thromboembolism? Eur J Contracept Reprod Health Care 5:105–112, 2000.
36. Anderson F Jr, Spencer F: Risk factors for venous thromboembolism. Circulation 107(23 Suppl 1):I9–I16, 2003.
37. Cade JF: High risk of the critically ill for venous thromboembolism. Crit Care Med 10:448–450, 1982.
38. Belch JJ, Lowe GD, Ward AG, et al: Prevention of deep vein thrombosis in medical patients by low-dose heparin. Scott Med J 26:115–117, 1981.
39. Hirsch DR, Ingenito EP, Goldhaber SZ: Prevalence of deep venous thrombosis among patients in medical intensive care. JAMA 274:335–337, 1995.
40. Heit J: Risk factors for venous thromboembolism. Clin Chest Med 24:1–12, 2003.
41. Kearon C: Natural history of venous thromboembolism. Circulation 107(23 Suppl 1):I22–I30, 2003.
42. Prandoni P, Cogo A, Bernardi E, et al: A simple ultrasound approach for detection of recurrent proximal-vein thrombosis. Circulation 88:1730–1735, 1993.
43. Sevitt S, Gallagher N: Venous thrombosis and pulmonary embolism. A clinico-pathological study in injured and burned patients. Br J Surg 48:475–489, 1961.
44. Prandoni P, Bernardi E: Upper extremity deep vein thrombosis. Curr Opin Pulm Med 5:222–226, 1999.
44a. Baskin JL, Pui CH, Reiss U, et al: Management of occlusion and thrombosis associated with long-term indwelling central venous catheters. Lancet 374:159–169, 2009.
45. Moser KM, LeMoine JR: Is embolic risk conditioned by location of deep venous thrombosis? Ann Intern Med 94:439–444, 1981.
46. Huisman MV, Buller HR, ten Cate JW: Utility of impedance plethysmography in the diagnosis of recurrent deep-vein thrombosis. Arch Intern Med 148:681–683, 1988.
47. Moser KM, Fedullo PF, LitteJohn JK, Crawford R: Frequent asymptomatic pulmonary embolism in patients with deep venous thrombosis. [see comments]. JAMA 271:223–225, 1994 [published erratum appears in JAMA 271:1908, 1994].
48. Huisman MV, Buller HR, ten Cate JW, et al: Unexpected high prevalence of silent pulmonary embolism in patients with deep venous thrombosis. Chest 95:498–502, 1989.
49. Schulman S, Rhedin AS, Lindmarker P, et al: A comparison of six weeks with six months of oral anticoagulant therapy after a first episode of venous thromboembolism. Duration of Anticoagulation Trial Study Group [see comments]. N Engl J Med 332:1661–1665, 1995.
50. Prandoni P, Lensing AW, Cogo A, et al: The long-term clinical course of acute deep venous thrombosis. Ann Intern Med 125:1–7, 1996.
51. Prandoni P, Lensing AW, Prins MH, et al: Residual venous thrombosis as a predictive factor of recurrent venous thromboembolism. Ann Intern Med 137:955–960, 2002.
52. Wood KE: Major pulmonary embolism: Review of a pathophysiologic approach to the golden hour of hemodynamically significant pulmonary embolism. Chest 121:877–905, 2002.

53. Huet Y, Lemaire F, Brun-Buisson C, et al: Hypoxemia in acute pulmonary embolism. Chest 88:829–836, 1985.
54. D'Angelo E: Lung mechanics and gas exchange in pulmonary embolism. Haematologica 82:371–374, 1997.
55. Prediletto R, Paoletti P, Fornai E, et al: Natural course of treated pulmonary embolism. Evaluation by perfusion lung scintigraphy, gas exchange, and chest roentgenogram. Chest 97:554–561, 1990.
56. Severinghaus JW, Swenson EW, Finley TN, et al: Unilateral hypoventilation produced in dogs by occluding one pulmonary artery. J Appl Physiol 16:53–60, 1961.
57. Manier G, Castaing Y, Guenard H: Determinants of hypoxemia during the acute phase of pulmonary embolism in humans. Am Rev Respir Dis 132:332–338, 1985.
58. D'Alonzo GE, Bower JS, DeHart P, Dantzker DR: The mechanisms of abnormal gas exchange in acute massive pulmonary embolism. Am Rev Respir Dis 128:170–172, 1983.
59. Chernick V, Hodson WA, Greenfield LJ: Effect of chronic pulmonary artery ligation on pulmonary mechanics and surfactant. J Appl Physiol 21:1315–1320, 1966.
60. Bjork L, McNeil BJ: Blood flow in pulmonary and bronchial arteries in acute experimental pneumonia and pulmonary embolism. Acta Radiol Diagn (Stockh) 18:393–399, 1977.
61. Dalen JE, Haffajee CI, Alpert JS 3rd, et al: Pulmonary embolism, pulmonary hemorrhage and pulmonary infarction. N Engl J Med 296:1431–1435, 1977.
62. Ellis FH Jr, Grindlay JH, Edwards JE: The bronchial arteries. II. Their role in pulmonary embolism and infarction. Surgery 31:167–179, 1952.
63. Schraufnagel DE, Tsao MS, Yao YT, Wang NS: Factors associated with pulmonary infarction. A discriminant analysis study. Am J Clin Pathol 84:15–18, 1985.
64. Tsao MS, Schraufnagel D, Wang NS: Pathogenesis of pulmonary infarction. Am J Med 72:599–606, 1982.
65. Jandik J, Endrys J, Rehulova E, et al: Bronchial arteries in experimental pulmonary infarction: Angiographic and morphometric study. Cardiovasc Res 27:1076–1083, 1993.
66. Wood KE: Major pulmonary embolism: Review of a pathophysiologic approach to the golden hour of hemodynamically significant pulmonary embolism. Chest 121:877–905, 2002.
67. Elliott CG: Pulmonary physiology during pulmonary embolism. Chest 101(4 Suppl):163S–171S, 1992.
68. McIntyre KM, Sasahara AA: The hemodynamic response to pulmonary embolism in patients without prior cardiopulmonary disease. Am J Cardiol 28:288–294, 1971.
69. McIntyre KM, Sasahara AA: Hemodynamic alterations related to extent of lung scan perfusion defect in pulmonary embolism. J Nucl Med 12:166–170, 1971.
70. McIntyre KM, Sasahara AA: Correlation of pulmonary photoscan and angiogram as measures of the severity of pulmonary embolic involvement. J Nucl Med 12:732–738, 1971.
71. McIntyre KM, Sasahara AA: Hemodynamic and ventricular responses to pulmonary embolism. Prog Cardiovasc Dis 17:175–190, 1974.
72. Smulders YM: Pathophysiology and treatment of haemodynamic instability in acute pulmonary embolism: The pivotal role of pulmonary vasoconstriction. Cardiovasc Res 48:23–33, 2000.
73. Azarian R, Wartski M, Collignon MA, et al: Lung perfusion scans and hemodynamics in acute and chronic pulmonary embolism. J Nucl Med 38:980–983, 1997.
74. Donnamaria V, Palla A, Petruzzelli S, et al: Early and late follow-up of pulmonary embolism. Respiration 60:15–20, 1993.
75. Menendez R, Nauffal D, Cremades MJ: Prognostic factors in restoration of pulmonary flow after submassive pulmonary embolism: A multiple regression analysis. Eur Respir J 11:560–564, 1998.
76. Murphy ML, Bulloch RT: Factors influencing the restoration of blood flow following pulmonary embolization as determined by angiography and scanning. Circulation 38:1116–1126, 1968.
77. Palla A, Donnamaria V, Petruzzelli S, Giuntini C: Follow-up of pulmonary perfusion recovery after embolism. J Nucl Med Allied Sci 30:23–28, 1986.
78. Walker RH, Goodwin J, Jackson JA: Resolution of pulmonary embolism. Br Med J 4:135–139, 1970.
79. Wartski M, Collignon MA: Incomplete recovery of lung perfusion after 3 months in patients with acute pulmonary embolism treated with antithrombotic agents. THESEE Study Group. Tinzaparin ou Heparin Standard: Evaluation dans l'Embolie Pulmonaire Study. J Nucl Med 41:1043–1048, 2000.
80. James WS 3rd, Menn SJ, Moser KM: Rapid resolution of a pulmonary embolus in man. West J Med 128:60–64, 1978.
81. Ribeiro A, Lindmarker P, Johnsson H, et al: Pulmonary embolism: One-year follow-up with echocardiography doppler and five-year survival analysis. Circulation 99:1325–1330, 1999.
82. Cranley JJ, Canos AJ, Sull WJ: The diagnosis of deep venous thrombosis. Fallibility of clinical symptoms and signs. Arch Surg 111:34–36, 1976.
83. Haeger K: Problems of acute deep venous thrombosis. I. The interpretation of signs and symptoms. Angiology 20:219–223, 1969.
84. Anand SS, Wells PS, Hunt D, et al: Does this patient have deep vein thrombosis? JAMA 279:1094–1099, 1998.
84a. Konstantinides S: Clinical practice. Acute pulmonary embolism. N Engl J Med 359:2804–2813, 2008.
85. Wells PS, Lensing AW, Davidson BL, et al: Accuracy of ultrasound for the diagnosis of deep venous thrombosis in asymptomatic patients after orthopedic surgery. A meta-analysis. Ann Intern Med 122:47–53, 1995.
86. Wells PS, Hirsh J, Anderson DR, et al: A simple clinical model for the diagnosis of deep-vein thrombosis combined with impedance plethysmography: potential for an improvement in the diagnostic process. J Intern Med 243:15–23, 1998.
87. Ryu JH, Olson EJ, Pellikka PA: Clinical recognition of pulmonary embolism: Problem of unrecognized and asymptomatic cases. Mayo Clin Proc 73:873–879, 1998.
88. Goldhaber SZ, Hennekens CH, Evans DA, et al: Factors associated with correct antemortem diagnosis of major pulmonary embolism. Am J Med 73:822–826, 1982.
89. Stein PD, Terrin ML, Hales CA, et al: Clinical, laboratory, roentgenographic, and electrocardiographic findings in patients with acute pulmonary embolism and no pre-existing cardiac or pulmonary disease. Chest 100:598–603, 1991.
90. Stein PD, Henry JW: Clinical characteristics of patients with acute pulmonary embolism stratified according to their presenting syndromes. Chest 112:974–979, 1997.
91. Value of the ventilation/perfusion scan in acute pulmonary embolism. Results of the prospective investigation of pulmonary embolism diagnosis (PIOPED). The PIOPED Investigators [see comments]. JAMA 263:2753–2759, 1990.
92. Monreal M, Ruiz J, Olazabal A, et al: Deep venous thrombosis and the risk of pulmonary embolism. A systematic study. Chest 102:677–681, 1992.
92a. Piazza G, Goldhaber SZ: Pulmonary embolism in heart failure. Circulation 118:1598–1601, 2008.
93. Afzal A, Noor HA, Gill SA, et al: Leukocytosis in acute pulmonary embolism. Chest 115:1329–1332, 1999.
94. Stein PD, Afzal A, Henry JW, Villareal CG: Fever in acute pulmonary embolism. Chest 117:39–42, 2000.
95. Rabinov K, Paulin S: Roentgen diagnosis of venous thrombosis in the leg. Arch Surg 104:134–144, 1972.
96. Fraser JD, Anderson DR: Deep venous thrombosis: Recent advances and optimal investigation with US. Radiology 211:9–24, 1999.
97. Pezzullo JA, Perkins AB, Cronan JJ: Symptomatic deep vein thrombosis: Diagnosis with limited compression US. Radiology 198:67–70, 1996.
98. Frederick MG, Hertzberg BS, Kliewer MA, et al: Can the US examination for lower extremity deep venous thrombosis be abbreviated? A prospective study of 755 examinations. Radiology 199:45–47, 1996.
99. Badgett DK, Comerota MC, Khan MN, et al: Duplex venous imaging: role for a comprehensive lower extremity examination. Ann Vasc Surg 14:73–76, 2000.
100. Strothman G, Blebea J, Fowl RJ, Rosenthal G: Contralateral duplex scanning for deep venous thrombosis is unnecessary in patients with symptoms. J Vasc Surg 22:543–547, 1995.
101. Kearon C, Julian JA, Newman TE, Ginsberg JS: Noninvasive diagnosis of deep venous thrombosis. McMaster Diagnostic Imaging Practice Guidelines Initiative [see comments]. Ann Intern Med 128:663–677, 1998.

102. Heijboer H, Buller HR, Lensing AW, et al: A comparison of real-time compression ultrasonography with impedance plethysmography for the diagnosis of deep-vein thrombosis in symptomatic outpatients. N Engl J Med 329:1365–1369, 1993.
103. Heijboer H, Cogo A, Buller HR, et al: Detection of deep vein thrombosis with impedance plethysmography and real-time compression ultrasonography in hospitalized patients. Arch Intern Med 152:1901–1903, 1992.
104. Ginsberg JS, Wells PS, Hirsh J, et al: Reevaluation of the sensitivity of impedance plethysmography for the detection of proximal deep vein thrombosis [see comments]. Arch Intern Med;154:1930–1933, 1994.
105. Wells PS, Hirsh J, Anderson DR, et al: Comparison of the accuracy of impedance plethysmography and compression ultrasonography in outpatients with clinically suspected deep vein thrombosis. A two-centre paired-design prospective trial. Thromb Haemost 74:1423–1427, 1995.
106. Huisman MV, Buller HR, ten Cate JW, Vreeken J: Serial impedance plethysmography for suspected deep venous thrombosis in outpatients. The Amsterdam General Practitioner Study. N Engl J Med 314:823–828, 1986.
107. Huisman MV, Buller HR, ten Cate JW: Utility of impedance plethysmography in the diagnosis of recurrent deep-vein thrombosis. Arch Intern Med 148:681–683, 1988.
108. Evans AJ, Sostman HD, Witty LA, et al: Detection of deep venous thrombosis: Prospective comparison of MR imaging and sonography. J Magn Reson Imaging 6:44–51, 1996.
109. Kanne JP, Lalani TA: Role of computed tomography and magnetic resonance imaging for deep venous thrombosis and pulmonary embolism. Circulation 109(12 Suppl 1):I15–I21, 2004.
110. Loud PA, Katz DS, Bruce DA, et al: Deep venous thrombosis with suspected pulmonary embolism: Detection with combined CT venography and pulmonary angiography. Radiology 219:498–502, 2001.
111. Stein PD, Fowler SE, Goodman LR, et al: Multidetector computed tomography for acute pulmonary embolism. N Engl J Med 354:2317–2327, 2006.
112. Kelly J, Rudd A, Lewis RR, Hunt BJ: Plasma D-dimers in the diagnosis of venous thromboembolism. Arch Intern Med 162:747–756, 2002.
113. Stein PD, Hull RD, Patel KC, et al: D-Dimer for the exclusion of acute venous thrombosis and pulmonary embolism: A systematic review. Ann Intern Med 140:589–602, 2004.
113a. Adam SS, Key NS, Greenberg CS: D-dimer antigen: current concepts and future prospects. Blood 113:2878–2887, 2009.
114. Perrier A, Desmarais S, Miron MJ, et al: Non-invasive diagnosis of venous thromboembolism in outpatients [see comments]. Lancet 353:190–195, 1999.
115. Wells PS, Anderson DR, Rodger M, et al: Evaluation of D-dimer in the diagnosis of suspected deep-vein thrombosis. N Engl J Med 349:1227–1235, 2003.
116. Constans J, Boutinet C, Salmi LR, et al: Comparison of four clinical prediction scores for the diagnosis of lower limb deep venous thrombosis in outpatients. Am J Med 115:436–440, 2003.
117. Wells PS, Anderson DR, Bormanis J, et al: Value of assessment of pretest probability of deep-vein thrombosis in clinical management. Lancet 350:1795–1798, 1997.
118. Schutgens RE, Ackermark P, Haas FJ, et al: Combination of a normal D-dimer concentration and a non-high pretest clinical probability score is a safe strategy to exclude deep venous thrombosis. Circulation 107:593–597, 2003.
119. Worsley DF, Alavi A, Aronchick JM, et al: Chest radiographic findings in patients with acute pulmonary embolism: Observations from the PIOPED Study. Radiology 189:133–136, 1993.
120. Stein PD, Dalen JE, McIntyre KM, et al: The electrocardiogram in acute pulmonary embolism. Prog Cardiovasc Dis 17:247–257, 1975.
121. Kucher N, Walpoth N, Wustmann K, et al: QR in V1—An ECG sign associated with right ventricular strain and adverse clinical outcome in pulmonary embolism. Eur Heart J 24:1113–1119, 2003.
122. Stein PD, Goldhaber SZ, Henry JW, Miller AC: Arterial blood gas analysis in the assessment of suspected acute pulmonary embolism [see comments]. Chest 109:78–81, 1996.
123. McConnell MV, Solomon SD, Rayan ME, et al: Regional right ventricular dysfunction detected by echocardiography in acute pulmonary embolism. Am J Cardiol 78:469–473, 1996.
124. Nass N, McConnell MV, Goldhaber SZ, et al: Recovery of regional right ventricular function after thrombolysis for pulmonary embolism. Am J Cardiol 83:804–806, A810, 1999.
125. Krivec B, Voga G, Zuran I, et al: Diagnosis and treatment of shock due to massive pulmonary embolism: Approach with transesophageal echocardiography and intrapulmonary thrombolysis. Chest 112:1310–1316, 1997.
126. Miniati M, Monti S, Pratali L, et al: Value of transthoracic echocardiography in the diagnosis of pulmonary embolism: Results of a prospective study in unselected patients. Am J Med 110:528–535, 2001.
127. Goldhaber SZ: Echocardiography in the management of pulmonary embolism. Ann Intern Med 136:691–700, 2002.
128. Konstantinides S, Geibel A, Olschewski M, et al: Importance of cardiac troponins I and T in risk stratification of patients with acute pulmonary embolism. Circulation 106:1263–1268, 2002.
129. ten Wolde M, Tulevski II, Mulder JW, et al: Brain natriuretic peptide as a predictor of adverse outcome in patients with pulmonary embolism. Circulation 107:2082–2084, 2003.
130. Hamel E, Pacouret G, Vincentelli D, et al: Thrombolysis or heparin therapy in massive pulmonary embolism with right ventricular dilation: Results from a 128-patient monocenter registry. Chest 120:120–125, 2001.
131. Anderson DR, Kahn SR, Rodger MA, et al: Computed tomographic pulmonary angiography vs ventilation-perfusion lung scanning in patients with suspected pulmonary embolism: A randomized controlled trial. JAMA 298:2743–2753, 2007.
132. Miniati M, Pistolesi M, Marini C, et al: Value of perfusion lung scan in the diagnosis of pulmonary embolism: Results of the Prospective Investigative Study of Acute Pulmonary Embolism Diagnosis (PISA-PED). Am J Respir Crit Care Med 154:1387–1393, 1996.
133. Henry JW, Stein PD, Gottschalk A, et al: Scintigraphic lung scans and clinical assessment in critically ill patients with suspected acute pulmonary embolism. Chest 109:462–466, 1996.
134. Kipper MS, Moser KM, Kortman KE, Ashburn WL: Long-term follow-up of patients with suspected pulmonary embolism and a normal lung scan. Perfusion scans in embolic suspects. Chest 82:411–415, 1982.
135. Hull RD, Raskob GE, Coates G, Panju AA: Clinical validity of a normal perfusion lung scan in patients with suspected pulmonary embolism. Chest 97:23–26, 1990.
136. van Beek EJ, Kuyer PM, Schenk BE, et al: A normal perfusion lung scan in patients with clinically suspected pulmonary embolism. Frequency and clinical validity. Chest 108:170–173, 1995.
137. van Beek EJ, Brouwers EM, Song B, et al: Lung scintigraphy and helical computed tomography for the diagnosis of pulmonary embolism: A meta-analysis. Clin Appl Thromb Hemost 7:87–92, 2001.
138. Goodman LR, Lipchik RJ, Kuzo RS, et al: Subsequent pulmonary embolism: Risk after a negative helical CT pulmonary angiogram—Prospective comparison with scintigraphy. Radiology 215:535–542, 2000.
139. Tapson VF, Carroll BA, Davidson BL, et al: The diagnostic approach to acute venous thromboembolism. Clinical practice guideline. American Thoracic Society. Am J Respir Crit Care Med 160:1043–1066, 1999.
140. British Thoracic Society guidelines for the management of suspected acute pulmonary embolism. Thorax 58:470–483, 2003.
141. Hirsh J, Hoak J: Management of deep vein thrombosis and pulmonary embolism: A statement for healthcare professionals from the Council on Thrombosis (in consultation with the Council on Cardiovascular Radiology), American Heart Association. Circulation 93:2212–2245, 1996.
142. Guidelines on diagnosis and management of acute pulmonary embolism. Task Force on Pulmonary Embolism, European Society of Cardiology. Eur Heart J 21:1301–1336, 2000.
143. Hull RD, Raskob GE, Pineo GF, Brant RF: The low-probability lung scan. A need for change in nomenclature. Arch Intern Med 155:1845–1851, 1995.

144. Miniati M, Pistolesi M, Marini C, et al: Value of perfusion lung scan in the diagnosis of pulmonary embolism: Results of the Prospective Investigative Study of Acute Pulmonary Embolism Diagnosis (PISA-PED). Am J Respir Crit Care Med 154:1387–1393, 1996.
145. Stein PD, Terrin ML, Gottschalk A, et al: Value of ventilation/perfusion scans versus perfusion scans alone in acute pulmonary embolism. Am J Cardiol 69:1239–1241, 1992.
146. Hartmann IJ, Hagen PJ, Melissant CF, et al: Diagnosing acute pulmonary embolism: Effect of chronic obstructive pulmonary disease on the performance of D-dimer testing, ventilation/perfusion scintigraphy, spiral computed tomographic angiography, and conventional angiography. ANTELOPE Study Group. Advances in New Technologies Evaluating the Localization of Pulmonary Embolism. Am J Respir Crit Care Med 162:2232–2237, 2000.
147. Hiorns MP, Mayo JR: Spiral computed tomography for acute pulmonary embolism. Can Assoc Radiol J 53:258–268, 2002.
148. Ruiz Y, Caballero P, Caniego JL, et al: Prospective comparison of helical CT with angiography in pulmonary embolism: Global and selective vascular territory analysis. Interobserver agreement. Eur Radiol 13:823–829, 2003.
149. Oser RF, Zuckerman DA, Gutierrez FR, Brink JA: Anatomic distribution of pulmonary emboli at pulmonary angiography: Implications for cross-sectional imaging [see comments]. Radiology 199:31–35, 1996.
150. Stein PD, Henry JW: Prevalence of acute pulmonary embolism in central and subsegmental pulmonary arteries and relation to probability interpretation of ventilation/perfusion lung scans. Chest 111:1246–1248, 1997.
151. Regni MV: Pulmonary embolism and spiral computerized tomographic scans. Curr Opin Pulm Med 15:430–438, 2009.
152. Goodman LR, Curtin JJ, Mewissen MW, et al: Detection of pulmonary embolism in patients with unresolved clinical and scintigraphic diagnosis: Helical CT versus angiography. AJR.Am J Roentgenol 164:1369–1374, 1995.
153. Sostman HD, Layish DT, Tapson VF, et al: Prospective comparison of helical CT and MR imaging in clinically suspected acute pulmonary embolism. J Magn Reson Imaging 6:275–281, 1996.
154. de Monye W, van Strijen MJ, Huisman MV, et al: Suspected pulmonary embolism: Prevalence and anatomic distribution in 487 consecutive patients. Advances in New Technologies Evaluating the Localisation of Pulmonary Embolism (ANTELOPE) Group. Radiology 215:184–188, 2000.
155. White RH, Zhou H, Murin S: Death due to recurrent thromboembolism among younger healthier individuals hospitalized for idiopathic pulmonary embolism. Thromb Haemost 99:683–690, 2008.
156. Brenner DJ, Hall EJ: Computed tomography—An increasing source of radiation exposure. N Engl J Med 357:2277–2284, 2007.
157. Hurwitz LM, Yoshizumi TT, Reiman RE, et al: Radiation dose to the female breast from 16-MDCT body protocols. AJR Am J Roentgenol 186:1718–1722, 2006.
158. Moores LK, Jackson WL Jr, Shorr AF, Jackson JL: Meta-analysis: Outcomes in patients with suspected pulmonary embolism managed with computed tomographic pulmonary angiography. Ann Intern Med 141:866–874, 2004.
159. van Strijen MJ, de Monye W, Schiereck J, et al: Single-detector helical computed tomography as the primary diagnostic test in suspected pulmonary embolism: A multicenter clinical management study of 510 patients. Ann Intern Med 138:307–314, 2003.
160. Hull RD, Raskob GE, Ginsberg JS, et al: A noninvasive strategy for the treatment of patients with suspected pulmonary embolism. Arch Intern Med 154:289–297, 1994.
161. Hull RD, Raskob GE, Pineo GF, Brant RF: The low-probability lung scan. A need for change in nomenclature. Arch Intern Med 155:1845–1851, 1995.
162. Turkstra F, Kuijer PM, van Beek EJ, et al: Diagnostic utility of ultrasonography of leg veins in patients suspected of having pulmonary embolism. Ann Intern Med 126:775–781, 1997.
163. Rosen MP, Sheiman RG, Weintraub J, McArdle C: Compression sonography in patients with indeterminate or low-probability lung scans: Lack of usefulness in the absence of both symptoms of deep-vein thrombosis and thromboembolic risk factors. AJR Am J Roentgenol 166:285–289, 1996.
164. Wells PS, Ginsberg JS, Anderson DR, et al: Utility of ultrasound imaging of the lower extremities in the diagnostic approach in patients with suspected pulmonary embolism. J Intern Med 250:262–264, 2001.
165. Perrier A: Diagnosis of acute pulmonary embolism: An update. Schweiz Med Wochenschr 130:264–271, 2000.
166. Hurwitz LM, Yoshizumi T, Reiman RE, et al: Radiation dose to the fetus from body MDCT during early gestation. AJR Am J Roentgenol 186:871–876, 2006.
167. Wells PS, Anderson DR, Rodger M, et al: Excluding pulmonary embolism at the bedside without diagnostic imaging: Management of patients with suspected pulmonary embolism presenting to the emergency department by using a simple clinical model and D-dimer. Ann Intern Med 135:98–107, 2001.
168. Kruip MJ, Slob MJ, Schijen JH, et al: Use of a clinical decision rule in combination with D-dimer concentration in diagnostic workup of patients with suspected pulmonary embolism: A prospective management study. Arch Intern Med 162:1631–1635, 2002.
169. Kruip MJ, Leclercq MG, van der Heul C, et al: Diagnostic strategies for excluding pulmonary embolism in clinical outcome studies. A systematic review. Ann Intern Med 138:941–951, 2003.
170. Nilsson T, Carlsson A, Mare K: Pulmonary angiography: A safe procedure with modern contrast media and technique. Eur Radiol 8:86–89, 1998.
171. Zuckerman DA, Sterling KM, Oser RF: Safety of pulmonary angiography in the 1990s. J Vasc Interv Radiol 7:199–205, 1996.
172. Wicki J, Perneger TV, Junod AF, et al: Assessing clinical probability of pulmonary embolism in the emergency ward: A simple score. Arch Intern Med 161:92–97, 2001.
173. Miniati M, Monti S, Bottai M: A structured clinical model for predicting the probability of pulmonary embolism. Am J Med 114:173–179, 2003.
174. Miniati M, Bottai M, Monti S, et al: Simple and accurate prediction of the clinical probability of pulmonary embolism. Am J Respir Crit Care Med 178:290–294, 2008.
175. Asif A, Preston RA, Roth D: Radiocontrast-induced nephropathy. Am J Ther 10:137–147, 2003.
176. Greer IA: Thrombosis in pregnancy: Maternal and fetal issues. Lancet 353:1258–1265, 1999.
177. Winer-Muram HT, Boone JM, Brown HL, et al: Pulmonary embolism in pregnant patients: Fetal radiation dose with helical CT. Radiology 224:487–492, 2002.
178. Bergqvist D, Agnelli G, Cohen AT, et al: Duration of prophylaxis against venous thromboembolism with enoxaparin after surgery for cancer. N Engl J Med 346:975–980, 2002.
179. Prevention of fatal postoperative pulmonary embolism by low doses of heparin. An international multicentre trial. Lancet 2:45–51, 1975.
180. Geerts WH, Bergqvist D, Pineo GF, et al: Prevention of venous thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th ed). Chest 133(6 Suppl):381S–453S, 2008.
181. Koch A, Ziegler S, Breitschwerdt H, Victor N: Low molecular weight heparin and unfractionated heparin in thrombosis prophylaxis: Meta-analysis based on original patient data. Thromb Res 102(4):295–309, 2001.
182. Comerota AJ, Katz ML, White JV: Why does prophylaxis with external pneumatic compression for deep vein thrombosis fail? Am J Surg 164:265–268, 1992.
183. Proctor MC, Greenfield LJ, Wakefield TW, Zajkowski PJ: A clinical comparison of pneumatic compression devices: The basis for selection. J Vasc Surg 34:459–463 2001 [discussion appears 463–454].
184. Francis CW, Marder VJ, Evarts CM, Yaukoolbodi S: Two-step warfarin therapy. Prevention of postoperative venous thrombosis without excessive bleeding. JAMA 249:374–378, 1983.
185. Hull RD, Pineo GF, Stein PD, et al: Timing of initial administration of low-molecular-weight heparin prophylaxis against deep vein thrombosis in patients following elective hip arthroplasty: A systematic review. Arch Intern Med 161:1952–1960, 2001.
186. Planes A, Vochelle N, Darmon JY, et al: Risk of deep-venous thrombosis after hospital discharge in patients having undergone

total hip replacement: Double-blind randomised comparison of enoxaparin versus placebo. Lancet 348:224–228, 1996.
187. Hull RD, Pineo GF, Stein PD, et al: Extended out-of-hospital low-molecular-weight heparin prophylaxis against deep venous thrombosis in patients after elective hip arthroplasty: A systematic review. Ann Intern Med 135:858–869, 2001.
188. Lassen MR, Bauer KA, Eriksson BI, Turpie AG: Postoperative fondaparinux versus preoperative enoxaparin for prevention of venous thromboembolism in elective hip-replacement surgery: A randomised double-blind comparison. Lancet 359:1715–1720, 2002.
189. Turpie AG, Bauer KA, Eriksson BI, Lassen MR: Postoperative fondaparinux versus postoperative enoxaparin for prevention of venous thromboembolism after elective hip-replacement surgery: A randomised double-blind trial. Lancet 359:1721–1726, 2002.
190. Girard TD, Philbrick JT, Fritz Angle J, Becker DM: Prophylactic vena cava filters for trauma patients: A systematic review of the literature. Thromb Res 112:261–267, 2003.
191. Anderson FAJ, Wheeler HB, Goldberg RJ, et al: Physician practices in the prevention of venous thromboembolism. Ann Intern Med 115:591–595, 1991.
192. Bratzler DW, Raskob GE, Murray CK, et al: Underuse of venous thromboembolism prophylaxis for general surgery patients: Physician practices in the community hospital setting. Arch Intern Med 158:1909–1912, 1998.
193. Kearon C, Kahn SR, Agnelli G, et al: Antithrombotic therapy for venous thromboembolic disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th ed). Chest 133(6 Suppl):454S–545S, 2008.
194. Wheeler AP, Jaquiss RD, Newman JH: Physician practices in the treatment of pulmonary embolism and deep venous thrombosis. Arch Intern Med 148:1321–1325, 1988.
195. Bernardi E, Piccioli A, Oliboni G, et al: Nomograms for the administration of unfractionated heparin in the initial treatment of acute thromboembolism—An overview. Thromb Haemost 84:22–26, 2000.
196. Raschke RA, Reilly BM, Guidry JR, et al: The weight-based heparin dosing nomogram compared with a "standard care" nomogram. A randomized controlled trial. Ann Intern Med 119:874–881, 1993.
197. Bates SM, Weitz JI, Johnston M, et al: Use of a fixed activated partial thromboplastin time ratio to establish a therapeutic range for unfractionated heparin. Arch Intern Med 161:385–391, 2001.
198. Levine MN, Hirsh J, Gent M, et al: A randomized trial comparing activated thromboplastin time with heparin assay in patients with acute venous thromboembolism requiring large daily doses of heparin. Arch Intern Med 154:49–56, 1994.
199. Hull RD, Raskob GE, Rosenbloom D, et al: Optimal therapeutic level of heparin therapy in patients with venous thrombosis. Arch Intern Med 152:1589–1595, 1992.
200. Hull RD, Raskob GE, Brant RF, et al: The importance of initial heparin treatment on long-term clinical outcomes of antithrombotic therapy. The emerging theme of delayed recurrence. Arch Intern Med 157:2317–2321, 1997.
201. Anand S, Ginsberg JS, Kearon C, et al: The relation between the activated partial thromboplastin time response and recurrence in patients with venous thrombosis treated with continuous intravenous heparin. Arch Intern Med 156:1677–1681, 1996.
202. Gould MK, Dembitzer AD, Sanders GD, Garber AM: Low-molecular-weight heparins compared with unfractionated heparin for treatment of acute deep venous thrombosis. A cost-effectiveness analysis [see comments]. Ann Intern Med 130:789–799, 1999.
203. Kearon C, Ginsberg JS, Julian JA, et al: Comparison of fixed-dose weight-adjusted unfractionated heparin and low-molecular-weight heparin for acute treatment of venous thromboembolism. JAMA 296:935–942, 2006.
204. Dolovich LR, Ginsberg JS, Dpiletos JD, et al: A meta-analysis comparing low-molecular-weight heparin with unfractionated heparin in the treatment of venous thromboembolism. Arch Intern Med 160:181–188, 2000.
205. Segal JB, Bolger DT, Jenckes MW, et al: Outpatient therapy with low molecular weight heparin for the treatment of venous thromboembolism: A review of efficacy, safety, and costs. Am J Med 115:298–308, 2003.
206. Hull RD, Raskob GE, Rosenbloom D, et al: Heparin for 5 days as compared with 10 days in the initial treatment of proximal venous thrombosis. N Engl J Med 322:1260–1264, 1990.
207. Chong BH: Heparin-induced thrombocytopenia. J Thromb Haemost 1:1471–1478, 2003.
208. Morris TA, Castrejon S, Devendra G, Gamst AC: No difference in risk for thrombocytopenia during treatment of pulmonary embolism and deep venous thrombosis with either low-molecular-weight heparin or unfractionated heparin: A meta-analysis. Chest 132:1131–1139, 2007.
209. Warkentin TE, Kelton JG: Temporal aspects of heparin-induced thrombocytopenia. N Engl J Med 344:1286–1292, 2001.
210. Wallis DE, Workman DL, Lewis BE, et al: Failure of early heparin cessation as treatment for heparin-induced thrombocytopenia. Am J Med 106:629–635, 1999.
211. Warkentin TE, Greinacher A, Koster A, Lincoff AM: Treatment and prevention of heparin-induced thrombocytopenia: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th ed). Chest 133(6 Suppl):340S–380S, 2008.
212. Lewis BE, Wallis DE, Leya F, et al: Argatroban anticoagulation in patients with heparin-induced thrombocytopenia. Arch Intern Med 163:1849–1856, 2003.
213. Warkentin TE, Levine MN, Hirsh J, et al: Heparin-induced thrombocytopenia in patients treated with low-molecular-weight heparin or unfractionated heparin. N Engl J Med 332:1330–1335, 1995.
214. Streiff MB: Vena caval filters: A comprehensive review. Blood 95:3669–3677, 2000.
215. Decousus H, Leizorovicz A, Parent F, et al: A clinical trial of vena caval filters in the prevention of pulmonary embolism in patients with proximal deep-vein thrombosis. Prevention du Risque d'Embolie Pulmonaire par Interruption Cave Study Group. N Engl J Med 338:409–415, 1998.
216. Decousus H: Eight-year follow-up of a randomized trial investigating vena cava filters in the prevention of PE in patients presenting a proximal DVT: The PREPIC trial. J Thromb Haemost 1(Suppl):OC440, 2003.
217. Mismetti P, Rivron-Guillot K, Quenet S, et al: A prospective long-term study of 220 patients with a retrievable vena cava filter for secondary prevention of venous thromboembolism. Chest 131:223–229, 2007.
217a. Masuda M, Nakajima N: Our experience of surgical treatment for chronic pulmonary thromboembolism. Ann Thorac Cardiovasc Surg 7:261–265, 2001.
218. Tapson VF, Witty LA: Massive pulmonary embolism. Diagnostic and therapeutic strategies. Clin Chest Med 16:329–340, 1995.
219. Kasper W, Konstantinides S, Geibel A, et al: Management strategies and determinants of outcome in acute major pulmonary embolism: Results of a multicenter registry. J Am Coll Cardiol 30:1165–1171, 1997.
220. Goldhaber SZ, Visani L, De Rosa M: Acute pulmonary embolism: Clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). Lancet 353:1386–1389, 1999.
221. Urokinase Pulmonary Embolism Trial. Phase 1 results: A cooperative study. JAMA 214:2163–2172, 1970.
222. Layish DT, Tapson VF: Pharmacologic hemodynamic support in massive pulmonary embolism. Chest 111:218–224, 1997.
223. Wood KE: The presence of shock defines the threshold to initiate thrombolytic therapy in patients with pulmonary embolism. Intensive Care Med 28:1537–1546, 2002.
224. Konstantinides S: The case for thrombolysis in acute major pulmonary embolism: Hemodynamic benefits and beyond. Intensive Care Med 28:1547–1551, 2002.
225. Wan S, Quinlan DJ, Agnelli G, Eikelboom JW: Thrombolysis compared with heparin for the initial treatment of pulmonary embolism: A meta-analysis of the randomized controlled trials. Circulation 110:744–749, 2004.
226. Dalen JE, Alpert JS, Hirsh J: Thrombolytic therapy for pulmonary embolism: Is it effective? Is it safe? When is it indicated? Arch Intern Med 157:2550–2556, 1997.
227. Konstantinides S, Geibel A, Heusel G, et al: Heparin plus alteplase compared with heparin alone in patients with submassive pulmonary embolism. N Engl J Med 347:1143–1150, 2002.

228. Meneveau N, Ming LP, Seronde MF, et al: In-hospital and long-term outcome after sub-massive and massive pulmonary embolism submitted to thrombolytic therapy. Eur Heart J 24:1447–1454, 2003.
229. Rose PS, Punjabi NM, Pearse DB: Treatment of right heart thromboemboli. Chest 121:806–814, 2002.
230. Chartier L, Bera J, Delomez M, et al: Free-floating thrombi in the right heart: Diagnosis, management, and prognostic indexes in 38 consecutive patients. Circulation 99:2779–2783, 1999.
231. Grifoni S, Olivotto I, Cecchini P, et al: Short-term clinical outcome of patients with acute pulmonary embolism, normal blood pressure, and echocardiographic right ventricular dysfunction. Circulation 101:2817–2822, 2000.
232. Doerge HC, Schoendube FA, Loeser H, et al: Pulmonary embolectomy: Review of a 15-year experience and role in the age of thrombolytic therapy. Eur J Cardiothorac Surg 10:952–957, 1996.
233. Gray HH, Morgan JM, Paneth M, Miller GA: Pulmonary embolectomy for acute massive pulmonary embolism: An analysis of 71 cases. Br Heart J 60:196–200, 1988.
234. Gray HH, Miller GA, Paneth M: Pulmonary embolectomy: Its place in the management of pulmonary embolism. Lancet 1:1441–1445, 1988.
235. Aklog L, Williams CS, Byrne JG, Goldhaber SZ: Acute pulmonary embolectomy: A contemporary approach. Circulation 105:1416–1419, 2002.
236. Uflacker R: Interventional therapy for pulmonary embolism. J Vasc Interv Radiol 12:147–164, 2001.
237. Kearon C, Gent M, Hirsh J, et al: A comparison of three months of anticoagulation with extended anticoagulation for a first episode of idiopathic venous thromboembolism [see comments]. N Engl J Med 340:901–907, 1999.
238. Agnelli G, Prandoni P, Becattini C, et al: Extended oral anticoagulant therapy after a first episode of pulmonary embolism. Ann Intern Med 139:19–25, 2003.
239. Agnelli G, Prandoni P, Santamaria MG, et al: Three months versus one year of oral anticoagulant therapy for idiopathic deep venous thrombosis. Warfarin Optimal Duration Italian Trial Investigators. N Engl J Med 345:165–169, 2001.
240. Pinede L, Ninet J, Duhaut P, et al: Comparison of 3 and 6 months of oral anticoagulant therapy after a first episode of proximal deep vein thrombosis or pulmonary embolism and comparison of 6 and 12 weeks of therapy after isolated calf deep vein thrombosis. Circulation 103:2453–2460, 2001.
241. Eichinger S, Minar E, Bialonczyk C, et al: D-Dimer levels and risk of recurrent venous thromboembolism. JAMA 290:1071–1074, 2003.
242. Khamashta MA, Cuadrado MJ, Mujic F, et al: The management of thrombosis in the antiphospholipid-antibody syndrome. N Engl J Med 332:993–997, 1995.
243. Crowther MA, Ginsberg JS, Julian J, et al: A comparison of two intensities of warfarin for the prevention of recurrent thrombosis in patients with the antiphospholipid antibody syndrome. N Engl J Med 349:1133–1138, 2003.
244. Moll S, Ortel TL: Monitoring warfarin therapy in patients with lupus anticoagulants. Ann Intern Med 127:177–185, 1997.
245. Ridker PM, Goldhaber SZ, Danielson E, et al: Long-term, low-intensity warfarin therapy for the prevention of recurrent venous thromboembolism. N Engl J Med 348:1425–1434, 2003.
246. Kearon C, Ginsberg JS, Kovacs MJ, et al: Comparison of low-intensity warfarin therapy with conventional-intensity warfarin therapy for long-term prevention of recurrent venous thromboembolism. N Engl J Med 349:631–639, 2003.
247. Dalen JE, Banas JS, Brooks HL, et al: Resolution rate of acute pulmonary embolism in man. N Engl J Med 280:1194–1199, 1969.
248. Tow DE, Wagner HN Jr: Recovery of pulmonary arterial blood flow in patients with pulmonary embolism. N Engl J Med 276:1053–1059, 1967.
249. The Urokinase Pulmonary Embolism Trial. A national cooperative study. Circulation 47(2 Suppl):II1–II108, 1973.
250. Fedullo PF, Auger WR, Kerr KM, Rubin LJ: Chronic thromboembolic pulmonary hypertension. N Engl J Med 345:1465–1472, 2001.
251. Pengo V, Lensing AW, Prins MH, et al: Incidence of chronic thromboembolic pulmonary hypertension after pulmonary embolism. N Engl J Med 350:2257–2264, 2004.
252. Lang I, Kerr K: Risk factors for chronic thromboembolic pulmonary hypertension. Proc Am Thorac Soc 3:568–570, 2006.
253. Bonderman D, Jakowitsch J, Adlbrecht C, et al: Medical conditions increasing the risk of chronic thromboembolic pulmonary hypertension. Thromb Haemost 93:512–516, 2005.
254. Auger WR, Permpikul P, Moser KM: Lupus anticoagulant, heparin use, and thrombocytopenia in patients with chronic thromboembolic pulmonary hypertension: A preliminary report. Am J Med 99:392–396, 1995.
255. Bonderman D, Turecek PL, Jakowitsch J, et al: High prevalence of elevated clotting factor VIII in chronic thromboembolic pulmonary hypertension. Thromb Haemost 90:372–376, 2003.
256. Ignatescu M, Kostner K, Zorn G, et al: Plasma Lp(a) levels are increased in patients with chronic thromboembolic pulmonary hypertension. Thromb Haemost 80:231–232, 1998.
257. Bonderman D, Wilkens H, Wakounig S, et al: Risk factors for chronic thromboembolic pulmonary hypertension. Eur Respir J 33:325–331, 2009.
258. Moser KM, Auger WR, Fedullo PF: Chronic major-vessel thromboembolic pulmonary hypertension. Circulation 81:1735–1743, 1990.
259. Wolf M, Boyer-Neumann C, Parent F, et al: Thrombotic risk factors in pulmonary hypertension. Eur Respir J 15:395–399, 2000.
260. Fedullo PF, Rubin LJ, Kerr KM, et al: The natural history of acute and chronic thromboembolic disease: The search for the missing link. Eur Respir J 15:435–437, 2000.
261. Moser KM, Bloor CM: Pulmonary vascular lesions occurring in patients with chronic major vessel thromboembolic pulmonary hypertension [see comments]. Chest 103:685–692, 1993.
262. Riedel M, Stanek V, Widimsky J, Prerovsky I: Long-term follow-up of patients with pulmonary thromboembolism. Late prognosis and evolution of hemodynamic and respiratory data. Chest 81:151–158, 1982.
263. Lewczuk J, Piszko P, Jagas J, et al: Prognostic factors in medically treated patients with chronic pulmonary embolism. Chest 119:818–823, 2001.
264. Meignan M, Rosso J, Gauthier H, et al: Systematic lung scans reveal a high frequency of silent pulmonary embolism in patients with proximal deep venous thrombosis. Arch Intern Med 160:159–164, 2000.
265. Auger WR, Moser KM: Pulmonary flow murmurs: A distinctive physical sign found in chronic pulmonary thromboembolic disease. Clin Res 37:145A, 1989.
266. D'Alonzo GE, Bower JS, Dantzker DR: Differentiation of patients with primary and thromboembolic pulmonary hypertension. Chest 85:457–461, 1984.
267. Morris TA, Auger WR, Ysrael MZ, et al: Parenchymal scarring is associated with restrictive spirometric defects in patients with chronic thromboembolic pulmonary hypertension. Chest 110:399–403, 1996.
268. Kapitan KS, Buchbinder M, Wagner PD, Moser KM: Mechanisms of hypoxemia in chronic thromboembolic pulmonary hypertension. Am Rev Respir Dis 139:1149–1154, 1989.
269. Fishman AJ, Moser KM, Fedullo P: Perfusion lung scans vs pulmonary angiography in evaluation of suspected primary pulmonary hypertension. Chest 84:679–683, 1983.
270. Bailey CL, Channick RN, Auger WR, et al: "High probability" perfusion lung scans in pulmonary venoocclusive disease. Am J Respir Crit Care Med 162:1974–1978, 2000.
271. Ryan KL, Fedullo PF, Davis GB, et al: Perfusion scan findings understate the severity of angiographic and hemodynamic compromise in chronic thromboembolic pulmonary hypertension. Chest 93:1180–1185, 1988.
272. King MA, Ysrael M, Bergin CJ: Chronic thromboembolic pulmonary hypertension: CT findings. AJR Am J Roentgenol 170:955–960, 1998.
273. Moser KM, Fedullo PF, Finkbeiner WE, Golden J: Do patients with primary pulmonary hypertension develop extensive central thrombi? Circulation 91:741–745, 1995.

274. Auger WR, Fedullo PF, Moser KM, et al: Chronic major-vessel thromboembolic pulmonary artery obstruction: Appearance at angiography. Radiology 182:393–398, 1992.
275. Shure D, Gregoratos G, Moser KM: Fiberoptic angioscopy: Role in the diagnosis of chronic pulmonary arterial obstruction. Ann Intern Med 103:844–850, 1985.
276. Kerr KM, Auger WR, Fedullo PF, et al: Large vessel pulmonary arteritis mimicking chronic thromboembolic disease. Am J Respir Crit Care Med 152:367–373, 1995.
277. Fedullo PF, Auger WR, Kerr KM, Kim NH: Chronic thromboembolic pulmonary hypertension. Semin Respir Crit Care Med 24:273–286, 2003.
278. Jamieson SW, Kapelanski DP, Sakakibara N, et al: Pulmonary endarterectomy: Experience and lessons learned in 1,500 cases. Ann Thorac Surg 76:1457–1462 2003 [discussion appears 1462–1454].
279. Olman MA, Auger WR, Fedullo PF, Moser KM: Pulmonary vascular steal in chronic thromboembolic pulmonary hypertension. Chest 98:1430–1434, 1990.
280. Levinson RM, Shure D, Moser KM: Reperfusion pulmonary edema after pulmonary artery thromboendarterectomy. Am Rev Respir Dis 134:1241–1245, 1986.
281. Moser KM, Metersky ML, Auger WR, Fedullo PF: Resolution of vascular steal after pulmonary thromboendarterectomy. Chest 104:1441–1444, 1993.
282. Mares P, Gilbert TB, Tschernko EM, et al: Pulmonary artery thromboendarterectomy: A comparison of two different postoperative treatment strategies. Anesth Analg 90:267–273, 2000.
283. Rubens F, Wells P, Bencze S, Bourke M: Surgical treatment of chronic thromboembolic pulmonary hypertension. Can Respir J 7:49–57, 2000.
284. D'Armini AM, Cattadori B, Monterosso C, et al: Pulmonary thromboendarterectomy in patients with chronic thromboembolic pulmonary hypertension: Hemodynamic characteristics and changes. Eur J Cardiothorac Surg 18:696–701, 2000 [discussion appears 701–692].
285. Tscholl D, Langer F, Wendler O, et al: Pulmonary thromboendarterectomy—Risk factors for early survival and hemodynamic improvement. Eur J Cardiothorac Surg 19:771–776, 2001.
286. Hagl C, Khaladj N, Peters T, et al: Technical advances of pulmonary thromboendarterectomy for chronic thromboembolic pulmonary hypertension. Eur J Cardiothorac Surg 23:776–781, 2003 [discussion appears 781].
287. Birkmeyer JD, Siewers AE, Finlayson EV, et al: Hospital volume and surgical mortality in the United States. N Engl J Med 346:1128–1137, 2002.
288. Kramm T, Mayer E, Dahm M, et al: Long-term results after thromboendarterectomy for chronic pulmonary embolism. Eur J Cardiothorac Surg 15:579–583, 1999 [discussion appears 583–584].
289. Archibald CJ, Auger WR, Fedullo PF, et al: Long-term outcome after pulmonary thromboendarterectomy. Am J Respir Crit Care Med 160:523–528, 1999.
290. Zoia MC, D'Armini AM, Beccaria M, et al: Mid term effects of pulmonary thromboendarterectomy on clinical and cardiopulmonary function status. Thorax 57:608–612, 2002.
291. McLaughlin VV, Genthner DE, Panella MM, et al: Compassionate use of continuous prostacyclin in the management of secondary pulmonary hypertension: A case series. Ann Intern Med 130:740–743, 1999.
292. Ono F, Nagaya N, Okumura H, et al: Effect of orally active prostacyclin analogue on survival in patients with chronic thromboembolic pulmonary hypertension without major vessel obstruction. Chest 123:1583–1588, 2003.
293. Suntharalingam J, Treacy CM, Doughty NJ, et al: Long-term use of sildenafil in inoperable chronic thromboembolic pulmonary hypertension. Chest 134:229–236, 2008.
294. Hughes RJ, Jais X, Bonderman D, et al: The efficacy of bosentan in inoperable chronic thromboembolic pulmonary hypertension: A 1-year follow-up study. Eur Respir J 28:138–143, 2006.
295. Nagaya N, Sasaki N, Ando M, et al: Prostacyclin therapy before pulmonary thromboendarterectomy in patients with chronic thromboembolic pulmonary hypertension. Chest 123:338–343, 2003.
296. Morris W, Knauer CM: Cardiopulmonary manifestations of schistosomiasis. Semin Respir Infect 12:159–170, 1997.
297. Muth CM, Shank ES: Gas embolism. N Engl J Med 342:476–482, 2000.
298. Butler BD, Hills BA: The lung as a filter for microbubbles. J Appl Physiol 47:537–543, 1979.
299. Palmon SC, Moore LE, Lundberg J, Toung T: Venous air embolism: A review. J Clin Anesth 9:251–257, 1997.
300. Tibbles PM, Edelsberg JS: Hyperbaric-oxygen therapy. N Engl J Med 334:1642–1648, 1996.
301. Johnson MJ, Lucas GL: Fat embolism syndrome. Orthopedics 19:41–48, 1996 [discussion appears 48–49].
302. Gossling HR, Pellegrini VD Jr: Fat embolism syndrome: A review of the pathophysiology and physiological basis of treatment. Clin Orthop Relat Res 165:68–82, 1982.
303. Bruecke P, Burke JF, Lam KW, et al: The pathophysiology of pulmonary fat embolism. J Thorac Cardiovasc Surg 61:949–955, 1971.
304. Richards RR: Fat embolism syndrome. Can J Surg 40:334–339, 1997.
305. King MB, Harmon KR: Unusual forms of pulmonary embolism. Clin Chest Med 15:561–580, 1994.
306. Davies S: Amniotic fluid embolus: A review of the literature. Can J Anaesth 48:88–98, 2001.
306a. Conde-Agudelo A, Romero R: Amniotic fluid embolism: an evidence-based review. Am J Obstet Gynecol 201:445.e1–13, 2009.
307. Clark SL: New concepts of amniotic fluid embolism: A review. Obstet Gynecol Surv 45:360–368, 1990.
308. Clark SL: Amniotic fluid embolism. Crit Care Clin 7:877–882, 1991.
309. Clark SL, Hankins GD, Dudley DA, et al: Amniotic fluid embolism: Analysis of the national registry. Am J Obstet Gynecol 172:1158–1167, 1995 [discussion appears 1167–1159].
310. Julander I: Staphylococcal septicaemia and endocarditis in 80 drug addicts. Aspects on epidemiology, clinical and laboratory findings and prognosis. Scand J Infect Dis Suppl 41:49–55, 1983.
311. Clarke DE, Raffin TA: Infectious complications of indwelling long-term central venous catheters. Chest 97:966–972, 1990.
312. Robertson CH Jr, Reynolds RC, Wilson JE 3rd: Pulmonary hypertension and foreign body granulomas in intravenous drug abusers. Documentation by cardiac catheterization and lung biopsy. Am J Med 61:657–664, 1976.
313. Ward S, Heyneman LE, Reittner P, et al: Talcosis associated with IV abuse of oral medications: CT findings. AJR Am J Roentgenol 174:789–793, 2000.
314. Pare JP, Cote G, Fraser RS: Long-term follow-up of drug abusers with intravenous talcosis. Am Rev Respir Dis 139:233–241, 1989.

CHAPTER 52

PULMONARY HYPERTENSION

Richard N. Channick, MD • Lewis J. Rubin, MD

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INTRODUCTION

Idiopathic pulmonary arterial hypertension (IPAH; formerly primary pulmonary hypertension [PPH]) is a disease in which there is a persistent elevation of pulmonary artery pressure without demonstrable cause. There is expert agreement that the definition of pulmonary hypertension, as was required for entry into the PPH registry of the United States National Institutes of Health (NIH)[1] and for inclusion in all recent clinical trials, is a resting mean pulmonary artery pressure greater than or equal to 25 mm Hg. A pulmonary artery occlusion pressure, or left ventricular end-diastolic pressure less than 16 mm Hg, in the setting of pulmonary hypertension, is compatible with a diagnosis of pulmonary arterial hypertension (PAH).

CLASSIFICATION

The classification of PAH has undergone several revisions since the 1960s; the latest—and hence the current "gold standard"—is shown in Table 52-1.[2] This revised classification system includes additions to WHO group 1 (PAH) of chronic hemolytic anemias and schisosomiasis based on emerging evidence that these disorders produce an arteriopathy strikingly similar to other forms of PAH.

EPIDEMIOLOGY

What is now called IPAH first was described at autopsy by Romberg in 1891.[3] Patients with pulmonary hypertension of unknown cause were reported infrequently over the next 60 years, with two cases identified from 10,000 consecutive autopsies at Massachusetts General Hospital.[4] However, the condition was recognized more commonly after the advent of cardiac catheterization. Wood in 1950[5] detected 6 cases of what he called "idiopathic pulmonary hypertension" among 233 unselected British patients with presumed congenital heart disease, 152 of whom were catheterized. One year later, the term "primary pulmonary hypertension" was introduced by Dresdale and associates[6] in a detailed clinical and hemodynamic study of similar patients.

Since these original studies, IPAH has been reported with increased frequency. Shephard and colleagues[7] and Chapman and coworkers[8] described 14 patients with the condition in 1957; in 1958, Yu[9] reviewed the findings in 55 persons older than 12 years reported previously in the literature. Wolcott and colleagues[10] selected 23 cases from among Mayo Clinic patients seen from 1946 to 1965. A review of 17,901 autopsies performed on persons older than 1 year from 1944 to 1981 at the Johns Hopkins Hospital yielded 24 cases of IPAH; this amounted to a prevalence of 0.13% of all

TABLE 52-1. Fourth World Symposium Diagnostic Classification of Pulmonary Hypertension (2009)

GROUP 1: PULMONARY ARTERIAL HYPERTENSION (PAH)
Idiopathic PAH
Heritable PAH
- BMPR2
- ALK1, endoglin (with or without hereditary hemorrhagic telangiectasia)
- Unknown genes

Drug- and toxin-induced
Associated with:
- Connective tissue diseases
- HIV infection
- Portal hypertension
- Congenital heart disease
- Schistosomiasis
- Chronic hemolytic anemia

Persistent pulmonary hypertension of the newborn

GROUP 1′: PULMONARY VENO-OCCLUSIVE DISEASE (PVOD) AND/OR PULMONARY CAPILLARY HEMANGIOMATOSIS (PCH)

GROUP 2: PULMONARY HYPERTENSION OWING TO LEFT HEART DISEASE
Systolic dysfunction
Diastolic dysfunction
Valvular disease

GROUP 3: PULMONARY HYPERTENSION OWING TO LUNG DISEASES AND/OR HYPOXEMIA
Chronic obstructive pulmonary disease
Interstitial lung disease
Other pulmonary diseases with mixed restrictive and obstructive pattern
Sleep-disordered breathing
Alveolar hypoventilation disorders
Chronic exposure to high altitude
Developmental abnormalities

GROUP 4: CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION (CTEPH)

GROUP 5: PULMONARY HYPERTENSION WITH UNCLEAR MULTIFACTORIAL MECHANISMS
Hematologic disorders: myeloproliferative disorders, splenectomy
Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis: lymphangioleiomyomatosis, neurofibromatosis, vasculitis
Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure on dialysis

ALK1, activin-like kinase type 1; BMPR2, bone morphogenetic protein receptor type 2; HIV, human immunodeficiency virus.

patients.[11] The IPAH registry included 187 cases collected from 32 centers between 1981 and 1985.[1] In 1984, Rich and Brundage[12] noted that IPAH was found at autopsy in approximately 1% of patients with cor pulmonale.

IPAH customarily has been considered a disease of young women. Indeed, all of Wood's[5] six patients were women between 20 and 45 years of age, as were the three patients described by Dresdale and associates.[6] An overall female-to-male ratio of 1.7:1 was found in the U.S. registry. However, IPAH has been reported in both sexes within a wide age range. For example, the mean age of patients in the registry series was 36 years, with a range of 1 to 81 years.[1] The disease appears to affect older men and women in equal numbers, although most younger patients continue to be female. It should be noted that, although in the NIH registry 7% of "IPAH" patients were over age 65, it is unclear how rigorously left-sided heart disease was excluded.[1] Given the high frequency of left ventricular diastolic dysfunction, for example, one wonders how many of these older "IPAH" patients actually were closer to diagnostic group 2.

PATHOLOGY

Wood in 1958[13] divided pulmonary hypertension into six types: *passive*, as seen with increased pulmonary venous pressure due to raised left atrial or ventricular pressure; *hyperkinetic*, caused by increased pulmonary blood flow; *obstructive*, resulting from pulmonary embolism or thrombosis; *obliterative*, manifested by a reduction of pulmonary vascular capacity; *vasoconstrictive*, brought about by functional and presumably reversible vasospasm; and *polygenic*, arising in two or more of the preceding ways. Vasoconstrictive pulmonary hypertension occurred most characteristically in response to alveolar hypoxia and usually responded to the inhalation of oxygen or the injection of acetylcholine into the pulmonary artery. Reversible vasoconstriction also was seen as an added component of the passive hypertension of mitral stenosis and the hyperkinetic hypertension caused by congenital left-to-right intracardiac shunts before the onset of Eisenmenger's syndrome. The histologic lesions observed in these reversible kinds of pulmonary hypertension consisted of medial hypertrophy of the pulmonary artery and scant intimal hyperplasia.

Also in 1958, Heath and Edwards[14] documented the pathology of hypertensive pulmonary vascular disease in a study of 67 patients with congenital heart disease and 2 patients with IPAH. These investigators argued that the progression of lesions in these patients was so stereotyped as to allow division of the structural effects of pulmonary hypertension into six grades as follows: grade 1, medial hypertrophy of the pulmonary arteries and arterioles without intimal changes; grade 2, medial hypertrophy with cellular intimal proliferation; grade 3, medial hypertrophy, intimal proliferation, and intimal fibrosis; grade 4, progressive generalized vascular dilation and occlusion by intimal fibrosis and fibroelastosis; grade 5, appearance of dilation lesions, including vein-like branches of occluded pulmonary arteries, plexiform lesions, angiomatoid lesions, and cavernous lesions; and grade 6, necrotizing arteritis.

Heath and Edwards' grading system[14] focused on the muscular pulmonary arteries 100 to 1000 μm in size. Grades 1 and 2, which were characterized by medial thickening, were comparable with the reversible vasoconstrictive phase of Wood's scheme.[13] In grades 3 and 4, intimal changes led to progressive obstruction of the vessels, which then dilated in the presence of high pressure. Some of the dilated areas evolved into microaneurysms in which there was endothelial proliferation and the formation of in situ thrombosis; these made up the characteristic plexiform lesions. In grade 5, the dilation became rigid, and hemosiderin was extruded from vessels that either burst or allowed the diapedesis of erythrocytes. Grade 6 was seen rarely and involved perivascular neutrophilic inflammation and fibrinoid necrosis.

Heath and Edwards[14] lumped the pathology of congenital heart disease and IPAH together, and a large series of patients with the latter disorder was not available until 1970. In that year, Wagenvoort and Wagenvoort[15] described the morphology of the pulmonary vessels of 150 persons in whom the diagnosis of IPAH had been made on clinical grounds. Despite their common diagnosis, the cases could be divided into several groups on histologic analysis: chronic pulmonary thromboembolism, chronic pulmonary venous hypertension, pulmonary veno-occlusive disease, sarcoidosis, chronic bronchitis and pulmonary emphysema, pulmonary schistosomiasis, and vasoconstrictive IPAH. The patients with the last disorder were the largest group, consisting of 36 men and 74 women with a mean age of 23 years and an age range of 4 days to 69 years.

The lesions that Wagenvoort and Wagenvoort[15] attributed to vasoconstrictive IPAH were strikingly similar to those described earlier by Heath and Edwards[14] and Wood.[13] The earliest abnormalities were medial hypertrophy of the muscular pulmonary arteries and muscularization of the arterioles. These findings were especially prominent in children and were the only irregularities found in young infants. Although the medial thickening might be interpreted as a persistence of the high-resistance fetal circulation, it was considerably greater than that observed in infants of the same age. Less marked in children but apparent in all adults studied were intimal proliferation and laminar intimal fibrosis that gave an onionskin appearance to the pulmonary arteries. This pattern was not seen in any patients with initially unsuspected chronic pulmonary thromboembolism and also was absent from an additional 20 patients with known thromboembolic disease.

Dilation lesions, including the plexiform variety, were observed in 77 patients with vasoconstrictive IPAH and 1 patient with schistosomiasis (who also had *Schistosoma mansoni* ova) but was not evident in persons with chronic pulmonary thromboembolism or other disorders.[15] Necrotizing arteritis occurred in 34 patients with chronic pulmonary thromboembolism; it never involved the veins as it does in pulmonary veno-occlusive disease. Wagenvoort and Wagenvoort[15] noted that vasculitis occurred only in persons with advanced disease and probably was a result rather than a cause of pulmonary hypertension, in contrast to the true pulmonary vasculitides. They believed that the progression of lesions in PPH was entirely consistent with a vasoconstrictive mechanism.

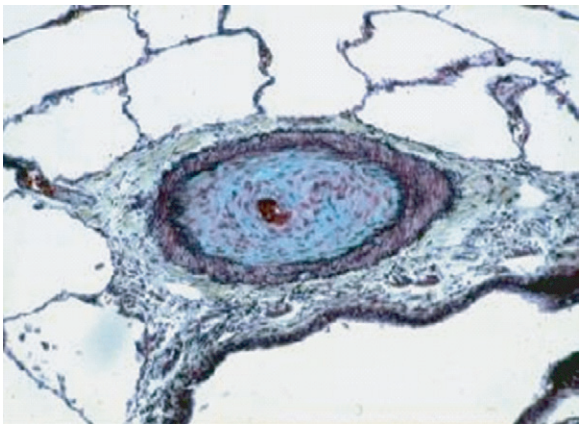

FIGURE 52-1 ■ Typical advanced pulmonary arteriopathy in idiopathic pulmonary arterial hypertension (IPAH). Note the proliferative changes in all three vessel layers, including intimal hyperplasia, medial hypertrophy, and adventitial fibrosis.

Subsequent investigators[16] confirmed the findings of Wagenvoort and Wagenvoort,[15] including the histologic distinctions between IPAH, chronic pulmonary thromboembolism, and pulmonary veno-occlusive disease. A typical arteriopathic muscular artery is shown in Figure 52-1.

Despite the distinct pathologic findings in IPAH, there is more recent evidence that the pathologic arteriopathic changes are, in fact, not unique to this disease and have been reported in congenital heart disease, connective tissue disease,[17] and chronic thromboembolic disease.[18] For this reason, in addition to the risk of lung biopsy in patients with pulmonary hypertension, one rarely obtains pathologic tissue prior to lung transplant or death.

PATHOGENESIS AND ETIOLOGY

A dramatic change has taken place over the last several years in our thinking regarding the pathogenesis of IPAH. The "paradigm" has shifted from one of vasoconstriction to one of growth and proliferation. There are several lines of evidence suggesting that IPAH develops as a result of abnormal proliferation of vascular smooth muscle cells affecting all three layers of the vessel wall and leading to intimal hyperplasia, medial hypertrophy, and adventitial proliferation. What initiates this abnormal growth is not entirely known, but there are several clues. The concept of genetic predisposition toward growth and proliferation has more recently emerged. Mutations in the bone morphogenic protein receptor 2 (*BMPR2*) gene have been reported in patients with the familial form of IPAH.[19] This gene contributes to the apoptotic process through a complex series of messenger proteins, as part of the transforming growth factor-β (TGF-β) family of genes. Thus emerges the possibility that

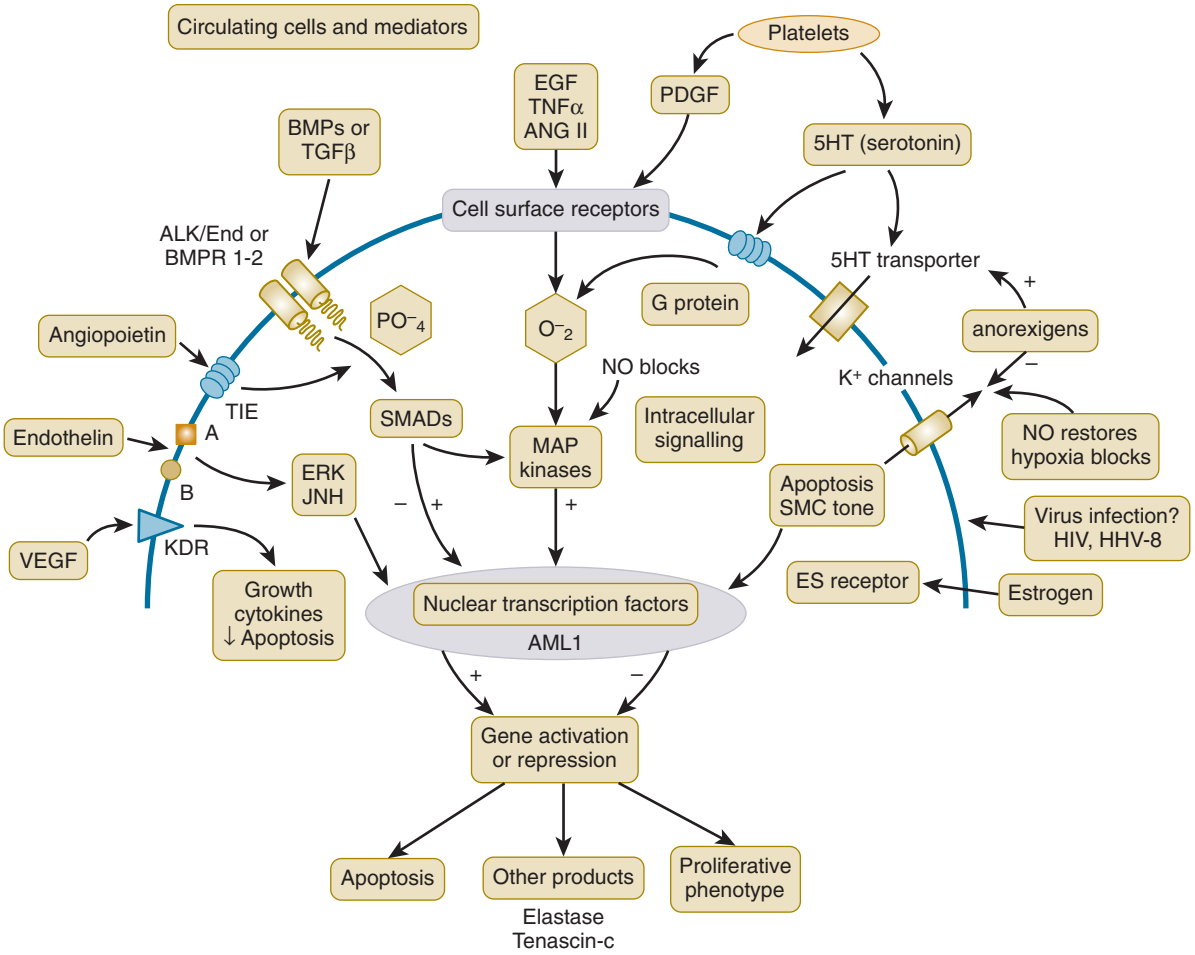

FIGURE 52-2 ■ Schematic of the possible pathogenetic factors in IPAH.

pulmonary arteriopathy is a failure of normal apoptosis. Some investigators have even referred to IPAH as "cancer of the pulmonary artery." Although this is an attractive hypothesis, the story is not that simple. For one, the presence of a *BMPR2* mutation is not always associated with the development of IPAH. It is likely that another genetic or acquired insult is required to initiate the arteriopathic process. Defects in a specific voltage-gated potassium ion channel, the Kv1.5 channel, have been found in the pulmonary artery smooth muscle cells from patients with IPAH.[19] A defect or deficiency of this channel allows excess calcium to enter the cell and thus promotes both cell contraction and growth. Overexpression of the serotonin transporter has been described in patients with IPAH.[20] This genetic defect might lead to increased internalization of serotonin and subsequent smooth muscle cell growth. Recent interest has focused on the role of impaired apoptosis on the development of proliferative arteriopathy in IPAH. It is clear that functional mutations seen in the *BMPR2* gene with resultant abnormal downstream signaling results in impaired apoptosis.[21–23]

In addition to potential genetic defects, several abnormalities in endothelial cell function have been found, many of which are likely a result of some vascular insult. The basis for currently approved therapeutics is the deficiency in prostacyclin and nitric oxide release and the excess in endothelin-1 and its receptor expression in patients with pulmonary hypertension.[24–27] The complex cellular and molecular processes contributing to IPAH are shown in Figure 52-2.

OTHER FORMS OF PULMONARY ARTERIAL HYPERTENSION

Etiologies other than IPAH leading to PAH are worth discussing because they may be considerably more common than IPAH and share many features. Patients with the scleroderma spectrum of diseases, most notably limited scleroderma (previously CREST [calcinosis cutis, Raynaud's phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia]) have been reported to have pulmonary hypertension in up 40% of cases.[28–30] Pulmonary vascular involvement is associated with worse survival in scleroderma.[31] Other connective tissue diseases associated with PAH, albeit less commonly, include systemic lupus erythematosis,[32–34] mixed connective tissue disease,[35–37] and rheumatoid arthritis.[38–40]

Congenital heart disease is a well-recognized "risk factor" for development of PAH. In 1958, Wood[13] coined the term "Eisenmenger's complex" to describe pulmonary hypertension at the systemic level due to high pulmonary vascular resistance (PVR), with reversed shunting through a large ventricular septal defect. Subsequently, the term has been used to describe pulmonary hypertension with cyanosis with any systemic to pulmonary circulatory shunt. The likelihood of developing pulmonary hypertension depends on the size of the defect. However, patients with even small atrial septal defects can develop pulmonary hypertension. These patients may, in fact, have IPAH and the atrial septal defect merely serves as a "trigger" in a susceptible patient.

In patients with ventricular septal defects, it has been shown that 3% of patients with a defect of 1.5 cm or smaller will develop Eisenmenger's syndrome whereas half of patients with a large defect will develop significant pulmonary hypertension, which will also appear earlier than in atrial septal defect, often in infancy.[41] PAH due to true Eisenmenger's syndrome is associated with a longer natural history and apparent adequate right ventricular compensation. In addition, the defect may actually function as a protective mechanism, providing a route for blood to reach the underfilled left ventricle.

The effects of drugs and toxins on the human pulmonary circulation have been graphically demonstrated in the past. Between 1967 and 1970 in Switzerland, Austria, and Germany, a 20-fold increase in pulmonary hypertension was observed after the introduction of aminorex, an appetite suppressant resembling epinephrine and amphetamine.[42] The pulmonary lesions produced by this agent resembled plexogenic pulmonary arteriopathy in every respect. Although the case against aminorex was weakened by the facts that 20% of patients with idiopathic pulmonary hypertension in Central Europe did not take the drug, only 1 in 1000 persons taking the drug actually developed pulmonary hypertension, and an animal model could not be created.[43] The case was strengthened by the observation that the incidence of pulmonary hypertension decreased to its previous level after aminorex was withdrawn from the market. Pulmonary hypertension has been associated with another family of appetite suppressants with similar chemical structure, fenfluramine and dexfenfluramine.[44] In a case-controlled prospective study performed in Europe, the risk of developing pulmonary hypertension was increased by 20-fold in individuals who used these drugs for periods exceeding 3 months. Reversible pulmonary hypertension has been reported after discontinuation of a similar agent.[45] Interestingly, application of both aminorex and fenfluramine to pulmonary artery smooth muscle cells results in K channel function alterations that are similar to those observed in cells from patients with "spontaneous" IPAH.[46]

Illicit drug use has been observed with increasing frequency as a cause of severe pulmonary hypertension. An especially strong association between methamphetamine use and PAH was found in a single-center case-control study.[47] In that study, patients with PAH and no other identifiable risk factors were 10 times more likely to have used methamphetamine than a control group of patients with other forms of PAH.

Portal hypertension is another disease associated with PAH. Mantz and Craige[48] first described simultaneous occurrence of portal and pulmonary hypertension in a patient with portal vein thrombosis and speculated that multiple emboli emanating from portacaval anastomoses were responsible for the pulmonary hypertension. Naeye in 1960[49] reported six cases of coexisting portal and pulmonary hypertension and also implicated embolization from the portal vein. A subsequent large retrospective autopsy study found pulmonary hypertensive changes in 0.73% of patients with portal hypertension.[50] A subsequent study in patients undergoing liver transplantation found an incidence of pulmonary hypertension of 4%.[51] The mechanism of pulmonary hypertension development in portal hypertension is not known. One hypothesis is that portosystemic shunting allows vasoactive substances, normally cleared in the liver, to reach the pulmonary vasculature. Hemodynamically, patients with portapulmonary hypertension tend to have higher cardiac outputs and lower PVRs.[52] Despite more favorable hemodynamics, the mortality risk following liver transplantation has been shown to be approximately 50% in patients with even mild pulmonary hypertension (PVR > 250 dynes/sec/cm^{-5}).[53] Knowledge regarding the high mortality in patients with portapulmonary hypertension undergoing orthotopic liver transplantation has led to development of aggressive strategies for screening and treatment of these patients prior to surgery.[54,55] The association between HIV and PAH is well known.[56–59] In several studies, the incidence of pulmonary hypertension in HIV has been reported as high as 0.5%. The mechanism of HIV-associated pulmonary hypertension is not known, although theories include release of cytokines and growth factors and the presence of human herpesvirus 8 (HHV8), a promoter of angiogenesis such as occurs in Kaposi's sarcoma. One report noted the presence of HHV8 in the cells from plexiform lesions in 10 of 16 patients with PPH.[60] Subsequent reports, however, failed to reveal HHV8 in plexiform lesions.[61,62] Pulmonary hypertension can occur in all stages of HIV, including patients with no detectable viral load. There is the suggestion that many of these patients have a concomitant history of illicit intravenous drug use in as many as 42% of cases.[63] At the authors' Pulmonary Hypertension Center, the vast majority of patients with HIV-associated PAH have a methamphetamine use history, suggesting the possibility that stimulant drugs contribute substantially to the risk of PAH in HIV patients. Clinical and hemodynamic features of HIV-associated pulmonary hypertension are similar to those of IPAH, although, in one study of 112 patients,[64] the survival rate was lower.

SYMPTOMS

Dyspnea is the cardinal symptom of IPAH, occurring in more than 95% of patients in the major clinical series.[1] Breathlessness is the presenting symptom in 60% of patients and usually is noted first on exertion, but

eventually occurs at rest. Its mechanism is probably complex: the most likely cause for the dyspnea of pulmonary hypertension is the inadequacy of cardiac output relative to metabolic requirements.[65] Reeves and Groves[66] have postulated that stretch receptors on the main pulmonary arteries also may be involved. Regardless of its mechanism, Packer[67] stresses that the severity of dyspnea does not correlate with the elevation of pulmonary artery pressure in patients with IPAH.

Closely related to dyspnea are sensations of fatigue and weakness, reported by a majority of patients with IPAH.[1] These sensations usually are experienced before the general disability that is present with advanced disease. They presumably reflect impaired tissue oxygenation resulting from the depressed cardiac output in patients with IPAH. This impairment is usually evident during cardiac catheterization as both a low cardiac output and a decreased mixed venous oxygen pressure (P_{O_2}).

Substernal chest pain also commonly is reported in patients with IPAH.[68] It frequently occurs on exertion, radiates to the left shoulder or axilla, and is relieved by rest. The pain has been likened to angina pectoris and has been attributed to coronary insufficiency in the presence of increased right ventricular work and hypoxemia, a concept supported by the occasional relief produced by nitroglycerin. However, pain may be present in young patients without coronary artery disease, prompting Viar and Harrison[68] to argue that the pain is caused by distention of the pulmonary artery, whose afferents enter the nervous system along the same pathways as afferents from the heart. Another plausible but unproven explanation is that the chest pain of IPAH is variant angina in patients with generalized vasospastic disease.

Syncope occurs in some patients with IPAH and may be its initial manifestation. This symptom also is experienced first on exertion but may happen later at rest. The syncope probably is caused by a decrease in cerebral blood flow that follows an increase in pulmonary artery pressure and a decrease in cardiac output. Dresdale and associates[6] speculated that cardiac output would be especially depressed in patients with concurrent coronary insufficiency and right ventricular failure.

Another symptom associated with IPAH is hemoptysis that presumably stems from microvascular rupture under the high pulmonary artery pressure. In addition, hoarseness may result from pressure of the enlarged main pulmonary artery on the recurrent laryngeal nerve. Peripheral edema and ascites may develop after the onset of right ventricular failure.

PHYSICAL FINDINGS

Patients with early IPAH may manifest no physical abnormality. However, signs of pulmonary hypertension and a decreased cardiac output should be evident with advanced disease. As Wood[13] observed, the hands and feet of a patient with severe pulmonary hypertension are cold, the peripheral pulse is diminished, the blood pressure is likely to be low, and the pulse pressure is reduced. Signs of systemic venous hypertension should be present, including a prominent jugular venous *a* wave, which is exaggerated by abdominal compression (hepatojugular reflux) and transmitted to the liver in a presystolic hepatic pulse, and prominent *c-v* waves, which are indicative of tricuspid regurgitation. Palpation of the chest should reveal a right ventricular lift at the left sternal border that is sustained throughout the pressure-overloaded cardiac contraction, in contrast to the unsustained parasternal impulse felt in pure volume overload.

On auscultation of the chest, the second heart sound is closely split, and the second (pulmonic) component is accentuated. The valvular closure sound should increase in intensity on inspiration and may become palpable as pulmonary artery pressure rises. A systolic ejection click reflecting sudden distention of the right ventricular wall also may be heard. A murmur of tricuspid regurgitation heard best along the left sternal border and increasing in intensity with inspiration, is frequent. A pulmonic regurgitant murmur may become evident after dilation of the main pulmonary artery and its valve annulus. Diastolic vibration of the aortic valve leaflet (Graham Steell murmur) may be present along with third and fourth heart sounds. In addition to these findings, patients with right-sided heart failure usually have peripheral edema and abdominal distention due to ascites. If tricuspid regurgitation is present, the liver may become pulsatile.

Cyanosis occurs with variable frequency in patients with IPAH and is likely to be a late phenomenon. It is most marked during exercise but also may be present at rest. Peripheral vasoconstriction and impaired oxygenation of arterial blood due to mixed venous hypoxemia resulting from the decreased cardiac output appear to be the most common mechanisms. Patients in whom right atrial pressure equals or exceeds left atrial pressure may develop severe hypoxemia and cyanosis because of opening of the foramen ovale with subsequent right-to-left shunting of blood. In addition to cyanosis, vascular plethora may be observed in hypoxemic patients with secondary polycythemia. With the exception of patients with cirrhosis and pulmonary hypertension, clubbing is not a usual manifestation of IPAH. The presence of clubbing warrants a careful search for other causes of pulmonary vascular disease.

DIAGNOSIS

Although pulmonary hypertension may be appreciated on physical examination, IPAH cannot necessarily be distinguished from the other causes of pulmonary hypertension by examination alone. The major entities in the differential diagnosis are chronic pulmonary thromboembolism; cardiac disorders, such as congenital heart disease, mitral stenosis, and left atrial tumors; and pulmonary veno-occlusive disease (discussed subsequently). Although the severity of pulmonary hypertension may be assessed by physical examination, laboratory evaluation is required for precise quantification.

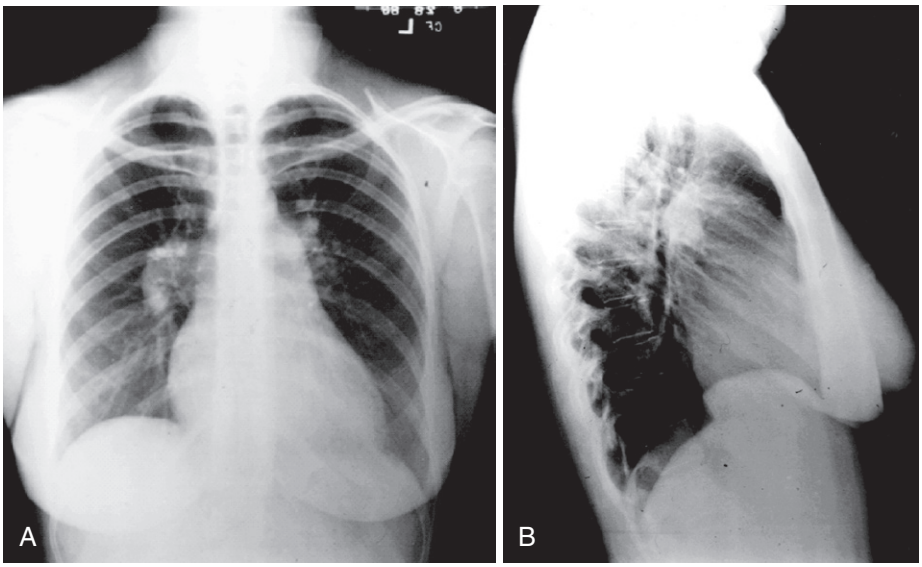

FIGURE 52-3 ■ Typical chest radiograph in IPAH. Note the clear lung fields, cardiomegaly, and the decrease in retrosternal airspace on the lateral film, indicating right ventricular enlargement.

Blood studies are an important part of the laboratory evaluation. The complete blood count is particularly helpful in documenting polycythemia, which is present in hypoxemic patients with PAH.

The plain chest radiograph is potentially useful in suggesting the presence of pulmonary hypertension and in providing clues of underlying conditions such as parenchymal lung disease (Fig. 52-3). In patients with IPAH, the radiograph characteristically reveals protrusion of the main pulmonary artery, increased width of the descending branch of the right pulmonary artery, peripheral oligemia, and an increase in the cardiothoracic ratio.

Systemic arterial blood gas analysis in patients with IPAH usually reveals a low arterial carbon dioxide pressure ($Paco_2$) and a normal pH, reflecting chronic respiratory alkalosis. The systemic arterial oxygen pressure (Pao_2) may be normal or abnormal, but the alveolar-to-arterial Po_2 difference usually is increased. Several mechanisms have been proposed for the hypoxemia of patients with IPAH, including diffusion impairment caused by a reduction in the number of pulmonary vessels coupled with the shortened time spent by erythrocytes in traversing the pulmonary circulation; ventilation-perfusion mismatching due to alterations in pulmonary blood flow and concomitant conditions such as bronchospasm; and right-to-left intracardiac shunting through a patent foramen ovale. Dantzker and Bower[69] demonstrated with the multiple inert gas elimination technique that the hypoxemia is caused by a combination of ventilation-perfusion mismatching, intrapulmonary shunt, and a low mixed venous Po_2 resulting from a reduced cardiac output.

Pulmonary function tests performed in patients with IPAH usually reveal normal expiratory flow rates with normal or mildly reduced lung volumes. The modest restrictive defect has been attributed to diminished distensibility of the pulmonary vessels.[70] The diffusing capacity for carbon monoxide often is reduced to a mild or moderate degree.

Exercise testing serves to bring out physiologic abnormalities in patients with IPAH if these abnormalities are not present at rest. Characteristically, patients with pulmonary hypertension achieve their target heart rate and anaerobic threshold at low levels of exercise, often accompanied by a reduction in the arterial Po_2 or an increase in the alveolar-to-arterial Po_2 difference. The dead space–to–tidal volume ratio either fails to decrease as it should in healthy persons or actually increases during graded exercise. Recent data suggest that cardiopulmonary exercise testing with hemodynamic measurements (level 4 test) can distinguish various forms of exercise-induced pulmonary hypertension.[71] Submaximal exercise testing by the 6-minute walk test is extremely useful as a prognostic marker and in following patients on therapy. Six-minute walk distance has served as the primary outcome end point in several pivotal pulmonary hypertension clinical trials.

The electrocardiogram usually discloses right ventricular hypertrophy in patients with advanced IPAH. Electrocardiographic criteria for right ventricular hypertrophy include a QRS axis in the frontal plane that is greater than or equal to 110 degrees, an R wave in lead V_1 that is greater than 5 mm, an R-to-S ratio in V_1 that is greater than 1, and an R-to-S ratio in lead V_6 that is less than 1. Patients also may manifest right atrial enlargement with a symmetrical and peaked P wave in lead II that is greater than 2.5 mm in amplitude. ST segment depression and T-wave inversion may be seen in the anterior chest leads. These abnormalities may not be present if pulmonary hypertension is not pronounced or if patients are young.

The echocardiogram may be helpful in documenting pulmonary hypertension and in ruling out conditions such as mitral valve disease and left ventricular systolic or diastolic dysfunction. IPAH has been associated in

one-dimensional echocardiography with midsystolic notching, diminution of the *a* dip, prolongation of the right ventricular preejection period, increased right ventricular systolic dimensions, and midsystolic fluttering of the pulmonary valve.[72–74] Two-dimensional echocardiography helps quantitate right atrial and right ventricular size and may identify systolic flattening or diastolic bulging of the interventricular septum due to increased pulmonary artery pressure.[74] Pulmonary artery pressure can be estimated by measuring the velocity of the tricuspid regurgitant jet using the equation:

$$\text{RV systolic pressure} = \text{TR velocity}^2 \times 4 + \text{estimated CVP}$$

where RV is right ventricular; TR is tricuspid regurgitation; and CVP is central venous pressure. The precision of the pulmonary artery systolic estimate compared with right heart catheterization measurement is controversial, with studies suggesting both good and poor concordance. Intracardiac shunting may be observed after the intravenous injection of microbubbles. More advanced echocardiographic techniques such as tissue Doppler[75] and calculation of the tricuspid annular shortening (TAPSE)[76] may provide more precise information.

Perfusion lung scanning has been used primarily to differentiate IPAH from chronic pulmonary thromboembolism. D'Alonzo and associates[77] studied 25 patients; in all 8 patients with chronic pulmonary thromboembolism, lung scans indicated a high probability of embolic disease due to multiple segmental defects, whereas 17 patients with IPAH had scans that were normal or indicated a low probability of embolism. This study suggests that lung scans are highly specific in differentiating the two conditions. If chronic thromboembolic pulmonary hypertension is suspected, pulmonary angiography is recommended to confirm the diagnosis and assess surgical accessibility.

In the evaluation of IPAH, right heart catheterization is mandatory to document the presence and severity of pulmonary hypertension, rule out cardiac causes, and determine if there is acute pulmonary vasoreactivity using pharmacologic agents. Hemodynamic values, especially right atrial pressure and cardiac index, correlate closely with survival.[78] Cardiac chamber and pulmonary arterial pressures are recorded, and the wedge pressure is measured to rule out disease at the level of the left ventricle, left atrium, or large pulmonary veins. Cardiac output is measured, and from it and vascular pressures, the pulmonary and systemic vascular resistances are calculated. Blood gas samples are taken to determine oxygen contents in the two circulations. These and other variables may be studied at rest or during exercise. Left-to-right intracardiac shunts may be excluded by the measurements of blood oxygen contents in the various cardiac chambers and by indicator techniques.

Cardiac catheterization in patients with IPAH may reveal elevated right atrial pressure, pulmonary arterial pressures that are increased often to systemic levels, and depression of cardiac output. PVR generally is increased, whereas systemic vascular resistance is in the normal range.

Virtually identical hemodynamic and clinical findings may be encountered in the rare form of PAH termed *pulmonary veno-occlusive* disease (PVOD). Like IPAH, PVOD appears to be a morphologic rather than an etiologic entity. In addition, PVOD tends to afflict infants, children, and young adults, although patients older than 60 years have been reported. However, in the adults with veno-occlusive disease who have been reported, there is a slight male preponderance. A familial occurrence of veno-occlusive disease also has been noted. Veno-occlusive disease has been associated with viral syndromes, toxin exposure, and chemotherapy. The characteristic histologic feature of PVOD is obstruction of pulmonary venules and veins by intimal fibrosis; intravascular fibrous septa, which usually are considered pathognomonic of recanalized thrombi, are nearly always present.[79] These findings have led to the speculation that thrombosis is an essential pathogenetic mechanism in most cases, but the factors causing or contributing to thrombus formation are completely unknown.

Of considerable interest is the observation that narrowing or obliteration of pulmonary arteries is found in approximately half the cases of PVOD.[79] The morphologic appearance of the arterial lesions indicates that they also were produced by organization of intravascular thrombi and that the abnormalities were not merely secondary to pulmonary venous obstruction with attendant medial hypertrophy and arterial hypertension. These observations raise the question whether there are two variations of the same basic disorder: the classic form of PVOD, in which the arteries are spared, and a generalized form, in which both arteries and veins are involved. PVOD cannot be distinguished with certainty from IPAH by right heart catheterization unless the pulmonary capillary wedge pressure is elevated. Apart from the difficulties of successfully wedging a catheter in patients with pulmonary hypertension, whether the wedge pressure is elevated depends on whether the venous obstruction is in the venules or the large veins. This is because the pressure actually measured at the tip of a catheter positioned in an obstructed pulmonary artery, by either wedging or inflating a balloon, is the pressure in the next freely communicating downstream vessel. Accordingly, if venules are occluded, as is often the case in PVOD, the next freely communicating vessel may be a vein in which the pressure is normal. In contrast, if (large) veins are the sites of occlusion, then the pulmonary venous pressure is likely to be elevated proximally and to be detectable at catheterization. Indeed, the wedge pressure may vary in different sites within the lung in patients with veno-occlusive disease. The chest radiograph may show signs of pulmonary hypertension with prominent Kerley B lines in the absence of other signs of left-sided heart failure, and this is often the most useful clue to the diagnosis in a patient with unexplained severe pulmonary hypertension. Computed tomography (CT) scanning may reveal interlobular septal thickening, pleural effusions, and enlarged pulmonary arteries. The perfusion lung scan may show defects suggestive of thromboembolism but with unremarkable pulmonary angiograms.[80] In addition, patients with veno-occlusive disease may

develop acute pulmonary edema in response to pharmacologic agents that reduce upstream PVR and increase cardiac output, such as prostacyclin. This phenomenon probably is caused by an increase in pulmonary blood volume in the face of downstream vascular obstruction. A recent analysis of PVOD cases suggested that bronchoalveolar lavage could be useful, as patients with PVOD almost always had increased hemosiderin-laden macrophages in bronchoalveolar lavage (BAL) fluid.[81]

Acute vasodilator testing is performed using a short-acting agent. Commonly used drugs include inhaled nitric oxide, adenosine, and prostacyclin. Oxygen and nitrates are not adequate testing agents in patients with IPAH. Criteria for defining vasoresponsiveness are discussed later, but fundamentally acute testing is performed to identify patients who will benefit from long-term calcium channel blocker therapy.

TREATMENT AND PROGNOSIS

IPAH is now a treatable disease. Clear-cut short- and long-term benefits are seen with currently available therapies. To optimize a patient's outcome, a comprehensive medical approach is essential. Once the diagnostic process in a patient with pulmonary hypertension is complete, and the patient is characterized as having IPAH (WHO group 1), therapy should be initiated. But many questions arise regarding IPAH therapy. What are the goals and expected outcomes of IPAH therapy? Which drug should be used first? When should another therapy be added? Should more than one therapy be used? In what order? When should transplantation be considered? Are there published guidelines in which experts have evaluated the quality of evidence and issued a "grade" for the therapy?

Therapy for IPAH may be subdivided into "supportive" or "conventional" therapies, defined as empirical treatments or recommendations for which there is no prospective, randomized, controlled data, and "specific" or "targeted" therapies, which have been tested and approved by regulatory authorities for the treatment of PAH.

Supportive Therapies

Exercise and Physical Activity

There is no evidence-based guidance regarding physical activity or exercise in PAH. Patients should avoid activities that lead to undue symptoms such as severe dyspnea, chest pain, light-headedness, or syncope. However, low- to moderate-levels of exercise to prevent deconditioning and improve mental outlook are appropriate. One recent study demonstrated that exercise and respiratory training is safe and results in measurable improvements in subjective and objective parameters.[82] Mereles and coworkers[82] randomized 30 patients (23 with PAH and 7 with chronic thromboembolic pulmonary hypertension) to exercise training versus no change in treatment. In addition to being safe, patients in the exercise-training group had improved their quality of life scores, functional class, maximal oxygen consumption, and 6-minute walk distance (of 111 m compared with the placebo group).

Avoidance of Altitude

Hypobaric hypoxia causes pulmonary vasoconstriction and, thus, can worsen the pulmonary hypertension in PAH patients. Patients with PAH not infrequently report symptomatic worsening when traveling to elevations above 1000 m. It is generally recommended that patients flying on commercial airliners (pressurized to 1500–2400 m) or traveling to elevation above 5000 feet use supplemental oxygen. Not surprising, patients with severe PAH residing at high elevations often improve if they move to sea level.

Avoidance of Pregnancy

Pregnancy and especially delivery are extremely risky in patients with PAH.[83] Although there are rare case reports of patients managed with epoprostenol and undergoing successful pregnancies and deliveries,[84,85] it is strongly recommended that women of childbearing potential use appropriate methods of birth control to avoid pregnancy. In terms of which birth control method is preferable, no consensus exists. Some experts recommend avoiding estrogen-containing hormonal contraceptives. Medroxyprogesterone acetate (Depo-Provera) is an effective, convenient agent commonly used in PAH patients. It should be noted that in patients on endothelin-receptor antagonists such as bosentan or ambrisentan, an additional barrier method of birth control should be used.

Warfarin

There is strong rationale for the use of anticoagulants in PAH. Many of the endothelial cell abnormalities that predispose patients to pulmonary arteriopathy also increase thrombosis. The presence of heart failure and an indwelling central venous catheter are independent risk factors for thromboembolic events, which are poorly tolerated by patients with an already marginal pulmonary vascular reserve. In addition, microscopic thrombotic lesions in the pulmonary vasculature are well appreciated in PAH patients.

Warfarin is the anticoagulant most frequently used in patients with PAH. In clinical trials with PAH drugs, about 50% to 85% of patients are on anticoagulants at study entry. However, anticoagulation has risks (i.e., bleeding) as well as the need for frequent monitoring. What data justify the use of warfarin in PAH? Three studies have examined the effects of warfarin in IPAH or anorexigen-induced PAH.[86–88] All three were retrospective analyses with some patients on warfarin. All three demonstrated better survival in patients on warfarin than those not anticoagulated. In an early study by Fuster and colleagues,[86] 120 patients with a clinical diagnosis of IPAH were studied; anticoagulation improved survival at 3 years (49% vs. 21%). However, of note, the overall

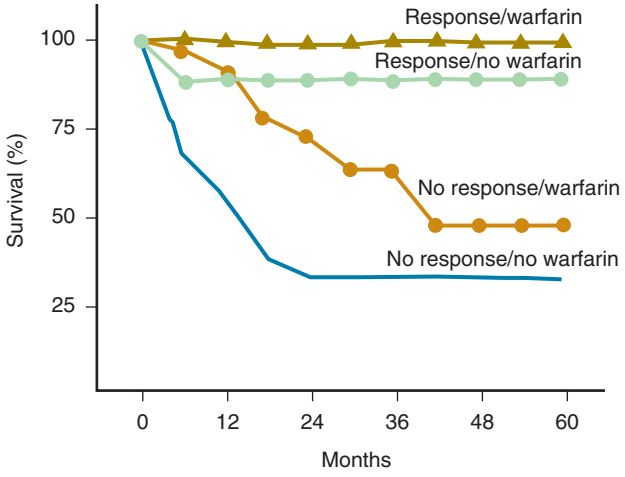

FIGURE 52-4 ■ Survival in patients with IPAH based on acute vasoreactivity and treatment with warfarin. In patients who were not vasoreactive, warfarin was associated with a modest survival advantage versus nonreactive patients who were not on warfarin. (Redrawn from Rich S, Kaufmann RN, Levy PS: The effect of high doses of calcium-channel blockers on survival in primary pulmonary hypertension. N Engl J Med 327:76–81, 1992.)

5-year survival for the entire cohort was only 21%. In addition, 57% of the patients in whom autopsy was performed had predominantly thrombotic lesions noted, raising the question of whether some of these "IPAH" patients may have been misdiagnosed and actually had chronic thromboembolic pulmonary hypertension. In the Rich and associates' study,[87] which primarily looked at the long-term benefit of calcium channel blockers in IPAH, a survival benefit with warfarin was noted predominantly in patients who were "nonresponders" to calcium channel blockers (Fig. 52-4). The third retrospective study, by Frank and coworkers,[88] compared survival in aminorex-induced PAH and IPAH with and without anticoagulation. In both groups, the use of oral anticoagulant therapy was associated with better survival, with the longest mean survival observed in anticoagulated aminorex-PAH patients (8.3 years vs. 6.1 years for nonanticoagulated aminorex-PAH patients).

Although these three retrospective studies all suggest a survival benefit with warfarin in PAH, it is important to note that none of the studies were conducted during the "modern" era of effective, targeted PAH therapies, which are already associated with better survival than that seen in these "historical" studies. Whether warfarin further improves outcome in patients on these therapies (e.g. endothelin receptor antagonists, phophodiesterase-5 inhibitors, prostanoids) remains unclear.

Despite the serious limitations in the existing data, published guidelines recommend, with a "B" grade, that patients with IPAH be treated with warfarin.[89] There is less guidance regarding the use of anticoagulation in other forms of PAH, such as that associated with congenital systemic-to-pulmonary shunts or associated with connective tissue diseases. There may be specific cases in which warfarin would be indicated, such as in patients with advanced heart failure, indwelling central venous catheters, or erythrocytosis. Conversely, if there are patients at increased risk for bleeding (thrombocytopenia, history of hemoptysis or gastrointestinal bleeding), withholding anticoagulation, given the limited data, may be prudent.

Supplemental Oxygen

The benefits of supplemental oxygen in PAH patients, unlike patients with pulmonary hypertension associated with lung diseases such as chronic obstructive pulmonary disease (COPD),[90,91] are not clear. In fact, most PAH patients are not hypoxemic, at least at rest. Mild hypoxemia, when present, is likely on the basis of reduced mixed venous oxygen saturation caused by low cardiac output with mild ventilation/perfusion inequality. The presence of more profound hypoxemia in a PAH patient should raise suspicion for underlying parenchymal lung disease, systemic to pulmonary shunting, PVOD, pulmonary capillary hemangiomatosis, or pulmonary arteriovenous malformations as seen in patients with Osler-Weber-Rendu–associated pulmonary hypertension.

Although oxygen is a pulmonary vasodilator, there are no long-term studies supporting its efficacy. However, the consensus is that if arterial P_{O_2} is less than 60 mm Hg or systemic arterial O_2 saturation is less than 90% at rest, supplemental oxygen is indicated. One exception to this approach is in patients with Eisenmenger's syndrome, with hypoxemia due to right-to-left shunting. In this group, the use of supplemental oxygen remains controversial.[92,93] There is no general agreement about whether exercise-only systemic arterial O_2 desaturation warrants oxygen supplementation. In addition, the "stigma" of nasal cannulae for a PAH patient often limits compliance outside the home.

Diuretics

Diuretics have long been a mainstay of therapy for heart failure, including right ventricular failure. Both total-body and intravascular volume overload are common in PAH patients. In pivotal trials of PAH drugs, the majority of patients entered the studies on chronic diuretic therapy.[94,95]

In addition to causing symptomatic peripheral edema, volume overload of the right ventricle can cause compression of the left ventricle and contribute to decreased cardiac output and prerenal azotemia. Thus, it is a common observation that in decompensated PAH patients, aggressive diuresis leads to clinical and physiologic improvements. Despite the benefits of diuretics in PAH patients, there are no controlled studies to guide the clinician in using these agents.

A loop diuretic is frequently employed first. Although furosemide is often the loop diuretic of choice, there is some evidence that torsemide might be more efficacious without increased side effects.[96] In addition, in patients with marked extravascular fluid accumulation and poor intestinal absorption, intravenous diuretic therapy is frequently needed. Anti-aldosterone drugs (e.g., spironol-

actone) are commonly combined with loop diuretics in PAH patients. Whether data suggesting a morbidity and mortality benefit of spironolactone in left-sided heart failure[97] can be extrapolated to right-sided heart failure is not known.

In some cases, addition of a thiazide diuretic to the regimen is appropriate. The combination of metolazone and furosemide has been found by the authors to be effective in causing a brisk diuresis. However, marked hypokalemia can occur with this regimen.

Although it is possible that in some PAH patients, the right ventricle is preload dependant and therefore overdiuresis can be detrimental, this has not been the authors' experience. More often, aggressive diuresis (1–3 L negative fluid balance per day) leads to improvement in renal function and blood pressure, consistent with improved cardiac output.

Calcium Channel Antagonists

In 1958, Paul Wood[5] first defined the clinical entity of pulmonary hypertension with reference to the "vasoconstrictive factor." It is not surprising, then, that a search for pulmonary vasodilators as effective therapies ensued. Agents including phentolamine,[98] tolazine,[99] captopril,[100] and hydralazine[101] were evaluated in uncontrolled reports. Results, although variable, were not overwhelmingly favorable. No systematic studies of these medications were carried out.

Out of the myriad of oral antihypertensive agents emerged calcium channel blockers. Ostensibly, this class of agents "made sense" for treating pulmonary hypertension. Calcium channel blockers have acceptable side effect profiles and are potent pulmonary as well as systemic vasodilator agents. The role of intracellular cytosolic calcium in the vasoconstriction of pulmonary artery smooth cells was well established. Thus, blocking influx of calcium into the cells seemed desirable.

In a highly quoted paper, Rich and associates[87] described favorable survival in a subgroup of IPAH patients treated with either diltiazem or nifedipine. In that study, patients manifesting acute pulmonary vasoreactivity with calcium channel blockers, defined as an acute decrease in mean pulmonary arterial pressure and PVR of at least 20%, had a 5-year survival of 94%. In contrast, patients who did not have an acute response had only a 55% 5-year survival. In addition, predicted survival for the "acute responders," using an equation based on hemodynamics at time of diagnosis, was significantly worse than the observed survival. Although not a placebo-controlled study, these data suggested a benefit with calcium channel blockers in some IPAH patients.

The Rich and associates' study,[87] although seminal, likely led to overuse of calcium channel blockers, not only for IPAH but for other forms of PAH as well. Calcium channel blockers are not selective pulmonary vasodilators. In addition, calcium channel blockers have potential negative inotropic effects. Thus, in patients with minimal or no acute pulmonary vasoreactivity, the negative effects of calcium channel blockers can become predominant, with potential for catastrophic consequences.

A subsequent, large retrospective study by Sitbon and colleagues[102] has further narrowed the role of calcium channel blockers in IPAH patients. In that study, 557 IPAH patients were tested for acute pulmonary vasoreactivity using either intravenous prostacyclin (e.g., epoprostenol) or inhaled nitric oxide. Seventy patients (about 13%) had an acute response (at least a 20% fall in mean pulmonary artery pressure and PVR) and were treated with calcium channel blockers. However, only half of those "acute responders" (about 7% of the total) did "well" long term on calcium channel blockers, defined as being alive and in functional class I or II at 5-year follow-up (see Fig. 52-2). The long-term survivors had less severe disease as assessed by hemodynamics at baseline and had reached a lower mean pulmonary artery pressure with acute vasodilator challenge than the long-term calcium channel blocker failures (33 mm Hg vs. 46 mm Hg). In other words, rather than the percent drop in mean pulmonary artery pressure during an acute test, the absolute mean pulmonary artery pressure reached appeared to be better in defining the patients that would benefit long term with calcium channel blockers. These data have been codified into evidence-based guidelines,[89] which define potential calcium channel blocker candidates as IPAH patients in whom, during an acute pulmonary vasoreactivity test, the mean pulmonary artery pressure decreases by at least 10 mm Hg to a level below 40 mm Hg, with no decrease in cardiac output.

The method for performing acute pulmonary vasoreactivity testing varies among pulmonary hypertension centers. Most frequently, one of three short-acting pulmonary vasodilators is used in the cardiac catheterization laboratory (i.e., inhaled nitric oxide, intravenous adenosine, or intravenous epoprostenol). Using a short-acting agent prevents refractory systemic hypotension that could result when a PAH patient with minimal pulmonary vasoreactivity is given a systemic vasodilator. A distinct advantage of inhaled nitric oxide is the absence of systemic hemodynamic effects, the very rapid "on-off" properties of the drug (i.e., half-life 20 seconds), and the absence of side effects. With inhaled nitric oxide, an acute pulmonary vasoreactivity test with repeat hemodynamic measurements can be accomplished in less than 20 minutes.

Targeted Therapies

PAH-specific therapies have been available since 1995, when intravenous epoprostenol was approved by the U.S. Food and Drug Administration (FDA), based on the first prospective randomized, controlled trial done in PAH. Since then, an additional five therapies have been approved for PAH: subcutaneous and intravenous treprostinil, inhaled iloprost, the oral endothelin receptor antagonists bosentan and ambrisentan, and the phosphodiesterase-5 inhibitor sildenafil. These therapies were developed to offset the imbalance in endothelial-derived mediators seen in PAH: excessive endothelin-1 production, deficient prostacyclin, and abnormal nitric oxide production (Fig. 52-5).

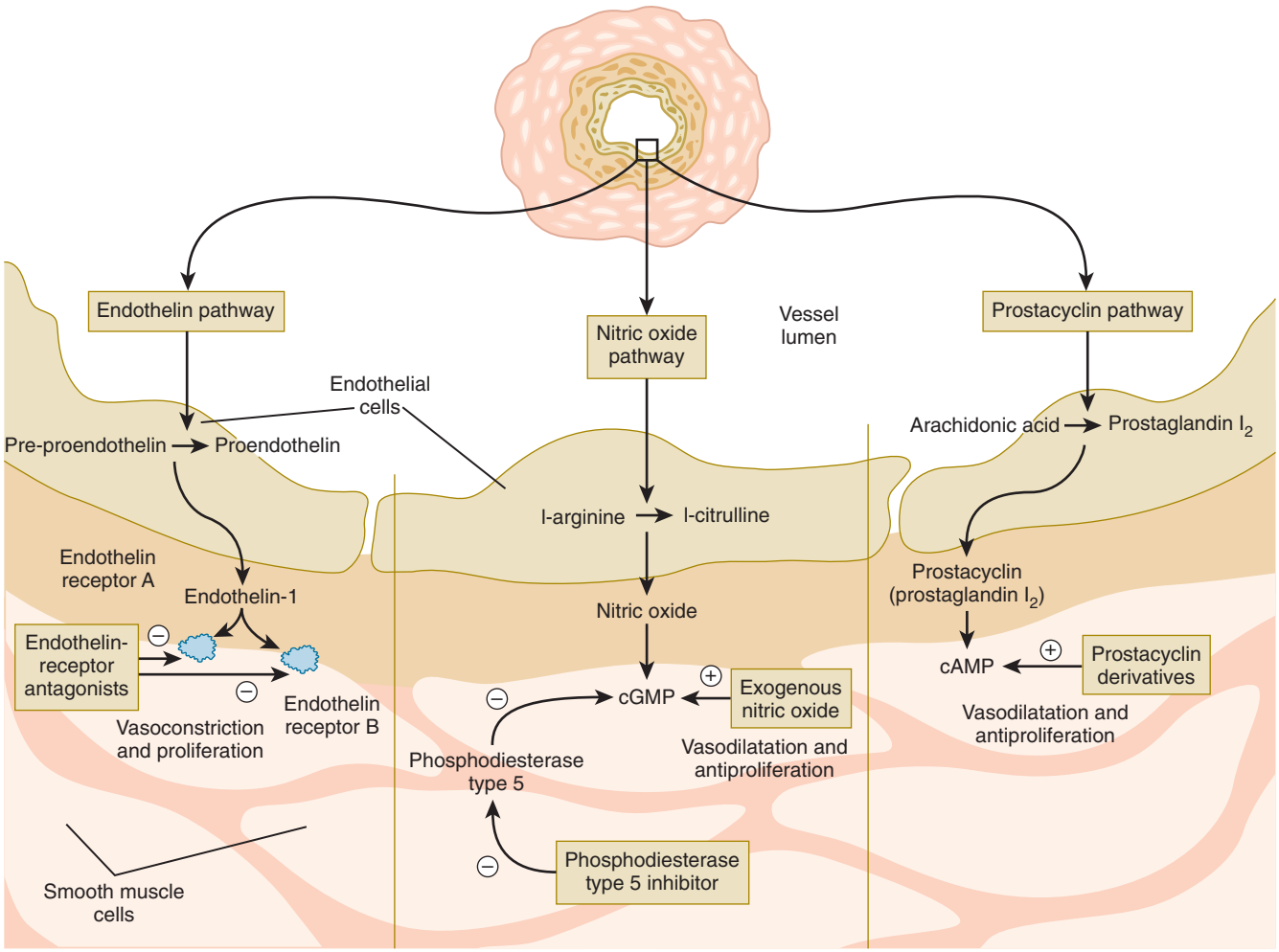

FIGURE 52-5 ■ Schematic of three abnormal endothelial mediator pathways that are targeted by current therapies.

Prostacyclin Analogues

Epoprostenol. Epoprostenol (Flolan) was first approved by the FDA on September 20, 1995, for the indication of "long-term intravenous treatment of primary pulmonary hypertension in New York Heart Association (NYHA) class III and class IV patients." Continuous intravenous infusions of prostacyclin (prostaglandin I_2, epoprostenol) have been used, either as a primary mode of treatment or as a bridge to transplantation, and produce sustained improvement in hemodynamics and exercise tolerance as well as prolonged survival. In this first randomized, prospective study,[94] 81 patients with NYHA class III or IV symptoms, despite treatment with conventional therapy, which included oral vasodilators, digoxin, diuretics, and supplemental oxygen, were randomized to either continuous intravenous epoprostenol plus conventional therapy or conventional therapy alone for 12 weeks. The primary outcome was the change in exercise capacity, as measured by the 6-minute walk test. Secondary outcomes included change in hemodynamics, quality of life, NYHA functional class and survival. At 12 weeks, the 6-minute walk distance improved in the continuous intravenous epoprostenol group by 32 m and decreased by 15 m in the conventional therapy group. Mean pulmonary artery pressure, cardiac index, and PVR significantly improved in the epoprostenol group. There were also significant improvements in the epoprostenol group when measuring quality of life and NYHA functional class. Eight patients died during the 12-week study and all were in the conventional treatment arm. Notably, this is the only PAH trial ever to show, compared with a control group, a beneficial effect on survival.

Follow-up studies have confirmed the long-term benefits of epoprostenol on survival compared with historical controls, with 5-year survival estimates of greater than 60% in treated patients,[103] a great improvement from the median survival of less than 3 years in the "pre-epoprostenol" era. Interestingly, the benefits of epoprostenol may be progressive. In one report of four patients,[104] chronic epoprostenol infusions resulted in normalization or near-normalization of pulmonary hemodynamics, allowing transitioning to oral medications. Despite its benefits, chronic use of epoprostenol is complex and requires an indwelling central venous catheter, continuous-infusion pump, and daily preparation of the medication. In addition numerous side effects including jaw claudication, leg and foot pain, diarrhea, rash, and

weight loss occasionally with ascites occur. The complexities of dosing prostacyclin and assessing response to the therapy obligate a dedicated team, typically present only at large pulmonary hypertension centers.

Treprostinil Sodium. Treprostinil sodium (Remodulin) is a tricyclic benzindene analogue of prostacyclin that is chemically stable at room temperature and has a half-life of approximately 4 hours. In a double-blind, randomized, controlled trail, 470 patients with IPAH (58%), PAH associated with connective tissue disease or associated with congenital systemic pulmonary shunts with WHO functional class II, III, or IV were randomized to continuous subcutaneous treprostinil or placebo for 12 weeks.[105] As with other PAH trials, the primary outcome measure was exercise capacity as defined as placebo-corrected improvement in 6-minute walk distance. In addition, "reinforcing" principal end points included a composite score assessing signs and symptoms of pulmonary hypertension, dyspnea fatigue rating, and clinical worsening (number of patients dying, undergoing lung transplantation, or discontinuation of the study drug). The placebo-corrected improvement in 6-minute walk distance was 16 m ($P = 0.006$). Thirteen patients in the treprostinil group and 16 patients in the placebo group died, required lung transplantation, or discontinued therapy secondary to clinical worsening. Borg dyspnea scores and quality of life measures were significantly improved in the treprostinil group compared with placebo. Patients treated with treprostinil had improved pulmonary hemodynamics, including significant improvement in mean right atrial pressure, mean pulmonary artery pressure, cardiac index, PVR, and mixed venous oxygen saturation. Review of the treprostinil subset analysis suggested that significantly higher doses than with epoprostenol were needed to get efficacy. Infusion site difficulties were the major adverse event, with 200 (85%) patients in the treprostinil group versus 62 (27%) in the placebo arm reporting site pain.

Subsequent to approval of subcutaneous treprostinil, the intravenous route was approved based on bioequivalence. There has not been a prospective, randomized, controlled trial of intravenous treprostinil, but two uncontrolled reports have been published.[106,107]

Iloprost. Iloprost is a stable prostacyclin analogue approved by the FDA in the inhaled formulation. Inhaled iloprost is delivered via ultrasonic nebulizer directly to the lungs. It received FDA approval in December 2004 based on the Aerosolized Iloprost Randomized study (AIR), a double-blind, placebo-controlled trial that randomized 203 patients with NYHA class III or IV IPAH (50%) or PAH associated with anorexigans, scleroderma, or chronic thromboembolic pulmonary hypertension to receive 2.5 μg or 5 μg inhaled iloprost versus placebo six or nine times per day for 12 weeks.[108] The primary outcome was a combined end point: At least 10% improvement in 6-minute walk distance in the treatment group and improvement in at least one NYHA functional class. Secondary outcome measures included change in 6-minute walk distance and NYHA class, dyspnea index scores, pulmonary hemodynamics and quality of life, and clinical worsening (defined as deterioration, death, or need for transplantation). Seventeen patients in the iloprost group versus 5 in the placebo arm met the combined primary end point, which was statistically significant with an estimated odds ratio of 3.97. Cardiac output, systemic arterial oxygen saturation, and mixed venous oxygen saturation as measured at "peak" following an inhalation increased significantly and the PVR and right atrial pressure decreased significantly in the iloprost group at 12 weeks as compared with the placebo group. Adverse events included syncope, flushing, and jaw pain in the iloprost group.

Endothelin Receptor Antagonists

In humans, two endothelin (ET)-1 receptor subtypes are found, ET-A and ET-B. Antagonism of one or both receptors has been shown to be an effective treatment strategy for IPAH, with two FDA-approved therapies, bosentan and ambrisentan. A third agent, sitaxsentan, was not approved in the United States but is available in Europe and other countries.

Bosentan. Bosentan is a potent, nonpeptide, oral ET-A and B receptor antagonist, with higher affinity for the ET-A subtype receptor. Bosentan received FDA approval in November 2001 for patients with WHO functional class III or IV PAH. The first double-blind, placebo-controlled trial randomized 32 patients with IPAH (84%) or pulmonary hypertension associated with scleroderma with NYHA class III to bosentan or placebo for 12 weeks.[109] The primary end point was the placebo-corrected change in 6-minute walk distance, with secondary end points including change in pulmonary hemodynamics, WHO functional class, Borg dyspnea index, and clinical worsening. The placebo-corrected improvement in 6-minute walk distance was 76 m in favor of the bosentan group, In addition, pulmonary hemodynamics, especially cardiac index and PVR, were favorably affected by bosentan (Fig. 52-6). There were asymptomatic increases in liver aminotransferases in 2 patients on bosentan, but these returned to baseline without discontinuing or changing the dose.

The larger BREATHE-1 (Bosentan Randomized Trial of Endothelin Antagonist Therapy) trial, which randomized 213 patients with IPAH (70%) and pulmonary hypertension associated with connective tissue disease with WHO functional class III and IV to placebo or bosentan at 125 mg or 250 mg twice daily, confirmed the efficacy and safety of bosentan over 16 weeks.[95] At 16 weeks, a placebo-corrected 6-minute walk distance improvement of 44 m was noted ($P < 0.001$) (Fig. 52-7A). There were also improvements in the Borg dyspnea score and time to clinical worsening in both bosentan groups. Increases in liver aminotransferases greater than eight times the upper limit of normal was again noted in the bosentan group and was dose-dependent with 2 patients in the 125-mg group and 5 patients in the 250-mg group.

In addition to the just-discussed "pivotal" trials of bosentan, a recently published randomized, controlled trail of bosentan in PAH patients less functionally impaired (WHO class II), the EARLY (Endothelin Antagonist Trial in Mildly Symptomatic Pulmonary Arterial Hypertension Patients) trial demonstrated a benefit in reducing PVR and preventing clinical worsening at 6

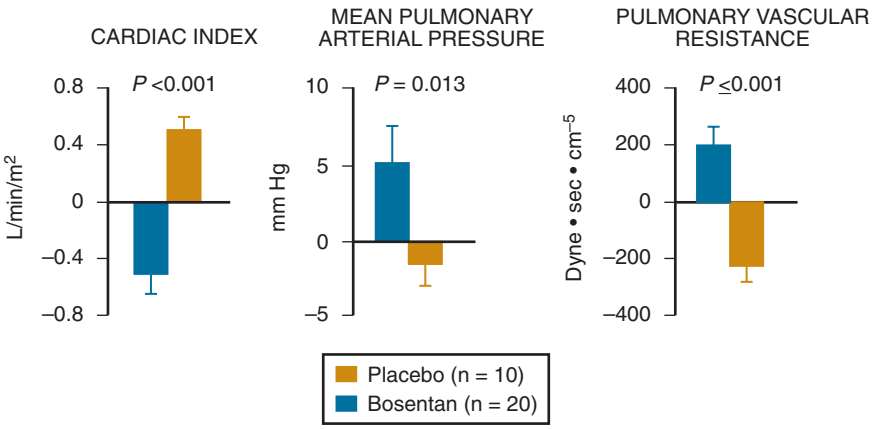

FIGURE 52-6 ■ Hemodynamic effects of bosentan in pulmonary arterial hypertension (PAH) patients. Bosentan-treated patients had significantly improved cardiac output, pulmonary vascular resistance, and pulmonary arterial pressure compared with those receiving placebo. (Adapted from Channick RN, Simonneau G, Sitbon O, et al: Effects of the dual endothelin-receptor antagonist bosentan in patients with pulmonary hypertension: A randomised placebo-controlled study. Lancet 358:1119–1123, 2001.)

months. No statistically significant effect on 6-minute walk distance was seen, although baseline walk distance was greater than 400 m, confirming that this cohort had better baseline exercise capacity.[110]

Ambrisentan. Ambrisentan is a specific ET-A receptor antagonist approved for PAH, functional classes II and III at doses of 5 mg or 10 mg once daily. Following a phase 2 dosing study showing favorable pulmonary hemodynamic effects,[111] two randomized, controlled trials of ambrisentan (Ambrisentan in Pulmonary Arterial Hypertension, Randomized, Double-Blind, Placebo-Controlled, Multicenter, Efficacy Studies [ARIES] 1: 5 mg, 10 mg, placebo; ARIES 2: 2.5 mg, 5 mg, placebo) enrolled a total of 394 patients.[112] Both trials achieved the primary end point of placebo-corrected improvement in 6-minute walk distance (see Fig. 52-7B). In ARIES-2, there was a significant improvement in time to clinical worsening in the treatment group as compared with placebo. There was a trend toward improvement in time to clinical worsening in the ARIES-1 study, but it was not statistically significant ($P = 0.3$). WHO functional class improvement was significant in ARIES-1 and there was a trend toward improvement in ARIES-2 but did not reach statistical significance ($P = 0.1$). Two hundred ninety-eight patients were enrolled and followed in the long-term extension study over 48 weeks. Eighteen patients required additional therapies (prostanoids [PD-5] inhibitors). Of the 280 patients continued on ambrisentan monotherapy, the improvement in 6-minute walk distance at 12 weeks was 40 m and maintained at 39 m. Although there was no patient with elevations in serum aminotransferases more than three times the upper limit of normal while on ambrisentan, in the trials, long-term follow-up has revealed cases of transaminase elevations that resolve upon discontinuation of ambrisentan.

Both approved endothelin receptor antagonists require monthly liver function test monitoring and have teratogenic properties, necessitating monthly pregnancy tests in women of childbearing age (see package inserts).

Phosphodiesterase Type 5 Inhibitors

Sildenafil. Sildenafil (Revatio) was approved by the FDA in June 2005 for the indication of symptomatic IPAH. The pivotal trial of sildenafil, SUPER-1 (Sildenafil Use in Pulmonary Arterial Hypertension) trial, was a 12-week randomized, double-blind, placebo-controlled trial comparing placebo, 20 mg, 40 mg, and 80 mg three times daily.[113] The study design was similar to other trials. In the sildenafil 20-mg group at 12 weeks, the placebo-corrected 6-minute walk distance was 45 m. In the 40-mg group, the improvement was 46 m, and in the 80-mg group, it was 50 m (see Fig. 52-7C). There was no significant effect of sildenafil on Borg dyspnea score or time to clinical worsening. There was an improvement in the percentage of patients with improved functional class, particularly with the higher doses of sildenafil (7% in placebo group, 28% in the 20-mg group, 36% in the 40-mg group, and 42% in the 80-mg group). However, despite the dose-related improvements in hemodynamics and WHO functional class in patients on higher dosages of sildenafil, the FDA approved only the 20-mg dose of sildenafil in the treatment of IPAH. This medication appeared well-tolerated and there were no laboratory abnormalities noted. Common adverse events included flushing, epistaxis, and gastritis. Use with nitrates is contraindicated.

Combination Therapy

There is strong rationale for combining drugs to treat IPAH. To date, however, there are very limited controlled data.

The PACES (Pulmonary Arterial Hypertension Combination Study of Epoprostenol and Sildenafil) trial randomized 267 patients with IPAH (79%) or PAH associated with connective tissue disease, anorexigen use, or corrected congenital-systemic shunts, on stable epoprostenol therapy to either additional sildenafil or placebo for 16 weeks.[114] Patients were on continuous epoprostenol as baseline therapy for an average of 2.91 and 2.75 years, in the treatment and placebo arms, respectively. They were randomized to either sildenafil 20 mg three times a day or placebo for 4 weeks and up-titrated to 80 mg three times a day or placebo up-titration. The primary outcome measurement was exercise capacity as measured by 6-minute walk test. The placebo-corrected 6-minute walk distance improvement in the sildenafil-epoprostenol group was 28.8 m. Hemodynamic improvements in the sildenafil-epoprostenol group compared

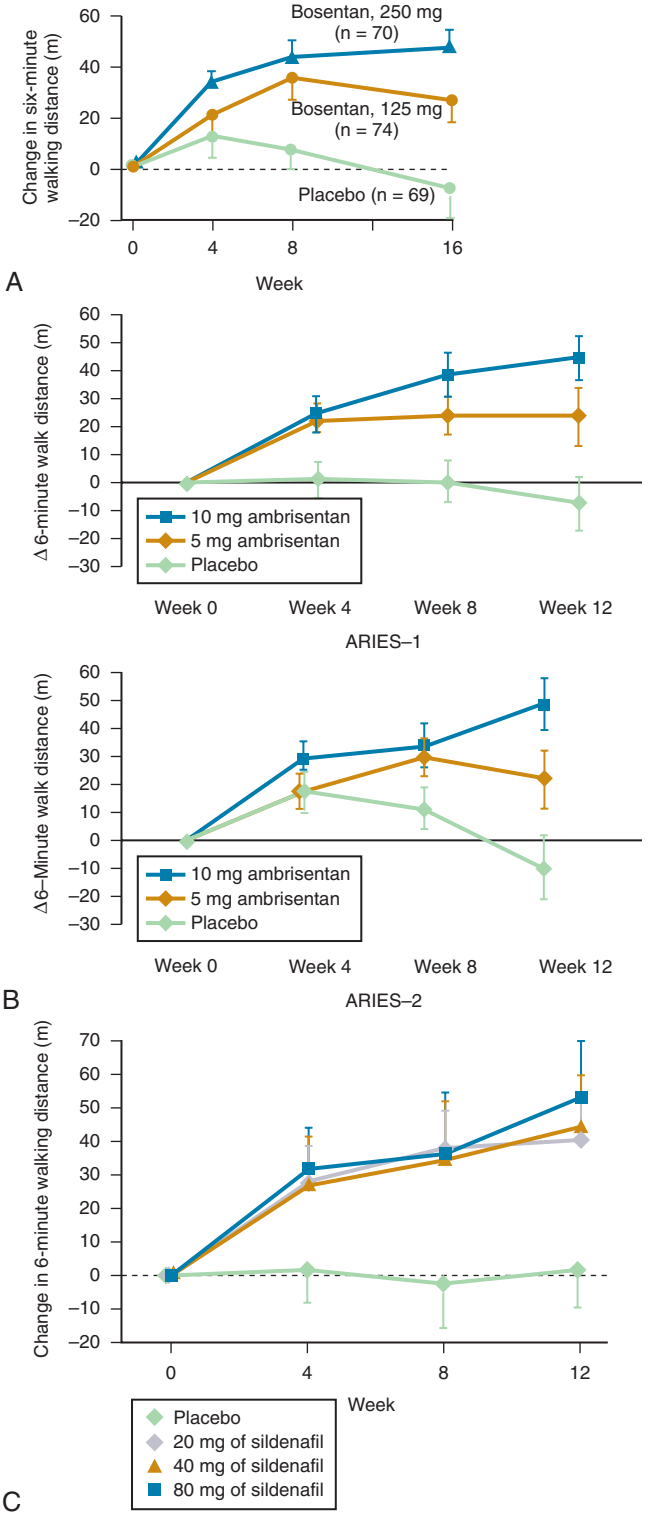

FIGURE 52-7 ■ Six-minute walk effects of the three currently approved oral therapies for PAH. All agents (**A,** bosentan; **B,** ambrisentan; **C,** sildenafil) demonstrated significant placebo-corrected improvements in 6-minute walk distance, which was the primary end point in each pivotal trial. (Data from references 95, 112, and 113.)

with placebo-epoprostenol were noted. Although mortality was not a prespecified end point, during the 16 week trial, there were 7 deaths, all of which occurred in the placebo-epoprostenol group.

The STEP (Iloprost Inhalation Solution, Safety and Pilot Efficacy) trial randomized 67 patients with IPAH (55%) and pulmonary hypertension associated with connective tissue disease, repaired congenital heart disease, HIV, or anorexigen use on stable therapy with bosentan for at least 4 months to inhaled iloprost or placebo for 12 weeks.[115] The study was designed primarily as a safety study, but efficacy end points were also evaluated, including 6-minute walk test, with secondary end points including functional class, Borg dyspnea score, pulmonary hemodynamics, and time to clinical worsening (defined as PAH-related death, hospitalization, study discontinuation from worsening pulmonary hypertension, initiation of new PAH-specific therapy, lung transplantation, or atrial septostomy). At 12 weeks, there was a borderline statistically significant placebo-corrected improvement in 6-minute walk test of 26 m in the bosentan-inhaled iloprost group ($P = 0.05$). In addition, there was a significant improvement in both the functional class and the time to clinical worsening in the iloprost-bosentan group compared with placebo-bosentan.

The addition of inhaled treprostinil (currently under FDA review) to oral PAH therapy has been evaluated and shown to be beneficial, first in a pilot study[116] and then in the pivotal TRIUMPH-1 (Treprostinil Sodium Inhalation Used in the Management of Pulmonary Arterial Hypertension) study,[117] a 12-week study that compared the addition of inhaled treprostinil versus placebo to either bosentan or sildenafil in 235 patients with NYHA functional class III and IV. The primary outcome was change in 6-minute walk test with secondary end points including change in functional class, Borg dyspnea score, signs and symptoms of pulmonary hypertension and clinical worsening. The 6-minute walk test improved significantly by 20 m in the treprostinil arm as compared with placebo. There were no significant changes in the secondary end points. Inhaled treprostinil appeared to be safe, with the most frequent adverse events reported as cough, headache, and nausea.

Clearly, further study is needed to elucidate the role of add-on or combination therapy. Importantly, the development of longer-term, event-driven trials will be necessary, because add-on therapy may provide less incremental improvement, as evidenced by the relatively modest effects on 6-minute walk distance seen in the STEP and TRIUMPH studies.

Lung Transplantation

Lung transplantation is a viable option when all therapies for IPAH have been tried without success. According to recent United Network of Organ Sharing (UNOS) data, a minority of lung transplants is done for IPAH and these are usually double-lung transplants. The primary goal of lung transplantation is to provide a survival benefit; however, in certain situations (e.g., COPD), a significant improvement in quality of life is also deemed as important as an end point.

In patients failing maximal medical therapy, lung transplantation is the "ultimate" option. According to the International Society of Heart and Lung Transplantations, current recommendations for consideration of transplantation include persistent NYHA class III or IV on maximal medical therapy, low or declining 6-minute walk test, failing therapy with intravenous epoprostenol, cardiac failure with cardiac index less than 2 L/min/m^2, and elevated right atrial pressure (>15 mm Hg).[118] Considerations for referral to a transplant center include any patient with rapidly progressive disease or NYHA functional class III or IV, regardless of therapeutic options. The lung allocation scoring system, although not perfect, has enabled more appropriate listing of IPAH patients. Patients who are declining will, hopefully, receive higher scores, allowing shorter waiting times and, presumably, better outcomes. In patients doing well on oral therapies alone, evaluation for transplantation is no longer necessary.

One-year survival after lung transplantation for pulmonary hypertension was estimated at 80% in one series.[119]

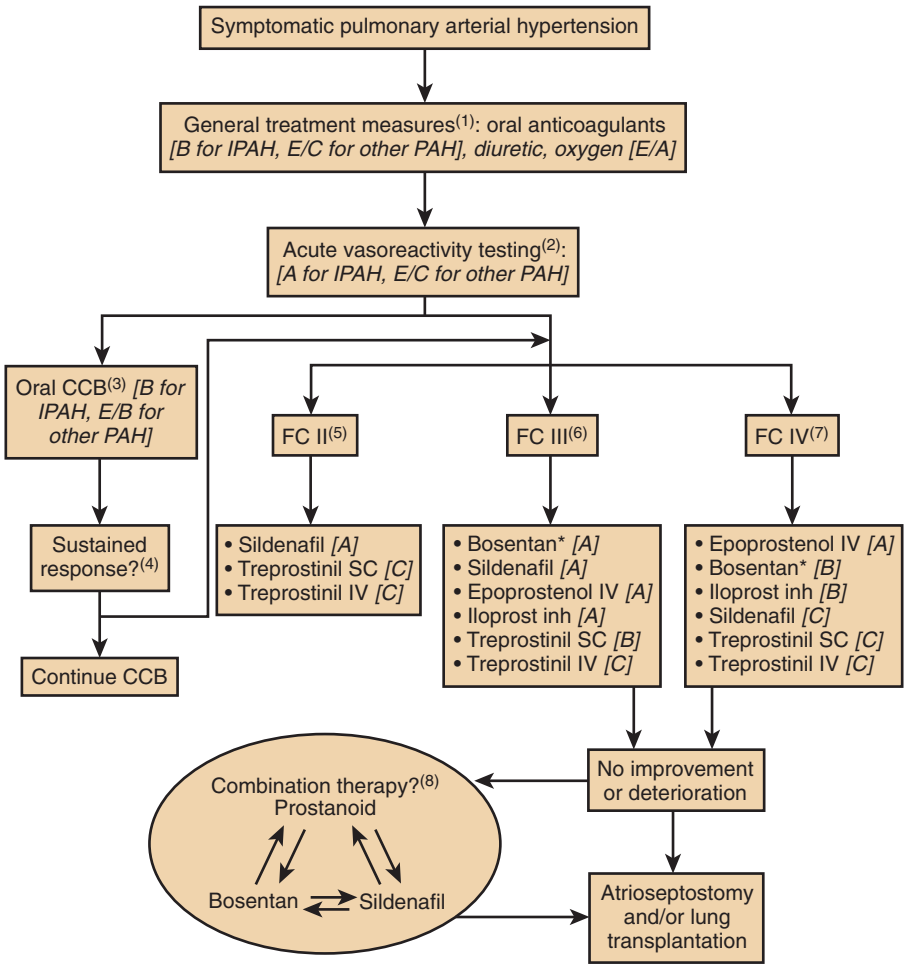

FIGURE 52-8 ■ Evidence-based treatment algorithm for PAH. The recommended therapies presented in this algorithm have been evaluated mainly in patients with IPAH, or PAH associated with connective tissue disease or anorexigen use. Extrapolation to other forms of PAH should be made with caution. Country-specific regulatory agency approval status and functional class indications for PAH medications vary. (1) Anticoagulation should be considered for patients with IPAH, and patients with an indwelling catheter for the administration of an IV prostanoid, in the absence of contraindications. Diuretics and oxygen should be added as necessary. (2) A positive acute vasodilator response is defined as a fall in mean PPA ≥ 10 mm Hg to ≤40 mm Hg, with an unchanged or increased cardiac output when challenged with inhaled nitric oxide, intravenous (IV) epoprostenol, or IV adenosine. (3) Consideration should be given to using a PAH-specific medication such as a phosphodiesterase 5 inhibitor, endothelin receptor antagonist, or prostanoid as first-line treatment instead of a calcium channel blocker (CCB) in patients with PAH that is not IPAH or PAH associated with anorexigen use, or in those in an advanced functional class (FC) given the exceedingly low long-term response rate to CCB monotherapy in the former and poor prognosis in the latter. (4) Sustained response to CCB therapy is defined as being in functional class I or II with normal or near-normal hemodynamics after several months of treatment. (5) First-line therapy for functional class III includes bosentan, sildenafil, epoprostenol, inhaled (inh) iloprost, and subcutaneous (SC) or IV treprostinil (see text for details). (7) Most experts recommend IV epoprostenol as first-line treatment for unstable patients in functional class IV. (8) Randomized controlled trials studying add-on combination treatment regimens are underway. *[A]*, strong recommendation; *[B]*, moderate recommendation; *[C]*, weak recommendation; *E/A*, strong recommendation based on expert opinion only; *E/B*, moderate recommendation based on expert opinion only; *E/C*, weak recommendation based on expert opinion only; *, not in order of preference. (Adapted from Badesch DB, Abman SH, Simonneau G, et al: Medical therapy for pulmonary arterial hypertension: Updated ACCP evidence-based clinical practice guidelines. Chest 131:1917–1928, 2007.)

In a recent article by the group from Pittsburgh,[120] the actuarial survival of all lung transplants for IPAH from 1994 to 2006 was 86% at 1 year, 75% at 5 years, and 66% at 10 years.

However, despite these recommendations, a minority of patients undergo lung transplantation for IPAH. This is likely related to the surge of treatments now available to treat IPAH.

Overall Therapeutic Strategy: Challenges

With several effective medical therapies and lung transplantation available for treatment of IPAH, how does one decide what therapy to use, when to reassess, when to add or change therapy, and what to add or change? Several consensus committees have attempted to evaluate the evidence for approved therapies and grade recommendations for these treatments. An algorithm recently published by an American College of Chest Physicians Consensus Group[89] is shown in Figure 52-8. Supportive therapies including diuretics, warfarin, and oxygen are considered. An acute vasoreactivity test is recommended for IPAH patients, and if a positive response is seen, calcium channel blocker treatment is recommended. For the patients without acute vasoreactivity, recommendations are given regarding specific therapies, based on the initial functional class. Oral therapies have been given "A" recommendations for less severely limited patients, intravenous epoprostenol for functional class IV patients.

Less specific guidance is given regarding combination therapy or timing of lung transplantation, given less data on these interventions. In practice, when a patient either fails to improve adequately or worsens on initial therapy, additional medications are often utilized. However, if such patients can be enrolled in a clinical trial evaluating "add-on" therapy, this route is probably preferable.

Survival

Long-term survival data are emerging in the era of IPAH treatment. In patients treated with epoprostenol, two papers demonstrated survival estimates of approximately 60% at 3 years.[103,121] In these retrospective studies, favorable survival was best predicted by response to therapy (improvement in 6-minute walk distance, functional class, and PVR). Survival data are also available for other therapies. For example, in 169 IPAH patients enrolled in the two pivotal trials of bosentan, estimated survival at 1 and 2 years was 96% and 89%, respectively, as compared with the predicted survival of 69% and 57%[95,122] (based on a validated equation calculating predicted survival from baseline hemodynamics). It should be acknowledged that there are no prospective, controlled survival data with the newer agents, given obvious ethical concerns about such trials in the era of existing therapy.

Experimental Therapies

The clinical therapeutics development landscape in PAH continues to evolve. Several new, novel agents are being evaluated, including a new-generation, tissue-targeted endothelin receptor antagonist, inhaled vasoactive intestinal peptide, a guanylate cyclase inhibitor, and a nitric oxide synthase coupler. In addition, antineoplastic agents such as imatinib and sorafinib that, through kinase inhibition, attack the excessive growth of cells, are being evaluated in IPAH.

KEY POINTS

- Pulmonary hypertension has been classified by WHO into 5 groups: (1) PAH, (2) pulmonary hypertension with heart disease, (3) pulmonary hypertension with lung disease, (4) pulmonary hypertension with pulmonary thromboembolism, and (5) miscellaneous.
- PAH has further been classified into (1) idiopathic IPAH, (2) heritable, (3) related to other conditions, (4) PPH of the newborn, and (5) PVOD.
- Heritable pulmonary hypertension has been associated with bone morphogenic protein receptor 2 (BMPR2), but mutations are not always associated with pulmonary hypertension, indicating other defects or insults are required. Evidence also supports involvement of a voltage-gated potassium ion channel and serotonin transporter.
- The basis for treatment of IPAH stems from deficiencies in prostacyclin and nitric oxide release and excess endothelin-1 found in patients with pulmonary hypertension.
- Pulmonary hypertension can be diagnosed to some extent by physical examination, chest radiology, electrocardiography, and echocardiography, but establishing the diagnosis with certainty requires a right-sided cardiac catheterization, which can check for left heart failure and response to a pulmonary vasodilator.
- Therapy includes moderate exercise, warfarin, oxygen, and calcium channel blockers.
- Targeted therapy with the prostacyclins, phosphodiesterase inhibitors, and endothelin receptor antagonists has made major improvements in the life of patients with PAH.

References

1. Rich S, Dantzker DR, Ayres SM, et al: Primary pulmonary hypertension: A national prospective study. Ann Intern Med 107:216–223, 1987.
2. Simonneau G, Robbins IM, Beghetti M, et al: Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol 54(1 Suppl):S43–54, 2009.
3. Romberg E: Über sklerose der Lungenarterien. Dtsch Arch Klin Med 48:197–215, 1891.
4. Goodale F Jr, Thomas WA: Primary pulmonary arterial disease. Arch Pathol 58:568–575, 1954.
5. Wood P: Congenital heart disease. Br Med J 18:693–698, 1950.
6. Dresdale DT, Schultz M, Michtom RJ: Primary pulmonary hypertension. Am J Med 18:686–705, 1951.
7. Shepherd JT, Edwards JE, Burchell HB, et al: Clinical, physiological, and pathological considerations in patients with idiopathic pulmonary hypertension. Br Heart J 19:70–82, 1957.
8. Chapman DW, Abbott JP, Latson J: Primary pulmonary hypertension: Review of literature and results of cardiac catheterization in ten patients. Circulation 12:35–46, 1957.
9. Yu PN: Primary pulmonary hypertension. Ann Intern Med 49:1138–1161, 1958.
10. Walcott G, Burchell HB, Brown AL: Primary pulmonary hypertension. Am J Med 49:70–79, 1970.
11. McDonnell PJ, Toye PA, Hutchins GM: Primary pulmonary hypertension and cirrhosis: Are they related? Am Rev Respir Dis 127:437–441, 1983.
12. Rich S, Brundage BH: Primary pulmonary hypertension: Current update. JAMA 251:2252–2254, 1984.
13. Wood P: Pulmonary hypertension with special reference to the vasoconstrictive factor. Br Heart J 28:557–570, 1958.
14. Heath D, Edwards JE: The pathology of hypertensive pulmonary vascular disease: A description of six grades of structural changes in the pulmonary arteries with special reference to congenital cardiac septal defects. Circulation 18:533–547, 1958.
15. Wagenvoort CA, Wagenvoort N: Primary pulmonary hypertension: A pathologic study of the lung vessels in 156 clinically diagnosed cases. Circulation 42:1163–1184, 1970.
16. Anderson EG, Simon G, Reid L: Primary and thromboembolic pulmonary hypertension: A quantitative pathological study. J Pathol 110:273–293, 1973.
17. Jamison BM, Michel RP: Different distribution of plexiform lesions in primary and secondary pulmonary hypertension. Hum Pathol 26:987–993, 1995.
18. Moser KM, Bloor CM: Pulmonary vascular lesions occurring in patients with chronic major vessel thromboembolic pulmonary hypertension. Chest 103:685–692, 1993.
19. Deng Z, Morse JH, Slager SL, et al: Familial primary pulmonary hypertension (gene PPH1) is caused by mutations in the bone morphogenic protein receptor-II gene. Am J Hum Genet 67:737–744, 2000.
20. Yuan JX, Aldinger AM, Juhaszova M, et al: Dysfunctional voltage-gated K+ channels in pulmonary artery smooth muscle cells of patients with primary pulmonary hypertension. Circulation 98:1400–1406, 1998.
21. Perros F, Montani D, Dorfmüller P, et al: Platelet-derived growth factor expression and function in idiopathic pulmonary arterial hypertension. Am J Respir Crit Care Med 178:81–88, 2008.
22. Yang X, Long L, Southwood M, et al: Dysfunctional Smad signaling contributes to abnormal smooth muscle cell proliferation in familial pulmonary arterial hypertension. Circ Res 96:1053–1063, 2005.
23. Morrell NW, Yang X, Upton PD, et al: Altered growth responses of pulmonary artery smooth muscle cells from patients with primary pulmonary hypertension to transforming growth factor-beta(1) and bone morphogenetic proteins. Circulation 104:790–795, 2001.
24. Christman BW, McPherson CD, Newman JH, et al: An imbalance between the excretion of thromboxane and prostacyclin metabolites in pulmonary hypertension. N Engl J Med 327:70–75, 1992.
25. Giaid A, Saleh D: Reduced expression of endothelial nitric oxide synthase in the lungs of patients with pulmonary hypertension. N Engl J Med 333:214–221, 1995.
26. Giaid A, Yanagisawa M, Langleben D, et al: Expression of endothelin-1 in the lungs of patients with pulmonary hypertension. N Engl J Med 328:1732–1739, 1993.
27. Humbert M, Montani D, Perros F, et al: Endothelial cell dysfunction and cross talk between endothelium and smooth muscle cells in pulmonary arterial hypertension. Vascul Pharmacol 49:113–118, 2008.
28. Schachna L, Wigley FM, Chang B, et al: Age and risk of pulmonary arterial hypertension in scleroderma Chest 124:2098–2104, 2003
29. Mukerjee D, St. George D, Coleiro B, et al: Prevalence and outcome in systemic sclerosis associated pulmonary arterial hypertension: Application of a registry approach. Ann Rheum Dis 62:1088–1093, 2003.
30. Wigley FM, Lima JA, Mayes M, et al: The prevalence of undiagnosed pulmonary arterial hypertension in subjects with connective tissue disease at the secondary health care level of community-based rheumatologists (the UNCOVER study). Arthritis Rheum 52:2125–2132, 2005.
31. Lee P, Langevitz P, Alderdice CA: Mortality in systemic sclerosis (scleroderma). Q J Med 82:139–148, 1992.
32. Fayemi AO: Pulmonary vascular disease in systemic lupus erythematosus. Am J Clin Pathol 65:284–290, 1976.
33. Gross M, Esterly JR, Earle RH: Pulmonary alterations in systemic lupus erythematosus. Am Rev Respir Dis 105:572–577, 1972.
34. Matthay RA, Schwarz MI, Petty TL, et al: Pulmonary manifestations of systemic lupus erythematosus: Review of twelve cases of acute lupus pneumonitis. Medicine 54:397–409, 1974.
35. Derderian SS, Tellis CJ, Abbrecht PH, et al: Pulmonary involvement in mixed connective tissue disease. Chest 88:45–48, 1985.
36. Jones MB, Osterholm RK, Wilson RB, et al: Fatal pulmonary hypertension and resolving immune-complex glomerulonephritis in mixed connective tissue disease. Am J Med 65:855–863, 1978.
37. Wiener-Kronish JP, Solinger AM, Warnock ML, et al: Severe pulmonary involvement in mixed connective tissue disease. Am Rev Respir Dis 124:499–503, 1981.
38. Petty TL, Wilkins M: The five manifestations of rheumatoid lung. Dis Chest 49:75–82, 1966.
39. Kay JM, Banik S: Unexplained pulmonary hypertension with pulmonary arteritis in rheumatoid disease. Br J Dis Chest 71:53–59, 1977.
40. Yousem SA, Colby TV, Carrington CB: Lung biopsy in rheumatoid arthritis. Am Rev Respir Dis 131:770–777, 1985.
41. Vongpatanasin W, Brickner E, Hillis D, et al: The Eisenmenger syndrome in adults. Ann Intern Med 128:745, 1998.
42. Follath F, Burkart F, Schweizer W: Drug-induced pulmonary hypertension? Br Med J 1:265–266, 1971.
43. Kay JM, Smith P, Heath D: Aminorex and the pulmonary circulation. Thorax 26:262–270, 1971.
44. Abenhaim L, Moride Y, Brenot F, et al: Appetite-suppressant drugs and the risk of primary pulmonary hypertension: International Primary Pulmonary Hypertension study group. N Engl J Med 335:609–616, 1996.
45. Nall KC, Rubin LJ, Lipskind S, et al: Reversible pulmonary hypertension associated with anorexigen use. Am J Med 91:97–99, 1991.
46. Weir EK, Reeve HL, Huang JMC, et al: Anorexic agents aminorex, fenfluramine, and dexfenfluramine inhibit potassium current in rat pulmonary vascular smooth muscle and cause vasoconstriction. Circulation 94:2216–2220, 1996.
47. Chin K, Channick RN, Rubin LJ: Is methamphetamine use associated with idiopathic pulmonary arterial hypertension? Chest 130:1657–1663, 2006.
48. Mantz FA, Craige E: Portal axis thrombosis with spontaneous portacaval shunt and resultant cor pulmonale. Arch Pathol 52:91–97, 1951.
49. Naeye RL: "Primary" pulmonary hypertension with coexisting portal hypertension: A retrospective study of six cases. Circulation 22:376–384, 1960.
50. Hadengue A, Benhayoun MK, Lebrec D, Benhamou JP: Pulmonary hypertension complicating portal hypertension: Prevalence and relation to splanchnic hemodynamics. Gastroenterology 100:520–528, 1991.

51. Herve P, Lebrec D, Brenot F, et al: Pulmonary vascular disorders in portal hypertension. Eur Respir J 11:1153–1166, 1998.
52. Kuo PC, Plotkin JS, Johnson LB, et al: Distinctive clinical features of portapulmonary hypertension. Chest 112:980–986, 1997.
53. Krowka MJ, Plevak DJ, Findlay JY, et al: Pulmonary hemodynamics and perioperative cardiopulmonary-related mortality in patients with portapulmonary hypertension undergoing liver transplantation. Liver Transpl Surg 6:443–650, 2000.
54. Swanson KL, Wiesner RH, Nyberg SL, et al: Survival in portapulmonary hypertension: Mayo Clinic experience categorized by treatment subgroups. Am J Transplant 8:2445–2453, 2008.
55. Krowka MJ, Swanson KL, Frantz RP, et al: Portapulmonary hypertension: Results from a 10 year screening algorithm. Hepatology 44:1502–1510, 2006.
56. Coplan NL, Shimony RY, Joachim HL et al: Primary pulmonary hypertension associated with human immunodeficiency viral infection. Am J Med 89:96–99, 1990.
57. Mette SA, Palevsky HI, Pietra GG, et al: Primary pulmonary hypertension in association with human immunodeficiency virus: A possible viral etiology for some forms of hypertensive pulmonary arteriopathy. Am Rev Respir Dis 145:1196–1200, 1992.
58. Speich R, Jenni R, Opravil M, et al: Primary pulmonary hypertension in HIV infection. Chest 100:1268–1271, 1991.
59. Sitbon O, Lascoux-Combe C, Delfraissy JF, et al: Prevalence of HIV-related pulmonary arterial hypertension in the current antiretroviral therapy era. Am J Respir Crit Care Med 177:108–113, 2008.
60. Cool CD, Rai PR, Yeager ME, et al: Expression of human herpesvirus 8 in primary pulmonary hypertension. N Engl J Med 349:1113–1122, 2003.
61. Bendayan D, Sarid R, Cohen A, et al: Absence of human herpesvirus 8 DNA sequences in lung biopsies from Israeli patients with pulmonary arterial hypertension. Respiration 75:155–157, 2008.
62. Bresser P, Cornelissen MI, van der Bij W, et al: Idiopathic pulmonary arterial hypertension in Dutch Caucasian patients is not associated with human herpes virus-8 infection. Respir Med 101:854–856, 2007.
63. Mesa RA, Edell ES, Dunn WF: Human immunodeficiency virus infection and pulmonary hypertension: Two new cases and a review of 86 reported cases. Mayo Clin Proc 73:37–45, 1998.
64. Nunes H, Humbert M, Jagot J-L, et al: Hypertension arerielle pulmonaire et infection par le VIH. Sang Thrombose Vaisseaux 10:555–562, 1998.
65. Levine S, Huckabee WE: Ventilatory response to drug-induced hypermetabolism. J Appl Physiol 38:827–833, 1975.
66. Reeves JT, Groves BM: Approach to the patient with pulmonary hypertension. *In* Weir EK, Reeves JT (eds): Pulmonary Hypertension. Mt. Kisco, NY: Futura Publishing, 1984, pp 1–44.
67. Packer M: Vasodilator therapy for primary pulmonary hypertension. Ann Intern Med 103:258–270, 1985.
68. Viar WN, Harrison TR: Chest pain in association with pulmonary hypertension: Its similarity to the pain of coronary disease. Circulation 5:1–11, 1952.
69. Dantzker DR, Bower JS: Mechanisms of gas exchange abnormality in patients with chronic obliterative pulmonary vascular disease. J Clin Invest 64:1050–1055, 1979.
70. Scharf SM, Feldman NT, Graboys TB, et al: Restrictive ventilatory defect in a patient with primary pulmonary hypertension. Am Rev Respir Dis 118:409–413, 1978.
71. Tolle JJ, Waxman AB, Van Horn TL, et al: Exercise-induced pulmonary hypertension. Circulation 118:2183–2189, 2008.
72. Weyman AE, Dillon JC, Feigenbaum H, et al: Echocardiographic patterns of pulmonic valve motion with pulmonary hypertension. Circulation 50:905–910, 1974.
73. Nanda NC, Gramiak R, Robinson TI, et al: Echocardiograph evaluation of pulmonary hypertension. Circulation 50:575–581, 1974.
74. Lew W, Karliner JS: Assessment of pulmonary valve echogram in normal subjects and in patients with pulmonary arterial hypertension. Br Heart J 42:147–161, 1979.
75. López-Candales A, Rajagopalan N, Dohi K, et al. Normal range of mechanical variables in pulmonary hypertension: A tissue Doppler imaging study. Echocardiography 25:864–872, 2008.
76. Forfia PR, Fisher MR, Mathai SC, et al: Tricuspid annular displacement predicts survival in pulmonary hypertension. Am J Respir Crit Care Med 174:1034–1041, 2006.
77. D'Alonzo G, Bower JS, Dantzker DR: Differentiation of patients with primary and thromboembolic pulmonary hypertension. Chest 85:457–462, 1984.
78. D'Alonzo GE, Barst RJ, Ayres SM, et al: Survival in patients with primary pulmonary hypertension: Results from a national prospective registry. Ann Intern Med 115:343–349, 1991.
79. Wagenvoort CA, Wagenvoort N, Takahashi T: Pulmonary veno-occlusive disease: Involvement of pulmonary arteries and review of the literature. Hum Pathol 16:1033–1041, 1985.
80. Bailey CL, Channick RN, Auger WR, et al: "High probability" perfusion lung scans in pulmonary venoocclusive disease. Am J Repir Crit Care Med 163:1974–1978, 2000.
81. Rabiller A, Jaïs X, Hamid A, et al: Occult alveolar haemorrhage in pulmonary veno-occlusive disease. Eur Respir J 27:108–113, 2006.
82. Mereles D, Ehlken N, Kreuscher S: Exercise and respiratory training improve exercise capacity and quality of life in patients with severe chronic pulmonary hypertension. Circulation 114:1448–1449, 2006.
83. Nelson DM, Main E, Crafford W, et al: Peripartum heart failure due to primary pulmonary hypertension. Obstet Gynecol 62:58s–63s, 1983.
84. Nootens M, Rich S: Successful management of labor and delivery in primary pulmonary hypertension. Am J Cardiol 71:1124–1125, 1993.
85. Bendayan D, Hod M, Oron G, et al: Pregnancy outcome in patients with pulmonary arterial hypertension receiving prostacyclin therapy. Obstet Gynecol 106:1206–1210, 2005.
86. Fuster V, Steele PM, Edwards WD, et al: Primary pulmonary hypertension: Natural history and the importance of thrombosis. Circulation 70:580–587, 1984.
87. Rich S, Kaufmann RN, Levy PS: The effect of high doses of calcium-channel blockers on survival in primary pulmonary hypertension. N Engl J Med 327:76–81, 1992.
88. Frank H, Miczoch J, Huber K, et al: The effect of anticoagulant therapy in primary and anorectic drug-induced pulmonary hypertension. Chest 1132:714–721, 1997.
89. Badesch DB, Abman SH, Simonneau G, et al: Medical therapy for pulmonary arterial hypertension: Updated ACCP evidence-based clinical practice guidelines. Chest 131:1917–1928, 2007.
90. Long-term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chrnoic bronchitis and emphysema. Report of the Medical Research Council Working Party. Lancet i:681–686, 1981.
91. Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: A clinical trial. Nocturnal Oxygen Therapy Trial Group. Ann Intern Med 93:391–398, 1980.
92. Sandoval J, Aguirre JS, Pulido T: Nocturnal oxygen therapy in patients with the Eisenmenger syndrome. Am J Respir Crit Care Med 164:1682–1687, 2001.
93. Bush A, Busst C, Booth K, et al: Does prostacyclin enhance the selective pulmonary vasodilator effect of oxygen in children with congenital heart disease? Circulation 74:135–144, 1986.
94. Barst RJ, Rubin LJ, Long WA, et al: A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. N Eng J Med 334:296–302, 1996.
95. Rubin LJ, Badesch DB, Barst RJ, et al: Bosentan therapy for pulmonary arterial hypertension. N Engl J Med 346:896–903, 2002.
96. Murray MD, Deer MM, Ferguson JA, et al: Open-label randomized trial of torsemide compared with furosemide therapy for patients with heart failure. Am J Med 11:513–520, 2001.
97. Pitt B, Znnad F, Remme WJ, et al: The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Sudy Investigators. N Engl J Med 341:709–717, 1999.
98. Froom P, Ortiz C: Primary pulmonary hypertension and oral phentolamine. Ann Intern Med 91:495–496, 1979.
99. Weir EK, Rubin LJ, Ayres SM, et al: The acute administration of vasodilators in primary pulmonary hypertension. Experience

from the National Institutes of Health Registry on Primary Pulmonary Hypertension. Am Rev Respir Dis 140:1623–1630, 1989.
100. Leier CV, Bambach D, Nelson S, et al: Captopril in primary pulmonary hypertension. Circulation 67:155–161, 1983.
101. Rubin LJ, Peter RH: Oral hydralazine therapy for primary pulmonary hypertension. N Engl J Med 302:69–73, 1980.
102. Sitbon O, Humbert M, Jais X, et al: Long-term response to calcium channel blockers in idiopathic pulmonary arterial hypertension. Circulation 111:3105–3111, 2005.
103. Mclaughlin VV, Shillington A, Rich S: Survival in primary pulmonary hypertension: The impact of epoprostenol therapy. Circulation 106:1477–1482, 2002.
104. Kim NH, Channick RN, Rubin LJ: Successful withdrawal of long-term epoprostenol therapy for pulmonary arterial hypertension. Chest 124:1612–1615, 2003.
105. Simonneau G, Barst RJ, Galie N, et al: Continuous subcutaneous infusion of treprostinil, a prostacyclin analogue, in patients with pulmonary arterial hypertension: A double-blind, randomized, placebo-controlled trial. Am J Respir Crit Care Med 165:800–804, 2002.
106. Tapson VF, Gomberg-Maitland M, McLaughlin VV, et al: Safety and efficacy of IV treprostinil for pulmonary arterial hypertension: A prospective, multicenter, open-label, 12-week trial. Chest 129:683–688, 2006.
107. Gomberg-Maitland M, Tapson VF, Benza RL, et al: Transition from intravenous epoprostenol to intravenous treprostinil in pulmonary hypertension. Am J Respir Crit Care Med 172:1586–1589, 2005.
108. Olschewski H, Simonneau G, Galie N, et al: Inhaled iloprost for severe pulmonary hypertension. N Engl J Med 347:322–329, 2002.
109. Channick RN, Simonneau G, Sitbon O, et al: Effects of the dual endothelin-receptor antagonist bosentan in patients with pulmonary hypertension: A randomised placebo-controlled study. Lancet 358:1119–1123, 2001.
110. Galiè N, Rubin LJ, Hoeper M, et al: Treatment of patients with mildly symptomatic pulmonary arterial hypertension with bosentan (EARLY study): A double-blind, randomized controlled trial. Lancet 37:2093–2100, 2008.
111. Galie N, Badesch D, Oudiz R, et al: Ambrisentan therapy for pulmonary arterial hypertension. J Am Coll Cardiol 46:529–535, 2005.
112. Galie N, Olschewki H, Oudiz RJ, et al: Ambrisentan for the treatment of pulmonary arterial hypertension: Results of the Ambrisentan in Pulmonary Arterial Hypertension, Randomized, Double-Blind, Placebo-Controlled, Multicenter, Efficacy (ARIES) study 1 and 2. Circulation 117:3010–3019, 2008.
113. Galie N, Ghofrani HA, Torbicki A, et al: Sildenafil citrate therapy for pulmonary arterial hypertension. N Engl J Med 353:2148–2157, 2005.
114. Simonneau G, Rubin LJ, Galie N, et al: Addition of sildenafil to long-term epoprostenol therapy in patients with pulmonary arterial hypertension: A randomized trial. Ann Intern Med 149:521–530, 2008.
115. McLaughlin VV, Oudiz RJ, Frost A, et al: Randomized study of adding inhaled iloprost to existing bosentan in pulmonary arterial hypertension. Am J Respir Crit Care Med 174:1257–1263, 2006.
116. Channick RN, Olschewski H, Seeger W, et al: Safety and efficacy of inhaled treprostinil as add-on therapy to bosentan in pulmonary arterial hypertension. J Am Coll Cardiol 48:1433–1437, 2006.
117. McLaughlin VV, Rubin LJ, Benza R, et al: Triumph-1. Efficacy and safety of inhaled treprostinil sodium in patients with pulmonary arterial hypertension (PAH). Am J Respir Crit Care Med 177:A965, 2008.
118. Orens JB, Estenne M, Arcasoy S, et al: International Guidelines for the selection of lung transplant candidates: 2006 Update—A consensus report from the Pulmonary Scientific Council of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant 25:745–755, 2006.
119. Charman SC, Sharples LD, McNeil KD, et al: Assessment of survival benefit after lung transplantation by patient diagnosis. J Heart Lung Transplant 21:226–232, 2002.
120. Toyoda Y, Thacker J, Santos R, et al: Long-term outcome of lung and heart-lung transplantation for idiopathic pulmonary arterial hypertension. Ann Thorac Surg 86:1116–1122, 2008.
121. Sitbon O, Humbert M, Nunes H, et al: Long-term intravenous epoprostenol infusion in primary pulmonary hypertension: Prognostic factors and survival. J Am Coll Cardiol 40:780–788, 2002.
122. McLaughlin VV, Sitbon O, Badesch DB, et al: Survival with first-line bosentan in patients with primary pulmonary hypertension. Eur Respir J 25:244–249, 2005.

CHAPTER 53

PULMONARY VASCULITIS

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INTRODUCTION

Pulmonary vasculitis is a general term that encompasses a wide variety of specific diseases whose primary target is the vasculature of the lung. Pathologically it is characterized by the presence of cellular inflammation that infiltrates vessel walls, causes their destruction, and results in tissue necrosis. The clinical features of any particular disorder are determined by the site, size, and type of vessel involved as well as the relative amounts of vessel inflammation, destruction, and tissue necrosis present. While simple to define, the recognition, diagnosis, and management of the pulmonary vasculitides are among the most demanding challenges in medicine. Protean in their presentation and variable in their clinical evolution, their signs and symptoms fully overlap with infection, malignancy, connective tissue disease, and even medication reactions. Even in patients with a known vasculitis, separating active disease from complicating infection, drug toxicity, or some combination thereof will challenge the most resolute physician. Despite these hurdles, the astute clinician can make the diagnosis, initiate and manage therapy, as well as minimize complications by keeping some broad concepts in mind.

CLASSIFICATION

The major clinical benefit of classifying the vasculitides is to provide a framework that allows for an appreciation of the presenting features of disease. To this end, most current classification schemes are variations of the 1994 Chapel Hill nomenclature[1] and based on clinicopathologic presentations rather than etiology (Table 53-1). Unfortunately, most of the classification criteria currently used are relatively insensitive and nonspecific as diagnostic tools and cannot be used as such.[2] Thus, *the diagnosis of vasculitis relies upon the astute clinician recognizing patterns of disease made up of specific clinical, laboratory, imaging, and pathologic features* rather than strict adherence to a set of clinical diagnostic guidelines.

Using this approach, a scheme that classifies by vessel size (large, medium, and small) can be useful as it can suggest the clinical features associated with a particular disease. The large vessels are made up of the aorta and its largest branches (clinically affecting the extremities and head/neck), the medium-sized vessels are made up of the main visceral arteries (the renal, hepatic, coronary, and mesenteric vessels), while the small vessels are made up of the capillaries, venules, and arterioles. There can

TABLE 53-1. Classification of Vasculitis

PRIMARY IDIOPATHIC
Small Vessel
- Necrotizing granulomatous vasculitis (NGV)
- Churg-Strauss syndrome (CSS)
- Microscopic polyangiitis (MPA)
- Idiopathic pauci-immune glomerulonephritis
- Idiopathic capillaritis

Medium Vessel
- Polyarteritis nodosa (PAN)
- Kawasaki's disease

Large Vessel
- Takayasu's arteritis (TA)
- Giant cell arteritis (GCA)

PRIMARY IMMUNE COMPLEX MEDIATED
- Goodpasture's syndrome
- Henoch-Schönlein purpura
- Immunoglobulin A nephropathy
- Behçet's disease
- Essential cryoglobulinemia

SECONDARY VASCULITIS
Classic autoimmune disease
- Systemic lupus erythematosus (SLE)
- Rheumatoid arthritis (RA)
- Antiphospholipid antibody syndrome (APAS)

Infection
Paraneoplastic
Drug-induced (e.g., propylthiouracil)
Inflammatory bowel disease
Hypocomplementemic urticarial vasculitis

Data from references 1, 112.

be some overlap in the size of vessels affected as the small and large vessel vasculitides sometimes involve medium-sized arteries, but large and medium vessel vasculitides generally do not involve vessels smaller than arteries.

A second level of classification defines the vasculitides as antineutrophil cytoplasmic antibody (ANCA) positive or negative. The identification of these antibodies in the 1980s revolutionized the thinking regarding diagnosis and pathogenesis of vasculitis (see later). The vasculitides that are most commonly encountered in the practice of pulmonary medicine—the primary, idiopathic small vessel vasculitides—are also the ANCA-associated vasculitides and include necrotizing granulomatous vasculitis (NGV) (formerly Wegener's granulomatosis),[2a] Churg-Strauss syndrome (CSS), and microscopic polyangiitis (MPA).

A third approach to classification is sometimes used, defining the vasculitides by the presence or absence of granulomatous inflammation. Two of the ANCA-associated vasculitides (NGV and CSS), as well as the large vessel vasculitides (Takayasu's arteritis and giant cell arteritis), are characterized by the presence of granulomatous inflammation.

EPIDEMIOLOGY

The overall incidence and prevalence of vasculitis is unknown. All of the available epidemiologic studies contain significant flaws that limit their applicability. For example, the available data are neither geographically nor ethnically diverse, and the diagnostic criteria used vary from study to study. Furthermore, the availability of ANCA testing has significantly increased case finding. With these caveats in mind, giant cell arteritis is the most frequently recognized systemic vasculitis, with an annual incidence of 150 to 350 per million persons over age 50. Those of Nordic extraction appear at particularly high risk, especially in older age. The primary systemic vasculitides have an overall prevalence estimated at between 90 and 257 per million in European populations. Among the individual disorders, the annual incidence of NGV ranges from 4.9 to 10.5 per million, that of CSS from 0.5 to 4.2, and that of MPA from 2.7 to 11.6. Their prevalence ranges from 24 to 157 for NGV, 7 to 38 for CSS, and 0 to 66 for MPA. Among the secondary vasculitides, the best data are for rheumatoid arthritis–associated vasculitis (incidence of 12.5 per million, though with the advent of biologic therapy this appears to have fallen dramatically) and systemic lupus erythematosus (SLE)–associated vasculitis (3.6 per million).[3]

NORMAL VASCULAR ANATOMY AND HISTOLOGY

In a group of diseases pathologically defined by abnormalities of the vasculature, understanding the normal organization and location of the arterial and venous blood supplies in the lung is useful in appreciating their clinical features. The lung has a dual blood supply: the pulmonary and the bronchial circulations. The bronchial arteries arise from the systemic circulation (aorta and intercostal arteries) and form a plexus in the bronchial wall. The bronchial veins associate closely with the bronchial arteries, though neither is commonly affected in the pulmonary vasculitides.

During embryogenesis, the pulmonary arterial system forms in tandem with the branching bronchial buds and is recognized on histologic examination by its close proximity to the corresponding bronchi or bronchiole (Fig. 53-1A). In the normal lung, arteries and adjacent airways (either bronchi or bronchioles) are similarly sized, and size differences between the two can be an indication of pathology.[4] The arterial system consists of four components: elastic arteries, muscular arteries, arterioles, and capillaries. The elastic arteries are larger than 0.5 to 1.0 mm in diameter and can be macroscopically recognized. They are composed of an endothelial cell lining layer and a smooth muscle medial layer, and have well-developed, multiple elastic laminae. Muscular arteries are between 100 and 500 μm in diameter, and are composed of an endothelial cell lining, a smooth muscle medial layer bound by two elastic laminae (inner and

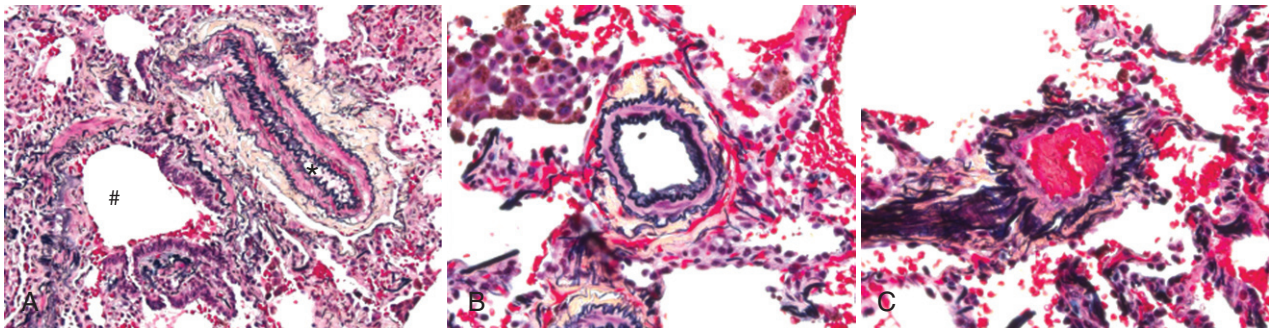

FIGURE 53-1 ■ **A,** Pentachrome (Movat) stain illustrating the relationship between pulmonary artery (*) and bronchiole (#). **B,** Small pulmonary artery in the peripheral lung showing internal and external elastic lamina in black. (Pentachrome/Movat stain.) **C,** Small pulmonary vein in peripheral lung showing one elastic lamina in black. (Pentachrome/Movat stain.)

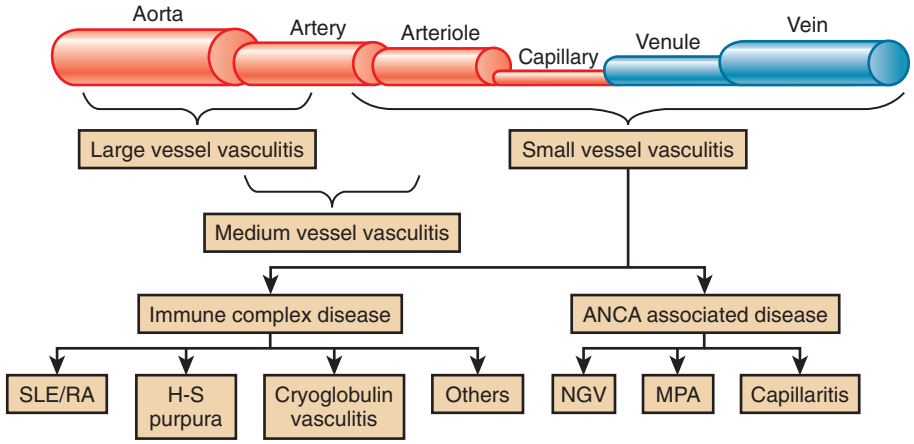

FIGURE 53-2 ■ Relationship between vessel size and mechanism. (See Table 53-1 for abbreviations.)

outer), and a collagenous adventitia. The smooth muscle layer progressively decreases in thickness until one reaches the arterioles, which are defined by a diameter of less than 100 µm and the absence of a muscular medial layer; however, they can become muscularized in a variety of disease states. The arterioles empty into the capillaries, which are characterized by the presence of a single layer of endothelial cells and an underlying basement membrane. They form part of the alveolar septa, and are the most common vessel affected in pulmonary vasculitis. On hematoxylin and eosin (H&E) stains of surgical lung biopsies, identifying the capillaries is difficult as a number of cells—endothelial cells, fibroblasts, and mononuclear inflammatory cells—are normal occupants of the alveolar septa.

The location of the pulmonary veins in the mature lung is typically within interlobular septa, as the embryonic pulmonary veins form branches that grow into the mesenchyme surrounding the lung buds. Pulmonary veins can be distinguished from pulmonary arteries by their single elastic lamina (see Fig. 53-1B and C). However, in the diseased lung, there can be reduplication of the elastic lamina, causing "arterialization" of the pulmonary veins, and anatomic location may be the only indicator as to the vessel type.

HISTOPATHOLOGY OF VASCULITIS

Although the diagnosis of vasculitis does not rely on pathology alone, both the diagnosis and a subclassification can be obtained from histopathology based on the size and location of the affected vessels (Fig. 53-2). The findings common to all the pulmonary vasculitides are inflammatory cell infiltration (inflammation) of the vessel wall with destruction of elastic laminae (in the case of arteries and veins) and, often, an accompanying fibrinoid necrosis. The lining endothelial cells may also show histologic abnormality, with subendothelial inflammation ("endothelialitis"), cellular disruption, and even loss of endothelial cells. The type of inflammation can vary widely; neutrophilic, eosinophilic, lymphoplasmacytic, or mixed infiltrates can all be seen. Granulomatous inflammation, consisting of poorly formed granulomas or multinucleated giant cells and/or epithelioid histiocytes, is of particular importance as one level of classification is based on its presence or absence (see earlier).

The term *capillaritis* is used to describe vasculitis of capillaries; however, it is often difficult to specifically identify the capillary on routine H&E stains, much less the endothelial disruption necessary to make the diagnosis. Therefore, identifying neutrophils and nuclear debris

(evidence of apoptosis) within alveolar septal walls is used as an indirect sign of capillaritis.

Not only do the size and type of vessel affected provide critical information, but changes to the associated lung parenchyma provide additional clues to the diagnosis. For example, a nodular parenchymal infiltrate is commonly seen in NGV, with microabscesses, necrosis, eosinophilic pneumonia, organizing pneumonia, and/or hemorrhage all adding important data. The specific pathologic findings associated with each entity are discussed in more detail later in the chapter.

PATHOGENESIS AND ETIOLOGY

Most of the vasculitic syndromes are hypothesized to be mediated by immunopathogenic mechanisms that occur in response to antigenic stimuli. Why some patients develop vasculitis in response to a particular stimulus, while others do not, is unknown. The etiology is likely multifactorial, including genetic predisposition, environmental exposures, and individual immune responses. Three broadly defined mechanisms have been proposed: directly pathogenic antibodies, immune complex deposition, and pathogenic T-cell responses. For each of these mechanisms, some combination of the direct immunologic attack and the endothelial and vascular wall response appears responsible for the histopathologic and subsequent clinical findings.[5]

A large variety of autoantibodies have been described in the vasculitic syndromes, including the anti–glomerular basement membrane (type IV collagen) antibodies seen in Goodpasture's syndrome, anti–endothelial cell antibodies, antilaminin antibodies, antiphospholipid (β2-glycoprotein 1) antibodies, and ANCAs among others. Of these, the best-studied mechanism is that hypothesized for the ANCA-associated vasculitides, especially WG.

The clinical syndrome was described in the 1930s[6–8]; however, it was not until 1982 that its closely associated autoantibodies, now known as ANCAs, were described.[9] While the role of ANCAs in the pathogenesis of disease is unknown, some clinical data suggest that, while not sufficient to cause disease alone, the presence of ANCAs appears to be required for the development or recurrence of systemic disease. These data include the link between the presence of these autoantibodies and the development of systemic vasculitic complications, ANCA-positive patients generally requiring systemic immunosuppressive therapy for disease control, and patients who become ANCA negative being at low risk of relapse. Mechanistically, the majority of the clinically significant ANCAs are directed against microbiocidal components used by neutrophils in host defense. These antibodies have been shown to have significant proinflammatory effects with activation of neutrophils, monocytes, and endothelial cells.[10] ANCAs stimulate the release of chemokines from neutrophils, monocytes, and endothelial cells; enhance the expression of cell adhesion molecules on endothelium; and activate primed neutrophils to release proteolytic enzymes and oxygen radicals.[11,12] Each of these steps would contribute to the vascular and tissue damage seen in vasculitis.

The trigger for ANCA production and persistence is also poorly understood. A role for active infection/inflammation in the disease pathophysiology has been proposed as there is evidence that chronic or concurrent infections can lead to disease exacerbation or relapse.[13–15] ANCA positivity has also been directed against a variety of antigens seen with viral, fungal, bacterial, and protozoal infection, as well as subacute bacterial endocarditis and cystic fibrosis.[16,17] It has been hypothesized that infections may give rise to ANCAs through molecular mimicry and contributes to their persistence through T- and B-cell stimulation by microbial superantigens.

Other potential mechanisms for the development of vasculitis include the direct invasion of the vessel wall by pathogenic organisms (e.g., bacterial, mycobacterial, spirochetal, rickettsial, fungal, viral) leading to an acute, direct vasculitic response as well as deposition of circulating immune complexes in the blood vessel wall. This deposition of immune complexes can lead to complement activation, anaphylatoxin production, and mast cell degranulation. Mast cell degranulation leads to release of vasoactive substances, and the anaphylatoxins can act as chemotactic agents for neutrophils, eosinophils, and mononuclear inflammatory cells. The prototypical disease for this mechanism is SLE, in which complexes of nuclear antigens such as DNA, immunoglobulins, and complement proteins lead to vascular injury.[18,19] Other immune complex–mediated vasculitides include rheumatoid vasculitis, Henoch-Schönlein purpura, and cryoglobulinemic vasculitis.

THE INITIAL DIAGNOSIS

Clinical Scenarios Suggestive of Vasculitis

The importance of the initial history in the evaluation of a patient with suspected vasculitis cannot be overemphasized. Symptoms that initially appear of only minor importance and unrelated must not be overlooked as both vasculitis and its mimics (connective tissue diseases, infection, malignancy, drug toxicity, etc.) present with and evolve through a variety of confusing clinical manifestations. Similarly, a careful physical examination may reveal otherwise asymptomatic disease that suggests the presence of a systemic disorder. To put some order to this, the identification of particular clinical scenarios can suggest the presence of a systemic vasculitis and the importance of its inclusion in the differential diagnosis.[20]

Destructive Upper Airway Lesions

Once primary infectious, allergic, and anatomic causes have been excluded, the presence of chronic refractory sinusitis and/or destructive soft tissue or bony lesions can prompt consideration of vasculitis.

Chest Imaging Findings of Cavitary or Nodular Disease

While a wide variety of nondiagnostic features may be seen on chest imaging when vasculitis involves the lung, the presence of nodular or cavitary disease should raise one's suspicion. While infection and malignancy are the most common explanations, in the correct clinical setting a vasculitis, particularly an ANCA-associated vasculitis, should be considered. For example, chest imaging findings of cavities are found in 35% to 50% and nodules in 55% to 70% of patients with NGV.[21,22]

Diffuse Alveolar Hemorrhage

Clinically defined by the presence of hemoptysis, diffuse alveolar opacities, and a drop in hematocrit, *diffuse alveolar hemorrhage* (DAH) refers to diffuse intra-alveolar bleeding generally from the alveolar capillaries and less frequently from the precapillary arterioles and postcapillary venules. However, the hemoptysis can be difficult to identify, often occurring only intermittently or not at all in up to one third of patients. The alveolar opacities do not have to be diffuse, and a drop in hematocrit can be difficult to document. Because of these caveats, DAH should be considered in patients with otherwise unexplained diffuse alveolar opacities, particularly when these opacities complicate symptoms of a connective tissue disease or new-onset renal insufficiency. An increase in the diffusion capacity of more than 30% over baseline can be suggestive of DAH. Bronchoalveolar lavage can be diagnostic when serially aspirated aliquots of fluid reveals persistently bloody return. On surgical lung biopsy, capillaritis, diffuse alveolar damage, or bland hemorrhage can be seen. When DAH is the complication of an ANCA-associated vasculitis, capillaritis can almost always be found; however, when partially treated, only bland hemorrhage may be seen. The finding of DAH with pulmonary capillaritis without an associated systemic vasculitis is termed *idiopathic pauci-immune pulmonary capillaritis,* and is classified within the family of primary idiopathic, small vessel vasculitis, despite generally being ANCA negative. The differential diagnosis of DAH includes diseases associated with the histopathologic finding of capillaritis (including both the primary idiopathic and secondary vasculitides) (Fig. 53-3) and in its absence (i.e., bland hemorrhage) (Table 53-2).

Acute Glomerulonephritis

Rapidly progressive glomerulonephritis is defined by an active urinary sediment, including hematuria (especially with dysmophic red cells), red cell casts, proteinuria (>500 mg/day), and a rising blood urea nitrogen and serum creatinine. The microscopic examination of the urine needs to be performed on a fresh urine sample as red cell casts and dysmophic red cells can quickly degenerate. Once rapidly progressive glomerulonephritis is identified, the differential diagnosis includes the ANCA-associated vasculitides, idiopathic pauci-immune glomerulonephritis (isolated small vessel renal vasculitis), SLE, Goodpasture's syndrome, postinfectious glomerulonephritis, immunoglobulin A (IgA) nephropathy, Henoch-Schönlein purpura, essential cryoglobulinemia, and membranoproliferative glomerulonephritis.[23–26]

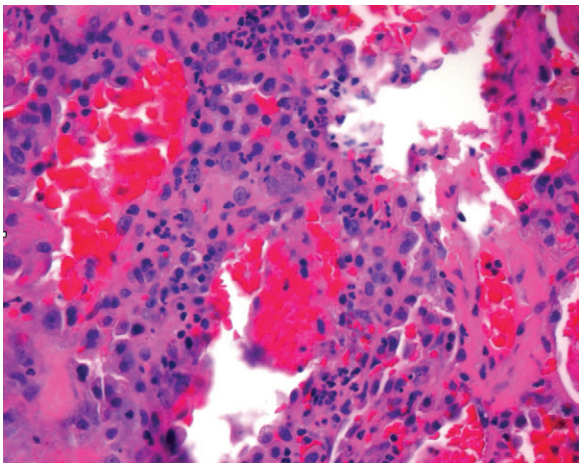

FIGURE 53-3 ■ Capillaritis showing disruption of the alveolar septa by infiltrates of neutrophils and nuclear debris. The septal borders are vague, indicating wall damage.

TABLE 53-2. Causes of Diffuse Alveolar Hemorrhage

WITH HISTOPATHOLOGIC CAPILLARITIS
Classic vasculitides
Primary idiopathic small vessel vasculitis
ANCA-associated—NGV, CSS, MPA
Isolated pulmonary capillaritis
Immune complex mediated
Goodpasture's syndrome
Essential cryoglobulinemia
Henoch-Schönlein purpura
Secondary vasculitis
Classic autoimmune disease—SLE, RA, PM/DM, SSc, MCTD
Primary antiphospholipid antibody syndrome
Lung or bone marrow transplantation
Drug-associated disease (chemotherapeutic agents, diphenylhydantoin)
Behçet's disease
WITHOUT CAPILLARITIS (BLAND HEMORRHAGE)
Idiopathic pulmonary hemosiderosis
Coagulopathy
Mitral stenosis
Inhalation injury (e.g., trimellitic anhydride)
Drug-associated disease (e.g., chemotherapeutic agents, penicillamine, amiodarone, nitrofurantoin)

ANCA, antineutrophil cytoplasmic antibody; CSS, Churg-Strauss syndrome; MCTD, mixed connective tissue disease; MPA, microscopic polyangiitis; NGV, necrotizing granulomatous vasculitis; PM/DM, polymyositis/dermatomyositis; RA, rheumatoid arthritis; SSc, systemic sclerosis; SLE, systemic lupus erythematosus.
Data from references 113, 114.

Pulmonary-Renal Syndrome

Pulmonary renal syndromes are classically defined as the presence of both DAH and rapidly progressive glomerulonephritis. However, whenever a destructive airway lesion or chest imaging findings of nodules or cavities occur with renal insufficiency, vasculitis should be considered. When this happens, the primary differential should includes the ANCA-associated vasculitides, Goodpasture's syndrome, and SLE.

Palpable Purpura

The presence of palpable purpura on physical examination implies a small vessel, cutaneous vasculitis.[27] The most common explanation is a cutaneous (hypersensitivity) vasculitis secondary to a drug reaction; however, the ANCA-associated vasculitides, cryoglobulinemia, connective tissue diseases, infections, and malignancy should all be considered.

Mononeuritis Multiplex

Defined by the occurrence of abnormalities in two or more peripheral nerve distributions, mononeuritis multiplex should raise particular suspicion.[28,29] A variety of other central or peripheral nervous system manifestations can also be seen, including pain, numbness, paresthesias, weakness, or loss of function (e.g., sudden onset of a footdrop or wristdrop).

Multisystem Disease

Unusual combinations of signs and symptoms that involve multiple organ systems either simultaneously or over time should raise the possibility of a vasculitis. This requires a high index of suspicion from the clinician as items such as constitutional symptoms (e.g., fever of unknown origin), unusual "rashes," migratory polyarthritis, or "chronic sinus disease" must be considered relevant when the primary clinical presentation is breathlessness, renal failure, or abnormal chest imaging.

Specific Testing

Antinuclear Cytoplasmic Antibodies

ANCAs were first described in the early 1980s in patients with vasculitis, glomerulonephritis, and NGV, and recognized by a pattern of diffuse immunofluorescent staining of ethanol-fixed neutrophils. Near the same time, a pattern of perinuclear immunofluorescent staining of ethanol-fixed neutrophils was described in patients with MPA and pauci-immune glomerulonephritis.[9] Currently, two specific indirect immunofluorescent staining patterns, cytoplasmic (c-ANCA) (Fig. 53-4A) and perinuclear (p-ANCA) (see Fig. 53-4B), are described. Each pattern is associated with specific antibodies against a variety of intracellular antigens in neutrophils and monocytes. c-ANCA are primarily, but not exclusively, directed against proteinase 3 (PR3, in azurophilic granules), while the p-ANCA are most commonly myeloperoxidase (MPO, also in azurophilic granules), but have a much wider group of potential intracellular targets. Specific enzyme-linked immunosorbent assay (ELISA) testing for PR3 and MPO is available and has clinical usefulness. These antibodies describe the group of small vessel vasculitides that commonly affect the lung: NGV, CSS, and MPA. These ANCA-associated small vessel vasculitides all involve the small vessels and share a number of clinical features. Renal involvement (when present) is similar (pauci-immune, crescentic, and focal necrotizing glomerulonephritis).

The diagnostic utility of ANCA testing is dependent upon the sensitivity, specificity, and positive predictive value of c-ANCA (or anti-PR3) for NGV and p-ANCA (or anti-MPO) for MPA and CSS. When these tests are applied indiscriminately, the positive predictive value of the testing declines dramatically. Mandl et al. demonstrated that, by using clinical guidelines to identify at-risk patients, the positive predictive value of the tests increased without reducing sensitivity.[30] While ANCA testing alone or PR3 and MPO ELISA testing alone are used by many centers as their initial screening test, the combination of ANCA immunofluorescent testing plus ELISA testing maximizes their sensitivity.[30-34]

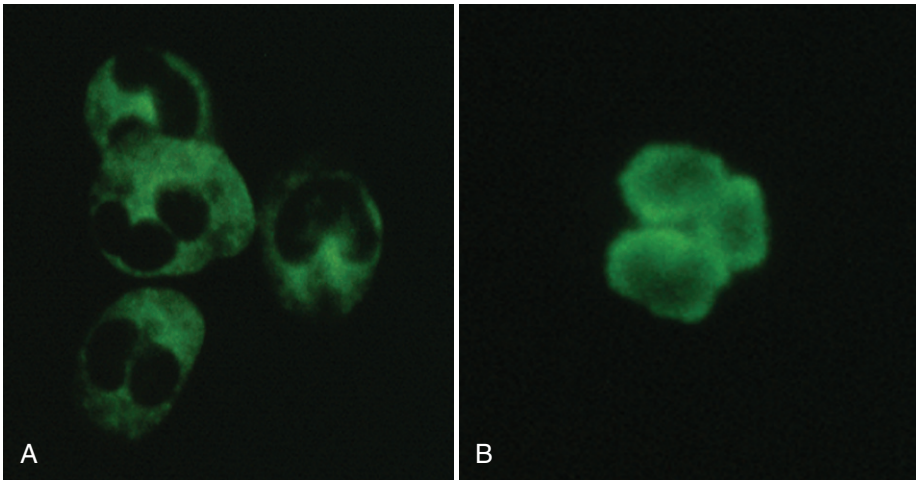

FIGURE 53-4 ■ Indirect immunofluorescent staining patterns of **(A)** c-ANCA and **(B)** p-ANCA.

With the caveats noted above, c-ANCA is highly sensitive (90% to 95%) in active, systemic NGV but slightly less so (65% to 85% sensitive) in organ-limited disease.[35] Specificity is approximately 90%. In the proper clinical setting, with a very high pretest probability of disease, a positive c-ANCA/anti-PR3 has sufficient positive predictive value that biopsy may be deferred.[36] Conversely, p-ANCA and anti-MPO generally lack sufficient sensitivity and may provide no more than suggestive evidence of CSS, MPA, or pauci-immune rapidly progressive glomerulonephritis, as they can be found in rheumatoid arthritis, Goodpasture's syndrome, and a wide variety of other clinical circumstances.[33]

Considerable attention has been focused on the utility of ANCA to assess disease activity, particularly the role of rising ANCA titers in predicting relapse.[37,38] Unfortunately, there appears to be no clear relationship between antibody titers and disease activity. In a recent prospective interventional study in which PR3-ANCA levels were routinely obtained, decreasing ANCA titers did not predict time to remission and increasing titers did not predict relapse. Increasing titers were associated with a relapse in only 40% of patients over a 12-month period. Therefore, the decision to modify therapy in patients with ANCA-associated vasculitis must be a clinical decision based on evidence of disease activity independent of ANCA titers.[35]

Based on high-quality evidence, recommendations have been offered that ANCA testing by immunofluorescence should be performed in the appropriate clinical context to detect the labeling pattern, and that all positive samples be tested for anti-PR3 and MPO specificity.[39] A positive test for c-ANCA targeted to PR3, or for p-ANCA targeted to MPO has a high sensitivity and specificity for the diagnosis of ANCA-associated vasculitis. It should also be recognized that the absence of a positive test does not rule out a diagnosis of vasculitis. ANCA testing should be performed in accredited laboratories that participate in external quality-control programs and undergo regular review of laboratory management and staff performing the assays.[40]

Other Laboratory Studies

Cultures of blood and other potentially affected organs (when tissue is obtained) should be performed to exclude infection. Routine laboratory studies (complete blood count with differential, chemistries, liver function tests, blood urea nitrogen and creatinine) should be obtained; however, the findings are generally nonspecific. An elevated erythrocyte sedimentation rate and elevated C-reactive protein lack specificity but are common. Urinalysis with microscopy should be performed on a fresh sample in all patients, as proteinuria and microscopic hematuria are common early findings in NGV and MPA. Anti–glomerular basement membrane antibodies should be obtained in all patients with pulmonary hemorrhage or a pulmonary-renal syndrome. Antinuclear antibodies and rheumatoid factor can be positive, although high titers—especially with the presence of disease-specific antibodies (e.g., anti-dsDNA, anti–SS-A/anti–SS-B, anti-RNP, anti–Scl-70, anticentromere, anti–JO-1)—favor a connective tissue disease. Immunoglobulin E should be obtained when CSS is being considered.

Chest Imaging

Plain chest radiographs and computed tomographic scanning will often be abnormal even in the absence of symptoms. Findings are best described in NGV and include nodular opacities and masses, particularly those that cavitate; diffuse ground-glass opacification when DAH is a possibility, airway stenoses, and ulcerations should raise the possibility of vasculitis. Adenopathy is not common and is more suggestive of infection or malignancy.[41]

Bronchoscopy

Bronchoscopy is primarily used to assess for the presence of malignancy, infection, stenotic or ulcerative upper airway or endobronchial lesions, pulmonary eosinophilia, and alveolar hemorrhage. Bronchoalveolar lavage should be grossly examined for evidence of alveolar hemorrhage, and then sent for culture (bacterial, fungal, and mycobacterial), cytology, and a differential count. Biopsies may provide important information that helps exclude infection or malignancy; however, they are rarely useful in making a positive diagnosis of vasculitis. When Hoffman et al.[42] performed 59 transbronchial biopsies in 48 patients with NGV, only 4 provided useful diagnostic features. Schnabel et al.[43] found that transbronchial biopsies provided support for a diagnosis of NGV in only 2 of 17 patients, while otolaryngologic examination and biopsy of the clinically involved areas of the upper respiratory tract yielded useful information in 13 of 19 NGV patients.

Diagnostic Biopsy

While a confident diagnosis may occasionally be made without tissue, diagnostic tissue biopsy remains necessary for a definitive diagnosis. While skin or upper airway tissue may be useful in some cases, when the lung is involved, definitive pathology generally requires a surgical lung biopsy. When Hoffman et al.[42] examined 82 open-lung biopsies in patients with small vessel vasculitis, diagnostic features were found in 90%. Renal biopsy is often performed to determine the cause of an acute glomerulonephritis. Specific features indicative of vasculitis, such as granulomatous inflammation or vascular necrosis, are rarely found; however, the presence of focal, segmental necrotizing glomerulonephritis without immune deposits (pauci-immune) is strongly suggestive of a systemic vasculitis.[42,44–46]

It is important to appreciate that the pathologic features of vasculitis often overlap with inflammatory lesions such as necrotizing infectious granulomas; all of the histopathologic features of vasculitis may not be present because of the timing of the biopsy and/or modification of the histology secondary to prior treatment, particularly corticosteroids. Because of this, it is critical

for the surgeon, pulmonologist, and pathologist to have a coordinated plan prior to the biopsy that includes the clinical differential diagnosis. This differential will dictate the appropriate specimens to collect and will include fresh tissue for culture and immunofluorescence (the presence of characteristic immunofluorescence patterns, such as IgA deposition in Henoch-Schönlein purpura, linear immunoglobulin G deposition in Goodpasture's syndrome, and irregular immunoglobulin and complement deposition in SLE, can be diagnostic) as well as for formalin fixation.

SPECIFIC CLINICAL DISORDERS

Being systemic disorders, apart from polyarteritis nodosa (PAN), virtually all of the vasculitides have been described to involve the lung. This involvement ranges from DAH to cavitary nodules, parenchymal inflammation, pleural disease, vascular aneurysms, and thrombotic and thromboembolic phenomena. A full accounting of each described disorder and their pulmonary manifestations is beyond the scope of this chapter. However, the primary idiopathic small vessel vasculitides deserve special attention.

Necrotizing Granulomatous Vasculitis (Formerly Wegener's Granulomatosis)

NGV is the most common of the ANCA-associated small vessel vasculitides, occurs at any age (generally 40 to 60), and equally affects the sexes. It is clinically recognized by its ability to involve the upper airway (e.g., chronic sinusitis and/or otitis, upper airway ulceration and/or structural deformity, subglottic or endobronchial stenosis); lower respiratory tract (e.g., chest symptoms of cough, chest pain, shortness of breath, hemoptysis, and/or chest imaging abnormalities); and kidney (e.g., glomerulonephritis) (Table 53-3). However, involvement of all three sites is neither necessary nor frequent at presentation. For example, even though 80% to 90% of patients will ultimately develop renal disease, as few as 40% will have renal involvement at time of first presentation.[42,47,48]

Constitutional symptoms (fever, asthenia, myalgias, arthralgias) and skin, eye, musculoskeletal, and peripheral and central nervous system disease are common.[26,42,47,48] Abnormal chest imaging occurs in the majority of patients, with alveolar, mixed, or interstitial opacities and nodular or cavitary disease.[21,22] A positive c-ANCA is seen in 90% to 95% of cases of active, systemic disease but in only 60% to 65% of cases of limited disease.[37,49-51]

The histopathology on surgical lung biopsy is dependent on the stage of the disease and whether there has been prior treatment. A small and medium vessel, necrotizing vasculitis with granulomatous inflammation and parenchymal necrosis, often with a geographic appearance, is characteristic (Fig. 53-5A).[52-56] The pathologic manifestations can be divided into major and minor histologic features. The three major features are (1) parenchymal necrosis, in the form of either geographic necrosis or neutrophilic microabscesses; (2) vasculitis (often small to medium-sized arteries, but can also involve veins and capillaries) (see Fig. 53-5B and C), and (3) granulomatous inflammation (see Fig. 53-5D). Although the inflammation in NGV is typically described as granulomatous, it is often mixed and includes granulomas, giant cells, neutrophils, lymphocytes, plasma cells, histiocytes, and eosinophils. The minor histologic criteria include organizing pneumonia (70% of cases), DAH (10% of cases), eosinophilia, and bronchocentric granulomatosis (1% of cases).[52,57] If the biopsy is performed early in the course of disease, some of the classic histologic findings may be absent. With prior treatment, there may be no significant inflammatory infiltrates and the only (nonspecific) clue may be scarring of arteries and/or airways.[58] A distinctive, but uncommon, histologic appearance in NGV is the presence of isolated capillaritis (see Fig. 53-3).

Prognostically, appropriately treated disease is associated with a 5-year survival rate of 75%. Death occurs from a variety of causes, including infection, cardiac disease, renal failure, and malignancy.[59] Poor outcomes correlate with advanced age, lack of otorhinolaryngology clinician involvement, more severe renal impairment, pulmonary involvement (particularly with alveolar hemorrhage), and low albumin and high-level anti-PR3 positivity.[60]

Churg-Strauss Syndrome

CSS is a specific ANCA-associated small vessel vasculitis that is clinically distinct from NGV and MPA (see Table 53-3), affects adults of all ages, and equally affects the sexes. Its presentation often overlaps with the eosinophilic lung diseases (chronic eosinophilic pneumonia, allergic bronchopulmonary mycosis, drug reactions, hypereosinophilic syndrome, parasitic infection, asthma/atopic disease) and difficult-to-control asthma/atopy. The syndrome is characterized by its own triad of (1) asthma, (2) hypereosinophilia, and (3) necrotizing vasculitis. The vasculitis classically has a three-phase presentation: the initial presence of atopy/rhinitis/sinusitis/asthma, followed by an eosinophilia, and a final vasculitic phase. However, the three phases do not need to occur sequentially, and the asthma may even postdate the vasculitis. Asthma is essentially universal, with common involvement of the upper airway.

In contrast to NGV and MPA, while pulmonary hemorrhage and glomerulonephritis may occur, they are much less common.[61-64] Significant cardiac disease (conduction abnormalities, systolic or diastolic dysfunction, intracavitary thrombus, pericarditis) and/or gastrointestinal disease (perforation, ischemia, bleeding) are dreaded and well-recognized complications.

ANCA is positive in a perinuclear immunofluorescent pattern (p-ANCA) in 40% to 70%, with peripheral eosinophilia (absolute eosinophil count >1500 cells/μL) almost universal at some point in the disease course.

Chest imaging is abnormal in two thirds of cases, with parenchymal opacities and less commonly nodules. Pleural effusions can be seen in 10%.

TABLE 53-3. Clinical Findings in the ANCA-Associated Vasculitides

	NGV	CSS	MPA
Constitutional	Commonly fatigue, malaise, fevers, and weight loss.	Common.	Very common. Generally precedes renal disease by months.
Pulmonary	70–95% of patients with respiratory symptoms or chest imaging abnormalities. Tracheobronchial and endobronchial disease in 10–50%.	Asthma essentially universal. Eosinophilic infiltrates in 30–50%. Diffuse alveolar hemorrhage in 0–20%.	25–55% of patients. 10–30% with diffuse alveolar hemorrhage. Fibrosis, focal infiltrates, and effusions rare.
Renal	50–90% of patients.	25–60% of patients.	Rapidly progressive glomerulonephritis is almost universal.
Upper Airway	70–95% of patients. Destructive or ulcerating lesions are suggestive.	Sinusitis in 20–70% of patients. Generally not destructive.	5–30% of patients, with sinus disease most common.
Musculoskeletal	Arthralgias, synovitis, and myalgias in up to 80% of patients.	Arthralgias and myalgias reported in up to 50% of patients.	Arthralgias and myalgias in at least 50% of patients.
Eyes	25–60% of patients. Vision-threatening disease including uveitis, ocular ulcers.	<5% of patients.	0–30% of patients. May be clinically silent.
Cardiac	5–30% of patients.	15–50% of patients and a major cause of mortality. Conduction delays or other ECG abnormality, systolic or diastolic dysfunction, pericarditis, or coronary artery vasculitis.	10–15% of patients. CHF and pericarditis have been described.
Gastrointestinal	<10% of patients.	15–60% of patients and a major cause of morbidity and mortality. Hemorrhage, abdominal pain, infarct, or perforated viscus.	35–55% of patients. Findings similar to PAN. Pain, bleeding, and ischemia. Rare visceral aneurysms.
Dermatologic	Up to 60% of patients. Palpable purpura, ulcers, nodules, or vesicles.	50–70% of patients. Nodules, papules, leukocytoclastic vasculitis with or without eosinophils.	35–60% of patients. Purpura common.
Neurologic	Both central and peripheral nervous system involvement.	Mononeuritis multiplex in 50–75% of patients. CNS in 5–40%.	Mononeuritis multiplex in 10–50% of patients.
Chest Imaging	Abnormal in >80% of patients. Alveolar, interstitial, or mixed opacities, often with nodular and/or cavitary disease.	Opacities in 40–75% of patients. Airways disease common (airway wall thickening, hyperinflation).	Opacities in 10–30% of patients. Pleural effusions in 5–20%.
ANCA	ANCA positive in >90% of patients and c-ANCA/anti-PR3 ELISA positive in >85% with generalized active disease.	ANCA positive in 40–70% of patients, with most of these being p-ANCA/anti-MPO positive.	ANCA positive in 50–75% of patients, with most of these being p-ANCA/anti-MPO positive.

ANCA, antineutrophil cytoplasmic antibody; c-ANCA, cytoplasmic ANCA; CHF, congestive heart failure; CNS, central nervous system; CSS, Churg-Strauss syndrome; ECG, electrocardiogram; ELISA, enzyme-linked immunosorbent assay; MPA, microscopic polyangiitis; MPO, myeloperoxidase; NGV, necrotizing granulomatous vasculitis; PAN, polyarteritis nodosa; p-ANCA, perinuclear ANCA; PR3, proteinase 3.
Data from references 21, 26, 42, 48, 61–64, 68, 75, 78, 109, 115–125.

Pathologically, both a necrotizing, small vessel vasculitis and an eosinophil-rich cellular infiltrate with necrotizing granulomas are seen.[65,66] The *diagnostic* findings on lung biopsy include eosinophilic pneumonia, necrotizing vasculitis, and granulomatous inflammation (Fig. 53-6A and B). The vasculitis consists of artery, vein, or capillary wall infiltration by lymphocytes and eosinophils. The granulomas often show central areas of necrosis with abundant necrotic eosinophils, surrounded by palisaded histiocytes and multinucleated giant cells. Findings *highly suggestive* of CSS include the combination of eosinophilic pneumonia and necrotizing vasculitis. Findings *suggestive* of CSS include the combination of eosinophilic pneumonia and parenchymal necrosis.[66]

Mortality is generally due to cardiac complications (up to half of CSS-related deaths), gastrointestinal complications, or status asthmaticus and respiratory failure.[61,62,67] While mortality rates of up to 40% were described in the 1970s, it is not clear from more recent data that adequately treated disease has an increased mortality.[68] Overall 5-year survival has been estimated at 68% to 100%.[60] A validated prognostic five-factor score has been defined. Made up of proteinuria (>1 g/24 hours), serum creatinine greater than 1.58 mg/dL, and clinically significant gastrointestinal, cardiac, or central nervous system involvement, each organ system involved counts as a score of 1. When two or more organs are involved, mortality is increased.[61]

Over the last several years, an association between the use of leukotriene inhibitors and CSS had been suggested in number of case reports and case series.[69,70] This led to the concern that leukotriene inhibitors may help promote

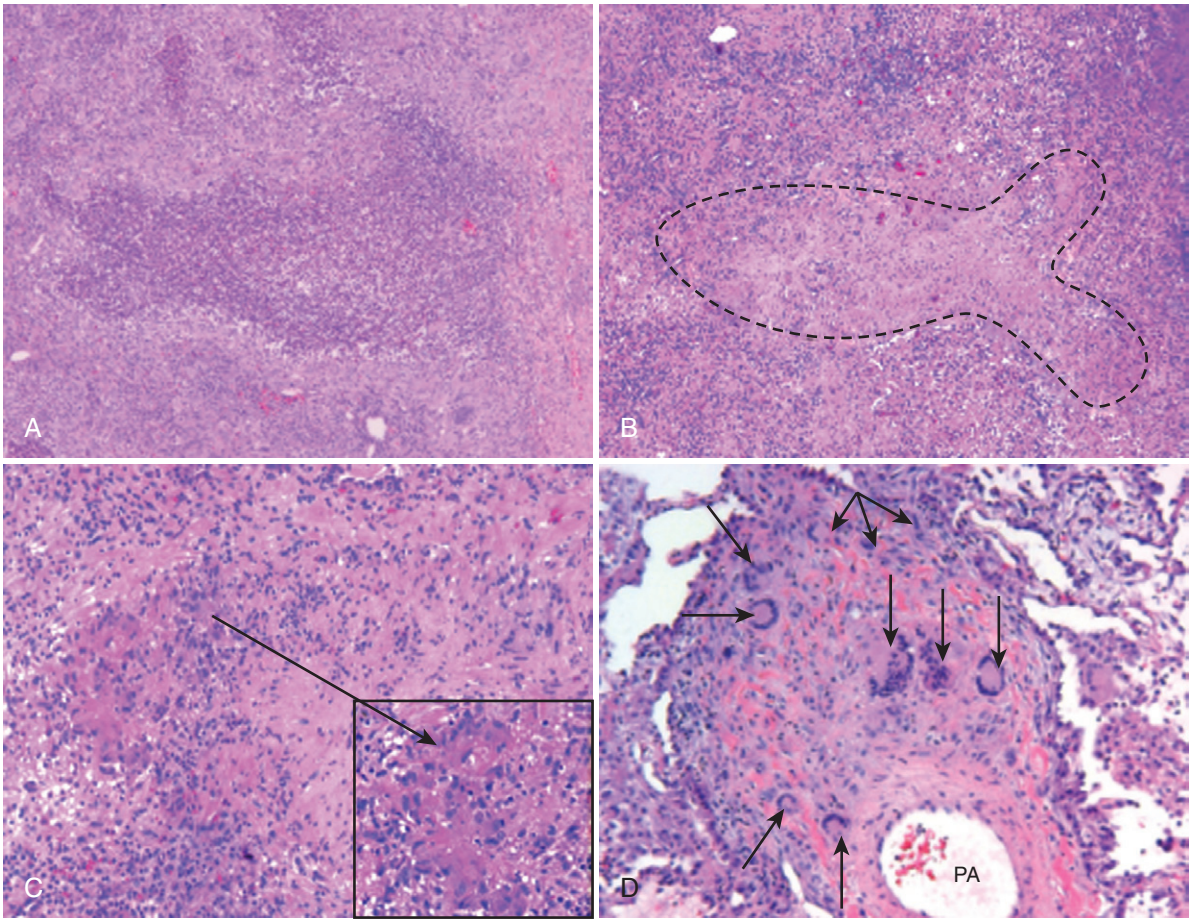

FIGURE 53-5 ■ **A,** Irregular outlines of geographic necrosis are typical of the parenchymal necrosis found in necrotizing granulomatous vasculitis. (Case courtesy of Dr. Christopher Bee.) **B,** Low-power view of a branching vessel demonstrating necrotizing vasculitis (Hematoxylin and eosin stain.) **C,** Higher power views of same vessel shown in **B.** Note the basophilic necrosis accompanied by chronic inflammation and vague granulomas (*inset*). **D,** Granulomatous inflammation (*arrows*) of the adventitia of a pulmonary artery (PA).

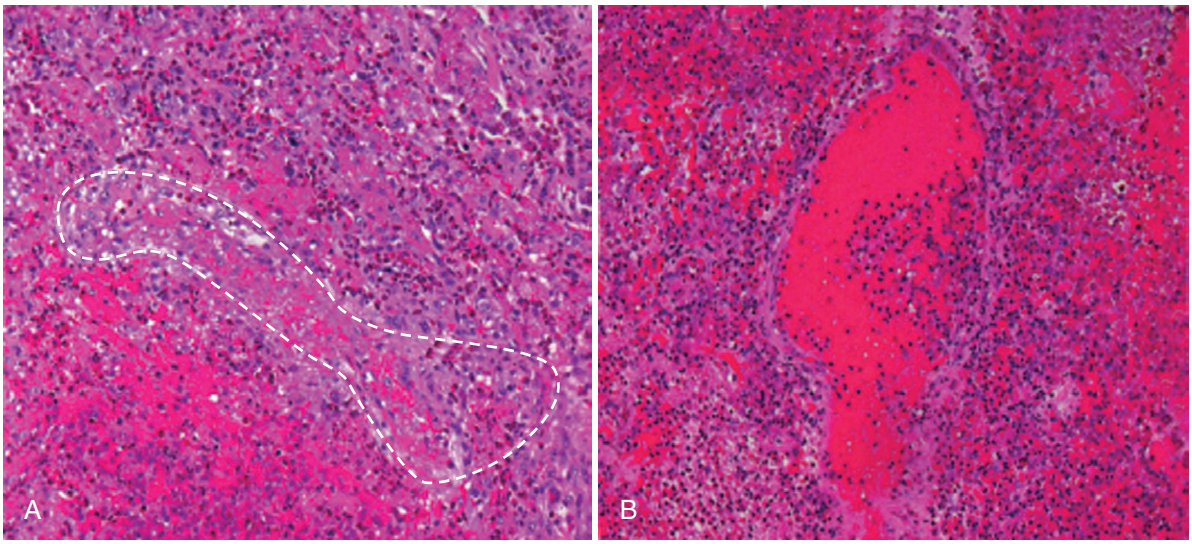

FIGURE 53-6 ■ **A,** Outline (*dotted line*) of a destroyed vessel in Churg-Strauss vasculitis. Note the marked eosinophilic infiltrates. **B,** A small vein showing destruction of its wall by eosinophils. There is an accompanying eosinophilic pneumonia characterized by numerous clusters of eosinophils within the air spaces. Hemorrhage is also present.

the biologic conversion of severe asthma/atopic disease to CSS.[71] However, recent analyses of postmarketing surveillance data and a number of patient cohorts have not offered supportive evidence of a pathogenic role for leukotriene receptor antagonists.[68,72–74] The appearance of CSS appears more likely to be related to the associated withdrawal of corticosteroids.

Microscopic Polyangiitis

Clinically, MPA is an ANCA-associated small vessel vasculitis generally heralded by weeks to months or longer of profound constitutional symptoms (fever, asthenia, myalgias, arthralgias) followed by the development of renal disease, generally rapidly progressive glomerulonephritis (see Table 53-3). It is more common in men, with an average age of onset in the sixth decade. Its clinical manifestations overlap considerably with those of PAN, explaining the decades of confusion over their relationship. The glomerulonephritis is essentially universal, whereas pulmonary involvement occurs in a minority of cases (10% to 30%).[75–77] In patients who develop lung disease, DAH/capillaritis is most common, while hemoptysis occurs in up to a third. Pulmonary fibrosis is uncommon, but associated with a high mortality rate. Skin disease occurs in over half of patients, most commonly with purpura. The peripheral nervous system (most commonly with mononeuritis multiplex) is involved more frequently than the central nervous system, and gastrointestinal involvement with bleeding and ischemia occurs with some frequency.[78] ANCA is positive in a perinuclear pattern in 50% to 75%.

Pathologically, a focal, segmental necrotizing vasculitis and a mixed inflammatory infiltrate without granulomata are seen. Vasculitis in MPA affects venules, capillaries, and arterioles. Neutrophilic capillaritis (see Fig. 53-3) is the classic histologic finding in the lung, with pulmonary alveolar hemorrhage and hemosiderin-laden macrophages (Fig. 53-7A–C). As the lesions heal, plugs of organizing pneumonia may fill air spaces, resulting in a pattern similar to brochiolitis obliterans with organizing pneumonia. Unlike the other small vessel vasculitides, MPA lacks granulomatous inflammation.

The overall 5-year survival rate has been estimated to range from 45% to 75%.[60] The prognostic five-factor score (see earlier) has been validated in MPA: the more organs that are involved, the worse the prognosis. The 5-year survival with a score of 0 is 88%, while a score of

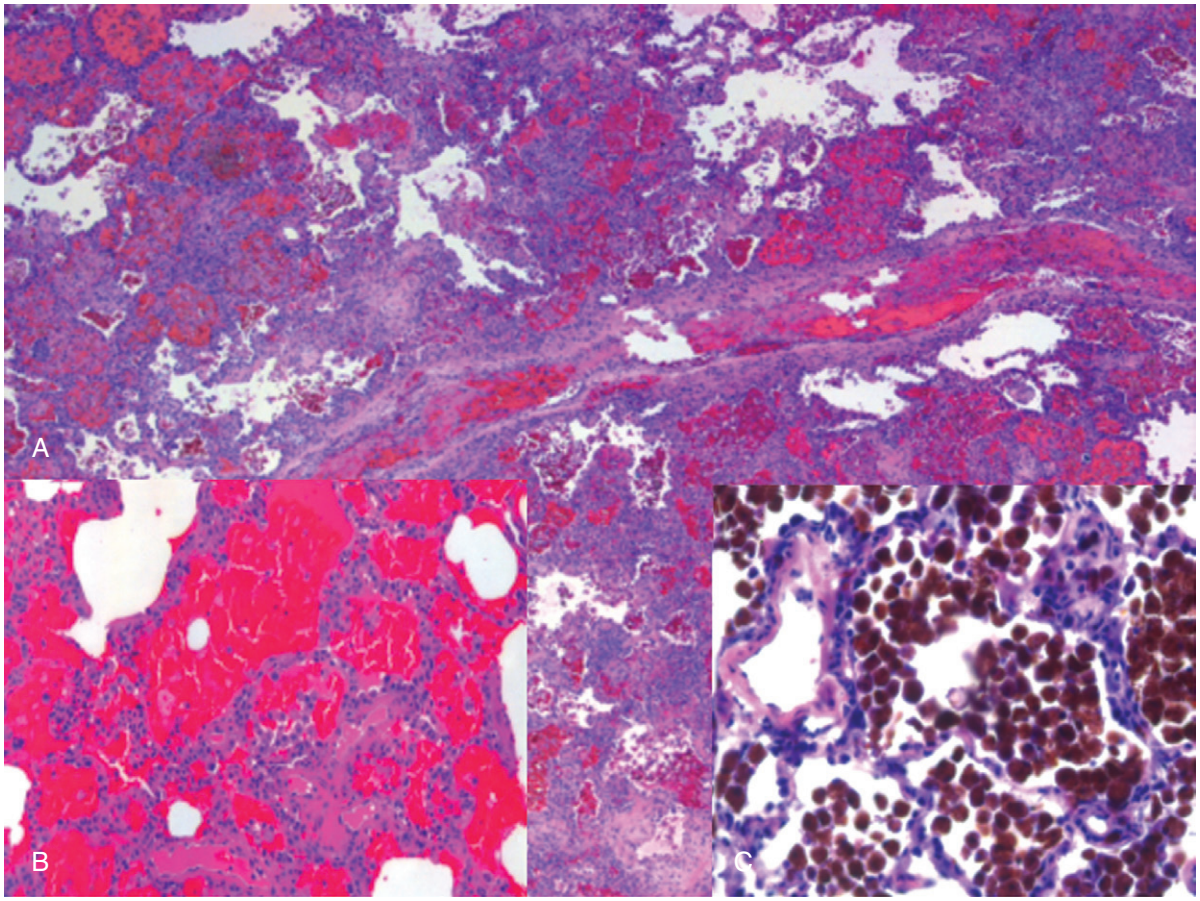

FIGURE 53-7 ■ **A,** Low-power view of diffuse alveolar hemorrhage. The air spaces are filled with red blood cells and the alveolar septa show concomitant inflammatory thickening. **B,** Alveolar hemorrhage demonstrating the smudged, homogeneous appearance of the disrupted red blood cells in the air spaces. Occasional hemosiderin-laden macrophages can be seen in the center. **C,** Hemosiderin-laden macrophages indicating chronic hemorrhage.

TABLE 53-4. European Vasculitis Study Group Disease Severity and First-Line Treatment Options for Induction Therapy

Disease Classification	Constitutional Symptoms	Renal Function	Threatened Organ Function	Treatment Options for Induction
Limited	No	Serum creatinine < 120 mmol/L (1.4 mg/dL)	No	Corticosteroids *or* methotrexate *or* azathioprine
Early generalized	Yes	Serum creatinine < 120 mmol/L (1.4 mg/dL)	No	Cyclophosphamide + corticosteroids *or* Methotrexate + corticosteroids
Active generalized	Yes	Serum creatinine < 500 mmol/L (5.7 mg/dL)	Yes	Cyclophosphamide + corticosteroids
Severe	Yes	Serum creatinine > 500 mmol/L (5.7 mg/dL)	Yes	Cyclophosphamide + corticosteroids + plasma exchange
Refractory	Yes	Any	Yes	Consider investigational or compassionate-use agents (see text).

Data from references 80, 98, 99, 101, 116, 126–132.

2 or greater is associated with 54% survival.[57] The intensity of therapy is therefore dictated by the number of organs involved. Relapses after successful induction therapy are common (25% to 33%)[75] but usually less severe and responsive to therapy.

TREATMENT

General Principles

As therapy for the vasculitides involves aggressive immunosuppression, treatment-related complications are common and can be severe. The risk of some complications is often directly associated with the intensity of immunosuppression. Therefore, rather than the diagnosis alone, often the disease severity dictates treatment intensity need to control the disease, while minimizing the risk of treatment-related adverse events. Similar to cancer therapy, treatment is divided into two parts, an initial "remission-induction" phase to control active disease and a "maintenance" phase to maintain disease remission while lowering treatment-related risk. Regardless of the phase of therapy, both disease-specific and drug-specific monitoring is required, focused on the early identification of disease activity, infection, or drug toxicity.

Clinicians should be familiar with the common toxicities associated with each drug and have a standard protocol for the monitoring of potential treatment-related side effects during both remission-induction and maintenance therapy. Not to be forgotten, oxygen therapy when needed, the treatment of comorbid disease, appropriate vaccinations, physical and occupational therapy, nutrition, and psychosocial support should be provided as they help to minimize the morbidity associated with these diseases.

As noted above, treatment recommendations depend upon an accurate assessment of disease severity. The European Vasculitis Study Group has devised a clinically useful grading system that categorizes the patient's disease as (1) limited, (2) early generalized, (3) active generalized, (4) severe, and (5) refractory. Clinical criteria and first-line treatment recommendations appear in Table 53-4.

Remission-Induction

Limited Disease

Limited disease refers to localized disease of the upper airway. There are no systemic symptoms, end-organ function is not threatened, and there is no renal involvement. Here, therapy can often be limited to a single agent such as corticosteroids, azathioprine, or methotrexate. Some authors have recommended trimethoprim-sulfamethoxazole alone for this group,[79] although it is not clear whether trimethoprim-sulfamethoxazole alone represents effective therapy (see later). For more aggressive, limited disease, therapy outlined for early generalized or active generalized disease may be necessary.

Early Generalized Disease

Early generalized disease differs from active generalized disease by the absence of a threat to specific organ function. While treatment recommendations have traditionally been similar for these (cyclophosphamide plus corticosteroids are the first-line therapy for both), the Methotrexate versus Cyclophosphamide for 'Early Systemic Disease' trial (NORAM) suggests that methotrexate is as efficacious as cyclophosphamide in the induction of disease remission in early generalized disease.[80–82] Thus, both agents represent acceptable first-line therapy in early disease.

Active Generalized Disease

Since Fauci's early studies,[48] cyclophosphamide plus corticosteroids have been the primary first-line therapy for

the treatment of active generalized disease. It has also recently been shown that pulsed intravenous cyclophosphamide is as effective as oral cyclophosphamide, with fewer side effects.[83–85]

Severe Disease

Severe disease is defined by impaired function of critical organs, such as severe renal disease (creatinine >5.7 mg/dL), DAH, or other organ-threatening disease. The addition of plasma exchange therapy to the standard cyclophosphamide plus corticosteroid regimen has been shown to be superior to high-dose, pulsed intravenous steroids at restoring renal function in patients with severe renal impairment.[86–92] Based upon several case reports and a case series, this strategy may also be effective for the treatment of DAH.[91] Additional therapies described at the case report level for patients with unresponsive DAH include activated human factor VII[93,94] and extracorporeal membrane oxygenation (used to "buy time" until other interventions have had a chance to work).[95]

Refractory Disease

Patients who have not responded to high-dose corticosteroids, cytotoxics, and plasma exchange are deemed to have refractory disease. There is no standard therapy that has been shown to work in this group of patients, and one must consider the use of novel or experimental agents. Treatments such as rituximab,[96–98] intravenous immune globulin, and antithymocyte globulin[99] have all been suggested.

Maintenance

Maintenance therapy to preserve disease control can hopefully be obtained with treatment associated with fewer and less severe adverse effects. During this phase of treatment, patients are generally converted to azathioprine or methotrexate, often combined with a low dosage of corticosteroids. As with all cytotoxic agents, these agents must be introduced with drug-specific monitoring to identify adverse effects as early as possible. Additional agents that have been used in selected patients include mycophenolate mofetil, leflunomide, and cyclosporine.[80,81,100–103]

The timing of transition from the induction agent to the maintenance therapy has been a subject of debate, with many physicians arguing that patients should have 12 months of induction therapy, while others have argued for using remission of clinical evidence of disease activity as the chief determinant of when to transition. The results of the Cyclophosphamide versus Azathioprine for Remission in Generalized Vasculitis (CYCAZAREM) trial demonstrated that patients with active generalized vasculitis may be transitioned from oral cyclophosphamide to azathioprine once a clinical remission (using defined criteria) has occurred (generally within 3 to 6 months) with no increase in the rate of relapse or disease activity scores or change in renal function.[98] The optimal duration of maintenance therapy is also a source of uncertainty. Absent convincing data, a number of experts have advocated for the use of at least 2 years of maintenance therapy before treatment cessation is considered.[104]

Another point of controversy has been the use of trimethoprim-sulfamethoxazole[15,105] or reduction of nasal *Staphylococcus aureus* carriage in the therapy of ANCA-associated small vessel vasculitis.[14,106] Studies have demonstrated a reduced frequency of disease relapse in patients who are maintained on trimethoprim-sulfamethoxazole compared to those without,[105] with additional work suggesting that this is related to *S. aureus* nasal carriage.[14,106] The European Vasculitis Study Group–sponsored Placebo-Controlled Trial of Nasal Mupirocin for the Prevention of Relapse (MUPIBAC) trial, in which patients are randomized to eradication of nasal *S. aureus* with topical mupirocin or placebo, hopefully will answer the question as to whether disease relapse is indeed related to *S. aureus* nasal carriage. Regardless of the results of this study, trimethoprim-sulfamethoxazole should be considered for *Pneumocystis jirovecii* prophylaxis in patients maintained on cyclophosphamide or other aggressive immunosuppression regimens, barring a sulfa allergy or other contraindication.

Monitoring for Complications

Monitoring for complications is mandatory in order to minimize the morbidity and mortality of both the disease and its treatment. When clinical deterioration occurs, infection, drug toxicity, disease relapse, or a new complication (such as deep venous thrombosis or thromboembolic disease[107]) should be considered. Infection is a major contributor to both morbidity and mortality and is frequently difficult to separate from disease activity. Up to 10% of patients treated with cyclophosphamide develop clinically important infections (i.e., pneumonia or sepsis) even in the absence of drug-induced leucopenia.[108] Combining high-dose glucocorticoids and cytotoxic therapy puts patients at especially high risk. Drug toxicity is also a common complication. In NGV patients treated with cyclophosphamide, cystitis is described in up to 12%, myelodysplastic syndrome in 8%, and solid malignancy in 5%.[109]

Historically, up to 50% of patients with an ANCA-associated vasculitis have suffered at least one relapse despite active treatment. Relapses are more common among patients with NGV (40% to 65%) and less common among patients with CSS (15% to 25%).[56,110] The features of clinical deterioration during a relapse may be similar to the patient's original presentation or may be novel, with symptoms and signs in previously unaffected organs. A relapse generally requires reinduction therapy. While disease relapse remains a clinical diagnosis at this time, a recent study applying a proteomic approach to identifying remission in NGV suggests that serum markers may one day permit accurate discrimination between quiescent and active disease.[111]

KEY POINTS

- Pulmonary vasculitis describes a variety of disorders characterized by their ability to cause vascular inflammation, destruction, and tissue necrosis in the lung.
- The presentation, clinical features, and evolution overlap fully with much more common diseases. The initial history is critical in the evaluation of a patient with suspected vasculitis.
- A confident diagnosis may occasionally be made without tissue; however, diagnostic tissue biopsy remains necessary for a definitive diagnosis.
- The ANCA-associated vasculitides—necrotizing granulomatous vasculitis, Churg-Strauss syndrome, and microscopic pulmonary angiitis—are the most commonly encountered vasculitides in the practice of pulmonary medicine.
- A number of high-quality randomized, controlled trials have allowed the development of evidence-based treatment recommendations with the expectation of a beneficial response.
- Therapy for the vasculitides involves aggressive immunosuppression; consequently, treatment-related complications are common and can be severe.

References

1. Jennette JC, Falk RJ, Andrassy K, et al: Nomenclature of systemic vasculitides: Proposal of an international consensus conference. Arthritis Rheum 37:187–192, 1994.
2. Sorensen SF, Slot O, Tvede N, Petersen J: A prospective study of vasculitis patients collected in a five year period: Evaluation of the Chapel Hill nomenclature. Ann Rheum Dis 59:478–482, 2000.

2a. Rosen MJ: Dr. Friedrich Wegener, the ACCP, and history. Chest 132:739–741, 2007.

3. Lane SE, Watts R, Scott DG: Epidemiology of systemic vasculitis. Curr Rheumatol Rep 7:270–275, 2005.
4. Yaegashi H, Takahashi T: The airway dimension in ordinary human lungs: A standardized morphometry of lung sections. Arch Pathol Lab Med Oct 118:969–974, 1994.
5. Khasnis A, Langford CA: Update on vasculitis. J Allergy Clin Immunol 123:1226–1236, 2009.
6. Klinger H: Grenzformen der periarteritis nodosa. Frankf Z Pathol 42:455–480, 1931.
7. Wegener F: Uber eine eigenartige rhinogene granulomatose mit besonderer beteiligung des arterien systems und der nieren. Beitre Pathol Anat Allg Pathol 102:36–68, 1939.
8. Wegener F: Uber eine generalisierte, septische of gefaberkrankungen. Verh Dtsch Patnol Ges 29:202–210, 1936.
9. Davies DJ, Moran JE, Niall JF, Ryan GB: Segmental necrotizing glomerulonephritis with antineutrophil antibody: Possible arbovirus aetiology? Br Med J 285:606, 1982.
10. Kallenberg CG, Stegeman CA, Heeringa P: Autoantibodies vex the vasculature. Nat Med 14:1018–1019, 2008.
11. Cid MC: New developments in the pathogenesis of systemic vasculitis. Curr Opin Rheumatol 8:1–11, 1996.
12. Ewert BH, Jennette JC, Falk RJ: Anti-myeloperoxidase antibodies stimulate neutrophils to damage human endothelial cells. Kidney Int 41:375–383, 1992.
13. Pinching AJ, Rees AJ, Pussell BA, et al: Relapses in Wegener's granulomatosis: The role of infection. Br Med J 281:836–838, 1980.
14. Stegeman CA, Tervaert JW, Sluiter WJ, et al: Association of chronic nasal carriage of *Staphylococcus aureus* and higher relapse rates in Wegener granulomatosis. Ann Intern Med 120:12–17, 1994.
15. DeRemee RA, McDonald TJ, Weiland LH: Wegener's granulomatosis: Observations on treatment with antimicrobial agents. Mayo Clin Proc 60:27–32, 1985.
16. Choi HK, Lamprecht P, Niles JL, et al: Subacute bacterial endocarditis with positive cytoplasmic antineutrophil cytoplasmic antibodies and anti-proteinase 3 antibodies. Arthritis Rheum 43:226–231, 2000.
17. Finnegan MJ, Hinchcliffe J, Russell-Jones D, et al: Vasculitis complicating cystic fibrosis. Q J Med 72:609–621, 1989.
18. Murin S, Wiedemann HP, Matthay RA: Pulmonary manifestations of systemic lupus erythematosus. Clin Chest Med 19:641–665, viii, 1998.
19. Churg A, Franklin W, Chan KL, et al: Pulmonary hemorrhage and immune-complex deposition in the lung: Complications in a patient with systemic lupus erythematosus. Arch Pathol Lab Med 104:388–391, 1980.
20. Mandl LA, Solomon DH, Smith EL, et al: Using antineutrophil cytoplasmic antibody testing to diagnose vasculitis. Arch Intern Med 162:1509–1514, 2002.
21. Cordier J-F, Valeyre D, Guillevin L, et al: Pulmonary Wegener's granulomatosis: A clinical and imaging study of 77 cases. Chest 97:906–912, 1990.
22. Reuter M, Schnabel A, Wesner F, et al: Pulmonary Wegener's granulomatosis: Correlation between high-resolution CT findings and clinical scoring of disease activity. Chest 114:500–506, 1998.
23. Bolton WK: Rapidly progressive glomerulonephritis. Semin Nephrol 16:517–526, 1996.
24. Couser WG: Glomerulonephritis. Lancet 353:1509–1515, 1999.
25. Madaio MP, Harrington JT: The diagnosis of glomerular diseases: Acute glomerulonephritis and the nephrotic syndrome. Arch Intern Med 161:25–34, 2001.
26. Frankel SK, Sullivan EJ, Brown KK: Vasculitis: Wegener granulomatosis, Churg-Strauss syndrome, microscopic polyangiitis, polyarteritis nodosa and Takayasu arteritis. Crit Care Clin 18:855–879, 2002.
27. Swerlick RA, Lawley TJ: Cutaneous vasculitis: Its relationship to systemic disease. Med Clin North Am 73:1221–1235, 1989.
28. Moore PM, Calabrese LH: Neurologic manifestations of systemic vasculitides. Semin Neurol 14:300–306, 1994.
29. Guillevin L, Lhote F, Gherardi R: Polyarteritis nodosa, microscopic polyangiitis, and Churg-Strauss syndrome: Clinical aspects, neurologic manifestations, and treatment. Neurol Clin 15:865–886, 1997.
30. Mandl LA, Solomon DH, Smith EL, et al: Using antineutrophil cytoplasmic antibody testing to diagnose vasculitis: Can test-ordering guidelines improve diagnostic accuracy? Arch Intern Med 162:1509–1514, . 2002
31. Russell KA, Wiegert E, Schroeder DR, et al: Detection of antineutrophil cytoplasmic antibodies under actual clinical testing conditions. Clin Immunol 103:196–203, 2002.
32. Hagen EC, Daha MR, Hermans J, et al: Diagnostic value of standardized assays for anti-neutrophil cytoplasmic antibodies in idiopathic systemic vasculitis. EC/BCR Project for ANCA Assay Standardization. Kidney Int 53:743–753, 1998.

33. Choi HK, Liu S, Merkel PA, et al: Diagnostic performance of antineutrophil cytoplasmic antibody tests for idiopathic vasculitides: Metaanalysis with a focus on myeloperoxidase antibodies. J Rheumatol 28:1584–1590, 2001.
34. Csernok E, Holle J, Hellmich B, et al: Evaluation of capture ELISA for detection of antineutrophil cytoplasmic antibodies directed against proteinase 3 in Wegener's granulomatosis: First results from a multicentre study. Rheumatology (Oxford) 43:174–180, 2004.
35. Finkielman JD, Lee AS, Hummel AM, et al: ANCA are detectable in nearly all patients with active severe Wegener's granulomatosis. Am J Med 120:643, 2007.
36. Langford CA: The diagnostic utility of c-ANCA in Wegener's granulomatosis. Cleve Clin J Med 65:135–140, 1998,
37. Boomsma MM, Stegeman CA, van der Leij MJ, et al: Prediction of relapses in Wegener's granulomatosis by measurement of antineutrophil cytoplasmic antibody levels: A prospective study. Arthritis Rheum 43:2025–2033, 2000.
38. Girard T, Mahr A, Noel LH, et al: Are antineutrophil cytoplasmic antibodies a marker predictive of relapse in Wegener's granulomatosis? A prospective study. Rheumatology (Oxford) 40:147–151, 2001.
39. Savige J, Gillis D, Benson E, et al: International Consensus Statement on Testing and Reporting of Antineutrophil Cytoplasmic Antibodies (ANCA). Am J Clin Pathol 111:507–513, 1999.
40. Mukhtyar C, Guillevin L, Cid MC, et al: EULAR recommendations for the management of primary small and medium vessel vasculitis. Ann Rheum Dis 68:310–317, 2009.
41. Ananthakrishnan L, Sharma N, Kanne JP: Wegener's granulomatosis in the chest: High-resolution CT findings. AJR Am J Roentgenol 192:676–682, 2009.
42. Hoffman GS, Kerr GS, Leavitt RY, et al: Wegener's granulomatosis: An analysis of 158 patients. Ann Intern Med 116:488–498, 1992.
43. Schnabel A, Holl-Ulrich K, Dalhoff K, et al: Efficacy of transbronchial biopsy in pulmonary vaculitides. Eur Respir J 10:2738–2743, 1997.
44. Jennette JC, Falk RJ: The pathology of vasculitis involving the kidney. Am J Kidney Dis 24:130–141, 1994.
45. Weiss MA, Crissman JD: Segmental necrotizing glomerulonephritis: Diagnostic, prognostic, and therapeutic significance. Am J Kidney Dis 6:199–211, 1985.
46. Hauer HA, Bajema IM, van Houwelingen HC, et al: Renal histology in ANCA-associated vasculitis: Differences between diagnostic and serologic subgroups. Kidney Int 61:80–89, 2002.
47. Anderson G, Coles ET, Crane M, et al: Wegener's granulomatosis: A series of 265 British cases seen between 1975 and 1985. A report by a sub-committee of the British Thoracic Society Research Committee. Q J Med 83:427–438, 1992.
48. Fauci AS, Haynes BF, Katz P, Wolff SM: Wegener's granulomatosis: Prospective clinical and therapeutic experience with 85 patients for 21 years. Ann Intern Med 98:76–85, 1983.
49. Noille B, Specks U, Ludemann J, et al: Anticytoplasmic autoantibodies: Their immunodiagnostic value in Wegener granulomatosis. Ann Intern Med 111:28–40, 1989.
50. Cohen-Tervaert JW, van der Woude FJ, Fauci AS, et al: Association between active Wegener's granulomatosis and anticytoplasmic antibodies. Arch Intern Med 149:2461–2465, 1989.
51. Kerr GS, Fleisher TA, Hallahan CW, et al: Limited prognostic value of changes in antineutrophil cytoplasmic antibody titers in patients with Wegener's granulomatosis. Adv Exp Med Biol 336:411–414, 1993.
52. Travis WD, Hoffman GS, Leavitt RY, et al: Surgical pathology of the lung in Wegener's granulomatosis. Am J Surg Pathol 15:315–333, 1991.
53. Lie JT: Illustrated histopathologic classification criteria for selected vasculitic syndromes. Arthritis Rheum 33:1074–1087, 1990.
54. Bligny D, Mahr A, Toumelin PL, et al: Predicting mortality in systemic Wegener's granulomatosis: A survival analysis based on 93 patients. Arthritis Rheum 51:83–91, 2004.
55. Neumann I, Kain R, Regele H, et al: Histological and clinical predictors of early and late renal outcome in ANCA-associated vasculitis. Nephrol Dial Transplant 20:96–104, 2005.
56. Gayraud M, Guillevin L, le Toumelin P, et al: Long-term followup of polyarteritis nodosa, microscopic polyangiitis, and Churg-Strauss syndrome: Analysis of four prospective trials including 278 patients. Arthritis Rheum 44:666–675, 2001.
57. Yousem SA: Bronchocentric injury in Wegener's granulomatosis: A report of five cases. Hum Pathol 22:535–540, 1991.
58. Mark EJ, Flieder DB, Matsubara O: Treated Wegener's granulomatosis: Distinctive pathological findings in the lung of 20 patients and what they tell us about the natural history of the disease. Hum Pathol 28:450–458, 1997.
59. Matteson EL, Gold KN, Bloch DA, Hunder GG: Long-term survival of patients with Wegener's granulomatosis from the American College of Rheumatology Wegener's Granulomatosis Criteria Cohort. Am J Med 101:129–134, 1996.
60. Phillip R, Luqmani R: Mortality in systemic vasculitis: A systematic review. Clin Exp Rheumatol 26(Suppl 51):S94–S104, 2008.
61. Guillevin L, Cohen P, Gayraud M, et al: Churg-Strauss syndrome: Clinical study and long-term follow-up of 96 patients. Medicine 78:26–37, 1999.
62. Guillevin L, Guittard T, Bletry O, et al: Systemic necrotizing angiitis with asthma: Causes and precipitating factors in 43 cases. Lung 165:165–172, 1987.
63. Lanham J, Elkon K, Pusey C, Hughes G: Systemic vasculitis with asthma and eosinophilia: A clinical approach to the Churg-Strauss syndrome. Medicine 63:65–81, 1984.
64. Guillevin L, Le Thi Huong D, Godeau P, et al: Clinical findings and prognosis of polyarteritis nodosa and Churg-Strauss angiitis: A study in 165 patients. Br J Rheumatol 27:258–264, 1988.
65. Churg J, Strauss L: Allergic granulomatosis, allergic angiitis, and periarteritis nodosa. Am J Pathol 27:277–301, 1951.
66. Katzenstein AL: Diagnostic features and differential diagnosis of Churg-Strauss syndrome in the lung: A review. Am J Clin Pathol 114:767–772, 2000.
67. Morgan JM, Raposo L, Gibson DG: Cardiac involvement in Churg-Strauss syndrome shown by electrocardiography. Br Heart J 62:462–466, 1989.
68. Keogh KA, Specks U: Churg-Strauss syndrome: Clinical presentation, antineutrophil cytoplasmic antibodies, and leukotriene receptor antagonists. Am J Med 115:284–290, 2003.
69. Weschler ME, Garpestad E, Flier SR, et al: Pulmonary infiltrates, eosinophilia, and cardiomyopathy following corticosteroid withdrawal in patients with asthma receiving zafirlukast. JAMA 279:455–457, 1998.
70. Weschler ME, Finn D, Gunawardena D, et al: Churg-Strauss syndrome in patients receiving montelukast as treatment for asthma. Chest 117:708–713, 2000.
71. Weller PF, Plaut M, Taggart V, Trontell A: The relationship of asthma therapy and Churg-Strauss syndrome: NIH workshop summary report. J Allergy Clin Immunol 108:175–183, 2001.
72. Jamaleddine G, Diab K, Tabbarah Z, et al: Leukotriene antagonists and the Churg-Strauss syndrome. Semin Arthritis Rheum 31:218–227, 2002.
73. Coulter D: Pro-active safety surveillance. Pharmacoepidemiol Drug Safety 9:273–280, 2000.
74. Lilly CM, Churg A, Lazarovich M, et al: Asthma therapies and Churg-Strauss syndrome. J Allergy Clin Immunol 109:S1–S19, 2002.
75. Guillevin L, Durand-Gasselin B, Cevallos R, et al: Microscopic polyangiitis: Clinical and laboratory findings in eighty-five patients. Arthritis Rheum 42:421–430, 1999.
76. Guillevin L, Lhote F: Treatment of polyarteritis nodosa and microscopic polyangiitis. Arthritis Rheum 41:2100–2105, 1998.
77. Akikusa B, Sato T, Ogawa M, et al: Necrotizing alveolar capillaritis in autopsy cases of microscopic polyangiitis: Incidence, histopathogenesis and relationship with systemic vasculitis. Arch Pathol Lab Med 121:144–149, 1997.
78. Lhote F, Guillevin L: Polyarteritis nodosa, microscopic polyangiitis and Churg-Strauss syndrome. Semin Respir Crit Care Med 19:27–45, 1998.
79. DeRemee RA: Wegener granulomatosis. Ann Intern Med 117:619–620, 1992 [author reply appears in Ann Intern Med 117:620–621, 1992].
80. Langford CA, Talar-Williams C, Sneller MC: Use of methotrexate and glucocorticoids in the treatment of Wegener's granulomato-

sis: Long-term renal outcome in patients with glomerulonephritis. Arthritis Rheum 43:1836–1840, 2000.
81. de Groot K, Muhler M, Reinhold-Keller E, et al: Induction of remission in Wegener's granulomatosis with low dose methotrexate. J Rheumatol 25:492–495, 1998.
82. Stone JH, Tun W, Hellman DB: Treatment of non-life threatening Wegener's granulomatosis with methotrexate and daily prednisone as the initial therapy of choice. J Rheumatol 26:1134–1139, 1999.
83. de Groot K, Adu D, Savage CO: The value of pulse cyclophosphamide in ANCA-associated vasculitis: Meta-analysis and critical review. Nephrol Dial Transplant 16:2018–2027, 2001.
84. Rihova Z, Jancova E, Merta M, et al: Daily oral versus pulse intravenous cyclophosphamide in the therapy of ANCA-associated vasculitis—preliminary single center experience. Prague Med Rep 105:64–68, 2004.
85. de Groot K, Harper L, Jayne DR, et al: Pulse versus daily oral cyclophosphamide for induction of remission in antineutrophil cytoplasmic antibody-associated vasculitis: A randomized trial. Ann Intern Med 150:670–680, 2009.
86. Pusey CD, Rees AJ, Evans DJ, et al: Plasma exchange in focal necrotizing glomerulonephritis without anti-GBM antibodies. Kidney Int 40:757–763, 1991.
87. Guillevin L, Lhote F, Cohen P, et al: Corticosteroids plus pulse cyclophosphamide and plasma exchanges versus corticosteroids plus pulse cyclophosphamide alone in the treatment of polyarteritis nodosa and Churg-Strauss syndrome patients with factors predicting poor prognosis: A prospective, randomized trial in sixty-two patients. Arthritis Rheum 38:1638–1645, 1995.
88. Gaskin G, Pusey C: Plasmapheresis in antineutrophil cytoplasmic antibody-associated systemic vasculitis. Ther Apher 5:176–181, 2001.
89. Frasca GM, Soverini ML, Falaschini A, et al: Plasma exchange treatment improves prognosis of antineutrophil cytoplasmic antibody-associated crescentic glomerulonephritis: A case-control study in 26 patients from a single center. Ther Apher Dial 7:540–546, 2003.
90. Bosch X, Font J, Mirapeix E, et al: Antimyeloperoxidase autoantibody-associated necrotizing alveolar capillaritis. Am Rev Respir Dis 146(5 Pt 1):1326–1329, 1992.
91. Klemmer PJ, Chalermskulrat W, Reif MS, et al: Plasmapheresis therapy for diffuse alveolar hemorrhage in patients with small-vessel vasculitis. Am J Kidney Dis 42:1149–1153, 2003.
92. Cole E, Cattran D, Magil A, et al: A prospective randomized trial of plasma exchange as additive therapy in idiopathic crescentic glomerulonephritis. The Canadian Apheresis Study Group. Am J Kidney Dis 20:261–269, 1992.
93. Henke D, Falk RJ, Gabriel DA: Successful treatment of diffuse alveolar hemorrhage with activated factor VII. Ann Intern Med 140:493–494, 2004.
94. Betensley AD, Yankaskas JR: Factor VIIa for alveolar hemorrhage in microscopic polyangiitis. Am J Respir Crit Care Med 166:1291–1292, 2002.
95. Ahmed SH, Aziz T, Cochran J, Highland K: Use of extracorporeal membrane oxygenation in a patient with diffuse alveolar hemorrhage. Chest 126:305–309, 2004.
96. Keogh KA, Wylam ME, Stone JH, Specks U: Induction of remission by B lymphocyte depletion in eleven patients with refractory antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum 52:262–268, 2005.
97. Jones RB, Ferraro AJ, Chaudhry AN, et al: A multicenter survey of rituximab therapy for refractory antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum 60:2156–2168, 2009.
98. Jayne D, Rasmussen N, Andrassy K, et al: A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. N Engl J Med 349:36–44, 2003.
99. Schmitt WH, Hagen EC, Neumann I, et al: Treatment of refractory Wegeners granulomatosis with antithymocyte globulin (ATG): An open study in 15 patients. Kidney Int 65:1440–1448, 2004.
100. Reinhold-Keller E, Fink CO, Herlyn K, et al: High rate of renal relapse in 71 patients with Wegener's granulomatosis under maintenance remission with low-dose methotrexate. Arthritis Rheum 47:326–332, 2002.
101. Haubitz M, de Groot K: Tolerance of mycophenolate mofetil in end-stage renal disease patients with ANCA-associated vasculitis. Clin Nephrol 57:421–424, 2002.
102. Nowack R, Gobel U, Klooker P, et al: Mycophenolate mofetil for maintenance therapy of Wegener's granulomatosis and microscopic polyangiitis: A pilot study in 11 patients with renal involvement. J Am Soc Nephrol 10:1965–1971, 1999.
103. Metzler C, Fink C, Lamprecht P, et al: Maintenance of remission with leflunomide in Wegener's granulomatosis. Rhematology (Oxford) 43:315–320, 2004.
104. Molloy ES, Langford CA: Does the dose of methotrexate influence the rate of relapse in patients with Wegener's granulomatosis? Nat Clin Pract Rheumatol 4:12–13, 2008.
105. Ohtake T, Kobayashi S, Honjou Y, et al: Generalized Wegener's granulomatosis responding to sulfamethoxazole-trimethoprim monotherapy. Intern Med 40:666–670, 2001.
106. Stegeman CA, Tervaert JW, de Jong PE, Kallenberg CGM: Trimethoprim-sulfamethoxazole for the prevention of relapses of Wegener's granulomatosis. N Engl J Med 335:16–20, 1996.
107. Allenbach Y, Seror R, Pagnoux C, et al: High frequency of venous thromboembolic events in Churg-Strauss syndrome, Wegener's granulomatosis and microscopic polyangiitis but not polyarteritis nodosa: A systematic retrospective study on 1130 patients. Ann Rheum Dis 68:564–567, 2009.
108. Bradley JD, Brandt KD, Katz BP: Infectious complications of cyclophosphamide treatment for vasculitis. Arthritis Rheum 32:45–53, 1989.
109. Reinhold-Keller E, Beuge N, Latza U, et al: An interdisciplinary approach to the care of patients with Wegener's granulomatosis. Arthritis Rheum 43:1021–1032, 2000.
110. Gordon M, Luqmani RA, Adu D, et al: Relapses in patients with a systemic vasculitis. Q J Med 86:779–789, 1993.
111. Stone JH, Rajapakse VN, Hoffman GS, et al: A serum proteomic approach to gauging the state of remission in Wegener's granulomatosis. Arthritis Rheum 52:902–910, 2005.
112. Jennette JC, Falk RJ: Small-vessel vasculitis. N Engl J Med 337:1512–1523, 1997.
113. Green RJ, Ruoss SJ, Kraft SA, et al: Pulmonary capillaritis and alveolar hemorrhage: Update on diagnosis and management. Chest 110:1305–1316, 1997.
114. Fontenot AP, Schwarz MI: Diffuse alveolar hemorrhage. *In* Schwarz MI, King TE (eds): Interstitial Lung Disease (4th ed). Hamilton, Ontario: BC Decker, 2003.
115. Romas E, Murphy BF, d'Apice AJ, et al: Wegener's granulomatosis: Clinical features and prognosis in 37 patients. Aust N Z J Med 23:168–175, 1993.
116. Frankel SK, Cosgrove GP, Brown KK: Small vessel vasculitis of the lung. Chron Respir Dis 2:75–84, 2005.
117. Hoffman GS, Specks U: Antineutrophil cytoplasmic antibodies. Arthritis Rheum 41:1521–1537, 1998.
118. Solans R, Bosch JA, Perez-Bocanegra C, et al: Churg-Strauss syndrome: Outcome and long-term follow-up of 32 patients. Rheumatology 40:763–771, 2001.
119. Guillevin L, Lhote F, Gayraud M, et al: Prognostic factors in polyarteritis nodosa and Churg-Strauss syndrome: A prospective study in 342 patients. Medicine 75:17–28, 1996.
120. Savage CO, Winearls CG, Evans DJ, et al: Microscopic polyarteritis: Presentation, pathology and prognosis. Q J Med 56:467–483, 1985.
121. Adu D, Howie AJ, Scott DG, et al: Polyarteritis and the kidney. Q J Med 62:221–237, 1987.
122. Serra A, Cameron JS, Turner DR, et al: Vasculitis affecting the kidney: Presentation, histopathology and long-term outcome. Q J Med 53:181–207, 1984.
123. D'Agati V, Chander P, Nash M, Mancilla-Jimenez R: Idiopathic microscopic polyarteritis nodosa: Ultrastructural observations on the renal vascular and glomerular lesions. Am J Kidney Dis 7:95–110, 1986.
124. Chumbley LC, Harrison EG Jr, DeRemee RA: Allergic granulomatosis and angiitis (Churg-Strauss syndrome): Report and analysis of 30 cases. Mayo Clin Proc 52:477–484, 1977.
125. Sinico RA, Di Toma L, Maggiore U, et al: Prevalence and clinical significance of antineutrophil cytoplasmic antibodies in Churg-Strauss syndrome. Arthritis Rheum 52:2926–2935, 2005.

126. Tesar V, Rihova Z, Jancova E, et al: Current treatment strategies in ANCA-positive renal vaculitis—lessons from European randomized trials. Nephrol Dial Transplant 18(Suppl 5):v2–v4, 2003.
127. Jayne D: Evidence-based treatment of systemic vasculitis. Rheumatology (Oxford) 39:585–595, 2000.
128. Jayne D: Update on the European Vasculitis Study Group Trials. Curr Opin Rheumatol 13:48–55, 2001.
129. Cohen Tervaert JW, Stegeman CA, Kallenberg CG: Novel therapies for anti-neutrophil cytoplasmic antibody-associated vasculitis. Curr Opin Nephrol Hypertens 10:211–217, 2001.
130. Langford CA, Sneller MC: Biologic therapies in the vasculitides. Curr Opin Rheumatol 15:3–10, 2003.
131. Kallenberg CGM, Tervaert JWC: New treatments of ANCA-associated vasculitis. Sarcoidosis Vasc Diffuse Lung Dis 17:125–129, 2000.
132. Bartolucci P, Ramanoelina J, Cohen P, et al: Efficacy of the anti-TNF-alpha antibody infliximab against refractory systemic vascuiltides: An open pilot study on 10 patients. Rhematology 41:1126–1132, 2002.

CHAPTER 54

PULMONARY ARTERIOVENOUS MALFORMATIONS AND OTHER VASCULAR ABNORMALITIES

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INTRODUCTION

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INTRODUCTION

Pulmonary vascular abnormalities occur in a variety of acquired and congenital conditions. These structural defects include vascular communications that either are confined to the pulmonary circulation, as is the case with pulmonary arteriovenous malformations, or join the systemic and pulmonary circulations, as with bronchopulmonary sequestration. Aneurysmal dilations of the pulmonary artery and its branches also occur and are considered in this chapter. Although all these conditions are rare, their diagnosis and treatment are important, because many are associated with complications that cause severe morbidity or mortality.

PULMONARY ARTERIOVENOUS MALFORMATIONS

Pulmonary arteriovenous malformations (PAVMs) are abnormal vascular structures that provide a direct capillary-free communication between the pulmonary and systemic circulations. They range in size from large complex structures consisting of a bulbous aneurysmal sac between dilated feeding arteries and draining veins (Fig. 54-1), to dilated smaller vessels (Fig. 54-2), to communications within the microvasculature (telangiectases). The true anatomic shunts of PAVMs are usually distinguished from the diffusion-perfusion defects that arise in patients with intrapulmonary vascular dilations secondary to the hepatopulmonary syndrome, which is fully described in Chapter 83.

Pulmonary arterial blood passing through these right-to-left (R–L) shunts cannot be oxygenated, which leads to hypoxemia. In addition, the absence of a filtering capillary bed allows particulate matter to reach the systemic circulation, where it impacts in other capillary beds, including the cerebral circulation, resulting in embolic cerebrovascular accidents (CVAs) and brain abscesses. It is crucial for the pulmonologist to assimilate the recent data demonstrating that—irrespective of PAVM size—all patients are at risk of paradoxical emboli. Importantly, recent data also confirm that most patients with clinically significant PAVMs do not have respiratory symptoms or profound hypoxemia. The incidence of

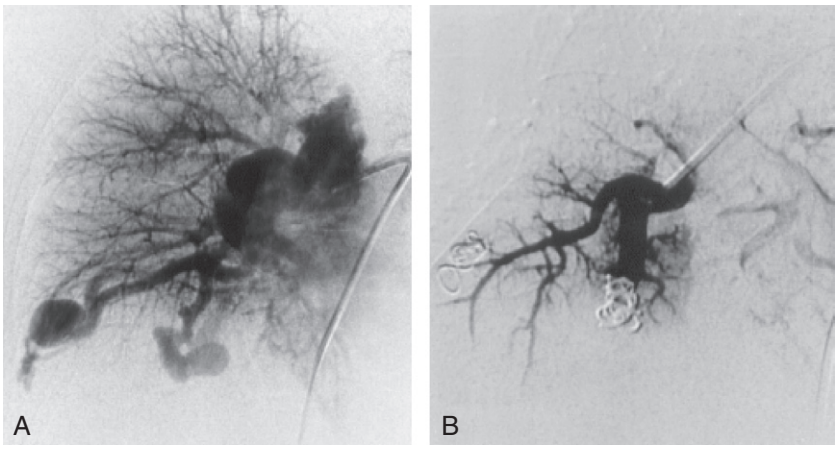

FIGURE 54-1 ■ Macroscopic right lower lobe pulmonary arteriovenous malformations (PAVMs) before **(A)** and after **(B)** embolization. Note embolization coils and restored perfusion of pulmonary arterial branches in **B.** Similar PAVMs were present in the left lung. Embolization over an 18-month period reduced the right-to-left shunt (and arterial oxygen saturation) from 32% (78% erect) to 3% (92% erect).

FIGURE 54-2 ■ Diffuse small pulmonary arteriovenous malformations in a patient left with a right-to-left shunt greater than 30% following maximal embolization. The patient declined transplantation; arterial oxygen saturation (erect) was unchanged at 78% to 79% over the next 12 years.

major, usually neurologic, complications approaches 50% (Table 54-1), with nearly 13% incidence of cerebral abscess and 27% of embolic stroke or transient ischemic attack recorded in all series. These complications can be limited if the underlying condition is recognized and treated with embolization using metal coils, balloons, or plug devices, the treatment of choice for almost all patients. Risk-benefit analyses are almost always in favor of treatment, though the possibility of contraindications needs to be considered.

TABLE 54-1. Features of Untreated Pulmonary Arteriovenous Malformations

	N	Mean (%)	Range (%)
RESPIRATORY			
Asymptomatic	260	49	25–58
Dyspnea	685	50	27–71
Chest pain	390	12	6–18
Hemoptysis	671	11	4–18
Hemothorax	1	1	0–2
Cyanosis	467	27	9–73
Clubbing	459	28	6–68
Bruit	455	31	3–58
CENTRAL NERVOUS SYSTEM			
Cerebral abscess	636	12.9	0–25
CVA/TIA	401	27	11–55
CVA	262	13.7	9.5–18
TIA	262	22.1	6.3–36
Migraine	266	44.7	38–57

CVA, cerebrovascular accident; TIA, transient ischemic attack.
Data from various sources referenced in text.

Etiology

New data highlight that the majority of PAVMs occur in individuals affected by the inherited vascular disorder hereditary hemorrhagic telangiectasia (HHT, or Osler-Weber-Rendu syndrome) (Table 54-2).[1,1a] In one series of 219 consecutive PAVM patients, a clinical diagnosis of HHT could be established in 93.6% of cases.[2] Additional cases may occur as a result of surgical treatments for several forms of complex cyanotic congenital heart disease, especially following surgical generation of cavopulmonary or atriopulmonary shunts, in which PAVMs may develop in the lung not receiving hepatic venous blood.[3,4] Traumatic PAVMs are rare.[5] Sporadic cases do occur, but many of these are, in fact, due to underlying, undiagnosed HHT; because the diagnosis of

TABLE 54-2. Clinical Features of Hereditary Hemorrhagic Telangiectasia

Curaçao Criteria*	Approximate Frequency (%)
Epistaxes (nose bleeds)	90
Mucocutaneous telangiectasia	80
GI bleeding	25
Pulmonary AVMs	50
Hepatic AVMs	20
Cerebral AVMs	10
Spinal AVMs	<1

*Rare noncriterion manifestations include juvenile polyposis,[19] pulmonary hypertension (see text), prothrombotic states,[127b] and immune dysfunction.[173]
AVMs, arteriovenous malformations; GI, gastrointestinal.

HHT is more difficult to make than many textbooks suggest, and because HHT features develop with age, many HHT patients go undiagnosed. In one recent series, 121 of 205 consecutive PAVM patients with HHT (59%; 95% confidence interval [CI], 52.2% to 65.5%) were unaware they had HHT when their PAVMs were diagnosed.[2] Sporadic PAVMs are usually single, and multiple PAVMs should raise particular suspicion that there is underlying HHT.[2,6,7] These considerations are particularly pertinent for children presenting with PAVMs.[8]

Hereditary Hemorrhagic Telangiectasia

HHT is a disorder of vascular development inherited as an autosomal dominant trait. It is usually underdiagnosed because clinical appreciation of mild phenotypes is poor. The lesions associated with HHT may remain silent and unnoticed for many years, and small lesions may never be detected unless specific screening is undertaken. Careful epidemiologic studies reveal a true incidence of 1 in 5000 to 8000 in France, Denmark, and Japan,[9–11] substantially higher than early figures based on analyses of medical records. Higher prevalences are described in isolated communities.[9,12] Because PAVMs affect approximately 50% of HHT patients,[13] the incidence of PAVMs may be estimated to be at least 1 in 10,000 to 16,000.

Clinical Features and Diagnosis. Many individuals with HHT are unaware they have the disease until the family history is unmasked by the question "Who in the family has nosebleeds?" Most patients will have nosebleeds at some stage of their life, often as children, and many meet the classical 19th century descriptions of having florid epistaxes, demonstrating mucocutaneous telangiectasia, and having needed iron supplementation (or required blood transfusions) due to nasal or gastrointestinal bleeding. The majority of patients are, however, minimally symptomatic and often unknown to the medical profession until a member of their family presents with a major complication. Even then, due to the late-onset penetrance, individuals of childbearing age may display no clinical evidence of HHT: Data suggest that, by the age of 16 years, 71% of individuals will have developed some sign of HHT, rising to over 90% by the age of 40 years.[14–16] However, these data mean that, during his or her childbearing years, an apparently unaffected child of an HHT patient still has a 5% to 20% chance of actually carrying the family's HHT disease gene.

To permit a high level of clinical suspicion without leading to overdiagnosis, international consensus diagnostic criteria were developed based on four findings: (1) spontaneous recurrent nosebleeds, (2) mucocutaneous telangiectasia, (3) visceral involvement, and (4) an affected first-degree relative.[1] When three criteria are present, "definite HHT" can be diagnosed; with two criteria, most commonly family history and nosebleeds, "suspected HHT" is diagnosed. With only one criterion, typically spontaneous nosebleeds, in a patient with neither a family history nor a first-degree relative of an HHT patient, and with no signs of the disease, the diagnosis of HHT is "unlikely" (see Table 54-2). A crucial issue for families (and medical practitioners) is that no child of a patient with HHT can be informed that he or she does not have HHT, unless the child has had a molecular diagnosis.

Genetics and Pathogenesis. HHT is a genetically heterogeneous condition. Three disease-associated genes have been identified. HHT type 1 (HHT1) is caused by mutations in *ENG,* encoding endoglin,[17] and HHT type 2 (HHT2) by mutations in *ACVRL1,* encoding activin receptor–like kinase (ALK1).[18] By April 2008, 311 different *ENG* mutations and 250 different *ACVRL1* mutations had been reported to the HHT Mutation Database (located at www.hhtmut.org/). Most families have a unique mutation; the individual number of reports corresponds to first-order decay kinetics, confirming the absence of common mutations. More rarely, mutations in *MADH4* cause HHT usually in association with juvenile polyposis (JPHT).[19] There are at least two further unidentified genes that can cause classical HHT, *HHT3* on chromosome 5q between *D5S2011* and *D5S2490,* and *HHT4* on chromosome 7p between *D7S2252* and *D7S510.*[20,21]

ENG and *ACVRL1* encode proteins expressed on vascular endothelial cells. Confirmation that the gene mutations cause HHT is available from experiments in transgenic mice, which demonstrate that some mice carrying one normal and one null copy of the respective gene (i.e., *endoglin*$^{+/-}$ or *ACVRL1*$^{+/-}$ heterozygote mice) display features of HHT.[22,23] Endothelial cells derived from HHT1 or HHT2 patients express approximately one half of the normal endoglin or ALK1 levels, respectively.[24,25] It is therefore believed that, in most if not all cases, HHT results from endoglin or ALK1 haploinsufficiency: in other words, a lack of sufficient protein for normal function. Dominant negative mutations in endoglin can be generated but appear to cause different phenotypes.[26] As endothelial cells derived directly from arteriovenous malformations (AVMs) in HHT1 patients also express half the normal levels of endoglin, these malformations do not appear to be due to an

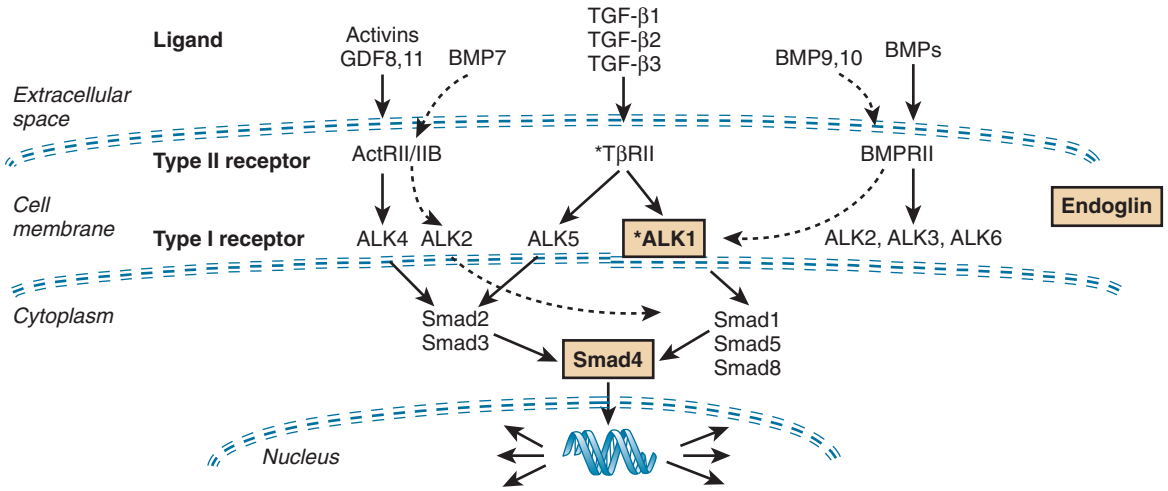

FIGURE 54-3 ■ TGF-β signaling pathway. Endoglin can interact with both type I and type II receptors. The genes mutated in HHT are highlighted in **bold.** (Adapted from Cole SG, Begbie ME, Wallace GMF, Shovlin CL: A new locus for hereditary haemorrhagic telangiactasia (HHT3) maps to chromosome 5. J Med Genet 42:577–582, 2005.)

additional local loss of endoglin expression due to a "second hit."[27] In 2009, interest in the role of angiogenesis in provoking or unmasking an HHT phenotype was renewed, owing to animal models, in particular, implicating a role for aberrant angiogenesis during wound healing.[28]

The genes mutated in HHT encode proteins that mediate signaling by the transforming growth factor-β (TGF-β) superfamily. Superfamily ligands such as TGF-βs, activins, and bone morphogenetic proteins (BMPs) affect cellular growth and differentiation through signal transduction cascades from transmembrane receptor complexes (Fig. 54-3). Generally, type II TGF-β receptors such as TGF-β receptor II and BMP receptor II (mutated in primary pulmonary arterial hypertension; see Chapter 52) bind the ligand directly, and recruit and activate type I receptors that activate downstream cytoplasmic signaling molecules via Smad-dependent and Smad-independent pathways.[29] Smad 4 mutations in JPHT implicate Smad-dependent pathways in HHT. Activated Smads translocate to the nucleus where, together with coactivators and corepressors, they influence transcriptional activation of target genes. As ALK1 is a type I receptor, and endoglin associates with different signaling receptors and can modify TGF-β1 signaling, the abnormal vessels in HHT were proposed to develop because of aberrant TGF-β signaling at some stage during vascular development and homeostasis. Current models include the "balance hypothesis" whereby the endothelial state depends on the predominant endothelial TGF-β type I receptor (ALK5/ALK1) and, hence, the Smad pathway utilized[30,31]; other models incorporate recent data that BMP-9 and BMP-10 are specific ALK1 ligands that can also bind endoglin.[32,33,33a] As additional HHT disease genes are identified, these will also likely play a part in this signaling pathway, possibly either as ligands, receptors, or downstream transducers of TGF-β family member signals.

Phenotype-Genotype Correlations. A characteristic finding is that different members of the same HHT family display different pattern of disease. This is also observed in the mouse models, suggesting that other genetic and environmental influences modify the HHT phenotype. The presence of specific *ENG* or *ACVRL1* mutations does not allow a strong prediction of the likely course of HHT because all features of HHT can be seen in both HHT1 and HHT2. Nevertheless, all recent large series support early observations that reported finding pulmonary and cerebral AVMs more commonly in patients with HHT1 (*ENG* mutations), and hepatic AVMs more commonly in those with HHT2 (*ACVRL1* mutations).[34–37] Although there was an initial suggestion that overall severity of disease is greater in HHT1 than HHT2,[38] this study predated the recognition of pulmonary hypertension (see later), and there was no difference in 90-month mortality in a later series.[34]

Cavopulmonary Shunts. In non-HHT patients, PAVMs commonly occur in those who have undergone surgical treatments of several forms of complex cyanotic congenital heart disease resulting in anastomoses between the superior vena cava and pulmonary arteries.[3] PAVMs associated with cavopulmonary or atriopulmonary shunts are macroscopically indistinguishable from sporadic and HHT-associated macroscopic PAVMs. Using angiography, PAVMs were detected in 31% of patients undergoing classic Glenn anastomoses after a mean follow-up of 6.8 years.[3] The only independent predictor of development of PAVMs was time after cavopulmonary shunting ($P < 0.05$), though there was a trend toward PAVMs developing more commonly in the presence of pulmonary hypertension in the contralateral lung.

The incidence of PAVMs rises substantially if microscopic AVMs detectable by contrast echocardiography are included[39]; moreover, microscopic arteriovenous shunting may develop within 2 hours of the procedure.[40]

Some have suggested that, following superior bidirectional cavopulmonary anastomosis (Kawashima procedure), the development of functional intrapulmonary shunts may be universal. In one study, technetium-99m–labeled albumin macroaggregates (^{99m}Tc-MAA) detected R–L shunts ranging from 11% to 64% of the cardiac output in the 17 patients studied, compared to 3% to 8% in controls.[41] Contrast-enhanced magnetic resonance (MR) angiography is emerging as a useful assessment modality for these patients.[42]

The key etiologic feature appears to be the route taken by hepatic venous effluent, because PAVMs develop in the lung that receives no or minimal hepatic venous return,[4,39] and can be treated either by rerouting the hepatic veins to the pulmonary arteries[43]; by reconnecting the pulmonary arteries[44]; or by incorporating the hepatic vein into the cavopulmonary system.[45] In the largest study, in 11 of the 15 survivors of 16 patients who underwent incorporation of the hepatic vein into the cavopulmonary system, hypoxemia improved from 76% (range, 56% to 85%) to greater than 93% at 2.8- to 10-year follow-up.[45] These observations, and data from patients with the hepatopulmonary syndrome (see Chapter 83), highlight the role of hepatic metabolism in influencing dilation and/or remodeling of the pulmonary vascular bed. Whether there will be common underlying mechanisms between the PAVMs that develop in the setting of cavopulmonary shunts and the vascular malformations found in HHT is unclear.

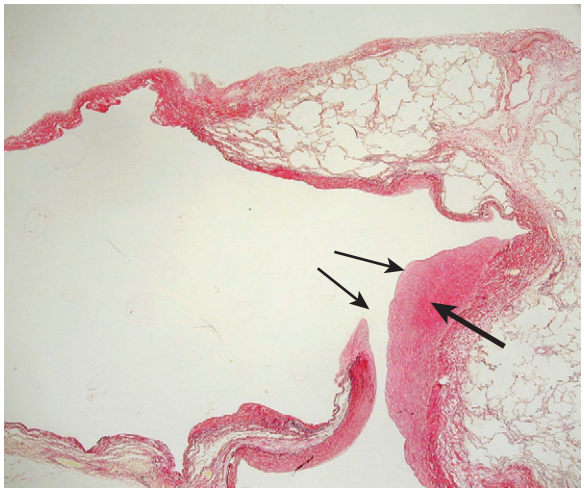

FIGURE 54-4 ■ Histopathology of a pulmonary arteriovenous malformation that ruptured in pregnancy. Note site of rupture (*narrow arrows*) at lower border, and region of endothelial intimal fibrous proliferation (*thick arrow*). (From Shovlin CL, Sodhi V, McCarthy A, et al: Estimates of maternal risks of pregnancy for women with hereditary haemorrhagic telangiectasia: Suggested approach for obstetrics services. BJOG 115:1108–1115, 2008.)

Pathophysiology

Anatomic Basis

Macroscopic (see Fig. 54-1) and microscopic or diffuse PAVMs are recognized. Dilated feeding arteries and dilated veins are characterized by walls of varying degrees of thickness even over relatively short segments, with disorganized adventitia. Medial thinning is observed, but also prominent are areas of focal thickening with abundant elastin tissue and a varying contribution of smooth muscle cells (Fig. 54-4).[27,46] Diffuse PAVMs have been defined as multiple small PAVMs affecting every segment of one or more lobes[47] or a single segment.[48]

PAVMs occasionally develop in the pre- or perinatal period.[49–52] Screening of vulnerable individuals over a period of years shows that PAVMs can develop in adult life in radiologically and/or physiologically normal vessels,[53,54] although it is likely that functional changes at a cellular or microscopic level predate the development of the macroscopic lesions. Once present, PAVMs tend to increase in size, particularly during puberty, in female patients during pregnancy,[53] or in the presence of pulmonary venous hypertension secondary to mitral stenosis or left ventricular dysfunction.[55] On rare occasions, spontaneous regression has been described.[56]

Physiologic Attributes at Rest

Right-to-Left Shunt. PAVMs provide an anatomic R–L shunt, with the proportion of the cardiac output using the shunt pathways (shunt fraction) varying widely, but reaching up to 60% in severe cases. In earlier series,[57–61] mean R–L shunt fractions were generally higher (23% to 38%) than found in later reports (8% to 13%),[2,62,63] in which earlier diagnosis had taken place owing to more energetic screening procedures.

Arterial P_{O_2} and oxygen saturation are inversely related to the size of the R–L shunt fraction.[64] The contribution of ventilation-perfusion mismatch to arterial hypoxemia in PAVMs is small, except in the occasional patient with significant coexisting lung disease. Calculations of the R–L shunt from arterial oxygen saturation measurements breathing air, often referred to as the venous admixture effect, are in good agreement with measurements of the anatomic R–L shunt,[59] confirming that the R–L shunt is the predominant cause of the arterial hypoxemia.

Pulmonary Hemodynamics. The absence of a microvascular network of capillary vessels means that the pulmonary vascular resistance (PVR) of PAVMs is less than that of the surrounding normal lung. The effect on the overall PVR depends on the proportion of the cardiac output flowing through the shunt channels. In one study of eight PAVM patients with large R–L shunt fractions (mean 31% ± 4% [standard error]), mean PVR and pulmonary artery pressure (P_{PA}) were 0.33 ± 0.08 (normal 0.5 to 1.3) mm Hg/L/min and 14 ± 0.6 (normal 12 to 16) mm Hg, respectively.[57] PVR was low, in spite of normal P_{PA}, because total pulmonary blood flow was high (8 ± 0.8 L/min [160% of predicted]). In later studies with smaller mean R–L shunt fractions (8.5% to 11.5%), mean pulmonary systolic and diastolic pressures have been in the normal range,[62–65] and recent studies have focused on the occasional presence of coexisting pulmonary

hypertension (see section on HHT-related pulmonary hypertension).

Pulmonary Function. Vital capacity is generally normal,[58–62] but was reduced to 51% to 81% of predicted values in 7 of 15 patients with large PAVMs and R–L shunts.[66] There is no airflow obstruction.[58,62,66] With large R–L shunts (>20%), the carbon monoxide diffusing capacity (D_{LCO}) is often moderately reduced (71% to 78%),[58,61,66] but in the majority of patients with less R–L shunting, D_{LCO} is equal to or greater than 90% of predicted (interquartile range, 76% to 100%).[62] The ratio of D_{LCO} to the measured alveolar volume (DL/VA, or KCO) is better preserved.[58,62] Values less than 70% are unusual[66]; in one study, only 16 of 63 patients had values less than 90% of predicted.[62] Those with the lowest D_{LCO} and DL/VA generally had widespread and small vascular malformations. In addition, data from patients following embolization (discussed later) indicate that, in some patients, a vascular steal through the low-resistance PAVMs also contributes to the low diffusion values.[62]

Physiologic Consequences of Posture and Exercise

Posture. PAVMs are more common in the lower than upper lobes,[7,58] hence for gravitational reasons, the shunt fraction tends to increase when patients stand up: R–L shunt increased from 28.7% to 39% in eight patients on standing.[59] Accordingly, arterial oxygen saturation falls considerably more in patients with PAVMs than in normal individuals, in whom the mean fall in arterial oxygen saturation on assuming the upright posture is only 0.3%.[67] The absolute decrease in arterial oxygen saturation (supine to erect) reflects the size of the R–L shunt, being generally larger for R–L shunts greater than 20%.[59,60,62,64]

Exercise. In the healthy lung, PVR falls on exercise to half its value at rest, because of dilation and recruitment of vessels predominantly in the pulmonary capillary bed. The effects of exercise on pulmonary hemodynamics in a PAVM-affected patient depend on the change in vascular resistance through the shunt channels in relation to the change in the resistance of the normal channels. It is not known what happens to the PVR of PAVMs as overall blood flow increases on exercise; in one group of eight PAVM patients with severe arterial hypoxemia on exercise (arterial oxygen saturation 74% ± 3%), there was an excessive increase in total pulmonary blood flow (142% of predicted) in relation to the observed oxygen consumption ($\dot{V}O_2$), resulting, in turn, in higher than predicted tissue oxygen delivery on exercise.[57] It is reasonable to suppose that, for PAVMs, which lack a capillary network and have dilated vessels, vascular resistance will fall somewhat less than that of normal lung, and the R–L shunt fraction will decrease on exercise. In one study comparing the R–L shunt at rest with that on maximal exercise, a fall in shunt fraction of 1% to 10% was demonstrated for four of six patients with larger and treatable PAVMs (postembolization residual shunts <10%), suggesting that these bigger sacs do not enlarge further as pulmonary flow increases.[60] In the same study, however, the R–L shunt fraction increased (38% to 47%) in the six patients with diffuse small PAVMs (feeding vessels ≤ 2 mm diameter), suggesting that the smaller PAVMs may be more compliant.[60]

The change in arterial oxygen saturation from rest to exercise depends both on the change in the shunt fraction and the fall in mixed venous oxygen saturation on exercise. For PAVM patients, overall, the fall in arterial oxygen saturation (rest to exercise) averaged 6% for mean shunts greater than 30%,[57,60] 3% for mean shunts of 20% to 25%,[58,60,62] and 1% to 2% for mean shunts less than 12%.[62] The importance of a fall in mixed venous oxygen saturation on exercise is demonstrated by a study involving 18 patients (R–L shunt at rest 42% ± 13%),[57] in whom R–L shunt fraction (which increased in 12 patients and decreased in 6) and arterial oxygen saturation were measured simultaneously. By interpolation, zero change in R–L shunt during submaximal exercise at 30 to 75 watts predicted a 3% fall in arterial oxygen saturation on exercise, reflecting the fall in mixed venous oxygen saturation on exercise.

Overall, gas-exchange efficiency in terms of the ventilatory equivalent ($\dot{V}E/\dot{V}O_2$) is abnormally high on exercise; observed values are directly related to the exercise R–L shunt, and inversely related to exercise arterial oxygen saturation.[57] Work capacity is well preserved in PAVM patients, even when arterial oxygen saturation on exercise is less than 80%. There is a relationship between exercise capacity in watts (as % of predicted) and the resting R–L shunt; for mean shunts greater than 20%, maximum power output was 65% to 75% of predicted, increasing to 75% to 85% of predicted for mean shunts of 10% to 15% and exceeding 90% for mean shunts less than 10%.[62,64]

Pulmonary Hypertension

Pulmonary hypertension has been recognized in a number of HHT patients.[55,61,68–70] As recently reviewed,[65] the causes of pulmonary hypertension in HHT are diverse, as in the normal population.[71] Two forms of pulmonary hypertension predominate in HHT, true pulmonary hypertension phenotypes,[61,69,72] and a postcapillary pulmonary hypertension occurring in the context of high-output cardiac failure secondary to hepatic AVMs, a potentially reversible form of pulmonary hypertension.[73] Mixed pictures are also observed.[65] The frequency of pulmonary hypertension and hepatic AVMs differs with HHT genotype: pulmonary hypertension phenotypes and hepatic AVMs are more common in HHT type 2—due to *ACVRL1* mutations—than in HHT type 1—due to *ENG* mutations.[69,71,74] Although pulmonary hypertension in HHT was initially considered attributable solely to *ACVRL1* mutations, there are now rare reports of pulmonary hypertension associated with *ENG* mutations, and both genes are to be included in the latest World Health Organization classification of pulmonary hypertension.

The overall prevalence of pulmonary hypertension in HHT is low. Catheter-based studies in a group of 143 PAVM/HHT patients, mean age 47 (range, 8 to 78) under-

going PAVM embolization, identified median (interquartile range) values for PPA as 23 (19 to 27) mm Hg systolic, 7 (5 to 9) mm Hg diastolic, and 13 (11 to 16) mm Hg mean, compared to normal values of 13 to 26, 6 to 16, and 7 to 19 mm Hg, respectively; there was a significant increase in PPA with age.[65] While PPA mean exceeded 20 mm Hg in 9 of 143 patients (6%), only 2 referred from services other than specialized pulmonary hypertension units had mean PPA values exceeding 35 mm Hg.[65] In an echocardiographic study of 68 HHT patients from a separate HHT population whose mean age was 51 years (range, 19 to 84), estimated systolic PPA values (40 to 58 mm Hg) were above the normal range in 9 (20.5%).[70]

Clinical Features

Respiratory Symptoms

Dyspnea. Dyspnea is the respiratory symptom most commonly reported by PAVM patients, but this is present in under 50% of all cases (see Table 54-1) and may not be appreciated until after the condition has been treated. One recent series of 219 consecutive PAVM patients stratified the proportion of dyspneic patients according to the degree of hypoxemia, and indicated that PAVMs generally result in symptomatic dyspnea only when resting arterial oxygen saturations are below 80%.[2,65]

Hemoptysis. The fragile vessels in HHT should be more prone to hemorrhage than normal pulmonary vessels but, surprisingly, hemoptysis and hemothorax are relatively rare features for PAVMs (see Table 54-1), with two important exceptions: (1) spontaneous and postembolization systemic arterial blood supply to PAVM sacs,[48,71] and (2) pregnancy-associated changes.[46] Both conditions place patients at higher risk of hemorrhage from PAVMs, which may be massive and life-threatening.

Chest Pain. Pleuritic chest pain of uncertain etiology occurs in up to 10% of PAVM patients (see Table 54-1). PAVM associations are likely to be overestimated, however, in series that do not correct for ascertainment bias of incidental PAVM detection following protocol-driven computed tomography (CT) scans for suspected pulmonary embolism.[2]

Strokes and Cerebral Abscess

PAVMs pose a substantial risk to patients because of paradoxical emboli leading to cerebral abscess or ischemic stroke, as repeatedly reported in high proportions of patients in historical series (see Table 54-1).[6,75,76] In a more recent series of 219 PAVM patients, in which correction was made for ascertainment bias (i.e., diagnosis of PAVMs because of the occurrence of stroke/abscess), the respective rates were 9% for cerebral abscess and 11.3% for ischemic stroke (Fig. 54-5).[2] Relative

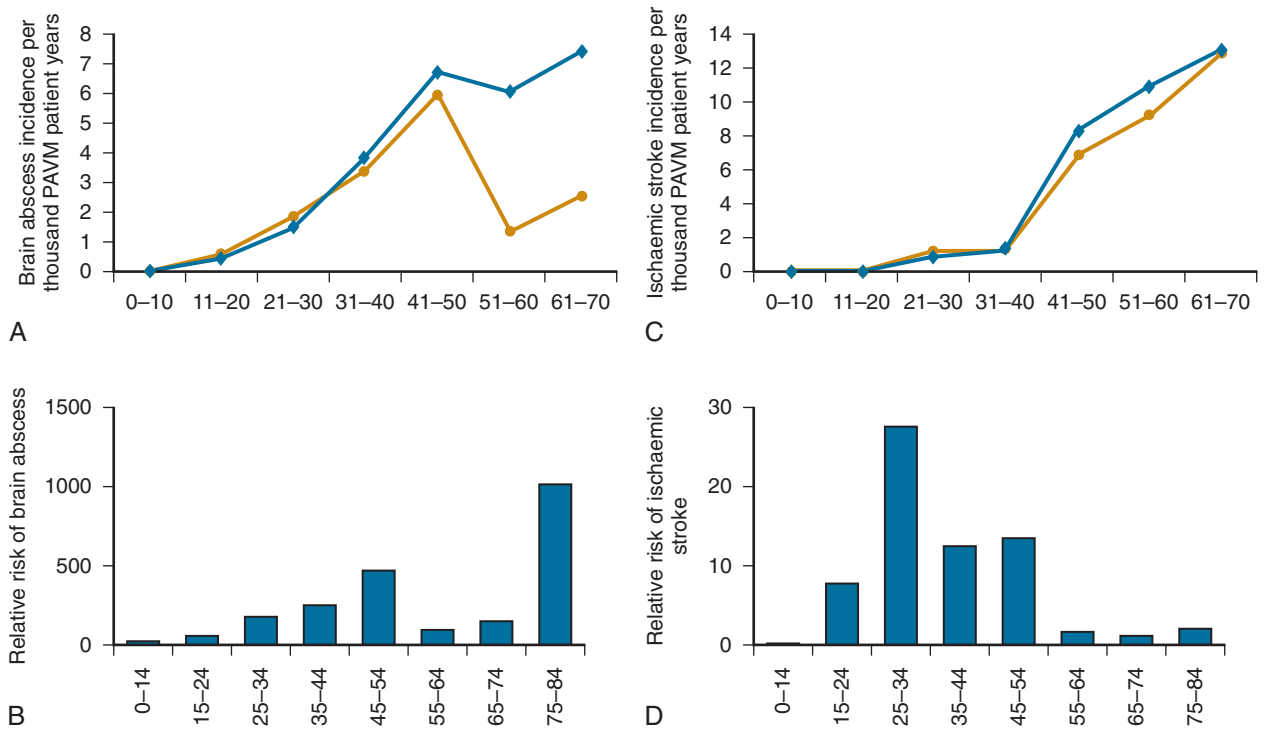

FIGURE 54-5 ■ Age-specific incidence rates and relative risks of brain abscess and ischemic stroke. Age-specific incidence rates of brain abscess **(A)** and ischemic stroke **(C)** for all patients (*diamonds/blue lines*), and patients excluding ascertainment bias (*solid circles/brown lines*). Relative risk (fold increase) for brain abscess **(B)** and ischemic stroke **(D)** for PAVM patients, excluding individuals who presented because of their stroke/abscess. Brain abscess rates are compared to the Olmsted County, Minnesota, series[77]; ischemic stroke to the U.K. Oxfordshire stroke study.[78] (Redrawn from Shovlin CL, Jackson JE, Bamford KB, et al: Primary determinants of ischaemic stroke and cerebral abscess are unrelated to severity of pulmonary arteriovenous malformations in HHT. Thorax 63:259–266, 2008.)

risks compared to control populations[77,78] were particularly high in young adults.[2] The risks of stroke/abscess for PAVM patients are poorly recognized and were not mentioned in a recent authoratitative set of guidelines for stroke prevention.[79] Evidence is now available that failure to recognize stroke/abscess risk leads to referral delays of 6.8 years (95% CI, 4.1 to 9.5 years) for patients with respiratory symptoms, and 7.5 years (95% CI, 4.3 to 10.8 years) for asymptomatic patients compared to 1.1 to 1.7 years for patients diagnosed either by post-stroke/abscess investigation or by screening programs.[2]

Small studies utilizing univariate analyses had suggested that neurologic complications were more common in patients with more severe PAVMs, defined by either PAVM size[80] or diffuse characteristics.[48] By contrast, a recent cohort study of 219 consecutive PAVM patients utilizing the Anderson Gill extension of the Cox proportional hazards models indicated that—contrary to expectations—there was no clear relationship between the risk of ischemic stroke or cerebral abscess and the presence of any of six markers of PAVM severity (symptoms, arterial oxygen saturation, R–L shunt, PAVM multiplicity, diameter of largest feeding vessel, or presence of small untreatable PAVMs); in addition, stroke risk was also unrelated to conventional neurovascular risk factors such as smoking, hypertension, diabetes mellitus, atrial fibrillation, and hypercholesterolemia.[2] There was a very strong association between ischemic stroke and low mean PPA (hazard ratio 0.89 [95% CI, 0.83 to 0.95] per mm Hg increase, $P < 0.0001$), as well as strong associations between cerebral abscess and male gender and dental microrganisms.[2]

Migraines

An excess of migraine first noted in HHT populations[81,82] was subsequently highlighted in observational PAVM series.[7,80] A clear association between migraine and the presence of PAVMs was established in a series of 538 HHT patients with a mean age of 39 years[83]: the overall migraine prevalence was 16%, compared to general population figures of 10% to 12%,[84] with a statistically significant excess of migraine in the patients with PAVMs compared to those without (21% vs. 13%, $P = 0.02$).[83] In a further study of 116 HHT patients, who were compared to an age- and sex-matched control group, there was a higher prevalence of migraine in both HHT patients with PAVMs (39.6% vs. 19.8%, $P < 0.001$) and HHT patients without detectable PAVMs (26.3% vs. 11.5%, $P = 0.003$).[85]

Pregnancy

Case reports and small series indicated that both PAVM hemorrhage,[46,86,87] and PAVM growth[53,86,87] could occur during pregnancy. A recent study of 484 pregnancies in women with HHT and PAVMs demonstrated that 1.0% (95% CI, 0.1% to 1.9%) of pregnancies resulted in a major PAVM bleed, and 1.0% (95% CI, 0.13% to 1.9%) resulted in maternal death.[46] In four women, the severity of PAVMs associated with life-threatening hemorrhage could be evaluated: two had small PAVMs associated with normal arterial oxygen saturations and near-normal R–L shunts; none had evidence of pulmonary hypertension.[46] Moreover, in women experiencing a life-threatening event, prior awareness of HHT or of a diagnosis of PAVM was associated with improved survival ($P = 0.041$).

Diagnosis

Classic PAVM cases with large R–L shunts are easy to diagnose because of cyanosis, clubbing, a vascular bruit, and characteristic chest radiographs displaying lobulated masses and dilated feeding arteries and draining veins. Detection of smaller PAVMs, however, often requires a high degree of clinical suspicion. Many patients are diagnosed as a result of a chest radiograph obtained either routinely or for nonspecific respiratory symptoms, often proven by subsequent thoracic CT scan. In other cases, PAVM screening in an at-risk population will be required in order to confirm or refute the diagnosis of PAVMs.

Radiology

Chest radiographs may demonstrate one or more well-circumscribed lobulated masses, connected by prominent blood vessels to the hilum (see Fig. 54-1). Careful scrutiny is required to detect lower lobe PAVMs, which may be partially obscured by one of the hemidiaphragms on posteroanterior chest radiographs, and which may present as subtle abnormalities, particularly for smaller PAVMs. Before 2007, there was a widespread opinion that the only PAVMs of clinical significance had feeding artery sizes larger than 3 mm, and the goals of many screening programs reflected this. Data presented in this era were that the chest radiograph was abnormal in 60% to 90% of instances.[58,62,88,89] It is anticipated that the frequency of positive standard frontal radiographs will fall further as smaller PAVMs are sought, in keeping with the recognition that these are an important cause of neurologic complications.[2,90]

Spiral (or helical) CT usually demonstrates the anatomy of PAVMs and their feeding vessels[91]; the radiation burden is greatly lessened and the resolution improved by the use of newer multislice (multidetector) CT protocols, which limit x-ray exposure to a single short breath-hold scan, and which allow elegant three-dimensional reconstructions of the images (see Fig. 19-21). Where there are difficulties with interpretation of dilated and apparently vascular structures, confirmation of R–L shunting may be helpful. Magnetic resonance imaging has been less effective than CT or pulmonary angiography because small PAVMs with rapid blood flow are not visualized.[92] Methodology, though, is improving,[93] and this modality provides no radiation exposure. But the frequency of its use may not increase as attention focuses on identification of smaller yet clinically significant PAVMs.

Measurement of Right-to-Left Shunt

Two techniques for measurement of R–L shunt are in common usage: (1) measurement of arterial P_{O_2} breathing 100% oxygen, and (2) ^{99m}Tc-MAA lung and kidney scans, both of which have proved useful in monitoring outcomes after coil or balloon embolization treatment for PAVMs.[58,62] R–L shunt measurements by either of these methods may confirm a diagnosis suspected on clinical grounds and provide useful follow-up data, but as shown in Table 54-3 (electronic version), they do not have sufficient sensitivity for use as a screen to exclude the presence of PAVMs.

100% Oxygen Breathing. In the classical technique, arterial P_{O_2} and hemoglobin concentration are measured after 100% oxygen has been breathed for 15 to 20 minutes, including periodic deep breaths, to wash nitrogen out of the lungs. In healthy subjects, the R–L physiologic shunt is usually less than 5% of the cardiac output and represents blood draining into the left atrium and ventricle from the bronchial and coronary circulations plus blood perfusing nonventilated alveoli. Rather than quoting the measured arterial P_{O_2} value, an estimated R–L shunt is usually calculated as a percent of the cardiac output using the shunt equation shown in the appendix; the resulting value depends on assuming an arteriovenous oxygen content difference, generally the standard amount of 5.0 mL/100 mL, even though the value is somewhat higher than that actually measured in the majority of PAVM patients: 4.4 mL/100 mL (attributed to the high resting cardiac output in PAVMs). Shunt size is therefore slightly underestimated: a 10% calculated shunt was measured as 11%.[63]

Radiolabeled Particles. This method measures a truly anatomic shunt, rather than a physiologic estimate of the anatomic shunt. After intravenous injection, ^{99m}Tc-radiolabeled human serum albumin particles (macroaggregates, 10 to 80 μm, or microspheres, 7 to 25 μm) normally impact in small branches of the pulmonary arterioles, generating the classical perfusion scan images (Fig. 54-6). In the presence of an anatomic shunt in the heart or lungs, a fraction of the particles, proportional to shunt flow, will escape into the systemic circulation and impact in systemic capillary beds. The R–L shunt can be measured following gamma camera measurements of activity over the lung fields and over the right kidney. Assuming 10% of the cardiac output goes to the right kidney, the R–L shunt is measured by the ratio of (right kidney counts × 10)/injected dose (*the kidney:dose method*), or (right kidney counts × 10)/[total lung counts + (right kidney counts × 10)] (*the kidney:lung method*).[60] Ideally, renal flow should be measured directly using a second tracer (*kidney2:lung method*), as the actual flow fraction to the right kidney deviated from the assumed 10% by ± 3% (standard deviation) absolute in one study.[63] The limits of agreement for a 100% O_2 shunt of 20% were 14% to 29% for the kidney:dose method,[64] 5% to 35% for the kidney:lung method, and 12% to 28% for the kidney2:lung method.[63] Owing to these differences, the methods cannot be used interchangeably in the follow-up of shunt size in a particular patient.

A B

FIGURE 54-6 ■ Right-to-left shunt quantification by radionuclide scans. **A,** In contrast to normal perfusion scans, the activity is not restricted to the lungs (included for reference). Renal images are used for quantification. **B,** Cerebral imaging illustrating risk of paradoxical microemboli.

Contrast Echocardiography. The method of contrast echocardiography (CE; synonym "echo-bubble") demonstrates intrapulmonary shunts by tracing the circulatory transit of microbubbles generated by intravenously injected echocontrast material. In contrast to intraventricular cardiac shunts—in which contrast passes immediately from the right to the left ventricle—R–L shunting through PAVMs results in a delayed appearance of microbubbles in the left side of the circulation, either the left ventricle or carotid artery. Bubbles arriving up to 10 cardiac cycles later have been associated with PAVMs[94]; most recent studies, however, utilize a delay of 3 to 4 cardiac cycles to distinguish PAVMs from a patent foramen ovale (Table 54-4, electronic version). Grading has been recommended based on the number of microbubbles appearing in the left ventricle on a single frame. Initial reports utilized a descriptive 5-point scale,[95] with individual groups interpreting this in varying ways (see Table 54-3). Specificity has been a concern (see Table 54-4): intrapulmonary shunting was demonstrated in 5 of 19 healthy subjects by injection of contrast directly into the pulmonary artery, bypassing any intracardiac shunt, in one early study,[96] and by CE in 7% of a more recent group of 100 control subjects, with a detection rate for patent foramen ovale of 6% in both controls and HHT patients.[97]

CE consistently detects more intrapulmonary R–L shunting in HHT patients than other PAVM screening modalities.[88,94–96,98] Initial reports in the adult HHT population suggested 100% sensitivity,[88] but false negatives have been reported.[99,100] Nevertheless, the negative predictive value of a negative CE assessed in several specialized units is of the order of 98%.[100] The positive predictive value of a positive result is more variable, with sensitivities in different studies ranging from 21% to 74% (see Table 54-3).

It was soon recognized that patients with lesser CE shunt severity were less likely to have a PAVM detected by subsequent studies. In a retrospective study of 104 patients[94] and a prospective study of 190 patients,[97] patients with grade 1 (minimal) opacification had a positive predictive value for PAVMs of 0 to 0.02 (see Table 54-4). In contrast, in another prospective study of 105 patients, grade 1 CE was associated with a positive predictive value of 0.22.[101] All three studies utilized CT scans as the "gold standard" and, where CT scan detection

rates were presented, positive detection rates were comparable (23% of full screened population, 74% of grades 2 and 3 shunt[97]; 36.5% of full screened population, 67% of grades 2 and 3 shunt[101]). Recent data suggest that shunt grade on CE may influence the likelihood that such lesions will be amenable to embolization therapy; in a prospective series of 105 patients with a positive R–L shunt, none of the patients with PAVMs on chest CT and a CE grade 1 or 2 shunt were candidates for embolotherapy.[101] However, in the other studies, grade 2 positive shunts were associated with PAVMs of a size amenable to embolization.[94,97]

Screening Patients

The overall incidence of PAVMs in the general population is so low (~0.01%) that targeted screening protocols are required. Dyspnea, hemoptysis, or other clinical symptoms are not appropriate to target screening because PAVM patients are often asymptomatic, and these symptoms occur commonly in the non-PAVM population. Suitable populations to screen would be patients with HHT (approximately 50% of whom have PAVMs), patients with cerebral abscesses, and any young patient with an embolic CVA, even if an apparent alternative cause is present.[102] The high proportions of HHT/PAVM patients undiagnosed at the time of their PAVM-induced ischemic stroke or cerebral abscess (in one series 66.7% and 64.3% respectively)[2] highlight the importance of robust PAVM screening programs for the HHT population. Screening HHT patients poses a particular difficulty as most individuals with HHT are unaware they have the disease, plus as demonstrated in Table 54-3, there are no cut-offs for available tests with sufficient sensitivity to rule out clinically significant PAVMs.

PAVM centers differ in the exact screening modalities employed, according to the particular expertise of the institution. Common to all programs are the policies of minimizing the radiation burden in an often young population, having a sensitive screen to detect all clinically significant PAVMs, and concern to avoid missing any treatable PAVMs: the choice usually lies between thoracic CT scans and CE. Many specialized PAVM units with extensive CE expertise utilize CE as a first-line screen for PAVMs, reserving the radiation exposure of CT scans for patients with a positive shunt and, potentially, a CE shunt of a particular severity.[101] At other institutions, CE is not used routinely due to time, training, and resource implications given the majority of scans will be positive, and the new generations of multislice CT scanners mean that a diagnosis of PAVMs can be made efficiently and quickly using a single-breath thoracic CT scan. Some centers will use pulmonary angiography as a tool to confirm the diagnosis, but in order to reduce the radiation burden, we prefer to restrict angiography to therapeutic embolization sessions.

Management

A "wait and see" policy is indicated only when physician and patient are fully informed of the risks of leaving PAVMs untreated, bearing in mind that PAVMs are not benign lesions that can be safely ignored.

Embolization

Percutaneous transcatheter embolization, which was introduced in 1978,[103,104] is now the treatment of choice for the vast majority of patients. More than 700 pulmonary AVM embolizations have been reported.

The technique of embolization at our institution has been described previously.[62] We start by administering prophylactic antibiotics 1 hour before the combined diagnostic and therapeutic procedure. First, a pigtail catheter is inserted to measure pulmonary artery pressure and to obtain angiograms of each lung. Then, the catheter is exchanged for one appropriate for emolization of the feeding vessels of the AVMs: usually with detachable metallic coils, plugs, or balloons, depending on the size and blood supply of the malformation. Occluding devices must be placed as close as possible to the neck of the malformation in an attempt to avoid the occlusion of normal pulmonary artery branches and to reduce the risk of the develoment of a bronchial arterial collateral supply to the sac (see later).

In individual patients, if the anatomy of the PAVMs precludes "conventional" embolization, other techniques are required such as packing the venous sac with coils. Treatment of particularly large and high-flow PAVMs may be achieved with coils inserted through the lumen of an occluding balloon catheter temporarily inflated to obliterate flow within the feeding vessel.[62] It is unclear how long occlusion is required in order to prevent flow: in one series of patients studied at a mean follow-up of 99 months (range, 63 to 123 months), 8 of 14 detachable silicone balloons were deflated at radiographic chest film follow-up, but at pulmonary angiographic follow-up all embolized malformations were without flow, irrespective of whether or not the balloons were visible.[105] Postembolization, residual shunting through untreatable (<2–3 mm diameter) arterial feeding vessels is common (Table 54-5). For example, in a series of 192 PAVM patients in whom feeding arteries less than 3 mm in diameter were embolized,[2] 70% had residual disease, a finding supported by other studies.[98,106,107]

Long-Term Outcome. Anatomic long-term results of transcatheter embolization have been evaluated by several centers. In the first study, a 2- to 21-year follow-up of after embolization of 64 PAVMs in 38 patients, the treatment success rate was 75%, with delayed recanalization requiring repeat embolization observed in 19%.[108] In a second study, a 1- to 7-year follow-up of 393 embolized PAVMs in 144 patients, recanalization was seen in 6.9% of patients.[105] In a further center, reperfusion was observed in 19 of 112 consecutive patients (17%), with recanalization the most common cause of reperfusion; factors associated with reperfusion included low number of and oversized coils, and proximal placement of coils, in one study,[109] and altered pulmonary hemodynamics (development of pulmonary hypertension or presence

TABLE 54-5. Pre- and Postembolization Results from Centers Treating Large Numbers of Patients with Pulmonary Arteriovenous Malformations

Center/Reference	No. Patients	R–L SHUNT (%)		ARTERIAL SO_2 (%)		Residual Shunt Present in (%)
		Pre	Post	Pre	Post	
BALTIMORE/YALE						
Pre-1983[174]	10	44	24	76–80*	82–92*	
1978–1987[7]	76			79–83*	90–94*	
1978–1995[110]	45			85–89*	93–97*	
1978–2006 (subgroup diffuse)[48]	36					
Unilateral				87±7	95±3	
Bilateral				79±8	85±7	
HAMMERSMITH						
1984–1990[66]	15	33	19	86†	92†	
1987–1994[58]	53	23	9	89	94	60
1994–1999[62]	66	13	6	93	96	72
SAN FRANCISCO						
1986–1991[61]	8	25	13	84–88*	92–96*	
NETHERLANDS						
1990–1995[106]	32	16.6	7.4	91–95*	93–97*	63
1988–2001[175]	112					
DENMARK						
1994–1998[107]	12	21‡	13‡	266 mm Hg§	439 mm Hg§	73

*Arterial oxygen saturation (SO_2) values derived from arterial PO_2 measurements via standard oxygen dissociation curve.
†R–L shunt and arterial SO_2 measured in semirecumbent or supine posture.
‡Calculated from arterial PO_2 assuming hemoglobin concentration of 13.9 g/dL and $C(a-V)O_2$ = 4.4 mL/100 mL.
§Arterial PO_2 values breathing 100% oxygen.

of hepatic AVMs) but not technical embolization parameters in another.[108]

Physiologic Outcome. Physiologic outcomes have improved with time, as shown in Table 54-5. Although substantial improvement in oxygenation is the rule for patients with preembolization hypoxemia,[61,65,106,110] the effects on other pulmonary function measurements are small. Vital capacity and forced expiratory volume in 1 second do not change.[58,62,64] There is a trend for the DL_{CO} and DL/VA (KCO) to improve,[58,64,66] and in one series of 60 patients, the 16 who had a low DL/VA preembolization showed significant improvement postembolization from 78% to 87% of predicted.[66] Exercise capacity, often relatively unimpaired preembolization, may improve in some patients,[64] and not necessarily in those in whom the DL/VA improves.[62] Arterial oxygen saturation at maximum exercise improves significantly, by 6% to 10% in groups with mean preembolization saturation values less than 82%,[62,64] and by 3% to 4% if mean preembolization saturation is 92% or higher.[62]

Clinical Outcome. After embolization in the majority of patients, there will be little improvement in dyspnea or exercise tolerance unless their PAVMs were associated with substantial R–L shunts and hypoxemia. In the authors' experience, hemoptysis often improves; rare preexisting chest pains do not. Clinical improvement therefore usually focuses on the expected improvement in neurologic risk, but until recently, no direct evidence of risk reduction had been presented. Two studies have now demonstrated the clinical efficacy of embolization in improving stroke/abscess risk,[2] and reducing the prevalence of migraine.[111] In the first, a cohort study of 219 consecutive individuals with PAVMs, no ischemic strokes or abscesses occurred in 58 of the 192 treated patients (30.2%) in whom all angiographically visible PAVMs were obliterated at embolization, and there was no evidence of recurrence during follow-up.[2] This group included 13 individuals who had had an ischemic stroke or brain abscess prior to PAVM embolization. Strokes/abscesses did occur in some patients postembolization in this series—as in others—due to small untreatable PAVMs (feeding artery diameter ≤ 2 to 3 mm) in addition to the PAVMs that had been embolized. Overall, the strongest model available demonstrates that embolization at a median age of 45 years significantly reduces the rate of ischemic stroke (P = 0.028).[2] Improvement in migraines following PAVM embolization was demonstrated in a prospective study of 84 patients, with a reduction in prevalence from 45% to 35% after 6 months (P = 0.01).[111] Improvement in migraine was also suggested by a study in a separate population.[112]

Risks of Embolization

In expert hands, embolization is efficacious and complications are rare, though the procedure is not without risk. Successive series highlight a learning curve, and smaller series have higher complication rates. The most common complication is transient pleurisy in up to 10% of patients, particularly those with peripheral PAVMs. Higher rates are seen for patients with diffuse PAVMs.[48] The mechanism for the pleurisy is unknown, but it appears unrelated to pulmonary infarction.[58,62] Angina, due to transient air bubble emboli, has been reduced by the technical advances reported in later series. There are occasional reports of long-term neurologic complications following paradoxical emboli.[113]

Development of Systemic Arterial Supply. The risk of massive hemoptysis from PAVM sacs that persist postembolization and that acquire a systemic arterial collateral blood supply was first highlighted in a small series published in 1998.[114] In view of the known importance of pulmonary-bronchial communications (see "Systemic-to-Pulmonary Vascular Communications" section later), it would not be unexpected for systemic collaterals to develop to supply an area of the pulmonary capillary bed that had lost its pulmonary arterial supply as a result of embolization. In one postembolization series, 13 of 32 patients demonstrated abnormally large arteries of bronchial, inferior phrenic, musculophrenic, internal mammary, or intercostal origin, and this group were more likely to have demonstrated clinical or angiographic evidence of pulmonary infarction as a result of the procedure.[115] Systemic supply is of consequence only if the fragile PAVM sac persists. None of the cases in Brillet and coworkers' series[115] experienced hemoptysis, in contrast to the majority of those in a smaller series.[114] To reduce the risk of development of systemic arterial collateral supply to any persistent sac, standard practice is to place embolization devices as close as possible to the neck of the malformation.[62] This is particularly difficult for patients with diffuse PAVMs, in whom sac persistence is inevitable. Expert institutions differ in the degree to which such PAVMs will be embolized. At our institution, more limited embolization is undertaken and in the presence of ongoing neurologic symptoms or hemoptysis, surgical resection is considered. Other approaches include dense packing of the most severely involved segmental arteries.[48]

Development of Pulmonary Hypertension. PAVM embolization may be expected to elevate PPA, because PAVMs provide low-resistance pathways for pulmonary blood flow. Data on PPA measurements pre- and postembolization were scarce. In three of the first four reported cases, each selected from larger series, PPA increased postembolization, whereas in the fourth it was unchanged.[61,73,116,117] There was also a report of worsening pulmonary hypertension after surgical resection of a PAVM.[118]

PPA measurements before and after successful PAVM embolization, as demonstrated by improved arterial oxygen saturation, were recently reported for 35 patients with measurements from two or more consecutive embolization sessions, and for 8 patients in whom PPA measurements were repeated at the end of embolization in the same session due to higher baseline PPA; there was no evidence of a sustained or acute change in PPA in the majority of patients, and in half, embolization led to a fall in PPA.[65]

Should embolization of PAVMs be performed in patients with severe preexisting pulmonary hypertension? This question was specifically addressed in a recent article evaluating risks-benefits in the light of new data regarding stroke risk,[2,118a] and data indicating that test balloon occlusion did not predict subsequent rise in PPA following definitive embolization.[65] The main indications for PAVM embolization are to reduce the risk of paradoxical embolic stroke/brain abscess, and, for individuals with hypoxemia, to improve dyspnea and exercise tolerance. Because the risk of paradoxical embolic stroke is substantially lower in individuals with higher PPA,[2] and symptomatic relief from dyspnea should not be expected for patients with pulmonary hypertension and arterial oxygen saturations higher than 90%, as was the case in all four patients with severe pulmonary hypertension in their series, the authors concluded that, for patients with preexisting severe pulmonary hypertension, the risks of PAVM embolization generally outweigh potential benefits.[65] It was recognized that the most difficult judgments relate to individuals with severe pulmonary hypertension and major hemoptysis.[118a]

Nonembolization Options

There are circumstances when PAVMs cannot be treated by embolization, the most common reason being that the feeding artery is too small (<2 mm diameter). It is doubtful that advances in transcatheter embolization techniques will permit routine embolization of feeding vessels of less than this size; thus, the issue arises of what to do with patients with small PAVMs not amenable to embolization.

Surgery. Surgery remained the treatment of choice until the 1980s, but was never the ideal solution for the multiple PAVMs of HHT; more recently, however, surgery has been a useful adjunctive therapy for selected cases. There may be circumstances in which small PAVMs are single or sufficiently localized for thoracoscopic resection if embolization is not feasible. At our institution, we reserve this for patients whose condition declares them to be at risk as evidenced by ongoing ischemic strokes or transient ischemic attacks following maximal embolization, as recommended by others.[119] In emergency situations, particularly associated with massive hemoptysis, lobectomy or pneumonectomy may be appropriate.[46,52]

Lung transplantation has been undertaken in a few patients with severe hypoxemia secondary to diffuse disease.[120,121] The long-term complications of untreated PAVMs, however, are likely in most cases to be less than transplantation-associated morbidity and mortality. Three PAVM patients in our clinic (one male, two female) who elected not to proceed with transplantation—after discussion of the risks at two different U.K. transplantation centers—have since remained stable over 15, 16,

and 19 years, respectively, and one patient has had three successful pregnancies. In a retrospective series of 36 patients with diffuse PAVMs for whom follow-up data were available for a mean of 8.5 years (range, 0.12 to 26 years), 24 of the 27 survivors were working or studying full time; one of the deaths was transplantation associated.[48]

Medical Management

Dental Issues. For patients with PAVMs and HHT, owing to the strong link between oral bacteria and cerebral abscess, antibiotic prophylaxis before dental and surgical procedures was recommended based on the endocarditis paradigm.[122-124] Furthermore, the evidence for an association between oral microorganisms and brain abscess was strengthened recently.[2] In the interim, however, the American Heart Association (AHA)[125] and British NICE[126] guidelines were published indicating that antibiotic prophylaxis is no longer required for most patients with structural heart disease at risk of infective endocarditis. This has led to confusion among dentists and medical practitioners caring for PAVM patients. A recent article exploring why PAVM/HHT patients do not fall into the groups considered by the AHA/NICE guidelines provided recommendations to reduce the risk of dental bacteremias, including the use of antibiotic prophylaxis prior to dental procedures.[127]

Pregnancy. In view of the risks of PAVM growth and rupture during pregnancy, female patients should be advised to defer pregnancy pending formal PAVM assesment and treatment. Pregnancies should be managed with close liaison between obstetricians, pulmonologists, and interventional radiologists, using appropriate "high-risk" obstetric management strategies.[46] Patients and their medical practitioners should be alerted to the possibility of hemoptysis or sudden severe dyspnea that requires urgent admission and management: embolization in the second and third trimesters is feasible and safe.[46,127a] The question of whether PAVM embolization should be offered to asymptomatic pregnant women differs between countries; at our institution it is not performed.[46]

Thromboembolic Risks. There are no data on maneuvers to reduce thromboembolic risks, but based on the high frequency of cerebral thromboembolic complications in these patients, and evidence that many have a prothrombotic state,[127b] we suggest that options such as cessation of hormonal therapy, or antiplatelet therapy, should be considered on a case-by-case basis for patients experiencing transient ischemic attacks, even if there is underlying HHT.

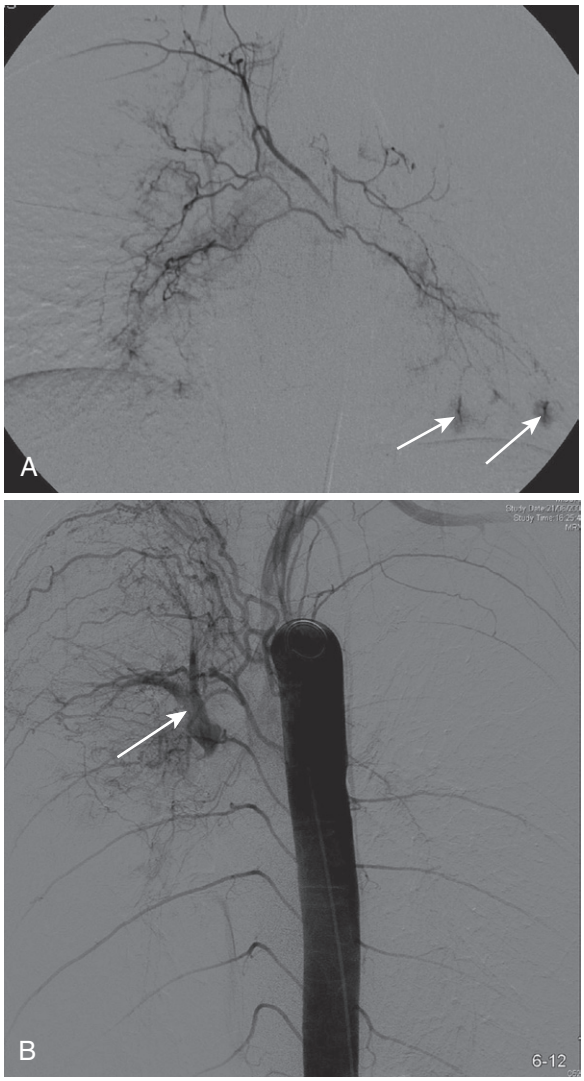

FIGURE 54-7 ■ Diagram showing normal and abnormal bronchial circulations. **A,** Selective digital subtraction angiogram showing normal bronchial arteries. Normal peripheral pulmonary artery branches are opacified (*arrows*) via normal bronchopulmonary anastomoses. **B,** Digital subtraction descending aortogram in a patient with hemoptysis due to previous right apical tuberculosis. There is bronchial and nonbronchial systemic artery hypertrophy supplying the right upper zone, with retrograde opacification of the entire right upper lobe pulmonary artery (*arrow*) via enlarged bronchopulmonary anastomoses.

SYSTEMIC-TO-PULMONARY VASCULAR COMMUNICATIONS

Anatomy

Communications between the systemic and pulmonary circulations are part of normal anatomy, since terminal branches of the bronchial microcirculation communicate with peripheral pulmonary artery branches (Fig. 54-7A). These vessels are functionally important in preventing lung infarction in the great majority of cases of pulmonary embolic disease. Their presence may be detected during specialized functional scans such as contrast-enhanced, time-resolved perfusion MR imaging of regions of the lung in which hypoxic pulmonary vasoconstriction reduces pulmonary arterial supply; late filling might reflect the systemic arterial component.[128]

Normally, there is a profound pressure drop between the systemic and pulmonary vessels, ascribed to *Sperrarterien,* or "blockading arteries," which were first described by von Hayek,[129] and visualized (by scanning electron microscopy of resin-injected sheep lungs) as deep focal constrictions within intrapulmonary bronchial arteries of 100 to 300-μm diameter.[130] In the presence of chronic intrapulmonary inflammatory disease, these normal bronchopulmonary anastomoses enlarge considerably (see Fig. 54-7B), increasing the perfusion pressure to the diseased lung, thereby increasing the likelihood of bleeding (see also Fig. 19-25).

In chronic inflammatory pulmonary disease, especially when located peripherally, additional systemic supply is recruited transpleurally through dense inflammatory adhesions between the lung and the chest wall. Direct communications between systemic arteries and the pulmonary circulation are also observed in several other settings (see later), such as when systemic arteries communicate with the pulmonary artery or its branch via the pulmonary ligament, which encloses the lung hilum. Intralobar sequestration (see "Bronchopulmonary Sequestration" section) is a developmental anomaly in which a systemic artery replaces a segmental pulmonary artery.

Adult (Acquired) Systemic-to-Pulmonary Communications

As noted, abnormally large systemic-to-pulmonary communications form part of the inflammatory response to the presence of chronically inflamed or necrotic lung tissue; the most frequent causes, according to Yoon and colleagues,[131] are pulmonary tuberculosis (usually chronic), aspergilloma (secondary to chronic sarcoidosis or tuberculosis), and bronchiectasis, including that caused by cystic fibrosis[132] (see Fig. 54-7B). Overlying pleural thickening provides transpleural access for systemic vessels from the intercostal, internal mammary, thyrocervical, axillary, and inferior phrenic arteries. For more proximal intrapulmonary disease, vascular hypertrophy and new vessel formation occurs within the bronchial circulation.

Fetal- and Perinatal Systemic-to-Pulmonary Artery Collaterals

During bronchial branching in the developing fetus, the dividing buds are supplied by a capillary plexus derived from the primitive aorta; this plexus later regresses as the growing lung advances and the developing pulmonary artery takes over. Between the 40th and 50th days of gestation, the lungs have a dual source of blood supply.[133,134] Systemic-to-pulmonary artery collaterals arising from the proximal or distal part of the aortic arch persist in later gestation and were detected and found to be functional in 88 of 133 (66%) premature, very-low-birth-weight (<1500 g) infants admitted to the neonatal intensive care unit at a mean gestational age of 28 ± 13 weeks; color Doppler scanning follow-up indicated that the systemic-to-pulmonary artery collaterals declined with maturity, until at 1 year of age only 2 of the original 88 infants still had collaterals.[135]

When present postnatally, these vessels, which provide additional extracardiac L–R shunts, effectively function as miniature patent ductus arterioses, placing the neonate at higher risk of heart failure, which developed in 11% of infants with systemic-to-pulmonary artery collaterals in one series.[135]

Aberrant Congenital Systemic-to-Pulmonary Communications

In addition to persistent fetal systemic-to-pulmonary artery collaterals, other congenital vascular anomalies are recognized, but rarely cause problems. The systemic artery is usually the internal mammary or a coronary artery. Iskandrian and colleagues[136] reported 12 patients with coronary-to-pulmonary artery communications, mostly discovered accidentally during routine coronary angiography for chest pain. Large-flow congenital systemic-to-pulmonary artery collaterals characteristically present in the second or third decade of life with a continuous murmur similar to that of a patent ductus arteriosus. Hearne and Burbank[137] reviewed 11 reported cases of communications between an internal mammary artery and the pulmonary arteries; 8 cases were considered to be congenital, 2 traumatic, and 1 neoplastic in origin.

Cavopulmonary Anastomoses

Systemic-to-pulmonary artery collaterals are a feature of Glenn/Fontan circulations constructed surgically as a palliative correction for tricuspid atresia or a functionally univentricular heart,[138] operations that are also associated with the development of PAVMs in the lung deprived of hepatic venous blood (see earlier section in this chapter). In a retrospective series by McElhinney and associates,[139] 59% of 76 patients had systemic-to-pulmonary artery collaterals on follow-up catheterization at approximately 2.5 years; their presence, however, was not associated with a poorer outcome.

Treatment

Treatment requirements depend upon the presence of symptoms. Even systemic-to-pulmonary artery collaterals derived from coronary arteries generally do not serve to "steal" blood flow from the coronary artery.[136] Whereas earlier cases from series spanning 1947 to 1979 were treated by ligation of the vessels and resection of the lobe, more recent cases were left untreated. Treatment is now offered in three settings: (1) for hemoptysis, the most common complication of acquired systemic-to-pulmonary artery collaterals; (2) for heart failure, predominantly affecting neonates with persistent fetal collaterals[135]; and (3) for patients with Fontan circulations in whom there is concern about induction of high-flow-induced pulmonary hypertension.[139]

Managements of Hemoptysis

Hemoptysis from systemic-to-pulmonary artery collaterals may be massive and require emergency management. Bronchoscopy may help to localize the source of bleeding,[140] but multidetector CT performed during the aortic phase of contrast enhancement is usually more helpful; CT angiograms document the underlying cause of bleeding in most instances and will also clearly demonstrate the presence or absence of hypertrophied bronchial or nonbronchial systemic arteries.[141] In an emergency, angiography takes precedence, with a view to embolization of the bleeding vessels. In 1977, Rémy and associates[142] reported their results of selective bronchial artery angiography and embolization on 105 patients with hemoptysis.

Bronchial artery or collateral vessel embolization is carried out at angiography with particulate polyvinyl alcohol; it is a highly specialized interventional radiology technique.[143,144] Complications are uncommon, but one of the most feared is that of a transverse myelitis, which may occur if inadvertent embolization is performed of a spinal artery arising from an intercostal or bronchial artery. The use of "superselective" coaxial catheters (3-French gauge), with peripheral placement of the tip in a stable position distal to normal arterial branches and without reflux after injection, has made the procedure much safer.[143-145] In 80% to 90% of cases, immediate control of hemoptysis will be achieved,[146] although 20% will rebleed in the first 6 months, and a further 50% will have significant hemoptyses on longer follow-up; repeat embolization is usually helpful in these individuals. While bronchial artery embolization is not curative and the risk of further hemoptysis is always present, embolization can be repeated several times.

Surgery is falling out of favor as first-line treatment for massive hemoptysis for three main reasons: (1) the patient's condition is often poor, (2) the disease is usually extensive and often bilateral, and (3) pleural thickening is present, and traversed by extensive collateral vessels and often adheres the lung to the chest wall. In 10 series, the average perioperative mortality for pleuropulmonary aspergilloma resection was 9% (range, 0 to 23%).[147] Increasingly, surgery is confined to low-risk cases in which recurrent hemoptysis is a problem.

BRONCHOPULMONARY SEQUESTRATION

Classification

Bronchopulmonary sequestration was first described by Pryce[148] in 1946 and defined by him as "an abnormal artery from the aorta supplying a bronchopulmonary mass or cyst which is dissociated from the normally connected bronchial tree." A distinction is usually made between intralobar sequestrations, which share a common visceral pleural investment with the adjacent normal lung tissue, and the much less frequent extralobar sequestrations, which have their own pleural lining that separates them from the remaining lung tissue. Both types have an abnormal systemic blood supply, most often from the thoracic aorta, but in roughly 20% of cases the artery originates from the abdominal aorta; atypical origins of the feeding vessels, even from coronary arteries, are well described. The venous drainage in intralobar sequestrations is generally via a pulmonary vein, whereas in the extralobar variety it is often via the azygous vein, but variations are common.[149]

Pathogenesis

During bronchial branching, which is completed in humans 16 weeks after conception, the dividing buds are supplied by a capillary plexus derived from the primitive aorta; this plexus later regresses. Growth arrest locally of the pulmonary artery during bronchial division may disrupt maturation and tracheobronchial integrity, as well as lead to persistence of the blood supply from the aorta. The developing lung bud lies in close proximity to the developing foregut, from which it is derived, which explains the high incidence of associated foregut anomalies and linkage with congenital cystic adenomatoid malformation. In 1987, Clements and Warner[150] developed an alternative nomenclature and anatomic classification that unifies these embryologically related anomalies, many of which are now being diagnosed in utero owing to the extensive use of prenatal imaging studies.[151]

Clinical Features

Most patients with sequestrations are symptomatic, and the diagnosis is made in 50% to 60% before the age of 20. Diagnosis in adults older than 50 is uncommon, but a series of 17 patients was recently reported.[152] According to a 1979 review of 540 cases by Savic and colleagues,[153] 15% of patients are asymptomatic.

Typically, symptoms develop during infancy or childhood and are characterized by chronic cough and recurrent pneumonias and episodes of acute bronchitis, which are related to underlying progressive bronchiectasis, scarring, and cyst formation in the poorly communicating sequestered lung. Hemoptysis is also common. Chest radiographs classically show a left basilar density, but involvement of the right basilar region also occurs; much less commonly, sequestrations may involve more superior intrapulmonary anatomic units.

The diagnosis depends on demonstrating the anomalous systemic arterial blood supply, which can reliably be shown by multislice (multidetector) CT techniques (Fig. 54-8), which as described in Chapter 19 allow three-dimensional reconstructions to be made that vividly display not only the arterial input but the venous drainage as well (see also Fig. 19-24). MR angiography is also a valuable means of diagnosing sequestration, and has the advantage of not involving ionizing radiation,[154] but this may be offset by longer imaging times when compared with CT, particularly in pediatric patients, in whom sedation is required.[149]

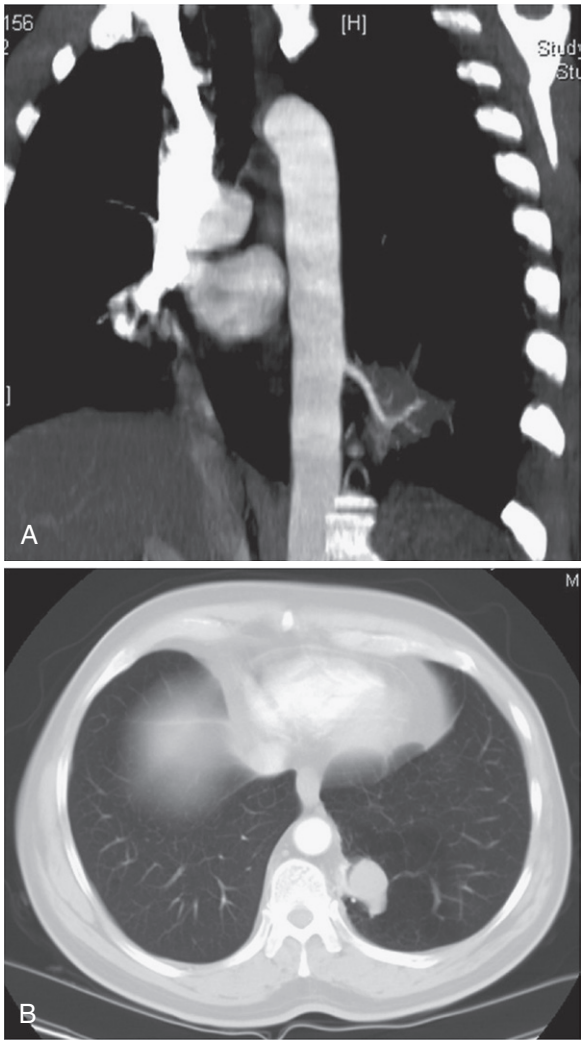

FIGURE 54-8 ■ Pulmonary sequestration presenting as a lung mass at the left lung base in an asymptomatic 55-year-old man (found on employment radiograph). **A,** Coronal reformation from contrast-enhanced multislice CT demonstrates the systemic arterial blood supply, which arises from the lower thoracic aorta and travels to a soft tissue mass in the left lower lobe. **B,** Axial image on a lung window demonstrates the soft tissue mass with hyperinflation of the surrounding lung due to disruption of the normal airway to this segment and resulting lung trapping.

Treatment

The recommended treatment of patients with symptomatic sequestrations is surgical removal of the affected lung, which often requires a lobectomy but which can sometimes be carried out by segmentectomy to conserve the normal portion of lung in patients with intralobar sequestrations. Recently, the feasibility of using video-assisted thoracic surgery has been demonstrated, but its final role in treatment is unknown.[155] A prerequisite of operative intervention is thorough definition of the origin and course of the aberrant arterial blood supply; Lee and coworkers[149] believe, also, that an additional surgical advantage lies in the demonstration of the venous drainage pathways by multislice CT examination. In patients in whom resection cannot be performed for technical reasons, ligation or embolization of the feeder artery is advised to prevent hemoptysis; embolization may also be performed preoperatively to help reduce blood loss.

PULMONARY ARTERY ANEURYSMS

Pulmonary artery aneuryms (PAAs) are rare vascular anomalies. Historically they were classified as peripheral (predominently tuberculous) or proximal (predominently syphilitic). It is now recognized that PAAs can develop in a wide range of clinical settings and that the distinction between large and medium to small vessels is by no means absolute.

Although tuberculosis and syphilis are no longer the main precipitating factors, there is still some merit and pathophysiologic basis to the proximal-versus-peripheral classification. Proximal PAAs develop primarily due to inherited defects in the vascular wall, or to trauma due to pulmonary hypertension or jets of blood impacting on specific sites, such as distal to pulmonary stenosis or opposite a patent ductus arteriosus. They can also result from focal endovascular infection or vasculitis, or disease of the vaso vasorum as in syphilis. Peripheral PAAs are more usually attributed to infection—either adjacent to an area of infected lung (as in Rasmussen's aneuryms), or due to endovascular seeding of infected foci—or to vasculitis. In many cases more than one etiologic factor is present, and it is not clear whether an intrinsic vascular defect, endovascular trauma, or infection is primarily responsible for the development of the aneurysm. Multiple aneurysms should raise the possibility of underlying Behçet's disease.

Pulmonary artery aneurysms are unstable structures: As the radius of the aneurysm increases, the wall tension (T) becomes higher at any given level of intravascular pressure, thus increasing the dilating force via the Laplace relationship:

$$T = \frac{pr}{2d}$$

where p is the intravascular pressure, r the radius of the aneurysm, and d the thickness of its wall. Although only some aneurysms continuously dilate via this vicious circle until they rupture, all have the potential to do so. The main risks of these unstable structures are pulmonary hemorrhage (which may be life-threatening from any site), and dissection for proximal lesions. In dissecting aneurysms, blood tracks within the arterial wall following an intimal tear. False or pseudoaneurysms occur when all layers of the wall are breached, but the blood is contained by the surrounding tissues or by clotting. If an aneurysm ruptures and is not contained in this way, blood may enter the bronchus sharing the common bronchovascular connective tissue sheath, causing hemoptysis and sometimes death from exsanguination.

Etiology and Pathogenesis

Infection

Small artery pseudoaneurysms are generally infective (mycotic) in origin, often mycobacterial or fungal. Pathologically, granulation tissue replaces a large part of the arterial wall. Tuberculosis and syphilis used to be the most common causes. Tuberculous Rasmussen's aneuryms, classically described as the tortuous abnormal vasculature of tuberculous cavity walls, were seen in 4% of autopsies (45 of 1114) in patients with chronic pulmonary tuberculosis, and caused death in the majority of those patients in whom they were present.[156] Rasmussen's aneuryms remain important; in 1984, they were reported in approximately 5% of cases of massive hemoptysis.[157] In contrast, in the era of untreated syphilis only 8 cases of proximal syphilitic PAA were found in 109,571 autopsies.[158]

Although the contribution of syphilis in particular has waned, infection remains a relatively common etiology, particularly secondary to tuberculosis or lung abscess. Other in situ pulmonary arterial wall infections occur from endovascular seeding from right-sided heart valve vegetations, typically in chronic drug abusers[159] or, in one case, from *Candida* endocarditis introduced by a Swan-Ganz catheter.[160]

Vascular Trauma

Large artery aneurysms have a variety of causes, the most common of which is congenital heart disease, especially patent ductus arteriosis; less common causes are pulmonary valve stenosis, atrial or ventricular septal defect, and Fallot's tetralogy. The mechanism is thought to be trauma to the artery wall from jets of blood ejected at high velocity by ventricular contraction. External sources of trauma include penetrating injuries such as stab wounds[161] and tube thoracostomy.[162] Disruption of the arterial wall during inflation of pulmonary artery balloon catheters has led to a significant number of false aneurysms, particularly in patients with preexisting pulmonary hypertension or on anticoagulants, though this remains a rare complication.[163] Catheterization can cause a pseudoaneurysm if the vessel wall is lacerated by the catheter tip and bleeding is contained, temporarily or permanently, by the surrounding tissues. Alternatively, a true aneurysm, with or without rupture, can develop if the catheter balloon is overinflated in a small branch of the pulmonary artery. Kearney and Shabot,[164] in a retrospective review of 32,442 in patients requiring catheterization from 1975 to 1991, found that catheter-induced pulmonary artery rupture associated with hemoptysis occurred in 10 patients (0.03% incidence). The risk factors were both technical, related to peripheral placement and overinflation of the balloon; and pathophysiologic, the most important of which was an age greater than 60 years, which reflects the greater fragility of pulmonary arteries in the elderly.

Weakness of the Arterial Wall

Vascular wall weakness may predispose to aneurysm formation. This most commonly occurs in the context of vasculitis, presumably from disease of the vasa vasorum, which originate from the bronchial circulation. Large artery aneurysms have been reported in patients with giant cell arteritis.[165] Multiple aneurysms may occur in Behçet's syndrome or in its variant, the Hughes-Stovin syndrome.[166] Pulmonary hypertension, when associated with atheromatous disease and cystic necrosis of the media, may lead to dissecting pulmonary artery aneurysms. Similarly, cystic necrosis and dissecting aneurysm are also caused by fibrillin deficiency in Marfan syndrome.[167] In many cases more than one etiologic factor is present, and it is not clear whether an intrinsic vascular defect, endovascular trauma, or infection is primarily responsible for the development of the aneurysm.

Diagnosis and Treatment

Pulmonary artery aneurysms usually come to light during the investigation of an unusual mass on a routine chest radiograph or during the workup for hemoptysis. Echocardiography (including transesophageal echocardiography), CT scanning, and MR imaging are replacing angiography as first-line diagnostic investigations.[168] In the absence of hemoptysis, treatment should first be directed to the underlying cause (such as infection, vasculitis, pulmonary hypertension, and congenital heart disease). Such measures may not be possible in patients with hemoptysis in whom emergency treatment of the aneurysm is required. When the aneurysm does not include the pulmonary trunk or main pulmonary arteries, embolization is the treatment of choice using metal coils or detachable silicone balloons. Embolization is also becoming the preferred choice for large artery aneurysms.[165] When a pulmonary artery pseudoaneurysm is demonstrated, usually during selective bronchial arteriography—because of pulmonary artery opacification via a systemic artery–to–pulmonary artery shunting—both bronchial and pulmonary artery embolization is likely to be necessary to control bleeding.[169]

Proximal aneurysms have been repaired by a variety of surgical techniques, including pulmonary artery banding or excision of the aneurysm and prosthetic patch replacement.[170] Stents and grafts inserted endovascularly are likely to replace open heart surgery in some instances.[171] Surgical resections in this group have been superceded as they result in excessive loss of parenchymal tissue, and carry a high morbidity and mortality. Lung tranplantation may be an option in patients with underlying primary pulmonary hypertension.[172]

Tables 54-3 and 54-4 can be found on Expert Consult

KEY POINTS

- Over 90% of PAVMs occur in individuals affected by the genetically determined vascular disorder hereditary hemorrhagic telangiectasia, which is inherited as an autosomal dominant trait with varying phenotypic patterns.
- Right-to-left shunting of blood through PAVMs leads to hypoxemia and paradoxical emboli presenting clinically as cerebral abscess or ischemic stroke.
- Diagnosis is facilitated by three-dimensional multislice CT techniques or contrast echocardiography. Two non-interchangeable techniques are available to quantify the magnitude of R–L shunting.
- Embolization of PAVMs with coils, plugs, or balloons generally decreases R–L shunting and the risk of paradoxical emboli. Small vessel malformations are difficult to close.
- Systemic to pulmonary communications are apt to be asymptomatic but may cause heart failure in neonates and hemoptysis in later life.
- Bronchopulmonary sequestrations are supplied by an abnormal systemic artery, usually from the aorta, and lack a normal communication with the tracheobronchial tree. Symptoms, if they develop, may start at a young age and are characterized by cough and recurrent infections. Treatment is surgical removal.
- Pulmonary artery aneurysms are rare vascular abnormalities of varying etiology, whose major complication is hemoptysis. Diagnosis is usually made by CT scanning or MR imaging. Treatment is directed at the underlying cause (infection, vasculitis, pulmonary hypertension, or congenital heart disease); hemoptysis is best treated by embolization.

References

1. Shovlin CL, Guttmacher AE, Buscarini E, et al: Diagnostic criteria for hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber syndrome). Am J Med Genet 91:66–67, 2000.

1a. Govani FS, Shovlin CL: Hereditary haemorrhagic telangiectasia: a clinical and scientific review. Eur J Hum Genet 17:860–871, 2009.

2. Shovlin CL, Jackson JE, Bamford KB, et al: Primary determinants of ischaemic stroke and cerebral abscess are unrelated to severity of pulmonary arteriovenous malformations in HHT. Thorax 63:259–266, 2008.

3. Kopf GS, Laks H, Stansel HC, et al: Thirty-year follow-up of superior vena cava-pulmonary artery (Glenn) shunts. J Thorac Cardiovasc Surg 100:662–671, 1990.

4. Srivastava D, Preminger T, Lock JE, et al: Hepatic venous blood and the development of pulmonary arteriovenous malformations in congenital heart disease. Circulation 92:1217–1222, 1995.

5. Manganas C, Iliopoulos J, Pang L, Grant PW: Traumatic pulmonary arteriovenous malformation presenting with massive hemoptysis 30 years after penetrating chest injury. Ann Thorac Surg 76:942–944, 2003.

6. Dines DE, Seward JB, Bernatz PE: Pulmonary arteriovenous fistulas. Mayo Clin Proc 58:176–181, 1983.

7. White RI Jr, Lynch-Nyhan A, Terry P, et al: Pulmonary arteriovenous malformations: Techniques and long-term outcomes of embolotherapy. Radiology 169:663–669, 1988.

8. Curie A, Lesca G, Cottin V, et al: Long-term follow-up in 12 children with pulmonary arteriovenous malformations: Confirmation of hereditary hemorrhagic telangiectasia in all cases. J Pediatr Surg 151:299–306, 2007.

9. Bideau A, Brunet G, Heyer E, et al: An abnormal concentration of cases of Rendu-Osler disease in the Valserine valley of the French Jura: A geneological and demographic study. Ann Hum Biol 19:233–247, 1992.

10. Kjeldsen AD, Vase P, Green A: Hereditary haemorrhagic telangiectasia: A population-based study of prevalence and mortality in Danish patients. J Intern Med 245:31–39, 1999.

11. Dakeishi M, Shioya T, Wada Y, et al: Genetic epidemiology of hereditary hemorrhagic telangiectasia in a local community in the northern part of Japan. Hum Mut 19:140–148, 2002.

12. Westermann CJ, Rosina AF, De Vries V, de Coteau PA: The prevalence and manifestations of hereditary hemorrhagic telangiectasia in the Afro-Caribbean population of the Netherlands Antilles: A family screening. Am J Med Genet 116:324–328, 2003.

13. Cottin V, Plauchu H, Bayle JY, et al: Pulmonary arteriovenous malformations in patients with hereditary hemorrhagic telangiectasia. Am J Respir Crit Care Med 169:994–1000, 2004.

14. Plauchu H, de Chadarévian JP, Bideau A, Robert JM: Age-related clinical profile of hereditary hemorrhagic telangiectasia in an epidemiologically recruited population. Am J Med Genet 32:291–297, 1989.

15. Porteous ME, Burn J, Proctor SJ: Hereditary haemorrhagic telangiectasia: A clinical analysis. J Med Genet 29:527–530, 1992.

16. Shovlin CL, Hughes JMB, Tuddenham EGD, et al: A gene for hereditary haemorrhagic telangiectasia maps to chromosome 9q3. Nat Genet 6:205–209, 1994.

17. McAllister KA, Grogg KM, Johnson DW, et al: Endoglin, a TGF-β binding protein of endothelial cells, is the gene for hereditary haemorrhagic telangiectasia type 1. Nat Genet 8:345–351, 1994.

18. Johnson DW, Berg JN, Baldwin MA, et al: Mutations in the activin receptor-like kinase 1 gene in hereditary haemorrhagic telangiectasia type 2. Nat Genet 13:189–195, 1996.

19. Gallione CJ, Repetto GM, Legius E, et al: A combined syndrome of juvenile polyposis and hereditary haemorrhagic telangiectasia is associated with mutations in *MADH4* (*SMAD4*). Lancet 363:852–859, 2004.

20. Cole SG, Begbie ME, Wallace GMF, Shovlin CL: A new locus for hereditary haemorrhagic telangiactasia (*HHT3*) maps to chromosome 5. J Med Genet 42:577–582, 2005.

21. Bayrak-Toydemir P, McDonald J, Akarsu N, et al: A fourth locus for hereditary hemorrhagic telangiectasia maps to chromosome 7. Am J Med Genet 140:2155–2162, 2006.

22. Bourdeau A, Dumont DJ, Letarte M: A murine model of hereditary hemorrhagic telangiectasia. J Clin Invest 104:1343–1351, 1999.

23. Park SO, Lee YJ, Seki T, et al: ALK5- and TGFBR2-independent role of ALK1 in the pathogenesis of hereditary hemorrhagic telangiectasia type 2. Blood 111:633–642, 2008.

24. Cymerman U, Vera S, Pece-Barbara N, et al: Identification of hereditary hemorrhagic telangiectasia type I in newborns by protein expression and mutation analysis of endoglin. Pediatr Res 47:24–35, 2000.

25. Abdalla SA, Pece-Barbara N, Vera S, et al: Analysis of ALK-1 and endoglin in newborns from families with hereditary hemorrhagic telangiectasia type 2. Hum Mol Genet 9:1227–1237, 2000.

26. Venkatesha S, Toporsian M, Lam C, et al: Soluble endoglin contributes to the pathogenesis of preeclampsia. Nat Med 12:642–649, 2006.
27. Bourdeau A, Cymerman U, Paquet ME, et al: Endoglin expression is reduced on normal vessels but still detectable in arteriovenous malformations of patients with hereditary haemorrhagic telangiectasia type I. Am J Pathol 156:911–923, 2000.
28. Park SO, Wankhede M, Lee YJ, et al: Real-time imaging of de novo arteriovenous malformation in a mouse model of hereditary hemorrhagic telangiectasia. J Clin Invest 119:3487–3496, 2009.
29. Derynck R, Zhang YE: Smad-dependent and Smad-independent pathways in TGF-beta family signalling. Nature 425:577–584, 2003.
30. Blanco FJ, Santibanez JF, Guerrero-Esteo M, et al: Interaction and functional interplay between endoglin and ALK-1, two components of the endothelial transforming growth factor-beta receptor complex. J Cell Physiol 204:574–584, 2005.
31. Pece-Barbara N, Vera S, Kathirkamathamby K, et al: Endoglin null endothelial cells proliferate faster and are more responsive to TGF-β1 with higher affinity receptors and an activated Alk1 pathway. J Biol Chem 280:27800–27808, 2005.
32. David L, Mallet C, Mazerbourg S, et al: Identification of BMP9 and BMP10 as functional activators of the orphan activin receptor-like kinase 1 (ALK1) in endothelial cells. Blood 109:1953–1961, 2007.
33. Scharpfenecker M, van Dinther M, Liu Z, et al: BMP-9 signals via ALK1 and inhibits bFGF-induced endothelial cell proliferation and VEGF-stimulated angiogenesis. J Cell Sci 120:964–972, 2007.

33a. Upton PD, Davies RJ, Trembath RC, Morrell NW: Bone morphogenetic protein (BMP) and activin type II receptors balance BMP9 signals mediated by activin receptor-like kinase-1 in human pulmonary artery endothelial cells. J Biol Chem 284:15794–15804, 2009.

34. Kjeldsen AD, Møller TR, Brusgaard K, et al: Clinical symptoms according to genotype amongst patients with hereditary haemorrhagic telangiectasia. J Intern Med 258:349–355, 2005.
35. Bayrak-Toydemir P, McDonald J, Markewitz B, et al: Genotype-phenotype correlation in hereditary hemorrhagic telangiectasia. Am J Med Genet 140A:463–470, 2006.
36. Sabbà C, Pasculli G, Lenato GM, et al: Hereditary haemorrhagic telangiectasia: Clinical features in ENG and ALK1 mutation carriers. J Thromb Haemost 5:1149–1157, 2007.
37. Lesca G, Olivieri C, Burnichon N, et al: Genotype-phenotype correlations in hereditary hemorrhagic telangiectasia: Data from the French-Italian HHT Network. Genet Med 9:14–22, 2007.
38. Berg J, Porteous M, Reinhardt D, et al: Hereditary haemorrhagic telangiectasia: A questionnaire based study to delineate the different phenotypes caused by *endoglin* and *ALK 1* mutations. J Med Genet 40:585–590, 2003.
39. Larsson ES, Solymar L, Eriksson BO, et al: Bubble contrast echocardiography in detecting pulmonary arteriovenous malformations after modified Fontan operations. Cardiol Young 11:505–511, 2001.
40. Ofoe VD, Pratap U, Slavik Z: Rapid onset of intravenous shunting after surgical repair of tetralagy of Fallot with pulmonary atresia. Cardiol Young 11:236–239, 2001.
41. Vettukattil JJ, Slavik Z, Lamb RK, et al: Intrapulmonary arteriovenous shunting may be a universal phenomenon in patients with the superior cavopulmonary anastemosis. Heart 83:425–428, 2000.
42. Goo HW, Yang D, Park IS, et al: Time-resolved three-dimensional contrast-enhanced magnetic resonance angiography in patients who have undergone a Fontan operation or bidirectional cavopulmonary connection: Initial experience. J Magn Reson Imaging 25:727–736, 2007.
43. Agnoletti G, Borghi A, Annecchino FP, Crupi G: Regression of pulmonary venous fistulas in congenital heart disease after redirection of hepatic venous flow to the lungs. Ann Thorac Surg, 2001: 72; 909–911.
44. AboulHosn J, Danon S, Levi D, et al: Regression of pulmonary arteriovenous malformations after transcatheter reconnection of the pulmonary arteries in patients with unidirectional Fontan. Congenit Heart Dis 2:179–184, 2007.
45. McElhinney DB, Kreutzer J, Lang P, et al: Incorporation of the hepatic veins into the cavopulmonary circulation in patients with heterotaxy and pulmonary arteriovenous malformations after a Kawashima procedure. Ann Thorac Surg 80:1597–1603, 2005.
46. Shovlin CL, Sodhi V, McCarthy A, et al: Estimates of maternal risks of pregnancy for women with hereditary haemorrhagic telangiectasia: Suggested approach for obstetrics services. BJOG 115:1108–1115, 2008.
47. Faughnan ME, Lui YW, Wirth JA, et al: Diffuse pulmonary arteriovenous malformations: Characteristics and prognosis. Chest 117:31–38, 2000.
48. Pierucci P, Murphy J, Henderson KJ, et al: New definition and natural history of patients with diffuse pulmonary arteriovenous malformations: Twenty-seven-year experience. Chest 133:653–661, 2008.
49. Higgins CB, Wexler L: Clinical and angiographic features of pulmonary arteriovenous fistulas in children. Radiology 119:171–175, 1976.
50. Koppen S, Korver CR, Dalinghaus M, Westermann CJ: Neonatal pulmonary arteriovenous malformation in hereditary haemorrhagic telangiectasia. Arch Dis Child Fetal Neonatal Ed 87:F226–F227, 2002.
51. Heling KS, Tennstedt C, Göldner B, Bollmann R: Prenatal diagnosis of intrapulmonary arteriovenous malformation: Sonographic and pathomorphological findings. Ultrasound Obstet Gynecol 19:514–517, 2002.
52. Ravasse P, Maragnes P, Petit T, Laloum D: Total pneumonectomy as a salvage procedure for pulmonary arteriovenous malformation in a newborn: Report of one case. J Pediatr Surg 38:254–255, 2003.
53. Shovlin CL, Winstock AR, Peters AM, et al: Medical complications of pregnancy in hereditary haemorrhagic telangiectasia. Q J Med 88:879–887, 1995.
54. Wallace GMF, Shovlin CL: A hereditary haemorrhagic telangiectasia family with pulmonary involvement is unlinked to the known HHT genes, *endoglin* and *ALK-1*. Thorax 55:685–690, 2000.
55. Chow LT, Chow WH, Ma KF: Pulmonary arteriovenous malformation: Progressive enlargement with replacement of the entire right middle lobe in a patient with concomitant mitral stenosis. Med J Aust 158:632–634, 1993.
56. Vase P, Holm M, Arendrup H: Pulmonary arteriovenous fistulas in hereditary hemorrhagic telangiectasia. Acta Med Scand 218:105–109, 1985.
57. Whyte MKB, Hughes JMB, Jackson JE, et al: Cardiopulmonary response to exercise in patients with intrapulmonary vascular shunts. J Appl Physiol 75:321–328, 1993.
58. Dutton JAE, Jackson JE, Hughes JMB, et al: Pulmonary arteriovenous malformations: Results of treatment with coil embolization in 53 patients. AJR Am J Roentgenol 165:1119–1125, 1995.
59. Ueki T, Hughes JMB, Peters AM, et al: Oxygen and ^{99m}Tc-MAA shunt estimations in patients with pulmonary arteriovenous malformations: Effects of changes in posture and lung volume. Thorax 49:327–331, 1994.
60. Whyte MKB, Peters AM, Hughes JMB, et al: Quantification of right to left shunt at rest and during exercise in patients with pulmonary arteriovenous malformations. Thorax 47:790–796, 1992.
61. Pennington DW, Gold WM, Gordon RL, et al: Treatment of pulmonary arteriovenous malformations by therapeutic embolization. Am Rev Resp Dis 145:1047–1051, 1992.
62. Gupta P, Mordin C, Curtis J, et al: Pulmonary arteriovenous malformations: Effect of embolization on right-to-left shunt, hypoxaemia and exercise tolerance in 66 patients. AJR Am J Roentgenol 179:347–355, 2002.
63. Mager JJ, Zanen P, Verzijlbergen F, et al: Quantification of right-to-left shunt with ^{99m}Tc-labelled albumin macroaggregates and 100% oxygen in patients with hereditary haemorrhagic telangiectasia. Clin Sci (London) 102:127–134, 2002.
64. Chilvers ER, Peters AM, George P, et al: Quantification of right to left shunt through pulmonary arteriovenous malformations using ^{99}Tc^{m} albumin microspheres. Clin Radiol 39:611–614, 1989.
65. Shovlin CL, Tighe HC, Davies RJ, et al: Embolisation of pulmonary arteriovenous malformations (PAVMs): No consistent effect on pulmonary artery pressure. Eur Respir J 32:162–169, 2008.
66. Chilvers ER, Whyte MKB, Jackson JE et al: Effect of percutaneous transcatheter embolization on pulmonary function, right-to-left shunt, and arterial oxygenation in patients with pulmonary

arteriovenous malformations. Am Rev Respir Dis 142:420–425, 1990.
67. Thompson RD, Jackson JE, Peters AM et al: Sensitivity and specificity of radioisotope right-left shunt measurements and pulse oximetry for the early detection of pulmonary arteriovenous malformations. Chest 115:109–113, 1999.
68. Sapru RP, Hutchison DC, Hall JI: Pulmonary hypertension in patients with pulmonary arteriovenous fistulae. Br Heart J 31:559, 1968.
69. Trembath RC, Thomson JR, Machado RD, et al: Clinical and molecular features of pulmonary hypertension in hereditary hemorrhagic telangiectasia. N Engl J Med 345:325–334, 2001.
70. Olivieri C, Lanzarini L, Pagella F, et al: Echocardiographic screening discloses increased values of pulmonary artery systolic pressure in 9 of 68 unselected patients affected with hereditary hemorrhagic telangiectasia. Genet Med 8:183–190, 2006.
71. Simonneau G, Galiè N, Rubin LJ, et al: Clinical classification of pulmonary hypertension. J Am Coll Cardiol 43:5S–12S, 2004.
72. Harrison RE, Flanagan JA, Sankelo M, et al: Molecular and functional analysis identifies ALK-1 as the predominant cause of pulmonary hypertension related to hereditary haemorrhagic telangiectasia. J Med Genet 40:865–871, 2003.
73. Haitjema T, ten Berg JM, Overtoom TT, et al: Unusual complications after embolization of a pulmonary arteriovenous malformation. Chest 109:1401–1404, 1996.
74. Chaouat A, Coulet F, Favre C, et al: Endoglin germline mutation in a patient with hereditary haemorrhagic telangiectasia and dexfenfluramine associated pulmonary arterial hypertension. Thorax 59:446–448, 2004.
75. Stringer CJ, Stanley AL, Bates RC, Summers JE: Pulmonary arteriovenous fistula. Am J Surg 89:1054–1080, 1955.
76. Sluiter-Eringa H, Orie NGM, Sluiter HJ: Pulmonary arteriovenous fistula: Diagnosis and prognosis in noncomplainant patients. Am Rev Respir Dis 100:177–188, 1969.
77. Nicolosi A, Hauser WA, Musicco M, Kurland LT: Incidence and prognosis of brain abscess in a defined population: Olmsted County, Minnesota, 1935–1981. Neuroepidemiology 10:122–131, 1991.
78. Bamford J, Sandercock P, Dennis M, et al: A prospective study of acute cerebrovascular disease in the community: The Oxfordshire Community Stroke Project 1981–1986. 1. Methodology, demography and incident cases of first ever stroke. J Neurol Neurosurg Psychiatry 51:1373–1380, 1988.
79. Sacco RL, Adams R, Albers G, et al: Guidelines for prevention of stroke in patients with ischemic stroke or transient ischemic attack: A statement for healthcare professionals from the American Heart Association/American Stroke Association Council on Stroke. Circulation 113:e409–e449, 2006.
80. Moussouttas M, Fayad P, Rosenblatt M, et al: Pulmonary arteriovenous malformations: Cerebral ischaemia and neurologic manifestations. Neurology 55:959–964, 2000.
81. Hodgson CH, Burchell HB, Good CA, Clagettt OT: Hereditary hemorrhagic telangiectasia and pulmonary arteriovenous fistula: Study of a large family. N Engl J Med 261:625–636, 1959.
82. Steele JG, Nath PU, Burn J, Porteous ME: An association between migrainous aura and hereditary haemorrhagic telangiectasia. Headache 33:145–148, 1993.
83. Post MC, Letteboer TG, Mager JJ, et al: A pulmonary right-to-left shunt in patients with hereditary haemorrhagic telangiectasia is associated with an increased prevalence of migraine. Chest 128:2485–2489, 2005.
84. Stewart WF, Shechter A, Rasmussen BK: Migraine prevalence: A review of population-based studies. Neurology 44:S17–S23, 1994.
85. Marziniak M, Jung A, Guralnik V, et al: An association of migraine with hereditary haemorrhagic telangiectasia independently of pulmonary right-to-left shunts. Cephalalgia 29:76–81, 2009.
86. Swinburne AJ, Fedullo AJ, Gangemi R, Mijangos JA: Hereditary telangiectasia and multiple pulmonary arteriovenous fistulas: Clinical deterioration during pregnancy. Chest 89:459–460, 1986.
87. Gammon RB, Miksa AK, Keller FS: Osler-Weber-Rendu disease and pulmonary arteriovenous fistulas: Deterioration and embolotherapy during pregnancy. Chest 98:1522–1524, 1990.
88. Kjeldsen AD, Oxhøj H, Andersen PE, et al: Pulmonary arteriovenous malformations: Screening procedures and pulmonary angiography in patients with hereditary hemorrhagic telangiectasia. Chest 116:432–439, 1999.
89. Haitjema T, Disch F, Overtoom TT, et al: Screening family members of patients with hereditary haemorrhagic telangiectasia. Am J Med 99:519–524, 1995.
90. Pollak JS, Saluja S, Thabet A, et al: Clinical and anatomic outcomes after embolotherapy of pulmonary arteriovenous malformations. J Vasc Interv Radiol 17:35–45, 2006.
91. Remy J, Remy-Jardin M, Wattinne L, Deffontaines C: Pulmonary arteriovenous malformations: Evaluation with CT of the chest before and after treatment. Radiology 182:809–816, 1992.
92. Gutierrez FR, Glazer HS, Levitt RG, Moran JF: NMR imaging of pulmonary arteriovenous fistulae. J Comput Assisted Tomogr 8:750–752, 1984.
93. Schneider G, Uder M, Koehler M, et al: MR angiography for detection of pulmonary arteriovenous malformations in patients with hereditary hemorrhagic telangiectasia. AJR Am J Roentgenol 190:892–901, 2008.
94. Zukotynski K, Chan RP, Chow CM, et al: Contrast echocardiography grading predicts pulmonary arteriovenous malformations on CT. Chest 132:18–23, 2007.
95. Barzilai B, Waggoner AD, Spessert C, et al: Two-dimensional contrast echocardiography in the detection and follow-up of congenital pulmonary arteriovenous malformations. Am J Cardiol 68:1507–1510, 1991.
96. Feinstein JA, Moore P, Rosenthal DN, et al: Comparison of contrast echocardiography versus cardiac catheterisation for detection of pulmonary arteriovenous malformations. Am J Cardiol 89:281–285, 2002.
97. Gazzaniga P, Buscarini E, Leandro G, et al: Contrast echocardiography for pulmonary arteriovenous malformations (PAVMs) screening: Does any bubble matter? Eur J Echocardiogr 10:513–518, 2009.
98. Lee WL, Graham AF, Pugash RA, et al: Contrast echocardiography remains positive after treatment of pulmonary arteriovenous malformations. Chest 123:351–358, 2003.
99. Nanthakumar K, Graham AT, Robinson TI, et al: Contrast echocardiography for detection of pulmonary arteriovenous malformations. Am Heart J 141:243–246, 2001.
100. van Gent MW, Post MC, Luermans JG, et al: Screening for pulmonary arteriovenous malformations using transthoracic contrast echocardiography: A prospective study. Eur Respir J 33:85–91, 2009.
101. van Gent MW, Post MC, Snijder RJ, et al: Grading of pulmonary right-to-left shunt with transthoracic contrast echocardiography: Does it predict the indication for embolotherapy? Chest 135:1288–1292, 2009.
102. Schussler JM, Phillips SD, Anwar A: Pulmonary arteriovenous fistula discovered after percutaneous patent foramen ovale closure in a 27-year-old woman. J Invasive Cardiol 15:527–529, 2003.
103. Porstmann W: Therapeutic embolization of arteriovenous pulmonary fistulas by catheter technique. *In* Kelop O (ed); Current Concepts in Pediatric Radiology. Berlin: Springer, 1977, pp 23–31.
104. Taylor BG, Cockerill EM, Manfredi F, Klatte EC: Therapeutic embolization of the pulmonary artery in pulmonary arteriovenous fistula. Am J Med 64:360–365, 1978.
105. Kaufman SL, Strandberg JD, Barth KH, et al: Therapeutic embolization with detachable silicone balloons: Long term effects in swine. Invest Radiol 14:157–161, 1978.
106. Haitjema TJ, Overtoom TT, Westermann CJ, Lammers JW: Embolisation of pulmonary arteriovenous malformations: Results and follow-up in 32 patients. Thorax 50:719–723, 1995.
107. Andersen PE, Kjeldsen AD: Long-term follow-up after embolization of pulmonary arteriovenous malformations with detachable silicone balloons. Cardiovasc Intervent Radiol 31:569–574, 2008.
108. Remy-Jardin M, Dumont P, Brillet PY, et al: Pulmonary arteriovenous malformations treated with embolotherapy: Helical CT evaluation of long-term effectiveness after 2–21-year follow-up. Radiology 239:576–585, 2006.
109. Milic A, Chan RP, Cohen JH, Faughnan ME: Reperfusion of pulmonary arteriovenous malformations after embolotherapy. J Vasc Intervent Radiol 16:1675–1683, 2005.

110. Lee D, White RI, Egglin T, et al: Embolotherapy of large pulmonary arteriovenous malformation: Long term results. Ann Thorac Surg 64:930–940, 1997.
111. Post MC, Thijs V, Schonewille WJ, et al: Embolization of pulmonary arteriovenous malformations and decrease in prevalence of migraine. Neurology 66:202–205, 2006.
112. Thenganatt J, Schneiderman J, Hyland RH, et al: Migraines linked to intrapulmonary right-to-left shunt. Headache 46:439–443, 2006.
113. Mager HJ, Overtoom TT, Mauser HW, Westermann KJ: Early cerebral infarction after embolotherapy of a pulmonary arteriovenous malformation. J Vasc Intervent Radiol 12:122–123, 2001.
114. Sagara K, Miyazono N, Inoue H, et al: Recanalization after coil embolotherapy of pulmonary arteriovenous malformations: Study of long term outcome and mechanism for recanalization. AJR Am J Roentgenol 170:727–730, 1998.
115. Brillet PY, Dumont P, Bouaziz N, et al: Pulmonary arteriovenous malformation treated with embolotherapy: Systemic collateral supply at multidetector CT angiography after 2–20-year follow-up. Radiology 242:267–276, 2007.
116. Terry PB, Barth KH, Kaufman SL, White RI Jr: Balloon embolization for the treatment of pulmonary arteriovenous fistulas. N Engl J Med 302:1189–1190, 1980.
117. Andrivet P, Lofaso F, Carette MF, et al: Haemodynamics and gas exchange before and after coil embolization of pulmonary arteriovenous malformations. Eur Respir J 8:1228–1230, 1995.
118. Rodan BA, Goodwin JD, Chen JT, Ravin CE: Worsening pulmonary hypertension after resection of arteriovenous fistula. AJR Am J Roentgenol 137:864–867, 1981.
118a. Shovlin CL, Gibbs JSR, Jackson JE: Management of pulmonary arteriovenous malformations in pulmonary hypertensive patients. A pressure to embolise? Eur Respir Rev 18:4–6, 2008.
119. Rodan BA, Goodwin JD, Chen JT, Ravin CE: Surgical treatment of recurrent transient ischemic attacks and hemoptysis in a young man with multiple pulmonary arteriovenous malformations. J Thorac Cardiovasc Surg 130:1456–1458, 2005.
120. Reynaud-Gaubert M, Thomas P, Gaubert JY, et al: Pulmonary arteriovenous malformations: Lung transplantation as a therapeutic option. Eur Respir J 14:1425–1428, 1999.
121. Svetliza G, De la Canal A, Beveraggi E, et al: Lung transplantation in a patient with arteriovenous malformations. J Heart Lung Transplant 21:506–508, 2002.
122. Swanson DL, Dahl MV: Embolic abscesses in hereditary hemorrhagic telangiectasia. J Am Acad Dermatol 24:580–583, 1991.
123. Mohler ER, Monahan B, Canty MD, Flockhart DA: Cerebral abscess associated with dental procedure in hereditary haemorrhagic telangiectasia. Lancet 338:508–509, 1991.
124. Chan P: Antibiotic prophylaxis for patients with hereditary hemorrhagic telangiectasia. J Am Acad Dermatol 26:282–283, 1992.
125. Wilson W, Taubert KA, Gewitz M, et al: Prevention of infective endocarditis: Guidelines from the American Heart Association. A guideline from the American Heart Association Rheumatic Fever, Endocarditis and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. J Am Dent Assoc 138:739–745, 747–760, 2008.
126. Wray D, Ruiz F, Richey R, et al: Prophylaxis against infective endocarditis for dental procedures—summary of the NICE guideline. Br Dent J 204:555–557, 2008.
127. Shovlin C, Bamford K, Wray D: Post NICE: Antibiotic prophylaxis prior to dental procedures for patients with pulmonary arteriovenous malformations (PAVMs) and hereditary haemorrhagic telangiectasia. Br Dent J 205:531–533, 2008.
127a. Gershon A, Faughnan M, Chon K, et al: Transcatheter embolotherapy of maternal pulmonary arteriovenous malformations during pregnancy. Chest 119:470–477, 2001.
127b. Shovlin CL, Sulainam NL, Govani FS, Begbie ME: Elevated Factor VIII in hereditary haemorrhagic telangiectasia (HHT): Association with venous thromboembolism. Thromb Haemost 98:1031–1039, 2007.
128. Eichinger M, Puderbach M, Kauczor H-U, Risse F: Improved visualization of delayed regional pulmonary perfusion in cystic fibrosis patients (abstract). Am J Respir Crit Care Med 177:456, 2008.
129. von Hayek H: The Human Lung. New York: Hafner, 1960.
130. Schraufnagel DE, Pearse DB, Mitzner WA, Wagner EM: Three-dimensional structure of the bronchial microcirculation in sheep. Anat Rec 243:357–366, 1995.
131. Yoon W, Kim YH, Kim JK, et al: Massive hemoptysis: Prediction of nonbronchial systemic arterial supply with chest CT. Radiology 227:232–238, 2003.
132. Brinson GM, Noone PG, Mauro MA, et al: Bronchial artery embolization for the treatment of hemoptysis in patients with cystic fibrosis. Am J Respir Crit Care Med 157:1951–1958, 1998.
133. Wells LJ, Boyden EA: The development of the bronchopulmonary segments in human embryos of the Horizons XVII to XIX. Am J Anat 95:163–201, 1954.
134. Haworth SG, Macartney FJ: Growth and development of pulmonary circulation in pulmonary atresia with ventricular septal defect and major aortopulmonary collateral arteries. Br Heart J 44:14–24, 1980.
135. Acherman RJ, Siassi B, Pratti-Madrid G, et al: Systemic to pulmonary collaterals in very low birth weight infants: Color Doppler detection of systemic to pulmonary connections during neonatal and early infancy period. Pediatrics 105:528–532, 2000.
136. Iskandrian AS, Kimbiris D, Bemis CE, Segal BL, et al: Coronary artery to pulmonary artery fistulas. Am Heart J 96:605–609, 1978.
137. Hearne SF, Burbank MK: Internal mammary artery-to-pulmonary artery fistulas: Case report and review of the literature. Circulation 62:1131–1135, 1980.
138. Fontan F, Baudet E: Surgical repair of tricuspid atresia. Thorax 26:240–248, 1971.
139. McElhinney DB, Reddy VM, Tworetzky W, et al: Incidence and implications of systemic to pulmonary collaterals after bi-directional cavopulmonary anastomosis. Ann Thorac Surg 69:1222–1228, 2000.
140. Dweik RA, Stoller JK: Role of bronchoscopy in massive hemoptysis. Clin Chest Med 20:89–105, 1999.
141. Remy-Jardin M, Bouaziz N, Dumont P, et al: Bronchial and nonbronchial systemic arteries at multi-detector row CT angiography: Comparison with conventional angiography. Radiology 233:741–749, 2004.
142. Rémy J, Arnaud A, Fardou H, et al: Treatment of hemoptysis by embolization of bronchial arteries. Radiology 122:33–37, 1977.
143. Marshall TJ, Jackson JE: Vascular intervention in the thorax: Bronchial artery embolization for haemoptysis. Eur Radiol 7:1221–1227, 1997.
144. Saluja S, Henderson KJ, White RI Jr: Embolotherapy in the bronchial and pulmonary circulations. Radiol Clin North Am 38:425–448, 2000.
145. White RI Jr: Bronchial artery embolotherapy for control of acute hemoptysis: Analysis of outcome. Chest 115:912–915, 1999.
146. Mal H, Rullon I, Mellot F, et al: Immediate and long-term results of bronchial artery embolization for life-threatening hemoptysis. Chest 115:996–1001, 1999.
147. Regnard JF, Icard P, Nicolosi M, et al: Aspergilloma: A series of 89 surgical cases. Ann Thorac Surg 69:898–903, 2000.
148. Pryce DM: Lower accessory artery with intralobular sequestration of the lung. J Pathol Bacteriol 58:457–467, 1946.
149. Lee EY, Siegel MJ, Sierra LM, Foglia RP: Evaluation of angioarchitecture of pulmonary sequestration in pediatric patients using 3D MDCT angiography. AJR Am J Roentgenol 183:183–188, 2004.
150. Clements BS, Warner JO: Pulmonary sequestration and related congenital bronchopulmonary-vascular malformations: Nomenclature and classification based on anatomical and embryological considerations. Thorax 42:401–408, 1987.
151. Liechty KW, Flake AW: Pulmonary vascular malformations. Semin Pediatr Surg 17:9–16, 2008.
152. Peterson G, Martin U, Singhai A, Criner GJ: Intralobar sequestration in the middle-aged and elderly adult: Recognition and radiographic evaluation. J Thorac Cardiovasc Surg 126:2086–2090, 2003.
153. Savic B, Birtel FJ, Tholen W, et al: Lung sequestration: Report of seven cases and review of 540 published cases. Thorax 34:96–101, 1979.
154. Tuite DJ, Francois C, Dill K, et al: Diagnosis and characterization of pulmonary sequestration using dynamic time-resolved magnetic resonance angiography. Clin Radiol 6:913–917, 2008.

155. Kestenholz PB, Schneiter D, Hillinger S, et al: Thoracoscopic treatment of pulmonary sequestration. Eur J Cardiothorac Surg 29:815–818, 2006.
156. Auerbach O: Pathology and pathogenesis of pulmonary arterial aneurysms in tuberculous cavities. Am Rev Tuberc 39:99–115, 1939.
157. Remy J, Lemaitre L, Lafitte JJ, et al: Massive haemoptysis of pulmonary arterial origin: Diagnosis and treatment. AJR Am J Roentgenol 143:963–969, 1984.
158. Deterling R, Clagett O: Aneurysm of the pulmonary artery: Review of the literature and report of a case. Am Heart J 34:471–499, 1947.
159. Benveniste O, Bruneel F, Bedos J, et al: Ruptured mycotic pulmonary artery aneurysm: An unusual complication of right-sided endocarditis. Scand J Infect Dis 30:626–629, 1998.
160. Roush K, Scala-Barnett DM, Donabedian H, Freimer EH: Rupture of a pulmonary artery mycotic aneurysm associated with candidal endocarditis. Am J Med Genet 84:142–144, 1988.
161. Savage C, Zwischenberger JB, Ventura KC, Wittich GR: Hemoptysis secondary to pulmonary pseudoaneurysm 30 years after a gunshot wound. Ann Thorac Surg 71:1021–1023, 2001.
162. Podbielski FJ, Wiesman IM, Yaghmai B, et al: Pulmonary artery pseudoaneurysm after tube thoracostomy. Ann Thorac Surg 64:1478–1480, 1997.
163. Ferretti GR, Thony F, Link KM, et al: False aneurysm of the pulmonary artery induced by a Swan-Ganz catheter: Clinical presentation and radiologic management. AJR Am J Roentgenol 167:941–945, 1996.
164. Kearney TJ, Shabot MM: Pulmonary artery rupture associated with the Swan-Ganz catheter. Chest 108:1349–1352, 1995.
165. Dennison AR, Watkins RM, Gunning AJ: Simultaneous aortic and pulmonary artery aneurysms due to giant cell arteritis. Thorax 40:156–157, 1985.
166. Durieux P, Bletry O, Huchon G, et al: Multiple pulmonary artery aneurysms in Behçet's disease and Hughes-Stovin syndrome. Am J Med 71:730–741, 1981.
167. Bartter T, Irwin RS, Nash G: Aneurysms of the pulmonary artery. Chest 94:1065–1075, 1988.
168. Khalil A, Parrot A, Nedelcu C, et al: Severe haemoptysis of pulmonary arterial origin: Signs and role of multidetector row CT angiography. Chest 133:212–219, 2008.
169. Sbano H, Mitchell AW, Ind PW, Jackson JE: Peripheral pulmonary artery pseudoaneurysms and massive haemoptysis. AJR Am J Roentgenol 184:1253–1259, 2005.
170. Kuwaki K, Morishita K, Komatsu K, Abe T: Graft replacement for huge aneurysm of the main pulmonary artery. Ann Thorac Surg 70:1714–1716, 2000.
171. Hannan RL, Miyaji K, Burke RP, Zahn EM: Endovascular stent graft treatment of a pulmonary artery pseudoaneurysm. Ann Thorac Surg 71:727–729, 2001.
172. Wekerle T, Klepetko W, Taghavi S, Birsan T: Lung transplantation for primary pulmonary hypertension and giant pulmonary artery aneurysm. Ann Thorac Surg 65:825–827, 1998.
173. Cirulli A, Loria MP, Darmbra P, et al: Patients with hereditary hemorrhagic telangiectasia (HHT) exhibit a deficit of polymorphonuclear cell and monocyte oxidative burst and phagocytosis: A possible correlation with altered adaptive immune responsiveness in HHT. Chest Pharm Des 12:1209–1215, 2006.
174. Terry P, White RI, Barth K, et al: Pulmonary arteriovenous malformations: Physiologic observations and results of balloon embolisation. N Engl J Med 308:1197–1200, 1983.
175. Mager JJ, Overtoom TT, Blauw H, et al: Embolotherapy of pulmonary arteriovenous malformations: Long-term results in 112 patients. J Vasc Interv Radiol 15:451–456, 2004.

CHAPTER 55

PULMONARY EDEMA AND ACUTE LUNG INJURY

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INTRODUCTION

Excessive extravascular water in the lungs (pulmonary edema) is a common clinical problem. It is always a manifestation of a serious underlying disease or disorder. Pulmonary edema can be life-threatening, but effective therapy is available to rescue patients from the deleterious consequences of disturbed lung fluid balance. The cause of the disturbance often can be identified and, in many instances, corrected. Because rational and effective therapy depends on understanding basic principles of normal and abnormal liquid and solute transport in the lungs, this chapter begins with a brief overview of the major factors that govern fluid filtration in the lungs before turning to the pathophysiology of pulmonary edema and acute lung injury (ALI). For further information, the reader is referred to the detailed description of the regulation of fluid balance in the lungs, including its anatomic basis and pharmacologic influences, that is provided in Chapter 6. This chapter emphasizes the diagnosis, treatment, and outcome of pulmonary edema and ALI, with an update from recent randomized clinical trials.

PATHOPHYSIOLOGY OF PULMONARY EDEMA AND ACUTE LUNG INJURY

Pulmonary edema occurs when fluid is filtered into the lungs faster than it can be removed. Accumulation of fluid can have serious consequences on lung function because efficient gas exchange cannot occur in fluid-filled alveoli. Lung structure relevant to edema formation and to the forces governing fluid and protein movement in the lungs has been the subject of classic and more recent reviews.[1-7]

There is always a net outward flux of fluid and protein crossing from the vascular space into the interstitium in the lungs because the balance of driving forces normally causes filtration out of the bloodstream and the microvascular endothelium is a leaky barrier. *Leaky* is a relative term: Lung lymph flow normally is less than 0.01% of lung blood flow. Because fluid filtration in the lungs is not limited to capillaries, the term *microvascular* is used throughout this chapter to refer to the sites where fluid exchange occurs. Because of the vast surface area of the lungs, most fluid and protein exchange in the lungs occurs across the interconnecting network of capillaries

embedded in the alveolar walls. Exchange can also occur across capillaries located in the interstitium at alveolar wall junctions (*corner vessels*) and across small interstitial arteries and veins. Their thick walls and small surface area probably limit fluid exchange in larger vessels in the lungs.

The essential factors that govern fluid exchange in the lungs are expressed in the Starling equation for the microvascular barrier:

$$Jv = LpS[(Pc - Pi) - \sigma d\,(\pi c - \pi i)]$$

where Jv is the net fluid-filtration rate (volume flow) across the microvascular barrier; Lp is the hydraulic conductivity ("permeability") of the microvascular barrier to fluid filtration (a measure of how easy it is for water to cross the barrier); S is the surface area of the barrier; Pc is the pulmonary capillary (microvascular) hydrostatic pressure; Pi is the interstitial ("perimicrovascular") hydrostatic pressure; πc is the capillary (microvascular) plasma colloid osmotic (or oncotic) pressure; πi is the interstitial (perimicrovascular) fluid osmotic pressure; and σd is the average osmotic reflection coefficient of the barrier (a measure of how effective the barrier is in hindering the passage of solutes from one side of the barrier to the other).

The microvascular hydrostatic pressure is the principal force that causes fluid filtration in the lungs. If blood were not flowing through the lungs, the opposing hydrostatic and osmotic forces on either side of the microvascular barrier would be equal, their sum would be zero, and there would be no filtration. It is the pumping action of the heart that causes blood to flow through the lungs, and the microvascular hydrostatic pressure generated in the process establishes the steady-state values of the other driving pressures and causes fluid to filter.[6,8]

According to the Starling equation, the balance between the prevailing transmural hydrostatic pressures (Pc − Pi) and the colloid osmotic pressures ($\pi c - \pi i$) provides the "driving force" for fluid filtration. The actual amount of filtrate that forms at any given driving force is determined by the integrity of the barrier to filtration, which is reflected in the conductivity (Lp) and reflection (σd) coefficients. The equation predicts the development of two fundamentally different kinds of pulmonary edema: the first, *increased pressure pulmonary edema*, occurs when the balance of the driving forces increases, forcing fluid across the barrier at a rate that can no longer be accommodated by lymphatic drainage; and the second, *increased permeability pulmonary edema*, occurs in the presence of ALI that damages the normal barriers to fluid filtration and allows increased conductance of liquid and protein in the lungs. There also is a third type of pulmonary edema caused by impaired lymphatic drainage of filtered fluid, but this has less clinical relevance and is not discussed in detail. The lymphatic drainage of the lungs is an important means of removing filtered fluid and proteins from the perimicrovascular interstitial space.[6,8]

Because the normal microvascular barrier is leaky, the alveolar barrier must serve as the principal protection against the accumulation of alveolar edema. Fluid and protein do not normally move into alveoli because the alveolar barrier has a low permeability even to small molecules (similar to cell membrane permeability) and because the fluid that is filtered is continuously being pumped back into the interstitium by alveolar epithelial cells,[2] drained away from the alveolar walls through the interstitium, and removed by lymphatic vessels and the lung microcirculation.

TABLE 55-1. Safety Factors That Protect the Lungs against Interstitial and Alveolar Edema Accumulation

1. Lung lymphatic system
2. Resorption into blood vessels
3. Drainage into the mediastinum
4. Drainage into the pleural space
5. Extremely low alveolar epithelial barrier permeability
6. Low alveolar surface tension (surfactant)
7. Active transport by alveolar and distal airway epithelial cells

The several factors (Table 55-1) that normally protect the lungs against edema have been called *safety factors*. Under normal conditions, the lymphatic system pumps filtered fluid and protein out of the lungs as rapidly as they are formed, even when filtration of fluid and protein from the bloodstream into the interstitium is increased. Increases in fluid and protein filtration across the microvascular barrier also can be drained away from the alveolar walls down the prevailing pressure gradient into the loose peribronchovascular connective tissue or can be resorbed directly into blood vessels.[4] The lung lymphatics can increase their pumping capacity manyfold, particularly when the microvascular wall has been injured.[6] When the balance of driving forces is upset by higher hydrostatic pressure, the increase in filtration of water across the microvascular barrier is much larger than that in protein flux because the microvascular barrier has a low protein conductance. This results in dilution ("washdown") of interstitial protein concentration and thereby an increase in the balance of the osmotic pressure opposing the higher hydrostatic pressure (because plasma protein concentration remains high). The interstitial gel is also hydrated. Exclusion volume for protein decreases, either because of swelling or because of alteration of composition as hyaluronan is washed out from the interstitium, reducing the concentration of protein by expanding the available volume.

The osmotic safety factors work only when the microvascular barrier is normal (increased pressure edema). If the endothelial barrier is injured and its functional integrity is compromised (increased permeability edema), barrier conductance increases and the osmotic reflection coefficient decreases, making this safety factor much less effective or completely ineffective. The compliance of the interstitial space also protects the lungs against edema. Increases in interstitial volume result in only small elevations of interstitial pressure until the interstitial volume is large. This keeps the hydrostatic driving pressure across the alveolar barrier suitably low. When

interstitial pressure is elevated to greater than pleural pressure, fluid flows across the visceral pleura into the pleural space, where its effects on lung function are relatively minor. Pleural fluid is drained by lymphatics in the parietal pleural and, even when pleural liquid accumulates, does not flow back from the pleural space into the lungs. The extremely low alveolar barrier solute conductance provides an osmotic force that favors absorption of water out of the air space rather than filtration of water into the air space. Fluid that does accumulate in the alveoli is pumped out by active ion transport.[2] There are several mechanisms that can up-regulate the rate of alveolar fluid clearance (see Chapter 10).

In summary, pulmonary edema results from increases in either driving pressures (increased pressure edema) or barrier conductance (increased permeability edema) or both mechanisms. What distinguishes the two types is barrier permeability, which is normal in increased pressure edema but abnormal in increased permeability edema. Fluid flow into the lungs is driven across the barrier in both types of edema by the balance of pressures.

Increased Pressure Edema

Increased pressure pulmonary edema (Fig. 55-1) is caused by an increase in the balance of driving forces for fluid filtration into the lungs. The essential feature of this edema is that the barriers to fluid and protein flow into the lungs are functionally intact. Increased pressure edema is often called *cardiogenic*, *high-pressure*, *hydrostatic*, or *secondary pulmonary edema* but more appropriately would be called *normal barrier pulmonary edema* because it is the barrier resistance to fluid and solute movement into the lungs that distinguishes the types of pulmonary edema.

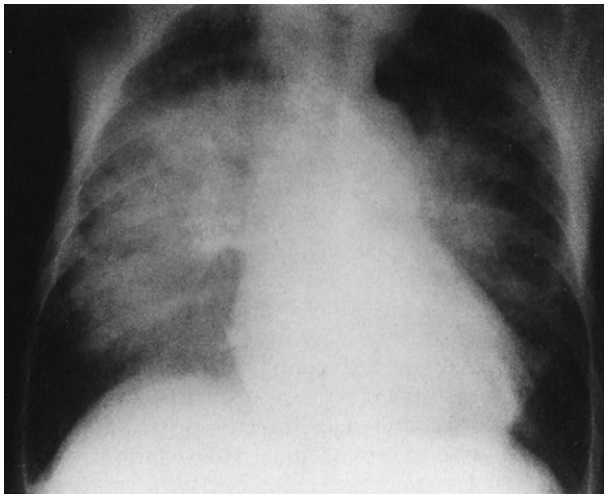

FIGURE 55-1 ■ Chest roentgenogram in a patient with increased pressure pulmonary edema. The heart is enlarged, and the vascular pedicle is widened. The "butterfly" pattern of edema (infiltrates centrally distributed, close to the heart and hila) is often seen with volume overload. The patient had chronic renal failure and volume overload.

Pathophysiology

The flow of fluid and protein into the lungs increases when the sum of driving pressures is elevated. If the rate of fluid accumulation exceeds the rate at which it can be removed, increased pressure edema occurs. Because the barriers limiting fluid and protein flow into the lungs are intact, the lungs are protected against edema by the normal safety factors. Especially important is the ability to protect against increases in the principal driving pressure, lung microvascular hydrostatic pressure. Because of the microvascular barrier's low protein conductance, fluid flow increases much more than protein flow with an elevation in microvascular hydrostatic pressure. Interstitial protein concentration is diluted both by this higher fluid flow relative to protein flow and by a diminished exclusion volume for proteins as the interstitial gel is hydrated and swells. Lower interstitial protein concentration (washdown or washout of interstitial proteins) results in lower perimicrovascular osmotic pressure and thereby a greater protein osmotic pressure difference across the barrier, opposing any rise in hydrostatic pressure. In experimental animals, slightly less than 50% of an increase in hydrostatic pressure is offset by the increase in osmotic pressure difference.[8] Increased pressure edema may be slow and gradual in onset and progression because any elevation in microvascular hydrostatic pressure is attenuated by a rise in osmotic pressure difference across the microvascular barrier, owing to a decline in interstitial protein osmotic pressure.

There are limits to the ability of widening osmotic pressure difference to oppose increases in hydrostatic pressure at the microvascular barrier. Because the barrier is leaky, some protein is always carried into the interstitial space with water by convection, and washdown is limited by the barrier osmotic reflection coefficient. These factors impose limits to the decrease in interstitial protein concentration such that the maximum osmotic pressure difference able to oppose an increase in hydrostatic pressure can at most about double, from close to 10 mm Hg to just over 20 mm Hg. This effect is also limited by the concentration of proteins in the vascular space. At low plasma protein concentrations, the capacity to oppose hydrostatic pressure increases is reduced[9] because the osmotic pressure difference across the barrier cannot be as large as normal. Lymphatic function is essential to this safety factor. Protein flow is greatly enhanced in increased pressure edema because proteins are swept into the lungs with water, and all the extravasated protein must be removed in lymph if washdown is to succeed. Lymphatic function may be compromised by an elevation in hydrostatic pressure at the outflow of the pulmonary lymphatic system into the large thoracic veins, which afford the back-pressure that must be pumped against,[10] and lymphatics in the lungs may be compressed by accumulating edema and rising pressure in the peribronchovascular connective tissue spaces. In long-standing or chronic high-pressure states (e.g., mitral stenosis), lymphatics have been said to proliferate and hypertrophy, improving the effectiveness of the lymphatic system for fluid and protein removal.[1]

TABLE 55-2. Effects of Vascular Congestion and Edema on Pulmonary Function and Lung Mechanics

VASCULAR CONGESTION
Increased diffusing capacity
Increased arterial P_{O_2}
Decreased compliance
Bronchoconstriction
INTERSTITIAL EDEMA
Increased closing volume
Decreased maximal expiratory flow
Increased ventilation-perfusion mismatching
Decreased arterial P_{O_2}
ALVEOLAR FLOODING
Increased closing volume (air trapping)
Increased vascular resistance
Decreased lung volume (especially vital and inspiratory capacities)
Decreased compliance
Decreased diffusing capacity
Right-to-left shunting of blood (severely compromised gas exchange)

The consequences of increased pressure edema on lung mechanics and gas exchange (Table 55-2) depend on how much edema accumulates.[11] Dehydration of normal subjects increases lung volumes and improves tests of ventilatory function,[12] indicating that water in the lungs affects even the normal condition. Early in the progression of edema, increases in hydrostatic pressure result in greater intrapulmonary blood volume (as vessels are recruited or distended by rising pressure), and the diffusing capacity of the lung for carbon monoxide may actually be greater than normal because pulmonary capillary blood volume is increased. Similarly, arterial oxygen pressure (P_{O_2}) may also rise because ventilated units are better perfused when vascular pressures increase.[13] The small, reversible changes in airflow resistance and dynamic compliance, unaffected by vagotomy, that occur in congested lungs appear to be due to reflex bronchoconstrictor responses, but only when baseline bronchial tone is normal.[14]

When interstitial edema is present, closing volume may be increased[15] and maximum expiratory flows may be decreased. These changes were originally believed to be due to a decrease in caliber of small airways caused by compression by rising volume and pressure in the peribronchovascular connective tissue spaces. This effect would have to be in airways larger than bronchioles, because bronchioles and smaller airways do not have loose connective tissue sheaths[1] and their diameter is a function of lung volume, not transpulmonary pressure.[16] Lung compliance may be decreased in interstitial edema, but changes have been found not to be related closely to the amount of lung water[1,17]; decreased lung compliance may be due to decreased lung volume, a reflex phenomenon, or to large airway compression.[18] Arterial P_{O_2} may fall as a result of ventilation-perfusion mismatching, but gas exchange is not seriously compromised until the alveoli are flooded.

With alveolar flooding, lung volumes are diminished.[13] This is most marked in measurements of vital capacity, with inspiratory capacity affected more than expiratory capacity. Airways may close at higher than normal distending pressures, resulting in trapping of larger volumes of gas in the lungs.[19] Lung compliance is reduced when alveolar edema is present because lung volume is decreased.[20] Gas exchange is, of course, severely compromised when flooded alveoli are perfused (right-to-left shunt),[21] and there is an increase in wasted ventilation (ventilation of units where no gas exchange occurs).

Airflow resistance increases more with increased pressure edema than with increased permeability edema, perhaps due to effects on the bronchial circulation: Bronchial veins drain into the right atrium, so increased systemic venous pressure would result in increased bronchial venous and capillary pressures.[21] In addition to changes in airway resistance, pulmonary vascular resistance increases as edema progresses.[22] The cause of decreased pulmonary blood flow with edema is believed to be compression of alveolar wall vessels by the weight of the edema fluid. Increased resistance to blood flow in extra-alveolar vessels occurs at low lung volumes.[23] Blood flow may also be redistributed: Flow decreases at the bases as lung volume is diminished by edema.[24]

Intact red blood cells are often found in the edema fluid in increased hydrostatic pressure edema. Their presence may be due to rupture of a small number of tiny blood vessels with very high pressure, probably at the base of the lungs, where pressure is highest, and mixing of extravasated cells with edema fluid. Increased pressure edema fluid has low protein concentration, and there is no evidence that new pathways for leaking blood into the air spaces are opened up as the pressure climbs. If new pathways were created, the protein concentration of the edema fluid would increase along with the pressure. Protein concentrations in edema fluid decrease as pressure increases, indicating that proteins are effectively sieved by the barrier (passing in proportion to their size).

Light and electron microscopic examination of human and animal lung tissue in increased pressure edema shows alveolar edema and hemorrhage; thickened interstitial compartments (especially large peribronchovascular fluid cuffs) with separated, dispersed collagen fibrils; and increased capillary surface area and volume.[25–29] More intercellular vesicles can be seen, but otherwise no detectable changes in the ultrastructure of the vascular endothelium occur, and the gap widths at intracellular junctions are not different from those in normal lungs. Electron-lucent zones (laminae rarae) may be seen in the basement membranes, particularly where the alveolar-capillary barrier is thinnest. Long-standing edema (e.g., in patients with mitral stenosis) can be associated with basement membrane thickening and increased distance between the alveoli and the capillaries; increases in fibroblasts, histiocytes, and bulky strands of collagenous fibers can be seen in the interstitium. Permeability might

be lowered across these widened barriers.[30] Dogs with pacing-induced chronic congestive heart failure developed a significant increase in the threshold for high-vascular-pressure edema formation (about a 50% reduction in the amount of water and protein cleared across the lung microvascular endothelial barrier at high pulmonary vascular pressures as compared with controls).[31] Morphometric analysis of the alveolar-capillary barrier showed that endothelial, interstitial, and epithelial thickness were increased compared with controls, indicating that remodeling confers an increase in the resistance to development of high-pressure–induced alveolar edema. Alveolar type II cells may be more numerous than in normal lungs, and alveolar macrophages proliferate.[29] Chronic, severe increased pressure edema may also become organized and fibrotic, may calcify, and may even result in bone formation.[32]

Mechanisms

The most common cause of increased pressure edema is elevated lung microvascular hydrostatic pressure. The sum of driving pressures might also be greater if perimicrovascular hydrostatic pressure or the osmotic pressure difference across the microvascular barrier were decreased. At the alveolar barrier, an increase in interstitial hydrostatic pressure, a decrease in alveolar hydrostatic pressure, or a decrease in osmotic pressure difference across the barrier might result in a greater sum of driving pressures. The possibilities are listed in Table 55-3.

Increased Microvascular Hydrostatic Pressure. Congestive heart failure is the most common cause of increased pressure edema. That is why increased pressure edema is often called "cardiogenic" even though the heart is not always primarily involved. Elevated pressures in the pulmonary microvasculature are usually due to left-sided heart failure, with elevated left atrial pressures transmitted retrograde into the pulmonary circulation. Common causes are left ventricular dysfunction (e.g., caused by acute myocardial infarction, severe coronary insufficiency, tachyarrhythmias, bradyarrhythmias, cardiomyopathies, constrictive pericarditis, aortic stenosis or regurgitation, mitral regurgitation, coarctation of the aorta, rupture of chordae tendineae or intraventricular septum, systemic hypertension) or mechanical obstruction of the left atrial outflow tract (e.g., as in mitral stenosis, left atrial myxoma). Left atrial pressure and subsequent pulmonary microvascular pressure can also be elevated by severe volume overloading in a patient with a normal or diseased heart.

An unusual cause of increased microvascular hydrostatic pressure is pulmonary venous hypertension in the absence of left ventricular or atrial disease, which can occur if the pulmonary veins are contracted (e.g., by possible muscular sphincters[33]), compressed, or obstructed (e.g., because of veno-occlusive disease or mediastinal fibrosis[34]). Bronchial venous hypertension does not appear to significantly increase fluid filtration in the lungs.[35]

Increases in fluid filtration can also be associated with increases in vascular pressure proximal to the filtration sites in the lungs. For example, pulmonary hypertension, in combination with depressed left ventricular function, has been implicated in the pathogenesis of cocaine-induced pulmonary edema.[36] Whether such increases lead to pulmonary edema depends on what happens to microvascular pressure. If high right-sided pressures are caused by increased resistance before the main site of filtration in the lungs (e.g., hypoxic pulmonary vasoconstriction of small arterial vessels,[37,38] primary pulmonary hypertension, pulmonary artery or valvular stenosis), edema does not occur. Conversely, if the lung vascular bed is only partially constricted or obstructed, or if the vascular surface area is greatly decreased (e.g., by lung resection), higher flow in perfused vessels leads to increased pressure edema[38] because microvascular pressures at the fluid exchange site are elevated in the overperfused lung. Pulmonary edema occurred in about 15% of patients after pneumonectomy and seemed to be exacerbated by administration of fresh frozen plasma,[39] probably because intravascular volume is increased by such transfusions. Any increase in blood flow through the lungs increases the pulmonary microvascular pressure at the fluid exchange sites even if the pulmonary venous pressure remains constant, because pulmonary microvascular pressure is the sum of pulmonary venous pressure plus the product of pulmonary venous resistance and blood flow.[1] High systemic venous pressure might also promote edema formation by raising the outflow pressure and thereby reducing the flow of lymph.[10]

The mechanisms of two less common causes of pulmonary edema, those occurring at high altitude and during severe neurologic insults, may involve increased microvascular hydrostatic pressure. *High-altitude pulmonary edema*,[40,41] which is also discussed in Chapter 65, appears to be caused by severe pulmonary hypertension that develops in susceptible individuals as a consequence of hypoxic vasoconstriction when the inspired P_{O_2} falls at altitude. Nonhomogeneous obstruction of the pulmonary vascular bed by exaggerated hypoxic vasoconstriction results in high blood flow and transmission

TABLE 55-3. Mechanisms of Increased Pressure Pulmonary Edema

INCREASED LUNG MICROVASCULAR HYDROSTATIC PRESSURE
Left ventricular dysfunction
Mechanical obstruction of left atrial outflow
Volume overload
Pulmonary venous hypertension
Overperfusion
Increased lymphatic outflow pressure
DECREASED PERIMICROVASCULAR HYDROSTATIC PRESSURE
INCREASED ALVEOLAR SURFACE TENSION
Inspiratory airway obstruction

of pressure to portions of the pulmonary vascular bed that are not protected by vasoconstriction, and pulmonary edema results from high intravascular pressure. Patients who develop high-altitude pulmonary edema have been found to have very high pulmonary arterial pressure (sometimes at systemic levels). The excessive rise in pressure precedes the development of the edema, and agents that lower pulmonary arterial pressure (e.g., oxygen, nifedipine, hydralazine, phentolamine, inhaled nitric oxide, and inhaled β_2-agonists) are effective in prevention or treatment, or both.

Postmortem edema fluid has been described as proteinaceous in high-altitude pulmonary edema, and measurements of edema fluid protein concentration have been made in two patients.[42] In one, the edema fluid–to–plasma protein concentration ratio (0.6) was in the range predicted for increased pressure edema; in the other, the ratio (0.8 in one sample, 1.1 in another) was in the range typical of increased permeability pulmonary edema. Bronchoalveolar lavage (BAL) fluid of six climbers with high-altitude pulmonary edema showed a marked increase in high-molecular-weight proteins (as well as many red blood cells and alveolar macrophages).[43] Because water is resorbed from edema fluid in the alveoli much faster than protein,[44,45] the protein concentration of edema fluid increases progressively as edema resolves. The high protein concentration of postmortem high-altitude pulmonary edema and BAL fluids may be due to observations made during a time when fluid was being resorbed from, rather than added to, alveoli.

As noted earlier, overperfusion of a restricted pulmonary vascular bed, even in the absence of hypoxia, causes increased pressure edema, not increased permeability edema.[38] This can explain why some cases of high-altitude pulmonary edema are correctly classified as increased pressure pulmonary edema. Evidence from climbers studied at high altitude suggests that high intravascular pressures cause physical damage to vascular walls (so-called stress failure), which has been shown to occur at extreme, but sometimes transient, increases in pulmonary vascular pressures in experimental animals.[46–48] Such structural failures need not occur in large numbers to explain even severe increased permeability edema, because edema would form readily and in a quantity driven by the prevailing elevated vascular pressure.[49] The suggestion has been made that high-altitude pulmonary edema results from the stress failure of overdistended, relatively thin-walled pulmonary arteries rather than from microvascular rupture,[50] which might help explain why the prevailing vasoconstriction does not seem to offer much protection to downstream vessels, why there are no reports of gradual progression through an indolent prodrome of increased pressure edema before stress failure occurs, and why high-altitude pulmonary edema is first detected radiographically in the central lung fields surrounding large vessels rather than in the lung bases and periphery.

Plasma selectins have been measured in subjects at high altitude.[51] Levels of E-selectin were inversely related to arterial oxygen saturation in control subjects and in subjects with acute mountain sickness and with high-altitude pulmonary edema. Because endothelial cells are the only known source of E-selectin, increased plasma levels were considered to be a sign of activation or injury of endothelial cells. Plasma levels of P-selectin were not found to be elevated at high altitude.

Alternative mechanisms for the increased permeability in high-altitude pulmonary edema have been proposed. However, inflammatory responses in high-altitude pulmonary edema are probably a consequence rather than a cause of the edema.[40,52,53] The rapid reversibility of high-altitude pulmonary edema with descent to lower elevation, oxygen therapy, or pharmacologic reduction of pulmonary vascular pressure is not characteristic of ALI and increased permeability pulmonary edema suspected to be caused by or related to inflammation. Also, some work supports the conclusion that this disorder is primarily a hydrostatic type of pulmonary edema.[54]

Neurogenic pulmonary edema[55] also may be related to elevated pulmonary vascular pressures. Measurements of edema fluid protein concentration relative to plasma protein concentration in 12 patients with neurogenic pulmonary edema have been reported.[56] Seven of the patients had ratios typical of increased pressure pulmonary edema, and the other 5 had ratios consistent either with increased permeability pulmonary edema or with sampling during the resolution phase of increased pressure pulmonary edema (when edema fluid protein concentration rises as fluid is resorbed from the alveoli at a faster rate than protein). Measurements in 8 patients had previously been reported; 2 of the measurements indicated increased pressure edema, and 6 indicated increased permeability edema or sampling during the resolution phase. Thus, half the cases of neurogenic pulmonary edema in which edema fluid protein concentration has been measured appear to involve increased pressure edema, and the fraction is perhaps even higher, depending on the timing of edema sampling.

Measurements of the alveolar-to-plasma protein concentration ratios in dogs with neurogenic pulmonary edema induced by intracisternal veratrine showed a wide range of values, indicating that both increased pressure and increased permeability mechanisms may be involved to varying degrees in that type of neurogenic pulmonary edema.[57] In other animal experiments, filtration increases in neurogenic edema[58–61] and edema following transient pulmonary hypertension[62] were attributable to increased pressure or increased vascular surface area, or both, perhaps in combination with acute lymphatic insufficiency. Animal studies can be difficult to interpret. Some models have been complicated by primary lung injury that is separate from effects on the central nervous system[63] or by evidence that vascular permeability was abnormal in control experiments[62] performed in surgically traumatized, acutely prepared animals.[64]

Both human and experimental neurogenic pulmonary edema can be associated with massive discharge of the sympathetic nervous system, resulting in systemic vasoconstriction and translocation of blood from the systemic to the pulmonary circulation, producing marked increases in pulmonary blood flow and vascular pres-

sures. Peak pulmonary arterial pressure can reach systemic levels. Hydrostatic pressure at the fluid exchange sites in the lungs can also be elevated by catecholamine-induced left ventricular dysfunction, increased pulmonary venous resistance, and mitral valve insufficiency secondary to left ventricular dilation. Thus, as in high-altitude pulmonary edema, high pulmonary vascular pressures could result in either increased pressure edema (from elevated microvascular hydrostatic pressure) or increased permeability edema (if pulmonary vascular pressures were high enough to cause stress failure of pulmonary vessels). Whether neurogenic pulmonary edema can occur by pressure-independent mechanisms remains controversial and unproved.[55] Some episodes of neurogenic edema may involve increased pressure; others appear to involve increased permeability. More information is needed to sort out the precise causes.

Decreased Perimicrovascular Hydrostatic Pressure. The sum of driving pressures would be greater if perimicrovascular hydrostatic pressure was diminished, thereby resulting in an increase in fluid and protein filtration at the microvascular barrier in the lungs. Pulmonary edema has been described in circumstances in which this might occur. The best clinical example is *postobstructive pulmonary edema* as a consequence of upper airway obstruction or its release, which can be caused, for example, by laryngospasm, endotracheal tube obstruction, foreign body aspiration, epiglottitis, croup, severe acute asthma, airway compression by tumors, strangulation, or hanging. High negative intrathoracic pressures generated by inspiratory attempts against the occluded airway are transmitted to the interstitium, promoting fluid movement into the interstitium. Mechanical effects on the cardiovascular system likely contribute to this kind of edema: High negative intrathoracic pressure causes increases in cardiac preload and afterload and in pulmonary blood flow, all of which increase the microvascular pressure that drives fluid out into the interstitium. Three patients with upper airway obstruction and pulmonary edema were reported, all with low edema fluid protein concentration relative to plasma protein concentration (ratios of 0.44, 0.31, and 0.52), indicating increased pressure pulmonary edema.[65]

Aspiration of air or fluid from the pleural space with consequent reexpansion of a collapsed lung could result in a decrease in perimicrovascular hydrostatic pressure as the lung expands to fill the thorax. So-called *reexpansion pulmonary edema* has been reported in experimental animals[66,67] and in patients[68,69] after lung reexpansion, but the high edema fluid protein concentration measured in three patients[70,71] indicated that reexpansion may result in an increased permeability edema rather than an increased pressure edema. However, one study of protein concentration in pulmonary edema fluid from patients with reexpansion edema indicates that hydrostatic mechanisms are important.[72] The increased permeability hypothesis was supported in studies of rabbits with experimental reexpansion edema.[73,74]

Reexpansion pulmonary edema may be a form of ischemia-reperfusion injury,[75] with the increase in lung microvascular permeability being related to restoration of blood flow, formation of oxygen free radicals, release of proinflammatory mediators, and activation of neutrophils. On reperfusion, pulmonary vascular resistance shifts more toward postcapillary venules, which elevates pressure in the microvascular vessels at the fluid exchange sites in the lungs and would aggravate edema formation across the injured barrier.[76] A patient with apparent reperfusion pulmonary edema complicating thrombolytic therapy for pulmonary embolism has been reported,[77] and reperfusion injury is probably one of the causes of the pulmonary edema that occurs in transplanted lungs.[78] Hemorrhagic and traumatic shock have also been conceived of as types of a "whole-body ischemia-reperfusion syndrome."[79]

If high alveolar surface tension were transmitted to the interstitium, perimicrovascular hydrostatic pressure would also be lowered, thereby increasing filtration across the microvascular barrier. Such an effect has been suggested by experimental findings in dog lungs.[80,81] The effect of alveolar surface tension on lung fluid balance is discussed later.

Decreased Transmural Osmotic Pressure Difference. The sum of driving pressures would be increased if the osmotic pressure difference opposing the hydrostatic pressure difference across the microvascular barrier were decreased (by lowering plasma protein concentration or by raising interstitial protein concentration), resulting in an increase in the sum of driving pressures for fluid and protein flow into the lungs. This theoretical mechanism of increased pressure edema has been the subject of study in experimental animals, with contradictory results. In some studies, hypoproteinemia was not found to increase lung microvascular liquid conductance or protein permeability.[82,83] Because the microvascular-perimicrovascular osmotic pressure gradient is generated by the microvascular hydrostatic pressure and by the barrier descriptors (conductivity and reflection coefficient), it is not possible to decrease the osmotic pressure gradient by depleting plasma proteins except transiently while a new steady state is being established. Although fluid flow would be increased temporarily, it would return to normal when a new steady state is reached, unless hydrostatic pressure or barrier characteristics were also changed. This is not to imply that protein concentrations are not important forces in lung fluid balance. Although an isolated decreased osmotic pressure gradient across the microvascular barrier cannot be sustained or be an important mechanism for increased pressure edema, the absolute concentration of protein has a profound effect on lung fluid balance when hydrostatic driving pressure is increased. When plasma osmotic pressure is low, the ability of the osmotic pressure gradient to widen in response to increased hydrostatic pressure is diminished, and edema accumulates at hydrostatic driving pressures lower than those needed to cause edema when protein concentration is normal.

Alveolar Barrier Function. The driving pressure for fluid and protein flow across the alveolar barrier would be elevated, resulting in increased pressure edema, if the interstitial hydrostatic pressure were raised

or if the alveolar hydrostatic pressure or the osmotic pressure difference across the alveolar barrier were lowered. Because the osmotic pressure difference across the barrier is established by the relevant hydrostatic forces and barrier descriptors (as across the microvascular barrier), an isolated decrease in the osmotic difference could result in only a transiently increased pressure filtration until a new steady state is achieved. This transient phenomenon would not be an important mechanism for increased pressure edema in the alveolar spaces.

Interstitial hydrostatic pressure rises as interstitial edema accumulates in the lungs.[4,84] Increased interstitial hydrostatic pressure would raise the sum of driving pressures across the alveolar barrier and could drive edema formation across the alveolar or airway epithelium. The role of interstitial hydrostatic pressure in edema formation is not simple, however. Although increased interstitial hydrostatic pressure favors edema formation across the alveolar barrier, it opposes edema formation across the microvascular barrier. The relative contributions of these disparate effects have not been separated. The osmotic pressure difference across the intact alveolar barrier provides a powerful force that opposes filtration increases driven by hydrostatic pressure. Because the barrier is normally virtually impermeable even to small solutes, filtration of water would result in a decrease in alveolar osmotic pressure. A decrease of only 1 mOsm (<0.5% of the normal alveolar osmotic pressure) would balance a 19 mm Hg increase in interstitial hydrostatic pressure.

Greater pressure filtration across the alveolar barrier would also result from an increase in the sum of driving pressures if alveolar hydrostatic pressure were lowered. This is complicated by the interrelation between alveolar and interstitial hydrostatic pressures.[4,85] A drop in alveolar hydrostatic pressure, which increases the sum of driving pressures across the alveolar barrier, also results in a lowering of interstitial hydrostatic pressure, which decreases the sum of driving pressures across the alveolar barrier but increases the sum of driving pressures across the microvascular barrier. The influence of alveolar surface tension on lung fluid balance has been investigated in dogs. Administration of a detergent aerosol resulted in loss of surfactant activity, higher alveolar surface tension, lower static compliance, atelectasis, and pulmonary edema; low protein concentration in alveolar edema fluid and left-hilar afferent lymph relative to plasma protein concentration indicated that this was an increased pressure type of pulmonary edema.[86,87] Because increased pressure edema can impair surface activity of dog lung extracts[88] and isolated rabbit lungs,[89] it is possible that changes in alveolar surface tension may accelerate edema formation. However, the notion that changes in alveolar surface tension in edema lead to a self-perpetuating vicious circle of edema formation is not borne out clinically.

The only kind of clinical pulmonary edema caused by transmural osmotic pressure differences is near drowning.[90,91] Seawater is three times more hyperosmotic (1000 mOsm) than plasma, so the volume of fluid in the air spaces after salt water aspiration increases threefold to reach osmotic equilibrium, thus markedly increasing the alveolar edema already present because of the volume of seawater itself in the alveoli. Osmotic equilibrium is reached in minutes as water is drawn from the vasculature into the alveoli by osmotic pressure.[90-92] Alveolar barrier function is not significantly compromised (unless perhaps the patient aspirates gastric contents or the seawater is contaminated or rich in particulate matter), and the alveolar edema is cleared very rapidly (50%–60% of excess alveolar fluid is cleared in 4 hr). However, transient, minimal disturbances in endothelial barrier function may occur if cellular water loss causes cell shrinkage, thereby opening up paracellular pathways (junctions between cells) for fluid and solute movement. Freshwater near drowning proceeds in the opposite fashion: osmotic equilibrium is reached rapidly by flow of water out of the alveoli into the interstitium and bloodstream. Severe hemodilution, with hemolysis and fibrinolysis, also occurs, and the rapid water flux and hypotonicity cause severe distortion of pulmonary ultrastructure, including damage to type I and type II cells, endothelial cell swelling, basement membrane detachment, and cell disruption. Both alveolar epithelium and microvascular endothelium can thus be injured by the hypotonic fluid, leading to increased permeability pulmonary edema rather than a normal barrier type of pulmonary edema.

Increased Permeability Edema and Acute Lung Injury

Increased permeability pulmonary edema (Fig. 55-2) is caused by an increase in liquid and protein conductance across the barriers in the lungs. The essential feature of

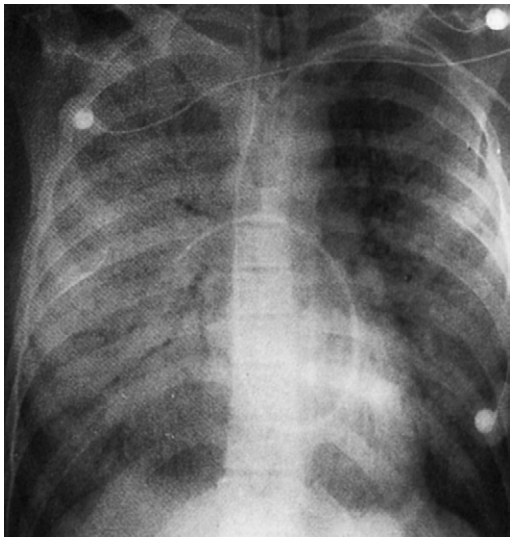

FIGURE 55-2 ■ Chest roentgenogram in a patient with increased permeability pulmonary edema. The heart is not enlarged, and the vascular pedicle is of normal size. Edema is peripheral and not gravitationally distributed. Air bronchograms are present, a finding more common in increased permeability edema than in increased pressure edema. The patient had drug overdose, coma, and hypotension.

this edema is that the integrity of the barrier to fluid and protein flow into the lung interstitium and the alveoli is altered. Increased permeability edema is sometimes called *noncardiogenic* or *primary pulmonary edema*, and the resulting clinical syndromes in humans are commonly lumped together as *ALI* or the *acute respiratory distress syndrome* (ARDS).[93,94]

Pathophysiology

Accumulation of fluid and protein increases when the lung endothelial and epithelial barriers are injured. If the rate of fluid accumulation exceeds the rate at which it can be removed, increased permeability edema occurs. Because the barriers limiting fluid and protein flow into the lungs do not function normally when the lungs are injured, the lungs are not protected against edema by the usual safety factors. Although increases in fluid and protein filtration across the barriers are removed by lymphatics and drained away from the alveolar walls as in increased pressure edema, much more fluid and protein are filtered at any given sum of driving pressures because the barriers to their flow are much less restrictive than normal. Edema formation in injured lungs is very sensitive to driving pressures.[49] Driving pressures are often increased when the lungs are injured because of the vasoconstrictive effects of inflammatory mediators such as thromboxanes, which may shift the main site of resistance to postcapillary venules, thus increasing hydrostatic pressure at the microvascular fluid exchange sites,[95] or because of effects on the heart as well as on the circulation. For example, elevated left atrial pressure, pulmonary venoconstriction, and an increase in cardiac output in sepsis can increase hydrostatic pressure at the microvascular fluid exchange sites.[96] Microvascular hydrostatic pressure in injured lungs is not related simply to pulmonary artery occlusion ("wedge") pressure, and such measurements can be misleading.

Because the barriers are leaky, protective osmotic pressure differences are lost across them; driving pressure is unopposed by osmotic pressure, and even normal hydrostatic pressure results in significant fluid and protein extravasation into interstitial and alveolar spaces. The ability of the lymphatics to pump the excess filtrate away is increased when the lungs are injured. Maximal lung lymph flow increases more when the microvascular wall has been injured than when hydrostatic pressure alone is increased (as a result of poorly understood "edema-dependent lymphatic factors"), but even this augmented lymphatic pumping capability is taxed at low driving pressures. If the epithelial barrier is injured, edema may accumulate readily in the alveoli, because most of the resistance to fluid and protein flow into the alveoli is in the epithelial barrier.[97,98] Increased permeability edema is often rapid in onset and progression because injured barriers offer much less resistance to flow and because hydrostatic driving pressure is unopposed by increases in osmotic pressure difference. Clinically, patients with increased permeability edema usually have a low intravascular hydrostatic pressure, commonly measured as a low or normal pulmonary capillary wedge pressure. In some cases, this reflects the low intravascular pressures associated with the underlying disease process (e.g., sepsis).

The consequences of increased permeability edema on lung mechanics and gas exchange depend on how much edema accumulates and how severe the causative lung injury is.[99] As with increased pressure edema, the major effects on pulmonary mechanics occur with alveolar flooding. In experimental lung injury, functional residual capacity was found to be decreased as a consequence of alveolar flooding, and this loss of ventilated units accounted for virtually all the observed decrease in static lung compliance.[100,101] Computed tomography has provided new insights into structure-function relationships in human ALI.[102,103] In the early stage of lung injury, when alveolar edema predominates, the lungs are characterized by a homogeneous alteration of vascular permeability, and edema accumulates evenly in all lung regions with a nongravitational distribution. Increased lung weight due to edema causes collapse of lung regions along the vertical axis through the transmission of hydrostatic forces (compression atelectasis, caused by the weight of edema). Thus, collapse occurs mainly in the dependent lung, where the superimposed weight from above is greatest.

Measurements of pulmonary mechanics in mechanically ventilated patients with ALIs[99] showed decreased static lung compliance as a consequence of this loss of ventilated lung. In addition, airflow resistance was increased as a result of decreased lung volume. Bronchospasm adds to the increase in airflow resistance and can be substantially reversed with bronchodilator inhalation.[104] Chest wall compliance was reduced, probably because of alterations of intrinsic mechanical properties of the chest wall by abdominal distention, chest wall edema, and pleural effusion.[99] Different respiratory mechanics and response to positive end-expiratory pressure (PEEP) during mechanical ventilation were reported in patients with ARDS originating from pulmonary disease (pneumonia, which caused consolidation) or from extrapulmonary disease (which caused edema and subsequent alveolar collapse).[105] Lung elastance was higher in pneumonia, whereas chest wall elastance and intra-abdominal pressure were higher in patients with extrapulmonary causes of their lung injuries. In pneumonia, PEEP appeared to distend normal alveoli, which are more compliant that involved alveoli, whereas in extrapulmonary causes of ALI, PEEP appeared to recruit previously collapsed alveoli.

Although the effects of surface forces on decreased lung compliance in ALI were believed to be small, results of experiments in isolated rabbit lungs indicated that increased permeability edema may result in more severe mechanical changes than equivalent degrees of increased pressure edema.[89] In contrast, experiments in awake sheep showed that similar degrees of pulmonary edema, regardless of the mechanism, caused similar changes in compliance and gas exchange.[21] Other experiments showed that dynamic and static lung compliance decreased early in evolving lung injury.[106] Surfactant is strongly thromboplastic, and coagulation may

compound surfactant depletion when plasma proteins enter the air spaces. The injured lung may release substances that can interfere with the normal low surface tension in the alveoli,[107] and activated polymorphonuclear leukocytes (PMNs) have been shown to impair surfactant function in vitro and to degrade the major surfactant apoprotein by a combination of proteolysis and oxidant-radical–mediated mechanisms.[108] Human lung surfactant obtained by BAL of patients at risk for ALI and patients with established ALIs has been reported to be abnormal in chemical composition and functional activity.[109] Abnormalities also could be caused by interactions between surfactant and edema proteins, because plasma proteins (especially fibrin monomers but also fibrinogen and albumin) interfere with surfactant function. Proteinaceous edema fluid has been associated with surfactant inhibition in various experimental models.[110–112] The role of surfactant in the development and treatment of ALI and the potential role for surfactant therapy are discussed in more detail later in this chapter.

As in increased pressure edema, gas exchange is severely compromised in increased permeability edema, owing both to intrapulmonary shunting of blood and to ventilation-perfusion inequalities.[113,114] The available evidence taken together does not support the concept that tissue oxygenation may be further compromised by an abnormality in the regulation of oxygen extraction, which has been hypothesized to occur in patients with ALI (so-called pathologic dependency).[115,116]

Patients with early ALI have a marked increase in their pulmonary dead-space fraction, indicating that many ventilated lung units are not well perfused, although intrapulmonary shunting may also contribute to the elevated dead space.[117] This finding explains why the minute ventilation is twice normal (~12 L/min) at the onset of the ARDS. An elevated pulmonary dead-space fraction also has been reported in pediatric patients with ALI.[118]

Mechanical and gas-exchange abnormalities change with time during the course of ALI. The early, exudative stage of injury, in which edema predominates, is characterized by small effective alveolar space (so-called baby lung) and true shunt; the later, proliferative stage of injury, in which fibrosis and remodeling predominate, is characterized by small and stiff lungs, with superimposed emphysema-like alterations (bullous disease), decreased alveolar ventilation, and ventilation-perfusion maldistribution rather than true shunt.

Other consequences of ALI (beyond those related to edema formation) probably depend on the cause and extent of injury. Bronchoconstriction, caused by injury and mediator release, may add to mechanical and gas-exchange abnormalities. Vascular reactivity to hypoxia and other stimuli may also be altered in the injured lung's vascular bed.[119–121] Perhaps because lung metabolic function is compromised, the injured lung may add or fail to extract vasoactive substances (e.g., biogenic amines, arachidonic acid metabolites, and drugs) from the blood, and angiotensin-converting enzyme (ACE) activity may be abnormal.[122] This could have effects on the heart and the systemic circulation as well as on the pulmonary circulation. Changes in the surface of microvascular endothelial cells may lead to activation of the clotting cascade.[123] Disseminated intravascular coagulation, often associated with endotoxemia and gram-negative infections, is an ominous complication associated with thromboses, hemorrhage, and endothelial cell injury in the lungs and other organs. Abnormalities of fibrin turnover[124] and lung fibrinogen uptake[125] have been reported in ALIs. There is also mounting evidence that there is a procoagulant and antifibrinolytic environment in the distal air spaces and the plasma of patients with early lung injury.[126,127] Pulmonary vascular resistance between arteries and veins also may increase as a result of morphologic alterations of the microvascular endothelium or disruption and loss of the pulmonary vascular bed.[128] If the lungs have severe structural damage, mechanical and gas-exchange abnormalities may be much greater than can be explained by edema accumulation alone.

The light and electron microscopic appearance of human[128–136] and animal[137–139] lung tissue in ALI is variable. Lung morphology depends on the severity and the duration of injury and the treatments administered in addition to the cause of injury. Exudative, proliferative, and fibrotic changes usually appear in sequence.

The earliest changes are marked by widespread alveolar and interstitial edema and hemorrhage. Injury to alveolar ducts may be particularly severe. Hyaline membranes, composed of precipitated plasma proteins, fibrin, and necrotic debris, can be seen. The alveolar epithelium may be more extensively damaged than the vascular endothelium, even if the underlying insult is bloodborne. Widespread, local areas of destruction of type I alveolar epithelial cells alternate with normal-appearing alveoli. The injured alveolar epithelium is swollen, disorganized, discontinuous, and often lifted off exposed, but usually intact, basement membranes, which are covered by hyaline membranes. Type I cells are more severely damaged than type II cells, and the thin cytoplasmic extensions of the cells far from the nucleus covering the thin side of the alveolar-capillary barrier may be most severely affected. The interstitium is widened by edema (especially in peribronchovascular cuffs) and may be choked with leukocytes, platelets, red blood cells, fibrin, and debris (especially near the alveolar walls). The thick portion of the alveolar interstitium is usually involved more than the thin portion. The microvascular endothelium is relatively preserved, usually showing little other than irregular, focal thickening as a result of cytoplasmic swelling or vacuoles and greater numbers of luminal leukocytes. Intracapillary thrombi are rare in this and subsequent phases. Large endothelial gaps are not seen, probably because they would be incompatible with even brief survival because massive edema pours across even small, focal gaps. The alveolar capillary is the usual site of injury, but some insults involve other vessels (e.g., focal gaps in arterioles less than 1 mm in diameter in air emboli–induced lung injury).

The exudative phase is followed by a proliferative phase, which begins within the first week after onset of injury.[133,140] The relative contributions of the original insult, repair processes, and effects of therapies to this

and subsequent phases are not well known, but some of the abnormalities that occur after the initial exudative phase seem to be related to the effects of traditional modes of mechanical ventilation that used tidal volumes between 12 and 15 mL/kg predicted body weight. In the proliferative phase, fluid has been reabsorbed from the air spaces. Fibrin may be prominent in alveoli and interstitium, and there is infiltration with inflammatory cells and fibroblasts (which may have been activated very early in the course of lung injury). The alveolar epithelium is often cuboidal, made up largely of proliferating type II cells. The air-blood barrier can be greatly thickened by interstitial and epithelial enlargement. The pulmonary vascular bed may be partially or completely disrupted, and structural alterations may greatly reduce its surface area. The proliferative phase can present clinically as an inflammatory syndrome with fever, leukocytosis, low systemic vascular resistance, diffuse alveolar infiltrates, diffuse and intense pulmonary uptake of gallium, and neutrophilia on BAL, all in the absence of any infection.[141]

A final stage may follow, often about 2 weeks after the initial insult, in which fibrotic changes of the alveolar ducts, alveoli, and interstitium predominate. Alveoli may be obliterated, alveolar walls coalesced, and functional lung units lost. The lungs may be emphysema-like, with extensive bullous changes.[133] Even severe changes at any stage may be reversible, with slow recovery toward normal lung function in patients who survive.[142,143]

Mechanisms

Most of the conditions that have been associated with ALI in humans are listed in Table 55-4. The most common causes are pneumonia, sepsis, gastric aspiration, and major trauma. The insult to the lungs occurs via either the airways or the bloodstream. The exact mechanisms by which the lungs are injured have been the subject of intense investigation in humans, animal models, and cellular systems.[94] Human studies have provided descriptive data about the events that occur in the air spaces before and after the onset of lung injury. Studies using BAL in patients before and after the onset of ALI have shown that there is a major acute inflammatory response that begins before ALI is clinically recognized, peaks during the first 1 to 3 days of clinically defined ALI, and resolves slowly over 7 to 14 days in patients who remain intubated.[141-143] These studies have shown the complexity of the evolving inflammatory responses, which are characterized by the accumulation of acute response cytokines and their naturally occurring inhibitors, oxidants, proteinases and antiproteinases, lipid mediators, growth factors, and collagen precursors involved in the repair process.[144-155] Extensive efforts have been made to find single biologic markers that predict the onset or the outcome of ALI, but these have met with only limited success.[156]

Hypotheses about mechanisms of lung injury have been tested in animal models and in vitro studies, and several reviews have summarized the findings.[157] The existing animal models do not completely reproduce all of the aspects of ALI in humans, in part because human ALI evolves over a longer period of time than can be studied in the laboratory. In addition, the lungs of humans are exposed not only to the initial injurious insult but also to the therapies that are used to treat ALI, such as mechanical ventilation. Experiments with isolated cells have been useful to test specific concepts, but the

TABLE 55-4. Clinical Disorders Associated with Acute Lung Injury

INFECTIOUS CAUSES
Gram-negative or gram-positive sepsis
Bacterial pneumonia
Viral pneumonia
Fungal pneumonia
Parasitic infections
Mycobacterial disease

ASPIRATION
Gastric acid
Food and other particulate matter
Fresh or sea water (near drowning)
Hydrocarbon fluids

TRAUMA
Lung contusion
Fat emboli
Nonthoracic trauma
Thermal injury (burns)
Blast injury (explosion, lightning)
Overdistention (mechanical ventilation)
Inhaled gases (phosgene, ammonia)

HEMODYNAMIC DISTURBANCES
Shock of any etiology
Anaphylaxis
High-altitude pulmonary edema
Reperfusion
Air embolism
Amniotic fluid embolism

DRUGS
Heroin
Methadone
Propoxyphene
Naloxone
Cocaine
Barbiturates
Colchicine
Salicylates
Ethchlorvynol
Interleukin-2
Protamine
Hydrochlorothiazide

HEMATOLOGIC DISORDERS
Disseminated intravascular coagulation
Incompatible blood transfusion
Rh incompatibility
Antileukocyte antibodies
Leukoagglutinin reactions
Post–cardiopulmonary bypass, pump oxygenator

METABOLIC DISORDERS
Pancreatitis
Diabetic ketoacidosis

NEUROLOGIC DISORDERS
Head trauma
Grand mal seizures
Increased intracranial pressure (any cause)
Subarachnoid or intracerebral hemorrhage

MISCELLANEOUS DISORDERS
Lung reexpansion
Upper airway obstruction

complexity and redundancy of intact biologic systems are not reproduced in simplified experimental systems. Most experimental work purposely limits a study to a single causative agent; however, this turns the reality of clinical complexity into the simplicity of a single experimental pathway. Increased permeability edema in humans is likely to be caused by interactions between a number of different pathways acting in parallel or in series.

Studies in isolated organs and small animals in which hemodynamic variables are not measured can be difficult to evaluate because indices of lung injury, usually measured by the appearance of markers in lungs, lavage fluid, or perfusate, are not determined solely by the barrier function of the microvasculature. For example, when the vascular endothelium is injured, fluid and protein movement from the vascular space into the lungs is extremely sensitive to hydrostatic driving pressures and surface area for filtration,[49] and the effects of experimental interventions may be caused by changes in these parameters and not solely by changes in microvascular barrier function. The effects of microvascular driving pressures and surface area can be difficult to evaluate even in large, instrumented animals. In sheep and goats, interpretation of lung lymph fluid and protein flow changes are further complicated by contributions from lymphatics outside the lungs,[158,159] physical forces acting on lymphatics,[160] and possible intranodal modification of lymph.[161] Data from experimental animal models suggest that there are at least two broad categories of mechanisms of ALI: those that are *indirect* (i.e., requiring the participation of intermediary mechanisms, such as host defenses) and those that are *direct* (i.e., not requiring intermediary mechanisms, with injury probably occurring as a result of contact between an offending substance and lung tissue). These categories overlap because, once the lungs are injured, inflammatory responses occur, which may compound the primary mechanism of injury. Three major hypotheses about the mechanism of ALI are discussed next. Each is discussed separately, but they are interrelated. A recent review provides specific information on animal models of ALI.[157]

Infection. ALI develops in 20% to 45% of patients with severe sepsis.[162–164] Increased microvascular permeability to albumin has been shown to accompany human sepsis,[165] and infection and the sepsis syndrome are major causes of ALI in humans.[166] Patients who develop shock in response to known or suspected infection have a particularly high incidence of ALI, and the mortality of patients with ALI associated with infection, the sepsis syndrome, or bacteremia is increased.[166–169] ALI also appears to predispose the lungs to infection, and delayed infection is an important cause of morbidity in patients who survive the initial lung insult.[170–173]

The mechanism by which infection and the sepsis syndrome injure the lungs is not certain.[174] It seems likely that lung injury may be related to factors other than direct damage by bacteria or other microorganisms because prognosis has not been found to be related to documented bacteremia or pneumonia.[175,176] In experimental animals, intravenous infusions of live *Pseudomonas aeruginosa*,[177] endotoxins from *Escherichia coli*,[178–180] and surgically induced peritonitis[181] all resulted in increased permeability pulmonary edema in sheep. Instillation of endotoxin into the airways of sheep also led to lung inflammation with variable degrees of lung injury.[182,183] *P. aeruginosa* has also been reported to cause lung injury in pigs, and *E. coli* endotoxin has been reported to injure the lungs of baboons[184] and dogs[185] and to result in neutrophilic alveolitis in rats.[186] ALI caused by endotoxin in sheep is believed to be an inflammatory response mediated at least in part by PMNs and by tumor necrosis factor (TNF). Endotoxin can also affect the clotting system and metabolic functions of the lungs,[187] and it may dispose the lung to the development of pulmonary infections by increasing adherence of bacteria to endothelium.[188] However, ALI in septic humans does not appear to be necessarily related to endotoxemia, because endotoxin may be undetectable or present only in low concentrations in septic patients. In one study, endotoxin was detected in plasma samples of 74% of patients believed to be at risk who subsequently developed ARDS, 64% of patients who already had ARDS, and 22% of patients believed to be at risk who did not develop ARDS.[189] Exoproducts of bacteria, such as elastase and *Pseudomonas* exoenzyme U, also have been shown to injure the lungs.[190,191]

In addition to a direct role in the pathogenesis of lung injury, bacterial products and mechanical stretch interact in a synergistic and bidirectional manner to enhance lung inflammation and injury.[192,192a] Gram-negative lipopolysaccharide (LPS) causes an acute inflammatory response in the lungs of humans.[193] Bacterial LPS enhanced the responses of human alveolar macrophages to positive-pressure ventilation,[194] and pretreatment of rats with intravenous LPS enhanced cytokine production in the lungs during mechanical ventilation ex vivo.[195] In turn, mechanical ventilation with moderate or large tidal volumes increases the sensitivity of lung macrophages to LPS in vitro and increases the expression of the LPS recognition molecule, CD14, on lung cells in vivo.[196] Mechanical ventilation also amplifies the effects of circulating LPS on lung inflammation.[197] Endotoxin recognition pathways are increased in the lungs of patients with ARDS, and the biologic effects of LPS are amplified in the lungs of patients with lung injury.[198,199] Bacterial LPS and mechanical ventilation interact to activate a series of key biologic transcription modules in the lungs.[200] The synergism between bacterial products and mechanical stretch suggests that interrupting these pathways could limit some forms of ALI in humans.[192]

Increased pressure edema and increased permeability edema are associated with impaired antibacterial defenses,[201,202] and bacterial infections worsen ALI in dogs,[203] baboons,[204] and hamsters.[205] The cause of impaired bacterial defenses in ALI is not known. Bactericidal properties of the alveolar lining material might be altered in injured or flooded lungs, and alterations in surfactant concentration and function may be important.[206] Although PMNs may be present in large numbers in the BAL fluid of patients with ALI, evidence indicates the function of these PMNs is compromised.[207,208]

Inflammation. Substantial evidence implicates host defenses and inflammatory responses in the underlying mechanism of many ALIs. Neutrophils, complement, and

other humoral mediators of inflammation, injury, and repair are discussed in detail in Chapter 17. The neutrophil has a dual role in inflammation and lung injury. PMNs are a vital component of host defenses, and patients with severe neutropenia are at increased risk of bacterial and fungal infections. Conversely, PMNs release toxic oxygen radicals, proteases, and other biologically active mediators that initiate inflammation. Other important cells include alveolar[209] and pulmonary intravascular macrophages[210] and eosinophils.[211] The major mediators of the acute inflammatory response (innate immunity) are listed in Table 55-5. Normally, the pulmonary circulation contains a very large pool of marginated PMNs,[212] which must change shape to squeeze through the lung capillaries. When PMNs are activated, they stiffen and become less distensible. Such PMNs are retained for longer periods of time in the pulmonary microcirculation. Endothelial activation leads to increased expression of leukocyte adhesion molecules, providing a second mechanism to slow the transit of PMNs through the lungs.[213,214] Trapped PMNs respond to chemotactic gradients generated by chemokines produced by alveolar macrophages and mesenchymal cells and migrate into the air spaces.[215] Activated PMNs generate and release toxic substances (e.g., oxygen metabolites[216] and granular constituents, such as proteases, and cationic lysosomal enzymes) that disrupt the function of the microvascular and epithelial barriers, which normally limit liquid and protein flow out of the vascular space and into the alveolar spaces, leading to increased permeability edema. New experimental data provides evidence that neutrophil-mediated acute lung injury may be potentiated by platelets, with additional evidence that aspirin can prevent lung injury in mice from either acid-induced lung injury and transfusion-induced lung injury.[216a]

TABLE 55-5. Possible Inflammatory Mediators of Lung Injury

CHEMOTACTIC FACTORS
Complement fragments
Oxidized lipids
Alveolar macrophage derived
Metabolites of arachidonic acid
TOXIC OXYGEN METABOLITES
Superoxide anion ($O_2^-\cdot$)
Hydrogen peroxide (H_2O_2)
Hydroxyl radical (·OH)
Peroxynitrite
Products of lipid peroxidation
Myeloperoxidase-halide–hydrogen peroxide products
Hypohalous acid
Halogenated amines
INFLAMMATORY HORMONES
Monokines and lymphokines (e.g., interleukins, tumor necrosis factor, endothelin)
Growth factors
ADHESION MOLECULES
Integrins
Selectins
PROTEOLYTIC ENZYMES
Leukocyte granular proteases
Kallikrein
VASOACTIVE SUBSTANCES
Metabolites of arachidonic acid
Amines
Kinins
Platelet-activating factors
Nitric oxide
CLOTTING FACTORS

Inflammatory responses also have the potential to induce injury to lung cells by activating cell death pathways, which lead to apoptosis.[217] Bacterial products, such as *Pseudomonas* exoenzyme U, and mechanical stretch may lead to direct cellular necrosis.[190,191] Apoptosis is mediated by a family of death receptors,[218] which include the TNF receptors and the Fas receptor. The Fas ligand (FasL) is a 45-kd peptide that is shed from the cell surface by the action of metalloproteinases such as matrilysin. Biologically active soluble FasL (sFasL) accumulates in the lungs of patients with ARDS and induces apoptotic death of human lung epithelial cells in vitro.[219] Human sFasL induces epithelial cell death in the lungs of rabbits,[220] and a monoclonal antibody that activates membrane Fas causes alveolar wall apoptosis and fibrosis in the lungs of mice.[220,221] Apoptosis and inflammation pathways intersect, as stimulation of membrane Fas induces cytokine production in human macrophages[222] and inflammation in the lungs of rabbits and mice.[220,223] In addition, lung injury may be able to trigger apoptosis pathways in distant organs, such as the kidney, perhaps by increasing the concentrations of circulating sFasL.[224] Thus, inflammatory responses may trigger cell death pathways, and cell death pathways triggered by sFasL can induce inflammation in the lung alveolar environment. Human studies implicate apoptosis in human lung injury.[225]

Direct Toxicity. Inflammation is not required for all forms of ALI. ARDS occurs in neutropenic patients,[226,227] and a clinical trial using granulocyte colony-stimulating factor to increase the number and activation state of circulating neutrophils in patients with severe pneumonia was not associated with an increased incidence of ARDS.[228] Lung injuries that do not require the participation of PMNs have been reported in animal models. Examples include injuries caused by ethchlorvynol in dogs[229]; by oleic acid in isolated dog lungs[230]; by oxygen in rats[231]; by thrombin infusions in dogs[232]; by *E. coli* endotoxin in rabbits,[233] and by *E. coli* septicemia in baboons.[234] Important species differences exist in the mechanisms involved. For example, in some species, PMN depletion lessens the injuries caused by oleic acid,[235] thrombin infusions,[236,237] and phorbol myristate acetate.[238]

Direct lung injuries are also thought to occur in humans. Putative agents that directly injure the lungs include mechanical forces during mechanical ventilation[239–241]; toxic and corrosive chemicals and gases (e.g., hydrochloric and other acids, ozone, ammonia, chlorine, phosgene, nitrogen dioxide, the vapors of cadmium and

mercury, combustion products, and oxygen, especially at high concentrations); ionizing radiation; aspiration of fresh water (near drowning) or hydrocarbon compounds (e.g., kerosine, gasoline, and dry-cleaning fluid); high temperatures (parenchymal lung burns from fires or explosions); and mechanical injuries (e.g., lung contusion from nonpenetrating chest trauma or blast injury from explosions or lightning).

Many of these injuries develop rapidly, supporting the idea that injury is caused directly by contact with the respiratory epithelium in the airways, the alveolar walls, or both. It is likely that inflammatory pathways are rapidly activated after many types of direct lung injury, as probably occurs after aspiration of gastric secretions (one of the most common causes of clinical ALI). Lung injury occurs rapidly, especially to the epithelium, and is related in part to the low pH of the aspirated stomach contents and also to proinflammatory cytokines in gastric juices.[242,243] Aspiration of gastric contents with pH greater than 2.5 is relatively benign, whereas aspiration of gastric contents with pH less than 2.5 causes severe pulmonary injury in rabbits, rats, and mice. Aspirated acid is quickly neutralized when it contacts lung tissue, but within hours, proinflammatory mediators are released and the injured lung becomes infiltrated with PMNs; then fibrin accumulates in the alveolar spaces and further structural damage is seen on histologic examination. The important role of mechanical stretch is suggested by the National Institutes of Health (NIH) ARDS Network study, which tested two different tidal volume settings in patients with established ARDS.[244] Patients ventilated with lower tidal volumes had a significantly lower mortality, and this was associated with a more rapid fall in circulating concentrations of interleukin-6 than in those receiving higher tidal volumes. In an earlier study, Ranieri and associates[245] found that a lung-protective strategy of mechanical ventilation was associated with a faster decline in inflammatory parameters in BAL fluid, suggesting that reducing stretch reduces inflammation.

Host Factors. Host factors have important effects on susceptibility to ALI. Poorly controlled diabetes is an important risk factor for infections that can lead to ALI, although some epidemiologic evidence suggests that diabetics are actually at a decreased risk for lung injury.[246] Chronic alcoholism increases susceptibility to sepsis and ALI, most likely by altering oxidant/antioxidant balance in the lungs by depleting glutathione in the alveolar microenvironment.[247,248] Genetic determinants also affect susceptibility to inflammation, sepsis, and ALI. The inflammatory response in the lungs of patients with ALI is triggered by innate immunity pathways, and normal people vary a great deal in the intensity of their innate immune responses to bacterial and viral products.[249] Modern rapid DNA sequencing methods have led to the identification of many different single nucleotide polymorphisms (SNPs) that change the base sequence of host DNA. Whether or not these SNPs alter gene function or change amino acid sequence of encoded proteins, SNPs serve as DNA markers that provide clues to genetic determinants of disease. An increasing number of SNPs have been associated with either the onset or the outcome of ALI (reviewed in Gao and coworkers[250]),[251,252] in some cases by altering key proinflammatory pathways in blood or lungs.[253–255]

DIAGNOSIS

The diagnosis of advanced pulmonary edema, particularly when caused by heart failure, is usually easy. Unraveling the cause of other kinds of pulmonary edema may not be so straightforward, particularly in patients with increased permeability edema.

Clinical Assessment

Symptoms and Signs

The clinical manifestations of pulmonary edema vary with its severity and depend on the underlying pathophysiology and the extent to which excess fluid has accumulated in the lungs. Basic initial symptoms are dyspnea, cough, and tachypnea. Wheezing may be heard and may present a problem in differential diagnosis, but patients with asthma generally do not have other symptoms and signs of congestive heart failure or pulmonary edema.[256] Patients who develop increased pressure edema may complain only of vague fatigue, mild pedal edema during the day, or exertional or paroxysmal nocturnal dyspnea. Once alveolar flooding has occurred, the diagnosis of pulmonary edema is not subtle. Patients with alveolar edema usually have severe dyspnea, tachypnea, and cough that is often productive of frothy and sometimes blood-tinged edema fluid. Crackles and rhonchi are heard over the chest, and wheezing may be present. The patient may be cyanotic if alveolar flooding has seriously compromised gas exchange. Cheyne-Stokes respiration is common in severe congestive heart failure and does not necessarily portend a poor immediate prognosis.[257]

Development of edema is often insidious in increased pressure pulmonary edema because the alveoli are protected by the normal safety factors (see Table 55-1). In contrast, in increased permeability edema, alveolar flooding usually occurs rapidly and the onset of symptoms may occur over a short period of time. Edema that occurs suddenly (or unexpectedly) sometimes is called "flash pulmonary edema."

Because pulmonary edema is always a sign of an underlying pathologic process, its cause must be identified so that effective therapy can be directed at the underlying problem producing abnormal transvascular fluid and solute flow into the lungs. Increased pressure edema is usually caused by cardiac failure and thus is usually accompanied by a history of heart disease. This can include signs and symptoms of any of the causes of chronic and acute congestive heart failure, such as coronary insufficiency, hypertension, valvular heart disease, and severe volume expansion. Elevated jugular venous pressure, cardiac enlargement, gallop rhythms, heart murmurs, arrhythmias, large tender liver, and peripheral edema suggest an underlying abnormality of cardiac

function. However, pulmonary edema may be the only manifestation of silent myocardial infarction or diastolic dysfunction of the left ventricle.[258]

History and physical examination may also be helpful in differentiating increased permeability edema from increased pressure edema and in identifying a possible cause of ALI. Patients with increased permeability edema usually do not have signs or symptoms of underlying cardiac disease. The cause of ALI may be suggested by a history of exposure (e.g., to toxic gases or chemicals, near drowning, drug ingestion, trauma), the clinical setting (e.g., sepsis, pneumonia, emesis, seizures, pancreatitis, burns, high altitude), or the physical findings (e.g., chest trauma, long bone fractures, coma, shock). Because infection and the sepsis syndrome are major causes of ALI in humans, a thorough search must be made for signs and symptoms of an infectious cause. Pulmonary and intra-abdominal sources are the most common sites of infection, and all patients should be examined carefully, with special attention being paid to abdominal, rectal, and pelvic examinations. Most patients with ALI are febrile, whether or not an infection is clinically apparent.

Diagnostic Studies and Definitions

Laboratory and other diagnostic studies are helpful, but by the time many of the results are abnormal, the diagnosis is usually obvious. In the special case of pulmonary edema suspected to be caused by saltwater near drowning, measurement of plasma magnesium level can help determine whether or not a patient has aspirated or swallowed seawater, or both: Severe hypermagnesemia (6.7 mg/dL; normal range, 1.6–2.7 mg/dL) has been reported because of the high concentration (around 125 mg/dL) of magnesium normally found in seawater.[90] Appropriate cultures for microorganisms and toxicology screens of blood and urine are useful in identifying underlying causes of ALIs. Sputum or trachea aspirate examination, bronchoscopy with protected-specimen brushing, or BAL with quantitative cultures are all useful in diagnosing pneumonia in ventilated patients, even those who are being treated with antimicrobial drugs.[173,175,176,259] Lung biopsy can provide a specific diagnosis in some patients with ALIs,[260,261] but the results often are not helpful because lung injuries caused by diverse underlying conditions have the same appearance and because specific therapies may not be available.

The criteria for the diagnosis of ALI have been somewhat controversial. Two definitions have gained some acceptance: the expanded definition of ALI[262] and the American-European Consensus Conference definition.[263]

TABLE 55-6. Expanded Definition of Acute Lung Injury

Phase (acute or chronic)
Lung injury score (see Table 55-7)
Etiology (underlying cause or association; see Table 55-4)
Nonpulmonary organ dysfunction

The expanded definition of ALI has four elements (Table 55-6). The first element establishes the time at which the diagnosis is made and separates the group of patients suffering from the immediate consequences of ALI from those who have progressed to more indolent, chronic disease. This is an important distinction because the causes of morbidity and mortality, appropriate supportive and specific therapy, and prognosis differ between the two phases. The second element is the actual Lung Injury Score (Table 55-7), which provides an assessment of the severity of lung injury, taking into account supportive therapy, such as mechanical ventilation with PEEP and oxygen supplementation. This score is important because not all lung injuries are of equal

TABLE 55-7. Components and Individual Values of the Lung Injury Score

	Value
1. CHEST ROENTGENOGRAM SCORE	
No alveolar consolidation	0
Alveolar consolidation confined to 1 quadrant	1
Alveolar consolidation confined to 2 quadrants	2
Alveolar consolidation confined to 3 quadrants	3
Alveolar consolidation in all 4 quadrants	4
2. HYPOXEMIA SCORE	
$PaO_2/FIO_2 \geq 300$	0
PaO_2/FIO_2 225–299	1
PaO_2/FIO_2 175–224	2
PaO_2/FIO_2 100–174	3
$PaO_2/FIO_2 < 100$	4
3. PEEP SCORE (WHEN VENTILATED)	
PEEP ≤ 5 cm H_2O	0
PEEP 6–8 cm H_2O	1
PEEP 9–11 cm H_2O	2
PEEP 12–14 cm H_2O	3
PEEP ≥ 15 cm H_2O	4
4. RESPIRATORY SYSTEM COMPLIANCE SCORE (WHEN AVAILABLE)	
Compliance ≥ 80 mL/cm H_2O	0
Compliance 60–79 mL/cm H_2O	1
Compliance 40–59 mL/cm H_2O	2
Compliance 20–39 mL/cm H_2O	3
Compliance ≤ 19 mL/cm H_2O	4
The final value is obtained by dividing the aggregate sum by the number of components that were used.	

	Score
No lung injury	0
Mild to moderate lung injury	0.1–2.5
Severe lung injury (ARDS)	>2.5

ARDS, acute respiratory distress syndrome; PaO_2/FIO_2, arterial oxygen tension to inspired oxygen concentration ratio; PEEP, positive end-expiratory pressure.

From Murray JF, Matthay MA, Luce JM, et al: An expanded definition of the adult respiratory distress syndrome. Am Rev Respir Dis 138:720–723, 1988.

severity and severity changes over time. The term *acute respiratory distress syndrome* is applied only to the most severe injuries (those that yield a score > 2.5); milder lung injuries, termed "mild to moderate," may have a better prognosis and may differ from ARDS in other important aspects. The third element, etiology, separates the many underlying disorders that can result in ALI (see Table 55-4, which is not meant to be an exhaustive or exclusive list). Multiple etiologies may be present. Finally, the fourth element, which was separated when the expanded definition of ALI was first proposed, recognizes the occurrence of injury to organs other than the lungs. This is important because injury is often not limited to the lungs. Dysfunction of other organs is common,[264] and prognosis varies between isolated pulmonary and generalized systemic disorders.

The Glasgow Coma Scale is widely used to assess neurologic status. Criteria have been proposed to evaluate abnormalities in renal, cardiovascular, hepatic, gastrointestinal, and hematologic function, all of which can complicate or coexist with ALI. The Acute Physiology and Chronic Health Evaluation (APACHE) II scoring system and the Simplified Acute Physiology Score have been used to define an individual patient's overall severity of injury.[265]

The American-European Consensus Conference Definition (Table 55-8) also has four elements: (1) timing (onset must be "acute"); (2) oxygenation (arterial P_{O_2}/F_{IO_2} [fractional concentration of oxygen in inspired gas] ≤ 300 mm Hg, regardless of the level of PEEP, for the diagnosis of ALI to be made, and arterial P_{O_2}/F_{IO_2} ≤ 200 mm Hg, regardless of PEEP level, for the diagnosis of ARDS to be made); (3) chest radiograph (bilateral infiltrates seen on frontal view); and (4) pulmonary artery wedge pressure (≤18 mm Hg when measured, or no clinical evidence of left atrial hypertension).

The two definitions differ in the exact criteria that must be met for a diagnosis to be established, but they identify similar patients[266] and are complementary. The power of the Consensus Conference definition is that it was reached by consensus and that it is also easy to remember. The advantages of the expanded definition are that it provides a grading system (the Lung Injury Score) whereby equally injured patients can be grouped and compared and the progress (or lack thereof) of any individual patient's course over time can be measured; that it recognizes the distinct phases of the progression of lung injuries (early vs. late disease); that it separates the different underlying conditions that are associated with ALI (conditions in which the exact etiology and mechanism of ALI may differ); and that it recognizes and requires identification of associated extrapulmonary disease (which has profound effects on mortality of patients with ALIs).

Despite these clinical criteria, defining ALI and ARDS is not without problems.[267] The most serious deficiency of both definitions is the failure to link the underlying pathophysiology of ALI to the functional abnormalities that are at the core of the definitions (i.e., data are lacking that link any particular arterial P_{O_2}/F_{IO_2} to any particular change in the structure or function of the relevant barriers in the lungs or to the degree of edema). What defines ALI in a meaningful way is the altered barrier permeability of the lungs. What defines ARDS in a meaningful way is structural damage to the lung microvascular endothelial barrier, the alveolar epithelial barrier, or both. Many respiratory disorders can reach the definitions' thresholds for "diagnosis," and many ALIs, especially mild ones, fail to reach them at all. For example, bacterial pneumonia may not be a different disease when it crosses some arbitrary threshold and meets criteria for ALI or ARDS; venous air emboli–induced and heroin-induced pulmonary edemas are ALIs, even if they fail to disturb oxygenation sufficiently to satisfy an arbitrary definition of ALI or ARDS. In small numbers of patients, the Lung Injury Score has correlated with bedside measurements of lung vascular permeability[268–270] and with the extent of abnormalities on computed tomography.[271] In the future as current research work evolves, the clinical definitions need to be supplemented with biologic criteria to help categorize ALI and ARDS into more specific disease entities.

The Consensus Conference definition also has limitations. First, it requires that timing be acute, but it neither specifies the degree of acuity required nor accounts for the considerable heterogeneity in the course of patients with ALIs, each progressing, or not progressing, at its own given pace, through exudative, proliferative, and recovery phases. Second, it requires an arbitrary pulmonary artery wedge pressure (or no clinical evidence of left atrial hypertension), but left atrial hypertension or the lack thereof is not part of the basic pathophysiology of ALI. It is the pulmonary microvascular pressure that matters when the lungs are injured, and that pressure can be low, normal, or (often) elevated. However, the Consensus Conference definition is simple to apply and has facilitated enrollment of patients in clinical trials.[94]

Both definitions have been faulted for failing to allow early diagnosis and for failing to accurately predict mortality.[272,273] Regarding mortality, the relevant question about any definition is not whether it can predict who

TABLE 55-8. American-European Consensus Conference Definition of Acute Lung Injury and Acute Respiratory Distress Syndrome

TIMING
Acute
OXYGENATION (REGARDLESS OF PEEP LEVEL)
P_{aO_2}/F_{IO_2} ≤ 300 = acute lung injury
P_{aO_2}/F_{IO_2} ≤ 200 = acute respiratory distress syndrome
CHEST RADIOGRAPH
Bilateral infiltrates on frontal view
PULMONARY ARTERY WEDGE PRESSURE
≤18 mm Hg when measured, *or*
No clinical evidence of left atrial hypertension

P_{aO_2}/F_{IO_2}, arterial oxygen tension to inspired oxygen concentration ratio; PEEP, positive end-expiratory pressure.

will live and who will die, but rather whether it can correctly identify and distinguish who has ALI and who does not. Death is often not directly related to ALI, but rather to nonpulmonary organ dysfunction, chronic liver disease, or sepsis.[273] The severity of the oxygenation defect, which is what the definitions measure, does not have major prognostic value early in the course of clinical lung injury. Finally, assessment of the accuracy of definitions[266] is difficult because there is no "gold standard" for ARDS against which the accuracy of any given definition can be measured.

Chest Radiographs

The plain chest radiograph is the most practical laboratory study available for the detection of pulmonary edema.[274–277] Disadvantages are that chest radiographs are insensitive to small changes in lung water and are only semiquantitative.[1,278] An additional limitation is that chest radiographs are not consistently helpful in distinguishing increased pressure edema from increased permeability edema.[279–281] These disadvantages are balanced by the advantages that chest radiographs are noninvasive, inexpensive, easily repeatable, readily available, and free of side effects.

Before alveolar flooding, the plain chest radiograph can show distended vascular shadows (particularly in the upper lung fields), enlargement and loss of definition of hilar structures, development of septal lines (Kerley's lines), loss of peribronchial and perivascular definition (cuffing), and perihilar haze indicating the presence of interstitial pulmonary edema. Acinar shadows, often confluent and creating irregular, patchy increases in lung density that obscure vascular markings, indicate the presence of alveolar edema. Air bronchograms may be observed in severe edema. Because the radiographic signs of interstitial and alveolar edema are determined by gas and blood volumes and their distribution in the lungs in addition to the presence of edema, the recognition and quantitation of edema are not precise, and the radiographic appearance of edema is strongly influenced by the lung volume at the time the film is made. The chest roentgenogram score is an integral part of the Lung Injury Score, but the interpretation of chest radiographs is not well standardized and significant interobserver variations have been reported.[282]

Arterial Blood Studies

Although not specific, the arterial P_{O_2}, carbon dioxide pressure (P_{CO_2}), and pH are the most informative laboratory indicators of overall pulmonary function in patients with pulmonary edema. Arterial blood studies are not sensitive to early edema. Arterial P_{O_2} may actually rise in the earliest stages of increased pressure edema because the increase in vascular pressures distributes blood flow more uniformly to well-ventilated units. Interstitial pulmonary edema does not usually affect oxygen uptake in the lungs beyond modest hypoxemia caused by ventilation-perfusion mismatching. In contrast, alveolar flooding seriously compromises gas exchange. Hypoxemia is due to right-to-left shunting of blood resulting from perfusion of alveoli that cannot be ventilated because they are fluid filled or collapsed. Ventilation-perfusion abnormalities also contribute to the hypoxemia of edema. In two studies of groups of patients with diverse lung injuries, oxygenation appeared to depend more on the vasoconstrictive ability of the pulmonary circulation (i.e., the ability to reduce perfusion of damaged and edematous areas of the lungs) than on the amount of edema present.[283,284]

Arterial P_{CO_2} is often low in edema, especially in the early stages, when tachypnea results in alveolar hyperventilation. An elevated P_{CO_2} (more common with severe edema) indicates alveolar hypoventilation, which can be caused by underlying lung disease, increased metabolic production of carbon dioxide (perhaps related to increased work of breathing), increased wasted ventilation (ventilation of poorly perfused alveoli or airways leading to flooded, nonventilated alveoli), or mechanical impairment caused by weak respiratory muscles.[285] Elevated P_{CO_2} does not necessarily indicate a poor prognosis[286] and often resolves with treatment of pulmonary edema.

Acid-base disturbances are common in increased pressure edema but often do not correlate with severity, morbidity, or mortality.[287] When edema is mild, tachypnea results in hyperventilation and consequent respiratory alkalosis (and subsequent compensating metabolic acidosis). When edema is severe or the lungs have been injured, many patients develop metabolic acidosis as a result of tissue hypoxia, increased work of breathing, intrinsic lung lactate production, or all of these.[286,288] Attempts to correct acidosis with parenteral bicarbonate administration usually are not necessary; rather, the underlying cause must be identified and treated appropriately. Respiratory acidosis caused by alveolar hypoventilation can be treated either by noninvasive ventilation or by invasive mechanical ventilation with endotracheal intubation. Metabolic acidosis can often be corrected by alleviating hypoxemia and improving cardiac function; the possibility of underlying disease amenable to surgery (e.g., intestinal ischemia or infarction, perforation of a viscus) or pancreatitis should not be overlooked.

Pulmonary Edema Fluid Protein Concentration Measurement

When florid pulmonary edema is present, measurement of protein concentration in simultaneously collected edema fluid (suctioned through an endotracheal tube) and plasma provides a rapid, noninvasive method for distinguishing increased pressure edema from increased permeability edema.[156] Because the microvascular barrier is functionally intact in increased pressure edema, plasma proteins remain largely confined to the intravascular space, and edema fluid protein concentration is low relative to plasma protein concentration (the ratio of edema fluid to plasma protein concentration generally <0.65). Because the microvascular barrier is injured and cannot effectively confine plasma proteins to the vascular space in increased permeability edema, edema fluid

protein concentration is high relative to plasma protein concentration (ratio of edema fluid to plasma protein concentration generally >0.75). Intermediate values (between 0.65 and 0.75) may indicate that both types of edema are present and suggest the relative contributions of each. Measurement of the ratio of edema fluid to plasma protein concentration has been shown to be a simple method for separating the types of pulmonary edema in numerous reported series of patients with pulmonary edema.[78,289–294] Three studies indicated that an increasing protein concentration in serial measurements of edema fluid in ALIs was a good sign, reflecting an intact epithelial barrier and net removal of edema fluid from the alveoli.[78,293,294] There is new evidence that the edema fluid to plasma protein ratio has prognostic value as well as diagnostic value.[294a] Such measurements need to be correlated with the patient's clinical condition, because an increasing protein concentration in edema fluid over time might also mean that increased permeability edema was complicating what had been increased pressure edema or that the lungs were injured more severely or more extensively as time passed.

Edema fluid can be collected by inserting a standard 14- to 18-gauge catheter through an endotracheal tube and advancing it into a wedged position in the distal air spaces (similar to the procedure for wedging a bronchoscope). Gentle suction is applied as the catheter is slowly withdrawn, and fluid is collected in a small trap. Several attempts may be needed; if no fluid can be suctioned, the clinician should try changing the patient's position. Samples grossly contaminated with airway secretions (which have a very low protein concentration, <1.0 g/dL), such as mucus, pus, and debris, should be discarded. Protein concentrations can be measured by the clinical laboratory or estimated quickly at the bedside from the protein scale of a handheld refractometer.

BAL has been used as a research and diagnostic tool that may also yield useful information about the cellular biochemical and microbial composition of the air space,[156,295] but lavage is not useful as a method to measure alveolar protein concentration, because the instilled saline dilutes alveolar fluid by approximately 50- to 100-fold, depending on the method that is used.[156]

Pulmonary Function Tests

With the exception of arterial blood gas analyses, by the time results of conventional tests of pulmonary function are abnormal in patients with pulmonary edema, the diagnosis is usually obvious or the patient is too sick to study. The general sequence of developing abnormalities as edema accumulates was discussed earlier in this chapter. The earliest abnormality detectable by conventional studies in increased pressure edema is a rise in diffusing capacity of the lung for carbon monoxide caused by an increase in pulmonary capillary blood volume as a result of pulmonary vascular congestion. Closing volume may be greater when interstitial edema is present, but consistent changes in routine pulmonary function tests are generally not found until the alveoli begin to flood and vital capacity begins to diminish. Because pulmonary function tests are neither sensitive nor specific in edema, provide no information for separating the two types of edema, and are difficult to perform in patients who are ill, such tests are not useful in the diagnosis of pulmonary edema.

Hemodynamic Measurements

Pulmonary vascular pressures are sometimes recommended as helpful for differentiating increased pressure edema from increased permeability edema. However, measurement of vascular pressures in the lungs is expensive and invasive and can be associated with significant morbidity and mortality,[296–298] although one study reported no excess morbidity or mortality in patients with ARDS who had a pulmonary arterial catheter inserted.[299] The problems with measuring and interpreting pulmonary artery occlusion pressures have been reviewed.[297,300–302]

Measurement of Lung Water and Barrier Function

Measurement of the amount of water in the lungs could be useful in detecting early pulmonary edema and in assessing its clinical course and response to treatment. However, no ideal technique is available. Methods in use or under investigation focus on either measurement of lung density or equilibration of tracers with water in the lungs.[1,303] Interest in such measurements assumes that accurate knowledge about lung water would be useful in diagnosis and would be beneficial in the treatment of patients with pulmonary edema. Recent work with a single thermal indicator for measuring extravascular lung water has shown promise based on several studies.[304–307]

Lung Density Methods

Because lung density is determined by air and blood as well as extravascular tissue and water contents, densitometric techniques are only semiquantitative, and baseline lung densities vary widely. These techniques are most useful when a series of studies can be compared in order to estimate changes in lung water content. They are of little use in early edema because lung fluid filtration can increase greatly before lung water content actually increases. The most widely used method is the plain chest roentgenogram, because it is readily available, is relatively inexpensive, is noninvasive, and can be repeated frequently at little risk to the patient. Unfortunately, it is insensitive (lung water must increase by >30% before being recognizable) and nonspecific (other interstitial or alveolar processes produce similar radiographic shadows). More precise density measurements may be made with techniques such as transmission computed tomography,[308,309] but the problem of separating changes in gas and blood volumes from changes in water content remains. Similar information may be gathered from transthoracic γ-ray attenuation[310] or Compton scattering.[311] It might be possible to relate changes in sound

speed across the lungs to lung water content,[312] but such measurements would also depend on lung volume. A theoretically related technique, transthoracic bioelectric impedance analysis, attempts to relate the resistance to an alternating electrical current passed through the thorax to the amount of water in the lungs.[313]

Nuclear magnetic resonance imaging[314] and positron emission tomography[315] techniques for measuring lung water are also under investigation. Their theoretical advantages are the noninvasive measurement of density without ionizing radiation (in the case of nuclear magnetic resonance imaging) and lack of effects of ventilation and perfusion abnormalities; their disadvantages are that the hardware for both techniques is expensive and not readily available and the slow scanning time and cumbersome equipment are not suitable for studying seriously ill patients.

Tracer Methods

Attempts have been made to assess lung water by measuring either the rates of equilibration of a diffusible indicator and an intravascular indicator (multiple-indicator dilution technique) or the uptake of inhaled gases (soluble-gas technique). Both methods have been the subject of considerable investigation, but neither method is in clinical use. These methods are limited by the inhomogeneous distribution of the tracers and the complexity of the equipment needed to make measurements.

Multiple-Indicator Dilution Techniques. These are invasive techniques based on measuring differences in transit-time volumes between two indicators, one nondiffusible (restricted to the intravascular space) and one diffusible (able to enter the extravascular space).[316] Suitable tracers are injected into a systemic vein or the right side of the heart, and time-concentration curves are recorded from a systemic artery. Because the diffusible tracer can in theory equilibrate with a much larger volume (extravascular and intravascular volumes) than the nondiffusible tracer (intravascular volume only), the differences in concentrations of the two tracers over time after traveling through the lungs can be used to calculate both blood flow and extravascular mass (mainly water) of the lungs.

Such techniques are limited by several factors: time, which may not allow the diffusible tracer to reach areas of the lungs remote from the microvascular bed; blood flow inhomogeneities, which restrict the tracers to perfused portions of the vascular bed; inhomogeneity of water distribution in the lungs; recirculation of the indicator; measurement of mass (e.g., dry lung, blood vessels, heart) in addition to water mass; and a host of technical details concerning the appropriateness of the indicators and the methods of their injection, withdrawal, and measurement, and calculation of concentration over time. The major problems are underestimation of lung water in pulmonary edemas in which uneven distribution of blood flow develops, which occurs in most lung injuries, and insensitivity (a 50% increase in measured lung water may be significant, but edema is obvious by that time).

Two methods have been the subject of considerable research, the thermal-dye method[317] and the multiple-isotope method.[318] The thermal-dye method has come closest to clinical use, and a refinement of the method (using a fluorescent indicator) allows measurements to be made with an indwelling catheter without blood withdrawal. The major problems are underestimation of lung water, particularly when vascular perfusion inequalities exist in the lungs or large volumes of edema are present, and accuracy of measurement of thermal changes.[319] Prospective evaluations of extravascular lung water measurements by the thermal-dye method versus pulmonary artery wedge pressures to guide the hemodynamic management of critically ill patients claimed superiority of the lung water technique[320,321]; benefit may have accrued as a result of restrained fluid therapy. The multiple-isotope method requires blood withdrawal for tracer measurement and, like the thermal-dye method, underestimates water content if there is perfusion inhomogeneity.[322] This latter method appears to provide a better estimation of lung permeability–surface area product than of lung water content.

Measurement of Barrier Function

Because transvascular fluid flow into the lungs can be abnormal long before lung water content increases, and because the two types of edema can be separated on the basis of differences in barrier function, detection of increased transvascular fluid flow into the lungs and measurement of barrier integrity might be more helpful than measurement of lung water content in edema. Clinical distinction between increased pressure edema and increased permeability edema is difficult.[323] A simple and practical method exists to evaluate barrier integrity (edema fluid protein concentration measurements, discussed earlier), and several methods have been studied to detect early edema and changes in barrier function. However, none is in routine clinical use.

Detection of Lung Injury

Because lung injury occurs before measurements of barrier integrity or transvascular fluid flow are abnormal, methods to detect lung injury before the appearance of abnormal liquid and solute transport might be of help. Early detection of lung injury would be especially valuable if therapies were developed on the basis of the mechanisms of lung injuries. Although tests to determine the causes of lung injuries are not available, methods such as studies of the metabolic functions of the lung and a variety of specific lung injury makers are being investigated to detect whether lungs have been injured.

Changes in Metabolic Functions of the Lung

The lungs are involved in the metabolism of a variety of biologically active substances. Because the removal and metabolism of such substances depend on endothelial cell function, alterations in metabolic function in the lungs might be sensitive early tests of endothelial cell

injury. Abnormal levels, activities, or uptakes of various substances (e.g., ACE, vasoactive amines, metabolites of arachidonic acid, endothelin-1, certain drugs) have been detected when the lungs are injured. Unfortunately, the finding of normal or abnormal uptake by the lungs is neither specific nor sensitive for all ALIs; metabolic functions can be influenced by drugs, cardiac output, vascular surface area, and hypoxia or hyperoxia, and serious lung injury can occur without changes in metabolic function. Although alterations in metabolic functions of the lungs are not clinically useful indicators of endothelial cell function at this time, their potential use for early detection of lung injury justifies continuing investigation.

Biologic Markers of Lung Injury

Potential markers of ALI have been the subject of several comprehensive reviews.[156,324,325] There is considerable interest in finding a simple blood, urine, or BAL test that could identify patients at risk who are destined to develop ALI, or who are in the earliest stages of ALI, or that could predict the outcome of patients with injured lungs. To be of clinical use, such a marker would have to be practical and inexpensive to measure as well as sensitive and specific for ALI; with the exception of measurements of edema fluid protein concentration relative to plasma protein concentration (discussed earlier), none has become clinically useful yet. There may be many reasons for the lack of progress in identifying suitable markers: many (if not most) patients cannot be enrolled into studies of early or predictive markers because they already have injured lungs when they present or injury occurs very soon after the causative insult; ARDS is not a disease, but rather a symptom complex that may result from diverse causes; injury to the lungs is often overwhelming, and subtle differences in potential markers may be missed; measurements of potential markers in biologic fluids may not reflect what is happening at the tissue and cellular levels; and there has been limited uniformity among studies in diagnostic criteria and design (e.g., suitable controls, such as patients with increased pressure pulmonary edema and severe lung disease other than ALI, are often not studied; measurements of putative markers are often made at a single time rather than regularly over the course of ALI). The result is that it might never be possible to find a suitable single marker, but new work shows the potential value of using more than one biologic marker.[326] Considerable progress has been made in studying biologic markers for their pathogenetic significance.[325,327]

Products of complement activation were proposed as markers but were later shown to be poorly correlated with lung injury.[328,329] Measurement of circulating endotoxin was not appropriately sensitive or specific for the presence or the risk of developing lung injury. Release or activity of ACE has not been found to be sensitive or specific for ALIs. von Willebrand factor antigen was useful as a plasma marker of impending ALI in septic patients, and one study confirms that von Willebrand factor antigen levels are elevated in the edema fluid and plasma of patients with ALI and correlate with poor clinical outcomes.[330] Other biochemical and inflammatory markers have been found to have some association with lung injury and mortality, including most recently surfactant protein D.[331] Elevated levels of interleukin-6 in the plasma are also associated with mortality.[244] So far at least, no simple biologic marker has been identified that can be used as elevations in cardiac enzymes are used to diagnose acute myocardial infarction.

Because PMNs are associated with the mechanism of many lung injuries, detection of their presence in the lungs, tests of their function, or measurement of their toxic metabolites might be useful. For example, increased hydrogen peroxide has been measured in the breath and urine of patients with ALIs,[332,333] presumably reflecting the presence of oxygen metabolites in their injured lungs. Evidence of oxidant activity was also reported in BAL fluid.[334] Other mediators of inflammation might be appropriately considered as well. For example, TNF-α has been detected in blood[335] and BAL fluid, but an association between TNF and the development of ARDS was not found,[336] and TNF was found to be elevated in patients with severe congestive heart failure[337]; various lipoxygenase products of arachidonic acid metabolism have been detected in pulmonary edema fluid,[149] BAL fluid,[338] plasma, and urine[339]; and elastase has been detected in BAL fluid.[340–343] In addition to these possible markers, sporadic reports of abnormal substances or abnormal levels of normally occurring substances detected in fluids obtained from small groups of patients with ALI are continually being reported. Often, there is overlap between levels in patients who have ALIs and those who do not. The results are often of interest to illustrate the wide variety of abnormalities that can be detected when the lungs are injured and to suggest the complexity of the underlying pathophysiology.

Several studies from multicenter clinical trials have reported the independent predictive value of some plasma markers for mortality and other clinical outcomes in patients with ALI. The biologic markers of greatest predictive value are surfactant protein D,[344] interleukin-6 and interleukin-8,[345] von Willebrand factor antigen,[346] soluble TNF-α receptors I and II,[347] intercellular adhesion molecule-1,[348] protein C and plasminogen activator-1,[349,350] and the receptor for glycation end products (RAGE).[351,352] Because ALIs follow a wide variety of insults and range in severity, and because many abnormalities detected in ALI are found in other severe illnesses of diverse etiology that do not involve the lungs, it seems unlikely that any single marker will be found that unequivocally identifies the risk or the presence of ALI. Focus on particular subgroups of patients with common causes of injury and study of much larger groups of better diagnosed patients might be helpful. An approach that has not received much attention is investigation of the sensitivity and specificity of combinations of markers. In support of this approach, one recent study found that combinations of three plasma biomarkers had a statistically significant better prognostic value for predicting death than the use of standard clinical predictors alone.[352a] The new field of targeted proteomics will

expand this kind of investigation and perhaps identify patterns of protein abnormalities that can be found in the plasma, edema fluid, and BAL fluid of the air spaces of the lung in ARDS.[353–356]

TREATMENT

Treatment of pulmonary edema requires adequate life support followed by specific therapy directed at the factors that led to accumulation of water in the extravascular spaces of the lungs. Rational therapy also requires a correct diagnosis and an understanding of the nature of the underlying disease state and of the strategies that might prove useful in limiting further edema accumulation and favor fluid removal from the lungs.[357]

Immediate Therapy

Patients with alveolar edema are often severely ill and require immediate treatment for acute respiratory failure. The basic principles of treatment of hypoxemic respiratory failure are discussed in Chapters 84 and 85. Essential requirements for patients with pulmonary edema include preservation of the airway, provision of adequate ventilation, and maintenance of satisfactory oxygenation. New methods for the noninvasive measurement of blood gases have made monitoring of their oxygen saturation possible, which can be useful in assessing the adequacy of oxygen support and the effects of therapy. Blood pressure and other forms of circulatory support may also be needed.

Hydrostatic Pulmonary Edema

If the patient is not hypotensive, morphine sulfate, 5 to 10 mg, or its equivalent, should be given intravenously slowly over several minutes (rapid injection can cause pulmonary vasoconstriction and increased permeability via histamine release from the lungs). Morphine is an extremely useful drug in the treatment of cardiogenic pulmonary edema because it is a potent vasodilator as well as a central nervous system sedative and because it does not depress myocardial contractility. Its vasodilating effects can substantially reduce pulmonary capillary pressure and may improve depressed cardiac output. The work of the heart is lessened by the vasodilating, bradycardic, and sedative effects of morphine. Cautiously administered morphine usually does not cause respiratory failure or aggravate existing carbon dioxide retention associated with acute pulmonary edema, but the patient must be closely watched if he or she is not intubated and receiving assisted ventilation. Hypotension following morphine administration indicates that too much drug was given or that the intravascular volume is lower than suspected.

If medical care is not immediately available, two historical treatments for increased pressure pulmonary edema can be lifesaving. First, rotating tourniquets can act to reduce blood volume (and thereby pulmonary perfusion pressure) by trapping blood in the extremities, away from the pulmonary circulation. Tourniquets, or blood pressure cuffs inflated to less than systolic pressure, are applied to three of the four extremities and rotated every 15 minutes. The purpose is to decrease venous return, not to stop all blood flow to the extremities. Care must be taken that the tourniquets are rotated and that venous return from any extremity is not obstructed for more than 45 minutes at a time. A study of patients with left ventricular dysfunction following myocardial infarction showed trapping of considerable blood volume in the periphery by tourniquets, but variable and sometimes unfavorable effects on left ventricular function.[358] Second, phlebotomy[359] (100–500 mL) can be used to reduce blood volume in acute pulmonary edema when the patient is not in shock and if drugs and supportive care are not available.

When supportive care is available, positive airway pressure, supplied by a tight-fitting face mask[360,361] or by mechanical ventilation after endotracheal intubation, performs the same function as rotating tourniquets without risking loss of limbs: High pressure in the thorax impedes venous return and traps blood volume peripherally, which has the same usually beneficial but sometimes unfavorable effects on left ventricular function as tourniquets. Positive airway pressure, mechanical ventilation, or both can also help reverse some of the physiologic disturbances that can contribute to the development of pulmonary edema: improved oxygenation can increase myocardial oxygen supply, mechanical ventilation can be of benefit to decrease the work of breathing and thus lower the work of the heart, and left ventricular afterload can be reduced when positive pleural pressure replaces the wide swings in negative pressure that occur with spontaneous ventilation. A recent clinical trial showed no improvement in mortality in patients with acute cardiogenic pulmonary edema who were treated with continuous positive airway pressure or bilevel positive airway pressure by mask as compared with supplemental oxygen alone.[362]

Major Options

After emergency treatment has been instituted, there are three major therapeutic options: vasodilators, diuretics, and inotropic agents. The goal of therapy with these agents is to lower the hydrostatic pressure at the filtration sites in the pulmonary vascular bed while maintaining adequate systemic delivery of oxygen. The choice of therapy is dictated by the patient's condition and the cause of the pulmonary edema.

Perhaps the most controversial topic in management is the role of bedside right-sided heart catheterization. One prospective cohort study of critically ill patients showed that flotation heart catheterization was associated with increased 30-, 60-, and 180-day mortality.[298] Subgroup analysis did not reveal any patient group for which right-sided heart catheterization was associated with improved outcome, and patients with acute respiratory failure and multiple organ system failure were at greatest hazard to do worse when a pulmonary artery catheter was placed. This was an observational study,

not a randomized clinical trial, and the reasons for lack of benefit from right-sided heart catheterization were not clear: the pulmonary artery catheter might directly worsen outcome, for example, if its risks and deleterious effects outweighed any benefits; benefits might not be realized if interpretations of hemodynamic measurements were incorrect (lack of skill and knowledge is a common problem in the interpretation of such measurements); the pulmonary artery catheter might be a marker for an aggressive style of care that increases mortality; or changes in therapy in response to hemodynamic information from pulmonary artery catheters might increase mortality. The study cohort appeared to exclude the possibility that right-sided heart catheterization was used in sicker patients, thus resulting in higher mortality (the patients with and without pulmonary artery catheters were matched for severity of illness). In addition to increased mortality, bedside flotation heart catheterization was associated with increased costs and use of resources. As a result of this observational study, the National Heart, Lung, and Blood Institute (NHLBI) sponsored clinical trials to assess the clinical usefulness of pulmonary artery catheterization in critically ill patients. The ARDS Network clinical trial of 1000 patients demonstrated that there was advantage to using a pulmonary arterial catheter versus a central venous catheter in patients with ALI.[363] There were no major complications with the use of pulmonary artery catheterization in this trial, but on balance, the results showed no benefit in most patients with ALI. Similarly, a different clinical trial reported no clinical benefit from the use of pulmonary artery catheters in surgical patients with preoperative cardiac dysfunction, and the patients who had pulmonary artery catheters had a increased incidence of pulmonary embolism, perhaps because they were sicker.[364,365] On balance, pulmonary artery catheters provide a great deal of clinically useful physiologic information, but the information gained does not alter clinical outcome, and their use has declined dramatically. Some patients with shock might still benefit from a pulmonary artery catheter.[366]

Vasodilators

Vasodilators are useful pharmacologic agents for treatment of acute increased pressure pulmonary edema. Their effects occur in minutes. Through dilation of veins, vascular capacitance is increased and blood is redistributed peripherally, thereby lowering the driving pressure for fluid filtration in the lungs; through dilation of arteries, systemic vascular resistance (cardiac afterload) falls, cardiac output and stroke volume increase, and the heart works more efficiently. In addition to morphine, three classes of vasodilators may be useful in pulmonary edema: venodilators (e.g., nitrates), arteriolar dilators (e.g., phentolamine, hydralazine), and mixed dilators (e.g., nitroprusside).

Sodium nitroprusside, a direct-acting venous and arteriolar dilator, is a commonly used agent in acute pulmonary edema. Its advantages are that the effects are immediate, its half-life is short, and cardiac output is maintained by arteriolar dilation and subsequent increased cardiac stroke volume even as central blood volume is lowered (thereby reducing pressure in the pulmonary vascular bed). Its main disadvantage is that invasive hemodynamic monitoring (i.e., an arterial cannula for continuous measurement of systemic blood pressure) is required because the dose must be carefully titrated to avoid profound hypotension. Prolonged infusions can result in cyanide or thiocyanate toxicity; the earliest sign is metabolic acidosis. Arterial oxygenation can deteriorate during therapy with any vasodilator if increased pulmonary blood flow and inhibition of hypoxia-mediated pulmonary vasoconstriction result in relatively increased perfusion of a nonventilated, fluid-filled, or collapsed lung. Therapy with both nitroprusside and nitroglycerin can be complicated by methemoglobinemia, and all nitrates can precipitate increased intracranial or intraocular pressure.

Nitroprusside is usually started at 10 μg/min by intravenous infusion and increased by 5 to 10 μg every 3 to 5 minutes until the desired effect is achieved. Arterial pressure should not be allowed to fall below 60 mm Hg diastolic, and peak systolic pressure should be kept higher than 90 mm Hg. Most patients require 50 to 100 μg/min to achieve the desired effects.

Nitroglycerin and other nitrates are also direct-acting vasodilators, but their predominant effect is on the venous capacitance bed. Intravenous nitroglycerin may be particularly useful in patients with increased pressure pulmonary edema associated with acute myocardial infarction or myocardial insufficiency. Nitroglycerin consistently dilates intercoronary collateral vessels, thereby improving blood flow to ischemic or marginally perfused regions of myocardium. Nitroprusside infusion does not consistently have this effect and may actually result in a decrease in collateral blood flow to ischemic regions of the heart. Nitroglycerin may also be useful in patients with borderline hypotension; because its effects (at least at lower infusion rates) are predominantly venodilating, systemic arterial pressure can be preserved while increased venous capacitance leads to lower driving pressures for fluid filtration in the lungs. At higher doses, nitroglycerin also exerts arteriolar dilator effects similar to those of nitroprusside. The major disadvantage of intravenous nitroglycerin is that invasive hemodynamic monitoring is generally required.

Intravenous nitroglycerin infusion is started at 10 to 15 μg/min and increased 5 to 10 μg/min every 3 to 5 minutes until mean arterial pressure falls (usually by >20 mm Hg), the pulmonary vascular pressure is brought to the desired level (if it is being measured), headache becomes intolerable, or angina (if present) is relieved. Development of tachycardia during nitroglycerin infusion can indicate that cardiac filling pressures and cardiac output have fallen to low levels. Nitroprusside, which preserves cardiac output, might be a more appropriate therapeutic option under this circumstance.

Isosorbide dinitrate can also be given intravenously. In patients with severe pulmonary edema, the combination of high-dose isosorbide dinitrate plus low-dose furosemide was found to be more effective (50% fewer acute

myocardial infarctions) than the combination of high-dose furosemide plus low-dose isosorbide dinitrate. The onset of action of intravenous isosorbide dinitrate is rapid (peak vasodilation at 5 min), but the short half-life (about half an hour) requires frequent repeat dosing when it is given by bolus injection. Usually, 3 mg is injected intravenously every 5 minutes until oxygen saturation increases, arterial blood pressure falls more than 30%, or systolic pressure is less than 90 mm Hg. The effective cumulative dose is generally around 12 mg.

Other nitrates can also be useful, especially in increased pressure pulmonary edema, if the patient is not so critically ill that urgent intravenous therapy is required. *Transdermal nitroglycerin* ointment, 0.5 to 2 inches, and oral isosorbide dinitrate, 20 to 100 mg, are effective venodilators with prolonged duration of action (3–5 hr). The advantage of ointment is that it can be wiped off if necessary, but both agents have the disadvantage that effects cannot be as precisely controlled as in intravenous therapy. Tolerance to the effects of transdermal nitroglycerin can develop rapidly but can be restored after a nitrate-free interval (usually overnight).

Other vasodilators may be useful in the treatment of selected cases of acute increased pressure pulmonary edema but have not been widely used. *ACE inhibitors*, such as captopril and enalapril, act both to reduce pulmonary vascular pressure and to increase cardiac output. The ACE inhibitors have proved to be useful agents in the treatment of more indolent pulmonary edema states. However, their use is not recommended in the setting of acute myocardial infarction. A placebo-controlled, randomized, double-blind clinical trial of intravenous enalaprilat (1 mg over 2 hr) in a small number of congestive heart failure patients with acute pulmonary edema showed reduced pulmonary capillary wedge pressure, increased renal blood flow, and slightly improved oxygenation with therapy.[367]

Diuretics

Patients with symptoms of pulmonary edema may also benefit from administration of diuretic agents.[368] These drugs may exert a modest immediate effect by increasing venous capacitance and decreasing the relative perfusion of flooded alveoli (acting as vasodilators), but their principal mechanism of action is to increase sodium and water excretion by the kidneys. The resultant diuresis causes a decrease in left ventricular volume and pressure and thereby a reduction in the pressure at the filtration sites in the lungs. The effects of therapy may be delayed for hours to days. The potent loop diuretic *furosemide*, 20 to 40 mg by slow intravenous injection, is the most useful agent in pulmonary edema. Furosemide is equally effective when administered by continuous infusion: a loading dose of 80 mg is followed by a continuous infusion at 10 to 20 mg/hr; if there is no response in an hour, the loading dose is given again and the infusion rate is doubled. Equivalent doses of other loop diuretics (bumetanide, torsemide, or ethacrynic acid) should have the same effects. Because these drugs cause excretion of substantial amounts of potassium and chloride in addition to sodium and water, their use can be associated with severe hypokalemic, hypochloremic metabolic alkalosis and an increased tendency for development of cardiac arrhythmias if potassium balance is not carefully corrected. Oral or parenteral administration of potassium chloride is usually necessary. Potassium-sparing diuretics, such as *spironolactone*, may also be of some benefit, but the delayed onset of their relatively mild diuretic action makes them less useful than the loop diuretics in the treatment of acutely ill patients.

If the patient is hypotensive or in frank shock, diuretics are usually not of much benefit, because poor renal perfusion limits any effects they might have on the nephron. In this circumstance, continuous venovenous ultrafiltration can reduce intravascular volume even in patients who require vasopressors for blood pressure support.

If the patient has severely diseased kidneys, diuresis may not be an option. In this circumstance, continuous arteriovenous hemofiltration with or without countercurrent dialysis[369,370] or venovenous ultrafiltration,[371] should be considered. These techniques represent considerable advances over traditional hemodialysis, which was often impossible in hemodynamically unstable patients (especially those with low cardiac output or hypotension), and peritoneal dialysis, which was both slow and poorly tolerated. Hemofiltration can be instituted, maintained, and managed successfully by well-trained intensive care unit nurses and physicians, and it is not complicated by hypotension because the circuits have small volumes, and pressures are low. Considerable fluid (≤200–300 mL/hr) can be removed gradually, with the amount being titrated to the patient's cardiovascular status.

Reduction of blood volume by diuresis (or other means) may not be possible or beneficial in all patients. If the patient is hypotensive, responds to intravascular volume reduction with dramatic decreases in cardiac output and delivery of oxygen to tissues, or develops significant tachycardia, another approach to therapy must be considered in addition to, or in combination with, blood volume reduction.

The value of diuretics in patients with ALI is discussed later.

Inotropic Agents

Patients with pulmonary edema who have poor cardiac output and hypotension may benefit from inotropic agents, which can be useful in managing patients with hypotension caused by cardiac pump failure, mechanical ventilation, or therapy directed at reducing thoracic blood volume. Inotropic agents increase cardiac output and therefore can lower the driving pressure for fluid filtration in the lungs by improving myocardial contractility.

Catecholamines are the most useful agents in the acute situation. Actions of these drugs are related to the magnitude of their effects on α- and β-adrenergic receptors: α stimulation results in peripheral vasoconstriction; β_1 stimulation results in cardiac stimulation; and β_2 stim-

ulation results in vasodilation (and bronchodilation). Relatively nonselective agonists, such as norepinephrine, increase cardiac contractility, but their usefulness is somewhat limited by their tendency to raise systemic vascular resistance (which in turn limits the improvement in cardiac output) and to increase myocardial oxygen consumption because of increased heart rate and afterload. The selective β-agonist isoproterenol causes large increases in cardiac output and decreases in pulmonary capillary pressure, but its vasodilatory effects often lead to reductions in arterial pressure and increases in heart rate. The myocardium may become increasingly irritable, and myocardial ischemia can be aggravated by reduction of arterial diastolic pressure. The drugs most commonly used to provide short-term, intravenous inotropic support in acute pulmonary edema are *dopamine* (the immediate precursor in the endogenous synthesis of norepinephrine) and the synthetic catecholamine *dobutamine*.

At low doses, dopamine increases cardiac contractility, improves cardiac output without causing significant changes in heart rate or myocardial oxygen consumption, reduces systemic vascular resistance, and can directly increase renal blood flow by stimulating dopaminergic receptors, thereby increasing urine output and salt and water excretion. It is particularly useful when hypotension complicates pulmonary edema; its vasopressor activity raises systemic blood pressure while cardiac output is maintained or increased. Ventricular filling pressures are often unchanged or even raised by dopamine infusion, however, and the pressure for fluid filtration in the lungs may actually increase. Venoconstriction may aggravate this stronger force for edema accumulation in the lungs by redistributing blood volume toward the thorax. For this reason, a vasodilator (e.g., nitroglycerin and nitroprusside) may also be given in order to reverse some of the undesired vasopressor effects of dopamine. When hypotension is a major concern, a predominant venodilator (e.g., intravenous nitroglycerin, nitroglycerin ointment) can be administered with dopamine to reduce thoracic blood volume while arterial pressure is supported. Dopamine can also be used to counteract hypotension caused by nitroprusside infusions. Measurement of pulmonary vascular pressure, in addition to systemic blood pressure, may be helpful when vasodilators are also being infused. As the dose of dopamine is increased, α stimulation begins to occur along with the release of endogenous norepinephrine from nerve endings. This produces a pressor effect but also increases heart rate, ventricular irritability, and arrhythmias. Increased filling pressures in the heart also aggravate the tendency for edema formation in the lungs. Intravenous dopamine therapy is started at 2 to 5 μg/kg/min, and the dose is titrated to produce the desired effects. Doses greater than 10 to 15 μg/kg/min are usually associated with prominent α effects, and such therapy may be complicated by arteriolar vasoconstriction so intense that digital necrosis may occur. Dopamine must be infused through a large-bore, secure catheter because tissue infiltration results in necrosis from local vasoconstriction.

Dobutamine differs from dopamine in that dobutamine does not cause systemic vasoconstriction. It is primarily a positive inotropic agent but also has a mild vasodilating effect. Dobutamine increases cardiac output because it has a direct inotropic effect and because systemic vascular resistance is decreased. Filling pressures in the heart tend to fall with dobutamine infusions (rather than rise, as with dopamine), which is beneficial relative to the forces governing fluid filtration in the lungs. Dobutamine might also increase the rate of alveolar fluid clearance,[372] but the clinical relevance of this effect is also unknown. Renal blood flow tends to increase with dobutamine infusions because cardiac output improves (rather than because renal dopaminergic receptors are stimulated, as with dopamine). Dobutamine is particularly useful for the treatment of pulmonary edema due to cardiac decompensation resulting from decreased ventricular contractility.

Dobutamine infusions are started at 2 to 3 μg/kg/min, and the dose is increased every 10 to 30 minutes until the desired effects are produced. Effects may be delayed several minutes, and the maximal effect of any dose occurs after 10 minutes or more. The usual dose is 5 to 15 μg/kg/min. Side effects are common when the dose exceeds 15 μg/kg/min. Arrhythmias may occur, and tachycardia indicates the dose is too high and stroke volume is not adequate. In this circumstance, myocardial oxygen demands are excessively increased by the rapid heart rate in the presence of positive inotropy. Myocardial oxygen supply is decreased because coronary perfusion pressures are reduced and diastolic perfusion time is shortened. Dobutamine therapy is most successful when left ventricular filling pressures are kept at 18 to 20 mm Hg or higher. Dobutamine should be administered cautiously to patients with atrial fibrillation because the drug facilitates atrioventricular nodal conduction and may cause an increase in ventricular rate. Digitalis may be a more appropriate inotropic agent in that circumstance.

The lives of a limited number of patients with severe pulmonary edema refractory to immediate drug therapies might be saved by temporary mechanical support of hemodynamics (i.e., intra-aortic balloon pumps or ventricular-assist devices). Extrapulmonary gas exchange,[373] or heart transplantation, lung transplantation, or both[374] (see Chapter 89) can be appropriately offered to limited number of patients, but the possibilities can be considered only if all other therapeutic options have been exhausted.

Therapeutic Strategy

The possible therapeutic options that have been discussed are directed at the immediate treatment of patients with life-threatening pulmonary edema. Therapy must be clearly goal oriented, responsive to the underlying pathophysiology, and frequently reassessed until the patient is stable. In hydrostatic pulmonary edema, the common goal of therapy is to reduce the transudation of fluid into the lungs. Because the rate of edema formation increases exponentially with increases in pulmonary vas-

cular pressures,[375] pressure control is crucial for successful therapy.

Increased Pressure Edema

The acute recognition and management of congestive heart failure has been the subject of comprehensive reviews.[376] With hydrostatic pulmonary edema, the goal of therapy is to reduce the hydrostatic pressure causing edema formation in the lungs. The major objective is to achieve a net negative fluid balance without adversely affecting myocardial performance. The work of the heart must be reduced as much as possible by restricting physical activity and preventing pain and anxiety, which act to increase the work of the heart by increasing sympathetic tone. As the heart fails, cardiac performance is reflexly preserved by progressive increases in vascular volumes that act to increase cardiac stroke volume and work (the Frank-Starling mechanism). This compensatory increase in preload of the left ventricle results in pulmonary venous hypertension and raises the driving pressure for fluid filtration out of the pulmonary microcirculation. As heart failure worsens, cardiac output falls, pulmonary and systemic venous pressures rise, systemic vascular resistance increases, and edema, in the lungs and in the periphery, becomes the major manifestation of compromised cardiac function. In patients with increased pressure pulmonary edema, a reduction of vascular volume and an increase in cardiac output cause the driving pressure for edema formation to decrease. Because the normal safety factors protecting the lungs from edema driven by high filtration pressures are intact, the pressure need be lowered only to near normal. At pulmonary capillary wedge pressures less than 20 mm Hg, fluid filtration in the lungs usually should not be sufficient to cause pulmonary edema. Patients with severe cardiac failure may tolerate higher pressures (because baseline barrier permeability is lowered in the lungs and lymphatic removal capability is increased) and may require such pressures to maintain cardiac output. Therapy is directed at reducing the work the heart must perform and at increasing the heart's efficiency for the work it must do. Some patients with severe hydrostatic pulmonary edema require mechanical ventilation with positive-pressure ventilation. The resolution of alveolar edema in these patients is not simply a function of lowering lung vascular pressures; other mechanisms that augment alveolar fluid clearance are important.[377]

Most patients with acute pulmonary edema caused by cardiac failure have systolic dysfunction, but a sizable minority (~30%) have diastolic dysfunction. Cardiac contraction is normal, but relaxation is impaired. Because the ventricle does not relax normally, end-diastolic pressure is increased, thereby increasing hydrostatic pressure in the lung microcirculation. Acute diastolic dysfunction producing pulmonary edema is now recognized as a common manifestation of acute myocardial ischemia or uncontrolled hypertension. Other causes include diabetes mellitus, aortic stenosis, infiltrative cardiomyopathies, endocardial fibroelastosis, hypothermia, septic shock, elevated thoracic pressures from mechanical ventilation, and pericardial effusion. Causal or aggravating conditions should be corrected (e.g., revascularization for coronary artery disease, control of systemic hypertension). The goal of therapy in acute diastolic dysfunction is to lower elevated filling pressures (by the cautious use of diuretics and nitrates) without significantly reducing cardiac output. These patients are prone to develop hypotension in response to diuretics and nitrates because adequate cardiac output depends on elevated filling pressures in the heart. Because systolic function is normal, positive inotropic agents do not help and can actually aggravate ischemia.

In the setting of acute increased pressure pulmonary edema, it is especially important to identify and treat correctable causes of heart failure. Acute myocardial infarction, ongoing myocardial ischemia, arrhythmias, valvular lesions, systemic hypertension, ventricular septal rupture, rheumatic or other inflammatory myocarditis, digitalis intoxication, pulmonary embolism, infection, thyrotoxicosis, or severe anemia may have caused the heart to fail and must be corrected. Cardiac patients presenting with pulmonary edema may not complain of chest pain, but most of them have significant coronary artery disease, and pulmonary edema may be the only manifestation of silent myocardial ischemia.

Increased Permeability Edema

The strategy for managing patients with ALI and increased permeability pulmonary edema differs from that for patients with increased pressure pulmonary edema because the endothelial and epithelial barriers are damaged in permeability edema, whereas they are normal in high-pressure edema. The problem is not that the driving pressure for edema formation is abnormally high, but that edema forms even at low driving pressures. The goals of therapy (Table 55-9) are to treat the cause of lung injury, to provide support while the repair phase begins, to use a lung-protective ventilator strategy that will not worsen the lung injury, and to reduce as

TABLE 55-9. Acute Lung Injury: Important Principles of Management

MINIMIZE EDEMA ACCUMULATION
Ensure lowest possible pulmonary microvascular pressure
Reduce vascular volume
FIND AND TREAT INFECTION
PROVIDE SUPPORTIVE THERAPY
Administer oxygen
Use lung-protective ventilation
Optimize blood pressure and cardiac output
DO MORE GOOD THAN HARM
Avoid hypotension
Avoid volume overload
Avoid oxygen toxicity
Avoid infection

much as possible the driving pressures for fluid movement across the injured barriers into the lungs.

The cause of lung injury may not always be apparent. If the cause is not obvious, it should be assumed to be infection, which is the most common treatable underlying cause of ALI. Although the patient is often seriously ill, diagnostic studies must be performed to identify a possible source of infection, so that appropriate drainage and antimicrobial therapy can be instituted. Plain chest roentgenograms usually are not helpful. Abdominal sonograms and computed tomography scans can be diagnostically useful. Sepsis from intra-abdominal infection is common and may be especially difficult to identify. Many of these infections require surgical drainage if antimicrobial drug therapy is to be effective. Because specific therapy for ALI is not usually available (unless the cause is a localized infection), supportive therapy is extremely important. The initial concerns are to support ventilation and circulation. Patients with ALI may be hemodynamically unstable, and ventilatory support can be complicated by hypotension or frank shock. PEEP, which may be required for adequate oxygenation, may compound the problem by impeding venous return to the heart and decreasing cardiac function.

Patients with low pulmonary capillary wedge pressures (<10 mm Hg) or central venous pressure (<4 mm Hg) and systemic hypotension require fluid resuscitation to support blood pressure and end-organ perfusion. If the patient has active, ongoing blood loss or the hemoglobin concentration is low (<7.0 g/dL), packed red blood cells are effective not only to expand intravascular volume and restore blood pressure but also to increase the oxygen-carrying capacity of the blood. Patients who are not bleeding and who have normal hemoglobin concentrations should be resuscitated with crystalloid solutions. Because the barriers restricting colloid movement from the vascular space into the lungs are not functioning normally when the lungs are injured, osmotic pressure differences favoring fluid movement into the vascular space cannot be established in the lungs; therefore, there is no advantage to fluid resuscitation with expensive colloid solutions.

Patients whose hypotension does not respond to fluid resuscitation or who have normal (>10 mm Hg) or elevated pulmonary capillary wedge pressure require vasopressors or positive inotropic agents. If systemic vascular resistance is elevated, dobutamine is appropriate. For patients with septic shock, generalized vasodilation resulting in low systemic vascular resistance is the major hemodynamic abnormality.[378] Dopamine and norepinephrine, with their vasopressor properties, are often useful to support blood pressure.

Aggressive hemodynamic and ventilatory support of critically ill patients can be detrimental if complications of therapies become more significant problems than the underlying disease itself. Strategies to increase systemic oxygen delivery (e.g., with inotropes, intravascular fluids, and blood transfusions) or to achieve supranormal values for the cardiac index or normal values for mixed venous oxygen saturation did not improve mortality when applied to all critically ill patients, but did improve outcome in patients with sepsis who were treated very early in their course.[379,380] A recent ARDS Network clinical trial showed that after the initial treatment of shock in the first 24 hours, a strategy to restrict fluids to reduce intravascular pressures (central venous pressure or the pulmonary arterial wedge pressure) improved clinical outcomes in patients with ALI.[381]

A multicenter, randomized, controlled clinical trial of transfusion requirements in critically ill patients with euvolemia after initial treatment showed that a restrictive strategy of red cell transfusions (in which red cells were transfused if the hemoglobin concentration dropped below 7.0 g/dL and hemoglobin concentrations were maintained at 7.0–9.0 g/dL) was at least as effective as and was possibly superior to a liberal transfusion strategy (in which transfusions were given when the hemoglobin concentration fell below 10.0 g/dL and hemoglobin concentrations were maintained at 10.0–12.0 g/dL), with the possible exception of patients with active coronary ischemic syndromes, such as acute myocardial infarction and unstable angina.[382]

Lung-Protective Ventilator Strategies. In experimental animals, ventilation with high tidal volumes can increase vascular filtration pressures; produce stress fractures of microvascular endothelium, alveolar epithelium, and basement membranes; and cause lung rupture (so-called ventilation-induced lung injury).[239,383,384] The injury appears to be due to increased lung excursions at high volumes (so-called volutrauma), not high airway pressure per se, because it can be prevented by limiting thoracic motion (e.g., by placing the chest in a cast). Because the evidence from animal experiments and small clinical trials seemed compelling,[385,386] clinical studies were done to test the potential benefit of lower tidal volumes and reduced airway pressures. In a large multicenter trial, mortality was reduced from 40% to 31% with a 6-mL/kg ideal body weight tidal volume strategy that also limited plateau airway pressure to less than 30 cm H_2O.[244] In this large clinical trial of 861 patients, the small tidal volume approach also was associated with a lower incidence of nonpulmonary organ failure. The protocol for carrying out the lung-protective ventilatory strategy is described in detail in Table 55-10. The results of this trial have transformed management of patients with ALI. In fact, a follow-up clinical study has indicated that ventilation with this level of tidal volume and plateau pressure limitation used in the original NIH ARDS Network trial is associated with an overall reduction of mortality to 26%.[387] In this study, elevated levels of PEEP did not decrease mortality, but the basic lung-protective strategy was validated as effective for reducing mortality.

Interestingly, results from an Italian study showed that a low tidal volume strategy in ARDS patients attenuated the inflammatory response in both the lungs and the bloodstream, as measured by a reduction in neutrophil and cytokine concentrations in BAL fluid and a reduction in cytokines in circulating blood.[245] Other studies have confirmed that low tidal volume lung-protective ventilation is associated with reduction in inflammatory markers in the lung.[244] There is also evidence that

TABLE 55-10. National Institutes of Health ARDS Network: Lower Tidal Volume Ventilation for Acute Lung Injury/Acute Respiratory Distress Syndrome Protocol Summary

Ventilator mode	Volume assist-control													
Tidal volume	≤6 mL/kg PBW*													
Plateau pressure	≤30 cm H_2O													
Ventilation set rate/pH goal	6–35, adjusted to achieve arterial pH ≥ 7.30 if possible													
Inspiratory flow (I:E)	Adjust flow to achieve I:E = 1:1–1:3													
Oxygenation goal	65 mm Hg ≤ Pa_{O_2} ≤ 80 mm Hg *or* 88% ≤ Sp_{O_2} ≤ 95%													
F_{IO_2}/PEEP COMBINATIONS:														
F_{IO_2}	0.3	0.4	0.4	0.5	0.5	0.6	0.7	0.7	0.7	0.8	0.9	0.9	0.9	1.0
PEEP (cm H_2O)	5	5	8	8	10	10	10	12	14	14	14	16	18	18, 22, 24
(Further increases in PEEP to 34 cm H_2O allowed but not required.)														
Weaning	Attempts to wean by pressure support required when F_{IO_2}/PEEP ≤ 0.40/8													

*PBW:
Male PBW = 50 + 2.3 [height (inches) − 60] *or*
50 + 0.91 [height (cm) − 152.4]
Female PBW = 45.5 + 2.3 [height (inches) − 60] *or*
45.5 + 0.91 [height (cm) − 152.4]

ARDS, acute respiratory distress syndrome; F_{IO_2}, fraction of inspired oxygen; I:E, ratio of the duration of inspiration to the duration expiration; Pa_{O_2}, partial pressure of oxygen in arterial blood; PBW, predicted body weight; PEEP, positive end-expiratory pressure; Sp_{O_2}, oxyhemoglobin saturation by pulse oximetry.
From Brower RG, Ware LB, Berthiaume Y, et al: Treatment of ARDS. Chest 120:1347–1367, 2001.

there probably is reduction in alveolar epithelial injury based on a decline in surfactant protein D levels in the plasma of patients treated with the lung-protective ventilatory strategy.[331] More clinical and experimental work is being done to determine the mechanisms responsible for the lung-protective effect. It is clear that use of the lung-protective ventilatory strategy is not associated with an adverse effect on hemodynamics or an increased need for supportive therapies, including intravenous fluids, diuretics, vasopressors, sedation, or neuromuscular blockade.[388]

A number of adjuncts to conventional mechanical ventilation have been proposed and studied in small numbers of patients, including prone positioning extrapulmonary gas exchange (oxygenation, carbon dioxide removal, or both),[389] liquid ventilation, tracheal gas insufflation, permissive hypercapnia, and high-frequency ventilation.[390] All of these adjuncts are investigational, and their use should probably be restricted to controlled clinical trials. Repositioning the patient is the simplest and least invasive of these techniques.[391] Turning patients with severe respiratory failure to the prone position can result in improved pulmonary gas exchange,[392] probably as a result of increased ventilation of dorsal lung units and more favorable matching of ventilation and perfusion. Turning critically ill, mechanically ventilated patients from the supine to the prone position is not an easy task, however, and there are risks involved (e.g., extubation, kinked ventilator tubing, disconnection of catheters, hemodynamic instability, pressure sores on the face). Not all patients respond by improving their oxygenation. A randomized trial showed no benefit of prone positioning for patients with acute respiratory failure, including ALI.[393,394]

Prevention of ventilator-associated pneumonia has been the subject of a comprehensive review and a meta-analysis.[370] Although a relation between gastric colonization with gram-negative bacilli and nosocomial pneumonia in intensive care unit patients has been shown,[395] selective decontamination of the digestive tract does not appear to significantly improve mortality even though respiratory tract infections are prevented.[396] The simple approach of increasing the angle of the head of the bed to 45 degrees is beneficial in reducing nosocomial infection.[397] Simple precautions, such as meticulous handwashing and removal of unnecessary catheters, should be followed.

The literature from the patients' point of view is sparse: Only a few group studies and scattered personal observations about patient experiences in intensive care units have been reported.[398] No reports of what it is like to have pulmonary edema could be found. A critical care text has sections dealing with nursing perspectives but no section on patient perspective, and both nurses and patients are slighted in this textbook. The limited information available indicates that many patients had significant amnesia for most of their intensive care unit stay and poor insight into their condition. Many survivors experience depression, which tends to diminish over a prolonged recovery time. Some experience posttraumatic stress disorder. Patient experience and longer-term outcomes are important areas that have only recently been better studied.[143,399]

Specific Pharmacologic Therapies. Therapeutic agents that have a rational place in our incomplete understanding of the pathogenesis of ALIs and that have been studied in patients with ALIs and sepsis disorders include corticosteroids, ibuprofen, nitric oxide, prostaglandin E_1 (PGE_1), liposomal prostaglandins E_1 and E_2, surfactant, antiendotoxin and anti–TNF-α antibodies, platelet-activating factor receptor antagonist, interleukin-1 receptor antagonist, ketoconazole, *N*-acetyl-

cysteine, oxothiazolidine carboxylate, and pentoxifylline. None of these agents has shown any benefit on mortality in large-scale, prospective, randomized, controlled clinical trials. There have been sporadic reports indicating that other agents might be useful. The state of clinical trials in ARDS was the subject of conference reports in 1992,[400] and in 2000,[94] which summarized the status of possible therapies and the opportunities and challenges faced in evaluating them. Another recent review summarizes the data.[401] The establishment of the ARDS clinical trials network by the NHLBI has already fostered the conduct of large, well-designed studies to define the efficacy and appropriate use of therapy for ALI; additional trials on the value of glucocorticoids late in the evolution of ARDS have just been completed, and a study on the efficacy of reducing lung vascular pressures is under way.

Whether or not newer anti-inflammatory therapies will be useful in patients with ALI remains an important question. Although inflammatory reactions can damage tissue, it is important to remember that inflammation plays an important beneficial role in the elimination of invading microorganisms. Because inflammatory pathways are redundant, blocking any one inflammatory mediator (or even multiple mediators) may have little or no effect on the overall inflammatory response. If the mechanisms of lung injury differ after various clinical events, the application of therapy directed at particular mechanisms would not be appropriate until all the underlying mechanisms are recognized. The moderate incidence of severe ALI among patients admitted with high-risk diagnoses[402] complicates the problem. Finally, the timing of therapy is likely to be an important factor.

Corticosteroids. Of the possible pharmacologic agents for treatment of ALIs, corticosteroids have the longest history. Despite a seemingly compelling rationale for their use in the setting of ALI from sepsis, four separate, prospective, randomized, double-blind, placebo-controlled trials of high-dose methylprednisolone therapy failed to show any benefit.[403] Corticosteroid therapy did not prevent the development of ALI or decrease its incidence in patients with the sepsis syndrome. Neither did it hasten the reversal of ARDS, lower mortality, or improve respiratory function. Moreover, corticosteroids were associated with both a greater 14-day mortality rate in patients who developed ALI and an increased frequency of associated infections. Corticosteroids also were ineffective in the sepsis syndrome[404] and may have caused harm. Thus, corticosteroids should not be given to patients at risk for or with developing ALIs unless there is some other indication, such as a history of recent steroid therapy or another reason to suspect adrenal insufficiency. One exception may be the fat embolism syndrome. A prospective, randomized, double-blind, placebo-controlled trial of corticosteroid treatment in 64 patients with long bone fractures showed that high-dose methylprednisolone effectively prevented the development of the fat embolism syndrome,[405] and short-course corticosteroid therapy appears to be appropriate in such patients, particularly in those who developed the characteristic petechial rash.

The generally disappointing results of corticosteroid trials in ALI have not discouraged investigators. Because of the diversity of underlying causes and the changing character of ALIs as they progress, some investigators believe that corticosteroids might be beneficial in subsets of patients or when given at a particular time (e.g., during the proliferative phase) or for a more sustained period.[406] Results of studies of corticosteroid therapy late in the course of ARDS (so-called rescue therapy) were encouraging, and a small (24-patient), randomized, double-blind, placebo-controlled clinical trial in patients with severe ARDS whose Lung Injury Score had failed to improve by the seventh day of respiratory failure showed improvement in lung injury and other organ dysfunction scores, and reduced mortality in the treated patients.[407] However, an NHLBI-sponsored trial of corticosteroid therapy (methylprednisolone 2 mg/kg) beginning on day 7 to 21 of ARDS showed no reduction in 60- or 180-day hospital mortality in patients treated with corticosteroids compared with placebo.[408] In addition, there were important neuromuscular complications in patients treated with methlprednisolone.

One major lesson learned from the experience with corticosteroids as early or late treatment for ALI is that no matter how compelling the rationale for their use might be based on preclinical studies, well-designed and executed large-scale clinical trials must be conducted before a promising therapy is accepted for clinical use.

Surfactant. The possibility of administering exogenous surfactant in the treatment of ALI has attracted considerable attention.[409] The rationale for such therapy is based on abnormalities of surfactant composition and function that have been found in ALIs and on the approval of an artificial surfactant (colfosceril [Exosurf]) for clinical use. Surfactant therapy has revolutionized the treatment of neonatal respiratory distress syndrome. Among the many possible benefits of surfactant therapy are stabilized alveoli, improved respiratory compliance, decreased work of breathing, improved gas exchange and consequently decreased need to administer toxic concentrations of oxygen, and enhanced phagocytosis and bronchial transport; these advantages plus surfactant's antibacterial and antiviral activity should reduce the possibility of lung infection. Surfactant might also inhibit the respiratory burst of PMNs and might modulate lung fibroblast and macrophage activity to decrease release of inflammatory mediators.

Results in experimental models have been mixed, but taken as a whole, they appear to indicate that animals are not harmed by surfactant therapy and that improved gas exchange and lung compliance are reasonable possibilities. A preliminary communication indicated that colfosceril could be administered safely to ventilated patients with sepsis-induced ARDS, but no differences were found in any physiologic parameters when compared with control subjects, and a dose-dependent trend in reduction of mortality did not reach statistical significance.[410] The pilot trial was followed by a large-scale, prospective, double-blind, randomized, placebo-controlled clinical trial of aerosolized surfactant in patients with sepsis-induced ARDS.[411] This study showed no significant

effect on 30-day survival, length of stay in the intensive care unit, duration of mechanical ventilation, or physiologic function. A more recent large clinical trial of recombinant surfactant protein C demonstrated no reduction in mortality or in the duration of mechanical ventilation in patients with the ARDS.[412]

Antioxidants. Clinically, *N*-acetylcysteine has advanced farther than any other therapeutic strategy because of the hypothetical role of oxidants in the pathogenesis of ALI. *N*-Acetylcysteine is unique among the free radical scavengers because it is already in widespread clinical use for acetaminophen and paracetamol overdose, conditions for which it has been found to be safe and effective. It is also novel among anti-inflammatory agents being tested for human therapy because it acts selectively to quench oxygen radicals rather than globally to suppress leukocyte function. *N*-Acetylcysteine appears to act both directly, by scavenging oxygen free radicals, and indirectly, by metabolism into glutathione, which is an important endogenous antioxidant.

Experimental animal studies were encouraging. Results from a randomized, double-blind pilot trial in 30 patients with ALI showed that plasma and red blood cell glutathione levels were decreased in the presence of ALI and could be increased by *N*-acetylcysteine administration. Improvements were shown in chest radiograph edema scores, pulmonary vascular resistance, shunt fraction, static compliance, cardiac output, oxygen delivery, and oxygen consumption.[413] Four subsequent small clinical trials in ALI patients examining the effects of *N*-acetylcysteine or oxothiazolidine carboxylate (Procysteine), which also acts to augment glutathione stores, have been conducted.[414] Enthusiasm for this type of therapy has been tempered by the possibility that antioxidants could compromise defenses against infection.

Pentoxifylline. Pentoxifylline is a phosphodiesterase inhibitor that increases cyclic adenosine monophosphate in PMNs and inhibits their inflammatory function.[415] Pentoxifylline has been in clinical use for many years in the treatment of intermittent claudication, based on its purported ability to increase the flexibility of red blood cells and thereby reduce blood viscosity and increase capillary blood flow. The hypothesized role of leukocytes in ALI led to studies in experimental models that have demonstrated prevention or attenuation of various ALIs in several species, apparently by inhibiting PMN function.[416] However, a related compound, lisofylline, failed to show efficacy in a large phase III NHLBI trial.[417]

Treatments for Sepsis. Two different monoclonal antibodies against endotoxin have been investigated as therapy for sepsis, the most common antecedent to ALI and ARDS: HA-1A human (also known as Centoxin or nebacumab) and E5 murine (also known as Xomen).[418] The underlying rationale for therapy with these agents and the two original clinical trials that were reported have been critiqued, an economic assessment of HA-1A monoclonal antibody for gram-negative sepsis has been made, and a detailed analysis of the original trials and the questions raised about them and regarding the cost and resulting ethical dilemmas[419] was published.

In patients with sepsis and a documented gram-negative infection who were not in shock, ARDS (as defined previously in a trial of corticosteroids in patients with ALI) occurred in 14% of the patients in the E5 murine trial; 60% (6 of 10) of those treated with the E5 antibody died, compared with 78% (7 of 9) of those treated with placebo. In the second E5 trial, the antibody appeared to offer some protection against development of ARDS in sepsis patients, but there was no effect on survival.[418] In the HA-1A trial, ALI (ARDS as defined by the expanded definition of ALI) occurred in 11% of the patients with documented gram-negative bacteremia; data on the resolution of lung injury were not published, but major complications of sepsis, which included the patients with ARDS, resolved in 62% of the treated patients compared with 42% of those given placebo. A subsequent publication discussed the results of HA-1A therapy in the 63 septic patients with ARDS from the larger trial: The antibody did not reverse acute respiratory failure or improve long-term survival.[420]

In addition to these antiendotoxin antibodies, large-scale clinical trials in patients with sepsis syndrome treated with inhibition of TNF-α[421] and of interleukin-1[422] have been reported. Neither showed a significant difference in mortality in patients who received the inhibitors as compared with those who received placebo. No differences in the frequency of continuing or new organ system failures, such as occurs in ARDS, were found in the anti–TNF-α trial. In the interleukin-1 receptor antagonist trial, a secondary analysis of the results indicated that survival time might have been increased for patients with ARDS (28-day mortality of 44% for placebo and 34% for antibody, with the improvement occurring in the sickest patients).

Conversely, one large clinical trial has reported efficacy of activated protein C for reducing mortality in severe sepsis. In this randomized, placebo-controlled clinical trial, mortality was reduced by 6%.[423] The most common source of severe sepsis was pneumonia, and 75% of the patients were mechanically ventilated and 75% were in shock. Because of the potential for inducing serious bleeding, patients were excluded from the trial who had a history of recent surgery, recent bleeding, severe trauma, or other factors that would increase the risk of bleeding. The mechanisms by which activated protein C works to reduce mortality are probably multifactorial. There is evidence that activated protein C reverses the procoagulant environment induced by severe sepsis and also that it has anti-inflammatory effects that may reduce cytokine-induced organ injury. Because of the relationship of organ injury in severe sepsis to the pathogenesis of ALI, there is interest in the possibility that treatment such as activated protein C might be efficacious for patients with ALI.[424,425] Other therapies that might inhibit coagulation and inflammation are also potentially worth testing in clinical trials. There has been some controversy regarding the results of the activated protein C trial, and some experts recommended further trials to evaluate the efficacy of this agent, particularly because two other clinical trials using anticoagulants did not show efficacy in patients with severe sepsis.

Consequently, a new placebo-controlled, double-blind clinical trial of activated protein C has been initiated to test its efficacy in severe sepsis. One recent clinical trial of 75 patients showed no benefit of activated protein C therapy for patients with ALI primarily on nonseptic etiologies.[426]

Prostaglandin E_1 and Inhaled Nitric Oxide. Another potential pharmacologic treatment of ALI was PGE_1, a vasodilator with anti-inflammatory properties. However, a 13-center, randomized, double-blind, placebo-controlled clinical trial showed no improvement in survival (mortality rate at 30 days was 60% in the treated group, 48% in the placebo group).[427] Reduction in systemic and pulmonary vascular resistance and evidence of increased oxygen availability and consumption were counterbalanced by such adverse effects as diarrhea, hypotension, fever, and cardiac arrhythmias. The trial was not designed to resolve the role of PGE_1 in patients at risk for developing ALI, so the question of any prophylactic benefit was left unanswered. A smaller, independent study from one institution found PGE_1 to be an effective vasodilator, but it did not influence the development of multiple organ failure or affect mortality of patients with ALI. A secondary report from the larger trial emphasized a purported benefit of PGE_1 on oxygenation in a subset of patients, even though survival was not improved; other studies have indicated that the drug causes deterioration of pulmonary gas exchange and aggravation of arterial hypoxemia by increasing perfusion of underventilated or unventilated lung areas. Another secondary report from the trial emphasized purported beneficial effects with PGE_1 therapy on hemodynamic performance, hepatic function, and leukocyte availability, but such effects were rather subtle, and their clinical significance was not obvious.

Inhaled nitric oxide can also improve oxygenation and lower pulmonary vascular pressure in patients with ARDS, but it does not lead to a sustained improvement in oxygenation as compared with conventional therapy,[428] and it has no beneficial effects on mortality.[429,430] Use of these drugs in patients with ALI is not recommended, although inhaled nitric oxide may have some value as a form of rescue therapy for ARDS patients with profound hypoxemia.

There is now preclinical data that the use of bone marrow-derived mesenchymal stem cells has potential value for the treatment of severe acute lung injury. In several of the studies, there is evidence that paracrine factors released by the cells can elaborate anti-inflammatory cytokines that decrease lung injury as well as growth factors such as keratinocyte growth factors that can enhance recovery from acute lung injury.[430a]

OUTCOME

Resolution of Edema

Until recently, much less was known about recovery from pulmonary edema than about its formation. Water (and extravasated proteins and cellular debris) must be removed from the alveoli and the interstitial spaces to restore the lungs to their normal condition. Edema could be cleared from the lungs by five routes: lymphatics, airways, blood vessels, the pleural space, and the mediastinum. Cellular debris and particulate matter must be removed from the alveoli by macrophages or must be expectorated from the airways.

The considerable advances in our understanding of the clearance of fluid and solute from the alveoli have been the subject of several reviews.[2,431–433] Active sodium chloride transport across the alveolar epithelial barrier into the interstitium drives edema fluid removal from the air spaces (see Chapter 10). The uninjured alveolar epithelium has a remarkable ability to clear fluid from the air spaces rapidly: for example, serial edema fluid protein concentration measurements relative to simultaneous plasma protein concentrations in a saltwater near drowning patient showed that 50% to 60% of excess alveolar fluid in the lungs was removed over the course of just 4 hours.[90] In experimental studies in rabbits, instillation of 4 mg/kg of seawater into the lungs resulted in a 300% increase in alveolar fluid volume in less than 5 minutes from mostly pure water drawn in osmotically from the plasma by the hyperosmolar (881 ± 29 mOsm) instillate, 80% of which was cleared from the alveoli in 6 hours.[434] Equivalent volumes of iso-osmotic (292 ± 6 mOsm) saline instilled into rabbit lungs were cleared at a similar rate. In neither circumstance was there evidence of injury to the alveolar epithelial barrier, which has been found to be more resistant than the endothelial barrier to a wide range of injuries, including ischemia, alveolar and intravenous endotoxin and bacteria, intravenous oleic acid, acid aspiration, saltwater aspiration, hyperoxia, intratracheal bleomycin, septic and hypovolemic shock, and rewarming after severe hypothermia. Even when mild to moderate alveolar injury occurs, the capacity to transport salt and water is often preserved; in severe injury, when the barrier is physically disrupted, the capacity to clear edema is lost, of course, and the vascular endothelium becomes the limiting barrier between the vascular system and the air spaces. Clinically, the capacity to remove some alveolar edema fluid (as indicated by increase in the edema fluid–to–plasma protein concentration ratio) in the first 12 hours after the development of ALI is a favorable prognostic finding, associated with a mortality of only 20%; in contrast, the inability to resorb alveolar edema fluid early in the course of ALI was associated with a mortality of nearly 80%.[293] The results of this earlier study were confirmed in a larger, more recent study.[294] Thus, the function of the alveolar epithelial barrier early in the course of ALI may be a useful prognostic index, perhaps because it serves as a marker of the severity and extent of lung injury.

Lung Na^+,K^+-ATPase activity was increased in rats recovering from experimental thiourea-induced increased permeability pulmonary edema.[435] Alveolar fluid clearance can be increased by salmeterol in uninjured, ex vivo human lungs.[436] Experimental studies have shown that alveolar fluid clearance can be increased pharmacologically (e.g., by catecholamines), even in the presence

of ALI and alveolar edema,[2] raising the potential of therapy to hasten the resolution of alveolar edema.

Because clearance of protein from flooded alveoli is much slower (1%–2%/hr) than clearance of fluid (10%–20%/hr),[431,437] the protein left behind becomes concentrated. The rising protein concentration in the alveoli as fluid is resorbed does not affect fluid clearance, because precipitated protein exerts no osmotic pressure and the concentration of soluble macromolecules is too small to counteract the differences in ion concentration resulting from transepithelial transport. Removal of fluid from flooded alveoli may be slowed, especially when lung vascular permeability is increased, if the fluid clots. Clotting can occur because extravasation of plasma into the air spaces may lead to activation of the clotting system by surfactant or macrophage-derived procoagulants.

Fluid cleared from alveolar spaces into the alveolar interstitium can leave the lungs by flowing into the lymphatic capillaries or by moving down the prevailing pressure gradient into the loose peribronchovascular connective tissue spaces or directly into the pleural space as well. Large amounts of fluid in the air spaces may be partially cleared into peribronchovascular cuffs through the hypothesized leaky terminal-airway epithelium,[438,439] leaving alveolar fluid and solute behind to be cleared more slowly through the more impermeable alveolar epithelium.

Most of the interstitial water in pulmonary edema is in the peribronchovascular loose connective tissue spaces rather than in the alveolar walls. Because the lymphatic capillaries are arranged to drain only the alveolar wall interstitium, this route for edema removal is not significant for most interstitial water. A study in goats showed that lung lymph originated mainly from alveolar wall interstitial fluid, and the contribution of the lung lymphatic system to the clearance of interstitial edema in bronchoalveolar cuffs and interlobular septa was small. The maximum possible contribution by lung lymphatics to the clearance of interstitial edema liquid was below 10%, and airway loss of liquid by evaporation was about twice the rate of lymphatic clearance.[440] In a study of in situ perfused sheep lungs with experimental low- and high-protein pulmonary edema, during recovery from pulmonary edema, interstitial liquid was resorbed into the circulation in inverse proportion to its protein concentration, and only a very small fraction of interstitial edema was cleared by the lung lymphatics during recovery from either type of edema.[441] Some fluid from the loose peribronchovascular interstitium may drain directly into the bloodstream by crossing the walls of blood vessels in the lungs. A study of isolated sheep lungs made edematous by raising vascular pressures showed that the primary route of edema clearance was by vascular resorption; 60% of filtered water was cleared over 3 hours, 42% by reabsorption into the bloodstream, and 18% by lymphatic, pleural, and mediastinal drainage.[442] Edema may also drain into the pleural space. Pleural effusions are more common in increased pressure pulmonary edema (occurring in about 25%–50% of patients, usually on the right side if the edema is unilateral), but are present in ALIs as well (occurring in about 35% of patients).[443–445] Formation and removal of pleural effusions are discussed in detail in Chapter 68. As much as 25% to 30% of pulmonary edema fluid may leave the lungs through the pleural space.[445,446] A significant portion of the interstitial edema probably follows the prevailing pressure gradient in the lungs to drain into the mediastinum, where it could be picked up by initial lymphatics.

Short-term alveolar protein clearance appears to proceed primarily by paracellular diffusion and is size dependent.[7] Most proteins are cleared intact rather than being degraded into smaller fragments (although a few specific proteins, such as vasoactive intestinal peptide and gastrin, are degraded before being cleared). An albumin-binding protein (albondin) is expressed on lung microvascular endothelial cells, and an antibody to this protein reacts with cellular proteins of alveolar epithelial cells, which also appear to have albondin-like binding sites for albumin. A polymeric immunoglobulin receptor has also been described. The significance of these receptors is unclear. The general consensus is that transcytosis (transport via vesicles) is not a major mechanism for clearing bulk quantities of albumin or other proteins from the alveolar space. Over the long term, cellular mechanisms, principally phagocytosis and catabolism by macrophages, account for most protein clearance from the alveolar space. All insoluble, precipitated proteins are removed in this way. Macrophages are also ultimately responsible for removing senescent and dead PMNs and other debris. The small ciliated surface area of the distal air spaces seems to indicate that the mucociliary route could account for only a minor fraction of alveolar protein clearance, although proteins might reach the mucociliary escalator along currents in the alveolar fluid layer. Even were this to occur, removal would be very slow (the half-time for mucociliary clearance of particles from the alveolar space is more than 4 wk). Complete clearance of alveolar protein from pulmonary edema by any route is slow.[7]

Little is known about the mechanisms and signals that regulate endothelial barrier function or how increased endothelial permeability is returned to normal.[447] The mechanisms of resolution of lung inflammation are also poorly understood.

Increased Pressure Edema

The outcome of increased pressure pulmonary edema is determined by the underlying cause and the treatment that is used. Because most increased pressure pulmonary edema is caused by heart disease, outcome is largely determined by the patient's cardiac function. Patients with pulmonary edema that is uncomplicated by acute myocardial infarction can be expected to do well (mortality rate, <10%).[448] In the presence of acute myocardial infarction, the prognosis is worse. However, thrombolytic therapy and coronary angioplasty and stent placement have improved the survival of patients with pulmonary edema complicating acute myocardial infarction. Patients who recover from increased pressure pulmonary edema caused by cardiac disease require

long-term outpatient management aimed at preventing recurrent episodes.

Some patients develop increased pressure pulmonary edema from noncardiac causes. Most cases are iatrogenic, being caused by massive volume overload or therapy with drugs that can affect cardiac function. This is a common cause of pulmonary edema in pregnant women, as discussed in Chapter 81. These patients can be expected to do well if the cause of the edema is removed.[449]

Increased Permeability Edema

The incidence of ALI is unknown. Many authors recite the 1972 NIH speculation that there are about 150,000 new cases each year (an incidence of about 75 cases/100,000 population/yr). Some estimates indicated that the NIH figure might have been too high,[450] but the large numbers of patients enrolled in the NHLBI ARDS clinical trials since 1996 suggest that the original NIH estimate may have been reasonably accurate. A careful prospective study in King County, Washington, with demographics similar to those for the United States also indicates that the original estimate of 75 to 85 cases/100,000 is correct.[451] The outcome of ALI and resultant increased permeability pulmonary edema is determined by the underlying cause, the extent of injury, and the treatment strategy. The reported mortality rates range from 20% to 90%, but yearly ARDS mortality rates reported from a single institution in the decade between 1983 and 1993 showed a significant decrease over time that occurred in patients younger than 60 years and in those with sepsis syndrome as their risk factor for ARDS.[452] In addition, the reported mortality in major epidemiologic and therapeutic trials of ARDS in the 20 years between 1975 and 1995 decreased. The explanation may be related to use of less injurious ventilator modes, more effective treatment of infection, and better nutritional supplementation.

ALI and increased permeability pulmonary edema are complications that occur late in the natural history of other diseases. The prognosis worsens as the number and the severity of underlying diseases increase.[94] Patients with sepsis have significantly higher mortality than patients with other clinical disorders associated with the development of ALI.[94] Medical patients have a higher mortality than surgical patients. Mortality is much higher in patients with chronic liver disease[273] or histories of chronic alcohol abuse.[453] Besides damaging the liver, chronic ethanol ingestion may reduce alveolar type II cell glutathione content and impair surfactant synthesis and secretion.[454] Mortality has been reported to increase with age, but the increased mortality of older ARDS patients might be due in part to decisions to withdraw supportive care, not to the medical futility of life-sustaining therapies for older patients.[455,456] Respiratory deaths are less common than deaths from the underlying disease, from nonpulmonary organ dysfunction, or from infection. Nosocomial pneumonia is an important clinical problem in patients who have sustained ALI. Patients with self-limited causes of injury (e.g., venous air emboli, fat emboli, isolated lung contusion and other trauma, massive blood transfusions, postictal pulmonary edema, heroin pulmonary edema) and those with milder degrees of edema have a greater chance of survival and often clear their edema rapidly (Fig. 55-3).

The long-term outlook for patients who survive diffuse lung injury, even if it is severe, has improved.[457–460] Most recover to have normal chest roentgenograms, no complaints of dyspnea on exertion, normal lung volumes and airflow, and normal resting and exercise arterial blood gas findings and shunt fraction. Some patients have residual airway hyperreactivity. The most common abnormality is a reduced diffusing capacity, which tends to improve gradually. Not surprisingly, patients with the most days on positive-pressure ventilation and those with the lowest static lung compliance during the course of their ALIs are most likely to experience residual pulmonary impairment. Laryngotracheal stenosis, a consequence of prolonged endotracheal intubation, should be considered in patients with persistent exertional dyspnea.[461] Histologic abnormalities usually also gradually regress. Some longer-term patient follow-up studies demonstrate that a significant fraction of ARDS survivors have persistent disabilities 6 to 12 months after discharge from the

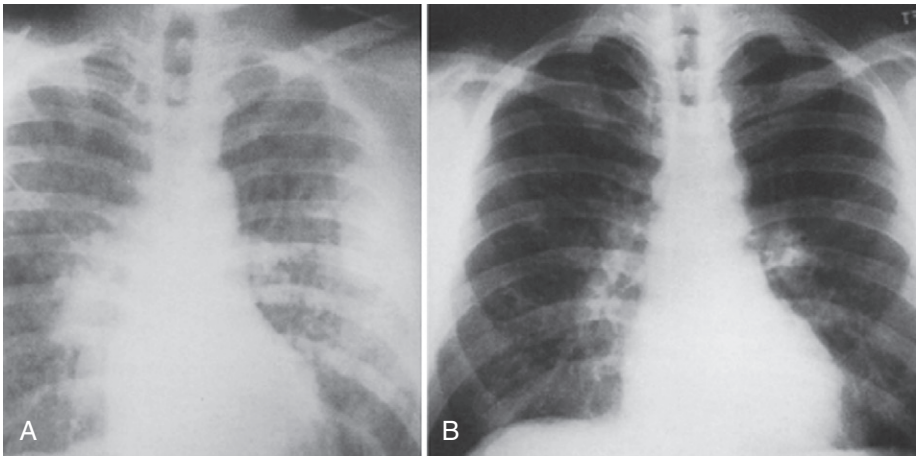

FIGURE 55-3 ■ Chest roentgenograms in a patient with heroin-induced increased permeability pulmonary edema. **A,** At the time of the initial film, the heart was not enlarged, the vascular pedicle was normal, and edema was patchy, peripheral, and not gravitationally distributed. **B,** Forty-eight hours later, the chest film was normal and the patient had fully recovered. Increased permeability pulmonary edema may resolve rapidly if the initiating agent of lung injury is transient and mild and the chronic phase of parenchymal lung injury (type II cell hyperplasia, fibrosis, connective tissue deposition, vascular remodeling) does not develop.

hospital, although this may not be specific for ARDS but rather may be a consequence of critical illness.[399]

Healing often involves some degree of fibrosis.[462,463] The fibroproliferative reaction to ALI seems to begin very early in the course of ALI.[153,464,465] Patients who develop fibrosis are less likely to survive than those who do not.[466] How much of this problem is due to disease and how much to treatment is not known. It may be possible to modify vigorous fibrotic reactions to lung injury, but the consequences of such therapy are unknown. It might also be possible to accelerate reconstitution of alveolar structure in injured lungs; for example, keratinocyte growth factor (fibroblast growth factor-7), which promotes alveolar epithelial hyperplasia in rodents, reduced mortality when given as pretreatment to rats exposed to hyperoxia,[467] and soluble and insoluble fibronectin increased alveolar wound healing in vitro.[468] More information about repair and healing might open new possibilities for therapy.[463,469]

Although several pharmacologic therapies for ARDS have not been effective in decreasing mortality,[94,390] the 30% reduction in mortality achieved with a lung-protective ventilatory strategy represents a major advance in understanding how to prevent ventilator-induced worsening of lung injury in these patients.[244,387]

OVERVIEW

Among the significant advances since the late 1960s has been the acquisition of important new knowledge concerning the physiology of fluid, solute, and protein transport in healthy and diseased lungs. Pulmonary edema—the abnormal accumulation of extravascular fluid in the lung—is a pathologic state that occurs when fluid is filtered into the lungs faster than it can be removed. The many causes of pulmonary edema have been grouped into two main pathophysiologic categories: increased pressure edema that results from an increase in the hydrostatic or osmotic forces (or both) that act across the barriers that normally restrict movement of fluid and solutes in the lungs and increased permeability edema from ALI that results from a breakdown of the normal barrier properties of the endothelium or the epithelium of the lung, or both. Although these two different types of pulmonary edema share many features, they can usually be distinguished clinically and they have different treatment requirements and prognoses. This distinction is possible by careful clinical, radiologic, and physiologic evaluation. However, increased permeability and elevated lung vascular pressure often coexist, as illustrated by the results of a large clinical trial in which pulmonary arterial wedge pressure and cardiac output was measured in 500 patients with ALI.[363] Although cardiac output was normal in the vast majority of patients, the initial pulmonary arterial wedge pressure was greater than 18 mm Hg in 29% of the patients, even though they also had good evidence for increased lung permeability from an infectious or noninfectious cause.[363]

Major advances in the treatment of ALI have occurred because of the successful application of lung-protective ventilatory strategies early to patients with clinical lung injury (see Table 55-10). A low tidal volume (6 mL/kg ideal body weight) coupled with a plateau pressure limit (<30 cm H_2O) is still the only therapy proven to reduce mortality in patients with ALI.[244,387] New insights into the pathogenesis of ALI suggest that other therapies may also prove to lower mortality in this common syndrome of severe acute respiratory failure.

A major development has been the ability to conduct large, prospective, randomized clinical trials sponsored by the NHLBI to test a variety of therapies that provide supportive care for patients, including mechanical ventilation, fluid therapy, and pharmacologic agents. For example, the recent 1000-patient fluid and catheter treatment trial demonstrated that the use of the pulmonary arterial catheter for most cases of ALI does not improve clinical outcomes,[363] although there are some patients with shock who may still benefit from the hemodynamic information provided by a pulmonary artery catheter.[366] Also, this trial demonstrated that a fluid conservative management strategy can reduce the duration of mechanical ventilation in patients with ALI.[381]

KEY POINTS

- Diagnosis of the cause of pulmonary edema should include detailed history, thorough physical examination, and selected laboratory data including the chest radiograph, the electrocardiogram, cardiac enzymes, and in some patients, microbiologic cultures, an echocardiogram, and occasionally, a pulmonary artery catheterization.
- ALI pulmonary edema may be complicated by the presence of elevated pulmonary intravascular pressures, especially from coexistent cardiac failure or volume overload.
- Treatment for cardiogenic pulmonary edema should include the immediate administration of supplemental oxygen and pharmacologic measures to reduce preload.
- The diagnosis of ALI should always initiate a thorough search for a treatable infection.
- If the patient with ALI requires intubation and positive-pressure ventilation, then the ventilation should be done with 6 mL/kg tidal volume with a plateau pressure less than 30 cm H_2O.

References

1. Staub NC: Pulmonary edema. Physiol Rev 54:678–811, 1974.
2. Matthay MA, Folkesson HG, Clerici C: Lung epithelial fluid transport and the resolution of pulmonary edema. Physiol Rev 82:569–600, 2002.
3. Taylor A: Capillary fluid filtration: Starling forces and lymph flow. Circ Res 49:557–575, 1981.
4. Lai-Fook SJ: Mechanical factors in lung liquid distribution. Annu Rev Physiol 55:155–179, 1993.
5. Bhattacharya J: Physiological basis of pulmonary edema. *In* Matthay MA, Ingbar D (eds): Pulmonary Edema. New York: Marcel Dekker, 1998, pp 1–36.
6. Staub NC: The pathogenesis of pulmonary edema. Prog Cardiovasc Dis 23:53–80, 1980.
7. Hastings R, Folkesson HG, Matthay MA: Mechanisms of alveolar protein clearance in the intact lung. Am J Physiol Lung Cell Mol Physiol 286:L679–L689, 2004.
8. Erdmann AJ III, Vaughan TRJ, Brigham KL, et al: Effect of increased vascular pressure on lung fluid balance in unanesthetized sheep. Circ Res 37:271–284, 1975.
9. Guyton AC, Lindsey AW: Effect of elevated left atrial pressure and decreased plasma protein concentration on the development of pulmonary edema. Circ Res 7:649–657, 1959.
10. Drake RE, Dhother S, Teauge RA, et al: Lymph flow in sheep with rapid cardiac ventricular pacing. Am J Physiol 272:R1595–R1598, 1997.
11. Snapper JR: Lung mechanics in pulmonary edema. Clin Chest Med 6:393–412, 1985.
12. Javaheri S, Bosken CH, Lim SP, et al: Effects of hypohydration on lung functions in humans. Am Rev Respir Dis 135:597–599, 1987.
13. Noble W, Kay JC, Obdrzalek J: Lung mechanics in hypervolemic pulmonary edema. J Appl Physiol 49:681–687, 1975.
14. Lloyd T: Reflex effects of left heart and pulmonary vascular distension on airways of dogs. J Appl Physiol 49:620–626, 1980.
15. Lemen R, Jones JG, Graf PD, et al: Closing volume changes in alloxan-induced pulmonary edema in anesthetized dogs. J Appl Physiol 30:224–227, 1975.
16. Klingele TG, Staub NC: Terminal bronchiole diameter changes with volume in isolated, air-filled lobes of cat lung. J Appl Physiol 30:224–227, 1971.
17. Emery DL, Shown B, Batra G, et al: Changes in collateral ventilation with increased vascular pressure and edema formation. J Appl Physiol 53:70–74, 1982.
18. Ploysongsang Y, Zocchi L, Michel RP, et al: Partitioning of respiratory mechanics in pulmonary interstitial edema in dogs (abstract). Fed Proc 44:1910, 1985.
19. Hughes JMB, Rosenzweig DY: Factors affecting trapped gas volume in perfused dog lungs. J Appl Physiol 29:332–339, 1970.
20. Said S, Longacher JW, Davis RK, et al: Pulmonary gas exchange during induction of pulmonary edema in anesthetized dogs. J Appl Physiol 19:403–407, 1964.
21. Bernard GR, Pou NA, Coggeshall JW, et al: Comparison of the pulmonary dysfunction caused by cardiogenic and noncardiogenic pulmonary edema. Chest 108:798–803, 1995.
22. Bhattacharya J, Nakahara K, Staub NC: Effect of edema on pulmonary blood flow in the isolated perfused dog lung lobe. J Appl Physiol 48:444–449, 1980.
23. Murray JF: Effects of lung inflation on pulmonary arterial pressure in dogs with pulmonary edema. J Appl Physiol 45:442–450, 1978.
24. Raj JU, Bland RD, Lai-Fook SJ: Microvascular pressures measured by micropipettes in isolated edematous rabbit lungs. J Appl Physiol 60:539–545, 1986.
25. Hovig T, Nicolaysen A, Nicolaysen G: Ultrastructural studies of the alveolar-capillary barrier in isolated plasma-perfused rabbit lungs: Effects of EDTA and of increased capillary pressure. Acta Physiol Scand 82:417–431, 1971.
26. De Fouw D, Berendsen PB: Morphological changes in isolated perfused dog lungs after acute hydrostatic edema. Circ Res 43:72–82, 1978.
27. Coalson JJ, Jacques WW, Campbell GS, et al: Ultrastructure of the alveolar-capillary membrane in congenital and acquired heart disease. Arch Pathol 83:377–391, 1967.
28. Hurley J: Types of pulmonary microvascular injury. Ann N Y Acad Sci 384:269–285, 1982.
29. Bachofen H, Bachofen M, Weibel ER: Ultrastructural aspects of pulmonary edema. J Thorac Imaging 3:1–7, 1988.
30. Davies SW, Wilkinson P, Keegan J, et al: Pulmonary microvascular permeability in patients with severe mitral stenosis. Br Heart J 65:89–93, 1991.
31. Townsley M, Fu Z, Mathieu-Costello O, et al: Pulmonary microvascular permeability: Responses to high vascular pressure after induction of pacing-induced heart failure in dogs. Circ Res 77:317–325, 1995.
32. Felson B: Thoracic calcifications. Chest 56:330–343, 1969.
33. Schraufnagel DE, Patel KR: Sphincters in pulmonary veins: An anatomic study in rats. Am Rev Respir Dis 141:721–726, 1990.
34. Sande MA, Alonso DR, Smith JP, et al: Left atrial tumor presenting with hemoptysis and pulmonary infiltrates. Am Rev Respir Dis 102:258–263, 1970.
35. Charan NB, Turk GM, Hey DH: Effect of increased bronchial venous pressure on lung lymph flow. J Appl Physiol 59:1249–1253, 1985.
36. Lang SA, Maron MB: Hemodynamic basis for cocaine-induced pulmonary edema in dogs. J Appl Physiol 71:1166–1170, 1991.
37. Bland RD, Demling RH, Selinger SL, et al: Effects of alveolar hypoxia on lung fluid and protein transport in unanesthetized sheep. Circ Res 40:269–274, 1977.
38. Landolt CC, Matthay MA, Albertine KH, et al: Overperfusion, hypoxia, and increased pressure cause only hydrostatic pulmonary edema in anesthetized sheep. Circ Res 52:335–341, 1983.
39. van der Werff YD, van der Houwen HK, Heijmans PJM, et al: Postpneumonectomy pulmonary edema: A retrospective analysis of incidence and possible risk factors. Chest 111:1278–1284, 1997.
40. Bartsch P: High altitude pulmonary edema. Respiration 64:435–443, 1997.
41. Hultgren H: High-altitude pulmonary edema. *In* Matthay MA, Ingbar D (eds): Pulmonary Edema. New York: Marcel Dekker, 1998, pp 355–378.
42. Hackett PH, Bertman J, Rodriguez G, et al: Pulmonary edema fluid protein in high-altitude pulmonary edema. JAMA 256:36, 1986.
43. Schoene R, Swenson ER, Pizzo CJ, et al: The lung at high altitude: Bronchoalveolar lavage in acute mountain sickness and pulmonary edema. J Appl Physiol 64:2605–2613, 1988.
44. Matthay MA, Landolt CC, Staub NC: Differential liquid and protein clearance from the alveoli of anesthetized sheep. J Appl Physiol 53:96–104, 1982.
45. Matthay MA, Berthiaume Y, Staub NC: Long-term clearance of liquid and protein from the lungs of unanesthetized sheep. J Appl Physiol 59:928–934, 1985.
46. West J, Colice GL, Lee Y-J, et al: Pathogenesis of high-altitude pulmonary oedema: Direct evidence of stress failure of pulmonary capillaries. Eur Respir J 8:523–529, 1995.
47. West JB, Mathieu-Costello O: Vulnerability of pulmonary capillaries in heart disease. Circulation 92:622–631, 1995.
48. West JB, Mathieu-Costello O: Structure, strength, failure, and remodeling of the pulmonary blood-gas barrier. Annu Rev Physiol 61:543–572, 1999.
49. Huchon G, Hopewell PC, Murray JF: Interactions between permeability and hydrostatic pressure in perfused dogs' lungs. J Appl Physiol 50:905–911, 1981.
50. Jerome EH, Severinghaus JW: High-altitude pulmonary edema. N Engl J Med 334:662–663, 1996.
51. Grissom C, Zimmerman GA, Whatley RE: Endothelial selectins in acute mountain sickness and high-altitude pulmonary edema. Chest 112:1572–1578, 1997.
52. Kleger G-R, Bärtsch P, Vock P, et al: Evidence against an increase in capillary permeability in subjects exposed to high altitude. J Appl Physiol 81:1917–1923, 1996.
53. Kubo K, Hanaoka M, Hayano T, et al: Inflammatory cytokines in BAL fluid and pulmonary hemodynamics in high-altitude pulmonary edema. Respir Physiol 111:301–310, 1998.
54. Swenson E, Maggiorini M, Mongovin S, et al: Pathogenesis of high-altitude pulmonary edema: Inflammation is not an etiologic factor. JAMA 287:2228–2235, 2002.

55. Maron MB, Pilati CF: Neurogenic pulmonary edema. *In* Matthay MA, Ingbar D (eds): Pulmonary Edema. New York: Marcel Dekker, 1998, pp 319–354.
56. Smith WS, Matthay MA: Evidence for a hydrostatic mechanism in human neurogenic pulmonary edema. Chest 111:1326–1333, 1997.
57. Maron MB: Analysis of airway fluid protein concentration in neurogenic pulmonary edema. J Appl Physiol 62:470–476, 1987.
58. Simon R, Bayne LL, Tranbaugh RF, et al: Elevated pulmonary lymph flow and protein content during status epilepticus in sheep. J Appl Physiol 52:91–95, 1982.
59. Jones T, Townsley MI, Weidner WJ: Effects of intracranial and left atrial hypertension on lung fluid balance in sheep. J Appl Physiol 52:1324–1329, 1982.
60. van der Zee H, Neumann PH, Minnear FL, et al: Effects of transient intracranial hypertension on lung fluid and protein exchange. J Appl Physiol 54:178–184, 1983.
61. Peterson BT, Ross JC, Brigham KL: Effect of naloxone on the pulmonary vascular responses to graded levels of intracranial hypertension in anesthetized sheep. Am Rev Respir Dis 128:1024–1029, 1983.
62. Minnear FL, Barie PS, Malik AB: Effects of transient pulmonary hypertension on pulmonary vascular permeability. J Appl Physiol 55:983–989, 1983.
63. Luce JM, Huseby JS, Robertson HT: Increasing intracranial pressure with air causes air embolism, not neurogenic pulmonary edema. J Appl Physiol 50:967–970, 1981.
64. Townsley M, McClure DE, Weidner WJ: Assessment of pulmonary microvascular permeability in acutely prepared sheep. J Appl Physiol 56:857–861, 1984.
65. Kallet RH, Daniel BM, Gropper M, et al: Acute pulmonary edema following upper airway obstruction: Case reports and brief review. Respir Care 43:476–480, 1998.
66. Miller W, Toon R, Palat H, et al: Experimental pulmonary edema following re-expansion of pneumothorax. Am Rev Respir Dis 108:664–666, 1973.
67. Pavlin J, Cheney FW: Unilateral pulmonary edema in rabbits after reexpansion of collapsed lung. J Appl Physiol 46:31–35, 1979.
68. Trapnell D, Thurston JGB: Unilateral pulmonary oedema after pleural aspiration. Lancet 1:1367–1369, 1970.
69. Shaw T, Caterine JM: Recurrent re-expansion pulmonary edema. Chest 86:784–786, 1984.
70. Marland A, Glauser FL: Hemodynamic and pulmonary edema protein measurements in a case of reexpansion pulmonary edema. Chest 81:250–251, 1982.
71. Suzuki S, Tanita T, Koike K, et al: Evidence of acute inflammatory response in reexpansion pulmonary edema. Chest 101:275–276, 1992.
72. Sue RD, Matthay MA, Ware LB: Hydrostatic mechanisms may contribute to the pathogenesis of human re-expansion pulmonary edema. Intensive Care Med 30:1921–1926, 2004.
73. Pavlin D, Nessly ML, Cheney FW: Increased pulmonary vascular permeability as a cause of re-expansion edema in rabbits. Am Rev Respir Dis 124:422–427, 1981.
74. Jackson R, Veal CF, Alexander CB, et al: Re-expansion pulmonary edema: A potential role for free radicals in its pathogenesis. Am Rev Respir Dis 137:1165–1171, 1988.
75. Heffner JE: Mechanisms underlying ischemia/reperfusion injury of the lung. *In* Matthay MA, Ingbar D (eds): Pulmonary Edema. New York: Marcel Dekker, 1998, pp 379–412.
76. Allison RC, Kyle J, Adkins WK, et al: Effect of ischemia reperfusion or hypoxia reoxygenation on lung vascular permeability and resistance. J Appl Physiol 69:597–603, 1990.
77. Ward BJ, Pearse DB: Reperfusion pulmonary edema after thrombolytic therapy of massive pulmonary embolism. Am Rev Respir Dis 138:1308–1311, 1988.
78. Ware L, Golder JA, Finkbeiner WE, et al: Alveolar epithelial fluid transport capacity in reperfusion lung injury after lung transplantation. Am J Respir Crit Care Med 159:980–988, 1999.
79. Modelska K, Pittet J-F: Increased-permeability edema following hemorrhagic and traumatic shock. *In* Matthay MA, Ingbar D (eds): Pulmonary Edema. New York: Marcel Dekker, 1998, pp 299–318.
80. Albert RK, Lakshminarayan S, Hildebrandt J, et al: Increased surface tension favors pulmonary edema formation in anesthetized dogs' lungs. J Clin Invest 63:1015–1018, 1979.
81. Beck KC, Lai-Fook SJ: Alveolar liquid pressure in excised edematous dog lung with increased static recoil. J Appl Physiol 55:1277–1283, 1983.
82. Dodek PM, Rice TW, Bonsignore MR, et al: Effects of plasmapheresis and of hypoproteinemia on lung liquid conductance in awake sheep. Circ Res 58:269–280, 1986.
83. Parker RE, Wickersham NE, Roselli RJ, et al: Effects of hypoproteinemia on lung microvascular protein sieving and lung lymph flow. J Appl Physiol 60:1293–1299, 1986.
84. Bhattacharya J, Gropper MA, Staub NC: Interstitial fluid pressure gradient measured by micropuncture in excised dog lung. J Appl Physiol 56:271–277, 1984.
85. Lai-Fook SJ, Beck KC: Alveolar liquid pressure measured by micropipettes in isolated dog lung. J Appl Physiol 53:737–743, 1982.
86. Nieman GF, Bredenberg CE: High surface tension pulmonary edema induced by detergent aerosol. J Appl Physiol 58:129–136, 1985.
87. Bredenberg C, Nieman GF, Paskanik AM, et al: Microvascular membrane permeability in high surface tension pulmonary edema. J Appl Physiol 60:253–259, 1986.
88. Said S, Avery ME, Davis RK, et al: Pulmonary surface activity in induced pulmonary edema. J Clin Invest 44:458–464, 1965.
89. Seeger W, Wolf HRD, Stahler G, et al: Alteration of pressure-volume characteristics due to different types of edema induction in isolated rabbit lungs. Respiration 44:273–281, 1983.
90. Cohen DS, Matthay MA, Cogan MG, et al: Pulmonary edema associated with salt water near-drowning: New insights. Am Rev Respir Dis 146:794–796, 1992.
91. Folkesson HG, Effros RM: Aspiration syndromes: Acid, salt water, and fresh water. *In* Matthay MA, Ingbar DH (eds): Pulmonary Edema. New York: Marcel Dekker, 1998, pp 269–298.
92. Folkesson HG, Kheradmand F, Matthay MA: The effect of salt water on alveolar epithelial barrier function. Am J Respir Crit Care Med 150:1555–1563, 1995.
93. Ashbaugh DG, Bigelow DB, Petty TL, et al: Acute respiratory distress in adults. Lancet 2:319–323, 1967.
94. Ware LB, Matthay MA: The acute respiratory distress syndrome. N Engl J Med 342:1334–1349, 2000.
95. Cope DK, Grimbert F, Downey JM, et al: Pulmonary capillary pressure: A review (see comments). Crit Care Med 20:1043–1056, 1992.
96. Robbins I, Newman JH, Brigham, KL: Increased-permeability pulmonary edema from sepsis/endotoxin. *In* Matthay M, Ingbar, DH (eds): Pulmonary Edema. New York: Marcel Dekker, 1998, pp 203–245.
97. Gorin AB, Stewart PA: Differential permeability of endothelial and epithelial barriers to albumin flux. J Appl Physiol 47:1315–1324, 1979.
98. Montaner JSB, Tsang J, Evans KG, et al: Alveolar epithelial damage: A critical difference between high pressure and oleic acid–induced low pressure pulmonary edema. J Clin Invest 77:1786–1796, 1986.
99. Pelosi P, Cereda M, Foti G, et al: Alterations of lung and chest wall mechanics in patients with acute lung injury: Effects of positive end-expiratory pressure. Am J Respir Crit Care Med 152:531–537, 1995.
100. Grossman RF, Jones JG, Murray JF: Effects of oleic acid–induced pulmonary edema on lung mechanics. J Appl Physiol 48:1045–1051, 1980.
101. Slutsky AS, Scharf SM, Brown R, et al: The effect of oleic acid–induced pulmonary edema on pulmonary and chest wall mechanics in dogs. Am Rev Respir Dis 121:91–96, 1980.
102. Gattinoni L, D'Andrea L, Pelosi P, et al: Regional effects and mechanism of positive end-expiratory pressure in early adult respiratory distress syndrome (see comments). JAMA 269: 2122–2127, 1993 [published erratum appears in JAMA 270:1814, 1993].
103. Pelosi P, D'Andrea L, Vitale G, et al: Vertical gradient of regional lung inflation in adult respiratory distress syndrome. Am J Respir Crit Care Med 149:8–13, 1994.

104. Wright PE, Carmichael LC, Bernard GR: Effect of bronchodilators on lung mechanics in the acute respiratory distress syndrome (ARDS). Chest 106:1517–1523, 1994.
105. Gattinoni L, Pelosi P, Suter PM, et al: Acute respiratory distress syndrome caused by pulmonary and extrapulmonary disease: Different syndromes? Am J Respir Crit Care Med 158:3–11, 1998.
106. Byrne K, Cooper KR, Carey PD, et al: Pulmonary compliance: Early assessment of evolving lung injury after onset of sepsis. J Appl Physiol 69:2290–2295, 1990.
107. Tierney DF, Johnson RP: Altered surface tension of lung extracts and mechanics. J Appl Physiol 20:1253–1260, 1965.
108. Ryan SF, Ghassibi Y, Liau DF: Effects of activated polymorphonuclear leukocytes upon pulmonary surfactant in vitro. Am J Respir Cell Mol Biol 4:33–41, 1991.
109. Gregory TJ, Longmore WJ, Moxley MA, et al: Surfactant chemical composition and biophysical activity in acute respiratory distress syndrome. J Clin Invest 88:1976–1981, 1991.
110. Holm BA, Notter RH, Finkelstein JN: Surface property changes from interactions of albumin with natural lung surfactant and extracted lung lipids. Chem Phys Lipids 38:287–298, 1985.
111. Lewis JF, Ikegami M, Jobe AH: Altered surfactant function and metabolism in rabbits with acute lung injury. J Appl Physiol 69:2303–2310, 1990.
112. Kobayashi T, Nitta K, Ganzuka M, et al: Inactivation of exogenous surfactant by pulmonary edema fluid. Pediatr Res 29:353–356, 1991.
113. Lamy M, Fallat RJ, Koeniger E, et al: Pathologic features and mechanisms of hypoxemia in adult respiratory distress syndrome. Am Rev Respir Dis 114:267–284, 1976.
114. Dantzker DR, Brook CJ, Dehart P, et al: Ventilation-perfusion distributions in the adult respiratory distress syndrome. Am Rev Respir Dis 120:1039–1052, 1979.
115. Russell JA, Phang PT: The oxygen delivery/consumption controversy: Approaches to management of the critically ill. Am J Respir Crit Care Med 149:533–537, 1994.
116. Phang PT, Cunningham KF, Ronco JJ, et al: Mathematical coupling explains dependence of oxygen consumption on oxygen delivery in ARDS. Am J Respir Crit Care Med 150:318–323, 1994.
117. Nuckton TJ, Alonso JA, Kallet RH, et al: Pulmonary dead-space fraction as a risk factor for death in the acute respiratory distress syndrome. N Engl J Med 346:1281–1286, 2002.
118. Coss-Bu J: Dead space ventilation in critically ill children with lung injury. Chest 123:2050–2055, 2003.
119. Hill NS, Rounds S: Vascular reactivity is increased in rat lungs injured with alpha-naphthylthiourea. J Appl Physiol 54:1693–1701, 1983.
120. Hutchison AA, Ogletree ML, Snapper JR, et al: Effect of endotoxemia on hypoxic pulmonary vasoconstriction in unanesthetized sheep. J Appl Physiol 58:1463–1468, 1985.
121. Domino KB, Cheney FW, Eisenstein BL, et al: Effect of regional alveolar hypoxia on gas exchange in pulmonary edema. Am Rev Respir Dis 145:340–347, 1992.
122. Wiedemann HP, Matthay MA, Gillis CN: Pulmonary endothelial cell injury and altered lung metabolic function: Early detection of the adult respiratory distress syndrome and possible functional significance. Clin Chest Med 11:723–736, 1990.
123. Dvorak HN, Senger DR, Dvorak AM, et al: Regulation of extravascular coagulation by microvascular permeability. Science 227:1059–1061, 1985.
124. Idell S, Koenig KB, Fair DS, et al: Serial abnormalities of fibrin turnover in evolving adult respiratory distress syndrome. Am J Physiol 261:L240–L248, 1991.
125. Quinn DA, Carvalho AC, Geller E, et al: ^{99m}Tc-fibrinogen scanning in adult respiratory distress syndrome. Am Rev Respir Dis 135:100–106, 1987.
126. Ware LB, Fang X, Matthay MA: Protein C and thrombomodulin in human acute lung injury. Am J Physiol Lung Cell Mol Physiol 285:L514–L521, 2003.
127. Prabhakaran P, Ware LB, White KE, et al: Elevated levels of plasminogen activator inhibitor-1 in pulmonary edema fluid are associated with mortality in acute lung injury. Am J Physiol Lung Cell Mol Physiol 285:L20–L28, 2003.
128. Snow RL, Davies P, Pontoppidan H, et al: Pulmonary vascular remodeling in the adult respiratory distress syndrome. Am Rev Respir Dis 126:887–892, 1982.
129. Fein A, Grossman R, Jones J, et al: The value of edema fluid protein measurements in patients with pulmonary edema. Am J Med 67:32–38, 1979.
130. Bachofen M, Weibel ER: Alterations of the gas exchange apparatus in adult respiratory insufficiency associated with septicemia. Am Rev Respir Dis 116:589–615, 1977.
131. Pratt PC, Vollmer RT, Shelburne JD, et al: Pulmonary morphology in a multihospital collaborative extracorporeal membrane oxygenation project. I. Light microscopy. Am J Pathol 95:191–214, 1979.
132. National Heart, Lung, and Blood Institute: Extracorporeal Support for Respiratory Insufficiency: A Collaborative Study in Response to RFP-NHLBI-73-20. Bethesda, MD: U.S. Department of Health, Education, and Welfare, 1979.
133. Bachofen M, Weibel ER: Structural alterations of lung parenchyma in the adult respiratory distress syndrome. Clin Chest Med 3:35–56, 1982.
134. Albertine K: Ultrastructural abnormalities in increased-permeability pulmonary edema. Clin Chest Med 6:345–369, 1985.
135. Tomashefski JF Jr: Pulmonary pathology of the adult respiratory distress syndrome. Clin Chest Med 11:593–619, 1990.
136. Anderson WR, Thielen K: Correlative study of adult respiratory distress syndrome by light, scanning, and transmission electron microscopy. Ultrastruct Pathol 16:615–628, 1992.
137. Meyrick B, Brigham KL: Acute effects of *Escherichia coli* endotoxin on the pulmonary microcirculation of anesthetized sheep: Structure:function relationships. Lab Invest 48:458–470, 1983.
138. Schoene RB, Robertson HT, Thorning DR, et al: Pathophysiological patterns of resolution from acute oleic acid lung injury in the dog. J Appl Physiol 56:472–481, 1984.
139. Albertine K, Wiener-Kronish JP, Koike K, et al: Quantification of damage by air emboli to lung microvessels in anesthetized sheep. J Appl Physiol 57:1360–1368, 1984.
140. Meduri G, Eltorky M, Winer-Muram HT: The fibroproliferative phase of late adult respiratory distress syndrome. Semin Respir Infect 10:1184–1188, 1995.
141. Headley A, Tolley E, Meduri GU: Infections and the inflammatory response in acute respiratory distress syndrome. Chest 111:1306–1321, 1997.
142. McHugh LG, Milberg JA, Whitcomb ME, et al: Recovery of function in survivors of the acute respiratory distress syndrome. Am J Respir Crit Care Med 150:90–94, 1994.
143. Herridge MS, Cheung AM, Tansey CM, et al: One-year outcomes in survivors of the acute respiratory distress syndrome. N Engl J Med 348:683–693, 2003.
144. Donnelly SC, Strieter RM, Kunkel SL, et al: Interleukin-8 and development of adult respiratory distress syndrome in at-risk patient groups (see comments). Lancet 341:643–647, 1993.
145. Goodman RB, Strieter RM, Martin DP, et al: Inflammatory cytokines in patients with persistence of the acute respiratory distress syndrome. Am J Respir Crit Care Med 154:602–611, 1996.
146. Park WY, Goodman RB, Steinberg KP, et al: Cytokine balance in the lungs of patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 164:1896–1903, 2001.
147. Pugin J, Ricou B, Steinberg KP, et al: Proinflammatory activity in bronchoalveolar lavage fluids from patients with ARDS: A prominent role for interleukin-1. Am J Respir Crit Care Med 153:1850–1856, 1996.
148. Ricou B, Nicod L, Lacraz S, et al: Matrix metalloproteinases and TIMP in acute respiratory distress syndrome. Am J Respir Crit Care Med 154:346–352, 1996.
149. Ratnoff WD, Matthay MA, Wong MY, et al: Sulfidopeptide-leukotriene peptidases in pulmonary edema fluid from patients with the adult respiratory distress syndrome. J Clin Immunol 8:250–258, 1988.
150. Verghese GM, McCormick-Shannon K, Mason RJ, et al: Hepatocyte growth factor and keratinocyte growth factor in the pulmonary edema fluid of patients with acute lung injury: Biologic and clinical significance. Am J Respir Crit Care Med 158:386–394, 1998.

151. Madtes DK, Rubenfeld G, Klima LD, et al: Elevated transforming growth factor-α levels in bronchoalveolar lavage fluid from patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 158:424–430, 1998.
152. Clark JG, Milberg JA, Steinberg KP, et al: Type III procollagen peptide in the adult respiratory distress syndrome: Association of increased peptide levels in bronchoalveolar lavage fluid with increased risk for death. Ann Intern Med 122:17–23, 1995.
153. Chesnutt AN, Matthay MA, Tibayan FA, et al: Early detection of type III procollagen peptide in acute lung injury: Pathogenic and prognostic significance. Am J Respir Crit Care Med 156:840–845, 1997.
154. Sittipunt C, Steinberg KP, Ruzinski JT, et al: Nitric oxide and nitrotyrosine in the lungs of patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 163:503–510, 2001.
155. Zhu S, Ware LB, Geiser T, et al: Increased levels of nitrate and surfactant protein A nitration in the pulmonary edema fluid of patients with acute lung injury. Am J Respir Crit Care Med 163:166–172, 2001.
156. Pittet J-F, Mackersie RC, Martin TR, et al: Biological markers of acute lung injury: Prognostic and pathogenetic significance (state of the art). Am J Respir Crit Care Med 155:1187–1205, 1997.
157. Matute-Bello G, Frevert CW, Martin TR: Animal models of acute lung injury. Am J Physiol Lung Cell Mol Physiol 295:L379–L399, 2008.
158. Koike K, Albertine KH, Staub NC: Intrathoracic sources of caudal mediastinal lymph node efferent lymph in sheep. J Appl Physiol 60:80–84, 1986.
159. Chanana AD, Joel DD: Contamination of lung lymph following standard and modified procedures in sheep. J Appl Physiol 60:809–816, 1986.
160. Laine G, Drake RE, Zavisca FG, et al: Effect of lymphatic cannula outflow height on lung microvascular permeability estimations. J Appl Physiol 57:1412–1416, 1984.
161. Adair T, Montani J-P, Guyton AC: Modification of lymph by sheep caudal mediastinal node: Effect of intranodal endotoxin. J Appl Physiol 57:1597–1601, 1984.
162. Bone RC, Fisher CJ, Clemmer TP, et al: Methylprednisolone Severe Sepsis Study Group: Early methylprednisolone treatment for septic syndrome and the adult respiratory distress syndrome. Chest 92:1032–1036, 1987.
163. Luce JM, Montgomery AB, Marks JD, et al: Ineffectiveness of high-dose methylprednisolone in preventing parenchymal lung injury and improving mortality in patients with septic shock. Am Rev Respir Dis 138:62–68, 1988.
164. Ziegler EJ, Fisher CJ, Sprung CL, et al: Treatment of gram negative bacteremia and septic shock with HA-1A human monoclonal antibody against endotoxin: A randomized, double-blind, placebo-controlled trial. N Engl J Med 324:429–436, 1991.
165. Anderson RR, Holliday RL, Driedger AA, et al: Documentation of pulmonary capillary permeability in the adult respiratory distress syndrome accompanying human sepsis. Am Rev Respir Dis 119:869–877, 1979.
166. Eisner MD, Thompson T, Hudson LD, et al: Efficacy of low tidal volume ventilation in patients with different clinical risk factors for acute lung injury and the acute respiratory distress syndrome. Am J Respir Crit Care Med 164:231–236, 2001.
167. Kaplan RL, Sahn SA, Petty TL: Incidence and outcome of the respiratory distress syndrome in gram-negative sepsis. Arch Intern Med 139:867–869, 1979.
168. Bell RC, Coalson JJ, Smith JD, et al: Multiple organ system failure and infection in adult respiratory distress syndrome. Ann Intern Med 99:293–298, 1983.
169. Torres A, Serra-Batlles J, Ferrer A, et al: Severe community-acquired pneumonia: Epidemiology and prognostic factors. Am Rev Respir Dis 144:312–318, 1991.
170. Montgomery A, Stager M, Carrico C, et al: Causes of mortality in patients with the adult respiratory distress syndrome. Am Rev Respir Dis 132:485–489, 1985.
171. Seidenfeld JJ, Pohl DF, Bell RC, et al: Incidence, site, and outcome of infections in patients with the adult respiratory distress syndrome. Am Rev Respir Dis 134:12–16, 1986.
172. Meduri GU: Host defense response and outcome in ARDS. Chest 112:1154–1158, 1997.
173. Sutherland KR, Steinberg KP, Maunder RJ, et al: Pulmonary infection during the acute respiratory distress syndrome. Am J Respir Crit Care Med 152:550–556, 1995.
174. Wiener-Kronish JP, Sawa T, Kurahashi K, et al: Pulmonary edema associated with bacterial pneumonia. *In* Matthay MA, Ingbar DH (eds): Pulmonary Edema. New York: Marcel Dekker, 1998, pp 247–267.
175. Delclaux C, Roupie E, Blot F, et al: Lower respiratory tract colonization and infection during severe acute respiratory distress syndrome: Incidence and diagnosis. Am J Respir Crit Care Med 156:1092–1098, 1997.
176. Chastre J, Trouillet JL, Vuagnat A, et al: Nosocomial pneumonia in patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 157:1165–1172, 1998.
177. Brigham KL, Woolverton WC, Blake LH, et al: Increased sheep lung vascular permeability caused by *Pseudomonas* bacteremia. J Clin Invest 54:792–804, 1974.
178. Brigham KL, Bowers RE, Haynes J: Increased sheep lung vascular permeability caused by *Escherichia coli* endotoxin. Circ Res 45:292–297, 1979.
179. Traber DL, Adams T, Henriksen N, et al: Reproducibility of cardiopulmonary effects of different endotoxins in the same sheep. J Appl Physiol 54:1167–1171, 1983.
180. Gabel JC, Hansen TN, Drake RE: Effect of endotoxin on lung fluid balance in unanesthetized sheep. J Appl Physiol 56:489–494, 1984.
181. Judges D, Sharkey P, Cheung H, et al: Pulmonary microvascular fluid flux in a large animal model of sepsis: Evidence for increased pulmonary endothelial permeability accompanying surgically induced peritonitis in sheep. Surgery 99:222–234, 1986.
182. Brodgen K, Cutlip RC, Lehmkuhl HD: Response of sheep after localized deposition of lipopolysaccharide in the lung. Exp Lung Res 7:123–132, 1984.
183. Wiener-Kronish JP, Albertine KH, Matthay MA: Differential responses of the endothelial and epithelial barriers of the lung in sheep to *Escherichia coli* endotoxin. J Clin Invest 88:864–875, 1991.
184. Guenter CA: Role of leukocytes in the lung after endotoxin administration. Adv Exp Med Biol 23:77–85, 1971.
185. Kinnebrew PS, Parker JC, Falgout HJ, et al: Pulmonary microvascular permeability following *E. coli* endotoxin and hemorrhage. J Appl Physiol 52:403–409, 1982.
186. Chang JC, Lesser M: Quantification of leukocytes in bronchoalveolar lavage samples from rats after intravascular injection of endotoxin. Am Rev Respir Dis 129:72–75, 1984.
187. Heflin AC, Brigham KL: Prevention by granulocyte depletion of increased vascular permeability of sheep lung following endotoxemia. J Clin Invest 68:1253–1260, 1981.
188. Thomas PD, Hampson FW, Hunninghake GW: Bacterial adherence to human endothelial cells. J Appl Physiol 65:1372–1376, 1988.
189. Parsons PE, Worthen GS, Moore EE, et al: The association of circulating endotoxin with the development of the adult respiratory distress syndrome. Am Rev Respir Dis 140:294–301, 1989.
190. Sato H, Frank DW, Hillard CJ, et al: The mechanism of action of the *Pseudomonas aeruginosa*-encoded type III cytotoxin, ExoU. EMBO J 22:2959–2969, 2003.
191. Kudoh I, Wiener-Kronish JP, Hashimoto S, et al: Exoproduct secretions of *Pseudomonas aeruginosa* strains influence severity of alveolar epithelial injury. Am J Physiol 267:L551–L556, 1994.
192. Martin T: Interactions between mechanical and biological processes in acute lung injury. Proc Am Thorac Soc 5:291–296, 2008.
192a. Smith LS, Gharib SA, Frevert CW, Martin TR: Effects of age on the synergistic interactions between lipopolysaccharide and mechanical ventilation in mice. Am J Respir Cell Mol Biol epub, 2009.
193. O'Grady NP, Preas HL, Pugin J, et al: Local inflammatory responses following bronchial endotoxin instillation in humans. Am J Respir Crit Care Med 163:1591–1598, 2001.
194. Pugin J, Dunn I, Jolliet P, et al: Activation of human macrophages by mechanical ventilation in vitro. Am J Physiol Lung Cell Mol Physiol 275:L1040–L1050, 1999.
195. Tremblay L, Valenza F, Ribeiro SP, et al: Injurious ventilatory strategies increase cytokines and c-fos m-RNA expression in an isolated rat lung model. J Clin Invest 99:944–952, 1997.

196. Moriyama K, Ishizaka A, Nakamura M, et al: Enhancement of the endotoxin recognition pathway by ventilation with a large tidal volume in rabbits. Am J Physiol Lung Cell Mol Physiol 286:L1114–L1121, 2004.
197. Altemeier WA, Matute-Bello G, Gharib SA, et al: Modulation of lipopolysaccharide-induced gene transcription and promotion of lung injury by mechanical ventilation. J Immunol 175:3369–3376, 2005.
198. Martin TR, Rubenfeld GD, Ruzinski JT, et al: Relationship between soluble CD14, lipopolysaccharide binding protein, and the alveolar inflammatory response in patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 1515:937–944, 1997.
199. Martin TR: Recognition of bacterial endotoxin in the lungs. Am J Respir Cell Mol Biol 23:128–132, 2000.
200. Gharib SA, Liles WC, Matute-Bello G, et al: Computational identification of key biologic modules and transcription factors in acute lung injury. Am J Respir Crit Care Med 173:653–658, 2006.
201. LaForce F, Mullane JF, Boehme RF, et al: The effect of pulmonary edema on antibacterial defenses of the lung. J Lab Clin Med 82:634–648, 1973.
202. Mullane J, LaForce FM, Huber GL: Variations in lung water and pulmonary host defense mechanisms. Am Surg 39:630–636, 1973.
203. Esrig BC, Fulton RL: Sepsis, resuscitated hemorrhagic shock and shock lung: An experimental correlation. Am Surg 182:218–227, 1975.
204. Campbell GD, Coalson JJ, Johanson WG: The effect of bacterial superinfection on lung function after diffuse alveolar damage. Am Rev Respir Dis 129:974–978, 1984.
205. Johanson WG, Higuchi JH, Woods DE, et al: Dissemination of *Pseudomonas aeruginosa* during lung infection in hamsters: Role of oxygen-induced lung injury. Am Rev Respir Dis 132:358–361, 1985.
206. Wright J: Pulmonary surfactant: A front line of lung host defense. J Clin Invest 111:1453–1455, 2003.
207. Martin TR, Pistorese BP, Hudson LD, et al: The function of lung and blood neutrophils in patients with the adult respiratory distress syndrome: Implications for the pathogenesis of lung infections. Am Rev Respir Dis 144:254–262, 1991.
208. Chollet-Martin S, Jourdain B, Gilbert C, et al: Interactions between neutrophils and cytokines in blood and alveolar spaces during ARDS. Am J Respir Crit Care Med 153:594–601, 1996.
209. Sibille Y, Reynolds HY: Macrophages and polymorphonuclear neutrophils in lung defense and injury: State of the art. Am Rev Respir Dis 141:471–501, 1990.
210. Warner AE, Brain JD: The cell biology and pathogenic role of pulmonary intravascular macrophages. Am J Physiol 258:L1–L12, 1990.
211. Hoidal JR: The eosinophil and acute lung injury. Am Rev Respir Dis 142:1245–1246, 1990.
212. Hogg JC, Doerschuk CM: Leukocyte traffic in the lung. Annu Rev Physiol 57:97–114, 1995.
213. Mulligan MS, Varani J, Dame MK, et al: Role of endothelial-leukocyte adhesion molecule 1 (ELAM-1) in neutrophil-mediated lung injury in rats. J Clin Invest 88:1396–1406, 1991.
214. Hidalgo A, Chang J, Jang JE, et al: Heterotypic interactions enabled by polarized neutrophil microdomains mediate thromboinflammatory injury. Nat Med 15:384–391, 2009.
215. Albelda SM: Endothelial and epithelial cell adhesion molecules. Am J Respir Cell Mol Biol 4:195–203, 1991.
216. Weiss SJ: Tissue destruction by neutrophils. N Engl J Med 320:365–376, 1989.
216a. Looney MR, Nguyen JX, Hu Y, et al: Platelet depletion and aspirin treatment protect mice in a two-event model of transfusion-related acute lung injury. J Clin Invest 119:3450-3461, 2009.
217. Martin TR, Nakamura M, Matute-Bello G: The role of apoptosis in acute lung injury. Crit Care Med 31:S184–S188, 2003.
218. Kuwano K, Hara N: Signal transduction pathways of apoptosis and inflammation induced by the tumor necrosis factor receptor family. Am J Respir Cell Mol Biol 22:147–149, 2000.
219. Matute-Bello G, Liles WC, Steinberg KP, et al: Soluble Fas-ligand induces epithelial cell apoptosis in humans with acute lung injury (ARDS). J Immunol 163:2217–2225, 1999.
220. Matute-Bello G, Winn RK, Jonas M, et al: Fas (CD95) induces alveolar epithelial cell apoptosis in vivo: Implications for acute pulmonary inflammation. Am J Pathol 158:153–161, 2001.
221. Hagimoto N, Kuwano K, Miyazaki H, et al: Induction of apoptosis and pulmonary fibrosis in mice in response to ligation of Fas antigen. Am J Respir Cell Mol Biol 17:272–278, 1997.
222. Park DR, Thomsen AR, Frevert CW, et al: Fas (CD95) induces pro-inflammatory cytokine responses by human monocytes and monocyte-derived macrophages. J Immunol 170:6209–6216, 2003.
223. Matute-Bello G, Liles WC, Frevert CW, et al: Recombinant human Fas ligand induces alveolar epithelial cell apoptosis and lung injury in rabbits. Am J Physiol Lung Cell Mol Physiol 281:L328–L335, 2001.
224. Imai Y, Parodo J, Kajikawa O, et al: Injurious mechanical ventilation and end-organ epithelial cell apoptosis and organ dysfunction in an experimental model of acute respiratory distress syndrome. JAMA 289:2104–2112, 2003.
225. Albertine K, Soulier MF, Wang Z, et al: Fas and Fas ligand are up-regulated in pulmonary edema fluid and lung tissue of patients with acute lung injury and the acute respiratory distress syndrome. Am J Pathol 161:1783–1796, 2002.
226. Laufe MD, Simon RH, Flint A, et al: Adult respiratory distress syndrome in neutropenic patients. Am J Med 80:1022–1026, 1986.
227. Maunder RJ, Hackman RC, Riff E, et al: Occurrence of the adult respiratory distress syndrome in neutropenic patients. Am Rev Respir Dis 133:313–316, 1986.
228. Nelson S, Belknap SM, Carlson RW, et al: A randomized controlled trial of filgrastim as an adjunct to antibiotics for treatment of hospitalized patients with community-acquired pneumonia. J Infect Dis 178:1075–1080, 1998.
229. Fairman RP, Glauser FL, Falls R: Increases in lung lymph and albumin clearance with ethchlorvynol. J Appl Physiol 50:1151–1155, 1981.
230. Hofman WF, Ehrhart IC: Permeability edema in dog lung depleted of blood components. J Appl Physiol 57:147–153, 1984.
231. Schwartz JS, Spragg RG, Loomis WH, et al: Oleic acid causes high permeability edema in blood-free perfused rabbit lungs (abstract). Clin Res 30:74A, 1982.
232. Lindquist P, Saldeen T, Sandler H: Pulmonary damage following pulmonary microembolism in the dog: Effect of various types of treatment. Acta Clin Scand 142:15–19, 1976.
233. Gaynor E: The role of granulocytes in endotoxin-induced vascular injury. Blood 41:797–808, 1973.
234. Pingleton W, Coalson JJ, Guenter CA: Significance of leukocytes in endotoxic shock. Exp Mol Pathol 22:183–194, 1975.
235. Eiermann G, Dickey BF, Thrall RS: Polymorphonuclear leukocyte participation in acute oleic acid–induced lung injury. Am Rev Respir Dis 128:845–850, 1983.
236. Tahamont M, Malik AB: Granulocytes mediate the increase in pulmonary vascular permeability after thrombin embolism. J Appl Physiol 54:1489–1495, 1983.
237. Heath C, Lai L, Bizios R, et al: Pulmonary hemodynamic effects of antisheep serum–induced leukopenia. J Leukoc Biol 39:385–397, 1986.
238. Shasby DM, VanBenthuysen KM, Tate RM, et al: Granulocytes mediate acute edematous lung injury in rabbits and isolated rabbit lungs perfused with phorbol myristate acetate: Role of oxygen radicals. Am Rev Respir Dis 125:443–447, 1982.
239. Dreyfuss D, Saumon G: Ventilator-induced lung injury: Lessons from experimental studies. Am J Respir Crit Care Med 157:294–323, 1998.
240. Dos Santos CC, Slutsky A: The contribution of biophysical lung injury to the development of biotrauma. Annu Rev Physiol 68:585–618, 2006.
241. Vlahakis NE, Hubmayr R: Cellular stress failure in ventilator-injured lungs. Am J Respir Crit Care Med 171:1328–1342, 2005.
242. Matthay MA, Rosen GD: Acid aspiration induced lung injury: New insights and therapeutic options. Am J Respir Crit Care Med 154:277–278, 1996.
243. Brégeon F, Papazian L, Delpierre S, et al: Role of proinflammatory activity contained in gastric juice from intensive care unit patients

to induce lung injury in a rabbit aspiration model. Crit Care Med 36:3205–3212, 2008.
244. The ARDS Network: Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 342:1301–1308, 2000.
245. Ranieri VM, Suter PM, Tortorella C, et al: Effect of mechanical ventilation on inflammatory mediators in patients with acute respiratory distress syndrome: A randomized controlled trial. JAMA 282:54–61, 1999.
246. Moss M, Guidot DM, Steinberg KP, et al: Diabetic patients have a decreased incidence of acute respiratory distress syndrome. Crit Care Med 28:2187–2192, 2000.
247. Moss M, Parsons PE, Steinberg KP, et al: Chronic alcohol abuse is associated with an increased incidence of acute respiratory distress syndrome and severity of multiple organ dysfunction in patients with septic shock. Crit Care Med 31:869–877, 2003.
248. Moss M, Guidot DM, Wong-Lambertina M, et al: The effects of chronic alcohol abuse on pulmonary glutathione homeostasis. Am J Respir Crit Care Med 161:414–419, 2000.
249. Wurfel MM, Park WY, Radella F, et al: Identification of high and low responders to lipopolysaccharide in normal subjects: An unbiased approach to identify modulators of innate immunity. J Immunol 175:2570–2578, 2005.
250. Gao L, Barnes KC: Recent advances in genetic predisposition to clinical acute lung injury. Am J Physiol Lung Cell Mol Physiol 296:L713–L725, 2009.
251. Ye SQ, Simon BA, Maloney JP, et al: Pre-B-cell colony-enhancing factor as a potential novel biomarker in acute lung injury. Am J Respir Crit Care Med 171:361–370, 2005.
252. Bajwa EK, Yu CL, Gong MN, et al: Pre-B-cell colony-enhancing factor gene polymorphisms and risk of acute respiratory distress syndrome. Crit Care Med 35:1290–1295, 2007.
253. Marshall RP, Webb S, Bellingan GJ, et al: Angiotensin converting enzyme insertion/deletion polymorphism is associated with susceptibility and outcome in acute respiratory distress syndrome. Am J Respir Crit Care Med 166:646–650, 2002.
254. Sapru A, Wiemels JL, Witte JS, et al: Acute lung injury and the coagulation pathway: Potential role of gene polymorphisms in the protein C and fibrinolytic pathways. Intensive Care Med 32:1293–1303, 2006.
255. Wurfel MM, Gordon AC, Holden TD, et al: Toll-like receptor 1 polymorphisms affect innate immune responses and outcomes in sepsis. Am J Respir Crit Care Med 178:710–720, 2008.
256. Snashall P, Chung KF: Airway obstruction and bronchial hyperresponsiveness in left ventricular failure and mitral stenosis. Am Rev Respir Dis 144:945–956, 1991.
257. Hoffman R, Agatston A, Krieger B: Cheyne-Stokes respiration in patients recovering from acute cardiogenic pulmonary edema. Chest 97:410–412, 1990.
258. Graham SP, Vetrovec GW: Comparison of angiographic findings and demographic variables in patients with coronary artery disease presenting with acute pulmonary edema versus those presenting with chest pain. Am J Cardiol 68:1614–1618, 1991.
259. Meduri GU, Wunderink RG, Leeper KV, et al: Management of bacterial pneumonia in ventilated patients: Protected bronchoalveolar lavage as a diagnostic tool. Chest 101:500–508, 1992.
260. Warner DO, Warner MA, Divertie MB: Open lung biopsy in patients with diffuse pulmonary infiltrates and acute respiratory failure. Am Rev Respir Dis 137:90–94, 1988.
261. Patel S, Karmpaliotis D, Ayas NT, et al: The role of open-lung biopsy in ARDS. Chest 125:197–202, 2004.
262. Murray JF, Matthay MA, Luce JM, et al: An expanded definition of the adult respiratory distress syndrome. Am Rev Respir Dis 138:720–723, 1988.
263. Bernard GR, Artigas A, Brigham KL, et al: The American-European Consensus Conference of ARDS: Definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med 149:818–824, 1994.
264. Matuschak GM: Lung-liver interactions in sepsis and multiple organ failure syndrome. Clin Chest Med 17:83–98, 1996.
265. Knaus W, Draper EA, Wagner DP, et al: APACHE II: A severity of disease classification system. Crit Care Med 13:818–829, 1985.
266. Moss M, Goodman PL, Heinig M, et al: Establishing the relative accuracy of three new definitions of the adult respiratory distress syndrome (see comments). Crit Care Med 23:1629–1637, 1995.
267. Schuster DP: What is acute lung injury? What is ARDS? Chest 107:1721–1726, 1995.
268. Sinclair DG, Braude S, Haslam PL, et al: Pulmonary endothelial permeability in patients with severe lung injury: Clinical correlates and natural history. Chest 106:535–539, 1994.
269. Groeneveld ABJ, Raijmakers PGHM, Teule GJJ, et al: The ^{67}gallium pulmonary leak index in assessing the severity and course of the adult respiratory distress syndrome. Crit Care Med 24:1467–1472, 1996.
270. Groeneveld ABJ, Raijmakers PGHM: The ^{67}gallium-transferrin pulmonary leak index in patients at risk for the acute respiratory distress syndrome. Crit Care Med 26:685–691, 1998.
271. Owens CM, Evans TW, Keogh BF, et al: Computed tomography in established adult respiratory distress syndrome: Correlation with lung injury score. Chest 106:1815–1821, 1994.
272. Knaus WA, Sun X, Hakim RB, et al: Evaluation of definitions for adult respiratory distress syndrome. Am J Respir Crit Care Med 150:311–317, 1994.
273. Doyle RL, Szaflarski N, Modin GW, et al: Identification of patients with acute lung injury: Predictors of mortality. Am J Respir Crit Care Med 152:1818–1824, 1995.
274. Staub NC: Clinical use of lung water measurements: Report of a workshop. Chest 90:588–594, 1986.
275. Bombino M, Gattinoni L, Pesenti A, et al: The value of portable chest roentgenography in adult respiratory distress syndrome: Comparison with computed tomography. Chest 100:762–769, 1991.
276. Winer-Muram H, Rubin SA, Miniati M, et al: Guidelines for reading and interpreting chest radiographs in patients receiving mechanical ventilation. Chest 102:565S–570S, 1992.
277. Suh R, Aberle DR: Radiographic manifestations of pulmonary edema. *In* Matthay MA, Ingbar DH (eds): Pulmonary Edema. New York: Marcel Dekker, 1998, pp 85–119.
278. Coates G, Powles ACP, Morrison SC, et al: The effects of intravenous infusion of saline on lung density, lung volumes, nitrogen washout, computed tomographic scans, and chest radiographs in humans. Am Rev Respir Dis 127:91–96, 1983.
279. Aberle DR, Wiener-Kronish JP, Webb RW, et al: Hydrostatic versus increased permeability pulmonary edema: Diagnosis based on radiographic criteria in critically ill patients. Radiology 168:73–79, 1988.
280. Rocker G, Rose DH, Manhire AR, et al: The radiographic differentiation of pulmonary edema. Br J Radiol 62:582–586, 1989.
281. Thomason J, Ely EW, Chiles C, et al: Appraising pulmonary edema using supine chest roentgenograms in ventilated patients. Am J Respir Crit Care Med 157:1600–1608, 1998.
282. Rubenfeld GD, Caldwell E, Granton J, et al: Interobserver variability in applying a radiographic definition for ARDS. Chest 116:1347–1353, 1999.
283. Brigham K, Kariman K, Harris TR, et al: Correlation of oxygenation with vascular permeability-surface area but not with lung water in humans with acute respiratory failure and pulmonary edema. J Clin Invest 72:339–349, 1983.
284. Harris T, Bernard GR, Brigham KL, et al: Lung microvascular transport properties measured by multiple indicator dilution methods in patients with adult respiratory distress syndrome: A comparison between patients reversing respiratory failure and those failing to reverse. Am Rev Respir Dis 141:272–280, 1990.
285. Estenne M, Yernault J-C: The mechanism of CO_2 retention in cardiac pulmonary edema. Chest 86:936–938, 1984.
286. Aberman A, Fulop M: The metabolic and respiratory acidosis of acute pulmonary edema. Ann Intern Med 76:173–184, 1972.
287. O'Donovan R, McGowan JA, Lupinacci L, et al: Acid-base disturbances in cardiogenic pulmonary edema. Nephron 57:416–420, 1991.
288. De Backer D, Creteur J, Zhang H, et al: Lactate production by the lungs in acute lung injury. Am J Respir Crit Care Med 156:1099–1104, 1997.
289. Sprung C, Rackow EC, Fein IA, et al: The spectrum of pulmonary edema: Differentiation of cardiogenic, intermediate, and noncar-

diogenic forms of pulmonary edema. Am Rev Respir Dis 124:718–722, 1981.
290. Carlson RW, Schaeffer RC, Carpio M, et al: Edema fluid and coagulation changes during fulminant pulmonary edema. Chest 79:43–49, 1981.
291. Carlson R, Schaeffer RC, Michaels SG, et al: Pulmonary edema fluid: Spectrum of features in 37 patients. Circulation 60:1161–1169, 1979.
292. Sprung CL, Long WM, Marcial EH, et al: Distribution of proteins in pulmonary edema: The value of fractional concentrations. Am Rev Respir Dis 136:957–963, 1987.
293. Matthay MA, Wiener-Kronish JP: Intact epithelial barrier function is critical for the resolution of alveolar edema in humans. Am Rev Respir Dis 142:1250–1257, 1990.
294. Ware LB, Matthay MA: Alveolar fluid clearance is impaired in the majority of patients with acute lung injury and the acute respiratory distress syndrome. Am J Respir Crit Care Med 163:1376–1383, 2001.
294a. Ware LB, Fremont RD, Bastarache JA, et al: Determining the etiology of pulmonary oedema by the oedema fluid-to-plasma protein ratio. Eur Respir J epub, 2009.
295. Steinberg KP, Mitchell DR, Maunder RJ, et al: Safety of bronchoalveolar lavage in patients with adult respiratory distress syndrome. Am Rev Respir Dis 148:556–561, 1993.
296. Connors A, Castele RJ, Farhat NZ, et al: Complications of right heart catheterization: A prospective autopsy study. Chest 88:567–572, 1985.
297. Matthay MA, Chatterjee K: Bedside catheterization of the pulmonary artery: Risks compared with benefits. Ann Intern Med 109:826–834, 1988.
298. Connors AF, Speroff T, Dawson NV, et al: The effectiveness of right heart catheterization in the initial care of critically ill patients. JAMA 276:889–897, 1996.
299. Richard C, Warszawski J, Anguel N, et al, for the French Pulmonary Artery Catheter Study Group: Early use of the pulmonary artery catheter and outcomes in patients with shock and acute respiratory distress syndrome: A randomized controlled trial. JAMA 290:2713–2720, 2003.
300. O'Quinn R, Marini JJ: Pulmonary artery occlusion pressure: Clinical physiology, measurement, and interpretation. Am Rev Respir Dis 128:319–326, 1983.
301. Robin ED: The cult of the Swan-Ganz catheter: Overuse and abuse of pulmonary flow catheters. Ann Intern Med 103:445–449, 1985.
302. Raper R, Sibbald WJ: Misled by the wedge? The Swan-Ganz catheter and left ventricular preload. Chest 89:427–434, 1986.
303. Staub NC: The hemodynamics of pulmonary edema. Bull Eur Physiopathol Respir 22:319–322, 1986.
304. Perkins GD, McAuley DF, Thickett DR, Gao F: The Beta-Agonist Lung Injury trial (BALTI): A randomized placebo-controlled clinical trial. Am J Respir Crit Care Med 173:281–287, 2006.
305. Licker M, Tschopp JM, Robert J, et al: Aerosolized salbutamol accelerates the resolution of pulmonary edema after lung resection. Chest 133:845–852, 2008.
306. Phillips CR, Chesnutt MS, Smith SM: Extravascular lung water in sepsis-associated acute respiratory distress syndrome: Indexing with predicted body weight improves correlation with severity of illness and survival. Crit Care Med 36:69–73, 2008.
307. Matthay MA: Measurement of extravascular lung water in patients with pulmonary edema. Am J Physiol Lung Cell Mol Physiol 294:L1021–L1022, 2008.
308. Stark P, Jasmine J: CT of pulmonary edema. Crit Rev Diagn Imaging 29:245–255, 1989.
309. Forster B, Mueller NL, Mayo JR, et al: High-resolution computed tomography of experimental hydrostatic pulmonary edema. Chest 101:1434–1437, 1992.
310. Simon D, Murray JF, Staub NC: Measurement of pulmonary edema in intact dogs by transthoracic gamma ray attenuation. J Appl Physiol 47:1228–1233, 1979.
311. Gamsu G, Kaufman L, Swann SJ, et al: Absolute lung density in experimental canine pulmonary edema. Invest Radiol 14:261–269, 1979.
312. Rice DA: Sound speed in pulmonary parenchyma. J Appl Physiol 54:304–308, 1983.
313. Nierman DM, Eisen DI, Fein ED, et al: Transthoracic bioimpedance can measure extravascular lung water in acute lung injury. J Surg Res 65:101–108, 1996.
314. Caruthers S, Paschal CB, Pou NA, et al: Regional measurements of pulmonary edema by using magnetic resonance imaging. J Appl Physiol 84:2143–2153, 1998.
315. Kaplan J, Calandrino FS, Schuster DP: A positron emission tomographic comparison of pulmonary vascular permeability during the adult respiratory distress syndrome and pneumonia. Am Rev Respir Dis 143:150–154, 1991.
316. Effros RM: Lung water measurements with the mean transit time approach. J Appl Physiol 59:673–683, 1985.
317. Böck J, Lewis FR: Clinical relevance of lung water measurement with the thermal-dye dilution technique. J Surg Res 48:254–265, 1990.
318. Chinard FP: Estimation of extravascular lung water by indicator-dilution techniques. Circ Res 37:137–145, 1975.
319. Allison R, Carlile PV, Gray BA: Thermodilution measurement of lung water. Clin Chest Med 6:439–467, 1985.
320. Eisenberg PR, Hansbrough JR, Anderson D, et al: A prospective study of lung water measurements during patient management in an intensive care unit. Am Rev Respir Dis 136:662–668, 1987.
321. Mitchell JP, Schuller D, Calandrino FS, et al: Improved outcome based on fluid management in critically ill patients requiring pulmonary artery catheterization (see comments). Am Rev Respir Dis 145:990–998, 1992.
322. Dawson C, Bronikowski TA, Linehan JH, et al: Influence of pulmonary vasoconstriction on lung water and perfusion heterogeneity. J Appl Physiol 54:654–660, 1983.
323. Sibbald W, Cunningham DR, Chin DN: Non-cardiac or cardiac pulmonary edema? A practical approach to clinical differentiation in critically ill patients. Chest 84:452–461, 1983.
324. Connelly KG, Repine JE: Markers for predicting the development of acute respiratory distress syndrome. Annu Rev Med 48:429–445, 1997.
325. Levitt JE, Gould MK, Ware LB, Matthay MA: The pathogenetic and prognostic value of biologic markers in acute lung injury. J Intensive Care Med 24:151–167, 2009.
326. McClintock D, Zhuo H, Wickersham N, et al: Biomarkers of inflammation, coagulation and fibrinolysis predict mortality in acute lung injury. Crit Care 12:R41, 2008.
327. Frank JA, Parsons PE, Matthay MA: Pathogenetic significance of biological markers of ventilator-associated lung injury in experimental and clinical studies. Chest 130:1906–1914, 2006.
328. Weinberg PF, Matthay MA, Webster RO, et al: Biologically active products of complement and acute lung injury in patients with the sepsis syndrome. Am Rev Respir Dis 130:791–796, 1984.
329. Parsons PE, Giclas PC: The terminal complement complex (sC5b-9) is not specifically associated with the development of the adult respiratory distress syndrome. Am Rev Respir Dis 141:98–103, 1990.
330. Ware LB, Conner E, Matthay MA: von Willebrand factor antigen is an independent marker of poor outcome in patients with early acute lung injury. Crit Care Med 29:2325–2331, 2001.
331. Eisner M, Parsons P, Matthay MA, et al: Acute Respiratory Distress Syndrome Network: Plasma surfactant protein levels and clinical outcomes in patients with acute lung injury. Thorax 58:983–988, 2003.
332. Baldwin S, Simon RH, Grum CM, et al: Oxidant activity in expired breath of patients with adult respiratory distress syndrome. Lancet 1:11–14, 1986.
333. Sznajder J, Fraiman A, Hall JB, et al: Increased hydrogen peroxide in the expired breath of patients with acute hypoxemic respiratory failure. Chest 96:606–612, 1989.
334. Cochrane C, Spragg R, Revak SD: Pathogenesis of the adult respiratory distress syndrome: Evidence of oxidant activity in bronchoalveolar lavage fluid. J Clin Invest 71:754–761, 1983.
335. Hyers TM, Tricomi SM, Dettenmeier PA, et al: Tumor necrosis factor levels in serum and bronchoalveolar lavage fluid of patients with the adult respiratory distress syndrome. Am Rev Respir Dis 144:268–271, 1991.
336. Parsons PE, Moore FA, Moore EE, et al: Studies on the role of tumor necrosis factor in adult respiratory distress syndrome. Am Rev Respir Dis 146:694–700, 1992.

337. Levine B, Kalman J, Mayer L, et al: Elevated circulating levels of tumor necrosis factor in severe chronic heart failure. N Engl J Med 323:236–241, 1990.
338. Stephenson A, Lonigro AJ, Hyers TM, et al: Increased concentrations of leukotrienes in bronchoalveolar lavage fluid of patients with ARDS or at risk for ARDS. Am Rev Respir Dis 138:714–719, 1988.
339. Bernard GR, Korley V, Chee P, et al: Persistent generation of peptido leukotrienes in patients with the adult respiratory distress syndrome. Am Rev Respir Dis 144:263–267, 1991.
340. Lee C, Fein AM, Lippmann M, et al: Elastolytic activity in pulmonary lavage fluid from patients with adult respiratory distress syndrome. N Engl J Med 304:192–196, 1981.
341. McGuire W, Spragg RG, Cohen AB, et al: Studies on the pathogenesis of the adult respiratory distress syndrome. J Clin Invest 69:543–553, 1982.
342. Idell S, Kucich U, Fein A, et al: Neutrophil elastase-releasing factors in bronchoalveolar lavage from patients with adult respiratory distress syndrome. Am Rev Respir Dis 132:1098–1105, 1985.
343. Wewers MD, Herzyk DJ, Gadek JE: Alveolar fluid neutrophil elastase activity in the adult respiratory distress syndrome is complexed to alpha-2-macroglobulin. J Clin Invest 82:1260–1267, 1988.
344. Cheng IW, Ware LB, Greene KE, et al: Prognostic value of surfactant proteins A and D in patients with acute lung injury. Crit Care Med 31:20–27, 2003.
345. Parsons PE, Eisner MD, Thompson BT, et al: Lower tidal volume ventilation and plasma cytokine markers of inflammation in patients with acute lung injury. Crit Care Med 33:1–6, 2005.
346. Ware LB, Eisner MD, Thompson BT, et al, The Acute Respiratory Distress Syndrome Network: Significance of von Willebrand factor in septic and nonseptic patients with acute lung injury. Am J Respir Crit Care Med 170:766–772, 2004.
347. Parsons PE, Matthay MA, Ware LB, Eisner MD: Elevated plasma levels of soluble TNF receptors are associated with morbidity and mortality in patients with acute lung injury. Am J Physiol Lung Cell Mol Physiol 288:L426–L431, 2005.
348. Calfee CS, Eisner MD, Parsons PE, et al: Soluble intercellular adhesion molecule-1 and clinical outcomes in patients with acute lung injury. Intensive Care Med 35:248–257, 2009.
349. Ware LB, Fang X, Matthay MA: Protein C and thrombomodulin in human acute lung injury. Am J Physiol Lung Cell Mol Physiol 285:L514–L521, 2003.
350. Prabhakaran P, Ware LB, White KE, et al: Elevated levels of plasminogen activator inhibitor-1 in pulmonary edema fluid are associated with mortality in acute lung injury. Am J Physiol Lung Cell Mol Physiol 285:L20–L28, 2003.
351. Uchida T, Shirasawa M, Ware LB, et al: Receptor for advanced glycation end-products is a marker of type I cell injury in acute lung injury. Am J Respir Crit Care Med 173:1008–1015, 2006.
352. Calfee CS, Ware LB, Eisner MD, et al: Plasma receptor for advanced glycation end products and clinical outcomes in acute lung injury. Thorax 63:1083–1089, 2008.
352a. Ware LB, Koyama T, Billheimer DD, et al: Prognostic and pathogenetic value of combining clinical and biochemical indices in patients with acute lung injury. Chest epub, 2009.
353. Hirsch J, Hansen KC, Burlingame AL, Matthay MA: Proteomics: Current techniques and potential applications to lung disease. Am J Physiol Lung Cell Mol Physiol 287:L1–L23, 2004.
354. Ware LB, Matthay MA: Beyond fishing: The role of discovery proteomics in mechanistic lung research. Am J Physiol Lung Cell Mol Physiol 296:L12–L13, 2009.
355. Bowler R, Duda B, Chan ED, et al: A proteomic analysis of pulmonary edema fluid and plasma in patients with acute lung injury. Am J Physiol Lung Cell Mol Physiol 286:L1095–L1104, 2004.
356. Chang DW, Hayashi S, Gharib SA, et al: Proteomic and computational analysis of bronchoalveolar proteins during the course of the acute respiratory distress syndrome. Am J Respir Crit Care Med 178:701–709, 2008.
357. Staub NC: Pulmonary edema: Physiologic approaches to management. Chest 74:559–564, 1978.
358. Klein H, Brodsky E, Ninio R, et al: The effect of venous occlusion with tourniquets on peripheral blood pooling and ventricular function. Chest 103:521–527, 1993.
359. Eiser A, Lieber JJ, Neff MS: Phlebotomy for pulmonary edema in dialysis patients. Clin Nephrol 47:47–49, 1997.
360. Jasmer RM, Luce JM, Matthay MA: Noninvasive positive pressure ventilation for acute respiratory failure: Underutilized or overrated? Chest 111:1672–1678, 1997.
361. Antonelli M, Conti G, Rocco M, et al: A comparison of noninvasive positive-pressure ventilation and conventional mechanical ventilation in patients with acute respiratory failure. N Engl J Med 339:429–435, 1998.
362. Gray A, Goodacre SM, Newby DE, et al: Noninvasive ventilation in acute cardiogenic pulmonary edema. N Engl J Med 359:142–151, 2008.
363. Wheeler AP, Bernard GR, Thompson BT, et al: Pulmonary-artery versus central venous catheter to guide treatment of acute lung injury. N Engl J Med 354:2213–2224, 2006.
364. Sandham J, Hull RD, Brant RF, et al: A randomized, controlled trial of the use of pulmonary-artery catheters in high-risk surgical patients. N Engl J Med 348:5–14, 2003.
365. Parsons P: Progress in research on pulmonary arterial catheters. N Engl J Med 348:66–68, 2003.
366. Ware LB, Matthay MA: Clinical practice: Acute pulmonary edema. N Engl J Med 353:2788–2796, 2005.
367. Annane D, Bellissant E, Pussard E, et al: Placebo-controlled, randomized, double-blind study of intravenous enalaprilat efficacy and safety in acute cardiogenic pulmonary edema. Circulation 94:1316–1324, 1996.
368. Brater DC: Diuretic therapy. N Engl J Med 339:387–395, 1998.
369. Garzia F, Todor R, Scalea T: Continuous arteriovenous hemofiltration countercurrent dialysis (CAVH-D) in acute respiratory failure (ARDS). J Trauma 31:1277–1285, 1991.
370. Kollef MH: The prevention of ventilator-associated pneumonia. N Engl J Med 340:627–634, 1999.
371. Susini G, Zucchetti M, Bortone F, et al: Isolated ultrafiltration in cardiogenic pulmonary edema. Crit Care Med 18:14–17, 1990.
372. Tibayan FA, Chesnutt AN, Folkesson HG, et al: Dobutamine increases alveolar liquid clearance in ventilated rats by beta-2 receptor stimulation. Am J Respir Crit Care Med 156:438–444, 1997.
373. Kolla S, Awad SS, Rich PB, et al: Extracorporeal life support for 100 adult patients with severe respiratory failure. Ann Surg 226:544–556, 1997.
374. Grover F, Fullerton DA, Zamora MR, et al: The past, present, and future of lung transplantation. Am J Surg 173:523–533, 1997.
375. Ehrhart I, Hofman WF: Relationship of fluid filtration to lung vascular pressure during edema. J Appl Physiol 70:202–209, 1991.
376. Gheorghiade M, Cody RJ, Francis GS, et al: Current medical therapy for advanced heart failure. Am Heart J 135:S231–S248, 1998.
377. Verghese GM, Ware LB, Matthay BA, et al: Alveolar epithelial fluid transport and the resolution of clinically severe hydrostatic pulmonary edema. J Appl Physiol 87:1301–1312, 1999.
378. Wheeler AP, Bernard GR: Treating patients with severe sepsis. N Engl J Med 340:207–214, 1999.
379. Gattinoni L, Brazzi L, Pelosi P, et al: A trial of goal-oriented hemodynamic therapy in critically ill patients. N Engl J Med 333:1025–1032, 1995.
380. Rivers E, Nguyen B, Havstad S, et al: Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 345:1368–1377, 2001.
381. Wiedemann HP, Wheeler AP, Bernard GR, et al: Comparison of two fluid-management strategies in acute lung injury. N Engl J Med 354:2564–2575, 2006.
382. Hebert P, Wells G, Blajchman MA, et al: A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. N Engl J Med 340:409–417, 1999.
383. Webb HH, Tierney DF: Experimental pulmonary edema due to intermittent positive pressure ventilation with high inflation pressures: Protection by positive end-expiratory pressure. Am Rev Respir Dis 110:556–565, 1974.
384. Parker JC, Townsley MI, Rippe B, et al: Increased microvascular permeability in dog lungs due to high peak airway pressures. J Appl Physiol 57:1809–1816, 1984.

385. Slutsky AS, Tremblay LN: Multiple system organ failure: Is mechanical ventilation a contributing factor? Am J Respir Crit Care Med 157:1721–1725, 1998.
386. Marini JJ: Evolving concepts in the ventilatory management of acute respiratory distress syndrome. Clin Chest Med 17:555–575, 1996.
387. The Acute Respiratory Distress Syndrome Network: A trial of mechanical ventilation with higher versus lower positive end-expiratory pressures in patients with acute lung injury and acute respiratory distress syndrome. N Engl J Med 351:327–336, 2004.
388. Cheng I, Eisner M, Thompson T, et al: Acute effects of tidal volume strategy on hemodynamics, fluid balance, and sedation in acute lung injury. Crit Care Med 33:63–70, 2005.
389. Morris AH, Wallace CJ, Menlove RL, et al: Randomized clinical trial of pressure-controlled inverse ratio ventilation and extracorporeal CO_2 removal for adult respiratory distress syndrome (see comments). Am J Respir Crit Care Med 149:295–305, 1994 [published erratum appears in Am J Respir Crit Care Med 149(3 Pt 1):838, 1994].
390. Brower RG, Ware LB, Berthiaume Y, et al: Treatment of ARDS. Chest 120:1347–1367, 2001.
391. Albert PK: The prone position in acute respiratory distress syndrome: Where we are, and where do we go from here. Crit Care Med 25:1453–1454, 1997.
392. Pelosi P, Tubiolo D, Mascheroni D, et al: Effects of the prone position on respiratory mechanics and gas exchange during acute lung injury. Am J Respir Crit Care Med 157:387–393, 1998.
393. Guerin C, Gaillard S, Lemasson S, et al: Effects of systemic prone positioning in hypoxemic acute respiratory failure: A randomized clinical trial. JAMA 292:2379–2387, 2004.
394. Curley MA, Hibberd PL, Fineman LD, et al: Effect of prone positioning on clinical outcomes in children with acute lung injury: A randomized controlled trial. JAMA 294:229–237, 2005.
395. Heyland D, Mandell LA: Gastric colonization by gram-negative bacilli and nosocomial pneumonia in the intensive care unit: Evidence for causation. Chest 101:187–193, 1992.
396. Dematte J, Sznajder JI: Effects of selective digestive decontamination on lung injury and outcome: The verdict is not yet in. Chest 112:304–306, 1997.
397. Collard H, Saint S, Matthay MA: Prevention of ventilator-associated pneumonia: An evidence-based systematic review. Ann Intern Med 136:494–501, 2003.
398. Turner J, Briggs S, Springhorn HE, et al: Patients' recollection of intensive care unit experience. Crit Care Med 18:966–968, 1990.
399. Girard TD, Kress JP, Fuchs BD, et al: Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (awakening and breathing controlled trial): a randomised controlled trial. Lancet 12:126-134, 2008.
400. Petty T, Bone RC, Gee MH, et al: Contemporary clinical trials in acute respiratory distress syndrome. Chest 101:550–552, 1992.
401. Cepkova M, Brady S, Sapru A, et al: Biological markers of lung injury before and after the institution of positive pressure ventilation in patients with acute lung injury. Crit Care 10:R126, 2006.
402. Hudson LD, Milberg JA, Anardi D, et al: Clinical risks for development of the acute respiratory distress syndrome. Am J Respir Crit Care Med 151:293–301, 1995.
403. Bernard GR, Luce JM, Sprung CL, et al: High-dose corticosteroids in patients with the adult respiratory distress syndrome. N Engl J Med 317:1565–1570, 1987.
404. Slotman G, Fisher CJ, Bone RC, et al: Detrimental effects of high-dose methylprednisolone sodium succinate on serum concentrations of hepatic and renal function indicators in severe sepsis and septic shock. Crit Care Med 21:191–195, 1993.
405. Schonfeld S, Ploysongsang Y, DiLisio R, et al: Fat embolism prophylaxis with corticosteroids: A prospective study in high-risk patients. Ann Intern Med 99:438–443, 1983.
406. Hooper RG: ARDS: Inflammation, infections, and corticosteroids. Chest 100:889–890, 1991.
407. Meduri GU, Headley AS, Golden E, et al: Effect of prolonged methylprednisolone therapy in unresolving acute respiratory distress syndrome: A randomized controlled trial (see comments). JAMA 280:159–165, 1998.
408. Steinberg KP, Hudson LD, Goodman RB, et al: Efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome. N Engl J Med 354:1671–1684, 2006.
409. Lewis JF, Jobe AH: Surfactant and the adult respiratory distress syndrome. Am Rev Respir Dis 147:218–233, 1993 [published erratum appears in Am Rev Respir Dis 147:following 1068, 1993].
410. Weg J, Balk RA, Tharratt RS, et al: Safety and potential efficacy of an aerosolized surfactant in human sepsis-induced adult respiratory distress syndrome. JAMA 272:1433–1438, 1994.
411. Anzueto A, Baughman RP, Guntupalli KK, et al: Aerosolized surfactant in adults with sepsis-induced acute respiratory distress syndrome. N Engl J Med 334:1417–1421, 1996.
412. Spragg RG, Lewis JF, Walmrath HD, et al: Effect of recombinant surfactant protein-C based surfactant on the acute respiratory distress syndrome. N Engl J Med 351:884–892, 2004.
413. Bernard GR: *N*-Acetylcysteine in experimental and clinical acute lung injury. Am J Med 91:54S–59S, 1991.
414. Bernard GR, Wheeler AP, Arons MM, et al.: A trial of antioxidants *N*-acetylcysteine and procysteine in ARDS. Chest 112:164–172, 1997.
415. Raffin T: Acute lung injury and pentoxifylline. Crit Care Med 18:1485–1486, 1990.
416. McDonald RJ: Pentoxifylline reduces injury to isolated lungs perfused with human neutrophils. Am Rev Respir Dis 144:1347–1350, 1991.
417. The Acute Respiratory Distress Syndrome Network: Randomized, placebo-controlled trial of lisofylline for early treatment of acute lung injury and acute respiratory distress syndrome. Crit Care Med 30:1–6, 2002.
418. Bone R, Balk RA, Fein AM, et al: A second large controlled clinical study of E5, a monoclonal antibody to endotoxin: Results of a prospective, multicenter, randomized, controlled trial. Crit Care Med 23:994–1006, 1995.
419. Luce JM: Introduction of new technology into critical care practice: A history of HA-1A human monoclonal antibody against endotoxin. Crit Care Med 21:1233–1241, 1993.
420. Bigatello L, Greene RE, Sprung CL, et al: HA-1A in septic patients with ARDS: Results from the pivotal trial. Intensive Care Med 20:328–334, 1994.
421. Abraham E, Wunderink R, Silverman H, et al: Efficacy and safety of monoclonal antibody to human tumor necrosis factor alpha in patients with sepsis syndrome: A randomized, controlled, double-blind, multicenter clinical trial. TNF-alpha MAb Sepsis Study Group. JAMA 273:934–941, 1995.
422. Fisher C, Dhainaut J-FA, Opal SM, et al: Recombinant human interleukin-1 receptor antagonist in the treatment of patients with sepsis syndrome: Results from a randomized, double-blind, placebo-controlled trial. JAMA 271:1836–1843, 1994.
423. Bernard GR, Vincent JL, Laterre PF, et al: Efficacy and safety of recombinant human activated protein C for severe sepsis. N Engl J Med 344:699–709, 2001.
424. Prabhakaran P, Ware LB, White KE, et al: Elevated levels of plasminogen activator inhibitor-1 in pulmonary edema fluid are associated with mortality in acute lung injury. Am J Physiol Lung Cell Mol Physiol 285:L20–L28, 2003.
425. Idell S: Adult respiratory distress syndrome: Do selective anticoagulants help? Am J Respir Med 1:383–391, 2002.
426. Liu KD, Levitt J, Zhuo H, et al: Randomized clinical trial of activated protein C for the treatment of acute lung injury. Am J Respir Crit Care Med 178:618–623, 2008.
427. Bone RC, Slotman G, Maunder R, et al: Randomized double-blind, multicenter study of prostaglandin E_1 in patients with the adult respiratory distress syndrome. Prostaglandin E_1 Study Group (see comments). Chest 96:114–119, 1989.
428. Matthay MA, Pittet J-F, Jayr C: Just say NO to inhaled nitric oxide for the acute respiratory distress syndrome (editorial). Crit Care Med 26:1–2, 1998.
429. Dellinger RP, Zimmerman JL, Taylor RW, et al: Effects of inhaled nitric oxide in patients with acute respiratory distress syndrome: Results of a randomized phase II trial. Inhaled Nitric Oxide in ARDS Study Group (see comments). Crit Care Med 26:15–23, 1998.
430. Luhr O, Nathorst-Westfelt U, Lundin S, et al: A retrospective analysis of nitric oxide inhalation in patients with severe acute

lung injury in Sweden and Norway 1991–1994. Acta Anaesth Scand 41:1238–1246, 1997.
430a. Lee JW, Fang X, Gupta N, et al: Allogeneic human mesenchymal stem cells for treatment of E. coli endotoxin-induced acute lung injury in the ex vivo perfused human lung. Proc Natl Acad Sci USA 106:16357-16362, 2009.
431. Hastings RH, Grady M, Sakuma T, et al: Clearance of different-sized proteins from the alveolar space in humans and rabbits. J Appl Physiol 73:1310–1316, 1992.
432. Matalon S, O'Brodovich H: Sodium channels in alveolar epithelial cells: Molecular characterization, biophysical properties, and physiological significance. Annu Rev Physiol 61:627–661, 1999.
433. Saumon G, Basset G: Electrolyte and fluid transport across the mature alveolar epithelium. J Appl Physiol 74:1–15, 1993.
434. Folkesson HG, Kheradmand F, Matthay MA: The effect of salt water on alveolar epithelial barrier function. Am J Respir Crit Care Med 150:1555–1563, 1994.
435. Zuege D, Suzuki S, Berthiaume Y: Increase of lung sodium-potassium-ATPase activity during recovery from high-permeability pulmonary edema. Am J Physiol 271:L896–L909, 1996.
436. Sakuma T, Folkesson HG, Suzuki S, et al: Beta-adrenergic agonist stimulated alveolar fluid clearance in ex vivo human and rat lungs. Am J Respir Crit Care Med 155:506–512, 1997.
437. Berthiaume Y, Albertine KH, Grady M, et al: Protein clearance from the air spaces and lungs of unanesthetized sheep over 144 h. J Appl Physiol 67:1887–1897, 1989.
438. Staub NC: Alveolar flooding and clearance. Am Rev Respir Dis 127:S45–S51, 1983.
439. Conhaim RL: Airway level at which edema liquid enters the air space of isolated dog lungs. J Appl Physiol 67:2234–2242, 1989.
440. Kambara K, Longworth KE, Serikov VB, et al: Effect of interstitial edema on lung lymph flow in goats in the absence of filtration. J Appl Physiol 72:1142–1148, 1992.
441. Fukue M, Serikov VB, Jerome EH: Recovery from increased pressure or increased leakiness edema in perfused sheep lungs. J Appl Physiol 77:184–189, 1994.
442. Pearse DB, Wagner EM, Sylvester JT: Edema clearance in isolated sheep lungs. J Appl Physiol 74:126–132, 1993.
443. Wiener-Kronish JP, Broaddus VC: Interrelationship of pleural and pulmonary interstitial liquid. Annu Rev Physiol 55:209–226, 1993.
444. Wiener-Kronish JP, Matthay MA, Callen PW, et al: Relationship of pleural effusions to pulmonary hemodynamics in patients with congestive heart failure. Am Rev Respir Dis 132:1253–1256, 1985.
445. Wiener-Kronish JP, Matthay MA: Pleural effusions associated with hydrostatic and increased permeability pulmonary edema. Chest 93:852–858, 1988.
446. Broaddus VC, Wiener-Kronish JP, Staub NC: Clearance of lung edema into the pleural space of volume-loaded anesthetized sheep. J Appl Physiol 68:2623–2630, 1990.
447. Lum H, Malik AB: Regulation of vascular endothelial barrier function. Am J Physiol 267:L223–L241, 1994.
448. Wiener R, Moses HW, Richeson JF, et al: Hospital and long term survival of patients with acute pulmonary edema associated with coronary artery disease. Am J Cardiol 60:33–35, 1987.
449. DiFederico EM, Harrison M, Matthay MA: Pulmonary edema in a woman following fetal surgery. Chest 109:1114–1117, 1996.
450. Thomsen G, Morris AH: Incidence of the adult respiratory distress syndrome in the state of Utah. Am J Respir Crit Care Med 152:965–971, 1995.
451. Rubenfeld GD, Caldwell EC, Martin DM, et al: The incidence of acute lung injury (ALI) in adults in the US: Results of the King County Lung Injury Project. Am J Respir Crit Care Med 165:A219, 2002.
452. Milberg JA, Davis DR, Steinberg KP, et al: Improved survival of patients with acute respiratory distress syndrome (ARDS): 1983–1993. JAMA 273:306–309, 1995.
453. Moss M, Bucher B, Moore FA, et al: The role of chronic alcohol abuse in the development of acute respiratory distress syndrome in adults. JAMA 275:50–54, 1996.
454. Holguin F, Moss IM, Brown LAS, et al: Chronic ethanol ingestion impairs alveolar type II cell glutathione homeostasis and function and predisposes to endotoxin-mediated acute edematous lung injury in rats. J Clin Invest 101:761–768, 1998.
455. Suchyta M, Clemmer TP, Elliott CG, et al: Increased mortality of older patients with acute respiratory distress syndrome. Chest 111:1334–1339, 1997.
456. Ely E, Wheeler AP, Thompson BT, et al: Recovery rate and prognosis in older persons who develop acute lung injury and the acute respiratory distress syndrome. Ann Intern Med 136:25–36, 2002.
457. Ghio AJ, Elliott CG, Crapo RO, et al: Impairment after adult respiratory distress syndrome: An evaluation based on American Thoracic Society recommendations. Am Rev Respir Dis 139:1158–1162, 1989.
458. Elliott CG: Pulmonary sequelae in survivors of the adult respiratory distress syndrome. Clin Chest Med 11:789–800, 1990.
459. McHugh LG, Milberg JA, Whitcomb ME, et al: Recovery of function in survivors of the acute respiratory distress syndrome. Am J Respir Crit Care Med 150:90–94, 1994.
460. Hert R, Albert RK: Sequelae of the adult respiratory distress syndrome. Thorax 49:8–13, 1994.
461. Elliott CG, Rasmusson BY, Crapo RO: Upper airway obstruction following adult respiratory distress syndrome: An analysis of 30 survivors. Chest 94:526–530, 1988.
462. Bitterman PB: Pathogenesis of fibrosis in acute lung injury. Am J Med 92:39S–43S, 1992.
463. Chapman HA: Disorders of lung matrix remodeling. J Clin Invest 113:148–157, 2004.
464. Pugin J, Verghese G, Widmer MC, et al: The alveolar space is the site of intense inflammatory and profibrotic reactions in the early phase of acute respiratory distress syndrome. Crit Care Med 27:304–312, 1999.
465. Olman M, White KE, Ware LB, et al: Pulmonary edema fluid from patients with early lung injury stimulates fibroblast proliferation through IL-1beta–induced IL-6 expression. J Immunol 172:2668–2677, 2004.
466. Martin C, Papazian L, Payan M-J, et al: Pulmonary fibrosis correlates with outcome in the adult respiratory distress syndrome. Chest 107:196–200, 1995.
467. Panos RJ, Bak PM, Simonet WS, et al: Intratracheal instillation of keratinocyte growth factor decreases hyperoxia-induced mortality in rats. J Clin Invest 96:2026–2033, 1995.
468. Garat C, Kheradmand F, Albertine KH, et al: Soluble and insoluble fibronectin increases alveolar epithelial wound healing in vitro. Am J Physiol 271:L844–L853, 1996.
469. Matthay MA: Fibrosing alveolitis in the adult respiratory distress syndrome (editorial). Ann Intern Med 122:65–66, 1995.

CHAPTER 56

COR PULMONALE

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INTRODUCTION

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INTRODUCTION

The term *cor pulmonale,* or pulmonary heart disease, has been used rather loosely for many years to describe three broad groups of patients, all of whom have pulmonary hypertension resulting in progressive right ventricular hypertrophy, right ventricular dilation, and eventual cardiac decompensation from (1) disorders that primarily affect ventilatory drive or musculoskeletal respiratory mechanics; (2) pulmonary airway, infiltrative, fibrotic, or vascular diseases; and (3) disease in which the clinical picture as it affects the lungs and pulmonary circulation is the consequence of a primary cardiovascular disorder. To clarify matters, in 1963, an expert committee appointed by the Director General of the World Health Organization (WHO) recommended a definition based on morbid anatomy. Specifically, the committee defined chronic cor pulmonale as "hypertrophy of the right ventricle resulting from diseases affecting the function and/or the structure of the lung, except when these pulmonary alterations are the result of diseases that primarily affect the left side of the heart or congenital heart disease."[1] Subsequently, the WHO organized a major symposium on pulmonary hypertension that was held in Evian, France, in September 1998; from that meeting, which was attended by experts from around the world, a revised classification of pulmonary hypertension emerged,[2] which included replacing the terms "primary" and "secondary" pulmonary hypertension with a clinically meaningful classification. Eleven years later, the classification was again modified at the Fourth World Symposium on Pulmonary Hypertension in Dana Point, California (Table 56-1).[3] The resulting classification of pulmonary hypertension is generally accepted as the "gold standard" today. This chapter on cor pulmonale primarily deals with the group of disorders classified by this expert committee as "Pulmonary Hypertension Associated with Lung Diseases and/or Hypoxemia." We limit our discussion mainly to diseases that affect the airways and lung parenchyma, the pulmonary vasculature, or alveolar ventilation. Pulmonary thromboembolism (Chapter 51), pulmonary hypertension and related disorders (Chapter 52), and pulmonary vasculitis (Chapter 53) are discussed elsewhere.

PULMONARY CIRCULATION

The major pulmonary arteries normally have less medial thickening than the systemic arteries, reflecting the

TABLE 56-1. Fourth World Symposium Diagnostic Classification of Pulmonary Hypertension (2009)

GROUP 1: PULMONARY ARTERIAL HYPERTENSION (PAH)
Idiopathic PAH
Heritable PAH
- BMPR2
- ALK1, endoglin (with or without hereditary hemorrhagic telangiectasia)
- Unknown genes

Drug- and toxin-induced
Associated with:
- Connective tissue diseases
- HIV infection
- Portal hypertension
- Congenital heart disease
- Schistosomiasis
- Chronic hemolytic anemia

Persistent pulmonary hypertension of the newborn

GROUP 1′: PULMONARY VENO-OCCLUSIVE DISEASE (PVOD) AND/OR PULMONARY CAPILLARY HEMANGIOMATOSIS (PCH)

GROUP 2: PULMONARY HYPERTENSION OWING TO LEFT HEART DISEASE
Systolic dysfunction
Diastolic dysfunction
Valvular disease

GROUP 3: PULMONARY HYPERTENSION OWING TO LUNG DISEASES AND/OR HYPOXEMIA
Chronic obstructive pulmonary disease
Interstitial lung disease
Other pulmonary diseases with mixed restrictive and obstructive pattern
Sleep-disordered breathing
Alveolar hypoventilation disorders
Chronic exposure to high altitude
Developmental abnormalities

GROUP 4: CHRONIC THROMBOEMBOLIC PULMONARY HYPERTENSION (CTEPH)

GROUP 5: PULMONARY HYPERTENSION WITH UNCLEAR MULTIFACTORIAL MECHANISMS
Hematologic disorders: myeloproliferative disorders, splenectomy
Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis: lymphangioleiomyomatosis, neurofibromatosis, vasculitis
Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure on dialysis

ALK1, activin-like kinase type 1; BMPR2, bone morphogenetic protein receptor type 2; HIV, human immunodeficiency virus.

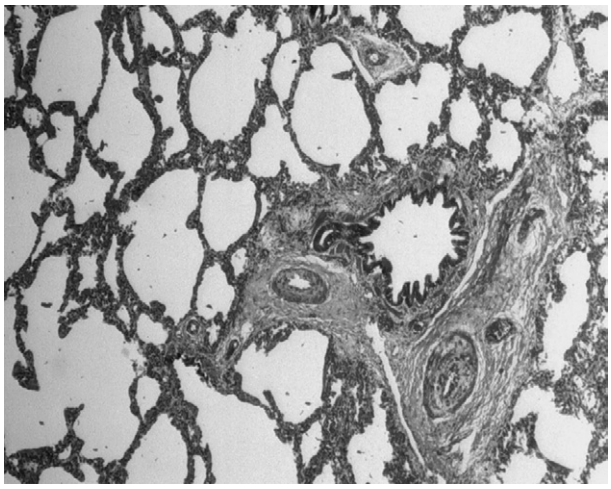


FIGURE 56-1 ■ A microscopic section from the lung of a patient who had chronic pulmonary hypertension. The small branches of the pulmonary artery are seen in juxtaposition to a terminal bronchiole. There is intimal thickening and marked medial hypertrophy.

fact that the pressures in the pulmonary arteries are approximately one fifth to one sixth of those normally found in the systemic arteries. In the systemic arteries, the ratio of medial thickness to external arterial diameter is 20% to 25%, but in the pulmonary arteries it is closer to 5%.[4] Postmortem casts of the human pulmonary arterial tree show there to be 17 branching orders, from the main pulmonary artery to the alveoli, that follow closely the branching pattern of the bronchial tree.[5,6] The number of vessels increases by a factor of approximately three with each branching order. As these vessels branch, their overall diameter ratio remains relatively constant, ensuring that the resistance to blood flow is minimal.

Muscular branches of the pulmonary artery, vessels with a luminal diameter between 100 and 1000 μm, have circular muscle fibers capable of causing vasoconstriction. These branches also demonstrate muscle hypertrophy in patients with chronic pulmonary hypertension (Fig. 56-1). True pulmonary arterioles, comparable to systemic arterioles, are not seen normally in the pulmonary circulation. Vessels smaller than 100 μm in diameter at the terminal end of the pulmonary arteries are usually referred to as pulmonary arterioles, but they normally have little or no medial smooth muscle. However, with chronic pulmonary hypertension, a single smooth muscle cell layer may extend longitudinally down these vessels. Therefore, normal pulmonary arterioles lack a true muscular media capable of reacting with vigorous vasoconstriction, but they still are capable of distending. Resistance to blood flow through the normal lung lies primarily in the capillary bed, but regulation resides chiefly in the very small branches of the pulmonary arterial system, and these branches are the major sites of the muscularization that is seen in patients who develop pulmonary hypertension. These vessels are less distensible in response to passive increases in pressure, and they can actively vasoconstrict in the presence of hypoxia. The pulmonary capillaries do not have smooth muscle cells within their walls and therefore do not contribute to pulmonary vasoconstriction. However, they can dilate to some extent during vascular engorgement, and numerous vessels are available for recruitment, both of which occur when pulmonary vein pressure rises. Although the pulmonary capillaries, which are literally suspended in

air, cannot vasoconstrict, their diameter can decrease in response to increases in intra-alveolar or intrapleural pressure. Their caliber may also decrease if there is perivascular inflammation or interstitial transudation of fluid.

Pulmonary Artery Pressure

Pulmonary artery pressure (PPA) in the normal resting recumbent adult averages 22/9 mm Hg, with a mean of 15 mm Hg. Pulmonary hypertension in the adult is said to be present when the resting pressure is higher than 30/15 mm Hg or the mean pressure is more than 25 mm Hg or 30 mm Hg with exercise. Commonly, pulmonary hypertension observed in cor pulmonale represents the net effect of a variety of different mechanisms. For example, in chronic obstructive pulmonary disease (COPD), a mixture of bronchitis and emphysema, the following effects on the pulmonary circulation may be seen: (1) reduction in the cross-sectional area of the pulmonary vasculature, reflecting anatomic loss of pulmonary capillaries from alveolar wall destruction; (2) increased pulmonary vascular resistance from hypoxic pulmonary vasoconstriction, with or without additional vasoconstriction resulting from hypercapnia and/or inflammation-induced vasoconstrictive stimuli and vascular remodeling; (3) medial hypertrophy of muscular pulmonary arteries and muscularization of the arterioles; (4) increased resistance to pulmonary blood flow resulting from polycythemia; (5) increased cardiac output and pulmonary blood flow from hypoxemia-induced systemic arteriolar vasodilation, which, in turn, raises PPA; and (6) an increase in intra-alveolar pressure with increasing lung inflation, which compresses pulmonary capillaries. Pulmonary hypertension may be variable—from mild elevations with exercise that return to normal with rest; to marked elevations in PPA associated with acute respiratory failure, but with restoration to the high-normal or mildly elevated range once ventilatory insufficiency is improved; to fixed severe pulmonary hypertension.

Disturbances in respiratory function ultimately affect the pulmonary circulation predominantly by production of alveolar hypoxia, regardless of whether obstructive or restrictive ventilatory insufficiency (or a combination of the two) is present, and regardless of the mechanism of abnormal gas exchange and whether it is caused by an anatomic or functional disturbance. In hypoxemia, with or without hypercapnia, PPA rises out of proportion to pulmonary capillary pressure owing to precapillary vasoconstriction, resulting in an increase in the work of the right ventricle and its subsequent remodeling.

Pulmonary Artery Wedge Pressure

The pulmonary artery wedge pressure is normally obtained during cardiac catheterization in the laboratory or at the bedside by occluding a small branch of the pulmonary artery in which the catheter is positioned, either by inflating a balloon at the end of the catheter or by wedging an end-hole catheter into the distal vessels. This extends the manometric system encompassed by the wall of the catheter, and the static column of fluid within it, to incorporate the walls of the vessel distal to the end of the catheter and the static column of blood within it (see Fig. 6-1 in Chapter 6). The extended manometric system then measures the pressure in the distal capillary-sinusoidal bed of the lung, where blood is still freely flowing (i.e., near the origin of the pulmonary venous system). Because the flow between the pulmonary capillaries and the left atrium normally is a low-resistance network, the pulmonary artery wedge pressure is usually within 1 or 2 mm Hg of left atrial pressure. Therefore, it is possible to estimate pulmonary vascular resistance by dividing the transpulmonary pressure gradient (mean PPA minus the pulmonary artery wedge pressure) by the cardiac output.

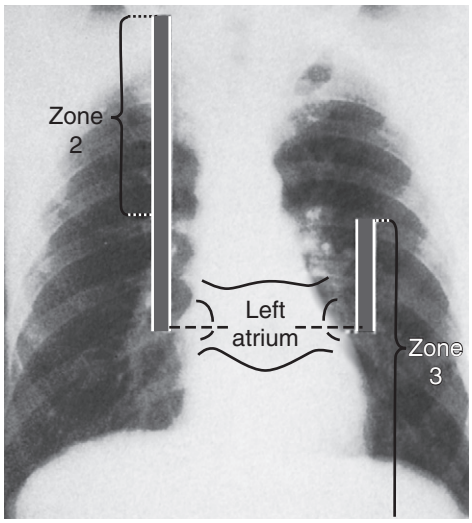


FIGURE 56-2 ■ Chest radiograph showing the distribution of zones in normal human lungs in the upright position. The *solid bar* on the left shows the height "reached" by pulmonary artery pressure, and the *bar* on the right shows the height "reached" by pulmonary vein pressure; both pressures are referenced to the mid-left atrium. More of the lungs are in zone 3 than zone 2, and there is no zone 1.

Although the apices of the lungs in a person who is sitting or standing are normally in West's zone 2 (Fig. 56-2), if PPA decreases, zone 1 relationships may develop (for further discussion, see Chapter 6). Under these conditions, estimates of left atrial pressure from pulmonary artery wedge pressures from zone 1 regions are difficult to obtain and may be inaccurate. However, because most measurements of pulmonary artery wedge pressures are made with the patient supine and the lungs mainly in zone 3, this is ordinarily not a significant practical problem. Should it be desirable to have measurements of pulmonary vascular resistance or estimations of accurate pulmonary artery wedge pressure while the patient is sitting or standing, the pulmonary artery catheter should be wedged in the dependent (posterobasal) portions of the lung: that is, in areas in which the vessel is below the level of the left atrium. Alternately, one may reasonably use total pulmonary resistance or the ratio of the mean PPA to the pulmonary blood flow when studying patients with pulmonary hypertension unrelated to left-sided heart events, in whom pulmonary vein pressures are presumably normal and, therefore, low. It should also be noted that the pulmonary artery wedge

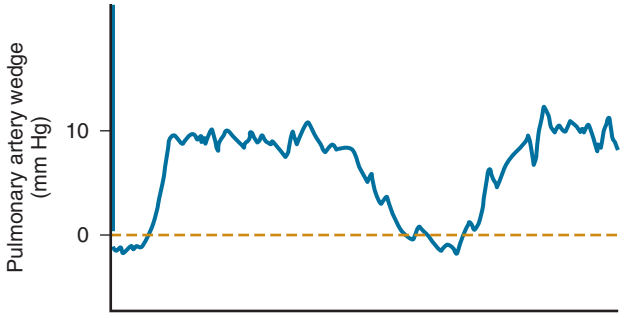


FIGURE 56-3 ■ Pulmonary artery wedge pressure in a patient with chronic obstructive lung disease. Note that the wedge pressure is normal. A prominent fall in wedge pressure is observed with the onset of inspiration as intrapleural pressure falls.

pressure may not reflect left atrial pressure if a patient is receiving positive-pressure ventilation. If there are wide swings in intrapleural pressure, the wedge pressure should be estimated at end-expiration and not as mean pressure (Fig. 56-3).

PATHOPHYSIOLOGY OF THE PULMONARY CIRCULATION

The normal pulmonary circulation, which is composed of highly compliant pulmonary arteries and a rich capillary network with a large recruitment capability, can accommodate large increases in blood flow (e.g., during exercise or with left-to-right congenital intracardiac shunts) without a significant rise in PPA. For example, this capillary reserve can be demonstrated in a healthy person at the time of cardiac catheterization by transient balloon occlusion of the left or right main pulmonary artery. No rise or only a small rise in the resting PPA results, despite the fact that the entire cardiac output must now go through the pulmonary circulation of only one lung.[7] Similarly, after recovering from pneumonectomy, patients often have only slightly raised resting PPA values.

Oxygen is the major mediator of pulmonary autoregulation, with pulmonary vasodilation occurring in regions where the partial pressure of oxygen is high and vasoconstriction occurring in lung regions that are poorly oxygenated so that blood flow is preferentially directed to areas that are better oxygenated. Hypoxic pulmonary vasoconstriction is the major mechanism implicated for the development of pulmonary hypertension in patients with lung disease; however, significant structural changes within the pulmonary vascular tree may also occur, which lead to destruction of the pulmonary capillary bed and contribute to the development of pulmonary hypertension. Early in the natural history of lung diseases, the resting pressure in the pulmonary artery is usually normal, and because of the large capillary reserve within the lung, it may not be readily apparent that significant capillary destruction is taking place until almost half of the capillary bed is destroyed.

The pathophysiology of pulmonary hypertension associated with advanced respiratory diseases is generally distinct from that of the pulmonary arterial hypertensive disorders, although they do share some similar mechanistic pathways. The vascular remodeling process in interstitial lung diseases and pulmonary arterial hypertension involve changes in all three levels of the vessel wall: the adventitia, media, and intima (luminal side). However, unlike the pulmonary arterial hypertensive disorders, which are characterized by marked intimal proliferation, adventitial collagen and extracellular matrix deposition, and plexigenic lesions, such severe findings are not generally present in patients with pulmonary hypertension associated with chronic obstructive or restrictive lung disorders.

Hypoxic Pulmonary Vasoconstriction

Several stimuli may result in precapillary pulmonary vasoconstriction with resultant pulmonary hypertension. Of these, the most potent and most important, alveolar hypoxia, may be present under a variety of circumstances.[8] Pulmonary vasoconstriction can occur in perfectly healthy lungs. For example, the pulmonary hypertension observed in persons living at high altitudes is caused by chronic hypoxemia despite the presence of hyperventilation with resultant hypocapnia. Similarly, hypoventilation sufficient to produce alveolar hypoxia and hypercapnia, which may occur in morbidly obese patients, results in pulmonary hypertension secondary to pulmonary vasoconstriction. Other causes of primary hypoventilation, whether it arises centrally or from weakness of the muscles of respiration, may also cause pulmonary hypertension secondary to inadequate alveolar ventilation. Hypercapnia, which is primarily mediated by an increase in hydrogen ion concentration, worsens pulmonary vasoconstriction, augmenting the pressure increase expected from a comparable degree of hypoxia alone.

It is of interest to contrast the consequences of hypoxic pulmonary vasoconstriction in healthy residents residing at high altitude and in patients with COPD with cor pulmonale residing at sea level. In the former case, a combination of alveolar hypoxia, hyperventilation, and hypocapnia is present; in the latter case, hypoxia is often associated with hypoventilation and hypercapnia. Subjects residing at high altitudes have an increased hematocrit and a decreased plasma volume. Their stroke volume and cardiac output tend to be low. In contrast, patients with COPD tend to have normal or increased blood volume, and their cardiac output is generally normal or even increased. Healthy subjects, even those residing at very high altitudes, normally do not develop right ventricular failure despite the presence of hypoxia and pulmonary artery hypertension, which suggests that acidemia and hypercapnia are important contributing elements to impaired right ventricular function in patients with COPD.

Low alveolar P_{O_2} increases PPA in a somewhat hyperbolic dose-response curve, with the pressure rising much more rapidly when arterial P_{O_2} values fall below 75 mm Hg. Nevertheless, there is still marked individual variability in the level of PPA at a given high altitude. In part this may be explained by differences in individual sensitivity to ventilatory drive produced by hypoxia, with some persons hyperventilating more than others.

However, some of the variability lies in the difference in pulmonary vasoconstrictive response, which probably reflects an inherited difference in pulmonary vascular reactivity. This latter viewpoint is supported by observations of the high-altitude pulmonary hypertensive disease among cattle known as *brisket disease.*[9] When cattle native to low altitudes are exposed to high altitudes for grazing, P_{PA} climbs only moderately in some, but in others the pressure climbs steeply. Cattle with either hyporesponsive or hyperresponsive pulmonary vascular reactivity transmit these phenotypes as a genetic trait from parents to offspring.[10]

Just as it has been suggested that genetic traits may play a role in the pulmonary pressor response to the hypoxia of high altitude, one explanation for the observation that some patients with COPD develop pulmonary hypertension, whereas others do not, attributes this variability to inherited differences in the ventilatory sensitivity to hypoxia and carbon dioxide or in pulmonary vascular reactivity, or both.[11]

Most patients who develop resting pulmonary hypertension with COPD are both hypoxemic and hypercarbic; presumably, the hypercarbic patients have a low ventilatory sensitivity to carbon dioxide, because, as noted, hypoxemic residents at high altitudes hyperventilate and are hypocarbic. It is therefore reasoned that some patients who are born with a normal ventilatory sensitivity to carbon dioxide and hypoxia have an increased ventilatory effort in response to obstructive lung disease and therefore maintain relatively normal blood gases. In contrast, a patient who responds with a low ventilatory sensitivity fails to compensate and consequently develops an insufficient ventilatory drive to overcome airway resistance, ultimately causing hypercapnia, hypoxemia, and pulmonary vasoconstriction.

Virtually all patients with COPD, whether characterized by the now obsolete terms "pink puffers" and "blue bloaters," have increased drive to breathe when evaluated by the mouth occlusion pressure ($P_{0.1}$) test.[12] The clinical differences between the groups are now believed to result from differences in the pattern of breathing and, probably, in intrapulmonary gas exchange.[13] It remains true, however, that in general the more abnormal the P_{O_2} and P_{CO_2} values in patients with COPD, the more severe the pulmonary hypertension and polycythemia and the greater the likelihood of cor pulmonale.

Pulmonary Vascular Remodeling

The presence of chronic hypoxemia and ventilatory insufficiency in patients with chronic respiratory diseases is well known to lead to pulmonary vascular remodeling, characterized by prominent medial smooth muscle hypertrophy, distal smooth muscle proliferation with neomuscularization of normally unmuscularized small pulmonary vessels, and mild intimal changes.[14] Hypoxic vasoconstriction increases pulmonary vascular resistance and pressure, wall stress, and shear force, and these mechanical forces in turn lead to a cascade of mediators and cellular changes that contribute to the remodeling process.

COPD is the most common and most studied lung disease associated with pulmonary hypertension and cor pulmonale. Significant structural changes occur in the pulmonary circulation in patients with COPD. The presence of hypoxemia and chronic ventilatory insufficiency is associated with hypoxic pulmonary vasoconstriction and early evidence of intimal thickening with medial hypertrophy in the smaller branches of the pulmonary arteries.[15] Vascular smooth muscle cells are laid down longitudinally within the intima, and hypertrophy of these cells and smooth muscle cells within the media becomes prominent. Localized thrombosis in situ can occur, obliterating parts of the pulmonary vascular tree. Progressive destruction of capillaries that course along alveoli that are being destroyed or coalescing into bullae further diminishes the cross-sectional area of the pulmonary vascular tree. The structural changes together with the effects of vasoconstriction result in a significant increase in pulmonary vascular resistance. The consequence is pulmonary arterial hypertension, which in itself may cause further structural damage to the smaller branches of the pulmonary circulation and serve as a stimulus for the development of medial hypertrophy and dilation of the larger branches of the pulmonary artery. If these developments are long-standing, prominent atherosclerotic changes may be seen in the main pulmonary artery and its major branches.[16]

The association of pulmonary hypertension with interstitial lung disease (ILD) is less well characterized than that with COPD; recent studies, however, have led to a greater understanding of the pathophysiologic mechanisms involved in the development of pulmonary hypertension in these patients. The ILDs most commonly associated with pulmonary hypertension include connective tissue disease–related ILD, sarcoidosis, idiopathic pulmonary fibrosis, and histiocytosis X. Pulmonary hypertension has been reported to develop in these patients through multiple, often diverse mechanisms, but chiefly from hypoxic pulmonary vasoconstriction and associated remodeling. In addition, vascular narrowing is worsened both by a reduction in pulmonary vascular distensibility from surrounding fibrosis and by hypoxia from mismatching between the distributions of ventilation and perfusion. Ultimately, large portions of the pulmonary vascular bed may be destroyed or obliterated from progressive parenchymal fibrosis, inflammation, perivascular fibrosis, and/or thrombotic angiopathy.[17–19]

The degree of pulmonary hypertension seen in patients with COPD and cystic fibrosis is usually, but with some exceptions, reported to be mild or moderate, often paralleling the degree of hypoxemia.[20,21] In a cohort of 500 patients with COPD and cor pulmonale, Stevens and colleagues[22] found that only 6 patients had severe elevations of P_{PA}, defined as mean P_{PA} greater than 50 mm Hg, and that the severity of P_{PA} increases did not appear to be related to the severity of underlying lung disease. Moreover, the direct correlation between arterial P_{O_2} and P_{PA} is not great. In a study of 120 patients with severe emphysema evaluated for entry into the National Emphysema Treatment Trial, multiple stepwise regression analysis revealed that arterial P_{O_2} was not an

independent predictor of mean PPA, and that indices of emphysema severity and PPA did not correlate either.[23] Studies in patients with ILD showed that the presence of pulmonary hypertension does not tend to correlate well with lung volumes, whereas diffusion impairment (reduced transfer factor for carbon monoxide) and the need for oxygen supplementation were predictors of pulmonary hypertension.[24,25]

Several studies suggest that vascular remodeling in patients with mild COPD without concomitant hypoxemia is a component of early-stage disease as evidenced by increased inflammatory cell density in the adventitia and increased thickness of the intima of pulmonary arteries.[26,27] Furthermore, endothelial lesions have been shown to be present in cigarette smokers without chronic airflow obstruction.[28] A study investigated the development of pulmonary arterial hypertension in patients with moderate to severe airflow obstruction who neither met criteria for long-term oxygen therapy nor had resting pulmonary arterial hypertension; 76 of 131 (58%) had exercise-induced pulmonary arterial hypertension. Five years later, 25% of the subjects had developed resting pulmonary arterial hypertension, including 32% who had exercise-induced pulmonary arterial hypertension at baseline.[29] These studies suggest that factors other than hypoxemia alone play a role in the development of pulmonary vasoconstriction and remodeling leading to pulmonary arterial hypertension.

As is the case with COPD, most patients with pulmonary hypertension associated with interstitial pulmonary fibrosis have mild to moderate elevations in PPA; however, occasional patients may present with severe pulmonary hypertension at or near systemic levels. A study of gene expression patterns in patients with interstitial pulmonary fibrosis who develop pulmonary hypertension reported abnormal vascular phenotypes, suggesting they may have an intrinsic vasculopathy.[30] Different mechanisms may contribute to the development of pulmonary hypertension among the various lung disorders. In patients with connective tissue diseases, for example, antibody-mediated vascular inflammation (vasculitis), in situ thrombosis and/or thromboembolism (related to a hypercoagulable state), and left ventricular diastolic dysfunction may be involved in the development of pulmonary hypertension. In addition, these patients may have coexistent pulmonary artery hypertension that is unrelated to the parenchymal lung disease. The pulmonary hypertension in patients with pulmonary histiocytosis X may be severe owing to the presence of an intrinsic proliferative pulmonary vasculopathy in the absence of advanced parenchymal destruction. In rare cases of histiocytosis X, pulmonary veno-occlusive disease has also been reported.[31] In patients with sarcoidosis and pulmonary hypertension, advanced fibrosis is usually the cause; however, granulomatous vasculopathy involving the pulmonary veins and arteries, as well as extrinsic compression of the large pulmonary arteries by lymphadenopathy, may also play a role. In addition, cardiac sarcoidosis can lead to pulmonary venous hypertension.[32] Studies by Shorr et al.[33,34] indicated that the need for supplemental oxygen in patients with pulmonary sarcoidosis was an independent predictor of pulmonary hypertension on multivariate analysis, whereas neither spirometric measures nor the need for corticosteroids was predictive of pulmonary hypertension.

The fact that the presence and degree of pulmonary hypertension in patients with interstitial pulmonary fibrosis cannot fully be explained by the degree of pulmonary fibrosis or hypoxemia alone has led to the theory that the development of fibrosis and vascular narrowing may be pathogenetically linked. Vasoactive and/or profibrotic mediators that have been implicated in the pathogenesis of both interstitial pulmonary fibrosis and idiopathic pulmonary fibrosis in patients or experimental models include increased endothelin-1 expression and reduced levels of nitric oxide (NO) synthase and prostaglandin E_2.[35,36] Endothelin-1 is a potent vasoconstrictor and mitogen, and NO is a pulmonary vasodilator and inhibitor of fibrosis. Other potential mediators associated with pulmonary hypertension in patients with ILD include thromboxane A_2, tumor necrosis factor-α, platelet-derived growth factor, transforming growth factor-β, and fibroblast growth factor.[37–39]

RIGHT VENTRICLE

The normal right ventricle is crescent shaped and has a wall thickness less than 0.6 cm (Fig. 56-4). Its weight is usually less than 65 g in men, and less than 50 g in women.[16] Embryologically, the right ventricle develops from two separate components: the bulbus cordis, which becomes the outflow tract, and the sinus venosus, which becomes the inflow tract. These are separated by a muscular ridge, the crista supraventricularis. Normally, the right ventricle contracts almost sequentially from inflow to outflow, thus effectively emptying its volume into the low-impedance pulmonary circulation. In the absence of cardiac disease, the right ventricle plays an almost passive role in maintaining cardiac output in accordance with the venous return and Starling's law of the heart. In fact, in congenital tricuspid atresia, early surgical approaches involved bypass of the right ventricle through anastomosis of the right atrium directly to the pulmonary artery (the so-called Fontan procedure), which resulted in perfusion of the pulmonary circulation from an elevated central venous pressure. However, it should also be noted that a damaged right ventricle with residual high central venous pressures resulting from an inferior myocardial infarction is associated with a distinctly reduced survival rate.

Because of the shape of the right ventricle, it is difficult to measure the right ventricular volume accurately by radiographic or echocardiographic techniques. In a series of 15 subjects without heart disease, right ventricular end-diastolic volume in the supine position measured by a thermodilution technique, which probably overestimates volumes, averaged 103 ± 24.4 mL/m^2.[40] With passive assumption of an upright posture by tilting, right ventricular end-diastolic volume falls due to gravitational pooling of blood within the distensible venous tree. In a separate series of eight subjects without heart

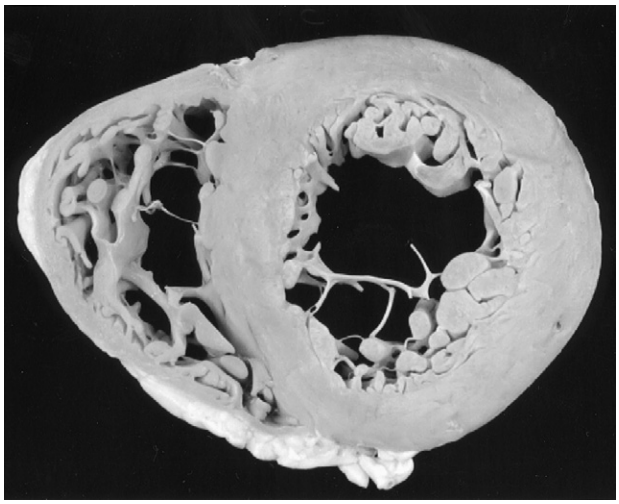


FIGURE 56-4 ■ A transverse section through a normal heart illustrates a somewhat crescent-shaped right ventricular cavity, together with the presence of prominent trabeculae carneae. Note that the myocardial thickness of the normal left ventricle is considerably greater than that of the right ventricle.

FIGURE 56-5 ■ Transverse section of a heart from a patient who had severe pulmonary hypertension showing dilation of the right ventricular cavity, which has a more spherical shape than the heart shown in Figure 56-4. Marked wall thickness of the right ventricle caused by massive hypertrophy is seen. The trabeculae carneae are also hypertrophied, and endocardial sclerosis is visible on several of them. The left ventricle is relatively normal, with protrusion of the posteromedial and anterolateral papillary muscles into the cavity. The bright white patches on the lateral free wall and posterolateral septum are highlight artifacts caused by reflection of the flash during photography.

disease, end-diastolic volume fell a mean of 16.3 mL/m^2 from a mean baseline of 98.1 ± 23.3 mL/m^2. This fall in right ventricular end-diastolic volume causes less of an end-diastolic fiber stretch and results in a fall in stroke volume with the assumption of an upright position. At the same time, aortic baroreceptor stimulation reflexively increases heart rate by about 12 beats/min, thus compensating for an average stroke volume fall of approximately 13.3 mL/m^2; therefore, cardiac output is maintained in essentially the same range as in a recumbent patient at rest.[41]

Acute increases in right ventricular afterload result in a significant fall in stroke volume[42]; in contrast, the left ventricle can accommodate an acute increase in afterload with little change in stroke output. Chronic pulmonary hypertension with a corresponding increase in right ventricular work results in uniform hypertrophy of the right ventricle. As a result, right ventricular weight increases as right ventricular wall myocytes thicken and exhibit enlarged nuclei. Varying degrees of interstitial fibrosis occur. As the ventricle further hypertrophies, it becomes increasingly able to expel the stroke output against high pulmonary vascular resistance and maintain cardiac output. Patients with idiopathic pulmonary arterial hypertension or with severe mitral stenosis and pulmonary vascular disease have been observed in whom the right ventricle maintained a pulmonary artery systolic pressure significantly higher than the systemic pressure.

In patients with COPD, hypoxic vasoconstriction is associated not only with right ventricular hypertrophy but also with right ventricular dilation. The normal crescent shape of the right ventricle is progressively transformed into a more spherical structure that is better able to generate an increased stroke work (Fig. 56-5).

The increase in right ventricular work associated with pulmonary hypertension, which results in both hypertrophy and dilation of the right ventricle, produces a significant increase in right ventricular myocardial oxygen consumption. At the same time, an increase in wall thickness tends to decrease right ventricular endocardial coronary perfusion. Furthermore, an increase in end-diastolic pressure occurs as right ventricular stiffness increases during diastole, adding to the compromise of endocardial coronary perfusion. Taken together, these factors result in an imbalance between right ventricular myocardial oxygen demand and supply. Nevertheless, in several studies the end-diastolic pressure-volume relationship, even in the presence of resting pulmonary hypertension, suggested well-preserved right ventricular contractility in patients with COPD. Only the additional presence of acidemia or infection precipitates right ventricular failure. When chronic hypercapnia with acidosis is present in patients with alveolar hypoventilation, the ability of the right ventricle to increase its work appears to be significantly impaired, and right ventricular end-diastolic pressure increases (i.e., there is a shift to the right in the family of Starling curves).

This impairment of myocardial contractility in the presence of hypercapnia probably plays a significant role in producing decompensated pulmonary heart disease in response to acute increases in arterial P_{CO_2} associated with exacerbations of COPD and accompanying decreases in alveolar ventilation. Recordings of right ventricular and pulmonary artery systolic pressures may show pulsus alternans similar to that often seen in left ventricular failure (Fig. 56-6). The development of right ventricular volume overload with ventricular dilation results in a decreased ejection fraction, because stroke volume tends to be maintained close to the normal range

in decompensated cor pulmonale.[43] With exercise, patients with COPD significantly raise their right ventricular afterload, which causes further increases in right ventricular end-diastolic volume and decreases in ejection fraction. It is likely that this deterioration in hemodynamics with exercise is a major factor limiting the ability of such patients to exercise normally.

Figure 56-7 describes the pathophysiology of right ventricular failure in patients with pulmonary hypertension. Right ventricular dilation and wall thinning result in increased right ventricular wall stress that, along with increased heart rate, leads to further increases in myocardial oxygen consumption. Increased myocardial oxygen consumption compounded by decreased myocardial perfusion as previously described results in right ventricular ischemia and worsening right ventricular function. In addition, as pulmonary pressures rise and the right ventricle dilates, severe tricuspid regurgitation ensues, which further compromises right ventricular forward cardiac output, thereby limiting left ventricular filling. Furthermore, right ventricular dilation in the setting of an intact pericardium compromises left ventricular filling through several mechanisms. A shift of the interventricular septum toward the left ventricle and an increase in intrapericardial pressure reduce left ventricular distensibility and transmural left ventricular filling pressure, which represents the true preload of the left ventricle. As a consequence of decreased left ventricular preload, the systemic cardiac output is significantly compromised, initially with exercise and eventually even at rest. With rising right atrial pressures in patients with a patent foramen ovale, significant right-to-left atrial shunting can occur, resulting in systemic oxygen desaturation and further worsening systemic oxygen delivery.[44]

In the presence of right ventricular failure and elevated central venous pressure when the patient stands up, neither right ventricular end-diastolic volume nor stroke volume decreases. Consequently, heart rate does not change. This lack of postural reflex compensation is attributable to failure of any incremental gravitational pooling of blood in the venous tree, because of increased plasma volume, increased tissue pressure from edema with decreasing venous distensibility, and increased venomotor tone.[41]

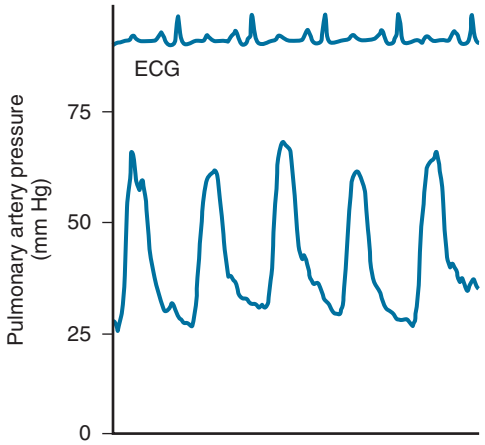
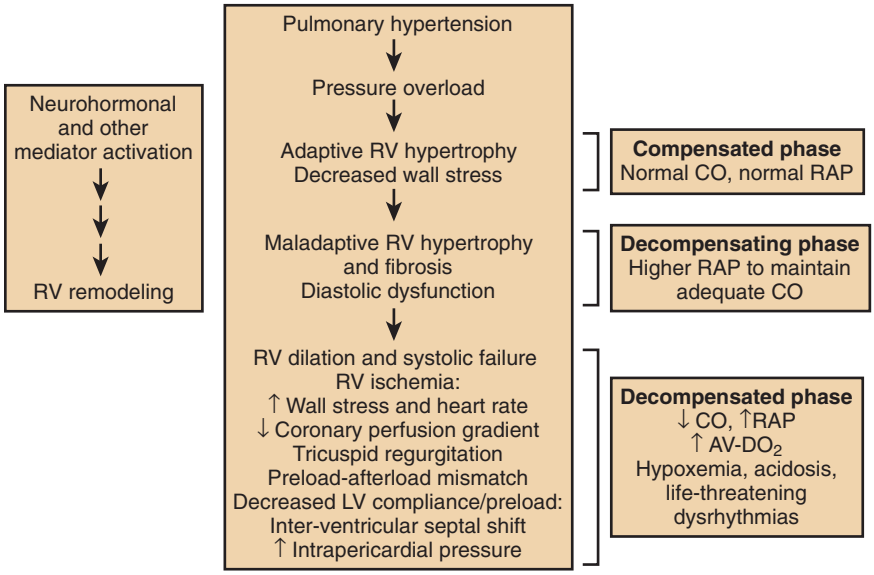


FIGURE 56-6 ■ A recording of the pulmonary artery pressure at the time of cardiac catheterization in a patient with cor pulmonale and heart failure, illustrating pulsus alternans in the pulmonary artery.

LEFT VENTRICLE

Controversy has existed over the years as to whether the left ventricle eventually fails when right ventricular failure results from chronic cor pulmonale. Part of the uncertainty has stemmed from the fact that the early studies of patients with cor pulmonale secondary to



AV-DO_2 = arteriovenous oxygen difference; CO = cardiac output; RAP = right atrial pressure; LV = left ventricular; RV = right ventricular

FIGURE 56-7 ■ Pathophysiology of right ventricular dysfunction in pulmonary hypertension.

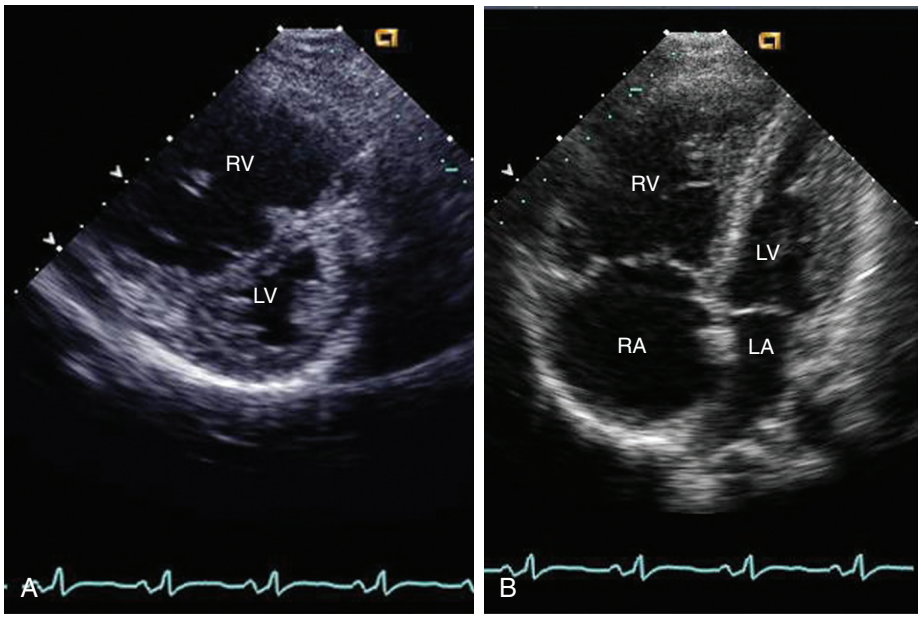


FIGURE 56-8 ■ **A,** Short-axis two-dimensional echocardiographic image of the right ventricle (RV) and left ventricle (LV) in diastole. Notice the enlarged RV with flattening of the interventricular septum (IVS), which causes the LV to assume a "D" shape. These findings, occurring in diastole, are indicative of RV volume overload. **B,** Apical four-chamber, two-dimensional echocardiographic view of all four cardiac chambers showing an enlarged right atrium (RA) and right ventricle (RV) with small, compressed left cardiac chambers. LA, left atrium; LV, left ventricle.

COPD included chiefly middle-aged or older men with a history of heavy cigarette smoking, who were likely to have coexisting coronary artery disease. Failure of the left ventricle in some of these patients may have reflected coexisting coronary artery disease rather than the natural history of decompensated pulmonary heart disease. Nevertheless, although left ventricular ejection performance is unimpaired, cardiac catheterization studies have revealed abnormal left ventricular end-diastolic pressure-volume relationships.[45] Echocardiographic studies also showed progressive impairment of left ventricular diastolic function that correlated with the severity of pulmonary hypertension.[46] It is likely that this results, in large part, from bulging of the interventricular septum from the hypertrophied and dilated right ventricle into the cavity of the left ventricle, and ventricular interdependence exerted by pericardial constraint.[44,47] As a result, left ventricular diastolic geometry becomes distorted (Fig. 56-8),[48] and filling characteristics may be altered such that a higher filling pressure is required to accomplish the same end-diastolic fiber stretch needed for a given stroke work, in accordance with Starling's law of the heart.

Furthermore, measurements of pulmonary artery wedge pressure as a reflection of left heart filling pressure can be distorted because of the increase in intra-alveolar pressures, as well as the large swings in intrathoracic pressure with resultant large swings in wedge pressure tracings seen in patients with COPD (see Fig. 56-3), and increases in intrapericardial pressure. This is particularly troublesome when the patient is receiving positive end-expiratory pressure from a mechanical ventilator. As mentioned, pulmonary artery wedge pressures should always be estimated at end-expiration rather than attempting to measure the mean wedge pressure. Furthermore, with severe right-sided heart failure and marked elevation in right atrial pressure, coronary sinus pressure increases significantly. This can result in an increase in left ventricular wall dimension limiting left ventricular distensibility. This mechanism leading to reduced left ventricular preload appears to act independently of diastolic ventricular interaction caused by right ventricular enlargement as previously described.[49]

NEUROHORMONES

Significant neurohormonal abnormalities occur in patients with cor pulmonale. Plasma catecholamine levels generally rise in patients with decompensated pulmonary heart disease in a manner comparable to that seen in patients with heart failure secondary to primary myocardial disorders. It is clear that increased sympathetic activity is present with decompensation from cor pulmonale, resulting in high plasma levels of circulating catecholamines and stimulation of the renin-angiotensin-aldosterone systems. In the measurements by Anand and associates,[50] vasopressin actually rose to a higher level than was seen in comparable patients with failure not associated with COPD. Because cardiac output is often normal or may even be increased in decompensated pulmonary heart disease, it is likely that the decrease in systemic vascular resistance resulting from both hypercapnia and hypoxia leads to a reflex increase in circulating catecholamines and other neural hormones. Central sympathetic stimulation may also be encouraged by the

direct effect of the increased P_{CO_2} on the central nervous system.

Recently, the neuropeptide vasoactive intestinal polypeptide (VIP) has been of significant interest in pulmonary hypertension. VIP primarily functions as a neurotransmitter and acts as a potent systemic and pulmonary vasodilator; it has been shown to inhibit platelet activation and vascular smooth muscle cell proliferation. These effects are mediated by stimulation of specific VIP receptors resulting in activation of the cyclic adenosine monophosphate and cyclic guanosine monophosphate (GMP) systems.[51–56] A deficiency of this neuropeptide has been found in the serum and lung tissue of patients with idiopathic pulmonary arterial hypertension. Chronic treatment with inhaled VIP in eight patients with idiopathic pulmonary arterial hypertension resulted in improved cardiopulmonary hemodynamics, exercise performance, and dyspnea.[57] The role of VIP in pulmonary hypertension associated with lung diseases or hypoxemia or both has yet to be investigated. However, given the findings described previously in idiopathic pulmonary arterial hypertension, VIP and its receptors represent rational and promising targets for the development of therapeutic strategies in other forms of pulmonary hypertension.

Angiotensin II

Angiotensin II is a potent vasoconstrictor of the pulmonary vascular bed. The pulmonary vasculature appears to be even more sensitive to the vasoconstrictor effects of angiotensin II than is the systemic vascular bed. This is noteworthy because increased circulating levels of angiotensin II and aldosterone are found in patients with cor pulmonale secondary to COPD who have hypoxia and hypercapnia.[58] Activation of the renin-angiotensin-aldosterone systems, together with hypoxemia, is probably an underlying pathophysiologic mechanism responsible for the elevation in pulmonary vascular resistance that is observed in patients with decompensated pulmonary heart disease.

A dose-response relationship of pulmonary vascular resistance to the infusion of angiotensin II has been observed in normal subjects.[59] In patients with pulmonary heart disease, lowering pulmonary vascular resistance and dropping P_{PA} is the ideal therapeutic goal. Angiotensin II inhibitors might be expected to produce this effect. They have been demonstrated to improve survival in patients with systolic heart failure caused by either coronary disease or idiopathic dilated cardiomyopathy. Could such a benefit be expected in patients whose right-sided heart failure results from COPD despite the earlier disappointing experience with vasodilators? Although such vasodilators are capable of reducing pulmonary vascular resistance, they may actually aggravate hypoxemia. Increased hypoxemia can result from administration of pulmonary vasodilators because perfusion may improve in areas of impaired ventilation, thereby worsening arterial hypoxemia. It is encouraging to note that the angiotensin-converting enzyme (ACE) inhibitor lisinopril has been demonstrated experimentally to attenuate significantly the pulmonary pressor response to hypoxic pulmonary vasoconstriction in healthy human volunteers.[60] In addition, angiotensin II receptor blockade has been shown to produce a similar effect in hypoxic pulmonary vasoconstriction in humans.[44] However, studies performed to date have not elucidated a role for ACE inhibitors or angiotensin II receptor antagonists in the treatment of cor pulmonale.

NATRIURETIC PEPTIDES

The family of natriuretic peptides includes atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP), and C-type natriuretic peptide (CNP). Circulating ANP and BNP levels are elevated severalfold in patients with cor pulmonale, even in the absence of impaired left ventricular function.[61] Presumably, right atrial distention or overactivity in response to increased right ventricular afterload is the stimulus for their release. CNP, which appears to be normal in the usual patient with congestive heart failure of left-sided origin, is elevated in patients with cor pulmonale, although not as extensively as ANP and BNP.[62] The elevation of CNP appears to be endothelial in origin, suggesting that its stimulus for release may be either arterial hypoxemia or endothelial damage occurring in cor pulmonale. ANP, BNP, and CNP have approximately equivalent pulmonary vasorelaxant activities. Although ANPs appear to have little effect on resting vasopulmonary artery tone, they do appear to interact with the vasoactive response of hypoxic pulmonary vasoconstriction. Experimentally, they can attenuate the increased pulmonary hypertension produced by hypoxia.[63] It has also been shown that BNP levels increase in proportion to the extent of right ventricular dysfunction in pulmonary hypertension.[64]

A recent study enrolled 44 patients with right ventricular overload, 18 of whom had atrial septal defect and 26 of whom had idiopathic pulmonary arterial hypertension or thromboembolic pulmonary hypertension. Plasma BNP and ANP levels were measured and right heart catheterization was performed. Right and left ventricular ejection fraction, myocardial mass, and chamber volumes were determined using electron beam computed tomography (CT). Plasma BNP and ANP levels were elevated in these patients compared to control subjects. Furthermore, the BNP-to-ANP ratios were significantly higher in patients with right ventricular pressure overload compared to volume overload. Levels of BNP correlated positively with pulmonary vascular resistance and right atrial pressure, but negatively with cardiac output and right ventricular ejection fraction. Long-term vasodilator therapy was also associated with reduced plasma BNP concentration. Another study of 60 patients with idiopathic pulmonary arterial hypertension established by right heart catheterization evaluated the long-term prognostic significance of BNP and other neurohormones.[65] On multivariate analysis, baseline plasma BNP was an independent predictor of mortality; patients with a supramedian level of baseline BNP (>150 pg/mL) had a significantly lower survival rate than those with an inframedian level ($P < 0.05$). Hence, BNP may serve as a

prognostic indicator in patients with idiopathic pulmonary arterial hypertension. In a study of 176 patients with various lung diseases, elevated serum BNP level predicted the presence of pulmonary hypertension and was a risk factor for death, independent of lung functional impairment or hypoxemia in both uni- and multivariate analysis.[24]

Patients with cor pulmonale, who demonstrate alveolar hypoxia and elevated circulating angiotensin II levels, have a dose-related decrease in PPA during an infusion of ANP.[66,67] The pulmonary pressor response to infused angiotensin II in humans appears to be significantly attenuated by BNP, but not by ANP. A similar effect is noted in response to hypoxic pulmonary pressor changes. Therefore, it is likely that BNP is the predominant natriuretic peptide modulating the response of the pulmonary vasculature to hypoxia and angiotensin II. BNP may play an important role in attenuating the pressor response that is likely to occur in humans through the actions of alveolar hypoxia and elevated angiotensin II levels. In patients with left-sided heart failure, the human recombinant BNP nesiritide has been shown to suppress endothelin and aldosterone levels, suggesting other mechanisms for the attenuating effect of this peptide on pulmonary vasoconstriction.[68] These findings suggest the possible clinical use of neutral endopeptidase inhibitors that increase circulating levels of endogenous natriuretic peptides by inhibiting their degradation.[69] Such agents might prove useful if added to ACE inhibitors and angiotensin II receptor antagonists in the management of chronic cor pulmonale characterized by alveolar hypoxia and pulmonary hypertension. However, this hypothesis has yet to be tested.

ENDOTHELIN-1

Endothelin-1 (ET-1) is a 21–amino acid peptide secreted by vascular endothelial cells in response to various stimuli, including pulsatile stretch, sheer stress, neurohormones, cytokines, growth factors, and thrombin. The secretion of ET-1 has been shown to be increased by hypoxemia in humans. The effects of ET-1 are mediated by the endothelin A (ET_A) and endothelin B (ET_B) receptors. ET_A is localized on vascular smooth muscle cells and ET_B is expressed on vascular smooth muscle cells, endothelial cells, and fibroblasts. The effects of ET-1 include vasoconstriction, hyperplasia, hypertrophy, fibrosis, and increased vascular permeability. Activation of ET_B receptors on endothelial cells mediates release of prostacyclin (prostaglandin I_2) and NO, which exert vasodilatory and antiproliferative effects while also inhibiting ET-1 production by endothelial cells. Furthermore, the pulmonary endothelial ET_B receptors are responsible for the pulmonary clearance of up to 50% of circulating ET-1.[70]

Increased ET-1 production has been described in patients with pulmonary hypertension. Increased ET-1 levels and increased expression of receptors have been shown to be present in plexiform lesions of the lung in patients with pulmonary hypertension.[70,71] High plasma levels of ET-1 have been observed in patients with pulmonary hypertension, and this elevation correlated with disease severity and adverse prognosis.[71–75] It has been demonstrated that ET-1 concentration is elevated in the sputum and urine of patients with COPD compared to normal subjects; moreover, urinary levels increase further during COPD exacerbations.[76,77] In addition, plasma ET-1 levels have been shown to be increased in subjects who exhibit oxyhemoglobin desaturation with exercise or at night.[78,79] In another study, patients with COPD and pulmonary hypertension were shown to have elevated transpulmonary ET-1 levels.[80] Increased plasma levels and lung tissue expression of ET-1 have also been identified with or without pulmonary hypertension.[71,81] These observations suggest that ET-1 plays an important role in mediating the development or perpetuation of pulmonary hypertension in various disease states, and hence is a rational therapeutic target.

SYMPTOMS AND SIGNS

Mild pulmonary hypertension reflected in small chronic elevations in right ventricular pressure generally causes minimal, if any, clinical, radiologic, or electrocardiographic findings. When moderate or severe pulmonary hypertension develops (mean PPA > 40 mm Hg), symptoms are often those associated with the underlying pulmonary disease. Most commonly, these are dyspnea on exertion, chronic cough productive of mucoid sputum (particularly in the morning hours), variable degrees of wheezing, and noticeable occasional cyanosis; clubbing of the fingers may be present. Moderate or severe pulmonary hypertension by itself (e.g., in patients with idiopathic pulmonary arterial hypertension) may result in only minimal or nonspecific symptoms. In addition to exertional dyspnea and fatigue, some patients experience dizziness or even exertional syncope, attributable to the inability to increase cardiac output during exercise in the face of a marked increase in pulmonary vascular resistance. Furthermore, these patients may have chest pain owing to right ventricular ischemia or stretching of the main pulmonary artery.

When resting PPA is sufficiently elevated, patients may eventually reach a point at which the right ventricle cannot meet the need for increased stroke work without a significant increase in right heart filling pressures. The resultant increase in central venous pressure is associated with developing symptoms of right-sided heart failure, such as peripheral edema, right upper quadrant discomfort nocturia, and easy fatigability. On examination, the patient is often cyanotic and sitting upright with tachypnea, prominent use of the accessory muscles of respiration, and arms extended holding on to the edges of the mattress. In COPD, pulsus paradoxus may be present. The chest may be hyperinflated. There may also be audible wheezing, particularly if the process of decompensation has been relatively acute and associated with a superimposed respiratory infection. Sinus tachycardia is often present; however, atrial and ventricular arrhythmias are also common.[82] Evidence of fluid reten-

tion may include dependent edema and some degree of ascites. The liver is enlarged and tender to palpation, and may be pulsatile, reflecting the presence of severe tricuspid insufficiency. Similarly, the neck veins are distended and, when tricuspid insufficiency is present, show a large *c-v* wave with rapid *y* descent; in addition, there may be a prominent *a* wave reflecting the increased force of right atrial contraction.

On examination of the chest, there may be a left parasternal systolic lift, owing to the overactivity of the enlarged right ventricle, and a thud felt over the pulmonary area as the pulmonary valve closes. The heart sounds are often difficult to hear if the patient has underlying COPD. The pulmonic component of the second heart sound (S_2) is accentuated and occurs earlier than usual, so the normal splitting may be abolished and a single loud S_2 heard. Normally not heard at the apex, the pulmonic component of S_2 may now be clearly heard. A high-pitched systolic ejection click may be heard in the second and third left intercostal spaces next to the sternum. It is often followed by a soft, localized systolic ejection murmur produced by ejection of the stroke volume into a dilated pulmonary artery. An S_3 gallop arising from the right side of the heart may be heard in the fourth and fifth interspaces immediately to the left of the sternum or even next to the xiphoid process. A presystolic S_4 gallop may also be heard, reflecting the increased forcible contraction of the right atrium with expulsion of blood into the hypertrophied and dilated right ventricle. Often tricuspid regurgitation is present, and this results in a prominent blowing pansystolic murmur in the same location, which may increase somewhat with inspiration. When prominent pulmonary hypertension is present, a diastolic murmur of pulmonary incompetence may be heard; this murmur, known as Graham Steell's murmur, is a soft, blowing decrescendo diastolic murmur, usually well localized to the second and third left intercostal spaces next to the sternum.

Acute respiratory failure is characterized by hypoxemia and hypercapnia, or by their worsening if they are chronically present when the patient is stable, and often requires hospitalization. Dyspnea becomes intense, and the patient is usually bedridden and visibly tachypneic. Coughing is likely to be exacerbated and sputum production increased. Congestive heart failure, if not present earlier, is now clearly evident in most cases. If it was chronically present before the exacerbation of respiratory failure, it will markedly worsen. The patient may exhibit confusion, insomnia, lethargy, and marked fatigue. Fever may be present if the episode has been precipitated or aggravated by an infectious process such as community-acquired pneumonia.

Chest Radiograph

The appearance of the chest radiograph depends in large part on the underlying cause for the presence of pulmonary hypertension. Generally, however, the main pulmonary artery segment is enlarged, together with large right and left descending pulmonary arteries. In contrast, there is abrupt tapering of the peripheral vessels, resulting in disproportionately large central pulmonary arteries and attenuated distal vessels. A right descending pulmonary artery with a diameter greater than 16 mm suggests pulmonary hypertension.[83] Enlargement of the right ventricle, which may be observed on echocardiography, is often not appreciated on the chest radiograph. If hyperinflation of the lungs is present, the overall diameter of the cardiac silhouette may not be increased, although the heart may have a globular appearance. Often some encroachment on or filling in of the retrosternal space by an enlarged right ventricle may be seen in a lateral view.

Pleural effusions (see Chapter 73) are seldom seen in patients presenting with pure cor pulmonale unless coexisting left ventricular dysfunction and failure are also present. The reason is evident in the mechanisms that govern fluid formation and clearance across the pleural membranes, which were largely set forth by Staub and coworkers[84] and are illustrated in Figure 73-4. The small amount of fluid that is normally present is filtered across the parietal pleura; removal of fluid occurs through lymphatic stomas that are also located in the parietal pleura. The visceral pleura plays little or no role in pleural fluid turnover in the normal lungs, but does serve as an important escape route for excess interstitial fluid that accumulates in the lungs during the evolution of cardiogenic pulmonary edema (see Chapter 55).

Given this analysis of the dynamics of pleural fluid exchange, pleural effusions might be expected in patients with chronic cor pulmonale and elevated right heart filling pressures, because they have increased systemic venous pressures, which must raise capillary pressures within the parietal pleura. Increased fluid transudation into the parietal pleural interstitium and then into the pleural space would be expected. Failure to find pleural effusions under these circumstances undoubtedly reflects the capacity of the parietal lymphatics to markedly increase their fluid removal capacity, by almost 20-fold. These mechanisms would appear to be substantiated by the findings of a prospective study of 37 patients admitted for congestive heart failure in whom the presence of pleural effusions correlated with the values of pulmonary artery wedge pressure but not with the right atrial pressure.[85] In a subsequent retrospective study of 18 patients with long-term right atrial or pulmonary hypertension or both, but with normal pulmonary artery wedge pressures, no pleural effusions were seen.[86] However, patients have been observed with chronic cor pulmonale and acute exacerbation of cardiac decompensation resulting from a superimposed respiratory infection who demonstrate transient small pleural effusions during the acute episode. It is of interest that cattle with brisket disease accumulate transudates in the thoracic cavity as well as in the abdominal cavity and pericardial sac.[87]

Electrocardiogram

The electrocardiogram can be quite helpful in establishing the presence of chronic cor pulmonale.[88] Characteristically, the P wave has a "p pulmonale" pattern with

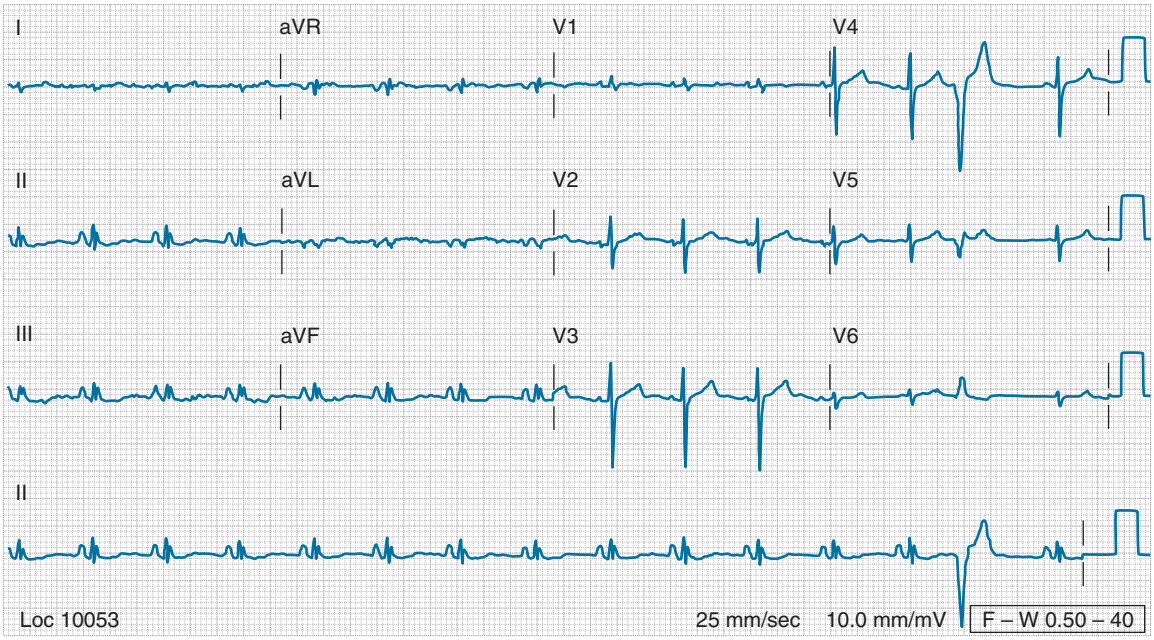


FIGURE 56-9 ■ An electrocardiogram in a patient with chronic cor pulmonale reveals prominent "p pulmonale" and other characteristic features (see text).

right-axis deviation resulting in an increase in its amplitude in leads II, III, and aVF to more than 2.5 mm (Fig. 56-9). The P wave may also be tall in the right precordial leads. The QRS vector in the frontal plane often shifts to the right in cor pulmonale, and a low-voltage QRS complex is common if lung hyperinflation is present. Prominent S waves are seen in leads I, II, and III, probably reflecting hypertrophy of the crista supraventricularis; an incomplete right bundle-branch block pattern is also frequently observed. When pulmonary arterial hypertension is moderate or severe, the more classic findings of right ventricular hypertrophy may dominate the electrocardiogram, which exhibits tall R waves in V_1 with an R/S ratio of more than 1, and a prominent S wave in V_5 and V_6 with an R/S ratio of less than 1. The presence of electrocardiographic evidence of cor pulmonale in patients with COPD is a poor prognostic sign.[89]

Echocardiography

Echocardiography is the most widely used and accepted screening tool for the presence of pulmonary hypertension and the evaluation of right ventricular structure and function. An echocardiographic examination can assist the clinician in eliminating various nonpulmonary causes of secondary pulmonary hypertension, such as left ventricular failure from coronary disease or dilated congestive cardiomyopathy, aortic or mitral valve disease, and congenital heart disease with left-to-right shunt. An estimation of the pulmonary artery systolic pressure can be determined in 36% to 86% of patients with pulmonary hypertension by taking advantage of the presence of tricuspid regurgitation and using continuous-wave Doppler to obtain the tricuspid regurgitant jet velocity.[90] The pressure gradient across the tricuspid valve between the right atrium and ventricle is calculated using the modified Bernoulli equation ($4v^2$), where v is the tricuspid regurgitant jet velocity, and this figure is then added to the right atrial pressure (estimated by the size and collapsibility of the inferior vena cava) to obtain an estimate of the right ventricular systolic pressure, which is equal to the pulmonary artery systolic pressure in the absence of pulmonary valve stenosis.

Additionally, there is usually pulmonary valve insufficiency detectable by Doppler echocardiography in the presence of pulmonary hypertension, which permits an estimation of pulmonary artery diastolic pressure. The size of the right atrium and the right ventricle can be determined and the contractile state of the right ventricle assessed. Flattening or leftward shift of the interventricular septum during systole suggests right ventricular pressure overload, whereas interventricular septal flattening during diastole is indicative of right ventricular volume overload. If right heart filling pressure (equal to right atrial pressure) is increased, it is usually associated with dilation of the inferior vena cava, which fails to collapse with respiratory maneuvers such as sniffing. The pulmonary velocity time integral can be used as a surrogate measure to estimate stroke volume and it can be monitored longitudinally in conjunction with the estimated pulmonary artery systolic pressure to assess response to therapy. Supine cycle ergometry with Doppler echocardiography can assess changes in PPA and provide insight into exertional symptoms.

Figure 56-10 illustrates a Doppler echocardiographic examination in a patient with COPD who presented with severe respiratory distress. The possibility of coexisting coronary disease, which arises frequently in the older male patient, led to the question of whether the patient was in respiratory distress from pulmonary congestion secondary to left ventricular failure or whether the problem reflected pulmonary hypertension and

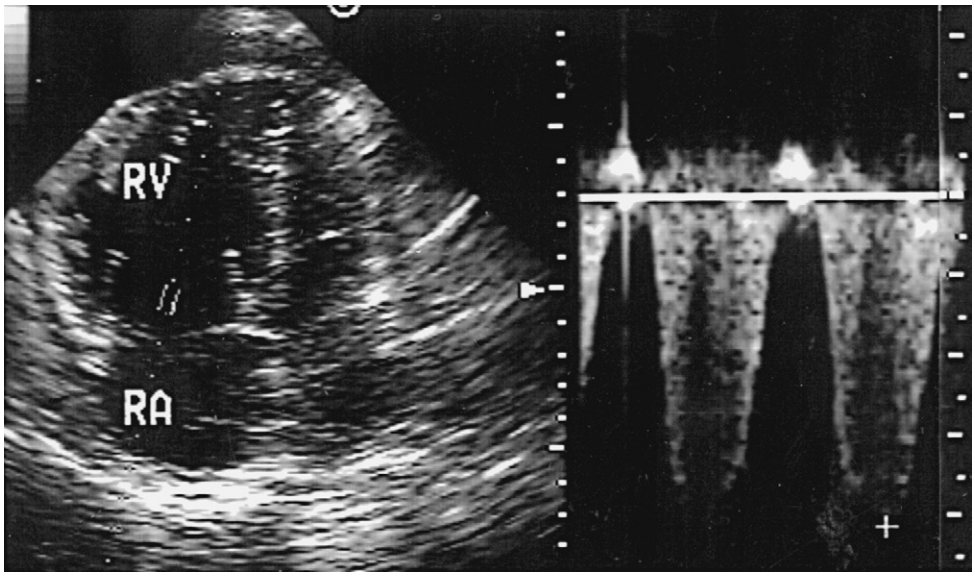


FIGURE 56-10 ■ *Left,* Normal left ventricular volume is seen on this echocardiogram of a patient with chronic obstructive pulmonary disease who presented with acute severe respiratory distress; normal contractility also was observed during recording. The right ventricle (RV) is markedly dilated (see text). *Right,* Estimation of the degree of pulmonary hypertension using continuous-wave Doppler measurement of the velocity jet from the tricuspid insufficiency that was present. A 55 mm Hg peak systolic pressure gradient between the RV and right atrium (RA) was calculated, indicating moderate to severe pulmonary arterial hypertension.

ventilatory insufficiency arising from decompensated pulmonary heart disease. The figure clearly illustrates that the left ventricle is small, and it was seen to have normal contractility during analog recording. In contrast, the right ventricle was severely dilated and was observed to have a significantly decreased right ventricular systolic contractile function. Right atrial enlargement was present as well. Although tricuspid insufficiency was not a major clinical problem in this particular patient, there was sufficient tricuspid insufficiency to permit Doppler estimation of the degree of pulmonary hypertension, which is often the case when pulmonary hypertension is present. The right section of Figure 56-10 illustrates a continuous-wave Doppler jet demonstrating that a peak systolic gradient of at least 55 mm Hg was present between the right ventricle and right atrium, indicating moderate to severe pulmonary hypertension.

Athough right ventricular ejection fraction was the most commonly used index of right ventricular function in the past, it is highly dependent on loading conditions and may not accurately reflect contractility. Moreover, echocardiography is less accurate than magentic resonance imaging (MRI)– and radionuclide angiography–derived right ventricular ejection fraction methods. In a study of 32 patients with advanced lung disease, Schenk and colleagues[91] found that, among various echocardiographic parameters, right ventricular end-diastolic area and fractional area change from the apical four-chamber view correlated best with MRI-derived right ventricular volume and ejection fraction, respectively. Newer Doppler-derived indices of right ventricular function, the tricuspid annular plane excursion (TAPSE)[91a] and right ventricular myocardial performance index (RVMPI),[91b] have both been shown to have prognostic value in patients with idiopathic pulmonary arterial hypertension and they are being studied in other classes of pulmonary hypertension. Three-dimensional echocardiography is a promising technique that could lead to a more accurate assessment of right ventricular volume and ejection fraction; however, difficulties in delineation of the anterior wall and infundibular plane still need to be overcome.

The presence of hyperinflation of the lungs impairs the transmission of ultrasound and can result in suboptimal transthoracic echocardiographic imaging. The sensitivity and specificity of Doppler echocardiography to predict the presence of pulmonary hypertension range from 0.79 to 1.0 and from 0.6 to 0.98, respectively,[90] and the actual echo-Doppler–derived estimate of pulomary artery systolic pressure may be imprecise compared with right heart catheterization.[92,93] If sufficient lung hyperinflation prevents adequate transthoracic examination, one may resort to transesophageal echocardiography (TEE) to clarify the problem. Often patients in this situation are intubated, and a transesophageal study probe can be slipped into the esophagus with relative ease. A much better delineation of cardiac function and any cardiac pathology can be obtained with TEE than is possible with a transthoracic probe. It is important to note that the estimation of pulmonary artery systolic pressure via echo-Doppler alone cannot fully address pulmonary hypertension, and in doubtful cases or when therapies directed at the pulmonary vasculature are being contemplated, a diagnostic right heart catheterization must be considered.

Computed Tomography

Chest CT is often used to visualize the pulmonary parenchyma in patients with respiratory disease. With this imaging modality, the size of the pulmonary artery can

be measured, and in patients with moderate to severe pulmonary hypertension, enlargement of the main pulmonary artery or an increased diameter of the pulmonary artery (>29 mm) may be documented. However, in a study of 65 patients with advanced idiopathic pulmonary fibrosis, main pulmonary artery diameter on high-resolution chest CT failed to differentiate between those who did or did not have pulmonary hypertension diagnosed with right heart catheterization.[94] Therefore, CT does not appear to be a reliable modality to screen for pulmonary hypertension. However, dilated right heart chambers on contrast-enhanced CT imaging would be suggestive but not diagnostic of cor pulmonale in patients with severe parenchymal lung changes.

Magnetic Resonance Imaging

MRI is the most accurate method for assessing right ventricular volume and ejection fraction. Compared with the normal left ventricular volume, the right ventricular volume is larger (66 ± 12 mL/m^2, range 44 to 89 mL/m^2 vs. 75 ± 13 mL/m^2, range 49 to 101 mL/m^2, respectively) and the ejection fraction is lower (67 ± 5%, range 57% to 78% vs. 61 ± 7%, range 47% to 76%, respectively).[95] Phase-contrast MRI has the capability to accurately calculate flow characteristics, including cardiac output, valvular regurgitant fraction, and shunt fraction. Because of its ability to penetrate diseased lungs and its high temporal resolution, the image quality of MRI to assess cardiac structures is superior to that of echocardiography, especially in patients with advanced lung disease. Although high cost, relatively long image acquisition time, and lack of widespread availability limit its use compared with echocardiography, cardiac MRI is increasingly being used as a standard tool for the evaluation of right ventricular structure and function in patients with pulmonary arterial hypertension. Its application in patients with respiratory diseases and cor pulmonale has yet to be evaluated.

Hemodynamics

Hemodynamic measurements in patients with decompensated pulmonary heart disease secondary to COPD are subject to error. Use of the direct Fick method to estimate cardiac output at the time of cardiac catheterization is complicated when hypoxemia is present. Hypoxemia may be caused both by shunting across the lungs, from perfusion of unventilated or poorly ventilated alveoli, and by a decrease in oxygen diffusion reflecting alveolar-capillary block from associated fibrosis, parenchymal infiltrative disease, inflammation, and/or edema. Consequently, true pulmonary blood flow, in terms of pulmonary capillary blood flow, is only approximated when systemic arterial oxygen content difference is used to calculate the arteriovenous oxygen content across the lungs. Further problems are provided by the fact that there may be difficulty in estimating oxygen consumption if the patient is receiving therapeutic oxygen.

Measurements of pulmonary blood flow by the use of indicator dilution curves such as thermodilution may also be spurious in patients with pulmonary shunting of blood and in those with very low cardiac outputs. In fact, the clinician should measure the oxygen saturation of pulmonary artery blood from the indwelling pulmonary artery catheter and verify that it is substantially lower than normal before accepting a thermodilution readout that cardiac output is markedly depressed. However, within these limitations, it would appear that cardiac output in patients with decompensated pulmonary heart disease from hypoxic pulmonary vasoconstriction is generally in the normal range or even increased due to the systemic vasodilation produced by hypoxemia; this finding contrasts with that in idiopathic pulmonary arterial hypertension, chronic obstructive embolic disease, mitral stenosis with pulmonary vascular disease, or decompensated heart failure caused by primary myocardial disease, in which low-output states are usually present. Hemodynamic studies in COPD patients with and without heart failure consistently show a normal cardiac output.[96,97] Measurements performed by Anand and associates[50] in nine patients with peripheral edema due to COPD and in six patients after recovery demonstrated that patients with edema had severe salt and water retention, reduction in renal blood flow and glomerular filtration rate, and a neurohormonal activation comparable to that seen in patients with congestive heart failure due to primary myocardial disease; these occurred despite the fact that mean cardiac output was normal, as was mean pulmonary artery wedge pressure. Therefore, after treatment that resulted in an increase in arterial P_{O_2} and a fall in P_{CO_2}, the patients became free from edema, with a corresponding increase in renal blood plasma flow and normalization of glomerular filtration rate.

In patients with pulmonary arterial hypertension as classified in Table 56-1, right heart catheterization is required to assess the hemodynamic severity and hence prognosis of pulmonary hypertension, to establish the pre- versus postcapillary etiology, to perform an oxygen saturation assessment across the right heart structures, to search for the presence of a congenital systemic-to-pulmonary shunt, to measure pulmonary vascular resistance, and to perform acute vasoreactivity testing to guide therapy as well as to monitor safety of treatment with calcium channel blockers.[2] It is not known if acute vasodilator therapy testing is of any utility in patients with pulmonary hypertension and cor pulmonale associated with diseases of the respiratory system or hypoxemia.

DIFFERENTIAL DIAGNOSIS

There are many causes of pulmonary artery hypertension, as noted in Table 56-1. At times, the underlying cause may be difficult to establish. Specific symptoms and signs of the basic disorder often help to establish the cause of pulmonary hypertension. For example, mitral stenosis noted on physical examination or by echocardiographic examination may represent the underlying cause of pulmonary hypertension. Early in the natural history of mitral stenosis, only passive pulmonary hypertension occurs; however, after prolonged elevation of left atrial and pulmonary vein pressure, P_{PA} rises out of proportion to the raised left atrial pressure from reflex

pulmonary vasoconstriction. Radiographic evidence of increased interstitial markings reflecting increased lung vascular volume from high pulmonary blood flow suggests the presence of congenital heart disease with a congenital systemic-to-pulmonary shunt. The diagnosis of idiopathic pulmonary arterial hypertension can be made only after other causes of increased obstruction to pulmonary blood flow have been eliminated. Obstructive pulmonary vascular disease caused by appetite suppressants or other toxic substances; pulmonary hypertension associated with occasional cases of portal hypertension; silent deep venous thrombotic disease that has resulted in multiple, relatively silent pulmonary emboli with subsequent pulmonary hypertension; and pulmonary vasculitis from systemic lupus erythematosus, scleroderma, or other collagen vascular diseases are but a few examples in which the underlying cause must be sought, beginning with a careful medical history and physical examination, to explain the basis of the pulmonary hypertension.

The diagnosis of chronic cor pulmonale due to obstructive or restrictive ventilatory insufficiency is usually rapidly established because these patients either have evidence of pulmonary parenchymal disease (e.g., radiographic evidence of pulmonary infiltrative or fibrotic disease, lung hyperinflation, radiologic findings suggesting bronchiectasis), present with symptoms or physical findings that suggest underlying pulmonary disease (e.g., bronchial wheezing, history of chronic bronchitis with a chronic productive cough), or have abnormalities of pulmonary function testing. Other patients present with evidence of chest wall deformities that may interfere with respiration (e.g., kyphoscoliosis). Morbid obesity may suggest the presence of the pickwickian syndrome or primary alveolar hypoventilation. Pulmonary edema on chest radiography, with dilation of the left side of the heart, indicates that COPD is not the cause, and suggests the presence of comorbid conditions affecting the left ventricle. Pulmonary edema may also occur without overt left ventricular failure in patients with acute respiratory distress syndrome (see Chapter 55).

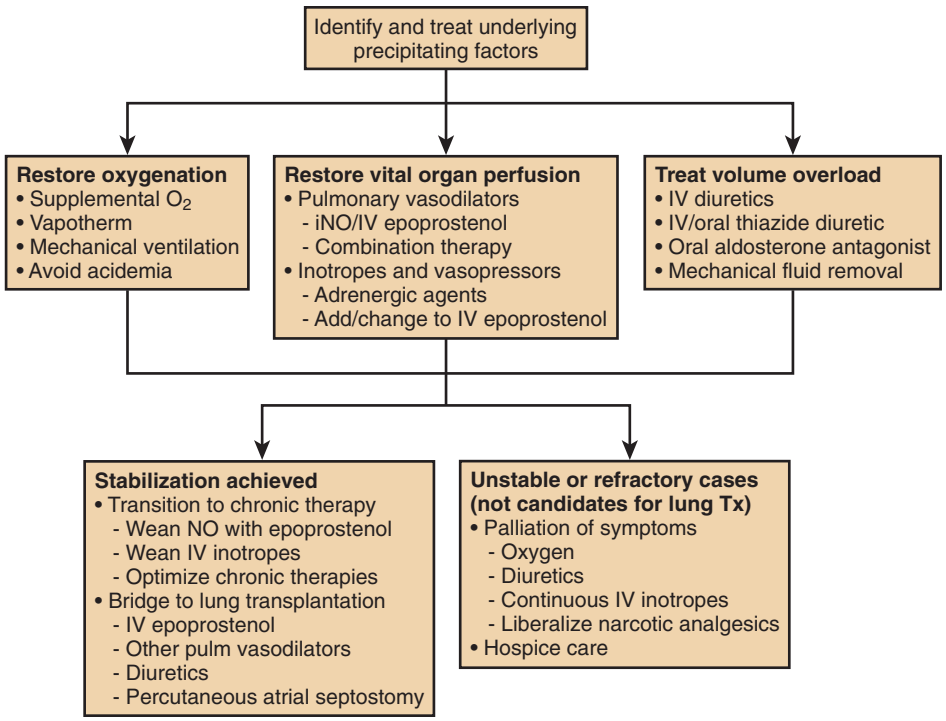
TREATMENT

The goals of treatment for cor pulmonale are similar to those for treating left-sided heart failure and include relief of symptoms, improvement of functional capacity, slowing of disease progression, and reducing morbidity and mortality. These goals can be attained, in part, by addressing the major operative pathophysiologic mechanisms: hypoxemia, acidemia, pulmonary hypertension, and neurohormonal activation.[44] Useful guidelines for the diagnosis and treatment of pulmonary hypertension have recently been published.[97a] Hemodynamic goals are very important in right-sided heart failure associated with pulmonary hypertension: (1) reduce right ventricular internal and external afterload (right ventricular wall stress and pulmonary vascular resistance, respectively) utilizing oxygen therapy and pulmonary vasomodulating agents; (2) decrease right ventricular preload, effecting a reduction in right ventricular wall stress and improving left ventricular filling (diuretics); and (3) augment right ventricular contractility. The therapeutic strategies for cor pulmonale are delineated in Table 56-2, and Figure 56-11 proposes an algorithmic approach to the management of acute decompensated right ventricular failure.[98,99] Certainly, treatment must be directed to the specific underlying pulmonary disorder leading to cor pulmonale (see Table 56-2). In the management of chronic cor pulmonale, diet and lifestyle modifications are important. These include smoking cessation, sodium restriction, weight loss, and exercise training to improve functional performance. Structured rehabilitation programs and breathing training have been shown to be useful.[44,100] Patients with severe pulmonary arterial hypertension, especially those with a history of syncope, should avoid overexertion. In addition, pregnancy and high altitudes (>4000 feet) should also be avoided in this setting. Oral anticoagulation is considered the standard of care in patients with moderate to severe pulmonary arterial hypertension. One retrospective and one prospective trial have suggested a mortality benefit.[101,102] In the

TABLE 56-2. Therapeutic Strategies for Cor Pulmonale

DIET AND LIFESTYLE
Smoking cessation
Weight loss
Sodium restriction
Judicious exercise training
Structured rehabilitation and breathing training programs
Avoidance of overexertion
Avoidance of pregnancy
Avoidance of high altitudes
INTERVENTIONS
Treatment of underlying condition
COPD (bronchodilators, corticosteroids, antibiotics, oxygen)
Interstitial lung disease (immunosuppression, oxygen, interferon gamma [investigational])
Sleep-disordered breathing and alveolar hypoventilation disorders (CPAP, BiPAP, surgery)
Chronic exposure to high altitudes (return to sea level)
Chronic thromboembolic disease (anticoagulation, inferior vena cava filters, thromboendarterectomy)
Supplemental oxygen
Pulmonary vasodilators
Anticoagulation
Diuretics
Digitalis glycosides (chronic therapy)
Nonglycoside inotropes (low-dose dobutamine or dopamine in acute severe right heart decompensation with hypoperfusion)
Lung volume-reduction surgery
Lung transplantation
Heart-lung transplantation (PAH secondary to complex congenital heart disease)
Percutaneous blade-balloon atrial septostomy (investigational)
Severe right-sided heart failure
Recurrent syncope

BiPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure; PAH, pulmonary arterial hypertension.



IV = intravenous; NO = nitric oxide; Tx = transplantation.

FIGURE 56-11 ■ Management of acute decompensated right ventricular failure in pulmonary arterial hypertension.

management of chronic cor pulmonale with excessive right ventricular preload, diuretic therapy is the mainstay of therapy to alleviate dyspnea, hepatic congestion, and peripheral edema. Decompression of the right ventricle with diuretics may also improve right ventricular performance by reducing its preload and wall stress. With resultant reductions in intrapericardial pressure and potential attenuation of interventricular septal shift toward the left ventricle, left ventricular filling may increase, resulting in improved systemic cardiac output.

Management of patients with decompensated pulmonary heart disease must focus on improvement of the underlying pulmonary disorder if compensation is to be restored. The precipitating event for decompensation in patients with stabilized chronic cor pulmonale from either COPD or infiltrative lung disease is often an associated upper respiratory infection. Increased secretions and infection are likely to tip the balance toward further alveolar hypoxemia, hypercapnia, and acidemia, which aggravate pulmonary hypertension and worsen ventricular contractility, resulting in cardiac decompensation.

Improvement in right ventricular performance is best accomplished not only by correcting acidemia, but also by reducing the afterload facing the right ventricle (i.e., reducing P_{PA}). Correction of arterial hypoxemia through the administration of an increased concentration of oxygen in inspired air lowers P_{PA} in patients with hypoxic pulmonary vasoconstriction. Improvement in alveolar ventilation with intubation and mechanical ventilation helps eliminate the acute hypercapnia and acidemia that depress myocardial contractility. Therapy with digoxin is controversial, and its effects on right ventricular function are unclear; it produces a modest increase in cardiac output in patients with pulmonary hypertension and right ventricular failure,[102] thereby increasing pulmonary blood flow and reducing right-sided heart filling pressure. However, it does not lower P_{PA}.[103] Short-term treatment with digoxin in patients with right ventricular dysfunction from pulmonary hypertension is associated with a significant reduction in circulating levels of catecholamines, and this may be a mechanism for its reported favorable hemodynamic effects in some studies.[102] It is unknown at this time if digoxin exerts beneficial effects on progression of right ventricular failure, morbidity, or survival, and therefore its use remains controversial. It must be emphasized that patients with COPD are particularly sensitive to digoxin, and close attention to dosage and electrolyte balance to prevent digitalis toxicity is necessary.

Often, an episode of acute cardiac decompensation in a patient who has chronic pulmonary hypertension due to COPD is caused by an underlying pneumonitis or superimposed bronchitis. Patchy areas of atelectasis may also play a role. Empirical antimicrobials (see Chapter 39) should be administered until cultures identify the causative organism and allow more specific treatment to be used. β_2-Agonists such as albuterol are widely accepted as standard management. Not only are they bronchodilators, but they acutely produce a fall in pulmonary artery pressure and a rise in right ventricular ejection fraction with no significant fall in arterial P_{O_2}.[44,104] Anticholinergic drugs such as ipratropium bromide are also useful bronchodilators. Theophylline seems to lessen dyspnea and may be helpful in improving ventilation, but it has

considerable toxicity and is now seldom used. Finally, short-term corticosteroids appear useful in accelerating recovery from exacerbations of acute respiratory failure in patients with COPD and should be given as early as possible.

Sleep disorders are common in patients with COPD and can contribute to nocturnal hypoxemia and hypercapnia, leading to increased pulmonary vasoconstriction. As described in Chapter 79, continuous positive airway pressure can exert beneficial effects by keeping both upper and lower airways open and improving gas exchange. In patients with obstructive sleep apnea, continuous positive airway pressure is associated with improved ventricular function and survival and reduced hematocrit.[105-107]

If severe polycythemia is present, phlebotomy may be helpful, although clinicians are frequently reluctant to undertake this type of therapy today. In cattle with brisket disease, cardiac output and coronary blood flow increased without a rise in PPA when phlebotomy was performed.[108] Hypoxic patients also show improvement in right ventricular ejection fraction, exercise tolerance, and neuropsychological function after phlebotomy.[44]

The role of ACE inhibitors,[109] angiotensin II receptor blockers, or aldosterone receptor blockers in chronic cor pulmonale has not been independently studied in large randomized, double-blind, clinical trials, and their potential long-term benefits are unknown.

Oxygen

Young adults living at high altitudes have distinctly raised PPA values that fall to normal if they leave to live at sea level for several years. Such observations, combined with the clinical, pathologic, and physiologic data observed in patients with COPD, emphasize the importance of hypoxia in the genesis of pulmonary hypertension. They also suggest that continuous domiciliary oxygen therapy might reduce pulmonary arterial hypertension in patients with COPD and thereby improve outcome. Controlled trials evaluating long-term oxygen administration showed improvement in survival, although they failed to demonstrate a clear and consistent reduction in pulmonary hypertension.

Two major randomized trials have been carried out. In the British Medical Research Council evaluation of long-term domiciliary oxygen in chronic hypoxic cor pulmonale, long-term oxygen administration for at least 15 hr/day appeared to prevent further rises in PPA, compared with no oxygen administration in control patients[110]; it also lessened mortality. In a National Institutes of Health study in the United States, 12 hours of nocturnal oxygen therapy was compared with continuous therapy; continuous oxygen proved distinctly more favorable, with a lessened mortality rate at 2 years.[111] Additionally, a decrease was seen in pulmonary vascular resistance, contrasted to a small rise in the group receiving only nocturnal therapy. Furthermore, oxygen therapy has been shown to relieve renal vasoconstriction and improve oxygen delivery to critical organs such as the heart and brain.[112]

Based on the results of these studies, it is clear that severely hypoxemic patients with COPD should be provided home oxygen therapy, with a goal of continuous therapy but with at least 15 hr/day of oxygen. However, it must be remembered that the acute administration of *high* concentrations of oxygen to a patient with hypoxic cor pulmonale can have adverse effects on breathing and carbon dioxide removal, particularly if the patient is already displaying alveolar hypoventilation as evidenced by hypercapnia. This is important to keep in mind when evaluating a patient's pulmonary artery hypertensive response to oxygen administration in the catheterization laboratory, and when determining the dose for use at home. Patients given domiciliary oxygen need to be observed closely when they are initially being instructed on the use of this therapy to ensure that arterial oxygen saturation actually rises: flow rates of 1 to 3 L/min generally suffice. Further information about the long-term use of oxygen in pulmonary rehabilitation is provided in Chapter 94.

Vasodilators

The recommendations for the treatment of pulmonary arterial hypertension with pulmonary vasodilators are based on studies of patients with idiopathic pulmonary arterial hypertension or pulmonary arterial hypertension associated with connective tissue diseases, most commonly the scleroderma spectrum of disorders. To date, no large-scale studies or guidelines have been developed with respect to vasodilator therapy for patients with pulmonary hypertension secondary to lung diseases with or without hypoxemia. Management algorithms for patients with pulmonary arterial hypertension include right heart catheterization for diagnostic as well as therapeutic indications. Protocols for vasoreactivity testing with short-acting acute vasodilators may include testing high-flow oxygen, inhaled NO up to 20 ppm, parenteral epoprostenol, or parenteral adenosine. A reduction in the pulmonary vascular resistance by more than 20% from baseline identifies a group of "responders," which comprises less than 15% of the pulmonary arterial hypertension population, but which includes those who may respond to a hemodynamically monitored trial of calcium channel blockers, such as nifedipine, diltiazem, or amlodipine. Verapamil should be avoided as it can exert substantial negative inotropic effects and worsen right ventricular function. In the treatment of idiopathic pulmonary arterial hypertension, high-dose calcium channel blockers have been shown to improve New York Heart Association (NYHA) functional classification and to induce echocardiographically demonstrated regression of right ventricular hypertrophy. Patients who responded to calcium channel blockade had a reported 5-year survival of 94% compared to 30% in the nonresponders.[101]

It has been far less common to evaluate and subsequently use pulmonary vasodilators as chronic therapy in patients with cor pulmonale due to COPD or diffuse parenchymal disease. Attempts to date have not significantly affected long-term function or survival. One

reason is that initial acute pulmonary vasodilating responses to an agent may not persist when the agent is used chronically. For example, in a study of 53 patients with COPD and pulmonary hypertension, the decrease in pulmonary vascular resistance after initial use of the calcium antagonist nifedipine was 23% at rest and 35% during exercise. However, after an average of 13 months of treatment, the decrease in pulmonary vascular resistance was no longer significant.[113] Side effects from calcium channel blockers include worsening hypoxemia secondary to increased ventilation-perfusion mismatch and right-to-left shunting through a patent foramen ovale in the setting of greater reduction in systemic vascular resistance relative to pulmonary vascular resistance. Peripheral edema is also a frequent consequence of calcium channel blockade and may limit its long-term tolerance. Those patients who fail to respond to acute vasodilator testing or who have severe right ventricular failure, adverse effects with calcium channel blockers, or hypotension should be considered for treatment with oral bosentan (Tracleer), a dual endothelin receptor antagonist; subcutaneously infused treprostinil (Remodulin); or intravenously infused epoprostenol (Flolan).

Of major concern in patients with pulmonary hypertension due to lung diseases is that the pharmacologic reversal of hypoxic pulmonary vasoconstriction with vasodilators may increase pulmonary blood flow to poorly ventilated or nonventilated alveoli, with the net effect that arterial P_{O_2} may fall despite a drop in PPA. What is frequently unappreciated is that ventilation-perfusion matching also affects carbon dioxide elimination. Minute ventilation may increase to compensate for the retention of carbon dioxide; therefore, although arterial P_{O_2} may fall, hypercapnia may not worsen.[114] In patients with advanced COPD, one small study reported a decrease[115] and another no change[116] in P_{O_2} after inhaled NO. In patients with respiratory failure from COPD, P_{O_2} did decrease with epoprostenol treatment.[117] However, in stable COPD patients treated with amlodipine and felodipine, there was no significant fall in P_{O_2}.[118,119] Another practical problem limiting the use of pulmonary vasodilators is that often they also are systemic vasodilators and may result in significant hypotension. Physicians should be on the lookout for the occasional patient with pulmonary hypertension from recurrent pulmonary embolism, because of the considerable benefit from thromboendarterectomy.[120]

Endothelin Receptor Antagonists

Bosentan (Tracleer) is an orally administered competitive receptor antagonist that blocks both the ET_A and ET_B receptors. It was approved for the treatment of pulmonary arterial hypertension to improve exercise tolerance and functional capacity, and delay the time to clinical worsening in patients with WHO functional class III or IV symptoms. In a 12-week randomized, prospective, double-blind, placebo-controlled trial of 32 subjects with either primary pulmonary hypertension or pulmonary arterial hypertension associated with connective tissue disease, patients treated with bosentan (125 mg twice daily) improved their performance on the 6-minute walk test by a placebo-corrected treatment effect of 76 m ($P = 0.02$) and showed improvement in cardiopulmonary hemodynamics.[121] A similarly designed 16-week trial, the BREATHE-1 study, was carried out on 213 subjects with WHO classification III or IV symptoms. At 16 weeks the placebo-corrected mean improvement in 6-minute walk distance was 44 m ($P = 0.0002$) for the patients randomized to the bosentan arm. Bosentan therapy was associated with a significant improvement in WHO functional classification ($P = 0.042$) and an insignificant improvement in Borg dyspnea index score ($P = 0.059$). At 16 weeks, bosentan delayed the time to clinical deterioration. Ninety-five percent of patients on bosentan were free of adverse clinical events compared to 75% of the control patients. In a subgroup of 48 subjects who continued in the double-blind extension up to 28 weeks, 89% of those in the bosentan group compared to 63% in the placebo arm were event free ($P = 0.0015$).[122]

Therapy with bosentan has been associated with potential liver injury, teratogenic effects, and modest reductions in hemoglobin concentration. Close monitoring of liver transaminases and hemoglobin is recommended. Pregnancy must be prevented with reliable barrier contraception as hormonal contraceptive therapy is unreliable in the presence of concomitant bosentan treatment. Monthly pregnancy tests are recommended. Side effects from bosentan include nasal congestion, pharyngitis, dyspepsia, and peripheral edema. Although bosentan has been shown to be beneficial in patients with pulmonary arterial hypertension, its role in the treatment of patients with hypertension associated with disorders of the respiratory system has yet to be determined in large-scale trials. Studies are underway to investigate its utility in pulmonary arterial hypertension due both to COPD and to ILD.

The selective ET_A receptor antagonist ambrisentan was approved by the Food and Drug Administration for the treatment of WHO functional class II and III pulmonary arterial hypertension based on the results of the ARIES-1 and ARIES-2 studies.[123] Studies 1 and 2 were concurrent, double-blind, placebo-controlled trials carried out in the United States and Europe that randomized 202 and 192 patients with pulmonary hypertension to placebo or ambrisentan, 5 or 10 mg and 2.5 or 5 mg, respectively, once daily for 12 weeks. The primary end point, 6-minute walk distance, increased in all ambrisentan groups. In ARIES-1, the mean placebo-corrected treatment effects in 6-minute walk distance were 31 m ($p = 0.008$) and 51 m ($p = 0.001$) for the 5- and 10-mg ambrisentan doses, respectively. In ARIES-2, the mean placebo-corrected treatment effects were 32 m ($p = 0.022$) and 59 m ($p < 0.001$) for the 2.5- and 5-mg ambrisentan doses, respectively. In ARIES-2, improvements in time to clinical worsening and quality of life (Short Form-36 score) were observed. In the ARIES-1 trial, improvements in WHO functional class were shown. Improvements in Borg dyspnea score and BNP were observed in both studies. Ambrisentan was also well tolerated and associated with a low risk of aminotransferase abnormalities. No patient treated with

ambrisentan developed aminotransferase elevation greater than three times the upper limit of normal. Ambrisentan has not been studied in pulmonary hypertension associated with pulmonary diseases.

Prostacyclin and Its Analogues

Prostaglandins are synthesized by the pulmonary vascular endothelium. Neonatal calves that develop severe pulmonary hypertension when exposed to chronic hypobaric hypoxia have been shown to have a relative deficit in prostaglandin production in their pulmonary arteries; this suggests that prostaglandins may play a role in the development of pulmonary hypertension by the lack of vasodilatory stimuli.[124] Normal subjects exposed acutely to high-altitude hypoxia release both vasoconstrictive and vasoactive eicosanoids, with vasoconstrictors being released initially and vasodilators being released several days later.[125] Furthermore, the medium to small pulmonary arteries of patients with idiopathic pulmonary arterial hypertension exhibit reduced expression of prostacyclin synthase compared with arteries from control subjects.[126]

Epoprostenol (Flolan) is a systemic and pulmonary vasodilator that also inhibits platelet aggregation, affects vascular remodeling, and opposes the effects of thromboxane A_2.[127] These effects are mediated by enhanced adenyl cyclase activity resulting in increased cyclic adenosine monophosphate in vascular smooth muscle cells and platelets. As a result of its ultrashort half-life and instability, epoprostenol use is limited to continuous intravenous infusion through a permanent indwelling central venous catheter and portable infusion pump. Side effects of the drug include flushing, headache, nausea, vomiting, diarrhea, myalgias, arthralgias, paresthesias, and jaw pain. Other adverse effects of epoprostenol therapy are consequences of the complex delivery system, including pump malfunction, catheter-related infections, and thrombosis. Based on studies in patients with documented pulmonary arterial hypertension, epoprostenol has been approved for the long-term treatment of patients with NYHA functional class III or IV symptoms due to idiopathic pulmonary arterial hypertension, pulmonary arterial hypertension associated with connective tissue disorders, or chronic thromboembolic disease. An early randomized trial in 24 patients with idiopathic pulmonary arterial hypertension revealed that continuous intravenous administration of epoprostenol by portable infusion pump resulted in substantial hemodynamic and symptomatic improvement over 8 weeks.[128] Barst and associates,[129] in a nonblinded study, randomly assigned 81 patients with idiopathic or familial pulmonary arterial hypertension to receive either a continuous intravenous epoprostenol infusion added to conventional therapy or conventional therapy alone. The intravenous dosage, which was given continuously by infusion pump through an implanted catheter, was determined by the dosage tolerated in an earlier, short-term, dose-ranging phase of the study. By the end of 12 weeks, epoprostenol resulted in symptomatic and hemodynamic improvement, and improved survival.

A group of 69 patients with idiopathic pulmonary arterial hypertension were similarly given a continuous intravenous infusion of epoprostenol through an implanted catheter using a portable, battery-operated infusion pump, with an initial maximum dose titrated to symptoms or to a drop in systemic blood pressure greater than 10 mm Hg.[130] Patients were monitored up to 3 years, during which time 13 of the patients died, including 3 among 9 patients who underwent single-lung transplantation. However, 18 of the patients were monitored for 330 to 700 days and demonstrated an echocardiographically determined estimated mean fall in the right ventricular minus right atrial systolic pressure gradient from 84.1 ± 24.1 to 62.7 ± 18.2 mm Hg ($P < 0.01$). McLaughlin and colleagues[131] evaluated 27 patients with idiopathic pulmonary arterial hypertension who were given epoprostenol over a mean of 16.7 ± 5.2 months. By increasing the rate of infusion by an average 2.5 ng/kg/min each month, a 53% decline in pulmonary vascular resistance was achieved at the time of restudy.

Another study enrolled 111 subjects with pulmonary arterial hypertension associated with the scleroderma spectrum of connective tissue disorders. The patients were randomized to epoprostenol plus background conventional therapy versus conventional therapy alone for 12 weeks. Epoprostenol patients demonstrated an improvement in placebo-corrected median 6-minute walk distance by 99.5 m ($P < 0.003$) as well as improvements in cardiopulmonary hemodynamics and a reduction in dyspnea.[132]

All of these studies suggest the desirability of using chronic infusions of epoprostenol in patients with severe pulmonary arterial hypertension to improve exercise capacity, functional class, and survival. However, therapy with this agent is limited by its side-effect profile and complex delivery system. Hence, alternatives to epoprostenol are being sought and studies with stable prostacyclin analogues have been pursued. Large studies of epoprostenol in pulmonary arterial hypertension associated with lung diseases have not been undertaken. Because in one small study, patients with respiratory failure secondary to COPD treated with epoprostenol experienced reductions in P_{O_2}, further studies of epoprostenol in this patient population must be performed before deciding on its clinical value.[125]

Treprostinil (Remodulin) is a stable prostacyclin analogue with pharmacodynamic actions similar to epoprostenol but with a longer half-life. It can be administered either via continuous subcutaneous or intravenous infusion with a small pump or by inhalation. This agent was approved for treatment of patients with WHO classification II, III, or IV symptoms due to pulmonary arterial hypertension based on favorable results of a pivotal 12-week prospective, randomized, double-blind, placebo-controlled trial.[133] This study enrolled 470 subjects with idiopathic pulmonary arterial hypertension, pulmonary arterial hypertension associated with connective tissue disease, or congenital systemic-to-pulmonary shunts. Treprostinil improved exercise capacity with a between-treatment-group difference in median 6-minute walk distance of 16 m ($P < 0.006$). Treprostinil improved

dyspnea, quality of life, and cardiopulmonary hemodynamics. Patients who appear to tolerate higher doses of treprostinil and who have more severe disease appear to derive the most benefit from the agent. However, 85% of patients did experience infusion site pain, which required premature discontinuation of the infusion in 8% of the subjects; it is this side effect that may limit increased dosing with the agent and also its long-term usage.[133]

In an open-labeled study in 16 patients with pulmonary hypertension who had not been treated with other specific antihypertensive therapy, intravenous treprostinil was associated with significant improvements in exercise capacity.[134] At 6 weeks of treatment the mean 6-minute walk distance was 378 m ($p = 0.008$), and at 12 weeks of treatment mean 6-minute walk distance was 400 m ($p = 0.001$), compared to the baseline of 319 m. Adverse events were similar to those seen with other prostanoids. Although no head-to-head trial has been performed to date of intravenous treprostinil versus intravenous epoprostenol, this study supports the use of intravenous treprostinil, which is already premixed and more stable with a longer half-life in patients for whom intravenous epoprostenol may not be the best alternative.

Recently, the FDA approved a new form of treprostonil (Tyvaso), a solution for inhalation, based upon the results of the TRIUMPH-1 Trial, which are not yet published, but which showed a 20-meter improvement in the 6-minute walk distance in patients who received inhaled treprostinil compared to those who received inhaled placebo ($p = 0.0005$ at peak effect).

Inhalational iloprost is a stable prostacyclin analogue that has been shown to selectively dilate the pulmonary arterial bed while exerting preferential vasodilation in well-ventilated lung regions. After inhalation, its vasodilatory effects last from 30 to 90 minutes. A prospective, double-blind, placebo-controlled, randomized 12-week trial enrolled 203 patients with NYHA functional class III or IV symptoms due to idiopathic pulmonary arterial hypertension and pulmonary arterial hypertension associated with appetite suppressant use, scleroderma, and inoperable chronic thromboembolic disease.[135] Iloprost-treated patients had improvement in the combined primary end point of 6-minute walk distance and NYHA functional class in the absence of clinical deterioration or death compared to the placebo group ($P = 0.007$); dyspnea was also improved.[135] Inhaled iloprost has been studied as an add-on therapy to stable oral bosentan monotherapy in the STEP Trial, a safety study with secondary efficacy end points.[136] In this randomized trial of 67 patients with pulmonary hypertension, iloprost was well tolerated and safe. In addition, compared to placebo, significantly more patients assigned to the inhaled iloprost arm demonstrated at least a one-class improvement in the NYHA functional classification. Treatment with add-on iloprost was also associated with delayed time to clinical worsening.

The effects of various delivery methods of the prostanoids and other vasodilators were evaluated in eight patients with severe pulmonary hypertension associated with pulmonary fibrosis: intravenous prostacyclin, inhaled NO, aerosolized epoprostenol, and calcium channel blockers were compared in randomized order.[137] Aerosolized epoprostenol resulted in preferential pulmonary vasodilation and significant reduction in mean PPA and pulmonary vascular resistance. There was no change in systemic arterial pressure, arterial oxygen saturation and pulmonary right-to-left-shunt. Inhaled NO also produced selective pulmonary vasodilation and decreased the pulmonary right-to-left shunt. However, intravenous epoprostenol and calcium channel blockers were not pulmonary selective. Both agents resulted in a significant drop in systemic arterial pressure. Furthermore, epoprostenol infusion resulted in a marked increase in right-to-left shunt flow. In a patient with severe dyspnea and decompensated right-sided heart failure, aerosolized iloprost exerted acute effects on hemodynamics and gas exchange similar to inhaled epoprostenol, but the effects lasted longer. Long-term therapy with inhaled iloprost resulted in improved clinical status. Certainly more studies on the role of these agents alone or in combination with existing agents are required in patients with pulmonary hypertension secondary to lung disease.

Oral Phosphodiesterase V Inhibitors

Sildenafil (Viagra) is a selective inhibitor of cyclic GMP–specific phosphodiesterase type V, which is found in abundance in the smooth muscle cells of the pulmonary vascular bed. Attenuated degradation of cyclic GMP by sildenafil increases intracellular levels of this mediator, resulting in smooth muscle cell relaxation and vasodilation. When administered acutely to patients with pulmonary arterial hypertension or pulmonary hypertension in the context of lung fibrosis, sildenafil exerts potent effects on cardiopulmonary hemodynamics with significant reductions in pulmonary vascular resistance without increasing left-sided filling pressures or worsening hypoxemia.[138–142] It has also been shown to potentiate the effect of other agents such as inhaled iloprost and NO.[142–144] Chronic administration in adults and children with pulmonary hypertension appears to improve exercise distance and symptoms.[142–146] Sildenafil is well tolerated, but some subjects have experienced headache, flushing, dyspepsia, myalgias, impaired blue-green color discrimination, dizziness, hypotension, and nasal congestion. Use of sildenafil with concomitant nitrates is contraindicated due to potential life-threatening hypotension.

A large prospective, randomized, double-blind, placebo-controlled trial of 278 subjects with pulmonary arterial hypertension compared the effects of three oral doses of sildenafil (20 mg, 40 mg, and 80 mg three times daily) to placebo on exercise capacity, symptoms, and cardiopulmonary hemodynamics. Six-minute walk distance improved by 50 m for the 80-mg group, 46 m for the 40-mg group, and 45 m for the 20-mg group compared to placebo. When the sildenafil data were pooled, 35% of sildenafil-treated patients had improvement of one functional class compared to 7% of patients in the placebo arm. There was no significant difference in cardiopulmonary hemodynamics. Sildenafil was well toler-

ated. The most common adverse event was headache. A long-term trial with patients on the 80-mg dose is ongoing.[147]

Sildenafil was studied as add-on therapy to stable intravenous epoprostenol in a 16-week multinational, double-blind, placebo-controlled study.[148] Two hundred sixty-seven patients with pulmonary hypertension on stable epoprostenol were randomized to receive sildenafil 20 mg three times daily, titrated up to 80 mg three times daily at 4-week interval as tolerated, or placebo. At the end of the 16-week study period, more than 80% of patients were able to reach the 80-mg three times daily dose. There were seven deaths in the placebo group and none in the sildenafil group. Significantly fewer patients in the sildenafil arm sustained clinical worsening events (death, transplantation, hospitalization, and increase in epoprostenol dose). Furthermore, the placebo-adjusted increase in mean 6-minute walk distance was 26 m ($p < 0.0009$) in favor of the sildenafil-treated group.

The effects of sildenafil have been evaluated in patients with interstitial lung disease in small, open-label studies. Sixteen hospitalized patients with pulmonary fibrosis and precapillary pulmonary hypertension were administered inhaled NO and then randomized to receive open-label intravenous epoprostenol (mean dose 8 ng/kg/min) or oral sildenafil (mean dose 50 mg three times daily).[149] All three agents reduced the pulmonary vascular resistance index to a similar extent. However, only inhaled NO and sildenafil reduced the pulmonary vascular resistance–to–systemic vascular resistance ratio. Intravenous epoprostenol also decreased mean systemic arterial pressure and pulmonary artery P_{O_2}, owing to worsening ventilation-perfusion matching. By contrast, inhaled NO and sildenafil maintained ventilation-perfusion matching. Therefore, in patients with pulmonary fibrosis, sildenfil exerted a selective pulmonary arterial vasodilatory effect without worsening hypoxemia. Another open-label chronic study evaluated the effect of sildenafil on exercise capacity in patient with idiopathic pulmonary fibrosis and precapillary pulmonary hypertension.[150] Fourteen patients received open-label sildenafil 20 to 50 mg three times daily for 12 weeks. At study period, of the 11 patients who completed the 6-minute walk test, 9 demonstrated an improvement in the mean 6-minute walk distance of 49 m (90% confidence interval [CI], 17.5 to 84 m). Sildenafil was discontinued in two patients for adverse events (diarrhea, hypotension). Of the 11 patients who completed the study, 1 patient had mild diarrhea and headache, another patient had headache, and a third experienced blurry vision. Based on these small but encouraging studies, a National Institutes of Health double-blind, placebo-controlled, randomized study is now underway to evaluate the effect of sildenafil in a large cohort of patients with pulmonary fibrosis and pulmonary hypertension.

Recently, a second oral phosphodiesterase V inhibitor, tadalafil, was approved for the treatment of patients with pulmonary arterial hypertension. Tadalafil, 40 mg daily, significantly improved the distance walked in 6 minutes and the time to clinical worsening compared to patients taking placebo.[150a]

Nitric Oxide

NO is produced within endothelial cells by activity of the enzyme NO synthase in response to various stimuli. NO activates guanylate cyclase, which leads to increased smooth muscle cell cyclic GMP, resulting in vasodilation. In the pulmonary capillaries, inhaled NO is inactivated by binding to hemoglobin and forming nitrosylmethemoglobin. Therefore, inhaled NO specifically dilates the pulmonary vasculature and is inactivated before it reaches the systemic circulation.[151] In subjects with severe pulmonary arterial hypertension, inhaled NO at 40 ppm was shown to decrease pulmonary vascular resistance 5% to 68% from baseline with no change in systemic vascular resistance, whereas intravenous epoprostenol reduced both the pulmonary and systemic vascular resistances. Other effects of NO include suppression of smooth muscle cell proliferation and platelet aggregation.[152,153]

Inhaled NO may affect airway tone through a variety of different mechanisms. It also significantly affects pulmonary vascular tone.[154] Both pulmonary arterial and venous endothelial cells are capable of producing NO. Using an NO synthase inhibitor in 11 healthy volunteers, Stamler and colleagues[155] demonstrated that NO regulates normoxic pulmonary vascular tone. Furthermore, when volunteers were made hypoxic, inhalation of 40 ppm NO reversed pulmonary vasoconstriction without causing systemic vasodilation.[156]

Endothelial damage with impaired NO production has been proposed as contributing to both acute and chronic pulmonary hypertension.[157] In a study of pulmonary artery rings obtained from 22 patients with COPD undergoing heart-lung transplantation, impaired endothelium-dependent pulmonary artery relaxation was observed and was related to the preoperative levels of hypoxemia and hypercapnia. Additionally, reduced relaxation was significantly correlated to the degree of intimal fibromuscular thickening.[158] The inhalation of NO at 40 ppm by awake lambs reversed pulmonary hypertension caused by breathing a hypoxic gas mixture within 3 minutes.[159]

There is a reduction in the expression of NO synthase in the pulmonary arteries of patients with idiopathic pulmonary arterial hypertension, and the degree of expression is inversely correlated with total pulmonary resistance. Hypoxia markedly lessens NO synthase activity, decreasing NO release, and this deficiency in patients with chronic pulmonary hypertension may contribute to their increase in pulmonary vascular resistance.[160,161]

In persistent newborn pulmonary hypertension, inhaled NO has proved to be of clinical value.[162,163] Furthermore, in patients with idiopathic pulmonary arterial hypertension, inhaled NO has been used to predict those patients who might safely and effectively respond to calcium channel blockers. However, in patients with COPD, intermittent NO inhalations are not commonly used therapeutically, in part because of costs and practical difficulties, including toxicity associated with chronic use, but also because of concern that systemic oxygenation might worsen due to increased local ventilation-perfusion mismatches, as often occurs with other vasodilators. However, NO theoretically should vasodi-

late only those areas it reaches as it is being inhaled, thereby increasing blood flow only to areas being ventilated and improving ventilation-perfusion matching. It would seem reasonable, therefore, to test patients with severe COPD associated with acute respiratory failure (as well as patients with obliterative or idiopathic pulmonary arterial hypertension) for their responsiveness to this potential therapeutic agent as an acute intervention. However, at present there does not appear to be a clinically meaningful role for its chronic use.

Angiotensin-Converting Enzyme Inhibitors

Studies in rats exposed to chronic hypoxia in a barochamber and then transferred to an environment of normoxia revealed that enalapril reduced the content and concentration of collagen significantly, suggesting that partial regression of cardiac fibrosis may occur with enalapril, independent of the reduction in pressure load.[164] In another study of chronically hypoxic rats, the ACE inhibitor quinapril reduced the development of pulmonary hypertension. This was seen both early and after pulmonary hypertension was established. The degree of medial thickness in alveolar duct blood vessels was significantly reduced by quinapril treatment, and stains of vascular smooth muscle cells showed that quinapril appeared to inhibit either vascular smooth muscle cell proliferation or growth, or sometimes both.[165]

Experimental observations in normal volunteers demonstrated that the infusion of saralasin (an angiotensin II receptor blocker) not only produces pulmonary vasodilation when the renin-angiotensin system has been stimulated but also attenuates pulmonary vasoconstriction in response to acute hypoxia.[166] The results of studies in patients with chronic cor pulmonale have been inconsistent. When enalapril was added to conventional treatment in 30 patients with chronic cor pulmonale, not only was pulmonary hypertension decreased but renal vascular resistance fell, resulting in increased renal blood flow and improved glomerular filtration rate.[167] In contrast, the acute effects of captopril were studied in 15 patients with severe COPD who were recovering from right-sided heart failure. Although captopril reduced systemic arterial pressure, it failed to decrease pulmonary vascular resistance in these patients with hypoxic pulmonary hypertension, nor were there any changes in breathing frequency, minute ventilation, or pulmonary gas exchange compared with controls.[168]

Angiotensin II, type I, receptor blockade attenuates the pulmonary vasoconstrictive response of acute hypoxia in normal subjects.[169] This has led to studies of the efficacy of these drugs in patients with COPD and pulmonary hypertension, but with normal left ventricular systolic function. In an acute study evaluating the response to losartan, an angiotensin II receptor blocker, after at least 1 week of therapy, nine patients with COPD had a significant reduction in both mean P_{PA} and total pulmonary vascular resistance; this was associated with a significantly lower plasma aldosterone level compared with patients receiving placebo. Although losartan produced its maximal effects 4 hours after administration, it did not alter oxygen saturation in patients with hypoxemic cor pulmonale.

The inconsistency in results with ACE inhibition may reflect the small size and short duration of the studies, as well as variations in inclusion criteria. In the study by Kiely and associates,[169] all patients had documented pulmonary vascular reactivity as assessed by a significant fall in P_{PA} in response to acute oxygen administration. It is possible that there are other patients in whom failure to demonstrate such vascular reactivity to 100% oxygen would result in a failure to demonstrate benefit from the use of an angiotensin II receptor blocker or ACE inhibitor. At present, there would appear to be no routine role for these agents in COPD. Whether ultimately there may be therapeutic value for their use in patients with cor pulmonale and pulmonary hypertension awaits the results of larger, randomized, double-blind clinical trials.

Natriuretic Peptides

In patients with COPD, infusion of ANP has been shown to reduce P_{PA} and increase the cardiac index.[170] Both ANP and BNP infusions have been shown to produce dose-related pulmonary vasodilation in patients with cor pulmonale without worsening arterial oxygen saturation or affecting systemic hemodynamics. Both agents suppress aldosterone production, and BNP has been demonstrated to suppress ET-1 levels.[68,171] There is no information to date on the long-term safety or efficacy of natriuretic peptides or neutral endopeptidase inhibitors that prevent natriuretic peptide degradation in cor pulmonale.

Nonglycoside Inotropes

Figure 56-11 delineates a suggested approach to the management of acute decompensated right ventricular failure in pulmonary arterial hypertension.[98] In the setting of severe acute right ventricular decompensation with hypoperfusion, low-dose intravenous infusion of dopamine and dobutamine (1 to 2 mg/kg/min) may improve cardiac output, blood pressure, and renal perfusion. Oxygen and dopamine have been shown to be equipotent renal vasodilators in hypoxic COPD. Low-dose dopamine infusion (2 to 5 mg/kg/min) can increase cardiac output, reduce pulmonary vascular resistance, and improve oxygen delivery.[172] Higher infusions of dopamine (10 mg/kg/min) have been shown to increase diaphragmatic blood flow and contraction.[173] Although they are effective in acute decompensated right ventricular failure, the value of these agents or of chronic oral phosphodiesterase isoform III inhibitors in chronic cor pulmonale is yet to be determined.

Surgery

The role of lung volume-reduction surgery in severe emphysema[174] is covered in Chapter 39, and that of lung and heart transplantation in cor pulmonale is covered in detail in Chapter 95. Lung transplantation is generally

reserved for suitable candidates who continue to be highly symptomatic despite optimal medical therapy and will derive a significant improvement in quality of life from the procedure. The first-year survival following lung transplantation is approximately 65% to 70% and the 5-year survival is approximately 50%, being largely limited by the development of bronchiolitis obliterans.[175]

Atrial Septostomy

Patients with idiopathic pulmonary arterial hypertension and a patent foramen ovale demonstrate a better survival compared to similar patients without a patent foramen ovale.[176] As a result, atrial septostomy, which involves the creation of a perforation in the atrial septum by use of a catheter-based blade, followed by graded balloon inflation across the atrial perforation, has been utilized in carefully selected patients with severe right-sided heart failure and recurrent syncope.[177,178] This technique increases the right-to-left shunt through the atrial communication, decreases right atrial pressure, and increases left ventricular filling, thereby decompressing the right ventricle and improving cardiac output. Atrial septostomy can reduce syncope and improve exercise performance. However, this procedure is limited by resultant arterial oxygen desaturation, frequent closure of the atrial septal communication, and the potential for paradoxical emboli. It is also associated with a high procedure-related mortality rate. Therefore, this investigational technique should be performed only by experienced operators when other options are not available or are inappropriate, or to serve as a bridge to lung transplantation.[179]

Percutaneous blade-balloon septostomy has not been studied in patients with cor pulmonale in association with other disorders of the respiratory system. The arterial hypoxemia resulting from this procedure can be life-threatening, especially in this population, mitigating any potential beneficial effects on cardiopulmonary hemodynamics.

NATURAL HISTORY

Any advanced lung disease can be associated with pulmonary hypertension and eventual potential progression to right heart failure. In a study of 374 patients with advanced lung disease referred for lung transplantaion 25% had pulmonary hypertension by right heart catheterization.[92] A study of 176 consecutive patients evaluated circulating BNP concentrations and severity of pulmonary hypertension in patients with various chronic lung diseases with a mean follow-up of 1 year.[24] Right heart catheterization, pulmonary function testing, and a 6-minute walk test were performed. Significant pulmonary arterial hypertension (mean PPA >35 mm Hg) was identified in approximately one fourth of all patients (31.8% of patients with ILD) and resulted in reduced exercise capacity and survival. Elevated BNP levels identified significant pulmonary hypertension and predicted mortality, serving as a risk factor of death independent of pulmonary functional impairment or hypoxemia.[24] COPD is the cause of chronic cor pulmonale in more than 80% of all cases.[180] Therefore, the natural history of cor pulmonale reflects the natural history of COPD. The American Thoracic Society reported that the death rate in 1991 from COPD was 18.6 per 100,000 persons, resulting in its ranking as the fourth leading cause of death. This represented a rise of 32.9% from 1979. In the United States, cor pulmonale accounts for approximately 80,000 deaths per year.[181]

Patients with COPD may or may not have pulmonary hypertension at rest. Furthermore, the progression of pulmonary hypertension in COPD is slow.[5] Among patients who are found to have normal pressures at rest, changes in pulmonary hemodynamics are frequently minimal over time. For example, in a group of 61 patients without initial pulmonary arterial hypertension, all of whom had arterial hypoxemia, a second cardiac catheterization on average 93.4 months later revealed an average change in mean PPA from 15.5 ± 2.4 to 19.6 ± 7.0 mm Hg.[182] In a second group of 32 patients who had pulmonary hypertension on their first catheterization, there was a nonsignificant rise in mean PPA, from 27.7 ± 6.0 to 31.0 ± 9.3 mm Hg, after an average delay of 60 months.[183] Hemodynamic worsening, defined as an increase of 5 mm Hg or more, occurred in approximately one third of patients and was clearly related to worsening of hypoxemia. Mortality in the group with hemodynamic worsening was significantly higher than in those with stable hemodynamics. Now, there is no doubt that the development of cor pulmonale worsens overall prognosis and increases long-term mortality.[184]

A long-term survival experience for COPD in a group who initially required hospitalization and who were in the age range of 50 to 54 years was reported from Finland.[185] Among 2727 new COPD patients, the estimated cumulative survival rate for men with COPD after 10 years was 60.1%, and for women it was 78.0%. However, the primary cause of death among patients initially hospitalized with COPD was ultimately COPD in only 22.1% of cases, with other causes such as coronary artery disease playing a prominent role. Nevertheless, it is clear that the prognosis for COPD patients in their 50s who require hospital treatment is poor.

Prognostic factors in COPD patients receiving long-term oxygen therapy have been analyzed by Oswald-Mammosser and colleagues.[186] Eighty-four patients underwent right-sided heart catheterization before institution of long-term oxygen therapy. These patients had a mean age of 63 years; they had a persistent arterial P_{O_2} of less than 55 mm Hg or an arterial P_{O_2} between 55 and 60 mm Hg and either signs of cor pulmonale or a mean PPA of 25 mm Hg or greater. When actuarial survival curves were plotted with consideration of a number of variables, it was found that the 5-year survival rate for patients with an initial mean PPA of 25 mm Hg or less was 62.2%, whereas it was only 36.3% in the 40 remaining patients who had an initial mean PPA higher than 25 mm Hg. Therefore, it would appear that the level of the PPA at the time a patient undergoes long-term oxygen therapy is a better prognostic indicator than are such

factors as forced expiratory volume in 1 second, the degree of hypoxemia, or the level of hypercapnia. It is also clear that pulmonary hypertension in patients with COPD is associated with increased hospitalization[187] and higher mortality rate[188] compared to COPD patients without pulmonary hypertension. Only 33% of patients with COPD and pulmonary hypertension survive 4 years after diagnosis, compared with 64% of patients without pulmonary hypertension.[189] A mean PPA of 20 to 25 mm Hg or more is associated with a poor prognosis. In one study, the 5-year survival of patients with COPD receiving long-term oxygen therapy was found to be 48%.[186]

The development of pulmonary hypertension in patients with ILD and, specifically, idiopathic pulmonary fibrosis is associated with worsening symptoms, functional impairment, and increased morbidity and mortality.[32,190–192] In a retrospective study of 136 patients with idiopathic pulmonary fibrosis, the median survival of those with estimated systolic PPA of greater than 50 mm Hg by echocardiography was less than 1 year ($p = 0.009$) compared to 4.8 years for patients without pulmonary hypertension (systolic PPA < 35 mm Hg), and 4.1 years for patients with mild pulmonary hypertension (systolic PPA 36 to 50 mm Hg).[190] In a study of 79 patients with idiopathic pulmonary fibrosis referred for lung transplantation who had a right heart catheterization, 32% (24 of 79) had pulmonary hypertension documented by a mean PPA greater than 25 mm Hg.[191] The 1-year survival rates were lower (72%) in those patients with pulmonary hypertension compared to idiopathic pulmonary fibrosis patients without pulmonary hypertension (94.5%; $p = 0.002$).[191] Furthermore, patients with pulmonary hypertension who had lower DL_{CO} values were more likely to require supplemental oxygen, and to exhibit shorter 6-minute walk test distances as well as a lower arterial oxygen saturation nadir. Five-year survival of idiopathic pulmonary fibrosis patients with pulmonary hypertension is also significantly curtailed. In one study of 78 patients with pulmonary hypertension, using a cutoff based on a receiver operating curve, the 5-year survival rate was 62% for the group ($n = 37$) with mean PPA less than 17 mm Hg compared to 16.7% for the group ($n = 24$) with mean PPA greater than 17 mm Hg ($p < 0.001$). The relative risk of death was higher at 2.20 (95% CI, 1.40 to 3.45) for the high mean PPA group.[193] According to an analysis of 2972 patients with advanced idiopathic pulmonary fibrosis listed for lung transplantation between 1995 and 2004, those with pulmonary hypertension were 1.62 times more likely to die after being listed for transplantation compared to those without pulmonary hypertension.[192]

Management of patients with pulmonary hypertension associated with ILD includes treating the underlying ILD, providing supplemental oxygen, and treating the right heart failure. There are no studies evaluating the efficacy of anticoagulation in this condition. Vasomodulating therapy for pulmonary hypertension in ILD is currently under investigation in larger studies, but at this time remains an off-label use. In pulmonary hypertension with ILD, one must weigh the potential benefit of reducing right ventricular afterload to alleviate symptoms and improve exercise capacity, quality of life, and morbidity and mortality versus the potential risks of worsening hypoxemia from increased ventilation-perfusion mismatch and acute pulmonary edema in cases of ILD associated with pulmonary veno-occlusive disease. Lung transplantation remains a life-saving procedure for this diagnosis.[32]

KEY POINTS

- The term *cor pulmonale* is defined by the WHO as "hypertrophy of the right ventricle resulting from diseases affecting the function and/or the structure of the lung, except when these pulmonary alterations are the result of diseases that primarily affect the left side of the heart or congenital heart disease."
- The pathogenesis of pulmonary hypertension in patients with chronic pulmonary disease involves combinations of hypoxic pulmonary vasoconstriction and pulmonary vascular remodeling related to anatomic restriction and/or obliteration of the pulmonary vascular bed from alveolar destruction, fibrosis, inflammation, thrombosis, and the effects of mitogenic mediators that are related to the specific underlying lung disease.
- Management of patients with pulmonary hypertension associated with cor pulmonale includes treating the underlying lung disease, administering supplemental oxygen, and treating right heart failure with diuretics, vasomodulating agents, and contractility agents as needed.
- Vasomodulating agents approved for the treatment of the pulmonary arterial hypertensive disorders include endothelin receptor antagonists, phosphodiesterase V inhibitors, and prostacyclin analogues; however, these agents have yet to be proven efficacious for the treatment of pulmonary hypertension associated with chronic pulmonary disease.
- Pulmonary hypertension is present in approximately 25% of patients with advanced lung disease and is associated with significantly worse symptoms and functional impairment, and with increased morbidity and mortality.

References

1. Report of an Expert Committee. Chronic cor pulmonale: Clinical progress. Circulation 27:594, 1963.
2. Rich S, Rubin LJ, Abenhail L, et al: Executive summary from the World Symposium on Primary Pulmonary Hypertension (Evian, France, September 6–10, 1998). Geneva: World Health Organization. Available at http://www.who.int/ncd/cvd/pph.html.
3. Simonneau G, Robbins I, Beghetti M, et al: Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol 54:S43–S54, 2009.
4. McGoon MD, Fuster V, Freeman WK, et al: Pulmonary hypertension. *In* Giuliani ER, Gersh BJ, McGoon MD (eds): Mayo Clinic Practice of Cardiology (3rd ed). St. Louis: Mosby, 1986, pp 1815–1836.
5. MacNee W: Pathophysiology of cor pulmonale in chronic obstructive pulmonary disease: Part one. Am J Respir Crit Care Med 150:833–852, 1994.
6. Horsfield K: Morphometry of the small pulmonary arteries in man. Circ Res 42:593–597, 1978.
7. Widimsky J: Pressure, flow and volume changes of the lesser circulation during pulmonary artery occlusion in healthy subjects and patients with pulmonary hypertension. Prog Respir Res 5:224–236, 1970.
8. Budey MM, Arroliga AC, Wiedemann NP, Matthay RA: Cor pulonale: An overview. Semin Respir Crit Care Med 24:233–244, 2003.
9. Hecht HH, Kuida H, Lange RL: Brisket disease: II. Clinical features and hemodynamic observations in altitude-dependent right heart failure in cattle. Am J Med 32:171–183, 1962.
10. Will DH, Horrell JF, Reeves JT, et al: Influence of altitude and age on pulmonary arterial pressure in cattle. Proc Soc Exp Biol Med 150:564–567, 1975.
11. Grover RF: Chronic hypoxic pulmonary hypertension. *In* Fishman AP (ed): The Pulmonary Circulation: Normal and Abnormal. Mechanisms, Management, and the National Registry. Philadelphia: University of Pennsylvania Press, 1990, pp 283–299.
12. Sorli J, Grassino A, Lorange G, et al: Control of breathing in patients with chronic obstructive lung disease. Clin Sci Mol Med 54:295–304, 1978.
13. Sassoon CSH, Hassell KT, Mahutte CK: Hyperoxic-induced hypercarbia in stable chronic obstructive pulmonary disease. Am Rev Respir Dis 135:907–911, 1987.
14. Presberg KW, Dincer HE: Pathophysiology of pulmonary hypertension due to lung disease. Curr Opin Pulm Med 9:131–138, 2003.
15. Edwards J: Pulmonary hypertension of cardiac and pulmonary origins: Pathologic origins. Prog Cardiovasc Dis 9:205–226, 1966.
16. Bove EK, Scott RC: The anatomy of chronic cor pulmonale secondary to intrinsic lung disease. Prog Cardiovasc Dis 9:227–238, 1966.
17. Hopkins N, McLoughlin P: The structural basis of pulmonary hypertension in chronic lung disease: remodeling, rarefaction or angiogenesis? J Anat 201:335–348, 2002.
18. Pietra GG, Capron F, Stewart S, et al: Pathologic assessment of vasculopathies in pulmonary hypertension. J Am Coll Cardiol 43(12 Suppl S):25S–32S, 2004.
19. Strange C, Highland KB: Pulmonary hypertension in interstitial lung disease. Curr Opin Pulm Med 11:452–455, 2005.
20. Boushy SF, North LB: Hemodynamic changes in chronic obstructive pulmonary disease. Chest 72:565–570, 1977.
21. Fraser KL, Tullis DE, Sasson Z, et al: Pulmonary hypertension and cardiac function in adult cystic fibrosis: Role of hypoxemia. Chest 115:1321–1328, 1999.
22. Stevens D, Sharma K, Szidon P, et al: Severe pulmonary hypertension associated with COPD. Ann Transplant 5:8–12, 2000.
23. Scharf SM, Iqbal M, Keller C, et al: Hemodynamic characterization of patients with severe emphysema. Am J Respir Crit Care Med 166:314–322, 2002.
24. Leuchte HH, Baumgartner RA, Nounou ME, et al: Brain natriuretic peptide is a prognostic parameter in chronic lung disease. Am J Respir Crit Care Med 173:744–750, 2006.
25. Shorr AF, Wainright JL, Cors CS, et al: Pulmonary hypertension in patients with pulmonary fibrosis awaiting lung transplant. Eur Respir J 30:715–721, 2007.
26. Peinado VI, Barbera JA, Abate P, et al: Inflammatory reaction in pulmonary muscular arteries of patients with mild chronic obstructive pulmonary disease. Am J Respir Crit Care Med 159:1605–1611, 1999.
27. Santos S, Peinado VI, Ramirez J, et al: Characterization of pulmonary vascular remodeling in smokers and patients with mild COPD. Eur Respir J 19:632–638, 2002.
28. Hale KA, Ewing SL, Gosnell BA, Niewoehner DE: Lung disease in long-term cigarette smokers with and without chronic air-flow obstruction. Am Rev Respir Dis 130:716–721, 1984.
29. Kessler R, Faller M, Weitzenblum E, et al: "Natural history" of pulmonary hypertension in a series of 131 patients with chronic obstructive lung disease. Am J Respir Crit Care Med 164:219–224, 2001.
30. Gagermeier J, Dauber J, Yousem S, et al: Abnormal vascular phenotypes in patients with idiopathic pulmonary fibrosis and secondary pulmonary hypertension. Chest 128(6 Suppl):601S, 2005.
31. Hamada K, Teramoto S, Narita N, et al: Pulmonary veno-occlusive disease in pulmonary Langerhans' cell granulomatosis. Eur Respir J 15:421–423, 2000.
32. Ryu JH, Krowka MJ, Pallika PA, et al: Pulmonary hypertension in patients with interstitial lung diseases. Mayo Clin Proc 82:342–350, 2007.
33. Shorr AF, Davies DB, Nathan SD, et al: Outcomes for patients with sarcoidosis awaiting lung transplantation. Chest 122:233–238, 2002.
34. Shorr AF, Davies DB, Nathan SD, et al: Predicting mortality in patients with sarcoidosis awaiting lung transplantation. Chest 124:922–928, 2003.
35. Giaid A, Yanagisawa M, Tuder RM, et al: Expression of endothelin-1 in the lungs of patients with pulmonary hypertension. N Engl J Med 328:1732–1739, 1993.
36. Giaid A, Saleh D: Reduced expression of endothelial nitric oxide synthase in the lungs of patients with pulmonary hypertension. N Engl J Med 333:214–221, 1995.
37. Presberg KW, Dincer HE: Pathophysiology of pulmonary hypertension due to lung disease. Curr Opin Pulm Med 9:131–138, 2003.
38. Nathan SD, Noble PW, Steen V, et al: Idiopathic pulmonary fibrosis and pulmonary hypertension: Connecting the dots. Am J Respir Crit Care Med 175:875–880, 2007.
39. Behr J, Ryu JH: Pulmonary hypertension in interstitial lung disease. Eur Respir J 31:1357–1367, 2008.
40. Rapaport E, Wong M, Ferguson RE, et al: Right ventricular volumes in patients with and without heart failure. Circulation 31:531–541, 1965.
41. Rapaport E, Wong M, Escobar EE, et al: The effect of upright posture on right ventricular volumes in patients with and without heart failure. Am Heart J 71:146–152, 1966.
42. Klinger JR, Hill NS: Right ventricular dysfunction in chronic obstructive pulmonary disease. Chest 99:715–723, 1991.
43. Matthay RA, Berger HJ, Davies RA, et al: Right and left ventricular exercise performance in chronic obstructive pulmonary disease: Radionuclide assessment. Ann Intern Med 93:234–239, 1980.
44. Missov E, De Marco T: Cor pulmonale. Curr Treat Options Cardiovasc Med 2:149–158, 2000.
45. Krayenbuehl HP, Turnia J, Hess O: Left ventricular function in chronic pulmonary hypertension. Am J Cardiol 41:1150–1158, 1978.
46. Tutar E, Kaya A, Gèulec S, et al: Echocardiographic evaluation of left ventricular diastolic function in chronic cor pulmonale. Am J Cardiol 83:1414–1417, 1999.
47. Vizza CD, Lynch JP, Ochoa LL, et al: Right and left ventricular dysfunction in patients with severe pulmonary disease. Chest 113:576–583, 1998.
48. Schena M, Clini E, Errera D, et al: Echo-Doppler evaluation of left ventricular impairment in chronic cor pulmonale. Chest 109:1446–1451, 1996.
49. Watanabe J, Levine MJ, Bellotto F, et al: Effects of coronary venous pressure on left ventricular diastolic distensibility. Circ Res 67:923–932, 1990.

50. Anand IS, Chandrashekhar Y, Ferrari R, et al: Pathogenesis of congestive state in chronic obstructive pulmonary disease. Circulation 86:12–21, 1992.
51. Gunaydin S, Imai Y, Takanashi Y, et al: The effects of vasoactive intestinal peptide on monocrotaline induced pulmonary hypertensive rabbits following cardiopulmonary bypass: A comparative study with isoproterenol and nitroglycerine. Cardiovasc Surg 10:138–145, 2002.
52. Greenberg B, Rhoden K, Barnes PJ: Relaxant effects of vasoactive intestinal peptide and peptide histidine isoleucine in human and bovine pulmonary arteries. Blood Vessels 24:45–50, 1987.
53. Iwabuchi S, Ono S, Tanita T, et al: Vasoactive intestinal peptide causes nitric oxide-dependent pulmonary vasodilation in isolated rat lung. Respiration 64:54–58, 1997.
54. Soderman C, Eriksson LS, Juhlin-Dannfelt A, et al: Effect of vasoactive intestinal polypeptide (VIP) on pulmonary ventilation-perfusion relationships and central haemodynamics in healthy subjects. Clin Physiol 13:677–685, 1993.
55. Cox CP, Linden J, Said SI: VIP elevates platelet cyclic AMP (cAMP) levels and inhibits in vitro platelet activation induced by platelet-activating factor (PAF). Peptides 5:325–328, 1984.
56. Maruno K, Absood A, Said SI: VIP inhibits basal and histamine-stimulated proliferation of human airway smooth muscle cells. Am J Physiol 268:L1047–L1051, 1995.
57. Petkov V, Mosgoeller W, Ziesche R, et al: Vasoactive intestinal peptide as a new drug for treatment of primary pulmonary hypertension. J Clin Invest 111:1339–1346, 2003.
58. MacNee W: Pathophysiology of cor pulmonale in chronic obstructive pulmonary disease: Part two. Am J Respir Crit Care Med 150:1158–1168, 1994.
59. Lipworth BJ, Dagg KD: Vasoconstrictor effects of angiotensin II on the pulmonary vascular bed. Chest 105:1360–1364, 1994.
60. Cargill RI, Lipworth BJ: Lisinopril attenuates acute hypoxic pulmonary vasoconstriction in humans. Chest 109:424–429, 1996.
61. Lang CC, Coutie WJ, Struthers AD, et al: Elevated levels of brain natriuretic peptide in acute hypoxaemic chronic obstructive pulmonary disease. Clin Sci 85:529–533, 1992.
62. Cargill RI, Barr CS, Coutie WJ: C-type natriuretic peptide levels in cor pulmonale and in congestive heart failure. Thorax 49:1247–1249, 1994.
63. Zhao L, Hughes JM, Winter RJ: Effects of natriuretic peptides and neutral endopeptidase inhibition in isolated perfused rat lung. Am Rev Respir Dis 146:1198–1201, 1992.
64. Nagaya N, Nishikimi T, Okano Y, et al: Plasma brain natriuretic peptide levels increase in proportion to the extent of right ventricular dysfunction in pulmonary hypertension. J Am Coll Cardiol 31:202–208, 1998.
65. Nagaya N, Nishikimi T, Uematsu M, et al: Plasma brain natriuretic peptide as a prognostic indicator in patients with primary pulmonary hypertension. Circulation 102:865–870, 2000.
66. Adnot S, Andrivet P, Chabrier PE, et al: Atrial natriuretic factor in chronic obstructive lung disease. J Clin Invest 83:986–993, 1989.
67. Cargill RI, Lipworth BJ: Atrial natriuretic peptide and brain natriuretic peptide in cor pulmonale. Chest 110:1220–1225, 1996.
68. Aronson D, Burger AJ: Intravenous nesiritide (human B-type natriuretic peptide) reduces plasma endothelin-1 levels in patients with decompensated congestive heart failure. Am J Cardiol 90:435–438, 2002.
69. Thompson JS, Morice AH: Neutral endopeptidase inhibitors and the pulmonary circulation. Gen Pharmacol 27:581–585, 1996.
70. Dupuis J: Endothelin-receptor antagonists in pulmonary hypertension. Lancet 358:1113–1114, 2001.
71. Giaid A, Yanagisawa M, Langleben D, et al: Expression of endothelin-1 in the lungs of patients with pulmonary hypertension. N Engl J Med 328:1732–1739, 1993.
72. Stewart DJ, Levy RD, Cernacek P, Langleben D: Increased plasma endothelin-1 in pulmonary hypertension: Marker or mediator of disease? Ann Intern Med 114:464–469, 1991.
73. Morelli S, Ferri C, Polettini E, et al: Plasma endothelin-1 levels, pulmonary hypertension, and lung fibrosis in patients with systemic sclerosis. Am J Med 99:255–260, 1995.
74. Kaur S, Frishman WH, Singh I, et al: Endothelin as a therapeutic target in the treatment of cardiovascular disease. Heart Dis 3:176–188, 2001.
75. Galie N, Grigrioni F, Bacchi-Reggiani L: Relation of endothelin-1 to survival in patients with primary pulmonary hypertension. Eur J Clin Invest 26:A48, 2001.
76. Chalmers GW, Macleod KJ, Sriram S, et al: Sputum endothelin-1 is increased in cystic fibrosis and chronic obstructive pulmonary disease. Eur Respir J 13:1288–1292, 1999.
77. Sofia M, Mormile M, Faraone S, et al: Increased 24-hour endothelin-1 urinary excretion in patients with chronic obstructive pulmonary disease. Respiration 61:263–268, 1994.
78. Faller M, Kessler R, Sapin R, et al: Regulation of endothelin-1 at rest and during a short steady-state exercise in 21 COPD patients. Pulm Pharmacol Ther 11:151–157, 1998.
79. Trakada G, Marangos M, Spiropoulos K: Mechanisms of endothelin-1 elevation in chronic obstructive pulmonary disease patients with nocturnal oxyhemoglobin desaturation. Respiration 68:134–139, 2001.
80. Celik G, Karabiyikoglu G: Local and peripheral plasma endothelin-1 in pulmonary hypertension secondary to chronic obstructive pulmonary disease. Respiration 65:289–294, 1998.
81. Uguccioni M, Pulsatelli L, et al: Endothelin-1 in idiopathic pulmonary fibrosis. J Clin Pathol 48:330–334, 1995.
82. Shih H-T, Webb CR, Conway WA: Frequency and significance of cardiac arrhythmias in chronic obstructive lung disease. Chest 94:44–48, 1988.
83. Matthay RA, Schwartz MI, Ellis JH, et al: Pulmonary artery hypertension in chronic obstructive pulmonary disease: Chest radiographic assessment. Invest Radiol 16:95–100, 1981.
84. Staub NC, Wiener-Kronish JP, Albertine KH: Transport through the pleura: Physiology of normal liquid and solute exchange in the pleural space. *In* Chrétien J, Bignon J, Hirsch A (eds): The Pleura in Health and Disease. New York: Marcel Dekker, 1985, pp 169–193.
85. Wiener-Kronish JP, Matthay MA, Callen PW: Relationship of pleural effusions to pulmonary hemodynamics in patients with congestive heart failure. Am Rev Respir Dis 132:1253–1256, 1985.
86. Wiener-Kronish JP, Goldstein R, Matthay RA, et al: Lack of association of pleural effusion with chronic pulmonary arterial and right atrial hypertension. Chest 92:967–970, 1987.
87. Jensen R, Pierson RE, Braddy PM, et al: Brisket disease in yearling feedlot cattle. J Am Vet Med Assoc 169:515–517, 1976.
88. Phillips RW: The electrocardiogram in cor pulmonale secondary to pulmonary emphysema: A study of 18 cases proved by autopsy. Am Heart J 56:352–371, 1958.
89. Incalzi RA, Fuso L, De Rosa M, et al: Electrocardiographic signs of chronic cor pulmonale: A negative prognostic finding in chronic obstructive pulmonary disease. Circulation 99:1600–1605, 1999.
90. McGoon M, Gutterman D, Steen V, et al: Screening, early detection, and diagnosis of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. Chest 126(1 Suppl):14S–34S, 2004.
91. Schenk P, Globits S, Koller J, et al: Accuracy of echocardiographic right ventricular parameters in patients with different end-stage lung diseases prior to lung transplantation. J Heart Lung Transplant 19:145–154, 2000.
91a. Forfia PR, Fisher MR, Mathai SC, et al: Tricuspid annular displacement predicts survival in pulmonary hypertension. Am J Respir Crit Care Med 174:1034–1041, 2006.
91b. Yeo TC, Dujardin KS, Tei C, et al: Value of a Dopper-derived index combining systolic and diastolic time intervals in predicting outcome in primary pulmonary hypertension. Am J Cardiol 81:1157–1161, 1998.
92. Arcasoy SM, Christie JD, Ferrari VA, et al: Echocardiographic assessment of pulmonary hypertension in patients with advanced lung disease. Am J Respir Crit Care Med 167:735–740, 2003.
93. Nathan SD, Shlobin OA, Barnett SD, et al: Right ventricular systolic pressure by echocardiography as a predictor of pulmonary hypertension in idiopathic pulmonary fibrosis. Respir Med 102:1305–1310, 2008.
94. Zisman DA, Karlamangla AS, Ross DJ, et al: High-resolution chest CT findings do not predict the presence of pulmonary hypertension in advanced idiopathic pulmonary fibrosis. Chest 132:773–779, 2007.

95. Lorenz CH, Walker ES, Morgan VL, et al: Normal human right and left ventricular mass, systolic function, and gender differences by cine magnetic resonance imaging. J Cardiovasc Magn Reson 1:7–21, 1999.
96. Murphy ML, Dinh H, Nicholson D: Chronic cor pulmonale. Dis Mon 35:663–718, 1989.
97. Bristow JD, Morris JF, Kloster FE: Hemodynamics of cor pulmonale. Prog Cardiovasc Dis 9:239–258, 1966.
97a. Galie N, Hoeper MM, Humbert M, et al: Guidelines for the diagnosis and treatment of pulmonary hypertension. The task force for the diagnosis and treatment of pulmonary hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). Eur Respir J 34:1219–1263, 2009.
98. De Marco T, McGlothlin D: Managing right ventricular failure in PAH: An algorithmic approach. Adv Pulm Hypertens 4:16–26, 2005.
99. Haddad F, Doyle R, Murphy DJ, Hunt SA: Right ventricular function in cardiovascular disease, part II: Pathophysiology, clinical importance, and management of right ventricular failure. Circulation 117:1717–1731, 2008.
100. Saroea HG: Chronic obstructive pulmonary disease: Major objectives of management. Postgrad Med 94:113–116, 121–122, 1993.
101. Rich S, Kaufmann E, Levy PS: The effect of high doses of calcium-channel blockers on survival in primary pulmonary hypertension. N Engl J Med 327:76–81, 1992.
102. Rich S, Seidlitz M, Dodin E, et al: The short-term effects of digoxin in patients with right ventricular dysfunction from pulmonary hypertension. Chest 114:787–792, 1998.
103. Ferrer MI, Harvey RM, Cathcart RT, et al: Some effects of digoxin upon the heart and circulation in man: Digoxin in chronic cor pulmonale. Circulation 1:161–186, 1950.
104. MacNee W, Wathen CG, Hannan WJ, et al: Effects of pirbuterol and sodium nitroprusside on pulmonary haemodynamics in hypoxic cor pulmonale. Br Med J (Clin Res Ed) 287:1169–1172, 1983.
105. He J, Kryger MH, Zorick FJ, et al: Mortality and apnea index in obstructive sleep apnea: Experience in 385 male patients. Chest 94:9–14, 1988.
106. Partinen M, Jamieson A, Guilleminault C: Long-term outcome for obstructive sleep apnea syndrome patients: Mortality. Chest 94:1200–1204, 1988.
107. Krieger J, Sforza E, Barthelmebs M, et al: Overnight decrease in hematocrit after nasal CPAP treatment in patients with OSA. Chest 97:729–730, 1990.
108. Tsagaris TJ, Sutton RB, Anderson FL: Effect of phlebotomy on coronary blood flow in calves with brisket disease. Proc Soc Exp Biol Med 142:560–563, 1973.
109. Rich S, Martinez J, Lam W, Rosen KM: Captopril as treatment for patients with pulmonary hypertension: Problem of variability in assessing chronic drug treatment. Br Heart J 48:272–277, 1982.
110. Stuart-Harris C, Flenley DC, Bishop JH, et al: Report of the Medical Research Council Working Party: Long-term domiciliary oxygen therapy in chronic cor pulmonale complicating chronic bronchitis and emphysema. Lancet 1:681–686, 1981.
111. Nocturnal Oxygen Therapy Trial Group: Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: A clinical trial. Ann Intern Med 93:391–398, 1980.
112. Reihman DH, Farber MO, Weinberger MH, et al: Effect of hypoxemia on sodium and water excretion in chronic obstructive lung disease. Am J Med 78:87–94, 1985.
113. Gassner A, Sommer G, Fridrich L, et al: Differential therapy with calcium antagonists in pulmonary hypertension secondary to COPD. Chest 98:829–834, 1990.
114. Weinberger SE, Schwartzstein RM, Weiss JW: Hypercapnia. N Engl J Med 321:1223–1231, 1989.
115. Barbera JA, Roger N, Roca J, et al: Worsening of pulmonary gas exchange with nitric oxide inhalation in chronic obstructive pulmonary disease. Lancet 347:436–440, 1976.
116. Yoshida M, Taguchi O, Gabazza EC, et al: Combined inhalation of nitric oxide and oxygen in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 155:526–529, 1997.
117. Archer SL, Mike D, Crow J, et al: A placebo-controlled trial of prostacyclin in acute respiratory failure in COPD. Chest 109:750–755, 1996.
118. Sajkov D, McEvoy RD, Cowie RJ, et al: Felodipine improves pulmonary hemodynamics in chronic obstructive pulmonary disease. Chest 103:1354–1361, 1993.
119. Sajkov D, Wang T, Frith PA, et al: A comparison of two long-acting vasoselective calcium antagonists in pulmonary hypertension secondary to COPD. Chest 111:1622–1630, 1997.
120. Archibald CJ, Auger WR, Fedullo PF, et al: Long-term outlook after pulmonary thromboendarterectomy. Am J Respir Crit Care Med 160:523–528, 1999.
121. Channick RN, Simonneau G, Sitbon O, et al: Effects of the dual endothelin-receptor antagonist bosentan in patients with pulmonary hypertension: A randomised placebo-controlled study. Lancet 358:1119–1123, 2001.
122. Rubin LJ, Badesch DB, Barst RJ, et al: Bosentan therapy for pulmonary arterial hypertension. N Engl J Med 346:896–903, 2002.
123. Galie N, Olschewski H, Oudiz RJ, et al: Ambrisentan for the treatment of pulmonary arterial hypertension: Results of the ambrisentan in pulmonary arterial hypertension, randomized, double-blind, placebo-controlled, multicenter, efficacy (ARIES) study 1 and 2. Circulation 117:3010–3019, 2008.
124. Badesch DB, Orton C, Zapp LM, et al: Decreased arterial wall prostaglandin production in neonatal calves with severe chronic pulmonary hypertension. Am J Respir Cell Mol Biol 1:489–498, 1989.
125. Richalet J-P, Hornych A, Rathat C, et al: Plasma prostaglandins, leukotrienes and thromboxane in acute high altitude hypoxia. Respir Physiol 85:205–215, 1991.
126. Tuder RM, Cool CD, Geraci MW, et al: Prostacyclin synthase expression is decreased in lungs from patients with severe pulmonary hypertension. Am J Respir Crit Care Med 159:1925–1932, 1999.
127. Friedman R, Mears JG, Barst RJ: Continuous infusion of prostacyclin normalizes plasma markers of endothelial cell injury and platelet aggregation in primary pulmonary hypertension. Circulation 96:2782–2784, 1997.
128. Rubin LJ, Mendoza J, Hood M, et al: Treatment of primary pulmonary hypertension with continuous intravenous prostacyclin (epoprostenol). Ann Intern Med 112:485–491, 1990.
129. Barst RJ, Rubin LJ, Long WA, et al: A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. N Engl J Med 334:296–301, 1996.
130. Shapiro SM, Oudiz RJ, Cao T, et al: Primary pulmonary hypertension: Improved long-term effects and survival with continuous intravenous epoprostenol infusion. J Am Coll Cardiol 30:343–349, 1997.
131. McLaughlin VV, Genthner DE, Panella MM, et al: Reduction in pulmonary vascular resistance with long-term epoprostenol (prostacyclin) therapy in primary pulmonary hypertension. N Engl J Med 338:273–277, 1998.
132. Badesch DB, Tapson VF, McGoon MD, et al: Continuous intravenous epoprostenol for pulmonary hypertension due to the scleroderma spectrum of disease: A randomized, controlled trial. Ann Intern Med 132:425–434, 2000.
133. Simonneau G, Barst RJ, Galie N, et al: Continuous subcutaneous infusion of treprostinil, a prostacyclin analogue, in patients with pulmonary arterial hypertension: A double-blind, randomized, placebo-controlled trial. Am J Respir Crit Care Med 165:800–804, 2002.
134. Tapson VF, Gomberg-Maitland M, McLaughlin VV, et al. Safety and efficacy of IV treprostinil for pulmonary arterial hypertension: A prospective multi-center, open-label, 12-week trial. Chest 129:683–688, 2006.
135. Olschewski H, Simonneau G, Galie N, et al: Inhaled iloprost for severe pulmonary hypertension. N Engl J Med 347:322–329, 2002.
136. McLaughlin VV, Oudiz RJ, Frost A, et al: Randomized study of adding inhaled iloprost to existing bosentan in pulmonary arterial hypertension. Am J Respir Crit Care Med 174:1257–1263, 2006.
137. Olschewski H, Ghofrani HA, Walmrath D, et al: Inhaled prostacyclin and iloprost in severe pulmonary hypertension secondary to lung fibrosis. Am J Respir Crit Care Med 160:600–607, 1999.

138. Prasad S, Wilkinson J, Gatzoulis MA: Sildenafil in primary pulmonary hypertension. N Engl J Med 343:1342, 2000.
139. Kleinsasser A, Loeckinger A, Hoermann C, et al: Sildenafil modulates hemodynamics and pulmonary gas exchange. Am J Respir Crit Care Med 163:339–343, 2001.
140. Michelakis E, Tymchak W, Lien D, et al: Oral sildenafil is an effective and specific pulmonary vasodilator in patients with pulmonary arterial hypertension: Comparison with inhaled nitric oxide. Circulation 105:2398–2403, 2002.
141. Ghofrani HA, Wiedemann R, Rose F, et al: Sildenafil for treatment of lung fibrosis and pulmonary hypertension: A randomised controlled trial. Lancet 360:895–900, 2002.
142. Ghofrani HA, Rose F, Schermuly RT, et al: Oral sildenafil as long-term adjunct therapy to inhaled iloprost in severe pulmonary arterial hypertension. J Am Coll Cardiol 42:158–164, 2003.
143. Watanabe H, Ohashi K, Takeuchi K, et al: Sildenafil for primary and secondary pulmonary hypertension. Clin Pharmacol Ther 71:398–402, 2002.
144. Ghofrani HA, Wiedemann R, Rose F, et al: Combination therapy with oral sildenafil and inhaled iloprost for severe pulmonary hypertension. Ann Intern Med 136:515–522, 2002.
145. Erickson S, Reyes J, Bohn D, Adatia I: Sildenafil (Viagra) in childhood and neonatal pulmonary hypertension. J Am Coll Cardiol 39:402A, 2002.
146. Abrams D, Schulze-Neick I, Magee AG: Sildenafil as a selective pulmonary vasodilator in childhood primary pulmonary hypertension. Heart 84:E4, 2000.
147. Ghofrani HA: Efficacy and safety of sildenafil citrate in pulmomonary arterial hypertension: Results of a multinational randomized, double-blind, placebo-controlled trial (sildenafil use in pulmonary arterial hypertension study SUPER-1). Paper presented at 70th Annual International Scientific Meeting of the American College of Chest Physicians, Seattle, Washington, 2004.
148. Simmoneau G, Rubin LJ, Galie N, et al: Safety and efficacy of sildenafil-epoprostenol combination therapy in patients with pulmonary arterial hypertension. Am J Respir Crit Care Med 175:A300, 2007.
149. Ghofrani HA, Wiedemann R, Rose F, et al: Sildenafil for treatment of lung fibrosis and pulmonary hypertension: A randomized controlled trial. Lancet 360:895–900, 2002.
150. Collard HR, Anstrom KJ, Schwarz MI, Zisman DA: Sildenafil improves walk distance in idiopathic pulmonary fibrosis. Chest 131:897–899, 2007.
150a. Galie N, Brundage BH, Ghofrani HA, et al: Tadalafil therapy for pulmonary arterial hypertension. Circulation 119:2894–2903, 2009.
151. Rimar S, Gillis CN: Selective pulmonary vasodilation by inhaled nitric oxide is due to hemoglobin inactivation. Circulation 88:2884–2887, 1993.
152. Zapol WM, Rimar S, Gillis N, et al: Nitric oxide and the lung. Am J Respir Crit Care Med 149:1375–1380, 1994.
153. Nong Z, Hoylaerts M, Van Pelt N, et al: Nitric oxide inhalation inhibits platelet aggregation and platelet-mediated pulmonary thrombosis in rats. Circ Res 81:865–869, 1997.
154. Hart CM: Nitric oxide in adult lung disease. Chest 115:1407–1417, 1999.
155. Stamler JS, Singel J, Loscaizo J: Biochemistry of nitric oxide and its redox-activated forms. Science 258:1898–1902, 1992.
156. Frostell CG, Blomqvist H, Hedenstierna G, et al: Inhaled nitric oxide selectively reverses human hypoxic pulmonary vasoconstriction without causing systemic vasodilation. Anesthesiology 78:427–435, 1993.
157. Johns RA: EDRF/Nitric oxide: The endogenous nitrovasodilator and a new cellular messenger. Anesthesiology 75:927–931, 1991.
158. Dinh-Xuan AT, Higenbotham TW, Clelland CA, et al: Impairment of endothelium-dependent pulmonary-artery relaxation in chronic obstructive lung disease. N Engl J Med 324:1539–1547, 1991.
159. Frostell C, Fratacci M-D, Wain J-C: Inhaled nitric oxide: A selective pulmonary vasodilator reversing hypoxic pulmonary vasoconstriction. Circulation 83:2038–2047, 1991.
160. Al-Ali MK, Howarth PH: Nitric oxide and the respiratory system in health and disease. Respir Med 92:702–715, 1998.
161. Dinh-Xuan AT: Endothelial modulation of pulmonary vascular tone. Eur Respir J 5:757–762, 1992.
162. Roberts JD, Polaner DM, Lang P, et al: Inhaled nitric oxide in persistent pulmonary hypertension of the newborn. Lancet 340:818–819, 1992.
163. Kinsella JP, Neish SR, Shaffer E, et al: Low-dose inhalational nitric oxide in persistent pulmonary hypertension of the newborn. Lancet 340:819–820, 1992.
164. Pelouch V, Kolar F, Ost'adal B, et al: Regression of chronic hypoxia-induced pulmonary hypertension, right ventricular hypertrophy, and fibrosis: Effect of enalapril. Cardiovasc Drugs Ther 11:177–185, 1997.
165. Nong Z, Stassen JM, Moons L, et al: Inhibition of tissue angiotensin-converting enzyme with quinapril reduces hypoxic pulmonary hypertension and pulmonary vascular remodelling. Circulation 94:1941–1947, 1996.
166. Kiely DG, Cargill RI, Lipworth BJ: Angiotensin II receptor blockade and effects on pulmonary hemodynamics and hypoxic pulmonary vasoconstriction in humans. Chest 110:698–703, 1996.
167. Mahajan SK, Sharma VK, Thakral S: Effect of enalapril on renal profile and right ventricular dimensions in chronic cor pulmonale. J Assoc Physicians India 44:323–324, 1996.
168. Zielinski J, Hawrylkiewicz I, Gorecka D, et al: Captopril effects on pulmonary and systemic hemodynamics in chronic cor pulmonale. Chest 90:562–565, 1986.
169. Kiely DG, Cargill RI, Wheeldon NM, et al: Haemodynamic and endocrine effects of type 1 angiotensin II receptor blockade in patients with hypoxaemic cor pulmonale. Cardiovasc Res 33:201–208, 1997.
170. Adnot S, Andrivet P, Chabrier PE, et al: Atrial natriuretic factor in chronic obstructive lung disease with pulmonary hypertension: Physiological correlates and response to peptide infusion. J Clin Invest 83:986–993, 1989.
171. Cargill RI, Lipworth BJ: Atrial natriuretic peptide and brain natriuretic peptide in cor pulmonale: Hemodynamic and endocrine effects. Chest 110:1220–1225, 1996.
172. Howes TQ, Deane CR, Levin GE, et al: The effects of oxygen and dopamine on renal and aortic blood flow in chronic obstructive pulmonary disease with hypoxemia and hypercapnia. Am J Respir Crit Care Med 151:378–383, 1995.
173. Chan TY: Low-dose dopamine in severe right heart failure and chronic obstructive pulmonary disease. Ann Pharmacother 29:493–496, 1995.
174. Cooper JD, Patterson GA: Lung volume reduction surgery for severe emphysema. Semin Thorac Cardiovasc Surg 8:52–60, 1996.
175. International Society of Heart and Lung Transplantation: ISHLT Lung Transplant Registry Slides 2004. Available at http://www.ishlt.org (accessed December 13, 2004).
176. Rozkovec A, Montanes P, Oakley CM: Factors that influence the outcome of primary pulmonary hypertension. Br Heart J 55:449–458, 1986.
177. Rich S, Dodin E, McLaughlin VV: Usefulness of atrial septostomy as a treatment for primary pulmonary hypertension and guidelines for its application. Am J Cardiol 80:369–371, 1997.
178. Sandoval J, Gaspar J, Pulido T, et al: Graded balloon dilation atrial septostomy in severe primary pulmonary hypertension: A therapeutic alternative for patients nonresponsive to vasodilator treatment. J Am Coll Cardiol 32:297–304, 1998.
179. Rothman A, Beltran D, Kriett JM, et al: Graded balloon dilation atrial septostomy as a bridge to lung transplantation in pulmonary hypertension. Am Heart J 125:1763–1766, 1993.
180. Vance JW: Management of patients with cor pulmonale—acute and chronic. Prog Cardiovasc Dis 9:470–483, 1967.
181. American Thoracic Society: Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 152(Suppl):S77–S120, 1995.
182. Weitzenblum E, Sautegeau A, Ehrhart M, et al: Long-term course of pulmonary arterial pressure in chronic obstructive pulmonary disease. Am Rev Respir Dis 130:993–998, 1984.
183. Weitzenblum E, Loiseau A, Hirth C, et al: Course of pulmonary hemodynamics in patients with chronic obstructive pulmonary disease. Chest 75:656–662, 1979.

184. Han MK, McLaughlin VV, Criner GJ, Martinez FJ: Pulmonary diseases and the heart. Circulation 116:2992–3005, 2007.
185. Keistinen T, Tuuponen T, Kivela S-L: Survival experience of the population needing hospital treatment for asthma or COPD at age 50–54 years. Respir Med 92:568–572, 1998.
186. Oswald-Mammosser M, Weitzenblum E, Quiox E, et al: Prognostic factors in COPD patients receiving long-term oxygen therapy: Importance of pulmonary artery pressure. Chest 107:1193–1198, 1995.
187. Kessler R, Faller M, Fourgaut G, et al: Predictive factors of hospitalization for acute exacerbation in a series of 64 patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 159:158–164, 1999.
188. Dallari R, Barozzi G, Pinelli G, et al: Predictors of survival in subjects with chronic obstructive pulmonary disease treated with long-term oxygen therapy. Respiration 61:8–13, 1994.
189. Scharf SM: Pulmonary heart disease. *In* Baum GL, Crapo JD, Celli BR (eds): Textbook of Pulmonary Heart Disease. Philadelphia: Lippincott-Raven, 1998, pp 1311–1326.
190. Nadrous HF, Pellikka PA, Krowka MJ, et al: The impact of pulmonary hypertension on survival in patients with idiopathic pulmonary fibrosis. Chest 128:2393–2399, 2005.
191. Lettieri CJ, Nathan SD, Barnett SD, et al: Prevalence and outcomes of pulmonary arterial hypertension in advanced idiopathic pulmonary fibrosis. Chest 129:746–752, 2006.
192. Shorr AF, Wainright J, Lettieri C, Helman D: The impact of pulmonary hypertension on survival in patients with idiopathic pulmonary fibrosis listed for lung transplant. Chest 132:428S, 2007.
193. Hamada K, Nagai S, Tanaka S, et al: Significance of pulmonary arterial pressure and diffusion capacity of the lung as prognosticators in patients with idiopathic pulmonary fibrosis. Chest 131:650–656, 2007.

CHAPTER 57

IDIOPATHIC INTERSTITIAL PNEUMONIAS

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INTRODUCTION

CLINICAL AND HISTOLOGIC CLASSIFICATION OF INTERSTITIAL LUNG DISEASE

CLINICAL, RADIOLOGIC, AND PHYSIOLOGIC FEATURES OF INTERSTITIAL LUNG DISEASES
Past History
Symptoms
Physical Findings
Radiographic Features
Functional Assessment
Laboratory Findings
Bronchoalveolar Lavage
Histologic Diagnosis

DIAGNOSIS AND MANAGEMENT OF THE IDIOPATHIC INTERSTITIAL PNEUMONIAS
Idiopathic Pulmonary Fibrosis
Acute Exacerbations of Interstitial Pulmonary Fibrosis
Familial Pulmonary Fibrosis
Nonspecific Interstitial Pneumonia
Respiratory Bronchiolitis–Associated Interstitial Lung Disease/Desquamative Interstitial Pneumonia
Acute Interstitial Pneumonia
Cryptogenic Organizing Pneumonia
Lymphocytic Interstitial Pneumonia
Conclusion

INTRODUCTION

The term *interstitial lung disease (ILD)*, in general, implies inflammatory-fibrotic infiltration of the alveolar walls (septa) resulting in profound effects on the capillary endothelium and the alveolar epithelial lining cells (Fig. 57-1). Under normal conditions, small numbers of interstitial macrophages, fibroblasts, and myofibroblasts reside within the interstitium. Other components of the interstitium include the matrix proteins of the lung, consisting of collagen-related macromolecules and the noncollagenous proteins such as fibronectin and laminin.

In many of the ILDs, interstitial fibrosis follows injury to the gas-exchanging units. This injury increases alveolar permeability, enabling the serum contents to enter the alveolar spaces. Fibroblastic proliferation and excessive collagen deposition, the histologic hallmarks of ILD, occur either as a direct result of the injury, as a result of an inflammatory cell response that releases proinflammatory and profibrotic cytokines, or as a consequence of the regenerative and reparative processes taking place at the epithelial and endothelial surfaces. Moreover, fibroblastic proliferation and collagen accumulation also occur within airway lumina and walls of small airways (alveolar ducts, respiratory bronchioles, and terminal bronchioles).

ILDs include many entities that injure the lung parenchyma, producing diseases with similar clinical, radiographic, and physiologic features. Some occur in the setting of other conditions, such as connective tissue disease; others are idiopathic. The primary goal of the clinician is to determine if the patient does or does not have idiopathic pulmonary fibrosis (IPF)/usual interstitial pneumonia (UIP) (see later).

CLINICAL AND HISTOLOGIC CLASSIFICATION OF INTERSTITIAL LUNG DISEASE

The exact prevalence and incidence of the ILDs are unknown. Studies suggest a prevalence of 80.9/100,000 for men compared with 67.2/100,000 for women. Similarly, the overall incidence of ILD is slightly more

common in men (31.5/100,000/yr) than in women (26.1/100,000/yr) and increases with age. For example, among men and women 75 years of age or older, the prevalence of IPF was 250/100,000 and the incidence was 160/100,000/yr.[1]

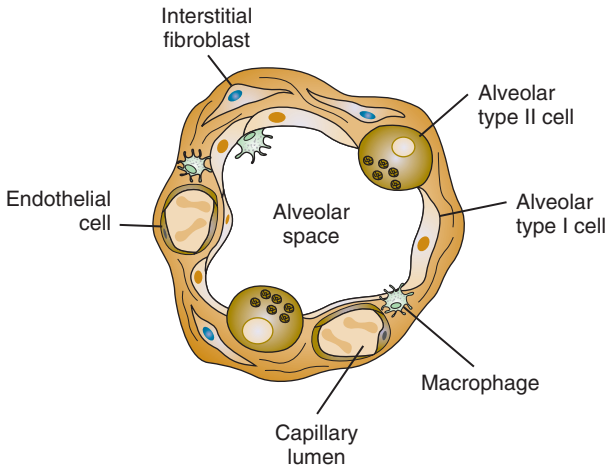


FIGURE 57-1 ■ Schematic depiction of the lung parenchyma surrounding an alveolar space shows the major cells that line and lie within the interstitial space.

A clinical classification of the ILDs is shown in Table 57-1.[2] Although the diagnosis of ILD due to occupational exposure, a medication, or a connective tissue disease may be obvious, the primary and idiopathic ILDs are difficult to diagnose on clinical grounds alone. This chapter presents an approach for the evaluation of these patients with emphasis on the idiopathic interstitial pneumonias (IIPs). An alternative method of histopathologic classification depends on the resultant pattern of injury found on lung biopsy. As seen in Table 57-2, dissimilar clinical entities may result in similar histologic appearances.

The causes of ILDs are daunting, but they are linked by many common features: clinical presentation, radiographic appearance, physiologic abnormalities, and in some instances, histologic findings. Nevertheless, a specific diagnosis can be made in many patients from the results of a careful history and certain laboratory tests. Bronchoscopy with bronchoalveolar lavage (BAL) and, often, transbronchial biopsy are useful in the diagnosis of some causes of interstitial infiltration. Thoracoscopic or open-lung biopsy is required for a definitive diagnosis of the remaining cases. Further information about many of the specific members of the interstitial disease family in this section is found in Chapters 57 through 63. Additional discussion of other causes of ILD is found

TABLE 57-1. Clinical Classification of the Interstitial Lung Diseases

CONNECTIVE TISSUE DISEASES
Scleroderma
Polymyositis-dermatomyositis
Systemic lupus erythematosus
Rheumatoid arthritis
Mixed connective tissue disease
Ankylosing spondylitis

TREATMENT-RELATED OR DRUG-INDUCED DISEASES
Antibiotics (nitrofurantoin, sulfasalazine)
Antiarrhythmics (amiodarone, tocainide, propranolol)
Anti-inflammatories (gold, penicillamine)
Anticonvulsants (dilantin)
Chemotherapeutic agents (mitomycin C, bleomycin, busulfan, cyclophosphamide, chlorambucil, methotrexate, azathioprine, BCNU [carmustine], procarbazine)
Therapeutic radiation
Oxygen toxicity
Narcotics

PRIMARY (UNCLASSIFIED) DISEASES
Sarcoidosis
Primary pulmonary Langerhans cell histiocytosis (eosinophilic granuloma)
Amyloidosis
Pulmonary vasculitis
Lipoid pneumonia
Lymphangitic carcinomatosis
Bronchoalveolar carcinoma
Pulmonary lymphoma
Gaucher's disease
Niemann-Pick disease
Hermansky-Pudlak syndrome
Neurofibromatosis
Lymphangioleiomyomatosis
Tuberous sclerosis
Acute respiratory distress syndrome
AIDS
Bone marrow transplantation
Postinfectious
Eosinophilic pneumonia
Alveolar proteinosis
Diffuse alveolar hemorrhage syndromes
Alveolar microlithiasis
Metastatic calcification

OCCUPATIONAL AND ENVIRONMENTAL DISEASES

Inorganic
Silicosis
Asbestosis
Hard-metal pneumoconiosis
Coal worker's pneumoconiosis
Berylliosis
Talc pneumoconiosis
Siderosis (arc welder)
Stannosis (tin)
Organic (hypersensitivity pneumonitis)
Bird breeder's lung
Farmer's lung
(For complete listing, see Chapter 66)

IDIOPATHIC FIBROTIC DISORDERS
Acute interstitial pneumonitis (Hamman-Rich syndrome)
Idiopathic pulmonary fibrosis/usual interstitial pneumonia
Familial pulmonary fibrosis
Respiratory bronchiolitis/desquamative interstitial pneumonitis
Cryptogenic organizing pneumonia
Nonspecific interstitial pneumonia
Lymphocytic interstitial pneumonia (Sjögren's syndrome, connective tissue disease, AIDS, Hashimoto's thyroiditis)
Autoimmune pulmonary fibrosis (inflammatory bowel disease, primary biliary cirrhosis, idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia)

AIDS, acquired immunodeficiency syndrome.

TABLE 57-2. Histologic Patterns in the Interstitial Lung Diseases and Their Disease Associations

Histologic Patterns	Clinical Associations
Usual interstitial pneumonia	Idiopathic pulmonary fibrosis; connective tissue diseases (uncommon); asbestosis; hypersensitivity pneumonitis; chronic aspiration pneumonia; chronic radiation pneumonitis; Hermansky-Pudlak syndrome; neurofibromatosis
Nonspecific interstitial pneumonia	Idiopathic; connective tissue diseases; drugs; hypersensitivity pneumonitis; diffuse alveolar damage; infections; lymphocytic interstitial pneumonia; AIDS; chronic eosinophilic pneumonia; infections; hemosiderosis; alveolar proteinosis
Diffuse alveolar damage	Acute interstitial pneumonia (Hamman-Rich syndrome); acute respiratory distress syndrome; drugs (cytotoxic agents, heroin, cocaine, paraquat, ethchlorvynol, aspirin); toxic gas inhalation; radiation therapy; oxygen toxicity; connective tissue disease; infections (*Legionella*, *Mycoplasma*, viral)
Organizing pneumonia	Cryptogenic organizing pneumonia; organizing stage of diffuse alveolar damage; diffuse alveolar hemorrhage; drugs (amiodarone, cocaine); infections; connective tissue diseases; hypersensitivity pneumonitis; eosinophilic pneumonia; Wegener's granulomatosis
Desquamative interstitial pneumonia/respiratory bronchiolitis	Cigarette smoking; idiopathic; connective tissue diseases; primary pulmonary Langerhans cell histiocytosis; asbestosis; hard-metal pneumoconiosis (cobalt); Gaucher's disease; Niemann-Pick disease; Hermansky-Pudlak syndrome; drugs (nitrofurantoin, amiodarone)
Lymphocytic interstitial pneumonia	Idiopathic; hypogammaglobulinemia; autoimmune diseases, including Hashimoto's thyroiditis, lupus erythematosus, primary biliary cirrhosis, Sjögren's syndrome, myasthenia gravis, chronic active hepatitis; AIDS; allogeneic bone marrow transplantation
Eosinophilic pneumonia	Idiopathic acute and chronic; tropical filarial eosinophilia; parasitic infections; allergic bronchopulmonary aspergillosis; allergic granulomatosis of Churg and Strauss; hypereosinophilic syndrome; AIDS
Alveolar proteinosis	Pulmonary alveolar proteinosis; acute silicosis; aluminum dust; AIDS; myeloproliferative disorder
Diffuse alveolar hemorrhage	
With capillaritis	Wegener's granulomatosis; microscopic polyangiitis; systemic lupus erythematosus; polymyositis; scleroderma; rheumatoid arthritis; mixed connective tissue disease; lung transplantation; drugs (retinoic acid, propylthiouracil, dilantin); Behçet's disease; cryoglobulinemia; Henoch-Schönlein purpura; pauci-immune glomerulonephritis; immune complex glomerulonephritis
Without capillaritis	Idiopathic pulmonary hemosiderosis; systemic lupus erythematosus; Goodpasture's syndrome; diffuse alveolar damage; pulmonary veno-occlusive disease; mitral stenosis; lymphangioleiomyomatosis
Amyloid deposition	Primary amyloidosis; multiple myeloma; lymphocytic interstitial pneumonia
Granuloma	Sarcoidosis; hypersensitivity pneumonitis; pulmonary Langerhans cell histiocytosis; silicosis; intravenous talcosis; berylliosis; lymphocytic interstitial pneumonia; infections

AIDS, acquired immunodeficiency syndrome.

elsewhere in the book: the pneumoconioses in Chapter 65, hypersensitivity pneumonitis in Chapter 66, and drug-induced pulmonary disease in Chapter 72.

CLINICAL, RADIOLOGIC, AND PHYSIOLOGIC FEATURES OF INTERSTITIAL LUNG DISEASES

The hallmarks of an ILD are progressive dyspnea and cough, an abnormal chest radiograph, and impaired pulmonary function tests.[2] However, 5% to 10% of symptomatic patients eventually diagnosed as having ILD have normal chest radiographs at the time of presentation. There are also dyspneic patients with or without abnormal chest radiographs in whom routine pulmonary function tests (flows, volumes, and diffusing capacity) are normal. Exercise testing, which stresses the cardiopulmonary system and measures gas exchange, may unmask abnormalities in these situations. Furthermore, high-resolution computed tomography (HRCT) scans and BAL can detect abnormalities in the presence of normal radiographs and physiologic tests in patients at high risk for development of ILD, such as those with connective tissue disease, asbestos exposure, or hypersensitivity pneumonitis, and those taking drugs known to injure the lung.

Past History

ILD occurring in a patient with an established connective tissue disease is obvious; however, there are patients in whom the lung disease precedes the more typical manifestations by months to several years (see Chapter 58).

Occupational History

The occupational history is of obvious importance. It should be thorough and detailed, because a long latency period may occasionally exist between exposure and the appearance of clinical impairment and disability. The exposure may have been of short duration but high intensity. Hypersensitivity pneumonitis, which can manifest either as recurrent acute or subacute pneumonitis or as an insidious form with slowly progressive dyspnea, must be excluded (see Chapter 66). A growing list of

occupational and environmental antigens can cause granulomatous pneumonitis.

Drug History

A review of the medications used in the recent and distant past is important. Uncommonly, the lung disease may appear weeks to years after the drug has been discontinued (see Chapter 72). Aspiration (often silent) of gastric contents because of gastroesophageal reflux (GER) can lead to the insidious development of ILD,[3] as can the nocturnal use of oily nose drops or use of mineral oil as a laxative.[4]

Smoking History

Determining any history of tobacco use is important. More than 90% of patients with pulmonary Langerhans cell histiocytosis (PLCH) of the lung are smokers at the time of diagnosis; this is also true for respiratory bronchiolitis. Of patients with Goodpasture's syndrome who smoked, 100% had diffuse alveolar hemorrhage, whereas only 20% of a nonsmoking group had pulmonary disease in addition to the renal involvement.[5] Tobacco use also appears to enhance the development of interstitial fibrosis in an asbestos-exposed population. The risk of asbestosis in exposed smokers was 13 times that in a nonsmoking asbestos-exposed cohort. Most patients with IPF have a history of tobacco abuse. Hypersensitivity pneumonitis, conversely, infrequently appears in the active smoker. Also, the incidence of sarcoidosis is higher in nonsmokers.

Family History

Familial associations (with an autosomal dominant pattern) have been identified in cases of IPF, sarcoidosis, tuberous sclerosis, and neurofibromatosis, Niemann-Pick disease, Gaucher's disease, and Hermansky-Pudlak syndrome are inherited in an autosomal recessive fashion[6–8] (see "Familial Pulmonary Fibrosis," later).

Gender

There are ILDs with a sex predilection. Lymphangioleiomyomatosis occurs exclusively in women. In addition, many connective tissue diseases more commonly affect women. Occupational causes are more likely in men. However, transmission of inorganic dust, either from clothes or by living in the vicinity of a manufacturing or mining facility, has resulted in asbestosis and berylliosis in women, children, and men not employed in the industry.

Symptoms

Progressive *dyspnea* is usually the most common symptom, but cough can be prominent, particularly in those patients with lymphangitic carcinomatosis in which the bronchial lymphatic channels are infiltrated.

Cough is a prominent symptom in ILDs that affect small airways or are bronchocentric in location, such as sarcoidosis, respiratory bronchiolitis, organizing pneumonia, pulmonary Langerhans cell granulomatosis, and hypersensitivity pneumonitis.

Wheezing, an unusual symptom in ILD, has been reported with lymphangitic carcinomatosis, chronic eosinophilic pneumonia, respiratory bronchiolitis, and hypersensitivity pneumonitis.

Substernal chest pain, an unusual complaint for most ILDs, is frequent in sarcoidosis. *Pleuritic-type chest pain* may accompany connective tissue and drug-related ILDs. The sudden appearance of *chest pain* due to a pneumothorax can be the presenting manifestation or complicate preexisting PLCH, lymphangioleiomyomatosis, tuberous sclerosis, or neurofibromatosis.

Hemoptysis is typical for the diffuse alveolar hemorrhage syndromes, lymphangioleiomyomatosis, pulmonary veno-occlusive disease, and long-standing mitral valve disease. However, alveolar hemorrhage may be present without hemoptysis. Hemoptysis occurring in a patient with an established ILD raises the possibility of a complicating malignancy.

Symptoms in patients with ILD are present for months to years and progress at varying rates. Several interstitial reactions are acute (days to several weeks). These are often confused with atypical pneumonias because they cause diffuse radiographic opacities and may be associated with fever. Included are acute interstitial pneumona (AIP; Hamman-Rich syndrome), acute eosinophilic pneumonia, some cases of hypersensitivity pneumonitis, occasionally drug-related ILDs, some cases of organizing pneumonia, the diffuse alveolar hemorrhage syndromes, and the acute immunologic pneumonias that occur with connective tissue diseases.

Physical Findings

The most typical physical finding is bibasilar inspiratory crackles. Crackles are less likely in the granulomatous diseases. Bilateral inspiratory crackles may also be present in a symptomatic patient with a negative chest radiograph. Clubbing of the digits, which in most cases indicates advanced fibrotic disease, is a common finding in patients with the idiopathic or familial forms of pulmonary fibrosis. However, the appearance of digital clubbing in a patient with an established case of ILD could indicate an underlying bronchogenic carcinoma. With advanced fibrosis, causing chronic hypoxemia, clinical signs of pulmonary hypertension and cor pulmonale appear. Attention to potential extrapulmonary physical findings or other manifestations may reveal a specific diagnosis (Table 57-3).

Radiographic Features

Although standard chest radiography is not as sensitive for detection of ILD as the HRCT scan, it is the logical starting point and the most practical way of identifying and defining disease.

TABLE 57-3. Extrapulmonary Physical Findings and Clinical Manifestations in the Interstitial Lung Diseases

Finding	Examples
Systemic hypertension	Connective tissue disease; neurofibromatosis; some diffuse alveolar hemorrhage syndromes
Erythema nodosum	Sarcoidosis; connective tissue disease; Behçet's syndrome
Maculopapular rash	Drug-induced; amyloidosis; lipoidosis; connective tissue diseases; Gaucher's disease
Heliotrope rash	Dermatomyositis
Albinism	Hermansky-Pudlak syndrome
Discoid lupus	Systemic lupus erythematosus
Neurofibroma	von Recklinghausen's disease
Telangiectasia	Scleroderma
Raynaud's phenomenon	Connective tissue disease
Cutaneous vasculitis	Systemic vasculitides; connective tissue disease
Subcutaneous nodules	von Recklinghausen's disease; rheumatoid arthritis
Calcinosis	Dermatomyositis; scleroderma
Uveitis	Sarcoidosis; Behçet's syndrome; ankylosing spondylitis
Scleritis	Systemic vasculitis; systemic lupus erythematosus; scleroderma; sarcoidosis
Keratoconjunctivitis sicca	Lymphocytic interstitial pneumonia
Salivary gland enlargement	Sarcoidosis, lymphocytic interstitial pneumonia
Peripheral lymphadenopathy	Sarcoidosis; lymphangitic carcinomatosis; lymphocytic interstitial pneumonia; lymphoma
Hepatosplenomegaly	Sarcoidosis; pulmonary Langerhans cell histiocytosis; connective tissue disease; amyloidosis; lymphocytic interstitial pneumonia
Pericarditis	Radiation pneumonitis; connective tissue disease
Myositis	Connective tissue disease; drugs (L-tryptophan)
Bone involvement	Pulmonary Langerhans cell histiocytosis; sarcoidosis; Gaucher's disease; lymphangitic carcinomatosis
Arthritis	Connective tissue disease; systemic vasculitis; sarcoidosis
Diabetes insipidus	Pulmonary Langerhans cell histiocytosis; sarcoidosis
Glomerulonephritis	Systemic vasculitis; connective tissue disease; Goodpasture's syndrome; sarcoidosis
Nephrotic syndrome	Amyloidosis; drug-induced (gold, penicillamine); systemic lupus erythematosus
Renal mass	Lymphangioleiomyomatosis; tuberous sclerosis

Plain Roentgenography

Ziskind and coworkers[9] classified the diffuse lung diseases according to the pattern on chest radiographs—alveolar filling and primarily interstitial patterns (reticular or nodular). Although computed tomography (CT) scanning has supplanted the chest radiograph in the assessment of diffuse parenchymal lung diseases, it is still very useful to recognize these patterns.

Alveolar Filling Pattern (Table 57-4). Alveolar filling is recognized by a homogeneous opacity that can be diffuse or patchy and is characterized by confluent nodules with ill-defined outer borders, air bronchograms, and obliteration or silhouetting of normal structures such as the diaphragm, heart, and intrapulmonary blood vessels (Fig. 57-2). Another feature is the acinar rosette or air alveologram, which indicates consolidation of the alveolus and small airways distal to an unobstructed terminal bronchiole (Fig. 57-3). Several have associated hilar adenopathy (e.g., sarcoidosis, pulmonary lymphoma). In patients with alveolar proteinosis, sparing of the lung parenchyma immediately adjacent to the diaphragm is seen. In chronic eosinophilic pneumonia, the pattern has been referred to as the radiographic negative of pulmonary edema, because the alveolar opacities are most prominent in the periphery. A similar alveolar

TABLE 57-4. Interstitial Lung Diseases Producing an Alveolar Filling Pattern on Chest Radiograph

Alveolar proteinosis (proteinaceous fluid)
Alveolar cell carcinoma (malignant cells)
Bronchioloalveolar metastases (malignant cells from pancreas, breast)
Pulmonary lymphoma (malignant lymphocytes)
Lymphocytic interstitial pneumonia (lymphoplasmacytic cells)
Alveolar sarcoid (lymphocyte-macrophage alveolitis or confluent granuloma)
Desquamative interstitial pneumonia (macrophages)
Diffuse alveolar hemorrhage (red blood cells; hemosiderin-filled macrophages)
Eosinophilic pneumonia (eosinophils, macrophages; lymphocytes)
Alveolar microlithiasis (calcium-phosphate microliths)
Bronchiolitis obliterans with organizing pneumonia (Masson bodies)
Mineral oil aspiration (lipid-filled macrophages)
Acute hypersensitivity pneumonia (lymphoplasmacytic cells)

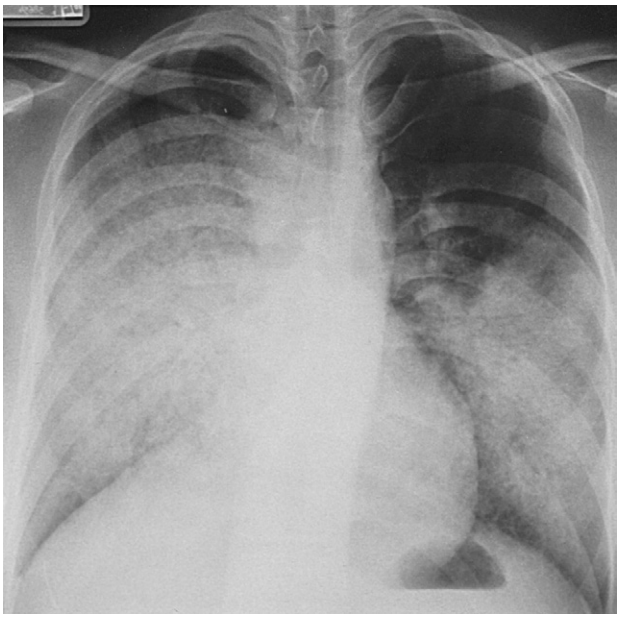


FIGURE 57-2 ■ Chest radiograph shows a characteristic pattern of alveolar filling disease in a patient with diffuse alveolar hemorrhage. Note the homogeneous consolidation with obliteration of the right heart border and the pulmonary vasculature in addition to air bronchograms.

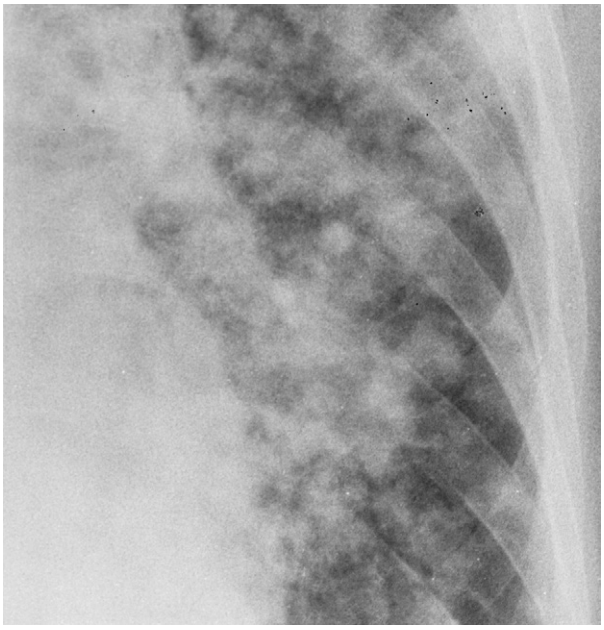


FIGURE 57-3 ■ Detailed view of chest radiograph shows alveolar nodules in a patient with alveolar cell carcinoma. Note the ill-defined nodules and distal air alveolograms.

pattern has also been reported to occur in some patients with organizing pneumonia (Fig. 57-4).

Interstitial Pattern. Radiographic interstitial opacities become apparent when the interstitial compartment becomes infiltrated and widened by inflammatory cells, excessive collagen, granulomatous inflammation, or smooth muscle proliferation. In other instances,

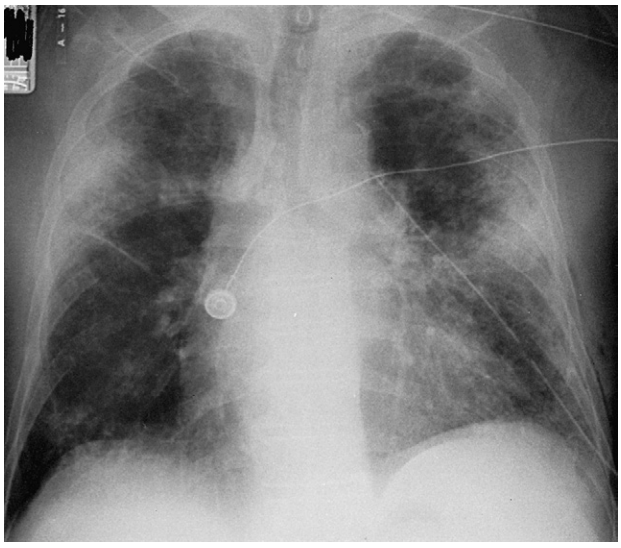


FIGURE 57-4 ■ Chest radiograph of a patient with organizing pneumonia shows bilateral peripheral alveolar opacities. A similar appearance is seen in chronic eosinophilic pneumonia.

malignant cells or amyloid deposits expand this compartment. These opacities appear as nodules, linear reticular opacities, or a combination of linear shadows and nodules ("reticulonodular" opacities).

Nodular Pattern. Nodules of varying size characterize the granulomatous lung diseases. Miliary nodules accompany infectious granulomas and noninfectious granulomas (e.g., sarcoidosis, PLCH, silicosis, and hypersensitivity pneumonitis) and some malignant diseases (e.g., melanoma, hypernephroma, and lymphoma) (Fig. 57-5). However, linear opacities possibly representing an underlying cellular interstitial infiltrate are also visible.

Linear or Reticular. Linear or reticular interstitial changes are seen in most ILDs (Fig. 57-6). It is typical for many ILDs (e.g., IPF, the connective tissue diseases, asbestosis, cytotoxic drug–induced disorders) to have the greatest concentration of the reticular opacities in the lower lung zones. The term *radiographic honeycomb lung* refers to a reticular and cystic pattern that correlates with the histologic "honeycombing." These small cystic structures, which are best seen in the lower and peripheral lung zones, indicate an underlying advanced fibrotic change (Fig. 57-7).

A criticism of the alveolar-interstitial classification is that a mixed pattern is often found. For example, interstitial fibrosis may eventually be superimposed on a disease that was primarily alveolar, such as alveolar proteinosis, diffuse alveolar hemorrhage, eosinophilic pneumonia, or organizing pneumonia. Sarcoidosis, a disease characterized by interstitial granuloma, can be alveolar in appearance due to either coalescence of granulomas with compression of adjacent lung or a lymphocyte-macrophage alveolitis. Dense fibrosis from any fibrotic lung disease can compress adjacent lung, producing homogeneous shadows. The appearance of alveolar

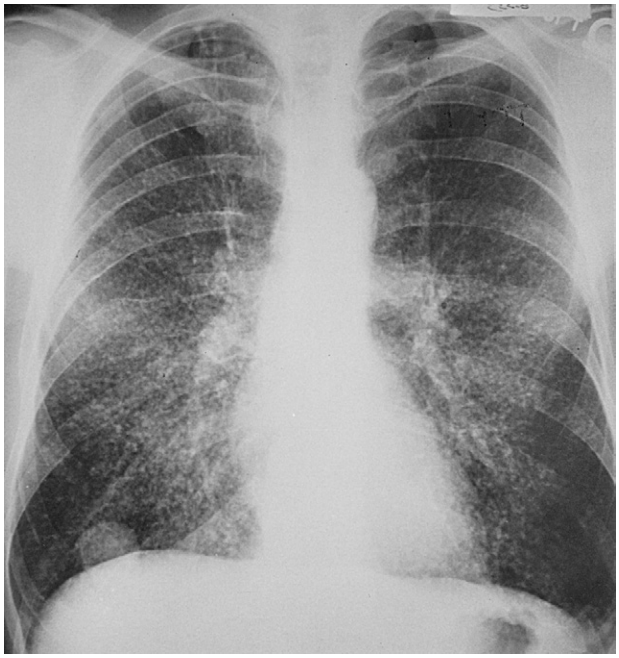


FIGURE 57-5 ■ Chest radiograph shows miliary interstitial nodulation in a patient with metastatic malignant melanoma. A large mass is also present in the right lower lobe.

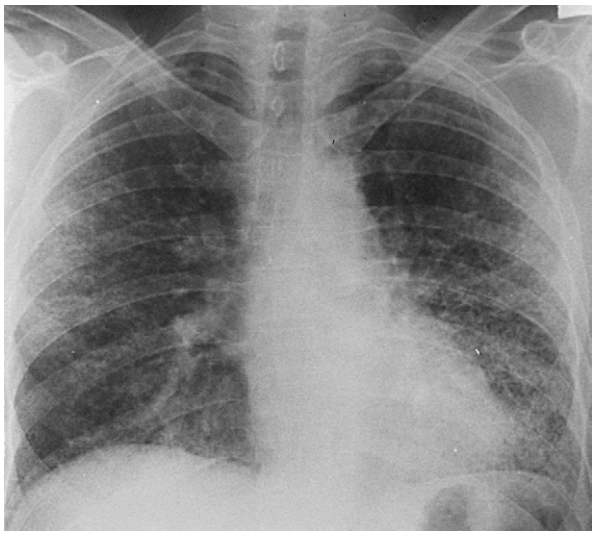


FIGURE 57-6 ■ Chest radiograph shows diffuse bilateral lower lung predominant reticular opacities in a patient with idiopathic pulmonary fibrosis (IPF).

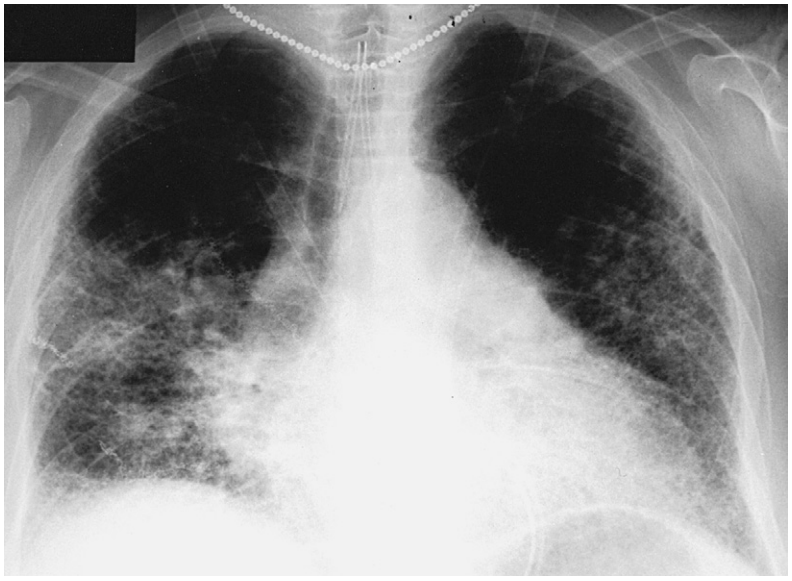


FIGURE 57-7 ■ Chest radiograph shows characteristic features of honeycomb lung. A network of 2- to 3-mm cystic spaces is distributed throughout the lung fields. This patient with end-stage IPF also had pulmonary hypertension and was receiving oxygen through a transtracheal catheter.

opacities during the course of an ILD may represent renewed activity of the primary disease, superimposed infection, or development of alveolar cell carcinoma or adenocarcinoma.[10,11]

Other Radiographic Features. Several distinctive patterns may accompany the interstitial changes and may point to a diagnosis (Table 57-5). There are a group of interstitial diseases, often granulomatous, in which the radiographic changes are more prominent in the upper lung zones (Fig. 57-8). There are interstitial diseases that are bronchiolocentric, resulting in either maintenance or expansion of the lung volume. If an ILD is superimposed on emphysema, the lung volumes often are preserved. The majority of ILDs result in a gradual reduction of the lung volumes. In fact, lower lobe volume loss and traction bronchiectasis are typical for the advanced stages of these diseases.[10–12] Short horizontal lines at the lung periphery (Kerley's B lines), representing thickened interlobular septa, are seen after obstruction of the pulmonary lymphatics (Fig. 57-9). Pneumothorax is often the presenting manifestation of PLCH or lymphangioleiomyomatosis. Diaphragmatic pleural calcification in a patient with interstitial opacities is indicative of asbestos exposure. Pleural thickening and pleural effusion

TABLE 57-5. Radiographic Features of the Interstitial Lung Diseases

Feature	Diseases
Upper zone–predominant disease	Radiation pneumonitis; neurofibromatosis; chronic sarcoidosis; pulmonary Langerhans cell histiocytosis; silicosis; chronic hypersensitivity pneumonitis; chronic eosinophilic pneumonia; ankylosing spondylitis; nodular rheumatoid arthritis; berylliosis; drug-induced (amiodarone, gold, BCNU [carmustine]); radiation
Increased lung volumes	Lymphangioleiomyomatosis; chronic sarcoidosis; chronic pulmonary Langerhans cell histiocytosis; tuberous sclerosis; neurofibromatosis
Radiographic honeycomb lung	Idiopathic pulmonary fibrosis; connective tissue disease; asbestosis; drug-induced; lymphocytic interstitial pneumonia; chronic aspiration pneumonia; hemosiderosis; Hermansky-Pudlak syndrome; alveolar proteinosis
Pneumothorax	Pulmonary Langerhans cell histiocytosis; lymphangioleiomyomatosis; tuberous sclerosis; neurofibromatosis
Kerley's B lines	Lymphangitic carcinomatosis; lymphangioleiomyomatosis; left atrial hypertension (mitral valve disease, veno-occlusive disease); lymphoma; amyloidosis
Lymphadenopathy	Sarcoidosis; lymphoma; lymphangitic carcinomatosis; lymphoid interstitial pneumonia; berylliosis; amyloidosis; Gaucher's disease
Pleural disease	Lymphangitic carcinomatosis; connective tissue disease; asbestosis (pleural calcification); lymphangioleiomyomatosis (chylous effusion); drug-induced (nitrofurantoin, radiation); sarcoidosis
Eggshell calcification of lymph nodes	Silicosis; sarcoidosis; radiation

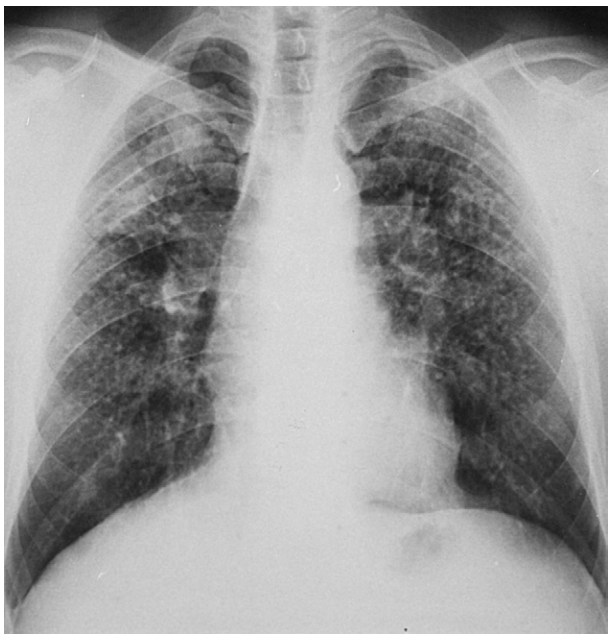


FIGURE 57-8 ■ Chest radiograph shows uncomplicated silicosis. Note the nodular interstitial disease with predilection for the middle and upper lung zones.

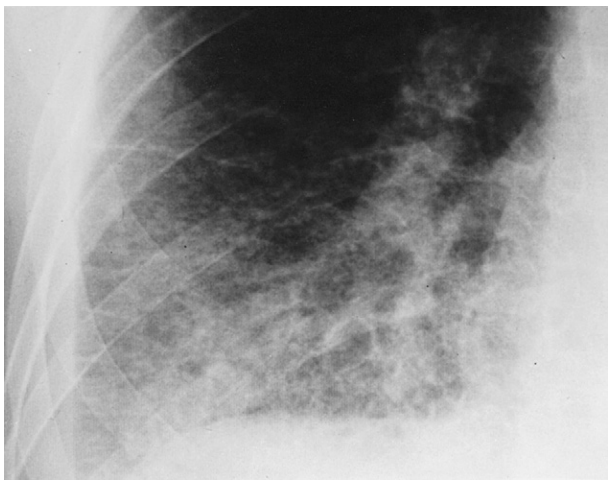


FIGURE 57-9 ■ Detailed view of right lung shows Kerley's B lines and pleural effusion in a patient with lymphangitic carcinomatosis.

may complicate the course of the connective tissue–associated ILDs (with the exception of polymyositis-dermatomyositis). Chronic hypoxemia results in radiographic evidence of pulmonary hypertension.

Computed Tomography

Conventional chest radiographic assessment for ILD may miss up to 10% of cases.[13] Conventional CT, obtained using 8- to 10-mm slices, offers little more for the detection of radiographic-negative ILD. HRCT, obtained with less than 3-mm slices, enables better visualization of fine parenchymal detail and therefore the detection of early air space filling or interstitial change (Fig. 57-10). In cases of suspected ILD with negative conventional radiography, it is important to perform HRCT with prone and supine views. Dependent lung density can mask interstitial change, and vascular engorgement of the dependent portion of lung mimics septal thickening on the supine view. Abnormalities that persist on the prone view are indicative of disease.

In patients with abnormal chest radiographs, the diagnostic accuracy increases with HRCT evaluation. In cases of IPF, peripheral reticular opacities, lower zone subpleural honeycombing, and traction bronchiectasis are seen (Fig. 57-11).[14] In the connective tissue diseases, asbestosis, and some drug-induced ILD, the results on

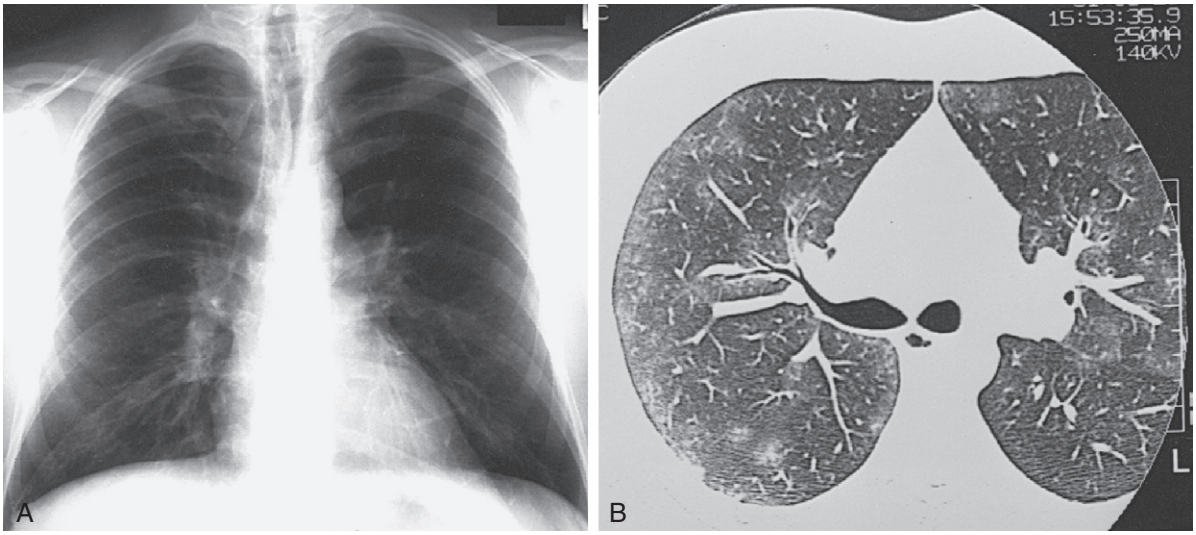


FIGURE 57-10 ■ **A,** A normal chest radiograph from a 45-year-old man with established hypersensitivity pneumonitis. At the time, his arterial oxygen pressure (Po_2) while breathing room air was 48 mm Hg. **B,** A high-resolution computed tomography (CT) image of the same patient demonstrates patchy ground-glass areas of air space–filling opacities.

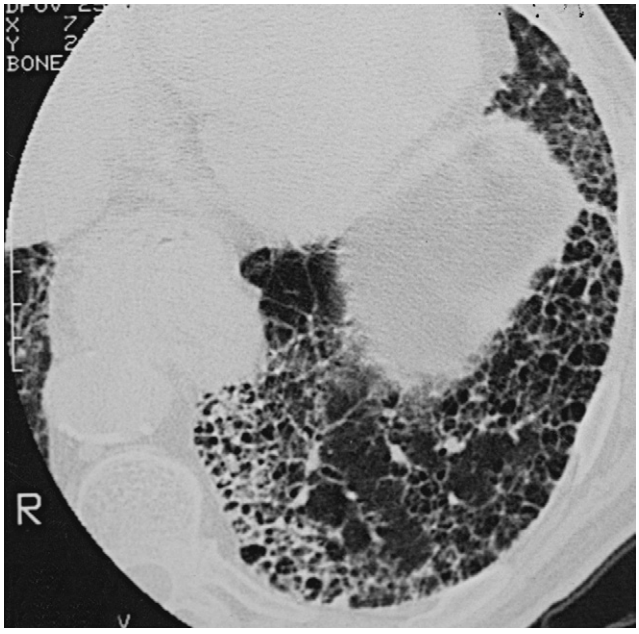


FIGURE 57-11 ■ High-resolution CT image of advanced IPF shows extensive honeycomb changes.

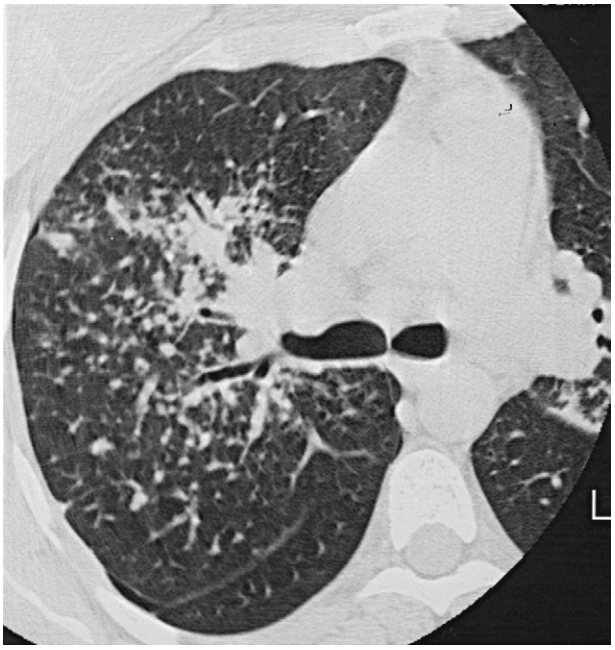


FIGURE 57-12 ■ High-resolution CT image from a patient with sarcoidosis shows hilar lymphadenopathy and nodular disease as well as dense air space filling.

HRCT, as on chest radiography, are indistinguishable from those of IPF or nonspecific interstitial pneumonia (NSIP). In scleroderma, a disease in which the prevalence rate of ILD approaches 100% in autopsy series, HRCT detects disease in 45% to 75% of patients when conventional radiography is negative.[15,16]

In sarcoidosis, in addition to the hilar and mediastinal adenopathy, nodules deposited along bronchovascular bundles and interlobular septa, air space filling due to the lymphocyte-macrophage alveolitis, and linear densities secondary to fibrotic scarring can be seen (Fig. 57-12). In patients with hypersensitivity pneumonitis, air space–filling centrilobular nodules and linear opacities without adenopathy are present. The HRCT can be normal in symptomatic patients with biopsy-proved hypersensitivity pneumonitis.[17] In patients with PLCH, the combination of centrilobular nodules and cysts, most prominent in the upper lobes and occasionally accompanied by a pneumothorax, is characteristic (Fig. 57-13). In earlier PLCH, coalescence of the nodules produces an air space–filling pattern.

In lymphangioleiomyomatosis, the HRCT is typical, revealing rounded, thin-walled cysts throughout (Fig.

FIGURE 57-13 ■ High-resolution CT image from a patient with pulmonary Langerhans cell histiocytosis shows diffuse centrilobular nodulation and cyst formation.

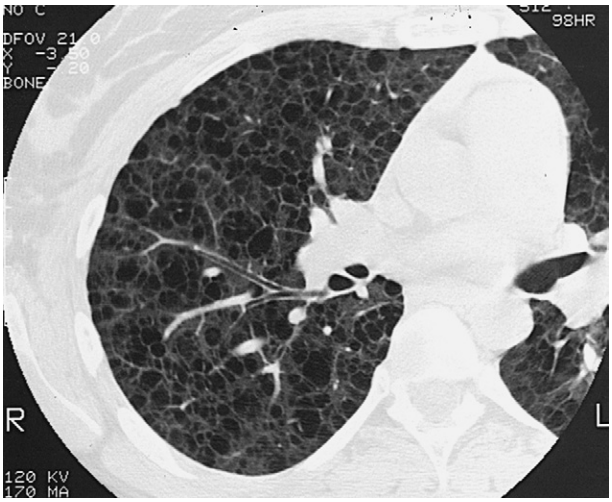


FIGURE 57-14 ■ High-resolution CT image from a patient with lymphangioleiomyomatosis shows characteristic thin-walled cysts throughout the parenchyma.

57-14). A pneumothorax or pleural effusion (chylous) may accompany this change. Except for the pleural effusion, identical findings are present in tuberous sclerosis. Lymphangitic carcinomatosis produces a beaded-chain appearance of the interlobular septa that correlates with Kerley's B lines seen with conventional radiography. In asbestos-related disease, noncalcified pleural plaques and early ILD are often difficult to detect, and the HRCT is more sensitive than conventional chest radiography.

Functional Assessment

In ILD, there are characteristic alterations of the lungs' mechanical properties and impairment of gas exchange at the alveolar-capillary interface. Assessment of ventilatory function and the mechanical properties of the lungs, as well as gas exchange, particularly during exercise, are vital components of the initial evaluation of patients with suspected ILD. In addition, serial measurements of function enable the physician to determine progression of the disease and the effects of therapeutic intervention.

Ventilatory Function

Ventilatory function tests provide an indirect index of alterations to the impedance to respiration offered by the elastic resistance to distention of the lungs and the frictional resistance to airflow in the tracheobronchial tree. Clinically, alterations of the mechanical properties of the respiratory system are also reflected in the pattern of breathing that is adopted by the patient. These patients tend to breathe rapidly and shallowly, because a larger tidal volume would require an inordinate increase in work of breathing to overcome the greatly increased elastic resistance.

Elastic Resistance

ILD is associated with an increase in elastic resistance (or decreased compliance), and this can be seen in a plot of the static transpulmonary pressure (i.e., at points of no flow) at differing decrements of lung volume from total lung capacity (TLC) to residual volume. In most patients with ILD, the plot of the volume-pressure relationship of the lungs is characteristically shifted downward and to the right, with a reduced slope (i.e., compliance is low) and a markedly increased coefficient of elastic recoil (maximum elastic recoil pressure, TLC). Conversely, as is demonstrated in Figure 57-15, there is significant variation in the position of the volume-pressure curve in patients with IPF and sarcoidosis,[18] and the correlation between alterations of the elastic properties (and lung volume compartments) and the degree of fibrosis present is poor. This is, at least in part, a consequence of the impact of smoking, which appears to differ in the two disorders. In patients with IPF who smoke, the volume-pressure curve is shifted upward and to the left, whereas in smokers with sarcoidosis, it is shifted downward and to the right.[18]

Measurements of lung volume reflect changes in position of the volume-pressure curve of the lungs. This is because alterations of the elastic recoil of the lung or chest wall disturb the balance between the elastic forces of the lungs, which act in an expiratory direction, and those of the chest wall, which act in an inspiratory direction. In patients with ILD, the TLC, functional residual capacity, and residual volume are generally lower than expected (Fig. 57-16). A lower than expected TLC (and vital capacity) in association with a normal functional residual capacity and a greater than expected residual volume generally reflects a mixed restrictive and obstructive disorder. However, because maximum effort is necessary to determine the inspiratory capacity and the expiratory reserve volume, a less than maximal inspiration or expiration, because of either weak respiratory

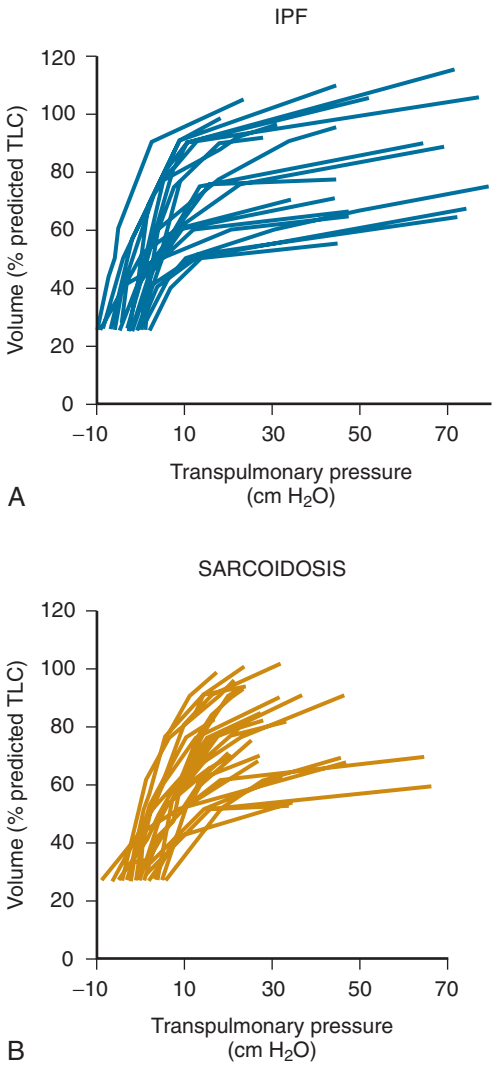


FIGURE 57-15 ■ Multiple recordings show volume-pressure characteristics in patients with IPF (**A**) and sarcoidosis (**B**). Note the marked variation of position and shape in both disorders. TLC, total lung capacity. (Redrawn from Hanley ME, King TE Jr, Schwarz MI, et al: The impact of smoking on mechanical properties of the lungs in idiopathic pulmonary fibrosis and sarcoidosis. Am Rev Respir Dis 144:1102, 1991.)

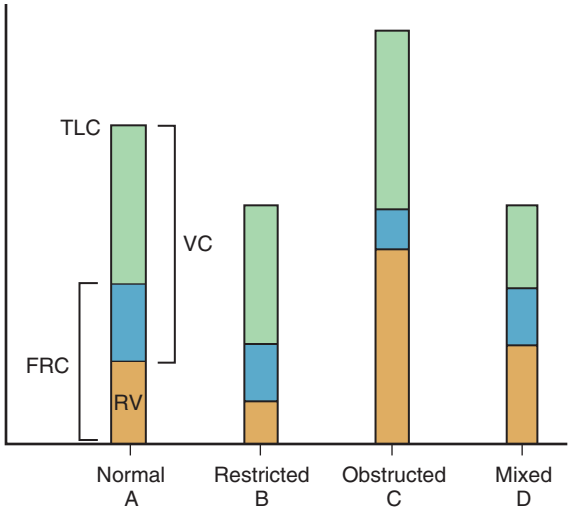


FIGURE 57-16 ■ Bar graphs show total lung capacity (TLC) and its subdivisions in healthy persons (**A**) compared with the typical abnormalities found in patients with restrictive disorders (**B**), obstructive disorders (**C**), and mixed disorders (**D**). FRC, functional residual capacity; RV, residual volume; VC, vital capacity. (Redrawn from Cherniack RM: Pulmonary Function Testing. Philadelphia: WB Saunders, 1992, p 212.)

muscles or poor effort, leads to the same findings. Similar qualifications apply to the vital capacity, which is often used as an index of alterations of elastic resistance. In addition, as can be seen in Figure 57-16, a low vital capacity is not specific for restrictive disorders, because it is also lower than expected in patients with airflow limitation (because of an increased residual volume).

Flow Resistance

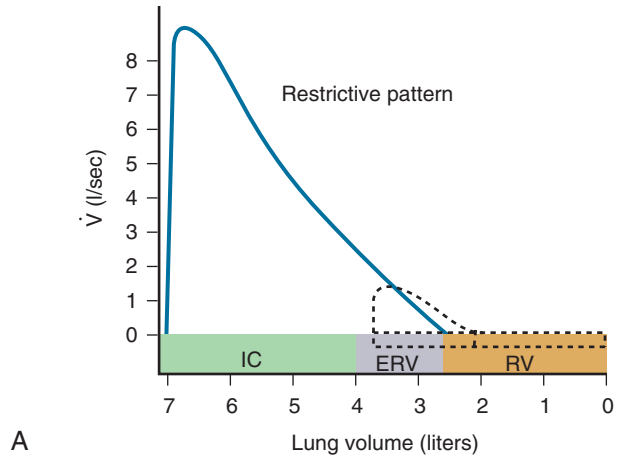
Measurement of lung volume is important when evaluating airflow resistance. This can be assessed directly from the relationship between the rate of airflow and the resistive component of the transpulmonary pressure.

In clinical practice, various indirect measures of flow resistance can be used: the forced expiratory volume in 1 second (FEV_1); the mean expiratory flow rate between 25% and 75% of the forced vital capacity (FVC), that is, $FEF_{25\%-75\%}$; the maximal expiratory flow rate ($\dot{V}max$) at a particular proportion (such as 75%, 50%, or 25%) of the FVC (from a flow-volume curve); the FEV_1/FVC ratio; or the FEV_1–to–vital capacity ratio. Low flow rates or a low FEV_1/FVC ratio (i.e., <70% of predicted) is believed to indicate expiratory airflow limitation. However, like airway resistance, $\dot{V}max$ values depend on the state of expansion of the airways (i.e., lung volume). The FEV_1/FVC ratio will be overestimated, and the degree of flow limitation underestimated, in the patient who does not exhale fully because of severe dyspnea or muscular weakness, pain, or poor effort.

Airflow resistance is not generally thought to be increased in ILD. As is seen in Figure 57-17, $\dot{V}max$ is low in ILD, not because of an increase in flow resistance but rather because the flow rates are being achieved at low lung volumes. In fact, in uncomplicated ILD, $\dot{V}max$ values are greater than expected at any particular lung volume (isovolume) because the lung elastic recoil pressure, which is the driving pressure for flow in the peripheral airways, is increased.[19] As a corollary, a $\dot{V}max$ lower than expected at a particular lung volume in a patient who is suffering from a restrictive disorder indicates an increase of flow resistance in the more peripheral (upstream) airways. An increase in upstream resistance has been reported in patients with IPF, hypersensitivity pneumonitis, and asbestos exposure.

Gas Exchange

Alterations of gas exchange are readily assessed by analysis of the arterial oxygen pressure (P_{O_2}) and carbon dioxide pressure (P_{CO_2}) and calculation of the



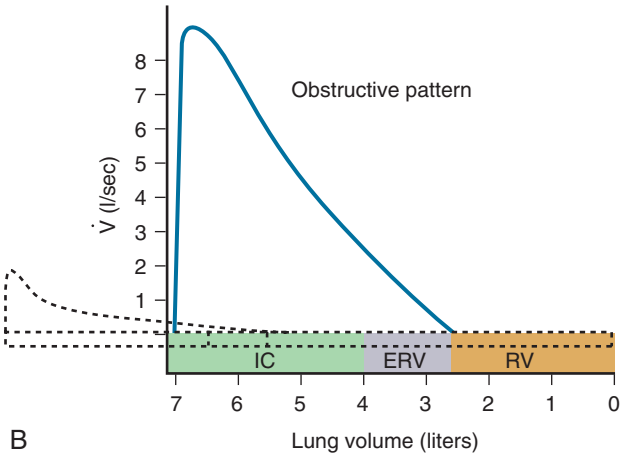
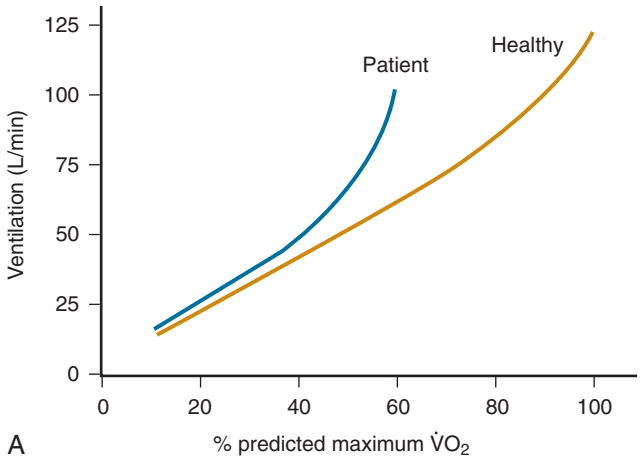


FIGURE 57-17 ■ Schematic volume-flow ($\dot{V}$) curves in a healthy person (*solid line*) are compared with those in patients (*dotted lines*) with a restrictive disorder (**A**) and with an obstructive disorder (**B**). Lung volume is reduced in the restrictive disorder, and maximum expiratory flow rates are low because they are achieved at low lung volumes. Flow rates are higher than expected at low lung volumes because the driving pressure (lung elastic recoil) is increased. ERV, expiratory residual volume; RV, residual volume. (Redrawn from Cherniack RM: Pulmonary Function Testing. Philadelphia: WB Saunders, 1992, p 218.)



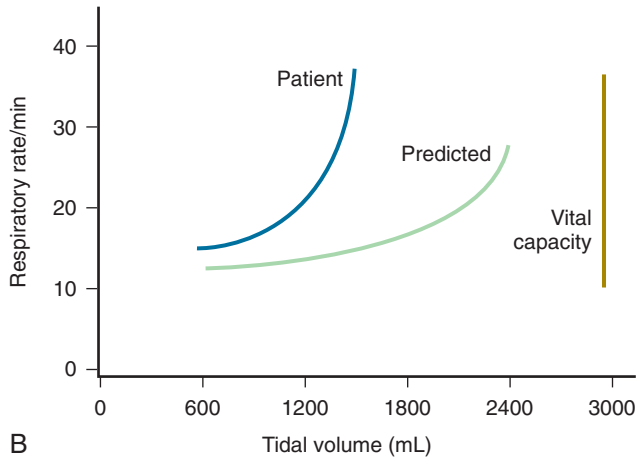


FIGURE 57-18 ■ Schematic curves show the ventilatory response (**A**) and respiratory pattern (**B**) during increasing exercise workloads expressed as a percentage of the predicted maximum oxygen uptake ($\dot{V}o_2$) in a healthy person and in a patient with IPF. (Redrawn from Cherniack RM: Pulmonary Function Testing. Philadelphia: WB Saunders, 1992, p 248.)

alveolar-arterial P_{O_2} difference ((A – a)P_{O_2}), both at rest and during exercise.

In patients with ILD, arterial blood analysis while at rest usually reveals hypoxemia and an increased (A – a)P_{O_2}, along with hypocapnia. In addition, the diffusing capacity for carbon monoxide ($D_{L_{CO}}$) is reduced, primarily because of a reduction in the alveolar-capillary surface available for gas exchange. The disturbance of gas exchange generally accompanies abnormalities in ventilatory function,[20] but gas exchange may be normal at rest in a significant number of patients. Similarly, the resting $D_{L_{CO}}$ may be only slightly reduced in patients who demonstrate a mild restrictive disorder or normal gas exchange while at rest, or both.

The $D_{L_{CO}}$ is generally greater than expected in those cases associated with recent pulmonary hemorrhage because the red blood cells in the pulmonary alveoli take up carbon monoxide readily. Sequential measurements of the $D_{L_{CO}}$ within minutes may aid in the establishment of the diagnosis of alveolar hemorrhage.[21] When there is fresh blood in the alveolar spaces, each successive $D_{L_{CO}}$ value will be lower as the hemoglobin in the alveoli becomes saturated with carbon monoxide.

Exercise

In most patients, gas exchange is disturbed during exertion, even in those with normal gas exchange at rest. Assessment of gas exchange during exercise provides the best correlation with the severity of disease[22] and is probably the most important physiologic determination in patients with ILD.

In general, patients with the most severe restrictive disease have the poorest exercise tolerance. As is shown in Figure 57-18, ventilation generally rises excessively

during exercise and may approach the ventilatory ceiling. Characteristically, the respiratory frequency rises inordinately with increasing exercise loads because of the increased work that would be required to overcome the elastic resistance of the lungs if the tidal volume were to increase.

The excessive ventilation is frequently preferentially distributed to areas of lung that have normal compliance but diminished perfusion (i.e., high ventilation-perfusion ratio); as a result, unlike the normal response, the calculated dead space (V_D) and the ratio of dead space to tidal volume (V_D/V_T) rise in association with rapid, shallow breathing. The increase in cardiac output with exercise and the rapid transit of blood through the pulmonary capillaries along with its redistribution in the lungs lead to a greater maldistribution of ventilation-perfusion ratios. This results in a rise in $(A - a)P_{O_2}$ and a fall in arterial P_{O_2} (Fig. 57-19). Except for heavy exercise, when the transit through the circulation is exceptionally rapid, it is unlikely that a reduced ability of oxygen to diffuse across a thickened alveolar-capillary membrane plays a significant role in the hypoxemia.

Laboratory Findings

Table 57-6 summarizes the results of laboratory tests that suggest or support the diagnosis of a specific ILD.

Bronchoalveolar Lavage

BAL is a technique employed to sample the distal airways via the instillation of sterile saline through a wedged fiberoptic bronchoscope. After aspiration, the contents, which are thought to represent the cellular, immunologic, and biochemical milieu of the alveolar structures, can be analyzed. The results of BAL for the evaluation of ILD have been difficult to interpret because of the lack of standardized techniques for both the performance of the procedure and the subsequent analysis of the data.[23,24] Furthermore, in some of the earlier studies, correlative data between lung biopsies and BAL were not obtained. Often, the treatment or smoking status of the patient was not considered. A multicenter publication has set forth the methods of performing and analyzing the results of BAL.[25] This study involved a large cohort of normal subjects of varying age and race who were compared with patients with documented ILD. Smoking affects the BAL

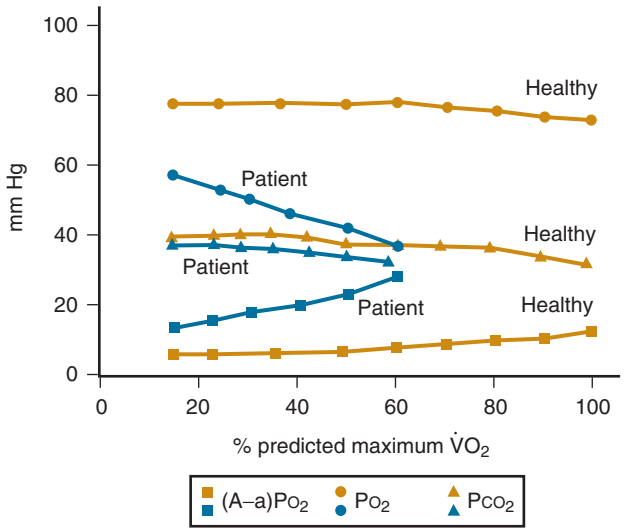


FIGURE 57-19 ■ The changes in arterial P_{O_2}, alveolar-arterial P_{O_2} difference ($(A - a)P_{O_2}$), and arterial carbon dioxide pressure (P_{CO_2}) during increasing exercise workloads expressed as the percentage of predicted maximum oxygen uptake ($\dot{V}_{O_2}$) in a healthy person and a patient with IPF. Testing performed at altitude (5280 feet). (Redrawn from Cherniack RM: Pulmonary Function Testing. Philadelphia: WB Saunders, 1992, p 249.)

TABLE 57-6. Laboratory Findings in the Interstitial Lung Diseases

Finding	Diseases
Leukopenia	Sarcoidosis; connective tissue disease; lymphoma; drug-induced
Leukocytosis	Systemic vasculitis; hypersensitivity pneumonitis; lymphoma
Eosinophilia	Eosinophilic pneumonia; sarcoidosis; systemic vasculitis; drug-induced (sulfa, methotrexate)
Thrombocytopenia	Sarcoidosis; connective tissue disease; drug-induced; Gaucher's disease; idiopathic pulmonary fibrosis
Hemolytic anemia	Connective tissue disease; sarcoidosis; lymphoma; drug-induced; idiopathic pulmonary fibrosis
Normocytic anemia	Diffuse alveolar hemorrhage syndromes; connective tissue disease; lymphangitic carcinomatosis
Urinary sediment abnormalities	Connective tissue disease; systemic vasculitis; drug-induced
Hypogammaglobulinemia	Lymphocytic interstitial pneumonia
Hypergammaglobulinemia	Connective tissue disease; sarcoidosis; systemic vasculitis; idiopathic pulmonary fibrosis; asbestosis; silicosis; lymphocytic interstitial pneumonia; lymphoma
Serum autoantibodies	Connective tissue disease; systemic vasculitis; sarcoidosis; idiopathic pulmonary fibrosis; silicosis; asbestosis; lymphocytic interstitial pneumonia
Serum immune complexes	Idiopathic pulmonary fibrosis; lymphocytic interstitial pneumonia; systemic vasculitis; connective tissue disease; pulmonary Langerhans cell histiocytosis
Serum angiotensin-converting enzyme	Sarcoidosis; hypersensitivity pneumonitis; silicosis; acute respiratory distress syndrome; Gaucher's disease
Antibasement membrane antibody	Goodpasture's syndrome
Antineutrophil cytoplasmic antibody	Systemic vasculitis

results of both normal subjects and patients by amplifying the macrophage and eosinophil populations.[25]

BAL is a useful investigative tool in many ILDs. Cytologic analysis of BAL specimens can be diagnostic for lymphangitic carcinomatosis, alveolar cell carcinoma, and pulmonary lymphoma. If the eosinophil level exceeds 40% (normal, <2%), eosinophilic pneumonia is usually the cause of the diffuse pulmonary infiltration. BAL eosinophilia of a lesser degree may occur with some connective tissue diseases, IPF, or organizing pneumonia.

The finding of periodic acid–Schiff–positive lipoproteinaceous bodies in the lavage liquid was originally thought to be diagnostic for pulmonary alveolar proteinosis but has proved to be nonspecific. In cases of diffuse alveolar hemorrhage, red blood cells and hemosiderin-laden macrophages dominate the lavage specimen.

Lavage lymphocytosis (>35% lymphocytes) predominates in some diseases. Sarcoidosis and hypersensitivity pneumonitis are most common. Others include lymphocytic interstitial pneumonia (LIP), pulmonary lymphoma, berylliosis, and some drug-induced ILDs. Smaller but increased percentages of lymphocytes (normal range, 15%) can be seen with these entities in addition to a number of other ILDs, including IPF, organizing pneumonia, connective tissue diseases, and some pneumoconioses.[26] In patients with suspected asbestos-related disease, one or more asbestos bodies per high-powered field in the BAL specimen indicate significant exposure, but this does not establish the diagnosis of asbestosis. Because of the vertical gradient of asbestos bodies recovered in the lungs of patients with asbestosis, if lavage is used to document previous asbestos exposure, samples should be obtained from a basal segment of one of the lower lobes. A diagnosis of berylliosis is confirmed when lavaged lymphocytes undergo proliferation after exposure to the mineral in vitro.

In the BAL recovered from patients with PLCH, all inflammatory cells are increased even though their percentages remain unchanged. Electron microscopy demonstrates increased numbers of Langerhans cells. This monocyte, which is thought to be central in the pathogenesis, has a typical pentilaminar body (Birbeck granule) in the cytoplasm, as revealed by electron microscopy. Langerhans cells have been described in other fibrotic lung diseases, but not in numbers equivalent to those of PLCH.[27]

Other applications of BAL include disease staging (i.e., cellular infiltrates versus fibrosis on lung biopsies) and the prediction of therapeutic responsiveness. For example, in both the connective tissue diseases and IPF, BAL lymphocytosis is associated with a cellular histology (as opposed to fibrosis) and an improved response to treatment. Furthermore, the overall survival rate in these patients is increased. Conversely, the combination of lavage neutrophilia and eosinophilia without lymphocytosis often portends progressive unresponsive disease. In sarcoidosis, a disease characterized by increases in the number of T-helper ($CD4^+$) lymphocytes in the lung, it has been suggested that clinical deterioration may be expected if the BAL lymphocyte level exceeds 28%. More recent data indicate that the level of BAL lymphocytes has no value in predicting the clinical outcome in sarcoidosis.

The assessment of potential ILD in populations at risk is another role for BAL. For example, in patients with scleroderma and rheumatoid arthritis in whom clinical, radiologic, and physiologic evidence of ILD is lacking, BAL studies have revealed increases in inflammatory cell populations.

Histologic Diagnosis

The final step in the evaluation of a patient with ILD is to decide whether tissue is needed for diagnosis. As previously noted, the diagnosis of connective tissue, occupational, or drug-related ILD is often obvious after a careful history has been taken. In cases of idiopathic and primary ILD (see Table 57-1), the diagnosis may not be as obvious, although clinical, laboratory, and radiologic findings are often suggestive. Furthermore, the diagnosis of IPF, a commonly encountered disorder, in most situations can be established only by lung biopsy.

Transbronchial Biopsy

As a matter of practicality, transbronchial biopsy can be performed during the bronchoscopy for BAL. Transbronchial biopsy is relatively safe and is often diagnostic of sarcoidosis, diffuse malignancy, alveolar proteinosis, or eosinophilic pneumonia. Other entities are less frequently confirmed by this procedure. A transbronchial biopsy interpretation, which describes only inflammation, fibrosis, or both, is not evidence for IPF or any other entity listed in Table 57-1. Furthermore, even in clinically confirmed cases of connective tissue or drug-induced ILD, several different histologic patterns may evolve (see Table 57-2), and lung biopsy is often undertaken to predict prognosis and therapeutic responsiveness, particularly if BAL and HRCT are inconclusive.

Surgical Lung Biopsy

If the transbronchial biopsy, clinical, and lavage data are inconclusive and the patient is not at high risk, a video thoracoscopic or open-lung biopsy should be performed. Moreover, there is a poor correlation between the results of transbronchial and open-lung biopsies unless the transbronchial biopsy yields a specific diagnosis. Therefore, when the transbronchial biopsy is inconclusive and a definitive diagnosis is required, open- or thoracoscopic lung biopsy is indicated.[28]

DIAGNOSIS AND MANAGEMENT OF THE IDIOPATHIC INTERSTITIAL PNEUMONIAS

The IIPs comprise seven clinical-radiologic-pathologic entities that are sufficiently different from one another to be designated as separate diseases. The classification, diagnosis, our understanding of the pathogenic mecha-

nisms and management of the IIPs continue to evolve.[2,29,30] As a group, they can be distinguished from other forms of ILD by clinical methods including history, physical examination, chest radiology laboratory studies, and pathology.[29] Importantly, however, several of them are frequently secondary to a known cause which must be carefully investigated (e.g., cryptogenic organizing pneumonia [COP], NSIP, LIP). Furthermore, the histologic patterns are distinctive but not specific, and they can be seen not only in the idiopathic setting but also in a variety of other conditions.[31] Tables 57-7 and 57-8 provide an overview of the key clinical and pathologic features of the IIPs.

Idiopathic Pulmonary Fibrosis

IPF is a common ILD of unknown etiology. IPF is a well-defined clinical entity with characteristic clinical, radiographic, physiologic, and pathologic manifestations.[29–31] The exact prevalence of this condition is unknown. In a recent study using narrow case-finding criteria, the prevalence ranged from 0.8 to 64.7/100,000 individuals; comparable figures for incidence were 0.4 to 27.1/100,000 persons. Extrapolating these rates to the overall U.S. population, prevalence was estimated to be 14.0/100,000 (incidence, 6.8/100,000).[32] Both the prevalence and the incidence of IPF increase markedly with age.

Clinical Features

IPF occurs in middle age, usually between 50 and 70 years of age. In fact, it is quite uncommon for a patient to present before the age of 40. The typical patient presents with the insidious onset of exertional breathlessness and a nonproductive cough. Constitutional symptoms are uncommon, but weight loss, fever, fatigue,

TABLE 57-7. Contrasting Pathologic Features of the Idiopathic Interstitial Pneumonias

Features	UIP	DIP	RB-ILD	AIP	NSIP	COP
Temporal appearance	Variegated	Uniform	Uniform	Uniform	Uniform	Uniform
Interstitial inflammation	Scant	Scant	Scant	Scant	Usually prominent	Usually moderate
Fibrosis	Patchy	Variable, diffuse, moderate	Variable, focal, mild	Typically no, but may evolve to fibrosis	Variable, diffuse	No
Fibroblast proliferation	Fibroblast foci prominent	No	No	Diffuse	Occasional, diffuse or rare fibroblast foci	Intra-alveolar (Masson bodies)
Honeycomb change	Yes	No	No	No	Rare	No
Intra-alveolar macrophage accumulation	Occasional, focal (smokers)	Yes, diffuse	Peribronchiolar	No	Occasional, patchy	Foamy macrophages common
Hyaline membranes	No	No	No	Occasional, focal	No	No

AIP, acute interstitial pneumonia; COP, cryptogenic organizing pneumonia; DIP, desquamative interstitial pneumonia; NSIP, nonspecific interstitial pneumonia; RB-ILD, respiratory bronchiolitis–associated interstitial lung disease; UIP, usual interstitial pneumonia.

Adapted from Katzenstein ALA, Myers JL: Idiopathic pulmonary fibrosis: Clinical relevance of pathologic classification. Am J Respir Crit Care Med 157:1301–1315, 1998; and King TE Jr: Idiopathic interstitial pneumonia. *In* Schwarz MI, King TE Jr (eds): Interstitial Lung Diseases (4th ed). Hamilton, Ontario: BC Dekker, 2003, pp 701–786.

TABLE 57-8. Contrasting Clinical Features of the Idiopathic Interstitial Pneumonias

Features	UIP	DIP	RB-ILD	AIP	NSIP	COP
Mean age at onset (yr)	60s	40s	40s	50s	50s	50s
Onset	Insidious	Insidious	Insidious	Acute	Subacute, insidious	Acute or subacute
History of cigarette smoking	About two thirds	Most	Most	Not known	Uncommon	About half
Mortality rate (mean survival)	68% (5–6 yr)	27% (12 yr)	0%	62% (1–2 mo)	~25% in 10 yr	10% in 5 yr
Response to steroids	Poor	Good	Good	Poor	Good	Excellent
Complete recovery possible	No	Yes	Yes	Yes, very rarely	Yes	Yes (≤70% of patients)

AIP, acute interstitial pneumonia; COP, cryptogenic organizing pneumonia; DIP, desquamative interstitial pneumonia; NSIP, nonspecific interstitial pneumonia; RB-ILD, respiratory bronchiolitis–associated interstitial lung disease; UIP, usual interstitial pneumonia.

Adapted from Katzenstein ALA, Myers JL: Idiopathic pulmonary fibrosis: Clinical relevance of pathologic classification. Am J Respir Crit Care Med 157:1301–1315, 1998; and King TE Jr: Idiopathic interstitial pneumonia. In Schwarz MI, King TE Jr (eds): Interstitial Lung Diseases (4th ed). Hamilton, Ontario, Canada: BC Decker, 2003, pp 701–786.

myalgias, or arthralgia is occasionally present. Although patients may present with only a nonproductive cough, all patients experience dyspnea with exertion as the disease progresses. Most patients have these symptoms for months to years prior to definitive evaluation, usually around 12 to 18 months. Recently, an accelerated variant of IPF was described.[33] These patients, usually male smokers, present for evaluation a few months after the onset of symptoms with severe functional derangement and display rapid progression and shorter survival than typical IPF patients.

The physical examination is rarely normal. Most patients have bibasilar late inspiratory fine crackles (Velcro crackles) on chest examination. Clubbing of the fingers is seen in 40% to 75% of patients and is a late finding in the disease course. Cardiac examination is usually normal except in the middle or late stages of the disease, when findings of pulmonary hypertension (e.g., augmented P_2, right-sided lift, and S_3 gallop) and cor pulmonale may become evident. Similarly, cyanosis is a late manifestation indicating advanced disease. Spontaneous pneumothorax rarely occurs.

Blood and Serologic Studies

An elevated erythrocyte sedimentation rate, low-titer antinuclear antibodies, and rheumatoid factor have been identified in some of these patients.

Chest Imaging Studies

Chest Roentgenography. The typical finding in patients with IPF is peripheral reticular opacities with a netlike appearance of linear or curvilinear densities, with predominance at the lung bases (Fig. 57-20). A coarse reticular pattern or multiple cystic or honeycombed areas (i.e., coarse reticular pattern with translucencies measuring 0.5–1.0 cm in diameter) are roentgenographic findings that correlate with advanced disease and poor prognosis (see Figs. 57-6 and 57-7). Chest roentgenographic evidence of reduced lung volumes is usually present unless there is associated obstructive airway disease.

Pleural abnormalities are uncommon in IPF; their presence should suggest another diagnosis, such as collagen vascular disease (especially rheumatoid arthritis or systemic lupus erythematosus), mitral valve disease, congestive heart failure, asbestosis, infection, drug-induced lung disease, or lymphangitic carcinomatosis (see Table 57-5).

Computed Tomography Scan. CT plays a major role in the evaluation of pulmonary parenchymal diseases, especially IPF.[14,34] HRCT is useful in the differentiation of IPF from other ILDs, the determination of the extent and severity of disease activity, and most importantly, the detection of disease, especially in patients with normal or minimal change on plain chest roentgenograms. HRCT findings in IPF include a marked peripheral (subpleural) distribution of the interstitial densities. The involvement is patchy, with areas of reticulation intermingled with areas of normal tissue, often associated with cystic spaces 2 to 4 mm in diameter (see Fig. 57-11). Early disease appears as patchy, predominantly peripheral, subpleural reticular opacities and minor degrees of honeycomb change. In more advanced disease, a more diffuse reticular pattern in the lower lung zones with thickened interlobular septa and intralobular lines progresses to traction bronchiectasis and subpleural fibrosis.[12]

One of the key findings indicating the diagnosis of IPF is the presence of honeycomb cysts in a basilar subpleural distribution. Honeycomb changes appear on the HRCT scan as variably sized cystic spaces that share walls and frequently stack upon one another in several layers.[35] Ground-glass opacities are common but of mild severity and characteristically much less extensive than the reticular pattern. Architectural distortion, which reflects lung fibrosis, is often prominent.

Combined lower lobe pulmonary fibrosis and upper lobe emphysema has been recently described as a new computer tomography–defined syndrome (Fig. 57-21).[36,37] Smoking appears to be the predominant risk factor for this disorder. Patients with this entity are primarily males with a mean age of 65 years who have relatively preserved lung volumes but marked reductions in D_{LCO} on pulmonary function testing. Limited data suggest that these patients with IPF and coexisting emphysema are more likely to require long-term oxygen therapy, develop pulmonary hypertension, and may have worse outcome than those without emphysema.[38]

Identification of a relationship between pulmonary function testing and HRCT findings remains incomplete. FVC, D_{LCO}, arterial PO_2 measured at peak exercise, and oxygen desaturation during exercise are the physiologic parameters that best correlate with the global extent of disease on HRCT.[39,40] In one study, D_{LCO} was the physiologic characteristic most highly correlated with HRCT findings.[41] Serial HRCT scanning showed that the changes over time in the total extent of the disease were similar to those changes observed in D_{LCO} and FVC.[40] HRCT plays an important role but has not replaced lung biopsy in the diagnosis and assessment of most ILDs. In the case of IPF, connective tissue diseases (particularly scleroderma) and asbestosis may cause a similar HRCT appearance (except for the presence of parenchymal bands of fibrosis and pleural plaques in patients with asbestosis). Patients with chronic hypersensitivity pneumonitis can have similar reticular opacity or honeycombing, but often lack the bibasilar predominance seen in IPF.[42]

Studies evaluating the ability of HRCT scanning to diagnose IPF accurately have found that HRCT significantly increases the level of diagnostic confidence. In general, the sensitivity for a confident diagnosis is low (~48%) but the specificity is high (~95%).[43–47] The accuracy of a confident diagnosis of IPF made on HRCT by a trained observer appears to be about 90%.[42,48–50] Less experienced observers are substantially less accurate than experienced observers.[48] An HRCT pattern highly suggestive of the diagnosis of IPF is associated with a very poor prognosis.[51] Patients with basilar honeycombing have a worse survival than those without honeycombing on the HRCT scan but with a histopathologic

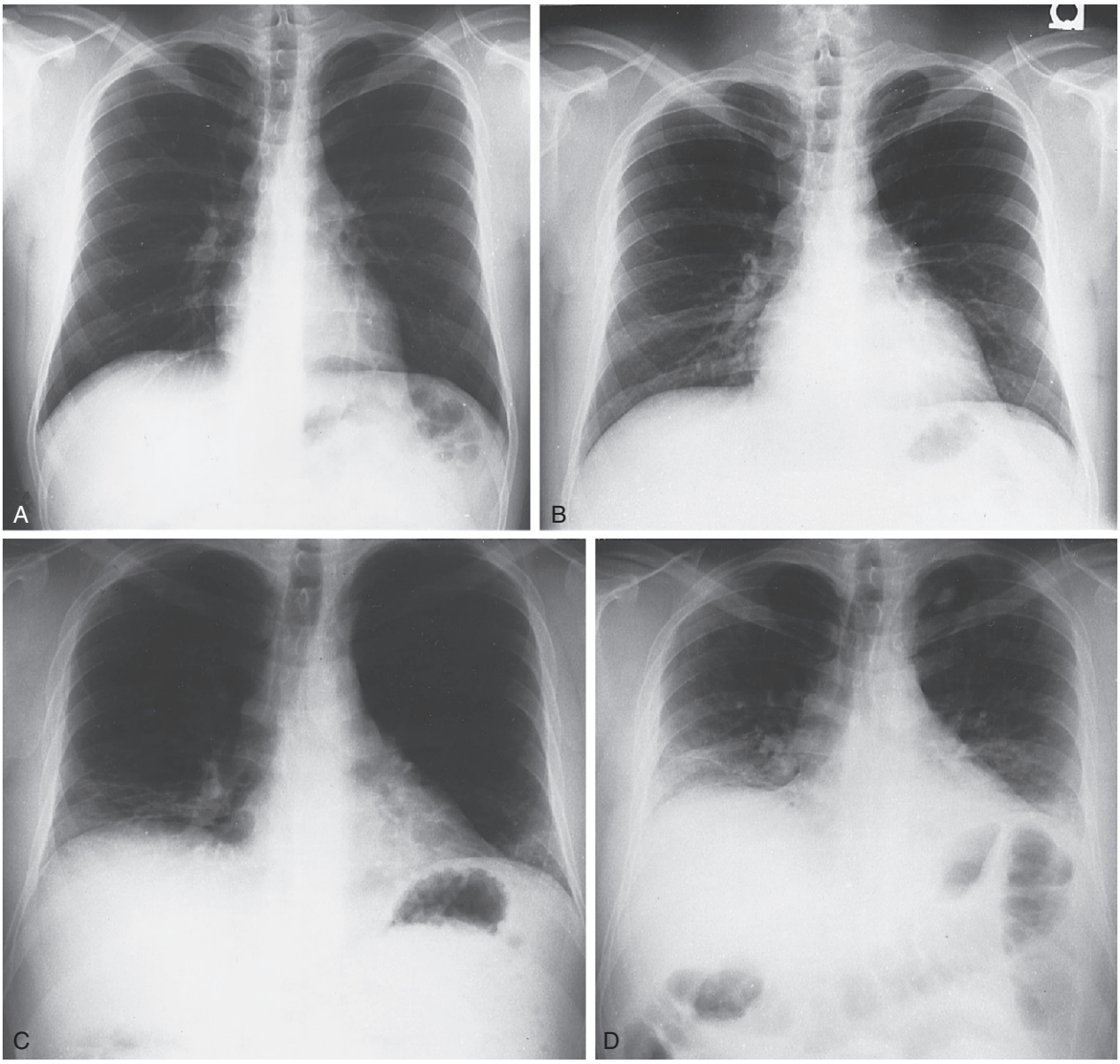


FIGURE 57-20 ■ Serial chest radiographs from a patient with IPF. **A,** The posteroanterior radiograph of the chest was obtained at the time of onset of breathlessness with exercise and mild cough. The chest appears normal. **B,** The follow-up film reveals progressive loss of lung volume and bibasilar, predominantly reticular opacities. The patient had stopped regular exercise because of breathlessness with exertion. **C,** Progressive changes are evident, with severe loss of lung volume. Predominantly in the lower lung zone are seen diffuse, bilateral, coarse reticular opacities typical of the radiographic appearance of the middle to late stage of pulmonary fibrosis. **D,** Continued disease progression is evident, with honeycombing and pulmonary hypertension. Open-lung biopsy revealed usual interstitial pneumonia with extensive fibrosis and histologic honeycombing. Treatment with corticosteroids and cyclophosphamide (Cytoxan) was started, but the patient experienced a progressive decline in functional status and died 6 months after lung transplantation.

diagnosis of UIP.[35] In a multivariate analysis of a large multicenter trial, it was found that extent of reticulation and honeycombing on HRCT is an important independent predictor of mortality in patients with IPF.[41]

Other Imaging Techniques

Gallium Scanning. Lung scanning with radioactive gallium (^{67}Ga) is a noninvasive test for staging the "alveolitis" found in ILDs, particularly sarcoidosis. Unfortunately, ^{67}Ga lung scanning is not recommended in the routine evaluation of IPF because inflammation is not a prominent feature, it is difficult to interpret, it is not specific, and a negative scan does not exclude disease.

Ventilation-Perfusion Lung Scanning. Ventilation-perfusion lung scanning is not recommended as a routine part of the evaluation. In most parenchymal diseases, ventilation-perfusion scanning reveals an inhomogeneous reduction of blood flow, ventilation, or both. Two types of perfusion abnormalities occur in IPF:

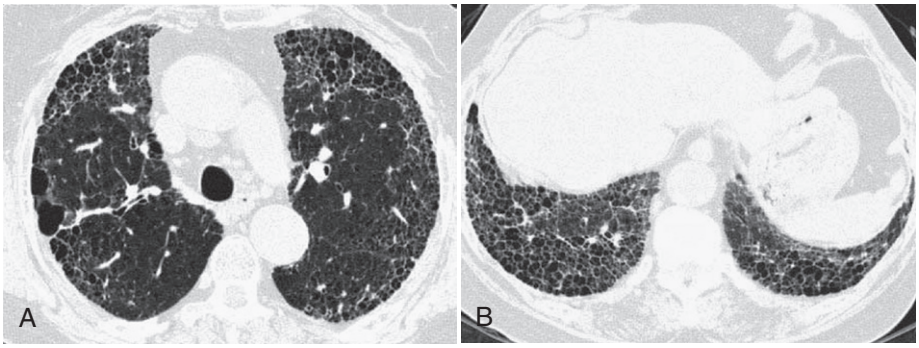


FIGURE 57-21 ■ Combined pulmonary fibrosis and emphysema. CT images from a 69-year-old woman with a 12-month history of worsening cough and dyspnea. She is a current heavy smoker. **A,** Upper zones of the lungs show emphysema and mild patchy peripheral reticular opacities. **B,** Lower zones of the lungs show emphysema and architectural distortion with patchy peripheral reticular opacities and extensive honeycombing lesions.

nonsegmental inhomogeneities, probably due to a localized loss of the capillary bed, most often in the lower lobes; and increased perfusion of the upper lung zones, resulting from pulmonary hypertension, which induces an upward shift in the gradient of capillary perfusion. Ventilation scans often reveal patchy, nonsegmental areas of decreased ventilation, reflecting regions of airway obstruction or alveolar destruction. Patchy areas of high and low ventilation-perfusion matching usually occur, with a few areas of well-maintained ventilation-perfusion matching. These findings of mismatching of ventilation and blood flow help explain the hypoxemia and high Vd/Vt ratio found in many of these patients at rest.

Magnetic Resonance Imaging for Differentiating Inflammation and Fibrosis

Although the traditional approach to lung imaging using HRCT consisting of 1-mm slices is increasingly being augmented by novel methods, the role of these techniques in IPF and other ILDs remains uncertain. MRI has several advantages over CT, including speed of imaging, lack of ionizing radiation, and ability to identify tissue characteristics at a nuclear level that may allow for novel assessments of lung function and microstructure.[52] In a recent study, 10 patients with IPF and 16 with NSIP were examined by comparing 3-T MRI of the lung to the morphologic findings on surgical biopsy.[53] Inflammation-predominant biopsy sites showed an early enhancement pattern on dynamic studies and high-signal intensity on T2-weighted triple-inversion black-blood turbo spin-echo (TSE) images compared with fibrotic areas. These results indicate that qualitative analysis of dynamic T1-weighted three-dimensional turbo field-echo magnetic resonance images obtained at 3-T may be helpful for differentiating inflammation- and fibrosis-predominant lesions.

Imaging of Fibrogenesis by Positron Emission Tomography. The putative role of physiologic imaging using ^{18}F-2-fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET) scans in IPF has been recently explored in few patients without clear results.[54] In general, the lungs of patients with IPF appear to show increased uptake of FDG on PET. Some studies have suggested that cis-4-^{18}F-fluoro-L:-proline [^{18}F-proline] may be a reliable marker for fibrosis formation. Recently, this radioligand was tested for in patients with IPF.[55] PET acquisition was performed 1, 2, and 3 hours after injection of 400 MBq ^{18}F-proline. Surprisingly, low uptake of ^{18}F-proline was found in the lungs of all patients with IPF. The highest uptake was seen at 2 hours postinjection, with a decline at 3 hours past injection. The authors speculate that this low uptake may be due to the slow nature of fibrogenesis or to the relatively low dose of proline that can be used. Further research is needed to know if imaging through PET has a role in the diagnosis or prognosis of ILDs.

Pulmonary Function Tests

The lung volumes (TLC, functional residual capacity, and residual volume) are reduced in IPF. Early on, the lung volumes may be normal, especially in patients with superimposed chronic obstructive pulmonary disease (COPD). Lung volumes are higher in smokers with IPF compared with those who have never smoked.[18] As mentioned previously, a group of smokers develop a combined IPF and emphysema and show almost normal lung volumes, even in advanced disease.[36,37] Expiratory flow rates (FEV_1 and FVC) may be decreased because of the reduction in lung volume, but the FEV_1/FVC ratio is maintained. Because of the increased static elastic recoil found in these patients, flow rates (at any given lung volume) are often increased (see Figs. 57-15A and 57-17).

Patients with IPF are tachypneic, with rapid shallow breaths, probably because of increased work of breathing. This rapid respiratory rate presumably results from altered mechanical reflexes, caused by the increased elastic load, vagal mechanisms, or both, because no defined chemical basis for the hyperventilation has been identified (see Fig. 57-18).

The D_{LCO} is reduced, often prior to the loss of lung volume. The decrease in the D_{LCO} results from both a contraction of the pulmonary capillary volume and the presence of ventilation-perfusion abnormalities. Resting arterial blood gases are usually abnormal, revealing

hypoxemia and respiratory alkalosis. The major cause of resting hypoxemia is ventilation-perfusion mismatching, and it is not due to either impaired oxygen diffusion, as was originally suspected, or to anatomic shunts. With exercise, the (A – a) P_{O_2} widens, and the arterial P_{O_2} and oxygen saturation fall. During maximal exercise, 20% to 30% of the exercise-induced widening of the (A – a) P_{O_2} may be caused by some impairment of oxygen diffusion. Importantly, the abnormalities identified at rest do not accurately predict the magnitude of the abnormalities seen with exercise (see Fig. 57-19). In addition, gas exchange during exercise has been demonstrated to be a sensitive parameter for following the clinical course.

In patients with IPF, a highly significant correlation has been reported between the 6-minute walk distance test (6MWD) and $D_{L_{CO}}$ as well as $\dot{V}_{O_2}$max and is a strong predictor of mortality.[56] The 6MWD is difficult to perform in patients with advanced lung disease, however, and variability is common.

The 15-steps Climbing Test Oximetry has been found useful for estimating ventilatory reserve in patients with COPD and for predicting postoperative complications of lung resection.[57] In a recent study, it was shown that the desaturation measured by the 15-steps Oximetry Test in IPF patients is comparable with the desaturation measured by the cardiopulmonary exercise test and the 6MWD test, suggesting it may be a reliable tool for monitoring IPF progression and for evaluating the need for oxygen supplementation. This test may serve as a surrogate marker of $\dot{V}_{O_2}$max and an alternative to the 6MWD in this setting.[57]

During exercise, patients with IPF increase their minute ventilation primarily by increasing their respiratory frequency (see Fig. 57-18). This method of increase differs from that in normal subjects, in whom increased ventilation during mild exercise occurs by an increase in the tidal volume (V_T) rather than respiratory rate. Thus, patients with IPF have elevated minute ventilation during exercise that is in part related to the increase in V_D. In addition, the V_D/V_T ratio is increased at rest and is maintained or decreases only slightly with exercise. Occasionally, the V_D/V_T ratio increases in ILDs that have a prominent pulmonary vascular component, such as scleroderma or Langerhans cell histiocytosis.

Pulmonary Hemodynamics

New evidence suggests pulmonary arterial hypertension (PAH) is relatively common in IPF and may contribute substantially to functional status, quality of life, morbidity, and mortality.[58] The prevalence of PAH complicating the course of patients with IPF has been reported to occur in 32% to 85% of patients, being more frequent in advanced disease.[58] The most appropriate method to detect PAH noninvasively is transthoracic (Doppler) echocardiography. Unfortunately, echocardiography may be inaccurate in estimating pulmonary arterial systolic pressure in patients with ILD.[59] Right heart catheterization (RHC) is the "gold standard" for the hemodynamic evaluation of the pulmonary circulation and diagnosis of PAH but is an invasive technique. RHC may be necessary, however, to document the severity of PAH and potential right ventricular dysfunction. Abnormalities in gas exchange and exercise capacity seem to have a significant association with PAH in IPF. Thus, exaggerated exercise oxygen desaturation, out-of-proportion reduction of $D_{L_{CO}}$, and supplemental oxygen requirement should raise suspicion of (and may be a useful surrogate for) the presence of underlying PAH.[59,60] Brain natriuretic peptide (BNP) concentrations predicted moderate to severe PAH with 100% sensitivity and high specificity (89%) in a small cohort of patients with pulmonary fibrosis.[61] This study requires further validation.

Pathologic vascular findings in IPF consist of changes in the arteries, arterioles, and venules as well as destruction of the capillary bed.[62] Advential thickening around the pulmonary vessels reflects an increase of connective tissue. Smooth muscle cell hypertrophy and proliferation and collagen and elastin accumulation occur in the media of the small muscular pulmonary arteries, and distal pulmonary arterioles become muscularized. In addition, there may be extensive intimal hyperplasia, fibrosis, and reduplication of the inner elastic lamina in the small muscular pulmonary arteries in IPF.

Supplemental oxygen is the most obvious choice for prevention or treatment of PAH; however, there are no data supporting favorable effects of oxygen on survival in PAH associated with IPF. Vasodilators agents are currently being studied, but one must recognize that decreased physiologic vasoconstriction in low ventilation-perfusion lung units may worsen shunt and hypoxemia in IPF.

Endothelin-1 (ET-1) receptor antagonists have been useful in patients with PAH (mostly in primary PAH or associated with connective tissue disease). Clinical trials in PAH associated to IPF are ongoing (Table 57-9). Prostacyclin (prostaglandin I_2 [PGI_2]) analogues used via inhalation could maintain (or even improve) ventilation-perfusion matching and could have a beneficial effect targeting PAH. In one study, inhaled iloprost decreased mean pulmonary artery pressure without changes in shunt flow,[63] suggesting the utility of selective pulmonary vasodilation in patients with PAH/IPF. A randomized clinical trial of inhaled iloprost for this patient group has been recently completed, although the results have not yet been published.[64] Sildenafil, a phosphodiesterase-5 inhibitor, promotes vasodilation and decreases smooth muscle proliferation and vascular remodeling. In an open-label study of treatment with sildenafil for 3 months in a small cohort of patients with PAH and IPF, a modest but significant improvement in 6MWD was noticed.[65] Several randomized clinical trials are currently ongoing (see Table 57-9).

Abnormalities during Sleep

Many patients with IPF, especially those with low daytime arterial oxygen saturation or a history of snoring during sleep, develop sleep disturbances characterized by reduced rapid eye movement sleep, lighter and more fragmented sleep, and hypoxemia during rapid eye movement sleep. Severe hypoxemia occurs in the

TABLE 57-9. Ongoing Clinical Trials in Patients with Idiopathic Pulmonary Fibrosis

Drug	Aim/Mechanism of Action	Sponsor	ClinicalTrials.gov Identifier
QAX576	It may down-regulate IL-13	Novartis	NCT00532233
FG-3019	It blocks CTGF	FibroGen	NCT00074698
Bosentan (BUILD-3)	Inhibitor of ET-1	Actelion	NCT00391443
Macitentan	Inhibitor of ET-1	Actelion	NCT00903331
Bosentan	Indicated for PAH	UCLA; Actelion	NCT00625469
Ambrisentan (ARTEMIS-IPF)	Inhibitor of ET-1 (selective for ET-A)	Gilead Sciences	NCT00768300
Pirfenidone	Antifibrotic effects in vitro and in experimental models	InterMune	NCT00287729
Zileuton	Inhibitor of leukotrienes	University of Michigan	NCT00262405
Gleevec (imatinib mesylate)	Tyrosine kinase inhibitor	Daniels, Craig E., MD, Novartis	NCT00131274
Octreotide (somatostatin analogue)	Anti-inflammatory and antifibrotic properties in vitro and in vivo	Institut National de la Santé et de la Recherche Médicale, France	NCT00463983
GC1008	Antibody that neutralizes TGF-β	Genzyme	NCT00125385
Inhaled IFN-γ	Anti-fibrotic effects	New York University School of Medicine; National Center for Research Resources, Stony Brook University; Respironics	NCT00563212
Inhaled IFN-γ	Same as previous	New York University School of Medicine	NCT00212563
Tetrathiomolybdate	Copper chelating agent	University of Michigan; Coalition for Pulmonary Fibrosis	NCT00189176
BIBF 1120	Inhibits profibrotic growth factors	Boehringer Ingelheim Pharmaceuticals	NCT00514683
NAC alone or with azathioprine and prednisone	Effect of the antioxidant NAC	NHLBI	NCT00650091
Thalidomide	Indicated for cough. Suppresses functional up-regulation of sensory fibers within the respiratory tract	Johns Hopkins University	NCT00600028
Sildenafil	Indicated for PAH	University of California, Los Angeles, and Pfizer	NCT00625079
Sildenafil	Indicated for PAH	NHLBI; Pfizer	NCT00517933
Sildenafil	Indicated for PAH	Department of Veterans Affairs	NCT00359736
Inhaled Iloprost	Indicated for PAH; Secondary purpose: to evaluate antifibrotic properties	Actelion	NCT00109681
CNTO 888	Phase II study	Centocor	NCT00786201
Losartan	An antagonist of angiotensin type 1 receptor	H. Lee Moffitt Cancer Center and Research Institute; NCI	NCT00879879
Interferon-alfa lozenges	Reduce the frequency and severity of coughing	Amarillo Biosciences; Texas Tech University Health Sciences Center	NCT00690885

CTGF, connective tissue growth factor; ET-1, endothelin-1; ET-A, endothelin receptor A; IFN-γ, interferon-γ; IL-13, interleukin-13; NAC, *N*-acetylcysteine; NCI, National Cancer Institute; NHLBI, National Heart, Lung, and Blood Institute; PAH, pulmonary arterial hypertension; TGF-β, transforming growth factor-β. From http://clinicaltrials.gov/ct2; search for Clinical trials: idiopathic pulmonary fibrosis.

absence of obstructive sleep apnea or changes in breathing pattern. Tachypnea persists during sleep. Identification and correction of the sleep disturbance may reduce morbidity and improve quality of life and patient survival. In a recent study, obstructive sleep apnea was confirmed in two thirds of IPF patients with complaints suggestive of sleep apnea. An increased body mass index and a significant impairment in pulmonary function testing may be predictors of obstructive sleep apnea in this population.[66]

Histopathology

The gross appearance of the lungs in IPF reveals a distinctive nodular pleural surface, sometimes with a marked cirrhotic appearance. The histopathologic pattern in IPF is UIP. UIP is characterized by a pattern quite distinguishable even on low-power magnification because of its characteristic heterogeneous, predominantly subpleural distribution (Fig. 57-22). This striking heterogeneous appearance is characterized by the presence of small areas of residual normal or nearly normal lung interspersed among extensively scarred parenchyma and microscopic honeycombing (areas characterized by enlarged air spaces lined by bronchiolar epithelium, often filled with mucin and variable numbers of inflammatory cells) abutting areas of active proliferation of fibroblasts and myofibroblasts (Figs. 57-23 through 57-25).[67] These discrete areas of fibroblastic proliferation have been termed *fibroblastic foci* and are essential to

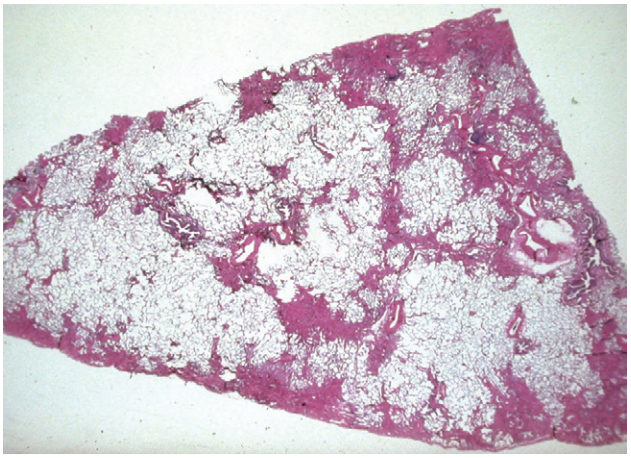


FIGURE 57-22 ■ Usual interstitial pneumonia pattern often shows a striking subpleural distribution. This low-power photomicrograph is from an area without the usual remodeling of the lung architecture with cystic (honeycomb) changes. (Courtesy of Thomas V. Colby, MD, Mayo Clinic, Scottsdale, AZ.)

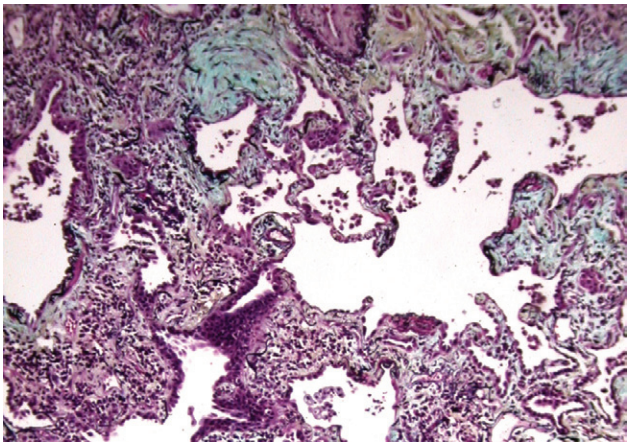


FIGURE 57-24 ■ Usual interstitial pneumonia pattern. Two fibroblastic foci of loose organizing connective tissue are seen in the top center and top right of the photomicrograph adjacent to an area of dense fibrosis. (Courtesy of Thomas V. Colby, MD, Mayo Clinic, Scottsdale, AZ.)

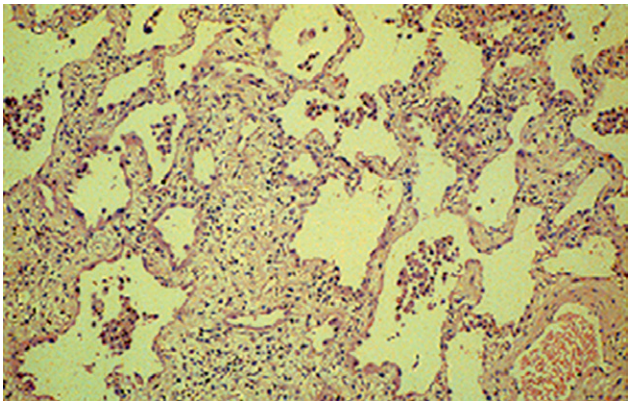


FIGURE 57-23 ■ Photomicrograph of usual interstitial pneumonia shows residual lymphoplasmacytic inflammation and collagen deposition broadening alveolar walls. (Original magnification ×10.)

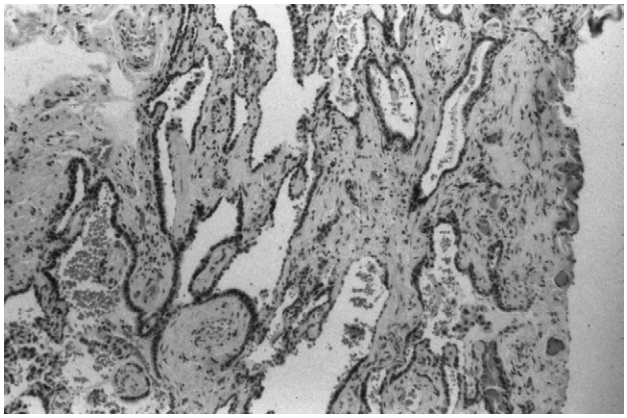


FIGURE 57-25 ■ Photomicrograph of honeycomb lung in IPF. There is total disruption of the lung architecture by bands of fibrous tissue forming cystic spaces. The spaces are lined by metaplastic epithelium. (Original magnification ×10.)

the histopathologic diagnosis of UIP[68] (see Fig. 57-24). Fibroblastic foci are composed of small dome-shaped collections of spindle-shaped fibroblasts and myofibroblasts within myxoid stroma, covered by hyperplastic alveolar lining cells. Generally, minimal interstitial inflammation is present in UIP; if present in significant amounts, the histopathologic diagnosis should be reconsidered. However, chronic inflammation, lymphoid aggregates with germinal centers, and even acute inflammation may be prominent around honeycomb areas, likely related to poor clearance from the areas of scarred lung.[67]

Bronchogenic carcinoma (all histologic types) has been identified with increased frequency in advanced IPF.[69] It has been postulated that carcinoma arises from the metaplastic bronchiolar epithelium that develops in these patients, but the pathogenic mechanisms are unclear. Interestingly, a number of the reported cases occurred in patients with familial IPF.

Etiologic Factors and Pathogenic Mechanisms

The inciting factors in the development of IPF are unknown. A widely held hypothesis is that this disorder occurs in susceptible individuals following some unknown stimuli. Inciting agents initiate an uncontrolled cascade of events that evolve to the fibrotic process. Smoking presents the most significant association with IPF, particularly for individuals who were ever smokers, with odds ratios (ORs) varying from 1.6 to 9.4.[70] The same association has been found in familial IPF. In a family-based case-control study of familial interstitial pneumonia, Steele and colleagues[71] identified 111 families, with 309 affected and 360 unaffected individuals. Adjusting for age and gender, ever smoking was strongly associated with familial interstitial pneumonia (OR, 3.6; 95% confidence interval [CI], 1.3–9.8). Some occupational and environmental exposures—primarily to wood

and metal dusts—have shown increased association with IPF.[70] The presence of Epstein-Barr virus found in some patients has led to speculation that chronic viral infection might play a role in the etiology of IPF,[72] but this virus has been found in other fibrotic lung diseases, as well as in many controls. Higher incidence of gastroesophageal reflux (GER) has been found in patients with IPF.[73] GER is frequent, however, in the normal population, as well as in patients with other advanced lung diseases, including cystic fibrosis, COPD, and fibrosis associated with scleroderma.[74]

The role of host genetic factors and their interactions with environmental factors leading to IPF is unknown. Numerous gene polymorphisms have been examined, and only a few of them have demonstrated confirmed (usually weak) association. Moreover, putative associations have not been corroborated in independent cohorts.

An important advance in our understanding of ILD has been the recognition that UIP appears to be a distinct pathophysiologic entity characterized by minimal inflammation and chronic fibroproliferation due to abnormal parenchymal wound healing.[75,76] This paradigm suggests the pathologic process of UIP is the result of persistent remodeling (abnormal wound healing) of the lung parenchyma. Multiple "microinjuries" damage and activate alveolar epithelial cells, which in turn provoke a profibrotic microenvironment.[77] Alveolar epithelial cells secrete growth factors and induce migration and proliferation of fibroblasts and differentiation into myofibroblasts. Aggregates of subepithelial fibroblasts-myofibroblasts (fibroblastic foci) and alveolar epithelial cells produce matrix-metalloproteinases 2 and 9 that may increase basement membrane disruption and allow fibroblast-myofibroblast migration into the alveolar spaces. In addition, alveolar epithelial cells induce an antifibrinolytic environment in the alveolar spaces, enhancing wound clot formation. Current evidence suggests that the tissue-factor–dependent extrinsic pathway is the predominant mechanism by which the coagulation cascade is locally activated in the lungs of patients with pulmonary fibrosis.[78] Both intra-alveolar and interstitial myofibroblasts secrete extracellular matrix proteins, mainly collagens. An imbalance between interstitial collagenases and tissue inhibitors of metalloproteinases provokes the progressive deposition of extracellular matrix.[79] Signals responsible for myofibroblast apoptosis seem to be absent or delayed in UIP, increasing cell survival.[80] These myofibroblasts produce angiotensinogen and hydrogen peroxide that have been implied in alveolar epithelial cell death, further impairing reepithelialization.[81,82] Although the molecular mechanisms that lead to end-stage pulmonary fibrosis in the IIPs are poorly understood, data support this "abnormal wound healing" hypothesis in UIP.[83–87] At least in part, the abnormal communication between alveolar epithelial cells and myofibroblasts may be provoked by an aberrant recapitulation of embryologic programs.[88,89]

One of the intriguing observations regarding IPF is that the disease is clearly associated with aging; it usually occurs in individuals older than 50 years, reaching a peak in subjects of 60 to 65 years old. In this context, two recent studies have shown that mutations in the genes encoding telomerase components are implicated in familial pulmonary fibrosis.[90,91] The same investigators demonstrated that patients with sporadic IPF have shorter leukocyte telomeres than age-matched controls and that some of them (10%–25%) had telomere lengths below the first percentile for their age.[92,93] Importantly, it was also determined that IPF patients had short telomeres in alveolar epithelial cells, suggesting that these cells may be the main lung culprit of this pathologic process.[92] Telomeres play a central role in cell fate and aging by adjusting the cellular response to stress and growth stimulation on the basis of previous cell divisions and DNA damage; their shortening has been associated with aging and several diseases.[94,95]

Diagnosis

The most definitive method of establishing a diagnosis is by surgical lung biopsy.[96] Open- or thoracoscopic lung biopsy is indicated because it provides an accurate diagnosis; it excludes neoplastic and infectious processes that occasionally mimic chronic, progressive interstitial disease; it may also identify a more treatable process than originally suspected (e.g., chronic hypersensitivity pneumonitis); and it provides a better assessment of disease activity.[28] Some studies have addressed the accuracy of the combined clinical and radiographic diagnosis of IPF.[43,45] In both studies, clinicians were blinded to the results of the surgical lung biopsies, which were used as the gold standard for diagnosis. The clinical diagnosis of IPF had a sensitivity of 48% and a specificity of 89% compared with the histopathologic diagnosis, which had a sensitivity of 62% and a specificity of 97%.[43,45] These studies argue that when the clinical and radiographic diagnoses are consistent, IPF can be confidently diagnosed. They also demonstrate, however, that this consistency is present in only about half of patients with biopsy-confirmed UIP. Furthermore, experts in the field performed these studies, and it is unclear how the outcome would vary with community physicians less familiar with these processes. In this context, significant disagreement has been reported regarding the diagnosis of IIPs between physicians based in communities compared with those in academic centers.[97] Importantly, community physicians were more likely to make a diagnosis of IPF, which has important implications, as individual patients with other ILDs (e.g., hypersensitivity pneumonitis, NSIP, or collagen vascular disease–associated ILD) are more likely to respond to immunosuppressive treatment, whereas patients with IPF should be referred, whenever possible, for participation in therapeutic trials or evaluated for lung transplant. In addition, this study also confirms that a multidisciplinary team approach between clinicians, radiologists, and pathologists improves interobserver agreement and enhances diagnosis specificity.[97]

Staging of Disease Activity and Predicting Outcome

The long-term survival in IPF is distinctly poor, with only a 20% to 30% survival 5 years after the time of diagnosis.[98] However, the rate of progression is variable. Attempts to predict who will respond to treatment have been largely disappointing primarily because the disease is relentlessly progressive with all the therapies used until now.

Clinical Features. Younger patients tend to have less fibrosis than do older patients, and younger patients and women survive longer than older patients and men. In a recent study, it was found that the percentage of monthly worsening in oxygen saturation is high in males, suggesting differences in disease progression according to gender and may explain the better survival of females with IPF.[99] Current smoking (i.e., at the time of presentation) was associated with improved survival in patients with IPF whereas heavy smoking (i.e., higher number of pack-years) was associated with a worse prognosis.[22] In addition, pulmonary fibrosis combined with emphysema and the accelerated variant of IPF that display the worst survival seems to be more frequent in smokers.[33,36,37]

In a recent study, it was shown that the Medical Research Council (MRC) Chronic Dyspnea Score estimated at the time of diagnosis is predictive of survival and may aid clinicians in assessing the prognosis of new cases of IPF.[100]

Serum Studies. The presence of immunologic markers, including autoantibodies, elevated sedimentation rates, circulating immune complexes, and increased serum immunoglobulins, has not been shown to influence the overall natural history of IPF.

Serum surfactant protein (SP) A and SP-D have prognostic value for mortality in patients with IPF.[101] A recent study showed that after controlling for known clinical predictors of mortality, an increased serum SP-A level is a strong and independent predictor of early mortality among patients with IPF. A prediction model containing SP-A and SP-D was substantially superior to a model with clinical predictors alone.[102]

Chest Roentgenography and High-Resolution Computed Tomography Scanning. A general pattern of evolution is seen in serial chest roentgenograms. The early changes include hazy opacities with reduction in lung volumes that progress to a reticular pattern and finally end in coarser, cystic areas of honeycombed lung. Unfortunately, the chest roentgenogram is not a useful monitor of the degree and extent of lesions. In fact, the only roentgenographic abnormality that correlates with the histologic pattern is honeycombing. Furthermore, the roentgenogram may demonstrate no changes even while clinically apparent physiologic deterioration is occurring. Another major problem with using the chest roentgenogram to follow the disease course or to estimate the stage of disease is that there is considerable interobserver variability in the interpretation of these studies.

HRCT scanning in IPF may be useful in staging disease activity. The finding of a higher extent of ground-glass opacities and a lower extent of reticular opacities on the initial HRCT identifies those patients with early disease who are the most likely to survive longer and respond (transiently) to corticosteroids.[103] Patients with a typical HRCT appearance of UIP experience the highest mortality.[51]

In a recent study, it was shown that by univariate logistic regression analysis, greater extent of fibrosis and lower skewness and kurtosis values by HRCT predicted short-term mortality during follow-up. The multivariate logistic regression analysis showed that the single best predictor of mortality during follow-up was the visual extent of fibrosis on CT images, and there was little additional predictive power to be gained from the more quantitative measures.[104]

Pulmonary Physiologic Tests. Reductions in the vital capacity correlate with the degree of fibrosis present and show a relationship with the overall histologic derangements. A marked reduction in the vital capacity (<50% of predicted) is associated with pulmonary hypertension and a reduced 2-year survival. Patients with normal Dl_{CO} values usually do not have significant gas-exchange abnormalities, whereas patients with values below 70% of predicted frequently have such changes at rest or with exercise. Survival is longer in patients with a more normal Dl_{CO} (>45% of predicted value). A marked reduction of the Dl_{CO} and resting hypoxemia are associated with pulmonary hypertension and decreased survival.

Patients with advanced disease and severe fibrotic process have greater abnormalities of the (A – a) Po_2 when compared with those with early disease and core preserved lung architecture. Alterations in gas exchange during exercise when compared with other indices of lung function correlate best with histopathologic findings. Serial measurements of gas exchange during exercise appear to be the best predictors of survival. In a recent study, it was demonstrated that the predictive ability of serial changes in physiology varied when patients are stratified by the presence/absence of desaturation 88% during a baseline 6MWT. For patients with baseline saturation less than 88%, the strongest observed predictor of mortality was serial change in DL_{CO}. For patients with saturation greater than 88% during their baseline walk test, serial decreases in FVC and increases in desaturation area significantly predicted subsequent mortality.[105] In summary, pulmonary function testing is useful in establishing the presence of impairment in IPF and following its course and response to therapy. The severity of the initial abnormalities in FVC, DL_{CO}, arterial Po_2, and (A – a)Po_2, as well as oxygen desaturation on a 6MWD,[56] correlate with poorer survival. Likewise, changes in DL_{CO}, TLC, FVC, arterial Po_2, oxygen saturation, and (A – a)Po_2 during follow-up are predictive of survival time after adjustment for baseline values.[106,107]

Bronchoalveolar Lavage. It has been suggested that the BAL cellular constituents reflect the state of the pulmonary inflammatory response. Unfortunately, many studies have failed to demonstrate a clear distinction between diseases based on the predominant cell type present in the lavage specimens. IPF is characterized by a severalfold increase in the total number of

inflammatory cells recovered from the respiratory tract with an increase in the percentage of neutrophils and eosinophils. Studies evaluating the association of BAL fluid cellular constituents and mortality have yielded conflicting results about the prognostic value of BAL and were limited by the size of the study cohort and the duration of follow-up.[108]

Turner-Warwick and Haslam[109] found that patients who failed to improve had elevated neutrophil and eosinophil counts throughout their course. Recent findings tend to confirm these findings, suggesting that increased BAL fluid neutrophil percentage may be an independent predictor of early mortality among persons with IPF.[110] The impact was most important in the first year of follow-up and attenuated with time.

In one study, it was found that SP-A is reduced in IPF, and decreases in its concentration referenced to total phospholipid (a marker of surfactant to normalize to the surface sampled by lavage and recovery) predict an adverse clinical outcome and poorer survival.[101]

Histopathology. Until recently, no specific histologic feature, other than end-stage fibrosis and honeycombing, has been shown to correlate with survival in UIP.[75,111] It has been proposed that the earliest and most characteristic manifestation of ongoing lung injury in UIP is the development of multiple fibroblastic foci.[67,68] The prognostic significance of these aggregates of fibroblasts and myofibroblasts in surgical lung biopsies from patients with IPF is unclear, and several studies have given contradictory results.[111-115] The effect of sample size, tissue sampling bias, and the different techniques for assessing the number of foci may account for these results. In general, detailed quantification of fibroblast foci on surgical lung biopsies may not be a consistent predictor of patient survival in this disease.

Prediction Models. Several investigators have attempted to identify parameters that best predict the clinical course and prognosis of IPF.[56,106,116-118] Individual changes in dyspnea score, TLC, FVC, arterial Po_2, oxygen saturation, or (A – a)Po_2 over 6 and 12 months may be useful as surrogate end points in monitoring therapeutic efficacy in individual patients. Prediction models based on combining multiple baseline clinical, radiologic, or physiologic measurements have been derived from large groups of carefully selected patients with IPF and appear to perform well as predictors of outcome.[22,117] Using hierarchical multivariable analysis of clinical, radiologic, and extensive physiologic variables (CRP), King and associates[22] developed a model that allows clinicians to make more precise prognostic estimations about patients with IPF. This model included the parameters of age, smoking history, clubbing, extent of profusion of interstitial opacities, presence or absence of pulmonary hypertension on the chest radiograph, percent predicted TLC, and arterial Po_2 at the end of maximal exercise. Although the CRP score is an accurate predictor of survival in IPF, it requires both detailed radiographic analysis and exercise physiologic measurements, neither of which is readily available to many physicians. This may limit its utility as a predictor of survival for those in general practice.

Wells and coworkers[117] identified a composite physiologic index (CPI) closely reflecting the morphologic extent of pulmonary fibrosis while accounting for the extent of emphysema (a finding commonly present in smokers with IPF). The CPI correlated strongly with disease extent on CT and mortality and was more accurate than any individual pulmonary function test.[117] However, its value in clinical practice appears limited.

Outcome and Causes of Death. Clinical deterioration in patients with IPF is expected. Most patients experience episodes of worsening shortness of breath, decreased exercise tolerance, or other decline in functional status during the course of their illness. Disease progression may be difficult to distinguish from disease-associated complications and adverse effects of therapy[119] (Table 57-10).

In a study of 42 consecutive patients with IPF who underwent a postmortem over a 9-year period, it was found that IPF by itself was the immediate cause of death in half of the patients either by acute exacerbation or from the gradual progression of the disease.[120] Other respiratory causes of death included pneumonia and aspiration. Cardiovascular disease including arrhythmia, myocardial infarction, and severe cor pulmonale was found to be the cause of death in 20% of subjects. Evidence of pulmonary hypertension was present in the

TABLE 57-10. Mortality from Disease or Therapy: Percent of All Deaths

PROGRESSIVE RESPIRATORY FAILURE
Gradual progression or acute exacerbation
Mortality: 39%
BRONCHOGENIC CARCINOMA
Mortality: 10%
Excess risk of 14:1 compared with general population; same histologic distribution as seen in population
CARDIOVASCULAR DISEASE
Mortality: 24%
Right ventricular hypertrophy, cor pulmonale due to progressive, long-standing pulmonary hypertension and right-sided heart failure
Left ventricular heart failure usually due to concurrent ischemic heart disease
PULMONARY INFECTION
Mortality: 2%–4%
Increased incidence: corticosteroids and cytotoxic therapy may further increase risk
PULMONARY EMBOLISM
Mortality: 3%–7%
Pulmonary angiography frequently required to make diagnosis
PNEUMOTHORAX
Occurs less often than in other interstitial lung diseases
May be difficult to manage

Adapted from Panos RJ, Mortenson RL, Niccoli SA, et al: Clinical deterioration in patients with idiopathic pulmonary fibrosis: Causes and assessment. Am J Med 88:396–404, 1990.

postmortem of 45% patients and was the immediate cause of death in 2 of them. Pulmonary embolism appears to be relatively common in IPF lung transplant recipients, although its prevalence is unknown.[121] Importantly, it has been shown that patients with IPF have a higher prevalence of coronary artery disease.[122] Also, patients with clinically stable IPF exhibit not only right ventricle diastolic and systolic dysfunction but also impaired left ventricle diastolic filling, while the systolic function is preserved.[123]

Therapeutic Approach

IPF is a progressive and fatal disorder without spontaneous remission, and no therapy to date has been shown to be effective. Although the natural history of IPF has not been appropriately defined, data thus far suggest the median survival after diagnosis, with or without treatment, is 2 to 3 years. Any therapy of IPF, regardless of the agent used, requires at least 1 year before its effectiveness can be assessed. For many years, IPF was treated with high dose of corticosteroids and/or immunosuppressive drugs. The basis for the use of anti-inflammatory therapies in this disease was the concept that a chronic inflammatory infiltrate led to progressive extracellular matrix deposition.

In recent years, several adequate randomized, controlled clinical trials of sufficient numbers of patients with IPF have been performed using putative "antifibrotic" drugs, but none thus far has shown significant improvements in outcome. Combination therapy with prednisone, azathioprine, and *N*-acetylcysteine (NAC) has been suggested as a reasonable choice for patients with mild to moderate disease.

Corticosteroids. Corticosteroids alone were the mainstay for the treatment of IPF, but there was never any randomized, placebo-controlled study.[124,125] However, the response to corticosteroid treatment in IPF has been almost uniformly poor.[126] In addition, significant complications can result from corticosteroid therapy, affecting the quality of life. Currently, there is no indication for the use of corticosteroids alone in the treatment of IPF.

Immunomodulatory and Antifibrotic Agents. Because of the poor responsiveness of IPF to corticosteroids, immunomodulatory agents (azathioprine or cyclophosphamide alone or in combination with corticosteroids) have been tried.[127–130]

Azathioprine. Azathioprine is a purine analogue that appears to act by the substitution of purines in DNA synthesis and by inhibiting adenine deaminase, which affects lymphocyte functions. Azathioprine has been reported to suppress natural killer cell activity, antibody production, and antibody-dependent cellular cytotoxicity. Older studies suggested azathioprine and low-dose prednisone might be useful in the treatment of patients with IPF.[128] The recommended dose for azathioprine in IPF was approximately 2 mg/kg, although the optimal dose for treating the disorder is as yet undetermined. Generally, the dose is 75 to 100 mg/day and does not exceed 150 mg/day.

Hematologic adverse effects include leukopenia, anemia, thrombocytopenia, pure red cell aplasia, and pancytopenia. Gastrointestinal complaints are the most frequent side effects, including nausea and vomiting and, less commonly, peptic ulcer disease and diarrhea. Mild elevation of hepatic enzymes has been described in approximately 5% of patients treated with azathioprine. Pulmonary complications of interstitial pneumonitis and diffuse alveolar damage (DAD) have been reported in some renal transplant recipients. The carcinogenic potential of azathioprine remains to be fully defined.

N-Acetylcysteine. In a recent double-blind, randomized, placebo-controlled multicenter study, it was found that NAC, a molecular precursor to the naturally occurring antioxidant glutathione, added to prednisone and azathioprine at a dose of 600 mg three times daily, decreases the drop or preserves vital capacity and Dl_{CO} better than does prednisone and azathioprine alone after approximately 1 year of follow-up.[131] No mortality benefit was identified in this study. The efficacy of NAC monotherapy has not been examined.

Cyclophosphamide. Cyclophosphamide was formerly used as a second-line drug in patients who either failed or could not tolerate corticosteroid treatment. Cyclophosphamide is an alkylating agent of the nitrogen mustard group that is absorbed orally and activated in the liver to several cytotoxic compounds. Its mode of action is the depletion of lymphocytes, thereby suppressing lymphocyte function. The recommended dose is 2 mg/kg/day given orally as a single dose, usually with oral prednisone at 0.25 mg/kg/day. Few data are available on the length of therapy. However, a large retrospective study of well-defined, matched patients with IPF suggested that treatment with combined corticosteroid and cyclophosphamide therapy does not improve survival compared with untreated patients.[127]

In addition, cyclophosphamide therapy also has severe side effects including leukopenia, thrombocytopenia, hematuria secondary to hemorrhagic cystitis (forced fluids and frequent bladder emptying are recommended to prevent this problem), gastrointestinal symptoms (including anorexia, nausea, and vomiting), bone marrow suppression, azoospermia and amenorrhea, infection, and the development of a hematologic malignant disease.

Other Agents. A number of other immunosuppressive or putative antifibrotic agents have been reported in individual cases or in small groups of patients with IPF without success. In vitro studies suggest several mechanisms by which *Colchicine* may interrupt the processes of collagen synthesis and deposition; it may have anti-inflammatory effects as well. On the basis of these mechanisms of action, colchicine has been used as a potential therapeutic agent in IPF, but there are no data affirming the efficacy of colchicine in IPF.[132–134] *Penicillamine* inhibits collagen synthesis by interfering with collagen cross-linking and is a suppressor of T-cell function. Limited studies have not shown efficacy in idiopathic pulmonary fibrosis.[134] *Interferon beta-1a* has been shown to reduce fibroblast migration/proliferation and inhibits collagen production by fibroblasts. Unpublished

randomized clinical trials in the United States and Canada failed to show any benefit.[135,136] *Captopril* inhibits the angiotensin-converting enzyme and completely abrogates Fas-induced apoptosis in human alveolar epithelial cells. It also has been shown to inhibit fibroblast proliferation in vitro, and reduce the fibrotic lung response in vivo. A small trial showed no effect.[137] *Chlorambucil* and *vincristine sulfate*, given alone or with corticosteroids, showed no beneficial effect.[138]

New Therapeutic Approaches. Based on the new knowledge about the pathogenic mechanisms involved in IPF, and the poor results obtained with immunosuppressive drugs, newer immunomodulatory or antifibrotic agents have been tried in patients with IPF.

Interferon-γ A large, controlled trial with interferon gamma-1b noted no difference in primary end point (progression-free survival) or most secondary end points.[139] In patients defined as having milder disease (FVC ≥ 55%; defined post hoc) or treatment-adherent, a potential survival benefit was suggested.[140] However, a much larger controlled trial (826 patients) with survival as the primary end point was recently discontinued based upon lack of efficacy. The overall mortality was of 14.5% in the IFN gamma-1b and of 12.7% in the placebo group.[141] A trial using interferon-γ as a nebulized mist is now ongoing (see Table 57-9).

Pirfenidone. Pirfenidone (5-methyl-1-phenyl-2-(1H)-pyridone) is a novel antifibrotic and anti-inflammatory agent that inhibits the progression of fibrosis in animal models. Raghu and colleagues[142] reported the results of a phase II, open-label study evaluating pirfenidone. They found that pirfenidone was well tolerated with minimal side effects. In addition, treatment with pirfenidone appeared to allow discontinuation or tapering of prednisone and immunosuppressive therapy without further loss of lung function. A multicenter, randomized, double-blind, placebo-controlled study of pirfenidone versus placebo was carried out in Japanese patients with IPF, although it was stopped at 9 months.[143] Pirfenidone was effective in stabilizing the lung function and reducing the number of patients who experienced acute exacerbation of their disease (5/35 placebo-treated patients compared with 0/72 pirfenidone-treated patients).[143] A large randomized, double-blind, placebo-controlled trial has recently been completed. Unpublished data suggest a treatment benefit may exist.

Endothelin-Receptor Antagonists. ET-1 contributes to the fibrotic phenotype of fibroblasts and is a downstream mediator of profibrotic responses to transforming growth factor-β (TGF-β).[144] In a rat model, it was found that ET-1 is involved in the pathogenesis of lung fibrosis and that blockage of its receptors reduces the fibrosis.[145] *Bosentan* is a dual ET-1 receptor antagonist (ET_A and ET_B) that has been shown to be effective in the treatment of PAH. Recently, a large, randomized, multinational, double-blind, placebo-controlled trial in patients with IPF was reported.[146] A total of 154 were included in the all-treated set (bosentan, $n = 71$; placebo, $n = 83$). Bosentan did not show an improvement over placebo with respect to 6MWD (primary end point), but patients treated with this drug showed a tendency to delayed time to death or disease progression, a predefined secondary end point. A surprising and unexplained finding was that this treatment effect was significant in the subset of patients who underwent surgical lung biopsy for confirmation of diagnosis. A new clinical trial with bosentan is currently ongoing. *Ambrisentan*, a selective ET_A antagonist, is also being studied in a large clinical trial.

Etanercept. The introduction of targeted biologic agents directed against tumor necrosis factor-α (TNF-α) has represented a novel and exciting avenue for the treatment of a variety of diseases. Elevated levels of this cytokine have been detected in experimental lung fibrosis and in patients with IPF as well. In a recent study, the effect of etanercept, a recombinant soluble human TNF receptor which binds to TNF and neutralizes its activity in vitro, was explored in IPF patients.[147] Sixty-five patients (etanercept, $n = 34$; placebo, $n = 31$) completed the 48 weeks of treatment. No statistically significant differences were observed between treatment groups in the three primary end points: changes in FVC%, DI_{CO}%, and the $(A - a)Po_2$ difference (at rest) at 48 weeks. However, this can be due in part to the modest number of subjects included in the trial. In post-hoc analysis, using rate of disease progression by death or absolute reduction in FVC (L), a tendency favoring etanercept was observed.

Ongoing clinical trials are summarized in Table 57-9.

Lung Transplantation

Since the late 1980s, lung transplantation has been used for the management of a wide range of severe lung disorders, with progressive disease unresponsive to pharmacologic treatment with evidence supporting quality of life and survival benefit for lung transplant recipients. The American Thoracic Society has published guidelines for the selection of IPF patients who should be considered potential transplant candidates.[148]

Unfortunately, given the scarcity of donors and the aging and disease complications of IPF patients, transplantation is indicated only in carefully selected patients. Early referral for consideration of transplant is highly desirable. It allows an orderly process for assessment, management of areas of concern, and patient education before active listing.[148]

Transplantation should be considered for patients who have signs or symptoms of progressive disease (including rest or exercise oxygen desaturation) with failure to improve or maintain lung function while being pharmacologically treated. Guidelines for referral and transplantation according to the international guidelines for the selection of lung transplant candidates updated in 2006 are as shown in Table 57-11.[148]

The 1-year and 5-year survival rates following lung transplantation for IPF according to the 2004 International Society for Heart and Lung Transplantation/United Network of Organ Sharing (ISHLT/UNOS) International Registry reporting experience over the previous 12 years was 68% and 40%, respectively.[149] Recently, survival of patients receiving transplantation for IPF ($n = 82$) was compared with survival of patients receiving transplanta-

TABLE 57-11. Guidelines for Referral and Transplantation of Patients with Idiopathic Interstitial Pneumonia

GUIDELINES FOR REFERRAL

1. Histologic or radiographic evidence of UIP irrespective of vital capacity.
2. Histologic evidence of fibrotic NSIP.

GUIDELINES FOR TRANSPLANTATION

1. Histologic or radiographic evidence of UIP and any of the following:
   a. A DL_{CO} < 39% predicted.
   b. A ≥ 10% decrement in FVC during 6 months of follow-up.
   c. A decrease in pulse oximetry below 88% during a 6-MWT.
   d. Honeycombing on HRCT (fibrosis score > 2).
2. Histologic evidence of NSIP and any of the following:
   a. A DL_{CO} < 35% predicted.
   b. A ≥ 10% decrement in FVC or 15% decrease in DL_{CO} during 6 months of follow-up.

DL_{CO}, diffusing capacity for carbon dioxide; FVC, forced vital capacity; HRCT, high-resolution computed tomography; 6-MWT, 6-minute walking test; NSIP, nonspecific interstitial pneumonia; UIP, usual interstitial pneumonia.

tion for non-IPF diagnoses (n = 387). Survival estimates after transplantation for IPF were 95%, 73%, 56%, and 44% at 30 days and 1, 3, and 5 years, somewhat worse than for matched non-IPF patients (P = .03). Survival for double- versus single-lung transplantation was 81% versus 67% at 1 year and 55% versus 34% at 5 years; however, among matched non-IPF patients, corresponding survivals were 88% versus 71% at 1 year and 72% versus 48% at 5 years (P = .3). These findings suggest survival after lung transplantation for IPF is worse than for other indications and that survival may be improved by double-lung transplant.[150]

Regular review of patients on the waiting list is required to detect complications that may impact on suitability for transplantation. Unfortunately, many IPF patients die while waiting. In this context, the lung allocation score was restructured in 2005 to an algorithm based on survival probability on the waiting list and after transplantation. The aim was to decrease the number of patients who die on the waiting list. A recent study shows that recipient diagnoses changed with an increase in IPF and a decrease in emphysema and cystic fibrosis.[151]

Rehabilitation

Twelve weeks of combined inpatient and home-based rehabilitation program (respiratory muscle training and bicycle riding to the limits of the patient's tolerance) has been shown to improve the quality of life and sensation of dyspnea in patients with ILD, despite changes in pulmonary function tests.[152] Currently, the effects of pulmonary rehabilitation on shortness of breath, exercise capacity, symptom control, mental health, cognitive function, and quality of life are being studied by the National Jewish Medical and Research Center and Mordecai Palliative Care Research Fund.

Acute Exacerbations of Interstitial Pulmonary Fibrosis

Some patients with IPF may experience a rapid deterioration in respiratory status after a period of relative stability.[153] This acute worsening may be related to viral or bacterial infection, aspiration by GER, or thromboembolic event. A growing body of evidence, however, indicates many of these acute, clinically significant episodes are of unknown etiology; these have been termed *acute exacerbations of IPF*.[153] The overall incidence of acute exacerbations in the IPF population remains unknown but has been suggested to range from 5% to 10%.[153,154] An analysis of the cause of death in the placebo arm of a large randomized clinical trial, however, showed that almost half of the deaths were acute in their onset after a period of decompensation that lasted 4 weeks or less, suggesting that acute exacerbations may be more frequent than usually believed.[155]

There is no established consensus on the diagnosis of acute exacerbation of IPF. Most definitions include a combination of the following data (occurring over < 4 wk): (1) severe worsening of dyspnea; (2) worsening hypoxemia (i.e., a fall in arterial P_{O_2} > 10 mm Hg); (3) new radiographic opacities, usually bilateral ground-glass opacities and consolidation superimposed on the reticular/honeycomb IPF pattern; (4) absence of an alternative explanation, such as infection, left heart failure, or pulmonary embolism.[153,156–158] It has been suggested that the pattern of the new ground-glass opacities may differ in the patients with acute exacerbation and that these differences might have prognostic implications.[158,159] Although radiographs of most patients typically show ground-glass attenuation at the periphery, near areas of underlying honeycombing, some demonstrate a multifocal or diffuse pattern in previously uninvolved areas. Such cases seem to have a worse prognosis than patients with only peripheral involvement.[160] Biopsies of most of these patients have a histopathologic pattern of DAD superimposed on underlying UIP. Occasionally, lungs may show features of prominent acute organizing pneumonia and extensive fibroblastic foci.[156,161] Cell profiles on BAL usually show an increase of neutrophils or both neutrophils and lymphocytes.

The etiology and pathogenesis of the acute exacerbations remain unknown. Disordered epithelial cell integrity, acute inflammation, excessive cytokines and matrix metalloproteinases release, and an antifibrinolytic alveolar milieu are all likely involved. Increased levels of interleukin-8 (IL-8) and α-defensin have been reported in some patients, suggesting the importance of neutrophils.[153] Exaggerated levels of serum ST2 protein, an orphan receptor with unknown natural ligand, have also been reported.[162] Importantly, ST2 is preferentially expressed on type 2 T helper (Th2) polarized cells expressing predominantly IL-4, IL-5, or IL-10 in vitro and ex vivo, indicating a role for activated (predominantly

Th2) lymphocytes.[163] More recently, antibodies to annexin-1 were detected in the sera and BAL fluids from half of patients with acute exacerbation of IPF, supporting the hypothesis that pulmonary epithelial apoptosis may be important in this pathologic event.[164]

Once infections and other causes of worsening have been excluded, treatment has generally consisted of enhanced immunosuppression with pulse doses of methylprednisolone (0.5–1 g/day). Some studies have also reported the use of additional immunosuppression with cyclophosphamide or cyclosporine, but no convincing evidence of benefit has been demonstrated. Unfortunately, no data from controlled trials have proved the efficacy of any treatment for this condition.

Familial Pulmonary Fibrosis

The clinical, radiographic, physiologic, and morphologic manifestations of familial IPF are indistinguishable from the sporadic form of the disease.[2,165] There may be a slight male predominance, and women tend to have a more favorable prognosis.[6,166] It is estimated that familial cases account for 0.5% to 2.2% of all patients with IIPs, with a prevalence of 1.34 cases/106 population in the United Kingdom.[166] In Finland, it was estimated that the prevalence for familial IPF was 5.9/million population.[167] The familial form explained 3.3% to 3.7% of all Finnish cases of IPF diagnosed according to the revised American Thoracic Society/European Respiratory Society international guidelines. Geographic clustering has been noted, suggesting a recent founder effect in patients with familial IPF.[166,167] Importantly, familial pulmonary fibrosis has been associated with multiple pathologic subsets of the IIPs: desquamative interstitial pneumonitis (DIP),[168] LIP,[169] and UIP.[6]

The genetic basis of familial pulmonary fibrosis is unclear and probably involves several genes. Thomas and associates[6] showed that mutations in the SP-C gene (*SFTPC*) are associated with familial DIP and NSIP and may cause type II cellular injury. The authors hypothesized that the presence of two different pathologic diagnoses in affected relatives sharing this mutation indicates that in this kindred, these diseases may represent pleiotropic manifestations of the same central pathogenesis.[6] Multiple heterozygous mutations in *SFTPC* have been reported in association with children suffering from ILD (DIP or NSIP), including familial and sporadic occurrences.[170,171] In addition, a deficiency of SP-C has been described in a small kindred suffering from a poorly defined form of interstitial pneumonitis, despite no sequence variation in *SFTPC*.[172] Taken together, these findings support a model in which misfolded pro–SP-C or SP-C can cause type II alveolar cell injury that results in ILD.[173] In the Finland families, *ELMOD2*, a functionally uncharacterized gene, was identified as a novel candidate gene for susceptibility in familial IPF.[174]

In a recent study, 111 families with two or more cases of IIP among first-degree family members having 309 affected and 360 unaffected individuals were evaluated. Older age, male sex, and having ever smoked cigarettes were associated with the development of IIP. Evidence of aggregation of disease was highly significant among sibling pairs, and 20 pedigrees demonstrated vertical transmission, consistent with autosomal dominant inheritance.[71] As reported previously, a substantial proportion of families displayed phenotypically heterogeneous IIP.

Nonspecific Interstitial Pneumonia

NSIP originated as a histopathologic categorization reserved for surgical lung biopsies not demonstrating a clearly identifiable pattern.[175] The histopathologic pattern of NSIP is found in a wide variety of diseases of known cause (e.g., hypersensitivity pneumonitis, drug-related, acquired immunodeficiency syndrome [AIDS]–related, and collagen-vascular diseases).[176] Moreover, many patients diagnosed with idiopathic NSIP meet the case definition of undifferentiated connective tissue disease, suggesting that idiopathic NSIP might actually be an autoimmune disease.[177] In addition, it is estimated that up to 15% to 20% of patients who present with a chronic ILD either have an occult connective tissue disease or subsequently develop a clinically overt connective tissue disease. In this particular group of patients, the initial clinical presentation may be essentially indistinguishable from that of several IIPs (especially NSIP and UIP).[178] Consequently, NSIP as a clinical form of IIP remains uncertain.[29]

Clinical Features

The presentation is quite similar to other forms of idiopathic pneumonias (see Tables 57-7 and 57-8). Most patients are middle-aged adults with a subacute onset of symptoms approximately 8 months prior to diagnosis.[175,176,179] Two thirds of the patients are women, and unlike patients with IPF, 70% are never smokers.[176] Cough and dyspnea are the main clinical manifestations. Serologic abnormalities (antinuclear antibodies and rheumatoid factor) are common. BAL findings do not discriminate between UIP and NSIP and have no prognostic value once the distinction between the two has been made histologically.[180]

Chest Imaging Studies

Chest Roentgenography. In patients with early NSIP, the chest radiograph may be normal. In advanced disease, bilateral reticular or hazy opacities are the most prominent abnormality. The lower lung lobes are more frequently involved, but an obvious apical-basal gradient, as seen in UIP, is usually absent.[175,176]

Computed Tomography Scan. In a recent review of 61 cases of confirmed idiopathic NSIP, the parenchymal abnormalities predominantly involved the lower lungs in the craniocaudal dimension. The most common HRCT features were a reticular pattern, traction bronchiectasis, and lobar volume loss (77%).[176] Ground-glass attenuation was present in nearly half of the cases, although it is a common manifestation in other series (Fig. 57-26). Other findings in advanced NSIP include

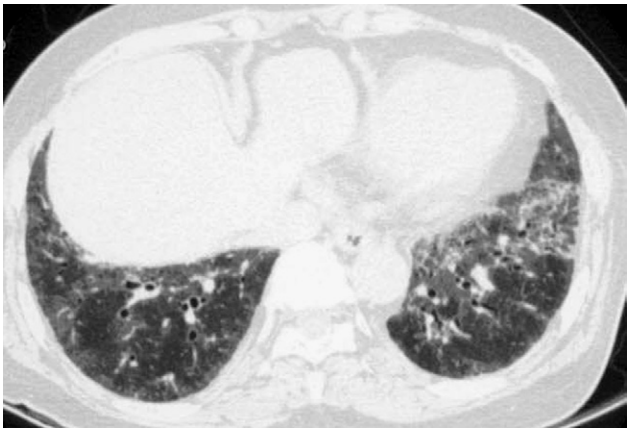


FIGURE 57-26 ■ High-resolution chest CT image from a patient with nonspecific interstitial pneumonia shows bilateral, patchy, ground-glass opacities without evidence of subpleural honeycombing.

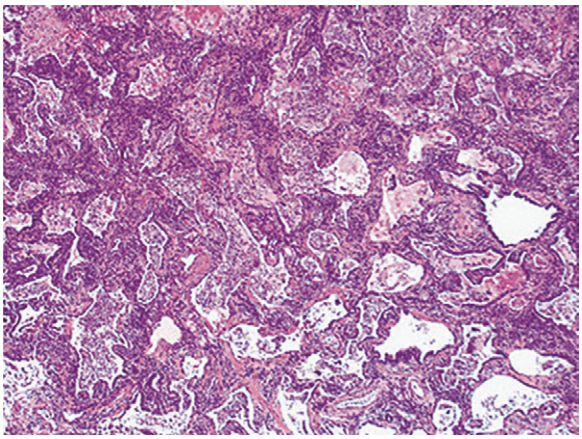


FIGURE 57-27 ■ Photomicrograph of nonspecific interstitial pneumonia. Note the lymphoplasmacytic cells expanding the interstitial compartment. Alveolar macrophages are present also. (Original magnification ×10.)

subpleural cysts. Compared with those of UIP, these cysts are smaller and limited in extent.[181] The major CT differential diagnosis for NSIP is UIP. Favoring the diagnosis of NSIP are homogeneous lung involvement without an obvious apical-basal gradient, extensive ground-glass abnormalities, a finer reticular pattern, and micronodules. Importantly, during follow-up, ground-glass opacities in NSIP patients usually do not evolve to areas of honeycombing. By contrast, progression of ground-glass attenuation to honeycombing is common in UIP and indicates irreversible fibrosis.[182]

Pulmonary Function Tests

Pulmonary function testing shows a typical restrictive ventilatory defect with gas-exchange abnormalities commonly found.

Pathologic Features

The histopathologic pattern of NSIP is characterized by temporally and spatially homogeneous lung involvement. This homogeneity is a key feature in differentiating the NSIP pattern from the UIP pattern. It is characterized by varying degrees of inflammation and fibrosis, with some cases having a primarily chronic inflammatory/cellular pattern (cellular NSIP) and most cases revealing a mixed cellular-fibrotic pattern (fibrotic NSIP)[175,176] (Figs. 57-27 and 57-28). Cellular NSIP is less common than fibrosing NSIP; it exhibits uniform alveolar septal infiltrates of lymphocytes and plasma cells. Neutrophils, eosinophils, and histiocytes are inconspicuous. Although NSIP may have significant fibrosis, it usually appears temporally uniform, and fibroblastic foci and honeycombing, if present, are rare. Fibrotic NSIP can be difficult to reliably distinguish from UIP, and significant interobserver variability among expert histopathologists exists.[183]

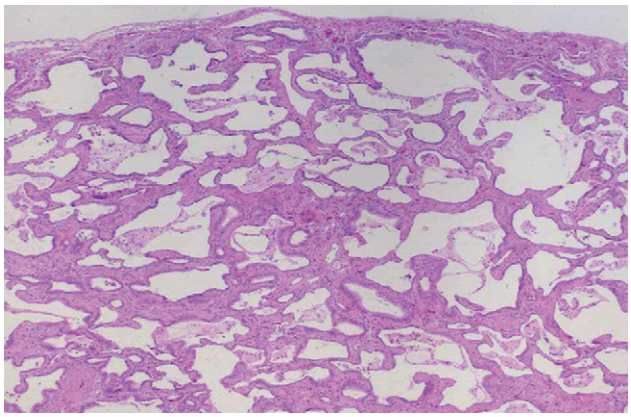


FIGURE 57-28 ■ Photomicrograph of nonspecific interstitial pneumonia with a mixed cellular-fibrotic pattern. The alveolar walls are thickened by dense collagen and a few lymphocytes and plasma cells. The fibroblastic foci that are commonly found in the usual interstitial pneumonia pattern are not present in this lesion.

Differential Diagnosis

Clinically, the most common diagnosis confused with fibrotic NSIP is IPF.[175,176,179] Patients who are known to be immunocompromised are not included in this group of patients. It is essential that the pathologist not use "UIP" or "NSIP" to refer to any nonclassifiable interstitial pneumonia because some of these cases represent a sampling error due to an inadequate lung biopsy. Importantly, most of the NSIP patients may have an ill-defined or inadequately evaluated connective tissue disease, drug-induced ILD, chronic hypersensitivity pneumonitis, recent acute lung injury (pneumonia or acute respiratory distress syndrome), or organizing pneumonia.[29,68,184–188] The NSIP pattern on surgical lung biopsy should prompt the clinician to revisit the clinical data, carefully looking for these conditions.

Although it has been suggested NSIP may represent early UIP, this possibility is unlikely for several reasons.

NSIP seems to occur predominantly in nonsmoker women whereas UIP occurs in smoker men.[176] Early UIP (as well as advanced UIP) does not have significant inflammation but rather has scattered fibroblast foci. Finally, the patchwork pattern that is so characteristic of UIP is not seen in NSIP, and therefore, one would have to postulate that during progression, some areas of NSIP reverted to normal whereas others evolved into fibrosis to become UIP.[67]

Clinical Course and Outcome

Several retrospective studies indicate the survival rate of patients with idiopathic NSIP is significantly higher than those with UIP.[176,179,189] This difference persists even after adjusting for age, gender, smoking history, and physiologic variables. The longest survival is observed in patients with a purely cellular pattern, indicating that prognosis depends primarily on the extent of fibrosis.[68,176] In the surgical lung biopsy, some patients may exhibit an NSIP pattern in one lobe and a UIP pattern in another.[190] Survival rate of these patients is similar to those with UIP. Corticosteroids combined with azathioprine may be more effective than corticosteroids alone.

Respiratory Bronchiolitis–Associated Interstitial Lung Disease/Desquamative Interstitial Pneumonia

Respiratory bronchiolitis–associated interstitial lung disease (RB-ILD) and DIP are related and, in some cases, inseparable conditions that probably represent different stages of the same process.[191,192] These diseases represent a distinct clinical syndrome found in current heavy smokers. The term respiratory *bronchiolitis-associated interstitial lung disease* is more anatomically accurate, as it conveys important pathogenic implications compared with the older term "desquamative interstitial pneumonia." Both (primarily RB-ILD) account for 15% to 20% of biopsied patients with IIPs (see Tables 57-7 and 57-8).[191,192] Importantly, respiratory bronchiolitis is an accurate histologic marker of cigarette smoking, and it may be found many years after smoking ceases.[193] The level of cytoplasmic pigmentation of macrophages and the presence of peribronchial fibrosis correlate with the pack-year smoking history.[193] Moreover, it was recently reported that those with significant lifetime secondhand smoke exposure, especially in the previous 12 months, have significant increases in ground-glass opacities on HRCT, suggesting an early or subclinical respiratory bronchiolitis/DIP.[194] Furthermore, RB/DIP-like histologic changes (1) are exceedingly common in PLCH, (2) may be sufficiently severe to cause the appearance of ground-glass attenuation on HRCT, and (3) correlate with the cumulative exposure to cigarettes smoked.[195] Although cigarette smoking is considered the main cause of RB-ILD/DIP, genetic abnormalities of surfactant function, specifically mutations in the SP-B, SP-C, and ABCA3 genes account for an increasing number of ILDs, including DIP.[196,197] In addition, DIP can be observed in various occupational or drug exposures.

Clinical Features

RB-ILD and DIP primarily afflict cigarette smokers between the third and the sixth decades of life. There is a male preponderance, with men affected nearly twice as often as women. Patients with either RB-ILD or DIP commonly present with insidious exertional dyspnea and persistent nonproductive cough. Less frequently, patients with DIP experience fatigue and weight loss. Coarse, bibasilar end-inspiratory crepitations are frequent findings on physical examination, whereas finger clubbing is uncommon.

Chest Imaging Studies

Chest Roentgenography. The chest radiograph is insensitive for detection of RB-ILD and is often normal. Sometimes, bronchial wall thickening or reticular opacities can be seen. Chest radiographs of DIP are nonspecific and usually reveal bilateral ground-glass opacities. Middle and lower lung field involvement with normal-appearing lung volumes predominates.[198] Air bronchograms can be found when this process surrounds the airways. The honeycomb pattern is rare.

Computed Tomography Scan. The key HRCT features of RB-ILD include central bronchial wall thickening proximal to segmental bronchi, peripheral bronchial wall thickening distal to segmental bronchi, centrilobular nodules, and areas of ground-glass opacity[198–202] (Fig. 57-29). Ground-glass opacifications may be diffuse or patchy, without basal or peripheral predominance.[202] The predominant abnormality in DIP is the bilateral, moderately symmetrical, peripheral and predominantly basal ground-glass attenuation. Tiny thin-walled cysts are noted in the ground-glass areas in 60% of cases. Honeycombing pattern is rarely found.[201,203,204]

There is occasional overlap in appearances between RB-ILD and DIP, although the ground-glass attenuation of DIP is usually more extensive, and nodules are infrequent or absent.[200]

Bronchoalveolar Lavage

BAL fluid in patients with RB-ILD/DIP is characterized by mild to moderate increases in total cell numbers, moderate to marked eosinophilia (a feature that in the absence of biopsy might raise the consideration of chronic eosinophilic pneumonia), and moderate neutrophilia.[180,198]

Pulmonary Function Tests

Pulmonary function testing may be normal but usually shows mild to moderate restriction, normal or slightly reduced diffusing capacity, and mild hypoxemia. A mixed obstructive-restrictive pattern is common, although an isolated increase in residual volume may be seen.

Pathologic Features

The cardinal feature of RB-ILD is the accumulation of alveolar macrophages within the membranous and respiratory bronchioles, variably extending into neighboring alveolar ducts and alveoli. Macrophages are characterized by glassy eosinophilic cytoplasm, usually with brown and finely granular pigmentation (representing constituents of cigarette smoke).[192,200,205] There is often a chronic inflammatory cell infiltrate in bronchiolar and surrounding alveolar walls. The changes are patchy at low magnification and have a distinctly bronchiolocentric distribution without the associated interstitial pneumonia necessary for a diagnosis of DIP (Fig. 57-30).[192] Bedrossian and coworkers[206] coined the term *DIP-like reaction* to identify prominent intra-alveolar macrophage accumulation around space-occupying pulmonary lesions. This DIP-like pattern can be seen in a number of other processes, including Langerhans cell histiocytosis, drug reactions (e.g., amiodarone), chronic alveolar hemorrhage, eosinophilic pneumonia, pneumoconioses (e.g., talcosis, hard-metal disease, asbestosis), obstructive pneumonias, and exogenous lipoid pneumonia. In these cases, however, the DIP-like reaction is usually minimal, without the uniform involvement of lung parenchyma seen in true cases of RB-ILD/DIP.

The histologic hallmark of DIP is the uniform filling of the alveolar spaces by cohesive clusters of numerous pigmented alveolar macrophages, including occasional multinucleated cells, eosinophils, and lymphocytes.[192] Alveolar septa are thickened by a sparse inflammatory infiltrate and lined by uniform hyperplastic type II pneumocytes. Peribronchiolar lymphoid hyperplasia is seen in the majority of cases (Fig. 57-31).[192,207]

The majority of DIP cases show a difference in the degree of pathologic change from one lobule to the next in a given biopsy specimen. Architectural destruction is usually observed. Akira and colleagues[204] have pointed out the presence of dilated alveolar ducts and bronchioles and/or pulmonary cysts, which corresponded to cystic spaces on HRCT.

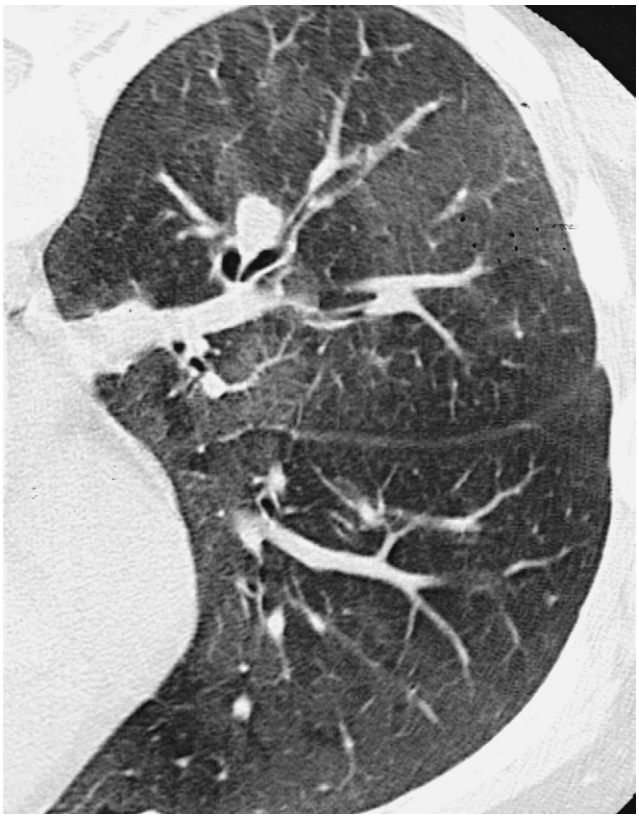


FIGURE 57-29 ■ High-resolution CT image from a patient with desquamative interstitial pneumonia shows diffuse ground-glass opacities (gray-appearing areas).

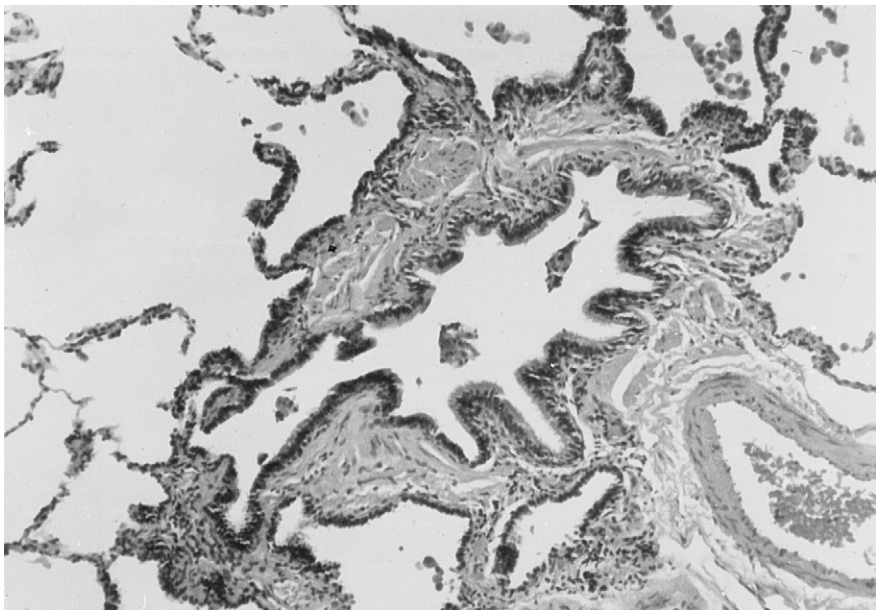


FIGURE 57-30 ■ Photomicrograph of respiratory bronchiolitis shows an ectatic small airway, with thickened walls and evidence of extension of the bronchiolar metaplastic epithelium into the immediately surrounding alveoli. Intraluminal macrophages are also present within the peribronchiolar alveolar spaces.

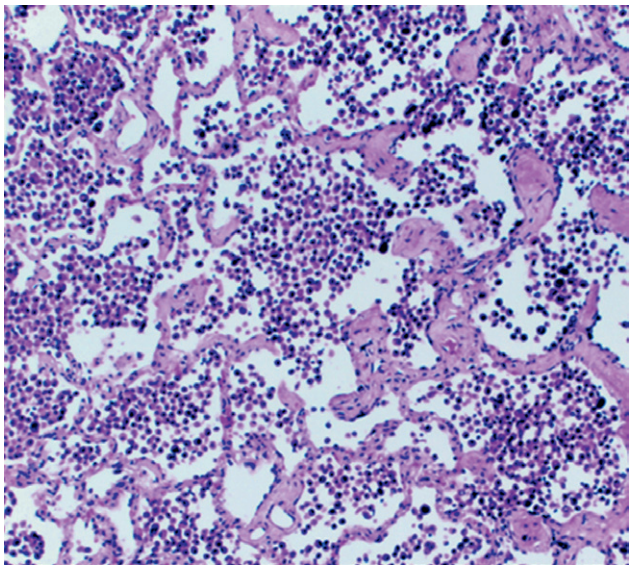


FIGURE 57-31 ■ Photomicrograph of desquamative interstitial pneumonia showing the characteristic dense collections of macrophages filling alveolar lumens. (Original magnification ×100.)

Clinical Course and Outcome

Because there has not been a longitudinal study of a large group of subjects, the clinical course and prognosis of RB-ILD are unknown. Most studies suggest a favorable response to quitting smoking and use of corticosteroids, with documented improvement in lung function and chest radiographs[205]; few deaths secondary to progressive lung disease have been reported.

Patients with the DIP stage of this process also have a good prognosis. Carrington and associates[208] reported a 28% mortality after an average survival of 12 years. Other studies have shown similar results, but additional study of a larger number of subjects is needed.[203–205] In a more recent study, symptomatic improvement (i.e., improved cough, dyspnea, or both) with prednisone treatment was noted in 24% of patients with DIP and 55% of patients with RB-ILD. Objective improvement with prednisone treatment, as evidenced by improvement in pulmonary function measurements or parenchymal infiltrates seen on chest radiography or CT scans, was noted in 33% of patients with DIP and 64% of patients with RB-ILD.[209] Unfortunately, these positive responses tended to be transient in half of the patients with tapering and discontinuation of prednisone treatment. This regression back to the baseline status occurred even in the absence of smoking.[209]

Nevertheless, because smoking plays a major role in the pathogenesis, smoking cessation is always indicated in these patients. In a recent study, both clinical symptoms and DL_{CO} improved significantly following smoking cessation, as did ground-glass opacities and centrilobular nodules seen on the initial HRCT examination.[210] Corticosteroids may be required in refractory or recurrent cases but should not be instituted in the absence of smoking cessation.

Acute Interstitial Pneumonia

AIP is a rare, fulminant form of lung injury that presents acutely (days to weeks from onset of symptoms), usually in a previously healthy individual.[211] AIP likely represents a subset of cases of idiopathic acute respiratory distress syndrome and is what Hamman and Rich[212] described and termed "acute diffuse interstitial fibrosis" (see Tables 57-7 and 57-8).

Clinical Features

Most patients are over the age of 40 years (mean age, 50 yr; range, 7–83 yr). Men and women are equally affected, and cigarette smoking does not seem to increase the risk for development of AIP. A prodromal illness, lasting usually 7 to 14 days before presentation, is common. The clinical signs and symptoms include fever, cough, and shortness of breath. Routine laboratory studies are nonspecific and generally not helpful.

Chest Imaging Studies

Chest Roentgenography. Diffuse, bilateral, air space opacification is seen on chest radiograph.[213,214]

Computed Tomography Scan. The typical HRCT features of AIP are bilateral, multifocal or diffuse areas of ground-glass opacity and consolidation, usually without pleural effusion.[35] A predominantly subpleural distribution may be seen. These radiographic findings are similar to those seen in acute respiratory distress syndrome; however, patients with AIP are more likely to have a symmetrical, bilateral distribution with a lower lobe predominance.[215] In the early phase of AIP, ground-glass opacities and less extensive areas of consolidation are the dominant CT pattern, reflecting the presence of alveolar septal edema and hyaline membranes.[35] During the organizing phase of the disease, HRCT findings consistent with evolving fibrosis are often present, including traction bronchiectasis, reticular opacities, and architectural distortion.[216] In this phase, consolidations resulting from intra-alveolar fibrosis may also be present. Mild honeycombing, usually involving less than 10% of the lung, may be seen on CT examination.

Pulmonary Function Tests

Most patients have moderate to severe hypoxemia and develop respiratory failure.

Pathologic Features

A surgical lung biopsy is required to confirm the diagnosis of AIP.[192,217] The histopathologic pattern of AIP includes DAD, which can be categorized into an early exudative phase and a chronic organizing phase, depending on the timing of the biopsy in relation to the lung insult. DAD develops after an acute injury to the alveolar capillary basement membranes.[211] It is most commonly seen in the acute respiratory distress syndrome or in immunosuppressed patients who have received cyto-

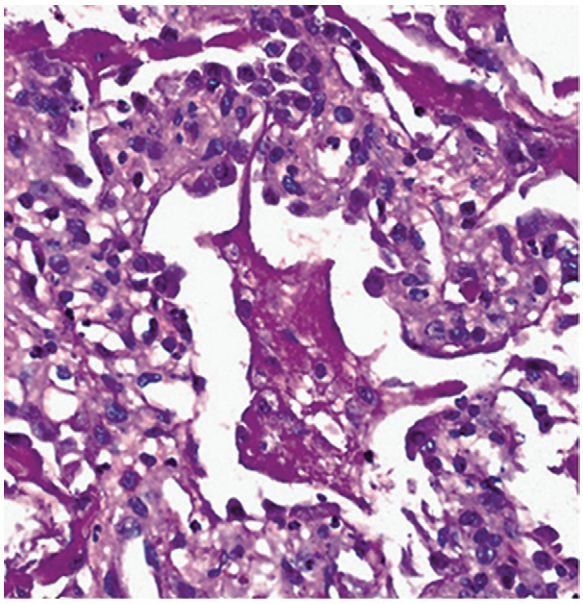


FIGURE 57-32 ■ Photomicrograph of acute interstitial pneumonia shows diffuse alveolar damage. Note the hyaline membranes within alveolar spaces and edema and inflammatory cell infiltration of the alveolar wall. (Original magnification ×10.)

toxic drugs or who have developed diffuse infectious pneumonias.[218]

After the endothelial-epithelial injury, there is leakage of serum proteins and red blood cells into the alveolar spaces. The alveolar epithelium becomes necrotic and is sloughed, and the interstitium becomes edematous. Hyaline membranes, recognized as eosinophilic debris and consisting of necrotic epithelial cells, protein, and fibrin, form within alveolar spaces (Fig. 57-32). In the reparative or organizing stage of DAD, there is proliferation and hyperplasia of the alveolar type II epithelial cells, often showing nuclear enlargement and prominent nucleoli. Extensive fibroblast proliferation is a dominant finding. Alveolar septa are uniformly thickened and distorted by proliferating fibroblasts and myofibroblasts within a myxoid basophilic matrix.[192] Fibrin thrombi are often present. With protracted or repeated parenchymal injury, irreversible fibrosis and honeycomb lung result.

Clinical Course and Outcome

Treatment is largely supportive and consists of mechanical ventilation and oxygen supplementation. Corticosteroids seem to be effective in the early phase of disease. Recently, chest ultrasound has become an attractive new tool for assessing lung status in ventilated critically ill patients. It is noninvasive, easily repeatable at the bedside, and provides an accurate evaluation of the respiratory status of patients with acute lung injury. It appears to be useful to diagnose lung consolidation, alveolar-interstitial syndrome, and pleural effusion.[219] According to most studies, the mortality from AIP appears to be high (>50%), with the majority of patients dying within 3 months of presentation. Most survivors of AIP experienced recurrences and chronic, progressive ILD.[214] However, significant lower hospital mortality (12.5%) with no evidence of either recurrent or progressive disease has been also described.[220]

Cryptogenic Organizing Pneumonia

COP is a specific clinicopathologic syndrome characterized by a "pneumonia-like" illness, with excessive proliferation of granulation tissue inside the alveolar spaces associated with chronic inflammation in the surrounding alveoli. The pathologic process may also involve the small airways (bronchiolitis obliterans with organizing pneumonia [BOOP]) (see Tables 57-7 and 57-8). Organizing pneumonia can be cryptogenic (COP) or associated with a number of lung injuries (e.g., postinfectious, drug-related, connective tissue disease–related, posttransplant, hypersensitivity pneumonitis, radiation [breast cancer], aspiration of particulate matter). There are no major differences in clinical features of COP and secondary organizing pneumonia.[221,222] BOOP may also be seen accompanying other histopathologic patterns (e.g., UIP). The diagnosis of COP is reserved for isolated organizing pneumonia in patients without an identifiable associated disease. The term *idiopathic BOOP* historically encompassed COP but is no longer recommended for this idiopathic condition.

Clinical Features[223]

The incidence of COP is similar in both men and women. The mean age at presentation is about 50 to 55 years (range, 21–80 yr). Patients with COP are frequently very specific about the timing of their disease onset. This is because the disease onset is recent (usually < 2 mo) and is often dramatic, with the development of a flulike illness characterized by cough, mild dyspnea, fever, malaise, fatigue, and weight loss. Physical examination usually discloses focal sparse crackles but may be almost normal. Finger clubbing is rare in patients with COP.

Routine laboratory studies are nonspecific. A leukocytosis without increase in eosinophils is seen in approximately half the patients. The initial erythrocyte sedimentation rate is frequently elevated in patients with COP.

Chest Imaging Studies

Chest Roentgenography. The roentgenographic manifestations are distinctive, usually including unilateral or bilateral patchy consolidations that resemble pneumonic infiltrates in the presence of normal lung volumes.[224,225] A peripheral distribution of the infiltrates, very similar to that thought to be "virtually pathognomonic" for chronic eosinophilic pneumonia, is commonly seen in COP.[224,226,227] Irregular linear or nodular interstitial opacities are rarely present as the only radiographic manifestation.[228] Honeycombing is rare and is seen only as a late manifestation in the few patients with progressive disease. Other radiographic abnormalities, such as pleural effusion, pleural thickening, hyperinflation, and cavities, are uncommon.

Computed Tomography Scan. CT scans of the lung reveal patchy air space consolidation, small nodular

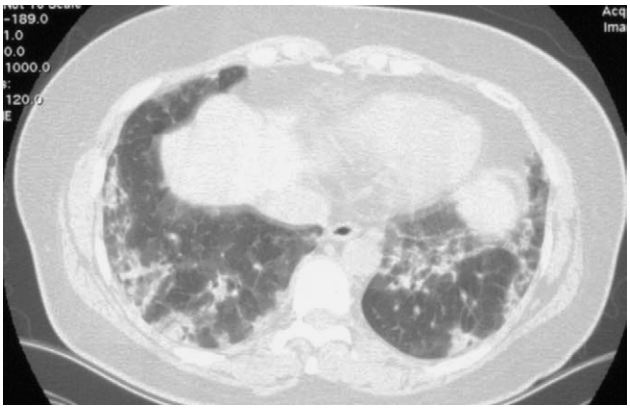


FIGURE 57-33 ■ High-resolution CT image from a patient with cryptogenic organizing pneumonia shows patchy areas of consolidation and diffuse ground-glass opacities (gray-appearing areas).

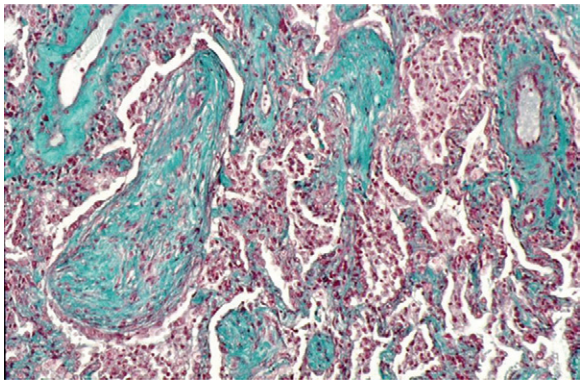


FIGURE 57-34 ■ Photomicrograph indicates organizing pneumonia. Immature connective tissue and proliferating fibroblasts appearing light blue (pentachrome stain) are present in alveolar ducts and alveolar spaces, and there is an interstitial infiltrate consisting of mononuclear cells. (Original magnification ×40.)

opacities, and bronchial wall thickening and dilation, most frequently in the periphery of the lung and often in the lower lung zones[224,228–231] (Fig. 57-33). Frequently, the CT findings are far more extensive than are expected by review of the plain chest film. These opacities have a tendency to migrate, changing in location and size, even without treatment. The CT finding of consolidation is associated with partial or complete resolution, whereas reticular opacities are associated with persistent or progressive disease.[232] Sometimes, COP shows unique findings such as the reversed halo sign, which is defined as central ground-glass opacity surrounded by more dense air space consolidation of crescentic and ring shapes. This sign is seen in around 20% of patients who have COP.[233] The presence of enlarged nodes is less common in COP than in the other IIPs.[234]

Focal organizing pneumonia has been described as a discrete form of COP and presents as an isolated focal lesion on chest imaging.[235] Many of these patients are asymptomatic and the lesion is discovered by chest x-ray or CT. It may be suspected to be a putative lung cancer, because most patients have a smoking history and are middle-aged or older.[236]

Pulmonary Function Tests

Pulmonary function is usually impaired, with a restrictive defect being most common, although obstructive defect (FEV_1/FVC ratio < 70%) is found in almost one fifth of subjects with COP, mostly in current or former smokers. Gas-exchange abnormalities are extremely common, with resting and exercise arterial hypoxemia. The DL_{CO} is reduced (<80% of predicted) in three fourths of patients.

Bronchoalveolar Lavage

An increase in lymphocytes (20%–40%), neutrophils (10%), and eosinophils (5%), with the level of lymphocytes higher than that of eosinophils, is the most common pattern at differential cell count.[237] BAL lymphocytes are activated and the CD4/CD8 ratio is usually decreased. An increase of plasma cells and/or mast cells may also be seen.

Pathologic Features

The diagnosis of COP depends on both the clinical setting and the finding of the characteristic pathologic features. Intraluminal fibrotic buds (Masson bodies) seen in respiratory bronchioles, alveolar ducts, and alveoli are the prominent feature.[237–240] Other pathologic features include foamy cells in the alveolar spaces, prominent type II cell hyperplasia, interstitial infiltrates, and fibrinous exudates.

Organizing pneumonia is recognized by the appearance in the small airways of intraluminal collections of proliferating fibroblasts and myofibroblasts that produce mucopolysaccharides and collagen. It is most prominent in the alveolar ducts but extends distally to the alveolar lumina and proximally to membranous bronchioles (Fig. 57-34). Masson bodies may also extend from one alveolus to the next through the interalveolar pores, giving a characteristic "butterfly pattern."[237] Organizing penumonias also show an interstitial lymphoplasmacytic infiltrate and hyperplasia of the type II epithelial cells. The organizing process, which may extend into the membranous bronchioles, produces an intraluminal polypoid bronchiolitis obliterans (Fig. 57-35). Organizing pneumonia represents a common reparative response to injury occurring in a variety of ILDs. If the injury is unresponsive to treatment, progression to irreversible fibrosis and honeycomb lung can result.

Clinical Course and Outcome

Corticosteroid therapy results in complete clinical, radiologic, and physiologic recovery in two thirds of patients. One third demonstrates recurrent or persistent disease. If reticular opacities are present on the chest radiograph or CT image, COP is less likely to respond to corticosteroids. In general, clinical improvement is rapid, within several days or a few weeks. Occasionally, recovery is quite dramatic. Relapses can occur when the corticosteroids are withdrawn, usually within 1 to 3 months.

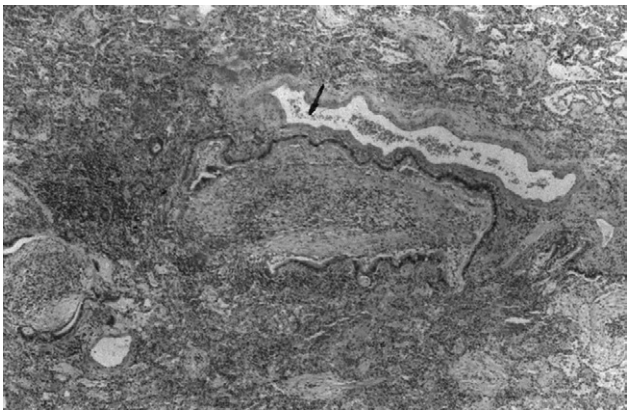


FIGURE 57-35 ■ Photomicrograph of organizing pneumonia shows a typical inflammatory polyp extending into the lumen of a terminal bronchiole. (Original magnification ×40.)

Most relapsed patients will improve when retreated with corticosteroids. It has been suggested that COP may also respond to macrolide therapy, but studies are scanty.[241] Spontaneous improvement may occur over 3 to 6 months in a few patients.[241-243] A seasonal (early spring) occurrence of COP with relapse every year at the same period has been reported.[244] Few of the patients with COP die as a result of this illness, but those prone to develop a rapidly progressive fatal form of organizing pneumonia have a clinical course similar to the "Hamman-Rich syndrome" (AIP).[245] In such patients, the diagnosis is usually delayed or missed.

The majority of cases of focal organizing pneumonia are cryptogenic, do not recur after surgical resection, and do not require corticosteroid therapy.[236,246]

TABLE 57-12. Diseases Associated with Lymphocytic Interstitial Pneumonitis

IDIOPATHIC DISEASE WITHOUT DYSPROTEINEMIA
DISEASE WITH DYSPROTEINEMIA
Hypogammaglobulinemia
Monoclonal or polyclonal gammopathy
AUTOIMMUNE DISEASE
Sjögren's syndrome
Primary biliary cirrhosis
Myasthenia gravis
Hashimoto's thyroiditis
Pernicious anemia
Autoimmune hemolytic anemia
Systemic lupus erythematosus
ALLOGENEIC BONE MARROW TRANSPLANTATION
ACQUIRED IMMUNODEFICIENCY SYNDROME
VIRAL INFECTIONS
Human immunodeficiency virus
Epstein-Barr virus
HTLV-1
MISCELLANEOUS
Tuberculosis
Celiac sprue
Dilantin
Post-*Legionella* pneumonia
Surfactant protein C deficiency

HTLV-1, human T-cell lymphotrophic virus type 1.
Adapted from Cosgrove GP, Fessler MB, Schwarz MI: Lymphoplasmacytic infiltrations of the lung. *In* Schwarz MI, King TE Jr (eds): Interstitial Lung Diseases (4th ed). Hamilton, Ontario: BC Decker, 2003, p 827.

Lymphocytic Interstitial Pneumonia

LIP is an uncommon pathologic process characterized by the presence of widespread, monotonous sheets of lymphocytic infiltration in the interstitium of the lung.[247] In addition to being differentiated from other IIPs, it must be distinguished from lymphocytic infiltrations associated with pseudolymphoma, primary lymphomas, lymphomatoid granulomatosis, benign lymphocytic angiitis and granulomatosis, plasma cell interstitial pneumonia, and angioimmunoblastic lymphadenopathy.

LIP has been associated with a variety of clinical conditions, including autoimmune diseases (especially Sjögren's syndrome), dysproteinemia, human immunodeficiency virus infection, variable immunodeficiency syndromes, and bone marrow transplantation. Once underlying systemic diseases have been excluded, LIP is called idiopathic. As an idiopathic disease, LIP is infrequent. It is far more common as a secondary disease in association with systemic disorders, most notably Sjögren's syndrome (Table 57-12).

Clinical Features

The clinical manifestations of LIP are dominated by those related to the underlying disease, such as Sjögren's syndrome. LIP occurs more commonly in women, usually in the fourth to sixth decade of life. It is also seen in children, particularly those with hypogammaglobulinemia or AIDS. Progressive dyspnea and cough are the most common presenting symptoms, although weight loss, pleuritic pain, arthralgias, and fever also occur. Bibasilar crackles on chest examination, cyanosis, and finger clubbing are common physical findings.

Chest Imaging Studies

Chest Roentgenography. The chest roentgenogram is nonspecific, with reticular opacities being the most frequent abnormality. A mixed alveolar-interstitial pattern appears as the disease progresses because of the coalescence of the opacities. Cysts, honeycombing, and pulmonary hypertension are also late manifestations.[248] Pleural effusions are infrequent and suggest a complicating lymphoma.

Computed Tomography Scan. The main parenchymal abnormalities on the initial CT scan consisted of ground-glass attenuation, thickening of interlobular septa, centrilobular nodules, thin-walled perivascular cysts, and air space consolidation[249] (Fig. 57-36). In contrast to the subpleural, lower lung cystic changes in UIP, the cysts of LIP are usually within the lung parenchyma throughout the mid lung zones and presumably result

FIGURE 57-36 ■ High-resolution CT image from a patient with lymphocytic interstitial pneumonia shows diffuse cysts.

from air trapping due to peribronchiolar cellular infiltration.[248] The cysts may be seen in up to 80% of the patients and are typically few in number and measure less than 3 cm in diameter. On follow-up CT, most patients improved, although several showed increased extent of disease. With the exception of cysts, the parenchymal opacities were reversible. New cysts developed in a few patients; these developed mainly in areas with centrilobular nodules on initial CT. Honeycombing was seen on follow-up CT in several patients in areas of previous air space consolidation on the initial CT.[249]

Pulmonary Function Tests

A restrictive defect including reduced FVC, elevated FEV_1/FVC, and reduced TLC is commonly seen and is often associated with a reduction in the D_{LCO} and arterial hypoxemia.

Bronchoalveolar Lavage

A striking T-cell lymphocytosis is seen on BAL.

Pathologic Features

Surgical lung biopsy is required for the diagnosis in almost all cases. The lymphocytic infiltration is usually extensive and severe, involving the alveolar septa and peribronchiolar and perivascular interstitium (Fig. 57-37). Reactive lymphoid follicles are often present and distributed along the peribronchiolar regions. The lymphocytes are polytypic (both B and T cells may be found), distinguishing them from the monotypic lymphocytic infiltrates characteristic of pulmonary lymphoma. The number of plasma cells and macrophages is also increased in these infiltrates.

LIP is distinguished from DIP and NSIP by the presence of monotonous sheets of lymphocytes infiltrating the interstitium and alveolar lumina.[250] Other features include the interstitial accumulation of macrophages, noncaseating granulomas, perivascular amyloid deposits, and germinal lymphoid centers. Conversion to a low-grade pulmonary lymphoma or progression to end-stage honeycomb lung may follow.[247,251]

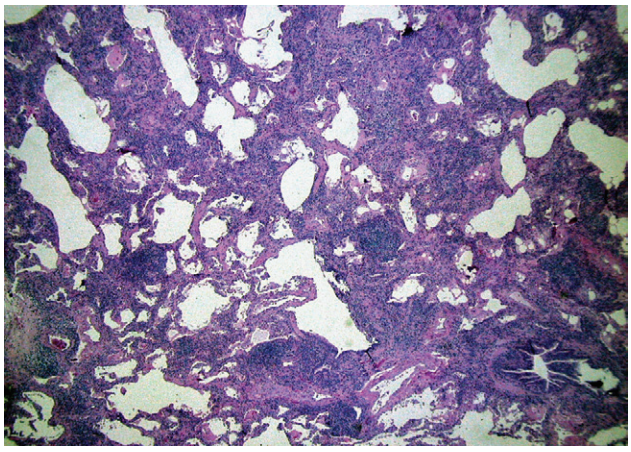


FIGURE 57-37 ■ Photomicrograph of lymphocytic interstitial pneumonia shows diffuse lymphoid infiltrate that extends through the pulmonary interstitium. (Original magnification ×10.)

Clinical Course and Outcome

The clinical course of idiopathic LIP is unknown. In cases in which LIP is associated with another disease, the underlying disease largely determines the outcome. Marked improvement or complete resolution follows corticosteroid therapy in many case reports. Progressive pulmonary fibrosis, cor pulmonale, and death can occur despite therapy. Infection is a common complication in these patients, especially those with an associated dysproteinemia. Progression to pulmonary or systemic lymphoma occurs but appears to be quite rare, and it is likely that this group of patients had malignant lymphoma from the outset.

Conclusion

Careful histopathologic evaluation has shown the traditionally clinical diagnosis of IIP to be more difficult and the findings to be more heterogeneous than was once thought. The subclassification of the IIPs, based on clinicopathologic criteria, has important therapeutic and prognostic implications. All patients with suspected IIP should be carefully evaluated with an in-depth history and physical examination, pulmonary function testing, bronchoscopy, and HRCT scanning by physicians experienced in the care of such patients. The most important diagnosis for clinicians to establish is whether or not IPF is present. Although the clinical and radiographic diagnosis of IPF can be made confidently in some cases, patients whose diagnosis is unclear after a thorough clinical and radiographic evaluation should undergo surgical lung biopsy to establish the underlying histopathology. New insight into the pathophysiology of IPF suggests a distinctly fibroproliferative process, and antifibrotic therapies are under evaluation. Referral for lung transplantation should be pursued early in those patients with progressive disease unresponsive to therapy. As our understanding of the pathogenic mechanisms of the IIPs grows, we will surely develop promising new agents that may significantly affect the morbidity and mortality of patients with these often devastating diseases.

KEY POINTS

Approach to the Patient with Interstitial Lung Disease

- ILDs include inflammatory and fibrotic diseases that ultimately disrupt the alveolar-capillary interface, leading to hypoxemia. ILDs usually lead to restrictive physiology, but airway involvement can cause obstruction or mixed physiology.
- ILDs arise in many clinical settings, including connective tissue disease; occupational, environmental and drug exposures; and primary pulmonary disorders.
- In many cases, the fundamental question to be answered is whether a patient has IPF or not.
- A careful detailed history and physical examination can be critical to uncovering clues that lead the thoughtful clinician to an accurate diagnosis.
- Characteristic radiographic features as well as certain laboratory tests can be helpful in delineating among possible causes of ILD. Pulmonary function testing is usually abnormal in patients with ILD. When it is normal, exercise challenge will often elicit underlying derangements in gas exchange.
- Ultimately, histopathologic examination of lung tissue obtained by surgical lung biopsy may be necessary to confirm a specific diagnosis in ILD.

Idiopathic Interstitial Pneumonias

- The IIPs are a subgroup of ILDs of unknown etiology and variable clinical course.
- IPF is the most common and is progressive, irreversible, and lethal. It has no effective treatment, although several clinical trials are ongoing.
- It is suggested that when possible, patients should be enrolled in a clinical trial and evaluated for lung transplant.
- Recent evidence indicates that 10% to 15% of IPF patients die from a rapid deterioration (acute exacerbation) that may be related to viral or bacterial infection, aspiration by gastroesophageal reflux, or thromboembolic event, or—most commonly—of unidentified cause.
- NSIP is characterized by diffuse, temporally and geographically homogenous cellular infiltrates (cellular NSIP) or fibrosis (fibrotic NSIP). NSIP is often associated to collagen vascular diseases, drug-induced disease, and hypersensitivity pneumonitis among others. In general, patients with NSIP (especially cellular NSIP) fare better than those with IPF.

References

1. Coultas DB, Zumwalt RE, Black WC, Sobonya RE: The epidemiology of interstitial lung diseases. Am J Respir Crit Care Med 150:967–972, 1994.
2. Schwarz MI, King TE Jr (ed): Interstitial Lung Disease (4th ed). Hamilton, Ontario: BC Decker, 2003.
3. Raghu G: The role of gastroesophageal reflux in idiopathic pulmonary fibrosis. Am J Med 115(Suppl 3A):60S–64S, 2003.
4. Bandla HP, Davis SH, Hopkins NE: Lipoid pneumonia: A silent complication of mineral oil aspiration. Pediatrics 103:E19, 1999.
5. Donaghy M, Rees AJ: Cigarette smoking and lung haemorrhage in glomerulonephritis caused by autoantibodies to glomerular basement membrane. Lancet 2:1390–1393, 1983.
6. Thomas AQ, Lane K, Phillips J 3rd, et al: Heterozygosity for a surfactant protein C gene mutation associated with usual interstitial pneumonitis and cellular nonspecific interstitial pneumonitis in one kindred. Am J Respir Crit Care Med 165:1322–1328, 2002.
7. Parker MS, Rosado Shipley W, de Christenson ML, et al: The Hermansky-Pudlak syndrome. Ann Diagn Pathol 1:99–103, 1997.
8. Anderson PD, Huizing M, Claassen DA, et al: Hermansky-Pudlak syndrome type 4 (HPS-4): Clinical and molecular characteristics. Hum Genet 113:10–17, 2003.
9. Ziskind MM, Weill H, Buechner HA, Brown M: Recognition of distinctive radiologic patterns in diffuse pulmonary disease. Arch Intern Med 114:108–112, 1964.
10. Muller NL, Miller RR: Computed tomography of chronic diffuse infiltrative lung disease. Part 1. Am Rev Respir Dis 142:1206–1215, 1990.
11. Muller NL, Miller RR: Computed tomography of chronic diffuse infiltrative lung disease. Part 2. Am Rev Respir Dis 142:1440–1448, 1990.
12. Desai SR, Wells AU, Rubens MB, et al: Traction bronchiectasis in cryptogenic fibrosing alveolitis: Associated computed tomographic features and physiological significance. Eur Radiol 13:1801–1808, 2003.
13. Epler GR, McLoud TC, Gaensler EA, et al: Normal chest roentgenograms in chronic diffuse infiltrative lung disease. N Engl J Med 298:934–939, 1978.
14. Hunninghake GW, Lynch DA, Galvin JR, et al: Radiologic findings are strongly associated with a pathologic diagnosis of usual interstitial pneumonia. Chest 124:1215–1223, 2003.
15. Schurawitzki H, Stiglbauer R, Graninger W, et al: Interstitial lung disease in progressive systemic sclerosis: high-resolution CT versus radiography. Radiology 176:755–759, 1990.
16. Harrison NK, Glanville AR, Strickland B, et al: Pulmonary involvement in systemic sclerosis: The detection of early changes by thin section CT scan, bronchoalveolar lavage and ^{99m}Tc-DTPA clearance. Respir Med 83:403–414, 1989.
17. Lynch DA, Rose CS, Way D, King TE Jr: Hypersensitivity pneumonitis: Sensitivity of high-resolution CT in a population-based study. AJR Am J Roentgenol 159:469–472, 1992.

18. Hanley ME, King TE Jr, Schwarz MI, et al: The impact of smoking on mechanical properties of the lungs in idiopathic pulmonary fibrosis and sarcoidosis. Am Rev Respir Dis 144:1102–1106, 1991.
19. Cherniack R (ed): Pulmonary Function Testing. Philadelphia: WB Saunders, 1992.
20. Fulmer JD, Roberts WC, von Gal ER, Crystal RG: Morphologic-physiologic correlates of the severity of fibrosis and degree of cellularity in idiopathic pulmonary fibrosis. J Clin Invest 63:665–676, 1979.
21. Greening AP, Hughes JM: Serial estimations of carbon monoxide diffusing capacity in intrapulmonary haemorrhage. Clin Sci (Lond) 60:507–512, 1981.
22. King TE Jr, Tooze JA, Schwarz MI, et al: Predicting survival in idiopathic pulmonary fibrosis: Scoring system and survival model. Am J Respir Crit Care Med 164:1171–1181, 2001.
23. Costabel U, Guzman J: Bronchoalveolar lavage. *In* Schwarz MI, King TE (eds): Interstitial Lung Diseases (4th ed). Hamilton, Ontario: BC Decker, 2003, pp 114–133.
24. Rottoli P, Bargagli E: Is bronchoalveolar lavage obsolete in the diagnosis of interstitial lung disease? Curr Opin Pulm Med 9:418–425, 2003.
25. Bronchoalveolar lavage constituents in healthy individuals, idiopathic pulmonary fibrosis, and selected comparison groups. The BAL Cooperative Group Steering Committee. Am Rev Respir Dis 141:S169–S202, 1990.
26. Ohshimo S, Bonella F, Cui A, et al: Significance of bronchoalveolar lavage for the diagnosis of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 179:1043–1047, 2009.
27. Kawanami O, Basset F, Ferrans VJ, et al: Pulmonary Langerhans' cells in patients with fibrotic lung disorders. Lab Invest 44:227–233, 1981.
28. Bensard DD, McIntyre RC Jr, Waring BJ, Simon JS: Comparison of video thoracoscopic lung biopsy to open lung biopsy in the diagnosis of interstitial lung disease. Chest 103:765–770, 1993.
29. American Thoracic Society/European Respiratory Society: International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. This joint statement of the American Thoracic Society (ATS), and the European Respiratory Society (ERS) was adopted by the ATS board of directors, June 2001, and by the ERS Executive Committee, June 2001. Am J Respir Crit Care Med 165:277–304, 2002.
30. American Thoracic Society: Idiopathic pulmonary fibrosis: Diagnosis and treatment. International consensus statement. American Thoracic Society (ATS), and the European Respiratory Society (ERS). Am J Respir Crit Care Med 161:646–664, 2000.
31. Travis WD, Colby T, Koss MN: Non-neoplastic Disorders of the Lower Respiratory Tract. Atlas of Nontumor Pathology 2002.
32. Raghu G, Weycker D, Edelsberg J, et al: Incidence and prevalence of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 174:810–816, 2006.
33. Selman M, Carrillo G, Estrada A, et al: Accelerated variant of idiopathic pulmonary fibrosis: Clinical behavior and gene expression pattern. PLoS One 2:e482, 2007.
34. Wittram C, Mark EJ, McLoud TC: CT-histologic correlation of the ATS/ERS 2002 classification of idiopathic interstitial pneumonias. Radiographics 23:1057–1071, 2003.
35. Gotway MB, Freemer MM, King TE Jr: Challenges in pulmonary fibrosis. 1: Use of high resolution CT scanning of the lung for the evaluation of patients with idiopathic interstitial pneumonias. Thorax 62:546–553, 2007.
36. Cottin V, Nunes H, Brillet PY, et al: Combined pulmonary fibrosis and emphysema: A distinct underrecognised entity. Eur Respir J 26:586–593, 2005.
37. Jankowich MD, Polsky M, Klein M, Rounds S: Heterogeneity in combined pulmonary fibrosis and emphysema. Respiration 75:411–417, 2008.
38. Mejia M, Carrillo G, Rojas-Serrano J, et al: Idiopathic pulmonary fibrosis and emphysema: Decreased survival associated with severe pulmonary arterial hypertension. Chest 136:10–15, 2009.
39. Wells AU, King AD, Rubens MB, et al: Lone cryptogenic fibrosing alveolitis: A functional-morphologic correlation based on extent of disease on thin-section computed tomography. Am J Respir Crit Care Med 155:1367–1375, 1997.
40. Xaubet A, Agusti C, Luburich P, et al: Pulmonary function tests and CT scan in the management of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 158:431–436, 1998.
41. Lynch DA, David Godwin J, Safrin S, et al: High-resolution computed tomography in idiopathic pulmonary fibrosis: Diagnosis and prognosis. Am J Respir Crit Care Med 172:488–493, 2005.
42. Lynch DA, Newell JD, Logan PM, et al: Can CT distinguish hypersensitivity pneumonitis from idiopathic pulmonary fibrosis? AJR Am J Roentgenol 165:807–811, 1995.
43. Hunninghake GW, Zimmerman MB, Schwartz DA, et al: Utility of a lung biopsy for the diagnosis of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 164:193–196, 2001.
44. Johkoh T, Muller NL, Cartier Y, et al: Idiopathic interstitial pneumonias: Diagnostic accuracy of thin-section CT in 129 patients. Radiology 211:555–560, 1999.
45. Raghu G, Mageto YN, Lockhart D, et al: The accuracy of the clinical diagnosis of new-onset idiopathic pulmonary fibrosis and other interstitial lung disease: A prospective study. Chest 116:1168–1174, 1999.
46. Swensen SJ, Aughenbaugh GL, Myers JL: Diffuse lung disease: Diagnostic accuracy of CT in patients undergoing surgical biopsy of the lung. Radiology 205:229–234, 1997.
47. Aziz ZA, Wells AU, Hansell DM, et al: HRCT diagnosis of diffuse parenchymal lung disease: Inter-observer variation. Thorax 59:506–511, 2004.
48. Grenier P, Valeyre D, Cluzel P, et al: Chronic diffuse interstitial lung disease: Diagnostic value of chest radiography and high-resolution CT. Radiology 179:123–132, 1991.
49. Mathieson JR, Mayo JR, Staples CA, Muller NL: Chronic diffuse infiltrative lung disease: Comparison of diagnostic accuracy of CT and chest radiography. Radiology 171:111–116, 1989.
50. Tung KT, Wells AU, Rubens MB, et al: Accuracy of the typical computed tomographic appearances of fibrosing alveolitis. Thorax 48:334–338, 1993.
51. Flaherty KR, Thwaite EL, Kazerooni EA, et al: Radiological versus histological diagnosis in UIP and NSIP: Survival implications. Thorax 58:143–148, 2003.
52. van Beek EJ, Hoffman EA: Functional imaging: CT and MRI. Clin Chest Med 29:195–216, vii, 2008.
53. Yi CA, Lee KS, Han J, et al: 3-T MRI for differentiating inflammation- and fibrosis-predominant lesions of usual and nonspecific interstitial pneumonia: Comparison study with pathologic correlation. AJR Am J Roentgenol 190:878–885, 2008.
54. Meissner HH, Soo Hoo GW, Khonsary SA, et al: Idiopathic pulmonary fibrosis: Evaluation with positron emission tomography. Respiration 73:197–202, 2006.
55. Lavalaye J, Grutters JC, van de Garde EM, et al: Imaging of fibrogenesis in patients with idiopathic pulmonary fibrosis with cis-4-[(18)F]-fluoro-L: -Proline PET. Mol Imaging Biol 11:123–127, 2009.
56. Lama VN, Flaherty KR, Toews GB, et al: Prognostic value of desaturation during a 6-minute walk test in idiopathic interstitial pneumonia. Am J Respir Crit Care Med 168:1084–1090, 2003.
57. Rusanov V, Shitrit D, Fox B, et al: Use of the 15-steps climbing exercise oximetry test in patients with idiopathic pulmonary fibrosis. Respir Med 102:1080–1088, 2008.
58. Nathan SD, Noble PW, Tuder RM: Idiopathic pulmonary fibrosis and pulmonary hypertension: Connecting the dots. Am J Respir Crit Care Med 175:875–880, 2007.
59. Arcasoy SM, Christie JD, Ferrari VA, et al: Echocardiographic assessment of pulmonary hypertension in patients with advanced lung disease. Am J Respir Crit Care Med; 167:735–740, 2003.
60. Lettieri CJ, Nathan SD, Barnett SD, et al: Prevalence and outcomes of pulmonary arterial hypertension in advanced idiopathic pulmonary fibrosis. Chest 129:746–752, 2006.
61. Leuchte HH, Neurohr C, Baumgartner R, et al: Brain natriuretic peptide and exercise capacity in lung fibrosis and pulmonary hypertension. Am J Respir Crit Care Med 170:360–365, 2004.
62. Patel NM, Lederer DJ, Borczuk AC, Kawut SM: Pulmonary hypertension in idiopathic pulmonary fibrosis. Chest 132:998–1006, 2007.
63. Olschewski H, Ghofrani HA, Walmrath D, et al: Inhaled prostacyclin and iloprost in severe pulmonary hypertension secondary to lung fibrosis. Am J Respir Crit Care Med 160:600–607, 1999.

64. Inhaled iloprost in adults with abnormal pulmonary pressure and associated with idiopathic pulmonary fibrosis. Available at http://clinicaltrials.gov
65. Collard HR, Anstrom KJ, Schwarz MI, Zisman DA: Sildenafil improves walk distance in idiopathic pulmonary fibrosis. Chest 131:897–899, 2007.
66. Mermigkis C, Chapman J, Golish J, et al: Sleep-related breathing disorders in patients with idiopathic pulmonary fibrosis. Lung 185:173–178, 2007.
67. Katzenstein AL, Mukhopadhyay S, Myers JL: Diagnosis of usual interstitial pneumonia and distinction from other fibrosing interstitial lung diseases. Hum Pathol 39:1275–1294, 2008.
68. Katzenstein AL, Myers JL: Idiopathic pulmonary fibrosis: Clinical relevance of pathologic classification. Am J Respir Crit Care Med 157:1301–1315, 1998.
69. Le Jeune I, Gribbin J, West J, et al: The incidence of cancer in patients with idiopathic pulmonary fibrosis and sarcoidosis in the UK. Respir Med 101:2534–2540, 2007.
70. Taskar VS, Coultas DB: Is idiopathic pulmonary fibrosis an environmental disease? Proc Am Thorac Soc 3:293–298, 2006.
71. Steele MP, Speer MC, Loyd JE, et al: Clinical and pathologic features of familial interstitial pneumonia. Am J Respir Crit Care Med 172:1146–1152, 2005.
72. Stewart JP, Egan JJ, Ross AJ, et al: The detection of Epstein-Barr virus DNA in lung tissue from patients with idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 159:1336–1341, 1999.
73. Raghu G, Freudenberger TD, Yang S, et al: High prevalence of abnormal acid gastro-oesophageal reflux in idiopathic pulmonary fibrosis. Eur Respir J 27:136–142, 2006.
74. D'Ovidio F, Singer LG, Hadjiliadis D, et al: Prevalence of gastroesophageal reflux in end-stage lung disease candidates for lung transplant. Ann Thorac Surg 80:1254–1260, 2005.
75. Selman M, King TE, Pardo A: Idiopathic pulmonary fibrosis: Prevailing and evolving hypotheses about its pathogenesis and implications for therapy. Ann Intern Med 134:136–151, 2001.
76. Gauldie J: Pro: Inflammatory mechanisms are a minor component of the pathogenesis of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 165:1205–1206, 2002.
77. Selman M, Pardo A: Role of epithelial cells in idiopathic pulmonary fibrosis: From innocent targets to serial killers. Proc Am Thorac Soc 3:364–372, 2006.
78. Chambers RC: Procoagulant signalling mechanisms in lung inflammation and fibrosis: Novel opportunities for pharmacological intervention? Br J Pharmacol 153(Suppl 1):S367–S378, 2008.
79. Selman M, Ruiz V, Cabrera S, et al: TIMP-1, -2, -3, and -4 in idiopathic pulmonary fibrosis. A prevailing nondegradative lung microenvironment? Am J Physiol Lung Cell Mol Physiol 279:L562–L574, 2000.
80. Thannickal VJ, Horowitz JC: Evolving concepts of apoptosis in idiopathic pulmonary fibrosis. Proc Am Thorac Soc 3:350–356, 2006.
81. Wang R, Ramos C, Joshi I, et al: Human lung myofibroblast-derived inducers of alveolar epithelial apoptosis identified as angiotensin peptides. Am J Physiol 277:L1158–L1164, 1999.
82. Waghray M, Cui Z, Horowitz JC, et al: Hydrogen peroxide is a diffusible paracrine signal for the induction of epithelial cell death by activated myofibroblasts. FASEB J 19:854–856, 2005.
83. Sheppard D: Pulmonary fibrosis: A cellular overreaction or a failure of communication? J Clin Invest 107:1501–1502, 2001.
84. Gauldie J, Kolb M, Sime PJ: A new direction in the pathogenesis of idiopathic pulmonary fibrosis? Respir Res 3:1, 2002.
85. Zuo F, Kaminski N, Eugui E, et al: Gene expression analysis reveals matrilysin as a key regulator of pulmonary fibrosis in mice and humans. Proc Natl Acad Sci U S A;99:6292–6297, 2002.
86. Selman M, Pardo A: The epithelial/fibroblastic pathway in the pathogenesis of idiopathic pulmonary fibrosis. Am J Respir Cell Mol Biol 29:S93–S97, 2003.
87. Selman M, Pardo A, Barrera L, et al: Gene expression profiles distinguish idiopathic pulmonary fibrosis from hypersensitivity pneumonitis. Am J Respir Crit Care Med 173:188–198, 2006.
88. Selman M, Pardo A, Kaminski N: Idiopathic pulmonary fibrosis: Aberrant recapitulation of developmental programs? PLoS Med 5:e62, 2008.
89. Konigshoff M, Balsara N, Pfaff EM, et al: Functional Wnt signaling is increased in idiopathic pulmonary fibrosis. PLoS One 3:e2142, 2008.
90. Armanios MY, Chen JJ, Cogan JD, et al: Telomerase mutations in families with idiopathic pulmonary fibrosis. N Engl J Med 356:1317–1326, 2007.
91. Tsakiri KD, Cronkhite JT, Kuan PJ, et al: Adult-onset pulmonary fibrosis caused by mutations in telomerase. Proc Natl Acad Sci U S A 104:7552–7557, 2007.
92. Alder JK, Chen JJ, Lancaster L, et al: Short telomeres are a risk factor for idiopathic pulmonary fibrosis. Proc Natl Acad Sci U S A 105:13051–13056, 2008.
93. Cronkhite JT, Xing C, Raghu G, et al: Telomere shortening in familial and sporadic pulmonary fibrosis. Am J Respir Crit Care Med 178:729–737, 2008.
94. Garcia CK, Wright WE, Shay JW: Human diseases of telomerase dysfunction: Insights into tissue aging. Nucleic Acids Res 35:7406–7416, 2007.
95. Aubert G, Lansdorp PM: Telomeres and aging. Physiol Rev 88:557–579, 2008.
96. Flaherty KR, King TE Jr, Raghu G, et al: Idiopathic interstitial pneumonia: What is the effect of a multidisciplinary approach to diagnosis? Am J Respir Crit Care Med 170:904–910, 2004.
97. Flaherty KR, Andrei AC, King TE Jr, et al: Idiopathic interstitial pneumonia:Do community and academic physicians agree on diagnosis? Am J Respir Crit Care Med 175:1054–1060, 2007.
98. Noble PW: Idiopathic pulmonary fibrosis: Natural history and prognosis. Clin Chest Med 27:S11–S16, v, 2006.
99. Han MK, Murray S, Fell CD, et al: Sex differences in physiological progression of idiopathic pulmonary fibrosis. Eur Respir J 31:1183–1188, 2008.
100. Manali ED, Stathopoulos GT, Kollintza A, et al: The Medical Research Council chronic dyspnea score predicts the survival of patients with idiopathic pulmonary fibrosis. Respir Med 102:586–592, 2008.
101. McCormack FX, King TE Jr, Bucher BL, et al: Surfactant protein A predicts survival in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med;152:751–759, 1995.
102. Kinder BW, Brown KK, McCormack FX, et al: Serum surfactant protein-A is a strong predictor of early mortality in idiopathic pulmonary fibrosis. Chest 135:1557–1563, 2009.
103. Gay SE, Kazerooni EA, Toews GB, et al: Idiopathic pulmonary fibrosis: Predicting response to therapy and survival. Am J Respir Crit Care Med 157:1063–1072, 1998.
104. Best AC, Meng J, Lynch AM, et al: Idiopathic pulmonary fibrosis: Physiologic tests, quantitative CT indexes, and CT visual scores as predictors of mortality. Radiology 246:935–940, 2008.
105. Flaherty KR, Andrei AC, Murray S, et al: Idiopathic pulmonary fibrosis: Prognostic value of changes in physiology and six-minute-walk test. Am J Respir Crit Care Med 174:803–809, 2006.
106. Collard HR, King TE Jr, Bartelson BB, et al: Changes in clinical and physiologic variables predict survival in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 168:538–542, 2003.
107. Martinez FJ, Flaherty K: Pulmonary function testing in idiopathic interstitial pneumonias. Proc Am Thorac Soc 3:315–321, 2006.
108. Watters LC, Schwarz MI, Cherniack RM, et al: Idiopathic pulmonary fibrosis. Pretreatment bronchoalveolar lavage cellular constituents and their relationships with lung histopathology and clinical response to therapy. Am Rev Respir Dis 135:696–704, 1987.
109. Turner-Warwick M, Haslam PL: The value of serial bronchoalveolar lavages in assessing the clinical progress of patients with cryptogenic fibrosing alveolitis. Am Rev Respir Dis 135:26–34, 1987.
110. Kinder BW, Brown KK, Schwarz MI, et al: Baseline BAL neutrophilia predicts early mortality in idiopathic pulmonary fibrosis. Chest 133:226–232, 2008.
111. King TE Jr, Schwarz MI, Brown K, et al: Idiopathic pulmonary fibrosis: Relationship between histopathologic features and mortality. Am J Respir Crit Care Med 164:1025–1032, 2001.
112. Nicholson AG, Fulford LG, Colby TV, et al: The relationship between individual histologic features and disease progression in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 166:173–177, 2002.

113. Flaherty KR, Colby TV, Travis WD, et al: Fibroblastic foci in usual interstitial pneumonia: Idiopathic versus collagen vascular disease. Am J Respir Crit Care Med 167:1410–1415, 2003.
114. Enomoto N, Suda T, Kato M, et al: Quantitative analysis of fibroblastic foci in usual interstitial pneumonia. Chest 130:22–29, 2006.
115. Hanak V, Ryu JH, de Carvalho E, et al: Profusion of fibroblast foci in patients with idiopathic pulmonary fibrosis does not predict outcome. Respir Med 102:852–856, 2008.
116. Latsi PI, du Bois RM, Nicholson AG, et al: Fibrotic idiopathic interstitial pneumonia: The prognostic value of longitudinal functional trends. Am J Respir Crit Care Med 168:531–537, 2003.
117. Wells AU, Desai SR, Rubens MB, et al: Idiopathic pulmonary fibrosis: A composite physiologic index derived from disease extent observed by computed tomography. Am J Respir Crit Care Med 167:962–969, 2003.
118. Flaherty KR, Mumford JA, Murray S, et al: Prognostic implications of physiologic and radiographic changes in idiopathic interstitial pneumonia. Am J Respir Crit Care Med 168:543–548, 2003.
119. Panos RJ, Mortenson RL, Niccoli SA, King TE Jr: Clinical deterioration in patients with idiopathic pulmonary fibrosis: Causes and assessment. Am J Med 88:396–404, 1990.
120. Daniels CE, Yi ES, Ryu JH: Autopsy findings in 42 consecutive patients with idiopathic pulmonary fibrosis. Eur Respir J 32:170–174, 2008.
121. Nathan SD, Barnett SD, Urban BA, et al: Pulmonary embolism in idiopathic pulmonary fibrosis transplant recipients. Chest 123:1758–1763, 2003.
122. Kizer JR, Zisman DA, Blumenthal NP, et al: Association between pulmonary fibrosis and coronary artery disease. Arch Intern Med 164:551–556, 2004.
123. Papadopoulos CE, Pitsiou G, Karamitsos TD, et al: Left ventricular diastolic dysfunction in idiopathic pulmonary fibrosis: A tissue Doppler echocardiographic [corrected] study. Eur Respir J 31:701–706, 2008.
124. Mapel DW, Samet JM, Coultas DB: Corticosteroids and the treatment of idiopathic pulmonary fibrosis. Past, present, and future. Chest 110:1058–1067, 1996.
125. Richeldi L, Davies HR, Ferrara G, Franco F: Corticosteroids for idiopathic pulmonary fibrosis. Cochrane Database Syst Rev 3:CD002880, 2003.
126. Collard HR, King TE Jr: Treatment of idiopathic pulmonary fibrosis: The rise and fall of corticosteroids. Am J Med 110:326–328, 2001.
127. Collard HR, Ryu JH, Douglas WW, et al: Combined corticosteroid and cyclophosphamide therapy does not alter survival in idiopathic pulmonary fibrosis. Chest 125:2169–2174, 2004.
128. Raghu G, Depaso WJ, Cain K, et al: Azathioprine combined with prednisone in the treatment of idiopathic pulmonary fibrosis: A prospective double-blind, randomized, placebo-controlled clinical trial. Am Rev Respir Dis 144:291–296, 1991.
129. Johnson MA, Kwan S, Snell NJ, et al: Randomised controlled trial comparing prednisolone alone with cyclophosphamide and low dose prednisolone in combination in cryptogenic fibrosing alveolitis. Thorax 44:280–288, 1989.
130. Zisman DA, Lynch JP 3rd, Toews GB, et al: Cyclophosphamide in the treatment of idiopathic pulmonary fibrosis: A prospective study in patients who failed to respond to corticosteroids. Chest 117:1619–1626, 2000.
131. Demedts M, Behr J, Buhl R, et al: High-dose acetylcysteine in idiopathic pulmonary fibrosis. N Engl J Med 353:2229–2242, 2005.
132. Douglas WW, Ryu JH, Swensen SJ, et al: Colchicine versus prednisone in the treatment of idiopathic pulmonary fibrosis. A randomized prospective study. Members of the Lung Study Group. Am J Respir Crit Care Med 158:220–225, 1998.
133. Douglas WW, Ryu JH, Schroeder DR: Idiopathic pulmonary fibrosis: Impact of oxygen and colchicine, prednisone, or no therapy on survival. Am J Respir Crit Care Med 161:1172–1178, 2000.
134. Selman M, Carrillo G, Salas J, et al: Colchicine, D-penicillamine, and prednisone in the treatment of idiopathic pulmonary fibrosis: A controlled clinical trial. Chest 114:507–512, 1998.
135. Raghu R, Bozic CR, Brown K: Trial of interferon beta-1a (INFbeta-1a) in idiopathic pulmonary fibrosis (IPF): Characteristics of patients with and without surgical lung biopsy [Abstract]. Am J Respir Crit Care Med 161:A527, 2000.
136. Raghu R, Bozic CR, Brown K: Feasibility of a trial of interferon beta-1a (IFNbeta-1a) in the treatment of idiopathic pulmonary fibrosis (IPF) [Abstract]. Am J Respir Crit Care Med 163:A707, 2001.
137. Carrillo G, Estrada A, Mejia M: Inhaled beclomethasone and colchicine (IBC) versus inhaled beclomethasone, colchicine and captopril (IBCCAP) in patients with idiopathic pulmonary fibrosis (IPF) [Abstract]. Am J Respir Crit Care Med 161:A528, 2000.
138. Meuret G, Fueter R, Gloor F: Early stage of fulminant idiopathic pulmonary fibrosis cured by intense combination therapy using cyclophosphamide, vincristine, and prednisone. Respiration 36:228–233, 1978.
139. Raghu G, Brown KK, Bradford WZ, et al: A placebo-controlled trial of interferon gamma-1b in patients with idiopathic pulmonary fibrosis. N Engl J Med 350:125–133, 2004.
140. King TE Jr, Safrin S, Starko KM, et al: Analyses of efficacy end points in a controlled trial of interferon-gamma1b for idiopathic pulmonary fibrosis. Chest 127:171–177, 2005.
141. King TE Jr, Albera C, Bradford WZ, et al, for the INSPIRE Study Group: The effect of interferon gamma-1b on survival in patients with idiopathic pulmonary fibrosis (INSPIRE): A multicentre randomised placebo-controlled trial. Lancet 374:222–228, 2009.
142. Raghu G, Johnson WC, Lockhart D, Mageto Y: Treatment of idiopathic pulmonary fibrosis with a new antifibrotic agent, pirfenidone: Results of a prospective, open-label phase II study. Am J Respir Crit Care Med 159:1061–1069, 1999.
143. Azuma A, Nukiwa T, Tsuboi E, et al: Double-blind, placebo-controlled trial of pirfenidone in patients with idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 171:1040–1047, 2005.
144. Shi-wen X, Kennedy L, Renzoni EA, et al: Endothelin is a downstream mediator of profibrotic responses to transforming growth factor beta in human lung fibroblasts. Arthritis Rheum 56:4189–4194, 2007.
145. Park SH, Saleh D, Giaid A, Michel RP: Increased endothelin-1 in bleomycin-induced pulmonary fibrosis and the effect of an endothelin receptor antagonist. Am J Respir Crit Care Med 156:600–608, 1997.
146. King TE Jr, Behr J, Brown KK, et al: BUILD-1: A randomized placebo-controlled trial of bosentan in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 177:75–81, 2008.
147. Raghu G, Brown KK, Costabel U, et al: Treatment of idiopathic pulmonary fibrosis with etanercept: An exploratory, placebo-controlled trial. Am J Respir Crit Care Med 178:948–955, 2008.
148. Orens JB, Estenne M, Arcasoy S, et al: International guidelines for the selection of lung transplant candidates: 2006 update—A consensus report from the Pulmonary Scientific Council of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant 25:745–755, 2006.
149. Trulock EP, Edwards LB, Taylor DO, et al: The Registry of the International Society for Heart and Lung Transplantation: Twenty-first official adult lung and heart-lung transplant report—2004. J Heart Lung Transplant 23:804–815, 2004.
150. Mason DP, Brizzio ME, Alster JM, et al: Lung transplantation for idiopathic pulmonary fibrosis. Ann Thorac Surg 84:1121–1128, 2007.
151. Kozower BD, Meyers BF, Smith MA, et al: The impact of the lung allocation score on short-term transplantation outcomes: A multicenter study. J Thorac Cardiovasc Surg; 135:166–171, 2008.
152. Jastrzebski D, Gumola A, Gawlik R, Kozielski J: Dyspnea and quality of life in patients with pulmonary fibrosis after six weeks of respiratory rehabilitation. J Physiol Pharmacol 57(Suppl 4):139–148, 2006.
153. Collard HR, Moore BB, Flaherty KR, et al: Acute exacerbations of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 176:636–643, 2007.
154. Hyzy R, Huang S, Myers J, et al: Acute exacerbation of idiopathic pulmonary fibrosis. Chest 132:1652–1658, 2007.
155. Martinez FJ, Safrin S, Weycker D, et al: The clinical course of patients with idiopathic pulmonary fibrosis. Ann Intern Med 142:963–967, 2005.
156. Silva CI, Muller NL, Fujimoto K, et al: Acute exacerbation of chronic interstitial pneumonia: High-resolution computed tomography and pathologic findings. J Thorac Imaging 22:221–229, 2007.

157. Churg A, Muller NL, Silva CI, Wright JL: Acute exacerbation (acute lung injury of unknown cause) in UIP and other forms of fibrotic interstitial pneumonias. Am J Surg Pathol 31:277–284, 2007.
158. Kim DS, Park JH, Park BK, et al: Acute exacerbation of idiopathic pulmonary fibrosis: Frequency and clinical features. Eur Respir J 27:143–150, 2006.
159. Akira M, Hamada H, Sakatani M, et al: CT findings during phase of accelerated deterioration in patients with idiopathic pulmonary fibrosis. AJR Am J Roentgenol 168:79–83, 1997.
160. Akira M, Kozuka T, Yamamoto S, Sakatani M: Computed tomography findings in acute exacerbation of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 178:372–378, 2008.
161. Parambil JG, Myers JL, Ryu JH: Histopathologic features and outcome of patients with acute exacerbation of idiopathic pulmonary fibrosis undergoing surgical lung biopsy. Chest 128:3310–3315, 2005.
162. Tajima S, Oshikawa K, Tominaga S, Sugiyama Y: The increase in serum soluble ST2 protein upon acute exacerbation of idiopathic pulmonary fibrosis. Chest 124:1206–1214, 2003.
163. Lohning M, Stroehmann A, Coyle AJ, et al: T1/ST2 is preferentially expressed on murine Th2 cells, independent of interleukin 4, interleukin 5, and interleukin 10, and important for Th2 effector function. Proc Natl Acad Sci U S A 95:6930–6935, 1998.
164. Kurosu K, Takiguchi Y, Okada O, et al: Identification of annexin 1 as a novel autoantigen in acute exacerbation of idiopathic pulmonary fibrosis. J Immunol 181:756–767, 2008.
165. Lee HL, Ryu JH, Wittmer MH, et al: Familial idiopathic pulmonary fibrosis: Clinical features and outcome. Chest 127:2034–2041, 2005.
166. Marshall RP, Puddicombe A, Cookson WO, Laurent GJ: Adult familial cryptogenic fibrosing alveolitis in the United Kingdom. Thorax 55:143–146, 2000.
167. Hodgson U, Laitinen T, Tukiainen P: Nationwide prevalence of sporadic and familial idiopathic pulmonary fibrosis: Evidence of founder effect among multiplex families in Finland. Thorax 57:338–342, 2002.
168. Buchino JJ, Keenan WJ, Algren JT, Bove KE: Familial desquamative interstitial pneumonitis occurring in infants. Am J Med Genet Suppl 3:285–291, 1987.
169. Wright JA, Pennington JE: Familial lymphoid interstitial pneumonitis. J Pediatr 111:638, 1987.
170. Nogee LM, Dunbar AE 3rd, Wert SE, et al: A mutation in the surfactant protein C gene associated with familial interstitial lung disease. N Engl J Med 344:573–579, 2001.
171. Nogee LM, Dunbar AE 3rd, Wert S, et al: Mutations in the surfactant protein C gene associated with interstitial lung disease. Chest 121:20S–21S, 2002.
172. Amin RS, Wert SE, Baughman RP, et al: Surfactant protein deficiency in familial interstitial lung disease. J Pediatr 139:85–92, 2001.
173. Whitsett JA: Genetic basis of familial interstitial lung disease: Misfolding or function of surfactant protein C? Am J Respir Crit Care Med 165:1201–1202, 2002.
174. Hodgson U, Pulkkinen V, Dixon M, et al: ELMOD2 is a candidate gene for familial idiopathic pulmonary fibrosis. Am J Hum Genet 79:149–154, 2006.
175. Katzenstein AL, Fiorelli RF: Nonspecific interstitial pneumonia/fibrosis. Histologic features and clinical significance. Am J Surg Pathol 18:136–147, 1994.
176. Travis WD, Hunninghake G, King TE Jr, et al: Idiopathic nonspecific interstitial pneumonia: Report of an American Thoracic Society project. Am J Respir Crit Care Med 177:1338–1347, 2008.
177. Kinder BW, Collard HR, Koth L, et al: Idiopathic nonspecific interstitial pneumonia: Lung manifestation of undifferentiated connective tissue disease? Am J Respir Crit Care Med 176:691–697, 2007.
178. Tzelepis GE, Toya SP, Moutsopoulos HM: Occult connective tissue diseases mimicking idiopathic interstitial pneumonias. Eur Respir J 31:11–20, 2008.
179. Bjoraker JA, Ryu JH, Edwin MK, et al: Prognostic significance of histopathologic subsets in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 157:199–203, 1998.
180. Veeraraghavan S, Latsi PI, Wells AU, et al: BAL findings in idiopathic nonspecific interstitial pneumonia and usual interstitial pneumonia. Eur Respir J 22:239–244, 2003.
181. Johkoh T, Muller NL, Colby TV, et al: Nonspecific interstitial pneumonia: Correlation between thin-section CT findings and pathologic subgroups in 55 patients. Radiology 225:199–204, 2002.
182. Misumi S, Lynch DA: Idiopathic pulmonary fibrosis/usual interstitial pneumonia: Imaging diagnosis, spectrum of abnormalities, and temporal progression. Proc Am Thorac Soc 3:307–314, 2006.
183. Nicholson AG, Colby TV, du Bois RM, et al: The prognostic significance of the histologic pattern of interstitial pneumonia in patients presenting with the clinical entity of cryptogenic fibrosing alveolitis. Am J Respir Crit Care Med 162:2213–2217, 2000.
184. Douglas WW, Tazelaar HD, Hartman TE, et al: Polymyositis-dermatomyositis–associated interstitial lung disease. Am J Respir Crit Care Med 164:1182–1185, 2001.
185. Kim DS, Yoo B, Lee JS, et al: The major histopathologic pattern of pulmonary fibrosis in scleroderma is nonspecific interstitial pneumonia. Sarcoidosis Vasc Diffuse Lung Dis 19:121–127, 2002.
186. Lantuejoul S, Brambilla E, Brambilla C, Devouassoux G: Statin-induced fibrotic nonspecific interstitial pneumonia. Eur Respir J 19:577–580, 2002.
187. Vourlekis JS, Schwarz MI, Cool CD, et al: Nonspecific interstitial pneumonitis as the sole histologic expression of hypersensitivity pneumonitis. Am J Med 112:490–493, 2002.
188. Arakawa H, Yamada H, Kurihara Y, et al: Nonspecific interstitial pneumonia associated with polymyositis and dermatomyositis: Serial high-resolution CT findings and functional correlation. Chest 123:1096–1103, 2003.
189. Leslie KO: Historical perspective: A pathologic approach to the classification of idiopathic interstitial pneumonias. Chest 128:513S–519S, 2005.
190. Flaherty KR, Travis WD, Colby TV, et al: Histopathologic variability in usual and nonspecific interstitial pneumonias. Am J Respir Crit Care Med 164:1722–1727, 2001.
191. Craig P, Wells AU, Doffman S: Desquamative interstitial pneumonia, respiratory bronchiolitis and their relationship to smoking. Histopathology 45:275–282, 2004.
192. Visscher D, Myers JL: Histologic spectrum of idiopathic interstitial pneumonias. Proc Am Thorac Soc 3:322–329, 2006.
193. Fraig M, Shreesha U, Savici D, Katzenstein AL: Respiratory bronchiolitis: A clinicopathologic study in current smokers, ex-smokers, and never-smokers. Am J Surg Pathol 26:647–653, 2002.
194. Vierikko T, Jarvenpaa R, Uitti J: The effects of secondhand smoke exposure on HRCT findings among asbestos-exposed workers. Respir Med 102:658–664, 2008.
195. Vassallo R, Jensen EA, Colby TV: The overlap between respiratory bronchiolitis and desquamative interstitial pneumonia in pulmonary Langerhans cell histiocytosis: High-resolution CT, histologic, and functional correlations. Chest 124:1199–1205, 2003.
196. Doan ML, Guillerman RP, Dishop MK: Clinical, radiological and pathological features of ABCA3 mutations in children. Thorax 63:366–373, 2008.
197. Deutsch GH, Young LR, Deterding RR, et al: ChILD Research Co-operative. Diffuse lung disease in young children: Application of a novel classification scheme. Am J Respir Crit Care Med 176:1120–1128, 2007.
198. Kawabata Y, Takemura T, Hebisawa A: Eosinophilia in bronchoalveolar lavage fluid and architectural destruction are features of desquamative interstitial pneumonia. Histopathology 52:194–202, 2008.
199. Park JS, Brown KK, Tuder RM, et al: Respiratory bronchiolitis–associated interstitial lung disease: Radiologic features with clinical and pathologic correlation. J Comput Assist Tomogr 26:13–20, 2002.
200. Wells AU, Nicholson AG, Hansell DM: Challenges in pulmonary fibrosis. 4: Smoking-induced diffused interstitial lung diseases. Thorax 62:904–910, 2007.
201. Hartman TE, Primack SL, Swensen SJ, et al: Desquamative interstitial pneumonia: Thin-section CT findings in 22 patients. Radiology 187:787–790, 1993.
202. Holt RM, Schmidt RA, Godwin JD, Raghu G: High resolution CT in respiratory bronchiolitis–associated interstitial lung disease. J Comput Assist Tomogr 17:46–50, 1993.

203. Hartman TE, Primack SL, Kang EY, et al: Disease progression in usual interstitial pneumonia compared with desquamative interstitial pneumonia. Assessment with serial CT. Chest 110:378–382, 1996.
204. Akira M, Yamamoto S, Hara H, et al: Serial computed tomographic evaluation in desquamative interstitial pneumonia. Thorax 52:333–337, 1997.
205. Yousem SA, Colby TV, Gaensler EA: Respiratory bronchiolitis–associated interstitial lung disease and its relationship to desquamative interstitial pneumonia. Mayo Clin Proc 64:1373–1380, 1989
206. Bedrossian CW, Kuhn C 3rd, Luna MA, et al: Desquamative interstitial pneumonia–like reaction accompanying pulmonary lesions. Chest 72:166–169, 1977.
207. Liebow AA, Steer A, Billingsley JG: Desquamative interstitial pneumonia. Am J Med 39:369–404, 1965.
208. Carrington CB, Gaensler EA, Coutu RE, et al: Natural history and treated course of usual and desquamative interstitial pneumonia. N Engl J Med 298:801–809, 1978.
209. Ryu JH, Myers JL, Capizzi SA, et al: Desquamative interstitial pneumonia and respiratory bronchiolitis–associated interstitial lung disease. Chest 127:178–184, 2005.
210. Nakanishi M, Demura Y, Mizuno S, et al: Changes in HRCT findings in patients with respiratory bronchiolitis–associated interstitial lung disease after smoking cessation. Eur Respir J 29:453–461, 2007.
211. Olson J, Colby TV, Elliott CG: Hamman-Rich syndrome revisited. Mayo Clin Proc 65:1538–1548, 1990.
212. Hamman L, Rich A: Acute diffuse interstitial fibrosis of the lungs. Bull Johns Hopkins Hosp 74:177–212, 1944.
213. Primack SL, Hartman TE, Ikezoe J, et al: Acute interstitial pneumonia: Radiographic and CT findings in nine patients. Radiology 88:817–820, 1993.
214. Vourlekis JS, Brown KK, Cool CD, et al: Acute interstitial pneumonitis. Case series and review of the literature. Medicine (Baltimore) 79:369–378, 2000.
215. Bonaccorsi A, Cancellieri A, Chilosi M, et al: Acute interstitial pneumonia: Report of a series. Eur Respir J 21:187–191, 2003.
216. Ichikado K, Johkoh T, Ikezoe J, et al: Acute interstitial pneumonia: High-resolution CT findings correlated with pathology. AJR Am J Roentgenol 168:333–338, 1997.
217. Askin FB: Acute interstitial pneumonia: Histopathologic patterns of acute lung injury and the Hamman-Rich syndrome revisited. Radiology 188:620–621, 1993.
218. Leslie KO, Colby TV, Swensen SJ (eds): Anatomic Distribution and Histopathologic Patterns of Interstitial Lung Disease (4th ed). Hamilton, Ontario: BC Decker, 2003.
219. Bouhemad B, Zhang M, Lu Q, Rouby JJ: Clinical review: Bedside lung ultrasound in critical care practice. Crit Care 11:205, 2007.
220. Quefatieh A, Stone CH, DiGiovine B, et al: Low hospital mortality in patients with acute interstitial pneumonia. Chest 124:554–559, 2003.
221. Sveinsson OA, Isaksson HJ, Sigvaldason A, et al: Clinical features in secondary and cryptogenic organising pneumonia. Int J Tuberc Lung Dis 11:689–694, 2007.
222. Drakopanagiotakis F, Polychronopoulos V, Judson MA: Organizing pneumonia. Am J Med Sci 335:34–39, 2008.
223. Wright L, King TE Jr: Cryptogenic organizing pneumonia (idiopathic bronchiolitis obliterans organizing pneumonia): An update. Clin Pulm Med 4:152–158, 1997.
224. Muller NL, Guerry-Force ML, Staples CA, et al: Differential diagnosis of bronchiolitis obliterans with organizing pneumonia and usual interstitial pneumonia: Clinical, functional, and radiologic findings. Radiology 162:151–156, 1987.
225. Chandler PW, Shin MS, Friedman SE, et al: Radiographic manifestations of bronchiolitis obliterans with organizing pneumonia vs usual interstitial pneumonia. AJR Am J Roentgenol 147:899–906, 1986.
226. Davison AG, Heard BE, McAllister WA, Turner-Warwick ME: Cryptogenic organizing pneumonitis. Q J Med 52:382–394, 1983.
227. Bartter T, Irwin RS, Nash G, et al: Idiopathic bronchiolitis obliterans organizing pneumonia with peripheral infiltrates on chest roentgenogram. Arch Intern Med 149:273–279, 1989.
228. Oikonomou A, Hansell DM: Organizing pneumonia: The many morphological faces. Eur Radiol 12:1486–1496, 2002.
229. Nishimura K, Itoh H: Is CT useful in differentiation between BOOP and idiopathic UIP? *In* Harasawa M, Fukuchi Y (eds): Interstitial Pneumonia of Unknown Etiology. Tokyo: University of Tokyo Press, 1989, pp 317–324.
230. Muller NL, Staples CA, Miller RR: Bronchiolitis obliterans organizing pneumonia: CT features in 14 patients. AJR Am J Roentgenol 154:983–987, 1990.
231. Preidler KW, Szolar DM, Moelleken S, et al: Distribution pattern of computed tomography findings in patients with bronchiolitis obliterans organizing pneumonia. Invest Radiol 31:251–255, 1996.
232. Lee JS, Lynch DA, Sharma S, et al: Organizing pneumonia: Prognostic implication of high-resolution computed tomography features. J Comput Assist Tomogr 27:260–265, 2003.
233. Kim SJ, Lee KS, Ryu YH, et al: Reversed halo sign on high-resolution CT of cryptogenic organizing pneumonia: Diagnostic implications. AJR Am J Roentgenol 180:1251–1254, 2003.
234. Souza CA, Muller NL, Lee KS, et al: Idiopathic interstitial pneumonias: Prevalence of mediastinal lymph node enlargement in 206 patients. AJR Am J Roentgenol 186:995–999, 2006.
235. Kohno N, Ikezoe J, Johkoh T, et al: Focal organizing pneumonia: CT appearance. Radiology 189:119–123, 1993.
236. Maldonado F, Daniels CE, Hoffman EA, et al: Focal organizing pneumonia on surgical lung biopsy: Causes, clinicoradiologic features, and outcomes. Chest 132:1579–1583, 2007.
237. Cordier JF: Cryptogenic organising pneumonia. Eur Respir J 28:422–446, 2006.
238. Myers JL, Katzenstein AL: Ultrastructural evidence of alveolar epithelial injury in idiopathic bronchiolitis obliterans–organizing pneumonia. Am J Pathol 132:102–109, 1988.
239. Katzenstein AL, Myers JL, Prophet WD, et al: Bronchiolitis obliterans and usual interstitial pneumonia. A comparative clinicopathologic study. Am J Surg Pathol 10:373–381, 1986.
240. Guerry-Force ML, Muller NL, Wright JL, et al: A comparison of bronchiolitis obliterans with organizing pneumonia, usual interstitial pneumonia, and small airways disease. Am Rev Respir Dis 135:705–712, 1987.
241. Stover DE, Mangino D: Macrolides: A treatment alternative for bronchiolitis obliterans organizing pneumonia? Chest 128:3611–3617, 2005.
242. Yamamoto M, Ina Y, Kitaichi M: Bronchiolitis obliterans organizing pneumonia (BOOP): Profile in Japan. *In* Harasawa M, Fukuchi Y, Morinari H (eds): Interstitial Pneumonia of Unknown Etiology. Tokyo: University of Tokyo Press, 1989, pp 61–70.
243. Barroso E, Hernandez L, Gil J, et al: Idiopathic organizing pneumonia: A relapsing disease. 19 years of experience in a hospital setting. Respiration 74:624–631, 2007.
244. Spiteri MA, Klenerman P, Sheppard MN, et al: Seasonal cryptogenic organising pneumonia with biochemical cholestasis: A new clinical entity. Lancet 340:281–284, 1992.
245. Cohen AJ, King TE Jr, Downey GP: Rapidly progressive bronchiolitis obliterans with organizing pneumonia. Am J Respir Crit Care Med 149:1670–1675, 1994.
246. Melloni G, Cremona G, Bandiera A, et al: Localized organizing pneumonia: Report of 21 cases. Ann Thorac Surg 83:1946–1951, 2007.
247. Koss MN, Hochholzer L, Langloss JM, et al: Lymphoid interstitial pneumonia: Clinicopathological and immunopathological findings in 18 cases. Pathology 19:178–185, 1987.
248. Ichikawa Y, Kinoshita M, Koga T, et al: Lung cyst formation in lymphocytic interstitial pneumonia: CT features. J Comput Assist Tomogr 18:745–748, 1994.
249. Johkoh T, Ichikado K, Akira M, et al: Lymphocytic interstitial pneumonia: Follow-up CT findings in 14 patients. J Thorac Imaging 15:162–167, 2000.
250. Liebow AA, Carrington CB: Diffuse pulmonary lymphoreticular infiltrations associated with dysproteinemia. Med Clin North Am 57:809–843, 1973.
251. Turner RR, Colby TV, Doggett RS: Well-differentiated lymphocytic lymphoma. A study of 47 patients with primary manifestation in the lung. Cancer 54:2088–2096, 1984.

CHAPTER 58

THE LUNGS AND CONNECTIVE TISSUE DISEASES

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INTRODUCTION

The lung may be involved in all connective tissue diseases (CTDs). The involvement is often subclinical, but its true extent may be masked by exercise limitation due to musculoskeletal features of the CTD. Patterns of lung involvement vary considerably within each CTD. The differential diagnosis is made even wider by inclusion of the drug-induced pulmonary reactions (Table 58-1) and the opportunistic infections secondary to therapy for the lung disease (Table 58-2), which may present with features indistinguishable from diffuse lung disease.

It is not surprising that the lung is involved frequently in CTDs because these are systemic syndromes, but it is disappointing that little is known about the true incidence and prevalence of lung disease because of the dearth of well-controlled prospective, unselected series. Imprecision of nomenclature has also confused the issue. With this background, the aims of this chapter are to highlight the ways in which the lung may be involved in the most common CTDs and to indicate, when appropriate, the most usual pattern of lung disease for each CTD, with an emphasis on approaches to diagnosis and efficient management.

SYSTEMIC SCLEROSIS (SCLERODERMA)

The preliminary criteria for classification of systemic sclerosis (SSc) require that one major or two or more of three minor criteria be present (Table 58-3).[1] The skin changes may affect the entire extremity or the face, neck, and trunk (thorax and abdomen). Scleroderma is traditionally classified on the basis of skin disease extent. Limited disease can involve the face, but the trunk and limbs proximal to the elbows and knees are spared. Diffuse disease can involve any part of the body.

Epidemiology and Risk Factors

The incidence of SSc is approximately 2 to 20/100,000/yr, with a peak incidence in the fourth to sixth decades. The prevalence is 30 to 120/100,000, with a 3:1 to 8:1 female preponderance.[2] Mortality rates have been

TABLE 58-1. Drug Toxicity: Patterns of Lung Disease That Have Been Reported as Adverse Effects of Drugs Commonly Used to Treat Connective Tissue Diseases

Pulmonary Effect	Penicillamine	Methotrexate	Gold	Cyclophosphamide	Sulfasalazine
Hypersensitivity pneumonitis		+	+		
Pulmonary infiltrate with eosinophilia		+	+		+
Interstitial pulmonary fibrosis			+	+	
Obliterative bronchiolitis	+		+		
Organizing pneumonia	+	+	+		+
Pleural effusion, thickening		+		+	+
Alveolar hemorrhage, vasculitis	+				+

TABLE 58-2. Immunosuppressive Therapy: Common Drugs Used in the Treatment of the Major Pulmonary Complications of Connective Tissue Diseases

Drug	Dose	Duration	Comments	Monitoring
Azathioprine	2.5 mg/kg/day Maximum 200 mg/day	Continuous	• Maximal effect may not be evident for 6–9 mo but has better adverse effect profile than cyclophosphamide • May be used long term. • Starting dose 50 mg daily with monitoring full blood count in case of thiopurine methyltransferase deficiency; maintenance dose from 1 mo.	Full blood count Liver function tests
Cyclophosphamide Oral	2 mg/kg/day	Variable	Oral cyclophosphamide may be used continuously or substituted at 3 mo for azathioprine because of more favorable adverse effect profile in DLD.	Full blood count Liver function tests Urinalysis for blood
IV	15 mg/kg monthly for 1–6 mo	Variable	• IV therapy for rapid induction of remission at 2–4 mg/kg/day for 3–4 days, especially for vasculitis. • Pulsed IV cyclophosphamide may be given at 1- to 3-mo intervals with better adverse effect profile and lower long-term cumulative dose, particularly in nonvasculitic disease.	
Cyclosporin A	5 mg/kg/day	Continuous	• Bioavailability variable, thus blood monitoring necessary. • May be used in combination with prednisolone	Blood pressure Urea and creatinine Cyclosporin A level
Methotrexate	7.5–25 mg/wk	Continuous	• Little information to support use except as second-line therapy after first-line treatment. • Pulmonary toxicity may be limiting	Full blood count Liver function tests
Prednisolone	1 mg/kg/day or 20 mg alternate days	Continuous	Prednisolone used alone in high dose for cellular DLD and then titrated to control. In conjunction with immunosuppressants, the low-dose regimen is used.	Blood pressure Blood glucose Weight Bone densitometry
Methylprednisolone	500–1000 mg	3–5 days	Used for aggressive induction of remission, particularly for vasculitis or acute pneumonitis, then followed by maintenance therapy of prednisolone or prednisolone plus immunosuppressive agent.	

DLD, diffuse lung disease; IV, intravenous(ly).

remarkably consistent over the years, varying from 0.9 to 1.5/million for men and 2.1 to 3.8/million for women in the United States. The disease occurs worldwide. Although scleroderma clusters in families with other autoimmune disease, there are very few reports of first-degree relatives having SSc. Genetic involvement in the disease has been determined by the identification of chromosomal abnormalities and by studies of the major histocompatibility complex genes. Although many of the early studies were serologic, more recently, polymerase chain reaction technology has been employed. With this latter approach, an association between diffuse lung disease and human leukocyte antigens (HLA)–DR3, HLA-DR52a, HLA-DRB1*11, and HLA-DPB1*1301 has been recognized.[3,4]

Chemically Induced Scleroderma-like Disorders

A variety of agents are known to induce SSc-like disease, often with lung involvement, including D-penicillamine, tryptophan, bleomycin, pentazocine, and (particularly in

TABLE 58-3. Systemic Sclerosis (Scleroderma)

CRITERIA FOR DIAGNOSIS*
Major
Thickening of the skin of the hands
Minor
Sclerodactyly (i.e., the changes of the major criterion but limited to the fingers)
Digital pitting scars or loss of substance from the finger pad: depressed areas at tips of fingers or loss of digital pad tissue as a result of ischemia
Bibasilar pulmonary fibrosis
LUNG MANIFESTATIONS
Interstitial pulmonary fibrosis
Organizing pneumonia
Isolated pulmonary vascular disease
Aspiration pneumonia (secondary to esophageal dysmotility)
Chest wall restriction

*The major or two or more minor criteria required for diagnosis.

men) the industrial agents vinyl chloride, benzene, toluene, and trichloroethylene.[5] Silica exposure increases the odds ratio of SSc, and silicosis increases the rate even further.[6] The toxic oil syndrome, first recognized in Madrid in 1981, results from ingestion of an adulterated cooking oil containing rapeseed oil denatured with aniline.[7] This provokes a scleroderma-like syndrome with pulmonary involvement. The association with silicone breast implants is unproved.

Pulmonary Manifestations

More is known about the pulmonary complications of SSc than any other CTD. Pulmonary involvement has emerged as the major cause of excess morbidity and mortality in SSc.[8] The patterns of lung disease with which SSc may present are variable and are shown in Table 58-3.

Interstitial Pulmonary Fibrosis

Pathogenesis. Of all of the lung problems in the CTDs, most is known about the pathophysiology of interstitial pulmonary fibrosis SSc. There are several distinct, but related, aspects of pathogenesis.

Predisposition. There is good evidence that individuals are predisposed genetically to develop SSc, and there are emerging markers that define risks for diffuse lung disease. The importance of genetics to SSc is illustrated by a study of Choctaw Indians residing in southeastern Oklahoma. The prevalence of SSc in full-blooded Choctaws is roughly 1:200, which is significantly higher than that found in non–full-blooded Choctaws (1:3000) and strikingly higher than the global prevalence of SSc in other Native Americans in Oklahoma (1:10,000).[9]

Class II major histocompatibility complex associations increase the risk of interstitial pulmonary fibrosis in SSc. The relative risk is increased if the anti-DNA topoisomerase (Scl-70) antibody is present. Recent studies have shown that there is an association between Scl-70 and an allele of the major histocompatibility complex *DPB1* gene.

The genetic susceptibility probably results in injury and an immune response. It has been shown that there are highly restricted T-cell responses to epitopes of DNA topoisomerase 1, both in healthy individuals and in those with SSc. Thus, in individuals with Scl-70–responsive T-cell clones, the autoantibody may be responsible for driving the immune response. In the lung, there is an accumulation of "memory-type" CD45 Ro lymphocytes and secondary lymphoid follicles with true germinal centers within lung biopsy samples.[10] Furthermore, the T cells present within the lung express cytokines of both the T helper 1 (Th1) and the T helper 2 (Th2) subsets.[11]

Inflammation Amplification. A wide variety of cytokines identified in bronchoalveolar lavage (BAL) fluid clearly contribute to the cascade of inflammation in the lungs.[12] The most striking of these are interleukin-8 (neutrophil chemoattractant and activator), tumor necrosis factor-α (TNF-α; an early cytokine involved in many pathologic processes), macrophage inflammatory protein-1α (important in neutrophil chemotaxis), and RANTES (regulated on activation normal T cell expressed and secreted; important in T-cell and eosinophil recruitment and activation). It is clear, therefore, that the downstream events of the initiation result in the release of a number of proinflammatory cytokines that are responsible for further recruitment and activation of inflammatory cells at disease sites.

Fibrogenetic Factors. The hallmark of SSc in both lung and skin is the accumulation of connective tissue matrix cells and proteins.[13,14] Many factors have been studied in this regard, and a wide variety of growth factors have been identified. Perhaps the most striking of these is connective tissue growth factor, which appears to depend on transforming growth factor-β (TGF-β) for up-regulation and has a potent effect on collagen production, as evidenced by collagen gel retraction studies.[15,16] TGF-β is found in high amounts in the lungs of patients with SSc,[17] and when TGF-β signaling is inhibited, minor epithelial injury leads to extensive fibrosis.[18] Endothelin (ET)-1 and coagulation cascade proteins are also present in high amounts in BAL fluid.[13,19] Fibroblasts from patients with lung disease exhibit dysregulated type I collagen biosynthesis and impaired messenger RNA down-regulation. The balance of ET receptors (A and B) is modified in the lungs of patients with scleroderma, with a consistent decrease in ET_A and an increase in ET_B receptors.[14,20] ET-1 may contribute to epithelial-mesenchymal transition of airway epithelial cells, resulting in fibrosis.[21]

A number of parallel events result in the development of lung injury and subsequent fibrosis. It is simplistic to target any one of these as being the important factor, but there seems little doubt that the key cytokines in the cascade include TNF-α (because it occurs very early in

disease and has been shown in animal models to be a pivotal factor in lung fibrosis)[22] and TGFr-β (which colocalizes with collagen gene up-regulation and is important in connective tissue growth factor release). Other important cytokines may include hepatocyte growth factor and insulin-like growth factor-II.[23,24] The balance of Th1 to Th2 cytokines is also key because, when the shift is in favor of Th2 cytokines, such as in idiopathic pulmonary fibrosis, the prognosis is worse and there is a much higher eosinophil influx into the lung, in comparison with patients with SSc, in whom the Th1/Th2 ratio is balanced and there is less eosinophil influx per unit lung involvement.[11]

Clinical Features. The prevalence of lung disease in SSc depends on the method used for detection. Symptoms or signs of lung disease are common. Dyspnea occurs in roughly 55% of patients (range, 21%–80%).[25] Cough, a less frequently reported symptom, tends to be dry and nonproductive. Hemoptysis is rare but may complicate carcinoma or bronchial telangiectasia.[26] Fine crackles are heard at the lung bases and are of a "Velcro" character. Pleural rub is almost never heard. Pleuritic chest pain is uncommon. Pneumothorax is even less common. Digital clubbing is extremely rare. Secondary pulmonary hypertension with appropriate clinical features of right ventricular strain, raised jugular venous pressure, and ankle edema may be seen during the terminal stages of the disease.

Chest radiographic abnormalities are present in 25% to 67% of patients, and lung function is impaired in up to 90%, although a large subset of patients has only a minor reduction in gas transfer. The lung is involved more commonly in patients with diffuse than with limited cutaneous SSc (i.e., involving skin proximal to the elbow), but the extent of skin involvement does not correlate with lung function changes. Patients are often symptom free, even with moderate pulmonary function impairment. Rarely, scleroderma of the chest wall may cause extrathoracic restriction.

Lung disease may be the first manifestation of SSc. In this setting, a history of Raynaud's phenomenon is often helpful. In addition, careful examination of the capillaries in the nail beds reveals the typical feature associated with scleroderma: abnormal loops associated with capillary "dropout." The presence of autoantibodies, particularly antinuclear antibodies, is helpful in suggesting a CTD etiology (Table 58-4).

Imaging. Chest radiography typically shows a reticular pattern in the lung bases and periphery in early disease. There is obvious loss of volume with more extensive reticular shadowing in more advanced disease. In this situation, honeycombing may be present (Fig. 58-1A).

Computed tomography (CT) has revolutionized the interpretation of the pattern and extent of disease. Disease is again localized to the peripheral rim, occurring earliest at the bases and posteriorly. As disease becomes more advanced, it progresses superiorly, centrally, and anteriorly. Esophageal dilation is common, which can be helpful in the diagnosis if the lung disease is the first manifestation of the systemic disease (see Fig. 58-1B and C).[27] The pattern may be "ground-glass" (reflecting either fine intralobular fibrosis or a more cellular histopathology) or an overtly fibrotic "reticular" pattern, consisting of intersecting linear abnormalities, often associated with traction bronchiectasis.[28] Honeycomb change is present in up to one third of cases but is usually limited in extent.[29]

CT extent correlates extremely well with lung function, particularly gas transfer. Strikingly, individuals with idiopathic pulmonary fibrosis have much more hypoxia than those with SSc once the extent of disease on CT has been taken into account.[30] The extent of individual patterns (ground-glass vs. reticular) is associated with the type of inflammatory cell found in BAL. More extensive reticular (consistent with more fibrosis) disease is associated with high neutrophil numbers, and this influx therefore appears to depend on disease extent regardless of disease type.[31]

Gallium scans provide no added value. Technetium-99m–labeled diethylenetriaminepentaacetic (DTPA) acid clearance has been used in some medical centers to identify early disease and to predict prognosis.[32] A more rapid clearance of this isotope is indicative of a loss of epithelial cell integrity, and rapid clearance indicates uptake from the air space into the circulation. A persistently rapid clearance rate confers an increased risk of subsequent lung function deterioration, and a persistently normal clearance rate predicts lung function stability.

Lung Function Tests. The interstitial pulmonary fibrosis of SSc is characterized by a restrictive ventilatory defect of mechanical function, which results in reduced pulmonary compliance, vital capacity, and total lung capacity. Residual volume is decreased. Diffusing capacity for carbon monoxide (DL_{CO}) is reduced and may be the only abnormality in early disease. Blood gas analysis usually reveals a reduced arterial oxygen pressure (Po_2) with a normal or low arterial carbon dioxide pressure (Pco_2). Hypoxia is usually not marked until very late in the disease process.

There have been a number of studies of rate of change of lung function in SSc.[33,34] In one study, 27 of 38 patients lost more than 30 mL of vital capacity per year (the normal rate of decline).[34] A second study showed that vital capacity loss was greater in patients who had evidence of an active alveolitis on BAL.[33] Rates of decline are often higher within 2 years of onset of SSc, emphasizing the importance of identifying lung disease early. Lower forced vital capacity (FVC) within 3 years of disease onset predicts decline in pulmonary function.[35]

Exercise lung function testing increases ventilation-perfusion mismatching and also increases diffusion abnormalities so that hypoxia results with widening of the alveolar-arterial gradient. Minute ventilation increases generally as a consequence of increased ventilation rate rather than tidal volume. Dead space ventilation may increase on exercise, with a rise in the dead space–to–tidal volume ratio. For a given degree of lung involvement defined by CT, abnormalities on exercise gas exchange are worse in patients with idiopathic pulmonary fibrosis than in those with interstitial pulmonary fibrosis in association with SSc.

TABLE 58-4. Autoantibodies in Connective Tissue Disease

CTD	Autoantibody	Target	Comments
SSc	Anticentromere	Centromere proteins (CENP A-F)	20%–40% total SSc, wide racial variation 70%–80% limited cutaneous variant with pulmonary hypertension
	Scl-70	DNA topoisomerase 1	28%–70% total SSc, wide racial variation; >30% diffuse cutaneous disease with ILD
	PM-Scl	—	Scleroderma-myositis overlap syndromes
	Antinucleolar	RNA polymerase-1	8%–20% SSc suggests poorest 10-yr survival, renal crisis
	Ku	DNA binding proteins	Scleroderma-myositis overlap syndromes
Rheumatoid arthritis	Rheumatoid factor	IgG	Seropositive disease more frequent with pulmonary nodules
	Antinuclear antibody	—	—
	Histone	Histone proteins	5% rheumatoid vasculitis
SLE	dsDNA	dsDNA	50%–75%, strong association with nephritis
	ANA	—	90%–95%
	Ro/La	RNA transcription factors	60%/20%
	Histone	Histone proteins	>90% drug-induced lupus, 20%–30% primary SLE
	Sm	—	10% whites and 30% African Americans and Chinese
	Lupus anticoagulant	Phospholipid	20%–30%
MCTD	U1-RNP	Small nuclear proteins	Myositis overlap syndromes (10% SSc)
	U2-RNP	—	Myositis, SLE, SSc
DM/PM	Jo-1	Histidyl tRNA synthetase	20%–30% inflammatory myopathy but 50%–100% when associated with diffuse fibrosing lung disease
	PL-7	Threonyl tRNA synthetase	<3% antisynthetase syndrome
	PL-12	Alanyl tRNA synthetase	<3% antisynthetase syndrome
	EJ	Glycyl tRNA synthetase	<2% antisynthetase syndrome
	OJ	Isoleucyl tRNA synthetase	<2% antisynthetase syndrome
	Mi-2	Nuclear proteins	<8% DM, associated with acute onset of classic DM
	Ku	Nuclear proteins	Associated with myositis-CTD overlap syndromes
Antiphospholipid syndrome	Anticardiolipin Lupus anticoagulant	Membrane phospholipids	Disease diagnosis depends on presence of clinical features
Relapsing polychondritis	Anticartilage	Cartilage	Unknown sensitivity
	Anticollagen	Collagen	
Sjögren's syndrome	Ro (SS-A)	RNA transcription factors	40%–50% primary Sjögren's syndrome (25%–30% SLE)
	La (SS-B)		50% Sjögren's (10% SLE)

ANA, antinuclear antibody; CTD, connective tissue disease; DM/PM, dermatomyositis/polymyositis; dsDNA, double-stranded DNA; IgG, immunoglobulin G; ILD, interstitial lung disease; MCTD, mixed connective tissue disease; SSc, systemic sclerosis; SLE, systemic lupus erythematosus; tRNA, transfer RNA.

Bronchoalveolar Lavage. BAL may identify alveolitis in SSc before the onset of pulmonary symptoms.[36] A neutrophil alveolitis has been described by some authors to predict more progressive disease.[33,37,38] However, it has been shown that an increase in neutrophils reflects an increase in the extent of disease on CT, particularly the reticular pattern, and this increase is, therefore, likely a marker of more extensive disease rather than an independent index of progressive disease.[31,39,40] BAL should not be used alone to determine whether treatment should be started. Many patients with apparently normal BAL findings may exhibit progressive disease. BAL is, therefore, not recommended routinely for the diagnosis or monitoring of SSc-related interstitial disease.

Biopsy. Surgical lung biopsy is largely not required in the diagnosis of SSc-related interstitial disease. If the pattern of disease is at all atypical after review of the less invasive indices, lung biopsy is recommended. No extra information is obtained by a transbronchial biopsy; therefore, surgical biopsy is required in this situation. Examples of circumstances in which biopsy is indicated include an unusual pattern of disease on CT, marked pleural disease, or clinical features of an overlap syndrome.

Pathologically, the most common pattern is nonspecific interstitial pneumonia, with thickening of the alveolar walls with inflammatory cells (mononuclear cells, granulocytes, and plasma cells), connective tissue matrix cells, and proteins combined with intra-alveolar inflammation (predominantly by macrophages), type II pneumocyte proliferation, and vascular obliteration. The distribution is subpleural and basal and is maximal in posterior segments, with the macroscopic findings of the lung surface taking on a fine nodular, "cirrhotic" appearance in the early stages and honeycombing with more advanced disease.[38] This pattern differs from usual

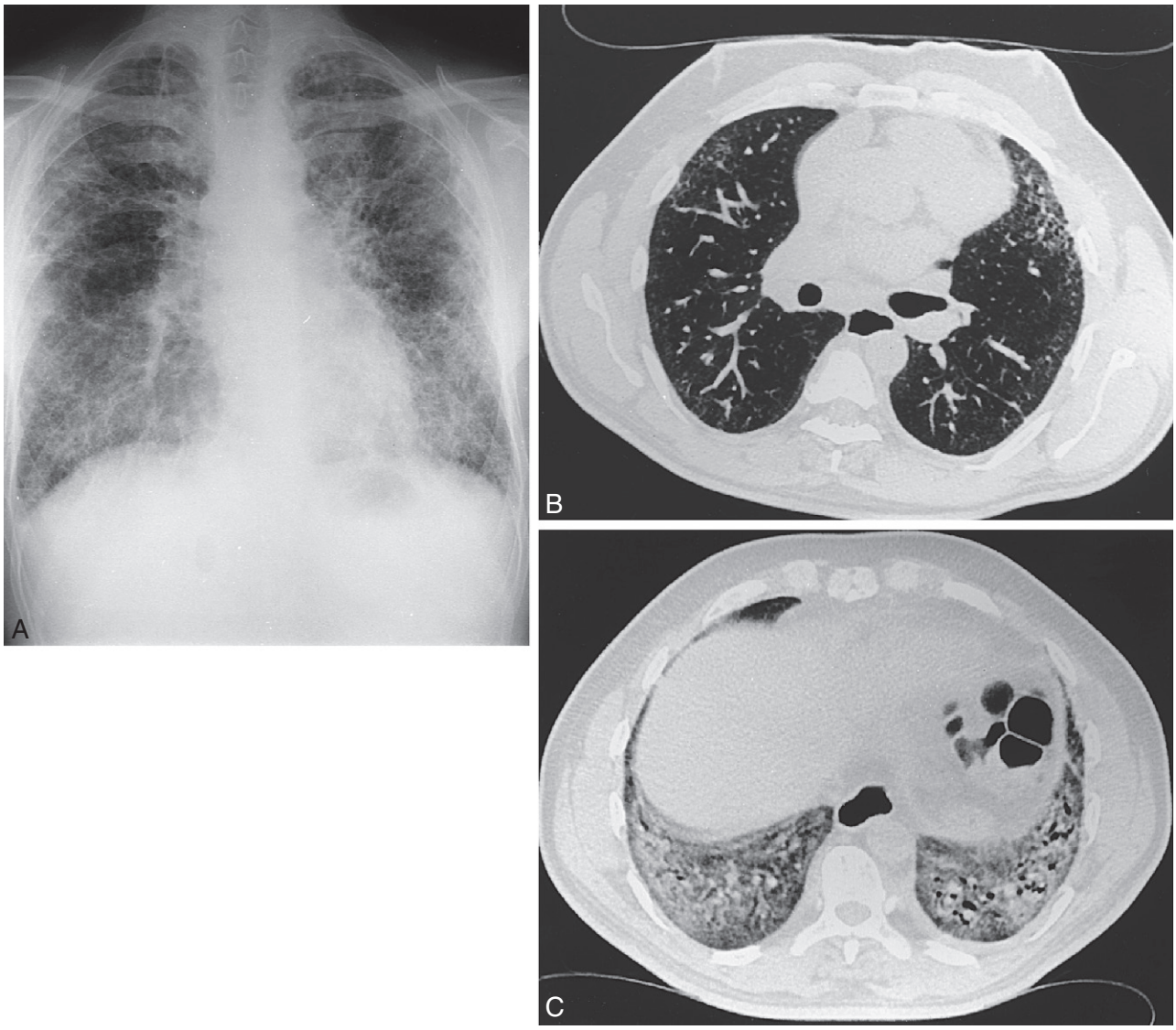

FIGURE 58-1 ■ Radiographic appearances in patients with systemic sclerosis. **A,** Chest radiograph from a patient with systemic sclerosis. Note the widespread, predominantly peripheral pattern of reticular opacities. The heart borders and the diaphragm are obscured. **B,** Computed tomography (CT) scan taken at a level just below the carina in a patient with systemic sclerosis. Note the peripheral reticular pattern that in this case is more prominent anteriorly. In this patient with subtle disease, the dilated esophagus is a clue as to the true cause of the fibrosing lung disease. **C,** CT scan taken at the level of the diaphragm in a patient with more extensive interstitial pulmonary fibrosis in the context of systemic sclerosis. Note in particular the very dilated airways, indicating that the apparent "ground-glass"/consolidation pattern is dense fibrosis. Again, the dilated esophagus indicates that this disease is likely to be part of systemic sclerosis.

interstitial pneumonia in exhibiting a homogeneous pattern of pathology. Much less commonly, the usual interstitial pneumonia pattern of histopathology is seen. One of the hallmarks of usual interstitial pneumonia is a heterogeneous appearance, with normal alveoli seen in the same section as areas of extensive alveolar remodeling.[41] These pathologic differences may denote disease subsets with differences in outcome. Electron microscopy shows early endothelial and epithelial cell injury, even without abnormalities on light microscopy. Autopsy studies show diffuse lung disease in up to 80% of cases and pulmonary vascular disease in up to 30%. In some patients with a more accelerated course of disease, histopathologic examination has shown a diffuse alveolar damage pattern.[42]

Serologic Investigations. Although SSc is traditionally defined on the basis of the extent of the skin disease, as outlined previously, the pattern of autoantibodies appears to be a much stronger determinant of the associated internal organ involvement.[43,44] Antinuclear antibodies are found in 90% to 100% of patients with SSc (roughly 30% of normal individuals have antinuclear antibodies at a titer of 1:40). Three major autoantibodies include anticentromere, occurring in 57% of patients with limited cutaneous disease; anti-topoisomerase (Scl-70), occurring in 40% of patients with diffuse disease; and PM-Scl,

occurring in a small fraction of cases in association with the polymyositis overlap syndrome. It is rare to have both Scl-70 and anti-centromere antibodies. Diffuse lung disease is rare in the presence of anti-centromere antibodies, and a protective role for this autoantibody has been argued but not substantiated. Interstitial pulmonary fibrosis is strongly associated with the Scl-70 antibody and with diffuse scleroderma. Limited cutaneous disease associates with vascular disease and the anti-centromere antibody. Both forms of lung disease may progress to pulmonary hypertension. Other autoantibody studies that have shown associations with organ involvement include a nucleolar pattern with diffuse lung disease and pulmonary hypertension[45]; the antibody B23 that recognizes this nucleolar phosphoprotein, with pulmonary hypertension and is associated with the presence of the anti-fibrillarin antibody; and anti-Th/To antibodies with "intrinsic" pulmonary hypertension and diffuse lung disease.

Prognosis. The prognosis of interstitial pulmonary fibrosis in SSc depends on the extent of disease at presentation. Worse lung function, particularly vital capacity and DL_{CO}, indicates a poorer outcome, and similar observations have been made based on extent of disease on CT as the criterion.[45a] A simple staging system using CT extent (above and below 20%), and FVC at presentation (above and below 70%), is highly discriminatory for both progression and death (Fig. 58-2).[46] Although crude mortality rates are 3.9%/yr for men and 2.6%/yr for women, lung disease remains the most common cause of death in patients with SSc.[47] In one series of causes of death, lung disease was the most common, accounting for 21% of all deaths.[47a] There is also an increased risk of lung cancer in SSc.[47b]

Treatment. A wide variety of treatments for interstitial pulmonary fibrosis in SSc have been explored.[48,49] Most of these include immunosuppression. A number of uncontrolled reports suggested an advantage of

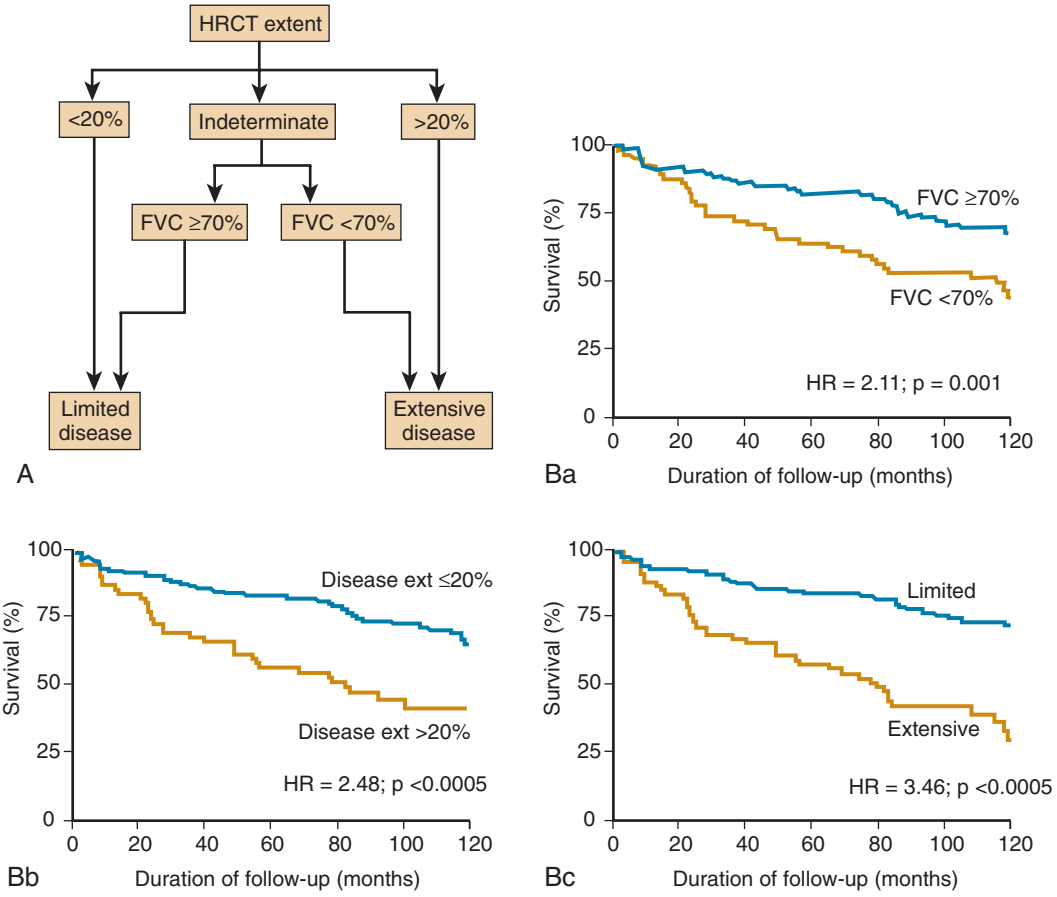

FIGURE 58-2 ■ Staging algorithm for interstitial lung disease due to systemic sclerosis. **A,** Flow diagram of limited/extensive staging system with use of high-resolution computed tomography (HRCT) scores and pulmonary function test data. Identification of overtly minimal/limited disease is based on disease extent threshold of 20% on HRCT versus severe/extensive disease that is identified by HRCT disease extent greater than 20%. In cases with an indeterminate extent of disease on HRCT, a forced vital capacity (FVC) threshold of 70% is used to separate the cases into limited or extensive disease. The HRCT scans are scored at five levels for total disease extent, extent of reticulation, proportion of ground glass, and coarseness of reticulation. **B,** Survival compared between patient subgroups with (*a*) FVC levels above and below a threshold value of 70%; (*b*) HRCT disease extent above and below a threshold value of 20%; and (*c*) limited disease (HRCT extent ≤ 10%, or when HRCT extent was 10%–30%, FVC ≥ 70%) versus extensive disease (HRCT > 30%, or when HRCT extent was 10%–30%, FVC < 70%). ext, extent. (Data from Goh NS, Desai SR, Veeraraghavan S, et al: Interstitial lung disease in systemic sclerosis: A simple staging system. Am J Respir Crit Care Med 177:1248–1254, 2008.)

treatment with cyclophosphamide, together with prednisolone, to improve lung function and prognosis.[50,51] The Scleroderma Lung Study demonstrated a small but significant benefit of oral cyclophosphamide over placebo for FVC, skin scores, as well as quality of life and dyspnea scores at 12 months.[52] The oral cyclophosphamide treatment regimen used most commonly is 2 mg/kg/day orally up to a maximum of 150 mg with moderately low dosages of prednisolone at 10 mg/day or 20 mg every other day. Close scrutiny with full blood counts, liver function tests, and urine testing for evidence of hemorrhagic cystitis is needed.

However, intravenous cyclophosphamide may have a better side effect profile.[53] Studies of intravenous cyclophosphamide (750–1000 mg/m^2) given at 2- to 4-week intervals for 6 to 12 months tended toward significance, as judged by CT and pulmonary function data.[54,55]

The question of *Pneumocystis* prophylaxis is not resolved. Some medical centers use cotrimoxazole three times a week if immunosuppressive agents are being given. A study of interferon-γ showed a greater deterioration in lung function at 1 year than with placebo.[56]

It has been observed that steroid therapy is associated with scleroderma renal crisis, both with high-dose therapy[57] and, more recently, with prednisolone doses of less than 10 mg daily.[58] However, confounding by severity cannot be excluded, as patients with more aggressive systemic disease are more likely to receive corticosteroids, although occasional cases of renal crisis are undoubtedly linked to high-dose corticosteroid therapy. Thus, low-dose steroid therapy remains justified as an invaluable adjunct to the treatment of lung disease, although renal function should be monitored from time to time. A number of retrospective studies support the use of mycophenolate mofetil[59–61]; however, a definitive controlled study has not been performed.

End-stage lung disease has been treated with single-lung transplantation provided there is no evidence of disease activity in other organs. There appears to be no greater mortality in this group than in individuals with primary diffuse lung disease. In terminal disease that is not amenable for transplantation, consideration must be given to regular oxygen therapy, treatment of supervening heart failure, and infection.

Pulmonary Vascular Disease in Systemic Sclerosis

Unlike the other CTDs, vascular involvement in SSc is caused by concentric fibrosis of small arterioles replacing the normal intima and media, but the plexiform lesions and fibrinoid necrosis of primary pulmonary hypertension are not seen. Isolated vascular disease occurs mainly in the limited form of SSc. Associated features are those of the CREST syndrome (calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasias) with prominent telangiectasia, esophageal disease, abnormal nail fold capillaries (dilated capillaries and dropout of capillary loops), and a positive anti-centromere antibody. Chest radiography, CT scanning, and BAL are all normal. Lung function studies show an isolated fall in D_{LCO}. When damage to the pulmonary vascular bed is extensive (gas transfer <50% of predicted), the risk of pulmonary hypertension increases.[62] Mortality rates are increased with increasing pulmonary hypertension.[63,63a]

DTPA clearance measurements are usually normal in patients with pure pulmonary vascular disease in scleroderma and help to differentiate vascular disease from early diffuse disease in patients with an isolated fall in D_{LCO}. Doppler echocardiography has been shown to correlate with measurements of pulmonary artery pressures made at right heart catheterization. Qualitative features found on echocardiography may also suggest pulmonary hypertension in the absence of a tricuspid regurgitant jet, precluding measurement of the gradient across the tricuspid valve and, thus, an estimate of pulmonary artery pressure. These include right ventricular dilation and right ventricular hypertrophy. Overall, echocardiography is moderately sensitive for the diagnosis of pulmonary arterial hypertension (PAH; 47%–88%).[64,65] However, echocardiography is less accurate at borderline and mild levels of pulmonary hypertension. Stress (exercise) echocardiography may be able to identify preclinical PAH.[66,67] NT-proBNP, released from cardiac ventricles in response to stretch, is elevated in SSc and is inversely related to gas transfer. Elevated NT-proBNP levels may predict the development of pulmonary hypertension in SSc.[68,69]

Although there are a number of emerging therapeutic options, optimal treatment of pulmonary vascular disease in SSc has not yet been defined. Calcium channel antagonists may be helpful, but often the dosage required to improve the pulmonary vasculature causes unacceptable drops in left-sided pressures and peripheral edema. Angiotensin-converting enzyme inhibitors can be helpful. Prostacyclin analogues cause potent pulmonary and systemic vasodilation and inhibit platelet aggregation. Intravenous and subcutaneous prostacyclin analogues have been shown to lead to improved pulmonary vascular resistance, pulmonary pressure, and 6-minute walk distances in the acute and longer term.[70–72] Exact dosage regimens need to be validated, however. Inhaled iloprost may also improve exercise capacity and cardiopulmonary hemodynamics.[73] Oral ET-1 receptor antagonists have been shown to improve exercise capacity and hemodynamics in patients with PAH and CTD (including SSc).[74–76] Sildenafil, a phosphodiesterase-5 inhibitor, leads to an improvement in exercise capacity and hemodynamics in patients with PAH (including patients with SSc).[77,78] The correct balance of these therapies, including combination therapy, is yet to be determined in controlled studies. Emerging therapies, such as the platelet-derived growth factor antagonist imatinib, show promise in animal studies.[79]

Other Pulmonary Complications

Aspiration pneumonia is extremely uncommon, particularly considering the prevalence of esophageal dysfunction in SSc. Pleural disease is uncommon. Rarely, the extent of skin tightness over the chest wall produces an

extrinsic restriction of ventilation. Occasionally, the first manifestation of pulmonary parenchymal disease is organizing pneumonia. This responds well to corticosteroid therapy, as does organizing pneumonia in other contexts.

RHEUMATOID ARTHRITIS

The American Rheumatism Association revised criteria for the classification of rheumatoid arthritis (RA) require that at least four of the criteria listed in Table 58-5 be satisfied for a minimum of 6 weeks.[80]

Epidemiology and Risk Factors

The reported incidence of RA ranges from 0.2 to 3.0/1000 person-years (<0.5/1000 person-years in most surveys), with a rising incidence with increasing age into the seventh decade. In adult whites, the prevalence of RA ranges from 0.5% to 2%, with a male-to-female ratio between 1:2 and 1:4. Depending on disease severity (as judged by disability scales and the need for long-term corticosteroid therapy), the age-matched mortality rate of RA is up to twofold higher than in the general population, with this increased mortality being attributed to cardiorespiratory complications.[81,82] The prevalence of RA is similar throughout the world. Evidence in support of a genetic predisposition includes familial and twin clustering and associations between RA and HLA-DRB1 alleles.[83] Hormonal factors may play a role, judging from the female preponderance of RA and a reduced incidence during pregnancy. Infectious agents and socioeconomic factors have not been shown to be etiologically important.

TABLE 58-5. Rheumatoid Arthritis

CRITERIA FOR DIAGNOSIS*
Morning stiffness (lasting at least 1 hr)
Arthritis (soft tissue swelling or fluid) of three or more joints (PIP, MCP, wrist, elbow, knee, ankle, MTP joints)
Arthritis of hand joints (swelling of at least one wrist, MCP, or PIP joint)
Symmetrical arthritis (i.e., simultaneous arthritis of the same joints on both sides of the body)
Rheumatoid nodules
Serum rheumatoid factor positivity (at a level such that <5% of normal controls are positive)
Radiographic hand or wrist changes typical of rheumatoid arthritis
LUNG MANIFESTATIONS
Interstitial pulmonary fibrosis
Organizing pneumonia
Obliterative bronchiolitis
Follicular bronchiolitis
Bronchiectasis
Vasculitis
Nodules
Pleural disease
Lymphocytic interstitial pneumonia
Drug induced

*At least four criteria for a minimum of 6 wk.
MCP, metacarpophalangeal; MTP, metatarsophalangeal; PIP, proximal interphalangeal.

Pulmonary Manifestations

Pleuropulmonary manifestations are multiple and are listed in Table 58-5.

Interstitial Pulmonary Fibrosis

The interstitial pulmonary fibrosis of RA has a male predominance (male-to-female ratio, 3:1).[84] High titers of rheumatoid factor[85] and the presence of rheumatoid nodules[86,87] are associated with an increased prevalence of pulmonary fibrosis in RA. Smoking is a risk factor for the development of overt pulmonary fibrosis in RA[85,88] and has also been associated with subclinical disease.[89,90] In the presence of HLA-DR susceptibility genes, smoking is strongly associated with development of anti-citrulline–positive RA.[88]

In early disease, a lymphocytic interstitial infiltrate is often the predominant abnormality,[91] and prominent peribronchiolar follicles, containing aggregates of lymphocytes with germinal centers, are often seen.[92] In long-standing disease, fibrosis predominates, often resulting in cystic changes or honeycombing. It is difficult to estimate the exact prevalence of subcategories of interstitial pulmonary fibrosis because, in historical series, histologic descriptions of "interstitial fibrosis" have not been detailed. Both nonspecific interstitial pneumonia and usual interstitial pneumonia are present in significant and likely similar proportions of patients with interstitial fibrosis.[93,94] However, it seems that usual interstitial pneumonia is associated with a better outcome in CTD than in an idiopathic setting.[41,95,96] Minor pulmonary fibrosis is common in RA; in one open-lung biopsy series performed in volunteers with RA (some without clinical evidence of interstitial lung disease), pulmonary fibrosis was seen in 60% of patients.[97]

Reductions in D_{LCO} are found in 40% of unselected RA patients.[98] However, radiologically overt pulmonary fibrosis is found in only 1% to 5% of RA patients (based on three large chest radiographic series).[86,89,99] In the largest prospective series reported to date, 150 consecutive patients were screened for pulmonary disease.[100] Of these, 19% had CT evidence of interstitial fibrosis, which was often subtle; 43% of those with interstitial abnormalities also had emphysematous bullae (previous or current smoking history). Chest radiography identified abnormalities in only 14% of the whole cohort, but physiologic abnormalities were seen in 82% (gas transfer) and 14% (restrictive pattern of ventilatory defect).[100] Disease severity as judged by CT reflects functional impairment.[101–103]

Severe progressive disease requiring hospitalization may be associated with cor pulmonale and respiratory failure and has a poor prognosis, with a 5-year survival

rate of less than 50%[45]; however, a large subgroup of patients have more indolent disease that progresses little during prolonged follow-up. A strong predictor of decline is a gas transfer less than 55% of predicted at presentation.[104] The most frequent symptom is exertional dyspnea, although this may be masked by a general loss of mobility due to systemic disease. The clinical picture is usually identical to that of idiopathic pulmonary fibrosis, with bilateral, predominantly basal crackles and tachypnea, cyanosis, and right heart failure in advanced disease. Finger clubbing, which is occasionally striking, is more prevalent than in other CTDs.

Organizing Pneumonia

Organizing pneumonia (bronchiolitis obliterans with organizing pneumonia) is characterized by plugs of granulation tissue in the air spaces distal to and including the terminal bronchioles, associated with lymphocytic infiltration within well-preserved bronchiolar walls and the surrounding lung interstitium. The term *bronchiolitis obliterans with organizing pneumonia* has caused confusion among clinicians, stimulating the recent use of the term *proliferative bronchiolitis*. Organizing pneumonia has a very different profile from the entity of bronchiolitis obliterans (also found in RA), with a clinical presentation of pneumonia (as opposed to airflow obstruction), multifocal consolidation on chest radiograph and CT, a restrictive functional defect, and a much higher chance of responsiveness to corticosteroids than bronchiolitis obliterans (with a good outcome in 15 of the first 17 reported cases) (Fig. 58-3).[105] Organizing pneumonia is more common in RA than in other CTDs (with the possible exception of polymyositis). In a series of 40 patients with RA undergoing open-lung biopsy, organizing pneumonia (6 cases) had a prevalence similar to that of interstitial fibrosis (5 cases),[106] although organizing pneumonia might have been overrepresented owing to an acute presentation (and thus a perceived need to reach a definitive histologic diagnosis). The good prognosis generally seen in organizing pneumonia has been emphasized in the medical literature, but a minority of RA

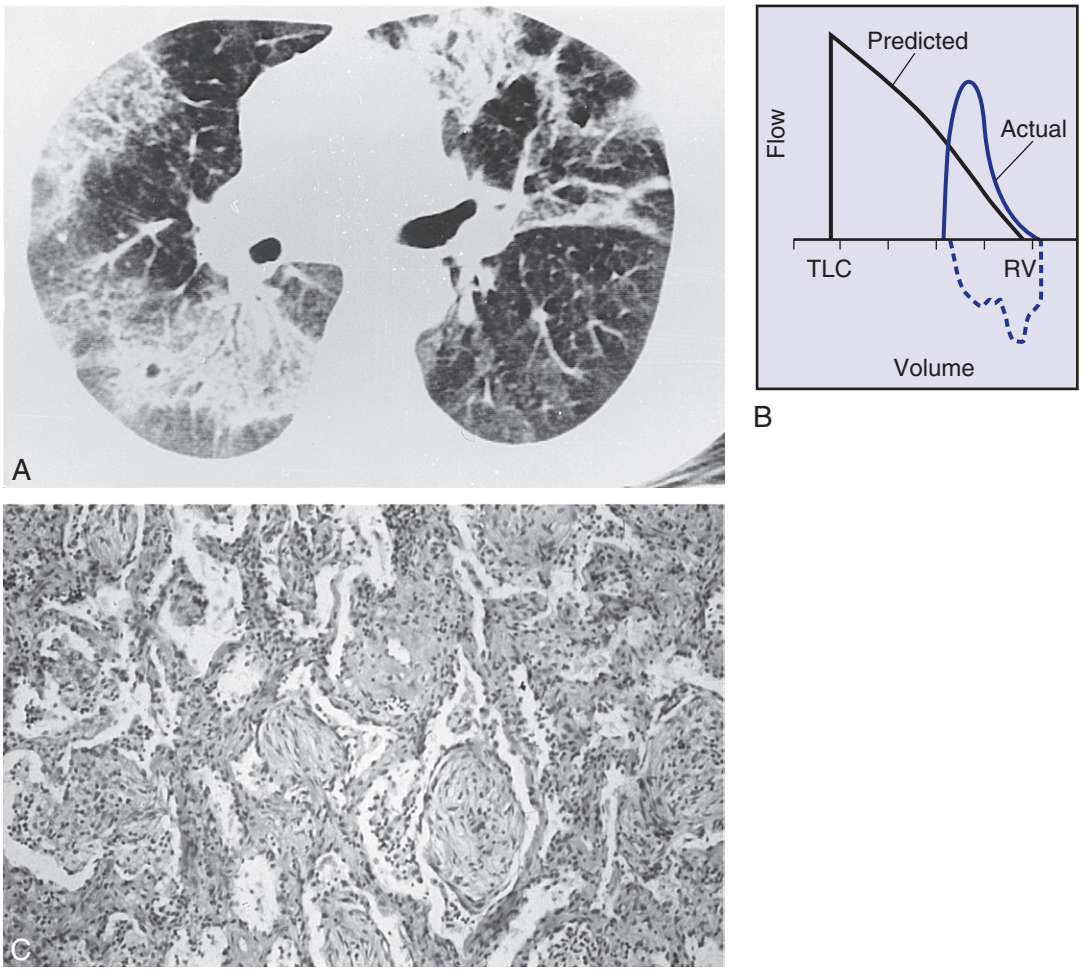

FIGURE 58-3 ■ **A,** CT scan from a patient with rheumatoid arthritis and organizing pneumonia. Note the bilateral pattern of air space consolidation. **B,** A flow-volume loop from the same patient as in **A.** The flow-volume loop is shifted to the right by comparison with the ideal predicted loop, but the flow rates are relatively well preserved. RV, residual volume; TLC, total lung capacity. **C,** Surgical lung biopsy specimen from another patient with organizing pneumonia in the context of rheumatoid arthritis. The alveoli and respiratory bronchioles are filled with loosely packed connective tissue.

patients progress to respiratory failure and death despite treatment.

Obliterative Bronchiolitis

Obliterative bronchiolitis (OB) in RA has now been described in numerous case reports and small series. OB (synonymous with bronchiolitis obliterans and constrictive bronchiolitis) (Fig. 58-4) is characterized histologically by destruction of the bronchiolar wall by granulation tissue, effacement of the lumen, and eventual replacement of the bronchiole by fibrous tissue. There is circumstantial evidence to suggest that OB may be preceded by an inflammatory exudate; prominent bronchiolar inflammation may be found in patients with the shortest symptomatic course.[107] The expression of HLA antigens B40 and DR1 is increased in OB associated with RA (but not in isolated OB).[108]

In early descriptions, the hallmark of OB was a rapidly progressive, often fatal, course; however, because clinician awareness of the disease was then low, patients with advanced and progressive disease were undoubtedly overrepresented. There is great heterogeneity in the speed of progression, with some patients having indolent disease[109]; the use of CT in RA patients with suspected pulmonary complications has now identified a subgroup with occult bronchiolitis, often admixed with interstitial lung disease. The prevalence of unsuspected OB in unselected RA patients remains uncertain, with unexplained airflow obstruction identified in a significant minority (including many nonsmokers) in one study[110] but no increase in the prevalence of pulmonary function abnormalities suggestive of isolated small airway disease in two subsequent controlled series.[111,112]

Two major associations with the development of OB in RA have been reported. It is likely that secondary

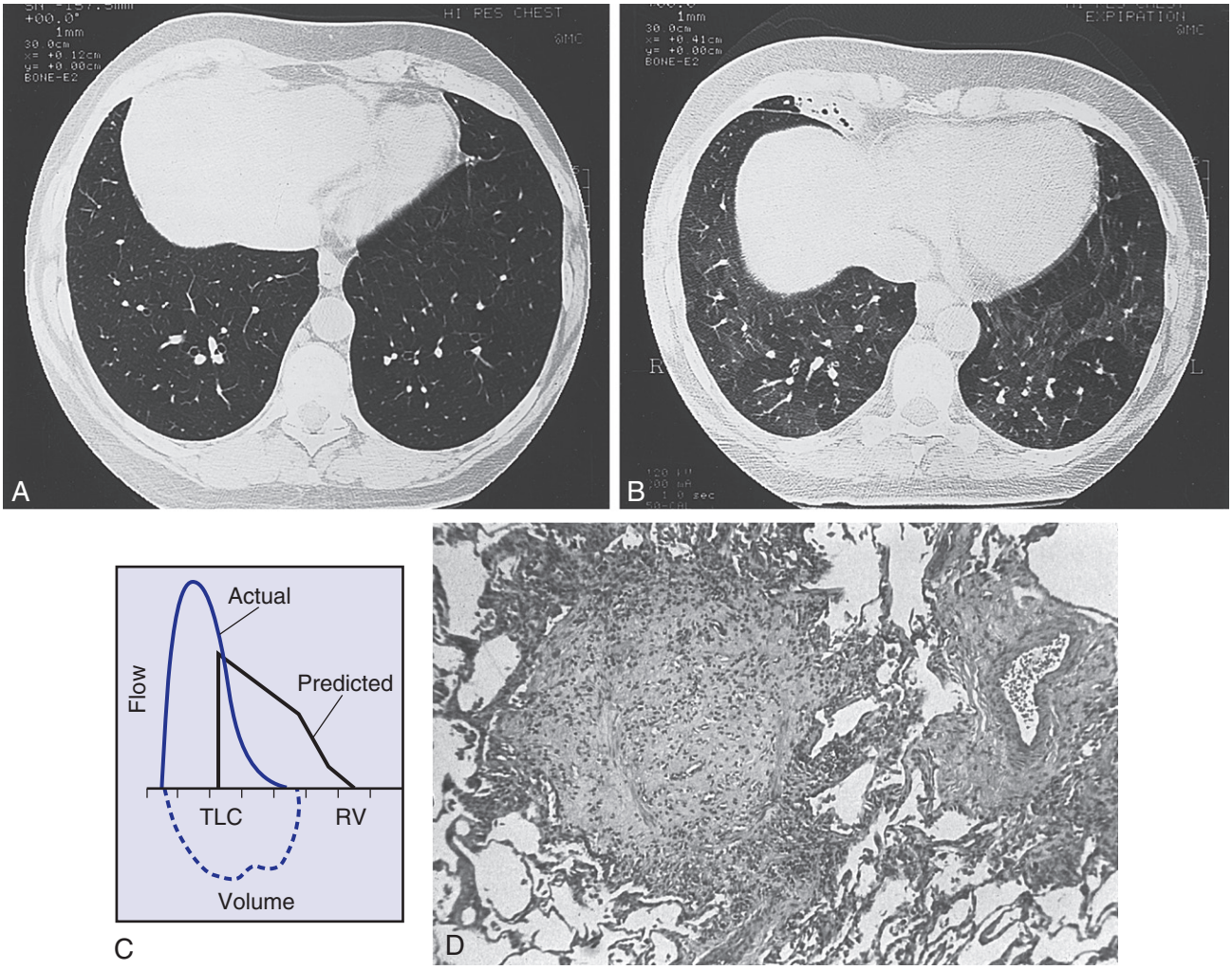

FIGURE 58-4 ■ Inspiratory and expiratory CT sections were obtained from a patient with rheumatoid arthritis with obliterative bronchiolitis. **A,** The inspiratory image is essentially normal. **B,** On the expiratory CT scan, there is extensive regional inhomogeneity, the reduced density resulting from regional vasoconstriction or regional gas trapping. **C,** A flow-volume curve from the same patient as in **A** and **B** shows marked elevation of total lung capacity (TLC) and residual volume (RV) associated with characteristic concavity of the expiratory limb, indicating airflow obstruction. **D,** Surgical lung biopsy specimen from a patient with obliterative bronchiolitis. A slitlike residual orifice is visible, but otherwise, the whole of this terminal bronchiole is effaced by dense fibrous tissue. Note that the surrounding alveoli are normal.

Sjögren's syndrome is an important predisposing factor, being associated with OB in five of six RA patients in one series[109]; the spectrum of histologic abnormalities in these cases, ranging from peribronchiolar lymphocytic infiltration to small airway destruction, was analogous to changes seen in the parotid gland in Sjögren's syndrome. As the presence or absence of Sjögren's syndrome is not documented in many case reports of OB in RA, the etiologic importance of Sjögren's syndrome remains uncertain.

More contentious is the reported association between OB and the use of penicillamine, first reported in the late 1970s.[113] After a number of case reports and small series, a significantly higher prevalence of OB was identified in RA patients who took penicillamine (3 of 133) than in other RA patients (0 of 469) in a large cohort.[107] It is possible that the development of OB and the use of penicillamine are both markers of more aggressive RA and are linked for this reason; however, OB developed less than 1 year after penicillamine was begun in 19 of the first 20 cases,[107] and thus the association is unlikely to be entirely spurious. Because OB has been reported in many RA patients not taking penicillamine, it is likely that an underlying predisposition to OB in RA is unmasked by penicillamine (which disrupts collagen linkage and thus interferes with tissue repair). A relationship between OB and gold therapy has been suggested but is not endorsed by recent clinical experience.

Follicular Bronchiolitis

Follicular bronchiolitis (FB) is characterized by external compression of bronchioles by hyperplastic lymphoid follicles, with variable lymphocytic infiltration of the bronchiolar wall. FB is associated more commonly with RA than with other CTDs[114] and is often found incidentally at lung biopsy in RA patients with interstitial pulmonary fibrosis. No causative mechanism has been identified, and it is unclear whether FB predisposes to the subsequent development of OB. When found in isolation, FB simulates interstitial lung disease, with reticular or nodular opacities on chest radiography and a pattern of functional impairment that may be restrictive or obstructive. Clinically significant isolated FB is rare in RA, but its recognition is important because a response to corticosteroid therapy, although not the rule, is much more likely than in OB; in six of the first nine reported cases, disease stabilized or regressed with treatment.[105] In a CT study of patients with histopathologically proven FB, the most prominent features were centrilobular and peribronchial nodules together with patchy ground-glass increases in attenuation in a bronchocentric distribution.[115]

Bronchiectasis

The prevalence of bronchiectasis is higher in RA than in other CTDs (Fig. 58-5). One literature review identified 289 patients with bronchiectasis associated with RA reported since 1928; however, because respiratory symptoms preceded the systemic manifestations of RA in 90%, it is likely that chance association accounts for a high proportion of early reported cases.[116] Although associated with long-standing RA in one study,[117] on prospective evaluation of 50 RA patients, bronchiectasis was present on 30% of CT scans.[118] Bronchiectasis in RA is not associated with more aggressive systemic disease and is often clinically silent, with little or no sputum production and a less progressive and disabling course than in patients with idiopathic bronchiectasis.

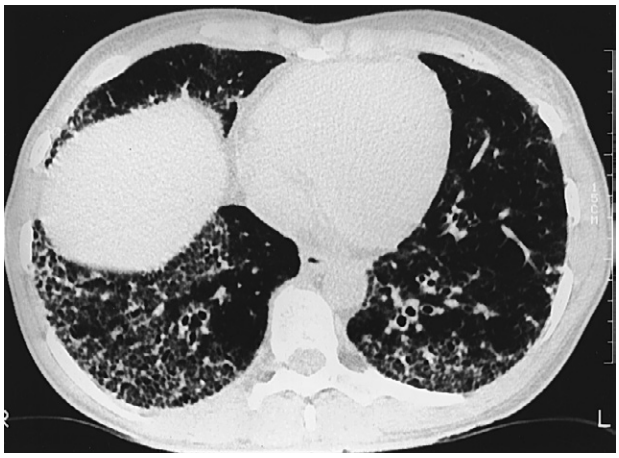

FIGURE 58-5 ■ Bronchiectasis in rheumatoid arthritis (RA). CT scan taken at the level of the diaphragm in a patient with RA. The typical reticular pattern of fibrosing alveolitis in the context of RA can be seen in the right lung. In the left lung, there are similar but less advanced changes. In addition, and notably remote from the fibrotic areas, there are airways that are clearly bronchiectatic.

Pulmonary Vasculitis

It is surprising that pulmonary vasculitis is reported only rarely in RA, given the relatively high prevalence of systemic vasculitis in the disease. Pulmonary hypertension resulting from pulmonary vascular disease (as opposed to extensive pulmonary fibrosis) is uncommon, although occasional cases of pulmonary vasculitis have been found at autopsy.[114] Similarly, diffuse alveolar hemorrhage is a rare complication of RA.

Pulmonary Rheumatoid Nodules

Pulmonary rheumatoid nodules may be single or multiple, are found on chest radiography in less than 1% of RA patients,[87] and are usually associated with rheumatoid nodules elsewhere in the body,[119] although they occasionally precede the development of systemic disease. Nodules are well circumscribed, with central necrotic material contained by palisading epithelioid cells and surrounded by fibrosis and lymphocytic infiltration. Nodule cavitation occasionally causes hemoptysis, and pneumothorax may result from the rupture of subpleural nodules. Diffuse infiltration by small nodules leading to respiratory failure has been reported.[120] However, nodules generally present as asymptomatic abnormalities on chest radiography and may vary in size according to underlying rheumatoid activity; thus, when solitary, their growth as judged by chest radiography may simulate

malignancy. Caplan's syndrome consists of the association of single or multiple nodules with coal worker's pneumoconiosis, which is often trivial, in keeping with the suggestion that nodule formation results from a hypersensitivity reaction to inhaled coal dust perhaps amplified by immunologic overactivity.

Pleural Disease

Pleural disease is seen at autopsy in approximately 50% of patients,[87] and 20% give a history of pleuritic chest pain.[121] However, pleural effusions are found in less than 5%,[85,86] usually in men,[119] and are frequently asymptomatic, often being identified on routine chest radiography. In a minority, pleuritic pain and fever are prominent, and the exclusion of empyema (which may be more prevalent in RA) is required. Occasionally, effusions may develop acutely in association with pericarditis or exacerbations of arthritis; more typically, radiographic abnormalities are chronic, often remaining unchanged for years. The fluid is an exudate, with a low glucose level (correlating poorly with serum glucose),[122] a low pH, and usually, a predominant lymphocytosis (although a neutrophilia is occasionally found). Pleural fluid rheumatoid factor levels tend to mirror serum levels and have little independent diagnostic value.

Other Pulmonary Complications

Other pulmonary complications of RA are rare. Lymphocytic interstitial pneumonia is an occasional finding at lung biopsy[106] and responds variably to corticosteroid therapy. Apical fibrosis mimicking the lung disease of ankylosing spondylitis has been reported.[123] Extensive apical cavitation in the absence of nodules or other causes of fibrocavitary disease (including tuberculosis) has been described in a handful of cases and may follow a fulminant course.[124] Amyloid has been reported occasionally. The incidence of pulmonary hypertension increases with time from diagnosis.[125] Lower respiratory tract infection is increased in frequency in RA; bronchopneumonia is a common terminal event, accounting for 15% to 20% of deaths in RA patients.[126,127] An increase in lung cancer has been reported in RA patients.[128]

Drug-Induced Pulmonary Disease

Drug-induced pulmonary disease is a particular problem in RA because of the widespread use of methotrexate in routine clinical practice, and it has been reported in 3% to 18% of RA patients treated with methotrexate.[129,130] Methotrexate pneumonitis is potentially life threatening. It presents with cough, dyspnea, fever, widespread crackles, and pulmonary infiltrates on chest radiography and CT, which may be focal or diffuse.[131] Although the presentation is sometimes explosive, more often, the onset is subacute (with symptoms evolving for up to 2 months before diagnosis)[131]; 50% of cases are diagnosed within 4 months of initiation of methotrexate therapy. As the clinical and radiographic features are nonspecific, methotrexate-induced lung disease should always be suspected in the treated patient presenting with progressive lung disease. Unfortunately, histologic findings are nonspecific, although prominent lymphocytic infiltration increases the probability of a methotrexate-injured lung.[132] There is conflicting evidence on whether preexisting lung disease predisposes to lung injury caused by methotrexate, but the published evidence does not suggest that functional impairment is an absolute contraindication to its use (although particular caution is warranted when pulmonary reserve is grossly compromised, and patients with previous methotrexate toxicity should not be retreated).[131,133] Pulmonary methotrexate toxicity is associated with a mortality rate of 15% to 20%[131]; because the lymphocytic component of disease is wholly or partially reversible, immediate withdrawal of methotrexate and the early institution of steroid therapy are warranted.

Pulmonary toxicity in RA has also been documented with sulfasalazine, gold therapy, and penicillamine (discussed earlier). Pulmonary infiltrates (due to organizing pneumonia) associated with sulfasalazine occur most commonly in the upper lobes; this side effect is rare in RA, with only a handful of cases reported (most cases occurred in ulcerative colitis).[134] Pulmonary disease induced by gold takes the form of alveolar opacities adjacent to bronchovascular bundles, best demonstrated by high-resolution CT, and often associated with fever or skin rash, relatively low rheumatoid factor titers, and a BAL lymphocytosis.[135] In most patients with sulfasalazine or gold toxicity, lung disease largely regresses with withdrawal of the agent and corticosteroid therapy.

There have been a number of reports of pulmonary toxicity relating to anti-TNF-α therapies including etanercept and infliximab. Toxicity ranges from infection (with particular focus on reactivation of tuberculosis) to interstitial disease and vasculitis.[136,137] Leflunomide has also been associated with pulmonary rheumatoid nodules and interstitial disease.[138,139]

Pulmonary Function Tests

Patterns of functional impairment in RA have been variable in unselected populations, with predominant airflow obstruction a frequent finding in one cohort[110] but reductions in D_{LCO} ascribed to occult interstitial fibrosis in at least 40%.[98] Inconsistencies in published data can be ascribed to the confounding effects of smoking and variations in the type and severity of associated pulmonary disease. Airflow obstruction may result from bronchiectasis or OB. Interstitial pulmonary fibrosis, organizing pneumonia, and lymphocytic interstitial pneumonia give rise to restrictive defects. Pleural disease may also be restrictive but is usually distinguished by elevation of the gas transfer index (KCO).

Radiologic Features

In chest radiographic series of unselected patients with RA, appearances indicative of interstitial lung disease are found in 1% to 5% of cases.[85,86,99,102] In interstitial pulmonary fibrosis, appearances are indistinguishable from

idiopathic pulmonary fibrosis, with symmetrical basal interstitial opacification in limited disease and diffuse coarse reticular abnormalities in extensive disease. Rheumatoid nodules are usually radiologically discrete and small but are often multiple and may reach up to 7 cm in diameter; in Caplan's syndrome, nodules appear in crops, often grow rapidly, and may cavitate. Other chest radiographic findings in RA include focal consolidation (in organizing pneumonia, infectious pneumonia, and lung disease induced by methotrexate), hyperinflation (in OB), and pleural thickening or effusion.

The CT appearances of interstitial pulmonary fibrosis in RA are similar to those in idiopathic pulmonary fibrosis,[139a] with the most common abnormality being a reticular pattern (irregular linear opacities with cyst formation or honeycombing, typically subpleural and most extensive posteriorly and at the lung bases, except in extensive disease). Ground-glass attenuation, consisting of a patchy or diffuse increase in lung density, is likely to denote inflammatory histologic appearances or fine intralobular fibrosis, as in other fibrosing lung diseases.

The cardinal CT feature of organizing pneumonia is patchy bilateral air space consolidation (often with associated ground-glass attenuation), which is often predominantly subpleural,[140] but may have a bronchovascular distribution.[141] Small nodules (≤1 cm in diameter) are common in organizing pneumonia; small pleural effusions and limited fibrosis (probably resulting from prolonged untreated inflammation) are occasional findings.

In bronchiolitis, bronchiolar structures are occasionally visualized directly on CT as centrilobular micronodular opacities and peripheral branching structures, denoting marked thickening of the bronchiolar wall; this appearance may be most frequent in FB.[142] In OB, areas of reduced lung density in a patchy distribution ("mosaic perfusion") are associated with a reduction in the caliber of pulmonary vessels in areas of decreased attenuation, indicative of regional hypoxic vasoconstriction in areas of severe bronchiolitis. Bronchiectasis and bronchial wall thickening on CT are common in constrictive bronchiolitis.

Treatment of Pulmonary Complications

The treatment of pulmonary disease has usually consisted of corticosteroid therapy, with or without immunosuppressive agents. Owing to small numbers, regimens have remained anecdotal. Organizing pneumonia and methotrexate pneumonitis often respond well to treatment. Regression of disease is highly variable in FB and lymphocytic interstitial pneumonia and is virtually never seen in OB. Lung function may improve in response to treatment in interstitial pulmonary fibrosis, but more often, the goal is to prevent further progression of disease, especially when extensive.

SYSTEMIC LUPUS ERYTHEMATOSUS

Systemic lupus erythematosus (SLE) is an inflammatory multisystem disorder of unknown etiology with protean clinical and laboratory manifestations and a variable course and prognosis. The 1982 revised American College of Rheumatology criteria for the diagnosis of SLE require that a minimum of four of the criteria listed in Table 58-6 be satisfied (although SLE is sometimes diagnosed with fewer than four criteria).[143]

TABLE 58-6. Systemic Lupus Erythematosus

CRITERIA FOR DIAGNOSIS*
Malar rash
Discoid rash
Photosensitivity skin rash
Oral or nasopharyngeal ulceration
Nonerosive arthritis involving two or more peripheral joints
Serositis (pleuritis or pericarditis)
Renal disorder (persistent proteinuria or cellular casts)
Neurologic disorder (unexplained seizures or psychosis)
Hematologic disorder (hemolytic anemia, leukopenia, lymphopenia, or thrombocytopenia)
Immunologic disorder (positive LE cell, anti-DNA antibody, anti-Sm antibody, false-positive syphilis serology)
Elevated antinuclear antibodies
LUNG MANIFESTATIONS
Acute lupus pneumonitis
Interstitial pulmonary fibrosis
Pulmonary vasculitis
Diffuse alveolar hemorrhage
Pulmonary hypertension
Shrinking lung syndrome
Antiphospholipid antibody syndrome
Organizing pneumonia
Pleural disease

*Minimum of four criteria required.
LE, lupus erythematosus.

Epidemiology and Risk Factors

SLE occurs throughout the world; the reported prevalence ranges from 12 to 50/100,000 population, and the incidence ranges from 1.8 to 7.6/100,000 population/yr.[144] There is a 6- to 10-fold female excess, and the disease is three times more common in African Americans than in whites. The 5-year survival rate exceeds 90%, but the mortality rate is three times higher than in the general population. Support for a genetic contribution to disease includes a high prevalence in monozygotic twins, familial clustering, and associations between SLE and HLA-DR2, HLA-DR3, and the C4A null allele.[145] No infectious or other environmental factor has been shown to play a major etiologic role.

Pulmonary Manifestations

Pleuropulmonary manifestations of SLE are listed in Table 58-6.

Diffuse Lung Disease

Diffuse lung disease on lung biopsy or at autopsy has been reported in 4%, 33%, and 70% of SLE patients.[146-148] These striking inconsistencies undoubtedly reflect major variations in the histologic diagnostic criteria: In the series with the highest prevalence, trivial interstitial thickening was categorized as "pulmonary fibrosis" but likely represented the minor residuum of infection or inflammatory complications of SLE. Only 3% of SLE patients have clinical evidence of diffuse lung disease at the onset of systemic disease, and a disease resembling interstitial pulmonary fibrosis develops during follow-up in less than 5%.[149] Risk factors for pulmonary fibrosis in SLE include increasing age, pneumonitis, and anti-RNP antibodies.[150]

Interstitial Pneumonia. The clinical presentation (dyspnea, cough, predominantly basal crackles, a restrictive lung function defect or isolated reduction in D_{LCO}, basal opacities on chest radiography) is similar to idiopathic pulmonary fibrosis. Features not typical of idiopathic pulmonary fibrosis include variably associated pleuritic pain, a paucity of patients with morphologically extensive or functionally severe lung fibrosis, and the frequent presence of enlarged peribronchiolar lymphoid follicles at lung biopsy (although other histologic findings are indistinguishable from usual interstitial pneumonia). Partial regression of disease with corticosteroids in 9 of 14 cases in one series[151] suggests that an empirical trial of therapy is usually warranted.

Acute Lupus Pneumonitis. Although seen in less than 2% of SLE patients, acute lupus pneumonitis is often life threatening, with a mortality rate of more than 50% (once respiratory failure has supervened) despite treatment.[152] The predominant histologic feature of diffuse alveolar damage is nonspecific, and it has been argued that acute lupus pneumonitis is merely a manifestation of aspiration or bacterial infection.[146] However, well-documented striking responses to corticosteroids and immunosuppressive agents after antibiotic failure suggest strongly that the disorder is a true, albeit rare, entity. Acute lupus pneumonitis is not to be confused with organizing pneumonia ("bronchiolitis obliterans with organizing pneumonia"), discussed elsewhere in this chapter and reported in only a handful of adult patients with SLE, or with lymphocytic interstitial pneumonia, described in a small number of patients with SLE.

Extrapulmonary Restriction

Extrapulmonary restriction, resulting in exertional dyspnea, a restrictive functional defect, and marked decrease of D_{LCO}, is a well-recognized complication of SLE. The "shrinking lung syndrome" was first described in patients with severe restriction and a marked reduction in lung volume on chest radiography, and it is generally ascribed to diaphragmatic weakness (Fig. 58-6).[153] However, the use of sniff pressures to evaluate diaphragmatic strength may be confounded by concurrent lung restriction or airflow obstruction; in one study, with the use of alternative methods to evaluate diaphragmatic function, the characteristic restrictive defect was attributed to an "unspecified restriction in chest wall expansion."[154] No treatment of proven efficacy currently exists, although a handful of patients have improved in association with corticosteroid or immunosuppressive therapy.[155] The disorder is almost always self-limited, although sometimes it is severe.

Diffuse Alveolar Hemorrhage

Although seen more frequently in SLE than in other CTDs, diffuse alveolar hemorrhage is rare in SLE. The typical presentation of acute dyspnea and extensive pulmonary opacities on chest radiography may mimic acute lupus pneumonitis, especially in the absence of hemoptysis.[156] Diffuse alveolar hemorrhage is often life threatening, with a mortality rate similar to that of acute lupus pneumonitis; however, because the two diseases are both treated empirically with corticosteroid and immunosuppressive therapy, the important differential diagnosis is opportunistic infection. Patients with SLE have

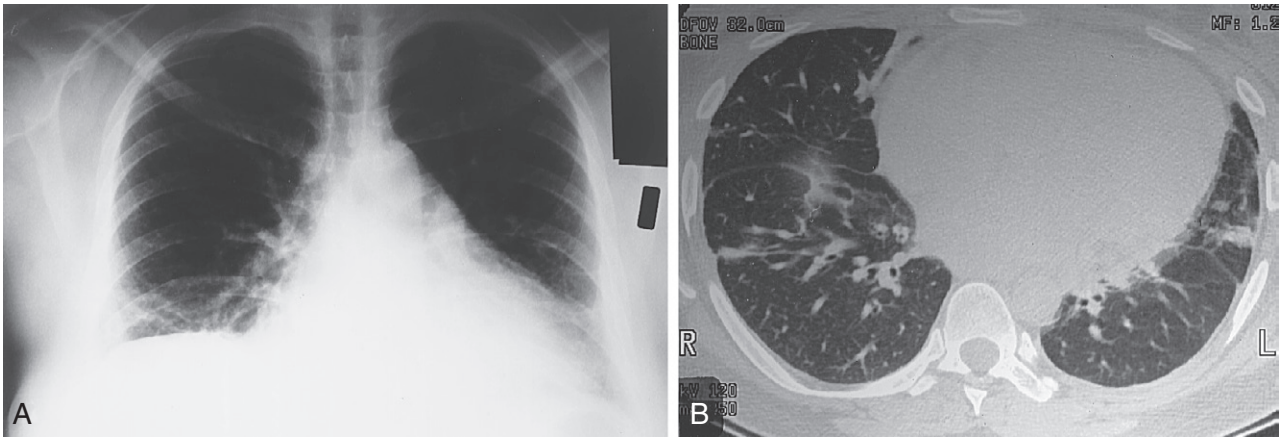

FIGURE 58-6 ■ **A,** Chest radiograph from a patient with systemic lupus erythematosus shows marked elevation of both hemidiaphragms, in keeping with "the shrinking lung syndrome." **B,** On a CT scan from the same patient as in **A,** linear abnormalities are seen that denote subsegmental atelectasis resulting from regional hypoventilation (due to diaphragmatic weakness). The heart is enlarged.

underlying defects in most arms of the immune system and are at added risk of fulminant infection with the use of corticosteroids or immunosuppressive agents.[157] In this context, a misdiagnosis of acute lupus pneumonitis or diffuse alveolar hemorrhage may lead to a potentially disastrous increase in immunosuppression. Thus, the performance of BAL to exclude opportunistic infection may be crucial in SLE patients with unexplained extensive pulmonary opacities.

Pulmonary Hypertension

Pulmonary hypertension was once considered rare in SLE, but it is now reported with increasing frequency[158] and has a 2-year survival rate of less than 50% in severe disease. Abnormalities indicative of subclinical pulmonary hypertension are found on echocardiography in 10% of SLE patients, usually in association with Raynaud's phenomenon,[159] and thus, it is likely that pulmonary hypertension results from vasoconstriction rather than pulmonary vasculitis (which is seldom identified in SLE); in autopsied patients with pulmonary hypertension, overt vasculitis is rare.

Important alternative mechanisms for pulmonary hypertension include vasculitis and thromboembolism.[160] Thromoboembolism has a high prevalence in SLE, especially in patients with antiphospholipid antibodies (which cross-react with coagulation factors).[161,162] In a 1993 study of 842 SLE patients, immunoglobulin G anticardiolipin antibodies were present more frequently than immunoglobulin M antibodies (24% vs. 13%), but both were associated with a 30% prevalence of thrombosis (as opposed to 10% in other SLE patients).[163] Patients with antiphospholipid antibody syndrome also have a higher incidence of impaired lung function than normal controls.[164] In view of the multiplicity of mechanisms potentially responsible for pulmonary hypertension, vasodilators and anticoagulation have all been advocated empirically for patients with the pulmonary vascular disease of SLE. Corticosteroid or immunosuppressive agents may be effective therapy for SLE-associated pulmonary hypertension.[160] In a small series of patients given chronic epoprostenol, measures of pulmonary hypertension, pulmonary vascular resistance, and exercise capacity all improved.[165]

Pleural Disease

Pleural disease is the most common pulmonary manifestation of SLE. Clinical or radiographic evidence of pleural involvement is seen in 20% of patients at the onset of systemic disease and occurs in at least 50% at some time[166] (with pleural abnormalities at autopsy in 50%–100%). Pleural disease is often asymptomatic, but pleuritic pain may be recurrent or intractable. The fluid is usually serosanguineous (but occasionally hemorrhagic) and exudative, with a neutrophilia in patients with pleurisy but a predominant lymphocytosis in chronic effusions.[166] The nonspecific histologic appearance of fibrinous pleuritis is not diagnostically useful. The identification of lupus erythematosus cells has largely fallen out of favor because technical difficulties greatly reduce the sensitivity of the test in confirming that a pleural effusion is due to SLE.[167] The measurement of pleural fluid antinuclear antibody titers may be more diagnostically useful when the etiology of pleural disease is in doubt.[168]

SJÖGREN'S SYNDROME

Sjögren's syndrome is an autoimmune disorder characterized by lymphocytic infiltration of the lachrymal, salivary, conjunctival, and pharyngeal mucosal glands, with variable involvement of extraglandular tissue. The cardinal clinical features of keratoconjunctivitis sicca (dry eyes) and xerostomia (dry mouth) may occur in isolation (primary Sjögren's syndrome, typically seen in women older than age 40) but are more often associated with CTDs such as RA, SSc, or SLE (secondary Sjögren's syndrome). Sicca symptoms are common in lung disease, however, and need to be carefully evaluated.[169] Variable diagnostic criteria are used internationally; in one proposed diagnostic algorithm, sicca symptoms are mandatory, with supportive evidence including ocular signs (positive Schirmer test, rose bengal score > 3), typical histologic appearances on salivary gland biopsy, antibodies to Ro (SS-A) or La (SS-B), or reduced salivary flow.[170]

Epidemiology and Risk Factors

The reported prevalence of primary Sjögren's syndrome ranges from 0.5% to 3.0%. The etiology of the disease is unknown. There is some evidence to suggest a genetic predisposition, including familial clustering and an association with HLA-Dw2 and HLA-Dw3, but no environmental triggers have been identified.

Pulmonary Manifestations

Pulmonary involvement is common in Sjögren's syndrome. In early series, primary and secondary Sjögren's syndromes were combined; it is likely that many of the pulmonary abnormalities seen in secondary Sjögren's syndrome were ascribed to the underlying CTD. Careful evaluation of patients with primary Sjögren's syndrome has shown that cough and dyspnea are common,[171] with objective evidence of pulmonary abnormalities in approximately one fourth of cases.[172] Lung involvement usually consists of lymphocytic infiltration similar to that seen in salivary glands and resulting in tracheobronchial disease or interstitial lung disease, depending on whether involvement is limited to secretory glandular tissue or is more widespread. However, population studies of respiratory involvement in Sjögren's syndrome have been hampered by variations in diagnostic criteria, failure to discriminate between primary and secondary Sjögren's syndrome, and failure to control for confounding features such as drug treatment and smoking. Lung manifestations include diffuse lung disease and tracheobronchial disease.

In a CT study of 35 patients, the most prevalent findings were large and/or small airway disease (n = 19) and diffuse lung disease (n = 12, including 7 in whom the features were suggestive of lymphocytic interstitial pneumonia). The patterns of physiologic abnormalities were consistent with the predominant CT pattern.[173]

Diffuse Lung Disease

Although often asymptomatic, diffuse lung disease in Sjögren's syndrome may present with cough, dyspnea, crackles on auscultation, reticular or nodular opacities on chest radiography, and a restrictive pattern of functional impairment. Interstitial involvement can be classified as pulmonary fibrosis, lymphocytic interstitial pneumonia, or lymphoma. Pulmonary fibrosis has been reported in up to 10% of patients with primary Sjögren's syndrome[174] and most frequently takes the form of fibrotic nonspecific interstitial pneumonia.[175] Although a presentation typical of extensive or progressive interstitial pulmonary fibrosis is rare and interstitial disease in Sjögren's syndrome is often regarded as clinically insignificant, Gardiner and coworkers[174] found that patients with primary Sjögren's syndrome complaining of dyspnea (~10%) have a high prevalence of histologic abnormalities (fibrosis or lymphocytic infiltration) on transbronchial biopsy.[174] A 10-year follow-up study of 30 patients showed that most patients do not develop progressive lung disease, although the total gas transfer level fell significantly in 7 cases.[176]

Lymphocytic interstitial infiltration may take the form of lymphocytic interstitial pneumonia, pseudolymphoma (extensive pulmonary lymphocytic infiltration with the formation of lymphoid follicles), or pulmonary lymphoma. Lymphocytic interstitial pneumonia, historically believed to be the most common diffuse lung disease in Sjögren's syndrome (Fig. 58-7),[177] is characterized by a diffuse lymphocytic infiltrate, with or without histiocytes and multinucleated giant cells, most prominent around bronchioles. Pseudolymphoma, characterized by pulmonary infiltration, may regress spontaneously and often responds well to corticosteroid therapy; however, some patients progress to pulmonary lymphoma. The prevalence of lymphoma is increased 40- to 50-fold in Sjögren's syndrome[178]; pulmonary lymphoma has a highly variable clinical and radiographic presentation, with the spectrum of disease ranging from diffuse interstitial involvement to discrete (often perihilar) masses. It is now believed that all lymphocytic interstitial pneumonia may represent malignant disease of varying nature.

Organizing pneumonia (bronchiolitis obliterans with organizing pneumonia) has been reported in Sjögren's syndrome but occurs less frequently than in RA or polymyositis. A response to corticosteroid therapy is usual but not invariable.

Tracheobronchial Disease

Tracheobronchial disease may take the form of loss of mucous secretion in the trachea (xerotrachea), chronic bronchitis, or small airway disease. Xerotrachea occurs in up to 25% of patients with primary Sjögren's syndrome and consists of atrophy of tracheobronchial mucous glands in association with a lymphoplasmocytic infiltrate, manifesting clinically as a relentless dry cough and endobronchial inflammation at bronchoscopy.[179] It is likely that similar histologic abnormalities in bronchi and bronchioles account for an increased prevalence of bronchial hyperresponsiveness, reported in 40% to 60% of patients with primary and secondary Sjögren's syndrome.[180]

Subclinical bronchiolitis may be common in Sjögren's syndrome. In the interstitial lung disease of Sjögren's syndrome, lymphocytic infiltration is more prominent around small bronchioles, resulting in a BAL lymphocytosis[181]; thus, it is likely that the occasional cases of isolated lymphocytic bronchiolitis, presenting with a clinical picture of chronic obstructive pulmonary disease, represent a more limited form of lymphocytic infiltration. The evaluation of airflow at low lung volumes in unselected patients with primary and secondary Sjögren's syndrome has demonstrated a high prevalence of small airway dysfunction[171]; aerosol penetration from central airways to the lung periphery is reduced,

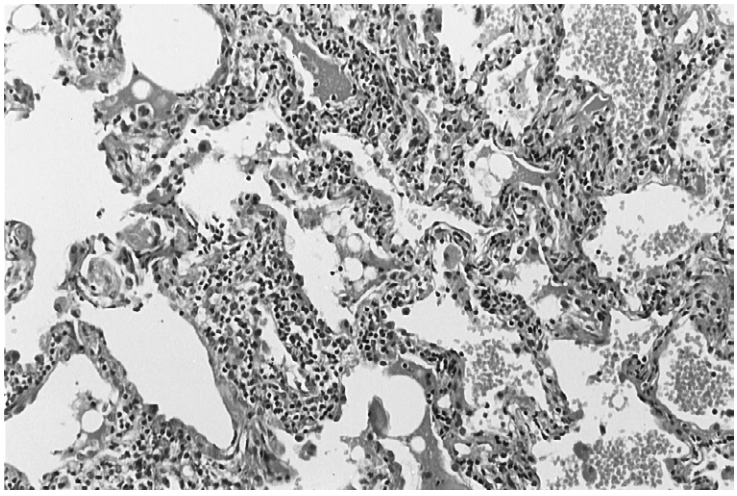

FIGURE 58-7 ■ Surgical lung biopsy specimen taken from a patient with diffuse lung disease in the context of Sjögren's syndrome. Note the dense lymphocytic infiltrate within the interstitium. (Courtesy of Dr. Andrew Nicholson, Royal Brompton Hospital, London, UK.)

indicating small airway obstruction.[182] These abnormalities, indicating either OB or mucous plugging, may contribute to an increased prevalence of bronchopneumonia but do not evolve into severe OB (which is not generally a feature of Sjögren's syndrome, except in occasional cases with associated RA). FB has been reported in a handful of patients with primary Sjögren's syndrome but may occur more frequently in secondary Sjögren's syndrome; in a number of reported cases of FB associated with RA, the presence of Sjögren's syndrome is not explicitly excluded. FB and diffuse bronchiolar lymphocytic infiltration may be part of the same spectrum of disease, but the relationship between the two disorders is uncertain.

POLYMYOSITIS AND DERMATOMYOSITIS

The defining criteria for polymyositis (PM) and dermatomyositis (DM) are listed in Table 58-7. For PM, a definite diagnosis is made if the first four features are present, a probable diagnosis is made if any three of the first four features are present, and a possible diagnosis is made if any two of the first four features are present. For DM, the typical rash must be present, plus any three of the first four for a definite diagnosis, two of the first four for a probable diagnosis, and one of the first four for a possible diagnosis (Bohan and Peter's criteria).[183]

The skin problems of DM include the presence of scaly cutaneous eruptions affecting extensor surfaces of the finger joints (Gottron's tubercles) and the characteristic edema and violaceous or purplish, heliotrope rash that surrounds the eyelids. Proximal muscle weakness tends to be insidious, progressive, and painless, affecting head, neck, and limb girdles and eventually involving the muscles of the tongue and pharynx and the respiratory muscles. Pulmonary complications occur in approximately 45% of patients and are the most frequent cause of death.

TABLE 58-7. Polymyositis with Dermatomyositis

CRITERIA FOR DIAGNOSIS
Symmetrical proximal muscle weakness
Muscle biopsy specimen showing myositis
Elevation of serum skeletal muscle enzymes
Characteristic electromyographic pattern of myositis
Typical rash of dermatomyositis
LUNG MANIFESTATIONS
Interstitial pulmonary fibrosis
Acute pneumonitis (with diffuse alveolar damage)
Organizing pneumonia
Aspiration pneumonia
Pulmonary vasculitis and alveolar hemorrhage
Respiratory muscle weakness

Epidemiology and Risk Factors

The inflammatory myopathies are relatively rare, affecting 2 to 10/100,000 population, with a female-to-male predominance of 2.5:1 and with a bimodal age distribution peaking in childhood and in the fourth to fifth decades. DM appears to have a higher expression of HLA-B8/DR3, HLA-B14, and HLA-B40, whereas PM associates with HLA-B8/DR3 and in African Americans with HLA-B7 and HLA-DRw6.[184] There are multiple manifestations of lung disease, as listed in Table 58-7. The presence of diffuse lung disease has been associated with two HLA haplotypes: HLA-DRB1*1302-DQA1*0102-DQB1*0604 and HLA-DRB1*0405-DQA1*03-DQB1*0401.[185] The prevalence of lung disease varies from series to series, and often the respiratory symptoms are masked by muscle fatigue. Nonetheless, pulmonary complications of the disease can be a frequent cause of death. In combined series, the prevalence of diffuse lung disease can be up to 64%. The disease may present with pulmonary symptoms, and in one series this was the case in 21 of 70 patients.[186]

Pulmonary Manifestations

Diffuse Lung Disease

Diffuse lung disease is the most common problem encountered in the context of DM with PM and may occur in up to 32% of patients.[187] The prevalence of diffuse lung disease may be less common in patients with amyotrophic DM, and is three to five times more common in women than men, most commonly presenting in the fifth decade. The pattern of diffuse lung disease often mimics that of chronic idiopathic pulmonary fibrosis, but an acute, rapidly progressive form of acute pneumonitis can occur.[188] Organizing pneumonia may also be the presenting feature (Fig. 58-8). The histopathologic features associated with these forms of presentation include usual interstitial pneumonia in patients with an interstitial pulmonary fibrosis pattern, diffuse alveolar damage in the acute pneumonitis and organizing pneumonia.[189–191] In a large series of 70 patients, Douglas and colleagues[186] reported that 82% of patients who were biopsied had the nonspecific interstitial pneumonia pattern of histopathology. It has been shown that one of the characteristic features of chronic diffuse lung disease in PM with DM is a combination of the features of organizing pneumonia and interstitial pulmonary fibrosis on high-resolution CT.[192] One report described an acute presentation of pulmonary capillaritis with alveolar hemorrhage in association with PM.[193]

Clinical Features. The clinical features of diffuse lung disease in PM with DM depend on the nature of the lung process. Dyspnea and nonproductive cough are the most common presenting symptoms. Breathlessness on exertion without wheeze is common, and if the myopathy is severe, orthopnea may be striking. Hemoptysis may occur if there is capillaritis. Pleural disease is uncommon. Pulmonary involvement can develop prior to the systemic disease and occur at any time in the disease

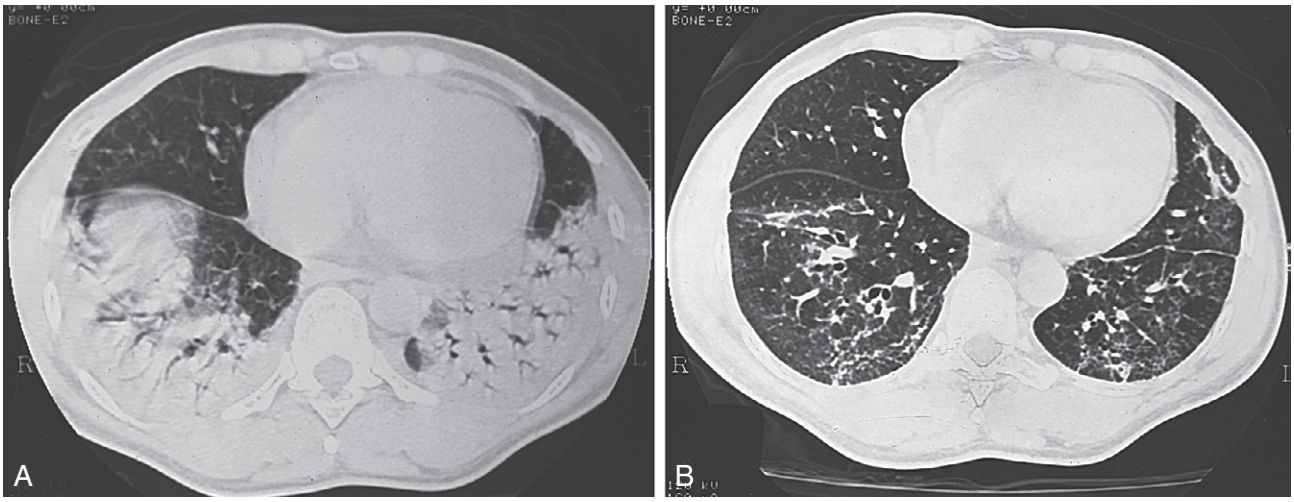

FIGURE 58-8 ■ **A,** CT scan shows dense consolidation that denotes organizing pneumonia in a patient with polymyositis. As shown in this example, the disease tends to be most prominent posteriorly in the lower lobes. **B,** After treatment, the dense consolidation has regressed, but there is extensive residual linear opacification, representing residual fibrosis and resulting in traction bronchiectasis on the right and a restrictive functional defect.

course. There is no correlation between the severity of pulmonary parenchymal involvement and the systemic musculoskeletal manifestations. Rarely, patients present acutely with or progress rapidly to acute respiratory failure.

Imaging. Chest radiography findings depend on lung disease. Chronic diffuse lung disease is associated with peripheral reticular opacities, particularly in the lung bases as for interstitial pulmonary fibrosis. Acute pneumonitis can result in ground-glass opacification on chest radiography and alveolar hemorrhage with areas of consolidation.

High-resolution CT is more sensitive and specific than chest radiography, highlighting the distributions of the different processes. CT findings include thickened interlobular septa, linear opacities, ground-glass opacification, and patchy consolidation. A combination of consolidation with a peripheral reticular pattern is highly characteristic.[194] Traction bronchiectasis and honeycombing are less common. The consolidation may evolve into a reticular pattern.[195] DM and PM are well-recognized paraneoplastic phenomena, so it is sometimes difficult to determine which condition presented first.[196] Screening for occult carcinoma is recommended with mammography, abdominal CT, pelvic ultrasonography, and tumor markers.

Pulmonary Function. Lung function tests show a restrictive ventilatory defect with reduced gas transfer. In recent hemorrhage or marked myopathy, there may be a disproportionate preservation of the D_{LCO}. However, it must be remembered that acute hemorrhage can occur in the context of previous chronic disease, and so the D_{LCO} may be normal or subnormal but elevated from a level that was previously lower. Severe reduction in D_{LCO} is associated with increased mortality.

Bronchoalveolar Lavage. BAL lymphocytosis and neutrophilia have been described in diffuse lung disease associated with DM/PM. The significance of BAL is debated, but it appears that neutrophilia on BAL is associated with clinical deterioration.[197]

Laboratory Tests. Several studies have reported no association between creatine kinase levels and respiratory disease. In fact, the presence of a low creatine kinase has been associated with more rapidly progressive diffuse lung disease.[198,199] Studies of autoantibodies have highlighted the association between the presence of antibodies to aminoacyl transfer RNA (tRNA) synthetases, inflammatory myopathies, and diffuse lung disease.[198] These antibodies help define the clinical antisynthetase syndrome: the coexistence of myositis, diffuse lung disease, and arthritis. The most common autoantibody is Jo-1 (a cytoplasmic antihistidyl tRNA synthetase), occurring in 20% to 30% of patients with inflammatory myopathy and correlating strongly with the presence of diffuse lung disease. Jo-1 antibodies are present in 50% to 100% of cases of inflammatory myopathy and diffuse lung disease, in contrast to less than 5% of patients without diffuse lung disease. A variety of novel autoantibodies have been described with affinity for other tRNA synthetase molecules: PL-12, PL-7, EJ, OJ, and Ku.[200]

Other Pulmonary Manifestations

Muscular weakness may lead to aspiration pneumonia in up to 20% of patients and is usually associated with dysphagia. Respiratory muscle weakness and hypercapneic respiratory failure occurs in up to 25% of patients, although severe respiratory failure requiring ventilatory support is less common. Bilateral diaphragmatic paralysis has been reported.

Treatment of Pulmonary Complications

Diffuse lung disease is a serious complication of DM/PM and is associated with increased mortality.[201] The clinical course and prognosis of DM/PM-associated diffuse lung disease is heterogeneous and depends on the histologic pattern of disease. The decision to treat, and the choice of therapy, therefore, needs to be individualized. Corticosteroids are the preferred initial therapy. Oral prednisolone (0.75–1.0 mg/kg/day) is usual, but intravenous corticosteroids are required in more severe or rapidly progressive disease. Immunosuppressive therapy may be used in patients who are steroid resistant or experiencing adverse effects from corticosteroids. There are some reports of efficacy of cyclophosphamide,[202,203] cyclosporine A,[204] and azathioprine.[204a,204b] In refractory cases, methotrexate and intravenous immunoglobulin should be considered. Mycophenolate has been shown to be safe and effective in treatment of the systemic disease, but no controlled studies have been performed in DM/PM-related lung disease.

Organizing pneumonia responds well to corticosteroids alone. Vasculitis may require a combination of high-dose prednisolone and immunosuppression. Occasionally, the myositis may resolve on treatment but the lung disease progresses; these cases may be very difficult to control.

MIXED CONNECTIVE TISSUE DISEASE

Mixed connective tissue disease (MCTD) is defined by the presence of features of SLE, SSc, and PM (Sjögren's syndrome may also be seen) in association with high titers (>1:1600) of autoantibody directed against the extractable nuclear antigen U1-RNP.[205,206] Criteria that have been suggested for the diagnosis of MCTD include the presence of antibody to the U1 ribonuclear protein together with the clinical features of hand edema, synovitis, Raynaud's phenomenon, acrosclerosis, and myositis. At least three of these clinical features are needed in addition to the autoantibody finding. A fourth clinical feature is required if the initial three are Raynaud's phenomenon, edema, and acrosclerosis. The difference between MCTD and overlap syndrome may be semantic, but the former often presents more acutely and with greater specificity for U1-RNP. MCTD may differentiate into specific rheumatologic diseases. This differentiation may be genetically determined.[207]

Other overlap syndromes are reported in which clinical features of more than one CTD are present in the same patient. Although MCTD tissue disease remains the most clearly definable, other overlap syndromes occur both with and without typical autoantibody association. Of the former, overlapping clinical features found in association with U2-RNP and U3-RNP and the tRNA synthetase–associated diseases (see earlier) can be considered to be part of an overlap syndrome. Antibodies to PM-Scl, KU, and U2-RNP are associated with overlaps of SSc and PM.[206]

The prevalence of MCTD is unclear, but it is estimated at 1 in 10,000, with a 9:1 female preponderance, most frequently presenting in the fourth decade. Pleuropulmonary complications occur in 20% to 85% of patients, but diffuse lung disease (most commonly a nonspecific interstitial pneumonia CT pattern) is the most common lung complication.[208] In a CT study of 41 patients, the major abnormalities were ground-glass appearances in all, subpleural micronodules in 40 of 41, and nonseptal linear opacities in 32 of 41.[209] Pleural effusions occur in patients with other clinical features of SLE, and are usually small, exudative, and often resolve spontaneously. Pulmonary hypertension may also occur.[210] Respiratory muscle weakness, diffuse alveolar hemorrhage, and small airway disease are less common complications.

Survival is difficult to quantify owing to the heterogeneity of disease. Individual disease course tends to be similar to that of the CTD most closely resembled in that patient. Survival is better if the diffuse lung disease is associated with U1-RNP positivity than with no U1-RNP. Treatment depends on the nature of the lung disease and is identical to the approaches used for the other CTDs. Pleural effusions are often responsive to corticosteroids. A combination of low-dose prednisolone and an immunosuppressant (such as cyclophosphamide or azathioprine) is generally used to treat interstitial fibrosis, with an approach similar to that for SSc.

UNDIFFERENTIATED CONNECTIVE TISSUE DISEASE

Up to 25% of patients with autoimmune features do not fulfill American College of Rheumatology criteria for a specific CTD, and a large proportion never progress to a "differentiated" CTD. Interstitial lung disease may complicate undifferentaited connective tissue diseases,[211] but little is known about the prognosis or treatment of interstitial lung disease in this context.

RELAPSING POLYCHONDRITIS

Relapsing polychondritis is a rare disease characterized by recurrent progressive cartilaginous inflammation. Episodic, painful, cartilaginous inflammation occurs, resulting eventually in the widespread degeneration of cartilaginous structures. The diagnosis of relapsing polychondritis requires the presence of three or more of the following clinical features[212]: bilateral auricular chondritis; nonerosive, seronegative inflammatory polyarthritis; nasal chondritis; ocular inflammation; respiratory tract involvement (either upper or lower respiratory tract); cochlear with or without vestibular abnormality; and positive biopsy specimen. The presence of anticartilage antibodies may be helpful in the diagnosis.

The condition affects men and women equally and has a peak incidence between 40 and 60 years of age. It is considered an autoimmune process, and autoanti-

FIGURE 58-9 ■ Relapsing polychondritis. **A,** Loss of cartilage in this individual's nose results in a "saddle" deformity. **B,** Chest radiograph of the same individual as in **A** demonstrates tracheal narrowing. **C,** Tracheal narrowing and thickening shown more graphically in the CT scan. **D,** Thickening of the segmental bronchi is seen together with patchy attenuation ("mosaicism"), which indicates small airway involvement.

bodies have been found directed against cartilage and type II collagen. A weak association with HLA-DR4 has been reported.[213] Diagnosis is chiefly clinical but can be confirmed at biopsy of affected cartilage, including tracheal rings.

Relapsing polychondritis is usually multifocal, affecting cartilage of the ear (85%–94%), nose (54%–57%) (Fig. 58-9A), upper respiratory tract (31%–48%), and ribs. In addition, patients frequently suffer ocular inflammation, nonerosive arthropathy (52%), and vestibulocochlear dysfunction.[212,214] It may occur in association with a wide range of other conditions, especially CTD and vasculitis. Approximately 30% of patients have a preexisting CTD.

Respiratory involvement probably accounts for around 10% of deaths in this condition. Up to 25% of cases present with focal or generalized respiratory tract involvement. The larynx and upper trachea are the most common focal areas involved, but large or small airways may also be affected. Laryngotracheal involvement is a poor prognostic determinant. Destruction and obstruction of the glottis, trachea, and bronchi may lead to airway stricture, collapse, and distal infection (see Fig.

58-9B and C).[215] Pulmonary parenchymal disease is rare, with the exception of pulmonary vasculitis.

Clinical presentation is determined by the site of cartilaginous involvement. Upper airway involvement typically presents with wheezing and hoarseness. Lung function testing shows diminution in maximal inspiratory (large, extrathoracic airways) and expiratory (smaller, intrathoracic airways) flow rates, suggesting airway collapse while static recoil pressures are preserved. Radiography may show ectopic airway cartilage calcification or large airway narrowing, but is often insensitive. However, high-resolution CT scanning shows tracheal ring thickening, airway wall attenuation, and calcification. Dynamic CT scanning may show airway collapse on expiratory maneuvers and can help to localize the large airway disease.[216] Bronchoscopy may show endobronchial inflammation or stenosis and is useful in the exclusion of mechanical obstruction. Endobronchial biopsy may be diagnostic but is insensitive. Laryngoscopy and bronchoscopy are associated with risk of acute airway compromise, however.[215]

Treatment depends on disease severity. Mild cases may be controlled with nonsteroidal anti-inflammatory drugs, but troublesome relapses may require short-term high-dose corticosteroid therapy. In acute airway involvement, high-dose intravenous corticosteroid is used. In one large review of 159 reported cases, three fourths of the patients required chronic corticosteroid therapy, which in that series, decreased the frequency, duration, and severity of flare-ups but did not prevent disease progression.[217] Steroid-resistant lesions have been treated with immunosuppressive agents such as cyclophosphamide. Despite short-term improvement with steroid and immunosuppressive therapy, relapse and disease progression are common. Tracheostomy and stenting are occasionally indicated, but other surgical treatment is difficult owing to the diffuse nature of involvement and risk of relapse.[218] In one study, the use of multiple, self-expandable stents via fiberoptic bronchoscopy in five patients requiring mechanical ventilation resulted in improvement in four patients who were all able to live without mechanical ventilation for up to 20 months.[219] Newer self-expanding silicone stents have been used with variable effect in palliative cases.[220] Intraluminal stents may be complicated by hemorrhage, tracheal erosion, ulceration, or airway obstruction, however. Survival has been reported at 94% at 8 years[221] and is variable.

BEHÇET'S SYNDROME

Behçet's syndrome occurs predominantly in the countries bordering the Mediterranean Sea. Prevalence estimates approach 80 to 370/100,000 population in Turkey. Men and women are affected equally, and age of onset is usually in the second or third decade. There is an association between the HLA-B51 allele and, more controversially, more severely affected patients; relative risk of HLA-B51 carriers is roughly 13:1 in Turkey. Herpes simplex type 1 and streptococci have been suggested as causative agents.[222] Diagnosis requires the presence of recurrent oral ulceration occurring at least three times in a 12-month period and two of the four minor features listed in Table 58-8.[223] Mucocutaneous ulceration is the clinical hallmark, with aphthous oral and genital ulceration seen in almost all patients. Other cutaneous features include erythema nodosum, an acneiform rash, and papular lesions of cutaneous vasculitis. Uveitis is the major cause of morbidity, but systemic vasculitis may affect all systems.

TABLE 58-8. Behçet's Syndrome

CRITERIA FOR DIAGNOSIS
Major (required)
Recurrent aphthous ulceration occurring at least three times in a 12-mo period
Minor (two of four)
Recurrent genital ulceration
Ocular disease
Skin lesions (erythema nodosum, skin ulcers)
Positive pathergy test (a 2-mm erythematous papule or pustule at the prick site 48 hr after the application of a sterile hypodermic 20- to 22-gauge needle that obliquely penetrated avascular antecubital skin to a depth of 5 mm)

Pulmonary involvement is seen in 1% to 7% and tends to affect HLA-B51–positive younger males (<25 yr) more severely. The major pulmonary manifestations are pulmonary vasculitis,[224] pulmonary artery aneurysms, arterial and venous thromboses, pulmonary infarction, organizing pneumonia, and pleurisy.[225] Symptoms include dyspnea, chest pain, and recurrent hemoptysis that can be massive and fatal.[226]

The cardinal histologic feature is vasculitis affecting arterial and venous vessels of all sizes. Pulmonary arterial aneurysms are surrounded by inflammatory infiltrates and have thickened intima and degeneration of the elastic lamina with thrombosis. Arterial and venous thromboses, pulmonary infarcts, and occasionally, pleural effusion also occur.[227] The radiographic abnormalities are nonspecific but may include the features of small airway disease, pulmonary hemorrhage, vascular occlusion, or mass lesions representing arterial aneurysm(s).[228,229] Prognosis is variable. The disease course is relapsing-remitting. Pulmonary artery aneurysm carries the worst prognosis, with a 2-year survival of 70%.

Treatment is complex and depends on presentation. Steroids and immunosuppressive agents are used to control vasculitis, particularly in cases of pulmonary artery aneurysm, in which eventual regression is sometimes observed. Cyclosporin A and FK506 have been successful in some patients.[225] Anticoagulants may be required for control of thrombosis but should be used only if immunosuppression is insufficient, because there is a significant risk of hemorrhage. Pulmonary embolization and surgical resection have been reported to be

successful, but surgical treatment of aneurysms can result in aneurysms at the anastomosis site.[230]

ANKYLOSING SPONDYLITIS

Ankylosing spondylitis (AS) is a seronegative spondyloarthritis developing in 0.05% to 1.5% of the general population and is associated with the major histocompatibility antigen HLA-B27.[231] The prevalence of AS is higher in white males, with a male-to-female ratio of 10:1. The cardinal site of disease is the vertebral column. As the disease progresses, inflammation leads to fibrosis and ossification, with ankylosis of the vertebral joints. Peripheral joint arthritis is seen in approximately one third of patients, and extra-articular features include aortic regurgitation, uveitis, pulmonary disease, and extrapulmonary restriction.

Lung disease, mainly upper zone fibrosis, can occur in up to 30% of case series but fibrobullous disease is less common. In a series of 2080 patients with AS, this pattern was seen in only 1% to 2% of patients.[232] Limited interstitial lung disease, small airway disease, bronchiectasis, and paraseptal emphysema are frequently present even when chest radiographic appearances are normal.[233–235] In another study, abnormalities were seen in 15 of 21 patients, comprising thickened interlobular septa (33%), bronchial wall thickening (29%), pleuropulmonary abnormalities (29%), and linear septal thickening (29%).[236] Pulmonary involvement, often subclinical, is an early manifestation of AS.[237] A subclinical lymphocytic alveolitis may be evident with BAL.[238] Histologically, lung abnormalities consist of a variable mixture of lymphocytic infiltration, fibrosis, and bullous change. On chest radiography, diffuse reticular opacities in the upper zones are usually symmetrical and are seldom extensive except in patients with severe spinal disease[239] or a long history of AS.[232] However, apical fibrosis occasionally may precede the development of extrapulmonary disease. No proven treatment exists to prevent the development of apical fibrosis; resistance to corticosteroid therapy is the rule.

Cavities may develop within distorted fibrotic apical tissue and are sometimes colonized by mycobacteria or fungi, especially *Aspergillus fumigatus,* which are isolated in up to 60% of AS patients with apical cavitation.[240] Life-threatening hemoptysis is an occasional complication of mycetoma formation within cavities and may be controllable by bronchial artery embolization; the resection of a mycetoma is a treatment of last resort owing to the high prevalence of postoperative bronchopleural fistula or empyema. Advanced apical fibrosis is often associated with apical pleural thickening, but pleural disease is seldom seen adjacent to normal lung parenchyma elsewhere in the thorax. There is an increased (≤10%) prevalence of pneumothorax in AS patients with apical fibrosis,[232] probably due to subpleural bullous degeneration in advancing disease.

Extrapulmonary restriction due to immobilization of the chest wall (costovertebral ankylosis) is an occasional complication of AS. Extrapulmonary restriction is often asymptomatic and associated with surprisingly little impairment in pulmonary function, perhaps because the diaphragm is able to make a major contribution in the presence of a high resting volume. Lung volumes may be mildly reduced, but gas transfer is almost always preserved in the absence of parenchymal disease.[241]

MARFAN SYNDROME

Marfan syndrome (MS) is an autosomal dominant condition of variable penetrance affecting approximately 5/100,000 population. MS is characterized by abnormalities of fibrous connective tissue with abundant type I collagen (in some cases due to mutations on chromosome 15), especially in the skeleton (long limbs, arachnodactyly, pectus excavatum, kyphoscoliosis), eyes (subluxation of the lens), and cardiovascular system (aortic or mitral regurgitation, aortic aneurysm). The reduced life expectancy of MS is largely attributable to cardiac complications; there is no effective treatment to reverse disease or to slow progression.

Respiratory complications can be subdivided into pulmonary and extrapulmonary abnormalities. Ten percent to 15% of patients with MS, have pulmonary involvement. The most common pulmonary complication is pneumothorax (often recurrent and bilateral). The high prevalence of pneumothorax in MS of 5% to 10%[242] (over 100-fold higher than in the general population) can be ascribed to the rupture of subpleural bullae. Localized bulla formation with a predilection for the lung apex[243] is an occasional striking finding in young patients. Emphysema is present on chest radiography in the majority of MS patients with pneumothoraces.[242,244] Generalized emphysema in nonsmoking patients with MS may become evident at any age and is sometimes fatal in childhood.[245] Underlying apical fibrosis has been reported in a handful of cases. Other less frequent parenchymal manifestations include congenital malformations of the middle lobes (which may be absent or rudimentary) and an increased prevalence of bronchopneumonia.[242]

Thoracic cage involvement is present in greater than 50% of MS patients. Isolated pectus excavatum in MS is seldom associated with significant impairment in lung function. However, occasionally kyphoscoliosis is associated with fatal cor pulmonale.[246] It is likely that nocturnal desaturation amplifies hypoxia due to kyphoscoliosis. Increased upper airway collapsibility during sleep is common in MS, accounting for an association between MS and obstructive sleep apnea.[247]

KEY POINTS

- In CTD the lung can be involved by a wide variety of patterns of pathology affecting the trachea through the parenchyma to the pleura.
- Sometimes, pulmonary manifestations may precede systemic features of the CTD.
- Often, combinations of patterns exist that flag the likelihood of CTD being the underlying problem. Some patterns of lung disease are more common in one CTD than the others. Specific pathologic entities that occur in these diseases do not generally follow the same course as their idiopathic counterparts.
- Common drugs used in the treatment of CTDs may result in major pulmonary complications.
- Increasing recognition of the pulmonary manifestations of these protean disorders is resulting in better outcomes and remains a growing field.

References

1. Preliminary criteria for the classification of systemic sclerosis (scleroderma). Subcommittee for scleroderma criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Arthritis Rheum 23:581–590, 1980.
2. Silman A, Black CM, Welsh KI: Epidemiology, demographics, genetics. *In* Clements PJ, Furst DE (eds): Systemic Sclerosis. Baltimore: Williams & Wilkins, 1996, pp 23–50.
3. Gilchrist FC, Bunn C, Foley PJ, et al: Class II HLA associations with autoantibodies in scleroderma: A highly significant role for HLA-DP. Genes Immunol 2:76–81, 2001.
4. Fonseca C, Lindahl GE, Ponticos M, et al: A polymorphism in the CTGF promoter region associated with systemic sclerosis. N Engl J Med 357:1210–1220, 2007.
5. Silver RM: Scleroderma and pseudoscleroderma: Environmental exposure. *In* Clements PJ, Furst DE (eds): Systemic Sclerosis. Baltimore: Williams & Wilkins, 1996, pp 81–98.
6. Rodnan GP, Benedek TG, Medsger TA Jr, Cammarata RJ: The association of progressive systemic sclerosis (scleroderma) with coal miners' pneumoconiosis and other forms of silicosis. Ann Intern Med 66:323–334, 1967.
7. Tabuenca JM: Toxic-allergic syndrome caused by ingestion of rapeseed oil denatured with aniline. Lancet 2:567–568, 1981.
8. Steen VD, Medsger TA: Changes in causes of death in systemic sclerosis, 1972–2002. Ann Rheum Dis 66:940–944, 2007.
9. Arnett FC, Howard RF, Tan F, et al: Increased prevalence of systemic sclerosis in a Native American tribe in Oklahoma. Association with an Amerindian HLA haplotype. Arthritis Rheum 39:1362–1370, 1996.
10. Petrek M, Pantelidis P, Southcott AM, et al: The source and role of RANTES in interstitial lung disease. Eur Respir J 10:1207–1216, 1997.
11. Majumdar S, Li D, Ansari T, et al: Different cytokine profiles in cryptogenic fibrosing alveolitis and fibrosing alveolitis associated with systemic sclerosis: A quantitative study of open lung biopsies. Eur Respir J 14:251–257, 1999.
12. Bolster MB, Ludwicka A, Sutherland SE, et al: Cytokine concentrations in bronchoalveolar lavage fluid of patients with systemic sclerosis. Arthritis Rheum 40:743–751, 1997.
13. Cambrey AD, Harrison NK, Dawes KE, et al: Increased levels of endothelin-1 in bronchoalveolar lavage fluid from patients with systemic sclerosis contribute to fibroblast mitogenic activity in vitro. Am J Respir Cell Mol Biol 11:439–445, 1994.
14. Shi-Wen X, Denton CP, McWhirter A, et al: Scleroderma lung fibroblasts exhibit elevated and dysregulated type I collagen biosynthesis. Arthritis Rheum 40:1237–1244, 1997.
15. Gauldie J, Jordana M, Cox G: Cytokines and pulmonary fibrosis. Thorax 48:931–935, 1993.
16. Sime PJ, Xing Z, Graham FL, et al: Adenovector-mediated gene transfer of active transforming growth factor-beta1 induces prolonged severe fibrosis in rat lung. J Clin Invest 100:768–776, 1997.
17. Corrin B, Butcher D, McAnulty BJ, et al: Immunohistochemical localization of transforming growth factor-beta 1 in the lungs of patients with systemic sclerosis, cryptogenic fibrosing alveolitis and other lung disorders. Histopathology 24:145–150, 1994.
18. Hoyles RK, Khan K, Shiwen X, et al: Fibroblast-specific perturbation of transforming growth factor beta signaling provides insight into potential pathogenic mechanisms of scleroderma-associated lung fibrosis: Exaggerated response to alveolar epithelial injury in a novel mouse model. Arthritis Rheum 58:1175–1188, 2008.
19. Gray AJ, Bishop JE, Reeves JT, et al: Partially degraded fibrin(ogen) stimulates fibroblast proliferation in vitro. Am J Respir Cell Mol Biol 12:684–690, 1995.
20. Abraham DJ, Vancheeswaran R, Dashwood MR, et al: Increased levels of endothelin-1 and differential endothelin type A and B receptor expression in scleroderma-associated fibrotic lung disease. Am J Pathol 151:831–841, 1997.
21. Jain R, Shaul PW, Borok Z, Willis BC: Endothelin-1 induces alveolar epithelial-mesenchymal transition through endothelin type A receptor-mediated production of TGF-beta1. Am J Respir Cell Mol Biol 37:38–47, 2007.
22. Piguet PF, Collart MA, Grau GE, et al: Requirement of tumour necrosis factor for development of silica-induced pulmonary fibrosis. Nature 344:245–247, 1990.
23. Bogatkevich GS, Ludwicka-Bradley A, Highland KB, et al: Impairment of the antifibrotic effect of hepatocyte growth factor in lung fibroblasts from African Americans: Possible role in systemic sclerosis. Arthritis Rheum 56:2432–2442, 2007.
24. Hsu E, Feghali-Bostwick CA: Insulin-like growth factor-II is increased in systemic sclerosis–associated pulmonary fibrosis and contributes to the fibrotic process via Jun N-terminal kinase– and phosphatidylinositol-3 kinase–dependent pathways. Am J Pathol 172:1580–1590, 2008.
25. Alton E, Turner-Warwick M: Lung involvement in scleroderma. *In* Jayson MIV, Blac CM (eds): Systemic Sclerosis: Scleroderma. London: John Wiley, 1988, pp 181–205.
26. Kim JH, Follett JV, Rice JR, Hampson NB: Endobronchial telangiectasias and hemoptysis in scleroderma. Am J Med 84:173–174, 1988.
27. Vonk MC, van Die CE, Snoeren MM, et al: Oesophageal dilatation on high-resolution computed tomography scan of the lungs as a sign of scleroderma. Ann Rheum Dis 67:1317–1321, 2008.
28. Launay D, Remy-Jardin M, Michon-Pasturel U, et al: High resolution computed tomography in fibrosing alveolitis associated with systemic sclerosis. J Rheumatol 33:1789–1801, 2006.
29. Goldin JG, Lynch DA, Strollo DC, et al: High-resolution CT scan findings in patients with symptomatic scleroderma–related interstitial lung disease. Chest 134:358–367, 2008.
30. Wells AU, Hansell DM, Rubens MB, et al: Functional impairment in lone cryptogenic fibrosing alveolitis and fibrosing alveolitis associated with systemic sclerosis: A comparison. Am J Respir Crit Care Med 155:1657–1664, 1997.

31. Wells AU, Hansell DM, Haslam PL, et al: Bronchoalveolar lavage cellularity: Lone cryptogenic fibrosing alveolitis compared with the fibrosing alveolitis of systemic sclerosis. Am J Respir Crit Care Med 157:1474–1482, 1998.
32. Wells AU, Hansell DM, Harrison NK, et al: Clearance of inhaled 99mTc-DTPA predicts the clinical course of fibrosing alveolitis. Eur Respir J 6:797–802, 1993.
33. Silver RM, Miller KS, Kinsella MB, et al: Evaluation and management of scleroderma lung disease using bronchoalveolar lavage. Am J Med 88:470–476, 1990.
34. Schneider PD, Wise RA, Hochberg MC, Wigley FM: Serial pulmonary function in systemic sclerosis. Am J Med 73:385–394, 1982.
35. Plastiras SC, Karadimitrakis SP, Ziakas PD, et al: Scleroderma lung: initial forced vital capacity as predictor of pulmonary function decline. Arthritis Rheum 55:598–602, 2006.
36. Wallaert B, Dugas M, Dansin E, et al: Subclinical alveolitis in immunological systemic disorders. Transition between health and disease? Eur Respir J 3:1206–1216, 1990.
37. Witt C, Borges AC, John M, et al: Pulmonary involvement in diffuse cutaneous systemic sclerosis: Broncheoalveolar fluid granulocytosis predicts progression of fibrosing alveolitis. Ann Rheum Dis 58:635–640, 1999.
38. Bouros D, Wells AU, Nicholson AG, et al: Histopathologic subsets of fibrosing alveolitis in patients with systemic sclerosis and their relationship to outcome. Am J Respir Crit Care Med 165:1581–1586, 2002.
39. Goh NS, Veeraraghavan S, Desai SR, et al: Bronchoalveolar lavage cellular profiles in patients with systemic sclerosis–associated interstitial lung disease are not predictive of disease progression. Arthritis Rheum 56:2005–2012, 2007.
40. Strange C, Bolster MB, Roth MD, et al: Bronchoalveolar lavage and response to cyclophosphamide in scleroderma interstitial lung disease. Am J Respir Crit Care Med 177:91–98, 2008.
41. Flaherty KR, Colby TV, Travis WD, et al: Fibroblastic foci in usual interstitial pneumonia: Iidiopathic versus collagen vascular disease. Am J Respir Crit Care Med 167(10):1410–1415, 2003.
42. Muir TE, Tazelaar HD, Colby TV, Myers JL: Organizing diffuse alveolar damage associated with progressive systemic sclerosis. Mayo Clin Proc 72:639–642, 1997.
43. Hesselstrand R, Scheja A, Shen GQ, et al: The association of antinuclear antibodies with organ involvement and survival in systemic sclerosis. Rheumatology (Oxford) 42:534–540, 2003.
44. Mitri GM, Lucas M, Fertig N, et al: A comparison between anti-Th/To- and anticentromere antibody–positive systemic sclerosis patients with limited cutaneous involvement. Arthritis Rheum 48:203–209, 2003.
45. Hakala M: Poor prognosis in patients with rheumatoid arthritis hospitalized for interstitial lung fibrosis. Chest 93:114–118, 1988.
45a. Assassi S, Del Junco D, Sutter K, et al: Clinical and genetic factors predictive of mortality in early systemic sclerosis. Arthritis Rheum 61:1403–1411, 2009.
46. Goh NS, Desai SR, Veeraraghavan S, et al: Interstitial lung disease in systemic sclerosis: A simple staging system. Am J Respir Crit Care Med 177:1248–1254, 2008.
47. Bryan C, Howard Y, Brennan P, et al: Survival following the onset of scleroderma: Results from a retrospective inception cohort study of the UK patient population. Br J Rheumatol 35:1122–1126, 1996.
47a. Altman RD, Medsger TA Jr, Bloch DA, Michel BA: Predictors of survival in systemic sclerosis (scleroderma). Arthritis Rheum 34:403–413, 1991.
47b. Rosenthal AK, McLaughlin JK, Gridley G, Nyren O: Incidence of cancer among patients with systemic sclerosis. Cancer 76:910–914, 1995.
48. Lynch JP 3rd, McCune WJ: Immunosuppressive and cytotoxic pharmacotherapy for pulmonary disorders. Am J Respir Crit Care Med 155:395–420, 1997.
49. Dheda K, Lalloo UG, Cassim B, Mody GM: Experience with azathioprine in systemic sclerosis associated with interstitial lung disease. Clin Rheumatol 23:306–309, 2004.
50. Steen VD, Lanz JK Jr, Conte C, et al: Therapy for severe interstitial lung disease in systemic sclerosis. A retrospective study. Arthritis Rheum 37:1290–1296, 1994.
51. White B, Moore WC, Wigley FM, et al: Cyclophosphamide is associated with pulmonary function and survival benefit in patients with scleroderma and alveolitis. Ann Intern Med 132:947–954, 2000.
52. Tashkin DP, Elashoff R, Clements PJ, et al: Cyclophosphamide versus placebo in scleroderma lung disease. N Engl J Med 354:2655–2666, 2006.
53. Guillevin L, Cordier JF, Lhote F, et al: A prospective, multicenter, randomized trial comparing steroids and pulse cyclophosphamide versus steroids and oral cyclophosphamide in the treatment of generalized Wegener's granulomatosis. Arthritis Rheum 40:2187–2198, 1997.
54. Latsi PI, Wells AU: Evaluation and management of alveolitis and interstitial lung disease in scleroderma. Curr Opin Rheumatol 15:748–755, 2003.
55. Hoyles RK, Ellis RW, Wellsbury J, et al: A multicenter, prospective, randomized, double-blind, placebo-controlled trial of corticosteroids and intravenous cyclophosphamide followed by oral azathioprine for the treatment of pulmonary fibrosis in scleroderma. Arthritis Rheum 54:3962–3970, 2006.
56. Black CM, Silman AJ, Herrick AI, et al: Interferon-alpha does not improve outcome at one year in patients with diffuse cutaneous scleroderma: Results of a randomized, double-blind, placebo-controlled trial. Arthritis Rheum 42:299–305, 1999.
57. Steen VD, Medsger TA Jr: Case-control study of corticosteroids and other drugs that either precipitate or protect from the development of scleroderma renal crisis. Arthritis Rheum 41:1613–1619, 1998.
58. DeMarco PJ, Weisman MH, Seibold JR, et al: Predictors and outcomes of scleroderma renal crisis: The high-dose versus low-dose D-penicillamine in early diffuse systemic sclerosis trial. Arthritis Rheum 46:2983–2989, 2002.
59. Plastiras SC, Vlachoyiannopoulos PG, Tzelepis GE: Mycophenolate mofetil for interstitial lung disease in scleroderma. Rheumatology (Oxford) 45:1572, 2006.
60. Gerbino AJ, Goss CH, Molitor JA: Effect of mycophenolate mofetil on pulmonary function in scleroderma-associated interstitial lung disease. Chest 133:455–460, 2008.
61. Zamora AC, Wolters PJ, Collard HR, et al: Use of mycophenolate mofetil to treat scleroderma-associated interstitial lung disease. Respir Med 102:150–155, 2008.
62. Black CM, du Bois RM: Organ involvement: Pulmonary. *In* Clements PJ, Furst DE (eds): Systemic Sclerosis. Baltimore: Williams & Wilkins, 1996, pp 299–331.
63. Johnson SR, Swinton JR, Granton JT: Prognostic factors for survival in scleroderma associated pulmonary arterial hypertension. J Rheumatol 35:1584–1590, 2008.
63a. McLaughlin V, Humbert M, Coghlan G, et al: Pulmonary arterial hypertension: the most devastating vascular complication of systemic sclerosis. Rheumatology (Oxford) 48 Suppl 3:iii25–31, 2009.
64. Mukerjee D, St. George D, Knight C, et al: Echocardiography and pulmonary function as screening tests for pulmonary arterial hypertension in systemic sclerosis. Rheumatology (Oxford) 43:461–466, 2004.
65. Hsu VM, Moreyra AE, Wilson AC, et al: Assessment of pulmonary arterial hypertension in patients with systemic sclerosis: Comparison of noninvasive tests with results of right-heart catheterization. J Rheumatol 35:458–465, 2008.
66. Pignone A, Mori F, Pieri F, et al: Exercise Doppler echocardiography identifies preclinic asymptomatic pulmonary hypertension in systemic sclerosis. Ann N Y Acad Sci 1108:291–304, 2007.
67. Steen V, Chou M, Shanmugam V, et al: Exercise-induced pulmonary arterial hypertension in patients with systemic sclerosis. Chest 134:146–151, 2008.
68. Allanore Y, Borderie D, Avouac J, et al: High N-terminal pro-brain natriuretic peptide levels and low diffusing capacity for carbon monoxide as independent predictors of the occurrence of precapillary pulmonary arterial hypertension in patients with systemic sclerosis. Arthritis Rheum 58:284–291, 2008.
69. Choi HJ, Shin YK, Lee HJ, et al: The clinical significance of serum N-terminal pro-brain natriuretic peptide in systemic sclerosis patients. Clin Rheumatol 27:437–442, 2008.

70. Menon N, McAlpine L, Peacock AJ, Madhok R: The acute effects of prostacyclin on pulmonary hemodynamics in patients with pulmonary hypertension secondary to systemic sclerosis. Arthritis Rheum 41:466–469, 1998.
71. Badesch DB, McLaughlin VV, Delcroix M, et al: Prostanoid therapy for pulmonary arterial hypertension. J Am Coll Cardiol 43(12 Suppl S):56S–61S, 2004.
72. Oudiz RJ, Schilz RJ, Barst RJ, et al: Treprostinil, a prostacyclin analogue, in pulmonary arterial hypertension associated with connective tissue disease. Chest 126:420–427, 2004.
73. Olschewski H, Simonneau G, Galie N, et al: Inhaled iloprost for severe pulmonary hypertension. N Engl J Med 347:322–329, 2002.
74. Kuhn KP, Byrne DW, Arbogast PG, et al: Outcome in 91 consecutive patients with pulmonary arterial hypertension receiving epoprostenol. Am J Respir Crit Care Med 167:580–586, 2003.
75. Rubin LJ, Badesch DB, Barst RJ, et al: Bosentan therapy for pulmonary arterial hypertension. N Engl J Med 346:896–903, 2002.
76. Denton CP, Pope JE, Peter HH, et al: Long-term effects of bosentan on quality of life, survival, safety and tolerability in pulmonary arterial hypertension related to connective tissue diseases. Ann Rheum Dis 67:1222–1228, 2008.
77. Hayakawa I, Shirasaki F, Hirano T, et al: Successful treatment with sildenafil in systemic sclerosis patients with isolated pulmonary arterial hypertension: Two case reports. Rheumatol Int 26:270–273, 2006.
78. Galie N, Ghofrani HA, Torbicki A, et al: Sildenafil citrate therapy for pulmonary arterial hypertension. N Engl J Med 353:2148–2157, 2005.
79. Schermuly RT, Dony E, Ghofrani HA, et al: Reversal of experimental pulmonary hypertension by PDGF inhibition. J Clin Invest 115:2811–2821, 2005.
80. Arnett FC, Edworthy SM, Bloch DA, et al: The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 31:315–324, 1988.
81. Gabriel SE, Crowson CS, Kremers HM, et al: Survival in rheumatoid arthritis: A population-based analysis of trends over 40 years. Arthritis Rheum 48:54–58, 2003.
82. Sihvonen S, Korpela M, Laippala P, et al: Death rates and causes of death in patients with rheumatoid arthritis: A population-based study. Scand J Rheumatol 33:221–227, 2004.
83. Nepom GT: Major histocompatibility complex–directed susceptibility to rheumatoid arthritis. Adv Immunol 68:315–332, 1998.
84. Gladman DD, Anhorn KA: HLA and disease manifestations in rheumatoid arthritis—A Canadian experience. J Rheumatol 13:274–276, 1986.
85. Hyland RH, Gordon DA, Broder I, et al: A systematic controlled study of pulmonary abnormalities in rheumatoid arthritis. J Rheumatol 10:395–405, 1983.
86. Jurik AG, Davidsen D, Graudal H: Prevalence of pulmonary involvement in rheumatoid arthritis and its relationship to some characteristics of the patients. A radiological and clinical study. Scand J Rheumatol 11:217–224, 1982.
87. Shannon TM, Gale ME: Noncardiac manifestations of rheumatoid arthritis in the thorax. J Thorac Imaging 7:19–29, 1992.
88. Klareskog L, Stolt P, Lundberg K, et al: A new model for an etiology of rheumatoid arthritis: Smoking may trigger HLA-DR (shared epitope)–restricted immune reactions to autoantigens modified by citrullination. Arthritis Rheum 54:38–46, 2006.
89. Gilligan DM, O'Connor CM, Ward K, et al: Bronchoalveolar lavage in patients with mild and severe rheumatoid lung disease. Thorax 45:591–596, 1990.
90. Gochuico BR, Avila NA, Chow CK, et al: Progressive preclinical interstitial lung disease in rheumatoid arthritis. Arch Intern Med 168:159–166, 2008.
91. Scadding JG: The lungs in rheumatoid arthritis. Proc R Soc Med 62:227–238, 1969.
92. DeHoratius RJ, Abruzzo JL, Williams RC Jr: Immunofluorescent and immunologic studies of rheumatoid lung. Arch Intern Med 129:441–446, 1972.
93. Yoshinouchi T, Ohtsuki Y, Fujita J, et al: Nonspecific interstitial pneumonia pattern as pulmonary involvement of rheumatoid arthritis. Rheumatol Int 26:121–125, 2005.
94. Lee HK, Kim DS, Yoo B, et al: Histopathologic pattern and clinical features of rheumatoid arthritis–associated interstitial lung disease. Chest 127:2019–2027, 2005.
95. Rajasekaran A, Shovlin D, Saravanan V, et al: Interstitial lung disease in patients with rheumatoid arthritis: Comparison with cryptogenic fibrosing alveolitis over 5 years. J Rheumatol 33:1250–1263, 2006.
96. Park JH, Kim DS, Park IN, et al: Prognosis of fibrotic interstitial pneumonia: Idiopathic versus collagen vascular disease-related subtypes. Am J Respir Crit Care Med 175:705–711, 2007.
97. Cervantes-Perez P, Toro-Perez AH, Rodriguez-Jurado P: Pulmonary involvement in rheumatoid arthritis. JAMA 243:1715–1719, 1980.
98. Roschmann RA, Rothenberg RJ: Pulmonary fibrosis in rheumatoid arthritis: A review of clinical features and therapy. Semin Arthritis Rheum 16:174–185, 1987.
99. Walker WC, Wright V: Pulmonary lesions and rheumatoid arthritis. Medicine (Baltimore) 47:501–520, 1968.
100. Dawson JK, Fewins HE, Desmond J, et al: Fibrosing alveolitis in patients with rheumatoid arthritis as assessed by high resolution computed tomography, chest radiography, and pulmonary function tests. Thorax 56:622–627, 2001.
101. Biederer J, Schnabel A, Muhle C, et al: Correlation between HRCT findings, pulmonary function tests and bronchoalveolar lavage cytology in interstitial lung disease associated with rheumatoid arthritis. Eur Radiol 14:272–280, 2004.
102. Zrour SH, Touzi M, Bejia I, et al: Correlations between high-resolution computed tomography of the chest and clinical function in patients with rheumatoid arthritis. Prospective study in 75 patients. Joint Bone Spine 72:41–47, 2005.
103. Wells AU, Hansell DM, Rubens MB, et al: Fibrosing alveolitis in systemic sclerosis: Indices of lung function in relation to extent of disease on computed tomography. Arthritis Rheum 40:1229–1236, 1997.
104. Dawson JK, Fewins HE, Desmond J, et al: Predictors of progression of HRCT diagnosed fibrosing alveolitis in patients with rheumatoid arthritis. Ann Rheum Dis 61:517–521, 2002.
105. Wells AU, du Bois RM: Bronchiolitis in association with connective tissue disorders. Clin Chest Med 14:655–666, 1993.
106. Yousem SA, Colby TV, Carrington CB: Lung biopsy in rheumatoid arthritis. Am Rev Respir Dis 131:770–777, 1985.
107. Wolfe F, Schurle DR, Lin JJ, et al: Upper and lower airway disease in penicillamine treated patients with rheumatoid arthritis. J Rheumatol 10:406–410, 1983.
108. Sweatman MC, Markwick JR, Charles PJ, et al: Histocompatibility antigens in adult obliterative bronchiolitis with or without rheumatoid arthritis. Dis Markers 4:19–26, 1986.
109. Begin R, Masse S, Cantin A, et al: Airway disease in a subset of nonsmoking rheumatoid patients. Characterization of the disease and evidence for an autoimmune pathogenesis. Am J Med 72:743–750, 1982.
110. Geddes DM, Webley M, Emerson PA: Airways obstruction in rheumatoid arthritis. Ann Rheum Dis 38:222–225, 1979.
111. Andonopoulos AP, Constantopoulos SH, Drosos AA, Moutsopoulos HM: Pulmonary function of nonsmoking patients with rheumatoid arthritis in the presence and absence of secondary Sjögren's syndrome, a controlled study. Respiration 53:251–258, 1988.
112. Sassoon CS, McAlpine SW, Tashkin DP, et al: Small airways function in nonsmokers with rheumatoid arthritis. Arthritis Rheum 27:1218–1226, 1984.
113. Geddes DM, Corrin B, Brewerton DA, et al: Progressive airway obliteration in adults and its association with rheumatoid disease. Q J Med 46:427–444, 1977.
114. Yousem SA, Colby TV, Carrington CB: Follicular bronchitis/bronchiolitis. Hum Pathol 16:700–706, 1985.
115. Howling SJ, Hansell DM, Wells AU, et al: Follicular bronchiolitis: Thin-section CT and histologic findings. Radiology 212:637–642, 1999.
116. Despaux J, Polio JC, Toussirot E, et al: Rheumatoid arthritis and bronchiectasis. A retrospective study of fourteen cases. Rev Rhum Engl Ed 63:801–808, 1996.

117. Shadick NA, Fanta CH, Weinblatt ME, et al: Bronchiectasis. A late feature of severe rheumatoid arthritis. Medicine (Baltimore) 73:161–170, 1994.
118. Perez T, Remy-Jardin M, Cortet B: Airways involvement in rheumatoid arthritis: Clinical, functional, and HRCT findings. Am J Respir Crit Care Med 157:1658–1665, 1998.
119. Kelly CA: Rheumatoid arthritis: Classical rheumatoid lung disease. Baillieres Clin Rheumatol 7:1–16, 1993.
120. Fellbaum C, Domej W, Popper H: Rheumatoid arthritis with extensive lung lesions. Thorax 44:70–71, 1989.
121. Walker WC, Wright V: Rheumatoid pleuritis. Ann Rheum Dis 26:467–474, 1967.
122. Dodson WH, Hollingsworth JW: Pleural effusion in rheumatoid arthritis. Impaired transport of glucose. New Engl J Med 275:1337–1342, 1966.
123. Strohl KP, Feldman NT, Ingram RH Jr: Apical fibrobullous disease with rheumatoid arthritis. Chest 75:739–741, 1979.
124. Yue CC, Park CH, Kushner I: Apical fibrocavitary lesions of the lung in rheumatoid arthritis. Report of two cases and review of the literature. Am J Med 81:741–746, 1986.
125. Udayakumar N, Venkatesan S, Rajendiran C: Pulmonary hypertension in rheumatoid arthritis—Relation with the duration of the disease. Int J Cardiol 127:410–412, 2008.
126. Mutru O, Koota K, Isomaki H: Causes of death in autopsied RA patients. Scand J Rheumatol 5:239–240, 1976.
127. Koota K, Isomaki H, Mutru O: Death rate and causes of death in RA patients during a period of five years. Scand J Rheumatol 6:241–244, 1977.
128. Khurana R, Wolf R, Berney S, et al: Risk of development of lung cancer is increased in patients with rheumatoid arthritis: A large case control study in US veterans. J Rheumatol 35:1704–1708, 2008.
129. Alarcon GS, Kremer JM, Macaluso M, et al: Risk factors for methotrexate-induced lung injury in patients with rheumatoid arthritis. A multicenter, case-control study. Methotrexate-Lung Study Group. Ann Intern Med 127:356–364, 1997.
130. St. Clair EW, Rice JR, Snyderman R: Pneumonitis complicating low-dose methotrexate therapy in rheumatoid arthritis. Arch Intern Med 145:2035–2038, 1985.
131. Kremer JM, Alarcon GS, Weinblatt ME, et al: Clinical, laboratory, radiographic, and histopathologic features of methotrexate-associated lung injury in patients with rheumatoid arthritis: A multicenter study with literature review. Arthritis Rheum 40:1829–1837, 1997.
132. Salaffi F, Manganelli P, Carotti M, et al: Methotrexate-induced pneumonitis in patients with rheumatoid arthritis and psoriatic arthritis: Report of five cases and review of the literature. Clin Rheumatol 16:296–304, 1997.
133. Cannon GW: Methotrexate pulmonary toxicity. Rheum Dis Clin North Am 23:917–937, 1997.
134. Camus P, Piard F, Ashcroft T, et al: The lung in inflammatory bowel disease. Medicine (Baltimore) 72:151–183, 1993.
135. Tomioka R, King TE Jr: Gold-induced pulmonary disease: Clinical features, outcome, and differentiation from rheumatoid lung disease. Am J Respir Crit Care Med 155:1011–1020, 1997.
136. Mutlu GM, Mutlu EA, Bellmeyer A, Rubinstein I: Pulmonary adverse events of anti-tumor necrosis factor-alpha antibody therapy. Am J Med 119:639–646, 2006.
137. Askling J, Dixon W: The safety of anti-tumour necrosis factor therapy in rheumatoid arthritis. Curr Opin Rheumatol 20:138–144, 2008.
138. Balakrishnan C, Dasgupta B: Pulmonary adverse events with leflunomide—Myth or reality? Rheumatology (Oxford) 46:372, 2007 [author reply 373].
139. Ju JH, Kim SI, Lee JH, et al: Risk of interstitial lung disease associated with leflunomide treatment in Korean patients with rheumatoid arthritis. Arthritis Rheum 56:2094–2096, 2007.
139a. Kim EJ, Collard HR, King TE Jr: Rheumatoid arthritis-associated interstitial lung disease: the relevance of histopathologic and radiographic pattern. Chest 136:1397–1405, 2009.
140. Alasaly K, Muller N, Ostrow DN, et al: Cryptogenic organizing pneumonia. A report of 25 cases and a review of the literature. Medicine (Baltimore) 74:201–211, 1995.
141. Lee KS, Kullnig P, Hartman TE, Muller NL: Cryptogenic organizing pneumonia: CT findings in 43 patients. AJR Am J Roentgenol 162:543–546, 1994.
142. Wells AU: Computed tomographic imaging of bronchiolar disorders. Curr Opin Pulm Med 4:85–92, 1998.
143. Tan EM, Cohen AS, Fries JF, et al: The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 25:1271–1277, 1982.
144. Gladman D, Urowitz MB: Systemic lupus erythrmatosus: Clinical features. *In* Klippel JH, Diepee PA (eds): Rheumatology. London: Mosby, 1998, pp 7.1.1-7.1-18.
145. Reinersten JL, Klippel JH, Johnson AH, et al: Family studies of B lymphocyte alloantigens in systemic lupus erythematosus. J Rheumatol 9:253–262, 1982.
146. Haupt HM, Moore GW, Hutchins GM: The lung in systemic lupus erythematosus. Analysis of the pathologic changes in 120 patients. Am J Med 71:791–798, 1981.
147. Miller LR, Greenberg SD, McLarty JW: Lupus lung. Chest 88:265–269, 1985.
148. Gross M, Esterly JR, Earle RH: Pulmonary alterations in systemic lupus erythematosus. Am Rev Respir Dis 105:572–577, 1972.
149. Eisenberg H, Dubois EL, Sherwin RP, Balchum OJ: Diffuse interstitial lung disease in systemic lupus erythematosus. Ann Intern Med 79:37–45, 1973.
150. Bertoli AM, Vila LM, Apte M, et al: Systemic lupus erythematosus in a multiethnic US Cohort LUMINA XLVIII: Factors predictive of pulmonary damage. Lupus 16:410–417, 2007.
151. Weinrib L, Sharma OP, Quismorio FP Jr: A long-term study of interstitial lung disease in systemic lupus erythematosus. Semin Arthritis Rheum 20:48–56, 1990.
152. Orens JB, Martinez FJ, Lynch JP 3rd: Pleuropulmonary manifestations of systemic lupus erythematosus. Rheum Dis Clin North Am 20:159–193, 1994.
153. Gibson CJ, Edmonds JP, Hughes GR: Diaphragm function and lung involvement in systemic lupus erythematosus. Am J Med 63:926–932, 1977.
154. Laroche CM, Mulvey DA, Hawkins PN, et al: Diaphragm strength in the shrinking lung syndrome of systemic lupus erythematosus. Q J Med 71:429–439, 1989.
155. Oud KT, Bresser P, ten Berge RJ, Jonkers RE: The shrinking lung syndrome in systemic lupus erythematosus: Improvement with corticosteroid therapy. Lupus 14:959–963, 2005.
156. Badsha H, Teh CL, Kong KO, et al: Pulmonary hemorrhage in systemic lupus erythematosus. Semin Arthritis Rheum 33:414–421, 2004.
157. Nived O, Sturfelt G, Wollheim F: Systemic lupus erythematosus and infection: A controlled and prospective study including an epidemiological group. Q J Med 55:271–287, 1985.
158. Asherson RA, Hackett D, Gharavi AE, et al: Pulmonary hypertension in systemic lupus erythematosus: A report of three cases. J Rheumatol 13:416–420, 1986.
159. Simonson JS, Schiller NB, Petri M, Hellmann DB: Pulmonary hypertension in systemic lupus erythematosus. J Rheumatol 16:918–925, 1989.
160. Pope J: An update in pulmonary hypertension in systemic lupus erythematosus—Do we need to know about it? Lupus 17:274–277, 2008.
161. Alarcon-Segovia D, Deleze M, Oria CV, et al: Antiphospholipid antibodies and the antiphospholipid syndrome in systemic lupus erythematosus. A prospective analysis of 500 consecutive patients. Medicine (Baltimore) 68:353–365, 1989.
162. Paran D, Fireman E, Elkayam O: Pulmonary disease in systemic lupus erythematosus and the antiphospholpid syndrome. Autoimmun Rev 3:70–75, 2004.
163. Cervera R, Khamashta MA, Font J, et al: Systemic lupus erythematosus: Clinical and immunologic patterns of disease expression in a cohort of 1,000 patients. The European Working Party on Systemic Lupus Erythematosus. Medicine (Baltimore) 72:113–124, 1993.
164. Paran D, Fireman E, Levartovsky D, et al: Pulmonary dysfunction in systemic lupus erythematosus and anti-phospholipid syndrome patients. Scand J Rheumatol 36:285–290, 2007.

165. Robbins IM, Gaine SP, Schilz R, et al: Epoprostenol for treatment of pulmonary hypertension in patients with systemic lupus erythematosus. Chest 117:14–18, 2000.
166. Good JT Jr, King TE, Antony VB, Sahn SA: Lupus pleuritis. Clinical features and pleural fluid characteristics with special reference to pleural fluid antinuclear antibodies. Chest 84:714–718, 1983.
167. Naylor B: Cytological aspects of pleural, peritoneal and pericardial fluids from patients with systemic lupus erythematosus. Cytopathology 3:1–8, 1992.
168. Leechawengwong M, Berger HW, Sukumaran M: Diagnostic significance of antinuclear antibodies in pleural effusion. Mt Sinai J Med 46:137–139, 1979.
169. Kurumagawa T, Kobayashi H, Motoyoshi K: Potential involvement of subclinical Sjögren's syndrome in various lung diseases. Respirology 10:86–91, 2005.
170. Vitali C, Bombardieri S, Moutsopoulos HM, et al: Preliminary criteria for the classification of Sjögren's syndrome. Results of a prospective concerted action supported by the European Community. Arthritis Rheum 36:340–347, 1993.
171. Papathanasiou MP, Constantopoulos SH, Tsampoulas C, et al: Reappraisal of respiratory abnormalities in primary and secondary Sjögren's syndrome. A controlled study. Chest 90:370–374, 1986.
172. Gardiner P: Primary Sjögren's syndrome. Baillieres Clin Rheumatol 7:59–77, 1993.
173. Taouli B, Brauner MW, Mourey I, et al: Thin-section chest CT findings of primary Sjögren's syndrome: Correlation with pulmonary function. Eur Radiol 12:1504–1511, 2002.
174. Gardiner P, Ward C, Allison A, et al: Pleuropulmonary abnormalities in primary Sjögren's syndrome. J Rheumatol 20:831–837, 1993.
175. Ito I, Nagai S, Kitaichi M, et al: Pulmonary manifestations of primary Sjögren's syndrome: A clinical, radiologic, and pathologic study. Am J Respir Crit Care Med 171:632–638, 2005.
176. Davidson BK, Kelly CA, Griffiths ID: Ten year follow up of pulmonary function in patients with primary Sjögren's syndrome. Ann Rheum Dis 59:709–712, 2000.
177. Strimlan CV, Rosenow EC 3rd, Divertie MB, Harrison EG Jr: Pulmonary manifestations of Sjögren's syndrome. Chest 70:354–361, 1976.
178. Kassan SS, Thomas TL, Moutsopoulos HM, et al: Increased risk of lymphoma in sicca syndrome. Ann Intern Med 89:888–892, 1978.
179. Constantopoulos SH, Drosos AA, Maddison PJ, Moutsopoulos HM: Xerotrachea and interstitial lung disease in primary Sjögren's syndrome. Respiration 46:310–314, 1984.
180. La Corte R, Bajocchi G, Potena A, et al: Bronchial hyperreactivity in systemic sclerosis patients: Influence of associated Sjögren's syndrome. Ann Rheum Dis 54:636–639, 1995.
181. Dalavanga YA, Constantopoulos SH, Galanopoulou V, et al: Alveolitis correlates with clinical pulmonary involvement in primary Sjögren's syndrome. Chest 99:1394–1397, 1991.
182. Fairfax AJ, Haslam PL, Pavia D, et al: Pulmonary disorders associated with Sjögren's syndrome. Q J Med 50:279–295, 1981.
183. Bohan A, Peter J: Polymyositis and dermatomyositis (second of two parts). N Engl J Med 292:403–407, 1975.
184. Oddis CV, Medsger TA Jr: Inflammatory myopathies. Baillieres Clin Rheumatol 9:497–514, 1995.
185. Horiki T, Ichikawa Y, Moriuchi J, et al: HLA class II haplotypes associated with pulmonary interstitial lesions of polymyositis/dermatomyositis in Japanese patients. Tissue Antigens 59:25–30, 2002.
186. Douglas WW, Tazelaar HD, Hartman TE, et al: Polymyositis-dermatomyositis–associated interstitial lung disease. Am J Respir Crit Care Med 164:1182–1185, 2001.
187. Schnabel A, Reuter M, Biederer J, et al: Interstitial lung disease in polymyositis and dermatomyositis: Clinical course and response to treatment. Semin Arthritis Rheum 32:273–284, 2003.
188. Won Huh J, Soon Kim D, Keun Lee C, et al: Two distinct clinical types of interstitial lung disease associated with polymyositis-dermatomyositis. Respir Med 101:1761–1769, 2007.
189. Nobutoh T, Kohda M, Doi Y, Ueki H: An autopsy case of dermatomyositis with rapidly progressive diffuse alveolar damage. J Dermatol 25:32–36, 1998.
190. Fata F, Rathore R, Schiff C, Herzlich BC: Bronchiolitis obliterans organizing pneumonia as the first manifestation of polymyositis. South Med J 90:227–230, 1997.
191. Shinohara T, Hidaka T, Matsuki Y, et al: Rapidly progressive interstitial lung disease associated with dermatomyositis responding to intravenous cyclophosphamide pulse therapy. Intern Med 36:519–523, 1997.
192. Mino M, Noma S, Taguchi Y, et al: Pulmonary involvement in polymyositis and dermatomyositis: Sequential evaluation with CT. AJR Am J Roentgenol 169:83–87, 1997.
193. Schwarz MI, Sutarik JM, Nick JA, et al: Pulmonary capillaritis and diffuse alveolar hemorrhage. A primary manifestation of polymyositis. Am J Respir Crit Care Med 151:2037–2040, 1995.
194. Hayashi S, Tanaka M, Kobayashi H, et al: High-resolution computed tomography characterization of interstitial lung diseases in polymyositis/dermatomyositis. J Rheumatol 35:260–269, 2008.
195. Akira M, Hara H, Sakatani M: Interstitial lung disease in association with polymyositis-dermatomyositis: Long-term follow-up CT evaluation in seven patients. Radiology 210:333–338, 1999.
196. Chow WH, Gridley G, Mellemkjaer L, et al: Cancer risk following polymyositis and dermatomyositis: A nationwide cohort study in Denmark. Cancer Causes Control 6:9–13, 1995.
197. Komocsi A, Kumanovics G, Zibotics H, Czirjak L: Alveolitis may persist during treatment that sufficiently controls muscle inflammation in myositis. Rheumatol Int 20:113–118, 2001.
198. Targoff IN: Humoral immunity in polymyositis/dermatomyositis. J Invest Dermatol 100:116S–123S, 1993.
199. Kuroda T, Morikawa H, Satou T, et al: A case of dermatomyositis complicated with pneumomediastinum successfully treated with cyclosporin A. Clin Rheumatol 22:45–48, 2003.
200. Cavazzana I, Ceribelli A, Quinzanini M, et al: Prevalence and clinical associations of anti-Ku antibodies in systemic autoimmune diseases. Lupus 17:727–732, 2008.
201. Cottin V, Thivolet-Bejui F, Reynaud-Gaubert M, et al: Interstitial lung disease in amyopathic dermatomyositis, dermatomyositis and polymyositis. Eur Respir J 22:245–250, 2003.
202. Marie I, Dominique S, Rémy-Jardin M, et al: [Interstitial lung diseases in polymyositis and dermatomyositis] (French). Rev Med Interne 22:1083–1096, 2001.
203. Yamasaki Y, Yamada H, Yamasaki M, et al: Intravenous cyclophosphamide therapy for progressive interstitial pneumonia in patients with polymyositis/dermatomyositis. Rheumatology (Oxford) 46:124–130, 2007.
204. Miyake S, Ohtani Y, Sawada M, et al: Usefulness of cyclosporine A on rapidly progressive interstitial pneumonia in dermatomyositis. Sarcoidosis Vasc Diffuse Lung Dis 19:128–133, 2002.
204a. Bunch TW: Prednisone and azathioprine for polymyositis: long-term followup. Arthritis Rheum 24:45–48, 1981.
204b. Rowen AJ, Reichel J: Dermatomyositis with lung involvement, successfully treated with azathioprine. Respiration 44:143–146, 1983.
205. Amigues JM, Cantagrel A, Abbal M, Mazieres B: Comparative study of 4 diagnosis criteria sets for mixed connective tissue disease in patients with anti-RNP antibodies. Autoimmunity Group of the Hospitals of Toulouse. J Rheumatol 23:2055–2062, 1996.
206. Maddison PJ: Overlap syndromes and mixed connective tissue disease. Curr Opin Rheumatol 3:995–1000, 1991.
207. Gendi NS, Welsh KI, Van Venrooij WJ, et al: HLA type as a predictor of mixed connective tissue disease differentiation. Ten-year clinical and immunogenetic followup of 46 patients. Arthritis Rheum 38:259–266, 1995.
208. Prakash UB: Respiratory complications in mixed connective tissue disease. Clin Chest Med 19:733–746, ix, 1998.
209. Kozuka T, Johkoh T, Honda O, et al: Pulmonary involvement in mixed connective tissue disease: High-resolution CT findings in 41 patients. J Thorac Imaging 16:94–98, 2001.
210. Fagan KA, Badesch DB: Pulmonary hypertension associated with connective tissue disease. Prog Cardiovasc Dis 45:225–234, 2002.
211. Kinder BW, Collard HR, Koth L, et al: Idiopathic nonspecific interstitial pneumonia: Lung manifestation of undifferentiated connective tissue disease? Am J Respir Crit Care Med 176:691–697, 2007.

212. Zeuner M, Straub RH, Rauh G, et al: Relapsing polychondritis: Clinical and immunogenetic analysis of 62 patients. J Rheumatol 24:96–101, 1997.
213. Lang B, Rothenfusser A, Lanchbury JS, et al: Susceptibility to relapsing polychondritis is associated with HLA-DR4. Arthritis Rheum 36:660–664, 1993.
214. Lee-Chiong TL Jr: Pulmonary manifestations of ankylosing spondylitis and relapsing polychondritis. Clin Chest Med 19:747–757, ix, 1998.
215. Eng J, Sabanathan S: Airway complications in relapsing polychondritis. Ann Thorac Surg 51:686–692, 1991.
216. Lee KS, Ernst A, Trentham DE, et al: Relapsing polychondritis: Prevalence of expiratory CT airway abnormalities. Radiology 240:565–573, 2006.
217. McAdam LP, O'Hanlan MA, Bluestone R, Pearson CM: Relapsing polychondritis: Prospective study of 23 patients and a review of the literature. Medicine (Baltimore) 55:193–215, 1976.
218. Shah R, Sabanathan S, Mearns AJ, Featherstone H: Self-expanding tracheobronchial stents in the management of major airway problems. J Cardiovasc Surg (Torino) 36:343–348, 1995.
219. Sarodia BD, Dasgupta A, Mehta AC: Management of airway manifestations of relapsing polychondritis: Case reports and review of literature. Chest 116:1669–1675, 1999.
220. Gildea TR, Murthy SC, Sahoo D, et al: Performance of a self-expanding silicone stent in palliation of benign airway conditions. Chest 130:1419–1423, 2006.
221. Trentham DE, Le CH: Relapsing polychondritis. Ann Intern Med 129:114–122, 1998.
222. Yazici H, Yurdakul S, Hamuryudan V: Behçet's syndrome. *In* Klippel JH, Diepee PA (eds): Rheumatology, 2nd ed. London: Mosby, 1998, pp 7.26.1–7.26.6.
223. Criteria for diagnosis of Behçet's disease. International Study Group for Behçet's Disease. Lancet 335:1078–1080, 1990.
224. Uzun O, Akpolat T, Erkan L: Pulmonary vasculitis in Behçet disease: A cumulative analysis. Chest 127:2243–2253, 2005.
225. Erkan F, Gul A, Tasali E: Pulmonary manifestations of Behçet's disease. Thorax 56:572–578, 2001.
226. Raz I, Okon E, Chajek-Shaul T: Pulmonary manifestations in Behççet's syndrome. Chest 95:585–589, 1989.
227. Tunaci A, Berkmen YM, Gokmen E: Thoracic involvement in Behçet's disease: Pathologic, clinical, and imaging features. AJR Am J Roentgenol 164:51–56, 1995.
228. Ahn JM, Im JG, Ryoo JW, et al: Thoracic manifestations of Behçet syndrome: Radiographic and CT findings in nine patients. Radiology 194:199–203, 1995.
229. Ozer C, Duce MN, Ulubas B, et al: Inspiratory and expiratory HRCT findings in Behçet's disease and correlation with pulmonary function tests. Eur J Radiol 56:43–47, 2005.
230. Tuzun H, Besirli K, Sayin A, et al: Management of aneurysms in Behçet's syndrome: An analysis of 24 patients. Surgery 121:150–156, 1997.
231. Schlosstein L, Terasaki PI, Bluestone R, Pearson CM: High association of an HL-A antigen, W27, with ankylosing spondylitis. N Engl J Med 288:704–706, 1973.
232. Rosenow E, Strimlan CV, Muhm JR, Ferguson RH: Pleuropulmonary manifestations of ankylosing spondylitis. Mayo Clin Proc 52:641–649, 1977.
233. Casserly IP, Fenlon HM, Breatnach E, Sant SM: Lung findings on high-resolution computed tomography in idiopathic ankylosing spondylitis—Correlation with clinical findings, pulmonary function testing and plain radiography. Br J Rheumatol 36:677–682, 1997.
234. Kiris A, Ozgocmen S, Kocakoc E, et al: Lung findings on high resolution CT in early ankylosing spondylitis. Eur J Radiol 47:71–76, 2003.
235. Souza AS Jr, Muller NL, Marchiori E, et al: Pulmonary abnormalities in ankylosing spondylitis: Inspiratory and expiratory high-resolution CT findings in 17 patients. J Thorac Imaging 19:259–263, 2004.
236. Turetschek K, Ebner W, Fleischmann D, et al: Early pulmonary involvement in ankylosing spondylitis: Assessment with thin-section CT. Clin Radiol 55:632–636, 2000.
237. Baser S, Cubukcu S, Ozkurt S, et al: Pulmonary involvement starts in early stage ankylosing spondylitis. Scand J Rheumatol 35:325–327, 2006.
238. Jeandel P, Bonnet D, Chouc PY, et al: [Demonstration of subclinical pulmonary alveolitis in spondylarthropathies] (French). Rev Rhum Ed Fr 61:301–309, 1994.
239. Chakera TM, Howarth FH, Kendall MJ, et al: The chest radiograph in ankylosing spondylitis. Clin Radiol 26:455–459, 1975.
240. Davies D: Ankylosing spondylitis and lung fibrosis. Q J Med 41:395–417, 1972.
241. Hunninghake GW, Fauci AS: Pulmonary involvement in the collagen vascular diseases. Am Rev Respir Dis 119:471–503, 1979.
242. Wood JR, Bellamy D, Child AH, Citron KM: Pulmonary disease in patients with Marfan syndrome. Thorax 39:780–784, 1984.
243. Turner JA, Stanley NN: Fragile lung in the Marfan syndrome. Thorax 31:771–775, 1976.
244. Hall JR, Pyeritz RE, Dudgeon DL, Haller JA Jr: Pneumothorax in the Marfan syndrome: Prevalence and therapy. Ann Thorac Surg 37:500–504, 1984.
245. Dominguez R, Weisgrau RA, Santamaria M: Pulmonary hyperinflation and emphysema in infants with the Marfan syndrome. Pediatr Radiol 17:365–369, 1987.
246. Wanderman KL, Goldstein MS, Faber J: Cor pulmonale secondary to severe kyphoscoliosis in Marfan's syndrome (letter). Chest 67:250–251, 1975.
247. Cistulli PA, Sullivan CE: Sleep apnea in Marfan's syndrome. Increased upper airway collapsibility during sleep. Chest 108:631–635, 1995.

CHAPTER 59

SARCOIDOSIS

Wonder Drake, MD • Lee S. Newman, MD, MA

INTRODUCTION

BACKGROUND

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INTRODUCTION

Sarcoidosis is a multisystem, inflammatory disorder characterized by noncaseating granulomas that can infiltrate almost any organ but, most commonly, involves the lungs. Most often occurring in adulthood, sarcoidosis often presents with hilar lymphadenopathy, pulmonary infiltration, and eye and skin lesions. Because of its many and varied clinical manifestations and its worldwide prevalence, this disorder can mimic other inflammatory and infectious disorders. Major targets include the lungs, lymphatics, eyes, skin, liver, bone, heart, and neurologic system.[1] The American Thoracic Society criteria for the diagnosis of pulmonary sarcoidosis includes (1) the presence of a consistent clinical and radiographic picture; (2) the demonstration of noncaseating granulomas on biopsy; and (3) exclusion of other conditions that can produce granulomatous inflammation, including infections, autoimmune disorders, and inhalational diseases, as discussed later in the "Differential Diagnosis" section.[2]

BACKGROUND

Jonathan Hutchinson published the first description of sarcoidosis in 1877, reporting a patient who had developed multiple raised purple skin lesions over 2 years. He subsequently described several similar cases and suggested that they represented a distinct clinical entity. In 1899, Caesar Boeck reported a case of skin lesions similar to Hutchinson's and provided a name for this condition when he used the term "multiple benign sarkoid of the skin," referring to the histologic appearance that he thought resembled sarcoma. He subsequently published descriptions of similar pathology in multiple other organs, including lung and lymph nodes. The name *sarcoidosis* was derived from these descriptions.[1,2]

EPIDEMIOLOGY

Sarcoidosis occurs worldwide, with the highest incidence occurring in United States (among African Americans) and Sweden. The incidence of sarcoidosis in the Asian population appears to be lower than in white and black populations.[3] In most populations, there is a consistent predilection for adults aged 40 years or younger, peaking in 20- to 29-year old subjects. Another consistent observation across ethnic groups is a preponderance for affecting females more than males. However, there is some variation in the age-specific incidence of sarcoidosis across ethnic groups. For African Americans, the peak incidence occurs in the fourth decade of life; for Japanese, the male incidence rates peaked in the 20- to 34-year-old group. However, among women, the incidence appears biphasic, for example, among Japanese

and Scandinavian women, there is a second higher peak for those older than 50 years.[3] Disease can occur in children and the elderly as well. A recent study of childhood sarcoidosis among Danish children revealed that it carries a favorable prognosis, with complete resolution in approximately 75%, the majority recovering within 6 years of diagnosis.[4] The published rates likely underestimate the frequency of this disorder because many cases may go undiagnosed or be misdiagnosed.

Ethnic variation in clinical presentation is also observed among sarcoidosis subjects. The Japanese frequently present with ocular and cardiac involvement. An acute form of sarcoidosis, comprised of bilateral hilar lymphadenopathy, arthritis, and erythema nodosum (Löfgren's syndrome), is more common among Southern Europeans. African American sarcoidosis subjects are more likely to present with more frequent involvement of the eye, liver, bone marrow, extrathoracic lymph nodes, and skin other than erythema nodosum.[5]

ETIOLOGY AND PATHOGENESIS

The cause of sarcoidosis remains unknown. However, there is much evidence to support the hypothesis that the disease develops when a genetically susceptible individual is exposed to a specific environmental antigen.

Environment

Spatial and Temporal Clustering

A shared environmental exposure, or possibly person-to-person transmission, is suggested by spatial and temporal clustering of cases, reports of community outbreaks, and reports of work-related risk for health care workers and firefighters. Careful environmental investigation of new cases sometimes uncovers clusters of disease and may suggest sources of antigen exposures or exposures to known causes of granulomatous disease. For example, clusters of disease have been found among nurses and groups of firefighters.[6,7] A case-control study of a sarcoidosis cluster on the Isle of Man demonstrated that a significantly greater percentage of cases than controls reported previous contact with a sarcoidosis patient.[8] A multicenter case-control study of the etiology of sarcoidosis (A Case Control Etiologic Study of Sarcoidosis [ACCESS]) examined 706 case-control pairs.[9] The study recruited newly diagnosed, pathology-confirmed cases, excluded cases of possible tuberculosis or chronic beryllium disease, and used random-digit telephone dialing to recruit controls matched for age, gender, race, and ethnicity from 10 centers. Questionnaires were used to obtain information about previous occupational and environmental exposures, as well as family history of sarcoidosis. The study found weak but statistically significant associations for several occupational and environmental exposures, including those potentially related to microbial bioaerosols and pesticides. A previous case-control study had more specifically evaluated rural exposures as potential risk factors for sarcoidosis; the authors found, even in multivariable models, a significant and dose-dependent association existed between exposure to wood stoves or fireplaces and the development of sarcoidosis.[10] Still another case-control investigation enrolled African American individuals with sarcoidosis and collected detailed job histories from them and from sibling controls.[11] Several job titles and job exposures were found to be associated, both positively and negatively, with disease risk. The authors concluded that work involving exposure to metals or high humidity may place individuals at increased risk of developing sarcoidosis but that identification of specific relevant exposures was quite difficult in the face of complex occupational exposures.[11]

Infectious Agents

The observation of transmissibility infers that infectious agents may have a role in sarcoidosis pathogenesis. Among the putative microorganisms, mycobacteria and proprionibacteria remain leading candidates. More recent studies from independent laboratories have demonstrated the presence of mycobacterial nucleic acids and proteins in sarcoidosis granulomas. One study used a limited proteomics approach to detect tissue antigens that were poorly soluble in neutral detergent and resistant to protease digestion. Using matrix-assisted laser desorption ionization–time-of-flight mass spectrometry (MALDI-TOF), they identified 16 of 75 peptide sequences that corresponded to *Mycobacterium tuberculosis* katG and one potential match for *M. tuberculosis* topoisomerase. They also found antimkatG immunoglobulin G (IgG) in the sera of 12 of 25 (48%) sarcoidosis subjects compared with 0 of 11 purified protein derivative (PPD)–healthy controls and four of 10 (40%) PPD+ controls.[12] In addition, polymerase chain reaction (PCR) analysis for mycobacterial nucleic acids have revealed the presence of conserved genes such as 16S rRNA, rpoB, and superoxide dismutase A.[13,14] A meta-analysis of studies from 1980 to 2000 that evaluated the presence of mycobacteria using molecular techniques in biologic samples found an overall positive association for the presence of mycobacterial nucleic acids within sarcoidosis granulomas.[15] The detection of T helper 1 (Th1) cellular immune responses to mycobacterial virulence factors in peripheral blood mononuclear cells and bronchoalveolar lavage (BAL) has been reported.[16,17] It has been shown that molecular analysis of sarcoidosis granulomas can identify microbial proteins that induce systemic Th1 immune responses in the same sarcoidosis subjects.[14]

Likewise, interesting data involving Japanese sarcoidosis subjects have suggested an association with *Proprionibacterium* species. It has been observed that *P. acnes* can be frequently isolated from patients with sarcoidosis.[18] Ishige and coworkers[19] reported that 15 of 15 sarcoidosis tissue samples were positive for propionibacterial (*P. acnes* or *P. granulosum*) rRNA by PCR analysis, compared with only 3 patients positive for mycobacterial DNA; conversely, 2 of 15 tissue samples from patients with tuberculosis were positive for propionibacteria and 15 of 15 were positive for mycobacteria. These results

were extended in a study involving 259 patients from five centers from Japan, Italy, Germany, and England.[20] Propionibacterial DNA was detected in all but 2 of 108 sarcoidosis lymph node samples compared with *M. tuberculosis* DNA that was found in 0% to 9% of these samples.[20] Of note, propionibacterial DNA was detected in 0% to 60% of *M. tuberculosis* or control samples. A study from an independent laboratory in Greece reported the presence of *Mycobacterium* and *Propionibacterium* nucleic acids in sarcoidosis specimens from Greece.[21] A study of successful culture and PCR analysis for *Proprionibacterium* species from lung tissues and lymph nodes from subjects with and without sarcoidosis suggested that *P. acnes* is a common commensal in peripheral lung tissues and mediastinal lymph nodes.[22]

Immunology

Autoantigens

In addition to infectious agents, autoantigens have been proposed to have a role in sarcoidosis pathogenesis. A recent report described isolation of common autoantigens from sarcoidosis BAL T cells of DRB1*0301-positive patients. From the BAL cells, human leukocyte antigen (HLA)-DR molecules were affinity purified and bound peptides acid eluted. Subsequently, peptides were separated by reversed-phase high-power liquid chromatography and analyzed by liquid chromatography mass spectrometry. Antigen, previously associated with autoimmune disease, such as vimentin and adenosine triphosphatase (ATP) synthase were identified.[23] The presence of antiendothelial cell antibodies has been reported among sarcoidosis subjects. The quantity of antibody appeared to correlate with disease severity and the need for immunosuppressive therapy.[24]

Immune Response

Although the etiology of sarcoidosis is not known, significant insight into sarcoidosis pathogenesis has been achieved through investigation of the sarcoidosis immune response. The core of sarcoidosis immunopathogenesis is the presentation of antigen(s) by host macrophages in the context of major histocompatibility complex (MHC) class II alleles, which are then recognized by antigen-specific $CD4^+$ T cells.

Sarcoidosis is mediated primarily through $CD4^+$ Th cells and cells derived from the mononuclear phagocytes.[25] $CD4^+$ T lymphocytes spontaneously proliferate, releasing interleukin-2 (IL-2) and interferon-γ (IFN-γ) in vitro. The IL-2 stimulates further T-lymphocyte proliferation and chemotaxis, recruiting more T lymphocytes to the affected site. IFN-γ amplifies the immune response through its effects on multiple target cells. The release of inflammatory cytokines serves to recruit additional peripheral blood monocytes to the affected organ, where they differentiate into exudate macrophages that show enhanced antigen-presenting capacity and release tumor necrosis factor-α (TNF-α) and IL-1β, both of which promote granuloma formation. These cells accumulate within the affected tissue, where they become increasingly organized, and form noncaseating granulomas. This infiltrative process is thought to be mediated primarily by $CD4^+$ T lymphocytes and mononuclear phagocytes, although other inflammatory cells (e.g., mast cells, fibroblasts) as well as epithelial and endothelial cells contribute to the nonspecific inflammatory response, leading to increased tissue permeability and cell migration. Because of chemoattractant signals, an elevated lymphocyte count and a marked increase in the $CD4^+$/$CD8^+$ T-lymphocyte ratio is observed in the affected organs of patients with active sarcoidosis. Several reviews describe in detail the current state of knowledge on the immune and inflammatory events.[26–28]

The recruitment of mononuclear cells in sarcoidosis is enhanced by the production of chemokines, including RANTES (regulated on activation, normal T cell expressed and secreted), monocyte chemoattractant protein-1, macrophage inflammatory protein-1α, and IL-8, all released by alveolar macrophages.[29] In addition, there is increased expression of adhesion molecules, such as intercellular adhesion molecule-1, vascular cell adhesion molecule-1, and the selectins, which promote cell binding.[30–34] Effector cells such as dendritic cells and macrophages function by presenting antigen to T cells and by producing proinflammatory cytokines, such as IL-12 and IL-15. IL-12 induces the differentiation of naive $CD4^+$ T lymphocytes into Th1 cells and promotes the release of IFN-γ. Th1 cells in sarcoidosis are antigen-activated $CD4^+$ T lymphocytes and produce IFN-γ and IL-2, resulting in a delayed-type hypersensitivity immune response. IL-15 acts synergistically with IL-2 and TNF-α to stimulate T-lymphocyte proliferation.

Sarcoidosis antigen–specific T lymphocytes generated during the initial host response play a central role in mediating the subsequent inflammatory events within the lung. Once naive T lymphocytes are activated, they undergo clonal expansion and differentiation into effector and memory T lymphocytes. In sarcoidosis, most of the T lymphocytes appear to have been previously stimulated, likely in regional lymph nodes, and to have migrated back to the affected organ.[35] Studies of the T-lymphocyte antigen receptor (TCR) repertoire in sarcoidosis demonstrate that the disorder is initiated by an antigen-specific immune response, based on observed oligoclonal expansion of T-lymphocyte subsets bearing particular, restricted α/β TCRs. Lymphocytes bearing γ/δ TCRs are likely to play some supporting role in the pathogenesis of this disorder, although the body of evidence most strongly supports the importance of T cells that bear particular α/β TCRs on their surface.[35,36]

In light of potential immunotherapeutic advances, it is noteworthy that TNF-α up-regulates endothelial cell adhesion molecules involved in leukocyte binding, stimulates T-lymphocyte release of IFN-γ, and enhances T-lymphocyte proliferation, among many other potential roles in inflammation. IL-1β may be needed in granuloma formation because it stimulates exudate macrophage production of IL-8 and granulocyte-macrophage colony-

stimulating factor, which, in turn, promotes monocyte differentiation and resultant macrophage proliferation. The net result is an amplification loop involving antigen recognition, proinflammatory cytokine release, cell activation, recruitment, and granuloma formation. Pathogenic aspects of granuloma formation and maintenance in sarcoidosis, as compared with other granulomatous disorders, have been the subject of recent reviews.[37,38]

Fibrosis

The progression from granulomatous inflammation to increasing amounts of fibrosis portends a poor prognosis. Factors leading from granuloma to fibrosis are poorly understood, but probably involve changes in local cytokine production toward a Th2 cell pattern (IL-4, IL-5) and increases in growth factor expression, including transforming growth factor-β (TGF-β), basic fibroblast growth factor, and insulin-like growth factor-1.[39]

Anergy

Many investigators have noted the presence of an immune paradox within sarcoidosis subjects: intense immune responses in affected organs, yet a state of peripheral anergy indicated by suppression of immune responses to common antigens such as tetanus, *Candida*, and PPD.[40] Some investigations have linked this observation of T cell anergy to T regulatory cell activity. Naturally occurring regulatory T cells are capable of suppressing proliferation and cytokine production of activated T cells via cell-cell contact. One study was able to demonstrate an accumulation of T regulatory cells in sarcoidosis BAL fluid, granulomas, and the peripheral blood of subjects with active disease. The sarcoid T regulatory cells were unable to completely down-regulate the production of inflammatory cytokines associated with granuloma formation, such as TNF-α, but did exhibit strong antiproliferative activity in the systemic circulation, which was felt to induce the observed anergic state seen in some sarcoidosis patients.[41] Another recent study identified the diminished systemic myeloid dendritic cell function as a contributor to anergy among sarcoidosis subjects. This diminished function also correlated the clinical pulmonary severity as determined by chest radiographs.[42]

Genetics

Familial Clustering

The observation of familial clustering of sarcoidosis cases, an increased incidence among monozygotic twins compared with non-twin siblings, as well as variations in disease susceptibility by race led to investigations of the role of genetics in sarcoidosis immunopathogenesis. Although the variation in incidence, severity, and manifestations of disease among different racial and ethnic groups may be consistent with either an environmental or a genetic contribution, observations of familial clustering of disease and the presence of disease two to four times more commonly in monozygotic than in dizygotic twins clearly demonstrate the importance of genetic factors. Previous studies have shown that up to 19% of affected African American families and 5% of white families have more than one member affected.[43,44] Results of ACCESS further support these observations. An analysis of nearly 11,000 first-degree and over 17,000 second-degree relatives of the 706 cases and controls revealed an overall adjusted familial relative risk of developing sarcoidosis of 4.7 (95% confidence interval, 2.3–9.7). Investigations of German families with more than one affected member similarly support a genetic contribution to disease development. Specifically, evaluations of the distribution of HLA and angiotensin-converting enzyme (ACE) polymorphic alleles in these families suggest an excess of specific alleles among affected first-degree relatives.[45–47] Given these observations, it is likely that multiple genes, rather than a single gene, account for the genetic predisposition to disease.

HLA Class II Associations

A number of chronic inflammatory diseases are associated with genes along the MHC class II region. Sarcoidosis is no exception. ACCESS enrolled biopsy-confirmed cases (736 total) from 10 centers in the United States, and performed high-resolution typing to define HLA class II associations with sarcoidosis. Of 474 matched cases and controls (948 total samples), the *HLA-DRB1* alleles were differentially distributed ($P < .0001$). The *HLA-DRB1*1101* allele was associated with sarcoidosis in blacks and whites ($P < .01$). In addition, there was a population-attributable risk of 16% in blacks and 9% in whites.[48] In contrast, *HLA-DQB1*0201* is associated with a good prognosis in African Americans as well as among British and Dutch patients.[49,50] Another analysis found that possession of the allele *DQB1*0602* has been associated with a poor outcome among African American and Dutch sarcoidosis patients.[51,52] This fact, along with HLA associations that are limited to clinical subsets of sarcoidosis, suggests that HLA phenotype is, at best, a modifier of disease susceptibility in a larger genetic, environmental, and immunologic context. Nonetheless, analysis of HLA associations may eventually deliver insights into the etiologic factors driving sarcoidosis or provide tools for prognostication.[53]

Of note, a body of work from Sweden in patients with Löfgren's syndrome and with acute, remitting sarcoidosis demonstrated a strong association between a lung-restricted expansion of Vα2.3 $CD4^+$ T cells and the expression of one of two specific antigen-presenting molecules (HLA-DRB3*0101, HLA-DRB3*0301) discussed earlier.[54] These data suggest that the combination of a specific T-cell antigen receptor and a particular HLA antigen presentation molecule interacts with the putative sarcoidosis antigen to trigger this acute form of disease. Genes such as Toll-like receptor 4, BTNL2, TGF-β, and annexin A11 have been shown to have associated with the clinical course of sarcoidosis patients.[55–59]

Investigation of other candidate genes in the MHC region has also yielded significant associations. Trans-

porter of antigenic peptide (TAP)-1 and TAP-2 are transporters critical in the processing of antigen prior to presentation through MHC class I, although some data suggest that they may play a role in delivery of antigen to the MHC class II complex as well. Evaluation of TAP-1 and TAP-2 polymorphisms in British and Polish sarcoidosis patients and controls revealed associations in each ethnic group of specific but distinct TAP-2 alleles with disease.[60] Similarly, specific polymorphic alleles in the TNF promoter have been associated with specific disease phenotypes in some studies.

A study has demonstrated a significantly increased frequency of the less common allele of the TNF-308 promoter polymorphism in patients with Löfgren's syndrome.[61] This allele has also been found in unexpectedly high frequencies in patients with cardiac sarcoidosis.[62] However, in two other studies, including one using a subpopulation from the ACCESS study, no difference was found in the TNF promoter-308 allele frequencies between cases and controls.[63,64] Investigation of the TNF-857 polymorphism in a British and Dutch population demonstrated an association between the less common -857T allele and sarcoidosis.[65] Taken together, these results support the existence of specific genetic variants, or more likely combinations of variants, within the MHC locus on chromosome 6 that contribute significantly to sarcoidosis disease risk.

Other Candidate Genes

There has also been evaluation of numerous genes outside of the MHC region with regard to their potential role in sarcoidosis susceptibility. Studies of many of these candidate genes have yielded negative or conflicting results. Of note among these is the ACE gene, selected because of the observed elevations in ACE levels in some sarcoidosis patients. This gene contains a polymorphism characterized by either the presence or the absence of a particular (287-base pair) fragment within the gene. Most studies have found no association of this polymorphism with sarcoidosis. However, one case-control study in African American subjects determined that homozygosity (the absence of this fragment in both copies of the gene) was associated with sarcoidosis susceptibility, particularly in cases with a family history of sarcoidosis.[66]

Several studies have found associations between sarcoidosis and specific alleles of polymorphisms in the IL-1α, the complement receptor 1, and various C-C chemokine receptor genes. The latter are of particular interest, as studies in three distinct populations (Japanese, Czech, and Dutch) have identified both strong positive and negative associations between specific polymorphic alleles and sarcoidosis.[67–69] Spagnolo and colleagues[69] evaluated haplotypes of four polymorphisms in the C-C chemokine receptor 2 gene in a Dutch population. They determined that haplotype 2 (A at nucleotide position 6752, A at 3000, T at 3547, and T at 4385) was strongly associated with Löfgren's syndrome, even after adjusting for other known risk factors for this sarcoidosis variant, such as HLA haplotype and female sex.

CLINICAL PRESENTATION

The clinical presentation of sarcoidosis ranges from an incidental chest radiographic finding in an asymptomatic patient to chronic progressive organ dysfunction. Usually, the disease appears between the ages of 20 and 50; however, both childhood and geriatric cases occur with some regularity. The vast majority of patients (~90%) have pulmonary involvement. However, sarcoidosis may affect any organ and, therefore, may present with symptoms referable to any organ. Patients may also present with nonspecific constitutional symptoms, including fatigue, fever, anorexia, and weight loss.

Acute Sarcoidosis

A distinct subgroup of sarcoidosis patients is characterized by an acute presentation, classically with Löfgren's syndrome. This syndrome, initially described by Sven Löfgren in 1946, is defined by acute erythema nodosum with bilateral hilar lymphadenopathy, fever, and polyarthritis. Symptoms are typically abrupt in onset and have a transient course. A vesicular or maculopapular rash, acute iritis, conjunctivitis, and Bell's palsy may also be features of acute disease. Chest radiographs typically are normal or show significant hilar and mediastinal lymphadenopathy, without pulmonary infiltrates. Arrhythmias may occur due to acute granulomatous cardiac involvement. In general, acute disease has a higher probability of spontaneous resolution. Although relapse may occur, it is thought to be less common than in those patients with a more chronic presentation. Prognosis of patients with an acute onset of sarcoidosis is generally good.

Chronic Sarcoidosis

Another subgroup of patients, often characterized by a more gradual, insidious onset, is more likely to develop chronic disease. Other risk factors for chronic disease include the presence of lupus pernio, which is a persistent, disfiguring, violaceous rash over the nose, cheeks, and ears, and the presence of multiorgan involvement at the time of diagnosis. Chronic eye involvement includes chronic uveitis, cataracts, glaucoma, or keratoconjunctivitis sicca, which can be confused with Sjögren's syndrome. Bone involvement is also much more common in chronic than acute cases, as are pulmonary infiltrates, nephrocalcinosis, and cor pulmonale. Persistence of disease and recurrence after treatment are common in the chronic form.

CLINICAL FEATURES AND DIAGNOSIS

Pulmonary Sarcoidosis

The lung is the most commonly involved organ in sarcoidosis, with physiologic or radiographic abnormalities, or both, demonstrable in more than 90% of patients.[1]

Symptoms and physical examination findings are nonspecific. Patients may present with cough, shortness of breath, and/or chest pain with crackles, wheezing, or a normal lung examination. Lung physiology is similarly nonspecific. Patients may have normal lung function, even with radiographic abnormalities, or may demonstrate restriction, obstruction, abnormal gas exchange, or a combination of these. Some studies report that the most frequent abnormalities are in the vital capacity and diffusing capacity, suggesting restrictive physiology; however, at least one study of newly diagnosed patients found airflow limitation to be the most common defect.[70] Airflow limitation may be due to endobronchial involvement, which can result in significant local stenosis. In general, measures of gas exchange provide greater sensitivity for sarcoidosis lung impairment and response to treatment than do measures of lung volume and airflow.

The radiologic patterns in sarcoidosis are classically described by the Scadding staging system, which is based on the chest radiograph. However, this staging system is increasingly being supplanted by use of imaging tools that have greater sensitivity, such as spiral/thin-section computed tomography (CT). The chest radiographic stages (0-IV) do not correspond to the chronologic progression of disease, but do correlate with likelihood of future radiographic and symptomatic disease resolution. A normal chest radiograph, or stage 0 disease, is seen in 5% to 10% of patients at presentation. Of note, in literature comparing chest radiographic to CT findings in sarcoidosis, up to one half of patients with stage 0 disease have pulmonary parenchymal abnormalities on CT scan.[71,72] In addition, 20% to 30% of these patients have physiologic abnormalities.[73] This group has a low likelihood of disease progression. Stage I disease (Fig. 59-1) is characterized by bilateral hilar and mediastinal lymphadenopathy, classically in the hila, right paratracheal region, and aortopulmonary window. Although the lungs appear normal radiographically in stage I disease, the majority of these patients will have diagnostic findings on transbronchial biopsies. Stage I disease is the most common radiographic presentation, and the majority (55%–90%) of these patients will demonstrate spontaneous resolution.[2] On CT scanning, stage I patients may also demonstrate adenopathy at less typical sites, such as the anterior and posterior mediastinum or axilla, as well as lymph node calcification.[72] A stage II radiograph reveals bilateral hilar or mediastinal adenopathy, or both, as well as pulmonary opacities (Fig. 59-2). Only 40% to 70% of these patients will experience spontaneous remission.[2] The parenchymal abnormalities may be nodular, reticular, or ground-glass and tend to occur in the middle and upper lung zones. In these patients, a classic CT appearance includes 2- to 10-mm nodules in a perilymphatic distribution around the hila, along bronchovascular bundles, and in the subpleural region. Nodular coalescence may occur. A stage III radiograph (Fig. 59-3) also shows parenchymal abnormalities and an absence of hilar or mediastinal lymphadenopathy.[72] Presentation with stage III is associated with only a 10% to 20% likelihood of spontaneous resolution. Finally, a stage IV radiograph demonstrates fibrosis, seen predominantly in the middle and upper lung zones, and is often associated with conglomerate mass formation, upper lobe volume loss, hilar retraction, peripheral bullae, and cystic lesions (Figs. 59-4 and 59-5). Once fibrosis is evident, spontaneous resolution does not occur.

A feared complication in patients with stage IV disease who develop cystic lesions is *Aspergilloma*. Symptoms may include a change in cough and sputum production, accelerated dyspnea, and especially hemoptysis. Imaging studies usually show cavitation, masses, or classic mycetomas with a mass within an increasing-sized cavity.

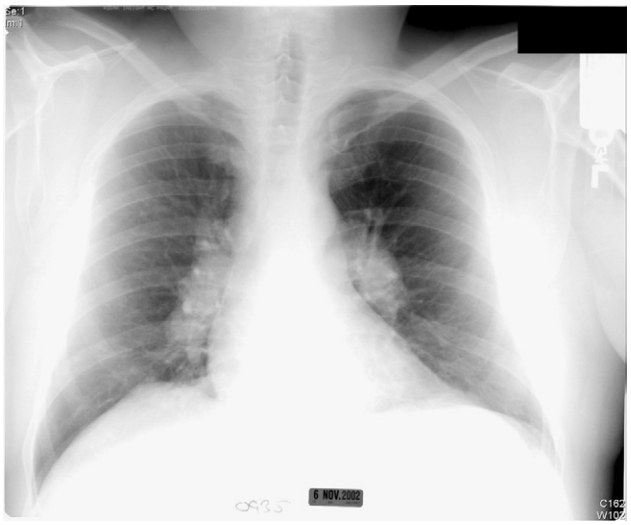

FIGURE 59-1 ■ Posteroanterior chest radiograph of stage I sarcoidosis. Important features include prominent hilar lymphadenopathy and normal appearing lungs.

FIGURE 59-2 ■ Posteroanterior chest radiograph of stage II sarcoidosis. Relevant findings include bilateral hilar lymphadenopathy and bilateral reticular and nodular interstitial infiltrates.

FIGURE 59-3 ■ Posteroanterior chest radiograph of stage III sarcoidosis. Characteristic findings include reticular and nodular interstitial infiltrates with an upper lung predominance and the absence of lymphadenopathy.

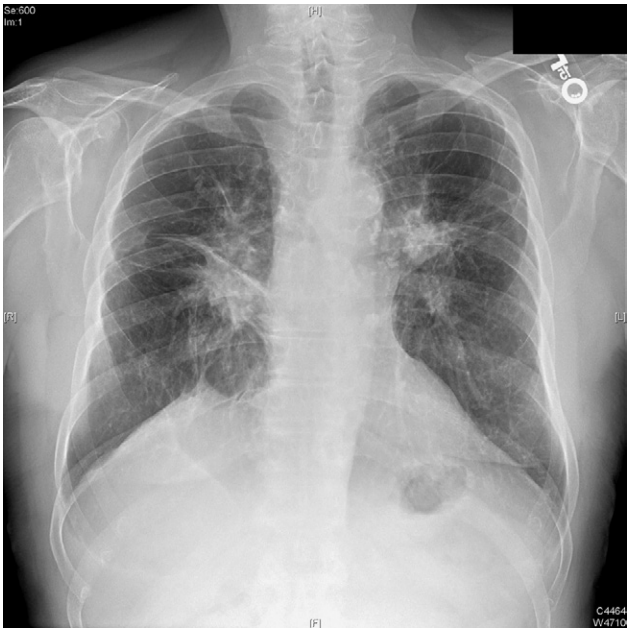

FIGURE 59-4 ■ Posteroanterior chest radiograph of stage IV sarcoidosis. This image demonstrates conglomerate mass formation, upper lobe volume loss, and hilar retraction.

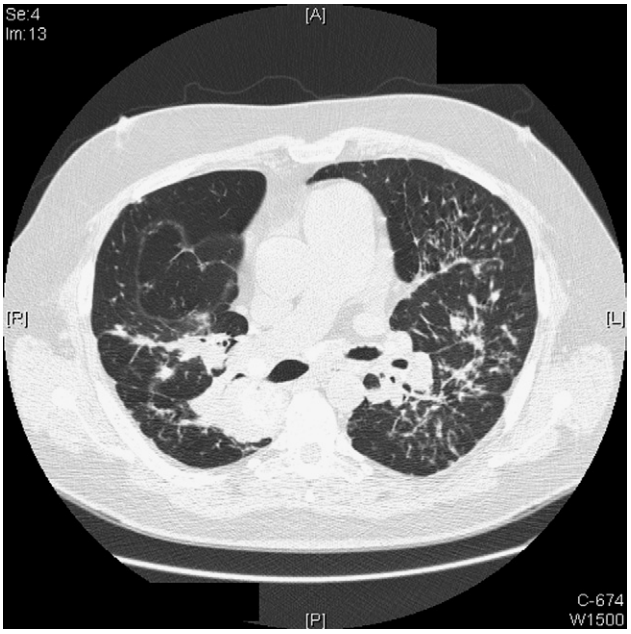

FIGURE 59-5 ■ High-resolution computed tomography scan of a patient with stage IV sarcoidosis demonstrates bilateral central fibrotic (conglomerate) masses with extensive central calcification, as well as parenchymal nodular abnormalities and septal thickening.

Diagnosis may be suggested by sputum cultures positive for fungi; skin tests for *Aspergillus* may be falsely negative due to the anergy.

Endobronchial involvement is another common presentation of pulmonary sarcoidosis. In one study, nearly half of all endobronchial biopsies demonstrated granulomatous inflammation.[74] In this group of 62 patients, positive endobronchial biopsies were associated with more progressive disease. In another study of patients with documented endobronchial disease, up to 10% had stenoses significant enough to result in an asthma-like syndrome, with airflow limitation, localized wheezing, and abnormal gas exchange.[75] Patients with endobronchial involvement have intractable cough. Airway obstruction may also result from bronchial distortion due to scarring in stage IV disease.[72]

Other pulmonary manifestations include various forms of pleural disease, including pleural effusion, pleural thickening, pleural nodules, pneumothorax, and chylothorax. Prevalence estimates for pleural involvement vary widely, depending on definition and method of assessment, from less than 1% to 96%. A review of the literature identified 145 biopsy-proven cases of pleural involvement.[76] Pleural disease was observed in all stages of disease (although radiographic stage was not always reported). The age range for all forms of pleural disease was 30 to 50 years, with an even distribution between men and women. In the majority of cases (>80%), the pleural involvement was unilateral, with the right side affected more often than the left (53% vs. 29%).[76] Pleural effusions should be diagnosed as being due to sarcoidosis only after careful exclusion of other etiologies, because one series reported that up to 40% of effusions in sarcoidosis patients may be due to other diagnoses, including reported cases of tuberculous effusion and mesothelioma.[77,78] Most of the effusions are small with lymphocytic exudates, although several eosinophilic effusions have been reported. Effusions have been reported to resolve spontaneously as well as with steroid therapy. Pleural thickening may be the most common sarcoid-related pleural abnormality, with CT studies reporting a prevalence of 11% to 71%.[76] High-resolution

CT has enhanced the detection of pleural disease, especially for pleural nodules, which have been reported in 22% to 76% of patients.[76]

Pneumothorax is a rare complication, and the relationship of the pneumothoraces to disease remains unclear. Some authors postulate that subpleural blebs (e.g., in advanced fibrocystic disease) or necrosis of subpleural granulomas cause the pneumothorax, whereas others have suggested that the occurrence is coincidental. The role of corticosteroids in treating this complication is similarly unclear.[76]

Chylothorax has also been reported in nine cases, with three of these confirming the presence of lymphadenopathy or adhesions obstructing the thoracic duct.[76]

Another rare form of pulmonary involvement with sarcoidosis that deserves special mention is *necrotizing sarcoid granulomatosis*. Liebow[79] first described this entity in 1973 in a publication that defined five idiopathic forms of pulmonary angiitis and granulomatosis. These were Wegener's granulomatosis, limited Wegener's disease, lymphomatoid granulomatosis, bronchocentric granulomatosis, and necrotizing sarcoid granulomatosis. Numerous case reports and case series have since documented the existence of this distinct entity. Patients may be asymptomatic at presentation or may have systemic symptoms, such as fever, malaise, fatigue, and weight loss; chest symptoms such as cough, chest pain, and dyspnea; or symptoms related to sites of extrathoracic involvement such as the eye or central nervous system. The typical radiographic appearance consists of solitary or multiple pulmonary nodules that often necrose and cavitate. Associated parenchymal opacification has also been described. These abnormalities are found in a distribution similar to that of sarcoidosis, subpleurally and along bronchovascular bundles, and may also be associated with lymphadenopathy. Necrotizing sarcoid granulomatosis is distinguished from sarcoidosis by the presence of cavitation on radiographic studies and the presence of necrosis and granulomatous vasculitis on histopathology, as described later. Typically the clinical course is benign and steroid-responsive; however, individual cases with severe extrathoracic involvement and initial critical illness have also been reported.[37,80]

The presence of bilateral hilar or mediastinal adenopathy (or both) in the absence of other symptoms or in the context of other features of Löfgren's syndrome is often adequate for a presumptive diagnosis of sarcoidosis. However, definitive diagnosis of intrathoracic involvement requires biopsy. It is generally recommended that patients with sarcoidosis have tissue confirmation of their diagnosis, especially if their disease is persistent or fails to fit conventional clinical patterns of multiorgan involvement, or if immunosuppressive treatment is being considered. The procedure of choice in most cases is transbronchial biopsy, which yields a diagnosis in 40% to 90% of procedures, depending on operator experience, the number of biopsies taken, and the Scadding stage.[2] Based on our clinical experience, a minimum of six good transbronchial biopsies are needed to maximize the yield from this procedure.[81]

Real-time endobronchial ultrasound (EBUS)–guided transbronchial needle aspiration (TBNA) has reported a sensitivity of approximately 90% in the diagnosis of sarcoidosis.[82] Other findings on bronchoscopy that support a diagnosis of sarcoidosis but are not diagnostic include BAL lymphocytosis (>10% lymphocytes) and an elevated CD4/CD8 ratio in the BAL fluid (>2:1).[83,84] These BAL criteria are rarely used in clinical practice. They are influenced by whether or not the patient has recently smoked (proportionately increasing the percentage of macrophages), and by the immunosuppressive treatment the patient has received (which can reduce the percentage of lymphocytes). Other supportive data may include an elevated serum ACE level, a positive gallium scan, or the presence of anergy.

If bronchoscopic biopsies are nondiagnostic, other options include mediastinoscopy, video-assisted thoracoscopic lung biopsy, and open-lung biopsy. If mediastinal adenopathy is present on CT scan, then many clinicians consider mediastinoscopy to be the procedure of choice because of the need to rule out malignancies such as lymphoma. It should be noted that in some cases, the tissue diagnosis can be made without a chest procedure. For example, some patients who have typical clinical and radiographic features and who have other organ involvement, such as skin nodules, sinus symptoms, or salivary gland symptoms, can have biopsies of those organs to demonstrate the presence of granulomas. In such cases, it is usually not necessary to do bronchoscopy or thoracoscopy.

The characteristic feature on lung biopsy is the noncaseating granuloma. As demonstrated in Figure 59-6, this is classically described as a well-formed, noncaseating epithelioid cell granuloma surrounded by a rim of lymphocytes and fibroblasts, with varying degrees of peripheral collagen deposition. The granulomas are found in a perilymphatic distribution, classically subpleurally and along bronchovascular bundles (Fig. 59-7). The

FIGURE 59-6 ■ A cluster of multiple noncaseating granulomata with surrounding normal lung parenchyma. The *arrow* indicates a multinucleated giant cell within a granuloma. (Original magnification ×100.) (Courtesy of Carlyne Cool, MD, National Jewish Medical and Research Center.)

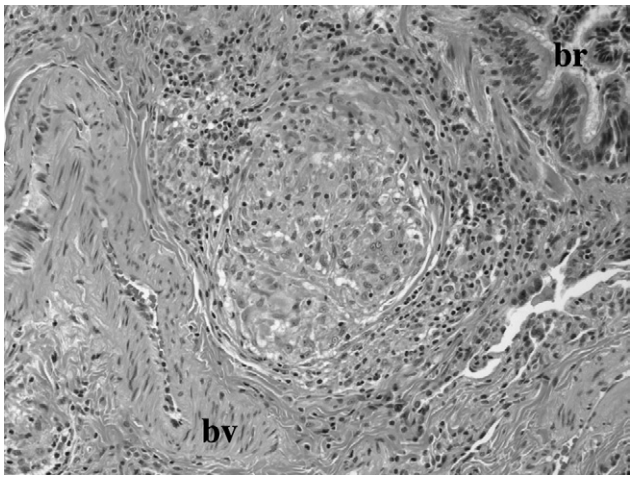

FIGURE 59-7 ■ View of a well-formed noncaseating granuloma located between a blood vessel (bv) and a bronchiole (br). (Original magnification ×200.) (Courtesy of Carlyne Cool, MD, National Jewish Medical and Research Center.)

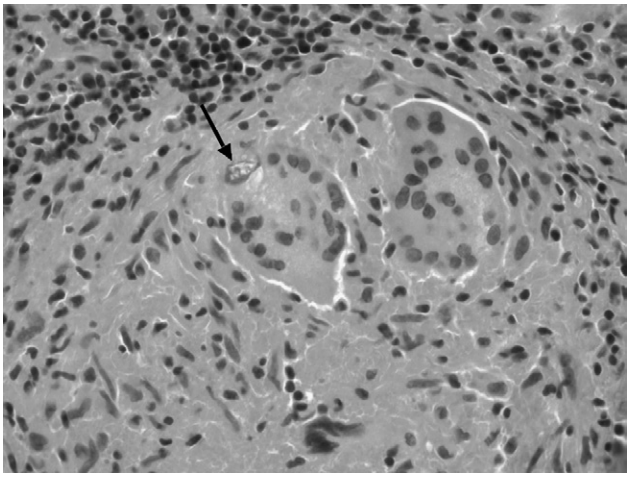

FIGURE 59-8 ■ A Schaumann body (*arrow*) within a multinucleated giant cell within a sarcoidosis granuloma of a pulmonary lymph node. (Original magnification ×400.) (Courtesy of Carlyne Cool, MD, National Jewish Medical and Research Center.)

granulomas may contain cytoplasmic inclusions within giant cells, such as asteroid bodies (star-shaped crystals consisting of microfilaments, microtubules, and other components embedded in a matrix) or Schaumann's bodies (small concentric laminated calcifications composed of calcium salts, iron, and a mucopolysaccharide matrix) (Fig. 59-8).[85]

This appearance is typical of sarcoidosis in the lung as well as in other organs. As noted previously, the diagnosis of sarcoidosis also requires exclusion of other possible etiologies of both the clinical and the pathologic presentation (see later discussion). The distinguishing histopathologic feature of necrotizing sarcoid granulomatosis is the presence of central necrosis within granulomas and a necrotizing granulomatous vasculitis. The appearance is similar to that of Wegener's granulomatosis, although the latter has a less extensive granulomatous reaction, a more severe clinical course, and positive cytoplasmic antineutrophil cytoplasmic antibodies in most cases.

Extrapulmonary Sarcoidosis

A characteristic of sarcoidosis is the potential for the development of granulomatous inflammation in virtually any organ. Confidence in the diagnosis of sarcoidosis rises if there is involvement elsewhere, in addition to lung and thoracic lymphatics. Key characteristics of some of the more commonly affected organs are described in this section.

Ears, Nose, and Throat

There is a range of otorhinolaryngologic presentations, including salivary gland involvement sometimes resulting in severe xerostomia, otitis media, vestibular symptoms, and hearing loss. However, nasal and paranasal sinus involvement can be the most difficult to diagnose and treat properly. Presenting symptoms are usually nonspecific, including nasal congestion, postnasal drip and sinus pressure, headaches, and infections. Sometimes, these will be associated with clinical features suggestive of sarcoidosis, such as lupus pernio (violaceous rash described later), nasal deformities such as saddle nose deformity, and nasal mucosal abnormalities such as friability with crusting, bleeding, and submucosal nodules. Rarely, these nodules may erode through the hard or soft palate, resulting in oral ulcerations or fistulous tracts. Other rare complications of nasal and sinus disease include epiphora (chronic tearing due to intranasal lacrimal tract outlet obstruction); anosmia (loss of the sense of smell due to direct involvement of the olfactory epithelium or obstruction of the olfactory cleft); and mass lesions with intraorbital or intracranial invasion. Even in cases with features suggestive of sarcoidosis, definitive diagnosis relies on biopsy evidence of granulomatous inflammation and exclusion of other infections and inflammatory etiologies (e.g., fungal or mycobacterial infection, Wegener's granulomatosis, rhinoscleroma).

There are a number of management strategies for sinonasal sarcoidosis, depending on disease severity. Krespi and associates[86] have proposed a staging system for nasal involvement that provides some general guidelines for therapy. Stage I nasal involvement is defined as mild nasal disease without paranasal sinus disease. These patients can typically be managed successfully with saline nasal spray, nasal irrigation, and topical nasal steroids. Stage II nasal involvement is moderate disease, with involvement of both nasal and paranasal sinuses; it is typically treated with both stage I therapy and intralesional steroids. Stage III nasal disease is characterized by severe, often irreversible, nasal and sinus disease that usually requires the therapeutic interventions of stages I and II, as well as systemic therapy. Courses of systemic antibiotics are also required for many patients who develop secondary infection related to mucus stasis or sinus ostium obstruction. Surgical interventions have traditionally been avoided owing to concerns

about worsening tissue destruction and inflammation; however, some reports suggest surgery can be performed safely and successfully in selected cases. Examples of surgical indications include severe nasal obstruction that has failed to respond to medical therapy, sinus obstruction with chronic infection, and need for biopsy for diagnosis.[87]

Peripheral Lymph Nodes

Lymphadenopathy is observed most commonly in the hilar and mediastinal lymph nodes (≤90% of patients); however, a minority of patients (5%–30%) have peripheral lymphadenopathy.[2] The nodes are typically nontender, mobile, and located in the cervical, axillary, epitrochlear, and inguinal regions.

Heart

Autopsy studies reveal that sarcoidosis involvement of the myocardium occurs in approximately 40% of patients, although clinical symptoms are present in approximately 10%.[88,89] Clinical manifestations most commonly include arrhythmias, conduction abnormalities, and congestive heart failure. Treatment includes immunosuppressant therapy, permanent pacemakers in the setting of conduction abnormalities, and implantable cardioverter-defibrillators in patients at risk for sudden cardiac death.[90] The "gold standard" for the diagnosis of cardiac sarcoidosis is endomyocardial biopsy. Although it carries high specificity, there is low sensitivity. Biopsy is typically performed from the right side of the heart, whereas sarcoidosis involvement tends to involve the basal and lateral regions of the left ventricle.

New cardiac-imaging techniques have emerged with permit noninvasive identification of cardiac sarcoidosis with high sensitivity. Gadolinium enhancement patterns and signal intensity on T2-weighted images on cardiac magnetic resonance imaging (MRI) can distinguish sarcoid involvement from ischemic scars. Fluorodeoxyglucose positron emission tomography (FDG-PET) imaging can also identify cardiac sarcoidosis lesions.[91,92] A recent study indicates that a history of cardiac symptoms, especially palpitations, as well as abnormalities on electrocardiography, Holter monitoring, or transthoracic echo, is sensitive and specific for cardiac sarcoidosis. Sarcoidosis lesions seen on cardiac MRI or PET scanning do not predict arrhythmias in patients with preserved cardiac function.[93]

Skin

Skin involvement is found in approximately 25% of sarcoidosis patients.[2] The two most classic skin lesions are erythema nodosum and lupus pernio. Erythema nodosum typically presents as raised, tender, red nodules, 1 to 2 cm in diameter, on the anterior surface of the lower legs. As described earlier, lupus pernio is a rare lesion consisting of purplish plaques typically found over the nose, cheeks, lips, and ears. It is observed more commonly in African American women and is associated with chronic, severe disease. More common skin abnormalities include red-brown to orange macules and papules, keloids, and hyper- or hypopigmentation. With the exception of the two classic lesions, definitive evidence of skin involvement relies on biopsy demonstrating noncaseating granulomas.

Eyes

Ocular involvement occurs in 11% to 83% of sarcoidosis patients.[2] The most common presentation is uveitis, with a higher prevalence of anterior uveitis in African Americans and of posterior uveitis in whites.[94] Anterior uveitis typically presents acutely, with pain, photophobia, lacrimation, and redness, but may have a more chronic course. Posterior uveitis is typically gradual in onset and is more likely to result in visual morbidity. Conjunctival nodules are another common, although usually asymptomatic, presentation. In fact, the diagnosis of sarcoidosis can sometimes be made with conjunctival biopsy, even in patients without any ocular symptoms. Although the yield varies depending on the presence of conjunctival follicles, other ocular abnormalities, and extraocular disease, small series of conjunctival biopsies have found yields of 33% to 70%, even without evident conjunctival disease.[95] Although less common, lacrimal gland enlargement is a characteristic finding (Fig. 59-9). In addition to posterior uveitis, the posterior segment of the eye may be affected with vitreous hemorrhage, cataracts, glaucoma, and retinal ischemia with neovascularization. Patients with disease of the posterior segment of the eye have a higher prevalence of central nervous system involvement.[96] Annual ophthalmologic evaluation with slit-lamp examination is recommended to evaluate for ocular involvement. Microvascular involvement can be detected using fluorescein angiography. Vigilance for ocular involvement is extremely important, as about 10% of patients with sarcoid-associated uveitis develop blindness in at least one eye.[97]

Nervous System

Neurosarcoidosis has been described in both the central and the peripheral nervous systems but is clinically evident in less than 10% of patients.[2] The most common form of central nervous system involvement is meningeal infiltration and inflammation. This may manifest clinically with cranial neuropathies, hydrocephalus, head-

FIGURE 59-9 ■ Enlargement of lacrimal glands in a sarcoidosis patient.

aches, and encephalopathy. Granulomatous inflammation of the cranial nerves most commonly presents as a unilateral seventh nerve palsy, but has been reported in every cranial nerve. Central lesions occur much less commonly and often present clinically when there is pituitary involvement. Clinical syndromes include diabetes insipidus and hyperprolactinemia. Peripheral neuropathy has also been described. Diagnostic tests that may be helpful include MRI for brain lesions and leptomeningeal involvement; cerebrospinal fluid examination, which typically reveals a lymphocytic pleocytosis and elevated protein in central nervous system disease; and electrodiagnostic studies and nerve biopsy for peripheral neuropathy. Although the sensitivity and specificity of many of these studies in neurosarcoidosis is not well defined, MRI with gadolinium is the preferred imaging study for sarcoidosis patients with central nervous system symptoms, with a sensitivity in this patient population of 82%.[98,99]

Endocrine Glands

Abnormal calcium metabolism is the most common endocrine disorder in sarcoidosis. Both hypercalcemia and hypercalciuria occur because of increased 1,25-dihydroxyvitamin D production by activated macrophages in sarcoidal granulomas.[100] Left untreated, these abnormalities can result in the formation of renal calculi, precipitation of calcium salts in the kidney itself (nephrocalcinosis), and sometimes, renal failure. Other unusual renal sequelae of sarcoidosis include interstitial nephritis and granulomatous masses.[2]

Parotid Gland

Parotid enlargement is a classic but rare disease feature. Heerfordt's syndrome, or uveoparotid fever, is characterized by parotid enlargement with fever, facial palsy, and anterior uveitis.

Liver and Spleen

Clinically apparent liver disease, such as palpable hepatomegaly or symptomatic cholestasis, is a rare complication of sarcoidosis. However, liver function test abnormalities are commonly observed.[2] Male gender, hepatomegaly, splenomegaly, and normal chest radiograph were associated with hepatic sarcoidosis. On multivariate analysis, male gender (odds ratio [OR] 2.8, $P = .012$), and splenomegaly (OR 9.2, $P < .0001$) were more prevalent in the group with liver disease. Liver involvement can also be detected radiographically, with hepatomegaly or nodular lesions detected on abdominal CT or MRI.[101] The demonstration of hepatic sarcoidosis after interferon therapy for hepatitis C has been reported.[102] These new lesions typically respond to steroid therapy. Splenic involvement is also rarely symptomatic, but is common, as determined by studies of fine-needle aspiration biopsies. Rarely, massive splenomegaly may occur and may cause thrombocytopenia or other cytopenias.[103]

FIGURE 59-10 ■ Joint and bone involvement in the hands of a sarcoidosis patient.

Joints

Although arthralgias are common in patients with Löfgren's syndrome, other forms of sarcoidosis less commonly demonstrate joint involvement. Arthralgias occur in 25% to 39% of patients, but deforming arthritis is rare.[2] Between 3% and 13% of patients display bony involvement,[104] although the increasing use of MRI may increase future estimates of the frequency of osseous sarcoidosis. Classically, if the bones are involved, plain radiographs or MRI will demonstrate bone cysts in the phalanges, although virtually any bone can be affected. Figure 59-10 illustrates the effects of bony involvement and arthritis in the hands of a sarcoidosis patient. Symptomatic muscle involvement, characterized by nodules, acute myositis, or chronic myopathy, is also rare; however, in systemic sarcoidosis without clinical manifestations of muscle disease, 20% to 75% of cases are found to have granulomas on muscle biopsy.[105]

Blood

Hematologic abnormalities are also seen, with as many as 40% of patients demonstrating anemia, leukopenia, lymphopenia, or a combination of these.[2] Thrombocytopenia is rare but can be the consequence of bone marrow involvement or splenic enlargement with platelet destruction.

Other Sites

Other unusual sites of biopsy-confirmed disease have been the subject of extensive reviews, including one by Judson and colleagues[106] that defines definite, probable, and possible criteria for organ involvement. These criteria were used to describe the case population in the ACCESS study.[106]

DIFFERENTIAL DIAGNOSIS

The diagnosis of sarcoidosis is made by exclusion of other conditions. Table 59-1 summarizes the major categories of both infectious and noninfectious disorders that must be considered prior to accepting the idiopathic diagnosis. Diagnostic considerations for pulmonary granulomatous inflammation include infections with mycobacteria, bacteria, fungi, spirochetes, and protozoa.

TABLE 59-1. Differential Diagnosis of Granulomatous Disease and Relevant Testing with Clinical Suspicion

Cause	Granulomatous Disease	Confirmatory Data
Infectious agents		
Mycobacteria	Tuberculosis, atypical mycobacterial infection	PPD; sputum or BAL culture
Fungi	Histoplasmosis, coccidioidomycosis	Serologic testing (histo); sputum or biopsy stains, serologies, skin tests (cocci)
Bacteria	Brucellosis	Culture (low yield); serologies
Spirochetes	Syphilis	RPR
Parasites	Leishmaniasis, toxoplasmosis	Tissue biopsy, culture, leishmanin test (leishmaniasis); serologies; BAL, lung biopsy cultures (toxoplasmosis)
Neoplasms	Carcinoma, sarcomas, malignant nasal granuloma	Full sectioning and histopathologic examination of lymph nodes
HP	Farmers' lung, bird breeder's lung, suberosis (HP secondary to moldy cork), bagassosis (HP secondary to moldy sugar cane)	Detailed history for likely exposures; examination of biopsies for other features characteristic of HP; precipitins
Metals	Chronic beryllium disease, zirconium or aluminum granulomas	Detailed history for likelihood of exposure; blood and/or BAL beryllium lymphocyte proliferation test
Silicates	Silicosis with granulomatous inflammation	Detailed history for likelihood of exposure; review of radiographic findings for features of silicosis; biopsy microanalysis for dust
Vasculitic granulomatoses and autoimmune disorders	Wegener's granulomatosis, Churg-Strauss syndrome, lymphomatoid granulomatosis, polyarteritis nodosa, bronchocentric granulomatosis, systemic lupus erythematosus, primary biliary cirrhosis, juvenile rheumatoid arthritis	Pathologic review for features of vasculitis; autoantibody studies, including c-ANCA, p-ANCA, ANA, anti-dsDNA, rheumatoid factor
Other conditions	Chronic granulomatous disease (children), Whipple's disease, lymphocytic infiltration after cancer chemotherapy, Blau syndrome, local sarcoidal reactions	

ANA, antineutrophil antibody; BAL, bronchoalveolar lavage; c-ANCA, cytoplasma antineutrophil cytoplasmic antibody; dsDNA, double-stranded deoxyribonucleic acid; HP, hypersensitivity pneumonitis; p-ANCA, perinuclear antineutrophil cytoplasmic antibody; PPD, purified protein derivative (of tuberculin); RPR, rapid plasma reagin test.

Diseases caused by occupational and environmental inhaled agents must also be considered, including hypersensitivity pneumonitis due to inhaled organic and inorganic antigens, metal-induced disorders such as chronic beryllium disease,[107] and silicosis.[108] In addition to the infectious and exposure-related diagnoses noted previously, other diagnostic considerations include Wegener's granulomatosis and idiopathic interstitial pneumonias such as lymphocytic interstitial pneumonia.

Chronic beryllium disease is of particular interest because it is clinically, radiographically, and histopathologically indistinguishable from sarcoidosis. Chronic beryllium disease is distinguished from sarcoidosis by a history of beryllium exposure and by laboratory evidence of immunologic sensitization to beryllium using blood or lavage cells in a beryllium lymphocyte proliferation test. A study from Israel illustrates the need to exclude chronic beryllium disease prior to accepting a diagnosis of sarcoidosis.[109] In this study, Fireman and coworkers[109] performed the blood beryllium lymphocyte proliferation test in 14 patients in their sarcoidosis clinic who, on repeat questioning, reported employment in industries with the potential for beryllium exposure (e.g., metal extraction, ceramics, electronics, space and atomic engineering, dental laboratories). Three of the 14 patients were found to be beryllium-sensitized and were therefore diagnosed as having chronic beryllium disease. Similar findings of chronic beryllium disease cases masquerading as sarcoidosis have been reported in a German cohort.[110] These studies highlight the importance of a thorough occupational history in patients with granulomatous lung disease.

The finding of noncaseating granulomas in lymph nodes is associated with a similarly broad differential diagnosis. Mycobacterial infection, brucellosis, toxoplasmosis, and cat-scratch disease can all cause a granulomatous lymphadenitis. Neoplasms, including Hodgkin's and non-Hodgkin's lymphoma and metastatic carcinoma, can cause lymph node enlargement and stimulate a sarcoid-like reaction. Therefore, when granulomas are identified on lymph node biopsy, the entire node must be examined histopathologically to exclude these diagnoses. Of note, nonthoracic lymph node granulomas without an identified etiology or evidence of other organ involvement are referred to as "granulomatous lesions of unknown significance," and are not sufficient to make a diagnosis of sarcoidosis. The differential diagnosis of noncaseating granulomas in other organs is similar. Other specific entities that can produce noncaseating granulomas include foreign body reactions in the skin, schistosomiasis, primary biliary cirrhosis, and Crohn's disease.[1,2]

The distinction between sarcoidosis and autoimmune disorders deserves specific mention. Sarcoidosis has been associated with elevation of various autoantibodies in serum, including nonspecific elevations of rheumatoid factor and antinuclear antibodies.[111] Several researchers have suggested an association between sarcoidosis and autoimmune endocrinopathies, as well as antiphospholipid antibodies.[112] The putative link between sarcoidosis and autoimmunity is supported by cases of concurrent diagnoses, as well as by some of the obvious similarities in clinical presentations between sarcoidosis and the autoimmune diseases.

Although sarcoidosis is rare in children, when it does occur in preschool children, it may mimic the manifestations of juvenile rheumatoid arthritis with skin, eye, and joint involvement without lung disease. Distinction between the two entities usually requires biopsy of skin, synovium, lymph node, or liver.[113] In contrast, in adults, the clinical presentations of rheumatoid arthritis and sarcoidosis are quite distinct. Interestingly, the coexistence of the two diseases with biopsy verification of both has been demonstrated in numerous case reports, suggesting a possible etiologic similarity.[114] Sjögren's syndrome and sarcoidosis may also coexist and be difficult to distinguish, particularly when there is lung involvement.[115] Both diseases can present with keratoconjunctivitis sicca, parotid swelling, lung involvement, and cutaneous anergy. Some authors suggest that labial minor salivary gland biopsy or lung biopsy can distinguish between the two diseases, but even biopsy findings are sometimes inconclusive.

EVALUATION AND MANAGEMENT

The recommended baseline evaluation and follow-up testing of sarcoidosis patients are shown in Table 59-2.[1] These recommendations are based on the major organs that are usually targeted by sarcoidosis. Other tests may be appropriate for evaluation and management, depending on the particular organs affected.

As a general principle, because there is no single sensitive or specific diagnostic test for sarcoidosis, the diagnosis depends on establishing the compatible clinicopathologic picture and excluding other granulomatous diseases. Ideally, the evaluation should provide histologic confirmation of disease and negative cultures and special stains for organisms.

The clinical impact of sarcoidosis depends on the extent of granulomatous inflammation and the particular organs affected. In determining the extent and severity of disease, clinicians should use available noninvasive tools as much as possible to assess which organs are clinically involved and to assess the extent and severity of organ injury. Asymptomatic organ involvement may be missed but is usually of mild or no clinical significance with three significant exceptions. A slit-lamp examination is recommended for all patients with suspected sarcoidosis to look for clinically undetected uveitis. Subclinical hypercalciuria, even in the absence of hypercalcemia, is associated with nephrolithiasis, and thus a baseline 24-hour urine calcium measurement is advisable. Periodic electrocardiograms should also be obtained to screen for rare, but potentially life-threatening, cardiac arrhythmias and conduction abnormalities.

A baseline complete blood count is recommended to evaluate for anemia, leukopenia, and thrombocytopenia. Serum calcium and liver enzymes may reflect organ involvement meriting treatment. Serum ACE activity is frequently elevated in sarcoidosis. This elevation is not specific but can be of use in monitoring the progression of disease and the response to therapy unless patients are being treated with an ACE inhibitor, which will lower ACE levels.

Tests demonstrating cutaneous anergy may help suggest a diagnosis of sarcoidosis, but the anergy panel is neither sensitive nor specific. Kveim-Siltzbach skin testing—using a preparation of sarcoidosis spleen that is intradermally injected—has been used in the past to help establish a diagnosis of sarcoidosis in patients with unexplained erythema nodosum, uveitis, liver granulomas, or hypercalciuria. This is not approved for general use in the United States and is not recommended.

TABLE 59-2. Recommended Baseline and Follow-up Clinical Evaluation for Sarcoidosis

BASELINE

- Detailed history, including occupational, environmental, and travel history to evaluate for exposure to known causes of granulomatous diseases (see Table 59-1).
- Physical examination with a focus on lungs, lymphatics, skin, eyes, liver, heart, nervous system, joints.
- Biopsy of an affected organ, with special stains, cultures for acid-fast bacillus and fungus to rule out infectious etiologies of granulomas.
- Chest radiography (posteroanterior and lateral).
- Full pulmonary function tests, including spirometry, lung volumes, and an assessment of gas exchange (e.g., diffusing capacity of carbon monoxide, arterial blood gases at rest and with exercise).
- Electrocardiogram.
- Ophthalmologic examination, including slit-lamp examination.
- Laboratory evaluation, including liver function tests, renal function tests, serum calcium, and a complete blood count with differential.
- Urinalysis and 24-hr urine collection for calcium and creatinine excretion.

OTHER TESTS

- To rule out other diagnostic possibilities (e.g., tuberculin skin test [with anergy panel], blood beryllium lymphocyte proliferation test).
- For clinical staging of organ system involvement and severity (e.g., computed tomography scan, magnetic resonance imaging, Holter monitoring, electromyogram, gallium scan).

FOLLOW-UP

Monitoring for resolution or progression:

- Track organs previously involved, using least invasive methods.
- Monitor for new involvement of common target organs annually or sooner if symptoms dictate.

Given the high likelihood of pulmonary involvement at some point in the course of sarcoidosis, we recommend that the extent of lung disease be thoroughly evaluated. Typically, this would include pre- and post-bronchodilator spirometry, lung volumes by body plethysmography, diffusing capacity, and in many cases, one or more direct measures of gas exchange. These include room air arterial blood gas measurements at rest and with exercise; a fall in arterial oxygen saturation during exercise is among the most sensitive indicators of lung impairment in sarcoidosis and other forms of diffuse lung disease. Baseline imaging studies, consisting at minimum of posteroanterior and lateral chest radiographs, should also be obtained. CT of the thorax using spiral and thin-section algorithms provides much greater detail of parenchymal abnormalities, including nodules, ground-glass, septal lines, and adenopathy, but is not required as a baseline study.[2] Generally, patients found to have pulmonary involvement can be followed with the simplest and least invasive testing. For example, in a patient found to have a low diffusing capacity, it is often possible to follow that test, along with spirometry and chest radiographs, rather than routinely performing more invasive studies such as exercise testing with arterial blood gases or serial chest CT scanning (which carries a greater cancer risk in this young population, especially among women).

Gallium-67 citrate scanning adds no specificity to the diagnosis of sarcoidosis, except in the case of patients with lacrimal and salivary gland involvement, in which case the so-called panda sign is observed due to increased uptake in those sites.[116] The "lambda" sign indicating hilar lymphadenopathy is also suggestive but not diagnostic.

Monitoring for disease progression, regression, or response to therapy should be customized, relying on the least invasive markers of disease activity and vital organ involvement, taking into consideration the relative sensitivity of the clinical tools available for monitoring. The clinician must remain vigilant given the tendency of this disorder to relapse and to erupt in new or previously subclinical organs.

TREATMENT

It is not known why some sarcoidosis patients recover and others progress. Even after an apparent recovery, a small proportion of patients may relapse months to years later. Factors associated with worse prognosis include older age at time of diagnosis, African American race, duration of illness greater than 6 months, pulmonary opacities, splenomegaly, lupus pernio, and number of organs involved. A more favorable prognosis has been found in patients with Lofgren's syndrome who expressed *HLA-DRB1*0301*.[117] It is important to recognize that the disease can spontaneously resolve without treatment and that some patients with sarcoidosis are disabled by their illness. The current paradigm for institution of therapy is based upon the presence of organ dysfunction. Thus, most treatment protocols incorporate a period of observation without treatment whenever possible.

Corticosteroids

A detailed summary of current pharmacotherapy in sarcoidosis has been the subject of several recent reviews.[118,119] This section addresses general treatment of sarcoidosis. Oral corticosteroids remain the first-line therapy in most cases. Corticosteroids inhibit proinflammatory cytokine production, including that of IL-1, IL-2, the IL-2 receptor, IFN-α, TNF, and perhaps, various colony-stimulating factors (CSFs) such as IL-3. In addition, corticosteroids, even in very low concentrations, inhibit the synthesis of a variety of proinflammatory enzymes, including the macrophage products collagenase, elastase, and plasminogen activator. Lymphocyte proliferation in vitro and delayed-type hypersensitivity in vitro are also inhibited by corticosteroids.

The use of oral corticosteroids in sarcoidosis is aimed at the relief of symptoms with intended improvement in quality of life and modulation of disease activity to prevent serious morbidity and mortality related to vital organ damage. It is debatable whether all of these goals can be achieved, especially in light of the side effects of corticosteroids.

In a systematic review, Paramothayan and Lasserson[120] identified all of the randomized trials of oral or inhaled corticosteroids in pulmonary sarcoidosis that included a control group. Their goal was to assess the beneficial and adverse effects of corticosteroid therapy. In synthesizing the data from eight studies that met their requirements for inclusion, the authors concluded that oral corticosteroids improved chest radiographs after 6 to 24 months of treatment and produced a small improvement in lung function and gas exchange. They found no data to suggest that systemic corticosteroid therapy alters long-term disease progression. Only two of these studies examined the efficacy of inhaled corticosteroid therapy. These demonstrated no effect on chest radiographic appearance and no consistent effects on lung function. In another review, Reich[121] suggested that corticosteroid-treated patients with a recent diagnosis of stage II or III sarcoidosis might derive more long-term harm than benefit, that the effect on those with disease of more intermediate duration is neutral, and that patients with chronic progressive pulmonary disease respond favorably, at least in the intermediate term. Obviously, the paucity of randomized, controlled clinical trials—especially for all of the various forms of sarcoidosis organ involvement—limits the conclusions that can be drawn. A review of the American Thoracic Society consensus statement[2] would suggest that patients with acute pulmonary sarcoidosis (stage I disease with isolated bilateral hilar adenopathy) *not* be treated because of the generally excellent outcome in the absence of therapy and the potential that corticosteroids may be detrimental if used in these acute cases.

Studies examining outcome at greater than 2 years suggest no significant benefit from corticosteroid therapy in asymptomatic sarcoidosis patients with more advanced

forms of pulmonary involvement.[122,123] In a British Thoracic Society study,[124] patients not meeting the indications for immediate therapy were observed for 6 months. At that point, using a strategy of alternate assignment, they were designated either to receive long-term corticosteroid therapy or to receive corticosteroids only as indicated symptomatically. Analysis of data at 2 years suggested that the long-term therapy group experienced only mild improvements in pulmonary function and reported numerous steroid side effects.

Based on the available literature and a survey of clinical practice in the United States and abroad, it is our general recommendation that whenever possible, corticosteroids should not be initiated until after a period of clinical observation of 3 to 6 months, unless there is a life- or sight-threatening indication to treat immediately. Urgent indications for treatment include eye disease that has failed to improve with topical therapy, cardiac involvement (e.g., cardiomyopathy, heart block, or serious arrhythmias), neurologic involvement (e.g., hypothalamic or pituitary dysfunction or other central nervous system involvement), hypercalcemia, hypercalciuria with associated renal insufficiency or recurrent nephrolithiasis, severe disfiguring skin lesions, severe thrombocytopenia with bleeding diathesis, progressive hepatic failure, severe incapacitating osseous or muscle involvement, and severe pulmonary involvement that is significantly impairing gas exchange. If no such urgent indications have intervened during the 3 to 6 months of observation, patients would be observed closely for pulmonary and other organ function. After these observation months, the persistence or progression of organ dysfunction would then be an indication for a trial period of treatment. Figure 59-11 offers a reasonable strategy for the use of corticosteroids and, as discussed later, methotrexate, in the treatment of acute-onset sarcoidosis.

There is no consensus regarding the optimal initial dosage of corticosteroids. The American Thoracic Society consensus statement[2] reports a usual starting dose of 20 to 40 mg of prednisone, or its equivalent, daily or on alternate days. The British Thoracic Society study[124] similarly used 30 mg of prednisolone (potency equivalent to prednisone) daily as a starting dose in both their long-term and their selective therapy groups. We typically start therapy at a dosage of 20 to 40 mg of prednisone daily or on alternate days, although we use higher doses (to a maximum of 60 mg daily) for severe disease, such as symptomatic cardiac involvement. Patients are seen back in the clinic 8 to 12 weeks later, at which time clinical, radiologic, physiologic, and laboratory assessments are repeated and patients are examined for side effects. Those who objectively improve on corticosteroids initiate a taper of corticosteroids to as low a dose as is tolerated without return of symptoms of organ dysfunction—usually 5 to 10 mg daily or on alternate days. The American Thoracic Society statement[2] recommends that for those who response to steroids, treatment should be continued for at least 1 year. Patients who become stable on high-dose corticosteroids but who have yet to improve are maintained at the same dosage, unless they have developed significant side effects. If intolerable side effects occur, or if the disease worsens, patients are considered candidates for the addition of a second-line immunosuppressive agent. If patients suffer relapse on maintenance therapy, we reinitiate higher dose prednisone and consider second-line, steroid-sparing options.[1,2,118] Patients who have evidence of a clinical response to corticosteroids over the time course described earlier are reevaluated using objective measures prior to attempts to withdraw immunosuppressive medication completely. In some patients, the disease remains quiescent off all

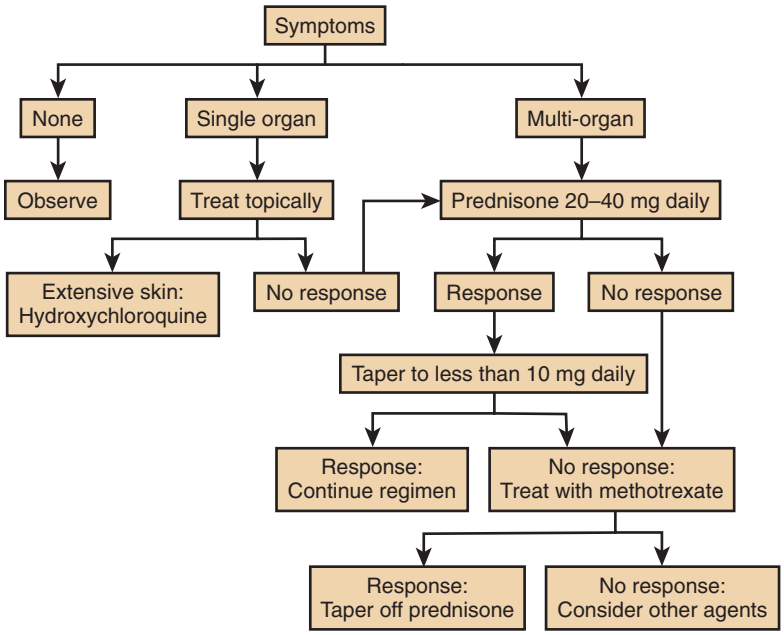

FIGURE 59-11 ■ A suggested treatment strategy for acute sarcoidosis (within 5 yr of diagnosis). Severe single organ sarcoidosis, including neurologic or cardiac, should be treated the same as multiorgan sarcoidosis. (Redrawn from Baughman RP, Costabel U, du Bois RM. Treatment of sarcoidosis. Clin Chest Med 29:535, 2008. © Elsevier Inc.)

corticosteroids. Unfortunately, in others, the disease relapses, requiring that therapy be restarted for purposes of symptomatic relief and clinical control of failing organs. Even patients who are believed to have entered remission should be followed periodically, given the propensity for sarcoidosis to relapse and given the lack of available information about predictors of long-term prognosis.

Other Immunosuppressive Agents

The use of other immunosuppressive agents in sarcoidosis should be reserved for those patients who experience symptomatic disease progression despite the use of systemic corticosteroids or who require systemic therapy but cannot tolerate the side effects of steroids. In general, there has been less clinical experience and fewer published studies testing the efficacy of other immunosuppressive agents, either as single agents or as steroid-sparing agents.

Methotrexate

Methotrexate has emerged as the preferred second-line immunosuppressive drug, especially when used as a steroid-sparing agent (see Fig. 59-11). Methotrexate's mechanisms of action is thought to be generated by the anti-inflammatory effects of adenosine accumulation; also Genestier and associates[125] have reported that methotrexate diminishes antigen-stimulated T-cell proliferation both in vitro and in T cells taken from patients taking methotrexate. There has only been one published randomized, controlled trial of methotrexate in sarcoidosis.[126] The primary end point of this small study was steroid dose after 6 to 12 months; although interpretation of the results was limited by a high dropout rate, there was a suggestion of a steroid-sparing effect in this population. The largest published experience comes from Baughman and Lower,[128] who reported improvement in 33 of 50 patients treated with methotrexate for a minimum of 2 years. Those with cutaneous and musculoskeletal involvement showed the greatest response. Twenty-five of 30 patients who were also receiving corticosteroids were able to decrease corticosteroid dosage; 13 discontinued corticosteroids entirely. A follow-up report of 209 patients showed that 52% on methotrexate entered remission and 16% remained stable, with or without low-dose prednisone.[128] Other reports confirm the beneficial effects of methotrexate in cutaneous and musculoskeletal sarcoidosis.[129,130] In a study by Kaye and colleagues,[130] low-dose methotrexate (average 10 mg/wk, range 7.5–15 mg), when used for an average of 30 months, controlled clinical symptoms in patients with musculoskeletal involvement and helped reduce corticosteroid dose. In most studies, treatment doses of methotrexate range from 5 to 15 mg/wk, usually taken as a single or divided oral dose taken 1 day/wk. Methotrexate may take up to 6 months to become effective in sarcoidosis. During this period, patients are usually maintained on corticosteroids. Leflunomide is a cytotoxic agent that has been used to treat pulmonary sarcoidosis patients, with fewer associated cases of interstitial pneumonitis than methotrexate.[131,132]

Cyclosporin A

Case reports on the benefits of cyclosporin A in sarcoidosis have not been supported by later larger cohort studies.[133,134] The first study to examine cyclosporine A in a more rigorous fashion found that cyclosporine A, administered at doses that achieved a blood level between 150 and 250 ng/mL, failed to produce clinical improvement in 20 patients who had pulmonary involvement, despite 6 months of therapy.[133] Cyclosporin A was undetectable in BAL fluid, suggesting poor penetration of cyclosporin A into the lung as a reason for its failure. A more recent randomized, controlled trial found the combination of prednisone and cyclosporin A to be no better and possibly worse than prednisone alone in treating pulmonary sarcoidosis.[134]

Azathioprine

Despite anecdotal reports and frequent use of azathioprine, there are few published studies examining the drug's efficacy in sarcoidosis. One group reported objective improvement in 7 of 10 patients with pulmonary sarcoidosis after receiving 150 mg/day of azathioprine for 6 months.[135] Some data suggest that it may be efficacious for extrapulmonary disease,[136] although side effects often limit the acceptance of this option. More recent case series evaluated combined therapy with azathioprine and corticosteroids in patients with chronic pulmonary sarcoidosis. A retrospective review of 10 patients demonstrated sustained improvement in lung function in only 2 patients, but a prospective evaluation of 11 patients demonstrated symptomatic relief and improvement in lung physiology and radiographic abnormalities in 9 after an average of 20 months of therapy. Thus, azathioprine may be an effective second-line agent in some sarcoidosis patients.[137,138]

Antimalarials

Chloroquine has proved effective in treating cutaneous manifestations of sarcoidosis,[139] hypercalcemia and hypercalciuria associated with sarcoidosis, and steroid-refractory neurosarcoidosis.[140,141] Generally, chloroquine therapy is initiated at a dosage of 500 mg/day and may be titrated up to a maximum of 1000 mg/day and decreased to a low of 250 mg/day. Because of the potential for significant ophthalmologic toxicity, hydroxychloroquine is often used instead, at a dosage of 200 to 400 mg daily. In 1967, the British Tuberculosis Association[142] reported the first controlled trial on the use of antimalarials in sarcoidosis. They observed some benefit early in attenuating symptoms of pulmonary sarcoidosis but showed little effect on disease outcome when comparing treatment and control groups at 6 months. A more recent trial examined the efficacy of

chloroquine therapy in chronic pulmonary sarcoidosis.[143] During an initial run-in phase, all subjects received chloroquine therapy for 6 months and demonstrated a significant improvement in several lung physiologic parameters. During the subsequent randomization phase, subjects were assigned to receive maintenance therapy with low-dose (250 mg/day) chloroquine or to be observed off therapy. With a mean of 19.7 months of follow-up, the maintenance group demonstrated significantly slower decline in lung function and a trend toward fewer relapses. Thus, although chloroquine and hydroxychloroquine are more commonly employed for extrathoracic disease, they may have a role in pulmonary disease as well.

Cyclophosphamide

Cyclophosphamide is employed in selected cases of corticosteroid-refractory sarcoidosis.[144,145] It appears beneficial for both cardiac sarcoidosis and neurosarcoidosis—in the latter case, even following failure of both corticosteroid and methotrexate therapy. If used, oral cyclophosphamide is given at a dose of 1 to 2 mg/kg/day to a maximum dose of 150 mg/day. Therapy is maintained for several months before tapering. In one open-label study, the investigators used intravenous pulse cyclophosphamide therapy for the treatment of neurosarcoidosis at a dosage of 0.75 to 1.5 g monthly.[145]

Anti–Tumor Necrosis Factor-α Therapy

Based on our present understanding of cytokine expression in sarcoidosis, it is logical to expect that anti–TNF-α therapies, either via inhibition of TNF production with thalidomide or pentoxifylline or via direct inhibition of TNF activity with etanercept or infliximab, should prove effective.[116]

There are individual published cases and small case series data supporting the use of thalidomide in treatment of patients with several forms of cutaneous sarcoidosis, including lupus pernio.[146–150] Pentoxifylline, at high doses, improved lung function in a group of patients with mild pulmonary sarcoidosis.[151]

A prospective, open-label study examined the treatment of sarcoidosis with etanercept, a dimeric fusion protein consisting of the extracellular binding domain of two human TNF receptors bound to the F_c portion of human IgG1.[152] This complex specifically binds TNF and inactivates it. Seventeen patients with progressive pulmonary sarcoidosis and on no other immunosuppressive agents were enrolled and followed for 3 to 12 months. The study was terminated prior to the full planned enrollment owing to excessive treatment failures, defined as a deterioration in two or three of the following: lung function (<10% decline in forced expiratory volume in 1 second, forced vital capacity, total lung capacity, or diffusing capacity for carbon monoxide), dyspnea score, and chest radiograph appearance. The authors concluded that etanercept should not be further studied as a therapeutic option for patients with stage II or III pulmonary sarcoidosis. Several shortcomings of this study are worth noting. First, at baseline, all of the mean lung function values were within the normal range. Therefore, this may have been a negative study because the subjects were too healthy to experience a significant benefit from etanercept. Second, patients were not permitted to be on any other immunosuppressive therapy. Because studies in other inflammatory disorders have demonstrated efficacy of TNF blockers in conjunction with other agents, this stipulation may have doomed the study to fail from the outset. Finally, the authors concluded that the drug deserves no further investigation despite the successful responses of nearly one third of the patients studied. It is, therefore, still certainly possible that for a subset of sarcoidosis patients with more significant pulmonary dysfunction and possibly on concomitant immunosuppressive therapy, this therapy will be effective.

In various case reports, infliximab, a chimeric humanized monoclonal antibody that binds TNF, has been used successfully in the treatment of lupus pernio, neurosarcoidosis, and progressive cutaneous sarcoidosis.[153–158] In one case, investigators reported clinical response in a sarcoidosis patient who presented with severe protein-losing enteropathy, hypoalbuminemia, and proximal myopathy.[159] A recent double-blind, randomized study demonstrated that infliximab therapy improved extrapulmonary sarcoidosis compared with placebo, as assessed by extrapulmonary physician organ severity tool. All patients in the study were required to be receiving a stable dose of corticosteroid or another immunosuppressant to control their pulmonary sarcoidosis. Therefore, the results of the present trial suggest that infliximab provides additional benefit for extrapulmonary sarcoidosis beyond that achieved with standard sarcoidosis treatment.[160]

It is worth noting that use of anti-TNF therapies has been associated with a significantly increased risk of active tuberculosis; therefore, any patient being considered for such therapy must be screened for previously untreated or active tuberculosis.[161] If screened using PPD, other positive controls should be included because of the potential for anergy. Special stains and cultures of lung tissue and BAL can also be used to help exclude tuberculosis.

Combination Treatment Regimens

Combined regimens are coming into increasing favor as treatments for sarcoidosis, although there have been few trials. Most combination treatment regimens for sarcoidosis are corticosteroids plus a second-line agent. The corticosteroid is then slowly tapered over a 3- to 6-month period as allowed by the patient's clinical status, leaving the second drug as the main therapeutic agent. In one study, the combination of cyclosporin A plus oral fluocortolone and oral methotrexate was studied in an open-label, uncontrolled trial in steroid-refractory patients.[162] All 11 patients entered remission. These preliminary results need to be confirmed with a larger, prospective, controlled trial.

Management of Treatment Complications: Aspergilloma

In the face of immunosuppression, sarcoidosis patients are at risk of aspergilloma. The underlying goal of any therapeutic intervention for aspergilloma is the prevention of massive, life-threatening hemoptysis, which may occur in up to 26% of patients with mycetomas.[163] Unfortunately, even with identified risk factors for a poor prognosis, including the severity of underlying lung disease, immunosuppression (including corticosteroids), and underlying sarcoidosis, the likelihood of significant hemoptysis is difficult to predict. Current practice guidelines and a review of the literature suggest that observation, without any therapeutic intervention, is appropriate in asymptomatic patients.[163,164] However, the optimal management of those patients with mild hemoptysis or systemic symptoms, or both, and the overall utility of medical interventions are unclear. There have been no prospective, randomized, double-blind, placebo-controlled trials. However, the available evidence suggests possible utility of endobronchial or intracavitary amphotericin B and of oral itraconazole in selected patients.[163] For those who do develop massive hemoptysis, bronchial artery embolization can sometimes be used as a bridge to surgery.[163,164] Unfortunately, although surgical resection is the definitive treatment, it carries a very high morbidity and mortality, the latter ranging from 1.5% to 23%.[165] In summary, this is a challenging clinical problem with little in the way of strong evidence to guide therapeutic decisions.

Lung Transplantation

Patients with severe and progressive pulmonary disease despite exhaustive medical therapy may be candidates for lung transplantation. The decision regarding timing of proceeding to transplantation is a difficult one; generally, patients with severe and irreversible disease with a life expectancy of less than 3 years are considered. This assessment can be quite challenging in sarcoidosis, as a retrospective study of sarcoidosis patients awaiting transplantation demonstrates. In this study, 23 of 43 patients died while awaiting transplantation; further analysis demonstrated that elevated right atrial pressure consistent with pulmonary hypertension was the only independent predictor of mortality.[165] A similar retrospective cohort study examined mortality of sarcoidosis patients listed for lung transplantation throughout the United States between 1995 and 2000. Among the 405 patients for whom adequate follow-up data were available, 111, or 27.4%, died while awaiting transplantation. The mortality prediction model found an association of higher mortality with African American race, amount of supplemental oxygen needed, and mean pulmonary artery pressure.[166] These data suggest that the development of a predictive model of life expectancy to assist in deciding the time of transplantation referral, as exists for such diseases as cystic fibrosis and primary pulmonary hypertension,[167] may improve survival to transplantation in this population.

There are several other issues unique to sarcoidosis patients that must be evaluated prior to proceeding to transplantation.[167] One is the search for and treatment of other etiologies of pulmonary dysfunction, such as bronchiectasis, often found in patients with stage IV disease, and congestive heart failure. Treatment of these disorders may yield enough clinical improvement to delay the need for transplantation. The presence of severe nonpulmonary disease, especially neurologic and cardiac disease, excludes patients from consideration for lung transplantation. Heart-lung transplantation can be considered for patients with severe cardiac and pulmonary involvement.

Another potential contraindication to transplantation, particularly in patients with end-stage fibrocystic disease, is the presence of one or more mycetomas (most commonly aspergillomas). Resection of mycetomas carries a high mortality and high incidence of postoperative complications. In addition, even with the successful removal of mycetomas, concern remains regarding the presence of residual subclinical invasive or noninvasive *Aspergillus* infection or colonization that may place the patient at high risk of severe and invasive infection on posttransplantation immunosuppressive therapy.[167] One case of an end-stage sarcoidosis patient with mycetomas who died from invasive *Aspergillus* infection after heart-lung transplantation has been reported.[168] In addition, a review of the lung transplantation experience at one center revealed that mycetomas were present in the explanted lungs of 3% of recipients. Most of those with mycetomas had sarcoidosis (six of nine). Posttransplantation mortality was significantly increased in this population, with better survival associated with aggressive pre- and posttransplantation antifungal therapy.[169]

The decision to proceed with single- versus double-lung transplantation depends largely on the infectious issues raised previously. If individuals with bilateral bronchiectasis or bilateral mycetomas are considered for transplantation, they should undergo double-lung transplantation. However, in most end-stage sarcoidosis patients, single-lung transplantation is considered adequate.[167] Another interesting feature of transplantation in this patient population is the recurrence of sarcoidosis in lung allografts, documented in numerous reports.[170–173] This has typically been observed on surveillance transbronchial biopsies and is rarely clinically significant. Lung transplant outcomes in this population have not been well studied. Several reviews of small series of patients demonstrate survival and obliterative bronchiolitis rates comparable with those reported in transplantation for other diseases.[174–177]

KEY POINTS

- Sarcoidosis is a multisystem, inflammatory disorder characterized by noncaseating granulomas that can infiltrate virtually any organ, but most commonly involves the lungs.
- Sarcoidosis should be considered in any patient presenting with systemic and multiorgan symptoms or whenever granulomatous inflammation is discovered on histology in any organ.
- Immunologic evidence suggest that sarcoidosis granulomas form as a result of (1) antigen exposure, (2) an antigen-specific cell-mediated immune response, and (3) inflammatory, or innate immune, responses that amplify and perpetuate the antigen-specific immunologic reaction.
- It is not known why some sarcoidosis patients recover and others progress. Persistence or progression of organ dysfunction is an indication for initiation of a trial period of treatment, usually with corticosteroids.
- Therapeutic advances based on an understanding of immune mechanisms will likely improve our approaches to medical management of this enigmatic condition.
- Further understanding derived from large, careful epidemiologic and genetic studies will also hopefully provide important clues about disease pathogenesis and potential pathways to prevention of this potentially devastating illness.

References

1. Iannuzzi MC, Rybicki BA, Teirstein AS: Sarcoidosis. N Engl JMed 357:2153–2165, 2007.
2. Statement on sarcoidosis: Joint statement of the American Thoracic Society (ATS), the European Respiratory Society (ERS) and the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) adopted by the ATS Board of Directors and by the ERS Executive Committee, February 1999. Am J Respir Crit Care Med 160:736–755, 1999.
3. Morimoto T, Azuma A, Abe S, et al: Epidemiology of sarcoidosis in Japan. Eur Respir J 31:372–379, 2008.
4. Milman N, Hoffman AL: Childhood sarcoidosis: Long-term follow-up. Eur Respir J 3:592–598, 2008.
5. Baughman RP, Teirstein AS, Judson MA, et al: Clinical characteristics of patients in a case control study of sarcoidosis. Am J Respir Crit Care Med 164:1885–1889, 2001.
6. Edmondstone WM: Sarcoidosis in nurses: Is there an association? Thorax 43:342–343, 1988.
7. Izbicki G, Chavko R, Banauch GI, et al: World Trade Center "sarcoid-like" granulomatous pulmonary disease in New York City Fire Department rescue workers. Chest 13:1414–1423, 2007.
8. Hills SE, Parkes SA, Baker SB: Epidemiology of sarcoidosis in the Isle of Man—2: Evidence for space-time clustering. Thorax 42:427–430, 1987.
9. ACCESS Research Group: Design of A Case Control Etiologic Study of Sarcoidosis (ACCESS). J Clin Epidemiol 52:1173–1186, 1999.
10. Kajdasz DK, Lackland DT, Mohr LC, et al: A current assessment of rurally linked exposures as potential risk factors for sarcoidosis. Ann Epidemiol 11:111–117, 2001.
11. Kucera GP, Rybicki BA, Kirkey KL, et al: Occupational risk factors for sarcoidosis in African-American siblings. Chest 123:1527–1535, 2003.
12. Song Z, Marzilli L, Greenlee BM, et al: Mycobacterial catalase-peroxidase is a tissue antigen and target of the adaptive immune response in systemic sarcoidosis. J Exp Med 201:755–767, 2005.
13. Drake WP, Pei Z, Collins R, et al: Molecular analysis of sarcoidosis specimens for *Mycobacterium* nucleic acids. Emerg Infect Dis 8:1334–1341, 2002.
14. Allen ST, Evans W, Hajizadeh R, et al: Superoxide dismutase A antigens derived from molecular analysis of sarcoidosis granulomas elicit systemic Th-1 immune responses. Respir Res 9:36, 2008.
15. Gupta D, Agarwal R, Aggarwal AN, et al: Molecular evidence for the role of mycobacteria in sarcoidosis: A meta-analysis. Eur Respir J 30:508–516, 2007.
16. Drake WP, Dhason R, Hajizadeh R, et al: Cellular recognition of *Mycobacterium* ESAT-6 and katG peptides in systemic sarcoidosis. Infect Immun 75:527–530, 2007.
17. Chen ES, Walstrom J, Song Z, et al: T cell responses to mycobacterial catalase-peroxidase profile a pathogenic antigen in systemic sarcoidosis. J Immunol 181:8784–8796, 2008.
18. Ichikawa H, Kataoka M, Hiramatsu J, et al: Quantitative analysis of propionibacterial DNA in bronchoalveolar lavage cells from patients with sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis 25:15–20, 2008.
19. Ishige I, Usui Y, Takemura T, et al: Quantitative PCR of mycobacterial and propionibacterial DNA in lymph nodes of Japanese patients with sarcoidosis. Lancet 354:120–123, 1999.
20. Eishi Y, Suga M, Ishige I, et al: Quantitative analysis of mycobacterial and propionibacterial DNA in lymph nodes of Japanese and European patients with sarcoidosis. J Clin Microbiol 40:198–204, 2002.
21. Gazouli M, Ikonomopoulos J, Trigidou R, et al: Assessment of mycobacterial, proprionibacterial, and HHV-8 DNA in tissues of Greek patients with sarcoidosis. J Clin Microbiol 40:3060–3063, 2002.
22. Ishige I, Eishi Y, Takemura T, et al: *Propionibacterium acnes* is the most common bacterium commensal in peripheral lung tissue and mediastinal lymph nodes from subjects without sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis 22:33–42, 2005.
23. Wahlström J, Dengjel J, Persson B, et al: Identification of HLA-DR–bound peptides presented by human bronchoalveolar lavage cells in sarcoidosis. J Clin Invest 117:3576–3582, 2007.
24. Inui N, Matsui T, Suda T, et al: Anti-endothelial cell antibodies in patients with sarcoidosis. Chest 133:955–960, 2008.
25. Hunninghake GW, Gadek JE, Kawanami O, et al: Inflammatory and immune processes in the human lung in health and disease: Evaluation by bronchoalveolar lavage. Am J Pathol 97:199–206, 1979.
26. Vourlekis JS, Sawyer RT, Newman LS: Sarcoidosis: Developments in etiology, immunology, and therapeutics. Adv Intern Med 45:209–257, 2000.
27. Moller DR, Chen ES: What causes sarcoidosis? Curr Opin Pulm Med 8:429–434, 2002.
28. Gerke AK, Hunninghake G: The immunology of sarcoidosis. Clin Chest Med 29:379–390, 2008.

29. Ziegenhagen MW, Muller-Quernheim J: The cytokine network in sarcoidosis and its clinical relevance. J Intern Med 253:18–30, 2003.
30. Kim DS, Paik SH, Lim CM, et al: Value of ICAM-1 expression and soluble ICAM-1 level as a marker of activity in sarcoidosis. Chest 115:1059–1065, 1999.
31. Berlin M, Lundahl J, Skold CM, et al: The lymphocytic alveolitis in sarcoidosis is associated with increased amounts of soluble and cell-bound adhesion molecules in bronchoalveolar lavage fluid and serum. J Intern Med 244:333–340, 1998.
32. Pforte A, Schiessler A, Kressenstein S, et al: ICAM-1 expression on alveolar macrophages and in serum of sarcoidosis patients. J Clin Lab Immunol 46:125–135, 1995.
33. Dalhoff K, Bohnet S, Braun J, et al: Intercellular adhesion molecule 1 (ICAM-1) in the pathogenesis of mononuclear cell alveolitis in pulmonary sarcoidosis. Thorax 48:1140–1144, 1993.
34. Striz I, Wang YM, Kalaycioglu O, et al: Expression of alveolar macrophage adhesion molecules in pulmonary sarcoidosis. Chest 102:882–886, 1992.
35. Moller DR: T-cell receptor genes in sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis 15:158–164, 1998.
36. Moller DR: Involvement of T cells and alterations in T cell receptors in sarcoidosis. Semin Respir Infect 13:174–183, 1998.
37. Ma Y, Gal A, Koss MN. The pathology of pulmonary sarcoidosis: Update. Semin Diagn Pathol 24:150–161, 2007.
38. Rosen Y: Pathology of sarcoidosis. Semin Respir Crit Care Med 28:36–52, 2007.
39. Moller DR: Pulmonary fibrosis of sarcoidosis: New approaches, old ideas. Am J Respir Cell Mol Biol 29:S37–S41, 2003.
40. Lecossier D, Valeyre D, Loiseau A, et al: Antigen-induced proliferative response of lavage and blood T lymphocytes. Comparison of cells from normal subjects and patients with sarcoidosis. Am Rev Respir Dis 144:861–868, 1991.
41. Miyara M, Amoura Z, Parizot C, et al: The immune paradox of sarcoidosis and regulatory T cells. J Exp Med 203:359–370, 2006.
42. Mathew S, Bauer KL, Fischoeder A, et al: The anergic state in sarcoidosis is associated with diminished dendritic cell function. J Immunol 181:746–755, 2008.
43. Harrington D, Major M, Rybicki BA, et al: Familial sarcoidosis: Analysis of 91 families. Sarcoidosis 11:240–243, 1994.
44. Rybicki BA, Maliarik MJ, Major M, et al: Genetics of sarcoidosis. Clin Chest Med 18:707–717, 1997.
45. Schurmann M, Reichel P, Muller-Myhsok B, et al: Angiotensin-converting enzyme (ACE) gene polymorphisms and familial occurrence of sarcoidosis. J Intern Med 249:77–83, 2001.
46. Schurmann M, Lympany PA, Reichel P, et al: Familial sarcoidosis is linked to the major histocompatibility complex region. Am J Respir Crit Care Med 162:861–864, 2000.
47. Schurmann M, Bein G, Kirsten D, et al: HLA-DQB1 and HLA-DPB1 genotypes in familial sarcoidosis. Respir Med 92:649–652, 1998.
48. Rossman MD, Thompson B, Federick M, et al: *HLA-DRB1*1101*: A significant risk factor for sarcoidosis in blacks and whites. Am J Hum Genet 73:720–735, 2003.
49. Iannuzzi MC, Maliarik MJ, Poisson LM, Rybicki BA: Sarcoidosis susceptibility and resistance HLA-DQB1 alleles in African Americans. Am J Respir Crit Care Med 167:1225–1231, 2003.
50. Sato H, Grutters JC, Pantelidis P, et al: HLA-DQB1*0201: A marker for good prognosis in British and Dutch patients with sarcoidosis. Am J Respir Cell Mol Biol 27:406–412, 2002.
51. Iannuzzi MC, Maliarik MJ, Poisson LM, et al: Sarcoidosis susceptibility and resistance HLA-DQB1 alleles in African Americans. Am J Respir Crit Care Med 167:1225–1231, 2003.
52. Voorter CE, Drent M, van den Berg-Loonen EM: Severe pulmonary sarcoidosis is strongly associated with the haplotype HLA-DQB1*0602-DRB1*150101. Hum Immunol 66:826–835, 2005.
53. Smith G, Brownell I, Sanchez M, et al: Advances in the genetics of sarcoidosis. Clin Genet 73:401–412, 2008.
54. Grunewald J, Wahlstrom J, Berlin M, et al: Lung restricted T cell receptor AV2S3 CD4 T cell expansions in sarcoidosis patients with a shared HLA-DRbeta chain conformation. Thorax 57:348–352, 2002.
55. Pabst S, Baumgarten G, Stremmel A et al: Toll-like receptor (TLR) 4 polymorphisms are associated with a chronic course of sarcoidosis. Clin Exp Immunol 143:420–426, 2006.
56. Rybicki BA, Walewski JL, Maliarik MJ, et al, and the ACCESS Research Group: The BTNL2 gene and sarcoidosis susceptibility in African Americans and Whites. Am J Hum Genet 77:491–499, 2005.
57. Spagnolo P, Sato H, Grutters JC, et al: Analysis of BTNL2 genetic polymorphisms in British and Dutch patients with sarcoidosis. Tissue Antigens 70:219–227, 2007.
58. Jonth AC, Silveira L, Fingerlin TE, et al: TGF-beta 1 variants in chronic beryllium disease and sarcoidosis. J Immunol 179:4255–4262, 2007.
59. Hofmann S, Franke A, Fischer A, et al: Genome-wide association study identifies ANXA11 as a new susceptibility locus for sarcoidosis. Nat Genet 40:1103–1106, 2008.
60. Foley PJ, Lympany PA, Puscinska E, et al: Analysis of MHC encoded antigen-processing genes TAP1 and TAP2 polymorphisms in sarcoidosis. Am J Respir Crit Care Med 160:1009–1014, 1999.
61. Swider C, Schnittger L, Bogunia-Kubik K, et al: TNF-alpha and HLA-DR genotyping as potential prognostic markers in pulmonary sarcoidosis. Eur Cytokine Netw 10:143–146, 1999.
62. Takashige N, Naruse TK, Matsumori A, et al: Genetic polymorphisms at the tumour necrosis factor loci (TNFA and TNFB) in cardiac sarcoidosis. Tissue Antigens 54:191–193, 1999.
63. Pandey JP, Frederick M: TNF-alpha, IL1-beta, and immunoglobulin (GM and KM) gene polymorphisms in sarcoidosis. Hum Immunol 63:485–491, 2002.
64. Yamaguchi E, Itoh A, Hizawa N, et al: The gene polymorphism of tumor necrosis factor-beta, but not that of tumor necrosis factor-alpha, is associated with the prognosis of sarcoidosis. Chest 119:753–761, 2001.
65. Grutters JC, Sato H, Pantelidis P, et al: Increased frequency of the uncommon tumor necrosis factor-857T allele in British and Dutch patients with sarcoidosis. Am J Respir Crit Care Med 165:1119–1124, 2002.
66. Maliarik MJ, Rybicki BA, Malvitz E, et al: Angiotensin-converting enzyme gene polymorphism and risk of sarcoidosis. Am J Respir Crit Care Med 158:1566–1570, 1998.
67. Hizawa N, Yamaguchi E, Furuya K, et al: The role of the C-C chemokine receptor 2 gene polymorphism V64I (CCR2–64I) in sarcoidosis in a Japanese population. Am J Respir Crit Care Med 159:2021–2023, 1999.
68. Petrek M, Drabek J, Kolek V, et al: CC chemokine receptor gene polymorphisms in Czech patients with pulmonary sarcoidosis. Am J Respir Crit Care Med 162:1000–1003, 2000.
69. Spagnolo P, Renzoni EA, Wells AU, et al: C-C chemokine receptor 2 and sarcoidosis: Association with Löfgren's syndrome. Am J Respir Crit Care Med 168:1162–1166, 2003.
70. Harrison BD, Shaylor JM, Stokes TC, et al: Airflow limitation in sarcoidosis—A study of pulmonary function in 107 patients with newly diagnosed disease. Respir Med 85:59–64, 1991.
71. Prabhakar HB, Rabinowitz CB, Gibbons FK, et al: Imaging features of sarcoidosis on MDCT, FDG PET, and PET/CT. AJR Am J Roentgenol. 190(3 Suppl):S1–S6, 2008.
72. de Boer S, Milne DG, Zeng I, Wilsher ML: Does CT scanning predict the likelihood of a positive transbronchial biopsy in sarcoidosis? Thorax 64:436–439, 2009.
73. McLoud TC, Epler GR, Gaensler EA, et al: A radiographic classification for sarcoidosis: Physiologic correlation. Invest Radiol 17:129–138, 1982.
74. Bjermer L, Thunell M, Rosenhall L, et al: Endobronchial biopsy positive sarcoidosis: Relation to bronchoalveolar lavage and course of disease. Respir Med 85:229–234, 1991.
75. Stjernberg N, Thunell M: Pulmonary function in patients with endobronchial sarcoidosis. Acta Med Scand 215:121–126, 1984.
76. Soskel NT, Sharma OP: Pleural involvement in sarcoidosis. Curr Opin Pulm Med 6:455–468, 2000.
77. Hamacher J, Losa F, Im Hof V, et al: [Tuberculous pleuritis in pre-existent sarcoidosis] (German). Schweiz Med Wochenschr 121:577–582, 1991.
78. Matsuzawa K, Hamada K, Tokuyama T, et al: [Photomicrographs of a pleural biopsy specimen, showing malignant mesothelioma and necrosis—Malignant pleural mesothelioma in a patient with sarcoidosis] (Japanese). Nihon Kyobu Shikkan Gakkai Zasshi 35:687–691, 1997.

79. Liebow AA: The J. Burns Amberson lecture—Pulmonary angiitis and granulomatosis. Am Rev Respir Dis 108:1–18, 1973.
80. Quaden C, Tillie-Leblond I, Delobbe A, et al. Necrotising sarcoid granulomatosis: Clinical, functional, endoscopical and radiographical evaluations. Eur Respir J 26:778–785, 2005.
81. Gilman MJ, Wang KP: Transbronchial lung biopsy in sarcoidosis: An approach to determine the optimal number of biopsies. Am Rev Respir Dis 122:721–724, 1980.
82. Oki M, Saka H, Kitagawa C, et al: Real-time endobronchial ultrasound-guided transbronchial needle aspiration is useful for diagnosing sarcoidosis. Respirology 12:863–868, 2007.
83. Winterbauer RH, Lammert J, Selland M, et al: Bronchoalveolar lavage cell populations in the diagnosis of sarcoidosis. Chest 104:352–361, 1993.
84. Costabel U, Ohshimo S, Guzman J: Diagnosis of sarcoidosis. Curr Opin Pulm Med 14:455–461, 2008.
85. Ma Y, Gal A, Koss MN: The pathology of pulmonary sarcoidosis: update. Semin Diagn Pathol 24:150–161, 2007.
86. Krespi YP, Kuriloff DB, Aner M: Sarcoidosis of the sinonasal tract: A new staging system. Otolaryngol Head Neck Surg 112:221–227, 1995.
87. Tami TA: Sinonasal sarcoidosis: Diagnosis and management. Semin Respir Crit Care Med 23:549–554, 2002.
88. Roberts WC, McAllister HA Jr, Ferrans VJ: Sarcoidosis of the heart: A clinicopathologic study of 35 necropsy patients (group 1) and review of 78 previously described necropsypatients (group 11). Am J Med 63:86–108, 1977.
89. Silverman KJ, Hutchins GM, Bulkley BH: Cardiac sarcoid: A clinicopathologic study of 84 unselected patients with systemic sarcoidosis. Circulation 58:1204–1211, 1978.
90. Ayyala US, Nair AP, Padilla ML: Cardiac sarcoidosis. Clin Chest Med 29:493–508, 2008.
91. Kim JS, Judson MA, Donnino R, et al: Cardiac sarcoidosis. Am Heart J 157:9–21, 2009.
92. Smedema JP, Snoep G, van Kroonenburgh MP, et al: Evaluation of the accuracy of gadolinium-enhanced cardiovascular magnetic resonance in the diagnosis of cardiac sarcoidosis. J Am Coll Cardiol 45:1683–1690, 2005.
93. Mehta D, Lubitz SA, Frankel Z, et al: Cardiac involvement in patients with sarcoidosis: Diagnostic and prognostic value of outpatient testing. Chest 133:1426–1435, 2008.
94. Rothova A: Ocular involvement in sarcoidosis. Br J Ophthalmol 84:110–116, 2000.
95. Hershey JM, Pulido JS, Folberg R, et al: Non-caseating conjunctival granulomas in patients with multifocal choroiditis and panuveitis. Ophthalmology 101:596–601, 1994.
96. Stanbury RM, Graham EM, Murray PI: Sarcoidosis. Int Ophthalmol Clin 35:123–137, 1995.
97. Rothova A, Suttorp-van Schulten MS, Frits Treffers W, et al: Causes and frequency of blindness in patients with intraocular inflammatory disease. Br J Ophthalmol 80:332–336, 1996.
98. Teirstein A: Neuromuscular sarcoidosis. Semin Respir Crit Care Med 23:505–512, 2002.
99. Vagal AS, Shipley R, Meyer CA: Radiological manifestations of sarcoidosis. Clin Dermatol 25:312–325, 2007.
100. Sharma OP: Vitamin D, calcium, and sarcoidosis. Chest 109:535–539, 1996.
101. Kahi CJ, Saxena R, Temkit M, et al: Hepatobiliary disease in sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis 23:117–123, 2006.
102. Adla M, Downey KK, Ahmad J: Hepatic sarcoidosis associated with pegylated interferon alfa therapy for chronic hepatitis C—Case report and review of literature. Dig Dis Sci 53:2810–2812, 2008. Epub 2008;March 5.
103. Thadani U, Aber CP, Taylor JJ: Massive splenomegaly, pancytopenia and haemolytic anaemia in sarcoidosis. Acta Haematol 53:230–240, 1975.
104. Wilcox A, Bharadwaj P, Sharma OP: Bone sarcoidosis. Curr Opin Rheumatol 12:321–330, 2000.
105. Zisman DA, Shorr AF, Lynch JP: Sarcoidosis involving the musculoskeletal system. Semin Respir Crit Care Med 23:555–570, 2002.
106. Judson MA, Baughman RP, Teirstein AS, et al: Defining organ involvement in sarcoidosis: The ACCESS proposed instrument. ACCESS Research Group. A Case Control Etiologic Study of Sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis 16:75–86, 1999.
107. Newman LS: Metals that cause sarcoidosis. Semin Respir Infect 13:212–220, 1998.
108. Safirstein BH, Klukowicz A, Miller R, et al: Granulomatous pneumonitis following exposure to the World Trade Center collapse. Chest 123:301–304, 2003.
109. Fireman E, Haimsky E, Noiderfer M, et al: Misdiagnosis of sarcoidosis in patients with chronic beryllium disease. Sarcoidosis Vasc Diffuse Lung Dis 20:144–148, 2003.
110. Müller-Quernheim J, Gaede KI, Fireman E, et al: Diagnoses of chronic beryllium disease within cohorts of sarcoidosis patients. Eur Respir J 27:1190–1195, 2006.
111. Weinberg I, Vasiliev L, Gotsman I: Anti-dsDNA antibodies in sarcoidosis. Semin Arthritis Rheum 29:328–331, 2000.
112. Nakamura H, Genma R, Mikami T, et al: High incidence of positive autoantibodies against thyroid peroxidase and thyroglobulin in patients with sarcoidosis. Clin Endocrinol (Oxf) 46:467–472, 1997.
113. Sakurai Y, Nakajima M, Kamisue S, et al: Preschool sarcoidosis mimicking juvenile rheumatoid arthritis: The significance of gallium scintigraphy and skin biopsy in the differential diagnosis. Acta Paediatr Jpn 39:74–78, 1997.
114. Fallahi S, Collins RD, Miller RK, et al: Coexistence of rheumatoid arthritis and sarcoidosis: Difficulties encountered in the differential diagnosis of common manifestations. J Rheumatol 11:526–529, 1984.
115. Mansour MJ, Al-Hashimi I, Wright JM. Coexistence of Sjögren's syndrome and sarcoidosis: A report of five cases. J Oral Pathol Med 36:337–341, 2007.
116. Oates E, Metherall J: Images in clinical medicine: Sarcoidosis. N Engl J Med 329:1394, 1993.
117. Grunewald J, Eklund A: Löfgren's syndrome: Human leukocyte antigen strongly influences the disease course. Am J Respir Crit Care Med 179:307–312, 2009.
118. Baughman RP, Costabel U, du Bois RM: Treatment of sarcoidosis. Clin Chest Med 29:533–548, 2008.
119. Doherty CB, Rosen T: Evidence-based therapy for cutaneous sarcoidosis. Drugs 68:1361–1383, 2008.
120. Paramothayan S, Lasserson T: Treatments for pulmonary sarcoidosis. Respir Med 102:1–9, 2008.
121. Reich JM: Adverse long-term effect of corticosteroid therapy in recent-onset sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis 20:227–234, 2003.
122. Young R: Pulmonary sarcoidosis: A prospective evaluation of glucocorticoid therapy. Ann Intern Med 7:207–212, 1970.
123. Harkleroad LE, Young RL, Savage PJ, et al: Pulmonary sarcoidosis: Long-term follow-up of the effects of steroid therapy. Chest 82:84–87, 1982.
124. Gibson GJ, Prescott RJ, Muers MF, et al: British Thoracic Society Sarcoidosis study: Effects of long-term corticosteroid treatment. Thorax 51:238–247, 1996.
125. Genestier L, Paillot R, Fournel S, et al: Immunosuppressive properties of methotrexate: Apoptosis and clonal deletion of activated peripheral T cells. J Clin Invest 102:322–328, 1998.
126. Baughman RP, Winget DB, Lower EE: Methotrexate is steroid sparing in acute sarcoidosis: Results of a double blind, randomized trial. Sarcoidosis Vasc Diffuse Lung Dis 17:60–66, 2000.
127. Lower EE, Baughman RP: Prolonged use of methotrexate for sarcoidosis. Arch Intern Med 155:846–851, 1995.
128. Baughman RP, Lower EE: Alternatives to corticosteroids in the treatment of sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis 14:121–130, 1997.
129. Webster GF, Razsi LK, Sanchez M, et al: Weekly low-dose methotrexate therapy for cutaneous sarcoidosis. J Am Acad Dermatol 24:451–454, 1991.
130. Kaye O, Palazzo E, Grossin M, et al: Low-dose methotrexate: An effective corticosteroid-sparing agent in the musculoskeletal manifestations of sarcoidosis. Br J Rheumatol 34:642–644, 1995.
131. Emery P, Breedveld FC, Lemmel EM, et al: A comparison of the efficacy and safety of leflunomide and methotrexate for the treatment of rheumatoid arthritis. Rheumatology (Oxford) 39:655–665, 2000.
132. Baughman RP, Lower EE: Leflunomide for chronic sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis 21:43–48, 2004.

133. Martinet Y, Pinkston P, Saltini C, et al: Evaluation of the in vitro and in vivo effects of cyclosporine on the lung T-lymphocyte alveolitis of active pulmonary sarcoidosis. Am Rev Respir Dis 138:1242–1248, 1988.
134. Wyser CP, van Schalkwyk EM, Alheit B, et al: Treatment of progressive pulmonary sarcoidosis with cyclosporin A: A randomized controlled trial. Am J Respir Crit Care Med 156:1371, 1997.
135. Pacheco Y, Marechal C, Marechal F, et al: Azathioprine treatment of chronic pulmonary sarcoidosis. Sarcoidosis 2:107–113, 1985.
136. Hof D: Long-term use of azathioprine as a steroid-sparing agent for chronic sarcoidosis. Am J Respir Crit Care Med 153:A870, 1996.
137. Lewis SJ, Ainslie GM, Bateman ED: Efficacy of azathioprine as second-line treatment in pulmonary sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis 16:87–92, 1999.
138. Muller-Quernheim J, Kienast K, Held M, et al: Treatment of chronic sarcoidosis with an azathioprine/prednisolone regimen. Eur Respir J 14:1117–1122, 1999.
139. Zic JA, Horowitz DH, Arzubiaga C, et al: Treatment of cutaneous sarcoidosis with chloroquine: Review of the literature. Arch Dermatol 127:1034–1040, 1991.
140. O'Leary TJ, Jones G, Yip A, et al: The effects of chloroquine on serum 1,25-dihydroxyvitamin D and calcium metabolism in sarcoidosis. N Engl J Med 315:727–730, 1986.
141. Sharma OP: Effectiveness of chloroquine and hydroxychloroquine in treating selected patients with sarcoidosis with neurological involvement. Arch Neurol 55:1248–1254, 1998.
142. British Tuberculosis Association: Chloroquine in the treatment of sarcoidosis: A report from the Research Committee of the British Tuberculosis Association. Tubercle 48:257–272, 1967.
143. Baltzan M, Mehta S, Kirkham TH, et al: Randomized trial of prolonged chloroquine therapy in advanced pulmonary sarcoidosis. Am J Respir Crit Care Med 160:192–197, 1999.
144. Demeter SL: Myocardial sarcoidosis unresponsive to steroids: Treatment with cyclophosphamide. Chest 94:202–203, 1988.
145. Lower EE, Broderick JP, Brott TG, et al: Diagnosis and management of neurological sarcoidosis. Arch Intern Med 157:1864–1868, 1997.
146. Carlesimo M, Giustini S, Rossi A, et al: Treatment of cutaneous and pulmonary sarcoidosis with thalidomide. J Am Acad Dermatol 32:866–869, 1995.
147. Rousseau L, Beylot-Barry M, Doutre MS, et al: Cutaneous sarcoidosis successfully treated with low doses of thalidomide. Arch Dermatol 134:1045–1046, 1998.
148. Lee JB, Koblenzer PS: Disfiguring cutaneous manifestation of sarcoidosis treated with thalidomide: A case report. J Am Acad Dermatol 39:835–838, 1998.
149. Oliver SJ, Kikuchi T, Krueger JG, et al: Thalidomide induces granuloma differentiation in sarcoid skin lesions associated with disease improvement. Clin Immunol 102:225–236, 2002.
150. Baughman RP, Judson MA, Teirstein AS, et al: Thalidomide for chronic sarcoidosis. Chest 122:227–232, 2002.
151. Zabel P, Entzian P, Dalhoff K, et al: Pentoxifylline in treatment of sarcoidosis. Am J Respir Crit Care Med 155:1665–1669, 1997.
152. Utz JP, Limper AH, Kalra S, et al: Etanercept for the treatment of stage II and III progressive pulmonary sarcoidosis. Chest 124:177–185, 2003.
153. Baughman RP, Lower EE: Infliximab for refractory sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis 18:70–74, 2001.
154. Petterson JA, Zochodne DW, Bell RB, et al: Refractory neurosarcoidosis responding to infliximab. Neurology 59:1660–1661, 2002.
155. Mallbris L, Ljungberg A, Hedblad MA, et al: Progressive cutaneous sarcoidosis responding to anti-tumor necrosis factor-alpha therapy. J Am Acad Dermatol 48:290–293, 2003.
156. Katz JM, Bruno MK, Winterkorn JM, et al: The pathogenesis and treatment of optic disc swelling in neurosarcoidosis: A unique therapeutic response to infliximab. Arch Neurol 60:426–430, 2003.
157. Sollberger M, Fluri F, Baumann T, et al: Successful treatment of steroid-refractory neurosarcoidosis with infliximab. J Neurol 251:760–761, 2004.
158. Carter JD, Valeriano J, Vasey JB, Bognar B: Refractory neurosarcoidosis: A dramatic response to infliximab. Am J Med 117:277–279, 2004.
159. Yee AM, Pochapin MB: Treatment of complicated sarcoidosis with infliximab anti-tumor necrosis factor-alpha therapy. Ann Intern Med 135:27–31, 2001.
160. Judson MA, Baughman RP, Costabel U, et al: Efficacy of infliximab in extrapulmonary sarcoidosis: Results from a randomised trial. Eur Respir J 31:1189–1196, 2008.
161. Keane J, Gershon S, Wise RP, et al: Tuberculosis associated with infiximab, a tumor necrosis factor alpha-neutralizing agent. N Engl J Med 345:1098, 2001.
162. Pia G, Pascalis L, Aresu G, et al: Evaluation of the efficacy and toxicity of the cyclosporine A-fluocortolone-methotrexate combination in the treatment of sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis 13:146–152, 1996.
163. Stevens DA, Kan VL, Judson MA, et al: Practice guidelines for diseases caused by *Aspergillus*. Infectious Diseases Society of America. Clin Infect Dis 30:696–709, 2000.
164. Soubani AO, Chandrasekar PH: The clinical spectrum of pulmonary aspergillosis. Chest 121:1988–1999, 2002.
165. Arcasoy SM, Christie JD, Pochettino A, et al: Characteristics and outcomes of patients with sarcoidosis listed for lung transplantation. Chest 120:873–880, 2001.
166. Shorr AF, Davies DB, Nathan SD: Predicting mortality in patients with sarcoidosis awaiting lung transplantation. Chest 124:922–928, 2003.
167. Judson MA: Lung transplantation for pulmonary sarcoidosis. Eur Respir J 11:738–744, 1998.
168. Kanj SS, Welty-Wolf K, Madden J, et al: Fungal infections in lung and heart-lung transplant recipients: Report of 9 cases and review of the literature. Medicine (Baltimore) 75:142–156, 1996.
169. Hadjiliadis D, Sporn TA, Perfect JR, et al: Outcome of lung transplantation in patients with mycetomas. Chest 121:128–134, 2002.
170. Bjortuft O, Foerster A, Boe J, et al: Single lung transplantation as treatment for end-stage pulmonary sarcoidosis: Recurrence of sarcoidosis in two different lung allografts in one patient. J Heart Lung Transplant 13:24–29, 1994.
171. Shah L. Lung transplantation in sarcoidosis. Semin Respir Crit Care Med 28:134–140, 2007.
172. Muller C, Briegel J, Haller M, et al: Sarcoidosis recurrence following lung transplantation. Transplantation 61:1117–1119, 1996.
173. Martinez FJ, Orens JB, Deeb M, et al: Recurrence of sarcoidosis following bilateral allogeneic lung transplantation. Chest 106:1597–1599, 1994.
174. Milman N, Burton C, Andersen CB, et al: Lung transplantation for end-stage pulmonary sarcoidosis: Outcome in a series of seven consecutive patients. Sarcoidosis Vasc Diffuse Lung Dis 22:222–228, 2005.
175. Walker S, Mikhail G, Banner N, et al: Medium term results of lung transplantation for end stage pulmonary sarcoidosis. Thorax 53:281–284, 1998.
176. Nunley DR, Hattler B, Keenan RJ, et al: Lung transplantation for end-stage pulmonary sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis 16:93–100, 1999
177. Shorr AF, Helman DL, Davies DB, Nathan SD: Sarcoidosis, race, and short-term outcomes following lung transplantation. Chest 125:990–996, 2004.

CHAPTER 60

DIFFUSE ALVEOLAR HEMORRHAGE AND RARE INFILTRATIVE DISORDERS OF THE LUNG

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RARE INFILTRATIVE DISORDERS OF THE LUNG
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Hermansky-Pudlak Syndrome
Dyskeratosis Congenita
Gaucher's Disease
Niemann-Pick Disease
Pulmonary Alveolar Microlithiasis

INTRODUCTION

This chapter discusses diffuse alveolar hemorrhage (DAH) and other rare infiltrative disorders of the lung. DAH is a life-threatening medical condition characterized by widespread hemorrhage from the pulmonary microcirculation (arterioles, capillaries, and venules). It can be seen in many different diseases, often as the primary manifestation. In the second section of the chapter, we discuss several rare infiltrative disorders of the lung, including neurofibromatosis, Hermansky-Pudlak syndrome, dyskeratosis congenita, Gaucher's disease, Niemann-Pick disease, and pulmonary alveolar microlithiasis.

DIFFUSE ALVEOLAR HEMORRHAGE

Unlike the more common forms of pulmonary hemorrhage that result from focal lesions (e.g., necrotizing pneumonia, bronchitis, bronchiectasis, malignancy, pulmonary infarction, arteriovenous malformation), DAH affects the majority of the alveolar capillary surface. DAH is a medical emergency that often results in acute respiratory failure and death. Pulmonologists must be prepared to promptly identify DAH, diagnose the underlying disease that is causing it, and institute appropriate medical therapy.

DEFINITION

DAH is defined by its pathology, which is characterized by intra-alveolar accumulation of erythrocytes (Fig. 60-1). There is often evidence of chronicity to the hemorrhage, with intra-alveolar hemosiderin-containing macrophages, erythrophagocytosis, and collections of free interstitial hemosiderin.[1] These findings can help distinguish true DAH from biopsy-related bleeding. Other features of

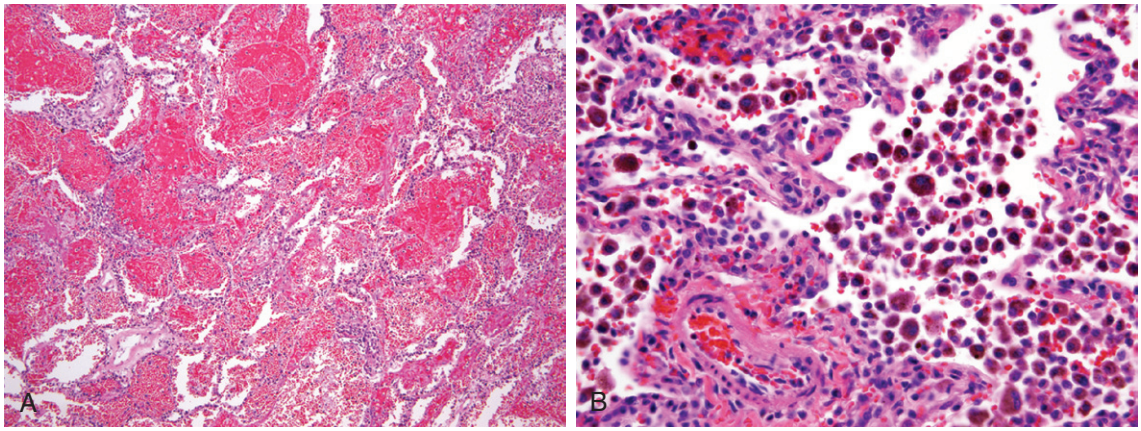

FIGURE 60-1 ■ Histopathology of diffuse alveolar hemorrhage. **A,** In acute diffuse alveolar hemorrhage, the alveoli show filling and distention by red blood cells admixed with fibrin. **B,** Chronic alveolar hemorrhage shows numerous hemosiderin-filled macrophages within air spaces. The alveolar septa may show mild fibrosis. (Images courtesy of Kirk Jones, MD, University of California, San Francisco.)

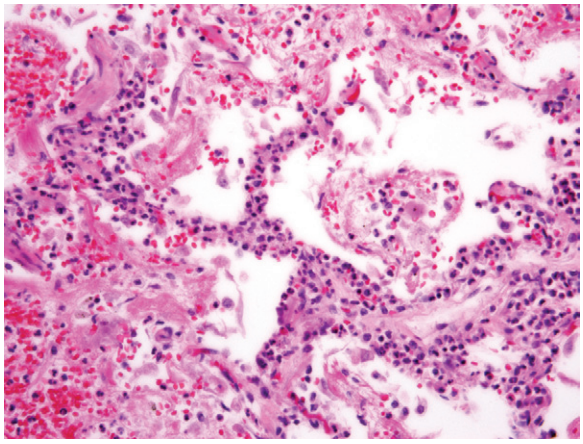

FIGURE 60-2 ■ Histopathology of diffuse alveolar hemorrhage accompanied by pulmonary capillaritis. Capillaritis is identified by accumulation of neutrophils within alveolar septa with accompanying fibrinoid necrosis and adherent alveolar fibrin within air spaces. (Images courtesy of Kirk Jones, MD, University of California, San Francisco.)

DAH include hyperplasia of the type II alveolar epithelial lining cells, intra-alveolar organization (organizing pneumonia), mononuclear cell infiltration of the alveolar interstitium, and small thrombi in the alveolar capillaries and venules.[1-3]

Many cases of DAH demonstrate neutrophilic inflammation of the alveolar interstitium known as *capillaritis* (Fig. 60-2).[4] Capillaritis is commonly associated with endothelial edema, injury, and localized fibrinoid necrosis.[2] Many of the neutrophils are undergoing leukocytoclasis and appear fragmented and pyknotic. Fragmentation of these cells leads to accumulation of nuclear dust in the lung parenchyma. Capillaritis may be central to the pathogenesis of many cases of DAH, with vascular injury and necrosis leading to loss of integrity of the epithelial-endothelial basement membranes and extravasation of red blood cells into the alveolar spaces.

CLINICAL PRESENTATION

History and Physical Examination

The classic clinical presentation of DAH includes hemoptysis, alveolar opacities on chest radiograph, and anemia.[5] However, many cases will demonstrate only one or two of these features; the absence of classic features does not rule out DAH. Other symptoms commonly reported are nonspecific (e.g., dyspnea, cough, chest pain, fever), although in some cases, disease-specific symptoms (e.g., sinusitis, rash, arthritis) may be present. In general, symptoms are usually of short duration, present from days to several weeks, and may be recurrent. The physical examination is likewise nonspecific, with inspiratory crackles common but not universal.

Radiology and Laboratory Evaluation

Laboratory evaluation often reveals anemia and leukocytosis. Serum creatinine levels may be elevated. Bronchoalveolar lavage (BAL) reveals a predominance of red blood cells and hemosiderin-containing macrophages.

The chest radiograph in DAH is generally abnormal, with bilateral alveolar opacities most commonly present (Fig. 60-3).[6] High-resolution computed tomography (HRCT) imaging is more sensitive for radiographic abnormalities showing bilateral "ground-glas" opacities or patchy consolidation (Fig. 60-4). With recurrent and chronic disease, reticulation may appear providing evidence of interstitial fibrosis. Kerley's B lines may occasionally be present.

Physiology

When measured, physiology may demonstrate restriction and gas exchange abnormalities, particularly in chronic cases. In acute DAH, an increase in the diffusing capacity for carbon monoxide (D_{LCO}) is often present, attributed to the increased binding of carbon monoxide

TABLE 60-1. Causes of Diffuse Alveolar Hemorrhage

VASCULITIS
Wegener's granulomatosis
Microscopic polyangiitis
Isolated pulmonary capillaritis
Mixed cryoglobulinemia
Behçet's syndrome
Henoch-Schönlein purpura
Pauci-immune glomerulonephritis

IMMUNOLOGIC
Goodpasture's syndrome
Connective tissue disease
Immune complex–associated glomerulonephritis
Acute pulmonary allograft rejection

COAGULATION DISORDERS

IDIOPATHIC PULMONARY HEMOSIDEROSIS

OTHER
Drugs/toxins
Diffuse alveolar damage
Mitral stenosis
Pulmonary veno-occlusive disease
Pulmonary capillary hemangiomatosis
Lymphangioleiomyomatosis/tuberous sclerosis

DIFFUSE INFILTRATIVE LUNG DISEASES

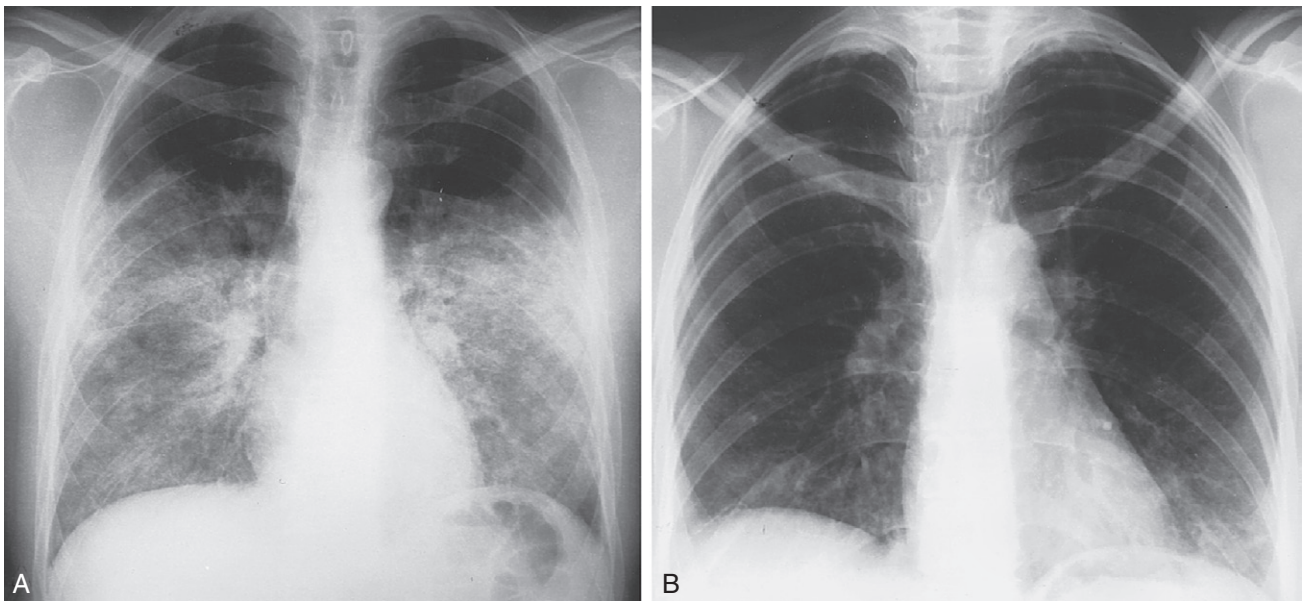

FIGURE 60-3 ■ Chest radiographs show diffuse alveolar opacities secondary to diffuse alveolar hemorrhage in patient with microscopic polyangiitis (**A**) and in a patient with Wegener's granulomatosis (**B**).

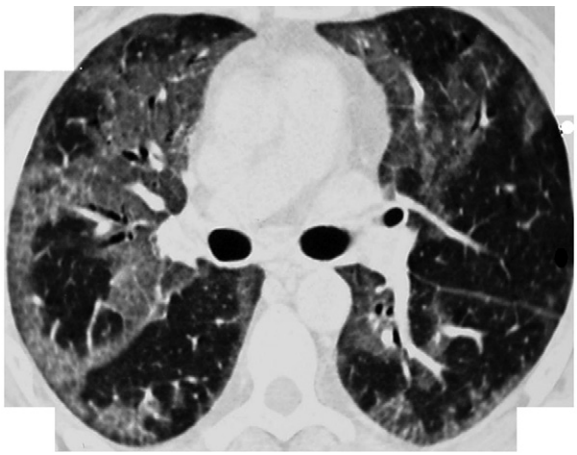

FIGURE 60-4 ■ High-resolution computed tomography scan of diffuse alveolar hemorrhage: confluent and patchy greyish areas.

to intra-alveolar hemoglobin.[7] This will generally resolve in 48 to 72 hours, as hemoglobin is degraded into hemosiderin.[8] Varying degrees of hypoxemia result from the ventilation-perfusion abnormalities produced by the alveolar hemorrhage, and patients often require ventilatory support.

CLASSIFICATION SCHEMA

There is no consensus classification schema for DAH, with clinical, histopathologic, and etiologic approaches all suggested.[5,9] One approach to classification is presented here (Table 60-1). The various causes of DAH are diverse; any source of injury to the alveolar microcirculation may contribute. The pathogenesis of DAH is thought to be primarily due to direct effects of autoantibodies on the alveolar capillary endothelium (Wegener's granulomatosis and microscopic polyangiitis), due to an

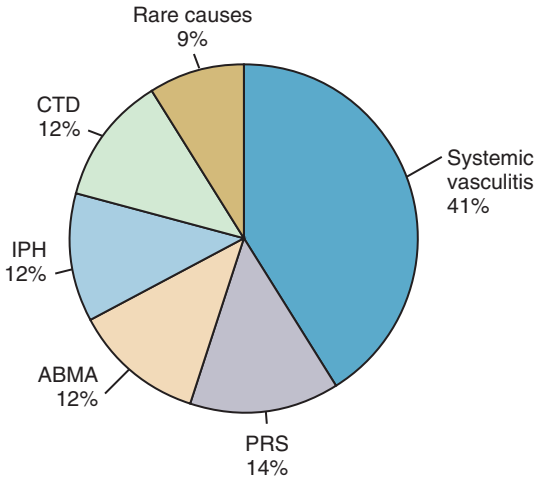

FIGURE 60-5 ■ Causes of diffuse alveolar hemorrhage. A retrospective review of 34 cases of diffuse alveolar hemorrhage found systemic vasculitis to be the most common cause (14 cases: 5 definite Wegener's, 6 probable Wegener's, and 3 unclassifiable), followed by unclassifiable pulmonary renal syndromes (PRS) (5 cases), Goodpasture's (4 cases), idiopathic pulmonary hemorrhage (4 cases), connective tissue disease (4 cases: 2 systemic lupus erythematosus, 1 rheumatoid arthritis, 1 juvenile rheumatoid arthritis), and other rare causes (3 cases: 2 idiopathic glomerulonephropathy, 1 immunoglobulin A [IgA] nephropathy); ABMA, anti–basement membrane antibody–mediated disease; CTD, connective tissue disease; IPH, idiopathic pulmonary hemorrhage. (Data from Travis WD, Colby TV, Lombard C, Carpenter H: A clinicopathologic study of 34 cases of diffuse pulmonary hemorrhage with lung biopsy confirmation. Am J Surg Pathol 14:1112–1125, 1990.)

antibody directed against the alveolar basement membrane (e.g., Goodpasture's syndrome), immune complex–mediated (e.g., systemic lupus erythematosus [SLE], Henoch-Schönlein purpura), or direct alveolar injury.[10]

Data on the relative frequency of the common causes of DAH are limited, but the most common cause of DAH appears to be systemic vasculitis, in particular Wegener's granulomatosis (Fig. 60-5). Other vasculitides are also implicated, including microscopic polyangiitis and isolated pulmonary capillaritis. A review of 34 cases of DAH found that vasculitis accounted for approximately half of the cases, followed by Goodpasture's syndrome (13%), idiopathic pulmonary hemosiderosis (IPH; 13%), connective tissue disease (13%).[1]

DIAGNOSTIC APPROACH

There are two steps to the diagnosis of DAH: identification of DAH and identification of its underlying cause. Both are essential to the timely evaluation of this life-threatening condition.

Diagnosis of Diffuse Alveolar Hemorrhage

The differential diagnosis for patients presenting with DAH is often broad because the classic findings of hemoptysis, alveolar opacities, and anemia are commonly absent. A thorough history and physical examination looking for evidence of potential associated conditions (e.g., connective tissue diagnosis, symptoms/signs of systemic vasculitis, anticoagulant medications) is essential, and initial studies should include a regular and an HRCT scan of the chest and complete blood count. If DAH remains in the differential diagnosis, the test of choice is fiberoptic bronchoscopy and this should be performed urgently.

Bronchoscopy with BAL is essential to the accurate identification of DAH. Serial BAL specimens should be obtained and sent for cell count and differential, with an increasing red blood cell count among sequential samples considered consistent with the diagnosis. Quantitative scoring of the hemosiderin concentration in alveolar macrophages obtained by BAL cytology has a good sensitivity for the diagnosis of DAH as well.[11] Importantly, BAL serves to rule out other conditions in the differential diagnosis such as infection, acute lung injury, and rare interstitial diseases such as acute eosinophilic pneumonia and pulmonary alveolar proteinosis.

Diagnosis of Underlying Cause

Once DAH has been identified, the underlying cause must be determined. Table 60-2 summarizes the differential clinical and laboratory features of some of the most common causes of DAH. In some cases, the etiology will be quite clear (e.g., history of SLE, drug exposure). In others, a careful laboratory evaluation is required. The presence of proteinuria and an abnormal urinary sediment (red blood cells and red blood cell casts) suggests an underlying glomerulonephritis consistent with the diagnosis of systemic vasculitis or Goodpasture's syndrome. Vasculitis is associated with the presence of antineutrophil cytoplasmic antibodies (ANCAs) directed against either proteinase 3 (c-ANCA) and myeloperoxidase (p-ANCA).[12] The c-ANCA level is more likely to be elevated in Wegener's granulomatosis, whereas P-ANCA is more likely to appear in microscopic polyangiitis, pauci-immune glomerulonephritis, and isolated pulmonary capillaritis. However, there can be crossover.[13] The diagnosis of Goodpasture's syndrome is supported by the presence of anti–glomerular basement membrane antibody (ABMA) in the serum. DAH in SLE is accompanied by reduced serum complement levels as well as the presence of antinuclear and native anti-DNA antibodies in the serum. Henoch-Schönlein purpura is characterized by the formation of immunoglobulin A (IgA) immune complexes present in the circulation and also bound to tissue.[14]

Role of Surgical Lung Biopsy

Surgical lung biopsy is rarely required for the diagnosis of DAH; BAL is generally sufficient. Whereas surgical lung biopsy can be useful in identifying the underlying cause of DAH, it is often nonspecific and most causes can be identified through clinical and serologic means.[1] Biopsy is most commonly considered in cases of

TABLE 60-2. Clinical Differentiation of Common Diffuse Alveolar Hemorrhage Syndromes

Syndrome	Anemia	Renal	Arthritis	Skin	ANA	dsDNA	RF	C_L	ABMA	c-ANCA (PR3)	p-ANCA (MPO)	Histopathology; Immunofluorescence
Wegener's granulomatosis	+	+	+	+	±	–	±	Normal	–	+	–	Capillaritis; ± granular
Microscopic polyangiitis	+	+	+	+	±	–	±	Normal	–	–	+	Capillaritis; No depositis
Isolated pulmonary capillaritis	+	–	–	–	–	–	–	Normal	–	–	–	Capillaritis; none
Goodpasture's syndrome	+	+	–	–	–	–	–	Normal	+	–	–	Bland or capillaritis; linear IgG
Systemic lupus erythematosus	+	+	+	±	+	+	±	Low	–	–	–	Bland or capillaritis; granular IgG
Idiopathic pulmonary hemosiderosis	+	–	–	–	–	–	–	Normal	–	–	–	Bland; none

ABMA, anti-basement membrane antibody; ANA, antinuclear antibody; c-ANCA (PR3), c-antineutrophil cytoplasmic antibody (antiproteinase-3); C_L, complement; dsDNA, anti-double stranded DNA antibody; IgG, immunoglobulin G; p-ANCA (MPO), p-antineutrophil cytoplasmic antibody (antimyeloperoxidase); RF, rheumatoid factor.

presumed vasculitis or Goodpasture's syndrome with equivocal serologies. Generally, these conditions are more easily confirmed by kidney biopsy, even in the absence of clinically evident renal involvement.[15]

SPECIFIC CAUSES OF DIFFUSE ALVEOLAR HEMORRHAGE

Vasculitis

Wegener's Granulomatosis

Wegener's granulomatosis is a systemic vasculitis that commonly involves the upper and lower respiratory tracts and kidneys. Other organs (e.g., eyes, skin) may be involved. DAH secondary to pulmonary capillaritis can either complicate an established case of Wegener's granulomatosis or represent the initial manifestation of the disease. Pulmonary capillaritis can be the sole histologic finding, or it can occur in combination with the more typical pathologic features of Wegener's granulomatosis. Examination of open-lung biopsy specimens from 87 patients with Wegener's granulomatosis revealed a 31% incidence of capillaritis, but in only 3 patients was this an isolated finding.[3] In another series, capillaritis was present in 17% of 35 patients, but never as an isolated finding.[16] In a postmortem study of 22 patients, capillaritis was the sole histologic feature in 3 cases and occurred in conjunction with the more typical granulomatous vasculitis in 7 cases.[17] In cases in which the typical histologic features (granulomatous inflammation, small and medium vessel vasculitis, and parenchymal necrosis) and clinical presentation (sinusitis, cavitary lung lesions) are absent and only DAH with or without a cutaneous leukocytoclastic vasculitis or a focal segmental necrotizing glomerulitis is present, the differentiation from microscopic polyangiitis is difficult. The specific diagnosis then depends on the ANCA pattern, with c-ANCA suggesting the diagnosis of Wegener's granulomatosis. In this disease, the characteristic histologic and clinical features may appear months to years after an initial presentation of DAH and capillaritis.[18] Circulating endothelial cells have been found in patients with Wegener's granulomatosis and in microscopic polyangiitis The presence of circulating endothelial cells may serve as a novel marker of active ANCA-positive vasculitis.[19]

Alveolar hemorrhage is often subclinical and recurrent in Wegener's granulomatosis (as well as microscopic polyangiitis), suggested by the presence of hemosiderin-laden macrophages on BAL. This pattern of frequently recurring DAH appears unique to the ANCA-associated vasculitides, because patients with collagen vascular disease–related DAH rarely manifest iron-positive macrophages.[20]

More than 40 cases of Wegener's granulomatosis with DAH and pulmonary capillaritis have been described. The rate of early mortality is 37%, and this mortality is most often due to acute respiratory or renal failure.[3,16–18,21,22] Renal disease in the form of a focal segmental necrotizing glomerulonephritis (Fig. 60-6), a cutaneous leukocytoclastic vasculitis, and arthritis often accompany the DAH. Treatment with high-dose corticosteroids and cyclophosphamide is the recommended therapy and, depending on the severity of the disease, can be initially administered intravenously. Azathioprine may be substituted for cyclophosphamide after remission.[23] Recurrences with tapering of the medications are to be expected. Disease activity is monitored by measurements of erythrocyte sedimentation rates, ANCA levels, serial diffusing capacities, and microscopic urine examinations. Recurrent or persistent disease after standard therapy may respond to intravenous immunoglobulin, although the response appears transient and side effects, including renal insufficiency, are frequent.[24]

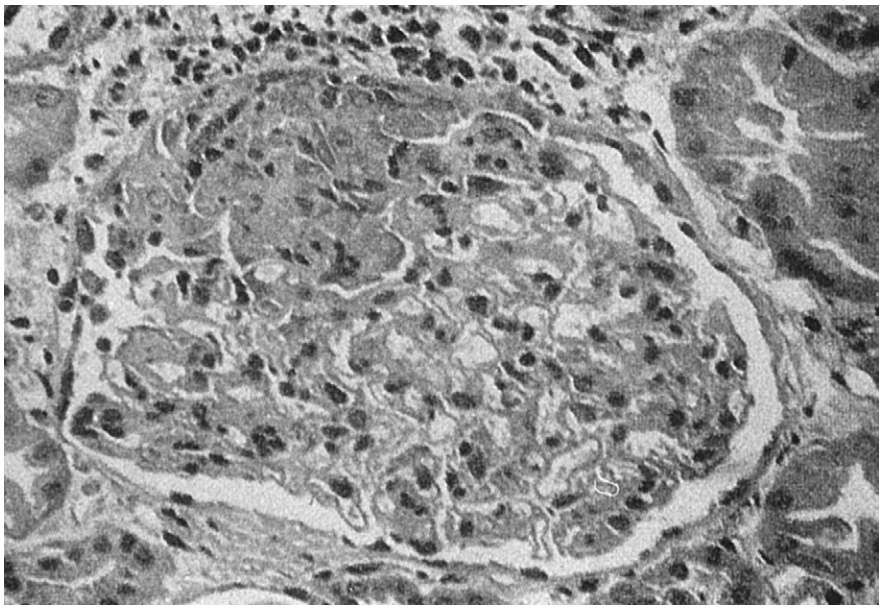

FIGURE 60-6 ■ Histopathology of a renal biopsy specimen demonstrates focal segmental necrotizing glomerulonephritis. (Original magnification ×40.)

Other novel therapies, including trimethoprim-sulfamethoxazole, antilymphocyte monoclonal antibodies, and tumor necrosis factor (TNF) inhibitors, have been tried with some success.[25]

As previously stated, the differentiation of Wegener's granulomatosis with DAH from microscopic polyangiitis is at times difficult because the clinical presentation, histopathologic findings, and serologic findings can be identical.[26] In fact, the response to treatment and the tendency for recurrences are similar. The differentiation can be established only after the development of the more typical upper airway disease and pathologic features of Wegener's granulomatosis.

Microscopic Polyangiitis

Microscopic polyangiitis is considered to be the small vessel variant of polyarteritis nodosa. It is a frequent cause of pulmonary capillaritis and DAH.[2,4,18,27–31] Microscopic polyangiitis is distinguishable from polyarteritis nodosa by the absence of medium-sized blood vessel involvement, the absence of asthma and systemic hypertension, and the relative sparing of the abdominal viscera. DAH has only rarely been documented as occurring with polyarteritis nodosa.[32]

The most consistent pathologic feature in microscopic polyangiitis is a focal segmental necrotizing glomerulonephritis, the renal lesion common to all systemic vasculitides. The lungs are involved by capillaritis in 20% to 30% of cases.[27,31] The alveolar hemorrhage tends to be severe and is often life-threatening. Other manifestations include fever, weight loss, cutaneous vasculitis, myalgias, arthralgias, diarrhea, and gastrointestinal bleeding from mucosal vasculitis that is often visible by direct examination, peripheral neuropathy, and in a few cases, sinusitis.[31,33,34] As with other vasculitides, the erythrocyte sedimentation rate is elevated, and nonspecific increases of serum rheumatoid factor and antinuclear antibody are found. Although circulating immune complexes are present in 45% of cases, tissue localization of these complexes is difficult to detect. Anti-DNA antibodies and hypocomplementemia, findings suggestive of SLE, are absent. A positive serum p-ANCA strongly supports the diagnosis. Antibodies to hepatitis B and C antigens are present in 33% of cases.[35]

Treatment consists of either oral or intravenous corticosteroids combined with cyclophosphamide or azathioprine.[23] Adjuvant treatment with plasmapheresis is recommended by some authors, but its additional efficacy is difficult to determine.[27,31] Outcome with early initiation of therapy for microscopic polyangiitis is generally good, with a 65% rate of 5-year survival. However, the presence of DAH contributes to an early mortality rate of 25%.[2,4,18,27–31] There is a tendency for recurrence with tapering of the medications. Intravenous immunoglobulin may be of use for resistant cases.[24] Factor VIIa has been used successfully with dramatic effects in one case of massive alveolar hemorrhage.[36]

The transition to pulmonary fibrosis and restrictive ventilatory impairment after recurrent DAH has been described,[8] and fibrotic lung disease has been reported as the presenting manifestation of microscopic polyangiitis.[37] There have been three cases of persistent, severe, irreversible airway dysfunction after recurrent episodes of DAH that complicated microscopic polyangiitis.[38] It is postulated that the combination of recurrent vascular obliteration from capillaritis and the release of neutral proteases and oxygen radicals from the overwhelming and recurrent burden of neutrophils causes permanent damage to the alveolar septa and results in emphysema.

Isolated Pulmonary Capillaritis

Isolated pulmonary capillaritis is a small vessel vasculitis confined to the lungs and without concomitant systemic involvement.[39] There are two forms: one with serum p-ANCA positivity and the other without this positive serology.[39,40] In one series, the latter type was the most frequent cause of pulmonary capillaritis and DAH.[39] Direct immunofluorescent studies of the lung in these patients have been negative. Although respiratory failure necessitating ventilatory support was frequent, response to corticosteroids and cyclophosphamide was good, and only one of eight patients died. Recurrences appeared in two subjects. During a 4-year follow-up period, clinical or serologic evidence for a systemic vasculitis or connective tissue disease did not appear.

Isolated forms of pulmonary capillaritis causing DAH must be distinguished from IPH, which is not associated with pulmonary capillaritis, as well as lung-limited forms of Goodpasture's syndrome, the initial presentation of collagen vascular disease, antiphospholipid antibody syndrome, and mitral stenosis. All patients who present with unexplained DAH should have an echocardiogram and undergo thoracoscopic or open-lung biopsy.

Mixed Cryoglobulinemia

Mixed cryoglobulinemia is a systemic vasculitis that is recognized by the presence of purpura, arthritis, hepatitis, and glomerulonephritis. It is thought to be an immune complex–induced disease, with most cases linked to hepatitis C (and less commonly hepatitis B) viral infection. Cutaneous vasculitis appearing as raised purpura is the clinical hallmark of this disease. Histologically, there is a perivascular polymorphonuclear infiltration with tissue extravasation and fragmentation in the dermis (leukocytoclastic vasculitis). The renal disease is a proliferative glomerulonephritis with positive granular immunofluorescence. Interstitial lung disease consisting of inflammation and fibrosis of the alveolar walls is the most common pulmonary manifestation.[41] There are two published cases of DAH with pulmonary capillaritis that complicated mixed cryoglobulinemia.[42,43]

Behçet's Syndrome

Behçet's syndrome is a chronic relapsing illness characterized by oral and genital ulceration, iridocyclitis, thrombophlebitis, and a multisystem disease consisting of a cutaneous vasculitis, arthritis, and meningoencephalitis.[44] Immune complexes have been identified in the

serum of active cases as well as in the lung and other organs.[44,45]

The lung is involved in 5% to 10% of cases of Behçet's syndrome. The pulmonary disease is typically a small vessel vasculitis affecting capillaries, venules, and arterioles. The renal disease is a focal segmental necrotizing vasculitis, as occurs in other systemic vasculitides. Immune complexes composed of IgG and complement have been identified in small pulmonary vessels in several cases.[44,45] In addition to alveolar hemorrhage, involvement of larger vessels can lead to aneurysms of the bronchial arteries, which can erode into bronchi, causing massive pulmonary hemorrhage and death.[46,47] Another potential cause for pulmonary hemorrhage in Behçet's syndrome is pulmonary arterial occlusion with infarction.[45] A review of 28 cases of pulmonary involvement in Behçet's syndrome emphasized several points: pulmonary complaints consisting of cough, hemoptysis, chest pain, and fever were more common in men than in women; pulmonary hemorrhage was the cause of death in 39%; and death usually occurred within 6 years of the first episode of hemoptysis. Other studies have confirmed the seriousness of this complication regardless of its cause.[46,47] Treatment consists of corticosteroids and immunosuppressive therapy.[48] Treatment with anti-TNF therapy has shown dramatic results in some case reports.[49]

Henoch-Schönlein Purpura

Henoch-Schönlein purpura, primarily a disease of children, also occurs in adults.[50] Adults typically present with palpable purpura (leukocytoclastic vasculitis) and glomerulonephritis.[14] The joints and gastrointestinal tract are commonly involved. Pulmonary involvement appears rare. In several large series, pulmonary disease, except for transient chest radiographic opacities, was not mentioned.[14] There have been proven cases of DAH with pulmonary capillaritis in patients with Henoch-Schönlein purpura.[51,52] In one, IgA immune complexes were present in the alveolar septa.[51] It is postulated that IgA immune complexes, which are present in the serum and kidneys of these patients, are responsible for the tissue damage that results in the clinical syndrome.[53] Corticosteroids were used in both cases and are generally recommended.

Pauci-immune Glomerulonephritis

Pauci-immune glomerulonephritis is one of three types of isolated renal vasculitides (the other two being immune complex–mediated glomerulonephritis and Goodpasture's syndrome). Pauci-immune glomerulonephritis lacks any immunoreaction product except for minimal accumulation of fibrin. It is histologically and immunologically similar to the glomerulonephritis of microscopic polyangiitis and Wegener's granulomatosis and is considered to represent a form of renal-limited vasculitis.[18] Up to 50% of affected patients develop pulmonary capillaritis and DAH, and a smaller number develop a full-blown systemic vasculitis indistinguishable from microscopic polyangiitis. Another indication that pauci-immune glomerulonephritis represents a limited form of vasculitis is the presence of serum p-ANCA in these patients. Because clinical manifestations are often limited to the lung and kidney, it can be confused with Goodpasture's syndrome.[18,53] Pauci-immune glomerulonephritis is distinguished by the absence of circulating basement membrane antibodies in the serum and by the negative findings of renal immunofluorescence studies. Treatment with high-dose corticosteroids plus immunosuppressive therapy with either cyclophosphamide or azathioprine is recommended.

Immunologic

Goodpasture's Syndrome

Whether the case reported by Goodpasture in 1919[54] describes the syndrome that bears his name is questionable. He described an 18-year-old man who died 6 weeks after an influenza infection and was found to have DAH, pleuritis, glomerulonephritis, splenic infarctions, and vasculitis of the small intestines. In 1965, an antibody to glomerular basement membrane (ABMA)—now identified as antibody against the NC1 domain of the α3 chain of type IV collagen—was identified in the kidneys and lungs of some patients with DAH and glomerulonephritis.[55,56] The diagnosis of Goodpasture's syndrome, also known as *ABMA disease*, is reserved for cases of DAH and glomerulonephritis in which this antibody appears in the serum, is bound to kidney and/or lung basement membranes in a linear manner by immunohistochemistry, or both.[18]

At least 90% of patients with Goodpasture's syndrome have a circulating ABMA.[57] The level of ABMA is not generally considered an accurate index of disease activity, although higher levels have been associated with more severe renal disease. In 60% to 80% of cases, the lung and renal disease appear simultaneously; in 5% to 10%, only the lung is affected; and in the remainder, renal disease exists by itself.[58,59] It is clear that ABMA is pathogenetic; however, the stimulus for its production remains unknown. The clinical onset of Goodpasture's syndrome has been temporarily related to infection with influenza A2 as well as to other respiratory infections, hydrocarbon exposure, and tobacco use.[60-62] The presence of histocompatibility human leukocyte antigens (HLA)-DRw2 and HLA-B7 (90% and 60%, respectively) in patients with Goodpasture's syndrome indicates that susceptible individuals are predisposed to disease that is often severe and progressive.[63,64] It is interesting to note that in some experimental models, the introduction of ABMA produces renal but not pulmonary disease. For deposition of this antibody to occur in the lung in those models, an additional injury that increases alveolar-capillary permeability is required.[65,66]

Men are more commonly affected (60%–80% of patients), and the concentration of cases is greatest between the ages of 20 and 30 years.[67,68] In older cases, the sex distribution is equal and the disease tends to be limited to the kidney.[61] Interestingly, DAH is more likely

to occur in patients who smoke.[61] The alveolar permeability is increased in most smokers and this is thought to be an important factor leading to DAH.[60] In one study, 100% of smokers with Goodpasture's syndrome developed both DAH and glomerulonephritis, whereas only 20% of nonsmokers developed DAH.[61] Resumption of cigarette smoking by patients who are in remission can result in recurrent episodes of DAH. Exposure to volatile hydrocarbons (e.g., petroleum products, turpentine, toluene, and pesticides) is associated with initiation, as well as exacerbations, of DAH.[58,59,69,70]

Symptoms most often refer to the lungs and consist of hemoptysis, cough, and dyspnea. Fatigue caused by iron-deficiency anemia and renal failure may predominate. Microscopic hematuria, proteinuria, and increases in the serum creatinine are often present, but gross hematuria with hypertension is unusual. The diffusing capacity may be increased during periods of active bleeding and is considered to be a useful monitor of new or recurrent DAH.[71] An increase of 30% above baseline is highly suggestive of an intra-alveolar hemorrhage, and this increase may precede pulmonary symptoms or radiographic changes. Chest radiography often reveals patchy air space abnormalities. HRCT scanning typically shows ground-glass opacities and consolidation and is more sensitive for DAH than plain chest radiography is.[72]

Pulmonary capillaritis is present in some cases of Goodpasture's syndrome, but the usual histologic appearance is bland pulmonary hemorrhage.[70] Alveolar wall necrosis, which is seen with systemic vasculitis, does not occur in Goodpasture's syndrome. The renal histologic findings are a focal segmental necrotizing glomerulonephritis with crescent formation. The major distinction between Goodpasture's syndrome and the other rapidly progressive glomerulonephritides is the presence of an uninterrupted linear deposition of immunoglobulin and complement along the glomerular basement membrane (Fig. 60-7). Identical findings are present on alveolar basement membranes.[73] Even when DAH dominates the clinical picture (i.e., there is no evidence of renal disease), renal biopsy will still reveal the typical linear staining.[74]

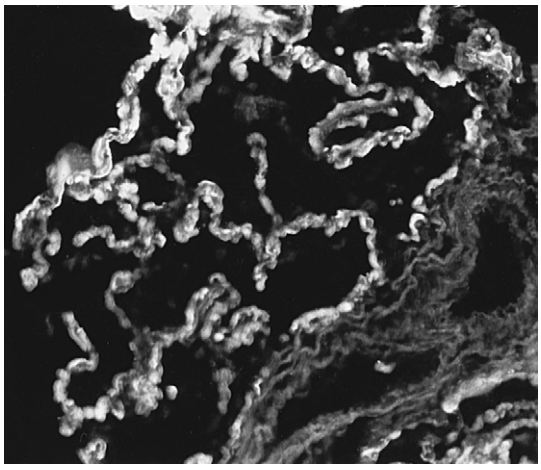

FIGURE 60-7 ■ Immunofluorescence study demonstrates linear staining (IgG) of alveolar walls in a patient with Goodpasture's syndrome. (Original magnification ×10.)

In the minority of patients without clinically evident renal involvement, DAH responds to oral or intravenous corticosteroids. Glomerulonephritis, if present, appears resistant to corticosteroid monotherapy. The combination of plasmapheresis (3–6 L daily for 2 weeks), corticosteroids, and cytotoxic drugs is effective, particularly in patients who do not have oligoanuria and do not require dialysis.[75–79] The combination of cyclophosphamide or azathioprine with corticosteroids leads to a dramatic fall in circulating ABMA, and oliguric dialysis-dependent subjects have responded to the point at which dialysis could be discontinued.[78,80] Anuric patients do not respond well to this combination therapy, and dialysis and renal transplantation are often necessary.[80] Case reports of successful treatment of refractory, life-threatening Goodpasture's syndrome with mycophenolate mofetil and anti-CD20 monoclonal antibody have been reported.[81,82] Bilateral nephrectomy, despite initial encouraging results for the control of DAH, no longer has a role in the management of Goodpasture's syndrome.

Over time, the survival rate in Goodpasture's syndrome has improved from 80% mortality at 6 months (half dying from DAH and the rest from renal insufficiency) to approximately 50% at 2 years.[68] With the aggressive treatment approach described previously, it is estimated that the 5-year survival rate exceeds 80% and fewer than 30% of patients require long-term dialysis. DAH is the usual cause of death, often being precipitated by a concomitant infection.[59] Spontaneous remission has occurred in cases without clinical evidence of renal disease, although this is not usual.[83] The most useful prognostic information comes from the kidney. Clinically, oliguric or anuric renal failure reduces the survival rate to 50% at 6 months. Histopathologically, less than 30% involvement of the glomeruli on biopsy predicts significant therapeutic response and improved survival. When 70% or more of glomeruli have formed crescents in conjunction with renal insufficiency, renal failure is progressive and often unresponsive to therapy, eventually necessitating dialysis.[80]

Connective Tissue Disease

Among the connective tissue diseases, DAH occurs most frequently in SLE.[18,84–86] It is unusual for DAH to be the initial manifestation of SLE, in contrast to acute lupus pneumonitis, which is often the initial manifestation.[87,88] Most patients with DAH have active lupus nephritis.[85] The onset of alveolar hemorrhage can be dramatic, producing severe gas-exchange abnormalities and necessitating mechanical ventilation. Reduced complement levels and increased serum titers of serum antinuclear antibodies confirm the diagnosis.

DAH must be distinguished from other causes of hemoptysis in SLE, specifically acute lupus pneumonitis. Acute lupus pneumonitis presents with fever, cough, and dyspnea. In 50% of cases, this is the initial manifestation of SLE.[88] It is an inflammatory condition, characterized histologically by organizing pneumonia, diffuse alveolar damage (DAD), cellular nonspecific interstitial

pneumonia, and occasionally, intra-alveolar hemorrhage. Although hemoptysis may accompany acute lupus pneumonitis, significant reductions of the hemoglobin are not to be expected. Unlike DAH, pleural and pericardial effusions are common in acute lupus pneumonitis. Other diagnostic considerations in the patient with suspected DAH include infectious pneumonias and pulmonary infarction associated with deep venous thrombosis with or without a circulating lupus anticoagulant.[89,90]

Histopathologic examination of DAH in patient with SLE generally reveals capillaritis, but bland pulmonary hemorrhage and DAD have been described.[88,91] Granular deposits of IgG and complement (C3) are commonly found in the alveolar interstitium and within the walls of intra-alveolar blood vessels (Fig. 60-8).[84,91–93] Capillaritis and immune complex deposition do not necessarily overlap. In one series of four patients with SLE and massive DAH associated with pulmonary capillaritis, only two demonstrated immune complexes by light and electron microscopic techniques.[94]

Treatment of DAH caused by SLE includes high-dose intravenous corticosteroids as well as azathioprine or cyclophosphamide. Plasmapheresis has been combined with chemotherapy in some cases, but it probably has little utility.[85] Broad-spectrum antibiotic coverage is recommended because of some evidence that infection may trigger the hemorrhage.[85] DAH is associated with a 50% mortality rate in SLE and can be recurrent in survivors.[87,91–95] Death is caused by massive hemorrhage, concurrent infection, or renal or central nervous system disease.

Rarely, DAH and glomerulonephritis occur in patients with rheumatoid arthritis,[96] scleroderma,[97] or mixed connective tissue disease. Isolated DAH with capillaritis has also been described in polymyositis, rheumatoid arthritis, and mixed connective tissue disease.[98,99] In polymyositis, DAH was the presenting manifestation, and in rheumatoid arthritis and mixed connective tissue disease, DAH and capillaritis followed the primary diagnosis (2–20 yr).[98,99] The absence of a systemic vasculitis in these cases, including glomerulonephritis, was unexpected.

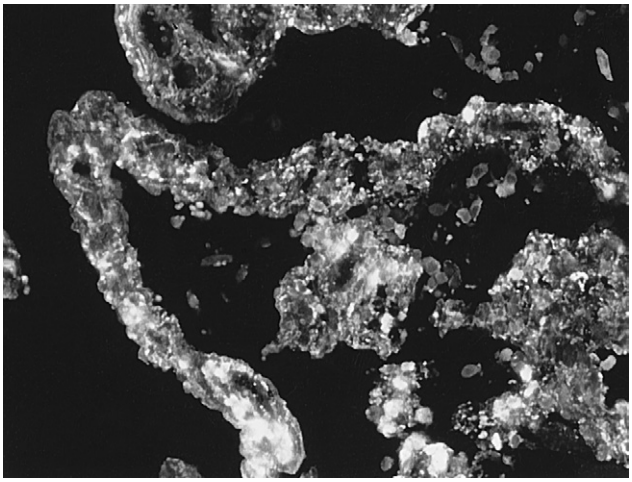

FIGURE 60-8 ■ Immunofluorescence study demonstrates granular deposition of IgG in the alveolar walls of a patient with systemic lupus erythematosus and diffuse alveolar hemorrhage. (Original magnification ×40.)

Immune Complex–Related Crescentic Glomerulonephritis

Immune complex–related crescentic glomerulonephritis is rarely accompanied by capillaritis and DAH.[1,100] Although the kidneys demonstrate granular immune deposits, immune complexes are not found in lung tissue.

Acute Pulmonary Allograft Rejection

Pulmonary capillaritis and DAH have been reported after lung transplantation for a variety of underlying diseases.[101] The suspected acute vascular rejection can occur weeks to months after the transplantation and may be the only histopathologic manifestation of allograft rejection. This represents a serious immunologic complication that threatens survival. In addition to standard anti-inflammatory therapy with corticosteroids and cytotoxic agents, plasmapheresis may be effective.

Coagulation Disorders

Coagulation disorders associated with DAH include disseminated intravascular coagulation,[102] idiopathic thrombocytopenic purpura,[103] thrombotic thrombocytopenic purpura,[104] acquired vitamin K deficiency,[105] and antiphospholipid antibody syndrome.[106] Uniquely among coagulation disorders, antiphospholipid antibody syndrome–associated DAH is sometimes associated with capillaritis.[107]

All anticoagulant medications have been associated with DAH, including coumadin and its derivatives,[108–110] thrombolytics,[111,112] and more recently, agents targeting the platelet glycoprotein IIb/IIIa.[113–115] In most iatrogenically anticoagulated patients, correction of the coagulation defect resolves the DAH.

DAH is common in patients with acute leukemia who have undergone induction chemotherapy and are thrombocytopenic.[116–118] Although thrombocytopenia surely contributes to the DAH, these patients also have evidence of DAD due to chemotherapy, oxygen toxicity, and infection that likely plays a central role.

Idiopathic Pulmonary Hemosiderosis

IPH is predominantly a disease of children, but adults represent approximately 20% of cases.[119,120] It is a diagnosis of exclusion,[119,120] and efforts to rule out other causes of DAH are essential. Among adults, men are more often affected, and there are reports of familial cases.[121] Some cases have occurred in the setting of celiac disease, and serum IgA levels are increased in 50% of cases.[122,123] The pathogenesis of IPH is not understood. Some cases may be secondary to environmental exposures, such as *Stachybotrys atra*, a toxigenic fungus that has been potentially linked to several cases of otherwise idiopathic alveolar hemorrhage.[124]

Recurrent hemoptysis due to DAH is the rule, ranging from intermittent blood-streaked sputum to life-threatening hemorrhage. Fever, cough, substernal chest pain, and fatigue secondary to iron-deficiency anemia are also reported. In selected pediatric cases, lymphadenopathy and hepatosplenomegaly are found. Renal disease is absent. In chronic recurrent disease, progressive dyspnea, finger clubbing, inspiratory crackles, and pulmonary fibrosis appear. Pulmonary function testing reveals a restrictive ventilatory defect with an increase in the D_{LCO} during periods of active bleeding. Chest imaging reveals diffuse ground-glass and ill-defined centrilobular nodules.[125] Measurements of serum antibodies reveal the absence of alternative etiology.

In adult cases, lung tissue is required to exclude the entity of isolated pulmonary capillaritis. The histologic examination of the lung in IPH reveals bland alveolar hemorrhage with hemosiderin accumulation.[120,126] There is hyperplasia of type II alveolar epithelial cells with capillary dilation and tortuosity. The iron content of the lung is increased, and it is the hemosiderin deposition in the interstitium that is thought to be the basis for collagen proliferation and parenchymal fibrosis. Pulmonary immune complexes are absent, differentiating IPH from isolated pulmonary Goodpasture's syndrome. Electron microscopic studies indicate degeneration of type I alveolar epithelial cells with exposure of and breaks in the basement membrane and discontinuity of the alveolar capillary structure.[126,127] Although nonspecific, these findings indicate a form of DAD.

Clinical benefit and recovery from the acute hemorrhage after corticosteroid therapy have been reported, but long-term benefit is unlikely.[120,128] Azathioprine has been successful in several cases.[126,129,130] Approximately 25% of patients are free of disease after the initial episode. Another 25% are free of active disease but have persistent dyspnea and anemia, and another quarter have persistent active disease that leads to fibrosis and severe restrictive lung disease. The rest have unresponsive disease with continued hemorrhage and death from respiratory failure. In those with persistent disease, the average survival is 3 to 5 years.[120,128] Adults have a better prognosis than children. Lung transplantation is controversial in this disease because IPH has been reported to recur after bilateral lung transplantation.[131]

Other Causes of Diffuse Alveolar Hemorrhage

Drugs/Toxins

There are many drugs that have been reported to cause DAH. Anticoagulants have been discussed previously. Most DAH due to drugs or toxins is associated with bland alveolar hemorrhage. This has been reported with abciximab, amiodarone, azathioprine, carbamazepine, cyclosporine, ara-C, dextran, docetaxel, fludarabine, hydralazine, methotrexate, radiographic contrast media, retinoic acid, sirolimus, TNF-α, and valproate.[132]

A few drugs have been associated with DAH and capillaritis, including tretinoin, propylthiouracil, phenytoin, and mitomycin.[133–137] DAH due to these drugs may also be associated with crescentic glomerulonephritis and elevated ANCA levels.

Penicillamine can result in DAH and an immune complex–mediated glomerulonephritis. Glomerular capillaries display a granular (as opposed to a linear) immunofluorescent pattern for IgG and C3.[138–141] Cases have appeared after as much as 20 years of treatment. Some authors have called this a drug-induced Goodpasture's syndrome, but the pattern of immunoglobulin deposition in the kidney differentiates this entity. Treatment with immunosuppressive therapy and even plasmapheresis may be required.[141]

Trimellitic anhydride is used for the manufacture of paints, epoxy resins, and plastics. DAH has been reported after the inhalation of fumes or dry powder, generally during spraying of this product on heated surfaces.[142–144] Antibodies to trimellitic anhydride in the serum and a latent period of 1 to 3 months both support an immunologic basis for this syndrome. Long-term physiologic impairment is unusual if further exposure is avoided.

Diffuse Alveolar Damage

DAD is the underlying histopathology of acute lung injury, and it has a variety of etiologies (Table 60-3). In DAD, the interstitium of the lung becomes edematous and the type I alveolar epithelial lining cells are sloughed. Neutrophilic inflammation and fibroblastic proliferation occurs, and hyaline membranes (eosinophilic strands of necrotic cells, protein, and fibrin) develop adjacent to the injured alveolar walls. In severe cases, red blood cells may enter the alveolar space as a result of injury to the alveolar-capillary interface, resulting in DAH. The neutrophilic inflammation in DAD-associated DAH is not as intense as it is in pulmonary capillaritis.

TABLE 60-3. Causes of Diffuse Alveolar Damage

ACUTE RESPIRATORY DISTRESS SYNDROME
Sepsis
Pneumonia (e.g., bacterial, viral, *Pneumocystis jirovecii* [*carinii*])
Trauma
Aspiration
Massive transfusion
Drugs (e.g., cytotoxic/chemotherapeutic agents, antibiotics)
CONNECTIVE TISSUE DISEASE
DIFFUSE LUNG DISEASE
Acute interstitial pneumonia
Acute exacerbation of idiopathic pulmonary fibrosis
RADIATION THERAPY
TOXIC INHALATION
Smoke
Ozone
Heavy metal fumes

Mitral Stenosis

Mitral stenosis can be clinically silent and, over time, can result in substantial pulmonary venous hypertension. In some cases, this can lead to the development of DAH.[145] The presentation can be dramatic, with massive hemoptysis occurring due to the rupture of engorged bronchial varicosities that develop as a result of long-standing left atrial hypertension. Less severe DAH may be recurrent and is often misdiagnosed, leading to chronic interstitial fibrosis. Radiographic findings consist of central ground-glass abnormalities and, in chronic cases, reticular abnormalities.[146] Repair or replacement of the stenotic mitral valve prevents recurrence.

Pulmonary Veno-occlusive Disease

Pulmonary veno-occlusive disease (PVOD) is a rare cause of pulmonary hypertension due to fibrous obliteration of small pulmonary veins and venules. PVOD affects men and women equally and involves all age groups, most commonly children and young adults.[147-149] Patients with PVOD present with dyspnea, syncope, and when severe, physical findings suggestive of cor pulmonale. Because PVOD is a postcapillary cause of pulmonary hypertension, paroxysmal nocturnal dyspnea, orthopnea, and DAH can also occur.

Right heart catheterization cannot easily distinguish PVOD from precapillary pulmonary hypertension because the pulmonary capillary wedge pressure is generally normal. Chest radiography shows signs of pulmonary hypertension; in some cases, interstitial opacities with septal thickening suggesting congestion as well as ground-glass abnormality from alveolar hemorrhage may be seen. Pleural effusions are common.

Pulmonary function studies reveal a reduced D_{LCO} with preservation of lung volumes, a physiologic picture similar to that found in other causes of pulmonary hypertension. Definitive diagnosis is achieved by lung biopsy, which demonstrates fibrous intimal obliteration of small pulmonary veins and venules, acute or recanalized thrombi, and hemosiderosis (Fig. 60-9).

Most cases of PVOD are idiopathic, but it has been reported after chemotherapy (e.g., carmustine, mitomycin, bleomycin) for malignant disease, bone marrow transplantation, and associated with connective tissue disease.[150-157] A mutation in the bone morphogenic protein receptor II gene (a gene associated with many cases of primary pulmonary hypertension) has been identified in a patient with idiopathic PVOD, suggesting an potential etiologic role.[158]

The use of pulmonary vasodilators in the treatment of PVOD is complicated and potentially harmful. Modest improvements with nifedipine and epoprostinol have been reported, but there have also been cases of these agents precipitating massive pulmonary edema and death.[159,160] Any trial of vasodilator therapy should be performed during right heart catheterization in an appropriate hospital setting. A few patients have had clinical responses to prednisone and azathioprine.[161,162] Anticoagulation for PVOD has been recommended based the potential role of thrombosis in the pathogenesis of PVOD and on limited data suggesting efficacy in patients with primary pulmonary hypertension. Anticoagulants should generally be avoided in patients who have had DAH.

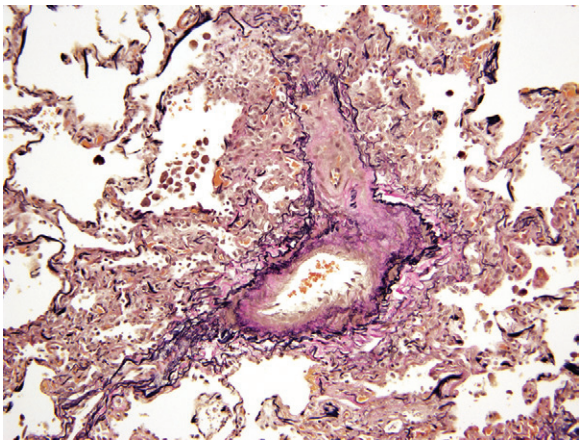

FIGURE 60-9 ■ Histopathology of pulmonary veno-occlusive disease. An elastic tissue stain (elastic van Gieson) shows marked intimal sclerosis with venous narrowing. These cases may show mild interstitial chronic inflammation and air space accumulation of hemosiderin-filled macrophages (hemosiderosis). (Images courtesy of Kirk Jones, MD, University of California, San Francisco.)

Pulmonary Capillary Hemangiomatosis

Pulmonary capillary hemangiomatosis (PCH) is a rare cause of pulmonary hypertension that can be associated with severe and recurrent DAH.[163-165] It is seen across age and gender. Patients universally present with dyspnea, often with evidence of right heart failure. Hemoptysis occurs in approximately one third of cases during the course of the disease.[163] Radiographic findings are nonspecific and commonly show alveolar opacities and evidence of pulmonary arterial hypertension. Pulmonary function test results are mixed, with both obstructive and restrictive changes described.[163] As with PVOD, right heart catheterization generally reveals a normal pulmonary capillary wedge pressure.

PCH is characterized by a proliferation of pulmonary capillaries, which infiltrate the interstitial, bronchial, and vascular structures of the lung (Fig. 60-10).[164] The exact mechanism of pulmonary hypertension and DAH is unclear, but mechanical rupture of hemangiomatous vessels in the setting of pulmonary arterial and venous occlusion and or thrombosis is likely responsible. Treatment of PCH with pulmonary vasodilators is generally contraindicated because worsening pulmonary edema and death have been reported as a result.[166,167] A few reports of treatment with recombinant interferon-alfa-2a suggest stabilization or improvement may occur.[163,168] Mean survival after diagnosis is usually 3 years, although successful treatment with lung transplantation has been reported.[163]

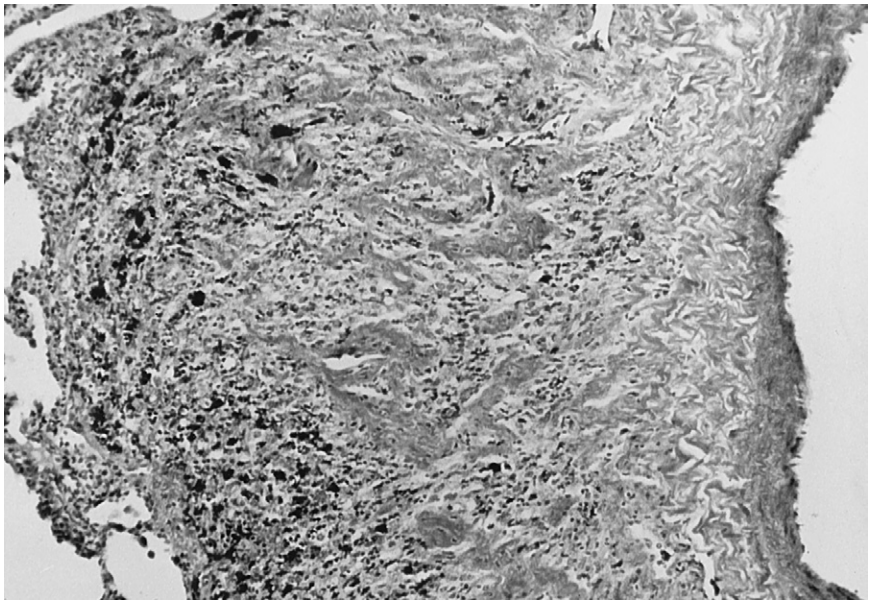

FIGURE 60-10 ■ Histopathology of pulmonary capillary hemangiomatosis. There is capillary proliferation in the wall of this large pulmonary vein. (Original magnification ×100.)

Lymphangioleiomyomatosis and Tuberous Sclerosis

Lymphangioleiomyomatosis (LAM) and tuberous sclerosis share a common pathobiology involving proliferation of smooth muscle in pulmonary interstitial, lymphatic, bronchial, and vascular structures (see Chapter 62 for a full discussion of these diseases).[169-171] Involvement of the pulmonary vasculature commonly results in episodes of alveolar hemorrhage. This alveolar bleeding is often focal; DAH is unusual. Pathologic specimens of the lung in LAM and tuberous sclerosis typically demonstrate focal areas of hemorrhage and hemosiderin deposition.

TABLE 60-4. Thoracic Manifestations of Neurofibromatosis

LUNG PARENCHYMAL
Interstitial lung disease
Metastatic neural tumor
MEDIASTINAL
Meningocele
Vagal nerve neurofibroma
CHEST WALL
Subcutaneous neurofibromas
Rib notching (inferior) from intercostal neurofibroma
Kyphoscoliosis
Apical neurofibroma (Pancoast's syndrome)

RARE INFILTRATIVE DISORDERS OF THE LUNG

Neurofibromatosis

There are two clinically and genetically distinct forms of neurofibromatosis termed neurofibromatosis 1 and neurofibromatosis 2. Lung disease is generally associated with neurofibromatosis 1, also known as von Recklinghausen's disease.[172] Neurofibromatosis 1 is an autosomal dominant disease caused by mutations in the NF1 gene at 17q11 and is characterized clinically by the appearance of cutaneous café au lait spots, subcutaneous neurofibromas, and Lisch nodule in the iris. The thoracic manifestations of neurofibromatosis are listed in Table 60-4. Interstitial lung disease occurs in 10% to 20% of affected patients, with dyspnea appearing between the third and the sixth decades.[173-177] Lower zone interstitial disease is the rule, with bullous disease eventually appearing in the upper zones. Physiologic testing early in the course of the disease reveals restrictive ventilatory impairment, but with time, an obstructive lung disease supervenes, because the fibrotic process in the lung involves not only the interstitium but also the small airways. Histopathology reveals cellular and fibrotic interstitial pneumonia.[173] Scar carcinoma has been reported as a complication of neurofibromatosis.[176]

Hermansky-Pudlak Syndrome

Hermansky-Pudlak syndrome is an autosomal recessive disorder characterized by occulocutaneous albinism and bleeding, found predominantly in inhabitants of Puerto Rico and southern Holland.[178-180] The biochemical defect is unknown, although putatively responsible genes have been identified and several mutations have been reported.[181] In patients with this disease, there is an accumulation of a chromolipid ceroid (related to lipofuscin) in the reticuloendothelial system. This result in partial tyrosine-negative albinism and a qualitative platelet defect. In addition, granulomatous colitis and progressive pulmonary fibrosis occur.

The interstitial lung disease is more likely to occur in women and develops during the second through fourth decades.[179] It progresses slowly and is unresponsive to treatment. Spirometry and measurement of lung volumes reveal restrictive lung disease. Chest radiography shows reticular opacities that progress to radiographic honeycomb lung over time. The histologic appearance is one of extensive interstitial fibrosis with filling of the alveolar spaces by ceroid-containing macrophages. These macrophages are identified in BAL and by subsequent staining with the Fontana-Masson silver reduction technique.

Dyskeratosis Congenita

Dyskeratosis congenita (DKC) is a rare inherited condition consisting most generally of mucocutaneous features including nail dystrophy, skin pigmentation, and oral leukoplakia.[182,183] Mutations in the genes encoding telomerase and telomere maintenance have been identified in nearly 50% of patients with this disease. Most patients with DKC are male, suggesting an X-linked pattern of inheritance.[184] Telomere length is important to control of cell division, and shortening of telomeres (either due to aging or inherited abnormalities) eventually leads to cellular senescence. In DKC, this most commonly manifests as bone marrow failure (isolated cytopenias to aplastic anemia).

Pulmonary fibrosis has been described in patients with DKC. These were initially described in patients following bone marrow transplant and may have been the result of increased susceptibility to chemotherapy-related pulmonary toxicity.[185] Since that time, additional cases of pulmonary fibrosis in patients with DKC have been reported.[186] There is little information on the histopathologic appearance of these cases. Approximately 11% of deaths in one cohort were due to pulmonary complications, with another 11% of deaths due to pulmonary complications of bone marrow transplantation.[186]

Gaucher's Disease

Gaucher's disease results from a deficiency in the enzyme glucocerebrosidase, a central component of ganglioside catabolism. The infantile form of Gaucher's disease, a hereditary disorder that is most common in Ashkenazi Jewish people, is uniformly fatal because of central nervous system involvement. However, the adult form (type 1 disease) is relatively benign and is associated with good long-term survival. This condition presents with hepatosplenomegaly, anemia, thrombocytopenia, long-bone erosions, and an increase in serum acid phosphatase. It is an autosomal recessive disease, the pathologic hallmark being the Gaucher cell. The Gaucher cell is a reticuloendothelial cell with a foamy cytoplasm due to the accumulation of glucocerebrosides. This leads to an excessive deposition of glucocerebrosides in the reticuloendothelial system, bone marrow, central nervous system, and occasionally, the lung.

Pulmonary disease occurs in only a small minority of adult cases.[187-189] Parenchymal disease, which consists of radiographically visible small nodules, appears during the first 3 decades of life. Pathologic examination reveals conglomerate masses of glucocerebroside-filled macrophages in the alveolar spaces and infiltrating the interstitium. Remarkably, there are limited to no acute or chronic inflammation or fibrosis. In addition to interstitial lung disease, affected patients are susceptible to lung infection. A single case of pulmonary hypertension from diffuse small vessel obstruction by these cells has been reported.[190] Although enzyme replacement (glucocerebrosidase) has therapeutic promise for many of the manifestations of Gaucher's disease, the interstitial lung disease appears unresponsive.[191]

Niemann-Pick Disease

Niemann-Pick disease results from a deficiency of sphingomyelinase that causes accumulation of sphingomyelin in the cells of the reticuloendothelial and central nervous systems.[192] As in Gaucher's disease, there is an infantile form of Niemann-Pick disease that is rapidly fatal. The adult form (type B disease), which appears during the second and third decades, is relatively benign, presenting with hepatosplenomegaly, hemostatic defects, platelet dysfunction, and occasionally, cerebellar ataxia. Interstitial lung disease, which appears as diffuse nodular infiltrates on the chest radiograph, is usually asymptomatic, although a mild restrictive ventilatory defect and reduced diffusing capacity have been reported.[193,194] As in Gaucher's disease, collections of foamy alveolar macrophages are found on lung biopsy.

Pulmonary Alveolar Microlithiasis

Pulmonary alveolar microlithiasis is an idiopathic rare disease in which concretions composed of calcium and phosphorus collect in alveolar spaces (Fig. 60-11).[195,196] In more than 50% of cases, a familial association is found.[197] A systemic disorder of calcium metabolism has not been identified, and the serum calcium and phosphate levels are normal. Most authors believe that

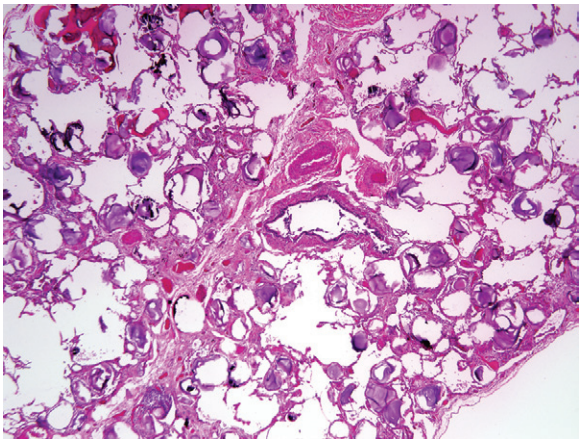

FIGURE 60-11 ■ Histopathology of pulmonary alveolar microlithiasis. Alveolar spaces are filled by lamellated, rounded microliths. (Images courtesy of Kirk Jones, MD, University of California, San Francisco.)

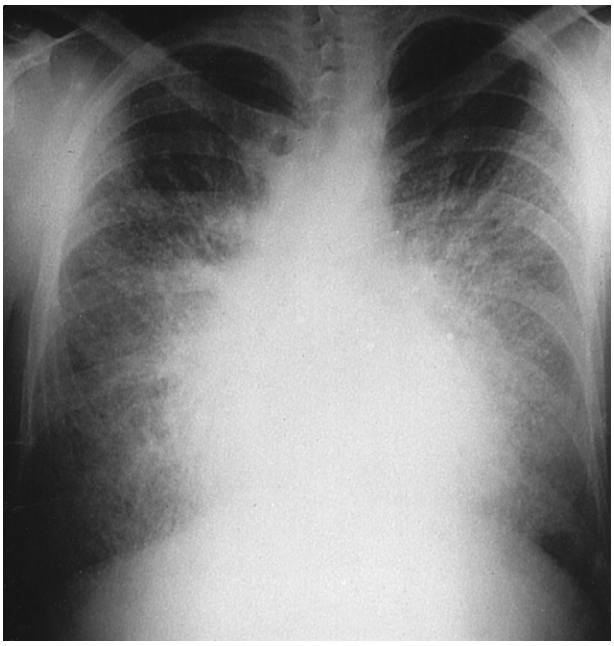

FIGURE 60-12 ■ Radiography of pulmonary alveolar microlithiasis.

the responsible mechanism is an inborn error of calcium metabolism that is confined to the lung and leads to precipitation of the salts.

Most cases of pulmonary alveolar microlithiasis are diagnosed during the third through fifth decades. Among familial cases, women are affected more often than men, but there is an equal distribution among the sporadic cases.[197,198] Cough and dyspnea are the most common presenting symptoms. Expectorated microliths have been reported.[195] Inspiratory crackles, finger clubbing, and signs of cor pulmonale may be present in more advanced disease.

The chest radiograph is characteristic and shows diffuse bilateral calcific opacities with predilection for the lower lung zones. This opacity is alveolar, producing air bronchograms and radiographic obliteration of the heart borders, pulmonary vessels, and diaphragmatic surfaces.[199] Chest computed tomography often demonstrates widespread intra-alveolar calcified nodules with a lower lobe and subpleural predominance, although early disease can be less conspicuous (Fig. 60-12).[200,201] Pulmonary function remains normal or only slightly impaired for a prolonged period after disease detection.[196] With time, the alveolar walls become fibrotic and a restrictive ventilatory defect with a reduced D_{LCO} develops. Technetium-99m bone scintigraphy or transbronchial lung biopsy can provide confirmation of the diagnosis.[202,203] Treatment is supportive. Whole-lung lavage has been tried without benefit.[204]

KEY POINTS

- DAH is an uncommon but striking condition that is associated with many different underlying disorders.
- DAH is a medical emergency that often results in acute respiratory failure and death.
- All of these diseases are rare, and many have a genetic basis.
- The classic clinical presentation of DAH includes hemoptysis, alveolar opacities on chest radiograph, and anemia.
- Most are diagnosable, and treatment is available for a few.
- Many of the disorders causing DAH appear to be immunologically mediated, either through injury to the capillary basement membrane by specific autoantibody or through deposition of immune complexes.
- Most conditions can be diagnosed by the presence of accompanying clinical features, laboratory abnormalities, and histologic findings, although overlap occurs.
- Bronchoscopy with serial BAL is essential to the accurate identification of DAH.
- Surgical lung biopsy is rarely required for the diagnosis of DAH.
- Many cases of DAH demonstrate neutrophilic inflammation of the alveolar interstitium known as capillaritis.
- The presence of proteinuria and an abnormal urinary sediment (red blood cells and red blood cell casts) suggests an underlying glomerulonephritis consistent with the diagnosis of systemic vasculitis or Goodpasture's syndrome.
- Accurate diagnosis is essential because aggressive treatment with corticosteroids, cytotoxic agents, and plasmapheresis (alone or in combination) is often helpful.

References

1. Travis WD, Colby TV, Lombard C, Carpenter H: A clinicopathologic study of 34 cases of diffuse pulmonary hemorrhage with lung biopsy confirmation. Am J Surg Pathol 14:1112–1125, 1990.
2. Mark E, Ramirez J: Pulmonary capillaritis and hemorrhage in patients with systemic vasculitis. Arch Pathol Lab Med 109:413–418, 1985.
3. Travis WD, Hoffman GS, Leavitt RY, et al: Surgical pathology of the lung in Wegener's granulomatosis. Review of 87 open lung biopsies from 67 patients. Am J Surg Pathol 15:315–333, 1991.
4. Spencer H: Pulmonary lesions in polyarteritis nodosa. Br J Tuberc Dis Chest 51:123–130, 1957.
5. Collard HR, Schwarz MI: Diffuse alveolar hemorrhage. Clin Chest Med 25:583–592, vii, 2004.
6. Cortese G, Nicali R, Placido R, et al: Radiological aspects of diffuse alveolar haemorrhage. Radiol Med (Torino) 113:16–28, 2008.
7. Greening AP, Hughes JM: Serial estimations of carbon monoxide diffusing capacity in intrapulmonary haemorrhage. Clin Sci (Lond) 60:507–512, 1981.
8. Nada AK, Torres VE, Ryu JH, et al: Pulmonary fibrosis as an unusual clinical manifestation of a pulmonary-renal vasculitis in elderly patients. Mayo Clin Proc 65:847–856, 1990.
9. Bosch X, Lopez-Soto A, Mirapeix E, et al: Antineutrophil cytoplasmic autoantibody-associated alveolar capillaritis in patients presenting with pulmonary hemorrhage. Arch Pathol Lab Med 118:517–522, 1994.
10. Schwarz MI, Brown KK: Small vessel vasculitis of the lung. Thorax 55:502–510, 2000.
11. Kahn F, Jones J, England D: Diagnosis of pulmonary hemorrhage in the immunocompromised host. Am Rev Respir Dis 136:155–160, 1987.
12. Schmitt WH, van der Woude FJ: Clinical applications of antineutrophil cytoplasmic antibody testing. Curr Opin Rheumatol 16:9–17, 2004.
13. Goeken JA: Antineutrophil cytoplasmic antibody—A useful serological marker for vasculitis. J Clin Immunol 11:161–174, 1991.
14. Roth DA, Wilz DR, Theil GB: Schönlein-Henoch syndrome in adults. Q J Med 55:145–152, 1985.
15. Colby TV, Fukuoka J, Ewaskow SP, et al: Pathologic approach to pulmonary hemorrhage. Ann Diagn Pathol 5:309–319, 2001.
16. Mark EJ, Matsubara O, Tan-Liu NS, Fienberg R: The pulmonary biopsy in the early diagnosis of Wegener's (pathergic) granulomatosis: A study based on 35 open lung biopsies. Hum Pathol 19:1065–1071, 1988.
17. Yoshikawa Y, Watanabe T: Pulmonary lesions in Wegener's granulomatosis: A clinicopathologic study of 22 autopsy cases. Hum Pathol 17:401–410, 1986.
18. Leatherman JW, Davies SF, Hoidal JR: Alveolar hemorrhage syndromes: Diffuse microvascular lung hemorrhage in immune and idiopathic disorders. Medicine (Baltimore) 63:343–361, 1984.
19. Woywodt A, Streiber F, de Groot K, et al: Circulating endothelial cells as markers for ANCA-associated small-vessel vasculitis. Lancet 361:206–210, 2003.
20. Schnabel A, Reuter M, Csernok E, et al: Subclinical alveolar bleeding in pulmonary vasculitides: Correlation with indices of disease activity. Eur Respir J 14:118–124, 1999.
21. Lenclud C, De Vuyst P, Dupont E, et al: Wegener's granulomatosis presenting as acute respiratory failure with anti-neutrophil-cytoplasm antibodies. Chest 96:345–347, 1989.
22. Travis WD, Carpenter HA, Lie JT: Diffuse pulmonary hemorrhage. An uncommon manifestation of Wegener's granulomatosis. Am J Surg Pathol 11:702–708, 1987.
23. Jayne D, Rasmussen N, Andrassy K, et al: A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. N Engl J Med 349:36–44, 2003.
24. Jayne DR, Chapel H, Adu D, et al: Intravenous immunoglobulin for ANCA-associated systemic vasculitis with persistent disease activity. Q J Med 93:433–439, 2000.
25. Thomas-Golbanov C, Sridharan S: Novel therapies in vasculitis. Expert Opin Investig Drugs 10:1279–1289, 2001.
26. Hall JB, Wadham BM, Wood CJ, et al: Vasculitis and glomerulonephritis: A subgroup with an antineutrophil cytoplasmic antibody. Aust N Z J Med 14:277–278, 1984.
27. Haworth SJ, Savage CO, Carr D, et al: Pulmonary haemorrhage complicating Wegener's granulomatosis and microscopic polyarteritis. Br Med J (Clin Res Ed) 290:1775–1778, 1985.
28. Imoto EM, Lombard CM, Sachs DP: Pulmonary capillaritis and hemorrhage. A clue to the diagnosis of systemic necrotizing vasculitis. Chest 96:927–928, 1989.
29. Thomashow BM, Felton CP, Navarro C: Diffuse intrapulmonary hemorrhage, renal failure and a systemic vasculitis. A case report and review of the literature. Am J Med 68:299–304, 1980.
30. Zashin S, Fattor R, Fortin D: Microscopic polyarteritis: A forgotten aetiology of haemoptysis and rapidly progressive glomerulonephritis. Ann Rheum Dis 49:53–56, 1990.
31. Savage CO, Winearls CG, Evans DJ, et al: Microscopic polyarteritis: Presentation, pathology and prognosis. Q J Med 56:467–483, 1985.
32. Guo X, Gopalan R, Ugbarugba S, et al: Hepatitis B–related polyarteritis nodosa complicated by pulmonary hemorrhage. Chest 119:1608–1610, 2001.
33. Guillevin L, Durand-Gasselin B, Cevallos R, et al: Microscopic polyangiitis: Clinical and laboratory findings in eighty-five patients. Arthritis Rheum 42:421–430, 1999.
34. Lauque D, Cadranel J, Lazor R, et al: Microscopic polyangiitis with alveolar hemorrhage. A study of 29 cases and review of the literature. Groupe d'Etudes et de Recherche sur les Maladies "Orphelines" Pulmonaires (GERM"O"P). Medicine (Baltimore) 79:222–233, 2000.
35. Bocanegra TS, Espinoza LR, Vasey FB, Germain BF: Pulmonary hemorrhage in systemic necrotizing vasculitis associated with hepatitis B. Chest 80:102–103, 1981.
36. Betensley AD, Yankaskas JR: Factor VIIa for alveolar hemorrhage in microscopic polyangiitis. Am J Respir Crit Care Med 166:1291–1292, 2002.
37. Eschun GM, Mink SN, Sharma S: Pulmonary interstitial fibrosis as a presenting manifestation in perinuclear antineutrophilic cytoplasmic antibody microscopic polyangiitis. Chest 123:297–301, 2003.
38. Schwarz MI, Mortenson RL, Colby TV, et al: Pulmonary capillaritis. The association with progressive irreversible airflow limitation and hyperinflation. Am Rev Respir Dis 148:507–511, 1993.
39. Jennings CA, King TE Jr, Tuder R, et al: Diffuse alveolar hemorrhage with underlying isolated, pauciimmune pulmonary capillaritis. Am J Respir Crit Care Med 155:1101–1109, 1997.
40. Bosch X, Josep F, Mirapeix E, et al: Antimyeloperoxidase autoantibody–associated necrotizing alveolar capillaritis. Am Rev Respir Dis 146:1326–1329, 1992.
41. Bombardieri S, Paoletti P, DiMunno O, et al: Lung involvement in essential mixed cryoglobulinemia. Am J Med 66:748–756, 1979.
42. Gomez-Tello V, Onoro-Canaveral JJ, de la Casa Monje RM, et al: Diffuse recidivant alveolar hemorrhage in a patient with hepatitis C virus–related mixed cryoglobulinemia. Intensive Care Med 25:319–322, 1999.
43. Ball JA, Young KR Jr: Pulmonary manifestations of Goodpasture's syndrome. Antiglomerular basement membrane disease and related disorders. Clin Chest Med 19:777–791, ix, 1998.
44. Chajek T, Fainaru M: Report of 41 cases and a review of the literature. Medicine (Baltimore) 54:179–196, 1975.
45. Gamble CN, Wiesner KB, Shapiro RF, Boyer WJ: The immune complex pathogenesis of glomerulonephritis and pulmonary vasculitis in Behçet's disease. Am J Med 6:1031–1039, 1979.
46. Raz I, Okon E, Chajek-Shaul T: Pulmonary manifestations in Behçet's syndrome. Chest 95:585–589, 1989.
47. Stricker H, Malinverni R: Multiple, large aneurysms of pulmonary arteries in Behçet's disease. Clinical remission and radiologic resolution after corticosteroid therapy. Arch Intern Med 149:925–927, 1989.
48. Yazici H, Pazarli H, Barnes CG, et al: A controlled trial of azathioprine in Behçet's syndrome. N Engl J Med 322:281–285, 1990.
49. Sfikakis PP: Behçet's disease: A new target for anti–tumour necrosis factor treatment. Ann Rheum Dis 61(Suppl 2):ii51–ii53, 2002.
50. Pillebout E, Thervet E, Hill G, et al: Henoch-Schönlein purpura in adults: Outcome and prognostic factors. J Am Soc Nephrol 13:1271–1278, 2002.
51. Kathuria S, Cheifec G: Fatal pulmonary Henoch-Schönlein syndrome. Chest 82:654–656, 1982.

52. Nadrous HF, Yu AC, Specks U, Ryu JH: Pulmonary involvement in Henoch-Schönlein purpura. Mayo Clin Proc 79:1151–1157, 2004.
53. Kauffmann RH, Herrmann WA, Meyer CJ, et al: Circulating IgA-immune complexes in Henoch-Schönlein purpura. A longitudinal study of their relationship to disease activity and vascular deposition of IgA. Am J Med 69:859–866, 1980.
54. Goodpasture E: The significance of certain pulmonary lesions in relation to the etiology of influenza. Am J Med Sci 158:863–870, 1919.
55. Butkowski RJ, Langeveld JP, Wieslander J, et al: Localization of the Goodpasture epitope to a novel chain of basement membrane collagen. J Biol Chem 262:7874–7877, 1987.
56. Hellmark T, Burkhardt H, Wieslander J: Goodpasture disease. Characterization of a single conformational epitope as the target of pathogenic autoantibodies. J Biol Chem 274:25862–25868, 1999.
57. Simpson IJ, Doak PB, Williams LC, et al: Plasma exchange in Goodpasture's syndrome. Am J Nephrol 2:301–311, 1982.
58. Kelly PT, Haponik EF: Goodpasture syndrome: Molecular and clinical advances. Medicine (Baltimore) 73:171–185, 1994.
59. McPhaul JJ Jr, Mullins JD: Glomerulonephritis mediated by antibody to glomerular basement membrane. Immunological, clinical, and histopathological characteristics. J Clin Invest 57:351–361, 1976.
60. Jones JG, Minty BD, Lawler P, et al: Increased alveolar epithelial permeability in cigarette smokers. Lancet 1:66–68, 1980.
61. Donaghy M, Rees AJ: Cigarette smoking and lung haemorrhage in glomerulonephritis caused by autoantibodies to glomerular basement membrane. Lancet 2:1390–1393, 1983.
62. Wilson CB, Smith RC: Goodpasture's syndrome associated with influenza A2 virus infection. Ann Intern Med 76:91–94, 1972.
63. Perl SI, Pussell BA, Charlesworth JA, et al: Goodpasture's (anti-GBM) disease and HLA-DRw2. N Engl J Med 305:463–464, 1981.
64. Rees AJ, Peters DK, Compston DA, Batchelor JR: Strong association between HLA-DRW2 and antibody-mediated Goodpasture's syndrome. Lancet 1:966–968, 1978.
65. Nakamura A, Yuasa T, Ujike A, et al: Fcgamma receptor IIB–deficient mice develop Goodpasture's syndrome upon immunization with type IV collagen: A novel murine model for autoimmune glomerular basement membrane disease. J Exp Med 191:899–906, 2000.
66. Reynolds J, Moss J, Duda MA, et al: The evolution of crescentic nephritis and alveolar haemorrhage following induction of autoimmunity to glomerular basement membrane in an experimental model of Goodpasture's disease. J Pathol 200:118–129, 2003.
67. Savage CO, Pusey CD, Bowman C, et al: Antiglomerular basement membrane antibody mediated disease in the British Isles 1980–1984. Br Med Journal (Clin Res Ed) 292:301–304, 1986.
68. Teague CA, Doak PB, Simpson IJ, et al: Goodpasture's syndrome: An analysis of 29 cases. Kidney Int 13:492–504, 1978.
69. Keogh AM, Ibels LS, Allen DH, et al: Exacerbation of Goodpasture's syndrome after inadvertent exposure to hydrocarbon fumes. Br Med J (Clin Res Ed) 288:188, 1984.
70. Lombard CM, Colby TV, Elliott CG: Surgical pathology of the lung in anti–basement membrane antibody–associated Goodpasture's syndrome. Hum Pathol 20:445–451, 1989.
71. Ewan PW, Jones HA, Rhodes CG, Hughes JM: Detection of intrapulmonary hemorrhage with carbon monoxide uptake. Application in Goodpasture's syndrome. N Engl J Med 295:1391–1396, 1976.
72. Primack SL, Miller RR, Muller NL: Diffuse pulmonary hemorrhage: Clinical, pathologic, and imaging features. AJR Am J Roentgenol 164:295–300, 1995.
73. Abboud RT, Chase WH, Ballon HS, et al: Goodpasture's syndrome: Diagnosis by transbronchial lung biopsy. Ann Intern Med 89:635–638, 1978.
74. Zimmerman SW, Varanasi UR, Hoff B: Goodpasture's syndrome with normal renal function. Am J Med 66:163–171, 1979.
75. Fort J, Espinel E, Rogriquez JA, et al: Partial recovery of renal function in an oligoanuric patient affected with Goodpasture's syndrome after treatment with steroids, immunosuppressives and plasmapheresis. Clin Nephrol 22:211–212, 1984.
76. Keller F, Offermann G, Schultze G, et al: Membrane plasma exchange in Goodpasture's syndrome. Am J Med Sci 287:32–36, 1984.
77. Levy JB, Turner AN, Rees AJ, Pusey CD: Long-term outcome of anti-glomerular basement membrane antibody disease treated with plasma exchange and immunosuppression. Ann Intern Med 134:1033–1042, 2001.
78. Bygren P, Freiburghaus C, Lindholm T, et al: Goodpasture's syndrome treated with staphylococcal protein A immunoadsorption. Lancet 2:1295–1296, 1985.
79. Johnson JP, Moore J Jr, Austin HA 3rd, et al: Therapy of anti–glomerular basement membrane antibody disease: Analysis of prognostic significance of clinical, pathologic and treatment factors. Medicine (Baltimore) 64:219–227, 1985.
80. Hind CR, Paraskevakou H, Lockwood CM, et al: Prognosis after immunosuppression of patients with crescentic nephritis requiring dialysis. Lancet 1:263–265, 1983.
81. Arzoo K, Sadeghi S, Liebman HA: Treatment of refractory antibody mediated autoimmune disorders with an anti-CD20 monoclonal antibody (rituximab). Ann Rheum Dis 61:922–924, 2002.
82. Garcia-Canton C, Toledo A, Palomar R, et al: Goodpasture's syndrome treated with mycophenolate mofetil. Nephrol Dial Transplant 15:920–922, 2000.
83. McCormick JR, Kass J, Skewes M: Goodpasture's syndrome. Compr Ther 13:25–32, 1987.
84. Hughson MD, He Z, Henegar J, McMurray R: Alveolar hemorrhage and renal microangiopathy in systemic lupus erythematosus. Arch Pathol Lab Med 125:475–483, 2001.
85. Zamora MR, Warner ML, Tuder R, Schwarz MI: Diffuse alveolar hemorrhage and systemic lupus erythematosus. Clinical presentation, histology, survival, and outcome. Medicine (Baltimore) 76:192–202, 1997.
86. Santos-Ocampo AS, Mandell BF, Fessler BJ: Alveolar hemorrhage in systemic lupus erythematosus: Presentation and management. Chest 118:1083–1090, 2000.
87. Eagen JW, Memoli VA, Roberts JL, et al: Pulmonary hemorrhage in systemic lupus erythematosis. Medicine (Baltimore) 57:545–560, 1978.
88. Matthay RA, Schwarz MI, Petty TL, et al: Pulmonary mainfestations of systemic lupus erythematosus: Review of twelve cases of acute lupus pneumonitis. Medicine (Baltimore) 54:397–409, 1975.
89. Howe HS, Boey ML, Fong KY, Feng PH: Pulmonary haemorrhage, pulmonary infarction, and the lupus anticoagulant. Ann Rheum Dis 47:869–872, 1988.
90. Alarcon-Segovia D, Deleze M, Oria CV, et al: Antiphospholipid antibodies and the antiphospholipid syndrome in systemic lupus erythematosus. A prospective analysis of 500 consecutive patients. Medicine (Baltimore) 68:353–365, 1989.
91. Gertner E: Diffuse alveolar hemorrhage in the antiphospholipid syndrome: Spectrum of disease and treatment. J Rheumatol 26:805–807, 1999.
92. Rodriguez-Iturbe B, Garcia R, Rubio L, Serano H: Immunohistologic findings in the lung in systemic lupus erythematosus. Arch Pathol Lab Med 101:342–344, 1977.
93. Desnoyers MR, Bernstein S, Cooper AG, Kopelman RI: Pulmonary hemorrhage in lupus erythematosus without evidence of an immunologic cause. Arch Intern Med 144:1398–1400, 1984.
94. Myers JL, Katzenstein AA: Microangiitis in lupus-induced pulmonary hemorrhage. Am J Clin Pathol 85:552–556, 1986.
95. Chang MY, Fang JT, Chen YC, Huang CC: Diffuse alveolar hemorrhage in systemic lupus erythematosus: A single center retrospective study in Taiwan. Ren Fail 24:791–802, 2002.
96. Smith BS: Idiopathic pulmonary haemosiderosis and rheumatoid arthritis. Br Med J 1:1403–1404, 1966.
97. Bar J, Ehrenfeld M, Rozenman J, et al: Pulmonary-renal syndrome in systemic sclerosis. Semin Arthritis Rheum 30:403–410, 2001.
98. Schwarz MI, Sutarik JM, Nick JA, et al: Pulmonary capillaritis and diffuse alveolar hemorrhage. A primary manifestation of polymyositis. Am J Respir Crit Care Med 151:2037–2040, 1995.
99. Schwarz MI, Zamora MR, Hodges TN, et al: Isolated pulmonary capillaritis and diffuse alveolar hemorrhage in rheumatoid arthritis and mixed connective tissue disease. Chest 113:1609–1615, 1998.

100. Beirne GJ, Kopp WL, Zimmerman SW: Goodpasture syndrome. Dissociation from antibodies to glomerular basement membrane. Arch Intern Med 132:261–263, 1973.
101. Badesch DB, Zamora M, Fullerton D, et al: Pulmonary capillaritis: A possible histologic form of acute pulmonary allograft rejection. J Heart Lung Transplant 17:415–422, 1998.
102. Robboy SJ, Minna JD, Colman RW, et al: Pulmonary hemorrhage syndrome as a manifestation of disseminated intravascular coagulation: Analysis of ten cases. Chest 63:718–721, 1973.
103. Buchanan GR, Moore GC: Pulmonary hemosiderosis and immune thrombocytopenia. Initial manifestations of collagen-vascular disease. JAMA 246:861–864, 1981.
104. Martinez AJ, Maltby JD, Hurst DJ: Thrombotic thrombocytopenic purpura seen as pulmonary hemorrhage. Arch Intern Med 143:1818–1820, 1983.
105. Drent M, Wessels S, Jacobs JA, Thijssen H: Association of diffuse alveolar haemorrhage with acquired vitamin K deficiency. Respiration 67:697, 2000.
106. Wiedermann FJ, Mayr A, Schobersberger W, et al: Acute respiratory failure associated with catastrophic antiphospholipid syndrome. J Intern Med 247:723–730, 2000.
107. Espinosa G, Cervera R, Font J, Asherson RA: The lung in the antiphospholipid syndrome. Ann Rheum Dis 61:195–198, 2002.
108. Barnett VT, Bergmann F, Humphrey H, Chediak J: Diffuse alveolar hemorrhage secondary to superwarfarin ingestion. Chest 102: 1301–1302, 1992.
109. Finley TN, Aronow A, Cosentino AM, Golde DW: Occult pulmonary hemorrhage in anticoagulated patients. Am Rev Respir Dis 112:23–29, 1975.
110. Erdogan D, Kocaman O, Oflaz H, Goren T: Alveolar hemorrhage associated with warfarin therapy: A case report and literature review. Int J Cardiovasc Imaging 20:155–159, 2004.
111. Awadh N, Ronco JJ, Bernstein V, et al: Spontaneous pulmonary hemorrhage after thrombolytic therapy for acute myocardial infarction. Chest 106:1622–1624, 1994.
112. Gopalakrishnan D, Tioran T, Emanuel C, Clark VL: Diffuse pulmonary hemorrhage complicating thrombolytic therapy for acute myocardial infarction. Clin Cardiol 20:298–300, 1997.
113. Choi RK, Lee NH, Lim DS, et al: Pulmonary hemorrhage after percutaneous coronary intervention with abciximab therapy. Mayo Clin Proc 77:1340–1343, 2002.
114. Khanlou H, Eiger G, Yazdanfar S: Abciximab and alveolar hemorrhage. N Engl J Med 339:1861–1863, 1998.
115. Yilmaz MB, Akin Y, Biyikoglu SF, et al: Diffuse alveolar hemorrhage following administration of tirofiban in a patient with acute coronary syndrome: A fatal complication. Int J Cardiol 93:81–82, 2004.
116. Raanani P, Segal E, Levi I, et al: Diffuse alveolar hemorrhage in acute promyelocytic leukemia patients treated with ATRA—A manifestation of the basic disease or the treatment. Leuk Lymphoma 37:605–610, 2000.
117. Golde DW, Drew WL, Klein HZ, et al: Occult pulmonary haemorrhage in leukaemia. Br Med J 2:166–168, 1975.
118. Smith LJ, Katzenstein AL: Pathogenesis of massive pulmonary hemorrhage in acute leukemia. Arch Intern Med 142:2149–2152, 1982.
119. Silverman ES, Mark EJ: Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 36-2002. A 32-year-old man with hemoptysis of nearly three decades' duration. N Engl J Med 347:1693–1701, 2002.
120. Cohen S: Idiopathic pulmonary hemosiderosis. Am J Med Sci 317:67–74, 1999.
121. Beckerman RC, Taussig LM, Pinnas JL: Familial idiopathic pulmonary hemosiderosis. Am J Dis Child 133:609–611, 1979.
122. Valassi-Adam H, Rouska A, Karpouzas J, Matsaniotis N: Raised IgA in idiopathic pulmonary haemosiderosis. Arch Dis Child 50:320–322, 1975.
123. Wright PH, Menzies IS, Pounder RE, Keeling PW: Adult idiopathic pulmonary haemosiderosis and coeliac disease. Q J Med 50:95–102, 1981.
124. Elidemir O, Colasurdo GN, Rossmann SN, Fan LL: Isolation of *Stachybotrys* from the lung of a child with pulmonary hemosiderosis. Pediatrics 104:964–966, 1999.
125. Seely JM, Effmann EL, Muller NL: High-resolution CT of pediatric lung disease: Imaging findings. AJR Am J Roentgenol 168:1269–1275, 1997.
126. Yeager H Jr, Powell D, Weinberg RM, et al: Idiopathic pulmonary hemosiderosis: Ultrastructural studies and responses to azathioprine. Arch Intern Med 136:1145–1149, 1976.
127. Irwin RS, Cottrell TS, Hsu KC, et al: Idiopathic pulmonary hemosiderosis: An electron microscopic and immunofluorescent study. Chest 65:41–45, 1974.
128. Kjellman B, Elinder G, Garwicz S, Svan H: Idiopathic pulmonary haemosiderosis in Swedish children. Acta Paediatr Scand 73:584–588, 1984.
129. Airaghi L, Ciceri L, Giannini S, et al: Idiopathic pulmonary hemosiderosis in an adult. Favourable response to azathioprine. Monaldi Arch Chest Dis 56:211–213, 2001.
130. Byrd RB, Gracey DR: Immunosuppressive treatment of idiopathic pulmonary hemosiderosis. JAMA 226:458–459, 1973.
131. Calabrese F, Giacometti C, Rea F, et al: Recurrence of idiopathic pulmonary hemosiderosis in a young adult patient after bilateral single-lung transplantation. Transplantation 74:1643–1645, 2002.
132. Camus P: Drug-induced infiltrative lung disease. *In* Schwarz MI, King TE Jr (eds): Interstitial Lung Diseases (4th ed). Hamilton, Ontario, Canada: BC Decker, 2003, pp 485–534.
133. Dhillon SS, Singh D, Doe N, et al: Diffuse alveolar hemorrhage and pulmonary capillaritis due to propylthiouracil. Chest 116:1485–1488, 1999.
134. Nicolls MR, Terada LS, Tuder RM, et al: Diffuse alveolar hemorrhage with underlying pulmonary capillaritis in the retinoic acid syndrome. Am J Respir Crit Care Med 158:1302–1305, 1998.
135. Polman AJ, van der Werf TS, Tiebosch AT, Zijlstra JG: Early-onset phenytoin toxicity mimicking a renopulmonary syndrome. Eur Respir J 11:501–503, 1998.
136. Srivastava A, Gottlieb D, Bradstock KF: Diffuse alveolar haemorrhage associated with microangiopathy after allogeneic bone marrow transplantation. Bone Marrow Transplantat 15:863–867, 1995.
137. Pirot AL, Goldsmith D, Pascasio J, Beck SE: Pulmonary capillaritis with hemorrhage due to propylthiouracil therapy in a child. Pediatr Pulmonol 39:88–92, 2005.
138. Sternlieb I, Bennet B, Scheinberg IH: D-Penicillamine induced Goodpasture's syndrome in Wilson's disease. Ann Intern Med 82:673–676, 1975.
139. Gavaghan TE, McNaught PJ, Ralston M, Hayes JM: Penicillamine-induced "Goodpasture's syndrome": Successful treatment of a fulminant case. Aust N Z J Med 11:261–265, 1981.
140. Louie S, Gamble CN, Cross CE: Penicillamine associated pulmonary hemorrhage. J Rheumatol 13:963–966, 1986.
141. Matloff DS, Kaplan MM: D-Penicillamine-induced Goodpasture's-like syndrome in primary biliary cirrhosis—Successful treatment with plasmapheresis and immunosuppressives. Gastroenterology 78:1046–1049, 1980.
142. Ahmad D, Morgan WK, Patterson R, et al: Pulmonary haemorrhage and haemolytic anaemia due to trimellitic anhydride. Lancet 2:328–330, 1979.
143. Herbert FA, Orford R: Pulmonary hemorrhage and edema due to inhalation of resins containing tri-mellitic anhydride. Chest 76:546–551, 1979.
144. Zeiss CR, Wolkonsky P, Chacon R, et al. Syndromes in workers exposed to trimellitic anhydride. A longitudinal clinical and immunologic study. Ann Intern Med 98:8–12, 1983.
145. Spence TH, Connors JC: Diffuse alveolar hemorrhage syndrome due to "silent" mitral valve regurgitation. South Med J 93:65–67, 2000.
146. Woolley K, Stark P: Pulmonary parenchymal manifestations of mitral valve disease. Radiographics 19:965–972, 1999.
147. Wagenvoort CA, Wagenvoort N, Takahashi T: Pulmonary veno-occlusive disease: Involvement of pulmonary arteries and review of the literature. Hum Pathol 16:1033–1041, 1985.
148. Pietra GG, Edwards WD, Kay JM, et al: Histopathology of primary pulmonary hypertension. A qualitative and quantitative study of pulmonary blood vessels from 58 patients in the National Heart, Lung, and Blood Institute, Primary Pulmonary Hypertension Registry. Circulation 80:1198–1206, 1989.

149. Palevsky HI, Pietra GG, Fishman AP: Pulmonary veno-occlusive disease and its response to vasodilator agents. Am Rev Respir Dis 142:426–429, 1990.
150. Lombard CM, Churg A, Winokur S: Pulmonary veno-occlusive disease following therapy for malignant neoplasms. Chest 92:871–876, 1987.
151. Troussard X, Bernaudin JF, Cordonnier C, et al: Pulmonary veno-occlusive disease after bone marrow transplantation. Thorax 39:956–957, 1984.
152. Hamada K, Teramoto S, Narita N, et al: Pulmonary veno-occlusive disease in pulmonary Langerhans' cell granulomatosis. Eur Respir J 15:421–423, 2000.
153. Hussein A, Trowitzsch E, Brockmann M: Pulmonary veno-occlusive disease, antiphospholipid antibody and pulmonary hypertension in an adolescent. Klin Padiatr 211:92–95, 1999.
154. Johnson SR, Patsios D, Hwang DM, Granton J: Pulmonary veno-occlusive disease and scleroderma associated pulmonary hypertension. J Rheumatol 33:2347–2350, 2006.
155. Kishida Y, Kanai Y, Kuramochi S, Hosoda Y: Pulmonary venoocclusive disease in a patient with systemic lupus erythematosus. J Rheumatol 20:2161–2162, 1993.
156. Saito A, Takizawa H, Ito K, et al: A case of pulmonary veno-occlusive disease associated with systemic sclerosis. Respirology 8:383–385, 2003.
157. Zhang L, Visscher D, Rihal C, Aubry MC: Pulmonary veno-occlusive disease as a primary cause of pulmonary hypertension in a patient with mixed connective tissue disease. Rheumatol Int 27:1163–1165, 2007.
158. Runo JR, Vnencak-Jones CL, Prince M, et al: Pulmonary veno-occlusive disease caused by an inherited mutation in bone morphogenetic protein receptor II. Am J Respir Crit Care Med 167:889–894, 2003.
159. Okumura H, Nagaya N, Kyotani S, et al: Effects of continuous IV prostacyclin in a patient with pulmonary veno-occlusive disease. Chest 122:1096–1098, 2002.
160. Palmer SM, Robinson LJ, Wang A, et al: Massive pulmonary edema and death after prostacyclin infusion in a patient with pulmonary veno-occlusive disease. Chest 113:237–240, 1998.
161. Hackman RC, Madtes DK, Petersen FB, Clark JG: Pulmonary venoocclusive disease following bone marrow transplantation. Transplantation 47:989–992, 1989.
162. Sanderson JE, Spiro SG, Hendry AT, Turner-Warwick M: A case of pulmonary veno-occlusive disease responding to treatment with azathioprine. Thorax 32:140–148, 1977.
163. Almagro P, Julia J, Sanjaume M, et al: Pulmonary capillary hemangiomatosis associated with primary pulmonary hypertension: Report of 2 new cases and review of 35 cases from the literature. Medicine 81:417–424, 2002.
164. Faber CN, Yousem SA, Dauber JH, et al: Pulmonary capillary hemangiomatosis. A report of three cases and a review of the literature. Am Rev Respir Dis 140:808–813, 1989.
165. Langleben D, Heneghan JM, Batten AP, et al: Familial pulmonary capillary hemangiomatosis resulting in primary pulmonary hypertension. Ann Intern Med 109:106–109, 1988.
166. Gugnani MK, Pierson C, Vanderheide R, Girgis RE: Pulmonary edema complicating prostacyclin therapy in pulmonary hypertension associated with scleroderma: A case of pulmonary capillary hemangiomatosis. Arthritis Rheum 43:699–703, 2000.
167. Humbert M, Maitre S, Capron F, et al: Pulmonary edema complicating continuous intravenous prostacyclin in pulmonary capillary hemangiomatosis. Am J Respir Crit Care Med 157:1681–1685, 1998.
168. White CW, Sondheimer HM, Crouch EC, et al: Treatment of pulmonary hemangiomatosis with recombinant interferon Alfa-2a. N Engl J Med 320:1197–1200, 1989.
169. Taylor JR, Ryu J, Colby TV, Raffin TA: Lymphangioleiomyomatosis. Clinical course in 32 patients. N Engl J Med 323:1254–1260, 1990.
170. Urban T, Lazor R, Lacronique J, et al: Pulmonary lymphangioleiomyomatosis. A study of 69 patients. Groupe d'Etudes et de Recherche sur les Maladies "Orphelines" Pulmonaires (GERM"O"P). Medicine 78:321–337, 1999.
171. Johnson S: Rare diseases. 1. Lymphangioleiomyomatosis: Clinical features, management and basic mechanisms. Thorax 54:254–264, 1999.
172. Riccardi V: Von Recklinghausen neurofibromatosis. N Engl J Med 305:1617–1627, 1981.
173. Massaro D, Katz S: Fibrosing alveolitis: Its occurrence, roentgenographic and pathologic features in von Recklinghausen's neurofibromatosis. Am Rev Respir Dis 93:934–942, 1966.
174. Massaro D, Katz S, Matthews MJ, Higgins G: Von Recklinghausen's neurofibromatosis associated with cystic lung disease. Am J Med 38:233–240, 1965.
175. Patchefsky AS, Atkinson WG, Hoch WS, et al: Interstitial pulmonary fibrosis and von Recklinghausen's disease. An ultrastructural and immunofluorescent study. Chest 64:459–464, 1973.
176. De Scheerder I, Elinck W, Van Renterghem D, et al: Desquamative interstitial pneumonia and scar cancer of the lung complicating generalised neurofibromatosis. Eur J Respir Dis 65:623–626, 1984.
177. Unger PD, Geller GA, Anderson PJ: Pulmonary lesions in a patient with neurofibromatosis. Arch Pathol Lab Med 108:654–657, 1984.
178. Hermansky F, Pudlak P: Albinism associated with hemorrhagic diatheses and unusual pigmented reticular cells in the bone marrow. Report of two cases of histochemical studies. Blood 14:162–169, 1959.
179. White DA, Smith GJ, Cooper JA Jr, et al: Hermansky-Pudlak syndrome and interstitial lung disease: Report of a case with lavage findings. Am Rev Respir Dis 130:138–141, 1984.
180. DePinho RA, Kaplan KL: The Hermansky-Pudlak syndrome. Report of three cases and review of pathophysiology and management considerations. Medicine 64:192–202, 1985.
181. Anderson PD, Huizing M, Claassen DA, et al: Hermansky-Pudlak syndrome type 4 (HPS-4): Clinical and molecular characteristics. Hum Genet 113:10–17, 2003.
182. Armanios M, Chen JL, Chang YP, et al: Haploinsufficiency of telomerase reverse transcriptase leads to anticipation in autosomal dominant dyskeratosis congenita. Proc Natl Acad Sci U S A 102:15960–15964, 2005.
183. Garcia CK, Wright WE, Shay JW: Human diseases of telomerase dysfunction: Insights into tissue aging. Nucleic Acids Res 35:7406–7416, 2007.
184. Dokal I: Dyskeratosis congenita in all its forms. Br J Haematol 110:768–779, 2000.
185. Yabe M, Yabe H, Hattori K, et al: Fatal interstitial pulmonary disease in a patient with dyskeratosis congenita after allogeneic bone marrow transplantation. Bone Marrow Transplant 19:389–392, 1997.
186. Knight S, Vulliamy T, Copplestone A, et al: Dyskeratosis Congenita (DC) Registry: Identification of new features of DC. Br J Haematol 103:990–996, 1998.
187. Schneider EL, Epstein CJ, Kaback MJ, Brandes D: Severe pulmonary involvement in adult Gaucher's disease: Report of three cases and review of the literature. Am J Med 63:475–480, 1977.
188. Terry RD, Sperry WM, Brodoff B: Adult lipoidosis resembling Neimann-Pick disease. Am J Pathol 30:263–286, 1954.
189. Miller A, Brown LK, Pastores GM, Desnick RJ: Pulmonary involvement in type 1 Gaucher disease: Functional and exercise findings in patients with and without clinical interstitial lung disease. Clin Genet 63:368–376, 2003.
190. Roberts WC, Fredrickson DS: Gaucher's disease of the lung causing severe pulmonary hypertension with associated acute recurrent pericarditis. Circulation ;35:783–789, 1967.
191. Altarescu G, Hill S, Wiggs E, et al: The efficacy of enzyme replacement therapy in patients with chronic neuronopathic Gaucher's disease. J Pediatr 138:539–547, 2001.
192. Lynn R, Terry RD: Lipid histochemistry and electron microscopy in adult Niemann-Pick disease. Am J Med 37:987–994, 1964.
193. Lever AM, Ryder JB: Cor pulmonale in an adult secondary to Niemann-Pick disease. Thorax 38:873–874, 1983.
194. Long RG, Lake BD, Pettit JE, et al: Adult Niemann-Pick disease: Its relationship to the syndrome of the sea-blue histiocyte. Am J Med 62:627–635, 1977.

195. Prakash UB, Barham SS, Rosenow EC, et al: Pulmonary alveolar microlithiasis. A review including ultrastructural and pulmonary function studies. Mayo Clin Proc 58:290–300, 1983.
196. Miro JM, Moreno A, Coca A, et al: Pulmonary alveolar microlithiasis with an unusual radiological pattern. Br J Dis Chest 76:91–96, 1982.
197. Sosman MC, Dodd GD, Jones WD, Pillmore GU: The familial occurrence of pulmonary alveolar microlithiasis. AJR Am J Roentgenol 77:947–1012, 1957.
198. Sears MR, Chang AR, Taylor AJ: Pulmonary alveolar microlithiasis. Thorax 26:704–711, 1971.
199. Balikian JP, Fuleihan FJ, Nucho CN: Pulmonary alveolar microlithiasis. Report of five cases with special reference to roentgen manifestations. AJR Am J Roentgenol 103:509–518, 1968.
200. Cluzel P, Grenier P, Bernadac P, et al: Pulmonary alveolar microlithiasis: CT findings. J Comput Assist Tomogr 15:938–942, 1991.
201. Korn MA, Schurawitzki H, Klepetko W, Burghuber OC: Pulmonary alveolar microlithiasis: Findings on high-resolution CT. AJR Am J Roentgenol 158:981–982, 1992.
202. Brown ML, Swee RG, Olson RJ, Bender CE: Pulmonary uptake of 99mTc diphosphonate in alveolar microlithiasis. AJR Am J Roentgenol 131:703–704, 1978.
203. Cale WF, Petsonk EL, Boyd CB: Transbronchial biopsy of pulmonary alveolar microlithiasis. Arch Intern Med 143:358–359, 1983.
204. Palombini BC, da Silva Porto N, Wallau CU, Camargo JJ: Bronchopulmonary lavage in alveolar microlithiasis. Chest 80: 242–243, 1981.

CHAPTER 61

EOSINOPHILIC LUNG DISEASES

Vincent Cottin, MD, PhD • Jean-François Cordier, MD

INTRODUCTION

EOSINOPHIL BIOLOGY

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Hypereosinophilic Syndrome

EOSINOPHILIC LUNG DISEASE OF DETERMINED CAUSE
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Idiopathic Interstitial Pneumonias
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INTRODUCTION

The eosinophilic lung diseases are a group of disorders (Table 61-1) characterized by the presence and presumed pathogenetic role of eosinophils in the lesional processes. They are mainly represented by the eosinophilic pneumonias, which are defined by a prominent infiltration of the lung parenchyma by eosinophils. The other eosinophilic lung diseases mainly involve the airways, as in the allergic bronchopulmonary mycoses. Asthma, in which the eosinophil is considered to play an important role, is not discussed in this chapter.

EOSINOPHIL BIOLOGY

The role of the eosinophil in homeostasis function, physiology, and pathophysiology has become better appreciated in recent years.[1-3] Eosinophils are multifunctional leukocytes implicated in innate and adaptative immunity, including numerous inflammatory reactions to parasitic helminth, bacterial, and viral infections.[3] They have been especially credited with a beneficial role in parasitic infestation; however, results from in vivo infection studies gave conflicting results.[3a]

The eosinophil[1-3] matures in the bone marrow under the action of cytokines and especially of interleukin (IL)-5 (involved in the differentiation of eosinophil precursors), IL-3, and granulocyte-macrophage colony-stimulating factor (GM-CSF). It then circulates in the blood for about 1 day before being attracted into tissues by complex processes including adhesion and attraction, diapedesis and chemotaxis, where they undergo apoptosis unless survival factors are present.

Major advances have been made in the understanding of molecular and intracellular pathways regulating eosinophil differentiation, priming, activation, and mediator secretion (with especially the role of vesicle-associated membrane protein [VAMP]–2 and VAMP-7, members of the SNARE complex [sensory nerve action potential

TABLE 61-1. Classification of the Eosinophilic Lung Diseases

EOSINOPHILIC LUNG DISEASE OF UNDETERMINED CAUSE

Idiopathic eosinophilic pneumonias
- Idiopathic chronic eosinophilic pneumonia
- Idiopathic acute eosinophilic pneumonia

Churg-Strauss syndrome

Hypereosinophilic syndrome

EOSINOPHILIC LUNG DISEASE OF DETERMINED CAUSE

Eosinophilic pneumonias of parasitic origin
- Tropical eosinophilia
- *Ascaris* pneumonia
- Eosinophilic pneumonia in larva migrans syndrome
- *Strongyloides stercoralis* infection
- Eosinophilic pneumonias in other parasitic infections

Eosinophilic pneumonias of other infectious causes

Allergic bronchopulmonary aspergillosis and related syndromes
- Allergic bronchopulmonary aspergillosis
- Other allergic bronchopulmonary syndromes associated with fungi or yeasts
- Bronchocentric granulomatosis

Drug, toxic agents, and radiation-induced eosinophilic pneumonias
- Drugs (typical, occasional, or exceptional eosinophilic pneumonia)
- Toxic agents (toxic oil syndrome)
- Eosinophilic pneumonia induced by radiation therapy to the breast

MISCELLANEOUS LUNG DISEASES WITH POSSIBLE ASSOCIATED EOSINOPHILIA

Organizing pneumonia

Asthma and eosinophilic bronchitis

Idiopathic interstitial pneumonias

Langerhans cell granulomatosis

Lung transplantation

Other lung diseases with occasional eosinophilia
- Sarcoidosis
- Paraneoplastic eosinophilic pneumonia

{*SNAP*} *Re*ceptors] in the regulation of granule fusion in eosinophils). The eosinophil contains two types of intracytoplasmic granules. The larger granules, characterized by an electron-dense crystalloid matrix, contain the characteristic cationic proteins. The smaller amorphous granules contain arylsulfatase and acid phosphatase. Activation of the eosinophil results in degranulation with the extracellular release of the eosinophil-specific proteins including major basic protein (MBP), eosinophil cationic protein (ECP), eosinophil-derived neurotoxin (EDN) (or eosinophil-protein X), and the enzymatic protein eosinophil peroxidase (EPO) and MBP homologue. The finding of vacuoles in the cytoplasm of the eosinophil and ultrastructural evidence of loss of electron density from the central core of the granules (inversion or disappearance of core density) characterizes morphologically the process of degranulation. Eosinophils also release proinflammatory cytokines, arachidonic acid–derived mediators, enzymes, reactive oxygen species, and matrix metalloproteases. They express a variety of surface proteins, including adhesion molecules, apoptotic signaling molecules, chemokines, complement receptors, chemotactic factor receptors, cytokine receptors, and immunoglobulin receptors. Thus, eosinophil accumulation and the release of toxic substances may in itself contribute to the pathophysiology of eosinophilic disorders.

Many biologic properties of the eosinophil are directed by T helper (Th) lymphocytes, but the eosinophil interacts in many allergic or inflammatory processes with other cells including mast cells and basophils, endothelial cells, macrophages, platelets, and fibroblasts. Eosinophils are capable of regulating mast cell function and histamine release. Activated eosinophils express the major histocompatibility complex II protein human leukocyte antigen (HLA)–DR, and possess the ability to participate to numerous immune functions, including antigen presentation and secretion of an array of cytokines capable of promoting effector T-cell proliferation. In addition, eosinophils are implicated in the regulation of Th1/Th2 balance, through synthesis of IL-4, promotion of IL-4, IL-5, and IL-13 secretion by $CD4^+$ T cells, and the synthesis of indoleamine 2,3-dioxygenase (indirectly promoting Th1 apoptosis).

Recruitment of the eosinophil to the lung mostly implicates IL-5 and the eotaxin subfamily of chemokines (itself regulated by the Th2 cell–derived IL-13 cytokine). Release of toxic granule proteins and lipid mediators by eosinophils may contribute to tissue damage and dysfunction; however, histopathologic lesions in eosinophilic pneumonias are largely reversible with treatment. One possible exception is represented by tissue damage associated with eosinophil infiltration in bronchial mucosa in asthma, especially in allergic bronchopulmonary aspergillosis (ABPA), and persistent airflow obstruction in Churg-Strauss syndrome (CSS). Corticosteroids are the most effective agents for reducing eosinophilia in the blood and tissues, by shortening the half-life of cytokines such as eotaxins, and inhibiting the cytokine-dependent survival of eosinophils.

A major impediment in eosinophil research is the inability of murine eosinophils to degranulate either in vivo or in vitro, in contrast with human eosinophils that differentially release their granule proteins after contact with different stimuli, and the difficulties of animal models in mimicking human eosinophilic lung disease. The recent availability of humanized anti-IL-5 antibody, which lowers eosinophil levels in the blood and in the lung in humans, and of genetically engineered mice such as those deficient in IL5 or in eosinophils, may hopefully contribute to a better understanding of the pathogenic role of eosinophils.[3b] There is, in any case, no doubt that the eosinophil plays a role in many inflammatory processes occurring in a variety of organs, and especially the respiratory tract. Because it has very characteristic morphology and staining properties, it is easy to detect in the tissues or biological fluids.

GENERAL FEATURES OF EOSINOPHILIC PNEUMONIAS

Historical Perspective

Reeder and Goodrich[4] published in 1952 a series of cases of pulmonary "infiltration with eosinophilia," including probable idiopathic chronic eosinophilic pneumonia (ICEP) and CSS. Crofton and coworkers[5] published a series of 16 cases of "pulmonary eosinophilia" with a review of 450 cases from the literature and proposed the following classification:

1. Simple pulmonary eosinophilia (Löffler's syndrome), defined by mild symptoms and transient infiltrates.
2. Prolonged pulmonary eosinophilia characterized by radiographic shadows persisting for over 1 month.
3. Tropical eosinophilia.
4. Pulmonary eosinophilia with asthma, a rather heterogeneous category.
5. Polyarteritis nodosa.

The authors mentioned "a continuum from the simple and transient abnormalities of Löffler's syndrome to the severe and often fatal manifestations of polyarteritis nodosa." Churg and Strauss reported in 1951[6] the eponym syndrome of "allergic granulomatosis, allergic angitiis, and periarteritis nodosa," and Carrington and colleagues [7] described the syndrome of ICEP. McCarthy and Pepys[8] later reported 27 cases of "cryptogenic pulmonary eosinophilias," 2 of whom developed systemic vasculitis.

Clinical Presentation

Eosinophilic pneumonia is a pneumonia in which the eosinophils are the most prominent inflammatory cells on histopathologic examination. Other inflammatory cells, especially lymphocytes and neutrophils, are often associated, but eosinophils clearly predominate. In clinical practice, the eosinophilic pneumonias may be separated into two main etiologic categories: (1) those in which a definite cause is found or (2) those of undetermined origin, that is, idiopathic (with the eosinophilic pneumonia being either solitary or included in a systemic disorder such as CSS).

A definite cause must be carefully investigated in any patient with eosinophilic pneumonia because it has practical consequences (e.g., stopping a drug responsible for iatrogenic eosinophilic pneumonia or treating a parasitic infection). When no cause is identified, the eosinophilic pneumonias may usually be included within well-characterized and individualized syndromes.

The eosinophilic pneumonias may manifest by different clinicoradiologic syndromes, namely Löffler's syndrome, chronic eosinophilic pneumonia, or acute eosinophilic pneumonia, mostly differing from one another by the pattern of disease onset. Extrapulmonary manifestations accompanying eosinophilic pneumonia are the hallmark of CSS and, to a lesser extent, hypereosinophilic syndrome (HES). The vast majority of cases respond dramatically to corticosteroid treatment and heal without significant sequelae.

Pathology

Histopathologic studies of eosinophilic pneumonia have mainly been done in patients with ICEP,[7,9,10] which was initially diagnosed by open-lung biopsy. The pathologic features described in ICEP may be considered as a common denominator of all categories of eosinophilic pneumonias, whatever their origin. Occasional pathologic studies in eosinophilic pneumonias of known cause have further shown some specific features such as a possible distinctive distribution of lesions (e.g., bronchocentric distribution in ABPA) or the presence of causal agents such as parasites or fungal hyphae.

In ICEP, the alveolar spaces are filled with eosinophils (Fig. 61-1). Macrophages are also present with some multinucleated giant cells scattered in the infiltrate; these may contain eosinophilic granules or Charcot-Leyden crystals.[7] An associated interstitial inflammatory cellular infiltrate is invariably present, consisting of eosinophils, lymphocytes, plasma cells, and histiocytes. A proteinaceous and fibrinous exudate accompanies the cellular eosinophilic infiltrate. Some eosinophilic microabscesses may be observed (foci of necrotic intra-alveolar eosinophils surrounded by macrophages or epithelioid cells with palisading arrangement). Morphologic (especially electron microscopic) as well as immunohistochemical studies have shown eosinophil degranulation within the site of eosinophilic pneumonia.[11] The global architecture of the lung remains intact, without necrosis or fibrosis.

Organization of the alveolar inflammatory exudate is a rather common finding,[7] suggesting some possible overlap between ICEP and organizing pneumonia. However, intraluminal organization in the distal air spaces is only sparse and never prominent in ICEP.

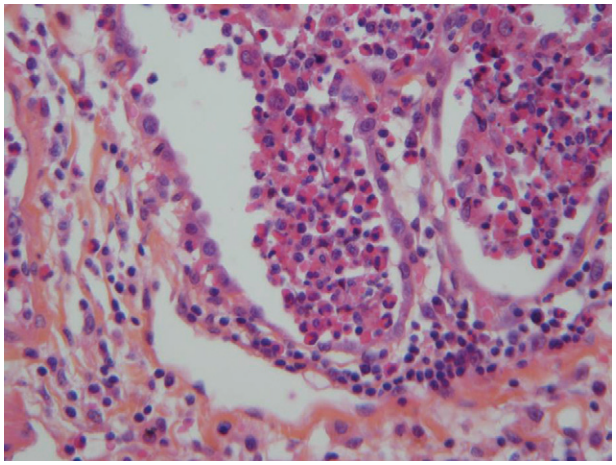

FIGURE 61-1 ■ Eosinophilic pneumonia. Accumulation of eosinophils within the alveolar lumen. (Courtesy of Françoise Thivolet-Béjui, MD, Department of Pathology, Louis-Pradel Hospital and Claude Bernard University, Lyon, France.)

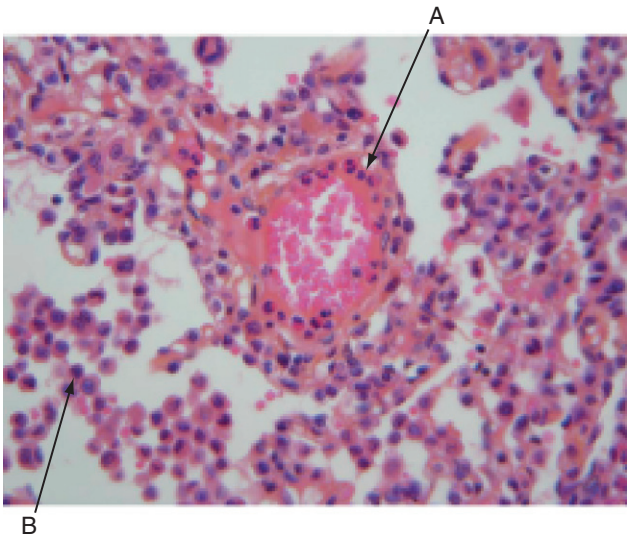

FIGURE 61-2 ■ Eosinophilic pneumonia. Eosinophils infiltrate the arteriolar wall (non-necrotizing vasculitis) (**A**) and are present within the alveolar lumen (**B**). (Courtesy of Françoise Thivolet-Béjui, MD, Department of Pathology, Louis-Pradel Hospital and Claude Bernard University, Lyon, France.)

Mucus plugs obstructing the small airways may be present in ICEP.[7]

A mild vasculitis involving both small arteries and venules is common, with perivascular cuffing and a few cells infiltrating the arterial media. In simple eosinophilic pneumonia, this vasculitis is *non-necrotizing* (Fig. 61-2).

The distribution of eosinophilic pneumonia is generally diffuse. However, it may be more focal in some cases, and the lesions may have an angiocentric or bronchiolocentric distribution in some etiologic groups of eosinophilic pneumonia.

The hilar lymph nodes associated with ICEP contain many eosinophils, and lymphoid hyperplasia is present.[7]

In idiopathic acute eosinophilic pneumonia (IAEP), the pathologic pattern includes intra-alveolar and interstitial eosinophilic infiltrates, diffuse alveolar damage, intra-alveolar fibrinous exudates, organizing pneumonia, and non-necrotizing vasculitis.[12]

Diagnosis

In clinical practice, the diagnosis of eosinophilic pneumonia is suspected in patients presenting with respiratory symptoms (dyspnea, cough, or wheezing), pulmonary opacities at chest imaging, and the demonstration of eosinophilia in the peripheral blood or, preferably, in the lung.

Although pathologic examination of the lung has been the "gold standard" to define eosinophilic pneumonia, lung biopsy is seldom necessary, and video-assisted thoracoscopic lung biopsy (which is a safe procedure) is necessary only in complex cases. Transbronchial lung biopsy may show characteristic features of eosinophilic pneumonia, but the small size of the specimen usually does not allow morphologic evidence of a possible etiologic process.

Bronchoalveolar lavage (BAL) has become a widely accepted noninvasive surrogate of lung biopsy for the diagnosis of eosinophilic pneumonia, although no study has definitely established a correlation between increased eosinophils at differential cell count and the finding of eosinophilic pneumonia at pathologic examination of the lung. In normal controls, BAL eosinophilia is lower than 1% of cells at differential count.[13] In contrast, BAL eosinophilia greater than 40% is found mainly in patients with chronic eosinophilic pneumonia, whereas BAL eosinophilia between 3% and 40% (and especially between 3% and 9%) may be found in various conditions, such as idiopathic pulmonary fibrosis, interstitial lung disease associated with connective tissue disorders, hypersensitivity pneumonitis, sarcoidosis, radiation pneumonitis, asthma, pneumoconioses, and infection.[14]

A conservative cutoff of 40% of eosinophils at BAL differential cell count has been adopted for the diagnosis of ICEP in clinical studies,[15,16] and a cutoff of 25% has been proposed for the diagnosis of IAEP.[17] For clinical practice, our recommendation is that a diagnosis of eosinophilic pneumonia is supported by alveolar eosinophilia when the eosinophils (1) are the predominant cell population (macrophages excepted) and (2) represent more than 25% and preferably more than 40% of differential cell count.

Although BAL is usually a safe procedure, it may not always be mandatory in typical cases. The diagnosis of eosinophilic pneumonia is usually accepted when both radiographic pulmonary opacities and peripheral blood eosinophilia are present, although alternative diagnoses such as bacterial or parasitic pneumonia, or pulmonary infiltrates related to Hodgkin disease, may also cause pulmonary opacities and peripheral eosinophilia. However, diagnosing eosinophilic pneumonia on the sole finding of blood eosinophilia and pulmonary opacities requires markedly elevated eosinophilia ($>1 \times 10^9$/L and preferably 1.5×10^9/L) together with typical clinicoradiologic features, because the finding of peripheral blood eosinophilia does not prove that the observed pulmonary opacities correspond to eosinophilic pneumonia. For example, BAL may occasionally be omitted for the diagnosis of Löffler's syndrome (as it occurs in ascariasis), with rather mild and nonspecific cough and wheezes, transient pulmonary opacities at chest radiograph, and frank blood eosinophilia. Conversely, peripheral blood eosinophilia may be missing in patients who have already received systemic corticosteroids, and it is often absent at presentation in IAEP. Nevertheless, BAL is recommended to confirm the diagnosis of eosinophilic pneumonia in most cases.

Once the diagnosis of eosinophilic pneumonia has been made, a thorough evaluation is necessary to investigate possible causes such as parasitic infection or drug or toxic exposure and to classify the case into one of the possible clinical entities (see Table 61-1).

EOSINOPHILIC LUNG DISEASE OF UNDETERMINED CAUSE

Either chronic or acute, the idiopathic eosinophilic pneumonias represent an eosinophilic pulmonary disorder without associated manifestations specific for any etiologic agent. ICEP is characterized by a progressive onset of symptoms over a few weeks with cough, increasing dyspnea, malaise, and weight loss. IAEP presents as an acute pneumonia (similar to acute lung injury or acute respiratory distress syndrome [ARDS]) with frequent respiratory failure necessitating mechanical ventilation.

Idiopathic Chronic Eosinophilic Pneumonia

Chronic eosinophilic pneumonia was defined as a distinct entity by Carrington and colleagues,[7] who described a series of 9 patients, with detailed clinical, radiologic, physiologic, and pathologic data. This syndrome was further confirmed and detailed by several series[10,16,18–20] and numerous case reports.

Clinical Features

ICEP occurs predominantly in women (with a 2:1 female-to-male ratio).[10,16] Although ICEP may occur in young people,[21,22] only 6% of patients are younger than 20 years old.[10] The incidence of ICEP peaks in the fourth decade,[10] with a mean age of 45 years at diagnosis.[16] A vast majority of patients with ICEP are nonsmokers,[10,16,19] suggesting that smoking might be protective.

A prior history of atopy is found in about half of the patients, with allergic rhinitis in 12%[10] to 24%,[16] drug allergy in about 10%,[10,16] nasal polyps in 5%[10] to 13%,[16] urticaria in 10%,[16] and eczema in 5%.[16]

Prior asthma is present in up to two thirds of the patients.[9,10,15,16,19,20] Asthma may also develop concomitantly with the diagnosis of ICEP in 15% of patients or develop after ICEP in 13%.[15] The presentation of ICEP is similar in asthmatics and nonasthmatics with the exception of higher total immunoglobulin (Ig) E in the former group.[15] ICEP may occur while asthmatic patients are on a desensitization program, but there is no proof that this may contribute to the development of ICEP. Asthma often gets worse after the occurrence of ICEP and requires long-term oral corticosteroid treatment even in the absence of recurrence of the eosinophilic pneumonia.[15]

The onset of ICEP is progressive, with a mean interval between the onset of symptoms and the diagnosis of 4 months in one series.[16] The most common respiratory symptoms are cough, dyspnea, and chest pain.[10,16] Dyspnea is usually not severe, although the necessity for mechanical ventilation after several months of progression of disease has been occasionally reported.[23] Hemoptysis occurs in about 10% of cases.[10,16] Wheezes at physical examination are found in one third of patients[10] and crackles in 38%.[16] Upper respiratory tract symptoms of chronic rhinitis or sinusitis are present in about 20% of patients.[16]

Systemic symptoms and signs are often prominent, with fever, weight loss (≥10 kg in about 10%). Asthenia, malaise, fatigue, anorexia, weakness, and night sweats are also common.

Imaging

The imaging features of ICEP are characteristic, although many of the features overlap with those found in cryptogenic organizing pneumonia (see Chapter 57). Peripheral opacities at chest x-ray are present in almost all cases[7,10,16,24–27] and are migratory in a quarter of the cases.[16] They usually consist of alveolar opacities with ill-defined margins, with a density varying from ground-glass to consolidation (Fig. 61-3). The classic pattern of "photographic negative or reversal of the shadows usually seen in pulmonary edema,"[26] highly evocative of ICEP,[26] is seen in only one fourth of patients.[10]

High-resolution computed tomography (HRCT) has further allowed description of the characteristic imaging features of ICEP. Whereas the opacities are bilateral in at least 50% of cases at chest x-ray,[10,19] the proportion of bilateral opacities may increase up to 97.5% at HRCT (Fig. 61-4).[16] Characteristic opacities predominate in the upper lobes[10,16,24] and are peripheral, with generally coexisting ground-glass and consolidation opacities at HRCT.[16,25,28] Consolidation with segmental or lobar atelectasis may be seen.[25] Septal line thickening is common.[28] Streaky or bandlike opacities parallel to the

FIGURE 61-3 ■ Chest radiograph of a patient with idiopathic chronic eosinophilic pneumonia shows bilateral alveolar opacities predominating in the upper lobes.

FIGURE 61-4 ■ Computed tomography (CT) scan of a patient with idiopathic chronic eosinophilic pneumonia shows bilateral symmetrical peripheral alveolar opacities.

chest wall may also be present.[25] Upon corticosteroid treatment, consolidation and ground-glass opacities rapidly show a decrease in size and extent, with possible change from consolidation to ground-glass opacities or inhomogeneous opacities, and later to streaky or band-like opacities.[25] Cavitary lesions are extremely rare and should lead to reconsideration of the diagnosis. Small pleural effusions are present in only 10% of cases at HRCT and mediastinal lymph node enlargement in 17%.[16]

Laboratory Studies

Peripheral blood eosinophilia over 6% was present in 88% of 111 cases in one literature review,[10] with a mean percentage of blood eosinophils at differential count of 26%. The mean blood eosinophilia was 5.5×10^9/L in our series, with eosinophils representing a mean of 32% of the total blood leukocyte count.[16] Because peripheral blood eosinophilia is often a diagnostic criterion of ICEP, the proportion of patients with ICEP and possible normal peripheral blood count is unknown.

Erythrocyte sedimentation rate is increased, and C-reactive protein level is elevated.[10,16,19] Total blood IgE level is increased in about half of cases and greater than 1000 kU/L in 15%.[16] Circulating immune complexes have been reported in ICEP in about one third of patients.[16] Antinuclear antibodies may occasionally be present.[16] Markedly increased urinary EDN level indicating active eosinophil degranulation is found in patients with ICEP.[29]

Bronchoalveolar Lavage

BAL has progressively replaced lung biopsy for the diagnosis of ICEP. Alveolar eosinophilia is a characteristic and constant feature in ICEP,[16,30] with a mean of 58% at differential cell count.[16] Alveolar eosinophilia may be associated with an increased percentage of neutrophils, mast cells, and lymphocytes.[16] BAL eosinophil cell count drops within a few days under corticosteroid treatment.[31] Sputum eosinophilia may also be present.[5,20]

BAL eosinophils of patients with ICEP show activation features such as the release of eosinophil proteins, which are taken up by macrophages.[32] ECP[33] and EDN[33] are increased in BAL fluid of patients with ICEP. Expression of HLA-DR in a patient with ICEP was present on 86% of alveolar eosinophils in contrast to 7% of blood eosinophils, suggesting compartmentalization of eosinophilic activation within the lung.[34] BAL lymphocytes are characterized by an accumulation of $CD4^+$ T cells that express activation surface antigens of memory T-cells ($CD45RO^+$, $CD45RA^-$, $CD62L^-$).[35] Recruitment of eosinophils to the lung involves various chemokines, which contribute to suppress Fas-induced apoptosis of eosinophils.[36]

Differential Diagnosis

Although ICEP is not a systemic disease, isolated and usually moderately severe extrapulmonary manifestations have been occasionally reported, including arthralgias, repolarization (ST-T) abnormalities on the electrocardiogram, pericarditis, altered liver biologic tests, eosinophilic lesions at liver biopsy, mononeuritis multiplex, diarrhea, skin nodule, immune complex vasculitis in the skin, and eosinophilic enteritis.[7,16,37] Such manifestations suggest an overlap between ICEP and CSS. Eosinophilic pneumonia similar to ICEP may be a presenting feature of CSS,[38,39] with patients often receiving corticosteroid treatment, which may prevent the development of overt systemic vasculitis. In a series of ICEP with especially high frequency of extrapulmonary signs (30%), some of which were quite evocative of the CSS, none of the patients treated with corticosteroids developed characteristic CSS or the idiopathic hypereosinophilic syndrome on follow-up.[37]

Lung Function Tests

Lung function tests in ICEP show an obstructive ventilatory defect in about half the patients[10,16] and a restrictive ventilatory defect in half the cases.[16] Hypoxemia defined by an arterial oxygen pressure (Pa_{O_2}) of 75 mm Hg or less was present in 64% of patients in a series[16]; CO transfer factor was less than 80% of predicted in 52%, and transfer coefficient was less than 80% of predicted in only 27%. An increased alveolar-arterial oxygen gradient has been reported in 90% of cases.[10] The impaired lung function tests normalize under treatment in most patients.[10] However, a ventilatory obstructive defect may develop over time in some patients, especially those with a markedly increased BAL eosinophilia at initial evaluation.[40]

Treatment and Prognosis

The natural course of untreated ICEP is not well known, because the dramatic response of ICEP to corticosteroids was observed shortly after these drugs became available.[10] Spontaneous resolution of ICEP may occur,[10,16] and death directly resulting from ICEP seems extremely rare. Symptoms improve within 1 or 2 weeks of corticosteroid treatment and even within 48 hours in about 80%[16] of

cases. Pulmonary opacities at chest x-ray clear rapidly. They disappeared within 1 week in 69% of patients in our series of patients treated with a mean initial dose of 1 mg/kg/day.[16] Almost all of our patients with ICEP treated with corticosteroids had a normal chest x-ray at their last follow-up visit.[16]

The optimal dose of corticosteroids is not established, but the usual doses vary between 20 and 60 mg/day. Our current recommendation is to start with 0.5 mg/kg/day of prednisone. Most patients require prolonged treatment (i.e., >6 mo) because of relapse while decreasing or after stopping the corticosteroid treatment. In one series, 58% of cases relapsed after corticosteroids had been discontinued and 21% while the corticosteroids were being tapered.[10] In our series, half of the patients relapsed after the corticosteroids had been weaned (with a mean delay of 72 wk) or were being tapered (the mean dose of corticosteroids at the time of relapse was 11 mg/day).[16] Relapses that may occur in the same areas of the lungs or in different areas[16] respond very well to resumed corticosteroid treatment; a dose of 20 mg/day of prednisone is usually sufficient to treat the relapses.

The clinical series in which follow-up is available clearly show that most patients need prolonged corticosteroid treatment: in our series with a mean 6.2 years of follow-up, only 31% were weaned at the last control visit.[16]

Relapses of ICEP are less frequent in patients with asthma, possibly because they often receive inhaled corticosteroids after stopping oral corticosteroids.[15,16] Inhaled corticosteroids might thus help in reducing the maintenance dose of oral corticosteroids, although they are not effective enough when given as monotherapy.[41]

Idiopathic Acute Eosinophilic Pneumonia

IAEP[12,17,20,42–45] differs from ICEP mainly by its acute onset, the severity of hypoxemia, the usual lack of increased blood eosinophils at presentation contrasting with frank eosinophilic alveolitis at BAL (BAL differential count with ≥25% eosinophils or predominance of eosinophils in open lung biopsy), and the absence of relapse after clinical recovery. Fever and bilateral opacities on chest x-ray are present in all patients. The absence of hypersensitivity to drugs, historical or laboratory evidence of infection, or other known cause of acute eosinophilic lung disease, are additional diagnostic criteria.[17] Our current diagnostic criteria of IAEP are listed in Table 61-2.[46]

TABLE 61-2. Diagnostic Criteria for Idiopathic Acute Eosinophilic Pneumonia

1. Acute onset of febrile respiratory manifestations (≤1 mo duration before consultation)
2. Bilateral diffuse opacities on chest radiography
3. Hypoxemia, with Pa_{O_2} on room air < 60 mm Hg, and/or Pa_{O_2}/Fi_{O_2} ≤ 300 mm Hg, and/or oxygen saturation on room air < 90%
4. Lung eosinophilia, with >25% eosinophils on BAL differential cell count (or eosinophilic pneumonia at lung biopsy)
5. Absence of infection, or of other known causes of eosinophilic lung disease (especially exposure to a drug susceptible to induce pulmonary eosinophilia)

Adapted from Allen JN, Pacht ER, Gadek JE, Davis WB: Acute eosinophilic pneumonia as a reversible cause of noninfectious respiratory failure. N Engl J Med 321:569–574, 1989; and Cottin V, Cordier JF: Eosinophilic pneumonias. Allergy 60:841–857, 2005.

Clinical Features

The average age at presentation is about 30 years[17,45]; but IAEP may occur in patients 20 years old or younger[21] and in older patients.[45] In contrast with ICEP, there is male predominance and no prior asthma history, although some patients may have a history of atopy.[20] Some patients had peculiar outdoor activities within the days before onset of disease, such as cave exploration, plant repotting, wood pile moving, smokehouse cleaning or motocross racing in dusty conditions.[17] Four patients from our series[45] had been exposed, respectively, to dust from indoor renovation work (two patients), gasoline tank cleaning, and explosion of a tear gas bomb. One case was reported in a New York City firefighter exposed to World Trade Center dust.[47]

A causative role of cigarette smoke seems established, because IAEP has developed soon after the initiation of smoking (especially when starting with large quantities) in numerous patients,[48–53] and challenge with cigarette smoking was positive in some of them,[48–51,53] but tolerance may develop in patients who resume smoking.[49–51] Flavoring components of smoked cigars have been suspected.[54] It is likely that inhalation of tobacco smoke or of any nonspecific injurious agent may initiate or contribute to the development of IAEP in individuals intrinsically prone to develop eosinophilic reactions to inhaled nonspecific causative agents. Recent alterations in smoking habits (e.g., beginning to smoke, restarting to smoke, or increasing the number of cigarettes smoked daily) especially within 1 month seem to play a major role in the onset of "idiopathic" AEP.[53] Increased levels of (1 → 3)-beta-D-glucan (a major component of the cell wall of most fungi and also one of the components of cigarette smoke) have been reported in BAL fluid of patients with IAEP.[52]

IAEP may develop acutely in previously healthy individuals, with symptoms at presentation consisting of cough, dyspnea, fever, and chest pain. It may also develop subacutely over a few weeks,[12] with no clinical difference between patients seen in a time interval of less than 7 days or 7 to 31 days from the first symptoms to the diagnosis of IAEP.[45] Abdominal complaints and also myalgias have been mentioned.[17] At physical examination, tachypnea and tachycardia are present, with crackles or, less often, wheezes on auscultation.

Imaging

Chest x-ray shows bilateral opacities, with mixed alveolar or interstitial opacities.[17,43–45] Bilateral pleural effusion

and Kerley B lines are common.[17] The chest x-ray returns to normal within 3 weeks,[17,43] with pleural effusions being the last abnormality to disappear.[17]

At computed tomography (CT) imaging, ground-glass opacities and air space consolidation are the most common patterns of parenchymal lesions, with poorly defined nodules and interlobular septal thickening seen in a majority of patients; pleural effusion present in at least two thirds of patients is usually bilateral.[17,27,43,45,55] We consider that bilateral pleural effusion and interlobular septal thickening are highly characteristic of IAEP in a patient with eosinophilic pneumonia.

Laboratory Studies

In contrast with ICEP, white blood cell count at presentation usually shows increased leukocytosis with a predominance of neutrophils, with eosinophils only rarely higher than 0.3×10^9/L, but the eosinophil count may rise to high values during the course of disease,[17,20,45] a finding very suggestive of IAEP. Eosinophilia is also present at pleural fluid differential cell count[17,49,56] and in the sputum.[20]

The IgE level may be raised in some patients,[56,57] and serum IgG and especially IgG2 and IgG4 levels may be reduced during the active phase of disease as compared with controls.[57] Serum levels of thymus and activation-regulated chemokine (TARC/CCL17) and KL6 are often increased in IAEP as opposed to other causes of acute lung injury (ALI).[58]

Bronchoalveolar Lavage

Given the usual lack of initial blood eosinophilia, BAL is the key to the diagnosis of IAEP, showing an average percentage of 37%[17] to 54%[45] eosinophils at differential cell count, with sterile bacterial cultures. After recovery, eosinophilia at BAL may persist for several weeks.[59] We consider that the finding of eosinophilia greater than 25% at BAL may obviate lung biopsy previously used for diagnosis, at least in immunocompetent patients.

Lung Function Tests

Hypoxemia may be severe and refractory to breathing 100% oxygen in some patients.[42,45] A majority of patients fit the definition of ALI (a pulmonary disorder characterized by an acute onset, bilateral opacities on chest x-ray, pulmonary artery wedge pressure ≤18 mm Hg when measured, or no evidence of left atrial hypertension, and a Pa_{O_2}/F_{IO_2} [fractional inspired oxygen concentration] ≤ 300 mm Hg) or the definition of ARDS (patients with ALI and with $Pa_{O_2}/F_{IO_2} \leq 200$ mm Hg). Mechanical ventilation, either noninvasive or with intratracheal intubation, is necessary in a majority of patients.[17,45] In contrast with ALI or ARDS, shock is exceptional[60,61] and extrapulmonary organ failure does not occur. F_{IO_2} may be decreased within a few hours of steroid treatment in many patients initially requiring oxygen.[17]

When performed in less severe cases, lung function tests have shown a mild restrictive ventilatory defect with normal forced expiratory volume in 1 second–to–forced vital capacity (FEV_1/FVC) ratio and reduced transfer factor.[57] Alveolar-arterial oxygen gradient is increased.[17] Lung function tests performed after recovery are normal in most patients, with possible ventilatory restriction in some of them.[17,62,63]

Lung Biopsy

Lung biopsy is seldom necessary. When done, it shows acute and organizing diffuse alveolar damage together with interstitial alveolar and bronchiolar infiltration by eosinophils, intra-alveolar eosinophils, and interstitial edema.[12,17,60,64]

Treatment and Prognosis

Recovery without corticosteroid treatment may occur,[45,58] demonstrating that improvement concomitant with corticosteroid treatment cannot be considered a diagnostic criterion of IAEP. However, when a diagnosis of IAEP is made, corticosteroid treatment is usually started with initially intravenous methyl prednisolone later changed to oral therapy that can be tapered over 2 to 4 weeks.[17] The response to corticosteroids occurs within 48 hours, allowing rapid weaning from the ventilator. Recovery is rapid with no significant clinical or imaging sequelae, and with no relapse after stopping corticosteroid treatment, in contrast with ICEP.

Although IAEP often presents clinically like ALI or ARDS, its prognosis is far better. The key to the diagnosis is eosinophilia at BAL, because blood eosinophilia is usually absent initially. A careful search for a cause of IAEP is mandatory, and especially infectious agents must be sought for in BAL fluid by cultures and appropriate staining.[65] Drug-induced IAEP must also be carefully excluded.

Churg-Strauss Syndrome

Although a subgroup of patients with periarteritis (polyarteritis) nodosa and associated asthma and eosinophilia had been previously characterized, Churg and Strauss described in 1951[6] the eponymous syndrome, mainly from autopsied cases. They described characteristic pathologic features consisting of granulomatous extravascular lesions as well as necrotizing, inflammatory, and granulomatous vascular changes, with an inflammatory exudate rich in eosinophils. The most frequent site of inflammation was the heart. In approximately half of the cases, a pneumonic process was found, with an eosinophil-rich exudate mixed with giant cells in the acute stage.

In the Chapel Hill Consensus Conference on the Nomenclature of Systemic Vasculitis,[66] CSS was included in the group of small vessel vasculitides and defined as an eosinophil-rich and granulomatous inflammation involving the respiratory tract, and necrotizing vasculitis affecting small to medium-sized vessels, and associated with asthma and eosinophilia. CSS is one of the pulmonary antineutrophil cytoplasmic antibodies

(ANCA)–associated vasculitides, together with Wegener's granulomatosis and microscopic polyangiitis, with ANCA present in approximately 40% of cases of CSS.

Because the diagnosis is now made earlier in the course of disease, lung biopsy is seldom necessary, and patients may receive corticosteroids before overt vasculitis has developed, the pathologic lesions of CSS currently observed[67,68] only rarely comprise all the characteristic features on a single biopsy from one organ. When typical features are present, both vasculitis (necrotizing or not, involving mainly the medium-sized pulmonary arteries) and granulomatous eosinophilic infiltration are seen. The extravascular granuloma consists of palisading histiocytes and giant cells. When present, the eosinophilic pneumonia in CSS is similar to ICEP. The early (prevasculitic) phase of CSS is characterized by eosinophilic infiltration of the tissues without vasculitis (perivascular eosinophilis are commonly found).

Clinical Features

The clinical features of CSS have been well defined.[69–74] It is a very rare systemic disease, which occurs especially in adults younger than 65[73,75]; it has been occasionally reported in children and adolescents. There is no sex predominance. The mean age of onset of vasculitis ranges from 38 to 49 years.[73,76]

Asthma, generally severe and becoming rapidly corticosteroid dependent, occurs at a mean age of about 35.[73] It usually precedes the onset of vasculitis by 3 years and up to 9 years.[69,73,76,77] The interval between asthma and the onset of vasculitis may be much longer in rare cases,[77] or they may be contemporaneous.[76] The severity of asthma typically increases progressively until the vasculitis develops, but it may attenuate when the vasculitis flourishes and further increase once the vasculitis recedes.[73,77]

Chronic rhinitis present in about three quarters of cases of CSS[73,82,83] is often accompanied by relapsing sinusitis and/or polyposis, with eosinophilic infiltration at histopathology.[84] Paranasal sinusitis has been reported in 61% of patients.[69] Crusty rhinitis may be present, but the rhinitis in CSS is distinctly much less severe than in Wegener's granulomatosis, with septal nasal perforation or saddle nose deformation being exceptional.

Asthenia, weight loss, fever, arthralgias, and myalgias (all of which are unusual in simple asthma) often herald the development of the extrapulmonary manifestations of vasculitis.

Heart damage that may be severe and lead to cardiac failure or sudden death[69,73,74,76,77] results especially from eosinophilic myocarditis and much less commonly from coronary arteritis.[90] Cardiac involvement is often insidious and asymptomatic and, thus, may be recognized only when left ventricular failure and dilated cardiomyopathy have developed. Heart failure may require heart transplantation, but recurrence of eosinophilic vasculitis is possible in the transplanted heart. However, myocardial impairment as well as coronary arteritis may markedly improve with corticosteroid treatment, thus necessitating a strict cardiac evaluation in any patient with suspected CSS, including electrocardiogram, echocardiography, serum level of troponin, and magnetic resonance imaging of the heart.[91] Pericarditis with limited effusion at echocardiography is common in CSS; occasionally, pericardial effusion may be more important and give rise to tamponade. In contrast with the idiopathic HES, endomyocardial involvement is not a common feature. Patients with CSS are at greater risk of venous thromboembolic events.[92]

Peripheral neurologic involvement mainly consists of mononeuritis multiplex, present in 77% of patients,[69] or asymmetrical polyneuropathy, with sudden onset of painful, focal or multifocal weakness or sensory loss, generally in the lower extremities. Cranial nerve palsies and central nervous system involvement are rare. Digestive tract involvement present in 31% of cases[69] usually manifests as isolated abdominal pain, but intestinal or biliary tract vasculitis may be present. Other digestive manifestations include diarrhea, ulcerative colitis, gastroduodenal ulcerations, perforations (esophageal, gastric, intestinal), digestive hemorrhage, and cholecystitis. Cutaneous lesions present in about half of patients[69] mainly consist of palpable purpura of the extremities, subcutaneous nodules (especially of the scalp and extremities), erythematous rashes, and urticaria. Renal involvement present in 26% of cases is usually mild,[69] in contrast with the other ANCA-associated vasculitides, namely, microscopic polyangiitis and Wegener's granulomatosis.

Imaging

Pulmonary opacities corresponding to eosinophilic pneumonia represent the most typical abnormalities on chest x-ray and have been reported in large series with a frequency of 37%[69] to 72%.[73] The pulmonary opacities are usually noted at presentation, but the chest x-ray remains normal throughout the course of the disease in some patients. The pulmonary opacities usually consist of ill-defined opacities, sometimes migratory, transient, and of varying density.[73,77–80] In contrast to Wegener's granulomatosis, pulmonary cavitary lesions are exceptional. Pleural effusion (usually mild) and phrenic nerve palsy may be observed.

The pulmonary opacities on thin-section CT mainly consist of areas of ground-glass attenuation or air space consolidation, with peripheral predominance or random distribution (Fig. 61-5); less common findings include centrilobular nodules, bronchial wall thickening or dilation, interlobular septal thickening, hilar or mediastinal lymphadenopathy, pleural effusion, or pericardial effusion[27,79–81] (Fig. 61-6). When present, pleural effusion should lead one to consider cardiomyopathy as a possible cause. Because these abnormalities are nonspecific, a correct diagnosis of CSS was made on CT in only 44% of 111 patients with eosinophilic lung diseases.[27]

Laboratory Studies

Peripheral blood eosinophilia is a major feature of CSS that usually parallels the vasculitis activity. Blood eosinophils are generally between 5 and 20×10^9/L, but they

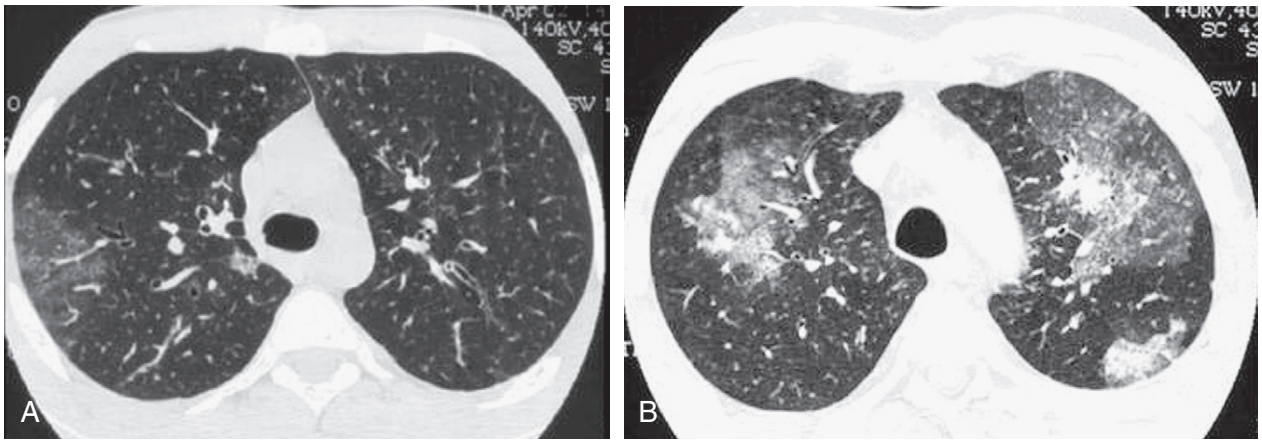

FIGURE 61-5 ■ CT scan of patients with Churg-Strauss syndrome shows ground-glass opacity of the right upper lobe (**A**) and bilateral central and peripheral opacities with varying density (**B**).

FIGURE 61-6 ■ Axial CT scan of a patient with Churg-Strauss syndrome, with lung consolidation and ground-glass opacities corresponding to eosinophilic pneumonia. In addition, pericardial effusion and bilateral pleural effusions are present due to cardiomyopathy.

may reach higher values.[69,73,77] Blood eosinophilia often disappears dramatically after the initiation of corticosteroid treatment (which may thus cause the absence of eosinophilia if blood tests are not done before starting corticosteroid treatment). Eosinophilia, sometimes greater than 60%, is found on BAL differential cell count[85] and in the pleural fluid when present.[86]

ANCA reported in 38% to 73% of patients are mainly perinuclear antineutrophil cytoplasmic antibody (p-ANCA) with myeloperoxidase specificity (much less often cytoplasmic antineutrophil cytoplasmic antibody [c-ANCA] with proteinase 3 specificity).[69,76,87,88] Serum IgE levels are markedly increased. The erythrocyte sedimentation rate and C-reactive protein level are increased, and anemia is common. High levels of urinary EDN have been reported, and these might represent an activity index of disease.[89]

Pathogenesis

The pathophysiology of CSS is not established. CSS may be considered as an autoimmune process involving T cells, endothelial cells, and eosinophils. Recent studies have identified possible defects in regulatory $CD4^+$ $CD25^+$ or $CD4^+$ $CD25^-$ T-cell lymphocytes (producing IL-10 and IL-2) in CSS (as compared with ICEP), possibly influencing progression and prognosis of disease.[93] Clonal $CD8^+/V\beta^+$ T cell expansions with effector memory phenotype and consistent with a hypothesis of persistent antigenic stimulation were found in peripheral blood lymphocytes by flow cytometry combined to analysis of T-cell antigen receptor (TCR)-γ gene rearrangement.[94] Some triggering or adjuvant factors (such as vaccines or desensitization) have been suspected to play a role in CSS.[95,96]

Although a family history of atopy and allergic rhinitis are often present, evidence of allergy (demonstration of specific IgE with corresponding clinical history) is present in less than one third of patients; when present, allergy in CSS mainly consists of perennial allergies especially to *Dermatophagoides*, with seasonal allergies less frequent than in asthmatic patients without CSS.[97] Genetic predisposition to develop CSS has been demonstrated in patients carrying the major histopathology complex DRB4 allele,[98] as well as the possibility of familial CSS.[99]

Other possible triggering factors include *Aspergillus*, allergic bronchopulmonary candidiasis, *Ascaris*, bird exposure, or smoked cocaine. Drug-induced eosinophilic vasculitis with pulmonary involvement has been reported in the past with sulfonamides used together with antiserum, and later with diflunisal,[100] macrolides,[101] and diphenylhydantoin.[102] CSS has also been reported in asthmatic patients treated with omalizumab, an anti-IgE antibody.[103–106]

The possible responsibility of leukotriene-receptor antagonists (montelukast, zafirlukast, pranlukast) in the development of CSS has generated much debate.[76,107–111] Although the association between leukotriene receptor antagonists and CSS is now established, there is

conflicting evidence whether it is the result of confounding by indication or a genuine causal association.[110] Whether the association is coincidental, whether some cases of smoldering CSS flare because of reducing oral or inhaled corticosteroids and/or adding leukotriene receptor antagonists, or whether these drugs really exert a role on the pathogenesis of the vasculitis is not established. However, CSS may occur following montelukast treatment in the absence of preexisting disease, may recur on rechallenge with leukotriene receptor antagonists, and may remit on withdrawal of this treatment without modifying the corticosteroid and/or immunosuppressive therapy.[108,110] We therefore consider that leukotriene receptor antagonists should be avoided in any asthma patient with eosinophilia and/or extrapulmonary manifestations compatible with smoldering CSS.

Diagnosis

The diagnosis of CSS may be difficult, because the clinician nowadays is more often faced with patients presenting with early and mild signs corresponding to the so-called formes frustes of CSS more or less suppressed by corticosteroid treatment for asthma, and which may later unmask especially when treatment is reduced or stopped.

The evolution of CSS usually follows three stages: asthma and rhinitis; tissue eosinophilia (such as a pulmonary disease resembling ICEP); and extrapulmonary eosinophilic disease with vasculitis. Diagnostic difficulties thus largely depend on the stage of disease at which the patient is seen. Although systemic disease is necessary to consider a diagnosis of CSS, it is extremely important that the diagnosis be established before severe organ involvement (especially cardiac) is present.

There are currently no established diagnostic criteria for CSS. Lanham and associates[73] have proposed three diagnostic criteria including (1) asthma, (2) eosinophilia exceeding 1.5×10^9/L, and (3) systemic vasculitis of two or more extrapulmonary organs. According to the classification criteria (which are not *diagnostic* criteria, however) of the American College of Rheumatology,[112] a sensitivity of 85% and a specificity of 99.7% are obtained if four or more of the six following criteria are present in a patient with proven systemic vasculitis: asthma; eosinophilia greater than 10% at differential blood cell count; mononeuritis (including multiplex) or polyneuropathy; fluctuating opacities on chest x-ray; bilateral maxillary sinusal abnormalities; or presence of extravascular eosinophils on a biopsy including a vessel. However, these diagnostic and classification criteria were proposed before ANCA were available. In the future, the presence of ANCA may probably be considered a major diagnostic criterion when present. A pathologic diagnosis of CSS is desirable, but not mandatory, in patients with characteristic clinical features and marked eosinophilia. The skin, nerve, and muscle are the most common sites where a pathologic diagnosis of vasculitis may be obtained.[69] Biopsy of the cutaneous lesions is the most common and simple procedure to obtain pathologic evidence of vasculitis. Lung biopsy is seldom done. Transbronchial biopsies usually do not show vasculitis or granulomata.

Differential Diagnosis

The borders separating CSS from the other ANCA-associated vasculitides and the other eosinophilic syndromes are sometimes difficult to establish. An eosinophilic variant of Wegener's granulomatosis has been described.[113] Concurrent CSS and pulmonary opacities and temporal arteritis (either with or without giant cells, either eosinophilic or not) has been described.[114] Distinguishing between mild CSS and ICEP with minor extrathoracic symptoms may also be difficult. Some mild vasculitis (non-necrotizing) is common on pathologic examination of the lung in patients with ICEP.[7] ICEP may further progress to CSS.[38] In addition, some cases of "limited" CSS have been reported[115] including those solely involving the lung or the heart. Formes frustes of CSS often consist of cases in which the disease has been controlled to a greater or lesser extent by corticosteroids given for asthma. Other cases are difficult to classify as either CSS or idiopathic HES. Careful clinical analysis, the presence of ANCA, the finding of a vasculitis and granulomas on biopsy, and molecular biologic analysis (in the cases of idiopathic HES) help in determining the final diagnosis.

Interestingly, two more recent studies have demonstrated that ANCA antibody status may characterize two distinct clinical phenotypes in CSS[87,88] (Table 61-3).

TABLE 61-3. Distinct Phenotypes of Churg-Strauss Syndrome

	Vasculitic Phenotype	Tissular Disease Phenotype
Respective frequency	~40%	~60%
ANCA	Present (mostly p-ANCA with anti-MPO specificity)	Absent
Predominant clinical and histopathologic features	Glomerular renal disease Peripheral neuropathy Purpura	Cardiac involvement (eosinophilic myocarditis) Fever
Predominant histopathologic features	Biopsy-proven vasculitis	Eosinophilic pneumonia

ANCA, antineutrophil cytoplasmic antibody; MPO, myeloperoxidase; p-ANCA, perinuclear antineutrophil cytoplasmic antibody.
Adapted from Sable-Fourtassou R, Cohen P, Mahr A, et al: Antineutrophil cytoplasmic antibodies and the Churg-Strauss syndrome. Ann Intern Med 143:632–638, 2005; and Sinico RA, Di Toma L, Maggiore U, et al: Prevalence and clinical significance of antineutrophil cytoplasmic antibodies in Churg-Strauss syndrome. Arthritis Rheum 52:2926–2935, 2005.

Hence, patients with ANCA, representing 38% of patients in both studies, have a *vasculitic phenotype* of disease with an increased frequency of extracapillary glomerular lesions, peripheral neuropathy, purpura, and biopsy-proven vasculitis. Conversely, CSS patients without ANCA have more frequent cardiac and pulmonary involvement (and fever), thus corresponding to an eosinophilic tissue disease phenotype of CSS. The latter might conceivably represent a variant of the HES with systemic manifestations.[88,116] The vasculitic phenotype of CSS is more frequent in patients carrying the major histopathology complex DRB4 allele[98] and, in those with the IL-10-3575/1082/592 TAC haplotype (part of the ancient haplotype IL10.2 correlated with increased IL-10 expression), is significantly associated with ANCA-negative CSS,[117] thus indicating that genetic predisposition may affect the phenotype of CSS.

Treatment and Prognosis

Corticosteroids are the mainstay of treatment of CSS and suffice in a large number of cases.[73,118,119] Initial methylprednisolone pulses, for 1 to 3 days, are useful in the most severe cases, then oral treatment is started, usually with 1 mg/kg/day of prednisone. Treatment is prolonged for several months with progressive reduction of doses. Relapses are common, and asthma often persists (or reappears if it had disappeared during high-dose corticosteroid treatment). Distinguishing relapse or persistence of so-called difficult asthma from relapse or persistence of CSS requires very precise evaluation taking into account the levels of blood eosinophils (generally $<1 \times 10^9$ in asthma without CSS relapse).

Cyclophosphamide therapy should be added to corticosteroids in patients with manifestations that could result in mortality or severe morbidity.[120] A retrospective study of patients with either polyarteritis nodosa or CSS[118] identified five factors with significant pronostic value and responsible for higher mortality (five factor score): proteinuria greater than 1 g/day; renal insufficiency with serum creatinine greater than 15.8 mg/L (140 μmol/L); gastrointestinal tract involvement; cardiomyopathy; and central nervous system involvement. Cardiomyopathy and central nervous system involvement were associated with a relative risk of mortality of 2.2 and 1.8, respectively (not statistically significant). The combination of immunosuppressors with corticosteroids improved disease control, despite associated infections (which could be decreased by using bolus instead of oral cyclophosphamide administration).[121,122] Mortality was associated with disease severity, and treatment with cytotoxic agents did not prevent relapses.[123] Although the optimal duration of therapy remains to be determined, 12 cyclophosphamide pulses were better able to control the disease than a 6-pulses regimen in patients with CSS and at least one poor prognosis factor at onset.[124] Corticosteroid treatment alone for CSS patients without poor prognostic factors at onset is efficient, with about half of the patients achieving complete remission without relapse.[125] Therefore, immunosuppressive therapy (most commonly with intravenous pulses of cyclophosphamide) in addition to corticosteroids is warranted in patients with poor prognostic factors at onset (e.g., five factor score ≥ 1). Oral azathioprine in addition to corticosteroids may be useful in patients who relapse under 20 mg/day or more of prednisone.

Subcutaneous interferon-alfa was successfully used mainly in CSS patients with severe disease.[126] High-dose intravenous immunoglobulins, cyclosporin A, and more recently, rituximab[127–130] have been occasionally used successfully. The anti-IgE omalizumab has been used successfully in patients with CSS to treat persistent asthma[131,132]; however, it does not control the systemic disease, and careful clinical monitoring is warranted.

The prognosis of CSS has improved considerably over time with almost 80% of patients alive at 5 years,[118] and 97% alive at 5 years in one recent series of CSS without poor-prognosis factors.[133] Most deaths during the first year of treatment are due to cardiac involvement.[134] In one series, CSS did not appear to confer increased mortality, a rather surprising finding.[76] As most patients continue to take oral corticosteroids over the long term, treatment-related side effects cause significant morbidity.[133] In addition, airflow obstruction due to uncontrolled asthma is present despite corticosteroids in many patients during follow-up, and persistent airflow obstruction may develop (38% of patients with at least 3 years follow-up in our series).[135] Airflow obstruction may not respond to inhaled bronchodilators, but may be still partly reversible with increased oral corticosteroid treatment.[135]

Hypereosinophilic Syndrome

The definition of the "idiopathic" HES proposed by Chusid and coworkers[136] in 1975 included (1) a persistent eosinophilia greater than 1.5×10^9/L for longer than 6 months, or death before 6 months associated with the signs and symptoms of hypereosinophilic disease, (2) a lack of evidence for parasitic, allergic, or other known causes of eosinophilia, and (3) presumptive signs and symptoms of organ involvement, including hepatosplenomegaly, organic heart murmur, congestive heart failure, diffuse or focal central nervous system abnormalities, pulmonary fibrosis, fever, weight loss, or anemia. The 14 cases they reported[136] included 2 patients with "prolonged benign hypereosinophilia," 3 with eosinophilic leukemia, and 1 with possible CSS. The later published cases of the idiopathic HES also proved heterogeneous, although patients with typical chronic disease shared some common complications, especially cardiac involvement.

Pathogenensis

In contrast with common hypereosinophilia, which is usually a reactive nonclonal process (as in parasitic disorders), several studies demonstrated that HES may result from a clonal proliferation of lymphocytes producing eosinophilopoetic chemokines ("lymphocytic variant" of HES), or from the clonal proliferation of the eosinophil cell lineage itself ("myeloproliferative variant" of HES, sometimes referred to as chronic eosinophilic

leukemia).[137-142] The term *idiopathic* should probably be abandoned in the classification of HES,[143] and may be appropriate only for the proportion of cases that cannot at present be classified in either category. In such genuinely idiopathic cases, innovative diagnostic tools such as the quantitative assessment of the *WT1* transcript in peripheral blood may help to differentiate HES from other causes of eosinophilia of determined cause.[144]

The **"lymphocytic variant"** of HES, which may account for about 30% of patients with HES, results from the production of chemokines (especially IL-5) which promote the accumulation of eosinophils by clonal Th2 lymphocytes (as demonstrated by clonal rearrangement of the TCR) bearing an aberrant immunologic phenotype (such as $CD3^-$ $CD4^+$). Lymphocyte phenotyping to detect a phenotypically aberrant T-cell subset, and analysis of the rearrangement of the TCR genes in search of T-cell clonality, should be performed on the peripheral blood (and bone marrow). Serum levels of IgE are elevated as a consequence of IL-4 and IL-13 production by Th2 lymphocytes.[143,145,146] Serum levels of IL-5 and TARC are increased.[147] The majority of reported patients was recruited from dermatology clinics and had papules or urticarial plaques infiltrated by lymphocytes and eosinophils (and in some of them, a cutaneous T-cell lymphoma or the Sezary syndrome was ultimately present). In such cases, the HES may be considered as a premalignant T-cell disorder.[145,146,148]

The **"myeloproliferative variant"** of HES (or chronic eosinophilic leukaemia), accounting for 20% to 30% of cases, is caused by a constitutively activated tyrosine kinase fusion protein created by fusion of *Fip1L1 – PDGFR-α* as a consequence of an interstitial chromosomal deletion of a region in the long arm of chromosome 4 (q12) not detectable by karyotype analysis.[149,150] Hepatomegaly, splenomegaly, mucosal ulcerations, severe cardiac manifestations resistant to corticosteroid treatment, anemia, thrombocytemia, increased serum vitamin B_{12}, leukocyte alkaline phosphatase and serum tryptase, and circulating leukocyte precursors are common and suggestive of the diagnosis, whereas cutaneous manifestations are infrequent. Diagnosis is confirmed by chromosomal rearrangement analysis and transcript study of the *Fip1L1 – PDGFR-α* fusion gene, which should be systematically performed in patients with HES. The fusion protein transforms hematopoietic cells and is inhibited by imatinib, a 2-phenylaminopyrimidine–based tyrosine kinase inhibitor originally used to treat chronic myelogenous leukemia. Imatinib proved efficient in the treatment of chronic myeloproliferative diseases and gastrointestinal stromal tumors (also characterized by aberrant constitutively activated tyrosine kinases). Imatinib proved efficient for several months in treating HES in patients refractory to corticosteroids, hydroxyurea, and/or interferon-α. Relapse occurred in one patient due to a mutation in *PDGFR-α* conferring resistance to imatinib (thus demonstrating that the FIP1L1-PDGFR-α fusion protein is the target of imatinib). Interestingly, IL-5 overexpression is necessary in mice to induce a condition similar to HES, suggesting that additional mechanisms may cooperate with the *Fip1L1 – PDGFR-α* fusion gene in disease etiology.[151]

Clinical Features

The pulmonary involvement in patients with eosinophilia of clonal origin has not been hitherto studied extensively, and especially has not been examined in cases classified according to the previously discussed two variants. However, lung or pleural involvement, although uncommon, has been mentioned in some cases[145,146,152] in patients with clonal lymphoid proliferations. The following data derived from older studies including cases with the two previously mentioned variants of HES may therefore need reevaluation in the future, and the prevalence of pulmonary involvement might be much lower than previously considered.

The HES is more common in men than in women (9:1), and occurs at ages between 20 and 50 years.[153] The onset is generally insidious, with eosinophilia discovered incidentally in 12% of the patients.[154] The mean eosinophil count at presentation was 20.1×10^9/L, with an average highest value of 44.4×10^9/L in one series.[155] Extremely high values of eosinophilia, in excess of 100×10^9/L, are found in some patients.[136]

The main presenting symptoms are weakness and fatigue (26%), cough (24%), and dyspnea (16%).[154] Cardiovascular involvement, present in 58% of the patients,[153] is a major cause of morbidity and mortality. Fibrotic thickening of the endocardium by collagen-rich connective tissue (endomyocardial fibrosis) is characteristic of cardiac disease in HES,[154,156] which differs from the cardiac involvement seen in CSS.[90] Endomyocardial fibrosis is preceded by an initial acute necrotic stage followed by a thrombotic process.[153] Cardiac manifestations include dyspnea, congestive heart failure, mitral regurgitation, and cardiomegaly.[154,157] Echocardiography demonstrates the classic features of HES consisting of mural thrombus, ventricular apical obliteration, and involvement of the posterior mitral leaflet.[158] The other manifestations of HES[153] include neurologic manifestations (thromboemboli, central nervous system dysfunction, and peripheral neuropathies), cutaneous manifestations (erythematous pruritic papules and nodules, urticaria, and angioedema).[153,159]

Imaging

Pulmonary involvement present in about 40% of patients[136,154] includes pleural effusion, pulmonary emboli, cough, and interstitial opacities. Severe coughing attacks were present in 40% of the cases in one series[155] with no other mention of bronchopulmonary disease. In another series,[157] cough was also the predominant feature, with bronchospasm and pulmonary opacities in 11/40 patients each.

CT findings in 5 patients consisted of small nodules with or without a halo of ground-glass attenuation and focal areas of ground-glass attenuation mainly in the lung periphery.[160] CT findings are poorly specific, and

a correct diagnosis was obtained in only one third of patients with the HES in a series of 111 patients with eosinophilic diseases.[27] Furthermore, some of the observed pulmonary imaging changes may correspond to pulmonary edema resulting from cardiac involvement, rather than genuine eosinophilic lung involvement.

Laboratory Studies

Only mild eosinophilia at BAL contrasting with high levels of eosinophilia in the blood has been reported in patients with the HES,[161,162] suggesting that eosinophilia may be compartmentalized in some patients with HES. Serum levels of mast cell tryptase may be elevated, and dysplastic mast cells may be found in the bone marrow, with some patients meeting minor criteria for systemic mastocytosis.[163]

Treatment and Prognosis

Imatinib has become the first-line therapy in patients with the myeloproliferative variant of HES, especially (but not exclusively) when the Fip1L1 – PDGFR-α fusion protein is present.[149,150] Corticosteroids may be used especially in the "lymphocytic variant" of HES (with response in only about half of the patients).[157,164] The anti-IL5 antibody mepolizumab has recently been shown to be beneficial as a corticosteroid-sparing agent in HES patients negative for the *Fip1L1 – PDGFR-α* fusion gene and requiring 20 to 60 mg/day of prednisone to maintain a stable clinical status and a blood eosinophil count of less than 1×10^9/L.[165] Other treatments include chemotherapeutic agents (hydroxyurea, vincristine, etoposide), cyclosporin A,[153,155,164] and interferon-alfa either as monotherapy[166–169] or in association with hydroxyurea, particularly in the myeloproliferative variant.[170,171]

Whereas the 3-year survival was only 12% in the first published series,[136] the prognosis has improved markedly in later series with about 70% survival at 10 years,[154] and 80% survival at 5 years and 42% at 10 and 15 years, respectively.[157] It is fascinating that advances in gene molecular biology may result in direct clinical benefit with a better prognosis for patients with an up-to-now almost untreatable disease.

EOSINOPHILIC LUNG DISEASE OF DETERMINED CAUSE

Eosinophilic Pneumonias of Parasitic Origin

The eosinophilic pneumonias related to parasite infestation probably represent the most common cause of eosinophilic pneumonia in the world. Parasitic eosinophilic pneumonia arises mainly in humans following infection by helminths (large multicellular worms) and especially nematodes (roundworms). The parasites may or may not be found at pathologic examination of the lung.

Tropical Eosinophilia

Clinical Features. Tropical eosinophilia[172] is a syndrome characterized by severe spasmodic bronchitis, leukocytosis, and high blood eosinophilia. The clinical manifestations of tropical pulmonary eosinophilia occur mainly in the second and third decades of life, with male predominance. It has been reported mostly in Indians, and occasionally in patients originating from India or Asia and living in North America or in Europe.[175,176] Tropical pulmonary eosinophilia is one of the most common causes of cough in tropical areas with endemic filariasis.[173] Patients develop a dry, hacking cough exacerbated at night (especially between 1 and 5 AM) and often associated with expiratory dyspnea and wheezing. Associated fever, loss of weight, and anorexia are common. Eosinophils, and sometimes Charcot-Leyden crystals, are present in the sputum. At chest x-ray, disseminated bilateral opacities are present.

Pathogenesis. Tropical eosinophilia is caused by the filarial nematodes *Wuchereria bancrofti* and *Brugia malayi* that infect more than 150 million persons in the world. The disease is endemic in the tropical and subtropical areas of coastal regions of Asia, southern and western Pacific, and Africa (less commonly in South and Central America). The adult worms reside in the lymphatic vessels, leading to lymphatic obstruction with subsequent elephantiasis. Humans are infected by infective larvae deposited in the skin by mosquitoes, which develop into mature worms within 6 to 12 months. First-stage larvae or microfilariae released from the fecund female's uterus circulate in the bloodstream from where they are ingested by the mosquitoes.

Patients with tropical pulmonary eosinophilia do not usually have clinical features of lymphatic filariasis. Microfilariae are usually not found in the blood or the lung. The circulating microfilariae are trapped in the lung vasculature where they release their antigenic contents, further triggering the inflammatory pulmonary reaction. The clinical features of tropical pulmonary eosinophilia largely result from an immune response of the host to the parasites.[174]

Although blood eosinophilia is high at the early stage (<2 wk) of pulmonary disease, no prominent eosinophilic infiltration is found in the lung. At this early stage, there is dense infiltration with histiocytes. Eosinophilic pneumonia is seen later (1–3 mo), with the formation of eosinophilic abscesses and granulomatous lesions characterized by the presence of foreign body giant cells, fibroblasts, and epithelioid cells; prominent eosinophilic infiltration is present at the periphery of the granuloma. Cases left untreated for 5 years or more eventually show pulmonary fibrosis with histiocytic infiltration.

Laboratory Studies. Blood eosinophilia is prominent, with more than 2×10^9 eosinophils/L in all cases, and up to 60×10^9/L in some cases.[177] IgE levels are increased. Antifilarial IgG antibodies are increased, as in all patients with filariasis. BAL shows intense alveolitis with a mean percentage of 54% of eosinophils with marked degranulation.[178] EDN may play an important role in the pathogenesis of pulmonary tropical eosi-

nophilia, as suggested by selective high levels of this eosinophilic granular protein in BAL.[179] In patients treated with diethylcarbamazine, BAL eosinophils drop within 2 weeks; blood eosinophils also decrease rapidly upon treatment.[178]

Persisting irregular basilar opacities are present in about two thirds of patients after 1 year. A "reticulonodular pattern" on chest CT is present in a majority of patients, with other features consisting of bronchiectasis, air trapping, and mediastinal lymphadenopathy.

Lung function tests show a restrictive ventilatory defect, with a reversible obstructive ventilatory defect and hypoxemia in about a quarter of the patients.[180,181]

Because microfilariae are not detectable in the blood, diagnosis is made in patients with residence for several months in an endemic area by the combination of the clinical, epidemiologic, and laboratory features including blood eosinophilia persisting for weeks with an absolute eosinophil count in the blood greater than 3×10^9/L, IgE levels exceeding 10,000 ng/mL, and markedly increased antifilarial IgG. Diagnosis is further supported by clinical improvement in the weeks following treatment. The current diagnostic criteria of tropical pulmonary eosinophilia include cough worse at night; residence in a filarial endemic area; eosinophil count greater than 3300 cells/mm^3; and clinical and hematologic response to diethylcarbamazine.[182]

Treatment. Diethylcarbamazine, which kills microfilariae and adult-stage worms, is the only effective drug for tropical pulmonary eosinophilia; corticosteroids in addition to diethylcarbamazine may be beneficial.

Ascaris Pneumonia

Pulmonary infiltrates with eosinophilia (Löffler's syndrome) may develop during the migration of the larvae of the parasite through the lung.

Ascaris lumbricoides, a nematode or roundworm, is the most common helminth infecting humans, especially children, in the tropical and subtropical areas. Mature females in the human intestine release large numbers of eggs. The eggs expelled with stools may survive for several months or years. The disease is transmitted through food or water contaminated by human feces. The infective larvae formed within eggs develop in the small intestine, penetrate through the intestinal wall, and migrate via the venous circulation to the lungs where they break out into the alveoli. They then migrate through the bronchi and trachea, are swallowed, and mature into adult worms in the small intestine.

Pulmonary manifestations occur during larval migration to the lungs. Usually, pulmonary symptoms are mild, with cough and wheezing, transient pulmonary opacities, and blood eosinophilia. Transient fever is present in the majority of patients, with possible pruritic eruption at the time of respiratory symptoms. Blood eosinophilia may be as high as 22×10^9/L.[183] Symptoms spontaneously resolve in a few days, whereas blood eosinophilia may remain elevated for several weeks. The diagnosis may be made by finding larvae in the sputum or gastric aspirates, but is more usually made by the delayed finding of the worm or ovae in the stool within 3 months of the pulmonary manifestations.

Intestinal ascariasis is treated with mebendazole for 3 days, or pyrantel palmoate and albendazole.[184]

Eosinophilic Pneumonia in Larva Migrans Syndrome

Visceral larva migrans[185] is a zoonotic infection caused in humans by *Toxocara canis*, a parasite infecting many dogs and other canines. Toxocariasis is found in all temperate and tropical areas of the world. Eggs released by female worms pass in feces of infected dogs, and the soil of public playgrounds in urban areas is therefore often contaminated with eggs of *Toxocara*. Children playing in contaminated areas may become infected, especially when they practice geophagia. Ingested eggs hatch in the intestine, migrate through the portal circulation, and invade the liver, lung, and other organs. However, in humans, the development of the parasite is blocked at the larval stage.

Visceral larva migrans occurs predominantly in children, the majority of whom remain asymptomatic and undiagnosed. When symptomatic, patients present with fever, pulmonary manifestations, seizures, and fatigue. Pulmonary manifestations in about 80% of cases consist of cough, wheezes, and dyspnea; pulmonary opacities at chest x-ray are present in approximately half the patients with pulmonary symptoms.[185] Severe pulmonary involvement, which is seen in about 17% of cases, may benefit from corticosteroids.[186]

Although uncommon in adults, toxocariasis is nevertheless a possible cause of pulmonary disease with eosinophilia that may be severe[187,188] and necessitate mechanical ventilation. Patients present with fever, dyspnea, and pulmonary opacities at chest x-ray. Wheezes or crackles are present at pulmonary auscultation. Blood eosinophilia may be present initially, or may develop only in the following days. Eosinophils are increased upon BAL differential cell count.

The diagnosis of toxocariasis is obtained by serologic methods, and especially by enzyme-linked immunosorbent assay (ELISA).

Visceral larva migrans usually requires only symptomatic treatment, the use of antihelmintics being controversial. Corticosteroids seem beneficial in cases with severe pulmonary involvement.

Strongyloides stercoralis Infection

Strongyloides stercoralis is an intestinal nematode that may cause severe autoinfection in immunocompromised patients. Strongyloidiasis is widely distributed in the tropics and subtropics. Human infection is acquired through the skin by contact with the soil of beaches or mud. Then larvae pass through the circulation to the lungs where they break into alveoli, ascend the trachea, are swallowed, and reside in the small intestine where they mature. Females deposit eggs that hatch into larvae that pass with feces. Eosinophilia is usually present in recently infected patients, but it is often absent in

disseminated disease.[189] *S. stercoralis* infection may persist for years and give rise thereafter to severe disseminated strongyloidiasis, which may affect all organs (hyperinfection syndrome), especially with immunosuppression from any cause.

Löffler's syndrome occurs when larvae migrate through the lungs after acute infection. Peripheral blood eosinophilia, in association with pneumonia, bronchospasm, or bronchitis, and abdominal pain or diarrhea, suggests strongyloidiasis in patients living, or having traveled, in endemic areas.

About 20% of hospitalized patients with strongyloidiasis have coexisting chronic lung disease.[190] Patients with chronic obstructive pulmonary disease or asthma receiving corticosteroids and immunocompromised patients are at risk of massive larval infection (hyperinfection syndrome) manifesting with fever, abdominal pain, ileus or small bowel obstruction, jaundice, or meningitis. Eosinophilia may or may not be present. Cough, wheezing, and dyspnea are associated with bilateral patchy opacities. Rhabditiform larvae may be recovered by BAL or bronchial washing[191,192] or in the sputum.[193]

Diagnosis of strongyloidiasis depends on the demonstration of larvae in the feces or in any secretion or tissue specimen (including sputum and BAL fluid). Immunodiagnostic assays by ELISA methods may be useful for diagnosis and screening.

Because of the risk of hyperinfection syndrome that persists for years, all infected patients are treated by thiabendazole when diagnosed.

Eosinophilic Pneumonias in Other Parasitic Infections

The dog hookworm *Ancylostoma brasiliense* causing cutaneous helminthiasis (creeping eruption) may produce, in 50% of cases, a typical Löffler syndrome with transitory migratory pulmonary infiltration and peripheral eosinophilia, with almost complete absence of clinical signs or symptoms of systemic disease. Pulmonary manifestations develop after the seventh day of cutaneous eruption. The human hookworms *Ancylostoma duodenale* and *Necator americanus* are other possible causes of Löffler's syndrome.

In early acute schistosomiasis (due to infection with either *Schistosoma haematobium* or *S. mansoni*), patients may develop transient multiple small pulmonary nodules on chest x-ray (best seen on CT scan) and eosinophilia.[194] In chronic schistosomiasis, embolization of ova in small arteries in the lungs results in granuloma formation, occlusion of pulmonary arteries, and further pulmonary hypertension.[195] The granuloma comprises lymphocytes, eosinophils, and giant cells. A posttreatment eosinophilic pneumonitis (also called lung shift, verminous pneumonia, and reactionary Löffler's-like pneumonitis) may develop.[196] It could result from parasitic antigen release following treatment.

The filarial parasite of dog *Dirofilaria immitis* (the pulmonary fluke) may occasionally develop into adult worms in the human lungs after inoculation of infective larvae by mosquitoes. It manifests mainly as solitary pulmonary nodules or masses with or without eosinophilia, but eosinophilic pulmonary infiltrates have been reported.

Other parasites causing rare pulmonary manifestations with eosinophilia include *Paragonimus westermani*, *Trichomonas tenax*, *Capillaria aerophila*, and *Clonorchis sinensis*.

Eosinophilic Pneumonias of Other Infectious Causes

Pulmonary infection with eosinophilia has been reported with the fungi *Coccidioides immitis*, *Bipolaris australiensis*, and *Bipolaris spicifera*. BAL eosinophilia has been reported in *Pneumocystis jirovecii* pneumonitis in patients with acquired immunodeficiency syndrome. Bacterial or viral pulmonary infection (e.g., tuberculosis, brucellosis, respiratory syncytial virus infection) may occasionally be a cause of eosinophilic pneumonia.

Allergic Bronchopulmonary Aspergillosis and Related Syndromes

Allergic Bronchopulmonary Aspergillosis

ABPA is distinct from the other pulmonary manifestations due to the fungus *Aspergillus* such as invasive pulmonary aspergillosis developing in immunocompromised patients or aspergilloma developing in preexistent pulmonary cavities. ABPA is characterized by asthma, eosinophilia, and bronchopulmonary manifestations with bronchiectasis secondary to a complex allergic and immune reaction to the presence of *Aspergillus* colonizing the airways. ABPA occurs in 1% to 2% of adults with previous asthma present for several years (with a prevalence of 1%–2%), and also in up to 7% to 10%[197,198] of patients in large series of cystic fibrosis. ABPA may be associated with allergic *Aspergillus* sinusitis,[199,200] which has been considered as a sinus equivalent of ABPA[200–205] and resulting in a syndrome called *sinobronchial allergic aspergillosis*.

Pathogenesis. ABPA may have an environmental (and especially occupational) dimension, as suggested by a study of workers in the bagasse-containing sites in sugar cane mills, where ABPA was diagnosed in 7% of workers who had chronic respiratory problems.[206]

Interestingly, an increased prevalence of heterozygotic cystic fibrosis transmembrane conductance regulator (CFTR) gene mutations has been reported in non–cystic fibrosis patients with ABPA or sinobronchial allergic mycosis,[207] suggesting that CFTR gene mutations could be involved in the development of these conditions without overt cystic fibrosis. Genetic susceptibility to develop ABPA has also been suggested by association with a polymorphism within the IL-4 receptor α-chain gene[208] and association with HLA DR subtypes.[209] Infection with nontuberculous mycobacteria may be seen with increased frequency in patients with ABPA.[210]

ABPA results from an immune and inflammatory reaction in the bronchi and the surrounding parenchyma in response to antigens from *Aspergillus* growing in mucous plugs in the airways of asthmatics. The immunologic response of the host includes—but is not restricted to—both type I hypersensitivity mediated by IgE antibodies and type III hypersensitivity with the participation of IgG and IgA antibodies and of a Th2 $CD4^+$ T-cell mediated immune response. Over time, the associated inflammatory reaction results in damage to the bronchial epithelium, submucosa, and adjacent pulmonary parenchyma.[211,212]

Clinical Features. The current primary diagnostic criteria include asthma, history of pulmonary infiltrates, proximal bronchiectasis, elevated serum IgE, and immunologic hypersensitivity to *A. fumigatus* such as immediate reaction to prick test for *Aspergillus* antigen, precipitating antibodies against *A. fumigatus*, and elevated specific IgE against *A. fumigatus*.[213,214] There are approximately 40 antigenic components that can bind with IgE antibodies, of which 22 recombinant *Aspergillus* allergens (named *Asp f1* to *Asp f22*) are identified.[215] Specific antibodies to *Asp f4* and *Asp f6* may be the most helpful for diagnostic purposes.[216]

Other common findings in patients with ABPA comprise the expectoration of mucous plugs, the presence of *Aspergillus* in sputum, and late skin reactivity to *Aspergillus* antigen.[213] In patients with ABPA, typical proximal bronchiectasis may be absent; such cases are designated ABPA-seropositive.[215] Five stages of ABPA have been distinguished: acute, remission, recurrent exacerbations, corticosteroid-dependent asthma, and fibrotic end stage. Pulmonary infiltrates or peripheral blood eosinophilia may be present only during the acute phase or recurrent exacerbations of the disease.

Imaging. Damage to the large bronchi is a major feature of ABPA, with mucous plugs containing *Aspergillus* obstructing the airways with subsequent atelectasis and bronchial wall damage. Proximal bronchiectases predominate in the upper lobes and are well visualized on CT.[217–219] In asthmatic patients, the presence of bronchiectasis affecting three or more lobes, centrilobular nodules, and mucoid impaction on CT scan are highly suggestive of ABPA (Fig. 61-7)[220]; because of its characteristic imaging presentation, the correct diagnosis of ABPA was made on CT scan in 84% of cases of ABPA in a series of patients with eosinophilic lung diseases.[27] Although surgery is seldom warranted, eosinophilic pneumonia may be found in resection specimens from patients with asthma and ABPA with chronic pulmonary consolidation.[217,221]

The acute stage of ABPA is characterized on imaging by either fleeting infiltrates due to eosinophilic pneumonia or mucus plugging with ensuing segmental, lobar, or even whole-lung atelectasis. Fever is present. Blood eosinophilia is generally greater than 1×10^9/L. Sputum and expectorated plugs contain eosinophils and Charcot-Leyden crystals. Serum levels of TARC are elevated and might be used as a marker for identification and monitoring of ABPA.[222,223] Mucoid impaction is typically characterized by a V-shaped lesion with the vertex pointing toward the hilum and atelectasis.[224]

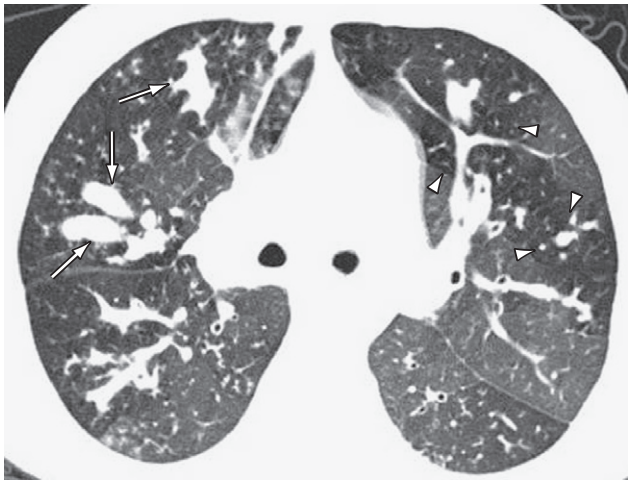

FIGURE 61-7 ■ Axial CT scan of a patient with allergic bronchopulmonary aspergillosis shows central bronchiectasis with mucoid impaction (*arrows*). Diffuse bilateral inhomogeneous lung opacity is present, with areas of low attenuation throughout the pulmonary parenchyma (*arrowheads*) representing mosaic perfusion resulting from a combination of large and small airway inflammation. (Courtesy of Michael B. Gotway, MD, Scottsdale Medical Imaging and the Department of Radiology, University of California, San Francisco.)

Treatment. The treatment of ABPA mainly relies on corticosteroids during attacks, with long-term corticosteroids maintained only in patients with frequent symptomatic attacks or evidence of progressive lung damage. Treatment of episodes of pulmonary consolidation may prevent the progression of ABPA to the fibrotic end stage.[225] Inhaled corticosteroids may reduce the need for long-term oral corticosteroids. Oral itraconazole is a useful adjunct to corticosteroids, allowing reduction of the doses of corticosteroids.[226,227] A double-blind, randomized, placebo-controlled study indicated that patients with corticosteroid-dependent ABPA generally benefit from concurrent itraconazole treatment; improvements included the immunologic and physiologic criteria and the corticosteroid dose, but there was no significant effect on pulmonary infiltrates.[228] Another randomized, double-blind, placebo-controlled study with itraconazole for 16 weeks in stable subjects with ABPA demonstrated that subjects receiving itraconazole had a decrease in sputum eosinophils, sputum ECP levels, serum IgE levels, and serum IgG levels to *A. fumigatus* and had fewer exacerbations than patients receiving placebo.[229] Itraconazole interacts with many medications and may further induce adrenal insufficiency.[230,231] Measuring total serum IgE level may be helpful for monitoring therapy.

Treatment with an anti-IgE recombinant antibody omalizumab may be useful in some cases.[232–234] The newer agent voriconazole has been successfully used in ABPA only in isolated case reports.[235,236]

Other Allergic Bronchopulmonary Syndromes Associated with Fungi or Yeasts

A similar syndrome of allergic bronchopulmonary disease may be produced by other fungi or yeasts including *Pseudallescheria boydii*, *Cladosporium herbarum*, *Candida albicans Stemphylium* sp., *Torulopsis* sp., *Curvularia lunata*, *Bipolaris* sp., *Rhizopus* sp., *Trichosporon terrestre*, *Fusarium vasinfectum*, and *Helminthosporium* sp.

Bronchocentric Granulomatosis

Bronchocentric granulomatosis[237] is an inflammatory and destructive process beginning within the bronchiolar walls and further extending into the surrounding parenchyma with a peribronchiolar distribution of the lesions.[238] The granulomatous inflammatory process destroys both the mucosa and the walls of the bronchioles, and the necrotic areas resulting from the destroyed bronchioles are often surrounded by palisading histiocytes. Eosinophils represent the major component of the cellular infiltrate. Scattered fungal hyphae may be demonstrated by the Grocott silver stain in some patients. A dense inflammatory infiltrate is, in most cases, present in the peribronchial tissue but may occasionally extend more distally in the parenchyma. In asthmatic patients with bronchocentric granulomatosis, eosinophils compose the major proportion of the infiltrate. Other possible changes include vascular inflammation and mucoid impaction.[238,239]

About half the patients with bronchocentric granulomatosis at lung pathologic examination are asthmatics who further present with fever and cough. A peripheral blood eosinophilia is common, generally greater than 1×10^9 eosinophils/L.[238,239] The radiographic features consist of masses, alveolar opacities or pneumonic consolidation, or reticulonodular opacities, which predominate in the upper lobes and are unilateral in a majority of patients.[240,241] Most of these patients fulfill the criteria for ABPA, and corticosteroids are efficient with an excellent prognosis, although recurrences are common.[238]

Eosinophilia is usually not conspicuous when bronchocentric granulomatosis occurs in patients without asthma (an infectious cause is found in some cases).

Drug, Toxic Agents, and Radiation-Induced Eosinophilic Pneumonias

Drugs

More than 80 drugs have been reported to cause eosinophilic pulmonary infiltrates (Table 61-4). However, the causality has not been established in many case reports, and thus, the number of drugs that can reliably be considered as a common cause of drug-induced eosinophilic pneumonia is much smaller. Drugs causing eosinophilic pneumonia are mainly nonsteroidal anti-inflammatory drugs and antibiotics.

Drug-induced eosinophilic lung disease may present in three main clinical settings: (1) some patients taking a drug for several months (or years) for the treatment of chronic disease progressively develop increasing dyspnea with cough and mild fever; (2) in asymptomatic patients, the interstitial lung disease may be discovered by routine chest x-ray; (3) some patients present with acute eosinophilic pneumonia sometimes requiring mechanical ventilation. Associated extrapulmonary iatrogenic manifestations, especially including cutaneous rashes, fever, or nausea, may be present.

All the drugs taken in the weeks or months preceding the clinical syndrome must be carefully recorded in any patient presenting with eosinophilic pneumonia, including illicit drugs (cocaine, heroin), the intake of which is often denied by the patient.

Transient interstitial infiltrates with eosinophilia (Löffler's syndrome), chronic eosinophilic pneumonia, and acute eosinophilic pneumonia have all been reported as drug-induced syndromes. Systemic eosinophilic vasculitis involving the lung (and thus closely resembling CSS) has also been reported.[102,242]

The regression of eosinophilic lung disease after stopping the drug is the best clue for an iatrogenic reaction. However, this may take a long time, and therefore, in many reported cases, corticosteroids have been given concomitantly with drug withdrawal, so that the responsibility of the drug cannot be definitely established. The only absolute proof of the drug responsibility is obtained by its reintroduction with ensuing relapse of pneumonia, but this may be dangerous and thus unethical if done only for scientific purposes. Careful reintroduction of a drug presumed to be the cause of eosinophilic pneumonia may be considered with careful monitoring only when no alternative treatment for a serious disease is available.

Presentation of eosinophilic drug-induced pneumonia is generally nonspecific. Although, in most cases, patients present with pulmonary manifestations compatible with ICEP (with the exception of possible associated pleural effusion and extrapulmonary manifestations including cutaneous rash), other patients present with features characteristic of IAEP. Therefore, in any case of "idiopathic" eosinophilic pneumonia, an iatrogenic cause must be systematically considered.

The eosinophilia-myalgia syndrome, which developed in 1989 in the United States, was related to the intake of contaminated preparations of L-tryptophan. It manifested with frequent dyspnea and cough, myalgia, fatigue, rash, paresthesia, swelling, and muscle weakness, with interstitial lung disease or infiltrates at CT in 13% of cases,[243] and peripheral blood eosinophilia. The outcome was favorable, especially in patients receiving corticosteroids.[243–245]

Toxic Oil Syndrome

Ingestion of denatured cooking oil was the cause of the toxic oil syndrome, which affected about 20,000 people in Spain in 1981.[246] This scleroderma-like disorder was characterized by an interstitial-alveolar pattern on chest imaging and eosinophilia during the first 4 months. In the acute phase, death was mainly due to respiratory

TABLE 61-4. Drugs That May Cause Eosinophilic Pneumonia

DRUGS WITH TYPICAL PULMONARY EOSINOPHILIA
Acetylsalicylic acid
Captopril
Diclofenac
Ethambutol
Fenbufen
Granulocyte-macrophage colony-stimulating factor
Ibuprofen
Minocycline
Naproxen
Para (4)-aminosalicylic acid
Penicillins
Phenylbutazone
Piroxicam
Pyrimethamine
Sulindac
Sulfamides-sulfonamides
Tolfenamic acid
Trimethoprim-sulfamethoxazole

DRUGS WITH OCCASIONAL PULMONARY EOSINOPHILIA
Bleomycin
Carbamazepine
Chlorpromazine
Cocaine
Desipramine
Dapsone
Febarbamate
Gold salts
Heroin
Imipramine
Isoniazid
Loxoprofen
Mephenesin
Methotrexate
Methylphedinate
Nitrofurantoin
Nomifensine
Pentamidine
Perindopril
Phenytoin
Propranolol
Sulfasalazine[275]
Trimipramine

DRUGS WITH EXCEPTIONAL EOSINOPHILIA
Amiodarone
Aminoglutethimide
Ampicillin
Beclomethasone
Bicalutamide
Bucillamine
Cephalosporins
Chloroquine
Chlorpropamide
Clarithromycin[276]
Clofibrate
Cromoglycate
Diflunisal
Erythromycin
Fludarabine[277]
Furazolidone
Glafenine
Indomethacin
Iodinated contrast medium
Levofloxacin
Maloprim
Maprotiline
Mesalazine (5-aminosalicylic acid)
Metronidazole
Nalidixic acid
Nilutamide
Paracetamol
Penicillamine
Procarbazine
Propylthiouracile
Oxaliplatin[278]
Ranitidine
Scotch-Guard
Streptomycin
Tenidap
Tetracycline
Tolazamide
Tosufloxacin tosilate
Trazodone
Troleandomycin
Venlafaxine

From Cordier JF: Eosinophilic pneumonias. *In* Schwarz MI, King Jr TE (eds): Interstitial Lung Disease (4th ed). London: BC Dekker, 2003, pp 657–700.

failure, whereas the chronic stage of disease was characterized by pulmonary hypertension, scleroderma, hepatic disease, sicca syndrome, polyneuropathy, joint contractures, and chronic pulmonary sequelae.

Radiation Therapy

Chronic eosinophilic pneumonia developing after radiation therapy for breast cancer has been reported.[247,248] It was seen in women with a history of asthma or allergy, at a median time of 3.5 months and up to 10 months after completion of radiotherapy for breast cancer. Dyspnea and cough were the main presenting symptoms, with pulmonary opacities at imaging being unilateral (irradiated lung) or bilateral, and possibly migratory. All patients had blood eosinophilia of 1.0×10^9 g/L or greater and/or eosinophilia greater than 40% on the BAL differential cell count. Patients rapidly improved with oral corticosteroids without sequelae, but some patients relapsed after treatment withdrawal. This syndrome is similar to the organizing pneumonia syndrome primed by radiation therapy to the breast,[249] with eosinophilic pneumonia occurring preferentially in patients with asthma or atopy. We hypothesize that eosinophilic pneumonia may develop upon radiation therapy preferentially in patients with a preexisting Th2-oriented lymphocyte response,[247,250,251] together with yet unidentified genetic predisposition, environmental factors, and/or additional triggers.

MISCELLANEOUS LUNG DISEASES WITH ASSOCIATED EOSINOPHILIA

Eosinophilia in blood and/or in BAL has been reported in some pulmonary disorders in which eosinophilic pneumonia is not a major finding.

Organizing Pneumonia

Organizing pneumonia is defined by the presence of buds composed of inflammatory cells, fibroblasts, and connective tissue within the lumen of distal air spaces. It may be secondary to various causes (such as infection or drug-induced reactions) or be cryptogenic. The typical clinical and imaging features (patchy alveolar infiltrates) of organizing pneumonia may closely mimic ICEP.[252] Furthermore, pathologic overlap of organizing pneumonia

and ICEP may be encountered, with foci of organizing pneumonia in ICEP and eosinophils in organizing pneumonia. In some cases, organizing pneumonia may represent the evolution of an untreated CEP.[252] Eosinophilia in BAL may be present in cryptogenic organizing pneumonia, but it is usually less than 20% at differential cell count.

Asthma and Eosinophilic Bronchitis

Infiltration of the airways by eosinophils is common in eosinophilic pneumonias, but may also be an isolated phenomenon. The eosinophil is considered to play a major role in the pathogenesis of asthma.[253] Eosinophilic inflammation of the airways present in the submucosa and epithelium of patients with asthma is correlated with severity of asthma.[254] Furthermore, BAL has shown mildly increased levels of eosinophils (usually <5%) on differential cell count in asthmatics, with the increase in eosinophils in the alveolar samples less than in bronchial samples.[255] Interestingly, although eosinophilic infiltration of the bronchi is common in the eosinophilic pneumonias, asthma is not a constant feature in such disorders.

Eosinophilic bronchitis (without asthma) with a high percentage of eosinophils (about 40%) in sputum is a cause of chronic cough responsive to corticosteroid treatment,[256] with normal lung function and absence of bronchial hyperreactivity.[257,258] Eosinophilic pneumonia does not occur. The observed values of sputum eosinophils are often much higher in eosinophilic bronchitis than in asthma.[258] The *FIP1L1 – PDGFR-α* fusion gene has been reported in one patient with eosinophilic bronchitis.[259] Prolonged treatment with inhaled corticosteroids may be beneficial.[256,260] Eosinophilic bronchitis is distinct from bronchial asthma, although it may in some cases evolve over time to irreversible airflow obstruction without asthma or to genuine asthma.[261,262]

Idiopathic Interstitial Pneumonias

Mildly increased levels of eosinophils may be found at BAL differential cell count in the idiopathic interstitial pneumonias (idiopathic pulmonary fibrosis, nonspecific interstitial pneumonia, cryptogenic organizing pneumonia). Increase of BAL eosinophils is associated with a poor clinical response to corticosteroids.[263–265]

Focal eosinophilic pneumonia has been reported in cases of usual interstitial pneumonia,[266] and focal eosinophils are a minor feature of nonspecific interstitial pneumonia.[267]

Langerhans Cell Granulomatosis

Pulmonary Langerhans cell granulomatosis (also designated as eosinophilic granuloma or pulmonary histiocytosis X) results from the proliferation of Langerhans cells. The pulmonary pathologic lesions consisting of nodules often assuming a bronchiolocentric stellate shape are composed of Langerhans cells with variable numbers of eosinophils, plasma cells, and lymphocytes. Eosinophils usually present in the initial active stage of disease contribute to the "eosinophilic granuloma." Numerous in about 25% of cases, they are usually situated at the periphery of the lesions. The eosinophils are rare or absent at the chronic stage of disease.

Lung Transplantation

Eosinophilic alveolitis in lung transplant recipients may be indicative of acute rejection (tissue eosinophilia is involved in rejection after renal, cardiac, hepatic, and pancreatic transplantation). However pulmonary eosinophilia in lung transplant recipients may also result from infectious agents such as *Aspergillus*, *Pseudomonas*, or coxsackievirus.[268]

Other Lung Diseases with Occasional Eosinophilia

Blood eosinophilia and tissue eosinophilia may be present in sarcoidosis, but are usually mild.[269] Pulmonary eosinophilia developed in two patients after transplantation for sarcoidosis, with bronchiolitis obliterans syndrome developing after resolution of pulmonary eosinophilia.[270] A case of ICEP overlapping with sarcoidosis and Behçet's disease has been reported.[271] Sarcoidosis developed in a patient with blood eosinophilia and a previous history of asthma and eosinophilic pneumonia.[272]

Eosinophilic pneumonia was reported in a patient with gastric cancer producing GM-CSF and IL-5.[273]

KEY POINTS

- Although they have lung and/or airways eosinophilia as a common denominator, the eosinophilic lung diseases correspond to a wide and heterogeneous spectrum of disorders.
- Eosinophilic lung disease may manifest clinically as a pulmonary disease of varying severity, ranging from chronic or transient infiltrates with mild symptoms to the acute severe eosinophilic pneumonia resembling ALI or ARDS and necessitating mechanical ventilation.
- Blood eosinophilia greater than 1×10^9 eosinophils/L (and preferably greater than 1.5×10^9/L) is of considerable help for suggesting the diagnosis. However, blood eosinophilia

KEY POINTS—CONT'D

may be absent (as in the early phase of IAEP or when patients are already taking corticosteroids).

- On BAL, high eosinophilia (>25%, and preferably >40%) may be considered diagnostic of eosinophilic pneumonia in a compatible setting.
- There is currently little if any indication for pulmonary biopsy in the diagnosis of the eosinophilic lung diseases.
- The etiologic diagnosis of eosinophilic lung diseases is crucial, and will be directed by the clinical syndrome.
  - Inquiry as to drug intake must be meticulous and any suspected drug should be withdrawn.
  - Travel history or residence in areas where parasites are endemic must be recorded, and laboratory investigations for parasitic causes must take into account the specific epidemiology of parasites throughout the world.
  - The appropriate diagnostic laboratory tests for parasites must be selected according to the instructions of a specialist.
  - The other known causes of eosinophilic lung disease must also be searched (with the help of a checklist if possible). If no cause is found, the eosinophilic lung disease is considered idiopathic.
- When present, extrathoracic manifestations raise the suspicion of a systemic eosinophilic disease such as CSS or HES, thus necessitating specific diagnostic investigations.
- Corticosteroids remain the cornerstone of symptomatic treatment for eosinophilic disorders, and these are necessary in the idiopathic eosinophilic pneumonias, ABPA flares, and the CSS (with the addition of cyclophosphamide in patients with poor-prognostic factors). The response to corticosteroids is usually dramatic in ICEP and in most cases of CSS, but relapses are common when tapering the doses or after stopping treatment.
- Imatinib, a tyrosine kinase inhibitor, has proved very effective in the treatment of the myeloproliferative variant of HES, a disorder heretofore resistant to treatment.

References

1. Marone G (ed): Human Eosinophils. Biological and Clinical Aspects, vol 76. Basel: S. Karger, 2000, p 250.
2. Rothenberg ME: Eosinophilia. N Engl J Med 338:1592–1600, 1998.
3. Hogan SP, Rosenberg HF, Moqbel R, et al: Eosinophils: Biological properties and role in health and disease. *In* Kay AB, Kaplan A, Bousquet J, Holt P (eds): Allergy and Allergic Diseases (2nd ed). Oxford: Blackwell Publishing, 2008, pp 258–294.

3a. Jacobsen EA, Taranova AG, Lee NA, Lee JJ: Eosinophils: singularly destructive effector cells or purveyors of immunoregulation? J Allergy Clin Immunol 119:1313–1320, 2007.

3b. Renninger ML, Seymour RE, Whiteley LO, et al: Anti-IL5 decreases the number of eosinophils but not the severity of dermatitis in Sharpin-deficient mice. Exp Dermatol 2009 (Epub ahead of print).

4. Reeder WH, Goodrich BE: Pulmonary infiltration with eosinophilia (PIE syndrome). Ann Intern Med 36:1217–1240, 1952.
5. Crofton JW, Linvingstone JL, Oswald NC, Roberts ATM: Pulmonary eosinophilia. Thorax 7:1–35, 1952.
6. Churg J, Strauss L: Allergic granulomatosis, allergic angiitis, and periarteritis nodosa. Am J Pathol 27:277–301, 1951.
7. Carrington C, Addington W, Goff A, et al: Chronic eosinophilic pneumonia. N Engl J Med 280:787–798, 1969.
8. McCarthy DS, Pepys J: Cryptogenic pulmonary eosinophilias. Clin Allergy 3:339–351, 1973.
9. Liebow AA, Carrington CB: The eosinophilic pneumonias. Medicine (Baltimore) 48:251–285, 1969.
10. Jederlinic PJ, Sicilian L, Gaensler EA: Chronic eosinophilic pneumonia. A report of 19 cases and a review of the literature. Medicine (Baltimore) 67:154–162, 1988.
11. Olopade CO, Crotty TB, Douglas WW, et al:. Chronic eosinophilic pneumonia and idiopathic bronchiolitis obliterans organizing pneumonia: Comparison of eosinophil number and degranulation by immunofluorescence staining for eosinophil-derived major basic protein. Mayo Clin Proc 70:137–142, 1995.
12. Tazelaar HD, Linz LJ, Colby TV, et al: Acute eosinophilic pneumonia: Histopathologic findings in nine patients. Am J Respir Crit Care Med 155:296–302, 1997.
13. The BAL Cooperative Group Steering Committee: Bronchoalveolar lavage constituents in healthy individuals, idiopathic pulmonary fibrosis, and selected comparison groups. Am Rev Respir Dis 141:S169–S202, 1990.
14. Velay B, Pages J, Cordier JF, Brune J: Hyperéosinophilie du lavage broncho-alvéolaire. Valeur diagnostique et corrélations avec l'éosinophilie sanguine. Rev Mal Respir 4:257–260, 1987.
15. Marchand E, Etienne-Mastroianni B, Chanez P, et al: Idiopathic chronic eosinophilic pneumonia and asthma: How do they influence each other? Eur Respir J 22:8–13, 2003.
16. Marchand E, Reynaud-Gaubert M, Lauque D, et al: Idiopathic chronic eosinophilic pneumonia. A clinical and follow-up study of 62 cases. Medicine (Baltimore) 77:299–312, 1998.
17. Pope-Harman AL, Davis WB, Allen ED, et al: Acute eosinophilic pneumonia. A summary of 15 cases and a review of the literature. Medicine (Baltimore) 75:334–342, 1996.
18. Pearson DJ, Rosenow EC: Chronic eosinophilic pneumonia (Carrington's). A follow-up study. Mayo Clin Proc 53:73–78, 1978.
19. Naughton M, Fahy J, FitzGerald MX: Chronic eosinophilic pneumonia. A long-term follow-up of 12 patients. Chest 103:162–165, 1993.
20. Hayakawa H, Sato A, Toyoshima M, et al: A clinical study of idiopathic eosinophilic pneumonia. Chest 105:1462–1466, 1994.

21. Wubbel C, Fulmer D, Sherman J: Chronic eosinophilic pneumonia: A case report and national survey. Chest 123:1763–1766, 2003.
22. Nathan N, Guillemot N, Aubertin G, et al: Chronic eosinophilic pneumonia in a 13-year-old child. Eur J Pediatr 167:1203–1207, 2008.
23. Libby DM, Murphy TF, Edwards A, et al: Chronic eosinophilic pneumonia: An unusual cause of acute respiratory failure. Am Rev Respir Dis 122:497–500, 1980.
24. Mayo J, Müller N, Road J, et al: Chronic eosinophilic pneumonia. CT findings in six cases. AJR Am J Roentgenol 153:727–730, 1989.
25. Ebara H, Ikezoe J, Johkoh T, et al: Chronic eosinophilic pneumonia: Evolution of chest radiograms and CT features. J Comput Assist Tomogr 18:737–744, 1994.
26. Gaensler EA, Carrington CB: Peripheral opacities in chronic eosinophilic pneumonia: The photographic negative of pulmonary edema. AJR Am J Roentgenol 128:1–13, 1977.
27. Johkoh T, Muller NL, Akira M, et al: Eosinophilic lung diseases: Diagnostic accuracy of thin-section CT in 111 patients. Radiology 216:773–780, 2000.
28. Arakawa H, Kurihara Y, Niimi H, et al: Bronchiolitis obliterans with organizing pneumonia versus chronic eosinophilic pneumonia: High-resolution CT findings in 81 patients. AJR Am J Roentgenol 176:1053–1058, 2001.
29. Cottin V, Deviller P, Tardy F, Cordier JF: Urinary eosinophil-derived neurotoxin/protein X: A simple method for assessing eosinophil degranulation in vivo. J Allergy Clin Immunol 101:116–123, 1998.
30. Pesci A, Bertorelli G, Manganelli P, et al: Bronchoalveolar lavage in chronic eosinophilic pneumonia. Analysis of six cases in comparison with other interstitial lung diseases. Respiration 54(Suppl 1):16–22, 1988.
31. Takahashi H, Arakawa Y, Oki K, et al: Analysis of bronchoalveolar lavage cells in chronic eosinophilic pneumonia before and during corticosteroid therapy. Int Arch Allergy Immunol 108(Suppl 1):2–5, 1995.
32. Janin A, Torpier G, Courtin P, et al: Segregation of eosinophil proteins in alveolar macrophage compartments in chronic eosinophilic pneumonia. Thorax 48:57–62, 1993.
33. Jorens PG, Van Overveld FJ, Van Meerbeeck JP, et al: Evidence for marked eosinophil degranulation in a case of eosinophilic pneumonia. Respir Med 90:505–509, 1996.
34. Beninati W, Derdak S, Dixon PF, et al: Pulmonary eosinophils express HLA-DR in chronic eosinophilic pneumonia. J Allergy Clin Immunol 92:442–449, 1993.
35. Mukae H, Kadota JI, Kohno S, et al: Increase of activated T-cells in BAL fluid of Japanese patients with bronchiolitis obliterans organizing pneumonia and chronic eosinophilic pneumonia. Chest 108:123–128, 1995.
36. Saita N, Yamanaka T, Kohrogi H, et al: Apoptotic response of eosinophils in chronic eosinophilic pneumonia. Eur Respir J 17:190–194, 2001.
37. Weynants P, Riou R, Vergnon JM, et al: Pneumopathies chroniques idiopathiques à éosinophiles. Étude de 16 cas. Rev Mal Respir 2:63–68, 1985.
38. Steinfeld S, Golstein M, De Vuyst P: Chronic eosinophilic pneumonia (CEP) as a presenting feature of Churg-Strauss syndrome (CSS). Eur Respir J 7:2098, 1994.
39. Hueto-Perez-de-Heredia JJ, Dominguez-del-Valle FJ, Garcia E, et al:. Chronic eosinophilic pneumonia as a presenting feature of Churg-Strauss syndrome. Eur Respir J 7:1006–1008, 1994.
40. Durieu J, Wallaert B, Tonnel AB: Long-term follow-up of pulmonary function in chronic eosinophilic pneumonia. Eur Respir J 10:286–291, 1997.
41. Minakuchi M, Niimi A, Matsumoto H, et al: Chronic eosinophilic pneumonia: Treatment with inhaled corticosteroids. Respiration 70:362–366, 2003.
42. Allen JN, Pacht ER, Gadek JE, Davis WB: Acute eosinophilic pneumonia as a reversible cause of non infectious respiratory failure. N Engl J Med 321:569–574, 1989.
43. Cheon JE, Lee KS, Jung GS, et al: Acute eosinophilic pneumonia: Radiographic and CT findings in six patients. AJR Am J Roentgenol 167:1195–1199, 1996.
44. King MA, Pope-Harman AL, Allen JN, et al: Acute eosinophilic pneumonia: Radiologic and clinical features. Radiology 203:715–719, 1997.
45. Philit F, Etienne-Mastroianni B, Parrot A, et al: Idiopathic acute eosinophilic pneumonia: A study of 22 patients. Am J Respir Crit Care Med 166:1235–1239, 2002.
46. Cottin V, Cordier JF: Eosinophilic pneumonias. Allergy 60:841–857, 2005.
47. Rom WN, Weiden M, Garcia R, et al: Acute eosinophilic pneumonia in a New York City firefighter exposed to World Trade Center dust. Am J Respir Crit Care Med 166:797–800, 2002.
48. Nakajima M, Manabe T, Niki Y, Matsushima T: Cigarette smoke–induced acute eosinophilic pneumonia. Radiology 207:829–831, 1998.
49. Shintani H, Fujimura M, Yasui M, et al: Acute eosinophilic pneumonia caused by cigarette smoking. Intern Med 39:66–68, 2000.
50. Shintani H, Fujimura M, Ishiura Y, Noto M: A case of cigarette smoking–induced acute eosinophilic pneumonia showing tolerance. Chest 117:277–279, 2000.
51. Nakajima M, Manabe T, Niki Y, et al: A case of cigarette smoking–induced acute eosinophilic pneumonia showing tolerance. Chest 118:1517–1518, 2000.
52. Kawayama T, Fujiki R, Honda J, et al:. High concentration of (1–>3)-beta-D-glucan in BAL fluid in patients with acute eosinophilic pneumonia. Chest 123:1302–1307, 2003.
53. Uchiyama H, Suda T, Nakamura Y, et al: Alterations in smoking habits are associated with acute eosinophilic pneumonia. Chest 133:1174–1180, 2008.
54. Al-Saieg N, Moammar O, Kartan R: Flavored cigar smoking induces acute eosinophilic pneumonia. Chest 131:1234–1237, 2007.
55. Daimon T, Johkoh T, Sumikawa H, et al: Acute eosinophilic pneumonia: Thin-section CT findings in 29 patients. Eur J Radiol 65:462–467, 2008.
56. Ogawa H, Fujimura M, Matsuda T, et al: Transient wheeze. Eosinophilic bronchobronchiolitis in acute eosinophilic pneumonia. Chest 104:493–496, 1993.
57. Matsuno O, Takenaka R, Hiroshige S, et al: Reduced IgG levels found during acute eosinophilic pneumonia, which normalize during recovery from disease. Respir Med 102:899–903, 2008.
58. Miyazaki E, Nureki S, Ono E, et al: Circulating thymus- and activation-regulated chemokine/CCL17 is a useful biomarker for discriminating acute eosinophilic pneumonia from other causes of acute lung injury. Chest 131:1726–1734, 2007.
59. Taniguchi H, Kadota J, Fujii T, et al: Activation of lymphocytes and increased interleukin-5 levels in bronchoalveolar lavage fluid in acute eosinophilic pneumonia. Eur Respir J 13:217–220, 1999.
60. Kawayama T, Fujiki R, Morimitsu Y, et al: Fatal idiopathic acute eosinophilic pneumonia with acute lung injury. Respirology 7:373–375, 2002.
61. Buddharaju VL, Saraceno JL, Rosen JM, et al: Acute eosinophilic pneumonia associated with shock. Crit Care Med 27:2014–2016, 1999.
62. Buchheit J, Eid N, Rodgers G, et al: Acute eosinophilic pneumonia with respiratory failure: A new syndrome? Am Rev Respir Dis 145:716–718, 1992.
63. Chiappini J, Arbib F, Heyraud JD, et al: Pneumopathie éosinophilique subaiguë idiopathique d'évolution favorable sans corticothérapie. Rev Mal Respir 12:25–28, 1995.
64. Mochimaru H, Kawamoto M, Fukuda Y, Kudoh S: Clinicopathological differences between acute and chronic eosinophilic pneumonia. Respirology 10:76–85, 2005.
65. Matsuno O, Ueno T, Takenaka R, et al: Acute eosinophilic pneumonia caused by *Candida albicans*. Respir Med 101:1609–1612, 2007.
66. Jennette JC, Falk RJ, Andrassy K, et al: Nomenclature of systemic vasculitides. Proposal of an international consensus conference. Arthritis Rheum 37:187–192, 1994.
67. Katzenstein AL: Diagnostic features and differential diagnosis of Churg-Strauss syndrome in the lung. A review. Am J Clin Pathol 114:767–772, 2000.
68. Churg A: Recent advances in the diagnosis of Churg-Strauss syndrome. Mod Pathol 14:1284–1293, 2001.

69. Guillevin L, Cohen P, Gayraud M, et al: Churg-Strauss syndrome. Clinical study and long-term follow-up of 96 patients. Medicine (Baltimore) 78:26–37, 1999.
70. Della Rossa A, Baldini C, Tavoni A, et al: Churg-Strauss syndrome: Clinical and serological features of 19 patients from a single Italian centre. Rheumatology (Oxford) 41:1286–1294, 2002.
71. Solans R, Bosch JA, Perez-Bocanegra C, et al: Churg-Strauss syndrome: Outcome and long-term follow-up of 32 patients. Rheumatology (Oxford) 40:763–771, 2001.
72. Churg A, Brallas M, Cronin SR, Churg J: Formes frustes of Churg-Strauss syndrome. Chest 108:320–323, 1995.
73. Lanham JG, Elkon K, Pusey C, Hughes G: Systemic vasculitis with asthma and eosinophilia: A clinical approach to the Churg-Strauss syndrome. Medicine (Baltimore) 63:65–81, 1984.
74. Reid AJC, Harrison BDW, Watts RA, et al: Churg-Strauss syndrome in a district hospital. Q J Med 91:219–229, 1998.
75. Mouthon L, le Toumelin P, Andre MH, et al: Polyarteritis nodosa and Churg-Strauss angiitis: Characteristics and outcome in 38 patients over 65 years. Medicine (Baltimore) 81:27–40, 2002.
76. Keogh KA, Specks U: Churg-Strauss syndrome: Clinical presentation, antineutrophil cytoplasmic antibodies, and leukotriene receptor antagonists. Am J Med 115:284–290, 2003.
77. Chumbley LC, Harrison EG, De Remee RA: Allergic granulomatosis and angiitis (Churg-Strauss syndrome). Report and analysis of 30 cases. Mayo Clin Proc 52:477–484, 1977.
78. Degesys GE, Mintzer RA, Vrla RF: Allergic granulomatosis: Churg-Strauss syndrome. AJR Am J Roentgenol 135:1281–1282, 1980.
79. Choi YH, Im JG, Han BK, et al: Thoracic manifestation of Churg-Strauss syndrome: Radiologic and clinical findings. Chest 117:117–124, 2000.
80. Kim YK, Lee KS, Chung MP, et a: Pulmonary involvement in Churg-Strauss syndrome: An analysis of CT, clinical, and pathologic findings. Eur Radiol 17:3157–3165, 2007.
81. Worthy SA, Muller NL, Hansell DM, Flower CDR: Churg-Strauss syndrome: The spectrum of pulmonary CT findings in 17 patients. AJR Am J Roentgenol 170:297–300, 1998.
82. Olsen KD, Neel HB 3rd, De Remee RA, Weiland LH: Nasal manifestations of allergic granulomatosis and angiitis (Churg-Strauss syndrome). Otolaryngol Head Neck Surg 88:85–89, 1995.
83. Srouji I, Lund V, Andrews P, Edwards C: Rhinologic symptoms and quality-of-life in patients with Churg-Strauss syndrome vasculitis. Am J Rhinol 22:406–409, 2008.
84. Bacciu A, Buzio C, Giordano D, et al: Nasal polyposis in Churg-Strauss syndrome. Laryngoscope 118:325–329, 2008.
85. Wallaert B, Gosset P, Prin L, et al: Bronchoalveolar lavage in allergic granulomatosis and angiitis. Eur Respir J 6:413–417, 1993.
86. Erzurum SC, Underwood GA, Hamilos DL, Waldron JA: Pleural effusion in Churg-Strauss syndrome. Chest 95:1357–1359, 1989.
87. Sable-Fourtassou R, Cohen P, Mahr A, et al: Antineutrophil cytoplasmic antibodies and the Churg-Strauss syndrome. Ann Intern Med 143:632–638, 2005.
88. Sinico RA, Di Toma L, Maggiore U, et al: Prevalence and clinical significance of antineutrophil cytoplasmic antibodies in Churg-Strauss syndrome. Arthritis Rheum 52:2926–2935, 2005.
89. Cottin V, Tardy F, Gindre D, et al: Urinary eosinophil-derived neurotoxin in Churg-Strauss syndrome. J Allergy Clin Immunol 96:261–264, 1995.
90. Ginsberg F, Parrillo JE: Eosinophilic myocarditis. Heart Fail Clin 1:419–429, 2005.
91. Baccouche H, Yilmaz A, Alscher D, et al: Images in cardiovascular medicine. Magnetic resonance assessment and therapy monitoring of cardiac involvement in Churg-Strauss syndrome. Circulation 117:1745–1749, 2008.
92. Allenbach Y, Seror R, Pagnoux C, et al: High frequency of venous thromboembolic events in Churg-Strauss syndrome, Wegener's granulomatosis and microscopic polyangiitis but not polyarteritis nodosa: A systematic retrospective study on 1130 patients. Ann Rheum Dis 68:564–567, 2009. Epub 2008;November 17.
93. Tsurikisawa N, Saito H, Tsuburai T, et al: Differences in regulatory T cells between Churg-Strauss syndrome and chronic eosinophilic pneumonia with asthma. J Allergy Clin Immunol 122:610–616, 2008.
94. Guida G, Vallario A, Stella S, et al: Clonal $CD8^+$ TCR-Vbeta expanded populations with effector memory phenotype in Churg-Strauss syndrome. Clin Immunol 128:94–102, 2008.
95. Mouthon L, Khaled M, Cohen P, et al: Antigen inhalation as a triggering factor in systemic small-sized-vessel vasculitis. Four cases. Ann Med Interne (Paris) 152:152–156, 2001.
96. Guillevin L, Guittard T, Bletry O, et al: Systemic necrotizing angiitis with asthma: Causes and precipiting factors in 43 cases. Lung 165:165–172, 1987.
97. Bottero P, Bonini M, Vecchio F, et al: The common allergens in the Churg-Strauss syndrome. Allergy 62:1288–1294, 2007.
98. Vaglio A, Martorana D, Maggiore U, et al: HLA-DRB4 as a genetic risk factor for Churg-Strauss syndrome. Arthritis Rheum 56:3159–3166, 2007.
99. Tsurikisawa N, Morita S, Tsuburai T, et al:. Familial Churg-Strauss syndrome in two sisters. Chest 131:592–594, 2007.
100. Rich MW, Thomas RA: A case of eosinophilic pneumonia and vasculitis induced by diflunisal. Chest 111:1767–1769, 1997.
101. Hubner C, Dietz A, Stremmel W, et al: Macrolide-induced Churg-Strauss syndrome in a patient with atopy. Lancet 350:563, 1997.
102. Yermakov VM, Hitti IF, Sutton AL: Necrotizing vasculitis associated with diphenylhydantoin: two fatal cases. Hum Pathol 13:182–184, 1983.
103. Ruppert AM, Averous G, Stanciu D, et al: Development of Churg-Strauss syndrome with controlled asthma during omalizumab treatment. J Allergy Clin Immunol 121:253–254, 2008.
104. Winchester DE, Jacob A, Murphy T: Omalizumab for asthma. N Engl J Med 355:1281–1282, 2006.
105. Puechal X, Rivereau P, Vinchon F: Churg-Strauss syndrome associated with omalizumab. Eur J Intern Med 19:364–366, 2008.
106. Bargagli E, Madioni C, Olivieri C, et al: Churg-Strauss vasculitis in a patient treated with omalizumab. J Asthma 45:115–116, 2008.
107. Lilly CM, Churg A, Lazarovich M, et al: Asthma therapies and Churg-Strauss syndrome. J Allergy Clin Immunol 109:S1–S19, 2002.
108. Nathani N, Little MA, Kunst H, et al: Churg-Strauss syndrome and leukotriene antagonist use: A respiratory perspective. Thorax 63:883–888, 2008.
109. Hauser T, Mahr A, Metzler C, et al: The leukotriene receptor antagonist montelukast and the risk of Churg-Strauss syndrome: A case-crossover study. Thorax 63:677–682, 2008. Epub 2008;February 14.
110. Beasley R, Bibby S, Weatherall M: Leukotriene receptor antagonist therapy and Churg-Strauss syndrome: Culprit or innocent bystander? Thorax 63:847–849, 2008.
111. Harrold LR, Patterson MK, Andrade SE, et al: Asthma drug use and the development of Churg-Strauss syndrome (CSS). Pharmacoepidemiol Drug Saf 16:620–626, 2007.
112. Masi AT, Hunder GG, Lie JT, et al: The American College of Rheumatology 1990 criteria for the classification of Churg-Strauss syndrome (allergic granulomatosis and angiitis). Arthritis Rheum 33:1094–1100, 1990.
113. Yousem SA, Lombard CM: The eosinophilic variant of Wegener's granulomatosis. Hum Pathol 19:682–688, 1988.
114. Vidal E, Liozon F, Rogues AM, et al: Concurrent temporal arteritis and Churg-Strauss syndrome. J Rheumatol 19:1312–1314, 1992.
115. Lie JT: Limited forms of Churg-Strauss syndrome. Pathol Annu 28:199–220, 1993.
116. Kallenberg CGM: Churg-Strauss syndrome: Just one disease entity? Arthritis Rheum 52:2589–2593, 2005.
117. Wieczorek S, Hellmich B, Arning L, et al: Functionally relevant variations of the interleukin-10 gene associated with antineutrophil cytoplasmic antibody-negative Churg-Strauss syndrome, but not with Wegener's granulomatosis. Arthritis Rheum 58:1839–1848, 2008.
118. Guillevin L, Lhote F, Gayraud M, et al: Prognostic factors in polyarteritis nodosa and Churg-Strauss syndrome. A prospective study in 342 patients. Medicine (Baltimore) 75:17–28, 1996.
119. Abu-Shakra M, Smythe H, Lewtas J, et al: Outcome of polyarteritis nodosa and Churg-Strauss syndrome. Arthritis Rheum 37:1798–1803, 1994.
120. Langford CA: Treatment of polyarteritis nodosa, microscopic polyangiitis, and Churg-Strauss syndrome: Where do we stand? Arthritis Rheum 44:508–512, 2001.

121. Chow CC, Mac-Moune Lai F: Allergic granulomatosis and angiitis (Churg-Strauss syndrome): Response to "pulse" intravenous cyclophosphamide. Ann Rheum Dis 48:605–608, 1989.
122. Guillevin L, Lhote F, Jarrousse B, Fain O: Treatment of polyarteritis nodosa and Churg-Strauss syndrome. A meta-analysis of 3 prospective controlled trials including 182 patients over 12 years. Ann Med Interne (Paris) 143:405–416, 1992.
123. Gayraud M, Guillevin L, le Toumelin P, et al: Long-term followup of polyarteritis nodosa, microscopic polyangiitis, and Churg-Strauss syndrome: Analysis of four prospective trials including 278 patients. Arthritis Rheum 44:666–675, 2001.
124. Cohen P, Pagnoux C, Mahr A, et al: Churg-Strauss syndrome with poor-prognosis factors: A prospective multicenter trial comparing glucocorticoids and six or twelve cyclophosphamide pulses in forty-eight patients. Arthritis Rheum 57:686–693, 2007.
125. Cohen P, Pagnoux C, Mahr A, et al: Treatment of Churg-Strauss (CSS) syndrome without poor prognostic factor at baseline with corticosteroids (CS) alone. Preliminary results of a prospective multicenter trial. Arthritis Rheum 48:S209, 2003.
126. Tatsis E, Schnabel A, Gross WL: Interferon-alpha treatment of four patients with the Churg-Strauss syndrome. Ann Intern Med 129:370–374, 1998.
127. Roccatello D, Baldovino S, Alpa M, et al: Effects of anti-CD20 monoclonal antibody as a rescue treatment for ANCA-associated idiopathic systemic vasculitis with or without overt renal involvement. Clin Exp Rheumatol 26:S67–S71, 2008.
128. Pepper RJ, Fabre MA, Pavesio C, et al: Rituximab is effective in the treatment of refractory Churg-Strauss syndrome and is associated with diminished T-cell interleukin-5 production. Rheumatology (Oxford) 47:1104–1105, 2008.
129. Kaushik VV, Reddy HV, Bucknall RC: Successful use of rituximab in a patient with recalcitrant Churg-Strauss syndrome. Ann Rheum Dis 65:116–117, 2006.
130. Koukoulaki M, Smith KG, Jayne DR: Rituximab in Churg-Strauss syndrome. Ann Rheum Dis 65:557–559, 2006.
131. Pabst S, Tiyerili V, Grohe C: Apparent response to anti-IgE therapy in two patients with refractory "forme fruste" of Churg-Strauss syndrome. Thorax 63:747–748, 2008.
132. Giavina-Bianchi P, Giavina-Bianchi M, Agondi R, Kalil J: Three months' administration of anti-IgE to a patient with Churg-Strauss syndrome. J Allergy Clin Immunol 119:1279–1280, 2007.
133. Ribi C, Cohen P, Pagnoux C, et al: Treatment of Churg-Strauss syndrome without poor-prognosis factors: A multicenter, prospective, randomized, open-label study of seventy-two patients. Arthritis Rheum 58:586–594, 2008.
134. Bourgarit A, le Toumelin P, Pagnoux C, et al: Deaths occurring during the first year after treatment onset for polyarteritis nodosa, microscopic polyangiitis, and Churg-Strauss syndrome: A retrospective analysis of causes and factors predictive of mortality based on 595 patients. Medicine (Baltimore) 84:323–330, 2005.
135. Cottin V, Khouatra C, Dubost R, et al: Persistent airflow obstruction in asthma of patients with Churg-Strauss syndrome and long-term follow-up. Allergy 64:589–595, 2009.
136. Chusid MJ, Dale DC, West BC, Wolff SM: The hypereosinophilic syndrome: Analysis of fourteen cases with review of the literature. Medicine (Baltimore) 54:1–27, 1975.
137. Bain BJ: Eosinophilic leukaemias and the idiopathic hypereosinophilic syndrome. Br J Haematol 95:2–9, 1996.
138. Brito-Babapulle F: Clonal eosinophilic disorders and the hypereosinophilic syndrome. Blood Rev 11:129–145, 1997.
139. Oliver JW, Deol I, Morgan DL, Tonk VS: Chronic eosinophilic leukemia and hypereosinophilic syndromes. Proposal for classification, literature review, and report of a case with a unique chromosomal abnormality. Cancer Genet Cytogenet 107:111–117, 1998.
140. Schoffski P, Ganser A, Pascheberg U, et al: Complete haematological and cytogenetic response to interferon alpha-2a of a myeloproliferative disorder with eosinophilia associated with a unique t(4;7) aberration. Ann Hematol 79:95–98, 2000.
141. Chang HW, Leong KH, Koh DR, Lee SH: Clonality of isolated eosinophils in the hypereosinophilic syndrome. Blood 93:1651–1657, 1999.
142. Bigoni R, Cuneo A, Roberti MG, et al: Cytogenetic and molecular cytogenetic characterization of 6 new cases of idiopathic hypereosinophilic syndrome. Haematologica 85:486–491, 2000.
143. Roufosse F, Cogan E, Goldman M: The hypereosinophilic syndrome revisited. Annu Rev Med 54:169–184, 2003.
144. Cilloni D, Messa F, Martinelli G, et al: WT1 transcript amount discriminates secondary or reactive eosinophilia from idiopathic hypereosinophilic syndrome or chronic eosinophilic leukemia. Leukemia 21:1442–1450, 2007.
145. Simon HU, Plotz SG, Dummer R, Blaser K: Abnormal clones of T cells producing interleukin-5 in idiopathic eosinophilia. N Engl J Med 341:1112–1120, 1999.
146. Roufosse F, Schandene L, Sibille C, et al: Clonal Th2 lymphocytes in patients with the idiopathic hypereosinophilic syndrome. Br J Haematol 109:540–548, 2000.
147. Kakinuma T, Nakamura K, Wakugawa M, et al: Thymus and activation-regulated chemokine in atopic dermatitis: Serum thymus and activation-regulated chemokine level is closely related with disease activity. J Allergy Clin Immunol 107:535–541, 2001.
148. Cogan E, Schandené L, Crusiaux A, et al: Clonal proliferation of type 2 helper T cells in a man with the hypereosinophilic syndrome. N Engl J Med 330:535–538, 1994.
149. Cools J, DeAngelo DJ, Gotlib J, et al: A tyrosine kinase created by fusion of the PDGFRA and FIP1L1 genes as a therapeutic target of imatinib in idiopathic hypereosinophilic syndrome. N Engl J Med 348:1201–1214, 2003.
150. Griffin JH, Leung J, Bruner RJ, et al: Discovery of a fusion kinase in EOL-1 cells and idiopathic hypereosinophilic syndrome. Proc Natl Acad Sci U S A 100:7830–7835, 2003.
151. Yamada Y, Rothenberg ME, Lee AW, et al: The FIP1L1-PDGFRA fusion gene cooperates with IL-5 to induce murine hypereosinophilic syndrome (HES)/chronic eosinophilic leukemia (CEL) –like disease. Blood 107:4071–4079, 2006.
152. Hirshberg B, Kramer MR, Lotem M, et al: Chronic eosinophilic pneumonia associated with cutaneous T-cell lymphoma. Am J Hematol 60:143–147, 1999.
153. Weller PF, Bubley GJ: The idiopathic hypereosinophilic syndrome. Blood 83:2759–2779, 1994.
154. Fauci AS, Harley JB, Roberts WC, et al: The idiopathic hypereosinophilic syndrome: Clinical, pathophysiologic and therapeutic considerations. Ann Intern Med 97:78–92, 1982.
155. Spry CJF, Davies J, Tai PC, et al: Clinical features of fifteen patients with the hypereosinophilic syndrome. Q J Med 205:1–22, 1983.
156. Roberts WC, Ferrans VJ: Pathologic anatomy of the cardiomyopathies. Idiopathic dilated and hypertrophic types, infiltrative types, and endomyocardial disease with and without eosinophilia. Hum Pathol 6:287–342, 1975.
157. Lefebvre C, Bletry O, Degoulet P, et al: Facteurs pronostiques du syndrome hyperéosinophilique. Étude de 40 observations. Ann Med Interne (Paris) 140:253–257, 1989.
158. Ommen SR, Seward JB, Tajik AJ: Clinical and echocardiographic features of hypereosinophilic syndromes. Am J Cardiol 86:110–113, 2001.
159. Kazmierowski JA, Chusid MJ, Parrillo JE, et al: Dermatologic manifestations of the hypereosinophilic syndrome. Arch Dermatol 114:531–535, 1978.
160. Kang EY, Shim JJ, Kim JS, Kim KI: Pulmonary involvement of idiopathic hypereosinophilic syndrome: CT findings in five patients. J Comput Assist Tomogr 21:612–615, 1997.
161. Cordier JF, Faure M, Hermier C, Brune J: Pleural effusions in an overlap syndrome of idiopathic hypereosinophilic syndrome and erythema elevatum diutinum. Eur Respir J 3:115–118, 1990.
162. Dussopt C, Schandené L, Perrin-Fayolle M, Pacheco Y: Augmentation du taux d'interleukine 5 sérique au cours d'un syndrome hyperéosinophilique. Presse Med 26:166, 1997.
163. Klion AD, Noel P, Akin C, et al: Elevated serum tryptase levels identify a subset of patients with a myeloproliferative variant of idiopathic hypereosinophilic syndrome associated with tissue fibrosis, poor prognosis, and imatinib responsiveness. Blood 101:4660–4666, 2003.
164. Parrillo JE, Borer JS, Henry WL, et al: The cardiovascular manifestations of the hypereosinophilic syndrome. Prospective study of

26 patients, with review of the literature. Am J Med 67:572–582, 1979.
165. Rothenberg ME, Klion AD, Roufosse FE, et al: Treatment of patients with the hypereosinophilic syndrome with mepolizumab. N Engl J Med 358:1215–1228, 2008.
166. Butterfield JH, Gleich GJ: Interferon-α treatment of six patients with the idiopathic hypereosinophilic syndrome. Ann Intern Med 121:648–653, 1994.
167. Butterfield JH, Gleich GJ: Response of six patients with idiopathic hypereosinophilic syndrome to interferon alfa. J Allergy Clin Immunol 94:1318–1326, 1994.
168. Ceretelli S, Capochiani E, Petrini M: Interferon-α in the idiopathic hypereosinophilic syndrome: Consideration of five cases. Ann Hematol 77:161–164, 1998.
169. Yoon TY, Ahn GB, Chang SH: Complete remission of hypereosinophilic syndrome after interferon-alpha therapy: Report of a case and literature review. J Dermatol 27:110–115, 2000.
170. Coutant G, Bletry O, Prin L, et al: Traitement des syndromes hyperéosinophiliques à expression myéloproliférative par l'association hydroxyurée-interféron alpha. A propos de 7 observations. Ann Med Interne (Paris) 144:243–250, 1993.
171. Demiroglu H, Dundar S: Combination of interferon-alpha and hydroxyurea in the treatment of idiopathic hypereosinophilic syndrome. Br J Haematol 97:928–930, 1997.
172. Weingarten RJ: Tropical eosinophilia. Lancet 1:103–105, 1943.
173. Malavige GN: Chronic cough. . . .and tropical pulmonary eosinophilia. BMJ 326:1036–1037, 2003.
174. Ong RK, Doyle RL: Tropical pulmonary eosinophilia. Chest 113:1673–1679, 1998.
175. Bartoloni A, Dini F, Farese A, et al: Tropical pulmonary eosinophilia. Report of a case. Ann Med Interne (Paris) 148:321–322, 1997.
176. Jiva TM, Israel RH, Poe RH: Tropical pulmonary eosinophilia masquerading as acute bronchial asthma. Respiration 63:55–58, 1996.
177. Rohatgi PK, Smirniotopoulos TT: Tropical eosinophilia. Semin Respir Med 12:98–106, 1991.
178. Pinkston P, Vijayan VK, Nutman TB, et al: Acute tropical pulmonary eosinophilia. Characterization of the lower respiratory tract inflammation and its response to therapy. J Clin Invest 80:216–225, 1987.
179. O'Bryan L, Pinkston P, Kumaraswami V, et al: Localized eosinophil degranulation mediates disease in tropical pulmonary eosinophilia. Infect Immun 71:1337–1342, 2003.
180. Udwadia FE: Tropical eosinophilia—A correlation of clinical, histopathologic, and lung function studies. Dis Chest 52:531–538, 1967.
181. Poh SC: The course of lung function in treated tropical pulmonary eosinophilia. Thorax 29:710–712, 1974.
182. Cooray JH, Ismail MM: Re-examination of the diagnostic criteria of tropical pulmonary eosinophilia. Respir Med 93:655–659, 1999.
183. Gelpi AP, Mustafa A: Ascaris pneumonia. Am J Med 44:377–389, 1968.
184. Khuroo MS: Ascariasis. Gastroenterol Clin North Am 25:553–577, 1996.
185. Schantz PM, Glickman LT: Current concepts in parasitology. Toxocaral visceral larva migrans. N Engl J Med 298:436–439, 1978.
186. Beshear JR, Hendley JO: Severe pulmonary involvement in visceral larva migrans. Am J Dis Child 125:599–600, 1973.
187. Roig J, Romeu J, Riera C, et al: Acute eosinophilic pneumonia due to toxocariasis with bronchoalveolar lavage findings. Chest 102:294–296, 1992.
188. Bartelink AK, Kortbeek LM, Huidekoper HJ, et al: Acute respiratory failure due to toxocara infection. Lancet 342:1234, 1993.
189. Igra-Siegman Y, Kapila R, Sen P, et al:. Syndrome of hyperinfection with *Strongyloides stercoralis*. Rev Infect Dis 3:397–407, 1981.
190. Davidson RA: Infection due to *Strongyloides stercoralis* in patients with pulmonary disease. South Med J 85:28–31, 1992.
191. Jamil SA, Hilton E: The strongyloides hyperinfection syndrome. N Y State J Med 92:67–68, 1992.
192. Williams J, Nunley D, Dralle W, Berk S: Diagnosis of pulmonary strongylodiasis by bronchoalveolar lavage. Chest 94:643–644, 1988.
193. Harris RA, Musher DM, Fainstein V, et al: Disseminated strongyloidiasis. Diagnosis made by sputum examination. JAMA 244:65–66, 1980.
194. Schwartz E, Rozenman J, Perelman M: Pulmonary manifestations of early schistosome infection among nonimmune travelers. Am J Med 109:718–722, 2000.
195. de Cleva R, Herman P, Pugliese V, et al: Prevalence of pulmonary hypertension in patients with hepatosplenic Mansonic schistosomiasis—Prospective study. Hepatogastroenterology 50:2028–2030, 2003.
196. Davidson BL, El-Kassimi F, Uz-Zaman A, Pillai K: The "lung shift" in treated schistosomiasis. Bronchoalveolar lavage evidence of eosinophilic pneumonia. Chest 89:455–457, 1986.
197. Geller DE, Kaplowitz H, Light MJ, Colin AA: Allergic bronchopulmonary aspergillosis in cystic fibrosis: Reported prevalence, regional distribution, and patient characteristics. Chest 116:639–646, 1999.
198. Mastella G, Rainisio M, Harms HK, et al: Allergic bronchopulmonary aspergillosis in cystic fibrosis. A European epidemiological study. Eur Respir J 16:464–471, 2000.
199. Shah A, Khan ZU, Chaturvedi S, et al: Concomitant allergic *Aspergillus* sinusitis and allergic bronchopulmonary aspergillosis associated with familial occurrence of allergic bronchopulmonary aspergillosis. Ann Allergy 64:507–512, 1990.
200. Shah A, Bhagat R, Panchal N, et al: Allergic bronchopulmonary aspergillosis with middle lobe syndrome and allergic *Aspergillus* sinusitis. Eur Respir J 6:917–918, 1993.
201. Ponikau JU, Sherris DA, Kern EB, et al: The diagnosis and incidence of allergic fungal sinusitis. Mayo Clin Proc 74:877–884, 1999.
202. Torres C, Ro JY, el-Naggar AK, et al: Allergic fungal sinusitis: A clinicopathologic study of 16 cases. Hum Pathol 27:793–799, 1996.
203. Schubert MS, Goetz DW: Evaluation and treatment of allergic fungal sinusitis. I. Demographics and diagnosis. J Allergy Clin Immunol 102:387–394, 1998.
204. Venarske DL, deShazo RD: Sinobronchial allergic mycosis: The SAM syndrome. Chest 121:1670–1676, 2002.
205. Leonard CT, Berry GJ, Ruoss SJ: Nasal-pulmonary relations in allergic fungal sinusitis and allergic bronchopulmonary aspergillosis. Clin Rev Allergy Immunol 21:5–15, 2001.
206. Mehta SK, Sandhu RS: Immunological significance of *Aspergillus fumigatus* in cane-sugar mills. Arch Environ Health 38:41–46, 1983.
207. Marchand E, Verellen-Dumoulin C, Mairesse M, et al: Frequency of cystic fibrosis transmembrane conductance regulator gene mutations and 5T allele in patients with allergic bronchopulmonary aspergillosis. Chest 119:762–767, 2001.
208. Knutsen AP, Kariuki B, Consolino JD, Warrier MR:. IL-4 alpha chain receptor (IL-4Ralpha) polymorphisms in allergic bronchopulmonary sspergillosis. Clin Mol Allergy 4:3, 2006.
209. Chauhan B, Santiago L, Kirschmann DA, et al: The association of HLA-DR alleles and T cell activation with allergic bronchopulmonary aspergillosis. J Immunol 159:4072–4076, 1997.
210. Mussaffi H, Rivlin J, Shalit I, et al: Nontuberculous mycobacteria in cystic fibrosis associated with allergic bronchopulmonary aspergillosis and steroid therapy. Eur Respir J 25:324–328, 2005.
211. Kauffman HF, Tomee JF, van der Werf TS, et al: Review of fungus-induced asthmatic reactions. Am J Respir Crit Care Med 151:2109–2116, 1995.
212. Patterson R, Grammer LC: Immunopathogenesis of allergic bronchopulmonary aspergillosis. *In* Patterson R, Greenberger PA, Roberts ML (eds): Allergic Bronchopulmonary Aspergillosis. Providence, RI: OceanSide, 1995, pp 35–38.
213. Rosenberg M, Patterson R, Mintzer R, et al: Clinical and immunologic criteria for the diagnosis of allergic bronchopulmonary aspergillosis. Ann Intern Med 86:405–414, 1977.
214. Patterson R, Greenberger PA, Roberts M: The diagnosis of allergic bronchopulmonary aspergillosis. *In* Patterson R, Greenberger PA, Roberts ML (eds): Allergic Bronchopulmonary Aspergillosis. Providence, RI: OceanSide, 1995, pp 1–3.

215. Greenberger PA: Allergic bronchopulmonary aspergillosis. J Allergy Clin Immunol 110:685–692, 2002.
216. Crameri R, Weichel M, Fluckiger S, et al: Fungal allergies: A yet unsolved problem. Chem Immunol Allergy 91:121–133, 2006.
217. Bosken C, Myers J, Greenberger P, Katzenstein AL: Pathologic features of allergic bronchopulmonary aspergillosis. Am J Surg Pathol 12:216–222, 1988.
218. Panchal N, Bhagat R, Pant C, Shah A: Allergic bronchopulmonary aspergillosis: The spectrum of computed tomography appearances. Respir Med 91:213–219, 1997.
219. Angus RM, Davies ML, Cowan MD, et al: Computed tomographic scanning of the lung in patients with allergic bronchopulmonary aspergillosis and in asthmatic patients with a positive skin test to *Aspergillus fumigatus*. Thorax 49:586–589, 1994.
220. Ward S, Heyneman L, Lee MJ, et al: Accuracy of CT in the diagnosis of allergic bronchopulmonary aspergillosis in asthmatic patients. AJR Am J Roentgenol 173:937–942, 1999.
221. McCarthy DS, Simon G, Hargreave FE: The radiological appearances in allergic broncho-pulmonary aspergillosis. Clin Radiol 21:366–375, 1970.
222. Latzin P, Hartl D, Regamey N, et al: Comparison of serum markers for allergic bronchopulmonary aspergillosis in cystic fibrosis. Eur Respir J 31:36–42, 2008.
223. Hartl D, Latzin P, Zissel G, et al: Chemokines indicate allergic bronchopulmonary aspergillosis in patients with cystic fibrosis. Am J Respir Crit Care Med 173:1370–1376, 2006.
224. Mintzer RA, Rogers LF, Kruglik GD, et al: The spectrum of radiologic findings in ABPA. Radiology 127:301–307, 1978.
225. Patterson R, Greenberger PA, Lee TM, et al: Prolonged evaluation of patients with corticosteroid-dependent asthma stage of allergic bronchopulmonary aspergillosis. J Allergy Clin Immunol 80:663–668, 1987.
226. Salez F, Brichet A, Desurmont S, et al: Effects of itraconazole therapy in allergic bronchopulmonary aspergillosis. Chest 116:1665–1668, 1999.
227. Wark P: Pathogenesis of allergic bronchopulmonary aspergillosis and an evidence-based review of azoles in treatment. Respir Med 98:915–923, 2004.
228. Stevens DA, Schwartz HJ, Lee JY, et al: A randomized trial of itraconazole in allergic bronchopulmonary aspergillosis. N Engl J Med 342:756–762, 2000.
229. Wark PA, Hensley MJ, Saltos N, et al: Anti-inflammatory effect of itraconazole in stable allergic bronchopulmonary aspergillosis: a randomized controlled trial. J Allergy Clin Immunol 111:952–957, 2003.
230. Parmar JS, Howell T, Kelly J, Bilton D: Profound adrenal suppression secondary to treatment with low dose inhaled steroids and itraconazole in allergic bronchopulmonary aspergillosis in cystic fibrosis. Thorax 57:749–750, 2002.
231. Skov M, Main KM, Sillesen IB, et al:. Iatrogenic adrenal insufficiency as a side-effect of combined treatment of itraconazole and budesonide. Eur Respir J 20:127–133, 2002.
232. van der Ent CK, Hoekstra H, Rijkers GT: Successful treatment of allergic bronchopulmonary aspergillosis with recombinant anti-IgE antibody. Thorax 62:276–277, 2007.
233. Zirbes JM, Milla CE: Steroid-sparing effect of omalizumab for allergic bronchopulmonary aspergillosis and cystic fibrosis. Pediatr Pulmonol 43:607–610, 2008.
234. Kanu A, Patel K: Treatment of allergic bronchopulmonary aspergillosis (ABPA) in CF with anti-IgE antibody (omalizumab). Pediatr Pulmonol 43:1249–1251, 2008.
235. Mulliez P, Croxo C, Roy-Saint GF, Darras A: Aspergillose bronchopulmonaire allergique traitée par voriconazole. Rev Mal Respir 23:93–94, 2006.
236. Erwin GE, Fitzgerald JE: Case report: Allergic bronchopulmonary aspergillosis and allergic fungal sinusitis successfully treated with voriconazole. J Asthma 44:891–895, 2007.
237. Liebow AA: Pulmonary angiitis and granulomatosis. Am Rev Respir Dis 108:1–18, 1973.
238. Katzenstein AL, Askin FB (eds): Katzenstein and Askin's Surgical Pathology of Non-neoplastic Lung Disease (3rd ed). Philadelphia: WB Saunders, 1997.
239. Katzenstein AL, Liebow AA, Friedmann PJ: Bronchocentric granulomatosis, mucoid impaction and hypersensitivity reaction to fungi. Am Rev Respir Dis 111:497–537, 1975.
240. Robinson RG, Wehnut WD, Tsou E, et al: Bronchocentric granulomatosis. Roentgenographic manifestations. Am Rev Respir Dis 125:751–756, 1982.
241. Ward S, Heyneman LE, Flint JD, et al: Bronchocentric granulomatosis: Computed tomographic findings in five patients. Clin Radiol 55:296–300, 2000.
242. Rich AR: The role of hypersensitivity in periarteritis nodosa as indicated by seven cases developing during serum sickness and sulfonamide therapy. Bull Johns Hopkins Hosp 71:123–141, 1942.
243. Hertzman PA, Clauw DJ, Kaufman LD, et al: The eosinophiliamyalgia syndrome: Status of 205 patients and results of treatment 2 years after onset. Ann Intern Med 122:851–855, 1995.
244. Strumpf IJ, Drucker RD, Anders KH, et al: Acute eosinophilic pulmonary disease associated with the ingestion of L-tryptophan containing products. Chest 99:8–13, 1991.
245. Tazelaar HD, Myers JL, Drage CW, et al: Pulmonary disease associated with L-tryptophan–induced eosinophilic myalgia syndrome. Clinical and pathologic features. Chest 97:1032–1036, 1990.
246. Alonso-Ruiz A, Calabozo M, Perez-Ruiz F, Mancebo L: Toxic oil syndrome. A long-term follow-up of a cohort of 332 patients. Medicine (Baltimore) 72:285–295, 1993.
247. Cottin V, Frognier R, Monnot H, et al: Chronic eosinophilic pneumonia after radiation therapy for breast cancer. Eur Respir J 23:9–13, 2004.
248. Solomon J, Schwarz M: Drug-, toxin-, and radiation therapy–induced eosinophilic pneumonia. Semin Respir Crit Care Med 27:192–197, 2006.
249. Crestani B, Valeyre D, Roden S, et al: Bronchiolitis obliterans organizing pneumonia syndrome primed by radiation therapy to the breast. Am J Respir Crit Care Med 158:1929–1935, 1998.
250. Miranowski AC, Ditto AM: A 59-year-old woman with fever, cough, and eosinophilia. Ann Allergy Asthma Immunol 96:483–488, 2006.
251. Cottin V, Cordier JF: Eosinophilic pneumonia in a patient with breast cancer: Idiopathic or not? Ann Allergy Asthma Immunol 97:557–558, 2006.
252. Cordier JF: Cryptogenic organising pneumonia. Eur Respir J 28:422–446, 2006.
253. Bousquet J, Chanez P, Vignola AM, et al: Eosinophil inflammation in asthma. Am J Respir Crit Care Med 150:S33–S38, 1994.
254. Bousquet J, Chanez P, Lacoste JY, et al: Eosinophilic inflammation in asthma. N Engl J Med 323:1033–1039, 1990.
255. Van Vyve T, Chanez P, Lacoste JY, et al: Comparison between bronchial and alveolar samples of bronchoalveolar lavage fluid in asthma. Chest 102:356–361, 1992.
256. Gibson PG, Fujimura M, Niimi A:. Eosinophilic bronchitis: Clinical manifestations and implications for treatment. Thorax 57:178–182, 2002.
257. Gibson PG, Dolovich J, Denburg J, et al: Chronic cough: eosinophilic bronchitis without asthma. Lancet 1:1346–1348, 1989.
258. Niimi A, Amitani R, Suzuki K, et al: Eosinophilic inflammation in cough variant asthma. Eur Respir J 11:1064–1069, 1998.
259. Chung KF, Hew M, Score J, et al: Cough and hypereosinophilia due to FIP1L1-PDGFRA fusion gene with thyrosine kinase activity. Eur Respir J 27:230–232, 2006.
260. Brightling CE: Chronic cough due to nonasthmatic eosinophilic bronchitis: ACCP evidence-based clinical practice guidelines. Chest 129:116S–121S, 2006.
261. Park SW, Lee YM, Jang AS, et al: Development of chronic airway obstruction in patients with eosinophilic bronchitis. A prospective follow-up study. Chest 125:1998–2004, 2004.
262. Brightling CE, Woltmann G, Wardlaw AJ, Pavord ID: Development of irreversible airflow obstruction in a patient with eosinophilic bronchitis without asthma. Eur Respir J 14:1228–1230, 1999.
263. Turner-Warwick ME, Haslam PL: The value of serial bronchoalveolar lavages in assessing the clinical progress of patients with cryptogenic fibrosing alveolitis. Am Rev Respir Dis 135:26–34, 1987.

264. Haslam PL, Turton CWG, Lukoszek A, et al: Bronchoalveolar lavage fluid cell counts in cryptogenic fibrosing alveolitis and their relation to therapy. Thorax 35:328–339, 1980.
265. Rudd RM, Haslam PL, Turner-Warwick M: Cryptogenic fibrosing alveolitis: Relationships of pulmonary physiology and bronchoalveolar lavage to response to treatment and prognosis. Am Rev Respir Dis 124:1–8, 1981.
266. Yousem SA: Eosinophilic pneumonia–like areas in idiopathic usual interstitial pneumonia. Mod Pathol 13:1280–1284, 2000.
267. Travis WD, Matsui K, Moss J, Ferrans VJ: Idiopathic nonspecific interstitial pneumonia: Prognostic significance of cellular and fibrosing patterns. Survival comparison with usual interstitial pneumonia and desquamative interstitial penumonia. Am J Surg Pathol 24:19–33, 2000.
268. Yousem SA: Graft eosinophilia in lung transplantation. Hum Pathol 23:1172–1177, 1992.
269. Renston JP, Goldman ES, Hsu RM, Tomashefski JF Jr: Peripheral blood eosinophilia in association with sarcoidosis. Mayo Clin Proc 75:586–590, 2000.
270. Gerhardt SG, Tuder RM, Girgis RE, et al: Pulmonary eosinophilia following lung transplantation for sarcoidosis in two patients. Chest 123:629–632, 2003.
271. Shijubo N, Fujishima T, Morita S, et al: Idiopathic chronic eosinophilic pneumonia associated with noncaseating epithelioid granulomas. Eur Respir J 8:327–330, 1995.
272. Asthma and eosinophilia in a 66-year-old woman. Am J Med 87:439–444, 1989.
273. Horie S, Okubo Y, Suzuki J, Isobe M: An emaciated man with eosinophilic pneumonia. Lancet 348:166, 1996.
274. Cordier JF: Eosinophilic pneumonias. *In* Schwarz MI, King Jr TE (eds): Interstitial Lung Disease (4th ed). London: BC Dekker, 2003, pp 657–700.
275. Parry SD, Barbatzas C, Peel ET, Barton JR: Sulphasalazine and lung toxicity. Eur Respir J 19:756–764, 2002.
276. Terzano C, Petroianni A: Clarithromycin and pulmonary infiltration with eosinophilia. BMJ 326:1377–1378, 2003.
277. Trojan A, Meier R, Licht A, Taverna C: Eosinophilic pneumonia after administration of fludarabine for the treatment of non-Hodgkin's lymphoma. Ann Hematol 81:535–537, 2002.
278. Gagnadoux F, Roiron C, Carrie E, et al: Eosinophilic lung disease under chemotherapy with oxaliplatin for colorectal cancer. Am J Clin Oncol 25:388–390, 2002.

CHAPTER 62

LYMPHANGIOLEIOMYOMATOSIS

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INTRODUCTION

Lymphangioleiomyomatosis (LAM) is a rare, neoplastic, systemic disease characterized by a genetic association with the neurocutaneous syndrome, tuberous sclerosis complex (TSC). There is a marked female gender predominance. It is characterized by cystic destruction of the lung, progressive dyspnea on exertion, recurrent pneumothorax, abdominal tumors, and chylous fluid accumulation in the chest and abdomen.[1,2]

LAM was first reported in a patient with TSC who presented with bilateral spontaneous pneumothorax in 1918[3] and in a patient without TSC in 1937.[4] In the 1950s through the late 1960s, there were solitary case reports or small case series with a varied and confusing pathologic nomenclature. Cornog and Enterline,[5] for example, described 6 cases of "lymphangiomyoma" and reviewed 14 cases in the literature with similar pathology that had been termed "lymphangioma," "lymphangiomyoma," "lymphangiopericytoma," "leiomyomatosis," "lymphangiomatosis malformation," and "intrathoracic angiomatous hyperplasia." Since the late 1970s, however, larger case studies have better defined the natural history, pathologic classification, and clinical presentation of LAM, including those of Silverstein and coworkers,[6] Corrin and colleagues,[7] Taylor and associates,[8] Kitaichi and coworkers,[9] Oh and colleagues,[10] Chu and associates,[11] Taveira-DaSilva and coworkers,[12] Hayashida and colleagues,[13] and Urban and associates.[14] Most significantly, recent synergistic interactions between pulmonary investigators, tuberous sclerosis geneticists, *Drosophila* biologists, and patient advocacy groups have resulted in truly significant progress in our understanding of the molecular and cellular basis of LAM.[15]

EPIDEMIOLOGY

LAM almost exclusively affects young women, primarily in their reproductive years. It occurs in the setting of tuberous sclerosis complex (TSC-LAM) and also in a sporadic form in women who do not have TSC (sporadic LAM [S-LAM]) (Table 62-1).[1,2]

TSC-LAM is typically accompanied by the multiple system involvement and varied clinical presentations that are associated with TSC. TSC is an autosomal dominant genetic disorder associated with development of hamartomas and dysplastic lesions in several organs,

TABLE 62-1. Comparison of TSC-LAM and S-LAM

	TSC-LAM	S-LAM
Estimated no. patients on earth	250,000	6000–15,000
Reported in males	+	+
Reported in children	+	+
Ascertainment	Screening, dyspnea, pneumothorax	Dyspnea, pneumothorax, chylothorax, incidentally on CT
Germline TSC mutations	+	–
Inheritable	+	–
TSC1/TSC2 mutations reported	33%/66%	0%/100%
Renal angiomyolipomas	93% Bilateral 81% Multiple 60%	33% Bilateral 19% Multiple 6%
Hepatic angiomyolipomas	33%	2%
Lymphangiomyomas	9%	29%
MMPH	+ (~12%)	Very rare (~1%)
CNS/skin/eye/cardiac lesions	+	–
Retroperitoneal, thoracic adenopathy	Rare	+
Dyspnea	Less common	More common
Chylothorax	Uncommon	33%
Pneumothorax	Less common	66%
Respiratory failure	Less common	More common

CNS, central nervous system; CT, computed tomography; LAM, lymphangioleiomyomatosis; MMPH, multifocal micronodular pneumocyte hyperplasia; S-LAM, sporadic lymphangioleiomyomatosis; TSC, tuberous sclerosis complex.

including cortical tubers, giant cell astrocytomas and subependymal nodules in the central nervous system; angiofibromas, Shagreen's patches, and ash leaf macules of the skin; and angiomyolipomas and cysts of the kidney.[16]

In S-LAM, by contrast, manifestations that accompany the pulmonary cystic changes include only renal and extrarenal angiomyolipomas and smooth muscle infiltration and obstruction of the lymphatic system. Clinical presentations consistent with LAM have also been described in a few males with TSC,[17] including three biopsy documented cases, two with TSC,[18,19] and one without evidence of TSC.[20]

Careful epidemiologic analyses of the ethnic and racial distribution of LAM have not been performed. Although the biases introduced by the rarity of the illness, the protean presentation, and the disproportionate reporting of LAM patients in large series from the United States, Europe, and Asia[9–12,14] might suggest a predilection of the disease for whites and Asians, as with TSC, it is likely that all races are affected and that countries and populations with the greatest access to health care resources are overrepresented in these studies.

The prevalence of LAM estimated from various international registries and surveys is approximately 2.5 cases per million in the United States (846 U.S. LAM patients are registered with the LAM Foundation [Sally Lamb, personal communication, The LAM Foundation]), 1.2 to 2.3 cases per million in Japan,[13] 0.9 cases per million in the United Kingdom,[21] and 1.3 cases per million in France.[14] LAM often presents in a protean manner, however, and it is likely that LAM is severalfold more common than these numbers suggest. Indeed, the calculated prevalence of TSC-LAM alone is significantly greater than 1 to 3 cases per million. Considering that the incidence of TSC is about 1/6000 births and that TSC occurs equally in both genders,[22] the estimated worldwide prevalence of TSC is approximately 1.2 to -1.5 million people, with 0.6 to 0.75 million of them being women. Cystic pulmonary changes are found in roughly one third of women with TSC,[23–25] suggesting a global TSC-LAM prevalence of approximately 250,000 individuals, or about 40 TSC-LAM cases per million people.

Although screening of TSC populations identifies a subset of patients who have a range of cystic change in the lung from very mild to severe, it has been estimated that pulmonary manifestations reach clinical significance in only about 5% to 10% of patients with TSC-LAM.[26] TSC-LAM is certainly underrepresented in large databases: TSC-LAM patients made up only about 10% to 15% of the 243 patients who enrolled in the National Heart, Lung, and Blood Institute (NHLBI) Registry and 9.5% of patients who are listed in the LAM Foundation database (Sally Lamb, personal communication, The LAM Foundation). Although TSC-LAM is predicted to be 10-fold more common than S-LAM, most (~90%) LAM patients who seek medical attention with pulmonary specialists have S-LAM. This observation is consistent with the notion that TSC-LAM identified through screening is often a milder disease than S-LAM, which reaches attention through progressive dyspnea or pneumothorax/chylothorax, and/or that other TSC comorbidities overshadow the pulmonary manifestations of TSC-LAM and prevent TSC-afflicted patients from seeking medical care for their lung disease.

GENETIC AND MOLECULAR BASIS OF TUBEROUS SCLEROSIS COMPLEX AND LYMPHANGIOLEIOMYOMATOSIS

Inheritance

Approximately two thirds of new TSC cases arise from de novo mutations, which occur during embryogenesis. Familial TSC, which results from inheritance of germline mutations, accounts for one third of new cases.[27] There have been several reports of familial TSC-LAM,[23,28] but mother-daughter transmission of S-LAM has never been reported.

Molecular Pathogenesis

Our understanding of the genetic and molecular basis of TSC and LAM has increased substantially since the late 1990s. The most significant findings have included that LAM is a neoplastic and metastatic process, that LAM is caused by mutations in TSC genes,[29] and that dysregulation of the Akt signaling pathway plays a central role in TSC and LAM cell growth, motility, and survival.[30,31]

Tumor Suppressor Proteins Control Cell Growth

Clinicians have long recognized that the lung disease that occurs in women with TSC is pathologically indistinguishable from that which occurs in women with S-LAM.[5,32] However, the demonstration that S-LAM and TSC-LAM are genetically linked was reported only relatively recently.[33] The lag period in our understanding was due, in part, to the failure to appreciate that a nonfamilial disease could share a common genetic basis with an inheritable disease. There are several precedents for this phenomenon among the class of diseases known as tumor suppressor syndromes (including neurofibromatosis and von Hippel–Lindau syndrome), of which TSC is a member.

Tumor suppressor proteins regulate orderly cell growth and differentiation by sensing the surrounding environment, transmitting signals to the nucleus, and directly affecting transcription, translation, survival, or cell division. In the classic "two-hit" paradigm,[34] a mutant copy of a tumor suppressor gene is inherited from one parent and a tumor or dysplastic lesion develops when the second "good" parental copy of the tumor suppressor gene is inactivated through a random, somatic mutation. This first (inherited) hit, often a point mutation or a small insertion or deletion, results in heterozygosity for the wild-type allele. The second mutational event is usually a large deletion, resulting in the loss of a chromosomal segment. A polymerase chain reaction (PCR) technique can be used to detect the "loss of heterozygosity (LOH)" for the wild-type allele caused by the deletion. When both copies of a tumor suppressor gene contain critical mutations, the protein produced by the gene becomes defective or deficient, protein function is lost, and cell growth, survival, and synthetic function become dysregulated.

The Tuberous Sclerosis Complex Proteins Regulate Signaling through the Akt Pathway

TSC is caused by inactivating mutations in either of the two known TSC loci, TSC1 on chromosome 9q34[35] and TSC2 on chromosome 16p13.[36] The proteins encoded by TSC1 and TSC2 are hamartin and tuberin, respectively. Hamartin has no informative homologies with other proteins in the National Center for Biotechnology Information (NCBI) database, whereas tuberin has a domain with GAP (GTPase-activating protein) homology.[37]

Until very recently, very little was known about the function of TSC proteins other than that they modulate cell growth. In 1999, it was reported that the enlarged eye cells phenotype of the mutant fruit fly, *Gigas*, was the result of genetic inactivation of the fly homologue for tuberin.[38] The loss of tuberin results in a defect in cell cycle control, which causes cells to repeat S phase without entering M phase. Several laboratories subsequently reported that tuberin and hamartin regulate signaling through the PI3K/PKB(Akt)/S6K pathway, which controls cellular size and proliferation.[39–41]

Our understanding of the function and positioning of the TSC proteins in the Akt/S6K pathway has been a rapidly evolving process, and the available data to date are modeled in Figure 62-1. Tuberin and hamartin associate into a complex that functions as a master regulator for the kinase, mTOR, or mammalian target of rapamycin (sirolimus), through an intermediate G protein called Rheb.[42,43] The intact tuberin/hamartin complex acts as a GAP for Rheb, and maintains Rheb in an inactivated, nonphosphorylated state (Rheb-GDP). Phosphorylation of tuberin by Akt inactivates the GAP activity of the tuberin/hamartin complex, increases the abundance of Rheb-GTP, drives association of mTOR with raptor (and mLST8 and PRAS40, not shown) to form the mTORC1 complex, and results in phosphorylation and activation of downstream kinases mTOR, S6K, and the initiation factor 4E-binding protein (4E-BP1). The association of mTOR with raptor (and mSIN1 and mLST8, not shown) to form mTORC2 results in activation of ROCK and rho kinase, cytoskeletal rearrangement, and cell movement through a separate pathway. Thus, genetic mutations that result in the absence or dysfunction of tuberin or hamartin, as occur in patients with tuberous sclerosis and LAM, ultimately cause constitutive activation of S6 and eIF4E, two proteins that are intimately involved in the regulation of protein translation, as well as Rho kinase, which regulates intracellular trafficking, cell adhesion, and cell movement. The end result is the inappropriate stimulation of protein synthesis, cell motility, and cell growth.[31] Multiple mTOR effectors and mTOR itself were found to be highly phosphorylated in tumors of rats,[44] mice,[45] and humans[46] with mutations in TSC genes. Sirolimus, a microbial product that binds the intracellular receptor FKBP12 (an FK-506–binding protein) to inhibit mTOR activity, extinguished phosphoS6 staining and caused widespread apoptosis in the rat renal tumors.[44]

Tuberous Sclerosis Complex Mutations Are Found in the Lung and Kidney Lesions of Patients with Sporadic Lymphangioleiomyomatosis

Tuberous sclerosis patients have germline mutations in TSC genes, but S-LAM patients do not.[47] Smolarek and coworkers[48] first implicated TSC genes in the pathogenesis of S-LAM by finding that LOH for TSC2 was present in the renal angiomyolipomas (AMLs) and lymph nodes from S-LAM patients. Proof that the loss of tuberin function was responsible for lung disease in LAM was provided by Carsillo and colleagues, who demonstrated the

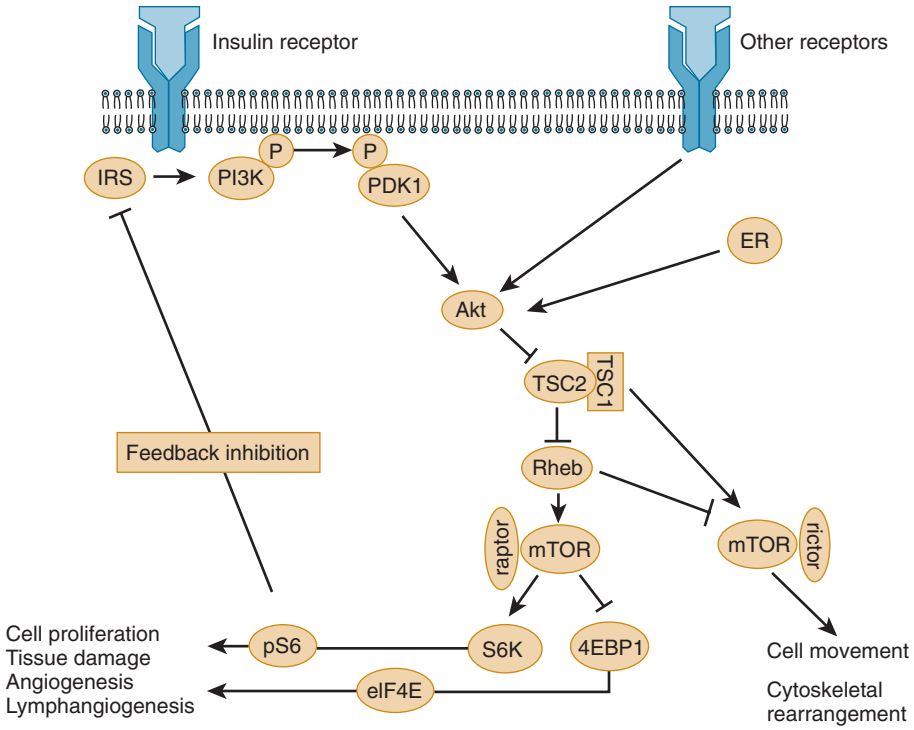

FIGURE 62-1 ■ Tuberous sclerosis proteins regulate signaling through the Akt growth and protein translation pathway. The binding of a ligand to a growth factor receptor (such as the insulin receptor) activates phosphatidylinositol-3-kinase (PI3K) followed by Akt. Activated pAkt phosphorylates tuberous sclerosis complex-2 (TSC2), which blocks its GTPase-activating protein (GAP) activity. When not phosphorylated, TSC2 complexed with TSC1 functions as a GAP for Rheb, maintaining Rheb in an inactivated Rheb-GDP state. Activated Rheb (Rheb-guanosine triphosphate [GTP]) is therefore abundant when TSC1 or TSC2 is missing or when TSC2 is phosphorylated. Rheb GTP activates mTOR, in a manner that is potentiated by the availability of amino acids, phosphatidic acid, and adenosine triphosphate, and blocked by the absence of these substrates or the presence of sirolimus. Activated mTOR complexed with raptor phosphorylates downstream targets S6K and 4E-BP1. pS6K phosphorylates S6 and 4E-BP1 releases eIF4E, which together activate the cellular translational machinery and promote cell growth. S6 also feeds back to inhibit upstream signaling, which restrains cell growth and "malignant" cellular behavior. Activated mTOR complexed with rictor signals through a divergent pathway to control cytoskeletal dynamics and cell movement through Rho kinases. (Adapted from Kwiatkowski DJ: Rhebbing up mTOR: New insights on TSC1 and TSC2, and the pathogenesis of tuberous sclerosis. Cancer Biol Ther 2:471–476, 2003.)

presence of missense and protein truncating TSC2 mutations associated with LOH in the abnormal lung and kidney tissue of patients with S-LAM.[33] Samples taken from the normal regions of lung and the kidney in those patients did not exhibit TSC mutations.[47] These findings were subsequently confirmed in 21 patients by Hino and associates,[49] and all S-LAM mutations described to date have been in the TSC2 locus.[33,49,50] These data indicate that S-LAM is caused by somatic mutations in both TSC2 alleles that occur after conception and result in defects or deficiency in tuberin. TSC1 and TSC2 mutations have been described in TSC-LAM,[23,51] and future studies may reveal TSC1 mutations to be causative in S-LAM as well.

Genetic Evidence Suggests That Lymphangioleiomyomatosis is a Metastatic Neoplasm

Cornog and Enterline[5] were the first to suggest that despite their benign appearance, cells that make up the LAM lesion are a clonal, neoplastic proliferation of smooth muscle cells. The demonstration of LOH in the lung, kidney, and lymph node lesions in LAM patients was the first indication that Cornog and Enterline's suspicions regarding neoplasia and clonality were correct.[48] Carsillo and colleagues[33] further demonstrated that the mutations present in the cells of the kidney tumor and lung lesion of a given individual with S-LAM were identical, suggesting that they arise from a common precursor.

A model for LAM was proposed in which the lung infiltration occurs as a consequence of benign metastasis of LAM cells from a remote and as yet unidentified source, such as the bone marrow, the lymphatic system,[52] the uterus,[53] or AMLs.[54] Reports of recurrence of LAM in the donor lung of LAM patients who had undergone lung transplant are also consistent with this metastatic theory[55-58]; in two cases, the recipient origin of lung metastases were proved by genetic and molecular techniques.[58,59] These data contradicted earlier reports that the recurrent lesions were derived from donor cells,[55,56] but in retrospect, the initial studies were limited by the spatial resolution that can be achieved with the immunohistochemical techniques used to colocalize cellular markers. Cells containing LOH for TSC genes have been isolated from the blood of LAM patients,[60] consistent with dissemination through the systemic circulation.

Other rare diseases that result from metastases of benign smooth muscle cells in women include leiomyomatosis peritonealis disseminate,[61] intravenous leiomyomatosis,[62] and benign metastasizing leiomyomatosis.[63] The metastatic theory of LAM suggests possible novel approaches for treatment based on preemptive removal of the source, once its identity is known.[29]

Role of Lymphangiogenesis and Lymphatic Spread in Dissemination of Lymphangioleiomatosis

Approximately 30% of LAM patients have axial abdominal or thoracic lymphadenopathy.[64] In some cases, LAM is restricted to the retroperitoneum, abdomen, or pelvis and is associated with normal lung parenchyma or only a very few lung cysts, consistent with regional spread from a subdiaphragmatic source.[65] Clusters of cells in the chylous pleural fluid of patients with LAM were first described by Valensi[66] in 1973. Later, Itami and coworkers[67] demonstrated that the clusters originated in the dilated lymphatic system and were composed of alpha smooth muscle actin–positive spindle cells enveloped by a single layer of endothelial cells. They suggested that LAM cell clusters could be used diagnostically to obviate the need for biopsy in patients with chylous manifestations of LAM. Data from Japan provide additional evidence that a likely source and mechanism of spread of LAM may be through the lymphatic circulation.[52,68,69] In a small autopsy series, Kumasaka and colleagues[52,70] described the presence of LAM cell clusters enveloped by lymphatic endothelial cells budding from the walls of lymphatic vessels.

Induction of lymphangiogenesis appears to play an important role in this process, based on abundant expression of lymphatic endothelial markers such as podoplanin (D2-40), LYVE-1, vascular endothelial growth factor receptor (VEGFR)-3, VEGF-C, and VEGF-D.[70] Two laboratories have recently reported that VEGF-D is elevated over three- to eightfold in the serum of patients with LAM, a finding that may prove to be useful for distinguishing LAM from other cystic lung diseases and for following response to therapy.[71,72] LAM cell clusters were also found in the lymphatic lumen, in regions between axial lymph nodes (retroperitoneal, mediastinal, and left venous angle) that were infiltrated with LAM cells, and in chylous fluids examined from patients with chylous ascites and chylothorax. They speculated that LAM cell clusters enter the venous circulation at the insertion of the thoracic duct into the junction of the left internal jugular and subclavian veins and disseminate throughout the pulmonary capillary bed. LAM cell emboli impacted in the lung vasculature may then proliferate intravascularly through a novel mechanism called "invasion-independent metastasis."[73,74]

Mechanisms of Matrix Remodeling in Lymphangioleiomyomatosis

Cystic destruction of the lung parenchyma causes progressive decline in lung function in patients with LAM, and proteases are believed to play a major role in the process. The spectrum of metalloproteinases that are aberrantly expressed in LAM has not been fully characterized, but matrix metalloproteinase (MMP)-2 is the most abundant of those studied to date. Overexpression of MMP-1, MMP-9, MT1-MMP, and MMP-14 has also been reported,[75] and serum levels of MMP-9 are elevated in patients with LAM.[76] MMP-1, MMP-2, and MMP-9 are able to degrade elastin, consistent with the loss and degradation of elastic fibers that is known to occur in LAM.[75] Zhe and associates have proposed that increased expression of serum response factor (SRF) may lead to MMP activation[77–80] and down-regulation of tissue inhibitor of metalloproteinase (TIMP)-3 in LAM cells,[77] leading to an imbalance of proteases and protease inhibitors. Recently, abundant expression of cathepsin K was reported in LAM, suggesting a possible pathogenic role.[81]

LAM lesions have also been reported to contain abundant tryptase-positive mast cells, which express basic fibroblast growth factor (bFGF) and receptors Bek (FGF-R-2) and Flg (FGF-R-1), as well as chymases, renin, angiotensin-converting enzyme, and angiotensin receptors type I and type II.[82,83] Insulin-like growth factors (IGFs) are involved in normal pulmonary development and in the pathogenesis of smooth muscle cell proliferation. IGF-I, IGF-II, IGF-I receptor, IGF-binding protein (IGFBP)-1, IGFBP-2, IGFBP-4, IGFBP-5, and IGFBP-6 are expressed in lung tissue from patients with LAM.[84] Carelli and coworkers[85] recently showed that $TSC2^{-/-}$ human smooth muscle cells derived from AMLs express the apoptosis inhibitor protein survivin when exposed to IGF-1. Transforming growth factor-β1 (TGF-β1), a profibrotic cytokine, is enriched in highly cellular areas of the LAM lesion.[85a] Targeting autocrine systems that promote fibroproliferative responses induced by bFGF, the renin-angiotensin system, IGFs, and TGF-β1 are possible therapeutic strategies for the future.

Preclinical Evidence and Human Trials

Estrogen

Estrogen-containing drugs have been implicated in the worsening of LAM. Estrogen regulates the transcription of many genes, and there is some evidence that estrogen can modulate signaling through the Akt pathway.[86,87] Estrogen may play a role in LAM cell migration, infiltration, proliferation, or secretion of destructive proteases.[31,87] Recently, estrogen was shown to promote pulmonary metastases and enhanced survival of TSC2 deficient cells in mice.[87a]

Sirolimus

Sirolimus, a natural macrolide immunosuppressant, has been shown to silence S6 phosphorylation, and induce apoptosis, necrosis, and tumor reduction of renal cystadenomas in TSC mutant (Eker) rats and the hepatic tumors of TSC heterozygous null mice.[88,89]

The demonstration that TSC mutations are present in patients with S-LAM has focused the attention of LAM scientists and trialists on the Akt pathway that has proved

to be central to TSC pathogenesis.[15] Goncharova and colleagues[90] reported abundant S6 phosphorylation and unregulated cell proliferation in LAM cells isolated from explanted LAM lungs harvested at lung transplant. They further demonstrated that sirolimus blocked the hyperphosphorylation of S6 and restored orderly cell growth.

These and other studies formed the basis for phase I/II trials of sirolimus in patients with tuberous sclerosis and LAM, the Cincinnati Angiomyolipoma Sirolimus Trial (CAST; NCT00457964).[91] In this open-label study, 25 patients with AMLs, including 6 patients with S-LAM and 12 with TSC-LAM and (7 with TSC alone), were treated for 1 year with sirolimus and followed with serial magnetic resonance imaging (MRI) studies of the kidneys, computed tomography (CT) scans of the lungs, and pulmonary function tests. AML volume of the 20 patients that reached the 1-year mark shrunk by an average of 47%, and forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) in 11 LAM patients still enrolled at a year increased by 118 mL and 390 mL, respectively. The residual volume fell by 440 mL, and cyst volume percent, a measurement of the fraction of the pulmonary parenchyma that is occupied by cysts, tended to decline on therapy but did not reach statistical significance.[92] Parameters that did not change included total lung capacity (TLC), 6-minute walk distance, and diffusing capacity for carbon monoxide (D_{LCO}). There were a number of adverse events while patients were taking the study article, including mouth ulcers and cholesterol elevations in most subjects and hospitalizations for pneumonia, diarrhea, cellulitis, pyelonephritis, palpitations, and mucositis.

In the second year of the trial, patients were observed off the study article at 6-month intervals. The average AML volume increased again and reached 77% of the original volume at 18 months and 86% at 24 months. In 25% of patients, however, AML size remained below 70% of baseline through the 2-year point. The FEV_1 and FVC declined off therapy at rates that are generally consistent with untreated LAM patients,[93] but remained 62 mL and 364 mL above baseline at 24 months, respectively. The effect of sirolimus on residual volume was durable in most patients, and residual volume remained 333 mL below baseline at 24 months, indicative of relief of gas trapping. Controlled trials will be required to determine if sirolimus has beneficial effects on lung function that outweigh the risks (NCT00414648).

CLINICAL FEATURES

The clinical onset of LAM usually occurs during the reproductive years, with a mean age at the onset of symptoms in the early to mid-30s.[8,9,14,94] Although new diagnoses of LAM have been reported in patients ranging in age from 12 to 75 years,[95,96] documented cases of the disease prior to menarche are rare. A number of reports in the literature describe women in whom the diagnosis was made after menopause.[8,9,14,94,97–100] LAM does not appear to be smoking-related, because the majority of patients in the largest case series were nonsmokers.[9,12,14]

Because LAM is rare and the symptoms are often nonspecific, the diagnosis is often delayed with a mean interval between the onset of symptoms and diagnosis of 5 to 6 years.[8,11,14,101] Initial incorrect diagnoses in these series typically included bronchial asthma, emphysema, chronic bronchitis, chronic obstructive pulmonary disease, sarcoidosis, diffuse panbronchiolitis (in Asia), and even idiopathic interstitial pneumonias including idiopathic pulmonary fibrosis.

In the patients reported by Urban and associates,[14] exertional dyspnea and spontaneous pneumothorax were the initial symptoms in 49% and 46% of patients, respectively. During the course of the illness, dyspnea developed in 87% of patients, and pneumothorax developed in 68% of patients. The first pneumothorax precedes the diagnosis of LAM in 82% of patients; in fact, most patients have two pneumothoraces before the diagnosis is made.[21,102] Pneumothorax is often recurrent.[7,11,14] In LAM patients who have a pneumothorax, the likelihood of an ipsilateral or contralateral recurrence is greater than 70%.[102] Pneumothorax most likely results from the rupture of subpleural blebs, but whether the event is triggered by progressive degradation of connective tissue matrix or airflow obstruction and overdistention of distal air spaces, or both, is unclear.

Other signs and symptoms of LAM, which may be present at the onset or may develop during the course of the disease, include fatigue, cough, hemoptysis (rarely massive), chest pain, and symptoms related to reflux of chylous fluid into pleural (33% of patients) and extrapleural locations, such as the peritoneum (chylous ascites) or pericardium (chylopericardium), airway (chyloptysis), and genitourinary tract (chyluria and chylous metrorrhea). It is likely that the chylous complications of LAM result from obstruction of lymphatic channels due to infiltration by smooth muscle cells.

AMLs, unusual hamartomas composed of fat, smooth muscle, and abnormal blood vessels, may occur in virtually any location in the chest and abdomen but are most common in the kidney. About 29–33% of S-LAM patients have renal AMLs, compared with about 88–93% of TSC or TSC-LAM patients.[23,103] AMLs are more commonly unilateral and solitary in S-LAM patients, and more commonly bilateral and multiple in TSC-LAM patients.[64] Blood vessels in AMLs are often tortuous and aneurysmal and are composed of cells with normal genotype and cells with TSC mutations,[104] which may partially explain their propensity to bleed. Spontaneous hemorrhage into AMLs may produce severe flank or abdominal pain, acute hypotension, and/or anemia, occasionally in association with circulatory collapse. Renal cysts are frequently present in patients with LAM; in TSC-LAM, polycystic kidney disease may occur due to a contiguous gene deletion of PKD1 which is adjacent to TSC2 on chromosome 16.[105] Rarely, LAM presents as retroperitoneal masses, including cystic lymphangioleiomyomas or adenopathy, which mimic lymphoma, ovarian or renal cancer, or other malignancy.[106,107]

There have been case reports of exacerbation of LAM associated with birth control pill use[108] or during pregnancy.[109–113] In a group of 69 patients with sporadic LAM,

the onset of pulmonary symptoms occurred during pregnancy in 9 of the 46 patients (20%) with a history of pregnancy before or at the time of diagnosis.[14] In this same group, a marked exacerbation of previously diagnosed pulmonary LAM was observed in 2 (14%) patients during pregnancy. The effect of pregnancy or exogenous estrogen use on LAM has not been systematically studied, however.

PHYSICAL EXAMINATION

The physical examination in LAM is often nonspecific. Lung auscultation is usually uninformative but may reveal crackles in 15% to 20% of patients and rhonchi or wheezing in less than 15%.[9,11,14] Clubbing is uncommon, being reported in 3% and 5% of patients in two larger case series.[9,11] Physical examination may also reveal evidence of pleural effusion, ascites, or pneumothorax, if present. Careful dermatologic, ocular, and dental surveys should be performed for evidence of TSC, including facial angiofibromas, subungual fibromas, palpable dysplastic cutaneous lesions called Shagreen's patches, hypomelanotic macules including those with ash leaf or confetti configurations, and dental pitting.[16]

IMAGING STUDIES

Early in the disease, the chest radiograph may appear normal or may suggest hyperinflation only. As the disease progresses, the chest radiograph demonstrates diffuse, bilateral, and symmetrical reticulondular infiltrates, which can progress to cysts, bullae, or a "honeycomb" appearance in the later stages.[9,14] Pleural effusion and pneumothorax may also be apparent (Fig. 62-2).

One characteristic chest radiographic feature of LAM is the preservation of lung volumes despite the presence of increased interstitial markings. This finding distinguishes LAM from most other interstitial lung diseases, in which alveolar septal and interstitial expansion tends to increase the lung's elastic recoil properties and decrease lung volumes. The chest radiograph may also reveal one of the common thoracic complications of LAM, either pneumothorax or chylous pleural effusion. The presence of a pneumothorax may allow visualization of cystic changes in the deflated lung, which are not visible in the fully inflated lung.

The high-resolution computed tomography (HRCT) chest scan is much more sensitive than the chest radiograph in detecting cystic parenchymal disease and is usually abnormal at the time of diagnosis, even when the chest radiograph and pulmonary function assessments are normal.[9,11,14,114] The CT shows diffuse, round, bilateral, thin-walled cysts of varying sizes ranging from 1 to 45 mm in diameter (see Fig. 62-2).[11,14] The numbers of cysts varies in LAM from a few to complete replacement of the normal lung tissue. The morphology of the cysts is useful in differentiating LAM from other cystic lung diseases. The presence of internal septa or a "centrilobular dot" consistent with a vessel is frequently seen in emphysema, but virtually never in LAM. In emphysema, the borders of the cystic spaces are difficult to discern, whereas in Langerhans cell histiocytosis, another LAM mimic, the cyst walls are thicker and more bizarre in shape. Other CT findings in LAM patients may include dilation of the thoracic duct or enlargement of mediastinal lymph nodes. Blinded expert radiologists can correctly identify LAM among a pool of CTs consisting of a variety of other cystic lung diseases about 72% of the time.[115] Other CT features include linear densities, (29%), ground-glass opacities (12%),[9] nodular densities (11%), hilar or mediastinal lymphadenopathy (9%), pleural effusion, pneumothorax, lymphangiomyomata, and dilated thoracic duct.[11,14]

In patients with TSC, nodular densities on HRCT may represent multifocal micronodular pneumocyte hyperplasia (MMPH), clusters of hyperplastic type II pneumocytes[23,116,117] (Fig. 62-3). MMPH may be present in males or females with TSC alone, but is very rare in

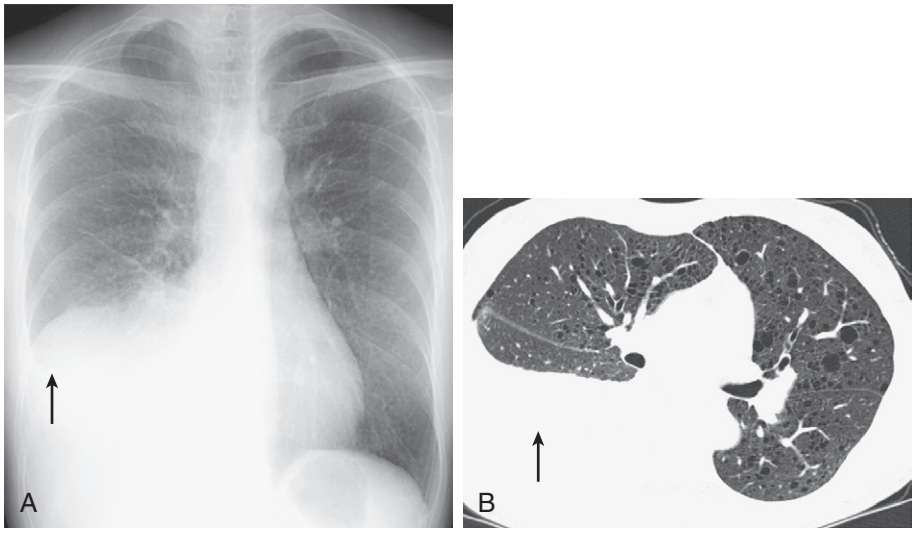

FIGURE 62-2 ■ Chest roentgenogram (**A**) and high-resolution computed tomography (HRCT; **B**) of a 40-year-old woman with sporadic lymphangioleiomyomatosis (LAM). Diffuse cystic changes and a right-sided chylothorax (*arrows*) are present.

patients with S-LAM.[118] MMPH has no known physiologic or prognostic consequences.

Chu and associates[11] reported that ventilation/perfusion scans were abnormal in 34/35 women with LAM. The most common abnormality was nonspecific, diffuse heterogeneity, usually grossly matched. These authors also described an "unusual," "speckling pattern" on the ventilation images in 74% of patients, consisting of "small, often peripheral collections of radioisotope."

LAM and AML lesions do not typically exhibit increased uptake of [(18)F]2-fluoro-2-deoxyglucose (FDG) on PET scanning. So other neoplasms (or sources of inflammation) should be considered in patients who are found to have positive studies.[118a]

Abnormalities on abdominal imaging, such as renal AML and enlarged lymphatic structures, are also common in LAM (Figs. 62-4 and 62-5). Fat density within a renal mass is pathognomonic of AMLs. AMLs are more frequently bilateral, larger, and more common in patients with TSC-LAM than in S-LAM patients, and AML size correlates with the prevalence of pulmonary cysts in patients with TSC.[23] Chu and associates[11] reported the results of abdominal CT and ultrasound imaging in 35 patients with LAM. Twenty-two (63%) of these patients were found to have solid renal masses. In 9 patients, the solid masses were multiple, and in 6, they were bilateral. Renal abnormalities with features suggesting AML were seen in 18 (51%) patients, consistent with prior studies.[119] These lesions were multiple in 6 patients, and bilateral in 4. Axial lymphadenopathy was also commonly seen in this series, including the presence of retroperitoneal nodes in 66% of patients. Less common findings were

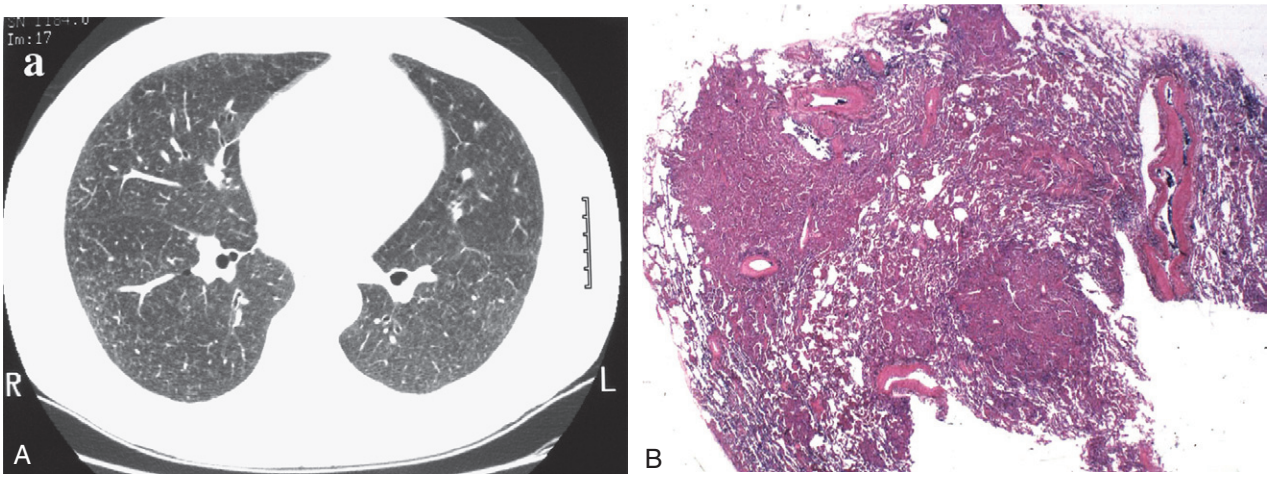

FIGURE 62-3 ■ Radiographic and histopathologic presentation of multifocal micronodular pneumocyte hyperplasia (MMPH). **A,** The HRCT of the chest of a patient with MMPH reveals miliary nodules throughout both lungs. **B,** The low-power view of lung biopsy from a patient with MMPH reveals diffuse nodular proliferation of alveolar type II cells.

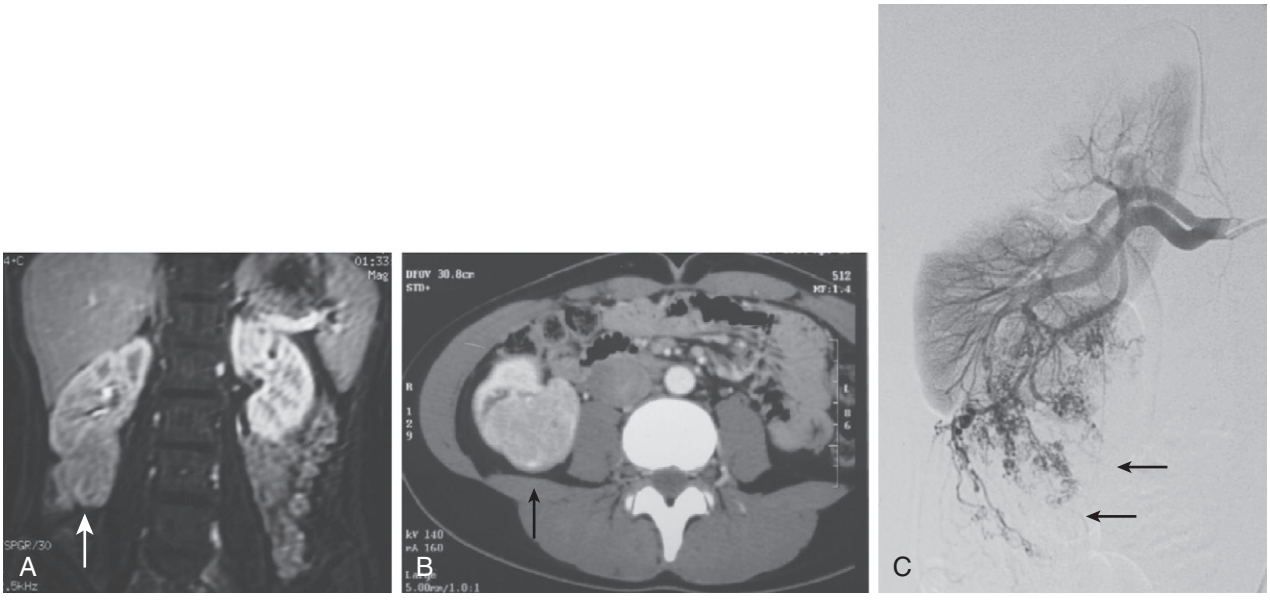

FIGURE 62-4 ■ Coronal (**A**) and sagittal (**B**) abdominal computed tomography (CT) scans and angiography (**C**) of a renal angiomyolipoma in a 16-year-old female with sporadic LAM. Note fat density within the tumor (*arrow*) in the right kidney. (Kindly provided from Dr. Shoji Samma, Nara Prefectural Nara Hospital, Japan.)

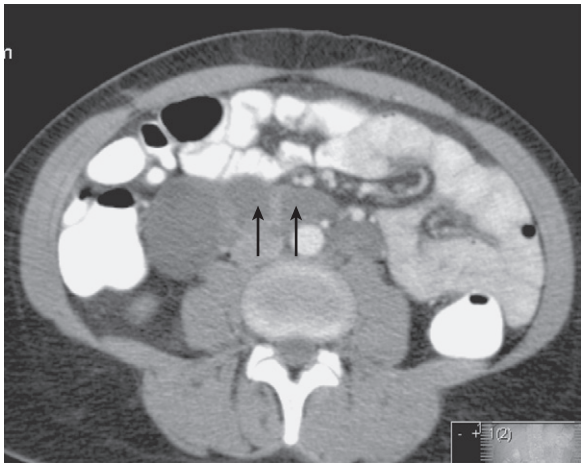

FIGURE 62-5 ■ Abdominal CT of cystic lymphangiomyomas (*arrows*) and retroperitoneal adenopathy in a patient with LAM.

ascites and renal cysts. Avila and coworkers[120] reported that abdominal lymphangioleiomyomas, often containing both cystic and solid components, were seen in 27 of 128 LAM patients.

Central nervous system abnormalities, such as cortical or subependymal tubers and astrocytomas, are common in patients with TSC, including those with TSC-LAM, but are not found in women with S-LAM. Moss and associates[121] reported that women with S-LAM and TSC-LAM may have an increased incidence of meningioma, but the significance of that finding has been questioned.[122]

PULMONARY FUNCTION TESTING

Pulmonary function testing in patients with LAM may be normal or may reveal obstructive, restrictive, or mixed patterns, with obstructive physiology being the most common abnormality. Quality controlled lung function data were collected prospectively by the NHLBI Registry,[103] a 5-year study of LAM patients in centers around the United States. Spirometry revealed obstructive changes in about 57% of patients and normal results in 34%.[103] Restriction, defined as a TLC value that is less than the lower limit of normal, was seen in 11%. Hyperinflation was unusual, present in about 6%. The average residual volume was 125% of predicted when measured by plethysmography, but was 103% of predicted determined with gas dilution methods. These data suggest that a significant proportion of gas trapped in the chest is not in communication with the airway. Approximately 25% of patients with obstructive physiology may demonstrate bronchodilator responsiveness.[12] The obstructive physiologic defect in LAM is primarily attributable to airflow obstruction and, to a lesser degree, to a modest increase in lung compliance.[123]

The most common finding on initial pulmonary function testing in various case series was abnormal gas transfer, as assessed by the D_{LCO}, described in 82% to 97% of patients.[8,9,11,14] Reduction in D_{LCO} and increase in residual volume are generally considered to be the earliest physiologic manifestations of LAM, and it is not unusual for D_{LCO} to be reduced out of proportion to FEV_1.[12]

Cardiopulmonary exercise testing in patients with LAM reveals that exercise-induced desaturation is often present, even in patients with normal or near normal D_{LCO} and FEV_1.[124,125] Crausman and colleagues[126] studied the mechanism of exercise limitation in 16 patients with LAM. They concluded that poor exercise performance was primarily due to airflow obstruction and increased dead-space ventilation, caused by pulmonary vascular disease or extensive cystic change. Cardiopulmonary exercise testing in a much larger cohort of patients with LAM revealed a reduced maximal oxygen consumption ($\dot{V}O_2max$) and anaerobic threshold in 217 patients.[124] Exercise-induced hypoxemia occurred even in patients who did not have resting abnormalities in FEV_1 and D_{LCO}. In most patients, exercise was felt to be ventilation limited, owing to airflow obstruction and increased dead-space ventilation.

Disease progression is usually accompanied by a progressive obstructive ventilatory defect, and decline in FEV_1 is the most commonly used parameter to monitor disease progression. Although resting pulmonary hypertension appears to be unusual in LAM, pulmonary arterial pressure often rises with low levels of exercise, related in part to hypoxemia.[125]

Taveira-DaSilva and coworkers[12] correlated lung function testing with lung histology in 74 patients and reported that a positive bronchodilator response was associated with a predominantly solid pattern of lung lesions (as opposed to cystic pattern), but not with airway inflammation (bronchiolitis), which was identified in 61% of lung biopsies. They also found that the D_{LCO} correlated with the lung $\dot{V}O_2max$ and the lung histology score (LHS), a quantification of the extent of involvement with cystic lesions and LAM cells. FEV_1 and D_{LCO} were the best predictors of $\dot{V}O_2max$, however.

PATHOLOGY

Grossly, LAM lungs are enlarged and diffusely cystic, with dilated air spaces as large as several centimeters in diameter[7,127] (Fig. 62-6). Microscopic examination of the lung reveals foci of smooth muscle cell infiltration of the lung parenchyma, airways, lymphatics, and blood vessels, associated with areas of thin-walled cystic change. LAM lesions contain a striking abundance of lymphatic channels, forming an anastomosing meshwork of slitlike spaces lined by endothelial cells. LAM cells have been observed to invade the airways, the pulmonary artery, the diaphragm, aorta, and retroperitoneal fat, to destroy bronchial cartilage and arteriolar walls, and to occlude the lumen of pulmonary arterioles.[7]

There are two major cell morphologies in the LAM lesion, small spindle-shaped cells and cuboidal epithelioid cells.[128] All LAM cells stain positively for smooth muscle actin, vimentin, and desmin (Fig. 62-7). The cuboidal cells within LAM lesions also react with a monoclonal antibody called HMB-45, developed against the premelanosomal protein gp-100, an enzyme in the mela-

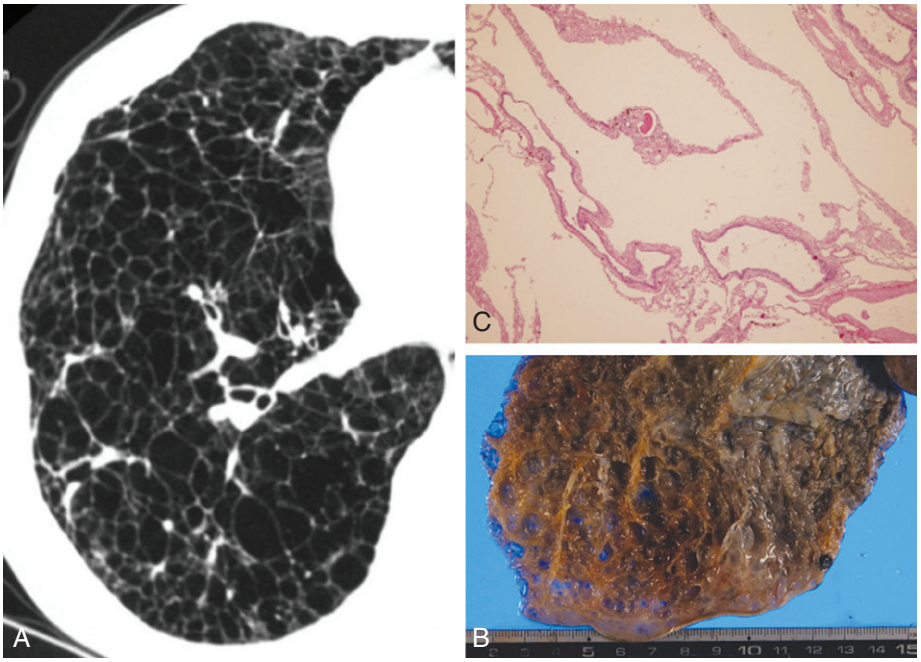

FIGURE 62-6 ■ HRCT (**A**) and pathologic gross specimen (**B**) of the autopsied lung from a 57-year-old woman with sporadic LAM. **C,** Microscopic with low magnification, hematoxylin and eosin (H&E) staining. Extensive cystic changes are evident in the terminal stages of LAM. (Kindly provided from Dr. Masanori Kitaichi, National Hospital Organization, Kinki-Chuo Chest Medical Center, Osaka, Japan.)

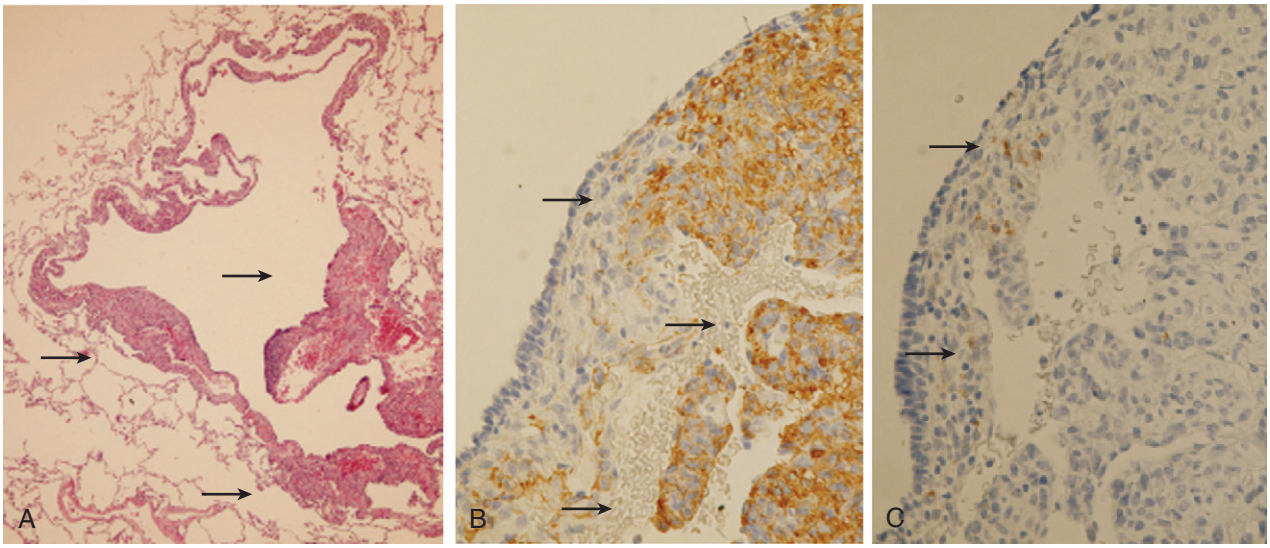

FIGURE 62-7 ■ Histopathology of a lung specimen from a 32-year-old woman with sporadic LAM. **A,** Smooth muscle cell proliferation (*arrow*), cystic change, and distorted pulmonary architecture characteristic of LAM (H&E staining). **B,** LAM nodule immunostained with alpha smooth muscle actin (SMA) (*arrow*). **C,** Scattered positive LAM cells immunostained with HMB-45 (*arrow*). (Kindly provided from Dr. Masanori Kitaichi, National Hospital Organization, Kinki-Chuo Chest Medical Center, Osaka, Japan.)

nogenesis pathway.[128] This immunohistochemical study is very useful diagnostically, because other smooth muscle–predominant lesions in the lung do not react with the antibody.[129] The spindle-shaped cells of the LAM lesion are more frequently proliferating cell nuclear antigen (PCNA)-positive than the cuboidal cells, consistent with a proliferative phenotype.[128] Compared with cigar-shaped normal smooth muscle, spindle-shaped LAM cells contain less abundant cytoplasm and are less eosinophilic. Estrogen and progesterone receptors may also be present in LAM lesions,[130,131] but not in normal lung tissue.[132] The smooth muscle–like cells of AMLs are morphologically and immunohistochemically similar to LAM cells, including reactivity with antibodies directed against actin, desmin, vimentin, and HMB-45 as well as estrogen and progesterone receptors.[133,134] Unlike the dilated air spaces in emphysema, the cystic spaces may be lined with hyperplastic type II cells.[135] Diffuse nodular

proliferation of type II cells indicative of MMPH may also occur in patients with TSC, in the presence or absence of the cystic pulmonary changes of LAM (see Fig. 62-3).[118]

DIAGNOSIS

The diagnosis of LAM is often delayed, and many patients are treated for several years for alternative diagnoses. Sadly, it is unusual for young dyspneic women with LAM to receive the correct diagnosis until a pneumothorax or chylothorax develops or interstitial lung disease or an AML is discovered. This unfortunate circumstance arises because the disease is rare, the symptoms are often nonspecific, and the radiographic manifestations can be protean. Many young women presenting with mild dyspnea are treated for asthma without extensive evaluation. Indeed, the findings of airflow limitation on spirometery discovered in LAM patients are consistent with asthma. Unless full pulmonary function testing is ordered, "red flags" such as reduced D_{LCO} will not be appreciated.

Clinical Diagnosis

In the proper clinical context, a diagnosis of LAM may be reasonably established based on radiographic findings alone. For instance, classic LAM cystic changes on HRCT of the lung along with a chylothorax documented by thoracentesis or CT evidence of fat-containing renal masses consistent with AMLs establishes the diagnosis with a high degree of certainty. There are rare exceptions, however, because lymphoma can present with pulmonary cystic change and chylothorax, and Birt-Hogg-Dube (BHD) can present pulmonary cystic change, fat-containing renal masses (angiolipomas), and angiofibromas. Pulmonary cystic change in a nonsmoking woman with TSC is consistent with LAM and does not usually require biopsy. In smoking patients with or without TSC, the diagnoses of pulmonary emphysema and Langerhans cell histiocytosis (pLCH)[136] must be seriously entertained. Serologies for Sjögren's syndrome antibody A (SS-A), SS-B, and alpha$_1$-antitrypsin level should be obtained. Serum VEGF-D is elevated three- to eightfold in patients with LAM[71] but not in patients with pulmonary emphysema, pLCH, lymphangiomatosis, or BHD and, if validated in larger studies, may prove to be useful in differentiating LAM from these disorders.[72]

In addition to an HRCT of the chest, patients with LAM should have a dedicated CT of the abdomen to screen for AMLs, lymphangiomyomas, uterine masses, and chylous ascites. Renal AMLs can be identified radiographically based on the presence of fat; biopsy may be required to rule out renal cell carcinoma in case the renal masses do not contain fat.

Differential Diagnosis

The primary differential in patients with a smoking history includes pLCH and pulmonary emphysema. The morphology of the cysts, which are devoid of distinct walls in emphysema and thicker walled, mid- and upper lung zone–predominant, and more irregularly shaped in pLCH, can be helpful in differentiating these disorders from LAM.[115] Diffuse subcentimeter nodular changes are often present in pLCH, but can also occur in TSC and TSC-LAM, where they represent MMPH.[118] Less common cystic lung diseases that can mimic LAM and should also be considered include Sjögren's syndrome,[137] Castleman's disease, follicular bronchiolitis and lymphocytic interstitial pneumonitis, hypersensitivity pneumonitis,[138] amyloidosis, lymphoma, light chain deposition disease,[139] and bronchopulmonary dysplasia/barotrauma. Thin-walled cystic lung lesions can also be associated with metastatic genitourinary neoplasms including endometrial stromal cell sarcoma,[140] low-grade leiomyosarcomas, and cystic benign metastasizing leiomyoma.[63]

BHD syndrome[141] can be difficult to distinguish from LAM. BHD is a rare tumor suppressor syndrome associated with spontaneous pneumothorax, skin lesions (fibrofolliculomas, trichodiscomas, acrochordons, and angiofibromas), bland, peripheral and subpleural pulmonary cysts devoid of smooth muscle infiltration (Fig. 62-8), and inherited renal neoplasms including oncocytomas, chromophobe adenomas, papillary renal cell carcinoma, and angiolipomas. Mutations in the folliculin gene *17p11.2* cause defects or deficiency in a protein of unknown function called folliculin and result in BHD or familial spontaneous pneumothorax.[142,143] It appears that BHD is also associated with aberrant signaling through

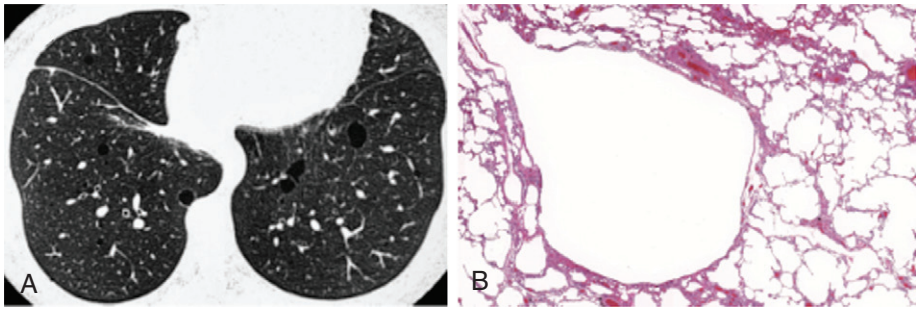

FIGURE 62-8 ■ Birt-Hogg-Dubé syndrome. HRCT (**A**) and histopathologic (**B;** H&E staining) presentation of the lung cysts. This 58-year-old patient had repeated bilateral pneumothoraces, facial fibrofolliculomas, and acrochordons and a family history of pneumothorax in a brother, son, and daughter. (Kindly provided from Dr. Takashi Ogura, Kanagawa Cardiovascular and Respiratory Center, Kanagawa, Japan; and Tamiko Takemura, Japanese Red Cross Medical Center, Tokyo, Japan.)

the Akt pathway, but the loss of regulation occurs upstream of mTOR.

Chylous diseases that involve the thorax including lymphangiomatosis, lymphangiectasis, and lymphatic dysplasia[144–147] may also be confused with LAM, although they do not typically produce cystic change in the lung.

Lung Biopsy

The diagnosis of LAM is most definitively established by lung biopsy. HMB-45 staining is highly specific for LAM and can be used to differentiate LAM from other causes of smooth muscle proliferation in the lung including idiopathic pulmonary fibrosis, benign metastasizing leiomyoma, and leiomyosarcoma. Successful bronchoscopic diagnoses, using transbronchial biopsies with appropriate immunohistochemical staining, have been reported but are the exception.[148] Video-assisted thoracoscopic lung biopsy is the preferred approach for making the diagnosis of LAM. Although there are few interventions for the most likely diseases in the differential other than smoking cessation, clarity regarding the diagnosis of LAM facilitates discussions regarding life planning, pregnancy, birth control, pneumothorax management, and candidacy for trials.

TREATMENT

There are no well-designed studies upon which to base therapeutic decisions in LAM, and there is no consensus regarding optimal treatment of the disease. The three largest recent series, from Japan,[9] England,[149] and France,[14] reviewed retrospective experiences with multiple therapies that can only be described as inconclusive. The definitions of evaluable treatments and response to therapy vary greatly. Each study reported a few responses, often in the chylous manifestations, but most patients progressed. The few apparent pulmonary responses were often based on soft end points, such as a 15% increase in FEV_1, and none of the studies was statistically powered to adequately address the question of therapeutic efficacy. The CAST trial described earlier suggested a possible beneficial effect of sirolimus on FEV_1, FVC, and residual volume in LAM, but the results will need to be validated in larger trials before the drug can be recommended for clinical use.[91] Multiple case reports of responses of AMLs and LAM (pre- and post-lung transplant) to sirolimus have recently appeared in the literature.[150–156]

The remarkable gender restriction in LAM, although unexplained, has provided the rationale for the empirical anti-estrogen strategies that have dominated the approach to LAM for the last several decades. The results are generally disappointing, and because proper trials with hormonal therapies have never been conducted, there remain no proven therapies for LAM based on antagonism of estrogen action. Bilateral oophorectomy has not been demonstrated to slow the rate of decline in lung function in LAM.[8] Enthusiasm for the use of progesterone, which became the standard of care following a single positive outcome published in a case report in 1987,[94] has likewise waned over time. In a retrospective study of 275 patients, Taveira-DaSilva and associates[101] found that progesterone treatment failed to slow the decline in FEV_1. In fact, in that study, intramuscular or oral progesterone therapy was associated with an accelerated rate of decline in D_{LCO} compared with untreated patients. The rate of decline in FEV_1 and D_{LCO} was also no different in patients treated with the gonadotropin-releasing hormone (GnRH) agonist triptorelin for 3 years compared with a well-characterized cohort of historical controls.[157] Other case series of GnRh agonist treatment have yielded conflicting results.[158–160]

In the face of such uncertainty, decisions of when and how to treat are best made jointly by the patient and physician after thorough discussions of the risks and limited available data. When feasible and available, enrollment in clinical trials should be offered to patients who qualify. Therapies that are most often discussed with patients who suffer progressive decline in lung function or worsening symptoms include progestins (both oral and intramuscular) and GnRH agonists. Oral progestins at doses that are just sufficient to suppress serum estrogen production are preferred over the suprapharmacologic intramuscular progesterone doses that have been propagated in the literature (e.g., Depo-Provera 400 mg intramuscularly every month). Progestins at such high doses can cause fluid retention, depression, and mood swings. GnRH agonists (e.g., leuprolide, buserelin acetate, goserelin) have been used in patients with LAM, but benefits are unproved and induction of early menopause is associated with psychological, vascular, and bony consequences in young women. There is no proven role for corticosteroids, immunomodulatory cytotoxic agents, or ovarian irradiation in the treatment of LAM. Ovariectomy is no longer widely recommended because the benefits are unknown.[8,9,14]

The management issues that should be addressed in patients with LAM are outlined in Table 62-2.

General Recommendations

Estrogen-containing medications may have adverse effects[108] and should be discontinued. A trial of bronchodilators should be considered in patients with LAM, because up to 17% to 25% of LAM patients have bronchodilator-responsive disease.[11,103] Extrapolating from chronic obstructive pulmonary disease populations, it is reasonable to speculate that oxygen use has beneficial effects in hypoxic patients. Oxygen should be administered to maintain oxyhemoglobin saturations of greater than 90% with rest, exercise, and sleep. Bone densitometry should be considered in all patients who are immobilized and/or on antiestrogen therapies, and appropriate therapy instituted for osteoporotic patients. Proper attention should be paid to cardiovascular health following natural or therapeutic menopause. Pulmonary rehabilitation seems to be particularly rewarding in this young, motivated population with obstructive lung disease, but studies to assess improvements in exercise tolerance, conditioning, and quality of life have not been done.

TABLE 62-2. Recommended Interventions, Studies and Immunizations in Patients with LAM

Interventions/ recommendations	• Stop smoking • Stop all estrogen containing medications • Counsel regarding pregnancy and air travel • Inform patient of symptoms/management of pneumothorax, chylothorax • Consider bronchodilator therapy • Consider oxygen therapy • Refer large angiomyolipomas (>4 cm diameter) for possible embolization • Refer for transplant evaluation for FEV_1 < 30%, disabling dyspnea or profound hypoxia
Studies	• High-resolution CT of the chest (every 1–3 yr) • Pulmonary function testing (every 6–12 mo) • $Alpha_1$-antitrypsin level, SS-A, SS-B, consider VEGF-D • Abdominal CT, MRI, or ultrasound for angiomyolipoma (every 6–12 mo) • Rule out TSC with head CT or MRI, dermatologic, and ophthalmologic examinations • Rest, sleep, exercise oximetry, 6-minute walk • Bone densitometry
Indications for lung biopsy	• Cystic pulmonary change without corroborating features of known TSC or angiomyolipomata. In smokers, lung biopsy may be required to distinguish LAM from emphysema and Langerhans cell histocytosis.
Immunizations	• Flu shot and pneumovax

CT, computed tomography; FEV_1, forced expiratory volume in 1 second; LAM, lymphangioleiomyomatosis; MRI, magnetic resonance imaging; SS-A, Sjögren's syndrome antibody A; SS-B, Sjögren's syndrome antibody B; TSC, tuberous sclerosis complex; VEGF-D, vascular endothelial growth factor-D.

Pregnancy

Patients should be advised that pregnancy has been reported to result in exacerbations of LAM in some cases.[109–113] However, the risk of pregnancy in LAM has not been rigorously studied, and decisions regarding the advisability of pregnancy should be made on an individual basis. Women diagnosed with LAM during pregnancy have high rates of pneumothorax, miscarriage, and premature birth.[161] In a survey of 318 patients who indicated on their LAM Foundation intake forms that they had had at least one pregnancy, 163 patients responded to a second inquiry regarding pneumothorax.[162] A total of 38 reported that they had a pneumothorax during pregnancy, consistent with a minimum incidence of pneumothorax in pregnancy of at least 10% (38/318). In a third of patients, the pneumothorax during pregnancy led to the diagnosis of LAM. Pneumothoraces occurred almost twice as frequently on the right as on the left and 4 women presented with bilateral spontaneous pneumothorax. Most pneumothoraces occurred during the second and third trimesters. This study and others[14,21] suggest that pregnancy is associated with pleural complications in patients with LAM. Unfortunately, the more pressing question of whether pregnancy accelerates the decline in lung function in LAM may never be fully addressed, because so few women with LAM choose to become pregnant and patients who are diagnosed with LAM during pregnancy rarely have baseline pulmonary function tests available.

Air Travel

LAM patients may be at increased risk of pneumothorax during air travel. Pollock-BarZiv and coworkers[163] found that 35% of LAM patients have been advised by their physician to avoid air travel, because of the theoretical risk of lung cyst rupture associated with atmospheric pressure changes during flight. In a survey of 276 patients who answered a questionnaire, there were 8 cases of radiographically documented pneumothorax associated with 454 flights. In 5 cases, however, symptoms that were consistent with pneumothorax may have been present prior to boarding. Other symptoms also occurred, including anxiety (22%), chest pain (12%), shortness of breath (14%), cyanosis (2%), and hemoptysis (0.4%) in 10% to 20% of flights. The conclusion from the study was that, although adverse events occurred during flight in patients with LAM, air travel is well tolerated by most LAM patients. A recent study of 281 LAM patients who had routine CXR after traveling to the National Institutes of Health identified 7 with acute pneumothorax. There was no difference in the incidence of pneumothorax in patients who traveled by ground versus air. The conclusion was that the occurrence of a pneumothorax with air travel was related to the high incidence of pneumothorax in the disease rather than the air travel itself.[163a] In advising LAM patients about air travel, it is reasonable to consider several factors, including a history of frequent or recent pneumothorax, extensive cystic disease on HRCT, and the overall extent of cardiopulmonary impairment. Patients with poor cardiopulmonary reserve may tolerate even small pneumothoraces poorly. It is prudent for LAM patients to seek medical evaluation including a chest radiograph prior to boarding a plane if pleuritic chest pain or unexplained persistent shortness of breath is present. Hypoxemia during flight presents independent risks. Patients should consult with their physicians regarding recommendations for on-board oxygen use.

Pleural Disease

Pneumothoraces occur in most patients with LAM and tend to recur, especially after conservative management such as observation, aspiration, or simple tube thoracostomy. Failure rates after pleurodesis are also surprisingly high for reasons that are not well explained; higher than in any other chronic lung disease. Over 65% of patients with LAM develop pneumothorax during the course of their illness, averaging 3.5 pneumothoraces per affected patient over a lifetime.[102] The size of cysts appears to correlate with risk of pneumothorax.[164] We advocate the use of a pleural symphysis procedure on the first pneumothorax, given the greater than 70% chance of recurrence. Chemical sclerosis, mechanical abrasion, talc poudrage, and pleurectomy have all been effective in patients with LAM.

Chyle does not generally cause pleural inflammation or fibrosis, and small stable chylous effusions rarely require intervention once the diagnosis of LAM is made. Shortness of breath may mandate drainage, however, and in some cases, repeatedly. Pleural symphysis may be required to prevent nutritional and lymphocyte deficiencies that can result from repeated taps or persistent drainage. Chemical pleurodesis is generally an effective therapy for chylothorax, as is mechanical abrasion and talc poudrage.[165]

Pulmonary Transplantation

Urban and associates[14] reported the outcome of transplant in 13 patients (associated with renal transplant in 1). The mean interval between time of onset of LAM and transplant was 7.8 ± 5.2 years (range, 2.1–16.8 yr). Mean FEV_1 before transplant was 0.57 ±.15 L. Boehler and colleagues[166] conducted a retrospective survey on 34 LAM patients who had undergone lung transplant. The actuarial survival after 2 years was 58%, which is similar to other lung disease categories. The incidence of perioperative bleeding appeared to be higher, especially in patients with extensive pleural adhesions related to prior pleural procedures, as were complications of pneumothorax and postoperative chylothorax. The United Network of Organ Sharing recorded 126 transplants for LAM from 1989 through 2007, including 77 double-lung transplants and 49 single-lung transplants. The 1-, 3-, and 5-year survival for single- and double-lung transplants were 87%, 73%, and 61%; and 92%, 83%, and 77%, respectively. These survival rates are equal to or better than those for other disease groups transplanted in the same timeframe. There have been four case reports of recurrence of LAM in the donor allograft.[56–58,167] The recurrences did not appear to contribute to death in any of these patients, and at the present time, we do not feel that recurrence should be considered in judging the candidacy of patients for transplant. More than half of LAM patients who have undergone lung transplantation have had a prior history of unilateral or bilateral pleural fusion procedures, and although postoperative bleeding risk is increased, the operative mortality and long-term survival do not appear to be affected.[102,166]

As with other obstructive lung diseases, referral for lung transplantation should be considered as the FEV_1 falls to less than 30% of the predicted value. Some patients that fail to meet this criterion may qualify based on other factors that profoundly affect quality of life, such as disabling dyspnea or problems maintaining oxygen saturation at high levels of supplemental oxygen. Although the question of bilateral versus unilateral transplantation has not been directly studied in LAM, bilateral lung transplantation produces better functional outcomes in other types of obstructive lung disease.[168] However, double-lung transplantation is not always feasible owing to the limited availability of organs and the urgency of the procedure in some patients.

Angiomyolipomas

Renal AMLs may require embolization or cauterization if bleeding occurs, which is thought to be more common when the diameter of the tumor exceeds 4 cm.[169] Others feel that the extent of aneurysmal change determines bleeding risk. Serial abdominal imaging should be performed to assess AML size at 6- to 12-month intervals. Nephron-sparing partial resections may be consider for very large tumors.[170] Nephrectomy is sometimes required for tumors with intravascular extension or other reasons, but is rarely the approach of choice for AMLs that can be managed by less invasive means.

PROGRESSION AND PROGNOSIS

Patients with LAM typically develop progressive airflow obstruction. In a cohort of patients in the United Kingdom, 10 years after symptom onset, 55% of 77 patients were breathless walking on flat ground and 10% were housebound.[171] The average annual rate of decline in FEV_1 and D_{LCO} in 275 patients studied in a single laboratory at the NHLBI was 75 ± 9 mL, and 0.69 ± 0.07 mL/min/mm Hg, respectively.[93] In other series from Europe, the rate of decline in FEV_1 was considerably higher, estimated at approximately 100 to 120 mL/yr.[14,172,173] There was some evidence in these studies that rate of decline in lung function correlates with initial D_{LCO}, with menopausal status, and with progesterone treatment. In patients with mild disease, the development of pneumothorax appears to correlate with a faster rate of decline in FEV_1.[164] A positive bronchodilator response, which was associated with a lower FEV_1, was found to be a predictor of more rapid rate of decline in FEV_1 over time.[12] Survival estimates vary widely, appear to be dependent on mode of presentation, and have generally trended upward over the past few decades, probably due to earlier recognition through more widespread use of CT scanning. The data from early, large case series indicate that 38% to 78% of patients are alive at 8.5 years from the time of disease onset.[8,9] Urban and associates[14] reported a 91% probability of survival at 8.5 years, 79% at 10 years, and 71% at 15 years. Hayashida and colleagues[13] reported that 5-, 10-, and 15-year survival probabilities for Japanese patients who presented with

pneumothorax as the sentinel event were 95%, 89%, and 89%, whereas the survival for those who presented with dyspnea were only 85%, 60%, and 47%. Matsui and coworkers[174] found that the actuarial survival, based on time from lung biopsy to death or transplant, was 85% and 71% after 5 and 10 years, respectively. These investigators also developed a lung histology scoring (LHS) system based on semiquantitative analyses of smooth muscle cell infiltration and cystic change, which correlated with survival. Using the Kaplan-Meier method, they found that patients with LHS scores of 1, 2, and 3 had 5- and 10-year survivals of 100%/100%, 81%/74%, and 63%/52%, respectively. Other negative prognostic indicators that have been reported include a reduced FEV_1/FVC, increased TLC, and a predominantly cystic, rather than smooth muscle hyperplastic, histology.[9] There are no prognostic data available for TSC-LAM, but the survival of patients identified through screening is almost certainly more favorable than that of patients who present with dyspnea.[23,25]

FUTURE CLINICAL TRIALS IN LYMPHANGIOLEIOMYOMATOSIS

Progress in the understanding of the genetic and molecular basis of LAM has suggested a number of potential candidate therapies beyond mTOR inhibitors that may be appropriate for testing in clinical trials (Fig. 62-9). These include Akt inhibitors, Rheb inhibitors (e.g., farnesyltransferase inhibitors and statins), selective estrogen receptor antagonists (e.g., fispemifene), aromatase inhibitors (e.g., letrozole), tyrosine kinase inhibitors (e.g., imatinib mesylate), metalloproteinase inhibitors (e.g., doxycycline), angiogenesis inhibitors (e.g., bevacizumab), Rho inhibitors, and lymphangiogenesis inhibitors (e.g., anti–VEGF-D antibody). Many of these drugs have been approved by the U.S. Food and Drug Administration or are in development for other indications. In the absence of a known effective treatment, participation in clinical trials should be encouraged.

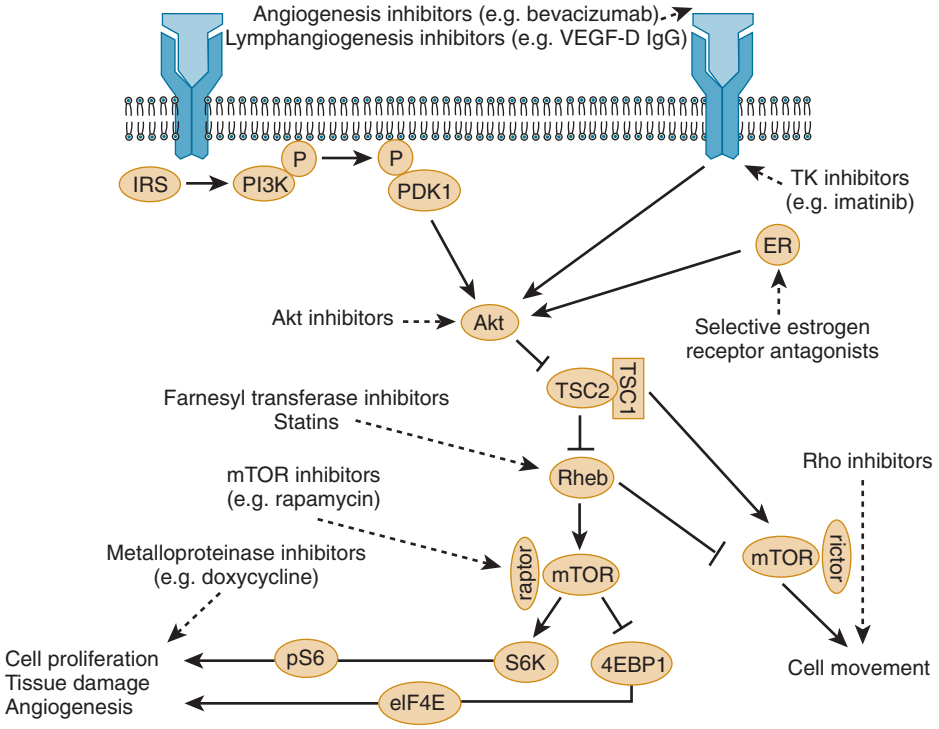

FIGURE 62-9 ■ Future therapeutic targets for LAM. Knowledge of the signaling pathways that are dysregulated in LAM patients has revealed a number of promising molecular targets for intervention. The constitutive activation of mTOR drives the inappropriate phosphorylation of S6 (pS6) when the TSC1 or TSC2 gene is missing or defective, as occurs in LAM patients. pS6 (and eIF4E) drives protein translation and inappropriate cellular proliferation, but also feeds back to inhibit the activation of immunoreactive secretin (IRS) and the downstream effector Akt. This feedback loop control can be defeated by the activation of Akt through other routes, such as the platelet-derived growth factor (PDGF) and estrogen receptor pathways (which may explain the gender restriction in LAM). In this regard, tyrosine kinase (TK) inhibitors such as imatinib and selective estrogen antagonists such as fispemiphene may have special utility in LAM to block alternative activation of Akt. mTOR inhibitors such as sirolimus and everolimus block mTOR signaling through binding to an accessory protein cell FKBP12, and statins and farnesyl transferase inhibitors block Rheb translocation to the membrane by inhibiting the lipid modification of the protein. Patients with LAM express elevated levels of the lymphangiogenic growth factor vascular endothelial growth factor-D (VEGF-D), which is currently being studied as a target in metastatic malignancy trials. Angiogenesis inhibitors such as bevacizumab and anti–VEGF-D antibody may block blood and lymphatic vessel recruitment required for tumor maintainance, respectively, and metalloproteinase inhibitors such as doxycycline may block lung matrix degradation that plays a role in tumor implantation, spread, and tissue destruction. Cell migration, infiltration, and metastasis are controlled by a rapamycin-insensitive mTOR pathway, but may be susceptible to inhibition by rho kinase inhibitors.

KEY POINTS

- LAM is the most gender-restricted illness in medicine, with the exception of diseases of the genitourinary tract. Only a few men with LAM have been reported.
- LAM affects about one third of women with the genetic disease tuberous sclerosis, but most LAM patients who present for pulmonary consultation have S-LAM.
- LAM is caused by mutations in tuberous sclerosis genes, which inactivate the regulatory TSC1/TSC2 complex and result in dysregulated signaling through the Akt growth pathway.
- LAM is characterized by smooth muscle infiltration and cystic destruction of the lung.
- LAM is a neoplasm that spreads through the bloodstream and the lymphatics.
- LAM most commonly presents with dyspnea and pneumothorax and less commonly with chylothorax, hemoptysis, or incidentally discovered abdominal masses or pulmonary cysts.
- The diagnosis of LAM can be established on clinical grounds, but may require tissue confirmation in patients who do not have corroborating features of pneumothorax, chylothorax, or tuberous sclerosis.
- There is no effective treatment for LAM, but clinical trials based on promising molecular targets are under way.
- Pregnancy can result in exacerbation of LAM.
- Pneumothorax in LAM should be aggressively managed, because the incidence of recurrence is exceedingly high.
- The clinical course of LAM is highly variable, but is generally slowly progressive, with 10-year survivals of approximately 80% to 90%.

References

1. Sullivan EJ: Lymphangioleiomyomatosis: A review. Chest 114:1689–1703, 1998.
2. McCormack FX: Lymphangioleiomyomatosis: A clinical update. Chest 133:507–516, 2008.
3. Lautenbacher R: Dysembriomes metotipiques des reins, carcinose submiliere aigue puomon avec amphyseme generalise et double pneumothorax. Ann Med Interne (Paris) 5:435–450, 1918.
4. von Stossel E: Uber muskulare Cirrhose der Lunge (Muscular cirrhosis of the lung). Beitr Klin Tuberk 90:432–442, 1937.
5. Cornog JL Jr, Enterline HT: Lymphangiomyoma, a benign lesion of chyliferous lymphatics synonymous with lymphangiopericytoma. Cancer 19:1909–1930, 1966.
6. Silverstein EF, Ellis K, Wolff M, et al: Pulmonary lymphangiomyomatosis. AJR Am J Roentgenol 120:832–850, 1974.
7. Corrin B, Leibow AA, Friedman PJ: Pulmonary lymphangiomyomatosis: A review. Am J Pathol 79:348–382, 1975.
8. Taylor JR, Ryu J, Colby TV, et al: Lymphangioleiomyomatosis. Clinical course in 32 patients. N Engl J Med 323:1254–1260, 1990.
9. Kitaichi M, Nishimura K, Itoh H, et al: Pulmonary lymphangioleiomyomatosis: A report of 46 patients including a clinicopathologic study of prognostic factors. Am J Respir Crit Care Med 151:527–533, 1995.
10. Oh YM, Mo EK, Jang SH, et al: Pulmonary lymphangioleiomyomatosis in Korea. Thorax 54:618–621, 1999.
11. Chu SC, Horiba K, Usuki J, et al: Comprehensive evaluation of 35 patients with lymphangioleiomyomatosis. Chest 115:1041–1052, 1999.
12. Taveira-DaSilva AM, Hedin C, Stylianou MP, et al: Reversible airflow obstruction, proliferation of abnormal smooth muscle cells, and impairment of gas exchange as predictors of outcome in lymphangioleiomyomatosis. Am J Respir Crit Care Med 164:1072–1076, 2001.
13. Hayashida M, Seyama K, Inoue Y, et al: The epidemiology of lymphangioleiomyomatosis in Japan: A nationwide cross-sectional study of presenting features and prognostic factors. Respirology 12:523–530, 2007.
14. Urban T, Lazor R, Lacronique J, et al: Pulmonary lymphangioleiomyomatosis. A study of 69 patients. Groupe d'Etudes et de Recherche sur les Maladies "Orphelines" Pulmonaires (GERM"O"P). Medicine (Baltimore) 78:321–337, 1999.
15. Juvet SC, McCormack FX, Kwiatkowski DJ, et al: Molecular pathogenesis of lymphangioleiomyomatosis: Lessons learned from orphans. Am J Respir Cell Mol Biol 36:398–408, 2007.
16. Gomez M, Sampson J, Whittemore V (eds): The Tuberous Sclerosis Complex (3rd ed). Oxford, England: Oxford University Press, 1999.
17. Dwyer JM, Hickie JB, Garvan J: Pulmonary tuberous sclerosis. Report of three patients and a review of the literature. Q J Med 40:115–125, 1971.
18. Aubry MC, Myers JL, Ryu JH, et al: Pulmonary lymphangioleiomyomatosis in a man. Am J Respir Crit Care Med 162:749–752, 2000.
19. Kim NR, Chung MP, Park CK, et al: Pulmonary lymphangioleiomyomatosis and multiple hepatic angiomyolipomas in a man. Pathol Int 53:231–235, 2003.
20. Schiavina M, Di Scioscio V, Contini P, et al: Pulmonary lymphangioleiomyomatosis in a karyotypically normal man without tuberous sclerosis complex. Am J Respir Crit Care Med 176:96–98, 2007.
21. Johnson SR, Tattersfield AE: Clinical experience of lymphangioleiomyomatosis in the UK. Thorax 55:1052–1057, 2000.
22. Sampson JR, Scahill SJ, Stephenson JB, et al: Genetic aspects of tuberous sclerosis in the west of Scotland. J Med Genet 26:28–31, 1989.
23. Franz DN, Brody A, Meyer C, et al: Mutational and radiographic analysis of pulmonary disease consistent with lymphangioleiomyomatosis and micronodular pneumocyte hyperplasia in women with tuberous sclerosis. Am J Respir Crit Care Med 164:661–668, 2001.
24. Costello LC, Hartman TE, Ryu JH: High frequency of pulmonary lymphangioleiomyomatosis in women with tuberous sclerosis complex. Mayo Clin Proc 75:591–594, 2000.
25. Moss J, Avila NA, Barnes PM, et al: Prevalence and clinical characteristics of lymphangioleiomyomatosis (LAM) in patients with tuberous sclerosis complex. Am J Respir Crit Care Med 164:669–671, 2001.

26. Krueger DA, Franz DN: Current management of tuberous sclerosis complex. Paediatr Drugs 10:299–313, 2008.
27. Dabora SL, Jozwiak S, Franz DN, et al: Mutational analysis in a cohort of 224 tuberous sclerosis patients indicates increased severity of TSC2, compared with TSC1, disease in multiple organs. Am J Hum Genet 68:64–80, 2001.
28. Slingerland JM, Grossman RF, Chamberlain D, et al: Pulmonary manifestations of tuberous sclerosis in first degree relatives. Thorax 44:212–214, 1989.
29. Astrinidis A, Henske EP: Tuberous sclerosis complex: Linking growth and energy signaling pathways with human disease. Oncogene 24:7475–7481, 2005.
30. Kwiatkowski DJ: Rhebbing up mTOR: New insights on TSC1 and TSC2, and the pathogenesis of tuberous sclerosis. Cancer Biol Ther 2:471–476, 2003.
31. Astrinidis A, Cash TP, Hunter DS, et al: Tuberin, the tuberous sclerosis complex 2 tumor suppressor gene product, regulates Rho activation, cell adhesion and migration. Oncogene 21:8470–8476, 2002.
32. Stovin PG, Lum LC, Flower CD, et al: The lungs in lymphangiomyomatosis and in tuberous sclerosis. Thorax 30:497–509, 1975.
33. Carsillo T, Astrinidis A, Henske EP: Mutations in the tuberous sclerosis complex gene TSC2 are a cause of sporadic pulmonary lymphangioleiomyomatosis. Proc Natl Acad Sci U S A 97:6085–6090, 2000.
34. Knudson AG: Two genetic hits (more or less) to cancer. Nat Rev Cancer 1:157–162, 2001.
35. van Slegtenhorst M, de Hoogt R, Hermans C, et al: Identification of the tuberous sclerosis gene TSC1 on chromosome 9q34. Science 277:805–808, 1997.
36. European Chromosome 16 Tuberous Sclerosis Consortium: Identification and characterization of the tuberous sclerosis gene on chromosome 16. Cell 75:1305–1315, 1993.
37. Wienecke R, Konig A, DeClue JE: Identification of tuberin, the tuberous sclerosis-2 product. Tuberin possesses specific Rap1GAP activity. J Biol Chem 270:16409–16414, 1995.
38. Ito N, Rubin GM: Gigas, a *Drosophila* homolog of tuberous sclerosis gene product-2, regulates the cell cycle. Cell 96:529–539, 1999.
39. Potter CJ, Huang H, Xu T: *Drosophila* Tsc1 functions with Tsc2 to antagonize insulin signaling in regulating cell growth, cell proliferation, and organ size. Cell 105:357–368, 2001.
40. Tapon N, Ito N, Dickson BJ, et al: The *Drosophila* tuberous sclerosis complex gene homologs restrict cell growth and cell proliferation. Cell 105:345–355, 2001.
41. Gao X, Pan D: TSC1 and TSC2 tumor suppressors antagonize insulin signaling in cell growth. Genes Dev 15:1383–1392, 2001.
42. Stocker H, Radimerski T, Schindelholz B, et al: Rheb is an essential regulator of S6K in controlling cell growth in *Drosophila*. Nat Cell Biol 5:559–565, 2003.
43. Ekblom P, Ekblom M, Fecker L, et al: Role of mesenchymal nidogen for epithelial morphogenesis in vitro. Development 120:2003–2014, 1994.
44. Kenerson HL, Aicher LD, True LD, et al: Activated mammalian target of rapamycin pathway in the pathogenesis of tuberous sclerosis complex renal tumors. Cancer Res 62:5645–5650, 2002.
45. Kwiatkowski DJ, Zhang H, Bandura JL, et al: A mouse model of TSC1 reveals sex-dependent lethality from liver hemangiomas, and up-regulation of p70S6 kinase activity in Tsc1 null cells. Hum Mol Genet 11:525–534, 2002.
46. El-Hashemite N, Zhang H, Henske EP, et al: Mutation in TSC2 and activation of mammalian target of rapamycin signalling pathway in renal angiomyolipoma. Lancet 361:1348–1349, 2003.
47. Astrinidis A, Khare L, Carsillo T, et al: Mutational analysis of the tuberous sclerosis gene TSC2 in patients with pulmonary lymphangioleiomyomatosis. J Med Genet 37:55–57, 2000
48. Smolarek TA, Wessner LL, McCormack FX, et al: Evidence that lymphangiomyomatosis is caused by TSC2 mutations: Chromosome 16p13 loss of heterozygosity in angiomyolipomas and lymph nodes from women with lymphangiomyomatosis. Am J Hum Genet 62:810–815, 1998.
49. Sato T, Seyama K, Fujii H, et al: Mutation analysis of the TSC1 and TSC2 genes in Japanese patients with pulmonary lymphangioleiomyomatosis. J Hum Genet 47:20–28, 2002.
50. Yu J, Astrinidis A, Henske EP: Chromosome 16 loss of heterozygosity in tuberous sclerosis and sporadic lymphangiomyomatosis. Am J Respir Crit Care Med 164:1537–1540, 2001.
51. Jones AC, Shyamsundar MM, Thomas MW, et al: Comprehensive mutation analysis of TSC1 and TSC2 and phenotypic correlations in 150 families with tuberous sclerosis. Am J Hum Genet 64:1305–1315, 1999.
52. Kumasaka T, Seyama K, Mitani K, et al: Lymphangiogenesis-mediated shedding of LAM cell clusters as a mechanism for dissemination in lymphangioleiomyomatosis. Am J Surg Pathol 29:1356–1366, 2005.
53. Kuramoto M, Kato M, Inoue Y: [Pulmonary lymphangiomyomatosis with tuberous sclerosis and endolymphatic stromal myosis of the uterus] (Japanese). Nihon Kyobu Shikkan Gakkai Zasshi 34:322–326, 1996.
54. Henske EP: Metastasis of benign tumor cells in tuberous sclerosis complex. Genes Chromosomes Cancer 38:376–381, 2003.
55. Bittmann I, Dose TB, Muller C, et al: Lymphagioleiomyomatosis: Recurrence after single lung transplantations. Hum Pathol 26:1420–1423, 1997.
56. Nine JS, Yousem SA, Paradis IL, et al: Lymphangioleiomyomatosis: Recurrence after lung transplantation. J Heart Lung Transplant 13:714–719, 1994.
57. O'Brien JD, Lium JH, Parosa JF, et al: Lymphangioleiomyomatosis recurrence in the allograft after single lung transplantation. Am J Respir Crit Care 151:2033–2036, 1995.
58. Bittmann I, Rolf B, Amann G, et al: Recurrence of lymphangioleiomyomatosis after single lung transplantation: New insights into pathogenesis. Hum Pathol 34:95–98, 2003.
59. Duffy K, Al-Saleem T, Karbowniczek M, et al: Mutational analysis of the von Hippel Lindau gene in clear cell renal carcinomas from tuberous sclerosis complex patients. Mod Pathol 15:205–210, 2002.
60. Crooks DM, Pacheco-Rodriguez G, DeCastro RM, et al: Molecular and genetic analysis of disseminated neoplastic cells in lymphangioleiomyomatosis. Proc Natl Acad Sci U S A 101:17462–17467, 2004.
61. Buckshee K, Verma A, Karak AK:. Leiomyomatosis peritonealis disseminata. Int J Gynaecol Obstet 61:191–192, 1998.
62. Dal Cin P, Quade BJ, Neskey DM, et al: Intravenous leiomyomatosis is characterized by a der(14)t(12;14)(q15;q24). Genes Chromosomes Cancer 36:205–206, 2003.
63. Shin MS, Fulmer JD, Ho KJ: Unusual computed tomographic manifestations of benign metastasizing leiomyomas as cavitary nodular lesions or interstitial lung disease. Clin Imaging 20:45–49, 1996.
64. Avila NA, Dwyer AJ, Rabel A, et al: Sporadic lymphangioleiomyomatosis and tuberous sclerosis complex with lymphangioleiomyomatosis: Comparison of CT features. Radiology 242:277–285, 2007.
65. Kebria M, Black D, Borelli C, et a: Primary retroperitoneal lymphangioleiomyomatosis in a postmenopausal woman: A case report and review of the literature. Int J Gynecol Cancer 17:528–532, 2007.
66. Valensi QJ: Pulmonary lymphangiomyoma, a probable forme frust of tuberous sclerosis. A case report and survey of the literature. Am Rev Respir Dis 108:1411–1415, 1973.
67. Itami M, Teshima S, Asakuma Y, et al: Pulmonary lymphangiomyomatosis diagnosed by effusion cytology. A case report. Acta Cytol 41:522–528, 1997.
68. Berner A, Franzen S, Heilo A: Fine needle aspiration cytology as a diagnostic approach to lymphangioleiomyomatosis. A case report. Acta Cytol 41:877–879, 1997.
69. Kamitani T, Yabuuchi H, Soeda H, et al: A case of lymphangioleiomyomatosis affecting the supraclavicular lymph nodes. J Comput Assist Tomogr 30:279–282, 2006.
70. Kumasaka T, Seyama K, Mitani K, et al: Lymphangiogenesis in lymphangioleiomyomatosis: Its implication in the progression of lymphangioleiomyomatosis. Am J Surg Pathol 28:1007–1016, 2004.

71. Seyama K, Kumasaka T, Souma S, et al: Vascular endothelial growth factor-D is increased in serum of patients with lymphangioleiomyomatosis. Lymphat Res Biol 4:143–152, 2006.
72. Young LR, Inoue Y, McCormack FX: Diagnostic potential of serum VEGF-D for lymphangioleiomyomatosis. N Engl J Med 358:199–200, 2008.
73. Sugino T, Yamaguchi T, Ogura G, et al: Morphological evidence for an invasion-independent metastasis pathway exists in multiple human cancers. BMC Med 2:9, 2004.
74. Sugino T, Kusakabe T, Hoshi N, et al: An invasion-independent pathway of blood-borne metastasis: A new murine mammary tumor model. Am J Pathol 160:1973–1980, 2002.
75. Fukuda Y, Ishizaki M, Kudoh S, et al: Localization of matrix metalloproteinases-1, -2, and -9 and tissue inhibitor of metalloproteinase-2 in interstitial lung diseases. Lab Invest 78:687–698, 1998.
76. Odajima N, Betsuyaku T, Nasuhara Y, et al: Matrix metalloproteinases in blood from patients with LAM. Respir Med 103:124–129, 2009.
77. Zhe X, Yang Y, Jakkaraju S, et al: Tissue inhibitor of metalloproteinase-3 downregulation in lymphangioleiomyomatosis: Potential consequence of abnormal serum response factor expression. Am J Respir Cell Mol Biol 28:504–511, 2003.
78. Hayashi T, Fleming MV, Stetler-Stevenson WG, et al: Immunohistochemical study of matrix metalloproteinases (MMPs) and their tissue inhibitors (TIMPs) in pulmonary lymphangioleiomyomatosis. Hum Pathol 28:1071–1078, 1997.
79. Matsui K, Takeda K, Yu ZX, et al: Role for activation of matrix metalloproteinases in the pathogenesis of pulmonary lymphangioleiomyomatosis. Arch Pathol Lab Med 124:267–275, 2000.
80. Zhe X, Yang Y, Schuger L: Imbalanced plasminogen system in lymphangioleiomyomatosis: Potential role of serum response factor. Am J Respir Cell Mol Biol 32:28–34, 2005
81. Chilosi M, Pea M, Martignoni G, et al: Cathepsin-k expression in pulmonary lymphangioleiomyomatosis. Mod Pathol 22:161–166, 2009.
82. Inoue Y, King TE, Barker E, et al: Basic fibroblast growth factor and its receptors in idiopathic pulmonary fibrosis and lymphangioleiomyomatosis. Am J Respir Crit Care Med 166:765–773, 2002.
83. Valencia JC, Pacheco-Rodriguez G, Carmona AK, et al: Tissue specific renin-angiotensin system in pulmonary lymphangioleiomyomatosis. Am J Respir Cell Mol Biol 35:40–47, 2006.
84. Valencia JC, Matsui K, Bondy C, et al: Distribution and mRNA expression of insulin-like growth factor system in pulmonary lymphangioleiomyomatosis. J Investig Med 49:421–433, 2001.
85. Carelli S, Lesma E, Paratore S, et al: Survivin expression in tuberous sclerosis complex cells. Mol Med 13:166–177, 2007.
85a. Evans SE, Colby TV, Ryu JH, et al: Transforming growth factor-beta 1 and extracellular matrix-associated fibronectin expression in pulmonary lymphangioleiomyomatosis. Chest 125:1063–1070, 2004.
86. Pedram A, Razandi M, Aitkenhead M, et al: Integration of the non-genomic and genomic actions of estrogen. Membrane-initiated signaling by steroid to transcription and cell biology. J Biol Chem 277:50768–50775, 2002.
87. Razandi M, Pedram A, Park ST, et al: Proximal events in signaling by plasma membrane estrogen receptors. J Biol Chem 278:2701–2712, 2003.
87a. Yu JJ, Robb VA, Morrison TA, et al: Estrogen promotes survival and pulmonary metastasis of tuberin-null cells. Proc Natl Acad Sci 106:2635–2640, 2009.
88. El-Hashemite N, Walker V, Zhang H, et al: Loss of Tsc1 or Tsc2 induces vascular endothelial growth factor production through mammalian target of rapamycin. Cancer Res 63:5173–5177, 2003.
89. Kenerson H, Dundon TA, Yeung RS: Effects of rapamycin in the Eker rat model of tuberous sclerosis complex. Pediatr Res 57:67–75, 2005.
90. Goncharova EA, Goncharov DA, Eszterhas A, et al: Tuberin regulates p70 S6 kinase activation and ribosomal protein S6 phosphorylation. A role for the TSC2 tumor suppressor gene in pulmonary lymphangioleiomyomatosis (LAM). J Biol Chem 277:30958–30967, 2002.
91. Bissler JJ, McCormack FX, Young LR, et al: Sirolimus for angiomyolipoma in tuberous sclerosis complex or lymphangioleiomyomatosis. N Engl J Med 358:140–151, 2008.
92. Schmithorst VJ, Altes TA, Young LR, et al: Automated algorithm for quantifying the extent of cystic change on volumteric chest CT: Initial results in lymphangioleiomyomatosis. AJR Am J Roentgenol 192:1037–1044, 2009.
93. Taveira-DaSilva AM, Steagall WK, Moss J: Lymphangioleiomyomatosis. Cancer Control 13:276–285, 2006.
94. Sieker HO, McCarty KS Jr: Lymphangiomyomatosis: A respiratory illness with an endocrinologic therapy. Trans Am Clin Climatol Assoc 99:57–67, 1987.
95. Awai K, Fujikawa K, Sato T, et al: Pulmonary lymphangiomyomatosis. Radiat Med 8:132–135, 1990.
96. Hancock E, Tomkins S, Sampson J, et al: Lymphangioleiomyomatosis and tuberous sclerosis. Respir Med 96:7–13, 2002.
97. Joliat G, Stalder H, Kapanci Y: Lymphangiomyomatosis: A clinicoanatomical entity. Cancer 31:455–461, 1973.
98. Sinclair W, Wright JL, Churg A: Lymphangioleiomyomatosis presenting in a postmenopausal woman. Thorax 40:475–476, 1985.
99. Baldi S, Papotti M, Valente ML, et al: Pulmonary lymphangioleiomyomatosis in postmenopausal women: Report of two cases and review of the literature. Eur Respir J 7:1013–1016, 1994.
100. Zanella A, Toppan P, Nitti D, et al: Pulmonary lymphangioleiomyomatosis: A case report in postmenopausal woman treated with pleurodesis and progesterone (medroxyprogesterone acetate). Tumori 82:96–98, 1996
101. Taveira-DaSilva AM, Stylianou MP, Hedin CJ, et al: Decline in lung function in patients with lymphangioleiomyomatosis treated with or without progesterone. Chest 126:1867–1874, 2004.
102. Almoosa KF, Ryu JH, Mendez J, et al: Management of pneumothorax in lymphangioleiomyomatosis: Effects on recurrence and lung transplantation complications. Chest 129:1274–1281, 2006.
103. Ryu JH, Moss J, Beck GJ, et al: The NHLBI lymphangioleiomyomatosis registry: Characteristics of 230 patients at enrollment. Am J Respir Crit Care Med 173:105–111, 2006.
104. Karbowniczek M, Yu J, Henske EP: Renal angiomyolipomas from patients with sporadic lymphangiomyomatosis contain both neoplastic and non-neoplastic vascular structures. Am J Pathol 162:491–500, 2003.
105. Brook-Carter PT, Peral B, Ward CJ, et al: Deletion of the TSC2 and PKD1 genes associated with severe infantile polycystic kidney disease—A contiguous gene syndrome. Nat Genet 8:328–332, 1994.
106. Matsui K, Tatsuguchi A, Valencia J, et al: Extrapulmonary lymphangioleiomyomatosis (LAM): Clinicopathologic features in 22 cases. Hum Pathol 31:1242–1248, 2000.
107. Avila NA, Kelly JA, Chu SC, et al: Lymphangioleiomyomatosis: Abdominopelvic CT and US findings. Radiology 216:147–153, 2000.
108. Shen A, Iseman MD, Waldron JA, et al: Exacerbation of pulmonary lymphangioleiomyomatosis by exogenous estrogens. Chest 91:782–785, 1987.
109. Hughes E, Hodder RV: Pulmonary lymphangiomyomatosis complicating pregnancy. A case report. J Reprod Med 32:553–557, 1987.
110. Yockey CC, Riepe RE, Ryan K: Pulmonary lymphangioleiomyomatosis complicated by pregnancy. Kans Med 87:277–278, 293, 1986.
111. Sleiman C, Mal H, Jebrak G, et al: Pulmonary lymphangiomyomatosis treated by single lung transplantation. Am Rev Respir Dis 145:964–966, 1992.
112. Kerr LA, Blute ML, Ryu JH, et al: Renal angiomyolipoma in association with pulmonary lymphangioleiomyomatosis: Forme fruste of tuberous sclerosis? Urology 41:440–444, 1993.
113. Johnson SR, Tattersfield AE: Pregnancy in lymphnagioleiomyomatosis. Am J Respir Crit Care Med 157:A807, 1998.
114. Muller NL, Chiles C, Kullnig P: Pulmonary lymphangiomyomatosis: Correlation of CT with radiographic and functional findings. Radiology 175:335–339, 1990
115. Koyama M, Johkoh T, Honda O, et al: Chronic cystic lung disease: Diagnostic accuracy of high-resolution CT in 92 patients. AJR Am J Roentgenol 180:827–835, 2003.
116. Popper HH, Juettner-Smolle FM, Pongratz MG: Micronodular hyperplasia of type II pneumocytes—A new lung lesion associated with tuberous sclerosis. Histopathology 18:347–354, 1991.

117. Lantuejoul S, Ferretti G, Negoescu A, et al: Multifocal alveolar hyperplasia associated with lymphangioleiomyomatosis in tuberous sclerosis. Histopathology 30:570–575, 1997.
118. Muir TE, Leslie KO, Popper H, et al: Micronodular pneumocyte hyperplasia. Am J Surg Pathol 22:465–472, 1998.
118a. Young LR, Franz DN, Nagarkatte P, et al: Utility of [18F]2-fluoro-2-deoxyglucose-PET in sporadic and tuberous sclerosis-associated lymphangioleiomyomatosis. Chest 136:926–933, 2009.
119. Bernstein SM, Newell JD Jr, Adamczyk D, et al: How common are renal angiomyolipomas in patients with pulmonary lymphangiomyomatosis? Am J Respir Crit Care Med 152:2138–2143, 1995.
120. Avila NA, Bechtle J, Dwyer AJ, et al: Lymphangioleiomyomatosis: CT of diurnal variation of lymphangioleiomyomas. Radiology 221:415–421, 2001
121. Moss J, DeCastro R, Patronas NJ, et al: Meningiomas in lymphangioleiomyomatosis. JAMA 286:1879–1881, 2001.
122. Franz DN: Meningiomas in women with lymphangioleiomyomatosis. JAMA 287:1397–1398, 2002.
123. Burger CD, Hyatt RE, Staats BA: Pulmonary mechanics in lymphangioleiomyomatosis. Am Rev Respir Dis 143:1030–1033, 1991.
124. Taveira-DaSilva AM, Stylianou MP, Hedin CJ, et al: Maximal oxygen uptake and severity of disease in lymphangioleiomyomatosis. Am J Respir Crit Care Med 168:1427–1431, 2003
125. Taveira-DaSilva AM, Hathaway OM, Sachdev V, et al: Pulmonary artery pressure in lymphangioleiomyomatosis: An echocardiographic study. Chest 132:1573–1578, 2007.
126. Crausman RS, Jennings CA, Mortenson RL, et al: Lymphangioleiomyomatosis: The pathophysiology of diminished exercise capacity. Am J Respir Crit Care Med 153:1368–1376, 1996.
127. Carrington CB, Cugell DW, Gaensler EA, et al: Lymphangioleiomyomatosis. Physiologic-pathologic-radiologic correlations. Am Rev Respir Dis 116:977–995, 1977.
128. Matsumoto Y, Horiba K, Usuki J, et al: Markers of cell proliferation and expression of melanosomal antigen in lymphangioleiomyomatosis. Am J Respir Cell Mol Biol 21:327–336, 1999.
129. Hoon V, Thung SN, Kaneko M, et al: HMB-45 reactivity in renal angiomyolipoma and lymphangioleiomyomatosis. Arch Pathol Lab Med 118:732–734, 1994.
130. McCarty KS Jr, Mossler JA, McLelland R, et al: Pulmonary lymphangiomyomatosis responsive to progesterone. N Engl J Med 303:1461–1465, 1980.
131. Colley MH, Geppert E, Franklin WA: Immunohistochemical detection of steroid receptors in a case of pulmonary lymphangioleiomyomatosis. Am J Surg Pathol 13:803–807, 1989.
132. Berger U, Khaghani A, Pomerance A, et al: Pulmonary lymphangioleiomyomatosis and steroid receptors. An immunocytochemical study. Am J Clin Pathol 93:609–614, 1990
133. Logginidou H, Ao X, Russo I, et al: Frequent estrogen and progesterone receptor immunoreactivity in renal angiomyolipomas from women with pulmonary lymphangioleiomyomatosis. Chest 117:25–30, 2000.
134. Henske EP, Ao X, Short MP, et al: Frequent progesterone receptor immunoreactivity in tuberous sclerosis–associated renal angiomyolipomas. Mod Pathol 11:665–668, 1998.
135. Matsui K, K Reimenschneider W, Hilbert SL, et al: Hyperplasia of type II pneumocytes in pulmonary lymphangioleiomyomatosis. Arch Pathol Lab Med; 124:1642–1648, 2000.
136. Vassallo R, Ryu JH, Schroeder DR, et al: Clinical outcomes of pulmonary Langerhans'-cell histiocytosis in adults. N Engl J Med 346:484–490, 2002.
137. Jeong YJ, Lee KS, Chung MP, et al: Amyloidosis and lymphoproliferative disease in Sjögren syndrome: Thin-section computed tomography findings and histopathologic comparisons. J Comput Assist Tomogr 28:776–781, 2004.
138. Silva CI, Churg A, Muller NL: Hypersensitivity pneumonitis: Spectrum of high-resolution CT and pathologic findings. AJR Am J Roentgenol 188:334–344, 2007.
139. Colombat M, Stern M, Groussard O, et al: Pulmonary cystic disorder related to light chain deposition disease. Am J Respir Crit Care Med 173:777–780, 2006.
140. Aubry MC, Myers JL, Colby TV, et al: Endometrial stromal sarcoma metastatic to the lung: A detailed analysis of 16 patients. Am J Surg Pathol 26:440–449, 2002.
141. Nickerson ML, Warren MB, Toro JR, et al: Mutations in a novel gene lead to kidney tumors, lung wall defects, and benign tumors of the hair follicle in patients with the Birt-Hogg-Dube syndrome. Cancer Cell 2:157–164, 2002.
142. Painter JN, Tapanainen H, Somer M, et al: A 4-bp deletion in the Birt-Hogg-Dube gene (FLCN) causes dominantly inherited spontaneous pneumothorax. Am J Hum Genet 76:522–527, 2005.
143. Chiu HT, Garcia CK: Familial spontaneous pneumothorax. Curr Opin Pulm Med 12:268–272, 2006.
144. Faul JL, Berry GJ, Colby TV, et al: Thoracic lymphangiomas, lymphangiectasis, lymphangiomatosis, and lymphatic dysplasia syndrome. Am J Respir Crit Care Med 161:1037–1046, 2000.
145. Tazelaar HD, Kerr D, Yousem SA, et al: Diffuse pulmonary lymphangiomatosis. Hum Pathol 24:1313–1322, 1993.
146. Swensen SJ, Hartman TE, Mayo JR, et al: Diffuse pulmonary lymphangiomatosis: CT findings. J Comput Assist Tomogr 19:348–352, 1995.
147. Swank DW, Hepper NG, Folkert KE, et al: Intrathoracic lymphangiomatosis mimicking lymphangioleiomyomatosis in a young woman. Mayo Clin Proc 64:1264–1268, 1989.
148. Guinee DG Jr, Feuerstein I, Koss MN, et al: Pulmonary lymphangioleiomyomatosis. Diagnosis based on results of transbronchial biopsy and immunohistochemical studies and correlation with high-resolution computed tomography findings. Arch Pathol Lab Med 118:846–849, 1994.
149. Johnson SR, Tattersfield AE: Treatment and outcome of lymphangioleiomyomatosis in the UK. Am J Respir Crit Care Med 155:A327, 1997.
150. Chen F, Omasa M, Kondo N, et al: Sirolimus treatment for recurrent lymphangioleiomyomatosis after lung transplantation. Ann Thorac Surg 87:e6–e7, 2009.
151. Egan JJ, Remund KF, Corris P: Sirolimus for lymphangioleiomyomatosis lesions. N Engl J Med 358:1963–1964, 2008 [author reply 1964].
152. Morton JM, McLean C, Booth SS, et al: Regression of pulmonary lymphangioleiomyomatosis (PLAM)–associated retroperitoneal angiomyolipoma post–lung transplantation with rapamycin treatment. J Heart Lung Transplant 27:462–465, 2008.
153. Ohara T, Oto T, Miyoshi K, et al: Sirolimus ameliorated post lung transplant chylothorax in lymphangioleiomyomatosis. Ann Thorac Surg 86:e7–e8, 2008.
154. Sugimoto R, Nakao A, Yamane M, et al: Sirolimus amelioration of clinical symptoms of recurrent lymphangioleiomyomatosis after living-donor lobar lung transplantation. J Heart Lung Transplant 27:921–924, 2008.
155. Taille C, Debray MP, Crestani B: Sirolimus treatment for pulmonary lymphangioleiomyomatosis. Ann Intern Med 146:687–688, 2007.
156. Wienecke R, Fackler I, Linsenmaier U, et al: Antitumoral activity of rapamycin in renal angiomyolipoma associated with tuberous sclerosis complex. Am J Kidney Dis 48:e27–e29, 2006.
157. Harari S, Cassandro R, Chiodini J, et al: Effect of a gonadotrophin-releasing hormone analogue on lung function in lymphangioleiomyomatosis. Chest 133:448–454, 2008.
158. de la Fuente J, Paramo C, Roman F, et al: Lymphangioleiomyomatosis: Unsuccessful treatment with luteinizing-hormone-releasing hormone analogues. Eur J Med 2:377–378, 1993.
159. Rossi GA, Balbi B, Oddera S, et al: Response to treatment with an analog of the luteinizing-hormone-releasing hormone in a patient with pulmonary lymphangioleiomyomatosis. Am Rev Respir Dis 143:174–176, 1991.
160. Schiavina M, Contini P, Fabiani A, et al: Efficacy of hormonal manipulation in lymphangioleiomyomatosis. A 20-year-experience in 36 patients. Sarcoidosis Vasc Diffuse Lung Dis 24:39–50, 2007.
161. Cohen MM, Freyer AM, Johnson SR: Pregnancy experiences among women with lymphangioleiomyomatosis. Respir Med 103:766–772, 2009.
162. Maurer J, Almoosa KF, McCormack FX, et al: Complications during pregnancy and childbirth in women with lymphangioleiomyomatosis. Submitted
163. Pollock-BarZiv S, Cohen MM, Downey GP, et al: Air travel in women with lymphangioleiomyomatosis. Thorax 62:176–180, 2007.

163a. Taveira-DaSilva AM, Burstein D, Hathaway OM, et al: Pneumothorax after air travel in lymphangioleiomyomatosis, idiopathic pulmonary fibrosis, and sarcoidosis. Chest 136:655–656, 2009.
164. Steagall WK, Glasgow CG, Hathaway OM, et al: Genetic and morphologic determinants of pneumothorax in lymphangioleiomyomatosis. Am J Physiol Lung Cell Mol Physiol 293:L800–808, 2007.
165. Ryu JH, Doerr CH, Fisher SD, et al: Chylothorax in lymphangioleiomyomatosis. Chest 123:623–627, 2003.
166. Boehler A, Speich R, Russi EW, et al: Lung transplantation for lymphangioleiomyomatosis. N Engl J Med 335:1275–1280, 1996.
167. Karbowniczek M, Astrinidis A, Balsara BR, et al: Recurrent lymphangiomyomatosis after transplantation: Genetic analyses reveal a metastatic mechanism. Am J Respir Crit Care Med 167:976–982, 2003.
168. Bando K, Paradis IL, Keenan RJ, et al: Comparison of outcomes after single and bilateral lung transplantation for obstructive lung disease. J Heart Lung Transplant 14:692–698, 1995.
169. De Luca S, Terrone C, Rossetti SR: Management of renal angiomyolipoma: A report of 53 cases. BJU Int 83:215–218, 1999.
170. Bissler JJ, Kingswood JC: Renal angiomyolipomata. Kid Int 66:924–934, 2004.
171. Johnson SR, Whale CI, Hubbard RB, et al: Survival and disease progression in UK patients with lymphangioleiomyomatosis. Thorax 59:800–803, 2004.
172. Lazor R, Valeyre D, Lacronique J, et al: Low initial KCO predicts rapid FEV_1 decline in pulmonary lymphangioleiomyomatosis. Respir Med 98:536–541, 2004.
173. Johnson SR, Tattersfield AE: Decline in lung function in lymphangioleiomyomatosis: Relation to menopause and progesterone treatment. Am J Respir Crit Care Med 160:628–633, 1999.
174. Matsui K, Beasley MB, Nelson WK, et al: Prognostic significance of pulmonary lymphangioleiomyomatosis histologic score. Am J Surg Pathol 25:479–484, 2001.

CHAPTER 63

PULMONARY ALVEOLAR PROTEINOSIS SYNDROME

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INTRODUCTION

Pulmonary alveolar proteinosis (PAP) is a rare disorder characterized by progressive accumulation of surfactant within pulmonary alveoli resulting in respiratory insufficiency and, in severe cases, respiratory failure.[1–3] Although the pathogenesis of PAP remained an enigma for much of the past 50 years, contributions from basic science, clinical medicine, and translational research and globalization of the PAP research community have taken this fascinating disorder from obscurity to clarity. Results have advanced our understanding of pathogenesis, epidemiology, clinical subtypes, prognosis, and natural history and have led to new methods to diagnose, evaluate, and treat patients (see references 1, 2, and 4–6 for recent reviews).

PAP is a syndrome and not a specific disease. Further, it is most appropriately considered in the larger context of disorders of surfactant homeostasis, which include disorders of surfactant production and disorders of surfactant clearance. The former include pulmonary surfactant metabolic dysfunction (PSMD) disorders, of which known diseases include genetic mutations in genes that encode surfactant proteins or proteins involved in surfactant lipid metabolism.[7] The latter include PAP, which can be divided into primary and

secondary forms depending on whether an underlying disease associated with development of PAP is absent or present, respectively.

Importantly, research on this rare but fascinating syndrome has illuminated the critical role of the cytokine granulocyte-macrophage colony-stimulating factor (GM-CSF) in the pathogenesis of PAP, pulmonary surfactant homeostasis, and immunity. Further, expanding knowledge about the regulatory role of GM-CSF in inflammation and autoimmunity has ushered in new potential treatment approaches to other more common diseases. This chapter provides an overview of the pathogenesis, classification, epidemiology, and clinical aspects of the PAP syndrome, emphasizing progress occurring since the previous edition of this textbook.

PATHOGENESIS

Surfactant Composition and Homeostasis

Surfactant is a complex mixture of 90% phospholipids and 10% surfactant proteins that functions at the air-liquid–alveolar wall interface to reduce surface tension, thereby preventing alveolar collapse. It is produced in type II alveolar epithelial cells, secreted into the alveolar space, and cleared by either recycling or catabolism in type II cells or uptake and catabolism by alveolar macrophages. Surfactant composition, production, and homeostasis are reviewed in detail in Chapter 9. Our current concepts of the mechanisms by which surfactant homeostasis is disrupted in PAP draw heavily on animal models of PAP in which the pathogenesis has been elucidated. These models and subsequent studies in humans have identified GM-CSF as a critical regulator of surfactant homeostasis (Fig. 63-1).

Granulocyte-Macrophage Colony-Stimulating Factor

GM-CSF is a 23-kD glycoprotein cytokine present in serum and tissues that signals via cell surface receptors comprising a GM-CSF–binding, low affinity α chain (CDw116) and a nonbinding, affinity-converting β chain (CD131).[8,9] While neither α nor β chains have intrinsic activities associated with intracellular signaling capabilities,[10] the β chain constitutively binds Janus activating kinase (JAK),[10] a tyrosine kinase involved in cytokine signaling. Ligand binding causes formation of αβJAK2 multimers and activation of JAK2, resulting in phosphorylation of α[11] and β chains, activation of other kinases,[10] and initiation of signaling via multiple pathways,[10,12] including the signal transducer of activation and transcription (STAT)-5.[13]

Murine Models of Disordered Surfactant Homeostasis

The first real clue to the pathogenesis of PAP was the observation that genetically manipulated mice deficient in GM-CSF developed a phenotype with features similar in nearly every respect to the common form of PAP in humans.[14] Detailed studies of these mice revealed that neither production of surfactant by type II cells nor its uptake by alveolar macrophages was altered.[14,15] Rather, the defect was impaired catabolism of surfactant in alveolar macrophages.[16] Further studies showed that pulmonary GM-CSF was critical for regulation of surfactant catabolism in alveolar macrophages,[17,18] and that this pathway was controlled by the transcription factor PU.1.[19] Many other functions of alveolar macrophages were concomitantly regulated by GM-CSF via PU.1,

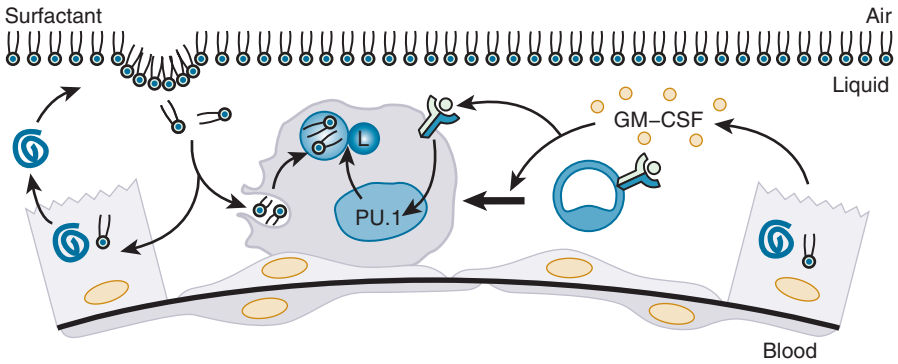

FIGURE 63-1 ■ Schematic of pulmonary surfactant homeostasis within an alveolus of a healthy individual. Surfactant lipids and proteins are synthesized in type II alveolar epithelial cells and secreted into the intra-alveolar space. Extracellular surfactant contributes to the surfactant layer present at the air-liquid-tissue interface, which plays a critical role by reducing surface tension within the alveolus. Surfactant lipids and proteins are removed from the extracellular surfactant by uptake and recycling in type II cells or by uptake and catabolism in alveolar macrophages. Granulocyte-macrophage colony-stimulating factor (GM-CSF), a critical regulator of surfactant catabolism in alveolar macrophages, functions by binding to heterologous receptors on alveolar macrophages and stimulating surfactant catabolism via the transcription factor PU.1. GM-CSF is also critical for stimulating the terminal differentiation of precursors into mature alveolar macrophages.

including cell adhesion; expression of Fc receptors, mannose receptors, and other receptors; phagocytosis; bacterial killing; and Toll-like receptor-4 signaling.[19] The diversity of functions coordinately regulated by GM-CSF via PU.1 indicated that pulmonary GM-CSF is a critical regulator of the terminal differentiation of alveolar macrophages in mice.

Genetically manipulated mice deficient in the β chain of the GM-CSF receptor develop PAP indistinguishable from that of GM-CSF–deficient mice.[20] Transplantation of bone marrow from wild-type mice corrected PAP in GM-CSF receptor–deficient mice, indicating that loss of GM-CSF signaling to myeloid cells (not lung epithelial cells) was the pathogenic lesion resulting in PAP in mice.[21]

Disruption of surfactant homeostasis also occurs in several other mouse models. For example, PAP develops in mice with severe combined immunodeficiency.[22] While the phenotype of this mouse is histologically similar to that of GM-CSF–deficient mice, the mechanism underlying the development of PAP is unknown. Pulmonary surfactant lipidosis occurs in transgenic mice with pulmonary overexpression of either interleukin (IL)-4[23] or IL-13 in airway epithelial cells[24]; however, both these models are phenotypically distinguished from the GM-CSF–deficient mouse by the presence of pulmonary inflammation, which is not a feature in GM-CSF–deficient mice. Surfactant lipid accumulation also occurs in surfactant protein (SP)-D–deficient mice.[25] However, these mice develop significant pulmonary inflammation and emphysema, and thus are phenotypically and mechanistically distinct from GM-CSF–deficient mice.[26] Inhalation of fine particulate silica (silica dioxide) by rodents produces alveolar proteinosis. Thus, silica inhalation serves as a model of secondary PAP (see later).[27]

Genetically modified mice with abnormalities of surfactant production exhibit disordered surfactant homeostasis to varying degrees but have a phenotype that differs markedly from that of GM-CSF knockout mice. For example, mice deficient in SP-B develop respiratory failure immediately after birth. Studies in these mice demonstrated that SP-B is critical to the processing of SP-C precursor protein, the organization of surfactant phospholipids in lamellar bodies, the formation of tubular myelin in the alveolus, the generation of surfactant films capable of reducing surface tension, and lung function during the early postnatal period.[28–30] Expression of mutant SP-C in mice causes a severe interstitial lung disease phenotype[31]; however, it is unclear whether the absence of mature, functional SP-C or the presence of abnormal SP-C is pathologically important for the development of this phenotype. Genetically modified mice deficient in ABCA3, a member of the ATP-binding cassette (ABC) transporter protein family expressed in alveolar type II cells, die from respiratory failure immediately after birth.[32] Studies in these mice have revealed that ABCA3 is a lipid transporter critical to lamellar body formation, and pulmonary surfactant biogenesis.[33] The phenotype of these murine is histologically, biochemically, and clinically distinct from that of GM-CSF–deficient or GM-CSF receptor–deficient mice.

Genetically modified mice deficient in ABCG1, a transmembrane protein, mediate cellular efflux of cholesterol, accumulate cholesterol in alveolar macrophages and type II cells, and develop pulmonary lipidosis, suggesting that ABCG1 is important in surfactant homeostasis.[34] In alveolar macrophages from both GM-CSF–deficient mice and patients with autoimmune PAP, impaired GM-CSF signaling results in reduced expression of ABCG1, and increased expression of a related family member, ABCA1, which is involved in cellular lipid efflux.[35]

Historical Overview of Human Disorders of Surfactant Homeostasis

PAP was initially described by Rosen in 1958 as a disorder characterized by the alveolar accumulation of lipoproteinaceous material, comprised of primarily phospholipids, a smaller amount of protein, and minimal amounts of carbohydrate.[36] The accumulated material was quickly identified as pulmonary surfactant, and a therapeutic approach was devised to remove the excess material by saline lung lavage. Notwithstanding, for 3 decades, it was unclear if the mechanism of surfactant accumulation in PAP involved an abnormality in production or clearance of surfactant. The rarity and heterogeneous nature of the syndrome probably contributed to the difficulty in establishing its pathogenesis. For example, the syndrome was associated with heavy silica inhalation, various hematologic disorders, and infections. However, in most cases, it occurred as an idiopathic disorder in previously healthy individuals with no obvious exposures other than smoking.

In 1976, Golde and colleagues reported that alveolar macrophages from PAP patients had excessive lipid accumulation, giant lysosomes, and impaired adhesion, chemotaxis, microbial killing, and survival.[37] The morphologic abnormalities were reproduced in normal monocyte-derived macrophages cultured with the proteinaceous lavage material from a PAP patient, suggesting that the lung macrophages were defective as a consequence of an abnormal pulmonary environment.

In 1981, Wasserman's group reported that both PAP patient serum and lung lavage fluid contained a substance that inhibited the growth of mononuclear cells in response to mitogens, and that the inhibiting substance did not appear to be immunoglobulin.[38] In 1987, Muller-Quernheim and associates identified a 40-kD protein found in the lavage fluid with macrophage-inhibiting effects.[39] Shortly thereafter, bronchoalveolar lavage (BAL) was reported to improve alveolar macrophage function in PAP. In 1996, prompted by the discovery of PAP in GM-CSF knockout mice, Seymour and colleagues reported that GM-CSF administration resulted in clinical improvement in one individual with idiopathic PAP.[40] Neither this individual nor any other humans have been identified to date as having GM-CSF deficiency,[41] and patients with idiopathic PAP were found to express GM-CSF normally.

In 1999, Nakata's group reported the presence of high levels of polyclonal, neutralizing immunoglobulin

G (IgG) autoantibodies in patients with idiopathic PAP.[42] This was a second important clue about the pathogenesis of PAP that has stimulated research in many areas, including pathogenesis, diagnosis, and therapy of PAP.

The first report of a genetic disturbance of surfactant homeostasis was the report of a PAP-like disease of unknown cause occurring in four siblings in 1981.[43] Subsequently, mutations in the genes encoding SP-B,[44] SP-C,[45] and ABCA3[7] (*SFTPB, SFTPC,* and *ABCA3,* respectively) have been reported to cause a spectrum of lung disease in humans, including variable degrees of disruption of surfactant homeostasis.

Dirksen and coworkers reported PAP in four cases in association with the absence of detectable GM-CSF receptor β chain on peripheral blood monocytes,[46] of which PAP was confirmed in three and SP-C mutation in one. Using biomarkers identified by studies in mice, a familial form of PAP caused by mutations in the gene encoding the GM-CSF receptor α chain (*CSF2RA*) was recently reported.[47]

Role of GM-CSF Autoantibodies

In 1999, Nakata's group identified the presence of neutralizing GM-CSF autoantibodies in the BAL fluid and serum of individuals with idiopathic PAP.[42,48] Subsequently, multiple studies confirmed the presence of GM-CSF autoantibodies with idiopathic PAP but not in secondary PAP, other lung diseases, PSMD disorders, or healthy individuals (Fig. 63-2).[1-3,49,50] GM-CSF autoantibodies are composed of IgG, predominantly of the IgG1, and IgG2 subclasses; are highly specific for GM-CSF; have a very high binding affinity (20 ± 7.5 pM); and are capable of neutralizing GM-CSF at levels up to many thousands times higher than the physiologic concentrations of GM-CSF in vivo.[49] Based on the available evidence, GM-CSF autoantibodies are presumed to be important in the pathogenesis of idiopathic PAP. Published reports have not established a causal role or even that GM-CSF autoantibodies affect alveolar macrophage function (Fig. 63-3). Supporting their potential role in pathogenesis, GM-CSF autoantibodies have been reported to impair neutrophil functions in humans and mice.[51] Endogenous neutrophil functions are impaired in patients with idiopathic PAP and GM-CSF–deficient mice in a remarkably similar pattern (Fig. 63-4). These results have shown that GM-CSF autoantibodies regulate neutrophil functions and suggest that a similar mechanism of control by GM-CSF may be present in humans and mice.

Serum GM-CSF autoantibodies are useful in diagnosis of idiopathic PAP, but levels do not correlate with disease severity,[50] casting doubt about their role in pathogenesis. Further, GM-CSF autoantibodies were detected in 4 of 1258 apparently healthy individuals in one report.[52] In another study, non-neutralizing autoantibodies were detected in 38 patients and neutralizing autoantibodies were detected in 3 of 425 patients with autoimmune diseases without evidence of PAP. The estimated concentrations of total GM-CSF autoantibodies in these latter three patients were 2.9, 8.6, and 17.3 μg/mL.[53] In contrast, the concentration of GM-CSF autoantibodies in 158 patients with idiopathic PAP was 113 ± 7 μg/mL,[1,49] while levels were less than 1 μg/mL in patients with secondary PAP, PSMD disorders, or other lung diseases.[1] GM-CSF autoantibodies are also the dominant anticytokine activity in pharmaceutical immunoglobulin, which is prepared from healthy individuals. Using improved detection methods, GM-CSF autoantibodies were demonstrated in all of 72 healthy individuals with no prior exposure to GM-CSF, albeit at low level (median [interquartile range] = 1.04 [0.63 to 1.7] μg/mL serum).[54] In this study, serum levels of endogenous GM-CSF autoantibodies in healthy individuals correlated inversely with endogenous, unstimulated neutrophil function (phagocytosis), suggesting they may play a physiologic role in healthy individuals. GM-CSF autoantibodies may also scavenge free GM-CSF in blood and tissues because serum GM-CSF concentrations were recently found to be much higher than previously reported, and more than 99% was bound to GM-CSF autoantibodies in healthy individuals and PAP patients.[54]

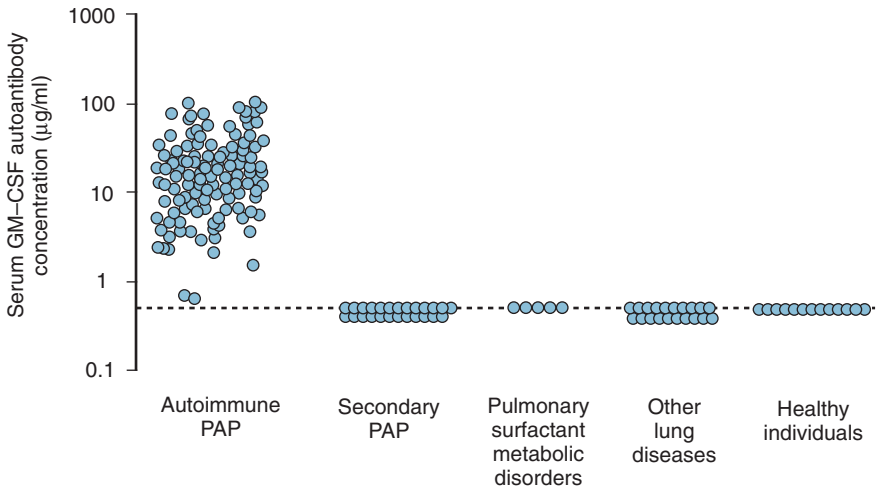

FIGURE 63-2 ■ Serum GM-CSF autoantibody levels in individuals with autoimmune PAP (n = 223), secondary PAP (n = 33), pulmonary surfactant metabolic dysfunction (n = 5), other lung diseases (n = 24), and in healthy controls (n = 13). The detection limit of the assay was 0.5 μg/mL of serum. (Some of these data were reported in Inoue et al.[3])

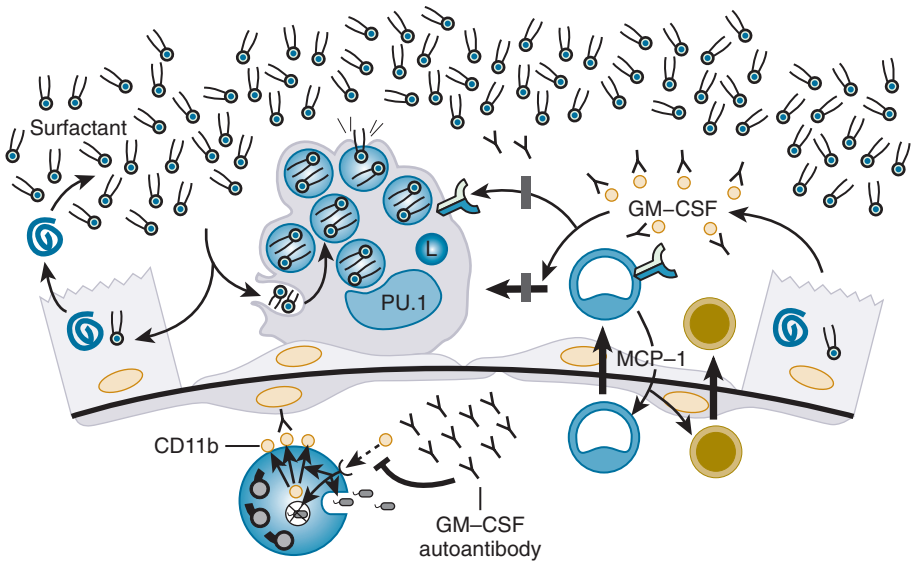

FIGURE 63-3 ■ Schematic of the pathogenic mechanism of autoimmune PAP. High levels of neutralizing GM-CSF autoantibodies bind to GM-CSF, eliminating its bioactivity in vivo. In the absence of GM-CSF, surfactant production continues, as does uptake into alveolar macrophages. However, in the absence of GM-CSF stimulation, levels of the transcription factor PU.1 fall within alveolar macrophages. Without PU.1, alveolar macrophages do not terminally differentiate and are unable to catabolize surfactant. With uptake proceeding and catabolism impaired, alveolar macrophages become engorged with surfactant-filled vesicles, which probably contributes to their dysfunction. Impaired pulmonary clearance of surfactant ensues, eventually leading to impaired gas transfer across the alveolar epithelium. GM-CSF autoantibodies also impair GM-CSF signaling to other cells (e.g., circulating neutrophils), thus impairing their innate immune and other GM-CSF–dependent functions.

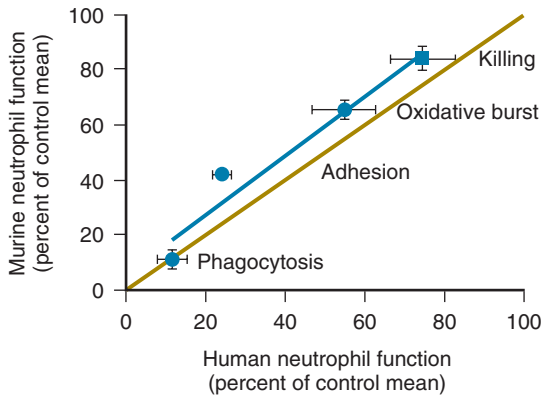

FIGURE 63-4 ■ Similarity of impairment of various corresponding neutrophil functions in GM-CSF–deficient mice and patients with autoimmune PAP. The *brown line* indicates equal impairment. The *blue line* indicates the similarity between the impairment in corresponding mouse and human functions (correlation coefficient = 0.94). (Redrawn from Uchida K, Beck DC, Yamamoto T, et al: GM-CSF autoantibodies and neutrophil dysfunction in pulmonary alveolar proteinosis. N Engl J Med 356:567–579, 2007.)

The apparent discrepancy between the high diagnostic utility of GM-CSF autoantibodies and a lack of correlation between their serum concentration and lung disease severity was reconciled by the hypothesis of a critical threshold level of GM-CSF autoantibodies necessary to reduce GM-CSF bioactivity to a level that impairs myeloid cell functions.[53] This value was calculated from published data to fall between 8 and 22 μg/mL[53] and determined experimentally to be between 10.7 and 19 μg/mL.[54] Together, published reports strongly suggest but do not prove that GM-CSF autoantibodies mediate the manifestations of patients with idiopathic PAP by impairing the functional ability of alveolar macrophages to catabolize surfactant lipids and proteins. Results also show that GM-CSF autoantibodies negatively regulate the basal functions of circulating neutrophils.

Genetic Factors

PAP has been reported in association with the absence of detectable GM-CSF receptor β protein on circulating leukocytes in four children,[46] and in one individual with sequence polymorphism in the gene (*CSF2RB*) encoding this receptor that causes a single amino acid change (isoleucine to threonine) at position 117 of the mature protein.[41] However, these studies did not definitively establish GM-CSF receptor β chain abnormalities as the cause of PAP. Recently, two studies reported PAP in association with abnormalities in the gene encoding the GM-CSF receptor α chain (*CSF2RA*).[47] In one report, biochemical, genetic, and molecular studies demonstrated that a point mutation causing a single, nonconservative amino acid change (glycine to arginine) at position 174 of the mature protein was the cause of reduced GM-CSF signaling in myeloid cells.[47] The defect was reproduced by cloning and expression of the abnormal complementary DNA in cultured cells. In the other study, bone marrow transplantation was successful in treating PAP. However, this patient succumbed to infection 4 months after transplantation. The absence or abnormalities of the GM-CSF receptor resulted in high

serum levels of GM-CSF. This appears to be a useful biomarker of GM-CSF receptor dysfunction, because screening of 122 previously collected serum samples from PAP patients who were negative for GM-CSF autoantibody revealed the presence of 5 cases with elevated GM-CSF levels and GM-CSF receptor α chain mutations.[55] Thus, the combination of an elevated serum GM-CSF level and the absence of detectable GM-CSF autoantibody in a child with PAP may indicate the presence of a GM-CSF receptor defect.

Mutations in three genes of the surfactant synthetic pathway, *SFTPB, SFTPC,* and *ABCA3,* disrupt surfactant production and function and cause respiratory disease in neonates, children, and older individuals.[56–59] SP-B and SP-C are hydrophobic peptides that reside within the surfactant phospholipid layer, which functions to reduce surface tension at the alveolar wall–liquid-air interface,[30] whereas ABCA3 likely transports lipids, including phosphatidylcholine, cholesterol, sphingomyelin, and phosphatidylglycerol, into lamellar bodies in alveolar type II cells where the surfactant complex is assembled, processed, and stored.

SFTPB is a relatively small gene (9.7 kb) encoding a 79–amino acid, hydrophobic protein. Infants homozygous for recessive loss-of-function mutations in *SFTPB* develop respiratory failure and die shortly after birth.[44,60] In contrast, individuals heterozygous for SP-B deficiency alleles have normal lung function.[61] More than 30 mutations have been identified to date in less than 100 infants with SP-B deficiency.[59,62] Two thirds have an insertional frameshift mutation caused by the replacement of a single nucleotide by three nucleotides at codon 121 (designated 121ins2). Among infants with SP-B deficiency, approximately 60% are homozygous for the 121ins2 mutation, 25% are heterozygous for this and another function-altering allele, and 15% have other mutations. SP-B deficiency is associated with the aberrant processing and secretion of an immature SP-C peptide, which may contribute to the respiratory failure associated with hereditary SP-B deficiency.[63]

SFTPC is also a small gene (3 kb) encoding a 35–amino acid hydrophobic protein. Known mutations in *SFTPC* are expressed in a dominant fashion and are associated with interstitial lung disease in neonates, children, and adults.[45,59,64–66] Twenty-five percent of individuals with SP-C–associated lung disease have a point mutation in *SFTPC* causing the substitution of threonine for isoleucine at codon 73 (I73T).[64] Immunohistochemical analysis of lung tissue from an infant with the I73T mutation demonstrated normal staining patterns for pro–SP-B, SP-B, and pro–SP-C. Although infants with this mutation can present with respiratory distress syndrome, most children with the mutation become symptomatic with interstitial lung disease beyond the newborn period.[64,67]

ABCA3 is a large gene (80 kb) encoding a 1704–amino acid protein. Autosomal recessive mutations in *ABCA3* can result in fatal surfactant deficiency in neonates[7,68] and chronic respiratory insufficiency in older children.[69] Function-altering mutations in *ABCA3* result in surfactant that is deficient in phosphatidylcholine and has decreased function, suggesting that ABCA3 has an important role in pulmonary surfactant phospholipid homeostasis.[70] A relatively common missense point mutation in *ABCA3* causing the substitution of a valine for glutamic acid at codon 292 (E292V) is associated with chronic interstitial lung disease in older children who are heterozygous for this and a different function-altering mutation on the other *ABCA3* allele.[69]

While disorders arising from function-altering mutations in *SP-B, SP-C,* and *ABCA3* disrupt surfactant homeostasis to varying degrees, they are easily distinguished from PAP by their surfactant dysfunction, disruption of alveolar wall architecture, and clinical course. Although sometimes referred to as congenital forms of PAP in the medical literature, these disorders are considered as distinct from PAP. In keeping with this concept, the term *pulmonary surfactant metabolic dysfunction disorders* has been proposed for this group of genetic disorders.

Disease Associations

PAP or PAP-like lung diseases have been reported in association with other medical conditions believed to cause PAP. In such cases, the lung disease is commonly referred to as "secondary PAP."[1,2] Systemic disorders associated with PAP include malignant and other hematologic diseases, nonhematologic malignancies, immune deficiency syndromes, chronic inflammatory syndromes, and chronic infections (Table 63-1). Chronic myelogenous leukemia and myelodysplastic syndrome are the most frequently reported hematologic disorders associated with PAP.[2,71–73] In one single-institution study, PAP occurred in 5.3% of patients with hematologic malignancies, and in 8.8% of those who were neutropenic.[72] Among 10 such patients, 5 had acute myeloid leukemia, 4 had chronic myelogenous leukemia, and 1 had acute lymphocytic leukemia. Of potential pathogenic importance, nine of these patients were neutropenic when they developed PAP, three had undergone bone marrow transplantation, and in most, PAP recovered spontaneously with recovery of bone marrow. In another report, a patient with acute lymphoid leukemia developed PAP during a period of neutropenia that resolved after treatment with granulocyte colony-stimulating factor.[74] A different study reported PAP in three patients with acute myeloid leukemia with GM-CSF receptor abnormalities, including reduced levels of the β chain (three of three) and undetectable α chain (two of three).[75]

Secondary PAP has been reported in the context of systemic disorders associated with various forms of immunodeficiency, including thymic alymphoplasia,[76] immunoglobulin A deficiency,[77] solid organ transplantation,[78] and acquired immunodeficiency syndrome.[79]

Although the mechanism(s) responsible for secondary PAP are poorly studied, two common themes emerge when the data are considered together. Medical conditions that reduce either the numbers or functions of myeloid cells may impair pulmonary clearance of surfactant by effects on alveolar macrophage numbers or function (i.e., surfactant catabolism). A reduction in either could alter the capacity of the alveolar macro-

TABLE 63-1. Underlying Systemic Disorders Reported in Association with PAP Syndrome

Disease Category/Underlying Disease	Reference
HEMATOLOGIC DISORDERS	72
Acute lymphocytic leukemia	74
Acute myeloid leukemia	75
Aplastic anemia	131
Chronic lymphocytic leukemia	132
Chronic myeloid leukemia	133
Myelodysplastic syndromes	73
Multiple myeloma	134
Lymphoma	71
Waldenstrom's macroglobulinemia	135
NONHEMATOLOGIC MALIGNANCIES	
Adenocarcinoma	136
Glioblastoma	136
Melanoma	137
IMMUNE DEFICIENCY AND CHRONIC INFLAMMATORY SYNDROMES	
Acquired immunodeficiency syndrome	138
Amyloidosis	139
Fanconi's syndrome	131
Agammaglobulinemia	140
Juvenile dermatomyositis	141
Renal tubular acidosis	142
Severe combined immunodeficiency disease	143
CHRONIC INFECTIONS	
Cytomegalovirus	144
Mycobacterium tuberculosis	145
Nocardia	146
Pneumocystis jirovecii (formerly *carinii*)	147

TABLE 63-2. Pulmonary Exposures Reported to Be Associated with PAP Syndrome

Exposure Category/Agent	Reference
DUSTS (INORGANIC)	
Aluminum	83, 84
Cement	148
Silica	80, 81
Titanium	85
ORGANIC DUSTS	
Agricultural	149
Bakery flower	80
Fertilizer	80
Sawdust	36
FUMES	
Chlorine	80
Cleaning products	80
Gasoline/petroleum	80
Nitrogen dioxide	150
Paint	85
Synthetic plastic fumes	80
Varnish	80

phage pool to clear surfactant from the lung surface. Further studies will be required to determine if this is, in fact, the case.

Environmental Factors

PAP or PAP-like lung disease has also been reported in association with varying degrees of inhalation exposure to environmental factors, including cigarette smoke, a wide variety of organic and inorganic dusts, and fumes and gases (Table 63-2). Epidemiologic studies (see later) have shown that PAP occurs more often in individuals who smoke. Reports linking PAP to other environmental exposures comprise case reports and small retrospective series, and in general, have not established a causal relationship between the exposure and development of PAP. Five of the 27 original patients reported by Rosen and colleagues had been exposed to wood dust.[36]

An early report on 138 PAP patients in one series found that about half had significant exposure to dust and fumes, of which the most common exposure was to inhaled silica, occurring in 10 individuals.[80] With the advent of occupational protective equipment in the workplace, this form of "acute silicoproteinosis"[81,82] is rare. Other case reports have documented the association of PAP with exposure to aluminum dust,[83] cellulose fibers, cement dust, titanium dioxide,[84,85] and nitrogen dioxide. In support of the link between silica and PAP are studies in rats demonstrating that inhalation of silica particles disrupts surfactant homeostasis, resulting in increased surfactant accumulation.[27,86] Further research is needed to determine what role, if any, environmental inhalation exposure plays in the pathogenesis of PAP.

Mechanisms of Disruption of Surfactant Homeostasis

In mice, a series of observations have established GM-CSF as a critical regulator of pulmonary surfactant homeostasis, including the following: (1) surfactant homeostasis requires the presence of GM-CSF in the lung, and PAP develops in the absence of either pulmonary GM-CSF or its receptor; (2) surfactant accumulation in GM-CSF–deficient mice is caused by decreased catabolism by alveolar macrophages, and not an increase in surfactant production; (3) pulmonary GM-CSF is required for normal expression of transcription factor PU.1 in alveolar macrophages, and enforced (i.e., retroviral-mediated) expression of PU.1 restores surfactant catabolism in alveolar macrophages from GM-CSF knockout mice; and (4) surfactant homeostasis can be restored in GM-CSF receptor β–deficient mice by transplantation of bone marrow from a wild-type mouse.

In humans, the pathogenesis is less clear, but recent studies support a similar role for GM-CSF as a critical

regulator of pulmonary surfactant homeostasis. These findings include the following: (1) high levels of GM-CSF autoantibodies are strongly and specifically associated with PAP; (2) GM-CSF autoantibodies are capable of neutralizing vastly more GM-CSF than is present physiologically; (3) in PAP patients, PU.1 expression is reduced in alveolar macrophages and increased by GM-CSF therapy; (4) interruption of GM-CSF signaling by function-altering mutations in the *CSF2RA* gene encoding the GM-CSF receptor α chain disrupt surfactant homeostasis and result in lung histopathology indistinguishable from that of GM-CSF knockout mice and idiopathic PAP in humans; (5) reduced expression of GM-CSF receptor β on leukocytes is associated with PAP in children and with development of PAP in leukemia patients; and (6) various disorders that transiently reduce the number and/or functions of myeloid cells are temporally related to the development and resolution of secondary PAP in humans. Importantly, a recent study involving passive transfer of highly purified GM-CSF autoantibodies into healthy nonhuman primates reproduced the typical pathologic findings of PAP, thus supporting the role of GM-CSF autoantibodies in the pathogenesis of PAP and the role of GM-CSF in surfactant homeostasis in primates.[87]

Available evidence suggests that GM-CSF regulates myeloid cell functions similarly in humans and mice. GM-CSF knockout mice and idiopathic PAP patients have remarkable similarity in (1) pulmonary histopathologic appearance of the lung; (2) cytologic and ultrastructural appearance of alveolar macrophages; (3) elevation of certain cytokines (monocyte chemotactic protein-1, macrophage colony-stimulating factor); (4) the pattern of differential impairment of various neutrophil functions; and (5) the increased occurrence of pulmonary and extrathoracic secondary infections.

A primary mechanism of PAP is the disruption of GM-CSF signaling to alveolar macrophages, either by the absence of GM-CSF (observed in mice, but not yet in humans), disruption of GM-CSF signaling by mutations in the GM-CSF receptor proteins (in mice and humans), or an autoimmune attack targeted at GM-CSF that neutralizes GM-CSF, eliminating GM-CSF bioactivity and myeloid cell stimulation in vivo (in humans and nonhuman primates) (see Fig. 63-3). GM-CSF, via PU.1, regulates catabolism of surfactant in alveolar macrophages (in mice and possibly humans). Surfactant accumulation in PAP is due to reduced clearance (in mice, and likely in PAP associated with GM-CSF autoantibodies or GM-CSF receptor defects in humans). However, the precise mechanism of this control is unknown. Since pulmonary surfactant is internalized into macrophages by endocytosis and catabolized in phagolysosomes, it is possible that interruption of GM-CSF signaling blocks the translocation of endocytosed surfactant to lysosomes. Such a mechanism has been demonstrated for adenovirus internalized by macrophages from GM-CSF–deficient mice, in which PU.1 redirects adenovirus-containing endosomes to lysosomes for destruction. Alternatively, GM-CSF deficiency may result in a key enzyme deficiency. Potentially supporting this possibility are data related to the peroxisome proliferator–activated receptor-γ (PPAR-γ), a ligand-activated transcription factor regulating genes involved in lipid metabolism and other pathways.[88] PPAR-γ messenger RNA and protein are expressed in alveolar macrophages in healthy individuals, decreased in PAP patients, and increased by GM-CSF therapy of PAP patients.[89] CD36, a lipid scavenger receptor regulated by PPAR-γ, is regulated in a similar pattern. However, PPAR-γ deficiency has been noted in several other disorders, including sarcoidosis, acute respiratory distress syndrome, and asthma, where there have been reports of surfactant abnormalities.[90] Further studies are required to determine the mechanism by which interruption of GM-CSF signaling leads to reduced catabolism of surfactant by alveolar macrophages.

Secondary mechanisms of PAP, although less well supported by experimental data, appear to involve a decrease in either the numbers or functions of myeloid cells, including alveolar macrophages. Such abnormalities are expected to decrease the capacity of the remaining alveolar macrophage population to clear pulmonary surfactant, resulting in its accumulation. This model is supported by the temporal relationship of the onset and resolution of PAP with the occurrence and resolution of myeloid cell suppression in hematologic disorders. Other secondary mechanisms of PAP—for example, due to inhalation of toxic fumes and dusts—are less clear. Presumably, they would involve a reduction in the ability of alveolar macrophages to clear surfactant. However, since overexpression of certain cytokines (IL-4, IL-13), or decreased expression of some surfactant proteins (SP-D) also increases surfactant production in mice, other potential mechanisms appear possible.

Mechanisms of PSMD involve mutations in genes of the surfactant synthetic pathway, including *SFTPB, SFTPC, ABCA3,* and likely others, and result in the production of biochemically and functionally abnormal surfactant. These disorders have a lung histopathology and clinical course that is markedly different from PAP caused by interruption of GM-CSF signaling. Further, the pathophysiology arises from surfactant deficiency rather than surfactant excess as in PAP. Thus, it seems appropriate to consider these disorders as distinct from PAP and not part of a spectrum of PAP.

NOMENCLATURE AND CLASSIFICATION

In the 50 years since PAP was first described as a lung disease "that consists of the filling of the alveoli by a PAS-positive proteinaceous material, rich in lipid,"[36] it has become recognized as a syndrome caused by various distinct diseases,[1] and is reported in the medical literature using numerous terms, resulting in a nomenclature that is redundant, inconsistent, and confusing. Terms have been based on the biochemical characteristics of the accumulated material (e.g., alveolar proteinosis, phospholipidosis), pathogenesis (e.g., silicoproteinosis, idiopathic), disease category (e.g., primary vs. secondary), and timing of symptom onset (e.g., congenital, acquired), and are redundant (e.g., idiopathic PAP, acquired PAP, pulmonary alveolar lipoproteinosis,

TABLE 63-3. Classification of Diseases Associated with Disruption of Surfactant Homeostasis

CLINICAL CATEGORY/DISEASE
Primary PAP
GM-CSF autoimmunity
CSF2RA dysfunction
CSF2RB dysfunction
GM-CSF mutations (mice)
Secondary PAP
Hematologic disease
Nonhematologic malignancy
Immune deficiency syndromes
Chronic inflammatory syndromes
Chronic infections
Pulmonary Surfactant Metabolic Dysfunction Disorders
SP-B deficiency
SP-C mutations
ABCA3 mutations

phospholipoproteinosis, alveolar lipoproteinosis, alveolar proteinosis, alveolar phospholipidosis, and alveolar lipophosphoproteinosis). Confusion arises from use of the same term for different diseases. For example, the term *congenital PAP* is used for the disease caused by mutations in *SFTPB* that is uniformly fatal at birth and caused by surfactant deficiency, and also for the disease caused by GM-CSF receptor deficiency that presents in children, is caused by surfactant accumulation, and can be treated successfully.

The foregoing discussion underscores the need for a classification and nomenclature that will facilitate clear communication about disorders of homeostasis necessary for clinical training, disease management, and research. Based on initial discussions of a global task force assembled by the Rare Lung Diseases Consortium, a simplified classified scheme is proposed (Table 63-3).

Disorders of surfactant homeostasis are separated into disorders of reduced clearance (PAP) or abnormal production (PSMD). PAP is further subdivided into primary and secondary categories, depending whether it is due to a primary disturbance of GM-CSF signaling or secondary to another disease, respectively. Primary PAP is composed of several specific disease mechanisms: an autoimmune disease caused by GM-CSF autoantibodies (autoimmune PAP), or one of several genetic diseases caused by mutations in *CSF2RA* or *CSFR2B.* A third disease, caused by GM-CSF deficiency, occurs in mice and is predicted but not yet observed in humans. Secondary PAP arises in association with several disease categories, including hematologic disorders, malignancy, immune deficiency syndromes, chronic inflammatory disorders, and chronic infections (see Table 63-1), and in association with certain inhalation exposures, especially silica (sandblasters) (see Table 63-2). PSMD disorders are those arising from mutations in genes of the surfactant synthesis pathway, including *SFTPB, SFTPC, ABCA3,* and likely others that have yet to be identified.[57] These disorders are included in a new classification of interstitial lung disease in young children.[91]

The plethora of terms used to report on the PAP syndrome are not recommended for continued use and should be replaced with the term *pulmonary alveolar proteinosis.* Terms referring to clinical presentation (i.e., acquired PAP, congenital PAP) should not be used when the underlying disease is known. For example, "SP-B deficiency" is far more informative than "congenital PAP," and more consistent with its pathogenesis as a disorder of surfactant deficiency (PSMD) rather than excessive surfactant accumulation (PAP). When the cause in unknown, the term *unclassified PAP* is preferred over "idiopathic PAP" because the latter is currently understood to be the disorder associated with high levels of GM-CSF autoantibodies.

EPIDEMIOLOGY

Disorders of surfactant homeostasis are found in worldwide distribution but are quite rare. Since the initial description of PAP, approximately 650 to 700 separate cases of PAP[2–4,36,46,47,92] and substantially fewer cases of PSMD[7,45,56–59,64,69,93–95] have been reported in the medical literature. A comprehensive meta-analysis of 410 separate cases of PAP representing all clinical subtypes and most or all cases of PAP reported in the medical literature through 1998 found that patients were more likely to be male (male:female ratio = 2.65:1.0), and that males predominated among smokers (male:female ratio = 2.78:1.0) but not among nonsmokers (male:female ratio = 0.69:1.0).[2] These results suggested that the high proportion of males among PAP patients may be explained by their higher frequency of tobacco use. This study also found the median age at diagnosis to be 39 years (39 in men and 35 in women). In a smaller study based on ethnic clustering in Israel, the incidence and prevalence of PAP were estimated to be 0.36 and 3.7 per million, respectively.[96] However, this report included only 15 cases, of which one was a PSMD disorder and others appear to be cases of primary and secondary PAP. More recent evaluations have refined these estimates for individual diseases. Consequently, the epidemiology of each is considered individually.

A large national, multicenter, registry-based study of PAP was recently conducted in Japan and identified 223 patients with autoimmune PAP.[3] This study reported a male predominance (male:female ratio = 2.1:1.0), and that males predominated among smokers (male:female ratio = 9.3:1.0) but not among nonsmokers (male:female ratio = 0.6:1.0).[3] The median age at the time of diagnosis was 53 years (52 in men and 55 in women). The prevalence was similar in nine non-overlapping geographic regions encompassing the entirety of Japan, and the case rate correlated closely with the regional population size. This result suggests the absence of an effect of climate on the prevalence. Further supporting this, PAP occurs in a worldwide distribution. An intensive screening

within the Niigata prefecture in Japan (population 2.41 million) estimated the incidence and prevalence of autoimmune PAP to be 0.49 ± 0.13 and 6.2 per million, respectively.[3] This registry found that, among noncongenital cases of PAP, 89.9% of cases were autoimmune, 9.7% were secondary, and 0.4% were unclassified.

Familial PAP caused by genetic mutations in the *CSF2RA* gene was recently reported in two female children ages 6 and 8.[47] The disease was suspected based on a series of biomarkers, including an elevated serum SP-D concentration and increased serum and lung lavage GM-CSF concentrations, and confirmed by biochemical, molecular, and genetic studies and by reproduction of the GM-CSF receptor signaling defect. Since this report, five other children ages 2 to 11 years old have been identified with PAP and genetic defects in the GM-CSF receptor α chain gene. Further, PAP has been associated with abnormalities in the GM-CSF receptor β chain.[41,46]

Secondary PAP accounts for approximately 10% of PAP in adults,[2,3] and occurs as a consequence of an underlying disease (see Table 63-1) or environmental exposure (see Table 63-2). Thus, the prevalence of secondary PAP is estimated to be approximately 0.34 per 100,000 individuals in the general population. The most common cause of secondary PAP is hematologic malignancy, in which PAP is reported to occur in up to 5.3 % of cases.[72] The occurrence of secondary PAP is a function of the underlying clinical condition and, in some cases, can resolve with successful treatment of the underlying disorder.

PSMD disorders occur in individuals with mutations in the genes involved in surfactant synthesis: *SFTPB, SFTPC,* and *ABCA3,* as discussed earlier. The incidence of SP-B deficiency is estimated to be approximately 1 per 1.5 million births. Among infants with respiratory distress syndrome of unknown etiology, mutations appear more commonly in *ABCA3* than in *SFTPB.*[57] The prevalence of the common disease-associated mutations in the *SFTPB* (121ins2), *SFTPC* (I73T), and *ABCA3* (E292V) genes are not well established. However, a recent study in ethnically diverse cohorts from Missouri, Norway, South Korea, and South Africa (n = 420) found the population-based frequencies of these mutations to be rare (<0.4%). Further, E292V was present in 3.8% of newborns with respiratory distress syndrome, suggesting it imparts an increased genetic risk for this syndrome.[56]

CLINICAL PRESENTATION

Autoimmune PAP typically presents as progressive dyspnea of insidious onset unless secondary infection is also present, in which case fever, cough, and rarely hemoptysis may also be present. The frequency of various symptoms was recently evaluated in a large contemporaneous cohort in Japan (Table 63-4). This nonspecific presentation may lead to months or years of misdiagnosis as "asthma" or "chronic bronchitis." The symptoms are frequently milder than expected from the radiographic findings, which should raise the suspicion of PAP. The physical examination is nonspecific.

TABLE 63-4. Frequency of Symptoms among Patients with Autoimmune PAP*

Symptom	Frequency (%)
Dyspnea	54
Cough	23
Sputum	4
Other	4
None (asymptomatic)	31

*Data for a contemporaneous group composed of 220 patients.
From Inoue Y, Trapnell BC, Tazawa R, et al: Characteristics of a large cohort of autoimmune pulmonary alveolar proteinosis patients in Japan. Am J Respir Crit Care Med 177:752–762, 2008.

Although lung examination is frequently normal despite a grossly abnormal chest radiograph, when findings are present, basilar crackles are most common. Cyanosis is seen in severe cases, while clubbing, hemoptysis, and fever are rare. Importantly, in the national PAP registry cohort in Japan, 31% of patients with obvious radiologic manifestations were asymptomatic.[3]

Familial PAP due to mutations in the GM-CSF receptor genes presented as progressive dyspnea in one of two sisters (age 6 years), while the other sister (age 8 years) was asymptomatic.[47] Others with this disease have presented with dyspnea of insidious onset. Thus, while this disease is newly described, very rare, and poorly studied, it appears quite similar to autoimmune PAP, except that it occurs in children instead of primarily in adults.

Secondary PAP usually arises in an individual with an underlying systemic disorder such as a hematologic malignancy/disease.[71,72,74,92,97,98] It can occur in the context of neutropenia or myeloid cell dysfunction related to the underlying disorder and can resolve with successful treatment of the underlying disorder.

PSMD disorders can present as a spectrum of lung disease ranging from respiratory distress syndrome in neonates and infants to interstitial lung disease in children, adolescents, and adults, depending on the exact nature of the underlying genetic mutations. SP-B deficiency typically presents as respiratory distress immediately after birth.[44,67,99] *ABCA3* mutations can result in fatal respiratory distress syndrome in neonates and interstitial lung disease in infants, children, and adolescents.[7,69,95,100] SP-C mutations can present as interstitial lung disease in children and adults.[45,59,65,66,94]

EVALUATION AND DIFFERENTIAL DIAGNOSIS

Radiographic Appearance

The chest radiograph in autoimmune and secondary PAP classically reveals patchy bilateral air space disease similar in appearance to that of pulmonary edema but without the other radiographic signs of left heart failure.[36,101] Occasionally, other patterns occur, including

mixed alveolar, interstitial, or nodular infiltrates, and asymmetrical or focal abnormalities. Effusions, adenopathy, and cardiomegaly are not features. The chest radiograph in familial PAP is similar except that the disease occurs in children, and it may be normal in mild cases.[47] The diagnostic value of the plain chest radiograph is limited by its lack of specificity.

Conventional 7- to 10-mm collimation chest computed tomography (CT) scans demonstrate bilateral areas of consolidation with poorly defined margins (Fig. 63-5).[102,103] High-resolution chest CT is superior to both conventional CT and chest radiography in the assessment of the pattern and distribution of abnormalities and may demonstrate lesions even when the radiograph is normal. The distribution of disease is variable and may reflect heterogeneity of underlying disease resulting in PAP. Several patterns are noteworthy. Areas of ground-glass opacification (GGO) often have sharply defined straight and angulated margins, giving them a "geographic" appearance. The sharp margination usually reflects lobular or lobar boundaries. A pattern of fine overlapping lines forming 3- to 10-mm polygonal shapes occurs in the majority of cases. Superimposition of these two patterns gives an appearance that has been described as "crazy paving," which is characteristic but not diagnostic of PAP.[104] In an ongoing study within the Japanese national PAP registry, autoimmune PAP was found to more commonly have a geographic appearance with crazy paving compared to secondary PAP.[104a]

Findings on the chest radiograph and high-resolution chest CT correlate with a restrictive ventilatory defect, reduced diffusing capacity, and hypoxemia.[103] Recently, a quantitative algorithm was reported permitting quantitative assessment of longitudinal changes in GGO, lung weight, and gas volume in patients with PAP.[105]

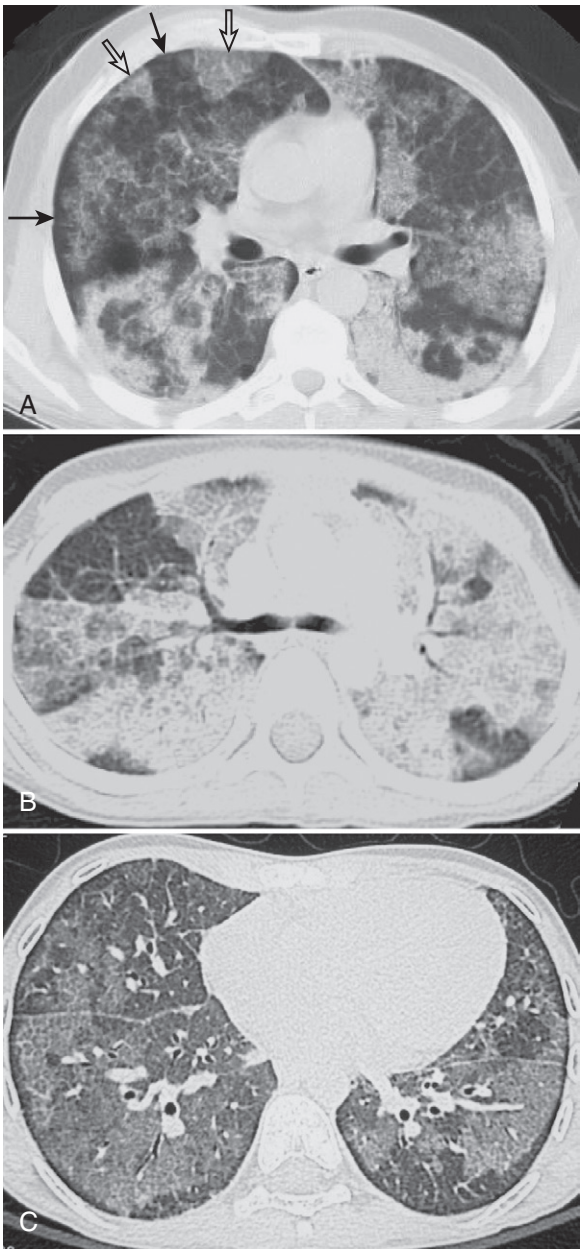

FIGURE 63-5 ■ Computed tomography of the chest illustrating differences in the radiographic appearance of the lungs in autoimmune PAP **(A),** familial GM-CSF receptor (alpha-chain) dysfunction **(B),** and secondary PAP in a child with lysinuric protein intolerance **(C).** Note the juxtaposition of highly abnormal secondary lobules (*open arrows*), adjacent to more normal-appearing secondary lobules (*solid arrows*). This is referred to as a "geographic" pattern and is common in autoimmune PAP, and also present in familial PAP due to GM-CSF receptor dysfunction. Infiltrates that are more homogeneous and less geographic are more common in secondary PAP **(C).**

Pulmonary Function Testing

The results of pulmonary function testing can be normal, but commonly show a restrictive ventilatory defect with mild impairment of the forced vital capacity and total lung capacity, and a disproportionate, severe reduction of the diffusing capacity for carbon monoxide.[2,3] Patients are typically mildly hypoxemic, with an elevated alveolar-arterial P_{O_2} difference and compensated respiratory alkalosis. The shunt fraction is elevated, compared to patients with other diffuse lung diseases.[106]

Bronchoscopy, Bronchoalveolar Lavage, and Transbronchial Biopsy

Bronchoscopic airway examination is typically unremarkable in PAP, and specimens are usually sent to assess the presence of infection or concomitant lung disease. In contrast, BAL specimens usually reveal characteristic gross, cytopathologic, and biochemical findings that are highly suggestive or diagnostic of PAP. In autoimmune, familial, and secondary clinical forms of PAP, the BAL fluid has a "milky" or "waxy" appearance, and upon standing forms sediment (Fig. 63-6). Cytologic examination of Papanicolaou-stained specimens reveal the BAL fluid to comprise granular, acellular, eosinophilic lipoproteinaceous material[107] and the sediment to contain fat globules. The most striking observation from a cytospin preparation or cell blocks of the BAL sediment is the gross appearance of the alveolar macrophage. These

FIGURE 63-6 ■ Gross appearance of the whole-lung lavage fluid from a patient with autoimmune PAP demonstrating the "milky" appearance and dense sediment (*right*) compared to normal saline (*left*). The lavage fluid was allowed to settle overnight in the refrigerator.

cells are enlarged and engorged with lipid material with a foamy, vacuolated appearance under light microscopy (Fig. 63-7). Electron microscopic examination of the sediment reveals the presence of tubular myelin, lamellar bodies, and fused membrane structures characteristic of pulmonary surfactant. The BAL cell differential in autoimmune PAP may be normal or reveal the presence of increased pulmonary lymphocytes composed of increased numbers of $CD4^+$ and $CD8^+$ cells.[108]

Biochemical analysis of BAL fluid reveals increased amounts of phospholipids and proteins, similar in composition to that of surfactant from healthy individuals.[109] Surfactant proteins are variably increased in the BAL fluid in PAP. This accumulated material in PAP has surface-active properties similar to those of normal pulmonary surfactant.

Surgical Lung Biopsy

Macroscopically, the cut surface of lung biopsy specimens in autoimmune and familial PAP reveals a geographic pattern of 2- to 3-cm grayish-yellow regions of firm consolidation that exudes fatty material. Microscopically, alveoli and terminal airways are filled with a fine eosinophilic material (Fig. 63-8) that stains strongly for

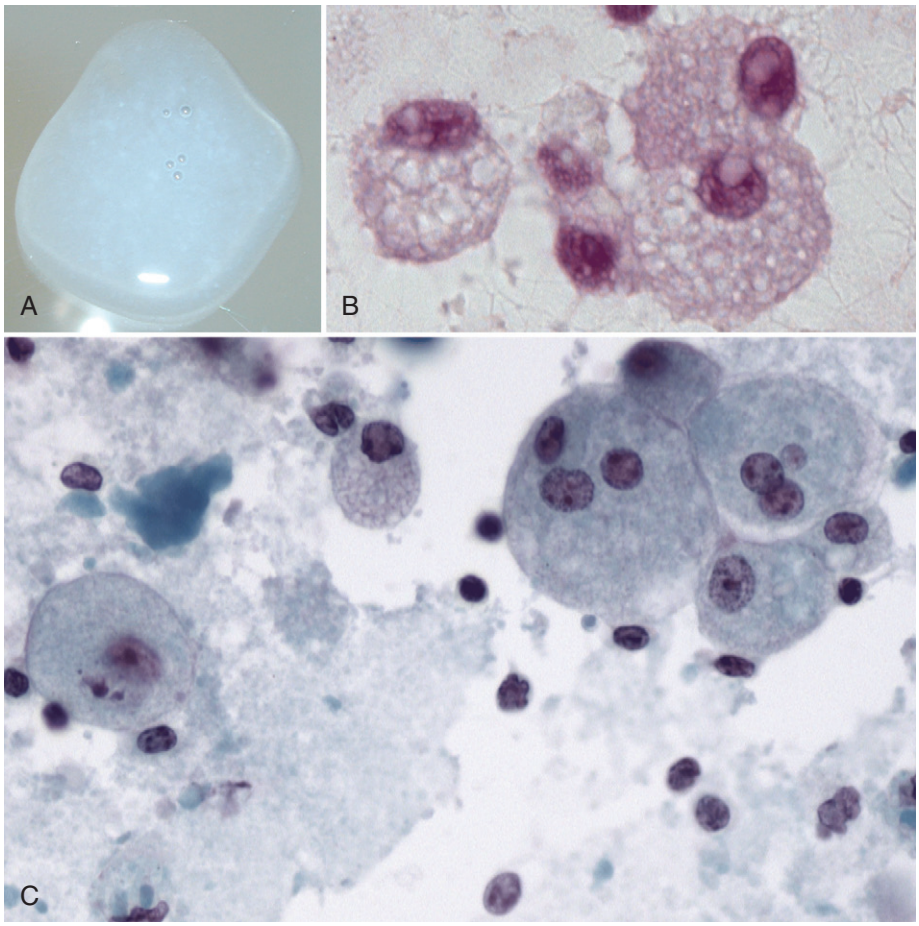

FIGURE 63-7 ■ Appearance of the sputum in autoimmune PAP. **A,** Gross appearance of freshly expectorated sputum from an afebrile patient. **B,** Sputum smear after staining with periodic acid–Schiff reagent. **C,** Sputum smear after staining with Papanicolaou reagent. Note the appearance of very large, foamy-appearing alveolar macrophages in **B** and **C**.

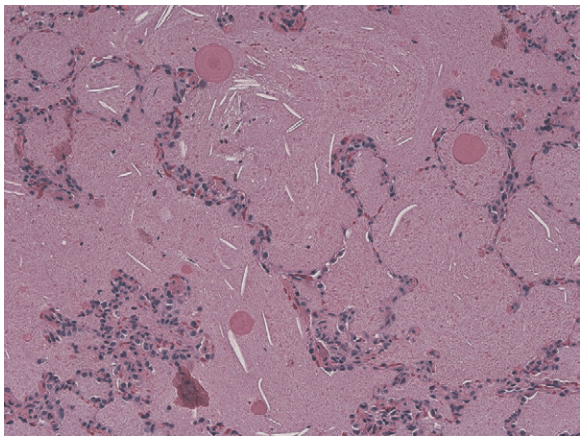

FIGURE 63-8 ■ Histopathologic appearance of the lung in autoimmune PAP. An open-lung biopsy was obtained from a patient with autoimmune PAP. The alveoli are completely filled with amorphous, acellular eosinophilic material contains cholesterol clefts and occasional eosinophilic bodies. The alveolar architecture is well preserved, and the alveolar walls are essentially unremarkable.

surfactant proteins (Fig. 63-9) with periodic acid–Schiff reagent (see Fig. 63-6). The alveolar wall and interstitial architecture are relatively well preserved, but lymphocyte infiltration and, occasionally, fibrosis can be seen. The vasculature appears normal. Electron microscopy, which is seldom necessary, reveals characteristic, concentrically laminated surfactant structures (lamellar body inclusions) within the granular material and in alveolar macrophages.[110]

Laboratory Studies

Routine laboratory studies are usually normal in PAP. Serum lactate dehydrogenase is typically elevated in proportion to lung disease severity, although this finding is nonspecific.[2,106] Serum levels of SP-A, SP-B, SP-D, C-reactive protein, and Krebs von den Lungen protein-6 (KL-6), a mucin-like protein secreted by alveolar epithelium, are increased in PAP and correlate with lung disease severity.[3,50,111] However, all of these biomarkers can be elevated in other lung diseases.[112,113] Thus, while not very helpful in establishing a diagnosis, these biomarkers may be useful in monitoring disease activity in patients with PAP.

In contrast to routine laboratory tests, several disease-specific biomarkers derived from clinical and basic research studies have emerged as useful tests for establishing the diagnosis of PAP as well as the clinical subtype. A high serum level of GM-CSF autoantibodies is helpful for establishing a diagnosis of autoimmune PAP, for which the sensitivity and specificity are reported to approach 100%.[114] Serum values above 3 μg/mL using a polyclonal standard,[1,51,54,114,115] or 0.5 μg/mL using a recently developed monoclonal standard,[116] are diagnostic of autoimmune PAP. Serial dilution is a useful but less well standardized method for titrating abnormal levels. The CD11b stimulation index is a measure of the ability of exogenous GM-CSF to bind to GM-CSF receptors on

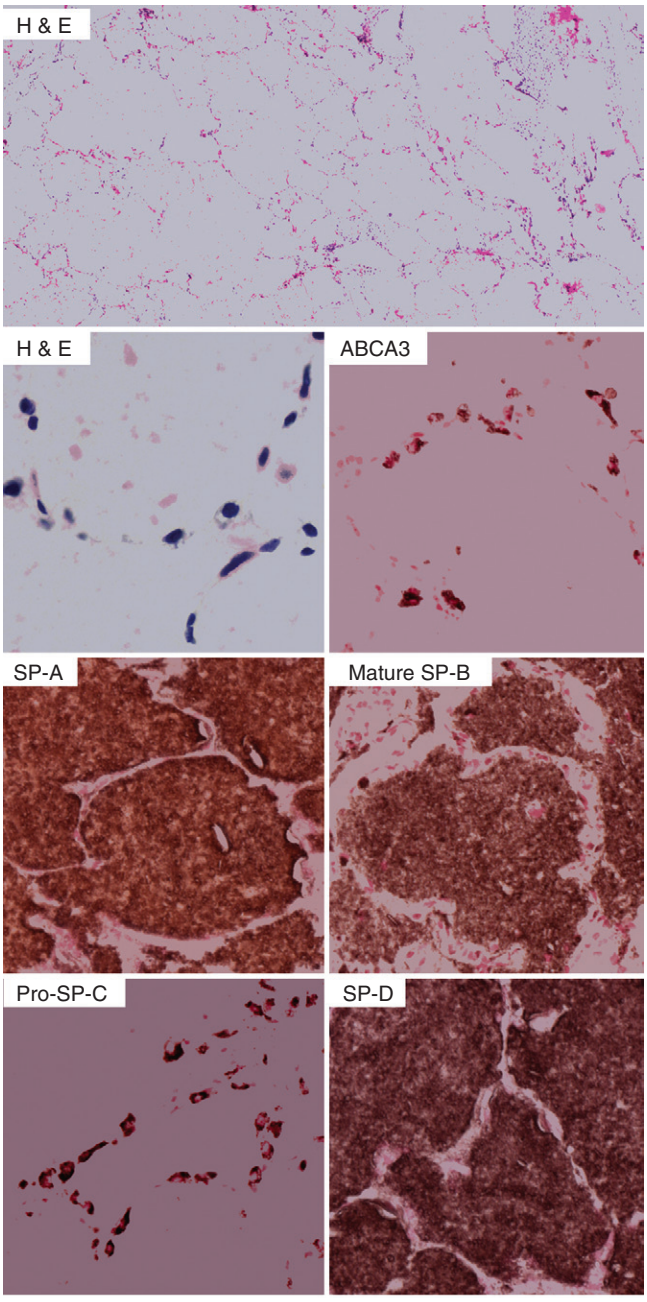

FIGURE 63-9 ■ Histopathologic appearance of the lung in familial PAP caused by function-altering mutations in the *CSF2RA* gene. An open-lung biopsy was obtained and stained with hematoxylin and eosin (H&E), or immunostained for ABCA3, SP-A, mature SP-B, pro–SP-C, or SP-D as indicated. Note the lymphocytosis in the low-powered H&E-stained section. (Data from Suzuki T, Sakagami T, Rubin BK, et al: Familial pulmonary alveolar proteinosis caused by mutations in *CSF2RA*. J Exp Med 205:2703–2710, 2008.)

neutrophils in fresh whole blood and increase the level of the cell surface CD11b.[51] In healthy individuals, the CD11b level rapidly increases at low concentrations of GM-CSF, whereas in patients with autoimmune PAP, the response is blunted or absent due to the presence of neutralizing GM-CSF autoantibodies. In familial PAP patients, who do not have GM-CSF autoantibodies, this test is also abnormal due to genetically impaired GM-CSF

receptor function.[47] In familial PAP, GM-CSF levels are elevated in serum and lung lavage, likely caused by the absence of receptor-mediated clearance.[47] These values range from 40 to 80 in serum and 400 to 1500 in lung lavage fluid.[47]

Approach to Diagnosis

The diagnosis of PAP should be suspected on the basis of a history of dyspnea of insidious onset with or without other symptoms and characteristic radiologic findings on high-resolution CT of the chest. Pulmonary function testing may be helpful if the disease is moderate or severe, but is normal in many patients.[3] In the context of these findings, a elevated serum GM-CSF autoantibody level is sufficient to establish the diagnosis of autoimmune PAP in previously healthy adult patients without other intercurrent illness or significant pulmonary exposures. Bronchoscopy with cytologic analysis of the BAL fluid is helpful and is further supported by transbronchial biopsy findings typical of PAP.[4,92] In many such cases, an open-lung biopsy is not necessary. However, if the diagnosis is still unclear or if secondary PAP is suspected, an open-lung biopsy may be needed. In such cases, it is important to rule out disorders that have radiologic, cytologic, or pathologic features similar to PAP.

In neonatal and pediatric cases of suspected disorders of surfactant homeostasis, it is important to establish if PAP or one of the PSMD disorders is present. The timing and severity of the presentation are helpful. Familial PAP can present between the ages of 1 and 11 years, while SP-B deficiency presents at birth, ABCA3 dysfunction presents over a wide range from neonates to adolescents, and SP-C dysfunction appears to present in children and adults. In familial PAP, the CD11b stimulation index and serum GM-CSF level will be abnormal. In the PSMD disorders, a lung biopsy is frequently needed. Genetic studies are generally a useful part of the workup of pediatric cases.

The diagnostic workup of individuals with disorders of surfactant homeostasis, including PAP and PSMD disorders, consists of routine clinical evaluations, a series of biomarker evaluations, and genetic tests capable of distinguishing among autoimmune PAP, secondary PAP, familial PAP caused by receptor dysfunction, and PSMD disorders (Fig. 63-10).

NATURAL HISTORY

The natural history of PAP has not been well studied. However, the clinical course of autoimmune PAP follows three distinct patterns: progressive deterioration, stable disease, or spontaneous resolution.[2] In Seymour and Presneill's comprehensive meta-analysis of PAP, the actuarial survival rates for 343 patients with acquired PAP were 78% ± 8% at 2 years, 75% ± 8% at 5 years, and 68% ± 9% at 10 years. More than 80% of the deaths attributable to PAP during a 5-year observation period occurred during the first 12 months after diagnosis. This study reported that, of the 69 deaths, death was caused by respiratory failure from PAP in 47 patients (72%), uncontrolled infection in 13 (20%), and unrelated causes in 5 cases (8%). A recent contemporaneous cohort of 223 autoimmune PAP patients reported no deaths over the 5-year period of the study, although it was not designed to report longitudinal results.[3]

Secondary Infections

Multiple studies have reported an unexpectedly increased incidence of secondary infections in patients with PAP.[2] Microbial pathogens include those commonly seen in community- and hospital-acquired infections but more commonly involve *Nocardia* spp. or opportunistic organisms.[2] However, such an increased risk of infections in PAP is controversial and supported by some[51] but not other[3,4] recent reports. GM-CSF–deficient mice also have increased mortality from infection and increased susceptibility to a wide variety of microbial pathogens, including bacteria, fungi, and mycobacteria. Further, myeloid cells from both patients with autoimmune PAP and GM-CSF–deficient mice have defects in innate immune functions, including phagocytosis, generation of reactive oxygen species, inflammatory signaling, and bacterial killing.[19,51,54,114,117] In both GM-CSF–deficient mice and PAP patients, infections can occur in the lungs and at extrathoracic locations, consistent with a systemic immune defect.

Pulmonary Fibrosis

Pulmonary fibrosis has been reported in association with PAP and has been reproduced in animal models of exposure to inhaled silica.[27,110] Further, exposure to oxygen or repeated whole-lung lavage have been suggested as potentially contributing to fibrosis. However, while not adequately studied, "end-stage lung disease" or irreversible scarring of the lung is rarely associated with PAP.

Spontaneous Resolution

Spontaneous improvement was reported to occur in cases of PAP in the initial description[36] and subsequent case series, although documentation is generally poor. In a comprehensive meta-analysis of 303 patients for whom adequate information was available, spontaneous improvement occurred in 24 (7.9%).

TREATMENT

Various therapeutic strategies have been proposed for PAP since its initial description (reviewed in the previous edition of this book). Whole-lung lavage emerged early, underwent multiple refinements to improve therapeutic efficiency, and has served as the standard therapy for nearly 5 decades. More recently, based on an understanding of the importance of GM-CSF in surfactant homeostasis and of neutralizing GM-CSF autoantibodies in the pathogenesis of the common form of PAP, new

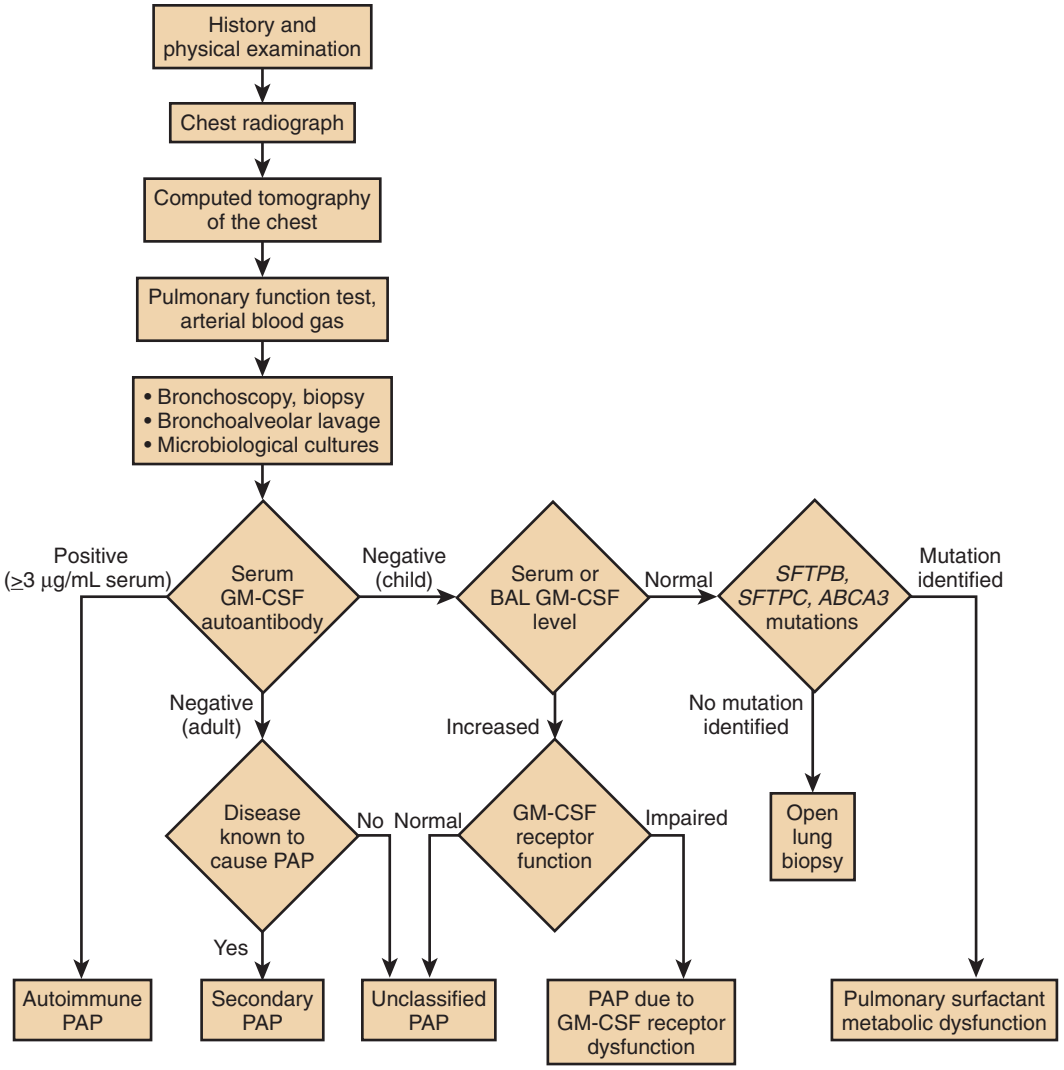

FIGURE 63-10 ■ Diagnostic algorithm for evaluation for individuals with PAP syndrome. In hereditary PAP caused by mutations in GM-CSF receptor genes *CSF2RA* or *CSF2RB,* further GM-CSF receptor function tests are needed to confirm and identify the specific nature of the defect. See text for details.

therapeutic strategies based on pathogenic mechanisms have emerged, including GM-CSF augmentation, plasmapheresis, and anti–B lymphocyte therapy.

Autoimmune PAP

Whole-Lung Lavage

Originally developed by Ramirez in the early 1960s, currently, whole-lung lavage is a procedure performed under general anesthesia in which large volumes (up to 50 L) of saline are infused into each lung to physically "wash out" the accumulated surfactant lipids and proteins while mechanical ventilation is provided to the other lung.[118–120] A number of procedural variations have been introduced, including the use of mechanical chest percussion, prone positioning, variation in the volume of infusate, and use of a hyperbaric chamber. Despite changes, whole-lung lavage has not been standardized with respect to the method (i.e., volume infused, use of mechanical percussion, the end point of an individual lavage procedure), indications for its use, methods for evaluating the treatment effectiveness, or timing of repeated procedures. The end point used clinically for terminating lung lavage in the operating room is a improvement in visual clearing of the lavage effluent. No studies have systematically evaluated the procedure, its utilization in clinical practice, or the efficacy or durability of clinical responses. Notwithstanding, it is widely held among practitioners to improve symptoms, radiographic findings, and gas exchange in PAP patients.[121,122]

Although safe in the vast majority of individuals, complications can include hypoxemia, pneumonia, sepsis, hydropneumothorax, and acute respiratory distress syndrome. The procedure is not performed in a patient with an active bacterial lung infection, since this can result in sepsis and shock. Bronchoscopic segmental or lobar lavage has been proposed as a safe alternative in patients in whom whole-lung lavage under general anesthesia is considered risky due to severe hypoxemia.[123]

TABLE 63-5. Therapeutic Response to Whole-Lung Lavage Therapy of Adults with PAP

Parameter	*n*	Mean Change ± SD	95% CI of the Mean	*P* Value*
Arterial P_{O_2} (mm Hg)	41	20.1 ± 14.3	15.6 to 24.6	<0.0001
(A − a)P_{O_2} (mm Hg)	21	−30.6 ± 18.0	−38.8 to −22.4	<0.0001
FEV_1 (L)	33	0.26 ± 0.47	0.09 to 0.42	<0.0034
VC (L)	40	0.50 ± 0.54	0.33 to 0.67	<0.0001
$D_{L_{CO}}$ (mL/mm Hg per minute)	25	4.4 ± 4.5	2.6 to 6.3	<0.0001

*Value is for the comparison of paired postlavage to prelavage data for individual patients for each parameter for only those patients with available data using a two-sample *t*-test.
(A − a)P_{O_2}, alveolar-arterial difference in oxygen tension; CI, confidence interval; $D_{L_{CO}}$, diffusing capacity of carbon monoxide; FEV_1, forced expiratory volume in 1 second; PAP, pulmonary alveolar proteinosis; VC, vital capacity.
From Seymour JF, Presneill JJ: Pulmonary alveolar proteinosis: progress in the first 44 years. Am J Respir Crit Care Med 166:215–235, 2002.

Other alternatives include performance in a hyperbaric chamber,[124] and use of complete cardiopulmonary bypass.[125]

A comprehensive literature review identified 231 individuals for whom sufficient whole-lung lavage data were available, and reported that lavage was associated with increased overall 5-year survival (94 ± 2% with lavage [n = 146] versus 85 ± 5% without lavage [n = 85]; P = 0.04).[2] This study also reported that the median number of whole-lung lavage procedures performed was two, and that 70% of patients underwent the procedure within 5 years of diagnosis. Among 55 individuals undergoing the procedure, the median duration of benefit was 15 months, and only 20% of patients remained free of recurrence at 3 years. Among 41 patients with adequate available data, arterial P_{O_2} improved by 20.1 mm Hg after whole-lung lavage (Table 63-5). The improvement in other pulmonary function test parameters was less impressive. More than 95% of patients respond to whole-lung lavage; however, a small fraction of patients did not respond despite aggressive lavage. Treatment-related improvement results from the physical removal of the accumulated surfactant and can occur within hours of completion of therapy.

In practice, the indications for whole-lung lavage therapy include dyspnea, exercise intolerance, and a desire to reduce the requirement for supplemental oxygen therapy. Reasonable indications for performing the procedure may include dyspnea limiting activities of daily living, arterial P_{O_2} less than 60 mm Hg while breathing room air, and a shunt fraction greater than 10% to 12%.

Granulocyte-Macrophage Colony-Stimulating Factor

Successful GM-CSF therapy of PAP was first demonstrated in a single patient in 1995.[40] GM-CSF was administered in subcutaneous daily doses of up to 6 μg/kg/day and resulted in reduction of the alveolar-arterial oxygen gradient and improved exercise tolerance within 35 days. Relapse occurred on discontinuance, but the treatment effects were restored on reinstitution of therapy. An international, multicenter follow-up study in 14 autoimmune PAP patients who received GM-CSF by subcutaneous injection in escalating doses (5 to 20 μg/kg/day) over a 3-month period reported an overall response rate of 43%.[126] A subsequent study in 21 autoimmune PAP patients receiving GM-CSF by subcutaneous administration in escalating doses (5 to 18 μg/kg/day) for 6 to 12 months reported an overall response rate of 48% as defined by a 10 mm Hg or greater improvement in room air arterial P_{O_2}.[127] Several single cases of subcutaneous GM-CSF therapy of PAP have reported similar findings. In aggregate, these results indicate that (1) subcutaneous GM-CSF therapy of autoimmune PAP results in objective improvement in about 50% of patients, (2) the therapeutic response is variable among patients, (3) the therapeutic response depends on the dose and duration of treatment, and (4) a lag of about 8 weeks occurs before a therapeutic response is seen. Although controversial, some but not all studies have reported that GM-CSF therapy is associated with a fall in the GM-CSF autoantibody level.

Several case reports and a recently completed larger study have evaluated aerosolized GM-CSF therapy of autoimmune PAP.[128] These studies have evaluated daily inhaled doses of GM-CSF ranging from 125 to 500 μg per patient per day. One recently completed study in 35 autoimmune PAP patients evaluated aerosolized GM-CSF given as induction therapy (250 μg on days 1 to 8 of 14, ×6 cycles) followed by maintenance therapy (125 μg on days 1 to 4 of 14, ×6 cycles). This study excluded patients who improved spontaneously during an initial observation period and thus only evaluated patients with unremitting/progressive disease. The overall response rate was 69%. Results suggested a somewhat higher clinical response rate for aerosol compared to subcutaneous GM-CSF administration. Further, while both routes appeared to be safe, local site reactions and other minor problems occurred in 85% of patients receiving subcutaneous GM-CSF, while no treatment-related side effects have been noted with inhaled GM-CSF.

Other Approaches

Other therapeutic strategies that have been tried in a few patients include plasmapheresis and B-lymphocyte depletion, both of which target the reduction in the level of GM-CSF autoantibodies. No conclusions can yet be drawn about the utility of such theoretically attractive

clinical therapeutic strategies. Lung transplantation has been performed successfully in a 41-year-old patient with PAP (probably autoimmune PAP), but the disease recurred 3 years later.[129]

Familial PAP

Whole-lung lavage and bone marrow transplantation have both been used successfully in familial PAP caused by *CSF2RA* mutations. Further work is needed to determine the safety of the latter, theoretically attractive approach.

Secondary PAP

Secondary PAP, in some cases caused by hematologic disorders, can resolve with resolution of the underlying disorder. Nonresolving secondary PAP can be effectively treated with whole-lung lavage. However, this has not been well studied.

Surfactant Metabolic Dysfunction Disorders

Therapy of these disorders depends on the disease and presentation; care is generally supportive and includes assessment of need for supplemental oxygen and nutritional support. In very young children, whole-lung lavage is extremely challenging and of uncertain efficacy, and an adapted technical approach to airway management is required during lavage.[130] Neonates may show transient improvement with exogenous surfactant administration. Lung transplantation is particularly considered in cases of SP-B deficiency and in severe and progressive disease from *ABCA3* mutations.

GAPS IN KNOWLEDGE AND FUTURE DIRECTIONS

Etiology

While our knowledge of the pathogenesis of the common form of PAP has improved substantially, its etiology remains obscure. Further, while it has been established that GM-CSF, via PU.1, is critical for surfactant homeostasis in humans and that GM-CSF autoantibodies mediate the pathogenesis of autoimmune PAP, the precise mechanism by which loss of GM-CSF signaling reduces surfactant catabolism in alveolar macrophages is not clear. Finally, the immunopathology of autoimmune PAP, while of particular interest, is largely unexplored.

In contrast, secondary PAP is less well studied in terms of pathogenesis, but in some cases, the etiology (i.e., loss of alveolar macrophages in hematologic disorders and after chemotherapy) is more clear. The extreme rarity of this disorder makes its study difficult.

The etiology of familial PAP is clear (i.e., genetic mutations in *CSFR2A*). However, the pathogenesis beyond the loss of GM-CSF signaling is unclear.

Surfactant metabolic dysfunction disorders are clear with respect to etiology, and continue to provide important information regarding surfactant production and processing.

Clinical Practice Guidelines

There are no standardized clinical practice guidelines for pulmonary alveolar proteinosis. While whole-lung lavage has been in use for nearly 5 decades, no studies have prospectively evaluated the indications for, timing of, or methods to monitor outcomes of the procedure. Nor has the procedure itself been standardized with respect to volume of infusate, use of mechanical percussion, hyperbaric oxygen, position or repositioning of the patient during the procedure, or objective methods for terminating the procedure. The Rare Lung Diseases Consortium has recently assembled a task force to address this unmet need and is developing a clinical consensus document.

Novel Therapeutic Approaches

Results of clinical trials show that inhaled GM-CSF in patients with autoimmune PAP is safe and effective. Current results show that the treatment effect is dependent on the dose and duration of therapy. However, existing results have not defined the optimal dose, timing, or duration of administration, which could potentially improve the current response rate. The mechanism of the therapeutic effect is also unclear with respect to lowering GM-CSF autoantibody levels. Further research is needed to evaluate other therapies, including plasmapheresis, anti–B lymphocyte therapy, and combination therapies. Examples of the latter include combining whole-lung lavage with aerosolized GM-CSF to reduce time to clearing and combining plasmapheresis and anti–B lymphocyte therapy to deplete GM-CSF autoantibodies.

Conclusion

PAP is a rare syndrome characterized by the accumulation of surfactant in the lungs and a variable clinical course ranging from respiratory failure to spontaneous improvement. It occurs in association with various disorders, but 90% of cases are caused by the presence of increased levels of neutralizing autoantibodies that block GM-CSF signaling to myeloid cells in vivo. The name of this common clinical form of PAP has been recommended to be changed to “autoimmune” in recognition of the new understanding of its pathogenesis. A new genetic disease, familial PAP, has been identified and has implicated GM-CSF as critical regulator of human surfactant homeostasis. A number of biomarkers have been developed to diagnose and manage individuals with various clinical forms of PAP. Current therapy with whole-lung lavage is effective in most patients with autoimmune and familial PAP. GM-CSF treatment of autoimmune PAP shows promise as safe and effective therapy, yet further clinical trials are needed to optimize the therapy.

KEY POINTS

- PAP is a rare syndrome with a prevalence of 6 to 7 per million in the general population that occurs in men, women, and children and in all ethnic backgrounds.
- Ninety percent of cases of PAP occur in individuals with high levels of GM-CSF autoantibodies, which eliminate GM-CSF bioactivity and presumably impair surfactant catabolism by alveolar macrophages. Nine percent to 10% of cases occur in individuals with an underlying disease associated with PAP that is presumed to impair surfactant catabolism in resident alveolar macrophages by reducing their number or functions.
- New diagnostic biomarkers are helpful in the differential diagnosis of clinical subtypes of PAP and pulmonary surfactant metabolic dysfunction disorders.
- Inhaled recombinant GM-CSF is a promising new pharmacologic approach that appears to be effective in individuals with autoimmune PAP.

References

1. Trapnell BC, Whitsett JA, Nakata K: Pulmonary alveolar proteinosis. N Engl J Med 349:2527–2539, 2003.
2. Seymour JF, Presneill JJ: Pulmonary alveolar proteinosis: Progress in the first 44 years. Am J Respir Crit Care Med 166:215–235, 2002.
3. Inoue Y, Trapnell BC, Tazawa R, et al: Characteristics of a large cohort of autoimmune pulmonary alveolar proteinosis patients in Japan. Am J Respir Crit Care Med 177:752–762, 2008.
4. Goldstein LS, Kavuru MS, Curtis-McCarthy P, et al: Pulmonary alveolar proteinosis: Clinical features and outcomes. Chest 114:1357–1362, 1998.
5. Shah PL, Hansell D, Lawson PR, et al: Pulmonary alveolar proteinosis: Clinical aspects and current concepts on pathogenesis. Thorax 55:67–77, 2000.
6. Venkateshiah SB, Thomassen MJ, Kavuru MS: Pulmonary alveolar proteinosis: Clinical manifestations and optimal treatment strategies. Treat Respir Med 3:217–227, 2004.
7. Shulenin S, Nogee LM, Annilo T, et al: *ABCA3* gene mutations in newborns with fatal surfactant deficiency. N Engl J Med 350:1296–1303, 2004.
8. Gearing DP, King JA, Gough NM, Nicola NA: Expression cloning of a receptor for human granulocyte-macrophage colony-stimulating factor. EMBO J 8:3667–3676, 1989.
9. Hayashida K, Kitamura T, Gorman DM, et al: Molecular cloning of a second subunit of the receptor for human granulocyte-macrophage colony-stimulating factor (GM-CSF): Reconstitution of a high-affinity GM-CSF receptor. Proc Natl Acad Sci U S A 87:9655–9659, 1990.
10. D'Andrea RJ, Gonda TJ: A model for assembly and activation of the GM-CSF, IL-3 and IL-5 receptors: Insights from activated mutants of the common beta subunit. Exp Hematol 28:231–243, 2000.
11. Matsuguchi T, Zhao Y, Lilly MB, Kraft AS: The cytoplasmic domain of granulocyte-macrophage colony-stimulating factor (GM-CSF) receptor alpha subunit is essential for both GM-CSF-mediated growth and differentiation. J Biol Chem 272:17450–17459, 1997.
12. Watanabe S, Itoh T, Arai K: Roles of JAK kinases in human GM-CSF receptor signal transduction. J Allergy Clin Immunol 98:S183–S191, 1996.
13. Lehtonen A, Matikainen S, Miettinen M, Julkunen I: Granulocyte-macrophage colony-stimulating factor (GM-CSF)-induced STAT5 activation and target-gene expression during human monocyte/macrophage differentiation. J Leukoc Biol 71:511–519, 2002.
14. Dranoff G, Crawford AD, Sadelain M, et al: Involvement of granulocyte-macrophage colony-stimulating factor in pulmonary homeostasis. Science 264:713–716, 1994.
15. Ikegami M, Ueda T, Hull W, et al: Surfactant metabolism in transgenic mice after granulocyte macrophage-colony stimulating factor ablation. Am J Physiol 270:L650–L658, 1996.
16. Yoshida M, Ikegami M, Reed JA, et al: GM-CSF regulates surfacant protein-A and lipid catabolism by alveolar macrophages. Am J Physiol Lung Cell Mol Physiol 280:L379–L386, 2001.
17. Huffman JA, Hull WM, Dranoff G, et al: Pulmonary epithelial cell expression of GM-CSF corrects the alveolar proteinosis in GM-CSF-deficient mice. J Clin Invest 97:649–655, 1996.
18. Reed JA, Ikegami M, Cianciolo ER, et al: Aerosolized GM-CSF ameliorates pulmonary alveolar proteinosis in GM-CSF-deficient mice. Am J Physiol 276:L556–L563, 1999.
19. Shibata Y, Berclaz PY, Chroneos ZC, et al: GM-CSF regulates alveolar macrophage differentiation and innate immunity in the lung through PU.1. Immunity 15:557–567, 2001.
20. Robb L, Drinkwater CC, Metcalf D, et al: Hematopoietic and lung abnormalities in mice with a null mutation of the common beta subunit of the receptors for granulocyte-macrophage colony-stimulating factor and interleukins 3 and 5. Proc Natl Acad Sci U S A 92:9565–9569, 1995.
21. Nishinakamura R, Wiler R, Dirksen U, et al: The pulmonary alveolar proteinosis in granulocyte macrophage colony-stimulating factor/interleukins 3/5 beta c receptor-deficient mice is reversed by bone marrow transplantation. J Exp Med 183:2657–2662, 1996.
22. Jennings VM, Dillehay DL, Webb SK, Brown LA: Pulmonary alveolar proteinosis in SCID mice. Am J Respir Cell Mol Biol 13:297–306, 1995.
23. Ikegami M, Whitsett JA, Chroneos ZC, et al: IL-4 increases surfactant and regulates metabolism in vivo. Am J Physiol Lung Cell Mol Physiol 278:L75–L80, 2000.
24. Homer RJ, Zheng T, Chupp G, et al: Pulmonary type II cell hypertrophy and pulmonary lipoproteinosis are features of chronic IL-13 exposure. Am J Physiol Lung Cell Mol Physiol 283:L52–L59, 2002.
25. Korfhagen TR, Sheftelyevich V, Burhans MS, et al: Surfactant protein-D regulates surfactant phospholipid homeostasis in vivo. J Biol Chem 273:28438–28443, 1998.
26. Ikegami M, Hull WM, Yoshida M, et al: SP-D and GM-CSF regulate surfactant homeostasis via distinct mechanisms. Am J Physiol Lung Cell Mol Physiol 281:L697–L703, 2001.
27. Heppleston AG, Wright NA, Stewart JA: Experimental alveolar lipo-proteinosis following the inhalation of silica. J Pathol 101:293–307, 1970.
28. Clark JC, Weaver TE, Iwamoto HS, et al: Decreased lung compliance and air trapping in heterozygous SP-B-deficient mice. Am J Respir Cell Mol Biol 16:46–52, 1997.
29. Lin S, Na CL, Akinbi HT, Apsley KS, Whitsett JA, Weaver TE. Surfactant protein B (SP-B) –/– mice are rescued by restoration of SP-B expression in alveolar type II cells but not Clara cells. J Biol Chem 274:19168–19174, 1999.
30. Whitsett JA, Weaver TE: Hydrophobic surfactant proteins in lung function and disease. N Engl J Med 347:2141–2148, 2002.
31. Glasser SW, Detmer EA, Ikegami M, et al: Pneumonitis and emphysema in sp-C gene targeted mice. J Biol Chem 278:14291–14298, 2003.

32. Hammel M, Michel G, Hoefer C, et al: Targeted inactivation of the murine *Abca3* gene leads to respiratory failure in newborns with defective lamellar bodies. Biochem Biophys Res Commun 359:947–951, 2007.
33. Ban N, Matsumura Y, Sakai H, et al: ABCA3 as a lipid transporter in pulmonary surfactant biogenesis. J Biol Chem 282:9628–9634, 2007.
34. Baldan A, Tarr P, Vales CS, et al: Deletion of the transmembrane transporter ABCG1 results in progressive pulmonary lipidosis. J Biol Chem 281:29401–29410, 2006.
35. Thomassen MJ, Barna BP, Malur AG, et al: ABCG1 is deficient in alveolar macrophages of GM-CSF knockout mice and patients with pulmonary alveolar proteinosis. J Lipid Res 48:2762–2768, 2007.
36. Rosen SG, Castleman B, Liebow AA: Pulmonary alveolar proteinosis. N Engl J Med 258:1123–1142, 1958.
37. Golde DW, Territo M, Finley TN, Cline MJ: Defective lung macrophages in pulmonary alveolar proteinosis. Ann Intern Med 85:304–309, 1976.
38. Stratton JA, Sieger L, Wasserman K: The immunoinhibitory activities of the lung lavage materials and sera from patients with pulmonary alveolar proteinosis (PAP). J Clin Lab Immunol 5:81–86, 1981.
39. Muller-Quernheim J, Schopf RE, Benes P, et al: A macrophage-suppressing 40-kD protein in a case of pulmonary alveolar proteinosis. Klin Wochenschr 65:893–897, 1987.
40. Seymour JF, Dunn AR, Vincent JM, et al: Efficacy of granulocyte-macrophage colony-stimulating factor in acquired alveolar proteinosis. N Engl J Med 335:1924–1925, 1996.
41. Bewig B, Wang XD, Kirsten D, et al: GM-CSF and GM-CSF beta c receptor in adult patients with pulmonary alveolar proteinosis. Eur Respir J 15:350–357, 2000.
42. Kitamura T, Tanaka N, Watanabe J, et al: Idiopathic pulmonary alveolar proteinosis as an autoimmune disease with neutralizing antibody against granulocyte/macrophage colony-stimulating factor. J Exp Med 190:875–880, 1999.
43. Teja K, Cooper PH, Squires JE, Schnatterly PT: Pulmonary alveolar proteinosis in four siblings. N Engl J Med 305:1390–1392, 1981.
44. Nogee LM, de Mello DE, Dehner LP, Colten HR: Brief report: Deficiency of pulmonary surfactant protein B in congenital alveolar proteinosis. N Engl J Med 328:406–410, 1993.
45. Nogee LM, Dunbar AE 3rd, Wert SE, et al: A mutation in the surfactant protein C gene associated with familial interstitial lung disease. N Engl J Med 344:573–579, 2001.
46. Dirksen U, Nishinakamura R, Groneck P, et al: Human pulmonary alveolar proteinosis associated with a defect in GM-CSF/IL-3/IL-5 receptor common beta chain expression. J Clin Invest 100:2211–2217, 1997.
47. Suzuki T, Sakagami T, Rubin BK, et al: Familial pulmonary alveolar proteinosis caused by mutations in *CSF2RA*. J Exp Med 205:2703–2710, 2008.
48. Tanaka N, Watanabe J, Kitamura T, et al: Lungs of patients with idiopathic pulmonary alveolar proteinosis express a factor which neutralizes granulocyte-macrophage colony stimulating factor. FEBS Lett 442:246–250, 1999.
49. Uchida K, Nakata K, Trapnell BC, et al: High-affinity autoantibodies specifically eliminate granulocyte-macrophage colony-stimulating factor activity in the lungs of patients with idiopathic pulmonary alveolar proteinosis. Blood 103:1089–1098, 2004.
50. Seymour JF, Doyle IR, Nakata K, et al: Relationship of anti-GM-CSF antibody concentration, surfactant protein A and B levels, and serum LDH to pulmonary parameters and response to GM-CSF therapy in patients with idiopathic alveolar proteinosis. Thorax 58:252–257, 2003.
51. Uchida K, Beck DC, Yamamoto T, et al: GM-CSF autoantibodies and neutrophil dysfunction in pulmonary alveolar proteinosis. N Engl J Med 356:567–579, 2007.
52. Meager A, Wadhwa M, Bird C, et al: Spontaneously occurring neutralizing antibodies against granulocyte-macrophage colony-stimulating factor in patients with autoimmune disease. Immunology 97:526–532, 1999.
53. Bendtzen K, Svenson M, Hansen MB, et al: GM-CSF autoantibodies in pulmonary alveolar proteinosis. N Engl J Med 356:2001–2002, 2007.
54. Uchida K, Nakata K, Suzuki T, et al: Granulocyte/macrophage colony-stimulating factor autoantibodies and myeloid cell in healthy individuals. Blood 113:2547–2556, 2009.
55. Carey BC, Suzuki T, Uchida K, et al: An algorithm for diagnosis of familial pulmonary alveolar proteinosis (PAP). Am J Respir Crit Care Med 179:A3679, 2009.
56. Garmany TH, Wambach JA, Heins HB, et al: Population and disease-based prevalence of the common mutations associated with surfactant deficiency. Pediatr Res 63:645–649, 2008.
57. Somaschini M, Nogee LM, Sassi I, et al: Unexplained neonatal respiratory distress due to congenital surfactant deficiency. J Pediatr 150:649–653, 2007.
58. Nogee LM: Genetics of pediatric interstitial lung disease. Curr Opin Pediatr 18:287–292, 2006.
59. Nogee LM: Alterations in SP-B and SP-C expression in neonatal lung disease. Annu Rev Physiol 66:601–623, 2004.
60. Ballard PL, Nogee LM, Beers MF, et al: Partial deficiency of surfactant protein B in an infant with chronic lung disease. Pediatrics 96:1046–1052, 1995.
61. Yusen RD, Cohen AH, Hamvas A: Normal lung function in subjects heterozygous for surfactant protein-B deficiency. Am J Respir Crit Care Med 159:411–414, 1999.
62. Whitsett JA, Wert SE, Trapnell BC: Genetic disorders influencing lung formation and function at birth. Hum Mol Genet 13(Spec No 2):R207–R215, 2004.
63. Vorbroker DK, Profitt SA, Nogee LM, Whitsett JA: Aberrant processing of surfactant protein C in hereditary SP-B deficiency. Am J Physiol 268:L647–L656, 1995.
64. Cameron HS, Somaschini M, Carrera P, et al: A common mutation in the surfactant protein C gene associated with lung disease. J Pediatr 146:370–375, 2005.
65. Hamvas A, Nogee LM, White FV, et al: Progressive lung disease and surfactant dysfunction with a deletion in surfactant protein C gene. Am J Respir Cell Mol Biol 30:771–776, 2004.
66. Nogee LM: Abnormal expression of surfactant protein C and lung disease. Am J Respir Cell Mol Biol 26:641–644, 2002.
67. Hamvas A: Inherited surfactant protein-B deficiency and surfactant protein-C associated disease: Clinical features and evaluation. Semin Perinatol 30:316–326, 2006.
68. Brasch F, Schimanski S, Muhlfeld C, et al: Alteration of the pulmonary surfactant system in full-term infants with hereditary ABCA3 deficiency. Am J Respir Crit Care Med 174:571–580, 2006.
69. Bullard JE, Wert SE, Whitsett JA, et al: *ABCA3* mutations associated with pediatric interstitial lung disease. Am J Respir Crit Care Med 172:1026–1031, 2005.
70. Garmany TH, Moxley MA, White FV, et al: Surfactant composition and function in patients with *ABCA3* mutations. Pediatr Res 59:801–805, 2006.
71. Carnovale R, Zornoza J, Goldman AM, Luna M: Pulmonary alveolar proteinosis: Its association with hematologic malignancy and lymphoma. Radiology 122:303–306, 1977.
72. Cordonnier C, Fleury-Feith J, Escudier E, et al: Secondary alveolar proteinosis is a reversible cause of respiratory failure in leukemic patients. Am J Respir Crit Care Med 149:788–794, 1994.
73. Shoji N, Ito Y, Kimura Y, et al: Pulmonary alveolar proteinosis as a terminal complication in myelodysplastic syndromes: A report of four cases detected on autopsy. Leuk Res 26:591–595, 2002.
74. Pamuk GE, Turgut B, Vural O, et al: Pulmonary alveolar proteinosis in a patient with acute lymphoid leukemia regression after G-CSF therapy. Leuk Lymphoma 44:871–874, 2003.
75. Dirksen U, Hattenhorst U, Schneider P, et al: Defective expression of granulocyte-macrophage colony-stimulating factor/interleukin-3/interleukin-5 receptor common beta chain in children with acute myeloid leukemia associated with respiratory failure. Blood 92:1097–1103, 1998.
76. Haworth JC, Hoogstraten J, Taylor H: Thymic alymphoplasia. Arch Dis Child 42:40–54, 1967.
77. Webster JR Jr, Battifora H, Furey C, et al: Pulmonary alveolar proteinosis in two siblings with decreased immunoglobulin A. Am J Med 69:786–789, 1980.
78. Yousem SA, Burke CM, Billingham ME: Pathologic pulmonary alterations in long-term human heart-lung transplantation. Hum Pathol 16:911–923, 1985.

79. Israel RH, Magnussen CR: Are AIDS patients at risk for pulmonary alveolar proteinosis? Chest 96:641–642, 1989.
80. Davidson JM, Macleod WM: Pulmonary alveolar proteinosis. Br J Dis Chest 63:13–28, 1969.
81. Xipell JM, Ham KN, Price CG, Thomas DP: Acute silicoproteinosis. Thorax 32:104–111, 1977.
82. Ziskind M, Jones RN, Weill H: Silicosis. Am Rev Respir Dis 113:643–665, 1976.
83. Miller RR, Churg AM, Hutcheon M, Lom S: Pulmonary alveolar proteinosis and aluminum dust exposure. Am Rev Respir Dis 130:312–315, 1984.
84. Humble S, Allan Tucker J, Boudreaux C, et al: Titanium particles identified by energy-dispersive X-ray microanalysis within the lungs of a painter at autopsy. Ultrastruct Pathol 27:127–129, 2003.
85. Keller CA, Frost A, Cagle PT, Abraham JL: Pulmonary alveolar proteinosis in a painter with elevated pulmonary concentrations of titanium. Chest 108:277–280, 1995.
86. Heppleston AG, Fletcher K, Wyatt I: Changes in the composition of lung lipids and the "turnover" of dipalmitoyl lecithin in experimental alveolar lipo-proteinosis induced by inhaled quartz. Br J Exp Pathol 55:384–395, 1974.
87. Sakagami T, Uchida K, Suzuki T, et al: Human GM-CSF autoantibodies cause pulmonary alveolar proteinosis. N Engl J Med 361:2679–2681, 2009.
88. Ricote M, Huang JT, Welch JS, Glass CK: The peroxisome proliferator-activated receptor (PPARgamma) as a regulator of monocyte/macrophage function. J Leukoc Biol 66:733–739, 1999.
89. Bonfield TL, Farver CF, Barna BP, et al: Peroxisome proliferator-activated receptor-gamma is deficient in alveolar macrophages from patients with alveolar proteinosis. Am J Respir Cell Mol Biol 29:677–682, 2003.
90. Culver DA, Barna BP, Raychaudhuri B, et al: Peroxisome proliferator-activated receptor gamma activity is deficient in alveolar macrophages in pulmonary sarcoidosis. Am J Respir Cell Mol Biol 30:1–5, 2004.
91. Deutsch GH, Young LR, Deterding RR, et al: Diffuse lung disease in young children: Application of a novel classification scheme. Am J Respir Crit Care Med 176:1120–1128, 2007.
92. Asamoto H, Kitaichi M, Nishimura K, et al: [Primary pulmonary alveolar proteinosis—clinical observation of 68 patients in Japan]. Nihon Kyobu Shikkan Gakkai Zasshi 33:835–845, 1995.
93. Cole FS, Hamvas A, Rubinstein P, et al: Population-based estimates of surfactant protein B deficiency. Pediatrics 105:538–541, 2000.
94. Nogee LM, Dunbar AE 3rd, Wert S, et al: Mutations in the surfactant protein C gene associated with interstitial lung disease. Chest 121:20S–21S, 2002.
95. Doan ML, Guillerman RP, Dishop MK, et al: Clinical, radiological and pathological features of *ABCA3* mutations in children. Thorax 63:366–373, 2008.
96. Ben-Dov I, Kishinevski Y, Roznman J, et al: Pulmonary alveolar proteinosis in Israel: Ethnic clustering. Isr Med Assoc J 1:75–78, 1999.
97. Hildebrand FL Jr, Rosenow EC 3rd, Habermann TM, Tazelaar HD: Pulmonary complications of leukemia. Chest 98:1233–1239, 1990.
98. Ohnishi T, Yamada G, Shijubo N, et al: Secondary pulmonary alveolar proteinosis associated with myelodysplastic syndrome. Intern Med 42:187–190, 2003.
99. Nogee LM, Garnier G, Dietz HC, et al: A mutation in the surfactant protein B gene responsible for fatal neonatal respiratory disease in multiple kindreds. J Clin Invest 93:1860–1863, 1994.
100. Young LR, Nogee LM, Barnett B, et al: Usual interstitial pneumonia in an adolescent with *ABCA3* mutations. Chest 134:192–195, 2008.
101. Wang BM, Stern EJ, Schmidt RA, Pierson DJ: Diagnosing pulmonary alveolar proteinosis: A review and an update. Chest 111:460–466, 1997.
102. Holbert JM, Costello P, Li W, et al: CT features of pulmonary alveolar proteinosis. AJR Am J Roentgenol 176:1287–1294, 2001.
103. Lee KN, Levin DL, Webb WR, et al: Pulmonary alveolar proteinosis: High-resolution CT, chest radiographic, and functional correlations. Chest 111:989–995, 1997.
104. Johkoh T, Itoh H, Muller NL, et al: Crazy-paving appearance at thin-section CT: Spectrum of disease and pathologic findings. Radiology 211:155–160, 1999.
104a. Ishii H, Trapnell BC, Tazawa R, et al: Comparative study of high resolution CT findings between autoimmune and secondary pulmonary alveolar proteinosis. Chest 136:1348–1355, 2009.
105. Robinson TE, Trapnell BC, Goris ML, et al: Quantitative analysis of longitudinal response to aerosolized GM-CSF in 2 adolescents with autoimmune pulmonary alverolar proteinosis. Chest 136:1348–1365, 2009.
106. Martin RJ, Rogers RM, Myers NM: Pulmonary alveolar proteinosis: Shunt fraction and lactic acid dehydrogenase concentration as aids to diagnosis. Am Rev Respir Dis 117:1059–1062, 1978.
107. Maygarden SJ, Iacocca MV, Funkhouser WK, Novotny DB: Pulmonary alveolar proteinosis: A spectrum of cytologic, histochemical, and ultrastructural findings in bronchoalveolar lavage fluid. Diagn Cytopathol 24:389–395, 2001.
108. Milleron BJ, Costabel U, Teschler H, et al: Bronchoalveolar lavage cell data in alveolar proteinosis. Am Rev Respir Dis 144:1330–1332, 1991.
109. Doyle IR, Davidson KG, Barr HA, et al: Quantity and structure of surfactant proteins vary among patients with alveolar proteinosis. Am J Respir Crit Care Med 157:658–664, 1998.
110. Clague HW, Wallace AC, Morgan WK: Pulmonary interstitial fibrosis associated with alveolar proteinosis. Thorax 38:865–866, 1983.
111. Honda Y, Kuroki Y, Matsuura E, et al: Pulmonary surfactant protein D in sera and bronchoalveolar lavage fluids. Am J Respir Crit Care Med 152:1860–1866, 1995.
112. Kuroki Y, Takahashi H, Chiba H, Akino T: Surfactant proteins A and D: Disease markers. Biochim Biophys Acta 1408:334–345, 1998.
113. Brasch F, Birzele J, Ochs M, et al: Surfactant proteins in pulmonary alveolar proteinosis in adults. Eur Respir J 24:426–435, 2004.
114. Presneill JJ, Nakata K, Inoue Y, Seymour JF: Pulmonary alveolar proteinosis. Clin Chest Med 25:593–613, viii, 2004.
115. Kitamura T, Uchida K, Tanaka N, et al: Serological diagnosis of idiopathic pulmonary alveolar proteinosis. Am J Respir Crit Care Med 162:658–662, 2000.
116. Inoue Y, Nakata K, Hamano E, et al: Clinical manifestations of Japanese patients with idiopathic pulmonary alveolar proteinosis. Am J Respir Crit Care Med 165:A155, 2002.
117. Seymour JF, Lieschke GJ, Grail D, et al: Mice lacking both granulocyte colony-stimulating factor (CSF) and granulocyte-macrophage CSF have impaired reproductive capacity, perturbed neonatal granulopoiesis, lung disease, amyloidosis, and reduced long-term survival. Blood 90:3037–3049, 1997.
118. Ben-Abraham R, Greenfeld A, Rozenman J, Ben-Dov I: Pulmonary alveolar proteinosis: Step-by-step perioperative care of whole lung lavage procedure. Heart Lung 31:43–49, 2002.
119. Wasserman K, Blank N, Fletcher G: Lung lavage (alveolar washing) in alveolar proteinosis. Am J Med 44:611–617, 1968.
120. Beccaria M, Luisetti M, Rodi G, et al: Long-term durable benefit after whole lung lavage in pulmonary alveolar proteinosis. Eur Respir J 23:526–531, 2004.
121. Selecky PA, Wasserman K, Benfield JR, Lippmann M: The clinical and physiological effect of whole-lung lavage in pulmonary alveolar proteinosis: A ten-year experience. Ann Thorac Surg 24:451–461, 1977.
122. Rogers RM, Levin DC, Gray BA, Moseley LW Jr: Physiologic effects of bronchopulmonary lavage in alveolar proteinosis. Am Rev Respir Dis 118:255–264, 1978.
123. Cheng SL, Chang HT, Lau HP, et al: Pulmonary alveolar proteinosis: Treatment by bronchofiberscopic lobar lavage. Chest 122:1480–1485, 2002.
124. van der Kleij AJ, Peper JA, Biervliet JD, et al: Whole lung lavage under hyperbaric conditions: 2. Monitoring tissue oxygenation. Adv Exp Med Biol 317:121–124, 1992.
125. Cohen ES, Elpern E, Silver MR: Pulmonary alveolar proteinosis causing severe hypoxemic respiratory failure treated with sequential whole-lung lavage utilizing venovenous extracorporeal membrane oxygenation: A case report and review. Chest 120:1024–1026, 2001.

126. Seymour JF, Presneill JJ, Schoch OD, et al: Therapeutic efficacy of granulocyte-macrophage colony-stimulating factor in patients with idiopathic acquired alveolar proteinosis. Am J Respir Crit Care Med 163:524–531, 2001.
127. Venkateshiah SB, Yan TD, Bonfield TL, et al: An open-label trial of granulocyte macrophage colony stimulating factor therapy for moderate symptomatic pulmonary alveolar proteinosis. Chest 130:227–237, 2006.
128. Tazawa R, Hamano E, Arai T, et al: Granulocyte-macrophage colony-stimulating factor and lung immunity in pulmonary alveolar proteinosis. Am J Respir Crit Care Med 171:1142–1149, 2005.
129. Parker LA, Novotny DB: Recurrent alveolar proteinosis following double lung transplantation. Chest 111:1457–1458, 1997.
130. McKenzie B, Wood RE, Bailey A: Airway management for unilateral lung lavage in children. Anesthesiology 70:550–553, 1989.
131. Eldar M, Shoenfeld Y, Zaizov R, et al: Pulmonary alveolar proteinosis associated with Fanconi's anemia. Respiration 38:177–179, 1979.
132. Breslow A, Snow P, Rosenberg MH: Pulmonary alveolar proteinosis and chronic lymphatic leukemia. Med Ann Dist Columbia 34:209–212, 1965.
133. Green D, Dighe P, Ali NO, Katele GV: Pulmonary alveolar proteinosis complicating chronic myelogenous leukemia. Cancer 46:1763–1766, 1980.
134. Tammaa M, Nasser W, Zaman M, Hernandez AM: Respiratory failure in an 83-year-old man with multiple myeloma: Pulmonary alveolar proteinosis. Tenn Med 102:37–39, 2009.
135. Loire R, Meunier P, Lenglet JP, et al: [Waldenstrom's disease with terminal pulmonary alveolar proteinosis]. Lyon Med 226:319–323, 1971.
136. Su KC, Lay SL, Perng RP, et al: Lung cancer may develop subsequently or coincidently with pulmonary alveolar proteinosis. Lung Cancer 58:144–148, 2007.
137. Schiller V, Aberle DR, Aberle AM: Pulmonary alveolar proteinosis: Occurrence with metastatic melanoma to lung. Chest 95:466–467, 1989.
138. Ruben FL, Talamo TS: Secondary pulmonary alveolar proteinosis occurring in two patients with acquired immune deficiency syndrome. Am J Med 80:1187–1190, 1986.
139. Ganguli PC, Lynne-Davies P, Sproule BJ: Pulmonary alveolar proteinosis, bronchiectasis and secondary amyloidosis: A case report. Can Med Assoc J 106:569 passim, 1972.
140. Patiroglu T, Akyildiz B, Patiroglu TE, Gulmez IY: Recurrent pulmonary alveolar proteinosis secondary to agammaglobulinemia. Pediatr Pulmonol 43:710–713, 2008.
141. Samuels MP, Warner JO: Pulmonary alveolar lipoproteinosis complicating juvenile dermatomyositis. Thorax 43:939–940, 1988.
142. Garcia Rio F, Alvarez-Sala R, Caballero P, et al: Six cases of pulmonary alveolar proteinosis: Presentation of unusual associations. Monaldi Arch Chest Dis 50:12–15, 1995.
143. Pessach I, Walter J, Notarangelo LD: Recent advances in primary immunodeficiencies: Identification of novel genetic defects and unanticipated phenotypes. Pediatr Res 65:3R–12R, 2009.
144. Ranchod M, Bissell M: Pulmonary alveolar proteinosis and cytomegalovirus infection. Arch Pathol Lab Med 103:139–142, 1979.
145. Witty LA, Tapson VF, Piantadosi CA: Isolation of mycobacteria in patients with pulmonary alveolar proteinosis. Medicine (Baltimore) 73:103–109, 1994.
146. Oerlemans WG, Jansen EN, Prevo RL, Eijsvogel MM: Primary cerebellar nocardiosis and alveolar proteinosis. Acta Neurol Scand 97:138–141, 1998.
147. Tran Van Nhieu J, Vojtek AM, Bernaudin JF, et al: Pulmonary alveolar proteinosis associated with *Pneumocystis carinii:* Ultrastructural identification in bronchoalveolar lavage in AIDS and immunocompromised non-AIDS patients. Chest 98:801–805, 1990.
148. McCunney RJ, Godefroi R: Pulmonary alveolar proteinosis and cement dust: A case report. J Occup Med 31:233–237, 1989.
149. Wuhrmann F, Mark GJ, Wick A, Marki HH: [Alveolar pulmonary proteinosis and aspergillosis with reactive reticulosis following silage work: A contribution on health hazards in agricultural work]. Schweiz Med Wochenschr 95:1738–1744, 1965.
150. Dawkins SA, Gerhard H, Nevin M: Pulmonary alveolar proteinosis: A possible sequel of NO_2 exposure. J Occup Med 33:638–641, 1991.

CHAPTER 64

ASTHMA IN THE WORKPLACE AND OCCUPATIONAL ASTHMA

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INTRODUCTION
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INTRODUCTION

Asthma affects 5% to 10% of people and about 10% of these individuals report that their symptoms are worse when they are at work and improve when they are away from work.[1] In addition, asthma in the workplace can provide important information on certain aspects of asthma, including physiopathology, diagnosis, and management.[2] Occupational asthma (OA) has the elements of an experiment, in which at-risk individuals can be examined before exposure starts and serially thereafter, during and after cessation of exposure. For example, apprentices starting work with exposure to high-[3,4] and low-molecular-weight[5] agents have been studied before and after their apprenticeship periods and, more recently, after several years in a working environment where they are either still or no longer exposed to the sensitizing agents.[6] It is also possible to examine workers with confirmed OA after they stop being exposed to see whether the asthma persists or is cured.[7] For instance, bronchial biopsies have recently been obtained and examined in workers with OA who were apparently cured.[8] This study showed that airway inflammation and remodeling were still present on average 14 years after exposure had stopped, which is instructive to our understanding of other forms of asthma.[9] OA can be reproduced by using specific inhalation challenges, which give information on late asthmatic reactions, a concept introduced by Professor Jack Pepys, who has been called the father of OA.[10]

DEFINITION AND CLASSIFICATION

Asthma in the workplace includes several types of asthmatic conditions (Fig. 64-1). This first includes OA or asthma caused by the workplace. In a recent re-edition of a textbook on *Asthma in the Workplace*, OA was defined as: "a disease characterized by variable airflow limitation and/or hyperresponsiveness and/or inflammation due to causes and conditions attributable to a particular occupational environment and not to stimuli encountered outside the workplace." Two types of OA are distinguished by their appearance following a latency period:

1. After a latency period (allergic): This category is characterized by work-related asthma appearing after a latency period and encompasses: (a) OA caused by most high- and certain low-molecular-weight agents for which an allergic (IgE-mediated) mechanism has been proved; and (b) OA induced by specific occupational agents (e.g., Western red

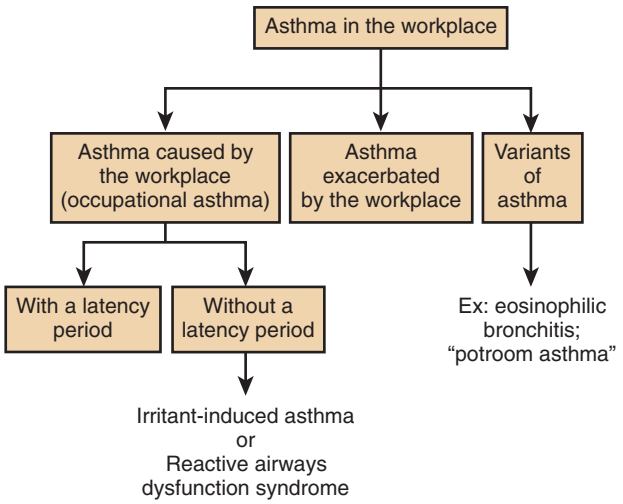

FIGURE 64-1 ■ Asthma in the workplace.

cedar) but the allergic mechanisms responsible have not yet been fully characterized.

2. Without a latency period (nonallergic): This category includes irritant-induced asthma or reactive airway dysfunction syndrome (RADS), which may occur after a single or multiple exposures to nonspecific irritants at high concentrations.[11]

OA, therefore, shares all functional and inflammatory features of common asthma. The first type of OA that occurs after a latency period is initiated in adult life and is caused solely by the workplace where, generally, a specific agent can be identified in its etiology. The other type of OA is rarer and is related to one (generally) or more inhalational accidents clearly identified by the worker at the workplace.

Besides OA, the majority of cases of asthma in the workplace are represented by asthmatic subjects who report that their symptoms are aggravated by exposure to the workplace. Little is known about this condition. Criteria for identification have been proposed by the Sentinel Event Notification System for Occupational Risks (SENSOR) project sponsored by the National Institute of Occupational Safety and Health (NIOSH).[12] These include (1) a physician's diagnosis of asthma; (2) an association between symptoms and work; (3) the onset of asthma symptoms or treatment within a period of 2 years before entering a new occupation; (4) increase in asthma symptoms or treatment upon entering a new occupation. As it is, this condition is mainly diagnosed through exclusion; that is, after excluding OA in a subject with asthma, the symptoms and the need for medication increase at work. This condition encompasses a socioeconomic burden that is equivalent to OA.[13] Indeed, even following confirmation that a worker does not suffer from OA, many frequently leave their workplace. Lemière and coworkers[14] have shown that the investigation of these subjects is more likely to show an increase in sputum neutrophils while at work, whereas, in the case of OA, there is an increase in eosinophils. Also, these subjects experience more important changes in peak expiratory flows (PEFs) while at work than what is found in well-controlled non–work-aggravated asthma, though of lesser magnitude than what is found in OA.[15]

There are variants of asthma in the workplace. Potroom asthma is an asthma-like condition that occurs in aluminum potroom workers, the cause being unknown. In recent years, many cases of occupational eosinophilic bronchitis have been described.[16] Workers affected by this condition principally report coughing. Airway responsiveness is normal. The only abnormality is the increase in eosinophils in induced sputum.

TABLE 64-1. Important Dates in the History of Asthma in the Workplace

Date	Event and Contributor
16th century	Olaus Magnus (Scandinavia) and Bernardino Ramazzini (Italy) first describe OA.
19th century	Thackrah in England and Patissier in France publish a more detailed account of OA.
First half of the 20th century	Castor beans, various gums, metal salts, and anhydrides incriminated as causes of OA.
1951	Fuchs and Valade identify isocyanates as a cause of OA.
1970s	Epidemics of OA due to enzymes in detergent workers.
	Development of specific inhalation challenges by Pepys.
1977	OA can cause permanent impairment even after removal from exposure, as shown by Chan-Yeung.
1979	Peak expiratory flows as a diagnostic tool proposed by Burge.
1985	Reactive airway dysfunction syndrome labeled by Brooks, Weiss, and Bernstein.
1990s	Epidemics of OA due to latex.
	Development of tools and scales to assess permanent impairment.
End of 20th century	Monitoring of airway inflammation as a diagnostic tool.

OA, occupational asthma.

HISTORICAL ASPECTS

Some of the important dates in the history of asthma and the workplace are listed in Table 64-1. In the 16th century, the Scandinavian physician Olaus Magnus and the Italian Bernardino Ramazzini first described difficult breathing occurring in grain handlers.[17] In the 19th century, Thackrah in England and Patissier in France described the occurrence of chronic bronchitis in workers exposed to malt, coffee, and flax. Castor beans, various gums (acacia, tragacanth), metal salts, and anhydrides were the first occupational sensitizing agents clearly identified in causing asthma in reports made in the beginning of the 20th century.[17] Diisocyanates, a still important cause of OA, were incriminated in 1951.[18]

Although the condition of irritant-induced asthma had been recognized a long time before as reviewed,[19] it was in 1985 that the label "reactive airway dysfunction syndrome" was first proposed.[20] The epidemics of OA due to enzymes incorporated in soaps in the 1970s[21] and due to the latex in gloves used by health professionals[22] have clearly demonstrated that the degree of exposure plays a key role and that the control of exposure can result in rapid diminution of sensitization and disease.

Various objective diagnostic means have been developed over recent years. Professor Pepys[23] proposed an experimental type of simulated exposure to agents suspected to cause OA. Monitoring of PEFs for periods at work and away from work were later proposed by Burge and colleagues.[24] More recently, monitoring of airway inflammation through induced sputum and exhaled nitric oxide has started being used.[25] Its usefulness in the diagnosis of OA is being evaluated at present. Although objective means are available and guidelines have been proposed,[26] it is known that the diagnosis is still principally based on clinical history,[27,28] which has a higher sensitivity than specificity.[29]

Chan-Yeung[30] was the first to show that workers with OA are often left with permanent asthma in 1970s, a relatively new concept because it was thought that removal from exposure would lead to a cure. Tools and scales to assess impairment were proposed in the 1990s.[31]

ETIOLOGIC AGENTS

OA can be caused by proteinaceous, high-molecular-weight, or chemical, low-molecular-weight agents. There are differences in the mechanisms, clinical manifestations, and means of diagnosis between these two classes of agents (Table 64-2). There are over 250 reported workplace sensitizers and there are many workplaces with such sensitizers. It is difficult for a physician to know all possible exposures that a patient could have. Fortunately, several websites—http://www.asmanet.com; http://www.csst.qc.ca; http://hazmap:nlm.nih.gov/; and http://toxnet.nlm.nih.gov/—and the appendix in the textbook *Asthma in the Workplace* contain up-to-date information on sensitizers and irritants causing asthma in the workplace.[32]

GENETIC, PHYSIOPATHOLOGIC ASPECTS, AND ANIMAL MODELS

Genetics

Because not all individuals exposed to the same levels of sensitizers develop asthma, host susceptibility factors are important, although little is known about this. Human leukocyte antigen (HLA) class II antigens (DR, DQ, DP) play a key role in antigen presentation to T lymphocytes and influence the specificity. They are also highly polymorphic. Their role has been examined in the development of OA due to a number of agents: high-molecular-weight allergens such as laboratory animals and low-molecular-weight compounds such as platinum salts, acid anhydride, diisocyanates, and plicatic acid as shown in Table 64-3. Some of the HLA class II antigens are associated with susceptibility whereas others are associated with protection.[33-39] It should be noted that in most occupational studies, the sample size is small and the magnitude of association illustrated by the odds ratio (OR) is low, suggesting that they are not major genetic determinants. However, HLA associations provide evidence of a specific immunologic response in asthma caused by low-molecular-weight sensitizers.

Many occupational agents such as welding fumes and ozone cause oxidative stress. However, even occupational sensitizers such as diisocyanates also cause oxidative stress by inducing monocytes to produce reactive oxygen species.[40] The presence of the GSTP1Val/Val genotype was found to confer protection against both

TABLE 64-2. Characteristics of High- and Low-Molecular-Weight Agents as a Cause of Occupational Asthma

	High-Molecular-Weight Agents	Low-Molecular-Weight Agents
Structure	Proteins, polysaccharides	Chemicals, metals
Duration of the latency period before receiving "sensitization"	Generally longer (e.g., flour)	Generally shorter (e.g., isocyanates)
Oculonasal symptoms	+++	+
Accompanying dermatitis	Rare	Possible
Immunologic mechanism	IgE-dependent	Generally not IgE-dependent. IgG, MCP-1 (isocyanates)
Cellular component	Eosinophils	Eosinophils and neutrophils
Feasibility of skin testing to elicit immediate reactions	Yes	No
Type of asthmatic reaction after challenge	Immediate, dual	Isolated late or atypical
Frequency of referral	One third	Two thirds
Diagnostic means	Numerous	More limited

Ig, immunoglobulin; MCP, macrophage chemotactic protein.

TABLE 64-3. HLA Antigen and Occupational Asthma from Selected Studies

Exposure	HLA Antigen	Cases	Controls	OR (95% CI)	Reference No.
Laboratory animal allergy					
Sensitization	HLA-DR7			1.82 (1.12–2.97)	33
	HLA-DR3			0.55 (0.31–0.97)	
Work-related chest symptoms	HLA-DR7			2.96 (1.64–5.37)	
	HLA-DR3			0.71 (0.35–1.45)	
Sensitization and work-related chest symptoms	HLA-DR7			3.81 (1.90–7.65)	
	HLA-DR3			0.57 (0.24–1.32)	
Complex platinum salts					34
All	HLA-DR3	18 (41)	15 (26)	2.3 (1.0–5.6)	
Low exposure		6 (55)	4 (22)	Infinite	
High exposure		12 (36)	11 (28)	1.6 (0.6–4.1)	
All	HLA-DR6	16 (36)	34 (60)	0.4 (0.2–0.8)	
Low exposure		2 (18)	12 (67)	0.1 (0.02–1.1)	
High exposure		14 (42)	22 (56)	0.5 (0.2–1.3)	
Acid anhydride					
Trimellitic anhydride	HLA-DR3	8/11	2/14		35
Phthalic anhydride		2/12	2/14		
Tetrachlorophthalic anhydride		5/7	0/0		
Total		15/30 (50)	4/28 (14)	16 $P < .05$	
Hexahydrophthalic anhydride	DQ5			4.3 (1.7–11)	36
	DQB1(*)0501	17 (33)	10 (14)	3.0 (1.2–7.4)	
	DR1	12 (32)	7 (14)	3.0 (1.2–11)	
Isocyanate	HLA-DQB1				37
	*0501	1/56	5/32 (16)	0.14 $P < .03$	
		(2)	0 (0)	9.8 $P < .04$	
	*0503	7/56 (13)			
	HLA-BAsp57				38
	Asp57+ homo	17 (57)	44 (32)		
	Asp57 hetero	12 (40)	73 (53)		
	Asp57– homo	1 (3)	21 (15)		
Western red cedar (plicatic acid)	HLA-DRB1				39
	*0101	4 (7.1)	15 (23.4)	0.25 (0.08–0.79)	
	HLA-DQB1				
	*0501	6 (10.7)	18 (28.1)	0.3 (0.11–0.82)	
	*0603	13 (23.2)	6 (9.4)	2.9 (1.01–8.17)	
	*0302	11 (19.1)	3 (4.7)	4.9 (1.28–18.56)	

Asp, aspartate; CI, confidence interval; HLA, human leukocyte antigen; hetero, heterozygous; homo, homozygous; OR, odds ratio.

asthma and nonspecific bronchial hyperresponsiveness induced by diisocyanates.[41] Another study found that the *N*-acetyltransferase slow acetyl genotype posed an eight-fold risk of toluene diisocyanate (TDI) asthma.[42]

A more recent study investigated the relationship between polymorphisms of interleukin-4 receptor antagonist (IL-4Ra), CD-14, and IL-13 in 62 inhalation-positive patients using 75 inhalation challenge–negative patients as controls. Among individuals exposed to hexamethylene diisocyanate, those with IL-4Ra II were at increased risk for asthma (OR 3.29, 95%, confidence interval [CI] 1.33–8.14). However, the combination of IL-4-Ra II and IL-13-receptor (IL-13RR) or IL-4Ra II and CD 14 CT genotypes as well as the triple combination of IL-4Ra II, IL-13RR, and CD 4 CT genotypes further increased the risk.[43]

Physiopathology

Occupational Asthma with a Latency Period

Irrespective of the etiology, the pathology in the airways of subjects with OA with latency is similar to what is found in non-OA. There is extensive epithelial desquamation associated with epithelial cell ciliary abnormalities, smooth muscle hyperplasia, presence of airway inflammation with increased numbers of total inflammatory cells, eosinophils, and lymphocytes in the airways of these subjects and presence of airway remodeling with subepithelial fibrosis.[44] Removal from exposure for a period ranging from 5 to 21 months in subjects with diisocyanate-induced asthma was associated with a reduction in subepithelial fibrosis, but also with persistence of inflammatory cell infiltration of the airways.[45] It

has recently been shown that airway eosinophilic inflammation and remodeling persist 10 years or more after cessation of exposure in subjects apparently cured, that is, without symptoms and with normal airway caliber and responsiveness.[8]

Immunologic, Immunoglobulin E–Mediated. High-molecular-weight agents, such as animal proteins and flour, act as complete antigens and induce the production of specific immunoglobulin E (IgE) antibodies. Certain low-molecular-weight occupational agents, such as platinum salts, trimellitic anhydride, and other acid anhydrides, also induce specific IgE antibodies by acting as haptens and binding with proteins to form functional antigens. As with common allergens, the inhaled occupational sensitizer binds to specific IgE antibodies on the surface of mast cells, basophils, and possibly macrophages and eosinophils, leading to a cascade of events that results in an influx of inflammatory cells into the airways as well as the release of inflammatory mediators. Clinically, an inhalational challenge with these agents in sensitized individuals leads to one of the following types of reactions: isolated early reaction (an asthmatic reaction that occurs in the first hour and that is maximum 10 to 20 minutes after end of exposure), isolated late (an asthmatic reaction that occurs 4 to 8 hours after ending exposure), biphasic reaction (combination of an early and a late reactions), or atypical (other patterns) reactions.

Immunologic, Non–Immunoglobulin E–Mediated. Many low-molecular-weight chemicals, including diisocyanates and plicatic acid, cause OA but do not induce specific IgE antibodies. In patients with Western red cedar asthma, specific IgE antibodies were found in only 20%.[46] These antibodies may reflect only prior red cedar exposure because they do not passively sensitize human lung fragments.[47] Specific IgE antibodies to TDI have been reported in 0% to 50% of workers with TDI-induced asthma.[48] This variation has been attributed to several reasons: the short half-life of the specific IgE antibodies to TDI of about 2 days,[49] the appearance of new antigenic determinants after the binding of specific IgE to TDI-human conjugate,[50] and the different methods of conjugation as well as the measurement of specific IgE antibodies. A conjugate of TDI vapor–exposed albumin was found to detect specific IgE antibodies in 40% to 50% of TDI-induced asthma, much higher than the conjugate prepared from the liquid phase of isocyanate.[51] The inability to detect specific IgE antibodies to such low-molecular-weight compounds as plicatic acid or diisocyanates may be due to the use of the wrong carrier protein, human serum albumin, which is the protein often used. Keratin in the lungs and skin was found to conjugate with hexamethylene diisocyanate through in vitro (human epithelial cell line) and in vivo (endobronchial biopsy samples) exposure.[52] The role of these proteins in the pathogenesis of diisocyanate-induced asthma needs to be assessed. Specific IgG antibodies are also demonstrated in diisocyanate-induced asthma.[53,54] Although they are sensitive in the diagnosis of TDI-induced asthma, their specificity is poor and their pathogenic significance unclear.

The characteristics of the inflammatory process in diisocyanate-induced asthma and Western red cedar asthma are similar to those of an IgE-dependent reaction. In both types of OA, evidence of cell-mediated immunity has been provided by bronchoalveolar lavage (BAL), bronchial biopsy, and induced sputum studies because the T lymphocytes showed markers of activation.[44,55] In isocyanate-induced asthma, an increase in $CD8^+$ cells and eosinophils was found in the peripheral blood of subjects during a late asthmatic reaction induced by challenge with the agent.[56] One study found that the majority of T cells from bronchial biopsies of these subjects exhibited the CD8 phenotype and produced interferon-γ (IFN-γ) and IL-5 with very few clones producing IL-4, suggesting that CD8 cells play a central role in OA without the production of IgE antibodies.[57] There is considerable controversy as to whether diisocyanate-induced asthma is due to a non-IgE or an IgE mechanism.[48] In a recent study, bronchial biopsies of patients with diisocyanate-induced asthma showed absence of both bronchial C-epsilon and IL-4 RNA message, which should be present if an IgE-mediated reaction had taken place, after an inhalation challenge with diisocyanate irrespective of the test response, suggesting that this is a non–IgE-mediated disease.[58]

The role of neutrophils in OA is unclear but could be important. Neutrophils are increased in the BAL fluid during the late asthmatic reaction,[59] and they are found when individuals with diisocyanate-induced asthma are exposed to a very low dose of TDI, levels much lower than would induce an asthmatic reaction.[60] In non-OA, the presence of neutrophils in the airways usually indicates severity of asthma in the absence of infection.[61] This could be due to oxidative stress with formation of reactive oxygen species arising from persistent airway inflammation.[62]

The sensitizing compound, when present in high levels, may also act as an irritant. Diisocyanates, for example, have been shown to stimulate sensory nerves to release substance P and other neuropeptides and inhibit the neutral endopeptidases that normally inactivate these substances.[63] Neuropeptides affect a variety of cells in the airways, resulting in cough, smooth muscle contraction, and mucus production.[64] These sensitizing chemicals may also have pharmacologic effects. High concentrations of plicatic acid have been shown to activate the classic complement pathway,[65] with generation of chemotactic factors leading to inflammatory response in the airways. The working environment is complex and workers are often exposed to multiple substances in the workplace. It is very likely that the airway inflammation found in patients with OA is the result of different mechanisms of exposure to an offending agent or to different substances.

Occupational Asthma without a Latency Period

Irritant-induced asthma is an example of nonimmunologically induced asthma or OA without latency. Subjects with RADS showed denudation of the mucosa and

fibrinohemorrhagic exudate in the submucosa,[66] followed by regeneration of the epithelium with proliferation of basal and parabasal cells, subepithelial edema, and marked thickening of the airway wall.[67] The underlying mechanism of irritant-induced asthma is not known, but in an animal model, extensive denudation of the epithelium[68,69] may result in airway inflammation because of a loss of epithelium-derived relaxing factors. Exposure of the nerve endings leads to neurogenic inflammation and nonspecific activation of mast cells with release of inflammatory mediators and cytokines. Epithelial damage, a key feature of the acute phase of the process, may also result in the marked airway remodeling that is probably responsible for the reduced reversibility of airflow obstruction in patients with RADS.[67]

Role of Irritant Exposure in Sensitization

There is increasing evidence that exposure to low levels of irritants may enhance specific sensitization to occupational agents. Combined ozone and platinum salt exposure significantly increased specific (platinum) and nonspecific bronchial hyperresponsiveness more often than did exposure to either ozone or the platinum salt alone.[70] The airway inflammation, epithelial damage, and modification of cellular tight junctions from ozone exposure lead to greater penetration of platinum salt into the subepithelial tissue and, thus, enhance the inflammatory response to platinum salt exposure.

Because, in many industries, exposure to low levels of irritant gases commonly occurs simultaneously with exposure to specific asthmagens, there greater emphasis should be put on reducing exposure to these gases as well as to the specific agents.

Animal Models

In OA, animal models are used: (1) to investigate exposure determinants, such as the route of exposure, respiratory or dermal, the dose, and the exposure duration and frequency; (2) to determine the role played by the immune system in order to reproduce the disease phenotype and to determine its pathogenesis; (3) to study potential interactions between allergens and pollutants; and (4) to identify novel agents or new modalities for treatment.

Occupational Asthma with a Latency Period

Table 64-4 shows some of the selected animal models of asthma due to occupational agents.[71–79] Some are high-molecular-weight allergens whereas others are low-molecular-weight compounds. All of them induce asthma with latency to indicate that some forms of immunologic mechanisms are involved. Interested readers should consult two recent reviews on animal models, one for protein respiratory sensitizers[80] and the other for low-molecular-weight chemicals.[81]

TABLE 64-4. Animal Models of Occupational Asthma

Agent—Purpose	Species	Exposure	Elicitation	Parameter Evaluated	Reference No.
HMW ALLERGENS					
Bacillus subtilis—to establish threshold limit value	Guinea pigs	Inhalation	Inhalation	Respiratory response—rapid shallow breathing	71
New enzyme protein in detergent industry	Guinea pigs	Intratracheal	Blood	Amount of antibodies produced	72
Latex—to identify the most active immunogenic fraction	Guinea pigs	Injection	Blood	PCA, passive systemic anaphylaxis	73
Latex—HEV b5	Mice	Intraperitoneal	Blood Lung lavage	Specific antibodies; IL-5 in lavage fluid	74
LMW COMPOUNDS					
Diisocyanate—to establish a model of TDI asthma	Guinea pigs	Inhalation—vapors	SIC with TDI-GPSA	Changes in pulmonary function	75
Diisocyanate—to determine the role of dermal exposure in TDI asthma	Guinea pigs	A single epicutaneous injection	SIC with TDI	Changes in pulmonary function Antibodies in blood	76
Diisocyanate—to study role of $CD4^+$ and $CD8^+$ T lymphocytes in TDI asthma	Mouse: Deficient in $CD4^+$ or $CD8^+$ T cells	Epicutaneous	SIC	BALF—eosinophils Skin—contact hypersensitivity	77
Acid anhydride—to establish a model of TMA lung	Guinea pig	Inhalation	SIC with TMA or TMA GPSA	Respiratory response Antibodies detection	78
Plicatic acid—Western red cedar—to establish a model	Rabbit	Plicatic acid-ovalbumin and adjuvant	Plicatic acid—OA conjugate	Respiratory response frequency and resistance	79

BALF, bronchoalveolar lavage fluid; GPSA, guinea pig serum albumin; HEV, hepatitis E virus; HMW, high-molecular-weight; IL, interleukin; LMW, low-molecular-weight; OA, ovalbumin; SIC, specific inhalation challenge test; T cells, T lymphocytes; TDI, toluene diisocyanate; TMA, trimellitic anhydride.

Guinea pigs, rats, and mice are commonly used, but occasionally, rabbits, monkeys, and dogs are also used. The mouse model has advantages because the IgE-mediated responses in mice and their antigenic repertoire are similar to those of humans. Sensitization can be initiated by either systemic or local (inhalation or dermal) exposures. Systemic sensitization is usually done through intraperitoneal injections whereas respiratory exposures can be done through inhalation, intratracheal, or intranasal route. The animals are usually challenged by the respiratory route when respiratory frequency and pulmonary resistance are measured. Measurement of nonspecific bronchial hyperresponsiveness can also be assessed by response to methacholine challenges. Blood samples and lung lavages can be collected for immunologic assessment such as measurement of specific antibodies, inflammatory cytokines, or chemokines. The tissue can be used to assay messenger RNA and the lung pathology assessed.

Animal models have been very helpful in increasing our understanding of the pathogenesis of OA. Studying the dose relationship between exposure and response may allow the determination of a threshold limit value of human exposure, as in the case of detergent enzymes.[72] However, one needs to be cautious in interpreting the results because most of the exposure situations in humans are quite different from laboratory conditions and the response in humans could be different from that in animals.

Occupational Asthma without a Latency Period

In an animal model of irritant-induced asthma caused by a single exposure of rats to chlorine 1500 ppm, it was shown that maximum changes in lung resistance and nonspecific bronchial hyperresponsiveness occurred in the first 3 days and persisted after 1 week.[68] These functional changes corresponded to the maximum pathologic changes when complete epithelial denudation was found. Neutrophils were increased in BAL. When lung tissue is exposed to chlorine, oxidation of component proteins is found with increased concentration of 3-nitrotyrosine and inducible nitric oxide synthase, along with the hypothesis that irritant-induced asthma is induced by an oxidative process.[69]

FREQUENCY

The frequencies of asthma in the workplace can be assessed by several means in either cross-sectional and longitudinal studies, and they are presented in Table 64-5.[3,4,6,12,82–86] First, several population-based studies have been carried out. Blanc and Toren,[1] in an often quoted review, proposed a median estimate of 9% to 15% of attributable risk of asthma due to work exposure. Becklake and associates[7] reviewed selected studies in which the population attributable risk (%) ranged from

TABLE 64-5. Means for Assessing the Frequency of Asthma in the Workplace and Examples

Type of Study*	Strengths	Weaknesses	Examples (Ref. Nos.)
POPULATION-BASED			
Epidemiologic surveys	Large samples. Subjects exposed to a vast number of agents. Possibility of using a job-exposure matrix. Avoid the "healthy worker" effect.	Mostly based on questionnaires. Very little objective confirmation. Costly.	82
Registers	Large samples. Subjects exposed to a vast number of agents. Not costly.	Indirect information. Misclassification likely.	83
OCCUPATION-BASED			
Epidemiologic surveys	Well-defined populations in high-risk workforces with possibility of control groups. Objective testing can be done. Possibility of obtaining information on preexposure host factors. Characterization of environment feasible.	Survivor bias. (Healthy worker effect.)	104 6 4
PATIENT- OR CLAIMANT-BASED			
Sentinel projects	Subjects assessed by specialists.	Referral biases Clinical impression not necessarily based on objective testing.	84 12
Patients referred to specialist clinics	Subjects assessed by specialists. Objective testing likely with firm diagnosis.	Referral biases.	85
Medicolegal registers	Diagnosis confirmed.	Referral biases.	86

*The design can be cross-sectional or longitudinal.

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3% in studies from Spain[87] and New Zealand[88] to 23% in Canada[89] and 33% in Singapore.[90] An important survey in the general population recently proposed that 10% to 25% of new cases of asthma confirmed by assessment of bronchial responsiveness were attributable to the workplace.[82] A source of controversy in the ascertainment of the condition is that it can be defined as either new-onset asthma or work-aggravated asthma and not necessarily OA.[91,92]

The prevalence of work-related respiratory symptoms suggestive of OA and of OA have been investigated in several different workplace surveys where workers were exposed to agents known to cause OA.[7] Highly variable prevalence figures have been proposed, depending on the way the cases were defined. Obviously, using only a questionnaire results in higher figures. Studies in which objective tests have been carried out to better ascertain cases have shown that as a rule of thumb, the prevalence is lower than 5% in workers exposed to high-molecular-weight agents and is between 5% and 10% in workers exposed to low-molecular-weight agents. The well-known survivor effect affects prevalence estimates.

Prevalence figures can also be obtained from registers. A population-based incidence study included the entire employed Finnish population. The cohort was followed for 10 years, using two registers, one of clinically established persistent asthma, the other of census data (for information on employment).[83] A total of nearly 50,000 incident cases of asthma were recorded and the fraction attributable to work was 29% for males and 17% for females. The proportion attributable to work was approximately 5%.[93] Higher frequencies of asthma and use of antiasthma medications have been found in workers of various trades—health care professionals,[94] cleaners,[95,96] electrical machinery workers,[97] and construction workers[90] being the most consistently reported ones. Recent figures from Surveillance of Work and Occupational Respiratory Disease (SWORD), the sentinel project based in the United Kingdom, show stabilization and even a reduction in the number of new cases of OA.[98] Similar surveillance systems have been initiated in the Canadian provinces of Quebec[99] and British Columbia,[100] in France,[101] and in South Africa.[102] Another means of collecting relevant information on frequency is by soliciting physicians to report possible cases with a sentinel-based approach. The SWORD[84] and the SENSOR[12] projects, respectively based in the United Kingdom and the United States, the most well-known and long-lived ones, reflect not only changes in frequencies but also changes in causal agents. Frequency can also be examined by consulting patient files in specialized referral clinics.[85] Finally, medicolegal statistics can be used. Figures from Finland and Quebec are particularly illustrative in this regard as they are probably less likely to be affected by underreporting because the system offers satisfactory compensation to workers with OA. Moreover, objective tools are used to diagnose the condition.[86]

Several prospective cohort studies have been carried out in selected high-risk professions to assess the incidence and determinants of probable OA among apprentices newly exposed to high-molecular-weight agents[3,4,103–107] and low-molecular-weight sensitizers.[5,108] The incidence is particularly high in apprentices exposed to animal-derived allergens, more so than in bakers and dental hygienists exposed to latex.[109] It is also higher during the apprenticeship period and diminishes during later exposure at the time of employment.[6]

Risk determinants for developing sensitization and disease have been examined in various studies.[7] Clearly, exposure and the degree of exposure, as shown by dose-response analysis, are the most significant determinants in most studies, having therefore an important impact on the prevention strategy in surveillance programs. Most occupational studies have shown that the higher the level of exposure, the higher the prevalence of sensitization. Table 64-6 shows some of these studies from

TABLE 64-6. Studies of Exposure-Response Relationships of Occupational Agents and Exposure Limits

Allergen	Source (Ref. No.)	No. Subjects	Lowest Effective Allergen Level	Exposure-Response Relationship	OEL in BC
Flour dust	110	230	1–2.4 mg/m^3	Sensitization	4 mg/m^3 for grain dust
	111	279	1.7 mg/m^3	Sensitization	
				Symptoms, PD20	
Alpha-amylase	112	178	0.25 ng/m^3	Sensitization	
Western red cedar	113	243	0.2–0.4 mg/m^3	FEV_1 decline	
Latex—NRL	114	145	0.6 ng/m^3	Sensitization, symptoms	1 ng/m^3
Acid anhydride					
TCPA	115	52	0.1–0.39 mg/m^3	Symptoms	0.04 mg/m^3
TMA	116	17	0.82 mg/m^3	Symptoms	
TMA	117	49	<0.04 mg/m^3	Symptoms, sensitization	
Isocyanates	118	84	5–10 ppb	Symptoms, lung function decline	0.005 ppm
Colophony	119	88	<0.01 mg/m^3	Asthma, lung function decline	
Platinum salts	120	78	≤2 µg/m^3	Sensitization, asthma	0.002 mg/m^3

FEV_1, forced expiratory volume in 1 second; NRL, natural rubber latex; OEL in BC, occupational exposure limits in British Columbia, Canada; ppb, parts per billion; ppm, parts per million; TCPA, tetrachlorophthalic anhydride; TMA, trimellitic anhydride.

which the lowest observed effective allergen levels were derived as well as the occupational threshold limit values in British Columbia, which were based on time-weighted averages.[110-120]

In OA, once sensitized, the degree of exposure is also a major determinant in the development of symptoms. However, the level of exposure required to induce symptoms is significantly lower after sensitization. Thus, the classic notion of time-weighted average exposure, short-term exposure limits, and ceiling limits for agents that are responsible for occupational diseases may not be relevant in OA.[121] For example, in diisocyanate exposure, it is not clear at this time whether peak levels of exposure are more important than the cumulative dose of exposure because one case report indicates the importance of intermittent high levels of exposure[122] whereas another indicates the level of continuous exposure.[123] In the case of high-molecular-weight agents only, personal factors that influence risk are atopy and, inconsistently, depending on the causal agent, smoking.[108] In a study of animal laboratory workers, the risk of sensitization in atopic subjects was found to increase when levels of exposure were low but the risk did not further increase with increasing exposure. In nonatopic subjects, the risk of sensitization increased with increasing exposure.[124] Some investigators suggested that genetic susceptibility is important when levels of exposure are low.[34]

DIAGNOSIS

The diagnosis of OA is a stepwise procedure that uses several tools (Fig. 64-2). Unfortunately, although guidelines have been proposed, objective confirmation of OA is often still not or only partially carried out.[125] The diagnosis of OA is too often made on clinical history alone, which is unacceptable when one considers the availability of objective tests for making the diagnosis.

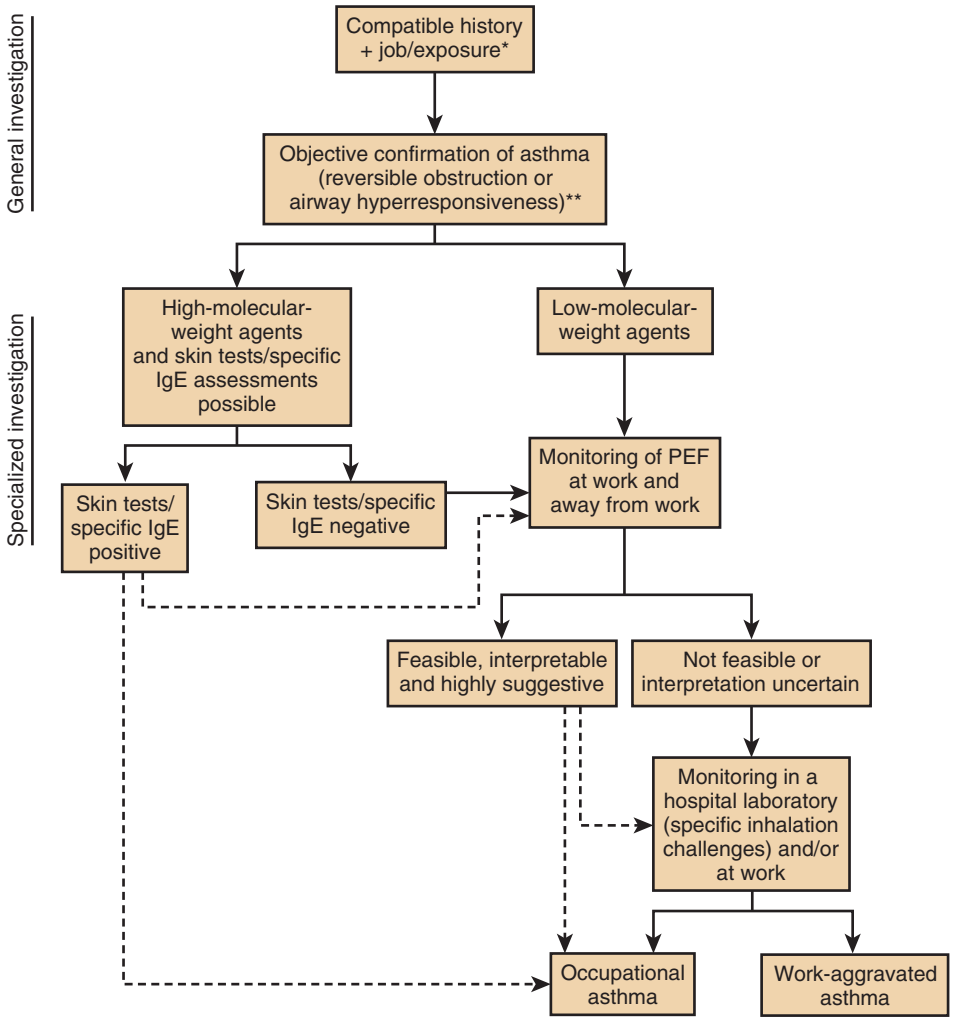

FIGURE 64-2 ■ The diagnosis of occupational asthma (OA). *Either the job or the exposure can result in increased risk. **Airway responsiveness can be ideally assessed at a time the worker is at work and has been symptomatic recently; even if a worker is no longer at work, airway responsiveness can persist in 75% of workers with OA. The *dashed lines* indicate that there are two possibilities. For example, even if interpretation of peak expiratory flow is suggestive of OA, some would prefer to carry on monitoring of airway function and inflammation.

The clinical questionnaire is the first step. It should obtain information on job title and exposure. For example, health care professionals represent a group at risk and a patient with asthma working in this field should be questioned on the products he or she may be exposed to at work. Information on products handled at work can be obtained by consulting material safety data sheets. However, these might not reveal the complete content of a product because manufacturers in the United States do not have to report on content that represents less than 1% of the total content of a product. If there is suspicion that a product can cause OA, the manufacturer needs to be contacted. In some instances, "walk-through" visits of the workplace need to be done to obtain more information on exposure. Often, workers can be exposed to several products that are known to cause OA.

Typically, respiratory symptoms begin to appear only on workdays and improve or disappear on weekends and vacations. However, with the progression of symptoms, patients may still be symptomatic on weekends. Workers should be questioned not only on the presence of classical asthma symptoms such as wheezing but also on nasal (i.e., the "united airway" concept) and ocular symptoms, especially in the case of exposure to high-molecular-weight agents for which the allergic mechanism is IgE-mediated.[126] A list of key symptoms to include has been published.[126] It has been shown that "open questionnaires" used by clinicians demonstrate satisfactory sensitivity but lack specificity.[29] Therefore, they should not be used alone in making a diagnosis that has considerable psychosocioeconomic impact (e.g., wrongly suggesting that a young worker leave his usual work for which he has been trained) and health consequences (e.g., wrongly suggesting that a worker stay at work with worsening asthma and the possibility of long-term sequelae).

If a worker has a history suggestive of asthma and has a job/exposure history compatible with OA, it is mandatory to confirm the diagnosis of asthma by objective testing, confirming either partial or complete reversibility of airway obstruction or airway hyperresponsiveness in the event that normal airway caliber is present. This assessment is best carried out toward the end of a week spent at work (i.e., on the Thursday or Friday afternoon of a normal week at work). Even if the worker is no longer at work, objective confirmation of asthma is still required because airway hyperresponsiveness is often still present after many exposure-free years in as much as 75% of workers affected with OA. If assessment of airway inflammation using induced sputum is available, this should also be examined. Workers may have normal function but airway inflammation can be present, especially in the case of eosinophilic bronchitis.

After confirming that a symptomatic at-risk worker has asthma, it is mandatory to refer her or him to a specialized center. Skin testing with some high-molecular-weight occupational allergens is feasible with cereals, in the case of bakers, or latex, for health professionals using gloves. If a technician exposed to laboratory animals has confirmed asthma and a positive skin test to rat urine, there is an 80% chance that exposure to rat urine in the laboratory will result in an asthmatic reaction.[127] Unfortunately, extracts of high-molecular-weight agents are rarely standardized and skin tests cannot be done with low-molecular-weight agents.

Serial monitoring of PEF can be initiated for periods at work and away from work. Such monitoring is complex. Workers need to be exposed and symptomatic at the time that this is carried out and meticulously and honestly record their breathing at least four times a day. Graphs have to be plotted and interpreted. The availability of computer-based reading may help the specialist.[24] This monitoring can be coupled with assessment of nonspecific bronchial hyperresponsiveness during periods at work and away from work as well as with monitoring of inflammatory parameters. Induced sputum adds information to monitoring of PEF[14] but monitoring of exhaled nitric oxide still has to be validated in the investigation of OA. In many instances, even after completing this investigation, the diagnosis is still uncertain and further testing is required. Finally, one should consider serial monitoring of airway function (forced expiratory volume in 1 second, forced vital capacity, airway responsiveness to methacholine) and inflammation (induced sputum) on days of controlled exposure to the potential causal agent in a hospital laboratory[128] or at work.[129] This monitoring that should be offered only in specialized centers and carried out in a standardized way, in a dose-response curve fashion, under the close supervision of an experienced technician.

EXPOSURE AND ENVIRONMENTAL MONITORING

Environmental monitoring is important in OA for identification of causative agents, determination of exposure dose-response relationship, establishment of threshold limit values, and subsequent control of exposure.

Traditional environmental monitoring has been carried out for chemicals and gases, but many agents causing OA are high-molecular-weight allergens such as proteins and polysaccharides. Progress and advancement in particle collection methods and immunochemistry since 1980 have enabled the characterization of complex mixtures of proteinaceous material and increased our understanding of bioaerosol exposure and its link to allergic lung disease.[121]

Exposure is the most important determinant in the development of OA (see "Frequency," earlier). Most occupational studies have shown that the higher the level of exposure, the higher the prevalence of sensitization. In OA, once sensitized, the degree of exposure is also a major determinant in the development of symptoms. However, the level of exposure required to induce symptoms is significantly lower after sensitization. Thus, the classic notion of time-weighted average exposure, short-term exposure limits and ceiling limits for agents that are responsible for occupational diseases may not be relevant in OA.[121] For example, in diisocyanate

exposure, it is not clear at this time whether peak levels of exposure are more important than the cumulative dose of exposure; one case report indicates the importance of intermittent high levels of exposure[122] whereas another indicates the level of continuous exposure.[123] In the case of flour, an exposure threshold has been proposed at 2 mg/m^3, at which risk of sensitization is significantly lower.[110]

Employers must ensure the availability of copies of the material safety data sheet for all materials used in the workplace. Moreover, an employer is required by law to make this information available to all workers in the workplace. Material safety data sheets are also available at the following websites: http://ccinfoweb.ccohs.ca/msds/search.html and www.ehs.cornell.edu/lrs/internetMSDS.htm. In the United States, the Occupational Safety and Health Administration (OSHA) requires suppliers to include information regarding a sensitizer if its concentration represents 1% or greater (≥0.1% in Canada) in a chemical product and to be listed as a hazardous ingredient.

MEDICOLEGAL ASPECTS AND COMPENSATION ISSUES

Numerous studies have shown that patients with documented OA may not recover after removal from exposure.[7] Even those apparently cured using clinical and functional criteria still have airway inflammation and remodeling 10 years or more after cessation of exposure.[8] Moreover, patients with OA (as well as with work-aggravated asthma) often become unemployed and suffer a loss of income after removal from exposure.[13,130–133] Even those workers who remain employed in the same workplace may suffer a reduction in income and an increase in medication costs over time.[132]

Given the permanent impairment and the economic loss from OA, the treating physician should support his or her patients in Workers' Compensation claims once the diagnosis has been established. Workers' Compensation is generally a no-fault compensation system paid for by employers or by insurance companies and differs from country to country. This variation is at times due to different ways of defining OA. In some industrialized countries, compensation of OA is based on a list or schedules of covered diseases. In others, objective evidence of work-relationship is necessary. It is in the patient's interest for the physician to obtain as much objective diagnostic information as possible before submitting the application so as to assist those with OA to change jobs and to avoid loss of employment for workers who do not have OA. Work-aggravated asthma is generally not accepted for compensation by medicolegal agencies unless unexpected working conditions occurred (e.g., an atopic asthmatic subject exposed to various molds as a result of dampness in a workplace and who reports that asthmatic symptoms worsened at work during a specific period or a lifeguard with asthma who has been exposed to higher than usual concentrations of chlorine in a swimming pool and who reports that the asthmatic condition worsened during this period).

In Quebec, Canada, the first level of compensation allocated at the time of diagnosis provides for an income replacement indemnity and complete costs for rehabilitation. This process lasts 1 to 2 years. The second level is based on a permanent disability indemnity that is allocated 2 years after diagnosis because, although improvement can still occur at a later stage, maximum improvement occurs in the first 2 years after cessation of exposure.[134] The criteria used for the determination of permanent impairment are the degree of airway obstruction, the degree of nonspecific bronchial hyperresponsiveness, and the need for medication as proposed by the American Thoracic Society[31] and the American Medical Association.[135] As a result, disability, that is, the impact of functional impairment and the psychosocial burden as a whole, is probably less than in other jurisdictions[136] with more than 80% of workers being employed when assessed 2 years after diagnosis, for a median direct cost recently estimated at $61,000 Canadian dollars (CAD) per claimant, this covering both readaptation and impairment/disability (including drugs for asthma).[137]

Whereas most industrialized countries have recognized OA as a compensable disease, work-aggravated asthma is not. Because the loss of income and suffering are the same irrespective of whether asthma is caused or exacerbated by work, the management and approach to compensation of work-aggravated asthma should be reconsidered.

PREVENTION AND SURVEILLANCE

Primary Prevention

Reduction of exposure is the key to primary prevention of OA and work-exacerbated asthma. This could be accomplished by substitution of the known hazardous substance with one that is less harmful, by improving ventilation, by enclosing the process, by modifying the process or the agent to reduce risk sensitization, and by improving housekeeping and work practices. There are many examples of successful reduction in OA and allergy due to reduction of exposure. In natural rubber latex allergy, avoiding use of the sensitizer by replacing latex gloves with nonlatex gloves and reducing the powder and the content of latex protein of gloves are measures that have led to a decline in the incidence of both OA and allergies to latex[22] as reflected in compensation data reported in Ontario[138] and in national statistics in Germany.[139] Encapsulation of detergent enzymes to reduce exposure was very successful in reducing sensitization and asthma.[21] In Ontario, Canada, the introduction of a surveillance program in 1983 for diisocyanates to include monitoring of diisocyanate concentrations in the workplace with a maximum allowable 8-hour time-weighted average of 5 ppb combined with a medical surveillance program was associated with a decline in new diisocyanate-induced asthma compensation

claims,[140] although similar declines have been noticed in other parts of the world where surveillance programs do not exist. The use of personal protective equipment such as respirators, gloves, coveralls, and goggles by the worker to reduce exposure is less desirable because compliance is poor.

The second measure in primary prevention is to identify susceptible workers and relocate them to areas free of known sensitizers. Atopy has been shown to be the most important personal risk factor for OA, whereas smoking is relevant in some types of OA owing to high-molecular-weight agents and some low-molecular-weight compounds such as acid anhydrides and platinum salts.[7] However, the prevalence of atopy in the general population is very high, close to 40%, and the rate of sensitization to the occupational agent is relatively low. Considering the high frequency of atopy, it is unrealistic to exclude atopic individuals from the workforce. Conversely, many countries now prohibit smoking in the workplace.

Another possible measure is to screen chemicals for respiratory sensitizing potential before their introduction into the market. As some low-molecular-weight compounds possess chemical structures that are more potent sensitizers than others, studies have been carried out to assess whether it is possible to develop quantitative structure-activity relationship models to predict the sensitizing potential of these compounds.[141,142] However, so far, there has been no validated protocol.

Secondary Prevention

Secondary prevention aims at early detection in workers with disease and removal of workers from further exposure to prevent the progression of the disease process with increasing morbidity and disability. Secondary prevention consists of a medical surveillance program together with environmental monitoring usually in high-risk industries. For high-molecular-weight allergens, a reasonable medical surveillance program of OA may include a symptom questionnaire, skin prick testing, and spirometry every 6 months for 2 years and once every year thereafter. In the detergent enzyme industry, such medical surveillance has proved to be very successful.[21] Workers who developed rhinitis or lower respiratory symptoms at work and had positive skin tests were removed from exposure. The rate of OA was significantly reduced as a result of these measures.

In asthma due to platinum salt allergy, skin prick testing using platinum salt in medical surveillance to detect and remove sensitized workers from further exposure resulted in a reduction of asthma.[143] However, when skin testing is not available, as in most low-molecular-weight compounds, the medical surveillance program is dependent on symptom questionnaires and spirometry. In Ontario, such a program was mandated by the Department of Labour—a questionnaire every 6 months and spirometry, if indicated by the questionnaire, as well as follow-up at least every 2 years thereafter. A referral was made for further investigation if the worker had symptoms of asthma or if there was a 15% drop in spirometry. This program initially increased the number of compensation claims followed by a progressive reduction.[140]

Tertiary Prevention

Tertiary prevention is directed at reducing the degree of impairment/disability in those with established disease. For OA with latency, the best prognosis is complete avoidance of further exposure to the sensitizing agent. An air-supply helmet respirator has been used by some sensitized workers when exposure is intermittent. Its use on a continuous basis may not be tolerated by workers.

IRRITANT-INDUCED ASTHMA AND REACTIVE AIRWAY DYSFUNCTION SYNDROME

It had long been thought that inhalational accidents resulted only in lung injury, causing edema and alteration of the alveolocapillary membrane, an example being the deleterious effect of toxic gases used in World War I.[19] It was only in 1983 that authors described the airway effect of inhalational accidents with development of airway hyperresponsiveness and irritant-induced asthma.[144] The label "RADS" and criteria for diagnosis were later proposed.[20] Whereas the label "RADS" is reserved for a single inhalational accident, Irritant-induced asthma may include more than one accident. The most mediated RADS events occurred at Bhopal in 1987 where methylisocyanate was responsible for the deaths of 2000 civilians[145] and at the World Trade Center site where firemen and civilians were exposed to dust.

RADS occurs after accidentally inhaling an agent generated at high concentrations. Theoretically, all types of agents can cause RADS but chlorine and ammonia are the most commonly reported agents. Vapors and aerosols are more likely to cause RADS than dry particles. The degree of exposure and the proximity of the emission are the most important determinants.[146] and there is no personal determinant. Table 64-7 compares some features of OA with a latency period and irritant-induced asthma. Although irritant-induced asthma is a type of OA, there are several differences between the two conditions (see Table 64-7). Coughing is the principal symptom and, commonly, the nose is also affected, workers complaining of acute burning in the nose. Workers typically arrive at the first aid unit or at the emergency department. Unfortunately, too often spirometry is not assessed and treatment with a bronchodilator and oxygen is initiated without giving parenteral and inhaled steroids, which should be the recommended course of action as early as possible after an inhalational accident.[147] Airway responsiveness should be part of the assessment. Typically, there is a discrepancy between the severity of symptoms and the low degree of airway hyperresponsiveness. If a worker is still symptomatic after 3 months, improvement will be minimal afterward.

TABLE 64-7. Differences between Occupational Asthma with a Latency Period and Irritant-Induced Asthma

	OA with a Latency period	IrIA
Latency period	Variable but at least a matter of weeks	Onset of symptoms within minutes or hours
Mechanisms	Immunologic sensitization	?
Physiopathology	Like common asthma	Massive epithelial desquamation with early deposition of collagen. No role of eosinophils. Oxidative process.
Frequency	85%–90% of all cases of OA	10%–15% of all cases of OA
Symptoms	Wheeze predominant	Cough predominant
Function	The degree of airway hyperresponsiveness to methacholine reflects severity.	Severity not reflected by the degree of responsiveness to methacholine.
Response to bronchodilator	+++	++
Response to inhaled steroids	+++	++
Improvement with time	Good in general	Moderate, little or absent

IrIA, irritant-induced asthma; OA, occupational asthma.

Irritant-induced asthma represents 10% to 15% of all cases of OA compensated by medicolegal agencies in Ontario[148] and Quebec.[149] Animal models in rats[68] and mice[69] exposed to chlorine have shown that early epithelial desquamation is massive, followed by an important generation of epithelial basal cells, edema, and early collagen deposition in the submucosal space. Inflammatory cells are minimally present. Although one study has shown that 25% of subjects with RADS had normal responsiveness approximately 2 years after an inhalational accident,[150] generally, the clinical, functional and pathological improvement is less than what is found in OA with a latency period.[151,152]

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KEY POINTS

- OA is caused by the workplace and may be associated with a latency period necessary for acquiring sensitization. OA can occur without a latency period, usually after inhalation of an irritating substance. This has different characteristics from asthma associated with latency.
- Asthmatic persons who report that their symptoms are aggravated by exposure in the workplace may also suffer significant disability.
- Asthma in the workplace can be suspected in 1 out of 10 adult-onset asthmatic subjects.
- OA can be caused by high-molecular-weight (proteins) and low-molecular-weight (chemicals) agents.
- OA caused by high-molecular-weight agents is IgE-mediated whereas the mechanism of OA caused by low-molecular-weight agents is generally unknown, although it is immunologically mediated.
- The diagnosis of OA should be confirmed by objective testing in addition to clinical questionnaires.
- The nature and intensity of exposure are the principal determinants of OA and are more important than personal determinants.
- OA should be diagnosed early to avoid permanent sequelae.
- Satisfactory compensation should be offered to claimants, the emphasis being on proper readaptation programs.
- Prevention should be focused on adequate environmental control.

References

1. Toren K, Blanc P: Asthma caused by occupational exposures is common—a systematic analysis of estimates of the population-attributable fraction. BMC Pulm Med 9:7, 2009.
2. Tarlo SM: Occupational asthma: A valid model for adult asthma? Curr Opin Allergy Clin Immunol 3:91–94, 2003.
3. Gautrin D, Ghezzo H, Infante-Rivard C, Malo JL: Natural history of sensitization, symptoms and diseases in apprentices exposed to laboratory animals. Eur Respir J 17:904–908, 2001.
4. Walusiak J, Hanke W, Gorski P, Palczynski C: Respiratory allergy in apprentice bakers: Do occupational allergies follow the allergic march? Allergy 59:442–450, 2004.
5. El-Zein M, Malo JL, Infante-Rivard C, Gautrin D: Incidence of probable occupational asthma and of changes in airway calibre and responsiveness in apprentice welders. Eur Respir J 22:513–518, 2003.
6. Gautrin D, Ghezzo H, Infante-Rivard C, et al: Long-term outcomes in a prospective cohort of apprentices exposed to high-molecular-weight agents. Am J Respir Crit Care Med 177:871–879, 2008.
7. Becklake MR, Chan-Yeung M, Malo JL: Epidemiological approaches in occupational asthma. *In* Bernstein IL, Chan-Yeung M, Malo JL, Bernstein DI (eds): Asthma in the Workplace (3rd ed): New York: Taylor & Francis, 2006, pp 37–85.
8. Sumi Y, Foley S, Daigle S, et al: Structural changes and airway remodelling in occupational asthma at a mean interval of 14 years after cessation of exposure. Clin Exp Allergy 37:1781–1787, 2007.
9. Maestrelli P, Saetta M: Recovery from adult-onset asthma and airway remodelling. Clin Exp Allergy 37:1733–1735, 2007.
10. Pepys J, Hutchcroft BJ: Bronchial provocation tests in etiologic diagnosis and analysis of asthma. Am Rev Respir Dis 112:829–859, 1975.
11. Bernstein IL, Bernstein DI, Chan-Yeung M, Malo JL: Definition and classification of asthma in the workplace. *In* Bernstein IL, Chan-Yeung M, Malo JL, Bernstein DI (eds): Asthma in the Workplace (3rd ed). New York: Taylor & Francis, 2006, pp 1–8.
12. Jajosky RA,Harrison R, Reinisch F, et al: Surveillance of work-related asthma in selected U.S. states using surveillance guidelines for state health departments—California, Massachusetts, Michigan, and New Jersey. MMWR CDC Surveill Summ 48:1–20, 1999.
13. Larbanois A, Jamart J, Delwiche JP, Vandenplas O: Socioeconomic outcome of subjects experiencing asthma symptoms at work. Eur Respir J 19:1107–1113, 2002.
14. Girard F, Chaboillez S, Cartier A, et al: An effective strategy for diagnosing occupational asthma. Induced sputum. Am J Respir Crit Care Med 170:845–850, 2004.
15. Chiry S, Cartier A, Malo JL, et al: Comparison of peak expiratory flow variability between workers with work-exacerbated asthma and occupational asthma. Chest 132:483–488, 2007.
16. Quirce S: Eosinophilic bronchitis in the workplace. Curr Opin Allergy Clin Immunol 4:87–91, 2004.
17. Pepys J, Bernstein IL: Historical aspects of occupational asthma. *In* Bernstein IL, Chan-Yeung M, Malo JL, Bernstein DI. (eds): Asthma in the Workplace (3rd ed). New York: Taylor & Francis, 2006, pp 9–35.
18. Fuchs S, Valade P: Étude clinique et expérimentale sur quelques cas d'intoxication par le Desmodur T (diisocyanate de toluylene 1-2-4 et 1-2-6). Arch Mal Profess 12:191–196, 1951.
19. Das R, Blanc PD: Chlorine gas exposure and the lung: A review. Toxicol Ind Health 9:439–455, 1993.
20. Brooks SM, Weiss MA, Bernstein IL: Reactive airways dysfunction syndrome (RADS): Persistent asthma syndrome after high level irritant exposures. Chest 88:376–384, 1985.
21. Juniper CP, How MJ, Goodwin BFJ: Bacillus subtilis enzymes: A 7-year clinical, epidemiological and immunological study of an industrial allergen. J Soc Occup Med 27:3–12, 1977.
22. Saary MJ, Kanani A, Alghadeer H, et al: Changes in rates of natural rubber latex sensitivity among dental school students and staff members after changes in latex gloves. J Allergy Clin Immunol 109:131–135, 2002.
23. Pepys J: Inhalation challenge tests in asthma. N Engl J Med 293:758–759, 1975.
24. Burge PS, Moscato G, Johnson A, Chan-Yeung M: Physiological assessment: Serial measurements of lung function and bronchial responsiveness. *In* Bernstein IL, Chan-Yeung M, Malo JL, Bernstein DI (eds): Asthma in the Workplace (3rd ed). New York: Taylor & Francis, 2006, pp 199–226.
25. Lemière C, Biagini RE, Zeiss CR: Immunological and inflammatory assessments. *In* Bernstein IL, Chan-Yeung M, Malo JL, Bernstein DI (eds): Asthma in the Workplace (3rd ed). New York: Taylor & Francis, 2006, pp 179–197.
26. Tarlo SM, Liss FGM: Evidence-based guidelines for the prevention, identification and, management of occupational asthma. Occup Environ Med 62:288–289, 2005.
27. Barber CM, Naylor S, Bradshaw LM, et al: Approaches to the diagnosis and management of occupational asthma amongst UK respiratory physicians. Respir Med 101:1903–1908, 2007.
28. Kopferschmitt-Kubler MC, Ameille J, Popin E, et al: Occupational asthma in France: A 1-year report of the Observatoire National de Asthmes Professionnels project. Eur Respir J 19:84–89, 2002.
29. Malo JL, Ghezzo H, L'Archevêque J, et al: Is the clinical history a satisfactory means of diagnosing occupational asthma? Am Rev Respir Dis 143:528–532, 1991.
30. Chan-Yeung M: Fate of occupational asthma. A follow-up study of patients with occupational asthma due to Western red cedar (*Thuja plicata*). Am Rev Respir Dis 116:1023–1029, 1977.
31. American Thoracic Society: Guidelines for the evaluation of impairment/disability in patients with asthma. Am Rev Respir Dis 147:1056–1061, 1993.
32. Malo JL, Chan-Yeung M: Agents causing occupational asthma with key references. *In* Bernstein IL, Chan-Yeung M, Malo JL, Bernstein DI (eds): Asthma in the Workplace (3rd ed). New York: Taylor & Francis, 2006, pp 825–866.
33. Jeal H, Draper A, Jones M, et al: HLA associations with occupational sensitization to rat lipocalin allergens: A model for other animal allergies? J Allergy Clin Immunol 111:795–799, 2003.
34. Newman Taylor AJ, Cullinan P, Lympany PA, et al: Interaction of HLA phenotype and exposure intensity in sensitization to complex platinum salts. Am J Respir Crit Care Med 160:435–438, 1999.
35. Young RP, Barker RD, Pile KD, et al: The association of HLA DR3 with specific IgE to inhaled acid anhydrides. Am J Respir Crit Care Med 151:219–221, 1995.
36. Jones MG, Nielsen J, Welch J, et al: Association of HLA-DQ5 and HLA-DR1 with sensitization to organic acid anhydrides. Clin Exp Allergy 34:812–816, 2004.
37. Bignon JS, Aron Y, Ju LY, et al: HLA class II alleles in isocyanate-induced asthma. Am J Respir Crit Care Med 149:71–75, 1994.
38. Balboni A, Baricordi OR, Fabbri LM, et al: Association between toluene diisocyanate–induced asthma and DQB1 markers: A possible role for aspartic acid at position 57. Eur Respir J 9:207–210, 1996.
39. Horne C, Quintana PJE, Keown PA, et al: Distribution of HLA class II DQB1 alleles in patients with occupational asthma due to Western red cedar. Eur Respir J 15:911–914, 2000.
40. Elms J, Beckett PN, Griffin P, Curran AD: Mechanisms of isocyanate sensitization. An in vitro approach. Toxicol In Vitro 15:631–634, 2001.
41. Mapp CE, Fryer AA, DeMarzo N, et al: Glutathione *S*-transferase GSTP1 is a susceptibility gene for occupational asthma induced by isocyanates. J Allergy Clin Immunol 109:867–872, 2002.
42. Piirila P, Wikman H, Luukkonen R, et al: Glutathione *S*-transferase genotypes and allergic responses to diisocyanate exposure. Pharmacogenetics 11:437–445, 2001.
43. Bernstein DI, Wang N, Campo P, et al: Diisocyanate asthma and gene-environment interactions with IL4RA, CD-14, and IL-13 genes. Ann Allergy Asthma Immunol 97:800–806, 2006.
44. Saetta M, DiStefano A, Maestrelli P, et al: Airway mucosal inflammation in occupational asthma induced by toluene diisocyanate. Am Rev Respir Dis 145:160–168, 1992.
45. Saetta M, Maestrelli P, DiStefano A, et al: Effect of cessation of exposure to toluene diisocyanate (TDI) on bronchial mucosa of subjects with TDI-induced asthma. Am Rev Respir Dis 145:169–174, 1992.

46. Tse KS, Chan H, Chan-Yeung M: Specific IgE antibodies in workers with occupational asthma due to Western red cedar. Clin Allergy 12:249–258, 1982.
47. Frew A, Chan H, Dryden P, et al: Immunologic studies of the mechanisms of occupational asthma caused by Western red cedar. J Allergy Clin Immunol 92:466–478, 1993.
48. Wisnewski A, Redlich CA, Mapp CE, Bernstein DI: Polyisocyanates and their prepolymers. *In* Bernstein IL, Chan-Yeung M, Malo JL, Bernstein DI (eds): Asthma in the Workplace (3rd ed). New York: Taylor & Francis, 2006, pp 481–504.
49. Tee RD, Cullinan P, Welch J, et al: Specific IgE to isocyanates: A useful diagnostic role in occupational asthma. J Allergy Clin Immunol 101:709–715, 1998.
50. Park HS, Kim Hy, Lee SK, et al: Diverse profiles of specific IgE response to toluene diisocyanate(TDI)-human serum albumin (HSA) conjugate to TDI-induced asthma patients. J Korean Med Sci 16:57–61, 2000.
51. Wisnewski AV, Stowe MH, Cartier A: Isocyanate vapor–induced antigenicity of human albumin. J Allergy Clin Immunol 113:1178–1184, 2004.
52. Wisnewski AV, Lemus R, Karol MH, Redlich CA: Isocyanate-conjugated human lung epithelial cell proteins: A link between exposure and asthma? J Allergy Clin Immunol 104:341–347, 1999.
53. Cartier A, Grammer L, Malo JL, et al: Specific serum antibodies against isocyanates: Association with occupational asthma. J Allergy Clin Immunol 84:507–514, 1989.
54. Bernstein DI, Cartier A, Cote J, et al: Diisocyanate antigen–stimulated monocyte chemoattractant protein-1 synthesis has greater test efficiency than specific antibodies for identification of diisocyanate asthma. Am J Respir Crit Care Med 166:445–450, 2002.
55. Frew A, Chan H, Lam S, Chan-Yeung M: Bronchial inflammation in occupational asthma due to Western red cedar. Am J Respir Crit Care Med 151:340–344, 1994.
56. Finotto S, Fabbri LM, Rado V, et al: Increase in numbers of CD8 positive lymphocytes and easinophils in peripheral blood of subjects with late asthmatic reactions induced by toluene diisocyanate. Br J Ind Med 48:116–121, 1991.
57. Maestrelli P, DelPrete GF, DeCarli M, et al: Activated CD8 T lymphocytes producing interferon-gamma (IFN-gamma) and interleukin-5 (IL-5) in bronchial mucosa of subjects sensitized to toluene diisocyanate (TDI). Scand J Work Environ Health 20:376–381, 1999.
58. Jones MG, Floyd A, Nouri-Aria KT, et al: Is occupational asthma to diisocyanates a non–IgE-mediated disease? J Allergy Clin Immunol 117:663–669, 2006.
59. Fabbri LM, Boschetto P, Zocca E, et al: Bronchoalveolar neutrophilia during late asthmatic reactions induced by toluene diisocyanate. Am Rev Respir Dis 136:36–42, 1987.
60. Lemière C, Romeo P, Chaboillez S, et al: Airway inflammation and functional changes after exposure to different concentrations of isocyanates. J Allergy Clin Immunol 110:641–646, 2002.
61. Douwes J, Gibson P, Pekkanen J, Pearce N: Non-eosinophilic asthma: Importance and possible mechanisms. Thorax 57:643–648, 2002.
62. Barnes PJ: Reactive oxygen species and airway inflammation. Free Radic Biol Med 9:235–243, 1990.
63. Chitano P, Di Blasi P, Lucchini RE, et al: The effects of toluene diisocyanate and of capsaicin on human bronchial smooth muscle in vitro. Eur J Pharmacol 270:167–173, 1994.
64. Mapp CE, Chitano P, Fabbri LM, et al: Evidence that toluene diisocyanate activates the efferent function of capsaicin-sensitive primary afferents. Eur J Pharmacol 180:113–118, 1990.
65. Chan-Yeung M, Giclas PC, Henson PM: Activation of complement by plicatic acid, the chemical compound responsible for asthma due to Western red cedar (*Thuja plicata*). J Allergy Clin Immunol 65:333–337, 1980.
66. Lemière C, Malo JL, Boutet M: Reactive airways dysfunction syndrome due to chlorine: Sequential bronchial biopsies and functional assessment. Eur Respir J 10:241–244, 1997.
67. Gautrin D, Boulet LP, Boutet M, et al: Is reactive airways dysfunction syndrome a variant of occupational asthma? J Allergy Clin Immunol 93:12–22, 1994.
68. Demnati R, Fraser R, Ghezzo H, et al: Time-course of functional and pathological changes after a single high acute inhalation of chlorine in rats. Eur Respir J 11:922–928, 1998.
69. Martin JG, Campbell HR, Iijima H, et al: Chlorine-induced injury to the airways in the mouse. Am J Respir Crit Care Med 168:568–574, 2003.
70. Biagini RE, Moorman WJ, Lewis TR, Bernstein IL: Ozone enhancement of platinum asthma in a primate model. Am Rev Respir Dis 134:719–725, 1986.
71. Thorne PS, Hillebrand J, Magreni C, et al: Experimental sensitization to subtilisin. I. Production of immediate and late onset pulmonary reaction. Toxicol Appl Pharmacol 86:112–123, 1986.
72. Sarlo K, Fletcher ER, Gaines WG, Ritz HL: Respiratory allergenicity of detergent enzymes in the guinea pig intratracheal test: Association with sensitization of occupationally exposed individuals. Fundam Appl Toxicol 39:44–52, 1997.
73. Aamir R, Safadi GS, Mandelik J, et al: A guinea pig model of hypersensitivity to allergenic fractions of natural rubber latex. Int Arch Allergy Immunol 110:187–194, 1996.
74. Hardy CL, Kenins L, Drew AC, et al: Characterization of a mouse model of allergy to a major occupational latex glove allergen Hev b 5. Am J Respir Crit Care Med 167:1393–1399, 2003.
75. Karol MH: The development of an animal model of TDI asthma. Bull Eur Physiopathol Respir 23:571–576, 1987.
76. Karol MH, Hauth BA, Riley EJ, Magreni CM: Dermal contact with toluene diisocyanate (TDI) induces respiratory tract hypersensitivity in guinea pigs. Toxicol Appl Pharmacol 58:221–230, 1981.
77. Herrick CA, Das J, Xu L, et al: Differential roles for CD4 and CD8 T cells after diisocyanate sensitization: Genetic control of TH2-induced lung inflammation. J Allergy Clin Immunol 111:1087–1094, 2003.
78. Pauluhn J, Eben A: Validation of a noninvasive technique to assess immediate or delayed onset of airway hypersensitivity in guinea pigs. J Appl Toxicol 11:423–431, 1991.
79. Chan H, Tse KS, Van Oostdam J, et al: A rabbit model of hypersensitivity to plicatic acid, the agent responsible for red cedar asthma. J Allergy Clin Immunol 79:762–767, 1987.
80. Ward MD, Selgrade MK: Animal models for protein respiratory sensitizers. Methods 41:80–90, 2007.
81. Arts JH, Kuper CF: Animal models to test respiratory allergy of low molecular weight chemicals: A guidance. Methods 41:61–71, 2007.
82. Kogevinas M, Zock JP, Jarvis D, et al: Exposure to substances in the workplace and new-onset asthma: An international prospective population-based study (ECRHS-II). Lancet 370:336–341, 2007.
83. Karjalainen A, Kurppa K, Martikainen R, et al: Work is related to a substantial portion of adult-onset asthma incidence in the Finnish population. Am J Resp Crit Care Med 164:565–568, 2001.
84. McDonald JC, Keynes HL, Meredith SK: Reported incidence of occupational asthma in the United Kingdom, 1989–97. Occup Environ Med 57:823–829, 2000.
85. Tarlo SM, Leung K, Broder I, et al: Asthmatic subjects symptomatically worse at work: Prevalence and characterization among a general asthma clinic population. Chest 118:1309–1314, 2000.
86. Bernstein Il, Keskinen H, Blanc PD, et al: Medicolegal aspects, compensation aspects, and evaluation of impairment/disability. In Bernstein IL, Chan-Yeung M, Malo JL, Bernstein DI (eds): Asthma in the Workplace (3rd ed). New York: Taylor & Francis, 2006, pp 319–351.
87. Kogevinas M, Antó JM, Soriano JB, et al: The risk of asthma attibutable to occupational exposures: A population-based study in Spain. Spanish Group of the European Asthma Study. Am J Respir Crit Care Med 154:137–143, 1996.
88. Fishwick D, Pearce N, D'Souza W, et al: Occupational asthma in New Zealanders: A population-based study. Occup Environ Med 54:301–306, 1997.
89. Becklake M, Ernst P, Chan-Yeung M, et al: The burden of asthma attributable to work exposures in Canada. Am J Respir Crit Care Med 153:A433, 1996.
90. Ng TP, Hong CY, Goh LG, et al: Risks of asthma associated with occupations in a community-based case-control study. Am J Ind Med 25:709–718, 1994.

91. Toren K, Brisman J, Olin AC, Blanc PD: Asthma on the job: Work-related factors in new-onset asthma and in exacerbations of pre-existing asthma. Respir Med 94:529–535, 2000.
92. Malo JL, Gautrin D: From asthma in the workplace to occupational asthma. Lancet 370:295–297, 2007.
93. Reijula K, Haahtela T, Klaukka T, Rantanen J: Incidence of occupational asthma and persistent asthma in young adults has increased in Finland. Chest 110:58–61, 1996.
94. Delclos GL, Gimeno D, Arif AA, et al: Occupational risk factors and asthma among health care professionals. Am J Respir Crit Care Med 175:667–675, 2007.
95. Zock JP, Kogevinas M, Sunyer J, et al: Asthma characteristics in cleaning workers, workers in other risk jobs and office workers. Eur Respir J 20:679–685, 2002.
96. Karjalainen A, Kurppa K, Martikainen R, et al: Exploration of asthma risk by occupation—Extended analysis of an incidence study of the Finnish population. Scand J Work Environ Health 28:49–57, 2002.
97. Arif AA, Whitehead LW, Delclos GL, et al: Prevalence and risk factors of work-related asthma by industry among United States workers: Data from the Third National Health and Nutrition Examination Survey (1988–94). Occup Environ Med 59:505–511, 2002.
98. McDonald JC, Chen Y, Zekveld C, Cherry NM: Incidence by occupation and industry of acute work-related respiratory diseases in the UK, 1992–2001. Occup Environ Med 62:836–842, 2005.
99. Provencher S, Labrèche FP, De Guire L: Physician based surveillance system for occupational respiratory diseases: The experience of PROPULSE, Québec, Canada. Occup Environ Med 54:272–276, 1997.
100. Contreras GR, Rousseau R, Chan-Yeung M: Occupational respiratory diseases in British Columbia, Canada in 1991. Occup Environ Med 51:710–712, 1994.
101. Ameille J, Pauli G, Calastreng-Crinquand A, et al; Observatoire National des Asthmes Professionnels:. Reported incidence of occupational asthma in France, 1996–99: The ONAP programme. Occup Environ Med 60:136–142, 2003.
102. Hnizdo E, Esterhuizen TM, Rees D, Lalloo UG: Occupational asthma as identified by the Surveillance of Work-related and Occupational Respiratory Diseases programme in South Africa. Clin Exp Allergy 31:32–39, 2001.
103. DeZotti R, Bovenzi M: Prospective study of work-related respiratory symptoms in trainee bakers. Occup Environ Med 57:58–61, 2000.
104. Gautrin D, Infante-Rivard C, Ghezzo H, Malo JL: Incidence and host determinants of probable occupational asthma in apprentices exposed to laboratory animals. Am J Respir Crit Care Med 163:899–904, 2001.
105. Archambault S, Malo JL, Infante-Rivard C, et al: Incidence of sensitization, symptoms and probable occupational rhinoconjunctivitis and asthma in apprentices starting exposure to latex. J Allergy Clin Immunol 107:921–923, 2001.
106. Gautrin D, Ghezzo H, Infante-Rivard C, Malo JL: Incidence and host determinants of work-related rhinoconjunctivitis in apprentice pastry-makers. Allergy 57:913–918, 2002.
107. Brisman J, Lillienberg L, Belin L, et al: Sensitization to occupational allergens in bakers' asthma and rhinitis: A case-referent study. Int Arch Occup Environ Health 76:167–170, 2003.
108. El-Zein M, Infante-Rivard C, Malo JL, Gautrin D: Is metal fume fever a determinant of welding related respiratory symptoms and/or increased bronchial responsiveness? A longitudinal study. Occup Environ Med 62:688–694, 2005.
109. Gautrin D, Ghezzo H, Infante-Rivard C, Malo J-L: Incidence and determinants of IgE-mediated sensitization in apprentices: A prospective study. Am J Respir Crit Care Med 162:1222–1228, 2000.
110. Houba R, Heederik D, Doekes G: Wheat sensitization and work-related symptoms in the baking industry are preventable. Am J Respir Crit Care Med 158:1499–1503, 1998.
111. Musk AW, Venables KM, Crook B, et al: Respiratory symptoms, lung function, and sensitisation to flour in a British bakery. Br J Ind Med 46:636–642, 1989.
112. Houba R, Heederik DJJ, Doekes G, van Run PEM: Exposure-sensitization relationship for a-amylase allergens in the baking industry. Am J Respir Crit Care Med 154:130–136, 1996.
113. Noertjojo HK, Dimich-Ward H, Peelen S, et al: Western red cedar dust exposure and lung function: A dose-response relationship. Am J Respir Crit Care Med 154:968–973, 1996.
114. Baur X: Cotton fluffs as latex allergen carriers in a glove factory. J Allergy Clin Immunol 111:177–179, 2003.
115. Liss GM, Bernstein D, Genesove L, et al: Assessment of risk factors for IgE-mediated sensitization to tetrachlorophthalic anhydride. J Allergy Clin Immunol 92:237–247, 1993.
116. Boxer MB, Grammer LC, Harris KE, et al: Six-year clinical and immunologic follow-up of workers exposed to trimellitic anhydride. J Allergy Clin Immunol 80:147–152, 1987.
117. Barker RD, van Tongeren MJA, Harris JM, et al: Risk factors for sensitisation and respiratory symptoms among workers exposed to acid anhydrides: A cohort study. Occup Environ Med 55:684–691, 1998.
118. Baur X, Marek W, Ammon J, et al: Respiratory and other hazards of isocyanates. Int Arch Occup Environ Health 66:141–152, 1994.
119. Burge PS: Occupational asthma due to soft soldering fluxes containing colophony (rosin, pine resin). Eur J Respir Dis 63(Suppl 123):65–67, 1982.
120. Calverley AE, Rees D, Dowdeswell RJ, et al: Platinum salt sensitivity in refinery workers: Incidence and effects of smoking and exposure. Occup Environ Med 52:661–666, 1995.
121. Swanson MC, Heederik D: Quantification of bio-active protein aerosols. *In* Bernstein IL, Chan-Yeung M, Malo JL, Bernstein DI. (eds): Asthma in the Workplace (3rd ed). New York: Taylor & Francis, 2006, pp 275–296.
122. Leroyer C, Perfetti L, Cartier A, Malo JL: Can reactive airways dysfunction syndrome (RADS) transform into occupational asthma due to "sensitisation" to isocyanates? Thorax 53:152–153, 1998.
123. Mastrangelo O, Paruzzolo P, Mapp C: Asthma due to isocyanates: A mail survey in a 1% sample of furniture workers in the Vaneto region. Med Lav 86:503–510, 1995.
124. Heederik D, Venables KM, Malmberg P, et al: Exposure-response relationships for work-related sensitization in workers exposed to rat urinary allergens: Results from a pooled study. J Allergy Clin Immunol 103:678–684, 1999.
125. Fishwick D, Bradshaw L, Henson M, et al: Occupational asthma: An assessment of diagnostic agreement between physicians. Occup Environ Med 64:185–190, 2007.
126. Vandenplas O, Ghezzo H, Munoz X, et al: What are the questionnaire items most useful in identifying subjects with occupational asthma? Eur Respir J 26:1056–1063, 2005.
127. Malo JL: A tribute to Tiffeneau's original contribution in the current issue of the journal. Allergy 61:1200–1201, 2006.
128. Vandenplas O, Cartier A, Malo JL: Occupational challenge Tests. *In* Bernstein IL, Chan-Yeung M, Malo JL, Bernstein DI (eds): Asthma in the Workplace (3rd ed). New York: Taylor & Francis, 2006, pp 227–252.
129. Rioux JP, Malo JL, L'Archevêque J, et al: Workplace specific challenges as a contribution to the diagnosis of occupational asthma. Eur Respir J 32:997–1003, 2008.
130. Marabini A, Ward H, Kwan S, et al: Clinical and socioeconomical features of subjects with red cedar asthma—A follow-up study. Chest 104:821–824, 1993.
131. Ameille J, Parion JC, Bayeux MC, et al: Consequences of occupational asthma on employment and financial status: A follow-up study. Eur Respir J 10:55–58, 1997.
132. Moscato G, Dellabianca A, Perfetti L, et al: Occupational asthma. A longitudinal study on the clinical and socioeconomic outcome after diagnosis. Chest 115:249–256, 1999.
133. Gassert TH, Hu H, Kelsey KT, Christiani DC: Long-term health and employment outcomes of occupational asthma and their determinants. J Occup Environ Med 40:481–491, 1998.
134. Malo JL, Ghezzo H: Recovery of methacholine responsiveness after end of exposure in occupational asthma. Am J Respir Crit Care Med 169:1304–1307, 2004.
135. Cocchiarella L, Andersson GBJ (eds): Guides to the Evaluation of Permanent Impairment (5th ed). Chicago: American Medical Association, 2001:102–104.
136. Yacoub MR, Lavoie K, Lacoste G, et al: Assessment of impairment/disability due to occupational asthma through a multidimensional approach. Eur Respir J 29:889–896, 2007.

137. Malo JL, L'Archevêque J, Ghezzo H: Direct costs of occupational asthma in Québec between 1988 and 2002. Can Respir J 15:413–416, 2008.
138. Liss GM, Tarlo SM: Natural rubber latex–related occupational asthma: Association with interventions and glove changes over time. Am J Ind Med 40:347–353, 2001.
139. Allmers H, Schmengler J, Skudlik C: Primary prevention of natural rubber latex allergy in the German health care system through education and intervention. J Allergy Clin Immunol 110:318–323, 2002.
140. Tarlo SM, Liss GM, Yeung KS: Changes in rates and severity of compensation claims for asthma due to diisocyanates: A possible effect of medical surveillance measures. Occup Environ Med 59:58–62, 2002.
141. Agius RM: Why are some low-molecular-weight agents asthmagenic? Occup Med 15:369–384, 2000.
142. Jarvis J, Seed MJ, Elton R, et al: Relationship between chemical structure and the occupational asthma hazard of low molecular weight organic compounds. Occup Environ Med 62:243–250, 2005.
143. Merget R, Caspari C, Kulzer SA, et al: Effectiveness of a medical surveillance program for the prevention of occupational asthma caused by platinum salts: A nested case-control study. J Allergy Clin Immunol 107:707–712, 2001.
144. Härkönen H, Nordman H, Korhonen O, Winblad I: Long-term effects of exposure to sulfur dioxide. Am Rev Respir Dis 128:890–893, 1983.
145. Cullinan P, Acquilla S, Dhara VR: Respiratory morbidity 10 years after the Union Carbide gas leak at Bhopal: A cross sectional survey. The International Medical Commission on Bhopal. BMJ 314:338–343, 1997.
146. Kern DG: Outbreak of the reactive airways dysfunction syndrome after a spill of glacial acetic acid. Am Rev Respir Dis 144:1058–1064, 1991.
147. Demnati R, Fraser R, Martin JG, et al: Effects of dexamethasone on functional and pathological changes in rat bronchi caused by high acute exposure to chlorine. Toxicol Sci 45:242–246, 1998.
148. Tarlo SM, Broder I: Irritant-induced occupational asthma. Chest 96:297–300, 1989.
149. Gautrin D, Bernstein IL, Brooks SM, Henneberger PK: Reactive airways dysfunction syndrome and irritant-induced asthma. *In* Bernstein IL, Chan-Yeung M, Malo JL, Bernstein DI (eds): Asthma in the Workplace (3rd ed). New York: Taylor & Francis, 2006, pp 579–627.
150. Malo JL, Cartier A, Boulet LP, et al: Bronchial hyperresponsiveness can improve while spirometry plateaus two to three years after repeated exposure to chlorine causing respiratory symptoms. Am J Respir Crit Care Med 150:1142–1145, 1994.
151. Malo JL, L'Archevêque J, Castellanos L, et al: Long-term outcomes of acute irritant-induced asthma. Am J Respir Crit Med 179:923–928, 2009.
152. Takeda N, Maghni K, Daigle S, et al: Long-term pathologic consequences of acute irritant-induced asthma. J Allergy Clin Immunol 124:975–981, 2009.

CHAPTER 65

PNEUMOCONIOSES AND OTHER MINERAL DUST–RELATED DISEASES

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FLOCK WORKER'S LUNG

INTRODUCTION

Definitions

The *Encyclopedia of Occupational Health and Safety* of the International Labour Organization (ILO)[1] defines pneumoconiosis as "the accumulation of dust in the lungs and the tissue reactions to its presence." The main reaction to mineral dust in the lungs is fibrosis. Not included in the definition of pneumoconiosis are conditions such as asthma, chronic obstructive pulmonary disease (COPD), and hypersensitivity pneumonitis in which there is no requirement for dust to accumulate in the lungs in the long term.

Accumulation of Dust in the Lung and Tissue Reactions

The *deposition* of dust in the lungs depends on the size and geometric and aerodynamic properties of the particles. Particle clearance is determined by the mucociliary escalator and cellular mechanisms, in particular, the macrophage (see Chapter 12). Dust *accumulation* in the lungs is determined by deposition and clearance. The biologic *response* depends upon the amount and duration of the accumulation and the nature of the dust. Tissue responses to inorganic dusts depend on particle size and the biologic activity of the dust, which in turn depends on its surface chemical and physical properties.[1] Some dusts, such as coal, are relatively inert and may accumulate in considerable amounts with minimal tissue response; others, in particular silica and asbestos, have potent biologic effects. Parenchymal responses include nodular fibrosis (the classic example is the silicotic nodule), diffuse fibrosis (the classic example is asbestosis), and macule formation with focal emphysema (the classic example is the coal dust macule).[2] Irregular and mixed fibrotic patterns also have been described as a consequence of mixed exposures involving other mineral dusts or fibers in addition to silica dust exposure.[3] For any given dust exposure, the severity of the tissue reaction appears to be related to the cumulative lung dust burden.

Exposure-Response Relationships

In epidemiologic studies, the dust burden in the lung can be assessed only indirectly. However, at an individual level, exposure can be estimated more directly from the job history, from the engineering history of the plant, including the efficiency of dust control, and from environmental measurements. Based on these estimates, convincing exposure-response relationships for pneumoconiosis can invariably be demonstrated in work force studies (Fig. 65-1; see also Fig. 65-9). At the public health level, the demonstration of exposure-response relationships is supportive evidence that the abnormality, dysfunction, or disease in question is causally related to the exposure.

The demonstration of exposure-response relationships also has implications for clinical practice. For instance, a clinical diagnosis of pneumoconiosis is strengthened greatly when there has been exposure to dust levels known to be associated with an increased risk of disease. Although exposure-response relationships generally describe the events in a work force, there may be heavily exposed individuals who remain unaffected and lightly exposed individuals with disease. Thus, environmental standards such as threshold limit values set by the American Conference of Government and Industrial Hygienists (ACGIH) are levels that if respected throughout an individual's working life, are unlikely to be associated with disease. However, dust sampling may be problematic and even in a workplace where average dust concentrations are below the threshold limit value, nearly half the samples exceed this value.[4] Thus, a clinician should not reject the diagnosis of pneumoconiosis solely on the grounds that exposure was too remote, too short, or in a workplace where the threshold limit value was maintained. The subject in question may be unusually susceptible, may have had an unusual exposure profile, or may retain more dust than others similarly exposed.

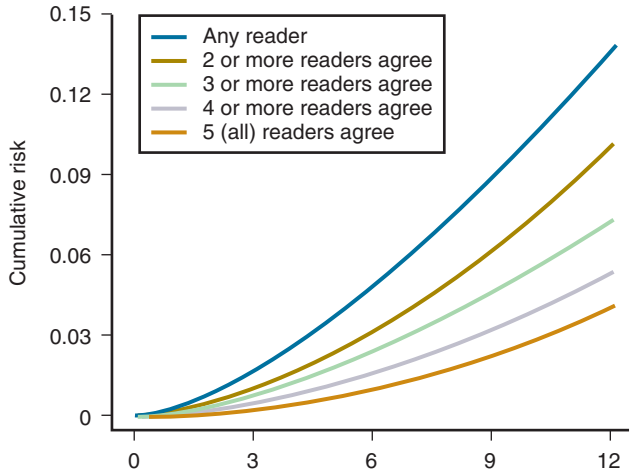

FIGURE 65-1 ■ The cumulative risk of developing silicosis in relation to cumulative exposure to respirable silica ($mg/m^3 \times yr$), lagged by 5 yr, among hard rock miners. The cohort consisted of all miners on the Ontario Workmen's Compensation Board's master file of miners who started work between 1941 and 1959 and were followed by chest radiography until their dust exposure ended or until 1982, whichever came first. The figure shows fitted Weibull models for one to five levels of reader consensus. The criterion for silicosis was a chest radiograph reading of small rounded opacities of profusion 1/1 or greater, using the International Labour Organization (ILO) standard reference films, on the miner's most recent film. The films of 32 of 2109 miners were considered by one or more readers to have silicosis and were retained for the purposes of this analysis. (Redrawn from Muir DCF, Shannon HS, Julian JA, et al: Silica exposure and silicosis among Ontario hardrock miners: III. Analysis and risk estimates. Am J Ind Med 16:29–43, 1989.)

Chest Imaging

The ILO standard films for the descriptive interpretation of the radiologic appearance of diffuse parenchymal lung

disease[5] were originally developed for epidemiologic studies of occupational lung disease but may also be used for clinical interpretation. Apart from improving consistency in the reading of parenchymal disease, which is notoriously subject to reader variability, they enable the clinician to set an individual case in the context of the available epidemiologic information.[5] Small opacities in the parenchyma are classified by shape and size: *p*, *q*, or *r* for rounded opacities (diameter, <1.5 mm, 1.5-3 mm, or >3 mm, respectively) and *s*, *t*, or *u* for irregular opacities (width, <1.5 mm, 1.5-3 mm, or >3 mm, respectively). Profusion category (or concentration) is next read on a 12-point scale (0/–, 0/0, 0/1, up to 3/2, 3/3, and 3/+) in comparison with the standard radiographs. Large opacities are classified as category A (for one or more such opacities with a diameter of 1 cm but not exceeding a combined diameter of 5 cm), category B (one or more opacities > 10 cm in diameter and whose combined area does not exceed one upper zone), and category C (>B). Provision is made to grade pleural thickening for width ($a \leq 5$ mm, $b > 5$ mm but < 10 mm, and $c \geq 10$ mm) and extent (*1* = up to one quarter, *2* = one quarter to one half, and *3* = over one half of the lateral chest wall). The extent of pleural calcification also is graded, and there are provisions for comment on other features.

In the United States, the National Institute of Occupational Safety and Health (NIOSH) administers the National Coal Workers' Health Surveillance Program, which provides coal miners with the opportunity of a periodic medical examination. The program incorporates quality control in terms of radiographic technique and reading procedures using the ILO classification and reader training. This involves training seminars for physicians who may qualify as "A" readers (i.e., attended the seminars) or "B" readers, who passed a comprehensive examination on the basis of 120 radiographs read into the ILO classification.

Chest radiographs are the cornerstone of surveillance for pneumoconiosis in the workplace. Computed tomography (CT) and high-resolution computed tomography (HRCT) have revolutionized clinical case evaluation. CT and HRCT are able to characterize lung and pleural lesions and their extent and confluence and are considerably more sensitive than the conventional chest radiograph. However, the chest radiograph remains the accepted method for surveillance and assessment because of its wide availability, acceptable cost and radiation dose, and the standardization of its reading.

Clinical Issues, Lung Function, and Principles of Management

The clinician is faced with two main tasks when evaluating a case of suspected pneumoconiosis. *First* to assess the nature of the disease process, including its site (airways or pulmonary parenchyma or pleura) and its extent, and to determine whether it has decreased the individual's performance in particular for his or her current job (evidence of impairment or disability). Assessment of impairment is based on symptoms and measurements of pulmonary function at rest and during exercise where indicated (see Chapter 27). Pneumoconiosis may be associated with apparently normal lung function or with a predominantly obstructive, restrictive, or mixed pattern of dysfunction. In the individual case, interpretation of results in terms of lung function profiles is usually done by the use of reference or predicted values. These may, however, be misleading given that those who undertake dusty occupations on average have higher initial spirometry and lung volumes than the general population, on whom most predicted values are based.[6] Thus, it is not appropriate to minimize the functional significance of pneumoconiosis on the grounds of apparently normal lung function. Assessment of disability is made in the wider context of whether the subject is fit for his or her job and, thus, requires expert knowledge of the job content. *Second*, is the need to determine whether there has been environmental or occupational exposure of duration, intensity, and character sufficient to account in full or in part for the patient's present condition. For this task, the key tool is the occupational history, which can be completed with the addition of the often extensive knowledge that the worker can provide concerning his or her occupations, the materials handled, and the processes involved. Because pneumoconiosis is a reaction to retained dust, it may appear and progress after exposure has ceased[7]; hence, the importance of a complete exposure history, including student summer jobs, military service, and short-term jobs. In addition, in industrialized countries, between 25% and 60% of men and up to 30% of women report exposure to dust or fumes at work,[8] further testimony to the fact that an occupational history is as essential as the smoking history in the practice of respiratory medicine. On occasions, it may be necessary to establish occupational exposure on the basis of analysis of biologic material (sputum, bronchoalveolar lavage (BAL), transbronchial or open-lung biopsy specimen) for the putative dust or its breakdown products. This is particularly so in cases in which the exposure is remote and the exposure history incomplete or unreliable. Figure 65-2 presents examples of cases in which the putative dust was demonstrated in the pathologic specimens. The case record in Figure 65-11 is an example of the use of lung dust burden measurements in establishing attributability.

Tuberculosis was a common complication of pneumoconiosis in the early part of the 20th century, when infection levels were high in parent populations from which work forces were drawn and drug therapy was not yet available. Although now relatively rare in industrialized countries, tuberculosis remains an important issue in industrializing countries and has increased dramatically, especially in South Africa, in response to the human immunodeficiency virus (HIV) epidemic.[9]

Pneumoconiosis does not regress and may appear and progress only after work exposure ceases.[7] In general, there should be no doubt that a worker with pneumoconiosis should have no further occupational dust exposure.[10] A rare exception would be in an older worker who is close to retirement for whom early retirement

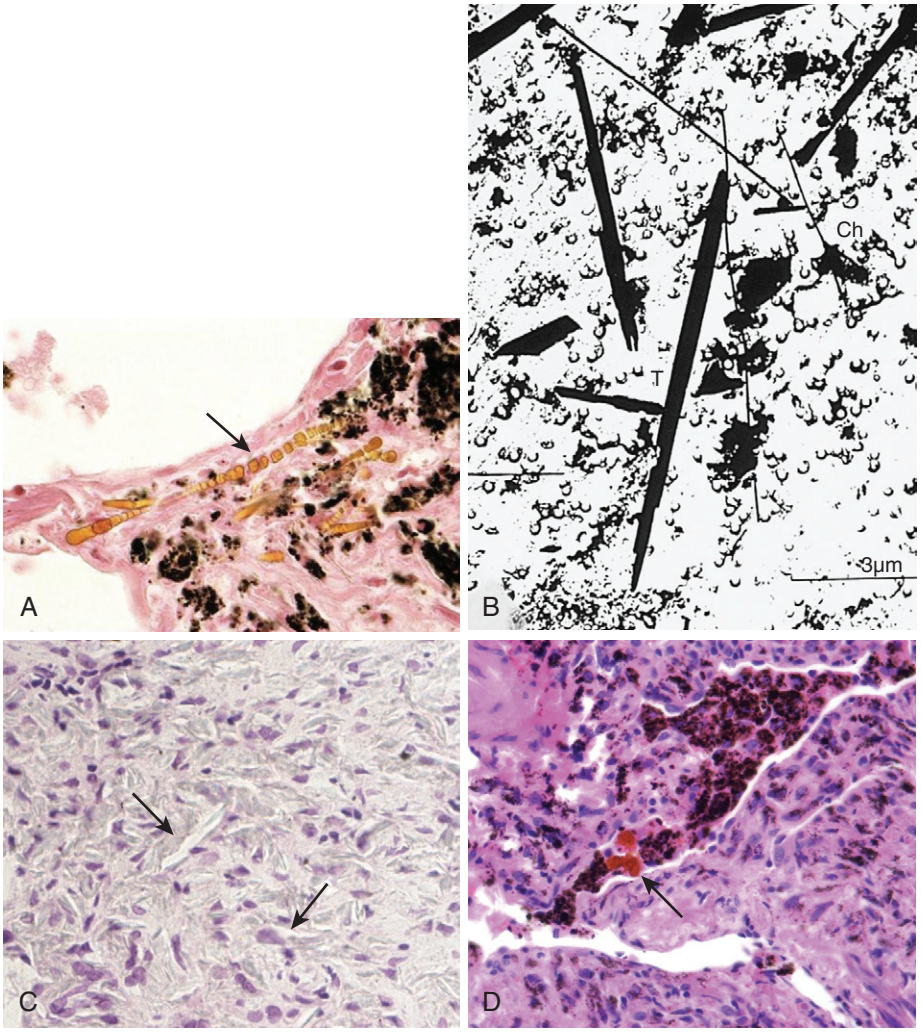

FIGURE 65-2 ■ The putative agent in the lung tissue in four cases of pneumoconiosis is demonstrated. **A,** Typical asbestos body (*arrow*) in the lung of a crocidolite asbestos miner with asbestosis, from South Africa. **B,** Lung digest from the case of a 67-year-old long-term chrysotile miner with asbestosis from the Thetford area, photographed on a filter of pore diameter 0.2 mm (pores are evident as small punched-out areas in the photograph). The thin fibers labeled *Ch* were identified as chrysotile using morphologic criteria and energy-dispersive x-ray spectrometry (EDS). The thick fibers labeled *T* were identified as tremolite by EDS. In this mining area, there is a small amount of tremolite in the mined ore that accumulates preferentially in the lung tissue.[142] Amphiboles such as crocidolite, amosite, and tremolite most frequently form the core of asbestos bodies. For each asbestos body found in lung tissue, the number of uncoated fibers is at least several orders of magnitude greater. **C,** Lung section from a 53-year-old man who worked in a mica milling factory. The mica (*arrows*) appears as birefringent (*bright white*) elongated particles. **D,** Lung from a foundry worker shows amorphous black carbon particles and a cluster of rounded iron-coated particles (*arrow*). Particle clusters like this frequently are seen in the lung sections of welders and of foundry workers who have had exposure to iron dusts and fumes. (**A, C,** and **D,** Courtesy of National Institute for Occupational Health, South Africa; **B,** courtesy of Drs. Bruce Case and R. S. Fraser, Department of Pathology, and Dr. Patrick Sébastien, formerly of the School of Occupational Health, McGill University, Montreal.)

would cause significant economic loss not covered by a compensation package.

The physician should be aware that each time the diagnosis of pneumoconiosis is substantiated, it carries with it several important public health implications. In many jurisdictions, the physician has the legal responsibility to report all cases of pneumoconiosis.[7] The diagnosis of pneumoconiosis reflects a failure of environmental controls in the workplace that may require intervention by an appropriate authority. There are differences in disease notification practice and compensation legislation among states and among countries, and physicians should be aware of the appropriate procedure in the location of their practice.

Epidemiology and Implications for Clinical Practice

Information on the distribution of these diseases within and between work forces and the factors that influence distribution provides the scientific base that the physician uses to reach a diagnosis, set prognosis, and plan management. Thus, knowledge of pneumoconiosis rates

in the industries located in the local area assists the physician in diagnosis. Likewise, determining prognosis depends on work force–based information, on knowing which factors influence disease progression favorably and unfavorably, and the likely effect of further exposure even at low levels.

In the discussion that follows, the various types of pneumoconioses are considered separately with respect to occupations at risk, pathophysiology and epidemiology, as well as the clinical issues of diagnosis, prognosis, and management. On all continents and in many countries, there are a substantial proportion of individuals exposed to dust at work and therefore potentially at risk for pneumoconiosis.[8] Lists of occupations and jobs at risk are never exhaustive (Table 65-1) but are a guide for use in general office practice, where it may be more important to raise the suspicion of a diagnosis of pneumoconiosis than to be knowledgeable about the particular exposures a given job title implies. Indeed, the latter often falls into the expertise of the industrial hygienist. For those in occupational health or occupational medicine practice, reference should be made to one of the more specialized texts that describe the occupations at risk in greater detail.[1,2,4,11]

TABLE 65-1. Industries and Occupations at Risk for Silicosis

Industries with Examples	Occupations Implicated
Mining, tunneling, and excavating	
Underground: gold, copper, iron, tin, uranium, civil engineering projects	Miner, driller, tunneler, developer, stoper
Surface: coal, iron, excavation of foundations	Mobile rig drill operator
Quarrying	
Granite, sandstone, slate, sand, chinastone/clay	Driller, hammerer, digger
Stonework	
Granite sheds, monumental masonry	Cutter, dresser, driller, polisher, grinder, mason
Foundries	
Ferrous and nonferrous metals	Molder, knockout man, fettler, coremaker, caster
Abrasives	
Production: silica flour, metal polish, and sandpapers, fillers in paint, rubber, and plastics	Crusher, pulverizer, and mixer; workers in the manufacture of abrasives
Sandblasting: oil rigs, tombstones, denim	Operators of high-speed jets
Ceramics	
Manufacture of pottery, stoneware, refractory bricks for ovens and kilns	Workers at any stage of process if products are dry
Others	
Glass making, boiler scaling, traditional crafts, stone grinders, gemstone workers, dental technicians, concrete reconstruction	

SILICOSIS

Definition

Silicosis is a fibrotic lung disease attributable to the inhalation of crystalline silica usually in the form of quartz and, less commonly, as cristobalite and tridymite.[1,12] Amorphous silica is relatively nontoxic; silicates such as asbestos, mica, and talc evoke a different type of pulmonary response and are considered separately.

Industries and Occupations Still at Risk

Silicosis is an ancient disease that continues to be a major disease worldwide in men and women exposed to silica dust in a variety of occupations.[1,13] Table 65-1 provides some common examples of industries in which workers are at risk for silica exposure. Construction and surface and underground rock drilling have all been subjects of Alert documents from NIOSH. Foundries are also a main source of silica dust.[1,7,14] More recent reports have shown a silicosis risk for workers involved with the repair, rehabilitation, or demolition of concrete structures[15] including roads.[16] Less common occupations associated with silicosis include workers producing stressed denim by sandblasting,[17] stone carvers,[18] and jewelers using chalk molds.[19]

Many of the current cases of silicosis come from industries using relatively new technology that, if unaccompanied by modern controls, may result in exposures to finer dust particles than in traditional industries and jobs. New types of pneumoconiosis often turn out to be silicosis in an industry not previously thought to be at risk or a mixed dust pneumoconiosis in which silica is implicated with other dusts.[20,21] Silicosis is often the result of exposure in the remote past and not in the current workplace. The risks for silicosis depend upon the levels of exposure, and although this can be controlled, there is evidence that dust levels may be monitored inappropriately and that the sampling accuracy may be poor in many workplaces.[14]

Outbreaks of silicosis and death from the disease continue to be reported worldwide,[7,14,18] even in countries with developed legislative systems and environmental surveillance programs, such as the United States,[22] Canada,[23] Europe,[24] and South Africa.[25] Recent U.S. data show a reduction in the rate of decline in deaths from silicosis after 1995 with an increased proportion of deaths in the age group younger than 45 years. These data indicate "that intense overexposures to respirable crystalline silica continue to occur despite the existence of legally enforceable limits."[26] In the United States, NIOSH has estimated that at least 1.7 million workers are exposed to silica, of whom between 1500 and 2360 will develop silicosis each year. Cases of silicosis have also been reported following general environmental exposure[27,28] and in agricultural workers.[29,29a]

Pathology

Three clinicopathologic types of silicosis have been described (Table 65-2): *chronic silicosis*, which typically

TABLE 65-2. Diseases Associated with Exposure to Silica Dust

SILICOSIS
Chronic silicosis
Accelerated silicosis
Acute silicosis (silicoproteinosis)
Progressive massive fibrosis

CHRONIC OBSTRUCTIVE LUNG DISEASE
Emphysema
Chronic bronchitis
Mineral dust–induced small airways disease

LUNG CANCER

MYCOBACTERIAL INFECTION
Mycobacterium tuberculosis
Nontuberculous mycobacteria

IMMUNE-RELATED DISEASES
Progressive systemic sclerosis
Rheumatoid arthritis
Chronic renal disease
Systemic lupus erythematosus

follows exposure, measured in decades rather than years, to respirable dust usually containing less than 30% quartz; *accelerated silicosis*, which follows shorter, heavier exposure; and *acute silicosis* (silicoproteinosis), which follows intense exposure to fine dust of high silica content, such as that found in sandblasting industries, for periods measured in months rather than years.[2,12]

Chronic silicosis is the most common form of the disease. The hallmark of chronic silicosis is the silicotic nodule, one of the few agent-specific lesions in pathology (Fig. 65-3A and B). The mature lesion is characterized by a central area of whorled hyalinized collagen fibers with a more peripheral zone of dust-laden macrophages. Birefringent particles can be seen in the nodule with light microscopy. Early in the course of the disease, dust-filled macrophages may be the most prominent finding. Silicotic nodules develop first in the hilar lymph nodes[30] and may be confined to this area; they may become encased in calcification and impinge on or erode into airways. The disease process next involves the lung parenchyma, where the nodules are discrete (3–5 mm in diameter), palpable and grayish-black in color. They are usually bilateral, involving the upper zones. Similar nodules can be found in the visceral pleura and often develop in the lymphatic drainage channels of the lung, particularly in the perivascular sheath.

In accelerated silicosis, the changes are similar to those seen in chronic silicosis. However, the nodules develop sooner (after 3–10 yr of exposure) and are more cellular than fibrotic.

With disease progression in both chronic and accelerated silicosis, the nodules may become confluent, leading to the development of *progressive massive fibrosis* (PMF) (see Fig. 65-3C), also known as *complicated silicosis*. These lesions, which are at least 1 cm in diameter (and often larger), usually involve the upper lobes. They tend to obliterate lung structure and may cavitate, which may be an indication of tuberculosis.[2] *Rheumatoid nodules* may also occur in the setting of silicosis and may be seen in subjects with rheumatoid arthritis or high levels of circulating rheumatoid factor.[2] These nodules may be larger than the usual silicotic lesion (≤5 cm in diameter) and have light gray necrotic centers surrounded by palisading histiocytes, fibroblasts, collagen, and neutrophils.[2] There may be silicotic nodules in the background. Rheumatoid nodules are less frequently associated with silica than with coal dust exposure (see subsequent discussion).

Acute silicosis shows all the features of pulmonary alveolar proteinosis (see Chapter 63). Silica particles and various biomarkers of tissue reaction can be identified in the proteinaceous material from the alveolar spaces as well as in lavage material.

The lungs of exposed individuals, whether or not they show silicosis, also may demonstrate the features of other diseases associated with occupational dust exposure, such as chronic bronchitis and emphysema. The pathologic features are similar whether associated with occupational exposure to dusts and fumes encountered in the workplace or with exposure to tobacco smoke. Small airway abnormalities, including fibrosis and pigmentation of respiratory bronchioles (see Fig. 65-3D), are seen in association with exposures to a variety of mineral dusts including those responsible for silicosis.[31] An association between silica exposure and idiopathic pulmonary fibrosis has also been noted.[32]

Silicotic nodules may also develop in the cervical and abdominal lymph nodes and, occasionally, in the liver, spleen, and bone marrow.[7]

Pathogenesis

The pathogenicity of silica dust is dependent on the physical, mechanical, and chemical properties of the particles. A review of this topic summarizes the processes whereby silica produces inflammation and fibrogenesis in the lung.[33] Silica-induced inflammation and fibrosis result from complex interactions between the particles and the lung macrophages, alveolar epithelial cells, fibroblasts, neutrophils, lymphocytes, and complex networks, stimulating the production of oxidants, chemokines, and cytokines. However, the cell mechanisms that initiate and drive the process of inflammation and fibrosis are not fully understood. The surface characteristics of the silica particles determine their redox potential and ability to react with hydrogen, oxygen, and nitrogen. There is agreement that freshly fractured silica, such as that generated during sandblasting, is more toxic to the alveolar macrophages than is "aged" silica, presumably because of its increased redox potential. Other minerals, particularly clay components, may adhere to the surfaces of silica particles, producing "coated" silica that is less toxic than uncoated silica dust. This may explain the relatively nonfibrogenic response to silica in

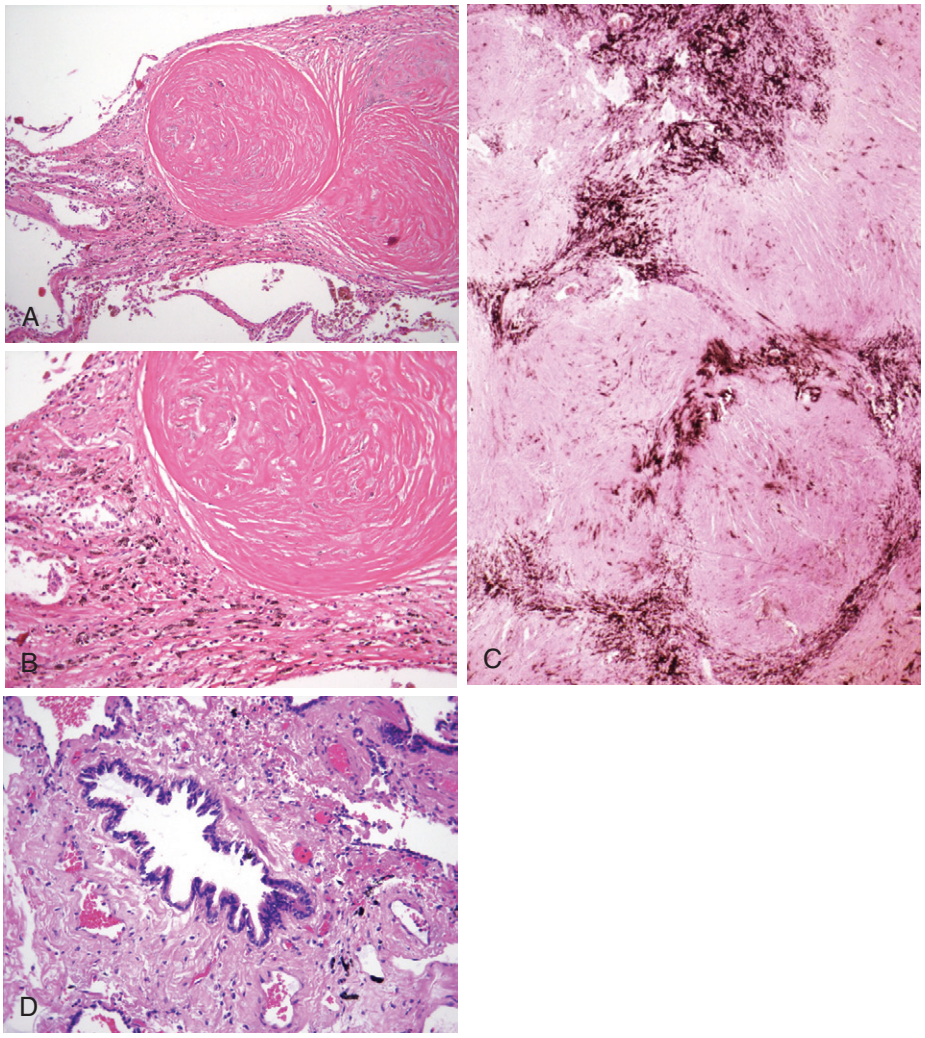

FIGURE 65-3 ■ Pathologic lesions of chronic silicosis. **A,** Silicotic nodule characterized by a central zone of a cellular hyalinized collagen with a whorled appearance and a peripheral zone of dust-laden macrophages. **B,** Silicotic nodule at higher magnification to show these characteristics to better advantage. **C,** Progressive massive fibrosis shows confluent silicotic nodules and aggregates of dust-laden macrophages. **D,** Mineral dust small airway disease characterized by peribronchiolar fibrous tissue containing a moderate amount of pigment. (Courtesy of National Institute for Occupational Health, South Africa.)

coal and hematite miners and the observation that the incidence of silicosis is decreased by concomitant exposure to other dusts. Silica particles smaller than 5 μm reach the lower respiratory tract and may enter the alveoli. There is some debate as to whether the fibrogenicity of the particles is dependent on their actual size. The intensity of the exposure determines the nature of the lung injury. Low-intensity exposure generally produces aggregates of fibrosis with relative sparing of the lung architecture, whereas high-intensity exposure has been shown in rats to cause widespread pulmonary inflammation and collagen deposition.

Tumor necrosis factor-α (TNF-α) and interleukin 1 (IL-1) play an important role in the initiation of silicosis, and experimental inhibition of these cytokines has been shown to prevent silicosis. Growth factors, including transforming growth factor-β (TGF-β), are important in fibrogenesis (and also have been implicated in carcinogenesis) in association with silica.[34,35] A review describes the immune response to silica in more detail and the role of innate and adaptive immunity.[36] Although the major determinant of silicosis is the level of exposure to silica-containing dust, individual susceptibility to the disease may play a role in its development and severity.[37,38]

Epidemiology: Secular Trends and Their Implications for the Clinician

Over the course of the 20th century, silicosis changed from a rapidly fatal disease to an indolent and disabling disorder. Reasons include improved environmental controls, falling rates of tuberculosis, and the advent of drug therapy for tuberculosis. Nevertheless, there is still well-warranted concern that this avoidable disease will remain

a significant cause of morbidity[7] and mortality in the 21st century.[39,40] The prevalence of silicosis is difficult to estimate, given the large number of industries at risk (see Table 65-1), the transient labor force in industrializing as well as in industrialized countries, and the frequent appearance (and progression) of disease after the worker has left the work force.[41,42] Despite the progress made, silicosis has been reported in workers from a variety of industries in persons starting work after 1970, and reported cases have been estimated to represent only a third of the total cases of silicosis.[13] The prevalence of silicosis in South Africa has been rising.[25] In calculating an individual's risk for silicosis, duration and intensity of exposure are of primary interest but peak exposure also may be important.[43] The physician should never dismiss the diagnosis of silicosis when that diagnosis is suggested by clinical and radiologic features, even when exposure appears to have been insignificant or in an occupation not known to be associated with silicosis.

Tuberculosis

The association between silicosis and tuberculosis has long been recognized. Rates for active tuberculosis in silicotic subjects range from 2- to 30-fold more than those in the same workforce without silicosis.[44] Factors that influence the development of tuberculosis in the subject with silicosis include the severity and type of disease (the risk is considerably higher in patients with acute and accelerated silicosis),[12] the prevalence of tuberculosis in the population from which the work force was drawn, as well as their age, general health and HIV status.[44–46] Exposure to silica, without silicosis, may also predispose individuals to tuberculosis.[44,45]

Tuberculosis is characterized by necrotizing epithelioid granulomas. These are never seen with silicosis alone. Although *Mycobacterium tuberculosis* is the usual organism, nontuberculous mycobacteria account for a large proportion of the mycobacterial disease in populations in which nontuberculosis mycobacterial disease is common.[7,47]

Airflow Obstruction and Chronic Bronchitis

Chronic obstructive pulmonary disease (COPD) and chronic bronchitis are common manifestations of long-term occupational exposure to environments contaminated by silica dust and can develop in silica-exposed individuals with or without silicosis.[7,48–50] Small airway abnormalities, including fibrosis and pigmentation of respiratory bronchioles (see Fig. 65-3D), are also seen in association with exposures to a variety of mineral dusts, including those responsible for silicosis.[31] In a study of adolescents and young adults working in a stone crushing plant, lung function changes were interpreted as evidence for impaired lung growth that was attributed to their very high respirable crystalline silica exposure.[51] Smoking can potentiate the effect of silica dust on airflow obstruction.[49]

Connective Tissue Diseases and Renal Disease

Associations have been reported between exposure to silica and certain connective tissue diseases including progressive systemic sclerosis, systemic lupus erythematosis, and as previously mentioned, rheumatoid arthritis.[7] Epidemiologic evidence indicates that the prevalence of rheumatoid arthritis is increased in those with exposure to silica as well as in those with silicosis.[52] It has also been suggested that rheumatoid arthritis may initiate or aggravate silicosis. Systemic sclerosis has been shown to be associated with silicosis[52] but may also be associated with silica dust exposure without silicosis.[7] The evidence for an association between lupus erythematosus and silicosis is strongest for acute or accelerated silicosis but is inconclusive for chronic silicosis.[7,52]

Renal disease has also been reported in silica-exposed workers. Some studies have implicated an immune complex glomerulitis or a direct toxic effect of silica.[7,11,52] A recent report has linked silicosis with ANCA positivity and possibly with vasculitis.[53]

Lung Cancer

In 1996, the International Agency for Research in Cancer (IARC)[54] classified silica dust as "carcinogenic to humans." The association between silicosis and lung cancer has been difficult to establish because of the high prevalence of smoking in silica-exposed workers and because of frequent concomitant radon exposure.[7] Studies of non-radon–exposed, nonsmoking workers with silicosis suggest a clear relationship between silicosis and lung cancer, but there remains some doubt as to whether silica exposure, in the absence of silicosis, carries an increased risk for lung cancer.[7,52,55–57]

Clinical Features

The symptoms and signs of chronic silicosis may be minimal. The main symptom is breathlessness, but in chronic silicosis, in the absence of other respiratory disease, even this symptom may be absent. It is not unusual for a patient with chronic silicosis to present without symptoms for assessment of an abnormal chest radiograph. The appearance of breathlessness may mark the development of a complication such as PMF or tuberculosis or may reflect associated airway disease. Cough and sputum production are common symptoms and usually relate to chronic bronchitis but may reflect the development of tuberculosis or lung cancer. Chest pain is not a feature of silicosis nor are systemic symptoms such as fever and weight loss, which should be attributed to tuberculosis or lung cancer until proved otherwise. Clubbing is also not a feature of silicosis and should raise concern about lung cancer.

In accelerated and acute silicosis, the time scale of symptom evolution is in years or months rather than in decades. In acute silicosis, breathlessness may become

disabling within months, followed by impaired gas exchange and respiratory failure.

Radiographic Features

Uncomplicated silicosis is characterized by the presence of small rounded opacities on the chest radiograph,[1,12,58] as graded in the ILO classification (as described previously).[5] In general, there is a good correlation between dust exposure, the amount of dust in the lungs, the lung pathology, and the chest radiograph.[59] However, occasionally, even advanced silicosis, determined by histology, may not be apparent on a chest radiograph.[60]

Silicotic nodules are usually symmetrically distributed and tend to occur first in the upper zones (Fig. 65-4), later, although not invariably, involving other zones. Occasionally, they are calcified, resembling microlithiasis. Enlargement of the hilar nodes may precede the development of the parenchymal lesions.[58] Eggshell calcification, when present, is strongly suggestive, although not pathognomonic, of silicosis (Fig. 65-5; see also Fig. 65-4). Pleural plaques may occur but are not a common feature.

PMF is characterized by the coalescence of small rounded opacities to form larger lesions; they are graded on the ILO scale according to size and extent (categories A-C). CT assessment is superior to the chest radiograph not only in assessing the presence and extent of silicotic nodulation but also in revealing early conglomeration (see Fig. 65-5).[61] With time, the mass lesions tend to contract, usually to the upper lobes, leaving hypertranslucent zones at their margins and often at the lung bases.

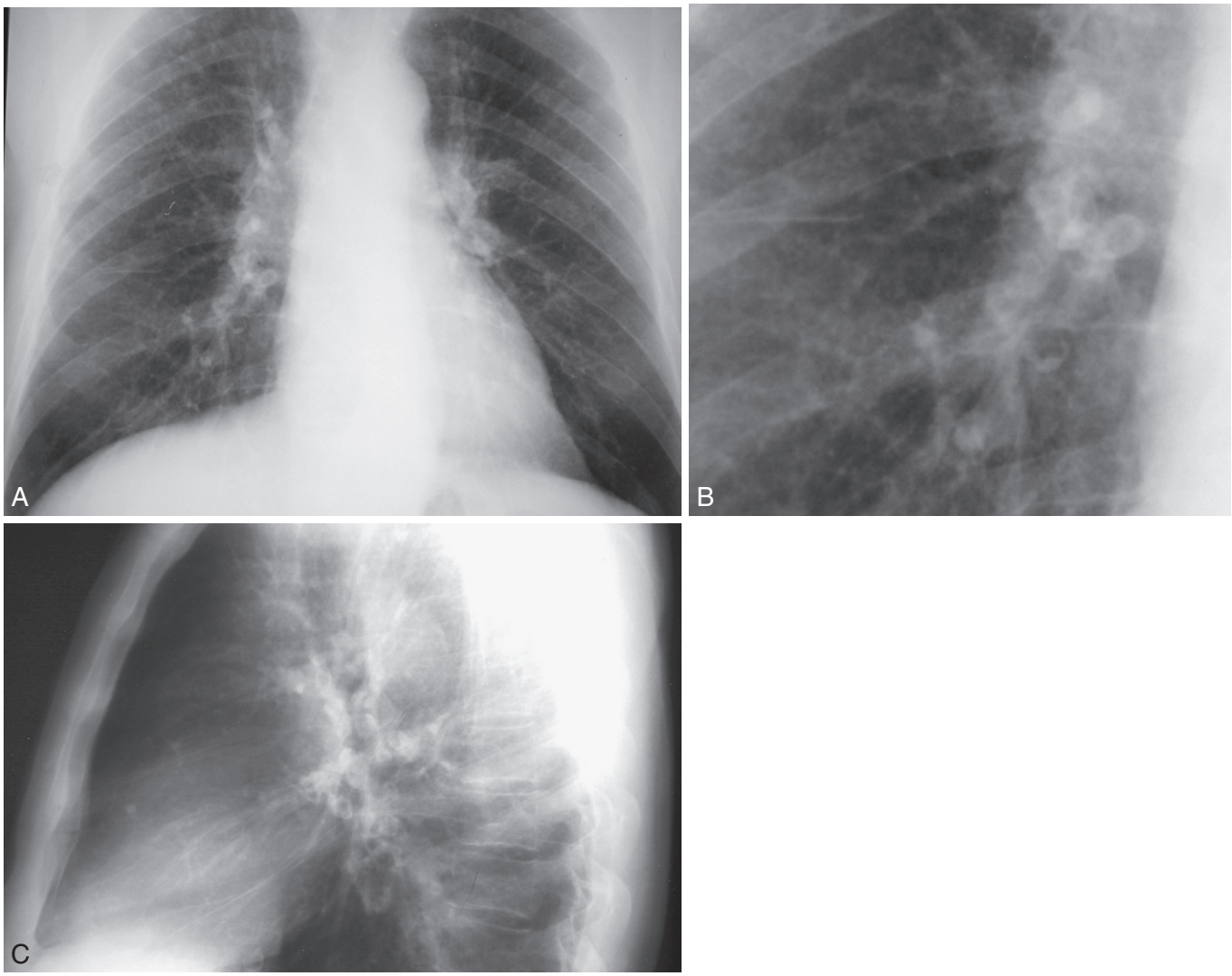

FIGURE 65-4 ■ **A,** Posteroanterior radiograph shows predominantly upper zone but, atypically, asymmetrical nodularity in keeping with silicosis. **B,** Close-up shows the right upper zone nodularity and "eggshell" calcification of the hilar lymph nodes. This latter feature strongly suggests that this radiograph represents silicosis, notwithstanding the patient's history of 30 years of underground work in a coal mine. **C,** Lateral view shows the eggshell calcification and also a larger and probably calcified nodule situated anteriorly. This latter feature is compatible with a healed primary tuberculous focus, and if this is supported by a positive test for tuberculosis, a course of treatment for latent tuberculosis infection should be offered. (Courtesy of Dr. J. H. M. MacGregor, University of Calgary.)

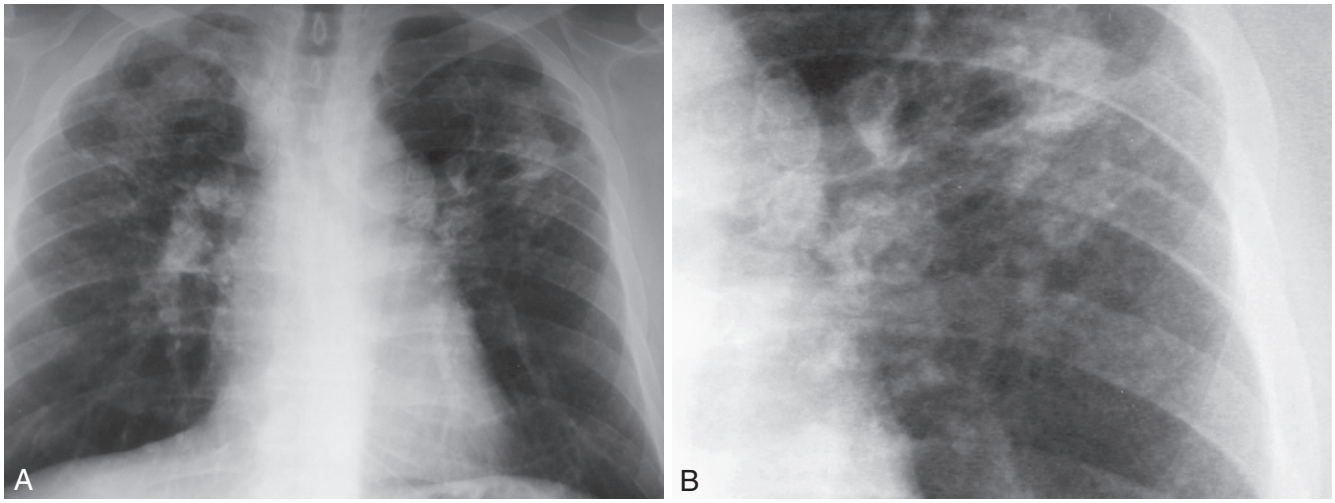

FIGURE 65-5 ■ **A,** Posteroanterior radiograph shows features of progressive massive fibrosis (PMF) with "eggshell" calcification of the hilar nodes, in keeping with complicated silicosis, in a man who had shoveled sand in a glass factory. **B,** Close-up view shows the PMF with a background of smaller nodules and the eggshell calcification. (Courtesy of Dr. J. H. M. MacGregor, University of Calgary.)

In this process, small rounded opacities, previously evident, may disappear, resulting in a picture that must be distinguished from tuberculosis. The rapid development of several large lesions suggests rheumatoid silicosis, but new lesions, especially if cavitated, should be regarded as evidence of mycobacterial disease. Acute silicosis is characterized radiologically by diffuse changes that usually display an air space and interstitial pattern rather than the usual nodularity.[1,62]

Lung Function

The lung function profile is determined by the extent of silicosis as well as associated or concomitant airway and vascular changes. In chronic silicosis, spirometric tests (forced expiratory volume in 1 second [FEV_1], FEV_1/FVC [forced vtital capacity], and maximal midexpiratory flow[31]) usually reflect airflow limitation.[7] Reduction in diffusing capacity of carbon monoxide (D_{LCO}) is generally apparent in more advanced chronic silicosis and probably reflects associated emphysema.[63]

In the accelerated and acute forms, functional changes are more marked and progression is more rapid. In acute silicosis, lung function shows a restrictive defect and impairment of gas exchange, which leads to respiratory failure and eventually to death from intractable hypoxemia. Interpretation of pulmonary function tests is discussed in Chapter 24.

Diagnosis and Complications

Silicosis is diagnosed on the basis of a history of exposure and the characteristic radiographic changes.[12] Problems arise when the history of exposure is remote, forgotten, or missed or has occurred outside of a recognized occupation. Occasionally, the radiologic features are unusual; examples include the presence of hilar lymphadenopathy or of large lung opacities in the absence of typical small nodules. Detection of silica in BAL material may suggest the diagnosis. Lung biopsy may be necessary to distinguish progressive massive fibrosis or other atypical features from lung cancer, tuberculosis, and other diagnoses. Biopsy material should be submitted for microanalysis for dust, including silica.

Less common complications include cor pulmonale, spontaneous pneumothorax, broncholithiasis, and tracheobronchial obstruction from enlarged calcified hilar nodes.[12] The diagnosis of active tuberculosis in the silicotic subject may be more difficult than in the nonsilicotic subject, but in general, a good sample of sputum or sputum induced by nebulized hypertonic saline sent for mycobacterial culture provides the diagnosis. The presence of cough, hemoptysis, weight loss, fever, or any new radiologic feature should be pursued with culture of sputum or BAL fluid or with culture and histologic examination of tissue. In many instances, it is the chest radiograph rather than the clinical features that gives the first indication of tuberculosis in the presence of silicosis, but it should be noted that those with silicosis are also at risk for extrapulmonary tuberculosis.[44]

Management and Control

Once established, the fibrotic process of chronic silicosis is thought to be irreversible. Management of the individual case is thus directed toward preventing progression and the development of complicated disease. A change in occupation to an environment free of silica-containing dust should be advised. The disease will generally progress even without further exposure,[41,42] but the rate of deterioration may be reduced.

Interventions to interrupt the inflammatory process that leads to chronic silicosis including the inhalation of aluminum or polyvinylpynidine-*N*-oxide and oral tetrandine have not been shown to be successful. There is currently interest in the use of lung lavage to remove

silica from the lung, but a favorable impact on progression of acute or chronic silicosis has not been demonstrated. Treatment of all forms of silicosis should be directed toward control of mycobacterial disease. This is especially true for acute and accelerated silicosis and silicosis in workers with HIV infection.[12,46] All subjects with silicosis should have a tuberculin skin test or an interferon-γ (IFN-γ) release assay[64] and, if positive in the absence of evidence of tuberculosis, be offered treatment for latent tuberculosis infection (see Chapter 34).

The interaction between silica exposure and smoking in the development of COPD,[49,50] tuberculosis,[65] and lung cancer makes it important to implement smoking-cessation programs in the workplace.

Because acute and accelerated silicosis carry such a poor prognosis and tend to occur in younger subjects,[66] consideration should be given for lung transplantation in such cases. (For lung transplantation, see Chapter 95.)

The most important aspect of the management of silicosis relates to its prevention. To achieve this, a sustained effort must be made to increase awareness of silicosis. Recent deaths from silicosis in younger subjects in the United States have occurred after exposure in the construction and manufacturing sectors, with none from mining.[66] Deaths of young people sandblasting denim[17] is a reminder that there is often a lack of awareness of the hazards of silica outside the traditional occupations associated with silicosis.[26]

COAL WORKERS' PNEUMOCONIOSIS

Definition and Occupations at Risk

Coal workers' pneumoconiosis (CWP) is a distinct pathologic entity resulting from the deposition of coal dust in the lungs.[1,2,4] The tissue reactions to deposits of dust include the *coal macule* and the *coal nodule* (simple CWP) and PMF (complicated CWP)[2] (Fig. 65-6).

The main occupation at risk for CWP is coal mining, an industry that in the 1970s, employed approximately 250,000 people in the United Kingdom and a comparable number in Western Europe.[8] Approximately 175,000 coal miners were employed in the United States in 1986; since then, there has been a steady decrease in the number to approximately 80,000 in 1999.[22] Coal is also mined in Eastern Europe, India, and China and on the African, Australian, and South American continents. With mechanization, output and potential for dust exposure have increased. Former as well as current coal workers are likely to continue to be seen with CWP.

Coal mine dust contains a variable amount of quartz depending on the nature of ore-bearing rock, the size of the coal seam, and the processes used to mine the seam (including the degree of mechanization). Coal miners may also develop silicotic nodules when the coal seams are in hard rock. Silicosis is more common in mines with a high grade of coal and in workers such as roof bolters who work outside of the coal seams.[2,4] Current evidence shows that coal mining, even in the absence of CWP, is associated with chronic bronchitis, chronic airflow limitation,[4,67,68] and emphysema.[2,4,68a]

Other occupations at risk for exposure to coal or carbon dust include coal trimming (which involves loading and stowing coal in stores or ships' holds), the mining and milling of graphite in carbon plants, the manufacture of carbon electrodes, and the manufacture and use of carbon black.

Pathology

The primary lesion in CWP is the *coal macule*, which can be seen (although not palpated) on macroscopic examination as a small (≤4 mm) pigmented lesion, distributed initially in the upper lobes, although the lower lobes may subsequently become involved.[2] On microscopic examination, the coal macule consists of a stellate aggregation of dust and dust-laden macrophages around respiratory bronchioles, with reticulin fibers and a variable amount of collagen (see Fig. 65-6).[2] *Focal emphysema*, a form of centriacinar emphysema, occurs within and around the coal macule, and together they form the characteristic lesion of CWP.[2] The *coal nodule* is a palpable lesion that, in addition to dust-laden macrophages and reticulin, contains a substantial number of haphazardly arranged collagen fibers.[2] Coal nodules, which

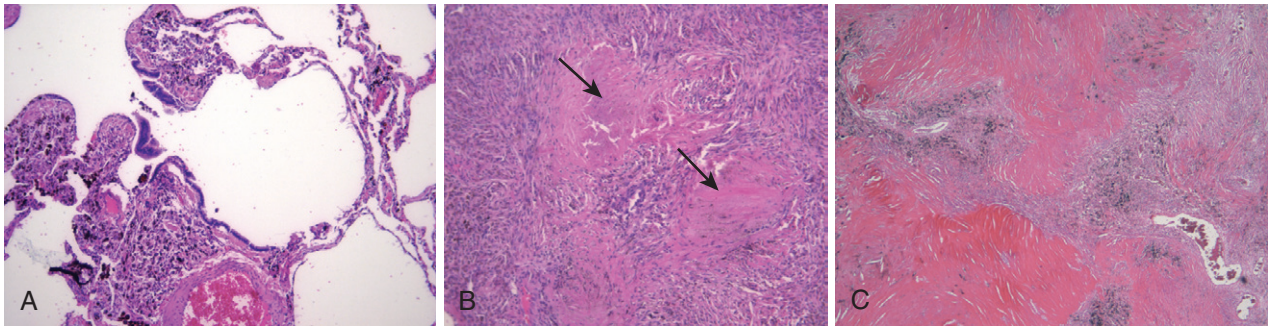

FIGURE 65-6 ■ Pathologic lesions of coal workers' pneumoconiosis: examples from South African coal miners. **A,** Coal macule shows an aggregation of dust and dust-laden macrophages in the wall of a distal airway in which reticulin and a few collagen fibers were demonstrated. **B,** Coal nodule consists of dust and dust-laden macrophages and dense, irregular depositions of collagen (*arrows*). This lesion would be palpable. There also was associated focal emphysema. **C,** Progressive massive fibrosis with coalescence of nodules and dense collagen deposition. (Courtesy of National Institute for Occupational Health, South Africa.)

result from exposure to coal dust admixed with silica, usually occur in association with coal macules.[1] Classic silicotic lesions are seen in approximately 12% of U.S. coal miners[2] and form when lung dust residue contains 18% or more quartz. Other features include subpleural dust deposits, enlargement of the hilar and mediastinal nodes, and on occasion, tattooing of the parietal pleural lymphatic channels by coal dust.

PMF (complicated CWP) is defined as a fibrotic pneumoconiotic lesion 1 cm or greater in diameter. These bulky, often irregular, well-defined, heavily pigmented rubbery black tissue masses usually occur in a background of severe simple CWP. PMF usually develops in the posterior segment of the upper lobes or apical segments of the lower lobes and is typically bilateral (Figs. 65-7 and 65-8). Microscopically, the lesions contain the

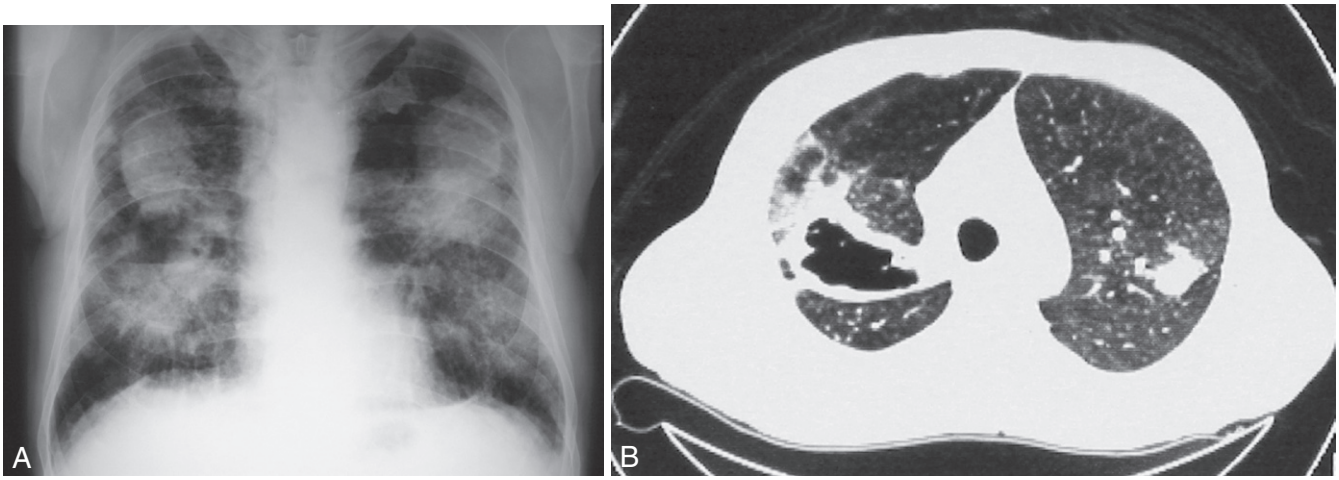

FIGURE 65-7 ■ **A,** Chest radiograph shows PMF with evidence of cavitation in the right lower zone. The film represents complicated coal worker's pneumoconiosis. **B,** Computed tomography scan shows the background nodularity and the lesions of PMF with cavitation on the right. (Courtesy of Dr. J. H. M. MacGregor, University of Calgary.)

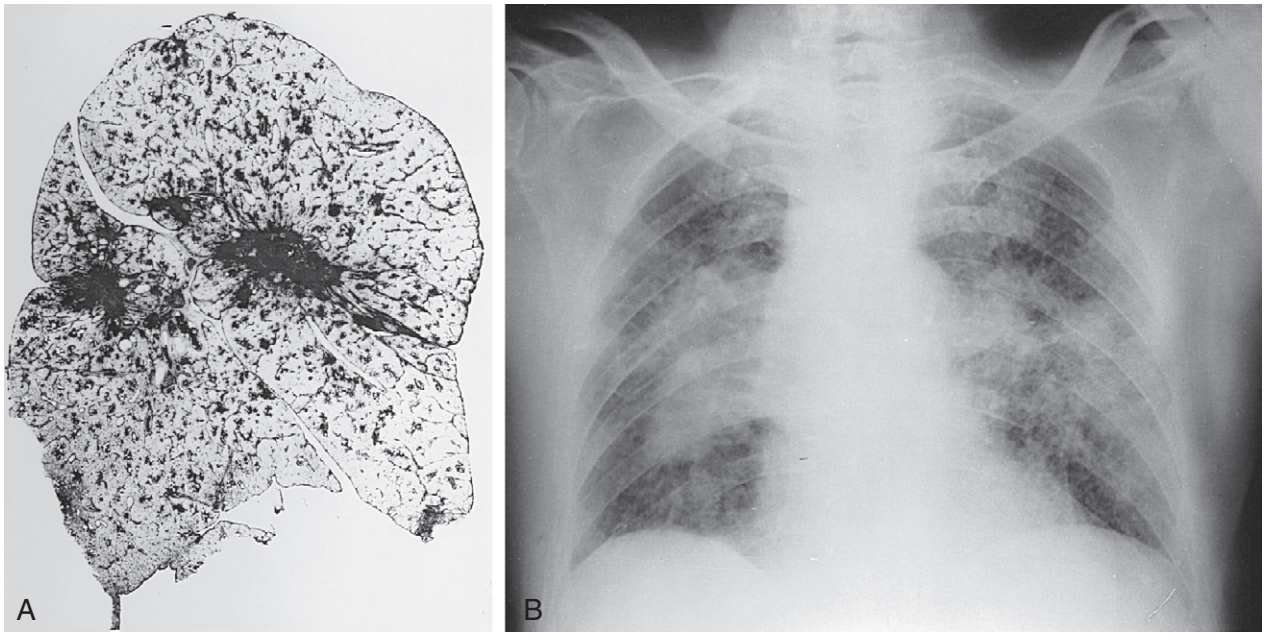

FIGURE 65-8 ■ **A,** Whole-lung section of a 71-year-old Appalachian coal miner. The miner was a nonsmoker and had worked for 28 years underground, primarily at face work. The midsagittal section of the left lung shows massive lesions in the superior segment of the lower lobe and in the central area of the upper lobe. PMF is seen against a background of simple nodular and macular coal workers' pneumoconiosis. In several areas, there is evidence of coalescence of nodules. There is mild focal emphysema associated with the coal dust macules. **B,** Chest radiograph shows features of PMF against a background of nodularity. The mass lesion on the right shows the propensity of PMF to move toward the hilum. The opacities are somewhat atypical for their predominantly lower zone situation. (Case from the National Institute of Occupational Safety and Health [NIOSH] W. Laqueur collection, courtesy of Drs. V. Vallyathan and F. H. Y. Green.)

same elements as the coal nodule (see Fig. 65-6C). They may impinge on and obliterate airways and vessels and cross interlobar fissures. Cavitation is not uncommon, probably as a consequence of ischemic necrosis.

Rheumatoid pneumoconiosis,[2] one variant of which is called Caplan's syndrome, is a form of CWP associated with rheumatoid arthritis or a rheumatoid diathesis. It is characterized by nodules that are larger than coal nodules (≤5 cm in diameter) and have smoother borders. Pigmentation is arranged in concentric laminations, and relative to PMF lesions, they contain little dust. These lesions may cavitate or calcify. The microscopic features are similar to those described for the rheumatoid silicotic lesion (see the discussion under the "Pathology" of "Silicosis"). Active areas in the nodules contain dust-laden macrophages, lymphocytes, polymorphonuclear leukocytes, and plasma cells. When activity ceases, they may collapse or calcify. Vasculitis is seen in vessels within and surrounding these lesions. Rheumatoid pneumoconiosis lesions were originally described in Welsh coal miners and are reported in Belgian coal miners, but are uncommon in North American coal miners.

Diffuse interstitial fibrosis has also been reported in coal miners; the fibrosis may contain black carbon pigment but is otherwise pathologically indistinguishable from usual interstitial fibrosis. However, it has a relatively benign clinical course compared with that of the same condition in the general population.[2]

Pathogenesis

The risk for CWP increases with the intensity and duration of exposure to coal dust. The effect of coal on the lung is also related to its rank, which is based on its carbon content. Anthracite ranks highest (93% carbon), followed by bituminous, subbituminous, and the lowest ranked lignite with the lowest carbon content.[2,4] In epidemiologic studies, CWP is more common in mines of high-rank coal than in those of low-rank coal. This may relate to the greater relative surface area of the coal dust particles, higher surface free radicals, and silica in the high-rank, rather than the low-rank, coal.[4] The coal dust macule and nodule are ascribed to the accumulation of large amounts of relatively inert dust in the lung. As the lung burden of dust increases, alveolar macrophages are activated and reactive oxygen species are released. These in turn trigger the release of cytokines, including interleukins and TNF, which set in motion the processes of inflammation and fibrogenesis that are responsible for the development of pneumoconiosis, and the release of proteases, which contribute to the associated emphysema. The fibrosis, however, is considerably less intense and extensive than that evoked by the more bioactive dusts, such as silica and asbestos.

Although the exact pathogenic mechanisms underlying the development of PMF remain in doubt, these lesions are thought to relate to the amount of coal dust accumulated in the lung, the proportion of inhaled silica in the dust and its surface bioactivity, individual immunologic and genetic factors, and whether tuberculosis is present.[2,4,38] Of these factors, the total dust burden appears to be the most important. In addition, there are striking differences in rates of simple pneumoconiosis and PMF between different coal pits, mining areas, and countries,[2,4] suggesting that other characteristics of the dust particles, including their shape, size, composition, bioactivity, and durability in lung tissue, also make a contribution to the risk of developing CWP and PMF.

Epidemiology and Natural History

Early studies of coal miners suggested that the occupation of coal mining and even the presence of CWP were not associated with higher mortality rates. These studies probably did not take the healthy worker effect into account, and more recent studies have shown that exposure to coal dust is associated with increased mortality.[69] Overall, in the United States, the mortality associated with CWP decreased by 36% between 1982 to 2000 compared with 1968 to 1981.[70]

Although the rates of CWP have been falling steadily in the United States and Europe, new cases continue to be detected.[1,22,71] The presence of PMF is associated with more severe adverse effects on the health and life expectancy of coal miners than those of simple CWP. Risk factors for PMF include the presence and stage of CWP, the intensity of dust exposure, and the age of the subject.[72] The role of silica in the development of PMF is controversial but is generally believed to be important.[2,4,72a] A study of coal miners with rapidly progressive CWP suggests that this might be a marker for the development of PMF. Risk factors for rapid progression of CWP included working at the face in smaller mines, younger age, and mining in eastern Kentucky and western Virgina.[71]

Rheumatoid Pneumoconiosis

Rheumatoid pneumoconiosis (Caplan's syndrome) was originally described as a variant of PMF in coal workers on the basis of its distinctive radiologic features. Active arthritis or circulating rheumatoid factor were commonly associated with rheumatoid pneumoconiosis.[1] At present, most evidence suggests that the presence of rheumatoid arthritis, a rheumatoid diathesis, or both, is a host factor that modifies the response of an individual to coal mine dust exposure. Conversely, dust exposure does not appear to be a risk factor for rheumatoid arthritis.[1] CWP does not appear to have an association with other connective tissue disorders.

Role of Silica

Although it is recognized that silica does not play a primary role in the causation of CWP, coal miners, especially those mining anthracite, may develop the lesions of silicosis. When present, silicosis is usually associated with CWP.[2] Although combined exposure to silica and coal dust may produce less silicosis than would a similar pure exposure to silica, silica exposure is nevertheless thought to contribute to the risk of developing PMF.[4]

Airflow Obstruction and Chronic Bronchitis

With the generally decreasing rates for CWP in most countries, the focus of interest has shifted to an examination of the relationship of coal mining exposure with chronic bronchitis and emphysema.[67,68a,73] Earlier studies demonstrated an association between occupational exposure and airflow limitation, but the confounding effects of smoking were not uniformly taken into account. The association between coal mining and obstructive lung disease has now been confirmed by several longitudinal studies that show that airflow limitation from coal dust exposure can occur independently from CWP and that the effect becomes comparable with that of smoking at exposure levels at which there is a risk for CWP.[50,74]

Mucus hypersecretion (chronic bronchitis) is common in coal workers but does not appear to play a direct role in their development of COPD. Mucus hypersecretion will generally resolve after withdrawal from dust exposure as it does after smoking cessation. Bronchial hyperresponsiveness appears to predispose coal workers to develop COPD. Longitudinal studies have shown that those with persistent airway hyperresponsiveness to methacholine over a 5-year period show a greater FEV_1 decline compared with those whose airway hyperresponsiveness reverses over the same time period.[75]

Tuberculosis and Cancer

Mycobacterial infection, either by *M. tuberculosis* or nontuberculous mycobacteria, has not been demonstrated to be more common in association with CWP in the absence of silicosis.[76] Most evidence suggests that the occupation of coal mining is not associated with lung cancer. An increased risk of stomach cancer has been documented,[2,4,77] but this was not apparent in a 23 year follow-up study of 8,899 coal miners.[69]

Clinical Features

Simple CWP is regarded as a disease state without symptoms or physical signs. The diagnosis is based on the radiologic features. The symptoms of cough and sputum reported by most coal miners are likely to be the consequence of dust-induced chronic bronchitis.[50] Breathlessness on effort is usually caused by associated chronic airflow limitation or by the development of PMF.[4] Respiratory impairment and disability develop as PMF progresses, although patients with category A PMF (lesions 1-5 cm in diameter) may be symptom free. Lesions of PMF that impinge on airways may cause abnormal breath sounds. Large or bilateral PMF lesions may be associated with hypoxemia and right heart failure. The presence of new lung lesions with rheumatoid arthritis, subcutaneous rheumatoid nodules, or positive rheumatoid factor raises the possibility of rheumatoid pneumoconiosis. The lung lesions may or may not develop concomitantly with joint disease.

Chest Radiography

The hallmark of simple CWP on the chest radiograph is the presence of small rounded opacities in the lung parenchyma.[1,58] (See the discussion of chest radiographs in the "Introduction" to this chapter.) Coal macules are usually associated with small (<1.5 mm) p nodules on the chest radiograph, but the radiograph may show no nodularity with mild to moderate grades of CWP. Large amounts of coal dust in the lungs are found in association with small, rounded p nodules. When the larger q and r nodules are visible radiologically, this usually reflects the presence of coal nodules and a higher proportion of quartz in the lungs.[78]

Because the chest radiograph has been shown to be insensitive to the presence of macules and nodules,[78] in individual cases, CT may be useful. Small rounded opacities are usually seen first in the upper zones and involve the other zones at a later stage; all lung zones are unlikely to be involved unless profusion category 3 is present.[1,58] The nodule profusion is closely related to the lung dust content at autopsy. Small irregular opacities also occur in a profusion up to 1/0 in association with increasing age and smoking and, in coal workers, may relate to coexisting fibrosis and emphysema. Small rounded opacities probably never regress but the presence of emphysema appears to reduce the reading of profusion on the chest radiograph. Some enlargement of hilar nodes is usual, but eggshell calcification is unusual.

PMF is diagnosed radiologically when the parenchymal opacities exceed 1 cm in diameter, a cutoff point that is arbitrary in what is obviously a continuous process, as shown by the pathologic demonstration of PMF without associated radiologic features.[78] Conversely, approximately one third of cases diagnosed as PMF on the radiograph have been shown, at autopsy, to represent other lesions, including tumors, rheumatoid nodules, or tuberculosis scars.[78] PMF lesions are more common in the upper lobes, are situated posteriorly, and are usually well demarcated from the adjacent lung. As PMF becomes more advanced, the lesions are nearly always bilateral (see Figs. 65-7 and 65-8). They may take on bizarre shapes, cavitate, or calcify. As the lesions shrink toward the hilum or to the apex, bullous lesions may be seen in the surrounding lung.

Lesions seen on the chest radiograph in rheumatoid pneumoconiosis are similar to those of PMF but are usually multiple and peripherally located. The lesions, which range in diameter from 0.5 to 5.0 cm, may appear within weeks. These lesions generally appear in the presence of lesser degrees of nodule profusion than are usual for PMF. They may cavitate, contain fluid levels, and show some calcification surrounding the cavity. In some cases, the lesions disappear, often completely, but may be followed at a later date by a fresh crop of lesions. The ILO classification of radiographs provides a

special notation for lesions thought to be rheumatoid pneumoconiosis.[5]

Lung Function

The controversy regarding the association between simple CWP and abnormal lung function has persisted largely because coal dust has been shown to cause both obstructive lung disease[79] and pneumoconiosis. In general, it is probably true that simple CWP is a condition with little demonstrable effect on lung function. In part, this may be due to the health selection effect into a dusty job.[50] Small irregular opacities and PMF have each been shown to be associated with abnormal lung function.[4,80] Lung function deficits in complicated CWP include reduction in FVC and FEV_1, increased total lung capacity (TLC) and residual volume, and decreased D_{LCO} (particularly in the presence of mixed rounded and irregular opacities). Similar changes have also been noted in nonsmoking coal miners without CWP.[4] Pulmonary hypertension may develop in proportion to the reduction of the vascular bed associated with advanced PMF.

Diagnosis, Complications, and Management

A history of occupational exposure to coal and a chest radiograph are the fundamental elements in the diagnosis of CWP. A CT scan of the chest may be used to demonstrate evidence of CWP when the features on the radiograph are inconclusive.

There are no data to suggest that CWP alone carries an increased risk for mycobacterial infection, either tuberculous or nontuberculous, but treatment of latent tuberculosis infection should be considered for coal workers who are thought to have had significant silica dust exposure or who have evidence of silicosis. Other complications include rheumatoid nodules, which are associated more commonly with coal mining than with gold mining exposure, and scleroderma, in which the opposite is true. Most evidence suggests that the occupation of coal mining is not associated with a risk of lung cancer, but there are some data to suggest and some to refute an increased risk of stomach cancer.[4,69]

The principles of management are those summarized in the "Introduction" to this chapter and elaborated in the section on "Silicosis." Younger subjects with radiologic disease of profusion category 1 or greater should be advised to change their occupation to one in which they are no longer exposed to dust because of their risk of developing PMF. Management of other dust-related, smoking-related, or dust- and smoking-related diseases, such as chronic bronchitis and emphysema, is less straightforward. Smoking-cessation counseling should be given on general principles. Although there are no data to show any interaction between smoking and CWP, both coal mining and smoking have the capacity to cause COPD.[68a]

ASBESTOS-RELATED FIBROSIS OF THE LUNGS (ASBESTOSIS) AND PLEURA

Asbestos Minerals

History and Uses

Asbestos is an ancient mineral exploited by humans from prehistoric times because of its durability and heat resistance and its fibrous nature, which enabled it to be spun.[1,81] Commercial use of asbestos, which started in the 19th century with open-pit mining, grew as mechanization replaced hand cobbing[1] and growth was exponential between the two world wars. Annual production peaked over 5 million tons in 1976 and stabilized at approximately 4 million tons in the early 1980s. Production began to fall in Europe and North America only in the late 1980s, when the ill health effects of exposure became a matter of increasing public concern.[1] By contrast, annual world production of the nonasbestos mineral silicates is almost eightfold greater (~30 million tons) than that of the asbestos mineral silicates.[82] The use of substitutes has increased proportionately as the use of asbestos has been restricted or banned, although in 2008, only 40 countries had banned or severely restricted the use of asbestos. On the African, Asian, and South American continents, asbestos continues to be in demand as a cheap, durable material for use in water reticulation and in housing projects for their rapidly urbanizing populations, and in many countries, the consumption of asbestos remains high and is increasing.[83]

The word *asbestos* (meaning "unquenchable" in Greek) is used currently as a collective term for naturally occurring mineral silicates of the serpentine and amphibole group. Despite different origins and physical and chemical properties, these silicates have in common a fibrous habit, that is, they occur naturally in bundles from which fibers can be easily separated.

What is meant by the term *fiber* is of more than academic importance because their dimensions are determinants of biologic potency. The mineralogist defines a fiber as a particle whose length to diameter (called "aspect") ratio is equal to or greater than 10:1, whereas the definition used by the Occupational Safety and Health Administration (OSHA) as a basis for standard setting is a particle more than 5 μm in length with an aspect ratio equal to or greater than 3:1.

Table 65-3 lists some of the mineral silicates found in human lung tissue and gives a general (but not exhaustive) indication of their commercial uses. From the point of view of health effects, the most important are asbestos fibers and man-made mineral fibers. Biologic potency (and disease-producing potential) depends in general on dose delivered to the target organ, fiber dimensions, and durability in the lung tissue. The role of each of these parameters may not be the same for all fibers and all disease entities.[82] Nonfibrous particles greater than 10 μm seldom reach the lung parenchyma, whereas fibers up to 200 μm can be found in the lungs if their diameter is less than 3 μm.[2]

TABLE 65-3. Mineral Silicates That Have Been Found in Human Lung Tissue*

Mineral: Group and Form	Location of Major Deposits, Commercial or Other	Main Commercial Uses and/or Other Sources of Human Exposure
ASBESTOS MINERALS		
Serpentine		
Chrysotile† (white asbestos)	Canada (Quebec, British Columbia, Yukon, Newfoundland‡), Russia, China (Szechwan), Brazil, Mediterranean countries (Cyprus, Corsica, Greece, Italy), southern Africa (South Africa, Zimbabwe, Swaziland)	Brake lining, shipbuilding and repair, polishing of precious stones, stone cutting, whetstone cutting, foundry operations (mainly for insulation) Asbestos cement products (pipes, gutters, tiles, roofing); insulation, fireproofing, reinforced plastics (fan blades, electric switchgear); textiles; friction materials; paper products; filters, spray-on products
Amphibole		
Crocidolite (blue asbestos)	South Africa (Northwest Cape‡), western Australia‡	Used in combination, mostly in cement but also in some of the products listed above
Amosite (brown asbestos)	South Africa (Northern Province, former Transvaal) Finland‡	
Anthophyllite		Filler in rubber and plastics
Tremolite	Contaminates ore in certain asbestos, talc, iron, and vermiculite mines; also found in some agricultural soils	May or may not be removed in processing; has rural domestic uses (e.g., stucco)
Cummington-grunerite	Contaminates ore in certain iron mines (often not fibrous)	No commercial use
NONASBESTOS MINERAL SILICATES		
Clay minerals (usually fine-grained, powder-like) such as kaolin and montmorillonite (bentonite)	40 countries, including China, United States (Georgia, North Carolina), United Kingdom (Cornwall), Czechoslovakia, Germany, Egypt, Japan	Functional filler in paper, plastic, bricks and cement, rubber, paint, etc.; fire clays, refractories, ceramics, lubricants
Attapulgite and sepiolite	United States (Georgia, Florida), Spain, Australia, South Africa	Oil absorbants; pesticide carriers; pet litter
Talcs (usually platelike but can roll into scrolls)	United States (Vermont, Montana, New York, California), Italy, Spain, Norway, China, Japan, Korea, Canada	Ceramics; paper making; cosmetics; pharmaceuticals; animal feed; fertilizer; anticaking; paints; varnishes; plastic reinforcer
Micas (usually flaky)		
Muscovite	United States (North Carolina, Georgia, and other states), France, Spain, China, India, Italy	Filler in plastics, drill sites, special paints; refractories; semiconductors; insulation; anticorrosion materials; welding rods
Vermiculite (expands when heated)	South Africa, United States (Montana, Virginia), Australia, Kenya	Absorbants (horticulture); plasters; boards; insulation; fire resistance
Wollastonite (occurs as needles or fibers in limestones)	United States (California, New York), Japan, former USSR, Finland, Mexico, Australia	Filler/flux in ceramic industry; used in latex and oil-based paint; in welding fluxes; asbestos substitute in hardboard, insulation, and brake linings
Zeolite (fibrous), e.g., Erionite§	Turkey (Cappadocia and Anatolia regions)§: noncommercial deposits	Houses constructed in erionite rock; soil-containing fibers mixed with tremolite; sepiolite used in stucco and plaster
Other (mainly nonfibrous)	Worldwide (in filling of lava cavities); mined in 16 countries, including several in Europe, in the United States, and in Japan	Pollutant and radioactive waste control; also used in catalysts, adsorbants, conditioners
MANMADE MINERAL FIBERS		
Glass wool and filament, rock wool, slagwool, ceramic fiber	Production in factories around the world	Many uses previously reserved for asbestos: glass filament used in mats, lamination, yarns; glass-rock and slagwool used as insulation in buildings and in car and naval construction; ceramic fiber used in reinforced cloth, disks, brakes, gaskets, board, and paper; high-performance ceramic fiber used in jet engines, spacecraft

*The list is not exhaustive, and the reader should consult other sources[1,2,84,151,152] for further information. Asbestos minerals invariably exhibit the fibrous habit; nonasbestos mineral silicates also may do so. Most silicate deposits are mineralogically heterogeneous, as are most of the commercial forms of the minerals.[151]

†Accounts for more than 90% of the world's commercial production; other fibers still used in combination with chrysotile.

‡Mining no longer in operation.

§One of three epidemics of mesothelioma in Turkish villages implicated erionite; in the other two, tremolite and/or chrysotile were implicated.[91] As of 2008, 40 countries have prohibited the use of asbestos or severely restricted its use, but in all countries, exemptions are allowed for certain uses. A prohibition decree was adopted to be enforced in the European Community in 2005. Currently, the Jeffrey Mine in Canada suspends its mining operations intermittently depending on demand.

Sources of Human Exposure

Given its many uses, the potential sources for human exposure to asbestos are legion, even today.[1] The list given in Table 65-3 should be regarded as a short guide for clinical use. The discussion that follows deals mainly with exposure to asbestos fibers; the principles, however, apply equally to exposure to other fibers.

In industrialized countries, and increasingly in industrializing countries, human exposure is most likely to be *occupational* and may occur in mining, milling, transporting, manufacturing, and applying or using raw fiber or manufactured products. In World War II, a major source of exposure was in the naval shipbuilding, repair, or refitting industries; in the post–World War II period, major sources of exposure were in the construction and transport industries, although exposures in shipbuilding, repair, or refitting continued to pose risks. Asbestos-containing materials in post–World War II buildings include boards, panels, surfacing, insulation, tile and floor covering, roofing, and caulking. Exposure also occurs in maintenance operations or demolition of plants and buildings in which asbestos-containing materials have been used. Other sources of human exposure occur during the removal of asbestos lagging or insulation from ships or buildings and the disposal of industrial waste, such as the dumps of defunct asbestos plants. In most industrialized countries, these sources of exposure have diminished in response to heightened public awareness and control regulations.[1,84] However, as recently as 2004, the U.S. Department of Labor estimated that 1.3 million workers remained exposed to asbestos in the workplace, notably in construction and general industry in the United States.[85] Data do suggest that asbestos exposure has decreased, although a recent study from the United States comparing those examined between 1980 and 1992 and those examined between 1993 and 2005 found an unexplained increase in crocidolite fibers in the lungs from 819 subjects with lung cancer, malignant mesothelioma, and asbestosis.[86]

Indirect occupational exposure, also called *bystander exposure*, describes the exposure of those whose trades require them to work in the vicinity of others who were working directly with asbestos or asbestos-containing materials. Examples are carpenters and welders who may work in close contact with insulators and laggers who mix asbestos on site, often in closed spaces. These exposures often occurred in the shipbuilding, repair, and refitting industries and the construction industries.

Domestic exposure occurred primarily as a consequence of fiber-laden work clothes being brought home. Domestic exposure still accounts for a small proportion of cases of asbestos-related disease, mainly pleural, and is reported to have accounted for up to 15% of malignant mesothelioma in one U.K. study.[87] Given the long incubation period of this tumor (from 20-40 yr), domestic exposure is likely to be the source of cases presenting well into the 21st century.[1,2]

Environmental and residential exposure occurs as a consequence of living in the neighborhood of asbestos mines, mills, or plants.[88] This source of exposure was first dramatically brought to medical attention in 1960 in a report of a cluster of 31 cases of malignant mesothelioma among residents and crocidolite asbestos miners of the Northwest Cape, South Africa.[89] New cases were reported from this area until 1995, and because occupational and environmental exposure continued until the 1970s, cases are expected to continue and to increase up to and beyond 2010.[90] A cohort study comparing the mortality experience of more than 4500 women living in the vicinity of the Quebec chrysotile mines with that of 1.375 million women from 60 reference areas in the province found 7 deaths from mesothelioma in women living in the asbestos mining area and none in the reference population.[88] Environmental exposures from nonindustrial sources have been documented among residents of rural areas in Eastern Europe where the soil is contaminated with various fibers.[91] In addition, epidemics of asbestos-related pleural disease, nonmalignant as well as malignant, have occurred among residents of Turkish villages whose homes were constructed in erionite tuff rock or who used erionite and tremolite in stucco and plaster[91] and in Da-yao, southwestern China, where crocidolite is present in the soil.[88,92] A major concern since the 1980s has been the potential risk of exposure to occupants of public buildings (including schools), commercial, and residential buildings constructed during the post–World War II period, when asbestos-containing materials were widely used in construction. A health review, mandated by the U.S. Congress concluded that exposure in buildings was less by an order of magnitude than that encountered in the workplace except for custodians and others responsible for building maintenance.[93] The report also provided estimates of lifetime cancer risk (see "Asbestosis, Asbestos Exposure, Lung Cancer, and Mesothelioma," later).

The Fate of Inhaled Fibers

Accumulation of fibers in the lung is the outcome of exposure, deposition, clearance, and retention, all processes that depend on fiber dimensions and the level, intensity, and profile of exposure.[94,95] Clearance of fibers from the lung is greater for short and for chrysotile fibers than for long and for amphibole fibers.[96] Retention of fibers is inhomogeneous, with more fibers being found in the lung regions with shorter pathways and greater accumulations of longer fibers with asbestosis than in lungs in which only airway lesions have developed.[96] Fibers equal to or less than 3 μm are phagocytosed by activated macrophages, then translocated to lymphatic channels, and eventually drained to the pleural space. Longer fibers are incompletely phagocytosed, often by more than one macrophage, and become the core of what were originally called *asbestos bodies* because of their association with asbestos exposure. Although most coated fibers in human lungs have been shown to contain asbestos (usually amphibole) when subjected to radiographic diffraction analysis,[2,81] the term *ferruginous bodies* has been suggested to underline the fact that other mineral fibers may undergo coating in human lungs. The mechanism by which fibers transmigrate to the parietal pleura to produce pleural plaques remains uncertain.[97]

In the lungs of exposed individuals, the number of uncoated, or bare, fibers (visible only on electron microscopy) exceeds the number of coated fibers (*asbestos* or *ferruginous* bodies), visible by light microscopy, by 5- to 10,000-fold.[82,98] For many years, the coated asbestos fiber, *asbestos body*, has been considered the hallmark of exposure, past or current, no doubt because of its distinctive structure and because it was readily visible under the light microscope. The presence of more than one coated fiber has been cited (and challenged) as a necessary criterion for the pathologic diagnosis of asbestosis even in a subject with an appropriate exposure history.[98] Asbestos bodies may be found in sputum or in BAL fluid when lung tissue levels are very high. They are also more commonly found when exposure has been recent and to amphibole rather than chrysotile fibers.[2,99,100] BAL fluid may also show characteristic cellular, biochemical, and mineralogic features in workers exposed to asbestos and especially in those with asbestosis.[101]

Exposure versus Dose-Response Relationships

Epidemiologic studies have consistently demonstrated exposure-response relationships for asbestos-related parenchymal lung fibrosis (Fig. 65-9).[102] There are differences in the slopes of the exposure-response relationships between industrial sectors, which probably reflect the fiber size (smaller fibers causing more disease) and the nature of the fibers, their retention, and their biopersistence in lung tissue (amphiboles causing more disease than chrysotile). For asbestos-related pleural disease, exposure-response relationships can also usually be demonstrated, but the residence time of the dust in the lungs is more important than the cumulative exposure.[95,97] Mineralogic analysis has also shown that the degree of fibrosis correlates with fiber concentration, both in chrysotile- and in amosite-exposed workers. The toxicity of mineral fibers is determined by their physical and aerodynamic properties, which determine deposition and retention. Also relevant in fibrogenesis and probably in carcinogenesis is the solubility of the fibers (which determines their survival in lung tissue) and their surface properties and electrical charge (which may affect their toxicity for cell membranes and the formation of free radicals).[2,33]

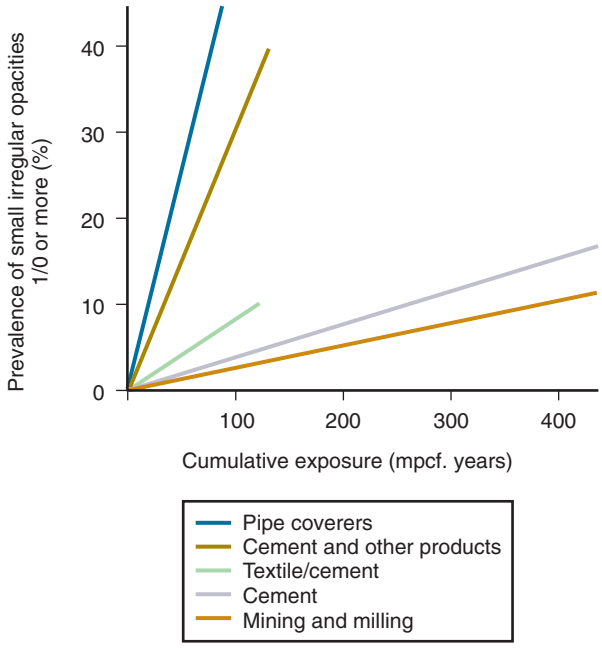

FIGURE 65-9 ■ The prevalence (%) of small irregular radiographic opacities (≥1/0) in relation to cumulative exposure in millions of particles per cubic foot × years (mpcf years) in different work forces exposed to asbestos. Idealized exposure-response relationships are shown for various sectors of the asbestos industry, including mining and milling, cement, and textile production (studies carried out in Quebec), and cement and other products and pipe covering (studies carried out in the United States). Further details are given elsewhere.[136] (Redrawn from Becklake MR: Occupational lung disease: Past record and future trend using the asbestos case as an example. Clin Invest Med 6:305–317, 1983.)

Asbestosis (Pulmonary Parenchymal Fibrosis)

Pathology and Pathogenesis

Asbestosis tends to be prominent in the lower lobes and in the subpleural areas. When disease is advanced, the lungs are small, streaks of fibrosis outline lobar and interlobar septa, and the visceral pleura is invariably thickened. Honeycombing may be prominent subpleurally and in the lower lobes. Unlike in silicosis, the tracheobronchial lymph nodes do not show characteristic changes and progressive massive fibrosis is unusual.[98] Advanced asbestos-related fibrosis is distinguishable from advanced fibrosis due to any other cause only by the presence of asbestos bodies or uncoated asbestos fibers (Fig. 65-10B).[2] At the other end of the disease spectrum, the lesions of mild asbestosis tend to occur at scattered sites and usually consist of foci of peribronchiolar fibrosis[103] with local chronic interstitial inflammation, accumulation of macrophages in the air spaces, and proliferation of type II pneumocytes. Second- and third-order bronchioles and alveolar ducts tend to be involved as the disease progresses and the fibrosis spreads to involve the alveolar interstitium (see Fig. 65-10A).

In general, the grade of pulmonary fibrosis relates to the fiber burden carried by the lungs.[2] On the basis of animal and human data,[33,104,105] the sequence of events leading to asbestosis is thought to commence with an alveolitis that may resolve if the fiber burden is low and the fibers are cleared. If the fiber load is low but retained, a nonprogressive distal airway lesion, mineral dust-induced peripheral airway disease, may develop.[33,96,103–105] If the dust load retained is high and phagocytosis of fibers by alveolar and interstitial macrophages is incomplete, fibronectin is released together with other proinflammatory and cytotoxic agents such as free oxygen radicals. These interact with and recruit fibroblasts to the site of the injury, where they proliferate and lay down collagen. If sustained, this leads to irreversible damage, loss of alveolar spaces, and the development of chronic interstitial lung fibrosis, asbestosis.[96]

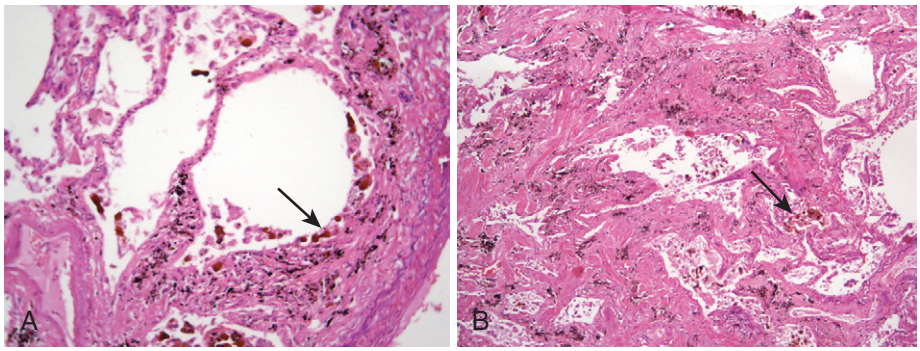

FIGURE 65-10 ■ Pathologic features of asbestosis: examples from South African asbestos workers. **A,** Asbestos bodies (*arrow*) with commencing fibrosis. The architecture of the surrounding lung parenchyma is preserved. **B,** Diffuse interstitial fibrosis with destruction of the lung architecture and honeycombing; asbestos bodies are seen in the air spaces and interstitial tissue (*arrow*). (Courtesy of National Institute for Occupational Health, South Africa.)

Epidemiology and Natural History

Clinical asbestosis, like clinical silicosis, is becoming less frequent and less severe as exposure levels in workplaces around the world are increasingly meeting currently recommended control levels.[95,106] However, in the United States, although mortality rates for the other pneumoconioses (CWP and silicosis) are declining, the rate for asbestosis has increased possibly by as much as tenfold between 1968 and 1999,[22,70] and are not expected to decrease before 2024,[70a] a similar trend was apparent in Australia,[107] while in the United Kingdom and Canada, rates of certification of death or disability from asbestosis are falling.[108,109] With low-level exposure to asbestos, the interval between exposure and disease increases.[95] The pattern of exposure also determines the nature of the disease. In occupations in which exposure is intermittent but of high intensity, the ratio of pleural to parenchymal radiologic abnormalities may exceed 20, whereas a 2:1 pleural-to-parenchymal ratio is more usual in occupations in which workers are more consistently exposed.[95,110] Exposure at a young age is an independent determinant of both attack and progression rates of parenchymal and pleural radiologic abnormalities, suggesting that residence time of dust in the lung is important in their pathogenesis.[95,110,111] Other determinants of progression are level and duration of exposure, cumulative exposure, and fiber type (more frequent after exposure to the amphiboles crocidolite and amosite or mixtures of amphibole and chrysotile than to chrysotile alone) (see Fig. 65-9).[95] Once established, radiologic asbestosis may remain static or it may progress; rarely has regression been recorded.[110] Radiologic asbestosis may appear and progress long after exposure ceases; in a study of chrysotile miners and millers in Quebec, appearance and progression rates of 31% and 9%, respectively, were recorded for pleuroparenchymal disease over an average follow-up period of 17 years after exposure.[95,110] Progression in the absence of further exposure relates to cumulative exposure up to the time of quitting.[95,111] Genetic features appear to play a role in determining the occurrence and extent of asbestos-induced lung fibrosis.[95,112,113]

Smoking deserves comment because of its role as a universal risk factor for respiratory disease, both malignant and nonmalignant. There is some evidence that the milder grades of radiologic small irregular opacities on the ILO classification may be caused by smoking. Pathologic studies do not show evidence of an association between asbestosis grade and smoking,[114] although there is evidence to suggest that smoking enhances the retention of fibers in the lungs.[2,114]

Clinical Features

Asbestosis has been called a monosymptomatic disease because the earliest, most consistently reported, and most distressing symptom is dyspnea. Dyspnea often precedes other evidence of disease and, therefore, may be underrated by the physician because of its subjective nature. However, the consistency of its relationship to exposure levels[95] suggests that it is related to early parenchymal asbestosis. Persistent dry cough is reported commonly, almost as frequently as dyspnea in some series,[97,115] and has been attributed to the stimulation of lung receptors. Chest tightness or pain, or both, are not uncommon and may be caused by acute asbestos-associated pleural reactions.

Basal crackles, an early and distinctive feature of asbestosis, are fine crisp persistent sounds, often heard first over axillary and basal regions and then more generally as the disease advances.[85] Other sounds, including coarse crackles and rhonchi, reflect airway disease that may be related to cigarette smoking or to dust in the occupational environment.[73] Clubbing of the fingers and, occasionally, the toes develops in some subjects. Late manifestations include respiratory and circulatory failure, and these, with cancer, are common causes of death.

Radiographic Features

The posteroanterior chest radiograph remains a key tool in the initial clinical diagnosis of asbestosis and in the health surveillance of exposed workers. The ILO classification[5] uses the term "small irregular opacities" to describe the irregular linear shadows that develop in the

lung parenchyma and obscure the normal bronchovascular arborization pattern seen in disease-free lungs. The parenchymal opacities are usually seen first in the lower lateral zones. As their profusion increases, the borders of the heart are obscured. Small rounded opacities are unusual when the exposure has been primarily to fibers but are more likely to be seen in workers who also have had silica exposure: for instance, asbestos cement workers.[1,16]

Early fibrotic changes are better visualized by HRCT with supplementary prone images,[101] particularly for subpleural parenchymal changes that may be obscured by overlying pleural fibrosis on the chest radiograph.[116] Visceral pleural thickening of the interlobar fissures is common.[97] Changes in the parietal pleura (see later) are also common, and the presence of pleural plaques (particularly if they are bilateral) or of pleural thickening provides additional evidence that the parenchymal disease is asbestos related. Hilar node enlargement is not a feature of asbestosis, and PMF lesions, including rheumatoid pneumoconiosis, are less common than in workers exposed to coal or silica. The radiologic features of well-developed disease seldom present a diagnostic problem; interpretation of the less marked changes is much more subjective, and hence, the use of ILO films and of HRCT are proportionately more valuable.[116,117] The CT scan is also useful in characterizing localized pleuropulmonary lesions, including rounded atelectasis, which must be distinguished from lung cancer because it usually presents as a solid localized lesion (Fig. 65-11). HRCT can also identify coexisting lung disease such as emphysema and distinguish subpleural fat from pleural thickening and plaques.

Lung Function

Established asbestosis is often, but certainly not always, associated with a restrictive lung function profile (see Chapter 24).[95] With less advanced radiologic disease, FVC and the D_{LCO} are reduced, and reduction in flow at low lung volumes ($FEF_{25\%-75\%}$ [mean forced expiratory flow between 25% and 75% of the FVC]) is a common finding in keeping with small airway abnormality.[31,97] In studies of exposed populations, a substantial proportion of subjects (up to half in some series)[110] exhibit a mixed or obstructive function profile in keeping with the parallel development of airway and parenchymal effects of working in dusty occupations contaminated by mineral dusts.[67] When repeated lung function tests are used to assess evolution of disease, simple volume measurements such as FVC appear to be the most useful.[81,110,118]

Diagnosis and Complications

Criteria for diagnosis depend on the purpose for which a diagnosis is required. Clinical diagnosis depends on establishing the presence, extent, and nature of pulmonary fibrosis and that the exposure has been of a duration and intensity sufficient to put the individual at risk for developing asbestosis. The fewer the features, the less certain the diagnosis; the more trivial the exposure, the less likely that it is causal. When radiologic or lung function changes are marginal, other imaging, including CT or HRCT, may be helpful. In the absence of what appears to be an adequate exposure history, it may be appropriate to perform a biopsy of the lung to establish the nature of the disease and the presence and burden of asbestos in the lung. Sputum analysis may be useful for identifying asbestos bodies as an indication of lung dust burden but is far less sensitive than BAL.[85,101,119] Diagnosis of asbestosis for the purpose of legal attributability calls for greater certainty and the use of criteria that vary according to the legal administrative system involved. Most published criteria consider histopathology as the best means of establishing the diagnosis.[96] In its absence, the following criteria are proposed: (1) a reliable history of asbestos exposure; (2) an appropriate lag time between exposure and detection; (3) evidence of lung fibrosis on the chest radiograph or HRCT scan; (4) a restrictive pattern of lung function; (5) bilateral fixed inspiratory crackles; and (6) clubbing of the fingers or toes, or both. Of these, history of exposure and radiographic evidence are considered essential and the others confirmatory.[96]

The individual with asbestosis is at increased risk for cancer of the lung[120,121] and, by virtue of asbestos exposure, is also at risk for mesothelioma. Working in a dusty occupation also puts the worker at risk for developing COPD.[67] Tuberculosis and rheumatoid pneumoconiosis are uncommon complications of asbestosis.

Asbestosis, Asbestos Exposure, Lung Cancer, and Mesothelioma

The observation reported in 1951 that lung cancer occurred more frequently in association with asbestosis than with several other types of pneumoconiosis was responsible for first directing attention to the potential of asbestos exposure for carcinogenesis.[122] Mortality studies of exposed workforces confirmed the excess lung cancer risk and showed it to be related to the intensity and duration of exposure[2,123] and to decrease after exposure ceases, thus providing evidence for causality.

In 1977, the IARC classified asbestos as a human carcinogen, the target sites being lung, larynx, and pleura.[1,121] The report stated that there is "no scientific documentation indicating that these entities [asbestosis and lung cancer] are interrelated in any way other than [by their being] associated causally with exposure to asbestos." Since that date, a considerable body of evidence has accumulated in support of this view that lung cancer is associated with asbestos exposure with or without asbestosis,[124–126] although there are still dissenting views.[2] Experimental studies (cellular and molecular) support this view and suggest that asbestos may have multiple roles in the pathogenesis of malignancy, a question that touches on the whole issue of the interrelationship of inflammation, fibrogenesis, and carcinogenesis because profibrotic mediators may promote carcinogenicity.[33] The lung cancer risk is enhanced by cigarette smoking (although the previously held multiplicative model has more recently been challenged[127]) but is also demonstra-

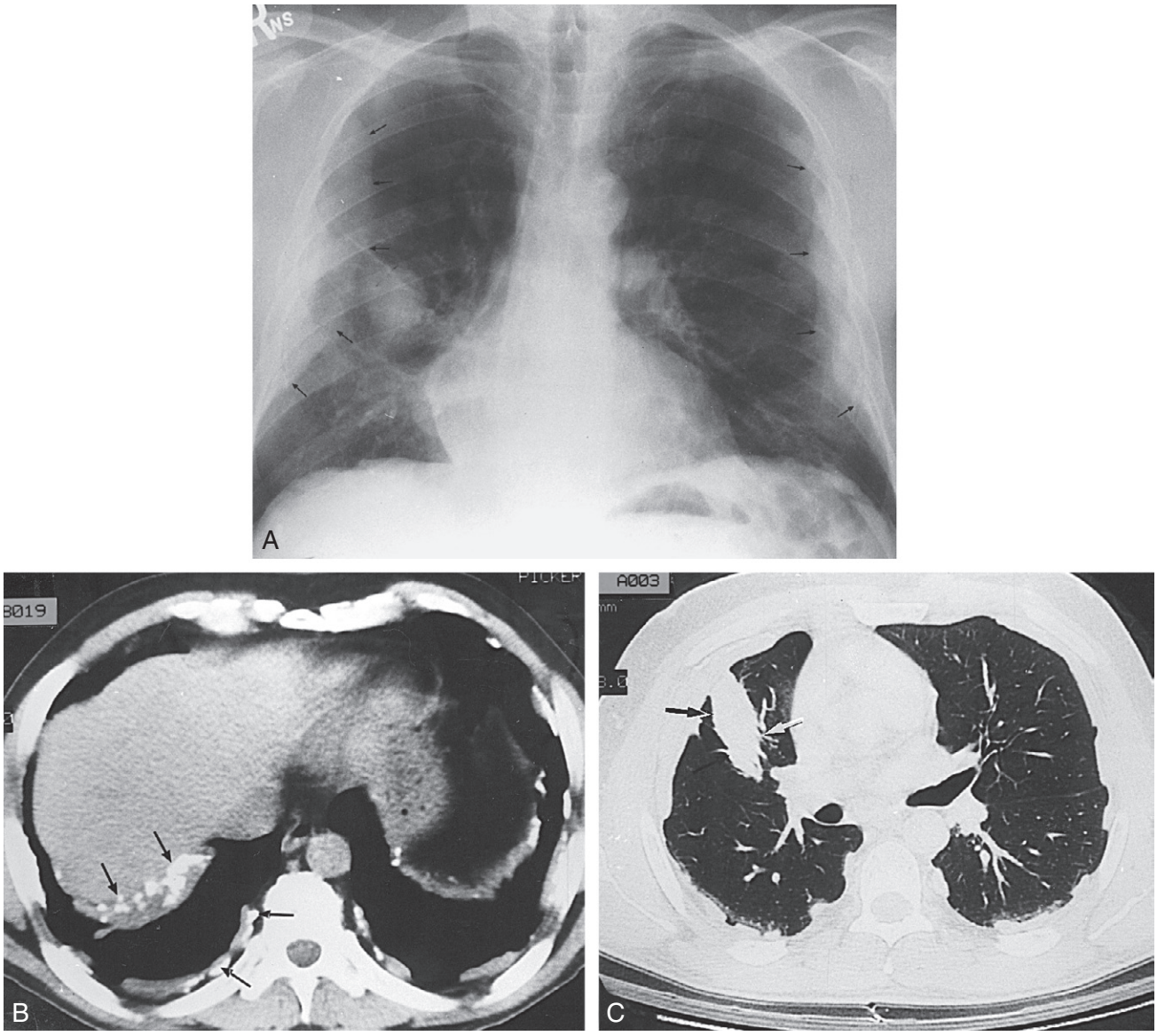

FIGURE 65-11 ■ Asbestos-related pulmonary parenchymal and pleural disease (bilateral pleural fibrosis and rounded atelectasis) in a 50-year-old man. The patient had worked as an electrician since the age of 17 years, first in construction for 10 years (with known exposure to asbestos), then briefly on naval ships during World War II, and in a chemical plant (with known exposure to talc) for the past 20 years. His exercise tolerance was excellent and his only complaint was a dry cough. Chest radiographic abnormalities had been noted 4 years previously. **A,** Posteroanterior chest radiograph shows bilateral diaphragmatic plaques, extensive bilateral pleural thickening (category c3 using the ILO reference radiographs), and a circumscribed lesion in the right mid-lung zone that had increased in size over the past year. **B,** On the computed tomography scan, the pleural plaques were shown to be much more extensive than appeared from the posteroanterior chest radiograph. Many plaques (*arrows*) were calcified. In addition, high-resolution computed tomography scan at multiple levels revealed bands of subpleural fibrosis related to the pleural plaques or thickening, or both. Lung volumes and carbon monoxide diffusing capacity were greater than 100% and 98% of predicted values, respectively. Because the circumscribed lesion (*arrows* in **C**) had enlarged over the past year, it was removed surgically. The lesion, which was nonmalignant and pleural based, consisting of pleural, subpleural, and interstitial fibrosis. Analysis of lung digest revealed the following: 36,000 asbestos bodies/g of dry lung tissue, and 7570 fibers/mg of dry lung tissue, more than half of which were asbestos fibers and less than 1% of which were talc. These findings implicated his earlier rather than his more recent occupational exposures as the cause of his pleural disease. (Dr. J. Kosiuk, Department of Radiology, Royal Victoria Hospital, Montreal, carried out the radiographic studies; Dr. A. Dufresne, School of Occupational Health, McGill University, carried out the lung dust analyses.)

ble in nonsmokers.[93,101,128] A 1999 analysis estimated the attributable proportion due to synergy to be as high as one third.[129] Other factors influencing the risk of lung cancer in exposed workforces include industry (risk greater in the textile vs. the asbestos cement industry), fiber type (risk greater when exposure is to amphibole-crocidolite, amosite or tremolite, or mixed amphibole-chrysotile than when it is only to chrysotile), and fiber dimensions (longer fibers are more carcinogenic than shorter fibers).[96,130]

The emergence of cancer as an important cause of death in asbestos-exposed individuals can be attributed

in part to workplace controls, introduced in the 1970s and implemented over the latter half of the 20th century, resulting in a decrease in the competing risk from asbestosis and greater chance of survival into the cancer age group. Lung dust burden studies in workers coming to autopsy with different asbestos-related diseases have confirmed that the dust burden associated with asbestosis is on average severalfold greater than that associated with asbestos-related lung cancer.[131] For instance, in chrysotile miners in Quebec, the fiber concentrations in those dying of asbestosis versus those dying of lung cancer versus nonexposed were 30 versus 13 versus 2 million chrysotile fibers per gram dry lung tissue; for those engaged in trades with asbestos exposure in the Pacific Northwest, where amosite was the dominant fiber, the equivalent figures were 10.0 versus 1.0 versus 0.7 million fibers per gram of dry lung tissue.[114] All histologic cell types of lung cancer have been shown to be associated with asbestos exposure, which further supports the direct role of asbestos, independently from asbestosis, as a carcinogen.[101] In addition to its biologic importance, the question is also of practical interest in terms of legal attributability, and this varies between jurisdictions. There is obviously a much stronger case for attributing lung cancer in a particular individual to asbestos exposure in the presence of asbestosis and in the absence of a smoking history than in the absence of asbestosis and in the presence of a smoking history. Despite the methodologic variation in asbestos fiber and body counting, all available information about exposure, including any measures of asbestos fiber in BAL or biopsy material, should be assembled in such evaluations; in other words, the presence of asbestosis should not be used as the only indicator of important occupational exposure.

Of great concern to the public has been the risk of cancer from attending school or working in a building constructed with asbestos-containing materials. The lifetime risk for premature cancer death from exposure at school from age 5 to 18 years has been estimated at 6 per million exposed, and for working in an office building with asbestos-containing material, at 4 per million exposed, compared with a risk of 2000 per million for 20 years employed in a workplace conforming to 0.1 fiber/mL, that is, in compliance with the current permissible exposure limit proposed by OSHA.[93] Malignant mesothelioma has been reported in 16 teachers from different parts of the United States, 12 of whom had no identified exposure outside of school employment, but other population studies have failed to show an increase in the incidence of mesothelioma in relation to the use of asbestos in buildings.[93] Residential environmental exposure has, however, been implicated in mesothelioma production.[88]

Pleural Plaques

Pathology and Pathogenesis

Pleural plaques are distinctive, smooth, white, raised, irregular lesions usually found on the parietal and rarely on the visceral pleura. They may vary from small to extensive ($\leq 50\,cm^2$) and are usually nonadherent. Common sites are the posterolateral mid-zones, where they may follow the rib contour, and on the diaphragm. They are less commonly found on the pleura adjacent to the mediastinum and pericardium and, rarely, in the apices and costophrenic sulci.[97] On microscopic section, pleural plaques consist of avascular, acellular, laminated collagen fibers arranged parallel to the surface or in whorls, with hyaline changes and occasional fibroblasts (Fig. 65-12). Macroscopic calcification is common, and microscopic calcification extremely common, especially in the parietal lesions. The lesions are usually covered by mesothelium. Fine asbestos fibers are seen on electron microscopy.[97] The lungs of patients from the general population who have plaques have been shown to contain a 50- to 250-fold excess of long, thin, mainly amphibole fibers.[2] In asbestos miners and millers in Quebec and in those engaged in the Pacific Northwest trades that involve exposure to asbestos, the lung burden is similar to that seen in association with lung cancer (see earlier).[114] Pleural plaques are thought to develop from the release of fibers into the pleural space by mechanisms open to conjecture.[2] Release or escape probably occurs from subpleural accumulations of usually short, fine fibers that are able to penetrate the deeper lung spaces and are cleared via subpleural lymphatic channels.[2] Within the pleural space, macrophage and cellular interactions may determine fiber localization and plaque formation. In the absence of macrophages, the pleural reaction tends to be disorganized and diffuse.[132] The parietal location may be due to the fact that for fibers, as for macrophages, the only exit from the pleural space is via stomas that communicate directly with the parietal pleural lymphatic channels. Pleural fibrosis and pleural plaques may have the same pathogenesis.[2]

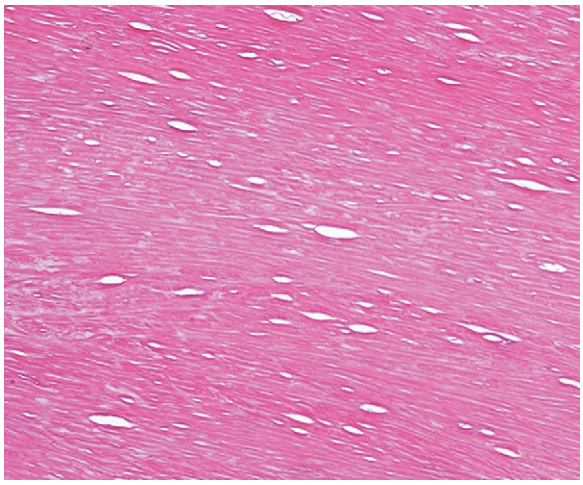

FIGURE 65-12 ■ Asbestos pleural plaque shows parallel acellular collagen fibers.

Clinical Features

Pleural plaques, in the absence of parenchymal disease, often do not cause signs and symptoms and are usually detected as an incidental finding on a routine chest radiograph. Their visualization depends on their thickness and the orientation of the x-ray beam. Only a modest proportion of those seen at autopsy are detected

on posteroanterior chest radiographs; oblique views increase the yield. CT and HRCT scans can identify plaques at an earlier, less well-developed stage and can differentiate plaques from extra pleural fat pads. In the past, pleural plaques have been labeled as "visiting cards" for asbestos exposure, implying that they had no impact on lung function at rest or on effort. In fact, in epidemiologic studies, lung volumes (mainly vital capacity and FVC) are on average modestly but consistently reduced. The DL_{CO} is generally normal and the diffusion constant Kco (DL_{CO}/TLC) may be increased because of the reduction in lung volume.[97,110,118] Increasingly too, it is recognized that in some individuals, pleural plaques may be associated with disability[133]; the underlying mechanism may be inhibition of inspiratory capacity during exercise resulting in an increase in the work of breathing.

Epidemiology

Pleural plaques continue to be the most frequent and often the only manifestation of asbestos exposure,[97,109,134] and asbestos exposure is the most common cause of pleural plaques. For instance, for the period 1996 to 1998, pleural plaques constituted 28% of 4393 incident cases of occupational respiratory disease reported to the Surveillance of Work and Occupational Respiratory Disease (SWORD) study, which has been operating in the United Kingdom since 1989.[134] Bilateral pleural plaques are more likely to be associated with occupational exposure than unilateral plaques, for which other causes should be considered.[85] Age and residence time of dust in the lungs are determinants of these distinctive pleural lesions[97]; smoking is considered to be a determinant by some[1] but not in general.[97] Domestic and residential exposures have been implicated in the production of pleural plaques (see earlier, the discussion of human exposure in the section on "Asbestos Minerals"), with remarkably high rates for pleural calcification (≤30%) being described in some rural communities in the eastern Mediterranean countries of Corsica, Greece, Cyprus, and Turkey.[91] Of greater concern to the patient and the clinician is the prognostic significance of plaques: in one study, they were associated with alveolitis, as reflected in bronchoalveolar cell counts,[132] and by implication, with an increased likelihood of developing parenchymal disease. The results of a Swedish cohort mortality study involving 1596 men were interpreted as showing that pleural plaques on the chest radiograph indicated significant exposure to asbestos, as well as an increased risk of mesothelioma and possibly also for lung cancer.[135] This risk raises the question of screening chest radiographs in those with pleural plaques, a topic that remains controversial in the absence of clear evidence of benefit.[85,135]

Pleural Fibrosis and Visceroparietal Reactions

Pathology

Like pleural plaques, pleural fibrosis and visceroparietal pleural reactions may be localized or diffuse and may vary in thickness from a milky discoloration of the lung surface to a thick, white peel encasing much of one or both lungs. The interlobar fissures are commonly involved.[101] Even severe visceral pleural disease may occur in the presence of minimal parenchymal reaction.[97,98] Occasionally, a localized pleural reaction may fold on itself and the surfaces synthesize, trapping the underlying lung and leading to a well-defined pleuroparenchymal lesion or pseudotumor, also called *rounded atelectasis*[97] (see Fig. 65-11). Asbestos bodies and fibers are usually found in the visceral pleura, the underlying parenchyma, or both,[97] and the lung dust burden usually reflects the occupational exposure but with electron microscopy fiber counts considerably less than those seen in asbestosis.

Epidemiology

Like pleural plaques, pleural fibrosis and visceroparietal reactions may occur in the absence of radiologic parenchymal fibrosis and are increasing in frequency.[97] The exposures implicated (see Table 65-3) are often short, heavy, remote, and related to amphiboles. Latency is usually long (>20 yr), reflected in the fact that these reactions relate to time since first exposure (a proxy for residence time of dust in the lung) and not to cumulative exposure dose.[97,110] In the United States, radiographic pleural abnormality has been reported in approximately 1% of men without known exposure.[97] Pleural fibrosis has been reported in association with environmental exposures from mining operations (see previous discussion under "Sources of Human Exposure") in Finland and South Africa and from nonmining (agricultural) operations in Bulgaria, Czechoslovakia, Poland, Greece, and Turkey. Epidemiologic studies are also consistent in showing that the presence of pleural fibrosis is associated with reduction in lung function, after any associated parenchymal fibrosis has been taken into account.[97,110,118]

Diagnosis

Pleural fibrosis is less specific for asbestos exposure than pleural plaques, and other causes need to be considered in the differential diagnosis. Diagnosis of asbestos-related pleural thickening is usually based initially on the chest radiograph. Clinical presentation, like that of pleural plaques, is often as an incidental abnormality detected on a routine chest radiograph. After careful inquiry, a remote history of exposure, often quite brief but usually heavy, can be obtained from the subject. Rounded atelectasis may present as a radiologic abnormality in an asymptomatic subject, usually with a clear history of exposure. Conversely, some subjects present with breathlessness[97] or chest pain, or both, with or without a history of acute episodes, attributed to benign pleural effusions (see later). Pleural fibrosis restricts the movement of the lungs; in the absence of associated parenchymal disease, clinical signs may be minimal, even though functional impairment is detectable. Impairment may be modest even in the presence of severe pleural disease.[97,110,136] In one study, any pleural abnormality was associated with an

average deficit of 0.22 L and 0.40 L for FEV_1 and FVC, respectively,[133] but pleural fibrosis occasionally becomes severe enough to precipitate respiratory and cardiac failure and to require pleurectomy.[97,137]

The radiologic and CT features of pleural fibrosis are discussed under "Pleural Plaques." Given a history of exposure, obliteration of the costophrenic angle is likely to represent the residuum of asbestos pleural effusion.[97] In rounded atelectasis, the CT scan is particularly useful in delineating the relationship of the rounded lesion to other pleural changes.[116] Nevertheless, the differential diagnosis of rounded atelectasis includes lung cancer, and in some cases, the diagnosis can be established only by surgery.

Benign Asbestos-Related Pleural Effusions

Benign asbestos-related pleural effusions may occur in lungs free of other stigmata of asbestos exposure or may mark an increase in the extent or severity of an already present pleural reaction. The term "benign" does not imply a lack of clinical significance but rather that the effusion is not associated with mesothelioma.[97] Benign asbestos-related pleural effusions usually occur within 15 years of the first exposure and may occur after exposure has ceased.[97] They are more common in persons in their 20s and 30s and may be the most common manifestation of asbestos pleural disease in that age group. The episodes are usually transient and may be silent but may be associated with chest tightness and, occasionally, pleural pain, fever, and dyspnea.[97] A pleural rub may be heard. The effusion is usually small, exudative, and blood-stained[2] and contains leukocytes. Asbestos bodies are rarely found in the fluid, but they may be seen in the underlying parenchyma on biopsy.[138] The sedimentation rate often is raised.[138] Diagnosis is by exclusion, and suggested criteria include (1) an exposure history; (2) the absence of other causes; and (3) absence of tumor on a 3-year follow-up.[96] Because cytologic examination of the pleural fluid is rarely conclusive, a thoracoscopic biopsy is usually required to exclude other causes; to establish the presence of fibers in the pleural fluid (rarely demonstrable), pleura (sometimes demonstrable), or the underlying lung parenchyma (not infrequently demonstrable); and to rule out malignancy, in particular malignant pleural mesothelioma. The usual pathologic findings in benign asbestos-related pleural effusion are those of chronic fibrous pleurisy with minimal cellularity.

The prognosis of benign asbestos-related pleural effusions is generally good; most clear spontaneously, whether it be the first episode or a recurrence. Recurrence may be on the opposite side. Although pleural effusion is a common form of presentation for mesothelioma (see Chapter 75), there is no evidence that a benign effusion signals a future pleural malignancy. It appears rather to represent a stage in the evolution of asbestos-related pleural fibrosis and also carries a risk of developing parenchymal fibrosis (asbestosis).[95] The pathogenesis is unknown.[2] Both mechanical irritation by fibers permeating the pleura and a direct cytotoxic effect on the surface mesothelial layer have been invoked.[97]

Management, Prevention, and Health Monitoring

The principles guiding clinical management of all asbestos-related lung and pleural conditions are no different from those guiding this management when there is no history of asbestos exposure. It is important to make the appropriate notification of a case of asbestos-related disease. Notification, together with any procedure related to compensation, depends on the local jurisdiction. Employment advice should be guided by knowledge of the impact of further exposure on the natural history of the disease processes[97,98,110] and by the risks for developing additional asbestos-related disease. It is important to emphasize that even in the absence of any further exposure, progression of all nonmalignant asbestos-related diseases may occur on the basis of dust load already in the lungs. Once there is definite parenchymal or pleural radiologic abnormality, the prudent option is to avoid all further exposure. Furthermore, continued exposure is likely to be associated with persistent industrial bronchitis, if present, and an increase in the risk of chronic airflow limitation.[73] The possible role of smoking in the initiation and progression of fibrotic parenchymal disease and its established role in multiplying the risk of lung cancer are strong indications for smoking-cessation advice to be given to the individual and for instituting smoking-cessation programs for workers in workplaces contaminated by asbestos dust.

No active treatment measures have been shown to influence the course of asbestosis. Corticosteroids and other anti-inflammatory and cytotoxic agents advocated for other interstitial lung diseases are less effective in asbestosis, possibly because the responsible agent remains in the lungs. Patients with end-stage asbestosis have been the recipients of lung and heart-lung transplants but technical difficulties may arise because of the associated pleural disease.

For the nonmalignant asbestos-related pleural disorders, the evidence is now reasonably clear that those with pleural fibrosis are at greater risk for parenchymal fibrosis in the future.[95] The presence of pleural fibrosis or pleural plaques is associated with increased risk for malignant pleural mesothelioma and lung cancer.[135]

Control and prevention of asbestos-related lung diseases are a public health issue reviewed elsewhere.[1] An international ban on asbestos has been advocated for its control as a public health measure.[139] However, issues associated with an international ban, imposed by the industrialized world, include the lack of inexpensive alternatives for asbestos, especially important in the industrializing world, which currently accounts for much of the asbestos use, and the lack of studies comparable with those conducted on asbestos to examine the safety and effectiveness of substitutes, including man-made fibers.[140] Concern certainly still exists about the potential ill health effects of the man-made substitutes[140,141] even though the most recent data do not suggest that those

exposed occupationally have an increased risk of lung cancer or mesothelioma.[142–144] A document from the American College of Chest Physicians highlights areas in which there is and is not consensus regarding the health effects of asbestos exposure.[138a]

Successful public control requires control of the work environment, setting and enforcing of standards, and preemployment or in-service health examinations for exposed workers as part of a health-monitoring program. Implicit in the latter examination, which has the elements of a screening examination, is the hope that early detection might avoid later damaging disease, a hypothesis still to be tested. Nor is the interpretation of small changes between examinations (in physical signs and in radiologic, lung function, and cytologic examinations) an easy task. Such examinations are best regarded as biologic monitoring (for the purpose of detecting average trends within a workforce) rather than as a method of case identification. Nevertheless, some individuals seek this type of health examination from their personal physician or clinic, and the clinician must make a best judgment on the basis of available information. For the current worker with no evidence of disease, whose exposure has occurred only since the present control levels (0.1 fiber/mL for a 50-yr working life) have been in place, ill-health effects are unlikely to be demonstrable by any practicable method of study, but for those with more than 10 years of exposure, a chest radiograph every 3 to 5 years is recommended.[85] Only a minority of those exposed are likely to develop radiologic changes, and only a minority of those with radiologic changes develop clinical manifestations and any degree of disablement. Furthermore, the additional chance of developing a carcinoma of the lung in the face of frank asbestosis is likely to be considerably lower than the 10% to 30% quoted on the basis of case data from subjects exposed before the 1960s when exposure levels were higher and asbestosis was, as far as can be judged, a more severe disease.[115] Quitting cigarette smoking should benefit the asbestos-exposed individual even more than the nonexposed individual because of the interaction of these two agents.[129,145] The mesothelioma risk, perhaps more disquieting for those with past occupational exposure, may also be expected to decline with time. Although in Europe and Australia, it had been estimated that this would occur only by the second decade of the 21st century,[146,147] a 2003 report from a British naval dockyard indicates that rates had already peaked in 1991 and have since fallen.[148] Similar trends have been observed in Sweden, where the rate in men peaked in 1995 and has subsequently fallen,[149] and in the Netherlands.[150] This improvement is attributed, at least in part, to the introduction of asbestos safety guidelines in the 1970s in the countries concerned.

NONASBESTOS MINERAL SILICATES AND LUNG DISEASE

Exposure to some of the nonasbestos mineral silicates listed in Table 65-3 has been associated with lung disease. Silicate dust particles are found in the lungs of most urban dwellers,[81] and in general, they appear to have low biologic activity.[151] Disease may develop after long, heavy exposure; initially, it is characterized by accumulation of dust-laden macrophages around respiratory bronchioles and, later, by fiber deposits with little mature collagen; the disease appears to progress in relation to lung dust overload.[91,151,152] Silicates are used widely as filling materials (kaolin, talc, and chlorite), as insulation (mica, vermiculite), and as absorbents (attapulgite, sepiolite), among other uses.[151] The clay minerals, talcs and mica (also called phyllosilicates because of their sheet structure),[151] constitute an important group. World production and use (estimated in 1991 as 5.3 million tons for talc alone) considerably exceeds that of the asbestos minerals, which peaked at 5 million tons in the late 1970s. Before a 1989 NATO Workshop, their toxicity as a group for humans had been studied little,[151] although three (talc, attapulgite, and sepiolite) had been evaluated for carcinogenic risk for humans by the IARC.[151] The information in this section is derived from the report of this workshop[151] and other sources.[2,105,153] Talc and, more often, mica particles may form the core of ferruginous bodies. In general, the nonfibrous silicates have pulmonary effects similar to those caused by coal, unless they contain fibrous forms of these minerals or are contaminated by asbestos fibers, in which case their effects are closer to those produced by asbestos. The biologic effects of silica (quartz) may be modulated by the presence of silicates.

Kaolin Pneumoconiosis

The lesions of kaolin pneumoconiosis tend to be cellular and dust packed.[151] In its simple form, this pneumoconiosis is not usually associated with clinical or lung function changes, but rarely. interstitial fibrosis or PMF may occur and be associated with impairment.[2] In 10 surveys of kaolin-exposed workforces, the radiologic prevalence of simple pneumoconiosis (mostly small round opacities) ranged from less than 1% to 26.3%, whereas complicated pneumoconiosis and pleural change were unusual.[153] In general, prevalence was related to level and duration of dust exposure and probably contamination by other materials, including silica. Although lung cancers have been mentioned in relation to kaolin exposure,[154] no cohort mortality studies have been reported.

Talc Pneumoconiosis

The lesions of talc pneumoconiosis include peribronchial and perivascular interstitial accumulations of dust-filled macrophages, ill-defined nodular lesions in which birefringent talc crystals can be seen, and foreign body granulomas.[2,151] In general, the disease evolves slowly, and progressive massive fibrosis occurs infrequently; tuberculosis may complicate the condition but might reflect concomitant silica exposure. Interstitial fibrosis also may occur. A granulomatous arteritis caused by talc embolism is described in drug addicts who use an

intravenous route for talc-containing drug tablets. Pleural changes, including plaques, are common; they are usually associated with mining exposures and may be due to contamination of mine dust by fiber (tremolite or anthophyllite).[2,151] Reactions to talc can be difficult to distinguish from those caused by silica or by asbestos, which often contaminate or even predominate in industrial grade talc.[2] In six surveys of talc-exposed workforces, prevalence of small opacities ranged from less than 1% to 37.2%, the latter in long-time workers and the lower rates in some studies in which exposure was to pure talc.[153,155] In three of seven cohort mortality studies in talc-exposed workers, excess deaths were recorded from nonmalignant respiratory disease, including pneumoconiosis. In addition, an excess of respiratory cancer mortality was found in five of the seven cohorts, but these findings must be interpreted with caution because they were based on only 13 or fewer deaths in each cohort. In four of these, coexposure to other carcinogenic agents (mineral fibers, radon, silica) could have been implicated.[153] Several cases of mesothelioma were reported, but all in cohorts exposed to fiber-contaminated dusts.[153]

Mica Pneumoconiosis

The lesions of mica pneumoconiosis comprise dust particles surrounded by reticulin but usually with relatively little cellular reaction, although there are case reports of interstitial fibrosis[156] in which granulomas also have been described.[153] In three surveys of mica-exposed workforces, the prevalence of radiologic pneumoconiosis ranged from 1% to 44%, the latter workforce being exposed to quartz-contaminated mica.[153] No mortality studies have been reported, but there has been one case report of a peritoneal mesothelioma in a mica-exposed worker.[153] Vermiculite, also a mica, does not appear to be toxic to the lungs of animals. However, in four surveys of vermiculite-exposed mine workers, the prevalence of radiologic pneumoconiosis ranged from less than 1% to 18% and of pleural changes from 3% to 28%; in a processing plant, rates were higher and were related to cumulative exposure.[151,153] Pleural effusions and pleural thickening have been reported in mica-exposed workforces but are thought to relate to amphibole contamination of vermiculite. Vermiculite mined in Libby, Montana, has been found to be contaminated with asbestos and to be associated with asbestosis, mesothelioma, and lung cancer in former miners, millers, and processors. The material has been widely used as insulation in buildings, which has raised concern for those exposed through building maintenance and renovation.[157] A case report of fatal asbestosis occurring 50 years after exposure to vermiculite from Libby in a California expansion plant emphasizes the risk from even brief but intense exposure to this material.[158] The lung biopsy fiber analysis showed 8 million fibers per gram of dry lung, a level certainly compatible with the diagnosis of asbestosis, of which 68% were tremolite. Pleural plaques had been noted on his chest film 10 years before evidence of interstitial lung disease became apparent.

The authors of a 1990 review[153] concluded that (1) there is little evidence that occupational exposure to pure kaolin, talc, mica, or vermiculite carries any important risk for health; (2) long and heavy exposure to kaolin and mica may result in low-grade radiographic changes, but clinically important pneumoconioses in workforces exposed to these phyllosilicates are likely to be the result of contamination by silica or asbestos fiber; (3) pleural lesions are common in talc-exposed workers but are probably caused by fiber contaminants; and (4) the increased rates of lung cancer or mesothelioma recorded in several exposed workforces probably result from exposure to fiber or silica contaminants of the ore or milled products.

Man-made Vitreous Fibers

The production of man-made vitreous fibers (MMVFs; including glass fibers and mineral wool, and refractory ceramic fibers as well as man-made mineral fibers such as carbon graphite, Kevlar-Aramid, silicon carbide, and aluminum oxide) has increased markedly since the restriction or banning of asbestos in several countries. As with asbestos fibers, determinants of MMVF toxicity are (1) their dimensions (greatest risk with fine, long fibers < 0.25 μm in diameter and > 8 μm in length); (2) their biopersistence, which can be altered in the production process according to the end use; and (3) dose to the target organ. MMVFs differ from asbestos fibers in being more soluble, less durable, and less biopersistent along a gradient: glass > rock > ceramic fibers.[159] Fibers are also coarser along a gradient: continuous glass filament > insulation wool > ceramic fibers > special purpose.[159] Airborne levels in plants manufacturing MMVFs are commonly lower than 1 fiber/mL and lower in most applications except the application of insulation in confined spaces.[159] Airborne fiber diameters, with the exception of ceramic fiber, are generally large (1 mm) and thus nonrespirable. Despite their intensely irritating effects on skin and mucous membranes, there is no firm evidence that these fibers produce lung fibrosis, pleural lesions, or nonspecific respiratory disease in humans. Refractory ceramic fibers may, however, enhance the effects of smoking in producing airway disease.[159,160] An increased standardized mortality ratio for lung cancer in several cohorts exposed to MMVFs is now thought to have been attributable to smoking[142,144] Nevertheless, several agencies have recommended exposures of 0.5 to 1 fiber/mL based on apparent excess working lifetime risk for lung cancer.[101] There is no evidence of an increased mesothelioma risk for MMVF workers.[143]

OTHER PNEUMOCONIOSES, OLD AND NEW

The pneumoconioses already discussed account for the majority of cases in most countries of the world. They exemplify a range of pulmonary reactions from minimal reaction to a large lung particulate dust load as in CWP

to a very specific fibrotic reaction to a comparatively small lung dust particulate load as in silicosis. In the case of mineral fibers, the pulmonary reaction appears to be determined by lung fiber load of a particular size range (the long, fine fiber) as well as by fiber durability.

Several long-recognized, well-catalogued but less common pneumoconioses, which fall into the group in which the dust load is heavy but pulmonary reaction minimal, have not yet been mentioned. They include the pneumoconioses resulting from inhalation of iron in welding fumes or in iron or hematite mine dust (siderosis), those that result from the inhalation of barytes by barium miners or workers (baritosis), and those that result from exposure to tin dust (stannosis). Other dusts that fall into this category include bismuth, manganese, Fuller's earth, and titanium. A more comprehensive list can be found elsewhere.[101] At the other end of the scale, lung disorders originally described as unusual or new forms of pneumoconiosis often turn out to be silicosis, which escaped recognition because exposure levels to quartz were higher than originally appreciated or the features of the pulmonary response were modified by the presence of other dusts. Examples include Labrador lung (after exposure of iron miners to ore dust containing silica and some anthophyllite fibers)[20] and disease in bentonite workers that also turned out to be silicosis.[161] The pneumoconiosis of foundry workers is also an example of a response to mixed dust, in which the proportion of quartz is a key determinant to the character of the response. Careful case reports by observant clinicians continue to identify interstitial lung disease associated with various exposures such as those associated with indium-tin oxide recently reported from Japan[162] and provide information to stimulate the epidemiologic studies necessary to place them in proper context.

BERYLLIUM LUNG DISEASE

Beryllium: Uses, Human Toxicity, and Exposures

Beryllium is a rare metal that has many applications in modern industry because of its light weight, tensile strength, high melting point (1500°C), excellent alloying properties (beryllium-copper are the most widely used), good thermal and electrical conductivity, resistance to corrosion, and ability to reduce the speed of nuclear fission.[1] Major sources are Argentina, Brazil, India, Zimbabwe, South Africa, and the United States. Its toxicity for humans was first recognized in Europe in the 1930s. In the United States, an epidemic of chronic beryllium disease (CBD) occurred as a result of exposure in the fluorescent light industry during the 1940s, leading to discontinuation of its use in that industry and the institution of engineering controls in other industries handling beryllium.[1] However, the number of cases continued to increase and, in 1987, reached 904 in a U.S. case registry.[163] Initially, a large number of cases of acute berylliosis, an acute, toxic pneumonitis, were documented but acute cases are now uncommon. Chronic berylliosis, a disease with features similar to those of sarcoidosis, continues to be reported. Cases arise from beryllium exposure in a wide variety of industries including the manufacture of alloys, ceramics, radiographic equipment, and vacuum tubes and in the extraction and smelting of beryllium. The number of individuals potentially exposed in the United States in 1987 was estimated between 30,000 and 800,000 in the following industries: aerospace, electronics, ceramics, metal, including refining of scrap metal, nuclear (reactors, weapons), telecommunications, tool and die, and welding.[163] A survey of 646 workers in a beryllium metal alloy and oxide production plant showed that 9.4% were sensitized to beryllium on the basis of their positive beryllium lymphocyte proliferation test (BeLPT) and 4.6% had evidence of disease.[164] A British registry of deaths from beryllium exposure found that most cases had been exposed as machinists or in the manufacture of fluorescent lamps.[165] Survival rates ranged from 1 to 29 years.[165] Cases of berylliosis have also been reported in residents living near a beryllium manufacturing facility[166] and in a wife who laundered her exposed husband's clothing.[167] Beryllium contamination inside the personal vehicles of workers has also been documented.[168] Sarcoidosis-like granulomatous lung disease in firefighters involved with rescue work at the World Trade Center is of uncertain origin and might suggest berylliosis or another environmental cause for granulomatous lung disease.[169]

Pathology and Immune Pathogenesis

Acute beryllium disease in humans has been attributed to toxic, dose-related lung injury characterized by acute inflammatory reactions in the upper airways, bronchiolitis, pulmonary edema, and chemical pneumonitis. Recovery is usual, but 17% of cases progress to CBD.[163] CBD is a multisystem disorder characterized by noncaseating granulomas that occur throughout the body, although their primary manifestation is in the lung.[2,163] On pathologic examination, CBD is characterized by the presence of a lymphocytic (helper/inducer T cells) alveolitis as well as noncaseating epithelioid granulomas indistinguishable from those of sarcoidosis. There is a variable amount of fibroblastic activity that progresses to interstitial fibrosis as the lesions mature. Granulomatous lesions may occasionally be found in other sites, including thoracic and abdominal lymph nodes, spleen, liver, kidneys, and adrenal glands.

Beryllium enters the body by inhalation and, occasionally, via the skin, where it acts as a specific antigen (alone or as a hapten through an IL-2 receptor pathway), leading to a proliferation of specific CD4 lymphocytes, release of lymphokines, and granuloma formation.[1] Because the agent persists in the lung, its slow release over time explains the appearance and progression of disease, even without further exposure.[1,2] There is evidence for an underlying genetic basis for susceptibility to beryllium disease, linked to a major histocompatibility complex (MHC) class II marker (human leukocyte antigen [HLA]-DPβ-1^{Glu69}) carrier status, which adds to the effect of the process (exposure) risk factor.[170,171]

Evidence for delayed hypersensitivity to beryllium may be assessed by the in vitro BeLPT on lymphocytes from blood or BAL.[172] Although these reactions are thought to indicate exposure and sensitization, not disease, in one series, six of eight sensitized individuals had granulomas on transbronchial biopsy.[173]

Beryllium is now considered to be a human carcinogen, especially in the presence of beryllium lung disease; in 1993, the IARC classified beryllium as a class 1 human carcinogen.[174]

Clinical Features

The clinical features of acute beryllium disease include cough, chest pain, blood-tinged sputum, crackles, and patchy airspace disease on the chest radiograph. The disorder is associated with high, and usually accidental, exposure and may present with an acute syndrome with features of acute respiratory distress syndrome or in a subacute form with features of pneumonitis.[175] High levels of exposure to beryllium may also cause irritation and inflammation of the upper respiratory tract and conjunctivitis.[163] Although resolution generally occurs within a year, historically, the acute form was associated with death in 10% of cases and 17% progressed to chronic berylliosis.[163] CBD may follow an acute beryllium pneumonitis but more usually develops without antecedent events. The clinical features of CBD are similar to those of pulmonary sarcoidosis, although extrapulmonary manifestations including hilar and mediastinal lymphadenopathy and splenomegaly are not as commonly observed.[163,176] There may be no associated symptoms,[172] but symptoms often include dyspnea, cough, chest pain, weight loss, fatigue, and arthralgias. Physical signs may include crackles, but signs of lung disease are often absent. Radiographic changes may precede the development of symptoms. The usual finding is ill-defined nodular or irregular opacities; hilar adenopathy is seen in approximately 40% of cases but is usually mild.[163] In the later stages of the disease, patchy fibrosis occurs with adjacent hyperinflation or distortion and extensive honeycombing. In CBD, pulmonary function usually shows a restrictive defect in advanced disease, but features including obstruction or isolated reduction in $D_{L_{CO}}$ may occur with mild or moderate disease.[177] The clinical course of CBD is variable. Some cases remain stable, some relapse and remit, and some progress inexorably.[163]

Diagnosis and Management

The diagnosis of CBD is based on documented exposure to beryllium, evidence of lung disease compatible with the diagnosis, and a positive BeLPT performed on blood or BAL fluid.[178] The BeLPT allowed for the introduction of three categories of beryllium-associated disorders: beryllium sensitization (positive blood or BAL BeLPT but negative biopsy), subclinical beryllium disease (positive BeLPT and biopsy but no clinical or radiologic features of the disease), and chronic berylliosis (positive BeLPT and biopsy with clinical and radiologic features of disease).[178]

Given the potentially long latency time for CBD and despite the generally lower exposures that have occurred since the 1950s and its decreasing frequency, CBD still should remain in the differential diagnosis of sarcoidosis. Clusters of sarcoidosis occurring in a workplace should alert the clinician to the possibility that these represent examples of chronic berylliosis. In this context, note should be made of the very wide range of occupations associated with potential exposure to beryllium

The most important step in case management is complete cessation of further exposure to beryllium, and this advice should also be given to exposed workers with a positive BeLPT, even in the absence of clinical and radiologic signs of disease, because of the high prevalence of lung granulomata associated with that finding.[173] Corticosteroid therapy has been recommended in CBD, and long-term steroid therapy is believed to alter the course of the disease favorably, although there are no reports of permanent cure.

HARD-METAL DISEASE

Hard-metal disease, first described in Germany in the 1940s, has now been reported from many countries. Hard metal is manufactured by a sintering process that involves pressurization plus heating to 1500°C a mixture of tungsten carbide powder (often with tantalum carbide or titanium carbide added) and 10% cobalt.[1] Because of their diamond-like hardness, extreme strength, and heat resistance, "hard-metal" products have wide application in industry as drill tips (from dental to engineering drilling and diamond polishing), cutting and tunneling tools, grinding wheels, molds, jet engines, and ferromagnets. Human exposure occurs in the manufacturing of hard-metal products and in their maintenance and use. The grinding of sintered pieces generates high dust and cobalt concentrations.

Work-related illness in hard-metal workers may be acute (rhinitis and asthma), subacute (fibrosing alveolitis), or chronic (diffuse and progressive interstitial fibrosis).[179] The interstitial fibrosis is characterized by unusual multinucleated giant cells comprising alveolar type II cells and macrophages that can be recovered from BAL. The interstitial lung disease which has been described with exposure to both tungsten carbide products and in diamond polishers[180] is thought to be a hypersensitivity pneumonitis to cobalt, which reacts with metallic carbides to produce active oxygen species.[181] A genetic association with some HLA-DP alleles may also be implicated.[182] This affords a plausible explanation of why only a small proportion of those exposed develop disease. A 1998 industry-wide cohort study in 10 facilities in France documented an increased mortality from lung cancer associated with simultaneous exposure to cobalt and tungsten carbide.[183] A review of workplace surveys indicates that interstitial disease is quite rare, whereas airway diseases including bronchitis and asthma are more frequent.[179,184] Both interstitial and airway disease may of course occur in the same individual. Diagnosis is based on an exposure history, a compatible clinical

presentation, and pathologic and mineralogic features on biopsy.[179,185] Both tungsten carbide and cobalt have now been identified in the centrilobular fibrotic lesions associated with hard-metal lung disease.[186] Prompt diagnosis and removal from exposure may reverse acute disease, including asthma, and prevent the development of chronic disease. There have been several reports of response to withdrawal from exposure and treatment with corticosteroid.[2] Prevention requires control of exposure; for monitoring workforce exposure, urinary cobalt may be useful.

SILICON CARBIDE (CARBORUNDUM) PNEUMOCONIOSIS

Carborundum pneumoconiosis is associated with exposure in the manufacture of carborundum, which is used as an abrasive because of its hardness. Under current exposure levels, this is generally a mild and nonprogressive disorder.[187] There is, however, some evidence that those exposed to this material, which has a silica and a fibrous component, are at risk for pneumoconiosis associated with lung dysfunction[188,189] and, possibly, for lung cancer.[190]

FLOCK WORKER'S LUNG

A specific interstitial lung disorder characterized by lymphocytic bronchiolitis and peribronchiolitis with lymphoid hyperplasia[191] has been described in workers involved with the manufacture of nylon flock.[192–194] The disorder appeared to be related to a specific form of cutting machine, but recent reports have shown restrictive lung disease in workers manufacturing rayon flock–coated cards[195] and workers exposed to polypropylene flock.[196]

KEY POINTS

General

- Chest radiography and occupational history are the mainstays for the diagnosis of pneumoconiosis, although CT and lung biopsy may be necessary, especially for asbestosis.
- Because of the many interactions between smoking and dust, it is important to implement smoking-cessation programs in the workplace.
- The treatment for most pneumoconiosis is removal from the workplace. Despite this, disease may progress and regression is not expected.

Silica

- Silicosis occurs in a wide range of new and older but less classical industries such as concrete rehabilitation, stone carving, and the sandblasting of denim jeans.
- Silica dust is a risk factor for tuberculosis and other mycobacterial lung diseases, lung cancer, COPD, and connective tissue diseases.
- Chronic silicosis may not be associated with respiratory symptoms even in the presence of extensive radiologic changes.
- Silicosis and HIV infection multiplicatively increase the risk of tuberculosis.

Coal

- Exposure to coal dust is not associated with an increased risk of tuberculosis or cancer of the respiratory system.
- Workers exposed to coal dust are at risk for developing COPD and chronic bronchitis.

Asbestos

- Asbestos-related diseases will occur for many decades because of the long latent period between exposure and disease and because asbestos is still widely encountered.
- Asbestos causes both benign and malignant disease.
- Pleural plaques, the most common manifestation of exposure, are generally an asymptomatic incidental radiologic finding but may be associated with an increased risk of malignant mesothelioma and lung cancer.
- Asbestos exposure is not a risk factor for the development of tuberculosis.

References

1. International Labour Office: Encyclopedia of Occupational Health and Safety (4th ed). Geneva: International Labour Office, 1998.
2. Churg A, Green FHY(eds): Pathology of Occupational Lung Disease (2nd ed). Baltimore: Williams & Wilkins, 1998.
3. Honma K, Abraham JL, Chiyotani K, et al: Proposed criteria for mixed-dust pneumoconiosis: Definition, descriptions, and guidelines for pathologic diagnosis and clinical correlation. Hum Pathol 35:1515–1523, 2004.
4. National Institute for Occupational Safety and Health: Occupational Exposure to Respirable Coal Mine Dust. Cincinnati, OH: U.S. Department of Health and Human Services, Public Health Services, Centers for Disease Control and Prevention, NIOSH, 1995.
5. International Labour Office: Guidelines for the Use of the ILO International Classification of Radiographs of Pneumoconioses (ed 2000). Geneva: ILO, 2003.
6. Becklake MR, White N: Sources of variation in spirometric measurements. Identifying the signal and dealing with noise. Occup Med 8:241–264, 1993.
7. American Thoracic Society: Adverse effects of crystalline silica exposure. Am J Respir Crit Care Med 155:761–768, 1997.
8. Becklake MR: Occupational pollution. Chest 96:372S–378S, 1989.
9. Corbett EL, Churchyard GJ, Clayton TC, et al: HIV infection and silicosis: The impact of two potent risk factors on the incidence of mycobacterial disease in South African miners. AIDS 14:2759–2768, 2000.
10. Carneiro AP, Barreto SM, Siqueira AL, et al: Continued exposure to silica after diagnosis of silicosis in Brazilian gold miners. Am J Ind Med 49:811–818, 2006.
11. National Institute for Occupational Safety and Health: NIOSH Hazard Review: Health Effects of Occupational Exposure to Respirable Crystalline Silica. Cincinnatti, OH: NIOSH, 2002.
12. Ziskind M, Jones RN, Weill H: Silicosis. Am Rev Respir Dis 113:643–665, 1976.
13. Rosenman KD, Reilly MJ, Kalinowski DJ, et al: Silicosis in the 1990s. Chest 111:779–786, 1997.
14. Valiante DJ, Rosenman KD: Does silicosis still occur? JAMA 262:3003–3007, 1989.
15. Akbar-Khanzadeh F, Milz S, Ames A, et al: Crystalline silica dust and respirable particulate matter during indoor concrete grinding—Wet grinding and ventilated grinding compared with uncontrolled conventional grinding. J Occup Environ Hyg 4:770–779, 2007.
16. Linch KD: Respirable concrete dust—Silicosis hazard in the construction industry. Appl Occup Environ Hyg 17:209–221, 2002.
17. Akgun M, Mirici A, Ucar EY, et al: Silicosis in Turkish denim sandblasters. Occup Med (Lond) 56:554–558, 2006.
18. Antao VC, Pinheiro GA, Kavakama J, et al: High prevalence of silicosis among stone carvers in Brazil. Am J Ind Med 45:194–201, 2004.
19. Murgia N, Muzi G, Dell'Omo M, et al: An old threat in a new setting: High prevalence of silicosis among jewelry workers. Am J Ind Med 50:577–583, 2007.
20. Edstrom HW, Rice DM: "Labrador lung": An unusual mixed dust pneumoconiosis. CMAJ 126:27–30, 1982.
21. Wagner JC, Pooley FD, Gibbs A, et al: Inhalation of china stone and china clay dusts: Relationship between the mineralogy of dust retained in the lungs and pathological changes. Thorax 41:190–196, 1986.
22. National Institute for Occupational Safety and Health: The Work-Related Lung Disease Surveillance Report, 2002. Cincinnatti, OH: NIOSH, 2003.
23. Finkelstein MM: Silicosis surveillance in Ontario from 1979 to 1992. Scand J Work Environ Health 21:55–57, 1995.
24. Cavariani F, Di Pietro A, Miceli M, et al: Incidence of silicosis among ceramic workers in central Italy. Scand J Work Environ Health 21:58–62, 1995/
25. Murray J, Kielkowski D, Reid P: Occupational disease trends in black South African gold miners. An autopsy-based study. Am J Respir Crit Care Med 153:706–710, 1996.
26. Centers for Disease Control and Prevention: Silicosis-related years of potential life lost (YPLL) before age 65 years, USA, 1968–2005. MMWRMorb Mortal Wkly Rep 57:771–775, 2008.
27. Norboo T, Angchuk PT, Yahya M, et al: Silicosis in a Himalayan village population: Role of environmental dust. Thorax 46:341–343, 1991.
28. Searl A, Nicholl A, Baxter PJ: Assessment of the exposure of islanders to ash from the Soufriere Hills volcano, Montserrat, British West Indies. Occup Environ Med 59:523–531, 2002.
29. Archer JD, Cooper GS, Reist PC, et al: Exposure to respirable crystalline silica in eastern North Carolina farm workers. AIHA J 63:750–755, 2002.

29a. Schenker MB, Pinkerton KE, Mitchell D, et al: Pneumoconiosis from agricultural dust exposure among young California farmworkers. Environ Health Perspect 117:988–994, 2009.

30. Murray J, Webster I, Reid G, et al: The relation between fibrosis of hilar lymph glands and the development of parenchymal silicosis. Br J Ind Med 48:267–269, 1991.
31. Churg A, Wright JL, Wiggs B, et al: Small airways disease and mineral dust exposure. Prevalence, structure, and function. Am Rev Respir Dis 131:139–143, 1985.
32. Baumgartner KB, Samet JM, Coultas DB, et al: Occupational and environmental risk factors for idiopathic pulmonary fibrosis: A multicenter case-control study. Collaborating Centers. Am J Epidemiol 152:307–315, 2000.
33. Mossman BT, Churg A:. Mechanisms in the pathogenesis of asbestosis and silicosis. Am J Respir Crit Care Med 157:1666–1680, 1998
34. Vanhee D, Gosset P, Boitelle A, et al: Cytokines and cytokine network in silicosis and coal workers' pneumoconiosis. Eur Respir J 8:834–842, 1995.
35. Williams AO, Knapton AD, Saffiotti U: Growth factors and gene expression in silica-induced fibrogenesis and carcinogenesis. Appl Occup Environ Hyg 10:1089–1098, 1995.
36. Huaux F: New developments in the understanding of immunology in silicosis. Curr Opin Allergy Clin Immunol 7:168–173, 2007.
37. Corbett EL, Mozzato-Chamay N, Butterworth AE, et al: Polymorphisms in the tumor necrosis factor-alpha gene promoter may predispose to severe silicosis in black South African miners. Am J Respir Crit Care Med 165:690–693, 2002.
38. Yucesoy B, Luster MI: Genetic susceptibility in pneumoconiosis. Toxicol Lett 168:249–254, 2007.
39. Mazurek JM, Attfield MD: Silicosis mortality among young adults in the United States, 1968–2004. Am J Ind Med 51:568–578, 2008.
40. Tse LA, Yu IT, Leung CC, et al: Mortality from non-malignant respiratory diseases among people with silicosis in Hong Kong: exposure-response analyses for exposure to silica dust. Occup Environ Med 64:87–92, 2007.
41. Ng TP, Chan SL, Lam KP: Radiological progression and lung function in silicosis: A ten-year follow-up study. BMJ 295:164–168, 1987.
42. Trapido AS, Mqoqi NP, Williams BG, et al: Prevalence of occupational lung disease in a random sample of former mineworkers, Libode District, Eastern Cape Province, South Africa. Am J Ind Med 34:305–313, 1998.
43. Buchanan D, Miller BG, Soutar CA: Quantitative relations between exposure to respirable quartz and risk of silicosis. Occup Environ Med 60:159–164, 2003.
44. Cowie RL: The epidemiology of tuberculosis in gold miners with silicosis. Am J Respir Crit Care Med 150:1460–1462, 1994.
45. Sherson D, Lander F: Morbidity of pulmonary tuberculosis among silicotic and nonsilicotic foundry workers in Denmark. J Occup Med 32:110–113, 1990.
46. Churchyard GJ, Kleinschmidt I, Corbett EL, et al: Mycobacterial disease in South African gold miners in the era of HIV infection. Int J Tuberc Lung Dis 3:791–798, 1999.
47. Sonnenberg P, Murray J, Glynn JR, et al: Risk factors for pulmonary disease due to culture-positive *M. tuberculosis* or nontuberculous mycobacteria in South African gold miners. Eur Respir J 15:291–296, 2000.
48. Cowie RL, Mabena SK: Silicosis, chronic airflow limitation, and chronic bronchitis in South African gold miners. Am Rev Respir Dis 143:80–84, 1991.

49. Hnizdo E, Vallyathan V: Chronic obstructive pulmonary disease due to occupational exposure to silica dust: A review of epidemiological and pathological evidence. Occup Environ Med 60:237–243, 2003.
50. American Thoracic Society: Occupational contribution to the burden of airway disease. Am J Respir Crit Care Med 167:787–797, 2003.
51. Green DA, McAlpine G, Semple S, et al: Mineral dust exposure in young Indian adults: An effect on lung growth? Occup Environ Med 65:306–310, 2008.
52. Calvert GM, Rice FL, Boiano JM, et al: Occupational silica exposure and risk of various diseases: An analysis using death certificates from 27 states of the United States. Occup Environ Med 60:122–129, 2003.
53. Bartunkova J, Pelclova D, Fenclova Z, et al: Exposure to silica and risk of ANCA-associated vasculitis. Am J Ind Med 49:569–576, 2006.
54. International Agency for Research in Cancer (IARC): Silica, Some Silicates, Coal Dust and Para-aramid Fibrils. Scientific Publication No. 68. Lyon, France: IARC, 1996.
55. McDonald AD, McDonald JC, Rando RJ, et al: Cohort mortality study of North American industrial sand workers. I. Mortality from lung cancer, silicosis and other causes. Ann Occup Hyg 45:193–199, 2001.
56. Wong O: The epidemiology of silica, silicosis and lung cancer: Some recent findings and future challenges. Ann Epidemiol 12:285–287, 2002.
57. Pelucchi C, Pira E, Piolatto G, et al: Occupational silica exposure and lung cancer risk: A review of epidemiological studies 1996–2005. Ann Oncol 17:1039–1050, 2006.
58. Fraser RS, Colman N, Muller NL, et al (eds): Fraser and Pare's Diagnosis of Diseases of the Chest (4th ed). Philadelphia: WB Saunders, 1999.
59. Verma DK, Ritchie AC, Muir D: Dust content of lungs and its relationships to pathology, radiology and occupational exposure in Ontario hardrock miners. Am J Ind Med 51:524–531, 2008.
60. Hnizdo E, Murray J, Sluis-Cremer GK, et al: Correlation between radiological and pathological diagnosis of silicosis: An autopsy population–based study. Am J Ind Med 24:427–445, 1993.
61. Begin R, Ostiguy G, Fillion R, et al: Computed tomography scan in the early detection of silicosis. Am Rev Respir Dis 144:697–705, 1991.
62. Marchiori E, Ferreira A, Muller NL: Silicoproteinosis: High-resolution CT and histologic findings. J Thorac Imaging 16:127–129, 2001.
63. Cowie RL, Hay M, Thomas RG: Association of silicosis, lung dysfunction, and emphysema in gold miners. Thorax 48:746–749, 1993.
64. Leung CC, Yam WC, Yew WW, et al: Comparison of T-Spot.TB and tuberculin skin test among silicotic patients. Eur Respir J 31:266–272, 2008.
65. Leung CC, Yew WW, Law WS, et al: Smoking and tuberculosis among silicotic patients. Eur Respir J 29:745–750, 2007.
66. Silicosis deaths among young adults—United States, 1968–1994. MMWR Morb Mortal Wkly Rep 47:331–335, 1998.
67. Becklake MR: Chronic airflow limitation:Its relationship to work in dusty occupations. Chest 88:608–617, 1985.
68. Coggon D, Newman Taylor A: Coal mining and chronic obstructive pulmonary disease: A review of the evidence. Thorax 53:398–407, 1998.
68a. Kuempel ED, Wheeler MW, Smith RJ, et al: Contributions of dust exposure and cigarette smoking to emphysema severity in coal miners in the United States. Am J Respir Crit Care Med 180:257–264, 2009.
69. Attfield MD, Kuempel ED: Mortality among U.S. underground coal miners: A 23-year follow-up. Am J Ind Med 51:231–245, 2008.
70. Changing patterns of pneumoconiosis mortality—United States, 1968–2000. MMWR Morb Mortal Wkly Rep 53:627–632, 2004.
70a. Antao VC, Pinheiro GA, Wassell JT: Asbestosis mortality in the USA: facts and predictions. Occup Environ Med 66:335–338, 2009.
71. Antao VC, Petsonk EL, Sokolow LZ, et al: Rapidly progressive coal workers' pneumoconiosis in the United States: Geographic clustering and other factors. Occup Environ Med 62:670–674, 2005.
72. Hurley JF, Alexander WP, Hazledine DJ, et al: Exposure to respirable coalmine dust and incidence of progressive massive fibrosis. Br J Ind Med 44:661–672, 1987.
72a. Laney AS, Petsonk EL, Attfield MD: Pneumoconiosis among underground bituminous coal miners in the United States: is silicosis becoming more frequent? Occup Environ Med 2009, Epub ahead of print.
73. Becklake MR: Occupational exposures: Evidence for a causal association with chronic obstructive pulmonary disease. Am Rev Respir Dis 140:S85–S91, 1989
74. Rudd R: Coal miners' respiratory disease litigation. Thorax 53:337–340, 1998.
75. Hodgins P, Henneberger PK, Wang ML, et al: Bronchial responsiveness and five-year FEV_1 decline: A study in miners and nonminers. Am J Respir Crit Care Med 157:1390–1396, 1998.
76. Isidro Montes I, Rego Fernandez G, Reguero J, et al: Respiratory disease in a cohort of 2,579 coal miners followed up over a 20-year period. Chest 126:622–629, 2004.
77. Swaen GM, Meijers JM, Slangen JJ: Risk of gastric cancer in pneumoconiotic coal miners and the effect of respiratory impairment. Occup Environ Med 52:606–610, 1995.
78. Vallyathan V, Brower PS, Green FH, et al: Radiographic and pathologic correlation of coal workers' pneumoconiosis. Am J Respir Crit Care Med 154:741–748, 1996.
79. Carta P, Aru G, Barbieri MT, et al: Dust exposure, respiratory symptoms, and longitudinal decline of lung function in young coal miners. Occup Environ Med 53:312–319, 1996.
80. Collins HP, Dick JA, Bennett JG, et al: Irregularly shaped small shadows on chest radiographs, dust exposure, and lung function in coalworkers' pneumoconiosis. Br J Ind Med 45:43–55, 1988.
81. Becklake MR: Asbestos-related diseases of the lung and other organs: Their epidemiology and implications for clinical practice. Am Rev Respir Dis 114:187–227, 1976.
82. Walton WH: Airborne Dusts. *In* Liddell D, Miller K (eds): Mineral Fibers and Health. Boca Raton, FL: CRC, 1991, pp 55–78.
83. Kazan-Allen L: Asbestos and mesothelioma: Worldwide trends. Lung Cancer 49(Suppl 1):S3–S8, 2005.
84. Selikoff I, Lee DHK (eds): Asbestos and Disease. New York: Academic, 1978.
85. American Thoracic Society: Diagnosis and initial management of nonmalignant diseases related to asbestos. Am J Respir Crit Care Med 170:691–715, 2004.
86. Roggli VL, Vollmer RT: Twenty-five years of fiber analysis: What have we learned? Hum Pathol 39:307–315, 2008.
87. McDonald JC, McDonald AD: Epidemiology of mesothelioma. *In* Liddell D, Miller K (eds): Mineral Fibers and Health. Boca Raton, FL: CRC, 1991.
88. Camus M, Siemiatycki J, Meek B: Nonoccupational exposure to chrysotile asbestos and the risk of lung cancer. N Engl J Med 338:1565–1571, 1998.
89. Wagner JC, Sleggs CA, Marchand P: Diffuse pleural mesothelioma and asbestos exposure in the North Western Cape Province. Br J Ind Med 17:260–271, 1960.
90. Kielkowski D, Nelson G, Rees D: Risk of mesothelioma from exposure to crocidolite asbestos: A 1995 update of a South African mortality study. Occup Environ Med 57:563–567, 2000.
91. Bignon J, Peto J, Souracci R, et al: Non-occupational Exposure to Mineral Fibers, Scientific Publication No. 90. Lyon, France: International Agency for Research in Cancer, 1989.
92. Luo S, Liu X, Mu S, et al: Asbestos related diseases from environmental exposure to crocidolite in Da-yao, China. I. Review of exposure and epidemiological data. Occup Environ Med 60:35–41, 2003.
93. Health Effects Institute: Asbestos Research: Asbestos in Public and Commercial Buildings. Cambridge, MA: Health Effects Institute, Asbestos Research, 1991.
94. Copes R, Thomas D, Becklake MR: Temporal patterns of exposure and nonmalignant pulmonary abnormality in Quebec chrysotile workers. Arch Environ Health 40:80–87, 1985.
95. Becklake M: Asbestosis. *In* Liddell D, Miller K (eds): Mineral Fibers and Health. Boca Raton, FL: CRC, 1991, pp 103–119.

96. Begin R, Samet JM, Shaikh RA: Asbestos. *In* Harber P, Schenker MB, Balmes JR (eds): Occupational and Environmental Respiratory Disease. St. Louis: Mosby, 1995, pp 293–329.
97. Ernst P, Zejda J: Pleural and airway disease associated with mineral fibers. *In* Liddell D, Miller K (eds): Mineral Fibers and Health. Boca Raton, FL: CRC, 1991, pp 121–134
98. Craighead JE, Abraham JL, Churg A, et al: The pathology of asbestos-associated diseases of the lungs and pleural cavities: Diagnostic criteria and proposed grading schema. Arch Pathol Lab Med 106:544–596, 1982.
99. Case BW, Sebastien P: Environmental and occupational exposures to chrysotile asbestos: A comparative microanalytic study. Arch Environ Health 42:185–191, 1987.
100. Dumortier P, Coplu L, de Maertelaer V, et al: Assessment of environmental asbestos exposure in Turkey by bronchoalveolar lavage. Am J Respir Crit Care Med 158:1815–1824, 1998.
101. Hendrick DJ, Burge PS, Beckett WS, et al (eds): Occupational Disorders of the Lung. London: WB Saunders, 2002.
102. Becklake MR: Occupational lung disease—Past record and future trend using the asbestos case as an example. Clin Invest Med 6:305–317, 1983.
103. Wright JL, Cagle P, Churg A, et al: Diseases of the small airways. Am Rev Respir Dis 146:240–262, 1992.
104. Green FH, Harley R, Vallyathan V, et al: Exposure and mineralogical correlates of pulmonary fibrosis in chrysotile asbestos workers. Occup Environ Med 54:549–559, 1997.
105. Harber P, Schenker MB, Balmes JR (eds): Occupational and Environmental Respiratory Disease. St. Louis: Mosby, 1995.
106. Becklake MR: The mineral dust diseases. Tuberc Lung Dis 73:13–20, 1992.
107. Smith DR, Leggat PA: 24 years of pneumoconiosis mortality surveillance in Australia. J Occup Health 48:309–313, 2006.
108. Meredith SK, Taylor VM, McDonald JC:. Occupational respiratory disease in the United Kingdom 1989: A report to the British Thoracic Society and the Society of Occupational Medicine by the SWORD project group. Br J Ind Med 48:292–298, 1991.
109. Provencher S, Labreche FP, De Guire L: Physician-based surveillance system for occupational respiratory diseases: The experience of PROPULSE, Quebec, Canada. Occup Environ Med 54:272–276, 1997.
110. Becklake MR: Asbestos and other fiber-related diseases of the lungs and pleura. Distribution and determinants in exposed populations. Chest 100:248–254, 1991/
111. Becklake MR, Liddell FD, Manfreda J, et al: Radiological changes after withdrawal from asbestos exposure. Br J Ind Med 36:23–28, 1979.
112. Horska A, Kazimirova A, Barancokova M, et al: Genetic predisposition and health effect of occupational exposure to asbestos. Neuro Endocrinol Lett 27(Suppl 2):100–103, 2006.
113. Franko A, Dolzan V, Arneric N, et al: The influence of genetic polymorphisms of GSTP1 on the development of asbestosis. J Occup Environ Med 50:7–12, 2008.
114. Becklake MR, Case BW: Fiber burden and asbestos-related lung disease: Determinants of dose-response relationships. Am J Respir Crit Care Med 150:1488–1492, 1994.
115. Huuskonen MS: Clinical features, mortality and survival of patients with asbestosis. Scand J Work Environ Health 4:265–274, 1978.
116. Gamsu G, Aberle DR, Lynch D: Computed tomography in the diagnosis of asbestos-related thoracic disease. J Thorac Imaging 4:61–67, 1989.
117. Muller NL, Miller RR: Computed tomography of chronic diffuse infiltrative lung disease. Part 2. Am Rev Respir Dis 142:1440–1448, 1990.
118. Miller A, Lilis R, Godbold J, et al: Relationship of pulmonary function to radiographic interstitial fibrosis in 2,611 long-term asbestos insulators. An assessment of the International Labour Office profusion score. Am Rev Respir Dis 145:263–270, 1992.
119. De Vuyst P, Dumortier P, Moulin E, et al: Diagnostic value of asbestos bodies in bronchoalveolar lavage fluid. Am Rev Respir Dis 136:1219–1224, 1987.
120. Hughes JM: Epidemiology of lung cancer in relation to asbestos exposure. *In* Liddell D, Miller K (eds): Mineral Fibers and Health. Boca Raton, FL: CRC, 1991, pp 136–145.
121. International Agency for Research in Cancer (IARC): Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man. Asbestos. Lyon, France: IARC, 1977.
122. Gloyne SR: Pneumoconiosis; a histological survey of necropsy material in 1205 cases. Lancet 1:810–814, 1951.
123. Becklake MR: Asbestos-related diseases of the lungs and pleura: Current clinical issues. Am Rev Respir Dis 126:187–194, 1982.
124. Finkelstein MM: Radiographic asbestosis is not a prerequisite for asbestos-associated lung cancer in Ontario asbestos-cement workers. Am J Ind Med 32:341–348, 1997.
125. Nelson HH, Christiani DC, Wiencke JK, et al: k-ras mutation and occupational asbestos exposure in lung adenocarcinoma: Asbestos-related cancer without asbestosis. Cancer Res 59:4570–4573, 1999.
126. Egilman D, Reinert A: Lung cancer and asbestos exposure: Asbestosis is not necessary. Am J Ind Med 30:398–406, 1996.
127. Liddell FD, Armstrong BG: The combination of effects on lung cancer of cigarette smoking and exposure in Quebec chrysotile miners and millers. Ann Occup Hyg 46:5–13, 2002.
128. International Agency for Research in Cancer (IARC): Mechanisms of Fiber Carcinogenesis. Scientific Publication No. 140. Lyon, France: IARC, 1996.
129. Erren TC, Jacobsen M, Piekarski C: Synergy between asbestos and smoking on lung cancer risks. Epidemiology 10:405–411, 1999.
130. McDonald JC, McDonald AD: Chrysotile, tremolite and carcinogenicity. Ann Occup Hyg 41:699–705, 1997.
131. Kayser K, Becker C, Seeberg N, et al: Quantitation of asbestos and asbestos-like fibers in human lung tissue by hot and wet ashing, and the significance of their presence for survival of lung carcinoma and mesothelioma patients. Lung Cancer 24:89–98, 1999
132. Constantopoulos SH, Dalavanga YA, Sakellariou K, et al: Lymphocytic alveolitis and pleural calcifications in nonoccupational asbestos exposure. Protection against neoplasia? Am Rev Respir Dis 146:1565–1570, 1992.
133. Bourbeau J, Ernst P, Chrome J, et al: The relationship between respiratory impairment and asbestos-related pleural abnormality in an active work force. Am Rev Respir Dis 142:837–842, 1990.
134. Meyer JD, Holt DL, Chen Y, et al: SWORD '99: Surveillance of work-related and occupational respiratory disease in the UK. Occup Med (Lond) 51:204–208, 2001.
135. Hillerdal G: Pleural plaques and risk for bronchial carcinoma and mesothelioma. A prospective study. Chest 105:144–150, 1994.
136. Kilburn KH, Warshaw R: Pulmonary functional impairment associated with pleural asbestos disease. Circumscribed and diffuse thickening. Chest 98:965–972, 1990.
137. Miller A, Teirstein AS, Selikoff IJ: Ventilatory failure due to asbestos pleurisy. Am J Med 75:911–919, 1983.
138. Hillerdal G, Ozesmi M: Benign asbestos pleural effusion: 73 exudates in 60 patients. Eur J Respir Dis 71:113–121, 1987/
138a. Banks DE, Shi R, McLarty J, et al: American College of Chest Physicians consensus statement on the respiratory health effects of asbestos. Results of a Delphi study. Chest 135:1619–1627, 2009.
139. LaDou J, Landrigan P, Bailar JC 3rd, et al: A call for an international ban on asbestos. Public Health Rev 29:241–246, 2001.
140. Siemiatycki J: Should Canadian health care professionals support the call for a worldwide ban on asbestos? CMAJ 164:495–497, 2001.
141. Camus M: A ban on asbestos must be based on a comparative risk assessment. CMAJ 164:491–494, 2001.
142. Marsh GM, Buchanich JM, Youk AO: Historical cohort study of US man-made vitreous fiber production workers: VI. Respiratory system cancer standardized mortality ratios adjusted for the confounding effect of cigarette smoking. J Occup Environ Med 43:803–808, 2001.
143. Marsh GM, Gula MJ, Youk AO, et al: Historical cohort study of US man-made vitreous fiber production workers: II. Mortality from mesothelioma. J Occup Environ Med 43:757–766, 2001.
144. Boffetta P, Andersen A, Hansen J, et al: Cancer incidence among European man-made vitreous fiber production workers. Scand J Work Environ Health 25:222–226, 1999.
145. Walker AM: Declining relative risks for lung cancer after cessation of asbestos exposure. J Occup Med 26:422–426, 1984.

146. Peto J, Decarli A, La Vecchia C, et al: The European mesothelioma epidemic. Br J Cancer 79:666–672, 1999.
147. Leigh J, Driscoll T: Malignant mesothelioma in Australia, 1945–2002. Int J Occup Environ Health 9:206–217, 2003.
148. Hilliard AK, Lovett JK, McGavin CR: The rise and fall in incidence of malignant mesothelioma from a British Naval Dockyard, 1979–1999. Occup Med (Lond) 53:209–212, 2003.
149. Hemminki K, Li X: Mesothelioma incidence seems to have leveled off in Sweden. Int J Cancer 103:145–146, 2003.
150. Segura O, Burdorf A, Looman C: Update of predictions of mortality from pleural mesothelioma in the Netherlands. Occup Environ Med 60:50–55, 2003.
151. Bignon J (ed): Health-Related Effects of Phyllosilicates. Berlin: Springer-Verlag, 1990.
152. Liddell D, Miller K (eds): Mineral Fibers and Health: Boca Raton, FL: CRC, 1991.
153. Cullinan P, McDonald JC: Respiratory disease from occupational exposure to nonfibrous mineral silicates. *In* Bignon J (ed): The Health-Related Effects of Phyllosilicates. Berlin: Springer-Verlag, 1990, pp 161–178.
154. Szadkowska-Stanczyk I, Szymczak W: Nested case-control study of lung cancer among pulp and paper workers in relation to exposure to dusts. Am J Ind Med 39:547–556, 2001.
155. Wegman DH, Peters JM, Boundy MG, et al: Evaluation of respiratory effects in miners and millers exposed to talc free of asbestos and silica. Br J Ind Med 39:233–238, 1982.
156. Landas SK, Schwartz DA: Mica-associated pulmonary interstitial fibrosis. Am Rev Respir Dis 144:718–721, 1991.
157. Sullivan PA: Vermiculite, respiratory disease, and asbestos exposure in Libby, Montana: Update of a cohort mortality study. Environ Health Perspect 115:579–585, 2007.
158. Wright RS, Abraham JL, Harber P, et al: Fatal asbestosis 50 years after brief high intensity exposure in a vermiculite expansion plant. Am J Respir Crit Care Med 165:1145–1149, 2002.
159. De Vuyst P, Dumortier P, Swaen GM, et al: Respiratory health effects of man-made vitreous (mineral) fibres. Eur Respir J 8:2149–2173, 1995.
160. Trethowan WN, Burge PS, Rossiter CE, et al: Study of the respiratory health of employees in seven European plants that manufacture ceramic fibres. Occup Environ Med 52:97–104, 1995.
161. Phibbs BP, Sundin RE, Mitchell RS: Silicosis in Wyoming bentonite workers. Am Rev Respir Dis 103:1–17, 1971.
162. Chonan T, Taguchi O, Omae K: Interstitial pulmonary disorders in indium-processing workers. Eur Respir J 29:317–324, 2007.
163. Kriebel D, Brain JD, Sprince NL, et al: The pulmonary toxicity of beryllium. Am Rev Respir Dis 137:464–473, 1988.
164. Kreiss K, Mroz MM, Zhen B, et al: Risks of beryllium disease related to work processes at a metal, alloy, and oxide production plant. Occup Environ Med 54:605–612, 1997.
165. Williams WJ: United Kingdom Beryllium Registry: Mortality and autopsy study. Environ Health Perspect 104S:949–951, 1996.
166. Maier LA, Martyny JW, Liang J, et al: Recent chronic beryllium disease in residents surrounding a beryllium facility. Am J Respir Crit Care Med 177:1012–1017, 2008.
167. Newman LS, Kreiss K: Nonoccupational beryllium disease masquerading as sarcoidosis: Identification by blood lymphocyte proliferative response to beryllium. Am Rev Respir Dis 145:1212–1214, 1992.
168. Sanderson WT, Henneberger PK, Martyny J, et al: Beryllium contamination inside vehicles of machine shop workers. Am J Ind Med Suppl 1:72–74, 1999.
169. Izbicki G, Chavko R, Banauch GI, et al: World Trade Center "sarcoid-like" granulomatous pulmonary disease in New York City Fire Department rescue workers. Chest 131:1414–1423, 2007.
170. Christiani DC, Mehta AJ, Yu CL: Genetic susceptibility to occupational exposures. Occup Environ Med 65:430–436, 2008.
171. Richeldi L, Kreiss K, Mroz MM, et al: Interaction of genetic and exposure factors in the prevalence of berylliosis. Am J Ind Med 32:337–340, 1997.
172. Kreiss K, Newman LS, Mroz MM, et al: Screening blood test identifies subclinical beryllium disease. J Occup Med 31:603–608, 1989.
173. Kreiss K, Mroz MM, Newman LS, et al: Machining risk of beryllium disease and sensitization with median exposures below 2 micrograms/m^3. Am J Ind Med 30:16–25, 1996.
174. Meeting of the IARC working group on beryllium, cadmium, mercury and exposures in the glass manufacturing industry. Scand J Work Environ Health 19:360–363, 1993.
175. Hardy HL: Beryllium disease: A clinical perspective. Environ Res 21:1–9, 1980.
176. Freiman DG, Hardy HL: Beryllium disease. The relation of pulmonary pathology to clinical course and prognosis based on a study of 130 cases from the U.S. beryllium case registry. Hum Pathol 1:25–44, 1970.
177. Cullen MR, Kominsky JR, Rossman MD, et al: Chronic beryllium disease in a precious metal refinery. Clinical epidemiologic and immunologic evidence for continuing risk from exposure to low level beryllium fume. Am Rev Respir Dis 135:201–208, 1987.
178. Newman LS, Kreiss K, King TE Jr, et al: Pathologic and immunologic alterations in early stages of beryllium disease. Re-examination of disease definition and natural history. Am Rev Respir Dis 139:1479–1486, 1989.
179. Balmes JR: Respiratory effects of hard-metal dust exposure. Occup Med 2:327–344, 1987.
180. Demedts M, Gheysens B, Nagels J, et al: Cobalt lung in diamond polishers. Am Rev Respir Dis 130:130–135, 1984.
181. Lison D, Lauwerys R, Demedts M, et al: Experimental research into the pathogenesis of cobalt/hard metal lung disease. Eur Respir J 9:1024–1028, 1996.
182. Potolicchio I, Mosconi G, Forni A, et al: Susceptibility to hard metal lung disease is strongly associated with the presence of glutamate 69 in HLA-DP beta chain. Eur J Immunol 27:2741–2743, 1997.
183. Moulin JJ, Wild P, Romazini S, et al: Lung cancer risk in hard-metal workers. Am J Epidemiol 148:241–248, 1998.
184. Auchincloss JH, Abraham JL, Gilbert R, et al: Health hazard of poorly regulated exposure during manufacture of cemented tungsten carbides and cobalt. Br J Ind Med 49:832–836, 1992.
185. Della Torre F, Cassani M, Segale M, et al: Trace metal lung diseases: A new fatal case of hard metal pneumoconiosis. Respiration 57:248–253, 1990.
186. Moriyama H, Kobayashi M, Takada T, et al: Two-dimensional analysis of elements and mononuclear cells in hard metal lung disease. Am J Respir Crit Care Med 176:70–77, 2007.
187. Durand P, Begin R, Samson L, et al: Silicon carbide pneumoconiosis: A radiographic assessment. Am J Ind Med 20:37–47, 1991.
188. Begin R, Dufresne A, Cantin A, et al: Carborundum pneumoconiosis. Fibers in the mineral activate macrophages to produce fibroblast growth factors and sustain the chronic inflammatory disease. Chest 95:842–849, 1989.
189. Marcer G, Bernardi G, Bartolucci GB, et al: Pulmonary impairment in workers exposed to silicon carbide. Br J Ind Med 49:489–493, 1992.
190. Masse S, Begin R, Cantin A: Pathology of silicon carbide pneumoconiosis. Mod Pathol 1:104–108, 1988.
191. Boag AH, Colby TV, Fraire AE, et al: The pathology of interstitial lung disease in nylon flock workers. Am J Surg Pathol 23:1539–1545, 1999.
192. Eschenbacher WL, Kreiss K, Lougheed MD, et al: Nylon flock–associated interstitial lung disease. Am J Respir Crit Care Med 159:2003–2008, 1999.
193. Kern DG, Crausman RS, Durand KT, et al: Flock worker's lung: Chronic interstitial lung disease in the nylon flocking industry. Ann Intern Med 129:261–272, 1998.
194. Chronic interstitial lung disease in nylon flocking industry workers—Rhode Island, 1992–1996. MMWR Morb Mortal Wkly Rep 46:897-901, 1997.
195. Antao VC, Piacitelli CA, Miller WE, et al: Rayon flock: A new cause of respiratory morbidity in a card processing plant. Am J Ind Med 50:274–284, 2007.
196. Atis S, Tutluoglu B, Levent E, et al: The respiratory effects of occupational polypropylene flock exposure. Eur Respir J 25:110–117, 2005.

CHAPTER 66

HYPERSENSITIVITY PNEUMONITIS

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INTRODUCTION

Hypersensitivity pneumonitis (HP), also known as extrinsic allergic alveolitis, constitutes a spectrum of granulomatous, interstitial, bronchiolar, and alveolar-filling lung diseases resulting from repeated inhalation of and sensitization to a wide variety of organic aerosols and low-molecular-weight chemical antigens. Increasing recognition of the ubiquity of environmental antigen exposures and improved diagnostic tools has led to identification of cases and outbreaks of HP in a wide variety of occupational and environmental settings. Disease typically is characterized by a lymphocytic alveolitis and granulomatous pneumonitis on pathologic examination.

HP remains a diagnostic challenge because of the spectrum of clinical findings and the lack of a simple "gold standard" for diagnosis. The diagnosis depends on a strong clinical index of suspicion, a careful exposure history, and the integration of a constellation of imaging, physiologic, and histopathologic findings that, by themselves, are nonspecific and mimic a variety of other chest illnesses. HP is both treatable and preventable if exposure is recognized and antigen abatement is effective. Unrecognized or untreated, the illness may lead to permanent sequelae including airway reactivity, emphysema, and interstitial fibrosis. Confirmation of the diagnosis often generates broader public health implications regarding potential risks from ongoing antigen exposure to others sharing the environment. Diagnosis of a case of HP should prompt a search for additional cases in the shared environment as well as initiation of measures to eliminate further exposure.

ETIOLOGY

The list of specific agents that cause HP is extensive, and new exposure circumstances and disease entities continue to be described. The distinctive and often colorful disease names for HP can be organized more simply into three major categories of causal antigens: microbial agents, animal proteins, and low-molecular-weight chemicals (Table 66-1). There are also an increasing number of pharmacologic agents that have been shown to cause hypersensitivity reactions in the lung, but these are beyond the scope of this chapter and are covered under the subject of drug-induced lung diseases (see Chapter 72).

TABLE 66-1. Etiologic Categories of Hypersensitivity Pneumonitis, with Examples

MICROBIAL AGENTS

Bacteria

Examples: Thermophilics, *Bacillus subtilis*, *Klebsiella*, *Epicoccum nigrum*, nontuberculous mycobacteria

Fungi

Examples: *Aspergillus*, *Penicillium*, *Cladosporium*, *Trichosporon*, *Alternaria*, *Aureobasidium*, *Cephalosporium* species, *Absidia corymbifera*, *Eurotium amstelodami*, *Wallemia sebi*

ANIMAL PROTEINS

Examples: Bird proteins, fish meal, rat urine, mollusk shell, wheat weevil, silkworm larvae

CHEMICAL SENSITIZERS

Examples: Isocyanates, acid anhydrides, pyrethrum, Pauli's reagent (sodium diazobenzene sulfate)

Microbial Agents

Microbial organisms, including bacteria and fungi, are common in indoor environments and probably cause many more cases of HP than are recognized clinically. Warm, moist environments often provide ideal circumstances for the amplification and proliferation of microbial antigens that, if aerosolized into the environment and inhaled, can cause sensitizing lung disease.

Bacteria

Bacteria are unicellular prokaryotic organisms that have adapted to a wide variety of ecologic habitats and segregate under different physical and chemical conditions in indoor and outdoor environments. Thermophilic actinomycetes are associated causally with the prototypical example of HP, farmer's lung disease (FLD), first described in 1932. These bacteria are found ubiquitously in the environment year round, thrive at 50°C to 55°C temperatures, and with moist conditions, secreting enzymes that cause decay of vegetable matter such as hay (FLD), sugar cane (bagassosis), and mushroom compost (mushroom worker's lung). They often are found contaminating ventilation and humidification systems (humidifier lung) where temperatures reach 60°C and stagnant water is present. Indoor bacteria that prefer lower temperatures also can cause HP, and case reports have been associated with *Bacillus* spp. in contaminated wood dust, *Klebsiella* spp. in humidifiers, and *Epicoccum* spp. associated with moisture from a basement shower. Metalworking fluid (MWF) aerosols may cause HP from exposure to mycobacterial antigens contaminating these fluids.[1-3] Recreational as well as occupational exposures to bacterially contaminated water aerosols can cause HP. Case reports and outbreaks have occurred in indoor swimming pools, termed "lifeguard lung,"[4] and from exposure to nontuberculous mycobacteria contaminating hot tubs.[5]

Fungi

Fungi are nonmotile, eukaryotic organisms that reproduce by means of spores designed for airborne transport (disseminators). Components of fungi capable of becoming airborne include spores, mycelial fragments, metabolites and partially degraded substrates, and toxins. Among the interior sites for mold growth are garbage containers, food storage areas, wallpaper, upholstery, areas of increased moisture such as shower curtains, window moldings, window air conditioners, damp basements, and emissions from cool mist vaporizers. Many fungal species have been associated causally with HP.[6] *Aspergillus* spp. have been associated with HP in soy sauce brewers; bird breeders; farmers; compost, sawmill, mushroom, greenhouse, tobacco, cane mill, grain, and brewery workers; and in those exposed to contaminated esparto grass used in the production of ropes, canvas, sandals, mats, baskets, and paper paste. Similarly, *Penicillium* spp. may cause HP in cork workers, cheese workers, peat moss processors, laboratory workers, farmers, onion and potato sorters, and tree cutters.[7] *Alternaria*, *Cladosporium*, *Aureobasidium*, *Paecilomyces*,[8] and many other fungal species have been associated with HP in sawmill workers, tree cutters, hardwood processors, and other wood handlers.

Fungal antigens often are implicated in HP cases associated with microbial contamination in homes.[9] Summer-type HP, the most prevalent form of the disease in Japan, is caused by seasonal mold contamination (mainly *Trichosporon asahii*, formerly *T. cutaneum* serotype II) in the home environment.[10,11] Domestic fungal exposure associated with decaying wood and damp walls in inner city dwellings is the most common cause of HP in Australia.[12] Multiple fungal species were identified in the homes of individuals with disease, suggesting that sensitizing microbial exposures may be complex mixtures and disease is not always attributable to a single, well-defined antigen.

Animal Proteins

Particulates from a variety of animal sources can cause HP when inhaled. Exposure to bird protein antigens, first described in 1960, is the most clinically important and well recognized and is referred to as "bird breeder's" or "bird fancier's lung." Avian antigens are complex high- and low-molecular-weight proteins found in the feathers, droppings, and serum of turkeys, chickens, geese, ducks, parakeets, parrots, budgerigars, pigeons, doves, love birds, canaries, and even native birds and are highly immunogenic.[13] Immunoglobulins, particularly IgA and IgG, are secreted from and coat birds' feathers, creating a fine dust called "bloom." Flying birds such as pigeons and parakeets produce the largest amount of bloom and are the birds most often associated with HP.[14] Pigeon fancier's lung may also be caused by IgG secreted on pigeon intestinal mucin.[15,16] Highest exposures to respirable avian antigens are associated with cleaning out bird lofts, cages, and coops.

Animal handlers, including laboratory and veterinary workers, are at risk for HP from exposure to inhaled animal proteins (including rats and gerbils) in pelts, serum, and excreta. Inhalation of grain infested with the wheat weevil *Sitophilus granarius* can cause a form of HP known as "miller's lung." Sericulturists engaged in silk production can develop HP from exposure to larval secretions and cocoon particulates.[17] Production workers exposed to mollusk shell dusts during cutting and polishing to make buttons may develop HP.[18]

Chemical Sensitizers

HP from inhalation exposure to low-molecular-weight chemicals is probably less common than the other causes, although some of these inorganic chemical antigens are widely used in industry. Isocyanates are used for large-scale production of polyurethane polymers in the manufacture of flexible and rigid foams, elastomers, adhesives, and surface coatings and are becoming increasingly recognized as a cause of HP. Acid anhydrides used in plastics, paints, and epoxy resins have been associated with an HP-like syndrome often accompanied by anemia.[19] Rare case reports of HP have been described from exposure to the pesticide pyrethrum; from Pauli's reagent (sodium diazobenzenesulfate) used in chromatography; and from copper sulfate used in Bordeaux mixture to spray vineyards. Other chemical exposures reported to cause HP include formaldehyde, dimethyl phthalate, and styrene, the latter used in boat manufacturing.[20,21]

EPIDEMIOLOGY

The worldwide prevalence of HP is unknown. Reported disease incidence, prevalence, and attack rates vary widely and depend on the populations studied, the nature and intensity of antigen exposure, the case definition chosen, and variable host factors. In Europe, HP constitutes 4% to 13% of all interstitial lung diseases.[22] Epidemiologic studies of agricultural workers and bird fanciers suggest that HP is quite common in some high-risk occupational settings. Early questionnaire surveys of farming communities found prevalence rates ranging from 2.3% to 20%. Country-wide reporting systems that collect data on clinically confirmed HP in Finnish farmers showed a mean annual incidence rate of 44 per 100,000,[23] similar to the Swedish rate of 23 per 100,000. The reported prevalence of pigeon breeder's disease varies between 1 and 100 per 1000 breeders.[24] Rates of avian HP in the United Kingdom averaged 0.9 cases per 100,000 person-years between the years 1991 and 2003.[25] Fewer data exist on the prevalence of HP in workers exposed to chemical antigens. Isocyanate-induced HP was identified in 8 (4.7%) of 167 workers employed in a wood chipboard manufacturing plant.[26] In a European survey of chest physicians reporting on acute work-related respiratory diseases between 1992 and 2001, there was an annual average HP incidence of 2 cases per million. Of the cases in which a causative agent was identified, 17% were due to various chemical agents, with isocyanates the most frequently reported.[27]

OCCUPATIONAL AND ENVIRONMENTAL EXPOSURES

Although the acute symptoms of HP are often attributed to intense, intermittent antigen exposure while more subtle, insidious symptoms are thought to result from lower level, more prolonged exposure, the paucity of environmental exposure data provides little insight into dose-response relationships. Insight into exposure-response relationships is further complicated by the fact that the latency period between exposure to an environmental antigen and onset of HP symptoms may vary from a few weeks to years.

Environmental risk factors—including antigen concentration, exposure duration, frequency and intermittency, particle size, antigen solubility, use of respiratory protection, and variability in work practices—may influence disease prevalence, latency, and severity. FLD is most common in late winter, when stored hay is used to feed cattle, and in regions with heavy rainfall and harsh winter conditions where feed is likely to become damp and, therefore, an ideal substrate for microbial proliferation. A seasonal variation in specific antibody levels has been described in patients with pigeon breeder's disease, with a peak in antibody production during late summer when highest exposures were associated with the sporting season. Thus, the most common forms of HP show both seasonal and geographic variation.

Indirect and apparently trivial antigen exposures have been associated with avian HP. Goose feather duvets, down comforters and pillows, feathers used for making fishing lures, and those contained in decorative wreaths have all been associated with cases of HP. These findings suggest that avian antigens are extremely potent inducers of immunologic lung disease, and a careful search for their presence must be included in the history taking of patients with suspected HP.

HOST FACTORS

Whereas many individuals may develop precipitating antibodies following antigen inhalation, fewer develop HP. Susceptibility to or protection from HP may be explained in part by genetic polymorphisms.[28] Polymorphisms in the major histocompatibility complex and in tumor necrosis factor-α (TNF-α) are associated with the development of HP.[29-31] Several polymorphisms have also been associated with decreased disease risk. Overexpression of GATA-3, a regulator of Th2 differentiation, attenuates disease by correcting the Th1 immune response.[32] Variants in the tissue inhibitor of metalloproteinase-3 appear to be protective against bird fancier's lung.[33,34]

HP occurs more frequently in nonsmokers than in smokers. Compared with former and never smokers, pigeon fanciers who smoked had a lower incidence of

precipitating antibodies to pigeon antigens and lower serum IgG and IgA antibody levels to pigeon proteins; this suggests that cigarette smoking depresses both T-independent and T-dependent responses to inhaled antigens.[35] Investigations into the biologic mechanisms by which smoking inhibits the development of granulomatous diseases have shown that nicotine exposure leads to a reduced cellular response, with reduced total bronchoalveolar lavage (BAL) cell count and lymphocyte count and decrease in lung tissue inflammation.[36] Other studies have shown that smoking induces relative increases in macrophages and decreases in lymphocytes and dendritic cells, perhaps promoting more effective clearance of antigens from terminal airways.[37,38] Although HP appears to occur more commonly in nonsmokers, prognosis is poorer in those with HP who smoke. Smokers with FLD had more frequent illness recurrence, were more likely to have insidious than acute symptoms, had lower percent predicted vital capacities, and had poorer 10-year survival in comparison with nonsmokers with FLD.[39]

HP can occur in infants and children, although incidence and prevalence are unknown. Avian proteins are the most common antigen associated with HP in the pediatric population. In one study of 86 pediatric HP cases, 70 were caused by birds.[40] Children are more likely to present with the subacute or chronic forms of HP than with acute illness.[41] Differential cell counts on BAL fluid of children with HP show a predominantly lymphocytic subpopulation; however, the CD4/CD8 ratio is usually within the normal range and an increased human leukocyte antigen (HLA)-DR expression may be found.[42] HP should be considered in the differential diagnosis of children with recurrent febrile respiratory illnesses and in those with unexplained interstitial lung disease. Parents should be questioned carefully regarding potential antigen exposures in the home, school, and avocation.

IMMUNOPATHOGENESIS

HP is characterized by the presence of activated T lymphocytes in BAL and an interstitial mononuclear cell infiltrate. The pathogenesis of HP is complex and involves (1) repeated antigen exposure; (2) immunologic sensitization of the host to the antigen; and (3) immune-mediated damage to the lung (Table 66-2). Repeated exposure to inhaled antigens usually results in a Th1 and $CD8^+$ T-lymphocyte–predominant inflammation.[43] Compared with sarcoidosis, the ratio of $CD4^+/CD8^+$ cells in HP is often less than 1. However, these ratios vary widely in patients with HP, with some having normal or increased $CD4^+/CD8^+$ ratios. Reasons for this variability are unclear, but the forms of HP (inflammatory vs. fibrotic) and the timing of last antigen exposure in relation to BAL may affect cellular phenotypes.

TABLE 66-2. Unifying Pathogenic Characteristics of Hypersensitivity Pneumonitis

Repeated antigen exposure
Immunologic sensitization of host
Lung is portal of entry and target organ
Immune inflammatory pulmonary infiltrate (T lymphocytes)
Chronic cellular immune response with ongoing antigen exposure

In humans, the cellular and inflammatory mediators that characterize HP have been examined using BAL and provide insights into the immunologic and inflammatory mechanisms that occur in the lung.[44] The BAL cellular profile of HP following antigen exposure begins with an influx of neutrophils, peaking 48 hours after exposure, and is followed by an increase in activated T cells ($CD4^+$).[45] An influx of macrophages and lymphocytes is seen between 48 and 72 hours. This cellular profile is associated with increases in inflammatory mediators. Macrophage inflammatory protein-1α, a chemotactic factors for lymphocytes, peaks early after exposure, between 4 to 6 hours, whereas monocyte chemoattractant protein-1 peaks later, between 48 and 72 hours.[46] Both cellular redistribution from peripheral blood to lung and in situ lymphocyte proliferation contribute to the increased number of lung T cells. Reactive oxygen species produced by macrophages contribute to alveolar damage.[47]

Several cytokines contribute to the development of granuloma formation including interferon-γ (IFN-γ), interleukin (IL)-12, IL-18, and TNF-α.[48] The development of a Th1 T-cell immune response is driven primarily by the cytokine IL-12, produced mainly by macrophages. Th1 cells secrete IL-12, IFN-γ, TNF-α, and TNF-β. Mouse models support the requirement of Th1 responses for the development of HP, whereas Th2-responsive mice are resistant to HP.[49] Natural killer cells also are increased in BAL from patients with HP in comparison with nonsmokers and those with sarcoidosis. Natural killer T cells augment the development of HP by secreting IL-4 and IFN-γ, modulating the Th1/Th2 balance.[50]

The cellular phenotype in chronic, fibrotic HP appears to be different from that of the acute or inflammatory form of disease. BAL from patients with chronic HP shows a loss of effector T-cell function and a higher $CD4^+/CD8^+$ ratio.[51] There is a skewing to Th2 activity associated with the development of fibrosis.[52,53]

Individual genetic factors may drive susceptibility to developing HP. Several genetic polymorphisms of HLA subtypes have been associated with HP.[30,54–56] However, the evidence is variable, and other studies have found no association with certain HLA subtypes. Polymorphisms in tissue inhibitor of metalloproteinase-3 have been shown to confer resistance to the development of HP.[33,34] The strongest evidence for the role of genetic factors in the pathogenesis of HP comes from gene expression profiles.[57] Lung biopsies from patients with idiopathic pulmonary fibrosis (IPF), nonspecific interstitial pneumonitis, and HP were profiled using microarray techniques. The gene expression profile from HP was easily distinguished from that of IPF and was found to

be enriched with genes that are functionally associated with inflammation, T-cell activation, and a heightened immune response. Many of the genes that were found to have a higher expression profile in HP have previously been implicated in the pathogenesis of HP.[58–60] Although gene expression profile studies provide strong evidence for individual susceptibility to the disease, more research is needed to confirm their functional role in the pathogenesis of HP.

HISTOPATHOLOGY

Irrespective of cause, the histopathologic changes of HP are similar but vary depending on the stage of illness at the time of biopsy. The classic histologic triad of HP includes (1) cellular bronchiolitis (airway-centered inflammation), (2) interstitial mononuclear cell infiltrates, and (3) scattered, small, non-necrotizing granulomas. Because the histopathologic findings of HP vary and overlap with other diseases such as usual interstitial pneumonitis (UIP), fibrosing nonspecific interstitial pneumonitis, organizing pneumonia, and centrilobular fibrosis,[61–64] additional clinical data must be considered in confirming the diagnosis.

Features of the inflammatory and acute forms of HP include a lymphocytic interstitial inflammatory cell infiltrate, poorly formed non-necrotizing granulomas, and cellular bronchiolitis[65,66] (Fig. 66-1). The interstitial infiltrates can closely resemble those found in nonspecific interstitial pneumonitis.[63] Granulomas may resolve after a period of antigen exposure avoidance.

Fibrotic and chronic forms of HP are characterized by airway-centered interstitial fibrosis and giant cells, often with minimal granulomatous inflammation (Fig. 66-2). Bridging fibrosis occurring between peribronchiolar and perilobular areas may provide evidence of chronic HP. In a review of 13 cases of chronic HP, three patterns were found: (1) a UIP-like pattern in a patchy subpleural distribution with obliteration of the lung architecture, often with fibroblast foci; (2) a homogeneous linear fibrosis similar to that of fibrotic nonspecific interstitial pneumonitis; and (3) irregular fibrosis in a peribronchiolar distribution.[64]

CLINICAL FEATURES

Signs and Symptoms

A thorough and detailed history is the cornerstone of HP diagnosis. It is also essential for planning exposure intervention (Table 66-3). A clinical history suggesting a temporal relationship between symptoms and certain activities is often the first clue to the diagnosis of HP, although such a pattern does not always occur. The work history should include a chronology of current and previous occupations, with a description of specific work processes and exposures. Antigen exposures capable of causing HP can occur in almost any indoor environment under appropriate circumstances, and a simple job title cannot be used to exclude potential risk.

The environmental history should explore exposure to pets and other domestic animals, particularly birds; hobbies such as gardening and lawn care, which may involve sensitizing chemical exposures like pyrethrins; recreational activities, for example, use of hot tubs and indoor swimming pools from which microbial bioaerosols can be generated; use of humidifiers, cool mist vaporizers, and humidified air conditioners, which can be sources of microbial bioaerosols; moisture indicators such as leaking, flooding, or previous water damage to carpets and furnishings; and visible mold or mildew contamination in occupied spaces. Use of medications (both prescription and nonprescription) should be elicited to assess possible drug-induced lung disease.

The classification of HP into distinct acute, subacute, and chronic forms can be misleading because clinical manifestations frequently overlap. Nevertheless, the varying presentations are associated with variable clinical findings. Acute HP typically begins 4 to 12 hours after exposure, with abrupt onset of viral-like respiratory and constitutional symptoms of cough, dyspnea, chest tightness, fevers, chills, malaise, and myalgias. Symptoms

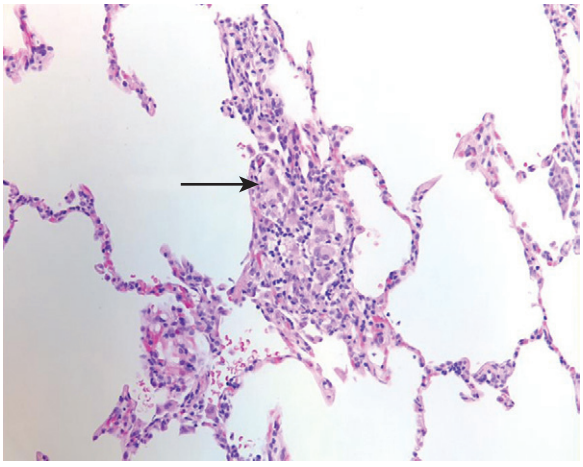

FIGURE 66-1 ■ Highlights of one of several poorly formed non-necrotizing granulomas (*arrow*) in the right middle lobe biopsy.

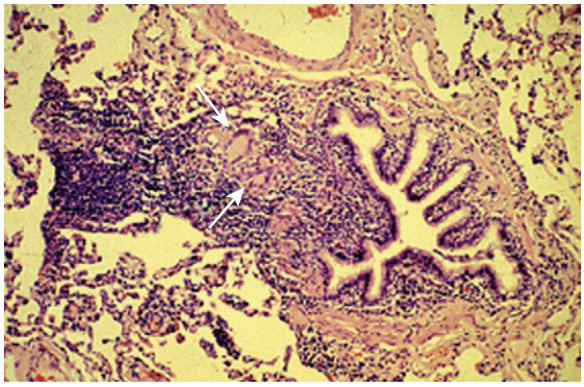

FIGURE 66-2 ■ Airway-centered interstitial fibrosis and giant cells (*arrows*), with granulomatous inflammation.

TABLE 66-3. Components of an Occupational and Environmental History for Patients with Suspected Hypersensitivity Pneumonitis

OCCUPATIONAL HISTORY
Chronology of current and previous occupations
Description of job processes and specific work practices
List of specific chemicals, dusts, and other aerosol exposures (e.g., grain dust; animal handling; food and plant processing; cooling towers, fountains, and other water sprays; metalworking fluids)
Review of material safety data sheets (MSDS) to identify known chemical sensitizers
Reports of industrial hygiene evaluations or environmental testing at the workplace
Symptom improvement away from work or symptom worsening with specific workplace exposures
Presence of persistent respiratory or constitutional symptoms in exposed coworkers
Use of respiratory protection at work
ENVIRONMENTAL AND RESIDENTIAL HISTORY
Pets and other domestic animals (especially birds)
Hobbies and recreational activities (especially those involving chemicals, feathers or fur, plant materials, and organic dusts)
Presence of humidifiers, dehumidifiers, evaporative coolers, clothes dryers vented indoors, and other humidity sources
Use of hot tubs or saunas
Leaking or flooding indoors
Water damage to carpets or furnishings
Visible fungal growth
Feather pillows, comforters, or bedding
Similar symptoms in other family members or home occupants

may be accompanied by physical findings of fever, tachypnea, tachycardia, and lung inspiratory crackles. Peripheral blood leukocytosis with neutrophilia and lymphopenia may be present. Eosinophilia is unusual. Symptoms of acute HP typically resolve spontaneously. Recurrent acute symptom episodes should prompt consideration of hypersensitivity lung disease and a careful historical search for relevant exposures.

The more insidious subacute presentations of illness also require a high degree of clinical suspicion to confirm the diagnosis and initiate appropriate management. Dyspnea and cough are the most commonly reported clinical symptoms. Patients frequently report sputum production, fatigue, malaise, chest tightness, and weight loss. Pulmonary examination findings often include basilar crackles, though in two large studies of HP, nearly 20% of patients with HP had a normal lung examination.[67,68] Wheezing may occur in some patients and likely reflects an antigen-mediated inflammatory effect on the airways. Cyanosis and right-sided heart failure occur with severe fibrotic disease. Digital clubbing is associated with a poorer prognosis.

Precipitating Antibodies

The finding of specific IgG-precipitating antibodies in the serum of a patient with suspected HP indicates exposure sufficient to generate a humoral immunologic response and may be a helpful diagnostic clue. Once thought to be the hallmark of HP, precipitating antibodies are unfortunately neither sensitive nor specific.[69] This is especially true if used as a screening tool.[70] In a large series of patients with bird fancier's lung, 92% had positive serum IgG antibodies, whereas 87% of controls also had positive precipitins.[68]

Despite advances in detection of serum antibodies, challenges in their use and interpretation persist.[71] False-negative results may occur because of poorly standardized antigens, improper quality controls, insensitive immunologic techniques, the wrong choice of antigen, or underconcentrated sera. More sensitive assays such as enzyme-linked immunosorbent assay for specific IgG antibodies may lead to confusion because of decreased specificity. Serum precipitins may disappear over time after exposure ceases. In cases associated with complex microbial bioaerosol exposures, disease may not be a reaction to one organism alone but a cumulative reaction to a number of airborne antigens, which may not be reflected in available laboratory antigen panels.

Other Laboratory Studies

Mild elevations in erythrocyte sedimentation rate, C-reactive protein, and immunoglobulins of IgG, IgM, or IgA isotypes are occasionally evident, reflecting acute or chronic inflammation. Antinuclear antibodies and other autoantibodies rarely are detected and, if found, suggest an underlying connective tissue disease. Skin tests for both immediate and delayed-type hypersensitivity reactions are not helpful in the diagnosis of HP.[70,72,73]

There is increasing evidence for Krebs von den Lungen-6 (KL-6) as a potential biomarker for HP. KL-6 is a mucin-like high-molecular-weight glycoprotein produced mainly by pulmonary epithelial cells. It is often elevated in the serum and BAL fluid of patients with diseases involving the small airways.[74-77] KL-6 has been studied in FLD and bird fancier's disease as a marker of disease activity and may correlate with pulmonary physiologic abnormalities.[78,79]

Physiology

Complete pulmonary function tests (PFTs), including lung volumes, spirometry, and diffusing capacity of carbon dioxide (D_{LCO}), should be obtained in all patients with suspected HP. Lung function abnormalities in acute HP are classically restrictive, with a decrease in forced vital capacity, total lung capacity, and diffusion capacity.[80,81] Hypoxemia is often present, and an exercise-induced decrease in arterial oxygen tension is an early sign of functional impairment. PFTs may be normal if performed after resolution of an acute episode.

PFTs may also fall within normal limits in subacute forms of HP, and findings may be misleading if no premorbid PFT values are available for comparison. Restrictive, obstructive, and combined defects in pulmonary function occur in subacute and chronic HP. Decreased

diffusion capacity also is commonly observed. Gas exchange abnormalities, particularly with exercise, may be marked. Nonspecific bronchial hyperreactivity measured by methacholine challenge has been described. HP should be considered in the differential diagnosis of nonsmokers presenting with physiologic findings of emphysema and in patients with airflow limitation and nonspecific bronchial hyperreactivity. Once diagnostic confirmation of HP is obtained, serial PFTs should be followed to assess response to therapy and to guide treatment decisions until recovery or stability of lung function is achieved.

Radiography

The chest radiograph in acute HP typically reveals a fine micronodular pattern or diffuse ground-glass opacities (Fig. 66-3A).[82,83] Hilar or mediastinal adenopathy rarely is seen on the plain radiograph. The chest film may be normal, particularly in early disease stages, and is a poor screening tool in populations at risk for HP. Radiographic abnormalities in acute illness regress or resolve over 4 to 6 weeks if further exposure is avoided. Radiographic manifestations of fibrotic HP include linear reticular opacities, volume loss, and honeycombing.

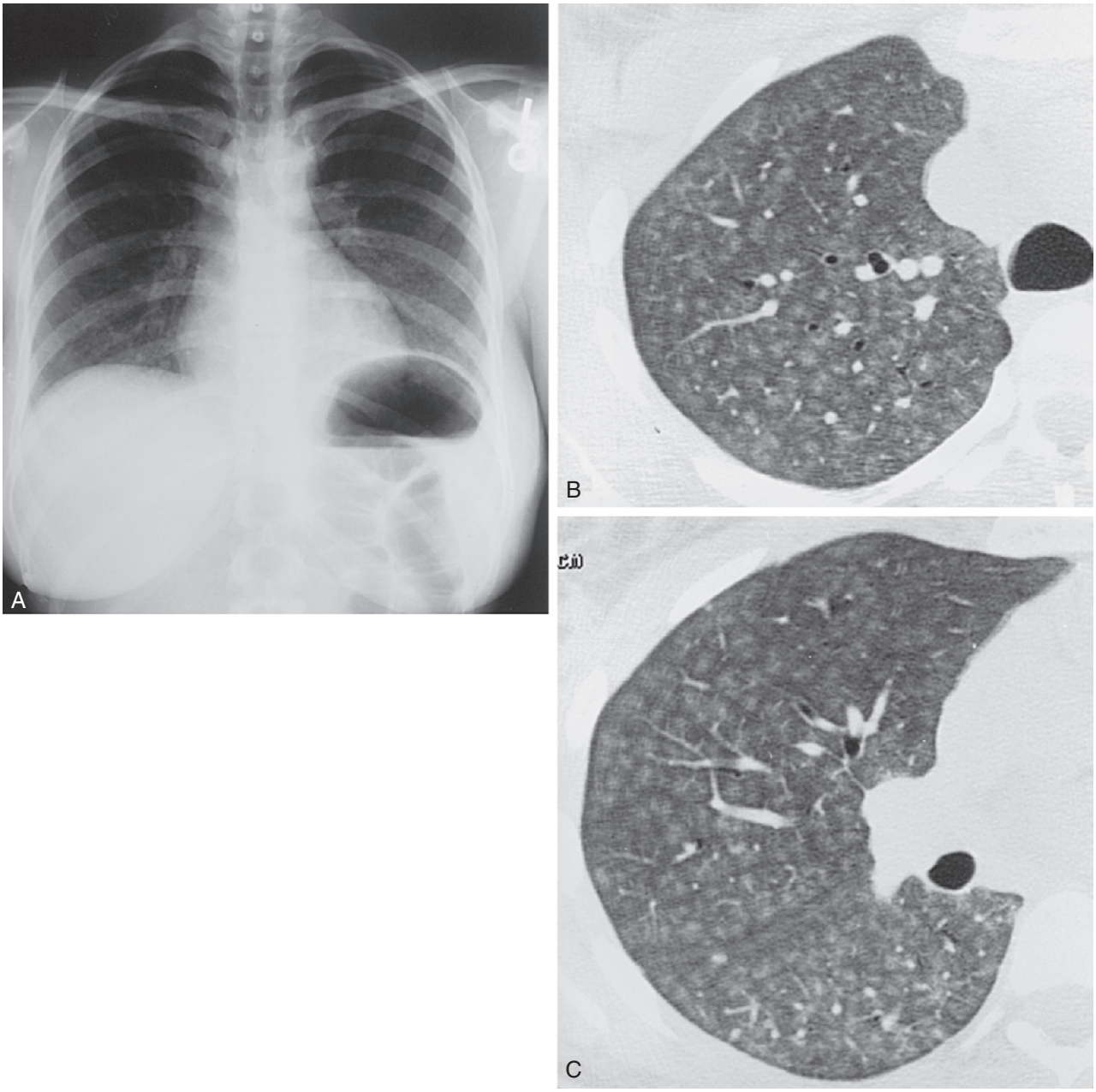

FIGURE 66-3 ■ **A,** Chest radiograph of a patient with hypersensitivity pneumonitis (HP) shows diffuse upper zone predominant micronodules. **B,** High-resolution (1.5-mm thin section) computed tomography (HRCT) image through the lung of the same patient shows profuse centrilobular micronodules. **C,** HRCT scan of a patient with chronic bird breeder's lung shows diffuse ground-glass attenuation with reticular opacities and centrilobular micronodules.

Chest computed tomography (CT) scanning is more sensitive than chest radiography in the diagnosis of HP and is useful in differentiating infectious and noninfectious parenchymal lung diseases.[84,85] The classic CT findings of HP include mosaic attenuation, ground-glass abnormalities, and centrilobular micronodules.[86,87] The finding of centrilobular micronodules probably reflects a cellular bronchiolitis (see Fig. 66-3B).[88] Diffuse ground-glass attenuation may be the predominant or only CT abnormality in some cases. The CT appearance of HP may be normal if disease is diagnosed early.[89] HP-associated effects on small airways are best assessed by expiratory imaging modalities that show areas of decreased attenuation.[90] In chronic HP, chest CT findings include fibrosis, reticular opacities, lobar volume loss, and honeycombing (see Fig. 66-3C). Focal areas of hyperlucency (mosaic pattern), perhaps due to bronchiolocentric inflammation with associated air trapping, may be a prominent feature[91] (Fig. 66-4). Mild reactive mediastinal lymphadenopathy is a common CT finding typically involving only a few nodes with a maximal short axis diameter less than 15 mm. The degree of fibrosis found on CT reflects a poorer prognosis in patients with HP[92,93] (Fig. 66-5). Notably, emphysema is a more common radiographic finding than fibrosis in chronic FLD.[94,95] Lung cysts have been reported in cases of subacute HP.[96] The use of CT scan alone to differentiate chronic HP from other fibrotic interstitial lung diseases is unreliable, with accurate diagnosis in 50% of patients in one series.[97]

Inhalation Challenge

The use of laboratory inhalation challenge in the diagnosis of HP is limited by the lack of standardized antigens and techniques. Inhalation of an aerosolized antigen suspected to be causative is most helpful when acute symptoms and clinical abnormalities are part of the disease presentation and likely to occur within hours after exposure. In some patients with acute symptoms, exposure to the suspect environment with postexposure monitoring of symptoms, temperature, leukocyte count, spirometry, DL_{CO}, and chest radiograph may be preferable to laboratory challenge. Inhalation challenge testing may be useful in distinguishing between insidious versus fluctuating types of chronic bird fancier's lung.[98] Interpretation of results is often difficult, and routine inhalation challenge is not recommended in most patients with suspected HP.[80]

Bronchoalveolar Lavage

BAL is a generally safe and sensitive tool to confirm the presence of alveolitis in patients with HP. Typically, a marked BAL lymphocytosis (30%–70%) without eosinophilia or neutrophilia is found, often with a $CD8^+$ lymphocyte predominance. Total white blood cell numbers are increased, often up to fivefold normal. The absolute number of macrophages is similar to that in controls, although their percentage in BAL is reduced because of the high percentage of lymphocytes.

The BAL cellular profile may vary considerably, depending on the stage of illness and the time interval between BAL and last antigen exposure. Cellular profiles provide insight into possible mechanisms of disease, particularly in chronic HP where effector T-cell function is lost, with shift toward a profibrotic Th2 profile.[51] The BAL lymphocytosis of HP may persist for years after apparent removal from antigen exposure and despite improvement in other clinical parameters, limiting its utility as a tool to follow the course and progression of disease or to assess adequacy of antigen avoidance.[99] Individuals exposed to HP antigens but without reported symptoms or other clinical abnormalities may develop a lymphocytic alveolitis, further limiting the diagnostic specificity of BAL. There appears to be little correlation between BAL findings and other clinical abnormalities, including radiographic changes, pulmonary function, and the presence of precipitating antibody.

FIGURE 66-4 ■ Chronic HP. Bilateral, diffuse ground-glass opacities with mosaic perfusion.

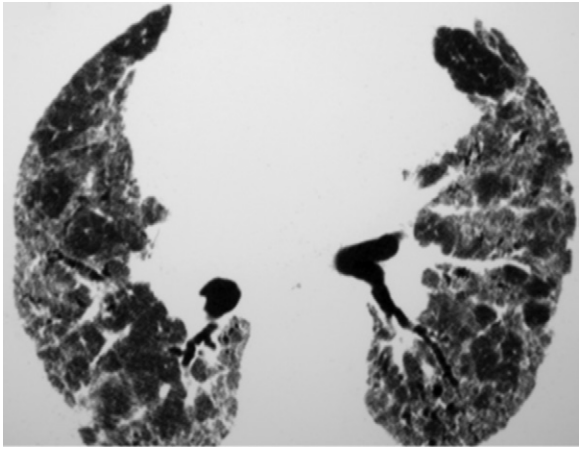

FIGURE 66-5 ■ Chronic HP. Chronic HP is manifest as lung fibrosis, with areas of reticulation, traction bronchiectasis, and architectural distortion, with a mid-lung predominance. (Courtesy of Dr. Michael Gotway.)

Lung Biopsy

Lung biopsy is indicated in patients without sufficient clinical criteria for definitive diagnosis or to rule out other diseases that require different management. In one study, transbronchial biopsies were found to have a relatively low yield of 38% in the diagnosis of interstitial lung disease.[100] Use of transbronchial biopsies should be considered in those patients who decline surgery or are at higher surgical risk. Interstitial lymphocytic inflammation, granulomas, and bronchiolar inflammation can be seen on transbronchial biopsy; however, appreciation of the prototypical airway-centered inflammation usually requires a surgical lung biopsy. Special stains and cultures are important to distinguish HP from infectious granulomatous conditions, including fungal and mycobacterial diseases. HP differs from sarcoidosis in the finding of inflammatory infiltrates at interstitial sites distant from granulomas, whereas in sarcoidosis, such infiltrates generally are found in and around the granulomas. Surgical lung biopsy is often necessary to confirm a diagnosis of subacute HP and is helpful when differentiating HP from other interstitial lung diseases.[62,64,101,102] Fibrotic HP may be difficult to distinguish from UIP. The diagnostic yield increases if biopsies are taken from multiple lobes.[103] Fibroblast foci commonly seen in UIP can also be seen in chronic HP.[61] The histopathologic finding of chronic bronchiolitis with or without peribronchiolar metaplasia in the setting of other findings consistent with UIP should raise the possibility of chronic HP.[103] Given the substantial overlap in the histologic appearance of these inflammatory processes, pathology without clinical correlation is often insufficient for diagnosis.

Diagnostic Approach

A thorough review of potential exposures to known antigens is essential as the cornerstone of treatment is elimination of further exposure. Diagnostic studies that should be considered on all patients with suspected HP can be found in Table 66-4. In patients with exertional dyspnea and normal or minimally abnormal PFTs, exercise physiology is often helpful in defining impairment and important in guiding treatment decisions, including the need for supplemental oxygen. Serum precipitins are helpful when positive in confirming the diagnosis in bird breeder's lung and in other circumstances in which the putative antigen has been identified. However, negative precipitins should not be used to exclude the diagnosis.

TABLE 66-4. Diagnostic Approach to the Patient with Possible Hypersensitivity Pneumonitis

Obtain detailed occupational and environmental exposure histories, along with regular clinical history
Physical examination, with attention to pulmonary findings
Pulmonary function, including spirometry, lung volumes, D_{LCO}
Chest radiograph
Chest high-resolution CT scan if chest film is negative or nonspecific
Assess exercise ventilatory and gas exchange parameters if exertional dyspnea is prominent
Consider serum precipitin analysis; negative results do not rule out HP, but a positive precipitin result helps confirm relevant antigenic exposures
FOB with BAL if diagnosis is in doubt; surgical lung biopsy may be indicated if FOB is nondiagnostic

BAL, bronchoalveolar lavage; CT, computed tomography; D_{LCO}, diffusing capacity of carbon dioxide; FOB, fiberoptic bronchoscopy; HP, hypersensitivity pneumonitis.

DIAGNOSTIC CRITERIA

A number of diagnostic criteria for HP have been proposed, but most lack validation.[104,105] Most criteria include the requirements of appropriate exposure, dyspnea on exertion, inspiratory crackles, and lymphocytic alveolitis (if BAL is done). Supportive criteria include recurrent febrile episodes; opacities on chest radiograph; decreased D_{LCO}; precipitating antibodies to causative antigens; granulomas on lung biopsy (usually not required); and improvement with contact avoidance. Stringent diagnostic criteria may underestimate milder cases of HP in which the chest radiograph is normal or when symptoms are subtle or insidious. Because a positive exposure history is part of the case definition for disease, absent or inadequate occupational and environmental history taking probably results in underrecognition of disease. Moreover, in up to 30% of cases with more complete exposure histories, no causal exposure is identifiable. The likelihood that unrecognized HP occurs also is based on several other factors: (1) the signs and symptoms of illness and clinical diagnostic findings are nonspecific and mimic many other diseases (Table 66-5); (2) early disease may be accompanied by a normal lung examination and resting pulmonary function as well as a normal chest radiograph; (3) many of the microbial antigens that cause HP proliferate in common environmental niches and relevant exposures may be difficult to elicit historically; and (4) precipitating antibodies are often negative and may disappear after exposure ceases, so that a patient with fibrotic lung disease from previous episodes of HP may not be recognized as such

NATURAL HISTORY AND PROGNOSIS

In acute HP, symptoms of fever, chills, and cough usually disappear within days after exposure ceases. Malaise, fatigue, and dyspnea may persist for several weeks. There is usually rapid improvement in lung vital capacity and D_{LCO} in the first 2 weeks after an acute attack, but mild abnormalities in pulmonary function often persist for several months. In general, single acute episodes are self-limited and do not require treatment other than avoidance of repeated exposure. Rarely, the disease may progress despite removal from exposure. Continued symptoms and progressive lung impairment have been

TABLE 66-5. Differential Diagnosis of Hypersensitivity Pneumonitis*

	Clinical Presentation	BAL Lymphocytosis	Histopathology
Asthma	++	+	–
Sarcoidosis	++	++	+
Inhalation fever (e.g., ODTS)	++	–	–
Viral/mycoplasma pneumonias	++	+	–
Mycobacterial infections	++	++	+
Fungal infections	+	+	+
Other ILD (collagen vascular, IPF)	+	+	+
Chronic beryllium disease	+	++	+
Lymphoma/leukemia	+	+	+
Toxic fume inhalation	+	–	–

*Designations reflect other illnesses compared with hypersensitivity pneumonitis (acute, subacute, or chronic presentation).
++, very similar; +, similar; –, dissimilar.
BAL, bronchoalveolar lavage; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; ODTS, organic duct toxic syndrome.

reported after recurrent acute attacks and even after a single severe attack.

The subacute and chronic forms of HP, with insidious symptoms and more subtle, progressive clinical abnormalities, are often recognized later in the course of illness and consequently have a poorer prognosis than acute disease. Overall, patients with HP appear to have an increased mortality rate when compared with the general population.[25] Patients with imaging evidence of fibrotic HP have a significantly worse prognosis overall when compared with those with nonfibrotic chronic HP.[86,93] The risk of death from HP increases with increased age.[92,101] Fatal diffuse alveolar damage has been described as a complication of chronic bird fancier's lung.[106]

Both emphysema (more common in late-stage FLD) and fibrosis (more common as an outcome of bird breeder's lung) are potential sequelae of HP. In a case-control study of 88 farmers with FLD,[107] emphysema was found significantly more often (23%) in those with FLD compared with matched control farmers (7%), occurring in 18% of nonsmoking and 44% of smoking FLD patients. Recurrent attacks of FLD were associated in this study with risk for emphysema. In another follow-up study of farmers with a history of FLD,[108] obstructive abnormalities from emphysema were the most common findings in those whose disease did not completely resolve; only 50% had no residual disease. In a study of Finnish farmers meeting strict diagnostic criteria for FLD,[109] the risk for asthma necessitating medication was found to increase within the first 3 years after a diagnosis of FLD, with significantly higher asthma prevalence rates in the population with FLD at 5-year follow-up compared with the reference population. Patients with HP from avian antigens appear to have a higher risk of developing fibrotic lung disease compared with those with FLD, with a poor 5-year survival similar to that of patients with IPF. Thus, although some patients with HP recover completely, permanent sequelae of the disease include asthma, emphysema, and (sometimes progressive) interstitial fibrosis.

No functional or biochemical marker exists to predict resolution or progression of disease. The BAL lymphocytosis associated with HP may persist for years after removal from exposure and despite clinical recovery. Age at diagnosis, duration of antigen exposure after onset of symptoms, and total years of exposure before diagnosis seem to have predictive value in the likelihood of recovery from pigeon breeder's lung disease.[110] A 23-year population-based study undertaken to investigate the mortality of HP showed that overall age-adjusted death rates increased between 1980 and 2002.[111] The authors suggest that this may be due to the concomitant decline in smoking rates in the United States and better disease recognition from use of thoracoscopic lung biopsy for diagnosis.[111] Wisconsin has the highest percentage of FLD-related deaths (81.9%), twice that of the nation as a whole. Death also increased with age, with rates of 0.01 per million in the 15- to 24-year-old group, compared with 0.80 per million in the 65-year-old and older group of patients with HP.[112]

TREATMENT

An accelerated decline in lung function with continued antigen exposure has been demonstrated for most forms of HP. Thus, early diagnosis and avoidance of exposure are the mainstays of treatment, with pharmacologic therapy an important adjunct in some cases.

Antigen Avoidance

Elimination of a causative antigen from the patient's environment not only is the first step in treatment but also prevents occurrence of hypersensitivity diseases in others exposed. For example, maple bark disease and bagassosis are now quite rare in the United States after changes in the handling of organic material, resulting in diminished opportunity for microbial growth. Removal of damaged and colonized areas, disinfection, and elimi-

nation of conditions leading to seasonal mold contamination have been effective in preventing recurrence of summer-type HP in Japan.[113] Outbreaks of HP traced to microbial contamination of ventilation systems were controlled by extensive modification and replacement of the systems and corresponding work areas.[114] In cases of home humidifier and hot tub lung, removal of the contaminated source is usually straightforward in eliminating ongoing exposure.

On-site investigation of the implicated work or home environment by an experienced industrial hygienist may be helpful in cases in which the exposure history is uncertain, particularly when disease is progressive. However, quantitative bioaerosol sampling for indoor microbial antigens is time-consuming, expensive, and not readily available to most clinicians and requires an experienced industrial hygienist and analytical laboratory. Even when properly performed, results are often difficult to interpret. Negative results should not be used to disprove disease or exposure. Avoidance of exposure by eliminating the offending antigen from the environment may be difficult in some circumstances. In five homes monitored serially after bird removal, antigen levels measured by inhibition enzyme-linked immunosorbent assay declined gradually despite extensive environmental control measures, with high levels still detectable at 18 months in one home.[115] Avian antigens can be found in homes without birds if wild bird excrement is deposited heavily outside the house and tracked in on shoes.

When elimination of the antigen is not feasible or the etiologic agent is not identified, exposure avoidance may be accomplished by removing the affected individual from the likely antigen-containing environment. This approach may be simple and adequate for recovery. However, the social consequences and economic disruption to the affected individual may preclude strict abstinence from exposure. When antigen exposure avoidance is likely to be inadequate, regular follow-up of pulmonary function, chest imaging, and symptoms is essential to assess response to treatment and to direct efforts to mitigate ongoing antigen exposure.

Pharmacologic Therapy

There are anecdotal reports of the beneficial effects of systemic steroids in acute attacks of HP, but controlled clinical trials are lacking. In cases in which pulmonary function abnormalities are minor and spontaneous recovery is likely with removal from exposure, steroids are probably unnecessary. More severe attacks may necessitate treatment with prednisone, typically beginning at 60 mg/day, plus supplemental oxygen for hypoxemia and other appropriate supportive measures. Prednisone usually is continued until there is significant symptomatic and functional improvement. Pulmonary function should be monitored within the first 4 weeks after initiation of treatment. If there is objective improvement, a gradual taper to minimum sustaining doses should follow; otherwise, steroids should be tapered and discontinued. Given the paucity of treatment studies and the known side effects of systemic corticosteroids, clinical judgment and careful medical follow-up must guide individual patient management.

The effect of corticosteroids on the long-term course of various forms of HP has received limited study. In one study, 36 patients, most having suffered only one acute attack of FLD, were assigned randomly to receive prednisolone or placebo for 2 months.[116] The steroid-treated group showed more rapid improvement in physiologic abnormalities (particularly D_{LCO}) at 1-month follow-up, but no differences were found between the treated and the untreated groups 5 years later. In a study of pigeon breeders with HP, there were no significant clinical outcome differences between cases who were treated with steroids and those who were not; the mean time for improvement or normalization of pulmonary function after treatment and removal from exposure was 3.4 months.[110]

Inhaled steroids and β-agonists may be helpful in patients with HP manifested by symptoms of chest tightness and cough and with airflow limitation on pulmonary function. There are as yet no data from controlled clinical trials on the efficacy of inhaled steroids in the treatment of HP. Cytotoxic agents such as cyclophosphamide, cyclosporin A,[117] and azathioprine have been used in patients with refractory progressive HP, but their efficacy is largely unexplored. Lung transplantation may be a last resort in patients unresponsive to medical therapy.

PREVENTION

Recognition of an index case of HP is often a sentinel health event, indicating the need for further investigation and intervention in the environment where others may be at risk and where opportunities for prevention may be identified. For example, indoor microbial contamination often is related to problems with control of moisture. Source dilution and administrative controls should be used when appropriate to reduce these indoor contaminants. Source control includes preventing leaking and flooding; removing stagnant water sources; eliminating aerosol humidifiers, hot tubs, and vaporizers; and maintaining indoor relative humidity below 70%. If humidifiers are used, frequent cleaning and water changes minimize the risk of microbial growth. Dilution of contaminants can be affected by increasing the amount of outdoor air in a building, and high-efficiency filters can be added to the ventilation system to clean recirculated air.

Work practices recommended to reduce the prevalence of FLD include efficient drying of hay and cereals before storage, use of mechanical feeding systems, and better ventilation of farm buildings. Education of potentially exposed workers in antigen avoidance and early symptom recognition may be helpful.

The efficacy of various types of respirators in preventing antigen sensitization and disease progression once sensitization has occurred is poorly studied. Helmet-type powered air purifying respirators have been used to

prevent episodic exposure in individuals with previous acute episodes of FLD. Respiratory protection has been examined in bird breeders with HP.[118] Serum antibody levels declined by 65% over 14 months in those wearing respirators in comparison with no decline in antibody levels in those without respirators; no data were reported on changes in symptoms or pulmonary function in the two groups. Prolonged wearing of respiratory protection is limited by the fact that most respirators are uncomfortable and cumbersome and interfere with communication. Dust respirators offer substantial, but in some cases incomplete, protection against organic dusts and are not recommended as preventive measures once sensitization has occurred.

KEY POINTS

- HP is a complex syndrome of varying clinical presentations, intensity/severity, and natural history.
- Many persons with mild or subclinical HP escape detection or are misdiagnosed as suffering from viral illnesses or asthma.
- Only a small proportion of exposed individuals develop clinically significant HP.
- Genetic factors are postulated to play a major role in determining an individual's risk of disease.
- HP occurs more frequently in nonsmokers than in smokers.
- Correct diagnosis is based upon: exposure history, clinical assessment, radiographic and physiologic findings.
- Absent or inadequate occupational and environmental history taking probably results in underrecognition of disease.
- The presence or absence of serum precipitins is of limited usefulness in the diagnosis of HP.
- HP is characterized by several histologic patterns of lung injury (in combination or alone).
- Removal from exposure to the suspected etiologic agent can be diagnostic and therapeutic.
- HP is both treatable and preventable if exposure is recognized and antigen abatement is effective.

References

1. Gupta A, Rosenman KD: Hypersensitivity pneumonitis due to metal working fluids: Sporadic or under reported? Am J Ind Med 49:423–433, 2006.
2. Wilson RW, Steingrube VA, Bottger EC, et al: *Mycobacterium immunogenum* sp. nov., a novel species related to *Mycobacterium abscessus* and associated with clinical disease, pseudo-outbreaks and contaminated metalworking fluids: An international cooperative study on mycobacterial taxonomy. Int J Syst Evol Microbiol 51:1751–1764, 2001.
3. Shelton BG, Flanders WD, Morris GK: *Mycobacterium* sp. as a possible cause of hypersensitivity pneumonitis in machine workers. Emerg Infect Dis 5:270–273, 1999.
4. Rose CS, Martyny JW, Newman LS, et al: "Lifeguard lung": Endemic granulomatous pneumonitis in an indoor swimming pool. Am J Public Health 88:1795–1800, 1998.
5. Aksamit TR: Hot tub lung: Infection, inflammation, or both? Semin Respir Infect 18:33–39, 2003.
6. Reboux G, Piarroux R, Mauny F, et al: Role of molds in farmer's lung disease in Eastern France. Am J Respir Crit Care Med 163:1534–1539, 2001.
7. Merget R, Sander I, Rozynek P, et al: Occupational hypersensitivity pneumonitis due to molds in an onion and potato sorter. Am J Ind Med 51:117–119, 2008.
8. Veillette M, Cormier Y, Israel-Assayaq E, et al: Hypersensitivity pneumonitis in a hardwood processing plant related to heavy mold exposure. J Occup Environ Hyg 3:301–307, 2006.
9. Temprano J, Becker BA, Hutcheson PS, et al: Hypersensitivity pneumonitis secondary to residential exposure to *Aureobasidium pullulans* in 2 siblings. Ann Allergy Asthma Immunol 99:562–566, 2007.
10. Ando M, Suga M, Nishiura Y, et al: Summer-type hypersensitivity pneumonitis. Intern Med 34: 707–712, 1995.
11. Ohtani Y, Ochi J, Mitaka K, et al: Chronic summer-type hypersensitivity pneumonitis initially misdiagnosed as idiopathic interstitial pneumonia. Intern Med 47:857–862, 2008.
12. Bryant DH, Rogers P: Allergic alveolitis due to wood-rot fungi. Allergy Proc 12:89–94, 1991.
13. Funke M, Fellrath JM: Hypersensitivity pneumonitis secondary to lovebirds: A new cause of bird fancier's disease. Eur Respir J 32:517–521, 2008.
14. Longbottom JL: Pigeon breeders' disease: Quantitative immunoelectrophoretic studies of pigeon bloom antigen. Clin Exp Allergy 19:619–624, 1989.
15. Baldwin CI, Calvert JE, Todd A, et al: IgG subclass responses to pigeon intestinal mucin in pigeon fanciers' lung. Eur J Med Res 5:128, 2000.
16. Baldwin CI, Allen A, Bourke S, et al: Mucin oligosaccharides and pigeon fanciers' lung. Adv Exp Med Biol 564:101–102, 2005.
17. Nakazawa T, Umegae Y: Sericulturist's lung disease: Hypersensitivity pneumonitis related to silk production. Thorax 45:233–234, 1990.
18. Orriols R, Manresa JM, Aliaga JL, et al: Mollusk shell hypersensitivity pneumonitis. Ann Intern Med 113:80–81, 1990.
19. Piirila P, Keskinen H, Anttila S, et al: Allergic alveolitis following exposure to epoxy polyester powder paint containing low amounts (<1%) of acid anhydrides. Eur Respir J 10:948–951, 1997.

20. Baccioglu A, Kalpaklioglu AF: An unusual form of formaldehyde-induced lung disease. Allergol Immunopathol (Madr) 35:110–112, 2007.
21. Volkman KK, Merrick JG, Zacharisen MC: Yacht-maker's lung: A case of hypersensitivity pneumonitis in yacht manufacturing. WMJ 105:47–50, 2006.
22. Thomeer M, Demedts M, Vandeurzen K: Registration of interstitial lung diseases by 20 centres of respiratory medicine in Flanders. Acta Clin Belg 56:163–172, 2001.
23. Terho O, Heinonen O, Lammi S: Incidence of clinically confirmed farmer's lung disease in Finland. Am J Ind Med 10:330, 1986.
24. Demedts M, Wells AU, Anto JM, et al: Interstitial lung diseases: An epidemiological overview. Eur Respir J Suppl 32:2s–16s, 2001.
25. Solaymani-Dodaran M, West J, Smith C, et al: Extrinsic allergic alveolitis: Incidence and mortality in the general population. Q J Med 100:233–237, 2007.
26. Vandenplas O, Malo JL, Dugas M, et al: Hypersensitivity pneumonitis–like reaction among workers exposed to diphenylmethane [correction to piphenylmethane] diisocyanate (MDI). Am Rev Respir Dis 147:338–346, 1993.
27. McDonald JC, Chen Y, Zekveld C, et al: Incidence by occupation and industry of acute work related respiratory diseases in the UK, 1992–2001. Occup Environ Med 62:836–842, 2005.
28. Schuyler M: Are polymorphisms the answer in hypersensitivity pneumonitis? Am J Respir Crit Care Med 163:1513–1514, 2001.
29. Aquino-Galvez A, Camarena A, Montano M, et al: Transporter associated with antigen processing (TAP) 1 gene polymorphisms in patients with hypersensitivity pneumonitis. Exp Mol Pathol 84:173–177, 2008.
30. Camarena A, Juarez A, Mejia M, et al: Major histocompatibility complex and tumor necrosis factor-alpha polymorphisms in pigeon breeder's disease. Am J Respir Crit Care Med 163:1528–1533, 2001.
31. Schaaf BM, Seitzer U, Pravica V, et al: Tumor necrosis factor-alpha-308 promoter gene polymorphism and increased tumor necrosis factor serum bioactivity in farmer's lung patients. Am J Respir Crit Care Med 163:379–382, 2001.
32. Matsuno Y, Ishii Y, Yoh K, et al: Overexpression of GATA-3 protects against the development of hypersensitivity pneumonitis. Am J Respir Crit Care Med 176:1015–1025, 2007.
33. Hill MR, Briggs L, Montano MM, et al: Promoter variants in tissue inhibitor of metalloproteinase-3 (TIMP-3) protect against susceptibility in pigeon breeders' disease. Thorax 59:586–590, 2004.
34. Janssen R, Kruit A, Grutters JC, et al: TIMP-3 promoter gene polymorphisms in BFL. Thorax 60:974, 2005.
35. Baldwin CI, Todd A, Bourke S, et al: Pigeon fanciers' lung: Effects of smoking on serum and salivary antibody responses to pigeon antigens. Clin Exp Immunol 113:166–172, 1998.
36. Blanchet MR, Israel-Assayag E, Cormier Y: Inhibitory effect of nicotine on experimental hypersensitivity pneumonitis in vivo and in vitro. Am J Respir Crit Care Med 169:903–909, 2004.
37. Robbins CS, Dawe DE, Goncharova SI, et al: Cigarette smoke decreases pulmonary dendritic cells and impacts antiviral immune responsiveness. Am J Respir Cell Mol Biol 30:202–211, 2004.
38. Sopori M: Effects of cigarette smoke on the immune system. Nat Rev Immunol 2:372–377, 2002.
39. Ohtsuka Y, Munakata M, Tanimura K, et al: Smoking promotes insidious and chronic farmer's lung disease, and deteriorates the clinical outcome. Intern Med 34:966–971, 1995.
40. Fan LL: Hypersensitivity pneumonitis in children. Curr Opin Pediatr 14:323–326, 2002.
41. Stauffer Ettlin M, Pache JC, Renevey F, et al: Bird breeder's disease: A rare diagnosis in young children. Eur J Pediatr 165:55–61, 2006.
42. Ratjen F, Costabel U, Griese M, et al: Bronchoalveolar lavage fluid findings in children with hypersensitivity pneumonitis. Eur Respir J 21:144–148, 2003.
43. Prince JE, Kheradmand F, Corry DB: Immunologic lung disease. J Allergy Clin Immunol 111(2 Suppl):S613–S623, 2003.
44. McSharry C, Anderson K, Bourke SJ, et al: Takes your breath away—The immunology of allergic alveolitis. Clin Exp Immunol 128:3–9, 2002.
45. Schuyler M, Gott K, Cherne A: Mediators of hypersensitivity pneumonitis. J Lab Clin Med 136:29–38, 2000.
46. Schuyler M, Gott K, Cherne A: Experimental hypersensitivity pneumonitis: Role of MCP-1. J Lab Clin Med 142:187–195, 2003.
47. Calhoun WJ: Enhanced reactive oxygen species metabolism of air space cells in hypersensitivity pneumonitis. J Lab Clin Med 117:443–452, 1991.
48. Chen B, Tong Z, Nakamura S, et al: Production of IL-12, IL-18 and TNF-alpha by alveolar macrophages in hypersensitivity pneumonitis. Sarcoidosis Vasc Diffuse Lung Dis 21:199–203, 2004.
49. Gudmundsson G, Hunninghake GW: Interferon-gamma is necessary for the expression of hypersensitivity pneumonitis. J Clin Invest 99:2386–2390, 1997.
50. Taniguchi M, Harada M, Kojo S, et al: The regulatory role of Valpha14 NKT cells in innate and acquired immune response. Annu Rev Immunol 21:483–513, 2003.
51. Barrera L, Mendoza F, Zuniga J, et al: Functional diversity of T-cell subpopulations in subacute and chronic hypersensitivity pneumonitis. Am J Respir Crit Care Med 177:44–55, 2008.
52. Sempowski GD, Derdak S, Phipps RP: Interleukin-4 and interferon-gamma discordantly regulate collagen biosynthesis by functionally distinct lung fibroblast subsets. J Cell Physiol 167:290–296, 1996.
53. Liu X, Kohyama T, Wang H, et al: Th2 cytokine regulation of type I collagen gel contraction mediated by human lung mesenchymal cells. Am J Physiol Lung Cell Mol Physiol 282:L1049–L1056, 2002.
54. Muers MF, Faux JA, Ting A, et al: HLA-A, B, C and HLA-DR antigens in extrinsic allergic alveolitis (budgerigar fancier's lung disease). Clin Allergy 12:47–53, 1982.
55. Rittner C, Sennekamp J, Mollenhauer E, et al: Pigeon breeder's lung: Association with HLA-DR 3. Tissue Antigens 21:374–379, 1983.
56. Selman M, Teran L, Mendoza A, et al: Increase of HLA-DR7 in pigeon breeder's lung in a Mexican population. Clin Immunol Immunopathol 44:63–70, 1987.
57. Selman M, Pardo A, Barrera L, et al: Gene expression profiles distinguish idiopathic pulmonary fibrosis from hypersensitivity pneumonitis. Am J Respir Crit Care Med 173:188–198, 2006.
58. Glass WG, Rosenberg HF, Murphy PM: Chemokine regulation of inflammation during acute viral infection. Curr Opin Allergy Clin Immunol 3:467–473, 2003.
59. Gudmundsson G, Monick MM, Hunninghake GW: Viral infection modulates expression of hypersensitivity pneumonitis. J Immunol 162:7397–7401, 1999.
60. Dakhama A, Hegele RG, Laflamme G, et al: Common respiratory viruses in lower airways of patients with acute hypersensitivity pneumonitis. Am J Respir Crit Care Med 159:1316–1322, 1999.
61. Ohtani Y, Saiki S, Kitaichi M, et al: Chronic bird fancier's lung: Histopathological and clinical correlation. An application of the 2002 ATS/ERS consensus classification of the idiopathic interstitial pneumonias. Thorax 60:665–671, 2005.
62. Hayakawa H, Shirai M, Sato A, et al: Clinicopathological features of chronic hypersensitivity pneumonitis. Respirology 7:359–364, 2002.
63. Vourlekis JS, Schwarz MI, Cool CD, et al: Nonspecific interstitial pneumonitis as the sole histologic expression of hypersensitivity pneumonitis. Am J Med 112:490–493, 2002.
64. Churg A, Muller NL, Flint J, et al: Chronic hypersensitivity pneumonitis. Am J Surg Pathol 30:201–208, 2006.
65. Coleman A, Colby TV: Histologic diagnosis of extrinsic allergic alveolitis. Am J Surg Pathol 12:514–518, 1988.
66. Cheung OY, Muhm JR, Helmers RA, et al: Surgical pathology of granulomatous interstitial pneumonia. Ann Diagn Pathol 7:127–138, 2003.
67. Hanak V, Golbin JM, Ryu JH: Causes and presenting features in 85 consecutive patients with hypersensitivity pneumonitis. Mayo Clin Proc 82:812–816, 2007.
68. Morell F, Roger A, Reyes L, et al: Bird fancier's lung: A series of 86 patients. Medicine (Baltimore) 87:110–130, 2008.
69. Fenoglio CM, Reboux G, Sudre B, et al: Diagnostic value of serum precipitins to mould antigens in active hypersensitivity pneumonitis. Eur Respir J 29:706–712, 2007.
70. Patel AM, Ryu JH, Reed CE: Hypersensitivity pneumonitis: Current concepts and future questions. J Allergy Clin Immunol 108:661–670, 2001.

71. Aberer W, Woltsche M, Woltsche-Kahr I, et al: IgG antibodies typical for extrinsic allergic alveolitis—An inter-laboratory quality assessment. Eur J Med Res 6:498–504, 2001.
72. Morell F, Codina R, Rodrigo MJ: Increased positivity of skin test and allergenic stability of glycerinated soybean hull extracts. Clin Exp Allergy 29:388–393, 1999.
73. Morell F, Roger A, Cruz MJ: Usefulness of specific skin tests in the diagnosis of hypersensitivity pneumonitis. J Allergy Clin Immunol 110:939, 2002.
74. Bandoh S, Fujita J, Ohtsuki Y, et al: Sequential changes of KL-6 in sera of patients with interstitial pneumonia associated with polymyositis/dermatomyositis. Ann Rheum Dis 59:257–262, 2000.
75. Kohno N: Serum marker KL-6/MUC1 for the diagnosis and management of interstitial pneumonitis. J Med Invest 46:151–158, 1999.
76. Kohno N, Awaya Y, Oyama T, et al: KL-6, a mucin-like glycoprotein, in bronchoalveolar lavage fluid from patients with interstitial lung disease. Am Rev Respir Dis 148:637–642, 1993.
77. Janssen R, Sato H, Grutters JC, et al: Study of Clara cell 16, KL-6, and surfactant protein-D in serum as disease markers in pulmonary sarcoidosis. Chest 124:2119–2125, 2003.
78. Janssen R, Grutters JC, Sato H, et al: Analysis of KL-6 and SP-D as disease markers in bird fancier's lung. Sarcoidosis Vasc Diffuse Lung Dis 22:51–57, 2005.
79. Takahashi T, Munakata M, Ohtsuka Y, et al: Serum KL-6 concentrations in dairy farmers. Chest 118:445–450, 2000.
80. Richerson HB, Bernstein IL, Fink JN, et al: Guidelines for the clinical evaluation of hypersensitivity pneumonitis. Report of the Subcommittee on Hypersensitivity Pneumonitis. J Allergy Clin Immunol 84:839–844, 1989.
81. Morais A, Winck JC, Delgado L, et al: Suberosis and bird fancier's disease: A comparative study of radiological, functional and bronchoalveolar lavage profiles. J Investig Allergol Clin Immunol 14:26–33, 2004.
82. Jaakkola J, Partanen K, Terho EO, et al: Radiographic grading of extrinsic allergic alveolitis. A comparison between a modified ILO classification and a descriptive method. Acta Radiol 32:461–466, 1991.
83. Akira M, Kita N, Higashihara T, et al: Summer-type hypersensitivity pneumonitis: Comparison of high-resolution CT and plain radiographic findings. AJR Am J Roentgenol 158:1223–1228, 1992.
84. Tomiyama N, Muller NL, Johkoh T, et al: Acute parenchymal lung disease in immunocompetent patients: Diagnostic accuracy of high-resolution CT. AJR Am J Roentgenol 174:1745–1750, 2000.
85. Johkoh T, Muller NL, Cartier Y, et al: Idiopathic interstitial pneumonias: Diagnostic accuracy of thin-section CT in 129 patients. Radiology 211:555–560, 1999.
86. Glazer CS, Rose CS, Lynch DA: Clinical and radiologic manifestations of hypersensitivity pneumonitis. J Thorac Imaging 17:261–272, 2002.
87. Raoof S, Naidich DP: Imaging of unusual diffuse lung diseases. Curr Opin Pulm Med 10:383–389, 2004.
88. Lynch DA, Rose CS, Way D, et al: Hypersensitivity pneumonitis: Sensitivity of high-resolution CT in a population-based study. AJR Am J Roentgenol 159:469–472, 1992.
89. Nasser-Sharif FJ, Balter MS: Hypersensitivity pneumonitis with normal high resolution computed tomography scans. Can Respir J 8:98–101, 2001.
90. Ng CS, Desai SR, Rubens MB, et al: Visual quantitation and observer variation of signs of small airways disease at inspiratory and expiratory CT. J Thorac Imaging 14:279–285, 1999.
91. Hansell DM, Wells AU, Padley SP, et al: Hypersensitivity pneumonitis: Correlation of individual CT patterns with functional abnormalities. Radiology 199:123–128, 1996.
92. Hanak V, Golbin JM, Hartman TE, et al: High-resolution CT findings of parenchymal fibrosis correlate with prognosis in hypersensitivity pneumonitis. Chest 134:133–138, 2008.
93. Sahin H, Brown KK, Curran-Everett D, et al: Chronic hypersensitivity pneumonitis: CT features comparison with pathologic evidence of fibrosis and survival. Radiology 244:591–598, 2007.
94. Cormier Y, Brown M, Worthy S, et al: High-resolution computed tomographic characteristics in acute farmer's lung and in its follow-up. Eur Respir J 16:56–60, 2000.
95. Malinen AP, Erkinjuntti-Pekkanen RA, Partanen PL, et al: Long-term sequelae of farmer's lung disease in HRCT: A 14-year follow-up study of 88 patients and 83 matched control farmers. Eur Radiol 13:2212–2221, 2003.
96. Franquet T, Hansell DM, Senbanjo T, et al: Lung cysts in subacute hypersensitivity pneumonitis. J Comput Assist Tomogr 27:475–478, 2003.
97. Silva CI, Muller NL, Lynch DA, et al: Chronic hypersensitivity pneumonitis: Differentiation from idiopathic pulmonary fibrosis and nonspecific interstitial pneumonia by using thin-section CT. Radiology 246:288–297, 2008.
98. Ohtani Y, Kojima K, Sumi Y, et al: Inhalation provocation tests in chronic bird fancier's lung. Chest 118:1382–1389, 2000.
99. Cormier Y, Belanger J, Laviolette M: Prognostic significance of bronchoalveolar lymphocytosis in farmer's lung. Am Rev Respir Dis 135:692–695, 1987.
100. Morell F, Reyes L, Domenech G, et al: [Diagnoses and diagnostic procedures in 500 consecutive patients with clinical suspicion of interstitial lung disease] (Spanish). Arch Bronconeumol 44:185–191, 2008.
101. Vourlekis JS, Schwarz MI, Cherniack RM, et al: The effect of pulmonary fibrosis on survival in patients with hypersensitivity pneumonitis. Am J Med 116:662–668, 2004.
102. Lacasse Y, Selman M, Costabel U, et al: Clinical diagnosis of hypersensitivity pneumonitis. Am J Respir Crit Care Med 168:952–958, 2003.
103. Trahan S, Hanak V, Ryu JH, et al: Role of surgical lung biopsy in separating chronic hypersensitivity pneumonia from usual interstitial pneumonia/idiopathic pulmonary fibrosis: Analysis of 31 biopsies from 15 patients. Chest 134:126–132, 2008.
104. Terho EO: Diagnostic criteria for farmer's lung disease. Am J Ind Med 10:329, 1986.
105. Cormier Y: Hypersensitivity pneumonitis. *In* Rom W (ed): Environmental & Occupational Medicine. Philadelphia: Lippincott-Raven, 1998, p 457.
106. Tasaka S, Kanazawa M, Kawai C, et al: Fatal diffuse alveolar damage from bird fanciers' lung. Respiration 64:307–309, 1997.
107. Erkinjuntti-Pekkanen R, Rytkonen H, Kokkarinen JI, et al: Long-term risk of emphysema in patients with farmer's lung and matched control farmers. Am J Respir Crit Care Med 158:662–665, 1998.
108. Lalancette M, Carrier G, Laviolette M, et al: Farmer's lung. Long-term outcome and lack of predictive value of bronchoalveolar lavage fibrosing factors. Am Rev Respir Dis 148:216–221, 1993.
109. Kokkarinen JI, Tukiainen HO, Terho EO: Asthma in patients with farmer's lung during a five-year follow-up. Scand J Work Environ Health 23:149–151, 1997.
110. de Gracia J, Morell F, Bofill JM, et al: Time of exposure as a prognostic factor in avian hypersensitivity pneumonitis. Respir Med 83:139–143, 1989.
111. Hoppin JA, Umbach DM, Kullman GJ, et al: Pesticides and other agricultural factors associated with self-reported farmer's lung among farm residents in the Agricultural Health Study. Occup Environ Med 64:334–341, 2007.
112. Bang KM, Weissman DN, Pinheiro GA, et al: Twenty-three years of hypersensitivity pneumonitis mortality surveillance in the United States. Am J Ind Med 49:997–1004, 2006.
113. Yoshida K, Ando M, Sakata T, et al: Prevention of summer-type hypersensitivity pneumonitis: Effect of elimination of *Trichosporon cutaneum* from the patients' homes. Arch Environ Health 44:317–322, 1989.
114. Woodard ED, Friedlander B, Lesher RJ, et al: Outbreak of hypersensitivity pneumonitis in an industrial setting. JAMA 259:1965–1969, 1988.
115. Craig TJ, Hershey J, Engler RJ, et al: Bird antigen persistence in the home environment after removal of the bird. Ann Allergy 69:510–512, 1992.
116. Kokkarinen JI, Tukiainen HO, Terho EO: Effect of corticosteroid treatment on the recovery of pulmonary function in farmer's lung. Am Rev Respir Dis 145:3–5, 1992.
117. Losa Garcia JE, Mateos Rodriguez F, Jimenez Lopez A, et al: Effect of cyclosporin A on inflammatory cytokine production by human alveolar macrophages. Respir Med 92:722–728, 1998.
118. Anderson K, Walker A, Boyd G: The long-term effect of a positive pressure respirator on the specific antibody response in pigeon breeders. Clin Exp Allergy 19:45–49, 1989.

CHAPTER 67

INDOOR AND OUTDOOR AIR POLLUTION

Mark D. Eisner, MD, MPH • John R. Balmes, MD

INTRODUCTION

AIR POLLUTANTS

Pollutants—What They Are and Why They Matter

General Properties, Sources, and Distribution of Pollutants

MECHANISMS OF DEFENSE AGAINST AIR POLLUTION–RELATED RESPIRATORY EFFECTS

Deposition of and Clearance of Particles

Gases—Deposition and Damage Is a Function of Solubility

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METHODS OF STUDYING THE HEALTH EFFECTS OF AIR POLLUTION

Epidemiologic Studies

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Air Pollution Studies—Putting It All Together

INDOOR AIR POLLUTION

Sources of Indoor Pollution

Indoor Combustion: The Major Source of Indoor Air Pollution

Secondhand Smoke and Obstructive Lung Disease

Gas Stove Exposure: A Cause of Asthma Exacerbation?

Wood Smoke Exposure—Respiratory Health Effects

Respiratory Effects of Kerosene Heater Use

Other Indoor Pollutants—The "Toxic" Indoor Environment

OUTDOOR AIR POLLUTION—ADVERSE RESPIRATORY EFFECTS OF SPECIFIC POLLUTANTS

Particulate Matter

Sulfur Dioxide

Nitrogen Dioxide

Ozone

INTRODUCTION

Catastrophic air pollution events in the Meuse Valley of Belgium (1930), Donora, Pennsylvania (1948), and London, England (1952), occurred when air stagnation caused very high levels of ambient pollutants, especially sulfur dioxide and particles. In each case, there was a marked increase in respiratory symptoms and mortality. These "fog disasters" provided incontrovertible evidence that air pollution can have immediate lethal consequences. Since this time, scientific investigations have uncovered a myriad of adverse respiratory health effects of air pollution, ranging from asthma exacerbation to respiratory mortality.

The respiratory system, because it is the portal of entry for air pollutants, suffers the major consequences of air pollution. This chapter reviews the key air pollutants, which are termed *criteria pollutants* by the U.S. Environmental Protection Agency (EPA), and how they affect the airways and lungs (Table 67-1). Both indoor and outdoor air pollution are considered. Respiratory health conditions that are most strongly linked with air pollution are reviewed.

AIR POLLUTANTS

Pollutants—What They Are and Why They Matter

Pollutants are substances that are present in the environment that can damage the physical environment or the living organisms that reside within it. Although pollution can include energy, such as noise, heat, or light, we

consider only chemical pollution in this chapter. Chemical pollution, which includes gas and particles, consists of either foreign substances introduced into the environment or naturally occurring substances that exceed levels that occur in nature in the absence of human intervention. Air pollution, which is a subset of chemical pollution, originates from mobile sources (e.g., vehicular traffic), stationary sources (e.g., factories, power plants, and refineries), and indoor sources (e.g., building materials, gas stoves, passive smoking, and cleaning products).[1–3]

Toxic air pollutants (air toxics) are a subset of air pollutants that may cause cancer or other serious health effects such as birth defects. These substances, such as benzene and cadmium, produce primarily nonrespiratory effects despite having the respiratory tract as a major portal of entry.

The major types of air pollutants that affect the respiratory system are sulfur dioxide (SO_2), nitrogen dioxide (NO_2), particles, and ozone (O_3) (Table 67-2). The principal sources of these pollutants are mobile and stationary sources. Ozone is a secondary pollutant that arises from the action of sunlight on nitrogen oxides and hydrocarbons present in motor vehicle exhaust. It is a major component of photochemical pollution or "smog." The respiratory health effects of these pollutants are considered later in the chapter. Carbon monoxide, which also enters via the respiratory tract, has primarily nonpulmonary toxicity and is not considered further in this chapter.

Indoor air quality has assumed increasing importance. As levels of outdoor ambient air pollution have decreased in many areas throughout the United States, the relative impact of indoor air pollution has increased. Moreover, North American residents spend the majority of their time indoors, increasing their exposure to indoor air pollutants.[4,5] At the same time, changes in home and office building construction have resulted in lower air exchange rates, increasing the levels of pollutants emitted indoors.[6] To adequately characterize personal exposure to air pollution, indoor air quality must be taken into account (see Fig. 67-1 later).

TABLE 67-1. National Primary Air Quality Standards in the United States (Criteria Pollutants)

Pollutant	Standard	Averaging Period
Carbon monoxide	9 ppm (10 mg/m^3)	8 hours
	35 ppm (40 mg/m^3)	1 hour
Nitrogen dioxide	0.053 ppm (100 μg/m^3)	1 year
Ozone	0.12 ppm	1 hour
	0.075 ppm	8 hours
Particulate matter <10 μm (PM_{10})	150 μg/m^3	24 hours
Particulate matter <2.5 μm ($PM_{2.5}$)	15 μg/m^3	1 year
	35 μg/m^3	24 hours
Sulfur dioxide	0.03 ppm (80 μg/m^3)	1 year
	0.14 ppm (365 μg/m^3)	24 hours
Lead	0.15 μg/m^3	Rolling 3-month average
	1.5 μg/m^3	3 months

General Properties, Sources, and Distribution of Pollutants

Sulfur oxides, particulate matter (PM), O_3, and NO_2 are the most widely encountered pollutants that cause adverse pulmonary health effects.[1–3] Sulfur dioxide is produced by the combustion of sulfur contained in fossil fuels such as coal and crude oil. The major sources of SO_2 pollution are power plants, oil refineries, smelters, and paper pulp mills. In the United States, SO_2 levels are generally higher in the northeastern and midwestern states, because sulfur-containing coal is used in power plants. Sulfur dioxide itself is a clear, highly water-soluble gas, so it is effectively absorbed by the mucosal surfaces of the upper airways. A very small proportion of inhaled SO_2 reaches the distal regions of the lungs, but susceptible persons with asthma may still suffer adverse respiratory health effects.[7,8] The SO_2 released into the atmosphere does not, however, remain uniquely in the form of a gas; rather, it undergoes chemical reactions with water, trace metals, and other pollutants to form

TABLE 67-2. Major Pollutants Associated with Adverse Pulmonary Effects

Pollutant	Outdoor Sources	Indoor Sources	Adverse Effects
Sulfur oxides	Power plants, oil refineries, smelters	Kerosene space heaters	Bronchoconstriction
Oxides of nitrogen	Motor vehicle exhaust, power plants, oil refineries	Gas stoves and furnaces, kerosene space heaters	Airway injury (respiratory bronchiolitis), impaired lung defenses, enhanced response to allergens
Ozone	Motor vehicle exhaust	Aircraft cabins, welding, copiers, ozone generators	Airway injury (respiratory bronchiolitis), decreased lung function, exacerbations of asthma, enhanced response to allergen
Particulate matter	Motor vehicle exhaust, power plants	Tobacco and wood smoke	Exacerbations of asthma and chronic obstructive pulmonary disease, increased cardiopulmonary mortality
Radon		Residential basements	Lung cancer
Polycyclic hydrocarbons	Diesel exhaust	Tobacco smoke	Lung cancer

particulate aerosols. The nature of particles generated from sulfur-containing fuels varies geographically, but sulfuric acid and various metallic, acidic, and ammonium sulfates are commonly present. The mixture of sulfur oxides and small particles may be blown great distances from its site of production, undergoing continuous transformation from gas to particle phase and ultimately becoming "acid rain" capable of profoundly affecting flora and fauna.[9]

In the western United States and many other areas of the world, particulate pollution is not driven by the combustion of sulfur-containing fuels. Atmospheric particulate air pollution arises from a variety of sources, including both natural (e.g., sea spray, windblown dust) and synthetic (e.g., power plants, motor vehicles) sources.[10,11] Moreover, particulate material that enters the atmosphere can be primary (particles emitted directly) or secondary (particles that form by complicated chemical reactions that occur in the atmosphere and involve gas-phase precursors such as SO_2 and nitrogen oxides). In North America, secondary particles comprise most of the fine-particle pollution.

Epidemiologic studies have focused on the size of particles in terms of aerodynamic diameter. Most particles have irregular shapes with geometric diameters that cannot be easily measured. The aerodynamic diameter is the diameter of a perfect sphere of unit density (1 g/mL) that has the same aerodynamic properties (e.g., settling velocity) as the particle in question. Larger particles are filtered in the nose and throat, but particles less than 10 μm in diameter (i.e., PM_{10}) can be deposited in the respiratory tract.[10,11] Fine particles, which are less than 2.5 μm in diameter ($PM_{2.5}$), penetrate the alveoli, and ultrafine particles ($PM_{0.1}$) can pass through the alveoli and spread to other organs.

Particle size also determines how far they travel and persist in the environment. Particles classified as "fine" (<2.5 μm) can travel for long distances and remain in the atmosphere for days to weeks; "coarse" particles (>2.5 μm) travel for rather short distances and have atmospheric half-lives of minutes to hours.[12] "Ultrafine" particles (<0.1 μm) are typically generated from combustion processes and have short atmospheric half-lives. For example, the concentration of ultrafine particles emitted from motor vehicles on a major roadway has a rapid falloff with distance from the roadway; the concentration is back to the background level at or beyond 300 m.[12]

Coarse particles (PM_{10}) are composed primarily of crustal (rock, soil), biologic (pollen, spores), and industrial components; they are formed primarily by mechanical processes that produce small particles from larger particles. Fine particles ($PM_{2.5}$) are composed mainly of varying amounts of water and six major components (sulfates, acids, nitrates, elemental carbon, organic carbon, and trace metals), several of which can be further subdivided on the basis of chemical constituents and sources.[13] They are formed from gases by nucleation, condensation, or liquid-phase reactions.

Ozone and nitrogen oxides arise primarily from the action of sunlight on emissions from internal combustion engines used by motor vehicles.[14] The most important of these products are unburned hydrocarbons and NO_2, which is an oxidation product of nitrogen oxide. In turn, nitrogen oxide arises from the fixation of atmospheric nitrogen with oxygen under conditions of high-temperature combustion. Ultraviolet irradiation of this mixture in the atmosphere results in a complex series of chemical reactions, producing O_3, alkyl nitrates, peroxyacyl nitrates, alcohols, ethers, acids, peroxyacids, and other organic and inorganic compounds that exist in both gas and particulate aerosol phases.[14] This mixture of pollutants typifies the "smog" found in areas with large numbers of automobiles and abundant sunlight, such as the Los Angeles basin.

Because O_3 and NO_2 are the gases present in highest concentration and they clearly cause toxic effects in animals and humans, they have been the oxidant pollutants most extensively studied. Both gases are relatively insoluble and poorly absorbed by the upper airways. A high proportion of the inhaled dose therefore reaches the peripheral portion of the lungs and can cause injury at any site from the upper airways to the alveoli.[15,16]

Outdoor urban air contains a number of known carcinogens, including polycyclic hydrocarbons, *n*-nitroso compounds, and asbestos. The concentrations of these carcinogens in ambient air, however, are quite low. Diesel exhaust, in particular, contains particles with polycyclic hydrocarbons as constituents. Epidemiologic studies have provided consistent evidence of an excess risk of lung cancer in workers exposed to diesel exhaust; it is a probable carcinogen in humans.[17–20] Several large population-based epidemiologic studies also have also linked lung cancer to long-term exposure to particulates, SO_2, and O_3 pollution.[21–25]

Although most attention has been given to pollutants present in outdoor air, it is now apparent that elevated concentrations of airborne contaminants are common inside homes, public buildings, and other indoor microenvironments.[6,26] There are two reasons why indoor air pollution has become an important determinant of health risk: (1) residents of the United States and other developed countries spend the majority of their time indoors, and (2) there are point sources of pollution indoors, such as secondhand cigarette smoke and gas stove use, that greatly increase the concentration of pollutants compared to outdoor air. Both indoor and outdoor pollution must be considered when assessing the total health effects of air pollution.

MECHANISMS OF DEFENSE AGAINST AIR POLLUTION–RELATED RESPIRATORY EFFECTS

The respiratory system, which encounters a myriad of particles and gases daily, has evolved an effective defense system for removing impurities from inhaled air. The various mechanisms of defense are interrelated and work in a coordinated manner. A perturbation of any defense mechanism, whether because of congenital deficiency, disease, or the effect of an inhaled pollutant itself, may

result in the breakdown of the coordinated defense system and the development of disease.

Deposition of and Clearance of Particles

The size of particles determines their site of deposition in the respiratory tract.[27] Large particles (diameter > 10 μm) are efficiently removed in the nose by simple filtration via the cilia. Those particles that are not removed by filtration will largely be deposited by a process termed *impaction.* The pathway through the nose, mouth, and branching airways is tortuous. Because inhaled particles cannot easily change direction to follow the abrupt changes in the pathway of airflow, they impact on the mucosa of the upper and lower respiratory tract. Airway bifurcations are especially prone to particle impaction. The complementary mechanisms of filtration and impaction are very efficient, so that few particles more than 10 μm reach the lower respiratory tract.

Smaller particles are less affected by filtration and impaction; the sites of their deposition are more determined by the processes of sedimentation and diffusion.[27] Sedimentation is the tendency for particles to fall at a constant rate under the influence of gravity. It is strongly influenced by particle density, particle diameter, and the viscosity of the surrounding gas. As air moves deeper into the lung, the airflow rate decreases and particles fall out of the air stream under the influence of gravity. Sedimentation is the predominant mechanism for deposition of particles of intermediate size (0.5 to 3.0 μm) in the smaller bronchi, bronchioles, and alveoli.

The smallest particles (<0.5 μm), however, are deposited by the mechanism of diffusion. These particles have random (brownian) motion and will impact the airway mucosa in the terminal bronchioles and alveoli, removing them from the stream of inspired air.

The pattern of breathing can influence the deposition of particles. A higher respiratory rate increases the velocity of airflow, promoting impaction of particles in the more proximal airways. Conversely, increased tidal volume results in deeper lung penetration by particles; because the respiratory rate is usually slower, there is more time for diffusion and sedimentation to deposit particles in the distal airways and alveoli.

After particles are deposited in the tracheobronchial tree, cough and mucociliary clearance are the most important mechanisms of defense. Cough is most effective for clearing particles that are deposited in the larger, more central airways. It is provoked by stimulation of afferent nerves that are most densely present in the mucosa of the larynx and branching points of the tracheobrochial tree, at which particles are most likely to be deposited.[28]

The "mucociliary escalator" is a critical system for clearing particles that are deposited in the trachobronchial tree; it operates over the respiratory tract from the proximal trachea to the terminal bronchioles. The mucus blanket is the product of secretion by goblet cells and serous cells of the epithelium and by the mucus cells and serous cells of the submucosal glands. The mucus blanket is propelled mouthward by the coordinated beating of epithelial cell cilia. The effective removal of particles by the mucociliary system thus requires secretion of glycoproteins by specialized secretory cells, maintenance of liquefaction by the transport of water and solute by airway epithelial cells, and coordinated function of airway cilia. Impairment of any of these functions, whether by congenital or acquired diseases affecting mucus or water secretion (e.g., cystic fibrosis, chronic bronchitis) or ciliary function (e.g., dysmotile cilia syndrome), leads to longer residence of particles in the airway and a greater likelihood of adverse health effects.

Some particles will be deposited in the distal airway and alveoli, beyond the reach of the mucociliary escalator. The central mechanism for clearing these particles involves the alveolar macrophage, which phagocytoses particles that are deposited in the gas-exchanging parts of the lung and either digests them or migrates to the respiratory bronchiole and ascends the mucociliary escalator. A smaller number of particle-laden macrophages migrate to peribronchial or perivascular connective tissue, which is a slow method of clearance that takes many weeks. Because macrophages are the primary phagocyte for inhaled PM, the carbon content of macrophages has been used as a biomarker of exposure to particulate pollution in epidemiologic studies.[29]

Gases—Deposition and Damage Is a Function of Solubility

For gaseous pollutants such as O_3, NO_2, and SO_2,the site of deposition in the respiratory tract is largely a function of its water solubility. For highly soluble gases, the nose serves an important defensive function, because the air inhaled transnasally is passed over the large, irregular surface of the turbinates. The promotion of turbulent flow prolongs contact with the mucosal surface, increasing adsorption. Under conditions of quiet breathing, when most air is inspired transnasally, this is an efficient system for removal. For example, the concentration of SO_2 that reaches the glottis is less than 2% of the concentration inspired at the nose.[30] Under other circumstances, the importance of the nose diminishes. The more rapid the inspiratory flow rate, the smaller the proportion of SO_2 removed. Furthermore, the mouth is substantially less efficient at absorbing gases than is the nose, and the proportion of air inhaled through the mouth increases as the ventilatory demands of exercise rise. Therefore, the dose of a soluble pollutant delivered to the lower airways is increased by exercise for three reasons: the inspiratory flow is higher, the proportion inhaled through the mouth is increased, and the total quantity inhaled over time is greater. The importance of the level of ventilation, which depends on the level of exercise, and of the oral-nasal distribution of breathing has perhaps best been shown in studies of the bronchoconstrictor response to SO_2, in which the greatest responses occur during oral breathing and the smallest responses during nasal breathing.[31] In addition, people with obstructive nasal disease also appear to be at greater

risk for adverse respiratory effects of soluble pollutant gases.

Oxidative Stress

Air pollution, especially particles and O_3, can increase the oxidative burden of the lung. To minimize oxidant damage to biologic molecules, the human lung has an integrated antioxidant system of enzymatic and expendable soluble antioxidants. This system includes several antioxidant defense mechanisms that detoxify reactive products or convert them to products that are quenched by other antioxidants. If the oxidant burden is sufficiently great, the reactive species may overwhelm or inactivate the antioxidant system. An imbalance between the production of reactive oxygen species (ROS) and reactive nitrogen species and antioxidant capacity leads to a state of "oxidative stress" that contributes to the pathogenesis of several respiratory diseases.[32,32a]

When imbalance occurs, the excess oxygen species induce a cellular stress response that activates a number of the redox-sensitive signaling cascades. This initial response is mediated in large part through the transcription factor nuclear factor erythroid 2–related factor 2, which leads to transcriptional activation of more than 200 antioxidant and detoxification enzymes that are collectively known as the phase 2 response.[33] Examples of phase 2 enzymes include heme oxygenase 1, glutathione-*S*-transferase isoenzymes, NADPH quinone oxidoreductase, catalase, superoxide dismutase, and glutathione peroxidase. If phase 2 responses fail to prevent a further increase in ROS production, damage to major cellular components, including membrane lipids, protein, carbohydrates, and DNA, will occur and inflammation and tissue damage may ensue.

There is also a connection between oxidative stress and inflammation in the lung. Proinflammatory effects are mediated by the redox-sensitive mitogen-activated protein kinase and nuclear factor-κB cascades that are responsible for the expression of cytokines, chemokines, and adhesion molecules.[34] Cytotoxic effects are associated with mitochondrial membrane damage, which leads to release of factors that induce apoptosis of lung cells.[35] Pathophysiologic consequences of pollutant-induced oxidant injury include airway inflammation leading to clinical exacerbation of asthma, increased susceptibility to infection, enhanced allergic responses and, if repetitive or chronic, airway remodeling.

METHODS OF STUDYING THE HEALTH EFFECTS OF AIR POLLUTION

In order to develop sound public policy aimed at protecting the public from the adverse health effects of pollutants, scientific studies are necessary both to elucidate the health effects of various pollutants and to define the threshold level at which the risk substantively increases. The scientific basis of public policy is based on several lines of evidence: epidemiologic studies of the association between air pollution exposure and occurrence of disease in the population, controlled human exposure studies conducted in the laboratory, effects of pollutants on lung structure and function in animals, and in vitro studies of toxicity. Each of these study types has advantages and disadvantages, and none alone can provide irrefutable proof of harmful effects from a particular pollutant under naturalistic conditions of exposure (Table 67-3). Standards are based, therefore, on the coherence of evidence provided by epidemiologic, clinical, animal, and in vitro research and are set to provide a margin of safety. Even so, it is recognized that harmful effects may occur in sensitive subgroups of the population even with exposure to lower levels of pollution.

Epidemiologic Studies

Epidemiologic studies have a special role in the evaluation of air pollution–related health effects, because they are the only method for studying the impact of air

TABLE 67-3. Methods for Studying Air Pollution

Method	Strengths	Weaknesses
Epidemiologic study	• Representative sample of general population • Naturalistic exposure • Broad range of pollutants • Wide range of health outcomes • Study of susceptible subgroups	• Chance, bias, confounding are threats to study validity • Difficulty separating effects of individual pollutants when they occur as multipollutant mixtures • Usually no information on biologic mechanisms
Controlled human exposure study	• Rigorous experimental design • Elimination of bias and confounding • Systematic control of exposure levels • Study of susceptible subgroups	• Acute effects do not necessarily predict chronic effects • Limited range of exposures and outcomes evaluated
Animal study	• Best method for evaluating impact of pollutants on structure and function of lung • Dose-response relationship (from minimal level producing health effects to death)	• Large interspecies response to pollutants • Applicability to humans often uncertain
In vitro study	• Elucidate cellular mechanisms • Rigorous experimental control	• Limited to available cell lines • Applicability to intact human organism often uncertain

pollution, as it is actually encountered, on large populations. Consequently, the strengths are the evaluation of a broad range of pollutants, a wide array of health effects, and a representative sample of the larger population. Epidemiologic studies, however, have to adequately address threats to study validity, principally chance, confounding, and other sources of bias. Moreover, epidemiologic studies, while they play a key role in support for regulatory intervention, must be supplemented by clinical, animal, and toxicology data before conclusions can be formulated about the risks of a specific pollutant.

For each putative pollution-related health effect, evidence must be compiled from published literature, synthesized, and evaluated for the likelihood of a causal effect. Typically, the criteria for evaluating whether a particular pollutant (e.g., particulate pollution) causes a specific respiratory disease (e.g., chronic obstructive pulmonary disease [COPD]) are those enumerated by Sir Austin Bradford Hill[36] and used by the U.S. Surgeon General beginning in 1964. These include strength of the association, consistency of the association, specificity of the association, temporal relationship, coherence, biologic plausibility, and exposure-response gradient. In this way, the totality of evidence can be evaluated and conclusions enumerated that provide the basis for regulatory decisions.

The issue of confounding is particularly complex in epidemiologic studies. A confounding variable is one that is associated with both the exposure under study and the outcome and creates the erroneous impression of a causal effect when none actually exists. For example, one might observe an association between a diet low in fruits and vegetables and lung cancer. An important confounder would be smoking, which is associated with both poor diet and lung cancer. In fact, it is smoking, and not poor diet that is the principle cause of lung cancer. Careful control of confounding is necessary to draw the correct conclusions from observed associations in epidemiologic studies.

Modern epidemiologic studies of air pollution–related health effects do account for potential confounding by age, cigarette smoking, occupational exposures, socioeconomic influences, and underlying medical illnesses. However, it is often difficult to be sure that all confounders have been identified and controlled. Since 1990, the use of daily time-series studies has increased, and these studies provide superior control of confounders that do not change over relatively short time periods.[37,38] These studies have led to important advances in the scientific understanding of what respiratory health effects are due to air pollution.

A major difficulty for large-scale epidemiologic studies is that most outdoor environments include a complex mixture of pollutants. Consequently, the several pollutants may interact to promote disease causation. Studying individual pollutants, one by one, might miss important health effects of exposure to the mixture of pollutants. A related issue is "multi-collinearity," which arises because air pollutant concentrations are correlated with one another, making it difficult to parse out the individual health effects of each pollutant. The modern use of multipollutant statistical modeling addresses these issues, but they remain challenges to valid epidemiologic inferences.[39,40]

In epidemiologic studies, the assignment of individual exposures still poses challenges. Many studies estimate individual exposure by mapping each individual subject's home (and sometimes workplace) relative to stationary pollution monitors. Recent advances have also allowed investigators to conduct personal direct monitoring of exposure to specific pollutants, but expense and other logistical considerations remain difficulties of these methods.[41] Another challenge is choosing the metric of exposure that is most relevant to disease causation, because area-based measures can provide multiple exposure metrics (e.g., hourly peaks, hourly averages, and 24-hour averages) for a wide variety of pollutants.

Controlled Human Exposure Research

Experimental studies expose human subjects to pollutants under carefully controlled conditions. Such studies can rigorously evaluate the impact of single or multiple pollutants on acute responses such as lung function or bronchial hyperresponsiveness. In addition to documenting the acute health effects of pollution, controlled human exposure studies can evaluate the minimal concentration of pollutants that causes reduction in lung function or other acute responses. They can also evaluate the effects of exercise, and consequently minute ventilation, on respiratory effects of pollution exposure. Controlled studies can also evaluate the effects of pollutants on susceptible subgroups of the population, such as adults with asthma. Moreover, measurement of biomarkers of inflammation, oxidative stress, and other pathophysiologic processes can provide mechanistic insights.

A major advantage of controlled human exposure studies is the (near) elimination of confounding and bias, because exposures are experimentally induced and carefully controlled. Because these studies evaluate acute effects, however, they cannot, by themselves, be easily extrapolated to the effects of more chronic or recurrent exposure. The finding that a brief exposure to O_3 causes acute decrements in lung function does not, for example, necessarily indicate that prolonged or repeated exposure will lead to the development of COPD. Controlled human exposure studies, when combined with epidemiologic and other study designs, can provide important data for establishing the causal effect of pollution on a respiratory health outcome.

Animal Research

Animal studies offer the most effective opportunity to elucidate the impact of air pollution on changes of lung structure and function. In addition, animal studies permit assessment of the effects of a range of concentrations, so that a dose-response curve can be constructed for outcomes ranging from the first measurable change in lung structure or function to death. Animal studies also afford a unique opportunity to dissect the pathogenetic mechanisms of pollution-related health effects.

The major limitation of animal studies is the large interspecies variations in response to pollutants. As such, applicability of animal studies to humans, especially for dose-response relationships, may not always be clear. Dogs, for example, can tolerate up to 200 ppm of SO_2 without developing significant bronchoconstriction, whereas guinea pigs appear to be especially sensitive to these bronchoconstriction effects.[42] Moreover, common human lung diseases, such as asthma and cystic fibrosis, do not occur in animals, precluding study of these susceptible subgroups for pollution-related effects.

In Vitro Research

Exposure of cell cultures to specific air pollutants has helped to elucidate the mechanisms of lung injury, inflammation, and other adverse respiratory health effects. Specifically, cell culture systems have been used to study the impact of particulate and other air pollutants on inflammatory cytokines, oxidative stress, DNA damage, and cytotoxicity.[43–49] Cultures of bronchial epithelial cells, monocytes, dendritic cells, and other cell lines have been useful for studying the mechanisms of air pollution on the respiratory system.

Air Pollution Studies—Putting It All Together

In sum, there is no single study design or discipline that can establish the health effects of air pollution and provide the basis for regulation. Epidemiologic studies are required, because they evaluate the impact of naturalistically occurring air pollution respiratory health outcomes on members of the general population. The previously mentioned limitations and pitfalls of epidemiologic study design require careful controlled human exposure studies, animal studies, and in vitro studies in order to formulate a conclusion that a specific pollutant causes a specific disease and what level of pollution begins to confer excess risk.

INDOOR AIR POLLUTION

Indoor air quality has been increasingly recognized as an important determinant of air pollution exposure. As levels of outdoor ambient air pollution have decreased in many areas throughout the United States, the relative impact of indoor air pollution has increased. Because North American residents spend the majority of their time indoors, exposure to indoor pollution may have substantive effects on health.[5] To adequately characterize personal exposure to air pollution, indoor air quality must be taken into account (Table 67-4).

Sources of Indoor Pollution

The concentration of indoor air pollutants depend on both indoor and outdoor emission sources (Fig. 67-1).[6,26,50]

TABLE 67-4. Indoor Air Pollutants

Category of Pollutant	Indoor Pollution Source
Combustion	Secondhand smoke
	Gas stoves, ovens, heaters, and fireplaces
	Wood smoke (stoves, fireplaces)
	Kerosene heaters
	Candles and incense
Building materials (emit volatile compounds)	Plywood
	Particle board
	Carpeting
	Paints
Cleaning materials	Bleach, ammonia, detergents

Outdoor emission sources determine outdoor pollution concentrations, which, in turn, can affect indoor air quality. The Six Cities Study clearly demonstrated the impact of outdoor air pollutant concentrations on indoor pollutant concentrations.[51] In addition to outdoor air pollution concentrations, the degree of penetration of outdoor pollution into the indoor environment depends largely on the rate of air infiltration from outdoors to indoors.[52] The rate of air infiltration is a complex function of the "tightness" of building construction and insulation, building location and orientation, number of exterior walls and windows, surrounding terrain and barriers, wind speed and direction, indoor-outdoor temperature gradient, and ventilation system type (e.g., heating, ventilation, and air-conditioning system) and efficiency.[6,26,52]

Time-activity patterns will influence personal exposure. The relative time spent indoors versus outdoors will affect the contribution of indoor pollutants to total personal exposure. Time spent in specific locations within the home will affect exposure to particular pollutants, as the distribution of indoor pollutant concentrations will vary among different zones of a building, especially for pollutants generated indoors.[52] In addition, activity level will affect metabolic rate and ventilatory rate, which will also influence personal exposure to indoor pollutants.[53]

Indoor Combustion: the Major Source of Indoor Air Pollution

Earlier in the chapter, the specific health effects of NO_2, SO_2, particulates, and O_3 were discussed. The major source of indoor pollution is from combustion, particularly secondhand smoke (SHS) exposure, gas stove use, and wood burning in stoves and fireplaces. Kerosene space heaters are also an important source of indoor air pollution. Table 67-4 shows the major indoor pollutants that are released from these sources and are associated with adverse pulmonary effects.

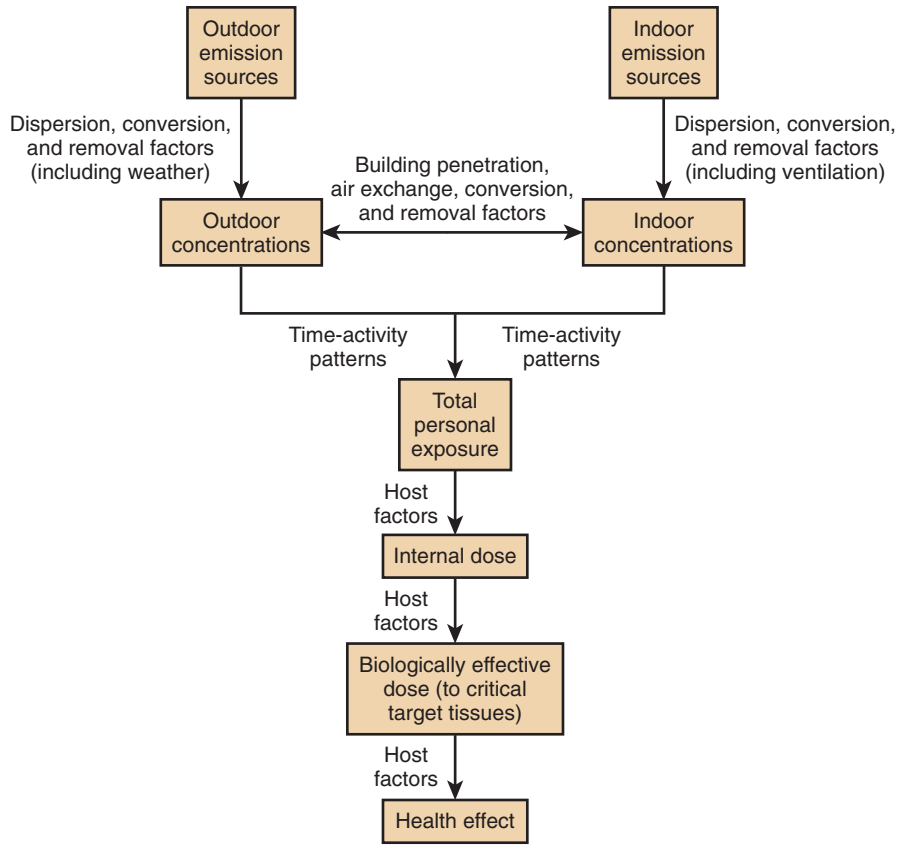

FIGURE 67-1 ■ Relationships among outdoor pollution, indoor pollution, and health effects.

Secondhand Smoke and Obstructive Lung Disease

SHS exposure is perhaps the best known and studied indoor pollutant. Strong evidence implicates it as a cause of lung cancer, coronary heart disease, and decreased life span.[54,55] In addition to these adverse health effects, SHS contains respiratory irritants, such as SO_2, ammonia, acrolein, and formaldehyde.[5] Passive smoking has also been linked with allergic phenomena, such as elevated serum immunoglobulin E levels.[56] As a consequence, SHS has the potential to induce new cases of asthma through irritant or sensitizing mechanisms. Among persons with established asthma, SHS exposure could adversely affect asthma control.

SHS is a complex mixture containing thousands of gas-phase and particulate substances. Of particular note, recent data indicate that passive smoking results in high levels of particulate air pollution. Homes where smoking is allowed have $PM_{2.5}$ levels up to 10 times higher than nonsmoking homes.[57] Workplace exposures can be even higher, especially in bars and casinos.

Numerous studies have evaluated the impact of SHS exposure on childhood asthma induction.[58] The 1997 California Environmental Protection Agency (CalEPA) report included a meta-analysis of 37 studies conducted between 1975 and 1995 that evaluated SHS exposure as a risk factor for induction of childhood asthma. The pooled relative risk for asthma was 1.44 (95% confidence interval [CI], 1.27 to 1.64). These data supported a causal association between environmental tobacco smoke and new onset of childhood asthma cases.[5] Since the CalEPA report, nearly 50 additional studies strongly support the original conclusion that SHS exposure is causally associated with new-onset asthma among children.[59]

SHS exposure also appears to be associated with new-onset asthma in adulthood. Cross-sectional, case-control, and cohort studies have suggested a link between SHS exposure and adult-onset asthma.[60–67] Workplace SHS exposure, in particular, appears to be related to adult asthma induction.[67] The CalEPA report, which was updated in 2006, concluded that the evidence was sufficient to implicate SHS as a cause of adult-onset asthma.[59]

SHS exposure may also cause other respiratory symptoms, such as wheezing, and impaired lung function.[64,68–71] In a cohort of older adults, lifetime home and workplace exposure to SHS was associated with a more rapid decline of lung function during a decade of follow-up.[72] Studies of bartenders, who have high occupational exposures to SHS, have revealed a strong link between SHS and poorer respiratory health. After smoke-free workplace laws were implemented in California, bartenders experienced a reduction of respiratory symptoms, such as cough, wheezing, and dyspnea, and improved lung function.[73] These findings have been replicated in studies from around the world.[74,75]

Beyond asthma induction, SHS exposure is a likely cause of asthma exacerbation in both children and adults. A previous review by the EPA (1992) concluded that: "There is now sufficient evidence to conclude that passive smoking is causally associated with additional episodes and increased severity of asthma in children who already have the disease."[5] Numerous subsequent studies indicate that SHS exposure, which is mostly due to parental smoking, causes increased symptoms, poorer pulmonary function, and other indicators of worsened asthma control among children with established asthma.[59] Similarly, SHS exposure, both at home and at work, appears to cause asthma exacerbation among adults.[69,76–81] Moreover, the negative impact of SHS exposure on pulmonary function appears to be greater among adults with asthma than in the general population.[69,74]

Emerging evidence now suggests that SHS exposure may also be a cause of COPD independent of personal cigarette smoking. A population-based study from the United States found that both cumulative home and work SHS exposure were associated with a greater risk of COPD, controlling for potential confounders.[82] A recent study from China found that self-reported cumulative lifetime SHS exposure at home and work was related to a greater risk of COPD, as defined by spirometry (Global Initiative for Chronic Obstructive Lung Disease [GOLD] stage I or greater).[83] Other epidemiologic studies also support an association between SHS exposure and the development of COPD, as defined by different metrics.[64,84–88] Among patients with established COPD, SHS exposure may increase the risk of respiratory symptoms, poor health status, and disease exacerbations.[89,90,90a,90b]

Gas Stove Exposure: A Cause of Asthma Exacerbation?

Because they have chronic airway inflammation, persons with asthma may be susceptible to the effects of NO_2 and other combustion products released by gas stoves. Few studies have examined the health effects of gas stove exposure among adults with asthma. Cross-sectional epidemiologic studies demonstrate an increased risk of prevalent childhood asthma cases in gas stove homes compared with electric stove homes,[91,92] although this has not been observed in adults.[65] In adults with established asthma, a prospective panel study found an association between gas stove use and increased risk of respiratory symptoms, restricted activity, and emergency department visits.[93] Another time-series analysis found a negative impact of gas stove use on daily peak expiratory flow and respiratory symptoms.[94] In contrast, a longitudinal U.K. cohort study found no effect of gas stove exposure on persistence of adult asthma or on respiratory symptoms among asthmatics[95]; the European Community Respiratory Health Survey investigators also found no clear link between gas stoves and asthma symptoms.[96] In a prospective cohort study of adults with asthma, we found no impact of gas stove exposure on asthma severity or other aspects of asthma status.[80] Moreover, there was no association between gas stove exposure and pulmonary function impairment in a population-based sample of U.S. adults.[97] There was also no relation between gas stove use or measured NO_2 level and lung function in adult asthma.[98] Overall, the evidence has not been sufficient to implicate gas stove use as an exacerbating factor in preexisting adult asthma. Among children with asthma, however, there is stronger evidence of a deleterious effect of indoor NO_2 exposure and poorer asthma control.[99,100]

Wood Smoke Exposure—Respiratory Health Effects

Wood smoke, which is produced from domestic fireplace or wood stove use, contains potent respiratory irritants such as formaldehyde, acrolein, nitrogen oxides, and SO_2. It is also a major source of particulate air pollution.[101] In previous studies, exposure to extremely high wood smoke levels has been linked with respiratory problems. After a work shift, forest firefighters experienced an acute decrement in pulmonary function.[102] Similarly, Florida wildfires were associated with increased emergency department visits for asthma and acute bronchitis.[103] In developing countries, where prolonged wood stove use in poorly ventilated homes occurs, wood smoke exposure has been associated with chronic respiratory symptoms and airway obstruction.[6,104,105] The exposure levels in such settings, however, are much higher than those encountered in modern buildings. Burning of other biomass fuels, such as crop residues or dung, can also lead to chronic respiratory symptoms and airflow obstruction in developing countries.

The respiratory health effects of residential wood smoke exposure in developed countries, which occurs at lower levels, are not as clear. Epidemiologic studies have examined respiratory symptoms, lung function, and asthma outcomes with mixed results.[80,93,99,106–110] Consequently, it remains unclear whether domestic wood smoke causes respiratory symptoms and asthma in developed countries.

Respiratory Effects of Kerosene Heater Use

Although kerosene heaters are less commonly used than other indoor heaters in developed countries, they can substantially increase indoor levels of fine particles ($PM_{2.5}$), sulfate aerosol ($SO4^{2-}$), and acidic aerosol (H^+), which have been linked with respiratory symptoms.[111] The existing evidence, however, is inconclusive about whether kerosene heater use is a cause of respiratory and asthma symptoms in developed countries.[91,99,112–115]

Other Indoor Pollutants—The "Toxic" Indoor Environment

Besides indoor combustion, there are many other sources of indoor pollutants. Building materials, such as plywood

or particle board, and carpeting can emit formaldehyde; furniture may release formaldehyde and volatile organic compounds (VOCs); paints, cleaning compounds, and photocopiers may release VOCs; and radon can arise from soil sources.[6,26] Cleaning with bleach and other compounds can release chlorine and ammonia gas, which are airway irritants. Combination of bleach and ammonia or other nitrogen sources can also produce choramine, which may induce upper and lower respiratory tract symptoms.[116] Of these substances, radon exposure has been associated with lung cancer.[117] Exposure to chlorine, chloramine, and VOCs may be linked with respiratory symptoms, some of which suggest asthma, but further evidence is needed before final conclusions can be drawn.[116,118,119]

OUTDOOR AIR POLLUTION—ADVERSE RESPIRATORY EFFECTS OF SPECIFIC POLLUTANTS

Particulate Matter

Since the catastrophic air pollution events of the Meuse Valley, Donora, and the London Fog, hundreds of epidemiologic studies have examined the health impacts of particulate air pollution. There is strong and consistent evidence that particulate pollution causes premature death, which is principally from cardiovascular and respiratory causes.[21,25,120–124] Both short-term exposure, measured as daily fluctuation of particulate pollutant levels, and longer term chronic exposures have been linked with mortality. In particular, the Harvard Six Cities Study and the American Cancer Society study have provided key insights into the long-term health impacts of particulate air pollution. Evidence linking PM_{10} and $PM_{2.5}$ to mortality is robust, but particularly strong for $PM_{2.5}$. Although particulate pollution is strongly correlated with other pollutants, such as SO_2, it has a strong independent effect on mortality.

Reduction in fine particulate air pollution translates into a longer life span for the population. A recent study examined 211 metropolitan counties throughout the United States to elucidate the impact of declining $PM_{2.5}$ levels on mortality from approximately 1980 to 2000.[122] A decrease in $PM_{2.5}$ of 10 $\mu g/m^3$ was associated with a mean increase in life expectancy of 0.61 years after taking into account measures of sociodemographic and smoking factors. During the 2 decades of the study, the average life expectancy increased 2.72 years. The authors estimated that up to 15% of this improvement in life span could be attributed to declining particulate pollution levels.

Particulate air pollution has a negative effect on respiratory health. Exposure to PM has been associated with lower respiratory tract symptoms, such as cough, wheezing, or shortness of breath.[125–127] Persons with asthma are particularly susceptible to developing lower respiratory symptoms after exposure to particulate pollution.[127a]

Particulate pollution is also associated with poorer lung function throughout the life span. The Children's Health Study conducted in Southern California, which followed thousands of children over many years, found that fine particulate pollution was linked to a reduced rate of lung function growth.[128–130] Another study used carbon content of airway macrophages as a biomarker of individual exposure to PM derived from fossil fuel; there was a dose-dependent inverse association between the carbon content of airway macrophages and lung function, including forced expiratory volume in 1 second (FEV_1), in children.[29] This study, because it used an airway-related biomarker of particulate exposure, provides key support for the connection between particulate exposure and impaired lung function in children.

Particulate pollution has also been linked to poorer lung function among adults, which may reflect decreased growth of lung function in childhood or accelerated decline subsequently.[128,131] In the German SALIA study, higher PM_{10} exposure during the past 5 years was negatively associated with forced vital capacity (FVC), FEV_1, and FEV_1/FVC.[132] This study also provided rare insight into the impact of particulate pollution on the risk of COPD. Higher PM_{10} was also related to an increased risk for COPD as defined by the GOLD criteria (stage I or greater; odds ratio, 1.33 per 7 $\mu g/m^3$; 95% CI, 1.03 to 1.72).[132] In support of a link between particulate pollution and COPD, other studies have linked ambient particle exposure to a greater risk of hospitalization and death from COPD.[133–137]

Importantly, declining particulate air pollution has translated into improved pulmonary function. A recent analysis of the SAPALDIA cohort examined the association between the 11-year change in air quality and lung function decline among 8047 adult subjects (4742 had complete follow-up).[138] Due to a broad range of air quality policies implemented in Switzerland, residential PM_{10} declined over this time period. An 11-year reduction of PM_{10} of 10 $\mu g/m^3$ was associated with a decreased rate of annual decline of lung function (9% for FEV_1, 6% for FEV_1/FVC ratio, and 16% for forced expiratory flow rate between 25% and 75% of the forced vital capacity [$FEF_{25-75\%}$]). The Harvard Six Cities Study also showed that declining fine particle levels were associated with reduced mortality in the United States.[120]

Asthma confers a particular vulnerability to the effects of particulate air pollution. Persons with asthma who are exposed to higher levels of particulate pollution have increased respiratory symptoms, poorer lung function (including peak expiratory flow and FEV_1), and a greater risk of exacerbations (emergency department visits, hospitalizations).[134,136,139–142]

Another important component of particulate pollution is diesel exhaust. Diesel exhaust from heavy-duty trucks and diesel-engine cars is a major contributor to particulate air pollution in many parts of the world. Diesel exhaust particle exposure has been linked with both oncologic and allergic diseases.

Diesel exhaust particles have a central carbon core and adsorbed organic compounds, including polycyclic aromatic hydrocarbons and other known carcinogens. Occupational exposure to diesel exhaust has been associated with an elevated risk of lung cancer; railroad

workers and truck drivers were at highest risk.[17,20,143–145] Toxicologic studies have confirmed the carcinogenic properties of diesel exhaust.[20]

Diesel exhaust exposure can cause acute deterioration of lung function among persons with asthma. A randomized crossover study randomly assigned adult subjects with mild to moderate asthma to walk along Oxford Street in London at lunchtime (the busiest shopping street, in which only diesel powered buses and taxis are allowed) or in Hyde Park for approximately 6 km.[146] Fine and ultrafine particle levels were approximately three times higher on Oxford Street than in Hyde Park. The maximal decline in FEV_1 was much greater for subjects walking on Oxford Street than in Hyde Park (−6.1% vs. −1.9%). These changes were accompanied by increases of biomarkers of neutrophilic inflammation and airway acidification. In sum, this study showed acute deleterious effects of diesel exhaust exposure on adults with asthma in a naturalistic setting. Other studies indicate that diesel exhaust may favor a Th2 immune response, further connecting this form of particulate pollution with allergic disease and asthma.[147]

Sulfur Dioxide

The major source of sulfur oxides in the ambient environment is the combustion of sulfur-containing fossil fuels such as coal and crude petroleum. Sulfur dioxide (SO_2) is the most important of the gas-phase sulfur oxides (SO_x) in terms of both atmospheric chemistry and health effects. Sulfur oxides are usually considered to include sulfur trioxide (SO_3) and gas-phase sulfuric acid (H_2SO_4), but neither is present in the atmosphere in concentrations that result in substantial human exposures except when there are industrial or transportation accidents. Sulfur dioxide is regulated by the EPA as a criteria pollutant.

Bronchoconstriction is the primary acute effect of SO_2 and is likely mediated by chemosensitive receptors in the tracheobronchial tree. In particular, persons with asthma are most sensitive to the effects of SO_2, which may result from preexisting airway inflammation that leads to enhanced release of mediators, alterations in the autonomic nervous system, and exaggerated response of the chemosensitive receptors.[148,149] Multiple controlled human exposure studies have observed symptomatic bronchoconstriction in exercising asthmatics following 5- to 10-minute exposures to SO_2 at concentrations that are similar to those found in ambient air.[150,151] In the published studies, 5% to 30% of relatively healthy asthmatic subjects experienced moderate or greater decrements in lung function (≥100% increase in specific airway resistance or ≥15% decrease in FEV_1) with exposures to SO_2 concentrations of 0.2 to 0.3 ppm during exercise.[31,151] At concentrations of 0.4 ppm or greater, a greater percentage (20% to 60%) of exercising asthmatic individuals experienced SO_2-induced bronchoconstriction. A clear concentration-response relationship has been demonstrated following exposures to SO_2 at concentrations between 0.2 and 1.0 ppm, in terms of both increasing severity of effect and proportion of asthmatic individuals affected.

The results of multiple epidemiologic studies show associations between short-term exposures (generally 24-hour averages) to ambient SO_2 and respiratory morbidity. These studies were conducted in areas where the mean ambient 24-hour average SO_2 concentration ranged from 1 to 30 ppb, with maximum values ranging from 12 to 75 ppb. Several multicity studies as well as single-city studies have found an association between 24-hour average SO_2 concentrations and respiratory symptoms in children, particularly those with asthma.[152–154] Limited epidemiologic evidence suggests that atopic children and adults are at increased risk for SO_2-induced respiratory symptoms.[155] Generally consistent associations also have been observed between ambient SO_2 concentrations and emergency department visits and hospitalizations for all respiratory causes, particularly among children and older adults (≥65 years), and for asthma.[156–160]

The observed associations of asthma symptoms with 24-hour average SO_2 exposures in epidemiologic studies are generally coherent with increases in symptoms reported in asthmatic subjects in controlled human exposure studies after 5- to 10-minute exposures; it is possible that these associations are determined in large part by peak exposures within a 24-hour period. In other words, the effects of SO_2 on respiratory symptoms and lung function observed in human experimental studies using peak exposures provide some biologic plausibility for the increased emergency department visits and hospital admissions observed in epidemiologic studies.

Only some of the published epidemiologic studies have assessed potential confounding by co-pollutants using multivariable regression models. In these studies, the effect of SO_2 on respiratory health outcomes appeared to be generally robust and independent of the effects of gaseous co-pollutants, including NO_2 and O_3, but this was not always the case for measures of particulate pollution.[158,161] A review by the EPA concluded that the observed effects of SO_2 on respiratory end points likely occur independent of the effects of other ambient air pollutants.

Several studies have assessed the effects of decreases in SO_2 concentrations on respiratory symptoms due to air quality regulations. In eastern Germany, a marked decline in ambient SO_2 concentrations (90% across the decade of the 1990s) was associated with a decrease in the prevalence of respiratory symptoms.[162] During the study period, however, decreases in other ambient air pollutants, including approximately 60% lower PM concentrations, also occurred. In a similar study of the effect of a 1990 regulation requiring use of low-sulfur fuel for power generation and on-road vehicles in Hong Kong, large reductions in ambient SO_2 concentrations of up to 80% were associated with reduced respiratory symptoms; in this study, reductions in ambient PM were less than 20%.[163] Although the improved respiratory symptoms observed in both of these intervention studies may be partially attributable to declining concentrations of air pollutants other than SO_2, the results nevertheless

provide support for a causal relationship between SO_2 and respiratory health.

Nitrogen Dioxide

The term *oxides of nitrogen* (NO_x) includes all forms of oxidized nitrogen compounds, including nitric oxide (NO), nitrogen dioxide (NO_2), and all other oxidized nitrogen-containing compounds formed from NO and NO_2. NO_x is emitted by combustion sources mainly as NO with smaller quantities of NO_2. Motor vehicle traffic and electric utilities are the two largest NO_x sources in the United States. Nitrogen oxide is the primary NO_x species emitted from most combustion sources, but is rapidly converted to NO_2; thus, NO_2 is the focus of most health effects studies. Nitrogen dioxide is another of the criteria pollutants regulated by the EPA to protect public health. It is an oxidant gas like O_3, but less potent. Although high concentrations sometimes found in silos are well known to cause the acute and sometimes lethal pulmonary edema of "silo-filler's disease,"[164] the much lower levels of NO_2 in outdoor air had not been definitively linked to adverse health effects in epidemiologic studies until the last decade. When it became apparent that indoor concentrations of NO_2 often exceeded outdoor concentrations, particularly in homes equipped with gas stoves, this discovery enabled epidemiologic study of this pollutant because indoor air is relatively free of the other pollutants normally associated with NO_2 in outdoor air. Research interest focused on the possibility that exposure to NO_2 in indoor air might increase the occurrence of respiratory infections, in part because of animal studies that exposure increased risk of experimental infections.[165]

Controlled human exposure studies provide evidence for increased airway responsiveness to both nonspecific and specific challenges in asthmatic subjects after short-term exposure to NO_2. The results of several older studies suggested that short-term (30- to 60-minute) exposures to NO_2 at concentrations in the range of 0.1 to 0.3 ppm may cause increased airway responsiveness to nonspecific bronchoconstrictor agents such as methacholine and histamine.[166] More recent studies involving allergen challenge in asthmatics suggest that NO_2 may enhance both allergen-induced bronchoconstriction and inflammatory responses after exposures as low as 0.26 ppm NO_2 for 30 minutes during rest.[167,168]

New evidence from a number of epidemiologic studies supports an association between ambient NO_2 and respiratory morbidity, especially among persons with asthma. In particular, a study that evaluated the effect of an intervention that reduced indoor exposure to NO_2 from gas heaters provided evidence of improvement in respiratory symptoms in asthmatic children.[169] Studies using community ambient monitors to assign exposures to NO_2 also found associations between ambient NO_2 and respiratory symptoms in asthmatic children.[152,153] Positive associations were observed in cities where the 24-hour average ambient concentrations were within the range of typical large U.S. urban areas. The results of multipollutant models generally showed that the NO_2 associations were robust to adjustment for co-pollutants including O_3, particles, and carbon monoxide.

Multiple epidemiologic studies also showed positive associations between short-term ambient NO_2 concentrations and emergency department visits and hospital admissions for respiratory causes, especially asthma.[161,170–172] These associations are particularly consistent for children and older adults (65+ years) when all respiratory diseases are the outcome, and for children and adults of all ages when asthma is the outcome.

In addition to the epidemiologic evidence that short-term exposure to ambient NO_2 can cause respiratory morbidity, long-term exposure to NO_2 has been associated with decreased rate of growth of lung function. Results from the longitudinal Children's Health Study indicated that decrements in lung function growth were substantial for boys and girls who lived in southern California communities with relatively high annual average ambient NO_2.[128] The mean annual NO_2 concentrations in the communities ranged from approximately 5 to 40 ppb, well below the current EPA national ambient air quality standard of 53 ppb as an annual average. Similar associations have also been found for PM, inorganic (mostly nitric) acid vapor, and proximity to traffic (<500 m) in this cohort; the high correlation among traffic-related pollutants makes it difficult to determine the independent effect of NO_2 on lung function growth.[128,173]

Because short-term exposures to NO_2 can induce greater airway responsiveness among asthmatic subjects in human experimental studies and are associated with respiratory outcomes, especially asthma, in epidemiologic studies, there is coherent evidence to support a short-term averaging time for air quality standards to control this pollutant.

Ozone

Ozone (O_3) is a colorless, pungent, relatively water-insoluble gas that occurs with other photochemical oxidants and fine particles to form "smog." Tropospheric O_3, or ground-level O_3, is an environmental air pollutant and is distinct from the stratospheric O_3 that occurs at altitudes of greater than 10 km (6.2 miles) above the earth's surface. O_3 is generated by a series of sunlight-driven reactions involving NO_x and volatile organic compounds from predominantly mobile (i.e., motor vehicle), but sometimes stationary sources. The meteorologic conditions that tend to foster the generation of O_3 are typically present from late spring to early fall. Peak concentrations of O_3 typically occur in mid-afternoon, after both the morning rush hour and several hours of bright sunlight. Indoor sources of O_3 include office equipment with electric motors or ultraviolet light, such as photocopy machines, and electrostatic devices, such as air purifiers and ion generators.

While O_3 has long been associated with southern California smog, many other areas of North America also experience high concentrations of this pollutant, especially Houston, Mexico City, and cities in the eastern

United States and Canada during the summer months. In these areas, there are many days each year when the current EPA national ambient air quality standard for O_3 is exceeded.

Ozone is a potent oxidant and is capable of reacting with a variety of extracellular and intracellular molecules. When these molecules include unsaturated lipids, free radicals and toxic intermediate products are generated that can lead to cellular damage or cell death.[174] Direct cytotoxicity is a major mechanism of O_3-induced tissue injury; secondary damage from the inflammatory response likely also plays a role.

Dosimetric studies indicate that much of the inhaled O_3 is deposited in the upper and proximal lower airways.[175] However, because of its relative water insolubility, a considerable fraction does penetrate to the distal airways and alveoli. At the tissue level, the dose is highest at these sites.[176] Increased inspiratory flow, which occurs with exercise, may overcome the upper airway "scrubbing mechanisms" and cause greater deposition of O_3 in the distal lung.[177]

Most of the research on the health effects of O_3 has focused on short-term exposure. In controlled human exposure studies, O_3 inhalation by healthy subjects causes mean decrements in FEV_1 and FVC that correlate with concentration, exposure duration, and minute ventilation.[178–180] These decrements in lung function are primarily a result of decreased inspiratory capacity rather than airway obstruction. The mechanism of the decreased inspiratory capacity appears to be neurally mediated involuntary inhibition of inspiratory effort involving stimulation of C fibers in the lungs.[181] Somewhat surprisingly, older subjects and those who are cigarette smokers demonstrate lower O_3-induced decrements in pulmonary function than healthy subjects.[182] The acute decrements in pulmonary function induced by O_3 usually resolve within 24 hours.

Respiratory symptoms appear to be associated with these mean decrements in pulmonary function. There is a correlation between the decline in FEV_1 and the probability of developing lower respiratory tract symptoms (e.g., substernal chest discomfort, cough, wheeze, and dyspnea).[180] Another adverse effect of short-term exposure to O_3 is enhanced airway responsiveness to nonspecific stimuli such as methacholine and histamine.[180] This effect may persist longer than the acute decrements in lung function and may occur even in individuals who do not experience a decline in their FEV_1.

Ozone exposure may induce adverse respiratory consequences through a variety of mechanisms. Nasal inflammatory changes, injury to type I alveolar cells, ciliated airway epithelial cell injury, infiltration of the airway mucosa by neutrophils, and increased bronchoalveolar lavage fluid neutrophils and inflammatory mediators have been observed after O_3 exposure.[183–185] Airway inflammation has been demonstrated after exposure to ambient concentrations with exercise.[186]

The effects of *chronic* O_3 exposure in humans have not been adequately defined. It has been hypothesized that chronic exposure would lead to emphysematous or fibrotic parenchymal changes; however, to date, animal toxicologic studies have failed to substantiate the induction of diffuse disease after long-term exposure to ambient concentrations. However, a recent study showed that O_3 exposure of neonatal rhesus monkeys led to abnormal development of conducting airways, especially with coexposure to house dust mites.[187] In addition, some epidemiologic studies, but not all, suggest that long-term residence of children in a high ambient O_3 environment can lead to remodeling of the small airways.[128,188]

Multiple epidemiologic studies show that high ambient O_3 concentrations are associated with an increased rate of asthma attacks and increased respiratory-related hospital admissions/emergency department visits for respiratory disease.[189] The biologic plausibility of these findings is supported by the results of controlled human exposure studies showing that O_3 increases nonspecific airway responsiveness, asthmatic subjects have a greater inflammatory response to exposure, and specifically sensitized asthmatic subjects have enhanced bronchoconstrictor responses to inhaled allergen.[190,191] In addition to the exacerbation of preexisting asthma, some evidence exists that exposure to O_3 could induce new cases of asthma; for example, children playing outdoor sports in polluted areas of the Los Angeles basin have a three- to fourfold increased risk of asthma.[192]

A newly documented effect of ambient O_3 is its association with greater mortality; this has been reported in both Europe and the United States.[193,194] Although this effect was first reported for respirable PM, both O_3 and fine PM are capable of generating oxidative stress and local inflammation in the deep lung. Similar to what has been observed in PM mortality studies, it appears that elderly people with preexisting heart and lung disease represent the group at greatest risk for O_3-related death. If excess oxidative stress is a critical step in a pathway that leads to early mortality in individuals with heart and lung disease, it is not surprising that exposure to both ambient O_3 and PM is associated with increased risk. Of additional concern, recent studies have suggested that young adults living in southern California have increased oxidative stress and cytogenetic damage compared to those living in northern California, perhaps related to differential exposure to O_3.[195,196]

In summary, tens of millions of persons in the United States are exposed to levels of O_3 above the current U.S. national ambient air quality standard. This exposure is capable of inducing both acute decrements in lung function and respiratory symptoms. Although these effects are transient, acute respiratory tract injury and inflammation can also be induced by short-term exposure to ambient concentrations of O_3. Exacerbations of asthma and increased risk of death of the elderly appear to be the most important health effects of short-term exposure. The long-term consequences of O_3-induced acute injury and inflammation are not well understood, but there is epidemiologic evidence consistent with airway remodeling.

KEY POINTS

- Although the hazard of air pollution for human health has been recognized for less than a century, great progress has been made in defining the sources, properties, and distribution of pollutants. More recently, the importance of indoor air pollution has become clear.
- Epidemiologic studies, taken together with controlled human exposure studies, animal studies, and in vitro studies, have delineated many of the serious respiratory health effects of air pollution. Significant questions remain, however, about the impact of multiple pollutants acting together, the effect of pollution on susceptible populations, and the minimum level at which the risk of health effects increases substantively. Further research is needed to define these important questions.
- Great progress has been made in clearing the air in the United States and other developed countries. But levels of indoor and outdoor pollutants remain higher than is desirable for human health. In developing countries, the problem is compounded by biomass smoke, which may very well be the world's leading cause of obstructive lung disease.
- Further research that addresses the important remaining questions in air pollution, especially the minimum threshold above which health effects begin to occur, will provide further impetus to refine regulation to protect public health.

References

1. American Thoracic Society: What constitutes an adverse health effect of air pollution? Official statement of the American Thoracic Society. Am J Respir Crit Care Med 161(2 Pt 1):665–673, 2000.
2. Health effects of outdoor air pollution. Part 2. Committee of the Environmental and Occupational Health Assembly of the American Thoracic Society. Am J Respir Crit Care Med 153:477–498, 1996.
3. Health effects of outdoor air pollution. Committee of the Environmental and Occupational Health Assembly of the American Thoracic Society. Am J Respir Crit Care Med 153:3–50, 1996.
4. Leech JA, Nelson WC, Burnett RT, et al: It's about time: A comparison of Canadian and American time-activity patterns. J Expo Anal Environ Epidemiol 12:427–432, 2002.
5. California Environmental Protection Agency: Health Effects of Exposure to Environmental Tobacco Smoke. Sacramento, CA: Office of Environmental Health Hazard Assessment, 1997.
6. Samet JM, Marbury MC, Spengler JD: Health effects and sources of indoor air pollution. Part I. Am Rev Respir Dis 136:1486–1508, 1987.
7. Laurent O, Pedrono G, Segala C, et al: Air pollution, asthma attacks, and socioeconomic deprivation: A small-area case-crossover study. Am J Epidemiol 168:58–65, 2008.
8. O'Connor GT, Neas L, Vaughn B, et al: Acute respiratory health effects of air pollution on children with asthma in US inner cities. J Allergy Clin Immunol 121:1133–1139, 2008.
9. Gorham E, Martin FB, Litzau JT: Acid rain: Ionic correlations in the eastern United States, 1980–1981. Science 225:407–409, 1984.
10. Brunekreef B, Forsberg B: Epidemiological evidence of effects of coarse airborne particles on health. Eur Respir J 26:309–318, 2005.
11. Wilson WE, Suh HH: Fine particles and coarse particles: Concentration relationships relevant to epidemiologic studies. J Air Waste Manag Assoc 47:1238–1249, 1997.
12. Zhu Y, Hinds WC, Kim S, Sioutas C: Concentration and size distribution of ultrafine particles near a major highway. J Air Waste Manag Assoc 52:1032–1042, 2002.
13. Almeida SM, Pio CA, Freitas MC, et al: Approaching $PM_{2.5}$ and $PM_{2.5-10}$ source apportionment by mass balance analysis, principal component analysis and particle size distribution. Sci Total Environ 368:663–674, 2006.
14. Finlayson-Pitts BJ, Pitts JN Jr: Tropospheric air pollution: Ozone, airborne toxics, polycyclic aromatic hydrocarbons, and particles. Science 276:1045–1052, 1997.
15. Miller FJ, Menzel DB, Coffin DL: Similarity between man and laboratory animals in regional pulmonary deposition of ozone. Environ Res 17:84–101, 1978.
16. Bauer MA, Utell MJ, Morrow PE, et al: Inhalation of 0.30 ppm nitrogen dioxide potentiates exercise-induced bronchospasm in asthmatics. Am Rev Respir Dis 134:1203–1208, 1986.
17. Garshick E, Laden F, Hart JE, et al: Lung cancer and vehicle exhaust in trucking industry workers. Environ Health Perspect 116:1327–1332, 2008.
18. Davis ME, Blicharz AP, Hart JE, et al: Occupational exposure to volatile organic compounds and aldehydes in the U.S. trucking industry. Environ Sci Technol 41:7152–7158, 2007.
19. Wichmann HE: Diesel exhaust particles. Inhal Toxicol 19(Suppl 1):241–244, 2007.
20. Ris C: U.S. EPA health assessment for diesel engine exhaust: A review. Inhal Toxicol 19(Suppl 1):229–239, 2007.
21. Dockery DW, Pope CA 3rd, Xu X, et al: An association between air pollution and mortality in six U.S. cities. N Engl J Med 329:1753–1759, 1993.
22. Beeson WL, Abbey DE, Knutsen SF: Long-term concentrations of ambient air pollutants and incident lung cancer in California adults: Results from the AHSMOG study. Adventist Health Study on Smog. Environ Health Perspect 106:813–823, 1998.
23. Beelen R, Hoek G, van den Brandt PA, et al: Long-term exposure to traffic-related air pollution and lung cancer risk. Epidemiology 19:702–710, 2008.
24. Beelen R, Hoek G, van den Brandt PA, et al: Long-term effects of traffic-related air pollution on mortality in a Dutch cohort (NLCS-AIR study). Environ Health Perspect 116:196–202, 2008.
25. Eftim SE, Samet JM, Janes H, et al: Fine particulate matter and mortality: A comparison of the Six Cities and American Cancer Society cohorts with a Medicare cohort. Epidemiology 19:209–216, 2008.
26. Samet JM, Marbury MC, Spengler JD: Health effects and sources of indoor air pollution. Part II. Am Rev Respir Dis 137:221–242, 1988.
27. Lippmann M, Yeates DB, Albert RE: Deposition, retention, and clearance of inhaled particles. Br J Ind Med 37:337–362, 1980.
28. Mazzone SB: An overview of the sensory receptors regulating cough. Cough 1:2, 2005.
29. Kulkarni N, Pierse N, Rushton L, Grigg J: Carbon in airway macrophages and lung function in children. N Engl J Med 355:21–30, 2006.
30. Frank NR, Yoder RE, Brain JD, Yokoyama E: SO_2 (^{35}S labeled) absorption by the nose and mouth under conditions of varying concentration and flow. Arch Environ Health 18:315–322, 1969.

31. Bethel RA, Erle DJ, Epstein J, et al: Effect of exercise rate and route of inhalation on sulfur-dioxide-induced bronchoconstriction in asthmatic subjects. Am Rev Respir Dis 128:592–596, 1983.
32. Li N, Xia T, Nel AE: The role of oxidative stress in ambient particulate matter-induced lung diseases and its implications in the toxicity of engineered nanoparticles. Free Radic Biol Med 44:1689–1699, 2008.

32a. Liu L, Poon R, Chen L, et al: Acute effects of air pollution on pulmonary function, airway inflammation, and oxidative stress in asthmatic children. Environ Health Perspect 117:668–674, 2009.

33. Cho HY, Reddy SP, Kleeberger SR: Nrf2 defends the lung from oxidative stress. Antioxid Redox Signal 8:76–87, 2006.
34. Nel A, Xia T, Madler L, Li N: Toxic potential of materials at the nanolevel. Science 311:622–627, 2006.
35. Xia T, Korge P, Weiss JN, et al: Quinones and aromatic chemical compounds in particulate matter induce mitochondrial dysfunction: Implications for ultrafine particle toxicity. Environ Health Perspect 112:1347–1358, 2004.
36. Hill AB: The environment and disease: Association or causation? Proc R Soc Med 58:295–300, 1965.
37. Goldberg MS, Burnett RT, Brook JR: Counterpoint: Time-series studies of acute health events and environmental conditions are not confounded by personal risk factors. Regul Toxicol Pharmacol 51:141–147, 2008 [discussion appears in Regul Toxicol Pharmacol 51:148–150, 2008].
38. Bateson TF, Schwartz J: Selection bias and confounding in case-crossover analyses of environmental time-series data. Epidemiology 12:654–661, 2001.
39. Clougherty JE, Wright RJ, Baxter LK, Levy JI: Land use regression modeling of intra-urban residential variability in multiple traffic-related air pollutants. Environ Health 7:17, 2008.
40. Kim JY, Burnett RT, Neas L, et al: Panel discussion review: Session two—Interpretation of observed associations between multiple ambient air pollutants and health effects in epidemiologic analyses. J Expo Sci Environ Epidemiol 17(Suppl 2):S83–S89, 2007.
41. Geyh AS, Xue J, Ozkaynak H, Spengler JD: The Harvard Southern California Chronic Ozone Exposure Study: Assessing ozone exposure of grade-school-age children in two Southern California communities. Environ Health Perspect 108:265–270, 2000.
42. Amdur MO, Underhill D: The effect of various aerosols on the response of guinea pigs to sulfur dioxide. Arch Environ Health 16:460–468, 1968.
43. Graff DW, Schmitt MT, Dailey LA, et al: Assessing the role of particulate matter size and composition on gene expression in pulmonary cells. Inhal Toxicol 19(Suppl 1):23–28, 2007.
44. Totlandsdal AI, Refsnes M, Skomedal T, et al: Particle-induced cytokine responses in cardiac cell cultures—the effect of particles versus soluble mediators released by particle-exposed lung cells. Toxicol Sci 106:233–241, 2008.
45. Brown DM, Hutchison L, Donaldson K, Stone V: The effects of PM10 particles and oxidative stress on macrophages and lung epithelial cells: Modulating effects of calcium-signaling antagonists. Am J Physiol Lung Cell Mol Physiol 292:L1444–L1451, 2007.
46. Garcon G, Dagher Z, Zerimech F, et al: Dunkerque City air pollution particulate matter-induced cytotoxicity, oxidative stress and inflammation in human epithelial lung cells (L132) in culture. Toxicol In Vitro 20:519–528, 2006.
47. Veranth JM, Cutler NS, Kaser EG, et al: Effects of cell type and culture media on interleukin-6 secretion in response to environmental particles. Toxicol In Vitro 22:498–509, 2008.
48. Jung EJ, Avliyakulov NK, Boontheung P, et al: Pro-oxidative DEP chemicals induce heat shock proteins and an unfolding protein response in a bronchial epithelial cell line as determined by DIGE analysis. Proteomics 7:3906–3918, 2007.
49. Porter M, Karp M, Killedar S, et al: Diesel-enriched particulate matter functionally activates human dendritic cells. Am J Respir Cell Mol Biol 37:706–719, 2007.
50. National Research Council, Committee on the Epidemiology of Air Pollutants: Epidemiology and Air Pollution. Washington, DC: National Academy Press, 1985.
51. Spengler JD, Ferris BG Jr, Dockery DW: Sulfur dioxide and nitrogen dioxide levels inside and outside homes and the implications on health effects research. Environ Sci Technol 13:1276–1280, 1979.
52. National Research Council, Committee on Indoor Pollutants: Indoor Pollutants. Washington, DC: National Academy Press, 1981.
53. Jaakkola MS, Jaakkola JJ: Assessment of exposure to environmental tobacco smoke. Eur Respir J 10:2384–2397, 1997.
54. Boffetta P: Involuntary smoking and lung cancer. Scand J Work Environ Health 28(Suppl 2):30–40, 2002.
55. National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health: The Health Consequences of Involuntary Exposure to Tobacco Smoke: A Report of the Surgeon General. Atlanta, GA: Centers for Disease Control and Prevention, Coordinating Center for Health Promotion, 2006.
56. Oryszczyn MP, Annesi-Maesano I, Charpin D, et al: Relationships of active and passive smoking to total IgE in adults of the Epidemiological Study of the Genetics and Environment of Asthma, Bronchial Hyperresponsiveness, and Atopy (EGEA). Am J Respir Crit Care Med 161(4 Pt 1):1241–1246, 2000.
57. Osman LM, Douglas JG, Garden C, et al: Indoor air quality in homes of patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 176:465–472, 2007.
58. Chilmonczyk BA, Salmun LM, Megathlin KN, et al: Association between exposure to environmental tobacco smoke and exacerbations of asthma in children. N Engl J Med 328:1665–1669, 1993.
59. Office of Environmental Health Hazard Assessment: Health Effects Assessment for Environmental Tobacco Smoke. Sacramento: California Environmental Protection Agency, 2005. Available at ftp://ftp.arb.ca.gov/carbis/regact/ets2006/app3part%20b.pdf (accessed February 24, 2006).
60. Kronqvist M, Johansson E, Pershagen G, et al: Risk factors associated with asthma and rhinoconjunctivitis among Swedish farmers. Allergy 54:1142–1149, 1999.
61. Hu FB, Persky V, Flay BR, Richardson J: An epidemiological study of asthma prevalence and related factors among young adults. J Asthma 34:67–76, 1997.
62. McDonnell WF, Abbey DE, Nishino N, Lebowitz MD: Long-term ambient ozone concentration and the incidence of asthma in nonsmoking adults: The AHSMOG Study. Environ Res 80(2 Pt 1):110–121, 1999.
63. Dayal HH, Khuder S, Sharrar R, Trieff N: Passive smoking in obstructive respiratory disease in an industrialized urban population. Environ Res 65:161–171, 1994.
64. Leuenberger P, Schwartz J, Ackermann-Liebrich U, et al: Passive smoking exposure in adults and chronic respiratory symptoms (SAPALDIA Study). Swiss Study on Air Pollution and Lung Diseases in Adults, SAPALDIA Team. Am J Respir Crit Care Med 150(5 Pt 1):1222–1228, 1994.
65. Ng TP, Hui KP, Tan WC: Respiratory symptoms and lung function effects of domestic exposure to tobacco smoke and cooking by gas in non-smoking women in Singapore. J Epidemiol Community Health 47:454–458, 1993.
66. Robbins AS, Abbey DE, Lebowitz MD: Passive smoking and chronic respiratory disease symptoms in non-smoking adults. Int J Epidemiol 22:809–817, 1993.
67. Jaakkola MS, Piipari R, Jaakkola N, Jaakkola JJ: Environmental tobacco smoke and adult-onset asthma: A population-based incident case-control study. Am J Public Health 93:2055–2060, 2003.
68. Jaakkola MS, Jaakkola JJ, Becklake MR, Ernst P: Effect of passive smoking on the development of respiratory symptoms in young adults: An 8-year longitudinal study. J Clin Epidemiol 49:581–586, 1996.
69. Eisner MD: Environmental tobacco smoke exposure and pulmonary function among adults in NHANES III: Impact on the general population and adults with current asthma. Environ Health Perspect 110:765–770, 2002.
70. Jaakkola MS, Jaakkola JJ, Becklake MR, Ernst P: Passive smoking and evolution of lung function in young adults: An 8-year longitudinal study. J Clin Epidemiol 48:317–327, 1995.
71. Strachan DP, Butland BK, Anderson HR: Incidence and prognosis of asthma and wheezing illness from early childhood to age 33 in a national British cohort. Br Med J (Clin Res Ed) 312:1195–1199, 1996.

72. Eisner MD, Wang Y, Haight TJ, et al: Secondhand smoke exposure, pulmonary function, and cardiovascular mortality. Ann Epidemiol 17:364–373, 2007.
73. Eisner MD, Smith AK, Blanc PD: Bartenders' respiratory health after establishment of smoke-free bars and taverns. JAMA 280:1909–1914, 1998.
74. Menzies D, Nair A, Williamson PA, et al: Respiratory symptoms, pulmonary function, and markers of inflammation among bar workers before and after a legislative ban on smoking in public places. JAMA 296:1742–1748, 2006.
75. Eisner MD: Banning smoking in public places: Time to clear the air. JAMA 296:1778–1779, 2006.
76. Blanc PD, Ellbjar S, Janson C, et al: Asthma-related work disability in Sweden. Am J Respir Crit Care Med 160:2028–2033, 1999.
77. Mannino DM, Siegel M, Rose D, et al: Environmental tobacco smoke exposure in the home and worksite and health effects in adults: Results from the 1991 National Health Interview Survey. Tob Control 6:296–305, 1997.
78. Sippel JM, Pedula KL, Vollmer WM, et al: Associations of smoking with hospital-based care and quality of life in patients with obstructive airway disease. Chest 115:691–696, 1999.
79. Eisner MD, Katz PP, Yelin EH, et al: Measurement of environmental tobacco smoke exposure among adults with asthma. Environ Health Perspect 109:809–814, 2001.
80. Eisner MD, Yelin EH, Katz PP, et al: Exposure to indoor combustion and adult asthma outcomes: Environmental tobacco smoke, gas stoves, and woodsmoke. Thorax 57:973–978, 2002.
81. Eisner MD, Klein J, Hammond SK, et al: Directly measured second hand smoke exposure and asthma health outcomes. Thorax 60:814–821, 2005.
82. Eisner MD, Balmes J, Katz PP, et al: Lifetime environmental tobacco smoke exposure and the risk of chronic obstructive pulmonary disease. Environ Health 4:7, 2005.
83. Yin P, Jiang CQ, Cheng KK, et al: Passive smoking exposure and risk of COPD among adults in China: The Guangzhou Biobank Cohort Study. Lancet 370:751–757, 2007.
84. Sezer H, Akkurt I, Guler N, et al: A case-control study on the effect of exposure to different substances on the development of COPD. Ann Epidemiol 16:59–62, 2006.
85. Jayet PY, Schindler C, Schwartz J, et al: Passive smoking exposure among adults and the dynamics of respiratory symptoms in a prospective multicenter cohort study. Scand J Work Environ Health 31:465–473, 2005.
86. Jindal SK, Aggarwal AN, Chaudhry K, et al: A multicentric study on epidemiology of chronic obstructive pulmonary disease and its relationship with tobacco smoking and environmental tobacco smoke exposure. Indian J Chest Dis Allied Sci 48:23–29, 2006.
87. Simoni M, Baldacci S, Puntoni R, et al: Respiratory symptoms/diseases and environmental tobacco smoke (ETS) in never smoker Italian women. Respir Med 101:531–538, 2007.
88. Maziak W, Ward KD, Rastam S, et al: Extent of exposure to environmental tobacco smoke (ETS) and its dose-response relation to respiratory health among adults. Respir Res 6:13, 2005.
89. Eisner MD, Balmes J, Yelin EH, et al: Directly measured secondhand smoke exposure and COPD health outcomes. BMC Pulm Med 6:12, 2006.
90. Eisner MD: Indoor air, passive smoking, and COPD. Am J Respir Crit Care Med 176:426–427, 2007.
90a. Eisner MD, Blanc PD, Omachi TA, et al: Socioeconomic status, race, and COPD health outcomes. J Epidemiol Community Health 2009 [Epub ahead of print].
90b. Eisner MD, Jacob P 3rd, Benowitz NL, et al: Longer term exposure to secondhand smoke and health outcomes in COPD: impact of urine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol. Nicotine Tob Res 11:945–953, 2009.
91. Maier WC, Arrighi HM, Morray B, et al: Indoor risk factors for asthma and wheezing among Seattle school children. Environ Health Perspect 105:208–214, 1997.
92. Lanphear BP, Aligne CA, Auinger P, et al: Residential exposures associated with asthma in US children. Pediatrics 107:505–511, 2001.
93. Ostro BD, Lipsett MJ, Mann JK, et al: Indoor air pollution and asthma: Results from a panel study. Am J Respir Crit Care Med 149:1400–1406, 1994.
94. Lebowitz MD, Collins L, Holberg CJ: Time series analyses of respiratory responses to indoor and outdoor environmental phenomena. Environ Res 43:332–341, 1987.
95. Moran SE, Strachan DP, Johnston ID, Anderson HR: Effects of exposure to gas cooking in childhood and adulthood on respiratory symptoms, allergic sensitization and lung function in young British adults. Clin Exp Allergy 29:1033–1041, 1999.
96. Jarvis D, Chinn S, Sterne J, et al: The association of respiratory symptoms and lung function with the use of gas for cooking. European Community Respiratory Health Survey. Eur Respir J 11:651–658, 1998.
97. Eisner MD, Blanc PD: Gas stove use and respiratory health among adults with asthma in NHANES III. Occup Environ Med 60:759–764, 2003.
98. Blanc PD, Eisner MD, Katz PP, et al: Impact of the home indoor environment on adult asthma and rhinitis. J Occup Environ Med 47:362–372, 2005.
99. Belanger K, Triche EW: Indoor combustion and asthma. Immunol Allergy Clin North Am 28:507–519, vii, 2008.
100. Hansel NN, Breysse PN, McCormack MC, et al: A longitudinal study of indoor nitrogen dioxide levels and respiratory symptoms in inner-city children with asthma. Environ Health Perspect 116:1428–1432, 2008.
101. Boman BC, Forsberg AB, Jarvholm BG: Adverse health effects from ambient air pollution in relation to residential wood combustion in modern society. Scand J Work Environ Health 29:251–260, 2003.
102. Betchley C, Koenig JQ, van Belle G, et al: Pulmonary function and respiratory symptoms in forest firefighters. Am J Indust Med 31:503–509, 1997.
103. Surveillance of morbidity during wildfires—Central Florida, 1998. MMWR Morb Mortal Wkly Rep 48:78–79, 1999.
104. Ozbay B, Uzun K, Arslan H, Zehir I: Functional and radiological impairment in women highly exposed to indoor biomass fuels. Respirology 6:255–258, 2001.
105. Perez-Padilla R, Regalado J, Vedal S, et al: Exposure to biomass smoke and chronic airway disease in Mexican women: A case-control study. Am J Respir Crit Care Med 154(3 Pt 1):701–706, 1996.
106. Honicky RE, Osborne JSD, Akpom CA: Symptoms of respiratory illness in young children and the use of wood-burning stoves for indoor heating. Pediatrics 75:587–593, 1985.
107. von Mutius E, Illi S, Nicolai T, Martinez FD: Relation of indoor heating with asthma, allergic sensitisation, and bronchial responsiveness: Survey of children in south Bavaria. BMJ 312:1448–1450, 1996.
108. Levesqu B, Allaire S, Gauvin D, et al: Wood-burning appliances and indoor air quality. Sci Total Environ 281:47–62, 2001.
109. Thorn J, Brisman J, Toren K: Adult-onset asthma is associated with self-reported mold or environmental tobacco smoke exposures in the home. Allergy 56:287–292, 2001.
110. Noonan CW, Ward TJ: Environmental tobacco smoke, woodstove heating and risk of asthma symptoms. J Asthma 44:735–738, 2007.
111. Leaderer BP, Naeher L, Jankun T, et al: Indoor, outdoor, and regional summer and winter concentrations of PM_{10}, $PM_{2.5}$, SO_4^{2-}, H^+, NH_4^+, NO_3^-, NH_3, and nitrous acid in homes with and without kerosene space heaters. Environ Health Perspect 107:223–231, 1999.
112. Triche EW, Belanger K, Beckett W, et al: Infant respiratory symptoms associated with indoor heating sources. Am J Respir Crit Care Med 166:1105–1111, 2002.
113. Venn AJ, Yemaneberhan H, Bekele Z, et al: Increased risk of allergy associated with the use of kerosene fuel in the home. Am J Respir Crit Care Med 164:1660–1664, 2001.
114. Triche EW, Belanger K, Bracken MB, et al: Indoor heating sources and respiratory symptoms in nonsmoking women. Epidemiology 16:377–384, 2005.
115. Beckett WS, Gent JF, Naeher LP, et al: Peak expiratory flow rate variability is not affected by home combustion sources in a group of nonsmoking women. Arch Environ Occup Health 61:176–182, 2006.
116. Jacobs JH, Spaan S, van Rooy GB, et al: Exposure to trichloramine and respiratory symptoms in indoor swimming pool workers. Eur Respir J 29:690–698, 2007.

117. Kreuzer M, Heinrich J, Wolke G, et al: Residential radon and risk of lung cancer in Eastern Germany. Epidemiology 14:559–568, 2003.
118. Medina-Ramon M, Zock JP, Kogevinas M, et al: Short-term respiratory effects of cleaning exposures in female domestic cleaners. Eur Respir J 27:1196–1203, 2006.
119. Medina-Ramon M, Zock JP, Kogevinas M, et al: Asthma symptoms in women employed in domestic cleaning: A community based study. Thorax 58:950–954, 2003.
120. Laden F, Schwartz J, Speizer FE, Dockery DW: Reduction in fine particulate air pollution and mortality: Extended follow-up of the Harvard Six Cities study. Am J Respir Crit Care Med 173:667–672, 2006.
121. Pope CA, Burnett RT, Thun MJ, et al: Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution. JAMA 287:1132–1141, 2002.
122. Pope CA 3rd, Ezzati M, Dockery DW: Fine-particulate air pollution and life expectancy in the United States. N Engl J Med 360:376–386, 2009.
123. Pope CA 3rd, Thun MJ, Namboodiri MM, et al: Particulate air pollution as a predictor of mortality in a prospective study of U.S. adults. Am J Respir Crit Care Med 151(3 Pt 1):669–674, 1995.
124. Krewski D, Burnett RT, Goldberg MS, et al: Validation of the Harvard Six Cities Study of particulate air pollution and mortality. N Engl J Med 350:198–199, 2004.
125. Schwartz J, Dockery DW, Neas LM, et al: Acute effects of summer air pollution on respiratory symptom reporting in children. Am J Respir Crit Care Med 150(5 Pt 1):1234–1242, 1994.
126. Neas LM, Dockery DW, Ware JH, et al: Concentration of indoor particulate matter as a determinant of respiratory health in children. Am J Epidemiol 139:1088–1099, 1994.
127. Dockery DW, Speizer FE, Stram DO, et al: Effects of inhalable particles on respiratory health of children. Am Rev Respir Dis 139:587–594, 1989.
127a. Gent JF, Belanger K, Triche EW, et al: Association of pediatric asthma severity with exposure to common household dust allergens. Environ Res 109:768–774, 2009.
128. Gauderman WJ, Avol E, Gilliland F, et al: The effect of air pollution on lung development from 10 to 18 years of age. N Engl J Med 351:1057–1067, 2004.
129. Gauderman WJ, Gilliland GF, Vora H, et al: Association between air pollution and lung function growth in southern California children: Results from a second cohort. Am J Respir Crit Care Med 166:76–84, 2002.
130. Gauderman WJ, McConnell R, Gilliland F, et al: Association between air pollution and lung function growth in southern California children. Am J Respir Crit Care Med 162(4 Pt 1):1383–1390, 2000.
131. Ackermann-Liebrich U, Leuenberger P, Schwartz J, et al: Lung function and long term exposure to air pollutants in Switzerland. Study on Air Pollution and Lung Diseases in Adults (SAPALDIA) Team. Am J Respir Crit Care Med 155:122–129, 1997.
132. Schikowski T, Sugiri D, Ranft U, et al: Long-term air pollution exposure and living close to busy roads are associated with COPD in women. Respir Res 6:152, 2005.
133. Chen Y, Yang Q, Krewski D, et al: Influence of relatively low level of particulate air pollution on hospitalization for COPD in elderly people. Inhal Toxicol 16:21–25, 2004.
134. Atkinson RW, Anderson HR, Sunyer J, et al: Acute effects of particulate air pollution on respiratory admissions: Results from APHEA 2 project. Air Pollution and Health: A European Approach. Am J Respir Crit Care Med 164(10 Pt 1):1860–1866, 2001.
135. Zanobetti A, Schwartz J, Dockery DW: Airborne particles are a risk factor for hospital admissions for heart and lung disease. Environ Health Perspect 108:1071–1077, 2000.
136. Halonen JI, Lanki T, Yli-Tuomi T, et al: Urban air pollution, and asthma and COPD hospital emergency room visits. Thorax 63:635–641, 2008.
137. Naess O, Nafstad P, Aamodt G, et al: Relation between concentration of air pollution and cause-specific mortality: Four-year exposures to nitrogen dioxide and particulate matter pollutants in 470 neighborhoods in Oslo, Norway. Am J Epidemiol 165:435–443, 2007.
138. Downs SH, Schindler C, Liu LJ, et al: Reduced exposure to PM10 and attenuated age-related decline in lung function. N Engl J Med 357:2338–2347, 2007.
139. Delfino RJ, Quintana PJ, Floro J, et al: Association of FEV_1 in asthmatic children with personal and microenvironmental exposure to airborne particulate matter. Environ Health Perspect 112:932–941, 2004.
140. Yu O, Sheppard L, Lumley T, et al: Effects of ambient air pollution on symptoms of asthma in Seattle-area children enrolled in the CAMP study. Environ Health Perspect 108:1209–1214, 2000.
141. Millstein J, Gilliland F, Berhane K, et al: Effects of ambient air pollutants on asthma medication use and wheezing among fourth-grade school children from 12 Southern California communities enrolled in The Children's Health Study. Arch Environ Health 59:505–514, 2004.
142. Islam T, Gauderman WJ, Berhane K, et al: Relationship between air pollution, lung function and asthma in adolescents. Thorax 62:957–963, 2007.
143. Garshick E, Laden F, Hart JE, et al: Lung cancer in railroad workers exposed to diesel exhaust. Environ Health Perspect 112:1539–1543, 2004.
144. Lipsett M, Campleman S: Occupational exposure to diesel exhaust and lung cancer: A meta-analysis. Am J Public Health 89:1009–1017, 1999.
145. McEntee JC, Ogneva-Himmelberger Y: Diesel particulate matter, lung cancer, and asthma incidences along major traffic corridors in MA, USA: A GIS analysis. Health Place 14:817–828, 2008.
146. McCreanor J, Cullinan P, Nieuwenhuijsen MJ, et al: Respiratory effects of exposure to diesel traffic in persons with asthma. N Engl J Med 357:2348–2358, 2007.
147. Chang Y, Senechal S, de Nadai P, et al: Diesel exhaust exposure favors TH2 cell recruitment in nonatopic subjects by differentially regulating chemokine production. J Allergy Clin Immunol 118:354–360, 2006.
148. Sheppard D, Wong WS, Uehara CF, et al: Lower threshold and greater bronchomotor responsiveness of asthmatic subjects to sulfur dioxide. Am Rev Respir Dis 122:873–878, 1980.
149. Linn WS, Venet TG, Shamoo DA, et al: Respiratory effects of sulfur dioxide in heavily exercising asthmatics: A dose-response study. Am Rev Respir Dis 127:278–283, 1983.
150. Balmes JR, Fine JM, Sheppard D: Symptomatic bronchoconstriction after short-term inhalation of sulfur dioxide. Am Rev Respir Dis 136:1117–1121, 1987.
151. Linn WS, Avol EL, Peng RC, et al: Replicated dose-response study of sulfur dioxide effects in normal, atopic, and asthmatic volunteers. Am Rev Respir Dis 136:1127–1134, 1987.
152. Mortimer KM, Neas LM, Dockery DW, et al: The effect of air pollution on inner-city children with asthma. Eur Respir J 19:699–705, 2002.
153. Schildcrout JS, Sheppard L, Lumley T, et al: Ambient air pollution and asthma exacerbations in children: An eight-city analysis. Am J Epidemiol 164:505–517, 2006.
154. van der Zee S, Hoek G, Boezen HM, et al: Acute effects of urban air pollution on respiratory health of children with and without chronic respiratory symptoms. Occup Environ Med 56:802–812, 1999.
155. Boezen HM, van der Zee SC, Postma DS, et al: Effects of ambient air pollution on upper and lower respiratory symptoms and peak expiratory flow in children. Lancet 353:874–878, 1999.
156. Wilson AM, Wake CP, Kelly T, Salloway JC: Air pollution, weather, and respiratory emergency room visits in two northern New England cities: An ecological time-series study. Environ Res 97:312–321, 2005.
157. Atkinson RW, Anderson HR, Strachan DP, et al: Short-term associations between outdoor air pollution and visits to accident and emergency departments in London for respiratory complaints. Eur Respir J 13:257–265, 1999.
158. Burnett RT, Cakmak S, Brook JR, Krewski D: The role of particulate size and chemistry in the association between summertime ambient air pollution and hospitalization for cardiorespiratory diseases. Environ Health Perspect 105:614–620, 1997.
159. Petroeschevsky A, Simpson RW, Thalib L, Rutherford S: Associations between outdoor air pollution and hospital admissions in Brisbane, Australia. Arch Environ Health 56:37–52, 2001.

160. Atkinson RW, Bremner SA, Anderson HR, et al: Short-term associations between emergency hospital admissions for respiratory and cardiovascular disease and outdoor air pollution in London. Arch Environ Health 54:398–411, 1999.
161. Ito K, Thurston GD, Silverman RA: Characterization of PM2.5, gaseous pollutants, and meteorological interactions in the context of time-series health effects models. J Expo Sci Environ Epidemiol 17(Suppl 2):S45–S60, 2007.
162. Heinrich J, Hoelscher B, Frye C, et al: Improved air quality in reunified Germany and decreases in respiratory symptoms. Epidemiology 13:394–401, 2002.
163. Peters J, Hedley AJ, Wong CM, et al: Effects of an ambient air pollution intervention and environmental tobacco smoke on children's respiratory health in Hong Kong. Int J Epidemiol 25:821–828, 1996.
164. Douglas WW, Hepper NG, Colby TV: Silo-filler's disease. Mayo Clin Proc 64:291–304, 1989.
165. Samet JM, Lambert WE, Skipper BJ, et al: A study of respiratory illnesses in infants and nitrogen dioxide exposure. Arch Environ Health 47:57–63, 1992.
166. Folinsbee LJ: Does nitrogen dioxide exposure increase airways responsiveness? Toxicol Ind Health 8:273–283, 1992.
167. Jenkins HS, Devalia JL, Mister RL, et al: The effect of exposure to ozone and nitrogen dioxide on the airway response of atopic asthmatics to inhaled allergen: Dose- and time-dependent effects. Am J Respir Crit Care Med 160:33–39, 1999.
168. Barck C, Sandstrom T, Lundahl J, et al: Ambient level of NO_2 augments the inflammatory response to inhaled allergen in asthmatics. Respir Med 96:907–917, 2002.
169. Pilotto LS, Nitschke M, Smith BJ, et al: Randomized controlled trial of unflued gas heater replacement on respiratory health of asthmatic schoolchildren. Int J Epidemiol 33:208–214, 2004.
170. Peel JL, Tolbert PE, Klein M, et al: Ambient air pollution and respiratory emergency department visits. Epidemiology 16:164–174, 2005.
171. Tolbert PE, Klein M, Peel JL, et al: Multipollutant modeling issues in a study of ambient air quality and emergency department visits in Atlanta. J Expo Sci Environ Epidemiol 17(Suppl 2):S29–S35, 2007.
172. Barnett AG, Williams GM, Schwartz J, et al: Air pollution and child respiratory health: A case-crossover study in Australia and New Zealand. Am J Respir Crit Care Med 171:1272–1278, 2005.
173. Gauderman WJ, Vora H, McConnell R, et al: Effect of exposure to traffic on lung development from 10 to 18 years of age: A cohort study. Lancet 369:571–577, 2007.
174. Pryor WA, Squadrito GL, Friedman M: A new mechanism for the toxicity of ozone. Toxicol Lett 82–83:287–293, 1995.
175. Hu SC, Ben-Jebria A, Ultman JS: Longitudinal distribution of ozone absorption in the lung: Quiet respiration in healthy subjects. J Appl Physiol 73:1655–1661, 1992.
176. Chang L, Miller FJ, Ultman J, et al: Alveolar epithelial cell injuries by subchronic exposure to low concentrations of ozone correlate with cumulative exposure. Toxicol Appl Pharmacol 109:219–234, 1991.
177. Hu SC, Ben-Jebria A, Ultman JS: Longitudinal distribution of ozone absorption in the lung: Effects of respiratory flow. J Appl Physiol 77:574–583, 1994.
178. McDonnell WF, Horstman DH, Hazucha MJ, et al: Pulmonary effects of ozone exposure during exercise: Dose-response characteristics. J Appl Physiol 54:1345–1352, 1983.
179. McDonnell WF 3rd, Horstman DH, Abdul-Salaam S, House DE: Reproducibility of individual responses to ozone exposure. Am Rev Respir Dis 131:36–40, 1985.
180. McDonnell WF, Kehrl HR, Abdul-Salaam S, et al: Respiratory response of humans exposed to low levels of ozone for 6.6 hours. Arch Environ Health 46:145–150, 1991.
181. Hazucha MJ, Bates DV, Bromberg PA: Mechanism of action of ozone on the human lung. J Appl Physiol 67:1535–1541, 1989.
182. Frampton MW, Morrow PE, Torres A, et al: Ozone responsiveness in smokers and nonsmokers. Am J Respir Crit Care Med 155:116–121, 1997.
183. Devlin RB, McDonnell WF, Mann R, et al: Exposure of humans to ambient levels of ozone for 6.6 hours causes cellular and biochemical changes in the lung. Am J Respir Cell Mol Biol 4:72–81, 1991.
184. Graham D, Henderson F, House D: Neutrophil influx measured in nasal lavages of humans exposed to ozone. Arch Environ Health 43:228–233, 1988.
185. Koren HS, Graham DE, Devlin RB: Exposure of humans to a volatile organic mixture. III. Inflammatory response. Arch Environ Health 47:39–44, 1992.
186. Kinney PL, Nilsen DM, Lippmann M, et al: Biomarkers of lung inflammation in recreational joggers exposed to ozone. Am J Respir Crit Care Med 154:1430–1435, 1996.
187. Fanucchi MV, Plopper CG, Evans MJ, et al: Cyclic exposure to ozone alters distal airway development in infant rhesus monkeys. Am J Physiol Lung Cell Mol Physiol 291:L644–L650, 2006.
188. Tager IB, Balmes J, Lurmann F, et al: Chronic exposure to ambient ozone and lung function in young adults. Epidemiology 16:751–759, 2005.
189. Gent JF, Triche EW, Holford TR, et al: Association of low-level ozone and fine particles with respiratory symptoms in children with asthma. JAMA 290:1859–1867, 2003.
190. Holz O, Mucke M, Paasch K, et al: Repeated ozone exposures enhance bronchial allergen responses in subjects with rhinitis or asthma. Clin Exp Allergy 32:681–689, 2002.
191. Kehrl HR, Peden DB, Ball B, et al: Increased specific airway reactivity of persons with mild allergic asthma after 7.6 hours of exposure to 0.16 ppm ozone. J Allergy Clin Immunol 104:1198–1204, 1999.
192. McConnell R, Berhane K, Gilliland F, et al: Asthma in exercising children exposed to ozone: A cohort study. Lancet 359:386–391, 2002.
193. Bell ML, McDermott A, Zeger SL, et al: Ozone and short-term mortality in 95 US urban communities, 1987–2000. JAMA 292:2372–2378, 2004.
194. Gryparis A, Forsberg B, Katsouyanni K, et al: Acute effects of ozone on mortality from the "Air Pollution and Health: A European Approach" project. Am J Respir Crit Care Med 170:1080–1087, 2004.
195. Chen C, Arjomandi M, Balmes J, et al: Effects of chronic and acute ozone exposure on lipid peroxidation and antioxidant capacity in healthy young adults. Environ Health Perspect 115:1732–1737, 2007.
196. Chen C, Arjomandi M, Qin H, et al: Cytogenetic damage in buccal epithelia and peripheral lymphocytes of young healthy individuals exposed to ozone. Mutagenesis 21:131–137, 2006.

CHAPTER 68

ACUTE PULMONARY RESPONSES TO TOXIC EXPOSURES

Paul D. Blanc, MD, MSPH

INTRODUCTION

PATHOGENESIS OF IRRITANT LUNG INJURY

GENERAL MANAGEMENT PRINCIPLES

CHRONIC SEQUELAE AND RESIDUAL EFFECTS

SPECIFIC EXPOSURES

Chlorine, Chloramines, Hydrochloric Acid, and Related Chemicals

Oxides of Nitrogen, Ozone, Sulfur Dioxide, and Acid Aerosols

Military and Crowd Control Agents

Cadmium, Mercury, and Other Toxic Metals

Metal Fume Fever, Polymer Fume Fever, Organic Dust Toxic Syndrome, and Other Inhalation Fevers

Fluorocarbon Aerosol Spray Pneumonitis

Hydrocarbon Pneumonitis and "Fire-Eater's Lung"

Paraquat

Smoke Inhalation

Pharmacologic Syndromes

Other Inhalant Exposures

INTRODUCTION

This chapter focuses on the acute effects on the lung after exposure to toxic substances. As used in this chapter, "acute" subsumes short-term exposures (minutes to hours), with the initial onset of pulmonary responses within a similarly rapid time period. Generally, the relevant toxicant exposures are of high intensity, far in excess of recommended safety limits for the workplace or the environment. The lung is the target organ for toxicity in the acute pulmonary responses addressed in this chapter. Importantly, *target organ* does not equate with *route of exposure*. For many acute exposures, inhalation is the route of delivery for toxins leading to the lung injury. However, in some instances, the route of delivery for the toxin may be by inhalation, yet the primary target organ for the toxic insult is not the lung (e.g., solvent inhalation that causes central nervous system depression). Inhalation exposures leading to nonpulmonary illnesses are not addressed here. In contrast, paraquat-induced lung injury and hydrocarbon aspiration, examples of ingested toxins with severe acute target organ effects on the lung, are discussed in this chapter.

Moreover, this chapter does not address brief exposures inducing acute responses mediated by anamnestic (i.e., allergic or other immune mediated) mechanisms. These responses require prior exposures that already have led to sensitization, such as occupational asthma (see Chapter 64) or hypersensitivity pneumonitis (see Chapter 66). There are also a number of toxicants causing unusual pulmonary syndromes after subacute (days to months) as opposed to acute exposure. Some of these syndromes have emerged in recent years associated with new technologies or novel toxicants, such as popcorn workers' lung and other flavor industry workers' disease linked to the chemical diacetyl,[1,2] flock workers' lung caused by very short synthetic textile fibers,[3,4] and ardystil lung, a dye chemical–induced organizing pneumonia.[5,6] Although beyond the scope of this chapter, some of these syndromes are discussed elsewhere (see Section L, "Infiltrative and Interstitial Lung Diseases," and elsewhere in Section M, "Environmental and Occupational Disorders").

PATHOGENESIS OF IRRITANT LUNG INJURY

Acute lung toxicity results from a variety of exposures but, nonetheless, is manifest by a narrow repertoire of injury. Irritant toxic substances can be encountered in

various physical states relevant to their inhalational properties. Such states include gases, vapors (i.e., the gaseous form of a substance that is a liquid or a solid at normal temperatures), fumes (i.e., an aerosol of solid material, often metals, of small particle size suspended in a gaseous medium [most <1.0 μm and many <0.1 μm] that has condensed from a vaporized state), and aerosols (i.e., liquid droplets or fine particulates dispersed in a gaseous medium; smoke is a subset of aerosol resulting from incomplete combustion). These exposures include heterogeneous toxic agents that are capable of causing extensive cell injury throughout the upper and lower respiratory tract. The primary location of respiratory tract injury and the onset of clinical symptoms are partly dependent on the solubility of the gas, vapor, fume, or aerosol involved, and in the case of fumes or aerosols, particle or droplet physical characteristics. Other factors that determine the injury pattern following exposure include amount of the toxic substance inhaled; duration of exposure to the inhalant; concentration of the inhalant in the ambient air; other physical properties (such as pH or chemical reactivity); and a variety of host factors, such as age, use of respiratory protection, and comorbid illness. Overwhelming exposures to any irritant inhalant, however, can cause extensive damage throughout the respiratory tract.

Ammonia[7] and sulfur dioxide[8] are examples of substances that are highly soluble in water. Such highly soluble substances cause immediate irritation of the conjunctival mucosa and upper airways. In contrast, oxides of nitrogen,[9] ozone,[10] and phosgene[11] have relatively low water solubility. For this reason, exposure to one of these agents may *not* be characterized by immediate symptoms of mucous membrane irritation. This may lead to more prolonged exposure and delay in seeking medical attention. Both more and less soluble irritant exposures can lead to distal lung injury, but in the case of highly soluble materials, a history of severe upper respiratory symptoms should precede the presentation of distal airway and alveolar damage.

Irritants reaching the lower respiratory tract, either because of their inherent physical characteristics or because of exposures that overwhelm the absorptive capacity of the upper airway, can injure both the lung epithelium and its endothelium. Pathophysiologically, irritant injury at this level leads to a nonspecific pattern of diffuse alveolar damage similar to that seen from a variety of different causes (see Chapters 55 and 60). The pathologic changes in fatal cases of irritant lung injury include focal and confluent areas of edema with protein-rich fluid in the alveolar spaces, hyaline membrane formation, and denudation of the alveolar epithelium.[12,13] In addition, mucous membranes of the bronchial and bronchiolar walls may be destroyed or denuded. A component of pulmonary hemorrhage may occur in irritant lung injury but typically is not a major clinical manifestation. Its presence should raise suspicion of other syndromes.[14]

On the cellular level, respiratory tract injury may be mediated through the deposition or formation of an acid, alkali, free radical, or other reactive chemical species. In most cases, the precise cellular mechanisms of injury from irritant inhalants have not been fully delineated. This is true even for relatively common irritants such as chlorine or even the chemical warfare agent phosgene, substances for which a great deal of human and experimental animal data exist.[15,16]

Acute irritant injury is the predominant, but not the only, pathophysiologic mechanism underlying acute toxic lung syndromes. In contrast to the anatomic distribution commonly seen in water-soluble irritant chemical–related injury, it may be difficult to delineate a descending, hierarchical pattern from upper airway to lower lung injury following exposure to a diverse group of agents. Many of these exposures lead to acute lung injury via a nonimmunologic mechanism (clinically, acute respiratory distress syndrome; pathologically, diffuse alveolar damage). Some of the diverse agents causing these syndromes are detailed subsequently in this chapter. Other toxin exposures produce various other syndromes, such as heavy metal pneumonitis,[17] hydrocarbon aspiration,[18] or paraquat lung injury.[19,20] The inhalation fever syndromes mark the principal exception to this in that the pathophysiology of this group of self-limited acute lung syndromes appears to be cytokine mediated, without obvious lung injury.[21]

GENERAL MANAGEMENT PRINCIPLES

Symptoms and signs of acute inhalation injury can be delayed in onset. Following removal from exposure while safeguarding the rescuing personnel, the next most important management decisions include protection of the airway (i.e., preemptive intubation may be required to prevent precipitous airway obstruction from progressive airway edema) and treatment of hypoxemia. The nasopharynx and larynx may manifest injuries earliest because they are exposed to the highest concentrations of inhaled water-soluble toxicants. Within a few hours after exposure, progressive airway edema, mucopurulent membrane production, and bronchorrhea may develop. Bronchoconstriction, peribronchial edema, and bronchial mucosal slough may result in the development of atelectasis. In the distal airways and alveoli, epithelial and endothelial injury leads to permeability-induced edema. This can manifest injury ranging from mild interstitial edema to diffuse alveolar damage. Pulmonary edema may be rapid following high-concentration toxicant exposure or may be delayed up to 24 to 48 hours. Diffuse alveolar damage after severe acute toxic lung injury should be managed consistent with the basic management of acute lung injury due to other causes (see Chapters 55, 89, and 90). This extends to the role of protective ventilation strategies.[22] Concomitant airway injury with acute bronchospasm often warrants treatment with bronchodilators because of the airway obstruction.

A beneficial role for corticosteroids in the acute phase of irritant and other chemically mediated forms of acute injury to the lungs has not been established by controlled trials in humans.[23,24] Experimental data suggest that if there is a beneficial effect of anti-inflammatory treatment

following toxic inhalation exposure, it is likely to be as an adjunct to bronchodilators for the management of airway obstruction. In a rat model, systemic corticosteroid treatment following chlorine inhalation showed a significant beneficial effect in terms of airway resistance and nonspecific airway responsiveness but not in a morphologic measure of injury. In a pig model, it was found that benefits were similar between inhaled and systemic corticosteroids.[25,26] Despite the lack of controlled evidence of efficacy, anecdotal reports of benefits from systemic corticosteroid use continue to appear.[23,27]

Prophylactic antibiotic drugs have not proved to be efficacious in toxic lung injury; antibiotics should be reserved for those patients with clinical evidence of infection, applying the recommended approach in fire smoke–related acute lung injury.[28] To date, convincing data do not support the use of other pharmacologic agents, such as antioxidants, in the generic treatment of toxic chemical lung injury.[23]

There are certain exposure-specific management issues that do occasionally arise. In paraquat-induced lung injury, for example, oxygen toxicity is a particular issue because of its specific mechanism of action, that is, high concentrations of oxygen may lead to more severe lung injury.[19] In paraquat as well, immunosuppressive therapy has been of particular interest and has yielded some promising data but remains to be adequately supported in randomized, controlled studies.[20] In the case of certain metal toxins, chelation may have a therapeutic role, as is addressed later in relation to the specific exposures involved. Inhalation fever is self-limited, so the principal clinical management issue is to exclude other exposures with less benign outcomes.[21]

CHRONIC SEQUELAE AND RESIDUAL EFFECTS

Among persons surviving symptomatic exposure to acute irritants, persistent structural and functional effects may occur. Long-term consequences to the upper airways (nose, pharynx, and larynx) can be sequelae of acute inhalational exposures; upper airway complaints including chronic rhinitis (*reactive upper airway dysfunction syndrome* [RUDS]), anosmia, and vocal cord dysfunction have been reported.[29–32]

Follow-up studies of more homogeneous populations evaluated after inhalation injury (with only a minority experiencing severe injury) suggest that airflow obstruction and nonspecific airway hyperresponsiveness are the most common persistent abnormalities of the conducting airways after irritant injury. Even so, epidemiologic data suggest that these outcomes occur only in a minority of those exposed.[33–35] The term *reactive airway dysfunction syndrome* (RADS) has been applied to the persistence of airway reactivity after acute exposure to respiratory irritants.[36–39] The more general term *irritant-induced asthma* has also been used to describe this condition.[40,41] Insofar as this syndrome represents a form of work-related asthma, it is addressed in Chapter 64.

Chronic injury to the lower airways and lung parenchyma are unusual sequelae of acute inhalational exposure. Long-term follow-up evaluation after recovery from acute respiratory distress syndrome due to heterogeneous causes (predominantly associated with sepsis) suggests that residual deficits in lung volumes, airflow, and gas exchange may persist long after recovery.[42] Bronchiolitis obliterans (BO),[43–50] bronchiectasis,[7,49,51–54] bronchiolitis obliterans with organizing pneumonia (BOOP),[55,56] and pneumomediastinum[57–59a] may all occur, but are rare complications. Irritants, in particular nitrogen oxide and related exposures, have long been known to cause BO.[60] Yet even with nitrogen dioxide, BO is an infrequent event; for example, only 1 case was found in a series of 20 moderate to severe exposures.[44] Pathologically, irritant-induced BO usually is characterized by intrabronchial granulation tissue (to which the term *proliferative bronchiolitis obliterans* is applied), as opposed to constrictive (obliterative) BO.[12,13] The latter appears to be the pathologic correlate of popcorn worker's lung[2] and has been reported in one case of BO following exposure in the World Trade Center disaster.[61] In addition to residual obstructive ventilatory deficits, restrictive deficits may also occur following severe irritant inhalation injury.[51,62] There is also some indication that an isolated reduction in residual volume may be noted in the follow-up of such cases.[63,64] Finally, nonspecific respiratory complaints after acute inhalation events can be a somatic manifestation of a psychological process.[65,66]

SPECIFIC EXPOSURES

Chlorine, Chloramines, Hydrochloric Acid, and Related Chemicals

Among the toxic agents causing pulmonary responses (Table 68-1), **chlorine** is a common and potent irritant inhalant accounting for substantial human morbidity.[15,67–69] Common forms of exposure include industrial leaks,[70] environmental releases occurring primarily during transport,[71,72] water purification,[73] swimming pool–related events,[27,74] household cleaning product misadventures,[75] and even homemade chemical bombs.[76] In the form of a yellow-green acrid gas, industrial and environmental releases typically present clear-cut exposure histories. Because the gas is heavier than air, higher contamination can be expected in low-lying areas (hence, its use in trench warfare in World War I).[77] However, other environmental conditions may supervene. Examples include one well-documented case of the gas rising along the heated outside wall of a factory where rooftop workers were exposed.[70] In another case, chlorine initially collected in a basement but then was sucked up into the central heating system of a dormitory.[78]

The history of exposure to chlorine may be less straightforward when inhalation occurs after de novo generation of gas from chlorine-containing liquids or powders. The most common *liquid* formulation associated with chlorine gas release is hypochlorite bleach, whereas the active chlorine component of dry *powdered*

TABLE 68-1. Selected Toxic Agents Causing Pulmonary Responses after Acute Exposure

Agent	Common Exposure Scenarios	References
Acid aerosols	Plating; microelectronics; other manufacturing	99, 114–118
Acrolein	Structural or wildland fires; other combustion	244, 248
Ammonia	Industrial refrigeration leaks; fertilizers	7, 270, 274
Brevetoxin	Aerosolization of "red tide" toxin	263, 264
Bromine	Water treatment; chemical manufacturing	46, 275–279
Cadmium fume	Flame cutting of soldered or sheet metal materials	153–156
Chloramines and nitrogen trichloride	Bleach + ammonia mix; chlorination + ammonia	79–81
Chlorine gas	Gas leak; water treatment; bleach + acid mix	15, 68–72
Chlorine dioxide	Pulp paper bleaching	105, 106
Crowd control agents (tear gas)	Military and police training and operations	144–146
Dimethyl sulfate	Industrial chemical yielding sulfuric acid	112, 113
Fluorocarbon polymers	Overheating polymers	120, 178, 184
Fluorocarbon sprays	Waterproofing and related aerosol sprays	214–218
Hydrocarbons	Aspiration of low-viscosity materials, "fire-eating"	18, 224, 228–231
Hydrogen sulfide	Sewers and manure pits; fossil fuel and geothermal production	282, 286–289
Mercury vapor	Gold extraction, heating cinnabar	158–164
Methyl bromide	Pesticide fumigant	280, 281
Methyl isocyanate	Pesticide manufacturing	289, 291
Methyl isothiocyanate	Breakdown product of metam sodium fumigant	292, 293
Mustard gas	Chemical warfare agent	51, 125–129
Nickel carbonyl	Nickel processing, metal reclamation	165–168
Nitrogen dioxide	Silage; combustion; explosives; welding; nitric acid mixes	9, 40, 94–97
Organic dusts/aerosols	Contaminated dust or bioaerosol generation	21, 200, 201
Organophosphates	Pesticide application; chemical warfare	137–139
Ozone	Bleaching; water treatment; plasma welding	102, 106
Paraquat	Herbicide skin contamination or ingestion	19, 234, 241
Phosgene	Chlorinated solvent breakdown by-product	11, 16, 132
Phosphine	Fumigation with aluminum or zinc phosphide, microelectronics	204–206
Sulfur dioxide	Refrigeration; cement manufacture; mining; pulp paper mills	8, 107–110
Tributyltin (bis[tributyltin] oxide)	Paint additive for mold inhibition	176
Vanadium	Ore processing; fossil fuel by-product, catalyst use	172, 175
Zinc chloride	Smoke bombs ("white smoke")	180, 192, 195
Zinc oxide fume	Welding galvanized steel; brass casting	137, 159, 168

bleaching cleansers is typically a chlorinated phosphate. In either liquid or powdered bleaches, the liberation of chlorine gas is pH dependent, occurring on contact with acids in common household products containing muriatic (hydrochloric), phosphoric, or hydrofluoric acid.[75] In contrast, mixing chlorine-containing products with ammonia leads to release of **chloramines** (monochloramine [NH_2Cl] and dichloramine [$NHCl_2$]) and related chemicals, especially nitrogen trichloride (NCl_3), chemicals whose irritant effects are attributed to in situ pulmonary reactions releasing chlorine, hypochlorous acid, and ammonia.[75,79,80] In chlorinated swimming pools, inadvertent mixing with nitrogen donors also occurs, with potential irritant effects attributed to nitrogen trichloride in particular.[79,81]

Irritant effects after inhalation of **hypochlorite** aerosols in confined spaces without a history of combining products (not an uncommon scenario when cleaning bathrooms) also can be associated with irritant effects. Similarly, in certain industrial operations, hydrochloric (hydrogen chloride in water) or hypochlorous acid aerosols are also respiratory irritants. Other sources of chlorine exposure occur in specific industrial processes that use a large number of inorganic chlorine derivatives. Worthy of particular mention are chlorine dioxide (used in pulp paper processing),[82] chlorinated silanes (gases used in microelectronics),[83] reactive metal halides (e.g., titanium or antimony chlorides),[17] and thionyl chloride (which breaks down to yield hydrogen chloride and sulfur dioxide).[46,84]

For chlorine and related chemicals, the acute respiratory response corresponds to the effective dose delivered to the lungs. All of these compounds appear to share a final common toxic pathway. As noted in the general discussion of acute toxic inhalations, water solubility is an important determinant of the dose reaching the lower airways. For chlorine, chlorine dioxide, chloramines, and nitrogen trichloride, lower solubility favors deeper penetration with a more effective delivered dose compared with an equivalent inhalation of acid aerosols.

However, exposure to any of these compounds is associated with some degree of immediate mucous membrane and upper airway irritation. In fact, the absence of acute irritant effects is not clinically consistent with chlorine gas or related exposures.

Chlorine inhalation may manifest any of the full spectrum of respiratory tract irritant effects, from minor mucosal responses to upper airway responses to diffuse alveolar damage.[27,70–77,85] Persistent airway hyperresponsiveness after irritant exposure has been associated particularly with chlorine gas and chlorine-containing products, although this may reflect the frequency of such exposures rather than a propensity for chlorine to have this effect.[15,40,41] There is also limited evidence that persons with underlying airway hyperreactivity may be more responsive to chlorine.[86]

Use of inhaled bronchodilators and steroids may be indicated for both acute and residual bronchospasm following chlorine inhalation. Although several case reports and series have touted the potential benefits of nebulized sodium bicarbonate inhalation in the acute treatment of chlorine or chloramine inhalation, the efficacy of this intervention has never been assessed in a controlled trial.[80,87–90] One small controlled trial administered inhaled bicarbonate 3 months or more after exposure in irritant-induced asthma.[91]

Oxides of Nitrogen, Ozone, Sulfur Dioxide, and Acid Aerosols

These inhalants are major air pollutants; the effects of low-level exposure are discussed in detail in Chapter 67. When they are inhaled in high concentrations, these irritants cause acute lung injury. Because of lower solubility, longer exposure with a greater predilection for lung injury may occur with ozone[10] and, even more commonly, nitrogen dioxide.[92] Nonetheless, with sulfur dioxide and acid aerosols, sufficient intensity of exposure leads to diffuse alveolar damage.

High-intensity exposure to **oxides of nitrogen** occurs through decomposition of organic matter as well as through other sources. Examples of exposure scenarios include nitrogen dioxide–induced lung injury among farmers (also known as silo filler's disease),[44,93,94] use of internal combustion engines in enclosed spaces (with large outbreaks associated with ice resurfacing equipment used in indoor skating rinks),[9,95–97] thermal degradation of polymers (e.g., in structural fires),[28] toxic gas produced by the detonation of explosives,[48,98] the release of gas through reactions of nitric acid breakdown in air or in reaction with metals or organic materials,[99–101] welding by-products, particularly when "gas-shielded" techniques are employed (manual inert gas welding or tungsten inert welding),[102] and the release of compressed nitrogen dioxide gas.[103] Historically, the detonation of explosives has been one of the most important sources of exposure to nitrogen oxides.[98] Nitric oxide, an inhalant used therapeutically, breaks down to nitrogen dioxide in the presence of oxygen and, thus, must be monitored with appropriate delivery devices.[104]

High-intensity occupational **ozone** exposure is unusual, but it can occur with welding conditions similar to those associated with oxides of nitrogen.[102] More recently, ozone in water treatment and in pulp paper bleaching also has emerged as a health issue; in the latter industry, there is often concomitant exposure to chlorine dioxide characterized by intermittent "gassings."[105,106]

Important sources of high-level **sulfur dioxide** exposure include mining and ore refining,[8] Portland cement manufacturing,[107] sulfur treatment of fruit,[108] and industrial releases.[109] Historically, sulfur dioxide has been and continues to be important in sulfite process pulp paper processing, where acute gas releases are superimposed on chronic lower-level exposure as with other irritant exposures in the paper industry.[105,106,110] In the past, sulfur dioxide was a common refrigerant.[111]

In ambient air pollution, **sulfuric acid** is an acid aerosol of primary concern, but this can be encountered in higher levels occupationally. Sulfuric acid exposure occurs both through direct use and through the breakdown of a highly toxic industrial chemical, dimethyl sulfate.[112,113] A number of other inorganic and organic acid vapors and aerosols are also important potential causes of acute lung injury, including chromic,[114] acetic,[115] formic,[116] and hydrofluoric acids.[101,117,118]

Hydrofluoric acid (hydrogen fluoride) inhalation, in addition to nonspecific irritant effects, can induce clinically significant hypocalcemia.[119] Exposures occur in manufacturing of both microelectronics and phosphate fertilizers, in household use of hydrofluoric acid rust removal agents (the mixture of which with hypochlorite bleach can evolve both chlorine and hydrogen fluoride), and in pyrolysis of fluorinated polymers.[120] Hydrogen fluoride is a chronic exposure problem in the aluminum smelting industry.[121] Hydrogen fluoride is also released as a breakdown product of sulfur hexafluoride, an electrical insulating liquid chemical used in equipment.[122]

Military and Crowd Control Agents

Sulfur Mustard

Unfortunately, chemical warfare agent exposures are not of mere historical interest.[77,123,124] Of the major World War I chemical weapons, only sulfur mustard (mustard gas) has been used "militarily" since World War II. Classified as a vesicant because of blistering induced by skin contact, mustard gas inhalation causes severe respiratory injury. Based largely on the Iranian experience of their Iraqi war veterans, sulfur mustard survivors can exhibit residual tracheobronchitis, asthma, bronchiectasis, bronchotracheomalacia, BO, and fibrosis.[51,124–129] Nitrogen mustards were sulfur mustard derivatives originally developed for military purposes but later applied medically; nonetheless, occupationally related acute lung injury has been reported through industrial release.[130]

Phosgene

Another World War I toxic gas, phosgene, is currently encountered as a chemical industry process chemical

and as a thermal breakdown product or ultraviolet photoreactant of chlorinated solvents (e.g., methylene chloride).[11,131] An occult cause of exposure can be inadvertent phosgene production from welding metals "degreased" with solvents.[102] Phosgene is the prototypic deeply penetrating inhalant exhibiting a delayed onset of symptoms (12–24 hr after exposure).[22,132,133]

Chloropicrin

Chloropicrin, another World War I gas, is a low-threshold irritant currently encountered in chemical manufacturing and as a component of fumigants.[134–136]

Neurotoxins

The modern chemical warfare armamentarium is dominated by systemic toxins developed from organophosphate pesticides; the nerve agent "VX" is prototypical.[137,138] These highly lethal neurotoxins have important respiratory effects, including manifestations of both muscarinic receptor stimulation (bronchorrhea and bronchospasm) and nicotinic receptor depolarization blockade (respiratory muscle paralysis); treatment is based on reversing enzyme inhibition and countering the effects of acetyl cholinesterase excess.[139]

Although the lung is typically the portal of entry for biologic warfare agents, this topic is beyond the scope of this chapter; infectious processes are covered elsewhere (e.g., see Chapter 69 for mediastinal involvement in anthrax).

Chloroacetopenone (Mace), Other Tear Gas Agents, and Zinc Chloride

Crowd control agents ("tear gases"), as opposed to the war gases, are intended to incapacitate persons via immediate mucous membrane irritation.[140] The agents in greatest use worldwide are chloroacetophenone ("mace"), and orthochlorobenzamalonitrile.[141,142] In addition to their mucous membrane effects, case reports have implicated these agents in lower respiratory injury and even persistent effects following high-intensity exposures (e.g., in enclosed buildings).[143–146] Unlike tear gas, exposure to smoke bomb releases (sometimes referred to as "white smoke") can cause severe lower respiratory injury; through a pyrotechnic reaction between hexachloroethane and zinc oxide, the potent respiratory irritant zinc chloride fume is released.[147,148] Military, police, and others exposed, often during ill-conceived training exercises, are at risk.[147–152]

Cadmium, Mercury, and Other Toxic Metals

Inhalation of certain metal fumes or metal vapors can cause an acute pneumonitis.[17] The two metals most important clinically are **cadmium** and **mercury**. In both instances, the most important factor in pulmonary insult is acute inhalation at a relatively high exposure level.

Cadmium

Exposure typically occurs through welding, brazing (high-temperature soldering) or flame-cutting metal or working with molten metal under conditions of inadequate ventilation.[153–156] In welding, brazing, and flame-cutting, the usual source of cadmium is the welding rod, brazing solder, or a metal coating, rather than the base metal itself.[102] In areas of the world where jewelry-making is carried out at a cottage industry level, cadmium use in silver-working can present a particular exposure risk.[157]

Mercury

High levels of the relatively volatile metal can be generated effectively from many nonenclosed operations, most notably through heated metal reclamation processes (e.g., home refining of mercury-gold amalgams or even reclaiming of mercury from electronic equipment).[158–162] Exposure has also occurred through burning mercury sulfide (Chinese red cinnabar) and mercuric oxide for medicinal purposes.[163,164]

Nickel Carbonyl

Nickel carbonyl is an organic metal derivative and potent pulmonary toxin, with exposure occurring through nickel refining, manufacturing processes in which it is used as a catalyst or intermediate, and metal recycling or reclaiming operations.[165–167] Inorganic nickel, although a sensitizing substance, is not associated with pneumonitis.

Other Metals

Other metals, including antimony, manganese, and beryllium, are sometimes cited as causes of acute lung injury consistent with metal pneumonitis, but there are few reports in the last 50 years providing documentation of such disorders.[7] A recent case report implicated copper dust inhalation with acute lung injury.[168]

Dangerous exposures to cadmium, mercury, and nickel carbonyl occur in part because these agents are not immediately irritating, analogous to the delayed symptoms after phosgene or nitrogen oxide gas inhalation. Patients typically present in respiratory distress 12 to 24 hours after exposure. Indeed, the exposure history often remains occult unless aggressively pursued. Metal pneumonitis from these materials also can include fever as a clinical manifestation of the toxic syndrome. However, the term *metal fume fever* should not be used in this context.[169]

The toxic mechanism in heavy metal pneumonitis is presumed to be inhibition of enzymatic and other critical cellular functions. Chelation treatment has not been shown to be effective in heavy metal pneumonitis due to cadmium or mercury, although chelation is often initiated in the case of mercury injury.[163,164] The agent dithiocarb (diethyldithiocarbamate) has been used as a chelating antidote for nickel carbonyl pneumonitis,

based on supportive animal data.[170,171] Disulfiram has been suggested as a potential alternative treatment, although experimental data to support this practice are weak.[167,171]

Two other metal compounds are well-documented bronchial irritants in humans. **Vanadium** (typically as a metal oxide), which is encountered in metal processing and, in lower concentrations, as a fossil fuel by-product, causes acute bronchitis.[172] Among boilermakers, vanadium-rich fuel oil ash is suspected to be a key exposure related to acute respiratory symptoms.[173] In a single case report, high-intensity exposure to ash from an oil-burning furnace was associated with diffuse alveolar damage; although vanadium was detectable in the residue, the toxic mechanism in this case was unclear.[174] In another case report, vanadium (as vanadyl pyrophosphate) was linked to pneumonitis.[175] **Tributyltin** (bis[tributyltin] oxide), an organotin compound employed as a mildew and mold retardant, is also an acute airway irritant.[176]

Metal Fume Fever, Polymer Fume Fever, Organic Dust Toxic Syndrome, and Other Inhalation Fevers

There are a number of febrile flulike pulmonary syndromes reflecting similar clinical responses to a diverse group of acute inhalational exposures.[21,177] Their hallmark is chills, fever, malaise, and myalgia with onset 4 to 8 hours after intense inhalation of fumes or organic dusts.[21,169,178] Common respiratory complaints include cough or mild dyspnea, but findings of chest radiographic opacities or hypoxemia are inconsistent with this disorder. Peripheral leukocytosis usually accompanies the syndrome; bronchoalveolar lavage shows a marked influx of neutrophils.[179–181] These syndromes all are self-limited, resolving clinically within 12 to 48 hours. Inhalation fevers share a common feature of tachyphylaxis, with a blunted response to daily repeated inhalation (and hence the name "Monday morning fever" among both brass founders and cotton mill workers).[21,182,183]

Signs or symptoms of pneumonitis should suggest alternative, less benign diagnoses, such as cadmium pneumonitis,[154,155] hypersensitivity pneumonitis (see Chapter 62), active infection (in the case of water-source aerosols), or inhalation of more toxic temperature-dependent fluoropolymer pyrolysis by-products (which include hydrogen fluoride and carbonyl fluoride).[129,184,185] Toxic pneumonitis due to fluorocarbon-containing aerosol sprays is an exposure scenario distinct from fluoropolymer pyrolysis by-product–caused polymer fume fever or acute lung injury and are dealt with separately (see later).

Metal fume fever is associated with **zinc oxide** inhalation from welding galvanized metal or brass working.[186] There is only limited clinical evidence that other metals (magnesium and copper) cause a similar response,[169,187] and experimental data further discount magnesium as a potential cause of fume fever.[188]

Polymer fume fever is associated with thermal breakdown products of fluoropolymers (e.g., Teflon and related materials).[178,189–191] The pathophysiologic mechanisms underlying the metal and polymer fume fever syndromes have not been established, but research suggests that pulmonary cytokines may play a key role.[192–195]

Organic dust toxic syndrome (ODTS) is associated with inhalation of materials contaminated with thermophilic bacteria and fungal spores, including wood chips,[196] straw,[197] silage,[198] grains and flour,[199] and textile raw materials.[183] The increasing industrialization of agricultural processes, especially the use of animal confinement techniques, is an additional source of exposure leading to ODTS, although these same settings can produce irritant gases such as hydrogen sulfide and ammonia.[200,201] ODTS has gone by various names, including pulmonary mycotoxicosis,[202] silo unloader's syndrome,[198] and mill fever.[203] One of the best documented historical outbreaks of ODTS occurred among individuals who work with stained (contaminated) cotton mattresses.[183] Inhalation of aerosols from contaminated water sources produces a self-limited febrile syndrome similar to ODTS. Some of these outbreaks are attributable to inhalation of *Legionella* species without actual infection (i.e., without clinical evidence of pneumonia) and are referred to as "Pontiac fever."[204–206] Water sources associated with contaminated aerosols causing inhalation fever syndromes can include saunas or hot tubs,[207,208] commercial (industrial) humidifying systems,[209,210] and metal machining cooling fluids.[211] Going along with these heterogeneous exposure scenarios, a variety of different names have been used for these syndromes, include humidifier fever,[210] sump bay fever,[212] and bath water fever.[207] As with ODTS, many of the same occupational and environmental conditions can lead to or be concomitant with cases of hypersensitivity pneumonitis and, more specific to waterborne aerosols, active respiratory infection. In addition to its self-limited nature, a key characteristic differentiating an outbreak of inhalation fever from other syndromes is its relatively high attack rate over a fairly short time period. As with metal fume fever and polymer fume fever, cytokines are presumed to be key mediators of the ODTS and water-borne aerosol-related inhalation fevers, with endotoxin and related factors being key exposure variables.[21,213]

Fluorocarbon Aerosol Spray Pneumonitis

Acute lung injury following inhalation exposure to commercial fluorocarbon-containing aerosol products is an important emerging syndrome first reported in the early 1990s.[214] This syndrome is distinct both from fluoropolymer fume fever as previously discussed and from exposure to irritant by-products from higher-temperature thermal breakdown of such polymers. A key feature of fluorocarbon aerosol pneumonitis is the onset of symptoms within several hours after using a spray product containing fluorocarbon polymers. Exposure can occur in an occupational setting (e.g., construction), but

consumer exposures from over-the-counter products is a common scenario. These exposures can be relatively brief with varying degrees of ventilation; importantly, exposure need not be in an enclosed space. Victims are usually naive to previous exposure; there is nothing in the condition to suggest a hypersensitivity mechanism. Application of multiple types of fluorocarbon-containing products have been linked to outbreaks; although waterproofing leather and fabric sprays have dominated the reports, other products include floor stain protector, rust-proofing spray, grout sealer, and ski wax.[214–221] The clinical presentations manifest a range of severity consistent with varying degrees of nonspecific acute lung injury; management is based on standard support care. The application of various descriptive labels based on the exposure scenario can obscure the consistent pattern of the syndrome.[217,222]

Hydrocarbon Pneumonitis and "Fire-Eater's" Lung

Hydrocarbon pneumonitis occurs with oral ingestion of hydrocarbons and associated aspiration. This is a prominent issue in the pediatric age group, accounting for many hospital admissions each year. The common hydrocarbons involved are mineral spirits, mineral seal oil (common in furniture polish), lamp oil, kerosene (paraffin), turpentine (pine oil), gasoline, and lighter fluid.[18,223–225] Even though these substances have systemic toxic effects such as central nervous system depression, life-threatening complications of ingestion are predominantly the result of concomitant hydrocarbon aspiration and subsequent pulmonary compromise, making the lung the target organ of concern in hydrocarbon ingestion. Pneumatocele is a recognized complication of hydrocarbon pneumonitis.[226] In contradistinction to aspiration hydrocarbon pneumonitis, the toxicity of hydrocarbon (solvent) vapor inhalation manifests primarily in either central nervous system or cardiac effects. Major pulmonary target organ damage associated with acute hydrocarbon exposure by inhalation is unusual but has been reported.[227]

"Fire-eater's lung" is an important variant of hydrocarbon pneumonitis.[228,229] Rather than children, this syndrome typically involves adolescents or young adults who are exposed through mishap during flame-blowing performances using a variety of different flammable materials. The substances used overlap with some of the reported pediatric exposures (kerosene, gasoline) but can also include other hydrocarbons such as jet fuel and, in France, an aromatic hydrocarbon enriched petroleum-distillate called "kerdan."[230,231] There has also been a case of citronella oil aspiration in a fire-eater.[228] As with hydrocarbon pneumonitis in children, fire-eater's lung can also be complicated by pneumatocele.[232] Although the term "acute lipoid pneumonia" has been used to refer to the "fire-eater's lung" syndrome, this is a misnomer.[233]

In both childhood and adult pneumonitis, hydrocarbon aspiration occurs at the time of initial ingestion event or subsequently with vomiting. Low viscosity of an ingested hydrocarbon is considered a major factor promoting aspiration (presumably for mechanical reasons), for example, with mineral seal oil.[18,224] Although theoretical consideration has been given to potential effects on surfactant as being mediators of hydrocarbon aspiration toxicity, the chemical pneumonitis of the syndrome appears to be nonspecific.

Paraquat

Paraquat is a widely used herbicide and a potent toxin. Ingestion rather than inhalation is the typical route of exposure associated with human toxicity. Systemic reactions following skin exposure have occurred almost exclusively owing to substantive direct exposure to the skin (soaking of the skin with paraquat) or when the skin integrity has been breached (e.g., preexisting skin lesions or burn). The theoretical risk of smoking contaminated materials has never been established clinically.

Most paraquat deaths result from suicidal intent.[19,234,235] Paraquat ingestion is a relatively uncommon method of suicide in the United States, but its incidence is greater in a number of other countries, perhaps related to patterns of crop utilization and ease of access.[234,236] Although paraquat ingestion leads to acute gastrointestinal tract necrosis and multiorgan failure, the lung is the target organ for toxicity among those surviving the immediate postingestion period. Diquat, a related dipyridyl herbicide, does not cause the syndrome of lung toxicity associated with paraquat.[237]

The pulmonary toxicity of paraquat, in contrast to its gastrointestinal effects, does not reflect caustic irritant injury. The major lung effect of paraquat toxicity is the development of pulmonary edema (usually observed 24–48 hr after ingestion). The pulmonary edema may evolve to a condition resembling acute respiratory distress syndrome (associated with histopathologic findings similar to those of diffuse alveolar damage), which may progress to induce an accelerated, chemically induced pulmonary fibrosis. After stabilization following acute multiorgan paraquat toxic effects, disease progression is marked by rapidly worsening respiratory distress, hypoxemia, and a restrictive ventilatory defect, with decreased lung compliance and diffusing capacity, ending in death from ventilatory failure within days to weeks.[19,234] Survivors may demonstrate modest and slow improvement in lung function.[238]

The mechanism of paraquat toxicity is attributed to the generation of superoxide radicals that may be partly iron dependent.[239] Consistent with an oxidant mechanism, supplemental oxygen and radiation therapy may worsen the outcome.[19,234,240] There are no known antidotes for paraquat poisoning, and enhanced elimination (hemoperfusion) has not demonstrated a clear benefit.[19,234] Plasma paraquat levels can be determined and may have a role in prognosticating survival.[241] Data suggest a possible benefit from immunosuppression, but this awaits confirmation through controlled clinical trials.[20] Death results from multiorgan failure and usually occurs within 1 to 2 weeks, but may be observed up to 6 weeks after ingestion.

Smoke Inhalation

The generic term *smoke inhalation* includes potential exposure to a wide array of substances because of the complex chemistry of heat decomposition and pyrolysis.[24,28] Although cytotoxic anoxia from carbon monoxide, cyanide, and oxidants represents a major manifestation of toxic insult from acute smoke inhalation, this *nonpulmonary target organ* effect is not covered here.[242–244] However, there are a number of chemical irritants produced as pyrolysis by-products that do have significant potential target organ pulmonary toxicity. In contrast to thermal injury to the respiratory tract, which is typically limited to upper airways, with laryngeal edema the major potential medical management problem,[24,245,246] smoke inhalation from fires can affect the entire respiratory tract through irritant injury.

In certain cases, irritant chemicals from fires result from liberation of preformed substances, but most commonly, the toxins of concern are formed de novo. These irritants are produced by the thermal degradation of both naturally occurring and synthetic polymers. The predominant by-products of heat breakdown are determined by the nature of the polymers consumed, but the precise mixture of agents released in any specific event may be difficult to predict, varying in particular according to temperature and oxygen availability.[78,247]

Generally, the chemical monomer precursor is not a significant polymer breakdown product, although residual monomers can be evolved under certain circumstances. For example, hydrogen chloride rather than vinyl chloride is released when polyvinyl chloride is burned. Many of the specific chemical irritants that can be released as common thermal breakdown by-products are addressed elsewhere in this chapter. These include the following: hydrochloric acid (hydrogen chloride), hydrofluoric acid (hydrogen fluoride), and other acids; ammonia; phosgene; and oxides of nitrogen. The zinc chloride "smoke" of smoke bombs (in contrast to the heterogeneous character of "natural smoke") is also discussed separately.

Aldehydes merit specific attention, however, because smoke from fires may represent the most common source of high-intensity irritant inhalant injury caused by this group of chemicals. These chemicals include formaldehyde, acetaldehyde, and acrolein. Of these aldehydes, **acrolein** (CH_2=CHCHO), although the most severe irritant, is least familiar to most health care providers. Acrolein, a highly reactive chemical, is formed as an important pyrolysis product of both synthetic (e.g., acrylic) and natural polymers.[248]

The general considerations concerning irritant exposure discussed previously, including air concentration and water solubility, come into play in smoke inhalation. These factors are further complicated by the potential interactive effects of multiple simultaneous exposures as well as the modifying impact of physical cofactors such as airborne respirable particulates (e.g., soot) that may serve as adsorbent carriers facilitating deep lung penetration. In practice, detailed exposure data delineating the irritant contents of a specific smoke exposure are rarely available. Information that may help to elucidate exposure conditions include identity of the products involved (e.g., specific synthetic polymers, if known), history of inhalation within an enclosed or confined space, evidence of thermal injury, and carboxyhemoglobin and methemoglobin levels as markers of inhalation severity based on other concomitant exposures (carbon monoxide and oxidants).[242–244]

Firefighters (both urban and wildland) and nonoccupationally exposed victims of irritant smoke inhalation have proved important groups in which to study acute inhalational syndromes. Large-scale conflagrations (e.g., urban "wildland" fires) can expose substantial numbers of people to irritant combustion by-products, as can smoke drift from intentional burning of agricultural residue. Studies of such populations have demonstrated acute and persistent airflow obstruction and increased nonspecific airway hyperresponsiveness after smoke inhalation.[249–257] Bronchiectasis and BO have both been associated with combustion by-product exposure.[46,49] The acute respiratory effects and potential sequelae of exposure to the plume generated by the destruction of the World Trade Center appear to relate to other factors such as alkaline (high-pH) dust from concrete, gypsum, and glass fibers, rather than to standard smoke particulate.[32,51,258,259]

Pharmacologic Syndromes

Certain natural and synthetic chemical exposures exert acute target organ lung effects mediated by specific mechanisms consistent with known pharmacologic actions. These chemicals are site-specific for key cellular functions leading to adverse respiratory effects. As noted previously, the most potent chemical warfare agents act through acetyl cholinesterase inhibition, with profound impacts on respiratory function.[137,138] Similar, albeit less potent, agents have widespread use as agricultural chemicals. Both **organophosphate** and **carbamate pesticides** lead to respiratory compromise as a principal toxic effect. For example, in one case series, a considerable number of poisonings from these pesticides led to respiratory failure, accompanied by a high case-fatality rate; in contrast, all the patients without concomitant respiratory failure survived.[260]

Inhaled **capsaicin**, of interest as a research tool to study *substance P*–mediated effects, is associated with cough in occupational settings (e.g., in chili pepper processing).[261] When used as a "personal defense spray," respiratory irritation has been reported, although ocular problems are more common.[262] Another naturally occurring toxin with a primary respiratory effect is **brevetoxin**. This toxin, produced by dinoflagellates, is associated with "red tides." Environmental inhalation exposure from airborne aerosols of **red tide** (due to wind and surf action) causes cough, sneeze, and wheeze.[263,264] The toxin appears to act by stimulating sodium channels in the lung. Respiratory irritation may also be a manifestation of *Pfiesteria* dinoflagellate toxin inhalation (although potential neurotoxicologic effects have been of more concern).[265,266]

Other Inhalant Exposures

Ammonia

Anhydrous **ammonia** is a gas at room temperature and ambient pressure, although ammonia more commonly is encountered in aqueous form (e.g., in cleaning solutions). In addition to incidents in the chemical industry and in hazardous transportation, commercial refrigeration systems and farming (fertilizer) represent important sources of potential exposure to ammonia gas.[7,267–273] Anhydrous ammonia release has also occurred from illicit methamphetamine laboratory operations, although such exposures are often in the context of conflagrations with concomitant thermal burns and other coexposures.[274] Ammonia has prominent irritant warning properties (such as burning eyes). It is linked with lung injury chiefly in settings of overwhelming exposure or where immediate escape has not been possible. Asthma and bronchiectasis both have been documented after ammonia exposure.[7,271] Acute ammonia exposure has also been reported to have residual upper airway effects, including decreased olfactory acuity.[29] Death may result from laryngeal edema and airway obstruction, acute pulmonary edema, or complications of the pneumonic process (e.g., bacterial superinfection).

Bromine and Methyl Bromide

Bromine is an irritant halogen. It usually is handled as a liquid rather than as a gas, but it vaporizes readily. Sources of bromine exposure other than environmental releases include chemical synthesis and water purification.[50,275–278] Bromine is a more potent irritant than chlorine and approximately a hundred times more irritating than ammonia.[279] **Methyl bromide** is a major industrial fumigant with far-greater potential for public exposure. Methyl bromide is also a potent respiratory irritant, but central nervous system effects may account for more important target organ toxicity in typical exposures.[280,281]

Hydrogen Sulfide

Hydrogen sulfide is a common by-product of petroleum extraction and refining as well as a potential hazard from the breakdown of organic materials (hence, its common name, "sewer gas").[282] Significant release can also occur through geothermal and volcanic sources.[283] Hydrogen sulfide is a respiratory irritant, but it is an even more potent cytotoxic asphyxiant, impairing cytochrome oxidase and cellular respiration. Therefore, in cases of severe hydrogen sulfide exposure, rapid cardiovascular collapse and death often overshadow any pulmonary organ effects, with irritant symptoms of importance only in lower intensity exposures.[282,284–288]

Methyl Isocyanate and Methyl Isothiocyanate

Methyl isocyanate (MIC) use is restricted to a narrow industrial application in the synthesis of pesticides. The mass fatalities at Bhopal, India, make MIC an important toxin for historical reasons. The toxicity of MIC was the result of its severe irritant properties leading to pulmonary edema.[289–291] No cyanide-mediated mechanism was involved. **Methyl isothiocyanate**, a breakdown product of the soil fumigant metam sodium, is an irritant chemically related to MIC that was also involved in a mass exposure episode, although less severe than the MIC release at Bhopal, and has also been associated with respiratory symptoms following agricultural application.[292,293] Urethane exposures do not involve MIC and do not have its toxicity; the isocyanates associated with urethane, such as toluene diisocyanate (TDI), diphenylmethane diisocyanate (MDI), and hexamethylene diisocyanate (HDI), are pulmonary irritants but are primarily of concern because of the sensitization they induce (see Chapter 64).

Miscellaneous Exposures

A number of other occupational and environmental agents result in acute pulmonary syndromes. Examples of such exposures include **diethylaminoethanol** and **cyclohexylamine** (both anticorrosive boiler additives),[294,295] **amitrole** and **glyphosphate** (both common herbicides),[296,297] **sodium azide** (used in a variety of chemical applications but important as a potential inhalant through automobile airbag deployment),[298] **diazomethane**, which is explosive but also highly toxic to the lung with a delayed onset similar to that of nitrogen dioxide,[299,300] **diborane** (an irritant gas used in manufacturing microelectronic equipment),[301,302] **barium** (inhalation can cause bronchospasm and respiratory muscle weakness in addition to life-threatening hypokalemia),[303] and **hydrogen selenide** (an irritant gas used in several industrial processes as well as being a potential metal processing by-product).[304,305]

Phosphine is an important agricultural fumigant with pulmonary and systemic toxicity that is generated on site as a gas given off by aluminum or zinc phosphide (e.g., in particular grain storage facilities or railway grain transport cars, where bystander exposure can occur); phosphine also has industrial applications, particularly in the production of microelectronics.[306–308a] **Acetic anhydride** (used in making epoxy and other resins) has also been associated with acute lung injury.[309] A distinctly different pattern of injury is associated with a related epoxy chemical, **trimellitic anhydride**, which causes severe pulmonary hemorrhage after subacute exposure.[16] **Osmium tetroxide** is a very potent respiratory irritant with terrorist weapon potential; fortunately, to date experience with human inhalation exposure has been limited.[310] **Carbon dioxide**, although a bulk asphyxiant and not a respiratory irritant, does cause shortness of breath and induces tachypnea; exposure can occur through natural geologic sources and through dry ice sublimation in an enclosed space.[311,312,312a]

Baby (talcum) powder aspiration is an inhalational pediatric acute pneumonitis occurring within hours of heavy exposure; infant inhalation of nontalcum powders has also led to pneumonitis.[313–315] Naturally occurring sources of exposure can also be associated with acute

and subacute lung responses, although these syndromes are poorly characterized.

Epidemiologically, *Stachybotrys chartarum* (*atra*) mold growth indoors in water-damaged residential structures was initially linked to a cluster of cases of pulmonary hemorrhage in infants, although the association was later retracted in a follow-up review by the U.S. Centers for Disease Control and Prevention.[316,317] The potential link between *Stachybotrys* and other human, predominantly nonpulmonary pathologies is even more questionable.[318] Other case reports have occasionally linked other molds or mold by-products with lung injury (as opposed to self-limited ODTS, discussed previously).[319] **Lycoperdonosis** is a potentially severe, acute pulmonary syndrome following intentional inhalation (sometimes as a natural medicinal treatment) of puffball mushroom (*Lycoperdon*) spores.[320,321,321a] The pathophysiology of the syndrome is not understood, but its high attack rate with heavy exposure suggests a toxic rather than an allergic or infective mechanism. Although toxic mushrooms with predominant muscarinic effects can cause bronchorrhea and bronchospasm, this would be anticipated to occur in the context of generalized cholinergic excess, similar to the anticholinesterase pesticides discussed previously.[322]

KEY POINTS

- Short-term inhalation exposures to toxic substances may have important effects on the lung as the target organ for damage.
- A number of substances cause acute respiratory tract toxicity, but the repertoire of pulmonary pathologic responses to such injury is fairly limited.
- Although modified by the solubility and other physical properties of the toxic agent, to a large degree, injury depends on the intensity and duration of exposure.
- Extensive injury can lead to acute pulmonary edema and diffuse alveolar damage.
- Specific exposures of importance include chlorine, oxides of nitrogen, sulfur dioxide, acid aerosols, toxic metal fumes, and pyrolysis by-products.
- Aside from acute irritant or toxic lung insult leading to airway injury and diffuse alveolar damage, other patterns of acute responses include the inhalation fevers (which are self-limited and appear to be cytokine mediated) and certain target-specific effects, such as those elicited by cholinesterase inhibition.
- Exposure by ingestion of some substances (e.g., hydrocarbons and paraquat) can cause important acute pulmonary target organ toxicity.
- Useful resources for information about specific toxins: National Library of Medicine's **TOXNET** (http://toxnet.nlm.nih.gov/) is a Web-based collection of resources covering toxicology, chemical safety, environmental health, and related areas. The **Household Products Database** (http://householdproducts.nlm.nih.gov/) is a consumer guide that provides information on the potential health effects of chemicals contained in more than 7000 common household products used inside and around the home. **Tox Town** (http://toxtown.nlm.nih.gov) is an interactive guide to commonly encountered toxic substances, public health, and the environment. **TOXMAP** (http://toxmap.nlm.nih.gov) is an interactive mapping site that helps users explore the geographic distribution of certain chemical releases, their relative amounts, and their trends over time. **Haz-Map** (http://hazmap.nlm.nih.gov) is an occupational health database designed for health and safety professionals and for consumers seeking information about the health effects of exposure to chemicals and biologicals at work. **WISER** (Wireless Information System for Emergency Responders) (http://wiser.nlm.nih.gov) is a system designed to assist first responders in hazardous material incidents.

References

1. Kreiss K, Gomma A, Kullman G, et al: Clinical bronchiolitis obliterans in workers at a microwave-popcorn plant. N Engl J Med 347:330–338, 2002.
2. van Rooy FGBGJ, Rooyakers JM, Prokop M, et al: Bronchiolitis obliterans syndrome in chemical workers producing diacetyl for food flavorings. Am J Respir Crit Care Med 176:498–540, 2007.
3. Kern DG, Crausman RS, Durand KTH: Flock worker's lung: Chronic interstitial lung disease in the nylon flocking industry. Ann Intern Med 129:261–272, 1998.
4. Kuschner W: What exactly is flock worker's lung? Chest 117:10–13, 2000.
5. Moya C, Anto JM, Newman Taylor AJ: Outbreak of organizing pneumonia in textile printing sprayers. Lancet 344:498–502, 1994.

6. Camus P, Nemery B: A novel cause for bronchiolitis obliterans organizing pneumonia: Exposure to paint aerosols in textile workshops. Eur Respir J 11:259–262, 1998.
7. Leduc D, Gris G, Lheureux P, et al: Acute and long-term respiratory damage following inhalation of ammonia. Thorax 47:755–757, 1992.
8. Rabonowitz S, Greyson ND, Weiser W, et al: Case report: Clinical and laboratory features of acute sulfur dioxide inhalation poisoning: Two year follow-up. Am Rev Respir Dis 139:556–558, 1989.
9. Karlson-Stiber C, Hojer J, Sjoholm A, et al: Nitrogen dioxide pneumonitis in ice hockey players. J Intern Med 239:451–456, 1996.
10. Menzel DB: Ozone: An overview of its toxicity in man and animals. J Toxicol Environ Health 13:183–204, 1984.
11. Snyder RW, Mishel HS, Christensen GC: Pulmonary toxicity following exposure to methylene chloride and its combustion product, phosgene. Chest 101:860–861, 1992.
12. Katzenstein, A-L: Katzenstein and Askin's Surgical Pathology of Non-neoplastic Lung Disease (4th ed). Edinburgh: Elsevier Saunders, 2006, pp 17–49.
13. Wright JL, Churg A: Diseases caused by gases and fumes. *In* Churg A, Green FHY (eds): Pathology of Occupational Lung Disease (2nd ed). Baltimore: Williams & Wilkins, 1998, pp 57–76.
14. Blanc PD, Golden JA: Unusual occupationally related disorders of the lung: Case reports and a literature review. Occup Med 7:403–422, 1992.
15. Das R, Blanc PD: Chlorine gas exposure and the lung. Toxicol Ind Health 9:439–455, 1993.
16. Pauluhn J, Carson A, Costa DL, et al: Workshop summary: Phosgene-induced pulmonary toxicity revisited: Appraisal of early and late markers of pulmonary injury from animal models with emphasis on human significance. Inhal Toxicol 19:789–810, 2007.
17. Nemery B: Metal toxicity and the respiratory tract. Eur Respir J 3:202–219, 1990.
18. Truemper E, Reyes De La Rocha S, Atkinson SD: Clinical characteristics, pathophysiology and management of hydrocarbon ingestion: Case report and review of the literature. Pediatr Emerg Care 3:187–193, 1987.
19. Dinis-Oliveira RJ, Duarte JA, Sánchez-Navarro A, et al: Paraquat poisonings: Mechanisms of lung toxicity, clinical features, and treatment. Crit Rev Toxicol 38:13–71, 2008.
20. Agarwal R, Srinivas R, Aggarwal AN, Gupta D: Immunosuppressive therapy in lung injury due to paraquat poisoning: A meta-analysis. Singapore Med J 48:1000–1005, 2007.
21. Blanc PD: Inhalation fever. *In* Rom WN, Markowitz SB (eds): Environmental and Occupational Medicine (4th ed). Philadelphia: Wolters Kluwer; Lippincott Williams & Wilkins 2007, pp 402–417.
22. Parkhouse DA, Brown RF, Jugg BJ, et al: Protective ventilation strategies in the management of phosgene-induced acute lung injury. Milit Med 172:295–300, 2007.
23. Russel D, Blaine PG, Rice P: Clinical management of casualties exposed to lung damaging agents: A critical review. Emerg Med J 23:421–424, 2006.
24. Lee AS, Mellines RB: Lung injury from smoke inhalation. Paediatr Respir Rev 7:123–128, 2006.
25. Demnati R, Fraser R, Martin JG, et al: Effects of dexamethasone on functional and pathological changes in rat bronchi caused by high acute exposure to chlorine. Toxicol Sci 45:242–246, 1998.
26. Wang J, Winskog C, Edston E, Walther SM: Inhaled and intravenous corticosteroids both attenuate chlorine gas–induced lung injury in pigs. Acta Anaesthesiol Scand 49:183–190, 2005.
27. Babu RV, Cardenas V, Sharma G: Acute respiratory distress syndrome from chlorine inhalation during a swimming pool acceded: A case report and review of the literature. J Intensive Care Med 23:275–280, 2008.
28. Demling RH: Smoke inhalation lung injury: An update. Eplasty 8:e27, 2008. (Downloaded 21 July 2008.)
29. Prudhomme JC, Shusterman DJ, Blanc PD: Acute-onset persistent olfactory deficit resulting from multiple overexposures to ammonia vapor at work. J Am Board Fam Pract 11:66–69, 1998.
30. Shusterman D: Upper and lower airway sequelae of irritant inhalations. Clin Pulm Med 6:18–31, 1999.
31. Perker JJ, Fennelly KP, Balkissoon R, et al: Irritant-associated vocal cord dysfunction. J Occup Environ Med 40:136–143, 1998.
32. de la Hoz RE, Shohet MR, Bienenfeld LA, et al: Vocal cord dysfunction in former World Trade Center (WTC) rescue and recovery workers and volunteers. Am J Ind Med. 51:161–165, 2008.
33. Blanc PD, Galbo M, Hiatt P, et al: Morbidity following acute irritant inhalation in a population-based study. JAMA 266:664–669, 1991.
34. Blanc PD, Galbo M, Hiatt P, et al: Symptoms, lung function and airway responsiveness following irritant inhalation. Chest 103:1699–1705, 1993.
35. Blanc PD: Chemical inhalation injury and its sequelae. West J Med 160:2–3, 1994.
36. Brooks SM, Weiss MA, Bernstein IL: Reactive airways dysfunction syndrome (RADS). Chest 88:376–384, 1985.
37. Alberts WM, Do Pico GA: Reactive airways dysfunction syndrome. Chest 109:1618–1626, 1996.
38. Blanc PD: RADS—A special entity? The role of irritant exposure in asthma. Proceedings of the first Jack Pepys Occupational Asthma Symposium. Am J Respir Crit Care Med 167:450–471, 2003.
39. Shakeri MS, Dick FD, Ayres JG: Which agents cause reactive airways dysfunction syndrome (RADS)? A systematic review. Occup Med (Lond) 58:205–211, 2008.
40. Tarlo S, Broder I: Irritant-induced occupational asthma. Chest 96:297–300, 1989.
41. Boulet LP: Increases in airway responsiveness following acute exposure to respiratory irritants: Reactive airway dysfunction syndrome or occupational asthma? Chest 94:476–481, 1988.
42. Suchyta MR, Elliot CG, Jensen RL, et al: Predicting the presence of pulmonary impairment in adult respiratory distress syndrome survivors. Respiration 60:103–106, 1993.
43. Yockey CC, Eden BM, Byrd RB: The McConnell missile accident: Clinical spectrum of nitrogen dioxide exposure. JAMA 244:1221–1223, 1980.
44. Zwemer FL, Pratt DS, May JJ: Silo filler's disease in New York State. Am Rev Respir Dis 146:650–653, 1992.
45. Lenci G, Wacker G, Schulz V, et al: [Bronchiolitis obliterans after inhalation of nitrogen dioxide (NO_2): Clinical, radiological, histological observations] (German). Pneumonologie 44:32–36, 1990.
46. Konichezsky S, Schatter A, Ezri T, et al: Thionyl-chloride–induced lung injury and bronchiolitis obliterans. Chest 104:971–973, 1993.
47. Janigan DT, Kiolp T, Michael R, et al: Bronchiolitis obliterans in a man who used his wood-burning stove to burn synthetic construction materials. CMAJ 156:1171–1173, 1997.
48. Segev JS, Mason UG, Worthen S, et al: Bronchiolitis obliterans: Report of three cases with detailed physiologic studies. Chest 83:169–174, 1983.
49. Tasaka S, Kanazawa M, Mori M, et al: Long-term course of bronchiectasis and bronchiolitis obliterans as late complication of smoke inhalation. Respiration 62:40–42, 1995.
50. Kraut A, Lilis R: Chemical pneumonitis due to exposure to bromine compounds. Chest 94:208–210, 1988.
51. Emad A, Rezaian GR: The diversity of the effects of sulfur mustard gas inhalation on respiratory system 10 years after a single, heavy exposure: Analysis of 197 cases. Chest 112:734–738, 1997.
52. Kass I, Zamel N, Dobry CA, et al: Bronchiectasis following ammonia burns of the respiratory tract. Chest 62:282–285, 1972.
53. Breton D, Jouvet P, de Blic J, et al: [Smoke inhalation injury: Two pediatric cases] (French). Arch Fr Pediatr 50:43–45, 1993.
54. Mahut B, Delacourt C, de Blic J, et al: Bronchiectasis in a child after acrolein inhalation. Chest 104:1286–1287, 1993.
55. Cantera Maortua JM, Martín Moreno S, Subhi Afmad I, Torres Nieto MA: [Bronchiolitis obliterans with organizing pneumonia. Secondary to chlorine gas inhalation?] (Spanish). Rev Clin Esp 188:217–218, 1991
56. Sheu BF, Lee CC, Young YR, et al: Delayed-onset bronchiolitis obliterans with organizing pneumonia associated with massive acetic acid steam inhalation. Thorax 63:570, 2008.
57. Gapany-Gapanavicius M, Yellin A, Almog S, Tirosh M: Pneumomediastinum. A complication of chlorine exposure from mixing household cleaning agents. JAMA 248:349–350, 1982.

58. Akdur O, Durukan P, Ikizceli I, et al: A rare complication of chlorine gas inhalation: Pneumomediastinum. Emerg Med J 23:e59, 2006 (Downloaded 24 July 2008.)
59. Lossos I, Abolnik I, Breuer R: Pneumomediastinum: A complication of exposure to bromine. Br J Ind Med 47:784, 1990.
59a. Serinken M, Karcioglu O, Evyapan F, Sungurtekin H: Bilateral pneumothorax following acute lung injury. Clin Toxicol 47:595–597, 2009.
60. Wagner JH: Bronchiolitis obliterans following the inhalation of acrid fumes. Am J Med Sci 154:511–522, 1917.
61. Mann JM, Sha KK, Kline G, et al: World Trade Center Dyspnea: Bronchiolitis obliterans with functional improvement: A case report. Am J Ind Med 48:225–229, 2005.
62. Piirla PL, Nordman H, Korhonen OS, et al: A thirteen-year follow-up of respiratory effect of acute exposure to sulfur dioxide. Scand J Work Environ Health 22:191–196, 1996.
63. Owens MW: Clinical significance of an isolated reduction in residual volume. Am Rev Respir Dis 136:1377–1380, 1987.
64. Buick JB, Lowry RC, Magee TRA: Is a reduction in residual volume a sub-clinical manifestation of hydrogen sulfide intoxication? Am J Ind Med 37:296–299, 2000.
65. Bowler RM, Mergler D, Huel G, et al: Psychological, psychosocial, and psychophysiological sequelae in a community affected by a railroad chemical disaster. J Trauma Stress 7:601–624, 1994.
66. Kovalchick DF, Burgess JL, Kyes KB, et al: Psychological effects of hazardous materials exposures. Psychosom Med 64:841–846, 2002.
67. Blanc PD, Galbo MS, Balmes JR, et al: Occupational factors in work-related inhalations: Inferences for prevention strategy. Am J Ind Med 25:783–791, 1994.
68. Winder C: The toxicology of chlorine. Environ Res A 85:105–114, 2001.
69. Horton DK, Berkowitz Z, Kaye WE: The public health consequences from acute chlorine releases, 1993–2000. J Occup Environ Health 44: 906–913, 2002.
70. Schwartz DA, Smith DD, Lakshminarayan S: The pulmonary sequelae associated with accidental inhalation of chlorine gas. Chest 97:820–825, 1990.
71. Jones RN, Hughes JM, Glindmeyer H, et al: Lung function after acute chlorine exposure. Am Rev Respir Dis 134:1190–1195, 1986.
72. Van Sickle D, Wenck MA, Belflower A, et al: Acute effects after exposure to chlorine gas released after a train derailment. Am J Emerg Med 27:1–7, 2009.
73. Fleta J, Calvo C, Zuniga J, et al: Intoxication of 76 children by chlorine gas. Hum Toxicol 5:99–100, 1986.
74. Vohra R, Clark RF: Chlorine-related inhalation injury from a swimming pool disinfectant in a 9-year old girl. Pediatr Emerg Care 22:254–257, 2006
75. Centers for Disease Control: Chlorine gas toxicity from mixture of bleach with other cleaning products—California. MMWR Morb Mortal Wkly Rep 40:619–621, 627–629, 1991.
76. Centers for Disease Control and Prevention: Homemade chemical bomb events and resulting injuries—Selected States, January 1996–March 2003. MMWR Morb Mortal Wkly Rep 52:662–664, 2003.
77. Eckert WG: Mass deaths by gas or chemical poisoning. Am J Forensic Med Pathol 12:119–125, 1991.
78. Hasan FM, Geshan A, Fuleihan FJD: Resolution of pulmonary dysfunction following acute chlorine exposure. Arch Environ Health 38:76–80, 1983.
79. Bernard A, Carbonelle S, Michel O, et al: Lung hyperpermeability and asthma prevalence in school children: Unexpected associations with the attendance at indoor chlorinated swimming pools. Occup Environ Med 60:385–394, 2003.
80. Pascuzzi TA: Mass casualties from acute inhalation of chloramine gas. Mil Med 163:102–104, 1998.
81. Jacobs JH, Spaan S, van Rooy GB, et al: Exposure to trichloramine and respiratory symptoms in indoor swimming pool workers. Eur Respir J 29:690–698, 2007.
82. Salisbury DA, Enarson DA, Chan-Yeung M, et al: First-aid reports of acute chlorine gassing among pulpmill workers as predictors of lung health consequences. Am J Ind Med 20:71–81, 1991.
83. Promisloff RA, Phan A, Lenchner GS, et al: Reactive airway dysfunction syndrome in three police officers following a roadside chemical spill. Chest 98:928–929, 1990.
84. Dunkel R, Wermke R, Felgenhauer N, et al: Short term thionylchloride exposure causing delayed airway obstruction (abstract). J Toxicol Clin Toxicol 37:417, 1999.
85. Shusterman D, Balmes J, Avila PC, et al: Chlorine inhalation produces nasal congestion in allergic rhinitics without mast cell degranulation. Eur Respir J 21:652–657, 2003.
86. D'Alessandro A, Kuschner W, Wong H, et al: Exaggerated responses to chlorine inhalation among persons with non-specific airway hyperreactivity. Chest 109:331–337, 1996.
87. Vinsel PJ: Treatment of acute chlorine gas inhalation with nebulized sodium bicarbonate. J Emerg Med 8:327–329, 1990.
88. Bosse GM: Nebulized sodium bicarbonate in the treatment of chlorine gas inhalation. Clin Toxicol 232:233–241, 1994.
89. Douidar SM: Nebulized sodium bicarbonate in acute chlorine inhalation. Pediatr Emerg Care 13:406–407, 1997.
90. Guloglu C, Kara IH, Erten PG: Acute accidental exposure to chlorine gas in the southeast of Turkey: A study of 108 cases. Environ Res A 88:29–33, 2002.
91. Aslan S, Kandiş H, Akgun M, et al: The effect of nebulized $NaHCO_3$ treatment on "RADS" due to chlorine gas inhalation. Inhal Toxicol 18:895–900, 2006.
92. Ainslie G: Inhalational injuries produced by smoke and nitrogen dioxide. Respir Med 87:169–174, 1993.
93. Douglas WW, Hepper NG, Colby TV: Silo-filler's disease. Mayo Clin Proc 64:291–304, 1989.
94. Leavey JF, Dubin RL, Singh N, Kaminsky DA: Silo-filler's disease, the acute respiratory distress syndrome, and oxides of nitrogen. Ann Intern Med 141:410–411, 2004.
95. Hedberg K, Hedberg CW, Iber C, et al: An outbreak of nitrogen dioxide induced respiratory illness among ice hockey players. JAMA 262:3014–3017, 1989.
96. Centers for Disease Control: Nitrogen dioxide and carbon monoxide intoxication in an indoor ice arena—Wisconsin, 1992. MMWR Morb Mortal Wkly Rep 41:383–385, 1992.
97. Kahan ES, Martin UJ, Spungen S, et al: Chronic cough and dyspnea in ice hockey players after an acute exposure to combustion products of a faulty ice resurfacer. Lung 185:47–54, 2007.
98. Ellis FP: The hazards of toxic gases in warships excluding agents of chemical warfare. *In* Cope VZ (ed): History of the Second World War: Medicine and Pathology. London: Her Majesty's Stationary Office, 1952, pp 304–318.
99. Hajela R, Janigan DT, Landrigan PL, et al: Fatal pulmonary edema due to nitric acid inhalation in three pulp-mill workers. Chest 97:487–489, 1990.
100. Shin JS, Lee S-W, Kim N-H, et al: Successful extracorporeal life support after potentially fatal pulmonary oedema cause by inhalation of nitric acid and hydrofluoric acid fumes. Resuscitation 75:184–188, 2007.
101. Murphy CM, Akbarnia H, Rose SR: Fatal pulmonary edema after acute occupational exposure to nitric acid. J Emerg Med Epub 2008;October 7 (ahead of print).
102. National Institute for Occupational Safety and Health: Criteria for a Recommended Standard: Welding, Brazing and Thermal Cutting. Publication No. 88-110. Cincinnati, OH: U.S. Department of Health and Human Services, 1988.
103. Tanaka N, Emoto T, Matsumoto T, et al: Inhalational lung injury due to nitrogen dioxide: High-resolution computed tomography findings in 3 patients. J Comput Assist Tomogr 31: 808–811, 2007
104. Quereshi MA, Shah NJ, Hemmen CW, et al: Exposure of intensive care nurses to nitric oxide and nitrogen dioxide during therapeutic use of inhaled nitric oxide in adults with acute respiratory distress syndrome. Am J Crit Care 11:147–153, 2002.
105. Toren K, Blanc PD: The history of pulp and paper bleaching with special emphasis on its respiratory health effects. Lancet 349:1316–1318, 1997.
106. Henneberger PK, Olin AC, Andersson E, et al: The incidence of respiratory symptoms and diseases among pulp mill workers with peak exposures to ozone and other irritant gases. Chest 128:3028–3037, 2005.
107. Centers for Disease Control: Sulfur dioxide exposure in Portland cement plants. MMWR Morb Mortal Wkly Rep 33:195–196, 1984.

108. Koksal N, Hasanoglu HC, Gokirmak M, et al: Apricot sulfurization: An occupation that induces an asthma-like syndrome in agricultural environments. Am J Ind Med 43:447–453, 2003.
109. Centers for Disease Control: Acute occupational exposure to sulfur dioxide—Missouri. MMWR Morb Mortal Wkly Rep 32:541–542, 1983.
110. Andersson E, Knutsson A, Hagberg S, et al: Incidence of asthma among workers exposure to sulphur dioxide and other irritant gases. Eur Respir J 27:720–725, 2006.
111. Galea M: Fatal sulfur dioxide inhalation. Can Med Assoc J 91:345–347, 1964.
112. Ip M, Wong K-L, Wong K-F, et al: Lung injury in dimethyl sulfate poisoning. J Occup Med 31:141–143, 1989.
113. Rippey JCR, Stallwood MI: Nine cases of accidental exposure to dimethyl sulphate—A potential chemical weapon. Emerg Med J 22:878–879, 2005.
114. National Institute for Occupational Safety and Health: Criteria for a Recommended Standard: Chromic Acid. Publication No. 73-11021. Cincinnati, OH: U.S. Department of Health, Education, and Welfare, 1973.
115. Kern DG: Outbreak of the reactive airways dysfunction syndrome after a spill of glacial acetic acid. Am Rev Respir Dis 144:1058–1064, 1991.
116. Yelon JA, Simpson RL, Gudjonsson O: Formic acid inhalation injury: A case report. J Burn Care Rehabil 17:241–242, 1996.
117. Wing J, Sanderson LM, Bender JD, et al: Acute health effects in a community after a release of hydrofluoric acid. Arch Environ Health 46:155–160, 1991.
118. Franzblau A, Sahakian N: Asthma following household exposure to hydrofluoric acid. Am J Ind Med 44:321–324, 2003
119. Upfal M, Doyle C: Medical management of hydrofluoric acid exposure. J Occup Med 32:726–731, 1990.
120. Zanen AL, Rietveld AP: Inhalation trauma due to overheating in a microwave oven. Thorax 48:300–302, 1993.
121. Taiwo OA, Sircar KD, Slade MD, et al: Incidence of asthma among aluminum workers. J Occup Environ Med 48:275–282, 2006.
122. Kraut A, Lillis R: Pulmonary effects of acute exposure to degradation products of sulphur hexafluoride during electrical cable repair work. Br J Ind Med 47:829–832, 1990.
123. Institute of Medicine, Pechura CM, Rall DP (eds): Veterans at Risk: The Health Effects of Mustard Gas and Lewisite. Washington, DC: National Academy Press, 1993.
124. Kales SN, Christiani DC: Acute chemical emergencies. N Engl J Med 350:800–808, 2004.
125. Freitag L, Firusian N, Stamatis G, et al: The role of bronchoscopy in pulmonary complications due to mustard gas inhalation. Chest 100:1436–1441, 1991.
126. Blanc PD: The legacy of war gas (editorial). Am J Med 106:689–690, 1999.
127. Blanc PD Occupational and environmental "orphan" respiratory diseases (editorial). Am J Respir Crit Care Med 173:253–254, 2006.
128. Bagheri MH, Hosseini SK, Mostafavi SH, Alalvi SA: High-resolution CT in chronic pulmonary changes after mustard gas exposure. Acta Radiol 44:241–245, 2003.
129. Ghanei M, Harandi AA: Long-term consequences from exposure to sulfur mustard: A review. Inhal Toxicol 19:451–456, 2007.
130. Wang GQ, Xia ZF: Tissue injury by hot fluid containing nitrogen mustard. Burns 33:923–926, 2007.
131. English JM: A case of probable phosgene poisoning. Br Med J 1:38, 1964.
132. Borak J, Diller WF: Phosgene exposure: Mechanisms of injury and treatment strategies. J Occup Environ Med 43:110–119, 2000.
133. Sciuto AM, Hurt HH: Therapeutic treatments of phosgene-induced lung injury. Inhal Toxicol 16:565–580, 2004.
134. TeSlaa G, Kaiser M, Biederman L, et al: Chloropicrin toxicity involving animal and human exposure. Vet Hum Toxicol 28:323–324, 1986.
135. Gonmori K, Muto H, Yamamoto T, et al: A case of homicidal intoxication by chloropicrin. Am J Forensic Med Pathol 8:135–138, 1987.
136. Centers for Disease Control and Prevention: Illness associated with drift of chloropicrin soil fumigant into a residential area—Kern County, California, 2003. MMWR Morb Mortal Wkly Rep 53:740–742, 2004.
137. Dunn MA, Sidell FR: Progress in medical defense against nerve agents. JAMA 262:649–652, 1989.
138. Danon YL, Shemer J (eds): Chemical Warfare Medicine: Aspects and Perspectives of the Persian Gulf War. Jerusalem, Israel: Gefen, 1994.
139. Nambiar MP, Gordon RK, Rezk PE, et al: Medical countermeasure against respiratory toxicity and acute lung injury following inhalation exposure to chemical warfare nerve agent VX. Toxicol Appl Pharmacol 219:142–150, 2007.
140. Reider MJ: Lacrimators. Clin Toxicol Rev 9:1–4, 1987.
141. Jones GRN: CS and its chemical relatives. Nature 235:257–261, 1972.
142. Beswick FW: Chemical agents used in riot control and warfare. Hum Toxicol 2:247–256, 1983.
143. Spark S, Giammona ST: Toxic effect of tear gas on an infant following prolonged exposure. Am J Dis Child 123:245–246, 1972.
144. Hu H, Fine JM, Epstein P, et al: Tear gas—Harassing agent or toxic chemical weapon? JAMA 262:660–663, 1989.
145. Roth VS, Franzblau A: RADS after exposure to a riot-control agent: A case report (letter). J Occup Environ Med 38:863–865, 1996.
146. Hill AR, Silverberg NB, Mayorga D, et al: Medical hazards of the tear gas CS. Medicine 79:234–240, 2000.
147. Brown RFR, Marrs TC, Rice P, et al: The histopathology of rat lung following exposure to zinc oxide/hexachlorethane smoke or instillation of zinc chloride followed by treatment with 70% oxygen. Environ Health Perspect 85:81–87, 1990.
148. Loh C-H, Chang Y-W, Lious S-H, et al: Case report: Hexachloroethane smoke inhalation: A rare cause of severe hepatic injuries. Environ Health Perspect 114:763–765, 2006.
149. Evans EH: Casualties following exposure to zinc chloride smoke. Lancet 2:368–369, 1945.
150. Schenker MR, Speizer FE, Taylor JO: Acute upper respiratory symptoms resulting from exposure to zinc chloride aerosol. Environ Res 25:317–324, 1981.
151. Pettila V, Takkunen O, Tukiainen P: Zinc chloride smoke inhalation: A rare case of severe acute respiratory distress syndrome. Intensive Care Med 26:215–217, 2000.
152. Huang KL, Chen CW, Chu SJ, et al: Systemic inflammation caused by white smoke inhalation in a combat exercise. Chest 133:722–728, 2008.
153. Anthony JS, Zamel N, Aberman A: Abnormalities in pulmonary function after brief exposure to toxic metal fumes. J Can Med Assoc 119:586–588, 1978.
154. Barnhart S, Rosenstock L: Cadmium chemical pneumonitis. Chest 86:789–791, 1984.
155. Fuortes L, Leo A, Ellerbeck PG, et al: Acute respiratory fatality associated with exposure to sheet metal and cadmium fumes. Clin Toxicol 29:279–283, 1991.
156. Panchal L, Vaideeswar P: Acute lung injury due to cadmium inhalation—A case report. Indian J Microbiol 49:265–266, 2006.
157. Sethi PK, Khandelwal D, Sethi N: Cadmium exposure: Health hazards of silver cottage industry in developing countries. J Med Toxicol 2:14–15, 2006.
158. Levin M, Jacobs J, Polos PG: Acute mercury poisoning and mercurial pneumonitis from gold ore purification. Chest 94:551–556, 1988.
159. Rowens B, Guerrero-Bentacourt D, Gottlieb CA, et al: Respiratory failure and death following acute inhalation of mercury vapor. Chest 99:185–190, 1991.
160. Moromisato DY, Anas N, Goodman G: Mercury inhalation poisoning and acute lung injury in a child: Use of high-frequency oscillatory ventilation. Chest 105:613–615, 1994.
161. Solis MT, Yuen E, Cortez PS, Goebel PJ: Family poisoned by mercury vapor inhalation. Am J Emerg Med 18:599–602, 2000.
162. Glezos JD, Albrecht JE, Gair RD: Pneumonitis after inhalation of mercury vapors. Can Respir J 13:150–152, 2006.
163. Ho BSJ, Lin J-L, Huang C-C, et al: Mercury vapor inhalation from Chinese red (cinnabar). J Toxicol Clin Toxicol 41:75–78, 2003.
164. Mohan S, Tamilarasan A, Buhl A: Inhalational mercury poisoning masquerading as toxic shock syndrome. Anaesth Intensive Care 22:305–306, 1994.

165. Zicheng S: Acute nickel carbonyl poisoning: A report of 179 cases. Br J Ind Med 43:422–424, 1986.
166. Scott LK, Grier LR, Arnold TC, Conrad SA: Respiratory failure from inhalational nickel carbonyl exposure treated with continuous high-volume hemofiltration and disulfiram. Inhal Toxicol 14:1103–1109, 2002.
167. Seet RC, Johan A, Teo CE, et al: Inhalational nickel carbonyl poisoning in waste processing workers. Chest 128:424–429, 2005.
168. Donoso A, Cruces P, Camacho J, et al: Acute respiratory distress syndrome resulting from inhalation of powdered copper. Clin Toxicol (Phila) 45:714–716, 2007.
169. Blanc P, Boushey HA: The lung in metal fume fever. Semin Respir Med 14:212–225, 1993.
170. Kurta DL, Dean BS, Krenzelok EP: Acute nickel carbonyl poisoning. Am J Emerg Med 11:64–66, 1993.
171. Bradberry SM, Vale JA: Therapeutic review: Do diethyldithiocarbamate and disulfiram have a role in acute nickel carbonyl poisoning? Clin Toxicol 37:259–264, 1999.
172. Irsigler GB, Visser PJ, Spangenberg PAL: Asthma and chemical bronchitis in vanadium plant workers. Am J Ind Med 35:366–374, 1999.
173. Woodin MA, Liu Y, Neuberg D, et al: Acute respiratory symptoms in workers exposed to vanadium-rich fuel-oil ash. Am J Respir Crit Care Med 37:353–363, 2000.
174. Ghio AJ, Gilbey JG, Roggli VL, et al: Diffuse alveolar damage after exposure to an oil fly ash. Am J Respir Crit Care Med 164:1514–1518, 2001.
175. Vandenplas O, Binard-van Cangh F, Gregoire J, et al: Fever and neutrophilic alveolitis caused by a vanadium-based catalyst. Occup Environ Health 59:785–787, 2002.
176. Wax PM, Dockstader L: Tributyltin use in interior paints: A continuing health hazard. Clin Toxicol 33:239–241, 1995.
177. Rask-Andersen A, Pratt DS: Inhalation fever: A proposed unifying term for febrile reactions to inhalation of noxious substances. Br J Ind Med 49:40, 1992.
178. Centers for Disease Control: Polymer-fume fever associated with cigarette smoking and the use of tetrafluoroethylene—Mississippi. MMWR Morb Mortal Wkly Rep 36:515–516, 521–522, 1987.
179. Volgelmeier C, Konig G, Bencze K, et al: Pulmonary involvement in zinc fume fever. Chest 92:946–948, 1987.
180. Blanc P, Wong H, Bernstein MS, et al: An experimental model of metal fume fever. Ann Intern Med 114:930–936, 1991.
181. Lecours R, Laviolette M, Cormier Y: Bronchoalveolar lavage in pulmonary mycotoxicosis (organic dust toxic syndrome). Thorax 41:924–926, 1986.
182. Drinker P, Thomson RM, Finn JL: Metal fume fever: II. Resistance acquired by inhalation of zinc oxide on two successive days. J Ind Hyg 9:98–105, 1927.
183. Neal PA, Schneiter R, Camanita BH: Report on acute illness among rural mattress makers using low grade, stained cotton. JAMA 119:1074–1082, 1942.
184. Robbins JJ, Ware RL: Pulmonary edema from Teflon fumes. N Engl J Med 271:360–361, 1964.
185. Evans EA: Pulmonary edema after inhalation of fumes from polytetra-fluoroethylene (PTFE). J Occup Med 15:599–601, 1973.
186. National Institute for Occupational Safety and Health: Occupational Exposure to Zinc Publication No. 76-104. Washington, DC: U.S. Department of Health, Education, and Welfare, 1976.
187. Borak J, Cohen H, Hethman TA: Copper exposure and metal fume fever: Lack of evidence for a causal relationship. Am Ind Hyg Assoc J 61:832–836, 2000.
188. Kuschner WG, Wong H, D'Alessandro A, et al: Human pulmonary responses to experimental inhalation of high concentration fine and ultrafine magnesium oxide particles. Environ Health Perspect 105:1234–1237, 1997.
189. Cavagna G, Finulli M, Vigliani EC: [Experimental study on the pathogenesis of Teflon fume fever] (Italian). Med Lav 52:251–261, 1961.
190. Lewis CE, Kerby GR: An epidemic of polymer fume fever. JAMA 191:375–378, 1965.
191. Wegman D, Peters JM: Polymer fume fever and cigarette smoking. Ann Intern Med 81:55–57, 1974.
192. Blanc PD, Boushey HA, Wong H, et al: Cytokines in metal fume fever. Am Rev Respir Dis 147:134–138, 1993.
193. Kuschner WG, D'Alessandro A, Wintermeyer SF, et al: Pulmonary responses to purified zinc oxide fume. J Investig Med 43:371–378, 1995.
194. Kuschner WG, D'Allesandro A, Wong H, et al: Early pulmonary cytokine responses to zinc oxide fume inhalation. Environ Res 75:7–11, 1997.
195. Fine JM, Gordon T, Chen LC, et al: Characterization of tolerance to inhaled zinc oxide in naive subjects and sheet metal workers. J Occup Environ Med 42:1085–1091, 2000.
196. Centers for Disease Control: Acute respiratory illness following occupational exposure to wood chips—Ohio. MMWR Morb Mortal Wkly Rep 35:483–484, 489–490, 1986.
197. Brinton WT, Vastbinder EE, Greene JW, et al: An outbreak of organic dust toxic syndrome in a college fraternity. JAMA 258:1210–1212, 1987.
198. May JJ, Stallones L, Darrow D, et al: Organic dust toxicity (pulmonary mycotoxicosis) associated with silo unloading. Thorax 41:919–923, 1986.
199. doPico GA, Flaherty D, Bhansali P, Chavaje N: Grain fever syndrome induced by inhalation of airborne grain dust. J Allergy Clin Immunol 69:435–443, 1982.
200. Schenker MB, Christiani D, Cormier Y, et al: Respiratory health hazards in agriculture. Am J Respir Crit Care Med 158:S1–S76, 1998.
201. Seifert SA, Von Essen S, Jacobitz K, et al: Organic dust toxic syndrome: A review. J Toxicol Clin Toxicol 41:185–193, 2003.
202. Emanuel DA, Wenzel FJ, Lawton BR: Pulmonary mycotoxicosis. Chest 67:293–297, 1975.
203. Taylor G: Acute systemic effects of inhaled occupational agents. *In* Merchant JA (ed): Occupational Respiratory Diseases. Washington, DC: U.S. Department of Health and Human Services, 1986, pp 607–625.
204. Glick TH, Gregg MB, Berman B, et al: Pontiac fever: An epidemic of unknown etiology in a health department: I. Clinical and epidemiologic aspects. Am J Epidemiol 107:149–160, 1978.
205. Goldberg DJ, Wrench JG, Collier PW, et al: Lochgoilhead fever: Outbreak of non-pneumonic legionellosis due to *Legionella micdadei*. Lancet 1:316–318, 1989.
206. Jones TF, Benson RF, Brown EW, et al: Epidemiological investigation of a restaurant-associated outbreak of Pontiac fever. Clin Infect Dis 37:1292–1296, 2003.
207. Muittari A, Kuusisto P, Sovijarvi A: An epidemic of bath water fever: Endotoxin alveolitis. Eur J Respir Dis 123(Suppl):108–116, 1982.
208. Atterholm I, Halberg T, Ganrot-Norlin K, Ringertz O: Unexplained acute fever after a hot bath. Lancet 1: 684–686, 1997.
209. Anderson K, Watt AD, Sinclair D, et al: Climate, intermittent humidification, and humidifier fever. Br J Ind Med 46:671–674, 1989.
210. Mamolen M, Lewis DM, Blanchet MA, Satink FJ, Vogt RL: Investigation of an outbreak of "humidifier fever" in a print shop. Am J Ind Med 23:483–490, 1993.
211. Simpson AT, Stear M, Groves JA, et al: Occupational exposure to metalworking fluid mist and sump fluid contaminants. Ann Occup Hyg 47:17–30, 2003.
212. Anderson K, McSharry CP, Clark C, et al: Sump bay fever: Inhalational fever associated with a biologically contaminated water aerosol. Occup Environ Med 53:106–111, 1996.
213. Wintermeyer SF, Kuschner WG, Wong H, et al: Pulmonary responses following wood chip mulch exposure. J Occup Environ Med 39:308–314, 1997.
214. Centers for Disease Control and Prevention: Severe acute respiratory illness linked to use of shoe sprays—Colorado, November 1993. MMWR Morb Mortal Wkly Rep 42:885–887, 1993.
215. Laliberte M, Sanfacon G, Blais R: Acute pulmonary toxicity linked to use of a leather protector. Ann Emerg Med 25:841–844, 1995.
216. Carson MF, White CM: Pneumonitis following inhalation of a commercially available water repellant. Clin Toxicol 39:179–180, 2001.
217. Wallace GM, Brown PH: Horse rug lung: Toxic pneumonitis due to fluorocarbon inhalation. Occup Environ Med 62:414–416, 2005.

218. Lazro-Blanchet C, Rusca S, Vernez D, et al: Acute pulmonary toxicity following occupational exposure to a floor stain protector in the building industry in Switzerland. Int Arch Occup Envrion Health 77:244–248, 2004.
219. Masaki Y, Suguyama K, Tanaka H, et al: Effectiveness of CT for clinical stratification of occupational lung edema. Ind Health 45:78–84, 2007.
220. Daubert GP, Spiller HA, Crouch BI, et al: Pulmonary toxicity following exposure to grout sealer. J Med Toxicol 5:125–129, 2009.
221. Bracco D, Favre J-P: Pulmonary injury after ski wax inhalation exposure. Ann Emerg Med 32:616–619, 1998.
222. Cormican LJ, Rees PJ: Hill walkers' lung. Respiration 73:836–839, 2006.
223. Klein BL, Simon JE: Hydrocarbon poisonings. Pediatr Clin North Am 33:411–419, 1986.
224. Dice WH, Ward G, Kelly J, et al: Pulmonary toxicity following gastrointestinal ingestion of kerosene. Ann Emerg Med 11:138–142, 1982.
225. Brook MP, McCarron MM, Mueller JA: Pine oil cleaner ingestion. Ann Emerg Med 18:391–395, 1989.
226. Mallavarapu RK, Katner HP: Pneumatocele complication acute hydrocarbon pneumonitis. Clin Toxicol (Phila) 46:911, 2008.
227. Nirenberg DW, Horowitz MB, Harris KM, et al: Mineral spirits inhalation associated with hemolysis, pulmonary edema, and ventricular fibrillation. Arch Intern Med 151:1437–1440, 1991.
228. Boots RJ, Weedon ZJ: Fire-eater's lung. Anaesth Intensive Care 36:449–453, 2008.
229. Kitchen JM, O'Brien DE, McLaughlin AM: Perils of fire eating. Thorax 63:401, 439, 2008.
230. Aboudara M, Yun J: A case of dire-eater's pneumonia in an active-duty soldier. MedGenMed 8:67, 2006.
231. Gentina T, Tillie-Leblond I, Birolleau S, et al: Fire-eaters lung. Medicine 80:291–297, 2001.
232. Guandalini M, Steinke K: Fire-eating: Hazards of hydrocarbon aspiration. Australas Radiol 51:567–569, 2007.
233. Trullás Vila JC, Pizarro Serra S, Noqué Xarau S, Soler Simón S: [Acute exogenous lipoid pneumonia in "fire-eaters". Description of two cases] (Spanish). Rev Clin Esp 207:240–242, 2007.
234. Bismuth C, Garnier R, Baud FJ, et al: Paraquat poisoning: An overview of the current status. Drug Safety 5:243–251, 1990.
235. Smith JC: Paraquat poisoning by skin absorption: A review. Hum Toxicol 7:15–19, 1988.
236. Im JQ, Lee KS, Han MC, et al: Paraquat poisoning: Findings on chest radiography and CT in 42 patients. AJR Am J Roentgenol 157:697–701, 1991.
237. Smith EA, Oehme FW: A review of selected herbicides and their toxicities. Vet Hum Toxicol 33:596–608, 1991.
238. Lin JL, Liu L, Leu ML: Recovery of respiratory function in survivors of paraquat intoxication. Arch Environ Health 50:432–439, 1995.
239. Van Der Wal NAA, Smith LL, Van Oirschot JFLM, et al: Effect of iron chelators on paraquat toxicity in rats and alveolar type II cells. Am Rev Respir Dis 145:180–186, 1992.
240. Saenghirunvattana S, Sermswan A, Piratchvej V, et al: Effect of lung irradiation on mice following paraquat intoxication. Chest 101:833–835, 1992.
241. Gil HW, Kang MS, Yang JO, et al: Association between plasma paraquat level and outcome of paraquat poisoning in 375 paraquat poisoning patients. Clin Toxicol (Phila) 46:515–518, 2008.
242. Summer W, Haponik E: Inhalation of irritant gases. Clin Chest Med 2:273–287, 1981.
243. Schwartz DA: Acute inhalational injury. Occup Med 2:297–318, 1987.
244. Miller K, Chang A: Acute inhalation injury. Emerg Med Clin North Am 21:533–557, 2003.
245. Haponik EF, Meyers DA, Munster AM, et al: Acute upper airway injury in burn patients: Serial changes of flow volume curves and nasopharyngoscopy. Am Rev Respir Dis 135:360–366, 1987.
246. Kuo DC, Jerrard DA: Environmental insults: Smoke inhalation, submersion, diving, and high altitude. Emerg Med Clin North Am 21:475–497, 2003.
247. Alarie Y: Toxicity of fire smoke. Crit Rev Toxicol 32:259–289, 2002.
248. Hale CA, Barkin PW, Jung W, et al: Synthetic smoke with acrolein but not HCl produces pulmonary edema. J Appl Physiol 64:1121–1133, 1988.
249. Sheppard D, Distefano S, Morse L, et al: Acute effects of routine firefighting on lung function. Am J Ind Med 9:333–340, 1986.
250. Stenton SC, Kelly CA, Waiters EH, et al: Induction of bronchial hyperresponsiveness following smoke inhalation injury. Br J Dis Chest 82:436–438, 1988.
251. Chia KS, Jeyaratnam J, Chan TB, et al: Airway responsiveness of firefighters after smoke exposure. Br J Ind Med 47:524–527, 1990.
252. Kinsella J, Carter R, Reid WH, et al: Increased airways reactivity after smoke inhalation. Lancet 337:595–597, 1991.
253. Liu D, Tager IB, Balmes JR, et al: The effect of smoke inhalation on lung function and airway responsiveness in wildland fire fighters. Am Rev Respir Dis 146:1469–1473, 1992.
254. Shusterman D, Kaplan JZ, Canabarro C: Immediate health effects of an urban wildfire. West J Med 158:133–138, 1993.
255. Long A, Tate RB, Neuman M, et al: Respiratory symptoms in a susceptible population due to burning of agricultural residue. Chest 113:351–357, 1998.
256. Park GY, Park JW, Jeong DH, et al: Prolonged airway and systemic inflammatory reactions after smoke inhalation. Chest 123:475–480, 2003.
257. Centers for Disease Control and Prevention. Monitoring health effects of wildfires using the BioSense system—San Diego County, California, October 2007. MMWR Morb Mortal Wkly Rep 57:741–744, 2008.
258. McGee JK, Chen LC, Cohen MD, et al: Chemical analysis of World Trade Center fine particulate matter for use in toxicologic assessment. Environ Health Perspect 111:972–980, 2003.
259. Herbstman JB, Frank R, Schwab M, et al: Respiratory effects of inhalation exposure among workers during the clean-up effort at the World Trade Center disaster site. Environ Res 99:85–92, 2005.
260. Tsao TC-Y, Juang Y-C, Lan R-S, et al: Respiratory failure of acute organophosphate and carbamate poisoning. Chest 98:631–636, 1990.
261. Blanc P, Liu D, Juarez C, Boushey HA: Cough in hot pepper workers. Chest 99:27–32, 1991.
262. Miller JJ, Skolnick J: Inhalation injury after capsaicin exposure. J Ky Med Assoc 104:103–105, 2006.
263. Abraham WM, Bourdelais AJ, Sabater JR, et al: Airway responses to aerosolized brevetoxins in an animal model of asthma. Am J Respir Crit Care Med 171:26–34, 2005.
264. Fleming LE, Kirkpatrick B, Backer LC, et al: Aerosolized red-tide toxins (brevetoxins) and asthma. Chest 131:187–194, 2007.
265. Haselow DT, Brown E, Tracy JK, et al: Gastrointestinal and respiratory tract symptoms following brief environmental exposure to aerosols during a *Pfiesteria*-related fish kill. J Toxicol Environ Health A 63:553–564, 2001.
266. Morris JG Jr: Human health effects and *Pfiesteria* exposure: A synthesis of available clinical data. Environ Health Perspect 109(Suppl):787–790, 2001.
267. Montague TJ, Macneil AR: Mass ammonia inhalation. Chest 77:496–498, 1980.
268. Flury KE, Dines DE, Rodarte JR, et al: Airway obstruction due to inhalation of ammonia. Mayo Clin Proc 64:291–304, 1989.
269. De La Hoz RE, Schlueter DP, Rom WN: Chronic lung disease secondary to ammonia inhalation injury: A report on three cases. Am J Ind Med 29:209–214, 1996.
270. Weisskopf MG, Drew JM, Hanrahan LP, et al: Hazardous ammonia releases: Public health consequences and risk factors for evacuation and injury, United States, 1993–1998. J Occup Environ Med 45:197–204, 2003.
271. White CE, Park MS, Renz EM, et al: Burn center treatment of patients with severe anhydrous ammonia injury: Case reports and literature review. J Burn Care Res 28:922–928, 2007.
272. Makarovsky I, Markel G, Dushnitsky T, Eisenkraft A: Ammonia—When something smells wrong. Israel Med Assoc J 10:437–543, 2008.
273. Centers for Disease Control and Prevention: Public health consequences among first responders to emergency events associated with illicit methamphetamine laboratories—Selected states, 1996–1999. MMWR Morb Mortal Wkly Rep 49:1021–1023, 2000.

274. Wells SM, Noonan C, Wells KM, et al: Effects of toxic gases: Methamphetamine inhalation. J Burn Care Res Epub 2008;December 3 (ahead of print).
275. Morabia A, Selleger C, Landry JC, et al: Accidental bromine exposure in an urban population: An acute epidemiological assessment. Int J Epidemiol 17:148–152, 1988.
276. Lossos IS, Abolnik I: Pneumomediastinum: A complication of exposure to bromine. Br J Ind Med 47:784, 1990.
277. Burns MJ, Linden CH: Another hot tub hazard: Toxicity secondary to bromine and hydrobromic acid exposure. Chest 111:816–819, 1997.
278. Inagaki N, Ishikawa M, Takeda M, et al: Case with bromine exposure leading to respiratory insufficiency. Chudoku Kenkyu 18:141–147, 2005.
279. Markovsky I, Markel G, Hoffman A: Bromine—The red cloud approaching. Isr Med Assoc J 9:677–679, 2007.
280. Hertzman J, Cullen MR: Methyl bromide intoxication in four field workers during removal of soil fumigation sheets. Am J Ind Med 17:321–326, 1990.
281. Centers for Disease Control: Unintentional methyl bromide gas release. MMWR Morb Mortal Wkly Rep 38:880–882, 1990.
282. Centers for Disease Control: Occupational fatality following exposure to hydrogen sulfide—Nebraska. MMWR Morb Mortal Wkly Rep 35:533–535, 1986.
283. Hansell AL, Horwell CJ, Oppenheimer C: The health hazards of volcanoes and geothermal areas. Occup Environ Med 63:149–156, 2006.
284. Jappinen P, Vilkka V, Marttila O, et al: Exposure to hydrogen sulphide and respiratory function. Br J Ind Med 47:824–828, 1990.
285. Parra O, Monso E, Gallego M, et al: Inhalation of hydrogen sulphide: A case of subacute manifestations and long term sequelae. Br J Ind Med 48:286–287, 1991.
286. Guidotti TL: Hydrogen sulphide. Occup Med 46:367–371, 1996.
287. Knight LD, Presnell SE: Death by sewer gas. Case report of a double fatality and review of the literature. Am J Forensic Med Pathol 26:181–185, 2005.
288. Yalamanchili C, Smith MD: Acute hydrogen sulfide toxicity due to sewer gas exposure. Am J Emerg Med 26:518e5–518e7, 2008.
289. Mehta PS, Mehta AS, Mehta SJ, et al: Bhopal tragedy's health effects: A review of methyl isocyanate. JAMA 264:2781–2787, 1990.
290. Dhra VR, Kriebel D: The Bhopal disaster: It's not too late for sound epidemiology (editorial). Arch Environ Health 48:436–438, 1993.
291. Dhara VR, Dhara R, Acquilla SD, Cullinan P: Personal exposure and long-term health effects in survivors of the union carbide disaster at Bhopal. Environ Health Perspect 110:487–500, 2002
292. Cone JE, Wugofski L, Balmes JR, et al: Persistent respiratory health effects after a metam sodium pesticide spill. Chest 106:500–508, 1994.
293. O'Malley M, Barry T, Ibara M, et al: Illness related to shank allocation of metam-sodium, Arvin, California, July, 2002. J Agromedicine 10:27–42, 2005.
294. Centers for Disease Control: Workplace exposures to corrosion-inhibiting chemicals from a steam humidification system—Ohio, 1988. MMWR Morb Mortal Wkly Rep 39:863–865, 1990.
295. Gadon ME, Melius JM, McDonald GJ, et al: New-onset asthma after exposure to the steam system additive 2-diethylaminoethanol. J Occup Med 36:623–626, 1994.
296. Balkisson R, Murray D, Hoffstein V: Alveolar damage due to inhalation of amitrole-containing herbicide. Chest 101:1174–1175, 1992.
297. Pushnoy LA, Avnon LS, Carel RS: Herbicide (Roundup) pneumonitis. Chest 114:1769–1770, 1998.
298. Gross KB, Haidar AH, Basha MA, et al: Acute pulmonary response of asthmatics to aerosols and gases generated by airbag deployment. Am J Respir Crit Care Med 150:408–414, 1994.
299. Ely TS: Diazomethane pneumonia. J Occup Med 10:326, 1968.
300. Stain JP, Nouvet G, Morere P: diazomethane[Poisoning by diazomethane poisoning] (French). Toxicol Eur Res 5:217–219, 1983.
301. Lowe HJ, Freeman G: Boron hydride (Borane) intoxication in man. Arch Ind Health 16:523–533, 1957.
302. Wald PH, Becker CE: Toxic gases used in the micro-electronics industry. Occup Med 1:105–117, 1986.
303. Jacobs IA, Taddeo J, Kelly K, et al: Poisoning as a result of barium styphnate explosion. Am J Ind Med 41:285–288, 2002.
304. Schecter A, Shanske W, Stenzler A, et al: Acute hydrogen selenide inhalation. Chest 77:554–555, 1980.
305. Banerjee BD, Dwivedi S, Singh S: Acute hydrogen selenide gas poisoning admissions in one of the hospitals in Delhi, India: A case report. Hum Exp Toxicol 16:276–278, 1997.
306. Feldstein A, Heumann M, Barnett M: Fumigant intoxication during transport of grain by railroad. J Occup Med 33:64–65, 1991.
307. Sudakin DL: Occupational exposure to aluminum phosphide and phosphine gas? A suspected case report and review of the literature. Hum Exp Toxicol 24:27–33, 2005.
308. Shadnia S, Mehrpour O, Abdollahi M: Unintentional poisoning by phosphine released from aluminum phosphide. Hum Exp Toxicol 27:87–89, 2008.
308a. Proudfoot AT: Aluminum and zinc phosphide poisoning. Clin Toxicol 47:89–100, 2009.
309. Sinclair JS, McManus DT, Ohara MD, et al: Fatal inhalation injury following an industrial accident involving acetic anhydride. Burns 20:469–470, 1994.
310. Makarovsky I, Markel G, Hoffman A, et al: Osmium tetroxide: A new kind of weapon. Isr Med Assoc J 9:750–752, 2007.
311. Centers for Disease Control and Prevention: Investigation of a home with extremely elevated carbon dioxide levels. West Virginia, December 2003. MMWR Morb Mortal Wkly Rep 53:1181–1182, 2004.
312. Centers for Disease Control and Prevention: Acute illness from dry ice exposure during Hurricane Ivan—Alabama, 2004. MMWR Morb Mortal Wkly Rep 53:1182–1183, 2004.
312a. Cantrell L, Young M: Fatal fall into a volcanic fumerole. Wilderness Environ Med 20:77–79, 2009.
313. Gould SR, Bernardo DE: Respiratory distress after talc inhalation. Br J Dis Chest 66:230–233, 1972.
314. Motomatsu K, Adachi H, Uno T: Two infant deaths after inhaling baby powder. Chest 75:448–450, 1979.
315. Silver P, Sagy M, Rubin L: Respiratory failure from corn starch aspiration: A hazard of diaper changing. Pediatr Emerg Care 12:108–110, 1996.
316. Centers for Disease Control and Prevention: Update: Pulmonary hemorrhage/hemosiderosis among infants—Cleveland, Ohio, 1993–1996. MMWR Morb Mortal Wkly Rep 46:33–35, 1997.
317. Centers for Disease Control and Prevention: Update: Pulmonary hemorrhage/hemosiderosis among infants—Cleveland, Ohio, 1993–1996. MMWR Morb Mortal Wkly Rep 49:180–184, 2000.
318. Terr AI: *Stachybotrys*: Relevance to human disease. Ann Allergy Asthma Immunol 87:57–63, 2001.
319. Yoshida K, Masayki A, Araki S: Acute pulmonary edema in a storehouse of moldy oranges: A severe case of the organic dust toxic syndrome. Arch Environ Health 44:382–384, 1989.
320. Strand RD, Neuhasuer EBD, Sornberger CF: Lycoperdonosis. N Engl J Med 277:89–91, 1967.
321. Centers for Disease Control and Prevention: Respiratory illness associated with inhalation of mushroom spores—Wisconsin, 1994. MMWR Morb Mortal Wkly Rep 43:525–526, 1994.
321a. Rubensohn M: Inhalation pneumonitis in a dog from spores of puffball mushrooms. Can Vet J 50:93, 2009.
322. Pauli JL, Foot CL: Fatal muscarinic syndrome after eating wild mushrooms. Med J Aust 182:294–295, 2005.
323. Hochstein C: Information Resources from the National Library of Medicine's Division of Specialized Information Services. Available at http://www.apha.org/membergroups/newsletters/sectionnewsletters/environ/winter08/natllibraryofmeds.htm (accessed January 2, 2009).

CHAPTER 69

BIOTERRORISM

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INTRODUCTION

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INTRODUCTION

Bioterrorism, once limited to military-directed biowarfare, has developed considerable prominence over the last decade due to increasing world threats and the anthrax outbreak in the United States in 2001. Clinicians and public health officials have become more aware of these rare diseases as local, state, and national directed programs increase detection, therapeutic options, and response to these agents. The agents of bioterrorism have some select features and characteristics that will allow clinicians and public health officials to appropriately detect and respond to one or multiple cases of febrile respiratory illnesses and respiratory failure.

Early recognition of bioterrorism agents can be difficult since the early prodromal phase of most agents is similar and often indistinguishable from other sources of febrile respiratory illnesses. Febrile respiratory illnesses and respiratory failure can signify a natural outbreak (such as severe acute respiratory syndrome [SARS], plague, tularemia, or a novel strain of influenza) or a bioterrorism event.[1,2] Most cases of febrile respiratory illnesses admitted to intensive care units (ICUs) are caused by community-acquired pneumonia, and up to 11% of these community-acquired pneumonia cases subsequently develop respiratory failure and acute respiratory distress syndrome (ARDS).[3,4] Although most cases of community-acquired pneumonia are recognizable, the rare and contagious causes (e.g., plague) can have a larger impact on the health care and public health systems.[2,5] Thus, early recognition of these rare infections becomes important for two reasons. Firstly, early infection control and public health preparedness strategies can be implemented to reduce spread in both the public and health care arena, particularly in the early phases of disease when patients are most contagious and likely to undergo aerosol-generating procedures by health care workers. Second, early detection of an intentional release of these agents is a bioterrorism event, and public health and law enforcement authorities can provide immediate investigation and support. Therefore, early suspicion of a bioterrorism event, along with early protective measures and public health contact, will reduce the likelihood of transmission to health care workers, visitors, patients, and ultimately the community.

Bioterrorism involves the deliberate release of viruses, bacteria, or their by-products (e.g., toxin) to cause morbidity and mortality in humans, animals, or plants.[6,7] All bioterrorism agents are naturally occurring organisms or toxins that can cause sporadic disease under natural circumstances, but on occasion, medical manipulation has been attempted to increase resistance to antibiotics or increase organism virulence.[7] This chapter provides an overview of the major agents of bioterrorism along with clues for detection, steps for public health response, and infection control interventions.

BIOTERRORISM: A HISTORICAL PERSPECTIVE

Bioterrorism has been around for centuries, from ancient Mesopotamia to current times.[7,8] The initial goal was to either incapacitate the enemy through death or stir great panic or fear into the population, leading to surrender. For example, in the 14th century, the Tartars would catapult plague-infected corpses into Kaffa, thereby leading to disease spread and the ultimate defeat of the city (and also starting the second wave of the Black Death in Europe).[9] In the New World, smallpox-infected blankets were distributed to native tribes from the West Indies to the Great Plains, with disastrous results. However, bioterrorism took form in the last 100 years with extensive biowarfare units in World War I and II.[7,8] Most notably, Unit 731 of the Japanese army in World War II used anthrax, plague, cholera, and typhoid on Chinese prisoners with great mortality, but transition to the battlefield was less successful.[7–9] The Cold War period saw both the United States and the former Soviet Union develop bioweapon stockpiles that have since been dismantled. However, over the past 25 years, an increase in individual-directed bioterrorism has occurred, culminating in the anthrax outbreak in 2001 that utilized the postal service for distribution, with 18 resulting cases.[7,8,10]

BASICS OF BIOTERRORISM

The route of transmission of bioterrorism agents can be by air (e.g., aerosol generation), food source (e.g., botulism), or water supply (e.g., gastroenteritis agents). Delivery can mimic naturally occurring disease, especially if the food or water supply to the public has been targeted. However, under aerosol generation, rapid increases in new cases are seen in low-risk populations, as seen with the anthrax cases in 2001.[11]

As most bioterrorism agents are infectious diseases, presentation of disease is usually covert, with health care workers seeing the initial cases as incubation periods vary and cases present over time. Particularly with contagious agents such as plague, smallpox, and viral hemorrhagic fevers, secondary infections will propagate the event to last weeks to months, stretching the capacity of the health care system.[2,7] Chemical and explosive forms of terrorism, however, are often overt and immediately known, with first responders in the field evaluating the initial cases and subsequent cases rarely occurring following the initial event. Therefore, subtle epidemiologic clues (such as an increase in pneumonia or a specific rash) may be the initial trigger to the clinician that a bioterrorism event has occurred.[12]

The Centers for Disease Control and Prevention (CDC) separated bioterrorism agents into three broad categories (A, B, and C) in 1999 based on ease of spread and severity of illness.[7,8,13,14] *Category A agents* are considered the highest risk to the public and national security for the following reasons: (1) easy person-to-person spread with many of the agents, (2) high mortality in those infected, (3) major public health impact causing panic and social disruption, and (4) requirement for specific and specialized public health emergency response (e.g., public prophylaxis or protective equipment)[7,8,13,14] (Table 69-1). *Category B agents* are moderately easy to spread and will result in moderate morbidity but low mortality in those infected. Less specific public health response is required (Table 69-2).[7] *Category C agents* are considered future or potential threats since they are easily available and can have a high mortality but have not been documented or engineered successfully (Table 69-3).[14] Although all of these agents can potentially cause serious disease, the category A agents, along with select category B agents, will be seen by clinicians and have the greatest impact on the public and health care system. These agents also present initially with a nonspecific prodromal phase with a few epidemiologic clues, thereby separating them from other less threatening causes of a febrile respiratory illness. Tables 69-4 to 69-8 list

TABLE 69-1. Centers for Disease Control and Prevention Category A Agents of Bioterrorism

Definition: Category A agents have the potential to be easily disseminated, have higher contagiousness, have high morbidity and mortality, and require increased public health preparedness

Anthrax (*Bacillus anthracis*)

Smallpox (variola major)

Plague (*Yersinia pestis*)

Tularemia (*Francisella tularensis*)

Botulism (*Clostridium botulinum* toxin)

Viral hemorrhagic fevers (filoviruses [e.g., Ebola, Marburg] and arenaviruses [e.g., Lassa, Machupo])

TABLE 69-2. Centers for Disease Control and Prevention Category B Agents of Bioterrorism

Definition: Category B agents are moderately easy to disseminate, carry a high morbidity but low mortality, and require public health laboratory and surveillance enhancements

PULMONARY AGENTS

Glanders (*Burkholderia mallei*)

Melioidosis (*Burkholderia pseudomallei*)

Psittacosis (*Chlamydophila psittaci*)

Q fever (*Coxiella burnetii*)

Ricin toxin from *Ricinus communis* (castor beans)

NONPULMONARY AGENTS

Brucellosis (*Brucella* species)

Epsilon toxin of *Clostridium perfringens*

Food safety threats (e.g., *Salmonella* species, *Escherichia coli* O157:H7, *Shigella*)

Staphylococcal enterotoxin B

TABLE 69-3. Centers for Disease Control and Prevention Category C Agents of Bioterrorism

Definition: Category C agents have the future potential for engineering for easy dissemination or high mortality

Influenza (novel strain)

Nipah virus

Typhus disease (*Rickettsia prowazekii*)

Viral encephalitis (alphaviruses [e.g., Venezuelan equine encephalitis, eastern equine encephalitis, western equine encephalitis])

Water safety threats (e.g., *Vibrio cholerae, Cryptosporidium parvum*)

FIGURE 69-1 ■ Anthrax lesion on the skin of the forearm caused by the bacterium *Bacillus anthracis.* The cutaneous ulceration has begun to turn black, hence the origin of the name "anthrax," after the Greek word for coal. (Courtesy of the Centers for Disease Control and Prevention/#2033 (James H. Steele). Available at http://phil.cdc.gov/phil/details.asp [accessed January 3, 2009].)

the unique features associated with category A agents: clinical syndromes, preferred diagnostic methods, radiologic features, treatment, and infection control and respiratory protection.

CDC CATEGORY A AGENTS

Anthrax

General

Anthrax is caused by a sporulating gram-positive rod, *Bacillus anthracis.* Its ecology has three distinct stages, a soil stage, animal infection, and human infection.[15,16] Anthrax is part of the normal soil flora, so local multiplication occurs if soil conditions are favorable. Otherwise, anthrax will persist for long periods of time in a spore form, resistant to decontamination and environmental influences. From the soil, disease spreads to herbivores, such as cattle, as they come into contact with highly infectious soil through grazing.[15,16]

Human disease largely occurs through contact with animal products, such as animal skins, where the bacillus form converts back to the spore form. In 2001, however, 22 cases of anthrax occurred in the United States as an act of bioterrorism through the postal system, placing anthrax on the forefront of bioterrorism.[10] Besides this outbreak in 2001, anthrax remains relatively rare in the United States, with most endemic and epizootic cases occurring in the Middle East. Most cases in the United States occur through handling of animal products, such as the 2006 cases associated with African animal hide drum skins.[16] The threat of anthrax as a bioterrorism and zoonotic agent still remains.

Disease occurs when the spore form is introduced subcutaneously or via inhalation, becomes the vegetative (bacillus) form, and starts replication.[15,16] Endotoxin secretion, along with a thick capsule that avoids phagocytosis, leads to local spread, edema, hemorrhage, and tissue necrosis. The anthax capsule, edema factor toxin, and lethal factor toxin act in concert to drive disease.[15,16]

Clinical Presentation

Three clinical disease syndromes occur with anthrax: cutaneous, gastrointestinal, and inhalational.[15–17] *Cutaneous anthrax* is the most common form worldwide, and has an incubation period of 7 to 14 days after inoculation of spores into the subcutaneous space. This is followed by a small, painless papule that can be pruritic. The papule enlarges and develops a central vesicle, followed by erosion into a painless black eschar (Fig. 69-1). Edema surrounds the tissues, and regional lymphadenopathy also may occur along with systemic symptoms of fever and malaise. The hands, arms, face, and neck are the most common areas affected.

With *inhalational anthrax,* the spores that reach the distal airways are brought into the mediastinal lymph nodes, where replication occurs followed by onset of disease.[15] The incubation period averages 1 to 7 days, followed by clinical symptoms of a nonspecific febrile illness, often mimicking influenza. However, within 24 hours, disease rapidly progresses with the development of respiratory failure, hemorrhagic mediastinitis, necrotizing pneumonia, shock, multiorgan failure and death (Table 69-4).[17] The development of shock and multiorgan failure can occur rapidly, and along with the hemorrhagic mediastinitis, is the clinical hallmark of anthrax.

Gastrointestinal anthrax is rare and occurs after the consumption of undercooked meats of infected animals, usually in family clusters. Bowel edema occurs, followed by mesenteric lymphadenitis and necrosis, with rapid progression to shock and death.[17]

The mortality for cutaneous anthrax remains low at less than 1% in treated patients (20% in untreated), while inhalational anthrax can carry a mortality of 89%.[15–17] The inhalational cases from 2001 in the United States had a lower mortality of 45%.[10]

TABLE 69-4. Unique Clinical Syndromes Associated with the CDC Category A Agents of Bioterrorism

Agent	Unique Clinical Finding/Syndrome
Anthrax	Hemorrhagic mediastinitis
Smallpox	Poxlike rash with systemic inflammatory response syndrome leading to septic shock
Plague	Sudden acute respiratory failure and sepsis
Tularemia	Patchy alveolar pneumonia with sepsis
Botulism	Descending flaccid paralysis
Viral hemorrhagic fevers (e.g., Eloba)	Sepsis with bleeding diathesis

TABLE 69-5. Preferred Diagnostic Methods for CDC Category A Agents

Agent	Laboratory Diagnostic Method
Anthrax	Culture of organism from blood or body fluid. Serology for uncultured cases. BSL 3 required at state and regional public health laboratory.
Smallpox*	EM or PCR of pox lesion. Viral isolation from skin/fluid. BSL 4 laboratory (CDC only).
Plague	Culture of organism from blood or sputum. Serology for uncultured cases. BSL 3+ at state or regional public health laboratory.
Tularemia	Serology or tissue histology. Difficult to culture. Performed at local, state, and regional public health laboratories.
Botulism	Isolation of toxin from blood or stool. Toxin identification (A–E) performed at state or regional public health laboratories.
Viral hemorrhagic fevers (e.g., Ebola)*	Serology or viral culture from blood/body fluid. BSL 4 at state or regional public health laboratory.

*Culture and/or species identification is performed at the CDC only.
BSL, bio-safety laboratory; CDC, Centers for Disease Control and Prevention; EM, electron microscopy; PCR, polymerase chain reaction.

TABLE 69-6. Radiologic Features of CDC Category A Agents of Bioterrorism

Agent	Radiologic Pulmonary Findings
Anthrax	Widening of mediastinum. May also have patchy alveolar opacities, pleural effusion, and lobar pneumonia but less likely.
Smallpox	Patchy alveolar opacities.
Plague	Diffuse, patchy, alveolar opacities.
Tularemia	Diffuse, patchy, alveolar opacities.
Botulism	Normal to lower lung volumes.
Viral hemorrhagic fevers (e.g., Ebola)	Diffuse alveolar opacities with areas of dense consolidation. Widened mediastinum and pleural effusions also reported.

Diagnosis

The diagnosis of anthrax is best performed by culture of the blood, sputum, pleural fluid, cerebrospinal fluid, or skin[16,18] (Table 69-5). Clinicians should notify the laboratory of suspected anthrax since spore formation during culture can occur, leading to spread to laboratory workers if not properly handled. Additionally, any suspect case of anthrax should involve the public health laboratories for confirmation and strain typing. Polymerase chain reaction (PCR) and enzyme-linked immunosorbent assay (ELISA)–based rapid assays exist and have a good sensitivity and specificity.[16,18]

The radiologic findings associated with anthrax include a widened mediastinum consistent with hemorrhagic mediastinitis, the hallmark of anthrax[15,16] (Table 69-6). However, in 2001, other findings including patchy alveolar opacities, lobar consolidation, and pleural effusions were also reported.[16] In each of these cases, a widened mediastinum was present on chest radiograph, with follow-up confirmation performed by computed tomography scan.

Treatment, Prophylaxis, and Prognosis

Treatment includes supportive therapy and antibiotics[17,18] (Table 69-7). Intensive care management with early and appropriate volume resuscitation along with lung-protective low-tidal-volume ventilation should be used if indicated.[2] Antibacterial treatment includes ciprofloxacin, doxycycline, and, if susceptible, penicillin.[17-19] In 2001, rifampin, clindamycin, or vancomycin in combination with ciprofloxacin was used.[17-19] The isolate in 2001 was resistant to penicillin. Appropriate pleural space drainage or the use of a central nervous ventriculoperitoneal shunt may also be used in individual cases. Corticosteroids were used to reduce edema and hemorrhage in some cases, but there is very limited data on their efficacy.[17] A live virus vaccine, which is toxigenic and uncapsulated, has been used in veterinary medicine to control disease in animals, but use in humans has been more limited due to a frequent dosing regimen, side effects, and efficacy concerns, and it is currently reserved for military personnel.[16,18] Exposure to aerosolized spores requires prophylaxis with either ciprofloxacin or doxycycline in adults, and amoxicillin as a second-line agent in children and pregnant women.[16,18]

Infection Control

Anthrax is not contagious as the vegetative bacillus form of disease exists during clinical infection[7,16] (Table 69-8). Contact with infected animals and animal products increases the likelihood of disease spread, so limiting contact or wearing appropriate personal protective equipment (PPE), particularly in endemic areas, is indicated.

TABLE 69-7. Treatment of Select CDC Category A Agents

Agent	Primary Treatment	Secondary Treatment
Anthrax	Ciprofloxacin 15 mg/kg IV twice daily	Clindamycin 900 mg IV three times daily
Plague	Gentamicin 5 mg/kg IV/IM daily	Ciprofloxacin 15 mg/kg IV twice daily
	Streptomycin 1 g IM daily	Chloramphenicol 15 mg/kg IV four times daily
Smallpox	Supportive care	Cidofovir*
	Vaccinia Immune Globulin 0.6 mg/kg IV/IM*	
Tularemia	Gentamicin 5 mg/kg IV/IM daily	Doxycycline 100 mg IV twice daily
	Streptomycin 1 g IM daily	Ciprofloxacin 15 mg/kg IV twice daily
		Chloramphenicol 15 mg/kg IV four times daily
Viral hemorrhagic fevers	Supportive care	Experimental with immune globulin from donors
	Ribiviron for Lassa fever	
Botulism	Trivalent antitoxin (A, B, E)	None
	Supportive care	

*Obtained through the CDC only (see http://www.bt.cdc.gov/agent/smallpox/vaccination/vig.asp).
CDC, Centers for Disease Control and Prevention; IM, intramuscularly; IV, intravenously.

TABLE 69-8. Infection Control and Respiratory Protection for CDC Category A Agents

Agent	Isolation	Baseline Protection	Protection in Higher Risk Procedures
Viral hemorrhagic fever	Airborne and contact	N95 mask	N95 mask or PAPR
Smallpox	Airborne and contact	N95 mask	N95 mask or PAPR
Botulism	None	None	Surgical
Plague*	Droplet and contact	N95 mask	N95 mask or PAPR
Tularemia	None	None	Surgical
Anthrax	None	None	Surgical

*Isolation can be stopped after 48 hours of appropriate antibacterial therapy.
PAPR, powered air-purifying respirator.

Smallpox

General

Variola virus is the causative agent of smallpox and is a member of the Poxviridae family.[20] Smallpox was eradicated worldwide in 1977 but now has regained interest as a potential bioterrorism agent.[20,21] Smallpox was endemic worldwide and at one point accounted for over 10% of all deaths worldwide until the last endemic case in Somalia in 1977.

It occurs in two forms, variola major and variola minor.[20,21] Variola major is the most common form of smallpox, has more severe disease with an extensive rash and fever, and carries a higher mortality (around 20% in the unvaccinated). Variola minor is less common and less severe, with mortality historically under 1%. Variola minor has a genetic sequence very similar to that of variola minor, with gene expression differences likely causing the variable mortality between the major and minor forms.

Smallpox is very contagious, with approximately half of all unvaccinated household contacts contracting disease.[20,21] However, after global eradication by 1977, routine vaccination for smallpox ceased worldwide.[22] However, due to an increasing unvaccinated population along with its contagiousness and ability to be transmitted by aerosol, smallpox is a CDC category A bioterrorism agent. Only two stockpiles of the virus remain (at the CDC and the Russian State Research Center) for continued research.[23,24]

Clinical Presentation

Smallpox infection occurs when the viral particles enter the respiratory tract, replicate locally, and then are carried to regional lymph nodes.[20,21] Subsequent viremia occurs with spread to lymphoid organs, followed by further viral amplification and the progression of symptoms. Variola major occurs in five main clinical categories: ordinary, modified, flat, hemorrhagic, and variola sine eruptione.[20,21]

Ordinary-type infection accounted for more than 70% of cases. After an incubation period of 10 to 14 days, disease onset (preeruptive phase) occurs with high fever, severe headache, and malaise. The preeruptive phase can last 2 to 4 days and is followed by the eruptive phase, which is characterized by rash. The lesions first appear as small erythematous macules on the mucous membranes, tongue, and face (herald spots).[20,21,25] Spread then occurs in a centrifugal fashion, with macules

FIGURE 69-2 ■ The maculopapular lesions on this patient's arm were caused by the smallpox virus, variola major. These lesions were in their pustular phase of development. (Courtesy of the Centers for Disease Control and Prevention/#10495 (Dr. John Noble Jr.). Available at http://phil.cdc.gov/phil/details.asp [accessed January 3, 2009].)

evolving into papules, then vesicles, and finally the classic pustules (pox) (Fig. 69-2) by day 5 to 7 of the rash (see Table 69-4). Fever usually resolves during the eruptive phase but may occur after the pustules develop. Crusting and healing begin by day 14 of the rash.

The *modified type* of variola major is similar to the ordinary type except for a more rapid but less severe rash, as this type was common in vaccinated individuals.[20,21,25] The *flat type* had pustules that remained flat and confluent and often occurred in children.

The *hemorrhagic type* was rare but very severe, with the lesions and mucous membranes becoming hemorrhagic.[20,21,25] This type was more common in pregnant women and rapidly led to multiorgan failure within a few days.

Patients with *variola sine eruptione* would have a fever but no rash; this type was often found in prior vaccinated individuals as well.

Diagnosis

Diagnosis is largely clinical, with the acute onset of fever followed by the characteristic rash of deep-seated vesicles or pustules[20,26] (see Table 69-5). For laboratory diagnosis, virus isolation from a skin lesion with reverse transcriptase–PCR confirmation is used, and is only performed at the CDC or World Health Organization laboratory.[20,26]

Radiologic findings in smallpox are limited largely to diffuse alveolar opacities from an inflammatory response associated with the primary infection[20,27] (see Table 69-6). Lobar opacities are seen and mostly associated with secondary bacterial pneumonia.

Treatment, Prophylaxis, and Prognosis

Treatment is largely supportive, with some evidence that cidofivir has activity in animal models[20,27,28] (see Table 69-7). Aggressive ICU support, including volume resuscitation, vasopressor support, and low-tidal-volume ventilation should be used for severe cases.[1] Vaccination early in disease may also reduce the severity of illness and is the mainstay for reducing spread and controlling disease in the community.[22] Vaccination can be administered within 4 days of exposure to a known case to provide protection.

Mortality from the ordinary type was around 20% from multiorgan failure and hypotension, with the flat and hemorrhagic types carrying a higher mortality and the modified and sine eruptione types carrying a much lower mortality. Complications include secondary bacterial skin infections and pneumonia, along with encephalitis, orchitis, and extensive scarring of the skin and corneas.[20,21]

Infection Control

Spread is through contact with infected lesions or respiratory secretions and thus full PPE, including gown, gloves, and face shield, is required.[28] CDC guidelines recommend airborne isolation with use of an N95 particulate respirator or a powered air-purifying respirator (PAPR) for respiratory protection, and all health care workers handling any smallpox patient must receive the vaccination[28] (see Table 69-8). Any suspected case of smallpox should involve public health officials immediately.

Plague

General

Yersinia pestis is the etiologic agent of plague and has caused a number of pandemics throughout human history.[9] Plague is a zoonosis, primarily affecting rodents, with humans and other animals (domestic cats) being accidental hosts.[29,30] The natural ecosystem of *Y. pestis* depends largely on the flea and rodent interaction, with seasonal variability noted based on environmental conditions. Infected fleas bite their rodent hosts, inoculating the rodent. Mortality in these animals remains lower than in other nonrodent mammals, and disease is passed from infected rodent to flea and the life cycle continues. Transmission to humans occurs by rodent-infected flea bites, infected animal scratches or bites, exposure to infected humans, and bioterrorism.[29,30] Transmission by infected flea bites is the most common mode, with squirrel, rabbit, domestic cats, and prairie dogs being the most common animals of transmission. Large rodent or other animal die-offs, particularly in more susceptible species, may herald a large epidemic in nature.[29,30] Plague is found worldwide, and in the United States endemic disease is found largely in the western states.

Clinical Presentation

Three clinical syndromes are associated with plague: bubonic plague (80% to 90% of cases), septicemic plague (10% of cases), and pneumonic plague (very rare).[29,30] After an incubation period of 2 to 7 days, symptoms usually occur and differ depending on clinical syndromes.

FIGURE 69-3 ■ An axillary bubo and edema exhibited by a plague patient. (Courtesy of the Centers for Disease Control and Prevention/#2061 (Margaret Parsons, Dr. Karl F. Meyer). Available at http://phil.cdc.gov/phil/details.asp [accessed January 3, 2009].)

In *bubonic plague,* a sudden onset of fevers, chills, and headache is followed by pain and swelling in the regional lymph nodes proximal to the site of the bite or scratch.[29,30] This lymph node (bubo) is characterized by intense tenderness with erythema and edema but without fluctuation (Fig. 69-3). Without treatment, disease disseminates, leading to complications such as pneumonia, meningitis, sepsis, and multiorgan failure. The development of a secondary pneumonia becomes extremely concerning as these patients are highly contagious.

Septicemic plague occurs with acute fever followed by sepsis without the presence of a bubo.[29,30] Additional symptoms such as nausea, vomiting, and diarrhea also complicate septicemic plague. Rapid sepsis, disseminated intravascular coagulation, and multiorgan failure develop quickly.

In *pneumonic plague,* most cases are secondary from bubonic or septicemic plague, but a primary pneumonic plague can occur after exposure to infected humans, animals, or aerosols in an intentional bioterror attack.[29,30] Due to the high contagiousness of plague, disease can spread rapidly with primary pneumonia as seen with past outbreaks in human history, subsequently creating a sustained pandemic. Initial cases in primary pneumonic plague have a very short incubation period of hours to a few days, followed by sudden onset of fever, cough, rapid onset of respiratory failure and ARDS, and death (see Table 69-4).

Diagnosis

The clinical diagnosis for plague can be difficult, but exposure to animals in an endemic area may be the first clue[29–31] (see Table 69-5). During intentional dissemination, multiple cases of severe, rapidly progressive pneumonia may be the first clue. Laboratory diagnosis is primarily by culture of the sputum or blood as *Y. pestis* grows well on most laboratory media. Serology and rapid diagnostic testing by ELISA or PCR is also available but is used primarily in field testing.[29–31]

A sudden and diffuse alveolar filling process is seen on chest radiographs consistent with acute lung injury[29,30] (see Table 69-6). Additional mediastinal lymphadenopathy may be present, as may be pleural effusion in later stage cases. Lobar opacities are less common.

Treatment, Prophylaxis, and Prognosis

The primary agent for antibacterial therapy has long been considered streptomycin, but based on its limited availability, gentamicin or doxycycline is preferred[29,30] (see Table 69-7). Most isolates are fully susceptible to gentamicin and doxycycline, as well as ciprofloxacin, which has been used in a more limited manner.[32] Chloramphenicol is preferred for cases of meningitis due to its ability to cross the blood-brain barrier. As most cases of primary pneumonia lead to multiorgan failure and acute lung injury, volume resuscitation, vasopressor support, and low-tidal-volume ventilation are indicated.[2] There is no evidence of corticosteroid benefit. Postexposure prophylaxis includes ciprofloxacin and doxycycline orally, with trimethoprim-sulfamethoxazole (if susceptible) or gentamicin for children and pregnant individuals.[32]

Infection Control

Due to the high rate of transmission of plague via aerosols, all patients should be on strict airborne isolation until at least 48 hours of antibiotics have been given[30] (see Table 69-8). Infection control measures include airborne isolation, including negative-pressure isolation. Appropriate PPE, including an N95 mask or PAPR, should be worn.

Tularemia

General

Tularemia is caused by the gram-negative bacterium *Francisella tularensis* and is a zoonotic disease, with humans as accidental hosts.[33] *Francisella tularensis* is found throughout the northern hemisphere and in a wide variety of wild and domesticated species. The organism persists in nature since it is passed transovarially in ticks, with disease coming after bites from infected vectors (ticks, flies, mosquitoes). Human infections occur by vector contact (ticks and flies), handling infected animals, improperly prepared animal meat, animal scratches and bites, drinking contaminated water, or aerosolization of the organism from the environment or in bioterrorism.[33–35] However, human-to-human transmission does not occur, largely since the organism is intracellular during infection and thus harder to spread from person to person.

Clinical Presentation

Approximately six distinct clinical syndromes occur with tularemia: ulceroglandular, glandular, typhoidal, pneumonic, oropharyneal, and oculoglandular.[36,37]

FIGURE 69-4 ■ Tularemia lesion on the dorsal skin of the right hand caused by the bacterium *Francisella tularensis.* (Courtesy of the Centers for Disease Control and Prevention/#2032 (Dr. Brachman). Available at http://phil.cdc.gov/phil/details.asp [accessed January 3, 2009].)

Ulceroglandular disease accounts for approximately 60% to 70% of cases.[36,37] Abrupt onset of fevers, chills, headache, and malaise occurs after an incubation period of 2 to 10 days. Most patients will have a single papuloulcerative lesion with a central eschar and associated tender lymphadenopathy (Fig. 69-4). In *glandular disease,* enlargement of lymph nodes occurs without the characteristic lesion (about 15% of cases).[36,37]

Pneumonic tularemia occurs with primary inhalation or hematogenous spread from typhoidal tularemia, and this is believed to be the main clinical presentation in a bioterrorism event with tularemia.[34] The incubation period tends to be shorter in these cases, with the rapid onset of pneumonia developing. Respiratory failure and ARDS develop rapidly (see Table 69-4).

Typhoidal tularemia is rare and can occur with or without pneumonia, as patients present with a febrile illness followed by sepsis without the glandular disease.[37] *Oropharyngeal tularemia* occurs rarely when undercooked infected meat or water is ingested and is associated with fever, pharyngitis, and cervical lymphadenopathy.[37]

Oculoglandular tularemia occurs with direct innoculatioin from contaminated fingers or accidental exposure. Besides conjunctival swelling and erythema, regional lymphadenopathy may be present.

Diagnosis

Francisella tularensis is very difficult to grow on culture media (requires cysteine), and since it is largely an intracellular organism, diagnosis is difficult[38,39] (see Table 69-5). Clinical suspicion must be high, particularly if the risk factors of vector exposure, animal exposure, or multiple community cases suggesting aerosolization occur. Therefore, serology by ELISA or histologic examination showing gram-negative intracellular organisms is the most likely method.[38,39] If serology is performed, a single elevated titer may not be specific and thus acute and convalescent titers are more predictive.[38,39]

Radiographic studies show patchy opacities bilaterally, lobar disease, and hilar adenopathy[40] (see Table 69-6). Pleural effusions and a miliary pattern can also occur, although this is less common. Hilar and mediastinal adenopathy may occur.

Treatment, Prophylaxis, and Prognosis

Similar to plague, aminoglycosides are the first treatment[39,41] (see Table 69-7). Gentamicin is preferred, with doxycycline or ciprofloxacin used as second-line therapy. For meningitis, chloramphenicol is preferred. In cases of exposure, doxycycline or ciprofloxacin is the preferred treatment, with trimethoprim-sulfamethoxazole or amoxicillin for children and pregnant patients.[39,41] Specific ICU management of tularemia includes supportive care and low-tidal-volume ventilation for ARDS. The overall mortality for tularemia is around 4%, but is thought to be higher in aerosolized disease that causes pneumonia or typhoidal tularemia.[36,37]

Infection Control

Human-to-human transmission does not occur, so once the diagnosis is confirmed, respiratory isolation can be lifted[37,41] (see Table 69-8). Reporting tularemia to public health officials varies across North America, but pneumonic or typhoidal cases, particularly if thought to be secondary to a bioterrorism event, should be reported.

Botulism

General

Clostridium botulinum, a gram-positive, spore-forming, obligate anaerobe, is the bacterium that produces and excretes botulinum toxin.[42,43] This neurotoxin is responsible for the clinical disease known as botulism and is the only category A agent that is a toxin. Seven serotypes of botulinum toxin exist, A through G, and are produced by different strains of *C. botulinum.* All act on the presynaptic nerve terminal of the neuromuscular junction and the cholinergic autonomic synapses. Disruption of neurotransmission occurs, leading to the clinical findings. Serotypes A, B, and E predominate in clinical disease, although any serotype can cause disease.[42,43] Serotypes C and D are predominately found in animal populations. Botulinum toxin is extremely lethal, with the median lethal oral dose estimated to be 1 ng/kg, although two to three times this dose may be needed for inhalation.[42,43]

Disease presents from potentially four different sources: food-borne, wound, infant, and intentional.[42,43] Food-borne disease occurs in outbreaks and is often associated with home-canned foods, such as fruits, vegetables, and fermented fish. Wound botulism has been associated with intravenous and subcutaneous injection of black tar heroin, mostly of Mexican origin. Infant botulism occurs sporadically in some western states, likely from spore acquisition from soil or raw honey, with subsequent toxin production in the gastrointestinal

tract. Finally, intentional release during a bioterrorism event may occur, with oral ingestion or aerosolization of the toxin.

Clinical Presentation

Clinical disease begins with the acute onset of bilateral cranial neuropathies with rapidly descending weakness (see Table 69-4). Of note, no fever is present and the patient maintains normal mentation.[42,43] The cranial neuropathies are usually symmetrical and often begin with oculomotor dysfunction. However, asymmetrical cranial nerve dysfunction has been reported.[44] Diplopia, dysphagia, ptosis, and facial weakness are the most common.[42,43] In food-borne exposure, gastrointestinal symptoms, including nausea and vomiting, may also occur. In infant botulism, poor feeding and lethargy may also be noted. Both wound and food-borne sources for botulism usually have an onset of symptoms at 12 to 36 hours after exposure and rapidly progress over the next 12 hours. If botulism is not suspected and treatment does not occur rapidly, eventual weakness and paralysis of respiratory muscles ensues, requiring mechanical ventilatory support.[44] Once the muscles of respiration are involved, mechanical support is required from 1 to 3 months.[44]

Diagnosis

Early and prompt diagnosis is essential since early treatment can alter the progression of weakness. Thus, the clinical findings of cranial nerve palsies, particularly in the appropriate clinical setting (e.g., heroin use) should prompt consideration (see Table 69-5). Laboratory diagnosis is by toxin or organism isolation, either in the spore or vegetative form.[45] Isolation of toxin from blood or stool is most reliable, and in some cases environmental isolation may be necessary to make the diagnosis.[45] The growth of *C. botulinum* from a stool or wound sample with the corresponding clinical findings can also confirm the diagnosis. Electromyography will also support the diagnosis if toxin and organism isolation is unsuccessful. There are no specific radiologic changes seen with botulism. Low lung volumes on chest radiographs may be seen but are not specific to the disease process (see Table 69-6).

Treatment, Prophylaxis, and Prognosis

Treatment must be started promptly and is directed at toxin neutralization[42,43,46] (see Table 69-7). An equine trivalent antitoxin (against serotypes A, B, and E) is available from state public health departments and the CDC and has been shown to decrease mortality in food-borne outbreaks as well as lessen the likelihood of respiratory failure in wound botulism.[46] Anaphylaxis and serum sickness have been reported. A human-derived antitoxin is available and is used in infant cases. Antibiotic administration is favored for wound botulism, with penicillin or clindamycin being the drugs of choice.[42,43] Since botulism results from exposure to the toxin, antibiotics are not recommended for food-borne and inhalational cases. In all cases of botulism without respiratory failure, routine monitoring of forced vital capacity is recommended, with early intubation if the vital capacity falls below 10 mL/kg (approximately 30% predicted). There is no direct prophylaxis for exposure, but in high-risk threats a vaccine directed against serotypes A and E is available and has been largely used in the military.[46] Death from botulism occurs from respiratory failure, so cases with prompt recognition and treatment have a low mortality.[44]

Infection Control

Since botulism is a toxin-based disease, infection control should follow universal precautions[42] (see Table 69-8). During an exposure to spores or toxin, decontamination should occur, although secondary infections in medical personnel have not been reported.

Viral Hemorrhagic Fevers

General

The hemorrhagic fever viruses include a wide number of geographically distributed viruses found worldwide, including Ebola and Marburg viruses and the viruses causing Rift Valley fever, Bolivian, Argentine, and Crimean-Congo hemorrhagic fevers, Lassa fever, yellow fever, and dengue fever.[47–49] Ebola and Marburg viruses are in the family Filoviridae, and Lassa virus as well as the viruses causing Bolivian (Machupo virus) and Argentine (Junin virus) hemorrhagic fever are in the family Arenaviridae. The Crimean-Congo and Rift Valley fever viruses belong to the Bunyaviridae family. Only the Filoviridae (Ebola and Marburg viruses) and Arenaviridae are listed as category A agents. The Filoviridae family serves as a classic template for viral hemorrhagic fevers and is largely discussed here.[47] Marburg virus has a single species, while Ebola virus has four different species that vary in virulence in humans.[48,49] Transmission appears to occur through contact with nonhuman primates and infected individuals. Settings for transmission have occurred in vaccine workers handling primate products, nonhuman primate food consumption, nosocomial transmission, and laboratory worker exposure. The use of hemorrhagic fever viruses in bioterrorism has also been postulated, largely based on their high contagiousness in aerosolized primate models.[48,49] The exact reservoir for these viruses was initially thought to be wild primates, but recently bats have been labeled as the reservoir, passing the infection on to nonhuman primates in the wild.

Clinical Presentation

The clinical manifestations of both Marburg and Ebola viruses are similar in presentation and pathophysiology, with morality being the only major difference between them.[49,50] The initial incubation period after exposure to either virus is 5 to 7 days, with clinical disease beginning

FIGURE 69-5 ■ Marburg virus rash. This posterior-oblique view of the back of a patient shows the measles-like maculopapular rash, which can appear on Marburg patients around the fifth day after the onset of symptoms, and usually may be found on the patient's chest, back, and stomach. This patient's skin blanched under pressure, which is a common characteristic of a Marburg virus rash. (Courtesy of the Centers for Disease Control and Prevention/#6571 (Dr. J. Lyle Conrad). Available at http://phil.cdc.gov/phil/details.asp [accessed January 3, 2009].)

with the onset of fever, chills, malaise, severe headache, nausea, vomiting, diarrhea, and abdominal pain.[49,50] Disease onset is abrupt, and over the next few days, symptoms worsen to include prostration, stupor, and hypotension. Shortly thereafter, impaired coagulation occurs with increased conjunctival and soft tissue bleeding. In some cases, more massive hemorrhage can occur in the gastrointestinal and urinary tracts, and in rare instances, alveolar hemorrhage can occur.[49,50] The onset of maculopapular rash on the arms and trunk also appears classic and may be a very distinctive sign (Fig. 69-5). Along with the bleeding and hypotension, multiorgan failure occurs eventually leading to death (see Table 69-4). Reports of outbreaks and cases have largely occurred in developing countries where critical care resources are more limited, thus experience with mechanical ventilation and the development of ARDS is not well documented.

Diagnosis

The diagnosis of viral hemorrhagic fevers becomes extremely important in order to initiate supportive care before the onset of shock, alert and involve the public health department, and institute infection control measures. However, diagnosis is difficult outside of the endemic area. Viral hemorrhagic fevers should be suspected in cases of an exposed laboratory worker or an acutely ill traveler from an endemic area (i.e., central Africa), or in the presence of some classic clinical findings with increasing cases within the community, suggesting a bioterrorism attack.[49] Outside of travel or laboratory exposure, the presence of a high fever, malaise and joint pain, conjunctival bleeding and bruising, confusion, and progression to shock and multiorgan failure should raise suspicion of a viral hemorrhagic fever, particularly if multiple cases are presenting in the community. Laboratory diagnosis includes antigen testing by ELISA or viral isolation by culture, but these tests are only performed by the CDC currently[49] (see Table 69-5).

Radiologic changes include a diffuse alveolar process consistent with acute lung injury[49,50] (see Table 69-6). As the disease progresses, the alveolar process can become dense as alveolar hemorrhage increases. Additional pleural effusions may also be present.

Treatment, Prophylaxis, and Prognosis

As no specific therapy is available, patient management includes supportive care, including a lung-protective strategy with low-tidal-volume ventilation if ARDS appears as part of the disease course[48–50] (see Table 69-7). With the arenavirus group (Lassa, Junin, and Machupo viruses) and the Bunyaviridae (Crimean-Congo hemorrhagic fever and Rift Valley fever viruses), ribavirin is recommended.[48–50] In a few cases in a Zaire outbreak in 1995, whole blood with immunoglobulin G antibodies against Ebola virus may have improved outcome, although analysis showed these patients were likely to survive anyhow.[47] If exposure occurs to a health care worker, there is no specific postexposure prophylaxis, and infection control and occupational health personnel should be involved, with potential quarantine measures for exposed individuals. Case fatality rates have reached 80% to 90% in the recent outbreak of Marburg virus in Angola, but Ebola virus case fatality rates appear lower at 50%.[47,49–51]

Infection Control

Although transmission appears to spread by droplet route, airborne precautions are recommended, with respiratory protection with an N95 mask or PAPR and placement of the patient in a respiratory isolation room[48–50] (see Table 69-8). Equipment should be dedicated to that individual, and all higher risk procedures should be done with adequate, full PPE. Any suspected case of viral hemorrhagic fever should immediately involve the public health officials and infection control department, as public health interventions and outbreak investigation will be paramount to reduce spread of disease within the community and to investigate any potential bioterrorism attack.

SELECT CDC CATEGORY B AGENTS

Direct Pulmonary Agents

Glanders (Burkholderia mallei)

The disease glanders is caused by the gram-negative bacterium *Burkholderia mallei.*[52] Glanders is primarily a disease of horses, and humans become secondarily infected through broken skin or droplet inhalation. Naturally occurring human infection is rare, but occupational cases (horse veterinarians) do occur sporadically.

In bioterrorism, aerosolization is the likely method. Glanders can occur as an acute or chronic skin infection, but with aerosolization, rapid pneumonia and/or sepsis will present.[52] Diagnosis is by culture, but since *B. mallei* is an uncommon organism, laboratories may misclassify it. Treatment includes supportive care as well as systemic antibiotics such as imipenem or a third-generation cephalosporin.[52] Ciprofloxacin is also an option. Since this is a rare disease, transmission to humans has not been documented, but universal precautions with droplet isolation for respiratory cases are recommended. Any suspect case should involve immediate contact with the public health department.

Melioidosis (Burkholderia pseudomallei)

Similar to glanders, melioidosis is caused by the gram-negative bacterium *Burkholderia pseudomallei.*[52,53] Unlike glanders, this bacterium has a natural reservoir in the soil and contaminated water and is spread through direct contact or inhalation. Thus, disease predominates during the rainy season. In bioterrorism, aerosolization will lead to a clinical picture of pneumonia or melioidosis sepsis.[52,53] With melioidosis, the incubation period can be highly variable, with some cases not presenting for extended periods while others may remain asymptomatic.[52–54] Most symptomatic cases will develop sepsis with multiple metastatic foci and eventually multiorgan failure. Diagnosis is by culture, which occurs readily by routine methods. Treatment involves imipenem or a third-generation cephalosporin, followed by a 20-week treatment with doxycycline and trimethoprim-sulfamethoxazole for metastatic foci eradication.[52,53]

Psittacosis (Chlamydophila psittaci)

Psittacosis is caused by an intracellular bacterium routinely associated with birds such as parrots, cockatiels, and canaries. *Chlamydophila psittaci* presents nonspecifically, and most cases often go undiagnosed.[55,56] As a category B bioterrorism agent, *C. psittaci* can cause morbidity with very low mortality. Intentional aerosolization would lead to multiple cases of nonspecific "atypical pneumonia" with cough, fever, and headache.[55,56] Diagnosis is difficult and relies on serology due to the difficulty in isolating the organism. Treatment is with doxycycline, a macrolide, or ciprofloxacin. Mortality is low at 1% in treated cases.[55,56] Universal precautions are required for patient care, although an N95 mask and coveralls are recommended for environmental decontamination.

Q Fever (Coxiella burnetii)

Q fever is a zoonotic disease caused by *Coxiella burnetii.* Cattle, sheep, and goats are the primary reservoirs of *C. burnetii,* and this disease is found worldwide.[57] *Coxiella burnetii* usually does not cause clinical disease in animals, but organisms are found in milk, urine, feces, amniotic fluids, and placenta. The organisms are resistant to heat and drying, and often cause infection by inhalation of environmental dust contaminated by dried placental material, birth fluids, and excrement. Incubation time is 1 to 2 weeks, after which only about one half of all infected persons develop a clinical illness.[57] The clinical illness is characterized by high fevers (often greater than 40° C/104° F), severe headache, myalgia, sore throat, nonproductive cough, nausea, vomiting, diarrhea, abdominal pain, and chest pain.[57,58] Fever usually lasts for 1 to 2 weeks. Thirty percent to 50% of patients with a symptomatic infection will develop pneumonia.

One percent to 2% of people with acute Q fever die of the disease.[57,58] A small percentage of those infected will develop chronic Q fever (infection that persists for more than 6 months). Complications of chronic Q fever include endocarditis. As many as 65% of persons with chronic Q fever will die of the disease. Making the diagnosis of Q fever requires serologic testing, most commonly using the indirect immunofluorescence assay.[57,58] Doxycycline 100 mg twice daily for 15 to 21 days is the treatment of choice for acute Q fever.[57,58] Quinolone antibiotics may be an effective alternative.

Ricin Toxin

Ricin is a potent biologic toxin (toxic protein) derived from part of the waste when castor beans (*Ricinus communis*) are processed during manufacture of castor oil.[59] Ricin acts as a toxin by the inhibition of protein synthesis; 0.2 mg (1/5000th of a gram) is thought to be the lethal dose. Symptoms begin within 4 to 12 hours after exposure. Systemic effects of ricin poisoning will depend upon route of exposure and exposure dosage. Signs and symptoms from oral ingestions would include vomiting and profuse diarrhea; fever, myalgia and arthralgia, hallucinations, and seizures may occur.[59] Hypovolemic shock and multiorgan failure may occur, and would represent the likely cause of death.[59]

After an inhalational exposure, the symptoms could include cough, respiratory distress, and bronchoconstriction. Influenza-like symptoms (fever, myalgia, and arthralgia) may occur, as well as hypotension, respiratory failure, and multiorgan failure.[59] Few symptoms and signs exist to separate this from other causes of respiratory failure, though excessive diaphoresis has been reported and would be unusual in other causes. No specific treatment or antitoxin exists. Treatment consists of decontamination and supportive therapy.[59]

Nonpulmonary Agents (Gastrointestinal and Toxin)

Brucellosis (Brucella Species)

Brucellosis is caused by a number of species within the genus *Brucella.* Disease is naturally common in livestock workers, particularly in areas of poor sanitation, where *Brucella* is found in the natural reservoir of domesticated animals.[60] *Brucella* is a category B agent due to its low mortality and prolonged incubation period.[61] After exposure through ingestion of contaminated food or intentional aerosolization, symptoms would develop after a

few weeks to months. Initially fevers would persist irregularly over weeks to months, followed by arthalgias, gastrointestinal symptoms, and possibly endocarditis.[60] Diagnosis is an epidemiologic link with isolation of the organism by blood culture. However, growth is slow, so all cultures should be kept for 4 weeks if the diagnosis is suspected. Treatment is with doxycycline for up to 6 weeks, with trimethoprim-sulfamethoxazole for children.[60] There are unique infection control precautions.

Epsilon Toxin of Clostridium perfringens

The *Clostridium* species produce a vast amount of toxins, and epsilon toxin is produced by *Clostridium perfringens* types B and D.[62] The toxin acts directly on the cell membrane, producing pores that cause nonselective permeability. *Clostridium perfringens* uses the toxin to gain access into the bloodstream from the gut. However, in bioterrorism, intentional release via ingestion or inhalation of the toxin without bacteria is most likely.[63] Rapid ingestion or inhalation would cause diffuse tissue edema that would manifest as central nervous system dysfunction (weakness, ataxia, confusion), pulmonary edema (shortness of breath, cough, bronchospasm, respiratory failure), nausea, vomiting, tachycardia, and hypotension.[62] Diagnosis requires clinical suspicion consistent with a bioterrorism attack, and toxin can be detected by PCR. Treatment is supportive, with penicillin if *C. perfringens* is released at the same time.[62]

Food Safety Threats (e.g., Salmonella Species, Escherichia coli O157:H7, Shigella)

Enteropathogenic gram-negative bacteria, such as *Escherichia coli, Salmonella,* and *Shigella,* constitute a large group of agents that make up food supply threats.[64] Public health officials are very familiar with these bacteria from numerous episodes of food contamination yearly, leading to localized outbreaks and large product recalls. In an intentional release, these agents will produce widespread gastrointestinal symptoms leading to significant morbidity but with low mortality. After an incubation period of 3 to 7 days, abdominal cramping, nausea, vomiting, and diarrhea occur. The diarrhea may be voluminous and bloody.[64] Diagnosis is by stool culture of the agents, and an aggressive public health investigation usually yields the initial agent, as bioterrorism will resemble a point-source outbreak.[65] Treatment is intravenous hydration as needed and, with some agents (*Salmonella, Shigella*), antibacterial therapy with ciprofloxacin.[65]

Staphylococcal Enterotoxin B

Staphylococcal enterotoxin B is a toxin produced by *Staphylococcus aureus* and commonly associated with food poisoning. Symptoms of food poisoning include vomiting and diarrhea several hours after ingesting food.[66] Naturally occurring, it is rarely lethal. The clinical presentation would depend on the route of administration. Oral administration (poisoning of food or water supplies) would present as vomiting and diarrhea.[66] If inhaled, respiratory failure with neurotoxic effects may be seen.[66]

RECOGNITION AND DETECTION OF A BIOTERRORISM EVENT

The recognition of a bioterrorism event versus a naturally occurring infection is paramount and relies on a high suspicion on behalf of the clinician. However, this recognition is difficult in the early stages of disease when many of the category A agents present with nonspecific symptoms.[67] In addition, these agents have their highest contagiousness during this initial period before more specific clinical or diagnostic features arise, increasing the likelihood of spread to health care workers and the community. Therefore, a systematic approach is advocated initially in all febrile respiratory illnesses, with suspicion and public health contact occurring when specific clinical findings or epidemiologic features are detected that lead the clinician to suspect a bioterrorism or emerging infectious disease event.[1,68]

Figure 69-6 outlines an approach to early isolation, testing, and involvement of institutional infection control and public health in cases of acute febrile illness. Upon admission, cases of acute febrile illness and respiratory failure should undergo initial diagnostic testing, including pretreatment Gram stain, respiratory culture, and urine antigen testing for *Legionella.* If an etiologic agent is identified on initial screening and clinical findings (i.e., gram-positive diplococci with a lobar pneumonia on radiograph), targeted treatment is performed with appropriate isolation based on the pathogen. However, if an agent is not easily identified in a patient with acute febrile illness, patients should be placed in isolation and further diagnostic testing should be performed. Additionally, if multiple simultaneous cases with similar symptoms or a case with an uncommon epidemiologic link (e.g., food source) is determined, patient isolation and contact with public health should occur. If certain clinical features subsequently arise, then specific diagnostic testing should be performed and public health authorities alerted. If no clear etiology is detected, then further evaluation is warranted with more invasive and expansive testing. Although bronchoscopy generates aerosols and can increase transmission risk, it should not be avoided in these cases as isolation and etiology becomes important from a public health perspective. Contact with both the public health authorities and institutional infection control is paramount throughout the process and should occur as early as possible when clinical suspicion of bioterrorism arises or when diagnostic tests do not yield results.

Once a bioterrorism agent is suspected, confirmation is performed by the public health authorities. Initial cases must meet a case definition for the suspected agent (see www.cdc.gov/bioterrorism/casedef.asp) before further evaluation occurs. In order to meet the case definition, at least one critical and distinguishing feature must be met along with other clinical and laboratory

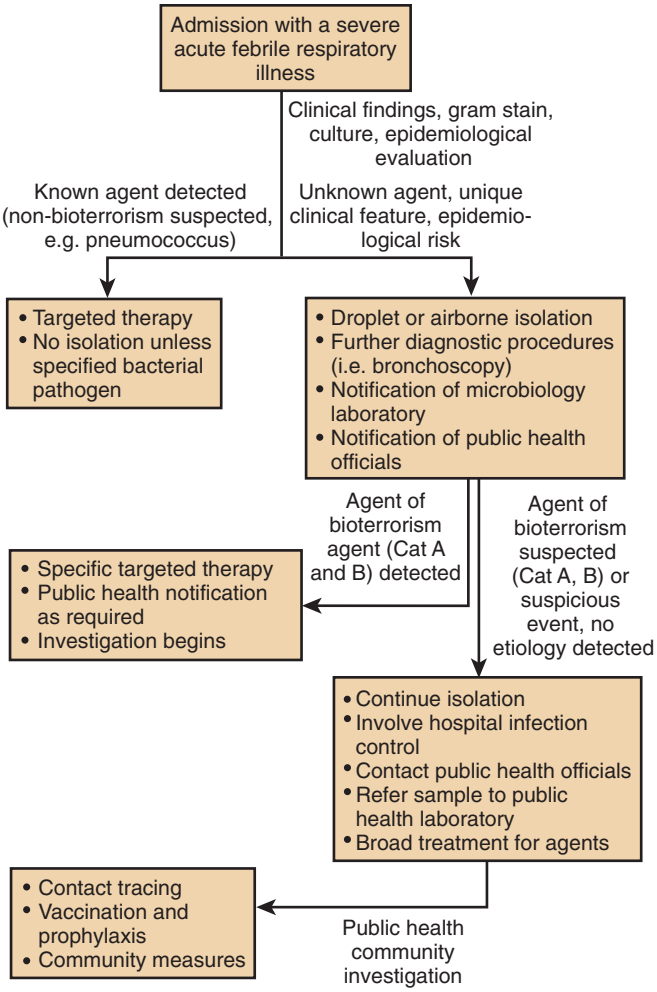

FIGURE 69-6 ■ General response to a febrile respiratory illness with respiratory failure.

features. After this stage, confirmatory diagnostic testing proceeds with selected methods that are usually performed at trained state or federal laboratories.

INFECTION CONTROL

Involvement of institutional infection control, microbiology, and public health should be started as early as possible. Ideally, notification should occur when one of four conditions is met: (1) a clinical or epidemiologic feature suggestive of bioterrorism (see Table 69-4), (2) an unexpected clinical link or increase in number of cases (e.g., pneumonia with respiratory failure), (3) if an extensive workup of a febrile respiratory illnesses has no direct results and an infectious disease is suspected, or (4) transmission of disease to health care workers occurs. Hospital-based infection control will assist in isolation and health care worker protection, and the hospital-based microbiology laboratory should be notified of suspected pathogens, allowing for worker protection and targeted testing of samples.[1,68] Finally, public health involvement will allow a broader bacterial, viral, and fungal testing, including subtyping and resistance testing. If the agent is a novel or emerging pathogen, as seen with SARS or avian influenza, early public health involvement will allow for rapid laboratory testing, epidemiologic investigation, case definition, and community prevention.

TABLE 69-9. Respiratory Care Procedures That Carry a Higher Risk for Disease Transmission in Patients with a CDC Category A Agent

Nebulization of medication
Endotrachial intubation
Nasotracheal suctioning
Noninvasive positive-pressure ventilation
Bag-valve-mask ventilation
Bronchoscopy
Humidified oxygen delivery
Non-rebreather mask without expiratory filter

The basic infection control requirements are outlined in Table 69-8. Anthrax and botulism are the only category A agents that are not contagious and do not require respiratory protection. If the number of cases exceeds the health care capacity for isolation, patient cohorting and accessory isolation measures can be used. Finally, higher risk procedures should be limited in these cases (Table 69-9). Aerosol-generating procedures are most common in ICU patients, and reducing unnecessary risky procedures will reduce patient and health care worker risk. However, these procedures should not be avoided if needed. Appropriate PPE should be worn by health care workers at all times, and if worn properly, disease transmission risk is low.[69]

PUBLIC HEALTH AND CRITICAL CARE RESPONSE

Acts of terrorism, such as conventional explosive devices or chemical attacks, result in a single point of mass casualties with an immediate critical area response. In contrast, as some of the category A agents are spread by contact and respiratory transmission, increasing cases will be seen after the initial outbreak. As these cases progress, the cumulative number of cases with severe respiratory illness will increase, putting stress on the critical care system and leading to a sustained need for emergency mass critical care (EMCC) from weeks to months. Sustained EMCC can lead to depletion of critical care resources, such as mechanical ventilation, specially trained staff, antibiotics and antivirals, and ICU bed capacity.[5] Thus, the unique issues associated with sustained EMCC have led to critical issues and advancements in planning and response to a bioterrorism or emerging infectious diseases outbreak.[70,71]

Recent consensus statements have recommended special critical care preparedness to include ICU capacity expansion, critical care resource storage, and the

coordination of critical care across communities to a regional and statewide level.[70,71] Capacity for critical care should be approximately three times normal ICU capacity, with all critically ill patients to be located in acute care hospitals (less severely ill patients will be diverted to alternate sites within the community). Each hospital should have enough supplies for 10 days per critically ill patient along with plans to have expanded care by non–critical care specialists in the case of a shortage.[72] ICU admission should be limited to the most severely ill (e.g., no observation). Most importantly, the identification of a triage mechanism is recommended for the allocation of scarce resources in sustained EMCC, with the most identified critical resource being mechanical ventilation and medical oxygen supply.[73] This triage mechanism would shift critical care from optimal care of the individual to optimal care for the population and would identify critically ill patients who may not get specific scarce resources during a period of limited supply in an outbreak. It would include inclusion and exclusion criteria for ICU admission along with a triage scoring mechanism for patient assessment. Recent publications have suggested the use of the Sequential Organ Failure Assessment (SOFA) score due to its use in sequential assessments and its ease of administration (less laboratory and data requirements). Additional triage scoring systems may be warranted in future outbreaks as disease and outbreak conditions change.

KEY POINTS

- Bioterrorism and emerging infectious diseases present unique and differing diagnostic and treatment options.
- Aggressive supportive care is the mainstay for all critically ill patients infected with a bioterrorism agent.
- Generally, many of the CDC category A agents present with a nonspecific prodrome that then develops into severe disease with specific epidemiologic hallmarks.
- The category B agents are very diverse but carry a lower morbidity and mortality, with a number of agents having few to no pulmonary manifestations.
- Early recognition relies on the astute clinician, with early involvement of public health and institutional infection control to reduce further spread to health care workers and the community.
- During an outbreak of a category A agent, mass critical care for a sustained period may be required, leading to depletion of critical patient care resources.

References

1. Sandrock C, Stollenwerk N: Acute febrile respiratory illness in the ICU: Reducing disease transmission. Chest 133:1221–1231, 2008.
2. Sandrock CE: Severe febrile respiratory illnesses as a cause of mass critical care. Respir Care 53:40–53, 2008 [discussion appears in Respir Care 53:57, 2008].
3. Bauer TT, Ewig S, Rodloff AC, Muller EE: Acute respiratory distress syndrome and pneumonia: A comprehensive review of clinical data. Clin Infect Dis 43:748–756, 2006.
4. Kao KC, Tsai YH, Wu YK, et al: Open lung biopsy in early-stage acute respiratory distress syndrome. Crit Care 10:R106, 2006.
5. Rubinson L, O'Toole T: Critical care during epidemics. Crit Care 9:311–313, 2005.
6. Hepburn MJ, Purcell BK, Paragas J: Pathogenesis and sepsis caused by organisms potentially utilized as biologic weapons: Opportunities for targeted intervention. Curr Drug Targets 8:519–532, 2007.
7. Moran GJ, Talan DA, Abrahamian FM: Biological terrorism. Infect Dis Clin North Am 22:145–187, 2008.
8. Kman NE, Nelson RN: Infectious agents of bioterrorism: A review for emergency physicians. Emerg Med Clin North Am 26:517–547, 2008.
9. Ligon BL: Plague: A review of its history and potential as a biological weapon. Semin Pediatr Infect Dis 17:161–170, 2006.
10. Update: Investigation of bioterrorism-related anthrax, 2001. MMWR Morb Mortal Wkly Rep 50:1008–1010, 2001.
11. Frazier AA, Franks TJ, Galvin JR: Inhalational anthrax. J Thorac Imaging 21:252–258, 2006.
12. Persell DJ, Robinson CH: Detection and early identification in bioterrorism events. Fam Community Health 31:4–16, 2008.
13. Daya M, Nakamura Y: Pulmonary disease from biological agents: Anthrax, plague, Q fever, and tularemia. Crit Care Clin 21:747–763, vii, 2005.
14. Mushtaq A, El-Azizi M, Khardori N: Category C potential bioterrorism agents and emerging pathogens. Infect Dis Clin North Am 20:423–441, x, 2006.
15. Dixon TC, Meselson M, Guillemin J, Hanna PC: Anthrax. N Engl J Med 341:815–826, 1999.
16. Kyriacou DN, Adamski A, Khardori N: Anthrax: From antiquity and obscurity to a front-runner in bioterrorism. Infect Dis Clin North Am 20:227–251, 2006.
17. Goldman DL, Casadevall A: Anthrax-associated shock. Front Biosci 13:4009–4014, 2008.
18. Swartz MN: Recognition and management of anthrax—an update. N Engl J Med 345:1621–1626, 2001.
19. Update: Adverse events associated with anthrax prophylaxis among postal employees—New Jersey, New York City, and the District of Columbia metropolitan area, 2001. MMWR Morb Mortal Wkly Rep 50:1051–1054, 2001.
20. Moore ZS, Seward JF, Lane JM: Smallpox. Lancet 367:425–435, 2006.
21. Henderson DA: Smallpox: Clinical and epidemiologic features. Emerg Infect Dis 5:537–539, 1999.
22. Metzger W, Mordmueller BG: Vaccines for preventing smallpox. Cochrane Database Syst Rev (3):CD004913, 2007.
23. Cleri DJ, Porwancher RB, Ricketti AJ, et al: Smallpox as a bioterrorist weapon: Myth or menace? Infect Dis Clin North Am 20:329–357, 2006.
24. Henderson DA: The looming threat of bioterrorism. Science 283:1279–1282, 1999.

25. Slifka MK, Hanifin JM: Smallpox: The basics. Dermatol Clin 22:263–274, 2004.
26. Seward JF, Galil K, Damon I, et al: Development and experience with an algorithm to evaluate suspected smallpox cases in the United States, 2002–2004. Clin Infect Dis 39:1477–1483, 2004.
27. Nafziger SD: Smallpox. Crit Care Clin 21:739–746, 2005.
28. Henderson DA, Inglesby TV, Bartlett JG, et al: Smallpox as a biological weapon: Medical and public health management. Working Group on Civilian Biodefense. JAMA 281:2127–2137, 1999.
29. Inglesby TV, Dennis DT, Henderson DA, et al: Plague as a biological weapon: Medical and public health management. Working Group on Civilian Biodefense. JAMA 283:2281–2290, 2000.
30. Prentice MB, Rahalison L: Plague. Lancet 369:1196–1207, 2007.
31. Koirala J: Plague: Disease, management, and recognition of act of terrorism. Infect Dis Clin North Am 20:273–287, 2006.
32. Galimand M, Carniel E, Courvalin P: Resistance of *Yersinia pestis* to antimicrobial agents. Antimicrob Agents Chemother 50:3233–3236, 2006.
33. Evans ME: Francisella tularensis. Infect Control 6:381–383, 1985.
34. Oyston PC, Sjostedt A, Titball RW: Tularaemia: Bioterrorism defence renews interest in *Francisella tularensis*. Nat Rev Microbiol 2:967–978, 2004.
35. Tarnvik A, Priebe HS, Grunow R: Tularaemia in Europe: An epidemiological overview. Scand J Infect Dis 36:350–355, 2004.
36. Evans ME, Gregory DW, Schaffner W, McGee ZA: Tularemia: A 30-year experience with 88 cases. Medicine (Baltimore) 64:251–269, 1985.
37. Sjostedt A: Tularemia: History, epidemiology, pathogen physiology, and clinical manifestations. Ann N Y Acad Sci 1105:1–29, 2007.
38. Hepburn MJ, Simpson AJ: Tularemia: Current diagnosis and treatment options. Expert Rev Anti Infect Ther 6:231–240, 2008.
39. Tarnvik A, Chu MC: New approaches to diagnosis and therapy of tularemia. Ann N Y Acad Sci 1105:378–404, 2007.
40. Rubin SA: Radiographic spectrum of pleuropulmonary tularemia. AJR Am J Roentgenol 131:277–281, 1978.
41. Dennis DT, Inglesby TV, Henderson DA, et al: Tularemia as a biological weapon: Medical and public health management. JAMA 285:2763–2773, 2001.
42. Dembek ZF, Smith LA, Rusnak JM: Botulism: Cause, effects, diagnosis, clinical and laboratory identification, and treatment modalities. Disaster Med Public Health Prep 1:122–134, 2007.
43. Sobel J: Botulism. Clin Infect Dis 41:1167–1173, 2005.
44. Sandrock CE, Murin S: Clinical predictors of respiratory failure and long-term outcome in black tar heroin-associated wound botulism. Chest 120:562–566, 2001.
45. Cai S, Singh BR, Sharma S: Botulism diagnostics: From clinical symptoms to in vitro assays. Crit Rev Microbiol 33:109–125, 2007.
46. Villar RG, Elliott SP, Davenport KM: Botulism: The many faces of botulinum toxin and its potential for bioterrorism. Infect Dis Clin North Am 20:313–327, ix, 2006.
47. Ebola: The virus and the disease. Wkly Epidemiol Rec 74:89, 1999.
48. Borio L, Inglesby T, Peters CJ, et al: Hemorrhagic fever viruses as biological weapons: Medical and public health management. JAMA 287:2391–2405, 2002.
49. Curtis N: Viral haemorrhagic fevers caused by Lassa, Ebola and Marburg viruses. Adv Exp Med Biol 582:35–44, 2006.
50. Gonzalez JP, Pourrut X, Leroy E: Ebolavirus and other filoviruses. Curr Top Microbiol Immunol 315:363–387, 2007.
51. Marburg haemorrhagic fever, Angola—update. Wkly Epidemiol Rec 80:125–126, 2005.
52. Gilad J: *Burkholderia mallei* and *Burkholderia pseudomallei:* The causative micro-organisms of glanders and melioidosis. Recent Patents Anti-Infect Drug Disc 2:233–241, 2007.
53. Peacock SJ: Melioidosis. Curr Opin Infect Dis 19:421–428, 2006.
54. Chan KP, Low JG, Raghuram J, et al: Clinical characteristics and outcome of severe melioidosis requiring intensive care. Chest 128:3674–3678, 2005.
55. Cunha BA: The atypical pneumonias: Clinical diagnosis and importance. Clin Microbiol Infect 12(Suppl 3):12–24, 2006.
56. Elliott JH: Psittacosis: A flu like syndrome. Aust Fam Physician 30:739–741, 2001.
57. Hartzell JD, Wood-Morris RN, Martinez LJ, Trotta RF: Q fever: Epidemiology, diagnosis, and treatment. Mayo Clin Proc 83:574–579, 2008.
58. Terheggen U, Leggat PA: Clinical manifestations of Q fever in adults and children. Travel Med Infect Dis 5:159–164, 2007.
59. Audi J, Belson M, Patel M, et al: Ricin poisoning: A comprehensive review. JAMA 294:2342–2351, 2005.
60. Franco MP, Mulder M, Gilman RH, Smits HL: Human brucellosis. Lancet Infect Dis 7:775–786, 2007.
61. Pappas G, Panagopoulou P, Christou L, Akritidis N: Brucella as a biological weapon. Cell Mol Life Sci 63:2229–2236, 2006.
62. Smedley JG 3rd, Fisher DJ, Sayeed S, et al: The enteric toxins of *Clostridium perfringens*. Rev Physiol Biochem Pharmacol 152:183–204, 2004.
63. Blazes DL, Lawler JV, Lazarus AA: When biotoxins are tools of terror: Early recognition of intentional poisoning can attenuate effects. Postgrad Med 112:89–92, 95–96, 98, 2002.
64. Khan AS, Swerdlow DL, Juranek DD: Precautions against biological and chemical terrorism directed at food and water supplies. Public Health Rep 116:3–14, 2001.
65. Crum NF, Wallace MR, Oldfield EC 3rd: New issues in infectious diarrhea. Rev Gastroenterol Disord 5(Suppl 3):S16–S25, 2005.
66. Salzman M, Madsen JM, Greenberg MI: Toxins: Bacterial and marine toxins. Clin Lab Med 26:397–419, ix, 2006.
67. Saks MA, Karras D: Emergency medicine and the public's health: Emerging infectious diseases. Emerg Med Clin North Am 24:1019–1033, 2006.
68. Muller MP, McGeer A: Febrile respiratory illness in the intensive care unit setting: An infection control perspective. Curr Opin Crit Care 12:37–42, 2006.
69. Interim recommendations for facemask and respirator use to reduce 2009 influenza A (H1N1) virus transmission. September 24, 2009. Available at www.cdc.gov/h1n1/masks (Accessed November 5, 2009).
70. Branson RD, Rubinson L: Mechanical ventilation in mass casualty scenarios. Respir Care 53:38–39, 2008.
71. Devereaux A, Christian MD, Dichter JR, et al: Summary of suggestions from the Task Force for Mass Critical Care summit, January 26–27, 2007. Chest 133:1S–7S, 2008.
72. Rubinson L, Hick JL, Curtis JR, et al: Definitive care for the critically ill during a disaster: Medical resources for surge capacity. Chest 133:32S–50S, 2008.
73. Devereaux AV, Dichter JR, Christian MD, et al: Definitive care for the critically ill during a disaster: A framework for allocation of scarce resources in mass critical care. Chest 133:51S–66S, 2008.

CHAPTER 70

HIGH ALTITUDE

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INTRODUCTION

ADAPTATION TO HIGH ALTITUDE
Pulmonary Adaptation
Cardiovascular Adaptation
Hematologic Adaptation
Tissue Adaptation
Central Nervous System Adaptation
Fluid Homeostasis and Renal Function

CHANGES IN COMMON SEA-LEVEL ACTIVITIES AT HIGH ALTITUDE
Sleep
Exercise

MALADAPTATION
Problems of Lowlanders on Ascent to High Altitude
Problems of High-Altitude Residents

PREEXISTING ILLNESS AND HIGH ALTITUDE
Respiratory Diseases
Altitude-Illness Medications and Underlying Medical Diseases

INTRODUCTION

Nearly 30 million people live at altitudes greater than 2500 m, primarily in the Rocky Mountains of North America, the Andes Mountains of South America, the Ethiopian Highlands of East Africa, and the Himalaya Mountains of south central Asia. These people have developed the ability to live and reproduce at elevations as high as 5000 m but, in some cases, develop chronic medical problems attributable to their high-altitude residence. In addition to long-term residents, many lowlanders venture to high altitude for work and recreation. These more acute exposures also pose the hazards of acute altitude illnesses or altitude-related exacerbations of preexisting diseases. With growing awareness of such risks, persons are seeking advice on traveling to these regions. It is, therefore, imperative that the counseling physician be able to provide guidance about minimizing risks and managing problems should they occur.

The purpose of this chapter is to review the normal adaptive processes that occur in response to high altitude, specifically the compensatory changes that occur in the transport of oxygen from the air to the tissues in the setting of decreased barometric pressure. We discuss acute and chronic adaptation and explore factors determining the limits of adaptation and performance at high altitude. We also review the consequences of maladaptation—the acute and chronic illnesses of high altitude—and discuss strategies for managing these situations. Finally, we present an approach to the traveler with underlying medical problems who is planning a trip to high altitude.

ADAPTATION TO HIGH ALTITUDE

Under normal conditions, the P_{O_2} diminishes as oxygen moves from air to the tissues. Ventilation, regional matching of ventilation and blood flow, diffusion of oxygen from the air to the blood, transport within the circulation, diffusion of oxygen from the blood into the tissue, and metabolism in the mitochondria are all links in this oxygen transport chain. As altitude increases, the barometric pressure declines (Table 70-1) and, as a result, the P_{O_2} at every step in this chain is lower than it would be at sea level. Compensatory processes occur at each step in the chain at different rates to raise the P_{O_2} and maintain adequate oxygen delivery and, thereby, facilitate tolerance of the hypoxic environment. As far back as Paul Bert, in the latter half of the 19th century, researchers have investigated the full spectrum of these adaptive responses. Hornbein and Schoene[1] and West et al.[2] have compiled extensive reviews of this vast literature, while West[3] has described the historic

TABLE 70-1. U.S. Standard Atmosphere: Altitude, Barometric Pressure, and Inspired Partial Pressure of Oxygen*

Altitude (meters)	Altitude (feet)	Barometric Pressure (mm Hg)	Inspired P_{O_2} (mm Hg)
0	0	760	159
1,000	3,280	674	141
2,000	6,560	596	125
3,000	9,840	526	110
4,000	13,120	463	97
5,000	16,400	405	85
6,000	19,680	354	79
8,000	26,240	268	56
8,848	29,028	253	43

*Values except 8,848 m are taken for mid-latitude (45°N). There is greater variation at higher altitudes.
Modified with permission from Altman PL, Dittmer DS (eds): Respiration and Circulation. Bethesda, Md: Federation of American Societies for Experimental Biology, 1971, pp 12–13.

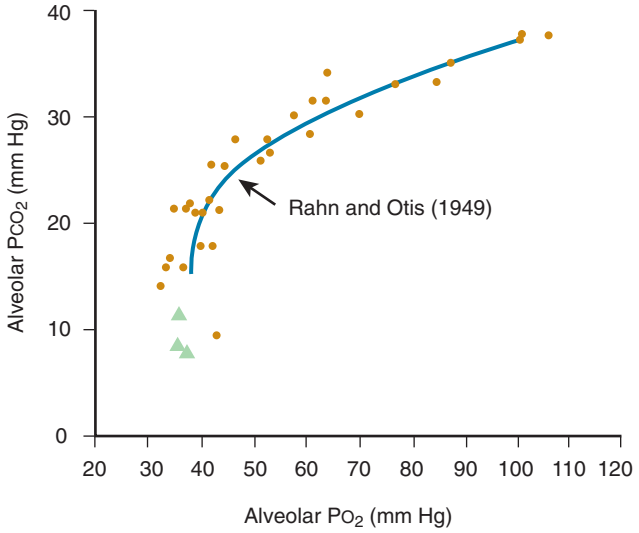

FIGURE 70-1 ■ Oxygen–carbon dioxide diagram demonstrating the alveolar gas composition in acclimatized subjects at high altitude. *Solid circles* represent data collected by Rahn and Otis (Rahn H, Otis B: Man's respiratory response during and after acclimatization to high altitude. Am J Physiol 157:445–449, 1949), while the *triangles* are measurements from three altitudes on Mt. Everest. At extreme altitudes, marked hyperventilation maintains alveolar P_{O_2} at approximately 35 mm Hg. (Redrawn from West JB, Hackett PH, Maret KH, et al: Pulmonary gas exchange on the summit of Mt. Everest. J Appl Physiol 55:678–687, 1983.)

achievements in the field. A summary of the key features of the adaptive responses to high altitude is provided in the following sections.

Pulmonary Adaptation

Control of Ventilation

Acute Response. Upon acute hypoxic exposure, alveolar ventilation increases. This response, referred to as the hypoxic ventilatory response (HVR), minimizes the drop in alveolar P_{O_2} (Fig. 70-1). There is interindividual variability in this response, which subsequently plays an important role in adaptation, maladaptation, and performance at high altitude. Large increases in ventilation are generally not seen until the arterial P_{O_2} falls below 60 mm Hg and, at any given altitude, ventilation continues to increase over weeks, in a process called ventilatory acclimatization. At extreme elevations, the increase in minute ventilation can be dramatic. Data obtained from a single individual on the summit of Mt. Everest (8848 m, barometric pressure ~253 mm Hg; see Fig. 70-1) revealed an alveolar P_{CO_2} of 7.5 mm Hg. As a result, despite an inspired P_{O_2} of only 43 mm Hg, the individual maintained an alveolar P_{O_2} of 34 mm Hg.

HVR is mediated in large part by peripheral chemoreceptors in the carotid body. Neural discharge from the whole carotid sinus nerve is related hyperbolically to decreasing arterial P_{O_2},[4] and surgical ablation of carotid body input (e.g., carotid endarterectomy or bilateral carotid body resection for intractable dyspnea) results in loss of the ventilatory response to acute hypoxia.[5]

The ventilatory response to a relatively constant hypoxic stimulus varies over time (Fig. 70-2). With initial exposure and the subsequent acute rise in minute ventilation, the arterial P_{CO_2} at the medullary and peripheral chemosensors decreases and depresses the ventilatory response.[6] Subsequently, over days, ventilation increases and continues to rise for months.[7] The classic explanation for this steady increase was that renal compensation for the respiratory alkalosis permitted full realization of the hypoxic stimulus to ventilation. However, measurement of blood pH reveals that hypocapnic alkalemia persists as ventilation increases, suggesting that other mechanisms beyond renal compensation, which is completed within 3 to 4 days, must be responsible for this change. It was proposed that a relative acidosis in the cerebrospinal fluid (CSF) and at medullary chemosensors trigger the increased ventilation, but lumbar CSF remains alkaline during high-altitude (3100 m) sojourns of up to 3 weeks, while during deacclimatization, hyperventilation persists even when arterial P_{CO_2} and blood and CSF pH have returned toward normal.[8] The pH of interstitial and intracellular fluid in the brain has also failed to show changes that could account for the increase in ventilation.[9] These results suggest that some mediator(s), other than hydrogen ion, sustain the hyperventilation during a high-altitude sojourn. One possible mediator may be erythropoietin (EPO) signaling in the brain via EPO receptors.[10] Another factor that promotes progressive hyperventilation is an increase over time in carotid body sensitivity to hypoxia.[11]

Intermittent Hypoxic Exposure. The sustained increase in ventilation described in the previous section generally pertains to exposures lasting days to weeks.

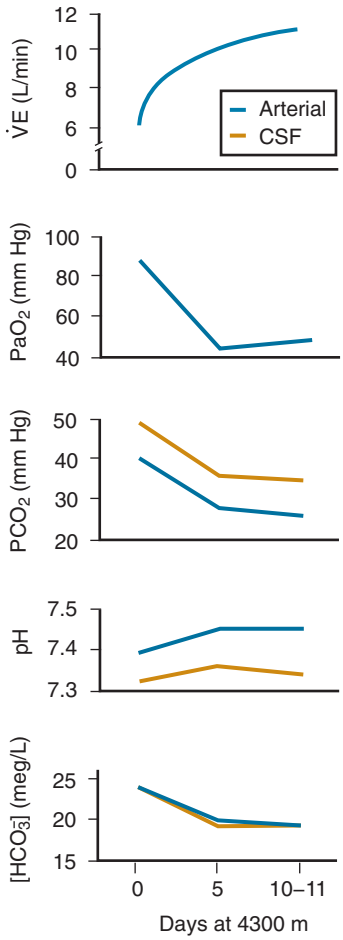

FIGURE 70-2 ■ Ventilatory acclimatization during a 10- to 11-day sojourn to 4300 m. Ventilation continues to increase as cerebrospinal fluid (CSF) acid-base alterations parallel plasma changes. HCO_3, bicarbonate; Pa_{O_2}, arterial oxygen tension; P_{CO_2}, carbon dioxide tension; $\dot{V}_E$, minute volume of ventilation. (Redrawn from Forster HV, Dempsey JA, Chosy LW: Incomplete compensation of CSF [H+] in man during acclimatization to high altitude [4300m]. J Appl Physiol 38:1067–1072, 1975.)

Shorter, intermittent exposures also affect ventilatory responses to both oxygen and carbon dioxide.[12] Studies have focused on the "dose" and frequency of the hypoxic stimulus necessary to induce a physiologic response. For example, 8 hours of exposure to isocapnic and poikilocapnic hypoxia (end-tidal P_{O_2} = 55 mm Hg) increases the chemosensitivity to carbon dioxide compared to controls,[13] while exposure to a simulated 4500-m altitude for 1 hr/day was associated with increased HVR, ventilatory equivalents ($\dot{V}_E/\dot{V}_{O_2}$), and arterial oxygen saturation (Sa_{O_2}) during postexposure hypoxia.[14]

Chronic Ventilatory Adaptation. Long-term high-altitude residents have lower minute ventilation and higher arterial P_{CO_2} than acclimatized lowlanders at the same elevation and have blunted ventilatory responses to acute hypoxia.[15] The blunted response occurs in conjunction with hypertrophy of the carotid bodies and may be an adaptive phenomenon in which the disadvantage of the lower arterial P_{O_2} is offset by the decreased energy expenditure associated with lower ventilation.

Pulmonary Function and Mechanics

On ascent, several changes occur in lung function. Vital capacity decreases in the first 24 hours and remains depressed over time at high altitude.[16] Proposed mechanisms for this observation include increased interstitial fluid volume, resulting in airway narrowing, air trapping, and delayed emptying of some lung units,[16] pulmonary vascular engorgement,[17] and decreased respiratory muscle strength.[18] Peak expiratory flow rates are increased and airway resistance is reduced.[19] The lower airway resistance is presumably due to decreased air density, which counteracts any airway narrowing that might occur due to hypoxia and hypocapnia.

In high-altitude residents, vital capacity is increased compared to non-native residents,[20] with the magnitude of the increase dependent on the length of stay at high altitude. Those born and raised at high altitude develop larger vital capacities than those who move to high altitude later in life.[21]

Gas Exchange

Ventilation and Perfusion Matching. The increase in ventilation during acute hypoxia is matched by increased cardiac output and pulmonary perfusion. Additionally, alveolar hypoxia triggers hypoxic pulmonary vasoconstriction (HPV), which increases pulmonary vascular resistance. These changes cause redistribution of blood flow to areas of the lung that are usually less well perfused at sea level and may, thereby, improve ventilation-perfusion matching ($\dot{V}_A/\dot{Q}$) and optimize gas exchange.

Diffusion. Several factors limit diffusion of oxygen from the alveolus to the blood at high altitude. Decreasing barometric pressure lowers the alveolar P_{O_2}, which, in turn, decreases the pressure gradient for diffusion such that, at altitudes above 2500 m, even the estimated pulmonary transit time at rest of 0.75 second may not be adequate for end-capillary equilibration of oxygen to occur; diffusion limitation is exacerbated during exercise due to the shortened transit time of blood across the pulmonary capillary and the fall in mixed venous P_{O_2}. Because the low arterial P_{O_2} lies on the steep portion of the oxygen-hemoglobin dissociation curve, a small decrease in P_{O_2} will result in a proportionately greater drop in pulmonary capillary oxygen content than occurs at sea level. West and Wagner[22] modeled these factors for the summit of Mt. Everest (barometric pressure ~250 mm Hg) and found that alveolar-capillary equilibration of oxygen is far from complete (Fig. 70-3).

With long-term residence at high altitude, the diffusing capacity of the lung increases, although the mechanism remains unclear. When compared to sojourners, high-altitude residents have a lower alveolar-arterial P_{O_2} difference, increased diffusing capacity, and, despite having lower minute ventilation, a higher arterial P_{O_2} at rest and during exercise.[23,24]

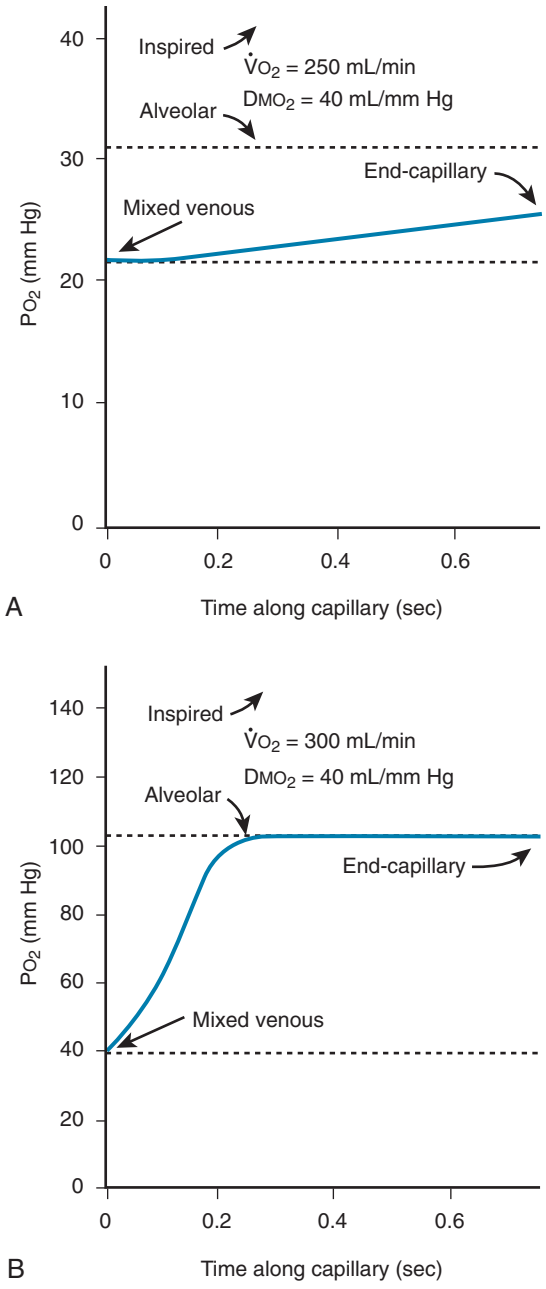

FIGURE 70-3 ■ Comparison of the calculated time course of oxygen tension (P_{O_2}) in the pulmonary capillary of a climber at rest on the summit of Mt. Everest (**A;** barometric pressure = 250 m, inspired P_{O_2} = 43 mm Hg) to sea-level values (**B;** barometric pressure = 760 mm Hg, inspired P_{O_2} =150 mm Hg). At sea level, there is adequate time for equilibration of alveolar and end-capillary oxygen, whereas at extreme altitude, even at rest, when transit time for the red blood cell is presumably similar to that at sea level, full equilibration is not realized, resulting in end-capillary blood that is not fully saturated. DMO_2, diffusion capacity of the alveolar capillary membrane; $\dot{V}O_2$, oxygen consumption. (Redrawn from West JB, Wagner PD: Predicted gas exchange on the summit of Mt. Everest. Respir Physiol 42:1–16, 1980.)

Cardiovascular Adaptation

Cardiac Response

With acute hypoxia and decreased arterial oxygen content, cardiac output increases in an effort to maintain oxygen delivery, such that for any given work rate, cardiac output is higher than at sea level. After about 1 week, the relationship between cardiac output and work rate returns to that seen at sea level. The increase in cardiac output is driven largely by an increase in heart rate rather than a change in stroke volume. Stroke volume declines upon initial exposure to high altitude and remains lower than sea level values despite acclimatization. This is not due to depressed myocardial function, as studies reveal evidence of preserved cardiac contractility in hypoxia,[25] and, instead, is likely due to diminished preload from a reduction in plasma volume. Systemic blood pressure is elevated in sojourners upon acute exposure to high altitude, likely due to increased sympathetic activity,[26] but decreases over time. In fact, in as little as 1 to 2 years after moving to high altitude, many people have lower systemic pressure, likely secondary to a vasodilatory effect of hypoxia on systemic arterial smooth muscle.

Hemodynamic Response

At high altitude, the low alveolar P_{O_2} triggers vasoconstriction in the pulmonary vasculature, a response known as *hypoxic pulmonary vasoconstriction.* Pulmonary artery pressure increases minimally until the alveolar P_{O_2} drops below 70 mm Hg, at which point a more marked rise ensues (Fig. 70-4). There is, however, substantial interindividual variability in this response,[27] part of which may be explained by the differences in iron stores between individuals.[27a]

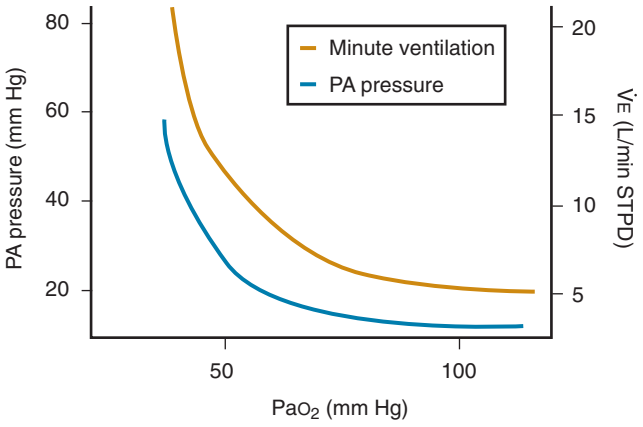

FIGURE 70-4 ■ Relationship of arterial oxygen tension (Pa_{O_2}) to minute ventilation ($\dot{V}_E$) and pulmonary arterial pressure (PA). Although there is variability among individuals, both the ventilatory and the pulmonary vascular response do not increase until Pa_{O_2} falls below 70 mm Hg. (Redrawn from Reeves JT, Wagner WW Jr, McMurtry F, et al: Physiological effects of high altitude on the pulmonary circulation. *In* Robertshaw D [ed]: International Review of Physiology: Environmental Physiology III. Baltimore: University Park Press, 1979, pp 289–310.)

Chronic hypoxic exposure results in even greater increases in pulmonary vascular resistance and pulmonary hypertension due to pulmonary vasoconstriction, hyperviscosity from polycythemia, and extensive vascular remodeling due to smooth muscle hypertrophy and collagen hyperproliferation. The precise time course of these changes is not clear. Groves et al.[28] exposed individuals to progressively lower inspired oxygen tensions during a simulated ascent of Mt. Everest (Operation Everest II) over a 40-day period and found that upon breathing a fractional concentration of oxygen in inspired gas (FIO_2) of 1.0, pulmonary artery pressures did not return to their sea-level baseline. This result suggests that some vascular remodeling had occurred in just a few weeks. Depending on the severity of changes, particularly the degree of intimal fibrosis, reversal of pulmonary hypertension may require months or years at low altitude.

Hematologic Adaptation

Erythropoietic Response

Hemoglobin concentration increases within 1 to 2 days of ascent and continues to rise for a number of weeks. The initial rise is due to hemoconcentration from the diuresis that occurs upon initial ascent; further changes are due to increased red blood cell production, which occurs as a result of hypoxia-mediated release of erythropoietin by the kidneys. Serum erythropoietin levels increase within 24 to 48 hours of ascent to high altitude, and then decline over 3 weeks as acclimatization progresses.[29] Both red blood cell volume and total blood volume increase. The erythropoietic response ceases on descent and the hematocrit returns to sea-level values in approximately 3 weeks.

Although the hematocrit generally increases with altitude, there is interindividual variability in the responses of both sojourners[30] and highlanders.[31] Similar variability is seen between different highland populations; Andean natives demonstrate greater erythropoiesis than either Himalayan or Ethiopian highlanders.[32] Whether the greater erythropoiesis in Andean natives is secondary to environmental exposures, such as high levels of cobalt in and around mining regions,[33] or to an up-regulation of the erythropoietic response to the renal sensing of hypoxia[34] is not clear.

While increasing hemoglobin concentration can augment arterial oxygen content, it may also impair oxygen delivery because, as the hematocrit approaches 60%, viscosity increases sufficiently to impair cardiac output.

Oxygen-Hemoglobin Affinity

Oxygen transport by blood is also influenced by the oxygen affinity of hemoglobin, as defined by the shape and position of the oxygen-hemoglobin dissociation curve. An important feature of the oxygen-hemoglobin relationship is the manner in which the dissociation curve steepens as the arterial PO_2 falls below 60 mm Hg. As a result, with ascent to high altitude, the arterial PO_2 falls into a range in which the oxygen content of hemoglobin drops precipitously with only small decreases in PO_2.

To mitigate the potentially large impact on oxygen delivery, adaptations occur in the oxygen-hemoglobin relationship. For example, with initial exposure to high altitude and the resultant respiratory alkalosis, the dissociation curve shifts to the left. This shift enhances oxygen loading in the lungs and increases arterial oxygen content but comes at the expense of potentially decreased oxygen off-loading in the tissues. Over time, the curve shifts back to the right in response to increased 2,3-diphosphoglycerate (2,3-DPG) concentrations and renal compensation for the respiratory alkalosis and improves oxygen off-loading in the tissues.

Coagulation

Studies at high altitude do not show consistent patterns of change in hemostasis, with conflicting results regarding the effect of high altitude on platelet counts, bleeding times, and markers of thrombin and fibrin formation.[35,36] Changes such as increased fibrinogen levels and prolonged clot lysis times have been noted in patients with high-altitude pulmonary edema (HAPE),[37] and taken as evidence that thrombosis and platelet aggregation may contribute to this disease. However, Bartsch et al.[38] performed careful longitudinal studies while subjects were developing HAPE and concluded that platelet and coagulation changes were epiphenomena and had no causative role. There may be a link between underlying coagulopathy and thromboembolic risk at altitude,[39] but more work is necessary on this question.

Tissue Adaptation

At the final stage of oxygen delivery, oxygen moves from plasma to the site of oxidative phosphorylation in the mitochondria. While driving pressures of only 1 to 2 mm Hg are necessary for diffusion from cytoplasm to the mitochondria, driving pressures of 10 mm Hg may be needed for movement from capillary plasma to the cytoplasm. At sufficiently high altitudes, the capillary PO_2 may fall to levels at which diffusion into the mitochondria is impaired. Morphologic and biochemical responses occur to overcome this problem. In general, evidence points to reduced diffusion distance from blood to mitochondria in muscle due to diminished fiber size, increased myoglobin concentration, and changes in the levels or activity of enzymes involved in oxidative metabolism. Finally, recent evidence indicates that cytoglobins, heme proteins expressed in many cells that have oxygen binding and transport characteristics similar to myoglobin, may be up-regulated in hypoxia and play a role in adaptive responses.[40]

Central Nervous System Adaptation

Cerebral Blood Flow

On acute exposure, hypoxia triggers an increase in cerebral blood flow that is, in part, offset by hypocapnic-

mediated cerebral vasoconstriction; the net result is a modest increase in cerebral blood flow,[41] which appears to be equally distributed between white and gray matter.[42] The acute cerebrovascular response may be biphasic in nature, with an initial decrease in cerebral blood flow due to acute hypocapnia followed by a subsequent increase triggered by arterial hypoxemia.[43] After 4 to 5 days, cerebral blood flow decreases but is still 13% greater than the sea-level value.[41] This increase in cerebral blood flow helps maintain oxygen delivery when arterial oxygen content is at its lowest until other adaptive mechanisms take effect and raise arterial oxygen content.

Cerebral Function

As one ascends, motor, sensory, and complex cognitive abilities are progressively impaired. New tasks are learned with difficulty at 3048 m, and simulated altitudes of 6100 m result in a decrement in sensory, perceptual, and motor performance. Short-term memory is impaired in climbers ascending without supplemental oxygen to 8500 m or higher.[44] Even acute, modest decreases in Sa_{O_2} to 85% impair mental concentration and fine motor coordination; a further decrease to 75% results in poor judgment, irritability, and decreased muscle function.

It is difficult to predict which individuals will experience neurologic dysfunction at high altitude, but combined data from a field study on Mt. Everest and a chamber study simulating an ascent of Mt. Everest (Operation Everest II) demonstrated that individuals with a high HVR and higher Sa_{O_2} had more pronounced neuropsychometric dysfunction.[45] One explanation for these findings is that those with a more brisk HVR might have greater hypocapnic cerebral vasoconstriction and, consequently, lower cerebral oxygen delivery.

A recent study in which brain magnetic resonance imaging (MRI) was performed on climbers who had ascended to summits between 5895 and 8848 m[46] demonstrated evidence of subcortical lesions suggestive of small infarctions. The study did not correlate these findings with symptoms or signs of neurologic dysfunction and did not include follow-up studies to determine if these lesions resolved, but the results raise the question as to whether high-altitude exposure causes permanent cerebral injury and whether the observed dysfunction at high altitude persists over time. Existing evidence suggests that the transient deterioration in learning, memory, and expression of verbal material returns to baseline within 1 year but that fine motor coordination problems may persist for longer periods of time.[45,47]

Cellular Adaptive Mechanisms

As with cytoglobin up-regulation in peripheral tissues, intracerebral expression of neuroglobin, another protein related to hemoglobin and myoglobin, is increased during hypoxic stress and may play a role in limiting neuronal injury.[48]

Fluid Homeostasis and Renal Function

Upon ascent to high altitude, diuresis and natriuresis occur and, as with the hypoxic ventilatory response, these peripheral chemoreceptor-mediated responses vary almost 10-fold between individuals over the first 24 to 48 hours at altitude.[49] Following acclimatization, further gains in elevation may lead to additional diuresis and natriuresis.[50] The mechanism underlying this observed diuresis and natriuresis is not clear, but it does not appear to result from changes in renin, angiotensin, aldosterone, or atrial natriuretic peptide levels. Acute hypoxia causes a two- to threefold increase in urinary protein excretion, with even higher levels seen in persons who develop high-altitude illness.

CHANGES IN COMMON SEA-LEVEL ACTIVITIES AT HIGH ALTITUDE

Sleep

Difficulty sleeping is a common problem at high altitude. In studies examining pharmacologic prophylaxis of acute mountain sickness (AMS), for example, over 70% of people receiving placebo reported poor quality sleep.[51] There is also objective evidence of impairment, increased arousals, sleep architecture changes, and an increased incidence of periodic breathing.[52] In addition, the most severe hypoxemia experienced by both sojourners and natives occurs during sleep, as steep, transient drops in oxygen saturation often accompany apneic periods.

The mechanisms underlying periodic breathing at high altitude have been reviewed elsewhere.[53] The consensus is that sleep eliminates most cortical influences on respiration, leaving hypoxemia via carotid chemoreceptors as the prominent drive. The effect of hypoxia-induced changes in P_{CO_2} on hypoxic drive may set up oscillations of ventilation in a poorly damped system. At moderate altitudes (<3000 m), this periodic breathing diminishes over several days as ventilatory acclimatization proceeds, but at higher altitudes periodic breathing persists for long periods of time.[54]

Periodic breathing during sleep at high altitude can be eliminated by breathing supplemental oxygen (Fig. 70-5) and can be reduced through the use of respiratory stimulants such as acetazolamide.[55] A review of trials of acetazolamide in AMS prophylaxis demonstrated that sleep was also improved in the acetazolamide groups compared to the placebo groups.[51,56] More recently, the benzodiazepine temazepam has also been shown to reduce the incidence of periodic breathing and improve measures of sleep quality without a negative effect on next-day reaction times or maintenance of wakefulness.[54] γ-Aminobutyric acid receptor agonists, including zolpidem and zaleplon, can also improve sleep quality and sleep architecture, but there is no evidence that either agent decreases periodic breathing.[57]

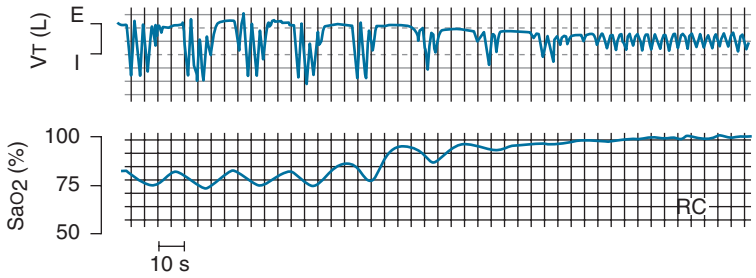

FIGURE 70-5 ■ Periodic breathing in a lowlander at 5400 m during sleep while breathing ambient air (*left half of tracings*) and oxygen (*right half of tracings*). *Upper panel* is tidal volume (V_T, inspiration downward), and *lower panel* is arterial oxygen saturation (Sa_{O_2}, %). (Redrawn from Lahiri S, Maret K, Sherpa MG: Dependence of high-altitude sleep apnea on ventilatory sensitivity to hypoxia. Respir Physiol 52:281–301, 1983.)

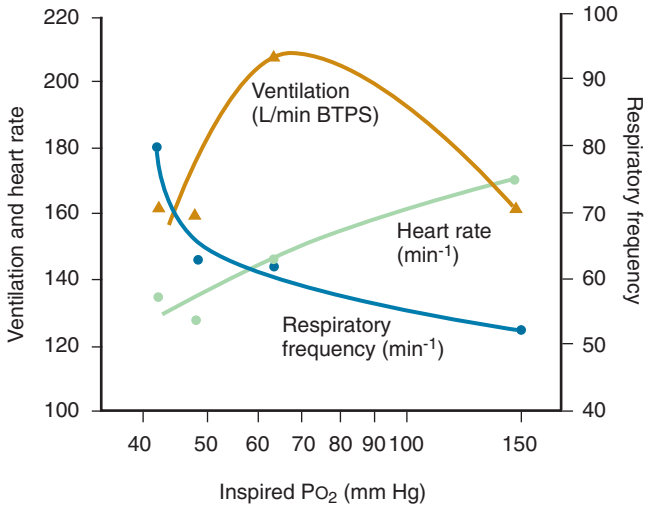

FIGURE 70-6 ■ Maximum minute ventilation ($\dot{V}_{E_{max}}$), respiratory frequency, and heart rate versus inspired P_{O_2}. At 6300 m, $\dot{V}_{E_{max}}$ is increased because of the stimulation to ventilation from hypoxia as well as a decreased density of the inspired air, whereas at over 8000 m, $\dot{V}_{E_{max}}$ is decreased, probably as a result of a diminished metabolic demand from low work rates. Frequency continues to increase. Maximum heart rate decreases with increasing altitude. (Redrawn from West JB, Boyer SJ, Graber DJ, et al: Maximal exercise at extreme altitudes on Mount Everest. J Appl Physiol 55:688–702, 1983.)

Exercise

Exercise at high altitude is different in many important respects from exercise at sea level.

Maximal Work

With acute and prolonged hypoxic exposures, maximal oxygen consumption ($\dot{V}_{O_2}$ max) and work capacity are decreased relative to sea-level values.[58,59] $\dot{V}_{O_2}$ max decreases about 10% per 1000 m of altitude gain, such that at approximately 0.5 atm, $\dot{V}_{O_2}$ max is about half of its sea-level value, and at 0.33 atm (as at the summit of Mt. Everest), $\dot{V}_{O_2}$ max is about 23% of that at sea level. Because maximum oxygen uptake is decreased at altitude, maximum minute ventilation and heart rate at peak exercise are also reduced compared to their sea-level values (Fig. 70-6).[58,59]

Ventilation

Because of the decrease in air density and the lower concentration of oxygen molecules, greater minute ventilation is required to achieve the same oxygen uptake at high altitude. As a result, the ventilatory response to exercise is augmented at altitude compared to sea level.[58,60] For example, the ventilation for a given metabolic rate (the ventilatory equivalent, $\dot{V}_E/\dot{V}_{O_2}$) in sojourners to 6300 m is almost four times as great as at sea level. The increase is a function of both the altitude attained and the strength of the individual's HVR.[60] The increase in ventilation comes at a price, however. The oxygen cost of breathing during exercise at extreme altitude may be as high as 40% of the overall metabolic rate at high levels of exercise and may result in allocation of cardiac output to respiratory muscles that could otherwise be dedicated to muscles of locomotion. Subjects also often experience extreme dyspnea that may affect the intensity and duration of exercise. Rest leads to rapid resolution of dyspnea in normal individuals, however.

Gas Exchange

Unlike at sea level, where arterial oxygen saturation remains constant with increasing work loads in most normal individuals, it decreases with increasing workloads following either short-duration[61] (Fig. 70-7) or long-duration high-altitude exposures.[58] Alveolar hypoxia decreases the driving gradient for diffusion, while pulmonary capillary transit time is shortened as a result of the increase in cardiac output, thereby creating a true diffusion limitation (see Fig. 70-3). $\dot{V}_A/\dot{Q}$ mismatching may also contribute to the observed gas exchange abnormalities[61]; nonuniform hypoxic pulmonary vascular response may lead to interstitial pulmonary fluid accumulation that, in turn, creates $\dot{V}_A/\dot{Q}$ heterogeneity and impairs gas exchange.

Cardiovascular Response

For any given submaximal work rate, cardiac output and heart rate are higher during exercise at altitude compared to sea level. Because maximum exercise capacity is reduced, peak heart rate and cardiac output are reduced relative to sea-level values. With acclimatization, cardiac output at submaximal workloads returns to sea-level values while heart rate remain elevated. Because maximum exercise capacity is not restored to sea-level

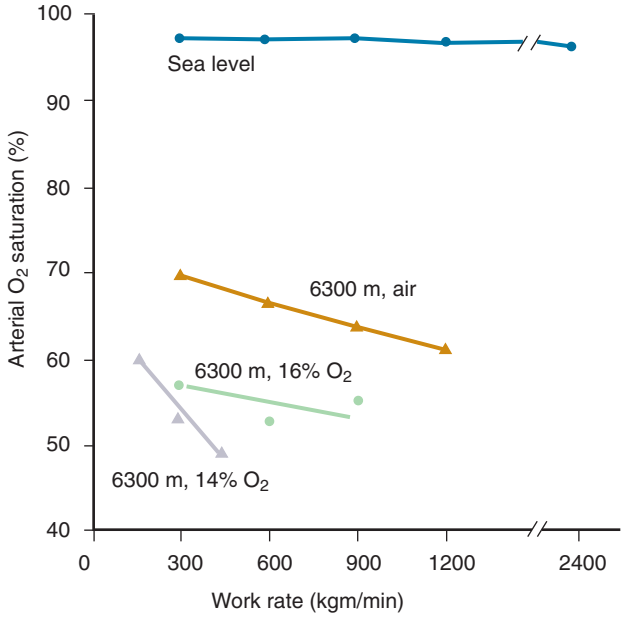

FIGURE 70-7 ■ Arterial oxygen saturation (%) does not decrease with exercise at sea level but drops progressively with higher workloads at greater altitudes due to a diffusion limitation of oxygen transfer across the alveolar-capillary interface. (Redrawn from West JB, Boyer SJ, Graber DJ, et al: Maximal exercise at extreme altitudes on Mount Everest. J Appl Physiol 55:688–702, 1983.)

values over time, maximum cardiac output, heart rate, and stroke volume all remain decreased following prolonged exposure.[25]

Pulmonary artery pressures reach high levels during exercise at high altitudes.[28] Whether these high pressures limit exercise capacity at altitude is not clear. On the one hand, because cardiac output is maintained at levels appropriate for the work rates attained, the increase in pulmonary vascular resistance in healthy sojourners to high altitude would not appear to limit exercise. However, in a recent field study of acclimatized individuals,[62] administration of the phosphodiesterase inhibitor sildenafil prior to a maximum exercise test at 5245 m improved pulmonary artery systolic pressure and maximum exercise capacity compared to placebo, but others have not confirmed this.[63,63a] Thus, it remains unresolved whether the rise in pulmonary artery pressures contributes to limiting exercise capacity at high altitude.

Exercise Performance at High Altitude

The effect of altitude on exercise performance varies based on the type of activity and the duration of stay at high altitude. Performance for running events of less than 2 minutes' duration at less than 3000 m altitude is not impaired and may even be slightly improved because of decreased air density. Performances in events of longer duration are predictably diminished and cannot be restored to sea-level capacity with prolonged stay at high altitude. Some improvements do occur with time, but overall performance does not return to sea-level values. Finally, as noted earlier, maximum oxygen consumption, peak heart rate, and peak minute ventilation are reduced at high altitude. Regardless of the duration of stay or the intensity of training, these values do not return to sea-level values.

Training at High Altitude

There is considerable interest in whether living and training at high altitude improves performance at lower elevations. In the past, many elite endurance athletes relocated to and trained at moderate altitudes of 2000 to 2500 m, but, unfortunately, the beneficial effects on performance after return to sea level were generally not realized, as athletes could not attain the same maximum speeds and power output during training at altitude that they needed to reach during their sea-level races. More recently, interest has been raised in using intermittent hypoxic exposure as an alternative means to apply the benefits of high-altitude acclimatization to sea-level performance. Beidleman et al.,[64] for example, found that intermittent exposure to 4300 m for 3 weeks improved ergometrics and strength in trained cyclists. In their landmark study, Levine and Stray-Gundersen[65] studied four well-matched groups of athletes: (1) those who lived low and trained low (1350 m), (2) those who lived low and trained high (3000 m), (3) those who lived high and trained high, and (4) those who lived high and trained low. The group that lived high and trained low seemed to have gained the benefit of hypoxic conditioning while not losing the intensity of training sessions. This advantage was presumably due to the modestly elevated hemoglobin from the altitude exposure, although there was individual variability in the erythropoietic response.[66]

Because of the limited access to high altitude for many athletes, recent interest has focused on "bringing the mountain to the athlete"[67] by having the athlete spend time each day in an oxygen-depleted tent that can be set up in the home or training center. The key question that has emerged from this practice and the studies noted previously, however, is what "dose" of hypoxic exposure is necessary to see a benefit in sea-level performance. A recent review of studies on the topic concluded that athletes needed to reside at 2000 to 2500 m for more than 4 weeks for greater than 22 hr/day in order to derive physiologic benefits from the live high–train low model.[67]

MALADAPTATION

The physiologic adaptations described previously give individuals the ability to tolerate high-altitude exposure. Whereas a person who makes a sudden ascent from sea level to the summit of Mt. Everest (8848 m) by helicopter, for example, would become unconscious within minutes and die soon thereafter, a climber using an appropriately slow ascent rate can complete the climb without obvious effects because the body adapts to the hypoxic environment. Regardless of the ultimate altitude achieved,[11] individuals who ascend too rapidly to altitudes above 2500 m may display maladaptive responses

and develop one of three forms of acute altitude illness: acute mountain sickness (AMS), high-altitude pulmonary edema (HAPE), and high-altitude cerebral edema (HACE). Because the risk of such illnesses decreases as individuals spend more time at altitude, long-term residents are not susceptible to these problems. However, several forms of chronic altitude illness, chronic mountain sickness, and right heart failure can affect these populations and represent important public health concerns.

Problems of Lowlanders on Ascent to High Altitude

Susceptibility to Altitude Illness

The incidence and severity of acute altitude illness depend on several factors, including the rate of ascent, the length of stay, and individual susceptibility. A trip to and from high altitude on the same day poses much less risk than an overnight stay because hypoxia is accentuated during sleep and because of more prolonged exposure associated with the overnight stay. Susceptibility to altitude illness varies considerably between individuals, but for a single individual the symptoms are often reproducible given the same rate of ascent and other circumstances. Whereas men and women are equally susceptible to AMS,[68,69] younger adults[68] and the obese[69,70] may be slightly more vulnerable to AMS. Recent trips to high altitude,[71] and residence at moderate altitude (>1900 m),[72] have a protective effect. Of note, being in good physical condition does not exert any protective effect.[73] There are insufficient data regarding whether preexisting illnesses increase susceptibility.

At present, there are no means to predict who will get sick upon ascent to high altitude. Variables such as HVR[74] and arterial oxygen saturation during hypoxic exposure[75] have been proposed as useful predictors for developing AMS, but have not been validated in further studies, and genetic differences such as the ACE gene polymorphism have no prognostic value.[76,76a] HAPE-susceptible individuals have been shown to have intense HPV and exaggerated pulmonary vascular responses to resting hypoxia and normoxic exercise[27,77] but this relationship has not been validated in prospective studies. In the end, the only useful predictive tool remains the patient's prior experience at high altitude, particularly when the ascent rate and altitude of the prior and planned sojourns are similar.

Acute Mountain Sickness

AMS is the most common form of acute altitude illness, affecting 22% to 50% of travelers to altitudes between 1850 and 4240 m.[68,69]

Clinical Presentation. AMS is marked by the presence of headache plus one or more other symptoms, including lassitude, insomnia, anorexia, nausea, dizziness, and, in severe cases, vomiting. Symptoms do not start immediately upon ascent but, instead, come on over many hours following arrival at altitudes above 2400 m (8000 feet), although the elevation at which symptoms begin varies between individuals. Affected persons frequently have difficulty sleeping and wake up the following morning with a severe headache. Although many people complain of a sense of oppression in the chest, there is rarely any respiratory distress or tachypnea so long as the patient is at rest.

On physical examination, many individuals manifest tachycardia, although a relative bradycardia has been documented in some case series.[78] Patients often appear slightly cyanotic with a dull, heavy look in their eyes. Localized crackles are present in 25% to 35% of the cases.[78] Decreased urine output in spite of adequate hydration and evidence of fluid retention may also be present.[68]

The symptoms and signs of AMS are nonspecific, and other items must be considered in the differential diagnosis, including dehydration, hypothermia, exhaustion, alcohol hangover, carbon monoxide poisoning, and respiratory or cerebral infections. The diagnosis is based solely on the clinical history, and there are no confirmatory laboratory tests. In order to say the person has AMS and not the more severe HACE, the patient must have normal neurologic and mental status examinations.

Natural Course of Untreated AMS. In a study of Indian soldiers[78] airlifted to 3300 to 5500 m, incapacitating illness lasted 2 to 5 days but full recovery often took longer; 38% recovered fully within 3 days, 40% were still ill after 1 week, and 13% had symptoms after 1 month. In tourists sleeping at a lower altitude (2700 m), symptoms lasted an average of 15 hours (range, 6 to 94 hours).[79] Most individuals tolerate or treat their own symptoms as the illness resolves over 1 to 3 days, but some persons with AMS seek medical help or are forced to descend. A small percentage of those with AMS (2% to 8%) proceed to develop HACE or HAPE, especially if ascent is continued in spite of illness.

Pathophysiology. Current concepts of pathophysiology emphasize the cerebral etiology of AMS. In very severe illness, elevated intracranial pressure and cerebral edema have been noted on neurologic imaging[80] and brain biopsy.[78] Brain MRI studies have demonstrated swelling in the white matter and none in the gray matter in patients with HACE,[80] a finding that suggests the edema is vasogenic in origin and initially confined to the white matter. Patients with AMS appear to have slightly increased brain volume (0.8% vs. 0.4%) and decreased intracerebral CSF volume by MRI versus those without symptoms.[81] Subsequent studies revealed conflicting data, with some reporting no evidence of changes consistent with cerebral edema[82] and others showing evidence of mild increases in brain volumes and evidence of cytotoxic edema in subjects with mild to moderate AMS.[83] It has been suggested that development of AMS may depend to some extent on the ability to shift CSF out of the cranium, and those individuals with smaller total CSF volumes may be at a disadvantage. This argument, referred to as the "tight-fit" hypothesis, might explain the possible difference in susceptibility between younger and older persons, as age-related increases in volume of sulci in the latter group may provide more room to accommodate mild brain swelling.[84]

Although the available evidence suggests cerebral edema plays a role in severe AMS, it remains unclear whether this causes milder forms of the disease. There is only one study of intracranial pressure in subjects with early AMS, and it failed to demonstrate an increase in CSF pressure.[84] Because headaches occur in early AMS at a time when edema and significant increases in intracranial pressure are unlikely, alternative explanations should be considered. The classic explanation that the headache and other symptoms of AMS are due to cerebral vasodilation alone seems unlikely, as attempts to link AMS symptom severity with middle cerebral artery blood flow velocity have shown no correlation.[85] Limited evidence that sumatriptan, a 5-hydroxytryptamine$_1$ receptor agonist, can prevent AMS[86] or treat high-altitude headaches[87] suggests that abnormal cerebrovascular reactivity or neuropeptide responses play a role in AMS pathophysiology. Another explanation is that hypoxia-induced changes in the blood-brain barrier alter permeability to plasma compounds with potential neurotoxicity or irritation. Studies in animals and cell cultures have established hypoxic-mediated increased permeability of the blood-brain barrier to large molecules, but this has not been observed in humans.[83] The mechanism underlying these blood-brain barrier changes is unclear, but factors such as oxygen free radical species and vascular endothelial growth factor have been proposed as possible explanations.[88,89]

The findings in severe AMS of possible cerebral edema, peripheral edema, and proteinuria also suggest there may be a defect in salt and water homeostasis, and an increase in capillary permeability. AMS-susceptible individuals have elevated aldosterone and antidiuretic hormone levels when compared with controls, while persons acclimatizing well exhibit diuresis, net water loss, and low antidiuretic hormone values.[90] A recent study confirmed the findings regarding antidiuretic hormone but found no difference in aldosterone levels between healthy controls and those with AMS.[91] These alterations in hormone levels cannot be attributed to a generalized increase in systemic capillary permeability or endothelial cell dysfunction, as subjects with and without AMS demonstrate no differences in the global transvascular escape of labeled protein.[92]

Hypoventilation may also contribute to the development of AMS. Acetazolamide and theophylline, two medications with respiratory stimulant properties, prevent the disorder,[56,93] while a brisk increase in ventilation on ascent to altitude has been associated with a lower incidence of AMS.[74] At the same time, however, prospective studies have not demonstrated a correlation between HVR measured prior to ascent and the development of AMS at high altitude.[94] Bartsch et al.[94] demonstrated that, as subjects developed AMS, they developed relative hypoventilation compared to well-adapting subjects, suggesting that HVR is blunted in response to AMS, rather than serving as its cause.

Prevention. A number of pharmacologic and nonpharmacologic measures prevent or ameliorate AMS. Because overly rapid ascent to too high an elevation is the leading risk factor for altitude illness, gradual ascent, with rest days for acclimatization, is considered the single best way to prevent all forms of altitude illness. Based on consensus opinion, it is recommended[81] that, above 3000 m, individuals should not increase their sleeping elevation by more than 300 to 500 m per night and should take an acclimatization day and sleep at the same elevation a second night every 3 to 4 days or after any large gain in elevation. This particular regimen has never been tested in a controlled study, but other studies[94a,94b] have established that graded ascent is associated with lower incidence of altitude illness. Strict adherence to the recommended ascent profile may be difficult due to differences in topography and travel schedules. Travelers should also avoid overexertion and refrain from heavy alcohol consumption or narcotic medication use, particularly before bedtime, in order to avoid hypoventilation, which can exacerbate the hypoxemia of high altitude. These strategies have never been subjected to rigorous study but represent commonsense measures in light of the physiologic changes at altitude.

Pharmacologic means can also be used to prevent AMS. The most commonly used medication for this purpose is acetazolamide.[56,68] Its principal action is renal carbonic anhydrase inhibition, which causes a bicarbonate diuresis and a metabolic acidosis, which, in turn, stimulates ventilation, increases alveolar P_{O_2} and enhances oxygen off-loading in the tissues. In effect, the drug speeds natural acclimatization by accelerating the pace of ventilatory adaptation by several days. Actions of acetazolamide on carbonic anhydrase elsewhere in the body, such as the peripheral and central chemoreceptors, may also contribute to its preventive role.[95]

Although there has been recent debate about the proper dosing regimen for AMS prophylaxis, a growing body of clinical evidence supports the use of either 125 mg or 250 mg twice a day (Table 70-2). Acetazolamide is well tolerated, with the most common side effect being paresthesias involving the hands, feet, and lips. Nausea and drowsiness occasionally occur, and carbonated beverages taste flat, probably secondary to the inhibition of hydration of carbon dioxide on the palate. Acetazolamide has a sulfonamide moiety and shares the cautions common to all sulfa drugs. The likelihood of a cross reaction is low (~7% to 10%),[96] but case reports describe fatal anaphylactic reactions in people with documented sulfa allergy who received acetazolamide.[97]

For patients who do not tolerate or cannot take acetazolamide, dexamethasone is an effective alternative for AMS prophylaxis.[98] Studies comparing dexamethasone and acetazolamide have revealed approximately equal effectiveness of the two drugs in preventing AMS.[99] Dexamethasone does not speed the acclimatization process and may be associated with reappearance of symptoms if it is abruptly discontinued. Suggested doses are listed in Table 70-2.

As noted earlier, theophylline can prevent AMS but, given the narrow therapeutic window of the medication, it should not be used for this purpose. Several studies demonstrate that gingko biloba can prevent AMS,[100,101] but given that there are also several negative trials[102,102a,103] and concerns about variability in gingko preparations from manufacturer to manufacturer,[102] this medication should not be used for AMS prophylaxis.

TABLE 70-2. Dosing and Use of Altitude Illness Medications in Normals and Patients with Underlying Disease

Medication	Dose in Normal Individuals	Liver Disease	Chronic Kidney Disease	Other Major Dosing Issues
Acetazolamide	*AMS Prevention:* 125 or 250 mg bid *AMS Treatment:* 250 mg bid	Use is contraindicated.	Avoid use in patients with GFR < 10 mL/min, metabolic acidosis, hypokalemia, hypercalcemia, and hyperphosphatemia or recurrent nephrolithiasis.	Avoid in patients on chronically high doses of aspirin or with ventilatory limitation (FEV_1 < 25% predicted). Caution in patients with documented sulfa allergy. Avoid concurrent use of topiramate.
Dexamethasone	*AMS Prevention:* 4 mg bid or 2 mg qid *HACE Treatment:* 8 mg once followed by 4 mg q6h	No contraindication; no dose adjustments necessary.	No contraindication; no dose adjustments necessary.	Expect elevated blood glucose values when used in diabetic patients. Avoid in patients at risk for peptic ulcer disease or upper GI bleeding. Caution in patients at risk for amebiasis or strongyloidiasis.
Nifedipine	*HAPE Prevention:* 20–30 mg of sustained-release version q12h *HAPE Treatment:* 20–30 mg of sustained-release version q12h	Reduced dose required (10 mg bid).	No contraindication; no dose adjustments necessary.	Caution in patients taking medications metabolized by CYP isozyme 3A4 and 1A2 pathways. Caution during concurrent use with other antihypertensive medications.
Tadalafil	*HAPE Prevention:* 10 mg bid *HAPE Treatment:* Unknown	*Child's Class A and B:* maximum 10 mg daily. *Child's Class C:* Do not use tadalafil.	Dose adjustments necessary if GFR < 50 mL/min: if GFR 30–50 mL/min, use 5-mg dose, maximum 10 mg in 48 hr; if GFR < 30 mL/min, no more than 5 mg.	Increased risk of gastroesophageal reflux. Caution in patients taking medications metabolized by CYP isozyme 3A4 pathway. Avoid concurrent use of nitrates or α-blockers.
Sildenafil	*HAPE Prevention:* 50 mg q8h *HAPE Treatment:* Unknown	Dose reductions recommended. Starting dose 25 mg tid. Avoid use in patients at risk for variceal bleeding.	Dose adjustments necessary if GFR < 30 mL/min.	Increased risk of gastroesophageal reflux. Caution in patients taking medications metabolized by CYP isozyme 3A4 pathway. Avoid concurrent use of nitrates or α-blockers.
Salmeterol	*HAPE Prevention:* 125 μg bid *HAPE Treatment:* Unknown	Insufficient data.	No contraindication; no dose adjustments necessary.	Avoid concurrent use of β-blockers, monoamine oxidase inhibitors, or tricyclic antidepressants. Possible adverse effects in coronary artery disease patients prone to arrhythmia.

AMS, acute mountain sickness; bid, twice daily; CYP, cytochrome P-450; FEV_1, forced expiratory volume in 1 second; GFR, glomerular filtration rate; GI, gastrointestinal; HACE, high-altitude cerebral edema; HAPE, high-altitude pulmonary edema; qid, four times daily; tid, three times daily.

In most cases, pharmacologic prophylaxis is not necessary; a slow ascent profile is usually sufficient to prevent AMS. Pharmacologic prophylaxis may be reserved for people with known susceptibility to AMS who are returning to altitudes at which they have been sick in the past, people flying into high-altitude destinations (e.g., La Paz, Bolivia), or people whose work mandates a rapid ascent (e.g., rescue teams). In other circumstances, it is reasonable to delay use of acetazolamide until the symptoms of AMS first develop, at which time it can be taken in the usual dosage until symptoms improve.

Treatment. In general, descent leads to resolution of all forms of altitude illness. Patients with mild illness may not require descent, however, and often recover by remaining at the same elevation and resting for a period of time. In more severe illness, descent is indicated and should continue until symptoms resolve. How much descent is required varies depending on the severity of the case; less severe illness may resolve with descent of only 300 m, while more severe illness may require further drops in altitude. At times, field conditions may be such that descent is infeasible and alternative treatments are necessary. Severely ill patients can be placed

on supplemental oxygen if gas tanks or an oxygen concentrator is available, or "low altitude" can be brought to the patient through the use of lightweight portable hyperbaric chambers. These chambers can be pressurized to 2 psi and effect a descent of approximately 1500 m. By means of a foot pump, sufficient gas flow is maintained to keep the carbon dioxide concentration low and the oxygen concentration close to 21%.[104] Studies demonstrate that the chamber is as effective as administering supplemental oxygen with an F_{IO_2} of 0.26 to 0.30, although the therapy is difficult to implement with claustrophobic individuals or those who are vomiting. As with oxygen therapy, relief of symptoms is generally immediate, but long treatment times are needed in severe illness and to ensure sustained improvement upon removal from the chamber.[104]

Acetazolamide can ameliorate symptoms of AMS and improve arterial oxygenation,[105] while aspirin,[78] ibuprofen,[106] and acetaminophen[106] have been shown to be treat the headache associated with AMS. Prochlorperazine is useful for treating nausea and vomiting and, unlike some other antiemetics, may actually increase HVR rather than depress ventilation.[107] Even if it is not being used for AMS prophylaxis, dexamethasone should be part of the high-altitude traveler's medical kit, especially in remote areas of the mountains, as rapid treatment of evolving symptoms with dexamethasone may keep patients ambulatory, allowing them to descend on their own without need for an expensive evacuation.

High-Altitude Cerebral Edema

HACE is a potentially fatal form of acute altitude illness defined by the onset of mental status changes and/or ataxia in a person with AMS, or by the presence of both neurologic signs in a person without AMS who has recently ascended to altitude.

In addition to ataxia and altered level of consciousness, many people develop an incapacitating headache, persistent nausea and vomiting, and debilitating lassitude. Affected individuals may also develop one of many neurologic symptoms and signs, including papilledema, visual changes, cranial nerve palsies, bladder dysfunction, abnormal reflexes, paresthesias, pareses, aphasia, clonus, hallucinations, seizures, and behavioral changes.[68] If the disease is not recognized and treated promptly, coma and death may ensue.

The incidence of HACE is difficult to assess because the boundary of progression from AMS may be hard to define and the symptoms and signs may be similar to those of cerebral hypoxia secondary to *severe* hypoxemia from pulmonary edema. Incidences of 0.53% to 1.25% have been reported.[78,108] At higher altitudes, HACE may affect 2% to 8% of those experiencing AMS and is more common in those with HAPE.[68,78] The differential diagnosis includes all other causes of encephalopathy, such as carbon monoxide poisoning, hypertensive crisis, severe cerebral hypoxia secondary to HAPE, meningitis, hypoglycemia, moderate to severe hypothermia, and migrainous encephalopathy. Because HACE is generally a problem of global neurologic dysfunction marked by gradual onset over a period of hours, the sudden onset and/or presence of focal neurologic deficits, high fevers, or neck stiffness should prompt consideration of alternative diagnoses. Diagnosis in the field is based on the clinical history and clinical examination. Heel-to-toe walking along a straight line is an effective test for the presence of ataxia. Where advanced diagnostic modalities are available, MRI reveals a pattern of reversible increased T2-weighted signal in the corpus callosum, and in particular the splenium, which may help differentiate HACE from other conditions.[80]

Pathology reports reveal gross cerebral edema in persons who die from HACE.[109] Findings included swelling and flattening of the cerebral gyri, compression of the sulci, herniation of cerebellar tonsils and unci, small petechial hemorrhages, and venous and sinus thromboses. Brain MRI performed in patients with nonfatal HACE also reveals evidence of hemosiderin deposition, a finding consistent with the presence of microhemorrhages.[110]

The definitive treatment for HACE is descent, although recovery is not as rapid as in AMS and HAPE, and descent of more than 1000 m may be necessary. Oxygen or hyperbaric therapy may be lifesaving temporizing measures if descent is not possible. In the only study of therapy, severe neurologic symptoms and signs responded to furosemide and betamethasone, although the drugs were not studied separately or in a prospective manner.[78] Dexamethasone is now routinely used in HACE management (see Table 70-2). Mannitol and glycerol have been suggested for treatment but are difficult to use safely in the field due to lack of adequate monitoring of serum osmolality and volume status, and should only be used in a hospital or clinic setting.

High-Altitude Pulmonary Edema

HAPE is the most common cause of death from high-altitude illness. It was previously misdiagnosed as pneumonia, bronchitis, or congestive heart failure until reports by Hultgren and colleagues[77] and Houston,[111] revealed it to be a distinct form of noncardiogenic pulmonary edema.

Clinical Presentation. HAPE typically occurs within 2 to 4 days of ascent to altitudes above 2400 m (8000 feet), most commonly beginning on the second night. In the early stages of the disease, individuals develop worsening exercise performance and require increasing amounts of time to recover from exertion. Individuals also complain of fatigue, weakness, and a persistent dry cough; symptoms of AMS may also be present. As the disease worsens, individuals become short of breath with minimal exertion. Dyspnea at rest, audible chest congestion, and production of pink frothy sputum are late findings in severe disease. Even in the absence of concurrent HACE, severe hypoxemia may produce mental changes, ataxia, and altered levels of consciousness.

On physical examination, the patient often appears better than one would expect based on blood gases and radiographic findings. Vital sign abnormalities may include low-grade temperatures to 38.5° C, as well as

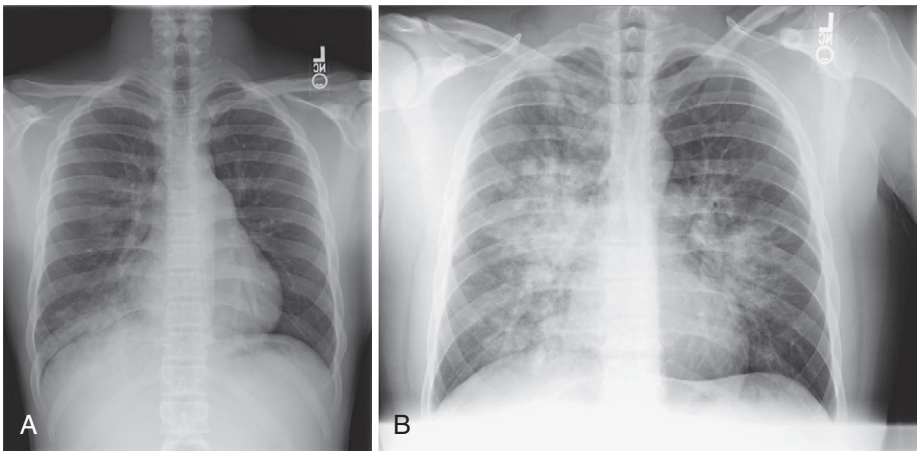

FIGURE 70-8 ■ **A,** Typical roentgenograph of high-altitude pulmonary edema in a 15-year-old boy. Note that the edema is unilateral, right sided, and predominantly in the right middle lobe. **B,** Severe high-altitude pulmonary edema in a 27-year-old man. Note the normal heart size and the presence of bilateral opacities in this case. (Both images courtesy of Peter Hackett.)

tachycardia and tachypnea. Crackles are initially heard in the right mid-lung fields and then more diffusely as the disease worsens. Generalized pallor and nail bed cyanosis may also occur. Radiographs and computed tomography scans show patchy, alveolar opacities, which may be limited to one area (the right lung field predominating initially) or generalized, depending on illness severity (Fig. 70-8). Arterial blood gases reveal severe hypoxemia. In a study at 4559 m, for example, individuals with HAPE had a mean Pa_{O_2} of 23 ± 3 mm Hg and an average saturation of 48 ± 8% versus 40 ± 5 mm Hg and 78 ± 7 % for healthy controls.[112] Pulmonary artery pressure is high, but pulmonary wedge pressure is normal and heart size is not increased.[77,113]

Pathologic Findings. A total of 22 autopsies have been reported in persons dying of HAPE.[78,114] A red cell–rich proteinaceous exudate with hyaline membranes is characteristic. All had some areas of pneumonitis with neutrophil accumulation but no evidence of bacterial accumulation. Pulmonary veins were not dilated. Most reports mention capillary and arteriolar thrombi and fibrin deposits, as well as hemorrhage and infarcts.

Bronchoalveolar lavage samples obtained within the first 24 hours of ascent to 4559 m demonstrated increased amounts of red blood cells and protein but an absence of inflammatory mediators and neutrophils,[115] while samples obtained later in the disease process show even more protein, neutrophilia, and evidence of inflammation marked by such inflammatory mediators as leukotriene B_4 thromboxane B_2,[116] and interleukin-1, -6, and -8 and tumor necrosis factor-α.[117]

Possible Mechanisms. HAPE is a form of noncardiogenic pulmonary edema. Left ventricular function and pulmonary capillary wedge pressure remain normal. Although the mechanisms underlying HAPE remain incompletely understood, it appears that elevated pulmonary artery pressures play a central role in the process, as multiple investigations have shown that affected individuals have markedly elevated pulmonary artery pressures when compared to healthy controls.[77,113]

HAPE-susceptible individuals have exaggerated HPV, which likely accounts for the elevated pulmonary artery pressures; multiple studies demonstrate that HAPE-susceptible individuals have abnormally high pulmonary artery pressure responses during hypoxic breathing and normoxic and hypoxic exercise as well as on ascent to high altitude before the onset of edema.[27,118] Lower HVR[119,120] and slightly lower lung volumes[120] may also contribute to increased pulmonary artery pressure by increasing alveolar hypoxia and reducing the number of recruitable vessels. Finally, evidence suggests that increased sympathetic tone[121] and alterations in vasoactive mediator (endothelin, nitric oxide) production by pulmonary endothelial cells[122,123] may also lead to stronger hypoxic pulmonary vasoconstriction.

Given the central importance of elevated pulmonary artery pressures in the pathogenesis of HAPE, the question is how these elevated pressures cause fluid accumulation when patients with severe pulmonary hypertension at sea level do not typically have pulmonary edema. Hultgren[124] has suggested that edema results from uneven hypoxic vasoconstriction, resulting in overperfusion of the microvasculature in areas of the lung where arteriolar vasoconstriction failed to protect downstream vessels. Uneven perfusion is suggested clinically by the typical patchy roentgenographic appearance (see Fig. 70-8) and by MRI studies in persons breathing hypoxic gas mixtures,[125,126] which demonstrate greater heterogeneous regional perfusion in HAPE-susceptible subjects.

The leak in overperfusion edema may be due to *capillary stress failure* in which high shear forces cause biomechanical stress and injury in the precapillary arterioles and capillaries.[127] The mechanism(s) by which high pressures and shear stress lead to a high permeability–type leak may involve a continuum of pressure-related phenomena by which pericellular and transcellular movement of plasma and even red cells occurs into the lung interstitium and subsequently into the alveolar space. At lower levels of pressure elevation,

stretch on collagen and other supporting extracellular matrix elements may induce dynamic and quickly reversible changes in barrier permeability[128] that, with greater duration and further pressure elevation, may lead to capillary rupture and alveolar hemorrhage, as seen in severe cases of HAPE.

Although the data largely establish a hydrostatic basis for HAPE, interest in the role of inflammation was raised when bronchoalveolar lavage studies on patients with HAPE demonstrated increased cellularity and the presence of chemotactic (leukotriene B_4) and vasoactive (thromboxane B_2) mediators compared to controls.[116] Swenson et al.[115] clarified the role of inflammation by performing bronchoalveolar lavage in HAPE-susceptible individuals and normal controls within the first 24 hours of arrival at 4559 m, well earlier than the lavage samples were obtained in the other studies. The lavage fluid demonstrated high protein and red blood cell content, the levels of which correlated with pulmonary artery pressures measured by echocardiography (Fig. 70-9), but no evidence of cytokine expression or neutrophil recruitment in the earliest phase of the disease. These findings solidified the notion that HAPE starts as a result of high intravascular pressure and not due to an inflammatory process.

While inflammation is not the primary factor in most cases, it may still play a role in certain situations. Respiratory viral infections have been shown to predispose to HAPE in children,[129] and anecdotal reports of viral infections preceding HAPE exist for adults. This suggests that viral infections may trigger inflammation, which makes the microvascular endothelium more vulnerable to increased pressures. Indeed, increased interstitial fluid accumulation has been documented during hypoxic exposure after priming by endotoxin or virus in animals.[130] This potential role for upper respiratory tract infections and subsequent inflammation may explain why HAPE has been seen at surprisingly low altitudes (1500 to 2400 m).[131]

Changes in fluid transport dynamics in the lung may also contribute to HAPE. Water and sodium transport by type I and II alveolar epithelial cells is important in normal lung fluid balance, and investigations in cell culture and animal models demonstrate that hypoxia decreases alveolar transepithelial sodium transport[132] and alveolar fluid clearance.[133] Subsequent studies in humans have examined transepithelial potential differences across the nasal mucosa as a model of alveolar epithelial function and demonstrate lower transepithelial nasal potentials in normoxia in HAPE-susceptible individuals versus nonsusceptible controls.[134] The reduced nasal potential difference was attributed to decreased sodium transport by the epithelial sodium channel. A more recent study confirmed the difference in nasal potential between HAPE-susceptible individuals and controls in normoxia, but it could not attribute these differences to alterations in epithelial sodium channel activity.[135] Transalveolar sodium transport can be increased by β_2-receptor stimulation, and a field study has reported successful prevention of HAPE with inhalation of salmeterol, a long-acting β_2-agonist.[134] However, given the multiple actions of this drug, including increased ventilatory response to hypoxia and tightening of cell-to-cell contacts, the contribution of enhanced alveolar fluid clearance to the study's positive outcome remains uncertain.[136]

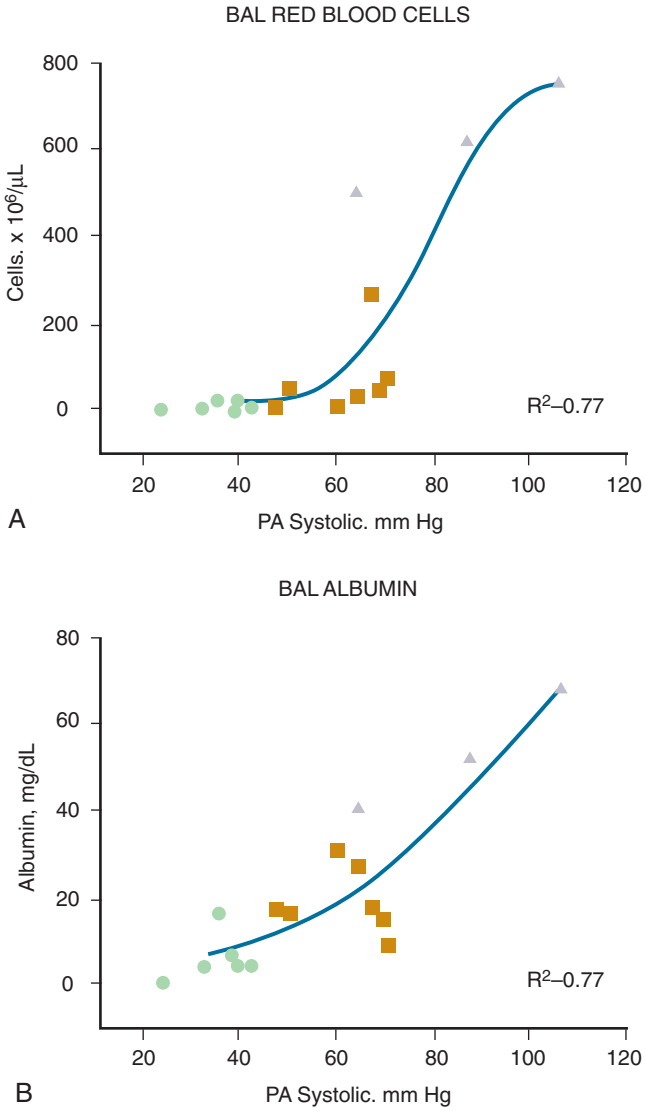

FIGURE 70-9 ■ The relationship between pulmonary artery pressure measured by echocardiography and the amount of red blood cells and albumin in bronchoalveolar lavage (BAL) fluid of normal and HAPE-susceptible (*triangles*) individuals at sea level and 4559 m. The *circles* in the lower left of both panels show values for red blood cells and albumin in normal subjects at low altitude (490 m) and the *squares* show values in the same subjects at altitude (4559 m). Correlation coefficients are provided for the best-fit curves of the data at high altitude. (From Swenson ER, Maggiorini M, Mongovin S, et al: Pathogenesis of high-altitude pulmonary edema: Inflammation is not an etiologic factor. JAMA 287:2228–2235, 2002.)

Allemann et al.[137] documented an increased incidence of patent foramen ovale (PFO) in HAPE-susceptible individuals at low and high altitude compared to healthy controls and argued that its presence may increase the risk of HAPE. It is not clear, however, whether the PFO actually causes HAPE or is a sequela of prior marked

rises in pulmonary artery pressure during sojourns to high altitude or during normoxic exercise, a feature of pulmonary vascular responses seen in HAPE-susceptible individuals.[138] Shunting through a PFO might act to lower pulmonary artery pressure by reducing total pulmonary blood flow, but the consequent greater arterial hypoxemia might increase pulmonary vascular resistance because the vasovasorum of the pulmonary arteries is fed by the bronchial arteries, and isolated bronchial arterial hypoxemia has been shown to increase HPV.[139]

Finally, it has been proposed that HAPE is a form of neurogenic pulmonary edema, as the presence of red blood cells, the spectrum of serum proteins in HAPE lavage fluid, and the absence of architectural damage are all features seen in this other form of noncardiogenic pulmonary edema.[140] Sympathetically mediated pulmonary venous constriction is thought to play a large role in neurogenic pulmonary edema,[141] while, as noted earlier, increased sympathetic activity may play a role in HAPE[121] and α-adrenergic blockade has been shown to decrease pulmonary artery pressure in HAPE.[142] What is lacking in HAPE, however, is the severe neurologic injury typically seen in neurogenic pulmonary edema. Although some HAPE patients have concurrent AMS or HACE, this is usually far less severe injury than the profound central nervous system alterations (e.g., subarachnoid hemorrhage) in most cases of neurogenic pulmonary edema. HAPE and neurogenic pulmonary edema are likely distinct processes that share features of a common final pathway to edema formation.

Prevention. The nonpharmacologic preventive measures previously described for AMS also apply to HAPE, with slow ascent being the most important strategy. Because unrecognizable subclinical pulmonary edema might be converted to clinical edema by exercise, avoidance of overexertion, especially when fatigued, may help prevent HAPE. Nifedipine has been shown to be effective in preventing HAPE in subjects with a past history of the illness.[143] Because the incidence of HAPE is low, prophylactic nifedipine should be reserved for known susceptible individuals. A single study established that high-dose inhaled salmeterol may be considered for prophylaxis,[134] although very high doses (2.5 times those used in asthma management) were used in the study and may be associated with side effects that affect patient tolerance. Salmeterol should not be used as monotherapy for prevention of HAPE and should only be considered as an add-on to other agents. More recently, the phosphodiesterase inhibitor tadalafil as well as dexamethasone, have also been shown to prevent disease in known susceptible individuals.[144] None of these medications, however, has been compared with nifedipine in head-to-head studies. Recommended doses for these medications are provided in Table 70-2.

Treatment. Proper treatment depends on the severity of the illness and the immediate setting. For patients developing HAPE in remote locations with limited access to care, the first priority is descent to lower elevation. The patient's level of exertion should be limited during descent as exertion may increase pulmonary artery pressure and worsen the pulmonary edema. If HAPE is diagnosed early, recovery is rapid with descents of only 500 to 1000 m, and the victim may be able to reascend cautiously 2 or 3 days later. If descent is infeasible due to weather or other factors, supplemental oxygen or a portable hyperbaric chamber should be an urgent priority.[145] If neither option is available, positive-pressure mask ventilation may improve oxygenation, although the effect on outcomes has not been established.[146] Keeping the patient warm may also be important, because cold stress elevates pulmonary artery pressure.[147]

Given the reduced margin for error in remote settings, the use of a pulmonary vasodilator such as nifedipine is warranted regardless of whether supplemental oxygen is available. The data supporting this practice are limited, however, and the recommendation is based largely on extensive clinical experience. A single study[148] demonstrated that nifedipine can be used to manage HAPE in the absence of descent or supplemental oxygen, but this study included a small number of patients and lacked a control group. Other pulmonary vasodilators such as tadalafil and sildenafil have not been studied for HAPE treatment, but reports in the literature indicate clinicians are using them for this purpose, often in conjunction with calcium channel blocker therapy.[149] Given the absence of data supporting benefit and the risk of provoking systemic hypotension, concurrent use of two pulmonary vasodilators should be avoided.

With access to hospitals or clinics, treatment with bed rest and oxygen may be sufficient and evacuation to lower elevations may be unnecessary. In well-selected patients with mild disease and adequate support (family, friends) to monitor their clinical course, it may even be feasible to send them home or to their hotel with supplemental oxygen rather than admitting them to the hospital.[150] Complete resolution of the edema may require 24 to 72 hours of oxygen therapy if treated near the altitude of onset, whereas removing the patient to a lower altitude results in more rapid improvement. Pulmonary vasodilators can be added in patients who worsen or fail to improve with conservative measures. There are no data regarding whether nifedipine is superior to phosphodiesterase inhibitors for this purpose, although there is more clinical experience with the less expensive nifedipine. A single case series documented the use of continuous positive airway pressure (CPAP) to relieve dyspnea in patients with HAPE,[131] but there are no controlled data to suggest this improves outcomes. Because fevers as high as 38.5°C have been described in HAPE, a finding of elevated temperature should not prompt administration of antibiotics unless the clinical picture is consistent with pneumonia. Patients who do not improve on an appropriate regimen should undergo investigations to identify other causes of hypoxemia and lung infiltrates.

Problems of High-Altitude Residents

Chronic Mountain Sickness

First described in Andean dwellers by Monge[151] in 1928 and often referred to as Monge's disease, chronic moun-

tain sickness (CMS) is the more commonly described form of chronic altitude illness. It occurs in persons born and living at high altitude as well as in lowlanders who move to high altitudes and stay for prolonged periods of time (>1 year). Excessive erythrocytosis, defined as a hematocrit above 60% to 70% or more than 2 standard deviations above the average value for healthy residents at a given high altitude, is an essential characteristic of the syndrome.

There are geographic and ethnic differences in the prevalence of CMS. It is rarely found in natives of the Tibetan plateau but is frequently encountered in the Andes, in the North American Rockies, and in other mountainous regions where lowlanders have moved, such as with Han Chinese who have been relocated to Tibet.[152,153] The reason for these regional differences is only speculative, but it is thought possibly to be secondary to more advantageous adaptations that the Tibetans have undergone because of the much greater duration of their existence on the Tibetan plateau compared with that of the Andeans. Especially relevant may be that Tibetans have much less HPV and lower hematocrits, as compared with other high-altitude populations. These may potentially be markers of more successful adaptation over a much longer period of time.

Clinical Presentation. Symptoms of CMS are similar to those found in persons suffering polycythemia at low altitude: headache, dizziness, lethargy, impaired memory and mentation, and poor sleep. Subsequent investigations reveal cyanosis, plethoric appearance, and elevated hematocrit and hemoglobin. The diagnosis can only be established by eliminating all other causes of polycythemia. Indeed, much confusion in the literature regarding incidence and other aspects of CMS may be due to inadequate validation of the diagnosis. Monge,[151] for example, noted a high frequency of bronchial complications in patients with CMS, whereas Kryger et al.[153] found evidence of lung disease in 50% of those with CMS in Leadville, Colorado. Indeed, when viewed as a syndrome, it is possible that many cases represent an interaction between some underlying chronic lung disease, high altitude, and, perhaps, heavy metal toxicity.[33]

Pathophysiology. Blunted HVR and relative hypoventilation are the likely initiating factors in CMS. Hypoventilation causes greater alveolar hypoxia and arterial hypoxemia, which, in turn, triggers more HPV and greater pulmonary hypertension, while the low arterial P_{O_2} leads to increased erythropoietin secretion and more red blood cell production.[153-155] At the same time, polycythemia may blunt ventilatory responses,[156,157] so cause and effect are not clear. Hypoxia itself may also contribute to the ventilatory depression, as evidenced by an increase in ventilation in some natives with CMS when given supplemental oxygen.

While the excessive polycythemia of CMS is likely due to greater hypoxemia, the actual hematocrit is often higher than expected for the measured Sa_{O_2},[158] suggesting that affected individuals may have exaggerated hematopoietic responses to a given hypoxic stimulus.[154] Severe nocturnal desaturation may also contribute to the development of polycythemia, as investigations in the Rocky Mountains revealed greater hypoxemia during sleep in patients with CMS compared to healthy controls.[159]

More recently, Jefferson et al.[33] found that a majority of subjects with CMS and excessive erythrocytosis in an Andean mining community had detectable serum concentrations of cobalt, a heavy metal known to independently stimulate renal erythropoietin production. This may help explain the higher incidence of CMS in high-altitude regions where mining is common.

Treatment. The key to treating CMS is to decrease the red cell mass. Improving oxygenation and thereby reducing the hypoxic stimulus for red blood cell production is the most physiologic approach to achieving this goal. Although relocation to a lower altitude is the definitive treatment for CMS, this approach is not feasible for many patients and other treatments are often employed. Phlebotomy has long been used, but despite the common practice and prompt subjective improvement, long-term benefits have not been well documented. Low-flow oxygen during sleep is probably effective, especially for those with marked sleep desaturation. By virtue of their ability to increase alveolar P_{O_2}, respiratory stimulants, including medroxyprogesterone[160] and acetazolamide,[161] are effective in decreasing hematocrit and treating CMS. Daily use of angiotensin-converting enzyme inhibitors can suppress erythropoietin secretion and decrease the need for phlebotomy.[162]

High-Altitude Pulmonary Hypertension

An alternative form of altitude-related disease in long-term residents has now been described in areas outside the Andes Mountains. Referred to as high-altitude pulmonary hypertension, it is marked by pulmonary hypertension and cor pulmonale without polycythemia. A recent consensus panel[163] defined the disease to be present if a resident at altitudes above 2500 m has a mean pulmonary artery pressure greater than 30 mm Hg or a systolic pulmonary artery pressure greater than 50 mm Hg, right ventricular hypertrophy, right heart failure, and moderate hypoxemia and lacks excessive erythrocytosis (hemoglobin < 21 g/dL in men and <19 g/dL in women). There is considerable overlap between this disease and subacute mountain sickness, a syndrome of pulmonary hypertension and right heart failure seen in lowlanders after weeks to months at high altitude,[164] with the major difference being the time spent at high altitude by the affected individual. There is also some debate as to whether this truly represents a separate entity from CMS or is simply a variant of the same disease.[155]

Affected individuals present with dyspnea, cough, cyanosis, peripheral edema, and physical examination findings consistent with right heart failure. Right-axis deviation, right ventricular hypertrophy, and P-pulmonale may be present on the electrocardiogram, while chest imaging reveals right ventricular and right atrial enlargement and prominence of the pulmonary arteries.[163] The pulmonary hemodynamics are similar to those seen in patients with CMS.[155] The optimal treatment for the disorder is relocation to lower elevation, but, as in CMS, descent may not be feasible and pharmacologic

options may be necessary. Unfortunately, aside from a small placebo-controlled trial that demonstrated that a 3-month course of the phosphodiesterase inhibitor sildenafil lowered pulmonary artery pressure by a modest amount (~6 to 7 mm Hg) and improved 6-minute walk distance,[165] larger studies of this and other pulmonary vasodilators are lacking and no formal treatment protocols exist at this time.

Reentry Pulmonary Edema

Some persons living for years at high altitude, who then descend to lower altitudes, develop HAPE on reascent. The phenomenon has been most often observed in Peru, where high-altitude residents can return from sea level to high altitude quite rapidly. Cases have also been reported in Leadville, Colorado, but reports are conspicuously absent from Nepal and Tibet, possibly because rapid return to high altitude is often less readily available. Authors have suggested that the incidence of HAPE on reascent may be higher than during initial ascent by sojourners,[166] but data on true incidence are lacking; children and adolescents may be more susceptible than adults.[166] It has been postulated that the increased muscularization of pulmonary arterioles that develops with chronic high-altitude exposure generates an inordinately high pulmonary artery pressure on reascent, causing the edema. Aside from a study by Marticorena and Hultgren[167] that demonstrated that treatment with bed rest alone may be sufficient in mild to moderate cases, no treatment trials have been conducted for reentry HAPE, and the disorder should be managed the same as HAPE in unacclimatized lowlanders.

PREEXISTING ILLNESS AND HIGH ALTITUDE

Given the prevalence of many common diseases, such as hypertension and chronic obstructive pulmonary disease (COPD), in the general population, it is likely that many high-altitude travelers have some underlying medical condition. This situation raises two important questions: (1) will the underlying disease predispose these individuals to high-altitude illness; and (2) will the added stress of hypoxia at high altitude worsen control of their underlying problems? To date, few studies have examined what happens to people with respiratory and other diseases when they visit high-altitude destinations, and even fewer data are available about how to treat them before and after their exposure. Several major categories of respiratory diseases are discussed in this section, while other major disease categories, including heart disease,[168] renal disease,[169] and diabetes,[170] are reviewed elsewhere.

Respiratory Diseases

High-altitude exposure poses several challenges to patients with lung disease that have been reviewed extensively elsewhere.[171] Several major forms of lung disease are considered here in brief.

COPD and Interstitial Lung Disease

A drop in barometric pressure and subsequent fall in inspired P_{O_2} place patients with severe COPD and interstitial lung disease at risk for arterial desaturation, particularly with exertion. During the pretravel evaluation, patients with moderate to severe COPD[172] and interstitial lung disease[173] should be tested to determine their predicted arterial P_{O_2} at high altitude. Those patients in whom the predicted value falls below 50 mm Hg, the same threshold used for determining supplemental oxygen needs on commercial air flight, should be provided a prescription for home oxygen, which they can arrange to fill at their destination (e.g., a ski resort town). An alternative strategy in patients with less severe disease would be to have them monitor their own pulse oximetry using a portable handheld device and fill a prewritten home oxygen prescription if their saturation falls below thresholds stipulated by their physician. COPD patients should travel with their controller medications and a supply of rescue medications in the event of an exacerbation. The sleeping elevation should be restricted to elevations below 3000 m because no studies have examined COPD or interstitial lung disease patients above this altitude.

Asthma

Changes in air temperature, humidity, and density may alter lung mechanics and airflow obstruction in patients with asthma, but field data demonstrate that mild, well-controlled asthmatic patients have decreased bronchial responsiveness at elevations as high as 5000 m and should tolerate travel up to these elevations.[171,174] Patients must have their asthma under good control prior to any trip to high altitude and should travel with both their controller medications and an adequate supply of rescue inhalers and prednisone for use in the event of an exacerbation.

Pulmonary Vascular Disease

Low alveolar oxygen tensions provoke HPV and increase pulmonary artery pressure. This response may provoke either acute right heart failure or HAPE in patients with primary or secondary pulmonary hypertension. No systematic studies have examined this issue, but several case reports and case series document the occurrence of HAPE in patients with pulmonary hypertension secondary to anatomic or nonanatomic causes.[171] Patients with known or suspected pulmonary hypertension should undergo echocardiography to measure pulmonary artery pressures. Travel to high altitude should be avoided in patients with moderate to severe disease, although the threshold used to proscribe travel is not clear. The available evidence suggests that mean pressures of about 40 mm Hg are sufficient to trigger HAPE, but a wide range of pressures have been documented in

case reports of this phenomenon at high altitude.[171] Patients with less severe disease should use nifedipine and should be encouraged to monitor their pulse oximetry either by using a handheld device or by periodically visiting a local clinic. Patients with congenital absence of a pulmonary artery should also avoid high-altitude travel, as these individuals are known to be susceptible to HAPE.[175]

Sleep Apnea

The limited available data suggest that the number of obstructive apneas is markedly decreased at high altitude. In a study of normal individuals with low baseline apnea-hypopnea indices, the obstructive sleep apnea (OSA) index fell from 5.5 ± 6.9 to 0.1 ± 0.3 events/hr at 5050 m,[176] while in a study of adult men with moderate OSA at baseline, the obstructive respiratory disturbance index fell from 25.5 ± 14.4 to 0.5 ± 0.5 events/hr at 2750 m.[177] The mechanism behind the decreased number of obstructive events is unclear but may relate to changes in air density, increased respiratory drives, and increased upper airway tone.[177]

In both studies, however, the decrease in obstructive events was offset by an increase in the incidence of central apneas. Whether these central events have the same impact as obstructive events on sleep quality and subsequent daytime performance is not known. Furthermore, to the extent that obstructive events persist at high altitude, one would expect greater arterial desaturation than at sea level. As a result, it would be prudent for people with severe OSA to travel to high altitude with their CPAP machine, provided reliable access to power sources can be arranged. Patients should be aware that machines lacking pressure-compensating features may not deliver the set pressure at high altitude, and higher pressures may be needed for adequate relief of symptoms. Recommendations for adjusting the set pressure have been made elsewhere.[178] Acetazolamide may also be considered for the purpose of decreasing the incidence of central apneas.

Thromboembolic Disease

Many case reports document arterial or venous thromboembolic events at high altitude, but a careful review of the cases reveals that most events occurred in people with underlying coagulopathy.[171] These findings fit with a recent study in which the most marked rises in thrombin-antithrombin complexes during hypobaric hypoxic exposure were seen in those with the factor V Leiden mutation or oral contraceptive use.[39] In the absence of clear data regarding thromboembolism risk at high altitude, people should simply continue their sea-level regimen upon travel to high altitude. There is no indication to start anticoagulation in those not previously on such medication. Efforts should be made to maintain mobility and good hydration throughout the trip. The international normalized ratio (INR) may change with trips to and from altitude,[179] and patients on warfarin should consider obtaining follow-up INR values upon returning from a long sojourn or periodically during prolonged stays at a new altitude.

Altitude-Illness Medications and Underlying Medical Diseases

As noted earlier, acetazolamide, dexamethasone, nifedipine, and the phosphodiesterase inhibitors play a large role in the prevention and treatment of high-altitude illness. The efficacy and safety of these medications in preventing and treating altitude illness has largely been established on the basis of studies in healthy individuals with no underlying medical disease. However, given the increasing numbers of people traveling to high altitude, it is possible that many of those using these medications for management of altitude illness will have underlying medical problems or will be using other medications that cause adverse drug interactions. Practical guidelines for the selection and dosing of the altitude illness medications in such patient populations have been reviewed elsewhere[180] and are summarized in Table 70-2.

KEY POINTS

- Important adaptive responses occur at every step of the oxygen transport chain that maintains oxygen delivery in the setting of lower ambient oxygen levels, but the magnitude of these changes varies among individuals and affects individual tolerance of this environment.
- Various aspects of sleep, including respiratory patterns, sleep architecture, and subjective impressions of sleep quality, are altered and contribute to poor sleep at high altitude. The number of obstructive apneas decreases at altitude, but this change is matched by an increase in the number of central events.
- Maximum exercise capacity is reduced at high altitude and does not recover to sea-level baseline values even with prolonged time and acclimatization at high altitude.
- An overly rapid ascent to too high an elevation is the primary reason people develop acute altitude illness, while undertaking a gradual ascent is the best nonpharmacologic means for preventing high-altitude illness.

KEY POINTS—CONT'D

- Acute mountain sickness is the most common form of acute altitude illness and is marked by the onset of headache plus one or more other symptoms, including light-headedness, gastrointestinal upset, fatigue, and poor sleep several hours following ascent to high altitude.
- High-altitude cerebral edema is an uncommon but potentially fatal form of altitude illness that is marked by the presence of ataxia and/or signs of global encephalopathy in patients with preceding symptoms of acute mountain sickness.
- High-altitude pulmonary edema is a noncardiogenic pulmonary edema that occurs primarily as a result of excessive rises in pulmonary artery pressure following acute ascent to high altitude.
- Long-term high-altitude residents are generally not susceptible to acute forms of high-altitude illness but are at risk for two forms of chronic altitude illness (chronic mountain sickness and high-altitude pulmonary hypertension) for which the optimal form of treatment is relocation to lower elevation.
- High-altitude travelers with underlying medical problems should be evaluated prior to their sojourn to determine whether their underlying problem may be adversely affected by high altitude or may increase the risk of acute altitude illness.
- The choice of medications for the prevention and treatment of high-altitude illness may need to be altered in patients with underlying medical problems or who are taking certain medications.

References

1. Hornbein TF, Schoene RB: High Altitude: An Exploration of Human Adaptation (Lung Biology in Health and Disease, Vol 161). New York: Marcel Dekker, 2001.
2. West JB, Schoene RB, Milledge JS: High Altitude Medicine and Physiology (4th ed). London: Hodder Arnold, 2007.
3. West JB: Highlife: A History of High Altitude Physiology and Medicine. Oxford, UK: Oxford University Press, 1998.
4. Smith CA, Dempsey JA, Hornbein TF: Control of breathing at high altitude. *In* Hornbein TF, Schoene RB (eds): High Altitude: An Exploration of Human Adaptation (Lung Biology in Health and Disease, Vol 161). New York: Marcel Dekker, 2001, pp 139–174.
5. Roeggla G, Roeggla M, Wagner A, Laggner AN: Poor ventilatory response to mild hypoxia may inhibit acclimatization at moderate altitude in elderly patients after carotid surgery. Br J Sports Med 29:110–112, 1995.
6. Daristotle L, Berssenbrugge AD, Engwall MJ, Bisgard GE: The effects of carotid body hypocapnia on ventilation in goats. Respir Physiol 79:123–135, 1990.
7. West JB: Rate of ventilatory acclimatization to extreme altitude. Respir Physiol 74:323–333, 1988.
8. Dempsey JA, Forster HV, Bisgard GE, et al: Role of cerebrospinal fluid [H^+] in ventilatory deacclimatization from chronic hypoxia. J Clin Invest 64:199–205, 1979.
9. Goldberg SV, Schoene RB, Haynor D, et al: Brain tissue pH and ventilatory acclimatization to high altitude. J Appl Physiol 72:58–63, 1992.
10. Soliz J, Gassmann M, Joseph V: Soluble erythropoietin receptor is present in the mouse brain and is required for the ventilatory acclimatization to hypoxia. J Physiol (Lond) 583:329–336, 2007.
11. Schoene RB, Roach RC, Hackett PH, et al: Operation Everest II: Ventilatory adaptation during gradual decompression to extreme altitude. Med Sci Sports Exerc 22:804–810, 1990.
12. Neubauer JA: Invited review: Physiological and pathophysiological responses to intermittent hypoxia. J Appl Physiol 90:1593–1599, 2001.
13. Ren X, Dorrington KL, Robbins PA: Respiratory control in humans after 8 h of lowered arterial PO_2, hemodilution, or carboxyhemoglobinemia. J Appl Physiol 90:1189–1195, 2001.
14. Katayama K, Sato Y, Morotome Y, et al: Intermittent hypoxia increases ventilation and Sao_2 during hypoxic exercise and hypoxic chemosensitivity. J Appl Physiol 90:1431–1440, 2001.
15. Lahiri S, DeLaney RG, Brody JS, et al: Relative role of environmental and genetic factors in respiratory adaptation to high altitude. Nature 261:133–135, 1976.
16. Jaeger JJ, Sylvester JT, Cymerman A, et al: Evidence for increased intrathoracic fluid volume in man at high altitude. J Appl Physiol 47:670–676, 1979.
17. Welsh CH, Wagner PD, Reeves JT, et al: Operation Everest II: Spirometric and radiographic changes in acclimatized humans at simulated high altitudes. Am Rev Respir Dis 147:1239–1244, 1993.
18. Deboeck G, Moraine JJ, Naeije R: Respiratory muscle strength may explain hypoxia-induced decrease in vital capacity. Med Sci Sports Exerc 37:754–758, 2005.
19. Mansell A, Powles A, Sutton J: Changes in pulmonary PV characteristics of human subjects at an altitude of 5,366 m. J Appl Physiol 49:79–83, 1980.
20. Brody JS, Lahiri S, Simpser M, et al: Lung elasticity and airway dynamics in Peruvian natives to high altitude. J Appl Physiol 42:245–251, 1977.
21. Frisancho AR: Functional adaptation to high altitude hypoxia. Science 187:313–319, 1975.
22. West JB, Wagner PD: Predicted gas exchange on the summit of Mt. Everest. Respir Physiol 42:1–16, 1980.
23. Dempsey JA, Reddan WG, Birnbaum ML, et al: Effects of acute through life-long hypoxic exposure on exercise pulmonary gas exchange. Respir Physiol 13:62–89, 1971.
24. Schoene RB, Roach RC, Lahiri S, et al: Increased diffusion capacity maintains arterial saturations during exercise in Quechua Indians of the Chilean Altiplano. Am J Hum Biol 2:663–668, 1990.
25. Reeves JT, Groves BM, Sutton JR, et al: Operation Everest II: Preservation of cardiac function at extreme altitude. J Appl Physiol 63:531–539, 1987.
26. Wolfel EE, Selland MA, Mazzeo RS, Reeves JT: Systemic hypertension at 4,300 m is related to sympathoadrenal activity. J Appl Physiol 76:1643–1650, 1994.
27. Grunig E, Mereles D, Hildebrandt W, et al: Stress Doppler echocardiography for identification of susceptibility to high altitude pulmonary edema. J Am Coll Cardiol 35:980–987, 2000.

27a. Smith TG, Talbot NP, Priva C, et al: Effects of iron supplementation and depletion on hypoxic pulmonary hypertension: two randomized controlled trials. JAMA 302:1444–1450, 2009.
28. Groves BM, Reeves JT, Sutton JR, et al: Operation Everest II: Elevated high-altitude pulmonary resistance unresponsive to oxygen. J Appl Physiol 63:521–530, 1987.
29. Knaupp W, Khilnani S, Sherwood J, et al: Erythropoietin response to acute normobaric hypoxia in humans. J Appl Physiol 73:837–840, 1992.
30. Ge RL, Witkowski S, Zhang Y, et al: Determinants of erythropoietin release in response to short-term hypobaric hypoxia. J Appl Physiol 92:2361–2367, 2002.
31. Schmidt W, Spielvogel H, Eckardt KU, et al: Effects of chronic hypoxia and exercise on plasma erythropoietin in high-altitude residents. J Appl Physiol 74:1874–1878, 1993.
32. Beall CM, Decker MJ, Brittenham GM, et al: An Ethiopian pattern of human adaptation to high-altitude hypoxia. Proc Natl Acad Sci U S A 99:17215–17218, 2002.
33. Jefferson JA, Escudero E, Hurtado ME, et al: Excessive erythrocytosis, chronic mountain sickness, and serum cobalt levels. Lancet 359:407–408, 2002.
34. Hochachka PW, Rupert JL: Fine tuning the HIF-1 'global' O_2 sensor for hypobaric hypoxia in Andean high-altitude natives. Bioessays 25:515–519, 2003.
35. Doughty HA, Beardmore C: Bleeding time at altitude. J R Soc Med 87:317–319, 1994.
36. Bartsch P, Haeberli A, Hauser K, et al: Fibrinogenolysis in the absence of fibrin formation in severe hypobaric hypoxia. Aviat Space Environ Med 59:428–432, 1988.
37. Singh I, Chohan IS, Mathew NT: Fibrinolytic activity in high altitude pulmonary oedema. Indian J Med Res 57:210–217, 1969.
38. Bartsch P, Straub PW, Haeberli A: Hypobaric hypoxia. Lancet 357:955–956, 2001.
39. Schreijer AJ, Cannegieter SC, Meijers JC, et al: Activation of coagulation system during air travel: A crossover study. Lancet 367:832–838, 2006.
40. Schmidt M, Gerlach F, Avivi A, et al: Cytoglobin is a respiratory protein in connective tissue and neurons, which is up-regulated by hypoxia. J Biol Chem 279:8063–8069, 2004.
41. Severinghaus JW, Chiodi H, Eger EI 2nd, et al: Cerebral blood flow in man at high altitude: Role of cerebrospinal fluid pH in normalization of flow in chronic hypocapnia. Circ Res 19:274–282, 1966.
42. Dyer EA, Hopkins SR, Perthen JE, et al: Regional cerebral blood flow during acute hypoxia in individuals susceptible to acute mountain sickness. Respir Physiol Neurobiol 160:267–276, 2008.
43. Steinback CD, Poulin MJ: Cardiovascular and cerebrovascular responses to acute isocapnic and poikilocapnic hypoxia in humans. J Appl Physiol 104:482–489, 2008.
44. Regard M, Oelz O, Brugger P, Landis T: Persistent cognitive impairment in climbers after repeated exposure to extreme altitude. Neurology 39:210–213, 1989.
45. Hornbein TF, Townes BD, Schoene RB, et al: The cost to the central nervous system of climbing to extremely high altitude. N Engl J Med 321:1714–1719, 1989.
46. Fayed N, Modrego PJ, Morales H: Evidence of brain damage after high-altitude climbing by means of magnetic resonance imaging. Am J Med 119:e161–e166, 2006.
47. Sharma VM, Malhotra MS: Ethnic variations in psychological performance under altitude stress. Aviat Space Environ Med 47:248–251, 1976.
48. Greenberg DA, Jin K, Khan AA: Neuroglobin: An endogenous neuroprotectant. Curr Opin Pharmacol 8:20–24, 2008.
49. Swenson ER: Renal function and fluid homeostasis. *In* Hornbein TF, Schoene RB (eds): High Altitude: An Exploration of Human Adaptation (Lung Biology in Health and Disease, Vol 161). New York: Marcel Dekker, 2001, pp 525–568.
50. Loeppky JA, Roach RC, Selland MA, et al: Body fluid alterations during head-down bed rest in men at moderate altitude. Aviat Space Environ Med 64:265–274, 1993.
51. Ellsworth AJ, Larson EB, Strickland D: A randomized trial of dexamethasone and acetazolamide for acute mountain sickness prophylaxis. Am J Med 83:1024–1030, 1987.
52. Weil JV: Sleep at high altitude. High Alt Med Biol 5:180–189, 2004.
53. Lahiri S, Maret KH, Sherpa MG, Peters RM: Sleep and periodic breathing at high altitude: Sherpa natives versus sojourners. *In* West JB, Lahiri S (eds): High Altitude and Man. Bethesda, MD: American Physiological Society, 1984, pp 73–90.
54. Nickol AH, Leverment J, Richards P, et al: Temazepam at high altitude reduces periodic breathing without impairing next-day performance: A randomized cross-over double-blind study. J Sleep Res 15:445–454, 2006.
55. Hackett PH, Roach RC, Harrison GL, et al: Respiratory stimulants and sleep periodic breathing at altitude: Almitrine versus acetazolamide. Am Rev Respir Dis 135:896–898, 1987.
56. Forwand SA, Landowne M, Follansbee JN, Hansen JE: Effect of acetazolamide on acute mountain sickness. N Engl J Med 279:839–845, 1968.
57. Beaumont M, Batejat D, Pierard C, et al: Zaleplon and zolpidem objectively alleviate sleep disturbances in mountaineers at a 3,613 meter altitude. Sleep 30:1527–1533, 2007.
58. West JB, Boyer SJ, Graber DJ, et al: Maximal exercise at extreme altitudes on Mount Everest. J Appl Physiol 55:688–698, 1983.
59. Sutton JR, Reeves JT, Wagner PD, et al: Operation Everest II: Oxygen transport during exercise at extreme simulated altitude. J Appl Physiol 64:1309–1321, 1988.
60. Schoene RB, Lahiri S, Hackett PH, et al: Relationship of hypoxic ventilatory response to exercise performance on Mount Everest. J Appl Physiol 56:1478–1483, 1984.
61. Gale GE, Torre-Bueno JR, Moon RE, et al: Ventilation-perfusion inequality in normal humans during exercise at sea level and simulated altitude. J Appl Physiol 58:978–988, 1985.
62. Ghofrani HA, Reichenberger F, Kohstall MG, et al: Sildenafil increased exercise capacity during hypoxia at low altitudes and at Mount Everest base camp: A randomized, double-blind, placebo-controlled crossover trial. Ann Intern Med 141:169–177, 2004.
63. Faoro V, Lamotte M, Deboeck G, et al: Effects of sildenafil on exercise capacity in hypoxic normal subjects. High Alt Med Biol 8:155–163, 2007.
63a. Fischler M, Maggiorini M, Dorschner L, et al: Dexamethasone but not tadalafil improves exercise capacity in adults prone to high-altitude pulmonary edema. Am J Respir Crit Care Med 180:346–352, 2009.
64. Beidleman BA, Muza SR, Fulco CS, et al: Intermittent altitude exposures improve muscular performance at 4,300 m. J Appl Physiol 95:1824–1832, 2003.
65. Levine BD, Stray-Gundersen J: "Living high-training low": Effect of moderate-altitude acclimatization with low-altitude training on performance. J Appl Physiol 83:102–112, 1997.
66. Chapman RF, Stray-Gundersen J, Levine BD: Individual variation in response to altitude training. J Appl Physiol 85:1448–1456, 1998.
67. Levine BD, Stray-Gundersen J: Dose-response of altitude training: How much altitude is enough? Adv Exp Med Biol 588:233–247, 2006.
68. Hackett PH, Rennie D: The incidence, importance, and prophylaxis of acute mountain sickness. Lancet 2:1149–1155, 1976.
69. Honigman B, Theis MK, Koziol-McLain J, et al: Acute mountain sickness in a general tourist population at moderate altitudes. Ann Intern Med 118:587–592, 1993.
70. Ri-Li G, Chase PJ, Witkowski S, et al: Obesity: Associations with acute mountain sickness. Ann Intern Med 139:253–257, 2003.
71. Schneider M, Bernasch D, Weymann J, et al: Acute mountain sickness: Influence of susceptibility, preexposure, and ascent rate. Med Sci Sports Exerc 34:1886–1891, 2002.
72. Muza SR, Rock PB, Zupan MF, et al: Residence at moderate altitude improves ventilatory response to high altitude. Aviat Space Environ Med 75:1042–1048, 2004.
73. Milledge JS, Beeley JM, Broome J, et al: Acute mountain sickness susceptibility, fitness and hypoxic ventilatory response. Eur Respir J 4:1000–1003, 1991.
74. Moore LG, Harrison GL, McCullough RE, et al: Low acute hypoxic ventilatory response and hypoxic depression in acute altitude sickness. J Appl Physiol 60:1407–1412, 1986.

75. Roach RC, Greene ER, Schoene RB, Hackett PH: Arterial oxygen saturation for prediction of acute mountain sickness. Aviat Space Environ Med 69:1182–1185, 1998.
76. Dehnert C, Weymann J, Montgomery HE, et al: No association between high-altitude tolerance and the ACE I/D gene polymorphism. Med Sci Sports Exerc 34:1928–1933, 2002.
76a. Kalson NS, Thompson J, Davies AJ, et al: The effect of angiotensin-converting enzyme genotype on acute mountain sickness and summit success in trekkers attempting the summit of Mt. Kilimanjaro (5895 m). Eur J Appl Physiol 105:373–379, 2009.
77. Hultgren HN, Lopez CE, Lundberg E, Miller H: Physiologic studies of pulmonary edema at high altitude. Circulation 29:393–408, 1964.
78. Singh I, Khanna PK, Srivastava MC, et al: Acute mountain sickness. N Engl J Med 280:175–184, 1969.
79. Montgomery AB, Mills J, Luce JM: Incidence of acute mountain sickness at intermediate altitude. JAMA 261:732–734, 1989.
80. Hackett PH, Yarnell PR, Hill R, et al: High-altitude cerebral edema evaluated with magnetic resonance imaging: Clinical correlation and pathophysiology. JAMA 280:1920–1925, 1998.
81. Hackett PH, Roach RC: High-altitude illness. N Engl J Med 345:107–114, 2001.
82. Fischer R, Vollmar C, Thiere M, et al: No evidence of cerebral oedema in severe acute mountain sickness. Cephalalgia 24:66–71, 2004.
83. Kallenberg K, Bailey DM, Christ S, et al: Magnetic resonance imaging evidence of cytotoxic cerebral edema in acute mountain sickness. J Cereb Blood Flow Metab 27:1064–1071, 2007.
84. Roach RC, Hackett PH: Frontiers of hypoxia research: Acute mountain sickness. J Exp Biol 204:3161–3170, 2001.
85. Baumgartner RW, Spyridopoulos I, Bartsch P, et al: Acute mountain sickness is not related to cerebral blood flow: A decompression chamber study. J Appl Physiol 86:1578–1582, 1999.
86. Jafarian S, Gorouhi F, Salimi S, Lotfi J: Sumatriptan for prevention of acute mountain sickness: Randomized clinical trial. Ann Neurol 62:273–277, 2007.
87. Bartsch P, Maggi S, Kleger GR, et al: Sumatriptan for high-altitude headache. Lancet 344:1445, 1994.
88. Bailey DM, Kleger GR, Holzgraefe M, et al: Pathophysiological significance of peroxidative stress, neuronal damage, and membrane permeability in acute mountain sickness. J Appl Physiol 96:1459–1463, 2004.
89. Tissot van Patot MC, Leadbetter G, Keyes LE, et al: Greater free plasma VEGF and lower soluble VEGF receptor-1 in acute mountain sickness. J Appl Physiol 98:1626–1629, 2005.
90. Bartsch P, Shaw S, Franciolli M, et al: Atrial natriuretic peptide in acute mountain sickness. J Appl Physiol 65:1929–1937, 1988.
91. Loeppky JA, Icenogle MV, Maes D, et al: Early fluid retention and severe acute mountain sickness. J Appl Physiol 98:591–597, 2005.
92. Kleger GR, Bartsch P, Vock P, et al: Evidence against an increase in capillary permeability in subjects exposed to high altitude. J Appl Physiol 81:1917–1923, 1996.
93. Fischer R, Lang SM, Steiner U, et al: Theophylline improves acute mountain sickness. Eur Respir J 15:123–127, 2000.
94. Bartsch P, Swenson ER, Paul A, et al: Hypoxic ventilatory response, ventilation, gas exchange, and fluid balance in acute mountain sickness. High Alt Med Biol 3:361–376, 2002.
94a. Block KE, Turk AJ, Maggiorini M, et al: Effect of ascent protocol on acute mountain sickness and success at Muztagh Ata, 7546 m. High Alt Med Biol 10:25–32, 2009.
94b. Beidleman BA, Fulco CS, Muza SR, et al: Effect of six days of staging on physiologic adjustments and acute mountain sickness during ascent to 4300 meters. High Alt Med Biol 10:253–260, 2009.
95. Swenson ER: Carbonic anhydrase inhibitors and ventilation: A complex interplay of stimulation and suppression. Eur Respir J 12:1242–1247, 1998.
96. Strom BL, Schinnar R, Apter AJ, et al: Absence of cross-reactivity between sulfonamide antibiotics and sulfonamide nonantibiotics. N Engl J Med 349:1628–1635, 2003.
97. Tzanakis N, Metzidaki G, Thermos K, et al: Anaphylactic shock after a single oral intake of acetazolamide. Br J Ophthalmol 82:588, 1998.
98. Johnson TS, Rock PB, Fulco CS, et al: Prevention of acute mountain sickness by dexamethasone. N Engl J Med 310:683–686, 1984.
99. Ellsworth AJ, Meyer EF, Larson EB: Acetazolamide or dexamethasone use versus placebo to prevent acute mountain sickness on Mount Rainier. West J Med 154:289–293, 1991.
100. Roncin JP, Schwartz F, D'Arbigny P: EGb 761 in control of acute mountain sickness and vascular reactivity to cold exposure. Aviat Space Environ Med 67:445–452, 1996.
101. Moraga FA, Flores A, Serra J, et al: Ginkgo biloba decreases acute mountain sickness in people ascending to high altitude at Ollague (3696 m) in northern Chile. Wilderness Environ Med 18:251–257, 2007.
102. Chow T, Browne V, Heileson HL, et al: Ginkgo biloba and acetazolamide prophylaxis for acute mountain sickness: A randomized, placebo-controlled trial. Arch Intern Med 165:296–301, 2005.
102a. van Patot MC, Keyes LE, Leadbetter G 3rd, Hackett PH: Ginkgo biloba for prevention of acute mountain sickness: does it work? High Alt Med Biol 10:33–43, 2009.
103. Gertsch JH, Basnyat B, Johnson EW, et al: Randomised, double blind, placebo controlled comparison of ginkgo biloba and acetazolamide for prevention of acute mountain sickness among Himalayan trekkers: The Prevention of High Altitude Illness Trial (PHAIT). BMJ 328:797, 2004.
104. Taber RL: Protocols for the use of portable hyperbaric chambers for the treatment of high altitude disorders. J Wild Med 1:181–192, 1990.
105. Grissom CK, Roach RC, Sarnquist FH, Hackett PH: Acetazolamide in the treatment of acute mountain sickness: Clinical efficacy and effect on gas exchange. Ann Intern Med 116:461–465, 1992.
106. Harris NS, Wenzel RP, Thomas SH: High altitude headache: Efficacy of acetaminophen vs. ibuprofen in a randomized, controlled trial. J Emerg Med 24:383–387, 2003.
107. Olson LG, Hensley MJ, Saunders NA: Augmentation of ventilatory response to asphyxia by prochlorperazine in humans. J Appl Physiol 53:637–643, 1982.
108. Wu T, Ding S, Liu J, et al: Ataxia: An early indicator in high altitude cerebral edema. High Alt Med Biol 7:275–280, 2006.
109. Houston CS, Dickinson J: Cerebral form of high-altitude illness. Lancet 2:758–761, 1975.
110. Kallenberg K, Dehnert C, Dorfler A, et al: Microhemorrhages in non-fatal high-altitude cerebral edema. J Cereb Blood Flow Metab 28:1635–1642, 2008.
111. Houston CS: Acute pulmonary edema of high altitude. N Engl J Med 263:478–480, 1960.
112. Bartsch P, Waber U, Haeberli A, et al: Enhanced fibrin formation in high-altitude pulmonary edema. J Appl Physiol 63:752–757, 1987.
113. Maggiorini M, Melot C, Pierre S, et al: High-altitude pulmonary edema is initially caused by an increase in capillary pressure. Circulation 103:2078–2083, 2001.
114. Dickinson J, Heath D, Gosney J, Williams D: Altitude-related deaths in seven trekkers in the Himalayas. Thorax 38:646–656, 1983.
115. Swenson ER, Maggiorini M, Mongovin S, et al: Pathogenesis of high-altitude pulmonary edema: Inflammation is not an etiologic factor. JAMA 287:2228–2235, 2002.
116. Schoene RB, Swenson ER, Pizzo CJ, et al: The lung at high altitude: Bronchoalveolar lavage in acute mountain sickness and pulmonary edema. J Appl Physiol 64:2605–2613, 1988.
117. Kubo K, Hanaoka M, Yamaguchi S, et al: Cytokines in bronchoalveolar lavage fluid in patients with high altitude pulmonary oedema at moderate altitude in Japan. Thorax 51:739–742, 1996.
118. Hultgren HN, Grover RF, Hartley LH: Abnormal circulatory responses to high altitude in subjects with a previous history of high-altitude pulmonary edema. Circulation 44:759–770, 1971.
119. Hackett PH, Roach RC, Schoene RB, et al: Abnormal control of ventilation in high-altitude pulmonary edema. J Appl Physiol 64:1268–1272, 1988.
120. Matsuzawa Y, Fujimoto K, Kobayashi T, et al: Blunted hypoxic ventilatory drive in subjects susceptible to high-altitude pulmonary edema. J Appl Physiol 66:1152–1157, 1989.

121. Duplain H, Vollenweider L, Delabays A, et al: Augmented sympathetic activation during short-term hypoxia and high-altitude exposure in subjects susceptible to high-altitude pulmonary edema. Circulation 99:1713–1718, 1999.
122. Busch T, Bartsch P, Pappert D, et al: Hypoxia decreases exhaled nitric oxide in mountaineers susceptible to high altitude pulmonary edema. Am J Respir Crit Care Med 163:368–373, 2001.
123. Sartori C, Vollenweider L, Loffler BM, et al: Exaggerated endothelin release in high-altitude pulmonary edema. Circulation 99:2665–2668, 1999.
124. Hultgren HN: High altitude pulmonary edema. *In* Hegnauer A (ed): Biomedical Problems of High Terrestrial Altitudes. Springfield, VA: Federal Scientific and Technical Information, 1967, pp 131–141.
125. Dehnert C, Risse F, Ley S, et al: Magnetic resonance imaging of uneven pulmonary perfusion in hypoxia in humans. Am J Respir Crit Care Med 174:1132–1138, 2006.
126. Hopkins SR, Garg J, Bolar DS, et al: Pulmonary blood flow heterogeneity during hypoxia and high-altitude pulmonary edema. Am J Respir Crit Care Med 171:83–87, 2005.
127. West JB, Mathieu-Costello O: Structure, strength, failure, and remodeling of the pulmonary blood-gas barrier. Annu Rev Physiol 61:543–572, 1999.
128. Parker JC, Ivey CL, Tucker JA: Gadolinium prevents high airway pressure-induced permeability increases in isolated rat lungs. J Appl Physiol 84:1113–1118, 1998.
129. Durmowicz AG, Noordeweir E, Nicholas R, Reeves JT: Inflammatory processes may predispose children to high-altitude pulmonary edema. J Pediatr 130:838–840, 1997.
130. Stelzner TJ, O'Brien RF, Sato K, Weil JV: Hypoxia-induced increases in pulmonary transvascular protein escape in rats: Modulation by glucocorticoids. J Clin Invest 82:1840–1847, 1988.
131. Gabry AL, Ledoux X, Mozziconacci M, Martin C: High-altitude pulmonary edema at moderate altitude (<2,400 m; 7,870 feet): A series of 52 patients. Chest 123:49–53, 2003.
132. Wodopia R, Ko HS, Billian J, et al: Hypoxia decreases proteins involved in epithelial electrolyte transport in A549 cells and rat lung. Am J Physiol Lung Cell Mol Physiol 279:L1110–L1119, 2000.
133. Vivona ML, Matthay M, Chabaud MB, et al: Hypoxia reduces alveolar epithelial sodium and fluid transport in rats: reversal by beta-adrenergic agonist treatment. Am J Respir Cell Mol Biol 25:554–561, 2001.
134. Sartori C, Allemann Y, Duplain H, et al: Salmeterol for the prevention of high-altitude pulmonary edema. N Engl J Med 346:1631–1636, 2002.
135. Mairbaurl H, Weymann J, Mohrlein A, et al: Nasal epithelium potential difference at high altitude (4,559 m): Evidence for secretion. Am J Respir Crit Care Med 167:862–867, 2003.
136. Bartsch P, Mairbaurl H: Salmeterol for the prevention of high-altitude pulmonary edema. N Engl J Med 347:1282–1285, 2002.
137. Allemann Y, Hutter D, Lipp E, et al: Patent foramen ovale and high-altitude pulmonary edema. JAMA 296:2954–2958, 2006.
138. Dehnert C, Bartsch P, Grunig E, Mereles D: High-altitude pulmonary edema and patent foramen ovale. JAMA 297:1432, 2007 [author reply appears in JAMA 297:1432–1433, 2007].
139. Marshall BE, Marshall C, Magno M, Lilagan P, Pietra GG: Influence of bronchial arterial PO_2 on pulmonary vascular resistance. J Appl Physiol 70:405–415, 1991.
140. Maron MB: Analysis of airway fluid protein concentration in neurogenic pulmonary edema. J Appl Physiol 62:470–476, 1987.
141. Malik AB: Pulmonary vascular response to increase in intracranial pressure: Role of sympathetic mechanisms. J Appl Physiol 42:335–343, 1977.
142. Hackett PH, Roach RC, Hartig GS, et al: The effect of vasodilators on pulmonary hemodynamics in high altitude pulmonary edema: A comparison. Int J Sports Med 13(Suppl 1):S68–S71, 1992.
143. Bartsch P, Maggiorini M, Ritter M, et al: Prevention of high-altitude pulmonary edema by nifedipine. N Engl J Med 325:1284–1289, 1991.
144. Maggiorini M, Brunner-La Rocca HP, Peth S, et al: Both tadalafil and dexamethasone may reduce the incidence of high-altitude pulmonary edema: A randomized trial. Ann Intern Med 145:497–506, 2006.
145. Hackett PH, Roach RC, Goldberg S, et al: A portable, fabric hyperbaric chamber for treatment of high altitude pulmonary edema (abstract). *In* Sutton JR, Coates G, Remmers JE (eds): Hypoxia: The Adaptations. Philadelphia: BC Decker, 1990, p 291.
146. Schoene RB, Roach RC, Hackett PH, et al: High altitude pulmonary edema and exercise at 4,400 meters on Mount McKinley: Effect of expiratory positive airway pressure. Chest 87:330–333, 1985.
147. Chauca D, Bligh J: An additive effect of cold exposure and hypoxia on pulmonary artery pressure in sheep. Res Vet Sci 21:123–124, 1976.
148. Oelz O, Maggiorini M, Ritter M, et al: Nifedipine for high altitude pulmonary oedema. Lancet 2:1241–1244, 1989.
149. Fagenholz PJ, Gutman JA, Murray AF, Harris NS: Treatment of high altitude pulmonary edema at 4240 m in Nepal. High Alt Med Biol 8:139–146, 2007.
150. Hultgren HN, Honigman B, Theis MK, Nicholas D: High-altitude pulmonary edema at a ski resort. West J Med 164:222–227, 1996.
151. Monge MC: La enfermedad de los Andes: Sindromes eritremicos. Ann Fac Med Univ San Marcos (Lima) 11:1–316, 1928.
152. Xie C-F, Pei S-X: Some physiological data on sojourners and native highlanders at three different altitudes in Xizang. *In* Shang LD (ed): Proceedings of Symposium on Tibet Plateau. New York: Gordon and Breach Science Publishers, 1981, pp 1449–1452.
153. Kryger M, McCullough R, Doekel R, et al: Excessive polycythemia of high altitude: Role of ventilatory drive and lung disease. Am Rev Respir Dis 118:659–666, 1978.
154. Winslow RM: Relationship between erythropoiesis and ventilation in high altitude natives. *In* Lahiri S, Cherniack NS, Fitzerland RS (eds): Response and Adaptation to Hypoxia: Organ to Organelle. New York: Oxford University Press, 1991, pp 143–156.
155. Penaloza D, Arias-Stella J: The heart and pulmonary circulation at high altitudes: Healthy highlanders and chronic mountain sickness. Circulation 115:1132–1146, 2007.
156. Hornbein TF, Roos A: Effect of polycythemia on respiration. J Appl Physiol 12:86–90, 1958.
157. Villafuerte FC, Cardenas-Alayza R, Macarlupu JL, et al: Ventilatory response to acute hypoxia in transgenic mice over-expressing erythropoietin: Effect of acclimation to 3-week hypobaric hypoxia. Respir Physiol Neurobiol 158:243–250, 2007.
158. Monge CC: Natural acclimatization to high altitudes: Clinical conditions in life at high altitudes. Sci Publications Pan Am Health Org 140:46–52, 1966.
159. Weil JV, Kryger MH, Scoggin CH: Sleep and breathing at high altitude. *In* Guilleminault C, Dement WC (eds): Sleep Apnea Syndromes. New York: Alan R. Liss, 1978, pp 119–136.
160. Kryger M, McCullough RE, Collins D, et al: Treatment of excessive polycythemia of high altitude with respiratory stimulant drugs. Am Rev Respir Dis 117:455–464, 1978.
161. Richalet JP, Rivera M, Bouchet P, et al: Acetazolamide: A treatment for chronic mountain sickness. Am J Respir Crit Care Med 172:1427–1433, 2005.
162. Plata R, Cornejo A, Arratia C, et al: Angiotensin-converting-enzyme inhibition therapy in altitude polycythaemia: A prospective randomised trial. Lancet 359:663–666, 2002.
163. Leon-Velarde F, Maggiorini M, Reeves JT, et al: Consensus statement on chronic and subacute high altitude diseases. High Alt Med Biol 6:147–157, 2005.
164. Anand IS, Malhotra RM, Chandrashekhar Y, et al: Adult subacute mountain sickness—a syndrome of congestive heart failure in man at very high altitude. Lancet 335:561–565, 1990.
165. Aldashev AA, Kojonazarov BK, Amatov TA, et al: Phosphodiesterase type 5 and high altitude pulmonary hypertension. Thorax 60:683–687, 2005.
166. Hultgren HN, Marticorena EA: High altitude pulmonary edema: Epidemiologic observations in Peru. Chest 74:372–376, 1978.
167. Marticorena E, Hultgren HN: Evaluation of therapeutic methods in high altitude pulmonary edema. Am J Cardiol 43:307–312, 1979.
168. Bartsch P, Gibbs JS: The effect of altitude on the heart and lungs. Circulation 116:2191–2202, 2007.

169. Luks AM, Johnson RJ, Swenson ER: Chronic kidney disease at high altitude: Risks and management. J Am Soc Nephrol 19:262–271, 2008.
170. Brubaker PL: Adventure travel and type 1 diabetes: The complicating effects of high altitude. Diabetes Care 28:2563–2572, 2005.
171. Luks AM, Swenson ER: Travel to high altitude with pre-existing lung disease. Eur Respir J 29:770–792, 2007.
172. Dillard TA, Berg BW, Rajagopal KR, et al: Hypoxemia during air travel in patients with chronic obstructive pulmonary disease. Ann Intern Med 111:362–367, 1989.
173. Christensen CC, Ryg MS, Refvem OK, Skjonsberg OH: Effect of hypobaric hypoxia on blood gases in patients with restrictive lung disease. Eur Respir J 20:300–305, 2002.
174. Cogo A, Basnyat B, Legnani D, Allegra L: Bronchial asthma and airway hyperresponsiveness at high altitude. Respiration 64:444–449, 1997.
175. Hackett PH, Creagh CE, Grover RF, et al: High-altitude pulmonary edema in persons without the right pulmonary artery. N Engl J Med 302:1070–1073, 1980.
176. Burgess KR, Johnson PL, Edwards N: Central and obstructive sleep apnoea during ascent to high altitude. Respirology 9:222–229, 2004.
177. Burgess KR, Cooper J, Rice A, et al: Effect of simulated altitude during sleep on moderate-severity OSA. Respirology 11:62–69, 2006.
178. Fromm RE Jr, Varon J, Lechin AE, Hirshkowitz M: CPAP machine performance and altitude. Chest 108:1577–1580, 1995.
179. Van Patot MC, Hill AE, Dingmann C, et al: Risk of impaired coagulation in warfarin patients ascending to altitude (>2400 m). High Alt Med Biol 7:39–46, 2006.
180. Luks AM, Swenson ER: Medication and dosage considerations in the prophylaxis and treatment of high-altitude illness. Chest 133:744–755, 2008.

CHAPTER 71

DIVING MEDICINE

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INTRODUCTION

Increased Pressure

Humans are exposed to increased pressure when submerged underwater and when subjected to elevated pressures in closed pressure vessels. Underwater exposure is experienced by divers, who are subject to increasing pressure directly proportional to depth (Table 71-1). Pressure vessels include hyperbaric chambers used for treatment of medical and diving-related diseases, pressurized tunnels and caissons used for underwater construction, and underwater habitats. As depth and pressure increase, the diver breathes gas of increased density using breathing equipment that provides oxygen and allows for elimination of carbon dioxide.

Relation to Altitude

Exposure to altitudes above 18,000 feet (0.5 atmosphere absolute [ATA]) may result in free gas formation in tissues due to supersaturation of inert gases dissolved at atmospheric pressure.[1] Divers with increased inert gas in their tissues from diving can develop free gas in these tissues when going to altitude after diving even though they follow established protocols for ascent from depth to the surface. Flying after diving is a common occurrence among sport divers, who may fly in commercial aircraft (about 8000 feet equivalent altitude) shortly after diving.

Water Immersion

Increases in intrathoracic blood volume occur with water immersion.[2] Intrathoracic pressure at end-expiration increases from −5 cm H_2O while standing in air to −2 cm H_2O during immersion,[3] and abdominal pressure increases from −6 cm H_2O in air to +12 cm H_2O during immersion.[4] This increased hydrostatic pressure prevents blood from pooling in the peripheral veins. The increase in transdiaphragmatic pressure and the absence of venous blood pooling increase venous return during

TABLE 71-1. Pressure Equivalents for Altitude and Depth

	Feet	ATA	mm Hg	psi
Altitude above sea level	12,000	0.636	483	9.3
	8,000	0.742	564	10.9
	4,000	0.863	656	12.7
Sea level	0	1	760	14.7
Depth in sea water	33	2	1,520	29.4
	66	3	2,280	44.1
	99	4	3,040	58.8
	132	5	3,800	73.5

ATA, atmospheres absolute; psi, pounds/square inch.

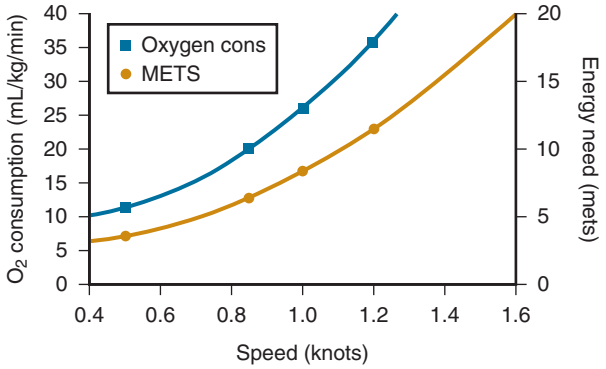

FIGURE 71-1 ■ Oxygen consumption and metabolic equivalents (METS) are shown for underwater swimming. (Data from Navy Department: U.S. Navy Diving Manual, Vol 1, Rev 3: Air Diving [Publication No. NAVSEA 0994-LP-001-9110]. Washington, DC: U.S. Navy Department, 1996.)

immersion. The magnitude of the increase in the intrathoracic blood volume during head-out immersion has been estimated to be 700 mL.[2] The central blood shifts result in an increase in cardiac output[5] and an increase in central venous pressure. The increase in intrathoracic blood volume causes a diuresis due to release of natriuretic hormones and suppression of antidiuretic hormone.

Breath-hold divers can develop sudden unconsciousness during ascent from long apneic dives.[6] This phenomenon is called *shallow water blackout* and is due to a progressive reduction in arterial P_{O_2} as the breath-hold diver ascends with decreasing ambient pressure and arterial P_{O_2} that is further reduced due to metabolic needs.

Thermal Exposure

Most diving is done in water with temperature below the skin temperature (30°C), and the diver loses heat throughout the dive. Therefore, hypothermia is a constant hazard in diving and occurs rapidly in the absence of protective garments even in relatively warm water (e.g., 22° to 23°C). Heat loss is inhibited in divers doing moderate work in water above 30°C, and hyperthermia can develop.

Cold stress evokes thermogenic responses, reflected by changes in oxygen consumption ($\dot{V}_{O_2}$). A rise in $\dot{V}_{O_2}$ upon exposure to cold water generates additional body heat in order to minimize core temperature change. A slower rise in $\dot{V}_{O_2}$ can occur in divers wearing thermal protection.

Peripheral vasoconstriction occurs in response to the stress of cold water diving. The magnitude of the vasoconstriction is dependent on body core temperature, which, in turn, is affected by the amount of thermal protection and the water temperature. Divers face heat loss even in tropical waters, which have temperatures ranging from 29° to 31°C.

Energy Needs for Diving

A scuba diver swimming underwater at a speed of 1.0 knot (about 100 feet/min) consumes about 25 mL of oxygen/kg per minute (Fig. 71-1).[7,8] This is a high workload and is uncommon in sport scuba diving. A diver with a maximum $\dot{V}_{O_2}$ of 40 mL/kg per minute would tolerate swimming at 1.3 knots for a few minutes but would become extremely tachypneic to compensate for lactate production. For a diver with a maximum $\dot{V}_{O_2}$ of 40 mL/kg per minute, sustainable swimming speed, working at 60% to 65% of maximum capacity, would be about 100 feet/min, whereas the diver with a maximum $\dot{V}_{O_2}$ of 25 mL/kg per minute would only be able to sustain a swimming speed of about 70 feet/min. Safety considerations suggest that the sport diver should be able to tolerate a sustained workload of about 24 mL/kg per minute (60% of maximum).[7,8] Scuba divers who maintain this level of physical conditioning can be expected to respond appropriately to most diving workloads. Poorly conditioned divers can experience severe dyspnea under even mildly stressful conditions that exceed their anaerobic threshold.

EQUIPMENT

Open-Circuit Scuba

The most commonly used breathing equipment in diving is the open-circuit scuba (self-contained underwater breathing apparatus). This equipment (Fig. 71-2) consists of a metal cylinder containing compressed air connected to a pressure regulator that lowers pressure first to about 150 psi over ambient pressure and then to ambient pressure with a demand-type regulator with a mouthpiece in the diver's mouth. This device delivers ambient-pressure air only when inhalation is initiated and allows flow that matches the minute volume of the diver. A typical scuba cylinder can supply approximately 2100 L of air at the surface (1 ATA). This volume is reduced in direct proportion to ambient pressure. For example, at a depth of 66 feet of seawater (fsw) or 3 ATA pressure, the effective volume of air is decreased to 700 L. With a minute

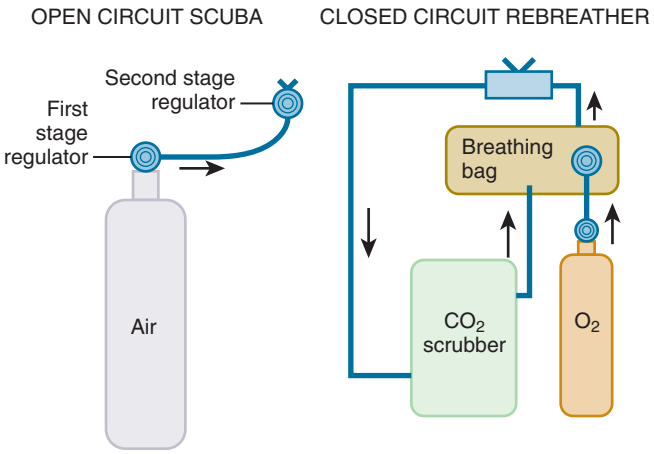

FIGURE 71-2 ■ The schematics show two types of self-contained diving systems. The open-circuit scuba is the system commonly used for recreational diving. Air is exhaled into the surrounding water. Rebreather systems allow exhaled breathing gas to be recycled through a carbon dioxide scrubber, mixed with additional breathing gas, and returned to the diver through a breathing bag. Breathing gas is replenished via a demand valve. This system can be used with 100% oxygen or oxygen-enriched air mixtures. Other forms of rebreather systems contain separate oxygen and inert gas supplies, and mixing is controlled with a small computer to maintain a constant oxygen partial pressure.

ventilation of 20 L/min, this air supply would last 105 minutes at the surface but only 35 minutes at 66 fsw. Open-circuit scuba is usually limited to depths above 200 feet because of limited air supply, nitrogen narcosis, and oxygen toxicity.

Closed-Circuit Scuba

The self-contained rebreather uses a carbon dioxide absorbent to remove exhaled carbon dioxide and replenishes only the oxygen used. Inert gas is conserved by recycling the exhaled gas through the carbon dioxide absorbent and then adding oxygen before the gas is rebreathed (see Fig. 71-2). Little gas is released into the surrounding water, oxygen can be carried in volumes adequate for several hours of exposure, and gas consumption is independent of depth. Although use of closed-circuit scuba in the past was confined to commercial and military divers, such rebreather systems now are becoming popular among recreational divers.

Surface-Supplied Equipment

Commercial diving often employs this form of equipment. The diver breathes compressed air or other gas mixtures pumped from the surface to the helmet, and the excess flows out through the bottom of the helmet. The modern diving helmet is attached at the collar to a diving suit so that air flows from the helmet into the suit to maintain an air layer for thermal protection. Modern systems contain a demand mask built into the helmet.

DISORDERS RELATED TO DIVING: NOMENCLATURE

Golding and coworkers[9] described a scheme for categorizing decompression-related disorders that has become the standard nomenclature. They described disorders related to supersaturation of inert gases in tissues with subsequent bubble formation as *decompression sickness* (DCS). They described a systemic form of DCS that involves the central nervous system, the lungs, and the circulation ("serious," type II) and a nonsystemic (peripheral) form that involves the skin, bones, and joints ("minor," type I). *Arterial gas embolism* is named separately based on different pathophysiologic mechanisms.

Francis and Smith[10] suggested the term *decompression illness* for these two disorders because they can be clinically difficult to separate and they require the same therapy; however, in this chapter, we use a pathophysiologic classification of the pressure disorders whenever possible.

PRESSURE EFFECTS: BOYLE'S LAW

Relation of Gas Volume to Depth

Boyle's law states that, if the temperature of a fixed mass of an ideal gas is kept constant, volume and pressure are inversely related. This relationship is described by the equation $P \cdot V = K$, where P is absolute pressure, V is volume, and K is a constant. Consequently, when the pressure is doubled, the volume is reduced to one half of the original volume. Because the gas volume is proportional to the absolute pressure, the volume change from 33 to 66 fsw (from 2 to 3 ATA) is less than the change from the surface to 33 fsw (from 1 to 2 ATA). Changes of depth in shallow water cause greater volume changes than equivalent changes of depth in deeper water. Rapid volume expansion resulting from depth changes in shallow water can cause tissue injury.

Barotrauma

With increased pressure, volume in the lungs, middle ear, paranasal sinuses, and gastrointestinal tract are reduced. Displacement of tissues into the diminishing volume of these spaces may cause tissue injury and may cause dysfunction of the organ involved. Middle ear barotrauma is the most common diving-related disorder encountered in divers.[11] Barotrauma can affect a paranasal sinus with an occluded orifice, a small residual air pocket left between a tooth filling and the base of the tooth, or the air space within a diving mask. All can produce tissue injury due to displacement of tissues into the diminishing air space. Although lung barotrauma on descent is possible by breath-hold diving to a depth that reduces the lung volume below the residual volume,[4] in practice this has not been observed because of the increased intrapulmonary blood volume and compression of the thorax.

Pulmonary Barotrauma and Arterial Gas Embolism

When a diver subjected to increasing pressure breathes from an air supply at depth, the breathing gas is pressurized to the ambient pressure so that pressure gradients from breathing supply to the airways are not altered as the diver descends. Ascent to the surface after breathing compressed air from depths as shallow as 4 feet can cause pulmonary barotrauma. Studies by Behnke[12] and by Polak and Adams[13] reported the features of lung barotrauma. Fatalities were identified in which an ascending diver with no evidence of pulmonary disease sustained pulmonary barotrauma due to inadequate exhalation during ascent. In some cases, obstruction of a single bronchus was thought to cause overexpansion of a lung segment. Later studies[14] provided further insight into mechanisms and prevention of pulmonary barotrauma.

Pathophysiology. Under experimental conditions, transpulmonary pressures (i.e., the difference between intratracheal and intrapleural pressures) of 95 to 110 cm H_2O are sufficient to disrupt pulmonary parenchyma and allow gases into the interstitium.[14] Extra-alveolar gas will migrate through perivascular sheaths of the pulmonary vasculature to cause mediastinal emphysema and pneumothorax.[14] Gas can also dissect into the retroperitoneum and into the subcutaneous tissues of the neck. When intrathoracic pressure drops after the pulmonary barotrauma, extra-alveolar gas can pass into ruptured blood vessels, travel to the left side of the heart, and enter the arterial circulation as gaseous emboli. The dissemination of gas bubbles throughout the arterial circulation causes injury to other organ systems and to skeletal muscle, which is evident by a rise in serum creatine kinase level.[15]

Pulmonary barotrauma can occur in divers who would not be considered at risk for lung overpressure. Tetzlaff and colleagues[16] suggested that prospective pulmonary function testing could be used as a means of separating individuals with a history of asthma who can dive safely from those who might be at risk for pulmonary barotrauma. They identified reduced midexpiratory flow at 25% of vital capacity in pulmonary barotrauma patients. The authors also performed computed tomography (CT) of the chest and found 13 lung abnormalities among the 15 patients with pulmonary barotrauma. Both studies suggest that occult lung disease and asthma may contribute to unexplained cerebral air embolism. However, other authors have disagreed with these interpretations.[17] Epidemiologic studies have not demonstrated a significant relationship between asthma and an increased risk for pulmonary barotrauma. In a retrospective study of submarine candidates undergoing submarine escape training, Benton and associates[18] identified a small forced vital capacity as a risk factor for pulmonary barotrauma.

Clinical Manifestations of Arterial Air Embolism. The brain is commonly involved. Loss of consciousness, hemiplegia, stupor, and confusion occur within minutes after the diver surfaces. Also frequently seen are seizures, vertigo, visual disturbances, sensory changes, headache, and circulatory collapse.[19] In a study of pulmonary barotrauma resulting from submarine escape training, Elliott and associates[19] found that most individuals fully recover if they are promptly recompressed.

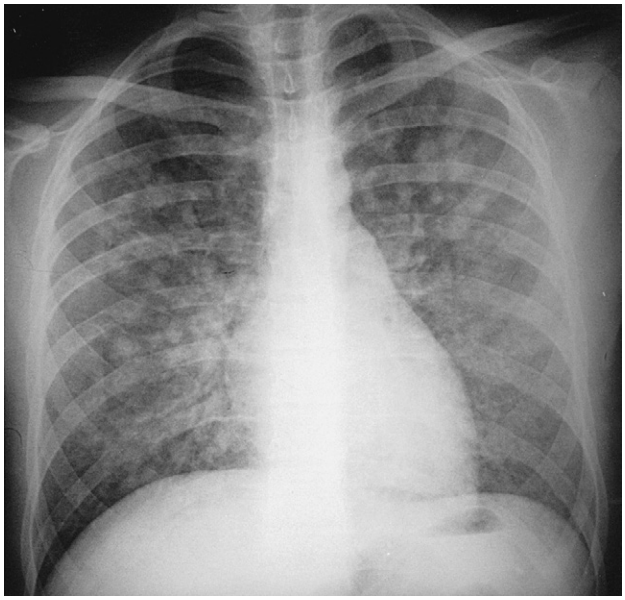

FIGURE 71-3 ■ Chest radiograph from a diver showing pulmonary barotrauma and near drowning. The diffuse pulmonary edema pattern is suggestive of water aspiration.

Victims of arterial gas embolism frequently suffer near drowning episodes when they lose consciousness in the water. Chest radiographs (Fig. 71-3) may show a diffuse lung edema pattern. About 5% of patients immediately develop apnea, unconsciousness, and cardiac arrest. This catastrophic course results from filling of the heart and great vessels with air. Many of these individuals are unresponsive to cardiopulmonary resuscitation and advanced life support measures.[20] Harker and coworkers[21] reported the pulmonary findings of 31 patients with cerebral air embolism from diving: 25% demonstrated pneumomediastinum; 10%, subcutaneous emphysema; 6%, pneumocardium; 3%, pneumoperitoneum; and 3%, pneumothorax. Fifty-two percent had pulmonary infiltrates indicating associated drowning.

Extra-alveolar gas can enter the mediastinum and the subcutaneous spaces of the neck and can enter the pleural space. Mediastinal emphysema is generally associated with mild substernal pain or no symptoms. The pain is described as either a dull ache or tightness and may be exacerbated by inspiration, coughing, or swallowing. The pain may radiate to any portion of the upper torso. Unless massive, this condition is not usually associated with respiratory symptoms. On physical examination, a crunching sound synchronous with cardiac action may be auscultated (Hamman's sign). The chest radiograph confirms the diagnosis. No treatment is usually necessary.

Air dissecting cephalad from the mediastinum causes subcutaneous emphysema in the neck. Swelling and crepitus in the root of the neck and supraclavicular fossa, sore throat, hoarseness, and dysphagia may result.

Radiographs may be helpful in detecting subtle cases, but CT scans are more sensitive and can be useful to confirm the diagnosis of barotrauma in doubtful cases. Brain MRI done within a few days of injury will show scattered grey and white matter lesions.[21a] When extra-alveolar gas ruptures into the pleural space, a pneumothorax results. Laboratory evaluation may show an elevated hematocrit level and elevation of several serum enzyme levels.[22] Treatment for arterial gas embolism requires recompression in a hyperbaric chamber (see later).

Middle Ear Barotrauma

Middle ear barotrauma occurs when the eustachian tube is blocked during descent and the middle ear space cannot equilibrate with the increasing ambient pressure. The tympanic membrane is displaced inward and may rupture. The middle ear may fill with blood from engorged mucous membranes. Infection and hearing loss are complications. Symptoms during descent include pain in the affected ear that increases with depth. Relief of pain without proper ventilation of the middle ear usually indicates that the tympanic membrane has ruptured. Cold water entering the middle ear when the tympanic membrane ruptures may cause vertigo due to unilateral vestibular stimulation. Late complications include bacterial otitis media, serous otitis media, and chronic tympanic membrane perforation.[11] In rare cases of middle ear barotrauma, the facial nerve is injured by the increased pressure and a temporary facial paralysis results.[23] A modified Valsalva maneuver is commonly used to equilibrate middle ear pressure. Because middle ear barotrauma causes edema and hemorrhage into the middle ear, equalization is usually impossible to achieve until healing is complete. The presence of middle ear barotrauma usually prohibits diving until it is resolved.

Alternobaric Vertigo. Vertigo occurs on ascent when the reduction of middle ear pressure is not uniform in both ears. The pressure imbalance causes differential stimulation of the labyrinths, resulting in vertigo. The sensation of vertigo may persist for 1 to 2 hours after diving and gradually disappears without therapy. Symptoms are similar to labyrinthitis and can include nausea, vomiting, and generalized malaise. Some subjects may be particularly susceptible to alternobaric vertigo if they have had previous injury or infection of the labyrinths. In susceptible individuals, use of moderate doses of antihistamines or decongestants may prevent symptoms. The disorder must be differentiated from vestibular DCS, which is usually associated with deeper, prolonged diving or saturation diving.

Inner Ear Barotrauma

Inner ear barotrauma occurs on descent in divers who perform a forceful Valsalva maneuver to equalize middle ear pressure. If the eustachian tube is blocked, middle ear pressure becomes progressively more negative relative to ambient pressure.[11,24] When a Valsalva maneuver is performed, intrathoracic pressure, central venous pressure, spinal fluid pressure, and inner ear pressure rise above ambient pressure, thereby increasing the gradient between the inner ear perilymph and the middle ear. If the pressure between the inner ear and middle ear becomes large enough, the round or oval window will rupture, and perilymph will leak from the inner ear to the middle ear. Symptoms include vertigo, nausea, vomiting, tinnitus, and loss of hearing on the affected side. Severity may vary, and some divers will complain of hearing loss, tinnitus, or vertigo only after diving.

Treatment varies from conservative therapy to surgical repair of the round or oval window. Vertigo and nausea can be treated with benzodiazepine medications. Tinnitus and reduced hearing may become chronic, particularly if no treatment is provided. Divers who exhibit clinical evidence of inner ear barotrauma with intact round and oval windows may have a pressure injury to the organ of Corti and the vestibular system.[25] Klingmann and colleagues found an increased prevalence of a patent foramen ovale (PFO) in divers with inner ear barotrauma.[26]

Sinus Barotrauma

When a sinus orifice is occluded, pressure within the sinus becomes negative with respect to ambient pressure, and mucosal blood vessels become engorged and eventually rupture. Pain over the affected sinus during descent and epistaxis on ascent are usual symptoms. Headache following a dive may indicate sphenoid sinus barotrauma. The disorder is usually self-limiting; treatment includes decongestants and maneuvers to drain the affected sinus. Persistence of blood in the sinus may result in bacterial sinusitis. Prevention is accomplished by avoiding diving with congestion of the nasopharynx and prudent use of decongestants. If a maxillary sinus orifice is occluded, the maxillary branch of the trigeminal nerve may be compressed during ascent and result in infraorbital paresthesias that usually resolve in 2 to 3 hours.

Less Common Forms of Barotrauma

Facial barotrauma (mask squeeze) occurs in the distribution of the diving mask. Facial edema, ecchymoses, and conjunctival hemorrhages are noted after diving. Retroorbital hematoma has been described as a complication.[27] The disorder is self-limiting; no treatment is needed.

Tooth barotrauma occurs on descent when air pockets under fillings or in areas of decay become compressed. Severe toothache results. Rarely, an air pocket under a filling expands on ascent and ejects the filling from the tooth. Careful dental work prevents this disorder.[28]

Gastrointestinal barotrauma occurs when air enters the stomach during diving due to faulty breathing apparatus or by air swallowing. On ascent, the expanding air will distend the stomach or intestine. Gastric distention can occlude the esophageal-gastric junction and prevent eructation. Distention of the stomach may cause stomach rupture and pneumoperitoneum.[29] The diver experiences abdominal pain, which increases during ascent. Treatment requires surgical repair of the ruptured viscus.

Divers with previous gastric surgery may be prone to gastric air trapping.[30]

DISSOLVED INERT GAS EFFECTS: HENRY'S LAW

Gas Solubility

Pressure determines the amount of gas that is dissolved in tissues and fluids of the body. A person subjected to increased ambient pressure takes up gases into the tissues of the body according to an exponential kinetics process. At equilibrium, the partial pressure of the gas and the solubility of the gas in the specific tissue (Table 71-2) determine dissolved gas content of tissues. Inert gases (nitrogen, helium) are limiting factors in diving because, as the diver ascends with increased dissolved gas in the tissues, these gases are able to supersaturate quickly and form a gas phase. Oxygen and carbon dioxide do not become supersaturated in most diving exposures.

Inert Gas Kinetics

Gases dissolve in tissues, fats, and water according to Henry's law: $Q = c \cdot P$, where c, a solubility coefficient, and P, the partial pressure of the gas, determine the quantity (Q) of dissolved inert gas. Solubility coefficients for water and lipid are provided in Table 71-2. Although Henry's law determines the amount of gas in the tissue, there is a finite time required for equilibrium to be achieved. Factors that affect the rate of entry include blood flow to the tissue and the rate of diffusion of gases into the tissue. Tissue gas concentration follows an asymptotic curve in which the tissue gas concentration approaches the maximum concentration for the given pressure after time has elapsed. These curves represent different body compartments that have different gas exchange characteristics.[31] Similar kinetics control the washout of inert gas from tissues when ambient pressure is reduced.

The majority of diving is of short duration (i.e., minutes to hours) and shallow exposure (i.e., in depths shallower that 200 feet). Such diving exposures allow only a few tissue compartments to reach equilibrium based on Henry's law, while most are not fully saturated. Divers can return to the surface from these short-duration dives by following a schedule of ascent based on depth and time.[31] Decompression tables have been incorporated into submersible wrist-mounted computers, which provide instantaneous information on decompression during diving.

When diving exposure is long enough, all tissues reach equilibrium at the new ambient pressure and are fully saturated with inert gas. Bond[32] demonstrated that divers could spend prolonged periods (weeks) under pressure, with all tissues saturated at the increased pressure, without serious physiologic changes. Working dives conducted with Bond's techniques have been performed at depths over 1000 feet in open sea for periods up to 3 to 4 weeks.

TABLE 71-2. Characteristics of Inert Gases*

Gas	Molecular Weight	Lipid Solubility†	Water Solubility	Narcotic Potential‡
Helium	4	0.015	0.009	0.23
Neon	20	0.019	0.009	0.28
Hydrogen	2	0.036	0.018	0.55
Nitrogen	28	0.067	0.013	1.00
Argon	40	0.140	0.026	2.32

*Solubility of the various gases in lipid is related to their narcotic potential. Helium is the least and argon the most narcotic gas in the list.
†Expressed as gas volume/solute volume at 1 bar.
‡Values relative to nitrogen.
Adapted from Bennett PB: Inert gas narcosis and HPNS. *In* Bove AA (ed): Bove and Davis' Diving Medicine (4th ed). Philadelphia: WB Saunders, 2004, pp 225–240.

Inert Gas Supersaturation in Tissues

When the diver ascends after breathing pressurized gas, tissues can become supersaturated with gas. When the degree of supersaturation becomes excessive, dissolved gas will leave solution and form free gas. Boycott and colleagues[33] first demonstrated that symptoms could be prevented by keeping the degree of supersaturation below a certain level. They suggested a 2 : 1 ratio of initial to final tissue partial pressure after ascent. Their concept of a critical pressure ratio is the basis for most decompression tables used to prevent DCS.

Boycott and colleagues[33] assumed that the body could be considered as a set of tissue compartments with different rates of gas uptake and elimination. Although these tissues do not represent discrete anatomic structures, they provide a convenient means to understand the kinetics of inert gas exchange. In most decompression tables, stops during ascent are selected to avoid excess supersaturation in tissues with specific gas-exchange rates (Fig. 71-4). Decompression procedures are well defined for air and other mixtures of nitrogen and oxygen; helium and oxygen; nitrogen, helium, and oxygen (trimix); hydrogen and oxygen; and a few rare earth gases such as argon and neon used in experimental exposures.

Decompression Sickness

Excess supersaturation causes dissolved gases to change phase to the gaseous form in blood and tissues.[34] Expansion of gases in blood and tissues on ascent results in damage and dysfunction of tissues and organs and venous gas embolism to the lungs. Sudden decompression following a long, deep dive can be fatal. DCS is the disorder caused by damage to organs and tissues as a result of free gas production and growth.

In the 19th century, Bert[35] described the pathophysiology of DCS. Several investigators in the early 20th century concluded from autopsies on divers and caisson workers that DCS is caused by free gas in the blood and tissues.[36] Based on free gas volume and location, they

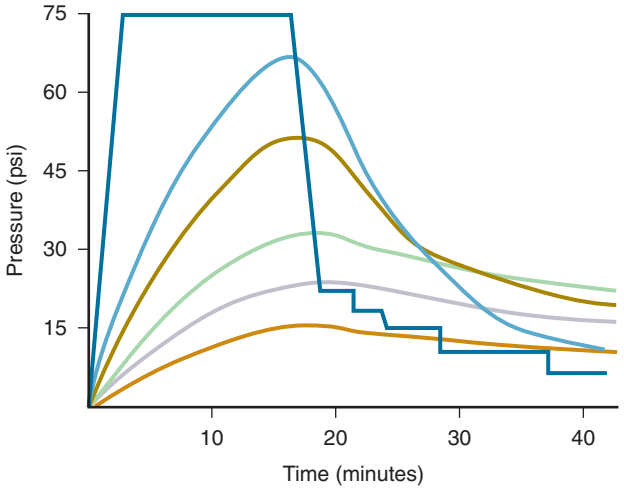

FIGURE 71-4 ■ Theoretical nitrogen gas concentrations are expressed in units of pressure for an exposure of 75 psi (5.1 ATA) following the depth-time profile indicated by the *dark blue line.* Curves are shown for five theoretical tissue compartments with different rates of gas exchange. Tissue gas concentration increases during exposure to pressure. When pressure is reduced, gas concentration in tissues begins to fall. Stops during return to baseline allow tissue concentration to fall to a safe level of supersaturation before reducing pressure further. (Data from Boycott AE, Damant GCC, Haldane J: The prevention of compressed air illness. J Hyg [Cambridge] 8:342–443, 1908.)

were able to explain the variety and severity of the symptoms. Paralysis resulted from free gas in the spinal cord, cerebral dysfunction was thought to result from free gas in the brain, and dyspnea was associated with free gas in the pulmonary circulation. Muscle and joint pain may be due to free gas in ligaments, fascia, periosteum, marrow, or nerve sheaths.

Hallenbeck and colleagues[37] described effects of free gas in blood and tissues that were not caused by mechanical obstruction. Subsequent studies identified clotting and platelet activation by bubbles, intravascular coagulation, plasma leakage from the intravascular space, hemoconcentration, and hypovolemia[38] as manifestations of bubble surface effects. Hematologic abnormalities are infrequent in mild cases.[39] Venous gas emboli are commonly present before overt symptoms of DCS appear.[40]

Free gas and tissue injury result in activation of the inflammatory cascade.[41] The inflammatory response causes fluid to leak into the interstitial tissues of the systemic and pulmonary vascular beds.[42] In severe cases, pulmonary edema, hypovolemia with significant plasma loss, and hemoconcentration will result.

Factors Affecting Risk of Decompression Sickness

The use of Doppler ultrasound for intravascular bubble detection has provided insight into the presence of bubbles following diving.[43] Many divers demonstrate venous gas emboli but no manifestations of DCS. The concept of a threshold or dose-response effect has been postulated, wherein a clinical disorder requires a certain volume of free gas whereas lesser amounts are asymptomatic.[44] However, the presence of venous bubbles in asymptomatic divers and aviators is associated with increased risk of developing symptoms of DCS after diving or altitude exposure.[45,46] Exercise and temperature during decompression have recently been shown to be risk factors for DCS. Repeated diving exposures over several months appears to lower DCS.[46a]

Patent Foramen Ovale. Moon and coworkers[47] reported 30 patients with a history of DCS who were studied with bubble contrast echocardiography for identification of a PFO. Sixty-one percent of 18 patients with serious DCS had shunting, whereas a 25% prevalence was seen in normal volunteers. Wilmshurst and associates[48] identified a single patient with paradoxical gas embolism through an atrial septal defect and suggested that the atrial septal defect augmented symptoms of DCS in this patient. Moon and coworkers[49] evaluated 90 divers with previous DCS who were studied using bubble contrast echocardiography and color flow Doppler to detect right-to-left shunting through a PFO. Fifty-nine of 90 had experienced serious decompression symptoms, whereas 31 had experienced pain only or mild symptoms.

Cerebral gas embolism is usually thought to be due to lung barotrauma. However, in the presence of a PFO, cerebral gas embolism can be caused by venous bubbles transiting the PFO.[50] Germonpré and associates[51] found that divers with cerebral DCS have a high incidence of large PFO compared to control subjects. The presence of a PFO may be associated with a two- to fourfold increase in the risk of DCS.[52] The high prevalence of PFO in the population and the very low incidence of DCS suggest that a PFO can only play a minor role in the pathophysiology of DCS. In some divers, an intrapulmonary shunt can allow venous bubbles to enter the left heart.[52a] There is no current need to close a PFO as a prophylactic measure.[53]

Age. Attempts to determine the impact of age on susceptibility to DCS have aroused much debate. A 10-year study by the U.S. Air Force on flight exposures ranging from 1500 to 30,000 feet show a threefold increase in susceptibility when comparing aviators 18 to 21 years of age with aviators 42 years of age and older.[54] The study suggests a trend toward increased DCS susceptibility in individuals over age 42. Carturan and colleagues[55] examined the effects of age and physical condition on venous bubble formation in sport divers. They found a correlation between bubble formation, increased age, and decreased physical condition. However, both of these studies have significant methodologic problems. Klingmann and coworkers reported an increased incidence of DCS in novice divers compared to more experienced divers.[56]

Clinical Manifestations

Sport and military divers have similar rates of type I and type II DCS (Table 71-3), whereas commercial divers have the highest incidence of DCS. Musculoskeletal DCS (type I) is the most common form. In the late 1990s, the incidence of DCS was about 2 in 10,000 dives for the sport diver.[57]

TABLE 71-3. Frequency and Incidence of Decompression Sickness (DCS) in Sport, Military, and Commercial Air Diving Populations

Source	Military	Sport	Commercial	All
Total dives*	648,488	2,577,680	43,063	3,269,231
Frequency				
Total DCS*	172	878	152	1,202
Type II DCS*	86	649	9	744
Incidence DCS†	2.65	3.41	35.3	3.68
Incidence DCS II†	1.33	2.52	2.09	2.28

*Values are number of events. Type II DCS is systemic, serious DCS.
†Incidence per 10,000 dives; DCS II, DCS type II.
Data from Bove AA: Risk of decompression sickness with patent foramen ovale. Undersea Biomed Res 25:175–178, 1998.

TABLE 71-4. Frequency of Decompression Sickness (DCS) Symptoms in 100 Cases

Symptom	Percentage of All DCS Symptoms
Skin itch	4
Headache	11
Fatigue/malaise	13
Bone/joint pain	54
Spinal/back pain	11
Spinal/neurologic	22
Respiratory	21

Data from Navy Department: U.S. Navy Diving Manual, Vol 1, Rev 3: Air Diving (Publication No. NAVSEA 0994-LP-001-9110). Washington, DC: U.S. Navy Department, 1996.

Symptoms of DCS can mimic a variety of other disorders (Table 71-4). Free gas entering the venous system will cause varying degrees of pulmonary vascular obstruction. A classic syndrome ("chokes") manifested by chest pain, dyspnea, and cough is described.[58] DCS is often associated with free gas in the blood and local tissue injury that activates an inflammatory process,[41] with damage to vascular endothelium, microvascular occlusion, and focal regions of tissue ischemia. A common manifestation of DCS in divers is spinal cord dysfunction, usually at levels below the diaphragm.[59] Symptoms include paresthesias, muscle weakness, paralysis of the lower extremities, bowel or bladder incontinence, urinary retention, and sexual impotence. Hawes and Massey[60] reviewed the neurologic manifestations of DCS. In cases of sudden ascent from deep depth ("blowup"), a massive DCS syndrome will occur with both cerebral and spinal neurologic symptoms, unconsciousness, hypovolemic shock, pulmonary edema, and a high mortality rate. A rare but important symptom of systemic (type II) decompression sickness is sudden acute neurologic hearing loss and vestibular dysfunction. DCS of this type usually occurs from deep, prolonged diving exposures and, if untreated, can result in permanent deafness.[61] Presence of a PFO (see earlier) can contribute to cerebral gas embolism in DCS.

The musculoskeletal form of DCS is manifested by pain in the extremities and joints.[62] Symptoms of local joint pain are often confused with pain from injuries, and the diagnosis of DCS may be missed. In some populations, a high incidence of osteonecrosis is found in divers who have experienced musculoskeletal DCS in the distant past or who have experienced deep, prolonged exposures in caisson work,[62] as well as in diving instructors[63] and in workers in commercial diving operations. An erythematous or purpuric skin rash (cutis marmorata) may also be a manifestation of DCS. A systematic method for diagnosing DCS is described by Grover and colleagues.[64]

Treatment

The clinical manifestations of arterial gas embolism and DCS often overlap, and treatment goals for both disorders include recompression and other adjunctive measures. The initial treatment of DCS and arterial gas embolism should always be a return to pressure by recompression in a hyperbaric chamber and administration of oxygen at increased ambient pressure (hyperbaric oxygen). Fluid replacement and antiplatelet agents are also a part of the initial treatment. Once stabilized with pressure and oxygen, the patient must be decompressed slowly to permit the inert gas to be carried away from tissues by the circulatory system and then to be exhaled by the lungs. With early treatment, DCS and air embolism generally have an excellent prognosis for recovery. When delay occurs, or when the injury is severe, permanent injury to the brain or spinal cord may result.

Hyperbaric Therapy. Treatment of DCS and arterial gas embolism should be instituted with recompression as soon as possible after the injury. A history and physical evaluation, including a neurologic examination and cognitive assessment, should be obtained before treatment when possible. Therapy is provided in a hyperbaric chamber by a trained medical team. Return to depth underwater is generally not a satisfactory method of recompression for DCS or air embolism. However, this treatment has been used in remote areas with a support team properly equipped and trained in open water

treatment. Hyperbaric therapy can be briefly delayed for further diagnostic studies only if the findings from such studies could influence the choice of therapy. The usual practice is to follow the standard protocols for pressure treatment outlined in the *U.S. Navy Diving Manual*[8] that involve a pressure exposure equivalent to a 60-foot depth in seawater (60 fsw) using intermittent oxygen therapy.

Most practitioners use a hyperbaric treatment protocol lasting about 6 hours (see Table 6 in *U.S. Navy Diving Manual*[8]) for treatment of types I and II DCS. Recompression therapy for cutis marmorata resulting from DCS has been recommended by some, but most cases, when not associated with other evidence of DCS, resolve spontaneously. Itching and erythema of the skin may also be noted following hyperbaric chamber exposures, but these skin findings alone do not require recompression therapy.

When a diver ascends from extreme depths with significant missed decompression, the practitioner may choose to use recompression tables that pressurize the diver to a "depth of relief," to use alternate gas mixtures (i.e., helium and oxygen), or to hold the diver for over 24 hours at a single depth to stabilize the medical status (saturation treatment).[65] For surface-supplied air and scuba divers, the principal treatment gases are oxygen and air. For treatment depths greater than 60 fsw (18 meters of seawater [msw]), enriched nitrogen-oxygen (nitrox) or helium-oxygen (heliox) may also be used. Helium-oxygen mixtures are sometimes used for treatments deeper than 200 fsw (60 msw).

Repeated hyperbaric oxygen treatments can be given, although end points for repetitive therapy are not well defined. Treatments can be administered until no further change of symptoms is found or for a fixed number of exposures (e.g., five). However, controlled trials to determine efficacy of repetitive treatments are not available. Treatment of arterial gas embolism follows similar protocols. Recompression to 60 fsw and oxygen therapy are usually successful.[66] Recompression to 165 fsw depth equivalent (5 ATA) is recommended if symptoms persist after recompression to 60 fsw.[8]

Supplemental Oxygen and Fluids. Early administration of supplemental oxygen on the surface is thought to be beneficial for treating both DCS and arterial gas embolism.[67] The recommended inspired concentration of oxygen is 100%. Intravenous fluid administration also may be a useful initial treatment. Central nervous system injury may be exacerbated by hyperglycemia, and glucose-containing intravenous solutions should be administered cautiously. Measurement of hematocrit and urine specific gravity is useful to guide fluid replacement therapy.

Diagnostic Testing

Chest radiography can be used to diagnose pneumothorax, pneumomediastinum associated with pulmonary overpressure accidents, and the pulmonary abnormalities associated with aspiration or capillary leakage associated with chokes. Chest or abdominal CT can also be used to diagnose pneumothorax, pneumomediastinum, or pneumoperitoneum. In most cases, it is not necessary to postpone recompression treatment in order to obtain radiographic studies. If pneumothorax is suspected, a chest radiograph can be helpful in making the decision to insert a chest tube. Neurologic and psychological testing may be useful in determining response to treatment when brain injury is present. Electronystagmography and audiography may be useful in distinguishing inner ear DCS from inner ear barotrauma. Inner ear DCS requires recompression, whereas inner ear barotrauma is managed with bed rest, avoidance of straining, and possibly surgical intervention. The circumstances causing the two syndromes are distinct (see earlier) and are helpful in the differential diagnosis; however, in the event the distinction cannot be made, recompression therapy may be of benefit. Central nervous system injury can be diagnosed by magnetic resonance imaging (MRI) and correlated with clinical findings.[68] MRI images of the brain in divers with no history of decompression-related disorders are also found to be abnormal in some studies[69]; the significance of MRI findings in these individuals is unclear. DCS case reviews provide some guidance on use of MRI in patients with DCS.[70]

Emergency Treatment

Because divers may be injured in areas remote from medical care, treatment measures should be instituted during transit to a hyperbaric chamber facility. Emergency treatment before transfer of an injured diver should include 100% oxygen by mask, aspirin 325 to 975 mg by mouth, and Ringer's lactate (or normal saline) intravenously. One study of oxygen, aspirin, intravenous fluids, and hydrocortisone 1 to 2 g intravenously during transit to a hyperbaric chamber found that two thirds of the cases had a favorable outcome[71]; however, it remains unproven whether emergency treatment alters long-term outcome. A favorable response to urgent care should not prolong transfer to the closest facility capable of providing recompression therapy.

INERT GAS NARCOSIS

Inert gas narcosis (nitrogen narcosis) results from breathing air at depths greater than 100 fsw.[72] Symptoms include loss of fine motor control and high-order mental skills, inappropriate response to emotional stress, hostility, and unconsciousness. Symptoms increase with depth from 100 feet. At 300 to 400 feet, unconsciousness may occur owing to the anesthetic effect of nitrogen at this pressure. In diving deeper than 200 feet, helium replaces nitrogen as the inert gas to prevent narcosis. Fatigue, heavy work, and hypothermia can augment the narcotic effect of nitrogen. Symptoms disappear immediately on ascending to a shallow depth. Often there is amnesia for the events that occurred below.[72] Nitrogen effects on nervous function are thought to have the same mechanism of action as anesthetic gases. Narcotic potential varies among the inert gases (see Table 71-2).

OXYGEN TOXICITY

Oxygen toxicity in divers primarily affects the central nervous system. Pulmonary oxygen toxicity is rare in diving, but may be of some concern in prolonged hyperbaric oxygen treatments. Acute toxicity to the brain usually occurs when oxygen partial pressure exceeds 1.4 ATA, although cases have been noted with P_{O_2} as low as 1.2 ATA. Higher partial pressures can be tolerated for brief periods. The affected diver may experience auditory or visual hallucinations, and commonly suffers a grand mal seizure. When underwater, a seizure can leads to drowning. Use of enriched oxygen mixtures by sport divers has increased the incidence of acute oxygen toxicity in this population. A detailed discussion of oxygen toxicity can be found in standard textbooks on diving.[73]

MEDICAL QUALIFICATIONS FOR DIVING

Military divers have the most stringent requirements, whereas recreational divers have the most relaxed requirements. Commercial divers, caisson and tunnel workers, and hyperbaric chamber workers all have unique standards. Disorders that limit cardiovascular or pulmonary function during exercise, physical deconditioning, metabolic disorders that limit exercise capacity, and certain physical handicaps can compromise diving safety.

Exercise Requirements

Workloads in diving vary based on the type of diving (see previous discussion). A diver swimming underwater at a speed of 1.0 knot consumes about 24 mL of oxygen per kilogram per minute.[74] Safety considerations suggest that divers should tolerate a sustained workload of about 24 mL/kg per minute to ensure safety under adverse diving conditions. Divers who do not achieve this level of fitness should avoid exposures that may require high levels of physical exertion.

Disorders Causing Sudden Unconsciousness

Seizure disorders are considered to be a contraindication to diving because a diver sustaining a seizure underwater is at risk for drowning and may compromise the safety of others who attempt a rescue. It has been recommended that a diving candidate with a history of a seizure disorder should be seizure free without antiseizure medications for 4 years before being considered for diving.[75] This recommendation, however, is not supported by clinical studies, although isolated cases of underwater seizures in epileptic divers have been recounted. Insulin-dependent diabetes mellitus is considered a contraindication to commercial and military diving due to the risk of hypoglycemia; however, special training for diabetic recreational divers has allowed safe diving for insulin-dependent sport divers.[76]

Pulmonary Disorders

Asthma has been a subject of controversy in diving because of possible air trapping and pulmonary overinflation during ascent. However, an increased risk for pulmonary barotrauma has not been supported by clinical observation.[77] Criteria for safe diving by patients with a history of asthma include evidence that midexpiratory flow is not reduced after exercise by greater than 50%. A more detailed discussion of issues related to asthma and diving has been published.[78] Clinical and operational experience suggests that patients with a history of spontaneous pneumothorax may be at risk for lung collapse and development of a progressively worsening tension pneumothorax during diving. Treatment requires immediate decompression of the pleural space through an intercostal needle or chest tube and may be difficult in remote diving sites.

Cardiac Disorders

Patients with coronary disease may develop angina pectoris, myocardial infarction, or sudden death while diving. Caruso and associates[79] found that the highest incidence of diving-related death from cardiovascular disease in divers occurs in the age range from 60 to 70 years (Fig. 71-5). Mebane and colleagues[80] reported the mortality experience from the Diving Alert Network. Of 33 cases of sudden death while diving, 31 were attributed to coronary disease, one was related to a cerebral vascular accident, and one was related to aortic stenosis. Screening of diving candidates for coronary disease is particularly important in the sport diving community, in which candidates at increased risk for

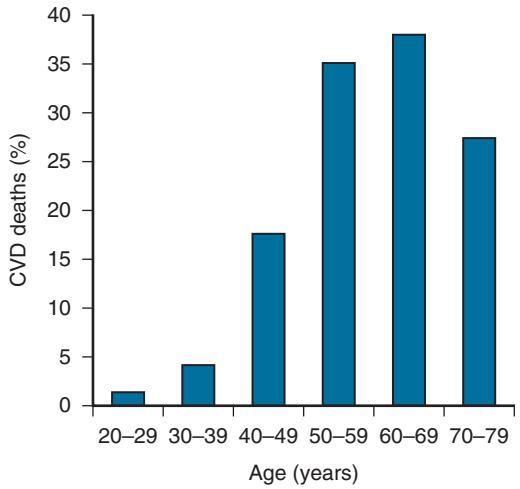

FIGURE 71-5 ■ Incidence of cardiovascular-related diving deaths as a percentage of all deaths in different age groups of recreational divers. (Data from Caruso JL, Bove AA, Uguccioni DM, et al: Recreational diving deaths associated with cardiovascular disease [abstract]. Undersea Hyperb Med 28:76, 2001.)

coronary disease due to age and chronic illness may present for training.

Diving candidates with atrial septal defects risk paradoxical embolism of gas bubbles that form in the venous circulation during decompression.[74] The presence of an atrial septal defect is considered to be a contraindication to diving. PFO effects on diving are discussed in an earlier section. A ventricular septal defect does not appear to produce a risk for paradoxical embolization of bubbles. Patients with a right-to-left shunt and arterial hypoxemia will normally have severely limited exercise capacity and should not dive. A detailed treatment of this topic can be found elsewhere.[74]

Diving-Induced Arrhythmias

Reflex bradycardia from diving has been described by a number of investigators.[81] This arrhythmia is thought to be related to facial immersion and cooling, and is found in diving mammals[82] as well as humans. The autonomic adjustments to apneic diving in marine mammals appear to be an oxygen-conserving reflex, but this effect does not appear to be significant in humans in spite of a well-developed reflex in many free divers. Ackerman and colleagues[83] described a series of drowning cases associated with a familial inherited long QT syndrome. The syndrome was confirmed by genetic testing. Although their cases were related to swimming, the same risk is likely to occur in divers with the long QT syndrome.

DROWNING

Drowning is reported as the leading cause of death in the approximately 100 to 150 scuba fatalities in the United States each year[84]; however, arterial gas embolism may be the precipitating factor or even the cause of death in many of these accidents.[85] In the United States, drowning of males is approximately five times more common than of females. As with fatal automobile accidents, the single most important factor in drowning incidents involving adults is alcohol, contributing to deaths in 30% to 70% of cases.[86] With scuba-related drowning incidents, the most common factor is entanglement or the diver running out of air at depth or in a cave. Although the terms *drowning* and *near drowning* have been used in the past to describe victims who respectively either died or survived (at least temporarily), it is simpler and preferable to use the term *drowning* for all individuals who suffer from submersion incidents.[87,88]

There is strong evidence that intentional hyperventilation before breath-hold diving is associated with drowning episodes.[6] Hyperventilation reduces the arterial P_{CO_2}, so the breath-hold breakpoint is prolonged sufficiently for hypoxemia to occur before the individual is forced to breathe. The hypoxemia in turn causes the individual to lose consciousness, and the submersion incident then occurs. This is termed *shallow water blackout*.

Hypothermia leading to drowning has been reported frequently; however, in diving fatalities this is an unusual occurrence due to the almost universal use of thermal protection by divers. Hypothermia reduces a person's ability to function until the point of unconsciousness or helplessness is reached. At that time, the victim's head falls into the water, resulting in drowning. Maximum breath-hold times of normally clothed individuals drop dramatically in cold water, further compromising their ability to survive in rough water where they may be intermittently submerged. However, in rare circumstances, hypothermia can have a protective effect on the drowning victim (see later).

Hypothermia is one of many conditions that can precipitate drowning by causing unconsciousness. In the case of scuba diving incidents, contamination of the diver's air supply with carbon monoxide produces rapid unconsciousness, and oxygen-induced seizures (see earlier) have been implicated as the cause of death in divers using oxygen-enriched air as a breathing mixture.

Pathophysiology

Approximately 10% to 15% of drowning victims may not aspirate fluid during immersion.[89] To account for the lack of aspiration in these individuals, it has been hypothesized that reflex laryngospasm occurs and persists until reflex ventilatory activity ceases. However, experimental data to support this hypothesis are lacking. In drowning victims who do not aspirate, the period of hypoxemia generally is as long as the immersion incident itself. If ventilation can be reestablished before the development of injury secondary to hypoxemia, recovery typically is rapid and uneventful. A review of early "dry" drowning studies does not support the dry drowning hypothesis.[90] It is much more likely that dry drowning actually represents arrhythmic death.

Unlike the victim without aspiration, the individual who aspirates remains hypoxemic, even after being removed from the fluid medium and even after ventilation is reestablished. As a result, in the latter group the period of hypoxemia is longer, and secondary damage to other organ systems is more likely to occur.[91] The continuing hypoxemia is most frequently due to direct lung injury from the aspirated fluid, which causes areas of low ventilation-perfusion ratio to develop. With saltwater aspiration, it is believed that hyperosmotic fluid causes transudation of fluid into alveoli, and the aspiration of debris (sand, diatoms, algae, etc.) causes a reactive exudate. As a result, alveoli become filled and are not ventilated. In freshwater aspiration, it is believed surfactant is washed out of the lungs, causing areas of focal alveolar collapse, leading to areas of shunt and low ventilation-perfusion ratio, and hypoxemia. These abnormalities persist until the lung damage resolves or until surfactant can be regenerated.

Victims often swallow large amounts of fluid during the drowning episode, so further decreases in ventilatory function may occur as a result of elevation of the diaphragm from gastric distention. Vomiting and aspiration of gastric contents may further complicate the drowning episode. Hypoxemia and decreased alveolar ventilation ($\dot{V}_{A_2}$) produce a number of consequences. Elevations of arterial P_{CO_2} and decreases in pH occur quickly.

Metabolic acidosis can be severe because the victim often struggles during the drowning episode. Finally, cardiovascular collapse may occur, resulting in cardiac arrest. If hypoxemia and decreased cardiac output persist long enough, anoxic cerebral damage can ensue.[92,93] Although electrolyte disturbances are usually not a significant problem in drowning, the exception to this situation appears to be drowning victims in the Dead Sea, where electrolyte concentrations are greater than those in normal seawater. Victims of drowning in that unique environment have major electrolyte abnormalities, which may be responsible for fatal arrhythmias in that group, whereas the marked hypertonicity of the fluid may explain the severe lung injury that these victims may receive.[94,95] The remaining specific consequence of drowning is aspiration pneumonia. The pathogens and the clinical picture of pneumonia associated with drowning have been reviewed extensively.[96]

Because cardiac arrest is secondary to hypoxemia in drowning, it takes a significant amount of time to occur. If the water in which the victim is immersed is cold enough, if the surface area–to-mass ratio of the victim is large enough, and if the victim swallows enough water, core temperature may decrease sufficiently that oxygen demands are markedly decreased. However, it is unclear whether this mechanism is adequate to explain the degree of cooling and the amount of cerebral protection that appears to occur in some incidents.

Clinical Presentation

The clinical presentation of drowning victims is highly variable. The patient who is unconscious and reported to be without vital signs at the site of the accident may be hemodynamically stable and neurologically intact in the emergency room, whereas the victim initially thought to be hemodynamically stable at the scene might deteriorate significantly before arrival at the hospital.

Cardiovascular System

Victims of significant drowning may suffer cardiac arrest and respond to resuscitative measures. Whether this represents premature cardiopulmonary resuscitation by inexperienced rescuers or a response to therapy is not certain. However, it is not uncommon for a victim to be brought to the emergency room still requiring cardiopulmonary resuscitation. If the patient "responds" to cardiopulmonary resuscitation at the scene of the rescue with a stable rhythm or if the patient never suffers a cardiac arrest, supraventricular tachycardias are commonly seen. If the patient presents with a viable rhythm, it will most likely be supraventricular tachycardia secondary to hypoxemia and acidosis.[92] Usually, however, the patient is hemodynamically intact (i.e., adequate blood pressure and pulse with a presumably adequate cardiac output). Some patients may have a primary cardiac arrest that may mimic a drowning episode. This is known to occur in patients with coronary ischemia and in patients with the long QT syndrome. The spectrum and frequency of cardiac channel defects in swimming-triggered arrhythmia syndromes may be greater than previously suspected.[97,98] Pathologic diagnoses may be further complicated by terminal aspiration secondary to agonal breathing after cardiac arrest, and thus postmortem analyses that depend upon aspiration may be misleading.[99,100]

TABLE 71-5. Average Blood Gas Measurements in Hospitalized Near-Drowning Victims Breathing Room Air upon Admission

	pH	$Paco_2$ (mm Hg)	Pao_2 (mm Hg)	Base Excess (mEq)
Fresh water	7.26	38	66	−9
Seawater	7.37	36	56	−5
All	7.30	37	62	−7

Data from Modell JH, Davis JH, Giammona ST, et al: Blood gas and electrolyte changes in human near-drowning victims. JAMA 203:337–343, 1968.

Pulmonary System

Patients with water aspiration may present with few or no respiratory complaints or with severe pulmonary edema.[101] The latter is probably due to direct lung injury and is not usually cardiac in origin. Patients who have aspirated any significant quantity of water frequently have a widened alveolar-arterial oxygen gradient and anything from mild to severe hypoxemia. Arterial P_{CO_2} can be low or elevated depending on alveolar ventilation (Table 71-5). Chest radiographs can show patchy infiltrates, which are most common in the periphery or in the medial basal regions, or frank pulmonary edema (see Fig. 71-4).[102] The pulmonary edema is a form of the acute respiratory distress syndrome.[102] The clinical course cannot be predicted with certainty by the radiographic picture of lung injury. Victims with clear-cut pulmonary difficulties may show minimal radiographic abnormalities, and those with minimal clinical injury may have severely abnormal radiographic pictures.

An interesting form of pulmonary edema found in divers was described by Wilmshurst and colleagues[103] and by Hampson and Dunford.[104] This is manifest as severe dyspnea while diving, associated with arterial hypoxemia, lung congestion, and a normal cardiovascular system. The syndrome may be related to negative-pressure pulmonary edema, a phenomenon well described in the anesthesia literature.[105] Chenaitia et al. reported a case of Takotsubo cardiomyopathy with similar symptoms.[105a]

Neurologic Status

The neurologic status of patients can also be quite varied. To compare results among different groups, a classification scheme has been suggested to describe these patients.[106] In this classification system, patients are placed into category A, B, or C based on their initial neurologic status. Category A patients are awake,

category B patients are blunted, and category C patients are comatose. Within category C, patients are further classified as C1, C2, or C3, depending on their best motor response. The C1 comatose patient has a decorticate response, the C2 patient has a decerebrate response, and the C3 patient has no motor response at all.

Treatment

Restoration of normal neurologic function, although unusual, has been described even after prolonged drowning-induced cardiac arrest.[107,108] As cardiac arrest in this setting is invariably due to hypoxemia and acidosis, the first goal must be to establish a reliable airway and to supply as high an inspired oxygen concentration as possible. Until the results of arterial blood gas determinations are available, 100% oxygen should be provided. Endotracheal intubation is the preferred method for establishing an airway. This approach needs to take into account the possibility of a concomitant unstable neck injury if there is associated trauma,[109] and the risk of aspiration. However, without signs or a history of trauma, the risks of an unstable cervical spine injury are very low.[110] At present there are insufficient data to warrant the routine use of the Heimlich maneuver in near drowning victims.[111]

Patients with cardiac arrest due to drowning can have a profound metabolic acidosis. The doses of bicarbonate required to reverse such acidosis may be far larger than the doses recommended for patients suffering cardiac arrest from primary heart disease.[112] If bicarbonate is to be given, arterial blood gas determinations are necessary to guide precise bicarbonate dosing. Concurrently, a nasogastric tube should be inserted to decompress the stomach, and body temperature readings should be obtained to rule out hypothermia. In the presence of a significantly lowered body temperature, aggressive rewarming measures should be instituted.

Once an adequate airway has been obtained and spontaneous cardiac activity achieved, an adequate arterial P_{O_2} must be established to ensure adequate oxygen delivery to the tissues. Generally, in the drowning victim, hemodynamic stability is relatively easy to achieve. Occasional patients will have marked decreases in blood pressure and cardiac output. The initial therapy for hypotension of most etiologies is a trial of fluids, but for a drowning victim with pulmonary edema, this may not be appropriate. As a result, this group of patients may require invasive hemodynamic monitoring. With knowledge of pulmonary artery wedge pressure and cardiac output, more rational decisions concerning the need for fluids or pressors can then be made. Isolated measurement of the central venous pressure is generally not an accurate method of judging intravascular volume status in the presence of noncardiac pulmonary edema. In the case of immersion pulmonary edema in a diver, the cause of hypoxemia is not water aspiration, and therapy should include diuretics to reduce lung congestion.[104]

Positive end-expiratory pressure is extremely effective in reversing the abnormal ventilation-perfusion relationships leading to hypoxemia. Usually only modest amounts of pressure are necessary to achieve adequate oxygenation, and the improvement in pulmonary function can be quite dramatic. Positive end-expiratory pressure apparently does not alter the course of the underlying pulmonary injury but rather allows for adequate oxygenation while the lung is recovering. It also allows this recovery to take place at a level of inspired oxygen that is not in itself toxic to the lung.[113] Usually the pulmonary injury resolves over a period of 48 to 72 hours, and ventilatory support in most circumstances is relatively brief, unless infection develops. Consequently, in patients who are able to tolerate it, nasal continuous or bilevel positive airway pressure may be a reasonable method for short-term ventilatory support. However, the risk of aspiration is not inconsequential with this treatment.[114] At present there are insufficient data to warrant the use of inverse-ratio ventilation in cases of drowning.[115] It may be prudent to manage some drowning victims with high-flow oxygen delivery systems for relatively brief periods before resorting to more invasive methods of providing adequate oxygenation.

The use of antibiotics in the drowning victim who aspirates ocean water or swimming pool water is generally necessary only for those individuals who become febrile, develop new pulmonary infiltrates, or develop purulent secretions.[116] Prophylactic antibiotics do not improve mortality or decrease morbidity.[92] Because most pulmonary infections in the near drowning victim appear to be hospital acquired, prophylactic antibiotics seem only to select for more resistant organisms.[117] In addition to clinical experience, experimental evidence also suggests that the use of prophylactic antibiotics is not indicated. If the victim aspirates heavily contaminated water with a known or suspected organism (as in the case of aspiration in a hot tub), the use of prophylactic antibiotics may be appropriate. A rare complication of drowning is the aspiration of sand or gravel.[118] Although bronchoscopy for the routine management of the drowning victim is probably not warranted, consideration for this procedure should be made when unexpected difficulties with mechanical ventilation occur.

Routine use of adrenocorticosteroids to treat the lung injury associated with near drowning is unwarranted. Experimental evidence with this form of aspiration as well as others strongly suggests that steroids do not improve the long-term outcome or short-term morbidity.[119] Artificial and animal-derived surfactants,[120] extracorporeal membrane oxygenation,[121] cardiopulmonary bypass,[122] and hypothermia[123] have also been used to treat the pulmonary injury associated with drowning. Any victim who has more than minimal respiratory symptoms, an abnormal chest radiograph, or abnormal arterial blood gas measurements should be observed, because pulmonary damage may not be clinically manifest for several hours after the incident.[124] Nearly all patients who will demonstrate significant problems of gas exchange will do so by 4 to 8 hours after the incident; therefore, consideration for discharge from the emergency department may be appropriate in people who can be observed in this fashion.[125] Indeed, current evidence suggests many victims can safely be

sent home by lifeguards after a water rescue.[126] In the setting of a diving accident, an unconscious victim may have sustained an air embolism as well. Whenever doubt exists, both conditions should be treated simultaneously.

Prognosis

The prognosis for the drowning victim depends mainly on the duration of immersion, the length of the anoxic period, and the degree of damage secondary to the anoxic episode. Patients who arrive at the hospital neurologically intact have an excellent prognosis and should survive neurologically unimpaired. Additionally, the occurrence of an apparent (i.e., undocumented) cardiac arrest does not in itself suggest a poor outcome; however, cardiac arrest that persists through the period of initial first aid and transport to the hospital is a poor prognostic sign. The presence of spontaneous respirations on presentation to the emergency department following cardiac arrest in the field is a good prognostic sign.[127] The duration of immersion correlates with the degree of damage secondary to the anoxic episode and therefore with the outcome. No prognostic test has proven to be a reliable basis for treatment decisions, and predictions concerning outcome cannot be made in the presence of severe hypothermia.

Conclusion

Diving and work in compressed air have produced occupational exposure to hazardous environments for over 100 years. In the past 50 years, diving has become a recreation participated in by millions of individuals throughout the world. Besides the medical support for commercial diving and the unique training needed by physicians who support military diving, any physician may encounter a recreational diver seeking consultation about an illness related to a diving exposure, or medical clearance for diving. Therefore, knowledge of the basic physiology and pathophysiology is important in understanding the patient's illness or evaluation requirements. Occasionally a physician may be confronted with treatment for an acute medical emergency related to diving exposure, such as DCS, arterial gas embolism, or drowning. This chapter provides a basic introduction and a basis for initiating treatment, seeking consultation, or furthering education in this interesting area of environmental medicine.

KEY POINTS

- Middle ear barotrauma is the most prevalent diving injury, while pulmonary barotrauma, although uncommon, is the most severe form of barotrauma injury due to the accompanying cerebral arterial gas embolism.
- Decompression sickness results from dissolution of dissolved inert gas and results in free gas formation in blood and tissues following inadequate decompression from exposure to increased pressure.
- Clinical manifestations of acute decompression sickness include disorders of the brain and spinal cord, musculoskeletal pain, chest pain, dyspnea, and skin rash occurring up to 24 hours following an exposure to increased pressure.
- Treatment of decompression sickness and arterial gas embolism should be instituted with recompression in a hyperbaric chamber as soon as possible after the injury.
- Assessment for fitness for diving includes consideration of the type of diving (recreational, commercial, military), and a number of chronic disorders that can be aggravated by the diving environment.
- Although drowning without aspiration is theoretically possible, the majority of drownings are associated with aspiration of water into the lungs and an accompanying hypoxemia.
- Goals of therapy for a drowning victim include reversing hypoxemia with positive-pressure ventilation and oxygen, treating metabolic acidosis, managing accompanying cardiac arrhythmias, and use of antibiotics when indicated.

References

1. Ryles MT, Pilmanis AA: The initial signs and symptoms of altitude decompression sickness. Aviat Space Environ Med 67:983–989, 1996.
2. Hong SK, Cerretelli P, Cruz JC, et al: Mechanics of respiration during submersion in water. J Appl Physiol 27:537–538, 1969.
3. Johnson LF, Lin YC, Hong SK: Gastroesophageal dynamics during immersion in water to the neck. J Appl Physiol 38:449–454, 1975.
4. Hong SK, Ting EY, Rahn H: Lung volumes at different depths of submersion. J Appl Physiol 23:18–22, 1967.
5. Arborelius M, Balldin UI, Lidja B, et al: Hemodynamic changes in man during immersion with the head above water. Aerosp Med 43:592–598, 1972.

6. Craig AB Jr: Causes of loss of consciousness during underwater swimming. J Appl Physiol 16:583–586, 1961.
7. Pendergast DR, Tedesco M, Nawrocki DM, et al: Energetics of underwater swimming with SCUBA. Med Sci Sports Exerc 28:573–580, 1996.
8. U.S. Navy Department: U.S. Navy Diving Manual, Vol 1, Rev 3: Air Diving (Publication No. NAVSEA 0994-LP-001-9110). Washington, DC: U.S. Navy Department, 1996.
9. Golding FC, Griffiths P, Hempleman HV, et al: Decompression sickness during construction of the Dartford Tunnel. Br J Ind Med 17:167–180, 1960.
10. Francis TJR, Smith DH: Describing Decompression Illness (42nd UHMS Workshop). Kensington, MD: Undersea and Hyperbaric Medical Society, 1991.
11. Hunter SE, Farmer JC: Ear and sinus problems in diving. *In* Bove AA (ed): Bove and Davis' Diving Medicine (4th ed). Philadelphia: WB Saunders, 2004, pp 431–460.
12. Behnke AR: Analysis of accidents occurring in training with the submarine "lung." US Naval Med Bull 30:177–184, 1932.
13. Polak B, Adams H: Traumatic air embolism in submarine escape training. US Naval Med Bull 30:165–177, 1932.
14. Schaefer KE, Nulty WP, Carey C, et al: Mechanisms in development of interstitial emphysema and air embolism on decompression from depth. J Appl Physiol 13:15–29, 1958.
15. Smith R, Neuman T: Elevation of serum creatine kinase in divers with arterial gas embolism. N Engl J Med 330:19–24, 1994.
16. Tetzlaff K, Reuter M, Leplow B, et al: Risk factors for pulmonary barotrauma in divers. Chest 112:654–659, 1997.
17. Neuman TS, Clausen JL: Recommend caution in defining risk factors for barotrauma. Chest 114:1791–1792, 1998.
18. Benton PJ, Francis THR, Pethybridge RJ: Spirometric indices and the risk of pulmonary barotrauma in submarine escape training. Undersea Hyperb Med 26:213–218, 1999.
19. Elliott DH, Harrison JAB, Barnard EEP: Clinical and radiographic features of 88 cases of decompression barotrauma. *In* Shilling CW, Beckett MW (eds): Proceedings of the Sixth Symposium on Underwater Physiology. Bethesda, MD: Federation of American Societies for Experimental Biology, pp 527–535, 1978
20. Neuman TS, Jacoby I, Bove AA: Fatal pulmonary barotrauma due to obstruction of the central circulation with air. J Emerg Med 16:413–417, 1998.
21. Harker CP, Neuman TS, Olson LK, et al: The roentgenographic findings associated with air embolism in sport scuba divers. J Emerg Med 11:443–449, 1993.

21a. Gao GK, Wu D, Yang Y, et al: Cerebral magnetic resonance imaging of compressed air divers in diving accidents. Undersea Hyperb Med 36:33–41, 2009.

22. Smith RM, Van Hoesen KB, Neuman TS: Arterial gas embolism and hemoconcentration. J Emerg Med 12:147–153, 1994.
23. Whelan TR: Facial nerve palsy associated with underwater barotrauma. Postgrad Med J 66:465–466, 1990.
24. Freeman P, Edmonds C: Inner ear barotrauma. Arch Otolaryngol 95:556–563, 1972.
25. Sheridan MF, Hetherington HH, Hull JJ: Inner ear barotrauma from scuba diving. Ear Nose Throat J 78:181, 184, 186–187, 1999.
26. Klingmann C, Praetorius M, Baumann I, Plinkert PK: Barotrauma and decompression illness of the inner ear: 46 cases during treatment and follow-up. Otol Neurotol 28:447–454, 2007.
27. Butler F: Orbital hemorrhage following facemask barotrauma. Undersea Hyperb Med 28:31–34, 2001.
28. Kieser J, Holborow D: The prevention and management of oral barotrauma. N Z Dent J 93:114–116, 1997.
29. Cramer FS, Heimbach RD: Stomach rupture as a result of gastrointestinal barotrauma in a SCUBA diver. J Trauma 22:238–240, 1982.
30. Hayden JD, Davies JB, Martin IG: Diaphragmatic rupture resulting from gastrointestinal barotrauma in a scuba diver. Br J Sports Med 32:75–76, 1998.
31. Vann RD: Mechanisms and risk of decompression sickness. *In* Bove AA (ed): Bove and Davis' Diving Medicine (4th ed). Philadelphia: WB Saunders, 2004, pp 127–164.
32. Bond G: New developments in high pressure living. Arch Environ Health 9:310–314, 1964.
33. Boycott AE, Damant GCC, Haldane J: The prevention of compressed air illness. J Hyg (Cambridge) 8:342–343, 1908.
34. Harvey EN, Barnes DK, McElroy WD, et al: Bubble formation in animals. I. Physical factors. J Cell Comp Physiol 24:1–22, 1944.
35. Bert P: Barometric Pressure: Researches in Experimental Physiology (Hitchcock MA, Hitchcock FA, transl). Columbus Book Co, 1943. Reprinted by the Undersea Medical Society, Bethesda, MD, 1978.
36. Erdman S: Aeropathy of compressed air illness among tunnel workers. JAMA 49:1665–1670, 1907.
37. Hallenbeck JM, Bove AA, Moquin R, et al: Accelerated coagulation of whole blood and cell free plasma by bubbling in vitro. Aerosp Med 44:712–714, 1973.
38. Bove AA, Hallenbeck JM: Changes in blood and plasma volumes in dogs during decompression sickness. Aerosp Med 45:49–55, 1974.
39. Boussuges A, Sainty JM, Juhan-Vague I, et al: Activation of coagulation in decompression illness. Aviat Space Environ Med 69:129–132, 1998.
40. Eftedal OS, Lydersen S, Brubakk AO: The relationship between venous gas bubbles and adverse effects of decompression after air dives. Undersea Hyperb Med 34:99–105, 2007.
41. Bove AA: Basis for drug therapy in decompression sickness. Undersea Biomed Res 9:91–112, 1982.
42. Levin LL, Stewart GJ, Lynch PR, et al: Blood and blood vessel wall changes induced by decompression sickness in dogs. J Appl Physiol 50:944–949, 1981.
43. Spencer MP: Decompression limits for compressed air determined by ultrasonically detected blood bubbles. J Appl Physiol 40:227–235, 1976.
44. Butler BD, Robinson R, Fife C, et al: Doppler detection of decompression bubbles with computer assisted digitization of ultrasonic signals. Aviat Space Environ Med 62:997–1004, 1991.
45. Conkin J, Waligora JM, Foster PP, et al: Information about venous gas emboli improves prediction of hypobaric decompression sickness. Aviat Space Environ Med 69:8–16, 1998.
46. Kumar VK, Waligora JM, Billica RD: Utility of Doppler-detectable microbubbles in the diagnosis and treatment of decompression sickness. Aviat Space Environ Med 68:151–158, 1997.

46a. Pontier JM, Guerrero F, Castagna O: Bubble formation and endothelial function before and after 3 months of dive training. Aviat Space Environ Med 80:15–19, 2009.

47. Moon RE, Camporesi EM, Kisslo JA: Patent foramen ovale and decompression sickness in divers. Lancet 1:513–514, 1989.
48. Wilmshurst PT, Byrne JC, Webb-Peploe MM: Relation between intraatrial shunts and decompression sickness in divers. Lancet 2:1302–1305, 1989.
49. Moon RE, Kisslo JA, Massey EW, et al: Patent foramen ovale (PFO) and decompression illness. Undersea Biomed Res 13(Suppl):15, 1991.
50. Wilmshurst PT, Treacher DF, Crowther A, et al: Effects of a patent foramen ovale on arterial saturation during exercise and on cardiovascular responses to deep breathing, Valsalva manoeuvre, and passive tilt: Relation to history of decompression illness in divers. Br Heart J 71:229–231, 1994.
51. Germonpré P, Dendale P, Unger P, Balestra C: Patent foramen ovale and decompression sickness in sports divers. J Appl Physiol 84:1622–1626, 1998.
52. Torti SR, Billinger M, Schwerzmann M, et al: Risk of decompression illness among 230 divers in relation to the presence and size of patent foramen ovale. Eur Heart J 25:1014–1020, 2004.

52a. Bakovic D, Glavas D, Palada I, et al: High-grade bubbles in left and right heart in an asymptomatic diver at rest after surfacting. Aviat Space Environ Med 79:626–628, 2008.

53. Moon RE, Bove AA: Transcatheter occlusion of patent foramen ovale: A prevention for decompression illness? Undersea Hyperb Med 31:271–274, 2004.
54. Sulaiman ZM, Pilmanis AA, O'Conner RB: Relationship between age and susceptibility to altitude decompression sickness. Aviat Space Environ Med 68:695–698, 1997.
55. Carturan D, Boussuges A, Vanuxem P, et al: Ascent rate, age, maximal oxygen uptake, adiposity, and circulating venous bubbles after diving. J Appl Physiol 93:1349–1356, 2002.

56. Klingmann C, Gonnermann A, Dreyhaupt J, et al: Decompression illness reported in a survey of 429 recreational divers. Aviat Space Environ Med 79:123–128, 2008.
57. Hart AJ, White SAS, Conboy PJ, et al: Open water scuba diving accidents in Leicester: Five years' experience. J Accid Emerg Med 16:198–200, 1999.
58. Neuman TS, Spragg RG, Wagner PD, et al: Cardiopulmonary consequences of decompression sickness. Respir Physiol 41:143–155, 1980.
59. Hallenbeck JM, Bove AA, Elliott DH: Mechanisms underlying spinal cord damage in decompression sickness. Neurology 25:308–316, 1975.
60. Hawes J, Massey EW: Neurologic injuries from scuba diving. Neurol Clin 26:297–308, xii, 2008.
61. Farmer JC, Thomas WG, Youngblood DG, et al: Inner ear decompression sickness. Laryngoscope 86:1315–1326, 1976.
62. McCallum RI, Walder DN: Bone lesions in compressed air workers. J Bone Joint Surg 48:207–235, 1966.
63. Cimsit M, Ilgezdi S, Cimsit C, Uzun G: Dysbaric osteonecrosis in experienced dive masters and instructors. Aviat Space Environ Med 78:1150–1154, 2007.
64. Grover I, Reed W, Neuman T: The SANDHOG criteria and its validation for the diagnosis of DCS arising from bounce diving. Undersea Hyperb Med 34:199–210, 2007.
65. Moon RE: Treatment of decompression illness. *In* Bove AA (ed): Bove and Davis' Diving Medicine (4th ed). Philadelphia: WB Saunders, 2004, pp 195–224.
66. Bove AA, Clark JM, Simon AJ, et al: Successful therapy of cerebral air embolism with hyperbaric oxygen at 2.8 ATA. Undersea Biomed Res 9:76–80, 1982.
67. Longphre JM, Denoble PJ, Moon RE, et al: First aid normobaric oxygen for the treatment of recreational diving injuries. Undersea Hyperb Med 34:43–49, 2007.
68. Reuter M, Tetzlaff K, Hutzelmann A, et al: MR imaging of the central nervous system in diving-related decompression illness. Acta Radiol 38:940–944, 1997.
69. Reul J, Weis J, Jung A, et al: Central nervous system lesions and cervical disc herniations in amateur divers. Lancet 345:1403–1405, 1995.
70. Yoshiyama M, Asamoto S, Kobayashi N, et al: Spinal cord decompression sickness associated with scuba diving: Correlation of immediate and delayed magnetic resonance imaging findings with severity of neurologic impairment—a report on 3 cases. Surg Neurol 67:283–287, 2007.
71. Saumarez RC, Bolt JF, Gregory RJ: Neurologic decompression sickness treated without recompression. Br Med J 1:151–152, 1973.
72. Bennett PB: Inert gas narcosis and HPNS. *In* Bove AA (ed): Bove and Davis' Diving Medicine (4th ed). Philadelphia: WB Saunders, 2004, pp 225–240.
73. Clark JM, Thom SR: Toxicity of oxygen, carbon dioxide, and carbon monoxide. *In* Bove AA (ed): Bove and Davis' Diving Medicine (4th ed). Philadelphia: WB Saunders, 2004, pp 241–260.
74. Bove AA: Cardiovascular disorders and diving. *In* Bove AA (ed): Bove and Davis' Diving Medicine (4th ed). Philadelphia: WB Saunders, 2004, pp 485–506.
75. Massey EW, Greer HD: Neurologic consequences of diving. *In* Bove AA (ed): Bove and Davis' Diving Medicine (4th ed). Philadelphia: WB Saunders, 2004, pp 461–474.
76. Scott DH, Marks AD: Diabetes and diving. *In* Bove AA (ed): Bove and Davis' Diving Medicine (4th ed). Philadelphia: WB Saunders, 2004, pp 507–518.
77. Neuman TS, Bove AA, O'Connor RD, et al: Asthma and diving. Ann Allergy 73:344–350, 1994.
78. Elliott DE: Are Asthmatics Fit to Dive? Kensington, MD: Undersea and Hyperbaric Medical Society, 1996.
79. Caruso JL, Bove AA, Uguccioni DM, et al: Recreational diving deaths associated with cardiovascular disease (abstract). Undersea Hyperb Med 28:76, 2001.
80. Mebane GY, Low N, Dovenbarger J: A review of autopsies on recreational scuba divers: 1989–1992. Undersea Hyperb Med 20(Suppl):70, 1993.
81. Irving L: Bradycardia in human divers. J Appl Physiol 18:489–491, 1963.
82. Irving L, Solandt OM, Solandt DY, Fischer KC: The respiratory metabolism of the seal and its adjustment to diving. J Cell Comp Physiol 7:137–151, 1935.
83. Ackerman MJ, Tester DJ, Porter CJ: Swimming, a gene-specific arrhythmogenic trigger for inherited long QT syndrome. Mayo Clin Proc 74:1088–1094, 1999.
84. McAniff JJ: United States Underwater Fatality Statistics, 1970–82, Including a Preliminary Assessment of 1983 Fatalities (Report No. URI-SSR-84-17). Providence: National Underwater Accident Data Center, University of Rhode Island, 1984.
85. Powers AT, Bass B, Stewart J, et al: A six year review of SCUBA diving fatalities in San Diego County. Undersea Biomed Res 19(Suppl):20, 1992.
86. Driscoll TR, Harrison JA, Steenkamp M: Review of the role of alcohol in drowning associated with recreational activity. Inj Prev 10:107–113, 2004.
87. Idris AH, Berg RA, Bierens JLM, et al: ILCOR Advisory Statement. Recommended guidelines for uniform reporting of data from drowning: The "Ulstein style." Resuscitation 59:45–57, 2003.
88. van Beeck EF, Branche CM, Szpilman D, et al: A new definition of drowning: Towards documentation and prevention of a global public health problem. Bulletin of the World Health Organization 83:853–856, 2005.
89. Modell JH, Davis JH, Giammona ST, et al: Blood gas and electrolyte changes in human near-drowning victims. JAMA 203:337–343, 1968.
90. Modell JH, Bellefleur M, Davis JH: Drowning without aspiration: Is this an appropriate diagnosis? J Forensic Sci 44:1119–1123, 1999.
91. Gu MN, Xiao JF, Huang YR, et al: Study of direct lung injury by sea water in canine models. Di Yi Jun Yi Da Xue Xue Bao 23:201–205, 2003.
92. Modell JH, Moya F, Newby EJ, et al: The effects of fluid volume in sea water drowning. Ann Intern Med 67:68–80, 1967.
93. Giammona ST, Modell JH: Drowning by total immersion: Effects on pulmonary surfactant of distilled water, isotonic saline and sea water. Am J Dis Child 114:612–616, 1967.
94. Yagil Y, Stalnikowicz R, Michaeli J, et al: Near drowning in the Dead Sea: Electrolyte imbalances and therapeutic implications. Arch Intern Med 145:50–53, 1985.
95. Seidel-Ode LR, Almog Y: Near drowning in the Dead Sea: A retrospective observational analysis of 69 patients. Israeli Med J 5:856–858, 2003.
96. Szpilman D: Near-drowning and drowning classification: A proposal to stratify mortality based on the analysis of 1,831 cases. Chest 112:660–665, 1997.
97. Choi G, Kopplin LJ, Tester DJ, et al: Spectrum and frequency of cardiac channel defects in swimming-triggered arrhythmia syndromes. Circulation 110:2119–2124, 2004.
98. Efremidis M, Loukas K, Pappas LK, et al: Swimming-triggered aborted sudden cardiac death in a patient with Andersen-Tawil syndrome. Int J Cardiol 112:e45–e47, 2006.
99. He F, Huang D, Liu L, et al: A novel PCR-DGGE-based method for identifying plankton 16S rDNA for the diagnosis of drowning. Forensic Sci Int 176:152–156, 2008.
100. Kakizaki E, Takahama K, Seo Y, et al: Marine bacteria comprise a possible indicator of drowning in seawater. Forensic Sci Int 176:236–247, 2008.
101. Lheureux P, Vincent JL, Brimioulle S: Fulminant pulmonary edema after near drowning: Remarkably high colloid osmotic pressure in tracheal fluid. Intensive Care Med 10:205–207, 1984.
102. Fine NL, Myerson DA, Myerson PJ, et al: Near drowning presenting as the adult respiratory distress syndrome. Chest 65:347–349, 1974.
103. Wilmshurst PT, Nuri M, Crowther A, Webb-Peploe MM: Cold-induced pulmonary oedema in scuba divers and swimmers and subsequent development of hypertension. Lancet 1:62–65, 1989.
104. Hampson NB, Dunford RG: Pulmonary edema of scuba divers. Undersea Hyperb Med 24:29–33, 1997.
105. Deepika K, Kenaan CA, Barrocas AM, et al: Negative pressure pulmonary edema after acute upper airway obstruction. J Clin Anesth 9:403–408, 1997.

105a. Chenaitia H, Coullange M, Benhamou L, Gerbeaux P: Takotsubo cardiomyopathy associated with diving. Eur J Emerg Med 2009 [Epub ahead of print].
106. Conn AW, Montes JE, Barker GA, et al: Cerebral salvage in near drowning following neurological classification by triage. Can Anaesth Soc J 27:201–210, 1980.
107. Sekar TS, McDonnell KF, Namsirikul P, et al: Survival after prolonged immersion in cold water without neurologic sequelae. Arch Intern Med 140:775–779, 1980.
108. Young RSK, Zaineraitis ED, Dooling EO: Neurologic outcome in cold-water drowning. JAMA 244:1233–1235, 1980.
109. Hwang V, Shofer FS, Durbin DR, Baren JM: Prevalence of traumatic injuries in drowning and near drowning in children and adolescents. Arch Pediatr Adolesc Med 175:50–53, 2003.
110. Watson RS, Cummins P, Quan L, et al: Cervical spine injuries among submersion victims. J Trauma 51:658–662, 2001.
111. Rosen P, Soto M, Harley J: The use of the Heimlich maneuver in near drowning. J Emerg Med 13:397–405, 1995.
112. Guidelines for cardiopulmonary resuscitation (CPR) and emergency cardiac care (ECC). JAMA 268:2171–2302, 1992.
113. Rutledge RR, Flor RJ: The use of mechanical ventilation with positive end expiratory pressure in the treatment of near drowning. Anesthesiology 38:194–196, 1973.
114. Lapinsky SE, Mount DB, Mackey D, et al: Management of acute respiratory failure due to pulmonary edema with nasal positive pressure support. Chest 105:229–231, 1994.
115. Shanholtz C, Brower R: Should inverse ratio ventilation be used in the adult respiratory distress syndrome? Am Rev Respir Dis 149:1354–1358, 1994.
116. Kizer KW: Resuscitation of submersion casualties. Emerg Med Clin North Am 1:643–652, 1983.
117. Hughes JA: Drowning—an overview. J Am Coll Emerg Physicians 6:172, 1977.
118. Dunagan DP, Cox JE, Chang MC, et al: Sand aspiration with near drowning: Radiographic and bronchoscopic findings. Am J Respir Crit Care Med 156:292–295, 1997.
119. Calderwood HW, Modell JH, Ruiz BC: The ineffectiveness of steroid therapy for treatment of fresh-water near drowning. Anesthesiology 43:642–650, 1975.
120. Onarheim H, Vik V: Porcine surfactant (Curosurf) for acute respiratory failure after near-drowning in 12 year old. Acta Anaesthesiol Scand 48:778–781, 2004.
121. Thalmann M, Trampitsch E, Haberfellner N, et al: Resuscitation in near drowning with extracorporeal membrane oxygenation. Ann Thorac Surg 72:607–608, 2001.
122. Eich C, Bräuer A, Timmermann A, et al: Outcome of 12 drowned children with attempted resuscitation on cardiopulmonary bypass: An analysis of variables based on the "Utstein Style for drowning." Resuscitation 75:42–52, 2007.
123. Varon J, Marik PE: Complete neurological recovery following delayed initiation of hypothermia in a victim of warm water near-drowning. Resuscitation 68:421–423, 2006.
124. Putman CE: Drowning: Another plunge. Am J Roentgenol Radium Ther Nucl Med 125:543–549, 1975.
125. Causey AL, Tilelli JA, Swanson ME: Predicting discharge in uncomplicated near-drowning. Am J Emerg Med 18:9–11, 2000.
126. Szpilman D: Near-drowning and drowning classifications: A proposal to stratify mortality based on the analysis of 1,831 cases. Chest 112:660–665, 1997.
127. Jacobsen WK, Mason LJ, Briggs BA, et al: Correlation of spontaneous respiration and neurologic damage in near drowning. Crit Care Med 11:487–489, 1983.

CHAPTER 72

DRUG-INDUCED PULMONARY DISEASE

Fabien Maldonado, MD • Andrew H. Limper, MD

INTRODUCTION

MECHANISMS OF DRUG-INDUCED PULMONARY INJURY

CHEMOTHERAPEUTIC AGENTS
Antibiotic-Derived Agents
Alkylating Agents
Antimetabolites
Nitrosoureas
Podophyllotoxins
Novel and Emerging Agents
Immunomodulatory Agents
Other Chemotherapeutic Agents
Radiation

ANTIMICROBIAL AGENTS
Nitrofurantoin
Sulfasalazine
Miscellaneous Antimicrobial Drugs

ILLICIT DRUGS
Heroin
Methadone and Propoxyphene
Methylphenidate
Cocaine
Talc Granulomatosis

CARDIOVASCULAR DRUGS
Angiotensin-Converting Enzyme Inhibitors
Amiodarone
Protamine
β-Adrenergic Antagonists
Tocainide and Flecainide

ANTI-INFLAMMATORY AGENTS
Aspirin
Other Nonsteroidal Anti-inflammatory Drugs
Gold
Penicillamine
Leflunomide
Biological Agents
Leukotriene Antagonists
Corticosteroids

DRUG-INDUCED SYSTEMIC LUPUS ERYTHEMATOSUS

INHALANTS
Oil
Oxygen

TRANSFUSION-RELATED ACUTE LUNG INJURY

RADIOGRAPHIC CONTRAST MEDIUM-INDUCED LEUKOSTASIS

MISCELLANEOUS DRUGS
Tocolytic-Induced Pulmonary Edema
Hydrochlorothiazide
Methysergide, Bromocriptine, and Cabergoline
Dextran
Amphetaminergic Agents
Esophageal Variceal Sclerotherapy
Tricyclic Antidepressant Overdose
Hydantoin
Dantrolene
Conclusion

INTRODUCTION

Adverse drug reactions have been the object of intense scrutiny since the early 1990s and have been recognized as a top safety priority by health care quality improvement organizations across the United States.[1] A groundbreaking report published in 1999 by the Institute of Medicine only intensified this attention by suggesting that medical errors, including medication errors, may be responsible for 98,000 patient deaths per year in the United States.[2] Specifically, medication errors and preventable adverse drug events may injure 1.5 million people and cost billions of dollars annually. Nonpreventable adverse drug reactions may occur in 2% to 5% of hospitalized patients.[3] Table 72-1 lists the classification of drug reactions.

We know relatively little about the pharmacokinetic properties of drugs in individual patients. Some metabolites last only a fraction of a second and are not measurable. Many drug-related injuries are not reproducible in animals and therefore cannot be studied in depth. Moreover, if a drug administered in the therapeutic dose range caused an adverse reaction in most of the patients who received it, the drug would not be usable. Thus, the very success of many drugs and the fact that only a small percentage of the population reacts adversely to drugs have also limited understanding of pulmonary toxicities. In spite of significant research in pharmacogenetics and drug metabolism, and except for a few instances, pulmonary complications often seem to occur in idiosyncratic fashion, likely determined by the patient's susceptibility profile, the chemical properties of the drug, and other environmental factors. Nevertheless, drug-induced pulmonary disease can be a significant problem. Analysis of a case series of open-lung biopsies in immunocompromised hosts with diffuse pulmonary disease disclosed that 21% of patients had disease that was likely to have been caused by a chemotherapeutic drug. Regulatory agencies have discouraged reports of adverse drug reactions that are neither unexpected nor serious except in the case of drugs recently approved for use. As such, the actual frequency of such adverse events remains unclear. It is estimated that less than 5% of all adverse drug-induced pulmonary diseases and overall less than 1% of serious and unexpected events are formally reported to the Food and Drug Administration (FDA).[1] The number of drugs associated with pulmonary toxicity is steadily increasing.[4] By 2009, more than 350 drugs have been identified to cause adverse pulmonary reactions. These reports are of various nature and quality, ranging from clear toxicities established in large series to isolated case reports of unequal interest. Some of these medications are listed in Table 72-2. To minimize mortality and significant morbidity, it is incumbent upon the clinician to keep in mind at least the more common drugs that may induce pulmonary disease.[5–9]

TABLE 72-1. Classification of Drug Reactions

Allergic or hypersensitivity reactions
Overdosage
Intolerance
Idiosyncratic reaction
Side effects
Secondary effects

MECHANISMS OF DRUG-INDUCED PULMONARY INJURY

Four mechanisms of drug injury to the lungs are recognized: (1) oxidant injury, such as during chronic nitrofurantoin ingestion; (2) direct cytotoxic effects (and these effects may be aggravated by oxidant injuries); (3) deposition of phospholipids within cells, such as produced by cationic amphophilic drugs such as amiodarone; and (4) immune-mediated injury through drug-induced systemic lupus erythematosus (SLE).[7,10–14] Although extensive investigation has been undertaken to look for other forms of immune system–mediated injury, only the SLE induced by drugs has been proven.

Oxidant-mediated injury is believed to play a significant role in several of the drug-induced pulmonary diseases, namely, the chronic fibrosis related to nitrofurantoin, and possibly many of the chemotherapeutic drug–induced pulmonary injuries.[15] In vitro, nitrofurantoin is capable of generating toxic oxygen-derived substances such as hydrogen peroxide, hydroxyl radical, superoxide, and singlet oxygen. These oxygen radicals generate singlet electron transfers that disrupt critical cell functions. Nitrofurantoin may produce pulmonary fibrosis by accelerating the generation of oxygen radicals within lung cells and by overwhelming the normal antioxidant protective mechanisms. This in turn incites inflammatory and fibrotic reactions.

It is postulated that chemotherapeutic drug injury represents a direct toxic reaction. Considerable research has been done on bleomycin-induced lung injury. Bleomycin does not have a major effect on the bone marrow or on immunocompetency. The exact mechanism of bleomycin lung injury is not fully known. However, epithelial cells in the lung and skin contain lower levels of a specific inactivating enzyme against bleomycin than do epithelial cells in other organs. Thus, the drug is allowed to accumulate within these cell and induce deoxyribonucleic acid (DNA) fragmentation.[11] Because bleomycin toxicity appears to be related to dosage and age, the toxicity probably is related to the levels of inactivating enzyme in certain individuals. Bleomycin apparently overwhelms this enzyme with a large total dose. It is also likely that there is a relative deficiency of the enzyme in individuals over 70 years of age. Some individuals of any age may be relatively deficient in this enzyme and hence especially sensitive to bleomycin lung toxicity.

The first cells to be affected by bleomycin are the type I alveolar epithelial cells. Repair of injured type I cells

TABLE 72-2. Classification of Drug-Induced and Related Pulmonary Diseases by Type of Medication

CHEMOTHERAPEUTIC
Cytotoxic
- Azathioprine
- *Bleomycin
- Busulfan
- Chlorambucil
- Cyclophosphamide
- Etoposide
- Interleukin-2
- Melphalan
- *Mitomycin C
- Nitrosoureas
- Procarbazine
- Tumor necrosis factor
- Vinblastine
- Zinostatin

Noncytotoxic
- *Bleomycin
- *Cytosine arabinoside
- *Gemcitabine
- *Methotrexate
- *Procarbazine

ANTIBIOTIC
- *Amphotericin B
- Nitrofurantoin
  - *Acute
  - Chronic
- Sulfasalazine

ANTI-INFLAMMATORY
- *Acetylsalicylic acid
- Gold
- Interferons
- Leukotriene antagonists
- Methotrexate
- Nonsteroidal anti-inflammatory agents
- *Penicillamine

ANALGESIC
- *Heroin
- *Methadone
- *Naloxone
- *Placidyl
- *Propoxyphene
- *Salicylates

CARDIOVASCULAR
- *Amiodarone
- Angiotensin-converting enzyme inhibitors
- Anticoagulants
- *β-Blockers
- Dipyridamole
- Flecainide
- *Protamine
- Tocainide

INHALANT
- Aspirated oil
- *Oxygen

INTRAVENOUS
- *Blood products
- *Ethanolamide maolate (sodium morrhuate)
- Ethiodized oil (lymphangiogram)
- Talc

MISCELLANEOUS
- Appetite suppressants
- Bromocriptine
- *Complement-mediated leukostasis
- Dantrolene
- *Hydrochlorothiazide
- Methysergide
- Radiation
- Systemic lupus erythematosus (drug-induced)
- *Tocolytic agents
- *Tricyclics
- L-Tryptophan

*Typically present as acute or subacute respiratory insufficiency.

is accomplished by type II cells, which proliferate and differentiate into type I cells to restore the normal air-blood barrier. The vulnerability of the type II cell to bleomycin depends on the state of its cell cycle. If it is in the resting G_0 phase, the cell appears resistant to bleomycin injury, whereas if the cell is proliferating or differentiating, atypical exaggerated metaplasia occurs. Consequently, with net loss of type I alveolar epithelial cells, a fibroblastic reparative process is initiated. Bleomycin can also stimulate fibroblasts directly to increase collagen synthesis. Type I cells are particularly vulnerable to injury by bleomycin, but in the steady state, the type II cell is generally considered to be injury resistant. By dosing bleomycin repeatedly, the likelihood increases that type II cells will be exposed during their vulnerable proliferative period.

Additional information indicates that bleomycin injures lung cells through the generation of reactive oxidants.[16] Antioxidant defenses may be of value in the amelioration of bleomycin-induced lung toxicity.[17] Accordingly, breathing supplementary oxygen potentiates bleomycin-induced oxidant injury. However, not all of the reactions to chemotherapeutic drugs are as dose and age related as bleomycin, nor does oxygen potentiate the toxicity of most drugs.

Amiodarone has brought to light another potential mechanism of drug-induced lung injury. Amiodarone has been demonstrated to produce phospholipidosis in alveolar macrophages and type II cells. In amiodarone pulmonary toxicity, there is a marked accumulation of abnormal alveolar macrophages containing lamellar inclusions, which in turn contain a variety of phospholipids.[12] It is not known whether this phospholipidosis is directly related to the accompanying interstitial pneumonitis. There are more than two dozen cationic amphophilic drugs known to induce a phospholipid storage disorder in cells, particularly in the lungs. It is believed that these drugs impair phospholipid catabolism. The process is reversible with discontinuation of the agent.

Drug-induced SLE is another established mechanisms of drug-induced pulmonary disease.[13] There are two groups of drugs associated with drug-induced SLE. The first group commonly elicits antinuclear antibody formation in a large percentage of the persons taking the drug, but only a small percentage of these persons develop clinical symptoms of SLE. The second group is made up of numerous drugs that have been reported to induce antinuclear antibodies only rarely, but virtually all persons afflicted develop SLE.

In drug-induced SLE, the antibodies are primarily directed against histones. In contrast, during idiopathic SLE, the antinuclear antibodies are heterogeneous and consist of antibodies recognizing native DNA, histones, and nonhistone ribonuclear proteins, as well as antibod-

ies formed against extranuclear host components such as clotting factors.[13] Exactly how drugs incite antibodies to nuclear protein is not clear, because these agents are in themselves nonimmunogenic. A current hypothesis proposes that the drug acts as an adjuvant or immunostimulant to augment responses to "self" antigens. Autoimmunity then develops from the clonal expansion of cell-reacting lymphocytes, which are ordinarily held in check by a balance of helper and suppressor influences.

CHEMOTHERAPEUTIC AGENTS

Chemotherapeutic agent are extensively used in solid and hematologic malignancies, but also are increasingly employed for their immunosuppressive properties in the management of various inflammatory disorders. Because of the severity of diseases in which they are employed, higher risk for potential adverse lung reactions are typically tolerated, hence pulmonary complications of chemotherapy are not uncommon in the clinical setting. It is, however, a diagnostic challenge for the clinician who has to determine the responsibility of the chemotherapeutic agent usually on the basis of a diagnosis of exclusion and decide to discontinue it, with the risk of depriving his or her patient of a potentially beneficial therapy. Oncology patients are prone to a number of pulmonary complications irrespectively of their chemotherapy regimen, including opportunistic infections, atypical presentations of common lung infections, radiation-induced lung injury, cardiogenic or noncardiogenic pulmonary edema, and, of course, metastatic lung involvement. The various presentations of drug-induced pulmonary disease must be rapidly differentiated from these other etiologies whose clinical presentations, including fever and diffuse radiographic abnormalities, may be extremely similar to chemotherapy-induced pulmonary reactions. Furthermore, virtually all histopathologic patterns have been described in the context of chemotherapy-induced lung disease, including usual interstitial pneumonia, nonspecific interstitial pneumonia, desquamative interstitial pneumonia, lymphocytic interstitial pneumonia, bronchiolitis obliterans with or without organizing pneumonia, and diffuse alveolar hemorrhage. Less commonly, non-necrotizing granulomatosis (methotrexate), alveolar proteinosis (busulfan), and pulmonary veno-occlusive disease (nitrosoureas) have also been reported. In addition, combination regimens are generally the rule, making it sometimes difficult to incriminate one agent over the other. Chemotherapy-associated pulmonary reactions have become a major problem, particularly in relation to therapeutic regimens containing bleomycin, methotrexate, cyclophosphamide, and a host of newer agents (Table 72-3).

Consistent criteria for drug-induced lung disease have not been officially established. Uncertainty that a given respiratory complication is linked to a particular drug is generally present. Furthermore, confirmation with rechallenge is to be avoided since it is often neither practical nor generally ethical. Hence, the diagnosis of cytotoxic lung damage rests upon an appropriate history of drug exposure, histologic evidence of lung injury, and, most importantly, the exclusion of other causes of the lung damage. Pulmonary manifestations are rarely specific enough to clearly point toward a drug effect. There is no single diagnostic test or tissue biopsy that can definitively confirm the diagnosis of chemotherapy-associated lung disease. Thus, a careful and thorough evaluation to eliminate the possibilities of other conditions producing these effects, particularly infection, is warranted. Clinicians caring for these patients must be aware of myriad chemotherapeutic agents that can injure the lungs. It is estimated that 10% to 20% of patients undergoing some type of chemotherapy will develop respiratory symptoms directly related to their treat-

TABLE 72-3. Pharmacologic Action of Selected Chemotherapeutic Agents with Associated Pulmonary Toxicities

ANTIBIOTIC-DERIVED AGENTS
Bleomycin
Mitomycin C

ALKYLATING AGENTS
Busulfan
Cyclophosphamide
Chlorambucil
Melphalan

ANTIMETABOLITES
Methotrexate
6-Mercaptopurine
Azathioprine
Cytosine arabinoside
Gemcitabine
Fludarabine

NITROSOUREAS
Bischloroethyl nitrosourea (BCNU)
Chloroethyl cyclohexyl nitrosourea (CCNU)
Methyl-CCNU

PODOPHYLLOTOXINS
Etoposide
Paclitaxel
Docetaxel

NOVEL ANTITUMOR AGENTS
All-*trans* retinoic acid (ATRA)
Gefitinib
Imatinib mesylate
Irinotecan

IMMUNE MODULATORY AGENTS USED IN MALIGNANCY
Interferons
Interleukin-2
Tumor necrosis factor-α

OTHER MISCELLANEOUS CHEMOTHERAPY AGENTS
Procarbazine
Zinostatin
Vinblastine

ment.[5,9] Thus, the clinician should maintain a high index of suspicion, and carefully screen for other competing causes of pulmonary injury that may affect these immune-compromised patients.

The clinical presentation of many chemotherapy drug effects is quite similar, with the exception that some present more acutely, whereas others tend to be more insidious in their onset. In general, nonproductive cough, dyspnea, and often fever begin weeks to years after the agent is first administered. Occasionally, symptoms may presently acutely as in the case of hypersensitivity reactions, or in a delayed fashion occurring years after discontinuation of the drug, perhaps reactivated by radiotherapy, a process called "radiation recall." Fever is common with most chemotherapeutic drug–induced pulmonary injury, but it may not be consistently present. Chills are usually absent and weight loss is often present. The chest radiograph in cases of chemotherapy-induced lung disease may be unremarkable for days or weeks before showing typical changes of a diffuse interstitial infiltrative pattern. Alternatively, there may be a diffuse mixed alveolar-interstitial pattern, which may occasionally be useful in recognizing early drug effects (Fig. 72-1). Auscultation of the lungs will frequently reveal crackles, which are also nonspecific. In some instances, small pleural effusions may be present during adverse drug reactions, but these are not consistently present. Clubbing has not been reported in any chemotherapeutic pulmonary toxicity.

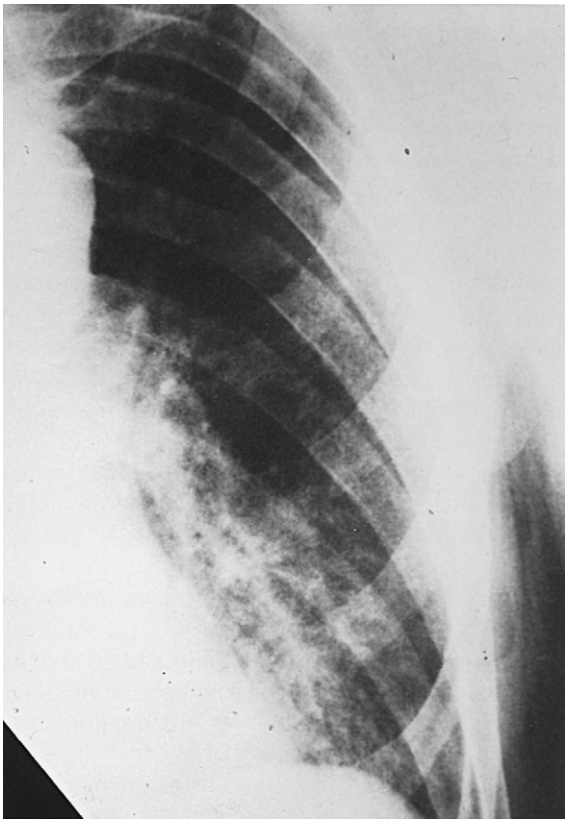

FIGURE 72-1 ■ A close-up chest roentgenogram showing an alveolar interstitial pattern that is characteristic but not diagnostic of cytotoxic lung disease.

The results of lung function studies are abnormal in almost all patients with cytotoxic drug–induced lung disease when compared with pretreatment testing. The carbon monoxide diffusing capacity may decrease before reduced volumes are detected. In addition, this decrease in carbon monoxide diffusing capacity may precede the onset of symptoms and radiographic changes by days or weeks.[5] In several prospective investigations, diffusing capacity has been used to detect early onset of pulmonary reactions, at which time the agents are discontinued to minimize progression into overt clinical disease.[18] Bronchoalveolar lavage may be another means of assessing early lung damage from these drugs; however, the results are often variable. In general, the greatest utility of bronchoalveolar lavage is to exclude infection.

Some reactions related to chemotherapeutic agents have been associated with cytologic atypia in affected pulmonary tissues. The histologic finding of markedly atypical type II pneumocytes, with relative fewer type I cells, has been reported. These type II pneumocytes may appear "bizarre"; however, the nuclear-to-cytoplasmic ratio remains normal, and there is no increase in mitotic activity in these cells.[7] Therefore, these changes should not be interpreted as a harbinger of malignancy. The simple presence of cytologic atypia cannot by itself definitely establish chemotherapy-associated lung injury. For instance, cytologic atypia may be present in occasional busulfan-treated patients without radiographic, clinical, or pathologic evidence of lung injury. In addition, cellular atypia can also be observed in the setting of a severe viral infection. In addition, tissue examination in chemotherapy-associated lung injury may demonstrate an inflammatory cell infiltrate in the interstitium as well as deposition of collagen in the septal walls. Lung remodeling can progress to severe fibrosis, resulting in respiratory insufficiency.

Antibiotic-Derived Agents

Bleomycin

Bleomycin is an antibiotics chemotherapeutic agent that was isolated in 1966 from *Streptomyces verticillus*. Its pulmonary toxicity was recognized early and has since been one of the main factors limiting its use in the clinical setting. It is by far the best understood type of drug-induced toxicity and represents in many aspects the prototype of "chemotherapy lung." The incidence of bleomycin lung toxicity ranges anywhere from zero to 46%, and pulmonary function testing and chest radiographs reveal that 20% of patients treated with bleomycin develop overt pulmonary disease, and as many as 3% die from pulmonary consequences of bleomycin therapy.[5,19]

The mechanisms by which bleomycin exerts its antineoplastic effects are diverse. Direct cytotoxic effect, prevention of neoangiogenesis by the tumor, stimulation of the production of various cytokines, and free radical generation via formation of a complex between ferrous

iron and oxygen are likely the most important.[20,20a,20b,20c] The latter effect may explain worsened bleomycin toxicity with high fraction of inspired oxygen. This is often a problem during anesthesia and in the postoperative recovery period.[21,22] This sensitivity to supplemental oxygen may persist for months and, perhaps, years after discontinuation of the drug. Several other contributing factors have been described. Perhaps one of the most consistent features of bleomycin-induced lung disease is the concept of cumulative toxicity. The incidence of pulmonary toxicity is significantly greater in those who have received a cumulative dose of over 450 units, with a 10% death rate in those having received a total dose greater than 550 units of bleomycin. However, doses as little as 50 units may occasionally suffice, especially when other synergic factors are present. Rapid rates of delivery by the intravenous route may also play a role, and slower infusion rates as well as intramuscular injections have been suggested.

Bleomycin is metabolized primarily by the kidneys. Hence, renal failure predisposes to impaired metabolism of the drug and increased toxicity. It is also inactivated by an enzyme, bleomycin hydrolase, present in most tissues except for the lungs and skin. This may explain the scleroderma-like skin changes occasionally observed with bleomycin. Radiotherapy is itself a common cause of pulmonary complications and is also thought to promote the generation of free radicals, toxic to both the tumor cells and surrounding tissues. The concomitant use of bleomycin and radiotherapy may be synergistic. In addition, as stated earlier, treatment with bleomycin may reactivate prior radiation-induced lung disease, a process called radiation recall. Pulmonary toxicity is also increased in patients over 70 years of age and in those with preexisting lung disease. There is good evidence that pediatric patients may also be at increased risk, with 70% of children treated with bleomycin for rhabdomyosarcoma developing pulmonary toxicity in one study.[23] Impaired or immature ability to process free radicals and inadequate kidney function may explain these differences. Finally, bleomycin toxicity may be synergistically increased by several other chemotherapeutic agents, including cyclophosphamide.

Although of uncertain value, determination of pretreatment carbon monoxide diffusing capacity and its frequent monitoring have been suggested in an attempt to predict subsequent clinical deterioration. Progressive fall in the carbon monoxide diffusing capacity should prompt withdrawal of further bleomycin administration.[24] Vital capacity and pulmonary capillary blood flow may be better predictors of lung toxicity.[25] In addition, the enhanced sensitivity of computed tomography scanning may also be useful in establishing an early diagnosis of bleomycin pneumonitis. In one series of 100 patients receiving bleomycin, thoracic computed tomography scans were abnormal in 38%, whereas the chest radiographs were abnormal in only 15%.[26] Serial imaging studies are not recommended in the absence of specific symptoms.

One study demonstrated that, if the patient survives the acute injury from bleomycin, pulmonary findings might improve substantially over time.[27] However, if significant fibrosis is present, the process may progress insidiously despite the administration of corticosteroids. Histological, end-stage bleomycin pneumonitis may be indistinguishable from idiopathic usual interstitial pneumonitis.

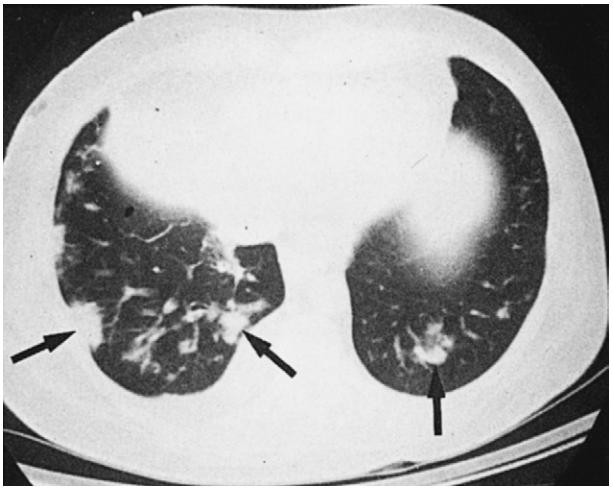

FIGURE 72-2 ■ A computed tomography scan of bleomycin pneumonitis showing a nodular pattern (*arrows*). The histologic features of this form of bleomycin-induced lung injury are typical of bronchiolitis obliterans with organizing pneumonitis.

Other forms of bleomycin-induced lung disease have been described, albeit less common. Hypersensitivity reactions are possible with an association of fever and peripheral blood or bronchoalveolar lavage eosinophilia.[5,18] Discontinuation of bleomycin and initiating corticosteroids usually brings about rapid reversal of this hypersensitivity variant of bleomycin pneumonitis.

An additional rare, but clinically important, presentation of bleomycin pneumonitis can occur: the clinical presentation of nodular pulmonary lesions mimicking tumor metastasis (Fig. 72-2).[28,29] These reactions to bleomycin have been described in the setting of lymphoma or seminoma, requiring surgical biopsy to differentiate bleomycin-associated lung injury from recurrence of the primary malignancy. These nodular lesions from bleomycin often exhibit the histologic pattern of bronchiolitis obliterans with organizing pneumonia.[7] Similar reactions have been described in association with other chemotherapeutic agents, including methotrexate, cyclophosphamide, chlorambucil, mitomycin, and interferon, and also with nonchemotherapeutic agents such as amiodarone, gold, and nitrofurantoin, and even in cases of radiation toxicity.[7] Pneumothorax and pneumomediastinum have also been described.

In suspected cases of bleomycin lung toxicity, discontinuation of the drug is warranted. Administration of corticosteroids is often recommended, but the evidence for this remains anecdotal at best. It would seem prudent to pay particular attention to avoid high fractions of inspired oxygen and concomitant radiotherapy and to monitor the kidney function carefully during the duration of treatment.

Mitomycin C

Mitomycin C is another antibiotic chemotherapeutic agent associated with pulmonary toxicity, which shares features similar to those induced by bleomycin. It has been employed in the management of bladder tumors, lung cancer, anal canal cancer, metastatic breast carcinoma, metastatic liver tumors, and esophageal malignancies. One series estimated the incidence of mitomycin-induced pneumonitis to be approximately 8%, with two additional series suggesting the incidence ranged from 12% to as high as 39%.[30,31] Similar to bleomycin-induced lung toxicity, the cumulative dose appears associated with the incidence of pulmonary manifestations in a linear fashion, with pulmonary fibrosis unlikely at doses less than 30 mg/m^2. Again, high fraction of inspired oxygen and radiotherapy may exacerbate this phenomenon. Concomitant administration of other chemotherapeutic agents such as bleomycin, doxorubicin, or cyclophosphamide may synergistically enhance pulmonary toxicity.

The symptomatology, radiographic abnormalities, and histologic findings of mitomycin-induced pneumonitis are similar to those of other alkylating drug toxicities. However, it has been suggested that the carbon monoxide diffusing capacity may not fall prior the onset of clinical symptoms, making it an unreliable predictor of overt lung disease.[31] In addition, a favorable response to corticosteroid therapy has also been quite dramatic in many of these patients, possibly greater than in other forms of chemotherapy-associated lung injury.

In addition to mitomycin-induced pneumonitis, there are reports of an unusual reaction to mitomycin C consisting of microangiopathic hemolytic anemia with associated noncardiogenic pulmonary edema and renal failure, in particular when associated with 5-fluorouracil.[32] This may be associated with pulmonary hypertension. Most of these patients developed side effects between 6 and 12 months after beginning mitomycin C chemotherapy. Up to one half of these patients evolve into the acute respiratory distress syndrome, with mortality as high as 95% in some series. The mortality in patients with mitomycin C–associated hemolytic uremic syndrome who do not develop acute respiratory distress syndrome is still in the range of 50%. In some instances, this unusual drug reaction appears to be precipitated by blood transfusions. Microangiopathic changes are present in the lungs and kidneys with intimal hyperplasia of the arterioles, along with prominent nuclear atypia of the capillary cells and capillary fibrin thrombi. Treatment is essentially supportive, with initiation of plasma exchange with or without dialysis and corticosteroids when deemed appropriate.

Other Antibiotic Chemotherapeutic Agents

A variety of other antibiotic chemotherapeutic agents have been associated with respiratory complications, although the very nature of combined chemotherapeutic regimens makes it difficult to definitely attribute the responsibility of one drug over another. Doxorubicin is an anthracycline agent notorious for causing cumulative cardiotoxicity with possible cardiogenic pulmonary edema. Rare cases of interstitial pneumonias have also been described, usually in combination with other drugs, typically with mitomycin C. Organizing pneumonia has rarely been reported. Infusion reactions with dyspnea may be observed in 5% to 10% of patients treated with pegylated liposomal doxorubicin. Epirubicin is a similar compound with fewer side effects. Pulmonary complications are rare but may occur in conjunction with other chemotherapeutic agents. Mitoxantrone is an anthracedione inhibitor of topoisomerase II essentially used in the treatment of multiple sclerosis. Rare cases of subacute interstitial pneumonias have been described. Cases of reactivation of prior radiation pneumonitis have also been observed with actinomycin D.[23]

Alkylating Agents

Busulfan

Busulfan has been used for the management of chronic myeloproliferative disorders. It was discovered in 1961 and found to be responsible for significant pulmonary toxicity shortly after. The average duration from the initiation of therapy to the onset of respiratory symptoms is roughly 3.5 years, ranging between 8 months and as late as 10 years. However, busulfan pulmonary toxicity can occur as soon as 6 weeks following initiation of therapy. The incidence of busulfan pulmonary toxicity is estimated to be 6%, with a reported range of 2.5% to 43%.[33] Busulfan-induced lung toxicity distinguishes itself from other forms of chemotherapy-induced lung disease in many ways. The mortality rate is extremely high, in the range of 80%.[23] No effective therapy has been identified, and discontinuation of the drug with or without initiation of corticosteroid therapy, although recommended, is of unclear value. No obvious aggravating factors have been identified, except perhaps the concomitant administration of other chemotherapeutic agents or radiotherapy. Age and cumulative dose do not seem to play any important role.

Dyspnea, fever, and cough begin in a more insidious fashion with busulfan than with many other chemotherapy lung toxicities. Such symptoms have even been reported to begin months after busulfan therapy has been discontinued. The chest radiograph in busulfan toxicity reveals a combined alveolar and interstitial process to a greater degree than in other chemotherapy reactions. This is likely due to a high degree of desquamation of injured epithelial cells into the alveolar spaces. This alveolar debris may be so extensive as to suggest alveolar proteinosis in some patients receiving busulfan. This form of alveolar proteinosis is more refractory to therapeutic lavage than is idiopathic alveolar proteinosis.

Cyclophosphamide

Cyclophosphamide is widely included in combination chemotherapy for hematologic malignancies and solid

tumors, including breast cancer. The incidence of pulmonary toxicity is estimated at around 1%, although accumulating evidence suggests that it may be largely underestimated. A case series from a large tertiary referral center only identified six patients over 20 years in whom cyclophosphamide was the only factor contributing toward pulmonary injury.[34] Clinical features of cyclophosphamide-associated pulmonary toxicity include fever, dyspnea, cough, gas-exchange abnormalities, parenchymal infiltrates, and pleural thickening. Two patterns of cyclophosphamide-induced lung toxicity have been described. First, an early-onset pneumonitis can occur within the first 1 to 6 months after institution of therapy. This form generally responds to withdrawal of cyclophosphamide. In contrast, a late-onset pneumonitis may develop after months or even years of therapy, and result in progressive lung fibrosis and bilateral pleural thickening. This late-onset variety unfortunately has minimal response to withdrawal of cyclophosphamide or to corticosteroid therapy.[34] The dose of cyclophosphamide and development of lung disease are not clearly related. Supplemental oxygen and radiotherapy may increase the likelihood of lung manifestations. Likewise, concomitant administration of other agents such as bleomycin, and perhaps carmustine, in preparation before bone marrow transplantation seem to accentuate the phenomenon. There have also been very rare reports of negative rechallenge with cyclophosphamide without subsequent recurrence of the pulmonary toxicity. For obvious reasons, this is generally not recommended.

Chlorambucil

This agent has been prescribed primarily for chronic lymphocytic disorders. The clinical presentation, chest radiographic abnormalities, and histologic features of chlorambucil-associated pneumonitis are remarkably similar to those described in other alkylating agent–induced pulmonary toxicities.[9] Cumulative doses in excess of 2 g seem to increase the risk significantly. The presentation is usually insidious, occurring 6 months to a year or more after the start of therapy. Surveillance of lung function, particularly diffusing capacity, may be of benefit in anticipating which patients will deteriorate and require discontinuation of the agent. Few data are available on the efficacy of corticosteroid therapy in chlorambucil-related lung toxicity.

Melphalan

Melphalan has been enlisted in the treatment of multiple myeloma. There have been relatively few well-documented cases of pulmonary toxicity associated with melphalan.[35] The course of melphalan-associated pulmonary injury varies from acute to more subacute in tempo. Patients present with insidious to abrupt onset of dyspnea, cough, and frequently fever. There are no particular clues for predicting which patients will develop side effects. The incidence of pulmonary side effects from melphalan must be generally low, in view of the fact that this agent has been widely employed in the long-term management of myeloma.

Ifosfamide

Ifosfamide is structurally related to cyclophosphamide and has been used in for the treatment of a variety of solid tumors, including lung, testicular, and breast cancer. Case reports of subacute interstitial pneumonias can be found in the literature, although the responsibility of ifosfamide remains unclear, as it was used in combination with other chemotherapeutic agents such as docetaxel. One case of fatal acute pneumonitis primarily due to ifosfamide has been reported. A case of methemoglobinemia has also been described, presumably secondary to the interaction between 4-thioifosfamide, a metabolite of ifosfamide, and glutathione and resultant oxidative stress.[36]

Other Alkylating Agents

Procarbazine is primarily used in the treatment of Hodgkin's lymphoma and glioblastoma multiforme. Rare cases of interstitial pneumonias have been reported, sometimes characterized by significant eosinophilia suggesting a hypersensitivity reaction. Progression to widespread and irreversible fibrosis seems rare.[37]

Oxaliplatin has been associated with laryngeal dysesthesia and was thought to be responsible for the development of diffuse alveolar damage, often in association with 5-fluorouracil. More typically, severe anaphylactic reactions during infusion of the drug can occur in about 1.3% of the cases. Eosinophilic pneumonia has also been rarely reported.[38,39]

Temozolomide is a second-generation alkylating agent now considered standard of care as an adjuvant therapy for glioblastoma in association with radiotherapy. It is also used in the treatment of metastatic melanoma. Few respiratory side effects have been described, mainly pharyngitis, sinusitis, cough, upper respiratory tract infection, and dyspnea. Pneumonitis was found to occur in up to 4.8% of patients in Phase II trials. One case of organizing pneumonia that resolved after discontinuation of treatment was described.[40]

Several cases of mild pneumonitis have been described with chlorozotocin, an alkylating agent used in the treatment of neuroendocrine tumors. All cases resolved with discontinuation of the drug and administration of corticosteroids.[41]

Antimetabolites

Methotrexate

Methotrexate is present in many combination regimens for malignancies, and also is used extensively for nonmalignant conditions, including psoriasis and rheumatoid arthritis. It interferes with the metabolism of folic acid, hence specifically targeting replicating cells and leading to a variety of well-described adverse effects, including bone marrow suppression, mucositis, alopecia, and

gastrointestinal manifestations. Pulmonary toxicity is thought to occur in about 10% of all patients treated, but is fortunately rarely fatal. Dyspnea, nonproductive cough, and fever usually commence a few days to several weeks after initiation of therapy. However, in rare cases, symptoms may be observed a few months or years after onset of therapy.[42] Methotrexate-associated pneumonitis is almost always reversible with or without the addition of corticosteroids. Eosinophilia is seen in at least half of the cases, and the disease is therefore believed to represent a hypersensitivity reaction.[5] The intriguing feature of this reaction is that the drug may be reinstituted following resolution of methotrexate pneumonitis without necessarily triggering a subsequent recurrence of symptoms or findings. In about one third of the patients, weakly formed granulomas are identified in lung biopsy, which is very unusual in other forms of chemotherapy-associated lung disease.[7] This in addition to the hilar lymphadenopathy occasionally present may mimic the typical manifestations of sarcoidosis. There is no cellular atypia, such as is seen in many other cytotoxic drug toxicities.

The chest radiograph tends to reveal a homogeneous infiltrate throughout all lung fields. Hilar adenopathy or pleural effusion occurs in at least 10% to 15% of patients with methotrexate lung toxicity. In distinct contrast to most of the other chemotherapy pulmonary toxicities, prospective investigations of patients receiving methotrexate have not demonstrated a diminished diffusing capacity that might predate subclinical toxicity. In addition, pulmonary toxicity in response to methotrexate does not appear to be dose related. There have been a few reports of fatal reactions occurring either from intrathecal methotrexate or from oral ingestion after previous intrathecal injections. Two other important manifestations associated with methotrexate should be mentioned. Opportunistic infections related to T-cell deficiency need to be excluded, in particular *Pneumocystis* pneumonia, which has been reported in a number of patients receiving methotrexate, either alone or in combination with corticosteroids.[43] Peculiar Epstein-Barr virus–related lymphomas that typically resolve after discontinuation of treatment have also been reported and may be directly related to an alteration in immune surveillance induced by methotrexate (as seen in posttransplantation lymphoproliferative disorders). The clinical presentation, chest radiography, and other clinical features can be quite similar to methotrexate lung.[43]

Azathioprine and 6-Mercaptopurine

There are over two dozen case reports of azathioprine-associated pneumonitis. However, the net overall incidence must be quite low, considering the widespread use of this agent for neoplastic as well as non-neoplastic conditions.[35] Nevertheless, the possibility of an azathioprine pneumonitis must be considered in any individual receiving this agent. Azathioprine is metabolized to 6-mercaptopurine, and there have been a handful of reports detailing cytotoxic interstitial pneumonitis in association with this metabolite.[6] However, most of these patients have also received other agents that potentially could be implicated in the lung injury described.

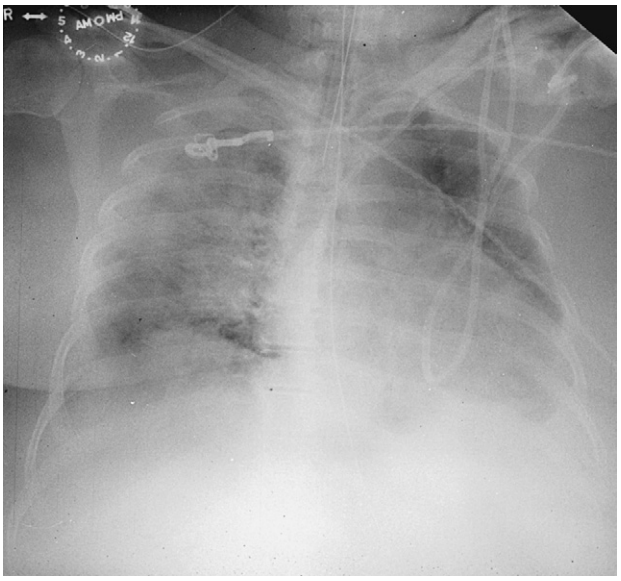

FIGURE 72-3 ■ A chest radiograph of a 44-year-old woman showing acute noncardiac pulmonary edema that resulted from cytosine arabinoside–induced pulmonary disease. Histologic examination typically demonstrates intense intra-alveolar proteinaceous material forming hyaline membranes, but little other reaction.

Cytosine Arabinoside

Cytosine arabinoside (ara-C) is a cytotoxic agent used to induce remission in acute leukemia and other hematologic malignancies prior to bone marrow transplantation. Intensive ara-C treatment regimens have been associated with rapidly fatal noncardiac pulmonary edema (Fig. 72-3).[6] Histologic examination of lung tissue during ara-C pulmonary toxicity reveals substantial accumulation of intra-alveolar proteinaceous material without the cellular atypia and mononuclear infiltration described with other cytotoxic drugs. In two large series, 13% to 28% of the patients with toxicity developed respiratory distress during the administration of the drug, and nearly one half developed symptoms within a month of completing drug administration. The mechanism underlying this reaction is unknown, and the associated mortality is high. Treatment for ara-C pulmonary toxicity is largely supportive, with mechanical ventilation, careful management of fluid status, and surveillance for superimposed infectious complications.

Gemcitabine

Gemcitabine is a pyrimidine analogue, with structure and activities similar to ara-C. It is highly active against non–small cell lung cancer, as well as breast, pancreatic, and ovarian cancers. It is usually well tolerated, with the most prevalent toxicity being bone marrow suppression,

FIGURE 72-4 ■ A computed tomography image of an individual with gemcitabine-induced lung disease. The pattern is a mixed alveolar and interstitial infiltration.

as well as nausea, rash, transaminase elevation, and edema in some cases. The evidence of pulmonary toxicity in association with gemcitabine has only recently emerged, and the incidence has probably been underestimated. Dyspnea has been reported in 10% of treated patients, with severe dyspnea reported in up to 5%.[44-46] Noncardiogenic pulmonary edema is thought to occur in 0.1% to 7% of all patients treated.[47] There are three major patterns of respiratory involvement in gemcitabine-related pulmonary toxicity. The first pattern is a nonspecific, self-limiting dyspnea occurring within hours to days of treatment. A second, relatively uncommon, pattern is that of an acute hypersensitivity reaction with bronchospasm. Lastly, a third pattern of severe respiratory involvement is occasionally seen. This is a severe idiosyncratic reaction with profound dyspnea and pulmonary infiltrates that may progress to life-threatening respiratory insufficiency within hours of infusion (Fig. 72-4). Most cases of gemcitabine-related pulmonary toxicity resolve with discontinuation of this drug. In cases of severe symptoms, discontinuation of the agent along with institution of corticosteroids, careful fluid management, and diuretic therapy may be warranted.[44] Cases of diffuse alveolar hemorrhage, pulmonary veno-occlusive diseases, and thrombotic microangiopathy have also been described.

Fludarabine

Fludarabine, another nucleoside analogue, is widely employed in the management of chronic lymphoproliferative disorders. The incidence of pulmonary toxicity related to fludarabine has been estimated to be approximately 8.6% in a series of 105 patients.[48-50] Affected individuals experience dyspnea as early as 3 days after the first round of chemotherapy, though later onset of pulmonary symptoms has also been reported. The chest radiograph reveals either interstitial or mixed alveolar-interstitial infiltrates. Nodular infiltrates have also been described. As is often the case with chemotherapeutic agents, particular attention should be given to the possibility of opportunistic infections. Most patients respond to discontinuation of the drug, and receive symptomatic and objective benefits from additional corticosteroid therapy.

Piritrexim

Piritrexim is an experimental oral inhibitor of the dihydrofolate reductase used in the treatment of parasitic infections, psoriasis, and transitional cell carcinoma. It is closely related to methotrexate, and pulmonary toxicity has been observed in up to 14% of patients.[51]

Nitrosoureas

Nitrosourea compounds have a role in the treatment of gliomas and other central nervous system tumors, as well as in conditioning protocols preceding autologous bone marrow stem cell transplantation. Pulmonary toxicity related to nitrosoureas is well recognized and represents one of the most common side effects of these agents.[52] In particular, bischloroethyl nitrosourea (BCNU, carmustine) has been described to induce both acute-onset pulmonary injury and delayed-onset pulmonary fibrosis, with a predilection for the upper lobes.[52] The incidence of pulmonary toxicity associated with the administration of BCNU varies from 1.5% to 20% and is dose related, with up to a 50% incidence of lung disease in those receiving a total dose of over 1500 mg/m^2. However, there have also been reports of pulmonary effects occurring with much lower doses. The duration of therapy before the onset of pulmonary toxicity for the acute variant of nitrosourea lung injury has generally ranged from 6 months to 3 years. There appears to be a synergistic effect with cyclophosphamide, with radiation therapy, and possibly with other chemotherapeutic agents. The outcome may be unpredictable and sometimes fatal. There have been fewer case reports of pulmonary toxicity with methylchloroethyl cyclohexyl nitrosourea (methyl-CCNU) and chloroethyl cyclohexyl nitrosourea (CCNU). Apparently, fever is less commonly associated with this form of pulmonary toxicity than with many other chemotherapeutic drugs. Therapy usually consists of withholding the offending agent, and institution of corticosteroids, which has variable and often only transient beneficial effects.[53]

A long-term complication of BCNU toxicity is upper lobe fibrosis that may appear many years after the completion of chemotherapy. O'Driscoll and colleagues followed 17 patients for up to 17 years, and 12 of the 17 (71%) developed delayed upper lobe fibrosis.[54] The fibrosis is insidious in onset and, once discovered, appears to be intractably progressive. Corticosteroid therapy has not proven to be effective in delayed BCNU upper lobe fibrosis. Another unusual reported complication that is almost exclusively associated with nitrosourea compounds is pneumothorax.[55] This may be related to the upper lobe fibrobullous changes present in patients with BCNU lung toxicity.

Cases of pulmonary fibrosis have also been reported with other nitrosourea agents, including lomustine (CCNU), semustine (methyl-CCNU), fotemustine (CENU)

and chlorozotocin (DCNU). Pneumothoraces have rarely been described with these agents.

Podophyllotoxins

Etoposide and Teniposide

Etoposide (VP-16), a topoisomerase II inhibitor, has been widely used in combination chemotherapy for non–small cell and small cell lung carcinoma. Despite its extensive use, only a few cases of etoposide-associated pulmonary toxicity have been reported.[56] Onset may occur shortly after the first round of chemotherapy. However, most of the associated cases present after prolonged treatment. Tissue examination reveals features of alveolar edema, diffuse alveolar damage, and atypical type II pneumocytes. Therapy consists of withdrawal of the agent and administration of corticosteroids, which provide variable improvement. In addition, etoposide may increase the intracellular levels of methotrexate, and combination of methotrexate and etoposide may synergistically increase the likelihood of adverse reactions.

Teniposide, another podophyllotoxin agent, is also associated with hypersensitivity reactions in 3.6% to 6.5% of the cases. This toxicity may present with dyspnea, bronchospasm, and hypertension.[51]

Paclitaxel

Paclitaxel is a highly potent chemotherapeutic agents used in the treatment of lung, breast, and ovarian carcinomas. Well-documented cases of pulmonary toxicity induced by paclitaxel can be found in the literature, but the frequency is unclear. Typical respiratory symptoms include cough, dyspnea, wheezing, and chest tightness that may occur within minutes of administration of the drug, suggesting a type I hypersensitivity reaction. Immunoglobulin E antibodies against paclitaxel itself or perhaps its vehicle, Cremophor EL, are thought to be responsible.[57] This reaction may occur in as many as 30% of patients, and premedication with corticosteroids is sometimes considered. Interstitial and reticulonodular infiltrates have been reported on chest radiographic studies.[58] Cases of transient pulmonary infiltrates and suspected interstitial pneumonitis have also been described. The true incidence of lung toxicity directly related to paclitaxel is not well understood. A prospective study of lung function in 33 patients receiving paclitaxel with carboplatin (an agent with little lung toxicity) in the setting of nonthoracic malignancy revealed an isolated decrease in diffusing capacity without other clinical or radiographic evidence of pulmonary toxicity.[59] In other studies, conducted on patients with lung carcinoma, significant early and late pulmonary toxicity has been noted in 10% and 68% of patients, respectively.[60] Attributing the toxicity directly to paclitaxel is confounded by the underlying thoracic neoplasm, as well as other cytotoxic agents used in these patients.[61] Nonetheless, clinicians should be aware of the potential of paclitaxel impairing pulmonary function.

Docetaxel

Docetaxel (Taxotere) is an additional taxane compound that has activity in the treatment of breast and non–small cell lung cancer. Occasional pulmonary toxicity based on a hypersensitivity reaction has been observed.[62] These patients have responded rapidly to corticosteroid therapy. Recently, a small case series has suggested that the combination of docetaxel and gemcitabine has a particular propensity to induce severe pulmonary toxicity.[63]

Novel and Emerging Agents

All-Trans Retinoic Acid

All-*trans* retinoic acid (ATRA) has been employed in acute promyelocytic leukemia, in which it promotes differentiation of myeloid precursors and stimulates the maturation of leukemic cells, thereby promoting remission. It has also been reported to reduce disseminated intravascular coagulation and hemorrhagic complications during promyelocytic leukemia. The main complication limiting its use is the development of the so-called retinoic acid syndrome, occurring in up to 25% of patients treated. This syndrome consists of diffuse edema, pleuropericardial effusions, and noncardiogenic pulmonary edema that may evolve into a generalized capillary leak syndrome. Hypotension and acute renal failure are commonly present. It may occur suddenly between days 2 and 21 of treatment. Its pathogenesis remain elusive, but it is thought to result from a massive release of cytokines from newly mature myeloid cells and adhesion of granulocytes to the pulmonary endothelium. Indeed, high leukocyte counts have been associated with an increased incidence of the syndrome in some, but not all, studies. In addition, multiple hemorrhagic complications have also been described. In one study, 9 of 35 patients with promyelocytic leukemia receiving ATRA developed respiratory distress.[64] Intravenous corticosteroid therapy seemed to be of benefit to these patients. Based upon these observations, an additional study has suggested that the incidence of ATRA-associated pulmonary complications may be reduced to roughly 10% through the use of preventative treatment with oral corticosteroids. The mortality associated with ATRA-induced pulmonary toxicity is estimated at around 9%. Tissue examinations of lungs affected by ATRA have revealed interstitial infiltration with maturing myeloid cells. However, the overall spectrum of the ATRA-associated pulmonary syndrome is continuing to evolve and includes the presence of myeloid cells and blasts in bronchoalveolar lavage fluid, nodular pulmonary infiltrates, pulmonary leukostasis, noncardiogenic pulmonary edema, acute respiratory distress syndrome, Sweet's syndrome, and diffuse alveolar hemorrhage.[65]

Tyrosine Kinase Inhibitors

Gefitinib (Iressa, ZD1839) is a selective tyrosine kinase inhibitor active on the epidermal growth factor receptor

(EGFR) used in patients with advanced non–small cell lung cancer who have failed to respond to platinum-based chemotherapy. Its use was recently restricted in the United States to patients already being treated with evidence of benefit, after the Phase III Iressa Survival Evaluation in Advanced Lung Cancer study showed no improvement in survival. Acute interstitial pneumonia has been associated with this drug, and the overall incidence of gefitinib-associated interstitial lung disease may be in the range of 1%, with a mortality rate approaching 30%.[28,66] A nested case-control study in an Asian population revealed an incidence of interstitial lung disease of 4.5 per 1000 person-weeks over a 12-week period.[67] Diffuse ground-glass opacities have been reported on computed tomography scan, with tissue examination demonstrating diffuse alveolar damage. Although some patients respond to withdrawal of the agent and institution of corticosteroid therapy, others progress to fulminant respiratory insufficiency. Hence, the clinician needs to remain mindful of this pulmonary complication of gefitinib therapy, and discontinue the agent if symptoms and radiographic abnormalities occur. In addition, erlotinib (Tarceva), another EGFR antagonist, has also been rarely associated with pulmonary toxicity, including fatalities. Recently, a limited number of cases showing pulmonary infiltration with eosinophilia, or other interstitial lung disease, have also been reported in association with imatinib mesylate (Gleevec, ST1571), an agent used in the treatment of chronic myelogenous leukemia and gastrointestinal stromal tumors.[68]

Irinotecan and Topotecan

Irinotecan, a semisynthetic camptothecin, has been employed for advanced colorectal cancer either alone or in combination with 5-fluorouracil, and in some lung cancer trials. Early studies of irinotecan in Japan documented a 1.8% incidence of pneumonitis.[69–71] In those studies, clinical features included dyspnea, fever, and reticulonodular pulmonary infiltrates. Empirical corticosteroids were recommended, but some patients progressed to fatal respiratory failure. In subsequent U.S. trials, cough and dyspnea were described in roughly 20% of treated patients.[72] However, many of these patients had intrathoracic malignancies. The reported incidence of serious pulmonary toxicity related to irinotecan was much lower in these subsequent trials (approximately 0.4%).[72] Radiotherapy and preexisting lung disease may increase the risk. Nonetheless, cases of serious irinotecan-associated interstitial pneumonitis have been reported in the United States. Patients with preexisting pulmonary disease may be at enhanced risk.

Topotecan is a similar agent and has rarely been reported to induce pulmonary toxicity, including cases of diffuse alveolar damage and constrictive bronchiolitis.

Monoclonal Antibodies

As our understanding of the pathogenesis of malignant processes continues to increase, the identification of specific target tumoral antigens had led to the development of specific immunotherapeutic tools, including monoclonal antibodies. Several new molecules have emerged as potentially beneficial adjunct agents in a variety of neoplastic processes.

Bevacizumab (Avastin) in a monoclonal antibody targeting the vascular endothelial growth factor, and designed to inhibit tumoral neoangiogenesis. It has been used in conjunction with conventional chemotherapeutic agents in the treatment of metastatic colon and nonsquamous non–small cell lung cancers. It is associated with hemorrhagic complications including fatal pulmonary hemorrhage thought to result from extensive tumor necrosis. As such, bevacizumab is contraindicated in patients with squamous cell histology and central nervous system metastases. Although it may seem counterintuitive, bevacizumab is though to increase the incidence of thromboembolic disease by twofold. This may be secondary to vascular injury with secondary exposure of the underlying endothelium with secondary activation of the coagulation cascade. Recently, cases of thrombotic microangiopathy with hypertension and acute renal failure have also been described. Cases of congestive heart failure have also been described, mostly in association with anthracycline agents, raising questions about this reported association.[73]

Cetuximab and panitumumab are two monoclonal antibodies directed against EGFR that are increasingly used in treatment of a number of neoplasms. They both have been associated with rare pulmonary toxicity. Interstitial lung disease has been reported in 0.4% of patients with cetuximab, and infusion reactions with bronchospasm and hoarseness may occur in 23% of the cases. Similar infusion reactions may occur with panitumumab and be severe in 1% of the cases.

Trastuzumab selectively binds the EGFR-2 (human epidermal growth factor receptor-2 [HER-2]) protein and is an adjuvant treatment of metastatic HER-2–positive breast cancer. As with other monoclonal antibodies, infusion reactions may present in 15% of the cases and are potentially associated with angioedema, fever, and bronchospasm. Trastuzumab reactions may also present as an acute or subacute interstitial pneumonia in approximately 0.5% of the cases, with a mortality rate estimated at 0.1%.

Rituximab is an anti-cd20 chimeric monoclonal antibody approved in 1997 for the treatment of non-Hodgkin's lymphoma. Its ever-increasing indications have led to an exponential increase in its use in a variety of diverse conditions from autoimmune inflammatory diseases to posttransplantation lymphoproliferative disorders. Pulmonary complications of rituximab appear fairly rare overall. A review of the literature in 2007 only identified 16 cases of interstitial lung disease assumed to be secondary to rituximab use. Specific patterns of lung injury have also been described in pathologic specimens, including diffuse alveolar hemorrhage and desquamative interstitial pneumonia, but the experience is often limited to isolated case reports.[74]

Immunomodulatory Agents

Interferons

Interferons have been used in a wide variety of malignant, infectious, and inflammatory disorders. Interferon alfa and interferon beta have been employed in the treatment of hairy cell leukemia, myeloma, T-cell lymphoma, chronic myelogenous leukemia, malignant pleural effusions, melanoma, renal cell carcinoma, and Kaposi's sarcoma. Interferon gamma has been included in investigative trials for mesothelioma, non–small cell lung carcinoma, and idiopathic pulmonary fibrosis.

Administration of interferons has been associated with a variety of pulmonary reactions. For instance, interferon alfa has been linked to severe exacerbation of bronchospasm in patients with preexisting asthma.[75] In addition, a granulomatous reaction indistinguishable from sarcoidosis has been described in relation to interferon therapy.[76] These toxicities usually respond to either reduction or withdrawal of the interferon treatment with or without the addition of corticosteroids. Noncaseating granulomas have been documented in the lung, lymph nodes, liver, and skin of affected patients.

Interferon-associated interstitial lung disease has also been reported.[77] Dyspnea and cough are observed and bilateral infiltrates are present on chest radiography. A CD8-predominant lymphocytic response is found in the bronchoalveolar lavage fluid, and a cellular interstitial pattern is present on histology. In some cases, interferon therapy has also been associated with bronchiolitis obliterans with organizing pneumonia.[78] Most affected patients respond to discontinuation of the interferon and administration of corticosteroids. Recently, interferon gamma has been used in idiopathic pulmonary fibrosis. A series has been reported in which four patients with advanced idiopathic pulmonary fibrosis developed acute hypoxemic respiratory failure during interferon gamma treatment.[79] This was not responsive to corticosteroids and was fatal in three cases. Interferon gamma is also associated with a high incidence of severe radiation pneumonitis when it is used in multimodality therapy for non–small cell lung carcinoma.

Rapamycin Analogs

Sirolimus was initially developed as an antifungal agent isolated from *Streptomyces hygroscopicus.* It is a macrolide antibiotic inhibitor of mTOR with antiproliferative and immunosuppressive properties essentially used to prevent rejection in solid-organ transplantation and as a coating agent in drug-eluting stents. It is currently under investigation for the treatment of lymphangioleiomyomatosis. Several patterns of drug toxicity have been described with sirolimus, including the subacute onset of interstitial pneumonitis (which usually resolves after discontinuation of therapy), bronchiolitis obliterans with organizing pneumonia, and diffuse alveolar hemorrhage. Rare cases of alveolar proteinosis and granulomatosis have also been reported. Typically, these pulmonary complications are reversible after discontinuation of therapy, but occasionally they represent a difficult diagnostic challenge in an immunosuppressed population prone to a variety of opportunistic infections.[80]

Everolimus is a similar inhibitor of the mTOR pathway that has been used as an immunosuppressive agent in solid-organ transplantation and is under investigation as an antineoplastic agent. Several types of pulmonary toxicity have been described, including bronchiolitis obliterans with organizing pneumonia and the subacute onset of interstitial pneumonitis.[81]

Temsirolimus is active against a variety of solid tumors, including endometrial cell carcinoma, breast cancer, and neuroendocrine tumors. It is FDA approved for the treatment of advanced renal cell carcinoma. In a retrospective review of 22 patients treated with temsirolimus, eight patients (36%) developed pulmonary complications. Half of these patients were symptomatic. On radiographic studies, two different patterns of involvement were identified consisting of ground-glass infiltrates or alveolar consolidation. Discontinuation of the drug is advised.[82]

Granulocyte-Macrophage and Granulocyte Colony-Stimulating Factors

Granulocyte-macrophage colony-stimulating factor and granulocyte colony-stimulating factor are widely applied in the treatment of bone marrow suppression following chemotherapy, thereby enhancing the immune response of treated patients. A number of case reports and small series have proposed that these biologic factors may potentiate pulmonary toxicity of other chemotherapeutic agents.[83] It has also been suggested that granulocyte-macrophage colony-stimulating factor may induce a recall phenomenon of toxicity from other drugs.

Other Chemotherapeutic Agents

Procarbazine

Procarbazine has found use in Hodgkin's disease and other lymphoproliferative disorders. Adverse pulmonary reactions related to procarbazine are fairly rare, with only a few cases of probable procarbazine pneumonitis being described.[35] These lung reactions may be cytotoxic in nature. In other patients, toxicity has been related to a rapid-onset hypersensitivity reaction associated with eosinophilia that declines after the drug has been discontinued.

Zinostatin

Zinostatin has been associated with occasional reports of pulmonary toxicity, usually only occurring in patients who have received the drug for prolonged periods of time.[35] Interestingly, this agent has been associated with the unique drug reaction of hypertrophy of the pulmonary vasculature, which may be associated with pulmonary hypertension.

Vinblastine

Vinblastine, a vinca plant alkaloid, is one of the oldest chemotherapeutic agents still in use. Vinblastine continues to be included in a wide variety of chemotherapeutic regimens for hematologic and solid malignancies. Traditionally, vinblastine was thought to have little if any pulmonary toxicity. However, reports have associated vinblastine with pulmonary complications when it is combined with other agents, particularly mitomycin C. This combination has been complicated by bronchospasm, interstitial pneumonitis, and a noncardiac pulmonary edema.[84,85]

Radiation

The acute effects of radiation can produce histologic changes mimicking cytotoxic lung responses and may occasionally involve areas of lung outside the port of radiation. The process is generally heralded by fever beginning 3 to 8 weeks after initiation of radiation therapy and may rapidly progress to a fatal outcome in spite of institution of corticosteroids. The disease may improve spontaneously but usually progresses to chronic radiation effects. Bronchoalveolar lavage fluid predominantly demonstrates lymphocytes in the involved lung as well as in the contralateral lung.[86] The chronic effects of radiation are well known. They begin 3 to 6 months or later after radiation therapy, and their primary effect is vascular. Recently, a form of radiation pneumonitis has been observed outside the treatment fields, usually in patients with breast cancer. Tissue examination has revealed bronchiolitis obliterans with organizing pneumonitis in these cases.[87]

ANTIMICROBIAL AGENTS

Nitrofurantoin

Acute Reaction

Nitrofurantoin pneumonitis may be one of the most common drug-induced pulmonary diseases.[88–90] Acute pulmonary reactions are probably underestimated. The incidence has been estimated to be anywhere from 1 in 550 to 1 in 5400 individuals.[90] The mechanism of the acute nitrofurantoin reaction is unknown. In spite of peripheral blood eosinophilia, eosinophils are not usually seen in the lung tissue.

The typical reaction begins a few hours to several days after initiation of therapy. It appears to be much more common in women, perhaps due to the increased use of this drug in women. Fever is present in the majority of cases, dyspnea is almost always present, and cough is present in about two thirds of cases. Other incidental findings include leukocytosis and eosinophilia in one third and an elevation in sedimentation rate in nearly one half of cases. The chest roentgenogram shows either an alveolar or an interstitial process or both. The reaction may be unilateral or asymmetrical and is generally most prominent at the bases. Pleural effusion has been found in one third of patients, most commonly unilaterally. Bronchospasm has been reported in a number of cases, but its incidence is unknown. It may occur in the absence of pulmonary parenchymal or pleural disease.[90]

The treatment consists of discontinuing the medication and providing supportive care. It is not known whether corticosteroids accelerate the resolution, and there is probably no indication for their use. There is also no role for rechallenge to confirm the diagnosis. Nitrofurantoin-induced SLE with pleuropulmonary disease and positive antinuclear antibody has also been reported. Little information is available on this form of lung disease.

Chronic Reaction

There is no clinical overlap between the acute and chronic pulmonary reaction to nitrofurantoin. Chronic reactions occur far less commonly than acute pulmonary reactions. In chronic reactions, fever and eosinophilia are much less common.[88,90,91] The onset of dyspnea and cough is usually insidious, beginning 6 months to many years after the chronic (either continuous or intermittent) use of nitrofurantoin. These reactions are more common in women.

The chest roentgenogram shows a diffuse interstitial process.[90,91] There is no associated bronchospasm or obstructive airway disease. Pulmonary function testing demonstrates a restrictive pattern. Bronchoalveolar lavage usually shows a lymphocytic reaction. Histologic analysis of lung tissue shows inflammatory cells and fibrosis. Clinically, radiologically, and histologically, this condition often mimics other forms of interstitial lung disease, including usual interstitial pneumonia, with the single exception that these patients have ingested nitrofurantoin chronically.

The literature varies as to the utility of corticosteroids. Our experience is that they are almost always required before significant resolution occurs. Others imply that the infiltrates resolve spontaneously on discontinuation of the medication.[91] Our policy is to observe the patient for 2 to 4 months after discontinuing nitrofurantoin and then repeating the chest roentgenogram and pulmonary function studies. If there is no improvement, a trial of corticosteroids is given.[92]

Sulfasalazine

Sulfasalazine is an antimicrobial drug that has been used for many years for the treatment of inflammatory bowel disease.[93] There appear to be two separate types of adverse pulmonary reactions: one is a pulmonary infiltrate and eosinophilia, and the other a bronchiolitis obliterans with organizing pneumonitis. The onset of symptoms of cough, dyspnea, and, in about half of cases, fever begins 1 to 8 months after initiation of continuous therapy. The dosage ranges from 1.5 to 8 g/day. The chest roentgenogram shows a variable pattern of lung infiltrates, ranging from upper lobe alveolar infiltrates to a diffuse interstitial process. Over half of the patients had significant blood eosinophilia, but none had migratory pulmonary infiltrates. The majority of the resolution

occurs within 1 week to 6 months after discontinuing the drug and, if necessary, adding corticosteroids. Sulfasalazine is metabolized to 5-aminosalicylic acid and sulfapyridine, both of which have been implicated in eosinophilic pneumonitis. In cases of suspected sulfasalazine-associated pulmonary disorders, it important to keep in mind that inflammatory bowel disease has been associated with a variety of pulmonary abnormalities independent of sulfasalazine use. Inflammatory bowel disease has been independently linked to airway inflammation, interstitial lung disease including bronchiolitis obliterans with organizing pneumonia, neutrophilic necrotic pulmonary nodules, and serositis. Most of these disorders respond to corticosteroid therapy.

Miscellaneous Antimicrobial Drugs

There are many scattered reports of unusual reactions to various antimicrobial drugs. In view of the wide use of these agents, the incidence is extremely small. Many of these reactions appear to be pulmonary infiltrates with eosinophilia. The polymyxin and aminoglycoside antibiotics are known to produce respiratory muscle weakness when they reach an excessive level in the blood.[94] Toxic levels in the blood occur in patients to whom these drugs are given by direct instillation into the peritoneal or pleural space, in persons with renal failure, or when the patient receiving them has been given a muscle-relaxing agent at the time of general anesthesia. These effects are reversible with physostigmine. The combined administration of granulocytes with amphotericin B may predispose some patients to transient deterioration in pulmonary function.[95]

ILLICIT DRUGS

Heroin

Although nitrofurantoin appears to be the most commonly reported prescribed drug with adverse pulmonary effects, heroin pulmonary edema may be the most common drug-induced pulmonary disease worldwide. Hospitals in all major cities of the United States receive hundreds of patients with heroin pulmonary edema. Heroin is diacetylmorphine and, because of its increased lipid solubility, it crosses the blood-brain barrier much more readily than morphine. There are several postulated mechanisms of heroin-induced noncardiac pulmonary edema. These include a direct toxic effect on the alveolar-capillary membrane, leading to an increased permeability and extravasation of fluid into the alveolar spaces; a neurogenic response to central nervous system injury; an allergic or hypersensitivity reaction; and an acute hypoxic effect on the alveolar-capillary membrane in association with secondary increased permeability. The hypoxemic theory is the one most commonly touted, but other causes of acute hypoxia, such as barbiturate overdosage with depression of the respiratory center, rarely result in noncardiac pulmonary edema.[56]

Heroin pulmonary edema can occur with the first intravenous use of the drug. It is believed that the effects of heroin are related to the dose. However, the exact dose is almost always unknown. Up to 40% of addicts hospitalized for acute drug overdose have acute pulmonary edema with severe hypoxemia and hypercapnia. The noncardiac pulmonary edema is indistinguishable at the outset from other forms of acute respiratory distress syndrome. The pulmonary capillary wedge pressure is usually within normal range. Typically, symptoms of dyspnea and somnolence begin within minutes of the intravenous "push," but reports of delayed onset of hours and even a few days have been published. The patient hypoventilates, producing hypoxemia and hypercapnia. The pupils are small. Auscultation of the lungs discloses crackles. The chest roentgenogram shows changes of noncardiac pulmonary edema. Acidosis can be metabolic as well as respiratory.

Up to one half of these patients vomit and aspirate, which leads to secondary bacterial infection. This should be suspected if the pulmonary infiltrates do not clear within 24 to 48 hours of treatment. Other pulmonary abnormalities include septic emboli from infected thrombophlebitis or tricuspid endocarditis. Treatment consists of assisted ventilation using positive end-expiratory pressure, oxygen, and intravenous naloxone to reverse the respiratory depression. This is usually sufficient treatment for the noncardiac pulmonary edema, which will reverse with time. Corticosteroids are unnecessary. Because up to half of these patients have aspirated and have bacterial infections, appropriate use of antimicrobial drugs is indicated.

Bronchiectasis and necrotizing bronchitis in chronic heroin abusers have been reported. These may be more sequelae of recurrent gastric aspiration than the effects of heroin, with or without pulmonary edema. Pulmonary function is abnormal in patients with pulmonary edema. Even after the roentgenographic clearance of the edema and the return of the lung volumes to normal, a reduction in the carbon monoxide diffusing capacity may persist. In chronic abusers of heroin and other illicit intravenous drugs, pulmonary function abnormalities are more likely to be related to talc granulomatosis (see later) than to sequelae of a single acute injury.

Methadone and Propoxyphene

Pulmonary sequelae similar to those associated with heroin have been reported with methadone and propoxyphene and likely have similar mechanisms. Treatment is the same as for heroin-induced sequelae. Addicts in drug rehabilitation programs have free access to methadone. They accumulate the drug illegally, dissolve it, and inject it. Noncardiac pulmonary edema has been reported in cases of both oral and intravenous overdose of methadone. Propoxyphene is a rapidly absorbed drug, and, even after oral ingestion, death can occur within 30 minutes from respiratory depression and arrest and noncardiac pulmonary edema. In some parts of the United States, propoxyphene is a commonly used drug in attempted suicide.

Methylphenidate

Methylphenidate may have more serious adverse side effects than either heroin or cocaine.[96,97] Methylphenidate can be abused either intravenously or orally. In one series of methylphenidate abuse, all 22 patients had chest pain and wheezing and most had abnormal pulmonary function tests and hemoptysis.[96] In another series, severe panlobular emphysema was found in seven patients who died as a result of the abnormalities.[97]

Cocaine

Cocaine use remains a major problem throughout the world, and there are increasing reports of adverse pulmonary effects from both intravenous and inhalation use of the drug. These are over and above the known cardiac effects of cocaine, which produces left ventricular failure with pulmonary congestion and edema. The principal long-term effects of cocaine are infection and aspiration, noncardiac pulmonary edema, particulate embolization, talcosis, diffuse alveolar damage, alveolar hemorrhage, intra-alveolar eosinophilic infiltration, lung mass with or without cavitation, and bronchiolitis obliterans with organizing pneumonia (Table 72-4).[98,99]

Talc Granulomatosis

Talc (magnesium silicate) is used as a filler in many medications intended for oral use. Addicts who abuse oral medications such as meperidine, methadone, propoxyphene, methylphenidate, amphetamines, and tripelennamine often crush the tablets, mix them with various solutions, and inject them intravenously. This results in the insidious onset of granulomatous interstitial fibrosis, granulomatous pulmonary arterial occlusion, or both.[98–100] This usually does not occur in heroin addicts, because heroin is mixed in soluble fillers such as quinine, lactose, or maltose. In large series of consecutive autopsies done on addicts, depending on the type of addiction, the incidence of talc granulomatosis ranges from 15% to 80%.

Dyspnea is the major symptom, cough occurs in some patients, and, in more advanced stages of pulmonary hypertension, symptoms of exercise-induced syncope and right-sided heart failure, and even sudden death, occur. The chest roentgenogram may be normal in up to half of patients with proven talc granulomatosis. Thus, a normal chest roentgenogram does not eliminate the possibility of this condition. Pulmonary function studies characteristically show a low diffusing capacity before any other abnormalities are evident, because of occlusion of pulmonary blood vessels. This may remain the only abnormality. Chest roentgenograms in these patients show diffuse micronodular densities varying in size between 1 and 3 mm, which may mimic alveolar microlithiasis. Therapy with corticosteroids provides little consistent improvement.

Histologically, the pulmonary tissue demonstrates granulomatous changes, with multinucleated giant cells, mononuclear inflammatory cells, lymphocytes, and fibrosis. Talc is detected by the presence of strongly birefringent crystals (using polarized light) within the granulomas. Bronchoalveolar lavage fluid shows an increased lymphocytosis, and intracellular and free talc have been identified in the bronchoalveolar lavage fluid. Talc retinopathy occurs in over half the patients. Talc emboli presenting as small, whitish, glistening foci near the macula within a small vessel are fairly characteristic.

TABLE 72-4. Principal Effects of Cocaine

Infection and aspiration leading to noncardiac pulmonary edema
Particulate embolization
Talcosis
Diffuse alveolar damage
Alveolar hemorrhage
Intra-alveolar eosinophilic infiltration
Lung mass with or without cavitation
Bronchiolitis obliterans with organizing pneumonia

CARDIOVASCULAR DRUGS

Angiotensin-Converting Enzyme Inhibitors

Angiotensin-converting enzyme (ACE) inhibitors are widely used for control of hypertension and in the management of congestive heart failure. Soon after their introduction, these agents were associated with nonproductive cough and more rarely with angioneurotic edema. Dry cough occurs in 5% to 20% of patients on ACE inhibitors, being reported with captopril, enalapril, lisinopril, and virtually all other ACE inhibitors. The mechanism of ACE inhibitor–induced cough likely involves accumulation of kinins and substance P, which are degraded by ACE and other endopeptidases. The cough generally is reported in the first few weeks after beginning therapy but may not be appreciated for a number of months. ACE cough is usually benign but can be quite annoying, and causes the discontinuation of these agents in half of the patients affected. Exacerbation of bronchospasm has been associated with ACE inhibitors only on very rare occasions. Fortunately, most patients can be switched to other classes of drugs. Rechallenge with a different ACE antagonist is not recommended as the cough will usually reoccur. Cough generally abates within 4 days of discontinuation of the agent, providing confirmation of the diagnosis. Of note, selective angiotensin receptor antagonists have much lower incidence of dry cough compared to ACE inhibitors and may represent a therapeutic option for many patients.

ACE inhibitors cause angioneurotic edema much less frequently; this condition is reported in 0.1% to 0.2% of patients receiving ACE inhibitors. This complication usually occurs within hours to, at most, 1 week after initiating therapy, and can be life-threatening. This reaction may be mediated by bradykinins but may also involve autoantibodies and complement system activa-

tion. Treatment involves airway protection, epinephrine, antihistamines, and corticosteroid administration. The ACE inhibitor must be discontinued and future use avoided in these patients.

Amiodarone

Amiodarone has significant benefit for ventricular and supraventricular dysrhythmias in patients who do not respond to most other antiarrhythmic agents. This drug is associated with a number of side effects, which include corneal microdeposits (in nearly 100% of the patients); peripheral neuropathy; liver dysfunction; thyroid dysfunction, including hypo- and hyperthyroidism; and bluish pigmentation of the skin. However, the most serious side effect is an interstitial pneumonitis, which occurs in up to 6% of patients and may be fatal.

The mechanism of amiodarone toxicity is unknown, but the toxicity is dose related and has distinctive histologic features. The histologic findings generally include foamy alveolar macrophages and type II pneumocytes containing lamellar inclusions. In one half of the patients on amiodarone who die of nonpulmonary causes, macrophages and type II pneumocytes contain a markedly increased amount of phospholipid.

The incidence of pulmonary toxicity from amiodarone varies widely but probably averages 4% to 6% of those patients on the drug.[12,101] The majority are men, but this may be related to increased use in men. Symptoms consist of insidious dyspnea, nonproductive cough, and occasionally a low-grade fever without chills, followed by subtle chest roentgenographic findings, which initially may be asymmetrical or even limited to the upper lobes. If the drug is continued, the process may diffusely involve the lungs with an interstitial or alveolar process. Pleural effusion is uncommon. Pleuritic chest pain occurs in about 10% of patients. Clubbing has not been reported. Crackles may be heard, but it is difficult to be certain whether these are due to pulmonary edema, because congestive heart failure is common in these patients. In about 20% of patients with amiodarone pneumonitis, the presentation will be acute, mimicking pneumonia.

Laboratory studies disclose a normal to mildly elevated leukocyte count, generally no eosinophilia, and an elevated sedimentation rate, with little or no reactivity to antinuclear antibody. Pulmonary function studies disclose a decrease in the total lung capacity and carbon monoxide diffusing capacity as well as hypoxemia. However, a decrease in the lung volumes and carbon monoxide diffusing capacity can occur as a result of congestive heart failure, and thus a change in these parameters is not diagnostic of impending clinical amiodarone pneumonitis. There are selected reports of using ^{67}Ga radionuclide lung scanning that may demonstrate its benefit in differentiating amiodarone pneumonitis from congestive heart failure.[102] There may be an increased predisposition to amiodarone pneumonitis if either pulmonary function or chest roentgenographic findings are abnormal before administration of the drug begins.

The majority of the patients who develop amiodarone pneumonitis have been taking the drug for at least a month, and some for a few years. Most are receiving at least 400 mg/day. However, there have been a number of reports of amiodarone pneumonitis occurring with as little as 200 mg/day. There are also reports of patients receiving 200 mg/day for months or even years and not developing amiodarone pneumonitis until the dose is boosted for purposes of better control of the arrhythmia. Generally, the systemic side effects from amiodarone, such as peripheral neuropathy and liver dysfunction, correlate with the serum levels, but this is not necessarily the case with the pulmonary toxicity. Perhaps the greater phospholipid turnover in the lung explains the greater chance for lung toxicity from amiodarone. The diagnosis of amiodarone pneumonitis is one of exclusion.

Normally, amiodarone pneumonitis is thought to be primarily an interstitial or alveolar process (or both) sometimes mimicking eosinophilic pneumonitis with peripheral infiltrates, but there are a number of reports of confluent lesions occurring as a result of amiodarone pneumonitis. Many of these lesions are bronchiolitis obliterans.[103,104] Computed tomography of the lung can further define these processes because amiodarone, being an iodinated compound, is radiopaque, and on a computed tomography scan the amiodarone pneumonitis lesions are denser than the surrounding soft tissue in the chest wall (Fig. 72-5). This latter finding may confirm the diagnosis.

Treatment consists of drug withdrawal and leads to a variety of responses. Some patients who were not treated with corticosteroids have died of pulmonary fibrosis and respiratory failure. Others have died in spite of being treated with corticosteroids. The majority respond to discontinuation of the drug and addition of corticosteroids, which are usually required for a period of at least

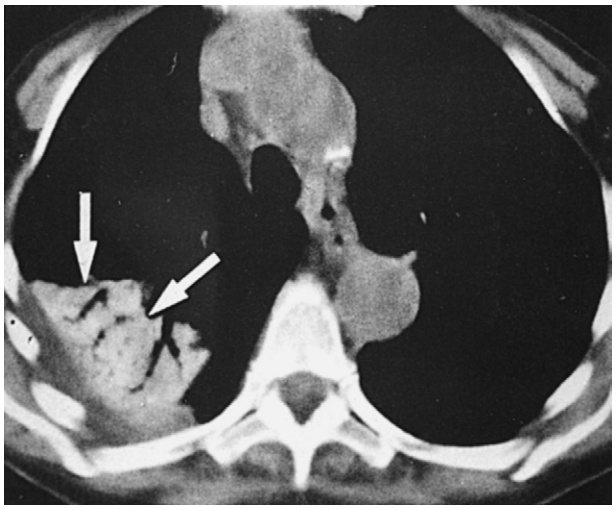

FIGURE 72-5 ■ A chest computed tomography (CT) scan showing confluent pulmonary masses (*arrows*) from amiodarone pneumonitis. Note that the masses are appreciably denser than the surrounding soft tissue in the chest wall in this CT scan obtained without contrast.

2 and perhaps 6 months or longer. There are many case reports of patients who continued on amiodarone because it was the only drug that controlled their ventricular dysrhythmia and who at the same time were given corticosteroids to suppress their pneumonic reaction.[105] For some patients, implantable automatic cardiac defibrillators provide a therapeutic option to chronic high-dose amiodarone therapy.

Initially, it was believed that tissue confirmation by biopsy was necessary to establish a diagnosis, although stopping the drug and adding corticosteroids may offer a presumptive diagnosis if the process clears. Bronchoalveolar lavage produces variable results.[12] The presence of foamy macrophages in lavage fluid or on biopsy only confirms exposure to the drug; their presence alone does not necessarily indicate amiodarone toxicity. Their absence does eliminate the diagnosis, however. Although not used frequently in recent years, a positive ^{67}Ga scan can be highly suggestive of an inflammatory pneumonitis rather than congestive heart failure. If the diagnosis has not been established, the clinician must decide whether to proceed with an open-lung biopsy to rule out other disease processes or to consider diminishing the dose or discontinuing the drug, or adding corticosteroids, or both. A lung biopsy usually reveals the foamy macrophages and epithelial cells, and variable inflammatory cell infiltration. In some cases, the tissue pattern of bronchiolitis obliterans with organizing pneumonia has been observed (Table 72-5). Reductions in sedimentation rate following discontinuation or reduction of amiodarone dosage may be of further value in establishing the diagnosis.

There are reports of postoperative acute respiratory distress syndrome in patients on amiodarone. Several of these patients have died as a result of the acute respiratory distress syndrome, which begins 18 to 72 hours after surgery. In one series, the acute respiratory distress syndrome occurred in 50% of the patients on or recently on amiodarone.[106] It has been postulated that the high fraction of inspired oxygen given during the operation and the postoperative period contributed to this complication.

TABLE 72-5. Drugs or Treatment Associated with the Induction of Bronchiolitis Obliterans with Organizing Pneumonitis

Bleomycin
Amiodarone
Gold
Penicillamine
Sulfasalazine
Radiation
Interferons
Methotrexate
Mitomycin C
Cyclophosphamide
Cocaine

Protamine

Protamine sulfate is used to reverse the anticoagulant effects of heparin following cardiovascular surgical procedures. Systemic hypotension is not uncommon following administration of this drug. However, there have been a number of cases of noncardiogenic pulmonary edema occurring within minutes to 1 or 2 hours after the administration of the drug.[107] It is frequently associated with an anaphylactic reaction and bronchospasm, an increase in pulmonary artery pressure with normal wedge pressure, and hypotension. In at least half of the patients there is a history of previous use of protamine, either in a similar situation or as protamine zinc insulin. Skin testing can confirm the sensitization. Therapy is supportive, including reintubation if the patient has been extubated, assisted ventilation with high inspired oxygen concentrations, administration of high-dose corticosteroids, and treatment of hypotension with an α-adrenergic agonist. In patients whose skin test is positive to protamine or who have a history of reaction to protamine, an alternative method of reversing the effects of heparin is to use intravenous hexadimethrine.

β-Adrenergic Antagonists

β-Adrenergic antagonists are among the most commonly prescribed drugs. β-Adrenergic receptors can be divided into excitatory β_1-receptors, located in the heart, and inhibitory β_2-receptors, located in the bronchi. The β-adrenergic blockers, or β-blockers, are competitive antagonists.

Propranolol was the first β-adrenergic antagonist introduced. It was quickly recognized that it had adverse effects on individuals with known obstructive lung disease. Studies have also demonstrated increased airway resistance in normal persons and in asymptomatic asthmatic patients who use propranolol.[108] Thus, this agent should be avoided in all patients with known obstructive lung disease, even those who are asymptomatic. The following β-adrenergic antagonists, presented in decreasing order of bronchoprovocation potential, are available for clinical use in the United States: propranolol, timolol, nadolol, metoprolol, atenolol, pindolol, and labetalol.[109]

Two features of β-adrenergic antagonists predict their potential for bronchoprovocation: their cardioselectivity and their intrinsic sympathomimetic activity. Generally, cardioselectivity is the more important of the two. If the drug is cardioselective, it has little effect on the inhibitory β-receptors located in the bronchial walls. Propranolol, timolol, and nadolol have essentially no cardioselectivity. Metoprolol has some cardioselectivity, and atenolol has considerable cardioselectivity, making atenolol the drug of choice in an individual with obstructive airway disease who needs a β-adrenergic antagonist. The other mechanism important in β-adrenergic antagonists is intrinsic sympathomimetic activity, with pindolol having strong intrinsic sympathomimetic activity. Labetalol is unique in that it has combined α- and β-antagonist effects. It is not cardioselective, nor does it have intrinsic sympathomimetic activity. Therefore, it is assumed that

it is its α-adrenergic antagonist potential that causes it to be bronchoprotective.

Thus, among the seven drugs listed, atenolol and then metoprolol and probably labetalol are the three that can be used with relative safety in persons with obstructive lung disease, if absolutely necessary. However, these should always be given in conjunction with an aerosolized β_2-adrenergic agent. Calcium channel blockers may be a good alternative to β-blocking drugs, if indicated, because they also may have some bronchodilating capabilities.

The same findings have been shown to occur in asthmatic patients receiving timolol eye drops for glaucoma. There are many case reports of the adverse effects of topical ocular timolol, including a number of fatal cases of status asthmaticus.[110] Topically applied timolol is absorbed through the conjunctiva and bypasses the liver, resulting in a higher concentration than when given orally. A novel ocular β-adrenergic antagonist, betaxolol, has been shown to be safer in patients with known airway disease. There are scattered reports of β-blocker–associated interstitial pneumonitis.[111] Propafenone is an additional membrane-stabilizing antiarrhythmic agent that is structurally similar to propranolol and has the potential to aggravate bronchospasm.[112]

Tocainide and Flecainide

Tocainide is used in the treatment of refractory ventricular arrhythmias. There are well over 100 known cases of acute interstitial pneumonitis beginning 3 weeks to several months after initiation of therapy.[113] The response to discontinuing the drug is good; corticosteroids may be necessary in some cases. Flecainide, another antidysrhythmic agent, has been reported to be associated with the acute respiratory distress syndrome and an interstitial lymphocytic pneumonitis.[114,115]

ANTI-INFLAMMATORY AGENTS

Aspirin

Anti-inflammatory agents are among the most commonly used drugs, and many have pulmonary side effects. Aspirin is the most commonly used drug in the world. In the United States, there are over 200 proprietary drugs that contain aspirin. It is estimated that up to 5% of asthmatics are sensitive to aspirin; ingestion may cause fatal aggravation of bronchospasm.[116] The exact cause of aspirin-sensitive asthma is unknown. One theory is that acetylsalicylic acid and similar compounds inhibit cyclooxygenase, and thus prevent the generation of cyclooxygenase products. If bronchodilator prostaglandins (such as prostaglandin E_2), are normally released by these individuals, their inhibition could cause bronchospasm.

The aspirin-asthma triad consists of asthma, rhinitis, and nasal polyposis. Almost always there are other associated side effects, such as cutaneous rashes and gastrointestinal symptoms. These adverse reactions are not dose related, because they can occur with very small doses. In addition, salicylate-induced noncardiac pulmonary edema can occur when the serum salicylate level is greater than 40 mg/dL. This can occur without an intentional overdosage in patients chronically ingesting salicylates. It occurs more commonly in elderly persons who are smokers than in younger nonsmokers. The mechanism is unknown, although it may be a direct effect on the alveolar capillary wall as a result of an increase in the capillary permeability. It may be related to the effect of salicylates on platelets or prostaglandins or occur through a central nervous system effect. It does not occur in every individual with very high serum salicylate levels. Because of the respiratory center stimulation by salicylates, hyperventilation occurs, resulting in a low arterial P_{CO_2}, frequently less than 20 mm Hg. In spite of hyperventilation, the arterial P_{O_2} may be paradoxically low because of the presence of pulmonary edema. In one review of the 177 consecutive patients admitted to an intensive care unit for salicylate intoxication, 47% had respiratory failure, 94% required mechanical ventilation, abnormal clotting studies were noted in 38%, and 36% were acidemic.[117] There was a 15% mortality. Treatment of salicylate-induced noncardiac pulmonary edema depends on the severity of the edema; some patients require intubation and even hemodialysis. Treatment with forced alkaline diuresis is often recommended, but this is dangerous in patients who already have pulmonary edema.

Leatherman and Schmitz have described a pseudosepsis syndrome associated with chronic salicylate ingestion.[118] Most patients had fever, leukocytosis, hypotension, and multiple organ failure, including acute respiratory distress syndrome. This condition is easily missed unless salicylate intoxication is suspected and the blood salicylate level is measured.

Other Nonsteroidal Anti-inflammatory Drugs

Most of the nonsteroidal anti-inflammatory agents can produce the same side effects as aspirin, including aggravation of asthma, noncardiac pulmonary edema, drug-induced SLE, and pulmonary infiltrates with eosinophilia. Naproxen may be more commonly associated with an infiltrate and eosinophilia than are the other agents.[119] A few agents can cause hypervolemia and, in turn, pulmonary edema through the mechanism of increased sodium retention through the kidneys.

Gold

Gold has been used since ancient times for treating various immunologic disorders, including rheumatoid arthritis. There are now a number of reports of diffuse interstitial pneumonitis and fibrosis associated with gold that are believed to be separate from that of rheumatoid lung. Interstitial pneumonitis is more commonly observed in patients taking sodium aurothiomalate than in those taking aurothioglucose, but this may reflect the more

common use of the former drug. Symptoms of dyspnea with or without fever begin insidiously several weeks to months after initiation of weekly intramuscular injections of gold. A few reports have demonstrated peripheral blood eosinophilia, but this is uncommon. Pleural effusion is not associated with this reaction.

In diffuse interstitial pneumonitis and fibrosis, the chest roentgenogram shows a predominantly interstitial process. Bronchoalveolar lavage usually demonstrates a high percentage of lymphocytes. Histologically, the lung demonstrates fibrosis with an interstitial infiltrate of lymphocytes and plasma cells and focal hyperplasia of type II pneumocytes. Electron microscopy demonstrates electron-dense structures within lysosomes of endothelial cells of the alveolar capillaries and interstitial macrophages. Microanalysis with an electron probe shows that these electron-dense structures contain gold, suggesting that a direct toxic effect might be an important mechanism in the pathogenesis of gold-induced pulmonary reactions. However, there are no control studies of lungs in patients who are taking gold but do not develop gold pneumonitis.

Other associated complications of gold are often present, such as dermatitis, neuropathy, and proteinuria. Secondary infections have not been reported as a complication of gold pneumonitis, nor have there been deaths reported from irreversible lung fibrosis. The treatment may be as simple as withdrawing the drug and allowing the process to resolve spontaneously. However, a number of patients have required corticosteroids for reversal. Gold pneumonitis is not thought to be related to rheumatoid fibrosis, in that the parenchymal disease improves spontaneously with stopping gold or almost always regresses with use of corticosteroids.

Penicillamine

There are three possible pulmonary complications with the use of penicillamine with no apparent overlap: penicillamine-induced SLE, bronchiolitis obliterans, and Goodpasture's syndrome. Some patients with penicillamine-associated pneumonitis or alveolitis have high titers of antinuclear antibodies. Penicillamine-induced disease appears to be one of the more common causes of drug-induced SLE. This condition should always be considered in the patient receiving penicillamine, especially if a pleural effusion is present. A normal concentration of sugar in the effusion fluid virtually eliminates the possibility of a rheumatoid effusion.

Penicillamine-associated bronchiolitis obliterans is probably underestimated in its incidence and severity. There is little information on pulmonary function in rheumatoid patients before initiation of penicillamine that compares patients who subsequently develop bronchiolitis obliterans with those who do not experience obstructive physiology. Perhaps there is a predisposing obstructive lung disease in the rheumatoid patient that is worsened by penicillamine in the form of a bronchiolitis obliterans. Corticosteroids have little benefit in treating this condition, which usually presents in an advanced state.

There have also been several case reports of penicillamine-associated Goodpasture's syndrome with diffuse alveolar hemorrhage.[120] If recognized early enough, appropriate therapy with hemodialysis, plasmapheresis, and immunosuppression may prevent a serious outcome.

Leflunomide

Several new agents have in recent years been found to be efficacious in the treatment of inflammatory conditions with a considerably improved safety profile when compared to the previous regimens used. Leflunomide received its FDA approval in 1998 and is currently used to treat rheumatoid arthritis as well as psoriatic arthritis. It is a pyrimidine synthesis inhibitor via inhibition of the dihydroorotate dehydrogenase enzyme and exerts mainly an immunomodulating effect, although it was also found to exert significant anti-inflammatory effects. Its main described adverse effect is liver toxicity, and it may act synergistically with methotrexate with a heightened degree of hepatotoxicity. More recently, several patterns of lung injury have been observed with leflunomide, mostly consisting of hypersensitivity reactions. In a postmarketing surveillance study, significant lung toxicity was identified in 61 of 5053 patients, with 24 patient deaths directly related to the pulmonary complications. Preexisting lung disease, and to a lesser degree loading dose, a smoking history, and low body weight, were identified as independent risk factors in multivariate analysis. A recent case-control study did not document a higher incidence of lung toxicity in individuals treated with leflunomide without preexisting lung disease or prior methotrexate use.[121] True hypersensitivity pneumonias have also been reported in case series, as defined by interstitial infiltrates associated with ill-defined granulomas.[122] Nonspecific infiltrates with or without eosinophilia have also been reported. Diffuse alveolar hemorrhage and pulmonary alveolar proteinosis are rarely encountered.

Biologic Agents

These agents have truly revolutionized the management of a number of chronic inflammatory conditions such as rheumatoid arthritis, inflammatory bowel diseases, and psoriasis. Anti–tumor necrosis factor-α (TNF-α) medications such as infliximab (a chimeric monoclonal antibody targeting TNF-α) or etanercept (a soluble TNF-α receptor) have been used with various success in these conditions by directly interfering with the very first steps of the inflammatory cascade. Not unexpectedly, infections are a major complication of these treatments—tuberculosis in particular, which may easily reactivate in a context of impaired T-cell immunity. Tuberculosis skin tests or blood assays for *Mycobacterium tuberculosis* are mandatory prior to initiation of treatment. Extrapulmonary manifestations seem relatively common (40 of 70 patients in an initial report), with most cases occurring in areas with a low incidence of tuberculosis, perhaps because these drugs tend to be used in more

developed countries. Interestingly, other opportunistic infections, including fungal lung infections, although described, are less of a concern with these agents. Multiple patterns of lung injury have been described with infliximab, including acute hypersensitivity reactions with or without eosinophilia, nonspecific interstitial pneumonitis, de novo usual interstitial pneumonia (UIP), or exacerbation of rheumatoid arthritis–associated UIP and vasculitis.[123] Two other anti–TNF-α medications, adalimumab and etanercept, have also been described in association with pulmonary fibrosis, but these associations are relatively weak and mainly based on isolated case reports.

Leukotriene Antagonists

Recent reports have associated zafirlukast and related leukotriene antagonists with manifestations of Churg-Strauss syndrome.[124,125] These potent agents have been employed in treating asthma. As zafirlukast is added to an asthmatic treatment regimen, corticosteroids are frequently tapered. A number of cases have been described with patients exhibiting pulmonary infiltrates, cardiomyopathy, and eosinophilia while receiving zafirlukast. It is currently unknown whether these medications actually trigger these reactions, or whether they are unmasking a preexistent infiltrative eosinophilic disorder as the corticosteroids are withdrawn. In either event, the pulmonary reaction responds to discontinuation of zafirlukast and reinstitution of corticosteroids.

Corticosteroids

Corticosteroids given in immunosuppressive doses are well known for predisposing patients to the development of opportunistic infections. A most unusual adverse effect of corticosteroids is mediastinal lipomatosis, the deposition of mediastinal fat, which produces a widening of the mediastinum that mimics lymphadenopathy or other neoplasms (Fig. 72-6). Clinically, these patients have a cushingoid appearance, with rounded facies and a "buffalo hump." The same kind of fat that deposits in the buffalo hump occurs in the mediastinum. The chest roentgenogram does not show the lumpiness usually expected with adenopathy. Computed tomography can usually make this diagnosis by establishing radiographic fat density throughout the mediastinal mass (see Fig. 72-6). Mediastinal lipomatosis does not necessitate tapering corticosteroids because the fat does not compromise vital structures.

DRUG-INDUCED SYSTEMIC LUPUS ERYTHEMATOSUS

Over 50 drugs have been reported to induce the SLE syndrome, but only 5 regularly induce antinuclear antibodies in patients taking them: hydralazine, procainamide, isoniazid, hydantoins, and penicillamine. Only a small percentage of the patients on these drugs develop the clinical syndrome that involves the pleuropulmonary system in over half the cases (see the earlier discussion on mechanisms of drug-induced injury). It is thought that patients who develop antinuclear antibodies to these drugs are "slow acetylators." Symptoms almost always begin insidiously after the patient has been taking the drug for many months or even years. Systemic signs and symptoms of polyarthralgia, myalgia, fever, pleurisy, and cutaneous lesions are common. However, renal disease is very uncommon, possibly because complement is not as often involved in the drug-induced form of SLE compared to the spontaneous type.

The antinuclear antibody assay is positive in all patients with drug-induced SLE. However, the test for anti-native (anti–double-stranded) DNA is negative. The complement level may or may not be abnormal. A Coombs' test is positive in about one third of patients. An elevated erythrocyte sedimentation rate and hypergammaglobulinemia are common nonspecific findings.

The chest roentgenographic findings of the drug-induced form of the disease are indistinguishable from spontaneous-onset SLE and include pleural effusions in one third of patients, basilar infiltrates, pneumonitis with atelectasis, and apparent cardiomegaly from pericardial effusion. Pleural fluid glucose is normal or at least correlates with the blood glucose levels.

The symptoms usually resolve once the drug is discontinued. However, occasionally it is necessary to add corticosteroids for more rapid resolution of disabling symptoms. If the offending drug cannot be discontinued for clinical reasons, the lowest dose should be used, along with the addition of corticosteroids.

INHALANTS

Oil

Aspirated oil can produce a variety of pulmonary diseases, ranging from an asymptomatic solitary nodule to diffuse disease with severe respiratory insufficiency.[126,127] Most commonly, however, the diseases present in an asymptomatic individual with an incidental finding of an abnormal chest roentgenogram that mimics a more serious process such as bronchogenic carcinoma. Because patients rarely consider oily nose drops, oily eye lubricants, or mineral oil as a medication, they rarely volunteer that they are taking oil-containing medications.

There are three types of oil: mineral oils, neutral oils, and animal fats. Mineral oils are the most commonly aspirated oils. Oily droplets are taken up by macrophages that eventually disintegrate and release the oil, which in turn inhibits ciliary activity. Thus, the oil is not expectorated and the cycle is repeated again. Eventually, a fibrotic or granulomatous reaction occurs. Neutral or vegetable oils (e.g., olive or castor oil) do not elicit a local reaction and are removed by expectoration. Animal fats (e.g., milk, butter) are rapidly hydrolyzed, with the liberated fatty acids producing tissue necrosis and

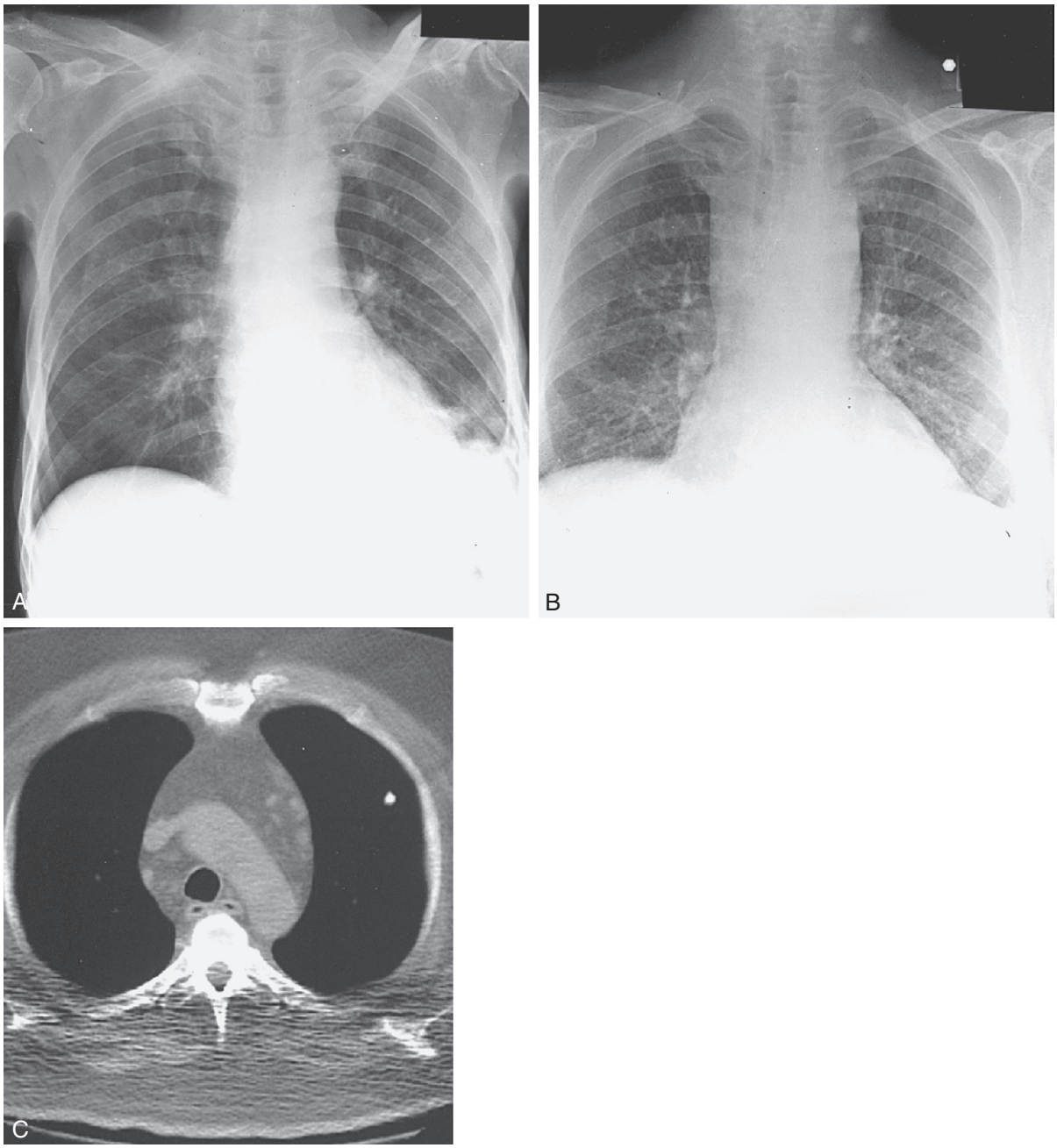

FIGURE 72-6 ■ Mediastinal lipomatosis in response to corticosteroids. **A,** Chest roentgenogram prior to systemic corticosteroid administration. **B,** Chest roentgenogram after corticosteroid administration shows widened mediastinum. **C,** Computed tomography scan of the chest shows mediastinal lipomatosis, with radiographic fat density surrounding the great vessels and tracheal shadows.

subsequent fibrosis. The diagnosis can be established with the demonstration of oil in the lung tissue. Computed tomography and magnetic resonance imaging have been used in diagnosing lipoid-induced infiltrates.[126] The "CT angiogram" sign, defined by the ability to distinguish the pulmonary vasculature within an area of consolidation, was once thought to be fairly specific for lipoid pneumonitis, but may be seen in a variety of unrelated conditions. Treatment involves the discontinuation of the oil-containing medication. Once this occurs, progression is unlikely.

Oxygen

Exposure to high concentrations of oxygen may contribute to or aggravate the acute respiratory distress syndrome. There are two theories as to the mechanism of oxygen-induced pulmonary disease. The first is that a high fraction of inspired oxygen induces formation and release of free oxidant radicals. These short-lived molecules damage DNA, destroy lipid membranes, and inactivate intracellular enzymes.[128] The other theory is that hyperoxia produces a direct injury to endothelial cells

and type I epithelial cells, which results in alveolar-capillary leak.[129]

Studies in volunteers breathing 100% oxygen for 6 to 48 hours produced variable effects, but in some a tracheobronchitis occurred, with symptoms of substernal burning, chest tightness, and nonproductive cough. It also produced a reduction in vital capacity and carbon monoxide diffusing capacity. The development of tolerance to hyperoxia appears to be related to the ability of the individual to increase the production of antioxidants, a mechanism that may be determined genetically.

The sequelae of oxygen toxicity are separable into two phases, the acute, or exudative, phase and the subacute proliferative phase; however, there is considerable overlap between the two phases, with the proliferative phase beginning after the fourth to seventh day. The exudative phase begins within 48 to 72 hours, depending on the fraction of inspired oxygen, and is associated with perivascular, interstitial, and alveolar edema with atelectasis, as well as alveolar hemorrhage. This phase appears to be reversible.

The proliferative phase is characterized by progressive resorption of exudates and hyperplasia of type II cells. This is followed by the deposition of collagen and elastin in the interstitium and hyaline membrane deposition. This is usually an irreversible phase. Clinically, hypoxemia and diminished compliance progress, requiring a greater fraction of inspired oxygen and assisted ventilation, further aggravating the problem. The chest roentgenogram shows an alveolar-interstitial pattern in an irregular distribution, with evidence of moderate loss of volume from patchy atelectasis.

There is no clinical way of diagnosing oxygen toxicity. A lung biopsy specimen may show changes consistent with oxygen toxicity, but the primary value of the biopsy is to exclude other causes of lung injury. Keeping the arterial P_{O_2} less than 80 mm Hg or the inspired fraction of oxygen below 0.40 to 0.50 minimizes the chance of oxygen toxicity developing. Barotrauma and ventilator-induced injury may accompany and be indistinguishable from oxygen toxicity.

TRANSFUSION-RELATED ACUTE LUNG INJURY

Acute alveolar damage as a result of transfusion reaction is probably one of the more rarely recognized adverse drug reactions, if one considers transfused blood or its products a form of drug. The damage is usually the result of donor antibodies against leukocyte antigens or donor leukocyte-specific immune cells reacting against the recipient's leukocytes.

In about 5% of the cases, the recipient's antileukocyte antibodies react against the donor leukocytes. The acute alveolar damage reaction is not a hemolytic transfusion reaction or an anaphylactic reaction. In a recently published nested case-control study, 74 (8%) of 901 critically ill patients who had received blood products developed transfusion-related acute lung injury (TRALI), as defined by onset within 6 hours of transfusion.[130] The main risk factors identified were sepsis and history of alcohol abuse. Transfusion with products from female donors, especially with a higher number of pregnancies, increased the odds of developing TRALI. The likelihood of a TRALI reaction also increased with the number of blood products given, the presence of anti–human leukocyte antigen class II antibodies and the concentration of lysophosphatidylcholine in the product.

The clinical presentation is that of onset of dyspnea, cough, fever, and hypotension within a few hours of receiving a transfusion. An urticarial rash occurs in about half of these patients. The onset of symptoms can occur in response to as little as 50 mL of transfused blood or blood products. Levels of C3 or C5 complement may decline within 12 to 36 hours of the onset of symptoms, further suggesting the diagnosis. The pulmonary artery wedge pressure is always normal. This is in contrast with transfusion-associated circulatory overload, which may present in a similar fashion, albeit with elevated left-sided filling pressures.

The source of the antibodies is almost always blood taken from multiparous women who have had three or more pregnancies. Approximately 7% of all multiparous women carry human leukocyte antigen antibodies in their blood.[131] It is recommended that donor blood of all multiparous women be screened for these antibodies and, if found, only the frozen or washed erythrocytes should be used.

The treatment of leukoagglutinin-mediated noncardiac pulmonary edema is supportive, including assisted ventilation if necessary and supplemental oxygen. It is unknown whether a short course of high-dose corticosteroids is beneficial, but it is certainly worth considering. The course of the noncardiac pulmonary edema is usually limited to 72 hours or less.

RADIOGRAPHIC CONTRAST MEDIUM–INDUCED LEUKOSTASIS

The symptoms and signs produced by complement-induced granulocyte aggregation associated with radiographic contrast media are frequently attributed to an allergic reaction and may cause noncardiac pulmonary edema. Anaphylaxis as a cause can be eliminated by the absence of urticaria or other rash, and by the absence of significant laryngeal edema or bronchospasm. Histologic examination of the lungs demonstrates aggregates of granulocytes obstructing microscopic pulmonary arterioles and capillaries. These findings can be overlooked if not carefully sought or if the autopsy or examination of lung tissue is not done within a few hours of the reaction.

Clinically, the onset of symptoms of dyspnea and hypoxemia begins within a few minutes to an hour of the injection of the radiographic contrast medium. There is not necessarily a history of an allergic reaction to iodine. Treatment is supportive and includes a trial of high-dose corticosteroids, although this may be ineffective.

The activation of complement and, in turn, the generation of C5a stimulates granulocytes to aggregate and to adhere to endothelium, releasing proteases and toxic

oxygen compounds. These, in turn, produce endothelial damage and capillary leakage. One study found high postmortem plasma histamine levels, which were thought to represent mast cell activation.[132]

MISCELLANEOUS DRUGS

Tocolytic-Induced Pulmonary Edema

Tocolytics are agents that have been widely used in the treatment of premature labor. The most commonly used drugs are terbutaline, albuterol, ritodrine, and other β-mimetic drugs. There are many reports of these agents inducing pulmonary edema in otherwise healthy women. The incidence varies from 0.5% to 5% of those receiving these drugs. Predisposing factors include the use of corticosteroids, twin gestation, fluid overload (particularly with saline), and anemia. The β-mimetic drugs typically stimulate β_2-adrenergic receptors, increase the maternal pulse rate and the cardiac output, and produce peripheral vasodilation. Hemodilution occurs and can be detected by a drop in the hemoglobin, hematocrit, and albumin. The blood pressure may drop as a result of the peripheral vasodilation and be a sign that too much tocolytic drug has been given.

A typical clinical scenario is as follows. In spite of the tocolytic agent, labor continues; the tocolytic agent is then stopped, and corticosteroids are added to accelerate fetal lung maturation. With the discontinuation of the tocolytic, the vasodilated vessels return to normal tone with a reduction of the intravascular volume. During delivery, further autotransfusion due to uterine contractions occurs, and pulmonary edema develops, usually in the postpartum period.

There are conflicting reports of the wedge pressure ranging from normal to elevated. In one study, patients with an elevated wedge pressure had normal left ventricular function by echocardiography. At this point, it is uncertain whether the pulmonary edema is truly cardiac or noncardiac in origin.

The treatment is oxygen and diuresis. In certain cases, consideration has been given to resuming the tocolytic agent merely to reproduce the peripheral vasodilation and allow an increase in the resumption of the intravascular volume that was present before the tocolytic agent was withdrawn. Corticosteroids aggravate the situation by their mineralocorticoid effect, which promotes fluid retention. The differential diagnosis includes aspiration of gastric contents, left-sided heart failure, amniotic fluid embolism, and overtransfusion.

Hydrochlorothiazide

There are over 40 reported cases of acute onset of diffuse pulmonary infiltrates associated with the ingestion of hydrochlorothiazide.[133] It may begin with the first dose or days later; 90% of cases occur in women who take the drug intermittently rather than daily, presumably for fluid retention. Symptoms consist of fairly rapid onset of dyspnea that clears within 48 to 72 hours of discontinuing the drug. A low-grade fever may be present. There is no eosinophilia and no positive antinuclear antibodies. The chest roentgenogram shows a diffuse bilateral alveolar-interstitial infiltrate. In the few cases studied, the pulmonary capillary wedge pressure was normal.

Methysergide, Bromocriptine, and Cabergoline

Methysergide, bromocriptine, and cabergoline are structurally similar and produce similar pleuropulmonary reactions. Methysergide is now rarely used to treat vascular headaches because there are better alternative drugs. Bromocriptine and cabergoline are used for the treatment of Parkinson's disease. The pleuropulmonary disease produced by both of these agents has an insidious onset. The predominant feature is pleural thickening and effusion, which is reversible by discontinuing the medication. Effusions are rarely large, are not commonly associated with pleuritic pain, and may show lymphocytosis.[134]

Dextran

Hyskon is a low-molecular-weight dextran that is capable of producing a noncardiac pulmonary edema.[135] It is used principally in hysteroscopic surgery, most often for improving fertility, during which the endometrial cavity is distended with approximately 500 mL of low-molecular-weight dextran. The incidence of noncardiac pulmonary edema increases significantly if more than 500 mL is used, endometrial surfaces are excessively irritated, or the procedure lasts more than 45 minutes. In addition to noncardiac pulmonary edema, coagulopathy can also occur.

Amphetaminergic Agents

In the 1960s, excess cases of pulmonary hypertension were associated with the potent anorexigen aminorex fumarate. More recently, pulmonary hypertension has been associated with dexfenfluramine, fenfluramine, and phenteramine.[136] Valvular heart disease has also been associated with these agents.[137] Although these agents have been removed from the market since 2004, a careful drug history must be taken to exclude this possibility in patients presenting with dyspnea, cardiovascular symptoms, or heart murmurs as manifestations typically persist despite discontinuation of the drugs. A recent retrospective study on 340 patients with pulmonary hypertension identified a history of stimulant use in 28.9% of them, including methamphetamine, amphetamine, and cocaine, emphasizing the importance of seeking this part of history that may not be easily volunteered by the patients.

Esophageal Variceal Sclerotherapy

Esophageal variceal sclerotherapy with either sodium morrhuate, sodium tetradecyl sulfate, or ethanolamine

oleate can lead to multiple abnormalities. Typically about 1 mL of one of these substances is injected into or around the varices, and up to 15 to 20 injections are made during a single procedure. Chest roentgenograms taken shortly after the procedure were abnormal in 85% of the cases at the Mayo Clinic, but this was rarely of clinical significance.[138] Pleural effusion occurred in about 25% of patients, mediastinal widening in 33%, atelectasis in 12%, and pulmonary infiltrates in 9%. Fever, chest pain, and difficulty in swallowing were common after the procedure but rarely amounted to a serious problem.

In the literature, pleural effusion occurred in anywhere from zero to 50% of the patients, and most of these patients were asymptomatic.[138] Effusions were more common when a large volume of fluid was injected and the volume per site was increased. Serious complications such as mediastinitis or frank esophageal rupture are rare, but should be suspected if the fever persists for more than 24 hours, the pleural effusion is large, or there is persistent chest pain. The acute respiratory distress syndrome can occur but happens in less than 1% of the patients in whom the procedure is carried out.

Tricyclic Antidepressant Overdose

Tricyclic antidepressant overdose is one of the more common causes of drug emergencies seen in the emergency room setting. About one third of the pulmonary complications that these patients develop are either noncardiac pulmonary edema or aspiration. If hypotension results, cardiac pulmonary edema can occur. Nearly 80% of the patients have an initially widened alveolar-arterial oxygen gradient. Mechanical ventilation may be required in up to three fourths of patients. The greater the drug level, the more likely the patient is to develop pulmonary complications. Nearly one half of the patients have an abnormal chest roentgenogram, and about 10% of the patients develop acute respiratory distress syndrome.

Hydantoin

There has been much confusion in the literature as to whether or not hydantoin produces parenchymal pulmonary disease and mediastinal adenopathy. Reports in the affirmative have been followed by a more detailed patient study refuting the possibility of pulmonary parenchymal disease.[139,140] The only two hydantoin-induced pulmonary diseases are drug-induced SLE and a few rare cases of hypersensitivity pneumonitis that show a predominance of lymphocytes found in the bronchoalveolar lavage fluid or biopsied tissue. The fact that hydantoin is one of the more commonly used drugs over extremely long periods of time and that it has not shown an obvious relationship for the induction of significant pulmonary disease makes it unlikely that there is a true relationship of any consequence.

Dantrolene

Dantrolene is a long-acting skeletal muscle relaxant used in treating patients with spastic neurologic disorders.[141] There have been several case reports of chronic pleural effusion or pericarditis, or both, associated with this drug. Peripheral blood eosinophilia was seen in some patients who were taking dantrolene.

Conclusion

Clinicians must maintain a high index of suspicion that unexplained pulmonary disease may be caused by medications. Most drug-induced pulmonary reactions are reversible if the drug is stopped in time. If necessary, additional measures such as judicious use of corticosteroids may be helpful. There are almost no diagnostic studies available that will confirm the presence of drug-induced lung disease. Rechallenging the patient with the suspected drug is dangerous and generally not indicated. If there is a question of whether or not a medication may be the cause of a particular pulmonary abnormality, one option is to call the medical director of the drug manufacturer, listed in the *Physicians' Desk Reference* (PDR). In addition, a useful website can be accessed at http://www.pneumotox.com.

KEY POINTS

- The frequency of drug-induced pulmonary toxicity may be underestimated, as the diagnosis is one of exclusion in the vast majority of cases.
- Most associations are based on anecdotal reports and circumstantial evidence.
- Potential mechanisms of lung injury include (1) oxidative injury, (2) direct cytotoxic effect, (3) accumulation of phospholipids, and (4) immune-mediated injury.
- Chemotherapy-induced lung toxicity should always be considered in the differential diagnosis of diffuse lung infiltrates as virtually all histopathologic presentations have been described.
- Even in situations in which cumulative toxicity is an issue, screening via serial imaging or physiologic studies is rarely helpful.

References

1. Nebeker JR, Barach P, Samore MH: Clarifying adverse drug events: A clinician's guide to terminology, documentation, and reporting. Ann Intern Med 140:795–801, 2004.
2. Kohn LT, Corrigan JM, Donaldson M (eds): To Err Is Human: Building a Safer Health System. Washington, DC: Institute of Medicine, 1999.
3. Classen DC, Pestotnik SL, Evans RS, Burke JP: Computerized surveillance of adverse drug events in hospital patients. JAMA 266:2847–2851, 1991.
4. Rosenow EC 3rd: The spectrum of drug-induced pulmonary disease. Ann Intern Med 77:977–991, 1972.
5. Limper AH: Drug induced lung disease: New developments. *In* Braunwald E (ed): Harrison's OnLine. New York: MacGraw-Hill Health Professions Division, 2000.
6. Cooper JAD Jr, White DA, Matthay RA: Drug-induced pulmonary disease. Part 2: Noncytotoxic drugs. Am Rev Respir Dis 133:488–505, 1986.
7. Myers JL: Pathology of drug-induced lung disease. *In* Katzenstein AL, Askin F (eds): Surgical Pathology of Non-neoplastic Lung Disease (2nd ed). Philadelphia: WB Saunders, 1990, pp 97–127.
8. Limper AH, Rosenow EC 3rd: Drug-induced interstitial lung disease. Curr Opin Pulm Med 2:396–404, 1996.
9. Rosenow EC 3rd, Limper AH: Drug-induced pulmonary disease. Semin Respir Infect 10:86–95, 1995.
10. Beinert T, Binder D, Stuschke M, et al: Oxidant-induced lung injury in anticancer therapy. Eur J Med Res 4:43–53, 1999.
11. Israel-Biet D, Labrune S, Huchon GJ: Drug-induced lung disease: Review. Eur Respir J 4:465–478, 1991.
12. Martin WJ 2nd, Rosenow EC 3rd: Amiodarone pulmonary toxicity: Recognition and pathogenesis (Part I). Chest 93:1067–1075, 1988.
13. Schoen RT, Trentham DE: Drug-induced lupus: An adjuvant disease? Am J Med 71:5–8, 1981.
14. Wesselius LJ: Pulmonary complications of cancer therapy. Compr Ther 18(3):17–20, 1992.
15. Rosenow EC 3rd, Myers JL, Swensen SJ, Pisani RJ: Drug-induced pulmonary disease: An update. Chest 102:239–250, 1992.
16. Oury TD, Thakker K, Menache M, et al: Attenuation of bleomycin-induced pulmonary fibrosis by a catalytic antioxidant metalloporphyrin. Am J Respir Cell Mol Biol 25:164–169, 2001.
17. Tamagawa K, Taooka Y, Maeda A, et al: Inhibitory effects of a lecithinized superoxide dismutase on bleomycin-induced pulmonary fibrosis in mice. Am J Respir Crit Care Med 161(4 Pt 1):1279–1284, 2000.
18. Jules-Elysee K, White DA: Bleomycin-induced pulmonary toxicity. Clin Chest Med 11:1–20, 1990.
19. Simpson AB, Paul J, Graham J, Kaye SB: Fatal bleomycin pulmonary toxicity in the west of Scotland 1991–95: A review of patients with germ cell tumours. Br J Cancer 78:1061–1066, 1998.
20. Chandler DB: Possible mechanisms of bleomycin-induced fibrosis. Clin Chest Med 11:21–30, 1990.

20a. Aesif SW, Anathy V, Havermans M, et al: In situ analysis of protein S-glutathionylation in lung tissue using glutaredoxin-l-catalyzed cysteine derivatization. Am J Pathol 175:36–45, 2009.

20b. Ghio AJ: Disruption of iron homeostasis and lung disease. Biochim Biophys Acta 1790:731–739, 2009.

20c. Iyer SS, Ramirez AM, Ritzenthaler JD, et al: Oxidation of extracellular cysteine/cystine redox state in bleomycin-induced lung fibrosis. Am J Physiol Lung Cell Mol Physiol 296:L37–45, 2009.

21. Goldiner PL, Carlon GC, Cvitkovic E, et al: Factors influencing postoperative morbidity and mortality in patients treated with bleomycin. Br Med J 1:1664–1667, 1978.
22. Ingrassia TS 3rd, Ryu JH, Trastek VF, Rosenow EC 3rd: Oxygen-exacerbated bleomycin pulmonary toxicity. Mayo Clin Proc 66:173–178, 1991.
23. Abid SH, Malhotra V, Perry MC: Radiation-induced and chemotherapy-induced pulmonary injury. Curr Opin Oncol 13:242–248, 2001.
24. Wolkowicz J, Sturgeon J, Rawji M, Chan CK: Bleomycin-induced pulmonary function abnormalities. Chest 101:97–101, 1992.
25. Sleijfer S, van der Mark TW, Schraffordt Koops H, Mulder NH: Decrease in pulmonary function during bleomycin-containing combination chemotherapy for testicular cancer: Not only a bleomycin effect. Br J Cancer 71:120–123, 1995.
26. Bellamy EA, Husband JE, Blaquiere RM, Law MR: Bleomycin-related lung damage: CT evidence. Radiology 156:155–158, 1985.
27. Van Barneveld PW, Sleijfer DT, van der Mark TW, et al: Natural course of bleomycin-induced pneumonitis: A follow-up study. Am Rev Respir Dis 135:48–51, 1987.
28. Cohen MH, Williams GA, Sridhara R, et al: FDA drug approval summary: Gefitinib (ZD1839) (Iressa) tablets. Oncologist 8:303–306, 2003.
29. Santrach PJ, Askin FB, Wells RJ, et al: Nodular form of bleomycin-related pulmonary injury in patients with osteogenic sarcoma. Cancer 64:806–811, 1989.
30. Linette DC, McGee KH, McFarland JA: Mitomycin-induced pulmonary toxicity: Case report and review of the literature. Ann Pharmacother 26:481–484, 1992.
31. Verweij J, van Zanten T, Souren T, et al: Prospective study on the dose relationship of mitomycin C-induced interstitial pneumonitis. Cancer 60:756–761, 1987.
32. Sheldon R, Slaughter D: A syndrome of microangiopathic hemolytic anemia, renal impairment, and pulmonary edema in chemotherapy-treated patients with adenocarcinoma. Cancer 58:1428–1436, 1986.
33. Fernandez HF, Tran HT, Albrecht F, et al: Evaluation of safety and pharmacokinetics of administering intravenous busulfan in a twice-daily or daily schedule to patients with advanced hematologic malignant disease undergoing stem cell transplantation. Biol Blood Marrow Transplant 8:486–492, 2002.
34. Malik SW, Myers JL, DeRemee RA, Specks U: Lung toxicity associated with cyclophosphamide use. Two distinct patterns. Am J Respir Crit Care Med 154(6 Pt 1):1851–1856, 1996.
35. Akoun GM, White JP: Treatment-induced respiratory disorders. *In* Dukes MNG (ed): Drug-Induced Disorders (Vol 3). Amsterdam: Elsevier, 1989, pp 1–377.
36. Hadjiliadis D, Govert JA: Methemoglobinemia after infusion of ifosfamide chemotherapy: First report of a potentially serious adverse reaction related to ifosfamide. Chest 118:1208–1210, 2000.
37. Mahmood T, Mudad R: Pulmonary toxicity secondary to procarbazine. Am J Clin Oncol 25:187–188, 2002.
38. Dimopoulou I, Bamias A, Lyberopoulos P, Dimopoulos MA: Pulmonary toxicity from novel antineoplastic agents. Ann Oncol 17:372–379, 2006.
39. Wilcox BE, Ryu JH, Kalra S: Exacerbation of pre-existing interstitial lung disease after oxaliplatin therapy: A report of three cases. Respir Med 102:273–279, 2008.
40. Maldonado F, Limper AH, Lim KG, Aubrey MC: Temozolomide-associated organizing pneumonitis. Mayo Clin Proc 82:771–773, 2007.
41. Ahlgren JD, Smith FP, Kerwin DM, et al: Pulmonary disease as a complication of chlorozotocin chemotherapy. Cancer Treat Rep 65:223–229, 1981.
42. Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 37-1990: A 28-year-old man with increasing dyspnea, dry cough, and fever after chemotherapy for lymphoma. N Engl J Med 323:737–747, 1990.
43. Hilliquin P, Renoux M, Perrot S, et al: Occurrence of pulmonary complications during methotrexate therapy in rheumatoid arthritis. Br J Rheumatol 35:441–445, 1996.
44. Gupta N, Ahmed I, Steinberg H, et al: Gemcitabine-induced pulmonary toxicity: Case report and review of the literature. Am J Clin Oncol 25:96–100, 2002.
45. Nelson R, Tarasoff P: Dyspnea with gemcitabine is commonly seen, often disease related, transient, and rarely severe. Eur J Cancer 31:197–198, 1995.
46. Rosado MF, Kett DH, Schein RM, et al: Severe pulmonary toxicity in a patient treated with gemcitabine. Am J Clin Oncol 25:31–33, 2002.
47. Sauer-Heilborn A, Kath R, Schneider CP, Hoffken K: Severe non-haematological toxicity after treatment with gemcitabine. J Cancer Res Clin Oncol 125:637–640, 1999.

48. Casper J, Knauf W, Blau I, et al: Treosulfan/fludarabine: A new conditioning regimen in allogeneic transplantation. Ann Hematol 83(Suppl 1):S70–S71, 2004.
49. Helman DL Jr, Byrd JC, Ales NC, Shorr AF: Fludarabine-related pulmonary toxicity: A distinct clinical entity in chronic lymphoproliferative syndromes. Chest 122:785–790, 2002.
50. Nusair S, Breuer R, Shapira MY, et al: Low incidence of pulmonary complications following nonmyeloablative stem cell transplantation. Eur Respir J 23:440–445, 2004.
51. Vahid B, Marik PE: Pulmonary complications of novel antineoplastic agents for solid tumors. Chest 133:528–538, 2008.
52. Massin F, Coudert B, Foucher P, et al: [Nitrosourea-induced lung diseases]. Rev Mal Respir 9:575–582, 1992.
53. Weinstein AS, Diener-West M, Nelson DF, Pakuris E: Pulmonary toxicity of carmustine in patients treated for malignant glioma. Cancer Treat Rep 70:943–946, 1986.
54. O'Driscoll BR, Hasleton PS, Taylor PM, et al: Active lung fibrosis up to 17 years after chemotherapy with carmustine (BCNU) in childhood. N Engl J Med 323:378–382, 1990.
55. Durant JR, Norgard MJ, Murad TM, et al: Pulmonary toxicity associated with bischloroethylnitrosourea (BCNU). Ann Intern Med 90:191–194, 1979.
56. Gurjal A, An T, Valdivieso M, Kalemkerian GP: Etoposide-induced pulmonary toxicity. Lung Cancer 26:109–112, 1999.
57. Shannon VR, Price KJ. Pulmonary complications of cancer therapy. Anesthesiol Clin North Am 16:563–586, 1998.
58. Ramanathan RK, Reddy VV, Holbert JM, Belani CP: Pulmonary infiltrates following administration of paclitaxel. Chest 110:289–292, 1996.
59. Dimopoulou I, Galani H, Dafni U, et al: A prospective study of pulmonary function in patients treated with paclitaxel and carboplatin. Cancer 94:452–458, 2002.
60. Robert F, Spencer SA, Childs HA, et al: Concurrent chemo-radiation therapy with cisplatin and paclitaxel for locally advanced non-small cell lung cancer: Long-term follow-up of a Phase I trial. Lung Cancer 37:189–199, 2002.
61. Robert F, Childs HA, Spencer SA, et al: Phase I/IIa study of concurrent paclitaxel and cisplatin with radiation therapy in locally advanced non-small cell lung cancer: Analysis of early and late pulmonary morbidity. Semin Radiat Oncol 9(2 Suppl 1):136–147, 1999.
62. Etienne B, Perol M, Nesme P, et al: [Acute diffuse interstitial pneumopathy following docetaxel (Taxotere): Apropos of 2 cases]. Rev Mal Respir 15:199–203, 1998.
63. Dunsford ML, Mead GM, Bateman AC, et al: Severe pulmonary toxicity in patients treated with a combination of docetaxel and gemcitabine for metastatic transitional cell carcinoma. Ann Oncol 10:943–947, 1999.
64. Frankel SR, Eardley A, Lauwers G, et al: The "retinoic acid syndrome" in acute promyelocytic leukemia. Ann Intern Med 117:292–296, 1992.
65. Nicolls MR, Terada LS, Tuder RM, et al: Diffuse alveolar hemorrhage with underlying pulmonary capillaritis in the retinoic acid syndrome. Am J Respir Crit Care Med 158:1302–1305, 1998.
66. Ieki R, Saitoh E, Shibuya M: Acute lung injury as a possible adverse drug reaction related to gefitinib. Eur Respir J 22:179–181, 2003.
67. Kudoh S, Kato H, Nishiwaki Y, et al: Interstitial lung disease in Japanese patients with lung cancer: A cohort and nested case-control study. Am J Respir Crit Care Med 177:1348–1357, 2008.
68. Rosado MF, Donna E, Ahn YS: Challenging problems in advanced malignancy: Case 3. Imatinib mesylate-induced interstitial pneumonitis. J Clin Oncol 21:3171–3173, 2003.
69. Fukuoka M, Niitani H, Suzuki A, et al: A Phase II study of CPT-11, a new derivative of camptothecin, for previously untreated non-small-cell lung cancer. J Clin Oncol 10:16–20, 1992.
70. Masuda N, Fukuoka M, Kusunoki Y, et al: CPT-11: A new derivative of camptothecin for the treatment of refractory or relapsed small-cell lung cancer. J Clin Oncol 10:1225–1229, 1992.
71. Yamada M, Kudoh S, Fukuda H, et al: Dose-escalation study of weekly irinotecan and daily carboplatin with concurrent thoracic radiotherapy for unresectable stage III non-small cell lung cancer. Br J Cancer 87:258–263, 2002.
72. Madarnas Y, Webster P, Shorter AM, Bjarnason GA: Irinotecan-associated pulmonary toxicity. Anticancer Drugs 11:709–713, 2000.
73. Herbst RS, Sandler AB: Non-small cell lung cancer and antiangiogenic therapy: What can be expected of bevacizumab? Oncologist 9(Suppl 1):19–26, 2004.
74. Wagner SA, Mehta AC, Laber DA: Rituximab-induced interstitial lung disease. Am J Hematol 82:916–919, 2007.
75. Bini EJ, Weinshel EH: Severe exacerbation of asthma: A new side effect of interferon-alpha in patients with asthma and chronic hepatitis C. Mayo Clin Proc 74:367–370, 1999.
76. Rubinowitz AN, Naidich DP, Alinsonorin C: Interferon-induced sarcoidosis. J Comput Assist Tomogr 27:279–283, 2003.
77. Kumar KS, Russo MW, Borczuk AC, et al: Significant pulmonary toxicity associated with interferon and ribavirin therapy for hepatitis C. Am J Gastroenterol 97:2432–2440, 2002.
78. Patel M, Ezzat W, Pauw KL, Lowsky R: Bronchiolitis obliterans organizing pneumonia in a patient with chronic myelogenous leukemia developing after initiation of interferon and cytosine arabinoside. Eur J Haematol 67:318–321, 2001.
79. Honore I, Nunes H, Groussard O, et al: Acute respiratory failure after interferon-gamma therapy of end-stage pulmonary fibrosis. Am J Respir Crit Care Med 167:953–957, 2003.
80. Pham PT, Pham PC, Danovitch GM, et al: Sirolimus-associated pulmonary toxicity. Transplantation 77:1215–1220, 2004.
81. Rothenburger M, Teerling E, Bruch C, et al: Calcineurin inhibitor-free immunosuppression using everolimus (Certican) in maintenance heart transplant recipients: 6 months' follow-up. J Heart Lung Transplant 26:250–257, 2007.
82. Duran I, Siu LL, Oza AM, et al: Characterisation of the lung toxicity of the cell cycle inhibitor temsirolimus. Eur J Cancer 42:1875–1880, 2006.
83. Vial T, Descotes J: Clinical toxicity of cytokines used as haemopoietic growth factors. Drug Saf 13:371–406, 1995.
84. Hoelzer KL, Harrison BR, Luedke SW, Luedke DW: Vinblastine-associated pulmonary toxicity in patients receiving combination therapy with mitomycin and cisplatin. Drug Intell Clin Pharm 20:287–289, 1986.
85. Rao SX, Ramaswamy G, Levin M, McCravey JW: Fatal acute respiratory failure after vinblastine-mitomycin therapy in lung carcinoma. Arch Intern Med 145:1905–1907, 1985.
86. Roberts CM, Foulcher E, Zaunders JJ, et al: Radiation pneumonitis: A possible lymphocyte-mediated hypersensitivity reaction. Ann Intern Med 118:696–700, 1993.
87. Arbetter KR, Prakash UB, Tazelaar HD, Douglas WW: Radiation-induced pneumonitis in the "nonirradiated" lung. Mayo Clin Proc 74:27–36, 1999.
88. Holmberg L, Boman G: Pulmonary reactions to nitrofurantoin: 447 cases reported to the Swedish Adverse Drug Reaction Committee 1966–1976. Eur J Respir Dis 62:180–189, 1981.
89. Holmberg L, Boman G, Bottiger LE, et al: Adverse reactions to nitrofurantoin: Analysis of 921 reports. Am J Med 69:733–738, 1980.
90. Prakash UBS: Pulmonary reaction to nitrofurantoin. Semin Respir Dis 2:71–75, 1980.
91. Robinson BW: Nitrofurantoin-induced interstitial pulmonary fibrosis: Presentation and outcome. Med J Aust 1:72–76, 1983.
92. Mendez JL, Nadrous HF, Hartman TE, Ryu JH: Chronic nitrofurantoin-induced lung disease. Mayo Clinic Proc 80:1298–1302, 2005.
93. Camus P, Piard F, Ashcroft T, et al: The lung in inflammatory bowel disease. Medicine (Baltimore) 72:151–183, 1993.
94. Warner WA, Sanders E: Neuromuscular blockade associated with gentamicin therapy. JAMA 215:1153–1154, 1971.
95. Levine SJ, Walsh TJ, Martinez A, et al: Cardiopulmonary toxicity after liposomal amphotericin B infusion. Ann Intern Med 114:664–666, 1991.
96. Parran TV Jr, Jasinski DR: Intravenous methylphenidate abuse: Prototype for prescription drug abuse. Arch Intern Med 151:781–783, 1991.
97. Schmidt RA, Glenny RW, Godwin JD, et al: Panlobular emphysema in young intravenous Ritalin abusers. Am Rev Respir Dis 143:649–656, 1991.
98. Forrester JM, Steele AW, Waldron JA, Parsons PE: Crack lung: An acute pulmonary syndrome with a spectrum of clinical

and histopathologic findings. Am Rev Respir Dis 142:462–467, 1990.
99. McCarroll KA, Roszler MH: Lung disorders due to drug abuse. J Thorac Imaging 6:30–35, 1991.
100. O'Donnell AE, Pappas LS: Pulmonary complications of intravenous drug abuse: Experience at an inner-city hospital. Chest 94:251–253, 1988.
101. Dusman RE, Stanton MS, Miles WM, et al: Clinical features of amiodarone-induced pulmonary toxicity. Circulation 82:51–59, 1990.
102. Xaubet A, Roca J, Rodriguez-Roisin R, et al: Bronchoalveolar lavage cellular analysis and gallium lung scan in the assessment of patients with amiodarone-induced pneumonitis. Respiration 52:272–280, 1987.
103. Camus P, Lombard JN, Perrichon M, et al: Bronchiolitis obliterans organising pneumonia in patients taking acebutolol or amiodarone. Thorax 44:711–715, 1989.
104. Piccione W Jr, Faber LP, Rosenberg MS: Amiodarone-induced pulmonary mass. Ann Thorac Surg 47:918–919, 1989.
105. Zaher C, Hamer A, Peter T, Mandel W: Low-dose steroid therapy for prophylaxis of amiodarone-induced pulmonary infiltrates. N Engl J Med 308:779, 1983.
106. Greenspon AJ, Kidwell GA, Hurley W, Mannion J: Amiodarone-related postoperative adult respiratory distress syndrome. Circulation 84(5 Suppl III):III-407–III-415, 1991.
107. Just-Viera JO, Fischer CR, Gago O, Morris JD: Acute reaction to protamine: Its importance to surgeons. Am Surg 50:52–60, 1984.
108. Chester EH, Schwartz HJ, Fleming GM: Adverse effect of propranolol on airway function in nonasthmatic chronic obstructive lung disease. Chest 79:540–544, 1981.
109. Reynolds RJ, Burford JG, George RB: Using beta-blockers safely in asthma and COPD patients. Respir Dis 2:95–113, 1982.
110. Everitt DE, Avorn J: Systemic effects of medications used to treat glaucoma. Ann Intern Med 112:120–125, 1990.
111. Gauthier-Rahman S, Akoun GM, Milleron BJ, Mayaud CM: Leukocyte migration inhibition in propranolol-induced pneumonitis: Evidence for an immunologic cell-mediated mechanism. Chest 97:238–241, 1990.
112. Ganau G, Lenzi T: Intravenous propafenone for converting recent onset atrial fibrillation in emergency departments: A randomized placebo-controlled multicenter trial. FAPS Investigators Study Group. J Emerg Med 16:383–387, 1998.
113. Feinberg L, Travis WD, Ferrans V, et al: Pulmonary fibrosis associated with tocainide: Report of a case with literature review. Am Rev Respir Dis 141:505–508, 1990.
114. Akoun GM, Cadranel JL, Israel-Biet D, Gauthier-Rahman S: Flecainide-associated pneumonitis. Lancet 337:49, 1991.
115. Cannon GW: Pulmonary complications of antirheumatic drug therapy. Semin Arthritis Rheum 19:353–364, 1990.
116. Ameisen JC, Capron A: Aspirin-sensitive asthma. Clin Exp Allergy 20:127–129, 1990.
117. Thisted B, Krantz T, Stroom J, Sorensen MB: Acute salicylate self-poisoning in 177 consecutive patients treated in ICU. Acta Anaesthesiol Scand 31:312–316, 1987.
118. Leatherman JW, Schmitz PG: Fever, hyperdynamic shock, and multiple-system organ failure: A pseudo-sepsis syndrome associated with chronic salicylate intoxication. Chest 100:1391–1396, 1991.
119. Londino AV Jr, Wolf GL, Calabro JJ, Perrone SJ: Naproxen and pneumonitis. JAMA 252:1853, 1984.
120. Peces R, Riera JR, Arboleya LR, et al: Goodpasture's syndrome in a patient receiving penicillamine and carbimazole. Nephron 45:316–320, 1987.
121. Suissa S, Hudson M, Ernst P: Leflunomide use and the risk of interstitial lung disease in rheumatoid arthritis. Arthritis Rheum 54:1435–1439, 2006.
122. Martin N, Innes JA, Lambert CM, et al: Hypersensitivity pneumonitis associated with leflunomide therapy. J Rheumatol 34:1934–1937, 2007.
123. Ostor AJ, Chilvers ER, Somerville MF, et al: Pulmonary complications of infliximab therapy in patients with rheumatoid arthritis. J Rheumatol 33:622–628, 2006.
124. Knoell DL, Lucas J, Allen JN: Churg-Strauss syndrome associated with zafirlukast. Chest 114:332–334, 1998.
125. Wechsler ME, Garpestad E, Flier SR, et al: Pulmonary infiltrates, eosinophilia, and cardiomyopathy following corticosteroid withdrawal in patients with asthma receiving zafirlukast. JAMA 279:455–457, 1998.
126. Laurent F, Philippe JC, Vergier B, et al: Exogenous lipoid pneumonia: HRCT, MR, and pathologic findings. Eur Radiol 9:1190–1196, 1999.
127. Lipinski JK, Weisbrod GL, Sanders DE: Exogenous lipoid pneumonitis. J Can Assoc Radiol 31:92–98, 1980.
128. Frank L, Massaro D: Oxygen toxicity. Am J Med 69:117–126, 1980.
129. Davis WB, Rennard SI, Bitterman PB, Crystal RG: Pulmonary oxygen toxicity: Early reversible changes in human alveolar structures induced by hyperoxia. N Engl J Med 309:878–883, 1983.
130. Gajic O, Rana R, Winters JL, et al: Transfusion-related acute lung injury in the critically ill: Prospective nested case-control study. Am J Respir Crit Care Med 176:886–891, 2007.
131. Popovsky MA, Abel MD, Moore SB: Transfusion-related acute lung injury associated with passive transfer of antileukocyte antibodies. Am Rev Respir Dis 128:185–189, 1983.
132. Vandenplas O, Hantson P, Dive A, Mahieu P: Fulminant pulmonary edema following intravenous administration of radiocontrast media. Acta Clin Belg 45:334–339, 1990.
133. Biron P, Dessureault J, Napke E: Acute allergic interstitial pneumonitis induced by hydrochlorothiazide. CMAJ 145:28–34, 1991.
134. Kinnunen E, Viljanen A: Pleuropulmonary involvement during bromocriptine treatment. Chest 94:1034–1036, 1988.
135. McLucas B: Hyskon complications in hysteroscopic surgery. Obstet Gynecol Surv 46:196–200, 1991.
136. Mark EJ, Patalas ED, Chang HT, et al: Fatal pulmonary hypertension associated with short-term use of fenfluramine and phentermine. N Engl J Med 337:602–606, 1997.
137. Connolly HM, Crary JL, McGoon MD, et al: Valvular heart disease associated with fenfluramine-phentermine. N Engl J Med 337:581–588, 1997.
138. Edling JE, Bacon BR: Pleuropulmonary complications of endoscopic variceal sclerotherapy. Chest 99:1252–1257, 1991.
139. Chamberlain DW, Hyland RH, Ross DJ: Diphenylhydantoin-induced lymphocytic interstitial pneumonia. Chest 90:458–460, 1986.
140. Michael JR, Rudin ML: Acute pulmonary disease caused by phenytoin. Ann Intern Med 95:452–454, 1981.
141. Miller DH, Haas LF: Pneumonitis, pleural effusion and pericarditis following treatment with dantrolene. J Neurol Neurosurg Psychiatry 47:553–554, 1984.

CHAPTER 73

PLEURAL EFFUSION

V. Courtney Broaddus, MD • Richard W. Light, MD

INTRODUCTION

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TRANSUDATIVE PLEURAL EFFUSIONS
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EXUDATIVE PLEURAL EFFUSIONS
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Actinomycosis
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Parasitic Diseases
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INTRODUCTION

The pleural space is bounded by two membranes, the visceral pleura covering the lung and the parietal pleura covering the chest wall and diaphragm. Into this space, normal liquid and protein enter from the systemic circulation and are removed by the parietal pleural lymphatics. Pleural pressure is subatmospheric and ensures inflation of the lung. Because the mesothelial boundaries are leaky, excess liquid can move across into this lower-pressure, high-capacitance space and collect as a pleural effusion. Thus, pleural effusions are common and of highly diverse etiologies. These effusions can form based on disease of the pleural membranes themselves or of thoracic or abdominal organs. Depending on the protein and lactate dehydrogenase (LDH) concentrations of the liquid and on the cellular composition, these effusions can be categorized initially as exudates or transudates. Exudative pleural effusions meet at least one of the following criteria, whereas transudative effusions meet none (Light's criteria): pleural fluid protein–to–serum protein ratio of more than 0.5, pleural fluid LDH–to–serum LDH ratio of more than 0.6, and pleural fluid LDH more than two thirds of the upper normal limit for serum. In this chapter, we discuss both the physiology and the pathophysiology of liquid movement in the pleural space.

THE PLEURA: FORM AND FUNCTION

These two pleural membranes meet at the hilar root of the lung. In the sheep, an animal with a pleural anatomy similar to that of humans, the surface area of the visceral pleura of one lung, including that invaginating into the lung fissures, is similar to that of the parietal pleura of one hemithorax, approximately 1000 cm^2.[1] The normal pleural space is approximately 18 to 20 μm in width, although it widens at its most dependent areas.[1] It has been shown that the pleural membranes do not touch each other and that the pleural space is a real, not a potential, space[1] (Fig. 73-1).

It is likely that the primary function of the pleural membranes is to allow extensive movement of the lung relative to the chest wall. If the lung adhered directly to the chest wall, its expansion and deflation would be more limited. Encased in its slippery coat, the lung, although still coupled mechanically to the chest wall, is able to expand across a breadth of several intercostal spaces. Nonetheless, in clinical and experimental studies, pleural symphysis has not been associated with large abnormalities in lung function.[2,3] The most common findings have been a decrease in volume of the affected lung and, in one study, of the opposite lung as well.[4] If pleural thickening accompanies pleural symphysis, abnormalities of lung function may result more from fibrothorax than from obliteration of the pleural space alone.

The visceral pleura may also provide mechanical support for the lung: contributing to the shape of the lung, providing a limit to expansion, and contributing to the work of deflation. Because the submesothelial connective tissue is continuous with the connective tissue of the lung parenchyma, the visceral pleura may help to distribute the forces produced by negative inflation pressures evenly over the lung. In this way, overdistention of alveoli at the pleural surface may be avoided, lessening the chance of rupture and pneumothorax.

One more recently recognized function of the pleural space is to provide a route by which edema can escape the lung.[5] As has been shown in several experimental studies of either hydrostatic or increased permeability lung edema,[6,7] the pleural space can function as an additional safety factor protecting against the development of alveolar edema. The formation of transudative effusions in patients with congestive heart failure (CHF) apparently reflects the movement of edema from the lung to a space where its effects on lung function are relatively small.

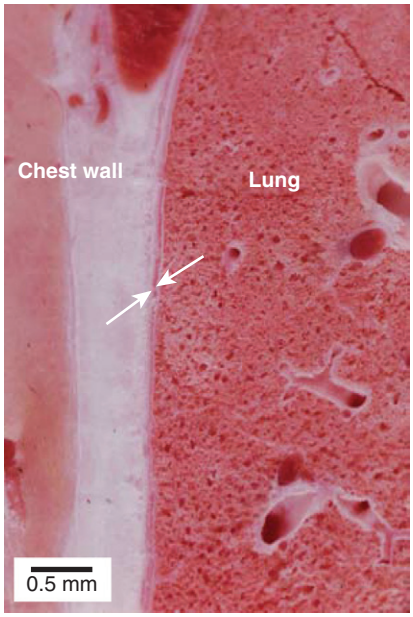

FIGURE 73-1 ■ The pleural space is depicted in a frozen sheep thorax by reflected-light microscopy. The pleural space is seen as a continuous dark band (between *arrows*) between the lung and the chest wall (labeled). (Courtesy of Kurt Albertine, PhD, University of Utah School of Medicine.)

EMBRYOLOGY AND ANATOMY

By 3 weeks of gestational age, the pleural, pericardial, and peritoneal spaces begin to form from the mesoderm and, by 9 weeks, the pleural cavity has become separated from both the pericardial and the peritoneal spaces.[8] Various cysts, diverticula, and defects can result from incomplete partitioning of the three mesodermal spaces. As the lung develops, the lung buds invaginate into the visceral pleura and, henceforth, retain a pleural covering.

The pleural membranes are smooth glistening coverings for the constantly moving lung. Overlying each pleural membrane is a single cell layer of mesothelial cells. These cells can vary in shape from flat to cuboidal or columnar, perhaps based on the degree of stretching of the underlying submesothelial tissue. These cells, the most numerous cell of the pleural space, may have a variety of functions important to pleural biology.[9] Mesothelial cells can secrete the macromolecular components of the extracellular matrix and organize them into mature matrix, phagocytose particles, produce fibrinolytic and procoagulant factors, and secrete neutrophil and monocyte chemotactic factors that may be important for inflammatory cell recruitment into the pleural spaces. The mesothelial cells also produce cytokines such as transforming growth factor-β, epidermal growth factor (EGF), and platelet-derived growth factor, cytokines that are important in pleural inflammation and fibrosis.

On their surface are microvilli, which are irregularly distributed over the pleural surfaces. Although microvilli presumably exist to increase surface area for metabolic activity, the function of these prominent features is unknown. Mesothelial cells produce hyaluronan but not mucin, express keratin microfilaments, stain negatively with epithelial-specific antibodies (Ber-EP4, B72.3, Leu. M1, and CEA), and stain positively for calretinin and mesothelin—all features that are important for histochemical and immunohistochemical identification of the cells in pleural effusions.[10,11]

The cells lie on a thin basement membrane overlying a varying region of connective tissue containing mostly collagen and elastin. Although the parietal pleural connective tissue layer is of a consistent thickness, the visceral connective tissue layer varies greatly. In a single individual, the visceral pleura varies from a thinner layer

at the cranial region to a thicker layer at the caudal region.[12] Analysis of the constituents of the visceral pleura has shown that there is more collagen relative to elastin than is found in the lung parenchyma, a finding consistent with a mechanical role for the pleura.[13] This connective tissue layer contains blood vessels and lymphatics and joins with the connective tissue of the lung.

Blood Supply

The parietal pleura is supplied by intercostal arteries[14] (Fig. 73-2A). The visceral pleura in humans, like that in sheep, is exclusively supplied by the bronchial circulation, which drains into pulmonary veins[12] (see Fig. 73-2B). The drainage route via pulmonary veins may have contributed to earlier confusion about whether the visceral pleural blood supply was from a systemic (bronchial) or a pulmonary circulation. Both pleurae in humans, therefore, have a systemic circulation, although the visceral pleural bronchial circulation may have a slightly lower perfusion pressure than the parietal pleural intercostal circulation because of its drainage into a lower-pressure venous system.

Lymphatics

If one injects carbon particles into the pleural space as a visible marker of lymphatic drainage pathways, one later finds that the black carbon has been taken up into lymphatics on the parietal side, not the visceral side (Fig. 73-3). The visceral pleura has extensive lymphatics, but they do not connect to the pleural space.[12] Demonstrated in rabbits, sheep, and now in humans, the parietal pleural lymphatics connect to the pleural space via stomata, holes of 8 to 10 μm in diameter that are formed by discontinuities in the mesothelial layer where mesothelium joins to the underlying lymphatic endothelium.[15–17] The stomata can accommodate particles as large as erythrocytes. In various experimental studies, these lymphatics have been shown to be the major route of exit of liquid from the pleural space.[18] From the stomata, liquid drains to lacunae, spider-like submesothelial collecting lymphatics, which then drain to infracostal lymphatics, to parasternal and periaortic nodes, to the thoracic duct, and into the systemic venous system. Lymphoid cells have been described lying within aggregates underneath morphologically different mesothelial cells, forming raised structures called *Kampmeier's foci* that may have an immune function, as shown for the peritoneal space.[9]

Nerve Supply

The parietal pleura contains sensory nerve fibers, supplied by the intercostal and phrenic nerves, and has long been thought to be the major site of pain sensation in the pleura. The costal and peripheral diaphragmatic regions are innervated by the intercostal nerves, and pain from these regions is referred to the adjacent chest wall. The central diaphragmatic region is innervated by

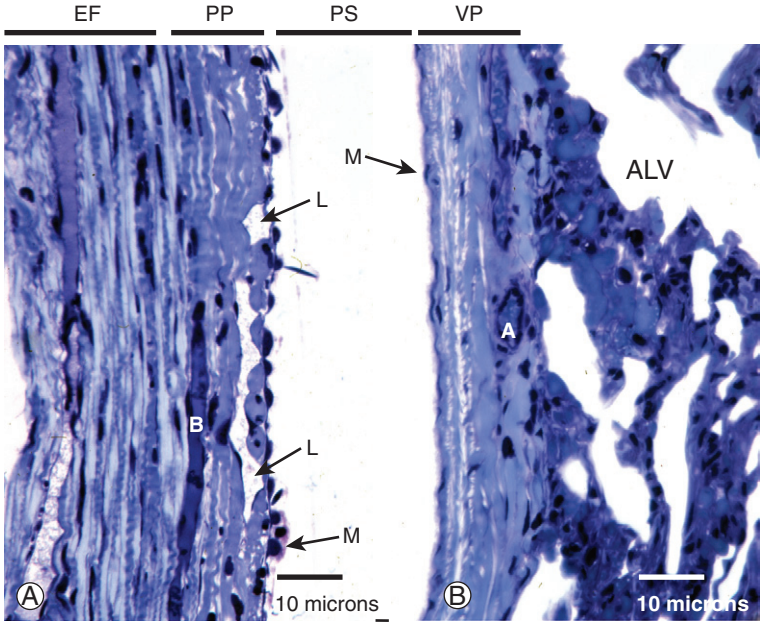

FIGURE 73-2 ■ Light micrograph shows the parietal and visceral pleurae of the sheep, an animal with a similar pleural anatomy to that of humans. Both membranes are covered by a single layer of mesothelial cells (M). The pleural membranes are shown separated by a distance similar to that for the pleural space (PS) of 18–20 microns. **A,** The parietal pleura (PP) is the layer of loose connective tissue between the PS and the dense connective tissue of the endothoracic fascia (EF). Within the loose connective tissue are blood microvessels (B) from the intercostal arteries, and lymphatic lacunae (L) that open into the pleural space via stomata. **B,** The visceral pleural (VP) lies between the pleural space (PS) and the alveoli (ALV). The blood supply to the visceral pleura is via the bronchial arteries (A), which drain into pulmonary veins. The pleura contains dense bands of elastin and collagen. (Reproduced with permission from Staub NC, Wiener-Kronish JP, Albertine KH: Transport through the pleura: Physiology of normal liquid and solute exchange in the pleural space. *In* Chrétien J, Bignon J, Hirsch A [eds]: The Pleura in Health and Disease. New York: Marcel Dekker, 1985, pp 174–175, by courtesy of Marcel Dekker, Inc.)

FIGURE 73-3 ■ Macroscopic photograph of lymphatic lacunae in the parietal pleura over an intercostal space. Colloidal carbon was instilled into the pleural space to label the draining lymphatics. When one looks down upon the pleura, the lymphatic lacunae (L) appear as broad cisterns. B, blood vessel. (Original magnification ×39.) (Reprinted by permission of Wiley-Liss, a division of Wiley and Sons, Inc., copyright owner. © From Albertine KH, Wiener-Kronish JP, Staub NC: The structure of the parietal pleura and its relationship to pleural liquid dynamics in sheep. Anat Rec 208:406, 1984.)

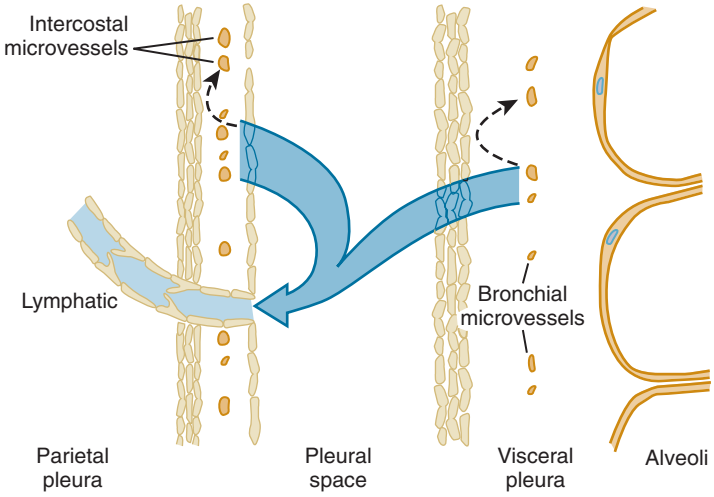

FIGURE 73-4 ■ Schema shows normal pleural liquid turnover. The initial microvascular filtrate in the parietal and visceral pleura is partly reabsorbed (*dashed arrows*). The remaining low-protein interstitial liquid flows across the leaky pleural mesothelial layers into the pleural space. The pleural liquid exits the pleural space via the parietal pleural lymphatic stomata. (Redrawn from Staub NC, Wiener-Kronish JP, Albertine KH: Transport through the pleura: Physiology of normal liquid and solute exchange in the pleural space. *In* Chrétien J, Bignon J, Hirsch A [eds]: The Pleura in Health and Disease. New York: Marcel Dekker, 1985, p 182, by courtesy of Marcel Dekker.)

the phrenic nerve, and pain from this region is referred to the ipsilateral shoulder. The visceral pleura has more recently been shown to have sensory nerve fibers that may participate in pain or other sensations such as dyspnea.[19] In addition, pleural adhesions may contain pain fibers and contribute to post-thoracotomy or post-pleurodesis pain.[20]

PHYSIOLOGY OF THE PLEURAL SPACE

Normal Pleural Liquid and Protein Turnover

Since the 1980s, a consensus has developed that normal pleural liquid arises from the systemic pleural vessels in both pleurae, flows across the leaky pleural membranes into the pleural space, and exits the pleural space via the parietal pleural lymphatics[21,22] (Fig. 73-4). In this way, the pleural space is analogous to other interstitial spaces of the body. There are several lines of evidence for this view.

1. Intrapleural pressure is lower than the interstitial pressure of either of the pleural tissues. This pressure difference constitutes a gradient for liquid movement into but not out of the pleural space.
2. The pleural membranes are leaky to liquid and protein. Whether tested in vitro[23,24] or in situ,[25] the pleura offers little resistance to liquid or protein movement.
3. Mesothelial cells express various transporters and aquaporins but these have not been shown to have a role in reabsorption of effusions.[26] Although normal pleural liquid has been reported to be alkaline with higher bicarbonate than plasma, there is no evidence for active mesothelial participation in generating a bicarbonate gradient, which can more likely be explained by a passive response to protein gradients (Donnan equlibrium).[26a]
4. The entry of pleural liquid is slow and compatible with known interstitial flow rates. By noninvasive studies of the equilibration of radiolabeled albumin, the entry rate of pleural liquid is approximately 0.01 mL/kg/hr in a sheep, or about 0.5 mL/hr or

12 mL/day in an adult human.[27] The halftime of pleural liquid turnover in sheep and rabbits is 6 to 8 hours.[27,28]

5. The protein concentration of normal pleural liquid is low in sheep[27] and probably in humans, which implies sieving of the protein across a high-pressure gradient. The protein concentration of sheep pleural liquid (10 g/L) and pleural–to–plasma protein concentration ratio (0.15) are similar to those of filtrates from high-pressure systemic vessels. By comparison, a filtrate from low-pressure pulmonary vessels has a higher protein concentration (45 g/L) and ratio (lymph–to–plasma protein concentration ratio 0.69).[29]
6. The majority of liquid exits the pleural space by bulk flow, not by diffusion or active transport. This is evident because the protein concentration of pleural effusions remains constant as the effusion is absorbed, as is expected with bulk flow. If liquid were absorbed by diffusion or active transport, proteins would diffuse at a slower rate, and the protein concentration would progressively increase. In addition, erythrocytes instilled into the pleural space are absorbed intact and in almost the same proportion as the liquid and protein.[18] This indicates that the major route of exit is via holes large enough to accommodate sheep erythrocytes (6–8 μm diameter). The only possible exit is via the parietal pleural stomata (10–12 μm diameter) into the pleural lymphatics. Of note, these lymphatics have a large capacity for absorption. When artificial effusions were instilled into the pleural space of awake sheep, the exit rate (0.28 mL/kg/hr) was nearly 30 times the baseline exit rate (0.01 mL/kg/hr).[18]

Pleural Pressure

The pleural pressure in humans is approximately −5 cm H_2O at midchest at functional residual capacity and −30 cm H_2O at total lung capacity.[30] If the compliance of the lung decreased, pleural pressures at the same lung volumes would be more negative. In one study of patients undergoing thoracentesis, those with more negative pleural pressures had a smaller improvement in lung volume than those with less negative pressures, presumably reflecting the presence of underlying diseased, noncompliant lung.[31]

Although the pleural space pressure is subatmospheric, gases do not accumulate there. The sum of all partial pressures of gases in capillary blood is approximately 700 mm Hg, or 60 mm Hg below atmospheric (water pressure [PH_2O] = 47, carbon dioxide pressure [P_{CO_2}] = 46, partial pressure of nitrogen [PN_2] = 570, and oxygen pressure [P_{O_2}] = 40 mm Hg). The subatmospheric pressure of dissolved gases in capillary blood helps to maintain the pleural space free of gas and facilitates absorption of any gas that does enter the pleural space. Of note, to increase the gradient favoring absorption of gas, one can lower the P_{N_2} in the blood by having a patient breathe increased concentrations of inspired oxygen. The oxygen displaces alveolar nitrogen, thereby lowering the P_{N_2} in capillary blood; because of the limited absorption of oxygen due to the plateau of the oxygen-hemoglobin dissociation curve, the increase in inspired oxygen does not add greatly to the P_{O_2} in capillary blood.

PATHOPHYSIOLOGY OF THE PLEURAL SPACE

Pleural Effusions

For pleural liquid to accumulate to form an effusion, it is likely that *both* the entry rate of liquid must increase and the exit rate must decrease. If only the entry rate increased, it would require a sustained rate more than 30 times normal to exceed the reserve lymphatic removal capacity; if the exit rate decreased, it would take more than a month at the normal entry rate of 12 mL/day to produce an effusion detectable by chest radiograph.[22] Thus, in the clinical setting, it is most likely that excess pleural liquid accumulates due to changes in *both* entry and exit rates.

Increased entry of liquid may result from increased filtration across systemic or pulmonary capillaries or entry of another liqud (e.g., chyle, cerebrospinal fluid [CSF], urine, intravenous fluids). Decreased exit of liquid may result from interference with lymphatic function (e.g., obstruction of the parietal pleural stomata, inhibition of lymphatic contractility, infiltration of draining parasternal lymph nodes, or elevation of the systemic venous pressure into which the lymph drains).[22] There are few studies on the rate of removal of liquid in humans; however, decreases in lymphatic clearance have been confirmed in patients with tuberculous and malignant effusions[32] and in those with the yellow nail syndrome, a disease of lymphatic function.[33] In some cases, it is likely that the same disease process acts both to increase the entry and to decrease the exit of liquid, whereas, in other cases, different disease processes may act cooperatively to produce an effusion.

To determine the origin of effusions, a classic and useful distinction is between transudates and exudates (see later, "Separation of Exudates from Transudates").[34] Transudates form by leakage of liquid across an intact capillary barrier owing to increases in hydrostatic pressures or decreases in osmotic pressures across that barrier. Transudates generally indicate that the pleural membranes are not themselves diseased. Exudates form from leakage of liquid and protein across an altered capillary barrier with increased permeability. The protein ratio, the LDH ratio, and the absolute pleural LDH concentration constitute Light's criteria.

Transudates include various low-protein liquids that arise from noninjured capillary beds. The majority of transudates are caused by CHF. These transudates have been shown to form from leakage of edema across normal pulmonary capillaries into the pulmonary interstitium and then across the leaky visceral pleura into the pleural space.[6,35] Other transudates, those associated

with the nephrotic syndrome or atelectasis, may form because of altered pressures (osmotic or hydrostatic) across the pleural capillaries. Some transudates, usually small, may develop primarily because of an isolated decrease in exit rate.[36] Hepatic hydrothorax and effusions from peritoneal dialysis develop when liquid flows from the peritoneal space into the lower pressure pleural space across macroscopic holes in the diaphragm. Finally, other *very* low protein fluids such as urine or CSF or intravenous liquids may find their way to the pleural space if their normal course is disrupted.

Exudates arise from injured capillary beds, in either the lung, the pleura, or adjacent tissues. Most exudates, such as those associated with pneumonia or pulmonary embolism, probably form following lung inflammation and injury when a high-protein lung edema leaks into the pleural space. Another large category of exudates arises from pleural injury due to inflammation, infection, or malignancy. Exudates can also form when exudative liquid in the mediastinum (esophageal rupture or chylothorax), retroperitoneum (pancreatic pseudocyst), or peritoneum (ascites with spontaneous bacterial peritonitis or Meigs' syndrome) finds its way into the lower-pressure pleural space.

As stated, for either transudates or exudates, lymphatic obstruction may contribute to the accumulation of the effusion. Nonetheless, because lymphatic clearance does not alter the pleural fluid protein concentration, the protein concentration gives information about the formation of the fluid, not its removal.[22]

Effects of Pleural Effusions on Lung and Cardiac Function

In the presence of a space-occupying liquid in the pleural space, the lung recoils inward, the chest wall recoils outward, and the diaphragm is depressed inferiorly and is sometimes inverted.[37] If the lung and chest wall have normal compliances, the decrease in lung volume accounts for approximately a third of the volume of the pleural effusion, and the increase in the size of the hemithorax accounts for the remaining two thirds. As a result, lung volumes are reduced by less than the pleural effusion volume. If the lung is otherwise normal, there is no evidence that an effusion causes significant hypoxemia, presumably because ventilation and perfusion decrease similarly. In fact, in one study, hypoxemia was noted only after liquid was removed by thoracentesis,[38] when perfusion presumably was restored while ventilation remained inadequate. In another study using multiple inert gas techniques to quantify ventilation-perfusion (V/Q) distributions, pleural effusion was associated with a small intrapulmonary perfusion shunt (6.9%) that did not change significantly when measured again 30 minutes after thoracentesis of approximately 700 mL (6.1%).[39] It appears, therefore, that the effects of pleural effusion and thoracentesis on oxygenation are variable and may depend on the underlying lung function.

Large pleural effusions may impair cardiac function, most likely by decreasing the distending pressures on the cardiac chambers and cardiac filling. In a study of 27 patients with large effusions occupying more than half the hemithorax, clinical and echocardiographic findings of cardiac tamponade were identified in most patients. These findings, including elevated jugular venous pressure, pulsus paradoxus, right ventricular diastolic collapse, or flow velocity paradoxus, resolved in all patients when studied again 24 hours after thoracentesis of more than 1.0 L.[40] Large pleural effusions, especially left-sided effusions, should be considered as potentially reversible causes of cardiac dysfunction.[41]

Common symptoms of patients with effusions are pleuritic chest pain, cough, and dyspnea. It appears that the three symptoms are due to different causes. Pleuritic chest pain derives from inflammation of the parietal pleura and possibly the visceral pleura. Occasionally, this symptom is accompanied by an audible or palpable pleural rub, reflecting the movement of abnormal pleural tissues. Cough may be due to distortion of the lung, in the same way as cough follows lung collapse from a pneumothorax. Dyspnea is most likely caused by the mechanical inefficiency of the respiratory muscles that are stretched by the outward displacement of the chest wall and the downward displacement of the diaphragm.[37] After the removal of large amounts of pleural liquid, dyspnea is generally relieved promptly, although the reduction in pleural liquid volume is associated with only small increases in lung volume and little improvement, or an actual decrease, in P_{O_2}. In one study, nine patients underwent removal of over 1800 mL of pleural liquid, and despite increases in vital capacity of only 300 mL, all patients experienced immediate relief of dyspnea.[42] Although the vital capacity changed little, patients could generate a more negative pleural pressure at the same lung volume after thoracentesis than before, indicating an improved efficiency of the respiratory muscles following the return of the chest wall and diaphragm to a more normal position after thoracentesis. This improved efficiency of respiration may explain the relief of dyspnea after removal of pleural liquid.

APPROACH TO PATIENTS WITH PLEURAL EFFUSION

Physical findings of a pleural effusion include dullness to percussion, decreased breath sounds, egophony at the upper level of the effusion, and decreased tactile fremitus. With large effusions, signs can include asymmetrical chest expansion or even bulging of the intercostal spaces. A systematic review concluded that the most useful physical findings were dullness to percussion and decreased tactile fremitus.[43]

The possibility of a pleural effusion should be considered in any patient with an abnormal chest radiograph. Increased densities on the chest radiograph are frequently attributed to parenchymal infiltrates when they actually represent pleural fluid. Free pleural fluid gravitates to the most dependent part of the thoracic cavity, which is the posterior costophrenic sulcus when the patient is upright. Therefore, if the posterior costo-

TABLE 73-1. Differential Diagnoses of Pleural Effusions

TRANSUDATIVE PLEURAL EFFUSIONS
- Congestive heart failure
- Pericardial disease
- Hepatic hydrothorax
- Nephrotic syndrome
- Peritoneal dialysis
- Urinothorax
- Myxedema
- Fontan procedure
- Central venous occlusion
- Subarachnoid-pleural fistula
- Veno-occlusive disease
- Bone marrow transplantation
- Iatrogenic

EXUDATIVE PLEURAL EFFUSIONS
- Neoplastic diseases
  - Metastatic disease
  - Mesothelioma
  - Primary effusion lymphoma
  - Pyothorax-associated lymphoma
- Infectious diseases
  - Pyogenic bacterial infections
  - Tuberculosis
  - Actinomycosis and nocardiosis
  - Fungal infections
  - Viral infections
  - Parasitic infections
- Pulmonary embolism
- Gastrointestinal disease
  - Esophageal perforation
  - Pancreatic disease
  - Intra-abdominal abscesses
  - Diaphragmatic hernia
  - Postabdominal surgery
- Collagen vascular diseases
  - Rheumatoid pleuritis
  - Systemic lupus erythematosus
  - Drug-induced lupus
  - Immunoblastic lymphadenopathy
  - Sjögren's syndrome
  - Churg-Strauss syndrome
  - Wegener's granulomatosis
- Postcardiac injury syndrome
- Post–coronary artery bypass surgery
- Asbestos exposure
- Sarcoidosis
- Uremia
- Meigs' syndrome
- Ovarian hyperstimulation syndrome
- Yellow nail syndrome
- Drug-induced pleural disease
  - Nitrofurantoin
  - Dantrolene
  - Methysergide
  - Bromocriptine
  - Procarbazine
  - Amiodarone
  - Dasatinib
- Radiation therapy
- Electric burns
- Iatrogenic injury
- Hemothorax
- Chylothorax

phrenic angle is blunted or if the posterior part of the diaphragm is not visible on the lateral chest radiograph, bilateral decubitus chest radiographs or an ultrasonic examination of the pleural space should be obtained to ascertain whether free pleural fluid is present. If the distance between the inside of the thoracic cavity and the outside of the lung is less than 10 mm, the pleural effusion is not likely to be clinically significant and, in any case, will be difficult to obtain by thoracentesis. If the distance is greater than 10 mm, an effort should be made to determine the cause of the pleural effusion.

Differential Diagnosis of Pleural Effusion

Many different diseases may have an accompanying pleural effusion (Table 73-1). The vigor with which various diagnoses are pursued should depend on the likelihood that the person has that particular disease. Table 73-2 shows rough estimates of the annual incidence of the most common causes of pleural effusions. CHF and cirrhosis are responsible for almost all transudative pleural effusions. Pneumonia, malignant pleural disease, pulmonary embolism, and gastrointestinal disease account for at least 90% of all exudative pleural effusions.

Separation of Exudates from Transudates

A diagnostic thoracentesis should be performed on nearly every patient with free pleural fluid that measures more than 10 mm on the decubitus radiograph. If the patient has obvious CHF, consideration can be given to postponing the thoracentesis until the heart failure is treated. However, if the patient is febrile or has pleuritic chest pain or if the effusions are not of comparable size on both sides, a thoracentesis should be performed without delay.

TABLE 73-2. Approximate Annual Incidence of Various Types of Pleural Effusions in the United States

Type of Effusion	Incidence
Congestive heart failure	500,000
Pneumonia (bacterial)	300,000
Malignant disease	200,000
Lung	60,000
Breast	50,000
Lymphoma	40,000
Other	50,000
Pulmonary embolization	150,000
Viral disease	100,000
Post–coronary artery bypass surgery	60,000
Cirrhosis with ascites	50,000
Gastrointestinal disease	25,000
Collagen vascular disease	6,000
Tuberculosis	2,500
Asbestos exposure	2,000
Mesothelioma	1,500

Adapted with permission from Light RW: Pleural Diseases (5th ed). Philadelphia: Lippincott Williams & Wilkins, 2007.

Thoracentesis is a safe procedure when performed by an experienced operator. Because of the small-bore needle required, it can be safely performed in patients with coagulopathies and thrombocytopenia and in patients on positive mechanical ventilation.[44] Descriptions of technique emphasize proper positioning of the patient, identification of the area of decreased tactile fremitus that is a sensitive physical finding for the level of the effusion, and adequate local anesthesia of parietal pleura as well as of the skin. The needle should run over the top of the rib to avoid the neurovascular bundle that travels in each intercostal space. Of note, this bundle travels in the middle of the intercostal space from the spine for approximately 5 to 6 inches (13 cm) before taking its safer position beneath the upper rib.[44] Thus, one should avoid thoracentesis medial to the midclavicular line.

Complications from thoracentesis include pneumothorax and hemothorax. Estimates of each complication from prospective studies are low (2%–6% for pneumothorax; 1% for hemothorax), with only half of the pneumothoraces requiring chest thoracostomy.[45] Pneumothorax is often associated with procedural events such as aspiration of air, multiple needle passes, and development of new symptoms. The risk for pneumothorax appears to be higher in patients with prior radiotherapy to the chest, multiple prior thoracenteses, or the use of vacuum bottles. In an uncomplicated thoracentesis that is well tolerated by the patient, there appears to be no value for routine chest radiography. In addition, routine post-thoracentesis radiographs rarely show new findings.[45] Thoracentesis may be safer when guided by ultrasound, although given the safety of the procedure in uncomplicated cases and the cost or inaccessibility of ultrasound, ultrasound can be selected for higher-risk procedures. For example, it would be appropriate to use ultrasound guidance for thoracentesis on small or multiloculated effusions or in patients with poor lung function or bullous lung disease.[44]

The first question that should be answered with the diagnostic thoracentesis is whether the patient has a transudative or an exudative pleural effusion (see "Pleural Effusions," earlier). The identification of transudates or exudates is made by analysis of the levels of protein and LDH in the pleural fluid and the serum. Exudative pleural effusions meet at least one of the following criteria, whereas transudative pleural effusions meet none[34]: (1) pleural fluid protein–to–serum protein greater than 0.50; (2) pleural fluid LDH–to–serum LDH greater than 0.60; and (3) pleural fluid LDH greater than two thirds of the upper normal limit for serum. If none of these criteria is met, the patient has a transudative pleural effusion, and the pleural surfaces can be ignored while the CHF, cirrhosis, or nephrosis is treated. In the rare cases in which malignancy has been associated with a transudate, extrapleural effects of the tumor or other causes such as concurrent CHF are the most likely cause as evidenced by the rarity of a positive cytology in those effusions.[22,46]

The previously discussed criteria may misidentify a transudative effusion as an exudative effusion in as many as 25% of cases. If a patient appears to have a transudative effusion clinically, additional tests can be assessed to verify its transudative etiology. If the difference between the protein concentration of serum and the pleura exceeds 3.1 gm/dL, the patient in all probability has a transudative effusion.[47] If pleural concentrations of N-terminal brain natriuretic peptide (NT-BNP) are elevated (>1300 pg/mL), the patient likely has a transudate from a cardiac cause.[48]

Most studies dichotomize pleural effusions into transudates or exudates based on a single cutoff point. An alternative approach recommended by Heffner and coworkers[49] is to use likelihood ratios for identifying whether a pleural fluid is a transudate or an exudate. The idea behind this approach is that the higher a value (e.g., the pleural fluid LDH), the more likely the effusion is to be an exudate, and the lower the value, the less likely the effusion is to be an exudate. When these likelihood ratios are used in conjunction with pretest probabilities using Bayes theorem, posttest probabilities can be derived. The difficulty in using this approach is that estimates of pretest probabilities vary significantly from physician to physician. Moreover, most physicians do not understand the mathematics involved. Nonetheless, this approach does emphasize that it is important to take into consideration the absolute value of the measurements. Very high or very low measurements are almost always indicative of exudates and transudates, respectively, whereas values near the cutoff levels can be associated with either transudates or exudates and can be considered *indeterminate*.

When dealing with a patient who has a high likelihood of having a transudative pleural effusion, the most cost-effective use of the laboratory is to order only protein and LDH levels on the pleural fluid and obtain other laboratory tests only if the fluid turns out to be an exudate. In one study of 320 pleural fluid specimens submitted for analysis, 83 were found to be transudative.[50] For these 83 effusions, 725 additional laboratory tests had been ordered, increasing both the cost and the incidence of false-positive tests (7/9). If one suspects initially that the patient has an exudate or if the fluid turns out to be an exudate, specimens can then be sent for cytology, glucose, cell count and differential, and cultures.

Differentiating Exudative Pleural Effusions

Once it has been determined that the patient has an exudative pleural effusion, one should attempt to determine which of the diseases listed in Table 73-1 is responsible for the effusion, remembering that pneumonia, malignancy, and pulmonary embolism account for the great majority of all exudative pleural effusions. In all patients with undiagnosed exudative pleural effusions, the appearance of the fluid should be noted, and the pleural fluid protein and LDH levels (if not already measured), glucose level, differential cell count, and microbiologic and cytologic studies should be obtained.[51] In selected patients, other tests on the pleural fluid, such as pH, amylase level, antinuclear antibody (ANA)

level, rheumatoid factor level, adenosine deaminase (ADA), lipid analysis, and so forth, may be of value. It is certainly not cost-effective, however, to obtain all these tests routinely on patients with undiagnosed exudative pleural effusions.

Appearance of Pleural Fluid

The gross appearance of the pleural fluid should always be described and its odor noted. If the pleural fluid smells putrid, the patient has a bacterial infection (probably anaerobic) of the pleural space. If the fluid smells like urine, the patient probably has a urinothorax. If the pleural fluid is bloody, a pleural fluid hematocrit should be obtained. If the pleural fluid hematocrit is greater than 50% that of the peripheral blood, the patient has a hemothorax and the physician should strongly consider inserting chest tubes. If the pleural fluid hematocrit is less than 1%, the blood in the pleural fluid has no clinical significance. If the pleural fluid hematocrit is between 1% and 50%, the patient most likely has malignant pleural disease, a pulmonary embolus, or a traumatically induced pleural effusion.[52]

The supernatant of the pleural fluid should be examined if the pleural fluid is turbid, milky, or bloody. If the pleural fluid is turbid when originally obtained, but the turbidity clears with centrifugation, the turbidity is due to cells or debris in the pleural fluid. If the turbidity persists after centrifugation, the patient probably has a chylothorax or a pseudochylothorax. These two entities can be differentiated by the patient's history, examination of the sediment for cholesterol crystals, and lipid analysis of the supernatant. With chylothorax, the disease process is acute, the pleural surfaces are not thickened, there are no cholesterol crystals present, and the pleural fluid triglyceride level is usually above 110 mg/dL (1.24 mmol/L). With pseudochylothorax, the disease process is usually chronic, the pleural surfaces are usually thickened, there may be cholesterol crystals, and the pleural fluid triglyceride level is usually not elevated. (For further discussion of chylothorax and pseudochylothorax, see Chapter 74.)

Pleural Fluid Protein

The pleural fluid protein level tends to be elevated to a comparable degree with all exudative pleural effusions and is, therefore, not generally useful in the differential diagnosis of an exudative pleural effusion. However, if the protein level is above 5.0 g/dL, the likelihood of the diagnosis of tuberculous pleurisy is increased. If the pleural fluid protein level is *very* low (<0.5 g/dL), the patient probably has a urinothorax, an effusion secondary to peritoneal dialysis, a leak of CSF into the pleural space, or an effusion secondary to the misplacement of a central intravascular line.

Pleural Fluid Lactate Dehydrogenase

Whereas pleural liquid protein and LDH arise from filtration from serum and thus serve as indicators of vascular permeability, LDH, as an intracellular enzyme, may also indicate the degree of cell turnover and/or the degree of inflammation within the pleural space. The pleural fluid LDH level is increased to a comparable degree in patients with all categories of exudative pleural effusions and, therefore, is of no utility in the differential diagnosis of exudative pleural effusion.[34] Likewise, the pleural fluid LDH isoenzymes are of limited use in the differential diagnosis of exudative pleural effusions. However, pleural fluid LDH concentration should be measured every time a diagnostic thoracentesis is performed because the level of LDH in the pleural fluid reflects the degree of inflammation in the pleural space. If the pleural fluid LDH concentration increases with serial thoracentesis, the degree of inflammation in the pleural space is worsening and the physician should be more aggressive in pursuing the diagnosis. Alternatively, if the pleural fluid LDH level decreases with serial thoracentesis, the pleural disease is resolving and observation of the patient is indicated.[53]

Pleural Fluid Glucose

A low glucose concentration probably indicates the coexistence of two abnormalities: a thickened, infiltrated pleura leading to an impaired diffusion of glucose into the pleural space plus increased metabolic activity leading to increased glucose utilization within the pleural space. The glucose level should be measured in all undiagnosed exudative pleural effusions because the demonstration of a reduced pleural fluid glucose level (<60 mg/dL, 3.33 mmol/L) narrows the diagnostic possibilities to seven: parapneumonic effusion, malignant effusion, tuberculous effusion, rheumatoid effusion, hemothorax, paragonimiasis, or the Churg-Strauss syndrome.[53] If a patient with a parapneumonic effusion has a pleural fluid glucose level below 40 mg/dL (2.22 mmol/L), tube thoracostomy should be considered. Many patients with rheumatoid pleural effusions have a pleural fluid glucose level below 30 mg/dL (1.66 mmol/L).[54] In contrast, most patients with pleural effusion secondary to systemic lupus erythematosus (SLE) will have a pleural fluid glucose level above 80 mg/dL (4.44 mmol/L).[55] Patients with malignant pleural disease and a low pleural fluid glucose level usually have a positive pleural fluid cytology.[56]

Pleural Fluid White Cell Count and Differential

Pleural liquid that is submitted for white cell count and differential should be sent in a tube with an anticoagulant to prevent the cells from clumping.[57] In the normal pleural space, the cell count has been reported to be 1700 cells/mm^3.[58] In effusions, the cell count has limited diagnostic value. A pleural fluid white blood cell count of 1000/mm^3 roughly separates transudative from exudative pleural effusion, whereas a pleural fluid white blood cell count above 10,000/mm^3 is most common with empyemas and parapneumonic effusions, but is also seen with pancreatitis, pulmonary embolism, collagen

vascular diseases, and occasionally, with malignancy and tuberculosis.[52]

The differential cell count on the pleural fluid is much more useful than the white cell count itself. The normal pleural space contains predominantly macrophages (75%) followed by lymphocytes (23%).[58] A change in differential from this normal distribution provides a clue to the underlying disease process. For the pleural fluid differential cell count, the cells should be partitioned into the following categories: polymorphonuclear leukocytes, eosinophils, small lymphocytes, mesothelial cells, and other mononuclear cells. Pleural effusions due to an acute disease process such as pneumonia, pulmonary embolization, pancreatitis, intra-abdominal abscess, or early tuberculosis contain predominantly polymorphonuclear leukocytes. Pleural effusions due to a chronic disease process contain predominantly mononuclear cells.

Pleural fluid eosinophilia (≥10% eosinophils by differential count) is most commonly due to air or blood in the pleural space. Interleukin-5 (IL-5) appears to be an important factor because the number and percentage of eosinophils in the pleural space are closely correlated with the pleural liquid IL-5 levels.[59] Occasionally, no pleural fluid eosinophils are found in the initial thoracentesis, but many eosinophils are seen in a subsequent thoracentesis most likely due to entry of air or blood caused by the initial thoracentesis.[60] With traumatic hemothorax, pleural fluid eosinophilia does not occur until the second week. The eosinophilia appears to be due to production of IL-5 by $CD4^+$ T cells within the pleural space.[61] At times, the pleural fluid eosinophilia associated with a hemothorax can lead to eosinophilia in the peripheral blood.[62] The bloody pleural effusion complicating pulmonary embolism frequently contains many eosinophils.[63] With pneumothorax, pleural eosinophilia appears within 3 days of the pneumothorax and reaches a peak after 6 days.[64]

After excluding air or blood as the underlying cause, the etiologies of 392 cases of eosinophilic pleural effusions have been reported as follows: idiopathic 40%, malignancy 17%, parapneumonic 13%, tuberculosis 6%, pulmonary embolism 4%, transudates 8%, and other 13%.[65] If the etiology of the eosinophilia is not evident, several unusual diagnoses should be considered. Benign asbestos pleural effusions are frequently eosinophilic. In one series, 15 of 29 patients (52%) with benign asbestos pleural effusions had pleural fluid eosinophilia.[60] Patients with pleural effusions secondary to drug reactions (nitrofurantoin or dantrolene) typically have pleural fluid eosinophilia.[53] The pleural fluid of patients with pleural paragonimiasis is typically eosinophilic with low glucose, low pH, and high LDH level.[66] The Churg-Strauss syndrome is the only other disease that produces this constellation of pleural fluid findings.[67]

Mesothelial cells line the pleural cavities. It is unusual to find mesothelial cells in effusions due to tuberculosis. However, the absence of mesothelial cells is also common with other conditions in which the pleura becomes coated with fibrin, such as a complicated parapneumonic effusion.

Small lymphocytes, when accounting for more than 50% of the white blood cells in an exudative pleural effusion, indicate that the patient probably has a malignant or a tuberculous pleural effusion. Ninety of 96 exudative pleural effusions (94%) in two series with more than 50% small lymphocytes were due to tuberculosis or malignant disease.[52,68] Because these two diseases can be diagnosed with needle biopsy of the pleura, the presence of pleural fluid lymphocytosis should alert the physician to consider needle biopsy of the pleura for diagnosis. In general, separation of pleural lymphocytes into T and B lymphocytes has not been useful diagnostically, because most lymphocytic effusions contain a predominance of T cells ($CD4^+$) whether the diagnosis is malignancy or tuberculosis.[69] Such partitioning can be useful diagnostically, however, when a diagnosis of chronic lymphocytic leukemia or lymphoma is suspected. With these diseases, the pleural lymphocytes are usually of B-cell origin.[70]

Pleural Fluid Cytology

A pleural fluid specimen from every patient with an undiagnosed exudative pleural effusion should be sent for cytopathologic studies. The first pleural fluid cytologic study is positive for malignant cells in up to 60% of the effusions caused by pleural malignancy.[52] If three separate specimens are submitted, up to 90% of effusions due to pleural malignancy have positive cytopathology. The percentage of cases in which cytologic study of the pleural fluid establishes the diagnosis of a malignant pleural effusion ranges from 40% to 87%.[52,71,72] The frequency of positive pleural fluid cytologic tests is dependent on the tumor type. For example, less than 25% of patients with Hodgkin's disease have positive cytology,[73] whereas most patients with adenocarcinomas have positive cytology.[72] The percentage of positive diagnoses is higher if both cell blocks and smears are prepared by standard protocols and examined by an experienced cytologist.[74] Each additional sample may increase diagnostic yield in part by providing a higher percentage of fresher cells as older degenerated cells are largely removed by the earlier thoracenteses. During thoracoscopy, pleural lavage has been found to increase the diagnostic yield, perhaps by harvesting more fresh cells for analysis.[75] The percentage of positive diagnoses is obviously dependent on the skill of the cytologist. Immunohistochemical stains of malignant cells are used to confirm a diagnosis and to specify tumor type, with many new markers recently available.[11,74]

Other Diagnostic Tests for Malignancy

Cytology may be nondiagnostic either because of a problem of specificity (e.g., the malignant cells cannot be differentiated from reactive mesothelial cells and "atypical" benign cells) or because of a problem of sensitivity (e.g., the malignant cells are rare). Several assays are being evaluated for their ability to increase the specificity of cytology for diagnosis of malignancy.[76] Fluorescent in situ hybridization (FISH) with chromosome-

specific probes can confirm abnormal numbers of specific chromosomes (aneuploidy), thereby confirming that abnormal cells are indeed malignant.[77] Early findings of malignancy including DNA methylation can be detected by methylation-specific polymerase chain reaction (PCR),[78] and gene expression patterns can help distinguish mesothelioma and adenocarcinoma.[79] EGF-receptor mutations can predict response to EGF-receptor tyrosine kinase inhibitors. Conversely, biomarkers have generally been disappointing due to nonspecificity. However, serum or pleural fluid mesothelin measurements hold promise for the diagnosis of mesothelioma[80] (see Chapter 75).

Culture and Bacteriologic Stains

Pleural fluid from patients with undiagnosed exudative pleural effusions should be cultured for bacteria (both aerobically and anerobically), mycobacteria, and fungi. Gram's stain should also be obtained. In the case of a probable complicated parapneumonic effusion with an initial negative Gram's stain, the sediment of the pleural fluid should be stained because the bacteria will be precipitated in the sediment along with the white blood cells and the debris.

One potentially useful adjunct is detection of bacterial antigens by countercurrent immunoelectrophoresis (CIE)[81] or latex agglutination[82] or of bacterial DNA by PCR.[83] The antigen-specific assays may be especially useful in children, whose common pathogens, *Staphylococcus aureus*, *Streptococcus pneumoniae*,[83a] and *Hemophilus influenzae*, have antigens available for identification. Amplification and sequencing of bacterial 16S ribosomal RNA has identified bacteria in pleural empyema, showing in one study that the bacteriology of pleural infections differed from that of pneumonia (see later, "Parapneumonic Effusions and Empyema").[84]

Other Diagnostic Tests for Pleural Fluid

Pleural Fluid pH and P_{CO_2}

The pleural fluid pH can be reduced to less than 7.20 with 10 different conditions: (1) complicated parapneumonic effusion, (2) esophageal rupture, (3) rheumatoid pleuritis, (4) tuberculous pleuritis, (5) malignant pleural disease, (6) hemothorax, (7) systemic acidosis, (8) paragonimiasis, (9) lupus pleuritis, or (10) urinothorax.[53] The decreased pleural fluid pH appears to result from lactic acid and carbon dioxide accumulation in the pleural fluid.[85] The pleural fluid pH is most useful in determining whether chest tubes should be inserted in patients with parapneumonic effusions.[86] A fall in the pleural fluid pH appears to be a sensitive indicator that the patient has a highly inflammatory parapneumonic pleural effusion that will require drainage.

The routine measurement of pleural fluid pH is recommended only in patients with parapneumonic effusions. In general, pleural fluids with a low pH also have a low glucose[85]; thus, pleural fluid glucose can be used as an alternative to the pH measurement. When the pleural fluid pH is used as a diagnostic test, it must be measured with the same care as arterial pH. The fluid should be collected anaerobically in a heparinized syringe and placed on ice. If the sample is left open to air, a spuriously high pH value can be obtained because of the rapid loss of carbon dioxide. The pH must be measured with a blood gas machine; a pH meter or indicator paper is not sufficiently accurate.[87] Pleural fluid pH, but not glucose, may be significantly altered by residual air or lidocaine in the syringe.[88] The pleural fluid glucose may be a preferable test when the accuracy of pH measurements cannot be assured.

Pleural Fluid Amylase

The pleural fluid amylase is elevated in patients with pleural effusions secondary to esophageal perforation, pancreatic disease, or malignant disease. However, because such a small percentage of effusions are due to esophageal perforation or pancreatic disease, the routine measurement of pleural fluid amylase is not indicated.[89] In the case of esophageal rupture, the origin of the amylase is the salivary glands.[90] In animal models of esophageal rupture, the pleural fluid amylase concentration is elevated within 2 hours of esophageal rupture.[91] In effusions due to pancreaticopleural fistulas, the amylase concentration is extremely high (>4000 IU/mL), reflective of the concentrations in pancreatic secretions.[92] In approximately 10% of malignant effusions, the pleural fluid amylase level is mildly elevated. The site of the primary tumor in such patients is usually not the pancreas.[93] Malignancy can be differentiated from pancreatic disease with amylase isoenzymes because the amylase with malignant effusions is primarily of the salivary type.[94]

Tests for Collagen Vascular Diseases

About 5% of patients with rheumatoid arthritis[95] and 50% of patients with SLE[96] have a pleural effusion sometime during the course of their disease. At times, the effusions may be the first manifestation of the disease; therefore, these diagnostic possibilities should be considered in patients with undiagnosed exudative pleural effusion.

Measurement of the ANA titer is the best screening test for lupus pleuritis, although it is now evident that a positive pleural fluid ANA is not specific for the diagnosis. Although all patients with lupus pleuritis have a positive pleural liquid ANA (>1:40), the finding of a positive ANA has been found in between 11% and 27% of other effusions.[97] Neither the titer of ANA, the ratio of pleura-to-plasma ANA, or the pattern of staining has been found to increase the specificity for SLE.[98] In fact, a positive pleural fluid ANA in patients without SLE may be associated with malignancy.[98] In patients with SLE, the lack of ANA in pleural liquid may have a high negative predictive value; in one study of patients with SLE and a pleural effusion of uncertain etiology, a lack of ANA (dsDNA, extractable nuclear antigens [ENA]) in the pleural fluid argued against the diagnosis of lupus pleuritis.[99]

When a rheumatoid pleural effusion is suspected, the clinical picture usually establishes the diagnosis. If any question exists, the level of rheumatoid factor in the pleural fluid should be measured. Only patients with rheumatoid pleuritis have a pleural fluid rheumatoid factor titer equal to or greater than 1:320 and equal to or greater than the serum titer.[100]

Adenosine Deaminase

ADA, a product of activated lymphocytes, catalyzes the conversion of adenosine to inosine and is important for normal immune function. The pleural fluid ADA levels are elevated in almost all patients with tuberculous pleuritis, but not with other conditions even when associated with lymphocytic effusions.[101] Despite earlier concerns about false-negative values in human immunodeficiency virus (HIV)–positive patients, ADA remains a sensitive marker for tuberculous pleurisy in patients with HIV.[102] An occasional patient with empyema, lymphoma, or leukemia may have elevated pleural fluid ADA levels; however, these entities should be relatively easy to differentiate from tuberculosis clinically. Because it is a highly sensitive test, the ADA can be a useful test to exclude the diagnosis of tuberculosis when the ADA level is low (<40 U/L).[103]

Interferon-γ

Interferon-γ (IFN-γ), a T-cell lymphokine, plays a critical role in the effective clinical response to *Mycobacterium tuberculosis*. Pleural liquid IFN-γ is elevated almost exclusively in tuberculous effusions.[104] IFN-γ release assays, however, have had variable results and have not added to the use of ADA or IFN-γ measurements for the diagnosis or exclusion of active pleural tuberculosis.[105]

Molecular Techniques for Diagnosis of Mycobacterium tuberculosis

Four molecular techniques are now available: PCR to detect specific mycobaterial DNA sequences in clinical specimens (pleural liquid or biopsy), nucleic acid probes to identify the organism in culture, restriction fragment length polymorphism to compare strains in epidemiologic studies, and gene-based susceptibility studies to screen for known genes associated with drug resistance.[106]

In theory, PCR tests have a great potential for providing a rapid, highly sensitive and specific diagnosis of mycobacterial infection. In practice, PCR amplification of clinical samples has been limited by a low sensitivity, often little better than culture itself.[107,107a] The decreased sensitivity may be due to degradation of the target DNA by sample processing or by inhibitors of amplification in clinical fluids. Before wide application of PCR assays, considerations will also include its cost and its current inability to identify antibiotic resistance of the organism. In the future, molecular techniques for diagnosis of tuberculosis and for other slow-growing microorganisms will likely prove increasingly important.

Useful Radiographic Tests in Patients with Suspected Pleural Disease

The possibility of a pleural effusion should be considered whenever a patient with an abnormal chest radiograph is evaluated. Two main factors influence the distribution of free fluid in the pleural space. First, the fluid collects in the most dependent part of the thoracic cavity because the lung is less dense than the pleural fluid. Second, because of their elastic recoil, the lobes of the lung, if normal, maintain their traditional shape at all stages of collapse.

When the patient is upright, the fluid first accumulates between the inferior surface of the lower lobe and the diaphragm. If there is less than 75 mL of fluid, it may occupy this position only, without overflowing into the costophrenic sinuses. When more fluid accumulates, it spills over into the posterior costophrenic angle and obliterates the posterior part of the diaphragm on the lateral projection. The possibility of a pleural effusion should be suspected whenever the posterior part of one or both diaphragms is obscured. The presence of a clinically significant amount of free pleural fluid can be excluded if both posterior costophrenic angles are clear.

When there are larger amounts of pleural fluid, the lateral costophrenic angle on the posteroanterior radiograph becomes blunted. Collins and associates[108] demonstrated that at least 175 mL of pleural fluid had to be injected into the pleural space of cadavers before the lateral costophrenic angle was blunted. In some of their cases, more than 500 mL of pleural fluid could be present without blunting the lateral costophrenic angle. As more fluid accumulates, the entire outline of the diaphragm on the affected side is lost, and the fluid extends upward around the anterior, lateral, and posterior thoracic walls, producing opacification of the lung base and the typical meniscus shape of the fluid.

The changes just discussed are suggestive rather than diagnostic of the presence of pleural fluid. Lateral decubitus radiographs or ultrasonic examination should be obtained in most instances when free pleural fluid is suspected. If the entire hemithorax is opacified, decubitus radiographs are of no use because there is no air-containing lung in the hemithorax. The basis for the use of the lateral decubitus view is that free fluid gravitates to the most dependent part of the pleural space. When a patient is placed in the lateral recumbent position, the free pleural fluid on the dependent side accumulates between the chest wall and the lung (Fig. 73-5). As little as 5 mL of pleural fluid can be demonstrated with properly exposed decubitus radiographs.[109] The amount of pleural fluid can be semiquantitated by measuring the distance between the inner border of the chest wall and the outer border of the lung (see Fig. 73-5). As already stated, when this distance is less than 10 mm, the amount of pleural fluid is small, and a diagnostic thoracentesis is usually not attempted.

Pleural fluid may become encapsulated by adhesions anywhere between the parietal and the visceral pleurae

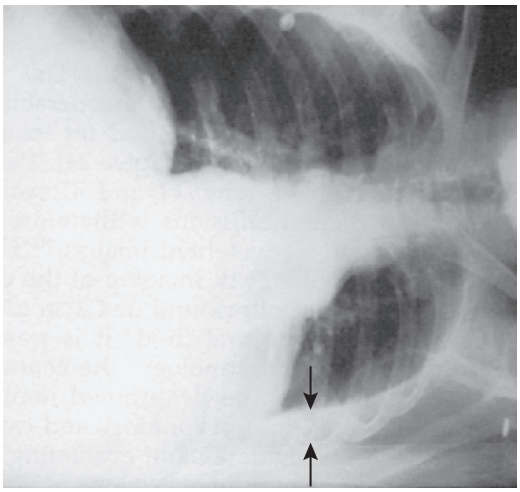

FIGURE 73-5 ■ Left lateral decubitus chest radiograph demonstrates the presence of free pleural fluid. The amount of pleural fluid can be semiquantified by measuring the distance between the two *arrows*.

or in the interlobar fissures. Such loculation occurs most frequently in association with conditions that cause intense pleural inflammation, such as complicated parapneumonic effusion or tuberculous pleuritis. When the loculation is situated between the lung and the chest wall, there is a characteristic radiographic picture. The loculation is D-shaped with the base of the D against the chest wall and the smooth convexity protruding inward toward the lung. The absence of air bronchograms helps differentiate a loculated pleural effusion from a parenchymal infiltrate. A definite diagnosis of loculated pleural effusion is best established by ultrasonography or computed tomography (CT).

Ultrasound

One way to document and locate loculated pleural fluid is with ultrasound. In the presence of pleural fluid, the proximal echoes from the skin, intercostal muscles, and parietal pleura are separated from the distal echoes arising from the visceral pleura and the lung by a central echo-free space. The advantages of ultrasound over CT are the ease and speed with which the examination can be performed, the lack of ionizing radiation, the relatively low cost, and the ability to provide continuous guidance for thoracentesis or pleural biopsy.[110]

The appropriate site for a thoracentesis can be identified using ultrasound, although its routine use is probably not cost-effective.[44] If a patient has a moderate or large effusion, ultrasound is indicated only if no fluid is obtained after two or three attempts. When ultrasound is used to identify the site for thoracentesis, it is important to perform the thoracentesis at the time of the ultrasonic examination. If the skin is marked and the patient returned to her or his room, thoracentesis is frequently unsuccessful, because the relationship between the skin and the pleural fluid may have changed. In addition, when the thoracentesis is performed at the time of the ultrasonic examination, there is immediate feedback that is valuable in improving the skill of the ultrasonographer (see Chapter 20).

Computed Tomography

CT is currently the best way to visualize the pleural space.[110] CT of the chest has its greatest utility in distinguishing parenchymal and pleural abnormalities. With current protocols involving the rapid injection of intravenous contrast medium, the unaerated perfused lung parenchyma will enhance, whereas the pleural abnormality will not.[111]

Chest CT is quite useful in distinguishing a parenchymal lung abscess located near the chest wall from an empyema with an air-fluid level. The most distinctive features are the margins of the abnormality. With empyema, the cavity walls are of uniform thickness both internally and externally and the adjacent lung is usually compressed. The angle of contact with the chest wall may be obtuse. In addition, most empyemas have a lenticular shape and demonstrate the "split-pleura" sign (Fig. 73-6A).[112] With lung abscess, the walls of the cavity are not of uniform thickness and the adjacent lung is not compressed. The angle of contact with the chest wall may be acute (see Fig. 73-6B).

In diffuse pleural disease, chest CT is useful in distinguishing malignant from benign causes. Features associated with malignancy include circumferential pleural thickening, pleural nodules, parietal thickening greater than 1 cm, and mediastinal pleural involvement.[113] The distinction of metastatic disease from mesothelioma can be difficult, although hilar adenopathy is more common with metastatic disease.[110]

CT angiography has become a first-line imaging test for the evaluation of pulmonary embolism[114] (see Chapter 51). The evaluation of a patient with a pleural effusion for pulmonary embolism can begin with a Doppler ultrasound of the lower extremities. If the ultrasound identifies thrombus, the patient can then be treated for thromboembolic disease. If it is negative, the patient may still have a pulmonary embolism. The standard approach had been to proceed to lung V/Q scanning. However, the interpretation of the perfusion lung scan is difficult in patients with pleural fluid because of shifting of the fluid when the patient moves from the supine position for the perfusion scan to the upright position for the ventilation scan. CT angiography instead is highly sensitive and specific for pulmonary emboli in the proximal, segmental pulmonary arteries.[114] In contrast to V/Q lung scanning, CT angiography can establish alternate diagnoses as well. Where CT angiography is not available, lung scanning can be used, perhaps after efforts to improve accuracy by withdrawing as much pleural liquid as possible. A diagnostic scan (normal or high probability) can then be used to either exclude the diagnosis or initiate anticoagulation. If nondiagnostic (e.g., of low or intermediate probability), the scan should be followed by pulmonary angiography.

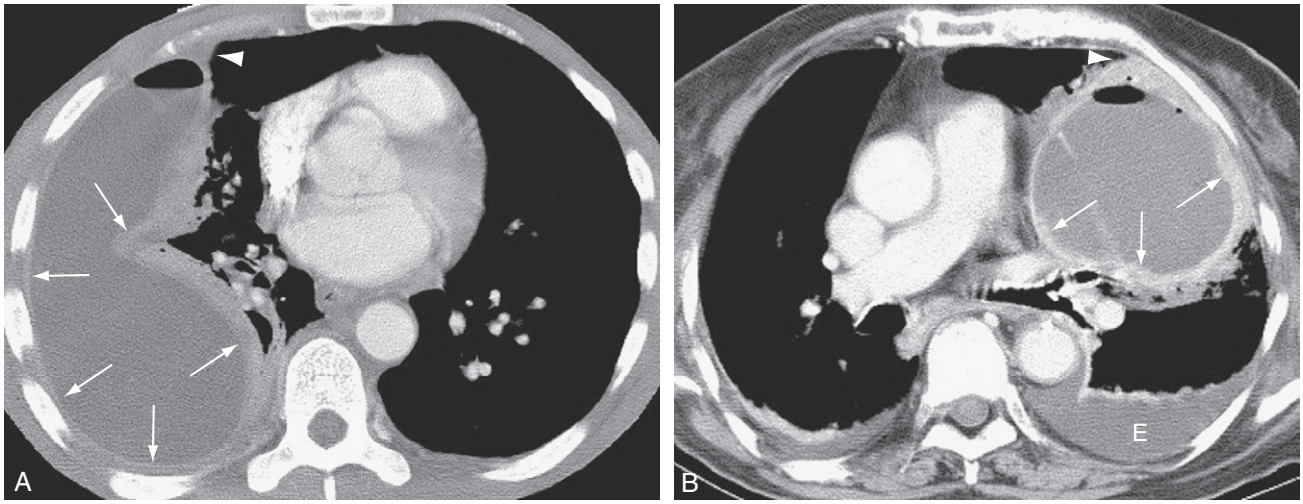

FIGURE 73-6 ■ Typical computed tomography (CT) features of a pleural empyema versus a lung abscess. **A,** Axial CT through the lower thorax in a patient with fever and pleuritic chest pain shows features typical of empyema, including the formation of obtuse angles between the lesion and the chest wall (*arrowhead*), a lenticular shape, a smooth internal surface (*arrows*), and mass effect on surrounding structures (note leftward shift of the heart and compression of intervening lung). Note enhancement and separation of the parietal and visceral pleura, representing the "split-pleura" sign (*arrows*) and the presence of an air-fluid level, indicating the presence of a bronchopleural fistula. **B,** Axial CT through the mid thorax in a patient with fever and cough productive of foul-smelling sputum shows features typical of a pulmonary abscess, including the formation of acute angles between the lesion and the chest wall (*arrowhead*), a round shape, a thick, irregular internal surface (*arrows*), and relatively little mass effect on the lung and mediastinum considering the large size of the lesion. The latter occurs because pulmonary abscesses tend to destroy adjacent lung more than they displace it. Note the presence of an associated pleural effusion (*E*). (Courtesy of Michael B. Gotway, MD, Scottsdale Medical Imaging and the Department of Radiology, University of California, San Francisco.)

Magnetic Resonance Imaging

Pleural effusions generally have long T1 and T2 values. The intensity of pleural effusions is therefore low to extremely low on T1-weighted images.[110] However, at the present time, magnetic resonance imaging (MRI) of the chest is less satisfactory than ultrasound or CT in identifying the presence of pleural fluid. It is possible that with improved MRI technology, the characteristics of pleural fluid can be determined noninvasively. At the present time, respiratory and cardiac motion is the major limitation in evaluating specific intensity patterns of fluid collections of various compositions.

Positron Emission Tomography and Positron Emission Tomography/Computed Tomography

Positron emission tomography (PET) visualizes tissues that are metabolically active by their concentration of the radioisotope ^{18}fluorodeoxyglucose. Because most malignant cells have a higher metabolic rate than non-malignant cells, PET can help differentiate malignant from benign lesions, help stage patients with malignancy, and help identify recurrence.[110] Introduced in 1998, PET/CT integrates the metabolic information of PET with the detailed anatomic information of CT. Compared with CT or PET alone, PET/CT can allow detection of additional lesions, localize them more accurately, characterize them as highly likely to be malignant, and discriminate malignant from surrounding normal tissue[115] (see Chapter 75).

Invasive Tests in Patients with Undiagnosed Exudative Pleural Effusions

In the patient with an undiagnosed exudative pleural effusion, there are several invasive tests that might be considered, including blind or image-guided needle biopsy of the pleura, bronchoscopy, pleuroscopy or video-assisted thoracoscopic surgery (VATS), and open biopsy of the pleura. It is important to remember that no diagnosis is ever established for approximately 20% of all exudative pleural effusions and that many resolve spontaneously, leaving no residua.[103,116] In patients with undiagnosed exudative pleural effusions, three factors should influence the vigor with which one pursues the diagnosis with invasive tests: (1) The symptoms and the clinical course of the patient. If the symptoms of the patient are minimal or if the symptoms are improving with time, a less aggressive approach is indicated. (2) The trend of the pleural fluid LDH level with time. If the pleural fluid LDH increases with serial thoracenteses, a more aggressive approach is indicated. (3) The attitude of the patient. If the patient is anxious to know the cause of the pleural effusion, a more aggressive approach should be taken.

Needle Biopsy of the Pleura

Small specimens of the parietal pleura can be obtained with needle biopsy, often called "blind" or "closed-needle" biopsy. The needles most commonly used for

this procedure are the Cope needle and the Abrams needle.[53] Because needle biopsy of the pleura is useful mainly to establish the diagnosis of malignant or tuberculous pleural effusions, this procedure should be considered when one of these diagnoses is suspected.

In malignant pleural disease, the needle biopsy of the pleura will be positive in 40% to 60% of patients.[116,117] Overall, the yield from pleural fluid cytology tends to be higher, probably because it samples cells dislodged from the entire pleura, whereas the needle biopsy can sample only from a localized area. In one series of 281 patients with malignant pleural effusions, the pleural biopsy was positive in 43%, whereas the pleural fluid cytology was positive in 58%.[116] In only 7% was the pleural biopsy positive and the pleural fluid cytology negative.[116] However, in a second series of 189 patients with malignant pleural effusions, the pleural biopsy was positive in 60%, whereas the cytology was positive in 52%. Both pleural fluid cytology and biopsy were positive in 33%, only the biopsy was positive in 27%, and only the cytology was positive in 19%.[117] A prudent approach to the patient with a suspected malignant pleural effusion is to obtain a pleural biopsy only if the cytology obtained at the time of the initial diagnostic thoracentesis is nondiagnostic. If the CT shows pleural thickening or nodularity, an image-guided pleural biopsy is an excellent option.[118]

Needle biopsy of the pleura has greater utility for the diagnosis of tuberculous pleuritis than of malignancy. The initial biopsy is positive for granulomas in 50% to 80% of patients.[119] The demonstration of granulomas on the pleural biopsy is virtually diagnostic of tuberculous pleuritis; caseous necrosis or acid-fast bacilli need not be demonstrated, although, on rare occasions, fungal diseases, sarcoidosis, or rheumatoid pleuritis can produce granulomatous pleuritis. When tuberculous pleuritis is suspected, a portion of the pleural biopsy specimen should be cultured for mycobacteria. In one series of 21 patients with tuberculous pleuritis, either the microscopic examination or the biopsy culture was positive in 20 of the 21 patients (95%).[120] If the initial biopsy is nondiagnostic and the patient has tuberculous pleuritis, a second biopsy will be diagnostic 10% to 40% of the time.[119,121]

The greatest value of needle biopsy for a patient with tuberculosis is obtaining material for culture of *M. tuberculosis* for the determination of drug susceptibility. Often, the presentation of a patient with a recent purified protein derivative (PPD) conversion and an exudative pleural effusion with lymphocytosis is classic and unlikely to be due to any diagnosis other than tuberculous pleurisy. The diagnosis can be further supported by measurements, where available, of pleural fluid ADA or IFN-γ. In those cases, treatment for tuberculosis can be offered with confidence without needle biopsy confirmation. However, when the patient may have been exposed to drug-resistant organisms, needle biopsy will increase the likelihood of obtaining organisms for culture and is recommended. Sputum induction can also be useful for culturing the organism, even when the patient is suspected to have only pleural involvement and the chest radiograph shows no pulmonary involvement; in this setting, sputum induction was shown to have a yield similar to that of culture of the pleural biopsy (52% vs. 62%).[122] Medical thoracoscopy has a higher yield than blind needle biopsy for obtaining pleural material for culture. When different approaches were compared in the same 51 patients, thoracoscopy obtained a positive culture of *M. tuberculosis* in 76% whereas the Abrams needle obtained a culture in 48%.[123] If the need for obtaining positive cultures is high, the more invasive diagnostic tests including medical thoracoscopy may be preferred.

The two major complications of needle biopsy of the pleura are pneumothorax and bleeding. Pneumothoraces large enough to require a chest tube occur in only about 1% of pleural biopsies.[116,124] It is likely that many pneumothoraces develop because of leakage of air through the biopsy needle and do not necessarily indicate puncture of the lung. A hemothorax can result if an intercostal artery or vein is inadvertently biopsied. In one older series, a fatal hemothorax occurred in 2 of 227 biopsy procedures.[124] The pleural biopsy needle can also be mistakenly inserted into the liver, spleen, or kidney, which can lead to hemorrhage in these organs. However, in general, bleeding complications are rare.

If no diagnosis is obtained after routine laboratory tests including cytology and one needle biopsy of the pleura, what can be said concerning the patient? Poe and colleagues[124] followed 143 such patients for 12 to 72 months, during which time 29 patients were diagnosed with malignant pleural disease and 1 patient with tuberculous pleuritis. In all 29 cases in which malignancy was eventually diagnosed, the diagnosis of malignant neoplasm was suggested by clinical criteria such as weight loss, constitutional symptoms, or a history of previous cancer. These authors concluded that most patients with undiagnosed exudative pleural effusions in whom the clinical picture does not suggest malignancy are best managed by observation. In those with symptoms suggestive of malignancy, image-guided pleural biopsy or thoracoscopy is probably the procedure of choice.

Image-Guided Pleural Biopsy

In patients with pleural abnormalities consistent with malignancy, CT-guided cutting-needle biopsies may supplant closed pleural biopsy for diagnosis.[125] In a randomized study of 50 patients with suspected malignant pleural effusions with negative cytology, those randomized to image-guided biopsy were more likely to be diagnosed (87% sensitivity) than those randomized to blind pleural biopsy (47%).[118] In situations in which the effusion is small or there is loculation or pleural thickening without an effusion, CT image-guided pleural biopsy is an excellent choice. PET/CT may increase the yield further by improving interpretation and selection of biopsy targets (see earlier).

Bronchoscopy

Another procedure that should be considered in the patient with an undiagnosed pleural effusion is bronchoscopy (see Chapter 22). If the patient has an

associated parenchymal lesion or hemoptysis, fiberoptic bronchoscopy will provide a diagnosis in nearly 75%.[126] Conversely, if the patient has neither a parenchymal abnormality nor hemoptysis, a diagnosis for the pleural effusion is established less than 10% of the time.[127] At the present time, CT scan of the chest should be performed in all patients with undiagnosed exudative pleural effusions. Bronchoscopy should then be performed only if the CT scan demonstrates parenchymal abnormalities or if the patient has hemoptysis. At the time of bronchoscopy, special attention is paid to those portions of the lung in which the parenchymal abnormalities were demonstrated.

Pleuroscopy or Video-Assisted Thoracoscopic Surgery

Pleuroscopy and VATS are discussed fully in Chapter 23. Pleuroscopy may be useful diagnostically in patients in whom the origin of a pleural effusion remains unclear after routine fluid analysis and needle biopsy of the pleura. In many cases, especially for the evaluation of malignancy, thoracoscopy may supplant needle biopsy because of a greater diagnostic yield and the added ability to provide a pleurodesis. Pleuroscopy can be performed by pulmonologists using local anesthesia and conscious sedation for direct visualization of the pleural surfaces, tissue sampling, and pleurodesis; thoracoscopy performed by thoracic surgeons, generally referred to as "video-assisted thoracoscopic surgery (VATS)," utilizes general anesthesia and single-lung ventilation by double-lumen intubation and allows greater access to the pleura and lung for surgical procedures.

Which patients with undiagnosed pleural effusions should undergo thoracoscopy? A diagnosis can be established in over 80% of patients with malignancy including those with mesothelioma.[128] Moreover, talc can be insufflated at the time of the procedure and this will control the effusion in the great majority of patients. Nonetheless, there are minor risks of the procedure, a need for postprocedure chest tube(s) and a procedure cost that should be considered. Pleuroscopy is, therefore, recommended for the patient with an undiagnosed pleural effusion after diagnostic thoracentesis and needle biopsy of the pleura in whom the diagnosis of malignancy is strongly suspected and in whom one wishes to establish this diagnosis.

Open Biopsy of the Pleura

Thoracotomy with direct biopsy of the pleura provides the best visualization of the pleura and the best biopsy specimens. Nowadays, the less invasive thoracoscopy can replace thoracotomy in most instances. The main indication for open pleural biopsy is progressive undiagnosed pleural disease that cannot be approached by or has failed to be diagnosed by thoracoscopy. In the past, for example, the diagnosis of malignant mesothelioma was usually made with open biopsy of the pleura, but now the diagnosis can be established in the majority of the cases with thoracoscopy.

It should be emphasized that open pleural biopsy does not always provide a diagnosis in patients with pleural effusions. Over the 11-year period from 1962 to 1972, 51 patients with pleural effusion at the Mayo Clinic had no diagnosis after an open pleural biopsy.[129] In 31 of these patients (61%), there was no recurrence of the pleural effusion, and no cause ever became apparent. However, 13 of the patients were eventually proved to have malignancy; 6 had lymphoma and 4 had malignant mesothelioma. Thus, observation of patients with undiagnosed pleural effusions is often warranted unless there is compelling reason to pursue the diagnosis of malignancy. Since the time of this study, there have been many improvements in diagnostic tests that may increase the diagnostic yield of invasive procedures.

TRANSUDATIVE PLEURAL EFFUSIONS

Transudative pleural effusions frequently accompany many common clinical disorders. It is noteworthy that the primary abnormality in most cases of transudative pleural effusions originates in organs other than the pleura or lungs, especially the heart, liver, and kidneys. This association emphasizes the fact that, although patients may visit their physicians for respiratory complaints, these symptoms may be caused by extrapulmonary disorders.

Congestive Heart Failure

CHF is probably the most common cause of pleural effusion.[53] The incidence of pleural effusion in patients with CHF is high. In one series of 60 patients with an exacerbation of stable CHF, chest CT scans demonstrated that 50 patients (83%) had a right-sided pleural effusion and 46 patients had a left-sided effusion. Approximately one third of the effusions had a volume that exceeded 700 mL.[130]

Pathophysiology

The pleural fluid that accumulates with CHF is related to the clearance of pulmonary interstitial fluid across a leaky mesothelium into the pleural space.[5] In studies in which sheep lungs were isolated in situ, volume loading led to an increased transudation across the lung into the pleural space.[6] The pleural fluid had the same protein concentration as that of the lung lymph and the interstitial edema liquid in the lung. The volume of pleural fluid constituted about 25% of all edema formed in the lung.[6] In the clinical situation, patients with CHF are much more likely to have a pleural effusion if there is radiologically apparent pulmonary edema.[131]

Clinical Manifestations

Patients with pleural effusion resulting from CHF usually have symptoms and signs of heart failure, such as dyspnea on exertion, orthopnea, nocturia, peripheral edema, distended neck veins, crackles, and a cardiac gallop. The

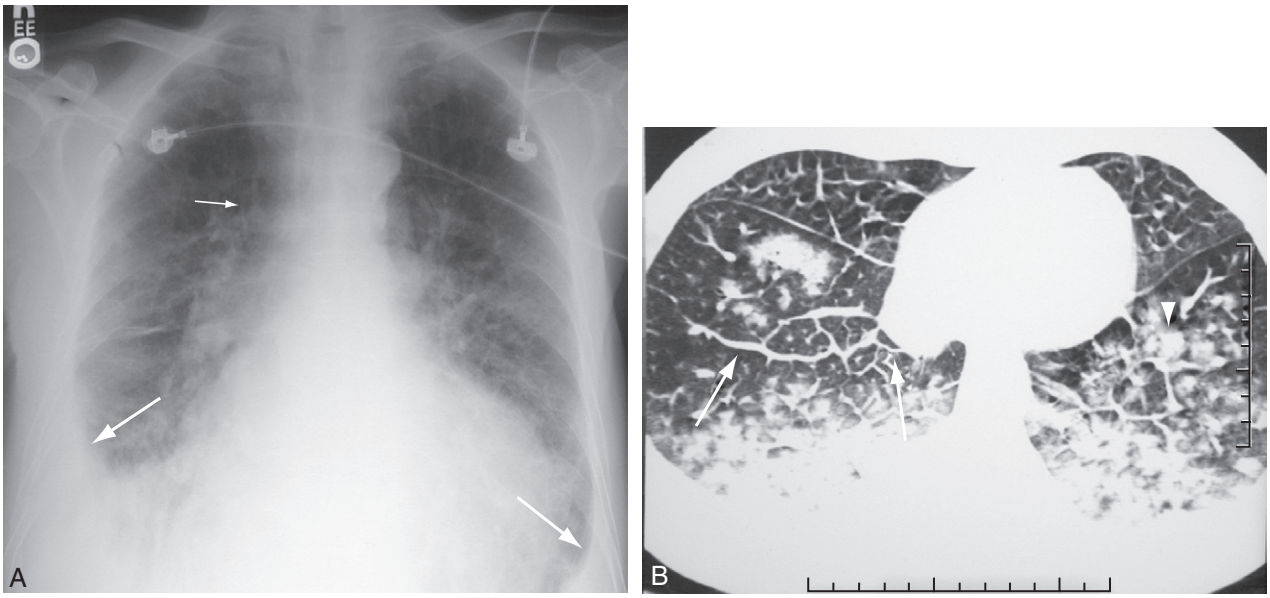

FIGURE 73-7 ■ Effusion from congestive heart failure. **A,** Frontal chest radiograph in a patient with pulmonary edema shows cardiomegaly, bilateral pleural effusions (*large arrows*), and central interstitial thickening, including Kerley's A lines (*small arrow*). Note that the right effusion is slightly larger than the left effusion. **B,** High-resolution computed tomography (HRCT) scan in a patient with pulmonary edema shows interstitial edema with bilateral, basilar centrilobular ground-glass opacity nodules (*arrowhead*) and smooth interlobular septal thickening (*arrows*). Bilateral pleural effusions are also present. (Courtesy of Michael B. Gotway, MD, Scottsdale Medical Imaging and the Department of Radiology, University of California, San Francisco.)

chest radiograph almost always reveals cardiomegaly in addition to the pleural effusion.

The pleural effusions that occur with CHF tend to be bilateral, with larger effusions on the right (Fig. 73-7A). On CT imaging, interstitial and alveolar edema can often be detected by the presence of thickened septae and patchy infiltrates (see Fig. 73-7B). In an autopsy study of 250 patients with CHF and pleural effusion, 88% of the patients had bilateral pleural effusions, with the mean volume of pleural fluid in the right pleural space (1084 mL) slightly greater than the mean volume of fluid in the left pleural space (913 mL).[132] Moreover, of the 35 patients who did have unilateral pleural effusions, 46% had either pulmonary embolism or pneumonia.[132] Weiss and Spodick[133] reported that 73% of 51 patients with CHF had bilateral effusions, 19% had unilateral right-sided effusions, and 9% had unilateral left-sided effusions.

The reason that effusions are generally larger on the right side may lie in the fact that they originate from the larger lung on the right side.[36] In volume-overloaded sheep, the rate of liquid leakage from the right lung was higher than from the left, likely due to the larger volume and surface area of the right lung.[6] In another study in awake sheep, there was no difference in the rate of absorption of effusions from the right and left pleural spaces,[18] suggesting that differences in formation are the cause of the difference in size.[18,36]

Although CHF is by far the most common cause of bilateral pleural effusions, an alternate explanation should be sought if there is no cardiomegaly. In one series of 78 patients with bilateral effusions but a normal-sized heart, only 4% of the effusions were caused by CHF.[134]

Diagnosis and Management

The diagnosis is usually suggested by the clinical picture of CHF. A diagnostic thoracentesis should be performed if the pleural effusion is unilateral, if bilateral effusions are not comparable in size, if the patient is febrile, if the patient has pleuritic chest pain, or if the patient does not have cardiomegaly.[53] If none of these conditions is met, one can treat the CHF and perform a diagnostic thoracentesis only if the effusion does not resolve.

The pleural fluid from a patient with CHF is usually a transudate, as defined previously by Light's criteria.[34] However, if the patient has been on diuretics, the pleural fluid protein and LDH ratios may be increased sufficiently that the pleural fluid meets Light's exudative criteria. A similar phenomenon has been described in the ascites literature.[135] The LDH ratio can also increase if intrapleural LDH increases due to injury from repeated taps and if serum LDH falls when diuresis reduces liver congestion.[135] Generally, if the effusion protein and LDH values meet Light's criteria for an exudate, it is only by a small amount.[49] The transudative nature of the pleural fluids can be established in such patients if the serum minus the pleural fluid protein level is greater than 3.1 gm/dL.[47] Measurement of pleural fluid N-terminal brain natriuretic peptide (NT-BNP) is useful in this setting because levels exceeding 1300 pg/mL are virtually diagnostic of CHF.[48] Pleural fluid BNP does not correlate well with NT-BNP and is not as useful in establishing the diagnosis of CHF.[48]

Patients with CHF and pleural effusion should be treated with afterload reduction, diuretics, and inotropes, as needed. When the heart failure is successfully managed, the pleural effusion usually resolves. If the

patient is markedly dyspneic when first evaluated, a therapeutic thoracentesis to relieve the dyspnea should be considered. Rarely, despite intensive therapy of the CHF, a patient has persistent large effusions. If such patients are dyspneic and if their dyspnea is relieved by a therapeutic thoracentesis, consideration can be given to controlling the effusions with a pleurodesis using a sclerosing agent, such as doxycycline or talc slurry, or the insertion of an indwelling catheter.

Pericardial Disease

There is a high incidence of pleural effusion in patients with pericardial disease. In one series of 35 patients with constrictive pericarditis, 60% of the patients had radiologically demonstrable pleural effusions.[136] Weiss and Spodick[137] reviewed 124 patients with pericardial disease and found that 35 (28%) had a pleural effusion. Of the 35 patients, 21 had only a left-sided pleural effusion, 2 had only a right-sided pleural effusion, and the remaining 12 were bilateral. However, in another series of 21 patients with constrictive pericarditis and pleural effusion, the pleural effusion was right-sided only in 9 (43%) and was bilateral in the remaining 12 (57%).[136]

The mechanism responsible for the pleural effusion associated with pericardial disease is not clear. In constrictive pericarditis, one explanation for the effusions is that the pulmonary and systemic capillary pressures are elevated secondary to the pericardial disease, resulting in a transudative pleural effusion. However, one would expect these effusions to be bilateral. In inflammatory pericardial disease, however, the pleural effusion tends to be left-sided and, although the characteristics of the fluid has not been well described, it is probable that the effusion forms from extension of the pericardial inflammation to the adjacent pleura.[137]

Hepatic Hydrothorax

The incidence of pleural effusions with cirrhosis is approximately 6%.[138,139] The incidence appears to be much higher if ascites is present; however, in some patients with hepatic hydrothorax, no ascites can be detected, presumably because all ascitic fluid moves to the pleural space because of prevailing pressure gradients and low-resistance diaphragmatic defects.[36,140]

Pathophysiology

The predominant mechanism leading to a pleural effusion in a patient with cirrhosis and ascites appears to be the movement of the ascitic fluid from the peritoneal cavity through defects in the diaphragm into the pleural space.[141] The decreased plasma oncotic pressure is only a secondary factor.

The diaphragmatic defects have been demonstrated in many ways. Lieberman and coworkers[138] introduced 500 to 1000 mL of air into the peritoneal cavity of five patients with cirrhosis, ascites, and pleural effusions and found that a pneumothorax developed in all patients within 48 hours. In addition, they were able to demonstrate air bubbles coming through an otherwise undetectable diaphragmatic defect at thoracoscopy in one of their patients. In two of their patients, diaphragmatic defects were demonstrated at postmortem examination.[138] By thoracoscopy, different types of defects, such as blebs or fenestrations, have been documented.[142] There are no direct lymphatic connections between the peritoneal and the pleural spaces. Thus, the connections between the spaces are either preexisting developmental defects or defects caused by trauma or stretching.

Clinical Manifestations

The clinical situation in patients with pleural effusions from cirrhosis and ascites is usually dominated by the cirrhosis and ascites. At times, however, the presence of a large pleural effusion may produce severe dyspnea. The pleural effusion associated with cirrhosis and ascites is frequently large and can occupy the entire hemithorax. The large effusions occur because the diaphragmatic defect permits fluid to flow from the peritoneal cavity into the pleural cavity until the pleural pressure approaches the peritoneal pressure. The pleural effusions are usually right-sided (80%) but occasionally are left-sided (17%) or bilateral (3%).[141]

Diagnosis and Treatment

The diagnosis of hepatic hydrothorax is usually easily established from the clinical picture. If doubt exists, the diagnosis can be confirmed by scanning the chest after ^{99m}Tc sulfur colloid is injected into the peritoneal cavity.[143] Both a paracentesis and a thoracentesis should be performed to confirm that the ascites and the pleural fluid are both transudates. Xiol and associates[144] performed thoracentesis on 60 patients with cirrhosis and ascites. The pleural fluid analysis yielded a diagnosis other than hepatic hydrothorax in 18 (30%) including 9 spontaneous bacterial pleuritis, 2 tuberculosis, 2 adenocarcinomas, 2 parapneumonic effusions, and 3 undiagnosed exudates. The protein level with hepatic hydrothorax in the pleural fluid is usually higher than that in the ascitic fluid but is still below 3.0 g/dL.[138] If the polymorphonuclear cell count is greater than 500 cells/μL, the diagnosis of spontaneous bacterial pleuritis in conjunction with spontaneous bacterial peritonitis should be considered.[145]

The initial management of the pleural effusion associated with cirrhosis and ascites should be directed toward treatment of the ascites. The patient should be given a low-salt diet and treated with diuretics. If diet and diuretics do not control the effusion, the most definitive treatment is liver transplantation.[140] Chest tube insertion should be avoided because drainage of the ascitic fluid through the chest tube can lead to massive protein depletion and even fatal cardiovascular collapse.[140,140a] The next best approach and a potentially useful bridge to transplantation is probably implantation of a transjugular intrahepatic portal systemic shunt (TIPS). TIPS is usually effective in the management of hepatic hydrothorax. Kinasewitz and Keddissi[140] summarized the lit-

erature on 115 patients who received TIPS for refractory hepatic hydrothorax and reported that the procedure controlled the hydrothorax in 80%, but 12% of the patients developed encephalopathy. If neither TIPS nor liver transplantation is feasible, the best alternative treatment is probably videothoracoscopy with closure of the diaphragmatic defects and pleurodesis. Cerfolio and Bryant[146] performed this procedure on 41 patients and reported a success rate of 80%.

Spontaneous Bacterial Pleuritis

Spontaneous bacterial pleuritis is, by definition, infection of a preexisting hepatic hydrothorax in which a parapneumonic infection has been excluded. Originally termed "spontaneous bacterial empyema," we prefer the term *pleuritis* to emphasize its similarity to spontaneous bacterial peritonitis and to indicate that its treatment does not require tube thoracostomy. In one series in Spain, 16 of 120 patients (13%) admitted with a diagnosis of hepatic hydrothorax had a spontaneous bacterial pleuritis.[145] The diagnosis is made if the pleural fluid culture is positive, the pleural fluid neutrophil count is greater than 250 cells/μL, and a pneumonic process has been excluded. If the pleural fluid neutrophil count is greater than 500 cells/μL and the pleural fluid cultures are negative, culture-negative spontaneous bacterial pleuritis is diagnosed.[145] In the series from Spain, 10 of 24 episodes (43%) of spontaneous bacterial empyema were not associated with bacterial peritonitis.[145] Appropriate treatment of spontaneous bacterial pleuritis requires systemic antibiotics, but tube thoracostomy does not appear to be necessary. It remains to be seen whether spontaneous bacterial pleuritis is a common occurrence in the United States.

Nephrotic Syndrome

There is a high incidence of pleural effusion in patients with the nephrotic syndrome. In one study of 52 patients, 21% had pleural effusions.[147] The mechanism responsible for the transudative pleural effusion associated with the nephrotic syndrome is probably the combination of decreased plasma oncotic pressure and increased hydrostatic pressure. The increased hydrostatic pressure is due to salt retention, which produces hypervolemia. The pleural effusions in patients with a nephrotic syndrome are usually bilateral and are frequently infrapulmonary in location.[147]

A diagnostic thoracentesis should be performed in all patients with the nephrotic syndrome and a pleural effusion to prove that the pleural fluid is a transudate. Nonetheless, the possibility of pulmonary embolism should always be considered in patients with the nephrotic syndrome and a pleural effusion. In one series of 36 patients with the nephrotic syndrome, 22% had pulmonary emboli.[148] If the pleural fluid is an exudate, a CT angiogram should be obtained.

The treatment of the pleural effusion associated with the nephrotic syndrome should be aimed at increasing the level of protein in the serum by decreasing the protein loss in urine. If this is unsuccessful, pleurodesis with a sclerosing agent should be considered in selected patients who are symptomatic from the pleural effusion.

Peritoneal Dialysis

Peritoneal dialysis is occasionally complicated by the development of an acute hydrothorax. In a review of 3195 patients receiving continuous ambulatory peritoneal dialysis in Japan, 1.6% developed a pleural effusion as a result of the movement of the dialysate from the peritoneal cavity into the pleural cavity.[149] The effusion developed within 30 days of initiation of the dialysis in 50% of the patients, but 18% had been receiving dialysis for more than a year before the effusion developed.[149] The effusions are right-sided in about 90%.[149,150]

The pleural fluid in these patients is characterized by a glucose level intermediate between that of the dialysate and that of the serum, a protein level below 10 g/L, and a low LDH level. The LDH level is higher and the glucose level is lower in the pleural fluid than in the ascitic fluid.[150] Although the communication closes spontaneously in some patients, a surgical approach is usually required if continuous ambulatory peritoneal dialysis is to be continued. The treatment of choice is probably thoracoscopy with closure of the diaphragmatic defects, followed by pleurodesis. Alternative treatments are pleurodesis alone or thoracotomy with repair of the diaphragmatic defects.

Urinothorax

Obstruction of the urinary tract resulting in a retroperitoneal urine collection (urinoma) can lead to a pleural effusion.[151] The mechanism by which the pleural fluid accumulates is unknown, but it is thought that this retroperitoneal urine collection drains along pressure gradients into the pleural space. The collection of fluid actually represents urine, and the pleural fluid smells like urine. Patients with urinothoraces have pleural fluid creatinine levels higher than those in serum, but about 10% of other effusions also meet this criteria.[151] When the urinary tract obstruction is relieved, the pleural effusion rapidly disappears.

Myxedema

A pleural effusion sometimes occurs as a complication of myxedema. Most patients with myxedema and pleural effusion have a concomitant pericardial effusion. In one series of 25 patients with pericardial effusions secondary to myxedema, 13 of the patients (52%) had concomitant pleural effusion.[152] When the pleural effusion occurs simultaneously with a pericardial effusion, the pleural fluid is usually a transudate.[152] The isolated pleural effusion seen in conjunction with myxedema is generally borderline between a transudate and an exudate. Although the mechanism of formation of the effusion is unknown, a decrease in lymphatic function due to low thyroid levels may contribute.[22] Thyroid replacement is the obvious treatment for pleural effusions associated with myxedema.

Fontan Procedure

With the Fontan procedure, an anastomosis is created between either the superior vena cava, the right atrium, or the inferior vena cava and the pulmonary artery to bypass the right ventricle, usually because of tricuspid atresia or a univentricular heart. Pleural effusion occurs in many patients after surgery and contributes significantly to postoperative morbidity. Pleural effusions are more likely to occur in patients who have significant aortopulmonary collateral vessels before surgery; thus, Spicer and colleagues[153] recommended that these vessels be embolized during preoperative angiography. The amount of pleural drainage postoperatively is decreased by about 50% if the Fontan circuit is fenestrated to allow shunt of deoxygenated blood to the systemic circulation.[154] Although the etiology of the effusions is still unknown, prolonged pleural effusions have also been correlated with higher preoperative pulmonary artery pressure, pulmonary vascular compliance or postoperative levels of salt and water hormones.[154a,154b,154c] The treatment of choice for these effusions is usually insertion of a pleuroperitoneal shunt. Alternative treatments are creation of a late fenestration to create a right-to-left shunt or chemical pleurodesis.

Other Causes of Transudative Pleural Effusions

On rare occasions, a subarachnoid-pleural fistula can develop that results in the accumulation of CSF in the pleural space. The pleural fluid looks like CSF with a very low protein and LDH level. Subarachnoid-pleural fistulae can occur following ventriculopleural shunting and with penetrating injuries, fractures, or surgery of the thoracic spine.[53] If there is doubt about the diagnosis, measurement of the pleural fluid β_2-transferrin is useful because only CSF contains this molecule.[155] The fistula rarely closes without surgical intervention.

Large, persistent transudative effusions can result from central venous obstruction, perhaps due to increases in venous pressure leading to increased formation of liquid and to decreases in lymphatic clearance. Venous obstruction as a cause of persistent transudative effusions should be considered in situations with prior instrumentation and have been reported from occlusions of the hemiazygous vein, brachiocephalic vein and superior vena cava. Relief of the obstruction can lead to resolution of the effusion.[156]

Patients with pulmonary veno-occlusive disease frequently have small pleural effusions.[157] The characteristics of the pleural fluid have not been described, but it is probably a transudate because the effusions are likely related to the increased interstitial fluid. Patients with right failure secondary to pulmonary hypertension frequently have small bilateral pleural effusions.[158]

Pulmonary embolism has been reported to be associated with a transudative pleural effusion. However, in a study of the pleural fluid findings in patients with pulmonary embolism, all 60 pleural fluids were exudates.[63] Pleural amyloidosis is associated with transudative effusions, probably due to a combination of heart failure and pleural infiltration with amyloid.[159] Cytokines such as vascular endothelial growth factor (VEGF) may play a role because, in a recent series, three out of four patients with persistent pleural effusions due to primary systemic amyloid improved with treatment with an antibody against VEGF, bevacizumab.[160]

EXUDATIVE PLEURAL EFFUSIONS

Exudative pleural effusions are common clinical problems. These effusions may develop as a result of inflammation, injury, or malignancy, which can involve the pleural surfaces, the adjacent lung, or more distant tissues, such as mediastinal or abdominal organs. Further discussion of effusions secondary to pleural tumors is presented in Chapter 75, and special types of effusions (chylothorax and hemothorax) are discussed in Chapter 74.

Parapneumonic Effusions and Empyema

A parapneumonic effusion is any pleural effusion associated with bacterial pneumonia, lung abscess, or bronchiectasis. Parapneumonic effusions are probably the most common exudative pleural effusion in the United States. The annual incidence of bacterial pneumonia in the United States is estimated to be 4 million.[161] Approximately 20% to 40% of patients hospitalized with bacterial pneumonia have an accompanying pleural effusion.[86,162] The morbidity and mortality in patients with pneumonia and pleural effusion are higher than in patients with pneumonia alone. In one study of patients with community-acquired pneumonia, the relative risk of mortality was 7.0 times higher for patients with bilateral pleural effusions and 3.4 times higher for patients with unilateral pleural effusions of moderate or greater size than for those without effusions.[163] Although it is possible that comorbidity from diseases such as CHF might cause both the effusions and the excess mortality, at least some of the increase in morbidity and mortality may be due to improper management of the pleural effusion.

When one is managing a patient with a parapneumonic effusion, the main decision to make is whether or not chest tubes should be inserted. The term *complicated parapneumonic effusion* was developed to refer to parapneumonic effusions that require tube thoracostomy for their resolution. An empyema is, by definition, pus in the pleural space. Approximately 60% of empyemas are parapneumonic, whereas 20% arise after thoracic surgical procedures, and the remaining 20% arise as complications of various conditions, such as thoracic trauma, esophageal perforation, thoracentesis, and subdiaphragmatic infection.[53]

Pathophysiology

The evolution of a parapneumonic pleural effusion can be divided into three stages, which are not sharply defined but rather represent a continuous spectrum. In

TABLE 73-3. Categorizing Risk for Poor Outcome in Patients with Parapneumonic Effusion

Pleural Space Anatomy		Pleural Fluid Bacteriology		Pleural Fluid Chemistry	Category	Risk of Poor Outcome	Drainage
A_o Minimal, free-flowing effusion (<10 mm on lateral decubitus)	*And*	B_x Culture and Gram stain results unknown	*And*	C_x pH, glucose unknown	1	Very low	No
A_1 Small to moderate free-flowing effusion (>10 mm and <half of the hemithorax)	*And*	B_o Negative culture and Gram stain	*And*	C_o pH ≥ 7.20 glucose > 60 mg/dL	2	Low	No
A_2 Large, free-flowing effusion (≥half of the hemithorax), loculated effusion, or effusion with thickened parietal pleura	*Or*	B_1 Positive culture and Gram stain	*Or*	C_1 pH < 7.20 glucose < 60 mg/dL	3	Moderate	Yes
		B_2 Pus			4	High	Yes

From Colice GL, Curtis A, Deslauriers J, et al: Medical and surgical treatment of parapneumonic effusions: An evidence-based guideline. Chest 118:1158–1171, 2000, with permission.

the first stage, the exudative stage, a focus of parenchymal infection leads to increased pulmonary interstitial fluid, some of which traverses the visceral pleura and causes the accumulation of a small sterile pleural effusion. The pleural fluid in this stage is an exudate with primarily polymorphonuclear leukocytes, a normal glucose level, and a normal pH. With institution of appropriate antibiotic therapy during this stage, both the pneumonic process and the pleural effusion resolve.

The next stage is the fibropurulent stage, characterized by infection of the previously sterile pleural fluid with the offending bacteria. In this stage, more pleural fluid accumulates and contains many polymorphonuclear leukocytes, bacteria, and cellular debris. In addition, fibrin is deposited as continuous sheets that cover both the visceral and the parietal pleura in the involved area. As this stage progresses, there is a tendency for the fibrin membranes to partition the involved pleural space into multiple locules. This loculation hinders extension of the empyema but makes complete drainage of the pleural space with chest tubes increasingly difficult. The pleural fluid pH and glucose levels decrease, and the LDH level increases progressively as this stage evolves.

In the last stage, the organization stage, fibroblasts grow into the exudate from both the visceral and the parietal pleural surfaces to produce an inelastic membrane. This membrane, sometimes called a *pleural peel*, can encase the lung and hinder the reexpansion of the underlying lung when the pleural fluid is evacuated. If the underlying lung cannot reexpand, consideration should be given to decortication, because it is virtually impossible to eradicate the infection if the space persists after the fluid is evacuated. However, if the infection is already controlled, the peel frequently resolves spontaneously over the ensuing 3 to 6 months.

Classification

An expert panel from the American College of Chest Physicians has developed a new categorization of patients with parapneumonic effusions.[164] This categorization is modeled somewhat on the tumor-node-metastasis (TNM) classification of tumors and is based upon the anatomy of the effusion, the bacteriology of the pleural fluid, and the chemistry of the pleural fluid (Table 73-3).

The *category 1* effusion is a small (<10 mm thickness on decubitus, CT or ultrasound studies) free-flowing effusion. Because the effusion is small, no thoracentesis is performed and the bacteriology and chemistry of the fluid are unknown. The risk of a poor outcome with a category 1 effusion is very low.

The *category 2* effusion is small to moderate in size (>10 mm thickness and < half the hemithorax) and is free flowing. The Gram stain and culture of the pleural fluid are negative and the pleural fluid pH is more than 7.20 or the glucose more than 60 mg/dL. The risk of a poor outcome with a category 2 effusion is low.

The *category 3* effusion meets at least one of the following criteria: (1) the effusion occupies more than half the hemithorax or is loculated or is associated with a thickened parietal pleura; (2) the Gram stain or culture is positive, or (3) the pleural fluid pH is less than 7.20 or the pleural fluid glucose is less than 60 mg/dL. The risk of a poor outcome with a category 3 effusion is moderate.

The *category 4* effusion is characterized by pleural fluid that is pus. The risk of a poor outcome with a category 4 effusion is high.

Bacteriology

The most recent comprehensive report on the bacteriology of complicated parapneumonic effusions comes from the large trial of intrapleural streptokinase in the United Kingdom.[84] In this study of 434 patients, the Gram stain was positive in 250 (58%) patients, the cultures grew a single aerobic growth in 151 (35%) patients, a single anaerobic growth in 29 (7%) patients, and a polymicrobial growth in 52 (12%) patients. Pleural fluid was available for molecular microbiologic analysis in 404 of the subjects. For 70 of the culture-negative cases, bacteria were identified by subsequent nucleic acid amplification. Overall, a microbiologic diagnosis was obtained in 320 patients (74%). In patients with

community-acquired pneumonia, the organisms most commonly responsible were *Streptococcus intermedius-anginosus-constellatus* (milleri) group (80), *S. pneumoniae* (71), other streptococcus species (25), *S. aureus* (34) (7 methicillin-resistant *Staphylococcus aureus* [MRSA]), gram-negatives (29), and anaerobes (67). In patients with hospital-acquired parapneumonic effusions, the most common organism was *S. aureus* (21) of which 15 were MRSA. The authors concluded that pleural infection differs from pneumonia in its bacteriology and, for community-acquired infection, should be treated with antibiotics for both aerobic and anaerobic bacteria.

Clinical Manifestations

Aerobic Bacterial Infections. Patients with aerobic bacterial pneumonia and pleural effusion initially have an acute febrile illness consisting of chest pain, sputum production, and leukocytosis. The incidence of pleuritic chest pain and the degree of leukocytosis are comparable whether or not there is an accompanying pleural effusion.[86]

Anaerobic Bacterial Infections. Patients with anaerobic bacterial infections involving the pleural space usually present with a subacute illness. In one series, the duration of symptoms before presentation averaged 10 days, with 70% of the patients having symptoms for more than 7 days.[165] Most patients with anaerobic pleuropulmonary infections have significant weight loss (mean, 13.2 kg in one series) as well as leukocytosis and mild anemia.[165] In addition, most patients have risk factors for aspiration of an anaerobic inoculum; these risk factors include alcoholism, an episode of unconsciousness, and infected gums.

Because of the nonspecificity of the symptoms associated with empyema, the diagnosis may not be considered and thus be delayed. In one series of 119 patients from England in the late 1980s, empyema was considered the most likely diagnosis by the admitting doctor in only 35 patients (29%).[166] In this same series, the diagnosis was delayed for more than 1 week after admission in 28 patients and for more than 1 month after admission in 5 patients.[166] In this series, the most common symptom was malaise (73%), and only 56% of the patients were febrile. In a more recent series from Canada, the mean delay from admission to the time of correct diagnosis was 44 days.[167]

Diagnosis

Parapneumonic effusion and empyema should be included in the differential diagnosis of all undiagnosed exudative effusions. The possibility of a parapneumonic effusion should be considered whenever a patient with a bacterial pneumonia is initially evaluated. If costophrenic angles show blunting or if the diaphragm is not visible throughout its length, bilateral decubitus chest radiographs or ultrasound should be obtained to evaluate the possibility of a pleural effusion.

With the involved side dependent, the amount of free pleural fluid can be semiquantitated by measuring the distance between the inside of the chest wall and the outside of the lung. If this distance is less than 10 mm, the effusion is not clinically significant, and thoracentesis is not indicated.[86,164] If the thickness of the fluid exceeds 10 mm, then a thoracentesis should be performed immediately.[164,168] Only by examining the pleural fluid can one distinguish a complicated from an uncomplicated parapneumonic effusion. The pleural fluid should be examined grossly for color, turbidity, and odor. Aliquots are sent for determination of the glucose, LDH, protein concentration, pH (if it can be performed with a blood gas machine),[87] a differential and total leukocyte count, Gram's stain, and aerobic and anaerobic bacterial cultures. In most instances, the pleural fluid should also be submitted for mycobacterial and fungal smears and cultures.

Not all patients with an acute illness, parenchymal infiltrates, and pleural effusion have an acute bacterial pneumonia. This clinical picture may also be seen with pulmonary embolization, acute pancreatitis, tuberculosis, Dressler's syndrome, and other diseases. The diagnostic workup of each patient should be individualized based on the clinical situation.

Treatment

When a patient with pneumonia and a pleural effusion is initially evaluated, an appropriate antibiotic must be selected, and the decision whether to initiate invasive therapy for the pleural effusion must be made. Bacterial cultures of the sputum, blood, and pleural fluid should be obtained before antibiotic therapy is instituted. Antibiotic therapy for bacterial pneumonia is discussed in Chapter 32.

Prognostic Factors. Findings that suggest that a more aggressive approach will be necessary for a parapneumonic effusion are listed in Table 73-4. The more purulent the pleural fluid, the lower the glucose level, and the lower the pH, the more likely the patient is to require increasingly invasive procedures for complete drainage. Other pleural fluid measurements that have been reported to be useful as markers for identifying complicated parapneumonic effusions include the pleural fluid myeloperoxidase level,[169] the complement

TABLE 73-4. Factors Suggesting That a More Invasive Approach Will Be Necessary for the Resolution of a Parapneumonic Effusion*

1. Pus is present in the pleural space.
2. Positive pleural fluid Gram stain.
3. Pleural fluid glucose < 60 mg/dL.
4. Pleural fluid pH < 7.20.
5. Positive pleural fluid culture.
6. Pleural fluid lactate dehydrogenase > three times upper normal limit for serum.
7. Loculated pleural fluid.

*Listed in order of decreasing seriousness.

activation product SC5b-9,[170] and the polymorphonuclear elastase level.[171] Additional studies are necessary to assess the utility of these measurements.

Overall Treatment Plan. The treatment options for patients with parapneumonic effusions and empyema, in order of increasing invasiveness, are diagnostic thoracentesis, therapeutic thoracentesis, tube thoracostomy, tube thoracostomy with thrombolytics, thoracoscopy, and thoracotomy with decortication. If the patient has any of the poor prognostic factors, it is likely that one of these treatments will be necessary. It is important not to continue any one treatment that is not working for more than a day or so.[172,173]

The effectiveness of a given treatment is evaluated by the clinical status of the patient together with the amount and the characteristics of the pleural fluid. If the patient appears to be responding, if the amount of pleural fluid is not large, and if the characteristics of the fluid are improving, the treatment should be considered successful. More invasive procedures are not indicated for pleural thickening or loculation alone. Chest CT scans are very useful in evaluating the adequacy of drainage of the pleural space.

Diagnostic versus Therapeutic Thoracentesis. To determine whether the patient has any of the prognostic factors listed in Table 73-4, a thoracentesis must be performed. Should a therapeutic or a diagnostic thoracentesis initially be performed? Because the risks of a diagnostic thoracentesis and a therapeutic thoracentesis are comparable, and a therapeutic thoracentesis might obviate the necessity for further procedures, a therapeutic thoracentesis is recommended.[172] If the pleural fluid never recurs, one need not worry about the pleural fluid. If the pleural fluid recurs after a therapeutic thoracentesis, poor prognostic findings in the initial pleural fluid indicate the need for more drainage—either an additional therapeutic thoracentesis or a tube thoracostomy. The absence of poor prognostic findings in a patient who is improving clinically indicates that additional drainage is not necessary. No more than three therapeutic thoracenteses are recommended.[172] If the pleural fluid cannot be completely removed because it is loculated, tube thoracostomy should be performed if any of the other poor prognostic factors listed in Table 73-4 are present. An alternative to therapeutic thoracentesis is to insert a small pigtail catheter.

Chest Tubes. Once it is decided that tube thoracostomy is necessary, there should be no delay in its performance, because a complicated parapneumonic effusion can progress from free-flowing pleural fluid to loculated pleural fluid within hours. In one older series of 47 anaerobic empyemas, 5 patients died, and all deaths were attributed to a delay in obtaining adequate pleural drainage.[165] In a subsequent series, a delay in instituting chest tube drainage was associated with a mortality increase from 3% to 16%.[174] The chest tube should be positioned in the most dependent part of the effusion.

There is no consensus on the optimal size of the chest tube for drainage.[168] In the past, relatively large (26–36 French) chest tubes were recommended because of the belief that smaller tubes would become obstructed by the thick fluid. However, it appears that many patients can be managed with much smaller tubes. In one study, 103 patients with empyema were treated with 8- to 12-French pigtail or 10- to 14-French Malecot catheters inserted with the Seldinger technique under either ultrasound or CT scan.[175] In this study, these small catheters served as the definitive treatment in 80 of the 103 patients (78%).[175] These results are as good as those reported in some series in which larger tubes were utilized.[174,176] The small chest tubes in the aforementioned two series were inserted percutaneously by interventional radiologists. It is likely that the excellent results are related to accurate image-guided placement of the catheter. If small tubes are used, regular flushing and suction is recommended to avoid catheter blockage.[168] If the pleural fluid is frank pus, it is still preferable to insert a large chest tube. The chest tube should be left in place until the volume of the pleural drainage per 24 hours is less than 50 mL and until the draining fluid becomes clear yellow.

Successful closed-tube drainage of a complicated parapneumonic effusion is associated with improvement in the clinical and radiologic status of the patient within 24 to 48 hours. If there is no significant improvement after this period, either the pleural drainage is unsatisfactory or the patient is receiving the wrong antibiotic. In such situations, the culture results should be reviewed and the adequacy of the pleural drainage should be assessed by chest radiographs, CT scans, or ultrasonic examination. If the pleural space is inadequately drained, another chest tube should be inserted, saline or a fibrinolytic agent can be injected intrapleurally (see later), or a more extensive surgical procedure should be performed. Inadequate drainage can be caused by poor positioning of the tube, obstruction of the chest tube, loculated pleural fluid, or inadequate expansion of the underlying lung caused by coating of the visceral pleura.

Intrapleural Thrombolytic Agents. Difficulties arise in the drainage of complicated parapneumonic effusions as a result of pleural loculations that are produced by fibrin membranes. The theory behind the use of intrapleural fibrinolytics is that they will degrade the fibrin membranes and facilitate drainage of the pleural fluid. However, in the most important study on the use of intrapleural fibrinolytics for the treatment of complicated parapneumonic effusion, the administration of streptokinase was not beneficial, even in subgroup analysis.[177] In this multicenter, randomized, controlled, double-blind study, 454 patients were randomized to receive 250,000 IU streptokinase or saline at a total volume of 30 mL twice a day. There was no difference in mortality, the need for surgical intervention, or the length of hospitalization. Accordingly, fibrinolytics are not recommended for routine use at the present time. An alternative fibrinolytic agent is tissue plasminogen activator (t-PA).[178] A second controlled trial is underway in the United Kingdom to assess the efficacy of t-PA, recombinant DNase, and the combination of the two agents. A study in rabbits demonstrated that the combination of t-PA and recombinant DNase drained empyema fluid better than either agent alone.[179] Although relatively safe, the issue of safety is still unre-

solved especially in those with coagulopathies or those receiving anticoagulant therapy.[179a]

Thoracoscopy. When the patient is not improving despite tube thoracoscopy, a more invasive procedure is needed. With thoracoscopy, the fibrin membranes creating the loculations are broken down and removed, the peel covering the visceral pleural can sometimes be removed and, at the end of the procedure, a chest tube is placed optimally in the pleural space.[180] Prior to thoracoscopy, a chest CT should be obtained to provide anatomic information about the size and the extent of the empyema cavity. The finding of a thickened visceral pleural peel without septations suggests that the empyema may be chronic and probably will not be amenable to thoracoscopic débridement alone. Most patients who undergo thoracoscopy need no additional therapy. When four studies with a total of 232 patients are combined, thoracoscopy was the definitive procedure in 77% of the patients.[181-184] After thoracoscopy, the median hospital stay ranged from 5.3 to 12.3 days, the median time for chest tube drainage postprocedure ranged from 3.3 to 7.1 days, and the overall mortality was 3%.[181-184]

Decortication. This procedure should be considered in patients who require additional drainage after tube thoracostomy and thoracoscopy.[180] With this procedure, a full thoracotomy is performed to remove all fibrous tissue and pus from the pleural space. The primary advantage that thoracotomy has over thoracoscopy is that decortication is easier to perform with thoracotomy. Decortication eliminates the pleural sepsis and allows the underlying lung to expand. Decortication is major thoracic surgery and should not be performed on patients who are markedly debilitated. It should not be performed just to remove thickened pleura, because such thickening usually resolves spontaneously over several months. After 6 months, however, if the pleural thickening persists and the pulmonary function is sufficiently reduced to limit the patient's activities, decortication should be considered.

Open Drainage (Eloesser Flap). With this relatively minor surgical procedure, which can be performed under local anesthesia, a U-shaped incision is made to provide a skin flap overlying the lower part of the empyema collection; the exposed rib segments and underlying parietal pleura are excised to open the empyema cavity; then, the skin flap is sutured inside the cavity to create a semipermanent opening into which one or more large-bore short tubes are inserted. The open-drainage procedure allows more complete drainage and frees the patient from attachment to chest-tube bottles.[185] After the procedure, the cavity should be irrigated daily with a mild antiseptic solution, and the drainage from the tubes can be collected in a colostomy bag placed over the tubes. Open drainage is preferred to decortication only in those patients who are thought to be too ill to tolerate the more extensive procedure. Patients treated by open drainage can expect to have an open chest wound for a prolonged period. In one series of 53 patients treated by an open-drainage procedure, the median time for healing the drainage site was over 120 days.[186]

Bronchopleural Fistula Complicating Empyema

When an empyema is complicated by the presence of a bronchopleural fistula, adequate pleural drainage is crucial. The pleural fluid that is not drained exteriorly with chest tubes is likely to drain interiorly throughout the tracheobronchial tree, producing a severe diffuse pneumonia. A bronchopleural fistula should be suspected whenever the chest radiograph reveals an air-fluid level or when the patient expectorates copious quantities of sputum while lying on one side (due to drainage of the empyema by gravity into the bronchial tree) and not while lying on the other side.

At times, it is difficult to determine whether an air-fluid level is in the lung or in the pleural space. It is important to make this differentiation because a lung abscess should be treated with antibiotics alone, whereas it is imperative to drain the pleural space if a bronchopleural fistula exists. Chest CT is quite valuable in making this differentiation, as described earlier in this chapter (see Fig. 73-6).

Postpneumonectomy Empyema

The incidence of empyema after pneumonectomy is about 7.5%.[187] This diagnosis should be suspected in any patient who undergoes pneumonectomy and becomes febrile, starts expectorating large amounts of sputum, has purulent drainage from the thoracotomy wound, or has a mediastinum that is midline or shifted to the contralateral side. The diagnosis is established with a diagnostic thoracentesis that reveals organisms on Gram stain or culture.

A postpneumonectomy empyema is an extremely serious complication because it is impossible to eliminate the space containing the infection and, consequently, it is difficult to sterilize the pleural space. Approximately 60% to 80% of patients with postpneumonectomy empyema have a bronchopleural or an esophagopleural fistula.[187,188] Therefore, all patients with this complication should undergo a chest CT scan and a bronchoscopy.

The treatment of a postpneumonectomy empyema involves two different aspects, draining the infected pleural fluid and closing the bronchopleural fistula. The pleural fluid is best drained by tube thoracostomy if the empyema develops in the first few days after pneumonectomy. Subsequently, most patients require open drainage. If the patient does not have a bronchopleural fistula, operative irrigation and filling of the residual space with an antibiotic-containing solution or thoracoscopic débridement may be curative.[188]

If a bronchopleural fistula is present, it must be treated. Attempts can be made to close the fistula bronchoscopically, but a thoracotomy with surgical closing of the fistula by use of an intrathoracic muscle transposition or a pedicled omental flap are usually required.[188]

Tuberculous Pleuritis

In many parts of the world, the most common cause of an exudative pleural effusion is tuberculosis. However,

in the United States, the annual incidence of tuberculous pleural effusion is below 1000; approximately 1 in every 30 cases of tuberculosis is tuberculous pleuritis.[189] In some African countries, the percentage of patients with tuberculosis who have a pleural effusion exceeds 30%.[190] The effect of HIV on the incidence of tuberculous pleurisy is still uncertain; in some studies, HIV appears to increase the incidence and in others not.[190] The confusion may lie in part due to the state of immunocompromise. The prevalence of tuberculous pleurisy is also higher in patients with CD4 counts above 200 than in those with CD4 counts below 200,[191] in keeping with our current understanding of the role of delayed hypersensitivity in the development of the effusion.

A pleural effusion as a manifestation of tuberculosis has been likened to a primary chancre as a manifestation of syphilis. Both are self-limited and of little immediate concern, but both may lead to serious disease many years later. Most instances of pleural effusion secondary to tuberculosis resolve spontaneously; however, if patients are not treated with antituberculous therapy, they have about a 50% likelihood of developing active tuberculosis in the subsequent 5 years.[192]

Pathogenesis

A tuberculous pleural effusion can either be a sequel to a primary infection acquired 3 to 6 months previously or represent reactivation tuberculosis. A molecular epidemiologic study has confirmed that tuberculous pleurisy is usually an early manifestation of tuberculosis infection.[193] Delayed hypersensitivity appears to play a large role in the pathogenesis of tuberculous pleuritis. In animal models, the intrapleural injection of tuberculous protein in sensitized animals results in the rapid appearance of an exudative pleural effusion.[194] When the animals are given antilymphocyte serum, the development of the effusion is suppressed. The observation that pleural fluid cultures are negative in approximately 80% of patients with tuberculous pleuritis suggests that delayed hypersensitivity also plays a large role in the development of tuberculous pleural effusions in humans. Although delayed hypersensitivity to tuberculous protein is believed to be primarily responsible for tuberculous pleuritis, approximately one third of patients with tuberculous pleuritis have a negative tuberculin skin test result when first evaluated. The negative skin test is thought to be due to the sequestration of circulating PPD-reactive lymphocytes or to suppressor cells, either adherent monocytes or Fc-bearing lymphocytes, which are found in the blood but not in the pleural space.[194]

Clinical Manifestations

Tuberculous pleuritis occurs as an acute illness in about two thirds of cases and as a chronic illness in the remaining one third. The acute illness is marked by cough and chest pain in about 75% of patients and often mimics a bacterial pneumonia with parapneumonic effusion. The chronic form is characterized by low-grade fever, weakness, and weight loss.

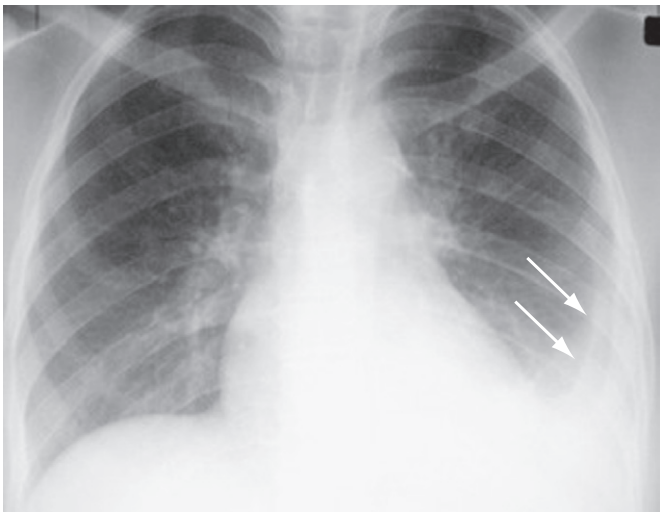

FIGURE 73-8 ■ Tuberculous effusion. Frontal chest radiograph in an immunocompromised patient with *Mycobacterium tuberculosis* infection shows left lower lobe consolidation (note absence of left diaphragm contour) and left pleural effusion (*arrows*). Smears and cultures of sputum were positive for *M. tuberculosis*. (Courtesy of Michael B. Gotway, MD, Scottsdale Medical Imaging and the Department of Radiology, University of California, San Francisco.)

Effusions secondary to tuberculous pleuritis are almost always unilateral (Fig. 73-8) and are usually small to moderate in size, although they may occupy the entire hemithorax. Up to 86% of patients will have coexisting parenchymal disease.[195] In such patients, the pleural effusion is almost always on the side of the parenchymal infiltrate and invariably indicates active parenchymal disease (see Fig. 73-8). It is likely that even in cases with no radiographic evidence of parenchymal involvement, the effusion is associated with a subpleural focus of infection. Evidence to support this contention is provided by a study in which the yield of sputum induction for *M. tuberculosis* was as high in patients with no radiographic evidence of parenchymal involvement (55%) as in those with evidence of parenchymal disease (45%).[122]

Pleural Fluid. The pleural fluid from patients with tuberculous pleuritis is an exudate that usually contains predominantly small lymphocytes. If symptoms have been present only a few days, neutrophils may be predominant. The pleural fluid glucose level is usually similar to that of serum but, at times, it is reduced. A pleural fluid protein level above 5.0 g/dL is suggestive of tuberculous pleuritis.

Diagnosis

The possibility of tuberculous pleuritis should be considered in every patient with an undiagnosed exudative pleural effusion, even though only a small percentage of such effusions are due to tuberculosis in the United States.[53] Since the late 1950s, the most common way to establish the diagnosis of tuberculous pleuritis has been via needle biopsy of the pleura. However, in recent years, three tests that can be performed on pleural fluid

have been developed that may be useful in establishing or excluding the diagnosis of tuberculous pleuritis: (1) the level of ADA in the pleural fluid, (2) the level of IFN-γ in the pleural fluid, and (3) the PCR for mycobacterial DNA. These studies are described in detail earlier in this chapter; as mentioned, one disadvantage of these tests is that they do not provide bacterial cultures for antibiotic sensitivity testing.

In all patients with an undiagnosed exudative pleural effusion, pleural fluid should be cultured for mycobacteria and have one of the aforementioned three tests performed on their pleural fluid. An induced sputum should also be sent for smear and culture because it will be positive in approximately 50%.[122] If the culture of the fluid or sputum is positive, treatment for tuberculosis should be initiated. If one of the other tests is positive for tuberculosis, the patient should also be treated for tuberculosis unless the patient has a disease that is known to be associated with a positive result or if there is no pleural fluid lymphocytosis. In areas with a high likelihood of resistant tuberculosis, one may also want to obtain pleural tissue for cultures via needle biopsy of the pleura or thoracoscopy. If the patient does not respond to therapy, then further investigations are warranted; needle biopsy of the pleura can be performed in questionable cases, but unless the likelihood of tuberculosis is high, the invasive diagnostic test of choice is usually thoracoscopy.

Treatment

Patients with tuberculous pleuritis should be treated with antituberculous medications in the same treatment regimens that are administered to patients with pulmonary tuberculosis; these are fully discussed in Chapter 34. With treatment, patients generally become afebrile within about 2 weeks, and the pleural effusion resolves within 6 weeks. On occasion, the pleural effusion worsens after antituberculous therapy is initiated[196] or a pleural effusion develops while a patient is being treated for tuberculosis.[197] In these situations, the possibility of a wrong diagnosis must be considered, but the paradoxical worsening can occur with the correct diagnosis and appropriate antituberculous medications.[196,197] Mild degrees of pleural fibrosis are present a year after therapy is begun in about 50% of patients. The presence of fibrosis is not related to the initial pleural fluid findings and is of limited clinical significance.[198]

The role of systemic corticosteroids in the treatment of tuberculous pleuritis remains controversial. A systematic literature review concluded that there was insufficient data to support evidence-based recommendations regarding the use of adjunctive corticosteroids in those with tuberculous pleurisy.[199] Use of corticosteroids may be considered for those who are markedly symptomatic, but only after the institution of appropriate antituberculosis therapy. Therapeutic thoracentesis is indicated if the patient has a moderate-sized or larger pleural effusion producing symptoms. Otherwise, complete drainage of the pleural space has no significant effects on the long-term outcome.[200]

Actinomycosis

More than 50% of patients with thoracic actinomycosis have pleural involvement.[201] In one series of 15 patients, 6 had pleural effusion, and an additional 6 had marked pleural thickening.[201] The characteristic chest radiographic finding is a localized lung lesion extending to the chest wall with pleural thickening or effusion. The pleural fluid with actinomycosis may be either frank pus with predominantly polymorphonuclear leukocytes or serous fluid with predominantly lymphocytes.

The diagnosis of actinomycosis should be considered when a chronic infiltrative pulmonary lesion extends to adjacent lobes through intralobar fissures. The presence of chest wall abscesses or draining sinus tracts suggests the diagnosis, as do bone changes consisting of periosteal proliferation or bone destruction. The definitive diagnosis is established with the demonstration of *Actinomyces israelii* by anaerobic cultures. Patients with pleural actinomycosis should be treated with high doses of penicillin or another suitable antimicrobial for prolonged periods. The management of the pleural effusion is similar to that for patients with any other bacterial pneumonia.

Nocardiosis

Pleural effusions develop in approximately 50% of patients with pulmonary nocardiosis.[202] Patients with pleural effusion secondary to nocardiosis almost always have an associated parenchymal infiltrate. The pleural fluid can range from serous fluid to frank pus, and pleural fluid cultures may or may not be positive. Because most patients who develop nocardiosis are immunosuppressed,[202] this diagnosis should be considered in the immunosuppressed patient with a parenchymal infiltrate and a pleural effusion. The diagnosis is established with aerobic cultures, which should be observed for at least 2 weeks, because *Nocardia asteroides* is a slow-growing organism. Patients with pleural nocardiosis should be treated with sulfonamides or suitable alternative antimicrobials, and the pleural effusion should be managed as any pleural effusion complicating a pneumonia.

Fungal Infections

Fungal infections of the lungs are discussed in Chapter 36. This section considers the pleural complications of aspergillosis, blastomycosis, coccidioidomycosis, cryptococcosis, and histoplasmosis. In addition, *Pneumocystis jirovecii* (formerly *carinii*) has been included.

Aspergillosis

The pleural space occasionally becomes infected with *Aspergillus*, usually *Aspergillus fumigatus*.[203] Pleural aspergillosis usually arises in one of two settings. Most commonly, it occurs in patients who were treated in the past with artificial pneumothorax therapy for tuberculosis. Pleural aspergillosis may also complicate lobectomy or pneumonectomy, in which situation, a bronchopleural fistula is almost always present.

The diagnosis of pleural aspergillosis should be suspected in any patient with a history of artificial pneumothorax therapy for tuberculosis who has signs and symptoms of a chronic infection, such as weight loss, malaise, low-grade fever, and chronic cough. The chest radiograph reveals increasing degrees of pleural thickening and usually an air-fluid level in the pleural space, indicating the presence of a bronchopleural fistula.[203] In some patients, fungus balls or mycetoma may be evident in either the lungs or the pleural space. The diagnosis is confirmed by the demonstration of *Aspergillus* on fungal cultures of the pleural fluid. Patients with pleural aspergillosis almost always have positive precipitin blood test results for antibodies against *Aspergillus*.

The optimal treatment for pleural aspergillosis is surgical removal of the involved pleura and resection of the involved lobe or the entire ipsilateral lung, if necessary.[203] Lung resection is usually necessary because the infection tends to invade and destroy the underlying lung. Surgery should be performed as early as possible to avoid progressive destruction of the lung. Itraconazole or amphotericin B should be administered systemically before and after the surgery to prevent postoperative pleural infection with *Aspergillus*. Some patients with pleural aspergillosis are too debilitated to undergo a major surgical procedure. Such patients should undergo open drainage (Eloesser flap) with daily insertion of gauze impregnated with amphotericin B.[204]

The clinical picture of postoperative *Aspergillus* pleural infections is similar to that of other postpneumonectomy infections. Once the diagnosis is established, a chest tube should be inserted, and the pleural space should be irrigated daily with 25 mg of amphotericin B or 75,000 U of nystatin. Over an extended period, most patients are cured with this treatment.

Blastomycosis

Infection with *Blastomyces dermatitidis* produces a pleural effusion in about 10% of patients, and an additional 40% or more have pleural thickening.[205] Patients with pleural blastomycosis have signs and symptoms similar to those of tuberculous pleuritis. The pleural fluid is usually an exudate with predominantly small lymphocytes, although polymorphonuclear leukocytes may predominate. Because pleural biopsy may reveal noncaseating granulomas, one should consider the diagnosis of blastomycosis in patients with a clinical picture compatible with tuberculous pleuritis and granulomas on pleural biopsy. The diagnosis is established by demonstrating the organism in secretions, pleural fluid, or histologic sections. Patients with pleural blastomycosis should be treated with itraconazole or amphotericin B, as described in Chapter 36.

Coccidioidomycosis

Two types of pleural disease arise in association with coccidioidomycosis. The first is associated with a primary benign infection and may or may not have concomitant parenchymal involvement. The second occurs when a coccidioidal cavity ruptures to produce a hydropneumothorax.

Primary Coccidioidomycosis. The incidence of pleural effusion in hospitalized patients with primary coccidioidomycosis is about 15%.[206] Most patients are febrile and have pleuritic chest pain. The pleural effusion is almost always unilateral and can occupy more than 50% of the hemithorax.[206] There is a coexisting parenchymal infiltrate in about 50%. The pleural fluid is an exudate containing predominantly small lymphocytes and frequently eosinophils; at times, the pleural fluid is pus.[206] Pleural fluid cultures are positive for *Coccidioides immitis* in about 20%, whereas cultures of pleural biopsy specimens are almost always positive.

Most patients with primary coccidioidomycosis and pleural effusion require no systemic antifungal therapy. Only patients with a negative skin test result or other evidence of dissemination should be treated. The complement fixation titers are usually high in patients with coccidioidal pleural effusion, and a high titer alone should not be used as an indication for treatment.

Rupture of Coccidioidal Cavity. Hydropneumothoraces develop in 1% to 5% of patients with chronic cavitary coccidioidomycosis. The rupture of the cavity into the pleural space is usually heralded by the development of an acute illness with systemic signs of toxicity. These patients should undergo tube thoracostomy immediately to drain the air and fluid from the pleural space. Most patients require a thoracotomy with a partial or total lobectomy, and most require some degree of decortication.

Cryptococcosis

Pleural involvement with cryptococcosis appears to result from extension of a primary subpleural cryptococcal nodule into the pleural space. About 50% of patients with pleural cryptococcosis have disseminated disease, and most have an accompanying parenchymal abnormality. Most patients who have a cryptococcal pleural effusion are immunosuppressed, and many of the patients have acquired immunodeficiency syndrome (AIDS).[207,208] The pleural fluid is an exudate, usually with a predominance of small lymphocytes.

Not all patients with pleural cryptococcosis require treatment with systemic antifungal therapy. Treatment should be initiated in patients with cryptococcal antigen in their blood or CSF; in immunosuppressed patients, including those with AIDS; and in those with enlarging effusions, especially if pleural cell counts and LDH concentrations are increasing.[53]

Histoplasmosis

Pleural effusion is rare with histoplasmosis. In one review of 259 patients with pulmonary histoplasmosis, only 1 had a pleural effusion.[209] Patients with pleural effusions secondary to histoplasmosis usually have a subacute illness characterized by low-grade fever and pleuritic chest pain. The chest radiograph usually reveals an infiltrate or a subpleural nodule in addition to the pleural effusion.[210] The pleural fluid is an exudate in which

lymphocytes predominate, and the pleural biopsy usually reveals noncaseating granulomas. No systemic treatment is usually necessary for a pleural effusion secondary to histoplasmosis because the effusion normally resolves spontaneously over several weeks. Systemic therapy should be administered if the effusion persists over 3 to 4 weeks or if the patient is immunosuppressed (see Chapter 36).

Pneumocytis jirovecii

Pleural effusions are rare in patients with *P. jirovecii* pneumonia (see Chapter 80), but they have been reported. The pleural effusion appears to be an extension of the pulmonary process, and concurrent pneumothoraces are common. The pleural fluid is an exudate with a relatively low protein level but an LDH level above the upper normal limit for serum. At times, organisms can be visualized in the pleural fluid.

Viral Infections

Viral infections probably account for a sizable percentage of undiagnosed exudative pleural effusions. However, the diagnosis is rarely established because it usually depends on the isolation of the virus or the demonstration of a significant increase in antibody titers to the virus. These studies are not routinely obtained on patients with undiagnosed pleural effusions.

Primary Atypical Pneumonia

The incidence of pleural effusions with so-called primary atypical pneumonia (usually caused by *Mycoplasma* or viruses) is as high as 20%.[211] The effusions associated with atypical pneumonia are usually small, are exudative, and contain predominantly neutrophils. Thoracentesis should be performed in such patients to exclude a complicated parapneumonic effusion.

Other Viruses

Viral infection is probably responsible for a much higher percentage of pleural effusion without parenchymal infiltrates than is generally recognized. In one epidemic, 559 soldiers in Turkey had an acute febrile illness characterized by pleuritic chest pain and a mononuclear cell–predominant pleural effusion without parenchymal infiltrates. No pathogens were demonstrated, and it was assumed that this self-limited disease was due to a virus, although serologic studies were not performed.[212]

Almost all patients with the hantavirus pulmonary syndrome (see Chapter 31) have a pleural effusion. Initially, the fluid is a transudate, probably resulting from cardiac dysfunction, but subsequently, the fluid becomes exudative.[213] Almost all patients with severe cases of dengue hemorrhagic fever also have pleural effusions, which are either right-sided or bilateral.[214] Pleural effusions have also been reported to result from infection with hepatitis, infectious mononucleosis, respiratory syncytial virus, influenza viruses, measles after the administration of inactivated virus vaccine, cytomegalovirus, herpes simplex virus, and Lassa fever virus.

Acquired Immunodeficiency Syndrome

As discussed in Chapter 80, pleural effusions occur in patients with AIDS, although less commonly than parenchymal infiltrates. In a series of 1225 consecutive hospital admissions of patients with AIDS in Jacksonville, FL, the incidence of pleural effusion was 15%.[215] The distribution of the diseases responsible for pleural effusions in patients with AIDS varies widely from series to series. In series from industrialized countries that included predominantly intravenous drug users, the most common cause is parapneumonic effusions; in contrast, in series with predominantly homosexuals, the most common cause is Kaposi's sarcoma. In series from Africa, tuberculosis is the most common cause.[216] Other causes of pleural effusions in patients with AIDS include body-cavity lymphoma, *P. jirovecii* (formerly *carinii*), opportunistic infections, renal failure, and CHF.

Patients with AIDS and parapneumonic effusions should be managed as any patient with a parapneumonic effusion, but the incidence of complicated parapneumonic effusion is higher in patients with AIDS.[217] The incidence of pleural effusion with pulmonary Kaposi's sarcoma is approximately 50%. Most patients with a pleural effusion due to Kaposi's sarcoma have bilateral parenchymal infiltrates. The diagnosis of pleural involvement is difficult and often depends on the demonstration of pulmonary Kaposi's sarcoma, by either bronchoscopic examination, high-resolution CT, or thoracoscopy. The pleural fluid is an exudate that is usually serosanguineous or hemorrhagic. Pleural fluid cytologic examinations are invariably negative with pleural Kaposi's sarcoma; pleural biopsy results are also usually negative because the parietal pleura is not involved.

Patients with AIDS with an exudative pleural effusion should have a diagnostic thoracentesis that includes bacterial, mycobacterial, and fungal cultures and measurement of the pleural fluid ADA or IFN-γ. If this does not establish a diagnosis, consideration should be given to performing thoracoscopy, at which time, a pleurodesis may be considered in symptomatic patients.

Parasitic Diseases

Parasitic infections of the lungs are discussed in Chapter 37. Those that may also involve the pleura—amebiasis, echinococcosis, and paragonimiasis—are also considered in this section.

Amebiasis

Pleural effusions arise by two different mechanisms in conjunction with amebic liver abscess. First, an amebic liver abscess may irritate the diaphragm and produce a sympathetic pleural effusion in a manner analogous to that of pyogenic liver abscess. Second, a pleural effusion develops when an amebic liver abscess ruptures into the pleural space through the diaphragm.[218]

The sympathetic effusion caused by pleural irritation by the amebic liver abscess is more common than the effusion caused by rupture of an abscess through the diaphragm.[218] The pleural fluid has not been well characterized. The diagnosis can be established by positive gel diffusion, indirect hemagglutination, or enzyme-linked immunosorbent assay (ELISA) tests, the results of which are positive in more than 98% of patients with extraintestinal invasive amebiasis.[218] Patients with amebic abscess and a sympathetic pleural effusion should be treated with antiamebic drugs, as described in Chapter 37.

The transdiaphragmatic rupture of an amebic liver abscess is usually heralded by an abrupt exacerbation of pain in the right upper quadrant and may be accompanied by a tearing sensation.[219] Shortly thereafter, progressive respiratory distress, sepsis, and occasionally shock develop. The pleural effusion is frequently massive, with opacification of the entire hemithorax and shift of the mediastinum to the contralateral side.[219] The diagnosis of amebic abscess with transdiaphragmatic rupture is suggested by the discovery of "anchovy paste"– or "chocolate sauce"–like pleural fluid on diagnostic thoracentesis. Patients with transdiaphragmatic rupture should undergo tube thoracostomy. The patients should also be treated with the same antiamebic drugs recommended for patients with amebic sympathetic effusions. Because bacterial infection of the pleural space complicates the process in about one third of patients, bacterial cultures of the pleural fluid should be obtained routinely. If bacterial infection is present, appropriate antibiotic therapy should be initiated.

Echinococcosis

Pleural involvement with hydatid disease can develop in one of three situations: (1) a pulmonary hydatid cyst may rupture into the pleural space; (2) a hepatic hydatid cyst or, on rare occasions, a splenic cyst may rupture through the diaphragm into the pleural space; or (3) the pleura maybe be primarily involved by the slowly enlarging cyst.[220] When a cyst ruptures into the pleural space, either an empyema or a pneumothorax can result.[220] In a series of 474 patients with pulmonary hydatid disease, 6% had pleural thickening or effusion.[221]

When a hydatid cyst ruptures into the pleural space, the patient develops acute symptoms, with sudden tearing chest pain, dyspnea, and shock from the antigenic challenge to the body. The cyst frequently also ruptures into the tracheobronchial tree, producing a bronchopleural fistula with a hydropneumothorax that may become secondarily infected.

The diagnosis of pleural echinococcosis is established by the demonstration of echinococcal scolices with hooklets in the pleural fluid or the pleural biopsy specimen. Eosinophils are frequently present in the pleural fluid unless it is secondarily infected. Patients with pleural echinococcosis should be immediately subjected to thoracotomy to remove the parasite, to excise the original cyst, and to close the bronchopleural fistula.[220] Patients with hydatid cysts should be treated with antiprotozoal therapy if all the cysts cannot be removed or when rupture of a cyst has occurred.

Paragonimiasis

Pleural disease is common with paragonimiasis (see also Chapter 37). In one series of 71 patients, 43 (61%) had pleural disease, including 20 with unilateral pleural effusions, 6 with bilateral pleural effusions, 6 each with unilateral and bilateral hydropneumothorax, and 5 with pleural thickening.[222] Paragonimiasis can occur in natives of the United States who have never left the country.

Patients with pleural paragonimiasis present with a chronic illness. There is a concomitant parenchymal infiltrate in approximately 50% of patients. The pleural fluid in patients with pleural paragonimiasis is characteristic. It is an exudate with a glucose level of less than 10 mg/dL (0.56 mmol/L), an LDH level of more than three times the upper limit of normal for serum, a pH below 7.10, and a differential revealing a high percentage of eosinophils.[66] In addition, cholesterol crystals are frequently present.[66] Pleural paragonimiasis is one of only two conditions in which the pleural fluid is characterized by a low pH, a low glucose level, and many eosinophils; the other is Churg-Strauss syndrome. Usually, there are no ova in the pleural fluid.

The diagnosis of pleural paragonimiasis is strongly suggested by the unique pleural fluid findings. The diagnosis is established definitively by demonstrating the typical operculated eggs in sputum, stool, or pleural fluid. A complement fixation titer above 1:8 for *Paragonimus westermani* is strongly suggestive of the diagnosis.[66] The treatment for paragonimiasis is discussed in Chapter 37.

Pulmonary Embolism

The diagnosis most commonly overlooked in the differential diagnosis of a patient with an undiagnosed pleural effusion is pulmonary embolism. It has been estimated that at least 500,000 persons develop venous thromboembolism annually in the United States. Because at least 30% of patients with pulmonary emboli have an associated pleural effusion,[223] over 150,000 pleural effusions secondary to pulmonary emboli should occur annually. Therefore, one should expect to see more cases of pleural effusion secondary to pulmonary embolization than to bronchogenic carcinoma. Nevertheless, in most large series, pulmonary embolization accounts for fewer than 5% of pleural effusions. The diagnosis and treatment of pulmonary embolism are discussed in Chapter 51.

Clinical Manifestations

Patients with pulmonary embolism can be divided into three categories, depending on their presenting symptoms: (1) pleuritic pain or hemoptysis, (2) isolated dyspnea, and (3) circulatory collapse. In the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study, 56% of the patients with pleuritic pain or hemoptysis had pleural effusion, and 26% of those with isolated dyspnea had pleural effusion, but none of the patients with circulatory collapse had pleural effusion.[223]

Approximately 50% of patients with paraembolic effusions have parenchymal infiltrates seen on chest radiographs.[224] The infiltrates are usually in the lower lobes, are pleural-based, and are convex toward the hilum. Paraembolic effusions are usually small; in one series, 48 of 56 patients (86%) had only blunting of the costophrenic angle, and no patient had an effusion that occupied more than one third of a hemithorax.[223] The pleural effusions may be unilateral or bilateral. In one study of 63 patients with pulmonary emboli and pleural effusion, the effusions were bilateral in 16 (25%).[225] Interestingly, in other studies using spiral CT angiography in patients suspected of having pulmonary embolism, those patients found to have pulmonary embolism were no more likely to have pleural effusions than those without embolism (50% vs. 58%[226]; 57% vs. 56%[227]). Patients suspected of having pulmonary embolism likely have other underlying conditions that predispose them to pleural effusions, such as CHF or pneumonia.

Pleural fluid analysis is of limited value in establishing the diagnosis of paraembolic effusion because there is nothing characteristic about the fluid. The pleural fluid is almost always an exudate.[63] The pleural fluid red blood cell count exceeds 100,000/μL in fewer than 20% and is below 10,000/μL in at least 30%. The pleural fluid white blood cell count can vary from under 100 to over 50,000/μL. The differential white blood cell count may reveal predominantly polymorphonuclear leukocytes or mononuclear cells.

Diagnosis

The diagnosis of pulmonary embolism is discussed in Chapter 51. The possibility of pulmonary embolization should be considered in every patient with a pleural effusion, even in the patient with obvious CHF. In an autopsy series of 290 patients with CHF and pleural effusion, 60 (21%) had pulmonary emboli.[132] When a paraembolic effusion is strongly suspected, the patient should be started on heparin treatment and a test for pulmonary embolism should be performed before a thoracentesis is attempted.[157]

In the patient with an undiagnosed pleural effusion for whom pulmonary embolism is suspected, CT angiography appears to be the preferred test because it also provides information about the lung parenchyma, the mediastinum, and the pleural surfaces that may provide clues to the etiology of the pleural effusion. Another reason to obtain the CT scan rather than a perfusion scan in patients with pleural effusions suspected of having pulmonary emboli is that the presence of the effusion makes the lung scan more difficult to interpret.

Treatment

The treatment of the patient with a paraembolic effusion is the same as for any patient with pulmonary emboli (see Chapter 51). The presence of bloody pleural fluid is not a contraindication to the administration of heparin or, if indicated, thrombolytic therapy.[224] Paraembolic effusions usually reach their maximum size within the first 3 days.[228] If the effusion increases in size after this time, the patient probably has recurrent emboli, a pleural infection, or a hemothorax and thus, a diagnostic thoracentesis should be performed. If the pleural fluid hematocrit value is greater than 50% of the peripheral hematocrit, a hemothorax is present. In this instance, anticoagulation should be discontinued, and tube thoracostomy should be performed.

Abdominal Diseases

As discussed in Chapter 83, many abdominal diseases can cause pulmonary signs and symptoms. This section describes the most important of these disorders that cause pleural effusion. The pleural effusions occurring in patients with chronic liver disease and ascites and in those with infectious hepatitis have already been discussed.

Esophageal Perforation

The diagnosis of esophageal rupture should always be considered in the differential diagnosis of exudative pleural effusions because, if this condition is not rapidly treated, the mortality increases, with current estimates ranging between 30% and 60%. Approximately 60% of patients with esophageal perforation have a pleural effusion, whereas about 25% have a pneumothorax.[229] The pleural effusion is usually left-sided (Fig. 73-9), but it might be right-sided or bilateral.

Esophageal perforation most commonly occurs as a complication of esophagoscopy and is more likely to occur when there is an attempt to remove a foreign body or to dilate an esophageal stricture.[230] Overall, the incidence of esophageal perforation with esophagoscopic

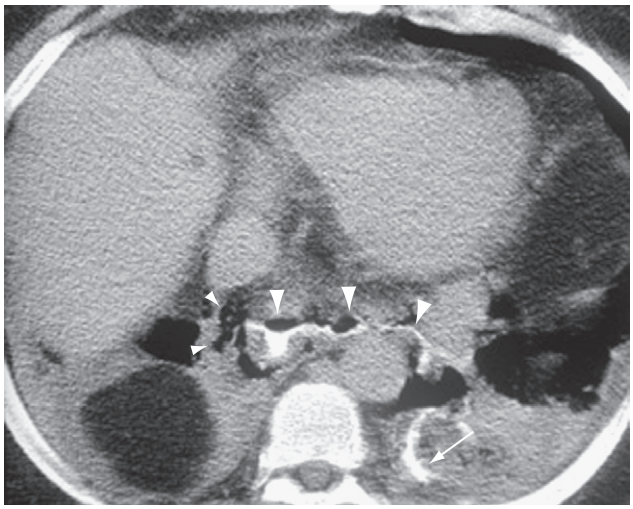

FIGURE 73-9 ■ Effusion due to esophageal perforation. Axial CT image through the lower thorax in a patient with chest pain shows pneumomediastinum (*small arrowheads*) and leakage of water-soluble oral contrast from the ruptured esophagus (*large arrowheads*) through the mediastinum into the left pleural space (*arrow*). (From Fadoo F, Ruiz DE, Dawn SK, et al: Helical CT esophagography for the evaluation of suspected esophageal perforation or rupture. AJR Am J Roentgenol 182:1177–1179, 2004.)

examination is 0.15% to 0.70%.[229] The insertion of a Blakemore-Sengstaken tube for esophageal varices can be complicated by esophageal rupture. Frequently, the diagnosis is missed in these patients because of the severity of their illness and the multiple coexisting problems.[229] Esophageal perforation may also result from transesophageal echocardiography, foreign bodies, esophageal carcinoma, gastric intubation, chest trauma, chest surgery, or vomiting (Boerhaave's syndrome).

Clinical Manifestations. The symptoms associated with esophageal perforation result from the acute mediastinitis produced by contamination of the mediastinum by the oropharyngeal contents. Most of the morbidity from esophageal perforation is caused by infection of the mediastinum and the pleural space by the oropharyngeal bacterial flora.[91]

A patient with an esophageal perforation is usually acutely ill. With a spontaneous rupture, there is frequently a sensation of tearing or bursting in the lower part of the chest or the epigastrium. The chest pain is characteristically excruciating and is often unrelieved by opiates. More than 50% of patients have small amounts of hematemesis. The presence of subcutaneous emphysema in the suprasternal notch is suggestive of the diagnosis. However, less than 10% of patients have subcutaneous emphysema within the first 4 hours of rupture.[231] When the esophagus is perforated during esophagoscopy, the endoscopist generally does not realize it; however, the patients usually develop persistent chest or epigastric pain within a few hours after the procedure.

Diagnosis. The diagnosis of esophageal rupture should be considered in all acutely ill patients with an exudative pleural effusion. The best screening test for esophageal rupture appears to be the level of amylase in the pleural fluid.[231] The pleural fluid amylase level is elevated owing to saliva, with its high amylase content, entering the pleural space.[90] The pleural fluid pH is usually decreased below 7.00 in patients with pleural effusion secondary to esophageal perforation due to the intense inflammatory response resulting from the mediastinitis and not the regurgitation of gastric juice into the pleural space. The demonstration of either squamous epithelial cells or food particles in the pleural fluid is highly suggestive of the diagnosis. Other findings suggestive of esophageal rupture are a chest tube output more than 500 mL/day or polymicrobial flora in the pleural fluid. The diagnosis is established when esophageal perforation is confirmed by contrast studies of the esophagus (see Fig. 73-9).

Treatment. The treatment of mediastinitis from esophageal perforation and other causes is discussed in detail in Chapter 83.

Pancreatic Disease

Three different types of nonmalignant pancreatic disease can have an accompanying pleural effusion: acute pancreatitis, chronic pancreatitis with pseudocyst, and pancreatic ascites.

Acute Pancreatitis. In a study of 133 patients with their first attack of acute pancreatitis, 50% of the patients had a pleural effusion on chest CT scan.[232] The effusion was bilateral in 51 (77%), unilateral left-sided in 10 (15%), and unilateral right-sided in 5 (8%). Patients with acute pancreatitis and a pleural effusion had more severe disease and a higher mortality rate than did those without effusions.[232] The exudative pleural effusion accompanying acute pancreatitis results from the diaphragmatic inflammation and transdiaphragmatic transfer of the exudative fluid arising from acute pancreatic inflammation.

The clinical picture is usually dominated by abdominal symptoms, including pain, nausea, and vomiting. However, at times, respiratory symptoms consisting of pleuritic chest pain and dyspnea may dominate the clinical picture. In addition to the small to moderate-sized pleural effusion, the chest radiograph may reveal an elevated diaphragm and basilar infiltrates. Demonstration of an elevated pleural fluid amylase level is highly suggestive of the diagnosis, but the diagnosis of esophageal rupture must be excluded. The pleural fluid is an exudate with predominantly polymorphonuclear leukocytes and a normal glucose level.

Patients with pancreatitis and a pleural effusion should be treated for their pancreatitis in the usual manner (see Chapter 83).

Chronic Pancreatic Pleural Effusion. Patients with chronic pancreatic disease sometimes have a large chronic pleural effusion. If the pancreatic ductal system is disrupted, a pseudocyst may form in the pancreas. A sinus tract may extend from the pseudocyst through the aortic or esophageal hiatus into the mediastinum. Once the sinus tract reaches the mediastinum, the process may be contained to form a mediastinal pseudocyst or it may rupture into one or both pleural spaces, resulting in a large chronic pleural effusion[92] (Fig. 73-10).

The clinical picture of patients with chronic pancreatic disease and pleural effusion is usually dominated by chest symptoms, such as dyspnea, cough, and chest pain. Most patients do not have abdominal symptoms

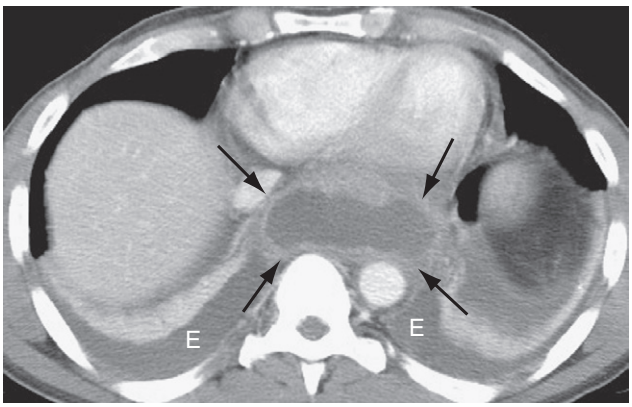

FIGURE 73-10 ■ Effusion due to pancreatic pseudocyst. Axial CT image through the lower thorax in a patient with chronic pancreatitis shows bilateral pleural effusions (E) and a cystic mass in the middle mediastinum (*arrows*) representing a pseudocyst. (Courtesy of Michael B. Gotway, MD, Scottsdale Medical Imaging and the Department of Radiology, University of California, San Francisco.)

because the pancreaticopleural fistula decompresses the pseudocyst. The pleural effusion is usually massive and recurs rapidly after thoracentesis.[92] The effusion is usually left-sided but may be right-sided or bilateral.

The key to the diagnosis is a markedly elevated pleural fluid amylase level, generally greater than 1000 U/L, whereas the serum level of amylase may be only mildly elevated. Patients with chronic pancreatic pleural disease are generally easily differentiated from those with malignant pleural effusion, who also may have an elevated pleural fluid amylase level, because the amylase level is much higher with the pseudocyst. In rare cases in which the differentiation is not obvious, the diagnosis can be made by measuring amylase isoenzymes because the amylase associated with malignancy is of the salivary, not the pancreatic, type.[94] Both ultrasound and CT are useful in establishing the diagnosis of pancreatic pseudocyst. Endoscopic retrograde cholangiopancreatography usually documents the fistulous tract or other pancreatic pathology.

Patients with chronic pancreatic pleural effusions should be given a trial of conservative therapy for 2 to 3 weeks consisting of nasogastric suction, no oral intake, suppression of pancreatic secretion with atropine, and repeated therapeutic thoracenteses.[92] The administration of a continuous infusion of somatostatin may decrease the secretions through the fistula and facilitate closure.[233] Conservative treatment is successful within 4 weeks in about 40% of patients. If conservative treatment fails, a laparotomy should be performed. The anatomy of the pancreatic ductal system should be assessed before surgery with endoscopic retrograde cholangiopancreatography or at the time of operation with operative pancreatography. If a sinus tract is found, it should be ligated or excised. The pancreas should be partially resected, drained with a Roux-en-Y loop, or both, depending on the pancreatographic findings.[92] An alternative approach is to attempt percutaneous abdominal pseudocyst drainage by use of CT guidance. Decortication of the pleura may be necessary for some patients in order to remove the thick pleural peel created by the intense inflammation caused by the presence of pancreatic enzymes.

Pancreatic Ascites. Some patients with pancreatic disease develop ascites characterized by high amylase and protein levels. If such patients should happen to have or develop a defect in their diaphragm, they develop a large pleural effusion as a result of the flow of fluid from the peritoneal cavity to the pleural cavity. The treatment for pancreatic ascites is the same as for pancreatic pleural effusion, except serial paracenteses rather than serial thoracenteses are performed.

Intra-abdominal Abscesses

Pleural effusions frequently occur with intra-abdominal abscesses. The possibility of an intra-abdominal abscess should be considered strongly in any patient with an undiagnosed exudative pleural effusion containing predominantly polymorphonuclear leukocytes, particularly when there are no pulmonary parenchymal infiltrates. The mechanism responsible for the development of the exudative pleural effusion is probably diaphragmatic irritation.

Subphrenic abscess is the intra-abdominal abscess most commonly associated with a pleural effusion; pleural effusions occur in approximately 80% of patients with subphrenic abscess.[234] The approximate incidence of effusions with other intra-abdominal abscesses is 40% in pancreatic abscesses, 30% in splenic abscess, and 20% in intrahepatic abscesses. With pancreatic abscess, the pleural fluid has a high amylase level.

Clinical Manifestations. Subphrenic abscess most commonly develops as a postoperative complication 1 to 3 weeks after intra-abdominal surgery.[234] Splenectomy and gastrectomy are particularly likely to be complicated by left subphrenic abscess. There is no antecedent abdominal surgery in approximately 10% of patients with subphrenic abscess.[234] The abscess may result from perforation of the stomach, duodenum, appendix, colon, or a diverticulum or from diverticulitis, cholecystitis, pancreatitis, or trauma. Most patients have fever, leukocytosis, and abdominal pain, but frequently, there are no localizing signs or symptoms.

Most patients with pyogenic intrahepatic abscesses have fever and anorexia. Abdominal pain is common, but frequently, it is not localized to the right upper quadrant. On physical examination, an enlarged, tender liver can be demonstrated. Laboratory tests reveal leukocytosis, anemia, elevated alkaline phosphatase levels, and hyperbilirubinemia.[235]

Pancreatic abscess usually follows an episode of acute pancreatitis. This diagnosis should be suspected if the patient does not respond to the initial therapy or if fever, abdominal pain, and leukocytosis develop within 3 weeks of the episode of acute pancreatitis. Splenic abscess is uncommon and usually occurs in patients with systemic infection. Bacterial endocarditis is the most common underlying infection.

The pleural fluid that accumulates in patients with intra-abdominal abscesses is an exudate with predominantly polymorphonuclear leukocytes. The pleural fluid white blood cell count may exceed 50,000/μL, but the pleural fluid pH and glucose concentration usually remain above 7.20 and 60 mg/dL (3.33 mmol/L), respectively. Only rarely does the pleural fluid become infected.

Diagnosis and Treatment. The diagnosis of intra-abdominal abscess is best established with an abdominal CT scan.[236] An abdominal CT scan should be obtained in every patient with an undiagnosed exudative neutrophilic pleural effusion if there are no parenchymal infiltrates. The appropriate treatment for a patient with an intra-abdominal abscess and a pleural effusion is drainage of the abscess combined with parenteral antibiotics.

Abdominal Surgery

Approximately 50% of patients undergoing abdominal surgery develop a pleural effusion in the first few days after surgery.[237,238] The incidence of postoperative pleural effusion is greater in patients undergoing upper abdominal surgery, in patients with postoperative atelectasis,

and in patients with free abdominal fluid at surgery.[237,238] The accumulation of pleural fluid within the first 72 hours after abdominal surgery is probably related to either diaphragmatic irritation or transdiaphragmatic movement of intra-abdominal fluid. A postoperative patient with a significant amount of pleural fluid, particularly when associated with fever, should have a diagnostic thoracentesis to rule out pleural infection as a cause of the effusion. In addition, the possibility of pulmonary embolization should be considered. If the effusion develops more than 72 hours after surgery, it is probably not related to the surgical procedure itself, and alternative explanations must be sought, such as pulmonary embolization, intra-abdominal abscess, and hypervolemia.

Liver Transplantation

Most patients who undergo an orthotopic liver transplantation develop a pleural effusion after surgery. In one study, 68% of 300 patients undergoing liver transplantation developed a pleural effusion, and the effusion occupied more than 25% of the hemithorax in 21 patients (7%).[239] The effusion was unilateral right-sided in 153 and bilateral in 53. The effusions are large enough to require therapeutic thoracentesis or tube thoracostomy in approximately 10%.[239] The natural history of these effusions is that they increase in size over the first 3 postoperative days and then gradually resolve over several weeks to several months. The pathogenesis of these effusions is probably related to injury or irritation of the right hemidiaphragm caused by the extensive right upper quadrant dissection. These pleural effusions can be largely prevented if a fibrin sealant is sprayed on the undersurface of the diaphragm around the insertion of the liver ligaments at the time of the transplantation.[240]

Bilious Pleural Effusion

Bilious pleural effusions are due to a fistula from the biliary tree to the pleural space.[241] The fistula may be secondary to trauma, suppurative complications of biliary tract infections, or surgery, particularly when biliary obstruction is present. The diagnosis should be suspected in any patient with an obstructed biliary tract. The pleural fluid usually appears bilious but, at times, the diagnosis may depend on the demonstration that the ratio of pleural fluid to serum bilirubin is greater than 1.0. Appropriate treatment consists of reestablishment of biliary drainage. The incidence of empyema with bilious pleural effusion is approximately 50%. Most patients who have a bilious pleural effusion require decortication and diaphragmatic repair.[53]

Miscellaneous Diseases

Rheumatoid Pleuritis

The pleura is occasionally involved in the course of rheumatoid arthritis. Approximately 5% of patients with rheumatoid arthritis have a pleural effusion, and approximately 20% experience pleuritic chest pain.[95,242] Rheumatoid pleurisy has a striking male predominance, despite the higher prevalence of rheumatoid disease in women; more than 10% of men, but less than 2% of women, with rheumatoid disease have a pleural effusion.[95,242] Additional information about rheumatoid pleuritis and other pulmonary manifestations of rheumatoid arthritis is found in Chapter 58.

Clinical Manifestations. Almost all patients with rheumatoid pleural effusions are older than 35 years. Approximately 80% are men and approximately 80% have subcutaneous nodules. The pleural effusion usually develops only after the arthritis has been present for several years[95] but, on rare occasions, a patient may present with a pleural effusion.

Patients with rheumatoid pleuritis may be asymptomatic or symptomatic with pleuritic chest pain, fever, or both[95,100] and some patients experience dyspnea secondary to the presence of pleural fluid. In most patients, the chest radiograph reveals a small or moderate-sized pleural effusion. In approximately 25% of patients, the effusion is bilateral.[95] With time, the effusion may alternate from one side to the other or may come and go on the same side. Other intrathoracic manifestations of rheumatoid disease are present in up to one third of patients.[95]

Diagnosis. The diagnosis is suggested by the clinical picture of rheumatoid arthritis and the presence of a pleural effusion. The pleural fluid with rheumatoid pleuritis is distinctive, characterized by a glucose level less than 30 mg/dL (1.67 mmol/L), a high LDH level (>twice the upper limit of normal), a low pH (<7.20), and a high rheumatoid factor titer (>1 : 320 and ≥ the serum titer).[100] Occasionally, the pleural fluid glucose is not reduced when the patient is first seen, but serial pleural fluid glucose determinations reveal progressively lower pleural fluid glucose levels. Another interesting characteristic of rheumatoid pleural effusions is their tendency to contain cholesterol crystals or high levels of cholesterol.[243] A unique cytologic appearance of elongated comet-shaped or "tadpole" cells is also considered specific for the diagnosis.[244]

With the characteristic pleural fluid findings, the primary alternative diagnosis to exclude is complicated parapneumonic effusion. The incidence of complicated parapneumonic effusion is high in patients with rheumatoid pleuritis,[245] so this differentiation is important. It is particularly important to examine the Gram stain of the pleural fluid and to culture the fluid both aerobically and anaerobically.

Prognosis and Treatment. The natural history of rheumatoid pleuritis varies. Most patients experience a spontaneous resolution within 3 months, but the effusion is persistent in an occasional patient, and massive pleural thickening sometimes develops. There are no studies that demonstrate that anti-inflammatory therapy has any influence on the course of rheumatoid pleuritis. The results after intrapleural corticosteroids have been mixed.[53] Decortication should be considered in patients with thickened pleura, who are symptomatic with dyspnea. This procedure is particularly difficult in

patients with rheumatoid pleuritis because it is not easy to develop a plane of dissection between the lung and the fibrous peel.

Lupus Pleuritis

Approximately 40% of patients with SLE or drug-induced lupus have a pleural effusion during the course of their disease.[96]

Clinical Manifestations. Most patients with lupus pleuritis have arthritis or arthralgias before the development of a pleural effusion. Almost all patients with lupus pleuritis have pleuritic chest pain, and most are also febrile. Lupus pleuritis frequently develops in association with an exacerbation of the underlying disease. The pleural effusions secondary to lupus are usually small and are bilateral in about 50% of patients.[246]

Many medications have been incriminated for producing drug-induced lupus erythematosus (see Chapter 72).[53] Hydralazine, procainamide, isoniazid, phenytoin, and chlorpromazine are the ones most commonly associated with drug-induced lupus, but there are more that 70 other drugs that possibly induce lupus. The presenting signs, symptoms, and radiographic abnormalities are similar, whether the pleuritis is due to spontaneous or to drug-induced lupus. The symptoms associated with drug-induced lupus characteristically abate within days of discontinuing the offending drug.

Diagnosis. The possibility of lupus pleuritis should be considered in any patient with an exudative pleural effusion of unknown cause. The pleural fluid can contain a predominance of either polymorphonuclear or mononuclear cells, depending on the timing of the thoracentesis in relation to the development of the symptoms.[55] Although it was believed in the past that elevated ANA titers in the pleural fluid were diagnostic of lupus pleuritis, it appears that such elevated titers are neither specific nor sensitive for diagnosing lupus pleuritis.[97,247] The diagnosis is based primarily on the clinical picture and the serologic findings for lupus.

Treatment. In contrast to rheumatoid pleuritis, the pleuritis with SLE responds to corticosteroid administration. It is recommended that patients with lupus pleuritis be treated with oral prednisone, 80 mg every other day, with rapid tapering once the symptoms are controlled. At times, the effusion is large, is symptomatic, and does not respond to corticosteroid therapy. In such a situation, consideration should be given to chemical pleurodesis. Of course, if the patient has drug-induced lupus, the offending drug should be withdrawn.

Post–Cardiac Injury Syndrome

This syndrome, which is also known as the postpericardiectomy or the post–myocardial infarction (Dressler's) syndrome, is characterized by combinations of pericarditis, pleuritis, and pneumonitis that develop after injury to the myocardium or pericardium.[248] In one report, noncomplicated post–cardiac injury syndrome (PCIS) was defined as the presence of temperature greater than 100.5°F, patient irritability, pericardial friction rub, and a small pericardial effusion with or without pleural effusion following cardiac trauma.[249] A complicated PCIS is defined as a noncomplicated PCIS plus the need for hospital readmission with or without the need for pericardiocentesis or thoracentesis.[249] PCIS has occurred after myocardial infarction, cardiac surgery, blunt chest trauma, percutaneous left ventricle puncture, and implantation of a pacemaker.[248] The incidence of PCIS is approximately 1% after myocardial infarction and is somewhat higher after cardiac surgery.[53] The exact pathogenesis of this syndrome is unknown, but it appears to have an immunologic basis.

Clinical Manifestations. The syndrome typically develops about 3 weeks after the injury, but it can occur any time between 3 days and 1 year. The two cardinal symptoms are fever and chest pain. The chest pain often precedes the onset of fever and can vary from an agonizing crush to a dull ache. At times, it may have a pleuritic component. Most patients have a pericardial friction rub, and echocardiography can demonstrate pleural fluid in more than 50% of the patients. Pulmonary infiltrates are present in about 50% of patients, and laboratory evaluation reveals leukocytosis with an elevated erythrocyte sedimentation rate.

A pleural effusion occurs in about two thirds of patients with PCIS.[248] The pleural effusions are bilateral and small in most patients. The pleural fluid is an exudate that is frequently serosanguineous or bloody. The pleural fluid differential may reveal either predominantly polymorphonuclear leukocytes or mononuclear cells, depending on the acuteness of the process.[248]

Diagnosis. The diagnosis of PCIS should be considered in any patient who develops a pleural effusion after injury to the heart. The diagnosis of the syndrome is established by the clinical picture and by excluding CHF, pulmonary embolism, and pneumonia.

Treatment. PCIS usually responds to treatment with anti-inflammatory agents, such as aspirin or indomethacin. Corticosteroids may be necessary in more severe cases.

Post–Coronary Artery Bypass Surgery

More than 600,000 patients undergo coronary artery bypass graft (CABG) surgery in the United States each year. Because approximately 10% of patients who undergo CABG surgery will develop a pleural effusion that occupies more than 25% of their hemithorax in the subsequent month,[250] CABG surgery is one of the more common causes of pleural effusions in the United States. The prevalence of small pleural effusions is high following CABG surgery. In one study, the prevalence of pleural effusions in 47 patients as detected by ultrasound was 89% at 7 days, 77% at 14 days, and 57% at 30 days.[251] In a study of 349 patients post-CABG, the prevalence of pleural effusion on chest radiograph 30 days postoperatively was 62%; 40 of the 349 patients (11%) had an effusion that occupied more than 25% of the hemithorax.[250] The pleural effusions after CABG surgery tend to be left-sided or bilateral, and if bilateral, the effusion is usually larger on the left.[250]

The primary symptom of a patient with a large pleural effusion post-CABG is dyspnea.[250] The presence of either chest pain or fever should alert the physician to an alternative diagnosis. When all patients with large pleural effusions after CABG surgery are considered, the effusions can be divided into those that are bloody and those that are serous. The bloody effusions are probably secondary to bleeding into the pleural space. They reach their maximal size within 30 days of surgery, are frequently associated with pleural fluid or peripheral eosinophilia or both, have a high pleural fluid LDH level,[252] and respond to one or two therapeutic thoracenteses.[252] In contrast, the cause of the serous pleural effusions is unknown. They tend to reach their maximal size more than 30 days after surgery, have more than 50% small lymphocytes, and have a relatively low pleural fluid LDH level.[252] Most of these late effusions can also be managed with one or two therapeutic thoracenteses,[250] but some are very refractory. It is unknown whether anti-inflammatory agents or diuretics are beneficial in the treatment of these effusions.

Other Collagen Vascular Diseases

Pleural effusions occasionally occur in the course of Churg-Strauss syndrome, Wegener's granulomatosis, and Sjögren's syndrome, which are described in detail in other chapters. The pleural disease that occurs with these diseases constitutes a relatively minor portion of the clinical picture.

Lung Transplantation

With lung transplantation, the lymphatics that normally drain the lung are severed. Accordingly, the fluid that normally leaves the lung via these lymphatics likely drains into the pleural space. The presence of chest tubes in the first few days after lung transplantation prevents the accumulation of pleural fluid. Pleural complications such as hemothorax, empyema, and persistent air leak contribute substantially to the postoperative morbidity and mortality. The incidence of pleural effusions at 3 months posttransplant is about 30% to 60%.[253,254] The incidence of effusion at 12 months is less than 10%.[254] The effusions are characteristically a lymphocyte-predominant exudate with a benign course.[253] However, patients who develop complications after lung transplantation are likely to develop pleural effusions. In one study, pleural effusions occurred with 74% of 19 episodes of acute rejection, 88% of 8 instances of chronic rejection, 55% of 11 episodes of infection, and 75% of 4 instances of lymphoproliferative disease.[255] (More details about lung transplantation are provided in Chapter 95.)

Asbestos Exposure

An otherwise unexplained pleural effusion may occur after exposure to asbestos, which may have been brief or intermittent, and in the immediate or distant past. Epler and coworkers[256] reviewed the medical histories of 1135 asbestos workers whom they had followed up for several years and found that 35 (3%) of the workers had pleural effusions for which there was no other ready explanation. The heavier the asbestos exposure, the more likely the patient is to develop a pleural effusion. The pleural effusion sometimes develops within 5 years of the initial exposure but, in one large series, the mean latency was 30 years.[257]

The pathogenesis of the pleural effusion occurring after asbestos exposure is unknown.[10] Asbestos fibers, both long and short, may move from the lung to the pleural space and lodge in the parietal pleura, where they appear to be concentrated in specific locations that correlate with the lymphatic drainage. Here, their presence leads to a continuous low-grade inflammation. This chronic inflammation can either decrease the lymphatic clearance of the pleural space or increase the permeability of the capillaries in the parietal pleura, either of which could lead to the development of an exudative pleural effusion. An immune mechanism has been invoked to explain the fluctuations in the degree of pleuritis with time.[257]

Clinical Manifestations. Patients with pleural effusion secondary to asbestos exposure have surprisingly few symptoms. In the series of Epler and coworkers,[256] 66% had no symptoms. The chest radiograph usually reveals a small to moderate-sized effusion, which is bilateral in about 10%. The pleural fluid is an exudate, and the pleural fluid differential can reveal either predominantly polymorphonuclear leukocytes or mononuclear cells. Interestingly, pleural fluid eosinophilia was present in 15 (52%) of the 29 patients with asbestos pleural effusions for whom pleural fluid differentials were reported.[60]

Diagnosis. The diagnosis of benign asbestos effusion is one of exclusion. It requires the following criteria: history of direct or indirect exposure to asbestos; exclusion of other causes, notably infection, pulmonary embolism, and malignancy; and follow-up of at least 2 years to verify that the effusion is benign.[257]

Prognosis. The natural history of the patient with an asbestos pleural effusion is one of chronicity, with frequent recurrences and sometimes the development of extensive fibrosis of the parietal pleura.[256] On average, the pleural effusion persists for 3 months but eventually clears and leaves no residual pleural disease. Massive pleural fibrosis develops in about 20% of patients, and ipsilateral blunting of the costophrenic angle occurs in another 20%.[256] Rounded atelectasis also develops in about 10% of patients. There is no known treatment for asbestos pleural effusion. Further information about asbestos-induced lung disease is provided in Chapter 65.

Sarcoidosis

The prevalence of pleural effusion with sarcoidosis (see Chapter 59) is about 1%.[258,259] Patients with pleural effusion due to sarcoid usually have extensive parenchymal sarcoidosis and, frequently, extrathoracic sarcoidosis.[258] The symptoms of pleural involvement with sarcoidosis vary; many patients have no symptoms, although an equal number have pleuritic chest pain or dyspnea.

The pleural effusions with sarcoidosis are usually small and are bilateral in approximately one third of cases. The pleural fluid is almost always an exudate, and its cell differential is characterized by predominantly small lymphocytes.[258,259] In the patient with known sarcoidosis, one can attribute the presence of the pleural effusion to sarcoid only when other causes of exudative lymphocyte-predominant pleural effusions, such as tuberculosis, are excluded. The pleural effusion secondary to sarcoidosis may resolve spontaneously, or corticosteroid therapy may be required for its resolution.

Uremia

Uremia may be complicated by a fibrinous pleuritis and pleural effusion.[53] The pathogenesis of the pleural effusion associated with uremia is unclear. It is probably somewhat analogous to that for uremic pericarditis because more than half of the patients with uremic pleuritis also have uremic pericarditis. The incidence of pleural effusions with uremia is approximately 3%. A close relationship does not appear to exist between the degree of uremia and the occurrence of a pleural effusion. The incidence of pleural effusion seen on chest CT in patients who are receiving chronic hemodialysis is approximately 50%. The etiologies of 100 effusions occurring in hospitalized patients with uremia were as follows: heart failure, 46; uremia, 16; parapneumonic, 15; atelectasis, 11; and miscellaneous, 12.[260]

The pleural effusion seen with uremia frequently occupies more than 50% of the hemithorax and is bilateral in about 20% of patients.[261] More than 50% of patients are symptomatic from the pleural disease, with fever (50%), chest pain (30%), cough (35%), and dyspnea (20%) being the most common symptoms. The pleural fluid is an exudate that is frequently serosanguineous or bloody. The differential white blood cell count reveals predominantly lymphocytes.[261] Pleural biopsy specimens invariably demonstrate chronic fibrinous pleuritis.

The diagnosis of uremic pleuritis is one of exclusion in the patient with chronic renal failure. After beginning dialysis, the effusion gradually disappears within 4 to 6 weeks in about 75% of patients. In the remaining patients, the effusion persists, progresses, or recurs. An occasional patient develops marked pleural thickening that may require decortication.

Meigs' Syndrome

Meigs and Cass[262] originally described a syndrome characterized by ascites and pleural effusion in association with solid benign ovarian tumors. Subsequently, it has become apparent that a similar syndrome can occur with benign cystic ovarian tumors, with benign tumors of the uterus (fibromyomas), and with low-grade ovarian malignant tumors without evidence of metastases.[53] The ascites appears to result from the secretion of large amounts of fluid by the tumors. VEGF plays an important role in the pathogenesis of the ascites and pleural fluid, because VEGF levels are high in both the ascites and the pleural fluid.[263] It is thought that the pleural effusion results from the ascitic fluid passing through defects in the diaphragm into the pleural space.

Patients with Meigs' syndrome usually have a chronic illness characterized by weight loss, pleural effusion, ascites, and a pelvic mass. It is important to realize that not all patients with this constellation of symptoms have a disseminated malignancy. Approximately 70% of the effusions are right-sided, and 20% are bilateral. The pleural fluid is usually an exudate with a relatively low white blood cell count (<1000/μL) and occasionally is bloody. The level of CA-125 in the pleural fluid may be elevated, and this should not be taken as an indication of malignancy.[263]

The diagnosis of Meigs' syndrome should be considered in all women who have a pelvic mass, ascites, and a pleural effusion. If the cytology of the pleural fluid is negative in such patients, a diagnostic laparoscopy or an exploratory laparotomy should be performed to determine whether there are peritoneal metastases. The diagnosis is confirmed when the ascites and the pleural fluid resolve after the primary neoplasm is removed and do not recur. The pleural fluid disappears from the chest within the first 2 weeks after surgery.

Endometriosis

An occasional patient with severe endometriosis presents with massive ascites. In one review, 10 of 27 patients (37%) also had a pleural effusion.[264] The effusions are usually right-sided but may be bilateral. The pleural fluid is a bloody or a chocolate-colored exudate. The serum carcinoembryonic antigen level may be elevated, suggesting ovarian carcinoma. Hormonal therapy, including gonadotropin-releasing hormone agonists, may be attempted, but frequently it is ineffective, and many patients require total abdominal hysterectomy plus bilateral salpingo-oophorectomy.[264]

Ovarian Hyperstimulation Syndrome

This syndrome is a serious complication of ovulation induction. The dramatic clinical picture is characterized by massive ovarian enlargement with multiple cysts, hemoconcentration, and the third-space accumulation of fluid.[263] The full-blown syndrome may be complicated by renal failure, hypovolemic shock, thromboembolic episodes, acute respiratory distress syndrome, and death. Although the pathophysiology of this syndrome is incompletely understood, it is likely that the increased capillary permeability is due to the up-regulation of VEGF expression in the ovarian granulosa cells by the exogenous human chorionic gonadotropin.[263]

Patients with the syndrome present within 2 to 3 weeks of receiving the human chorionic gonadotropin. Patients typically present with abdominal pain and distention, nonproductive cough, and dyspnea caused by the ascites, pleural effusion, or both. The pleural effusion is usually bilateral, and the pleural fluid is an exudate with predominantly neutrophils and a relatively low LDH level. The treatment of severe cases requires restoration of intravascular volume, correction of electrolyte abnormalities, and venous thromboembolism prophylaxis.[263]

Yellow Nail Syndrome

This syndrome consists of the triad of deformed yellow nails, lymphedema, and pleural effusions. The three entities may become manifest at widely disparate times and, therefore, are not all concurrently present in every patient. The basic abnormality responsible for this syndrome appears to be hypoplasia of the lymphatic vessels.[265,266]

Typically, the nails are pale yellow to greenish in color and are excessively curved from side to side. They are also thickened and may show transverse ridging or onycholysis (separation of nail from bed). The pleural effusions are bilateral in about 50% of cases and can be massive. Once a pleural effusion has developed with this syndrome, it tends to persist and to recur rapidly after thoracentesis.[265] The pleural fluid is usually a clear exudate with predominantly lymphocytes.[265] The pleural fluid LDH tends to be relatively low relative to the pleural fluid protein level.[53]

The diagnosis is usually established by the presence of the triad of pleural effusion, lymphedema, and yellow nails. The diagnosis may be difficult to establish if the pleural effusion is the first manifestation of the syndrome. There is no specific treatment for the syndrome, but if the effusion is large and is producing symptoms, the effusion can be treated with pleurodesis, parietal pleurectomy, or a pleuroperitoneal shunt.[53]

Drug Reactions Producing Pleural Effusions

Lupus-like syndromes occur in conjunction with the administration of many different medications and have been discussed earlier in this chapter and in Chapter 72. Although there are case reports of pleural disease associated with administration of many drugs,[267] the following drugs are known to induce pleural disease.

Nitrofurantoin. Pleuropulmonary reactions occasionally result from the administration of nitrofurantoin. Such reactions can have an acute or a chronic presentation.[268] The acute presentation occurs within 1 month of initiation of therapy and is manifested by dyspnea, nonproductive cough, and fever. About 20% of patients have an infiltrate and an effusion, and about 3% have only an effusion. Most patients have both peripheral eosinophilia (>350/μL) and lymphopenia (<1000/μL).[269] The chronic syndrome occurs when the patient has been taking nitrofurantoin for 2 months to 5 years and is much less common than the acute syndrome. Pleural effusion occurs in less than 10% of patients, and no patient with the chronic syndrome has had a pleural effusion without an infiltrate.[268]

The diagnosis of nitrofurantoin pleuropulmonary reaction should be suspected in all patients with a pleural effusion who are taking nitrofurantoin. If the drug is discontinued, the patient usually improves clinically within 1 to 4 days, and the chest radiograph becomes normal within a week with the acute syndrome, whereas the time course is much longer for the chronic syndrome.[268]

Dantrolene. Dantrolene sodium is a long-acting skeletal muscle relaxant with a chemical structure similar to that of nitrofurantoin. Its administration can lead to the development of pleural or pericardial disease.[270] The pleural effusion is unilateral and develops 2 months to 12 years after the initial administration of dantrolene. Patients may be febrile and may have pleuritic chest pain. The pleural fluid is an eosinophilic exudate with a normal glucose level.[270] When dantrolene is discontinued, the patient improves symptomatically within days, but it may take several months for the pleural effusion to resolve completely.

Methysergide. The administration of methysergide can lead to a pleuropulmonary disease similar to that seen with nitrofurantoin.[271] Symptoms consisting of chest pain, dyspnea, and fever develop 1 month to 3 years after methysergide therapy is initiated. The chest radiograph commonly shows bilateral loculated pleural effusions and pleural thickening.[271] When methysergide is discontinued, the symptoms of the patients improve. However, in one series of 13 patients, severe pleural fibrosis persisted in the 2 patients who had continued to take the drug for the longest period (18 and 36 mo) after the onset of the pleurisy.[271]

Ergot Alkaloids. The administration of ergot alkaloid drugs such as bromocriptine, ergotamine, dihydroergotamine, nicergoline, pergolide, and dopergine in the long-term treatment of Parkinson's disease can lead to pleuropulmonary changes.[267] As of 1988, a total of 23 patients had been reported. All the patients were men, and the drug had been taken for 6 months to 4 years before symptoms developed. Two to 5% of patients receiving long-term ergot alkaloid therapy develop pleuropulmonary disease. The incidence of pleural disease is higher if the patient has previous exposure to asbestos.[272] The chest radiograph reveals unilateral or bilateral pleural thickening or effusion in most patients. Analysis of the pleural fluid reveals an exudate with predominantly lymphocytes and frequently eosinophilia.[273] The natural history of pleuropulmonary disease during ergot alkaloid therapy is unclear. The disease progresses only in some of the patients who continue taking the drug.[273]

Procarbazine. There have been two detailed case reports in which pleuropulmonary reactions consisting of chills, cough, dyspnea, and bilateral pulmonary infiltrates with pleural effusion occurred after treatment with procarbazine.[53] In both cases, symptoms developed within hours after procarbazine therapy; in both instances, rechallenge with procarbazine again produced the infiltrates and pleural effusions. With discontinuation of the drug, the symptoms and radiographic changes resolved within several days.

Amiodarone. Amiodarone is an antiarrhythmic that may produce severe pulmonary toxicity (see Chapter 72). Pleural effusions occur as a manifestation of amiodarone toxicity, but they are uncommon. Most cases have concomitant parenchymal involvement, but cases have been reported in which there is none.[267] The pleural fluid is an exudate and may have predominantly lymphocytes, macrophages, or polymorphonuclear leukocytes.[267]

Interleukin-2. Recombinant IL-2 is sometimes used in the treatment of malignancies, especially melanoma or renal cell carcinoma. One of the primary side effects

of IL-2 administration is the development of pulmonary infiltrates and pleural effusion that are probably related to a generalized capillary leak syndrome.[53] The incidence of pleural effusion after IL-2 administration is approximately 50%.[267] The characteristics of the pleural fluid have not been described. After the IL-2 therapy is stopped, the effusions tend to disappear. However, in one study, 17% of patients still had a pleural effusion 4 weeks after cessation of therapy.[274]

Dasatinib. Dasatinib is an inhibitor of multiple tyrosine kinase receptors, used primarily for treating adults with chronic myeloid leukemia with resistance to prior therapy. Use of dasatinib is associated with a high incidence of pleural effusion. Qunitas-Cardama and associates[275] reported that effusions occurred in 35% of 135 patients receiving the drug and about half the effusions occupied more than 25% of the hemithorax. The effusions were bilateral in 80% of the patients. The effusions were mostly exudates. The effusions went away when dasatinib was discontinued or when steroids were administered. In a recent study, the effusions were less common when dasatinib was administered once rather than twice per day (14% incidence compared to 23–26% incidence), without loss of efficacy.[275a]

Trapped Lung

Effusions that are remarkably stable over time, recur after thoracentesis, and are resistant to diagnosis may be due to an underlying trapped lung (Fig. 73-11). Following an earlier episode of inflammation, a fibrous peel may form over the visceral pleura and can prevent the underlying lung from expanding fully, thereby "trapping" the underlying lung. The resulting negative pleural pressure leads to the development of a chronic pleural effusion.[276,277]

Patients with a chronic pleural effusion secondary to trapped lung are often asymptomatic but may have symptoms of dyspnea. Symptoms of acute pleural inflammation, such as pleuritic chest pain and fever, are distinctly uncommon, but the patient often gives a history of such events in the past. One characteristic of the pleural effusion secondary to trapped lung is that the amount of fluid is quite constant from one study to another. With trapped lung, the pleural fluid is often a borderline exudate; the ratio of pleural fluid to serum protein is about 0.5, and the ratio of pleural fluid LDH to serum LDH is about 0.6.

The diagnosis of pleural effusion secondary to trapped lung should be suspected in any patient with a stable, chronic pleural effusion, particularly if the patient has a history of uremia, thoracic radiation, or prior thoracic surgery.[277] The thickened visceral pleura can be demonstrated if 200 to 400 mL of air is injected into the pleural space at the time of a thoracentesis. At some institutions, pleural manometry is used routinely during a therapeutic thoracentesis; if the pleural pressure falls rapidly (>14–15 cm H_2O/L pleural fluid removed), air is allowed to enter the pleural space to return the pleural pressure to a more normal range (−5 cm H_2O) so that an air-contrast chest CT scan can be obtained to evaluate the visceral pleura.[277]

The definitive therapy for trapped lung is thoracotomy with decortication. However, this major surgery is indicated only in patients who are symptomatic from the trapped lung. If the patient is asymptomatic or minimally

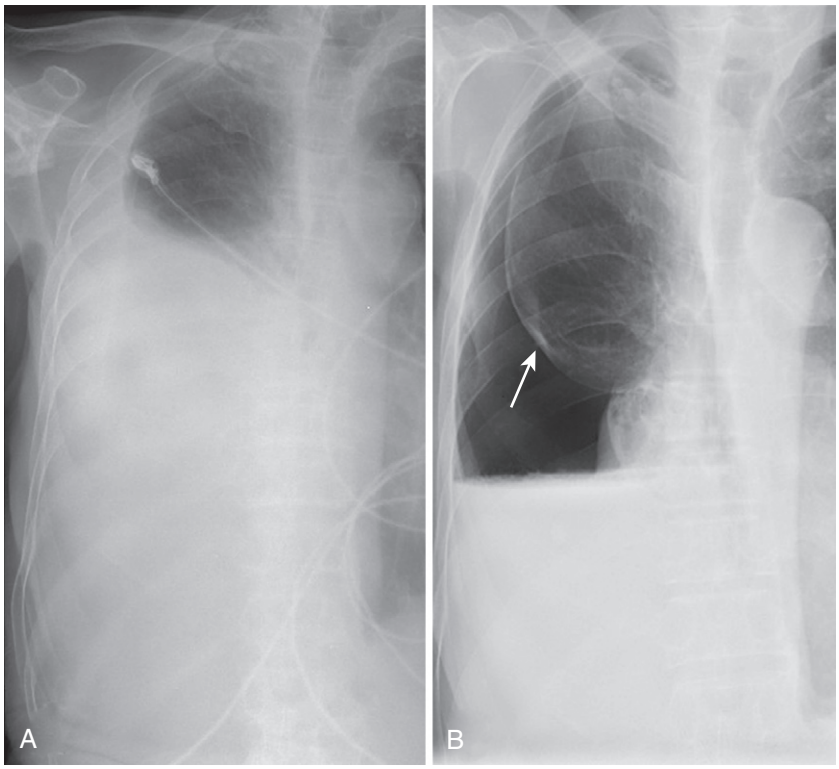

FIGURE 73-11 ■ Effusion with trapped lung. **A,** Frontal chest radiograph shows a large right pleural effusion. **B,** On a subsequent radiograph, the effusion has been partially drained, revealing the underlying lung with some visceral pleural thickening (*arrow*). The lung failed to reexpand despite negative intrapleural pressures. The intrapleural air entered the pleural space from the atmosphere along the drainage track. (Courtesy of Michael B. Gotway, MD, Scottsdale Medical Imaging and the Department of Radiology, University of California, San Francisco.)

symptomatic, the patient can be observed if the clinical picture, pleural fluid findings, and pleural pressure measurements are all compatible with the diagnosis of trapped lung.

Pleural Effusions Due to Misplaced Catheters

Both internal jugular and subclavian vein catheterization can be complicated by misplacement of the catheter tip into the mediastinum or pleural space that results in a large unilateral or bilateral pleural effusion. The pleural fluid may have the characteristics of the intravenous fluid, or it may be bloody from laceration of the blood vessels.[278] If the patient is receiving lipids through a central line, the fluid may look chylous.[279] The diagnosis of a misplaced central venous catheter should be considered in all patients with such lines who rapidly develop pleural effusions, and the patients should be evaluated by diagnostic thoracentesis.

Small pleural effusions may also develop after translumbar aortographic examination and after percutaneous transhepatic coronary vein occlusion. The effusions in these circumstances are usually small and resolve spontaneously.

In the past several years, the development of soft, flexible, small-bore polyurethane feeding tubes has made nasogastric and nasoenteric feeding more practical and comfortable for patients. However, misplacement of these tubes can lead to serious pleural complications. Pneumothorax is the most common complication, but infusion of the enteral formula into the pleural space, or the development of an empyema, or both, also occur relatively frequently.[280] These small flexible tubes are inserted with a stylet in place that enables easier advancement of the device. However, with the stylet in place, the tubing becomes stiff enough that it can perforate structures relatively easily. The risk is much greater if the patient has an endotracheal tube in place or is obtunded.[280] To prevent these complications, these tubes should be inserted only by experienced persons, and the tube should be immediately removed if the patient starts coughing. The tube should not be advanced if resistance is felt, and before feeding is initiated, the position of the tip of the tube should be confirmed radiographically.[281,282] If enteral solutions enter the pleural space, tube thoracostomy should be performed to remove the solution. In addition, the patient should be carefully observed for the development of an empyema.[280]

KEY POINTS

- Entry of normal fluid into the pleural space is slow, consistent with that found in other interstitial spaces of the body. Exit of fluid is mainly via parietal pleural lymphatics, which have a large reserve capacity and can accommodate increases in fluid formation without the development of an effusion.
- Pleural effusions develop when disease or combinations of diseases lead to an increase in fluid entry into the pleural space and a decrease in removal from the pleural space; both changes may be necessary for formation of an effusion.
- Excess fluid anywhere in the body can move to and enter the pleural space due to (1) subatmospheric pleural pressure (−5 to −30 cm H_2O), (2) the leaky mesothelial layer, (3) the high capacitance of the pleural space.
- Transudates usually result from systemic changes in hydrostatic and/or osmotic pressures that lead to collection of a relatively low protein and LDH fluid (pleural–to–serum protein ratio < 0.5 *and* pleural/serum LDH < 0.6 *and* LDH < two thirds the upper limit of normal [Light's criteria]).
- Transudates with a *very* low protein concentration (<0.5 g/dL) come from entry of CSF, urine, peritoneal dialysis fluid, or intravenous fluids into the pleural space.
- Exudates result from pleural or extrapleural injury or inflammation that can be due to a multitude of inflammatory, infectious, or malignant diseases, leading to effusions with a relatively high protein and/or LDH concentration.
- Most transudates arise from CHF. When the cause is unclear or when the protein and LDH ratios are not clearly transudative, as can happen after diuresis, the NT-BNP is a sensitive and specific marker for a cardiac etiology.
- Most exudates arise from either pneumonia, malignancy, or pulmonary embolism.
- No diagnosis is ever established for approximately 20% of all exudative pleural effusions and many resolve spontaneously, leaving no residua. The degree to which a diagnosis is pursued by invasive procedures will depend on (1) the symptoms and the clinical course of the patient, (2) the trend of the pleural fluid LDH level with time, and (3) the eagerness of the patient for a diagnosis.

References

1. Albertine KH, Wiener-Kronish JP, Bastacky J, et al: No evidence for mesothelial cell contact across the costal pleural space of sheep. J Appl Physiol 70:123–134, 1991.
2. Deschamps C, Rodarte JR: Effects of unilateral pleural symphysis on respiratory system mechanics and gas exchange in anesthetized dogs. Am Rev Respir Dis 137:1385–1389, 1988.
3. Ukale V, Bone D, Hillerdal G, et al: The impact of pleurodesis in malignant effusion on respiratory function. Respir Med 93:898–902, 1999.
4. Davidson FF, Glazier JB: Unilateral pleuritis and regional lung function. Ann Intern Med 77:37–42, 1972.
5. Broaddus VC, Light RW: What is the origin of transudates and exudates? Chest 102:658–659, 1992.
6. Broaddus VC, Wiener-Kronish JP, Staub NC: Clearance of lung edema into the pleural space of volume-loaded, anesthetized sheep. J Appl Physiol 68:2623–2630, 1990.
7. Wiener-Kronish JP, Broaddus VC, Albertine KH, et al: Relationship of pleural effusions to increased permeability pulmonary edema in anesthetized sheep. J Clin Invest 82:1422–1429, 1988.
8. Gray SW, Skandalakis JE (eds): Development of the Pleura. New York: Marcel Dekker, 1985.
9. Jantz MA, Antony VB: Pathophysiology of the pleura. Respiration 75:121–133, 2008.
10. Nishimura SL, Broaddus VC: Asbestos-induced pleural disease. Clin Chest Med 19:311–329, 1998.
11. Ordonez NG: What are the current best immunohistochemical markers for the diagnosis of epithelioid mesothelioma. A review and update. Hum Pathol 38:1–16, 2007.
12. Albertine KH, Wiener-Kronish JP, Roos PJ, et al: Structure, blood supply, and lymphatic vessels of the sheep's visceral pleura. Am J Anat 165:277–294, 1982.
13. Oldmixon EH, Hoppin FGJ: Comparison of amounts of collagen and elastin in pleura and parenchyma of dog lung. J Appl Physiol 56:1383–1388, 1956.
14. Albertine KH, Wiener-Kronish JP, Staub NC: The structure of the parietal pleura and its relationship to pleural liquid dynamics in sheep. Anat Rec 208:401–409, 1984.
15. Wang N-S: The preformed stomas connecting the pleural cavity and the lymphatics in the parietal pleura. Am Rev Respir Dis 111:12–20, 1975.
16. Li J: Ultrastructural study on the pleural stomata in human. Funct Develop Morphol 3:277–280, 1993.
17. Li Y-Y, Li J-C: Ultrastructure and three-dimensional study of the lymphatic stomata in the costal pleura of the rabbit. Microsc Res Tech 62:240–246, 2003.
18. Broaddus VC, Wiener-Kronish JP, Berthiaume Y, et al: Removal of pleural liquid and protein by lymphatics in awake sheep. J Appl Physiol 64:384–390, 1988.
19. Pintelon I, Brouns I, De Proost I, et al: Sensory receptors in the visceral pleura. Am J Respir Cell Mol Biol 36:541–551, 2007.
20. Montes JF, Garcia-Valero J, Ferrer J: Evidence of innervation in talc-induced pleural adhesions. Chest 130:702–709, 2006.
21. Staub NC, Wiener-Kronish JP, Albertine KH (eds): Transport through the Pleura: Physiology of Normal Liquid and Solute Exchange in the Pleural Space. New York: Marcel Dekker, 1985.
22. Broaddus VC: Physiology: Fluid and solute exchange in normal physiological states. *In* Light R, Lee Y (eds): Textbook of Pleural Diseases. London: Hodder Arnold, 2008, pp 43–48.
23. Payne DK, Kinasewitz GT, Gonzalez E: Comparative permeability of canine visceral and parietal pleura. J Appl Physiol 65:2558–2564, 1988.
24. Kim KJ, Critz AM, Crandall ED: Transport of water and solutes across sheep visceral pleura. Am Rev Respir Dis 120:883–892, 1979.
25. Negrini D, Townsley MI, Taylor AE: Hydraulic conductivity of the canine parietal pleura in vivo. J Appl Physiol 69:438–442, 1990.
26. Song Y, Yang B, Matthay MA, et al: Role of aquaporin water channels in pleural fluid dynamics. Am J Physiol Cell Physiol 279:C1744–C1750, 2000.

26a. Gilligan DR, Volk MC, Blumgart HL: Observations on the chemical and physical relation between blood serum and body fluids. J Clin Invest 13:365–381, 1934.

27. Wiener-Kronish JP, Albertine KH, Licko V, et al: Protein egress and entry rates in pleural fluid and plasma in sheep. J Appl Physiol 56:459–463, 1984.
28. Broaddus VC, Araya M: Liquid and protein dynamics using a new, minimally invasive pleural catheter in rabbits. J Appl Physiol 72:851–857, 1992.
29. Erdmann AJ, Vaughan TR, Brigham KL, et al: Effect of increased vascular pressure on lung fluid balance in unanesthetized sheep. Circ Res 37:271–284, 1975.
30. Murray JF (ed): The Normal Lung (2nd ed). Philadelphia: WB Saunders, 1986.
31. Light RW, Stansbury DW, Brown SE: The relationship between pleural pressures and changes in pulmonary function after therapeutic thoracentesis. Am Rev Respir Dis 133:658–661, 1986.
32. Leckie WJH, Tothill P: Albumin turnover in pleural effusions. Clin Sci 29:339–352, 1965.
33. Runyon BA, Forker EL, Sopko JA: Pleural-fluid kinetics in a patient with primary lymphedema, pleural effusions, and yellow nails. Am Rev Respir Dis 119:821–825, 1979.
34. Light RW, MacGregor MI, Luchsinger PC, et al: Pleural effusions: The diagnostic separation of transudates and exudates. Ann Intern Med 77:507–513, 1972.
35. Wiener-Kronish JP, Broaddus VC: Interrelationship of pleural and pulmonary interstitial liquid. Annu Rev Physiol 55:209–226, 1993.
36. Broaddus VC: Transudative pleural effusions. *In* Loddenkemper R, Antony V (eds): Pleural Diseases (European Respiratory Monograph). Sheffield, UK: ERS Journals, Ltd., 2002, pp 157–176.
37. Wang JS, Tseng CH: Changes in pulmonary mechanics and gas exchange after thoracentesis on patients with inversion of a hemidiaphragm secondary to large pleural effusion. Chest 107:1610–1614, 1995.
38. Brandstetter RD, Cohen RP: Hypoxemia after thoracentesis: A predictable and treatable condition. JAMA 242:1060–1061, 1979.
39. Agusti AGN, Cardus J, Roca J, et al: Ventilation-perfusion mismatch in patients with pleural effusion: Effects of thoracentesis. Am J Respir Crit Care Med 156:1205–1209, 1997.
40. Traylor JJ, Chan K, Wong I, et al: Large pleural effusions producing signs of cardiac tamponade resolved by thoracentesis. Am J Cardiol 89:106–108, 2002.
41. Light RW: Physiology: Changes with pleural effusion and pneumothorax. *In* Light R, Lee Y (eds): Textbook of Pleural Diseases. London: Hodder Arnold, 2008, pp 49–58.
42. Estenne M, Yernault J-C, de Troyer A: Mechanism of relief of dyspnea after thoracocentesis in patients with large pleural effusions. Am J Med 74:813–819, 1983.
43. Wong CL, Holroyd-Leduc J, Straus SE: Does this patient have a pleural effusion? JAMA 301:309–317, 2009.
44. Colt H: Drainage techniques. *In* Light RW, Lee YCG (eds): Textbook of Pleural Diseases. London: Hodder Arnold, 2008, pp 551–567.
45. Petersen WG, Zimmerman R: Limited utility of chest radiograph after thoracentesis. Chest 117:1038–1042, 2000.
46. Ashchi M, Golish J, Eng P, et al: Transudative malignant pleural effusions: Prevalence and mechanisms. South Med J 91:23–26, 1998.
47. Romero-Candeira S, Fernandez C, Martin C, et al: Influence of diuretics on the concentration of proteins and other components of pleural transudates in patients with heart failure. Am J Med 110:681–686, 2001.
48. Porcel J, Martinez-Alonso M, Cao G, et al: Biomarkers of heart failure in pleural fluid. Chest 136:671–677, 2009. Epub 2009;April 10.
49. Heffner JE, Highland K, Brown LK: A meta-analysis derivation of continuous likelihood ratios for diagnosing pleural fluid exudates. Am J Respir Crit Care Med 15:1591–1599, 2003.
50. Peterman TA, Speicher CE: Evaluating pleural effusions: A two-stage approach. JAMA 252:1051–1053, 1984.
51. Light RW: Pleural effusion. N Engl J Med 346:1971–1977, 2002.
52. Light RW, Erozan YS, Ball WC: Cells in pleural fluid: their value in differential diagnosis. Arch Intern Med 132:854–860, 1973.
53. Light RW (ed): Pleural Diseases (5th ed). Philadelphia: Lippincott, Williams & Wilkins, 2007.

54. Lillington GA, Carr DT, Mayne JG: Rheumatoid pleurisy with effusion. Arch Intern Med 128:764–768, 1971.
55. Good JTJ, King TE, Antony VB, et al: Lupus pleuritis: Clinical features and pleural fluid characteristics with special reference to pleural fluid antinuclear antibodies. Chest 84:714–718, 1983.
56. Sahn SA, Good JTJ: Pleural fluid pH in malignant effusions. Diagnostic, prognostic, and therapeutic implications. Ann Intern Med 108:345–349, 1988.
57. Conner BD, Lee YCG, Branca P, et al: Variations in pleural fluid WBC count and differential counts with different sample containers and different methods. Chest 123:1181–1187, 2003.
58. Noppen M, De Waele M, Li R, et al: Volume and cellular content of normal pleural fluid in humans examined by pleural lavage. Am J Respir Crit Care Med 162:1023–1026, 2000.
59. Mohamed KH, Abdelhamid AI, Lee YCG, et al: Pleural fluid levels of interleukin-5 and eosinophils are closely correlated. Chest 122:567–580, 2002.
60. Adelman M, Albelda SM, Gottlieb J, et al: Diagnostic utility of pleural fluid eosinophilia. Am J Med 77:915–920, 1984.
61. Schandene L, Namias B, Crusiaux A, et al: IL-5 in post-traumatic eosinophilic pleural effusion. Clin Exp Immunol 93:115–119, 1993.
62. Maltais F, Laberge F, Cormier Y: Blood hypereosinophilia in the course of posttraumatic pleural effusion. Chest 98:348–351, 1990.
63. Romero-Candeira S, Hernandez Blasco L, Soler MJ, et al: Biochemical and cytologic characteristics of pleural effusions secondary to pulmonary embolism. Chest 121:465–469, 2002.
64. Smit HJ, van den Heuvel MM, Barbierato SB, et al: Analysis of pleural fluid in idiopathic spontaneous pneumothorax: Correlation of eosinophil percentage with the duration of air in the pleural space. Respir Med 93:262–267, 1999.
65. Kalomenidis I, Light RW: Eosinophilic pleural effusions. Curr Opin Pulm Med 9:254–260, 2003.
66. Johnson RJ, Johnson JR: Paragonimiasis in Indochinese refugees. Am Rev Respir Dis 128:534–538, 1983.
67. Erzurum SE, Underwood GA, Hamilos DL, et al: Pleural effusion in Churg-Strauss syndrome. Chest 95:1357–1359, 1989.
68. Yam LT: Diagnostic significance of lymphocytes in pleural effusions. Ann Intern Med 66:972–982, 1967.
69. Elis A, Mulchanov I, Radnay J, et al: The diagnostic significance of polyclonal lymphocytosis in pleural effusions. N Z Med J 113:56–58, 2000.
70. Katz RL, Raval P, Manning JT, et al: A morphologic, immunologic, and cytometric approach to the classification of non-Hodgkin's lymphoma in effusions. Diagn Cytopathol 3:91–101, 1987.
71. Jarvi OH, Kunnas RJ, Laitio MT, et al: The accuracy and significance of cytologic cancer diagnosis of pleural effusions. Acta Cytol 16:152–157, 1972.
72. Dekker A, Bupp PA: Cytology of serous effusions. An investigation into the usefulness of cell blocks versus smears. AmJ Clin Pathol 70:855–860, 1978.
73. Melamed MR: The cytological presentation of malignant lymphomas and related diseases in effusions. Cancer 16:413–431, 1963.
74. Fetsch PA, Abati A: Immunocytochemistry in effusion cytology: A contemporary review. Cancer 93:293–308, 2001.
75. Mohamed KH, Mobasher AA, Yousef AI, et al: Pleural lavage: A novel diagnostic approach for diagnosing exudative pleural effusion. Lung 178:371–379, 2000.
76. Reis-Filho JS, Schmitt FC: Fluorescence in situ hybridization, comparative genomic hybridization, and other molecular biology techniques in the analysis of effusions. Diagn Cytopathol 33:294–299, 2005.
77. Fiegl M, Kaufmann H, Zojer N, et al: Malignant cell detection by fluorescence in situ hybridization (FISH) in effusions from patients with carcinoma. Hum Pathol 31:448–455, 2000.
78. Benlloch S, Galbis-Caravajal JM, Martin C, et al: Potential diagnostic value of methylation profile in pleural fluid and serum from cancer patients with pleural effusion. Cancer 107:1859–1865, 2006.
79. Holloway AJ, Diyagama DS, Opeskin K, et al: A molecular diagnostic test for distinguishing lung adenocarcinoma from malignant mesothelioma using cells collected from pleural effusions. Clin Cancer Res 12:5129–5135, 2006.
80. Creaney J, Robinson BWS: Serum and pleural fluid biomarkers for mesothelioma. Curr Opin Pulm Med 15:366–370, 2009.
81. Coonrod JD, Wilson HD: Etiologic diagnosis of intrapleural empyema by counterimmunoelectrophoresis. Am Rev Respir Dis 113:637–641, 1976.
82. Boersma WG, Lowenberg A, Holloway Y, et al: Rapid detection of pneumococcal antigen in pleural fluid of patients with community acquired pneumonia. Thorax 48:160–162, 1993.
83. Falguera M, Lopez A, Nogues A, et al: Evaluation of the polymerase chain reaction method for detection of *Streptococcus pneumonia* DNA in pleural fluid samples. Chest 122:2212–2216, 2002.
83a. Casado Flores J, Nieto Moro M, Berron S, et al: Usefulness of pneumococcal antigen detection in pleural effusion for the rapid diagnosis of infection by S. pneumoniae. Eur J Pediatr 2009 (Epub ahead of print).
84. Maskell N, Batt S, Hedley E, et al: The bacteriology of pleural infection by genetic and standard methods and its mortality significance. Am J Respir Crit Care Med 174:817–823, 2006.
85. Potts DE, Willcox MA, Good JTJ, et al: The acidosis of low-glucose pleural effusions. Am Rev Respir Dis 117:665–671, 1978.
86. Light RW, Girard WM, Jenkinson SG, et al: Parapneumonic effusions. Am J Med 69:507–512, 1980.
87. Cheng D-S, Rodriguez RM, Rogers J, et al: Comparison of pleural fluid pH values obtained using blood gas machine, pH meter and pH indicator strip. Chest 114:1368–1372, 1998.
88. Rahman NM, Mishra EK, Davies HE, et al: Clinically important factors influencing the diagnostic measurement of pleural fluid pH and glucose. Am J Respir Crit Care Med 178:483–490, 2008.
89. Branca P, Rodriguez RM, Rogers JT, et al: Routine measurement of pleural fluid amylase is not indicated. Arch Intern Med 161:228–232, 2001.
90. Sherr HP, Light RW, Merson MH, et al: Origin of pleural fluid amylase in esophageal rupture. Ann Intern Med 76:985–986, 1972.
91. Maulitz RM, Good JTJ, Kaplan RL, et al: The pleuropulmonary consequences of esophageal rupture: An experimental model. Am Rev Respir Dis 120:363–367, 1979.
92. Rockey DC, Cello JP: Pancreaticopleural fistula: Report of 7 patients and review of the literature. Medicine (Baltimore) 69:332–344, 1990.
93. Light RW, Ball WC: Glucose and amylase in pleural effusions. JAMA 225:257–260, 1973.
94. Kramer MR, Saldana MJ, Cepero RJ, et al: High amylase in neoplasm-related pleural effusion. Ann Intern Med 110:567–569, 1989.
95. Walker WC, Wright V: Rheumatoid pleuritis. Ann Rheum Dis 26:467–474, 1967.
96. Winslow WA, Ploss LN, Loitman B: Pleuritis in systemic lupus erythematosus: Its importance as an early manifestation in diagnosis. Ann Intern Med 49:70–88, 1958.
97. Khare V, Baethge B, Lang S, et al: Antinuclear antibodies in pleural fluid. Chest 106:866–871, 1994.
98. Wang DY, Yang PC, Yu WL, et al: Comparison of different diagnostic methods for lupus pleuritis and pericarditis: A prospective three-year study. J Formos Med Assoc 99:375–380, 2000.
99. Porcel JM, Ordi-Ros J, Esquerda A, et al: Antinuclear antibody testing in pleural fluid for the diagnosis of lupus pleuritis. Lupus 16:25–27, 2007.
100. Halla JT, Schrohenloher RE, Volanakis JE: Immune complexes and other laboratory features of pleural effusions. Ann Intern Med 92:748–752, 1980.
101. Jimenez Castro D, Diaz Nuevo G, Perez-Rodriguez E, et al: Diagnostic value of adenosine deaminase in nontuberculous lymphocytic pleural effusions. Eur Respir J 21:220–224, 2003.
102. Baba K, Hoosen AA, Langeland N, et al: Adenosine deaminase activity is a sensitive marker for the diagnosis of tuberculous pleuritis in patients with very low CD4 counts. PLoS One 3:e2788, 2008.
103. Ferrer JS, Muñoz XG, Orriols RM, et al: Evolution of idiopathic pleural effusion: A prospective, long-term follow-up study. Chest 109:1508–1513, 1996.

104. Villena V, Lopez-Encuentra A, Pozo F, et al: Interferon gamma levels in pleural fluid for the diagnosis of tuberculosis. Am J Med 115:365–370, 2003.
105. Hooper CE, Lee YC, Maskell NA: Interferon-gamma release assays for the diagnosis of TB pleural effusions: Hype or real hope? Curr Opin Pulm Med 15:358–365, 2009.
106. Su WJ: Recent advances in the molecular diagnosis of tuberculosis. J Microbiol Immunol Infect 35:209–214, 2002.
107. Forbes BA: Critical assessment of gene amplification approaches on the diagnosis of tuberculosis. Immunol Invest 26:105–116, 1997.
107a. Dheda K, Van-Zyl Smit RN, Sechi LA, et al: Clinical diagnostic utility of IP-10 and LAM antigen levels for the diagnosis of tuberculous pleural effusions in a high burden setting. PLOS One 4:e4689, 2009.
108. Collins JD, Burwell D, Furmanski S, et al: Minimal detectable pleural effusions. Radiology 105:51–53, 1972.
109. Moskowitz H, Platt RT, Schachar R, et al: Roentgen visualization of minute pleural effusion. Radiology 109:33–35, 1973.
110. Davies CL, Gleeson FV: Diagnostic radiology. *In* Light RW, Lee GYC (eds): Textbook of Pleural Diseases. London: Hodder Arnold, 2003, pp 210–237.
111. Bressler EL, Francis IR, Glazer GM, et al: Bolus contrast medium enhancement for distinguishing pleural from parenchymal lung disease: CT features. J Comput Assist Tomogr 11:436–440, 1987.
112. Stark DD, Federle MP, Goodman PC, et al: Differentiating lung abscess and empyema: Radiography and computed tomography. AJR Am J Roentgenol 141:163–167, 1983.
113. Leung AN, Muller NL, Miller RR: CT in differential diagnosis of diffuse pleural disease. AJR Am J Roentgenol 154:487–492, 1990.
114. Cronin P, Weg JG, Kazerooni EA: The role of multidetector computed tomography angiography for the diagnosis of pulmonary embolism. Semin Nucl Med 38:418–431, 2008.
115. De Wever W, Stroobants S, Coolen J, et al: Integrated PET/CT in the staging of nonsmall cell lung cancer: Technical aspects and clinical integration. Eur Respir J 33:201–212, 2009.
116. Prakash UBS, Relman HM: Comparison of needle biopsy with cytologic analysis for the evaluation of pleural effusion: Analysis of 414 cases. Mayo Clin Proc 60:158–164, 1985.
117. Bueno CE, Clemente G, Castro BC, et al: Cytologic and bacteriologic analysis of fluid and pleural biopsy specimens with Cope's needle. Arch Intern Med 150:1190–1194, 1990.
118. Maskell NA, Gleeson FV, Davies RJ: Standard pleural biopsy versus CT-guided cutting-needle biopsy for diagnosis of malignant disease in pleural effusions: A randomised controlled trial. Lancet 361:1326–1330, 2003.
119. Scerbo J, Keltz H, Stone DJ: A prospective study of closed pleural biopsies. JAMA 218:377–380, 1971.
120. Levine H, Metzger W, Lacera D, et al: Diagnosis of tuberculous pleurisy by culture of pleural biopsy specimens. Arch Intern Med 126:269–271, 1970.
121. Von Hoff DD, LiVolsi V: Diagnostic reliability of needle biopsy of the parietal pleura. Am J Clin Pathol 64:200–203, 1975.
122. Conde MB, Loivos AC, Rezende VM, et al: Yield of sputum induction in the diagnosis of pleural tuberculosis. Am J Respir Crit Care Med 167:723–725, 2003.
123. Diacon AH, Van de Wal BW, Wyser C, et al: Diagnostic tools in tuberculous pleurisy: A direct comparative study. Eur Respir J 22:589–591, 2003.
124. Poe RH, Israel RH, Utell MJ, et al: Sensitivity, specificity, and predictive values of closed pleural biopsy. Arch Intern Med 144:325–328, 1984.
125. Rahman NM, Gleeson FV: Image-guided pleural biopsy. Curr Opin Pulm Med 14:331–336, 2008.
126. Chang SC, Perng RP: The role of fiberoptic bronchoscopy in evaluating the causes of pleural effusions. Arch Intern Med 149:855–857, 1989.
127. Feinsilver SH, Barrows AA, Braman SS: Fiberoptic bronchoscopy and pleural effusion of unknown origin. Chest 90:516–519, 1986.
128. Casal RF, Eapen GA, Morice RC, et al: Medical thoracoscopy. Curr Opin Pulm Med 15:313–320, 2009.
129. Ryan CJ, Rodgers RF, Unni KK, et al: The outcome of patients with pleural effusion of indeterminate cause at thoracotomy. Mayo Clin Proc 56:145–149, 1981.
130. Kataoka H, Takada S: The role of thoracic ultrasonography for evaluation of patients with decompensated chronic heart failure. J Am Coll Cardiol 35:1638–1646, 2000.
131. Wiener-Kronish JP, Matthay MA, Callen PW, et al: Relationship of pleural effusions to pulmonary hemodynamics in patients with heart failure. Am Rev Respir Dis 132:1253–1256, 1985.
132. Race GA, Scheifley CH, Edwards JE: Hydrothorax in congestive heart failure. Am J Med 22:83–89, 1957.
133. Weiss JM, Spodick DH: Laterality of pleural effusions in chronic congestive heart failure. Am J Cardiol 53:951, 1984.
134. Rabin CB, Blackman NS: Bilateral pleural effusions: Its significance in association with a heart of normal size. J Mt Sinai Hosp NY 24:45–63, 1957.
135. Broaddus VC: Diuresis and transudative effusions—Changing the rules of the game. Am J Med 110:732–735, 2002.
136. Plum GE, Bruwer AJ, Clagett OT: Chronic constrictive pericarditis: Roentgenologic findings in 35 surgically proved cases. Mayo Clin Proc 32:555–566, 1957.
137. Weiss JM, Spodick DH: Association of left pleural effusions with pericardial disease. N Engl J Med 308:696–697, 1983.
138. Lieberman FL, Hidemura R, Peters RL, et al: Pathogenesis and treatment of hydrothorax complicating cirrhosis with ascites. Ann Intern Med 64:341–351, 1966.
139. Johnston RF, Loo RV: Studies to determine the source of the fluid and report of thirteen cases. Ann Intern Med 61:385–401, 1964.
140. Kinasewitz GT, Keddissi JI: Hepatic hydrothorax. Curr Opin Pulm Med 9:261–265, 2003.
140a. Outcomes of patients with chest tube insertion for hepatic hydrothorax. Hepatol Int 3:582–586, 2009.
141. Castellore J, Xiol X: Hepatic hydrothorax. *In* Light RW, Lee GYC (eds): Textbook of Pleural Diseases. London: Hodder Arnold, 2008, pp 455–463.
142. Huang P, Chang Y, Yang C, et al: The morphology of diaphragmatic defects in hepatic hydrothorax: Thoracoscopic finding. J Thorac Cardiovasc Surg 130:141–145, 2005.
143. Bhattacharya A, Mittal BR, Biswas T, et al: Radioisotope scintigraphy in the diagnosis of hepatic hydrothorax. J Gastroenterol Hepatol 16:317–321, 2001.
144. Xiol X, Castellote J, Cortes-Beut R, et al: Usefulness and complications of thoracentesis in cirrhotic patients. Am J Med 111:67–69, 2001.
145. Xiol X, Castellvi JM, Guardiola J, et al: Spontaneous bacterial empyema in cirrhotic patients: A prospective study. Hepatology 23:719–723, 1996.
146. Cerfolio R, Bryant A: Efficacy of video-assisted thoracoscopic surgery with talc pleurodesis for porous diaphragm syndrome in patients with refractory hepatic hydrothorax. Ann Thorac Surg 82:457–459, 2006.
147. Cavina G, Vichi G: Radiological aspects of pleural effusions in medical nephropathy in children. Ann Radiol Diagn 31:163–202, 1958.
148. Llach F, Arieff AI, Massry SG: Renal vein thrombosis and nephrotic syndrome: A prospective study of 36 adult patients. Ann Intern Med 83:8–14, 1975.
149. Nomoto Y, Suga T, Nakajima K, et al: Acute hydrothorax in continuous ambulatory peritoneal dialysis: A collaborative study of 161 centers. Am J Nephrol 9:363–367, 1989.
150. Tang S, Chui WH, Tang AW, et al: Video-assisted thoracoscopic talc pleurodesis is effective for maintenance of peritoneal dialysis in acute hydrothorax complicating peritoneal dialysis. Nephrol Dial Transplant 18:804–808, 2003.
151. Garcia-Pachon E, Romero S: Urinothorax: A new approach. Curr Opin Pulm Med 12:259–263, 2006.
152. Marks PA, Roof BS: Pericardial effusions associated with myxedema. Ann Intern Med 39:230–240, 1953.
153. Spicer RL, Uzark KC, Moore JW, et al: Aortopulmonary collateral vessels and prolonged pleural effusions after modified Fontan procedures. Am Heart J 131:1164–1168, 1996.
154. Lemler MS, Scott WA, Leonard SR, et al: Fenestration improves clinical outcome of the Fontan procedure: A prospective, randomized study. Circulation 105:207–212, 2002.
154a. Mascio CE, Wayment M, Colaizy TT, et al: The modified Fontan procedure and prolonged pleural effusions. Am Surg 75:175–177, 2009.

154b. Yun TJ, Im YM, Jung SH, et al: Pulmonary vascular compliance and pleural effusion duration after the Fontan procedure. Int J Cardiol 133:55–61, 2009.
154c. Francois K, Bove T, De Groote K, et al: Pleural effusions, water balance mediators and the influence of lisinopril after completion Fontan procedures. Eur J Cardiothorac Surg 36:57–62, 2009.
155. Huggins J, Sahn S: Duro-pleural fistula diagnosed by beta2-transferrin. Respiration 70:423–425, 2003.
156. Muthuswamy P, Alausa M, Reilly J: The effusion that would not go away. N Engl J Med 345:756–759, 2001.
157. Porcel JM, Light RW: Effusions from vascular causes. *In* Light RW, Lee YCG (eds): Textbook of Pleural Diseases. London: Hodder Arnold, 2008, pp 397–408.
158. Tang K, Robbins I, Light R: Incidence of pleural effusion in idiopathic and familial pulmonary arterial hypertension patients. Chest 136:688–693, 2009.
159. Berk JL, Keane J, Seldin DC, et al: Persistent pleural effusions in primary systemic amyloidiosis: Etiology and prognosis. Chest 124:969–977, 2003.
160. Hoyer RJ, Leung N, Witzig TE, et al: Treatment of diuretic refractor pleural effusions with bevacizumab in four patients with primary systemic amyloidosis. Am J Hematol 82:409–413, 2007.
161. Neiderman MS, Bass JB, Campbell GD: Guidelines for the initial management of adults with community-acquired pneumonia: Diagnosis, assessment of severity, and initial antimicrobial therapy. Am Rev Respir Dis 148:1418–1426, 1993.
162. Musher DM, Alexandraki I, Graviss EA, et al: Bacteremic and nonbacteremic pneumococcal pneumonia. A prospective study. Medicine (Baltimore) 79:210–221, 2000.
163. Hasley PB, Albaum MN, Li Y-H, et al: Do pulmonary radiographic findings at presentation predict mortality in patients with community-acquired pneumonia? Arch Intern Med 156:2206–2212, 1996.
164. Colice GL, Curtis A, Deslauriers J, et al: Medical and surgical treatment of parapneumonic effusions: An evidence-based guideline. Chest 118:1158–1171, 2000.
165. Bartlett JG, Finegold SM: Anerobic infections in the lung and pleural space. Am Rev Respir Dis 110:56–77, 1974.
166. Ferguson AD, Prescott RJ, Selkon JB: The clinical course and management of thoracic empyema. QJM 89:285–289, 1996.
167. Chu MW, Dewar LR, Burgess JJ, et al: Empyema thoracis: Lack of awareness results in a prolonged clinical course. Can J Surg 44:284–288, 2001.
168. Davies CL, Gleeson FV, Davies RJ: BTS guidelines for the management of pleural infection. Thorax 58(Suppl 2):II18–II28, 2003.
169. Alegre J, Jufresa J, Aléman C, et al: Pleural fluid myeloperoxidase as a marker of infectious pleural effusions. Eur J Intern Med 12:357–362, 2001.
170. Vives M, Porcel JM, Gazquez I, et al: SC5b-9: A test for identifying complicated parapneumonic effusions. Respiration 67:433–438, 2000.
171. Aléman C, Alegre J, Segura R, et al: Polymorphonuclear elastase in the early diagnosis of complicated pyogenic pleural effusions. Respiration 70:462–467, 2003.
172. Light RW, Rodriguez RM: Management of parapneumonic effusions. Clin Chest Med 19:373–382, 1998.
173. Lim TK, Chin NK: Empirical treatment with fibrinolysis and early surgery reduces the duration of hospitalization in pleural sepsis. Eur Respir J 13:514–518, 1999.
174. Ashbaugh DG: Empyema thoracis: Factors influencing morbidity and mortality. Chest 99:1162–1165, 1991.
175. Shankar S, Gulati M, Kang M, et al: Image-guided percutaneous drainage of thoracic empyema: Can sonography predict the outcome? Eur Radiol 10:495–499, 2000.
176. Ali I, Unruh H: Management of empyema thoracis. Ann Thorac Surg 50:355–359, 1990.
177. Maskell NA, Davies CW, Nunn AJ, et al: U.K. controlled trial of intrapleural streptokinase for pleural infection. N Engl J Med 352:865–874, 2005.
178. Froudarakis ME, Kouliatsis G, Steiropoulos P, et al: Recombinant tissue plasminogen activator in the treatment of pleural infections in adults. Respir Med 102:1694–1700, 2008.
179. Zhu Z, Hawthorne M, Guo Y, et al: Tissue plasminogen activator combined with human recombinant deoxyribonuclease is effective therapy for empyema in a rabbit model. Chest 129:1577–1583, 2006.
179a. Goralski JL, Bromberg PA, Haithcock V: Intrapleural hemorrhage after administration of tPA: a case report and review of the literature. Ther Adv Respir Dis 3:295–300, 2009.
180. Molnar T: Current surgical treatment of thoracic empyema in adults. Eur J Cardiothorac Surg 32:422–430, 2007.
181. Landreneau RJ, Keenan RJ, Hazelrigg SR, et al: Thoracoscopy for empyema and hemothorax. Chest 109:18–24, 1995.
182. Cassina PC, Hauser M, Hillejan L, et al: Video-assisted thoracoscopy in the treatment of pleural empyema: Stage-based management and outcome. J Thorac Cardiovasc Surg 117:234–238, 1999.
183. Lawrence DR, Ohri SK, Moxon RE, et al: Thoracoscopic débridement of empyema thoracis. Ann Thorac Surg 64:1448–1450, 1997.
184. Striffeler H, Gugger M, Im Hof V, et al: Video-assisted thoracoscopic surgery for fibrinopurulent pleural empyema in 67 patients. Ann Thorac Surg 65:319–323, 1998.
185. Deslauriers J, Jacques LF, Gregoire J: Role of Eloesser flap and thoracoplasty in the third millennium. Chest Surg Clin North Am 12:605–623, 2002.
186. Maruyama R, Ondo K, Mikami K, et al: Clinical course and management of patients undergoing open window thoracostomy for thoracic empyema. Respiration 68:606–610, 2001.
187. Pairolero PC: Empyema and bronchopleural fistula after pneumonectomy: Factors affecting incidence. Ann Thorac Surg 72:243–247, 2001.
188. Wain JC: Management of late postpneumonectomy empyema and bronchopleural fistula. Chest Surg Clin North Am 6:529–541, 1996.
189. Baumann MH, Nolan R, Petrini M, et al: Pleural tuberculosis in the United States: Incidence and drug resistance. Chest 131:1125–1132, 2007.
190. Mlika-Cabanne N, Brauner M, Kamanfu G, et al: Radiographic abnormalities in tuberculosis and risk of coexisting human immunodeficiency virus infection. Am J Respir Crit Care Med 152:794–799, 1995.
191. Jones BE, Young SMM, Antoniskis D, et al: Relationship of the manifestations of tuberculosis to CD4 cell counts in patients with human immunodeficiency virus infection. Am Rev Respir Dis 148:1292–1297, 1993.
192. Roper WH, Waring JJ: Primary serofibrinous pleural effusion in military personnel. Am Rev Respir Dis 71:616–634, 1955.
193. Ong A, Creasman J, Hopewell PC, et al: A molecular epidemiological assessment of extrapulmonary tuberculosis in San Francisco. Clin Infect Dis 38:25–31, 2004.
194. Ellner JJ, Barnes PF, Wallis RS, et al: The immunology of tuberculous pleurisy. Semin Respir Infect 3:335–342, 1988.
195. Kim H, Lee H, Kwon S, et al: The prevalence of pulmonary parenchymal tuberculosis in patients with tuberculous pleuritis. Chest 129:1253–1258, 2006.
196. Al-Majed SA: Study of paradoxical response to chemotherapy in tuberculous pleural effusion. Respir Med 90:211–214, 1996.
197. Gupta RC, Dixit R, Purohit SD, et al: Development of pleural effusion in patients during anti-tuberculosis chemotherapy. Indian J Chest Dis Allied Sci 42:161–168, 2000.
198. Barbas CSV, Cukier A, de Varvalho CRR, et al: The relationship between pleural fluid findings and the development of pleural thickening in patients with pleural tuberculosis. Chest 100:1264–1267, 1991.
199. Engel M, Matchaba P, Volmink J: Corticosteroids for tuberculous pleurisy. Cochrane Database Syst Rev 4:CD001876, 2007.
200. Lai YF, Chao TY, Wang YH, et al: Pigtail drainage in the treatment of tuberculous pleural effusions: A randomised study. Thorax 58:149–151, 2003.
201. Flynn MW, Felson B: The roentgen manifestations of thoracic actinomycosis. AJR Am J Roentgenol 110:707–716, 1970.
202. Feigin DS: Nocardiosis of the lung: Chest radiographic findings in 21 cases. Radiology 159:9–14, 1986.
203. Hillerdal G: Pulmonary aspergillus infection invading the pleura. Thorax 36:745–751, 1981.

204. Shirakusa T, Ueda H, Saito T, et al: Surgical treatment of pulmonary aspergilloma and *Aspergillus* empyema. Ann Thorac Surg 48:779–782, 1989.
205. Kinasewitz GT, Penn RL, George RB: The spectrum and significance of pleural disease in blastomycosis. Chest 86:580–584, 1985.
206. Merchant M, Romero A, Libke R, et al: Pleural effusion in hospitalized patients with coccidioidomycosis. Respir Med 102:537–540, 2008.
207. Wasser L, Talavera W: Pulmonary cryptococcosis in AIDS. Chest 92:692–695, 1987.
208. Conces DRJ, Vix VA, Tarver RD: Pleural cryptococcosis. J Thorac Imaging 5:84–86, 1990.
209. Connell JVJ, Mumh JR: Radiographic manifestations of pulmonary histoplasmosis: A 10-yr review. Radiology 121:281–285, 1976.
210. Weissbluth M: Pleural effusion in histoplasmosis. J Pediatr 88:894–895, 1976.
211. Fine NL, Smith LR, Sheedy PF: Frequency of pleural effusions in mycoplasma and viral pneumonias. N Engl J Med 283:790–793, 1970.
212. Alptekin F: An epidemic of pleurisy with effusion in Bitlis, Turkey: Study of 559 cases. US Armed Forces Med J 9:1–11, 1958.
213. Bustamante EA, Levy H, Simpson SQ: Pleural fluid characteristics in hantavirus pulmonary syndrome. Chest 112:1133–1136, 1997.
214. Setiawan MW, Samsi TK, Wulur H, et al: Dengue haemorrhagic fever: Ultrasound as an aid to predict the severity of the disease. Pediatr Radiol 16:1–4, 1998.
215. Afessa B: Pleural effusion and pneumothorax in hospitalized patients with HIV infection. Chest 117:1031–1037, 2000.
216. Light RW, Hamm H: Pleural disease and the acquired immune deficiency syndrome. Eur Respir J 10:2638–2643, 1997.
217. Gil Suay V, Cordero PJ, Martinez E, et al: Parapneumonic effusions secondary to community-acquired bacterial pneumonia in human immunodeficiency virus–infected patients. Eur Respir J 8:1934–1939, 1995.
218. Lyche KD, Jensen WA: Pleuropulmonary amebiasis. Semin Respir Infect 12:106–112, 1997.
219. Ibarra-Perez C: Thoracic complications of amebic abscess of the liver. Chest 79:672–676, 1981.
220. Aribas OK, Kanat F, Gormus N, et al: Pleural complications of hydatid disease. J Thorac Cardiovasc Surg 123:492–497, 2002.
221. Ozvaran MK, Ersoy Y, Uskul B, et al: Pleural complications of pulmonary hydatid disease. Respirology 9:115–119, 2004.
222. Im JG, Whang HY, Kim WS, et al: Pleuropulmonary paragonimiasis: Radiologic findings in 71 patients. AJR Am J Roentgenol 159:39–43, 1992.
223. Stein PD, Henry JW: Clinical characteristics of patients with acute pulmonary embolism stratified according to their presenting syndromes. Chest 112:974–979, 1997.
224. Bynum LJ, Wilson JEI: Radiographic features of pleural effusions in pulmonary embolism. Am Rev Respir Dis 117:829–834, 1978.
225. Porcel J, Madronero A, BPardina M, et al: Analysis of pleural effusions in acute pulmonary embolism: Radiological and pleural fluid data from 230 patients. Respirology 12:234–239, 2007.
226. Coche EE, Muller NL, Kim KI, et al: Acute pulmonary embolism: Ancillary findings at spiral CT. Radiology 207:753–758, 1998.
227. Shah AA, Davis SD, Gamsu G, et al: Parenchymal and pleural findings in patients with and patients without acute pulmonary embolism detected at spiral CT. Radiology 211:147–153, 1999.
228. Bynum LJ, Wilson JEI: Characteristics of pleural effusions associated with pulmonary embolism. Arch Intern Med 136:159–162, 1976.
229. Michel L, Grillo HC, Malt RA: Operative and nonoperative management of esophageal perforations. Ann Surg 194:57–63, 1981.
230. Bufkin BL, Miller JIJ, Mansour KA: Esophageal perforation: Emphasis on management. Ann Thorac Surg 61:1447–1451, 1996.
231. Abbott OA, Mansour KA, Logan WD, et al: Atraumatic so-called "spontaneous" rupture of the esophagus. J Thorac Cardiovasc Surg 59:67–83, 1970.
232. Lankisch PG, Droge M, Becher R: Pleural effusions: A new negative prognostic parameter for acute pancreatitis. Am J Gastroenterol 89:1849–1851, 1994.
233. Pederzoli P, Bassi C, Falconi M, et al: Conservative treatment of external pancreatic fistulas with parenteral nutrition alone or in combination with continuous intravenous infusion of somatostatin, glucagon or calcitonin. Surg Gynecol Obstet 163:428–432, 1986.
234. van der Sluis RF: Subphrenic abscess. Surg Gynecol Obstet 158:427–430, 1984.
235. Chu K-M, Fan S-T, Lai ECS, et al: Pyogenic liver abscess. Arch Surg 131:148–153, 1996.
236. Haaga JR, Weinstein AJ: CT-guided percutaneous aspiration and drainage of abscesses. AJR Am J Roentgenol 135:1187–1194, 1980.
237. Light RW, George RB: Incidence and significance of pleural effusion after abdominal surgery. Chest 69:621–626, 1976.
238. Nielsen PH, Jepsen SB, Olsen AD: Postoperative pleural effusion following upper abdominal surgery. Chest 96:1133–1135, 1989.
239. Golfieri R, Giampalma E, Morselli Labate AM, et al: Pulmonary complications of liver transplantation: Radiological appearance and statistical evaluation of risk factors in 300 cases. Eur Radiol 10:1169–1183, 2000.
240. Uetsuji S, Komada Y, Kwon AH, et al: Prevention of pleural effusion after hepatectomy using fibrin sealant. Int Surg 79:135–137, 1994.
241. Bergeron E, Beaulieu C, Passerini L, et al: Dropped gallstones causing transdiaphragmatic migration and thoracic empyema. Ann Thorac Surg 84:1760–1762, 2007.
242. Horler AR, Thompson M: The pleural and pulmonary complications of rheumatoid arthritis. Ann Intern Med 51:1179–1203, 1959.
243. Ferguson GC: Cholesterol pleural effusion in rheumatoid lung disease. Thorax 21:577–582, 1966.
244. Chou CW, Chang SC: Pleuritis as a presenting manifestation of rheumatoid arthritis: Diagnostic clues in pleural fluid cytology. Am J Med Sci 323:158–161, 2002.
245. Jones FL, Blodgett RC: Empyema in rheumatoid pleuropulmonary disease. Ann Intern Med 74:665–671, 1971.
246. Wang DY: Diagnosis and management of lupus pleuritis. Ann Intern Med 49:70–88, 2002.
247. Wang DY, Yang P-C, Yu WL, et al: Serial antinuclear antibodies titre in pleural and pericardial fluid. Eur Respir J 15:1106–1110, 2000.
248. Light RW: Pleural effusions following cardiac injury and coronary artery bypass graft surgery. Semin Respir Crit Care Med 22:657–664, 2001.
249. Mott AR, Fraser CDJ, Kusnoor AV, et al: The effect of short-term prophylactic methylprednisolone on the incidence and severity of postpericardiotomy syndrome in children undergoing cardiac surgery with cardiopulmonary bypass. J Am Coll Cardiol 37:1700–1706, 2001.
250. Light RW, Rogers JT, Moyers JP, et al: Prevalence and clinical course of pleural effusions at 30 days after coronary artery and cardiac surgery. Am J Respir Crit Care Med 166:1563–1566, 2002.
251. Vargas FS, Cukier A, Hueb W, et al: Relationship between pleural effusion and pericardial involvement after myocardial revascularization. Chest 105:1748–1752, 1994.
252. Sadikot RT, Rogers JT, Cheng DS, et al: Pleural fluid characteristics of patients with symptomatic pleural effusion after coronary artery bypass graft surgery. Arch Intern Med 160:2665–2668, 2000.
253. Shitrit D, Izbicki G, Fink G, et al: Late postoperative pleural effusion following lung transplantation: Characteristics and clinical implications. Eur J Cardiothorac Surg 23:494–496, 2003.
254. Ferrer JS, Roldan J, Roman A, et al: Acute and chronic pleural complications in lung transplantation. J Heart Lung Transplant 22:1217–1225, 2003.
255. Medina LS, Siegel MJ, Bejarano PA, et al: Pediatric lung transplantation: Radiographic-histopathologic correlation. Radiology 187:807–810, 1993.
256. Epler GR, McCloud CT, Gaensler EA: Prevalence and incidence of benign asbestos pleural effusion: diagnosis and cause. JAMA 267:617–622, 1982.

257. Hillerdal G: Nonmalignant pleural disease related to asbestos exposure. Clin Chest Med 6:141–152, 1985.
258. Soskel NT, Sharma OP: Pleural involvement in sarcoidosis. Curr Opin Pulm Med 6:455–468, 2000.
259. Huggins JT, Doelken P, Sahn SA, et al: Pleural effusions in a series of 181 outpatients with sarcoidosis. Chest 129:1599–1604, 2006.
260. Jarratt MJ, Sahn SA: Pleural effusions in hospitalized patients receiving long-term hemodialysis. Chest 108:470–474, 1995.
261. Berger HW, Rammohan G, Neff MS, et al: Uremic pleural effusion: A study in 14 patients on chronic dialysis. Ann Intern Med 82:362–364, 1975.
262. Meigs JV, Cass JW: Fibroma of the ovary with ascites and hydrothorax. Am J Obstet Gynecol 33:249–267, 1937.
263. Light RW: Pleural effusions due to obstetric and gynecological conditions. *In* Light RW, Lee YCG (eds): Textbook of Pleural Diseases. London: Hodder Arnold, 2008, pp 465–482.
264. Bhojawala J, Heller DS, Cracchiolo B, et al: Endometriosis presenting as bloody pleural effusion and ascites—Report of a case and review of the literature. Arch Gynecol Obstet 264:39–41, 2000.
265. Beer DJ, Pereira WJ, Snider GL: Pleural effusion associated with primary lymphedema: A perspective on the yellow nail syndrome. Am Rev Respir Dis 117:595–599, 1978.
266. Lewis M, Kallenbach JA, Zaltzman M, et al: Pleurectomy in the management of massive pleural effusion associated with primary lymphoedema: Demonstration of abnormal pleural lymphatics. Thorax 38:637–639, 1983.
267. Kalomenidis IT: Effusions caused by drugs. *In* Light RW, Lee YCG (eds): Textbook of Pleural Diseases. London: Hodder Arnold, 2008, pp 432–443.
268. Holmberg L, Boman G: Pulmonary reactions to nitrofurantoin: 447 cases reported to the Swedish Adverse Drug Reaction Committee, 1966–1976. Eur J Respir Dis 62:180–189, 1981.
269. Geller M, Flaherty DK, Dickie HA, et al: Lymphopenia in acute nitrofurantoin pleuropulmonary reactions. J Allergy Clin Immunol 59:445–448, 1977.
270. Petusevsky ML, Faling LJ, Rocklin RE, et al: Pleuropericardial reaction to treatment with dantrolene. JAMA 242:2772–2774, 1979.
271. Kok-Jensen A, Lindeneg O: Pleurisy and fibrosis of the pleura during methysergide treatment of hemicrania. Scand J Respir Dis 51:218–222, 1970.
272. Hillerdal G, Lee J, Blomkvist A, et al: Pleural disease during treatment with bromocriptine in patients previously exposed to asbestos. Eur Respir J 10:2711–2715, 1997.
273. McElvaney NG, Wilcox PG, Churg A, et al: Pleuropulmonary disease during bromocriptine treatment of Parkinson's disease. Arch Intern Med 148:2231–2236, 1988.
274. Vogelzang PJ, Bloom SM, Mier JW, et al: Chest roentgenographic abnormalities in IL-2 recipients. Incidence and correlation with clinical parameters. Chest 101:746–752, 1992.
275. Quintas-Cardama A, Kantarjian H, O'Brien S, et al: Pleural effusion in patients with chronic myelogenous leukemia treated with dasatinib after imatinib failure. J Clin Oncol 25:3908–3914, 2007.
275a. Porkka K, Khoury HJ, Paquette RL, et al: Dasatinib 100 mg once daily minimizes the occurrence of pleural effusion in patients with chronic myeloid leukemia in chronic phase and efficacy is unaffected in patients who develop pleural effusion. Cancer 2009 (Epub ahead of print).
276. Light RW, Jenkinson SG, Minh V, et al: Observations on pleural pressures as fluid is withdrawn during thoracentesis. Am Rev Respir Dis 121:799–804, 1980.
277. Huggins JT, Sahn SA, Heidecker J, et al: Characteristics of trapped lung: Pleural fluid analysis, manometry, and air-contrast chest CT. Chest 131:206–213, 2007.
278. Duntley P, Siever J, Korwes ML, et al: Vascular erosion by central venous catheter. Clinical features and outcome. Chest 101:1633–1638, 1992.
279. Wothuis A, Landewe RB, Theunissen PH, et al: Chylothorax or leakage of total parenteral nutrition? Eur Respir J 12:1233–1235, 1998.
280. Roubenoff R, Ravich WJ: Pneumothorax due to nasogastric feeding tubes: Report of four cases, review of the literature, and recommendations for prevention. Arch Intern Med 149:184–188, 1989.
281. Miller KS, Tomlinson JR, Sahn SA: Pleuropulmonary complications of enteral tube feedings. Chest 88:231–233, 1985.
282. Lo JO, Wu V, Reh D, et al: Diagnosis and management of misplaced nasogastric tube into the pulmonary pleura. Arch Otolaryngol Head Neck Surg 134:547–550, 2008.

CHAPTER 74

PNEUMOTHORAX, CHYLOTHORAX, HEMOTHORAX, AND FIBROTHORAX

Richard W. Light, MD • Y. C. Gary Lee, MBChB, PhD, FRACP

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INTRODUCTION

A pneumothorax is present when there is air in the pleural space. Pneumothoraces are classified as *spontaneous pneumothoraces,* which develop without preceding trauma or other obvious cause, and *traumatic pneumothoraces,* which develop as a result of direct or indirect trauma to the chest, including diagnostic or therapeutic maneuvers (*iatrogenic pneumothoraces*). Spontaneous pneumothoraces are subclassified as *primary* or *secondary.* A primary spontaneous pneumothorax presents in an otherwise healthy person without underlying lung disease. A secondary spontaneous pneumothorax complicates an underlying lung disease, most commonly chronic obstructive pulmonary disease (COPD).

Most pleural effusions prove to be either an exudate or a transudate according to the criteria provided in Chapter 73. Occasionally, the liquid contents turn out to be chyle, pseudochyle, or blood. This chapter describes the pathogenesis and clinical manifestations of chylothorax, pseudochylothorax, and hemothorax. Fibrothorax, the sequela of chronic organizing pleural disease of any origin, is also considered.

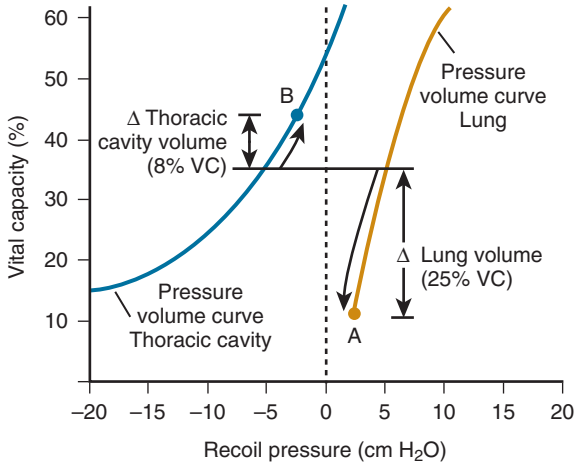

FIGURE 74-1 ■ Influence of a pneumothorax on the volumes of the lung and hemithorax. In this illustration, the pneumothorax has caused the intrapleural pressure to rise from –5 to –2.5 cm H_2O. The lung and thoracic cavity move on their respective pressure-volume curves (*dashed lines*) to new volumes for the lung **(A)** and thoracic cavity **(B).** Note that the volume of the hemithorax becomes larger as the volume of the lung becomes smaller. The changes in volumes of the hemithorax and lung are unequal because of the differences in the slopes of two pressure-volume curves. VC, vital capacity. (Redrawn from Light RW: Pleural Diseases [4th ed]. Philadelphia: Lippincott Williams & Wilkins, 2001, p 286.)

PATHOPHYSIOLOGY OF PNEUMOTHORAX

In normal subjects, the pressure in the pleural space is negative with respect to the alveolar pressure during the entire respiratory cycle. The pressure gradient between the alveoli and the pleural space—the transpulmonary pressure—is the result of the inherent elastic recoil of the lung. During spontaneous breathing, the pleural pressure is also negative with respect to the atmospheric pressure. The functional residual capacity, or resting end-expiratory volume of the lung, is the volume at which the inherent outward pull of the chest wall is equal to, but opposite in direction to, the inward pull (recoil) of the lung.[1]

When a communication develops between an alveolus or other intrapulmonary air space and the pleural space, air will flow from the alveolus into the pleural space until there is no longer a pressure difference or until the communication is sealed. Similarly, when a communication develops through the chest wall between the atmosphere and the pleural space, air will enter the pleural space until the pressure gradient is eliminated or the communication is closed. The influence of a pneumothorax on the volume of the hemithorax and the lung is illustrated in Figure 74-1. In this example, sufficient air has entered the pleural space to elevate the pleural pressure from −5 to −2.5 cm H_2O, so that the transpulmonary or recoil pressure has decreased from 5 to 2.5 cm H_2O. The amount of air necessary to effect this change in the pleural pressure can be seen to be equal to 33% of the patient's vital capacity: most of this pleural air (25% of the vital capacity) is accounted for by air displaced from the lung and the rest is accounted for by the expansion of the thoracic cavity along its pressure-volume curve (by 8% of the vital capacity). The rise in the pleural pressure also causes a shift of the mediastinum to the contralateral side, an enlarged hemithorax, and a depressed hemidiaphragm. These findings are expected and do not necessarily indicate that a tension pneumothorax is present.[1]

The main physiologic consequences of a pneumothorax are a decrease in the vital capacity (as illustrated in Fig. 74-1) and the arterial P_{O_2}. In patients with primary spontaneous pneumothorax, the decrease in the vital capacity is usually well tolerated. If the lung function of the patient is abnormal before the development of the pneumothorax, the decrease in vital capacity may lead to respiratory insufficiency with alveolar hypoventilation and respiratory acidosis.

Most patients with a pneumothorax have a reduced arterial P_{O_2} and an increase in the alveolar-arterial oxygen tension difference. In a series of 12 patients with spontaneous pneumothorax, the arterial P_{O_2} was below 80 mm Hg in 9 (75%) and was below 55 mm Hg in 2 patients, both of whom had secondary spontaneous pneumothorax.[2]

The reduction in arterial P_{O_2} appears to be due to the creation of regions of the lung both with low ventilation-perfusion ratios and with absent ventilation (shunt), and, occasionally, due to alveolar hypoventilation. Norris and coworkers[2] reported that the average right-to-left shunt in their 12 patients with spontaneous pneumothorax was more than 10%. Larger pneumothoraces were associated with greater shunts. When the pneumothorax

occupied less than 25% of the hemithorax, the shunt was not increased.[2]

After air is evacuated from the pleural space, the arterial P_{O_2} usually improves, but the improvement may take several hours. Norris and colleagues[2] evacuated the pleural air from three patients with an initial shunt above 20%; within 90 minutes, the shunt had decreased below 10% but it nonetheless remained above 5% in all patients. The delay in improvement may be related to the duration of the pneumothorax and the time necessary to expand collapsed alveoli.

PRIMARY SPONTANEOUS PNEUMOTHORAX

Incidence

In a study from the United Kingdom, the incidence of spontaneous pneumothorax was 24.0 and 9.8 per 100,000 per year for men and women, respectively,[3] and about one half of the pneumothoraces were primary spontaneous pneumothoraces. Extrapolating from these data, the annual incidence in the United States would be about 22,500.

Etiologic Factors

Primary spontaneous pneumothorax (PSP) is traditionally believed to result from rupture of a subpleural emphysematous bleb, which is usually located in the apex of the lung.[4] Blebs can be found in more than 75% of patients undergoing thoracoscopy for treatment of PSP.[4] The pathogenesis of these subpleural blebs and the trigger(s) of their rupture are unclear. Such blebs have been attributed to congenital abnormalities, inflammation of the bronchioles, and disturbances of the collateral ventilation.[4] There is a strong association between smoking and the development of a PSP. When four separate series of patients with PSP are combined, 461 of 505 patients (91%) with PSP were smokers or ex-smokers.[1] The occurrence of a spontaneous pneumothorax is related to the level of cigarette smoking. In men, the relative risk of a pneumothorax is 7 times higher in light smokers (1 to 12 cigarettes/day), 21 times higher in moderate smokers (13 to 22 cigarettes/day), and 102 times higher in heavy smokers (>22 cigarettes/day) than in nonsmokers.[5] It is probable that smoking-induced disease of small airways contributes to the development of the subpleural blebs.

Patients with PSP tend to be taller and thinner than control persons. In one study, military recruits with a pneumothorax were on average 2 inches taller and 25 pounds lighter than the typical military recruit.[1] An increased length of the chest may contribute to the formation of the subpleural blebs. Because pleural pressure falls about 0.20 cm H_2O per centimeter of vertical height, pleural pressure will be more negative at the apex of the lung in taller people; accordingly, the alveoli at their lung apex are subjected to a greater mean distending pressure. Over an extended period, this could lead to the formation of subpleural blebs in subjects genetically predisposed to bleb formation.

A tendency for the development of a PSP can be inherited. Some cases are due to an autosomal dominant gene with incomplete penetrance, the penetrance being lower in women (21%) than in men (50%). The Birt-Hogg-Dubé syndrome is an autosomal dominant condition characterized by an increased incidence of spontaneous pneumothorax, benign skin tumors, and renal tumors.[6] The genetic abnormality resides on chromosome 17p11.2 and involves mutations in the folliculin gene.[6] Approximately 40% of patients with the mutation will have a pneumothorax.[6] Pneumothorax also occurs with increased frequencies in those with the Marfan syndrome and homocystinuria.

Recent data have challenged the traditional concepts of air leak from one bleb supplied by one single airway. A study using inhaled fluorescein suggested that air may leak from more areas than just the blebs,[7] raising the possibility of "pleural porosity," in which the air leaks from multiple pores on the visceral pleura. Endobronchial one-way valve studies also found that occlusion of multiple segmental bronchi are necessary to stop air leaks.[8] This suggests that air is leaking either via multiple sites or via collateral ventilation, or both.

Clinical Manifestations

PSP most commonly occurs in those in their early 20s, and rarely after age 40. PSP usually develops while the patient is at rest, and rarely during heavy exercise.[1]

Chest pain and dyspnea are the two main symptoms. The chest pain usually has an acute onset and is localized to the side of the pneumothorax. A rare complication of PSP is Horner's syndrome, which is thought to result from traction on the sympathetic ganglion produced by a shift of the mediastinum.

On physical examination, the vital signs are usually normal, with the exception of a moderate tachycardia. A tension pneumothorax should be suspected if the pulse rate exceeds 140 beats/min or if hypotension, cyanosis, or electromechanical dissociation is present. The side with pneumothorax may be larger than the contralateral side and move less during the respiratory cycle. Tactile fremitus is absent, the percussion note is hyperresonant, and the breath sounds are absent or reduced on the affected side. In those with a right-sided pneumothorax, the lower edge of the liver may be shifted inferiorly. With a large pneumothorax, the trachea may be shifted toward the contralateral side.

Diagnosis

The diagnosis is usually suggested by the clinical history and the physical examination. The diagnosis is established by demonstrating a pleural line on the chest radiograph (Fig. 74-2). A visceral pleural line can be distinguished from other lines such as skinfolds by the following criteria. This line is defined by air density on either side of the line, whereas a skinfold is really an edge without air density on either side. A pleural line

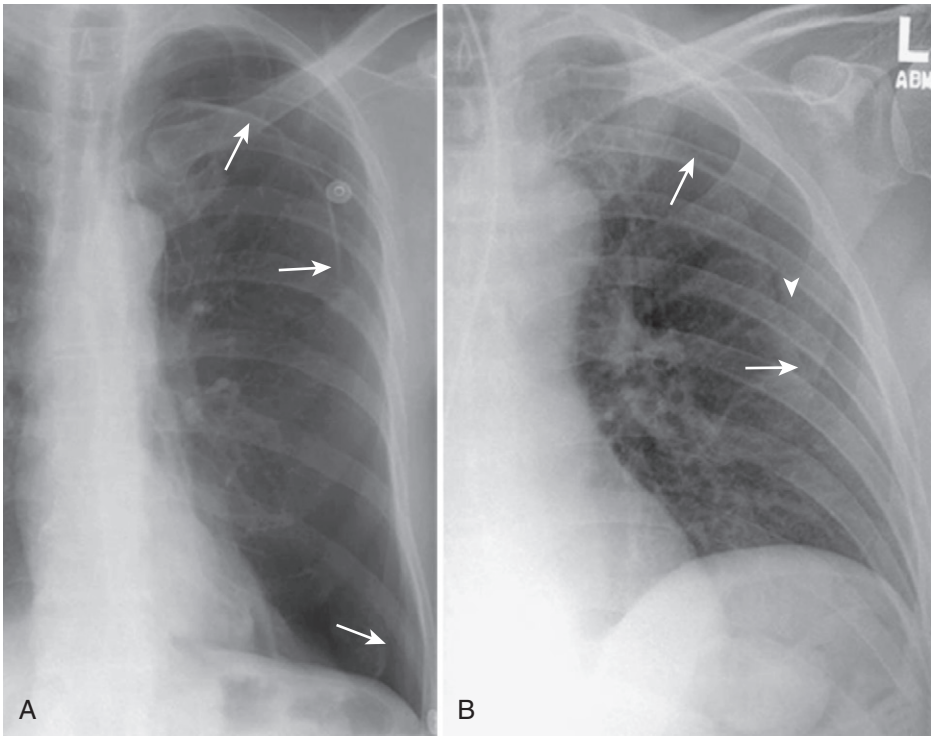

FIGURE 74-2 ■ **A,** Chest radiograph of a pneumothorax. The pleural line has lucency on either side, representing air in the pleural space on one side of the line and air in the lung on the other. The line is sharply demarcated and can be traced along its course (*lower arrow*). No blood vessels can be seen beyond the superior (*upper arrow*) and lateral (*middle arrow*) extent of the line. **B,** Chest radiograph of a skinfold (*arrows*) that could be mistaken for a pneumothorax. The border is more of an edge, with lucency on only one side. The edge is poorly defined and cannot be followed continuously (*lower arrow*). Blood vessels can be traced beyond the border of the fold (*arrowhead*). (Courtesy of Michael B. Gotway, MD, Scottsdale Medical Imaging and the Department of Radiology, University of California, San Francisco.)

should generally be sharp and well-defined, whereas a skinfold is often poorly defined, at least on one side. A pleural line can be followed continuously, roughly paralleling the chest wall inner contour so that, in the upright patient, it caps the apex of the lung (assuming no adhesions) and often tapers toward the lung base; a skinfold usually is not continuous, often fades at both ends, and often does not follow an anatomically sensible configuration. Finally, a pleural line should not be crossed by lung vessels, whereas a skinfold can show lung vessels beyond its edge.

In doubtful cases, lateral decubitus films (with the affected side up), or a computed tomography (CT) scan may facilitate the diagnosis. Expiratory films are only slightly more sensitive than inspiratory films in detecting pneumothoraces and are not routinely recommended.[4] A small pleural effusion is associated with a PSP in approximately 15% of cases and is manifested radiographically as an air-fluid level. When the pleural fluid is analyzed, it frequently contains a large percentage of eosinophils.[9] On rare occasions, spontaneous pneumothorax is complicated by brisk bleeding into the pleural space, producing a hemopneumothorax.[10] If the patient's vital signs are unstable in this situation, emergency surgery is indicated.[10]

When one is managing a patient with a pneumothorax, the amount of lung collapse should be estimated. One can first measure the lung and hemithorax "diameter": the distance from the lung root to the visceral pleural line (lung diameter) or to the chest wall (hemithorax diameter). Because the volumes of the lung and the hemithorax are roughly proportional to the cube of their diameters, one can estimate the degree of collapse (percent pneumothorax, or PTX%) by measuring average diameters of the lung and the hemithorax, cubing these diameters, and using the following equation, known as the Light index[1]:

$$\text{PTX\%} = 100\% \times [1 - (\text{diameter of the lung} / \text{diameter of the hemithorax})^3]$$

There is an excellent correlation ($r = 0.84$) between the Light index and the amount of air that can be aspirated from a pneumothorax.[11]

Recurrence Rates

Following a PSP, a patient is at risk of recurrence particularly in the months immediately after the first episode. Sadikot and associates[12] followed 153 patients with PSP for a mean of 54 months and reported that 39% had a recurrent ipsilateral pneumothorax, most within the first year. Of the 153 patients, 15% also developed a pneumothorax on the contralateral side.

There have been several attempts to predict who will develop recurrent pneumothorax. Patients who are tall, patients with a low body mass index, and those who

continue to smoke are more likely to have a recurrence.[13] Yet, there is no relationship between the number of blebs or the size of the blebs on CT, or the appearance of the lung at thoracotomy, and the risk of recurrence.[1] Once a patient has had one recurrence, the risk of another recurrence increases to more than 50% if no measure is taken to prevent the recurrence.[1]

Treatment

There are two goals to managing a patient with a PSP: to rid the pleural space of its air and to decrease the likelihood of a recurrence. Treatment options include observation, supplemental oxygen, simple aspiration of the pneumothorax, simple tube thoracostomy, tube thoracostomy with instillation of a pleurodesing agent, thoracoscopy with oversewing of the blebs and pleurodesis, and open thoracotomy. When selecting treatment for any given patient, it should be remembered that PSP is mainly a nuisance and rarely life-threatening. Recently, the American College of Chest Physicians[14] and the British Thoracic Society[15] have published guidelines on the treatment of spontaneous pneumothorax. The former guideline emphasized how few controlled studies exist on the treatment of pneumothorax.[14]

Observation

Once the communication between the alveoli and the pleural space is eliminated, the residual air in the pleural space will be gradually reabsorbed, albeit slowly. Kircher and Swartzel[16] estimated that 1.25% of the volume of the hemithorax is absorbed each 24 hours. For a patient with a 20% pneumothorax, it will take 16 days for pleural air to be absorbed spontaneously. Therefore, it is recommended that only asymptomatic patients with pneumothoraces occupying less than 15% of the hemithorax be considered for observation treatment. If the patient is hospitalized, supplemental oxygen should be administered to increase the rate of pleural air absorption.

Supplemental Oxygen

In pneumothorax, gases move in and out of the pleural space from the capillaries in the visceral and parietal pleura. The movement of each gas depends on the gradient between its partial pressure in the capillaries and in the pleural space, the blood flow per unit surface area available for gas exchange, and the solubility of each gas in the surrounding tissues. Normally, the sum of all the partial pressures in the capillary blood with a patient breathing room air is about 706 mm Hg (P_{H_2O} = 47, P_{CO_2} = 46, P_{N_2} = 573, and P_{O_2} = 40 mmHg). If it is assumed that the pleural pressure is approximately 0 when there is a pneumothorax, then the net gradient for gas absorption is only 54 mm Hg (760 − 706). If the patient is placed on 100% oxygen, however, the sum of all the partial pressures in the capillary blood will probably fall below 200 mm Hg (the P_{N_2} will approach 0, whereas the P_{O_2} will remain < 100 mm Hg). Accordingly, the net gradient for gas absorption will exceed 550 mm Hg or be 10 times greater than it was with the patient breathing room air.[1]

Indeed, the administration of supplemental oxygen accelerates the rate of pleural air absorption in clinical and experimental situations. Chernick and Avery[17] demonstrated that the administration of humidified 100% oxygen to rabbits with experimentally induced pneumothoraces increased the rate of absorption by about sixfold. Subsequent studies in patients with a spontaneous pneumothorax have demonstrated that pleural air is absorbed about four times faster when the patients are given high concentrations of supplemental oxygen to breathe.[18] It is recommended that hospitalized patients with any type of pneumothorax who are not subjected to aspiration or tube thoracostomy be treated with supplemental oxygen at high concentrations.

Simple Aspiration

The initial treatment for most patients with PSP greater than 15% of the volume of the hemithorax should be simple aspiration.[15,19] This procedure is successful in approximately 60% of patients with spontaneous pneumothorax. If successful, simple aspiration avoids hospitalization and there is less pain from the smaller tube. The recurrence rates appear to be similar after simple aspiration and after tube thoracostomy.[15,19]

With this procedure, a relatively small needle (~16 gauge) with an internal polyethylene catheter is inserted into the second anterior intercostal space at the mid-clavicular line after local anesthesia. An alternative site is selected if the pneumothorax is loculated or if adhesions are present. After the needle is inserted, it is extracted, leaving the catheter tip in the pleural space. A three-way stopcock and a 60-mL syringe are attached to the catheter. Air is manually withdrawn until no more can be aspirated. The catheter is then occluded for several hours. If the chest radiograph confirms that there has been no recurrence, the catheter is removed and the patient is discharged. Alternatively, the patient can be observed overnight or can be discharged with a Heimlich one-way valve attached to the catheter. If the total volume of air aspirated exceeds 4 L and no resistance has been felt, it is assumed that there has been no reexpansion, and alternative procedures are initiated.

Patients with their first PSP should be managed initially with simple aspiration on an outpatient basis. Consideration can be given to overnight observation in hospital for those who reside a long distance from the hospital. Patients should return in 24 to 72 hours for a follow-up chest radiograph. If aspiration is unsuccessful, then either thoracoscopy or tube thoracostomy should be undertaken.[20] Because of a low (<50%) likelihood of recurrence and because a PSP is a nuisance rather than life-threatening, maneuvers to prevent recurrence are usually unnecessary for patients with a first episode. Simple aspiration is not recommended for patients with secondary spontaneous pneumothoraces or with recurrent PSPs.

Tube Thoracostomy

For the past several decades, most patients with PSP have been managed initially with tube thoracostomy. It is recommended if simple aspiration proves ineffective and thoracoscopy is not readily available. It rapidly results in the reexpansion of the underlying lung and does not require prolonged hospitalization. In one series of 81 patients treated with tube thoracostomy, the average duration of hospitalization was only 4 days (range 3 to 6 days). Only three patients (4%) had persistent air leaks after several days of chest tube drainage.[21]

When a spontaneous pneumothorax is managed with tube thoracostomy, relatively small tubes (8 to 16 French) or pigtail catheters (8 to 10 French) appear to be as effective as larger tubes.[15] Because the risk of reexpansion pulmonary edema is greater when the lung is reexpanded rapidly, it is advisable to use a water-seal chamber and to avoid suction for the first 24 hours of tube thoracostomy.

After the lung has reexpanded and the air leak has ceased for 24 hours, the chest tube can be removed. Air leaks are present when there is bubbling through the water-seal chamber of the drainage system. If there is no bubbling on quiet respiration, the patient should be asked to cough. The absence of bubbling indicates there is no air leak. Whether clamping the tube before its removal is beneficial remains controversial.[14,15] If the lung remains unexpanded or if there is a persistent air leak 72 hours after tube thoracostomy, thoracoscopy or thoracotomy should be considered. There is no evidence that the intrapleural injection of a pleurodesing agent facilitates closure of a bronchopleural fistula.[21]

Tube Thoracostomy with Instillation of a Pleurodesing Agent

Because many patients with a PSP will have a recurrence, efforts have been made to diminish the recurrence rates by injecting pleurodesing agents into the pleural space at the time of the initial episode. The two agents most commonly used are talc slurry and doxycycline. The administration of one of these agents will reduce the recurrence rates from approximately 40% to 25% (Fig. 74-3).[22] However, because thoracoscopy with stapling of blebs and pleural abrasion reduces the recurrence rate to less than 5%,[23] the thoracoscopic procedure is preferred if available. If talc is used for pleurodesis, large-particle-size talc should be used to minimize the risks of acute lung inflammation.[24] A tetracycline derivative (e.g., doxycycline 500 mg) is preferred by some. Because the injection of a tetracycline derivative can be very painful, particularly in a patient with a pneumothorax and relatively normal pleura, heavy sedation should be given before sclerosis is attempted. (See also Chapter 75 on pleurodesis.) Bleomycin is not recommended for pneumothoraces because it does not produce a pleurodesis in animals with a normal pleura,[25] and has not been studied with pneumothorax in humans.

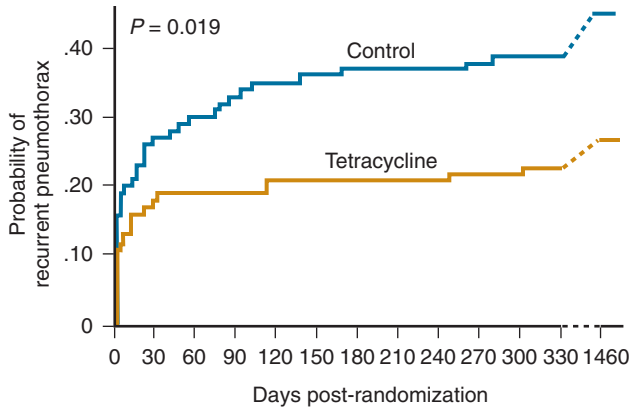

FIGURE 74-3 ■ Probability of recurrent pneumothorax after assignment to the tetracycline or the control group in the Veterans Administration cooperative study on spontaneous pneumothorax. (Redrawn from Light RW, O'Hara VS, Moritz TE, et al: Intrapleural tetracycline for the prevention of recurrent spontaneous pneumothorax. JAMA 264:2224–2230, 1990.)

Thoracoscopy

Patients with spontaneous pneumothorax are increasingly being managed with video-assisted thoracoscopic surgery (VATS) (see also Chapter 23). VATS is the procedure of choice if aspiration fails or if the patient has a recurrent pneumothorax. During VATS, attempts are made to eliminate the blebs responsible for the pneumothorax and to create a pleurodesis. The primary means by which the blebs are treated is with endo-stapling, which requires expensive consumables.[26] When this is a concern, the apical blebs and bullae can be managed by thoracoscopic suturing.[26] Pleurodesis is probably best induced by pleural abrasion.[27,28] Bleb stapling without pleurodesis has a higher recurrence rate, and is not recommended.

VATS is an effective management for PSP. In a meta-analysis of 27 studies, the recurrence rate was 5.4%. The most common complication of VATS for the treatment of PSP is a persistent air leak, which occurs in less than 5% of cases. VATS is preferred to thoracotomy because the hospitalization times are shorter (median 3 days) and the patient incurs less morbidity.[29]

Some have proposed that medical thoracoscopy or pleuroscopy with the insufflation of talc is the preferred way to manage PSP.[30] In one study of 59 patients, pleuroscopy with the insufflation of talc had a recurrence rate of 5% during a follow-up period of 5 years.[31] With pleuroscopy, the anesthesia is local and no treatment is provided for the blebs. Controlled studies are needed to determine whether pleuroscopy (which does not provide stapling of the blebs and pleural abrasion) is as effective as VATS.

Open Thoracotomy

When VATS is not available, open thoracotomy with oversewing of the blebs and pleural abrasion is a reasonable alternative. If a thoracotomy is performed for pneumothorax, a transaxillary mini-thoracotomy should be

performed to minimize the trauma and the length of the scar.[31] In a recent meta-analysis, the recurrence rate after open thoracotomy was only 1.1%, which was significantly less than that for thoracoscopy.[23] Various methods have been used for scarification of the pleural surfaces, ranging from visceral and parietal pleurectomy to pleural abrasion with dry sponges. Because all appear to be similarly effective, pleural abrasion with dry gauze is recommended because it is less traumatic than pleurectomy and does not appear to interfere with a subsequent thoracotomy.

Summary of Treatment

Most patients with their first PSP should be managed initially with simple aspiration of the pleural air with a plastic catheter. If this is ineffective, VATS should be performed promptly, with endo-stapling of blebs and pleural abrasion to create a pleurodesis. An alternative to VATS is open thoracotomy, which is associated with a significantly lower recurrence rate but which requires a longer hospital stay and produces more postoperative morbidity. When thoracoscopy is unavailable, patients who fail aspiration should be managed with tube thoracostomy with an attempt at pleurodesis with either doxycycline or talc, or thoracotomy. If, after 3 days of thoracostomy drainage, there is a persistent air leak or the lungs have not reexpanded, thoracotomy should be considered. Patients with recurrent PSP should undergo VATS or thoracotomy.

SECONDARY SPONTANEOUS PNEUMOTHORAX

A secondary spontaneous pneumothorax (SSP) complicates an underlying lung disease and thus is more serious than a primary pneumothorax because it further decreases the pulmonary function of a patient whose reserve is already diminished. In addition, the presence of the underlying lung disease makes management of the pneumothorax more difficult.

Incidence

The incidence of SSP is similar to that of PSP.[32] An estimated 15,000 new cases of SSP occur annually in the United States. Men over the age of 75 have the highest per capita rate of pneumothorax, 60 per 100,000 per year.[3]

Etiologic Factors

COPD is the most common underlying disease in patients with SSP, although almost every lung disease has been associated with SSP. In one series of 505 patients with SSP, 348 patients had COPD, 93 had tumors, 26 had sarcoidosis, 9 had tuberculosis, 16 had other pulmonary infections, and 13 had miscellaneous diseases.[33] Among patients with COPD, the incidence of SSP increases with progressive severity of the COPD. In the Veterans Administration cooperative study[22] on pneumothorax, 27% of the 229 participants had an FEV_1/FVC ratio below 0.40. One of the more common causes of SSP is *Pneumocystis jirovecii* (formerly *carinii*) infection in patients with acquired immunodeficiency syndrome (AIDS).[34] There is also a high incidence in cystic fibrosis. Of the more than 28,000 patients on the Cystic Fibrosis Foundation Registry, the incidence of pneumothorax was 3.4%.[35] Patients with lymphangioleiomyomatosis (Fig. 74-4; see Chapter 62) and histiocytosis X[36] (Langerhans cell histiocytosis; see Chapter 57) also have a high incidence of spontaneous pneumothorax.

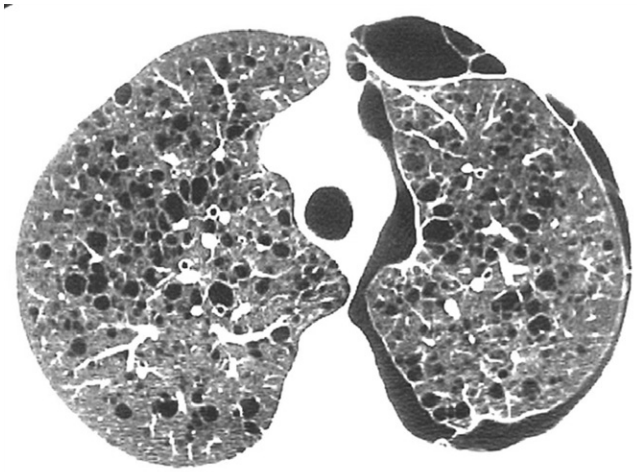

FIGURE 74-4 ■ Chest computed tomography scan of a patient with lymphangioleiomyomatosis. Note the numerous thin-walled cysts, rounded and relatively uniform in shape, and a pneumothorax on the left. (Courtesy of Dr. Lisete Teixeira, University of Sao Paulo, Brazil.)

Clinical Manifestations

In general, the clinical symptoms associated with SSP are more severe than those associated with PSP. In one series of 57 patients with COPD and pneumothorax,[37] all patients were dyspneic, 74% had chest pain on the side of the pneumothorax, 9% were cyanotic, and 7% were hypotensive. Although earlier studies reported a mortality rate that exceeded 10% with pneumothorax secondary to COPD,[37] in the large Veterans Administration cooperative study, the mortality rate from pneumothorax was only 1%.[22]

Diagnosis

The possibility of a pneumothorax should be considered in every patient with COPD who has a sudden increase in shortness of breath, particularly if there is associated chest pain. The physical examination of a patient with a SSP is less helpful in establishing the diagnosis than it is in a patient with a PSP. Patients with underlying disease may already have hyperexpanded lungs, decreased tactile fremitus, a hyperresonant percussion note, and distant breath sounds over both lung fields. Accordingly,

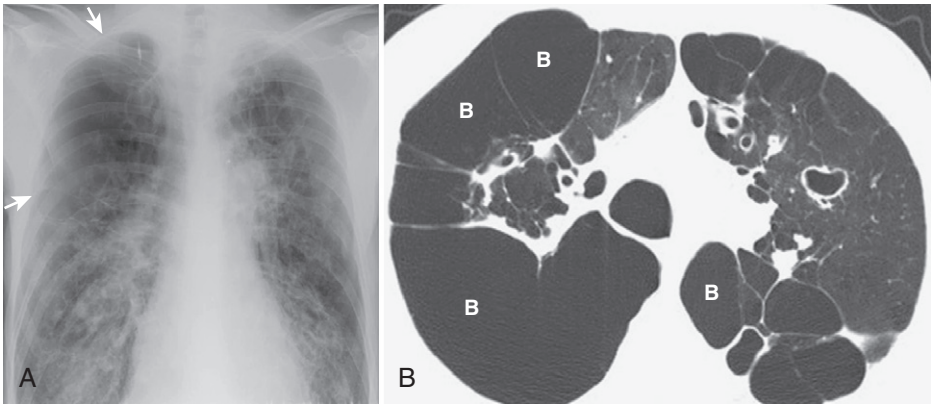

FIGURE 74-5 ■ **A,** Posteroanterior chest radiograph of a patient with cystic fibrosis and extensive bullous disease of the right apex that was initially mistaken for a pneumothorax. Note lucent area (*arrows*) within the right upper lung field. **B,** Computed tomography scan confirms the presence of bullae (B) and excludes pneumothorax. (Courtesy of Michael B. Gotway, MD, Scottsdale Medical Imaging and the Department of Radiology, University of California, San Francisco.)

when a pneumothorax develops, side-to-side differences in the physical examination may not be apparent.

The diagnosis of SSP is established by the demonstration of a pleural line on the chest radiograph. This line can be difficult to see in radiographs of patients with COPD because of their hyperlucent emphysematous lungs. Frequently, the presence of the pneumothorax is overlooked, particularly when the radiograph is overexposed. In patients with lung disease, the radiographic appearance of the pneumothorax can be altered by the underlying abnormalities. Areas of normal lung collapse more evenly and completely than do diseased areas with large bullae or severe emphysema, which have decreased elastic recoil and may trap gas.

It is important to distinguish a spontaneous pneumothorax from a large, thin-walled, air-containing bulla in patients with COPD. The apparent pleural line with a large bulla is usually concave toward the lateral chest wall because it represents the medial border of the bulla, whereas the pleural line with a pneumothorax is usually oriented convexly toward the lateral chest wall. At times, CT examination of the chest is necessary to make this differentiation (Fig. 74-5).

Recurrence Rates

The recurrence rates for SSPs are higher than those for PSPs if measures are not taken to prevent a recurrence. The recurrence rates are higher in those with SSP (~45%) than in patients with PSP (~30%) over a 3- to 5-year observation period.[12,22]

Treatment

Urgent evaluation is indicated for any patient suspected of having a SSP, because death has occasionally been reported before a chest tube can be inserted. Such deaths were reported in 3 of 57 patients (5%) with pneumothorax secondary to COPD[37] and in 3 of 15 patients (20%) with cystic fibrosis.[38] The high immediate mortality rate emphasizes that an important secondary treatment goal for these patients is reducing the likelihood of a recurrence.

The initial treatment for nearly every patient with a SSP should be tube thoracostomy. Simple aspiration is not recommended because it frequently is ineffective and cannot prevent recurrence. The evacuation of even a small pneumothorax can lead to a rapid improvement in symptoms. In patients requiring mechanical ventilation, a chest tube should be placed immediately because the pneumothorax is likely to enlarge during mechanical ventilation.

In those treated with tube thoracostomy, it is more difficult to expand the lung and air leaks persist longer in patients with SSP than in patients with PSP. In SSP caused by COPD, the median time for lung expansion is 5 days compared with 1 day for PSP,[37] and more patients require prolonged chest tube drainage. After 7 days of tube thoracostomy drainage, the lung remains unexpanded or the air leak persists in about 20% of patients with SSP.[37]

Following thoracostomy, most patients with SSP should be considered for thoracoscopy. Thoracoscopy should certainly be performed in patients with a persistent air leak or an unexpanded lung after 72 hours of tube thoracostomy. If the lung expands and the air leak ceases within the first 72 hours, an attempt should be made to prevent a recurrence. For preventing recurrences, thoracoscopy is superior to chemical pleurodesis (recurrence rates of about 5% vs. 20%, respectively).[12,22] If thoracoscopy is unavailable, chemical pleurodesis should be performed (as discussed earlier) to prevent a recurrent pneumothorax. Thoracotomy should be considered if air leak persists after 5 days and thoracoscopy is unavailable.

One consideration for patients with SSP is the effect that a pleurodesing agent might have on a future lung transplantation. In the past, prior attempts of ipsilateral pleurodesis excluded patients from lung transplantation due to the risk of excess bleeding. In 1998, however, a consensus conference statement on lung transplantation in cystic fibrosis stated that pleurodesis is not a

contraindication to lung transplantation.[39] However, pleurodesis is likely to make future lung transplantation more difficult, and consultation with a transplant surgeon is advisable.

Pneumothorax Secondary to *Pneumocystis* in Patients with AIDS

Patients with AIDS and *P. jirovecii* infection have a relatively high incidence of spontaneous pneumothorax. Approximately 5% of patients with AIDS who receive prophylactic pentamidine will have a spontaneous pneumothorax. Most patients with AIDS who have a spontaneous pneumothorax have a history of *P. jirovecii* infection, many are taking prophylactic pentamidine, and most have a recurrence of *P. jirovecii* infection.[1,34] The presence of multiple subpleural lung cavities, often associated with subpleural necrosis, may explain the high incidence of spontaneous pneumothorax.[1] Once such a patient has a pneumothorax, he or she is likely to experience a contralateral pneumothorax. It should be noted that iatrogenic pneumothoraces, particularly those related to mechanical ventilation or pulmonary procedures, are also common in patients with AIDS.[1,34]

Perhaps due to the necrotic lung surrounding the ruptured cavity, the spontaneous pneumothorax associated with AIDS and *P. jirovecii* infection is notoriously difficult to treat. In one report of 20 patients, the median duration of tube thoracostomy was 20 days; 11 patients underwent pleurodesis, whereas 5 patients had thoracotomy.[40]

Patients with AIDS and a spontaneous pneumothorax should be treated with tube thoracostomy. If the air leak persists for more than a few days, there are two options: a Heimlich valve or VATS. The intrapleural injection of a pleurodesing agent has not been shown to be effective in expediting closure of the leak. In general, the Heimlich valve is preferred because the patient can be managed as an outpatient.

If the patient cannot be managed with a Heimlich valve because the airflow through the bronchopleural fistula is too high, VATS can be performed. Wait[41] reported that 30 of 32 patients with AIDS and spontaneous pneumothorax were managed successfully with talc insufflation without endo-stapling. If operative intervention is planned, it should be carried out early to avoid prolonged air leak, hospitalization, and morbidity.

Pneumothorax Secondary to Tuberculosis

Between 1% and 3% of patients hospitalized for pulmonary tuberculosis will have a pneumothorax.[42] All such patients should be treated initially with tube thoracostomy. In one series of 28 patients, 7 of the 11 patients treated by observation or repeated pleural aspiration died,[42] compared with 1 of the 17 patients treated with tube thoracostomy (64% vs. 6%, respectively). Antituberculous chemotherapy should be given concomitantly with the tube thoracostomy. Thoracotomy should not be considered until the patient has received antituberculous chemotherapy for at least 6 weeks.

IATROGENIC PNEUMOTHORAX

Iatrogenic pneumothoraces are probably more common than PSPs and SSPs combined. In a study of 3430 patients in 12 intensive care units in France, 3.0% developed a pneumothorax.[43] The etiologies of the pneumothoraces in this study were mechanical ventilation in 42, central venous catheters in 28, thoracentesis in 21, and miscellaneous in 3.[43]

Currently, the leading cause of iatrogenic pneumothorax is transthoracic needle aspiration. The incidence of iatrogenic pneumothorax with this procedure is about 25%, and about 10% of the patients with pneumothorax receive tube thoracostomy.[1] This procedure is more likely to result in a pneumothorax if the patient has COPD, if the lesion is deep within the lung, or if the angle of the needle route is wide.[44,45] Various maneuvers such as positioning the patient with the biopsied side down or using the blood patch technique have not proved useful in diminishing the incidence of pneumothorax. A recent paper did demonstrate a significant reduction in pneumothoraces if the puncture access was sealed by instillation of NaCl 0.9% solution during extraction of the guide needle.[46]

Mechanical ventilation is another risk factor. In one early series of 553 patients undergoing mechanical ventilation, 4% developed a pneumothorax.[47] The frequency of the pneumothorax was increased if the patient had aspiration pneumonia (37%), was treated with positive end-expiratory pressure (15%), had intubation of the right main-stem bronchus (13%), or had COPD (8%).[47] In another study, the incidence of pneumothorax in 725 patients with acute respiratory distress syndrome was 6.9%.[48] In patients with acute respiratory distress syndrome, the incidence of barotrauma is higher if the ventilator plateau pressure exceeds 35 cm H_2O or if the lung compliance is below 30 mL/cm H_2O.

Other common causes of iatrogenic pneumothorax (with approximate incidences) are thoracentesis (2.5%), pleural biopsy (8%), and transbronchial lung biopsy (6%). Iatrogenic pneumothorax also frequently complicates cardiopulmonary resuscitation. Other procedures associated with the development of an iatrogenic pneumothorax include subclavian or internal jugular vein catheterization, tracheostomy, intercostal nerve block, mediastinoscopy, liver biopsy, and the insertion of small nasogastric tubes.[1] Radiofrequency ablation is increasingly used to treat lung tumors and carries a high incidence of pneumothorax (~30%).[49,50] In a series of 137 procedures, 27 resulted in symptomatic pneumothoraces requiring chest tube drainage.[51] In another series, the risks of pneumothorax was associated with the number of tumors ablated, electrode positions, and the electrode trajectory through aerated lung.[50]

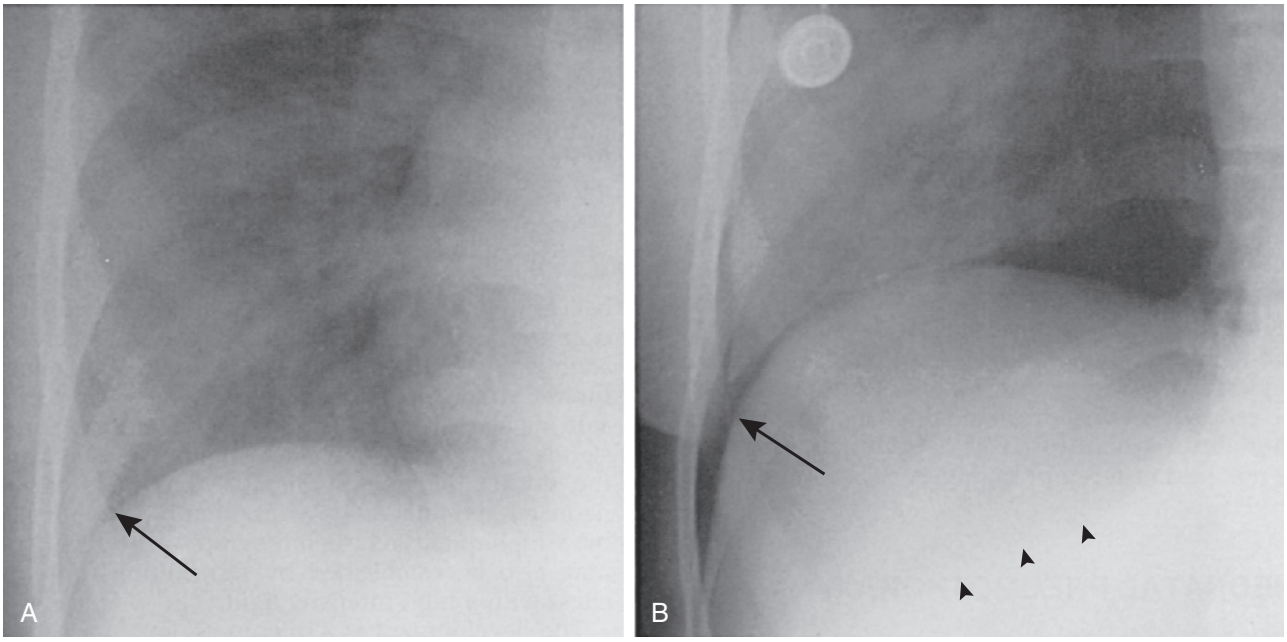

FIGURE 74-6 ■ Detailed views of the right costophrenic angle from successive supine chest radiographs taken before **(A)** and after **(B)** the development of a pneumothorax. Both illustrations show diffuse infiltrations in the right lower lung field. Note change in costophrenic angles (*arrows*) caused by air in the pleural space between the diaphragm and chest wall: the "deep sulcus" sign. Air in the anterior pleural space can also be recognized by an air-tissue interface (*arrowheads*).

Diagnosis

Iatrogenic pneumothorax should be suspected in any patient treated by mechanical ventilation whose clinical condition suddenly deteriorates. A sensitive indicator of the development of a pneumothorax in such patients is increased peak and plateau pressures if the patient is on a volume-cycled ventilator or a decreased tidal volume if the patient is on a pressure-cycled ventilator. The diagnosis should also be suspected in any patient who becomes more dyspneic after a medical or surgical procedure that is known to be associated with the development of a pneumothorax. It should be emphasized that symptoms from the pneumothorax may not be evident for 24 hours or longer after the procedure.[52] The diagnosis is readily confirmed by a chest radiograph. In patients with extensive pulmonary infiltrates, there may be little evidence of lung collapse, but the air in the pleural space may instead be indicated by the "deep sulcus" sign (Fig. 74-6).

Treatment

The treatment of iatrogenic pneumothorax differs from that of spontaneous pneumothorax in that preventing recurrence is not an issue. If the patient has at most minimal symptoms and the pneumothorax occupies less than 15% of the volume of the hemithorax, the patient can be observed. The administration of supplemental oxygen increases resolution (see previous section). If the patient has more than minimal symptoms or if the pneumothorax occupies more than 15% of the hemithorax, the procedure of choice is simple aspiration with a plastic catheter,[53] as described for PSP. If simple aspiration fails, tube thoracostomy should be performed. Small-bore chest tubes with Heimlich valves are quite effective in this situation.[54]

The management of patients with an iatrogenic pneumothorax secondary to positive-pressure mechanical ventilation should include tube thoracostomy to prevent the development of a tension pneumothorax. In a patient on positive pressure ventilation, tension pneumothorax can easily develop because the positive pressure during inspiration forces air into the pleural space under high pressure until it soon exceeds atmospheric pressure. If the patient continues to receive mechanical ventilation, the chest tube should be left in place for at least 48 hours after the air leak stops. At times, a bronchopleural fistula is so large that a high percentage of the total inspired volume exits through the chest tube. The air exiting through the chest tube still provides effective ventilation, however, because it contains levels of carbon dioxide similar to those of exhaled gas.[55] Although the use of high-frequency ventilators has been recommended in this situation, two studies in adults[56,57] have demonstrated that high-frequency ventilation does not consistently improve gas exchange or decrease the flow through the fistula.

TRAUMATIC (NON-IATROGENIC) PNEUMOTHORAX

The incidence of pneumothorax after blunt trauma depends on the severity of the trauma. The incidence of pneumothorax has exceeded 35% in some series.[58]

Mechanism

A traumatic pneumothorax can result from either penetrating or nonpenetrating chest trauma. With penetrating chest trauma, the wound allows air to enter the pleural space via the chest wall or via the visceral pleura from the tracheobronchial tree. With nonpenetrating trauma, a pneumothorax may develop if the visceral pleura is lacerated secondary to a rib fracture or dislocation. In the majority of patients with pneumothorax secondary to nonpenetrating trauma, however, there are no associated rib fractures. It is thought that the sudden chest compression abruptly increases the alveolar pressure, which may cause alveolar rupture. Air then enters the interstitial space and dissects toward either the visceral pleura or the mediastinum. A pneumothorax develops when either the visceral or the mediastinal pleura ruptures, allowing air to enter the pleural space.

Diagnosis and Treatment

The diagnosis of pneumothorax is made by the chest radiograph or the chest CT. A pneumothorax that is apparent on the chest CT, but not on the chest radiograph, is called an *occult* pneumothorax.[1] About 40% of traumatic pneumothoraces are occult.[59] In recent years ultrasonography performed by emergency room physicians or surgeons has been used increasingly to determine whether a pneumothorax is present.[59] Ultrasound is more sensitive that supine chest radiographs in identifying pneumothoraces,[59] but false positives are known to occur, especially in patients with underlying lung diseases (especially COPD).[60] (For additional information on ultrasonography, see Chapter 20.)

Most traumatic pneumothoraces should be treated initially with tube thoracostomy. If the patient has an occult pneumothorax or if the distance between the lung and chest wall does not exceed 1.5 cm, however, tube thoracostomy is probably not indicated unless the patient is receiving mechanical ventilation.[61] In one series, 333 patients with pneumothoraces less than 1.5 cm were initially managed without chest tubes, and only 33 (10%) subsequently required tube thoracostomy.[61] When traumatic pneumothoraces are treated with tube thoracostomy, the lung usually expands and the air leak ceases within 24 hours.[61] If the leak persists for more than a few days, consideration should be given to performing thoracoscopy to identify and repair the site of the air leak.[62]

Immediate thoracotomy is indicated for two uncommon diagnoses in any patient with a traumatic pneumothorax. The first diagnosis is fracture of the trachea, or a major bronchus, which usually occurs in the presence of an anterior or lateral fracture of one or more of the first three ribs. Most patients will have at least some hemoptysis.[63] Therefore, in patients with a traumatic pneumothorax, the presence of a large pneumothorax with continued leakage of air into the pleural space after tube thoracostomy, a fracture of one or more of the first three ribs, or hemoptysis should serve as an indication for fiberoptic bronchoscopy to assess the possibility of a bronchial tear.[63] Primary surgical repair of the tear usually results in full restoration of function of the distal lung.[63]

The second diagnosis to consider is traumatic rupture of the esophagus, which is almost always accompanied by a hydropneumothorax. A reliable screening test for esophageal rupture is measurement of the pleural fluid amylase concentration.[64] If this level is elevated, contrast radiographic studies of the esophagus should be performed. It is important to establish the diagnosis of esophageal rupture expeditiously because the mortality approaches 100% if surgical treatment is not performed promptly.

Air Travel and Pneumothorax

For patients who have suffered a pneumothorax, the Aerospace Medical Association suggests that flying be allowed 2 to 3 weeks after radiologic resolution of the pneumothorax.[65] One study of 12 patients with traumatic pneumothorax reported that the 10 patients who waited at least 14 days before travel were all asymptomatic in-flight, whereas 1 of 2 patients who flew earlier than 14 days developed respiratory distress in-flight with symptoms suggesting a recurrent pneumothorax.[66]

NEONATAL PNEUMOTHORAX

A spontaneous pneumothorax is present shortly after birth in 1% to 2% of all infants, and the pneumothorax is symptomatic in approximately half of these.[17,67] The incidence of spontaneous neonatal pneumothorax is twice as high in male as in female infants. Affected infants are usually full- or post-term.[17] Usually, the infant has a history of fetal distress requiring resuscitation or a difficult delivery with evidence of aspiration of meconium, blood, or mucus.[17]

There is a high incidence of pneumothorax in infants with neonatal respiratory distress syndrome. In one series of 295 newborn infants with the syndrome, 19% had a pneumothorax.[68] Pneumothorax developed in 29% of those requiring intermittent positive-pressure ventilation with positive end-expiratory pressure, in 11% of those requiring continuous positive airway pressure (CPAP), and in only 4% of those not requiring respiratory assistance.[68] In a series of 26,007 babies with birth weights between 401 and 1500 g born in 1999, the incidence of pneumothorax was 6.3%, but, in babies weighing less than 750 g, the incidence was 15%.[69]

Pathogenesis

The development of a spontaneous neonatal pneumothorax is related to the mechanical problems of expanding the lung for the first time. During the first few breaths of life, the transpulmonary pressures average 40 cm H_2O, with occasional pressures as high as 100 cm H_2O.[1] At birth, the alveoli usually open in rapid sequence, but, if bronchial obstruction is present from the aspiration of blood, meconium, or mucus, high transpulmonary pres-

sures may lead to rupture of the lung. A transpulmonary pressure of 60 cm H_2O ruptures an adult lung,[17] whereas a transpulmonary pressure of 45 cm H_2O ruptures a neonatal rabbit lung.[1]

Clinical Manifestations

With neonatal spontaneous pneumothorax, the signs vary from none to severe acute respiratory distress, depending on the size of the pneumothorax. With a small pneumothorax, there may be mild apneic spells with some irritability or restlessness. With a large pneumothorax, there may be severe respiratory distress with marked tachypnea, grunting, retractions, and cyanosis.[17] In newborn babies, the detection of pneumothorax by physical examination is often difficult because breath sounds are widely transmitted in the small neonatal thorax from the contralateral lung. The most reliable sign is a shift of the apical heart impulse away from the side of the pneumothorax.[17] The diagnosis of neonatal spontaneous pneumothorax is confirmed by a high-quality chest radiograph.

The development of a pneumothorax in a patient with neonatal respiratory distress syndrome is usually heralded by a change in the vital signs. In one series of 49 patients, cardiac arrest marked the development of the pneumothorax in 12 patients (24%); most of the other patients had a decrease in the blood pressure, pulse, or respiratory rate.[68] In another series, however, the earliest signs were an increase in the blood pressure, heart rate, or pulse pressure.[70] A pneumothorax in an infant with the neonatal respiratory distress syndrome is associated with mortalities exceeding 60% in some studies.

Treatment

An infant with a spontaneous pneumothorax who is asymptomatic or mildly symptomatic can be observed closely because the pneumothorax will usually resolve within a few days. It is necessary to observe the patient closely in case the pneumothorax enlarges or a tension pneumothorax develops.[17] Supplemental oxygen can hasten the resolution of the pneumothorax, but it should be administered with care because of the dangers of retrolental fibroplasia.[17] Tube thoracostomy should be performed on any neonate who is more than mildly symptomatic. One study demonstrated that 18-gauge venous catheters were comparable to 12-French chest tubes in managing pneumothorax in neonates.[71] Tube thoracostomy should be performed in virtually all infants with the neonatal respiratory distress syndrome and pneumothorax, because the pneumothorax further compromises the ventilatory status of the patient and tends to increase in size.

CATAMENIAL PNEUMOTHORAX

A catamenial pneumothorax is a pneumothorax that occurs in conjunction with menstruation (Fig. 74-7). Up until 2004, 229 cases had been reported.[72] However, catamenial pneumothorax is probably underdiagnosed and underreported. With catamenial pneumothorax, respiratory symptoms usually develop within 24 to 48 hours of the onset of the menstrual flow.[73] Most pneumothoraces are right sided, but left-sided and bilateral pneumothoraces have been reported.[73] Catamenial pneumothoraces tend to be recurrent. On average, patients have about five pneumothoraces before the diagnosis is recognized.

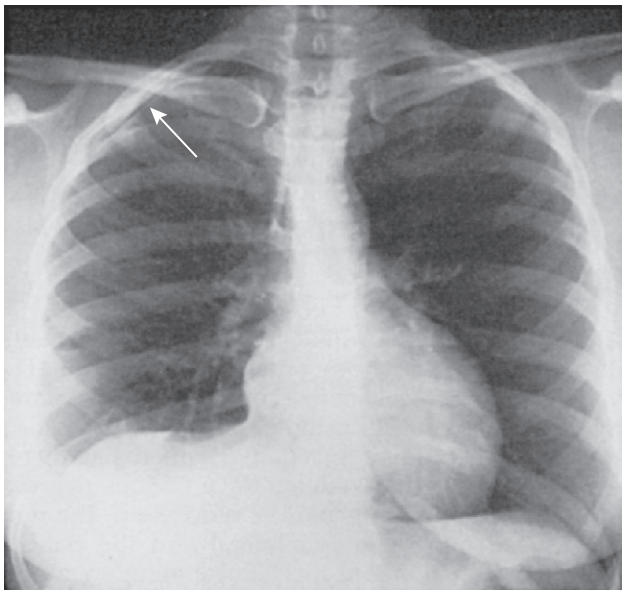

FIGURE 74-7 ■ Posteroanterior chest radiograph from a 32-year-old woman showing a small right-sided pneumothorax (*arrow*). This was the fourth episode with onset during menses. (Courtesy of Dr. Louis S. Lehman, San Francisco.)

Pathogenesis

The pathogenesis of catamenial pneumothorax is not definitely established. When the syndrome was initially described by Maurer and colleagues,[74] it was hypothesized that air gained access to the peritoneal cavity during menstruation and then entered the pleural cavity through a diaphragmatic defect. In a subsequent review of 18 patients who had undergone thoracotomy, however, diaphragmatic defects were demonstrable in only three, whereas six had pleural or diaphragmatic endometriosis.[75] However, in a more recent series of eight cases in which a careful thoracoscopic examination was performed, diaphragmatic abnormalities were detected in all; four patients had both diaphragmatic defects and endometriosis, three patients had only diaphragmatic endometriosis, and one patient had only a diaphragmatic defect.[76] It has been suggested that, with diaphragmatic endometriosis, the endometrial tissue undergoes cyclical necrosis leading to a diaphragmatic defect.[77] These authors concluded that diaphragmatic abnormalities play a fundamental role in the pathogenesis of catamenial pneumothorax.[77]

Diagnosis and Treatment

Any woman who has a spontaneous pneumothorax within the first 48 hours of her menstrual period should be suspected of having a catamenial pneumothorax. The treatment of catamenial pneumothorax is aimed at treating endometriosis, known or suspected, by suppressing the ectopic endometrium. This can be attempted by suppression of ovulation with oral contraceptives or by suppression of gonadotropins with danazol or gonadotropin-releasing hormone to produce a medical oophorectomy.[72] However, these measures are effective in less than 50% of patients.[72] Alternative treatments include thoracoscopy with stapling of blebs, closure of diaphragmatic defects and parietal abrasion or pleurectomy, or pleurodesis.[72]

TENSION PNEUMOTHORAX

A tension pneumothorax is present when the intrapleural pressure exceeds the atmospheric pressure throughout expiration and often during inspiration as well.[1] Most patients who develop a tension pneumothorax are receiving positive pressure to their airways, either during mechanical ventilation or during resuscitation.[1] For a tension pneumothorax to develop in a spontaneously breathing person, some type of one-way valve mechanism must be present so more air enters the pleural space on inspiration than leaves the pleural space on expiration, so air accumulates in the pleural space under positive pressure.[1]

Pathophysiology

The development of a tension pneumothorax is usually heralded by a sudden deterioration in the cardiopulmonary status of the patient. The explanation for this sudden deterioration is probably related to the combination of a decreased cardiac output due to impaired venous return and profound hypoxia due to ventilation-perfusion mismatches. In mechanically ventilated sheep, an induced tension pneumothorax (mean pleural pressure of +25 cm H_2O) reduced the cardiac output from 3.5 to 1.1 L/min.[78] The arterial P_{O_2} also fell from a baseline value of 159 to 59 mm Hg. Comparable reductions in cardiac output and oxygen saturation were seen in pigs[79] and in dogs[80] following induction of tension pneumothoraces. Similarly, in patients on mechanical ventilation who develop tension pneumothorax, there is a large drop in the cardiac output.[81]

Clinical Manifestations

Patients most commonly have a tension pneumothorax while they are receiving positive-pressure mechanical ventilation, during cardiopulmonary resuscitation,[82] or as a complication of hyperbaric oxygen therapy.[1] Occasionally, a tension pneumothorax will evolve during the course of a spontaneous pneumothorax. Tension pneumothorax can develop from improper connection of one-way flutter valves with small-caliber chest tubes.[83]

The clinical picture associated with the development of a tension pneumothorax is striking. The patient appears distressed, with rapid labored respirations, cyanosis, marked tachycardia, and profuse diaphoresis. The physical findings are those of a very large pneumothorax. Arterial blood gases reveal marked hypoxemia and sometimes respiratory acidosis.

Tension pneumothorax should be suspected in patients receiving mechanical ventilation who suddenly deteriorate. In this situation, the peak pressures on the ventilator usually increase markedly if the patient is on volume-type ventilation, whereas the tidal volumes decrease markedly if the patient is on pressure-support ventilation.[1] Tension pneumothorax should also be suspected in any patient undergoing cardiopulmonary resuscitation in whom ventilation becomes difficult. In one series of 3500 autopsies, an unsuspected tension pneumothorax was found in 12 cadavers; 10 of these had received mechanical ventilation, and 9 had undergone cardiopulmonary resuscitation.[84] Tension pneumothorax should also be suspected in patients with a known pneumothorax who deteriorate suddenly or in patients who have undergone a procedure known to cause a pneumothorax.

Diagnosis and Treatment

A tension pneumothorax is a medical emergency. One should not waste time trying to establish the diagnosis of tension pneumothorax radiologically because the clinical situation and the physical findings usually strongly suggest the diagnosis.[1] The patient should immediately be given high-flow supplemental oxygen to alleviate the hypoxia. Once the abnormal hemithorax is identified, a large-bore (14- to 16-gauge) catheter with needle should be immediately inserted into the pleural space through the second anterior intercostal space.[1] After the catheter and needle are inserted into the chest, the needle is removed and a large syringe containing a few milliliters of sterile saline is attached to the indwelling catheter. The plunger is then pulled out of the syringe. If air bubbles through the saline after withdrawing the plunger, the diagnosis of tension pneumothorax is established. If the fluid enters the pleural space from the syringe, the patient does not have a tension pneumothorax and the catheter should be removed.

If the procedure just described confirms the diagnosis of a tension pneumothorax, the catheter should be left in place and in communication with the atmosphere until air ceases to exit through the syringe. Additional air can be withdrawn from the pleural space with the syringe and the three-way stopcock. The patient should be prepared for immediate tube thoracostomy.

REEXPANSION PULMONARY EDEMA

Unilateral pulmonary edema (*reexpansion pulmonary edema*) may develop in certain patients whose lung has

rapidly reinflated after a period of collapse secondary to a pneumothorax or a pleural effusion. Patients with reexpansion pulmonary edema have various degrees of hypoxia and hypotension. On occasion, the pulmonary edema becomes bilateral, and the patient requires intubation and mechanical ventilation. On rare occasions, the syndrome is fatal; the seriousness of the syndrome is emphasized by the fact that it has been fatal in otherwise healthy, young persons. Although the incidence of reexpansion pulmonary edema is not known, it is probably relatively low because there were no instances of reexpansion pulmonary edema in the Veterans Administration cooperative study of more than 200 patients with spontaneous pneumothorax.[22] In a retrospective study of 320 episodes of pneumothorax, reexpansion pulmonary edema occurred in 3 patients (1.0%).[85] A literature review in 1988 revealed 53 cases of reexpansion pulmonary edema that was fatal in 11 (21%) cases.[86] This is likely an overestimation as nonfatal cases are less likely to be reported and many patients can be asymptomatic.[86a]

Pathophysiology

Reexpansion pulmonary edema appears to be due to increased permeability of the pulmonary vasculature. In both experimental animals and humans, the edema fluid has a high protein content, suggesting that edema forms due to increased capillary leak rather than increased hydrostatic pressure. It has been hypothesized that the mechanical stresses applied to the lung during reexpansion damage the capillaries and lead to pulmonary edema. Reperfusion injury due to reactive oxygen species (ROS) is another possibility. However, several animal studies[87-90] demonstrated that the administration of ROS-scavenging compounds such as dimethylthiourea, catalase, or superoxide dismutase all partially inhibit the neutrophilic infiltration associated with the development of reexpansion pulmonary edema, but do not impressively decrease the amount of edema in the experimental situation. Moreover, neutrophil depletion does not affect the amount of edema.

In humans, most cases of reexpansion pulmonary edema develop when the pneumothorax or pleural effusion has been present for at least 3 days and when negative pressure has been applied to the pleural space. Similar findings have been confirmed in experimental animal studies.

Clinical Manifestations

Patients with reexpansion pulmonary edema typically have pernicious coughing or chest tightness during or immediately after tube thoracostomy or thoracentesis. The symptoms usually progress for 12 to 24 hours, and serial chest radiographs reveal progressive ipsilateral pulmonary edema, which may progress to involve the contralateral lung. Treatment is primarily supportive, with the administration of supplemental oxygen and diuretics, and intubation and mechanical ventilation when necessary. One report suggested that the syndrome could be aborted if the patient is treated with CPAP within the first hour of the development of the syndrome.[90] Chest tubes should be placed to underwater-seal drainage if the syndrome develops.

Prevention

Because reexpansion pulmonary edema can be fatal, it is important to prevent it when possible. The possibility of its development should be considered in any patient with a large pneumothorax or pleural effusion subjected to tube thoracostomy or thoracentesis. When tube thoracostomy is performed for spontaneous pneumothorax, the tubes should initially be connected to an underwater-seal drainage apparatus rather than to negative pleural pressure. If underwater-seal drainage does not cause reexpansion of the underlying lung within 24 to 48 hours, then negative pressure can be applied to the pleural space.[1]

When a thoracentesis is performed, the procedure should be terminated if the patient develops tightness of the chest or experiences coughing. In a series of 941 thoracenteses, including 119 that drained more than 1500 mL, infiltrates consistent with reexpansion pulmonary edema were noted in only two patients (0.2%) from whom 1000 and 1200 mL of pleural fluid had been removed: neither was symptomatic or required treatment.[91]

CHYLOTHORAX

Pleural fluid can be milky or turbid. When this cloudiness persists after centrifugation, it is almost always due to high lipid content in the pleural fluid. High levels of lipid can accumulate in pleural liquid through two separate mechanisms. In one, chyle enters the pleural space following disruption of the thoracic duct, producing a chylothorax or chylous pleural effusion. In the second, large amounts of cholesterol or lecithin-globulin complexes accumulate in a pleural effusion to produce a pseudochylothorax or chyliform pleural effusion.[92] It is important to recognize and differentiate these two conditions because their etiology and management are completely different.

Pathophysiology

A chylothorax forms when the thoracic duct, which carries dietary fat in the form of chylomicrons, becomes disrupted. Chylomicrons are formed in the intestine, after which they enter the intestinal lacteal vessels and are then transported to the cisterna chyli. The thoracic duct leaves the cisterna chyli and passes through the aortic hiatus of the diaphragm on the anterior surface of the vertebral body between the aorta and the azygos vein into the posterior mediastinum. The thoracic duct then ascends extrapleurally in the posterior mediastinum along the right side of the anterior surface of the vertebral column. Between the level of the fourth and sixth thoracic vertebrae, the duct crosses to the left side of the vertebral column and continues cephalad to enter

the superior mediastinum between the aortic arch and the subclavian artery and the left side of the esophagus. As a result, rupture of the thoracic duct below the sixth thoracic vertebrae tends to produce right-sided chylothoraces, and rupture of the ascending duct above the sixth thoracic vertebra tends to produce left-sided chylothoraces.[92] Once the thoracic duct passes the thoracic inlet, it arches above the clavicle and passes anterior to the left subclavian artery, vertebral artery, and thyrocervical trunk to terminate in the region of the left jugular and subclavian veins.

Although the route just described is the typical one, there are wide anatomic variations throughout the course of the duct. For example, duplication or even triplication of the thoracic duct is present in 40% of the population. Also, many collateral vessels and lymphaticovenous anastomoses are known to exist. Presumably these channels transport the chyle to the blood following therapeutic ligation of the thoracic duct.

Chyle, the liquid drained from the thoracic duct, is a milky, opalescent fluid that usually separates into three layers on standing: a creamy uppermost layer containing chylomicrons, a milky intermediate layer, and a dependent layer containing cellular elements. Chyle is bacteriostatic,[92] is not irritating, and seldom induces pleural thickening.

The thoracic duct normally conveys between 1500 and 2500 mL of chyle daily. Ingestion of fat can increase the flow of lymph in the thoracic duct by 2- to 10-fold for several hours. Ingestion of liquid, but not protein or carbohydrate, also increases the flow, whereas starvation decreases chyle flow. The primary cellular component of chyle is the T lymphocyte. Prolonged loss of chyle can result in severe nutritional depletion, dehydration, electrolyte loss, and hypolipidemia as well as depletion of T- and B-cell lymphocytes and immunodeficiency.[92]

Etiology

Chylothorax can result from traumatic (including surgical) and nontraumatic causes: their relative frequencies vary among series. In a summary of five separate series totaling 143 patients, greater than 50% of chylothoraces were caused by tumors, especially lymphoma, followed by trauma.[1] However, a single institute series of 203 patients revealed trauma/surgery as the most common (50%) cause compared to nontraumatic causes (44%).[93] Idiopathic chylothorax accounts for 5% to 10% of cases.

The unpredictable anatomy of the thoracic duct and associated accessory lymphatics makes them vulnerable to injury during cardiovascular or thoracic surgical procedures, especially those involving the posterior mediastinum. Esophagectomy, for example, is complicated by chylothorax in 1% to 4% of cases.[94] Overall, the incidence of chylothorax after cardiothoracic operations is generally low (0.5% to 2.5%[95,96]). Surgical procedures that involve mobilization of the left subclavian artery are particularly likely to be complicated by chylothorax. Transplantation of the lung and heart (or both) can sever the lymphatic drainage and result in chylothoraces.[97] Chylothorax has been reported as a complication of a wide range of other operations, including esophagoscopy, stellate ganglion blockade, thoracic sympathectomy, high translumbar aortography, lung resections, thyroid surgery, and spinal surgery.[1] Bilateral chylothoraces can develop following bilateral neck dissection.[98] In the pediatric setting, chylothorax is particularly common after surgical repair of congenital diaphragmatic hernia (up to 10% of cases) and is usually left-sided.[99]

To aid in the identification of the thoracic duct during surgery, ingestion of cream (to increase the flow and size of the thoracic duct) before high-risk operations (e.g., esophagectomy) has been advocated.[100]

Nonsurgical trauma can also lead to chylothorax. The thoracic duct may be disrupted with penetrating injuries involving the neck or thorax. Nonpenetrating trauma in which the spine is hyperextended or a vertebra is fractured can lead to chylothorax, particularly if the injury occurs shortly after the ingestion of a fatty meal. Less impressive traumas such as weight lifting, straining, severe bouts of coughing or vomiting, childbirth, and vigorous stretching while yawning have been associated with chylothorax.[92] Chylothoraces secondary to closed trauma are usually on the right side, with the site of rupture in the region of the 9th or 10th thoracic vertebra.

Chylothoraces can also arise from transdiaphragmatic movement of chylous ascites,[101] as shown by radioisotope studies. Causes of chylous ascites include many of the causes of chylothorax. In addition, cirrhosis may be a cause of chyloascites and associated chylothorax. These chylothoraces are transudative, probably from dilution by low-protein cirrhotic ascitic fluid.

There are many other causes of chylothorax, but altogether they account only for a small percentage of all chylothoraces. Pulmonary lymphangioleiomyomatosis is discussed later in this chapter (see also Chapter 62).[102] Other disease entities associated with chylothorax are abnormalities of the lymphatic vessels, such as pulmonary lymphangiectasis, yellow nail syndrome, lymph node enlargement, mediastinal fibrosis, lymphangitis of the thoracic duct, tuberous sclerosis, amyloidosis, and Gorham's syndrome. Elevated pressure of the venous system into which the thoracic duct drains (e.g., superior vena caval or subclavian vein thrombosis/obstruction) is another cause of chylothorax.[92] In postsurgical patients, those with central venous thrombosis were five times more likely to develop chylothorax.[103] Chylothorax accounts for about one fifth of pleural effusions in patients with superior vena cava syndrome.[104]

Chylothorax with no identifiable cause is labeled *idiopathic*. Lymphoma, however, must be excluded.

Fetal and Neonatal Chylothorax

Fetal chylothorax is an uncommon but important condition that requires monitoring and management to avoid serious complications, including spontaneous abortion or death after birth.[105] Fetal chylothoraces are often termed *primary* fetal pleural effusions, as no obvious cause can be identified in most cases.[105] Congenital

lymphangiectasis is a rare condition that can produce fetal chylothorax.[106] Cytogenetic analysis of the cells (mainly lymphocytes) may help detect underlying chromosomal abnormalities.

Chylothorax is the most common type of neonatal pleural effusion.[105] It may be a result of persistent fetal chylothorax,[105] but can also be due to rupture of the thoracic duct from trauma during delivery, or to developmental abnormalities of the thoracic duct.[107] Increased venous pressure, especially from congenital heart diseases or from thrombosis of central venous catheters, is another recognized mechanism of neonatal chylothorax.[105] In many cases, the chylothorax is idiopathic. Of note, the pleural fluid remains clear rather than milky until milk feeding begins.[105]

Several molecules have been implicated in the development of chylothorax based on preclinical studies. The integrin $\alpha_9\beta_1$ is widely expressed in smooth muscles and is a receptor for extracellular matrix proteins and vascular cell adhesion molecule-1. Animal studies suggested that the α_9 subunit is required for the normal development of the lymphatic system, including the thoracic duct. Mice with homozygous null mutation of the α_9 subunit develop large bilateral congenital chylothoraces.[108] Vascular endothelial growth factor (VEGF)-C and -D were important in tumor-related lymphangiogenesis and chyloascites formation in mice bearing ovarian carcinoma. Chy-3–mutant mice, which carry a chromosomal deletion that includes VEGF-C, develop hypoplastic dermal lymphatic drainage and resultant chyloascites and lymphedema.[109] Another strain of transgenic mice with mutations in the *Pi3kca* (phosphoinositide 3-kinase) gene also develop defective lymphatics and chyloascites.[110]

Clinical Manifestations

The symptoms, physical findings, and radiographic features of chylothorax are the same as those encountered in patients with comparably sized pleural effusions of any cause. Pleuritic chest pain and fever are rare because chyle is not proinflammatory. Concurrent chylopericardium or chyloascites can occur.

With nontraumatic chylothorax, insidious onset of dyspnea on exertion is common. With traumatic chylothorax, there is usually a latent period of 2 to 10 days between the trauma and the clinical presentation of the pleural effusion.[111] During this latent period, chyle may accumulate in the posterior mediastinum to form a chyloma—visible radiologically as a posterior mediastinal mass[1]—which eventually ruptures into the pleural cavity, giving rise to a chylothorax.

Neonatal chylothorax may present with respiratory distress in the first few days of life. Fifty percent of the infants have symptoms within the first 24 hours, whereas 75% have symptoms by the end of the first week. Most neonatal chylothoraces are either right-sided or bilateral; only rarely are they left-sided.[107] There is a high frequency of neonatal chylothoraces in infants with hydramnios.[107] Fetal chylothorax is often diagnosed only on ultrasonography.

The main threat to life with chylothorax is inanition from malnutrition if the chyle is drained externally. The daily loss of 1.5 to 2.5 L of fluid rich in protein, fats, electrolytes, and lymphocytes will rapidly render patients malnourished and immunocompromised.

Diagnosis

The distinctive white, odorless, milky appearance should suggest the diagnosis, though chylothorax must be differentiated from empyema and pseudochylothorax. In empyema, the milky appearance is caused by suspended leukocytes and debris, which will sediment upon centrifugation, leaving a clear supernatant. In chylous and chyliform pleural effusions, the milky appearance is caused by high lipid levels and the supernatant will remain cloudy after centrifugation. The lipids in chyliform effusion are cholesterol or lecithin-globulin complexes rather than chylomicrons (as in chylothoraces).[112] It should be emphasized that the pleural fluid with chylothorax can occasionally be bloody or even clear yellow.

Pleural fluid and serum triglyceride and cholesterol levels should be measured. Patients who have a chylothorax usually have a pleural fluid triglyceride level above 110 mg/dL (1.24 mmol/L), a ratio of the pleural fluid to the serum triglyceride of greater than 1.0, and a ratio of the pleural fluid to the serum cholesterol of less than 1.0.[101] However, it should be remembered that fasting may significantly reduce the triglyceride level in the pleural fluid and produce false-negative results.[112a] If doubt persists after the lipid measurements, one approach is to feed the patient a high-fat meal before sampling the pleural fluid. Alternatively, the demonstration of chylomicrons in lipoprotein analysis of the pleural fluid confirms the diagnosis of chylothorax.[113] The latter is particularly valuable if the triglyceride level is in the equivocal range (50 to 110 mg/dL). It is important to differentiate chylous from chyliform pleural fluid (see later).

Typical chylous effusions are lymphocyte-rich effusions with exudative protein levels but low lactate dehydrogenase (LDH). The electrolyte composition of chyle is similar to that of serum, and the protein content is usually around 3 g/dL. Transudative chylothorax is usually due to concurrent conditions (especially hepatic cirrhosis) known to produce transudates. An elevated LDH in chylothorax should raise concerns of concurrent conditions (e.g., infection).[114] Magnetic resonance imaging (MRI) can confirm the high fat density of the pleural effusion and may support the diagnosis of chylothorax.

After establishing the diagnosis of a chylothorax, it is important to determine the cause. Because lymphoma is the most common (and treatable) cause of nontraumatic chylothorax, CT of the mediastinum and abdomen is mandatory to search for lymphadenopathy and is also useful in the diagnosis of lymphangioleiomyomatosis.

Bipedal lymphangiography or lymphoscintigraphy (e.g., with technetium-99m–labeled human serum albumin) is useful to help pinpoint the site of chyle leak along the thoracic duct.[115-117] Combination of

lymphoscintigraphy with three-dimensional MRI can provide additional anatomical and functional details of the lymphatic channels.[118]

It should be emphasized that examination of the pleura is unlikely to provide insight to the etiology of the chylothorax. Hence, pleural biopsy or thoracoscopy is not usually indicated in the workup of patients with a chylothorax.

Treatment

General Approaches

Management strategies for chylothoraces should be directed toward (1) maintaining nutrition and reducing the flow of chyle, (2) relieving dyspnea by removing the chyle, and (3) closure of the defect (Table 74-1).

Maintaining Nutrition and Reducing the Flow of Chyle. The main dangers to the patient are malnutrition and immunodeficiency from removal of a large volume of chyle; hence it is important to initiate definitive treatment of the chylothorax promptly.

Regardless of the cause, closure of the thoracic duct leak may be facilitated by reducing the flow of chyle. This can be achieved by using parenteral hyperalimentation to provide nutrition. Alternatively, a low-fat diet with most fats in the form of medium-chain triglycerides can reduce chyle flow because the medium-chain triglycerides are absorbed directly into the blood.[92] Input from an experienced dietitian is recommended.

A range of compounds have been tested to hasten the closure of thoracic duct leak. Most studies have used octreotide (a somatostatin analog)[119–122] in postoperative pediatric patients in uncontrolled trials, but evidence on its use in adults and for nontraumatic chylothoraces is relatively scarce; large controlled studies are urgently needed. In a series of chylothoraces in 85 children, 85% responded to dietary manipulation. Somatostatin therapy was successful in half of the remaining 15% of cases, but no factors were identified to predict octreotide response.[123] The mechanism of its action is not clear but is believed to be related to a reduction of intestinal fat (especially triglyceride) absorption and increased fecal fat excretion.[119] Common side effects include flushing, nausea, and diarrhea. Other agents examined include etilefrine[124]—a sympathomimetic drug that aimed to induce contraction of smooth muscles around the main thoracic duct—and factor XIII; the results of these agents need further verification.

TABLE 74-1. Management of a Chylothorax

Maintaining Nutrition and Reducing the Volume of Chyle Circulation
Dietary: medium-chain triglyceride diet or total parenteral nutrition
Octreotide
Relieving Dyspnea by Removing Chyle from the Pleural Cavity
Thoracentesis (short term only)
Tube thoracostomy (short term only)
Pleuroperitoneal or pleurovenous shunting
Pleurodesis
Treatment of the Underlying Defect
Thoracic duct embolization
Ligation of the thoracic duct (thoracoscopy or thoracotomy)
Clipping or fibrin glue to the thoracic duct leak
Radiotherapy for mediastinal lymphoma

Relieving Dyspnea by Removing Chyle. Thoracentesis or tube thoracostomy may be used initially, but every attempt should be made to minimize the duration of tube drainage to avoid malnutrition or immunosuppression.

Pleuroperitoneal shunts are advisable if the chylothorax fails to resolve quickly. This minimizes the risks of malnourishment or immunodeficiency because the lymph is not removed from the body. Some authors recommend pleuroperitoneal shunts as the first line of management as soon as the diagnosis is established. To date, most series on pleuroperitoneal shunts are based in pediatric populations. Pleuroperitoneal shunting is contraindicated if ascites is present, and is less likely to be successful if the chylothoraces result from central venous thrombosis.[125] Redirection of the chyle back into the systemic circulation has been performed successfully via pleurovenous shunts.[126] Use of indwelling pleural catheters for ambulatory drainage of chylothoraces has been reported in a retrospective series of 10 patients.[127]

Closure of the Defect. With traumatic chylothorax, the defect in the thoracic duct frequently closes spontaneously. If the pleuroperitoneal shunt is ineffective in draining the pleural space, or if the patient has a chest tube and the drainage of chyle continues unabated beyond 7 days, a more aggressive treatment plan is needed. In a series of 27 patients with chylothorax following lung resection, those with large-volume drainage (>500 mL per 24 hours) despite total parenteral nutrition were more likely to require reoperation.[96] In another series of patients with post–lung resection chylothorax, 13 of the 15 patients with lower initial drainage volume (mean 300 mL/day) responded to conservative treatment, whereas only 6 of 11 patients with larger drainage volume responded.[128]

Several options exist to control the chyle leak. Talc pleurodesis by slurry or poudrage has been successful in some reports.[129] Recently, lymphatic embolization and blockade has been shown in a large series of 42 patients to be safe, with a complete or partial response rate of 74%.[130] The thoracic duct is punctured transabdominally via a peritoneal cannula under fluoroscopic guidance and the duct is embolized with various devices (e.g., microcoils). In patients whose thoracic duct cannot be cannulated, disruption of the duct with needles may be sufficient to reduce or stop the chyle leak.[130] Retrograde embolization of the cisterna chyli has been attempted via a microcatheter passed through the thoracic duct for the treatment of chylous ascites.[131] Coils, gelatin sponge, and doxycycline have been used as embolization material.[131]

Surgical repair of the thoracic duct defect should be considered if lymphatic embolization is unavailable or

fails. Surgical ligation can often be achieved via VATS, but thoracotomy is sometimes required. The duct is ligated above and below the site of the leak or at the lowest point in the chest.[132] Various technical advances have been tried, including fibrin glue application around the leak,[133] use of robotic ligation,[134] and thermofusion of the thoracic duct using a computer-controlled diathermy system.[135] Ligation of the thoracic duct by laparoscopy has also been attempted with success.[136]

Ideally, the site of the leak should be identified preoperatively by a lymphangiography or lymphoscintigraphy. The identification of the thoracic duct can also be facilitated with preoperative oral administration of cream.[137]

If for technical reasons, the thoracic duct cannot be successfully ligated during VATS, a pleurodesis (e.g., partial pleurectomy or talc insufflation) should be performed to obliterate the pleural space during the operation.

Special Considerations

Nontraumatic Chylothorax. If the patient is known to have either lymphoma or metastatic carcinoma, the chylothorax can respond to mediastinal radiation. In one series, mediastinal radiation adequately controlled the chylothorax for the remainder of the patient's life in 68% of those with lymphoma and in 50% of those with metastatic carcinoma.[138] If radiation therapy fails, embolization, pleurodesis, or pleuroperitoneal shunting should be considered.[139]

If the cause of a nontraumatic chylothorax is unknown, the initial management is similar to that for a patient with a traumatic chylothorax, as discussed previously. A pleuroperitoneal shunt should be inserted to allow time for a thorough evaluation. If chest CT and lymphangiography are normal, the chylothorax can be assumed to be due to minor trauma, and spontaneous closure can be expected within weeks.

Fetal and Congenital Chylothorax. Congenital chylothorax, diagnosed either in utero or after birth, can cause developmental abnormalities and at times be fatal.[105] Congenital chylothorax was present in 3.2% of 598 patients with hydrop fetalis in one series, with a mortality of 5.9%.[140] If diagnosed in utero, maternal dietary restriction should be initiated.[141] Thoracentesis can be performed under ultrasound guidance to evacuate the chylothorax,[142] as large effusions can cause pulmonary hypoplasia and respiratory distress at birth.[105] If the chylothorax reaccumulates, pleuro-amniotic shunting should be considered.[143] In a small number of reported cases, ultrasound-guided intrapleural administration of OK-432[144] or maternal blood[145] has offered effective control of the chylothorax, presumably via creating a pleurodesis.

If the congenital chylothorax is diagnosed after birth, the baby should be treated conservatively with repeated thoracenteses to avoid respiratory compromise while nutrition is maintained by the parenteral route or with medium-chain triglycerides.[146] Feeding with centrifuged breast milk (which removes the fat content) was attempted in one small study.[147] Although the evidence supporting octreotide remains limited, it has a good safety profile and can be tried. If the chylothorax recurs after the third pleural aspiration, however, a pleuroperitoneal shunt should be placed. If the shunt is unsuccessful, thoracic duct ligation is recommended.[105]

Pulmonary Lymphangioleiomyomatosis. Pulmonary lymphangioleiomyomatosis (LAM) is a rare condition, affecting mostly women of reproductive age, and is characterized by progressive dyspnea, recurrent pneumothoraces, and chylous effusions (see Chapter 62). The reported incidence of chylothorax in patients with LAM ranges from 10%[148] to 30%.[149] It can occur in both the sporadic and the tuberous sclerosis complex–associated types of LAM—the former is associated with a higher incidence of chylothorax.[148] Whereas the mean age of presentation of LAM is in the early 30s,[150] the mean age of presentation of chylothorax is in the early 40s.[148] The chylothorax is usually unilateral but can be bilateral[148] or associated with chyloascites. The chylothorax is thought to be the result of the combination of perilymphatic proliferation of smooth muscle leading to lymphatic obstruction and of infiltration of the lymph nodes in the mediastinum and retroperitoneal space by immature smooth muscle cells.[151] CT scan is usually diagnostic for LAM (see Fig. 74-4). Typical LAM cell clusters can also be found in the chylous pleural fluid.[152]

The general principles for the management of a chylothorax secondary to LAM are similar to those for any nontraumatic chylothorax. The course of these chylothoraces is highly variable.[148] In some cases, simple thoracentesis for symptomatic relief is adequate.[148] However, in two series combined, 12 of the 19 LAM patients with chylothoraces required either pleurodesis or thoracic duct ligation to control the reaccumulation of chyle.[148,153]

It should be emphasized that lung transplantation is a treatment option for a proportion (19% in one series[154]) of patients with LAM. The morbidity and mortality of transplantation is increased in these patients, especially from intraoperative bleeding,[155] which is attributed to pleural adhesions from recurrent pneumothoraces. Although pleurodesis is not an absolute contraindication for future transplantation, a transplant surgeon should be consulted before subjecting LAM patients with a chylothorax to pleurodesis or surgical ligation of the thoracic duct.

PSEUDOCHYLOTHORAX (CHYLIFORM PLEURAL EFFUSIONS; CHOLESTEROL PLEURAL EFFUSIONS)

A pseudochylothorax (chyliform pleural effusion) may also produce milky turbid pleural fluid. The turbidity is related to high levels of cholesterol or lecithin-globulin complexes in the fluid. Pseudochylothoraces, with fewer than 200 reported cases in the literature,[156] are much less common than chylothoraces.

Pathogenesis

Although pseudochylothorax was first reported over a century ago, its precise pathogenesis remains unknown. Most patients with a pseudochylothorax have pleural surfaces that are markedly thickened and sometimes calcified, and the effusion is usually long-standing. It appears that, if an exudative effusion persists for a lengthy period—months to years—in a fibrotic area of grossly thickened pleura, it has a high tendency to become enriched with cholesterol.[92] However, increasing reports of pseudochylothoraces without chronic pleuritis or grossly thickened pleura challenge the traditional belief.[157]

Most of the cholesterol in chyliform pleural effusions is associated with high-density lipoproteins, in contrast to the cholesterol in acute exudates, which is mostly bound to low-density lipoproteins.[158] It has been hypothesized that, during acute inflammation, there is increased filtration of cholesterol into the pleural fluid.[158] In addition, the cholesterol can originate from degeneration of erythrocytes and leukocytes that enter the pleural space as part of the underlying disease process.[159] The thickened pleura inhibits the exit of cholesterol out of the pleural space.[158] Serum cholesterol levels and systemic cholesterol metabolism appear to be normal in patients with pseudochylothorax.

The most common situations in which chyliform pleural effusions occur are after tuberculous pleurisy (54%), including those cases treated with artificial pneumothorax. Successful treatment of an acute tuberculous pleurisy does not preclude the development of a pseudochylothorax.[156] Pseudochylothorax can develop in association with chronic rheumatoid pleurisy (9% of pseudochylothoraces) and rarely with paragonimiasis and trauma (including thoracic surgery).[160]

Clinical Manifestations

Pseudochylothorax commonly but not inevitably develops in patients with long-standing pleural effusions. The mean duration of the effusion is 5 years before it turns chyliform, but much shorter times of onset have been reported.[157,161] Many patients with chyliform pleural effusions are asymptomatic or at least no more symptomatic than when they initially developed the pleural effusion. When symptoms occur, they are usually related to the underlying disease process or to the pulmonary restriction produced by the effusion and the thickened pleura. In some cases, the effusion gradually enlarges with time, with resultant progressive dyspnea.[92]

Diagnosis

The pleural effusion is often chronic and associated with thickened or calcified pleura. The fluid is milky, and the differential diagnoses of chylothorax and empyema need exclusion (see earlier). The pleural fluid should be examined for cholesterol crystals—a diagnostic feature of pseudochylothorax. The cholesterol crystals give a distinct satin-like sheen to the pleural fluid and microscopically have a typical rhomboid appearance. Not all patients with chyliform pleural effusion have cholesterol crystals in their pleural fluid; however, most have an elevated pleural fluid cholesterol level (>250 mg/dL, or 6.45 mmol/L).[1] Pleural fluid triglyceride levels can be high in pseudochylothorax. CT chest scan can reveal a layering of fat in nondependent sites, as shown in a series of pseudochylothorax patients.[162]

Treatment

Tuberculosis should always be considered in patients with a pseudochylothorax, although tuberculous pseudochylothorax is usually culture negative.[156] We advise drainage only in symptomatic cases and treating with antituberculous chemotherapy only those patients with positive stain or culture for tuberculosis and those with enlarging effusions of suspected tuberculous origin (see Chapter 34).

When the patient's exercise capacity is limited by breathlessness, a therapeutic thoracentesis should be performed and can improve exercise tolerance.[159] Thoracentesis can be difficult because of the frequently thickened pleura and negative intrapleural pressure.[92] Limited evidence exists to support surgical decortication, which should only be considered if the patient is symptomatic and the underlying lung is believed to be functional.

HEMOTHORAX

Hemothorax is the presence of blood in the pleural space, specifically when the hematocrit of the pleural fluid is at least 50% that of the peripheral blood.[1] When bloody pleural fluid is obtained with a diagnostic thoracentesis, the hematocrit should always be measured. Frequently, even though the pleural fluid appears to be pure blood, the hematocrit of the fluid will be less than 5%.[1]

Traumatic Hemothorax

Blood may enter the pleural space from injury to the chest wall, diaphragm, lung, blood vessels, or mediastinum. On entering the pleural space, the blood coagulates rapidly but, presumably as a result of the physical agitation produced by movement of the heart and lungs, the clot may be defibrinated. Loculation may develop early in the course of hemothorax.

Diagnosis

The diagnosis of traumatic hemothorax should be suspected in any patient with penetrating or nonpenetrating trauma of the chest (Fig. 74-8). It should be emphasized that the hemothorax may not be apparent on the initial chest radiograph. In one series of 130 patients with hemothorax secondary to nonpenetrating trauma, the hemothorax was not appreciated on the initial chest radiograph in 24% of the patients.[163] Although

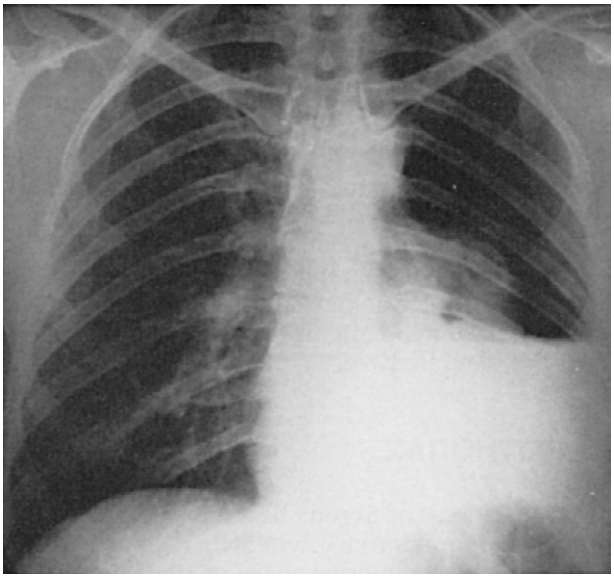

FIGURE 74-8 ■ Posteroanterior chest radiograph from a patient who suffered multiple injuries in an automobile accident. The patient had a hemopneumothorax. With the prompt institution of tube thoracostomy, the air and blood were evacuated from the pleural space and the chest radiograph was normal 1 week later.

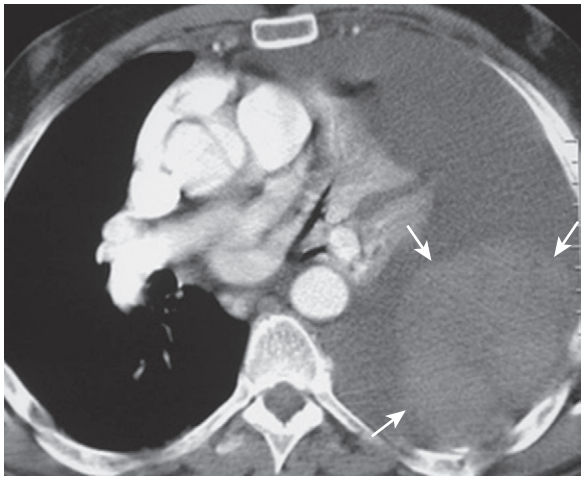

FIGURE 74-9 ■ Axial computed tomography scan of a patient with a large left hemothorax. The hyperdense region (*arrows*) indicates a retracted thrombus. Occasionally, unclotted erythrocytes can settle to the dependent area, creating a "fluid-fluid level," representing the so-called hematocrit sign. (Courtesy of Michael B. Gotway, MD, Scottsdale Medical Imaging and the Department of Radiology, University of California, San Francisco.)

the hemothorax was missed in some of the patients because the initial radiograph was obtained with the patient supine, other patients had no evidence of a hemothorax on the erect radiograph.[163]

The CT scan is more sensitive than the chest radiograph in detecting hemothoraces. In a study of 103 patients with blunt trauma,[58] thoracic CT detected a hemothorax in 21 patients (20%) in whom the routine chest radiograph showed no pleural fluid. When patients experience severe thoracic trauma, a CT scan of the chest is indicated for its ability to identify hemothorax as well as pneumothoraces, lung contusion, and bone fractures.[58] The diagnosis is established if the pleural fluid hematocrit is greater than 50% of that of the peripheral blood.

Ultrasound is now available in many emergency rooms, and has been applied for the detection of traumatic hemothoraces. In one study of 240 patients, ultrasonography was comparable to initial chest radiograph in detecting hemothoraces, with a specificity and sensitivity of 100% and 96%, respectively.[164] On CT scans, hyperdensity, due to the high hemoglobin content of retracted clot or sedimented blood, may point toward a hematoma (Fig. 74-9).[165]

Delayed hemithorax has been reported and, in one study of 36 patients, occurred in one third at 18 hours to 6 days following the initial blunt trauma. Most of these patients had multiple or displaced rib fractures.[166] However, in another series of 100 patients with penetrating thoracic trauma, none developed a hemothorax after 3 hours.[167]

A patient with a traumatic hemothorax should undergo immediate tube thoracostomy: it permits nearly complete evacuation of the blood from the pleural space; it can stop the bleeding from pleural lacerations by bringing the two pleural surfaces into apposition; it enables quantification of the degree of continued bleeding; and it may decrease the incidence of subsequent empyema. The blood drained from the pleural space may be autotransfused. The rapid evacuation of the blood from the pleural space may decrease the incidence of a subsequent fibrothorax.

It is recommended that the chest tube be inserted relatively high (fourth or fifth intercostal space) in the midaxillary line because the ipsilateral hemidiaphragm may be elevated secondary to the trauma. Alternatively, it should be inserted under image guidance. Large-bore chest tubes should be used because the blood frequently clots. Chest tubes should be removed as soon as they stop draining or cease to function, because they can serve as conduits for pleural infection.

Approximately 20% of patients with hemothorax require surgical intervention for suspected cardiac tamponade, vascular injury, pleural contamination, débridement of devitalized tissue, chest wounds, major bronchial air leaks, or continued pleural hemorrhage. Posttraumatic hemithorax was traditionally managed exclusively by thoracotomy, but advances in VATS have made it the procedure of choice in many centers,[168] with thoracotomy reserved only for massive acute hemorrhages. There are no precise criteria for the amount of pleural bleeding that should serve as an indication for thoracoscopy or thoracotomy, and each case must be individualized; however, if the bleeding is more than 200 mL/hr and shows no signs of slowing, surgical intervention should be seriously considered.

In a recent series, patients with active hemothorax drainage over 200 mL/hr were subjected to contrast-enhanced CT scan, which allowed identification of sites of bleeding intercostal arteries (by tracking the extravasation of the contrast). In all five patients, transcatheter arterial embolization successfully stopped the bleeding.[169]

Complications

The four main potential pleural complications of traumatic hemothorax are the retention of clotted blood in the pleural space, pleural infection, pleural effusion, and fibrothorax. In one retrospective series, 24 (1.4%) of 1728 chest trauma patients had a residual hemothorax.[170] Most patients with small to moderate amounts of clotted blood remaining in their pleural space have no residual pleural abnormalities even if no intervention is undertaken.[171] If more than 30% of the hemithorax is occupied by clotted blood, the hemithorax should be evacuated. Decisions regarding thoracoscopic evacuation should not be made from the plain chest radiograph alone and require CT studies.[172] VATS is the mainstay of management, and conversion to thoracostomy is seldom required.[168] The clotted blood should be evacuated within 7 days because after this time it begins to become organized and is much more difficult to remove.[168] In a prospective, randomized trial, VATS was more effective than thoracostomy tube drainage for removing retained hemothoraces. In this study, both the length of hospital stay (7 vs. 3.6 days) and the duration of tube drainage (4.5 vs. 2.5 days) were shorter in the group receiving VATS.[173] In another series, thoracoscopic evacuation performed within 3 days of admission was associated with a lower operative difficulty score (and shorter operation time) and shorter inpatient stay, compared with patients operated at later time points.[170]

Once the source of the bleeding is controlled, intrapleural administration of fibrinolytic agents (e.g., streptokinase or urokinase) may be safe in patients with hemothorax and retained clots, according to several descriptive studies.[174] However, there have been no comparative studies to confirm the efficacy of fibrinolysis versus conservative management or surgical evacuation.

Empyema occurs in 1% to 4% of patients with traumatic hemothoraces.[171,175] Empyema is more frequent in patients who are admitted in shock, have gross contamination of their pleural space, have associated abdominal injuries, or undergo prolonged pleural drainage.[171,175] The administration of prophylactic antibiotics (e.g., cefazolin 500 mg every 6 hours until tube removal) results in a significant decrease in the incidence of pleural infection.[176] The treatment of empyema complicating hemothorax is similar to that of any bacterial infection of the pleural space (see Chapters 32 and 73).

In more than 10% of patients with a traumatic hemothorax, a pleural effusion will develop after the chest tubes are removed.[171,175] Most such pleural effusions resolve spontaneously, leaving no residual pleural abnormalities. It is important to perform a diagnostic thoracentesis in such patients, however, to verify that no pleural infection is present.

Fibrothorax develops in less than 1% of patients with hemothorax. Fibrothorax appears to develop more frequently when a hemopneumothorax is present or when a hemothorax becomes infected. The definitive treatment for fibrothorax is decortication. Decortication for fibrothorax should be delayed for several months after the injury, however, to allow time for spontaneous resolution of the pleural thickening, which is often considerable.

Iatrogenic Hemothorax

Whenever a hemothorax is discovered, the possibility of an iatrogenic origin should be considered. The most common cause of iatrogenic hemothorax is thoracic surgery,[177] but perforation of a central vein or artery by a percutaneously inserted catheter[178] or leaking from the aorta after translumbar aortographic study are also common. Iatrogenic hemothorax can also follow thoracentesis, pleural biopsy, chest tube insertion, percutaneous lung aspiration or biopsy, transbronchial biopsy, endoscopic esophageal variceal therapy, and cardiopulmonary resuscitation. Patients with iatrogenic hemothoraces should be managed, as are patients with traumatic hemothoraces, with chest tubes and thoracoscopy or thoracotomy as needed.

Nontraumatic Hemothorax

Nontraumatic hemothoraces are distinctly uncommon. The most common cause is malignant pleural disease and the second most common cause is a complication of anticoagulation therapy for pulmonary embolization.[179] The cause of the hemothorax in some patients remains unknown despite exploratory thoracotomy.

A spontaneous hemothorax may result from rupture of an abnormal intrathoracic blood vessel, such as subpleural arteriovenous malformations, aneurysm of the aorta or pulmonary artery, patent ductus arteriosus, or coarctation of the aorta. Other causes of a spontaneous hemothorax include a complication of bleeding disorders (such as hemophilia or thrombocytopenia), a complication of spontaneous pneumothoraces, bronchopulmonary sequestration, thoracic endometriosis, chickenpox pneumonia, or intrathoracic extramedullary hematopoiesis. Spontaneous hemothorax is a rare but potentially life-threatening complication of neurofibromatosis, either from aneurysmal changes in large arteries (e.g., aorta) or from dysplastic changes in small vessels.

Mediastinal tumors can also produce a spontaneous large hemothorax, which can be bilateral. Blood can also accumulate in the pleural space due to pathologies of abdominal organs, such as rupture of a splenic artery aneurysm through the diaphragm, pancreatic pseudocysts, and rupture of hepatocellular carcinomas.

Hemothoraces can complicate anticoagulant therapy (warfarin[180] or heparin—low molecular weight[181] or unfractionated[179]) or intrapleural fibrinolytic therapy.[180] The hemothorax usually becomes apparent 4 to 7 days after anticoagulation therapy is initiated, but it may occur much later. When the hemothorax develops, the coagulation studies may be within the acceptable therapeutic range.[179]

Chest tubes should be inserted into patients with spontaneous hemothorax to remove the blood from the pleural space and to quantify the rate of bleeding. If brisk (>100 mL/hr) bleeding persists, emergency thoracotomy should be performed.

FIBROTHORAX

Dense fibrous tissue may form over the pleural surface for a variety of reasons. Pleural fibrosis usually follows intense inflammation of the pleura; however, the mechanisms following the inflammatory process leading up to fibrosis are unclear. Profibrotic cytokines, especially transforming growth factor-β (TGF-β), probably play a significant role. In various animal models, TGF-β, administered directly or via vector transfection, induces pleural fibrosis, and anti–TGF-β antibodies can inhibit pleural adhesion formation in empyema.[182]

A fibrothorax most commonly develops as a complication of an empyema or a hemothorax. Fibrothorax has also developed as a complication of tuberculosis, collagen vascular diseases, uremia, paragonimiasis, and drug reactions. Pleural fibrosis can be idiopathic, and isolated familial cases have been reported.[183] Whereas tuberculous pleuritis is common, fibrothorax is a rare complication.[184] In one study, restrictive functional sequelae were found in 10% of 81 patients with tuberculous pleuritis, but were mostly mild.[185] Neither the early drainage of the pleural effusion[186] nor the use of systemic corticosteroids[187] has significant impact on subsequent development of pleural thickening or restrictive lung function in patients with tuberculous pleuritis. Pleural fluid inflammatory markers are, at best, weak predictors of eventual pleural thickening.[185]

Asbestos exposure may also lead to a fibrothorax (also called diffuse pleural thickening), which is usually bilateral.[188] In these cases, extensive fibrosis of the visceral pleura develops, together with areas of adhesion with the parietal surfaces, thus obliterating the pleural space.[188] Diffuse pleural thickening is known to follow benign asbestos pleural effusions, and it has been suggested that this is a necessary precursor of fibrothorax.[189] In one series of 44 patients with diffuse pleural thickening, half had a history of benign asbestos effusion; conversely, 54% of those who had a benign asbestos effusion had residual pleural thickening.[189] Diffuse pleural thickening is usually,[188] but not inevitably, associated with heavy asbestos exposure, and its incidence increases with increasing time since first exposure.[189] The pleural fibrosis is often progressive, resulting in restrictive lung defects, especially if the costophrenic angle is obliterated.[190]

Pleural (with or without concurrent pulmonary) fibrosis can also occur with the use of ergot alkaloids (e.g., bromocriptine, pergolide, and methysergide).[180,191] It has been suggested that subjects with asbestos exposure may be more susceptible to bromocriptine-induced pleural fibrosis.[192] Onset of dyspnea from ergot-induced pleural fibrosis is usually insidious and in the majority of cases presents at least 6 months after starting the medication.[180] The pleural thickening is usually bilateral but can be unilateral, and may be associated with pleuritic pain. Constitutional symptoms and elevated serologic inflammatory markers have also been reported.[191] In the case of bromocriptine, the fibrothorax will stop progressing on cessation of the drug use, and may regress,[180] though complete resolution is rare. Corticosteroids are often administered, but their effectiveness has never been established.[180] Pleural fibrosis is often bilateral (if due to systemic causes) and may be associated with concurrent peritoneal fibrosis.[193]

Although pleural fibrosis is usually an undesirable event, it is commonly used therapeutically (pleurodesis) to control pleural effusions and pneumothoraces. Pleurodesis is the iatrogenic induction of pleural fibrosis, leading to symphysis of the visceral and parietal pleurae to obliterate the pleural space to prevent fluid or air reaccumulation.[194] Interestingly, pleurodesis has no major impact on pulmonary function, even after decades. A retrospective review of young patients treated 22 to 35 years ago for spontaneous pneumothoraces showed that those who received talc pleurodesis (n = 80) had a higher incidence of pleural thickening on radiographs, but minimal restrictive changes in their lung function when compared with those treated by simple drainage (n = 34).[195] Several small human and animal studies also revealed no significant impairment in lung volumes and gas exchange at rest or during exercise following pleurodesis.[194] Such observations imply that, for a fibrothorax to be clinically significant, it must involve either very extensive pleural fibrosis (in excess of therapeutic pleurodesis) or concomitant parenchymal fibrosis.

Diagnosis

In one large population screening study of over 70,000 subjects, pleural thickening was reported in 3.6% of radiologic examinations.[196] In typical cases, the diagnosis of fibrothorax can easily be made from the radiographic findings plus a history of a predisposing cause (e.g., an old injury or infection). Radiologically, a peel of uniform thickness surrounds the lung. Calcification occurs frequently on the inner aspect of the peel (Fig. 74-10) and provides an indicator by which the thickness of the peel may be accurately measured. Apparent pleural thickening can occur, especially in obese subjects (body mass index >30), presumably the result of extrapleural fat deposition.[197] A CT scan can easily discriminate between fat and thickening.

Recently, a new CT scoring system that quantifies the thickness of the pleura and the fractional circum-

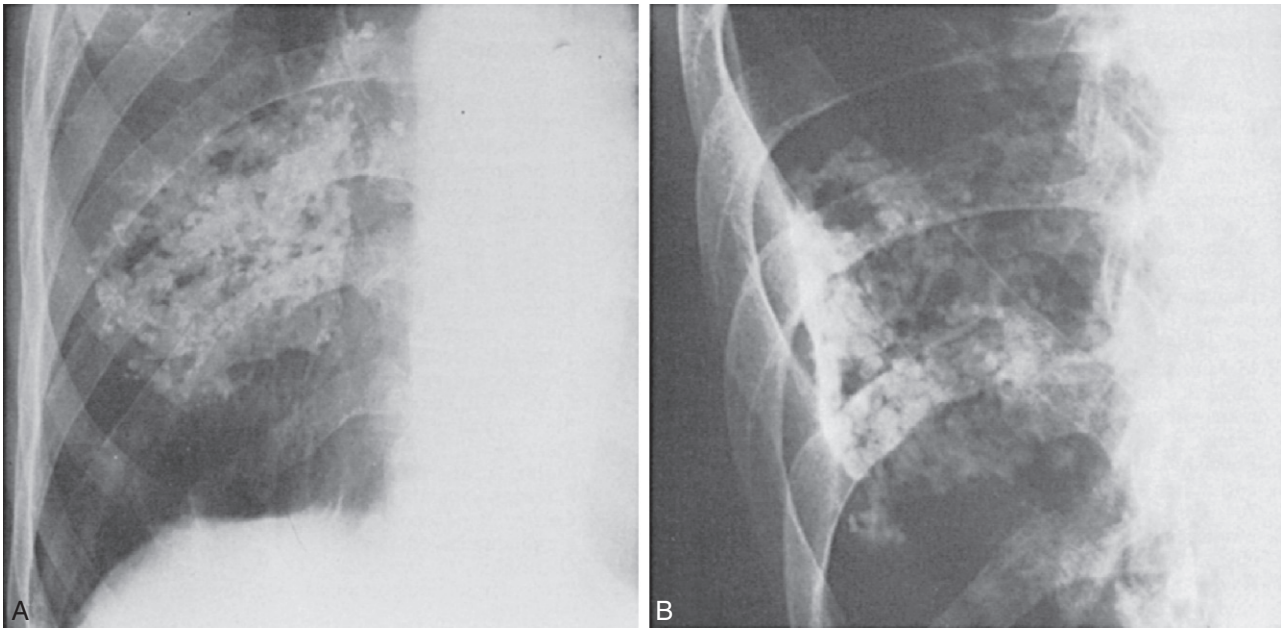

FIGURE 74-10 ■ Detailed views from posteroanterior **(A)** and oblique **(B)** chest radiographs of a 62-year-old man showing a localized fibrothorax with calcified plaque on the right. The patient had had right-sided empyema 32 years before. (From Hinshaw HC, Murray JF: Diseases of the Chest. Philadelphia: WB Saunders, 1980, p 912.)

ference of the hemithorax involved (as well as other pleural changes, such as rounded atelectasis and pleural plaques) has been shown to correlate with impairment in pulmonary function measures (especially total lung capacity and diffusing capacity).[198]

Routine pulmonary function testing usually reveals mild to severe restrictive ventilatory dysfunction.[189] In the case of asbestos-induced diffuse pleural thickening, the restriction arises from inflammatory involvement of the costal surfaces of the diaphragm and lower costal pleura, thus producing a pleurodesis that limits the movement of both the diaphragm and rib cage during inspiration.[199] The reduction in rib cage expansion is the main cause of restriction, because the diaphragm can still contribute by flattening of its dome on inspiration.[199] In one study, 95% of patients with asbestos-induced diffuse pleural thickening complained of exertional dyspnea.[200] Objective reduction of exercise work capacity had also been shown.[201]

Pulmonary function may be severely compromised in patients with an extensive fibrothorax. As a result of the marked pleural thickening, the hemithorax becomes contracted, and its mobility is reduced. As the fibrothorax progresses, the intercostal spaces may narrow, the size of the involved hemithorax may diminish, and the mediastinum may be displaced ipsilaterally. In patients with bilateral fibrothorax resulting from asbestos exposure, hypercapnic respiratory failure may develop and may be amenable to home noninvasive ventilation.[202]

Treatment

It should be emphasized that patients with a recent hemothorax, empyema, or tuberculous pleuritis frequently show marked spontaneous improvement in their symptoms and the degree of pleural thickening in the 3 to 6 months after the acute episode.[203] Patients with a fibrothorax should avoid drugs that can induce pleural fibrosis.

Decortication—surgical removal of the fibrous peel from the pleural surface—has been attempted to treat fibrothorax. However, the degree of improvement after decortication varies, with many series showing disappointing results.[204,205] Success in part depends on the condition of the underlying lung. If the underlying lung is normal, the vital capacity may improve after decortication but, if there is extensive parenchymal disease, the vital capacity may even decrease. The duration of the fibrothorax does not seem helpful in predicting the outcome. Surgical morbidity and mortality are not insignificant.[206] Therefore, decortication should be considered only if the pleural thickening has been present for several months and if the patient is significantly affected by exertional dyspnea. Decortication is a major surgical procedure and should not be performed on patients debilitated by other diseases.

If CT scans reveal significant parenchymal disease, decortication is not advisable. The results of decortication in patients with bilateral fibrothoraces secondary to asbestos exposure have been disappointing, probably a result of concomitant pulmonary fibrosis.[207]

KEY POINTS

- Simple aspiration is the recommended first step of air evacuation in most cases of primary spontaneous pneumothorax.
- Secondary spontaneous pneumothorax is potentially life-threatening, and prevention of recurrence should be considered even at the first episode of pneumothorax.
- Chylothorax is characterized by milky fluid and the presence of chylomicrons. Early intervention is advocated because prolonged drainage of chylous effusion can lead to malnutrition.
- Pseudochylothorax is characterized by cholesterol crystals, and should be differentiated from chylothorax because the etiology and management are different.
- A traumatic hemothorax should be drained and, if the bleeding rate is greater than 200 mL/hr, intervention targeting the underlying bleeding site by surgical or interventional radiologic means should be considered. Traumatic hemothorax can be complicated by retention of clotted blood in the pleural space, pleural infection, pleural effusion, and rarely fibrothorax.
- Pleural thickening may improve spontaneously during the 3 to 6 months after acute hemothorax, empyema, or tuberculous pleuritis. Decortication should be considered only if the pleural thickening has been present for several months and if the patient is significantly affected by exertional dyspnea.

References

1. Light RW: Pleural Diseases (5th ed). Baltimore: Lippincott, Williams & Wilkins, 2007.
2. Norris RM, Jones JG, Bishop JM: Respiratory gas exchange in patients with spontaneous pneumothorax. Thorax 23:427–433, 1968.
3. Gupta D, Hansell A, Nichols T, et al: Epidemiology of pneumothorax in England. Thorax 55:666–671, 2000.
4. Schramel FM, Sutedja TG, Braber JC, et al: Cost-effectiveness of video-assisted thoracoscopic surgery versus conservative treatment for first time or recurrent spontaneous pneumothorax [see comments]. Eur Respir J 9:1821–1825, 1996.
5. Bense L, Eklung G, Wiman LG: Smoking and the increased risk of contracting spontaneous pneumothorax. Chest 92:1009–1012, 1987.
6. Menko FH, van Steensel MA, Giraud S, et al: Birt-Hogg-Dube syndrome: diagnosis and management. Lancet Oncol 10:1199–1206, 2009.
7. Noppen M, Dekeukeleire T, Hanon S, et al: Fluorescein-enhanced autofluorescence thoracoscopy in patients with primary spontaneous pneumothorax and normal subjects. Am J Respir Crit Care Med 174:26–30, 2006.
8. Travaline JM, McKenna RJ, Degiacomo T, et al: Treatment of persistent pulmonary air leaks using endobronchial valves. Chest 136:355–360, 2009.
9. Smit HJ, Wienk MA, Schreurs AJ, et al: Do bullae indicate a predisposition to recurrent pneumothorax? Br J Radiol 73:356–359, 2000.
10. Wu YC, Lu MS, Yeh CH, et al: Justifying video-assisted thoracic surgery for spontaneous hemopneumothorax. Chest 122:1844–1847, 2002.
11. Noppen M, Alexander P, Driesen P, et al, for the Vlaamse Werkgroep voor Medische Thoracoscopie en Interventionele Bronchoscopie: Quantification of the size of primary spontaneous pneumothorax: Accuracy of the Light index. Respiration 68:396–399, 2001.
12. Sadikot RT, Greene T, Meadows K, Arnold AG: Recurrence of primary spontaneous pneumothorax. Thorax 52:805–809, 1997.
13. Guo Y, Xie C, Rodriguez RM, et al: Factors related to recurrence of spontaneous pneumothorax. Respirology 10:378–384, 2005.
14. Baumann MH, Strange C, Heffner JE, et al: Management of spontaneous pneumothorax: An American College of Chest Physicians Delphi Consensus Statement. Chest 119:590–602, 2001.
15. Henry M, Arnold T, Harvey J: BTS guidelines for the management of spontaneous pneumothorax. Thorax 58(Suppl II):II39–II52, 2003.
16. Kircher LTJ, Swartzel RL: Spontaneous pneumothorax and its treatment. JAMA 155:24–29, 1954.
17. Chernick V, Avery ME: Spontaneous alveolar rupture at birth. Pediatrics 32:816–824, 1963.
18. Northfield TC: Oxygen therapy for spontaneous pneumothorax. Br Med J 4:86–88, 1971.
19. Noppen M, Alexander P, Driesen P, et al: Manual aspiration versus chest tube drainage in first episodes of primary spontaneous pneumothorax: A multicenter, prospective, randomized pilot study. Am J Respir Crit Care Med 165:1240–1244, 2002.
20. Chen JS, Hsu HH, Tsai KT, et al: Salvage for unsuccessful aspiration of primary pneumothorax: Thoracoscopic surgery or chest tube drainage? Ann Thorac Surg 85:1908–1913, 2008.
21. Seremetis MG: The management of spontaneous pneumothorax. Chest 57:65–68, 1970.
22. Light RW, O'Hara VS, Moritz TE, et al: Intrapleural tetracycline for the prevention of recurrent spontaneous pneumothorax: Results of a Department of Veterans Affairs cooperative study. JAMA 264:2224–2230, 1990.
23. Barker A, Maratos EC, Edmonds L, Lim E: Recurrence rates of video-assisted thoracoscopic versus open surgery in the prevention of recurrent pneumothoraces: A systematic review of randomised and non-randomised trials. Lancet 370:329–335, 2007.
24. Light RW: Talc should not be used for pleurodesis. Am J Respir Crit Care Med 162:2024–2026, 2000.
25. Vargas FS, Wang NS, Lee HM, et al: Effectiveness of bleomycin in comparison to tetracycline as pleural sclerosing agent in rabbits. Chest 104:1582–1584, 1993.
26. Yim AP: Video-assisted thoracoscopic suturing of apical bullae: An alternative to staple resection in the management of primary spontaneous pneumothorax. Surg Endosc 9:1013–1016, 1995.
27. Casadio C, Rena O, Giobbe R, et al: Stapler blebectomy and pleural abrasion by video-assisted thoracoscopy for spontaneous pneumothorax. J Cardiovasc Surg (Torino) 43:259–262, 2002.
28. Bertrand PC, Regnard JF, Spaggiari L, et al: Immediate and long-term results after surgical treatment of primary spontaneous pneumothorax by VATS. Ann Thorac Surg 61:1641–1645, 1996.

29. Crisci R, Coloni GF: Video-assisted thoracoscopic surgery versus thoracotomy for recurrent spontaneous pneumothorax: A comparison of results and costs. Eur J Cardiothorac Surg 10:556–560, 1996.
30. Tschopp JM, Boutin C, Astoul P, et al: Talcage by medical thoracoscopy for primary spontaneous pneumothorax is more cost-effective than drainage: A randomised study. Eur Respir J 20:1003–1009, 2002.
31. Yim AP, Ng CS: Thoracoscopy in the management of pneumothorax. Curr Opin Pulm Med 7:210–214, 2001.
32. Melton LJ, Hepper NG, Offord KP: Incidence of spontaneous pneumothorax in Olmsted County, Minnesota: 1950 to 1974. Am Rev Respir Dis 120:1379–1382, 1979.
33. Weissberg D, Refaely Y: Pneumothorax. Chest 117:1279–1285, 2000.
34. Afessa B: Pleural effusion and pneumothorax in hospitalized patients with HIV infection: The Pulmonary Complications, ICU Support, and Prognostic Factors of Hospitalized Patients with HIV (PIP) Study. Chest 117:1031–1037, 2000.
35. Flume PA, Strange C, Ye X, et al: Pneumothorax in cystic fibrosis. Chest 128:720–728, 2005.
36. Mendez JL, Nadrous HF, Vassallo R, et al: Pneumothorax in pulmonary Langerhans cell histiocytosis. Chest 125:1028–1032, 2004.
37. Dines DE, Clagett OT, Payne WS: Spontaneous pneumothorax in emphysema. Mayo Clin Proc 45:481–487, 1970.
38. Boat TF, Di Sant' Agnese PA, Warwick WJ, Handwerger SA: Pneumothorax in cystic fibrosis. JAMA 209:1498–1504, 1969.
39. Yankaskas MR, Mallory GBJ, and the Consensus Committee: Lung transplantation in cystic fibrosis. Chest 113:217–226, 1998.
40. Sepkowitz KA, Telzak EE, Gold JW, et al: Pneumothorax in AIDS. Ann Intern Med 114:455–459, 1991.
41. Wait MA: AIDS-related pneumothorax. Ann Thorac Surg 64:290–291, 1997.
42. Wilder RJ, Beacham EG, Ravitch MM: Spontaneous pneumothorax complicating cavitary tuberculosis. J Thorac Cardiovasc Surg 43:561–573, 1962.
43. De Lassence A, Timsit JF, Tafflet M, et al: Pneumothorax in the intensive care unit: Incidence, risk factors, and outcome. Anesthesiology 104:5–13, 2006.
44. Vitulo P, Dore R, Cerveri I, et al: The role of functional respiratory tests in predicting pneumothorax during lung needle biopsy. Chest 109:612–615, 1995.
45. Saji H, Nakamura H, Tsuchida T, et al: The incidence and the risk of pneumothorax and chest tube placement after percutaneous CT-guided lung biopsy: The angle of the needle trajectory is a novel predictor. Chest 121:1521–1526, 2002.
46. Billich C, Muche R, Brenner G, et al: CT-guided lung biopsy: Incidence of pneumothorax after instillation of NaCl into the biopsy track. Eur Radiol 18:146–152, 2008.
47. de Latorre FJ, Tomasa A, Klamburg J, et al: Incidence of pneumothorax and pneumomediastinum in patients with aspiration pneumonia requiring ventilatory support. Chest 72:141–144, 1977.
48. Weg JG, Anzueto A, Balk RA, et al: The relation of pneumothorax and other air leaks to mortality in the acute respiratory distress syndrome. N Engl J Med 338:341–346, 1998.
49. Okuma T, Matsuoka T, Yamamoto A, et al: Frequency and risk factors of various complications after computed tomography-guided radiofrequency ablation of lung tumors. Cardiovasc Intervent Radiol 31:122–130, 2008.
50. Gillams AR, Lees WR: Analysis of the factors associated with radiofrequency ablation-induced pneumothorax. Clin Radiol 62:639–644, 2007.
51. Lencioni R, Crocetti L, Cioni R, et al: Response to radiofrequency ablation of pulmonary tumours: A prospective, intention-to-treat, multicentre clinical trial (the RAPTURE study). Lancet Oncol 9:621–628, 2008.
52. Choi CM, Um SW, Yoo CG, et al: Incidence and risk factors of delayed pneumothorax after transthoracic needle biopsy of the lung. Chest 126:1516–1521, 2004.
53. Yamagami T, Nakamura T, Iida S, et al: Management of pneumothorax after percutaneous CT-guided lung biopsy. Chest 121: 1159–1164, 2002.
54. Conces DJJ, Tarver RD, Gray WC, Pearcy EA: Treatment of pneumothoraces utilizing small caliber chest tubes. Chest 94:55–57, 1988.
55. Bishop MJ, Benson MS, Pierson DJ: Carbon dioxide excretion via bronchopleural fistulas in adult respiratory distress syndrome. Chest 91:400–402, 1987.
56. Bishop MJ, Benson MS, Sato P, Pierson DJ: Comparison of high frequency jet ventilation with conventional mechanical ventilation for bronchopleural fistula. Anesth Analg 66:833–838, 1987.
57. Albelda SM, Hansen-Flaschen JH, Taylor E, et al: Evaluation of high-frequency jet ventilation in patients with bronchopleural fistulas by quantitation of the airleak. Anesthesiology 63:551–554, 1985.
58. Trupka A, Waydhas C, Hallfeldt KK, et al: Value of thoracic computed tomography in the first assessment of severely injured patients with blunt chest trauma: Results of a prospective study. J Trauma 43:405–411, 1997.
59. Rowan KR, Kirkpatrick AW, Liu D, et al: Traumatic pneumothorax detection with thoracic US: Correlation with chest radiography and CT—initial experience. Radiology 225:210–214, 2002.
60. Slater A, Goodwin M, Anderson KE, Gleeson FV: COPD can mimic the appearance of pneumothorax on thoracic ultrasound. Chest 129:545–550, 2006.
61. Knottenbelt JD, van der Spuy JW: Traumatic pneumothorax: A scheme for rapid patient turnover. Br J Accident Surg 21:77–80, 1990.
62. Carrillo EH, Schmacht DC, Gable DR, et al: Thoracoscopy in the management of posttraumatic persistent pneumothorax. J Am Coll Surg 186:636–639, 1998.
63. Kunisch-Hoppe M, Hoppe M, Rauber K, et al: Tracheal rupture caused by blunt chest trauma: Radiological and clinical features. Eur Radiol 10:480–483, 2000.
64. Light RW, Lee YCG: Textbook of Pleural Diseases (2nd ed). London: Arnold, 2008.
65. Medical guidelines for air travel. Aerospace Medical Association, Air Transport Medical Committee, Alexandria, VA. Aviat Space Environ Med 67(10 Suppl):B1–B8, 1996.
66. Cheatham ML, Safcsak K: Air travel following traumatic pneumothorax: When is it safe? Am Surg 65:1160–1164, 1999.
67. Steele RW, Metz JR, Bass JW, DuBois JJ: Pneumothorax and pneumomediastinum in the newborn. Radiology 98:629–632, 1971.
68. Ogata ES, Gregory GA, Kitterman JA, et al: Pneumothorax in the respiratory distress syndrome: Incidence and effect on vital signs, blood gases, and pH. Pediatrics 58:177–183, 1976.
69. Horbar JD, Badger GJ, Carpenter JH, et al: Trends in mortality and morbidity for very low birth weight infants, 1991–1999. Pediatrics 110:143–151, 2002.
70. Goldberg RN: Sustained arterial blood pressure elevation associated with pneumothoraces: Early detection via continuous monitoring. Pediatrics 68:775–777, 1981.
71. Arda IS, Gurakan B, Aliefendioglu D, Tuzun M: Treatment of pneumothorax in newborns: Use of venous catheter versus chest tube. Pediatr Int 44:78–82, 2002.
72. Korom S, Canyurt H, Missbach A, et al: Catamenial pneumothorax revisited: Clinical approach and systematic review of the literature. J Thorac Cardiovasc Surg 128:502–508, 2004.
73. Johnson MM: Catamenial pneumothorax and other thoracic manifestations of endometriosis. Clin Chest Med 25:311–319, 2004.
74. Maurer ER, Schaal JA, Mendez FL: Chronic recurrent spontaneous pneumothorax due to endometriosis of the diaphragm. JAMA 168:2013–2014, 1958.
75. Lillington GA, Mitchell SP, Wood GA: Catamenial pneumothorax. JAMA 219:1328–1332, 1972.
76. Alifano M, Roth T, Broet SC, et al: Catamenial pneumothorax: A prospective study. Chest 124:1004–1008, 2003.
77. Bagan P, Le Pimpec Barthes F, Assouad J, et al: Catamenial pneumothorax: Retrospective study of surgical treatment. Ann Thorac Surg 75:378–381, 2003.
78. Carvalho P, Hilderbrandt J, Charan NB: Changes in bronchial and pulmonary arterial blood flow with progressive tension pneumothorax. J Appl Physiol 81:1664–1669, 1996.
79. Barton ED, Rhee P, Hutton KC, Rosen P: The pathophysiology of tension pneumothorax in ventilated swine. J Emerg Med 15:147–153, 1997.

80. Daly CM, Swalec-Tobias K, Tobias AH, Ehrhart N: Cardiopulmonary effects of intrathoracic insufflation in dogs. J Am Anim Hosp Assoc 38:515–520, 2002.
81. Beards SC, Lipman J: Decreased cardiac index as an indicator of tension pneumothorax in the ventilated patient. Anesthesiology 49:137–141, 1994.
82. Leigh-Smith S, Harris T: Tension pneumothorax—time for a rethink? Emerg Med J 22:8–16, 2005.
83. Mainini SE, Johnson FE: Tension pneumothorax complicating small-caliber chest tube insertion. Chest 97:759–760, 1990.
84. Ludwig J, Kienzle GD: Pneumothorax in a large autopsy population. Am J Clin Pathol 70:24–26, 1978.
85. Rozenman J, Yellin A, Simansky DA, Shiner RJ: Re-expansion pulmonary oedema following spontaneous pneumothorax. Respir Med 90:235–238, 1996.
86. Mahfood S, Hix WR, Aaron BL, et al: Reexpansion pulmonary edema. Ann Thorac Surg 45:340–345, 1988.
86a. Kim YK, Kim H, Lee CC, et al: New classification and clinical characteristics of reexpansion pulmonary edema after treatment of spontaneous pneumothorax. Am J Emerg Med 27:961–967, 2009.
87. Jackson RM, Veal CF, Beckman JS, Brannen AL: Polyethylene glycol-conjugated superoxide dismutase in unilateral lung injury due to re-expansion (re-oxygenation). Am J Med Sci 300:22–28, 1990.
88. Jackson RM, Veal CF, Alexander CB, et al: Re-expansion pulmonary edema: A potential role for free radicals in its pathogenesis. Am Rev Respir Dis 137:1165–1171, 1988.
89. Doerschuk CM, Allard MF, Oyarzun MJ: Evaluation of reexpansion pulmonary edema following unilateral pneumothorax in rabbits and the effect of superoxide dismutase. Exp Lung Res 16:355–367, 1990.
90. Smolle-Juettner FM, Prause G, Ratzenhofer B, et al: The importance of early detection and therapy of reexpansion pulmonary edema. Thorac Cardiovasc Surg 39:162–166, 1991.
91. Jones PW, Moyers JP, Rogers JT, et al: Ultrasound-guided thoracentesis: Is it a safer method? Chest 123:418–423, 2003.
92. Hillerdal G: Effusions from lymphatic disruptions. *In* Light RW, Lee YCG (eds): Textbook of Pleural Diseases. London: Arnold, 2003, pp 362–369.
93. Doerr CH, Allen MS, Nichols FCR, Ryu JH: Etiology of chylothorax in 203 patients. Mayo Clin Proc 80:867–870, 2005.
94. Alexiou C, Watson M, Beggs D, et al: Chylothorax following oesophagogastrectomy for malignant disease. Eur J Cardiothorac Surg 14:460–466, 1998.
95. Shimizu J, Hayashi Y, Oda M, et al: Treatment of postoperative chylothorax by pleurodesis with the streptococcal preparation OK-432. Thorac Cardiovasc Surg 42:233–236, 1994.
96. Shimizu K, Yoshida J, Nishimura M, et al: Treatment strategy for chylothorax after pulmonary resection and lymph node dissection for lung cancer. J Thorac Cardiovasc Surg 124:499–502, 2002.
97. Shitrit D, Izbicki G, Starobin D, et al: Late-onset chylothorax after heart-lung transplantation. Ann Thorac Surg 75:285–286, 2003.
98. Kamasaki N, Ikeda H, Wang ZL, et al: Bilateral chylothorax following radical neck dissection. Int J Oral Maxillofac Surg 32:91–93, 2003.
99. Hanekamp MN, Tjin A Djie GCM, van Hoek-Ottenkamp WG, Hazebroek FWJ, et al: Does V-A ECMO increase the likelihood of chylothorax after congenital diaphragmatic hernia repair? J Pediatr Surg 38:971–974, 2003.
100. Shackcloth MJ, Poullis M, Lu J, Page RD: Preventing of chylothorax after oesophagectomy by routine pre-operative administration of oral cream. Eur J Cardiothorac Surg 20:1035–1036, 2001.
101. Romero S, Martin C, Hernandez L, et al: Chylothorax in cirrhosis of the liver: Analysis of its frequency and clinical characteristics. Chest 114:154–159, 1998.
102. Avila NA, Dwyer AJ, Rabel A, Moss J: Sporadic lymphangioleiomyomatosis and tuberous sclerosis complex with lymphangioleiomyomatosis: Comparison of CT features. Radiology 242:277–285, 2007.
103. McCulloch MA, Conaway MR, Haizlip JA, et al: Postoperative chylothorax development is associated with increased incidence and risk profile for central venous thromboses. Pediatr Cardiol 29:556–561, 2008.
104. Rice TW, Rodriguez RM, Barnette R, Light RW: Prevalence and characteristics of pleural effusions in superior vena cava syndrome. Respirology 11:299–305, 2006.
105. Perkett EA: Pediatric pleural diseases. *In* Light RW, Lee YCG (eds): Textbook of Pleural Diseases. London: Arnold, 2003, pp 475–480.
106. Jacquemont S, Barbarot S, Boceno M, et al: Familial congenital pulmonary lymphangectasia, non-immune hydrops fetalis, facial and lower limb lymphedema: Confirmation of Njolstad's report. Am J Med Genet 93:264–268, 2000.
107. Van Aerde J, Campbell AN, Smyth JA, et al: Spontaneous chylothorax in newborns. Am J Dis Child 138:961–964, 1984.
108. Huang XZ, Wu JF, Ferrando R, et al: Fatal bilateral chylothorax in mice lacking the integrin α9β1. Mol Cell Biol 20:5208–5215, 2000.
109. Dellinger MT, Hunter RJ, Bernas MJ, et al: Chy-3 mice are Vegfc haploinsufficient and exhibit defective dermal superficial to deep lymphatic transition and dermal lymphatic hypoplasia. Dev Dyn 236:2346–2355, 2007.
110. Gupta S, Ramjaun AR, Haiko P, et al: Binding of Ras to phosphoinositide 3-kinase p110alpha is required for Ras-driven tumorigenesis in mice. Cell 129:957–968, 2007.
111. Miller JIJ: Diagnosis and management of chylothorax. Chest Surg Clin N Am 6:139–148, 1996.
112. Agrawal V, Sahn SA: Lipid pleural effusions. Am J Med Sci 335:16–20, 2008.
112a. McGrath EE, Blades Z, Anderson PB: Chylothorax: aetiology, diagnosis and therapeutic options. Respir Med 104:1–8, 2010.
113. Staats BA, Ellefson RD, Budahn LL, et al: The lipoprotein profile of chylous and nonchylous pleural effusions. Mayo Clin Proc 55:700–704, 1980.
114. Agrawal V, Doelken P, Sahn SA: Pleural fluid analysis in chylous pleural effusion. Chest 133:1436–1441, 2008.
115. Sachs PB, Zelch MG, Rice TW, et al: Diagnosis and localization of laceration of the thoracic duct: Usefulness of lymphangiography and CT. AJR Am J Roentgenol 157:703–705, 1991.
116. Browse NL, Allen DR, Wilson NM: Management of chylothorax. Br J Surg 84:1711–1716, 1997.
117. Stavngaard T, Mortensen J, Brenoe J, Svendsen LB: Lymphoscintigraphy using technetium-99m human serum albumin in chylothorax. Thorac Cardiovasc Surg 50:250–252, 2002.
118. Liu N, Wang C, Sun M: Noncontrast three-dimensional magnetic resonance imaging vs lymphoscintigraphy in the evaluation of lymph circulation disorders: A comparative study. J Vasc Surg 41:69–75, 2005.
119. Al-Zubairy SA, Al-Jazairi AS: Octreotide as a therapeutic option for management of chylothorax. Ann Pharmacother 37:679–682, 2003.
120. Buettiker V, Hug MI, Burger R, Baenziger O: Somatostatin: A new therapeutic option for the treatment of chylothorax. Intensive Care Med 27:1083–1086, 2001.
121. Evans J, Clark MF, Mincher L, Varney VA: Chylous effusions complicating lymphoma: A serious event with octreotide as a treatment option. Hematol Oncol 21:77–81, 2003.
122. Parames F, Freitas I, Fragata J, et al: Octreotide—additional conservative therapy for postoperative chylothorax in congenital heart disease. Rev Port Cardiol 28:799–807, 2009.
123. Cannizzaro V, Frey B, Bernet-Buettiker V: The role of somatostatin in the treatment of persistent chylothorax in children. Eur J Cardiothorac Surg 30:49–53, 2006.
124. Guillem P, Papachristos I, Peillon C, Triboulet JP: Etilefrine use in the management of post-operative chyle leaks in thoracic surgery. Interact Cardiovasc Thorac Surg 3:156–160, 2004.
125. Murphy MC, Newman BM, Roadgers BM: Pleuroperitoneal shunts in the management of persistent chylothorax. Ann Thorac Surg 48:195–200, 1989.
126. Urizar RE, Kolnacki K, Kaslovsky R, et al: Chylothorax fluid autoinfusion in a chronic hemodialysis patient. Pediatr Nephrol 18:403–406, 2003.
127. Jimenez CA, Mhatre AD, Martinez CH, et al: Use of an indwelling pleural catheter for the management of recurrent chylothorax in patients with cancer. Chest 132:1584–1590, 2007.
128. Le Pimpec-Barthes F, D'Attellis N, Dujon A, et al: Chylothorax complicating pulmonary resection. Ann Thorac Surg 73:1714–1719, 2002.

129. Mares DC, Mathur PN: Medical thoracoscopic talc pleurodesis for chylothorax due to lymphoma: A case series. Chest 114:731–735, 1998.
130. Cope C, Kaiser LR: Management of unremitting chylothorax by percutaneous embolization and blockage of retroperitoneal lymphatic vessels in 42 patients. J Vasc Interv Radiol 13:1139–1148, 2002.
131. Mittleider D, Dykes TA, Cicuto KP, et al: Retrograde cannulation of the thoracic duct and embolization of the cisterna chyli in the treatment of chylous ascites. J Vasc Interv Radiol 19:285–290, 2008.
132. Robinson CLN: The management of chylothorax. Ann Thorac Surg 39:90–95, 1985.
133. Suemitsu R, Ondo K, Fukuyama S, Ueda H: Late-period-onset chylothorax after a pulmonary resection for lung cancer: A case report. Ann Thorac Cardiovasc Surg 13:345–348, 2007.
134. Thompson KJ, Kernstine KH, Grannis FWJ, et al: Treatment of chylothorax by robotic thoracic duct ligation. Ann Thorac Surg 85:334–336, 2008.
135. Khelif K, Massarani F, Dassonville M, Laet MH: Thoracoscopic thoracic duct sealing with LigaSure in two children with refractory postoperative chylothorax. J Laparoendosc Adv Surg Tech A 17:137–139, 2007.
136. Vassallo BC, Cavadas D, Beveraggi E, Sivori E: Treatment of postoperative chylothorax through laparoscopic thoracic duct ligation. Eur J Cardiothorac Surg 21:556–557, 2002.
137. Janssen JP, Joosten HJ, Postmus PE: Thoracoscopic treatment of postoperative chylothorax after coronary bypass surgery. Thorax 49:1273, 1994.
138. Roy PH, Carr DT, Payne WS: The problem of chylothorax. Mayo Clin Proc 42:457–467, 1967.
139. Romero S: Nontraumatic chylothorax. Curr Opin Pulm Med 6:287–291, 2000.
140. Abrams ME, Meredith KS, Kinnard P, Clark RH: Hydrops fetalis: A retrospective review of cases reported to a large national database and identification of risk factors associated with death. Pediatrics 120:84–89, 2007.
141. Bartha JL, Comino-Delgado R: Fetal chylothorax response to maternal dietary treatment. Obstet Gynecol 97:820–823, 2001.
142. Tanemura M, Nishikawa N, Kojima K, et al: A case of successful fetal therapy for congenital chylothorax by intrapleural injection of OK-432. Ultrasound Obstet Gynecol 18:371–375, 2001.
143. Brito T, Oliveira C, Sousa L, et al: Congenital chylothorax: A case report. Ultrasound Obstet Gynecol 21:70–71, 2003.
144. Jorgensen C, Brocks V, Bang J, et al: Treatment of fetal chylothorax associated with pronounced hydrops with intrapleural injection of OK-432. Ultrasound Obstet Gynecol 21:66–69, 2003.
145. Parra J, Amenedo M, Muniz-Diaz E, et al: A new successful therapy for fetal chylothorax by intrapleural injection of maternal blood. Ultrasound Obstet Gynecol 22:290–294, 2003.
146. Beghetti M, La Scala G, Belli D, et al: Etiology and management of pediatric chylothorax. J Pediatr 136:653–658, 2000.
147. Chan GM, Lechtenberg E: The use of fat-free human milk in infants with chylous pleural effusion. J Perinatol 27:434–436, 2007.
148. Ryu JH, Doerr CH, Fisher SD, et al: Chylothorax in lymphangioleiomyomatosis. Chest 123:623–627, 2003.
149. Taylor JR, Ryu J, Colby TV, Raffin TA: Lymphangioleiomyomatosis: Clinical course in 32 patients. N Engl J Med 323:1254–1260, 1990.
150. Sullivan EJ: Lymphangioleiomyomatosis: A review. Chest 114: 1689–1703, 1998.
151. Kalassian KG, Doyle R, Kao P, et al: Lymphangioleiomyomatosis: New insights. Am J Respir Crit Care Med 155:1183–1186, 1997.
152. Hirama M, Atsuta R, Mitani K, et al: Lymphangioleiomyomatosis diagnosed by immunocytochemical and genetic analysis of lymphangioleiomyomatosis cell clusters found in chylous pleural effusion. Intern Med 46:1593–1596, 2007.
153. Johnson SR, Tattersfield AE: Clinical experience of lymphangioleiomyomatosis in the UK. Thorax 55:1052–1057, 2000.
154. Urban T, Lazor R, Lacronique J, et al: Pulmonary lymphangioleiomyomatosis: A study of 69 patients. Medicine 78:321–337, 1999.
155. Boehler A, Speich R, Russi EW, Weder W: Lung transplantation for lymphangioleiomyomatosis. N Engl J Med 335:1275–1280, 1996.
156. Garcia-Zamalloa A, Ruiz-Irastorza G, Aguayo FJ, Gurrutxaga N: Pseudochylothorax: Report of 2 cases and review of the literature. Medicine 78:200–207, 1999.
157. Wrightson JM, Stanton AE, Maskell NA, et al: Pseudochylothorax without pleural thickening—time to reconsider pathogenesis? Chest 136:1144, 2009.
158. Hamm H, Pfalzer B, Fabel H: Lipoprotein analysis in a chyliform pleural effusion: Implications for pathogenesis and diagnosis. Respiration 58:294–300, 1991.
159. Hillerdal G: Chyliform (cholesterol) pleural effusion—eleven new cases. Chest 86:426–428, 1985.
160. Garcia-Pachon E, Fernandez LC, Lopez-Azorin F, Padilla-Navas I: Pseudochylothorax in pleural effusion due to coronary artery bypass surgery. Eur Respir J 13:1487–1488, 1999.
161. Nogueras C, Monteagudo M, Vila M, et al: Recent-onset tuberculous pleurisy presenting as pseudochylothorax. Am J Med 113:166–168, 2002.
162. Song JW, Im JG, Goo JM, et al: Pseudochylous pleural effusion with fat-fluid levels: Report of six cases. Radiology 216:478–480, 2000.
163. Drummond DS, Craig RH: Traumatic hemothorax: Complications and management. Am Surg 33:403–408, 1967.
164. Ma OJ, Mateer JR: Trauma ultrasound examination versus chest radiography in the detection of hemothorax. Ann Emerg Med 29:312–315, 1997.
165. Wolverson MK, Crepps LF, Sundaram M, et al: Hyperdensity of recent hemorrhage at body computed tomography: Incidence and morphologic variation. Radiology 148:779–784, 1983.
166. Simon BJ, Chu Q, Emhoff TA, et al: Delayed hemothorax after blunt thoracic trauma: An uncommon entity with significant morbidity. J Trauma 45:673–676, 1998.
167. Seamon MJ, Medina CR, Pieri PG, et al: Follow-up after asymptomatic penetrating thoracic injury: 3 hours is enough. J Trauma 65:549–553, 2008.
168. Carrillo EH, Richardson JD: Thoracoscopy in the management of hemothorax and retained blood after trauma. Curr Opin Pulm Med 4:243–246, 1998.
169. Hagiwara A, Yanagawa Y, Kaneko N, et al: Indications for transcatheter arterial embolization in persistent hemothorax caused by blunt trauma. J Trauma 65:589–594, 2008.
170. Vassiliu P, Velmahos GC, Toutouzas KG: Timing, safety, and efficacy of thoracoscopic evacuation of undrained post-traumatic hemothorax. Am Surg 67:1165–1169, 2001.
171. Wilson JM, Boren CHJ, Peterson SR, Thomas AN: Traumatic hemothorax: Is decortication necessary? J Thorac Cardiovasc Surg 77:489–495, 1979.
172. Velmahos GC, Demetriades D, Chan L, et al: Predicting the need for thoracoscopic evacuation of residual traumatic hemothorax: Chest radiograph is insufficient. J Trauma 46:65–70, 1999.
173. Meyer DM, Jessen ME, Wait MA, Estrera AS: Early evacuation of traumatic retained hemothoraces using thoracoscopy: A prospective, randomized trial. Ann Thorac Surg 64:1396–1400, 1997.
174. Kimbrell BJ, Yamzon J, Petrone P, et al: Intrapleural thrombolysis for the management of undrained traumatic hemothorax: A prospective observational study. J Trauma 62:1175–1178, 2007.
175. Beall ACJ, Crawford HW, DeBakey ME: Considerations in the management of acute traumatic hemothorax. J Thorac Cardiovasc Surg 52:351–360, 1966.
176. Brunner RG, Vinsant GO, Alexander RH, et al: The role of antibiotic therapy in the prevention of empyema in patients with an isolated chest injury (ISS 9-10): A prospective study. J Trauma 30:1148–1153, 1990.
177. Waller DA, Edwards JG, Martin-Ucar AE: Surgery of the pleural cavity. *In* Light RW, Lee YCG (eds): Textbook of Pleural Diseases. London: Arnold, 2003, pp 513–525.
178. Krauss D, Schmidt GA: Cardiac tamponade and contralateral hemothorax after subclavian vein catheterization. Chest 99:517–518, 1991.
179. Rostand RA, Feldman RL, Block ER: Massive hemothorax complicating heparin anticoagulation for pulmonary embolus. South Med J 70:1128–1130, 1977.

180. Kalomenidis IT: Effusions due to drugs. *In* Light RW, Lee YCG (eds): Textbook of Pleural Diseases. London: Arnold, 2003, pp 383–393.
181. Mrug M, Mishra PV, Lusane HC, et al: Hemothorax and retroperitoneal hematoma after anticoagulation with enoxaparin. South Med J 95:936–938, 2002.
182. Lee YCG, Lane KB: The many faces of transforming growth factor beta in pleural diseases. Curr Opin Pulm Med 7:173–179, 2001.
183. Azoulay E, Paugam B, Heymann MF, et al: Familial extensive idiopathic bilateral pleural fibrosis. Eur Respir J 14:971–973, 1999.
184. Chan CH, Arnold M, Chan CY, et al: Clinical and pathological features of tuberculous pleural effusion and its long-term consequences. Respiration 58:171–175, 1991.
185. Candela A, Andujar J, Hernandez L, et al: Functional sequelae of tuberculous pleurisy in patients correctly treated. Chest 123:1996–2000, 2003.
186. Lai YF, Chao TY, Wang YH, Lin AS: Pigtail drainage in the treatment of tuberculous pleural effusions: A randomised study. Thorax 58:149–151, 2003.
187. Matchaba PT, Volmink J: Steroids for treating tuberculous pleurisy. Cochrane Database Syst Rev 2:CD001876, 2000.
188. Chapman SJ, Cookson WO, Musk AW, Lee YCG: Benign asbestos pleural disease. Curr Opin Pulm Med 9:266–271, 2003.
189. Musk AW, De Klerk NH: Benign asbestos pleural diseases. *In* Light RW, Lee YCG (eds): Textbook of Pleural Diseases (2nd ed). London: Arnold, 2008, pp 499–506.
190. Copley SJ, Lee YCG, Sivakumaran P, et al: Use of high resolution computed tomography (HRCT) to determine relative contribution of asbestos-induced pleuro-pulmonary disease and emphysema to lung function impairment (abstract). Am J Respir Crit Care Med 167:A987, 2003.
191. Pfitzenmeyer P, Foucher P, Dennewald G, et al: Pleuropulmonary changes induced by ergoline drugs. Eur Respir J 9:1013–1019, 1996.
192. Hillerdal G, Lee J, Blomkvist A, et al: Pleural disease during treatment with bromocriptine in patients previously exposed to asbestos. Eur Respir J 10:2711–2715, 1997.
193. Cottin V, Brillet PY, Combarnous F, et al: Syndrome of pleural and retrosternal "bridging" fibrosis and retroperitoneal fibrosis in patients with asbestos exposure. Thorax 63:177–179, 2008.
194. Davies HE, Lee YCG: Pleurodesis. *In* Light RW, Lee YCG (eds): Textbook of Pleural Diseases (2nd ed). London: Arnold, 2008, pp 569–582.
195. Lange P, Mortensen J, Groth S: Lung function 22–35 years after treatment of idiopathic spontaneous pneumothorax with talc poudrage or simple drainage. Thorax 43:559–561, 1988.
196. Pinsky PF, Freedman M, Kvale P, et al: Abnormalities on chest radiograph reported in subjects in a cancer screening trial. Chest 130:688–693, 2006.
197. Lee YCG, Runnion CK, Pang SC, et al: Increased body mass index is related to apparent circumscribed pleural thickening on plain chest radiographs. Am J Ind Med 39:112–116, 2001.
198. Copley SJ, Wells AU, Rubens MB, et al: Functional consequences of pleural disease evaluated with chest radiography and CT. Radiology 220:237–243, 2001.
199. Singh B, Eastwood PR, Finucane KE, et al: Effect of asbestos-related pleural fibrosis on excursion of the lower chest wall and diaphragm. Am J Respir Crit Care Med 160:1507–1515, 1999.
200. Yates DH, Browne K, Stidolph PN, Neville E: Asbestos-related bilateral diffuse pleural thickening: Natural history of radiographic and lung function abnormalities. Am J Respir Crit Care Med 153:301–306, 1996.
201. Picado C, Laporta D, Grassino A, et al: Mechanisms affecting exercise performance in subjects with asbestos-related pleural fibrosis. Lung 165:45–57, 1987.
202. Munoz X, Roger A, Pallisa E, et al: Ventilatory insufficiency due to asbestos-related diffuse pleural fibrosis successfully treated with noninvasive home mechanical ventilation. Respiration 68:533–536, 2001.
203. Diacon AH, Theron J, Schuurmans MM, et al: Intrapleural streptokinase for empyema and complicated parapneumonic effusions. Am J Respir Crit Care Med 71:519–522, 2004.
204. Fielding DI, McKeon JL, Oliver WA, et al: Pleurectomy for persistent pain in benign asbestos-related pleural disease. Thorax 50:181–183, 1995.
205. Gorur R, Yildizhan A, Yiyit N, et al: Spirometric changes after pleural decortication in young adults. Aust N Z J Surg 77:344–346, 2007.
206. Boffa DJ, Mason DP, Su JW, et al: Decortication after lung transplant. Ann Thorac Surg 85:1039–1043, 2008.
207. Hillerdal G: Non-malignant asbestos pleural disease. Thorax 36:669–675, 1981.

CHAPTER 75

TUMORS OF THE PLEURA

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INTRODUCTION

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INTRODUCTION

Tumors of the pleural space can be primary or secondary. The secondary tumor due to metastatic spread of malignancy usually from lung or breast cancer is the most common and is discussed first. Pleural metastatic disease is estimated to affect 200,000 persons/yr in the United States and serves as the most common cause of exudative pleural effusion after infection.[1] Unfortunately, because it represents metastatic spread, treatment goals are generally that of palliation, not cure. Survival is poor, with a median of 4 months.[2] Primary tumors of the pleural space are less common. The most common primary tumor, malignant mesothelioma, affects approximately 3000 persons/yr in the United States, although the incidence is growing worldwide.[1] Interestingly, despite its grim reputation, mesothelioma offers better survival than does metastatic pleural disease, with a median survival of less than 12 months.[3] Although curative treatments are not yet available, progress is being made. Other rare but interesting tumors such as solitary fibrous tumor of the pleura, primary effusion lymphoma, and pyothorax-associated lymphoma are discussed.

METASTATIC PLEURAL DISEASE

Types of Tumor

Certain tumors appear to have a predilection for metastasis to the pleura, particularly lung cancer, breast cancer, and lymphomas, and less commonly gastrointestinal and genitourinary malignancies (Table 75-1). In approximately half the cases of metastatic pleural disease, the patient will have an associated pleural effusion, most often exudative.[4] However, in up to 10% of the malignant pleural effusions, the tumor of origin is not identified.[5] After infectious diseases, malignant pleural effusions are the leading cause of exudative effusions.[1]

The pattern of metastatic spread can provide some clues to the identity of the primary tumor. Whereas malignant mesotheliomas generally originate on the parietal pleura and then spread to the visceral pleura, metastases due to bronchogenic carcinoma usually are first found on the visceral pleura and then spread to the parietal pleura. Metastatic pleural involvement is rarely found exclusively on the parietal pleura.[4] In addition, the side of a malignant effusion is usually the same as the tumor of origin in most cases of bronchogenic carci-

TABLE 75-1. Primary Tumors Responsible for Malignant Pleural Effusion*

Primary Tumor Site	Total (%)
Lung	37.5
Breast	16.8
Lymphoma	11.5
Gastrointestinal	6.9
Genitourinary	9.4
Other	7.3
Unknown	10.7

*A compilation of data from five different reports with a total of 2040 patients. The "other" category includes ovarian carcinoma, sarcomas, uterine and cervical carcinomas, and other carcinomas.
From Antunes G, Neville E, Duffy J, et al: BTS guidelines for the management of malignant pleural effusions. Thorax 58:ii29–ii38, 2003.

noma, with 17 out of 24 cases ipsilateral in one autopsy series.[6] In patients with pleural metastasis due to other cancers, evidence from two autopsy series suggests that the malignancy initially involves the visceral pleura and moves to the pleural space from there.[4,6]

Clinical Features

The most common symptom associated with malignant pleural disease is dyspnea, most often from the presence of a pleural effusion (see Chapter 73). Cough may also be caused by the presence of a pleural effusion. If the effusion is the cause of these symptoms, both dyspnea and cough can be relieved promptly by thoracentesis. When a thoracentesis fails to relieve these symptoms, tumor infiltration of lung or pleura or another medical condition should be suspected. Chest pain is often described as a "dull ache"; this may indicate involvement of the chest wall and sensory neurons of the parietal pleura and chest wall. Because sensory neurons are now known to lie in the visceral pleura, pain may not necessarily mean involvement of the parietal pleura and chest wall.[7] In one series, 34% of patients with malignant pleural effusion described a dull chest ache and 24% described a pleuritic chest pain.[8] Patients with benign causes of their effusions were more likely to describe pleuritic chest pain.[8] Systemic symptoms may include malaise and anorexia.

Malignant Pleural Effusions

Malignant pleural disease can exist without pleural effusion. In autopsy studies of patients with malignancy, malignant pleural disease was associated with an effusion in 55%[4] to 60%[6] of cases. It is increasingly recognized that malignant cells can reach the pleural space without effusion because cytology of pleural lavage can be positive in patients undergoing resection for lung cancer who have no effusion. In one study of more than 1200 patients with lung cancer without effusion undergoing curative surgical resection, 7.0% had positive pleural cytology on lavage at the time of resection.[9] The development of an effusion may depend on characteristics of the tumor cells because of either their secretion of bioactive mediators or their ability to initiate inflammatory, angiogenic, or fibrinolytic processes.[10]

Lung cancer is the most common cause of malignant pleural effusions[11] (see Table 75-1). Lung cancer and breast cancer together account for more than half of all malignant pleural effusions. Of the histologic types of bronchogenic cancers, adenocarcinomas are most frequently associated with malignant pleural effusions, but effusions may be seen with all types.[12]

Breast cancer is the second most common cause of malignant pleural effusions.[11,13] The time course of development of the effusion from the time of initial diagnosis of breast cancer is usually 2 years, but can be up to 20 years. The effusion usually is ipsilateral to the side of the original tumor (50%) but can also be contralateral (40%) and, less commonly, bilateral (10%).[14]

Lymphoma is the third most common cause in most series[11] but is possibly the most common cause in young adults.[13] Pleural effusions are common in both non-Hodgkin and Hodgkin lymphoma.[15] In patients with non-Hodgkin lymphoma, approximately 16% will develop malignant effusions and most will have the effusion at the time of initial diagnosis in association with evidence of disease elsewhere.[16] The high yield of pleural fluid cytology suggests frequent invasion of the pleural space.[17] Chylothorax may also develop in some patients with non-Hodgkin lymphoma. In Hodgkin lymphoma, effusions may be caused by hilar or mediastinal lymph node involvement as well as pleural involvement.[15]

Malignancies probably produce pleural effusions by both increasing the entry of liquid and by decreasing the normal exit of liquid (Table 75-2) (see Chapter 73). The entry of liquid can be increased by several mechanisms: (1) increased permeability of the pleural vessels by direct invasion of tumor cells, inflammatory and vasoactive cytokines (e.g., vascular endothelial growth factor [VEGF]), or injury (e.g., radiation-induced), (2) increased permeability of *pulmonary* vessels by infection, pulmonary embolism, or pulmonary infarct with movement of liquid from lung to pleural space, (3) increased hydrostatic forces due to venous obstruction or hypoproteinemia, and (4) entry of other sources of liquid such as chyle from a disrupted thoracic duct. The exit of liquid from the pleural space can be decreased by several mechanisms that would reduce lymphatic drainage: (1) infiltration of parietal pleural lymphatics or mediastinal lymph nodes, (2) lowered pleural pressure due to atelectasis from bronchial obstruction, or (3) elevated downstream central venous pressure, as from a superior vena cava (SVC) syndrome. We suspect that several factors combine to form a pleural effusion in association with malignancy.[18] The malignancy alone may be sufficient to tip the balance between the entry and the exit of liquid toward accumulation of excess pleural liquid. Alternatively, the malignancy may alter the balance gradually without the development of an overt effusion; the advent of another nonmalignant condition, such as heart failure or pneumonia, may then tip the balance and precipitate

TABLE 75-2. Pathophysiologic Mechanisms (Neoplastic and Paraneoplastic) by which Malignancy May Cause Pleural Effusions*

Means of Increasing Liquid	Mechanism	Site/Source	Examples
Increased entry	Increased vascular permeability	Pleural vessels	Invasion by tumor
			Cytokines (e.g., VEGF)
			Injury (e.g., radiation)
		Pulmonary vessels	Infection (e.g., postobstructive pneumonitis)
			Cytokines/injury
	Increased vascular hydrostatic gradient	Pleural vessels	Decreased pleural pressure (e.g., atelectasis)
			Increased venous pressure (e.g., SVC syndrome)
			Decreased plasma osmotic pressure (e.g., hypoproteinemia)
	Nonvascular source	Thoracic duct	Chylothorax
Decreased exit	Increased resistance to lymphatic flow	Pleural lymphatics	Infiltration of parietal pleura
		Lymph nodes	Infiltration of mediastinal lymph nodes
	Increased pressures opposing lymphatic flow		Decreased pleural pressure (e.g., atelectasis)
			Increased venous pressure (e.g., SVC syndrome)

*Most likely, both an increase in entry and a decrease in exit are required to produce a stable pleural effusion. Paraneoplastic refers to mechanisms taking place outside the pleural space.
SVC, superior vena cava; VEGF, vascular endothelial growth factor.
Adapted from Broaddus VC: Physiology: fluid and solute exchange in normal physiological states. *In* Light R, Lee Y (eds): Textbook of Pleural Diseases. London: Hodder Arnold, 2008, pp 43–48.

the appearance of a symptomatic pleural effusion. In these cases, malignancy may contribute to but not be the sole cause of the effusion.[18] Such processes may explain how malignancy can be associated with transudative effusions.[19]

In several animal studies, bioactive molecules involved in angiogenesis and permeability, such as VEGF, have been identified that may play key roles in accumulation of effusions in malignancy.[10] Understanding the mechanisms of effusion formation could lead to new therapeutic approaches such as inhibition of VEGF or the VEGF receptor or interfering with multiple actions including permeability and angiogenesis.

Pleural Fluid Analysis

The pleural fluid is almost always an exudate. The effusion may meet exudative criteria by the lactate dehydrogenase (LDH) only (either the ratio or the absolute level) and not by protein criteria.[20] Such an observation may indicate that an increased cell turnover and cell lysis is the source of the elevated LDH, whereas an increased vascular permeability needed to produce pleural fluid with increased protein concentration is not present. In some studies, perhaps 5% of malignant effusions are found to be transudates.[21] In most of these cases, the primary cause of these "malignant" transudative effusions appears to be congestive heart failure or other known cause of a transudate (e.g., SVC, volume overload), whereas the malignancy is in a secondary, contributing role.[21] Malignancy could be the primary cause of a transudate if, for example, the malignancy interfered with lymphatic absorption of pleural liquid.[18] In such cases, one could imagine that the accumulation of normal pleural liquid as an effusion would produce a transudate. In one interesting case report, a patient with metastatic colon cancer, but without other comorbid conditions, presented with transudative pleural effusions and negative cytology; within 1 month, the effusions were exudative with positive cytology.[22] Biopsy showed parietal pleural lymphatic infiltration, suggesting that the cause of the initial transudative effusion was primarily blockage of pleural liquid lymphatic clearance, followed by invasion of the pleural space and development of an exudate.

The effusion may be grossly bloody; indeed, malignant disease is the most common cause of bloody effusions.[23] However, about half of malignant effusions are not bloody in appearance and have pleural fluid red blood cell counts under 10,000 cells/μL.[23] On cell differential, a predominance of lymphocytes is usual, but a mononuclear or eosinophilic predominance does not exclude the diagnosis. The presence of pleural fluid eosinophilia (>10% eosinophils) has been thought to be unusual in malignant effusion and to argue against the diagnosis.[24] However, in a more recent study of 460 effusions, 20% of the eosinophilic effusions were found to be malignant; of note, 20% of non-eosinophilic effusions were also found to be malignant, showing not only that eosinophilic effusions could be malignant but also that the presence of eosinophilia did not alter the likelihood of malignancy.[25] Eosinophilia in many of these situations may be caused by other factors, such as the prior entry of air or blood into the pleural space. In another study in which care was taken to study only the initial thoracentesis to avoid artifacts due to prior entry of air or blood, eosinophilia was present in 12.6% of all effusions tapped and the presence of eosinophilia did not differentiate malignant from benign etiologies.[26]

The pleural glucose concentration is lower than 60 mg/dL in approximately 20% of malignant pleural

effusions.[27] Effusions with a low glucose level also tend to have a low pleural pH and may have a larger tumor burden in the pleural space. It would therefore be expected that those patients with a low pleural glucose or pH would have a shorter survival and a poorer response to pleurodesis, as has been reported.[28,29] However, more recent studies have found that pleural fluid pH may not be an accurate predictor of survival[30,31] and may also fail to predict which patients will respond to a pleurodesis.[30,32] Therefore, the pleural fluid pH or glucose should not be relied upon for selecting patients for pleurodesis. In fact, for survival, the best predictor may not lie in the pleural space; in one study, the best criteria for predicting survival was the Karnofsky score, a scale from 0 to 100 based on results of the history and physical examination (see "Prognosis and Staging," later).[31]

Pleural fluid amylase concentration is elevated in 10% of patients with malignant pleural effusions.[33] The origin of the amylase is not the pancreas, as shown by its identification as salivary rather than pancreatic amylase.[34] In one series of consecutive effusions, a very high amylase in malignant pleural fluid (>600 IU/L) was a poor prognostic factor.[33]

Radiographic Evaluation

The size of malignant effusions may vary greatly. Some may be small, amounting to a few milliliters and causing only blunting of the costophrenic angle, whereas others are large enough to obscure the hemithorax. In fact, malignancy is the most common cause of effusions that are either large, opacifying more than two thirds of hemithorax, or massive, opacifying the entire hemithorax. In one retrospective series of 766 patients, malignancy was found as the cause of 55% of large and massive effusions[35]; the other causes were pleural empyema and tuberculous effusions. Of these large malignant effusions, most were caused by lung or breast cancer. Interestingly, cytologic examination was no more likely to be positive in these large/massive effusions as in smaller ones (63% yield from large effusions; 53% from small).[35]

If the effusion is large, it is important to note the position of the mediastinum. It is expected that in an uncomplicated situation, the mediastinum will be shifted away from a large effusion. If the mediastinum is midline, one can suspect one of two things: (1) the pleural pressures are equal on the two sides, implying that significant lung collapse is present, offsetting the increase in pressure expected from the presence of the effusion or (2) the mediastinum is fixed in position and cannot shift in response to a pressure differential. If the mediastinum is shifted toward the side of the effusion, the pressure is most likely lower on the side of the effusion than on the other side; in that case, the lung must be unable to expand fully in response to this abnormally low pressure. Because the lung is restricted from expanding or is trapped, due either to mainstem bronchial obstruction or to infiltration by tumor, it is unlikely to reinflate with chest tube thoracostomy. In situations in which the mediastinum is shifted toward a massive effusion, placement of chest tubes is not recommended. Instead, a bronchoscopy would be a reasonable next step to investigate for bronchial obstruction as a possible reason for the failure of lung expansion.

Computed tomography (CT) has the advantage of providing detailed information about the pleural surfaces as well as about the lung parenchyma, chest wall, and mediastinum. Thus, one obtains clues about the identity of the tumor of origin as well as staging information. The typical features found in malignant pleural disease are pleural thickening (>1 cm), irregularity, and nodules (Fig. 75-1). In a prospective CT study of 40 patients with suspected malignant effusions, these pleural characteristics discriminated well between malignant and benign disease, with a sensitivity for malignancy of 84% and a specificity of 100%.[36] In a larger CT study of 211 consecutive patients with effusions, the most specific findings for malignancy were pleural nodules and nodular thickening.[37] Pleural thickening alone was not as specific and was seen in malignancy as well as empyema. Whereas the presence of pleural nodules was highly specific, it was not sensitive because only 17% of malignant effusions had associated pleural nodules. Interestingly, half of the patients with malignant effusions had no pleural abnormalities on the CT; other CT findings suggested malignancy such as the presence of a pulmonary mass, chest wall involvement, large mediastinal nodes, and hepatic metastases.[37]

Although magnetic resonance imaging (MRI) is not advocated for routine evaluation of malignant effusions, its excellent soft tissue contrast may be useful for detailed evaluation of tumor invasion.[38] It may be particularly useful in evaluating the chest wall and pleura in the apices of the hemithoraces.

Positron emission tomography (PET) with [^{18}F]fluorodeoxyglucose can be very useful for differentiating benign pleural abnormalities from malignancy[39] and provides useful information for staging in cases of

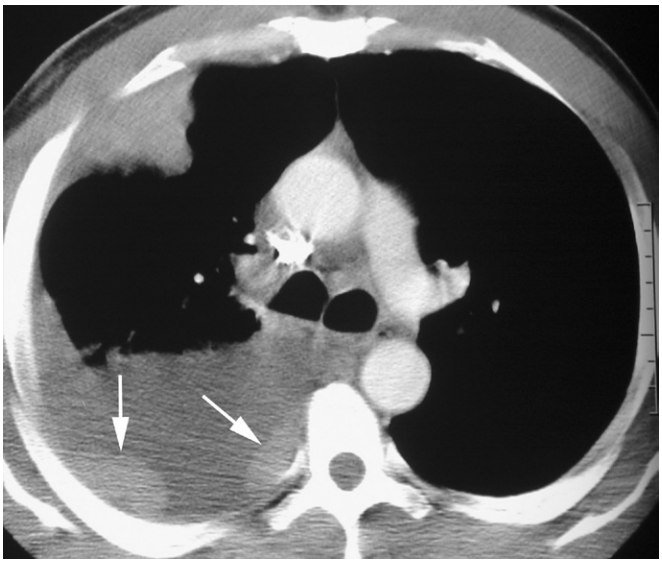

FIGURE 75-1 ■ Metastatic adenocarcinoma. Axial contrast-enhanced thoracic computed tomography (CT) scan shows right pleural effusion associated with enhancing nodular masses (*arrows*) emanating from the parietal pleura, later shown to be metastatic adenocarcinoma.

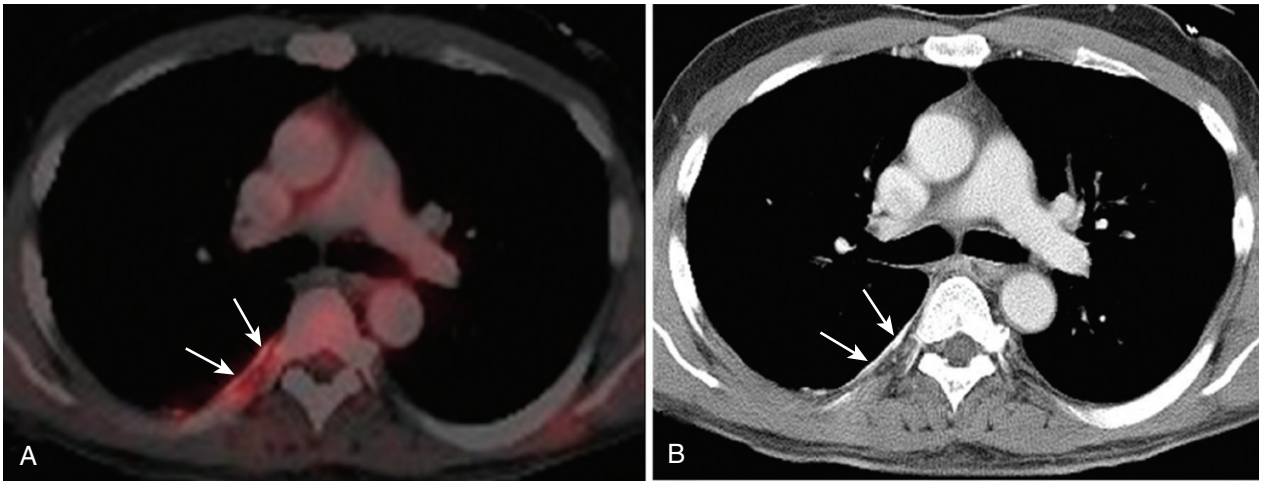

FIGURE 75-2 ■ Increased positron emission tomography (PET) scan activity at site of talc pleurodesis. **A,** A PET/CT scan obtained in a patient with a prior talc pleurodesis for recurrent pneumothorax shows increased pleural uptake (*arrows*). **B,** The axial thoracic CT image confirms that the area of increased PET uptake corresponds to an area of high attenuation characteristic of talc deposits. (Courtesy of Michael B. Gotway, MD, Scottsdale Medical Imaging and the Department of Radiology, University of California, San Francisco.)

documented malignancy. However, it may not always be able to differentiate pleural malignancy from benign pleural inflammation, such as that due to talc pleurodesis[40] (Fig. 75-2). In a patient with a history of talc pleurodesis, PET/CT can allow correlation of the increased uptake with areas of increased attenuation characteristic of talc deposits.[41]

Diagnosis

Cytology is reportedly diagnostic in approximately 60% of patients,[42] but the diagnostic yield varies with the type of tumor, extent of tumor involvement of the pleural space, and the skill of the cytologist (see Chapter 73). Cytology is more likely to be positive in adenocarcinoma than in squamous cell lung cancer, for example, perhaps because of the increased tendency of adenocarcinoma to invade the pleural space.[23] Interestingly, cytologic yield does not vary greatly with the size of the effusion; as mentioned, in one study, cytology was positive as often in large or massive effusions (63%) as in small or moderate-size effusions (53%).[35]

Biopsy may be necessary when cytology is negative or indeterminate. In the past, closed (or "blind") pleural biopsy was performed as a next step in cases in which cytology was negative. However, the patchy involvement of the parietal pleura by malignancy appears to make closed pleural biopsy a "hit or miss" technique and, not surprisingly, image-directed biopsies have been shown to be more accurate. In one randomized study comparing CT-guided biopsy with closed pleural biopsy using an Abrams needle, CT-guided biopsy was significantly more sensitive (87% vs. 47%) with a better negative predictive value (80% vs. 44%).[43] Pleuroscopy is a well-tolerated procedure that permits excellent visualization of the entire pleural surface (see also Chapter 23). Directed biopsies of suspicious areas detected metastatic pleural disease in nearly 100% of cases.[44] This technique has additional advantages, including the ability to provide large biopsies for immunohistochemical analysis or electron microscopy, the ability to provide information about the gross appearance of tumor, the ability to provide information for staging, the ability to lyse adhesions, and the ability to drain the pleural space for talc pleurodesis. It is worth remembering that metastatic disease can sometimes be diagnosed by fine-needle aspirates of abnormal lymph nodes in the cervical, supraclavicular, or other regions, bypassing invasive tests directed at the pleural space.

Biologic markers for malignancy may be identified as the molecular biology of cancer is better understood. Biomarkers in pleural fluid would potentially assist the cytologic diagnosis (see Chapter 73). Unfortunately, biomarkers have had indeterminate sensitivity and specificity, leading to overlap between malignant and nonmalignant conditions. One approach has been to combine tumor markers to improve diagnostic yield, although one may predict malignancy as well by using clinical characteristics (time of symptoms > 1 mo, absence of fever, serosanguineous fluid, and chest CT findings of malignancy).[45] For mesothelioma, detecting the molecule, mesothelin, a product of mesothelial cells, may have diagnostic utility in certain circumstances (see section on "Mesothelioma," later). The future of diagnosis may lie in genetic testing, either for features of malignancy (DNA methylation, mutations, microsatellites, telomerase, aneuploidy) or in the genetic expression fingerprint (microarray) characteristic of tumors.[46,47] Most exciting is the possibility that genetic testing of pleural cells may lead to the selection of therapy; for example, finding an epidermal growth factor receptor (EGFR) mutation in malignant pleural cells may predict response to appropriate EGFR inhibitors, such as gefitinib.[48]

Therapy and Palliation

The therapeutic and palliative approach to malignant pleural effusions is guided by several factors (Table 75-3).

TABLE 75-3. Options for Control of Symptomatic Malignant Effusions

Option	Patient Eligibility and Considerations
Chemotherapy	Chemoresponsive tumor
Thoracentesis	Slowly recurring effusion
	For patients with very short life expectancy
Pleurodesis	
Via chest tube	Lung able to reinflate
Via pleuroscopy	Can free up lung tacked down by adhesions
	When pleuroscopy already indicated for biopsies
Indwelling tunneled catheter	Good for outpatient situation
	Good for trapped lung
Pleuroperitoneal shunt	Patient must operate pump
	Good for trapped lung
	Excellent for chylothorax
Pleurectomy	
Via pleuroscopy	When other less invasive options have failed
Via thoracotomy	For patients with good status and life expectancy

The options are several and of increasing invasiveness. First of all, the clinician should determine that the effusion is causing either dyspnea or cough, symptoms that can be due to the volume of the effusion and its effect on lung and cardiac function (see Chapter 73). The most common and debilitating symptom caused by malignant effusions is dyspnea, and control of dyspnea can often be the primary focus of palliative therapy. Symptomatic effusions indicate the need to control the effusion, usually by obliterating the pleural space or by draining the effusion, either internally or externally. Important issues that help the clinician decide on the approach are whether the lung can reinflate fully, the clinical status of the patient, and the availability of approaches such as pleuroscopy. Obviously, the overall goal is to provide the greatest relief of symptoms using the least invasive, least morbid, and least expensive therapy. Management issues mainly focusing on palliation have been addressed in guidelines from the European Respiratory Society/American Thoracic Society (ERS/ATS)[49] and the British Thoracic Society.[11]

Systemic therapy with chemotherapy may be considered as dictated by the primary malignancy. Malignant pleural effusions that may respond to chemotherapy include those due to breast cancer, small cell lung cancer, and lymphoma.[14,50,51] Radiation therapy may be useful for treatment of the primary tumor or to treat local areas of chest wall invasion but is limited by the radiosensitive organs adjacent to the pleura, such as the lung and heart.

Repeated thoracentesis to remove a symptomatic effusion may be used in those unusual circumstances when the fluid reaccumulates slowly and the patient prefers this approach. Nonetheless, most malignant effusions recur rapidly and would need frequent drainage, making this approach useful in only a few cases, such as in a patient with a very short life expectancy.

Chemical pleurodesis can be considered when the lung can reinflate so it comes in contact with the parietal pleura. Even if contact can be achieved over a large but partial pleural surface area, pleurodesis may still be effective at preventing the rcurrence of large symptomatic effusions. Pleurodesis with talc is successful in most (70%–100%) cases[52] and is more effective than pleurodesis with other agents, including tetracycline and bleomycin.[49,52] Talc pleurodesis can be painful and, in a small percentage of patients, can lead to pulmonary edema and acute respiratory failure.[1] Evidence suggests that the smaller talc particles (<10 μm) can exit the pleural space and distribute systemically; in a randomized study, pleurodesis with graded talc (with most particles <10 μm removed) was associated with fewer complications than a mixed talc that included small particles.[53] Alternative sclerosing agents have been investigated, but currently, talc is the preferred agent because it is reported to have the highest success rates, followed by the tetracyclines and bleomycin. Nonetheless, there is significant variability in the practice of pleurodesis, as shown in a survey of pulmonologists in five countries.[54] Other agents include iodopovodine, nitrogen mustard, *Corynebacterium parvum*, OK432, and silver nitrate.[52]

The optimal mode of administration of talc is still unclear. Prospective trials have shown no benefit of large-bore tubes over small-bore tubes (12 French) for pleurodesis, although talc was used in a minority of these patients,[55] and no benefit from rotation of patients as determined by instillation of radiolabeled talc and by outcome.[56] Newer approaches that have shown promise include use of a small-bore catheter followed by outpatient talc instillation and removal of chest tubes as early as 24 hours after talc instillation.[57] Talc can be administered via slurry through chest tubes or by poudrage (insufflation) via pleuroscopy or video-assisted thoracoscopic surgery (VATS). In a prospective, randomized trial, talc slurry and poudrage were similar in efficacy; 71% of patients had a successful 30-day outcome following talc slurry and 78% following poudrage.[58] Interestingly, for the subgroup of patients with breast or lung cancer, poudrage may have been better than slurry (82% success with poudrage vs. 67% with slurry).[58] Pleuroscopy or VATS also has the ability to drain the pleural space completely at the time of talc instillation and lyse adhesions, steps that may increase the success of pleurodesis.

Chronic indwelling catheters have been shown to be effective alternatives to chemical pleurodesis. The catheter is inserted under local anesthesia and the patient drains the effusion via a daily or every other day protocol as an outpatient. This approach may be the only alternative when pleurodesis is not possible as, for example, when the lung cannot reexpand. It has now been recognized that not only can the indwelling catheters control symptoms but also, in many cases, can induce a symphysis allowing the tube to be removed without recurrence of the effusion. In a review of 263 patients with

malignant pleural effusions treated with indwelling, tunneled pleural catheters until drainage was less than 50 mL/day, the catheters could be removed in 58% of patients.[59] The average indwelling time for the catheter overall was 29 days. The success of the catheter alone was greater in those with breast and gynecologic tumors (70%–72%) and in those without a history of chest wall irradiation, those with positive cytology, and those with complete reexpansion of the underlying lung.[59] An added benefit of this outpatient approach is a reduction in hospitalization time, particularly attractive for a palliative procedure.[59a]

Pleuroperitoneal shunting is another alternative for palliation when the lung cannot reexpand or pleurodesis is unsuccessful, but is reserved primarily for patients with chylous effusions. Although it is a more invasive procedure, the pleuroperitoneal shunt allows the drainage of chyle into the abdomen, where it can be absorbed, and thus minimizes depletion of protein and lymphocyte populations. Rarely, malignant seeding along the chest wall can develop at the site of shunt insertion. Importantly, improvement in dyspnea is achieved in most patients (95%).[60] Of note, the external pump chamber must be manually compressed several times each day to move the pleural fluid into the peritoneal space.

Pleurectomy via thoracotomy can achieve a pleural symphysis when other treatment fails, but should be reserved for patients with an expected survival of longer than 6 months. This technique is reportedly very effective, but the operative mortality is relatively high (12.5%).[61] Pleurectomy via VATS has a lower operative mortality and morbidity. However, in a prospective study of 19 patients, the hospital stay was a median of 5 days and 2 patients developed recurrent effusions,[62] making chronic indwelling catheter placement more appealing for many of these patients.

Prognosis

The overall prognosis is poor for most patients with malignant pleural effusions. In an analysis of several studies with a total of over 400 patients, the median survival was 4.0 months.[2] The survival varied by tumor of origin; patients with malignant effusions from lung cancer had a lower median survival of 3.0 months, whereas those with pleural effusions from cancer of the breast had 5.0 months, from mesothelioma 6.0 months, and from lymphoma 9.0 months. When used to predict survival for any individual patient, pleural fluid pH or glucose is not sufficiently robust.[2] One of the strongest predictors appears to be the Karnofsky Performance Scale; in a prospective trial of 85 consecutive patients with malignant pleural effusions referred for pleuroscopic pleurodesis, those with a Karnofsky score above 70 had a median survival of 13.2 months, whereas those with a score below 30 had a median survival of 1.1 months.[31] Interestingly, in this study, when compared with other measures such as pleural fluid pH, glucose, or extent of carcinomatous involvement of the pleural surface, performance scoring was the only significant predictor of survival.

The poor life expectancy of patients with lung cancer and malignant pleural effusion has led to a revised staging classification for malignant pleural effusions[63] (see Chapter 47). In the 6th edition of the tumor-node-metastasis (TNM) classification, effective since 1997, malignancy of the pleural space was considered a T4 lesion, with a similar prognosis as other invasive lesions, and patients were staged as IIIB. However, in a comprehensive reassessment of staging and its effect on survival, patients with malignant pleural effusions were found to have a poorer prognosis than other T4M0 patients (8 mo vs. 13 mo), a prognosis that was closer to patients with metastatic disease to the opposite lung (10 mo).[63] In the revised staging system, pleural malignancy (malignant effusions or pleural nodular malignancy) is considered along with contralateral lung nodules as intrathoracic metastatic disease (M1a). Intrathoracic metastatic disease (M1a) is classified separately from extrathoracic metastatic disease (M1b) because of a somewhat better prognosis.[63]

MESOTHELIOMA

Incidence and Etiology

Malignant pleural mesothelioma is uncommon but can no longer be considered rare with almost 3000 cases/year diagnosed in the United States alone. The number of cases is anticipated to continue to increase in the United States and Western Europe until approximately 2020[64] due to the increase in occupational exposures to asbestos and asbestos-containing products that occurred after World War II. During the heyday of excitement about asbestos, asbestos was viewed as a modern breakthrough and was even used in such products as toothpaste[65] and cigarette filters![66] Unfortunately, after extensive use in industry and in building materials, asbestos fibers were discovered to be harmful, with multiple toxic effects leading to fibrosis and malignancy[67] (see later).

After 2020, the number of cases is anticipated to plateau and then gradually decline in these countries owing to the reduction in occupational exposures caused by restrictions on asbestos use, worker protection, and asbestos abatement efforts that were instituted from the mid-1970s to 1990s; nonetheless, many individuals will continue to be exposed incidentally (e.g., while performing home renovations). In those industrialized countries where the control of asbestos was delayed by several decades, as in Japan, the "epidemic" of mesothelioma will also be delayed by several decades. Unfortunately, asbestos continues to be mined, and its use is actually increasing in many developing countries.[68] Globally, there is a great disparity in asbestos use, with some countries adopting "asbestos bans" and others using asbestos without regulation. Interestingly, the United States does not have a ban although asbestos use has fallen to less than 1% of its historical peak.[69] In high-use countries, asbestos-induced lung cancer will also increase because of the multiplicative effects of

asbestos inhalation (including chrysotile) and cigarette smoking.[70]

Those with significant asbestos exposure and increased rates of mesotheliomas include workers in the asbestos industry, insulators, pipefitters, shipyard workers, brake mechanics, railroad workers, construction trades, carpenters, plumbers, electricians, painters, nonasbestos miners, welders, machinists, manufacturers of mineral products, and workers who perform maintenance and repair in buildings with asbestos insulation.[71] In addition, it is not uncommon to see women with asbestos-induced mesothelioma whose only clear asbestos exposure was from exposure to their spouses' contaminated clothing.[71a] Children who have been incidentally exposed can develop mesothelioma in early adult life. Incidence may rise due to recent population exposures such as from the dust that settled after the collapse of the World Trade Center.[72] In addition, recent use of nanoparticles and nanotubes raises concerns for unforeseen toxic effects analogous to those of asbestos.[73]

Other causes of mesothelioma have been postulated. Recently, there has been a great deal of controversy as to whether a simian virus (SV40) that contaminated the polio vaccine administered from 1955 through 1961 may be contributing to the development of mesotheliomas in the United States and other countries. SV40 is an intriguing candidate because it can immortalize cells by binding and inactivating both the retinoblastoma (Rb) protein and p53, key control steps for proliferation and apoptosis, respectively. In a review of 15 studies, mesothelioma tissues were 17 times more likely to have evidence of SV40 than were control tissues.[74] In cell and animal studies, SV40 may cooperate with asbestos in inducing damage and generating mesothelioma.[75] However, in humans, a causal relationship has not been established and epidemiologic studies to date have not shown an increase in the incidence of mesotheliomas in populations exposed to this virus.[76,77] Further complicating the analysis is the recognition that the presence of SV40 DNA sequences alone does not prove its role in tumor development. Viral proteins must be expressed and impair the function of cell proteins necessary for normal cell function. At this time, SV40 is still a subject of intense discussion, more as a possible co-carcinogen with asbestos than as a primary cause of mesothelioma. See arguments addressing the evidence for[78] and against[79] SV40 as a cause of mesothelioma.

Cigarette smoking is not associated with an increased incidence of mesotheliomas.[80] Silica or man-made vitreous fibers (rock/slag wool and fiberglass) have not been found to be associated with occupational mesotheliomas.[81,82] Excess cases of mesotheliomas have been identified in oil refinery workers; this risk was once thought to be due to exposure to petroleum oil and its products but is now attributed to occupational asbestos exposure.[83] Ionizing radiation may be a cause as well with a small increased risk in patients exposed to the radioactive contrast medium Thorotrast and in those who received therapeutic radiation for the treatment of lymphoma or breast cancer.[84]

Environmental asbestos exposures have been associated with the development of mesothelioma. Low-dose exposure in large populations may produce only "background" levels of asbestos in lung tissue but, because of the number of individuals exposed in that way, lead to an increase in the number of mesothelioma cases (similar to widespread exposure to sunlight and melanoma development). Exposure of occupants in buildings with asbestos-containing materials is generally not associated with increased asbestos fiber burden in the lung or an increase in mesothelioma incidence, unless the building materials are disturbed. Naturally-occurring asbestos can also be released into the air by home-building or road paving, leading to concern about increased risk for mesothelioma in exposed populations.[85] In Turkey, an extraordinarily high incidence of mesothelioma is found in certain villages in central Turkey with exposure to erionite dust, a nonasbestos crystalline fibrous form of the mineral zeolite. Finally, chronic inflammation of the pleura as in familial Mediterranean fever has been postulated to cause mesothelioma. At least four cases of mesothelioma have been reported in patients with this disease, presumably due to recurrent serositis.[86] Asbestos may still be an underlying cause or contributing factor in patients without a clear occupational exposure, given that fiber burden studies suggest that most urban dwellers have some asbestos fibers in their lungs.[87]

Although millions of workers have been exposed to significant amounts of asbestos, only a few develop mesothelioma, making it likely that there are genetic factors that increase susceptibility. Supporting the notion of genetic susceptibility is the identification of multiple clusters of this disease in families,[88] although clusters may also be explained by common environmental exposure to asbestos. Nonetheless, in the Cappadocian region of Turkey, where exposure to erionite is widespread, the susceptibility to mesothelioma appears to be inherited in an autosomal dominant pattern.[89]

Genetic Characteristics

Mesothelioma is characterized by a high degree of aneuploidy, but there is no single oncogene or tumor suppressor gene that has yet been found to underlie the tumor. The tumor suppressor genes most frequently implicated in mesothelioma are $p16^{INK4A}$-$p14^{ARF}$(9p21) and the neurofibromatosis type 2 (NF2) gene (22q12).[90] p53, a tumor suppressor mutated in most lung cancers and other solid tumors, is not frequently mutated in mesothelioma.[91] (For discussion of genetic abnormalities in lung cancer, see Chapter 45.) Nonetheless, abnormalities in the pathway that controls p53 function may still be present. Kras, a protooncogene frequently activated in lung cancer, is also not found to be abnormal in mesothelioma.[92] Studies of cytogenetics and loss of heterozygosity show consistent losses of chromosomal regions, suggesting that these regions may contain genes for key tumor suppressors. Losses are consistently found in regions 1p, 3p, 6q, 9p, 15q, and 22q. Growth-promoting genes suspected to play a role in mesothelioma include those coding for growth factors or growth factor

receptors (e.g., platelet-derived growth factor, EGFR). Gene expression profiling may provide additional insights into genetic abnormalities critical for mesothelioma and, in so doing, may also provide prognostic information, help with diagnosis, guide therapy, and suggest future therapeutic approaches.[93,94]

The long latency period between exposure to asbestos and development of mesothelioma suggests that multiple genetic abnormalities are required. Unlike the situation for bronchogenic carcinoma in which the natural history can be studied by repeatedly accessing the bronchial epithelium, the pleural space is not easily sampled, making the natural history of mesothelioma more opaque. Owing to their long, thin shape, asbestos fibers are inhaled deep into the lung and translocate from the lung to the pleural space; the fibers accumulate at the parietal pleura, where they can interact with mesothelial cells over decades. Along the way, the fibers are ingested by macrophages and induce a chronic inflammation. The fibers may also be internalized by mesothelial cells where they can both interfere with chromosome segregation leading to chromosome damage and generate reactive oxygen species via their iron content leading to oxidant injury to DNA.[95,96] In the process, the cells develop unregulated proliferation and an increased resistance to apoptosis.[97] The ability of asbestos fibers to produce the combination of chronic inflammation and of chromosomal and DNA damage may explain their potent carcinogenic effect. Damage or loss of key genetic areas containing tumor suppressors may be critical steps in generating mesothelioma. If SV40 contributes to this process, it may be by binding and inactivating key regulators of cell growth and survival, Rb and p53 proteins.

Clinical Features

The mean age at presentation is 60 years because of the long latency (usually 30–40 yr) from the time of first exposure to asbestos to the development of clinically evident disease.[64] The incidence is higher in men, presumably because more men have worked in asbestos-related trades.

Symptoms and physical findings are generally not specific for the disease. Most patients present with nonpleuritic chest pain or dyspnea.[98] Compared with that of metastatic pleural diseases, the pain from mesothelioma can be severe, aching, and often very difficult to control. Less common complaints are cough, fevers, chills, sweats, and fatigue. Fatigue, cachexia, and pain are common in advanced disease. Physical examination is usually only remarkable for signs related to the presence of a pleural effusion or mass. Later in the course of disease, one can often appreciate volume loss and decreased mobility of the chest wall on the side of the primary tumor. Occasionally, the tumor may extend directly into the chest wall and be detected as a tender or nontender chest wall mass.

Laboratory findings are also nonspecific and include anemia and thrombocytosis. Thrombocytosis (platelets >400,000/mm^3) can be seen in 40% of patients, may be due to production by the tumor of interleukin-6, and augurs a poor prognosis.[99,100] Measurement of mesothelin-family proteins in serum shows future promise for the diagnosis of mesothelioma and for monitoring of disease progression.[101]

Radiographic Evaluation

The most common findings on chest radiograph are a moderate to large unilateral pleural effusion or unilateral pleural thickening (nodular or smooth)[98] (Fig. 75-3). In a study of 99 patients with malignant mesothelioma, the most common finding on CT was a rindlike extension of tumor on the pleural surfaces (70%).[102] Other findings included circumferential lung encasement by multiple nodules (28%), pleural thickening with an irregular margin between the lung and the pleura (26%), and pleural thickening with pleural-based nodules (20%). Invasion of soft tissues and the chest wall with rib destruction may also be seen.[102] As the disease progresses and the lung becomes more encased with tumor, there is often volume loss with a shift of the mediastinum toward the side of the primary tumor (see Fig. 75-3). Signs of lymphatic metastasis may be seen but are more commonly evident late in the course of disease. Further tumor progression may lead to invasion into the contralateral chest. It is important to note that pleural plaques are often not visible; less than 20% of patients with mesothelioma may have radiographically apparent plaques.[103] Large mediastinal lymph nodes are more consistent with metastatic disease than with mesothelioma. Mediastinal adenopathy on chest radiographs or CT as the initial presentation of mesothelioma has been reported but is exceedingly rare,[104] although PET scanning often identifies active nodes that are normal in size and shape on imaging.[105] Radiographic features that favor the diagnosis of malignant mesothelioma over metastatic pleural disease were found by multivariate analysis to include

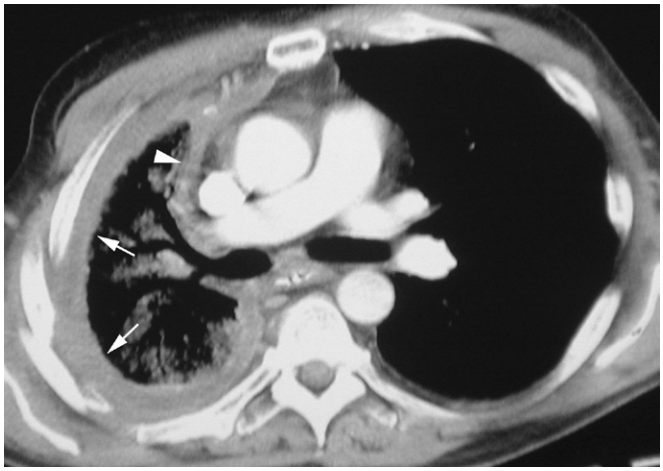

FIGURE 75-3 ■ Mesothelioma. Axial thoracic CT scan shows diffuse right pleural thickening (*arrows*) associated with marked volume loss in the right thorax. Note the presence of mediastinal pleural involvement (*arrowhead*).

FIGURE 75-4 ■ Mesothelioma. Magnetic resonance imaging (MRI) of the same patient as in Figure 75-3 with malignant mesothelioma shows invasion across the diaphragm by tumor (*arrow*).

rindlike pleural involvement, mediastinal pleural involvement, and pleural thickness more than 1 cm.[102]

Some clinicians prefer MRI over CT for staging and preoperative evaluation because, as reported in one study, MRI may demonstrate extent of disease and in particular chest wall and diaphragmatic invasion better than CT[106] (Fig. 75-4). However, this has not yet been shown to confer an important clinical advantage. In an earlier study, Heelan and coworkers[107] also found MRI superior in detection of tissue invasion in these areas, nonetheless, they found no improvement in staging and no alteration in therapy due to its use.

FDG-PET and particularly PET/CT show promise as tools to differentiate benign from malignant disease and as adjunctive tools for staging (Fig. 75-5). In a comparison of different diagnostic imaging techniques in patients with mesothelioma who then underwent surgery, PET/CT was more accurate than either PET, CT, or MRI alone.[108] It is hoped that functional assessment by PET may also be useful for monitoring response to therapy.[109]

In patients being considered for an extensive debulking procedure such as extrapleural pneumonectomy, every effort should be made to define the extent of disease, in particular to exclude patients with unsuspected extension beyond the pleura. A combination of imaging techniques may be selected to identify tumor spread.[110] However, even in patients with negative imaging, invasive approaches are often used to assure lack of tumor spread, such as preoperative endoscopic ultrasound with biopsy of suspicious nodes, mediastinoscopy, laparoscopy or thoracoscopic visualization of the contralateral pleura (see "Surgical Therapy," later).[111]

Diagnosis

The role of pleural fluid cytology in establishing a diagnosis is controversial, with some groups demonstrating a high level of diagnostic specificity and others demanding tissue histopathology.[112,113] Patterns of gene expression by microarray in cytologic samples may also help with diagnosis.[47] The only serum biomarker that is clinically useful is serum mesothelin which, in the serum, has a high specificity (>90%) but only a 50% sensitivity for the diagnosis.[101] Mesothelin biomarker levels in pleural fluid may also become useful in diagnosis.[114]

Closed pleural biopsy often misses malignant tissue, although it may be improved using CT guidance. In one study in which patients were randomly assigned to closed pleural biopsy or CT-guided biopsy, mesothelioma was diagnosed by closed pleural biopsy with a sensitivity of 55% (6/11) and by CT-guided biopsy with a sensitivity of 88% (8/9); although the difference was not significant because of small numbers, a similar diagnostic advantage of CT-guided biopsy was found for other pleural malignancies.[43] With current immunohistochemical stains, mesothelioma can usually, although not always, be differentiated from metastatic adenocarcinoma. It is often harder to differentiate mesothelioma from the benign mesothelial cell hyperplasias that often accompany inflammatory processes in the pleura. In uncertain cases, surgical biopsy is required to establish a definitive diagnosis. A surgical biopsy not only provides larger specimens for immunohistochemistry but also provides critical information about the biologic behavior of the tumor. The behavior of mesotheliomas is unique in that they usually start on the parietal pleural surface with multiple colonies of cells that coalesce and spread to the visceral pleura. Distant metastases are generally a very late finding. In contrast, metastatic adenocarcinomas are usually more prominent on the visceral pleural surface and often associated with distant metastasis. Benign inflammation lacks the surface irregularity usually (but not always) seen with malignant disease.

The preferred technique for surgical biopsy is via pleuroscopy (see Chapter 23). Not only does pleuroscopy have the advantage of obtaining large samples, but also it permits the drainage of effusions and the freeing up of a trapped lung.[115] In addition, if the lung is not trapped, talc can be insufflated at the end of the procedure to achieve a pleurodesis. The insertion site of the thoracoscope is an important consideration if tumor debulking is attempted in the future owing to the tendency of mesotheliomas to seed biopsy and chest tube sites.[112] Misdiagnosis with pleuroscopy has rarely been reported and, in those cases, was thought due to adhesions preventing access to the primary tumor.[116] If pleuroscopy cannot be performed due to the absence of pleural effusion, an incisional biopsy has an equally high diagnostic yield.

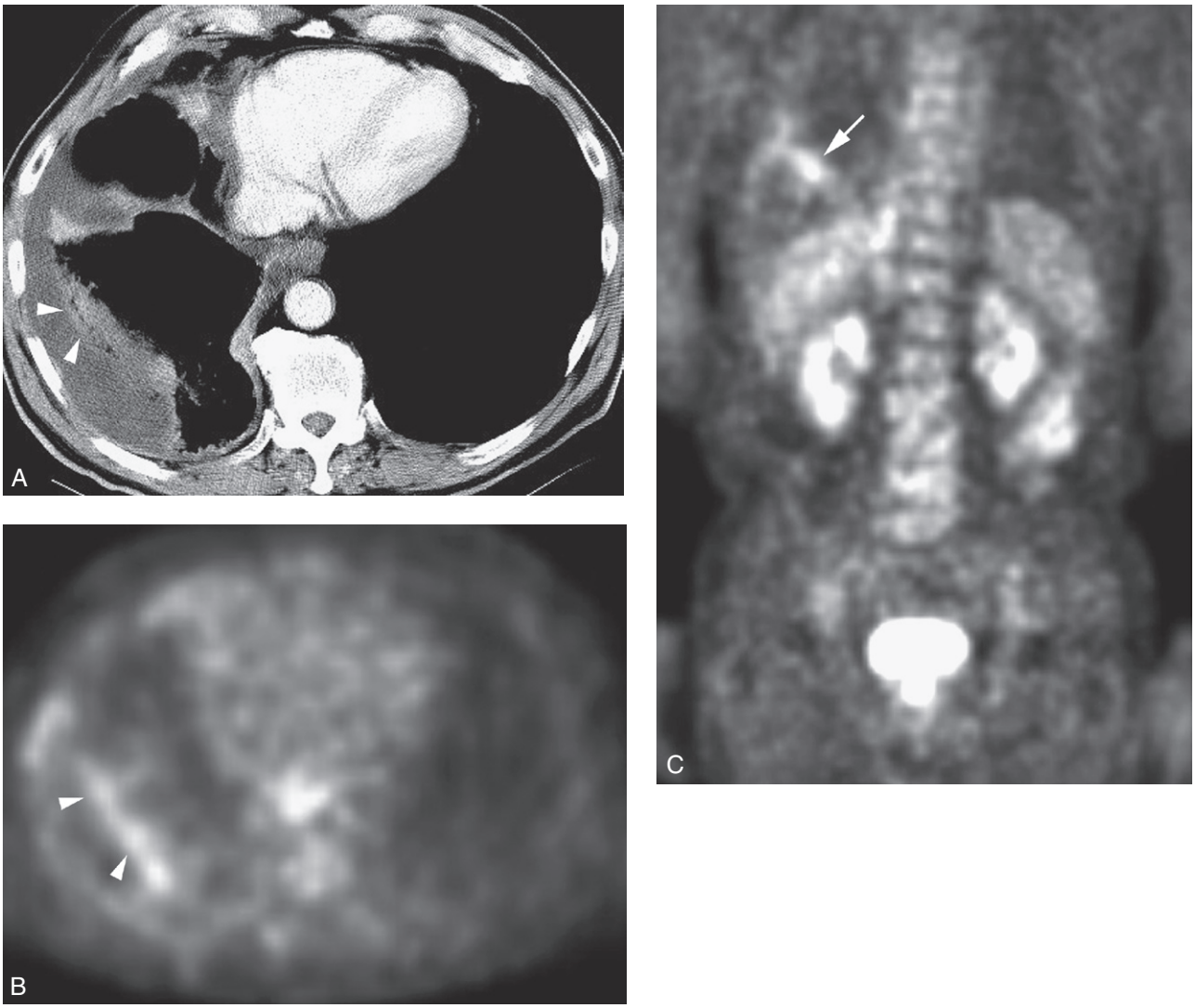

FIGURE 75-5 ■ Mesothelioma. **A,** Axial CT scan shows mesothelioma of the right chest with effusion and a thickened visceral pleura with underlying pulmonary atelectasis (*arrowheads*). **B,** Axial PET scan image indicates high activity in the area of thickened pleura, indicating likely involvement by tumor, suggesting at least a T2 lesion by International Mesothelioma Interest Group (IMIG) staging (*arrowheads*). The bright central uptake appears to indicate malignant involvement, either of a mediastinal lymph node or of the mediastinal pleura. **C,** Coronal view of PET also shows high activity of the visceral pleura in the fissure (*arrow*). (Courtesy of Michael B. Gotway, MD, Scottsdale Medical Imaging and the Department of Radiology, University of California, San Francisco.)

Intraoperative talc insufflation has been reported to have a greater than 95% success rate of preventing recurrent pleural effusion in this setting.[117] Talc pleurodesis does not apparently interfere with later attempts at surgical debulking. Talc pleurodesis does interfere with any intrapleural therapy that might be considered, such as intrapleural gene therapy now in clinical trials, so this potential therapeutic approach should be considered before pursuing pleurodesis. Talc pleurodesis can also confound interpretation of PET, which can show increased activity in areas of talc deposition for long periods of time following pleurodesis[40] (see Fig. 75-2 and discussion of PET, earlier). In such cases, PET/CT may be helpful by localizing the increased activity to areas of increased attenuation due to talc.[40]

Pathologic Features

The dilemma for the pathologist can be in differentiating mesothelioma both from metastatic adenocarcinoma and from reactive mesothelium. Because of the difficulties in establishing the diagnosis in some cases, an expert panel of pathologists from the United States and Canada was formed.[118] In their statement, they stressed the need for the pathologist to have information about the biologic behavior of the tumor from both radiographic and intraoperative observations. In addition, they stressed the need to obtain larger specimens to permit multiple immunohistochemical stains and perhaps electron microscopy. Ultrastructural features seen with electron microscopy that are typical of mesothelioma include cytoplasmic tonofilaments and long, sinuous, branching

microvilli.[119] In contrast, the microvilli of adenocarcinomas are relatively short, wide, and straight. For electron microscopy, some biopsy material must be preserved in glutaraldehyde, whereas formalin-fixed specimens can be analyzed by immunohistochemistry. Although a variety of immunohistochemical stains have been used to differentiate adenocarcinoma of the lung and mesothelioma, none is specific, especially with less well differentiated tumors. Use of a panel of immunohistochemical stains is recommended, with calretinin and cytokeratin 5/6 (or WT1) favoring mesothelioma, and CEA and MOC-31 (or B72.3, Ber-EP4, or BG-8) favoring adenocarcinoma.[120] Sarcomatous and biphasic mesothelioma raise special issues, usually in differentiating from other sarcomatous tumors.[120] Currently, immunohistochemical staining has been highly effective in diagnosis of mesothelioma, making electron microscopy usually unnecessary.

Prognosis and Staging

The median survival for patients with malignant mesothelioma is between 4 and 12 months from the time of diagnosis.[121] Regardless of therapy, patients with the epithelial cell type do best and those with the sarcomatous cell type the worst, with mixed or biphasic falling between the two other types.[121] In two separate studies, age, male gender, performance status, leukocytosis, and presence of chest pain were associated with a poorer prognosis.[100,122] Pathologic findings of microvessel density and tumor necrosis are poor prognostic factors.[123,124]

Staging is an issue for those patients in whom surgery is contemplated and continues to be controversial. Prior to the proposal of a TNM-based staging system by the International Mesothelioma Interest Group (IMIG),[125] there had been at least six other systems proposed for staging of mesotheliomas. None of the six was clearly shown to predict survival, including the most widely used Butchart staging system.[126] The TNM-based staging system is organized in a manner similar to the system currently in use for non–small cell carcinoma of the lung (Table 75-4). Further surgical studies at the Memorial Sloan Kettering supported the prognostic value of this system.[127,128] For example, patients with stage I disease had a median survival of 30 months and those with stage IV had a median survival of 8 months.[128] However, the Brigham group found it less useful for determination of surgical resectability and have proposed yet another staging system that is also widely used[129] (Table 75-5). It should be noted that this staging system requires resection to determine the involvement of surgical margins, limiting its applicability mostly to postsurgical staging.

Staging systems may be supplemented by prognostic scoring systems that do not require surgical staging. Prognostic scoring systems proposed by the European Organisation for Research and Treatment of Cancer (EORTC) and by the Cancer and Leukemia Group B (CALGB) incorporate performance status, histopathology, and other laboratory studies.[100]

TABLE 75-4. International Mesothelioma Interest Group Staging System for Malignant Pleural Mesothelioma

T1	Tumor limited to ipsilateral parietal pleura
T1a	No involvement of visceral pleura
T1b	Some scattered foci involving visceral pleura
T2	Tumor involving entire ipsilateral pleura, both visceral and parietal, plus one of the following: Invasion of diaphragmatic muscle, Or, confluent involvement of visceral pleura, including the fissures Or, invasion from visceral pleura into pulmonary parenchyma
T3	Tumor locally advanced but potentially resectable
T4	Tumor locally advanced and technically unresectable
NX	Regional nodes cannot be assessed
N0	No lymph node metastasis
N1	Metastasis to ipsilateral bronchopulmonary or hilar lymph nodes
N2	Metastasis to subcarinal or *ipsilateral* mediastinal nodes
N3	Metastasis to *contralateral* mediastinal or internal mammary nodes, or to any supraclavicular node
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis present

Stage	Description
Stage I	
Ia	T1aN0M0
Ib	T1bN0M0
Stage II	T2N0M0
Stage III	Any T3M0
	Any N1M0
	Any N2M0
Stage IV	Any T4
	Any N3
	Any M1

From Rusch VW: A proposed new international TNM staging system for malignant pleural mesothelioma from the International Mesothelioma Interest Group. Lung Cancer 14:1–12, 1996.

TABLE 75-5. The Brigham Staging System for Malignant Pleural Mesothelioma

Stage	Description
Stage I	Completely resectable
Stage II	Positive surgical margins and/or intrapleural adenopathy*
Stage III	Local extension and extrapleural disease
Stage IV	Distant metastasis

*Intrapleural adenopathy is any node present in the resected pleural envelope.

From Sugarbaker DJ, Norberto JJ, Swanson SJ: Surgical staging and work-up of patients with diffuse malignant pleural mesothelioma. Semin Thorac Cardiovasc Surg 9:356–360, 1997.

Therapy and Palliation

Surgical Therapy

The two potential goals of surgical therapy for mesothelioma are palliation of symptoms and debulking of tumor with therapeutic intent. Many believe that therapy should follow the paradigm of treatment developed for ovarian cancer because of the similarities in biologic behavior of the cancer and similar embryologic origin of the cells of the primary tumor.[130] In both diseases, surgical resection alone does not prevent disease recurrence. However, the approach of surgical debulking followed by systemic chemotherapy has shown significant success for the treatment of ovarian cancer. For surgical debulking of mesotheliomas, two surgical approaches are commonly employed: pleurectomy with decortication (P/D) or extrapleural pneumonectomy (EPP). P/D removes all gross disease from all pleural surfaces and preserves the underlying lung. EPP entails en bloc removal of the lung along with surrounding parietal pleura, pericardium, and diaphragm, with the pericardium and diaphragm then replaced by synthetic grafts. These are both technically challenging procedures and should be performed only by surgeons with extensive experience. EPP is especially difficult and was originally associated with an unacceptably high morbidity of 30%. However, with advances in surgical, anesthetic, and critical care techniques, and more exacting patient selection, experienced centers now report mortality rates of less than 4%, a rate comparable with that of standard pneumonectomy.[131] Both P/D and EPP are accomplished through an extended posterolateral thoracotomy and, as mentioned previously, talc pleurodesis is not a contraindication to either procedure and may actually facilitate the separation of the pleura from the chest wall.

Preoperative evaluation of patients considered for surgery includes a thorough assessment of tumor stage, cardiac function, and pulmonary function. Most surgery is confined to those with the epithelial cell morphology. If debulking surgery is to be of benefit, it is essential that tumor is early stage and confined to one hemithorax. Chest CT or MRI is the usual first step in staging. MRI is preferred by some centers for assessment of transdiaphragmatic extension of tumor (see Fig. 75-4), and many now request PET or PET/CT as well (see Fig. 75-5). Recognition that mediastinal lymph node involvement is a poor prognostic sign has prompted centers to require either cervical mediastinoscopy or endoscopic ultrasound with biopsy of suspicious nodes prior to EPP. Even with negative imaging studies, some groups perform extensive surgical staging with mediastinosopy as well as laparoscopy because mesothelioma often spreads through the diaphragm to the peritoneum.[111]

For patients who successfully complete such extensive screening, a few large series suggest that surgical debulking procedures may provide a survival advantage. In the first studies in which both surgeries were performed, it appeared as if pleurectomy was superior, with better survival than EPP.[127,132] However, in a follow-up report, the same investigators found that there was no difference in median survival between the two surgical debulking procedures.[128] Both series showed that failure after pleurectomy is more often local, whereas failure after EPP is more often extrathoracic. These results underscore the difficulty in eradicating mesothelioma with surgery alone.

Based on such studies showing that surgery alone is insufficient to cure mesothelioma, Sugarbaker and colleagues[131] at the Brigham and Women's Hospital have developed a strategy of tumor debulking using EPP followed by chemotherapy and high-dose radiation therapy to destroy residual tumor cells. This strategy was reported to yield a median survival of 19 months and a 5-year survival of 15%. However, patients with all three positive variables (an epithelial cell type, clean margins after resection, and negative lymph nodes) had a median survival of 51 months and a 5-year survival of 46%. Of note, patients with sarcomatous cell type did especially poorly. These results, although exciting, have been criticized for selection bias. Given the lack of prospective, randomized studies comparing surgery with or without adjuvant therapy with medical management or supportive care, the therapeutic or even palliative benefit of surgical debulking followed by chemotherapy and radiation therapy remains unknown. Some critics point out that there are some long-term survivors without treatment and that surgery may actually harm patients without improving survival.[133] For example, in one unrandomized, prospective study, 52 patients receiving surgery and other treatments (chemotherapy or radiotherapy) were compared with 64 patients without treatment. Although the treatments were felt to provide palliation, there was no significant difference in survival between treated and untreated patients.[134] Until randomized studies are performed, the best treatment plan for patients with mesothelioma will remain unknown.

Surgical debulking has been combined with a variety of other cytoreductive approaches to destroy residual tumor cells on the surface of the thoracic cavity including hyperthermia and photodynamic therapy, without convincing success. At this time, the value of surgical debulking and adjunctive measures such as hyperthermia, photodynamic therapy, intrapleural chemotherapy, immunotherapy, and radiation therapy is not known. It may be that an approach of debulking followed by some modality to eradicate residual tumor will improve outcome. However, until randomized trials are undertaken and a consensus is reached on staging, this will not be known with confidence.

Chemotherapy

Most patients with mesothelioma are not candidates for surgical or radiotherapy treatment and chemotherapy is their main option. There are two main regimens that are used in mesothelioma. The most commonly used now includes the multitargeted antifolate drug pemetrexed with a platinum drug such as cisplatinum. The use of this combination has been compared with cisplatin alone in a large phase III study of 456 patients.[135] Response rates

were significantly better in the pemetrexed/cisplatin arm than in the cisplatin-alone arm (41.3% vs. 16.7%), and survival was significantly better as well (median survival 12.1 mo vs. 9.3 mo). Importantly, the addition of folic acid and vitamin B_{12} significantly reduced toxicity without reducing the survival benefit.[135] The other regimen used commonly is the false nucleotide gemcitabine with a platinum agent. Nearly half of the patients on this doublet regimen noted symptom improvement, 33% had a partial response, and 60% had stable disease; no survival benefit was demonstrated compared with historical controls.[136] Similarly, treatment with the combination of gemcitabine and oxaliplatin has been reported to improve symptoms, but not to significantly improve survival (median survival of 13 mo).[137]

Newer Agents under Study. Studies of the molecular biology of mesothelioma and the cellular mechanisms leading to a malignant phenotype have led to the identification of several possible therapeutic targets for treatment of this disease. Some of these are already under investigation in clinical trials (see www.clinicaltrials.gov). For example, several receptor tyrosine kinases are aberrantly expressed in these tumors, including the EGFR.[138] Inhibitors of these proteins are now available in oral form and are being evaluated in patients with mesothelioma. However, so far, drugs blocking EGFR or platelet-derived growth factor (PDGF) receptor signaling, such as gefitinib and imatinib, have not proved to be of benefit when used as single agents. Other novel agents targeting growth factors found to be overexpressed in mesothelioma (e.g., VEGF and its receptor) are under investigation. Other agents under study include antiangiogenic agents (e.g., AZD2171, thalidomide, and PTK/ZK787), inhibitors of histone deacetylase superoylanilide and hydroxamic acid (SAHA), proteasome inhibitors, and histone deacetylase inhibitors (PXD101). Monoclonal antibodies labeled with toxins targeted to the mesothelioma cells are also being studied in immunotoxin trials.[139]

Radiation Therapy

Although in vitro studies suggest that mesothelioma is more sensitive to radiation than non–small cell lung cancer,[140] the clinical experience reported by radiation oncologists suggests that it is an especially radioresistant tumor. In addition, radiation of the involved chest is limited by the presence of radiosensitive organs and the extensive nature of the tumor. As a consequence, its use appears limited to adjunctive therapy for patients who have undergone EPP and to palliative treatment of painful chest wall lesions. Prophylactic chest wall irradiation may reduce the incidence of chest wall recurrences at incision sites, but there is no consensus on its use and randomized, controlled trials are needed.[141] An area of active ongoing research is the role of high-dose hemithorax irradiation after EPP for early-stage disease. In carefully staged patients, this approach has resulted in a marked reduction in local tumor recurrences, although nearly one half of patients subsequently developed isolated distant metastases.[142]

Immunotherapy

It is known that an immune response is induced by mesothelioma, but it is weak.[143] This knowledge has prompted a number of investigators to study different ways of strengthening that response. The intrapleural instillation of cytokines is limited by the short half-life of most cytokines, necessitating repeated injections or continuous infusion via a pleural catheter. Intrapleural interferon-γ twice weekly for 2 months was reported to induce response rate of 56% in early-stage disease.[144] A continuous intrapleural infusion of interleukin-2 induced a partial response in four of 21 patients and an overall survival of 16 months.[145] In both cases, side effects were minimal and consisted primarily of fever and constitutional symptoms. Studies in animals suggest that interferons have an antiproliferative effect on mesothelioma cells and enhance the cytotoxic effect of cisplatin. The results from these studies led to the development of a phase II trial of cisplatin-doxorubicin and interferon alfa-2b in advanced malignant mesothelioma.[146] The overall response rate was 29% and the median survival was 9.3 months with a 1-year survival of 45% and 2-year of 34%. However, severe myelosuppression was seen in 60% of patients, limiting the application of this treatment.[146]

Gene Therapy

Gene therapy strategies that have been investigated for the treatment of mesothelioma include mutation compensation, molecular chemotherapy, and genetic immunopotentiation. Mutation compensation attempts to block or replace abnormally expressed genes. The best example of this in mesothelioma is compensation for the absence of p16 gene expression, a consistent abnormality in mesothelioma. Reexpression of p16INK using an adenoviral vector improved survival in a murine model of mesothelioma.[147] Molecular chemotherapy is a technique of genetically modifying cancer cells to make them susceptible to a drug. For example, an adenoviral vector containing the herpes simplex thymidine kinase (HSVtk) gene has been injected into the pleural space of patients; the virus is taken up by mesothelioma cells and the HSVtk gene product makes the cells metabolize ganciclovir to a toxic by-product. In humans, such approaches have been limited by patchy viral uptake and the development of immunity to the virus.[148] Genetic immunopotentiation employs the genetic induction of an inflammatory antitumor response. For example, vaccinia virus carrying the gene for interleukin-2 has been studied in patients to determine toxicity.[149] Intratumoral injection was not only well tolerated but 50% of tumors were found to have T-cell infiltration. However, no tumor regression was seen. Recent gene therapy trials are focusing on the use of the interferon-beta gene to enhance immunity.[150]

Palliative Therapy

Pain is common and often disabling. Invasion of the chest wall can cause localized somatic pain, intercostal

nerve invasion or vertebral invasion can cause neuropathic pain, and lung invasion may cause diffuse visceral pain. Opioids, such as liquid morphine plus sustained release morphine, are the mainstay of pain control. Somatic pain responds to nonsteroidal anti-inflammatory drugs, and neuropathic pain requires an anticonvulsant such as carbamazepine or sodium valproate. Some patients require procedural pain relief as from intrathecal analgesia or nerve block.

Dyspnea and cough are often due to large pleural effusions or from tumor spread. The approach to palliation has been described for malignant pleural effusions earlier in this chapter, and some of these options are applicable to the effusions due to mesothelioma as well (see Table 75-3). Effusions due to mesothelioma can usually be controlled with pleurodesis or placement of an indwelling tunneled catheter. Pleurodesis with talc is an option if a patent pleural space is not needed later, as it would be for intrapleural therapy within clinical trials. Talc pleurodesis is reasonably effective and relatively inexpensive for this task. As described earlier, talc can be administered as a slurry through a chest tube or as an aerosol during thoracoscopy with equal effect. Regardless, with either technique, the affected lung must be capable of expanding so that the visceral and parietal pleura are in contact. Placement of a tunneled pleural catheter for chronic pleural drainage is another option for these patients, as described for "Malignant Pleural Effusions," earlier.

Psychosocial care is also very important in palliation given the fear, anger, and suffering associated with the disease.[151,152]

Chemoprevention and Screening

The existence of populations with known exposure to asbestos suggests that an effective chemoprevention strategy could reduce the incidence of mesothelioma. In one such study, former workers of the Wittenoom asbestos mines of Australia were assigned randomly to daily use of vitamin A (retinol) or β-carotene, without a placebo group.[153] Although not definitive, studies of retinol are continuing because of some early promising data. Such approaches have the potential of preventing a disease for which curative therapies do not yet exist.

Screening of high-risk populations has the potential of detecting early lesions that could respond better to therapy. Screening trials of high-risk populations are ongoing to determine the value of routine low-dose CT scanning.[154] The sensitivity of serum mesothelin is not sufficient for use as a marker for early-stage mesothelioma; biomarkers with greater sensitivity are needed.[114]

Additional information on clinical and basic research concerning mesothelioma can be found in reports of biannual meetings plus the website of the IMIG[155] (www.imig.org). Other independent websites are the National Cancer Institute (www.nci.nih.gov), Oncolink (Abramson Cancer Center, University of Pennsylvania) (www.oncolink.com), and for referral of patients for ongoing National Institutes of Health (NIH)-sponsored studies (www.clinicaltrials.gov).

SOLITARY FIBROUS TUMOR OF THE PLEURA

Solitary fibrous tumors are mesenchymal tumors that can arise not only in the pleura but also throughout the body.[156] The term "solitary fibrous tumor" is now used in preference to earlier terms such as "benign mesothelioma" or "localized mesothelioma" for several reasons: to distinguish it clearly from malignant mesothelioma, to acknowledge that it may contain malignancy within it, and also to recognize that its cellular origin is more likely from pleuripotential fibroblasts than from mesothelial cells.[1,157] These localized tumors of the pleura are more rare than malignant mesotheliomas, accounting for 8% of all benign pathologies of the chest and 10% of all pleural neoplasms.[158] More than 50% cause no symptoms and are identified as an incidental finding on radiographic examination.[159] When symptoms do occur, they are usually chronic and related to the mechanical effects of the tumor. Most commonly noted are cough, dyspnea, and chest pain.[157,160]

Paraneoplastic syndromes are associated with this tumor. Hypertrophic osteoarthropathy has been described in 14%[160] to 19%[157] and usually resolves over a few months following resection of the tumor.[157] Hypoglycemia has been described in between 4%[157] and 14%[160] of patients with solitary fibrous tumors, although the percentage may be elevated because the hypoglycemia may bring the patient to medical attention. The hypoglycemia arises from the production by the tumor of insulin-like growth factor II (IGF-II), which has insulin activity peripherally and at the liver.[161] As for other non–islet cell tumors associated with hypoglycemia, the hypoglycemia can be treated best by full resection of the tumor.[162] If this is not possible or while awaiting surgical resection, patients have been treated successfully with corticosteroids, which can suppress IGF-II production.[162]

Most solitary fibrous tumors arise from the visceral pleura, but some arise from the parietal.[160] In cases in which they appear within the lung parenchyma, the tumor border may be attached to the pleura via a pedicle or stalk. They are usually round and firm with clear borders and can grow to be several centimeters in diameter. On cut section, the tumor has a fibrous whorled appearance with occasional calcification, hemorrhage, and central necrosis. Cells are elongated and spindle-shaped on histologic examination. By immunohistochemistry, the solitary fibrous tumor can be distinguished from malignant mesothelioma by its staining for vimentin and CD34 (a hematopoietic progenitor cell antigen) and its lack of staining for keratin.[160,163]

Radiographic evaluation usually reveals a solitary circumscribed lesion (Fig. 75-6). It rarely may occupy the entire hemothorax, but the average size is about 6 cm. In one study, most of the masses appeared to have an atypical appearance for pleural-based tumors in that they appeared to form an acute angle with the chest wall on radiographic examinations.[164] This may be due to the size of the lesions and the tendency for them to hang from a pedicle into the lung.[164] In some cases, the mass

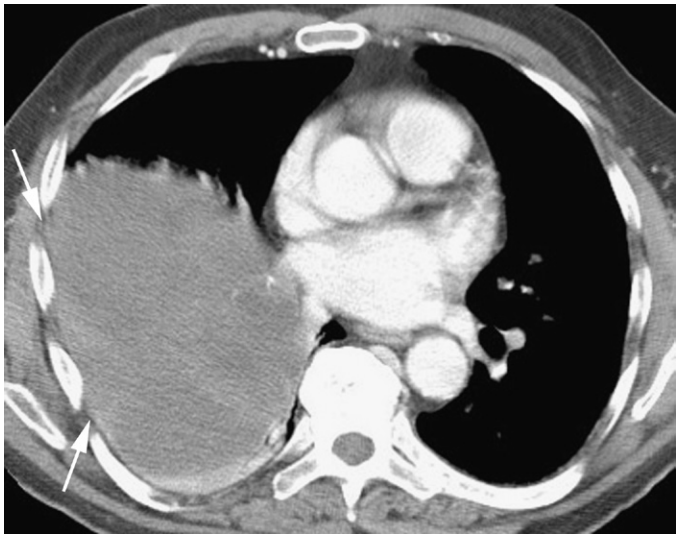

FIGURE 75-6 ■ Solitary fibrous tumor of the pleura. Axial CT image shows a large, somewhat heterogeneous mass in the right lower chest with extensive chest wall contact (*arrows*). (Courtesy of Michael B. Gotway, MD, Scottsdale Medical Imaging and the Department of Radiology, University of California, San Francisco.)

may be mobile due to the pedicle and occasionally movement can be documented using decubitus views. CT scans may reveal heterogeneous areas of enhancement in some larger tumors that correlate pathologically with areas of cystic necrosis and hemorrhage. All have contours that are smooth and lobulated without evidence of invasion into underlying tissues. Occasionally, dense calcification is seen.[165] MRI findings are consistent with a fibrous tumor with low signal on T1- and T2-weighted images.[166] There is little information about the use of PET to differentiate solitary fibrous tumors from malignant mesothelioma. However, the few cases in the literature support the finding of low or absent uptake of fluorodeoxyglucose on PET imaging of the solitary fibrous tumor.[167]

The diagnosis is strongly suggested by the chest radiograph and CT scan. If a paraneoplastic syndrome is present together with a large tumor of the pleural space, the diagnosis of solitary fibrous tumor is likely. Needle biopsy may be unhelpful and, even if malignancy is present within a portion of the tumor, may miss the areas of concern. Surgery is advised in most cases both for diagnosis by excision and for definitive treatment.

Surgical resection will be curative in most cases. When the tumor arises from the visceral pleura, surgical resection may involve wedge resection or lobectomy. Recurrences do occur and have been documented many years after resection, sometimes with malignant transformation.[157,168] Yearly chest radiographs are recommended to follow these patients after resection. Sometimes, return of a paraneoplastic syndrome can accompany a recurrence of the solitary fibrous tumor.[160]

Treatment of recurrent tumors can be difficult if reresection is not possible. Current approaches targeting VEGF and angiogenesis pathways have shown promise.[156]

PRIMARY EFFUSION LYMPHOMA

Primary effusion lymphoma (PEL) is a type of high-grade B-cell lymphoma that grows within the serous body cavities (pleural, peritoneal, and pericardial) without a detectable tumor mass (Fig. 75-7). Because of its tropism for serosal spaces, it is considered one of the entities within the group of body cavity lymphomas.[169] PEL is a body cavity lymphoma caused by the human herpes virus 8 (HHV8),[169] the same virus that is the etiologic cause of Kaposi's sarcoma. Most cases of PEL are found in homosexual men with advanced human immunodeficiency virus (HIV) disease. In a few cases, PEL has also been described in HIV-negative patients, usually elderly persons of Eastern European/Mediterranean descent, in an epidemiologic pattern similar to that of HIV-negative, classic Kaposi's sarcoma.[169] Many primary effusion lymphomas in HIV-positive patients are coinfected by Epstein-Barr virus (EBV),[169] suggesting a cooperative etiologic role between HHV8 and EBV. Nonetheless, the HHV8 is thought to be the primary etiologic factor and the identification of HHV8 is required for the diagnosis of PEL.[169]

PEL tends to occur as a late manifestation of HIV infection. Therefore, PEL should be considered in patients with advanced HIV disease with large exudative lymphocytic effusions. CT scan will show a small degree of pleural thickening, without any tumor mass or mediastinal adenopathy[170] (see Fig. 75-7). Pleural fluid may have a very elevated LDH level.[1] Cytologic examination will show pleomorphic large lymphocytes and suggest the diagnosis. The lymphocytes stain negatively for B- and T-cell antigens. Identification of HHV8 can be performed by extracting DNA from involved tissues followed by Southern blot analysis, by in situ hybridization of slides from paraffin-embedded samples, and by in situ reverse transcriptase polymerase chain reaction of cytologic smears or cell blocks.[171]

Treatment is usually attempted with a CHOP-like regimen (cyclophosphamide, doxorubicin, vincristine, and prednisone) and, if the patient is HIV-positive, antiretroviral therapy.[172] Some patients have shown benefit from antiretroviral therapy alone, suggesting that the immune reconstitution can be effective against the lymphoma.[172] Nonetheless, prognosis is poor, with a median survival of around 6 months. As more is learned

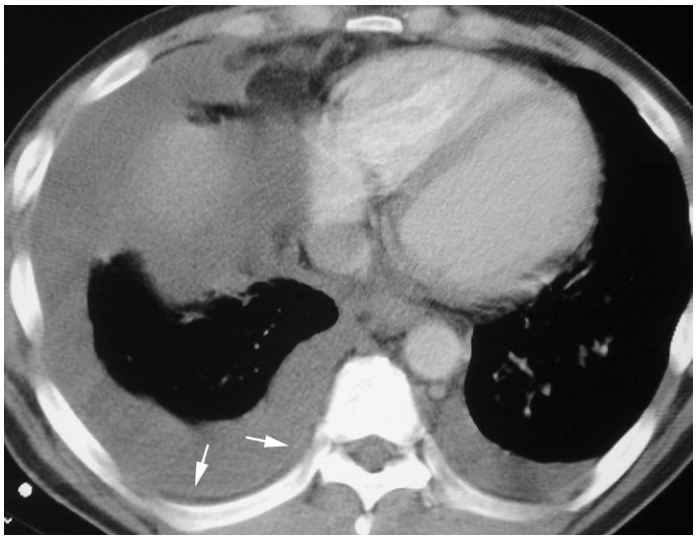

FIGURE 75-7 ■ Primary effusion lymphoma. On axial CT, the malignancy is manifest by bilateral effusions. *Arrows* indicate a minimally thickened parietal pleura, without nodularity. (Courtesy of Michael B. Gotway, MD, Scottsdale Medical Imaging and the Department of Radiology, University of California, San Francisco.)

of the life cycle of HHV8, there is hope for specific therapy targeting the causative virus.

PYOTHORAX-ASSOCIATED LYMPHOMA

Pyothorax-associated lymphoma (PAL) is an HHV8-negative body cavity lymphoma, associated with EBV.[169] It is a high-grade non-Hodgkin lymphoma occurring as a mass in the pleural space of patients with long-standing chronic pleural inflammation usually following artificial pneumothorax for pleuropulmonary tuberculosis.[173] This entity is mainly seen in Japan but has also been reported in Western countries.[173,174] The few series available report a strong association with EBV, with 70% of tumors having evidence of EBV in one study.[175] The cell type is usually B-cell with frequent plasmacytoid features, but occasionally an aberrant dual B/T phenotype may be seen.[174] As opposed to PEL, which is associated with systemic immunodeficiency as from HIV or old age, PAL is associated with a local pleural immunosuppression and antigenic stimulation.[169]

A relatively large review of 106 patients with PAL in Japan showed the median age at the time of diagnosis to be 64 years (range, 46–82 yr).[175] In these patients, there was at least a 20-year history of pyothorax (mean, 37 yr; maximum, 64 yr), and patients were predominately male (12:1). All had a history of chronic inflammation of the pleura, due to either artificial pneumothorax for treatment of pulmonary tuberculosis (80%) or tuberculous pleuritis (17%). Fever and/or back pain were the common symptoms on presentation, and chest radiograph or CT scan showed a localized pleural mass in an area of chronic pleural disease. There are no large series evaluating specific treatments for this disease. In some reports, it appears that patients may do better with radiotherapy than with chemotherapy.[176,177] In the review of 106 patient records, patients underwent a variety of treatments including surgical resection, chemotherapy with CHOP-like regimen or radiotherapy.[175] Patients appeared to respond initially to chemotherapy, but clinical outcome was poor with a 5-year survival of 22%.[175] In one patient undergoing treatment, the serum EBV load measured by a quantitative real-time polymerase chain reaction correlated well with tumor size, suggesting that monitoring of the serum EBV load might be helpful in the management of EBV-positive patients with this disease.[177] Recognition of the development of a pleural soft-tissue mass adjacent to a longstanding empyema cavity may allow earlier diagnosis and potentially better response to treatment.[178]

KEY POINTS

- Malignant effusions are most commonly due to lung cancer, followed by breast cancer and lymphoma.
- Malignant effusions are often diagnosed by cytology (60% of cases), which has a high yield for adenocarcinoma and a low yield for squamous cell carcinoma. If cytology is negative, image-guided biopsy and VATS have a high yield (80%–100%) for diagnosis.
- Malignancy may involve the pleural space without formation of an effusion. In the 7th edition of TNM staging for lung cancer, pleural malignancy with or without effusion is now classified as a metastatic lesion (M1a, intrathoracic metastasis).
- Palliation of malignant pleural effusions may include repeated taps, talc pleurodesis, indwelling catheter drainage, and even thoracotomy with pleurectomy, with the choice depending on the life expectancy of the patient and whether the lung can reexpand. Indwelling catheter drainage can lead to symphysis and catheter removal in many patients.
- Pleural mesothelioma should be considered in any patient with a persistent undiagnosed exudate, especially if there is a history of exposure to asbestos, chest pain, a rindlike nodular thickening of the pleura, and involvement of the mediastinal pleura. Diagnosis may be suggested by an elevated mesothelin in serum or pleural fluid but will require biopsy, often by VATS, for adequate tissue for panels of immunohistochemical stains.
- Pleural mesothelioma has been shown in a large prospective, randomized trial to respond to cisplatin plus pemetrexed; although not studied in a randomized trial, surgery may play a role in debulking and as a part of multimodality therapy including chemotherapy and radiotherapy.
- Solitary fibrous tumors are mesenchymal tumors that can involve the visceral pleura and are usually treated successfully with resection. If the tumors recur and cannot be resected again, targeted therapy is being used against VEGF and angiogenic pathways.
- Primary effusion lymphoma (PEL) and pyothorax-associated lymphoma (PAL) are both mostly B-cell body cavity lymphomas, the first presenting without a mass and the second as a mass. PEL is associated with systemic immunosuppression from HIV and is caused by HHV8; PAL is associated with long-standing pleural inflammation and with EBV.

References

1. Light RW (ed): Pleural Diseases (5th ed). Philadelphia: Lippincott, Williams & Wilkins, 2007.
2. Heffner JE, Nietert PJ, Barbieri C: Pleural fluid pH as a predictor of survival for patients with malignant pleural effusions. Chest 117:79–86, 2000.
3. Robinson BWS, Lake RA: Advances in malignant mesothelioma. N Engl J Med 353:1591–1603, 2005.
4. Rodriguez-Panadero F, Borderas Naranjo F, Lopez Mejias J: Pleural metastatic tumours and effusions. Frequency and pathogenic mechanisms in a post-mortem series. Eur Respir J 2:366–369, 1989.
5. Johnston WW: The malignant pleural effusion. A review of cytopathologic diagnoses of 584 specimens from 472 consecutive patients. Cancer 56:905–909, 1985.
6. Meyer PC: Metastatic carcinoma of the pleura. Thorax 21:437–443, 1966.
7. Pintelon I, Brouns I, De Proost I, et al: Sensory receptors in the visceral pleura. Am J Respir Cell Mol Biol 36:541–551, 2007.
8. Marel M, Stastny B, Melinova L, et al: Diagnosis of pleural effusions. Experience with clinical studies, 1986 to 1990. Chest 107:1598–1603, 1995.
9. Shintani Y, Ohta M, Iwasaki T, et al: Intraoperative pleural lavage cytology after lung resection as an independent prognostic factor for staging lung cancer. J Thorac Cardiovasc Surg 137:835–839, 2009.
10. Stathopoulos GT, Kalomenidis I: Animal models of malignant pleural effusion. Curr Opin Pulm Med 15:343–352, 2009.
11. Antunes G, Neville E, Duffy J, et al: BTS guidelines for the management of malignant pleural effusions. Thorax 58:ii29–ii38, 2003.
12. Chernow B, Sahn SA: Carcinomatous involvement of the pleura: An analysis of 96 patients. Am J Med 63:695–702, 1977.
13. Hsu C: Cytologic detection of malignancy in pleural effusion: A review of 5255 samples from 3811 patients. Diagn Cytopathol 3:8–12, 1987.
14. Fentiman IS, Millis R, Sexton S, et al: Pleural effusion in breast cancer: A review of 105 cases. Cancer 47:2087–2092, 1981.
15. Alexandrakis MG, Passam FH, Kyriakou DS, et al: Pleural effusions in hematologic malignancies. Chest 125:1546–1555, 2004.
16. Berkman N, Breuer R, Kramer MR, et al: Pulmonary involvement in lymphoma. Leuk Lymphoma 20:229–237, 1996.
17. Das DK, Gupta SK, Ayyagari S, et al: Pleural effusions in non-Hodgkin's lymphoma. A cytomorphologic, cytochemical and immunologic study. Acta Cytol 31:119–124, 1987.
18. Broaddus VC: Physiology: Fluid and solute exchange in normal physiological states. *In* Light R, Lee Y (eds): Textbook of Pleural Diseases. London: Hodder Arnold, 2008, pp 43–48.
19. Broaddus VC: Transudative pleural effusions. *In* Loddenkemper R, Antony V (eds): Pleural Diseases European Respiratory Monograph. Sheffield, UK: ERS, 2002, pp 157–176.
20. Light RW, MacGregor MI, Luchsinger PC, Ball WC Jr: Pleural effusions: The diagnostic separation of transudates and exudates. Ann Intern Med 77:507–513, 1972.
21. Ashchi M, Golish J, Eng P, et al: Transudative malignant pleural effusions: Prevalence and mechanisms. South Med J 91:23–26, 1998.

22. Fernandez C, Martin C, Aranda I, et al: Malignant transient pleural transudate: A sign of early lymphatic tumoral obstruction. Respiration 67:333–336, 2000.
23. Light RW, Erozan YS, Ball WC: Cells in pleural fluid: Their value in differential diagnosis. Arch Intern Med 132:854–860, 1973.
24. Adelman M, Albelda SM, Gottlief JE, et al: Diagnostic utility of pleural fluid eosinophilia. Am J Med 77:915–920, 1984.
25. Rubins JB, Raabe HB: Etiology and prognostic significance of eosinophilic pleural effusions. A prospective study. Chest 110:1271–1274, 1996.
26. Martinez-Garcia MA, Cases-Viedma E, Cordero-Rodriguez PJ, et al: Diagnostic utility of eosinophils in the pleural fluid. Eur Respir J 15:166–169, 2000.
27. Rodriguez-Panadero F, Lopez Mejias J: Low glucose and pH levels in malignant pleural effusions. Am Rev Respir Dis 139:663–667, 1989.
28. Rodriguez-Panadero F, Lopez-Mejias J: Survival time of patients with pleural metastatic carcinoma predicted by glucose and pH studies. Chest 95:320–324, 1989.
29. Sahn SA, Good JTJ: Pleural fluid pH in malignant effusions. Ann Intern Med 108:345–349, 1988.
30. Heffner JE, Heffner JN, Brown LK: Multilevel and continuous pleural fluid pH likelihood ratios for evaluating malignant pleural effusions. Chest 123:1887–1894, 2003.
31. Burrows CM, Mathews C, Colt HG: Predicting survival in patients with recurrent symptomatic malignant pleural effusions. Chest 117:73–78, 2000.
32. Heffner JE, Nietert PJ, Barbieri C: Pleural fluid pH as a predictor of pleurodesis failure. Chest 117:87–95, 2000.
33. Villena V, Perez V, Pozo F, et al: Amylase levels in pleural effusions: A consecutive unselected series of 841 patients. Chest 121:470–474, 2002.
34. Kramer MR, Saidan MJ, Cepero RJ, et al: High amylase levels in neoplasm related pleural effusion. Ann Intern Med 110:567–569, 1989.
35. Porcel JM, Vives M: Etiology and pleural fluid characteristics of large and massive effusions. Chest 124:978–983, 2003.
36. Traill ZC, Davies RJ, Gleeson FV: Thoracic computed tomography in patients with suspected malignant pleural effusions. Clin Radiol 56:193–196, 2001.
37. Arenas-Jimenez J, Alonso-Charterina S, Sanchez-Paya J, et al: Evaluation of CT findings for diagnosis of pleural effusions. Eur Radiol 10:681–690, 2000.
38. Knisely BL, Broderick LS, Kuhlman JE: MR imaging of the pleura and chest wall. Magn Reson Imaging Clin North Am 8:125–141, 2000.
39. Schaffler GJ, Wolf G, Schoellnast H, et al: Non-small cell lung cancer: Evaluation of pleural abnormalities on CT scans with ^{18}F FDG PET. Radiology 231:858–865, 2004.
40. Weiss N, Solomon SB: Talc pleurodesis mimics pleural metastases: Differentiation with positron emission tomography/computed tomography. Clin Nucl Med 28:811–814, 2003.
41. Kwek BH, Aquino SL, Fischman AJ: Fluorodeoxyglucose positron emission tomography and CT after talc pleurodesis. Chest 125:2356–2360, 2004.
42. Prakash US, Reiman HM: Comparison of needle biopsy with cytologic analysis for the evaluation of pleural effusions: Analysis of cytologic analysis in 414 cases. Mayo Clin Proc 60:158–164, 1985.
43. Maskell NA, Gleeson FV, Davies RJ: Standard pleural biopsy versus CT-guided cutting-needle biopsy for diagnosis of malignant disease in pleural effusions: A randomised controlled trial. Lancet 361:1326–1330, 2003.
44. Cardillo G, Facciolo F, Carbone L, et al: Long-term follow-up of video-assisted talc pleurodesis in malignant recurrent pleural effusions. Eur J Cardiothorac Surg 21:302–305, 2002 [discussion appears 305–306].
45. Ferrer J, Roldan J, Teixidor J, et al: Predictors of pleural maliginancy in patients with pleural effusion undergoing thoracoscopy. Chest 127:1017–1022, 2005.
46. Brock MV, Hooker CM, Yung R, et al: Can we improve the cytologic examination of malignant pleural effusions using molecular analysis? Ann Thorac Surg 80:1241–1247, 2005.
47. Holloway AJ, Diyagama DS, Opeskin K, et al: A molecular diagnostic test for distinguishing lung adenocarcinoma from malignant mesothelioma using cells collected from pleural effusions. Clin Cancer Res 12:5129–5135, 2006.
48. Zhang X, Zhao Y, Wang M, et al: Detection and comparison of epidermal growth factor receptor mutations in cells and fluid of malignant pleural effusion in non–small cell lung cancer. Lung Cancer 60:175–182, 2007.
49. Antony VB, Loddenkemper R, Astoul P, et al: Management of malignant pleural effusions. Eur Respir J 18:402–419, 2001.
50. Livingston RB, McCracken JD, Trauth CJ, et al: Isolated pleural effusion in small cell lung carcinoma: Favorable prognosis. Chest 81:208–211, 1982.
51. Elis A, Blickstein D, Mulchanov I, et al: Pleural effusion in patients with non-Hodgkin's lymphoma: A case-controlled study. Cancer 83:1607–1611, 1998.
52. Heffner JE, Klein JS: Recent advances in the diagnosis and management of malignant pleural effusions. Mayo Clin Proc 83:235–250, 2008.
53. Maskell NA, Lee YC, Gleeson FV, et al: Randomized trials describing lung inflammation after pleurodesis with talc of varying particle size. Am J Respir Crit Care Med 170:377–382, 2004. Epub 2004;May 13.
54. Lee YC, Baumann MH, Maskell NA, et al: Pleurodesis practice for malignant pleural effusions in five English-speaking countries: Survey of pulmonologists. Chest 1243:2229–2238, 2003.
55. Parulekar W, Di Primio G, Matzinger F, et al: Use of small-bore vs large-bore chest tubes for treatment of malignant pleural effusions. Chest 120:19–25, 2001.
56. Mager HJ, Maesen B, Verzijlbergen F, et al: Distribution of talc suspension during treatment of malignant pleural effusion with talc pleurodesis. Lung Cancer 36:77–81, 2002.
57. Spiegler PA, Hurewitz AN, Groth ML: Rapid pleurodesis for malignant pleural effusions. Chest 123:1895–1898, 2003.
58. Dresler CM, Olak J, Herndon JE, et al: Phase III intergroup study of talc poudrage vs talc slurry sclerosis for malignant pleural effusion. Chest 127:909–915, 2005.
59. Warren WH, Kim AW, Liptay MJ: Identification of clinical factors predicting Pleurx catheter removal in patients treated for malignant pleural effusion. Eur J Cardiothorac Surg 33:89–94, 2008.
59a. Efthymiou CA, Masudi T, Thorpe JA, et al: Malignant pleural effusion in the presence of trapped lung. Five-year experience of PleurX tunnelled catheters. Interact Cardiovasc Thorac Surg 9:961–964, 2009.
60. Genc O, Petrou M, Ladas G, et al: The long-term morbidity of pleuroperitoneal shunts in the management of recurrent malignant effusions. Eur J Cardiothorac Surg 18:143–146, 2000.
61. Fry WA, Khandekar JD: Parietal pleurectomy for malignant pleural effusion. Ann Surg Oncol 2:160–164, 1995.
62. Waller DA, Morritt GN, Forty J: Video-assisted thoracoscopic pleurectomy in the management of malignant pleural effusion. Chest 107:1454–1456, 1995.
63. Postmus PE, Brambilla E, Chansky K, et al: The IASLC Lung Cancer Staging Project: Proposals for revision of the M descriptors in the forthcoming (seventh) edition of the TNM classification of lung cancer. J Thorac Oncol 2:686–693, 2007.
64. Britton M: The epidemiology of mesothelioma. Semin Oncol 29:18–25, 2002.
65. Alleman JE, Mossman BT: Asbestos revisited. Sci Am 277:70–75, 1997.
66. Talcott JA, Thurber WA, Kantor AF, et al: Asbestos-associated diseases in a cohort of cigarette-filter workers. N Engl J Med 321:1220–1223, 1989.
67. Broaddus VC, Jaurand M-C: Asbestos fibers and their interaction with mesothelial cells in vitro and in vivo. *In* Robinson BWS, Chahinian P (eds): Mesothelioma. New York: Gordon and Breach Science/Harwood Academic, 2001.
68. Harris LV, Kahwa IA: Asbestos: Old foe in 21st century developing countries. Sci Total Environ 307:1–9, 2003.
69. Nishikawa K, Takahashi K, Karjalainen A, et al: Recent mortality from pleural mesothelioma, historical patterns of asbestos use, and adoption of bans: a global assessment. Environ Health Perspect 116:1675–1680, 2008.
70. Reid A, de Klerk NH, Ambrosini GL, et al: The risk of lung cancer with increasing time since ceasing exposure to asbestos and quitting smoking. Occup Environ Med 63:509–512, 2006.

71. Rake C, Gilham C, Hatch J, et al: Occupational, domestic and environmental mesothelioma risks in the British population: A case-control study. Br J Cancer 100:1175–1183, 2009.
71a. Ferrante D, Bertolotti M, Todesco A, et al: Cancer mortality and incidence of mesothelioma in a cohort of wives of asbestos workers in Casale Monferrato, Italy. Environ Health Perspect 115:1401–1405, 2007.
72. Landrigan PJ, Lioy PJ, Thurston G, et al: Health and environmental consequences of the World Trade Center disaster. Environ Health Perspect 112:731–739, 2004.
73. Kane AB, Hurt RH: Nanotoxicology: The asbestos analogy revisited. Nat Nanotechnol 3:378–379, 2008.
74. Carbone M, Pass HI, Miele L, et al: New developments about the association of SV40 with human mesothelioma. Oncogene 22:5173–5180, 2003.
75. Kroczynska B, Cutrone R, Bocchetta M, et al: Crocidolite asbestos and SV40 are cocarcinogens in human mesothelial cells and in causing mesothelioma in hamsters. Proc Natl Acad Sci U S A 103:14128–14133, 2006.
76. Engels EA, Katki HA, Nielsen NM, et al: Cancer incidence in Denmark following exposure to poliovirus vaccine contaminated with simian virus 40. J Natl Cancer Inst 95:532–539, 2003.
77. Strickler HD, Goedert JJ, Devesa SS, et al: Trends in U.S. pleural mesothelioma incidence rates following simian virus 40 contamination of early poliovirus vaccines. J Natl Cancer Inst 95:38–45, 2003.
78. Pass HI, Bocchetta M, Carbone M: Evidence of an important role for SV40 in mesothelioma. Thorac Surg Clin 14:489–495, 2004.
79. Shah KV: Causality of mesothelioma: SV40 question. Thorac Surg Clin 14:497–504, 2004.
80. Muscat J, Wydner E: Cigarette smoking, asbestos exposure and malignant mesothelioma. Cancer Res 51:2263–2267, 1991.
81. Coggiola M, Bosio D, Pira E, et al: An update of a mortality study of talc miners and millers in Italy. Am J Ind Med 44:63–69, 2003.
82. Marsh GM, Gula MJ, Youk AO, et al: Historical cohort study of US man-made vitreous fiber production workers: II. Mortality from mesothelioma. J Occup Environ Med 43:757–766, 2001.
83. Gennaro V, Finkelstein MM, Ceppi M, et al: Mesothelioma and lung tumors attributable to asbestos among petroleum workers. Am J Ind Med 37:275–282, 2000.
84. Goodman JE, Nascarella MA, Valberg PA: Ionizing radiation: A risk factor for mesothelioma. Cancer Causes Control 20:1237–1254, 2009.
85. Lee RJ, Strohmeier BR, Bundker KL, et al: Naturally occurring asbestos: a recurring public policy challenge. J Hazard Mater 153:1–21, 2008.
86. Lidar M, Pras M, Langevitz P, et al: Thoracic and lung involvement in familial Mediterranean fever (FMF). Clin Chest Med 23:505–511, 2002.
87. Kobayashi H, Watanabe H, Zhang WM, et al: A quantitative and histological study on pulmonary effects of asbestos exposure in general autopsied lungs. Acta Pathol Jpn 36:1781–1791, 1986.
88. Huncharek M: Non–asbestos-related diffuse malignant mesothelioma. Tumori 88:1–9, 2002.
89. Carbone M, Emri S, Dogan AU, et al: A mesothelioma epidemic in Cappadocia: Scientific developments and unexpected social outcomes. Nat Rev Cancer 7:147–154, 2007.
90. Murthy SS, Testa JR: Asbestos, chromosomal deletions, and tumor suppressor gene alterations in human malignant mesothelioma. J Cell Physiol 180:150–157, 1999.
91. Mor O, Yaron P, Huszar M, et al: Absence of p53 mutations in malignant mesothelioma. Am J Respir Cell Mol Biol 16:9–13, 1997.
92. Metcalf RA, Welsh JA, Bennett WP, et al: p53 and Kirsten-ras mutations in human mesothelioma cell lines. Cancer Res 52:2610–2615, 1992.
93. Singhal S, Wiewrodt R, Malden LD, et al: Gene expression profiling of malignant mesothelioma. Clin Cancer Res 9:3080–3097, 2003.
94. Pass HI, Liu Z, Wali A, et al: Gene expression profiles predict survival and progression of pleural mesothelioma. Clin Cancer Res 10:849–859, 2004.
95. Broaddus VC, Jaurand M-C: In vitro and in vivo. *In* Chahinian AP, Robinson BWS (eds): Mesothelioma. London: Martin Dunitz, 2002, pp 267–287.
96. Liu W, Ernst JD, Broaddus VC: Phagocytosis of crocidolite asbestos induces oxidative stress, DNA damage and apoptosis in mesothelial cells. Am J Respir Cell Mol Biol 23:371–378, 2000.
97. Leard LE, Broaddus VC: Mesothelial cell proliferation and apoptosis. Respirology 9:292–299, 2004.
98. Ruffie P, Minkin F, Cormier Y, et al: Diffuse malignant mesothelioma of the pleura in Ontario and Quebec: A retrospective study of 332 patients. J Clin Oncol 7:1157–1168, 1989.
99. Nakano T, Chahinian AP, Shinjo M, et al: Interleukin 6 and its relationship to clinical parameters in patients with malignant pleural mesothelioma. Br J Cancer 77:907–912, 1998.
100. Edwards JG, Abrams KR, Leverment JN, et al: Prognostic factors for malignant mesothelioma in 142 patients: Validation of CALGB and EORTC prognostic scoring systems. Thorax 55:731–735, 2000.
101. Robinson BW, Creaney J, Lake R, et al: Mesothelin-family proteins and diagnosis of mesothelioma. Lancet 362:1612–1616, 2003.
102. Metintas M, Ucgun I, Elbek O, et al: Computed tomography features in malignant pleural mesothelioma and other commonly seen pleural diseases. Eur J Radiol 41:1–9, 2002.
103. Ng CS, Munden RF, Libshitz HI: Malignant pleural mesothelioma: the spectrum of manifestations on CT in 70 cases. Clin Radiol 54:415–421, 1999.
104. Sussman J, Rosai J: Lymph node metastasis as the initial manifestation of malignant mesothelioma. Report of six cases. Am J Surg Pathol 14:819–828, 1990.
105. Francis RJ, Byrne MJ, van der Schaaf AA, et al: Early prediction of response to chemotherapy and survival in malignant pleural mesothelioma using a novel semiautomated 3-dimensional volume-based analysis of serial 18F-FDG PET scans. J Nucl Med 48:1449–1458, 2007.
106. Knuuttila A, Kivisaari L, Kivisaari A, et al: Evaluation of pleural disease using MR and CT. With special reference to malignant pleural mesothelioma. Acta Radiol 42:502–507, 2001.
107. Heelan RT, Rusch VW, Begg CB, et al: Staging of malignant pleural mesothelioma: Comparison of CT and MR imaging. AJR Am J Roentgenol 172:1039–1047, 1999.
108. Plathow C, Staab A, Schmaehl A, et al: Computed tomography, positron emission tomography, positron emission tomography/computed tomography, and magnetic resonance imaging for staging of limited pleural mesothelioma. Invest Radiol 43:737–744, 2008.
109. Ceresoli GL, Chiti A, Zucali PA, et al: Assessment of tumor response in malignant pleural mesothelioma. Cancer Treat Rev 33:533–541, 2007.
110. Wang ZJ, Reddy GP, Gotway MB, et al: Malignant pleural mesothelioma: Evaluation with CT, MR imaging, and PET. Radiographics 24:105–119, 2004.
111. Rice DC, Erasmus JJ, Stevens CW, et al: Extended surgical staging for potentially resectable malignant pleural mesothelioma. Ann Thorac Surg 80:1988–1992, 2005.
112. Boutin C, Rey F: Thoracoscopy in pleural malignant mesothelioma: A prospective study of 188 patients. Cancer 72:389–393, 1993.
113. Whitaker D: The cytology of malignant mesothelioma. Cytopathology 11:139–151, 2000.
114. Creaney J, Robinson BWS: Serum and pleural fluid biomarkers for mesothelioma. Curr Opin Pulm Med 15:366–370, 2009.
115. Grossebner MW, Arifi AA, Goddard M, et al: Mesothelioma—VATS biopsy and lung mobilization improves diagnosis and palliation. Eur J Cardiothorac Surg 16:619–623, 1999.
116. Blanc FX, Atassi K, Bignon J, et al: Diagnostic value of medical thoracoscopy in pleural disease: A 6-year retrospective study. Chest 121:1677–1683, 2002.
117. Yim AP, Chan AT, Lee TW, et al: Thoracoscopic talc insufflation versus talc slurry for symptomatic malignant pleural effusion. Ann Thorac Surg 62:1655–1658, 1996.
118. McCaughey W, Colby T, Battifora H, et al: Diagnosis of diffuse malignant mesothelioma: Experience of a US/Canadian Mesothelioma Panel. Mod Pathol 4:342–353, 1991.

119. Yang GC: Long microvilli of mesothelioma are conspicuous in pleural effusions processed by Ultrafast Papanicolaou stain. Cancer 99:17–22, 2003.
120. Ordonez NG: The immunohistochemical diagnosis of mesothelioma: a comparative study of epithelioid mesothelioma and lung adenocarcinoma. Am J Surg Pathol 27:1031–1051, 2003.
121. Zellos LS, Sugarbaker DJ: Diffuse malignant mesothelioma of the pleural space and its management. Oncology (Huntingt) 16:907–913, 2002.
122. Metintas M, Metintas S, Ucgun I, et al: Prognostic factors in diffuse malignant pleural mesothelioma: Effects of pretreatment clinical and laboratory characteristics. Respir Med 95:829–835, 2001.
123. Edwards JG, Cox G, Andi A, et al: Angiogenesis is an independent prognostic factor in malignant mesothelioma. Br J Cancer 85:863–868, 2001.
124. Edwards JG, Swinson DE, Jones JL, et al: Tumor necrosis correlates with angiogenesis and is a predictor of poor prognosis in malignant mesothelioma. Chest 124:1916–1923, 2003.
125. Rusch VW: A proposed new international TNM staging system for malignant pleural mesothelioma from the International Mesothelioma Interest Group. Lung Cancer 14:1–12, 1996.
126. Butchart E, Ashcroft T, Barnsley W, et al: Pleuropneumonectomy in the management of diffuse malignant mesothelioma of the pleura: Experience in 29 patients. Thorax 31:15–24, 1976.
127. Rusch VW, Venkatraman E: The importance of surgical staging in the treatment of malignant pleural mesothelioma. J Thorac Cardiovasc Surg 111:815–826, 1996.
128. Rusch VW, Venkatraman ES: Important prognostic factors in patients with malignant pleural mesothelioma, managed surgically. Ann Thorac Surg 68:1799–1804., 1999.
129. Sugarbaker DJ, Norberto JJ, Swanson SJ: Surgical staging and work-up of patients with diffuse malignant pleural mesothelioma. Semin Thorac Cardiovasc Surg 9:356–360, 1997.
130. Piquette GN, Timms BG: Isolation and characterization of rabbit ovarian surface epithelium, granulosa cells, and peritoneal mesothelium in primary culture. In Vitro Cell Dev Biol 26:471–481, 1990.
131. Sugarbaker DJ, Flores RM, Jaklitsch MT, et al: Resection margins, extrapleural nodal status, and cell type determine postoperative long-term survival in trimodality therapy of malignant pleural mesothelioma: Results in 183 patients. J Thorac Cardiovasc Surg 117:54–63, 1999.
132. Pass HI, Kranda K, Temeck BK, et al: Surgically debulked malignant pleural mesothelioma: Results and prognostic factors. Ann Surg Oncol 4:215–222, 1997.
133. Lee YCG, Light RW, Musk AW: Management of malignant pleural mesothelioma: A critical review. Curr Opin Pulm Med 6:267–274, 2000.
134. Law MR, Gregor A, Hodson ME, et al: Malignant mesothelioma of the pleura: A study of 52 treated and 64 untreated patients. Thorax 39:255–259, 1984.
135. Vogelzang NJ, Rusthoven JJ, Symanowski J, et al: Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. J Clin Oncol 21:2636–2644, 2003.
136. Nowak AK, Byrne MJ, Williamson R, et al: A multicentre phase II study of cisplatin and gemcitabine for malignant mesothelioma. Br J Cancer 87:491–496, 2002.
137. Schutte W, Blankenburg T, Lauerwald K, et al: A multicenter phase II study of gemcitabine and oxaliplatin for malignant pleural mesothelioma. Clin Lung Cancer 4:294–297, 2003.
138. Janne PA, Taffaro ML, Salgia R, et al: Inhibition of epidermal growth factor receptor signaling in malignant pleural mesothelioma. Cancer Res 62:5242–5247, 2002.
139. Hassan R, Ho M: Mesothelin targeted cancer immunotherapy. Eur J Cancer 44:46–53, 2008.
140. Carmichael J, Degraff WG, Gamson J, et al: Radiation sensitivity of human lung cancer cell lines. Eur J Cancer Clin Oncol 25:527–534, 1989.
141. Lee C, Bauman N, Swindell R, et al: Prophylactic radiotherapy to intervention sites in mesothelioma: A systematic review and survey of UK practice. Lung Cancer 66:150–156, 2009.
142. Senan S: Indications and limitations of radiotherapy in malignant pleural mesothelioma. Curr Opin Oncol 15:144–147, 2003.
143. Robinson C, Callow M, Stevenson S, et al: Serologic responses in patients with malignant mesothelioma: Evidence for both public and private specificities. Am J Respir Cell Mol Biol 22:550–556, 2000.
144. Boutin C, Viallat JR, Van Zandwijk N, et al: Activity of intrapleural recombinant gamma-interferon in malignant mesothelioma. Cancer 67:2033–2037, 1991.
145. Goey S, Eggermont A, Punt C, et al: Intrapleural administration of interleukin 2 in pleural mesothelioma: A phase I-II study. Br J Cancer 72:1283–1288, 1995.
146. Parra HS, Tixi L, Latteri F, et al: Combined regimen of cisplatin, doxorubicin, and alpha-2b interferon in the treatment of advanced malignant pleural mesothelioma: A phase II multicenter trial of the Italian Group on Rare Tumors (GITR) and the Italian Lung Cancer Task Force (FONICAP). Cancer 92:650–656, 2001.
147. Frizelle SP, Rubins JB, Zhou JX, et al: Gene therapy of established mesothelioma xenografts with recombinant p16INK4a adenovirus. Cancer Gene Ther 7:1421–1425, 2000.
148. Sterman DH, Kaiser LR, Albelda SM: Gene therapy for malignant pleural mesothelioma. Hematol Oncol Clin North Am 12:553–568, 1998.
149. Mukherjee S, Haenel T, Himbeck R, et al: Replication-restricted vaccinia as a cytokine gene therapy vector in cancer: Persistent transgene expression despite antibody generation. Cancer Gene Ther 7:663–670, 2000.
150. Sterman DH, Recio A, Carroll RG, et al: A phase I clinical trial of single-dose intrapleural IFN-beta gene transfer for malignant pleural mesothelioma and metastatic pleural effusions: High rate of antitumor immune responses. Clin Cancer Res 13:4456–4466, 2007.
151. Clayson H, Seymour J, Noble B: Mesothelioma from the patient's perspective. Hematol Oncol Clin North Am 19:1175–1190, 2005.
152. Hughes N, Arber A: The lived experience of patients with pleural mesothelioma. Int J Palliat Nurs 14:66–71, 2008.
153. de Klerk NH, Musk AW, Ambrosini GL, et al: Vitamin A and cancer prevention II: Comparison of the effects of retinol and beta-carotene. Int J Cancer 75:362–367, 1998.
154. Roberts HC, Patsios DA, Paul NS, et al: Screening for malignant pleural mesothelioma and lung cancer in individuals with a history of asbestos exposure. J Thorac Oncol 4:620–628, 2009.
155. Carbone M, Albelda SM, Broaddus VC, et al: Eighth international mesothelioma interest group. Oncogene 26:6959–6967, 2007.
156. Park MS, Araujo DM: New insights into the hemangiopericytoma/solitary fibrous tumor spectrum of tumors. Curr Opin Oncol 21:327–331, 2009.
157. Briselli M, Mark EJ, Dickersin GR: Solitary fibrous tumors of the pleura: Eight new cases and review of 360 cases in the literature. Cancer 47:2678–2689, 1981.
158. Mezzetti M, Panigalli T, Giudice FL, et al: Surgical experience of 15 solitary benign fibrous tumors of the pleura. Crit Rev Oncol Hematol 47:29–33, 2003.
159. Robinson LA, Reilly RB: Localized pleural mesothelioma. The clinical spectrum. Chest 106:1611–1615, 1994.
160. Rena O, Filosso PL, Papalia E, et al: Solitary fibrous tumour of the pleura: Surgical treatment. Eur J Cardiothorac Surg 19:185–189, 2001.
161. Le Roith D: Tumor-induced hypoglycemia. N Engl J Med 341:757–758, 1999.
162. Teale JD, Wark G: The effectiveness of different treatment options for non-islet cell tumour hypoglycaemia. Clin Endocrinol 60:457–460, 2004.
163. Chang YL, Lee YC, Wu CT: Thoracic solitary fibrous tumor: Clinical and pathological diversity. Lung Cancer 23:3–60, 1999.
164. Mendelson DS, Meary E, Buy JN, et al: Localized fibrous pleural mesothelioma: CT findings. Clin Imaging 15:105–108, 1991.
165. Lee KS, Im JG, Choe KO, et al: CT findings in benign fibrous mesothelioma of the pleura: Pathologic correlation in nine patients. AJR Am J Roentgenol 158:983–986, 1992.
166. Padovani B, Mouroux J, Raffaelli C, et al: Benign fibrous mesothelioma of the pleura: MR study and pathologic correlation. Eur Radiol 6:425–428, 1996.
167. Cortes J, Rodriguez J, Garcia-Velloso MJ, et al: [(18)F]-FDG PET and localized fibrous mesothelioma. Lung 181:49–54, 2003.

168. Harrison-Phipps KM, Nichols FC, Schleck CD, et al: Solitary fibrous tumors of the pleura: Results of surgical treatment and long-term prognosis. J Thorac Cardiovasc Surg 138:19–25, 2009.
169. Ascoli V, Lo-Coco F: Body cavity lymphoma. Curr Opin Pulm Med 8:317–322, 2002.
170. Morassut S, Vaccher E, Balestreri L, et al: HIV-associated human herpesvirus 8–positive primary lymphomatous effusions: Radiologic findings in six patients. Radiology 205:459–463, 1997.
171. Wakely PE Jr, Menezes G, Nuovo GJ: Primary effusion lymphoma: Cytopathologic diagnosis using in situ molecular genetic analysis for human herpesvirus 8. Mod Pathol 15:944–950, 2002.
172. Chen YB, Rahemtullah A, Hochberg E: Primary effusion lymphoma. Oncologist 12:569–576, 2007.
173. Androulaki A, Drakos E, Hatzianastassiou D, et al: Pyothorax-associated lymphoma (PAL): A Western case with marked angiocentricity and review of the literature. Histopathology 44:69–76, 2004.
174. Petitjean B, Jardin F, Joly B, et al: Pyothorax-associated lymphoma: A peculiar clinicopathologic entity derived from B cells at late stage of differentiation and with occasional aberrant dual B- and T-cell phenotype. Am J Surg Pathol 26:724–732, 2002.
175. Nakatsuka S, Yao M, Hoshida Y, et al: Pyothorax-associated lymphoma: A review of 106 cases. J Clin Oncol 20:4255–4260, 2002.
176. Aruga T, Itami J, Nakajima K, et al: Treatment for pyothorax-associated lymphoma. Radiother Oncol 56:59–63, 2000.
177. Shide K, Henzan H, Nagafuji K, et al: Dynamics of Epstein-Barr virus load in pyothorax-associated lymphoma. J Med Virol 70:137–140, 2003.
178. Ueda T, Andreas C, Itami J, et al: Pyothorax-associated lymphoma: imaging findings. Am J Roentgenol 194:76–84, 2010.

CHAPTER 76

TUMORS AND CYSTS OF THE MEDIASTINUM

David R. Park, MD • Eric Vallières, MD

INTRODUCTION

THE NORMAL MEDIASTINUM

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INTRODUCTION

The mediastinum is the region in the chest between the pleural cavities that contains the heart and other thoracic viscera except for the lungs. Interest in the mediastinum as a separate body region stems from the diversity and vital importance of the structures it contains, and the multiplicity of disease processes by which it can be affected. The nonspecific clinical manifestations of most of these disorders and the mediastinum's relative inaccessibility for diagnostic examination result in considerable challenges to the clinician evaluating mediastinal disease. This chapter begins by describing the normal anatomy and contents of the mediastinum, the clinical manifestations produced by mediastinal disease, and the means available for diagnostic investigation. It then describes the features of specific mediastinal tumors and cysts and outlines an overall clinical approach to the evaluation of mediastinal disease.

THE NORMAL MEDIASTINUM

The anatomy of the mediastinum can be described in several ways. Most clinicians simply divide the mediastinum into anterior, middle, and posterior compartments, as seen on the lateral chest radiograph (Fig. 76-1).[1]

The anterior compartment consists of everything lying forward of and superior to the heart shadow; its boundaries are the sternum, the first rib, and an imaginary curved line following the anterior heart border and brachiocephalic vessels from the thoracic inlet to

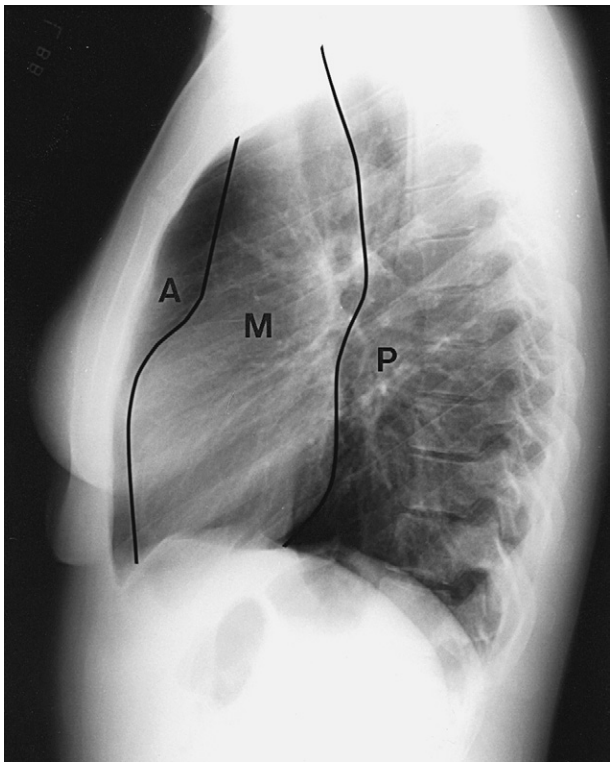

FIGURE 76-1 ■ By convention, the mediastinum is divided into anterior (A), middle (M), and posterior (P) compartments, according to its appearance on lateral chest radiograph. Although other more complex subdivisions exist, this one is most helpful to the clinician.

TABLE 76-1. Normal Mediastinal Contents

ANTERIOR COMPARTMENT
Thymus gland
Substernal extensions of thyroid and parathyroid glands
Lymphatic vessels and lymph nodes
Connective tissue
MIDDLE COMPARTMENT
Heart
Pericardium
Aortic arch and great vessels
Innominate veins and superior vena cava
Trachea and main bronchi
Hila
Lymph nodes
Phrenic and upper vagus nerves
Connective tissue
POSTERIOR COMPARTMENT
Esophagus
Descending aorta
Azygos and hemiazygos veins
Thoracic duct
Lymph nodes
Vagus nerves (lower portions)
Sympathetic chains
Connective tissue

the diaphragm. Within the anterior compartment lie the thymus gland, any substernal extensions of the thyroid and parathyroid glands, and lymphatic tissue (Table 76-1).

The middle compartment, dorsal to the anterior mediastinum, extends from the lower edge of the anterior heart border along the diaphragm and then cephalad along the posterior heart border and posterior wall of the trachea. It contains the heart, the pericardium, the aortic arch and its major branches, the innominate veins and superior vena cava, the pulmonary arteries and hila, the trachea, and several groups of lymph nodes. In addition, the phrenic and upper vagus nerves course through the middle mediastinal compartment.

The posterior compartment occupies the space between the back of the heart and trachea and the front of the posterior ribs and paravertebral gutters. It extends from the diaphragm cephalad to the first rib. In it are the esophagus, descending aorta, azygous and hemiazygous veins, paravertebral lymph nodes, and thoracic duct. The lower portions of the vagus nerve and sympathetic chains also lie within the posterior mediastinum.

This three-compartment model is consistent with embryonic development of the region and also with the characteristic distribution of individual disorders encountered clinically. Separation of mediastinal structures into anterior, middle, and posterior compartments follows logically from the appearance of the chest on conventional radiography. And, because evaluation of a mediastinal abnormality nearly always starts with a conventional chest radiograph, these compartments will likely remain the fundamental anatomic units of the mediastinum. However, other classifications exist. One, based on surgical landmarks, is used for the mapping of lymph node locations during mediastinal staging of bronchogenic carcinoma.[2] Many of the anatomic relationships of the mediastinal viscera and tissue planes are best appreciated on axial images such as shown schematically in Figure 77-1.[3]

CLINICAL SETTINGS AND PRESENTATIONS OF MEDIASTINAL DISEASE

Asymptomatic Mass

The incidental discovery of a mediastinal mass that has produced no symptoms is the most common presentation of primary mediastinal disease. At least half of all mediastinal masses are asymptomatic and detected by chest radiography performed for unrelated reasons. About 80% of such asymptomatic masses are benign, whereas more than half of those that produce symptoms are malignant.[4-6]

Effects of Compression or Invasion of Adjacent Tissues

Symptoms in patients with mediastinal mass lesions are usually due to compression by mass effect, or invasion of adjacent intrathoracic structures.[4,5] Chest pain, from traction on mediastinal tissues, tissue invasion, or bone erosion, is common. Cough also occurs frequently because of extrinsic compression of the trachea or bronchi, erosion into the airway, and sometimes post-obstructive pneumonia. Hemoptysis, hoarseness, or stridor also may be part of the clinical presentation. Invasion or irritation of the pleural surface may produce a pleural effusion, and can cause pain and dyspnea. Compression or direct invasion of the esophagus may lead to dysphagia. Rarely, anterior mediastinal tumors can cause pericarditis or pericardial tamponade, and masses in the middle mediastinum can produce right ventricular outflow obstruction and cor pulmonale.

The superior vena cava is especially vulnerable to extrinsic compression and obstruction because it is thin walled, its intravascular pressure is low, and it is relatively confined by lymph nodes and other more rigid structures. A "superior vena cava syndrome" results from increased venous pressure in the upper thorax, head, and neck,[7] and is characterized by dilation of collateral veins in the upper portion of the thorax and neck; edema and plethora of the face, neck, and upper torso; suffusion and edema of the conjunctiva; and cerebral symptoms, such as headache, disturbance of consciousness, and visual distortion (see Fig. 47-5 in Chapter 47). Tinnitus and epistaxis also may occur. All symptoms are exacerbated in the supine position. Numerous benign causes of superior vena cava syndrome are described,[8] but bronchogenic carcinoma and lymphoma are now the most common etiologies,[9,10] and fewer than 20% of cases are due to nonmalignant disease.[9,10]

Mediastinal masses can produce a variety of symptoms by invading or compressing nerves. These include hoarseness from recurrent laryngeal nerve involvement, Horner's syndrome from involvement of sympathetic ganglia, dyspnea from phrenic nerve involvement causing diaphragmatic paralysis, tachycardia secondary to vagus nerve involvement, and clinical manifestations of spinal cord compression.

Systemic Symptoms and Syndromes

Fever, anorexia, weight loss, and other systemic symptoms are nonspecific features of malignancy and inflammation that occur frequently in patients with mediastinal disease. In addition, primary mediastinal tumors are associated with a wide array of distinctive systemic syndromes (Table 76-2).[4,5,11–13] Some typically have endocrine activity, such as thyrotoxicosis sometimes seen with intrathoracic goiter; Cushing's syndrome, associated with thymomas and carcinoid tumors; gynecomastia, seen in patients with human chorionic gonadotropin–secreting germ cell tumors; hypertension, typical in patients with pheochromocytoma; and hypercalcemia, observed in patients with parathyroid adenoma and lymphoma. Hypoglycemia in patients with certain pleural tumors, teratomas, fibrosarcomas, and neurosarcomas is also believed to be the result of tumor products with endocrine activity.

TABLE 76-2. Systemic Syndromes Associated with Mediastinal Masses

Syndrome	Associated Conditions
ENDOCRINE EFFECTS	
Hypothyroidism or hyperthyroidism	Mediastinal goiter
Hypercalcemia	Parathyroid adenoma, lymphoma
Hypertension	Pheochromocytoma, ganglioneuroma, chemodectoma
Cushing's syndrome	Carcinoid, thymoma
Hypoglycemia	Mesenchymal tumor
Gynecomastia	Germ cell tumor
Diarrhea	Ganglioneuroma, neuroblastoma
AUTOIMMUNE EFFECTS	
Opsomyoclonus	Neuroblastoma
Myasthenia gravis	Thymoma
Red cell aplasia	Thymoma
Myocarditis	Thymoma
Hypogammaglobulinemia	Thymoma
CONGENITAL SYNDROMES	
Neurofibromatosis	Neurofibroma
Multiple endocrine neoplasia	Parathyroid adenoma, pheochromocytoma
UNKNOWN CAUSES	
Alcohol-induced pain	Hodgkin's disease
Fever and night sweats	Lymphoma

Thymomas are associated with numerous systemic syndromes, most of which appear to be autoimmune in origin.[4,5,12] The most familiar of these is myasthenia gravis; others include pure red blood cell aplasia, myocarditis, and hypogammaglobulinemia. Patients with thymoma also have an increased incidence of collagen vascular disease, Whipple's disease, and malignancy elsewhere in the body.

Other mediastinal tumors associated with systemic syndromes or diseases include carcinoid and parathyroid adenomas (multiple endocrine neoplasia), neurofibromas (neurofibromatosis), and lymphomas (fever of unknown origin and alcohol-induced pain). Osteoarthropathy is a known feature of primary pleural tumors, neurofibroma, and neurilemoma.

Investigation of the Mediastinum in Patients with Malignancy

The most common reason that clinicians evaluate the mediastinum is in the staging of patients with lung cancer. Whether and to what extent the mediastinum is involved is crucial to the management of patients with non–small cell lung cancer.[14] Although metastatic

involvement of the mediastinal lymph nodes has traditionally been considered a contraindication to surgical resection, increasing attention is being focused on multimodality treatment approaches for these patients, and treatment options are rapidly evolving. Regardless of the latest treatment options, careful preoperative evaluation of the mediastinum is crucial to the decision-making process.[15,16]

Nonthoracic malignancies also may metastasize to the mediastinum. This is particularly common with tumors originating in the head and neck, the esophagus, the genitourinary tract, the breasts, and the skin (malignant melanoma).

TECHNIQUES FOR VISUALIZING THE MEDIASTINUM AND ITS CONTENTS

The diagnostic evaluation of disorders of the mediastinum may be divided into two phases: noninvasive investigations via imaging, and invasive procedures to obtain tissue samples. The mediastinum is relatively inaccessible for examination or exploration. Accordingly, imaging studies play an important role in the initial evaluation of mediastinal disease. These include conventional radiographic studies, computed tomography (CT), magnetic resonance (MR) imaging, transthoracic and endoscopic ultrasonography, and various radionuclide studies.

Conventional Radiographic Techniques

Standard posteroanterior and lateral chest radiographs are the means by which most mediastinal abnormalities are first detected, and certain mediastinal mass lesions have characteristic findings (Table 76-3). For example, teratomas are usually anterior and may contain areas of calcium (sometimes teeth or bone), fat, and soft tissue. Neural tumors are usually far posterior, with sharply delineated margins. Pericardial cysts usually lie against the pericardium, on the diaphragm, or against the anterior chest wall. Bronchogenic cysts tend to lie against the trachea, carina, or main bronchus. These findings give clues to the possible origin of a mediastinal mass, but further imaging evaluation is usually required.

In the appropriate clinical settings, contrast studies remain important diagnostic tools in mediastinal disease. Barium esophagrams can demonstrate extrinsic compression, esophageal diverticulum, tumor invasion, or fistula formation.[4] Angiography can identify vascular compression or invasion, can define the vascular supply of tumors, and can sample blood for hormonal localization of certain tumors. Myelography may help to delineate intraspinal extension of posterior mediastinal tumors and to differentiate neurogenic neoplasms from meningoceles. For the most part, these techniques have been supplanted by CT and MR.

Computed Tomography

Evaluation of mediastinal disease is greatly facilitated by CT imaging. The transaxial plane of CT is well suited for assessment of mediastinal structures, most of which are oriented perpendicularly to this plane. Certain patterns and densities on CT images are virtually pathognomonic. These include the high density of calcified tissue, contrast-enhanced blood vessels, and the characteristic low

TABLE 76-3. Some Characteristic Imaging Findings in Mediastinal Disease

Feature	Likely Etiology
Huge mass on initial presentation	Neurogenic tumor Meningocele Mesenchymal tumor
Teardrop-shaped mass within interlobar fissure	Pericardial or bronchogenic cyst
Fat density on computed tomography scan	Mediastinal lipomatosis or lipoma
Calcification in mass	In rim of mass Cystic thymoma or thyroid adenoma Aneurysm Silicosis ("eggshell" calcification) In center of mass Thyroid adenoma Teratoma
Teeth or bone	Teratoma
Phleboliths	Hemangioma
Air-fluid level in mass	Esophageal disease Diaphragmatic hernia Developmental cyst Cystic teratoma Abscess
Mass with associated parenchymal infiltrate	Granulomatous infection Metastatic bronchogenic carcinoma Lymphoma with direct extension into lung Esophageal abnormality with aspiration pneumonitis Bronchial compression by primary mediastinal mass
Mass with associated pleural effusion	Metastatic malignancy with pleural involvement Granulomatous inflammation of lymph nodes
Superior vena cava obstruction	Recent onset Bronchogenic carcinoma Lymphoma Catheter-associated thrombosis Long-standing Mediastinal fibrosis
Erosion or destruction of bone	Arterial aneurysm Tumors of peripheral nerves or sympathetic ganglia Meningocele
Spine or rib deformity	Enteric cyst

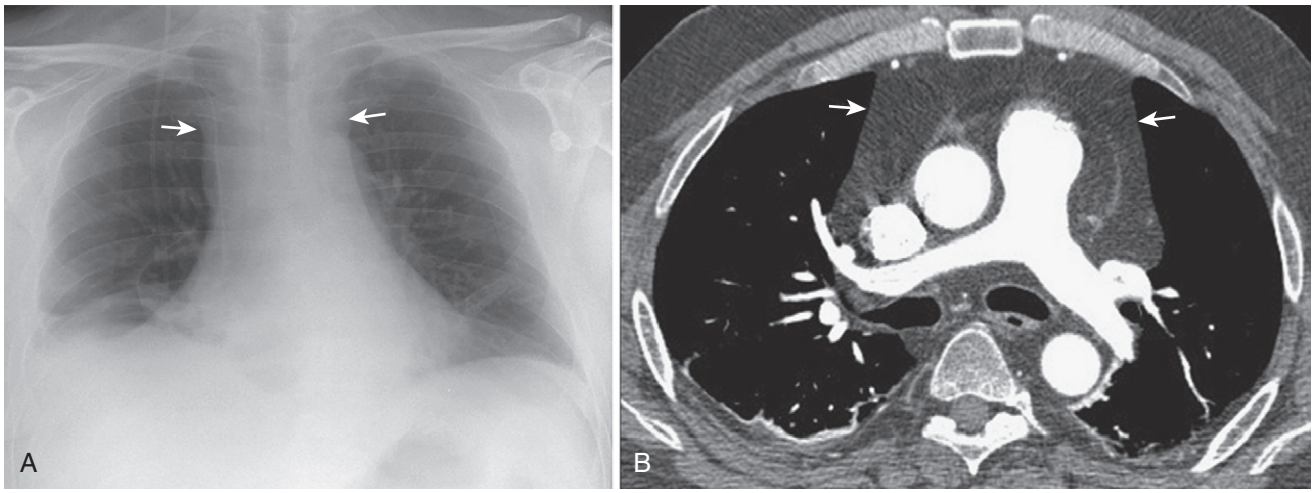

FIGURE 76-2 ■ Chest radiograph **(A)** showing diffuse mediastinal widening (*arrows*) and computed tomography (CT) scan **(B)** showing extensive fat deposition (*arrows*) in the anterior mediastinum in a patient with mediastinal lipomatosis. (Courtesy of Michael B. Gotway, MD, Scottsdale Medical Imaging and the Department of Radiology, University of California, San Francisco.)

density of fat (Fig. 76-2).[17] Normal anatomic variations and fluid-filled cysts can be distinguished confidently from other processes, and the site of origin of mediastinal masses can be better identified.[18] Characteristic CT findings in a variety of mediastinal disorders have now been described (see Table 76-3). A recent report described 100% specificity for the CT appearance of teratomas, thymolipomas, and omental fat herniation, but the overall accuracy of CT for predicting the diagnosis of all mediastinal masses was only 48%.[17]

Lymph nodes are readily identifiable on CT scan and can be categorized as normal in size and shape, enlarged, coalescent, or grossly replaced by tumor mass. Mediastinal lymph nodes greater than 1.0 cm in diameter in the short axis are considered to be abnormally enlarged. However, in numerous studies of the use of CT in mediastinal staging of lung cancer, the sensitivity of the 1.0-cm cutoff for detecting cancerous nodes by CT has ranged from 18% to 94% (reviewed in Gould and coworkers[19]). The specificity of the 1.0-cm cutoff in these studies ranged from 43% to 100%, although it was usually under 90%. Mediastinal lymph nodes greater than 2.0 cm in diameter are virtually always abnormal, and most nodes greater than 2.0 cm in diameter in patients with lung cancer contain metastatic disease. However, even in series of patients with proven bronchogenic carcinoma, benign findings were present in 10% of lymph nodes either larger than 2.0 cm in diameter or with evidence of central necrosis.[20] In another study, no cancer was found in 37% of lymph nodes 2 to 4 cm in diameter.[21] Thus normal-appearing nodes often contain metastatic cancer, while even markedly enlarged nodes with abnormal appearance may not.

Nevertheless, CT has become the initial imaging procedure of choice for the evaluation of the mediastinum in patients with a primary mediastinal mass[11-13] or with suspected lung cancer.[22] In the majority of patients, CT cannot establish a diagnosis with certainty. However, CT can precisely define the mediastinal anatomy and guide subsequent invasive diagnostic and staging procedures, or can confirm a clinical suspicion of extensive mediastinal involvement or visceral organ invasion that precludes curative resection.

Magnetic Resonance Imaging

MR assesses tissues by measuring radiofrequency-induced nuclear resonance emissions and is better suited than CT to evaluating vertically oriented structures and tissue boundaries[23,24] (Fig. 76-3). In addition, MR images of blood vessels are identifiable without the need for contrast enhancement (Fig. 76-4). Finally, metallic objects that cause artifact on CT scans do not interfere with MR, although some metallic devices may be subjected to magnetic forces.[25]

MR has use in evaluation of the mediastinum, both in general applications in chest disease[18,23,24] and in more specific circumstances such as bronchogenic carcinoma.[22] A large multicenter study comparing CT and MR in patients with lung cancer found similar accuracy for the detection of mediastinal node involvement, but MR was superior for detecting direct mediastinal tumor invasion.[26] Most authorities now recommend CT for routine staging purposes, and MR for defining anatomy in special circumstances such as prior to surgical resection of superior sulcus tumors or those invading the mediastinum, chest wall, or diaphragm.[15,22]

Both CT and MR have limitations. Both imaging techniques distinguish poorly between hilar masses and adjacent collapsed or consolidated lung. Both can also show displacement or compression of the esophagus or trachea by tumor, but often are unable to indicate whether there is also invasion of these structures. Most importantly, neither technique reliably distinguishes between benign and malignant causes for mediastinal lymph node enlargement.

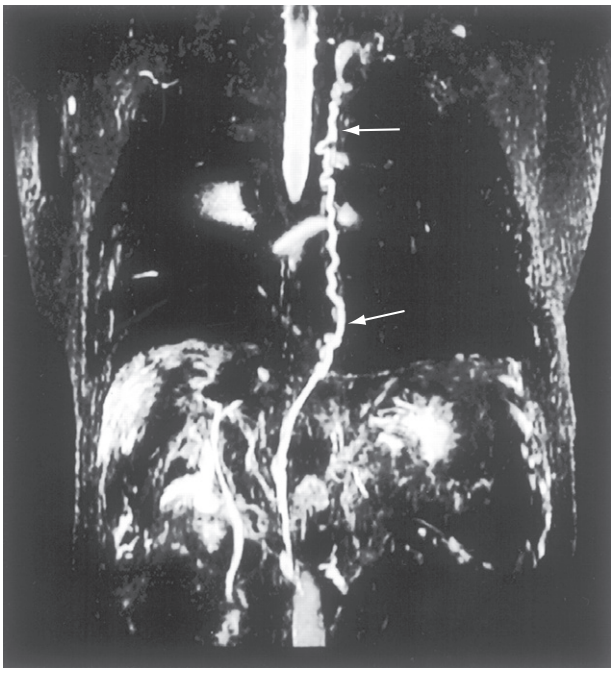

FIGURE 76-3 ■ Magnetic resonance lymphogram of the thoracic duct. The normal course of the thoracic duct can be seen crossing diagonally through the lower mediastinum from the patient's right to left and then ascending along the left mediastinum to reach the subclavian vein. In this case the duct is somewhat more dilated and tortuous than normal due to the presence of hepatic cirrhosis. (From Takahashi H, Kuboyama S, Abe H, et al: Clinical feasibility of noncontrast-enhanced magnetic resonance lymphography of the thoracic duct. Chest 124:2136–2142, 2003.)

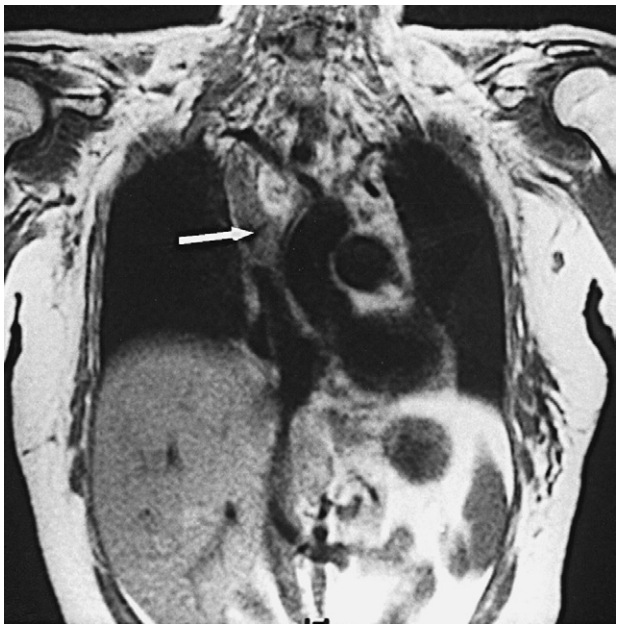

FIGURE 76-4 ■ Magnetic resonance imaging of a 52-year-old woman with multiple myeloma, experiencing symptoms of superior vena cava (SVC) obstruction following placement of an indwelling central venous catheter in preparation for bone marrow transplantation. Vertically oriented structures are clearly discernible, and black "flow void" is present within the heart and great vessels. The SVC is completely obstructed by thrombus (*arrow*).

Ultrasonography

Ultrasonography may be useful in confirming the cystic nature of mediastinal masses, although it cannot readily distinguish between benign and malignant cystic lesions. Both transthoracic and endoscopic ultrasound probes may be useful in the evaluation of mediastinal disease.[27] Ultrasound may be most useful in guiding endoscopic biopsy techniques, as discussed later in this chapter.[28]

Radionuclide Imaging

Radionuclide imaging studies rely on the localization of markers based on specific metabolic or immunologic properties of the target tissue. The spatial resolution of radionuclide scans is relatively poor, but the overall diagnostic accuracy may be good if a sufficiently specific probe is available. An additional appeal is the potential ability to stage a malignancy and identify distant metastases with a single scan of the entire body.

Planar imaging with gallium-67 (^{67}Ga) has been used in the evaluation of patients with sarcoidosis. Characteristic "lambda" and "panda" signs result from uptake in the lacrimal and salivary glands and the mediastinal lymph nodes.[29] However, the lack of specificity has relegated the use of ^{67}Ga scans to selected cases with high pretest probability, or to detect subclinical extrathoracic sites of involvement. ^{67}Ga scans are less accurate than CT for evaluating mediastinal spread of lung cancer.[30] Radioiodine scanning may detect ectopic thyroid tissue; a positive result is pathognomonic for that condition.[4] Various radionuclide studies used to characterize specific primary mediastinal masses are discussed later in this chapter.

Single-photon emission computed tomography (SPECT) permits imaging of standard gamma-emitting probes in an axial fashion similar to that of conventional CT. The accuracy of ^{201}Tl-SPECT for determining mediastinal node involvement by lung cancer compares favorably with CT, but is not sensitive or specific enough to supplant surgical staging.

Positron emission tomography (PET) is perhaps the most promising imaging technique available for use in the evaluation of the mediastinum.[19,31] PET technology relies on high-energy photon–emitting probes such as [^{18}F]fluorodeoxyglucose (FDG), which are chemically trapped within metabolically active cells. The result is a high signal-to-background ratio, excellent spatial resolution, and good accuracy (Fig. 76-5). PET is demonstrating increasing versatility in the evaluation of many forms of mediastinal disease.[32] Unfortunately, PET technology is costly and not universally available, and false-positive results can be caused by inflammatory conditions.

The role of PET in the mediastinal staging of lung cancer remains to be determined. Early experience found that PET detected mediastinal metastases with sensitivity and specificity ranging from 50% to 100% and 63% to 100%, respectively.[19] The American College of Surgeons Oncology Group reported the results of a prospective multicenter evaluation of PET in staging resectable non–small cell lung cancer[33]; in this realistic setting,

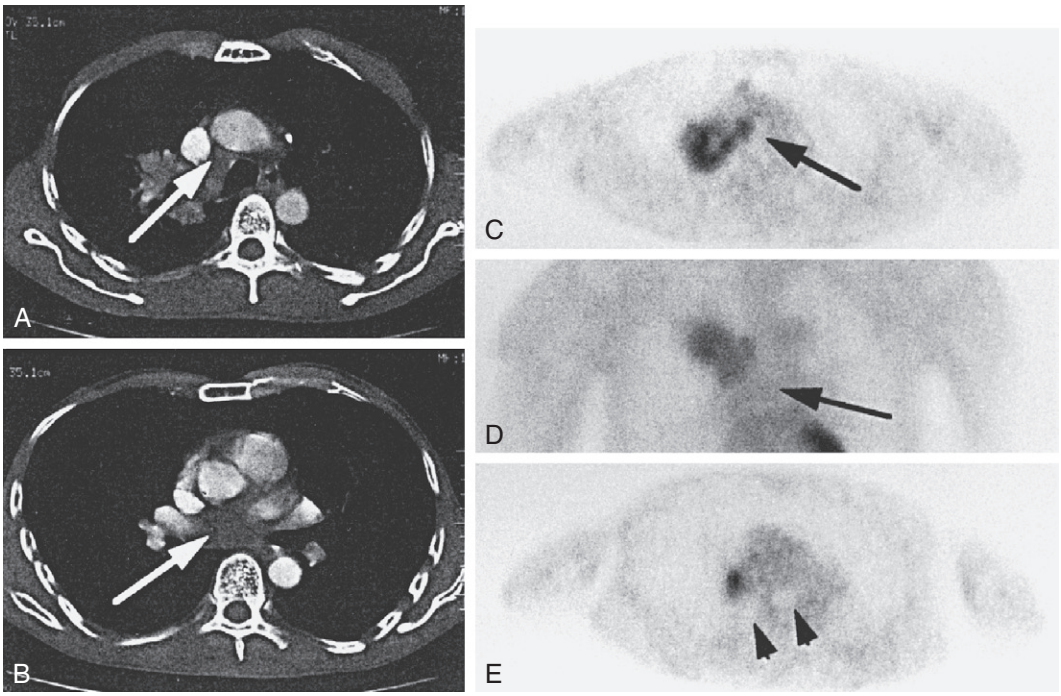

FIGURE 76-5 ■ Computed tomography (CT) and positron emission tomography (PET) scans of a patient with right upper lobe squamous cell carcinoma. The primary tumor and right paratracheal adenopathy **(A)** and subcarinal adenopathy **(B)** are evident on the standard CT images (*arrows*). PET images reveal probe uptake in the primary tumor and right paratracheal nodes on axial **(C)** (*arrow*) and coronal **(D)** views, but not in the subcarinal node on coronal **(D)** (*arrow*) and axial **(E)** views. The *arrowheads* in **E** point to the main bronchi. At mediastinoscopy, the right paratracheal nodes were found to be malignant, and the subcarinal nodes were enlarged but benign. (From Vansteenkiste JF, Stroobants SG, De Leyn PR, et al: Mediastinal lymph node staging with FDG-PET scan in patients with potentially operable non-small cell lung cancer: A prospective analysis of 50 cases. Leuven Lung Cancer Group. Chest 112:1480–1486, 1997.)

the sensitivity of PET in determining mediastinal nodal involvement was 61%, its specificity was 84%, the negative predictive value was 87%, and the positive predictive value was only 56%. PET may provide other helpful information. In a series from our institution, FDG-PET scans failed to detect mediastinal metastases in 8 of 118 patients with surgically established nodal stage, but identified unsuspected sites of distant metastasis and prevented unnecessary operations in 17% of patients.[34]

Technological advances such as co-registration of PET and CT images have improved the sensitivity of PET,[35] but at the cost of lower specificity and increased false-positive results.[36] Based on these experiences, it seems prudent to confirm both positive and negative FDG-PET findings if the findings of mediastinal involvement would alter the subsequent surgical approach (see also Chapters 21 and 47).

TECHNIQUES FOR OBTAINING MEDIASTINAL TISSUE

Definitive diagnosis of most mediastinal masses requires the evaluation of a tissue sample. Available approaches for biopsy of mediastinal lesions include needle aspiration and biopsy via transbronchial, percutaneous, or transesophageal approaches; and surgical biopsies obtained by more invasive procedures including mediastinoscopy, mediastinotomy, and thoracoscopy.

Needle Aspiration and Biopsy

Transbronchial Needle Aspiration

Transbronchial needle aspiration (TBNA) via the fiberoptic bronchoscope can yield definitive proof of the presence of malignancy in the mediastinum using a procedure less hazardous and costly than mediastinoscopy. Despite the proximity of major vessels and lung parenchyma to the areas routinely biopsied, TBNA appears to be a relatively safe procedure. Few significant complications (pneumothorax and hemomediastinum) have been reported in over 1500 reported procedures. Although experience with TBNA in patients receiving mechanical ventilation is limited, no complications were reported in a series of 8 patients.[37]

In the setting of bronchogenic carcinoma, a careful prospective study found that only 15% of patients with the established diagnosis of lung cancer had a positive result from TBNA but, in 69% of these, the TBNA specimen was the only preoperative evidence for mediastinal metastasis.[38] The true sensitivity and specificity of TBNA appear to range from 14% to 50% and 96% to 100%, respectively.[39,40] Thus, negative results require definitive operative confirmation, but the risk of false-positive TBNA results appears to be quite low. Nonetheless, to avoid generating false-positive results by aspirating malignant cells stirred up from elsewhere in the tracheobronchial tree, TBNA should be performed prior to

bronchial exploration or biopsy of any endobronchial lesions.[38,41]

The yield of TBNA is improved in patients with visible endobronchial lesions, with widening or erythema of the carina,[38,41] or with mediastinal adenopathy on plain radiographs and subcarinal adenopathy on CT.[42] The yield of TBNA can be improved by guidance of the biopsy needle using CT or especially using real-time endobronchial ultrasound (EBUS).[43–45] In addition, diagnostic algorithms combining EBUS-guided TBNA with PET scan identification of specific areas of concern may lead to improved diagnostic yields.[46,47]

Finally, TBNA may have utility in other clinical situations such as in the diagnosis of a variety of primary mediastinal masses and cysts, metastases from extrathoracic malignancies, and miscellaneous benign conditions,[48,49] and in the evaluation of mediastinal adenopathy associated with human immunodeficiency virus (HIV) infection.[50]

Percutaneous Needle Aspiration and Biopsy

Percutaneous needle aspiration and biopsy of mediastinal masses can be performed using ultrasound or, more often, CT guidance[51] (Fig. 76-6). Percutaneous needle aspiration of the mediastinum has acceptable morbidity and yields comparable to those from percutaneous biopsy of pulmonary lesions. As with TBNA, serious bleeding is seldom encountered,[51] and accurate diagnosis of a wide variety of lesions has been reported. Accuracy is enhanced when immediate cytopathologic examination is used to determine whether or not an adequate sample has been obtained.

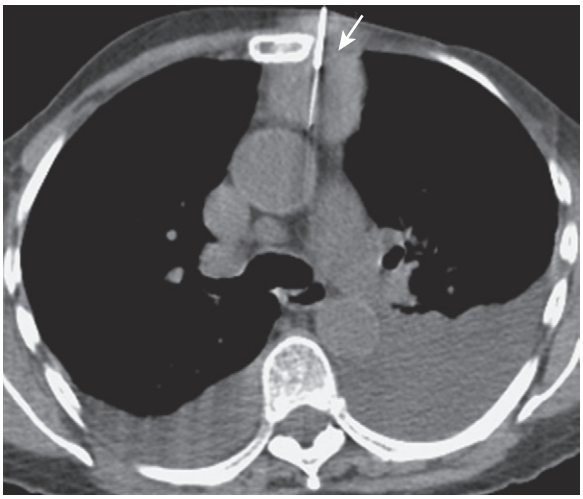

FIGURE 76-6 ■ Computed tomography–guided needle aspiration of an anterior mediastinal mass. The image shows the needle entering the mass by passing lateral to the sternum and medial to the internal mammary vessels (*arrow* = left internal mammary artery). Associated findings include a pretracheal lymph node and bilateral pleural effusions. (Courtesy of Michael B. Gotway, MD, Scottsdale Medical Imaging and the Department of Radiology, University of California, San Francisco.)

Endoscopic Ultrasound-Guided Needle Aspiration and Biopsy

Endoscopic ultrasound (EUS)–guided sampling relies on the placement of biopsy needles that are passed through the working channel of a gastroscope.[52] The proximity of the esophagus to areas of the mediastinum relatively inaccessible to mediastinoscopy, such as the posterior subcarinal lymph nodes, make this approach particularly useful in selected cases. Preliminary studies suggest that it is highly accurate and well tolerated.[28,53] EUS-guided biopsy has similar sensitivity compared to PET for lung cancer, and superior specificity (100%).[54] In selected cases, it can confirm the presence of mediastinal metastases and obviate the need for surgical staging procedures.[55] By combining EUS-guided biopsy and EBUS-guided TBNA, the mediastinum can be thoroughly sampled.[56]

Mediastinoscopy, Anterior Mediastinotomy, and Thoracoscopy

Mediastinoscopy allows direct inspection and biopsy of lymph nodes or other masses in the superior portion of the anterior mediastinum.[57] Although more invasive than any of the techniques discussed previously in this chapter, mediastinoscopy can provide large specimens for histologic examination, including entire lymph nodes, rather than the cellular aspirates or small tissue fragments produced by needle biopsy techniques.

Mediastinal anatomy from the mediastinoscopist's perspective is different from that based on the lateral chest radiograph as described earlier: for mediastinoscopy; structures are considered according to whether they lie anterior, posterior, or immediately to the right or left of the trachea.[2] Not all mediastinal lymph nodes can be reached by the mediastinoscope. Those readily accessible include the right paratracheal nodes to the level of the tracheal bifurcation, the left paratracheal nodes as far as the aortic arch, and the anterior subcarinal nodes.[18] Mediastinoscopy usually requires general anesthesia, but may be performed as an outpatient procedure when subsequent thoracotomy is not planned to follow immediately.[58]

Mediastinoscopy has utility in evaluating mediastinal adenopathy or mass lesions in a variety of settings, including the evaluation of complications of HIV infection.[59] However, its most frequent application is in the staging of bronchogenic carcinoma.[60] Either frozen section or imprint cytology methods can provide rapid, accurate results and facilitate immediate decisions about the feasibility of curative resection.[61,62]

Mediastinoscopy does have potential complications, including pneumothorax, hemorrhage, recurrent laryngeal nerve or phrenic nerve paralysis, injury to the trachea, esophageal perforation, thoracic duct laceration, air embolism, and mediastinitis. A recent retrospective review of 2137 consecutive mediastinoscopies in one center reported only one death attributable to the procedure (0.05%) and 12 complications (0.6%).[63] In a nearly

identical experience of 2145 procedures at another center, there were 23 complications (1.07%), one death (0.05%), and a 5.5% false-negative rate (mostly attributable to nodes not accessible at mediastinoscopy).[64]

The precise indications for mediastinoscopy in non–small cell lung cancer are controversial. The presence of enlarged nodes is an important indication for mediastinoscopy, so that patients with resectable tumors are not incorrectly assumed to have inoperable mediastinal spread (Fig. 76-7). Some advocate the routine use of mediastinoscopy in the evaluation of all cases of potentially resectable disease.[63,65] Others use mediastinoscopy more selectively and omit the procedure if all nodes are less than 1.0 cm or 1.5 cm in diameter by CT scan,[18] or if the primary tumor is small, peripheral, or located in either of the lower lobes.[66] Despite these guidelines, the decision to perform mediastinoscopy or anterior mediastinotomy for lung cancer staging remains a variable one that depends on local resources, personal experience, institutional biases, and treatment preferences for patients with minimal mediastinal nodal involvement.[67]

Video-assisted thoracoscopic surgery, usually considered a tool for the evaluation of pleural and lung abnormalities, can also be helpful in the management of mediastinal diseases. After dissection through the mediastinal pleura, mediastinal lymph nodes can be sampled to aid in the staging of malignancies such as esophageal carcinoma and for the diagnosis and resection of primary mediastinal tumors and cysts.[68-71]

FIGURE 76-7 ■ Axial computed tomographic image through the lower trachea shows a squamous cell carcinoma in the posterior right upper lobe (*) and right paratracheal lymphadenopathy (*arrow*). The right paratracheal lymph node, which was more than 2.0 cm in short-axis diameter, did not show abnormal tracer accumulation on positron emission tomography. It was surgically sampled and proven to be free of tumor. (Courtesy of Michael B. Gotway, MD, Scottsdale Medical Imaging and the Department of Radiology, University of California, San Francisco.)

THE MEDIASTINAL MASS

Definition

The next part of this chapter discusses the specific lesions that present as a mass in the mediastinum. Several of the conditions mentioned, such as thyroid and fat, are not tumors but are instead aberrantly located or overabundant normal tissues. Justification for their inclusion comes from their similar presentation to that of mediastinal tumors and the fact that in most instances they require the same evaluation as any other mediastinal mass. The clinical problem is a "mediastinal mass," and this discussion focuses on the main disease processes that are the cause of this presentation.

Classification and Incidence

Primary mediastinal masses are not uncommon, but their true incidence is difficult to ascertain. An overall incidence of one case per 100,000 population per year may be a reasonable estimation. The tumors and cysts that account for this incidence are individually much less frequent. Table 76-4 estimates the relative frequencies of the most common mediastinal tumors and cysts, based on the collection by Silverman and Sabiston of nearly 2400 cases from the literature.[4] More recent series suggest a similar pattern,[6,72] although Cohen and associates[6] have observed a rising incidence of mediastinal masses in general and an increasing proportion of

TABLE 76-4. Relative Frequencies of Mediastinal Masses in Adults and Children*

Lesion	Adults (%)	Children (%)
Thymoma	19	—
Developmental cysts	21	18
Bronchogenic	7	8
Pericardial	7	<1
Enteric	3	8
Other cysts	4	2
Neurogenic tumors	21	40
Lymphoma	13	18
Germ cell tumors	11	11
Endocrine (thyroid, parathyroid, carcinoid)	6	—
Mesenchymal tumors	7	9
Primary carcinoma	—	—
Other malignancies	3	4

*Based on Silverman and Sabiston's review of reported mediastinal masses in 1950 adults and 437 children. Data from Silverman NA, Sabiston DC Jr: Mediastinal masses. Surg Clin North Am 60:757–777, 1980.

lymphoma and malignant neurogenic tumors over the course of their 45-year survey. In general, neurogenic tumors, thymomas, and developmental cysts account for about 60% of all mediastinal masses. Lymphomas and germ cell tumors such as teratoma and seminoma account for about 25%, and a large number of other lesions, both benign and malignant, constitute the remaining 15%.

There are some differences in the incidence of mediastinal masses between adults and children: thymoma and thyroid masses rarely occur in infants and children, whereas neurogenic tumors are less common in adults. The likelihood of malignancy is higher in infants and children than in adults: in adults, about one fourth of all mediastinal mass lesions are malignant, whereas in children, the percentage is 40% to 45%.[4] In addition, HIV infection substantially alters the spectrum of mediastinal disease. In the HIV-positive population, mediastinal masses are most often due to granulomatous inflammation from mycobacterial and other infections, lymphoma, and other opportunistic processes; in addition, multiple diseases may be present simultaneously.[59] Finally, surgical case series are likely to underrepresent causes of mediastinal masses, such as goiter, that do not routinely lead to surgical intervention.

The most practical clinical classification of mediastinal masses is by their location, grouping together lesions that are characteristically found in the anterior, middle, and posterior mediastinal compartments. Table 76-5 lists the disorders that present as a mediastinal mass and the compartments in which they characteristically arise. This simple scheme is followed in this chapter, recognizing that such a classification ignores the fact that mediastinal masses may present in atypical mediastinal compartments (Fig. 76-8).

SPECIFIC MEDIASTINAL TUMORS AND CYSTS

Lesions Typically in the Anterior Mediastinum

Thymic Neoplasms

Thymoma is the most common neoplasm arising in the anterior mediastinum[4,5,18,73] and has been recognized more often recently because of increased aggressiveness in evaluating patients with myasthenia gravis.[4] Histologically, thymoma is composed of lymphocytes and epithelial cells and is described according to predominating cell type. However, a thymoma's histologic appearance correlates poorly with its biologic behavior and, clinically, these tumors are categorized according to their local invasiveness rather than their appearance under the microscope.[5] Thus, biologically aggressive thymomas are referred to as "invasive" rather than "malignant" thymoma.

The peak incidence of thymomas is between the ages of 40 and 60 years, with equal gender predilection. Two thirds of patients are asymptomatic at the time of diagnosis. The rest of the patients typically have nonspecific chest pain, cough, or dyspnea.[74] However, from 40% to 70% have at least laboratory evidence of one or more of the two dozen systemic "parathymic" syndromes that have been recognized.[4] Myasthenia gravis is the most frequent among these, reported in 10% to 50% of patients with thymoma,[4] and thought to be due to autoantibodies to the postsynaptic acetylcholine receptor.[75,76]

Radiographically, thymomas are usually detected near the junction of the heart and great vessels; typically, they

TABLE 76-5. Disorders Presenting as a Mass in the Mediastinum

ANTERIOR MEDIASTINUM	MIDDLE MEDIASTINUM	POSTERIOR MEDIASTINUM
Thymic neoplasms	Lymphadenopathy	Neurogenic tumors
Germ cell tumors	Reactive and granulomatous inflammation	Arising from peripheral nerves
Teratoma	Metastasis	Arising from sympathetic ganglia
Seminoma	Angiofollicular lymphoid hyperplasia (Castleman's disease)	Arising from paraganglionic tissue
Nonseminomatous germ cell tumors	Lymphoma	Meningocele
Embryonal cell carcinoma	Developmental cysts	Esophageal lesions
Choriocarcinoma	Pericardial cyst	Carcinoma
Lymphoma	Foregut duplication cysts	Diverticula
Hodgkin's disease	Bronchogenic cyst	Diaphragmatic hernia (Bochdalek's)
Non-Hodgkin's lymphoma	Enteric cyst	Miscellaneous
Thyroid neoplasms	Others	
Parathyroid neoplasms	Vascular enlargements	
Mesenchymal tumors	Diaphragmatic hernia (hiatal)	
Lipoma		
Fibroma		
Lymphangioma		
Hemangioma		
Mesothelioma		
Others		
Diaphragmatic hernia (Morgagni's)		
Primary carcinoma		

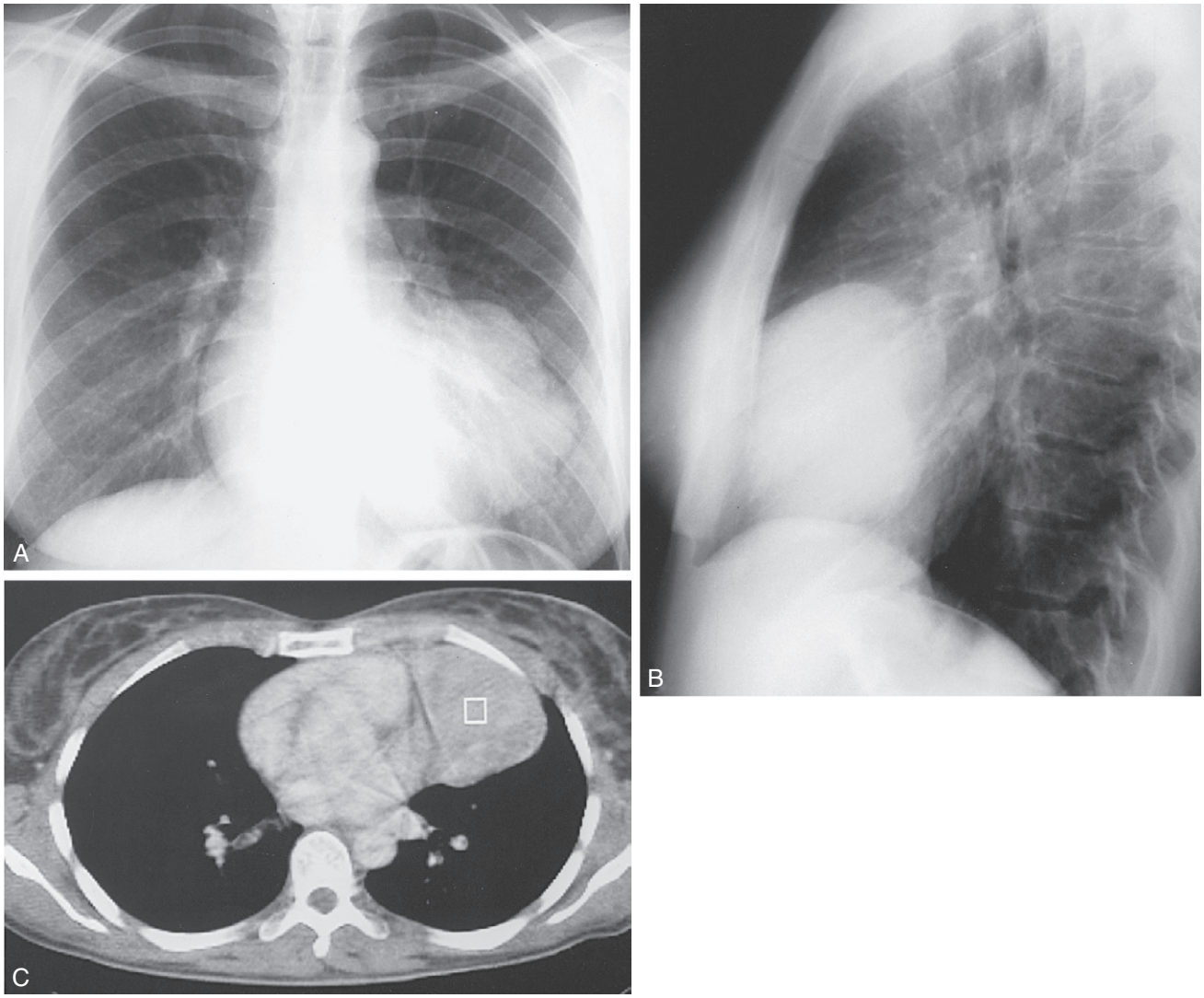

FIGURE 76-8 ■ Typical findings on chest radiographs (**A,** posteroanterior view; **B,** lateral view) and thoracic computed tomogram **(C)** showing a mass presenting in the anterior and middle mediastinum. At surgery, this mass proved to be a benign thymoma, originating in the anterior mediastinum and extending by a slender stalk into the middle radiographic compartment. (Courtesy of Dr. Robert Stevens, Wenatchee, WA.)

are round or oval and their margins are smooth or lobulated (Fig. 76-9).[77] Compared with thymic hyperplasia, which is typically symmetrical, thymoma usually distorts the gland's normal shape and extends to one side.[78] Thymoma is diagnosed with certainty only by examination of tissue. However, CT or MR can reveal gross invasion and continuity of a mediastinal mass with the thymus. Somatostatin receptor scintigraphy and FDG-PET imaging appear promising for discerning thymoma and other thymic tumors from benign thymic hyperplasia.

Thymomas are managed by resection, generally via a median sternotomy approach,[4,73] or via video-assisted thoracoscopic surgery.[70] Adjunctive treatment with postoperative radiotherapy is typically provided,[5,73,79] and the addition of preoperative or adjuvant chemotherapy appears promising for more advanced stages.[80-82]

Thymomas are neoplastic, but most have relatively benign biologic behavior. Patients whose tumors are fully encapsulated can expect survival equal to that of the general population. Invasive tumors have a poorer prognosis, with 50% to 77% 5-year and 30% to 55% 10-year survival.[83] Thymoma recurs after resection in nearly a third of patients.[83]

Other thymic mass lesions include benign conditions such as thymic hyperplasia, thymic cysts, and lipothymoma.[84] Thymic carcinoma is a histologically malignant process that invades locally and frequently metastasizes.[85,86] The prognosis depends on the histologic grade and the anatomic stage and is generally poor. Resection and combined chemoradiation therapy are advocated. Carcinoid tumors occasionally occur in the thymus.[87,88] They may cause Cushing's syndrome and be associated with multiple endocrine adenomatosis. Locally invasive carcinoids may be difficult to resect completely, but characteristically have a prolonged clinical course.[4] Interestingly, the thymus is also a common site for mediastinal Hodgkin's lymphoma, and normal thymic tissue may enlarge following chemotherapy for lymphoma (a

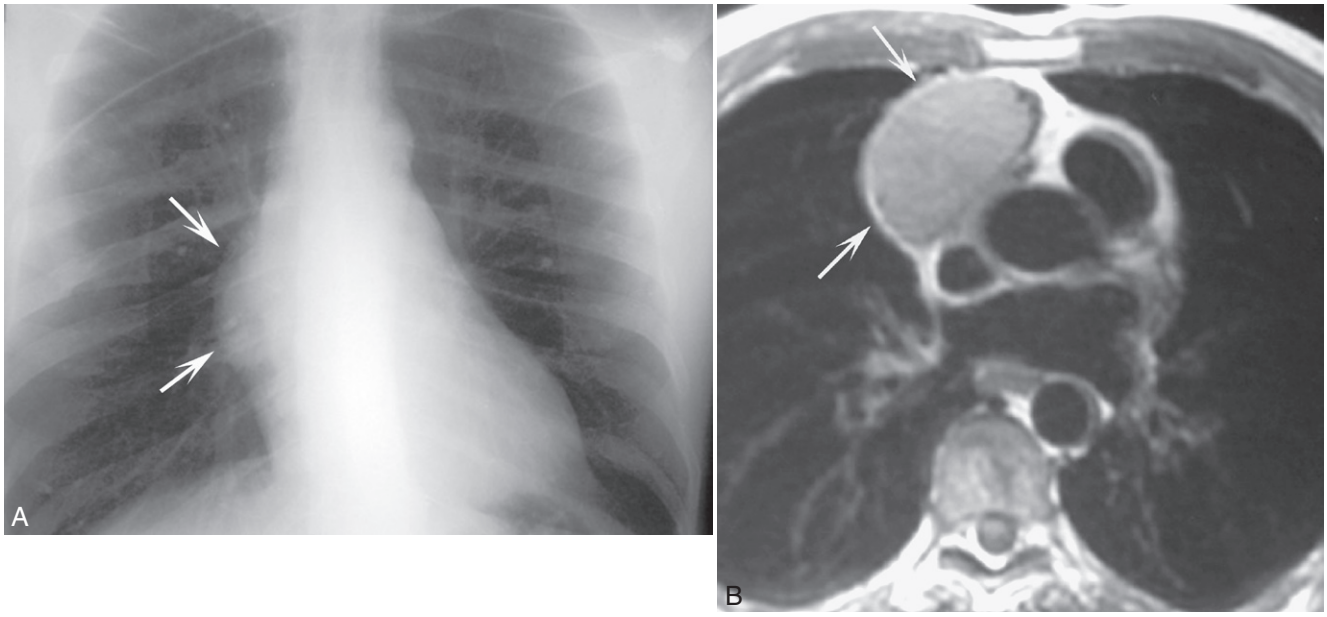

FIGURE 76-9 ■ ***A***, Frontal chest radiograph shows a smoothly marginated mass along the right side of the mediastinum (*arrows*). **B**, Axial magnetic resonance T1-weighted image through the base of the heart shows that the mass (*arrows*) is slightly hyperintense compared to the skeletal muscle and resides within the anterior mediastinum. Note the smooth, well-defined margins of the mass, consistent with an encapsulated thymoma. (Courtesy of Michael B. Gotway, MD, Scottsdale Medical Imaging and the Department of Radiology, University of California, San Francisco.)

process termed *thymic rebound*), mimicking recurrence of the primary disease.[89]

Germ Cell Tumors

Approximately 10% to 12% of primary mediastinal masses are derived from germinal tissues.[4,5,90] These neoplasms are classified into four main groups: teratoma and teratocarcinoma, seminoma, embryonal cell carcinoma, and choriocarcinoma. They are believed to arise from remnant multipotent germ cells that migrated abnormally during embryonic development.[91]

Teratomas are the most common germ cell tumors. By definition, they are made up of tissues foreign to the area in which they occur. Ectodermal derivatives predominate, but structures originating in all three primary germ cell layers may be found. When only the epidermis and its derivatives are present, the term *dermoid cyst* is appropriate. Teratomas arise most often in young adults, but have been reported in all age groups; men and women are affected with equal frequency. Most (80%) are benign, but teratocarcinoma, the malignant counterpart, is an aggressive, rapidly spreading neoplasm with a poor prognosis.

Most patients with teratomas have symptoms caused by the tumor; only about a third are asymptomatic.[4,92] Usual symptoms are pain, cough, and dyspnea. If the tumor erodes into a bronchus, the patient may have hemoptysis or even expectorate differentiated tissue such as hair (trichiptysis) or sebaceous material.[92] Teratomas have also ruptured into the pleural space, causing acute respiratory distress, or into the pericardium, causing pericardial tamponade.

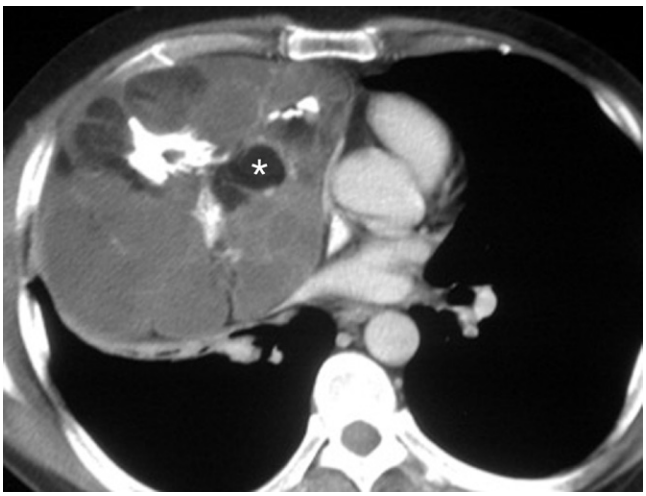

FIGURE 76-10 ■ Axial computed tomographic image through the base of the heart shows a large right-sided anterior mediastinal mass with heterogenous attenuation. Elements of calcium, soft tissue, and fat (*) are present. The presence of fat within an anterior mediastinal mass is consistent with teratoma. (Courtesy of Michael B. Gotway, MD, Scottsdale Medical Imaging and the Department of Radiology, University of California, San Francisco.)

On chest radiographs, if they are cystic, teratomas are generally smooth, rounded, and well circumscribed; if they are solid, they are more lobulated and asymmetrical. On CT scans, soft tissue, fat, and calcification (occasionally, fully-formed teeth and bone) can be identified, rendering this one of few mediastinal tumors that can be diagnosed confidently before operation[17] (Fig. 76-10). All

teratomas should be resected because they may be malignant and because, even if benign, they may enlarge and thus impinge on adjacent vital structures. In malignant teratoma, adjuvant combination chemotherapy may result in improved survival.[93]

Seminomas and nonseminomatous germ cell tumors nearly always cause symptoms and appear as a large anterior mediastinal mass on chest radiographs and CT images. PET scanning may be useful in staging these tumors, but may have greater value in identifiying residual disease and recurrence after medical treatment.[94]

Seminoma (dysgerminoma) occurs almost exclusively in men, usually in the third decade of life.[5] Most patients seek medical attention because of chest pain, dyspnea, cough, hoarseness, or dysphagia. Superior vena cava obstruction can occur. Seminomas are aggressive malignant tumors that extend locally and metastasize distantly, usually to skeletal bones. They may secrete human chorionic gonadotropin, but not alpha-fetoprotein. Factors associated with a poorer prognosis include age over 35 years; superior vena cava obstruction; supraclavicular, cervical, or hilar adenopathy; and fever.[95,96] Seminomas are extremely radiosensitive and may respond dramatically to chemotherapy even in cases with dissemination.[91,97] With aggressive cisplatin-based regimens, long-term survival for all mediastinal seminomas is approximately 80%.[91,98]

Nonseminomatous mediastinal germ cell tumors may be grouped into embryonal cell carcinoma and choriocarcinoma.[4,5,95] A nonseminomatous malignancy usually grouped with embryonal cell carcinoma is called endodermal sinus or yolk sac tumor. These highly malignant aggressive tumors often secrete human chorionic gonadotropin, alpha-fetoprotein, or carcinoembryonic antigen which may also produce clinical manifestations, such as gynecomastia, in 50% of patients.[5] Associations have been noted with Klinefelter's syndrome[99] and with hematologic malignancy.[100] Like seminoma, these tumors occur mainly in men in the third and fourth decades and are usually symptomatic. Most patients present with disseminated disease, and the prognosis has been less favorable than in seminoma.[5] Cisplatin-based treatment regimens have markedly improved the outcome, with over 50% of patients achieving long-term survival.[91,100] Long-term survival may be possible in those who undergo a complete surgical resection following chemotherapy.[101] Even disseminated and refractory malignant germ cell tumors may respond to aggressive chemotherapy[102] and salvage regimens involving bone marrow transplantation.[103,104]

Lymphoma

Lymphoma is a common cause of a mediastinal mass in both adults and children and represents between 10% and 20% of cases in most series.[4–6,72] Hodgkin's disease, or Hodgkin's lymphoma, has a bimodal distribution, arising in adolescents and young adults as well as in those over 50, whereas non-Hodgkin's lymphoma arises most commonly in older adults. Primary mediastinal B-cell lymphoma is a distinct subset of non-Hodgkin's lymphoma that shares features with nodular sclerosing Hodgkin's lymphoma.[105] Lymphoma is especially common as a thoracic complication in HIV-infected patients.[106,107] HIV-associated lymphomas are usually immunoblastic,[106] although Hodgkin's disease also is more common in patients with HIV infection than in the general population.[107,108]

Incidental discovery of a mass on a chest radiograph is a common presentation of lymphoma, although many patients have systemic symptoms or more localized complaints such as cough and chest pain. Tracheal compromise and superior vena cava obstruction are common, as are pericardial and pleural involvement, and Hodgkin's disease often involves the hilar nodes and lung parenchyma.[109] Resection is not a necessary part of therapy, but anterior thoracotomy or mediastinoscopy is usually required to confirm the diagnosis if a site outside the mediastinum is not evident for biopsy. The prognosis of Hodgkin's and other lymphomas has improved strikingly in the last 2 decades as more effective and less toxic combinations of radiotherapy and chemotherapy have evolved, and effective salvage regimens including bone marrow transplantation have been developed to treat relapsed disease.

Thyroid Lesions

In surgical series, ectopic thyroid glands account for fewer than 10% of mediastinal masses but, in clinical practice, these are probably more common. Thyroid tissue within the mediastinum is of two distinct origins. Most commonly, a cervical goiter extends substernally into the anterior mediastinum.[110] Primary intrathoracic goiter, presumably originating from an embryonic rest of heterotopic thyroid tissue, is rare. Most such goiters are in the anterior mediastinum, but they may occur in the middle or posterior mediastinum as well.[4,5] Intrathoracic goiter presents predominantly in women of middle age or older; although it is usually asymptomatic, the goiter may cause hoarseness, cough, or swelling of the face and arms. Intrathoracic thyroid tissue is easily recognized by radioactive iodine scanning,[111] and may be suspected on the basis of high radiodensity on CT scans, particularly after iodinated contrast injection.[112,113] Treatment is by resection.

Parathyroid Lesions

Mediastinal parathyroid tissue is said to account for as many as 10% of cases of hyperparathyroidism, and the mediastinum is the most common site for ectopic parathyroid adenomas in surgically-resistant hyperparathyroidism.[114] Half of ectopic parathyroid adenomas lie in the anterior mediastinum, usually near the thymus. Parathyroid cysts may enlarge sufficiently to appear as a mass on the chest radiograph and to produce symptoms.[115] Otherwise, location of aberrant functioning

parathyroid tissue can be a difficult clinical problem that may be aided preoperatively by CT, ultrasound, MR imaging and the sensitive technetium-99m sestamibi scanning.[116] Selective arteriography and venous sampling for parathormone levels have largely been supplanted by the sestamibi radionuclide scans.[116]

Technetium-99m sestamibi scans are highly accurate in the detection of aberrant parathyroid tissue.[117,118] Sestamibi, a lipophilic cationic molecule that is taken up by mitochondrial-rich cells, is accumulated and retained by hyperplastic parathyroid cells, a finding first described in 1989. The routine use of sestamibi scanning has been proposed as cost-effective because it may lessen the chance of protracted and/or failed cervical explorations in cases of primary hyperparathyroidism.[119,120] Parathyroid adenomas are cured by complete resection, and resection via video-assisted thoracoscopic surgery is increasingly advocated.[68]

Parathyroid carcinoma may be functional, resulting in varying degrees of hyperparathyroidism, but is also locally invasive and may metastasize.[121] Cure is possible with aggressive surgical management[122] that may be guided by imaging and functional localization studies.[123]

Mesenchymal Tumors

Included in this group of unusual mediastinal masses are lipomas, fibromas, mesotheliomas, and lymphangiomas, plus several other rare tumors (see Table 76-5).[4] They arise from connective tissue, fat, smooth muscle, striated muscle, blood vessels, or lymphatic channels and can occur in any region of the mediastinum. Histologically and clinically, they are not substantially different from their counterparts elsewhere in the body. Unless the lesion is very large, the presence of symptoms usually means that the lesion is malignant.[4,18]

Lipoma is the most common mesenchymal tumor of the mediastinum and is most often anterior. It may be encapsulated or unencapsulated, but in either case it is smooth and rounded with well-defined margins. The characteristic low density of lipomas on CT images (Fig. 76-11) permits a confident diagnosis unless there is associated inhomogeneity, invasion of surrounding tissues, or poor demarcation of the mass's perimeter, in which case malignancy (liposarcoma or lipoblastoma) or teratoma must be excluded.[18] Considerably more common than lipoma is mediastinal lipomatosis, or generalized overabundance of histologically normal unencapsulated fat.[124] Mediastinal lipomatosis appears on the conventional radiograph as a smooth widening or bulging of normal mediastinal contours, and its low homogeneous CT density confirms the diagnosis (see Fig. 76-2).[18] Compression or displacement of other mediastinal structures does not occur.

Sarcomas involving the mediastinum are rare but, if present, are more likely due to nerve sheath sarcoma, spindle cell sarcoma, leiomyosarcoma, or liposarcoma.[125] Prior radiation therapy appears to be a predisposing factor in some cases.[126]

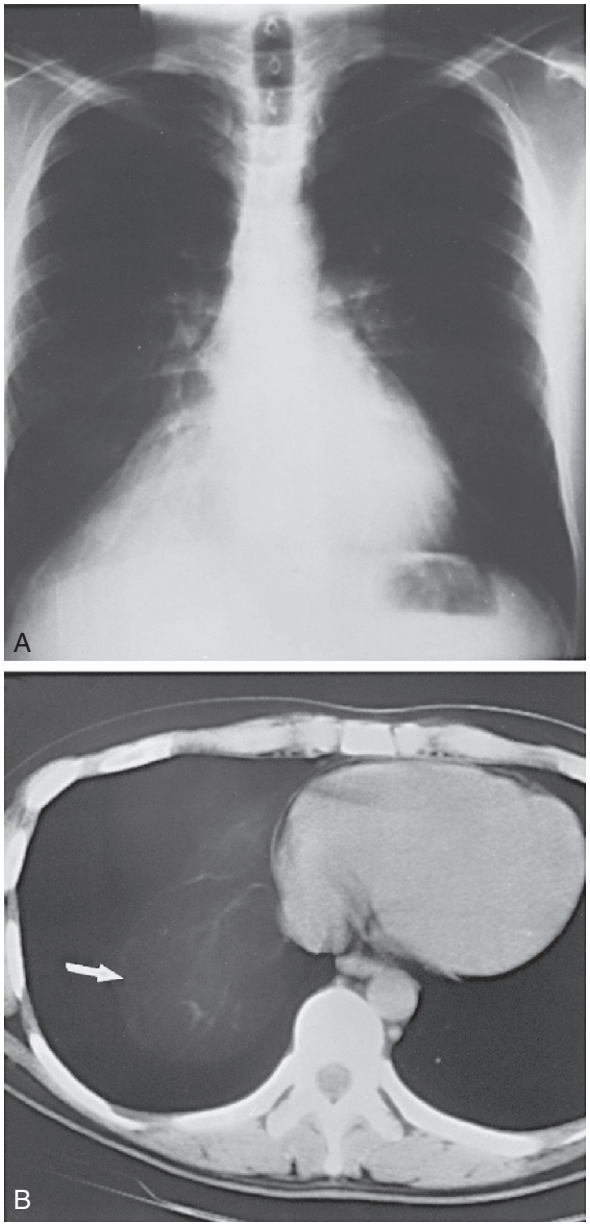

FIGURE 76-11 ■ **A**, Chest radiograph of a 31-year-old man showing an abnormality at the right cardiophrenic angle noted as an incidental finding. **B**, Computed tomogram demonstrates a well-circumscribed homogeneous fat-density mass characteristic of a mediastinal lipoma extending into the right hemithorax (*arrow*).

Lesions Typically in the Middle Mediastinum

Enlargement of Lymph Nodes

Enlargement of lymph nodes represents one of the most common causes of mediastinal abnormality on chest radiographs. Numerous classifications exist for the mediastinal lymph nodes, a comprehensive example of which is the 11-region scheme of the American Thoracic Society.[2] Figure 76-12 presents a simplified grouping of

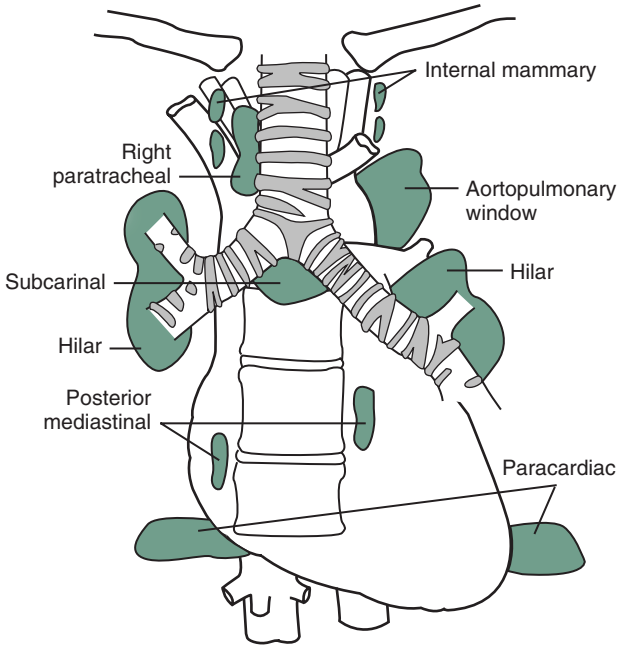

FIGURE 76-12 ■ Simplified schematic diagram depicting mediastinal lymph node groups. (Redrawn from McLoud TC, Meyer JE: Mediastinal metastases. Radiol Clin North Am 20:453–468, 1982.)

the main mediastinal nodes that corresponds to findings on conventional radiography and CT scans.[127] Nodes in the subcarinal, paratracheal, and hilar areas tend to be larger than those elsewhere,[128,129] but most authors consider 1.0-cm diameter at the short axis to be the upper limit of normal size.

Mediastinal lymph node enlargement is most often due to three general categories of disease process: lymphoma,[130] metastatic cancer,[127] and granulomatous inflammation such as that caused by sarcoidosis. Numerous less common causes are described, including Castleman's disease or angiofollicular lymphoid hyperplasia. Mediastinal adenopathy is common in HIV-infected patients and is usually induced by infection, although lymphoma, Kaposi's sarcoma, and other noninfectious processes may be responsible.[131] As discussed previously, lymph node enlargement can be detected accurately by CT and MR, but imaging studies cannot reliably distinguish between benign and malignant causes of node enlargement (see Fig. 76-7).

Developmental Cysts

Developmental cysts of various sorts comprise 10% to 20% of all mediastinal masses.[4,132] Most can be identified as pericardial, bronchogenic, or enteric on the basis of their lining tissues.[4] Bronchogenic and enteric cysts are often referred to as *foregut duplication cysts* because of their origin from aberrant portions of the ventral and dorsal foregut, respectively.

Pericardial cysts account for about one third of cystic masses in adults, but are much less common in children (see Table 76-4). They typically lie against the pericardium, diaphragm, or anterior chest wall in the right cardiophrenic angle. Rarely, pericardial cysts may communicate with the pericardial space. Although typically harmless, pericardial cysts may enlarge to cause right ventricular outflow obstruction,[133] or rupture and hemorrhage to cause pericardial tamponade[134] or sudden cardiac death.[135]

Bronchogenic cysts are typically found near the large airways, often just posterior to the carina, although they may be attached to the esophagus or even inside the pericardial space.[4] The cyst wall often contains cartilage and respiratory epithelium. Most are discovered incidentally and cause no symptoms; however, they may communicate with the tracheobronchial tree and become infected[136]; enlarge to cause airway obstruction,[137] pulmonary artery compression,[138] or hemodynamic collapse[139]; or rupture with disastrous consequences.[140] Spillage of cyst contents into the airway during anesthesia also has been reported.[141]

Enteric or enterogenous cysts are similar in location and appearance to bronchogenic cysts, but have digestive tract epithelium. They are relatively uncommon in adults, but are the most common cysts found in infants and children, in whom they may be associated with spinal extension and malformations of the vertebral column (called "neurenteric" cysts). Enteric cysts can occasionally be multiple and associated with duplications of other portions of the gastrointestinal tract.

Developmental cysts can usually be identified by CT or ultrasonography, and the diagnosis may be confirmed by aspiration cytology. MR imaging is valuable for confirming the cystic nature of these lesions and for evaluating possible spinal extension. In the appropriate clinical setting, benign cysts need not be resected unless they cause symptoms.[142] However, most authorities favor resection because of diagnostic uncertainties and the potential for development of complications.[136,140] Alternatives to thoracotomy include therapeutic aspiration[143,144] and thoracoscopic or mediastinoscopic excision.[69,145,146]

Vascular Masses and Enlargements

Although not technically masses, a variety of vascular lesions must be considered in the differential diagnosis of what appears to be a mediastinal mass seen on the chest radiograph.[5,147] These include poststenotic aortic dilation, aneurysms or tortuosity of the aorta and great vessels, aortic coarctation, innominate vein and superior vena cava aneurysm, persistent left vena cava, azygos and hemiazygos vein enlargement, anomalous pulmonary venous return, pulmonary venous varix, and cardiophrenic angle varices associated with portal hypertension.[148] Idiopathic dilation of the pulmonary trunk and pulmonary arterial hypertension of any cause may appear as a mediastinal mass, and traumatic aortic transection or more subtle vascular injuries may result in mediastinal hematoma.

Angiography has been the traditional means of diagnosing mediastinal masses of vascular origin but, in most cases today, CT imaging with intravenous contrast injection provides a more convenient diagnosis.[149,150] MR

imaging may permit definitive diagnosis without radiation or contrast exposure.

Diaphragmatic Hernia

Omental fat or other abdominal contents may protrude through the diaphragm via several potential routes, producing mediastinal mass lesions in any compartment.[18] A hernia through the foramen of Morgagni produces a cardiophrenic angle mass, usually on the right side in the anterior mediastinum. Bochdalek's hernia, in the posterior mediastinum, generally appears on the left side, presumably because the liver prevents herniation on the right. Herniation of fat around the esophagus is believed to precede hiatal hernia formation; either may appear as a mediastinal mass. In the latter instance, an air-fluid level is intermittently seen on horizontal beam films. Fine linear densities are often demonstrable in diaphragmatic fat herniations on CT imaging. These are thought to represent omental vessels within the hernia, and they may help differentiate a hernia from a lipoma.[18]

Lesions Typically in the Posterior Mediastinum

Neurogenic Tumors

Neoplasms arising from neural tissues constitute the largest single group of mediastinal masses,[4,5] accounting for about 20% of adult cases and twice that proportion in children (see Table 76-4). They are classified into those arising from peripheral nerves, from sympathetic ganglia, and from paraganglionic (chemoreceptor) tissue (Table 76-6). As a group, neurogenic tumors usually appear radiographically as a unilateral paravertebral mass.[4,151,152] Clinical manifestations include chest pain from nerve or bone erosion, dyspnea secondary to tracheal compression, and neurologic deficits resulting from spinal cord compression by intraspinal tumor extension. In addition, many neurogenic tumors are hormonally active.

TABLE 76-6. Neurogenic Tumors of the Mediastinum

Neoplasms Arising from Peripheral Nerves
Neurofibroma
Neurilemoma (schwannoma)
Neurosarcoma
Neoplasms Arising from Sympathetic Ganglia
Ganglioneuroma
Ganglioneuroblastoma
Neuroblastoma
Sympathicoblastoma
Neoplasms Arising from Paraganglionic Tissue
Pheochromocytoma
Paraganglioma (chemodectoma)

Tumors arising from peripheral nerves include neurofibromas, neurilemomas (also called schwannomas), and neurosarcomas. Neurofibromas contain both nerve sheath cells and nerve elements and are the most common tumor of this group. They are incompletely encapsulated and may grow quite large, producing symptoms by nerve compression or space occupation. Mediastinal neurofibroma may be one manifestation of von Recklinghausen's disease (neurofibromatosis). As with these tumors elsewhere, malignant degeneration into neurosarcoma eventually occurs in 10% to 15% of patients with von Reckinghausen's disease.[5]

Neurilemoma, or schwannoma, is another common neurogenic tumor that arises from the neural sheath. Most often seen in the third to fifth decade of life, neurilemoma usually causes no symptoms and appears as a well-circumscribed, homogeneous density on chest radiograph (Fig. 76-13A).[4,5] It is always completely encapsulated and does not invade surrounding tissues, although neurilemomas may extend into intervertebral foramina (see Fig. 76-13B and C). Treatment of both neurilemoma and solitary neurofibroma is resection.

Malignant tumors of nerve sheath origin are also known as malignant neurofibroma, malignant schwannoma, or neurogenic fibrosarcoma. These tumors behave aggressively, with both local invasion and distant metastasis. Half occur in patients with neurofibromatosis.[13] Treatment requires wide excision and usually adjuvant radiation.[13]

Tumors arising from nerve cells in sympathetic ganglia display a spectrum of neoplastic behavior ranging from ganglioneuroma, a benign tumor occurring mainly in children, to the malignant tumors ganglioneuroblastoma and neuroblastoma. Ganglioneuromas cause symptoms merely by mass effect, and are usually cured by surgical excision. Ganglioneuroblastomas have intermediate behavior and can invade locally but are less likely to metastasize.[5] Neuroblastoma rapidly displaces and invades adjacent structures and may be widely metastatic at the time of presentation.[153,154] These tumors often elaborate endocrine peptides and catecholamines, and are associated with diarrhea, fever, anorexia, and weight loss.[4] The propensity to produce catecholamines is used to advantage by imaging tumor uptake of the catecholamine precursor [^{123}I]-metaiodobenzylguanine (MIBG) for purposes of diagnosis, identification of distant tumor metastases and treatment.[155,155a] Treatment of neuroblastoma involves risk-based strategies that guide multimodality therapy.[156]

Neoplasms arising from paraganglionic or chemoreceptor tissue include pheochromocytomas, which are rare in the mediastinum and indistinguishable clinically or histologically from their counterparts in the abdomen, and paragangliomas (chemodectomas). Paragangliomas may secrete catecholamines just as do pheochromocytomas and thus may also be detected and perhaps treated with MIBG.[156a] They appear benign under the microscope and seldom metastasize, but spread locally in an aggressive fashion and thus have high morbidity and mortality rates.[4]

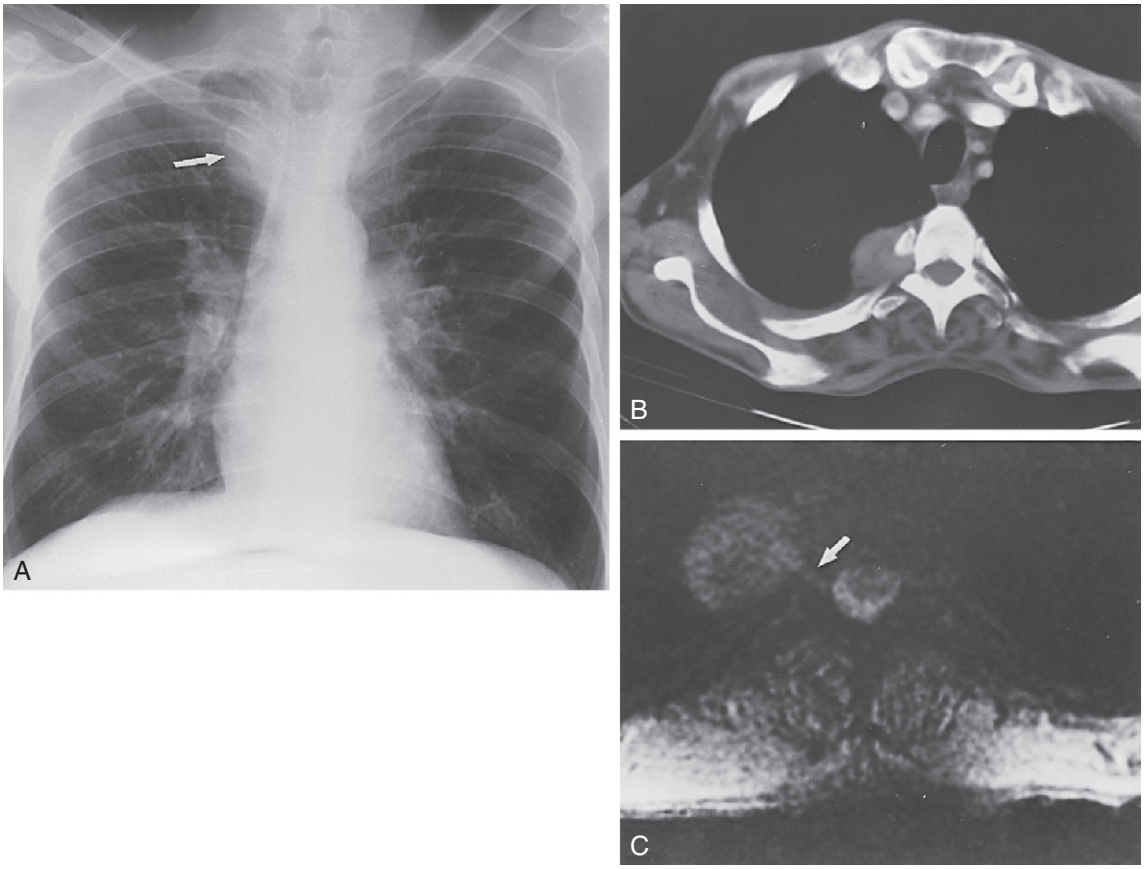

FIGURE 76-13 ■ Series of imaging studies of a 64-year-old asymptomatic man with a surgically proved neurilemoma, or schwannoma. **A**, Posteroanterior chest radiograph showing an incidental finding of a discrete mass behind the right clavicular head (*arrow*). **B**, Computed tomogram showing homogeneous, well-circumscribed appearance and posterior location adjacent to the vertebral column. **C**, Magnetic resonance image showing extension of the tumor into the intervertebral foramen (*arrow*).

Miscellaneous Mediastinal Masses

Numerous rare causes of mass lesions in the mediastinum have been described.[5] These include malignancies known as primary carcinoma and sarcoma of the mediastinum.[4] Primary carcinoma usually occurs in the anterior or middle mediastinum and is believed to be distinct from bronchogenic carcinoma and from other primary mediastinal neoplasms. It occurs primarily in adults, usually in men, and has an aggressive, rapidly fatal course with little response to therapy. Primary mediastinal sarcoma is a rare lesion of children, which otherwise clinically resembles primary carcinoma. Poorly differentiated carcinoma of the mediastinum ("Adkins tumor"[157]) is a rare neoplasm whose histology does not permit identification of a likely tissue or site of origin.

Miscellaneous benign causes of a mediastinal mass have been described. Pancreatic pseudocysts may extend into the mediastinum, usually through the aortic or esophageal hiatus.[5,158,159] They have been reported in all three mediastinal compartments. Hydatid cysts also rarely occur in the mediastinum.[5] The posterior mediastinum is occasionally the site of a thoracic duct cyst.[4,72] Also, extramedullary hematopoiesis in patients with chronic hemolytic anemia may appear as a mediastinal mass, often in a posterior location. Meningoceles, outgrowths of spinal meninges that protrude along the course of a spinal nerve, produce posterior mediastinal masses.

Finally, it must be remembered that masses found within any of the mediastinal compartments may be due to lesions more commonly found in another mediastinal compartment or due to those which have extended from another area in the mediastinum (see Fig. 76-8).

GENERAL APPROACH TO DIAGNOSTIC INVESTIGATION

Evaluation of a Mediastinal Mass

Occasionally, mass lesions in the mediastinum can be diagnosed based on clinical information and noninvasive test results alone, without need for a biopsy. Only a few masses fall into this category. These include mediastinal thyroid tissue, which can be identified by radioactive iodine scans, certain calcified lesions that have remained unchanged on serial radiographs, and mediastinal lipomatosis with typical CT findings. Determining that a mass is cystic does not unequivocally establish it as benign: solid tumors may become cystic (especially thymomas and degenerating nerve sheath tumors), and teratomas may be solid, cystic, or a combination of these. In addi-

tion, some cystic lesions become so densely packed with secreted material and detritus that they appear solid on CT. Lymphoma or other malignancy diagnosed by biopsy of tissues outside the thorax does not require separate demonstration that it is also the cause of a mediastinal mass. Confirmed active pulmonary tuberculosis or sarcoidosis usually warrants a trial of therapy and period of observation before invasive approaches are used to evaluate coexistent mediastinal abnormalities. However, for the large majority of mediastinal masses, thorough diagnostic evaluation must lead to examination of tissue obtained from the lesion.

Primary mediastinal tumors usually require biopsy in order to determine the cause. However, because most primary mediastinal masses should be removed regardless of the cause, consideration should be given to surgical resection as the initial invasive diagnostic approach. In general, even benign lesions should be removed because they may subsequently enlarge, compress vital mediastinal structures, hemorrhage, rupture, become infected, or, with varying degrees of likelihood, undergo malignant degeneration. In light of these factors, the basic focus of the diagnostic evaluation of a mediastinal mass is an orderly preparation for obtaining a tissue diagnosis or a complete resection. The goals should be to assess the patient's general health and suitability for operation, and clinical syndromes and laboratory clues suggesting a specific diagnosis (Table 76-7).

Conventional chest radiographs are the first diagnostic tool in all cases, and certain mediastinal mass lesions have characteristic appearances (see Table 76-3). A stable appearance, in comparison to older films, can obviate the need for further investigation in selected patients. Imaging by CT or MR will more completely depict the mass's size, location, density, homogeneity, and gross involvement of surrounding tissues than standard chest radiographs and will also help guide the surgeon. The need for specialized studies such as a thyroid scan, a sestamibi scan, or ^{123}I-MIBG will be dictated by the clinical setting and by suspicion of a specific diagnosis. Sometimes a more accessible site for biopsy is discovered on general evaluation of the patient, as in cases of lymphoma with extrathoracic lymphadenopathy. However, in most cases, tissue from the mediastinal mass must be obtained, and the optimal management of mediastinal tumors and cysts usually includes complete resection of the mass. Therefore, if the patient is a candidate for potentially curative surgical resection, surgery should be the next step in most cases. Surgery and anesthesia can be challenging, and approaches should be individualized.[160]

TABLE 76-7. Diagnostic Approach to the Primary Mediastinal Mass

History
Symptoms of local effects or complications
Systemic syndromes as clues to diagnosis (see Table 76-2)
Physical Examination
Physiologic compromise
Extrathoracic manifestations as clues to diagnosis (see Table 76-2)
Potential extrathoracic biopsy sites
General condition and candidacy for surgery
Chest Radiography and Computed Tomography
Anatomic location (see Table 76-5)
Appearance (size, shape, density, invasion)
Characteristic imaging features (see Table 76-3)
Special Imaging Studies
Thyroid scan (suspected goiter, abnormal thyroid function tests)
^{67}Gallium scan (suspected sarcoidosis)
Somatostatin receptor scintigraphy (suspected thymoma)
^{99m}Technetium sestamibi scan (suspected parathyroid adenoma)
^{123}I-MIBG scintigraphy (suspected catecholamine-producing neurogenic tumors)
Positron emission tomography (suspected lung cancer)
Laboratory Studies
Complete blood count
Routine chemistries (hypercalcemia, hypoglycemia)
Thyroid function tests (suspected goiter)
Anti–acetylcholine receptor antibody (myasthenic symptoms or mass contiguous with thymus)
Alpha-fetoprotein and β-human chorionic gonadotropin (suspected germ cell tumor)
Catecholamine levels (suspected neurogenic tumor)
Tissue Biopsy
Transbronchial needle biopsy (especially if bronchoscopy is already indicated)
Transthoracic or transesophageal needle biopsy (for accessible lesions when primary resection is not feasible)
Mediastinoscopy or mediastinotomy (for accessible lesions, if less invasive approaches are unsuccessful)
Primary Surgical Resection
Appropriate diagnostic approach when ultimate goal is resection and no evidence precludes therapeutic resection

Mediastinal Evaluation to Stage Bronchogenic Carcinoma

Mediastinal tissue sampling is central to the management of bronchogenic carcinoma because noninvasive assessment of the mediastinum usually cannot definitively confirm or exclude the presence of metastases, and because findings of mediastinal metastases may drastically alter the surgical and other therapeutic options. Thus, in patients who appear to be candidates for surgical resection, staging should consist of a deliberate search for metastases in the mediastinal lymph nodes.[16] To deny surgery to a patient with curable disease is a greater loss than to perform mediastinoscopy or even thoracotomy on a patient who is then found to be unresectable. It seems logical to progress through the staging process from diagnosis, to imaging of the mediastinum, to examination of nodal tissue, to surgical exploration, stopping the sequence on the confident discovery of metastatic disease but otherwise proceeding to resection. Which imaging procedures to employ, how to obtain diagnostic tissue, and what constitutes the confident identification of metastases that contraindicate surgery are decisions that must be made but have no absolute answers.

Finally, the general condition and wishes of the patient with lung cancer must enter into the clinical staging process. A systematic extrathoracic assessment may indicate that curative resection is not an option, either because the patient has obvious signs of distant metastases or because severe chronic pulmonary, cardiac, or other systemic disease precludes curative therapy.

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KEY POINTS

- The mediastinum is the space in the center of the chest, between the lungs, that contains all of the other thoracic viscera.
- The mediastinum contains numerous vital organs within a confined space that is surrounded by the bony thorax and is relatively inaccessible for examination.
- The mediastinum can be divided into three compartments based on anatomic boundaries that can be seen on a lateral chest radiograph.
- The *anterior* compartment lies between the sternum and the anterior border of the heart and great vessels. Anterior mediastinal masses include thymoma, germ cell tumors, lymphoma, and thyroid and parathyroid tumors.
- The *middle* compartment contains the heart and most of the great vessels, the trachea, and the phrenic and upper vagus nerves. Middle mediastinal masses include lymphadenopathy and developmental cysts.
- The *posterior* compartment lies between the posterior wall of the heart and trachea and the posterior chest wall. It contains the esophagus, thoracic duct, descending aorta and azygos/hemiazygos veins, and the sympathetic chains and lower vagus nerves. Posterior mediastinal masses are generally neurogenic tumors.
- Benign mediastinal tumors and cysts may cause problems due to compression of adjacent organs and structures, hemorrhage, infection, or rupture.
- Malignant mediastinal lesions can invade locally and can metastasize distantly.
- Whether benign or malignant, most mediastinal tumors and cysts should be resected either because they may be malignant or because even benign masses may enlarge and impinge on vital structures.

References

1. Fraser R, Paré J, Fraser R, et al: The normal chest. *In* Fraser R, ParéJ (eds): Synopsis of Diseases of the Chest (2nd ed). Philadelphia: WB Saunders; 1994, pp 1–116.
2. Clinical staging of primary lung cancer: American Thoracic Society node mapping scheme. Am Rev Respir Dis 127:659–669, 1983.
3. Maunder RJ, Pierson DJ, Hudson LD: Subcutaneous and mediastinal emphysema: Pathophysiology, diagnosis, and management. Arch Intern Med 144:1447–1453, 1984.
4. Silverman NA, Sabiston DC Jr: Mediastinal masses. Surg Clin North Am 60:757–777, 1980.
5. LeRoux BT, Kallichurum S, Shama DM: Mediastinal cysts and tumors. Curr Probl Surg 21:1–76, 1984.
6. Cohen AJ, Thompson L, Edwards FH, et al: Primary cysts and tumors of the mediastinum. Ann Thorac Surg 51:378–384, 1991.
7. Wudel LJ Jr, Nesbitt JC: Superior vena cava syndrome. Curr Treat Options Oncol 2:77–91, 2001.
8. Mahajan V, Strimlan V, van Ordstrand HS, et al: Benign superior vena cava syndrome. Chest 68:32–35, 1975.
9. Yellin A, Rosen A, Reichert N, et al: Superior vena cava syndrome: The myth—the facts. Am Rev Respir Dis 141:1114–1118, 1990.
10. Chen JC, Bongard F, Klein SR: A contemporary perspective on superior vena cava syndrome. Am J Surg 160:207–211, 1990.
11. Hoffman OA, Gillespie DJ, Aughenbaugh GL, et al: Primary mediastinal neoplasms (other than thymoma). Mayo Clin Proc 68:880–891, 1993.
12. Strollo DC, Rosado de Christenson ML, Jett JR: Primary mediastinal tumors. Part I: Tumors of the anterior mediastinum. Chest 112:511–522, 1997.
13. Strollo DC, Rosado de Christenson ML, Jett JR: Primary mediastinal tumors: Part II. Tumors of the middle and posterior mediastinum. Chest 112:1344–1357, 1997.
14. Mountain CF: Revisions in the International System for Staging Lung Cancer [see comments]. Chest 111:1710–1717, 1997.
15. Pretreatment evaluation of non-small-cell lung cancer. The American Thoracic Society and The European Respiratory Society. Am J Respir Crit Care Med 156:320–332, 1997.
16. Detterbeck F, Jantz M, Wallace M, et al: Invasive mediastinal staging of lung cancer: ACCP evidence-based clinical practice guidelines (2nd ed). Chest 132:202S–220S, 2007.
17. Ahn JM, Lee KS, Goo JM, et al: Predicting the histology of anterior mediastinal masses: Comparison of chest radiography and CT. J Thorac Imaging 11:265–271, 1996.
18. Naidich DP, Zerhouni EA, Siegelman SS: Computed Tomography and Magnetic Resonance of the Thorax (2nd ed). New York: Raven Press, 1991.
19. Gould MK, Kuschner WG, Rydzak CE, et al: Test performance of positron emission tomography and computed tomography for

mediastinal staging in patients with non-small-cell lung cancer: A meta-analysis. Ann Intern Med 139:879–892, 2003.
20. Ratto GB, Frola C, Cantoni S, et al: Improving clinical efficacy of computed tomographic scan in the preoperative assessment of patients with non-small cell lung cancer. J Thorac Cardiovasc Surg 99:416–425, 1990.
21. McLoud TC, Bourgouin PM, Greenberg RW, et al: Bronchogenic carcinoma: Analysis of staging in the mediastinum with CT by correlative lymph node mapping and sampling [see comments]. Radiology 182:319–323, 1992.
22. Quint LE, Francis IR, Wahl RL, et al: Preoperative staging of non-small-cell carcinoma of the lung: Imaging methods. AJR Am J Roentgenol 164:1349–1359, 1995.
23. Gamsu G, Sostman D: Magnetic resonance imaging of the thorax. Am Rev Respir Dis 139:254–274, 1989.
24. Link KM, Samuels LJ, Reed JC, et al: Magnetic resonance imaging of the mediastinum and its contents. J Thorac Imaging 8:34–53, 1993.
25. Dujovny M, Alp MS, Dujovny N, et al: Aneurysm clips: Magnetic quantification and magnetic resonance imaging safety. Technical note. J Neurosurg 87:788–794, 1997.
26. Webb WR, Gatsonis C, Zerhouni EA, et al: CT and MR imaging in staging non-small cell bronchogenic carcinoma: Report of the Radiologic Diagnostic Oncology Group. Radiology 178:705–713, 1991.
27. Wernecke K, Diederich S: Sonographic features of mediastinal tumors. AJR Am J Roentgenol 163:1357–1364, 1994.
28. Pedersen BH, Vilmann P, Folke K, et al: Endoscopic ultrasonography and real-time guided fine-needle aspiration biopsy of solid lesions of the mediastinum suspected of malignancy. Chest 110:539–544, 1996.
29. Sulavik SB, Spencer RP, Weed DA, et al: Recognition of distinctive patterns of gallium-67 distribution in sarcoidosis. J Nucl Med 31:1909–1914, 1990.
30. Dooms GC, Hricak H: Radiologic imaging modalities, including magnetic resonance, for evaluating lymph nodes. Western J Med 144:49–57, 1986.
31. Lowe VJ, Naunheim KS: Positron emission tomography in lung cancer. Ann Thorac Surg 65:1821–1829, 1998.
32. Puri V, Meyers B: Utility of positron emission tomography in the mediastinum: Moving beyond lung and esophageal cancer staging. Thorac Surg Clin 19:7–15, 2009.
33. Reed CE, Harpole DH, Posther KE, et al: Results of the American College of Surgeons Oncology Group Z0050 trial: The utility of positron emission tomography in staging potentially operable non-small cell lung cancer. J Thorac Cardiovasc Surg 126:1943–1951, 2003.
34. Vesselle H, Pugsley JM, Vallières E, et al: The impact of fluorodeoxyglucose F 18 positron-emission tomography on the surgical staging of non-small cell lung cancer. J Thorac Cardiovasc Surg 124:511–519, 2002.
35. Yang W, Fu Z, Yu J, et al: Value of PET/CT versus enhanced CT for locoregional lymph nodes in non-small cell lung cancer. Lung Cancer 61:35–43, 2008.
36. Lee B, von Haag D, Lown T, et al: Advances in positron emission tomography technology have increased the need for surgical staging in non-small cell lung cancer. J Thorac Cardiovasc Surg 133:746–752, 2007.
37. Ghamande S, Rafanan A, Dweik R, et al: Role of transbronchial needle aspiration in patients receiving mechanical ventilation. Chest 122:985–989, 2002.
38. Shure D, Fedullo PF: The role of transcarinal needle aspiration in the staging of bronchogenic carcinoma. Chest 86:693–696, 1984.
39. Schenk DA, Bower JH, Bryan CL, et al: Transbronchial needle aspiration staging of bronchogenic carcinoma. Am Rev Respir Dis 134:146–148, 1986.
40. Ratto GB, Mereu C, Motta G: The prognostic significance of preoperative assessment of mediastinal lymph nodes in patients with lung cancer. Chest 93:807–813, 1988.
41. Wang KP, Brower R, Haponik EF, et al: Flexible transbronchial needle aspiration for staging of bronchogenic carcinoma. Chest 84:571–576, 1983.
42. Harrow E, Halber M, Hardy S, et al: Bronchoscopic and roentgenographic correlates of a positive transbronchial needle aspiration in the staging of lung cancer. Chest 100:1592–1596, 1991.
43. Herth FJ, Becker HD, Ernst A: Ultrasound-guided transbronchial needle aspiration: An experience in 242 patients. Chest 123:604–607, 2003.
44. Yasufuku K, Nakajima T, Motoori K, et al: Comparison of endobronchial ultrasound, positron emission tomography, and CT for lymph node staging of lung cancer. Chest 130:710–718, 2006.
45. Yasufuku K, Nakajima T, Fujiwara T, et al: Role of endobronchial ultrasound-guided transbronchial needle aspiration in the management of lung cancer. Gen Thorac Cardiovasc Surg 56:268–276, 2008.
46. Kalade A, Eddie Lau W, Conron M, et al: Endoscopic ultrasound-guided fine-needle aspiration when combined with positron emission tomography improves specificity and overall diagnostic accuracy in unexplained mediastinal lymphadenopathy and staging of non-small-cell lung cancer. Intern Med J 38:837–844, 2008.
47. Rintoul R, Tournoy K, El Daly H, et al: EBUS-TBNA for the clarification of PET positive intra-thoracic lymph nodes—an international multi-centre experience. J Thorac Oncol 4:44–48, 2009.
48. Gay PC, Brutinel WM: Transbronchial needle aspiration in the practice of bronchoscopy. Mayo Clin Proc 64:158–162, 1989.
49. Trisolini R, Agli LL, Cancellieri A, et al: The value of flexible transbronchial needle aspiration in the diagnosis of stage I sarcoidosis. Chest 124:2126–2130, 2003.
50. Harkin TJ, Ciotoli C, Addrizzo-Harris DJ, et al: Transbronchial needle aspiration (TBNA) in patients infected with HIV. Am J Respir Crit Care Med 157:1913–1918, 1998.
51. Akamatsu H, Terashima M, Koike T, et al: Staging of primary lung cancer by computed tomography-guided percutaneous needle cytology of mediastinal lymph nodes. Ann Thorac Surg 62:352–355, 1996.
52. Krasnik M: Endoscopic transesophageal and endoscopic transbronchial real-time ultrasound-guided biopsy. Respiration 70:293–298, 2003.
53. Silvestri GA, Hoffman BJ, Bhutani MS, et al: Endoscopic ultrasound with fine-needle aspiration in the diagnosis and staging of lung cancer. Ann Thorac Surg 61:1441–1445, 1996.
54. Fritscher-Ravens A, Davidson BL, Hauber HP, et al: Endoscopic ultrasound, positron emission tomography, and computerized tomography for lung cancer. Am J Respir Crit Care Med 168:1293–1297, 2003.
55. Gress FG, Savides TJ, Sandler A, et al: Endoscopic ultrasonography, fine-needle aspiration biopsy guided by endoscopic ultrasonography, and computed tomography in the preoperative staging of non-small-cell lung cancer: A comparison study. Ann Intern Med 127:604–612, 1997.
56. Vilmann P, Puri R: The complete "medical" mediastinoscopy (EUS-FNA + EBUS-TBNA). Minerva Med 98:331–338, 2007.
57. Kelemen JJ 3rd, Naunheim KS: Minimally invasive approaches to mediastinal neoplasms. Semin Thorac Cardiovasc Surg 12:301–306, 2000.
58. Vallières E, Pagé A, Verdant A: Ambulatory mediastinoscopy and anterior mediastinotomy. Ann Thorac Surg 52:1122–1126, 1991.
59. Mouroux J, Riquet M, Padovani B, et al: Surgical management of thoracic manifestations in human immunodeficiency virus-positive patients: Indications and results. Br J Surg 82:39–43, 1995.
60. Ginsberg RJ: Evaluation of the mediastinum by invasive techniques. Surg Clin North Am 67:1025–1035, 1987.
61. Clarke MR, Landreneau RJ, Borochovitz D: Intraoperative imprint cytology for evaluation of mediastinal lymphadenopathy. Ann Thorac Surg 57:1206–1210, 1994.
62. de Montpréville VT, Dulmet EM, Nashashibi N: Frozen section diagnosis and surgical biopsy of lymph nodes, tumors and pseudotumors of the mediastinum. Eur J Cardiothorac Surg 13:190–195, 1998.
63. Hammoud ZT, Anderson RC, Meyers BF, et al: The current role of mediastinoscopy in the evaluation of thoracic disease. J Thorac Cardiovasc Surg 118:894–899, 1999.
64. Lemaire A, Nikolic I, Petersen T, et al: Nine-year single center experience with cervical mediastinoscopy: Complications and false negative rate. Ann Thorac Surg 82:1185–1189, 2006.

65. Boyle EM, Vallières E: Mediastinoscopy in the staging of lung cancer. Curr Surg 58:47–54, 2001.
66. Dillemans B, Deneffe G, Verschakelen J, et al: Value of computed tomography and mediastinoscopy in preoperative evaluation of mediastinal nodes in non-small cell lung cancer: A study of 569 patients. Eur J Cardiothorac Surg 8:37–42, 1994.
67. Ghosh S, Nanjiah P, Dunning J: Should all patients with non-small cell lung cancer who are surgical candidates have cervical mediastinoscopy preoperatively? Interact Cardiovasc Thorac Surg 5:20–24, 2006.
68. Prinz RA, Lonchyna V, Carnaille B, et al: Thoracoscopic excision of enlarged mediastinal parathyroid glands. Surgery 116:999–1004, 1994.
69. Hazelrigg SR, Landreneau RJ, Mack MJ, et al: Thoracoscopic resection of mediastinal cysts. Ann Thorac Surg 56:659–660, 1993.
70. Sugarbaker DJ: Thoracoscopy in the management of anterior mediastinal masses. Ann Thorac Surg 56:653–656, 1993.
71. Demmy TL, Krasna MJ, Detterbeck FC, et al: Multicenter VATS experience with mediastinal tumors. Ann Thorac Surg 66:187–192, 1998.
72. Adegboye VO, Brimmo AI, Adebo OA, et al: The place of clinical features and standard chest radiography in evaluation of mediastinal masses. West Afr J Med 22:156–160, 2003.
73. Kohman LJ: Controversies in the management of malignant thymoma. Chest 112:296S–300S, 1997.
74. Morgenthaler TI, Brown LR, Colby TV, et al: Thymoma. Mayo Clin Proc 68:1110–1123, 1993.
75. Lennon VA, Lambert EH: Myasthenia gravis induced by monoclonal antibodies to acetylcholine receptors. Nature 285:238–240, 1980.
76. Beekman R, Kuks JB, Oosterhuis HJ: Myasthenia gravis: Diagnosis and follow-up of 100 consecutive patients. J Neurol 244:112–118, 1997.
77. Rosado-de-Christenson M, Strollo D, Marom E: Imaging of thymic epithelial neoplasms. Hematol Oncol Clin North Am 22:409–431, 2008.
78. Rosado de Christenson ML, Galobardes J, Moran CA: Thymoma: Radiologic-pathologic correlation. Radiographics 12:151–168, 1992.
79. Curran WJ Jr, Kornstein MJ, Brooks JJ, et al: Invasive thymoma: The role of mediastinal irradiation following complete or incomplete surgical resection. J Clin Oncol 6:1722–1727, 1988.
80. Venuta F, Rendina EA, Longo F, et al: Long-term outcome after multimodality treatment for stage III thymic tumors. Ann Thorac Surg 76:1866–1872, 2003 (discussion appears in Ann Thorac Surg 76:1872, 2003).
81. Casey E, Kiel P, Loehrer PS: Clinical management of thymoma patients. Hematol Oncol Clin North Am 22:457–473, 2008.
82. Venuta F, Rendina E, Coloni GF: Multimodality treatment of thymic tumors. Thorac Surg Clin 19:71–81, 2009.
83. Blumberg D, Port JL, Weksler B, et al: Thymoma: A multivariate analysis of factors predicting survival. Ann Thorac Surg 60:908–913, 1995.
84. Rosado de Christenson ML, Pugatch RD, Moran CA, et al: Thymolipoma: Analysis of 27 cases. Radiology 193:121–126, 1994.
85. Hsu CP, Chen CY, Chen CL, et al: Thymic carcinoma: Ten years' experience in twenty patients. J Thorac Cardiovasc Surg 107:615–620, 1994.
86. Moran C, Suster S: Thymic carcinoma: Current concepts and histologic features. Hematol Oncol Clin North Am 22:393–407, 2008.
87. Wick MR, Rosai J: Neuroendocrine neoplasms of the mediastinum. Semin Diagn Pathol 8:35–51, 1991.
88. Economopoulos GC, Lewis JW Jr, Lee MW, et al: Carcinoid tumors of the thymus. Ann Thorac Surg 50:58–61, 1990.
89. Burns DE, Schiffman FJ: Beguiled by the gallium: Thymic rebound in an adult after chemotherapy for Hodgkin's disease. Chest 104:1916–1919, 1993.
90. Dehner LP: Germ cell tumors of the mediastinum. Semin Diagn Pathol 7:266–284, 1990.
91. Nichols CR: Mediastinal germ cell tumors. Semin Thorac Cardiovasc Surg 4:45–50, 1992.
92. Lewis BD, Hurt RD, Payne WS, et al: Benign teratomas of the mediastinum. J Thorac Cardiovasc Surg 86:727–731, 1983.
93. Dulmet EM, Macchiarini P, Suc B, et al: Germ cell tumors of the mediastinum: A 30-year experience. Cancer 72:1894–1901, 1993.
94. De Giorgi U, Pupi A, Fiorentini G, et al: FDG-PET in the management of germ cell tumor. Ann Oncol 16:90–94, 2005.
95. Knapp RH, Hurt RD, Payne WS, et al: Malignant germ cell tumors of the mediastinum. J Thorac Cardiovasc Surg 89:82–89, 1985.
96. Hurt RD, Bruckman JE, Farrow GM, et al: Primary anterior mediastinal seminoma. Cancer 49:1658–1663, 1982.
97. Bukowski RM, Wolf M, Kulander BG, et al: Alternating combination chemotherapy in patients with extragonadal germ cell tumors. A Southwest Oncology Group study. Cancer 71:2631–2638, 1993.
98. Kesler K, Einhorn L: Multimodality treatment of germ cell tumors of the mediastinum. Thorac Surg Clin 19:63–69, 2009.
99. Nichols CR, Heerema NA, Palmer C, et al: Klinefelter's syndrome associated with mediastinal germ cell neoplasms. J Clin Oncol 5:1290–1294, 1987.
100. Nichols CR, Roth BJ, Heerema N, et al: Hematologic neoplasia associated with primary mediastinal germ-cell tumors. N Engl J Med 322:1425–1429, 1990.
101. Kang C, Kim Y, Jheon S, et al: Surgical treatment of malignant mediastinal nonseminomatous germ cell tumor. Ann Thorac Surg 85:379–384, 2008.
102. Nichols CR, Catalano PJ, Crawford ED, et al: Randomized comparison of cisplatin and etoposide and either bleomycin or ifosfamide in treatment of advanced disseminated germ cell tumors: An Eastern Cooperative Oncology Group, Southwest Oncology Group, and Cancer and Leukemia Group B study. J Clin Oncol 16:1287–1293, 1998.
103. Nichols CR, Andersen J, Lazarus HM, et al: High-dose carboplatin and etoposide with autologous bone marrow transplantation in refractory germ cell cancer: An Eastern Cooperative Oncology Group protocol. J Clin Oncol 10:558–563, 1992.
104. Nichols CR, Saxman S: Primary salvage treatment of recurrent germ cell tumors: Experience at Indiana University. Semin Oncol 25:210–214, 1998.
105. Boleti E, Johnson P: Primary mediastinal B-cell lymphoma. Hematol Oncol 25:157–163, 2007.
106. Wang CY, Snow JL, Su WP: Lymphoma associated with human immunodeficiency virus infection. Mayo Clin Proc 70:665–672, 1995.
107. Straus DJ: Human immunodeficiency virus-associated lymphomas. Med Clin North Am 81:495–510, 1997.
108. L'Evy R, Colonna P, Tourani JM, et al: Human immunodeficiency virus associated Hodgkin's disease: Report of 45 cases from the French Registry of HIV-Associated Tumors. Leuk Lymphoma 16:451–456, 1995.
109. Strickler JG, Kurtin PJ: Mediastinal lymphoma. Semin Diagn Pathol 8:2–13, 1991.
110. Chin SC, Rice H, Som PM: Spread of goiters outside the thyroid bed: A review of 190 cases and an analysis of the incidence of the various extensions. Arch Otolaryngol Head Neck Surg 129:1198–1202, 2003.
111. Park HM, Tarver RD, Siddiqui AR, et al: Efficacy of thyroid scintigraphy in the diagnosis of intrathoracic goiter. AJR Am J Roentgenol 148:527–529, 1987.
112. Glazer HS, Molina PL, Siegel MJ, et al: High-attenuation mediastinal masses on unenhanced CT. AJR Am J Roentgenol 156:45–50, 1991.
113. Jennings A: Evaluation of substernal goiters using computed tomography and MR imaging. Endocrinol Metab Clin North Am 30:401–414, ix, 2001.
114. Jaskowiak N, Norton JA, Alexander HR, et al: A prospective trial evaluating a standard approach to reoperation for missed parathyroid adenoma. Ann Surg 224:308–320, 1996.
115. Hauet EJ, Paul MA, Salu MK: Compression of the trachea by a mediastinal parathyroid cyst. Ann Thorac Surg 64:851–852, 1997.
116. Judson BL, Shaha AR: Nuclear imaging and minimally invasive surgery in the management of hyperparathyroidism. J Nucl Med 49:1813–1818, 2008.
117. Caixas A, Berna L, Hernández A, et al: Efficacy of preoperative diagnostic imaging localization of technetium 99m-sestamibi scintigraphy in hyperparathyroidism. Surgery 121:535–541, 1997.

118. Thomas DL, Bartel T, Menda Y, et al: Single photon emission computed tomography should be routinely performed for the detection of parathyroid abnomalities utilizing Tc-99m sestamibi parathyroid scintigraphy. Clin Nucl Med 34:651–655, 2009.
119. Nilubol N, Beyer T, Prinz R, et al: Mediastinal hyperfunctioning parathyroids: Incidence, evolving treatment, and outcome. Am J Surg 194:53–56, 2007.
120. Fayet P, Hoeffel C, Fulla Y, et al: Technetium-99m sestamibi scintigraphy, magnetic resonance imaging and venous blood sampling in persistent and recurrent hyperparathyroidism. Br J Radiol 70:459–464, 1997.
121. Cordeiro AC, Montenegro FL, Kulcsar MA, et al: Parathyroid carcinoma. Am J Surg 175:52–55, 1998.
122. Vázquez Quintana E: Parathyroid carcinoma: Diagnosis and management. Am Surg 63:954–957, 1997.
123. Damadi A, Harkema J, Kareti R, et al: Use of pre-operative Tc99m-sestamibi scintigraphy and intraoperative parathyroid hormone monitoring to eliminate neck exploration in mediastinal parathyroid adenocarcinoma. J Surg Educ 64:108–112, 2007.
124. Homer JM, Wechsler RJ, Carter BL: Mediastinal lipomatosis. Radiology 128:657–661, 1978.
125. Burt M, Ihde JK, Hajdu SI, et al: Primary sarcomas of the mediastinum: Results of therapy. J Thorac Cardiovasc Surg 115:671–680, 1998.
126. Killion MJ, Brodovsky HS, Schwarting R: Pericardial angiosarcoma after mediastinal irradiation for seminoma: A case report and a review of the literature. Cancer 78:912–917, 1996.
127. McLoud TC, Meyer JE: Mediastinal metastases. Radiol Clin North Am 20:453–468, 1982.
128. Genereux GP, Howie JL: Normal mediastinal lymph node size and number: CT and anatomic study. AJR Am J Roentgenol 142:1095–1100, 1984.
129. Glazer GM, Gross BH, Quint LE, et al: Normal mediastinal lymph nodes: Number and size according to American Thoracic Society mapping. AJR Am J Roentgenol 144:261–265, 1985.
130. Filly R, Blank M, Castellino RA: Radiographic distribution of intrathoracic disease in previously untreated patients with Hodgkin's disease and non-Hodgkin's lymphoma. Radiology 120:277–281, 1976.
131. Haramati LB, Choi Y, Widrow CA, et al: Isolated lymphadenopathy on chest radiographs of HIV-infected patients. Clin Radiol 51:345–349, 1996.
132. Cioffi U, Bonavina L, De Simone M, et al: Presentation and surgical management of bronchogenic and esophageal duplication cysts in adults. Chest 113:1492–1496, 1998.
133. Ng AF, Olak J: Pericardial cyst causing right ventricular outflow tract obstruction. Ann Thorac Surg 63:1147–1148, 1997.
134. Borges AC, Gellert K, Dietel M, et al: Acute right-sided heart failure due to hemorrhage into a pericardial cyst. Ann Thorac Surg 63:845–847, 1997.
135. Fredman CS, Parsons SR, Aquino TI, et al: Sudden death after a stress test in a patient with a large pericardial cyst. Am Heart J 127:946–950, 1994.
136. Ribet ME, Copin MC, Gosselin B: Bronchogenic cysts of the mediastinum. J Thorac Cardiovasc Surg 109:1003–1010, 1995.
137. Lippmann M, Solit R, Goldberg SK, et al: Mediastinal bronchogenic cyst: A cause of upper airway obstruction. Chest 102:1901–1903, 1992.
138. Worsnop CJ, Teichtahl H, Clarke CP: Bronchogenic cyst: A cause of pulmonary artery obstruction and breathlessness. Ann Thorac Surg 55:1254–1255, 1993.
139. Fratellone PM, Coplan N, Friedman M, et al: Hemodynamic compromise secondary to a mediastinal bronchogenic cyst. Chest 106:610–612, 1994.
140. Zaugg M, Kaplan V, Widmer U, et al: Fatal air embolism in an airplane passenger with a giant intrapulmonary bronchogenic cyst. Am J Respir Crit Care Med 157:1686–1689, 1998.
141. Politis GD, Baumann R, Hubbard AM: Spillage of cystic pulmonary masses into the airway during anesthesia. Anesthesiology 87:693–696, 1997.
142. Bolton JW, Shahian DM: Asymptomatic bronchogenic cysts: What is the best management? [see comments]. Ann Thorac Surg 53:1134–1137, 1992.
143. Schwartz AR, Fishman EK, Wang KP: Diagnosis and treatment of a bronchogenic cyst using transbronchial needle aspiration. Thorax 41:326–327, 1986.
144. Tobert DG, Midthun DE: Bronchogenic cyst. J Bronch 3:295–299, 1996.
145. Urschel JD, Horan TA: Mediastinoscopic treatment of mediastinal cysts. Ann Thorac Surg 58:1698–1700, 1994.
146. Smythe WR, Bavaria JE, Kaiser LR: Mediastinoscopic subtotal removal of mediastinal cysts. Chest 114:614–617, 1998.
147. Kelley MJ, Mannes EJ, Ravin CE: Mediastinal masses of vascular origin: A review. J Thorac Cardiovasc Surg 76:559–572, 1978.
148. Wachsberg RH, Yaghmai V, Javors BR, et al: Cardiophrenic varices in portal hypertension: Evaluation with CT. Radiology 195:553–556, 1995.
149. Marotta R, Franchetto AA: The CT appearance of aortic transection. AJR Am J Roentgenol 166:647–651, 1996.
150. Gavant ML, Menke PG, Fabian T, et al: Blunt traumatic aortic rupture: Detection with helical CT of the chest [see comments]. Radiology 197:125–133, 1995.
151. Woo O, Yong H, Shin B, et al: Wide spectrum of thoracic neurogenic tumors: A pictoral review of CT and pathological findings. Br J Radiol 81:668–676, 2008.
152. Tanaka O, Kiryu T, Hirose Y, et al: Neurogenic tumors of the mediastinum and chest wall: MR imaging appearance. J Thorac Imaging 20:316–320, 2005.
153. Shields TW, Reynolds M: Neurogenic tumors of the thorax. Surg Clin North Am 68:645–668, 1988.
154. Mueller S, Matthay KK: Neuroblastoma: biology and staging. Curr Oncol Rep 11:431–438, 2009.
155. Taggart D, Dubois S, Matthay KK: Radiolabeled MIBG for imaging and therapy of neuroblastoma. Q J Nucl Med Mol Imaging 52:403–418, 2008.
155a. Taggart DR, Han MM, Quach A, et al: Comparison of I123 MIBG scan and FDG-PET to evaluate response after I131 MIBG therapy for relapsed neuroblastoma. J Clin Oncol 27:5343–5349, 2009.
156. Maris JM, Hogarty MD, Bagatell R, Cohn SL: Neuroblastoma. Lancet 369:2106–2120, 2007.
156a. Havekes B, Lai EW, Corssmit EP, et al: Detection and treatment of pheochromocytomas and paragangliomas: current standing of MIBG scintigraphy and future role of PET imaging. Q J Nucl Med Mol Imaging 52:419–429, 2008.
157. Adkins RBJ, Maples MD, Hainsworth JD: Primary malignant mediastinal tumors. Ann Thorac Surg 38:648–653, 1984.
158. Jaffe BM, Ferguson TB, Holtz S: Mediastinal pancreatic pseudocysts. Am J Surg 124:600–606, 1972.
159. Gupta R, Munoz J, Garg P, et al: Mediastinal pancreatic pseudocyst—a case report and review of the literature. Med Gen Med 9:8, 2007.
160. Erdos G, Tzanova I: Perioperative anaesthetic management of mediastinal mass in adults. Eur J Anaesthesiol 26:627–632, 2009.

CHAPTER 77

PNEUMOMEDIASTINUM AND MEDIASTINITIS

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INTRODUCTION

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INTRODUCTION

Pneumomediastinum (air in the mediastinum) and mediastinitis (infection or inflammation in the mediastinum) are disorders that involve the potential spaces and tissues of the mediastinum. Although both may occur together, as following esophageal rupture, the term *pneumomediastinum* usually refers to the presence of aberrant air in the mediastinum without accompanying infection and *mediastinitis* refers to infection or inflammation regardless of the presence of air. These conditions are seen in a variety of unique clinical circumstances. However, both tend to result either from breaches in the integrity of mediastinal structures or from spread to mediastinal structures from elsewhere in the body. Thus, anatomic considerations are similar for the two processes and are considered at the beginning of this chapter. The pathophysiology, clinical settings, management approaches, and clinical impact of pneumomediastinum and mediastinitis are quite different and are discussed separately.

GENERAL ANATOMIC CONSIDERATIONS

The mediastinum is traversed by air-filled structures (the trachea and esophagus) which may contain colonizing microorganisms. In addition, mediastinal lymph nodes drain the airways and lung parenchyma where inhaled organisms, antigens, and dusts are encountered. Consequently, entry of air or inflammatory and infectious materials into the mediastinum is readily accomplished by breaches in the integrity of these mediastinal structures or when materials deposited in the airways or distal lung are transported through the lymphatic system.

How air enters and moves through the mediastinum can be understood by referring to the soft tissue compartments of the neck, thorax, and abdomen, as illustrated in Figure 77-1. The visceral space surrounding the trachea, esophagus, and great vessels in the neck continues into the chest to envelop the mediastinal viscera and passes through the diaphragm with the esophagus to communicate with the retroperitoneal space. A continuum thus connects the viscera-containing spaces of the neck, chest, and retroperitoneum. This same space extends along the vessels and airways of the pulmonary hilum to merge with the distal bronchovascular sheaths (see Fig. 77-1).[1] Thus, it is possible for air that enters these tissue planes, or inflammation originating at any site in the mediastinum, to dissect and spread to involve any of the mediastinal structures.

In the remainder of this chapter, pneumomediastinum and the various forms of mediastinitis are discussed in turn.

PNEUMOMEDIASTINUM

Pneumomediastinum consists of air or other gas in the mediastinum. Also known as *mediastinal emphysema*, it is one of several forms of aberrant extra-alveolar air, or air outside the confines of the respiratory and gastrointestinal tracts. The others include subcutaneous emphysema, pulmonary interstitial emphysema,

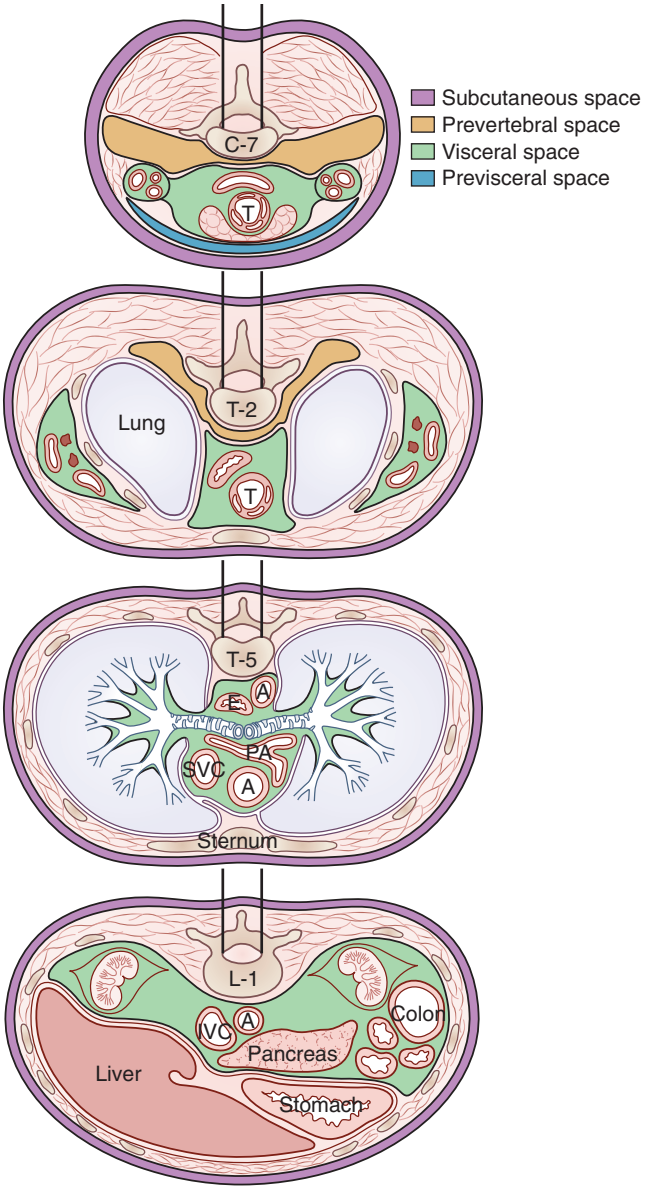

FIGURE 77-1 ■ Soft tissue compartments of the mediastinum (at levels of T2 and T5) in relation to those of the neck (at level of C7) and the upper abdomen (at level of L1) demonstrate continuity of the visceral space. (Redrawn from Maunder RJ, Pierson DJ, Hudson LD: Subcutaneous and mediastinal emphysema: Pathophysiology, diagnosis, and management. Arch Intern Med 144:1447–1453, 1984.)

pneumopericardium, pneumoperitoneum, pneumoretroperitoneum, pneumocephalus, and pneumorachis (air in the spinal canal). Pneumothorax, the most common life-threatening form of extra-alveolar air, is discussed elsewhere and mentioned only briefly here (see Chapter 74).

Extra-alveolar air in the form of pneumomediastinum and subcutaneous emphysema arises in a wide variety of clinical settings; the earliest to be recognized was during childbirth. In her "Observations" of 1617 (as cited by Gordon[2]), Louise Bourgeois, midwife to the queen of France, wrote, "I saw that she tried to stop crying out, and I implored her not to stop, for fear that her throat might swell." The first formal medical documentation of pneumomediastinum and subcutaneous emphysema during labor was by Simmons in 1784, and this association was reported in over 130 patients by 1927.[2] Within 2 decades thereafter, Hamman[3,4] had thoroughly established the clinical features of spontaneous pneumomediastinum and Macklin and Macklin[5] had elegantly elucidated its pathophysiology (see later). Little has been added to the pioneering descriptions of these investigators, but pneumomediastinum and other forms of extra-alveolar air occur today in a greater variety of clinical circumstances. In addition to childbirth, these include mechanical ventilation and other aspects of critical care, decompression in diving and other settings, chest trauma, asthma, and numerous other situations.[1]

Pathophysiology

The pathophysiology of pneumomediastinum depends on the clinical circumstances in which it is encountered. Pneumomediastinum most commonly results from alveolar rupture but can also result from air escaping from the upper respiratory tract, intrathoracic airways, or gastrointestinal tract. Gas can be generated by certain infections, and outside air can reach the mediastinum after trauma or surgery. These potential sources for mediastinal emphysema are summarized in Table 77-1 and discussed in the following sections.

Air Originating in the Upper Respiratory Tract

Mediastinal air dissecting downward from the head and neck can originate in several ways. Retropharyngeal abscess is a long-established cause of gas in the neck, but other infections including dental abscess, cervical adenitis, salivary gland infection, tonsillitis, and osteomyelitis of the facial bones can also produce this finding.[1,6] Odontogenic infections are said to be the most common of these.[7]

Dental extractions or drilling can be followed by pneumomediastinum. Passage of air into the soft tissues from the socket of an extracted tooth can be increased dramatically if positive pressure is applied at the mouth—as illustrated by the case of a soldier whose neck swelled on resumption of his duties as a bugler immediately after a tooth extraction.[8]

Injury to the paranasal sinuses, orbit, mandible, and other facial bones adjacent to the upper airways can provide access of air to the fascial planes of the neck, especially following nose blowing. Surgical procedures involving the upper respiratory tract may produce air in the neck via breaches in either the oropharyngeal mucosa or the trachea and skin. For instance, pneumomediastinum and subcutaneous emphysema are common after tracheotomy: these findings were noted in 13% of cases in one prospective series in adults.[9]

TABLE 77-1. Possible Origins of Air in the Mediastinum

UPPER RESPIRATORY TRACT
- Head and neck infection (odontogenic, salivary glands, cervical adenitis, tonsillitis, peritonsillar abscess, osteomyelitis of facial bones)
- Fractures (involving paranasal sinuses, orbit, mandibles, other facial bones)
- Other mucosal disruption (trauma, surgery, attempted endotracheal intubation)
- Dental procedures (extractions, air-turbine drilling)

INTRATHORACIC AIRWAYS
- Blunt or penetrating chest trauma
- Foreign body
- Iatrogenic (bronchoscopy, bronchial brushing, transbronchial biopsy, needle aspiration)
- Neoplasm

LUNG PARENCHYMA
- Direct disruption of alveoli (penetrating trauma, surgery, transbronchial biopsy, needle aspiration)
- "Spontaneous" alveolar rupture (between alveolus and adjacent bronchovascular sheath)*

GASTROINTESTINAL TRACT
- Esophageal perforation
- Via pneumoperitoneum or pneumoretroperitoneum (gastric or intestinal perforation, diverticulitis, pneumatosis cystoides intestinalis, endoscopy, biopsy, infection)

EXTERNAL TO THE BODY
- Penetrating trauma to neck or chest
- Surgical procedures (tracheotomy, mediastinoscopy, sternotomy)
- Via subcutaneous emphysema in association with chest tube insertion
- Artificial pneumothorax
- Artificial pneumoperitoneum

INFECTION WITH GAS-PRODUCING ORGANISMS
- Acute bacterial mediastinitis
- Head and neck infections

*See Table 77-2 for clinical settings.

Pneumomediastinum can also occur following attempts at endotracheal intubation or after overinflation of the endotracheal tube cuff when the hypopharyngeal mucosa or membranous trachea is injured.[10] Tracheal injury and esophageal rupture leading to pneumomediastinum can happen also when air is forced into the open mouth.[11,12]

Air Originating in the Intrathoracic Airways

Blunt thoracic trauma, particularly deceleration injury as sustained in motor vehicle crashes, may lacerate or fracture the trachea or main bronchi and allow air to enter the mediastinum.[13] Although this may occur in the proximal trachea, the majority of such injuries are within 3 cm of the carina, probably owing to the relative fixation of the airway at the carina and the development of a shearing force when the more mobile parts are displaced by the sudden impact.

Other potential sources of mediastinal air from the major intrathoracic airways include perforation by an aspirated foreign body and erosion by bronchogenic or esophageal neoplasm. Visceral perforation is associated with bronchoscopy much less frequently than with esophagoscopy. However, the increasing use of bronchoscopic biopsy techniques and endobronchial therapies for bronchial obstruction render this source for mediastinal air increasingly likely.

Air Originating in the Lung Parenchyma

Most instances of pneumomediastinum are the result of alveolar disruption. This may occur after direct injury to the lung parenchyma, which allows air to escape from torn alveoli and terminal bronchioles after penetrating thoracic trauma or from cut surfaces during surgery. The lung may be nicked in the course of tracheotomy or central venous access procedures, and this mechanism may also be the source of extra-alveolar air after percutaneous or transbronchial lung biopsy. The majority of cases of pneumomediastinum, however, follow "spontaneous" alveolar rupture.

Mechanism of Alveolar Rupture. Disruption of alveolar walls and entry of air into the bronchovascular sheath can result when a pressure gradient becomes sufficient to disrupt the alveolar walls at their bases and force air into the pulmonary interstitium, as depicted in Figure 77-2.[1,5,14] Although it has been speculated that a increase in intra-alveolar pressure was capable of producing alveolar rupture, animal experiments have demonstrated that an increase in alveolar volume, due to increased transpulmonary pressure, is a more important determinant of disruption of the alveolar walls.[15] This finding may explain the rarity of alveolar rupture following coughing and sneezing; contraction of muscles of the chest and abdominal walls counter the transient high intra-alveolar pressures.[16]

High alveolar volumes undoubtedly contribute to alveolar rupture after decompression due to decreases in external pressure.[16,17] The mechanism of alveolar rupture presumably relates to overdistention due to the expansion of gas trapped in the lungs during ascent.[18,19]

Pneumomediastinum and other forms of extra-alveolar air arising from the lung are almost always associated with parenchymal abnormalities in the affected lung both during mechanical ventilation[16,20] and during spontaneous ventilation.[1,5]

Spread of Air following Alveolar Rupture. Entry of air into the bronchovascular sheath, as depicted schematically in Figure 77-2, produces pulmonary interstitial emphysema. This is the initial consequence of alveolar rupture and may be the only overt manifestation of extra-alveolar air. According to Munsell,[21] Laennec called this condition "interlobular emphysema." Because the mean pressure in the mediastinum, like that in the pleural space, is always somewhat negative with respect to the

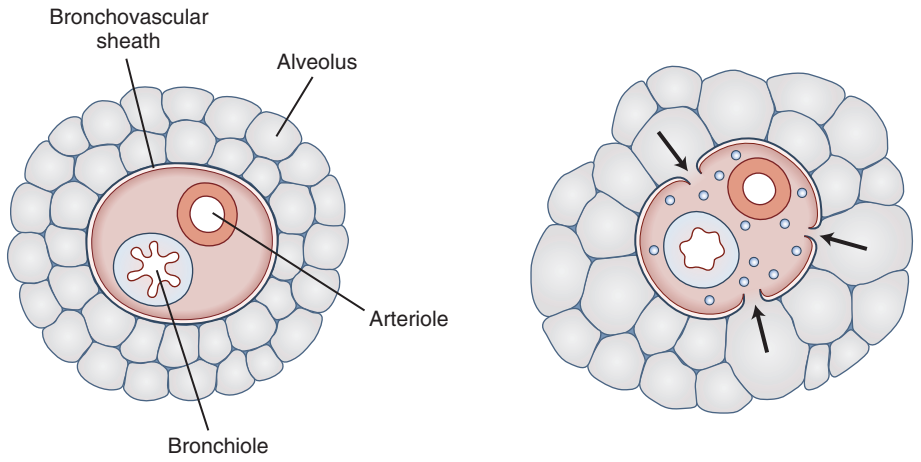

FIGURE 77-2 ■ Schematic diagram shows the mechanism of alveolar rupture into the bronchovascular sheath resulting from a momentary pressure gradient between them. (Redrawn from Maunder RJ, Pierson DJ, Hudson LD: Subcutaneous and mediastinal emphysema: Pathophysiology, diagnosis, and management. Arch Intern Med 144:1447–1453, 1984.)

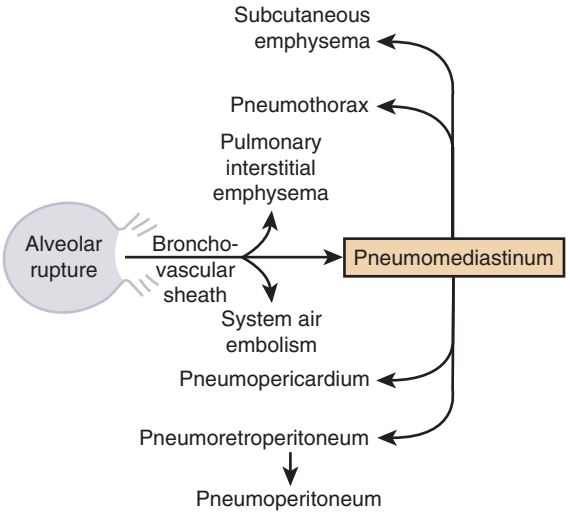

FIGURE 77-3 ■ The pathogenesis of the different forms of extra-alveolar air resulting from alveolar rupture.

pressure in the pulmonary parenchyma, the pressure difference causes air to move toward the mediastinum.[22] This is illustrated in Figure 77-3 and convincingly described in the 1944 paper by Macklin and Macklin,[5] which first confirmed the sequence in experimental animals:

> The first step … was air passing through numerous minute ruptures in the strained bases of the alveoli of the overinflated region into the underlying vascular sheaths. The air bubbles, at the very first minute, moved along the vascular sheaths, coalescing and gaining in size. This streaming of air through the pulmonic interstitium reminded one of the flow of a river that ever increases in size by addition of new tributaries as it proceeds on its course. Reaching the root of the lung, the train of air bubbles passed into and distended the mediastinum. With continued insufflation an actual overflow into the retroperitoneum, anterior mediastinum and subcutaneous tissues of the root of the neck and axillae occurred. In extreme cases the mediastinal wall ruptured, producing a pneumothorax.

These classic observations have since been confirmed in other studies but, conceptually, little has been added.

Entry of Air into the Pleural Space. Once in the mediastinum, air follows the path of least resistance and may rupture through the delicate mediastinal fascia and overlying pleura into the pleural space. This model is supported by observations that, in animal experiments, lower sustained inflation-hold pressures were required to produce pulmonary interstitial emphysema than to create a pneumomediastinum or pneumothorax and that, in most mechanically-ventilated patients in one clinical series, pneumomediastinum preceded pneumothorax.[23] Another mechanism for pneumothorax following alveolar rupture has been proposed, in which air dissects toward the periphery of the lung rather than toward the mediastinum and ruptures via subpleural blebs through the visceral surface of the lung. Which of these mechanisms most often accounts for "spontaneous" pneumothorax is uncertain.

Entry of Air into the Abdomen. Extra-alveolar air originating from disrupted alveoli may appear below the diaphragm as either *pneumoperitoneum* or *pneumoretroperitoneum*.[24] To reach the retroperitoneal space, air from the mediastinum usually travels via the loosely packed paraesophageal connective tissue across the diaphragm. The retroperitoneal air may then break through the peritoneum to enter the peritoneal space.

Entry of Air into the Vasculature. Extra-alveolar air also may enter pulmonary blood vessels resulting in *arterial air embolism*.[17,25] This complication is particularly common in the setting of decompression illness,[25] yet is relatively rare as a complication of mechanical ventilation, despite a high incidence of alveolar rupture and other forms of aberrant air.[26] The more common recognition of air embolism in decompression illness than in barotrauma due to mechanical ventilation may

relate to a larger volume of air entering the circulation, to a greater injury to the pulmonary venules and veins, to the relative ease in recognizing subtle forms of air embolism in otherwise healthy patients, or to the upright posture of ascending divers favoring clinically overt cerebral embolization of any air entering the systemic circulation. Also, during decompression, bubbles may form directly within systemic circulation, leading to arterial air embolism in the absence of pulmonary barotrauma.

Although commonly associated with cardiac septal defects or pulmonary arteriovenous shunts,[27] systemic air embolism can follow introduction of air into the venous system without the obvious presence of such right-to-left shunts.[28]

Air Originating in the Gastrointestinal Tract

Mediastinal air can originate from the gastrointestinal tract, either above or below the diaphragm. In *Boerhaave's syndrome*, rupture of the esophagus allows air and other material to enter the mediastinum.[29] In this circumstance, pneumomediastinum is accompanied by acute mediastinitis, as discussed later in this chapter. Pneumomediastinum can also result from esophageal perforation during upper gastrointestinal endoscopy[30] or following the ingestion of a caustic such as paraquat[31] or lye (sodium hydroxide).

Rarely, air or other gas originating in the retroperitoneal space can spread to the mediastinum.[1] Retroperitoneal causes of pneumomediastinum include perforation of a duodenal ulcer, ulcerative colitis, sigmoid diverticulitis, pneumatosis cystoides intestinalis, "rectal barotraumas,"[32] and procedures such as sigmoidoscopy, colonoscopy, and barium enema.[33]

Air Originating from External and Miscellaneous Sources

Pneumomediastinum can arise from air entering the body from external sources, particularly if positive pressure is applied at the subcutaneous tissue planes. Air can reach the mediastinum via the cervical soft tissues during tracheotomy,[9] via the chest wall during arthroscopic shoulder surgery,[34] or via the extremities as a result of industrial accidents.[35] Mediastinal air can also arise from a pneumothorax by an unusual mechanism: air in the pleural space can reach the subcutaneous tissues via the tube thoracostomy tract, can dissect to the neck, and can then penetrate down to the mediastinum. Pneumomediastinum has also been observed following the insufflation of air into the peritoneal cavity for tuberculosis treatment,[36] during the course of modern era laparoscopy,[37] and via the female genital tract during pelvic examination,[38] douche,[39] postpartum exercise,[40] or blowing into the vagina,[41–43] especially during pregnancy.[44]

Gas can form in the mediastinum during acute bacterial mediastinitis caused by gas-producing microbes. More commonly, pneumomediastinum associated with mediastinitis is due to communication with the gastrointestinal tract (as in Boerhaave's syndrome), respiratory tract (as in necrotizing pneumonia), or outside air (as in traumatic or poststernotomy mediastinitis). These conditions are described in more detail in the second part of this chapter.

Clinical Settings and Syndromes

Pneumomediastinum following alveolar rupture is encountered clinically in two general settings: "spontaneous" mediastinal emphysema and "barotrauma," or pneumomediastinum arising during positive-pressure ventilation or associated with other externally applied distending pressures (Table 77-2).

Spontaneous Pneumomediastinum

Voluntary Alterations in Breathing Pattern. Alveolar rupture can sometimes be induced by voluntary manipulations of the breathing pattern. A typical example

TABLE 77-2. Alveolar Rupture: Reported Clinical Settings

DUE TO ALTERATIONS OF SPONTANEOUS BREATHING PATTERNS

Voluntary Alteration in Breathing Pattern
- Marijuana smoking and cocaine inhalation
- Pulmonary function testing
- Mountain climbing—"voluntary pressure breathing"
- Wind instrument playing
- Yelling, shouting, and singing

Inadvertant Alteration in Breathing Pattern
- Childbirth
- Vomiting
- Seizures; status epilepticus
- Violent coughing; sneezing; hiccupping
- Heavy lifting; athletic competition
- Straining at stool

Intrinsic Airway and Lung Disease
- Asthma
- Atelectasis
- Bronchiolitis
- Pneumonia
- Influenza
- Measles
- Tuberculosis
- Silicosis
- Foreign body
- Tumor
- "Idiopathic" (Hamman's syndrome)

DUE TO RAPID CHANGES IN TRANSPULMONARY PRESSURE GRADIENT

Decrease in External Pressure from Decompression Causing Gas Expansion
- Scuba diving
- Air travel

Increase in Intrathoracic Pressure of External Origin
- Mechanical ventilation
- Continuous positive airway pressure
- Manual ventilation during resuscitation, anesthesia, or transport
- Equipment malfunction or misconnection in anesthesia or oxygen therapy
- Heimlich maneuver
- Deceleration injury

is pneumomediastinum reported after vigorous straining against a closed glottis during marijuana smoking[45] or after inhaling free-base cocaine,[46,47] during which users sometimes add additional external airway pressure by having an accomplice blow vigorously into their mouths through a cardboard tube.[48] Pneumomediastinum has also been reported in two college fraternity brothers following the recreational inhalation of nitrous oxide from disposable canisters.[49]

Mediastinal and subcutaneous emphysema occurred in a medical student after pulmonary function testing,[50] and these findings have also been observed in other healthy young individuals after dancing[51]; strenuous shouting, yelling, and singing[52]; playing the trumpet[53]; inflating a balloon[53,54]; and mountain climbing.[55] In mountaineers, alveolar rupture may be related to "voluntary pressure breathing," a practice originally proposed for fliers during World War II, that consists of slow, deep inhalations followed by forced exhalation through tightly pursed lips. This maneuver has been advocated by some climbers as a means of getting more oxygen into the blood, but it could well lead to alveolar rupture. The cases reported by Vosk and Houston[55] were members of the same climbing party and both had practiced "voluntary pressure breathing" during ascent.

Inadvertent Alteration of Breathing Pattern. Much more common than the voluntary maneuvers just discussed is the inadvertent manipulation of the breathing pattern in the course of straining or exertion such as during childbirth.[2] It has also been noted after vomiting in association with bulimia,[56] hyperemesis gravidarum,[57] diabetic ketoacidosis,[58] and other settings. Prolonged straining during convulsive seizures can be followed by mediastinal emphysema,[59] as can athletic competition,[60,61] violent coughing,[62] sneezing, hiccupping, and straining at stool.[1,5] It is reasonable to expect that any activity producing large momentary swings in intrathoracic pressure could result in alveolar rupture and pneumomediastinum.

Associated Airway and Lung Diseases. Localized airway obstruction can overdistend lung tissue, disrupt alveoli, and lead to all the reported forms of extra-alveolar air. This is easiest to visualize in the case of an obstructing foreign body,[63] but it may also explain the observation of extra-alveolar air in diffuse obstructive and parenchymal lung diseases. Pneumomediastinum is well described as a complication of acute asthma. Although chest radiographs are not routinely obtained during attacks of asthma, pneumomediastinum was noted in 5.4% of 479 radiographs of children admitted with asthma attacks.[64]

Parenchymal lung diseases associated with pneumomediastinum include atelectasis,[5] bronchiolitis,[65,66] pneumonia,[67,68] influenza,[5,21] measles,[69] and hematogenous tumor metastases.[70]

Idiopathic Pneumomediastinum. Although a history of a potential predisposing event or disease process is elicited in most patients with "spontaneous" pneumomediastinum, cases have been described without such associations and are known as *Hamman's syndrome*. Hamman's original patient was a 51-year-old physician in whom no predisposing factor could be identified.[71] Hamman later reported several additional cases of truly "idiopathic" pneumomediastinum; in modern series, patients been reported despite normal lung parenchyma as determined by chest computed tomography (CT).[3,72]

Pneumomediastinum Associated with Pressure Changes

Decreased Extrathoracic Pressure. Decreases in external pressure, such as during decompression events, may lead to alveolar overdistention and rupture. Alveolar rupture is a relatively common complication of sudden decompression.[17,25] Extra-alveolar air may develop following scuba diving,[73,74] during decompression in a hyperbaric chamber,[75] or with sudden barometric pressure changes during air travel.

Increased Intrathoracic Pressure. Externally applied positive airway pressure is another general category of clinical settings associated with extra-alveolar air. Most familiar within this category is "barotrauma" during mechanical ventilation.[16,76] Alveolar rupture during positive-pressure ventilation is thought to result from overdistention in an area with abnormal airways or lung parenchyma. Large delivered tidal volumes and high levels of positive end-expiratory pressure predispose to barotrauma, although the disease processes traditionally managed in this fashion are themselves associated with alveolar rupture.[16] Gammon and associates[23] found that the acute respiratory distress syndrome (ARDS) was the lung disease most commonly associated with barotrauma and, among ventilated patients, was the only independently associated risk factor for barotraumas.[20] Previously reported univariate associations between airway pressures and barotrauma may reflect that airway pressures serve as a marker of the severity of lung injury.[20] Further supporting this hypothesis, studies have found that the airway pressures and tidal volumes used were not different among those ARDS patients who developed and did not develop barotrauma.[77–79] In fact, it is likely that both the severity of underlying lung dysfunction and the particular styles of ventilator management that result in higher pressures and regional overdistention are responsible.[80]

Noninvasive forms of positive-pressure ventilation are associated with barotrauma less often than with conventional mechanical ventilation. This is probably because of the lower airway pressures used and the less severe lung diseases being treated. For instance, continuous positive airway pressure (CPAP) applied by mask was associated with pneumomediastinum in only 1 of 331 applications of this therapy, as cited in one review.[81]

Barotrauma is especially likely when air or oxygen is inadvertently insufflated under high pressure. Barotrauma is a well-documented complication of manual ventilation during cardiopulmonary resuscitation. Improperly connected oxygen tubing that prevented exhalation has resulted in life-threatening barotrauma,[82] as have similar errors following anesthesia and surgery.[83,84]

Extra-alveolar air can result from deceleration injury, even when there is no open chest wound or displaced rib fracture. Although such deceleration injuries most commonly result from motor vehicle accidents, they can also follow blows to the chest or falls into water with the glottis closed.[14,85] Pneumomediastinum has also been caused by resuscitation using the Heimlich maneuver.[86]

Arterial Air Embolism

Entry of aberrant air into the pulmonary vessels can result in systemic or arterial air embolism. This is particularly common in the setting of decompression illness (detectable in 3% of submarine escape trainees[87]) and is often accompanied by pneumomediastinum.[25] When a predisposing condition such as asthma is present, even ascents from the bottom of a swimming pool can cause air embolism.[88] The clinical manifestations depend on the amount and the distribution of the bubbles; cerebral air embolism is often fatal.[17,25,88]

As discussed previously, arterial air embolism is relatively rare as a complication of mechanical ventilation,[26] except after thoracotomy for penetrating lung injury. Fatal air embolism has also been reported after recreational inhalation of helium from a pressurized cylinder.[89]

Systemic air embolism may develop from circumstances other than alveolar rupture. Dramatic cases of air embolism have followed the rupture of an air-filled bronchogenic cyst during ascent in an aircraft[90] and the establishment of a bronchial–left atrial fistula due to a mediastinal abscess.[91]

Clinical Manifestations and Diagnosis

Symptoms, Physical Signs, and Laboratory Findings

Chest pain is the most common symptom reported by patients with pneumomediastinum.[1,72] It has been reported in 80% to 90% of patients with "spontaneous" mediastinal emphysema and may account for some cases of unexplained acute chest pain in otherwise healthy young people.[72,92] The pain is characteristically substernal in location and aggravated by movement, breathing, and position changes. It often radiates to the back, shoulder, or arm. Discomfort may extend into the neck, and retropharyngeal or perilaryngeal air dissection may give rise to dysphagia or dysphonia, with characteristic muffled voice. Dyspnea is present in about half of the cases.[72]

Physical examination reveals palpable crepitation in the neck and supraclavicular area in perhaps 50% of cases,[92] and cyanosis and neck vein distention have been observed.[21] The most characteristic physical finding in pneumomediastinum is Hamman's sign,[3,21] a crunching or clicking sound synchronous with the heartbeat, heard over the precordium, and increased in intensity during inspiration and in the left lateral decubitus position.[1,21,93] *Hamman's crunch* has been described as similar to the noise produced by rubbing two rubber balloons together.[21] Although considered by Hamman to be pathognomonic for mediastinal air, it can occasionally be heard in other circumstances such as pneumothorax without radiographic evidence for pneumomediastinum.[1]

Low-grade fever, along with mild to moderate leukocytosis,[1,21] likely results from reactive inflammation associated with air dissection in the mediastinum. Leukocyte counts of over 10,000/mm^3 in 16 of 23 patients and over 20,000/mm^3 in 5 of 23 were noted in one series, but returned to normal without treatment within 1 to 2 days.[21]

Electrocardiographic changes occur in some cases of pneumomediastinum without evidence of other cardiac abnormalities.[21] These may consist of diffusely low voltage, nonspecific axis shifts, ST-T wave changes, and ST segment elevation in the lateral precordial leads.[21] These changes are also observed in association with pneumothorax and may be in part related to physical displacement of mediastinal structures.

Radiographic Features

Pneumomediastinum is most often detected by standard chest radiography, and the finding of pneumomediastinum may be the first manifestation of extra-alveolar air. The diagnosis is usually made by demonstrating a thin line of radiolucency, best seen along the left heart border (Fig. 77-4).[1] Other common signs are the highlighting of the aortic knob, which is surrounded by increased radiolucency, and the "continuous diaphragm sign,"[94] an unbroken radiolucent line extending from one hemidi-

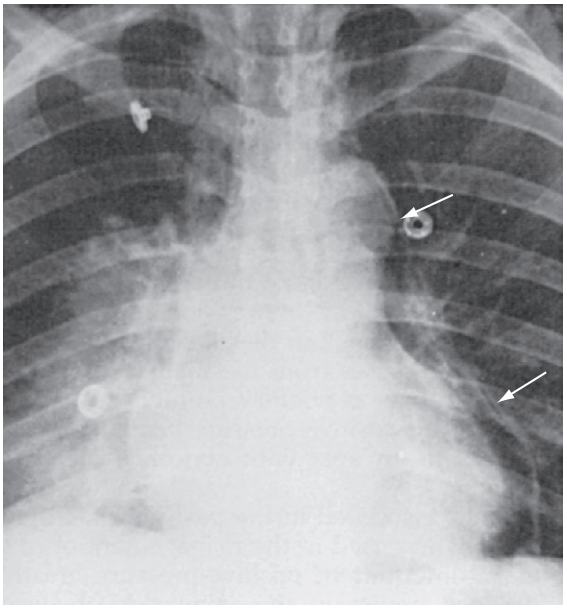

FIGURE 77-4 ■ Chest radiograph of a 47-year-old man who developed mediastinal emphysema while hospitalized for treatment of right lower lobe pneumonia shows displacement of the mediastinal pleura by air (*arrows*).

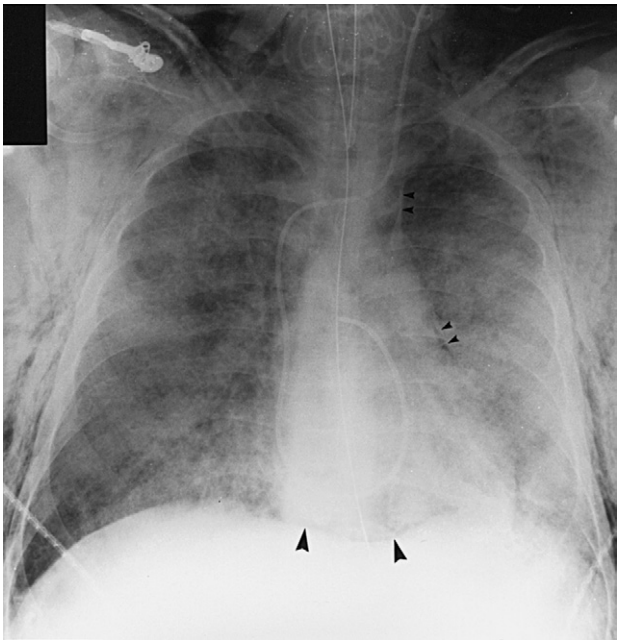

FIGURE 77-5 ■ The "continuous diaphragm sign" in a patient with pneumomediastinum that developed during mechanical ventilation for acute respiratory distress syndrome. An unbroken radiolucent line (*large arrowheads*) is visible from one hemidiaphragm to the other, rendering the inferior heart border clearly visible. Air is also present in the mediastinum (*small arrowheads*) and in the soft tissues of the shoulders, neck and chest wall.

aphragm to the other beneath the heart (Fig. 77-5). Mediastinal air may be easier to see on films taken in lateral projection, which may demonstrate retrosternal air or vertical lucent streaks outlining the aorta, pulmonary artery, or other mediastinal structures.[1] A variety of more subtle findings may be present.[95] Distinguishing between mediastinal emphysema and a small pneumothorax may be difficult. A film taken in the lateral decubitus position may show air rising to the most elevated portion of the thorax if it is free to move in the pleural space, whereas mediastinal air moves little with changes in position.[95]

Subcutaneous emphysema is readily detected as streaks or pockets of air outlining the visceral planes in the neck or within subcutaneous tissues. It often outlines the tissue compartments of the chest wall, clearly identifying the pectoral muscles. Both subcutaneous emphysema and pneumomediastinum are common findings in patients on mechanical ventilators,[96,97] being present in 7% of cases in one early series (Fig. 77-6).[96] These signs of alveolar rupture during positive-pressure ventilation are important clinical danger signals, because half or more will go on to pneumothorax.[23,97]

Chest CT is more accurate than plain radiographs for detecting aberrant air in all its forms and should be considered when important management decisions rest on a given distinction or when the underlying cause is not evident.[95] This is especially true in patients with pneumomediastinum due to blunt trauma, in which only 15% could be detected by plain chest radiographs.[98]

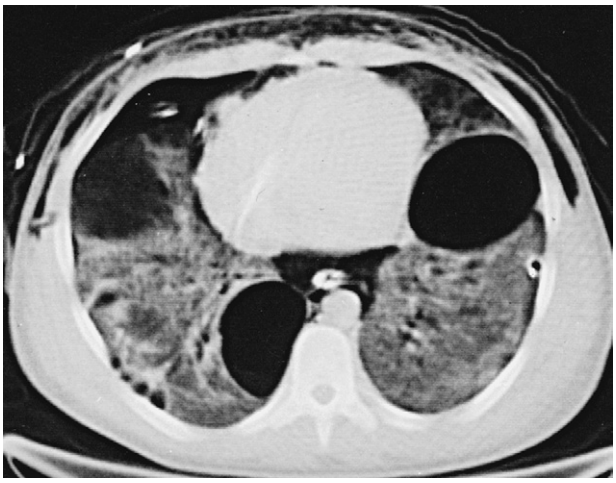

FIGURE 77-6 ■ Computed tomography (CT) scan of the chest shows pneumomediastinum associated with extensive subcutaneous emphysema in a patient undergoing mechanical ventilation for acute respiratory distress syndrome. Mediastinal air is seen in both the middle and the posterior mediastinal compartments.

Approach to Management

Natural History of Pneumomediastinum

In most cases of pneumomediastinum, the air tends to spread throughout the mediastinum and to vent out of the thorax into the subcutaneous tissue planes.[1] Subcutaneous emphysema can become massive and prove distressing to both patient and physician, but it is seldom dangerous in itself. Subcutaneous air collections will resolve spontaneously without surgical decompression once the primary air leak has sealed.

Management of Spontaneous Pneumomediastinum

Most cases of spontaneous pneumomediastinum can be linked to one or more predisposing factors such as bronchospasm, infection, or foreign body, and treatment or removal of these is followed by gradual resolution of the aberrant air. Pain and other symptoms should be alleviated and supplemental oxygen may hasten reabsorption, but specific therapy for pneumomediastinum is rarely needed. Most cases resolve with conservative management alone.[99] In fact, beyond the radiographs necessary to confirm the diagnosis, rarely is clinically useful information obtained from further diagnostic evaluation.[100]

Nonetheless, although pneumomediastinum rarely becomes physiologically significant, it can produce life-threatening cardiovascular collapse.[2,5,101] An early, well-documented incident was described by Laennec more than 150 years ago, as related by Munsell.[21] The great French clinician was called to see a small boy who had been run over by a dung cart: Laennec describes how his 4-year-old patient was placed in a tent with a candle for light. With the boy in extremis, Laennec inserted sharp sticks into the boy's neck, supraclavicular areas,

and anterior portion of the chest; a rapid, large outpouring of air extinguished the candle and the boy recovered. Modern medicine can add little more to this emergency decompression regimen except for the substitution of needles for sticks.

Other equally convincing, if less eloquently described, instances of life-threatening pneumomediastinum and its immediate surgical relief have been recorded.[101] Although surgical treatment of massive or symptomatic subcutaneous emphysema has been advocated, a careful examination of the literature reveals very few instances in which this has actually been carried out. Most experienced clinicians reserve invasive therapy for cases of increasing airway impingement or cardiovascular compromise. In these instances, small infraclavicular venting incisions seem to be the most prudent initial approach.[102]

Management of Pneumomediastinum during Positive-Pressure Ventilation

The appearance of mediastinal or subcutaneous air in a patient receiving positive-pressure ventilation is always a cause for concern. Discontinuation of positive-pressure ventilation, if possible, would seem advantageous for patients with ventilator-related extra-alveolar air in any form. Short of this, several adjustments should theoretically diminish the tendency of air to enter the mediastinum. Delivered tidal volumes and distending pressures should be reduced if possible. Positive end-expiratory pressure should be reduced or discontinued, and mean intrathoracic pressure should be minimized by adjusting inspiratory flow and timing. Patient-triggered pressure-limited ventilation (e.g., inspiratory pressure support) or low-rate intermittent mandatory ventilation would probably be preferable to mandatory volume-limited ventilation if clinically feasible.[103] Cough suppression should be considered.

Occult positive end-expiratory pressure, or "auto-PEEP," can augment air leakage. If present, auto-PEEP should be reduced[104] as, for example, by reducing minute ventilation and maximizing expiratory time. Finally, bronchospasm and other potentially reversible contributors to air trapping during mechanical ventilation should be treated vigorously.

Tracheobronchial disruption causing extra-alveolar air requires prompt diagnosis and surgical repair.[13] This condition should be considered in a patient with blunt thoracic trauma in the presence of extensive soft tissue emphysema, airway bleeding, or nonresolving pneumothorax[1,14] especially if, on chest radiography, the collapsed lung tissue appears to have fallen away from the hilum.[105] When these findings are present, emergent bronchoscopy should be carried out to establish the diagnosis.[1]

MEDIASTINITIS

The term *mediastinitis* encompasses a number of loosely related processes that induce inflammation of mediastinal structures. Most forms of mediastinitis are infectious, and variations in their clinical presentation depend largely on the chronicity of the underlying process rather than on the specific microbial cause. Thus, it seems logical to classify this family of disorders according to "acute" and "chronic" forms rather than into more specific etiologic categories. Acute mediastinitis is a distinct, usually catastrophic, disorder. The chronic forms of mediastinal inflammation cover a spectrum of disease, defined usually by radiographic or histologic features, that ranges from active granulomatous inflammation to "burned-out" mediastinal fibrosis.

Acute Mediastinitis

Acute mediastinitis was once a rare, dramatic, and usually fatal condition seen after rupture of the esophagus from forceful vomiting or in conjunction with penetrating trauma. With the proliferation of endoscopic procedures and the rise of cardiac surgery via median sternotomy, acute mediastinitis has become both more common and more varied in its clinical presentation. Because of this clinical variation, which may include relatively indolent infections, the term "suppurative mediastinitis" has been proposed as more accurate than "acute." In either case, a distinction is drawn between these disorders and chronic "granulomatous" and "fibrosing" mediastinitis.

Typical Clinical Features of Acute Mediastinitis

In the classic clinical description of acute mediastinitis, the onset is sudden and dramatic, with chills, high fever, and prostration. Patients are restless and irritable, with a sense of impending doom. Tachycardia, tachypnea, and signs of systemic toxicity are prominent. Most patients complain of severe substernal chest pain, worsened by breathing or coughing, and unrelieved by opiates. With involvement of the superior mediastinum, the pain may be referred into the neck and ear, whereas, with involvement of the posterior or inferior mediastinum, the pain may be radicular and radiate around the chest and between the scapulae. Examination may reveal supraclavicular fullness, tenderness over the sternum or sternoclavicular joints, and crepitus and other signs of mediastinal and subcutaneous emphysema. Hamman's sign (a crunching sound synchronous with cardiac systole, heard over the anterior thorax) is characteristic but not always present. Later, tracheal deviation, jugular venous distention, and other signs of compression of mediastinal structures may appear. These features are typical after spontaneous esophageal rupture as seen in Boerhaave's syndrome, but the presentation varies considerably in other settings.

Clinical Classification of Acute Mediastinitis

Involvement of different mediastinal regions tends to be associated with characteristic causes: superior mediastinal infection is most often the result of direct extension from neck infection; anterior mediastinal infection is

TABLE 77-3. Acute Mediastinitis: Etiologies and Clinical Settings

PERFORATION OF A THORACIC VISCUS
Esophagus
"Spontaneous": forceful vomiting (Boerhaave's syndrome); pneumatic trauma
Direct penetrating trauma
Impacted foreign body
Instrumentation: esophagoscopy; sclerotherapy; esophageal obturator airway
Erosion: carcinoma; necrotizing infection
Trachea or Main Bronchi
Direct penetrating trauma
Instrumentation: diagnostic bronchoscopy; therapeutic bronchoscopy; intubation
Foreign body
Erosion of carcinoma
DIRECT EXTENSION OF INFECTION FROM ELSEWHERE
Intrathoracic
Lung; pleura; pericardium; lymph node; paraspinous abscess
Extrathoracic
From above: retropharyngeal space; odontogenic
From below: pancreatitis
MEDIASTINITIS FOLLOWING STERNOTOMY FOR CARDIOTHORACIC SURGERY
"PRIMARY" MEDIASTINAL INFECTION
Inhalational anthrax

typical after surgery or penetrating wounds to the anterior thorax; and posterior mediastinal infection can arise from tuberculous or pyogenic spinal infections. The following discussion characterizes the clinical picture and management of acute mediastinitis in different settings classified according to the mechanism of mediastinal entry (Table 77-3).

Mediastinitis Resulting from Visceral Perforation

Boerhaave's syndrome refers to esophageal rupture associated with forceful vomiting, classically after overeating or excessive drinking. It is the most familiar example of acute mediastinitis,[106,107] although no longer the most common. Unilateral or bilateral hydropneumothorax is common and quickly progresses to empyema (Fig. 77-7). Spontaneous esophageal rupture can be difficult to diagnose, especially in the patient with altered sensorium who may delay seeking medical attention and who may not be able to relate a clear history. Adding to the clinician's confusion is the fact that lower esophageal rupture may be mistaken for an abdominal catastrophe.

The mechanism of esophageal rupture involves hydrostatic forces that overcome the tensile strength of the normal esophageal wall. A momentary rise in intragastric pressure, as in vomiting, trauma, seizure, or other straining, accompanied by relaxation of the lower esophageal sphincter, permits gastric contents to enter and distend

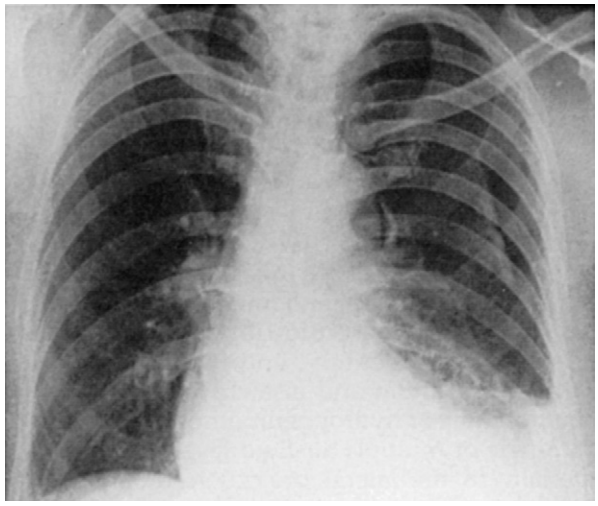

FIGURE 77-7 ■ Chest radiograph of a 64-year-old woman taken 16 hours after traumatic perforation of the esophagus. The classic features of pneumomediastinum and left-sided pneumothorax and pleural effusion are evident.

the lower esophagus. If the upper sphincter does not open to allow regurgitation of esophageal contents, hydrostatic pressure in the esophagus may rise to the point that its wall gives way at its weakest point. This is usually in the lower left posterolateral wall, where the muscle bundles in the longitudinal layer of the esophagus separate, allowing a bubble of mucosa to protrude into the mediastinum and burst. This mechanism may be similar to that in pneumatic esophageal rupture, which follows exposure of the esophagus to air under high pressure as, for example, after biting and puncturing an automobile tire inner tube or closing the mouth around the leaking valve of an automobile tire.[108] Rarely, rupture can occur even above the upper esophageal sphincter.[109]

In the present era, the most common cause of acute mediastinitis is esophageal perforation during diagnostic or therapeutic endoscopic procedures.[110] In a review of 54 esophageal perforations related to endoscopy or instrumentation, 35 instances were in patients with inoperable esophageal malignancy and 19 were in patients with benign disease. Most followed stent placement or dilation procedures.[111] The diagnosis was made within 2 hours in 94% of these patients. Of the 19 patients with benign disease, 14 were treated conservatively and 5 underwent surgical repair; there were no deaths among these patients, probably reflecting the influences of an empty gut lumen, prompt recognition of the complication, and immediate treatment.

Endoscopic injection sclerotherapy is associated with mediastinal complications.[110,112] Frank perforation, associated with necrosis of the esophageal wall and usually occurring 2 to 14 days after the procedure, has been reported in approximately 6% of patients. More common is pleural effusion, presumably associated with subclinical chemical mediastinitis without actual perforation, which has been noted in up to 14% of patients.[110,113] In most instances, this complication is benign and self-limited, responding to conservative therapy in this chronically ill patient population.[113]

Other reported causes of traumatic esophageal perforation include the use of the esophageal obturator airway and swallowed foreign bodies, particularly if the aim is to induce injury. One series describes six prison inmates who swallowed hypodermic needles fashioned in the shape of "stars" to win temporary reprieves from incarceration.[114] Unfortunately, all required surgical management and one patient experienced a lengthy and complicated hospital course. Accidental or intentional ingestion of caustic solutions such as paraquat or lye also can lead to esophageal perforation.[31]

The diagnosis of esophageal perforation depends on an appropriate degree of clinical suspicion. On the chest radiograph, the hallmarks are diffuse mediastinal widening and the presence of air in the mediastinum and elsewhere in soft tissues. Mediastinal air-fluid levels may be seen, and pneumothorax or hydropneumothorax may be present. CT can delineate these abnormalities clearly. Passage of ingested contrast material into the periesophageal or pleural space may be observed.[115,116]

Successful management of frank uncontained esophageal perforation requires early surgical repair, drainage of the mediastinum and often the pleural space, and administration of appropriate antibiotics.[117,118] Percutaneous catheter aspiration of mediastinal abscesses, under CT guidance, has been used when the infection is localized and the clinical setting is less urgent. Of 51 patients in a recent series, 3 died before intervention could be accomplished, 31 underwent standard thoracotomy and repair leading to 11 deaths, and 17 highly selected patients with minimal contamination were managed successfully with targeted drainage and antibiotic therapy.[119] In selected cases, esophageal perforation can be contained using endoscopically placed stents. Stenting appears to be most successful for the management of anastomotic leaks after esophageal surgery and may be less effective at controlling leaks after spontaneous esophageal rupture.[120,121]

Complications of acute mediastinitis after esophageal rupture may include localized abscess formation, extensive pleural empyema, and persistent esophagocutaneous fistulas. A prolonged stormy course is usual, and reexploration may be necessary to ensure adequate drainage. Reported mortality has varied due to differences in patient selection and management approaches. Timing of surgical drainage has been of prime importance in determining the clinical outcome. Modern series reporting the use of consistently aggressive surgical management cite 89% to 90% survival after spontaneous esophageal rupture.[122,123]

Other potential iatrogenic causes of mediastinitis include bronchoscopic airway perforation and migration of indwelling central venous catheters. Bronchoscopy is a much less frequently reported cause of mediastinitis than esophagoscopy. However, increasing use of laser and mechanical endobronchial procedures, often performed in the setting of malignancy with chronic airway colonization or postobstructive pneumonia, add to the likelihood of potential mediastinal complications. Intravascular catheters may be another source of acute mediastinitis when the catheter tip erodes through the vessel wall into the mediastinum. Instillation of hyperosmotic,[124] vessicant, or vasoactive substances via these catheters may induce a chemical, rather than an infectious, inflammation (Fig. 77-8).

Direct Extension of Infection from Other Sites

Infection can extend directly into the mediastinum from elsewhere.[125] Infection originating in periodontal tissues, in the tonsillar region, or after pharyngeal perforation may extend to the mediastinum via the prevertebral, visceral, or pretracheal spaces or carotid sheaths,[6,126] although the usual route is via the retropharyngeal space to the posterior mediastinum (Fig. 77-9).[127,128] Mediastinal infection of this type, which has been given the name *descending necrotizing mediastinitis*, is perhaps the most clinically devastating form of the disorder.[127–129]

Odontogenic infection is consistently the most common source of descending necrotizing mediastinitis.[125,130] Most infections are mixed, with both aerobic and anaerobic organisms; purulent pleural and pericardial involvement is common.[125]

In addition to the clinical signs described previously for acute mediastinitis after esophageal perforation, patients with this form of the disease may have widening of the retropharyngeal space, with or without associated air-fluid levels, anterior displacement of the tracheal air column, and loss of the normal cervical spine lordosis on lateral films of the neck. CT scans of the neck and chest are usually definitive (Fig. 77-10).[127]

Treatment of descending necrotizing mediastinitis requires aggressive surgical drainage, usually via a cervical approach.[125,125a] Whether or not to explore the mediastinum via a thoracic approach in addition depends on the imaging findings. Some authors have suggested that thoracic exploration be reserved for cases in which the infection extends below the level of the fourth vertebral body or the tracheal bifurcation.[125a] Others have argued that any evidence of mediastinal involvement should prompt transthoracic exploration and drainage.[125,130] This more aggressive approach is supported by findings of Corsten and coworkers[127] that the mortality rate of patients treated with cervical drainage alone was 47% compared with 19% when thoracic mediastinal drainage was added. Routine serial postoperative cervicothoracic CT imaging and aggressive reexploration and drainage guided by these imaging findings appear to reduce the mortality of this condition even further.[128] Although thoracoscopic and other percutaneous drainage procedures have been described and may be appropriate in selected patients, open surgical drainage and irrigation remains the standard approach.

Direct extension of infection from elsewhere in the chest is a rare cause of acute mediastinitis. Such extension can be associated with eroding neoplasms, with anterior chest wall and neck infections in injection drug users, or as a complication of vertebral or costal tuberculous infection. Penetrating chest injuries may result in acute mediastinitis, especially if the wound causes visceral perforation or is grossly contaminated, or if there

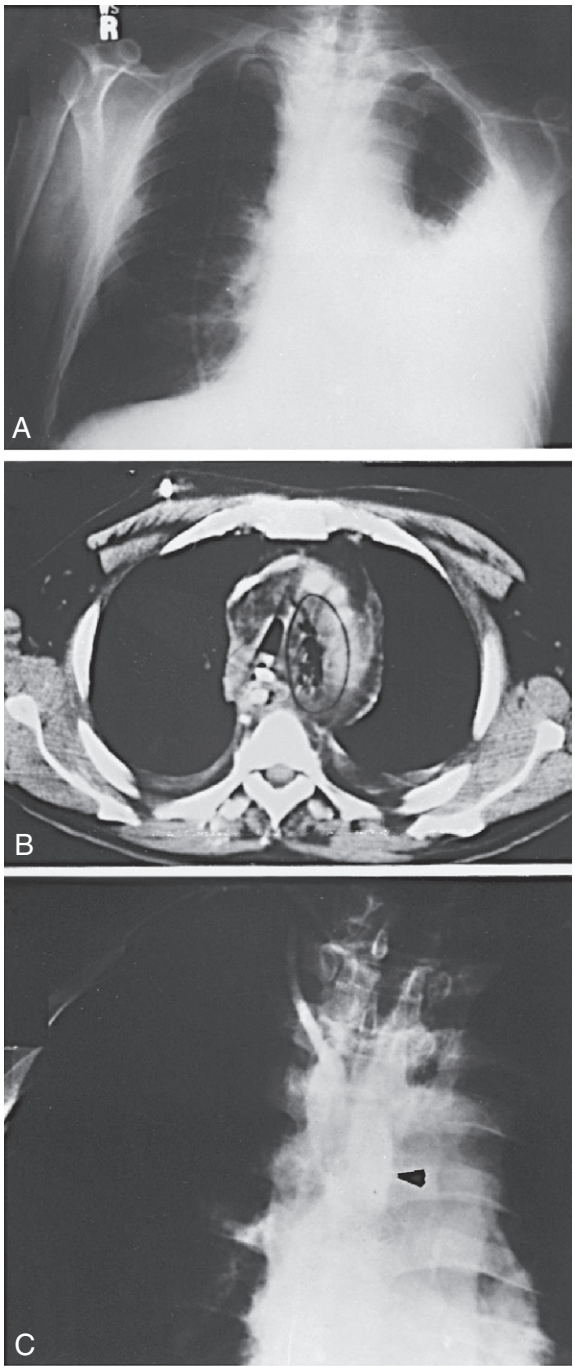

FIGURE 77-8 ■ Films of a 74-year-old man with mediastinitis due to erosion of an indwelling central venous catheter tip into the mediastinum. **A,** The chest radiograph shows mediastinal widening, radiolucency in the left upper mediastinum, left pleural effusion, and medial deviation of the catheter tip. **B,** The chest CT scan shows a gas-containing mediastinal abscess between the trachea and the contrast-enhanced great vessels (an indelible elliptical line was drawn around the area on the original film). **C,** Although blood could be aspirated from the catheter, contrast material injected through the catheter passed directly into the mediastinum (*arrowhead*).

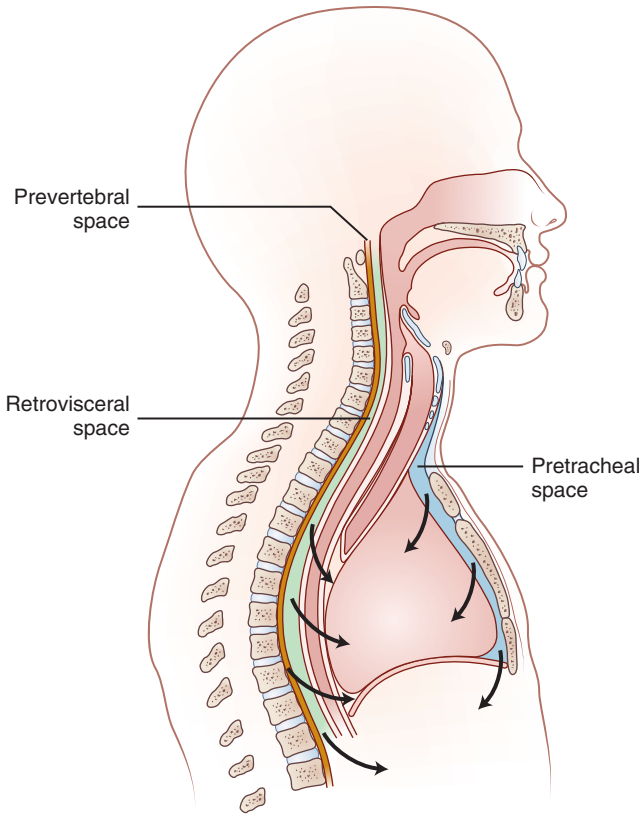

FIGURE 77-9 ■ The three deep spaces of the neck and their communication with the mediastinum. (Redrawn from Freeman RK, Vallières E, Verrier ED, et al: Descending necrotizing mediastinitis: An analysis of the effects of serial surgical débridement on patient mortality. J Thorac Cardiovasc Surg 119:260–267, 2000.)

has been a delay in reaching medical attention. In such instances, the diagnosis of acute mediastinitis may not be apparent if the patient has other serious injuries.

Pancreatitis has been reported to extend into the mediastinum, presenting as mediastinal widening with the clinical picture of acute mediastinitis. Spread in such a circumstance is presumably via the aortic and esophageal hiatuses. Both gastric and esophageal ulcers have been reported as causes of mediastinitis, sometimes eroding directly into the pericardium.

Mediastinitis after Cardiac Surgery

Whereas some forms of acute mediastinitis have been decreasing in frequency, mediastinitis after cardiac surgery has become an increasingly important entity.[131,132] Several cases of acute bacterial mediastinitis have occurred after heart and heart-lung transplantation.[133–135] Along with mediastinitis as a complication of endoscopy, this form illustrates the predominantly iatrogenic character of acute mediastinitis in the present era.

The incidence of mediastinal infection after cardiac surgery has been variously reported at 0.4% to 5.0%, but a more recent series reported rates of less than 1%.[136] Post-sternotomy mediastinitis has become a substantial

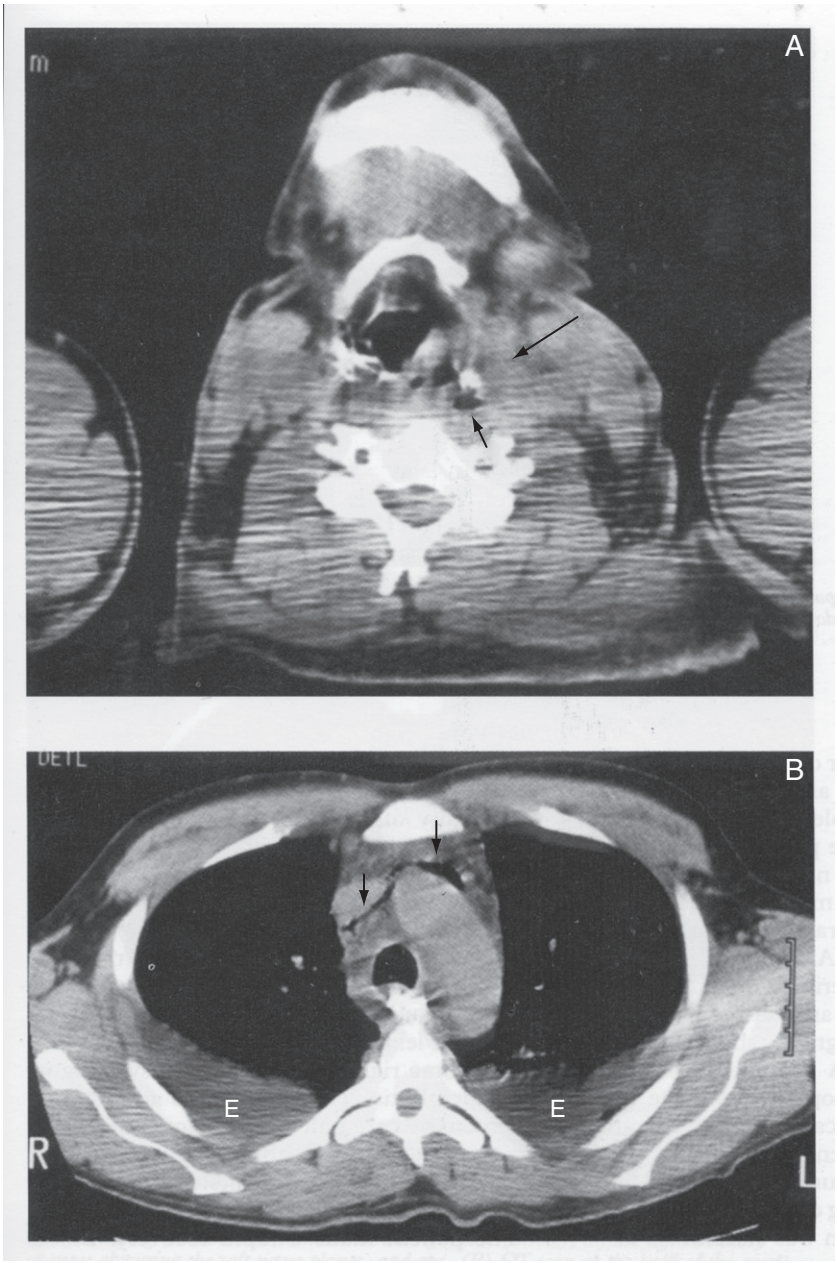

FIGURE 77-10 ■ CT scans of a 35-year-old man with descending necrotizing mediastinitis. **A,** At the level of the hyoid bone in the neck, there is gas in the retropharyngeal soft tissues (*short arrow*) and inflammatory changes in the parapharyngeal space (*long arrow*). **B,** At the level of the aortic arch in the chest, there is gas outlining the great vessels (*arrows*). There are inflammatory changes in the paratracheal tissues, and bilateral pleural effusions (empyema). (From Corsten MJ, Shamji FM, Odell PF, et al: Optimal treatment of descending necrotizing mediastinitis. Thorax 52:702–708, 1997.)

clinical problem not because of a high case incidence but because cardiac surgery via median sternotomy has become such a widely used procedure.

Risk factors that appear to predispose to development of mediastinitis after cardiac surgery have been reported in a myriad of case series.[136,137] Preoperative risk factors include advanced age and male gender, diabetes mellitus, obesity, the need for immunosuppressive therapy, smoking, obstructive lung disease, a history of previous sternotomy or mediastinal irradiation, and poor preoperative cardiac dysfunction and New York Heart Association functional class. Perioperative risk factors include shaving rather than clipping for hair removal, the use of bilateral internal mammary artery grafts, a longer duration of the surgical procedure and of perfusion time, greater use of cautery or bone wax, a low cardiac output state in the early postoperative period, and greater amounts of postoperative bleeding. The incidence of postoperative mediastinitis appears to be increased further if reoperation is required to control bleeding, if multiple valve replacement accompanies coronary artery bypass, or if the patient requires more than 48 hours of mechanical ventilation postoperatively.

The pathogenesis of mediastinitis following sternotomy is debated. Three possible routes of infection are postulated. Some authorities suspect that primary sternal instability leads to failure of the skin closure and subsequent penetration of bacteria through the wound.[138] Others suspect that a focus of sternal osteomyelitis is the initial site of infection, leading to secondary sternal instability and deeper penetration of the infection.[139,140] A third postulated mechanism is bacterial seeding of an

undrained mediastinal fluid collection.[136] In the acute stages, the mediastinal structures are enveloped with pliable fibrinous exudates; osteomyelitis, if present, is confined to the wound margins. Subacute infections are characterized by increasingly dense adhesions entrapping the visceral organs, sinus track formation, and more extensive sternal bone involvement.[136]

The epidemiology of cases within an institution suggests that sound infection control measures and careful asepsis in the operating room remain the most effective means of prevention.[136] Although definitive proof of their efficacy is still lacking, prophylactic antibiotics are widely used in the perioperative management of cardiac surgery patients.[136] The prophylactic intranasal application of mupirocin ointment has been shown to reduce by 50% the rate of *Staphylococcus aureus* nosocomial infections in carriers who undergo major surgery,[141] and there is a suggestion that its general use in cardiac surgery may significantly decrease the rates of post-sternotomy wound infections and osteomyelitis,[142] but there have been no confirmatory randomized, controlled trials.

The bacteriology of postoperative mediastinitis parallels that of early prosthetic valve endocarditis. *Staphylococcus epidermidis* and *S. aureus* have been the most frequent organisms in several series,[143,144] and as many as 40% of cases have mixed infections.[143] Methicillin-resistant *Staphylococcus aureus* (MRSA) is a relatively uncommon but virulent cause.[145] Rare organisms include anaerobes and Gram-negative bacilli,[143,146] *Candida* species,[143,147] and atypical mycobacteria (especially *Mycobacterium chelonei* and *Mycobacterium fortuitum*).[131] Infection with the last two groups tends to be more indolent and more likely to involve the sternum or costochondral tissues. Presentation within the first postoperative week is more often associated with gram-negative infection and also more likely to be accompanied by bacteremia, whereas presentation after the second week increases the likelihood that *Staphylococcus* is the infecting agent.[148]

Acute mediastinitis presenting after cardiac surgery tends to be less devastating than that seen in the settings described previously, perhaps because it remains relatively localized longer and tends to be recognized earlier. Typically, the clinical course consists of fever and systemic signs, followed by bacteremia and local signs of wound infection.[148] Drainage from the sternotomy incision and other localizing findings are present in the great majority of patients.[139,143,148]

The diagnosis is usually made at the time of reexploration of the sternotomy wound and rests on a high clinical suspicion in the appropriate setting. Distinguishing between superficial and deep wound infections may be difficult, especially if the clinical signs of infection are modest. CT is particularly helpful in identifying and discerning soft tissue swelling, fluid collections, and sternal erosion or dehiscence.[149] However, because swelling and fluid collections are common in the early postoperative period, their significance is much more clear when they persist or develop after 14 days.[149,150] Some authors use subxiphoid[151] or transsternotomy[140] needle aspiration in suspected cases, although, as with the other tests mentioned, such diagnostic maneuvers may delay treatment in a condition that can progress rapidly. Patients with fever, positive blood cultures, and wound abnormalities in the post-sternotomy period should probably be explored surgically.

As in other settings, therapy for post-sternotomy mediastinitis consists of early surgical exploration, débridement and drainage, irrigation, and administration of systemic antibiotics.[136,143,152,153] There has been disagreement in the past as to whether the incision should be left open or closed around drains for irrigation. Most authors now advocate early closure, even though reexploration may be necessary. This approach avoids both the respiratory and the cardiovascular compromises from the open chest wound and the longer hospital stay associated with open wounds.[136,143,153,154] A variety of surgical options exist for the débridement, establishment of irrigation, and buttressing and closure of sternal wounds.[153]

Reported mortality from mediastinitis after cardiac surgery varies considerably. Currently, most patients survive, with mortality rates of 20% to 40%.[136,148] Hospitalization of survivors is usually prolonged by this complication.[155]

"Primary Mediastinitis": Inhalational Anthrax

Anthrax, caused by infection with *Bacillus anthracis*, is primarily a disease of cattle, sheep, and goats and is most prevalent in the Middle East, although it is now recognized as an important disease of bioterrorism (see later). The most common form of anthrax is the cutaneous form, which is contracted by direct inoculation usually from handling hides or hair from infected animals. The less common form, inhalational anthrax, or *woolsorter's disease*, is contracted by inhaling *B. anthracis* spores from animal sources. Anthrax spores inhaled into the distal air spaces are ingested by alveolar macrophages and transported to the mediastinal lymph nodes, where they induce a hemorrhagic mediastinitis, followed by bacteremia, overwhelming sepsis, and usually death.[156–158]

Clinically, patients typically experience a biphasic illness with an initial insidious flulike illness lasting 2 to 4 days and characterized by fever, malaise, myalgias, and nonproductive cough. This is followed by a fulminant phase of acute mediastinitis, with respiratory distress, chest pain, cyanosis, and prostration.[157–160] The chest radiograph and CT typically show mediastinal widening and pleural effusions (Fig. 77-11).[161] The diagnosis is established by demonstration of gram-positive, boxcar-shaped bacilli in tissue or body fluid specimens or in the blood buffy coat. A direct fluorescent antibody test, polymerase chain reaction, and serologic tests are available for confirmation.

Sporadic anthrax is fortunately rare, with one report documenting only two confirmed cases in this country in 25 years.[162] However, anthrax has remained a very real concern because of its devastating clinical effects and its ominous potential as an agent of biologic warfare and

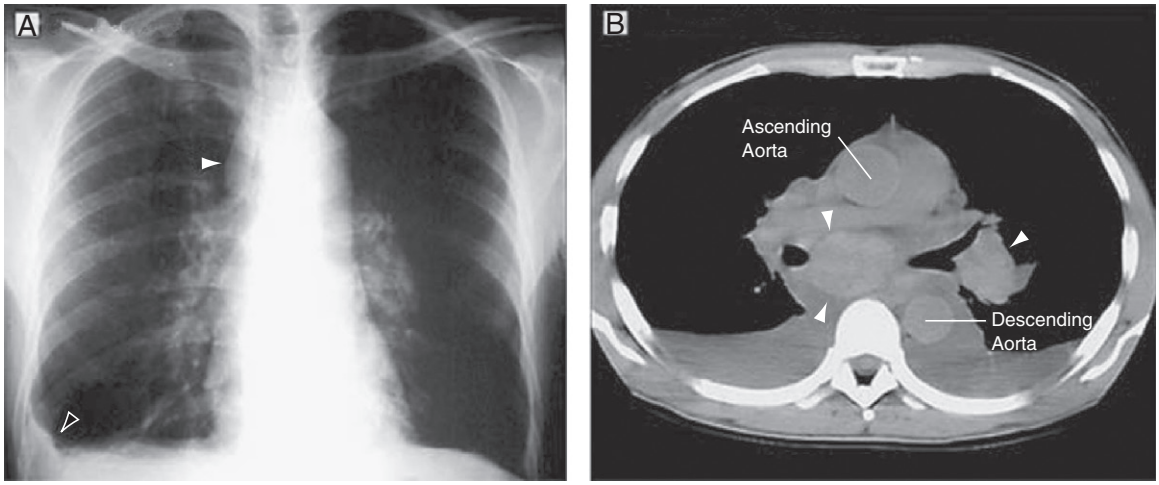

FIGURE 77-11 ■ Films from a 56-year-old man with inhalational anthrax. **A,** The chest radiograph shows a widened mediastinum (*white arrowhead*), perihilar infiltrates, and right pleural effusion (*dark arrowhead*). **B,** The noncontrast chest CT confirms mediastinal edema, mediastinal and hilar adenopathy, and bilateral pleural effusions. Note the large hyperattenuated, dense lymph nodes (*arrowheads*) in the subcarinal space and left hilum; such dense nodes are described with anthrax mediastinal adenitis and, in the setting of acute respiratory illness, can raise the suspicion for anthrax. (From Mayer TA, Bersoff-Matcha S, Murphy C, et al: Clinical presentation of inhalational anthrax following bioterrorism exposure. JAMA 286:2549–2553, 2001.)

bioterrorism.[157,158,163,164] In the fall of 2001, this potential was realized when *B. anthracis* spores were intentionally dispersed through the U.S. postal system. An outbreak followed, with many cases of cutaneous anthrax and at least 10 cases of inhalational anthrax identified by astute local physicians, local public health officers, and an investigative team headed by the U.S. Centers for Disease Control and Prevention.[159,160] All patients became ill within 4 to 6 days of presumed exposure, presented within 2 to 5 days of symptom onset, and had abnormal chest radiographs. Most had evidence of bacteremia.[159,160]

Inhalational anthrax has historically been a devastating disease even with appropriate treatment: 12 of 13 well-documented sporadic cases in the United States had fatal outcomes.[156] However, in the bioterrorism outbreak, prompt diagnosis and initiation of antibiotic therapy plus aggressive drainage of mediastinal and pleural collections resulted in the survival of 6 of the 10 patients.[159] High-dose intravenous penicillin has traditionally been the treatment of choice,[156] although penicillin-resistant strains have been reported.[165] Cephalosporin resistance is typical, and most patients in the bioterrorism outbreak were treated with multiple agents including a fluoroquinolone.[159] Future treatment will likely include passive immunization with anti-toxin antibodies.[165a]

Granulomatous Mediastinitis and Mediastinal Fibrosis

Mediastinal disease that is chronic in nature may be considered in the broad categories of granulomatous mediastinitis and mediastinal fibrosis. These conditions are not so much separate disease processes, however, as they are two ends of a spectrum of chronic inflammation and fibrosis. This pathophysiologic continuum is not evident in most of the literature, which mainly reports groups of cases at one or another end of the spectrum. Among the larger series, some have been based on pathologic material, selected according to the presence of granulomas or fibrosis; others have reported only cases of proved etiology, with mediastinal widening or mass on the chest radiograph, or who presented with superior vena cava (SVC) obstruction. Attempts to garner large numbers of cases from the literature[166,167] have necessarily been hampered by this lack of uniformity in selection. Further, because nearly all published series are retrospective, the clinical descriptions of chronic mediastinitis are incomplete and biased toward especially prominent or commonly recorded features.

Disorders falling along the continuum from active granulomatous mediastinitis to pure mediastinal fibrosis have been designated by the following terms: mediastinal adenitis, mediastinal granulomatosis, sclerosing mediastinitis, mediastinal collagenosis, fibrosing mediastinitis, and idiopathic fibroinflammatory lesion of the mediastinum. Conceptually, all these processes may be thought of as variations of a common process (Fig. 77-12).

Pathophysiology and Etiologies

The genesis of granulomatous mediastinitis and mediastinal fibrosis is most easily understood using histoplasmosis or tuberculosis as an example. Infection begins as a primary focus in the lung, which spreads to mediastinal lymph nodes and induces mediastinal adenitis and periadenitis. Eventually, a cluster of caseating lymph nodes breaks down into an irregular mass, heals by fibrous encapsulation, and in some cases, undergoes dense calcification. The thickness of the fibrotic capsule is the main determinant of the clinical picture: when 2

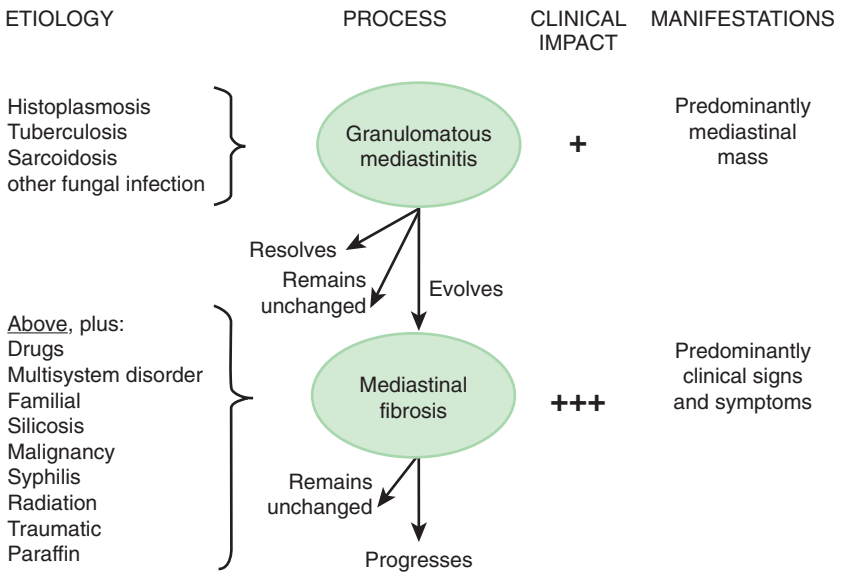

FIGURE 77-12 ■ Pathophysiologic relationships between granulomatous mediastinitis and mediastinal fibrosis.

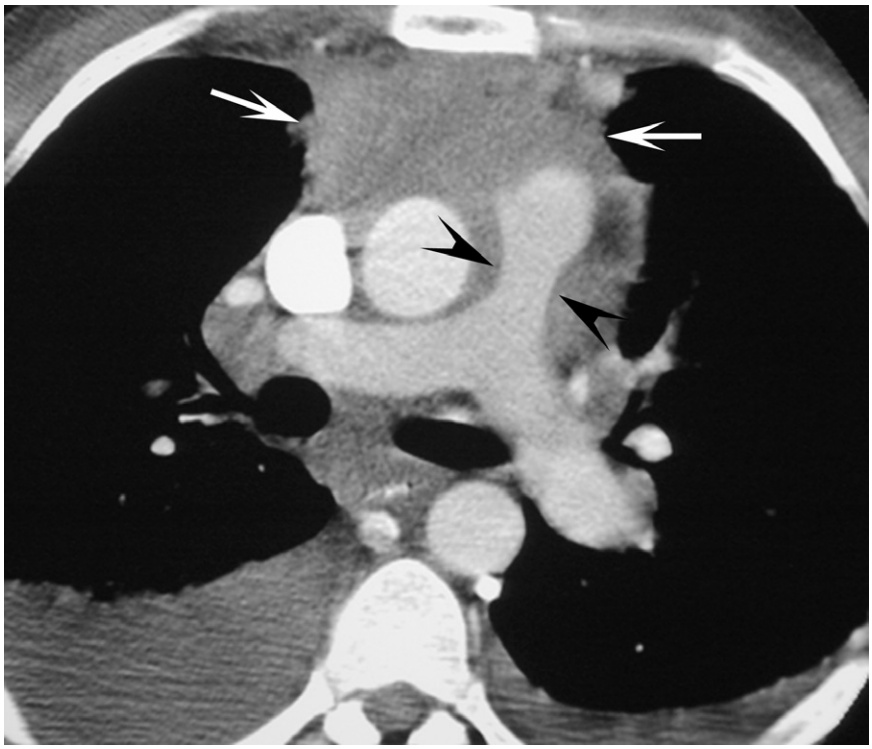

FIGURE 77-13 ■ Axial CT image through the main pulmonary artery shows abnormal soft tissue infiltrating the mediastinum (*arrows*), compressing the main pulmonary artery (*arrowheads*). The presence of mass effect on vessels and bronchi is characteristic of mediastinal fibrosis. (Courtesy of Michael B. Gotway, MD, Scottsdale Medical Imaging and the Department of Radiology, University of California, San Francisco.)

to 5 mm in thickness, it has little clinical impact, whereas, if the capsule reaches 6 to 9 mm, it can invade or interfere with adjacent tissues.[168,169] This benign localized "healing" process produces physiologically important effects because of the compact nature of the mediastinum and the importance and vulnerability of its structures (Fig. 77-13).

The symptoms and physiologic effects of this process are determined by the location of the involved lymph nodes. Most commonly, the involved lymph nodes are in the right perihilar region, perhaps accounting for the high prevalence of SVC obstruction in chronic mediastinitis. Later, in instances in which the process progresses to generalized fibrosis, the entire upper portion of the mediastinum may be involved.

The mechanism by which inflammation and fibrosis progress in some patients and not in others has been the subject of considerable debate. Goodwin and colleagues[168] postulated that prolonged gradual seepage of some soluble antigen or other substance from the involved lymph nodes causes fibrosis. Other authors reject this theory in favor of an abnormality in collagen organization that when provoked by various stimuli, leads to mediastinal fibrosis.[170] Whether either of these

concepts or some other mechanism is responsible, it is evident that the nature and vigor of the host's response is vitally important.

The development of both mediastinal and retroperitoneal fibrosis in the same patients, and of idiopathic isolated mediastinal fibrosis in others,[171] has led some investigators to postulate an autoimmune mechanism. The finding of mediastinal and retroperitoneal fibrosis, along with other forms of fibrosis in members of the same family, has led to the term *familial multifocal fibrosclerosis*. Fibrosing processes elsewhere in the body that could be related, in at least some cases, to mediastinal fibrosis include retroperitoneal fibrosis, Riedel's thyroiditis, sclerosing cholangitis, orbital pseudotumor, sclerosing cervicitis, ligneous perityphlitis of the cecum, and keloids.[170,172] Others have pointed out dissimilarities between mediastinal and retroperitoneal fibrosis and disagree with this unitary concept.[168]

Most cases of granulomatous mediastinitis are caused by histoplasmosis (especially in North America) or tuberculosis.[166,168,170,173] However, as the disease progresses from active caseous inflammation to largely acellular fibrosis, it becomes more and more difficult to establish the cause with certainty. In 180 cases reviewed by Schowengerdt and coworkers,[166] a definite diagnosis could be established in 33 of 103 examples of "granulomatous mediastinitis" but in only 3 of 77 categorized as "mediastinal fibrosis." Histoplasmosis and tuberculosis together accounted for 83% of the confirmed diagnoses.[166]

Granulomatous infection is the usual cause of mediastinal fibrosis, as diagrammed in Figure 77-12. However, the same histologic and clinical picture can be the ultimate result of other disease processes. Fibrosis associated with use of methysergide, a drug used in the control of severe vascular headache, is perhaps the best known of these. Sarcoidosis accounts for 11% of the cases of granulomatous mediastinitis of known cause in the review by Schowengerdt and coworkers.[166] Other reported noninfectious causes of mediastinal fibrosis include silicosis,[174] paraffin (as a late complication of plombage for tuberculosis), and traumatic mediastinal hematoma.[175] Nodular sclerosing Hodgkin's disease also may masquerade as mediastinal fibrosis,[176] emphasizing the importance of careful review of adequately representative biopsy samples when evaluating a mediastinal mass. Although there are reports of SVC and bronchial obstruction thought to be caused by mediastinal irradiation,[177] radiotherapy as a cause of mediastinal fibrosis must be distinctly unusual in view of its widespread use and the rare documentation of this complication.

Clinical Manifestations

On the continuum from active granulomatous mediastinitis to "burned-out" mediastinal fibrosis, the former tends to be asymptomatic and to be discovered incidentally by chest radiography; the latter tends to cause clinical manifestations.[178] In the largest collection of cases to date, 74% of the patients with granulomatous mediastinitis were asymptomatic, whereas all but 17% with fibrosis presented with symptoms or signs.[166] In 52 patients with mediastinal fibrosis and evidence of histoplasmosis reviewed by Loyd and associates,[167] initial symptoms included cough in 41%, dyspnea in 32%, hemoptysis in 31%, and chest pain in 23%. Clinical manifestations develop either because the fibrotic process invades or compresses mediastinal structures or because a calcified mass erodes into adjacent structures. These manifestations can be grouped into those related to involvement of the airways, the SVC, the esophagus, the major pulmonary vessels, and mediastinal nerves.

Airway Involvement. Clinical manifestations due to involvement of the trachea or major bronchi are common in patients with granulomatous mediastinitis or mediastinal fibrosis. Airway complications including dyspnea, cough, and hemoptysis were the most common clinical manifestations in several series[167,178] and constituted the most common indication for surgical intervention.[178] Any of the main airways may be compromised, but involvement of the right middle lobe is reported as most frequent and is often accompanied by features of the *right middle lobe syndrome*. A rare cause, bronchoesophageal fistula, may be heralded by simultaneous hemoptysis and hematemesis.[179]

Superior Vena Cava Obstruction. SVC obstruction has been the most frequent complication of granulomatous mediastinitis and mediastinal fibrosis in some series.[166,180] Although most patients with SVC obstruction have malignancy, benign causes account for about 3% to 6% of large published series,[181,182] of which most are due to granulomatous mediastinitis or mediastinal fibrosis.[173] SVC obstruction can occur at any stage of granulomatous or fibrotic involvement; in Schowengerdt's and coworkers series,[166] SVC obstruction was present in 77% of symptomatic patients with granulomatous mediastinitis and in 52% of symptomatic patients with mediastinal fibrosis.

The typical presentation is *superior vena cava syndrome*.[183] Because obstruction develops gradually, collateral channels tend to divert much of the venous flow (Fig. 77-14). Therefore, symptoms may be less prominent than might be expected and may improve with time.[173] However, even chronic SVC obstruction can cause serious complications such as hemorrhage from esophageal varices, recurrent upper extremity thrombophlebitis, and postphlebitic syndrome. Less commonly, the inferior vena cava or azygous vein can be involved.[166] Thoracic duct obstruction is rare[166] but can produce chylothorax and its associated clinical manifestations.

Esophageal Involvement. Esophageal involvement can include extrinsic compression, traction diverticulae, disturbances of esophageal motility, or bleeding. Symptoms of dysphagia, chest pain, and eructation can result.[166]

Pulmonary Vascular Involvement. Mediastinal fibrosis can involve major vessels on either side of the heart.[166,168,170] When this occurs, the prognosis can be serious. Progressive obstruction of one or both main pulmonary arteries can result in pulmonary hypertension, cor pulmonale, and refractory right-sided heart

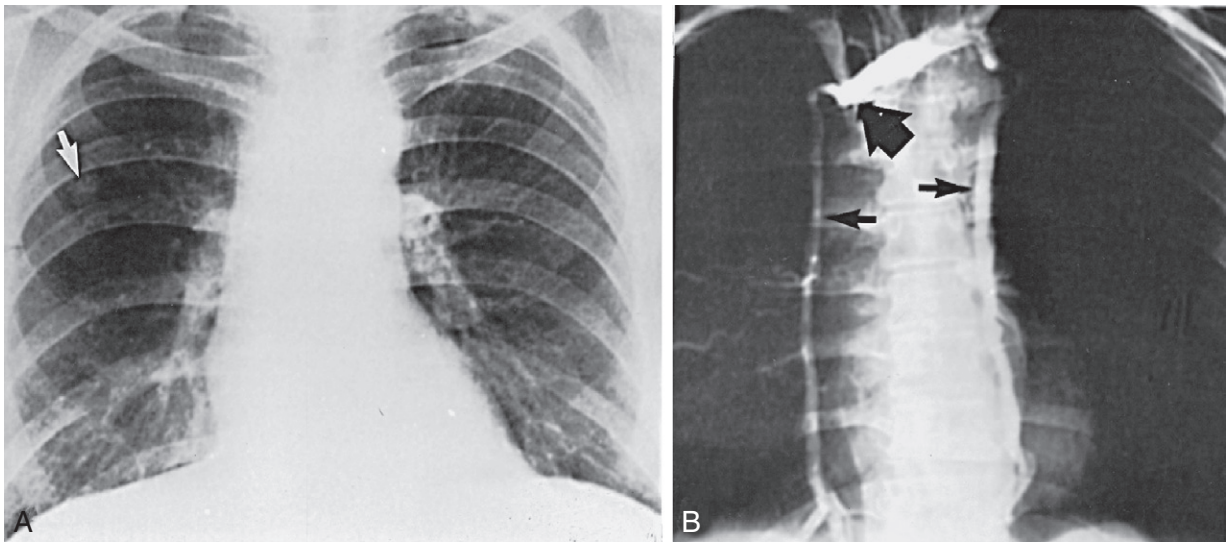

FIGURE 77-14 ■ Mediastinal fibrosis (in this instance from histoplasmosis) with superior vena cava obstruction and extensive collateral circulation. **A,** The standard frontal radiograph shows smooth widening of the superior mediastinum with a peripheral granuloma in the right lung (*arrow*). **B,** Another film taken just after rapid injection of contrast material into an antecubital vein shows complete obstruction of the superior vena cava (*thick arrow*), with filling of the internal mammary veins bilaterally (*thin arrows*). (From Fraser RG, Paré JAP, Paré PD, et al: Diagnosis of Diseases of the Chest [3rd ed, Vol. II]. Philadelphia: WB Saunders, 1989, p 955.)

failure.[184] Stenosis of proximal pulmonary veins can cause a clinical picture similar to that of severe valvular mitral stenosis, with pulmonary venous hypertension and recurrent episodes of hemoptysis. Pulmonary venous hypertension can be unilateral when the veins from only one lung are involved and, thus, may result in unilateral pulmonary edema and fibrosis.

Mediastinal Nerve Involvement. Entrapment or compression of the mediastinal nerves can cause a variety of disorders. Hoarseness can result from involvement of the recurrent laryngeal nerve,[166,170] diaphragmatic paralysis from involvement of one or both phrenic nerves, Horner's syndrome from impingement on autonomic ganglions or nerves, and persistent tachycardia from damage to the vagus nerve.

Diagnosis and Management

In most instances, surgical exploration is necessary to distinguish between benign and malignant causes for SVC syndrome, localized mediastinal mass, or other manifestation of chronic mediastinitis. In occasional cases, radiographs from previous years documenting an unchanged appearance or dense calcification within the mass will permit a confident diagnosis without operation.

Chest radiographs are abnormal in most patients. Granulomatous mediastinitis more often presents as a localized mass, usually in the right paratracheal area, and the later fibrotic state more frequently produces generalized widening of the superior portion of the mediastinum, but these characteristics vary.[170,173] Mass lesions tend to be smooth and lobulated,[173] and contrast studies in cases of SVC obstruction typically show the affected area to be smooth and tapered,[170] in contrast to the more ragged appearances usually seen with cancer. In some cases, the mediastinum is normal in appearance on standard chest radiographs, and venography or CT is necessary to demonstrate the anatomic basis of a clinically evident obstruction.[173]

The role of specific medical therapy for granulomatous mediastinitis or mediastinal fibrosis is unclear.[178] Some evidence suggests that selected cases with active inflammation associated with histoplasmosis may benefit from antifungal therapy,[180,185] but specific indications, if any, for antifungal therapy remain unknown. A similarly conservative approach should be taken to tuberculosis-related mediastinal complications, unless sputum or tissue samples are positive for mycobacteria or convincing clinical evidence of active tuberculosis is present.

The clinical manifestations of this disease appear to be the result of host factors as much as the infection itself. Accordingly, therapy has also been directed at the host inflammatory response. Anecdotal reports of treatment of mediastinal and retroperitoneal fibrosis with corticosteroids have reached opposite conclusions.[186,187] It appears that diffuse forms of fibrosis may be more likely to respond.[188] As in the case of antimicrobial therapy, the appropriate role for anti-inflammatory therapy for granulomatous mediastinitis and mediastinal fibrosis is at present unknown.[189]

At the time of exploration for diagnosis, some surgeons advise removal of as much of the inflammatory or fibrous mass as possible, in order to reduce its bulk and perhaps diminish its later impact on adjacent tissues.[189] Despite the difficulties presented by fibrotic and granulomatous encasement, surgical intervention may be quite successful in these patients.[178] Surgery to bypass an

obstructed vena cava is technically difficult and not always effective, although this may still be considered if bleeding esophageal varices or recurrent upper extremity thrombophlebitis occurs. Endovascular stent placement is another option.[190] Obstruction of major pulmonary vessels is a poor prognostic sign. Therapeutic options are limited, but surgical reconstruction, angiographic dilation and stent placement may be successful in selected cases.[191]

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KEY POINTS

- Pneumomediastinum refers to the presence of air or other gas in the mediastinum.
- The gas that causes pneumomediastinum usually originates from alveolar rupture in the lungs but may arise from the upper respiratory tract or the gastrointestinal tract (especially the esophagus).
- Treatment of pneumomediastinum depends primarily on successful management of the underlying disease process. Rarely, direct intervention is needed to decompress air in the mediastinum.
- Acute mediastinitis is usually a sudden and severe disease that is now most commonly caused by perforation of the esophagus during endoscopic procedures.
- "Spontaneous" rupture of the esophagus during vomiting and descending infections originating in the neck remain important causes of acute mediastinitis, and infectious complications after surgical procedures that incorporate sternotomy incisions are being encountered with increasing frequency.
- All forms of acute mediastinitis are life-threatening and require prompt diagnosis, imaging, surgical drainage, and antimicrobial treatment.
- Chronic mediastinitis results from granulomatous inflammation of the mediastinum and its fibrotic sequelae. Complications include bronchial obstruction, SVC syndrome, esophageal compression, and pulmonary vessel obstruction.
- Management or chronic mediastinitis is aimed at relief of these mechanical complications. The role of anti-inflammatory and antimicrobial therapy is at present unclear.

References

1. Maunder RJ, Pierson DJ, Hudson LD: Subcutaneous and mediastinal emphysema: Pathophysiology, diagnosis, and management. Arch Intern Med 144:1447–1453, 1984.
2. Gordon CA: Respiratory emphysema in labor: With two new cases and a review of 130 cases in the literature. Am J Obstet Gynecol 14:633–646, 1927.
3. Hamman L: Spontaneous mediastinal emphysema. Bull Johns Hopkins Hosp 64:1–21, 1939.
4. Hamman L: Mediastinal emphysema. JAMA 128:1–6, 1945.
5. Macklin MT, Macklin CC: Malignant interstitial emphysema of the lungs and mediastinum as an important occult complication in many respiratory diseases and other conditions: An interpretation of the clinical literature in the light of laboratory experiment. Medicine 23:281–352, 1944.
6. Moncada R, Warpeha R, Pickleman J, et al: Mediastinitis from odontogenic and deep cervical infection: Anatomic pathways of propagation. Chest 73:497–500, 1978.
7. Estrera AS, Landay MJ, Grisham JM, et al: Descending necrotizing mediastinitis. Surg Gynecol Obstet 157:545–552, 1983.
8. Turnbull A: A remarkable coincidence in dental surgery. Br Med J 1:1131, 1900.
9. Stauffer JL, Olson DE, Petty TL: Complications and consequences of endotracheal intubation and tracheotomy: A prospective study of 150 critically ill patients. Am J Med 70:65–76, 1981.
10. Marty Ané CH, Picard E, Jonquet O, et al: Membranous tracheal rupture after endotracheal intubation. Ann Thorac Surg 60:1367–1371, 1995.
11. Frascone RJ, Cicero JJ, Sturm JT: Pneumopericardium occurring during a high-speed motorcycle ride. J Trauma 23:163–164, 1983.
12. Curci MR, Dibbins AW, Grimes CK: Compressed air injury to the esophagus: Case report. J Trauma 29:1773–1775, 1989.
13. Wiot JF: Tracheobronchial trauma. Semin Roentgenol 18:15–22, 1983.
14. Robertson HT, Lakshminarayan S, Hudson LD: Lung injury following a 50-metre fall into water. Thorax 33:175–180, 1978.
15. Schaefer KE, McNulty WPJ, Carey C, et al: Mechanisms in development of interstitial emphysema and air embolism on decompression from depth. J Appl Physiol 13:15–29, 1958.
16. Pierson DJ: Alveolar rupture during mechanical ventilation: Role of PEEP, peak airway pressure, and distending volume. Respir Care 33:472–483, 1988.
17. Peirce ECI: Cerebral gas embolism (arterial) with special reference to iatrogenic accidents. Hyperbaric Oxygen Rev 1:161–184, 1980.
18. Melamed Y, Shupak A, Bitterman H: Medical problems associated with underwater diving. N Engl J Med 326:30–35, 1992.
19. Grim PS, Gottlieb LJ, Boddie A, et al: Hyperbaric oxygen therapy. JAMA 263:2216–2220, 1990.

20. Gammon RB, Shin MS, Groves RH Jr, et al:. Clinical risk factors for pulmonary barotrauma: A multivariate analysis. Am J Respir Crit Care Med 152:1235–1240, 1995.
21. Munsell WP: Pneumomediastinum. JAMA 202:689–693, 1967.
22. Macklin CC: Transport of air along sheaths of blood vessels from alveoli to mediastinum: Clinical implications. Arch Intern Med 64:913–926, 1939.
23. Gammon RB, Shin MS, Buchalter SE: Pulmonary barotrauma in mechanical ventilation. Patterns and risk factors. Chest 102:568–572, 1992.
24. Mularski RA, Sippel JM, Osborne ML: Pneumoperitoneum: A review of nonsurgical causes. Crit Care Med 28:2638–2644, 2000.
25. Strauss RH: Diving medicine. Am Rev Respir Dis 119:1001–1023, 1979.
26. Marini JJ, Culver BH: Systemic gas embolism complicating mechanical ventilation of adult respiratory distress syndrome. Ann Intern Med 110:699–707, 1989.
27. Foster PP, Boriek AM, Butler BD, et al: Patent foramen ovale and paradoxical systemic embolism: A bibliographic review. Aviat Space Environ Med 74:B1–B64, 2003.
28. Black M, Calvin J, Chan KL, et al: Paradoxic air embolism in the absence of an intracardiac defect. Chest 99:754–755, 1991.
29. Jaworski A, Fischer R, Lippmann M: Boerhaave's syndrome. Arch Intern Med 148:223–224, 1988.
30. Minocha A, Richards R: Pneumomediastinum as a complication of upper gastrointestinal endoscopy. J Emerg Med 9:325–329, 1991.
31. Chen KW, Wu MH, Huang JJ, et al: Bilateral spontaneous pneumothoraces, pneumopericardium, pneumomediastinum, and subcutaneous emphysema: A rare presentation of paraquat intoxication. Ann Emerg Med 23:1132–1134, 1994.
32. Mirzayan R, Cepkinian V, Asensio JA: Subcutaneous emphysema, pneumomediastinum, pneumothorax, pneumopericardium, and pneumoperitoneum from rectal barotrauma. J Trauma 41:1073–1075, 1996.
33. Bakker J, van Kersen F, Bellaar-Spruyt J: Pneumopericardium and pneumomediastinum after polypectomy. Endoscopy 23:46–47, 1991.
34. Lee HC, Dewan N, Crosby L: Subcutaneous emphysema, pneumomediastinum, and potentially life-threatening tension pneumothorax: Pulmonary complications from arthroscopic shoulder decompression. Chest 101:1265–1267, 1992.
35. Steffen T, Wedel A, Kluckert J, et al: Severe pneumomediastinum after high-pressure air-injection injury to the hand: A case of pneumomediastinum with an unusual cause. J Trauma 66:1243–1245, 2009.
36. Simmonds F: Air embolism and pneumomediastinum in artificial pneumoperitoneum. Lancet 1:530–533, 1946.
37. Chui PT, Gin T, Chung SC: Subcutaneous emphysema, pneumomediastinum and pneumothorax complicating laparoscopic vagotomy. Report of two cases. Anaesthesia 48:978–981, 1993.
38. Cass LJ, Dow EC, Brooks JR: Pneumoperitoneum following pelvic examination. Am J Gastroenterol 45:209–211, 1966.
39. Walker MA: Pneumoperitoneum following a douche. J Kans Med Soc 43:55, 1942.
40. Lozman H, Newman AJ: Spontaneous pneumoperitoneum occurring during postpartum exercises in the knee-chest position. Am J Obstet Gynecol 72:903–905, 1956.
41. Ashai S, Lipton D, Colon A, et al: Pneumoperitoneum secondary to cunnilingus. N Engl J Med 295:117, 1976.
42. Varon J, Laufer MD, Sternback GL: Recurrent pneumoperitoneum following vaginal insufflation. Am J Emerg Med 9:447–448, 1991.
43. Muramori K, Takahashi Y, Handa N, et al: Subcutaneous emphysema, pneumomediastinum, pneumothorax, pneumoperitoneum, and pneumoretroperitioneum by insufflation of compressed air at the external genitalia in a child. J Pediatr Surg 44:E5–E8, 2009.
44. Collins KA, Davis GJ, Lantz PE: An unusual case of maternal-fetal death due to vaginal insufflation of cocaine. Am J Forensic Med Pathol 15:335–339, 1994.
45. Hazouard E, Koninck JC, Attucci S, et al: Pneumorachis and pneumomediastinum caused by repeated Muller's maneuvers: Complications of marijuana smoking. Ann Emerg Med 38:694–697, 2001.
46. Seaman ME: Barotrauma related to inhalational drug abuse. J Emerg Med 8:141–149, 1990.
47. Sullivan TP, Pierson DJ: Pneumomediastinum after freebase cocaine use. AJR Am J Roentgenol 168:84, 1997.
48. Adrouny A, Magnusson P: Pneumopericardium from cocaine inhalation. N Engl J Med 313:48–49, 1985.
49. LiPuma JP, Wellman J, Stern H: Nitrous oxide abuse: A new cause for pneumomediastinum. Radiology 145:602, 1982.
50. Varkey B, Kory RC: Mediastinal and subcutaneous emphysema following pulmonary function tests. Am Rev Respir Dis 108:1393–1396, 1973.
51. Jabourian Z, McKenna EL, Feldman M: Spontaneous pneumomediastinum and subcutaneous emphysema. J Otolaryngol 17:50–53, 1988.
52. McMahon DJ: Spontaneous pneumomediastinum. Am J Surg 131:550–551, 1976.
53. Lorge H: The etiology of idiopathic pneumothorax. Am J Med Sci 199:635–641, 1940.
54. Mumford AD, Ashkan K, Elborn S: Clinically significant pulmonary barotrauma after inflation of party balloons. BMJ 313:1619, 1996.
55. Vosk A, Houston CS: Mediastinal emphysema in mountain climbers: Report of two cases and review. Heart Lung 6:799–805, 1977.
56. Mitchell JE, Seim HC, Colon E, et al: Medical complications and medical management of bulimia. Ann Intern Med 107:71–77, 1987.
57. Schwartz M, Rossoff L: Pneumomediastinum and bilateral pneumothoraces in a patient with hyperemesis gravidarum. Chest 106:1904–1906, 1994.
58. Watson JP, Barnett AH: Pneumomediastinum in diabetic ketoacidosis. Diabetic Med 6:173–174, 1989.
59. Kistner RW:. Acute mediastinal emphysema complicating eclampsia. N Engl J Med 244:873–875, 1951.
60. Millard CE: Pneumomediastinum. Chest 56:297–300, 1969.
61. Morgan EJ, Henderson DA: Pneumomediastinum as a complication of athletic competition. Thorax 36:155–156, 1981.
62. Kobak AJ, Abrams RH: Pregnancy complicated by massive subcutaneous emphysema of mediastinal origin (Hamman's syndrome). Am J Obstet Gynecol 57:789–792, 1949.
63. Gay BB: Radiologic evaluation of the nontraumatized child with respiratory distress. Radiol Clin North Am 16:91–112, 1978.
64. Eggleston PA, Ward BH, Pierson WE, et al: Radiographic abnormalities in acute asthma in children. Pediatrics 54:442–449, 1974.
65. Wohl MEB, Chernick V: Bronchiolitis. Am Rev Respir Dis 118:759–781, 1978.
66. Gapany-Gapanavicius M, Yellin A, Almog S, et al: Pneumomediastinum: A complication of chlorine exposure from mixing household cleaning agents. JAMA 248:349–350, 1982.
67. Ozonoff MB: Pneumomediastinum associated with asthma and pneumonia in children. AJR Am J Roentgenol 95:112–117, 1965.
68. Greenberg LF, Benham Kahn S: *Klebsiella* pneumonia with pneumothorax, pneumomediastinum, and pneumoperitoneum. Dis Chest 43:546–550, 1963.
69. Odita JC, Akamaguna AI: Mediastinal and subcutaneous emphysema associated with childhood measles. Eur J Pediatr 142:33–36, 1984.
70. Sharma S, Rajani M, Aggarwal S, et al: Spontaneous pneumothorax and pneumothorax in metastatic lung disease. Indian J Chest Dis Allied Sci 30:125–132, 1988.
71. Hamman L: Spontaneous interstitial emphysema of the lungs. Tr Assoc Am Physicians 52:311–319, 1937.
72. Gerazounis M, Athanassiadi K, Kalantzi N, et al: Spontaneous pneumomediastinum: A rare benign entity. J Thorac Cardiovasc Surg 126:774–776, 2003.
73. Boettger ML: Scuba diving emergencies: Pulmonary overpressure accidents and decompression sickness. Ann Emerg Med 12:563–567, 1983.
74. Rose DM, Jarczyk PA: Spontaneous pneumoperitoneum after scuba diving. JAMA 239:223, 1978.
75. Unsworth IP. Pulmonary barotrauma in hyperbaric chamber. Anaesthesia 28:675–678, 1973.
76. Pierson DJ: Barotrauma and bronchopleural fistula. *In* Tobin M (ed): Principles and Practice of Mechanical Ventilation. New York: McGraw-Hill, 1994.

77. Schnapp LM, Chin DP, Szaflarski N, et al: Frequency and importance of barotrauma in 100 patients with acute lung injury. Crit Care Med 23:272–278, 1995.
78. Weg JG, Anzueto A, Balk RA, et al: The relation of pneumothorax and other air leaks to mortality in the acute respiratory distress syndrome. N Engl J Med 338:341–346, 1998.
79. Boussarsar M, Thierry G, Jaber S, et al: Relationship between ventilatory settings and barotrauma in the acute respiratory distress syndrome. Intensive Care Med 28:406–413, 2002.
80. Kacmarek RM: Methods of providing mechanical ventilatory support. *In* Pierson D, Kacmarek R (eds): Foundations of Respiratory Care. New York: Churchill Livingstone, 1992, pp 953–972.
81. Branson RD, Hurst JM, DeHaven CBJ: Mask CPAP: State of the art. Respir Care 30:846–857, 1985.
82. Vestal BK, Vestal RE: Iatrogenic pneumothorax: An unusual cause. JAMA 235:1879–1880, 1976.
83. Chiles DG, Mannheimer WN, Miller FE: Pneumothorax, pneumomediastinum, and massive subcutaneous emphysema after general anesthetic: Report of a case. J Oral Surg 28:845–847, 1970.
84. Newton NI, Adams AP: Excessive airway pressure during anesthesia: Hazards, effects, and prevention. Anaesthesia 33:689–699, 1978.
85. Fraser R, Paré J, Fraser R, et al:. The normal chest. *In* Fraser R, ParéJ, Fraser R, ParéP (eds): Synopsis of Diseases of the Chest (2nd ed). Philadelphia: WB Saunders, 1994, pp 1–116.
86. Agia G, Hurst E: Pneumomediastinum following the Heimlich maneuver. Ann Emerg Med 8:473–475, 1979.
87. Ingvar DH, Adolfson J, Lindemark C: Cerebral air embolism during training of submarine personnel in free escape: An encephalographic study. Aerospace Med 44:628–635, 1973.
88. Weiss LD, Van Meter KW: Cerebral air embolism in asthmatic scuba divers in a swimming pool. Chest 107:1653–1654, 1995.
89. Pao BS, Hayden SR: Cerebral gas embolism resulting from inhalation of pressurized helium. Ann Emerg Med 28:363–366, 1996.
90. Zaugg M, Kaplan V, Widmer U, et al: Fatal air embolism in an airplane passenger with a giant intrapulmonary bronchogenic cyst. Am J Respir Crit Care Med 157:1686–1689, 1998.
91. Karmy-Jones R, Vallières E, Culver B, et al: Bronchial-atrial fistula after lung transplant resulting in fatal air embolism. Ann Thorac Surg 67:550–551, 1999.
92. Yellin A, Gapany-Gapanavicius M, Lieberman Y: Spontaneous pneumomediastinum: Is it a rare cause of chest pain? Thorax 38:383–385, 1983.
93. Holmes KD, McGuirt WF: Spontaneous pneumomediastinum: Evaluation and treatment. J Fam Pract 31:422, 425–426, 1990.
94. Levin B: The continuous diaphragm sign. Radiology 24:337–338, 1973.
95. Bejvan SM, Godwin JD: Pneumomediastinum: Old signs and new signs. AJR Am J Roentgenol 166:1041–1048, 1996.
96. Rohlfing BM, Webb WR, Schlobohm RM: Ventilator-related extraalveolar air in adults. Radiology 121:25–31, 1976.
97. Zimmerman JE, Dunbar BS, Klingenmaier CH: Management of subcutaneous emphysema, pneumomediastinum, and pneumothorax during respirator therapy. Crit Care Med 3:69–73, 1975.
98. Dissanaike S, Shalhub S, Jurkovich G: The evaluation of pneumomediastinum in blunt trauma patients. J Trauma 65:1340–1345, 2008.
99. Macia I, Moya J, Ramos R, et al: Spontaneous pneumomediastinum: 41 cases. Eur J Cardiothorac Surg 31:1110–1114, 2007.
100. Iyer V, Joshi A, Ryu J: Spontaneous pneumomediastinum: Analysis of 62 consecutive adult patients. Mayo Clin Proc 84:417–421, 2009.
101. Beg MH, Reyazuddin N, Ansari MM: Traumatic tension pneumomediastinum mimicking cardiac tamponade. Thorax 43:576–577, 1988.
102. Gries C, Pierson D: Tracheal rupture resulting in life-threatening subcutaneous emphysema. Respir Care 52:191–195, 2007.
103. Kacmarek RM: Management of the patient-ventilator system. *In* Pierson D, Kacmarek R (eds): Foundations of Respiratory Care. New York: Churchill Livingstone, 1992, pp 973–998.
104. Benson MS, Pierson DJ: Auto-PEEP during mechanical ventilation of adults. Respir Care 33:557–565, 1988.
105. Oh KS, Fleischner FG, Wyman SM: Characteristic pulmonary finding in traumatic complete transection of a main-stem bronchus. Radiology 92:371–377, 1969.
106. Bjerke HS: Boerhaave's syndrome and barogenic injuries of the esophagus. Chest Surg Clin North Am 4:819–825, 1994.
107. Brauer RB, Liebermann Meffert D, Stein HJ, et al: Boerhaave's syndrome: Analysis of the literature and report of 18 new cases. Dis Esophagus 10:64–68, 1997.
108. Bar-Maor J, Hayari L: Pneumatic perforation of the esophagus in children. J Pediatr Surg 27:1532–1533, 1992.
109. Roh J, Park C: Spontaneous pharyngeal perforation after forceful vomiting: The difference from classic Boerhaave's syndrome. Clin Exp Otorhinolaryngol 1:174–176, 2008.
110. Edling JE, Bacon BR: Pleuropulmonary complications of endoscopic variceal sclerotherapy. Chest 99:1252–1257, 1991.
111. Wesdorp ICE, Bartelsman JFWM, Huibregtse K, et al: Treatment of instrumental esophageal perforation. Gut 25:398–404, 1984.
112. Schuman BM, Beckman JW, Tedesco FJ, et al: Complications of endoscopic injection sclerotherapy: A review. Am J Gastroenterol 82:823–830, 1987.
113. Baydur A, Korula J: Cardiorespiratory effects of endoscopic esophageal variceal sclerotherapy. Am J Med 89:477–482, 1990.
114. Vassilev BN, Kazandziev PK, Losanoff JE, et al: Esophageal "stars": A sinister foreign body ingestion. South Med J 90:211–214, 1997.
115. Fraser RG, Paré JAP (eds): Diagnosis of Diseases of the Chest (2nd ed). Philadelphia: WB Saunders, 1979.
116. Gollub MJ, Bains MS: Barium sulfate: A new (old) contrast agent for diagnosis of postoperative esophageal leaks. Radiology 202:360–362, 1997.
117. Krizek TJ, Lease JG: Surgical management of suppurative mediastinitis. *In* Sabiston DJ (ed): Textbook of Surgery (14th ed). Philadelphia: WB Saunders, 1991, pp 1796–1800.
118. Wu J, Mattox K, Wall MJ: Esophageal perforations: New perspectives and treatment paradigms. J Trauma 63:1173–1184, 2007.
119. Griffin S, Lamb P, Shenfine J, et al: Spontaneous rupture of the oesophagus. Br J Surg 95:1115–1120, 2008.
120. Zisis C, Guillin A, Heyries L, et al: Stent placement in the management of oesophageal leaks. Eur J Cardiothorac Surg 33:451–456, 2008.
121. Salminen P, Gullichsen R, Laine S: Use of self-expandable metal stents for the treatment of esophageal perforations and anastamotic leaks. Surg Endosc 23:1526–1530, 2009.
122. Ohri SK, Liakakos TA, Pathi V, et al: Primary repair of iatrogenic thoracic esophageal perforation and Boerhaave's syndrome. Ann Thorac Surg 55:603–606, 1993.
123. Sakamoto Y, Tanaka N, Furuya T, et al: Surgical management of late esophageal perforation. Thorac Cardiovasc Surg 45:269–272, 1997.
124. Keung YK, Gendreau J, Barber A, et al: Acute mediastinitis secondary to leakage of parenteral nutrition from a migrated central venous catheter in a patient undergoing autologous bone marrow transplant. Bone Marrow Transplant 17:871–872, 1996.
125. Kiernan PD, Hernandez A, Byrne WD, et al: Descending cervical mediastinitis. Ann Thorac Surg 65:1483–1488, 1998.
125a. Ridder GJ, Maier W, Kinzer S, et al: Descending necrotizing mediastinitis: contemporary trends in etiology, diagnosis, management, and outcome. Ann Surg 2009 (Epub ahead of print).
126. Garatea-Crelgo J, Gay-Escoda C: Mediastinitis from odontogenic infection: Report of three cases and review of the literature. Int J Oral Maxillofac Surg 20:65–68, 1991.
127. Corsten MJ, Shamji FM, Odell PF, et al: Optimal treatment of descending necrotising mediastinitis. Thorax 52:702–708, 1997.
128. Freeman RK, Vallières E, Verrier ED, et al: Descending necrotizing mediastinitis: An analysis of the effects of serial surgical débridement on patient mortality. J Thorac Cardiovasc Surg 119:260–267, 2000.
129. Wheatley MJ, Stirling MC, Kirsh MM, et al: Descending necrotizing mediastinitis: Transcervical drainage is not enough. Ann Thorac Surg 49:780–784, 1990.
130. Marty-Ané CH, Berthet JP, Alric P, et al: Management of descending necrotizing mediastinitis: An aggressive treatment for an aggressive disease. Ann Thorac Surg 68:212–217, 1999.

131. Goodwin RAJ: Disorders of the mediastinum. *In* Fishman AP (ed): Pulmonary Diseases and Disorders. New York: McGraw-Hill, 1980, pp 1479–1486.
132. Newman LS, Szczukowski LC, Bain RP, et al: Suppurative mediastinitis after open heart surgery. Chest 94:546–553, 1988.
133. Karwande S, Renlund D, Olsen S, et al: Mediastinitis in heart transplantation. Ann Thorac Surg 54:1039–1045, 1992.
134. Baldwin R, Radovancevic B, Sweeney M, et al: Bacterial mediastinitis after heart transplantation. J Heart Lung Transplant 11:545–549, 1992.
135. Bassiri AG, Girgis RE, Theodore J: *Actinomyces odontolyticus* thoracopulmonary infections. Two cases in lung and heart-lung transplant recipients and a review of the literature. Chest 109:1109–1111, 1996.
136. El Oakley RM, Wright JE: Postoperative mediastinitis: Classification and management. Ann Thorac Surg 61:1030–1036, 1996.
137. Ulicny KS Jr, Hiratzka LF: The risk factors of median sternotomy infection: A current review. J Card Surg 6:338–351, 1991.
138. Stoney WS, Alford WC Jr, Burrus GR, et al: Median sternotomy dehiscence. Ann Thorac Surg 26:421–426, 1978.
139. Grossi EA, Culliford AT, Krieger KH, et al: A survey of 77 major infectious complications of median sternotomy: A review of 7,949 consecutive operative procedures. Ann Thorac Surg 40:214–223, 1985.
140. Culliford AT, Cunningham JJ, Zeff RH, et al: Sternal and costochondral infections following open-heart surgery: A review of 2594 cases. J Thorac Cardiovasc Surg 72:714–726, 1976.
141. Perl TM, Cullen JJ, Wenzel RP, et al: Intranasal mupirocin to prevent postoperative *Staphylococcus aureus* infections. N Engl J Med 346:1871–1877, 2002.
142. Kluytmans JA, Mouton JW, VandenBergh MF, et al: Reduction of surgical-site infections in cardiothoracic surgery by elimination of nasal carriage of *Staphylococcus aureus*. Infect Control Hosp Epidemiol 17:780–785, 1996.
143. Sarr MG, Gott VL, Townsend TR: Mediastinal infection after cardiac surgery. Ann Thorac Surg 38:415–423, 1984.
144. Demmy TL, Park SB, Liebler GA, et al: Recent experience with major sternal wound complications. Ann Thorac Surg 49:458–462, 1990.
145. Reddy S, Grayson A, Smith G, et al: Methicillin resistant *Staphylococcus aureus* infections following cardiac surgery: Incidence, impact, and identifying adverse outcome traits. Eur J Cardiothorac Surg 32:113–117, 2007.
146. Kohman LJ, Coleman MJ, Parker FB Jr: Bacteremia and sternal infection after coronary artery bypass grafting. Ann Thorac Surg 49:454–457, 1990.
147. Glower DD, Douglas JMJ, Gaynor JW, et al: *Candida* mediastinitis after a cardiac operation. Ann Thorac Surg 49:157–163, 1990.
148. Bor DH, Rose RM, Modlin JF, et al: Mediastinitis after cardiovascular surgery. Rev Infect Dis 5:885–897, 1983.
149. Misawa Y, Fuse K, Hasegawa T: Infectious mediastinitis after cardiac operations: Computed tomographic findings. Ann Thorac Surg 65:622–624, 1998.
150. Jolles H, Henry DA, Roberson JP, et al: Mediastinitis following median sternotomy: CT findings. Radiology 201:463–466, 1996.
151. Sarr MG, Watkins LJ, Stewart JR: Mediastinal tap as a useful method for the early diagnosis of mediastinal infection. Surg Gynecol Obstet 159:79–81, 1984.
152. Craver JM, Rand RP, Bostwick JI, et al: Management of postcardiotomy mediastinitis. *In* Waldhausen J, Orringer M (eds): Complications in Thoracic Surgery. St Louis: Mosby Year Book, 1991, pp 125–131.
153. Robicsek F: Postoperative sterno-mediastinitis. Am Surg 66:184–192, 2000.
154. El Gamel A, Yonan NA, Hassan R, et al: Treatment of mediastinitis: Early modified Robicsek closure and pectoralis major advancement flaps. Ann Thorac Surg 65:41–46, 1998.
155. Lazar HL, Fitzgerald C, Gross S, et al: Determinants of length of stay after coronary artery bypass graft surgery. Circulation 92:II20–II24, 1995.
156. LaForce FM: Anthrax. Clin Infect Dis 19:1009–1013, 1994.
157. Shafazand S, Doyle R, Ruoss S, et al: Inhalational anthrax: Epidemiology, diagnosis, and management. Chest 116:1369–1376, 1999.
158. Shafazand S: When bioterrorism strikes: Diagnosis and management of inhalational anthrax. Semin Respir Infect 18:134–145, 2003.
159. Jernigan JA, Stephens DS, Ashford DA, et al: Bioterrorism-related inhalational anthrax: The first 10 cases reported in the United States. Emerg Infect Dis 7:933–944, 2001.
160. Jernigan DB, Raghunathan PL, Bell BP, et al: Investigation of bioterrorism-related anthrax, United States, 2001: Epidemiologic findings. Emerg Infect Dis 8:1019–1028, 2002.
161. Mayer TA, Bersoff-Matcha S, Murphy C, et al: Clinical presentation of inhalational anthrax following bioterrorism exposure: Report of 2 surviving patients. JAMA 286:2549–2553, 2001.
162. Brachman PS: Inhalation anthrax. Ann N Y Acad Sci 353:83–93, 1980.
163. Abramova FA, Grinberg LM, Yampolskaya OV, et al: Pathology of inhalational anthrax in 42 cases from the Sverdlovsk outbreak of 1979. Proc Natl Acad Sci U S A 90:2291–2294, 1993.
164. Waterer GW, Robertson H: Bioterrorism for the respiratory physician. Respirology 14:5–11, 2009.
165. Lalitha MK, Thomas MK: Penicillin resistance in *Bacillus anthracis*. Lancet 349:1522, 1997.
165a. Schneemann A, Manchester M: Anti-toxin antibodies in prophylaxis and treatment of inhalation anthrax. Future Microbiol 4:35–43, 2009.
166. Schowengerdt CG, Suyemoto R, Main FB: Granulomatous and fibrous mediastinitis: A review and analysis of 180 cases. J Thorac Cardiovasc Surg 57:365–379, 1969.
167. Loyd JE, Tillman BF, Atkinson JB, et al: Mediastinal fibrosis complicating histoplasmosis. Medicine 67:295–310, 1988.
168. Goodwin RA, Nickell JA, DesPrez RM: Mediastinal fibrosis complicating healed primary histoplasmosis and tuberculosis. Medicine 51:227–246, 1972.
169. Worrell J, Donnelly E, Martin J, et al: Computed tomography and the idiopathic form of proliferative fibrosing mediastinitis. J Thorac Imaging 22:235–240, 2007.
170. Feigin DS, Eggleston JC, Siegelman SS: The multiple roentgen manifestations of sclerosing mediastinitis. Johns Hopkins Med J 144:1–8, 1979.
171. Cunningham T, Farrell J, Veale D, et al: Anterior mediastinal fibrosis with superior vena caval obstruction complicating the synovitis-acne-pustulosis-hyperostosis-osteomyelitis syndrome. Br J Rheumatol 32:408–410, 1993.
172. Comings DE, Skubi KB, Van Eyes J, et al: Familial multifocal fibrosclerosis. Findings suggesting that retroperitoneal fibrosis, mediastinal fibrosis, sclerosing cholangitis, Riedel's thyroiditis, and pseudotumor of the orbit may be different manifestations of a single disease. Ann Intern Med 66:884–892, 1967.
173. Fraser RG, Paré JAP, Paré PD, et al (eds): Diagnosis of Diseases of the Chest (3rd ed). Philadelphia: WB Saunders, 1989:955.
174. Ray RL, Truscott DE: Silicosis as a cause of superior vena cava obstruction. Br J Dis Chest 57:210–212, 1963.
175. Light AM: Idiopathic fibrosis of the mediastinum: A discussion of three cases and review of the literature. J Clin Pathol 31:78–88, 1978.
176. Flannery MT, Espino M, Altus P, et al: Hodgkin's disease masquerading as sclerosing mediastinitis. South Med J 87:921–923, 1994.
177. Dechambre S, Dorzee J, Fastrez J, et al: Bronchial stenosis and sclerosing mediastinitis: An uncommon complication of external thoracic radiotherapy. Eur Respir J 11:1188–1190, 1998.
178. Hammoud ZT, Rose AS, Hage CA, et al: Surgical management of pulmonary and mediastinal sequelae of histoplasmosis: a challenging spectrum. Ann Thorac Surg 88:399–403, 2009.
179. Kefri M, Dyke S, Copeland S, et al: Hemoptysis and hematemesis due to a broncholith: granulomatous mediastinitis. South Med J 89:243–245, 1996.
180. Urschel HC Jr, Razzuk MA, Netto GJ, et al: Sclerosing mediastinitis: Improved management with histoplasmosis titer and ketoconazole. Ann Thorac Surg 50:215–221, 1990.
181. Lokich JJ, Goodman R: Superior vena cava syndrome: Clinical management. JAMA 231:58–61, 1975.

182. Wychulis AR, Payne WS, Clagett OT, et al: Surgical treatment of mediastinal tumors: A 40-year experience. J Thorac Cardiovasc Surg 62:379–391, 1977.
183. Yellin A, Rosen A, Reichert N, et al: Superior vena cava syndrome: The myth—The facts. Am Rev Respir Dis 141:1114–1118, 1990.
184. Espinosa RE, Edwards WD, Rosenow ECD, et al: Idiopathic pulmonary hilar fibrosis: An unusual cause of pulmonary hypertension. Mayo Clin Proc 68:778–782, 1993.
185. Maholtz MS, Dauber JH, Yousem SA: Case report: Fluconazole therapy in histoplasma mediastinal granuloma. Am J Med Sci 307:274–277, 1994.
186. Field C, Arnold W, Gloster ES, et al: Steroid therapy as treatment for idiopathic fibrosis of the retroperitoneum and mediastinum. Pediatrics 78:936–938, 1986.
187. Gran JT: Chronic idiopathic mediastinal fibrosis presenting with malaise, pleuritis and thoracic back pain. Br J Rheumatol 32:757–759, 1993.
188. Sherrick AD, Brown LR, Harms GF, et al: The radiographic findings of fibrosing mediastinitis. Chest 106:484–489, 1994.
189. Dunn EJ, Ulicny KS Jr, Wright CB, et al: Surgical implications of sclerosing mediastinitis. A report of six cases and review of the literature. Chest 97:338–346, 1990.
190. Lanciego C, Pangua C, Chacon JI, et al: Endovascular stenting as the first step in the overall management of malignant superior vena cava syndrome. Am J Roentgenol 193:549–558, 2009.
191. Brown ML, Cedeno AR, Edell ES, et al: Operative strategies for pulmonary artery occlusion secondary to mediastinal fibrosis. Ann Thorac Surg 88:233–237, 2009.

CHAPTER 78

HYPOVENTILATION AND HYPERVENTILATION SYNDROMES

James Duffin, PhD • Eliot A. Phillipson, MD

INTRODUCTION

THE CONTROL OF BREATHING
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Organization of the Respiratory Control System
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HYPOVENTILATION SYNDROMES
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INTRODUCTION

Breathing is regulated by two anatomically distinct but functionally integrated elements referred to as the metabolic (or automatic) and the behavioral (or voluntary) respiratory control systems. The major components are shown in Figure 78-1. The metabolic system is concerned primarily with acid-base balance and blood gas homeostasis. Appropriate to this function, it receives afferent input from peripheral and central chemoreceptors that are sensitive to hydrogen ion concentration ($[H^+]$), P_{CO_2}, and P_{O_2} and from bronchopulmonary mechanoreceptors that are sensitive to the degree of lung stretch and rate of airflow. In contrast, the behavioral control system utilizes the ventilatory apparatus for functions whose primary purpose is not gas exchange, the most notable examples being speaking and singing. Disorders in the control of breathing can arise because of disturbances in either of these two control systems. In broad terms, defects in the behavioral system result in dysphasia, dyspraxia, or alveolar hyperventilation syndromes but do not produce clinically important hypoventilation syndromes. Rather, hypoventilation disorders arise because of either defects in the metabolic control system or defects in the respiratory neuromuscular apparatus, chest wall, lungs, or airways. Such disorders can be acute or chronic. Acute hypoventilation disturbances, which represent life-threatening emergencies, are considered in Chapter 90. This chapter deals with disturbances in respiratory control that result in chronic hypoventilation or chronic hyperventilation syndromes.

THE CONTROL OF BREATHING

Basic Principles

Breathing is responsible for providing sufficient oxygen for metabolism and for eliminating the carbon dioxide produced by metabolism. The respiratory control system accomplishes this goal by adjusting pulmonary ventilation so oxygen uptake in the lungs equals oxygen consumption by the tissues, and carbon dioxide elimination at the lungs equals carbon dioxide production by the tissues (Fig. 78-2). Under these conditions, pulmonary gas exchange matches metabolism, and P_{O_2} and P_{CO_2} remain constant at values satisfying physiologic requirements.

In the case of P_{O_2}, the requirement is relatively simple: it must be kept at a level sufficient to saturate arterial hemoglobin and to provide a pressure gradient that supplies tissue metabolic requirements for oxygen. Because hemoglobin saturation can be achieved over a wide range of P_{O_2} levels, P_{O_2} need not be closely regulated, as

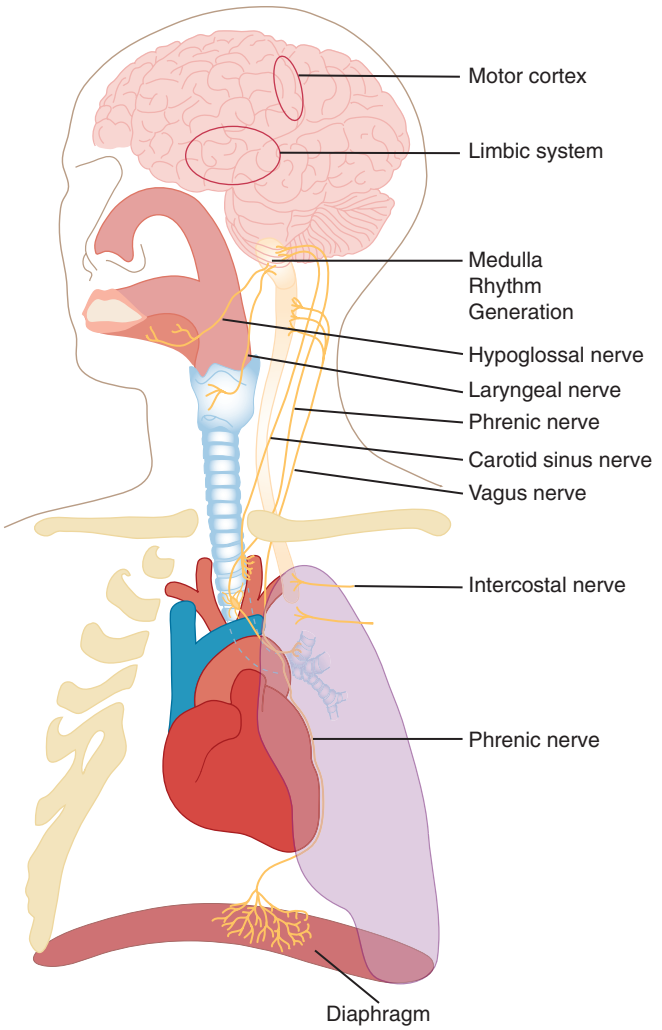


FIGURE 78-1 ■ A cartoon showing the major elements of the central nervous system participating in the metabolic and behavioral respiratory control systems and their anatomic relationships. The automatic respiratory rhythm is generated in the medulla and sent down the spinal cord to motoneurons connecting to the diaphragm via the phrenic nerve and the intercostal muscles via the intercostal nerves. The tongue and upper airway muscles are controlled via the hypoglossal and laryngeal nerves, respectively. The limbic system and motor cortex are the origin of emotional and voluntary control of respiration. Lung receptor signals are fed back to the medullary control center via the vagus nerve, and the carotid sinus nerve conveys the carotid body (peripheral chemoreceptor) drive to breathe.

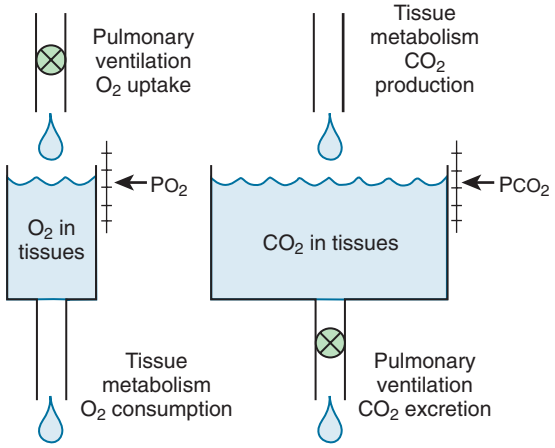


FIGURE 78-2 ■ A conceptual model showing the balance between metabolic requirements for the supply of oxygen and elimination of carbon dioxide, and the pulmonary gas exchange of O_2 and CO_2. Metabolic consumption of O_2 is represented by the drops of O_2 leaving the O_2 storage tank (mostly blood), and CO_2 production in the tissues is represented by the drops of CO_2 entering the CO_2 storage tank (body water). Pulmonary ventilation operates the O_2 inflow tap and the CO_2 outflow tap to control the O_2 uptake and CO_2 elimination represented by the drops. Note the difference in size of the tissue storage compartments of the two gases, as a result of which changes in P_{O_2} stores are fast and changes in P_{CO_2} stores in tissues such as the brain are slow.

long as tissue hypoxia is avoided. In contrast, the requirement for carbon dioxide elimination is less dependent on a pressure gradient because carbon dioxide diffuses much more readily through an aqueous environment than oxygen. However, P_{CO_2} must be controlled at a level that ensures that tissue $[H^+]$ remains within the narrow limits necessary for optimal protein function (normally 40 nM/L).[1] This requirement can be considered as the second goal of the respiratory control system, with renal regulation of ionic concentrations also involved.

Under resting conditions, P_{CO_2} is maintained within a narrow range by a negative feedback regulator involving two sets of chemoreceptors that sense $[H^+]$, one in the brain (central chemoreceptors) and one in the carotid bodies (peripheral chemoreceptors). When these chemoreceptors sense an increase in $[H^+]$, breathing is stimulated. This chemoreflex control system also protects against asphyxia by increasing the sensitivity of the peripheral chemoreceptors to $[H^+]$ under conditions of hypoxia. The regulation of blood gases is discussed in Chapter 4, and acid-base balance is examined in Chapter 7.

During exercise, however, rapid increases in metabolism must be accompanied by rapid changes in ventilation if pulmonary gas exchange is to match metabolism. In this situation, fast neural response mechanisms are activated, including afferent feedback from the exercising muscles and a parallel activation of ventilation with activation of the exercising muscles, termed *central command*.[2]

The two elements involved in matching pulmonary gas exchange to metabolic requirements, the chemoreflex and exercise control systems, collectively constitute the metabolic or automatic control system. However, other physiologic functions also utilize the ventilatory apparatus, notably speaking,[3] singing, and voluntary breath-holding[4] as well as emotions.[5] These activities have impact on the respiratory muscles through the behavioral control system.[6] Breath-holding exemplifies the competition that may exist between the behavioral and metabolic control systems for use of the respiratory

muscles. At the initiation of a breath-hold, voluntary control dominates and breathing is halted; but as the chemoreflex drive to breathe increases progressively, the metabolic control system overrides behavioral control and the breath-hold is terminated. In the process of this competition, the discrepancy between the chemoreflex drives to breathe, on the one hand, and the lack of ventilation, on the other, results in a sensation of dyspnea.[7]

Subsidiary to the metabolic and behavioral systems are other control systems, including those responsible for choice of efficient patterns of breathing in terms of tidal volume and respiratory rate,[8] and for protection of the airways by pulmonary reflexes, such as cough.[9] This hierarchical system of controllers can be put into perspective by examination of the organization of the central respiratory control system.

Organization of the Respiratory Control System

General Organization

Taken together, the demands of the various respiratory control systems vary from moment to moment, and may place conflicting demands on the respiratory muscles, which then act according to set priorities. The site of much of this competition is the respiratory motoneurons in the spinal cord, where the various drives to breathing arrive via separate pathways[6] (Fig. 78-3). The separation of the spinal pathways for behavioral and metabolic control in humans has been deduced from observations of spinal cord injuries that involve only one pathway. For example, some patients are able breathe on command but lack the automatic chemoreflex response to carbon dioxide, whereas others have a response to carbon dioxide but cannot voluntarily influence breathing.[10] Behavioral or voluntary control from the motor cortex arrives via the corticospinal tracts in the dorsolateral spinal cord; metabolic or automatic control from the central controller in the medulla arrives via ventrolateral spinal cord pathways, as do the inputs from hypothalamic, limbic, and reticular formation systems that mediate such behaviors as anxiety hyperventilation, the sudden gasp of a startle, the changes in breathing during sleep, and the response to sensory afferents such as pain.

The metabolic respiratory control system can be viewed as a complex hierarchical control system with multiple feedback loops (Fig. 78-4). The system is centered in the brain stem (medulla), where respiratory rhythm and drives are sent to the respiratory motoneurons in the spinal cord, based on feedback from various afferents. Details of this system are provided in reviews.[11] The afferent inputs to the system include those from the central chemoreceptors within the medulla, the peripheral chemoreceptors in the carotid bodies, and airway and lung receptors. These signals also reach higher areas of the central nervous system such as the pons, where they affect the patterning of breathing,[12] and the cortex, where they may contribute to respiratory sensations

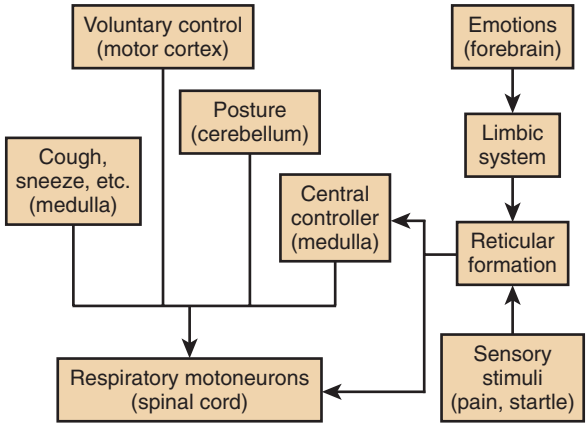


FIGURE 78-3 ■ A general scheme showing various drives to breathing controlling the spinal respiratory motoneurons, with the direct pathways on the left and the indirect pathways on the right. The voluntary control from the motor cortex and the respiratory rhythm from the central controller in the medulla reach the spinal motoneurons via separate spinal pathways, each of which may be damaged to separately disable voluntary and automatic respiratory control of the respiratory muscles. The reticular formation conveys emotional and sensory signals that affect breathing.

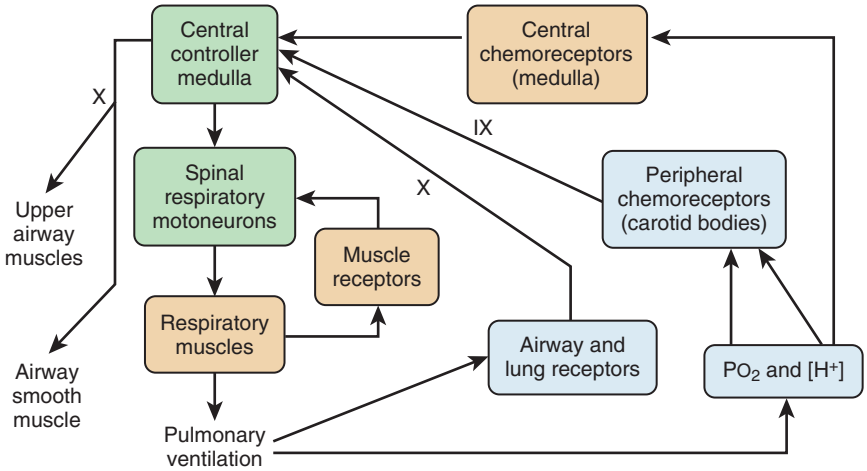


FIGURE 78-4 ■ A schematic diagram of some of the many feedback loops involved in the automatic control of breathing. The central controller rhythmically drives the respiratory muscles via the spinal motoneurons to ventilate the lung and control P_{CO_2}, which controls $[H^+]$ and P_{O_2}. Central and peripheral chemoreceptors feed back information about $[H^+]$ and P_{O_2} to the central controller in the medulla via the glossopharyngeal nerve (IX) (the chemoreflexes). Airway and lung receptors feed back information about irritants and lung volume to the central controller via the vagus nerve (X). Local spinal feedback assists with the control of the complex respiratory musculature.

such as dyspnea, but the pathways involved are mostly unknown. In addition to the medullary feedback loops, there are also local control loops to spinal motoneurons from respiratory muscle receptors, particularly in the intercostal muscles.

Spinal Organization

The spinal organization of respiratory motoneuron control is complex and not fully understood. Four groups of respiratory neurons have been identified in the spinal cord: upper cervical inspiratory neurons in C1-3; phrenic motoneurons and interneurons in C3-5; intercostal motoneurons and interneurons in T1-12; and abdominal motoneurons and interneurons in T6-L3. The interneurons within the motoneuron segments and those more remote in the upper cervical cord probably mediate the segmental and suprasegmental reflex control of the motoneurons.

The upper cervical inspiratory neurons are located bilaterally in longitudinal columns extending caudally from the medulla to mid-C3.[13] These neurons receive a direct drive from the medullary inspiratory neurons, as well as inputs from intercostal afferents. Their axons descend the spinal cord ipsilaterally as far as the upper lumbar segments, and arborize within the phrenic, intercostal, and abdominal motoneuron segments of the spinal cord. As yet, the functional connections of these neurons are undetermined because they do not appear to connect synaptically with spinal respiratory neurons.

The respiratory motoneurons, including the phrenic motoneurons driving the diaphragm, the intercostal motoneurons driving the intercostal muscles, and the abdominal motoneurons driving the abdominal muscles,[14] receive a rhythmic respiratory drive from two sources: the nearby respiratory interneurons in the spinal cord, and the respiratory neurons located in the medulla. These motoneurons produce a ramp of inspiratory nerve activity by an increasing firing frequency and by the recruitment of additional motoneurons. Because some medullary respiratory neurons are the source of the rhythmic drive to the spinal respiratory motor neurons, they are often referred to as respiratory premotor neurons.

Central Organization

The network that generates and transmits respiratory rhythm to the spinal respiratory motoneurons via bulbospinal projections, and to various respiratory muscles of the airway via cranial nerves, lies within the medulla and pons.[15] The medullary respiratory neurons are located in two main groups, longitudinally distributed on either side of the neuraxis, referred to as the ventral respiratory group (VRG) and the dorsal respiratory group (DRG), because of their relative anatomic positions. The groups are located near the obex, the point where the central canal widens into the fourth ventricle (Fig. 78-5). Not shown are the medullary elements sensing [H^+] that constitute the central chemoreceptors[16] that are located close to the ventral surface and elsewhere. These neuron populations have bursting activities that occur in different phases of the respiratory cycle: the most obvious are inspiration and expiration, but the expiratory phase is often divided into two parts, a postinspiratory or early expiratory portion and a late expiratory portion. Within

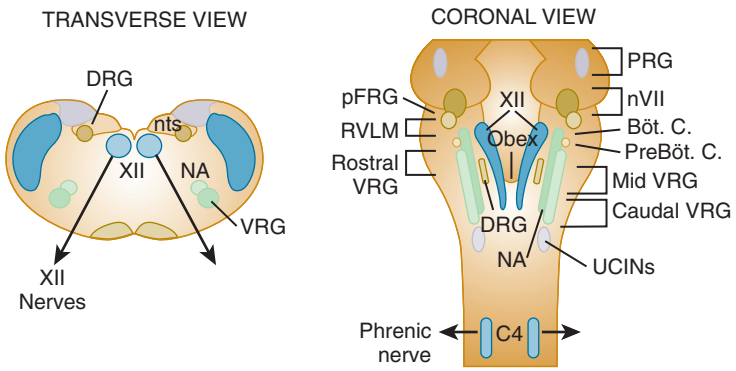


FIGURE 78-5 ■ A schematic diagram of the medulla showing the main groups of respiratory neurons. The coronal view has the cerebellum removed, and the transverse view is at the level of the obex. The two major groups of neurons are the ventral respiratory group (VRG) and the dorsal respiratory group (DRG); the latter is where vagal afferent inputs are processed. The ventral respiratory group (VRG) has been subdivided into a caudal part, where many expiratory premotor neurons are found, and a rostral part, where many premotor inspiratory neurons are found, based on the location of the obex, the point where the central canal surfaces into the fourth ventricle. An intermediate locus about the obex contains both inspiratory and expiratory neurons. Intermingled with these neurons are the cranial motor neurons of the nucleus ambiguous (NA). Caudal to the ventral respiratory group are the mysterious upper cervical inspiratory neurons (UCINs). Above the ventral respiratory group, as a rostral extension of it, lies the Bötzinger complex (Böt C) in the rostroventrolateral medulla (RVLM), containing a variety of neuron types, including cranial motor neurons and a major group of inhibitory expiratory neurons. Immediately rostral, near the facial nucleus (nVII), is the parafacial respiratory group (pFRG) associated with rhythm generation in neonates. Just caudal to the Bötzinger complex is the pre-Bötzinger complex (pre Böt C), whose neurons are also associated with rhythm generation in neonates. Other respiratory neurons involved in rhythm generation are found in the pons (pontine respiratory group, PRG). The hypoglossal motoneurons (XII) controlling the tongue are also shown.

each phase, the pattern of firing frequency may be augmenting, constant, or decrementing.

The caudal VRG contains many expiratory premotor neurons and the rostral VRG contains many premotor inspiratory neurons, whose axons course contralaterally within the medulla before descending the cord to the respiratory motoneurons and interneurons. Caudal to the VRG in the cervical spinal cord lie the upper cervical inspiratory neurons. The DRG includes the respiratory afferent relay neurons of the nucleus tractus solitarius. Pontine respiratory groups include the Kolliker fuse and parabrachial nuclei.[17] Other medullary neurons include the Bötzinger complex, rostral to the VRG, that inhibits medullary inspiratory activity during expiration as well as phrenic motor neurons, and two sites of pacemaker-type cells: the pre-Bötzinger complex (preBötC),[18] located between the Bötzinger complex and the VRG, and the parafacial respiratory group (pFRG), located beside the facial nucleus.[19] The abdominal motoneurons receive excitation from neurons in the pFRG via the caudal VRG premotor neurons.

The VRG also includes the cranial motoneurons of the nucleus ambiguus,[20] which leave the medulla ipsilaterally in the vagus or glossopharyngeal nerves, and innervate several different muscles of the airways.[21] Other cranial neurons include the hypoglossal motoneurons that lie close to the midline and innervate the tongue.[22] These various cranial motoneurons are respiratory in the sense that a component of their activity is related to the respiratory cycle; but they are also involved in other functions, such as speech and swallowing.[23] Because this dual function dictates the requirement for looser respiratory control than the respiratory pump muscles, the hypoglossal motoneurons, for example, are not driven by the same premotor neurons as the diaphragm.[24]

Pontine neurons exchange information with the medulla,[17] but their role as "apneustic" and "pneumotaxic" centers has changed to that involving more complex behaviors. The pons has profound influences on respiratory rhythm generation[25] and is involved in mechanoreceptor and chemoreceptor reflexes.[26] Other aspects include the role of the pons in vocalization,[3] exercise,[27] and nociception[28] and as a source of state-dependent control of respiratory activity, such as the control of airway muscles during sleep.[29]

The Respiratory Rhythm Generator

Current concepts of respiratory rhythm generation remain controversial, with two main theories in contention: the pacemaker hypothesis, and the network hypothesis. Definitive proof for these hypotheses is difficult to establish. Indeed, they have emerged largely from studies based on different experimental preparations (the network hypothesis derives from adult in vivo preparations, and the pacemaker hypothesis from neonatal in vitro preparations) and these differences may account for the different findings. This conflict between hypotheses may be resolved using a new perfused preparation that can be applied to both neonates and adults, the working heart–brain stem preparation.[30] Experiments with this preparation have already demonstrated the importance of synaptic inhibition in normal respiratory rhythm generation.[31]

In neonatal in vitro preparations, pacemaker-like neurons have been identified in two discrete regions in the rostroventrolateral medulla: the preBötC[18] and pFRG.[19] These two pacemaker populations may represent coupled inspiratory and expiratory rhythm generators. However, their interaction is a point of contention. Do the pFRG neurons represent a master rhythm generator that not only sets the expiratory rhythm but also entrains inspiratory bursts, or does the preBötC dominate? Neurons in the pFRG have been shown to excite preBötC neurons, and preBötC neurons have been shown to inhibit pFRG neurons. Perhaps the interaction is cooperative.[32]

Nevertheless, the network hypothesis, which suggests that respiratory rhythm results from the pattern of synaptic interconnections among neurons in a distributed network in the medulla and pons,[33] remains in contention with evidence that, when pacemakers are eliminated, respiratory rhythm continues, and when synaptic inhibition, essential for network rhythm generation, is suppressed, rhythm ceases. Recent experiments have led to the proposal that the generation of respiratory rhythm is organized as a hierarchy of mechanisms.[34] All network models have three basic principles in common. First, mutual inhibition must exist between at least two major groups of neurons of opposite respiratory phase (inspiratory and expiratory). Second, at least one of the neuron types must be self-limiting through an accommodative mechanism whereby the responsiveness of the neuron is decreased by its own activity. Third, a tonic drive to the neurons involved is necessary to produce the oscillation. Figure 78-6 shows proposed connection diagrams for models of two-phase[35,36] and three-phase[37] respiratory rhythm generators.

Control of Breathing Pattern

Two main types of receptors from the lungs and airways provide feedback information to the medullary controller that determines the pattern of breathing; specifically, rapidly adapting irritant receptors, and slowly adapting stretch receptors.[38] The rapidly adapting receptors are found throughout the airway from the nose to the alveoli, and are stimulated by irritants in the inspired air, and by rapid and excessive lung inflation or deflation. These receptors are classified as rapidly adapting because, following stimulation, their activation declines rapidly even if the stimulus persists. Some irritant receptors produce stereotyped patterns of breathing, such as coughing,[39] and all share the property of stimulating inspiration and inducing bronchoconstriction.[21] Stimulation of these receptors during an asthmatic attack exacerbates airway narrowing by producing reflex bronchoconstriction in addition to that produced by the local release of chemical mediators. The pattern of breathing induced by irritant receptor stimulation depends upon their location in the airway: nasal receptors (trigeminal nerves) result in sneezing; epipharyngeal receptors (glossopharyngeal

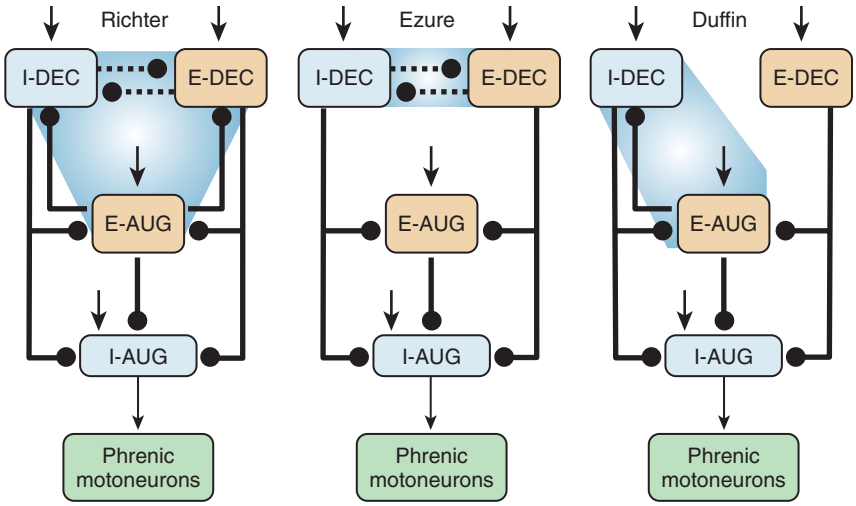


FIGURE 78-6 ■ Three conceptual models[36,37,135] of respiratory rhythm generation based upon inhibitory connections (*shaded area*) between inspiratory (I) and expiratory (E) neurons of the VRG with decrementing (DEC) and augmenting (AUG) patterns of activity. The E-AUG neurons are the Bötzinger complex expiratory neurons, and the E-DEC and I-DEC neurons are accommodating. These neurons control the output of the inspiratory augmenting neurons (I-AUG). The network requires a tonic excitation (*closed circles*) from the chemoreceptors to oscillate. The *dotted lines* indicate theoretical connections, while the *solid lines* indicate known connections.

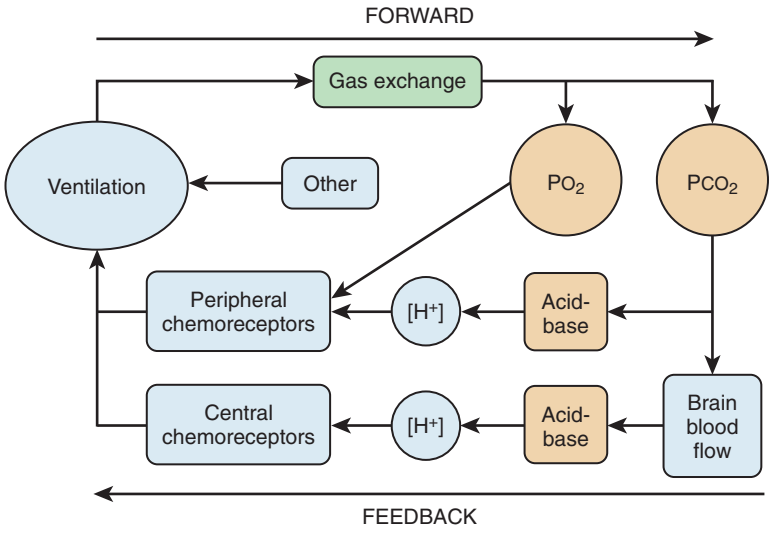


FIGURE 78-7 ■ A schematic diagram of the negative feedback chemoreflex control of breathing. Ventilation controls P_{CO_2} and P_{O_2} via the gas exchange in the lungs (the forward part of the control loop). P_{CO_2} controls brain blood flow, and central and peripheral $[H^+]$ via acid-base relationships. Central and peripheral chemoreceptors drive ventilation according to the levels of P_{O_2} and $[H^+]$ to form a chemoreflex (the feedback part of the control loop). The control system is termed "negative feedback" because an increase in ventilation decreases P_{CO_2}, which in turn decreases the chemoreceptor feedback driving ventilation. Note that "other" drives to breathe, such as wakefulness, behavior, and exercise, also affect ventilation. (Please see the text for more details.)

nerves) result in the aspiration or sniff reflex; laryngeal and tracheal receptors (vagus nerves) result in coughing; tracheal, bronchial, and bronchiolar receptors (vagus nerves) result in Head's paradoxical reflex and the deflation reflex; and juxtapulmonary capillary or J receptors (vagus nerves) result in rapid, shallow breathing.

The stretch receptors, which are located in the main airways of the bronchial tree, respond to lung inflation and produce afferent feedback to the medullary controller through the vagus nerves that is proportional to lung volume.[40] These receptors are responsible for the Hering-Breuer inflation reflex, whereby lung inflation switches respiratory phase from inspiration to expiration. This reflex is very apparent in animals, even at normal lung volumes, so that blockade or section of the vagi results in slow, deep breathing because inspiration continues to larger tidal volumes and longer inspiration times. In humans, however, the inflation reflex is weak, and difficult to demonstrate except at high lung volumes.[41] It is thought that the stretch receptors provide information to the central respiratory controller that enables a judgment to be made of the effectiveness of respiratory muscle activity. Such information may be used for adjustment of the breathing pattern in response to altered loading of the respiratory muscles.[8]

Although the level of ventilation required for metabolic gas exchange can be achieved by several different combinations of tidal volume and respiratory rate, there is a particular combination that will result in minimum work.[42] Stretch receptor information may help to determine this combination. In addition, stretch receptor information may also be sensed consciously, providing information with regard to lung volume and pulmonary ventilation. A discrepancy between the level of ventilation demanded by the central controller (which can also be sensed) and the actual pulmonary ventilation achieved is thought to produce the sensation of dyspnea.[43]

Chemoreflex Control of Breathing

General Organization

The chemoreflex control of breathing is based on a negative feedback loop (Fig. 78-7). When the central and

peripheral chemoreceptors sense an increase in $[H^+]$, breathing is stimulated via a chemoreflex arc that includes the central nervous system, respiratory muscles, and changes in alveolar ventilation, which results in an increased elimination of CO_2 and a fall in P_{CO_2} and $[H^+]$ at the chemoreceptor sites; hence the negative feedback designation of the system. However, in addition to chemoreflex drives to breathing, another tonic drive to breathe also contributes to ventilation, independently of the chemoreflexes and not behavioral in nature. This drive reflects the "state" of the subject, and is referred to as the "waking neural drive," because it is withdrawn during sleep.

The forward part of the loop (see Fig. 78-7) relates the dependence of P_{CO_2} and P_{O_2} on ventilation as the pulmonary gas exchange controls the elimination of CO_2 and uptake of O_2. Therefore, the forward part of the loop can be characterized by the relationships between ventilation and P_{CO_2} and P_{O_2}. Because P_{CO_2} is the major factor controlling the $[H^+]$ sensed by the chemoreceptors, we concentrate on that relationship. The alveolar air equation states that the product of ventilation and alveolar P_{CO_2} is proportional to the amount of carbon dioxide eliminated; hence, in any steady metabolic state, P_{CO_2} depends on carbon dioxide production divided by ventilation. This relationship, when graphed, has the geometric shape of a rectangular hyperbola, and is therefore referred to as the *metabolic hyperbola.* The feedback part of the loop is the increase in pulmonary ventilation in response to stimulation of the chemoreceptors by $[H^+]$ and is referred to as a *chemoreflex.* There are two, central and peripheral, which are defined by the location of their sensors.

Central Chemoreflex

The central chemoreceptors are located in the medulla (near the ventrolateral surface and scattered within the brain tissue) and respond to the $[H^+]$ of their local environment.[44] They are often thought of as CO_2 receptors because central $[H^+]$ is directly dependent on the P_{CO_2} of chemoreceptor tissue. Two factors complicate the physiology of the central chemoreceptors. First, the blood-brain barrier to polar solutes prevents changes in arterial $[H^+]$ from reaching the central environment, whereas carbon dioxide passes freely across the barrier. As a result, central $[H^+]$ may differ from arterial $[H^+]$. The central chemoreceptors are therefore somewhat isolated from arterial acid-base disturbances, except as they involve changes in arterial P_{CO_2}. Indeed, control of central acid-base status to keep central $[H^+]$ at normal values may result in differences in the relation between P_{CO_2} and central $[H^+]$ that produce shifts in the central chemoreflex ventilatory response to CO_2.[1]

Second, because the central chemoreceptors are in brain tissue, they are relatively slow in responding even to changes in P_{CO_2} in arterial blood, so the time constant for the central chemoreceptor response to a change in alveolar P_{CO_2} is about 100 seconds; hence, it takes 5 minutes (three time constants) for the system to respond fully to changes in inspired CO_2. Furthermore, increases in cerebral blood flow in response to increases in arterial P_{CO_2} will affect the relation between arterial P_{CO_2} and central chemoreceptor P_{CO_2}. If cerebral blood flow increases markedly with P_{CO_2}, the difference between central chemoreceptor P_{CO_2} and arterial P_{CO_2} declines as arterial P_{CO_2} increases. Measuring the ventilatory response of the central chemoreflex using a rebreathing technique, which measures only the central chemoreflex ventilatory response, may therefore differ from that using a steady-state technique, which measures both the central chemoreflex ventilatory response and the effect of the cerebral blood flow response.[45] The drive to breathe from the central chemoreceptors increases linearly with $[H^+]$ (or P_{CO_2}) above a chemoreceptor threshold, and the slope of this response is its sensitivity. The central chemoreflex response to any particular P_{CO_2} is therefore determined by both its sensitivity and its threshold (Fig. 78-8A).

Peripheral Chemoreflex

The peripheral chemoreceptors, located in the carotid bodies at the bifurcation of the carotid arteries, "taste" the blood approaching the brain. Signals from the receptors are sent to the respiratory controller in the medulla via the carotid sinus nerve (a branch of the glossopharyngeal or IXth cranial nerve).[46] The peripheral chemoreceptors respond to both the $[H^+]$ and the P_{O_2} of arterial blood, such that, in response to hypoxia, the sensitivity of the chemoreceptor response to $[H^+]$ or P_{CO_2} is increased (see Fig. 78-8B). Thus, the receptors are maximally stimulated by a simultaneous increase in $[H^+]$ and decrease in P_{O_2}—in other words, by asphyxia. Like the central chemoreflex, the drive to breathe from peripheral chemoreceptors increases linearly with $[H^+]$ (or P_{CO_2}) above a chemoreceptor threshold, with the slope of the response representing its sensitivity. Thus, the peripheral chemoreflex response to any particular P_{CO_2} is determined by both its sensitivity and its threshold. However, for the peripheral chemoreceptors, the sensitivity of the response also depends on the P_{O_2}, such that hypoxia increases the P_{CO_2} sensitivity markedly, and hyperoxia decreases it almost to zero.

The peripheral chemoreceptors have traditionally been considered to be primarily hypoxia sensors. Although correct in one sense, this notion is somewhat misleading as it implies an independent drive to breathe associated with hypoxia. Although the peripheral chemoreceptors do sense hypoxia, the only effect of hypoxia acutely (as noted previously) is to increase the sensitivity of the chemoreceptors to $[H^+]$ (or P_{CO_2}). This feature of the peripheral chemoreflex has two important clinical implications: if the P_{O_2} is high, there is little (if any) peripheral chemoreflex response to P_{CO_2}; and if the P_{CO_2} is low (and therefore below the ventilatory recruitment threshold), there is little (if any) peripheral chemoreflex response to hypoxia. However, in the presence of prolonged continuous or intermitted hypoxia, the chemoreflex may undergo modifications.[47]

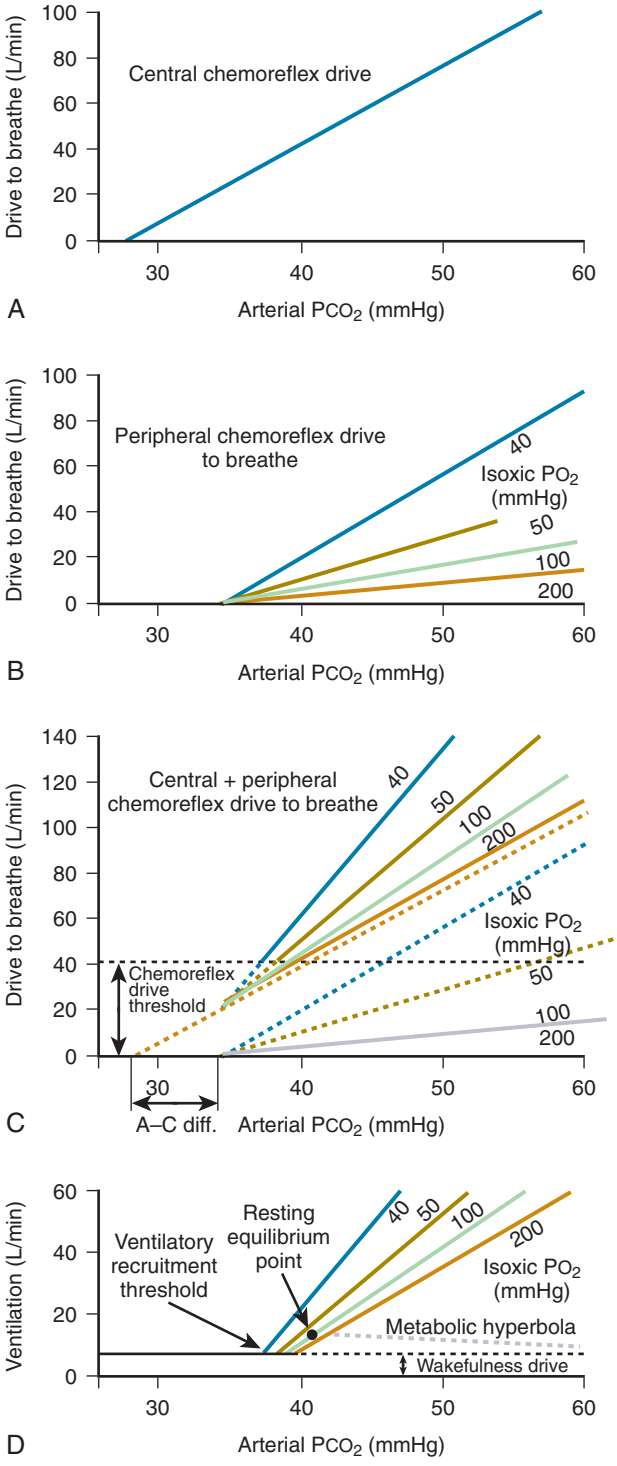


FIGURE 78-8 ■ A graphic solution for the negative feedback chemoreflex control of breathing. **A,** The central chemoreflex contribution to ventilatory drive, which depends entirely on medullary P_{CO_2} (via $[H^+]$). Note that the chemoreceptor threshold P_{CO_2}, when plotted against arterial P_{CO_2}, is less than that for the peripheral chemoreceptors because of the difference between the arterial P_{CO_2} and central chemoreceptor P_{CO_2} (A–C diff.). This arterial-to-central P_{CO_2} difference is affected by cerebral blood flow, itself responsive to changes in arterial P_{CO_2}. **B,** The peripheral chemoreflex contribution to ventilatory drive, which depends on P_{CO_2} (via $[H^+]$) and whose sensitivity varies with P_{O_2}. **C,** The central and peripheral ventilatory drives (*dotted lines*) are added to provide the total chemoreflex drive to breathe but only increase ventilation once a threshold is exceeded (*solid lines*). **D,** Finally, the chemoreflex drive to breathe is added to the wakefulness drive to breathe. The chemoreflex control of ventilation, dependent on both P_{CO_2} and P_{O_2}, is therefore shown as a series of isoxic lines. Below the threshold, ventilation is driven by the waking neural drive (*dotted line*). The intersection of the control lines with the metabolic hyperbola (*dashed line*) defines the equilibrium point of the forward and feedback components of the control system, and the resting ventilation and P_{CO_2}.

Chemoreflex Control System

The central and peripheral chemoreceptor drives to breathe summate to provide the chemoreflex drive to breathe, but do not affect pulmonary ventilation until the total ventilatory drive (neural signals from the chemoreceptors) exceeds a threshold, called the *drive threshold.* Thus, an increase in P_{CO_2} does not increase ventilation until a threshold P_{CO_2} has been exceeded, referred to as the *ventilatory recruitment threshold.* Above the ventilatory recruitment threshold, the ventilatory response to P_{CO_2} is usually linear, with a slope (sensitivity) varying with P_{O_2} (see Fig. 78-8C).[45] When P_{O_2} is high, the ventilatory response to carbon dioxide is due almost entirely to the central chemoreflex. When P_{CO_2} is below the ventilatory recruitment threshold, ventilation is main-

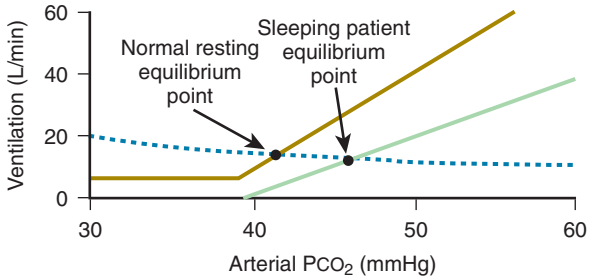


FIGURE 78-9 ■ An illustration of the use of the graphic approach to the chemoreflex control of breathing. The *dashed blue line* shows the metabolic hyperbola, the *brown line* shows the normal waking neural and chemoreflex drives to breathe, and the *pale green line* shows the drive to breathe in a sleeping patient with supplemental oxygen recovering from anesthesia. The intersection of the metabolic hyperbola and the chemoreflex drive shows the resting equilibrium ventilation and arterial P_{CO_2}, and illustrates the large increase in arterial P_{CO_2} for little decrease in ventilation that occurs during sleep.

tained above zero by the waking neural drive (see Fig. 78-8D). However, when this drive is lost during sleep, a P_{CO_2} below the ventilatory recruitment threshold results in apnea (see Chapter 79).

The graphic representation of the chemoreflex control of breathing is useful for predicting ventilation and P_{CO_2} under a variety of conditions. Figure 78-9 shows one example, that of a sleeping patient recovering from anesthesia and breathing supplemental oxygen. In this case the waking neural drive is absent, the peripheral chemoreflex drive is minimal because the P_{O_2} is high, and the central chemoreflex sensitivity is depressed by the anesthesia. As a result, the patient is operating on the flat portion of the metabolic hyperbola, and, under these conditions, a small decrease in ventilation results in a large increase in P_{CO_2}.

Stability

The stability of the chemoreflex control system is governed by the sensitivity or gain of the entire control loop, both forward and feedback portions (see Fig. 78-7). Increases in loop gain are associated with instability.[48] As the anesthetized patient in Figure 78-9 illustrates, moving the equilibrium point to increasing P_{CO_2} increases the ability of ventilation to change P_{CO_2} (i.e., the sensitivity or gain of the forward part of the loop is increased). However, at the same time the chemoreflex sensitivity (the feedback portion of the loop) has decreased in the sleeping patient, so overall the loop gain, which is the combination of the forward and feedback gains, is relatively unchanged.[49] The effect of cerebral blood flow control by arterial P_{CO_2} should also be considered; as P_{CO_2} increases, cerebral blood flow also increases, washing out CO_2 from brain tissue and reducing the stimulus to the central chemoreceptors. A reduction in the sensitivity of cerebral blood flow to arterial P_{CO_2} therefore increases the overall sensitivity of the central chemoreflex response to changes in arterial P_{CO_2}.[50]

HYPOVENTILATION SYNDROMES

General Principles and Diagnostic Approach

Pathogenesis

Alveolar hypoventilation exists when arterial P_{CO_2} increases above the normal range of 37 to 43 mm Hg. In clinically important hypoventilation syndromes, arterial P_{CO_2} is 45 mm Hg or higher and typically ranges from 50 to 70 mm Hg.[51] Numerous disease entities can result in chronic alveolar hypoventilation (Table 78-1), but in all cases the underlying mechanism involves a defect in either the sensors or the integrating neurons of the metabolic (automatic) respiratory control system or in the effector organs of breathing (i.e., the neuromuscular system or the ventilatory apparatus) (Table 78-2).

TABLE 78-1. Classification of Disorders Associated with Chronic Alveolar Hypoventilation

DISORDERS OF CHEMOSENSITIVITY
Carotid body dysfunction, trauma[136]
Prolonged hypoxia[137,138]
Metabolic alkalosis[139]

DISORDERS OF BRAIN-STEM INTEGRATING AND RHYTHM-GENERATING NETWORKS AND BRAIN-STEM MOTOR NEURONS
Bulbar poliomyelitis, encephalitis[140,141]
Infarction[78,142]
Neoplasms[143]
Sarcoidosis[144]
Demyelinating disorders[145]
Chronic drug administration[146]
Primary alveolar hypoventilation syndrome[147–149]

DISORDERS OF SPINAL CORD, PERIPHERAL NERVES, AND RESPIRATORY MUSCLES
Poliomyelitis[77,150,151]
Motor neuron disease[55,60,152,153]
Peripheral neuropathy[154]
Myasthenia gravis[150,155]
Muscular dystrophy[150,155–158]
Chronic myopathy[150,155–157]

DISORDERS OF CHEST WALL STRUCTURE
Obesity-hypoventilation syndrome[104,159–161]
Kyphoscoliosis[162]
Fibrothorax[162]
Post-thoracoplasty[162]
Ankylosing spondylitis[162]

DISORDERS OF LUNGS AND AIRWAYS
Chronic obstructive pulmonary disease (see Chapter 39)
Cystic fibrosis (see Chapter 41)
Laryngeal and tracheal stenosis[163,164] (see Chapter 43)
Obstructive sleep apnea syndrome (see Chapter 79)

TABLE 78-2. Mechanisms Underlying Chronic Alveolar Hypoventilation

Mechanisms Involved	Site or Type of Defect	Major Distinguishing Features
Sensors	Metabolic alkalosis	Alkaline pH
	Peripheral chemoreceptors	Impaired response to hypoxia
	Central chemoreceptors	Impaired response to hyperoxic hypercapnia
Controller	Brain-stem respiratory neurons or networks	Impaired chemoresponses
		Sleep-induced hypoventilation
		Normal ventilatory mechanics
Effectors	Neuromuscular apparatus	Reduced maximal respiratory pressures
	Ventilatory apparatus	Impaired ventilatory mechanics

Defects in the metabolic control system result in hypoventilation because abnormalities in blood gases and cerebral acid-base status are not sensed or, if sensed, do not produce an appropriate change in motor output of the medullary respiratory neurons. Patients with such defects fail to breathe normally in response to metabolic respiratory stimuli, but because the behavioral control system, respiratory motor pathways, and ventilatory apparatus are intact, they are capable of voluntarily driving respiration. As a result, patients with defects in the metabolic control system typically demonstrate normal ventilatory mechanics, but they have impaired responses to metabolic respiratory stimuli and often hypoventilate severely during sleep, when ventilation is critically dependent on the metabolic control system.[52]

As a result of chronic hypoventilation, such patients have a primary respiratory acidosis leading to a secondary increase in extracellular bicarbonate concentration.[53] In contrast, patients with a primary metabolic alkalosis may develop secondary hypoventilation as a compensatory response. This type of hypoventilation represents not a defect in respiratory control but rather an appropriate response of the metabolic control system to a disturbance in acid-base status. It can be said that patients with metabolic alkalosis "shouldn't" breathe, in contrast to those with control defects, who "won't" breathe, and those with mechanical defects, who "can't" breathe. However, the degree of hypoventilation that develops in response to metabolic alkalosis depends on several factors, including associated electrolyte disturbances and the sensitivity of the peripheral chemoreceptors to the accompanying hypoxia.[54] Thus, patients with weak hypoxic responsiveness tend to hypoventilate more than do patients with brisk hypoxic responsiveness.

Chronic hypoventilation resulting from defects in effector elements of the respiratory system (see Table 78-2) represents disturbances of ventilatory motor and mechanical function that do not in themselves mean that the metabolic control system is defective. Because the same effector elements also serve the behavioral control system, such patients are usually unable to breathe normally even when consciously attempting to do so. Hence, such defects are characterized either by reductions in the maximum respiratory pressures that can be generated voluntarily or by impairment of lung volumes and flow rates.[55] In the presence of such neural or mechanical defects, coexisting disturbances in respiratory control are often difficult to identify, because the neuromuscular or mechanical defect may preclude normal responses to chemical respiratory stimuli even when the control system is intact.

Physiologic and Clinical Consequences

Regardless of the underlying cause, the fundamental disturbance in all hypoventilation syndromes is a global reduction in the level of alveolar ventilation, resulting in an increase in alveolar P_{CO_2} and therefore in arterial P_{CO_2}. Because of the inverse relationship between alveolar P_{CO_2} and P_{O_2} defined by the alveolar air equation, the rise in alveolar P_{CO_2} produces an obligatory decrease in alveolar P_{O_2}, resulting in hypoxemia (Fig. 78-10). These disturbances are typically magnified during sleep because of further reductions in alveolar ventilation secondary to a reduction in overall respiratory drive (see Chapter 79).

The primary disturbances produced by alveolar hypoventilation lead to a series of secondary physiologic responses that in turn produce the clinical features of chronic hypoventilation (see Fig. 78-10). These features consist predominantly of hematologic, cardiovascular, and neurologic manifestations. There is considerable debate as to whether the cardiovascular and neurologic features of hypoventilation result from the chronic hypercapnia or from the chronic hypoxemia, but it appears likely that both disturbances play a role. For example, alleviation of hypoxemia alone by the administration of supplemental oxygen reverses the polycythemia and may attenuate the severity of pulmonary hypertension, but supplemental oxygen can also aggravate the degree of hypercapnia and the severity of neurologic complaints.[51]

Laboratory Assessment

The investigation of the patient with chronic alveolar hypoventilation involves the use of a series of laboratory tests that examine one or more components of the respiratory system (Fig. 78-11). Analysis of the pattern of test results usually enables localization of the site of the underlying defect to the metabolic control system, the respiratory neuromuscular system, or the ventilatory apparatus.

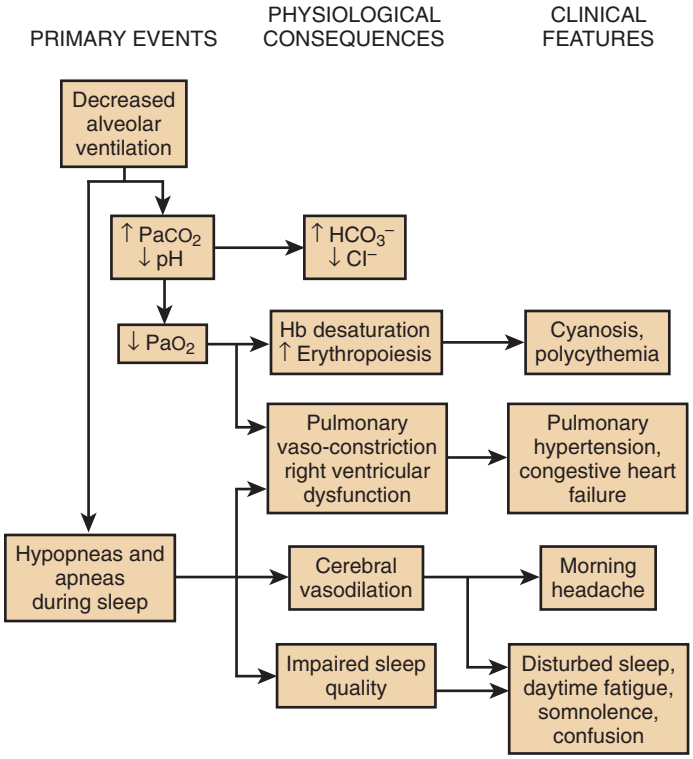
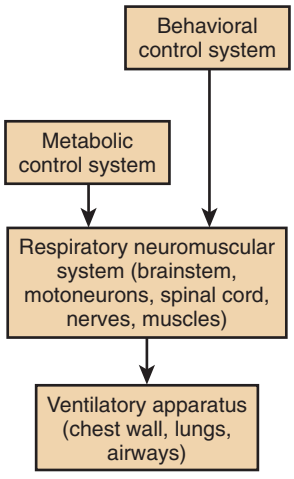


FIGURE 78-10 ■ Schema showing the primary events, physiologic responses, and clinical features resulting from alveolar hypoventilation. $Paco_2$, arterial Pco_2; Pao_2, arterial Po_2.



A-a PO2	Resistance and compliance of lungs, chest wall	Volumes, flows	Maximal inspiratory, expiratory pressures	Responses to CO_2, hypoxia		Sleep studies
				Ventilatory	P0.1 EMGdia	
Normal	Normal	May be abnormal	May be abnormal	Normal	Normal	Normal
Normal	Normal	Normal	Normal	↓	↓	Central apnea, hypopneas
Normal	Normal	↓	↓	↓	↓	Central apnea, hypopneas
Abnormal	Abnormal	↓	Normal	↓	Normal	Variable

FIGURE 78-11 ■ Pattern of laboratory test results in alveolar hypoventilation syndromes, based on the site of defect. (A-a)Po_2, alveolar-arterial Po_2 difference; EMGdia, diaphragmatic electromyogram; P0.1, pressure generated in first 1/10th second after airway occlusion.

Defects in Metabolic Control. The patient with a defect in the chemoreceptors or medullary integrating and premotor neurons that constitute the metabolic control system typically demonstrates impaired ventilatory responses to hypercapnia, hypoxia, asphyxia, and often exercise.[56] Because central drive is impaired, occlusion pressure responses and diaphragm electromyographic (EMG) responses to chemical stimuli are also diminished, although few systematic measurements have been reported in such patients. Furthermore,

during sleep such patients tend to hypoventilate even more than while awake, as a result of the loss of the stimulatory effect of wakefulness on breathing, and central apneas during sleep may be frequent.[51,57,58] In contrast, in the absence of intrinsic bronchopulmonary or chest wall disease, tests of respiratory system resistance and compliance give normal results and the alveolar-arterial P_{O_2} difference is not widened. Because the behavioral control system and neuromuscular apparatus are intact, such patients can usually hyperventilate voluntarily and can generate normal lung volumes and flow rates.[59] Similarly, tests of respiratory muscle activation and strength yield normal results, including normal maximum inspiratory and expiratory mouth pressures generated against an occluded airway, normal transdiaphragmatic pressure, and normal diaphragmatic EMG responses.

Neuromuscular Defects. Patients with defects in the spinal cord, respiratory nerves, or respiratory muscles resemble patients with disturbances in the control system, in that the former also have impaired ventilatory, occlusion pressure, and EMG responses to chemical respiratory stimuli.[60] In addition, however, patients with neuromuscular disease are unable to generate normal lung volumes (particularly total lung capacity), flow rates (particularly peak flow and maximum voluntary ventilation), and static respiratory pressures.[55]

Ventilatory Apparatus Defects. Patients with intrinsic disease of the lungs, airways, or chest wall demonstrate abnormalities in the values of respiratory resistance or compliance. Because of these abnormalities, values of lung volumes and flow rates are typically abnormal, and ventilatory responses to chemical respiratory stimuli are impaired. In contrast, because the respiratory neuromuscular system is intact in such patients, static tests of respiratory muscle strength and activity, which are not influenced by the resistance or compliance of the respiratory system, usually yield normal results.[61] Thus, maximum inspiratory and expiratory pressures, transdiaphragmatic pressure, and occlusion pressure and diaphragm EMG responses to hypercapnia or hypoxia may be normal.[62,63]

Primary Alveolar Hypoventilation

Primary alveolar hypoventilation is a disorder of unknown origin characterized by chronic hypercapnia and hypoxemia in the absence of identifiable neurologic disease, respiratory muscle weakness, or mechanical ventilatory defects. The disorder is considered to occur from a failure in the metabolic (or automatic) respiratory control system, which results in a diminished central respiratory drive. In most patients, hypoventilation is more severe during sleep, and apneic periods are common. In contrast, because the behavioral respiratory control system is intact, patients with primary alveolar hypoventilation are able to hyperventilate voluntarily and to reduce arterial P_{CO_2} to normal levels.

The clinical syndrome of primary alveolar hypoventilation in its isolated form is a relatively rare disease. However, an element of primary alveolar hypoventilation may play a role in several clinical disorders of the respiratory neuromuscular and ventilatory systems in which the degree of alveolar hypoventilation is out of keeping with the magnitude of underlying neuromuscular or mechanical defect. Such disorders include diseases of the respiratory muscles,[64] the obesity-hypoventilation syndrome,[65] and the "blue bloater" chronic obstructive pulmonary disease syndrome.[63] In these disorders, the impairment of the respiratory muscles or the increased mechanical impedance to breathing may unmask a weakness in central respiratory drive,[66] analogous to the weakness that can be uncovered in some otherwise healthy subjects by the imposition of mechanical ventilatory loads.[67] However, whether the underlying cause of decreased respiratory drive in such patients is the same as in patients with isolated primary alveolar hypoventilation is not known.

Pathogenesis

Primary alveolar hypoventilation is thought to result from a failure of the chemoreceptors or of the medullary neuronal networks that make up the metabolic respiratory control system. As such, it represents a pure disease of the respiratory controller rather than of the respiratory muscles or mechanical ventilatory apparatus. In the majority of patients, this interpretation is based on the clinical and laboratory features of the illness and not on the demonstration of specific lesions in any component of the metabolic control system. In fact, autopsy studies have reported neuropathologic findings in extremely few patients and have found either no abnormalities or only nonspecific lesions in the area of the medullary respiratory neurons.[2] However, studies in both animals and humans indicate an important role for genetic and metabolic factors in the pathogenesis of hypoventilation syndromes,[68] and specific mutations in the *PHOX2B* gene have now been identified in neonates and adults with the disorder.[69] In contrast to primary alveolar hypoventilation, lesions involving the medullary reticular formation have been demonstrated in several patients with central alveolar hypoventilation secondary to known neurologic disease.[70] In some infants who died of sudden infant death syndrome, which may represent a primary alveolar hypoventilation disorder, structural abnormalities of the carotid body chemoreceptors have been demonstrated.[71] Removal of the carotid bodies in experimental animals results in a chronic hypoventilation syndrome that closely resembles the human disorder.[72] However, no studies of carotid body structure have been reported in patients with primary alveolar hypoventilation.

Clinical Features

Primary alveolar hypoventilation occurs in all age groups, including infancy and childhood,[52] but the majority of reported cases in adults have been in men ages 20 to 50 years.[57] Occasional familial cases have been described.[73] In most patients, the development of symptoms is insidious, and the disease is often overlooked because

the patient is typically free of respiratory complaints. In particular, dyspnea is uncommon in this condition, in contrast to other hypoventilation disorders, and the arterial P_{CO_2} may be relatively normal when measured during wakefulness. Often, the diagnosis is first suspected only when the patient develops severe respiratory depression after conventional doses of anesthesia or sedation.

The common presenting complaints of patients with primary alveolar hypoventilation are lethargy, fatigue, daytime somnolence, disturbed sleep, and morning headache (see Fig. 78-10). Cyanosis and secondary polycythemia are also frequent. As the severity of chronic hypoventilation and hypoxemia increases, patients develop clinical evidence of pulmonary hypertension, right ventricular hypertrophy, and, eventually, congestive cardiac failure. The congestive heart failure is due to right ventricular dysfunction and is manifested by elevation of the jugular venous pressure, hepatomegaly, and peripheral edema.

Diagnosis

The key diagnostic findings in primary alveolar hypoventilation are hypercapnia, hypoxemia, and chronic respiratory acidosis in the absence of respiratory muscle weakness or mechanical ventilatory defects (see Fig. 78-11). The degree of blood gas abnormality is often surprising, in that arterial P_{CO_2} levels of 50 to 70 mm Hg and arterial P_{O_2} levels of 40 to 50 mm Hg may be associated with relatively mild symptoms. Typically, patients can voluntarily hyperventilate and reduce the arterial P_{CO_2} to normal or even to hypocapnic levels. As a result, hypercapnia may not be detected in a single arterial blood sample, but the presence of elevated serum bicarbonate should draw attention to the underlying chronic disturbance. The alveolar-arterial P_{O_2} difference is usually normal but may be elevated, presumably because of areas of low ventilation-perfusion matching or microatelectasis, although the mechanism has not been clearly defined.

In addition to normal lung volumes and airflow rates, patients with primary alveolar hypoventilation typically maintain a normal maximum voluntary ventilation and normal maximum inspiratory and expiratory airway pressures (see Fig. 78-11). In contrast, the ventilatory and occlusion pressure responses to hypercapnia are reduced or absent, and the responses to hypoxia are often diminished.[59] In most patients, some hypoxic chemosensitivity persists, in that inhalation of high oxygen concentrations further reduces the level of ventilation.[74] Paradoxically, in a few patients, supplemental oxygen produces an increase in ventilation, which suggests that chronic hypoxia may have contributed to central respiratory depression.[59] In the typical patient, the ventilatory response to exercise is also abnormal, with further increases in arterial P_{CO_2} and decreases in arterial P_{O_2}, in keeping with a failure of metabolic respiratory control. Breath-holding time may be markedly prolonged, without any accompanying sensation of dyspnea.[75]

Patients with primary alveolar hypoventilation are generally able to maintain rhythmic breathing during wakefulness, although at a lower-than-normal level of ventilation, because of the stimulatory effect of brainstem reticular activation on the respiratory neurons.[52,76] During sleep, however, breathing is critically dependent on the metabolic respiratory control system.[76] Hence, such patients are apt to cease rhythmic breathing during sleep. Sleep studies in patients with alveolar hypoventilation usually demonstrate a further deterioration in ventilation, with frequent episodes of central hypopnea or outright apnea followed by arousal or awakening. These sleep-related events presumably account for the clinical complaints of disturbed sleep and morning headache; they contribute to daytime fatigue, lethargy, and somnolence; and they play a role in the development of polycythemia and pulmonary hypertension. Support for this concept is derived from the fact that the daytime symptoms of primary alveolar hypoventilation, as well as the polycythemia and pulmonary hypertension, can be alleviated by improving nocturnal ventilation alone.[59]

Differential Diagnosis

Primary alveolar hypoventilation, in which there is no other identifiable neurologic disease, must be distinguished from central alveolar hypoventilation secondary to underlying neurologic disease (see Table 78-1), although the clinical and laboratory features of the two disorders are often very similar. This distinction requires a careful neurologic history and examination for evidence of other brain-stem or autonomic disturbances. The classic example of chronic alveolar hypoventilation secondary to brain-stem disease is that which follows bulbar poliomyelitis or encephalitis.[77] The disorder has also been reported in association with brain-stem vascular insufficiency or stroke, infections, neoplasms, sarcoidosis, multiple sclerosis, and autonomic insufficiency syndromes.[78] These secondary causes of central alveolar hypoventilation are usually signified by the other features of the underlying disease process and by the fact that the patient may not be able to increase the level of ventilation voluntarily. A form of subacute central alveolar hypoventilation that follows cervical spinal surgery has also been described.[79]

Primary alveolar hypoventilation can be confused with chronic disorders of the respiratory neuromuscular system (see Chapter 87) that are often unrecognized clinically (see Table 78-1). Included in this group of disorders is the postpolio syndrome, a form of chronic respiratory insufficiency that typically develops 20 to 30 years after recovery from poliomyelitis.[77] In addition to the history of polio many years earlier, such patients demonstrate weakness of the respiratory muscles (see Fig. 78-11), and many have developed kyphoscoliosis. Motoneuron disease, an idiopathic degeneration of motoneurons from anterior horn cells to cortex, can manifest as chronic respiratory failure, particularly when the phrenic motoneurons are involved.[80] The disease typically occurs in men ages 50 to 70 years and is distinguished from primary alveolar hypoventilation by the presence of muscle weakness and atrophy, often with fasciculation and spasticity. Laboratory investigation

reveals a pattern of test results typical of respiratory neuromuscular disease (see Fig. 78-11). Furthermore, the abnormalities are progressive, as is the clinical course of the disease; death, from respiratory complications, usually occurs 2 to 5 years after onset of the disease.

Unilateral diaphragmatic paralysis can result from phrenic nerve trauma, inflammation, or neoplastic infiltration, but in most cases the cause is unknown.[81] Patients with unilateral diaphragmatic paralysis are often asymptomatic and do not usually hypoventilate. Bilateral diaphragm weakness or paralysis can result from phrenic neuropathy or from intrinsic diaphragmatic disease, including muscular dystrophies, polymyositis, and acid-maltase deficiency.[82] Bilateral diaphragmatic disease may lead to severe chronic alveolar hypoventilation. Distinguishing features include the presence of orthopnea, paradoxical movement of the abdomen in the supine posture, deterioration in lung volumes and in arterial blood gas values in the supine posture, rapid deterioration in ventilation during a maximum voluntary ventilation maneuver, and reduction of the maximum inspiratory pressures that can be generated against an occluded airway. Transdiaphragmatic pressures, calculated from simultaneous measurement of esophageal and gastric pressures, are reduced or absent, and the EMG response of the diaphragm, recorded by an esophageal electrode, reveals a reduction in diaphragm discharge in response to transcutaneous phrenic nerve stimulation in the neck.[82]

Management

Patients with primary alveolar hypoventilation must be cautioned against the use of sedative medications, which may readily induce acute respiratory failure. Respiratory stimulants may be useful in some patients. Several pharmacologic agents, including methylxanthines and analeptics, have been used to treat patients with primary alveolar hypoventilation (Table 78-3), with variable but generally disappointing results. Long-term administration of progesterone has been beneficial in some patients, particularly those with mechanical ventilatory defects and an element of reduced respiratory drive, such as the obesity-hypoventilation syndrome and hypercapnic obstructive lung disease.[83] Acetazolamide is effective in increasing respiratory drive in patients with primary metabolic alkalosis superimposed on chronic carbon dioxide retention[84] but is not indicated in pure respiratory acidosis. A few patients with primary alveolar hypoventilation have responded favorably to long-term nocturnal oxygen administration, which suggests that cerebral hypoxia during sleep was aggravating the hypoventilation disorder.[59] In the majority of patients, however, supplemental oxygen aggravates the degree of nocturnal hypoventilation and further increases arterial carbon dioxide levels by removing hypoxic ventilatory drive.

In most patients with primary alveolar hypoventilation, neuromuscular disease, or the obesity-hypoventilation syndrome, mechanical ventilatory assistance is required for effective management (see Table 78-3). Noninvasive positive-pressure ventilation, often delivered through a nasal mask, is currently the preferred method of treatment,[85] but diaphragmatic pacing by electrophrenic stimulation can also be very effective.[86] The administration of such treatment only during sleep generally produces dramatic clinical improvement, with alleviation of daytime symptoms; reversal of daytime hypercapnia, polycythemia, and pulmonary hypertension; and prolongation of survival.[85]

TABLE 78-3. Management of Primary Alveolar Hypoventilation

Pharmacologic techniques	Respiratory stimulant drugs (progesterone, acetazolamide)
	Supplemental oxygen
Mechanical techniques	Rocking bed
	Negative-pressure ventilator
	Positive-pressure ventilator
	Phrenic nerve stimulation

HYPERVENTILATION SYNDROMES

Introduction

Hyperventilation refers to an increase in the rate of alveolar ventilation that is excessive for the rate of metabolic carbon dioxide production, resulting in a decrease in arterial P_{CO_2} to below the normal range of 37 to 43 mm Hg. Hyperventilation should be distinguished from tachypnea, an increase in respiratory frequency, and from hyperpnea, an increase in minute volume of ventilation. Neither of these latter conditions derives from nor implies a change in arterial P_{CO_2}. Hyperventilation is often associated with dyspnea, but not all patients with hyperventilation complain of shortness of breath; conversely, patients with dyspnea need not be hyperventilating.

Pathogenesis

Alveolar hyperventilation arises from excessive ventilatory drive that is mediated through either the behavioral or metabolic control systems (Fig. 78-12). Many pathophysiologic conditions and diseases can result in an increase in respiratory drive (Table 78-4). In some cases, the mechanism involved is well understood (e.g., hypoxemic sensitization of the peripheral chemoreceptors); in other cases, several potential mechanisms have been postulated but as yet have not been clearly established (e.g., hyperventilation associated with hepatic failure). Therefore, hyperventilation syndromes are best considered through the use of a clinical rather than mechanistic approach (see Table 78-4).

Hypoxemia

In most clinical settings, hypoxemia is a potent ventilatory stimulus and results in hyperventilation by virtue of

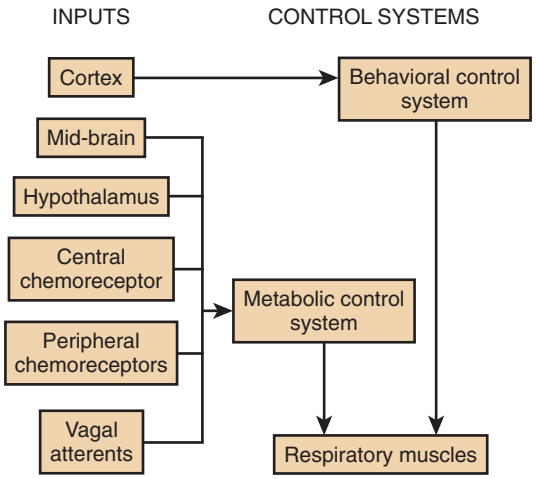


FIGURE 78-12 ■ A schematic diagram showing the main elements of the metabolic and behavioral respiratory control systems that are involved in alveolar hyperventilation. Disorders within sites affecting the metabolic control system include the midbrain, hypothalamus, central and peripheral chemoreceptors, and vagal afferents. The cortex is the site of behavioral control.

its action on the peripheral chemoreceptors (i.e., the carotid bodies). The response of minute volume of ventilation (or alveolar ventilation) to decreases in arterial P_{O_2} is not linear: it is substantially greater when arterial P_{O_2} falls below 60 mm Hg. In contrast, although the oxygen content per se of arterial blood is not the primary hypoxic stimulus of the carotid bodies, the ventilatory response to hypoxemia is relatively linear with regard to decreases in arterial oxygen saturation.[87] However, the magnitude of response is attenuated by reduced levels of arterial P_{CO_2} and increased levels of arterial pH (see "Control of Breathing" section). The hyperventilation associated with hypoxia can be dramatic, particularly in persons with normal ventilatory mechanics. For example, at the summit of Mount Everest, where arterial P_{O_2} was estimated to be 27 mm Hg, alveolar P_{CO_2} was reduced to 7.5 mm Hg.[88] Clinically, however, impaired mechanical properties of the chest wall or lungs often attenuate the degree of alveolar hyperventilation induced by hypoxia. Conversely, in many pulmonary disorders that produce hypoxemia, the associated hypocapnia may not be due to the hypoxia and persists even when the hypoxia is alleviated with supplemental oxygen.[89]

The degree of alveolar hyperventilation induced by hypoxia is highly variable; the variation is determined, at least in part, by genetic factors.[90] In addition, there also appears to be a temporal influence that may, in part, reflect the effects of hypoxia on cerebral blood flow, metabolism, and release of excitatory and inhibitory neuromodulators, all of which secondarily affect breathing.[91] Typically, the ventilatory response to acute hypoxia is initially brisk but then decreases after several minutes,[52] only to increase again after 12 to 24 hours as the longer term process of respiratory acclimatization comes into play.[47] However, sustained hypoxemia of many years' duration, as occurs in long-time residents at high altitudes and in patients with cyanotic congenital heart disease, is associated with considerable attenuation of hypoxic ventilatory drive.[92]

TABLE 78-4. Hyperventilation Syndromes

HYPOXEMIA
High altitude
Pulmonary disease
Cardiac shunts

PULMONARY DISORDERS
Pneumonia
Interstitial pneumonitis, fibrosis, edema
Pulmonary embolic or vascular disease
Bronchial asthma
Pneumothorax
Chest wall disorders

CARDIOVASCULAR DISORDERS
Congestive heart failure
Hypotension

METABOLIC DISORDERS
Acidosis (diabetic, renal, lactic)
Hyperthyroidism
Hepatic failure

NEUROLOGIC AND PSYCHOGENIC DISORDERS
Psychogenic or anxiety hyperventilation
Central nervous system infection, tumors, infarction

DRUG-INDUCED
Salicylates
Methylxanthine derivatives
Beta-adrenergic agonists
Progesterone

MISCELLANEOUS
Fever, sepsis
Pain
Pregnancy

From Phillipson EA: Disorders of ventilation. *In* Fauci AS, Braunwald E, Isselbacher KJ, et al (eds): Harrison's Principles of Internal Medicine (14th ed). New York: McGraw-Hill, 1998, pp 1476–1480.

Pulmonary Disorders

One of the most common causes of hyperventilation in patients with pulmonary disease is stimulation of bronchopulmonary receptors that reflexly increase ventilatory drive and, directly or indirectly, contribute to the sensation of dyspnea (see Chapter 28). These receptors, which are sensitive to a variety of mechanical and chemical stimuli, send impulses to the central nervous system through the afferent vagus nerves, resulting in cough, bronchoconstriction, and hyperventilation (see "Control of Breathing" section). Direct evidence implicating these receptors in the alveolar hyperventilation of lung disease is derived largely from animal studies,[93,94] but there are also supportive studies in a few patients who have undergone vagal blockade.[95] Indirect support for this notion is

derived from the fact that administration of supplemental oxygen to patients with hypoxemic interstitial or pulmonary vascular disease does not necessarily abolish the hyperventilation.[96]

Stimulation of chest wall receptors may contribute to the hyperventilation that accompanies asthma, pulmonary fibrosis, and restrictive chest wall disorders.[93] The mechanisms involved have not been clearly established but are thought to include stimulation of respiratory muscle spindles and other chest wall receptors. The same mechanisms may also play a role in the pathogenesis of dyspnea in these disorders.

Cardiovascular Disorders

Patients with congestive heart failure and states of low cardiac output typically hyperventilate at rest, during exercise, and even during sleep.[97–99] The mechanisms involved probably include stimulation of pulmonary vascular and interstitial receptors as a result of pulmonary congestion.[100] In addition, low cardiac output states and hypotension stimulate breathing through the arterial baroreceptors[101] and may also stimulate breathing secondary to "stagnant hypoxia" of the carotid body chemoreceptor cells.

Metabolic Disorders

Alveolar hyperventilation is a well-described compensatory response to metabolic acidosis. Although respiratory compensation is generally effective, physiologic compensation for metabolic acidosis is not complete. For example, in a severe metabolic acidosis that reduces serum bicarbonate concentration ($[HCO_3^-]$) to 8 mEq/L, the uncompensated arterial pH would be 6.92; with hyperventilation to 20 mm Hg (a typical response), pH increases to 7.22. The degree of compensation varies among patients, depending on differences in chemosensitivity and ventilatory mechanics, but in general a decrease in $[HCO_3^-]$ of 1 mEq/L results in a compensatory decrease in arterial P_{CO_2} of about 1 mm Hg.[102] The specific mechanisms involved in the hyperventilation of metabolic acidosis are controversial, but probably include stimulation of both the peripheral and central chemoreceptors.[103] Metabolic acidosis also increases the sensitivity of the peripheral chemoreceptors to hypoxia.

Hyperthyroidism is frequently associated with hyperventilation and increased ventilatory chemoreflexes, both of which return to normal after treatment.[104] Hyperventilation is also a common feature in patients with severe liver disease.[105] Several possible mechanisms have been proposed, including increased blood levels of progesterone, ammonia, and vasoactive intestinal peptide, and increased brain levels of ammonia and glutamine, all of which may stimulate respiration.[91] In addition, patients with severe hepatocellular dysfunction or portal hypertension may develop small pulmonary arteriovenous anastomoses ("spider nevi" of the lungs) or portal-pulmonary venous shunts, resulting in hypoxemia and hyperventilation due to stimulation of the peripheral chemoreceptors.

Neurologic and Psychogenic Disorders

Psychogenic hyperventilation[106] is thought to arise from anxiety or stress, both of which act on the behavioral respiratory control system (see Fig. 78-12). Increasingly recognized in recent years have also been the hyperventilation associated with panic attacks,[107] and an idiopathic form of chronic hyperventilation whose etiology may be distinct from psychogenic hyperventilation.[108] Apart from psychogenic causes, central neurogenic hyperventilation is relatively rare. Indeed, in many patients with intracranial disturbances who are hyperventilating, the immediate cause is either pulmonary edema or hypoxemia.[109] In rare cases, however, disorders of the midbrain and hypothalamus induce hyperventilation.[109–111] In addition, patients with head trauma or intracranial hemorrhage may hyperventilate as a secondary reaction to red blood cell glycolysis and acidosis in the cerebrospinal fluid, and patients with brain-stem infiltration by tumor may hyperventilate, possibly as a result of lactic acidosis produced by the malignant cells.[109,112] In other rare cases, severe cerebrovascular insufficiency or infarction is associated with hyperventilation, possibly by interference with the inhibitory influence normally exerted by cortical structures on the brain-stem respiratory neurons.[113]

Drug-Induced Hyperventilation

Several drugs cause hyperventilation[114] by stimulating the peripheral or central chemoreceptors or by direct action on the brain-stem respiratory neurons (see Table 78-4). The acid-base disturbance resulting from salicylate overdose is biphasic, consisting of an initial primary respiratory alkalosis followed by a metabolic acidosis that induces secondary hyperventilation.[115]

Miscellaneous Causes

Fever and sepsis, even in the absence of hypotension, are commonly associated with hyperventilation, over and above any associated increase in metabolic rate.[116] The mechanisms involved are not clear, but they could include either carotid body or hypothalamic stimulation by increased temperature. Pain is also frequently accompanied by hyperventilation.[117] The mechanisms involved may include adrenergic stimulation of the peripheral and central chemoreceptors.[118] In addition, painful stimuli may act through the behavioral control system. From a practical clinical standpoint, there is often concern that a painful arterial puncture required for blood gas assessment could result in a spuriously low arterial P_{CO_2} and inappropriate diagnosis of hyperventilation. However, there is little difference in arterial P_{CO_2} between samples obtained with and without the use of local anesthetic.[119] Chronic hyperventilation is a normal feature of pregnancy and of the luteal phase of the menstrual cycle. Although hormone-mediated factors may play a role,[120] the relationship involves complex changes in the wakefulness and central chemoreflex drives to breathing and in acid-base balance.[121]

Physiologic and Clinical Features

Respiratory

Because hyperventilation involves an increase in respiratory drive, respiratory muscle effort, and minute volume of ventilation, the most frequent symptom associated with hyperventilation is dyspnea. However, there is considerable discrepancy between the degree of hyperventilation, as assessed by arterial P_{CO_2}, and the degree of dyspnea.

From a physiologic standpoint, hyperventilation is clearly beneficial in patients who are hypoxemic because the alveolar hypocapnia is associated with an increase in alveolar P_{O_2} and with a varied increase in arterial P_{O_2} (dependent on pulmonary ventilation-perfusion inhomogeneities). The relationship among these variables is governed by the alveolar air equation (see Chapter 4). This physiologic consequence of hyperventilation is clinically important in patients with hypoxemic pulmonary disease and in healthy persons at high altitude. Indeed, the successful ascent of Mount Everest without the use of supplemental oxygen was critically dependent on the increase in alveolar and arterial P_{O_2} generated by profound alveolar hyperventilation.[88]

Conversely, alveolar hyperventilation can also have detrimental respiratory effects, including a decrease in or loss of respiratory drive immediately after cessation of the hyperventilation, secondary to the low arterial and cerebral P_{CO_2}. Under these conditions, hypoxemia can develop quickly without an associated return of respiratory drive or a sensation of dyspnea, because of the persisting hypocapnia that reverses at a considerably slower rate. This sequence of events has been implicated in the deaths of healthy underwater divers who, in advance of diving, voluntarily hyperventilate to decrease alveolar P_{CO_2} and increase alveolar oxygen stores, and thereby prolong underwater breath-holding time. A less dramatic but more common clinical problem resulting from hyperventilation during wakefulness is periodic breathing during sleep, with or without associated central sleep apnea. This sequence of events gives rise to the most common type of central sleep apnea syndrome (see Chapter 79).

Blood

Respiratory alkalosis produces a leftward shift in the oxygen-hemoglobin dissociation curve (the Bohr effect), which increases loading of oxygen onto hemoglobin in the lungs but decreases release of oxygen at the tissue level. This change can be beneficial or detrimental, depending on the specific conditions. In general, the detrimental effects of impaired oxygen release at the tissues outweigh the beneficial effects of increased oxygen loading in the lungs, because even under conditions of moderate hypoxemia, hemoglobin is well saturated with oxygen without a leftward shift of the dissociation curve (e.g., at an arterial P_{O_2} of 60 mm Hg, hemoglobin is 90% saturated). However, under conditions of severe hypoxia, as at very high altitudes or in utero, the loading of oxygen onto hemoglobin becomes critical to survival, and therefore a respiratory alkalosis and the resulting leftward shift of the dissociation curve can be beneficial.

Respiratory alkalosis also results in several electrolyte shifts that are clinically important, including hypokalemia, hypophosphatemia, and decreased ionizable calcium.[122] These shifts contribute to many of the clinical features of hyperventilation, including dizziness, peripheral parasthesias, carpopedal spasm, tetany, and muscle weakness.

Cardiovascular and Cerebrovascular

The most important clinical consequences of alveolar hyperventilation are those related to vasoconstriction that is secondary to alkalemia.[123] Severe alkalemia can induce cardiac arrhythmias (possibly related to electrolyte disturbances) and cardiac ischemia, which probably results from both acute coronary vasoconstriction and the increased oxygen affinity of hemoglobin.[123,124] Alkalemia also induces intense cerebrovascular constriction that can result in dizziness, visual impairment, syncope, and seizures.[125] Acutely, every 1 mm Hg decrease in arterial P_{CO_2} reduces cerebral blood flow by 2%,[126] resulting in cerebral hypoxia, as assessed by metabolic, electroencephalographic, and corneoretinal indices and by direct measurements of cerebral P_{O_2}.[127] In patients with sickle cell disease, the degree of cerebral hypoxia may be sufficient to induce red blood cell sickling and cerebral infarction.[128] In general, the severity of cerebral vasoconstriction induced by hyperventilation decreases within hours, as the degree of cerebral alkalosis is attenuated.[125]

Diagnosis

Although hyperventilation may be suspected clinically in the presence of tachypnea or noticeable hyperpnea, the diagnosis can be confirmed only by analysis of arterial blood gases and pH. The key measurements are the arterial P_{CO_2}, a decrease in which indicates the presence of hyperventilation, and the pH, which determines whether the disorder is classified as a primary respiratory alkalosis (increased pH) or a primary metabolic acidosis (decreased pH).[102,129] However, in mixed acid-base disorders, arterial pH may not be alkalemic despite primary alveolar hyperventilation. Measurement of arterial P_{O_2} and calculation of the alveolar-arterial P_{O_2} difference is also helpful, because a widened difference suggests a pulmonary disorder as the underlying cause of the hyperventilation. The finding of a decreased [HCO_3^-] establishes the chronic nature of the disorder. In patients with suspected psychogenic hyperventilation, measurements of minute volume of ventilation and of arterial or transcutaneous P_{CO_2} during sleep can be useful because the hyperventilation may not persist during sleep.

Once the presence of alveolar hyperventilation has been established, the underlying cause can generally be identified on the basis of history, physical examination, and knowledge of coexisting medical disorders (see Table 78-4). Three disorders may not be readily apparent

clinically and frequently give rise to "unexplained hyperventilation": pulmonary vascular disease (particularly chronic or recurrent thromboembolism), psychogenic or anxiety hyperventilation,[106] and idiopathic hyperventilation.[108] However, these disorders can usually be identified and distinguished on the basis of clinical and laboratory features. Hyperventilation secondary to pulmonary vascular disease is invariably accompanied by exertional dyspnea and often by exertional presyncope and clinical signs of pulmonary arterial hypertension. In addition, such patients usually have a widened alveolar-arterial P_{O_2} difference, often have a reduced pulmonary diffusing capacity for carbon monoxide, and usually maintain their hyperventilation during exercise. In contrast, patients with psychogenic hyperventilation typically complain of the need to sigh frequently and of dyspnea at rest and not necessarily during exercise.[130] Symptoms of acute hyperventilation, including parasthesias, carpopedal spasm, and tetany, are frequent, and anxiety is often prominent.[131] Half the patients present with cardiovascular symptoms, including palpitation, tachycardia, and chest pain, and about 25% present with neurologic complaints, including light-headedness, headache, or memory impairment.[125] In contrast to pulmonary vascular disease, in psychogenic hyperventilation the alveolar-arterial P_{O_2} difference and pulmonary function tests yield normal results, and during mild to moderate exercise, the hyperventilation tends to disappear. However, during exercise, heart rate and cardiac output may be high in relation to metabolic rate. In contrast, recent studies have demonstrated that hyperventilation persists during exercise in patients with the idiopathic form of the disorder.[108]

Management

Alveolar hyperventilation can often be managed by appropriate treatment of the underlying cause (see Table 78-4). However, in the few patients in whom alkalemia is thought to be inducing acute cerebral vasoconstriction, cardiac arrhythmias or ischemia, or parasthesias and tetany, inhalation of a low concentration of carbon dioxide can provide relief.

The long-term management of patients with disabling hyperventilation related to anxiety or panic attacks can be problematic. Careful explanation of the basis of the symptoms is helpful and reassures the patient that no serious cardiac or cerebral disorder is present. Such reassurance may be sufficient to allay the patient's anxiety. If not, more intense psychotherapy or medications that relieve anxiety maybe required.[132,133] Some patients have responded well to β-adrenergic antagonists or to an exercise program,[134] and very recently, end-tidal CO_2-guided breathing therapy has been demonstrated to produce long-term reductions in ventilation and in panic disorder severity.[107]

KEY POINTS

- The respiratory chemoreflexes are the primary building block of the metabolic control system.
- The voluntary control of breathing constitutes the behavioral control system.
- The behavioral and metabolic control systems compete for the use of the respiratory muscles.
- Automatic respiratory rhythm is generated in the medulla.
- Alveolar hypoventilation can result from numerous disease entities but is ultimately attributable to defects in the metabolic respiratory control system, the respiratory neuromuscular system, or the ventilatory apparatus. Detailed clinical and laboratory investigations can generally distinguish among these underlying mechanisms and locate the site of the defect.
- In most patients, alveolar hypoventilation is secondary to obstructive airway disease, mechanical chest wall disturbances, neurologic disease affecting the brain stem or spinal cord, or respiratory muscle weakness. In a small percentage of cases, no underlying cause can be found, and such patients are said to have primary alveolar hypoventilation, which is considered to represent a failure of the metabolic respiratory control system.
- Patients with primary alveolar hypoventilation are able to hyperventilate voluntarily, but during sleep, hypoventilation becomes more severe and central apneas are common.
- Management of patients with primary alveolar hypoventilation, as well as those with respiratory neuromuscular disorders, usually involves mechanical ventilatory assistance. Administration of such treatment only during sleep often produces dramatic clinical improvement and alleviates daytime symptoms.
- Hyperventilation can result from several diseases that produce an increase in respiratory drive, including disorders associated with hypoxemia, pulmonary vascular and interstitial

KEY POINTS—CONT'D

disease, congestive heart failure, metabolic acidosis, intracranial disorders, anxiety, and drugs.

- Patients who are hyperventilating may complain of dyspnea, but there is often a considerable discrepancy between the degree of hyperventilation, as assessed by arterial Pco_2, and the degree of dyspnea.
- Hyperventilation may produce important secondary effects on respiratory drive, on the unloading of oxygen from hemoglobin at the tissue level, and on cardiac and cerebral function.
- The underlying cause of hyperventilation can often be identified by the associated clinical features and measurements of arterial blood gases, pH, bicarbonate, and the alveolar-arterial Po_2 difference.
- The disorders that most frequently give rise to "unexplained hyperventilation" are pulmonary vascular disease, anxiety, and idiopathic hyperventilation.
- Treatment of hyperventilation is generally directed at the underlying disorder.

References

1. Duffin J: Role of acid-base balance in the chemoreflex control of breathing. J Appl Physiol 99:2255–2265, 2005.
2. Bell HJ: Respiratory control at exercise onset: an integrated systems perspective. Respir Physiol Neurobiol 152:1–15, 2006.
3. Jurgens U: Neural pathways underlying vocal control. Neurosci Biobehav Rev 26:235–258, 2002.
4. Phillipson EA, McClean PA, Sullivan CE, et al: Interaction of metabolic and behavioral respiratory control during hypercapnia and speech. Am Rev Respir Dis 117:903–909, 1978.
5. Homma I, Masaoka Y: Breathing Rhythms and Emotions. Exp Physiol 93:1011–1021, 2008.
6. Horn EM, Waldrop TG: Suprapontine control of respiration. Respir Physiol 114:201–211, 1998.
7. Manning HL, Mahler DA: Pathophysiology of dyspnea. Monaldi Arch Chest Dis 56:325–330, 2001.
8. Benchetrit G: Breathing pattern in humans: Diversity and individuality. Respir Physiol 122:123–129, 2000.
9. Fong J, Sandhu G, Ellaway P, et al: What do we know about how humans cough? Pulm Pharmacol Ther 17:431–434, 2004.
10. Shea SA: Behavioural and arousal-related influences on breathing in humans. Exp Physiol 81:1–26, 1996.
11. Duffin J, Tian GF, Peever JH: Functional synaptic connections among respiratory neurons. Respir Physiol 122:237–246, 2000.
12. St.-John WM, Paton JFR: Role of pontile mechanisms in the neurogenesis of eupnea. Respir Physiol Neurobiol 143:321–332, 2004.
13. Lipski J, Duffin J, Kruszewska B, et al: Upper cervical inspiratory neurons in the rat: An electrophysiological and morphological study. Exp Brain Res 95:477–487, 1993.
14. Iscoe S: Control of abdominal muscles. Prog Neurobiol 56:433–506, 1998.
15. Duffin J: Functional organization of respiratory neurones: A brief review of current questions and speculations. Exp Physiol 89:517–529, 2004.
16. Nattie E, Li A: Central chemoreception 2005: A brief review. Auton Neurosci 126-127:332–338, 2006.
17. Ezure K, Tanaka I: Distribution and medullary projection of respiratory neurons in the dorsolateral pons of the rat. Neuroscience 141:1011–1023, 2006.
18. Smith JC, Ellenberger HH, Ballanyi K, et al: Pre-Bötzinger complex: A brainstem region that may generate respiratory rhythm in mammals. Science 254:726–729, 1991.
19. Onimaru H, Homma I: A novel functional neuron group for respiratory rhythm generation in the ventral medulla. J Neurosci 23:1478–1486, 2003.
20. Hayakawa T, Takanaga A, Maeda S, et al: Monosynaptic inputs from the nucleus tractus solitarii to the laryngeal motoneurons in the nucleus ambiguus of the rat. Anat Embryol (Berl) 202:411–420, 2000.
21. Canning BJ, Fischer A: Neural regulation of airway smooth muscle tone. Respir Physiol 125:113–127, 2001.
22. Fregosi RF, Fuller DD: Respiratory-related control of extrinsic tongue muscle activity. Respir Physiol 110:295–306, 1997.
23. Sawczuk A, Mosier KM: Neural control of tongue movement with respect to respiration and swallowing. Crit Rev Oral Biol Med 12:18–37, 2001.
24. Peever JH, Shen L, Duffin J: Respiratory pre-motor control of hypoglossal motoneurons in the rat. Neuroscience 110:711–722, 2002.
25. Dutschmann M, Herbert H: The Kolliker-Fuse nucleus gates the postinspiratory phase of the respiratory cycle to control inspiratory off-switch and upper airway resistance in rat. Eur J Neurosci 24:1071–1084, 2006.
26. Song G, Poon C-S: Functional and structural models of pontine modulation of mechanoreceptor and chemoreceptor reflexes. Respir Physiol Neurobiol 143:281–292, 2004.
27. Plowey ED, Kramer JM, Beatty JA, et al: In vivo electrophysiological responses of pedunculopontine neurons to static muscle contraction. Am J Physiol Regul Integr Comp Physiol 283:R1008–R1019, 2002.
28. Jiang M, Alheid GF, Calandriello T, et al: Parabrachial-lateral pontine neurons link nociception and breathing. Respir Physiol Neurobiol 143:215–233, 2004.
29. Haxhiu MA, Mack SO, Wilson CG, et al: Sleep networks and the anatomic and physiologic connections with respiratory control. Front Biosci 8:D946–D962, 2003.
30. Paton JF: A working heart-brainstem preparation of the mouse. J Neurosci Meth 65:63–68, 1996.
31. Busselberg D, Bischoff AM, Paton JF, et al: Reorganisation of respiratory network activity after loss of glycinergic inhibition. Pflugers Arch 441:444–449, 2001.
32. Wittmeier S, Song G, Duffin J, et al: Pacemakers handshake synchronization mechanism of mammalian respiratory rhythmogenesis. Proc Nat Acad Sci U S A 105:18000–18005, 2008.
33. Duffin J, Ezure K, Lipski J: Breathing rhythm generation: Focus on the rostral ventrolateral medulla. NIPS 10:133–140, 1995.
34. Smith JC, Abdala AP, Koizumi H, et al: Spatial and functional architecture of the mammalian brain stem respiratory network: A hierarchy of three oscillatory mechanisms. J Neurophysiol 98:3370–3387, 2007.
35. Ezure K: Synaptic connections between medullary respiratory neurons and considerations on the genesis of respiratory rhythm. Prog Neurobiol 35:429–450, 1990.

36. Duffin J: A model of respiratory rhythm generation. NeuroReport 2:623–626, 1991.
37. Richter DW, Ballanyi K, Schwarzacher S: Mechanisms of respiratory rhythm generation. Curr Opin Neurobiol 2:788–793, 1992.
38. Widdicombe J: Airway receptors. Respir Physiol 125:3–15, 2001.
39. Bolser DC, Davenport PW: Functional organization of the central cough generation mechanism. Pulm Pharmacol Ther 15:221–225, 2002.
40. Schelegle ES, Green JF: An overview of the anatomy and physiology of slowly adapting pulmonary stretch receptors. Respir Physiol 125:17–31, 2001.
41. Bechbache RR, Chow HH, Duffin J, et al: The effects of hypercapnia, hypoxia, exercise and anxiety on the pattern of breathing in man. J Physiol (Lond) 293:285–300, 1979.
42. Milic-Emili J, Petit JM: Mechanical efficiency of breathing. J Appl Physiol 15:359–362, 1960.
43. Buchanan GF, Richerson GB: Role of chemoreceptors in mediating dyspnea. Respir Physiol Neurobiol 167:9–19, 2009.
44. Nattie EE, Li A: Central chemoreception is a complex system function that involves multiple brainstem sites. J Appl Physiol 106:1464–1466, 2009.
45. Ainslie PN, Duffin J: Integration of cerebrovascular CO_2 reactivity and chemoreflex control of breathing: mechanisms of regulation, measurement, and interpretation. Am J Physiol Regul Integr Comp Physiol 296:R1473–1495, 2009.
46. Iturriaga R, Varas R, Alcayaga J: Electrical and pharmacological properties of petrosal ganglion neurons that innervate the carotid body. Respir Physiol Neurobiol 157:130–139, 2007.
47. Duffin J, Mahamed S: Adaptation in the respiratory control system. Can J Physiol Pharmacol 81:765–773, 2003.
48. Khoo MCK: Determinants of ventilatory instability and variability. Respir Physiol 122:167–182, 2000.
49. Mahamed S, Hanly PJ, Gabor J, et al: Overnight changes of chemoreflex control in obstructive sleep apnoea patients. Respir Physiol Neurobiol 146:279–290, 2005.
50. Xie A, Skatrud JB, Barczi SR, et al: Influence of cerebral blood flow on breathing stability. J Appl Physiol 106:850–856, 2009.
51. Goldstein RS: Hypoventilation: Neuromuscular and chest wall disorders. Clin Chest Med 13:507–521, 1992.
52. Spengler CM, Gozal D, Shea SA: Chemoreceptive mechanisms elucidated by studies of congenital central hypoventilation syndrome. Respir Physiol 129:247–255, 2001.
53. Goldring RM, Turino GM, Heinemann HO: Respiratory-renal adjustments in chronic hypercapnia in man: Extracellular bicarbonate concentration and the regulation of ventilation. Am J Med 51:772–784, 1971.
54. Heinemann HO, Goldring RM: Bicarbonate and the regulation of ventilation. Am J Med 57:361–370, 1974.
55. Jackson CE, Rosenfeld J, Moore DH, et al: A preliminary evaluation of a prospective study of pulmonary function studies and symptoms of hypoventilation in ALS/MND patients. J Neurol Sci 191:75–78, 2001.
56. Barlow PB, Bartlett D Jr, Hauri P, et al: Idiopathic hypoventilation syndrome: Importance of preventing nocturnal hypoxemia and hypercapnia. Am Rev Respir Dis 121:141–145, 1980.
57. Bradley GW, Phillipson EA: Central sleep apnea. Clin.Chest Med 13:493–507, 1992.
58. McNicholas W, Phillipson E: Central hypoventilation syndromes and hypercapnic central sleep apnea. *In* McNicholas W, Phillipson E (eds): Breathing Disorders in Sleep. Philadelphia: Saunders, 2002, pp 239–245.
59. McNicholas WT, Carter JL, Rutherford R, et al: Beneficial effect of oxygen in primary alveolar hypoventilation with central sleep apnea. Am Rev Respir Dis 125:773–775, 1982.
60. Gupta R: Respiratory dysfunction in motor neuron disease. *In* Weiner W (ed): Respiratory Dysfunction in Neurologic Disease. New York: Futura, 1980, pp 71–81.
61. Whitelaw WA, Derenne J-P, Milic-Emili J: Occlusion pressure as a measure of respiratory center output in conscious man. Respir Physiol 23:181–199, 1975.
62. Altose MD, McCauley WC, Kelsen SG, et al: Effects of hypercapnia and inspiratory flow-resistive loading on respiratory activity in chronic airways obstruction. J Clin Invest 59:500–507, 1977.
63. Gelb AF, Klein E, Schiffman P, et al: Ventilatory response and drive in acute and chronic obstructive pulmonary disease. Am Rev Respir Dis 116:9–16, 1977.
64. Riley DJ, Santiago TV, Daniele RP, et al: Blunted respiratory drive in congenital myopathy. Am J Med 63:459–466, 1977.
65. Olson AL, Zwillich C: The obesity hypoventilation syndrome. Am J Med 118:948–956, 2005.
66. Mountain R, Zwillich C, Weil J: Hypoventilation in obstructive lung disease: The role of familial factors. N Engl J Med 298:521–525, 1978.
67. Schiffman PL, Westlake RE, Santiago TV, et al: Ventilatory control in parents of victims of sudden-infant-death syndrome. N Engl J Med 302:486–491, 1980.
68. Weil JV: Variation in human ventilatory control—genetic influence on the hypoxic ventilatory response. Respir Physiol Neurobiol 135:239–246, 2003.
69. Barratt S, Kendrick AH, Buchanan F, et al: Central hypoventilation with *PHOX2B* expansion mutation presenting in adulthood. Thorax 62:919–920, 2007.
70. Levin BE, Margolis G: Acute failure of automatic respirations secondary to a unilateral brainstem infarct. Ann Neurol 1:583–586, 1977.
71. Cole S, Lindenberg LB, Galioto FM Jr, et al: Ultrastructural abnormalities of the carotid body in sudden infant death syndrome. Pediatrics 63:13–17, 1979.
72. Bowes G, Andrey S, Kozar L, et al: Effect of chronic carotid body denervation on respiratory drive and stability in sleeping dogs. Am Rev Respir Dis 129(Suppl):A244, 1984.
73. Weese-Mayer DE, Berry-Kravis EM, Marazita ML: In pursuit (and discovery) of a genetic basis for congenital central hypoventilation syndrome. Respir Physiol Neurobiol 149:73–82, 2005.
74. Bubis MJ, Anthonisen NR: Primary alveolar hypoventilation treated by nocturnal administration of O_2. Am Rev Respir Dis 118:947–953, 1978.
75. Hyland RH, Jones NL, Powles ACP, et al: Primary alveolar hypoventilation treated with nocturnal electrophrenic respiration. Am Rev Respir Dis 117:165–172, 1978.
76. Phillipson E, Bowes G: Control of breathing during sleep. *In* Cherniack N, Widdicombe J (eds): Handbook of Physiology. Section 3: The Respiratory System. Vol II: Control of Breathing (Part 2). Bethesda, MD: American Physiological Society, 1986, pp 649–689.
77. Hsu AA, Staats BA: "Postpolio" sequelae and sleep-related disordered breathing. Mayo Clin Proc 73:216–224, 1998.
78. Smyth A, Riley M: Chronic respiratory failure: An unusual cause and treatment. Thorax 57:835–836, 2002.
79. Krieger AJ, Rosomoff HL: Sleep-induced apnea. 1: A respiratory and autonomic dysfunction syndrome following bilateral percutaneous cervical cordotomy. J Neurosurg 40:168–180, 1974.
80. Lo Coco D, Marchese S, Corrao S, et al: Development of chronic hypoventilation in amyotrophic lateral sclerosis patients. Respir Med 100:1028–1036, 2006.
81. Easton PA, Fleetham JA, de la Rocha A, et al: Respiratory function after paralysis of the right hemidiaphragm. Am Rev Respir Dis 127:125–128, 1983.
82. Derenne JP, Macklem PT, Roussos C: The respiratory muscles: Mechanics, control, and pathophysiology. Part III. Am Rev Respir Dis 118:581–601, 1978.
83. Skatrud JB, Dempsey JA, Bhansali P, et al: Determinants of chronic carbon dioxide retention and its correction in humans. J Clin Invest 65:813–821, 1980.
84. Bear R, Goldstein M, Phillipson E, et al: Effect of metabolic alkalosis on respiratory function in patients with chronic obstructive lung disease. Can Med Assoc J 117:900–903, 1977.
85. Robert D, Argaud L: Clinical review: Long-term noninvasive ventilation. Crit Care 11:210, 2007.
86. Weese-Mayer DE, Silvestri JM, Kenny AS, et al: Diaphragm pacing with a quadripolar phrenic nerve electrode: An international study. Pacing Clin Electrophysiol 19:1311–1319, 1996.
87. Weil JV, Byrne-Quinn E, Sodal IE, et al: Hypoxic ventilatory drive in normal man. J Clin Invest 49:1061–1072, 1970.
88. West JB, Hackett PH, Maret KH, et al: Pulmonary gas exchange on the summit of Mount Everest. J Appl Physiol 55:678–687, 1983.

89. Anthonisen N, Cherniack R: Ventilatory control in lung disease. *In* Hornbein T (ed): Regulation of Breathing (Part II). New York: Marcel Dekker, 1981, pp 965–987.
90. Kawakami Y, Yamamoto H, Yoshikawa T, et al: Chemical and behavioral control of breathing in adult twins. Am Rev Respir Dis 129:703–707, 1984.
91. Neubauer JA, Melton JE, Edelman NH: Modulation of respiration during brain hypoxia. J Appl Physiol 68:441–451, 1990.
92. Weil JV: Ventilatory control at high altitude. *In* Cherniack NS, Widdicombe JG (eds): Handbook of Physiology. Section 3: The Respiratory System. Vol II: Control of Breathing (Part 2). Bethesda, MD: American Physiological Society, 1986, pp 703–728.
93. Phillipson EA, Murphy E, Kozar LF, et al: Role of vagal stimuli in exercise ventilation in dogs with experimental pneumonitis. J Appl Physiol 39:76–85, 1975.
94. Cotton DJ, Bleecker ER, Fischer SP, et al: Rapid, shallow breathing after *Ascaris suum* antigen inhalation: Role of vagus nerves. J Appl Physiol 42:101–106, 1977.
95. Guz A, Noble M, Eisele J, et al: Experimental results of vagal blockade in cardiopulmonary disease. *In* Porter R (ed): Breathing: Hering-Breuer Centenary Symposium. London: Churchill, 1970, pp 315–329.
96. DiMarco AF, Kelsen SG, Cherniack NS, et al: Occlusion pressure and breathing pattern in patients with interstitial lung disease. Am Rev Respir Dis 127:425–430, 1983.
97. Bradley TD: Right and left ventricular functional impairment and sleep apnea. Clin Chest Med 13:459–479, 1992.
98. Naughton M, Benard D, Tam A, et al: Role of hyperventilation in the pathogenesis of central sleep apneas in patients with congestive heart failure. Am Rev Respir Dis 148:330–338, 1993.
99. Lorenzi-Filho G, Rankin F, Bies I, et al: Effects of inhaled carbon dioxide and oxygen on Cheyne-Stokes respiration in patients with heart failure. Am J Respir Crit Care Med 159:1490–1498, 1999.
100. Tkacova R, Hall MJ, Liu PP, et al: Left ventricular volume in patients with heart failure and Cheyne-Stokes respiration during sleep. Am J Respir Crit Care Med 156:1549–1555, 1997.
101. De Burgh Daly M: Interactions between respiration and circulation. *In* Cherniack NS, Widdicombe JG (eds): Handbook of Physiology. Section 3: The Respiratory System. Vol II: Control of Breathing (Part 2). Bethesda, MD: American Physiological Society, 1986, pp 529–594.
102. Gennari FJ, Goldstein MB, Schwartz WB: The nature of the renal adaptation to chronic hypocapnia. J Clin Invest 51:1722–1730, 1972.
103. Forster H, Dempsey J: Ventilatory adaptations. *In* Hornbein T (ed): Regulation of Breathing. Part I. New York: Marcel Dekker, 1981, pp 845–904.
104. Pino-Garcia JM, Garcia-Rio F, Diez JJ, et al: Regulation of breathing in hyperthyroidism: Relationship to hormonal and metabolic changes. Eur Respir J 12:400–407, 1998.
105. Stanley NN, Salisbury BG, McHenry LC Jr, et al: Effect of liver failure on the response of ventilation and cerebral circulation to carbon dioxide in man and in the goat. Clin Sci Mol Med 49:157–169, 1975.
106. Jack S, Rossiter HB, Warburton CJ, et al: Behavioral influences and physiological indices of ventilatory control in subjects with idiopathic hyperventilation. Behav Modif 27:637–652, 2003.
107. Meuret AE, Wilhelm FH, Ritz T, et al: Feedback of end-tidal pCO_2 as a therapeutic approach for panic disorder. J Psychiatr Res 42:560–568, 2008.
108. Jack S, Rossiter HB, Pearson MG, et al: Ventilatory responses to inhaled carbon dioxide, hypoxia, and exercise in idiopathic hyperventilation. Am J Respir Crit Care Med 170:118–125, 2004.
109. Plum F, Posner J: The Diagnosis of Stupor and Coma. Philadelphia: Davis, 1966.
110. Takahashi M, Tsunemi T, Miyayosi T, et al: Reversible central neurogenic hyperventilation in an awake patient with multiple sclerosis. J Neurol 254:1763–1764, 2007.
111. Nystad D, Salvesen R, Nielsen EW: Brain stem encephalitis with central neurogenic hyperventilation. J Neurol Neurosurg Psychiatry 78:107–108, 2007.
112. Tarulli AW, Lim C, Bui JD, et al: Central neurogenic hyperventilation: A case report and discussion of pathophysiology. Arch Neurol 62:1632–1634, 2005.
113. Johnston SC, Singh V, Ralston HJ 3rd, et al: Chronic dyspnea and hyperventilation in an awake patient with small subcortical infarcts. Neurology 57:2131–2133, 2001.
114. Hickey R, Severinghaus J: Regulation of breathing: Drug effects. *In* Hornbein T (ed): Regulation of Breathing (Part II). New York: Marcel Dekker, 1981, pp 1251–1312.
115. Millhorn DE, Eldridge FL, Waldrop TG: Effect of salicylate and 2,4-dinitrophenol on respiration and metabolism. J Appl Physiol 53:925–929, 1982.
116. Gaudio R Jr, Abramson N: Heat-induced hyperventilation. J Appl Physiol 25:742–746, 1968.
117. Aronson PR: Hyperventilation from organic disease. Ann Intern Med 50:554–559, 1959.
118. Heistad DD, Wheeler RC, Mark AL, et al: Effects of adrenergic stimulation on ventilation in man. J Clin Invest 51:1469–1475, 1972.
119. Morgan EJ, Baidwan B, Petty TL, et al: The effects of unanesthetized arterial puncture on PCO_2 and pH. Am Rev Respir Dis 120:795–798, 1979.
120. Bayliss DA, Millhorn DE: Central neural mechanisms of progesterone action: Application to the respiratory system. J Appl Physiol 73:393–404, 1992.
121. Jensen D, Duffin J, Lam Y-M, et al: Physiological mechanisms of hyperventilation during human pregnancy. Respir Physiol Neurobiol 161:76–86, 2008.
122. Brautbar N, Leibovici H, Finlander P, et al: Mechanism of hypophosphatemia during acute hyperventilation (abstract). Clin Res 28:387A, 1980.
123. Laffey JG, Kavanagh BP: Hypocapnia. N Engl J Med 347:43–53, 2002.
124. Chen CC, Chen SA, Tai CT, et al: Hyperventilation facilitates induction of supraventricular tachycardia: A novel method and the possible mechanism. J Cardiovasc Electrophysiol 12:1242–1246, 2001.
125. Magarian GJ: Hyperventilation syndromes: Infrequently recognized common expressions of anxiety and stress. Medicine (Baltimore) 61:219–236, 1982.
126. Raichle ME, Posner JB, Plum F: Cerebral blood flow during and after hyperventilation. Arch Neurol 23:394–403, 1970.
127. Kennealy JA, McLennan JE, Loudon RG, et al: Hyperventilation-induced cerebral hypoxia. Am Rev Respir Dis 122:407–412, 1980.
128. Arnow PM, Panwalker A, Garvin JS, et al: Aspirin, hyperventilation, and cerebellar infarction in sickle cell disease. Arch Intern Med 138:148–149, 1978.
129. Arbus GS, Herbert LA, Levesque PR, et al: Characterization and clinical application of the "significance band" for acute respiratory alkalosis. N Engl J Med 280:117–123, 1969.
130. Brashear RE: Hyperventilation syndrome. Lung 161:257–273, 1983.
131. Lewis BI: Hyperventilation syndrome: A clinical and physiological evaluation. Calif Med 91:121–126, 1959.
132. Rosenbaum JF: The drug treatment of anxiety. N Engl J Med 306:401–404, 1982.
133. van Doorn P, Folgering H, Colla P: Control of the end-tidal PCO_2 in the hyperventilation syndrome: Effects of biofeedback and breathing instructions compared. Bull Eur Physiopathol Respir 18:829–836, 1982.
134. Folgering H, Rutten H, Roumen Y: Beta-blockade in the hyperventilation syndrome: A retrospective assessment of symptoms and complaints. Respiration 44:19–25, 1983.
135. Ezure K: Reflections on respiratory rhythm generation. Prog Brain Res 143:67–74, 2004.
136. Wade JG, Larson CP Jr, Hickey RF, et al: Effect of carotid endarterectomy on carotid chemoreceptor and baroreceptor function in man. N Engl J Med 282:823–829, 1970.
137. Severinghaus JW, Bainton CR, Carcelen A: Respiratory insensitivity to hypoxia in chronically hypoxic man. Respir Physiol 1:308–334, 1966.
138. Weil JV, Byrne-Quinn E, Sodal IE, et al: Acquired attenuation of chemoreceptor function in chronically hypoxic man at high altitude. J Clin Invest 50:186–195, 1971.
139. Goldring RM, Cannon PJ, Heinemann HO, et al: Respiratory adjustment to chronic metabolic alkalosis in man. J Clin Invest 47:188–202, 1968.

140. Plum F, Swanson AG: Abnormalities in central regulation of respiration in acute and convalescent poliomyelitis. AMA Arch Neurol Psychiatry 80:267–285, 1958.
141. Solliday NH, Gaensler EA, Schwaber JR, et al: Impaired central chemoreceptor function and chronic hypoventilation many years following poliomyelitis. Case report. Respiration 31:177–192, 1974.
142. Devereaux MW, Keane JR, Davis RL: Automatic respiratory failure associated with infarction of the medulla: Report of two cases with pathologic study of one. Arch Neurol 29:46–52, 1973.
143. Hughes JM: Central respiratory failure reversed by treatment. Brain 90:675–680, 1967.
144. Daum JJ, Canter HG, Katz S: Central nervous system sarcoidosis with alveolar hypoventilation. Am J Med 38:893–898, 1965.
145. Boor JW, Johnson RJ, Canales L, et al: Reversible paralysis of automatic respiration in multiple sclerosis. Arch Neurol 34:686–689, 1977.
146. Marks CE Jr, Goldring RM: Chronic hypercapnia during methadone maintenance. Am Rev Respir Dis 108:1088–1093, 1973.
147. Rodman T, Close HP: The primary hypoventilation syndrome. Am J Med 26:808–817, 1959.
148. Rhoads GG, Brody JS: Idiopathic alveolar hypoventilation: Clinical spectrum. Ann Intern Med 71:271–278, 1969.
149. Richter T, West JR, Fishman AP: The syndrome of alveolar hypoventilation and diminished sensitivity of the respiratory center. N Engl J Med 256:1165–1170, 1957.
150. Newsom Davis J, Goldman M, Loh L, et al: Diaphragm function and alveolar hypoventilation. Q J Med 45:87–100, 1976.
151. Lane DJ, Hazleman B, Nichols PJ: Late onset respiratory failure in patients with previous poliomyelitis. Q J Med 43:551–568, 1974.
152. Sivak ED, Streib EW: Management of hypoventilation in motor neuron disease presenting with respiratory insufficiency. Ann Neurol 7:188–191, 1980.
153. Thorpy MJ, Schmidt-Nowara WW, Pollak CP, et al: Sleep-induced nonobstructive hypoventilation associated with diaphragmatic paralysis. Ann Neurol 12:308–311, 1982.
154. Goldstein RL, Hyde RW, Lapham LW, et al: Peripheral neuropathy presenting with respiratory insufficiency as the primary complaint: Problem of recognizing alveolar hypoventilation due to neuromuscular disorders. Am J Med 56:443–449, 1974.
155. Gibson GJ, Pride NB, Davis JN, et al: Pulmonary mechanics in patients with respiratory muscle weakness. Am Rev Respir Dis 115:389–395, 1977.
156. Inkley SR, Oldenburg FC, Vignos PJ Jr: Pulmonary function in Duchenne muscular dystrophy related to stage of disease. Am J Med 56:297–306, 1974.
157. Coccagna G, Mantovani M, Parchi C, et al: Alveolar hypoventilation and hypersomnia in myotonic dystrophy. J Neurol Neurosurg Psychiatry 38:977–984, 1975.
158. Hukins CA, Hillman DR: Daytime predictors of sleep hypoventilation in Duchenne muscular dystrophy. Am J Respir Crit Care Med 161:166–170, 2000.
159. Lopata M, Onal E: Mass loading, sleep apnea, and the pathogenesis of obesity hypoventilation. Am Rev Respir Dis 126:640–645, 1982.
160. Berger KI, Ayappa I, Chatr-Amontri B, et al: Obesity hypoventilation syndrome as a spectrum of respiratory disturbances during sleep. Chest 120:1231–1238, 2001.
161. Phipps PR, Starritt E, Caterson I, et al: Association of serum leptin with hypoventilation in human obesity. Thorax 57:75–76, 2002.
162. Bergofsky EH: Respiratory failure in disorders of the thoracic cage. Am Rev Respir Dis 119:643–669, 1979.
163. Shim C, Corro P, Park SS, et al: Pulmonary function studies in patients with upper airway obstruction. Am Rev Respir Dis 106:233–238, 1972.
164. Proctor DF: The upper airways II. The larynx and trachea. Am Rev Respir Dis 115:315–342, 1977.

CHAPTER 79

SLEEP-DISORDERED BREATHING

Grace W. Pien, MD • Allan I. Pack, MBChB, PhD

INTRODUCTION

PATHOGENESIS OF OBSTRUCTIVE SLEEP APNEA
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SLEEP HYPOVENTILATION SYNDROMES
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Conclusions

INTRODUCTION

Sleep-disordered breathing is an extremely common problem. The most common form of sleep-disordered breathing is caused by obstruction in the upper airway, and is called *obstructive sleep apnea (OSA)*. Apneas—cessation of breathing—can also occur as a result of temporary loss of neural output to the diaphragm, that is, central apnea. The term "mixed apnea" is also used when the apnea starts as a central event but becomes

TABLE 79-1. Definitions*

EVENTS

Apnea: Cessation of breathing lasting 10 seconds or longer. Obstructive: continued respiratory effort with paradoxical motion of rib cage and abdomen; central: absent respiratory effort.

Hypopnea: Different definitions used. Two alternative definitions are part of the scoring criteria advanced by the American Academy of Sleep Medicine:

1. Score a hypopnea if all of the following are present:
   a. Nasal pressure signal excursions; drop ≥30% of baseline for at least 10 seconds.
   b. There is a ≥4% desaturation from pre-event baseline.
   c. At least 90% of the event's duration must meet the amplitude reduction of criteria for hypopnea.
2. Score a hypopnea if all of the following are present:
   a. Nasal pressure signal excursions; drop ≥50% of baseline for at least 10 seconds.
   b. There is a ≥3% desaturation from pre-event baseline *or* the event is associated with an arousal. (The latter does not require a desaturation.)
   c. At least 90% of the event's duration must meet the amplitude reduction of criteria for hypopnea.

Respiratory Effort–Related Arousal (RERA): Pattern of progressively more negative esophageal pressure terminated by a sudden change in pressure to a less negative level and an arousal; events last 10 seconds or longer.

METRICS OF SEVERITY

Apnea-Hypopnea Index: Average number of apneas plus hypopneas per hour of sleep.

Respiratory Disturbance Index: Average number of apneas plus hypopneas plus RERAs per hour of sleep.

CONSENSUS DEFINITIONS OF SEVERITY

Normal: <5 episodes/hr

Mild sleep apnea: ≥5 and <15 episodes/hr

Moderate sleep apnea: ≥15 and <30 episodes/hr

Severe sleep apnea: ≥30 episodes/hr

CONCEPT OF SLEEP APNEA SYNDROME

Sleep-disordered breathing with complaint of excessive sleepiness.

*See also American Academy of Sleep Medicine.[7]

obstructive later in the same event. Mixed apnea should not be confused with mixed distributions of apnea, that is, where both pure obstructive and pure central apneas occur in the same individual during the same sleep period. Recently, a new term has been introduced—*complex apnea*—which is used when an individual initially has obstructive apneas, but central apneas occur once the individual is treated with nasal continuous positive airway pressure (CPAP).

Fundamental to the identification of these disorders is a description of the breathing events that occur during sleep. In adults, an *apnea* is defined as a cessation of breathing that lasts for more than 10 seconds (for summary of definitions, see Table 79-1). In obstructive apnea, paradoxical motion of the abdomen and rib cage occurs because of continued activation of the diaphragm. This paradoxical motion can be detected by sensors assessing rib cage and abdominal motion. In contrast, in a central apnea, rib cage and abdominal motion ceases. An example of both an obstructive apnea and a central apnea are shown in Figure 79-1 to illustrate this distinction.

Another type of event is a *hypopnea* (see Table 79-1), when respiration declines but does not completely stop. This decline in ventilation can lead to the same consequences as from apneas, for example, a fall in oxygen saturation. As with an apnea, the event is typically terminated by an arousal, that is, brief sudden change in sleep state that can be detected on the electroencephalogram.[1] Whereas, currently, there is one standard definition for apnea, there are a number of different definitions for hypopnea, for example, a greater than 50% reduction in airflow with a 4% fall in oxygen saturation; a discernible fall in airflow with a 3% fall in oxygen saturation, and/or termination of the event by an arousal. The latter definition does not require an oxygen desaturation event to occur. These different definitions of hypopneas lead to some confusion and result in different numbers of events being counted and scored from the same recording in the same subject.[2,3] Moreover, the technology used to assess airflow during sleep studies has changed over the years. Initially, it was based on nasal thermistors, but this has changed to assessment of small changes in nasal pressure with respiration. Nasal pressure is more quantitative, is a more linear signal for airflow than thermistors, and hence, can detect events that are missed by thermistors.[3] The major epidemiologic studies of sleep-disordered breathing that have been performed in the United States—the Wisconsin Sleep Cohort Study,[4] the Sleep Heart Health Study,[5] and the study in Dauphine County in Pennsylvania[6]—were initiated before nasal pressure recordings were available and are based on using thermistors to detect changes in nasal airflow. Hence, one cannot directly compare the number of events that would be identified in current studies with those obtained in these classic epidemiologic studies.

The severity of sleep-disordered breathing is assessed by counting the number of apneas and hypopneas during sleep and then dividing by total sleep time. This gives the event rate—apnea-hypopnea index (AHI), that is, number of apneas plus hypopneas per hour of sleep. By consensus,[7] based on published literature, the following cut-points are used (see Table 79-1): normal AHI < 5 episodes/hr; mild sleep apnea AHI ≥ 5 and < 15 episodes/hr; moderate sleep apnea AHI ≥ 15 and < 30 episodes/hr; and severe sleep apnea AHI ≥ 30 episodes/hr.

Another term that is used is the *upper airway resistance syndrome*. This syndrome was originally described by Guilleminault and associates[8–10] before the introduction of nasal pressure to identify changes in airflow. The original concept was that one might have an event with a progressive increase in upper airway resistance and,

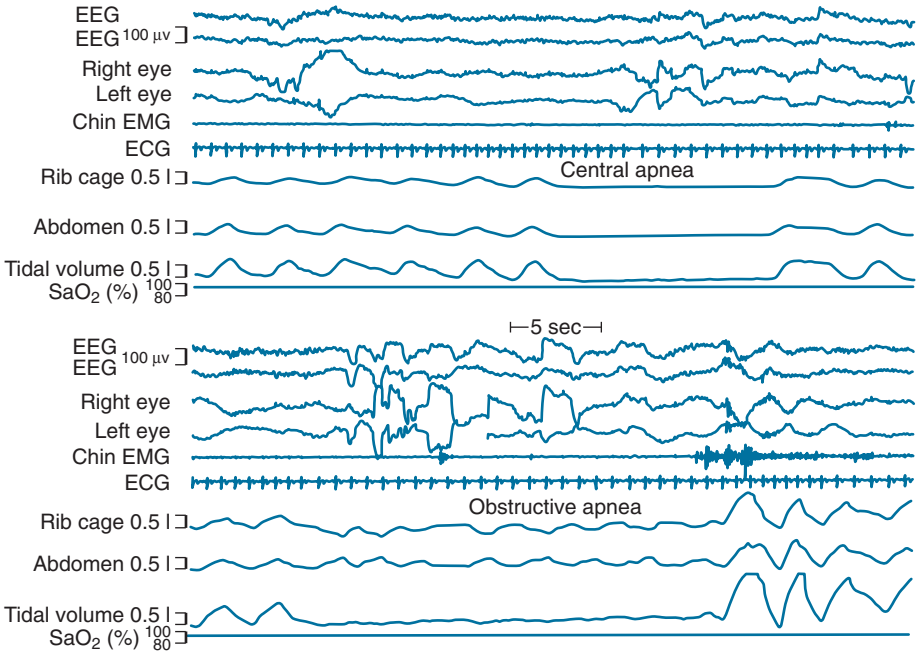

FIGURE 79-1 ■ Recorder tracings during polysomnographic study show distinction between central and obstructive apneas, using a respiratory inductive plethysmograph. *Upper and lower panels* form a continuous record in rapid eye movement sleep. Channels from the top down show the following: electroencephalogram (EEG), right and left eye movements, submental electromyogram (EMG), electrocardiogram (ECG), movements of rib cage and abdomen, tidal volume, and arterial oxygen saturation (SaO_2). Note that during central apnea, the absence of tidal volume excursion was accompanied by absence of rib cage and abdominal movements; during obstructive apnea, paradoxical rib cage and abdominal movements were present. (From Phillipson EA, Bowes G: Sleep disorders. *In* Fishman AP [ed]: Update: Pulmonary Diseases and Disorders. New York: McGraw-Hill, 1982, pp 256–273.)

hence, in snoring that terminated in an arousal. The event did not meet the definition of hypopnea. When the more sensitive nasal pressure measurements were used, some of these upper airway resistance events proved to be hypopneas. Moreover, in a provocative article about the upper airway resistance syndrome, Guilleminault and Chowdhuri[11] altered the concept somewhat. He and his colleague now describe an abnormally sensitive reaction to the normal increase in upper airway resistance that occurs during sleep. This is said to be more common in women and to present with symptoms of fatigue and other somatic symptoms. In a response to this point of view, Douglas[12] proposed that it is premature to consider this a syndrome until treatment benefits have been shown by appropriate interventions. Thus, the concept of the upper airway resistance syndrome remains controversial. Identification of this disorder would require recording esophageal pressure using an indwelling catheter, which most laboratories do not routinely perform. Given the concept, however, the group who developed definitions for all sleep-disordered events and syndromes[7] introduced a new term, the *respiratory effort–related arousal (RERA)*, in order to capture upper airway resistance events (see Table 79-1). Identification of this requires assessment of esophageal pressure. Studies of patients with moderate obstructive sleep-disordered breathing show that this type of event is relatively uncommon and that the vast majority of events are either apneas or hypopneas.[13] Whereas the respiratory disturbance index (RDI) was initially used interchangeably with the AHI, and in some studies still is, the most common use of the term "respiratory disturbance index" denotes the total event rate, that is, apneas plus hypopneas plus RERAs/hr of sleep.

The final aspect of definitions that must be considered before discussing other aspects of sleep-disordered breathing is the use of the term "sleep apnea syndrome." The epidemiologic studies from the Wisconsin Sleep Cohort[4] show that only the minority of subjects with evidence of sleep-disordered breathing actually complain of excessive sleepiness during the daytime. Because excessive sleepiness is such an important clinical consequence of sleep-disordered breathing, the term "sleep apnea syndrome" should be reserved for those patients who not only have abnormal breathing events during sleep of required frequency but also complain of daytime sleepiness. Simple questions can identify patients who are excessively sleepy,[14] and the most commonly used instrument to assess sleepiness is the Epworth Sleepiness Scale.[15-17] This simple questionnaire (Fig. 79-2) has eight questions in which the individual indicates the likelihood of dozing in eight different circumstances (see Fig. 79-2). The total range of the questionnaire is 0 to 24, and studies in several patient populations indicate that a score of more than 10 indicates excessive sleepiness. Although the instrument has been criticized on the grounds that some individuals (e.g., elderly subjects) might not experience the circumstances described in the questionnaire, it identifies robust treatment effects in placebo-controlled treatment trials of OSA.[18] A complete review of the definitions of sleep-disordered breathing syndromes is available.[7]

Epworth Sleepiness Scale

Situation	Score
Sitting and reading	
Watching TV	
Sitting inactive in public place	
Passenger in car	
Lying down to rest in afternoon	
Sitting talking to someone	
Sitting after lunch without alcohol	
In a car, stopped for minutes in traffic	
Total (normal #10)	

Dozing

0 = Never

1 = Slight chance

2 = Moderate chance

3 = High chance

FIGURE 79-2 ■ The Epworth Sleepiness Scale. This instrument asks patients about their likelihood of dozing in eight different situations over the past month.

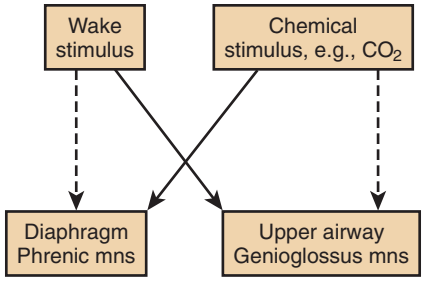

FIGURE 79-3 ■ Schematic illustrates that the relative role of the wakefulness stimulus for respiration and that coupled to chemical drive are different for the diaphragm and upper airway dilator muscles such as the genioglossus. (Reproduced with permission from Pack AI: Changes in the cardiorespiratory system during sleep. *In* Fishman AP (ed): Fishman's Pulmonary Diseases and Disorders (4th ed). New York: McGraw-Hill, 2008, pp 1689–1695.)

PATHOGENESIS OF OBSTRUCTIVE SLEEP APNEA

Neural Component

OSA occurs during sleep. Disordered breathing during sleep is the result of sleep-related alterations in neural control of the upper airway. The dimensions of the upper airway are protected by a large group of complex muscles—the upper airway dilator muscles. These muscles, which include the muscles of the soft palate and tongue, have multiple functions in swallowing and speech. With the onset of sleep, neural output to these muscles decline, resulting in an increase in upper airway resistance in all individuals. In addition, this increase in upper airway resistance causes a reduction in ventilation during sleep.

The motoneurons for upper airway dilator muscles receive input from the respiratory pattern generator in the brain stem, so their activity has a respiratory component. However, the fraction of the total drive to these neurons that is respiratory is considerably less than that to phrenic motoneurons (Fig. 79-3). Conversely, the activity of upper airway motoneurons is much more dependent on sleep/awake state than is the activity of the phrenic motoneurons. As a result, obstructive apneas are much more common than central apneas.

The basis for the dependency of upper airway motoneuron activity on sleep/awake state is complex and includes a number of different neuronal systems. During sleep, there is reduced activation of upper airway motoneurons by neuronal systems whose firing declines in non–rapid eye movement (NREM) and particularly rapid eye movement (REM) sleep (serotonin from the raphe, noradrenaline from the locus coeruleus, glutamate from the reticular formation, orexin from the lateral hypothalamus), as well as increased inhibition by glycine (for review, see Horner[19]) (see schematic, Fig. 79-4). Loss of the excitatory inputs, rather than an increase in inhibitory inputs, is the dominant factor for upper airway motoneurons.

The changes in neuronal activation during sleep also affect upper airway reflexes. The upper airway has a negative pressure reflex such that if the airway collapses, there is reflex activation of upper airway dilator muscles.[20] This is lost or attenuated during sleep.[21-23]

These changes in neural control of the upper airway during sleep occur in all individuals—both healthy controls, people who snore, and those with OSA. There is currently no evidence that subjects with sleep apnea have major differences in the sleep-related changes in neural activation, as compared with healthy subjects, although it is difficult to assess this in individual patients. Rather, the upper airway of patients with sleep apnea is much more susceptible to the normal changes in neural control with sleep. Two aspects that make the upper airway of patients with sleep apnea more susceptible are its smaller size, even during wakefulness, and its increased collapsibility.

Upper Airway Size

The upper airway in subjects with sleep apneas is smaller, as shown by studies using different imaging methods (for review, see Ahmed and Schwab[24]) (see example, Fig. 79-5). The reduction in airway size is particularly apparent in the lateral (not anteroposterior) dimension. Airway

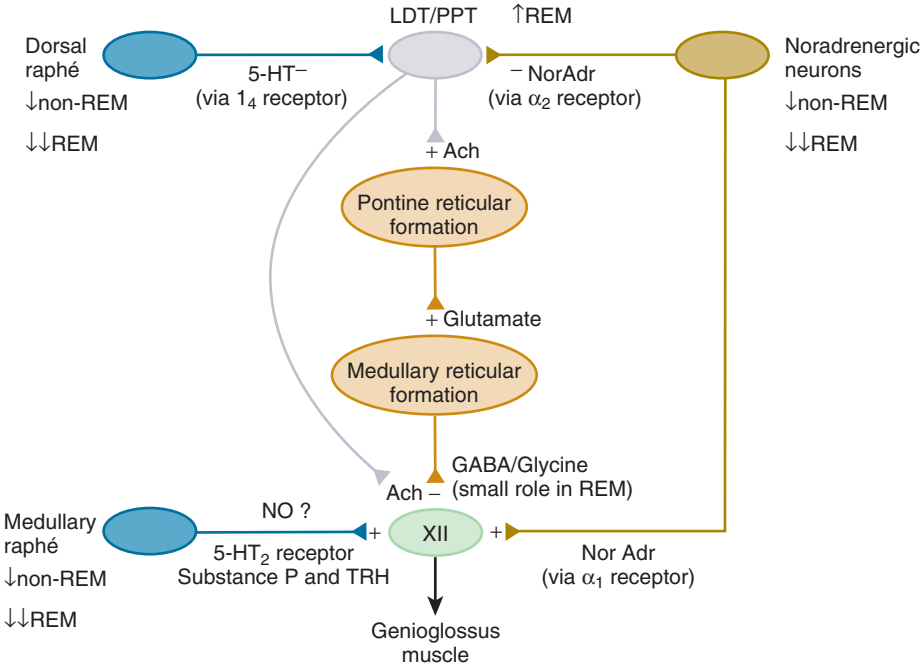

FIGURE 79-4 ■ Schematic shows the neuronal basis for changes in activity of upper airway motoneurons during sleep. 5-HT, serotonin; GABA, γ-aminobutyric acid; LDT/PPT, laterodorsal and pedunculopontine tegmental nuclei; NO, nitric oxide; REM, rapid eye movement; XII, hypoglossal motoneurons. For further details, see text. (Reproduced from Horner RL: Respiratory motor activity: Influence of neuromodulators and implications for sleep disordered breathing. Can J Physiol Pharmacol 85:155–165, 2007, with permission.)

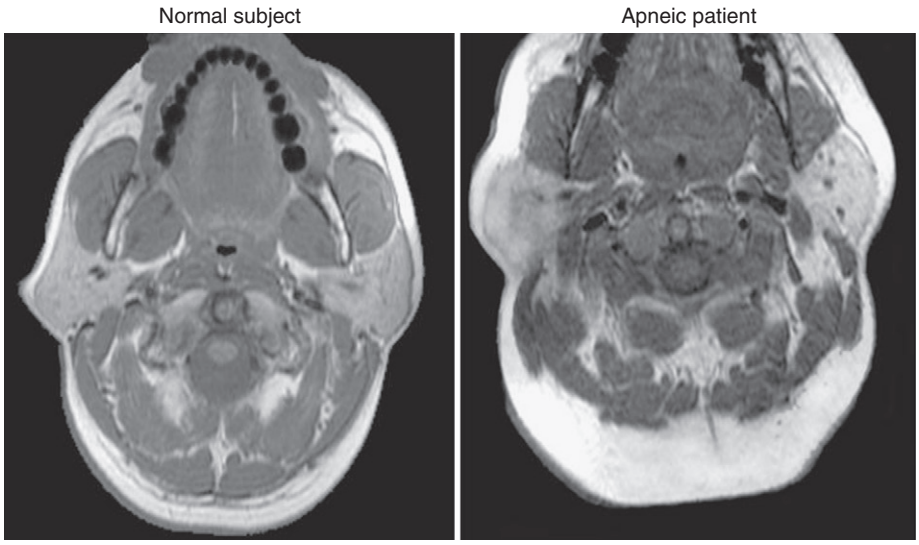

FIGURE 79-5 ■ Axial magnetic resonance imaging (MRI) of upper airway in normal subject (*left panel*) and apneic patient (*right panel*). In the middle of the image is the airway—small dark structure. It is much smaller in the apneics than the normal subject, particularly in the lateral dimension. There is much more subcutaneous fat (*white areas*) in the apneics. (Reproduced from Schwab RJ, Gupta KB, Gefter WB, et al: Upper airway and soft tissue anatomy in normal subjects and patients with sleep-disordered breathing. Significance of the lateral pharyngeal walls. Am J Respir Crit Care Med 152:1673–1689, 1995, with permission.)

size can be compromised by alterations in craniofacial dimensions, for example, small retrognathic mandible, or by increased size of upper airway soft tissues[25] (Fig. 79-6). Total soft tissue, tongue volume, and volume of the lateral walls are all increased in patients with OSA as compared with controls.[26] These differences are heritable and explain part of the genetic basis for OSA.[27]

Upper Airway Collapsibility

Patients with OSA also have a more collapsible airway. The upper airway behaves as a Starling resistor with a critical closing pressure (P_{crit}) at which the airway collapses.[28,29] The P_{crit} can be measured during sleep, and techniques are available to suddenly reduce upper airway

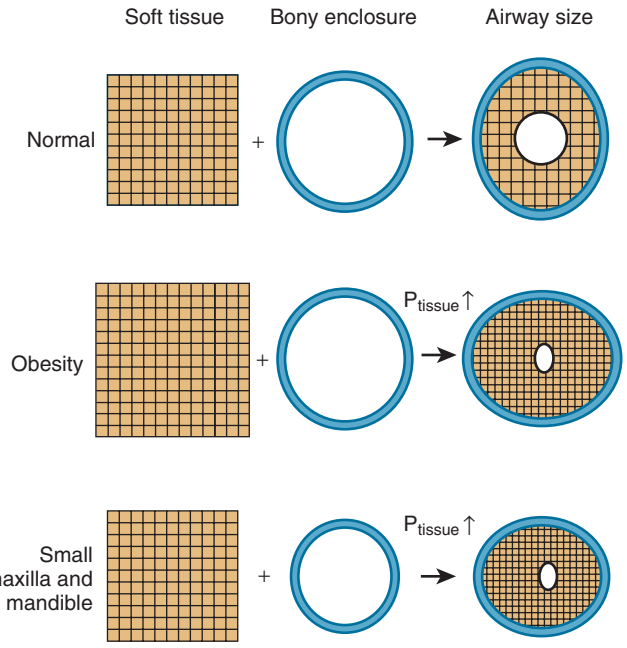

FIGURE 79-6 ■ Schematic shows the different mechanisms that can lead to compromise of upper airway size. The airway is the small open structure in the figures in the right column. The airway can be compromised by obesity that is associated with increased size of soft tissues, including tongue (*middle panel*), or by altered craniofacial dimensions (*bottom panel*). As the schematic shows, the reduction in airway dimensions is particularly in the lateral dimension rather than the anteroposterior. (Reproduced from Watanabe T, Isono S, Tanaka A, et al: Contribution of body habitus and craniofacial characteristics to segmental closing pressures of the passive pharynx in patients with sleep-disordered breathing. Am J Respir Crit Care Med 165:260–265, 2002, with permission.)

motor activity by suddenly altering intraluminal pressure in the upper airway, then measuring the biomechanical collapsibility of the airway. An even more direct method is to evaluate P_{crit} during anesthesia with paralysis, thereby completely eliminating motor activity, as reported by Isono and coworkers[30] (Fig. 79-7). Normal individuals have a negative P_{crit}, which means that significant negative intraluminal pressure is required to collapse the airway. For moderate sleep apnea, P_{crit} is more positive, whereas in severe sleep apnea, P_{crit} is actually positive, that is, these subjects require activation of upper airway dilator muscles to maintain patency of the upper airway. It has been proposed that there is increased activation of upper airway muscles during wakefulness in subjects with sleep apnea, thereby ensuring airway patency.[31]

Muscle Factors

There is also evidence that subjects with sleep apnea have damage to upper airway muscles, thereby creating a vicious circle.[32] This has been called the pharyngeal myopathy of OSA, and has been described in humans as well as in English bulldogs, the only natural animal model of OSA.[33] The concept is that the vibrations produced by snoring, combined with the large surges in intraluminal pressure, produce secondary changes in the muscles as well as the afferent and efferent nerve fibers that innervate the upper airway.[34,35] This concept was originally proposed by Friberg and colleagues[34,36] who coined the term "progressive snorers disease." A study of palatal tissue from patients with sleep apnea showed increased inflammatory cells in muscle and epithelium and increased expression of nerve cell adhesion molecule (NCAM) in muscle fibers,[37] which is seen when muscle fibers are denervated.[38,39] Hence, there is probably some degree of denervation of muscle fibers in the soft palate

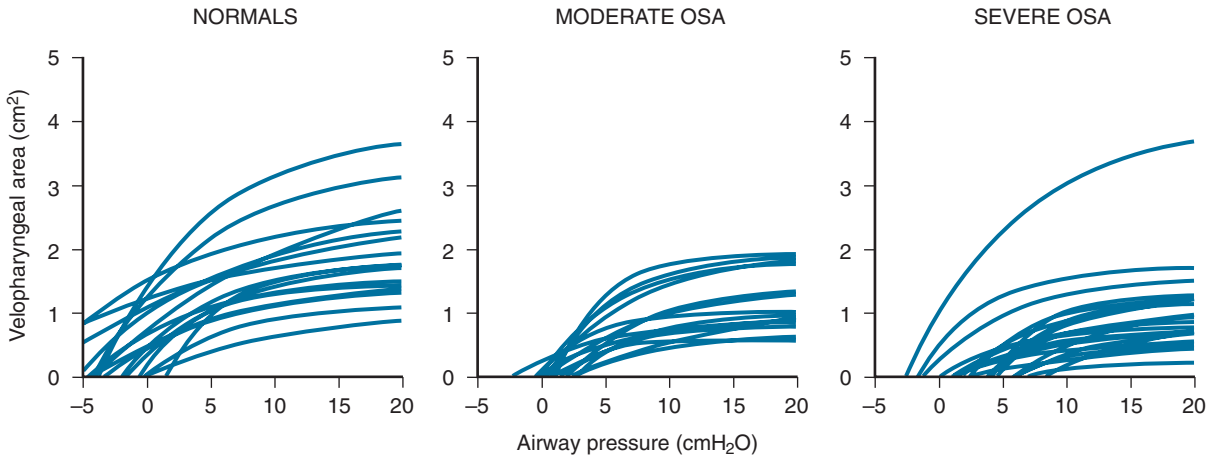

FIGURE 79-7 ■ Plots of velopharyngeal area against intraluminal pressure in a number of normal subjects (*left panel*), those with moderate obstructive sleep apnea (*middle panel*), and those with severe obstructive sleep apnea (*right panel*). In normals, airway area goes to zero at negative intraluminal pressure. In severe apneics, zero airway area occurs at positive pressures. Moderate obstructive sleep apnea subjects are intermediate. (Reproduced from Isono S, Remmers JE, Tanaka A, et al: Anatomy of pharynx in patients with obstructive sleep apnea and in normal subjects. J Appl Physiol 82:1319–1326, 1997, with permission.)

in patients with obstructive apneas. Whether this also occurs in other key muscles like the tongue is unknown. There is also evidence of damage to afferent fibers, with reduction in sensation in the upper airway of patients with sleep apnea.[35,40]

Fluid Shift at Night

An intriguing new concept is that fluid shifts from the legs to the torso, including upper airway structures, during sleep and recumbency play a role in the pathogenesis of OSA.[41–43] Application of pressure to the legs during sleep using antishock trousers, thereby enhancing fluid shift from the legs, increases upper airway dimensions[43] and increases airway collapsability.[42] Moreover, in nonobese subjects, with a body mass index (BMI) less than 30 mg/kg^2, the magnitude of fluid loss from the legs during sleep, as assessed by bioimpedance, is associated with the degree of sleep-disordered breathing.[41] The degree of fluid shift during sleep is associated with sedentary behavior during the day. Thus, particularly in elderly sedentary subjects, fluid accumulation in the legs during the day is likely to be part of the pathogenesis of OSA.

Different Phenotypes

These observations make it likely that specific pathogenetic mechanisms vary in patients with OSA. An additional mechanism is unstable action of the respiratory control system due to a phenomenon called "high loop gain," in which exaggerated neural inputs, for example, from chemoreceptors, produce higher than normal outputs.[44] Techniques to assess loop gain during sleep have been developed.[45] Accumulating evidence suggests that for some patients, a more collapsible upper airway is the major mechanism, whereas for others, high loop gain is more important.[46] Subjects with high loop gain might benefit from oxygen therapy, which reduces chemoreceptor responses and therefore loop gain.[47] However, oxygen is not a good strategy to treat sleep apnea, because it tends to lengthen apneas, further increasing arterial carbon dioxide pressure (Pa_{CO_2}) and reducing pH.

Arousals

The reason that oxygen lengthens apneas is that obstructive apneas are terminated by an arousal, that is, a sudden lightening of sleep state. Arousal is coupled to total ventilatory drive, that is, the magnitude of the neural output to phrenic and motoneurons for other pump muscles,[48,49] which depends in turn on the degree of hypoxia and hypercapnia. The role of arousals in the pathogenesis of OSA has been reviewed by Younes.[50] With arousal, there is a large increase in neural drive to the upper airway motoneurons as a consequence of the sudden change in sleep state. Arousal leads not only to sudden opening of the airway but also to a sudden increase in heart rate and in blood pressure owing to sympathetic activation.[51,52] Thus, arousals are not only beneficial in that they terminate the obstructive events but also potentially detrimental because of the cardiovascular effects.

CLINICAL RISK FACTORS FOR OBSTRUCTIVE SLEEP APNEA

These pathogenetic mechanisms relate directly to the clinical risk factors for OSA, which are summarized in Table 79-2.

Genetics

OSA aggregates in families, as shown in several different populations using relatively unique genealogic approaches: in the United States in the Cleveland Family Study[53]; in Scotland[54]; in Israel[55]; and in Iceland.[56] These studies in different populations have led to similar conclusions. The increased relative risk for having OSA in a first-degree relative of a patient with the disorder is 1.5 to 2.0.[53,56] Thus, obtaining a family history with respect to OSA and a history of snoring should be part of the routine evaluation of patients suspected of having sleep apnea. This genetic influence is mediated in part by obesity, which is a direct risk factor for sleep apnea. The genetic risk for OSA is, however, not due simply to obesity, because obesity-dependent and -independent genetic risks for sleep apnea have been described.[57] Although family aggregation has been demonstrated, genetic variants conferring risk for OSA have not yet been identified (for review, see Riha and associates[58]). Linkage studies have shown modest linkage peaks, but specific gene variants have not been found.[59–61] Association studies using candidate genes such as apolipoprotein E4 (ApoE4) have been performed, and both positive[62] and negative[63] associations have been reported. A genome-wide association study has not yet been conducted. The complexity of sleep-disordered breathing suggests that many different genes will contribute.

Upper Airway Anatomic Abnormalities

As outlined previously, patients with OSA have a smaller upper airway even in wakefulness.[24] Thus, anything that compromises upper airway anatomy is a risk factor for OSA. Sleep apnea is common in individuals with craniofacial disorders such as Treacher Collins and Pierre Robin

TABLE 79-2. Risk Factors for Obstructive Sleep Apnea in Adults

Obesity
Upper airway abnormalities
Craniofacial abnormalities
Endocrine diseases (hypothyroidism, acromegaly)
Postmenopausal status
Family aggregation

syndromes. In individuals who do not have specific craniofacial syndromes, there can be more subtle craniofacial differences such as retroposed mandibles and maxillas or reduced mandibular length. These differences can be quantified by analysis of digital photographs,[64] and the resulting data have some predictive value.[65]

Nasal obstruction is also a risk factor for OSA.[66] With increased nasal resistance, the intraluminal pressure in the pharynx is more negative if the subject has nasal breathing during sleep. This more negative intraluminal pharyngeal pressure facilitates airway collapse when the upper airway dilator muscles lose their tone during sleep.

Soft tissue abnormalities in the upper airway can also be a risk factor for OSA. Enlarged tonsils and adenoids are a major risk factor for OSA in children between the ages of 3 and 5 years (for recent reviews on pediatric sleep apnea, see Gozal and Kheirandish-Gozal[67] and Kheirandish-Gozal and Gozal[68]). Increased tongue size is also a risk factor, as occurs in patients with Down's syndrome, in whom OSA is common.[69] The macroglossia is often relative, that is, the tongue size is increased in relation to the craniofacial structure[70] even though it is not larger in absolute terms than in normal subjects. Occasional patients with upper airway tumors present with OSA.[71,72]

Thus, an important part of the evaluation of patients with OSA is to consider whether they might have upper airway abnormalities. Physicians should have a low threshold for referring patients for a detailed upper airway evaluation by an otolaryngologist, particularly when the reason for the OSA is not obvious.

Obesity

Obesity is the most important single risk factor for OSA in middle-aged adults. The increase in weight that confers risk can be modest, and many patients with OSA are not obese. Obesity has important interactions with other risk factors, such as craniofacial characteristics. The obesity risk was measured in a classic epidemiologic study from the Wisconsin Sleep Cohort.[4] Specifically, a 1 standard deviation in BMI triples the risk of OSA. The distribution of fat is important and patients with sleep apnea have increased neck circumference.[73] This link is so strong that measurement of neck circumference should be part of a routine physical examination.

The effect of obesity is not as marked in elderly subjects[74] so the role of obesity as a risk factor is less important in the elderly than in middle-aged subjects (Fig. 79-8). Several possibilities might underlie this observation: first, subjects with marked obesity are likely to die before becoming elderly; second, other pathophysiologic mechanisms might become increasingly important with age (e.g., the upper airway becomes more collapsible in elderly subjects)[75]; and third, sleep apnea seems to be a slowly progressive disorder that increases in severity with age.[76,77]

The mechanism by which obesity leads to OSA is unknown. Recent attention has focused on the concept that fat is deposited in the tongue, thereby increasing tongue size. Fat deposits in the tongue were originally demonstrated in an autopsy study, with the amount of tongue fat being associated with BMI.[78] Moreover, a polygenetic mouse model of obesity—the New Zealand Obese mouse—has an increased tongue size, as assessed by three-dimensional MRI, and a smaller upper airway than the relevant genetic control mouse.[79] Fat infiltration in the tongue of this mouse was demonstrated.[79] Increased tongue size is a common physical finding in sleep apnea patients with ridging of the tongue by the teeth.[80]

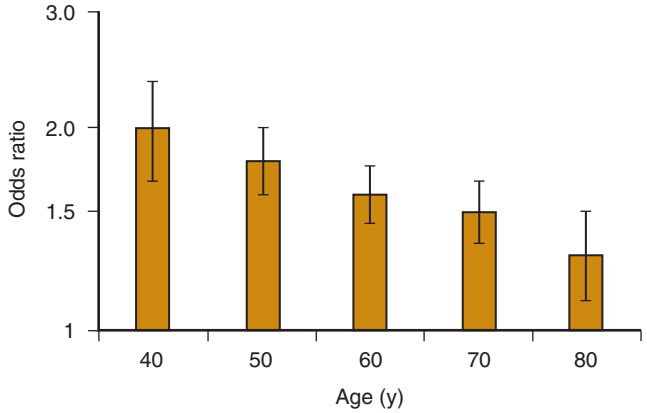

FIGURE 79-8 ■ Odds ratio (y-axis) in logarithmic scale for an apnea-hypopnea index of greater than 15 episodes/hr associated with a body mass increment of 5.3 kg/m^2, adjusted for sex and race. *Error bars* indicate 95% confidence intervals. The role of obesity declines with age. Data are from the Sleep Heart Health Study. (Reproduced from Young T, Shahar E, Nieto FJ, et al: Predictors of sleep-disordered breathing in community-dwelling adults: The Sleep Heart Health Study. Arch Intern Med 162:893–900, 2002, with permission.)

Endocrine Changes

Endocrine abnormalities also increase the risk for OSA. For example, OSA is more common in patients with hypothyroidism[81] and acromegaly.[82] Taking a detailed history, including questions relating to thyroid function, is important. Many practitioners have a low threshold for ordering thyroid function tests, particularly in individuals in whom the etiology of OSA is not obvious.

In females, sex hormones have a protective role. OSA is much less common in premenopausal than in postmenopausal women.[83,84] Moreover, epidemiologic studies show lower rates of OSA in postmenopausal women taking hormone replacement therapy than in those who were not.[83] The mechanism for this protective effect of female sex hormones is unknown. Because of the other adverse consequences of hormone replacement therapy,[85] estrogen is not recommended for postmenopausal women with OSA. Whereas OSA can occur in premenopausal women, the magnitude of the protective effect of female sex hormones is such that the diagnosis of OSA in premenopausal women should always be questioned.

CLINICAL PRESENTATION OF OBSTRUCTIVE SLEEP APNEA

In general, symptoms of OSA can be classified by their occurrence during nighttime (sleep) or daytime (wakefulness). During sleep, the majority of patients with OSA manifest loud, often disruptive snoring: in one study, nearly half of patients reported sleeping in a separate bedroom from their spouse or partner.[86] The bed partners of patients undergoing evaluation for sleep apnea can provide valuable history: in addition to snoring, the bed partner may describe apneic episodes, with periods of silence lasting 10 to 30 seconds or more that are terminated by snorting or choking sounds.[86] Although patients themselves are often unaware of whether they snore, they may perceive awakening with snoring, gasping, or choking or may experience dyspnea upon awakening.[87] Often, patients report awakening with a dry mouth, and some may complain of bruxism.[88] Many individuals with OSA experience nocturia, even in the absence of prostate disease, diuretic use, diabetes mellitus, or other contributory factors.[89,90] Patients with OSA usually describe unrefreshing or restless sleep, even after adequate time in bed for sleep.

The cardinal daytime complaint of patients with OSA is excessive daytime somnolence or fatigue. Individuals undergoing evaluation for OSA should be asked about whether they have experienced drowsiness with driving, because OSA increases the risk for fall-asleep crashes and near-misses.[91,92] Patients who fear driving restrictions (e.g., commercial drivers) may be very reluctant to reveal this history. A minority of patients complain of morning headaches. Because morning headaches can be a symptom of hypercapnia, patients with this complaint warrant additional evaluation for obesity hypoventilation, as described later.[93] Many individuals with OSA notice declines in cognition and performance, especially while performing tasks requiring concentration, cognitive processing, sustained attention, and executive functioning.[94] Patients and their families may also describe personality changes, depressive symptoms, decreased quality of life, and decreased libido.[95–97]

Epidemiology of Obstructive Sleep Apnea

A major community-based population study to document the prevalence of OSA was performed in middle-aged adults in the United States and reported the prevalence of OSA with daytime sleepiness to be between 2% to 4% in men and women between the ages of 30 and 60.[4] Since that time, a number of additional studies using large community samples have been performed in countries as diverse as Australia,[98] the United States,[6,83] China,[99,100] India,[101] Korea,[102] and Spain.[103] These studies are generally consistent in estimating the prevalence of OSA with symptoms to be approximately 3% to 8% in men and 1% to 5% in women.[4,6,83,98–102]

Prevalence estimates for OSA are affected by a number of factors. The characteristics of the population under study, such as the prevalence of obesity and the ethnicity of the population, can affect prevalence because these factors modify the risk for developing OSA. Different diagnostic methods for making the diagnosis of OSA can also cause estimates to vary or introduce bias. For example, methods to detect airflow and the willingness of people to undergo different types of testing vary in different locations. Variability in disease definitions (e.g., hypopnea definition[104,105] or AHI criteria defining OSA[83]) lead to different estimates of disease prevalence, even when studies use similar methods to collect data. The prevalence of sleep-disordered breathing events alone, without daytime symptoms, is considerably higher than the estimates cited above. For example, the Wisconsin Sleep Cohort Study found that 9% of women and 24% of men had an AHI of at least 5 events/hr.[4] In Pennsylvania, a community-based study estimated the prevalence of an AHI of at least 5 events/hr to be 17% in men; when the cutoff was increased to at least 15 events/hr, the prevalence was 7% in men and 2% in women.[83] Investigators in Spain observed that 26% of men and 28% of women had an AHI of at least 5 events/hr.[103]

Gender

Although data from early studies of OSA suggested that it was nearly exclusively a disease of males,[106,107] it is now well established that OSA is also common among women even though the prevalence of OSA is two to threefold higher in men than in women. Among women, several conditions increase the risk for sleep-disordered breathing. During pregnancy, nearly 25% of women have been reported to develop loud, regular snoring by the end of pregnancy[108]; further work is needed to determine the incidence of gestational sleep apnea. Data from several community-based studies show that the risk for OSA is approximately three times higher among postmenopausal women than among premenopausal women.[83,84] The higher prevalence of OSA among postmenopausal women is presumably related to declines in reproductive hormone levels. However, data describing how these hormone levels affect the anatomy and function of the upper airway or the control of breathing and ventilation leading to sleep-disordered breathing remain limited.[109–111] Women with polycystic ovarian syndrome, a common endocrine disorder of premenopausal women that is characterized by androgen excess and obesity, are at markedly increased risk for OSA, even when compared with weight-matched controls.[112,113]

Age

The prevalence of OSA increases with age through midlife, but appears to be relatively constant after the age of 60 to 65.[74] Among a sample of 385 elderly community-dwelling men and women at least 65 years of age, 81% had an AHI of at least 5 events/hr, and 62% had an AHI of at least 10.[114] In a community-based sample of men between 20 and 100 years of age, the odds ratio for

having an AHI of at least 10 events/hr was 6.6 (95% confidence interaval [CI] 2.6–16.7) for men between 65 and 100, as compared with men between 20 and 44 years of age.[6] The odds ratio for women between 65 and 100 years of age in this cohort having an AHI of at least 15 events/hr was 6.8 (95% CI 0.8–25.9) as compared with women 20 to 44 years old.[6,83] The Sleep Heart Health Study observed a plateau effect for the prevalence of OSA, beginning at approximately 60 years of age.[74] However, given the high overall prevalence of sleep-disordered breathing in individuals older than 65 years of age (>50% in several studies[74,103,104]) and conflicting reports regarding the risk for adverse outcomes,[115] controversy exists over the clinical significance of OSA in older people.

Ethnicity

The existing prevalence estimates for OSA are derived largely from white populations. However, a number of studies have been performed to characterize OSA in Asians as well as African Americans. Among other ethnic groups, data regarding the prevalence of OSA are very sparse. In midlife African Americans, the prevalence of OSA is similar to that in whites.[74,116] However, among African Americans younger than 25[116] or older than 65 years of age,[117] the prevalence of OSA appears to be higher as compared with either whites or African Americans in other age groups.

Several studies[99–102] have shown that despite a lower prevalence of obesity among Asians than in whites, the prevalence of OSA is similar in Asian and white population samples. Furthermore, after controlling for age and the extent of obesity, the severity of OSA tends to be higher in Asians than in whites.[118,119] The increased risk for OSA among Asians could be related in part to characteristics of the craniofacial anatomy.[118,120]

Snoring, one of the cardinal symptoms of OSA, is more common among Hispanic populations in the United States than in whites.[121,122] However, studies providing objective measurement of the prevalence of OSA in Hispanics and comparison with whites or other ethnic groups are not available. Studies in these and other ethnic groups are needed to provide a more complete understanding of the worldwide prevalence of OSA.

DIFFERENTIAL DIAGNOSIS OF EXCESSIVE SLEEPINESS

As noted previously, patients with OSA commonly complain of excessive sleepiness, and in managing these patients, it is important to consider the differential diagnosis of excessive sleepiness (Table 79-3).

TABLE 79-3. Differential Diagnosis of Excessive Daytime Sleepiness

Insufficient sleep syndrome
Restless legs syndrome
Narcolepsy
Delayed sleep-phase syndrome
Other medical conditions
Medications with sleepiness as a side effect
Kleine-Levin syndrome

Insufficient Sleep Syndrome

The insufficient sleep syndrome includes individuals who have no specific abnormality in their sleep but simply do not sleep enough. Insufficient sleep is extremely common in American society with about 35% of the population sleeping less than 6 hr/night.[123] For all patients being evaluated for a sleep disorder, a careful history should be taken about their sleep, including the time they go to bed, fall asleep, and wake up in the morning. The method of awakening also should be recorded, including whether they wake up spontaneously or use an alarm clock. Individuals with insufficient sleep will typically use an alarm clock to allow them to terminate their sleep. Insufficient sleep leads to performance impairments as well as metabolic consequences. Specifically, insufficient sleep affects glucose handling.[124] There is also an increase in ghrelin, which stimulates appetite, and a decrease in leptin, which inhibits appetite.[125] Thus, insufficient sleep is a risk factor for obesity.[126] Several excellent reviews about insufficient sleep are available.[127,128]

Restless Legs Syndrome

The restless legs syndrome is another common condition that leads to sleepiness. Patients with this disorder have abnormal sensations in their legs that come on typically in the evening, that is, before sleep, and are exacerbated by inactivity. Because of their time of occurrence and the effect of inactivity, these sensations can make sleep difficult. The symptoms of restless legs syndrome are exacerbated by iron deficiency. Thus, all patients suspected of having restless legs syndrome should have their serum iron and ferritin levels checked, and oral iron should be prescribed for patients who are iron deficient. Whereas restless legs syndrome can occur as a result of other conditions,that is, it is common in patients on renal dialysis and in pregnancy, a primary familial form also exists. Individuals with the familial form of restless legs syndrome typically present before they are 30 years of age.[129] Gene variants associated with restless legs syndrome have been identified in genome-wide association studies.[130,131] Whereas a number of different medications can be used for restless legs syndrome, dopamine agonists such as pramipexole (Mirapex) and ropinirole (Requip) can result in a dramatic reduction in symptoms (reviewed in Earley[132] and Trenkwalder and coworkers[133]).

Narcolepsy

Narcolepsy is another condition that can result in excessive sleepiness. Narcolepsy typically presents in the

second or third decade of life and has four cardinal features, including marked daytime sleepiness, cataplexy, hypnagogic or hypnopomic hallucinations, and sleep paralysis. These features reflect an intense pressure for REM sleep (dream sleep), such that aspects of REM sleep become apparent during wakefulness. Cataplexy is the sudden onset of muscle atonia, as occurs in REM sleep, that is precipitated in wakefulness by emotion. Laughter is the most common trigger. The atonia can be intense, such that the individual might fall to the floor. Hypnagogic or hypnopomic hallucinations are vivid dreams during wakefulness that occur either at sleep onset or at the end of sleep. Individuals with sleep paralysis wake up from sleep unable to move, because they are emerging from REM sleep and the REM-associated atonia has not been switched off. Although particularly common in narcolepsy, this phenomenon also occurs intermittently in otherwise healthy individuals.

Narcolepsy with cataplexy results from destruction of orexin-producing cells in the hypothalamus. These individuals have low levels of orexin in the cerebrospinal fluid.[134] This relationship with orexin deficiency is not found in individuals with other features of narcolepsy who do not have cataplexy.[134] Narcolepsy with cataplexy is associated with a particular human leukocyte antigen (HLA) (HLA DQBI*0602), which is present in about 80% of patients with this condition but is also found in approximately 25% of the general population.[135] The association between a particular HLA and narcolepsy with cataplexy suggests that the disorder may be an autoimmune disorder, with the autoimmune process leading to destruction of orexin-producing cells. Because this HLA is common in the general population, it raises a question about whether the autoimmune process requires an as yet unknown environmental trigger and/or the presence of other gene variants. The latter question has recently been addressed in a genome-wide association study comparing subjects with or without narcolepsy and cataplexy in a cohort in which all subjects (cases and controls) were HLA DQBI*0602–positive. With this design, an association with gene variants of the T-cell receptor alpha locus was identified.[136] Thus, narcolepsy with cataplexy seems to be an autoimmune disorder, and this is the first such disorder in which a role for a particular T-cell receptor gene variant has been identified.

Medications are commonly used to treat narcolepsy. The drug of choice for the excessive sleepiness is modafinil (Provigil), which promotes wakefulness. Occasional patients also require methylphenidate (Ritalin) or dexamphetamine in addition to modafinil to manage their sleepiness. When sleepiness is well managed, cataplexy improves, but in some patients, specific medications must be introduced for managing cataplexy. Tricyclic, monoamine oxidase inhibitor and selective serotonin reuptake inhibitor antidepressants improve cataplexy and γ-hydroxybutyrate (Xyrem) is approved by the U.S. Food and Drug Administration (FDA) for treatment of cataplexy based on the results of a placebo-controlled trial.[137] An excellent review of the management of narcolepsy is available.[138]

Delayed Sleep-Phase Syndrome

Abnormalities also occur in the circadian clock (for review, see Lu and Zee[139]). In such patients, sleep is usually normal, but it takes place at an abnormal time (i.e., it is phase shifted in relation to the light/dark cycle). These phase shifts are likely to be genetic, and heritability of the phase of the internal biologic "clock" has been shown in twin studies. The internal clock has a molecular mechanism, and since the mid 1990s, a great deal has been learned about the molecules involved (for review, see Siepka and colleagues[140]). Although a number of different feedback loops are involved, the core is a negative feedback loop in which clock proteins (three period molecules and two crytochromes) form a complex that is translocated to the nucleus to inhibit their own transcription. The role of genetic changes in producing phase shifts is shown by studies in the familial phase advance syndrome, a mendelian autosomal dominant condition. Patients with this syndrome go to sleep at around 7:30 PM and wake up at 4:00 AM, that is, they are profoundly phase advanced.[141] Two different mutations have been described in these patients—a single base mutation in the period two gene[142] and in casein kinase.[143] The latter enzyme is responsible for phosphorylating the clock proteins, and when phosphorylated, their degradation is accelerated.

Although the familial phase advance syndrome is proof of the concept of genetic variations, it is an uncommon condition. In contrast, the delayed sleep phase syndrome is much more common. Individuals with this abnormality have a marked phase delay. They may not be able to go to sleep until 3:00 AM or later, they sleep until noon, and their sleep is normal. These individuals function normally if they follow the timing of sleep set by their internal clock; however, they are constrained by the need to conform to expectations set by others. Thus, if they need to be at work at 8:00 AM or earlier, they will have inadequate sleep and be continually sleep deprived. This can be particularly troublesome for teenagers with delayed sleep-phase syndrome, because they need to wake up early to go to school. Techniques are available to shift the clock but are not particularly robust. Phase advance of the clock can be produced by melatonin in the evening and bright light in the morning.[144] Both of these interventions can advance the clock by about 1 hour. Thus, part of the management of patients with this disorder is to counsel them about activities and occupations that are compatible with their sleep-onset and -offset times.

Kleine-Levin Syndrome

A rare cause of sleepiness is the Kleine-Levin syndrome (for description of clinical features, see Arnulf and associates[145]). This typically presents in adolescents and individuals with this syndrome have intermittent episodes of intense hypersomnia. These episodes can last for days and the individuals may sleep for 20 hr/day. Associated features include markedly increased appetite during the

episodes and overt sexual behavior. The natural history of the disorder suggests that in later life, these episodes may disappear.

Other Conditions and Medications

Many other conditions can interrupt sleep and result in excessive sleepiness, including pulmonary conditions with nighttime cough, wheeze, and shortness of breath, and gastroesophageal reflux. Chronic pain at night is also a risk factor for sleep interruption and excessive sleepiness and is a prominent risk factor in older subjects complaining of sleepiness.[14]

Many medications also result in sleepiness as a side effect (e.g., antihistamines, some β-blocker drugs).[14] Thus, part of the evaluation of all patients with excessive sleepiness is to check whether their medications have sleepiness as a side effect.

DIAGNOSIS OF OBSTRUCTIVE SLEEP APNEA

The diagnosis of OSA is based on the presence of characteristic clinical symptoms and objective evidence of OSA. A number of patient questionnaires have been created to aid in the stratification of risk for OSA (e.g., Berlin Questionnaire,[146] Multivariable Apnea Prediction Index[87]). These questionnaires are most useful as screening tools in general populations.[147] Several clinical prediction models, which generally incorporate a combination of symptoms and anthropomorphic variables (e.g., BMI, neck circumference), also have been developed.[146–152] These models tend to be relatively sensitive (76%–96%) but not very specific (13%–54%).[153] Thus, there is a continuing need for better tools to objectively document sleep-disordered breathing.

Attended Polysomnography

The "gold standard" for the diagnosis of OSA remains full overnight polysomnography, performed in an attended laboratory setting. Full overnight polysomnography includes monitoring of electroencephalography (EEG), chin and anterior tibialis electromyography (EMG), oronasal airflow and snoring, thoracic and abdominal effort, electrocardiography (ECG), pulse oximetry, and body position. Scoring of sleep stages and arousals from sleep is performed from the EEG and EMG data. Apneas and hypopneas are scored according to the combination of oronasal airflow data, thoracoabdominal effort, and oxyhemoglobin saturation. The AHI, which indicates the severity of sleep-disordered breathing, is calculated based on the number of events per hour of sleep. In general, there is agreement across sleep laboratory facilities about the definition of apneas, that is, complete or near-complete cessation of airflow for at least 10 seconds,[4,105] with obstructive and central events differentiated by the presence or absence of chest and abdominal effort. However, the definition of hypopnea has varied according to the degree of desaturation (if any) that is required to accompany the event, whether arousals without desaturations define events, and whether diminution in airflow alone defines events.[104,105] These variations can lead to substantial disparities in the measured severity of sleep-disordered breathing.[104,105]

In clinical practice, the severity of sleep apnea is determined based on the number of apneas and hypopneas per hour of sleep. Fewer than 5 events/hr is normal, 5 to 15 events/hr represents mild disease, 15 to 30 events/hr defines moderate disease, and greater than 30 events/hr constitutes severe sleep apnea.[7] These definitions are helpful in classifying patients, and disease severity correlates with the likelihood of adverse outcomes (e.g., hypertension, cardiovascular mortality).[5,154] Nevertheless, these definitions fail to capture other significant aspects of OSA, such as the degree of oxyhemoglobin desaturation and nocturnal hypoxemia, or associated sleep disruption.

Unattended Sleep Studies

The increasing demand for evaluating sleep apnea and the relatively high costs associated with full-night attended polysomnography have led to the development of unattended sleep monitoring to evaluate patients for OSA. These studies are usually performed in patients' homes. For many patients, home sleep studies offer greater convenience and more closely replicate their usual night of sleep. The amount of data gathered during portable sleep studies spans a wide range: the most complex monitors can replicate the montage used in the laboratory, whereas other monitors do not monitor sleep and/or use fewer respiratory channels. Portable sleep monitors have been classified into four different types by the American Academy of Sleep Medicine according to the number of channels and types of recording. Attended laboratory polysomnographies are type 1 studies.[155] Type 2 studies are unattended, but generally collect EEG and electro-oculogram (EOG) data to allow sleep to be staged and include respiratory monitoring.[155] Type 3 devices must incorporate at least two airflow and/or respiratory effort channels, as well as oxygen saturation. Type 4 monitors record continuous single or dual bioparameters, typically including oxygen saturation or airflow.

Internationally, the use of portable sleep monitoring varies widely and is likely to be affected by a number of factors, including the availability of laboratory polysomnography and insurance guidelines regarding the reimbursement for portable studies. Even within the United States, substantial regional variation exists. The utility of these studies is likely to be greatest in two situations: for making the diagnosis of OSA in patients with relatively severe disease, because type 3 and 4 monitors, which frequently do not objectively measure sleep, are likely to underestimate the AHI; and for use among patients who may benefit from expedited diagnosis when laboratory polysomnography is not readily available.[156] Unattended monitoring is not recommended for cases in which central sleep apnea is suspected.

CONSEQUENCES OF OBSTRUCTIVE SLEEP APNEA

Pathophysiologic Mechanisms

The consequences of OSA follow from the physiologic changes that occur as a result of the apneic events. The apneic events are terminated by arousals that result in sleep being repetitively interrupted, that is, sleep fragmentation. This not only disturbs the continuity of sleep but also results in patients being "stuck" in the lighter stages of sleep and being deprived of both deep slow-wave sleep (stage N3) and REM sleep.

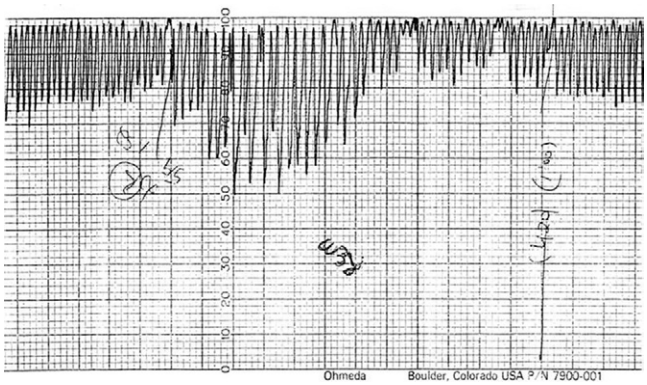

FIGURE 79-9 ■ Example of cyclical falls in oxygen saturation and then recovery in a patient with severe obstructive sleep apnea, as assessed by oximetry. The falls in oxygen in rapid eye movement (REM) sleep (middle of trace) are greater as the apneas were longer. The scale is 0% to 100% oxygen saturation. (Reproduced with permission from Pack AI: Changes in the cardiorespiratory system during sleep. *In* Fishman AP (ed): Fishman's Pulmonary Diseases and Disorders (4th ed). New York: McGraw-Hill, 2008, pp 1689–1695.)

The other major pathogenetic mechanism is the repetitive cyclical deoxygenation/reoxygenation with each event (see example, Fig. 79-9). It has been proposed by Lavie[157] that this is akin to repetitive ischemia/reperfusion with a burst of free radicals being produced with each reoxygenation. In this paradigm, OSA is an oxidative stress disorder, resulting not only in an increase in free radicals but also activation of nuclear factor-κB (NF-κB) with the production of downstream proinflammatory molecules.[158–160] Thus, OSA can lead to elevation of inflammatory biomarkers that are reduced with continuous positive airway pressure (CPAP) therapy.[161–167] However, not all studies agree on this point.[168,169] These pathways activated by OSA are the same pathways that are believed to be activated in obesity, so that both obesity and OSA can lead to overlapping pathogenetic consequences[170] (Fig. 79-10). Because obesity is a major risk factor for OSA, the coexistence of obesity and OSA can augment the pathogenetic consequences. Arnardottir and coworkers[170] have reviewed the molecular consequences of OSA.

Sequelae of Excessive Sleepiness

As described previously, sleep fragmentation and loss of deep NREM as well as REM sleep can lead to excessive sleepiness during the wakeful period. That REM sleep is chronically deprived in some patients with OSA is supported by the observation that when nasal CPAP is instituted for therapy, a dramatic increase in REM sleep occurs in many patients. Such patients report an almost miraculous effect of CPAP and indicate that they have not slept or felt as good for many years.

Excessive sleepiness results in people falling asleep at inappropriate times (e.g., while in conversation) and has a profound effect on quality of life. They can have difficulty coping at work and maintaining social

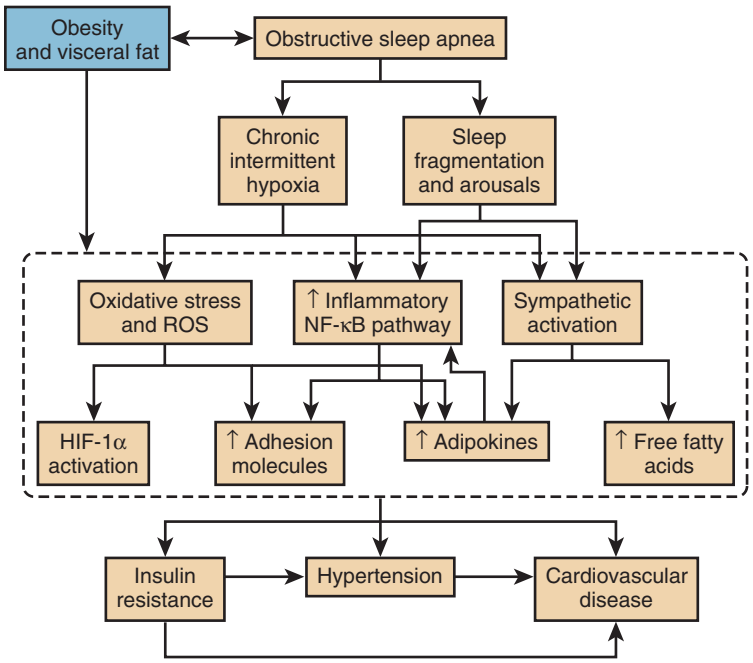

FIGURE 79-10 ■ Schematic illustrates the pathways involved in producing insulin resistance and cardiovascular disease as a result of obesity and obstructive sleep apnea. Both conditions affect the same molecular mechanisms. Because obesity is a risk factor for obstructive sleep apnea, determining the relative roles of these two conditions is challenging. HIF-1α, hypoxia-inducible factor-1α; NF-κB, nuclear factor κB; ROS, reactive oxygen species. (Reproduced from Arnardottir ES, Mackiewicz M, Gislason T, et al: Molecular signatures of obstructive sleep apnea in adults: A review and perspective. Sleep 32:447–470, 2009, with permission.)

relationships. OSA can lead to sexual dysfunction,[171] a finding that is replicated in animal models.[172] The adverse effect of OSA on quality of life and the positive effect of CPAP therapy have been shown in randomized trials.[173] Two specific quality of life instruments have been designed for use in patients with obstructive sleep apnea, and have shown that impaired quality of life improves with CPAP therapy. These include the Functional Outcomes of Sleepiness Questionnaire (FOSQ)[174] and the Sleep Apnea Quality of Life Instrument (SAQLI).[175] A new short form of the FOSQ instrument has been designed.[176]

Many patients with OSA suffer from depression. Epidemiologic studies reveal that the presence of untreated OSA is a risk factor for the development of depression.[97] Thus, symptoms of OSA should be sought in all patients presenting with depression, particularly those who are resistant to drug therapy for depression.

Patients with OSA and daytime somnolence are at significantly increased risk for vehicular accidents. This has been shown in several studies and a meta-analysis has been performed[92] (Fig. 79-11). Patients with untreated OSA have a twofold increase in the relative risk of automobile accidents. Studies show that in patients effectively treated with CPAP, the accident rates return to the same as the rest of the population.[177] This increased crash risk in patients with OSA is challenging to physicians, because if individuals are not treated, there are medicolegal implications. It is important, therefore, for practicing physicians to understand the relevant laws in their own state. Guidelines developed by the American Thoracic Society that were published in 1994[178] are being revised. A helpful discussion of this topic by several leading experts is recommended for the practicing physician.[179]

The increased rate of vehicular crashes is a particular issue for commercial drivers. Commercial drivers are largely male and tend to be more overweight than the general population.[180,181] Two studies, one in Australia[182] and one in the United States,[180,181] have shown a high prevalence of OSA in commercial drivers. Whereas the study in the United States also revealed associated impairment in driving tasks associated with OSA,[181] no data currently show that commercial drivers with OSA have an increased accident risk, because the relevant studies have not been done. Nevertheless, based on data from passenger car studies, an expert panel of the Federal Motor Carrier Safety Administration has recommended screening for OSA in commercial drivers at risk for the disorder as part of their routine medical assessment. These recommendations are published on the Federal Motor Carrier Safety Administration website (http://www.fmcsa.dot.gov/rules-regulations/TOPICS/mep/report/Sleep-MEP-Panel-Recommendations-508.pdf).

Insulin Resistance and Diabetes

Based on the mechanisms described previously, OSA might also lead to insulin resistance, a major risk factor for cardiovascular disease [for review, see Rader[183]]. The conclusion that OSA is an independent risk factor for insulin resistance (i.e., beyond the effects simply of obesity) is supported by association studies in general populations[184] and in a sleep center cohort.[185] Intervention data have also shown that treatment of OSA with CPAP improves insulin resistance,[186] although a second study was negative about this point.[187] Thus, OSA should be considered as part of the metabolic syndrome (Fig. 79-12).

The role of OSA as a risk factor for insulin resistance has led to studies in patients with type 2 diabetes, in whom OSA is extremely common.[188] Approximately 86% have at least mild sleep apnea (AHI > 5 events/hr), whereas 30.5% have moderate apnea and 22.6% severe sleep apnea. Thus, the presence of obesity and type 2 diabetes itself has a high positive predictive value for OSA. These data have led to the expectation that treatment of OSA in type 2 diabetics might improve glucose control, but existing studies conflict.[189,190] A negative study was performed in very obese subjects (mean BMI = 36.8 kg/m^2), raising the possibility that in the very obese, the effects of obesity are so overwhelming that

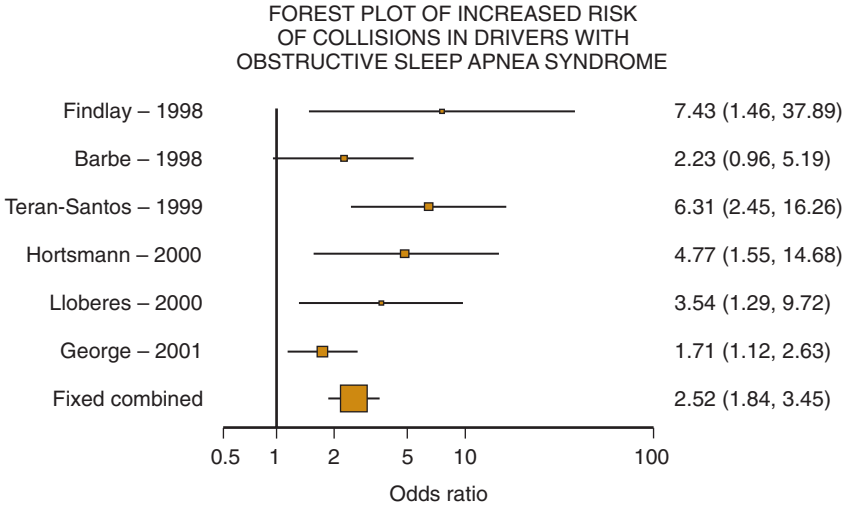

FIGURE 79-11 ■ Results of meta-analysis of studies assessing risk of collisions in drivers with untreated obstructive sleep apnea. The overall increased risk of crashes is slightly more than twofold. The original citations to the original studies are not provided, although the interested reader can obtain this information from the manuscript of Sassani and coworkers. (Reproduced from Sassani A, Findley LJ, Kryger M, et al: Reducing motor-vehicle collisions, costs, and fatalities by treating obstructive sleep apnea syndrome. Sleep 27:453–458, 2004, with permission.)

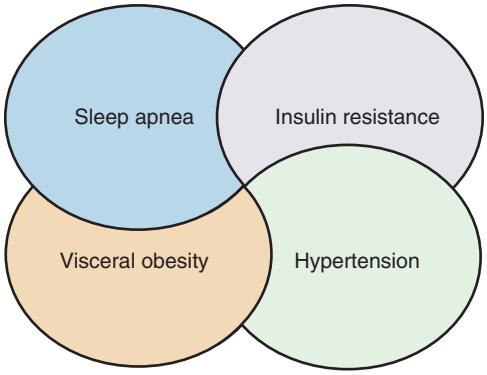

FIGURE 79-12 ■ A new concept of the metabolic syndrome. It includes not only insulin resistance, visceral obesity, and hypertension but also obstructive sleep apnea.

treatment of OSA has no effect. Further studies on this topic are needed.

CARDIOVASCULAR DISEASE

Hypertension

OSA is a risk factor for a number of cardiovascular sequalae [for review, see Pack and Gislason[191]], and the data are most convincing for hypertension. An animal model (dog) in which repetitive obstruction of the airway during sleep produced sustained hypertension during wakefulness, an effect that was reversed when the obstruction was no longer produced.[192] Moreover, when cyclic intermittent hypoxia mimicking that which occurs in OSA was produced in rats, sustained elevations of blood pressure occurred.[193]

Epidemiologic studies also show an independent association of OSA with hypertension after controlling for obesity in cross-sectional studies[5,194] and in the development of hypertension in a longitudinal cohort study.[195]

Randomized intervention studies with CPAP typically using sham CPAP as a placebo (i.e., application of CPAP with very low subtherapeutic pressures) also show improvements in blood pressure[196] (Fig. 79-13). Meta-analysis of these studies reveals that the average effect on blood pressure is small[197] (Fig. 79-14). However, one would not expect to see any improvement in blood pressure in some of these studies, because the inclusion and exclusion criteria excluded subjects with elevated blood pressure or who were on antihypertensive medications.[198] One study that included a large percentage of subjects with hypertension (42%) showed an average fall in mean blood pressure of 10 mm Hg.[199]

These results suggest that OSA might make individuals somewhat resistant to the effects of medical therapy for hypertension. OSA is common in refractory hypertension, defined as persistent hypertension despite treatment with a combination of three drugs.[200,201] Treatment of OSA in such individuals results in reduction of their blood pressure.[200,201] Thus, OSA should be considered in all patients with refractory hypertension.

Arrhythmias

OSA also is associated with cardiac arrhythmias. Whereas the early literature focused on heart block, recent attention has shifted to atrial fibrillation. Atrial fibrillation is more common in individuals with severe OSA than in those without OSA.[202] Patients with untreated OSA whose atrial fibrillation is controlled by cardioversion to sinus rhythm also more frequently relapse into atrial fibrillation.[203] Thus, OSA should be considered in all patients being evaluated for atrial fibrillation.

Cardiovascular Events

OSA has also been associated with cardiovascular events such as myocardial infarction and stroke in cross-sectional studies.[204] More definitive evidence comes from longitudinal follow-up of patients who refused therapy for OSA.[154,205,206] In these studies, there is an increased rate of cardiovascular events and cardiovascular mortality in patients with untreated severe OSA[154] (Fig. 79-15). Conversely, individuals with severe OSA who are treated with CPAP show no elevation of cardiovascular event rates as compared with controls.[154] One study also showed an increase in cardiovascular event rates in patients with moderate OSA.[207]

Whereas these data support the conclusion that treatment of OSA reduces cardiovascular risk, it may also be true that refusal of CPAP is a marker of general nonadherent behavior and that such individuals do not take other medications. Thus, the increased event rate might not be a specific effect of not being treated for OSA, but rather could be a result of poor adherence to health-promoting behaviors. If so, one might anticipate that there would be an association between medication use and CPAP use. One study found this to be true[208] whereas another study did not,[209] so this remains an open question.

Ultimately, there will be a need for randomized intervention studies of OSA treated with well-defined cardiovascular end points. Such a study is currently under way in Sweden[210] and a second much larger multicenter study is being conducted in Australia—the Sleep Apnea Cardiovascular Endpoints Study (SAVE) trial. The need for randomized intervention studies has been reviewed by Pack and Gislason.[191]

Current evidence raises questions about whether individuals with OSA who are not particularly symptomatic, that is, excessively sleepy, should be treated to reduce cardiovascular risk, but definitive data to support this recommendation are not available. CPAP is a safe and effective treatment if the individual can adhere to this therapy. On balance, it is prudent to share the current data with patients and to recommend therapy in such individuals, because they will likely benefit from therapy and there are no major risks. If the individuals cannot tolerate CPAP, more aggressive treatment is not warranted at this time.

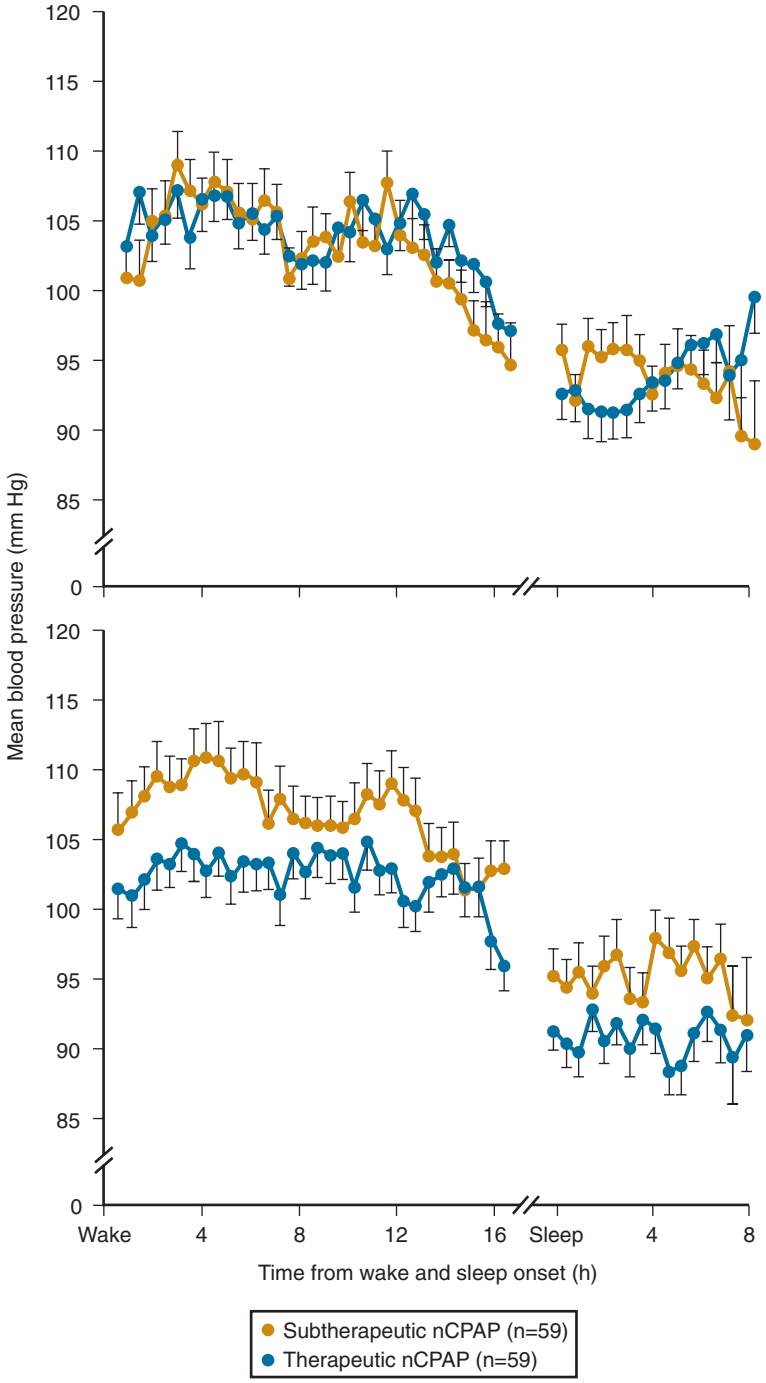

FIGURE 79-13 ■ Twenty-four-hour blood pressure in two groups of subjects with severe obstructive sleep apnea. One group was randomized into active continuous positive airway pressure (CPAP) for 1 month (*blue circles*—therapeutic nasal continuous positive airway pressure [nCPAP]) while the other group used sham CPAP (*brown circles*), that is, CPAP at a very low, ineffective pressure (labeled in the figure as subtherapeutic). Before treatment, the therapeutic group and subtherapeutic group had comparable blood pressures across the day (*top panel*). However, with active CPAP, there was a significant fall in blood pressure in the group on active CPAP but not in the sham group (*bottom panel*). (Reproduced from Pepperell JC, Ramdassingh-Dow S, Crosthwaite N, et al: Ambulatory blood pressure after therapeutic and subtherapeutic nasal continuous positive airway pressure for obstructive sleep apnoea: A randomised parallel trial. Lancet 359:204–210, 2002, with permission.)

ATHEROSCLEROSIS AND MECHANISMS FOR CARDIOVASCULAR EVENTS

OSA might lead to cardiovascular events in a number of ways. First, hypoxic events during sleep might precipitate cardiovascular events. This is believed to have happened to the famous National Football League (NFL) player, Reggie White. NFL players on both the offensive and the defensive lines have a high prevalence of OSA.[211] This hypothesis is supported by sleep studies in individuals who presented with a new myocardial infarction. Individuals with OSA are more likely to have their acute events between the hours of midnight and 6:00 AM as compared with those without OSA.[212]

An alternative hypothesis based on the concept that OSA is an oxidative stress disorder and leads to a proinflammatory state is that OSA can lead to atherosclerosis. For example, C57BL/6 male mice developed aortic atherosclerosis when they were fed a high-fat diet and subjected to cyclic intermittent hypoxia mimicking what occurs in OSA (Fig. 79-16).[213] Neither challenge on its own led to atherosclerosis,[213] suggesting that cyclic intermittent hypoxia and high-fat diet interact to produce

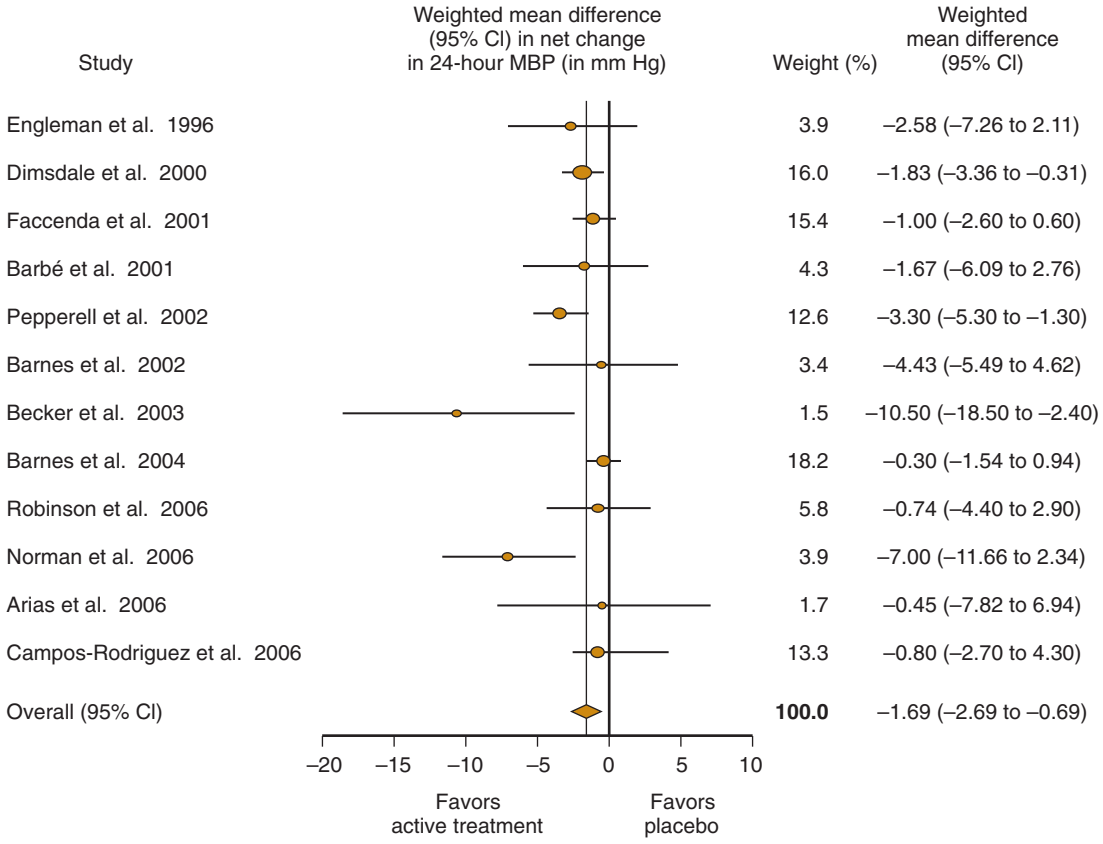

FIGURE 79-14 ■ Results of meta-analysis of effects of CPAP treatment on mean 24-hour blood pressure in patients with obstructive sleep apnea. There is overall a significant, albeit small, effect. Although the test for heterogeneity of results is not significant (P = .07), there was substantial variation between studies in the inclusion/exclusion criteria. One study excluded individuals with hypertension, another with sleepiness. Original articles are not cited but are available in the manuscript of Haentjens and coworkers. (Reproduced from Haentjens P, Van Meerhaeghe A, Moscariello A, et al: The impact of continuous positive airway pressure on blood pressure in patients with obstructive sleep apnea syndrome: Evidence from a meta-analysis of placebo-controlled randomized trials. Arch Intern Med 167:757–764, 2007, with permission.)

atherosclerosis even though the C57BL/6 male mice are relatively resistant to atherosclerosis.[214]

Another interesting hypothesis relates to atherosclerosis specifically in the carotid arteries. It has been proposed that the vibration produced by snoring is transmitted to the carotid artery and produces vessel wall damage. Vibration of rat tails leads to endothelial damage in blood vessels.[215] The time an individual spends snoring during the night in subjects who snore but have few apneas is strongly associated with the presence of plaques in the carotid artery but not the femoral artery.[216] This observation needs to be confirmed in other studies and then tested in intervention studies. If this concept is true, it will fundamentally change medical practice, because treating persistent snoring in individuals without OSA could be very beneficial.

MORTALITY

Not surprisingly, untreated OSA is associated with increased mortality.[217-219] This increased mortality is related to cardiovascular deaths and occurs largely in individuals with severe OSA. Interestingly, the survival curves for patients with severe OSA are identical whether or not patients complain of sleepiness.[217] This adds support for treating nonsomnolent patients with OSA.[220]

The increased mortality associated with sleep apnea is most marked in younger individuals and is not found in those over the age of 65 years.[221] Indeed, it has been argued that in the elderly, the presence of OSA might be protective because it is like ischemic preconditioning and can lead to increased vascular endothelial growth factor (VEGF) and collateral coronary vessels.[222] The evidence for this is not yet sufficient to modify clinical practice and not treat older adults with OSA.

TREATMENT OF OBSTRUCTIVE SLEEP APNEA

Treatment options for OSA generally fall into three categories: positive airway pressure (PAP), oral appliance therapy, and surgery. Among these, PAP is widely

accepted to be the most efficacious option (i.e., it works under ideal conditions, such as in the sleep laboratory), though the effectiveness of PAP therapy (i.e., whether it works in routine clinical care) is poorer, because of variability in the acceptance of and adherence to PAP therapy.

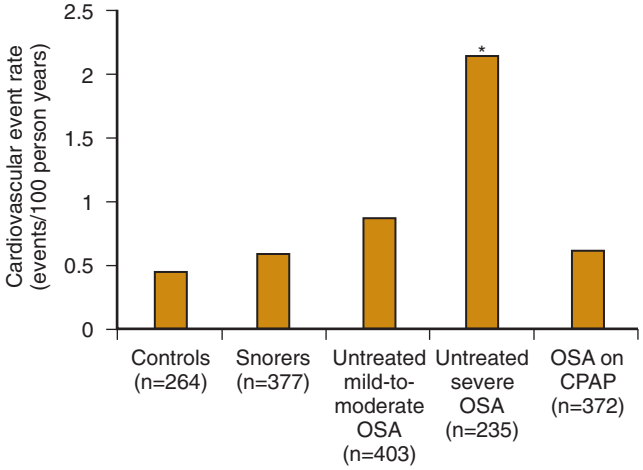

FIGURE 79-15 ■ Cardiovascular event rate over a 10-year period in five cohorts, all matched for age and body mass index (BMI). All subjects are male. Patients with untreated severe obstructive sleep apnea have a marked significant (*) increase in event rate compared with all other groups. Individuals with severe obstructive sleep apnea on CPAP have no increase in event rate. Data are from Marin and colleagues.[154] (Reproduced from Pack AI: Advances in sleep-disordered breathing. Am J Respir Crit Care Med 173:7–15, 2006, with permission.)

Positive Airway Pressure Devices

CPAP is the most commonly prescribed type of PAP therapy, and a number of studies have shown that CPAP is an effective treatment for excessive daytime sleepiness.[223–226] A meta-analysis of randomized, controlled trials for OSA demonstrated that improvements in subjective sleepiness (as measured by the Epworth Sleepiness Scale) were greatest in individuals with severe disease.[227] PAP treatment of individuals with severe OSA has been associated with a reduction in the rate of motor vehicle crashes.[177] Other studies examining the effect of PAP on general and disease-specific quality of life measures have mostly observed improvements with PAP therapy.[198,224,228,229]

CPAP delivers a preset level of pressurized air to the upper airway that prevents airway closure by acting as a "pneumatic splint" and is administered at a constant level throughout both inspiration and expiration. The appropriate level of therapy to eliminate apneas and hypopneas is determined during a CPAP titration study, which is usually performed during monitored overnight polysomnography; successful treatment strategies involving portable sleep monitoring and auto-setting continuous positive airway pressure (auto-PAP) titration have also been developed.[230–232] Treatment algorithms using predictive equations to determine the PAP prescription often require adjustments in pressure based on patient and bed partner report to establish a final treatment pressure.[231,233] The level of pressure needed to eliminate

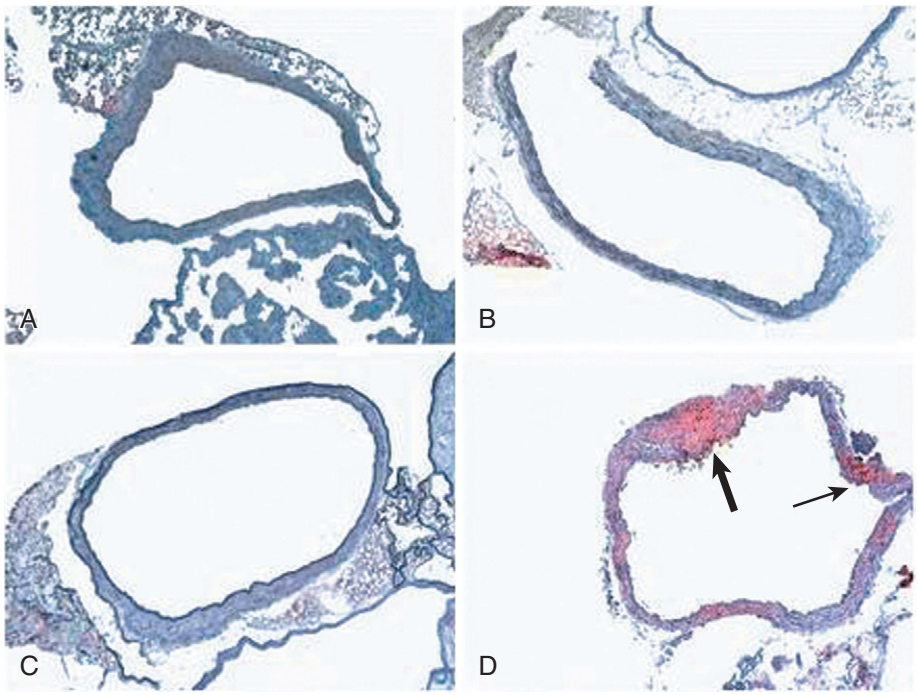

FIGURE 79-16 ■ Aortas of C57BL/6 male mice who received different interventions for 3 months. **A,** Normal diet, no intermittent hypoxia. **B,** Normal diet with cyclical intermittent hypoxia for 8 hr/day. **C,** High-fat diet, no intermittent hypoxia. **D,** High-fat diet and cyclical intermittent hypoxia for 8 hr/day. Only the last group developed atherosclerotic plaques (marked by *arrows*). (Reproduced from Savransky V, Nanayakkara A, Li J, et al: Chronic intermittent hypoxia induces atherosclerosis. Am J Respir Crit Care Med 175:1290–1297, 2007, with permission.)

sleep-disordered breathing events is affected by several factors. Body position during sleep can affect the degree of pressure needed, because the airway is generally more collapsible while the individual is in the supine position. Sleep stage can also affect the degree of pressure required, with higher pressures needed during REM sleep, when REM muscle hypotonia may cause the airway to be more collapsible.[234] Although alcohol and benzodiazepine use might be expected to increase the level of CPAP pressure needed, small studies looking at these factors have failed to show a need for higher pressures.[235–237]

In addition to CPAP therapy, there are several other modalities for delivering PAP, including bilevel positive airway pressure (BPAP), auto-PAP, and auto-setting bilevel positive airway pressure (auto-BPAP). An alternative mode of PAP, adaptive servoventilation (ASV), has been developed for use in patients with central or complex sleep apnea.

BPAP differs from CPAP in that BPAP delivers a higher fixed level of pressure during inspiration and a lower fixed pressure during expiration. For patients who require high levels of CPAP therapy to prevent airway collapse, the lower pressure administered during expiration can make PAP easier to tolerate.[238,239] For patients who require ventilatory support, such as patients with OSA and concomitant obesity hypoventilation or chronic obstructive pulmonary disease (COPD) with respiratory failure, BPAP also provides a pressure gradient for augmenting ventilation.[240,241] A backup respiratory rate is generally not set for patients with OSA receiving BPAP unless central apneas are also present.

Auto-PAP and BPAP devices respond to variations in flow limitation, airflow magnitude, airway impedance, and vibration (snoring) depending on the individual device algorithm.[236,242] These devices vary the level of pressure administered to the patient during each episode of use, allowing the delivery of the lowest pressure that overcomes airflow limitation, between a minimum and a maximum pressure determined by the provider. Auto-setting devices can be used in situations in which patients have difficulty tolerating a fixed, higher level of CPAP or BPAP, especially when sleep-disordered breathing events may be concentrated by sleep stage (e.g., REM-related apnea) or position. Nevertheless, greater adherence to auto-PAP devices than to CPAP has not been consistently demonstrated,[18,242] and adherence to auto-setting BPAP has not been extensively examined. Auto-setting devices can also be used for unattended titrations of PAP: data collected over several days or weeks can be analyzed to provide information about the pressure that is most likely to be effective.[230–232]

A variety of interfaces are available for delivery of PAP, including nasal masks, nasal-oral (full face) masks, nasal inserts ("pillows"), and hybrid nasal-oral masks. A trial of several different masks is sometimes necessary to find a well-fitting mask that is comfortable for the patient. Factors to consider in mask fitting include whether the patient is susceptible to claustrophobia, the use of eyeglasses, the presence of nasal congestion or facial hair, and the shape of the face and nasal bridge. The routine inclusion of a heated humidifier unit in line with the PAP device has been shown in some studies to result in greater adherence to therapy.[243–245]

Recent advances in technology have enabled PAP devices to record sophisticated measurements of adherence to therapy beyond the total number of hours of use. Data regarding the duration and patterns of nightly use, the degree of residual sleep-disordered breathing, and mask leak all create opportunities for augmenting patients' self-report regarding PAP adherence and allow for changes to therapy based on objective data (e.g., by correcting mask leak or by increasing pressure to correct an elevated residual AHI). Because adherence in the first week of PAP use is important in predicting longer-term use,[229,246] adherence monitoring and close follow-up after initiation of PAP should be key components of treatment programs.

Oral Appliance Therapy

Oral appliances for treating OSA are designed to maintain upper airway patency during sleep. Most oral appliances are mandibular advancement devices that advance the position of the lower jaw during sleep.[247] Tongue-retaining devices are less well studied. Mandibular advancement devices vary not only in their design features and material but also in the degree to which they are customized for individual patients. A recent Cochrane review of the effect of oral appliances in the treatment of OSA in adults found that CPAP was more effective in reducing the severity of OSA (i.e., AHI) and sleep disruption and at improving the minimum oxygen saturation during sleep.[248] However, compared with sham oral appliances, active oral appliance use reduces the severity of OSA and improves daytime sleepiness.[248]

Oral appliances are not generally considered first-choice treatment for patients with OSA in whom symptoms and sleep disruption are severe.[249] They are recommended for patients with mild to moderate OSA and those unable or unwilling to use PAP.[249] Overall, the ability of oral appliances to reduce the severity of sleep-disordered breathing to less than 10 events/hr has been estimated to be approximately 50%, and oral appliances reduce the mean AHI by approximately half.[250] The major problem with intraoral devices is that although on average, they produce improvement, there is variation in effectiveness between individuals, and some have no improvement (Fig. 79-17). Thus, sleep studies following treatment are essential to demonstrate the effectiveness of oral devices.

Surgical Treatment of Obstructive Sleep Apnea

The success of surgical treatments for OSA, aside from tracheotomy, is unpredictable and generally less effective than PAP therapy.[251] The objective of the surgical treatments for OSA is to relieve sites of upper airway obstruction within the naso-, oro-, and hypopharynx. A number of procedures have been developed, including

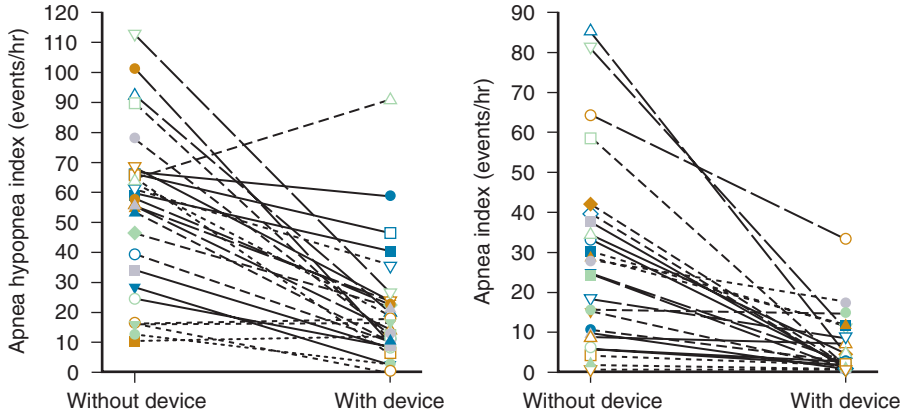

FIGURE 79-17 ■ Effect of an intraoral device on apnea-hypopnea index (*left panel*) and apnea index (*right panel*) in subjects with obstructive sleep apnea. Treatment improved sleep-disordered breathing when assessed across all subjects. In some cases, the improvement is dramatic, but some subjects do not improve and others get worse. (Reproduced from Henke KG, Frantz DE, Kuna ST: An oral elastic mandibular advancement device for obstructive sleep apnea. Am J Respir Crit Care Med 161:420–425, 2000, with permission.)

procedures to reduce soft palate redundancy, such as uvulopalatopharyngoplasty, uvulopalatal flap surgery, and laser-assisted uvulopalatoplasty.[251] Surgeries for nasal and palatal reduction, as well as tongue reduction or tongue advancement surgeries, are referred to as phase 1 surgeries and may be performed in combination or separately from phase 2 surgeries such as maxillomandibular advancement.[251] Although tracheotomy bypasses the upper airway and provides an effective cure for OSA,[252] this procedure is performed only rarely because it is not well accepted by patients. Tonsillectomy and adenoidectomy, a first-line intervention in children, does not reliably improve sleep-disordered breathing in adults.

Only a small number of clinical trials to assess the effectiveness of different surgical techniques for treatment of OSA have been performed.[253] Uvulopalatopharyngoplasty has been reported to reduce the AHI in patients with mild to moderate OSA to less than 50% of baseline or less than 20 events/hr in approximately 40% to 50% of cases. These are less stringent criteria as compared with PAP therapy, in which AHI is reduced to less than 5 events/hr.[254] Because the available evidence does not support widespread use of the surgical therapies, even among patients with mild to moderate OSA,[253,255] surgery should be limited to patients unwilling to consider other forms of treatment or as an adjunctive therapy (e.g., for relief of nasal obstruction to increase tolerance to PAP therapy).[251]

Alternative/Adjunctive Therapies for Obstructive Sleep Apnea

Because of the strong association between obesity and OSA, a major focus of long-term OSA treatment should be on weight loss. Data from two large cohort studies and a number of other studies show that apnea severity changes with changes in weight, although the magnitude of change is greater with weight gain than with weight loss.[76,77,256,257] In the minority of patients with purely positional apnea (usually in the supine position), maintaining alternative sleep postures (e.g., by using a body pillow) is an effective treatment strategy.

A flow diagram outlining an overall approach to treatment of OSA, based on the different modalities of therapy, is shown in Figure 79-18.

CENTRAL SLEEP APNEA

Central sleep apnea is less common than OSA.[258] Central sleep apnea is more complex, however, because a number of different mechanisms are involved. Central sleep apnea can be divided into hypercapnic and hypocapnic types. Hypercapnia occurs in neuromuscular diseases and in association with sleep-related hypoventilation. The apnea in this case is an extreme form of hypoventilation disorders that lead to hypercapnic central sleep apnea. The conditions in which this occurs include brain-stem lesions such as syringomyelia, spinal cord disorders, stroke, muscle disorders such as muscular dystrophy, and Shy-Drager syndrome (dysautonomia).

CONGENITAL HYPOVENTILATION

Chronic congenital hypoventilation is a rare form of hypercapnic central sleep apnea that presents in early childhood and is also known as Ondine's curse. Individuals with this disorder have relatively normal ventilation during wakefulness but a very blunted or absent response to hypercapnia.[259] These subjects hypoventilate when they fall asleep, due to central sleep apnea. During sleep, the ventilatory control system is much more dependent on the chemical drive to breathe when the wakefulness stimulus for respiration is lost.

The genetic basis of this disorder has been identified.[260] The majority of cases have an abnormal number

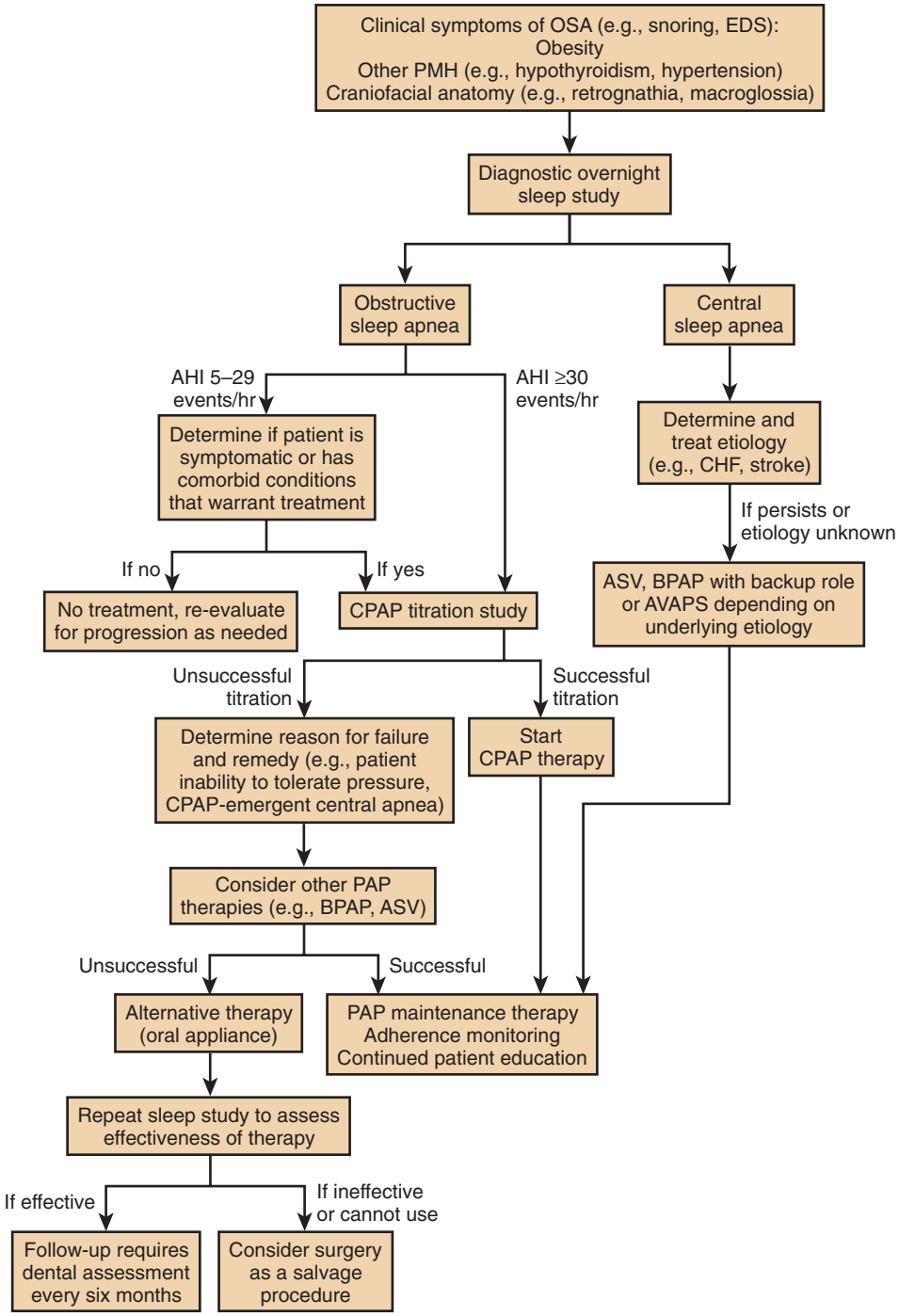

FIGURE 79-18 ■ Flow diagram outlines a treatment algorithm that can be used for diagnosis and management of obstructive sleep apnea. The algorithm has CPAP as a first-line therapy with intraoral devices as a second line. Upper airway surgery is essentially a salvage procedure that can be used to reduce the overall degree of sleep-disordered breathing when other modalities have failed.

of polyalanine repeats in exon 3 of the PHOX2B gene.[260] These mutations usually arise de novo and there is no family history. This gene is a transcription factor involved in development of the autonomic nervous system. Mice with increased polyalanine repeats in the gene have absent responses to hypercapnia, as do human patients, and marked instability of ventilation.[261] In normal individuals, there are usually 20 polyalanine repeats in this location in the gene. In patients with congenital hypoventilation, the number of repeats is typically 25 to 33 repeats. Interestingly, a few patients have been described who presented in adulthood (in their 20s) who had 25 repeats.[262] Other mutations in this gene can also lead to the syndrome.[263] Patients with congenital

hypoventilation also have associated Hirschprung's disease and neural crest tumors. The frequency of these associated conditions is higher in individuals with the rarer mutations of the gene than in those with the more common excess polyalanine repeats.[263]

Patients with congenital hypoventilation can be successfully treated if they are ventilated during the sleep period, because hypoventilation occurs only during sleep. Although this might be achieved by noninvasive ventilation using a face mask, this mode of ventilation is not secure. Therefore, these patients usually are treated by tracheostomy early in life for secure nocturnal ventilation using a positive-pressure ventilator. During the day, the tracheostomy is capped so that individuals can function normally. These patients often live into adulthood and need ongoing management of their nocturnal ventilation and their tracheostomy from physicians who care for adults.

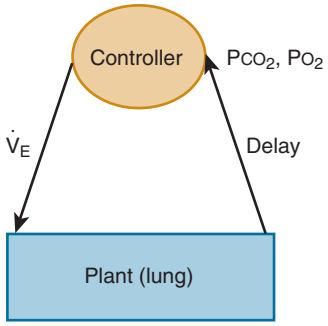

FIGURE 79-19 ■ Overview of control system for ventilatory control. The plant being regulated is the lung. The control variables are carbon dioxide pressure (P_{CO_2}) and oxygen pressure (P_{O_2}), which are served by the central and peripheral chemoreceptors. There is a delay between the plant and the controller. The controller adjusts ventilation ($\dot{V}_E$) in response to the changes in the chemical stimuli.

Hypocapnic Central Sleep Apnea

In contrast to congenital hypoventilation, hypocapnic sleep apnea has a different etiology resulting from alteration in the CO_2 apnea threshold during sleep.[264] During wakefulness, there is a strong drive to breathe that is not coupled to the chemical drive from Pa_{CO_2} and arterial oxygen pressure (Pa_{O_2}). This drive has been termed the "wakefulness stimulus." With the onset of sleep, this drive is lost, and the ventilatory control system becomes almost entirely dependent on the chemical drive to breathe. Thus, if subjects are artificially overventilated during wakefulness, rhythmic respiration is sustained even at low Pa_{CO_2}. In contrast, during sleep, dropping the Pa_{CO_2} by only a few torr below the awake Pa_{CO_2} can result in apnea (i.e., a CO_2-dependent apnea threshold emerges during sleep). Individuals hypoventilate during sleep as a result of the increase in upper airway resistance, so that Pa_{CO_2} rises approximately 2 to 6 torr during sleep. Because of the emergence of the CO_2-dependent apnea threshold during sleep, hypocapnia from any cause is a risk factor for central apnea, because such individuals will be closer to the sleep-related apnea threshold.

Another important concept in the pathogenesis of central apnea of the hypocapnic type is instability of the respiratory control system.[44] Any negative-feedback control system can produce self-sustaining oscillations when the overall response of the control system is high enough and there is a delay between the plant being controlled and the sensors (Fig. 79-19). The responsiveness of the control system is determined by overall loop gain, which is the product of the chemoreceptor response (increase in ventilation for a given increase in Pa_{CO_2} or fall in Pa_{O_2}) and plant gain, which is the change in Pa_{CO_2} for a given change in ventilation. Unstable operation of the respiratory control system results in self-sustaining oscillations in ventilation that are evident as periodic breathing. At the peak of ventilation, Pa_{CO_2} will be driven down to the CO_2-dependent apnea threshold and apnea will ensue.

In this type of apnea, arousals with interruption of sleep can occur but arousals will occur at the peak of ventilation not at the end of the apnea. As described previously, arousal is coupled to total ventilatory output. In unstable ventilation with hypocapnic central apnea, the maximum ventilatory output is at the peak of the ventilatory cycle, at which time an arousal may occur (Fig. 79-20). In contrast, in OSA, the peak ventilatory output to the diaphragm and other pump muscles occurs at the end of the apnea. This difference in the timing of arousals in these two different types of apnea is an important distinguishing feature.

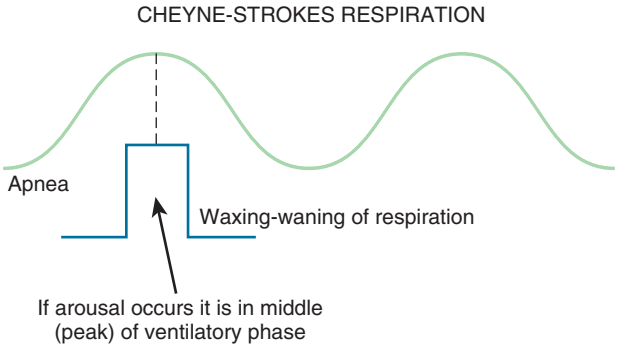

FIGURE 79-20 ■ Schematic shows the waxing and waning of ventilation that occurs in Cheyne-Stokes respiration. As illustrated, when arousal occurs in this type of sleep-disordered breathing, it occurs at the peak of the ventilatory phase, that is, maximal ventilatory output. In obstructive sleep apnea, the maximal ventilatory output occurs at the end of the apnea, and hence, this is when arousals occur. This different timing of the arousal can be helpful in distinguishing the different types of sleep-disordered breathing.

Periodic breathing with hypocapnic central apnea occurs at high altitude and in Cheyne-Stokes respiration. At high altitude, individuals are hypoxic, ventilation is stimulated and Pa_{CO_2} is reduced. The overall chemoreceptor sensitivity and, hence, loop gain are increased. This increase is due to augmentation of input from the peripheral chemoreceptor sensing hypoxia, that is, the

carotid body. Thus, unstable periodic breathing with central apneas can result with the relevant delay being between the lungs and the carotid body. Because this delay is short, the cycle times of these oscillations in ventilation is of the order of 20 seconds. This is the mechanism by which central apneas occur in normal subjects sleeping at high altitude. These apneas result in sleep fragmentation, excessive sleepiness, and other consequences. Central apneas at high altitude can be treated with acetazolamide (Diamox). This seems surprising because acetazolamide produces metabolic acidosis and is a ventilatory stimulant. However, animal studies show that acetazolamide has a different effect on the Pa_{CO_2} during eupnea in wakefulness and the CO_2-dependent apnea threshold.[265] Specifically, it increases the difference between the eupneic Pa_{CO_2} and the apnea threshold, making central apnea less likely.

Cheyne-Stokes Respiration

In contrast to periodic breathing at high altitude, the cycle times of the ventilatory oscillations in Cheyne-Stokes respiration are longer, of the order of 60 to 120 seconds (Fig. 79-21). These are mediated by the central rather than peripheral chemoreceptors, and hence, the relevant delay is between the lungs and the central chemoreceptors. Cheyne-Stokes respiration was originally described in two different independent reports by Irish physicians (Cheyne and Stokes) in the early part of the 19th century.[266,267] Cheyne-Stokes respiration is seen in patients with stroke, encephalopathies, heart failure, and other conditions.[268–270] Cheyne-Stokes respiration has been better studied in patients with heart failure than in patients with stroke.

Early reports from case series suggested that Cheyne-Stokes respiration is extremely common in patients with systolic heart failure.[271,272] Specific risk factors for the presence of Cheyne-Stokes respiration in patients with heart failure include age (risk is higher in those >65 years of age); male gender; presence of atrial fibrillation; and hypocapnia (Pa_{CO_2} < 38 mm Hg).[272] The permissive role of hypocapnia is further shown by studies in which the addition of even small amounts of CO_2 to the inspired air (~1%) profoundly attenuates central apneas in these patients.[273] Although this demonstrates the important role of hypocapnia, this intervention has not been used in large clinical studies.

Cheyne-Stokes respiration in patients with heart failure has a number of adverse consequences, including sleep fragmentation due to arousals resulting in excessive sleepiness and fatigue[274]; higher levels of circulating catecholamines[275]; increased ventricular ectopy[276]; and an increased rate of cardiovascular deaths.[277] Because of these effects, considerable attention has been paid to the question of whether treating Cheyne-Stokes ventilation in patients with heart failure can improve survival.

Different modalities to treat Cheyne-Stokes respiration have been used. Because of the factors involved in pathogenesis, oxygen administration helps to reduce chemoreceptor gain. Oxygen treatment reduces the overall percentage of the night that such subjects have Cheyne-Stokes respiration and the number of central apneas, but it does not completely abolish the abnormalities.[278] Theophylline also has been used,[279] but concerns about increased ventricular ectopy have limited its acceptance.

CPAP has received a great deal of attention in patients with Cheyne-Stokes breathing. This seems unusual because the problem in patients with Cheyne-Stokes respiration is central, rather than obstructive, apneas. Indeed, the mechanism by which CPAP treats Cheyne-Stokes is unknown. In these patients, CPAP is introduced in a different way than it is in OSA. In the latter, CPAP is titrated in the laboratory to eliminate obstructive events. In Cheyne-Stokes respiration, it is introduced at a low pressure, around 5 cm H_2O, and then increased nightly or over a period of days or even weeks depending on the patient's tolerance to the pressure. The CPAP is increased up to the tolerated amount or up

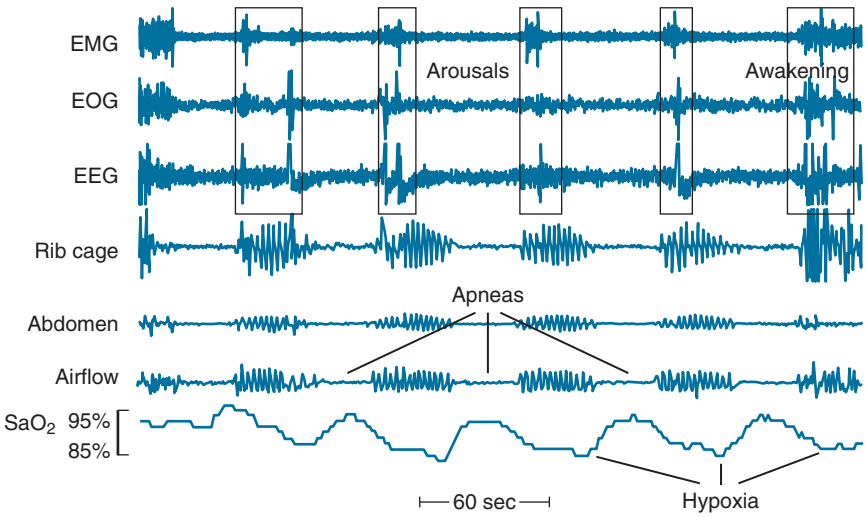

FIGURE 79-21 ■ Example of Cheyne-Stokes respiration. There is waxing and waning of airflow and rib cage and abdominal motion. During the apneas, there is no rib cage and abdominal motion, indicating the lack of respiratory effort, that is, central apnea. Oxygen saturation cycles with these episodes. Arousals occur during the ventilatory phase.

to a maximum of 10 cm H_2O. Early studies showed that CPAP improved ejection fraction[280] and reduced catecholamine levels.[275] In an initial randomized trial of CPAP compared with conservative management, individuals on CPAP had a reduced mortality over a 40-month period.[281]

These small studies led to a larger multicenter trial primarily in Canada—the CANPAP study. In this trial, 130 patients with systolic dysfunction and Cheyne-Stokes respiration were randomized to medical management of their heart failure and 128 were randomized to CPAP therapy.[282] There was no difference in heart transplant free survival (i.e., number living and not needing a heart transplant) between those treated with CPAP and the controls. Indeed, there was a significantly higher mortality in the CPAP treatment group between 12 and 18 months after starting therapy ($P = .02$).

One concern about this trial is that individuals on the CPAP arm were only partially treated. Because of this concern, the investigators performed a post-hoc analysis studying differences in mortality in those subjects who were effectively treated with CPAP.[283] They defined effective treatment as having an AHI less than 15 events/hr on CPAP. When examined in this way, the CPAP group had a markedly improved transplant-free survival as compared with the control group and those using CPAP whose sleep-disordered breathing was not suppressed by CPAP. Because this was an unplanned post-hoc analysis, these data cannot be used as a basis for recommending the use of CPAP therapy in these patients.

A new positive-pressure approach provides improved therapeutic efficacy in these patients. This was initially called auto-CS but is now called an "adaptive servoventilator." The fundamental concept of this approach is that there is a fixed expiratory (E) pressure while the inspiratory (I) pressure is varied on each breath (Fig. 79-22), that is, there is varied pressure support. The algorithm on which the I pressure is adjusted is based on maintaining a target ventilation. Thus, during the hypercapnic phase of the ventilatory cycle, the I pressure is reduced, while during hypoventilation, it is increased. The machine triggers breaths during the apneas. Thus, the device essentially does the converse of Cheyne-Stokes respiration and completely stabilizes ventilation. The E pressure, while fixed for a given subject, can be adjusted for different subjects so that this system can be used to relieve upper airway obstruction. This is of value in patients with Cheyne-Stokes respiration, who for part of the sleep period, might show classic Cheyne-Stokes respiration, while for other parts of the night, they may have obstructive events. The unstable cycling of neural output affects output to the upper airway dilator muscles as well as to the diaphragm. Thus, in these patients, there is a mixed distribution of apneas during the sleep period, with some central and some obstructive. Moreover, the proportion of these different types of apnea varies from night to night.[284] Thus, being able to deal simultaneously with Cheyne-Stokes respiration and obstructive apneas is beneficial in these patients in contrast to CPAP treatment for heart failure. Because of the variable nature of the output of this device, it is effective immediately. It nearly abolishes sleep-disordered breathing events in these patients on the first night of application and is much more effective in this regard than CPAP or BPAP therapy.[285] Improvements in sleepiness in patients with heart failure and Cheyne-Stokes respiration have been demonstrated.[274] A multicenter study evaluating transplant-free survival in heart failure patients with Cheyne-Stokes is in progress. The device can be used for other types of central apnea, and its efficacy in what has been called "complex sleep apnea" has been shown in small studies.[286]

Idiopathic Central Apnea

The idiopathic form of central sleep apnea resembles Cheyne-Stokes breathing, but these patients do not have heart failure and are otherwise normal. They have increased ventilation with hypocapnia during wakefulness and an increased ventilatory response to CO_2.[287] As in Cheyne-Stokes breathing in heart failure, addition of small amounts of CO_2 to the inspired air markedly attenuates the central apneas.[288] This is another example of the importance of the CO_2-dependent apnea threshold that emerges during sleep.

Complex Sleep Apnea

The term "complex sleep-disordered breathing" was initially coined by Thomas and colleagues[289] to describe a range of obstructive and central apnea patterns that included individual events with both central and obstruc-

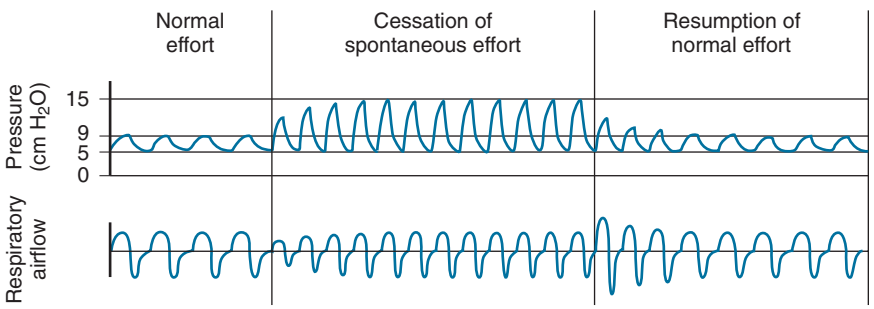

FIGURE 79-22 ■ Schematic shows the mechanism of action of the adaptive servoventilator. The pressure applied by the machine is in the *top panel* and the airflow in the *bottom panel*. The expiratory pressure is fixed on each breath but is titrated to relieve obstruction. The inspiratory (I) pressure is adjusted on each breath to maintain a target ventilation. Thus, in the period when ventilation is maintained, the I pressure is low, whereas it is increased during periods of reduced respiratory effort.

tive characteristics (mixed apneas), flow-limited breaths intermixed with periodic breathing, and variability in the degree of apnea dependent on sleep position, sleep stage, and time of night. These investigators also described a pattern of respiratory instability during sleep that occurred primarily during NREM periods of electroencephalographic cyclic alternating pattern, in which patients had periodic short cycles of obstructive events that responded incompletely to PAP and were minimized during REM sleep.[290]

More recently, the term "complex sleep apnea" has been used to describe central apneas or Cheyne-Stokes breathing that emerges during CPAP treatment of OSA.[291] Approximately 15% of a clinical sample of patients undergoing polysomnography who were characterized initially as having obstructive sleep apnea-hypopnea syndrome (OSAHS) without evidence of heart failure showed either a residual central apnea index of at least 5 events/hr despite elimination of events defining OSAHS or a prominent and disruptive pattern of Cheyne-Stokes respiration. These individuals were more obese than cases diagnosed with central sleep apnea and more likely to be male than patients initially diagnosed with OSA. Their other demographic characteristics and symptoms were generally similar to patients with OSAHS.[291] Additional studies have reported that 5% to 13% of patients treated with CPAP for OSA develop central apneas,[292,293] although it should be noted that a common syndromic definition has not been established.

Since the initial description, there has been debate about whether complex sleep apnea exists as a distinct entity or simply represents a variation in the response to CPAP therapy for OSA. Critics promote paying closer attention to whether the patient might in fact be over- or undertitrated on CPAP therapy, determining whether a mask leak may be causing residual events, scrutinizing whether occult heart failure is present, and examining whether medications (e.g., narcotics) might be contributing factors.[294] Several explanations for the emergence of central apneas with CPAP have been proposed, such as ventilatory control instability, which can induce central apneas as end-tidal CO_2 changes with the application of CPAP. Because men have higher loop gain than women (so that that they require a smaller degree of change in CO_2 to develop central apnea), this greater propensity for ventilatory instability could explain the greater likelihood of men to develop CPAP-emergent sleep apnea.[292] Other theories include an elevated CO_2 ventilatory response in patients with subclinical heart failure that precipitates Cheyne-Stokes respiration when CPAP is applied,[292] changes in CO_2 excretion that lead to central apneas,[295] worsened sleep fragmentation with initial CPAP treatment that leads to central apneas,[294] and a maladaptive response to CPAP therapy in which patients take larger than normal breaths, producing post-hypopnea pauses.[293]

Several approaches have been proposed for treating patients who have central apnea that emerges during CPAP therapy. Two studies have shown that in many patients, central apneas were a transient phenomenon during the CPAP titration night that resolved during further treatment with CPAP.[296,297] However, sample sizes were small, and one of the studies suggested that only half of patients improved with longer-term CPAP treatment.[296,297] Although central apneas may worsen when treated with BPAP alone,[298] BPAP used with a backup rate (i.e., noninvasive ventilation) appears to be an effective treatment for some patients with complex sleep apnea.[286,299]

Adaptive servoventilation (ASV), described earlier, is a relatively new PAP technology for treatment of central sleep apnea, mixed apnea, and periodic breathing that has also been used effectively for patients with the complex sleep apnea pattern.[286,299] In a retrospective, unblinded comparison study of CPAP, BPAP with a backup rate, and ASV for sleep-disordered breathing, ASV lowered the AHI to a greater degree than the other modalities and patients spent more time in REM sleep.[286] A prospective, randomized, crossover trial comparing ASV and BPAP for treatment of CPAP-emergent central apnea also showed that, although both modalities provided effective treatment, ASV was associated with a larger reduction in the AHI.[286]

SLEEP HYPOVENTILATION SYNDROMES

Central apneas can occur in the context of sleep-related hypoventilation syndrome. This syndrome occurs when there is an excessive increase in $PaCO_2$ during sleep. In normal adults, the $PaCO_2$ normally rises between 2 and 7 torr during sleep.[300–302] The diagnostic criteria for this have been defined, and each individual must fulfill criteria A and B.[7]

A. One or more of the following:
   a. Cor pulmonale.
   b. Pulmonary hypertension.
   c. Excessive daytime somnolence that is not better explained by other factors.
   d. Erythrocytosis.
   e. Hypercapnia during wakefulness ($PaCO_2$ > 45 torr).
B. Overnight monitoring demonstrates one or both of the following:
   a. An increase in $PaCO_2$ during sleep > 10 torr from awake supine values.
   b. Oxygen desaturation during sleep not explained by apnea or hypopnea events.

Many risk factors are associated with sleep-related hypoventilation syndromes including morbid obesity (BMI > 35 kg/m^2); chest wall restriction (e.g., kyloscoliosis); neuromuscular disease (e.g., amyotrophic lateral sclerosis); brain-stem or spinal cord lesions; idiopathic central alveolar hypoventilation (as described earlier); obstructive lung disease; or hypothyroidism. These risk factors interact with obesity and obstructive lung disease. Thus, it has been argued that one should consider sleep hypoventilation syndrome as an entity with a number of risk factors rather than as a number of distinct entities.[7] However, the literature typically treats the hypoventilation occurring with different risk factors as a specific entity, for example, obesity-hypoventilation syndrome.

Obesity-Hypoventilation Syndrome

Obesity hypoventilation is relatively common in severely obese subjects but is often not detected.[303] In one series, 31% of severely obese subjects had daytime hypercapnia without other reasons for this (mean $Paco_2$ = 52 torr). Somewhat surprisingly, only 13% of patients with obesity hypoventilation were treated with noninvasive ventilation during sleep.[303] Mortality was higher in the group with obesity hypoventilation than with simple obesity. Thus, obesity-hypoventilation syndrome is an important clinical problem, particularly with the rapid growth in obesity in the U.S. population.

In the majority of patients with obesity-hypoventilation syndrome, OSA with the characteristic symptoms and findings during the sleep study occurs. This is not surprising because obesity is the major risk factor for both conditions. However, about 10% of patients with obesity-hypoventilation syndrome do not have sleep-disordered breathing, and their AHI is less than 5 events/hr.[304–306] Thus, the presence of OSA is not an essential prerequisite for obesity-hypoventilation syndrome.

Although obesity is the major risk factor for the obesity-hypoventilation syndrome, not all obese subjects, including those with morbid obesity, hypoventilate during sleep. The mechanisms for hypoventilation in obesity include the mechanical mass loading effect of obesity, but also alteration in ventilatory control, probably as a result of central leptin resistance. Mice lacking leptin (ob/ob) have hypercapnia and a blunted ventilatory response.[307,308] This is not simply related to their obesity, because these ventilatory changes occur before they become profoundly obese.[307,308]

Certain features should arouse suspicion that obese individuals might have obesity-hypoventilation syndrome including daytime hypoxemia (patients with OSA have normal daytime blood gases); evidence of sustained desaturation on a sleep study, that is, nocturnal hypoxemia not simply related to recurring events; or a bicarbonate level of 27 mEq/L or greater on a routine electrolyte screen. Among patients with OSA (AHI > 5 events/hr) and obesity (BMI ≥ 30 kg/m^2), only 3% of patients with a bicarbonate lower than 27 mEq/L had obesity-hypoventilation syndrome whereas 50% of those with bicarbonate levels greater than 27 mEq/L had obesity-hypoventilation syndrme.[304] All of these findings should trigger an evaluation of blood gases while the patient is awake. Blood gas assessments before and shortly after sleep can document the sleep-related hypoventilation.

Management of these patients requires application of PAP during sleep. CPAP and noninvasive positive-pressure ventilation have been used. There is no standard protocol, but a useful approach has been described in a recent review.[305] The number of prospective randomized studies in this area is very limited.[309,310]

Application of positive pressure in these patients should be done in a setting with experienced technologists. In many patients, CPAP therapy is beneficial, although in about 50% of patients supplemental oxygen needs to be added to CPAP.[305] Whereas combined CPAP and oxygen is sufficient in many patients, some patients require noninvasive ventilation. For the latter, BPAP with a backup rate is typically used. Some of the patients requiring noninvasive ventilation can be identified during the sleep study because they have persistent oxyhemoglobin desaturation even though CPAP has abolished the apneas and hypopneas. Others may only be identified later when a repeat blood gas assessment on therapy shows persistent hypercapnia. No guidelines specify when to switch patients from CPAP to noninvasive ventilation. Because failure of CPAP therapy may take several weeks to be seen, physicians should have a low threshold for using noninvasive ventilation in these patients.[311] Recently, a new ventilatory modality has been used—the average volume-assured pressure support (AVAPS)—which combines pressure-limited and volume-limited modes of ventilation to ensure a more consistent tidal volume. Use of this method has been described in a small series of patients with obesity-hypoventilation syndrome.[310]

Because obesity is the major cause of this condition, these patients should be evaluated for bariatric surgery. Weight loss can be associated with substantial improvements in the degree of sleep-disordered breathing as well as daytime hypercapnia.[312] Patients with obesity-hypoventilation syndrome have an increased risk of complications with bariatric surgery, and untreated sleep apnea is a documented risk factor for death following bariatric surgery.[313] Thus, OSA and hypoventilation need to be well managed before surgery is planned. Indeed, all patients having bariatric surgery should undergo evaluation for sleep-disordered breathing and treatment should be initiated as needed.

Conclusion

In conclusion, a great deal has been learned since the original clinical recognition of OSA in the 1970s. The condition has moved from being considered a rarity, if it existed at all, to being seen as a highly prevalent disorder of major public health significance.[123] The discovery of CPAP by Sullivan and colleagues[314] provided a safe and effective therapy that has transformed the treatment of OSA and helped millions of people. The developing evidence about OSA as an independent risk factor for cardiovascular disease is opening a new chapter in this fascinating area. Despite these important advances, a lot remains to be discovered. Management of patients with sleep-disordered breathing is extremely gratifying because the treatments often result in significant improvement in people's lives.

KEY POINTS

- OSA is a common health problem worldwide, and prevalence increases with age. OSA is two to three times more common among men than women, but the risk rises significantly in women after menopause.
- OSA is associated with daytime somnolence, motor vehicle accidents, hypertension, and cardiovascular mortality and should be considered part of the metabolic syndrome.
- Pathogenetic factors in OSA include small upper airway size, changes in upper airway muscles and nerves, and individual differences in chemoreceptor sensitivity and arousal responses to apneas.
- CPAP is the standard of care in most patients with OSA, but oral appliances and surgical procedures are useful in selected patients.
- Periodic breathing at high altitude and Cheyne-Stokes respiration are forms of hypocapneic central sleep apnea resulting from the dependence of ventilatory control during sleep on the chemical drive to breathe.
- Individuals with obesity-hypoventilation syndrome have an excessive increase in arterial P_{CO_2} during sleep and usually have hypercapnia during wakefulness and a very high BMI. The pathogenetic mechanisms include mechanical mass loading of the chest wall and alterations in ventilatory control.

References

1. Gould GA, Whyte KF, Rhind GB, et al: The sleep hypopnea syndrome. Am Rev Respir Dis 137:895–898, 1988.
2. Montserrat JM, Farre R, Ballester E, et al: Evaluation of nasal prongs for estimating nasal flow. Am J Respir Crit Care Med 155:211–215, 1997.
3. Norman RG, Ahmed MM, Walsleben JA, et al: Detection of respiratory events during NPSG: nasal cannula/pressure sensor versus thermistor. Sleep 20:1175–1184, 1997.
4. Young T, Palta M, Dempsey J, et al: The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med 328:1230–1235, 1993.
5. Nieto FJ, Young TB, Lind BK, et al: Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study. Sleep Heart Health Study. JAMA 283:1829–1836, 2000.
6. Bixler EO, Vgontzas AN, Ten Have T, et al: Effects of age on sleep apnea in men: I. Prevalence and severity. Am J Respir Crit Care Med 157:144–148, 1998.
7. American Academy of Sleep Medicine: Sleep-related breathing disorders in adults: Recommendations for syndrome definition and measurement techniques in clinical research. The Report of an American Academy of Sleep Medicine Task Force. Sleep 22:667–689, 1999.
8. Guilleminault C, Stoohs R, Duncan S: Snoring (I). Daytime sleepiness in regular heavy snorers. Chest 99:40–48, 1991.
9. Guilleminault C, Stoohs R, Clerk A, et al: From obstructive sleep apnea syndrome to upper airway resistance syndrome: Consistency of daytime sleepiness. Sleep 15:S13–S16, 1992.
10. Guilleminault C, Stoohs R, Kim YD, et al: Upper airway sleep-disordered breathing in women. Ann Intern Med 122:493–501, 1995.
11. Guilleminault C, Chowdhuri S: Upper airway resistance syndrome is a distinct syndrome. Am J Respir Crit Care Med 161:1412–1413, 2000.
12. Douglas NJ: Upper airway resistance syndrome is not a distinct syndrome. Am J Respir Crit Care Med 161:1413–1416, 2000.
13. Cracowski C, Pepin JL, Wuyam B, et al: Characterization of obstructive nonapneic respiratory events in moderate sleep apnea syndrome. Am J Respir Crit Care Med 164:944–948, 2001.
14. Pack AI, Dinges DF, Gehrman PR, et al: Risk factors for excessive sleepiness in older adults. Ann Neurol 59:893–904, 2006.
15. Johns MW: A new method for measuring daytime sleepiness: The Epworth Sleepiness Scale. Sleep 14:540–545, 1991.
16. Johns MW: Reliability and factor analysis of the Epworth Sleepiness Scale. Sleep 15:376–381, 1992.
17. Johns MW: Daytime sleepiness, snoring, and obstructive sleep apnea. The Epworth Sleepiness Scale. Chest 103:30–36, 1993.
18. Ayas NT, Patel SR, Malhotra A, et al: Auto-titrating versus standard continuous positive airway pressure for the treatment of obstructive sleep apnea: Results of a meta-analysis. Sleep 27:249–253, 2004.
19. Horner RL: Respiratory motor activity: Influence of neuromodulators and implications for sleep disordered breathing. Can J Physiol Pharmacol 85:155–165, 2007.
20. Malhotra A, Fogel RB, Edwards JK, et al: Local mechanisms drive genioglossus activation in obstructive sleep apnea. Am J Respir Crit Care Med 161:1746–1749, 2000.
21. Horner RL, Innes JA, Morrell MJ, et al: The effect of sleep on reflex genioglossus muscle activation by stimuli of negative airway pressure in humans. J Physiol 476:141–151, 1994.
22. Wheatley JR, Tangel DJ, Mezzanotte WS, et al: Influence of sleep on response to negative airway pressure of tensor palatini muscle and retropalatal airway. J Appl Physiol 75:2117–2124, 1993.
23. Wheatley JR, White DP: The influence of sleep on pharyngeal reflexes. Sleep 16:S87–S89, 1993.
24. Ahmed MM, Schwab RJ: Upper airway imaging in obstructive sleep apnea. Curr Opin Pulm Med 12:397–401, 2006.
25. Watanabe T, Isono S, Tanaka A, et al: Contribution of body habitus and craniofacial characteristics to segmental closing pressures of the passive pharynx in patients with sleep-disordered breathing. Am J Respir Crit Care Med 165:260–265, 2002.
26. Schwab RJ, Pasirstein M, Pierson R, et al: Identification of upper airway anatomic risk factors for obstructive sleep apnea with volumetric magnetic resonance imaging. Am J Respir Crit Care Med 168:522–530, 2003.
27. Schwab RJ, Pasirstein M, Kaplan L, et al: Family aggregation of upper airway soft tissue structures in normal subjects and patients with sleep apnea. Am J Respir Crit Care Med 173:453–463, 2006.
28. Schwartz AR, Smith PL, Wise RA, et al: Induction of upper airway occlusion in sleeping individuals with subatmospheric nasal pressure. J Appl Physiol 64:535–542, 1988.
29. Schwartz AR, Gold AR, Schubert N, et al: Effect of weight loss on upper airway collapsibility in obstructive sleep apnea. Am Rev Respir Dis 144:494–498, 1991.

30. Isono S, Remmers JE, Tanaka A, et al: Anatomy of pharynx in patients with obstructive sleep apnea and in normal subjects. J Appl Physiol 82:1319–1326, 1997.
31. Mezzanotte WS, Tangel DJ, White DP: Waking genioglossal electromyogram in sleep apnea patients versus normal controls (a neuromuscular compensatory mechanism). J Clin Invest 89:1571–1579, 1992.
32. Petrof BJ, Hendricks JC, Pack AI: Does upper airway muscle injury trigger a vicious cycle in obstructive sleep apnea? A hypothesis. Sleep 19:465–471, 1996.
33. Petrof BJ, Pack AI, Kelly AM, et al: Pharyngeal myopathy of loaded upper airway in dogs with sleep apnea. J Appl Physiol 76:1746–1752, 1994.
34. Friberg D, Gazelius B, Hokfelt T, et al: Abnormal afferent nerve endings in the soft palatal mucosa of sleep apnoics and habitual snorers. Regul Pept 71:29–36, 1997.
35. Svanborg E: Upper airway nerve lesions in obstructive sleep apnea. Am J Respir Crit Care Med 164:187–189, 2001.
36. Friberg D, Ansved T, Borg K, et al: Histological indications of a progressive snorers disease in an upper airway muscle. Am J Respir Crit Care Med 157:586–593, 1998.
37. Boyd JH, Petrof BJ, Hamid Q, et al: Upper airway muscle inflammation and denervation changes in obstructive sleep apnea. Am J Respir Crit Care Med 170:541–546, 2004.
38. Sanes JR, Schachner M, Covault J: Expression of several adhesive macromolecules (N-CAM, L1, J1, NILE, uvomorulin, laminin, fibronectin, and a heparan sulfate proteoglycan) in embryonic, adult, and denervated adult skeletal muscle. J Cell Biol 102:420–431, 1986.
39. Covault J, Sanes JR: Neural cell adhesion molecule (N-CAM) accumulates in denervated and paralyzed skeletal muscles. Proc Natl Acad Sci U S A 82:4544–4548, 1985.
40. Kimoff RJ, Sforza E, Champagne V, et al: Upper airway sensation in snoring and obstructive sleep apnea. Am J Respir Crit Care Med 164:250–255, 2001.
41. Redolfi S, Yumino D, Ruttanaumpawan P, et al: Relationship between overnight rostral fluid shift and obstructive sleep apnea in nonobese men. Am J Respir Crit Care Med 179:241–246, 2009.
42. Su MC, Chiu KL, Ruttanaumpawan P, et al: Lower body positive pressure increases upper airway collapsibility in healthy subjects. Respir Physiol Neurobiol 161:306–312, 2008.
43. Shiota S, Ryan CM, Chiu KL, et al: Alterations in upper airway cross-sectional area in response to lower body positive pressure in healthy subjects. Thorax 62:868–872, 2007.
44. Khoo MC, Kronauer RE, Strohl KP, et al: Factors inducing periodic breathing in humans: A general model. J Appl Physiol 53:644–659, 1982.
45. Younes M, Ostrowski M, Thompson W, et al: Chemical control stability in patients with obstructive sleep apnea. Am J Respir Crit Care Med 163:1181–1190, 2001.
46. Wellman A, Jordan AS, Malhotra A, et al: Ventilatory control and airway anatomy in obstructive sleep apnea. Am J Respir Crit Care Med 170:1225–1232, 2004.
47. Wellman A, Malhotra A, Jordan AS, et al: Effect of oxygen in obstructive sleep apnea: Role of loop gain. Respir Physiol Neurobiol 162:144–151, 2008.
48. Gleeson K, Zwillich CW, White DP: The influence of increasing ventilatory effort on arousal from sleep. Am Rev Respir Dis 142:295–300, 1990.
49. Berry RB, Gleeson K: Respiratory arousal from sleep: Mechanisms and significance. Sleep 20:654–675, 1997.
50. Younes M: Role of arousals in the pathogenesis of obstructive sleep apnea. Am J Respir Crit Care Med 169:623–633, 2004.
51. Horner RL, Brooks D, Kozar LF, et al: Immediate effects of arousal from sleep on cardiac autonomic outflow in the absence of breathing in dogs. J Appl Physiol 79:151–162, 1995.
52. Nalivaiko E, Catcheside PG, Adams A, et al: Cardiac changes during arousals from non-REM sleep in healthy volunteers. Am J Physiol Regul Integr Comp Physiol 292:R1320–R1327, 2007.
53. Redline S, Tishler PV, Tosteson TD, et al: The familial aggregation of obstructive sleep apnea. Am J Respir Crit Care Med 151:682–687, 1995.
54. Mathur R, Douglas NJ: Family studies in patients with the sleep apnea-hypopnea syndrome. Ann Intern Med 122:174–178, 1995.
55. Pillar G, Lavie P: Assessment of the role of inheritance in sleep apnea syndrome. Am J Respir Crit Care Med 151:688–691, 1995.
56. Gislason T, Johannsson JH, Haraldsson A, et al: Familial predisposition and cosegregation analysis of adult obstructive sleep apnea and the sudden infant death syndrome. Am J Respir Crit Care Med 166:833–838, 2002.
57. Patel SR, Larkin EK, Redline S: Shared genetic basis for obstructive sleep apnea and adiposity measures. Int J Obes (Lond) 32:795–800, 2008.
58. Riha RL, Diefenbach K, Jennum P, et al: Genetic aspects of hypertension and metabolic disease in the obstructive sleep apnoea-hypopnoea syndrome. Sleep Med Rev 12:49–63, 2008.
59. Larkin EK, Patel SR, Elston RC, et al: Using linkage analysis to identify quantitative trait loci for sleep apnea in relationship to body mass index. Ann Hum Genet 72:762–773, 2008.
60. Palmer LJ, Buxbaum SG, Larkin EK, et al: Whole genome scan for obstructive sleep apnea and obesity in African-American families. Am J Respir Crit Care Med 169:1314–1321, 2004.
61. Palmer LJ, Buxbaum SG, Larkin E, et al: A whole-genome scan for obstructive sleep apnea and obesity. Am J Hum Genet 72:340–350, 2003.
62. Gottlieb DJ, DeStefano AL, Foley DJ, et al: APOE epsilon4 is associated with obstructive sleep apnea/hypopnea: The Sleep Heart Health Study. Neurology 63:664–668, 2004.
63. Larkin EK, Patel SR, Redline S, et al: Apolipoprotein E and obstructive sleep apnea: Evaluating whether a candidate gene explains a linkage peak. Genet Epidemiol 30:101–110, 2006.
64. Lee RW, Chan AS, Grunstein RR, et al: Craniofacial phenotyping in obstructive sleep apnea—A novel quantitative photographic approach. Sleep 32:37–45, 2009.
65. Lee RW, Petocz P, Prvan T, et al: Prediction of obstructive sleep apnea with craniofacial photographic analysis. Sleep 32:46–52, 2009.
66. Zonato AI, Bittencourt LR, Martinho FL, et al: Association of systematic head and neck physical examination with severity of obstructive sleep apnea-hypopnea syndrome. Laryngoscope 113:973–980, 2003.
67. Gozal D, Kheirandish-Gozal L: The multiple challenges of obstructive sleep apnea in children: Morbidity and treatment. Curr Opin Pediatr 20:654–658, 2008.
68. Kheirandish-Gozal L, Gozal D: The multiple challenges of obstructive sleep apnea in children: Diagnosis. Curr Opin Pediatr 20:650–653, 2008.
69. Shott SR, Amin R, Chini B, et al: Obstructive sleep apnea: Should all children with Down syndrome be tested? Arch Otolaryngol Head Neck Surg 132:432–436, 2006.
70. Guimaraes CV, Donnelly LF, Shott SR, et al: Relative rather than absolute macroglossia in patients with Down syndrome: Implications for treatment of obstructive sleep apnea. Pediatr Radiol 38:1062–1067, 2008.
71. Eloy JA, Carneiro E, Vibhute P, et al: A rare prevertebral ordinary lipoma presenting as obstructive sleep apnea: Computed tomographic and magnetic resonance imaging findings. Arch Otolaryngol Head Neck Surg 134:1001–1003, 2008.
72. Piccin O, Sorrenti G: Adult obstructive sleep apnea related to nasopharyngeal obstruction: A case of retropharyngeal lipoma and pathogenetic considerations. Sleep Breath 11:305–307, 2007.
73. Hoffstein V, Mateika S: Differences in abdominal and neck circumferences in patients with and without obstructive sleep apnoea. Eur Respir J 5:377–381, 1992.
74. Young T, Shahar E, Nieto FJ, et al: Predictors of sleep-disordered breathing in community-dwelling adults: The Sleep Heart Health Study. Arch Intern Med 162:893–900, 2002.
75. Eikermann M, Jordan AS, Chamberlin NL, et al: The influence of aging on pharyngeal collapsibility during sleep. Chest 131:1702–1709, 2007.
76. Peppard PE, Young T, Palta M, et al: Longitudinal study of moderate weight change and sleep-disordered breathing. JAMA 284:3015–3021, 2000.
77. Newman AB, Foster G, Givelber R, et al: Progression and regression of sleep-disordered breathing with changes in weight: The Sleep Heart Health Study. Arch Intern Med 165:2408–2413, 2005.
78. Nashi N, Kang S, Barkdull GC, et al: Lingual fat at autopsy. Laryngoscope 117:1467–1473, 2007.

79. Brennick MJ, Pack AI, Ko K, et al: Altered upper airway and soft tissue structures in the New Zealand Obese mouse. Am J Respir Crit Care Med 179:158–169, 2009.
80. Schellenberg JB, Maislin G, Schwab RJ: Physical findings and the risk for obstructive sleep apnea. The importance of oropharyngeal structures. Am J Respir Crit Care Med 162:740–748, 2000.
81. Grunstein RR, Sullivan CE: Sleep apnea and hypothyroidism: Mechanisms and management. Am J Med 85:775–779, 1988.
82. Grunstein RR, Ho KY, Sullivan CE: Sleep apnea in acromegaly. Ann Intern Med 115:527–532, 1991.
83. Bixler EO, Vgontzas AN, Lin HM, et al: Prevalence of sleep-disordered breathing in women: Effects of gender. Am J Respir Crit Care Med 163:608–613, 2001.
84. Young T, Finn L, Austin D, et al: Menopausal status and sleep-disordered breathing in the Wisconsin Sleep Cohort Study. Am J Respir Crit Care Med 167:1181–1185, 2003.
85. Prentice RL, Manson JE, Langer RD, et al: Benefits and risks of postmenopausal hormone therapy when it is initiated soon after menopause. Am J Epidemiol 170:12–23, 2009.
86. Kales A, Cadieux RJ, Bixler EO, et al: Severe obstructive sleep apnea—I: Onset, clinical course, and characteristics. J Chronic Dis 38:419–425, 1985.
87. Maislin G, Pack AI, Kribbs NB, et al: A survey screen for prediction of apnea. Sleep 18:158–166, 1995.
88. Ohayon MM, Li KK, Guilleminault C: Risk factors for sleep bruxism in the general population. Chest 119:53–61, 2001.
89. Hajduk IA, Strollo PJ Jr, Jasani RR, et al: Prevalence and predictors of nocturia in obstructive sleep apnea-hypopnea syndrome—A retrospective study. Sleep 26:61–64, 2003.
90. Moriyama Y, Miwa K, Tanaka H, et al: Nocturia in men less than 50 years of age may be associated with obstructive sleep apnea syndrome. Urology 71:1096–1098, 2008.
91. George CF, Nickerson PW, Hanly PJ, et al: Sleep apnoea patients have more automobile accidents. Lancet 2:447, 1987.
92. Sassani A, Findley LJ, Kryger M, et al: Reducing motor-vehicle collisions, costs, and fatalities by treating obstructive sleep apnea syndrome. Sleep 27:453–458, 2004.
93. Masa JF, Celli BR, Riesco JA, et al: The obesity hypoventilation syndrome can be treated with noninvasive mechanical ventilation. Chest 119:1102–1107, 2001.
94. Weaver TE George CF: Cognition and performance in patients with obstructive sleep apnea. *In* Kryger MH, Roth T, Dement WC (eds): Principles and Practice of Sleep Medicine. Philadelphia: Elsevier Saunders, 2005.
95. Reishtein JL, Pack AI, Maislin G, et al: Sleepiness and relationships in obstructive sleep apnea. Issues Ment Health Nurs 27:319–330, 2006.
96. McCall WV, Harding D, O'Donovan C: Correlates of depressive symptoms in patients with obstructive sleep apnea. J Clin Sleep Med 2:424–426, 2006.
97. Peppard PE, Szklo-Coxe M, Hla KM, et al: Longitudinal association of sleep-related breathing disorder and depression. Arch Intern Med 166:1709–1715, 2006.
98. Bearpark H, Elliott L, Grunstein R, et al: Snoring and sleep apnea. A population study in Australian men. Am J Respir Crit Care Med 151:1459–1465, 1995.
99. Ip MS, Lam B, Lauder IJ, et al: A community study of sleep-disordered breathing in middle-aged Chinese men in Hong Kong. Chest 119:62–69, 2001.
100. Ip MS, Lam B, Tang LC, et al: A community study of sleep-disordered breathing in middle-aged Chinese women in Hong Kong: Prevalence and gender differences. Chest 125:127–134, 2004.
101. Udwadia ZF, Doshi AV, Lonkar SG, et al: Prevalence of sleep-disordered breathing and sleep apnea in middle-aged urban Indian men. Am J Respir Crit Care Med 169:168–173, 2004.
102. Kim J, In K, You S, et al: Prevalence of sleep-disordered breathing in middle-aged Korean men and women. Am J Respir Crit Care Med 170:1108–1113, 2004.
103. Duran J, Esnaola S, Rubio R, et al: Obstructive sleep apnea-hypopnea and related clinical features in a population-based sample of subjects aged 30 to 70 yr. Am J Respir Crit Care Med 163:685–689, 2001.
104. Loube DI, Gay PC, Strohl KP, et al: Indications for positive airway pressure treatment of adult obstructive sleep apnea patients: A consensus statement. Chest 115:863–866, 1999.
105. Redline S, Kapur VK, Sanders MH, et al: Effects of varying approaches for identifying respiratory disturbances on sleep apnea assessment. Am J Respir Crit Care Med 161:369–374, 2000.
106. Block AJ, Boysen PG, Wynne JW, et al: Sleep apnea, hypopnea and oxygen desaturation in normal subjects. A strong male predominance. N Engl J Med 300:513–517, 1979.
107. Gislason T, Almqvist M, Eriksson G, et al: Prevalence of sleep apnea syndrome among Swedish men—An epidemiological study. J Clin Epidemiol 41:571–576, 1988.
108. Franklin KA, Holmgren PA, Jonsson F, et al: Snoring, pregnancy-induced hypertension, and growth retardation of the fetus. Chest 117:137–141, 2000.
109. White DP, Douglas NJ, Pickett CK, et al: Hypoxic ventilatory response during sleep in normal premenopausal women. Am Rev Respir Dis 126:530–533, 1982.
110. Pickett CK, Regensteiner JG, Woodard WD, et al: Progestin and estrogen reduce sleep-disordered breathing in postmenopausal women. J Appl Physiol 66:1656–1661, 1989.
111. Popovic RM, White DP: Upper airway muscle activity in normal women: Influence of hormonal status. J Appl Physiol 84:1055–1062, 1998.
112. Vgontzas AN, Legro RS, Bixler EO, et al: Polycystic ovary syndrome is associated with obstructive sleep apnea and daytime sleepiness: Role of insulin resistance. J Clin Endocrinol Metab 86:517–520, 2001.
113. Fogel RB, Malhotra A, Pillar G, et al: Increased prevalence of obstructive sleep apnea syndrome in obese women with polycystic ovary syndrome. J Clin Endocrinol Metab 86:1175–1180, 2001.
114. Ancoli-Israel S, Kripke DF, Klauber MR, et al: Periodic limb movements in sleep in community-dwelling elderly. Sleep 14:496–500, 1991.
115. Launois SH, Pepin JL, Levy P: Sleep apnea in the elderly: A specific entity? Sleep Med Rev 11:87–97, 2007.
116. Redline S, Leitner J, Arnold J, et al: Ventilatory-control abnormalities in familial sleep apnea. Am J Respir Crit Care Med 156:155–160, 1997
117. Ancoli-Israel S, Klauber MR, Stepnowsky C, et al: Sleep-disordered breathing in African-American elderly. Am J Respir Crit Care Med 152:1946–1949, 1995.
118. Li KK, Kushida C, Powell NB, et al: Obstructive sleep apnea syndrome: A comparison between Far-East Asian and white men. Laryngoscope 110:1689–1693, 2000.
119. Ong KC, Clerk AA: Comparison of the severity of sleep-disordered breathing in Asian and Caucasian patients seen at a sleep disorders center. Respir Med 92:843–848, 1998.
120. Sakakibara H, Tong M, Matsushita K, et al: Cephalometric abnormalities in non-obese and obese patients with obstructive sleep apnoea. Eur Respir J 13:403–410, 1999.
121. Schmidt-Nowara WW, Coultas DB, Wiggins C, et al: Snoring in a Hispanic-American population. Risk factors and association with hypertension and other morbidity. Arch Intern Med 150:597–601, 1990.
122. O'Connor GT, Lind BK, Lee ET, et al: Variation in symptoms of sleep-disordered breathing with race and ethnicity: The Sleep Heart Health Study. Sleep 26:74–79, 2003.
123. Colten HR, Altevogt BM (eds): Sleep Disorders and Sleep Deprivation: An Unmet Public Health Problem. Washington, DC: The National Academies Press, 2006.
124. Spiegel K, Leproult R, Van Cauter E: Impact of sleep debt on metabolic and endocrine function. Lancet 354:1435–1439, 1999.
125. Spiegel K, Tasali E, Penev P, et al: Brief communication: Sleep curtailment in healthy young men is associated with decreased leptin levels, elevated ghrelin levels, and increased hunger and appetite. Ann Intern Med 141:846–850, 2004.
126. Knutson KL Van Cauter E: Associations between sleep loss and increased risk of obesity and diabetes. Ann N Y Acad Sci 1129:287–304, 2008.
127. Knutson KL, Spiegel K, Penev P, et al: The metabolic consequences of sleep deprivation. Sleep Med Rev 11:163–178, 2007.

128. Durmer JS, Dinges DF: Neurocognitive consequences of sleep deprivation. Semin Neurol 25:117–129, 2005.
129. Winkelmann J, Muller-Myhsok B, Wittchen HU, et al: Complex segregation analysis of restless legs syndrome provides evidence for an autosomal dominant mode of inheritance in early age at onset families. Ann Neurol 52:297–302, 2002
130. Winkelmann J, Schormair B, Lichtner P, et al: Genome-wide association study of restless legs syndrome identifies common variants in three genomic regions. Nat Genet 39:1000–1006, 2007.
131. Stefansson H, Rye DB, Hicks A, et al: A genetic risk factor for periodic limb movements in sleep. N Engl J Med 357:639–647, 2007.
132. Earley CJ: Clinical practice. Restless legs syndrome. N Engl J Med 348:2103–2109, 2003.
133. Trenkwalder C, Hogl B, Winkelmann J: Recent advances in the diagnosis, genetics and treatment of restless legs syndrome. J Neurol 256:539–553, 2009.
134. Mignot E, Lammers GJ, Ripley B, et al: The role of cerebrospinal fluid hypocretin measurement in the diagnosis of narcolepsy and other hypersomnias. Arch Neurol 59:1553–1562, 2002.
135. Chabas D, Taheri S, Renier C, et al: The genetics of narcolepsy. Annu Rev Genomics Hum Genet 4:459–483, 2003.
136. Hallmayer J, Faraco J, Lin L, et al: Narcolepsy is strongly associated with the T-cell receptor alpha locus. Nat Genet 41:708–711, 2009.
137. U.S. Xyrem Multicenter Study Group: Sodium oxybate demonstrates long-term efficacy for the treatment of cataplexy in patients with narcolepsy. Sleep Med 5:119–123, 2004.
138. Mohsenin V: Narcolepsy—Master of disguise: Evidence-based recommendations for management. Postgrad Med 121:99–104, 2009.
139. Lu BS, Zee PC: Circadian rhythm sleep disorders. Chest 130:1915–1923, 2006.
140. Siepka SM, Yoo SH, Park J, et al: Genetics and neurobiology of circadian clocks in mammals. Cold Spring Harb Symp Quant Biol 72:251–259, 2007.
141. Jones CR, Campbell SS, Zone SE, et al: Familial advanced sleep-phase syndrome: A short-period circadian rhythm variant in humans. Nat Med 5:1062–1065, 1999.
142. Toh KL, Jones CR, He Y, et al: An hPer2 phosphorylation site mutation in familial advanced sleep phase syndrome. Science 291:1040–1043, 2001.
143. Xu Y, Padiath QS, Shapiro RE, et al: Functional consequences of a CKIdelta mutation causing familial advanced sleep phase syndrome. Nature 434:640–644, 2005.
144. Barion A, Zee PC: A clinical approach to circadian rhythm sleep disorders. Sleep Med 8:566–577, 2007.
145. Arnulf I, Lin L, Gadoth N, et al: Kleine-Levin syndrome: A systematic study of 108 patients. Ann Neurol 63:482–493, 2008.
146. Netzer NC, Stoohs RA, Netzer CM, et al: Using the Berlin Questionnaire to identify patients at risk for the sleep apnea syndrome. Ann Intern Med 131:485–491, 1999.
147. Ahmadi N, Chung SA, Gibbs A, et al: The Berlin Questionnaire for sleep apnea in a sleep clinic population: Relationship to polysomnographic measurement of respiratory disturbance. Sleep Breath 12:39–45, 2008.
148. Crocker BD, Olson LG, Saunders NA, et al: Estimation of the probability of disturbed breathing during sleep before a sleep study. Am Rev Respir Dis 142:14–18, 1990.
149. Deegan PC, McNicholas WT: Predictive value of clinical features for the obstructive sleep apnoea syndrome. Eur Respir J 9:117–124, 1996.
150. Flemons WW, Whitelaw WA, Brant R, et al: Likelihood ratios for a sleep apnea clinical prediction rule. Am J Respir Crit Care Med 150:1279–1285, 1994.
151. Rauscher H, Popp W, Zwick H: Model for investigating snorers with suspected sleep apnoea. Thorax 48:275–279, 1993.
152. Viner S, Szalai JP, Hoffstein V: Are history and physical examination a good screening test for sleep apnea? Ann Intern Med 115:356–359, 1991.
153. Rowley JA, Aboussouan LS, Badr MS: The use of clinical prediction formulas in the evaluation of obstructive sleep apnea. Sleep 23:929–938, 2000.
154. Marin JM, Carrizo SJ, Vicente E, et al: Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: An observational study. Lancet 365:1046–1053, 2005.
155. Chesson AL Jr, Berry RB, Pack A, et al: Practice parameters for the use of portable monitoring devices in the investigation of suspected obstructive sleep apnea in adults. Sleep 26:907–913, 2003.
156. Flemons WW, Littner MR, Rowley JA, et al: Home diagnosis of sleep apnea: A systematic review of the literature. An evidence review cosponsored by the American Academy of Sleep Medicine, the American College of Chest Physicians, and the American Thoracic Society. Chest 124:1543–1579, 2003.
157. Lavie L: Obstructive sleep apnoea syndrome—An oxidative stress disorder. Sleep Med Rev 7:35–51, 2003.
158. Ryan S, Taylor CT, McNicholas WT: Predictors of elevated nuclear factor-kappaB–dependent genes in obstructive sleep apnea syndrome. Am J Respir Crit Care Med 174:824–830, 2006.
159. Ryan S, Taylor CT, McNicholas WT: Selective activation of inflammatory pathways by intermittent hypoxia in obstructive sleep apnea syndrome. Circulation 112:2660–2667, 2005.
160. Ryan S, McNicholas WT, Taylor CT: A critical role for p38 map kinase in NF-kappaB signaling during intermittent hypoxia/reoxygenation. Biochem Biophys Res Commun 355:728–733, 2007.
161. Liu H, Liu J, Xiong S, et al: The change of interleukin-6 and tumor necrosis factor in patients with obstructive sleep apnea syndrome. J Tongji Med Univ 20:200–202, 2000.
162. Shamsuzzaman AS, Winnicki M, Lanfranchi P, et al: Elevated C-reactive protein in patients with obstructive sleep apnea. Circulation 105:2462–2464, 2002.
163. Yokoe T, Minoguchi K, Matsuo H, et al: Elevated levels of C-reactive protein and interleukin-6 in patients with obstructive sleep apnea syndrome are decreased by nasal continuous positive airway pressure. Circulation 107:1129–1134, 2003.
164. Minoguchi K, Tazaki T, Yokoe T, et al: Elevated production of tumor necrosis factor-alpha by monocytes in patients with obstructive sleep apnea syndrome. Chest 126:1473–1479, 2004.
165. Minoguchi K, Yokoe T, Tazaki T, et al: Increased carotid intima-media thickness and serum inflammatory markers in obstructive sleep apnea. Am J Respir Crit Care Med 172:625–630, 2005.
166. Kobayashi K, Nishimura Y, Shimada T, et al: Effect of continuous positive airway pressure on soluble CD40 ligand in patients with obstructive sleep apnea syndrome. Chest 129:632–637, 2006.
167. Bravo Mde L, Serpero LD, Barcelo A, et al: Inflammatory proteins in patients with obstructive sleep apnea with and without daytime sleepiness. Sleep Breath 11:177–185, 2007.
168. Guilleminault C, Kirisoglu C, Ohayon MM: C-reactive protein and sleep-disordered breathing. Sleep 27:1507–1511, 2004.
169. Sharma SK, Mishra HK, Sharma H, et al: Obesity, and not obstructive sleep apnea, is responsible for increased serum hs-CRP levels in patients with sleep-disordered breathing in Delhi. Sleep Med 9:149–156, 2008.
170. Arnardottir ES, Mackiewicz M, Gislason T, et al: Molecular signatures of obstructive sleep apnea in adults: A review and perspective. Sleep 32:447–470, 2009.
171. Budweiser S, Enderlein S, Jorres RA, et al: Sleep apnea is an independent correlate of erectile and sexual dysfunction. J Sex Med Epub 2009;June 29 (ahead of print).
172. Soukhova-O'Hare GK, Shah ZA, Lei Z, et al: Erectile dysfunction in a murine model of sleep apnea. Am J Respir Crit Care Med 178:644–650, 2008.
173. Siccoli MM, Pepperell JC, Kohler M, et al: Effects of continuous positive airway pressure on quality of life in patients with moderate to severe obstructive sleep apnea: Data from a randomized controlled trial. Sleep 31:1551–1558, 2008.
174. Weaver TE, Laizner AM, Evans LK, et al: An instrument to measure functional status outcomes for disorders of excessive sleepiness. Sleep 20:835–843, 1997.
175. Flemons WW, Reimer MA: Measurement properties of the Calgary Sleep Apnea Quality of Life Index. Am J Respir Crit Care Med 165:159–164, 2002.
176. Chasens ER, Ratcliffe SJ, Weaver TE: Development of the FOSQ-10: A short version of the Functional Outcomes of Sleep Questionnaire. Sleep 32:915–919, 2009.

177. George CF: Reduction in motor vehicle collisions following treatment of sleep apnoea with nasal CPAP. Thorax 56:508–512, 2001.
178. Sleep apnea, sleepiness, and driving risk. American Thoracic Society. Am J Respir Crit Care Med 150:1463–1473, 1994.
179. George CF, Findley LJ, Hack MA, et al: Across-country viewpoints on sleepiness during driving. Am J Respir Crit Care Med 165:746–749, 2002.
180. Gurubhagavatula I, Maislin G, Nkwuo JE, et al: Occupational screening for obstructive sleep apnea in commercial drivers. Am J Respir Crit Care Med 170:371–376, 2004.
181. Pack AI, Maislin G, Staley B, et al: Impaired performance in commercial drivers: Role of sleep apnea and short sleep duration. Am J Respir Crit Care Med 174:446–454, 2006.
182. Howard ME, Desai AV, Grunstein RR, et al: Sleepiness, sleep-disordered breathing, and accident risk factors in commercial vehicle drivers. Am J Respir Crit Care Med 170:1014–1021, 2004.
183. Rader DJ: Effect of insulin resistance, dyslipidemia, and intra-abdominal adiposity on the development of cardiovascular disease and diabetes mellitus. Am J Med 120:S12–S18, 2007.
184. Punjabi NM, Sorkin JD, Katzel LI, et al: Sleep-disordered breathing and insulin resistance in middle-aged and overweight men. Am J Respir Crit Care Med 165:677–682, 2002.
185. Ip MS, Lam B, Ng MM, et al: Obstructive sleep apnea is independently associated with insulin resistance. Am J Respir Crit Care Med 165:670–676, 2002.
186. Harsch IA, Schahin SP, Radespiel-Troger M, et al: Continuous positive airway pressure treatment rapidly improves insulin sensitivity in patients with obstructive sleep apnea syndrome. Am J Respir Crit Care Med 169:156–162, 2004.
187. Smurra M, Philip P, Taillard J, et al: CPAP treatment does not affect glucose-insulin metabolism in sleep apneic patients. Sleep Med 2:207–213, 2001.
188. Foster GD, Sanders MH, Millman R, et al: Obstructive sleep apnea among obese patients with type 2 diabetes. Diabetes Care 32:1017–1019, 2009.
189. Babu AR, Herdegen J, Fogelfeld L, et al: Type 2 diabetes, glycemic control, and continuous positive airway pressure in obstructive sleep apnea. Arch Intern Med 165:447–452, 2005.
190. West SD, Nicoll DJ, Wallace TM, et al: Effect of CPAP on insulin resistance and HbA1c in men with obstructive sleep apnoea and type 2 diabetes. Thorax 62:969–974, 2007.
191. Pack AI, Gislason T: Obstructive sleep apnea and cardiovascular disease: A perspective and future directions. Prog Cardiovasc Dis 51:434–451, 2009.
192. Brooks D, Horner RL, Kozar LF, et al: Obstructive sleep apnea as a cause of systemic hypertension. Evidence from a canine model. J Clin Invest 99:106–109, 1997.
193. Fletcher EC, Lesske J, Qian W, et al: Repetitive, episodic hypoxia causes diurnal elevation of blood pressure in rats. Hypertension 19:555–561, 1992.
194. Bixler EO, Vgontzas AN, Lin HM, et al: Association of hypertension and sleep-disordered breathing. Arch Intern Med 160:2289–2295, 2000.
195. Peppard PE, Young T, Palta M, et al: Prospective study of the association between sleep-disordered breathing and hypertension. N Engl J Med 342:1378–1384, 2000.
196. Pepperell JC, Ramdassingh-Dow S, Crosthwaite N, et al: Ambulatory blood pressure after therapeutic and subtherapeutic nasal continuous positive airway pressure for obstructive sleep apnoea: A randomised parallel trial. Lancet 359:204–210, 2002.
197. Haentjens P, Van Meerhaeghe A, Moscariello A, et al: The impact of continuous positive airway pressure on blood pressure in patients with obstructive sleep apnea syndrome: Evidence from a meta-analysis of placebo-controlled randomized trials. Arch Intern Med 167:757–764, 2007.
198. Faccenda JF, Mackay TW, Boon NA, et al: Randomized placebo-controlled trial of continuous positive airway pressure on blood pressure in the sleep apnea-hypopnea syndrome. Am J Respir Crit Care Med 163:344–348, 2001.
199. Becker HF, Jerrentrup A, Ploch T, et al: Effect of nasal continuous positive airway pressure treatment on blood pressure in patients with obstructive sleep apnea. Circulation 107:68–73, 2003.
200. Logan AG, Tkacova R, Perlikowski SM, et al: Refractory hypertension and sleep apnoea: Effect of CPAP on blood pressure and baroreflex. Eur Respir J 21:241–247, 2003.
201. Ruttanaumpawan P, Nopmaneejumruslers C, Logan AG, et al: Association between refractory hypertension and obstructive sleep apnea. J Hypertens 27:1439–1445, 2009.
202. Mehra R, Benjamin EJ, Shahar E, et al: Association of nocturnal arrhythmias with sleep-disordered breathing: The Sleep Heart Health Study. Am J Respir Crit Care Med 173:910–916, 2006.
203. Kanagala R, Murali NS, Friedman PA, et al: Obstructive sleep apnea and the recurrence of atrial fibrillation. Circulation 107:2589–2594, 2003.
204. Shahar E, Whitney CW, Redline S, et al: Sleep-disordered breathing and cardiovascular disease: Cross-sectional results of the Sleep Heart Health Study. Am J Respir Crit Care Med 163:19–25, 2001.
205. Peker Y, Hedner J, Norum J, et al: Increased incidence of cardiovascular disease in middle-aged men with obstructive sleep apnea: A 7-year follow-up. Am J Respir Crit Care Med 166:159–165, 2002.
206. Yaggi HK, Concato J, Kernan WN, et al: Obstructive sleep apnea as a risk factor for stroke and death. N Engl J Med 353:2034–2041, 2005.
207. Buchner NJ, Sanner BM, Borgel J, et al: Continuous positive airway pressure treatment of mild to moderate obstructive sleep apnea reduces cardiovascular risk. Am J Respir Crit Care Med 176:1274–1280, 2007.
208. Platt A, Field SH, Zhen C, et al: Does adherence to lipid-lowering medications predict CPAP adherence? Sleep 31:A150, 2008.
209. Marin JM, Carrizo S, Villar I, et al: Medication adherence in severe obstructive sleep apnea (OSA). Am J Respir Crit Care Med 177:A477, 2008.
210. Peker Y, Glantz H, Thunstrom E, et al: Rationale and design of the Randomized Intervention with CPAP in Coronary Artery Disease and Sleep Apnoea—RICCADSA trial. Scand Cardiovasc J 43:24–31, 2009.
211. George CF, Kab V, Kab P, et al: Sleep and breathing in professional football players. Sleep Med 4:317–325, 2003.
212. Kuniyoshi FH, Garcia-Touchard A, Gami AS, et al: Day-night variation of acute myocardial infarction in obstructive sleep apnea. J Am Coll Cardiol 52:343–346, 2008.
213. Savransky V, Nanayakkara A, Li J, et al: Chronic intermittent hypoxia induces atherosclerosis. Am J Respir Crit Care Med 175:1290–1297, 2007.
214. Paigen B, Morrow A, Holmes PA, et al: Quantitative assessment of atherosclerotic lesions in mice. Atherosclerosis 68:231–240, 1987.
215. Curry BD, Bain JL, Yan JG, et al: Vibration injury damages arterial endothelial cells. Muscle Nerve 25:527–534, 2002.
216. Lee SA, Amis TC, Byth K, et al: Heavy snoring as a cause of carotid artery atherosclerosis. Sleep 31:1207–1213, 2008.
217. Young T, Finn L, Peppard PE, et al: Sleep disordered breathing and mortality: Eighteen-year follow-up of the Wisconsin Sleep Cohort. Sleep 31:1071–1078, 2008.
218. Marshall NS, Wong KK, Liu PY, et al: Sleep apnea as an independent risk factor for all-cause mortality: The Busselton Health Study. Sleep 31:1079–1085, 2008.
219. Pack AI, Platt AB, Pien GW: Does untreated obstructive sleep apnea lead to death? Sleep 31:1067–1068, 2008.
220. Hedner J, Grote L: The link between sleep apnea and cardiovascular disease: Time to target the nonsleepy sleep apneics? Am J Respir Crit Care Med 163:5–6, 2001.
221. Lavie P, Lavie L, Herer P: All-cause mortality in males with sleep apnoea syndrome: Declining mortality rates with age. Eur Respir J 25:514–520, 2005.
222. Lavie L, Lavie P: Ischemic preconditioning as a possible explanation for the age decline relative mortality in sleep apnea. Med Hypotheses 66:1069–1073, 2006.
223. Engleman HM, Martin SE, Kingshott RN, et al: Randomised placebo controlled trial of daytime function after continuous positive airway pressure (CPAP) therapy for the sleep apnoea/hypopnoea syndrome. Thorax 53:341–345, 1998.
224. Montserrat JM, Ferrer M, Hernandez L, et al: Effectiveness of CPAP treatment in daytime function in sleep apnea syndrome: A

randomized controlled study with an optimized placebo. Am J Respir Crit Care Med 164:608–613, 2001.
225. Henke KG, Grady JJ, Kuna ST: Effect of nasal continuous positive airway pressure on neuropsychological function in sleep apnea-hypopnea syndrome. A randomized, placebo-controlled trial. Am J Respir Crit Care Med 163:911–917, 2001.
226. Redline S, Adams N, Strauss ME, et al: Improvement of mild sleep-disordered breathing with CPAP compared with conservative therapy. Am J Respir Crit Care Med 157:858–865, 1998.
227. Patel SR, White DP, Malhotra A, et al: Continuous positive airway pressure therapy for treating sleepiness in a diverse population with obstructive sleep apnea: Results of a meta-analysis. Arch Intern Med 163:565–571, 2003.
228. Jenkinson C, Davies RJ, Mullins R, et al: Comparison of therapeutic and subtherapeutic nasal continuous positive airway pressure for obstructive sleep apnoea: A randomised prospective parallel trial. Lancet 353:2100–2105, 1999.
229. Weaver TE, Kribbs NB, Pack AI, et al: Night-to-night variability in CPAP use over the first three months of treatment. Sleep 20:278–283, 1997.
230. Stradling JR, Barbour C, Pitson DJ, et al: Automatic nasal continuous positive airway pressure titration in the laboratory: Patient outcomes. Thorax 52:72–75, 1997.
231. Masa JF, Jimenez A, Duran J, et al: Alternative methods of titrating continuous positive airway pressure: A large multicenter study. Am J Respir Crit Care Med 170:1218–1224, 2004.
232. Mulgrew AT, Fox N, Ayas NT, et al: Diagnosis and initial management of obstructive sleep apnea without polysomnography: A randomized validation study. Ann Intern Med 146:157–166, 2007.
233. Oliver Z, Hoffstein V: Predicting effective continuous positive airway pressure. Chest 117:1061–1064, 2000.
234. Wiegand L, Zwillich CW, Wiegand D, et al: Changes in upper airway muscle activation and ventilation during phasic REM sleep in normal men. J Appl Physiol 71:488–497, 1991.
235. Berry RB, Desa MM, Light RW: Effect of ethanol on the efficacy of nasal continuous positive airway pressure as a treatment for obstructive sleep apnea. Chest 99:339–343, 1991.
236. Teschler H, Berthon-Jones M, Wessendorf T, et al: Influence of moderate alcohol consumption on obstructive sleep apnoea with and without AutoSet nasal CPAP therapy. Eur Respir J 9:2371–2377, 1996.
237. Berry RB, Patel PB: Effect of zolpidem on the efficacy of continuous positive airway pressure as treatment for obstructive sleep apnea. Sleep 29:1052–1056, 2006.
238. Sanders MH, Kern N: Obstructive sleep apnea treated by independently adjusted inspiratory and expiratory positive airway pressures via nasal mask. Physiologic and clinical implications. Chest 98:317–324, 1990.
239. Reeves-Hoche MK, Hudgel DW, Meck R, et al: Continuous versus bilevel positive airway pressure for obstructive sleep apnea. Am J Respir Crit Care Med 151:443–449, 1995.
240. Resta O, Guido P, Picca V, et al: Prescription of nCPAP and nBIPAP in obstructive sleep apnoea syndrome: Italian experience in 105 subjects. A prospective two centre study. Respir Med 92:820–827, 1998.
241. Schafer H, Ewig S, Hasper E, et al: Failure of CPAP therapy in obstructive sleep apnoea syndrome: Predictive factors and treatment with bilevel-positive airway pressure. Respir Med 92:208–215, 1998.
242. Berry RB, Parish JM, Hartse KM: The use of auto-titrating continuous positive airway pressure for treatment of adult obstructive sleep apnea. An American Academy of Sleep Medicine review. Sleep 25:148–173, 2002.
243. Massie CA, Hart RW, Peralez K, et al: Effects of humidification on nasal symptoms and compliance in sleep apnea patients using continuous positive airway pressure. Chest 116:403–408, 1999.
244. Neill AM, Wai HS, Bannan SP, et al: Humidified nasal continuous positive airway pressure in obstructive sleep apnoea. Eur Respir J 22:258–262, 2003.
245. Wiest GH, Harsch IA, Fuchs FS, et al: Initiation of CPAP therapy for OSA: Does prophylactic humidification during CPAP pressure titration improve initial patient acceptance and comfort? Respiration 69:406–412, 2002.
246. Budhiraja R, Parthasarathy S, Drake CL, et al: Early CPAP use identifies subsequent adherence to CPAP therapy. Sleep 30:320–324, 2007.
247. Chan AS, Lee RW, Cistulli PA: Non-positive airway pressure modalities: Mandibular advancement devices/positional therapy. Proc Am Thorac Soc 5:179–184, 2008.
248. Lim J, Lasserson TJ, Fleetham J, et al: Oral appliances for obstructive sleep apnoea. Cochrane Database Syst Rev 1:CD004435, 2006.
249. Ferguson KA, Cartwright R, Rogers R, et al: Oral appliances for snoring and obstructive sleep apnea: A review. Sleep 29:244–262, 2006.
250. Hoffstein V: Review of oral appliances for treatment of sleep-disordered breathing. Sleep Breath 11:1–22, 2007.
251. Won CH, Li KK, Guilleminault C: Surgical treatment of obstructive sleep apnea: Upper airway and maxillomandibular surgery. Proc Am Thorac Soc 5:193–199, 2008.
252. Guilleminault C, Simmons FB, Motta J, et al: Obstructive sleep apnea syndrome and tracheostomy. Long-term follow-up experience. Arch Intern Med 141:985–988, 1981.
253. Franklin KA, Anttila H, Axelsson S, et al: Effects and side-effects of surgery for snoring and obstructive sleep apnea—A systematic review. Sleep 32:27–36, 2009.
254. Walker-Engstrom ML, Tegelberg A, Wilhelmsson B, et al: 4-year follow-up of treatment with dental appliance or uvulopalatopharyngoplasty in patients with obstructive sleep apnea: A randomized study. Chest 121:739–746, 2002.
255. Sundaram S, Bridgman SA, Lim J, et al: Surgery for obstructive sleep apnoea. Cochrane Database Syst Rev 4:CD001004, 2005.
256. Dixon JB, Schachter LM, O'Brien PE: Sleep disturbance and obesity: Changes following surgically induced weight loss. Arch Intern Med 161:102–106, 2001.
257. Strobel RJ, Rosen RC: Obesity and weight loss in obstructive sleep apnea: A critical review. Sleep 19:104–115, 1996.
258. Eckert DJ, Jordan AS, Merchia P, et al: Central sleep apnea: Pathophysiology and treatment. Chest 131:595–607, 2007.
259. Weese-Mayer DE, Rand CM, Berry-Kravis EM, et al: Congenital central hypoventilation syndrome from past to future: Model for translational and transitional autonomic medicine. Pediatr Pulmonol 44:521–535, 2009.
260. Amiel J, Laudier B, Attie-Bitach T, et al: Polyalanine expansion and frameshift mutations of the paired-like homeobox gene PHOX2B in congenital central hypoventilation syndrome. Nat Genet 33:459–461, 2003.
261. Gallego J, Dauger S: PHOX2B mutations and ventilatory control. Respir Physiol Neurobiol 164:49–54, 2008.
262. Antic NA, Malow BA, Lange N, et al: PHOX2B mutation-confirmed congenital central hypoventilation syndrome: Presentation in adulthood. Am J Respir Crit Care Med 174:923–927, 2006.
263. Berry-Kravis EM, Zhou L, Rand CM, et al: Congenital central hypoventilation syndrome: PHOX2B mutations and phenotype. Am J Respir Crit Care Med 174:1139–1144, 2006.
264. Skatrud JB, Dempsey JA: Interaction of sleep state and chemical stimuli in sustaining rhythmic ventilation. J Appl Physiol 55:813–822, 1983.
265. Nakayama H, Smith CA, Rodman JR, et al: Effect of ventilatory drive on carbon dioxide sensitivity below eupnea during sleep. Am J Respir Crit Care Med 165:1251–1260, 2002.
266. Cheyne J: A case of apoplexy in which the fleshy part of the heart was converted into fat. Dublin Hosp Rep 2:216–223, 1818.
267. Stokes W (ed): The Diseases of the Heart and Aorta. Dublin, Ireland: Hodges & Smith, 1854.
268. Bassetti C, Aldrich MS, Chervin RD, et al: Sleep apnea in patients with transient ischemic attack and stroke: A prospective study of 59 patients. Neurology 47:1167–1173, 1996.
269. Siccoli MM, Valko PO, Hermann DM, et al: Central periodic breathing during sleep in 74 patients with acute ischemic stroke—Neurogenic and cardiogenic factors. J Neurol 255:1687–1692, 2008.
270. Bonnin-Vilaplana M, Arboix A, Parra O, et al: Sleep-related breathing disorders in acute lacunar stroke. J Neurol Epub 2009;July 22 (ahead of print).
271. Javaheri S, Parker TJ, Liming JD, et al: Sleep apnea in 81 ambulatory male patients with stable heart failure. Types and their

prevalences, consequences, and presentations. Circulation 97:2154–2159, 1998.
272. Sin DD, Fitzgerald F, Parker JD, et al: Risk factors for central and obstructive sleep apnea in 450 men and women with congestive heart failure. Am J Respir Crit Care Med 160:1101–1106, 1999.
273. Lorenzi-Filho G, Rankin F, Bies I, et al: Effects of inhaled carbon dioxide and oxygen on Cheyne-Stokes respiration in patients with heart failure. Am J Respir Crit Care Med 159:1490–1498, 1999.
274. Pepperell JC, Maskell NA, Jones DR, et al: A randomized controlled trial of adaptive ventilation for Cheyne-Stokes breathing in heart failure. Am J Respir Crit Care Med 168:1109–1114, 2003.
275. Naughton MT, Benard DC, Liu PP, et al: Effects of nasal CPAP on sympathetic activity in patients with heart failure and central sleep apnea. Am J Respir Crit Care Med 152:473–479, 1995.
276. Javaheri S, Corbett WS: Association of low Pa_{CO_2} with central sleep apnea and ventricular arrhythmias in ambulatory patients with stable heart failure. Ann Intern Med 128:204–207, 1998.
277. Lanfranchi PA, Braghiroli A, Bosimini E, et al: Prognostic value of nocturnal Cheyne-Stokes respiration in chronic heart failure. Circulation 99:1435–1440, 1999.
278. Javaheri S, Ahmed M, Parker TJ, et al: Effects of nasal O_2 on sleep-related disordered breathing in ambulatory patients with stable heart failure. Sleep 22:1101–1106, 1999.
279. Javaheri S, Parker TJ, Wexler L, et al: Effect of theophylline on sleep-disordered breathing in heart failure. N Engl J Med 335:562–567, 1996.
280. Naughton MT, Liu PP, Bernard DC, et al: Treatment of congestive heart failure and Cheyne-Stokes respiration during sleep by continuous positive airway pressure. Am J Respir Crit Care Med 151:92–97, 1995.
281. Sin DD, Logan AG, Fitzgerald FS, et al: Effects of continuous positive airway pressure on cardiovascular outcomes in heart failure patients with and without Cheyne-Stokes respiration. Circulation 102:61–66, 2000.
282. Bradley TD, Logan AG, Kimoff RJ, et al: Continuous positive airway pressure for central sleep apnea and heart failure. N Engl J Med 353:2025–2033, 2005.
283. Arzt M, Floras JS, Logan AG, et al: Suppression of central sleep apnea by continuous positive airway pressure and transplant-free survival in heart failure: A post hoc analysis of the Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnea and Heart Failure Trial (CANPAP). Circulation 115:3173–3180, 2007.
284. Tkacova R, Wang H, Bradley TD: Night-to-night alterations in sleep apnea type in patients with heart failure. J Sleep Res 15:321–328, 2006.
285. Teschler H, Dohring J, Wang YM, et al: Adaptive pressure support servo-ventilation: A novel treatment for Cheyne-Stokes respiration in heart failure. Am J Respir Crit Care Med 164:614–619, 2001.
286. Morgenthaler TI, Gay PC, Gordon N, et al: Adaptive servoventilation versus noninvasive positive pressure ventilation for central, mixed, and complex sleep apnea syndromes. Sleep 30:468–475, 2007.
287. Xie A, Rutherford R, Rankin F, et al: Hypocapnia and increased ventilatory responsiveness in patients with idiopathic central sleep apnea. Am J Respir Crit Care Med 152:1950–1955, 1995.
288. Xie A, Rankin F, Rutherford R, et al: Effects of inhaled CO_2 and added dead space on idiopathic central sleep apnea. J Appl Physiol 82:918–926, 1997.
289. Gilmartin GS, Daly RW, Thomas RJ: Recognition and management of complex sleep-disordered breathing. Curr Opin Pulm Med 11:485–493, 2005.
290. Thomas RJ, Terzano MG, Parrino L, et al: Obstructive sleep-disordered breathing with a dominant cyclic alternating pattern—A recognizable polysomnographic variant with practical clinical implications. Sleep 27:229–234, 2004.
291. Morgenthaler TI, Kagramanov V, Hanak V, et al: Complex sleep apnea syndrome:Is it a unique clinical syndrome? Sleep 29:1203–1209, 2006.
292. Lehman S, Antic NA, Thompson C, et al: Central sleep apnea on commencement of continuous positive airway pressure in patients with a primary diagnosis of obstructive sleep apnea-hypopnea. J Clin Sleep Med 3:462–466, 2007.
293. Endo Y, Suzuki M, Inoue Y, et al: Prevalence of complex sleep apnea among Japanese patients with sleep apnea syndrome. Tohoku J Exp Med 215:349–354, 2008.
294. Malhotra A, Bertisch S, Wellman A: Complex sleep apnea: It isn't really a disease. J Clin Sleep Med 4:406–408, 2008.
295. Skatrud JB, Dempsey JA, Badr S, et al: Effect of airway impedance on CO_2 retention and respiratory muscle activity during NREM sleep. J Appl Physiol 65:1676–1685, 1988.
296. Dernaika T, Tawk M, Nazir S, et al: The significance and outcome of continuous positive airway pressure–related central sleep apnea during split-night sleep studies. Chest 132:81–87, 2007.
297. Kuzniar TJ, Pusalavidyasagar S, Gay PC, et al: Natural course of complex sleep apnea—A retrospective study. Sleep Breath 12:135–139, 2008.
298. Johnson KG, Johnson DC: Bilevel positive airway pressure worsens central apneas during sleep. Chest 128:2141–2150, 2005.
299. Allam JS, Olson EJ, Gay PC, et al: Efficacy of adaptive servoventilation in treatment of complex and central sleep apnea syndromes. Chest 132:1839–1846, 2007.
300. Birchfield RI, Sieker HO, Heyman A: Alterations in blood gases during natural sleep and narcolepsy: A correlation with the electroencephalographic stages of sleep. Neurology 8:107–112, 1958.
301. Birchfield RI, Sieker HO, Heyman A: Alterations in respiratory function during natural sleep. J Lab Clin Med 54:216–222, 1959.
302. Bristow JD, Honour AJ, Pickering TG, et al: Cardiovascular and respiratory changes during sleep in normal and hypertensive subjects. Cardiovasc Res 3:476–485, 1969.
303. Nowbar S, Burkart KM, Gonzales R, et al: Obesity-associated hypoventilation in hospitalized patients: Prevalence, effects, and outcome. Am J Med 116:1–7, 2004.
304. Mokhlesi B, Tulaimat A, Faibussowitsch I, et al: Obesity hypoventilation syndrome: Prevalence and predictors in patients with obstructive sleep apnea. Sleep Breath 11:117–124, 2007.
305. Mokhlesi B, Tulaimat A: Recent advances in obesity hypoventilation syndrome. Chest 132:1322–1336, 2007.
306. Kessler R, Chaouat A, Schinkewitch P, et al: The obesity-hypoventilation syndrome revisited: A prospective study of 34 consecutive cases. Chest 120:369–376, 2001.
307. Tankersley C, Kleeberger S, Russ B, et al: Modified control of breathing in genetically obese (ob/ob) mice. J Appl Physiol 81:716–723, 1996.
308. Tankersley CG, O'Donnell C, Daood MJ, et al: Leptin attenuates respiratory complications associated with the obese phenotype. J Appl Physiol 85:2261–2269, 1998.
309. Piper AJ, Wang D, Yee BJ, et al: Randomised trial of CPAP vs bilevel support in the treatment of obesity hypoventilation syndrome without severe nocturnal desaturation. Thorax 63:395–401, 2008.
310. Storre JH, Seuthe B, Fiechter R, et al: Average volume-assured pressure support in obesity hypoventilation: A randomized crossover trial. Chest 130:815–821, 2006.
311. Al Dabal L, Bahammam AS: Obesity hypoventilation syndrome. Ann Thorac Med 4:41–49, 2009.
312. Sugerman HJ, Fairman RP, Baron PL, et al: Gastric surgery for respiratory insufficiency of obesity. Chest 90:81–86, 1986.
313. Longitudinal Assessment of Bariatric Surgery (LABS) Consortium, Flum DR, Belle SH, King WC, et al: Perioperative safety in the longitudinal assessment of bariatric surgery. N Engl J Med 361:445–454, 2009.
314. Sullivan CE, Issa FG, Berthon-Jones M, et al: Reversal of obstructive sleep apnoea by continuous positive airway pressure applied through the nares. Lancet 1:862–865, 1981.

CHAPTER 80

PULMONARY COMPLICATIONS OF HUMAN IMMUNODEFICIENCY VIRUS INFECTION

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INTRODUCTION

Since the recognition of the first cases of acquired immunodeficiency syndrome (AIDS) in 1981, our understanding of human immunodeficiency virus (HIV) and its myriad infectious and noninfectious complications has increased enormously. During this period, the prognosis for persons infected by HIV has undergone dramatic change in regions with access to effective combination antiretroviral therapy to suppress HIV replication and strategies to treat and prevent HIV-associated complications. These therapeutic advances have resulted in a dramatic decline in the incidence of new AIDS cases and in the number of AIDS-associated deaths in countries predominantly in North America and Western Europe, where this care is more widely and consistently available.[1] Unfortunately, access to medications is far from universal, a cure for HIV seems unlikely, and an HIV vaccine remains elusive. Therefore, efforts to prevent the spread of new HIV infection, to identify and treat those persons who are already HIV infected, and to slow the progression from HIV to AIDS continue to be worldwide priorities.

The lungs are one of the chief target organs of HIV disease and, accordingly, a major source of morbidity and mortality. The spectrum of pulmonary manifestations is broad, and many infectious and noninfectious complications have been recognized (Table 80-1).[2,3] These complications include diseases that are AIDS defining or HIV associated (such as *Pneumocystis* pneumonia or recurrent bacterial pneumonia), disorders that are not classified as HIV associated but appear to be more common in those with HIV infection (such as lung cancer, pulmonary arterial hypertension, and chronic obstructive pulmonary disease), and conditions whose association with HIV is inconclusive or purely coincidental (such as sarcoidosis). This chapter provides a brief review of the epidemiology of HIV infection and its immunologic abnormalities, followed by a diagnostic approach to the evaluation of pulmonary disease in an HIV-infected patient. Then, the major HIV-associated pulmonary diseases are discussed, with emphasis on clinical features, diagnosis, treatment, and prevention.

TABLE 80-1. Spectrum of Pulmonary Complications

INFECTIONS
Bacteria*
- *Streptococcus pneumoniae*
- *Haemophilus* species
- *Staphylococcus aureus*
- *Pseudomonas aeruginosa*
- Other bacteria

Mycobacteria
- *Mycobacterium tuberculosis*†
- *Mycobacterium avium* complex‡
- *Mycobacterium kansasii*‡
- Other mycobacteria‡

Fungi
- *Pneumocystis jirovecii* (formerly *P. carinii*)§
- *Cryptococcus neoformans*‡
- *Histoplasma capsulatum*‡
- *Coccidioides immitis*‡
- *Aspergillus* species (most often *A. fumigatus*)
- *Blastomyces dermatitidis*
- *Penicillium marneffei*
- Other fungi

Viruses
- Cytomegalovirus§
- Other viruses

Parasites
- *Toxoplasma gondii*¶
- Other parasites

MALIGNANCIES
Kaposi sarcoma§
Non-Hodgkin's lymphoma§
Bronchogenic carcinoma

INTERSTITIAL PNEUMONITIDES
Lymphocytic interstitial pneumonitis¶
Nonspecific interstitial pneumonitis

OTHER
Chronic obstructive pulmonary disease
Asthma
Pulmonary arterial hypertension
Sarcoidosis
Immune reconstitution inflammatory syndrome

*Acquired immunodeficiency syndrome (AIDS)–defining diagnosis in adults and adolescents (>13 years) if recurrent (≥2 episodes in 12 months). Not applicable as AIDS-defining diagnosis in children.
†AIDS-defining diagnosis in adults and adolescents. AIDS-defining diagnosis in children if extrapulmonary or disseminated.
‡AIDS-defining diagnosis if extrapulmonary or disseminated.
§AIDS-defining diagnosis.
¶AIDS-defining diagnosis if central nervous system is involved.
¶AIDS-defining diagnosis in children. Not applicable as AIDS-defining diagnosis in adults or adolescents.
Modified from Murray JF, Mills J: Pulmonary infectious complications of human immunodeficiency virus infection. Am Rev Respir Dis 141:1356–1372, 1582–1598, 1990.

EPIDEMIOLOGY

The AIDS epidemic has had a major impact throughout the world. Since the beginning of the epidemic, 25 million people have died from HIV-related causes.[4] Global estimates at the end of 2007 indicated that 33 million people were living with HIV; during that year, 2.7 million were newly infected and 2.0 million people died due to AIDS.[4] A disproportionate number of all the HIV-infected people in the world live in low- and middle-income countries, especially in sub-Saharan Africa, which has the world's highest prevalence of HIV infection, and which is where approximately 67% of all people with HIV live.[4] In the United States, although the national incidence and prevalence of HIV can only be estimated because of incomplete reporting, the Centers for Disease Control and Prevention (CDC) estimates that there are more than 1 million people living with HIV.[5] As survival has improved for HIV-infected patients after the introduction of combination antiretroviral therapy (ART), more people are living with HIV in the United States than ever before.[6]

In the United States and most developed countries, persons at highest risk for HIV infection are injection drug users (IDUs), men who have sex with men (MSM), and sex workers. Heterosexual contact is a predominant mode of HIV transmission worldwide.[7] In the United States from 2003 through 2006, the main risk for transmission of HIV was MSM (approximately 49% of cases), followed by high-risk heterosexual contact (33%); most of the remaining cases were attributable to IDU.[4] Overall, the proportion of cases with transmission of HIV because of high-risk heterosexual contact has increased over the course of the epidemic. In contrast, rates of perinatal transmission have declined, and the risk of HIV infection from transfusion of blood products is estimated to be as low as 1 in 2 million blood donations with current screening and testing methods.

The gender and racial/ethnic demographics of HIV-infected populations vary worldwide. Globally, women account for approximately 50% of people living with HIV.[4] In the United States, women now comprise an increasing percentage of adult AIDS cases, accounting for about 25% of new cases.[5] Whereas HIV was predominantly seen among non-Hispanic white MSM early in the epidemic, HIV is increasingly affecting minorities. In 2006, 49% of all new HIV/AIDS diagnoses in the United States occurred in blacks, with rates of HIV/AIDS cases of 67.7 per 100,000 in the black population, 25.5 per 100,000 in the Hispanic population, and 8.2 per 100,000 in the white population.[4]

IMMUNOLOGIC ABNORMALITIES

After infection with HIV and without effective ART, HIV-infected persons experience a gradual but inexorable loss of host immunity that has been characterized as a syndrome of immune dysregulation, dysfunction, and deficiency, involving many components of the immune system. HIV is tropic for $CD4^+$ lymphocytes and monocytes.[8] After initial infection, HIV leads to massive depletion of $CD4^+$ lymphocytes of the effector-memory type from mucosal-associated lymphoid tissue.[9] During the chronic phase of untreated HIV infection, generalized immune activation occurs and ultimately, progressive decline in the naïve and memory T-cell pool results in

systemic $CD4^+$ lymphocyte depletion.[9,10] As well as being decreased in number, T cells are also dysfunctional and mount abnormal host responses to T-cell–dependent antigens. In addition, HIV infection is associated with B-cell dysfunction. Abnormal polyclonal activation, hypergammaglobulinemia, and lack of specific antibody responses ensue. This combination of immune dysfunction, dysregulation, and depletion of $CD4^+$ lymphocytes results in a substantially increased risk for infections and other complications over the course of HIV infection. Effective combination ART substantially decreases opportunistic infections and mortality in HIV-infected patients.[1] The chronic immune activation that occurs in the second phase of HIV infection can be decreased by combination ART.[9]

HIV infection also causes alteration in several lines of host defense in the lung and respiratory tract that contribute to an increased risk for pulmonary infections. These include abnormalities in mucociliary function and soluble defense molecules within respiratory secretions.[11] Within the lung parenchyma, innate and adaptive immune responses to pathogens may be impaired.[12] For example, alveolar macrophages, a primary reservoir of HIV within the lung, have been shown to have deficiencies in pathogen recognition. Evidence also suggests that HIV results in chronic stimulation and activation of inflammatory cells within the alveolar space.[11] Furthermore, animal models suggest that HIV-related proteins may disrupt the barrier function of the alveolar epithelium.[11a] The consequences of this persistently increased inflammation on the pathogenesis of chronic lung disease in HIV-infected persons are poorly understood.

DIAGNOSTIC APPROACH

The evaluation of an HIV-infected patient with pulmonary disease is aimed at making a specific diagnosis. Whenever possible, definitive diagnosis is preferred to empirical therapy for a number of reasons. Although each of the HIV-associated pulmonary diseases has characteristic clinical and radiographic features, these features overlap. Occasionally, the presenting features are atypical, or more than one pulmonary disease is present. Without appropriate therapy, HIV-infected patients with pneumonia can progress rapidly to respiratory failure and death. The therapies used to treat HIV-associated pulmonary diseases have substantial toxicities and interactions with other medications that a patient may be receiving for prophylaxis, for a comorbid condition, or as part of combination ART.

The evaluation should begin with the history and physical examination. Laboratory testing should be performed and a chest radiograph obtained from patients with suspected pulmonary disease. Frequently, the results of this evaluation suggest a specific differential diagnosis and management plan. Occasionally, additional studies, including pulmonary function testing, chest computed tomography (CT), high-resolution CT, and gallium-67 (^{67}Ga) scanning, are needed to narrow the differential diagnosis and to refine the management plan.

Owing to their particular importance in the diagnostic evaluation of many patients with known or suspected HIV-related pulmonary disease, the value of $CD4^+$ lymphocyte counts and fiberoptic bronchoscopy are briefly reviewed here. The utility of other diagnostic tests are considered in the discussions of the specific disorders that follow this section.

$CD4^+$ Lymphocyte Count

The $CD4^+$ lymphocyte count is an excellent indicator of an HIV-infected patient's risk of developing a specific opportunistic infection or neoplasm. Many of the HIV-associated pulmonary diseases usually present at or below a characteristic $CD4^+$ lymphocyte count and seldom occur above that count.[13] The exceptions are diseases that can present in persons without HIV infection, such as bacterial pneumonia, tuberculosis, and non-Hodgkin's lymphoma. In HIV-infected persons, these diseases can present at any $CD4^+$ lymphocyte count, although their incidence increases and their characteristic presentation changes as the $CD4^+$ lymphocyte count declines (see subsequent disease discussion).

At $CD4^+$ lymphocyte counts less than 200 cells/μL, bacterial pneumonia is often accompanied by bacteremia, and *Mycobacterium tuberculosis* disease is often extrapulmonary or disseminated. Moreover, below this $CD4^+$ lymphocyte count, *Pneumocystis* and *Cryptococcus neoformans* pneumonia become important considerations, whereas neither typically occurs in a patient with a count significantly higher than 200 cells/μL. At $CD4^+$ lymphocyte counts below 50 to 100 cells/μL, endemic fungi, certain viruses (cytomegalovirus), nontuberculous mycobacteria (*Mycobacterium avium* complex [MAC]), and Kaposi sarcoma become important considerations. Many of these diseases present with extrapulmonary or disseminated manifestations that may dominate the clinical presentation.

The risk of opportunistic infections is best reflected by the current $CD4^+$ lymphocyte count.[14] Primary and secondary *Pneumocystis* prophylaxis can be safely discontinued in patients whose $CD4^+$ lymphocyte counts increase above 200 cells/μL for at least 3 months in response to ART; similar evidence has emerged indicating that it is safe to discontinue primary and secondary prophylaxis against MAC, *C. neoformans,* and *Toxoplasma gondii* when $CD4^+$ lymphocyte counts have been restored to greater than 100 cells/μL (MAC) to 200 cells/μL (*C. neoformans* and *T. gondii*) for at least 3 months for primary prophylaxis and 6 months for secondary prophylaxis.[14]

Fiberoptic Bronchoscopy

Since the beginning of the AIDS epidemic, fiberoptic bronchoscopy has been a cornerstone in the evaluation of HIV-associated pulmonary disease. In general, bronchoscopy should be considered for any known or suspected HIV-infected patient with pulmonary disease whose severity warrants a prompt and accurate diagnosis, for patients with suspected pulmonary Kaposi

sarcoma, for patients with suspected non-Hodgkin's lymphoma (if other diagnostic procedures are thought to be more hazardous or less likely to provide the diagnosis), for patients whose diagnosis remains unknown despite less invasive diagnostic studies (e.g., induced sputum), and for patients whose empirical therapy is failing.

The decision to perform bronchoalveolar lavage (BAL) with or without transbronchial biopsy (TBBX) depends on the suspected diagnosis and on the sensitivities of these procedures for that diagnosis. At the beginning of the AIDS epidemic, both BAL and TBBX were usually performed during the initial bronchoscopy. Studies demonstrated that the yield from these two procedures was complementary in identifying pathogens: The sensitivity of BAL was 86% and that of TBBX 87%; when the two procedures were combined, the sensitivity was 98% for all pathogens and 100% for *Pneumocystis.*[15] Currently, we perform only BAL during the initial bronchoscopy in cases in which *Pneumocystis* pneumonia (PCP) is the suspected pathogen.[16] Our experience is that the sensitivity of BAL fluid examination for *Pneumocystis* is 97% or higher, and, therefore, a negative BAL fluid examination for *Pneumocystis* rules out the diagnosis of PCP in all but the rarest of cases.

In contrast to PCP, TBBX improves the sensitivity of bronchoscopy for diagnosing a number of other important pathogens, including tuberculosis and endemic fungal pneumonias. Furthermore, tissue confirmation from TBBX or another biopsy specimen is mandatory to establish the diagnosis of invasive aspergillosis, cytomegalovirus pneumonia, and pulmonary non-Hodgkin's lymphoma. Therefore, when the clinical and radiographic features suggest one of these diseases, both BAL and TBBX are warranted during the initial bronchoscopy.

Other Invasive Procedures

Other less commonly used invasive procedures include diagnostic thoracenteses, which should be considered for any HIV-infected patient with pleural effusion in whom other studies are nondiagnostic or in whom there is a concern about empyema. Although the addition of pleural biopsy increases the sensitivity of this procedure for tuberculosis, pleural fluid culture alone is often sufficient to establish the diagnosis of bacterial and fungal infections, and pleural fluid cytology can establish the diagnosis of non-Hodgkin's lymphoma. Transthoracic needle aspiration of the lungs can be used to diagnose focal mass lesions and mediastinal adenopathy.[17] Video-assisted thoracoscopy has made a number of important contributions. As a result, open-lung biopsy is only rarely indicated in the evaluation of HIV-associated pulmonary disease, but when used, it establishes a diagnosis in most cases.[18,19]

INFECTIOUS COMPLICATIONS

The lungs are the principal targets of the many infections that lead to an AIDS diagnosis and are often involved in earlier stages of HIV disease as well. In this section, the major pulmonary infectious complications of HIV disease are reviewed according to the category of infectious microorganism that causes them (see Table 80-1).

Bacteria

Early in the AIDS epidemic, bacterial pneumonia accounted for only a small proportion of reported pulmonary diseases. Subsequently, bacterial pneumonia became recognized as a frequent complication of HIV infection and one that often preceded other opportunistic infections. As a result, recurrent bacterial pneumonia (defined as two or more episodes within 12 months) was included as an AIDS-defining illness in the 1993 CDC Expanded Surveillance Case Definition for AIDS.[20]

Prior to the combination ART era, Hirschtick and coworkers in the Pulmonary Complications of HIV Infection Study (PCHIS)[21] confirmed the increased incidence of community-acquired bacterial pneumonia in HIV-infected persons. In this study, there were 5.5 episodes of bacterial pneumonia per 100 person-years in the HIV-infected cohort compared with 0.9 episodes per 100 person-years in the HIV-seronegative control cohort ($P < 0.001$). Bacterial pneumonia was more common in HIV-infected patients than in the HIV-seronegative controls, even in the subset of HIV-infected patients with $CD4^+$ lymphocyte counts above 500 cells/μL ($P < 0.004$). Furthermore, the rate of bacterial pneumonia in the HIV-infected cohort increased as the $CD4^+$ lymphocyte count declined. The rate of bacterial pneumonia was 2.3 episodes per 100 person-years in subjects with a $CD4^+$ lymphocyte count above 500 cells/μL compared to 10.8 episodes per 100 person-years in subjects with a $CD4^+$ lymphocyte count below 200 cells/μL. The incidence of bacterial pneumonia was greater in IDUs (11.1 episodes per 100 person-years) than in either MSM (4.1 episodes per 100 person-years, $P < 0.001$) or female partners of HIV-infected men (3.8 episodes per 100 person-years, $P < 0.003$). Cigarette smoking was also associated with an increased incidence of bacterial pneumonia, especially in HIV-infected subjects with a $CD4^+$ lymphocyte count below 200 cells/μL.

During the combination ART era (1996 to present), the incidence of community-acquired bacterial pneumonia among HIV-infected persons has declined, although it has not declined to as great an extent as opportunistic pneumonias such as PCP.[22] In the CDC-sponsored Adult/Adolescent Spectrum of HIV Disease project, a prospective medical record review of HIV-infected persons of age 13 years or older conducted in 11 U.S. cities, the incidence of recurrent pneumonia declined from 22.0 per 1000 person-years in 1992 to 10.7 per 1000 person-years in 1997.[23] Other studies have reported similar decreases from the use of combination ART in both community-acquired pneumonia[24] and hospital-acquired pneumonia.[25]

Thus, combination ART is clearly associated with a decreased risk for bacterial pneumonia. Antiretroviral regimens that contain an HIV protease inhibitor (PI) may be associated with a further decreased risk of bacterial pneumonia.[24] Another potential reason for decreased

bacterial pneumonia among HIV-infected patients in the current era is the use of trimethoprim-sulfamethoxazole (TMP-SMX) as prophylaxis for PCP.[26]

Yet despite the significant decrease in incidence, bacterial pneumonia remains a common cause of morbidity and is associated with an increased mortality in HIV-infected patients in the combination ART era.[26] One reason for the persistence of bacterial pneumonia despite effective ART is the high prevalence of cigarette smoking in HIV-infected populations.[27] Cigarette smoking is associated with substantially increased rates of pneumonia in multiple studies of HIV-infected patients, at all $CD4^+$ lymphocyte cell counts.[21,26,28] IDU remains a significant risk factor for bacterial pneumonia in the combination ART era. Higher HIV RNA (viral load) may also be associated with increased risk for bacterial pneumonia, independent of $CD4^+$ lymphocyte count.[29] Additionally, impairments in neutrophil number and function can occur in HIV infection, which may be exacerbated by concomitant cigarette smoking and contribute to increased risk for bacterial pneumonia.[11]

Overall, *Streptococcus pneumoniae* and *Haemophilus* species are the most frequently identified bacteria causing community-acquired pneumonia in HIV-infected persons. *Staphylococcus aureus* can be isolated as a cause of community-acquired pneumonia in patients both with and without a history of IDU.[29,30] *Pseudomonas aeruginosa* is also an important cause of bacterial pneumonia in HIV-infected patients. In one study, *S. pneumoniae* and *P. aeruginosa* were the two most common bacteria seen in a series of 111 cases.[30] Although this series included community-acquired as well as hospital-acquired pneumonias, most cases of pneumococcal pneumonia (91%) as well as pseudomonal pneumonia (63%) were community acquired. Other bacteria that are occasionally identified as causes of community-acquired pneumonia in HIV-infected persons include atypical organisms such as *Legionella* species and *Mycoplasma pneumoniae.* Other causes of pneumonia that are less likely in HIV-uninfected persons but should be considered in HIV-infected patients include *Rhodococcus equi* and *Nocardia* species.

The two most common bacterial causes of hospital-acquired pneumonia in HIV-infected persons are *P. aeruginosa* and *S. aureus.* Both of these organisms are more likely to be isolated in patients with lower $CD4^+$ lymphocyte counts.[25,31] Staphylococcal pneumonia is frequently complicated by bacteremia, methicillin resistance, and high mortality.[25] *Streptococcus pneumoniae* and *Klebsiella pneumoniae* are also relatively frequent causes of pneumonia in HIV-infected hospitalized patients.[25]

Streptococcus pneumoniae and Haemophilus Species

Similar to published series of community-acquired bacterial pneumonia in non–HIV-infected populations, *S. pneumoniae* and *Haemophilus* species are the most frequently identified pathogens in people with HIV infection. In several studies, the two organisms have accounted for approximately 50% to 60% of cases combined.[21,31] In studies of bacterial pneumonia in the combination ART era, *S. pneumoniae* and *Haemophilus influenzae* remain two of the most commonly isolated bacterial organisms.[29]

Clinical Features. In HIV-infected persons, the clinical and radiographic features of bacterial pneumonia are similar to those in immunocompetent persons (see discussion in Chapter 32), with a few important exceptions.

$CD4^+$ Lymphocyte Count. Bacterial pneumonia can occur throughout the course of HIV infection and at any $CD4^+$ lymphocyte count. As the $CD4^+$ lymphocyte count declines, however, both the incidence of bacterial pneumonia and the frequency of bacteremia increase. The rate of pneumococcal bacteremia in HIV-infected patients has been estimated to be almost 100 times greater than that in age-matched non–HIV-infected persons.[32] Findings that confer greater risk for bacteremic pneumococcal pneumonia include alcohol abuse, cigarette smoking, recent hospitalization, and presence of comorbid illnesses.[33]

Chest Radiograph. As illustrated in Figure 80-1, the majority of bacterial pneumonias due to *S. pneumoniae* in HIV-infected patients present with segmental, lobar, or multilobar consolidation on chest radiograph.[34] Radiographic findings of pneumococcal pneumonia do not appear to be different among patients on ART compared to those not on ART.[35] Although less common, focal or diffuse alveolar patterns as well as interstitial infiltrates in association with *S. pneumoniae* or *H. influenzae* can also occur.[36,37] Studies suggest that a "classic" presentation with consolidation of anatomic units may be seen more frequently in pneumonias due to *S. pneumoniae* and, to a lesser extent, *Haemophilus* species than in those due to community-acquired *P. aeruginosa.*

Diagnosis. The diagnostic approach to bacterial pneumonia is the same for HIV-infected as for non–HIV-infected persons (see Chapter 32).[14,38] HIV-infected patients continue to be at increased risk for invasive pneumococcal disease in the combination ART era.[39] Definitive diagnosis is possible in the 25% to 80% of HIV-infected patients with pneumococcal pneumonia who present with bacteremia, and in the 5% to 25% of those with *H. influenzae* pneumonia with bacteremia. Thoracentesis should be considered for patients with pleural effusion, especially if the effusion is large or if there is concern about a possible empyema. Efforts to culture the causative bacteria to enable drug susceptibility testing are especially important in communities where drug-resistant bacteria are prevalent.

Pneumococcal urinary antigen testing offers the potential for early, specific diagnosis. In a study of 70 adults with pneumococcal pneumonia, 47 of whom were HIV infected, pneumococcal urinary antigen testing had a sensitivity of 81%, specificity of 98%, positive predictive value of 98%, and negative predictive value of 82%.[40] The test appeared to perform equally well in HIV-infected and HIV-uninfected persons.

Serum procalcitonin and C-reactive protein levels may assist in early differentiation of bacterial community-

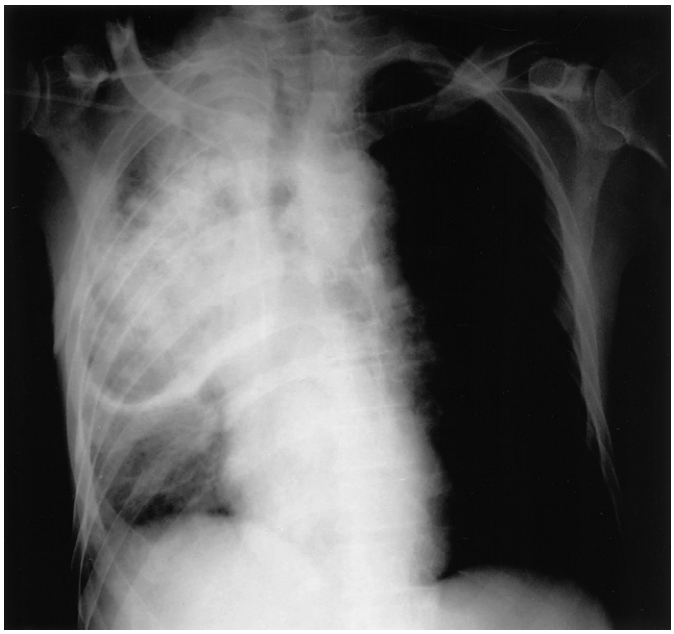

FIGURE 80-1 ■ Posteroanterior chest radiograph of an HIV-seropositive patient showing focal right lung consolidation. Culture of blood and sputum revealed *Streptococcus pneumoniae.* In HIV-infected persons, *S. pneumoniae* is the most frequently identified bacterial pathogen and is often accompanied by bacteremia, especially when the $CD4^+$ lymphocyte count is below 200 cells/μL. (Courtesy of L. Huang.)

acquired pneumonia and pulmonary tuberculosis in HIV-infected patients, as shown by the results of a study from South Africa; procalcitonin and C-reactive protein levels were found to be higher in patients with bacterial pneumonia compared to patients with pulmonary tuberculosis, although overlap occurred between the groups.[41] Because procalcitonin increases in response to microbial toxins and decreases in the presence of viral infections, levels are being used as a biologic marker of community-acquired pneumonia.[42]

Treatment. The principles of the treatment of patients with community-acquired pneumonia are similar for HIV-infected and non–HIV-infected persons.[14,38,43] The choice of antimicrobial agent should be based on a number of factors, such as the results of a sputum Gram stain, the presence of comorbid conditions (e.g., chronic obstructive pulmonary disease, congestive heart failure, alcohol use), the clinical and radiographic presentation, and the severity of the pneumonia. As for non–HIV-infected persons, treatment should be initiated promptly. Initial empirical therapy should include coverage against frequently identified organisms (e.g., *S. pneumoniae* and *Haemophilus* species). Prevailing drug resistance patterns must be considered when the antibiotic is selected. Empirical monotherapy with a macrolide is not advised in HIV-infected patients, particularly if they are already on macrolide prophylaxis for MAC, given increasing pneumococcal resistance rates.[14] Patients on TMP-SMX prophylaxis may be more likely to have penicillin- and TMP-SMX–resistant *S. pneumoniae.*[44] For patients with $CD4^+$ lymphocyte counts less than 100 cells/μL, especially if associated with recent hospitalization, neutropenia, and broad-spectrum antimicrobial use, consideration should be given to including coverage against *P. aeruginosa.*

Prevention. The National Institutes of Health (NIH), the CDC, and the HIV Medical Association of the Infectious Diseases Society of America (HIVMA/IDSA) recommend that the 23-valent polysaccharide pneumococcal vaccine be given to all HIV-infected patients with $CD4^+$ lymphocyte counts above 200 cells/μL and be considered for patients with $CD4^+$ lymphocyte counts below 200 cells/μL.[14] The efficacy of vaccination is believed to be the greatest when the patient's $CD4^+$ lymphocyte count is above 500 cells/μL.[45] Observational studies also suggest, however, that pneumococcal vaccination lowers risk for pneumonia even when $CD4^+$ lymphocyte counts are less than 200 cells/μL.[46] Revaccination can be considered for patients who were initially immunized when their $CD4^+$ lymphocyte count was below 200 cells/μL if their count has increased above 200 cells/μL in response to combination ART. The duration of the protective effect of primary pneumococcal vaccination in HIV-infected persons is unknown; revaccination 5 years after the initial vaccination may be appropriate.[14]

Pseudomonas aeruginosa

In addition to being a cause of nosocomial disease, *P. aeruginosa* is well recognized as a cause of community-acquired bacterial pneumonia in HIV-infected persons, especially those with advanced AIDS. In contrast to non–HIV-infected persons, the classic risk factors for *P. aeruginosa* infection are often absent in HIV-infected patients, and the disease often recurs.[47]

Pseudomonas aeruginosa infection produces a wide spectrum of disease in HIV-infected persons. The two most common presentations are pneumonia and bacteremia. Unlike pneumonia due to *S. pneumoniae* and *Haemophilus* species, however, pneumonia due to *P. aeruginosa* usually occurs at more profound degrees of immunosuppression, and the chest radiograph often reveals cavitary infiltrates. The usual symptoms include fever and cough that is productive, with dyspnea and chest pain seen less frequently.[48]

$CD4^+$ Lymphocyte Count. Most cases of *P. aeruginosa* pneumonia occur in HIV-infected patients with a $CD4^+$ lymphocyte count less than 100 cells/μL, and usually less than 50 cells/μL.[48,49]

Chest Radiograph. Although the chest radiograph may resemble that seen in pneumococcal or *Haemophilus* pneumonias with focal consolidation, a significant proportion of radiographs demonstrate cavitary infiltrates. Schuster and Norris[48] reported that half of 16 HIV-infected patients with *Pseudomonas* pneumonia had cavitary infiltrates on their admission chest radiograph, and another 3 patients (19%) had cavities on subsequent radiographs. Less striking results were noted in a study of 58 HIV-infected patients with *P. aeruginosa* infection in whom 24% of the 25 patients with pneumonia had cavitary infiltrates on chest radiograph.[50]

Other Bacteria

Legionella pneumonia is an infrequent cause of bacterial pneumonia in HIV-infected patients. Blatt and coworkers[51] reported eight cases of *Legionella pneumophila* pneumonia occurring in seven HIV-infected patients; five of the cases were nosocomial. The median $CD4^+$ lymphocyte count was 83 cells/μL (range, 38 to 155 cells/μL). Another series reported 15 cases of *Legionella pneumophila* pneumonia that spanned the combination ART era; 10 of the 15 cases occurred in persons who were receiving ART, and the mean $CD4^+$ lymphocyte count was 348 cells/μL.[52] Five of the 10 also had an undetectable HIV RNA level. The chest radiograph revealed alveolar infiltrates in all 15 cases, with 8 of the 15 having bilateral involvement. Extrapulmonary manifestations (gastrointestinal, $n = 3$; neurologic, $n = 4$) were also seen. Of note, 12 (80%) of the 15 persons developed respiratory failure and 3 died. Although *L. pneumophila* is the most common species identified, other *Legionella* species have also been reported. Rapid diagnosis of *Legionella* pneumonia can be attained with urinary antigen testing. However, cultures and/or serology should still be considered as part of the diagnostic evaluation, as the urinary antigen primarily detects *L. pneumophila* serogroup 1 and can have a lower sensitivity in cases of mild disease.[53] Its performance has also not been prospectively evaluated in HIV-infected patients.

There have been a number of reports of *R. equi* pulmonary disease occurring in HIV-infected persons. A review of over 100 reported cases of *R. equi* infection found that approximately two thirds occurred in HIV-infected persons, with pulmonary disease present in the majority.[54] HIV-infected persons were more likely to have *R. equi* bacteremia or extrapulmonary manifestations, or both, than persons without HIV infection. Most cases present when the $CD4^+$ lymphocyte count is less than 200 cells/μL and usually below 100 cells/μL.[54] In one multicenter series of 67 HIV-infected patients with *R. equi* infection, the mean $CD4^+$ lymphocyte count was 35 cells/μL (range, 1 to 183 cells/μL).[55] The chest radiograph often reveals cavitary lesions that may mimic tuberculosis or nocardiosis, or focal consolidation that may mimic bacterial pneumonia. Sputum, blood, bronchoscopy, and pleural fluid specimens can establish the diagnosis of *R. equi* pneumonia.[55] The optimum treatment regimen and duration have yet to be defined.[54] Combination antimicrobial therapy is generally recommended, and treatment for 6 months is often required; because relapses are common, chronic suppressive therapy is probably indicated.

There have been a handful of reports of *Nocardia* species infection in HIV-infected patients. *Nocardia asteroides* is the most common species identified, and the lung is the most commonly affected site. Most cases present when the $CD4^+$ lymphocyte count is below 200 cells/μL. In one series of 30 HIV-infected patients with nocardiosis, the mean $CD4^+$ lymphocyte count was 109 cells/μL (median 92 cells/μL; range, 12 to 266 cells/μL).[56] The presenting symptoms often mimicked tuberculosis. The chest radiograph usually reveals cavitary lesions or lobar or multilobar infiltrates, especially in the upper lung zones, although reticulonodular infiltrates, solitary masses, and pleural effusions can also be seen.[57] Sputum or bronchoscopy can establish the diagnosis of pulmonary nocardiosis. A modified acid-fast bacilli (AFB) stain may provide an early presumptive diagnosis in the proper clinical setting. Long-term TMP-SMX is the treatment of choice.

Mycobacteria

Early in the AIDS epidemic, mycobacteria were recognized as major sources of HIV-associated morbidity and mortality. Initially, HIV-infected patients were noted to develop disseminated MAC. Subsequently, the relationship between HIV and *M. tuberculosis* and nontuberculous mycobacteria such as *Mycobacterium kansasii* became clearer. Other nontuberculous mycobacteria are also occasionally identified as causes of pneumonia in HIV-infected persons.

Mycobacterium tuberculosis

Tuberculosis is the most prevalent opportunistic infection complicating the HIV epidemic worldwide. Although other pathogens may predominate in individual areas, no other pathogen poses as great a global threat to persons immunocompromised by HIV infection as *M. tuberculosis.* Moreover, unlike most of the HIV-associated opportunistic infections, *M. tuberculosis* is transmissible from person to person, including to those without HIV infection. In fact, it has been found that clusters of transmission of tuberculosis that include at least one HIV-infected person are larger, last longer, and have a shorter time period between successive cases than clusters of solely HIV-negative persons.[58] The disease is also curable and preventable.

The AIDS epidemic has contributed to a veritable explosion of tuberculosis throughout the world, but especially in low-income countries, where it is often the first manifestation of HIV and a leading cause of mortality. The World Health Organization estimated that, in 2007, of the 9.27 million new cases of tuberculosis worldwide, 1.37 million (14% of the total) occurred in

persons with HIV, most of whom lived in sub-Saharan Africa and Southeast Asia; of the 1.78 million total deaths from tuberculosis, 0.46 million (26%) were in HIV-infected persons.[59] Deaths from tuberculosis among HIV-infected people accounted for 23% of the estimated 2 million total HIV deaths in 2007.

The AIDS epidemic has also affected tuberculosis in the United States. Before 1985, the incidence of tuberculosis in the United States regularly declined by 5% to 6% per year. From 1985 through 1992, tuberculosis cases increased by 20%, which resulted in 51,700 additional cases of tuberculosis being reported in excess of that predicted by the annual decline previously noted.[60] Tuberculosis cases have decreased since 1992, with the 2008 incidence being the lowest reported since 1953, when national reporting began; however, the rate of decline has now slowed.[61] The proportion of tuberculosis cases with known HIV infection has also decreased from 15.0% in 2003 to 12.4% in 2006; however, the proportion of cases with HIV discovered at the time of tuberculosis diagnosis has increased from 28.7% in 2005 to 31.7% in 2006.[62]

It remains unclear whether HIV-infected persons are more likely to acquire tuberculous infection after exposure to *M. tuberculosis* than HIV-negative persons. Once an individual becomes infected, however, there is no doubt that HIV infection significantly increases the risk of developing primary tuberculosis as well as progressing from latent tuberculosis infection (LTBI) to active tuberculous disease. Instead of a 5% lifetime risk of "reactivation" disease, the risk among HIV-infected persons with LTBI in the pre–combination ART era has been estimated to be as high as 10% per year.

Multidrug-resistant tuberculosis (MDR-TB), defined as resistance to at least isoniazid and rifampin (also known as rifampicin in many countries), poses a particularly grim prospect for the HIV-infected person. The risk of drug-resistant tuberculosis has been reported to be greater among HIV-infected patients than among others, and drug-resistant tuberculosis appears to be associated with decreased survival.[63] In a multivariate analysis, HIV infection was found to be an independent risk factor for at least isoniazid resistance, for both isoniazid and rifampin resistance, and especially for rifampin monoresistance.[64] A meta-analysis of risk factors for MDR-TB in Europe found that HIV was an independent risk factor (odds ratio = 3.52).[65] In addition, HIV-infected patients treated with intermittent rifabutin-based therapy have been found to have a high risk of acquired rifamycin resistance, particularly if their $CD4^+$ lymphocyte count is less than 100 cells/μL.[66] Factors that lead to acquired drug resistance include an inadequate initial treatment regimen, patient nonadherence with the prescribed regimen, and the addition of a single drug to a failing regimen. Studies using restriction fragment length polymorphism analysis have shown that MDR-TB can also occur as a result of exogenous reinfection from a multidrug-resistant source.[67]

Extensively drug-resistant tuberculosis (XDR-TB), defined as resistance to at least isoniazid and rifampin (i.e., MDR-TB), plus resistance to any fluoroquinolone and to at least one second-line injectable drug, was first reported in 2006.[68] It has been documented in all regions of the world and in HIV-infected persons.[69,69a,69b] It is likely that the true extent of XDR-TB is unknown because many laboratories are unable to perform susceptibility tests, particularly to second-line drugs, and rely only on smear results for diagnosing tuberculosis. A case series of 53 persons with XDR-TB in South Africa found that, of the 44 patients who underwent HIV testing, all were HIV infected; 52 of the 53 patients died, and the median survival was only 16 days.[70] Epidemiologic evidence strongly suggested that the outbreak of XDR-TB was a result of person-to-person transmission, especially in a nosocomial setting.

Clinical Features. Worldwide, tuberculosis is the most common initial manifestation of underlying HIV infection. The clinical and radiographic features of tuberculosis in both HIV-infected and non–HIV-infected persons vary and are fully discussed in Chapter 34. HIV infection is independently associated with an increased risk for extrapulmonary tuberculosis.[71]

$CD4^+$ Lymphocyte Count. Tuberculosis may develop throughout the course of HIV infection, regardless of the $CD4^+$ lymphocyte count, but the incidence increases as the count decreases; tuberculosis is much less common in patients receiving ART but still occurs. The clinical expression of tuberculosis in HIV-infected persons is largely dependent on the degree of host immunosuppression as indicated by the $CD4^+$ lymphocyte count (Table 80-2).[72] HIV-infected persons with relatively early HIV disease typically present with a picture suggestive of reactivation tuberculosis, with disease usually limited to the lungs. In contrast, persons with more advanced HIV disease typically present with a picture reminiscent of primary pulmonary tuberculosis, often with disseminated or extrapulmonary tuberculosis. In a series of 97 HIV-infected patients with tuberculosis, Jones and colleagues[72] reported that extrapulmonary tuberculosis was seen in 30 (70%) of 43 patients with a $CD4^+$ lymphocyte count of 100 cells/μL or fewer, in 10 (50%) of 20 patients with a count between

TABLE 80-2. Manifestations of AIDS-Related Tuberculosis in "Early" and "Late" HIV Infection

Feature	Early Infection	Late Infection
Tuberculin skin test	Positive	Negative
Extrapulmonary	10–15%	More than 50%
Radiographic findings		
Distribution	Upper zones	Lower and middle zones
Cavitation	Common	Uncommon
Adenopathy	Uncommon	Common
Miliary	Uncommon	Common
Pleural effusion	Uncommon	Rare

Adapted from Murray JF: Cursed duet: HIV infection and tuberculosis. Respiration 57:210–220, 1990.

101 and 200 cells/μL, in 7 (44%) of 16 patients with a count between 201 and 300 cells/μL, and in only 5 (28%) of 18 patients with a count above 300 cells/μL. Virtually any extrapulmonary site may be involved; common sites include lymph nodes (usually cervical, supraclavicular, and axillary), bone marrow, genitourinary tract, central nervous system, and liver.[73]

Chest Radiograph. The prevalence of specific chest radiograph features of tuberculosis also depends on the degree of host immunosuppression. Disease occurring early in the course of HIV infection mirrors that encountered in immunocompetent persons: upper lung zone infiltrates, often with cavitation, on chest radiograph. However, tuberculosis occurring later in the course of HIV infection often presents with middle and lower lung zone infiltrates, as illustrated in Figure 80-2; with diffuse infiltrates, including a miliary pattern; or with a normal chest radiograph. As the $CD4^+$ lymphocyte count declines, cavitation becomes less common and intrathoracic adenopathy, as shown in Figure 80-3, becomes more common. Jones and colleagues[72] reported that adenopathy was seen on the radiographs of 20 (34%) of 58 HIV-infected patients with a $CD4^+$ lymphocyte count of 200 cells/μL or fewer compared with 4 (14%) of 29 patients with a $CD4^+$ lymphocyte count above 200 cells/μL ($P = 0.04$). Combination ART also affects the chest radiographic appearance in HIV-infected patients with tuberculosis; in one study of 209 patients, 82% of the patients receiving ART presented with a post-primary pattern of tuberculosis compared to 44% of the patients not receiving ART ($P < 0.001$).[74]

Diagnosis. The diagnostic approach to tuberculosis is the same for HIV-infected as for non–HIV-infected persons (see Chapter 34). Two to three sputum specimens should be examined for AFB and cultured for mycobacteria; a third sputum smear adds little to the diagnosis, but all three specimens, when available, should be cultured for mycobacteria.[74a] In patients with a nonproductive cough or scant secretions, sputum induction should be performed. In addition, the sensitivity of sputum mycobacterial culture for HIV-infected patients with pleural effusions due to tuberculosis has been reported to be as high as 77%, and samples from extrapulmonary sites have a higher sensitivity in those with advanced immunodeficiency.[75]

The "gold standard" diagnostic test for tuberculosis remains the isolation and identification of *M. tuberculosis* by culture or by polymerase chain reaction (PCR). Virtually any specimen can be studied for mycobacteria, including sputum, pleural fluid, urine, cerebrospinal fluid, and BAL fluid; Wang needle, fine-needle, and bone marrow aspirates; and all biopsy specimens. Blood cultures are specific and should be obtained, especially from those persons with a $CD4^+$ lymphocyte count below 200 cells/μL. All cultures positive for *M. tuberculosis* should be submitted for susceptibility testing, as the results are essential in identifying cases of drug resistance and in tailoring definitive treatment.

Treatment. New recommendations for the treatment of tuberculosis are described in Chapter 34. Because tuberculosis is transmissible, persons with suspected tuberculosis should be promptly started on empirical antituberculosis treatment to reduce the risk of transmission. The detection of AFB on smear or in culture, regardless of the source, is an indication for empirical antituberculosis treatment while final identification is awaited. HIV-infected persons with suspected tuberculosis should be started on four antituberculous

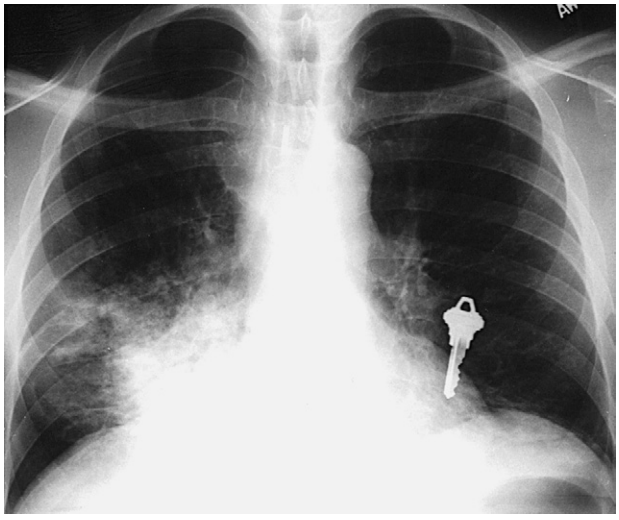

FIGURE 80-2 ■ Posteroanterior chest radiograph of an HIV-seropositive patient showing focal right lung consolidation with air bronchograms. Culture of sputum revealed *Mycobacterium tuberculosis* that was mono-rifampin resistant. Knowledge of the patient's $CD4^+$ lymphocyte count (<50 cells/μL) and understanding that tuberculosis can present with middle to lower lung zone consolidation during "late" HIV infection were instrumental in making the diagnosis of tuberculosis. The key was in the patient's pocket. (Courtesy of L. Huang.)

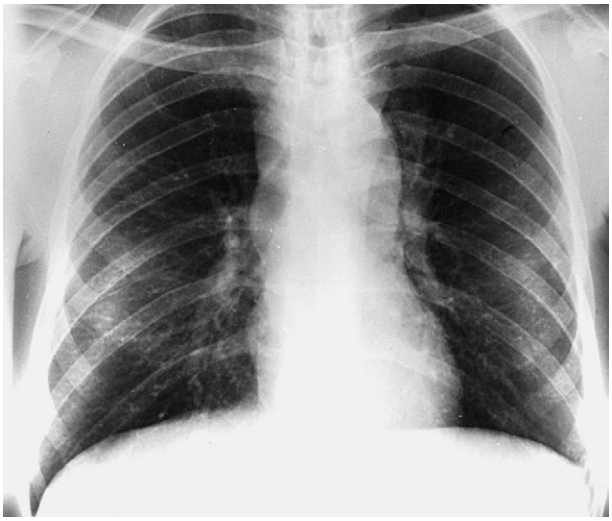

FIGURE 80-3 ■ Posteroanterior chest radiograph of an HIV-seropositive patient showing mediastinal adenopathy. Culture of biopsy material revealed *Mycobacterium tuberculosis.* Among HIV-infected persons, the proportion of cases that present with intrathoracic adenopathy on chest radiograph increases as the $CD4^+$ lymphocyte count decreases. (From Murray JF, Mills J: Pulmonary complications of HIV infection. Am Rev Respir Dis 141:1356–1372, 1582–1598, 1990.)

drugs: isoniazid, rifampin, pyrazinamide, and ethambutol along with pyridoxine.[76] When results of species identification and susceptibility testing become available, drug selection can be tailored as needed. In the United States, the response to therapy and the time to convert sputum cultures from positive to negative appear to be similar in HIV-infected and non–HIV-infected patients.[76] In sub-Saharan Africa, however, the likelihood of death, especially during the first 2 months of therapy, and of relapse following apparently successful treatment is considerably higher in HIV-infected than in non–HIV-infected patients.[77]

HIV-infected patients with tuberculosis are more likely to experience toxicity from antituberculous drugs than are non–HIV-infected persons. One series found that serious adverse events occurred in 40% of HIV-infected patients with tuberculosis compared to 26% of HIV-uninfected persons ($P = 0.008$).[78] HIV-infected patients are frequently receiving a number of additional medications, and it is often difficult to distinguish an adverse drug effect to antituberculous drugs from adverse effects from these other medications. As a result, the first-line antituberculous drugs (especially isoniazid and rifampin) should only be discontinued permanently if there is strong evidence that these medications were the cause.[76]

Moreover, HIV-infected patients who are receiving or who are initiating combination ART at the time that tuberculosis is diagnosed pose a special problem for the treatment of tuberculosis. HIV-infected patients with tuberculosis who begin therapy for both *M. tuberculosis* and HIV infection may develop immune reconstitution inflammatory syndrome (IRIS), a paradoxical reaction presenting as a temporary exacerbation of clinical and radiographic features, which appears to be more common among those starting ART within 6 weeks of initiating antituberculosis therapy and among those with disseminated tuberculosis.[79] However, ART use during tuberculosis treatment has been associated with improved survival and more rapid conversion of sputum smears and culture.[80] Once begun, it is crucial that ART be continued without interruption for maximum, durable results. The optimal timing for initiating combination ART in an HIV-infected patient who is being treated for tuberculosis remains to be defined, but it is generally recommended to wait at least 2 weeks or longer depending on the degree of immunocompromise.[14]

Furthermore, the simultaneous treatment of HIV and *M. tuberculosis* poses additional challenges in terms of drug interactions. Both HIV PIs and non-nucleoside reverse transcriptase inhibitors (NNRTIs) have significant interactions with the rifamycins, principally related to the induction or inhibition (or both) of the hepatic cytochrome P-450 (CYP) enzyme system.[76] Decreased drug levels are associated with the development of resistance by both HIV and *M. tuberculosis,* whereas increased drug levels are correlated with toxicity. Rifabutin is preferred to rifampin in persons receiving PIs as it is a less potent CYP 3A4 inducer than rifampin. Information on the interactions between specific antiretroviral drugs and different rifamycins is constantly being updated and can be found on such websites as the CDC website (http://www.cdc.gov/tb/). Clinicians caring for HIV-infected patients with tuberculosis should consult experts for aid in management prior to initiating tuberculosis or HIV therapy.

Prevention of Exposure. Because tuberculosis can be transmitted from person to person, HIV-infected persons should be advised to avoid settings in which they might be exposed to tuberculosis (i.e., jails, group homes, homeless shelters).[14] In hospitals and health care facilities, all persons with HIV infection and signs or symptoms compatible with tuberculosis should be placed in respiratory isolation until three sputum smears are negative or another disease is diagnosed. Prevention of transmission of drug-resistant tuberculosis is particularly important, both for those with and without HIV infection. In a modeling study, it was shown that mask use and a shift to outpatient therapy could prevent about one third of XDR-TB cases in a highly prevalent area; additional measures such as improved ventilation, rapid drug sensitivity testing, HIV treatment, and tuberculosis isolation facilities were also found to be effective preventive measures, but involuntary detention for XDR-TB treatment was thought to possibly lead to an increase in transmission.[81] Ultraviolet lights are also useful but costly.

Prevention of Disease. HIV-infected persons are at high risk for progressing from LTBI to active tuberculosis. Therefore, HIV-infected persons should be tested for LTBI by either a tuberculin skin test or interferon-γ (IFN-γ) release assay when HIV infection is first identified.[14,82] Repeat testing each year should be considered for persons who have a negative response to either test and who are at risk for exposure to *M. tuberculosis.* In addition, strong consideration should be given to retesting persons who initially had a negative test but subsequently experienced an increase in their $CD4^+$ lymphocyte count due to combination ART.

Several studies document that the risk of LTBI reactivation is virtually eliminated if an HIV-infected person who has been infected with a drug-susceptible organism takes adequate prophylaxis.[14,82] HIV-infected persons with a positive tuberculin skin reaction (5-mm rather than the conventional 10-mm induration), with a history of a positive tuberculin response who have not received prior treatment for LTBI or active tuberculosis, or with a positive IFN-γ release assay should receive isoniazid (daily or twice weekly) plus pyridoxine for 9 months.[14] An alternative treatment for LTBI is rifampin daily for 4 months; if the patient is also receiving ART with a PI or with delavirdine (an NNRTI), expert consultation should be sought. The two-drug regimen of rifampin plus pyrazinamide for 2 months is no longer recommended due to an increased incidence of severe hepatotoxicity and death.[83] At present, the routine use of preventive therapy in anergic or purified protein derivative (PPD)–negative, HIV-infected persons is not generally recommended.[14,82]

HIV-infected persons, including HIV-infected health care workers who have experienced a significant tuberculosis exposure (sufficient to cause PPD conversions in immunocompetent persons), should be offered appropriate chemoprophylaxis. HIV-seropositive persons who have converted their PPD test after exposure to MDR-TB

or anergic HIV-seropositive persons who have experienced a significant contact with MDR-TB should be offered prophylaxis based on the susceptibilities of the MDR-TB case to which they were exposed. Paramount in the management of such patients is the active involvement of an expert in the treatment of drug-resistant tuberculosis.

Mycobacterium avium Complex

As fully discussed in Chapter 35, the *Mycobacterium avium* complex consists of several related *Mycobacterium* species, including *M. avium* and *Mycobacterium intracellulare.* Until 1980, only 24 cases of disseminated MAC had been reported.[83] After the onset of the AIDS epidemic, the number of cases rose dramatically. With the increased use of combination ART, however, the incidence of disseminated MAC has declined since 1996.[1]

The pathogenesis of disseminated MAC is incompletely understood, but it is believed to result from primary acquisition of the microorganism, which is ubiquitous in the environment, rather than reactivation of latent infection.[84] These mycobacteria probably enter the body chiefly through the gastrointestinal tract and occasionally through the lungs.[85] Person-to-person transmission is believed to be unlikely. Nearly all cases of disseminated MAC are caused by *M. avium* serotypes, which suggests that there are important differences in exposure to or virulence of these particular strains.

Clinical Features. Although the lungs are an important potential portal of entry for MAC into the bloodstream, isolated MAC pulmonary disease is rare.[86] The most common clinical presentation of disseminated MAC disease is a febrile, wasting syndrome consisting of fever, night sweats, fatigue, anorexia, and weight loss; other manifestations include abdominal pain and chronic diarrhea, hepatosplenomegaly, lymphadenopathy, progressive anemia, and, rarely, extrabiliary obstructive jaundice.[87]

$CD4^+$ Lymphocyte Count. More than 95% of cases of disseminated MAC occur in HIV-infected patients whose $CD4^+$ lymphocyte count is 50 cells/μL or less.[87] Laboratory abnormalities include anemia, which is often severe, and an elevated alkaline phosphatase level. Other associated factors include a plasma HIV viral level greater than 100,000 copies/mL, history of previous opportunistic infection(s), and previous MAC colonization of the respiratory or gastrointestinal tract.[14]

Chest Radiograph. The chest radiograph is typically normal, even when the organism is cultured from respiratory tract secretions.[85] Focal pneumonia has been reported, but is extremely rare.[86] More frequently seen—but still uncommon—are endobronchial lesions without pneumonia.[88] These endobronchial lesions appear to be submucosal "pearls" that are teeming with AFB on biopsy. Many of the reported cases of isolated pulmonary MAC occurred in patients who received combination ART, thus raising the possibility that this particular manifestation is an example of immune reconstitution. Clinicians should be aware of this possibility when starting patients on ART as it may occur either in patients with diagnosed disease or in those with subclinical infection.

Diagnosis. In HIV-infected patients with MAC, the organism can be cultured from numerous sites, but the most productive sources are blood, bone marrow, liver, or lymph nodes.[81] The sensitivity of blood cultures for disseminated MAC has ranged from 86% to 98% of cases in which disseminated disease was confirmed by autopsy. The diagnosis of disseminated MAC can also be established by cultures from any normally sterile body site. Often, MAC is cultured from respiratory specimens such as sputum or BAL fluid, but this finding may not be indicative of either pulmonary or disseminated disease depending on the clinical situation.[85,89] If patients have abnormal chest radiographs with positive sputum cultures, the diagnostic criteria for nonimmunosuppressed hosts recommended by the American Thoracic Society and the Infectious Disease Society of America (ATS/IDSA), which are listed in Table 35-3, should be applied.[89] The pathologic findings of MAC infection are characteristic, but not definitive; AFB are remarkably abundant and are often packed within foamy macrophages or histiocytes; granulomas are usually absent or poorly formed.

Treatment. Although there are several efficacious treatment regimens, the optimal one for treating disseminated MAC is still debated.[14,89] As emphasized in Chapter 35, the key to any regimen is the inclusion of a macrolide: clarithromycin (500 mg twice daily) is preferred, but azithromycin (500 to 600 mg daily) can be substituted if needed. One of these should be combined with ethambutol (15 mg/kg/day) plus, as recommended by many experts, the addition of rifabutin (300 mg daily), although the principal benefit of rifabutin appears to be in decreasing the risk of macrolide drug resistance among those patients who responded to therapy.[90] As with tuberculosis, the use of rifabutin must be carefully scrutinized with concurrent administration of an NNRTI or a PI. Use of a third or fourth agent can be considered in patients with advanced immunosuppression, high mycobacterial burden, or the inability to use ART.[14] Currently, in the setting of combination ART with increases in the $CD4^+$ lymphocyte count to above 100 cells/μL for at least 6 months—and after a minimum of 12 months of a macrolide-based MAC treatment regimen—most patients have been able to discontinue therapy without relapse.[14]

Prevention. Although MAC can be found in environmental sources such as food and water, there are no specific recommendations regarding exposure avoidance as a prevention strategy. Similarly, although the presence of MAC in a stool or respiratory specimen is predictive of disseminated disease, routine screening of either is not recommended. The NIH, CDC, and HIVMA/IDSA guidelines recommend that MAC prophylaxis be administered to HIV-infected patients with a $CD4^+$ lymphocyte count less than 50 cells/μL and no clinical evidence of disseminated MAC; a number of different MAC prophylaxis regimens are available, including azithromycin (1200 mg weekly or 600 mg twice weekly), clarithromycin (500 mg twice daily), or rifabutin (300 mg daily).[14] If rifabutin is to be used, tuberculosis should first be ruled out. Primary MAC prophylaxis should be

discontinued in persons who have experienced a significant response to ART with an increase in their $CD4^+$ lymphocyte count to greater than 100 cells/μL for at least 3 months.[14]

Mycobacterium kansasii

As documented in Chapter 35, *M. kansasii* has a particular geographic distribution, predominantly in the southern and central United States.[89] Clusters of disease have also been reported in Europe, Asia, and Africa. Prior to the AIDS epidemic, infection and disease due to *M. kansasii* were uncommon; thereafter, a dramatic increase in the incidence associated with HIV infection was observed, even in nonendemic areas. Bloch and associates[91] found a cumulative incidence of *M. kansasii* infection of 2.4 cases per 100,000 HIV-infected adults in three counties in northern California, a rate that is almost five times higher than the national rate. Although *M. kansasii* pulmonary disease can be clinically indistinguishable from tuberculosis,[92] no person-to-person transmission has been documented, and infection is thought to occur from environmental sources.

$CD4^+$ Lymphocyte Count. Similar to tuberculosis in HIV-infected persons, *M. kansasii* pneumonia can occur at any $CD4^+$ lymphocyte count. Most HIV-infected patients with *M. kansasii,* however, have evidence of severe immunosuppression with $CD4^+$ lymphocyte counts below 100 cells/μL.[91-93] In a study from the combination ART era, Canueto-Quintero and colleagues[92] reported a mean $CD4^+$ lymphocyte count of 20 cells/μL among 25 HIV-infected patients with *M. kansasii.* Witzig and coworkers[93] found that 32 (65%) of 49 HIV-infected patients with *M. kansasii* had isolated pulmonary disease (mean $CD4^+$ lymphocyte count, 75 cells/μL), whereas the remainder had disseminated disease (mean $CD4^+$ lymphocyte count, 28 cells/μL).

Chest Radiograph. The chest radiographic findings of *M. kansasii* are varied. The most common radiographic findings resemble tuberculosis and include alveolar infiltrates, diffuse infiltrates, and cavities (see Fig. 35-5); masses, intrathoracic adenopathy, and pleural effusions have also been reported. In a series of 83 HIV-infected patients with *M. kansasii,* the most frequent findings were consolidation (66%) and nodules (42%); abnormalities were most often located in the mid-lung and lower lung zones (89%), and in 10%, the radiographs were normal.[94]

Diagnosis. The diagnosis of *M. kansasii* rests on its isolation and subsequent identification by culture. Pulmonary disease can be diagnosed by all of the techniques used for the diagnosis of tuberculosis. Unlike tuberculosis, however, in which identification of *M. tuberculosis* is diagnostic of disease, the identification of *M. kansasii* can occasionally represent colonization rather than disease.[95] As already mentioned, the ATS/IDSA have defined criteria for the diagnosis of nontuberculous mycobacterial pulmonary disease that includes *M. kansasii,* which can be found in Table 35-3 and in the paper by Griffith and colleagues.[89] In addition, the use of subtyping defined by PCR–restriction enzyme analysis of the *hsp65* gene may help distinguish pathogenic from nonpathogenic isolates.[96]

Treatment. The recommended regimen for treatment of *M. kansasii* pulmonary disease consists of isoniazid (300 mg daily), rifampin (600 mg daily), and ethambutol (15 mg/kg daily).[89] Patients should also receive pyridoxine (50 mg daily) during treatment. Patients who are taking PI or NNRTI therapy for HIV infection should receive rifabutin or clarithromycin in place of rifampin. Pyrazinamide is unacceptable as an alternative drug because all *M. kansasii* isolates are resistant. Patients should receive treatment for a minimum of 12 months after their cultures have converted to negative.

Prevention. There are no recommended prevention strategies for *M. kansasii.*

Other Mycobacteria

MAC and *M. kansasii* account for the great majority of nontuberculous mycobacterial infections complicating HIV disease. Other mycobacteria, however, have been occasionally identified.[87,97] Increased frequency of exposure or specific defects in host defenses might account for the predominance of MAC and to a lesser extent *M. kansasii* in AIDS patients, but the reasons for this striking disparity are unknown.

Fungi

Early in the AIDS epidemic, fungi were recognized as major sources of morbidity and mortality. Despite the overall decline in HIV-associated opportunistic infections in the United States, fungi remain frequent causes of disease. Several fungi can cause pulmonary disease in HIV-infected persons. *Pneumocystis jirovecii,* formerly *P. carinii,* previously classified as a protozoan but currently considered a fungus, remains the most common AIDS-defining opportunistic infection in the United States and Western Europe and is a common cause of HIV-associated pneumonia. *Cryptococcus neoformans,* the most common cause of meningitis in HIV-infected persons, often presents with an associated pneumonia. The endemic fungi *Histoplasma capsulatum, Coccidioides immitis, Penicillium marneffei,* and, to a lesser extent, *Blastomyces dermatitidis* are among the chief causes of HIV-associated disease seen in their particular geographic regions, and all have important pulmonary presentations. Finally, invasive aspergillosis is often a devastating pulmonary disease seen in HIV-infected persons with severe immunosuppression. Further information about fungal pulmonary diseases is provided in Chapter 36.

Pneumocystis jirovecii

PCP (shorthand for *P*neumocystis *p*neumonia) remains the most common AIDS-defining opportunistic infection in the United States, even though its overall incidence has declined substantially.[1] Early in the AIDS epidemic, PCP accounted for nearly two thirds of AIDS-defining

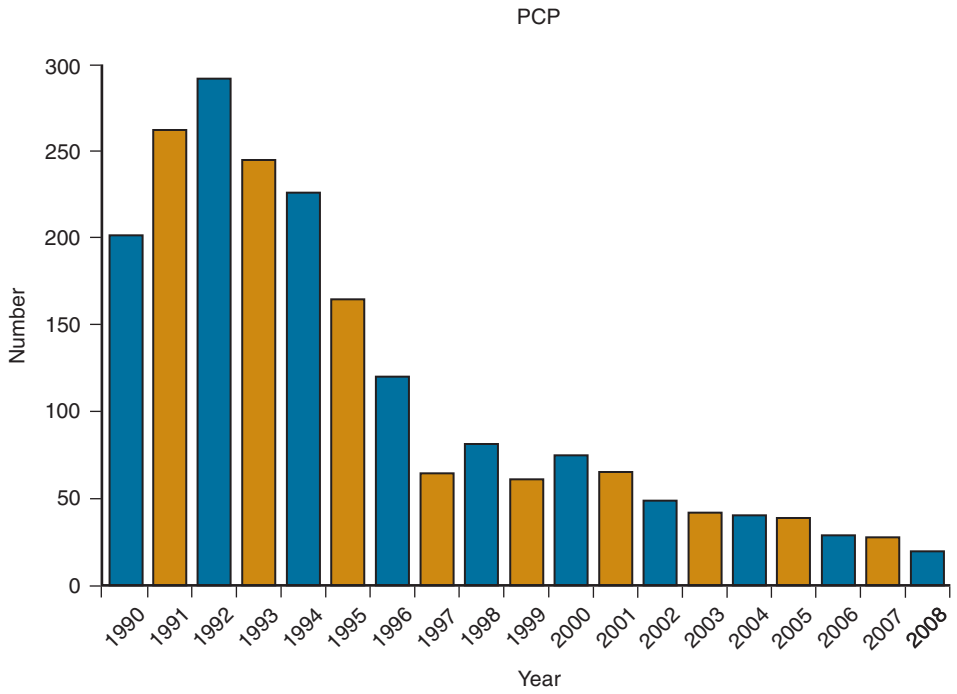

FIGURE 80-4 ■ Annual cases of *Pneumocystis* pneumonia diagnosed at San Francisco General Hospital (1990–2008).

diagnoses, and an additional 15% to 20% of patients developed PCP at some time during their HIV disease. Two factors—the use of combination ART and *Pneumocystis* prophylaxis—have dramatically reduced the overall number of cases (Fig. 80-4). Nevertheless, PCP continues to occur, chiefly among persons who are unaware of their HIV infection, those who fail to seek medical care, and those who fail to adhere to or respond to ART or *Pneumocystis* prophylaxis.[98,99]

History and Epidemiology. First identified early in the 20th century by Chagas, *Pneumocystis* was initially recognized as a human pathogen in the 1940s and 1950s. Despite over a half-century of experience, several gaps in our understanding of this omnipresent organism remain.[99,100] In fact, it was only in 1988 that initial homology studies indicated that *Pneumocystis* was a fungus rather than a protozoan, as previously classified.[101,102] One major obstacle that has impeded further advances has been the inability to reliably culture human *Pneumocystis* in vitro, forcing researchers to rely on animal models for growth and testing. Although mammals are the only known hosts of *Pneumocystis* and a number of mammals are susceptible to infection, *Pneumocystis* has been demonstrated to be species specific.[103] Although *Pneumocystis* can be easily transmitted between mammals of the same species, studies that have attempted to transmit *Pneumocystis* from one species to another have been unsuccessful.[103] In recognition of the host-species specificity of *Pneumocystis,* the *Pneumocystis* that causes *Pneumocystis* pneumonia in humans is now referred to as *P. jirovecii,* in honor of Otto Jirovec, the parasitologist who is credited with first identifying *Pneumocystis* as the cause of pulmonary disease in humans.[104,105]

The precise ecologic niche for *P. jirovecii* and its mode of transmission are unknown.[106,107] The inability to maintain human *Pneumocystis* in culture suggests that *P. jirovecii* may be unable to grow outside of its human host. Given its species specificity, it is doubtful that other mammals are the reservoir for *P. jirovecii.* This host-species specificity also implies coevolution of humans and *P. jirovecii* that, in turn, implies long-term carriage in its human host. It has been shown that infection with *P. jirovecii* is almost ubiquitous. Up to 85% to 100% of the U.S. population have specific antibodies directed against *P. jirovecii* by the age of 3 years.[108,109] Clearly, most of these individuals never develop PCP. In the setting of severe immunosuppression, however—such as typically occurs in untreated HIV infection—PCP can affect significant proportions of people. These studies and others suggest that reactivation of latent infection is a cause of *P. jirovecii* disease among immunocompromised hosts. In addition, outbreaks of newly acquired infection after de novo exposure to persons with PCP have been documented among immunocompromised patients in pediatric wards, cancer clinics or wards, transplantation units, and other confined spaces, which suggests possible person-to-person transmission of *P. jirovecii* and the rapid development of disease. Results of studies that have used molecular tools to detect *Pneumocystis* are consistent with transmission of *P. jirovecii* from patients with PCP to their household and hospital contacts,[110,111] probably via inhalation of a *Pneumocystis*-containing aerosol.

Hughes and colleagues[112,113] demonstrated that immunocompromised axenic rats maintained in germ-free isolators did not develop PCP despite 3 months of immunosuppression with dexamethasone. In a selective

manner, these rats were then exposed to potential sources of *P. carinii,* including air, food, and water. The rats that were exposed to filtered (sterile) air and to regular (unsterile) food and water did not develop PCP. However, rats exposed to room (unsterile) air but maintained on sterile food and water did develop PCP, implying that *P. carinii* is acquired as an airborne disease from de novo infection in the setting of immunocompromise. The duration of exposure necessary for transmission may be short. Soulez and associates[114] housed *Pneumocystis*-free severe combined immunodeficiency (SCID) mice near corticosteroid-treated non-SCID mice and found that a 1-day exposure was sufficient for transmission of *Pneumocystis* to the SCID mice. Transmission of *P. carinii* from PCP-infected SCID mice to other SCID mice via immunocompetent BALB/c mice that were colonized with *P. carinii* has been demonstrated.[115] Taken together, these studies offer a compelling extrapolation that humans are the reservoir for *P. jirovecii,* that person-to-person transmission occurs, and that PCP can result from a recent exposure both to humans with PCP and to humans who are colonized with *P. jirovecii.*[116] If correct, these studies have profound implications as to our current management of persons with PCP.

Risk Factors. Setting aside the question of whether person-to-person transmission of *P. jirovecii* is an important problem, the risk factors for the development of PCP among HIV-infected persons are clear. These risk factors for adults include a $CD4^+$ lymphocyte count less than 200 cells/μL, a history of PCP, and oropharyngeal candidiasis.[117,118]

$CD4^+$ Lymphocyte Count. Approximately 95% of adolescent and adult cases of PCP occur in HIV-infected patients whose $CD4^+$ lymphocyte count is below 200 cells/μL.[118] The Multicenter AIDS Cohort Study found a markedly increased risk for PCP among HIV-infected subjects with a $CD4^+$ lymphocyte count of 200 cells/μL or less at study entry.[117] These subjects had a nearly fivefold greater risk of developing PCP than did subjects who had a $CD4^+$ lymphocyte count higher than 200 cells/μL at study entry. This study also demonstrated that the presence of fever for 2 weeks or more and the development of thrush were independent predictors for PCP. Stansell and colleagues[118] found that the incidence of PCP increased as the $CD4^+$ lymphocyte count declined. Subjects with a $CD4^+$ lymphocyte count between 101 and 200 cells/μL had an incidence of 5.95 cases of PCP per 100 person-years, whereas those with a $CD4^+$ lymphocyte count of 100 cells/μL or less had 11.13 cases per 100 person-years.

Clinical Features. HIV-infected adults, unlike other immunocompromised persons, usually have a prolonged prodromal illness associated with PCP. Kovacs and coworkers[119] found nearly 1 month of symptoms before presentation in most HIV-infected patients with PCP. In this study, the median duration of symptoms in 40 HIV-infected patients was 28 days, which was significantly longer than the median duration of 5 days seen in the 37 patients with other immunosuppressive diseases ($p < 0.0002$). Kales and colleagues[120] reported a median duration of symptoms of 3 weeks in 143 HIV-infected patients with PCP and found that 72 patients (50%) had a duration of symptoms of 2 weeks or longer. This duration of symptoms can often be used to distinguish PCP from pyogenic pneumonia, which typically presents with 3 to 5 days of symptoms.

Classically, PCP presents with fever, a nonproductive cough, and dyspnea on exertion. In one series of 145 HIV-infected patients with PCP, fever was noted in 86%, cough in 91%, and dyspnea in 95% of patients.[120] High fevers, rigors, purulent sputum, and pleuritic chest pain are uncommon and can be used to distinguish PCP from pyogenic pneumonia. In a multivariate analysis, Selwyn and associates[121] found that the presence of purulent sputum was an independent predictor of bacterial pneumonia rather than of PCP or tuberculosis.

Physical examination of the chest may be normal. In the series reported by Kales and colleagues,[120] 78 patients (54%) with PCP had a normal lung examination. When abnormal, the most frequent findings on lung auscultation are inspiratory crackles, which have been reported to be associated with a greater disease severity and an increased mortality.[120]

Numerous studies have shown that the serum lactate dehydrogenase (LDH) level is increased in patients with PCP; however, an elevated serum LDH level does not establish the diagnosis of PCP, nor does a normal serum LDH value rule out the diagnosis. *S*-adenosylmethionine concentration,[122] β-D-glucan,[123] and KL-6[123] have also been reported to be potential diagnostic tools for PCP.

Chest Radiograph. Classically, PCP presents with bilateral, symmetrical reticular or granular opacities as illustrated in Figure 80-5[124]; these opacities typically begin in the perihilar region and extend outward as the disease severity increases. Occasionally, the opacities will be unilateral or asymmetrical. Thin-walled cysts, or pneumatoceles, are seen in 10% to 20% of cases (see Fig. 80-5).[125] Pneumatoceles may be present at the time of diagnosis or may develop during PCP therapy. Pneumatoceles may be single or multiple in number, and small or large in size, and predispose patients to pneumothorax, which is another radiographic presentation of PCP. Usually pneumatoceles resolve, but occasionally they persist despite successful therapy.

Virtually every possible radiographic finding, including focal, lobar, or segmental consolidation, nodules with or without cavitation, and a miliary pattern, can be seen occasionally.[125] Apical or upper lung zone disease that mimics tuberculosis (shown in Fig. 80-6) is typically associated with aerosolized pentamidine prophylaxis, although this presentation can be seen as well in patients taking oral prophylaxis or no preventive therapy. Intrathoracic adenopathy and pleural effusions are rarely due to PCP. These radiographic findings should prompt a search for an alternate or at least a coexisting process such as bacterial pneumonia, tuberculosis, fungal pneumonia, or pulmonary Kaposi sarcoma. PCP may also present with a normal chest radiograph. Published studies report the incidence of a normal radiograph to range from 0% to 39%.[124–126]

Diagnosis. The diagnosis of PCP rests on the microscopic visualization of the characteristic *P. jirovecii* cysts

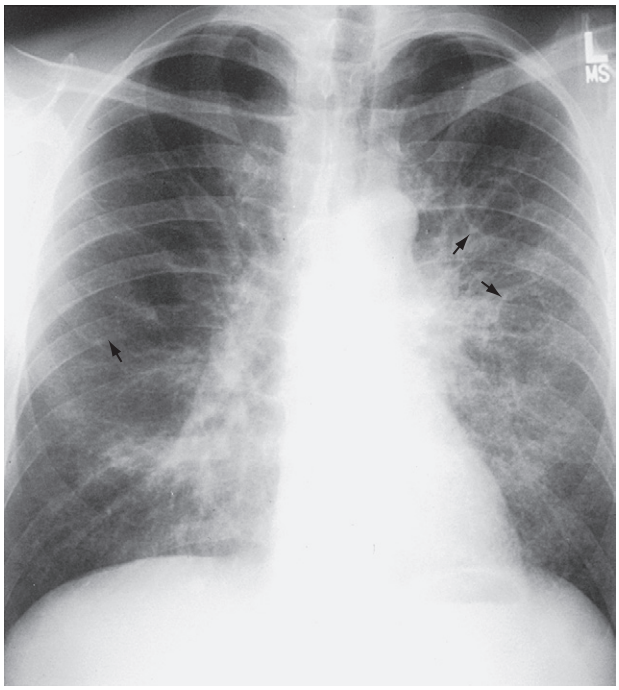

FIGURE 80-5 ■ Posteroanterior chest radiograph of an HIV-seropositive patient with *Pneumocystis* pneumonia showing bilateral, predominantly perihilar, granular opacities and three pneumatoceles (*arrows*). Pneumatoceles may be single or multiple in number, and small or large in size, and may predispose patients to pneumothorax. (Courtesy of L. Huang.)

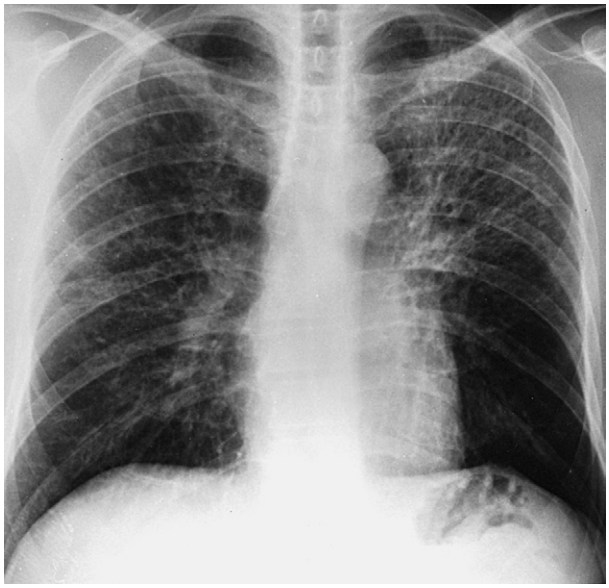

FIGURE 80-6 ■ Posteroanterior chest radiograph of an HIV-seropositive patient who had been receiving aerosolized pentamidine showing reticular infiltration, predominantly of the upper lung zones, secondary to relapsed *Pneumocystis* pneumonia (PCP). This radiographic presentation, however, may also be seen in patients on no PCP prophylaxis. (From Murray JF, Mills J: Pulmonary complications of HIV infection. Am Rev Respir Dis 141:1356–1372, 1582–1598, 1990.)

or trophic forms (or both) on stained respiratory specimens. *Pneumocystis jirovecii* can be detected in expectorated or induced sputum; in pulmonary secretions obtained by nasotracheal suction, BAL, or percutaneous aspiration of the lung parenchyma; and in pulmonary tissue obtained by transbronchial, thoracoscopic, or open-lung biopsy. Of these, sputum induction and BAL are the most widely used. The standard method for detection of *P. jirovecii* has been with cyst wall stains such as methenamine silver and toluidine blue-O or with Giemsa and Diff-Quik, which stain both the intracystic sporozoites and the trophic forms; monoclonal antibodies to *P. jirovecii,* which react with both cysts and trophic forms, are also used.[127] PCR-based techniques have also been employed and have been reported to be more sensitive but also less specific than either of the other methods.[127,128] However, the increased sensitivity of PCR-based assays has allowed for their pairing with noninvasive, rapid (60-second) procedures such as oropharyngeal washing (i.e., gargling) for the diagnosis of PCP. Several studies have reported sensitivities and specificities for PCP of a PCR-based assay using oropharyngeal washing that may permit its clinical use.[129]

A number of studies have examined the impact of PCP prophylaxis on the sensitivity of induced sputum and BAL examination for detecting the organisms.[130–133] Some authors reported a lower sensitivity of diagnostic studies for PCP among patients who were receiving aerosolized pentamidine compared with those having no prophylaxis, whereas others found no difference between the two groups. In patients undergoing bronchoscopy, the yield for *P. jirovecii* may be improved by performing upper lobe lavage or multiple-lobe lavage with or without a more sensitive staining technique (e.g., monoclonal antibodies).[132,133] Our practice is to perform BAL in the most affected lobe visualized on chest radiograph. For patients with diffuse radiographic disease, we usually perform a single lavage in the right middle lobe. For patients with, for example, an upper lung zone predominance on radiograph, however, we often lavage both an upper lobe and the right middle lobe. Despite the widespread use of TMP-SMX and dapsone for PCP prophylaxis, no studies have evaluated whether the yield of diagnostic studies is changed in persons receiving one of these medications. Our clinical experience suggests that, although the severity of chest radiograph abnormalities may be milder in patients receiving prophylaxis than in those receiving no prophylaxis, the high yields from both sputum induction and BAL remain the same.

Treatment. The treatment of choice for patients with mild, moderate, and severe PCP remains TMP-SMX, administered for 21 days. TMP-SMX possesses many benefits, including availability in both an intravenous and an oral form, availability as a single-drug combination, excellent oral bioavailability, and activity against many community-acquired bacteria that may cause concomitant pyogenic infection. The usual dose of TMP is 15 mg/kg/day (range, 15 to 20 mg/kg/day) and that of SMX is 75 mg/kg/day (range, 75 to 100 mg/kg/day), divided into three or four daily doses as described in Table 80-3. Dosing may be intravenous (recommended for patients

TABLE 80-3. Treatment and Prophylaxis Regimens for *Pneumocystis* Pneumonia*

Treatment Regimen	Dose(s), Frequency	Toxicities
Mild PCP† (Arterial P_{O_2} > 70 mm Hg **AND** alveolar-arterial O_2 difference < 35 mm Hg)		
Trimethoprim (TMP)-Sulfamethoxazole (SMX)	15–20 mg/kg (TMP component) daily (q6–8h)	Fever, dermatologic, gastrointestinal, hematologic
Trimethoprim plus	15–20 mg/kg daily (q6–8h)	Dermatologic, gastrointestinal, hematologic
Dapsone	100 mg once daily	
Clindamycin plus	1800 mg daily (q6–8h)	Dermatologic, gastrointestinal, hematologic
Primaquine	30 mg (base) once daily	
Atovaquone	750 mg thrice daily	Dermatologic, gastrointestinal
Moderate-Severe PCP‡ (Arterial $P_{O_2} \leq 70$ mm Hg **OR** alveolar-arterial O_2 difference ≥ 35 mm Hg)		
Trimethoprim (TMP)-Sulfamethoxazole (SMX)	15–20 mg/kg (TMP component) daily (q6–8h)	Fever, dermatologic, gastrointestinal, hematologic
Pentamidine	3–4 mg/kg once daily	Renal, pancreatic
Clindamycin plus	1800–2400 mg (q6–8h)	Dermatologic, gastrointestinal, hematologic
Primaquine	30 mg (base) once daily	

*Recommended duration of therapy = 21 days.
†Oral route is preferred for patients with mild PCP who are treated as outpatients.
‡Intravenous route is preferred (at least until clinical improvement) for patients with moderate-severe PCP. Adjunctive corticosteroids (prednisone 40 mg, PO, twice daily for 5 days, then 40 mg, PO, once daily for 5 days, then 20 mg, PO, once daily for 11 days or potency-equivalent solumedrol, IV) should also be administered.

with moderate or severe PCP) or oral. Unfortunately, adverse effects from TMP-SMX are frequent and include rash, fever, gastrointestinal complaints (nausea, vomiting), elevated liver transaminases, hyperkalemia, and bone marrow suppression, especially anemia and neutropenia. Often these effects develop during the second week of therapy. In a significant proportion of HIV-infected patients, the side effects are ultimately treatment limiting. Rare adverse reactions include Stevens-Johnson syndrome, toxic epidermal necrolysis, and a clinical syndrome resembling septic shock with hypotension, fever, pulmonary infiltrates, and renal and hepatic dysfunction. Studies are conflicting regarding the presence of potential TMP-SMX drug resistance.[134,135]

For patients with an allergy to or intolerance of TMP-SMX, alternative treatment regimens (see Table 80-3) include intravenous pentamidine, clindamycin plus primaquine, trimethoprim plus dapsone, trimetrexate (with or without dapsone), and atovaquone.[14] Similar to tuberculosis, HIV-infected patients with PCP who begin dual therapy for *Pneumocystis* and HIV infection may develop paradoxical reactions, a temporary exacerbation of clinical and radiographic features.[136] The diagnosis of paradoxical reactions is one of exclusion. Patients with paradoxical reactions only rarely require change or discontinuation of anti-*Pneumocystis* or antiretroviral therapies, and symptomatic therapy is recommended.

Corticosteroid Therapy. In 1990, the National Institutes of Health–University of California Expert Panel for Corticosteroids as Adjunctive Therapy for Pneumocystis Pneumonia[137] concluded that adjunctive corticosteroid therapy "can clearly reduce the likelihood of death, respiratory failure, or deterioration of oxygenation in patients with moderate-to-severe pneumocystis pneumonia." The panel recommended that adjunctive corticosteroids be given to adults or adolescents with documented or suspected PCP if they have an arterial P_{O_2} level less than 70 mm Hg or an alveolar-arterial P_{O_2} difference greater than 35 mm Hg. Adjunctive corticosteroids, either oral prednisone or intravenous methylprednisolone, should be started when specific anti-*Pneumocystis* treatment is begun.

Early in the AIDS epidemic, it was realized that acute respiratory failure secondary to PCP, if severe enough to warrant mechanical ventilation, had a mortality rate of 86% or greater.[137] Subsequent reports from individual hospitals confirmed this gloomy prognosis; 39 of 45 patients who were intubated and ventilated for PCP at San Francisco General Hospital from 1981 to 1985 died, a mortality rate of 87%.[138] Although the mortality associated with acute respiratory failure secondary to PCP remains significant (approximately 30% to 50%), encouraging progress has been made.[139,140]

Prevention. The natural reservoir for human *Pneumocystis* remains unknown. Both an environmental and a human reservoir have been suggested.[106,107] Whether PCP results solely from reactivation of latent infection or also from a recent infection is debated; as mentioned, reports of cluster outbreaks of PCP among different immunocompromised populations support the theory that PCP can result from person-to-person transmission. Accordingly, some authorities have argued that HIV-infected and other immunocompromised persons who are at risk for PCP should avoid close contact with any individuals who have PCP. Nevertheless, the current NIH, CDC, and HIVMA/IDSA guidelines for preventing opportunistic infections state that "although certain authorities might recommend that persons who are at risk for PCP not share a hospital room with a patient who has PCP based on animal studies and anecdotal human experience, data are insufficient to support this recommendation as standard practice."[14]

TABLE 80-4. Prevention of *Pneumocystis* Pneumonia

Prevention Regimens	Alternative Dosing	Comments
Trimethoprim-sulfamethoxazole 1 double-strength (DS) tablet daily	1 single-strength tablet daily 1 DS tablet thrice weekly	Also effective prophylaxis against *Toxoplasma gondii* and many bacterial pathogens
Dapsone 100 mg daily		Combine with pyrimethamine and leucovorin in persons who are *T. gondii* immunoglobulin G antibody positive. Consider combining with pyrimethamine and leucovorin when used for secondary prophylaxis
Atovaquone suspension 1500 mg daily, divided into 1–2 doses		Improved bioavailability compared to tablets
Aerosolized pentamidine 300 mg monthly via RespirGard II nebulizer		May be associated with increased risk of extrapulmonary disease

HIV-infected adults or adolescents (including those on ART) who have a $CD4^+$ lymphocyte count less than 200 cells/μL or a history of oropharyngeal candidiasis should receive primary *Pneumocystis* prophylaxis, and persons with prior PCP should receive secondary prophylaxis using one of the regimens shown in Table 80-4.[14] Once started, HIV-infected adults and adolescents should remain on prophylaxis for life, unless their $CD4^+$ lymphocyte counts increase from less than 200 cells/μL to greater than 200 cells/μL for at least 3 months as a result of ART; several studies have demonstrated that primary and secondary PCP prophylaxis can be safely discontinued in the vast majority of these persons.[14] In rare cases, however, PCP has recurred after the discontinuation of secondary PCP prophylaxis, despite an apparent ART-associated immune reconstitution.[141]

TMP-SMX, dapsone, atovaquone suspension, and aerosolized pentamidine are the standard options for PCP prophylaxis.[14] TMP-SMX is the first-line prophylaxis choice, both primary and secondary, against *Pneumocystis.* For those patients intolerant of TMP-SMX, dapsone and atovaquone are both oral drugs that can be used. Many authorities would add pyrimethamine to these drugs for patients with a history of PCP or a $CD4^+$ lymphocyte count less than 100 cells/μL, or both. For patients who are *T. gondii* immunoglobulin G antibody positive, pyrimethamine must be added. Aerosolized pentamidine remains an effective and well-tolerated prophylaxis option. However, caution must be exercised when using this drug for secondary prophylaxis or for a patient with a $CD4^+$ lymphocyte count below 100 cells/μL.

Cryptococcus neoformans

Cryptococcosis is a disease caused by the budding encapsulated yeast *C. neoformans.* It is the only encapsulated fungus that infects humans, both healthy (see Chapter 36) and immunocompromised, and India ink or mucicarmine staining can identify its polysaccharide capsule.[142] Serotyping based on antigenic differences in the polysaccharide capsule demonstrates that serotypes A and D are the most common cause of infection and disease. *Cryptococcus neoformans* infection occurs after inhalation of a yeast-containing aerosol. The yeast is global in distribution and is most commonly isolated from bird excrement, decaying fruit, and soil.

The incidence of cryptococcosis in HIV-infected persons has dramatically declined since the introduction of combination ART. In one population-based surveillance study, the annual incidence of cryptococcosis decreased from 66 per 1000 persons with AIDS in 1992 to 7 per 1000 persons in 2000 in the Atlanta area, and from 24 per 1000 persons with AIDS in 1993 to 2 per 1000 persons in 2000 in the Houston area.[143] Using national surveillance data, a study from France found a 46% decrease in the incidence of cryptococcosis in HIV-infected patients from the pre–combination ART period (1985–1996) to the combination ART period (1997–2001).[144]

Clinical Features. Although the portal of entry is the lung, cryptococcal pulmonary infection is often asymptomatic or minimally symptomatic, and the most commonly encountered manifestation of cryptococcal disease is meningitis.[144–146] In a large series of 106 HIV-infected patients with cryptococcal disease, 89 patients (84%) had meningitis, and only 4 patients (4%) had isolated pneumonia.[145] In a population-based surveillance study that included 1322 HIV-infected patients with cryptococcal disease, only 45 patients (3%) had pulmonary disease in the absence of both fungemia and meningitis.[143] However, autopsy studies suggest that pulmonary disease is underdiagnosed, particularly in settings where diagnostic facilities are limited.[147]

Most cases of pulmonary involvement are discovered serendipitously on routine chest radiograph rather than as a result of specific symptoms or signs. When present, the most frequent respiratory complaints are cough and dyspnea.[145,148] Pleuritic chest pain and productive cough have also been reported,[149] perhaps distinguishing pulmonary cryptococcosis from PCP. Although more rare, cases of acute respiratory failure can occur.[147]

$CD4^+$ Lymphocyte Count. Most cases of cryptococcosis occur in patients with a $CD4^+$ lymphocyte count less than 200 cells/μL, and usually below 100 cells/μL. A study of 1644 patients reported a median $CD4^+$ count of 24 cells/μL with a range of 0 to 480 cells/μL.[144]

Chest Radiograph. Cryptococcal pneumonia most commonly presents with diffuse bilateral interstitial infiltrates.[149,150] In one study, Meyohas and associates[151]

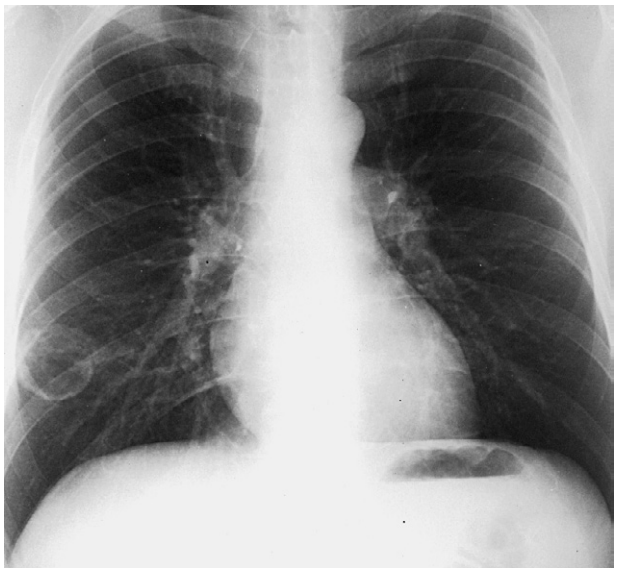

FIGURE 80-7 ■ Posteroanterior chest radiograph of an HIV-seropositive patient showing a solitary cavitary lesion in the right lower lung field. Culture of bronchoalveolar lavage fluid revealed *Cryptococcus neoformans*. In HIV-infected patients, cryptococcal disease can present with a wide range of chest radiographic findings, including a normal chest radiograph. (From Stansell JD: Fungal disease in HIV-infected persons: Cryptococcosis, histoplasmosis, and coccidioidomycosis. J Thorac Imaging 6:28–35, 1991.)

reported interstitial infiltrates in 60 of 92 radiographs (65%); in addition, focal consolidation (13%), nodular opacities (11%), cavitation (11%) (Fig. 80-7), pleural effusion (14%), and hilar adenopathy (27%) were noted. More rarely, radiographic findings include a miliary pattern,[152] solitary pulmonary nodules,[153] pulmonary masses,[154] isolated pleural effusion,[155] and pneumothorax[156] due to *C. neoformans*. Finally, cryptococcal pneumonia may also present with a normal chest radiograph; in the review by Meyohas and associates,[151] for example, normal radiographs were seen in 11% of the 92 cases.

Diagnosis. The diagnosis of cryptococcal infection begins with the cryptococcal antigen (CRAG) test. The test can be performed on serum, cerebrospinal fluid, urine, BAL fluid,[157] or pleural fluid. The serum CRAG test is sensitive and specific for cryptococcemia. A negative serum CRAG test virtually rules out the diagnosis of cryptococcal meningitis but can be seen in cases of isolated pulmonary cryptococcosis. A positive serum CRAG test should prompt an evaluation for disseminated disease, especially meningitis, but it can be seen in the presence of rheumatoid factor or infection with *Trichosporon beigelii*. Blood fungal cultures are specific and should be obtained as part of the diagnostic evaluation. New cutaneous lesions may be signs of dissemination, and their sudden appearance should prompt consideration for biopsy.

The diagnosis of pulmonary cryptococcosis is usually established by culture of sputum or BAL fluid and occasionally of pleural fluid. Biopsy specimens from TBBX and pleural biopsy can also be diagnostic. Batungwanayo and coworkers[149] found that BAL diagnosed 27 of 33 cases (sensitivity 82%) of cryptococcal pneumonia compared with TBBX, which diagnosed 10 of 21 cases (sensitivity 48%). In some cases, cultures are negative, but a BAL or pleural fluid CRAG test can establish the diagnosis.[151] Alternatively, because the treatment is identical, the diagnosis of pneumonia may be inferred in the presence of disseminated cryptococcal disease (e.g., meningitis) and a compatible radiographic presentation. However, caution must be exercised with this approach, because other opportunistic infections such as PCP may be present concurrently and can demonstrate identical radiographic findings.

Treatment. In contrast to cryptococcal meningitis, there are no randomized controlled trials for HIV-infected patients presenting with isolated cryptococcal pneumonia or with concurrent cryptococcal pneumonia and meningitis.[158] Some authorities would treat isolated cryptococcal pneumonia that is mild in severity with fluconazole alone (400 mg daily).[147] However, patients with clinically significant cryptococcal pneumonia should be considered at high risk for early deterioration and should be offered amphotericin B (0.7 mg/kg/day), with or without 5-fluorocytosine.[147] Treatment should be continued until the patient is clinically improved, at which point the patient can be switched to fluconazole (400 mg daily) to complete a 10- to 12-week course. The patient should then be maintained on fluconazole (200 mg daily) for life unless he or she experiences an increase in $CD4^+$ cell counts due to ART. Maintenance therapy can be discontinued in the vast majority of patients who have a $CD4^+$ lymphocyte count greater than 100 to 200 cells/μL for at least 6 months due to ART, who complete their initial 10- to 12-week course for cryptococcosis, and who remain asymptomatic.[14] Similar to tuberculosis and PCP, HIV-infected patients with cryptococcosis who begin dual therapy for *C. neoformans* and HIV infection may develop IRIS.[159] Patients who had cryptococcal meningitis may present with aseptic meningitis and have elevated intracranial pressure. In addition, patients with cryptococcal pneumonia and nodules on chest radiograph may develop cavitation of their nodules or new intrathoracic adenopathy.[159]

Primary Prevention. There are no specific recommendations regarding exposure avoidance or chemoprophylaxis for *C. neoformans*.[14] In addition, routine screening of asymptomatic persons with serum CRAG testing is not recommended.

Histoplasma capsulatum

Histoplasmosis is a disease caused by the dimorphic, soil-dwelling fungus *H. capsulatum*. The fungus is found on all continents except Antarctica, but it is most endemic to North America and the Caribbean basin.[142,160] The heaviest concentration is found in the Mississippi, Ohio, and St. Lawrence River valleys. In these areas, the fungus exists in microfoci related to the enrichment of the soil with bird or bat excrement, which helps to promote sporulation. In the soil, the fungus exists in a mycelial form with characteristic tuberculate

macroconidia. The hyphae also have microconidia that are easily aerosolized when disturbed. Inhalation of these microconidia leads to primary pulmonary infection that is usually clinically silent.

Once deposited in the alveoli, *H. capsulatum* transforms into its yeast (or parasitic) form, and an area of pneumonitis develops. During this period before cell-mediated immunity develops, the organism spreads to regional lymph nodes and to reticuloendothelial organs. Two to 3 weeks after exposure, about 40% of immunocompetent individuals develop a flulike syndrome with fever, chills, myalgias, a nonproductive cough, and chest pain. As emphasized in Chapter 36, 99% of these cases spontaneously resolve with the development of specific cell-mediated immunity. In contrast, progressive disseminated histoplasmosis develops in HIV-infected and other persons lacking cell-mediated immunity. Although most cases of HIV-associated histoplasmosis appear to result from de novo exposure, reactivation disease does occur. These cases account for the histoplasmosis seen in nonendemic areas such as San Francisco or New York.[161]

Clinical Features. Although the portal of entry is the lung, disseminated histoplasmosis most often presents as a febrile wasting illness in HIV-infected persons. In a large series of 72 HIV-infected patients with disseminated histoplasmosis, 69 patients (96%) presented with fever and weight loss; in approximately 10% of cases reviewed, the presentation is dramatic with a sepsis-like syndrome associated with hypotension, respiratory failure, liver and renal failure, and coagulopathy.[162] Prognosis in these patients is poor. Respiratory complaints at presentation, chiefly cough and dyspnea, are found in patients who are likely to have abnormal chest radiographs.[162,163]

$CD4^+$ Lymphocyte Count. Most cases of disseminated histoplasmosis occur in patients with a $CD4^+$ lymphocyte count less than 100 cells/μL and often below 50 cells/μL. Frequent laboratory findings include anemia, leukopenia, thrombocytopenia, and liver function test elevations. Serum LDH and serum ferritin elevations, often pronounced, have also been reported.[160]

Chest Radiograph. Disseminated histoplasmosis will present with a normal chest radiograph in a significant proportion of cases, ranging from approximately 35% to 55%.[150,162,164] In patients with abnormal findings, the most frequent are diffuse, coarse reticular or reticulonodular infiltrates as shown in Figure 80-8. Occasionally, alveolar infiltrates may occur[150]; focal opacities are less common but are seen in 7% to 11% of cases.[163] Hilar and mediastinal adenopathy and calcified granulomata are each found in less than 5% of patients, attesting to the low incidence of reactivation disease.[162]

Diagnosis. The diagnosis of histoplasmosis begins with the histoplasma polysaccharide antigen (HPA) test. The test can be performed on urine, serum, cerebrospinal fluid, or BAL fluid. The sensitivity of the HPA test is greater in urine (95%) than in serum (85%).[14] Although the urine HPA is sensitive in disseminated histoplasmosis, it is often negative in isolated pulmonary disease. With successful therapy HPA values fall, and during relapses HPA values rise (usually by ≥2 HPA units), which are useful features for assessing response to therapy and for evaluating possible relapse.[165] A false-positive HPA test can occur in patients with other disseminated fungal diseases (blastomycosis, paracoccidioidomycosis, and penicilliosis), but it has not been described in patients with coccidioidomycosis, cryptococcosis, aspergillosis, or candidiasis. A persistently positive HPA test indicates continued disease and warrants continued therapy. Definitive diagnosis requires isolation and identification of the fungus by culture. Blood fungal cultures are specific and should be obtained as part of the diagnostic evaluation. Wheat and colleagues[162] reported that fungal blood cultures were positive in 65 of their 72 cases (90%). Occasionally, the peripheral blood smear reveals intracellular yeast. Other potential diagnostic sources include bone marrow, lymph node, and skin. The diagnosis of pulmonary histoplasmosis can be established by direct examination and culture of sputum, BAL fluid, or TBBX.

FIGURE 80-8 ■ Posteroanterior chest radiographic close-up of the left mid-lung of an HIV-seropositive patient showing a medium to coarse reticulonodular pattern characteristic of disseminated fungal disease. (From Stansell JD: Fungal disease in HIV-infected persons: Cryptococcosis, histoplasmosis, and coccidioidomycosis. J Thorac Imaging 6:28–35, 1991.)

Treatment. Either amphotericin B or a lipid formulation of amphotericin B is the treatment of choice for HIV-infected patients with moderate to severe disseminated histoplasmosis, whereas itraconazole is an alternative for patients with mild disease.[14,166] Treatment with amphotericin B should be continued until the patient is clinically improved, at which point the patient can be

switched to twice-daily itraconazole to complete at least a 12-month course.

Primary Prevention. In those areas endemic for *H. capsulatum,* HIV-infected patients, especially if their $CD4^+$ lymphocyte counts are less than 150 cells/μL, should avoid activities that will potentially increase their exposure, including cleaning chicken coops; disturbing native soil beneath bird-roosting sites; cleaning, remodeling, or demolishing old buildings; and exploring caves.[14] Routine serologic testing, even in histoplasmosis-endemic areas, is not recommended. Current NIH, CDC, and HIVMA/IDSA guidelines do not recommend itraconazole for primary *H. capsulatum* prophylaxis, except perhaps in those who have a $CD4^+$ lymphocyte count less than 150 cells/μL, and who are at high-risk due to occupation or who live in hyperendemic regions.[14]

Coccidioides immitis

Coccidioidomycosis is a disease caused by the dimorphic, soil-dwelling fungi *C. immitis* and *Coccidioides posadasii.* As described in Chapter 36, the chief manifestation of coccidioidomycosis is as a mild flulike, often undiagnosed illness, from which most previously healthy people spontaneously recover. Chronic pulmonary disease occurs in roughly 5% of infected persons and disseminated disease in even fewer. By contrast, in HIV-infected persons coccidioidomycosis is an uncommon, but devastating, disseminated disease that is frequently fatal. The fungus is endemic to the semiarid regions of North America, notably the southwestern United States (central California, southern Arizona, southern New Mexico, and west Texas) and also northern Mexico.[142,167] California's southern San Joaquin Valley and southern Arizona are hyperendemic areas.[167] *Coccidioides* is also found in South America, especially central Argentina. In soil, the fungus exists in a mycelial form with characteristic arthrospores. When the soil is disrupted, the few-micrometer diameter arthrospores, which are just the right size for deposition in the distal airways and alveoli after inhalation, become airborne. After deposition in the lungs, the arthrospores transform into spherules that may develop several hundred endospores. Rupture of the spherules allows widespread dissemination of the endospores, which then form additional spherules, replicating the cycle. Although most cases of HIV-associated coccidioidomycosis appear to result from de novo inhalation exposure, reactivation disease does occur.

Clinical Features. The clinical presentation is often nonspecific; fever and chills (68%), night sweats (36%), and weight loss (50%) are common.[168] Although the portal of entry is the lung, coccidioidomycosis often presents with disseminated disease and meningitis. Other frequent sites include the skin, lymph nodes, liver, and skeletal system. In one study, 42% of HIV-infected patients with coccidioidomycosis presented with disseminated disease; overall, 25% of the patients in this series died.[169]

$CD4^+$ Lymphocyte Count. Most cases of disseminated coccidioidomycosis occur in patients with a $CD4^+$ lymphocyte count below 100 cells/μL and often fewer than 50 cells/μL.[168,169] Cerebrospinal fluid examination is warranted in all patients with suspected coccidioidomycosis.

Chest Radiograph. In a series of 91 HIV-infected patients with coccidioidomycosis, diffuse reticulonodular infiltrates (see Fig. 36-14) were seen in 65%; focal opacities were less common but occurred in 14% of cases and consisted of focal infiltrates, single or multiple nodules, and cavities.[168] Pleural effusion and hilar adenopathy were also reported, as well as normal chest radiographs.

Diagnosis. Unlike cryptococcosis and histoplasmosis, there is no specific antigen test available for diagnosing coccidioidomycosis. Thus, definitive diagnosis requires the isolation and identification of the fungus by culture or identification of pathognomonic giant spherules in cytologic or histologic preparations. In cases of suspected coccidioidomycosis, it is critical to alert the microbiology laboratory so that proper precautions can be implemented to prevent laboratory transmission. Serologic tests are useful in the evaluation of suspected coccidioidomycosis. Several studies have found an 80% to 90% sensitivity of complement fixation and tube precipitin tests.[170] False-negative titers usually occurred in the most severely immunocompromised patients with diffuse pulmonary disease; in those with positive tests, the titer appeared to reflect the disease activity and proved useful for monitoring response to therapy.[171]

Direct examination and culture of sputum, BAL fluid, or TBBX can establish the diagnosis of pulmonary coccidioidomycosis in HIV-infected patients. Singh and associates[168] found that sputum culture in 13 of 19 cases (68%) and cytology in 8 of 11 cases (73%) had a high yield. BAL fluid culture diagnosed 29 of 42 cases (69%), and BAL fluid cytology diagnosed 32 of 48 cases (67%); in addition, TBBX culture diagnosed 8 of 10 cases (80%), and biopsy histology diagnosed all 14 cases (100%).

Treatment. Either amphotericin B or a lipid formulation of amphotericin B is the treatment of choice for HIV-infected patients with severe (i.e., diffuse) pulmonary or disseminated coccidioidomycosis.[14,167] Treatment with amphotericin B should be continued until the patient is clinically improved, at which point the patient can be switched to fluconazole or itraconazole. In patients with clinically mild infection, such as focal pneumonia, fluconazole or itraconazole may be used at the outset.[14] In patients with diffuse disease, lifelong suppressive therapy with itraconazole or fluconzaole should be continued after initial treatment is complete. In patients who have had focal coccidioidal pneumonia, and who have had a sustained response to ART with $CD4^+$ lymphocyte counts above 250 cells/μL, therapy may be discontinued after 12 months, but periodic surveillance with chest radiograph and coccidioides serology is recommended.[14]

Primary Prevention. In areas endemic for *C. immitis,* HIV-infected persons should avoid activities that will potentially increase their exposure, such as

visits to construction or other sites where soil is being disturbed. Routine serologic testing is reasonable only in endemic areas; primary prophylaxis for persons living in or traveling to an endemic area is recommended only if serology test results are positive and $CD4^+$ lymphocyte count is below 250 cells/μL.[14]

Aspergillus Species

Species of *Aspergillus* are found worldwide, and exposure is universal. Nevertheless, disease is infrequent unless phagocyte number or function is reduced.[172] Presently, greater than 180 species within the *Aspergillus* genus have been identified. *Aspergillus fumigatus,* however, is the most common disease-causing species, and it accounts for approximately 90% of cases of invasive aspergillosis. Although invasive aspergillosis is a well-documented complication of various immunosuppressive disorders, particularly in patients with hematologic malignancy or organ transplantation, it is an uncommon problem in patients with HIV disease. Risk factors for the development of aspergillosis besides HIV-induced immunosuppression included use of corticosteroids, neutropenia, marijuana, and broad-spectrum antimicrobial drugs.[173] In the combination ART era, the incidence of invasive aspergillosis has further declined. Holding and coworkers[174] reported an aspergillosis incidence of 3.5 cases per 1000 person-years among HIV-infected subjects enrolled in the CDC-led Adult and Adolescent Spectrum of HIV Disease study.

Clinical Features. The entire spectrum of *Aspergillus*-related lung disease (see Chapter 36 for further details) has been observed in HIV-infected persons, from colonization of the respiratory tract or a preexisting cavity, to tracheobronchitis or obstructing bronchial aspergillosis, to invasive aspergillosis, by far the most severe manifestation.[173,175-177] Although most patients with invasive aspergillosis have a $CD4^+$ lymphocyte count lower than 50 cells/μL, the classic risk factors for the disease relate more to phagocyte number and function (as determined by neutropenia and use of corticosteroids or broad-spectrum antibiotics) than to absolute $CD4^+$ lymphocyte counts. Patients with aspergillosis typically present with fever, cough, dyspnea, and occasionally pleuritic chest pain. Hemoptysis is another presenting feature. The chest radiographic abnormalities are variable and include unilateral or bilateral infiltrates, cavitary lesions, nodular and pleural-based densities, and pleural effusions.[178]

Diagnosis. The definitive diagnosis of aspergillosis requires both demonstration of tissue invasion and isolation of the organism by culture. Neither sputum nor BAL is sufficient. Microscopy alone cannot distinguish *Aspergillus* species from *Fusarium* or *Pseudallescheria* species. The results of TBBX are usually negative, but specimens from sputum, BAL fluid, or percutaneous aspirates are often positive on culture. The absence of histologic proof of tissue invasion is always somewhat disquieting, especially in attempting to distinguish invasive disease from possible colonization of damaged airways. Repeated isolation of the fungus in large numbers with a compatible clinical setting makes the diagnosis more tenable.

Galactomannan antigen testing on serum or BAL specimens may be useful in the diagnosis of invasive pulmonary aspergillosis, although its performance has not been prospectively evaluated in HIV-infected patients with suspected aspergillosis. False-positive results can occur in patients who are on concomitant piperacillin-tazobactam or amoxicillin-clavulanate, and cross reactivity can occur with several other fungi.[179]

Treatment. Compared with the fungi previously discussed, there is relatively little experience treating HIV-infected patients with aspergillosis.[172] Voriconazole is the first-line recommended therapy.[14] Alternative agents include amphotericin, capsofungin, and posaconazole. Interactions with ART drugs must be considered. Even with the prompt institution of therapy, the prognosis is poor, undoubtedly in large part because aspergillosis, when it occurs, is nearly always a late complication of advanced HIV disease.

Prevention. Given the ubiquitous nature of *Aspergillus* species, it is impossible to prevent exposure to the organism. However, patients with advanced HIV disease should avoid activities that will potentially increase their exposure, including being near decaying vegetation (e.g., compost) and soil.

Blastomyces dermatitidis

Blastomycosis is a disease caused by the endemic, dimorphic fungus *B. dermatitidis.* Blastomycosis is coendemic with histoplasmosis throughout much of the central United States (see also Chapter 36), but it is much less common than histoplasmosis, and reports of HIV-associated blastomycosis are infrequent.[180,181]

Clinical Features. The largest case series reported 15 cases of HIV-associated blastomycosis; all but one had a $CD4^+$ lymphocyte count less than 200 cells/μL.[180] The authors noted two distinct patterns of disease: one group of patients had disease that was clinically limited to the respiratory system, whereas the other group had disseminated blastomycosis, commonly involving multiple organ systems, including the lungs. Eleven of 15 patients (73%) had abnormal chest radiographs, with diffuse interstitial or miliary disease (55%) being the most common radiographic finding. Definitive diagnosis requires the growth of *B. dermatitidis,* although visualization of the characteristic budding yeast form is strongly suggestive and warrants antifungal therapy while awaiting the results of culture.

Treatment. Intravenous amphotericin B is the treatment of choice for HIV-infected patients with severe disease.[180,181] Treatment with amphotericin B should be continued to a cumulative induction dose of 1.5 to 2.5 g. Patients who have improved can then be switched to oral itraconazole maintenance therapy for life, whereas those without significant improvement should continue taking amphotericin B. With prompt institution of therapy, most patients with disease limited to the lungs responded well; in contrast, patients with disseminated disease did poorly (40% mortality in 30 days).[180]

Penicillium marneffei

Penicilliosis is a disease caused by *P. marneffei,* a dimorphic, soil-dwelling fungus. With expansion of the HIV epidemic into southeastern Asia has come a dramatic increase in cases of penicilliosis.[182,183] *Penicillium marneffei* is endemic in southeastern Asian countries, and, in northern Thailand, it is the third most common opportunistic infection (after tuberculosis and cryptococcosis) in HIV-infected patients with AIDS, accounting for 15% to 20% of all AIDS-related illnesses. Disease is related to soil exposure, especially during the rainy season (May to October), and infection is probably acquired via inhalation.

Clinical Features. Most cases of penicilliosis occur in patients with a $CD4^+$ lymphocyte count less than 100 cells/μL. The clinical presentation is often mistaken for tuberculosis, cryptococcosis, or histoplasmosis. The most common symptoms include fever, weight loss, cough, and generalized papular skin lesions, usually with central umbilication.[184] Symptoms are often present for weeks. In addition to the cutaneous findings, physical examination often reveals peripheral lymphadenopathy and hepatomegaly. Anemia is a prominent laboratory finding.

Diagnosis. *Penicillium marneffei* is most commonly a disseminated disease in HIV-infected patients, and the diagnosis is usually made by blood fungal cultures. Other sites of diagnosis include the skin, lymph nodes, bone marrow, and lungs. In contrast to other *Penicillium* species that cause disease in humans, *P. marneffei* converts to a yeast form in its host, and yeast-laden macrophages can often be seen in peripheral blood, bone marrow aspirates, and touch preparations from tissue biopsies.

Treatment. Amphotericin B, followed by itraconazole, is the standard treatment for *P. marneffei* infection.[14] Mild forms of disease can be treated initially with itraconazole. The duration of amphotericin B treatment is 2 weeks, followed by an additional 10 weeks of itraconazole. This regimen is reported to have a greater than 97% response rate for disseminated *P. marneffei* infection.[185] Without secondary prophylaxis, however, most patients will suffer a relapse within 6 to 12 months. Secondary prophylaxis can be discontinued in patients who are started on ART and have a sustained $CD4^+$ lymphocyte count more than 100 cells/μL for more than 6 months.[14]

Prevention. Itraconazole may be effective as primary prophylaxis against *P. marneffei* for subjects in endemic areas.[186] Given the strong association with soil exposure, especially during the rainy season, HIV-infected patients living in endemic areas should avoid activities that will potentially increase their exposure. Current NIH, CDC, and HIVMA/IDSA guidelines suggest that HIV-infected patients avoid visiting endemic areas if possible.[14]

Candida Species

Despite the high frequency of mucocutaneous candidiasis in HIV-infected patients, pulmonary candidiasis is distinctly uncommon and is rarely diagnosed during life.[187] Because of the small number of documented cases of pulmonary candidiasis, neither the clinical features nor the treatment is well established. However, it is clear that tissue invasion must be demonstrated by biopsy for a convincing diagnosis; the mere identification of the fungus in respiratory secretions by culture alone is insufficient.

Viruses

Many viruses are known to cause pulmonary disease in immunosuppressed persons; however, only cytomegalovirus (CMV) is regarded as an important agent of pulmonary disease in HIV-infected persons. Although clearly the source of significant pathologic conditions in the retina, gastrointestinal tract, and nervous system, the role of CMV in producing pulmonary disease in HIV-infected persons is open to question. Many consider this ubiquitous virus a "passenger" rather than a pathogen in most instances. However, there are also clear instances in which documented pulmonary disease results from CMV.

Cytomegalovirus

Cytomegalovirus, a double-stranded DNA virus in the Herpesvirus family, is fully described in Chapter 31. The risk of exposure to CMV increases with age, and evidence of CMV infection is extremely common in healthy persons. In HIV-infected patients, CMV disease is believed to result chiefly from reactivation of latent infection. However, disease has been documented from de novo infection in recipients of solid organs, bone marrow, and blood (see Chapter 81), which raises the possibility that new infection or superinfection from exogenous sources may also occur in HIV-infected persons.

Clinical Features. Retinitis and gastrointestinal disease are the two most common forms of HIV-associated CMV disease. Cytomegalovirus is a frequent isolate from the BAL fluid of patients with advanced immunosuppression who undergo evaluation for opportunistic infections, notably *Pneumocystis.* Because CMV may be shed in respiratory secretions, its mere presence in BAL fluid cannot be construed as diagnostic of CMV pulmonary disease. When dual pulmonary infection is discovered, treatment directed against the coexisting disease and not against CMV usually results in clinical resolution.[188] However, there are clearly instances when CMV causes pulmonary disease, and the challenge clinicians face is to recognize when these occur.[189,190]

The most common symptoms of CMV pneumonia are cough, dyspnea, and fever. In the study by Salomon and associates,[190] these symptoms were seen in 94%, 94%, and 89%, respectively, of the 18 patients reported. Respiratory symptoms were present for up to 2 weeks in 50% and between 2 and 4 weeks in an additional 44%.

$CD4^+$ Lymphocyte Count. Most cases of CMV disease occur in patients with a $CD4^+$ lymphocyte count less than 50 cells/μL. In one study of 18 patients with biopsy-proven CMV pneumonia, the median $CD4^+$

lymphocyte count was 4 cells/μL.[190] The serum LDH has been reported to be elevated in CMV pneumonia.[190]

Chest Radiograph. The chest radiograph findings of CMV pneumonia vary and include reticular or ground-glass opacities, alveolar infiltrates, and nodules or nodular opacities.[190] Pleural effusions may be seen as well.

Diagnosis. When suspected CMV pulmonary disease occurs in conjunction with other end-organ disease (e.g., retinitis), CMV therapy must be initiated immediately. Treatment of one end-organ CMV disease in fact treats all, although the length of therapy can differ by organ system. The therapeutic dilemma is much greater when only the lungs appear to be afflicted. Patients suspected of having CMV pneumonitis should undergo a careful dilated retinal examination performed by an experienced ophthalmologist, even if there are no ocular complaints. Cytomegalovirus is usually a disseminated disease and commonly involves multiple organ systems in a single host. The only precise criterion for diagnosis of CMV pulmonary disease is the demonstration of widespread specific cytopathic changes in the lungs. Neither culture of BAL fluid[191] nor cytopathic inclusions on TBBX specimens are sufficient to make the diagnosis of CMV pneumonitis.

Treatment. Data for treatment of CMV pneumonia in HIV-infected patients are limited. Intravenous ganciclovir, foscarnet, or cidofovir and valganciclovir are the principal treatment options for CMV retinitis. With these drugs, an initial course of induction therapy is used, and should be continued until clinical improvement occurs; the length of induction therapy for CMV pneumonia, however, is undetermined. Some authorities have recommended a 21-day course for isolated CMV pneumonitis. The usefulness of maintenance therapy in preventing relapse of CMV pneumonitis is unclear.

Prevention. HIV-infected patients who are CMV immunoglobulin G negative should be given CMV-negative blood in the event that a transfusion is necessary. Disease from CMV is best prevented by maintaining $CD4^+$ lymphocyte counts above 100 cells/μL with ART.[14]

Other Viruses

Symptomatic pulmonary viral infection other than CMV is uncommon. Herpes simplex virus, while frequently cultured from BAL fluid, is usually a contaminant from upper airway carriage. Lower respiratory tract involvement is rare in HIV-infected persons (0.2% to 4% of autopsy cases) and appears to be more frequent in other immunosuppressed hosts. Herpes simplex virus pulmonary disease causes a focal pneumonia or a diffuse interstitial pneumonitis.[192] The focal pneumonias appear to result from contiguous spread of herpes simplex virus to the lung parenchyma and are often associated with necrotizing tracheobronchitis, whereas the diffuse interstitial pneumonias appear to be a manifestation of hematogenous herpes simplex virus dissemination.

Varicella-zoster virus is a rare cause of pneumonia in HIV-infected adult patients.[193] Epstein-Barr virus DNA has been identified in lung biopsy specimens of infants and children with lymphocytic interstitial pneumonitis, but the precise role of the virus in this disease is uncertain.[194] Influenza has been isolated from HIV-infected patients.[195] In this small series, neither the clinical presentation of influenza nor the rate of secondary complications appeared to be different from that in healthy persons. Nevertheless, it is generally recommended that all HIV-infected persons be vaccinated annually.[14]

Parasites

Of the classic unicellular and multicellular parasites that afflict otherwise healthy humans (see Chapter 37), several also cause pulmonary disease in HIV-infected hosts. Of these, *T. gondii* is the most frequent.

Toxoplasma gondii

Toxoplasmosis is a zoonosis caused by the intracellular protozoan *T. gondii,* with domestic cats as its definitive host but with an infectious reservoir that encompasses all animals. Transmission to humans occurs when raw or undercooked meat containing *T. gondii* is eaten. Domestic cat feces in litter boxes are an additional source of potential *T. gondii* infection. Vertical transmission can occur from mother to fetus. In HIV-infected patients, the overwhelming majority of cases of toxoplasmosis result from reactivation of chronic, latent infection. Thus, the keys to preventing toxoplasmosis are prevention of exposure for those not yet infected and prophylaxis for those already seropositive. The seroprevalence of *Toxoplasma* antibodies varies. In the United States, the seroprevalence is 10% to 50%, whereas in Western Europe, the seroprevalence may be as high as 90%.

Clinical Features. Central nervous system complications of *T. gondii* are well recognized in HIV disease and include encephalitis as well as focal brain abscess. Pulmonary involvement is uncommon, but can occur in patients with central nervous system or disseminated disease, or can present as isolated pneumonia.[196,197]

$CD4^+$ Lymphocyte Count. Toxoplasmosis presents at the lower range of $CD4^+$ lymphocyte counts. In a large study of 64 patients with pulmonary toxoplasmosis conducted in France, the mean (± standard deviation [SD]) $CD4^+$ lymphocyte count was 40 (±75) cells/μL.[197]

Chest Radiograph. The chest radiograph usually reveals bilateral infiltrates, either fine reticulonodular infiltrates indistinguishable from PCP or a coarse nodular pattern similar to that seen with tuberculosis or fungal pneumonias.[198] Pleural effusions can be seen, and a variety of other radiographic findings have also been described.[199]

Diagnosis. The diagnosis of pulmonary toxoplasmosis is usually established by bronchoscopy and study of BAL fluid. In one review, BAL fluid examination was diagnostic in 16 of 17 immunocompromised patients with pulmonary disease.[199]

Treatment. The treatment for pulmonary toxoplasmosis is identical to that for central nervous system toxoplasmosis. First-line treatment is sulfadiazine plus pyrimethamine with leucovorin to decrease the likelihood of hematologic toxicities associated with

pyrimethamine.[14] The preferred alternative regimen is clindamycin plus pyrimethamine with leucovorin.

Prevention. HIV-infected persons should be tested for *T. gondii* antibodies. Persons who are *Toxoplasma* antibody negative should be instructed to avoid potential sources of infection. Patients should receive primary prophylaxis once their $CD4^+$ lymphocyte count falls below 100 cells/μL.[14] As a practical matter, this is often accomplished when the $CD4^+$ lymphocyte count reaches 200 cells/μL or fewer because the prophylaxis of choice (TMP-SMX) is also the prophylaxis of choice for *Pneumocystis.* For patients who are intolerant of TMP-SMX, dapsone plus pyrimethamine (and leucovorin) or atovaquone plus pyrimethamine (and leucovorin) can be used. Primary and secondary *T. gondii* prophylaxis can be discontinued in HIV-infected persons on ART who have experienced an increase in their $CD4^+$ lymphocyte count to greater than 200 cells/μL for at least 3 to 6 months.[14]

Other Parasites

In general, helminth infections occur infrequently in HIV-infected persons.[200,201] Both pulmonary cryptosporidiosis and pulmonary microsporidiosis in HIV-infected patients with concurrent intestinal disease have been reported.[202] In these cases, aspiration from the gastrointestinal tract appears to be the most probable route of pulmonary infection. Occasionally, patients have presented with disseminated disease, raising the likely possibility of hematogenous spread. The most common respiratory symptoms are cough, dyspnea, and pleuritic chest pain. One review found that these symptoms were present in 77%, 58%, and 33%, respectively, of patients with cryptosporidial pulmonary disease.[202] The diagnosis of *Strongyloides stercoralis* pulmonary disease can be made by either sputum study or bronchoscopy.[203,204] *Strongyloides* hyperinfection syndrome has also been reported in HIV-infected patients,[205] but does not appear to be an important HIV-associated complication, even in countries where the parasite is endemic.[206]

NONINFECTIOUS DISORDERS

The evaluation of respiratory complications usually focuses on the diagnosis of HIV-associated opportunistic infections because of their frequency, the need for prompt therapy, and, in the case of tuberculosis, the concern for transmission to other persons, both HIV infected and non–HIV infected. However, as more people are living with HIV/AIDS and are living longer on effective ART, noninfectious complications and comorbid illnesses among these HIV-positive patients have increased in frequency.[207] In addition to an increased risk for infectious diseases, HIV-infected patients appear to have an increased risk for a number of noninfectious pulmonary diseases, including chronic obstructive pulmonary disease (COPD), lung cancer, and pulmonary arterial hypertension. Increasing age and a high prevalence of cigarette smoking combined with an independent risk from HIV infection itself may all contribute, in particular to increases in COPD and lung cancer. Noninfectious pulmonary diseases that may be encountered in HIV are reviewed here.

Malignancies

Two different HIV-associated malignancies, Kaposi sarcoma and non-Hodgkin's lymphoma, may involve the thorax, including the lung parenchyma, airways, pleura, or hilar or mediastinal lymph nodes. Intrathoracic disease from either neoplasm is usually a manifestation of disease already recognized elsewhere, but occasionally both Kaposi sarcoma and non-Hodgkin's lymphoma may present with isolated pulmonary disease.

Kaposi Sarcoma

The most common HIV-associated malignancy is Kaposi sarcoma, although its incidence has decreased dramatically with combination ART.[208,209] Kaposi sarcoma is an angioproliferative tumor that most commonly presents with mucocutaneous involvement. The lymph nodes, gastrointestinal tract, and lungs can also be involved. Significant advances have been made in our understanding of its pathogenesis, including its association with a human herpesvirus.[210]

The incidence of HIV-associated Kaposi sarcoma has always been significantly higher in MSM than in other HIV risk groups. Approximately 90% to 95% of cases occur in MSM, and it has been estimated that there is a 20,000- to 73,000-fold increased incidence of Kaposi sarcoma in HIV-infected MSM than in the overall population.[211] These observations suggested the presence of a possible sexually transmitted cofactor. In 1994, Chang and colleagues[212] identified DNA fragments present in HIV-associated Kaposi sarcoma specimens but absent in most non-Kaposi specimens. The nucleotide sequence of these fragments demonstrated homology to two known gamma- (lymphotropic) herpesviruses, suggesting that the fragments derived from a novel herpesvirus, subsequently named human herpesvirus 8 (HHV8) or Kaposi sarcoma–associated herpesvirus.[213] Since then, HHV8 has also been found in specimens from non–HIV-infected persons with classic, endemic (African), and transplant-associated Kaposi sarcoma. These and other findings argue for a central role of HHV8 in the pathogenesis of Kaposi sarcoma and provide new avenues for possible treatment of this disease.

Clinical Features. Pulmonary Kaposi sarcoma is detected clinically in approximately one third of patients with known Kaposi sarcoma, with the proportion detected at autopsy approaching 50% to 75%. Most but not all patients with clinically diagnosed pulmonary Kaposi sarcoma have concomitant mucocutaneous disease. Huang and coworkers[214] found that 85% of 168 consecutive patients diagnosed with pulmonary Kaposi sarcoma by bronchoscopy had evidence of mucocutaneous involvement at the time of bronchoscopy. The 15% without mucocutaneous involvement had pulmonary disease that ranged from isolated tracheal lesions to

diffuse endobronchial involvement that was ultimately fatal. A significant proportion of patients with pulmonary Kaposi sarcoma also have concurrent opportunistic infection. For example, in the study by Huang and coworkers,[214] 45 (27%) of the 168 patients with pulmonary Kaposi sarcoma had accompanying opportunistic infection, most frequently PCP. These observations underscore the need to evaluate each patient with Kaposi sarcoma who presents with respiratory symptoms not only for pulmonary Kaposi sarcoma but also for opportunistic infection. Patients with pulmonary Kaposi sarcoma who develop opportunistic infection may also experience a rapid progression of their Kaposi sarcoma that mimics an infectious process.

$CD4^+$ Lymphocyte Count. Pulmonary Kaposi sarcoma presents at the lower range of $CD4^+$ lymphocyte counts. In one study of 168 patients with pulmonary involvement from Kaposi sarcoma, the median $CD4^+$ lymphocyte count was 19 cells/μL; 68% had a $CD4^+$ lymphocyte count below 50 cells/μL, and only 4% had a $CD4^+$ lymphocyte count higher than 200 cells/μL.[214] Patients with Kaposi sarcoma pulmonary involvement appear to have lower $CD4^+$ lymphocyte counts than those without pulmonary involvement.

Chest Radiograph. Pulmonary Kaposi sarcoma characteristically presents with bilateral opacities in a central or perihilar distribution, as shown in Figure 80-9. Typical findings include linear densities, nodules or nodular opacities of varying size, pleural effusions, and intrathoracic adenopathy. Gruden and associates[215] reviewed the chest radiographic presentation of 76 consecutive patients with pulmonary Kaposi sarcoma diagnosed by bronchoscopy whose BAL was negative for infectious organisms. In this study, 95% of the radiographs had peribronchial cuffing and "tram track" opacities, with or without more extensive perihilar coalescent opacities. Small nodules or nodular opacities were seen in 78%, Kerley B lines in 71%, and pleural effusions in 53% of the radiographs. Although these radiographic findings strongly suggest the diagnosis of pulmonary Kaposi sarcoma in HIV-infected MSM, no radiograph is diagnostic for Kaposi sarcoma. Therefore, patients with suspected pulmonary Kaposi sarcoma should have their diagnosis confirmed.

Diagnosis. The diagnosis of pulmonary Kaposi sarcoma is usually established by bronchoscopy. The observation of characteristic endobronchial, red or violaceous, flat or slightly raised lesions is sufficient to diagnose pulmonary involvement (Fig. 80-10). However, the presence of these lesions does not preclude a concurrent infection, nor does their absence in the observable airway preclude more distal disease or parenchymal, pleural, or nodal involvement. Although endobronchial or transbronchial biopsy of the airway or parenchymal abnormalities, respectively, is usually unnecessary, we have occasionally established the diagnosis by TBBX in patients in whom there was a strong clinical suspicion for pulmonary Kaposi sarcoma but who had no endobronchial lesions detected. Patients with cutaneous Kaposi sarcoma who develop new respiratory complaints should undergo thorough evaluation to rule out an opportunistic infection or other process. However, patients in whom there is a strong clinical suspicion for pulmonary Kaposi sarcoma should undergo bronchoscopy as the initial procedure.

Kaposi sarcoma is ^{67}Ga scan negative. In contrast, opportunistic infections and non-Hodgkin's lymphoma are ^{67}Ga avid. Among HIV-associated pulmonary diseases, this unique feature of Kaposi sarcoma has created a

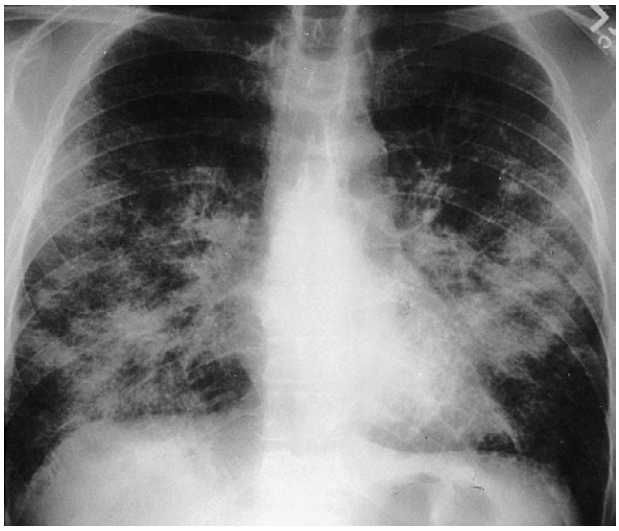

FIGURE 80-9 ■ Posteroanterior chest radiograph of an HIV-seropositive patient with pulmonary Kaposi sarcoma diagnosed by bronchoscopy showing the characteristic bilateral, perihilar distribution of abnormalities consisting of nodules and nodular opacities. Although most HIV-infected patients with pulmonary Kaposi sarcoma will have concomitant mucocutaneous Kaposi sarcoma, approximately 15% will have no evidence of cutaneous or oral involvement. (Courtesy of L. Huang.)

FIGURE 80-10 ■ Characteristic Kaposi sarcoma lesions in the trachea of an HIV-seropositive patient seen via bronchoscopy. (Courtesy of L. Huang.)

niche for the use of ^{67}Ga scans. In the absence of either a bronchoscopic or tissue diagnosis of pulmonary Kaposi sarcoma, its presence may be inferred by the finding of significant chest radiographic abnormalities and a negative ^{67}Ga scan.

Treatment. Tumors can regress in size and number in response to ART, and therefore all patients with Kaposi sarcoma should receive combination ART if no other contraindications exist.[216] Treatment of systemic disease also includes chemotherapy, with approved agents consisting of doxorubicin, daunorubicin, and paclitaxel; in addition, the antiviral agent cidofovir, although not effective on its own, may have a role as adjunctive therapy.[216] Mortality in patients with Kaposi sarcoma may be related to an increased rate of other malignancies, particularly lymphomas, in this population.[217] Survival in patients with pulmonary Kaposi sarcoma appears substantially worse when compared to patients without pulmonary involvement: 5-year overall survival was reported to be 49% in patients with pulmonary Kaposi sarcoma as compared to 82% in patients without pulmonary involvement ($p < 0.0001$).[218]

Non-Hodgkin's Lymphoma

Almost all HIV-associated non-Hodgkin's lymphomas are of B-cell origin. Most are classified as small, noncleaved Burkitt's, diffuse large cell with centroblastic features, or diffuse large cell with immunoblastic features.[219] Many patients have an advanced stage of disease at the time of presentation. Although initial data concerning non-Hodgkin's lymphoma in the combination ART era did not demonstrate as substantial a decrease in incidence as observed in Kaposi sarcoma, most studies now demonstrate that significant decreases occur in non-Hodgkin's lymphoma as well.[220]

Clinical Features. Most HIV-infected patients with non-Hodgkin's lymphoma present with widely disseminated disease and extranodal involvement.[221] Frequent extranodal sites include the liver, spleen, bone marrow, meninges, gastrointestinal tract, and pericardium. Intrathoracic involvement is seen in a smaller proportion. The reported incidence of intrathoracic disease varies from 0 to 31% of patients at the time of clinical diagnosis and is usually higher at the time of autopsy. Occasionally, the lung is the only site involved.

CD4$^+$ Lymphocyte Count. Non-Hodgkin's lymphoma can present at a wide range of CD4$^+$ lymphocyte counts. The median CD4$^+$ T-lymphocyte count is approximately 100 cells/μL, and 75% of patients have a CD4$^+$ lymphocyte count above 50 cells/μL. In one study of 38 patients with non-Hodgkin's lymphoma, the mean (±SD) CD4$^+$ lymphocyte count was 67 (±65) cells/μL.[222]

Chest Radiograph. The most common chest radiograph parenchymal findings include single (Fig. 80-11) or multiple nodules, nodular opacities or masses, lobar infiltrates, and diffuse interstitial infiltrates.[222] More rarely, cases of endobronchial lesions have been reported.[223] Pleural effusions are the most common radiographic abnormality, occurring in 40% to 70% of cases, and many are bilateral.[222] Bilateral hilar and mediastinal adenopathy can be found in up to 60% of patients. Isolated intrathoracic adenopathy without identifiable extrathoracic nodal involvement is a rare presentation for HIV-associated non-Hodgkin's lymphomas.

Diagnosis. The diagnosis of non-Hodgkin's lymphoma requires demonstration of malignant lymphocytes on cytology or biopsy specimens. Most often the diagnosis is made by needle aspiration or biopsy of an extrathoracic site. Persons who present with isolated intrathoracic involvement should undergo bronchoscopy with Wang needle biopsy, if abnormal nodes are within reach through the bronchoscope, and with TBBX.[222] For lesions outside the sampling distance of the bronchoscope, fluoroscopic or CT-guided fine-needle aspiration should be considered. Other options include mediastinoscopy

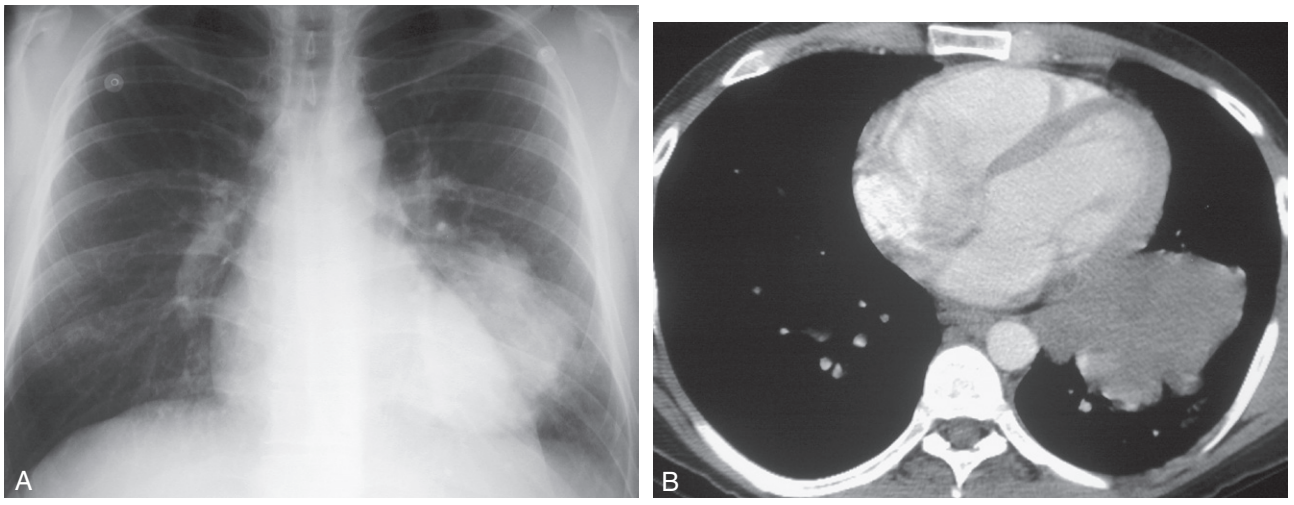

FIGURE 80-11 ■ **A,** Frontal chest radiograph from an AIDS patient with non-Hodgkin's lymphoma showing a large left lower lobe mass. **B,** Axial computed tomogram shows a mass in the left lower lobe without an air bronchogram, suggestive of a neoplasm. (Courtesy of Michael B. Gotway, MD, Scottsdale Medical Imaging and the Department of Radiology, University of California, San Francisco.)

and open-lung biopsy. For patients with pleural effusions, pleural fluid cytology, biopsy, or both are often diagnostic.[222] Pleural fluid is exudative, lymphocytic predominant, and often with very high levels of LDH.[222] The yield of pleural cytology is significantly higher in HIV-associated pulmonary lymphoma as opposed to HIV-negative cases.[224]

Treatment. Pulmonary involvement in non-Hodgkin's lymphoma is treated as part of systemic disease. Median survival from AIDS-related non-Hodgkin's lymphoma has greatly improved as a result of combining ART with systemic chemotherapy: from 8.3 months to 43.2 months in one analysis.[225] Chemotherapy of non-Hodgkin's lymphoma is frequently complicated by the development of opportunistic infections, particularly PCP, and by the presence of decreased bone marrow reserve. Therefore, *Pneumocystis* prophylaxis should be considered in all cases, regardless of $CD4^+$ lymphocyte count.

Primary Effusion Lymphoma

Classic primary effusion lymphoma is a distinct subtype of non-Hodgkin's lymphoma that presents with isolated effusions in body cavities, including the pleura, pericardium, and peritoneum.[226] The classic form of primary effusion lymphoma presents with lymphomatous effusions that occur in the absence of a discrete nodal or extranodal mass. A rare disease, these tumors are found nearly exclusively in HIV-infected MSM. HIV infection is usually advanced; in one study peripheral $CD4^+$ lymphocyte counts averaged 200 cells/μL.[226] HIV-infected patients with primary pleural effusion lymphoma typically present with symptoms related to the space-occupying nature of the effusion (i.e., dyspnea). Diagnosis is established by pleural fluid histology and identification of HHV8, which can be found in all cases.[227] Primary effusion lymphomas are of a null phenotype, lacking classic B-cell and T-cell markers.[216] Prognosis is poor, with median survival on the order of 6 months. Treatment options include combination ART and systemic chemotherapy. Agents known to have activity against intermediate- and high-grade non-Hodgkin's lymphoma may be used. A handful of cases have noted prolonged survival in patients treated with cidofovir or ganciclovir as adjunctive antiviral therapy.[216]

Multicentric Castleman's Disease

Multicentric Castleman's disease (MCD) is a rare lymphoproliferative disorder of the plasma cell type.[228] MCD can occur in association with Kaposi sarcoma in HIV-infected as well as in HIV-uninfected patients. Most patients with MCD are infected with HHV8, particularly if they are also infected with HIV. Common presenting symptoms and signs of systemic MCD include fever, weakness, generalized lymphadenopathy, anemia, and hypergammaglobulinemia. One series described 12 patients with histologically proven MCD with pulmonary involvement.[229] Symptoms of dyspnea and cough were common in this group; bilateral crackles were frequently described on physical examination. Chest imaging demonstrated reticular (n = 7) and/or nodular (n = 7) interstitial patterns, with mediastinal lymphadenopathy (n = 9) and bilateral pleural effusion (n = 3). In another study, bronchovascular nodularity, consolidation, and mediastinal lymphadenopathy were described on chest CT.[230] HHV8 may be detected on BAL. Diagnosis is based on pathologic evaluation of an involved lymph node or extranodal mass. Involved cells resemble immunoblasts, and are of B-cell lineage.[228] Prognosis is generally poor. Treatment options include systemic chemotherapy as well as monoclonal antibodies against CD20 (rituximab) and interleukin-6 receptor (altizumab); reports of sustained remission have been associated with rituximab therapy.[216] Cases of IRIS, some of them fatal, have been reported in patients with MCD initiated on ART.

Non–Small Cell Lung Cancer

The incidence of lung cancer is greater among HIV-infected persons than among HIV-uninfected persons. Whether this increased incidence is due to HIV infection or to other potential confounders such as increased smoking among HIV-infected populations remains somewhat controversial. Studies that account for potential confounding factors include work by Kirk and colleagues,[231] who analyzed lung cancer deaths in the combination ART era and found that HIV infection was associated with a hazard ratio of 3.6 for lung cancer (95% confidence interval [CI], 1.6 to 7.9), after controlling for smoking status as well as age, sex, and calendar period. Similarly, in a study by Engels and colleagues,[232] HIV infection was associated with a standardized incidence ratio of 2.5 (95% CI, 1.6 to 3.5) for lung cancer, adjusting for estimates of smoking prevalence. The incidence of lung cancer in HIV appears to be increased in the combination ART era, with one study finding an incidence of 0.8 per 10,000 person-years in the precombination ART era compared with 6.7 per 10,000 person-years following ART.[233] Whether this is due to an increased age of patients with HIV or other factors is unclear.

Clinical Features. A number of reports have suggested that bronchogenic carcinoma is increased in frequency, occurs at a younger age, and has a more aggressive course in HIV-infected patients. Most HIV-infected patients who develop bronchogenic carcinoma are cigarette smokers. Although all pathologic types are seen, adenocarcinoma has been the most frequent type reported, similar to that seen in non–HIV-infected patients younger than 40 years of age who develop bronchogenic carcinoma; squamous cell carcinoma is the second most frequently observed pathologic type.[232] HIV-infected patients may be more likely to have advanced-stage disease at presentation, although whether this is due to detection bias is uncertain, and age-matched data do not support this finding.[234] Bronchogenic carcinoma can develop at a wide range of $CD4^+$ lymphocyte counts. In the PCHIS study, the range of $CD4^+$ lymphocyte counts among the patients who developed lung cancer was 127 to 1026 cells/μL.[235] There is no apparent relationship between HIV viral load and use of ART with

lung cancer risk.[231] The characteristic presentation and radiographic finding of bronchogenic carcinoma, as described in Chapter 47, are similar in HIV-infected and HIV-uninfected patients.

Diagnosis and Treatment. The diagnosis and treatment of bronchogenic carcinoma in an HIV-infected patient is similar to that in a non–HIV-infected individual. HIV infection should be considered an important concurrent underlying medical problem, much the same as one would consider underlying cardiopulmonary disease. Overall, mortality in HIV-infected patients with lung cancer appears to be independent of HIV, and median survival in HIV-infected patients with lung cancer is similar to age-matched HIV-uninfected lung cancer patients.[234]

Pulmonary Arterial Hypertension

Since the 1980s, studies have reported an increased frequency of pulmonary arterial hypertension in the HIV-infected population, with a prevalence of approximately 0.5% compared to 1 to 2 cases per million in the non–HIV-infected population.[236] There is some debate about whether this diagnosis has decreased in the era of combination ART, but it still seems to be over-represented in HIV-infected individuals.[237] Data suggest that pulmonary arterial hypertension may be underdiagnosed in this population as screening echocardiograms detected increased pulmonary artery pressures in 35% of HIV-infected subjects compared to 7.7% of non–HIV-infected controls.[238]

Clinical Features

HIV-infected patients are significantly younger, and the proportion with New York Heart Association functional class III or IV significantly lower (50% vs. 75%, $P = 0.01$), than in non–HIV-infected subjects with idiopathic pulmonary arterial hypertension, and 1-year survival is approximately 51%.[239] Intravenous drug use is commonly reported in HIV-infected patients with pulmonary hypertension.[239] In a review of 131 cases of pulmonary hypertension in HIV-infected patients,[240] presenting symptoms and radiographic, pulmonary function, electrocardiographic, echocardiographic, and pathologic findings were similar to those found in non–HIV-related idiopathic pulmonary arterial hypertension (described in Chapter 52).

Treatment

Small studies have reported improved functional and hemodynamic parameters in subjects with HIV and pulmonary arterial hypertension during treatment with epoprostenol and bosentan.[241] Other treatments such as sildenafil and iloprost may also be useful.[242,243] Epoprostenol may be associated with intravascular infections in the HIV population, and high levels of sildenafil can be seen when used in combination with antiretrovirals, particularly ritonavir. Although still controversial, some studies have found a benefit in treating patients with ART or the combination of ART and bosentan.[236,244]

Obstructive Lung Disease

Obstructive lung disease occurs frequently in HIV-infected patients, and a variety of pulmonary function test abnormalities can be seen. The PCHIS researchers performed serial pulmonary function tests in more than 1100 HIV-infected subjects and demonstrated that advanced HIV infection, characterized by a $CD4^+$ lymphocyte count less than 200 cells/μL or HIV-associated symptoms, as well as race, cigarette smoking, and IDU, were associated with reductions in D_{LCO}.[245] A PCHIS multivariate analysis found that both PCP and bacterial pneumonia were independently associated with an accelerated decline in the forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), FEV_1/FVC, and D_{LCO}.[246] Studies have found that significant proportions of HIV-infected subjects self-report wheezing within the past 12 months,[247,247a] and have evidence of airflow obstruction: 33 of 99 persons with AIDS (33%) had decreased forced expiratory flow rates, and 20 of the 33 (61%) experienced a significant response to inhaled bronchodilators.[248]

HIV-infected patients may have asthma that precedes their HIV infection. In one clinic-based study, a history of asthma was reported in 21% and current asthma in 17% of 136 patients attending a primary care clinic for HIV infection.[249] On questioning, 61% of the current asthmatic patients reported subjective worsening of their asthma after becoming HIV infected, but the role of HIV itself is unclear. HIV-infected patients are more likely than non–HIV-infected patients to have bronchial hyperresponsiveness to methacholine.[247] $CD4^+$ lymphocyte counts greater than 200 cells/μL are associated with current asthma in those with HIV infection,[249] and one report has linked use of asthma medication to combination ART use in HIV-infected children, suggesting that immune responses are important.[250]

Obstructive airway disease, chronic bronchitis, and bronchiectasis are well-recognized sequelae of opportunistic infection[251,252]; however, evidence also suggests that HIV infection is associated with an increase in emphysema apart from the effects of opportunistic infections.[253] The impact of combination ART on emphysema and airway obstruction is mostly unknown, but a study of self-report and *International Classification of Diseases,* Ninth Revision, diagnoses of COPD in a cohort of HIV-seropositive and HIV-seronegative veterans found that HIV infection was an independent risk factor for COPD.[254]

Treatment

In general, treatment of asthma and COPD in patients with HIV infection should be similar to that for the non–HIV-infected population (see Chapters 38 and 39). PIs, particularly ritonavir, have been reported to increase systemic levels of inhaled or intranasal fluticasone, leading to Cushing's syndrome or adrenal suppression when the corticosteroids are tapered.[255] The use of high-dose inhaled steroids for COPD in patients with HIV also requires careful monitoring for oral candidiasis and bacterial pneumonia.[256]

Interstitial Pneumonitides

Although opportunistic infection and neoplasia dominate the clinical spectrum of HIV-associated pulmonary diseases, a small number of patients present with signs and symptoms that are attributable to one of the interstitial pneumonitides, lymphocytic interstitial pneumonitis (LIP) or nonspecific interstitial pneumonitis (NSIP).

Lymphocytic Interstitial Pneumonitis

Although described by Carrington and Liebow over 30 years ago, it remains speculative whether LIP is a pathogenically distinct entity or a disorder of multiple causes that all produce a similar pathologic reaction (see also Chapter 57). The facts that LIP occurs with increased frequency in HIV-infected persons (albeit rarely in adults) and is diagnostic of AIDS when it occurs in an HIV-infected child younger than 13 years of age favor the diverse-origin theory.

Clinical Features. The most striking feature of HIV-associated LIP is the effect of age on its incidence. Early in the AIDS epidemic, one third to one half of AIDS-defining diagnoses in HIV-infected children in industrialized countries were due to LIP. In contrast, LIP is rare in adults. We have encountered but a handful of biopsy-proven LIP cases in our experience with several thousand adult AIDS patients at San Francisco General Hospital, and there are only scattered case reports throughout the literature.[257]

The chest radiograph presentation of LIP is nonspecific, as shown in Figure 80-12, and is characterized by bilateral reticulonodular interstitial infiltrates with a middle to lower lung zone predominance.[258] Areas of alveolar opacity believed to result from bronchial compression caused by more severe lymphocytic infiltration may occur but are rare. Hilar or mediastinal adenopathy is occasionally seen. Chest CT scans may reveal small (2- to 4-mm) nodules, often in a peribronchovascular distribution, or diffuse areas of ground-glass opacity.[259]

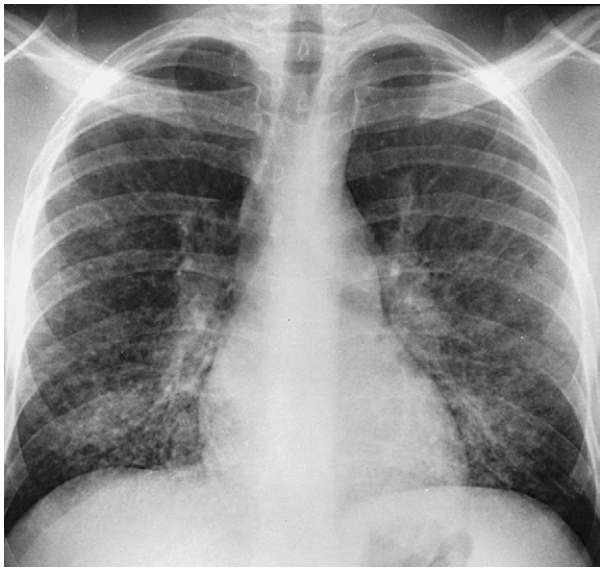

FIGURE 80-12 ■ Posteroanterior chest radiograph of an HIV-seropositive patient showing diffuse reticulonodular infiltration. Biopsy specimen revealed lymphocytic interstitial pneumonitis, a rare disorder in HIV-infected adults that is more frequently seen in HIV-infected children.

Diagnosis and Treatment. The definitive diagnosis of LIP requires histologic confirmation by biopsy. There are so few studies of LIP among HIV-infected adults that neither definitive therapy nor benefit of therapy has been determined. A few cases of LIP that responded to ART alone have been reported.[257,260]

Nonspecific Interstitial Pneumonitis

NSIP is a pulmonary disorder characterized histologically by infiltration of mononuclear cells, predominantly lymphocytes and plasma cells, into the peribronchiolar and perivascular interstitium (see also Chapter 57). NSIP has been reported with various frequencies in HIV-infected patients. Because it is a histologic diagnosis, its incidence depends on the frequency with which biopsy is performed during the diagnostic evaluation.

Clinical Features. The clinical features of NSIP are indistinguishable from those of PCP; however, NSIP may present at $CD4^+$ lymphocyte counts above 200 cells/μL, whereas PCP rarely (≤5%) does. For example, in a series of 67 HIV-infected patients with NSIP, the mean $CD4^+$ lymphocyte count in the patients with NSIP was 492 cells/μL compared with 57 cells/μL for the matched control subjects with PCP.[261] The chest radiographic presentation of NSIP is usually a nonspecific diffuse interstitial pattern, which is also indistinguishable from that of PCP; one study, however, reported that 16 of 36 (44%) patients with HIV-related NSIP had normal radiographs.[262]

Diagnosis and Treatment. The diagnosis of NSIP requires both histologic confirmation and the exclusion of other etiologies. The natural history of HIV-associated NSIP is poorly understood, but it usually resolves or stabilizes without therapy.[261] Observation is all that is required, with the proviso that, if the patient becomes severely ill, repeat bronchoscopy and biopsy are indicated to look for a different, usually infectious, disorder.

Sarcoidosis

Although sarcoidosis would seem an unlikely disorder among patients with HIV, a number of cases of sarcoidosis or sarcoid-like disease have been reported in this population. Many of these cases have been reported during the combination ART era and have correlated the use of ART with the development of sarcoidosis.[263,264] Whether sarcoidosis in HIV represents a manifestation of IRIS is debated. Approximately 75% of HIV-infected patients with sarcoidosis have $CD4^+$ lymphocyte counts above 200 cells/μL.[263]

Both the clinical and radiographic findings of sarcoidosis in HIV-infected patients mirror findings of sarcoidosis in HIV-uninfected patients.[263,264] As described in Chapter 59, granulomatous inflammation of the lungs and other involved organs is characteristic. Stains and cultures of tissue should be obtained and, to diagnose

sarcoid, must be negative for microorganisms (e.g., mycobacteria, fungi). Lymphocytic alveolitis with a high percentage of $CD4^+$ lymphocytes may be encountered.[265] Because no studies have evaluated treatment of sarcoidosis specifically in HIV-infected persons, until further data are available, management should follow guidelines as outlined for HIV-uninfected persons with sarcoidosis.

Immune Reconstitution Inflammatory Syndrome

"Immune reconstitution inflammatory syndrome" describes a paradoxical worsening of clinical status related to recovery of the immune system following a period of immunosuppression, which typically occurs after the initiation of ART in HIV-infected patients. IRIS is thought to occur as a result of reconstitution of the immune system leading to host inflammatory responses to previously recognized or subclinical infections. Immune reconstitution may also result from an inflammatory or immune response to cancer or self antigens, as cases of IRIS have been reported to present with worsening tumor or autoimmune disease.

Numerous different disease processes have been associated with IRIS. These include many infections, sarcoid, autoimmune conditions, and tumors.[266,267] Among infectious triggers, mycobacterial infections—particularly *M. tuberculosis* and MAC—are most frequently encountered. Fungal infections, including PCP and *Cryptococcus,* as well as viral infections, such as CMV, can also be exacerbated by IRIS. The majority of cases of IRIS occur within the first 1 to 3 months following the initiation of ART, although cases may present several months after the initiation of ART.[267] In most studies, IRIS is significantly associated with starting ART in close proximity to treatment for an acute opportunistic infection.[268,269]

In general, ART should be continued in patients who have IRIS, although careful review on a case-by-case basis is required.[14] Nonsteroidal anti-inflammatory agents and corticosteroids can be used to decrease inflammation. Steroids are recommended if the excessive inflammatory response can be particularly harmful, such as in lesions involving the central nervous system or causing airway compromise. Optimal dosage and duration have not been studied, but prednisone or methylprednisolone at approximately 1 mg/kg of body weight, gradually reduced over 1 to 2 weeks, may be used.[14]

KEY POINTS

- HIV infection results in immune dysregulation, dysfunction, and deficiency, with a progressive decline in the circulating $CD4^+$ lymphocyte count, particularly in patients not receiving effective combination antiretroviral therapy (ART). HIV infection also causes alteration in several lines of host defense in the lungs and respiratory tract.
- The peripheral $CD4^+$ lymphocyte count is a key factor that influences the risk for pulmonary complications in HIV-infected persons; the risk of opportunistic infections and HIV-associated malignancies increases progressively as $CD4^+$ lymphocyte counts decrease.
- Worldwide, tuberculosis is the most common infectious lung complication and a major cause of HIV-associated morbidity and mortality. Drug-resistant tuberculosis appears to be increasing in incidence and seems to have a predilection for persons infected with HIV.
- Bacterial pneumonia and *Pneumocystis* pneumonia (PCP) are also common infectious lung complications associated with HIV; noninfectious conditions that may be encountered with increased frequency in patients with HIV include lung cancer, idiopathic pulmonary arterial hypertension, and chronic obstructive pulmonary diseases.
- The differential diagnosis for pulmonary diseases in HIV-infected patients is broad, and the clinical features and radiographic findings of many diseases may overlap significantly. Definitive diagnosis is highly recommended in patients with HIV. When feasible, early bronchoscopy with bronchoalveolar lavage should be performed in patients with pneumonia who do not have an established microbiologic diagnosis.
- In HIV-infected patients recently started on combination ART, immune reconstitution inflammatory syndrome may occur with paradoxical worsening of conditions that include infections (such as tuberculosis, MAC, and PCP), malignancies (such as Kaposi sarcoma), and inflammatory diseases (such as sarcoidosis).

References

1. Palella FJ Jr, Delaney KM, Moorman AC, et al: Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. N Engl J Med 338:853–860, 1998.
2. Murray JF, Mills J: Pulmonary infectious complications of human immunodeficiency virus infection. Am Rev Respir Dis 141:1356–1372, 1582–1598, 1990.
3. White DA, Matthay RA: Noninfectious pulmonary complications of infection with the human immunodeficiency virus. Am Rev Respir Dis 140:1763–1787, 1989.

4. UNAIDS and World Health Organization: Report on the Global AIDS Epidemic. Geneva: World Health Organization, 2008.
5. Twenty-five years of HIV/AIDS—United States, 1981–2006. MMWR Morb Mortal Wkly Rep 55:585–589, 2006.
6. Epidemiology of HIV/AIDS—United States, 1981–2005. MMWR Morb Mortal Wkly Rep 55:589–592, 2006.
7. UNAIDS and World Health Organization: Report on the Global HIV/AIDS Epidemic. Geneva: World Health Organization, 2003.
8. Chinen J, Shearer WT: Molecular virology and immunology of HIV infection. J Allerg Clin Immunol 110:189–198, 2002.
9. Grossman Z, Meier-Schellersheim M, Paul WE, Picker LJ: Pathogenesis of HIV infection: What the virus spares is as important as what it destroys. Nat Med 12:289–295, 2006.
10. Derdeyn CA, Silvestri G: Viral and host factors in the pathogenesis of HIV infection. Curr Opin Immunol 17:366–373, 2005.
11. Shellito JE: Failure of host defenses in human immunodeficiency virus. Semin Respir Crit Care Med 25:73–84, 2004.

11a. Lassiter C, Fan X, Joshi PC, et al: HIV-1 transgene expression in rats causes oxidant stress and alveolar epithelial barrier dysfunction. AIDS Res Ther 6:1–10, 2009.

12. Beck JM: The immunocompromised host: HIV infection. Proc Am Thorac Soc 2:423–427, 2005.
13. Hanson DL, Chu SY, Farizo KM, Ward JW: Distribution of $CD4^+$ T lymphocytes at diagnosis of acquired immunodeficiency syndrome-defining and other human immunodeficiency virus-related illnesses. The Adult and Adolescent Spectrum of HIV Disease Project Group. Arch Intern Med 155:1537–1542, 1995.
14. Centers for Disease Control and Prevention: Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents: Recommendations from the CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. MMWR 58:1–207, 2009.
15. Broaddus C, Dake MD, Stulbarg MS, et al: Bronchoalveolar lavage and transbronchial biopsy for the diagnosis of pulmonary infections in the acquired immunodeficiency syndrome. Ann Intern Med 102:747–752, 1985.
16. Huang L, Hecht FM, Stansell JD, et al: Suspected *Pneumocystis carinii* pneumonia with a negative induced sputum examination: Is early bronchoscopy useful? Am J Respir Crit Care Med 151:1866–1871, 1995.
17. Gruden JF, Klein JS, Webb WR: Percutaneous transthoracic needle biopsy in AIDS: Analysis in 32 patients. Radiology 189:567–571, 1993.
18. Pass HI, Potter D, Shelhammer J, et al: Indications for and diagnostic efficacy of open-lung biopsy in the patient with acquired immunodeficiency syndrome (AIDS). Ann Thorac Surg 41:307–312, 1986.
19. LoCicero J 3rd: Does every patient with enigmatic lung disease deserve a lung biopsy? The continuing dilemma. Chest 106:706–708, 1994.
20. Centers for Disease Control and Prevention: 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. JAMA 269:729–730, 1993.
21. Hirschtick RE, Classroth J, Jordan MC, et al: Bacterial pneumonia in persons infected with the human immunodeficiency virus. Pulmonary Complications of HIV Study Group. N Engl J Med 333:845–851, 1995.
22. Grubb JR, Moorman AC, Baker RK, Masur H: The changing spectrum of pulmonary disease in patients with HIV infection on antiretroviral therapy. AIDS 20:1095–1107, 2006.
23. Jones JL, Hanson DL, Dworkin MS, et al: Surveillance for AIDS-defining opportunistic illnesses, 1992–1997. MMWR CDC Surveill Summ 48:1–22, 1999.
24. Sullivan JH, Moore RD, Keruly JC, Chaisson RE: Effect of antiretroviral therapy on the incidence of bacterial pneumonia in patients with advanced HIV infection. Am J Respir Crit Care Med 162:64–67, 2000.
25. Franzetti F, Grassini A, Piazza M, et al: Nosocomial bacterial pneumonia in HIV-infected patients: Risk factors for adverse outcome and implications for rational empiric antibiotic therapy. Infection 34:9–16, 2006.
26. Kohli R, Lo Y, Homel P, et al: Bacterial pneumonia, HIV therapy, and disease progression among HIV-infected women in the HIV Epidemiologic Research (HER) study. Clin Infect Dis 43:90–98, 2006.
27. Niaura R, Shadel WG, Morrow K, et al: Human immunodeficiency virus infection, AIDS, and smoking cessation: The time is now. Clin Infect Dis 31:808–812, 2000.
28. Gordon FM, Roediger MP, Girard PM, et al: Pneumonia in HIV-infected persons: Increased risk with cigarette smoking and treatment interruption. Am J Respir Crit Care Med 80:775–801, 1996.
29. Le Moing V, Rabaud C, Journot V, et al: Incidence and risk factors of bacterial pneumonia requiring hospitalization in HIV-infected patients started on a protease inhibitor-containing regimen. HIV Med 7:261–267, 2006.
30. Afessa B, Green B: Bacterial pneumonia in hospitalized patients with HIV infection: The Pulmonary Complications, ICU Support, and Prognostic Factors of Hospitalized Patients with HIV (PIP) Study. Chest 117:1017–1022, 2000.
31. Mundy LM, Auwaerter PG, Oldach D, et al: Community-acquired pneumonia: Impact of immune status. Am J Respir Crit Care Med 152:1309–1315, 1995.
32. Daley CL: Bacterial pneumonia in HIV-infected patients. Semin Respir Infect 8:104–115, 1993.
33. Grau I, Pallares R, Tubau F, et al: Epidemiologic changes in bacteremic pneumococcal disease in patients with human immunodeficiency virus in the era of highly active antiretroviral therapy. Arch Intern Med 165:1533–1540, 2005.
34. Janoff EN, Breiman RF, Daley CL, Hopewell PC: Pneumococcal disease during HIV infection: Epidemiologic, clinical, and immunologic perspectives. Ann Intern Med 117:314–324, 1992.
35. Rizzi EB, Schinina V, Rovighi L, et al: HIV-related pneumococcal lung disease: Does highly active antiretroviral therapy or bacteremia modify radiologic appearance? AIDS Patient Care STDS 22:105–111, 2008.
36. Schlamm HT, Yancovitz SR: *Haemophilus influenzae* pneumonia in young adults with AIDS, ARC, or risk of AIDS. Am J Med 86:11–14, 1989.
37. Garcia-Leoni ME, Moreno S, Rodeno P, et al: Pneumococcal pneumonia in adult hospitalized patients infected with the human immunodeficiency virus. Arch Intern Med 152:1808–1812, 1992.
38. Niederman MS, Mandell LA, Anzueto A, et al: Guidelines for the management of adults with community-acquired pneumonia: Diagnosis, assessment of severity, antimicrobial therapy, and prevention. Am J Respir Crit Care Med 163:1730–1754, 2001.
39. Jordano Q, Falco V, Almirante B, et al: Invasive pneumococcal disease in patients infected with HIV: Still a threat in the era of highly active antiretroviral therapy. Clin Infect Dis 38:1623–1628, 2004.
40. Boulware DR, Daley CL, Merrifield C, et al: Rapid diagnosis of pneumococcal pneumonia among HIV-infected adults with urine antigen detection. J Infect 55:300–309, 2007.
41. Schleicher GK, Herbert V, Brink A, et al: Procalcitonin and C-reactive protein levels in HIV-positive subjects with tuberculosis and pneumonia. Eur Respir J 25:688–692, 2005.
42. Niederman MS: Biological markers to determine eligibility in trials for community-acquired pneumonia: A focus on procalcitonin. Clin Infect Dis 47(Suppl 3):S127–S132, 2008.
43. Mandell LA, Bartlett JG, Dowell SF, et al: Update of practice guidelines for the management of community-acquired pneumonia in immunocompetent adults. Clin Infect Dis 37:1405–1433, 2003.
44. Pemba L, Charalambous S, von Gottberg A, et al: Impact of cotrimoxazole on non-susceptibility to antibiotics in *Streptococcus pneumoniae* carriage isolates among HIV-infected mineworkers in South Africa. J Infect 56:171–178, 2008.
45. Dworkin MS, Ward JW, Hanson DL, et al: Pneumococcal disease among human immunodeficiency virus-infected persons: Incidence, risk factors, and impact of vaccination. Clin Infect Dis 32:794–800, 2001.
46. Rodriguez-Barradas MC, Goulet J, Brown S, et al: Impact of pneumococcal vaccination on the incidence of pneumonia by HIV infection status among patients enrolled in the Veterans Aging Cohort 5-Site Study. Clin Infect Dis 46:1093–1100, 2008.
47. Manfredi R, Nanetti A, Ferri M, Chiodo F: *Pseudomonas* spp. complications in patients with HIV disease: An eight-year clinical and microbiological survey. Eur J Epidemiol 16:111–118, 2000.

48. Schuster MG, Norris AH: Community-acquired *Pseudomonas aeruginosa* pneumonia in patients with HIV infection. AIDS 8:1437–1441, 1994.
49. Boumis E, Petrosillo N, Girardi E, et al: Changing patterns in the etiology of HIV-associated bacterial pneumonia in the era of highly active antiretroviral therapy. Eur J Clin Microbiol Infect Dis 20:71–73, 2001.
50. Dropulic LK, Leslie JM, Eldred LJ, et al: Clinical manifestations and risk factors of *Pseudomonas aeruginosa* infection in patients with AIDS. J Infect Dis 171:930–937, 1995.
51. Blatt SP, Dolan MJ, Hendrix CW, Melcher GP: Legionnaires' disease in human immunodeficiency virus-infected patients: Eight cases and review. Clin Infect Dis 18:227–232, 1994.
52. Pedro-Botet ML, Sabria M, Sopena N, et al: Legionnaires disease and HIV infection. Chest 124:543–547, 2003.
53. Den Boer JW, Yzerman EP: Diagnosis of *Legionella* infection in Legionnaires' disease. Eur J Clin Microbiol Infect Dis 23:871–878, 2004.
54. Weinstock DM, Brown AE: *Rhodococcus equi:* An emerging pathogen. Clin Infect Dis 34:1379–1385, 2002.
55. Torres-Tortosa M, Arrizabalaga J, Villanueva JL, et al: Prognosis and clinical evaluation of infection caused by *Rhodococcus equi* in HIV-infected patients: A multicenter study of 67 cases. Chest 123:1970–1976, 2003.
56. Uttamchandani RB, Daikos GL, Reyes RR, et al: Nocardiosis in 30 patients with advanced human immunodeficiency virus infection: Clinical features and outcome. Clin Infect Dis 18:348–353, 1994.
57. Kramer MR, Uttamchandani RB: The radiographic appearance of pulmonary nocardiosis associated with AIDS. Chest 98:382–385, 1990.
58. DeRiemer K, Kawamura LM, Hopewell PC, Daley CL: Quantitative impact of human immunodeficiency virus infection on tuberculosis dynamics. Am J Respir Crit Care Med 176:936–944, 2007.
59. Global Tuberculosis Control: Epidemiology, Strategy, Financing (WHO/HTM/TB/2009.411). Geneva: World Health Organization, 2009.
60. Tuberculosis morbidity—United States, 1992. MMWR Morb Mortal Wkly Rep 42:696–697, 703–704, 1993.
61. Centers for Disease Control and Prevention: Trends in tuberculosis—United States, 2008. MMWR Morb Mortal Wkly Rep 58:249–253, 2009.
62. Branson BM, Handsfield HH, Lampe MA, et al: Revised recommendations for HIV testing of adults, adolescents, and pregnant women in health-care settings. MMWR Recomm Rep 55:1–17, 2006.
63. Sungkanuparph S, Eampokalap B, Chottanapund S, et al: Impact of drug-resistant tuberculosis on the survival of HIV-infected patients. Int J Tuberc Lung Dis 11:325–330, 2007.
64. Moore M, Onorato IM, McCray E, Castro KG: Trends in drug-resistant tuberculosis in the United States, 1993–1996. JAMA 278:833–837, 1997.
65. Faustini A, Hall AJ, Perucci CA: Risk factors for multidrug resistant tuberculosis in Europe: A systematic review. Thorax 61:158–163, 2006.
66. Burman W, Benator D, Vernon A, et al: Acquired rifamycin resistance with twice-weekly treatment of HIV-related tuberculosis. Am J Respir Crit Care Med 173:350–356, 2006.
67. Small PM, Shafer RW, Hopewell PC, et al: Exogenous reinfection with multidrug-resistant *Mycobacterium tuberculosis* in patients with advanced HIV infection. N Engl J Med 328:1137–1144, 1993.
68. Emergence of *Mycobacterium tuberculosis* with extensive resistance to second-line drugs—worldwide, 2000–2004. MMWR Morb Mortal Wkly Rep 55:301–305, 2006.
69. Wells CD, Cegielski JP, Nelson LJ, et al: HIV infection and multidrug-resistant tuberculosis: The perfect storm. J Infect Dis 196(Suppl 1):S86–S107, 2007.
69a. Kliiman K, Altraja A: Predictors of extensively drug-resistant pulmonary tuberculosis. Ann Intern Med 150:766–775, 2009.
69b. Gandhi NR, Shah NS, Andrews JR, et al: HIV co-infection in multidrug- and extensively drug-resistant tuberculosis results in high early mortality. Am J Respir Crit Care Med 2009. In Press.
70. Gandhi NR, Moll A, Sturm AW, et al: Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa. Lancet 368:1575–1580, 2006.
71. Ong A, Creasman J, Hopewell PC, et al: A molecular epidemiological assessment of extrapulmonary tuberculosis in San Francisco. Clin Infect Dis 38:25–31, 2004.
72. Jones BE, Young SM, Antoniskis D, et al: Relationship of the manifestations of tuberculosis to CD4 cell counts in patients with human immunodeficiency virus infection. Am Rev Respir Dis 148:1292–1297, 1993.
73. Shafer RW, Kim DS, Weiss JP, Quale JM: Extrapulmonary tuberculosis in patients with human immunodeficiency virus infection. Medicine 70:384–397, 1991.
74. Busi Rizzi E, Schinina V, Palmieri F, et al: Radiological patterns in HIV-associated pulmonary tuberculosis: Comparison between HAART-treated and non-HAART-treated patients. Clin Radiol 58:469–473, 2003.
74a. Monkongdee P, McCarthy KD, Cain KP, et al: Yield of acid-fast smear and mycobacterial culture for tuberculosis diagnosis in people with human immunodeficiency virus. Am J Respir Crit Care Med 180:903–908, 2009.
75. Conde MB, Loivos AC, Rezende VM, et al: Yield of sputum induction in the diagnosis of pleural tuberculosis. Am J Respir Crit Care Med 167:723–725, 2003.
76. Blumberg HM, Burman WJ, Chaisson RE, et al, for the American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: Treatment of tuberculosis. Am J Respir Crit Care Med 167:603–662, 2003.
77. Kang'ombe CT, Harries AD, Ito K, et al: Long term outcomes in patients registered with TB in Zomba, Malawi: Mortality at 7 years according to initial HIV status and type of TB. Int J Tuberc Lung Dis 8:829–836, 2004.
78. Breen RA, Miller RF, Gorsuch T, et al: Adverse events and treatment interruption in tuberculosis patients with and without HIV co-infection. Thorax 61:791–794, 2006.
79. Breen RA, Smith CJ, Bettinson H, et al: Paradoxical reactions during tuberculosis treatment in patients with and without HIV co-infection. Thorax 59:704–707, 2004.
80. Nahid P, Gonzalez LC, Rudoy I, et al: Treatment outcomes of patients with HIV and tuberculosis. Am J Respir Crit Care Med 175:1199–1206, 2007.
81. Basu S, Andrews JR, Poolman EM, et al: Prevention of nosocomial transmission of extensively drug-resistant tuberculosis in rural South African district hospitals: An epidemiological modelling study. Lancet 370:1500–1507, 2007.
82. Targeted tuberculin testing and treatment of latent tuberculosis infection: Joint statement of the American Thoracic Society/Centers for Disease Control and Prevention/Council of the Infectious Diseases Society of America. Am J Respir Crit Care Med 161:S221–S247, 2000.
83. Horsburgh CR Jr, Mason UG 3rd, Farhi DC, Iseman MD: Disseminated infection with *Mycobacterium avium-intracellulare:* A report of 13 cases and a review of the literature. Medicine 64:36–48, 1985.
84. Horsburgh CR Jr, Selik RM: The epidemiology of disseminated nontuberculous mycobacterial infection in the acquired immunodeficiency syndrome (AIDS). Am Rev Respir Dis 139:4–7, 1989.
85. Horsburgh CR Jr, Metchock BG, McGowan JE Jr, Thompson SE: Clinical implications of recovery of *Mycobacterium avium* complex from the stool or respiratory tract of HIV-infected individuals. AIDS 6:512–514, 1992.
86. Salama C, Policar M, Venkataraman M: Isolated pulmonary *Mycobacterium avium* complex infection in patients with human immunodeficiency virus infection: Case reports and literature review. Clin Infect Dis 37:e35–e40, 2003.
87. Jones D, Havlir DV: Nontuberculous mycobacteria in the HIV infected patient. Clin Chest Med 23:665–674, 2002.
88. Mehle ME, Adamo JP, Mehta AC, et al: Endobronchial *Mycobacterium avium-intracellulare* infection in a patient with AIDS. Chest 96:199–201, 1989.
89. Griffith DE, Aksamit T, Brown-Elliott BA, et al: An official ATS/IDSA statement: Diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. Am J Respir Crit Care Med 175:367–416, 2007.
90. Gordin FM, Sullam PM, Shafran SD, et al: A randomized, placebo-controlled study of rifabutin added to a regimen of clarithromycin and ethambutol for treatment of disseminated infection with

Mycobacterium avium complex. Clin Infect Dis 28:1080–1085, 1999.
91. Bloch KC, Zwerling L, Pletcher MJ, et al: Incidence and clinical implications of isolation of *Mycobacterium kansasii:* Results of a 5-year, population-based study. Ann Intern Med 129:698–704, 1998.
92. Canueto-Quintero J, Caballero-Granado FJ, Herrero-Romero M, et al: Epidemiological, clinical, and prognostic differences between the diseases caused by *Mycobacterium kansasii* and *Mycobacterium tuberculosis* in patients infected with human immunodeficiency virus: A multicenter study. Clin Infect Dis 37:584–590, 2003.
93. Witzig RS, Fazal BA, Mera RM, et al: Clinical manifestations and implications of coinfection with *Mycobacterium kansasii* and human immunodeficiency virus type 1. Clin Infect Dis 21:77–85, 1995.
94. Cattamanchi A, Nahid P, Marras TK, et al: Detailed analysis of the radiographic presentation of *Mycobacterium kansasii* lung disease in patients with HIV infection. Chest 133:875–880, 2008.
95. Marras TK, Daley CL: A systematic review of the clinical significance of pulmonary *Mycobacterium kansasii* isolates in HIV infection. J Acquir Immune Defic Syndr 36:883–889, 2004.
96. Taillard C, Greub G, Weber R, et al: Clinical implications of *Mycobacterium kansasii* species heterogeneity: Swiss National Survey. J Clin Microbiol 41:1240–1244, 2003.
97. Falkinham JO 3rd: Nontuberculous mycobacteria in the environment. Clin Chest Med 23:529–551, 2002.
98. Lundberg BE, Davidson AJ, Burman WJ: Epidemiology of *Pneumocystis carinii* pneumonia in an era of effective prophylaxis: The relative contribution of non-adherence and drug failure. AIDS 14:2559–2566, 2000.
99. Thomas CF Jr, Limper AH: Pneumocystis pneumonia. N Engl J Med 350:2487–2498, 2004.
100. Huang L, Morris A, Limper AH, Beck JM: An Official ATS Workshop Summary: Recent advances and future directions in pneumocystis pneumonia (PCP). Proc Am Thorac Soc 3:655–664, 2006.
101. Edman JC, Kovacs JA, Masur H, et al: Ribosomal RNA sequence shows *Pneumocystis carinii* to be a member of the fungi. Nature 334:519–522, 1988.
102. Stringer SL, Stringer JR, Blase MA, et al: *Pneumocystis carinii:* Sequence from ribosomal RNA implies a close relationship with fungi. Exp Parasitol 68:450–461, 1989.
103. Gigliotti F, Haidaris PJ, Haidaris CG, et al: Further evidence of host species-specific variation in antigens of *Pneumocystis carinii* using the polymerase chain reaction. J Infect Dis 168:191–194, 1993.
104. Stringer JR, Beard CB, Miller RF, Wakefield AE: A new name (*Pneumocystis jiroveci*) for *Pneumocystis* from humans. Emerg Infect Dis 8:891–896, 2002.
105. Huang L, Murray JF: A rose is a rose: But what about *Pneumocystis* pneumonia? Int J Tuberc Lung Dis 9:1297–1298, 2005.
106. Kovacs JA, Gill VJ, Meshnick S, Masur H: New insights into transmission, diagnosis, and drug treatment of *Pneumocystis carinii* pneumonia. JAMA 286:2450–2460, 2001.
107. Morris A, Beard CB, Huang L: Update on the epidemiology and transmission of *Pneumocystis carinii*. Microbes Infect 4:95–103, 2002.
108. Pifer LL, Hughes WT, Stagno S, Woods D: *Pneumocystis carinii* infection: Evidence for high prevalence in normal and immunosuppressed children. Pediatrics 61:35–41, 1978.
109. Peglow SL, Smulian AG, Linke MJ, et al: Serologic responses to *Pneumocystis carinii* antigens in health and disease. J Infect Dis 161:296–306, 1990.
110. Vargas SL, Ponce CA, Gigliotti F, et al: Transmission of *Pneumocystis carinii* DNA from a patient with *P. carinii* pneumonia to immunocompetent contact health care workers. J Clin Microbiol 38:1536–1538, 2000.
111. Miller RF, Ambrose HE, Novelli V, Wakefield AE: Probable mother-to-infant transmission of *Pneumocystis carinii* f. sp. *hominis* infection. J Clin Microbiol 40:1555–1557, 2002.
112. Hughes WT: Natural mode of acquisition for de novo infection with *Pneumocystis carinii*. J Infect Dis 145:842–848, 1982.
113. Hughes WT, Bartley DL, Smith BM: A natural source of infection due to *Pneumocystis carinii*. J Infect Dis 147:595, 1983.
114. Soulez B, Palluault F, Cesbron JY, et al: Introduction of *Pneumocystis carinii* in a colony of SCID mice. J Protozool 38:123S–125S, 1991.
115. Gigliotti F, Harmsen AG, Wright TW: Characterization of transmission of *Pneumocystis carinii* f. sp. *muris* through immunocompetent BALB/c mice. Infect Immun 71:3852–3856, 2003.
116. Morris A: Is there anything new in *Pneumocystis jirovecii* pneumonia? Changes in *P. jirovecii* pneumonia over the course of the AIDS epidemic. Clin Infect Dis 46:634–636, 2008.
117. Phair J, Munoz A, Detels R, et al: The risk of *Pneumocystis carinii* pneumonia among men infected with human immunodeficiency virus type 1. Multicenter AIDS Cohort Study Group. N Engl J Med 322:161–165, 1990.
118. Stansell JD, Osmond DH, Charlebois E, et al: Predictors of *Pneumocystis carinii* pneumonia in HIV-infected persons. Pulmonary Complications of HIV Infection Study Group. Am J Respir Crit Care Med 155:60–66, 1997.
119. Kovacs JA, Hiemenz JW, Macher AM, et al: *Pneumocystis carinii* pneumonia: A comparison between patients with the acquired immunodeficiency syndrome and patients with other immunodeficiencies. Ann Intern Med 100:663–671, 1984.
120. Kales CP, Murren JR, Torres RA, Crocco JA: Early predictors of in-hospital mortality for *Pneumocystis carinii* pneumonia in the acquired immunodeficiency syndrome. Arch Intern Med 147:1413–1417, 1987.
121. Selwyn PA, Pumerantz AS, Durante A, et al: Clinical predictors of *Pneumocysis carinii* pneumonia, bacterial pneumonia and tuberculosis in HIV-infected patients. AIDS 12:885–893, 1998.
122. Skelly MJ, Holzman RS, Merali S: S-adenosylmethionine levels in the diagnosis of *Pneumocystis carinii* pneumonia in patients with HIV infection. Clin Infect Dis 46:467–471, 2008.
123. Tasaka S, Hasegawa N, Kobayashi S, et al: Serum indicators for the diagnosis of pneumocystis pneumonia. Chest 131:1173–1180, 2007.
124. DeLorenzo LJ, Huang CT, Maguire GP, Stone DJ: Roentgenographic patterns of *Pneumocystis carinii* pneumonia in 104 patients with AIDS. Chest 91:323–327, 1987.
125. Kennedy CA, Goetz MB: Atypical roentgenographic manifestations of *Pneumocystis carinii* pneumonia. Arch Intern Med 152:1390–1398, 1992.
126. Opravil M, Marincek B, Fuchs WA, et al: Shortcomings of chest radiography in detecting *Pneumocystis carinii* pneumonia. J Acquir Immune Defic Syndr 7:39–45, 1994.
127. Shelhamer JH, Gill VJ, Quinn TC, et al: The laboratory evaluation of opportunistic pulmonary infections. Ann Intern Med 124:585–599, 1996.
128. Huggett JF, Taylor MS, Kocjan G, et al: Development and evaluation of a real-time PCR assay for detection of *Pneumocystis jirovecii* DNA in bronchoalveolar lavage fluid of HIV-infected patients. Thorax 63:154–159, 2008.
129. Larsen HH, Huang L, Kovacs JA, et al: A prospective, blinded study of quantitative touch-down polymerase chain reaction using oral-wash samples for diagnosis of *Pneumocystis* pneumonia in HIV-infected patients. J Infect Dis 189:1679–1683, 2004.
130. Levine SJ, Masur H, Gill VJ, et al: Effect of aerosolized pentamidine prophylaxis on the diagnosis of *Pneumocystis carinii* pneumonia by induced sputum examination in patients infected with the human immunodeficiency virus. Am Rev Respir Dis 144:760–764, 1991.
131. Fahy JV, Chin DP, Schnapp LM, et al: Effect of aerosolized pentamidine prophylaxis on the clinical severity and diagnosis of *Pneumocystis carinii* pneumonia. Am Rev Respir Dis 146:844–848, 1992.
132. Levine SJ, Kennedy D, Shelhamer JH, et al: Diagnosis of *Pneumocystis carinii* pneumonia by multiple lobe, site-directed bronchoalveolar lavage with immunofluorescent monoclonal antibody staining in human immunodeficiency virus-infected patients receiving aerosolized pentamidine chemoprophylaxis. Am Rev Respir Dis 146:838–843, 1992.
133. Read CA, Cerrone F, Busseniers AE, et al: Differential lobe lavage for diagnosis of acute *Pneumocystis carinii* pneumonia in

patients receiving prophylactic aerosolized pentamidine therapy. Chest 103:1520–1523, 1993.
134. Huang L, Crothers K, Atzori C, et al: Dihydropteroate synthase gene mutations in *Pneumocystis* and sulfa resistance. Emerg Infect Dis 10:1721–1728, 2004.
135. Stein CR, Poole C, Kazanjian P, Meshnick SR: Sulfa use, dihydropteroate synthase mutations, and *Pneumocystis jirovecii* pneumonia. Emerg Infect Dis 10:1760–1765, 2004.
136. Koval CE, Gigliotti F, Nevins D, Demeter LM: Immune reconstitution syndrome after successful treatment of *Pneumocystis carinii* pneumonia in a man with human immunodeficiency virus type 1 infection. Clin Infect Dis 35:491–493, 2002.
137. Consensus statement on the use of corticosteroids as adjunctive therapy for pneumocystis pneumonia in the acquired immunodeficiency syndrome. The National Institutes of Health–University of California Expert Panel for Corticosteroids as Adjunctive Therapy for Pneumocystis Pneumonia. N Engl J Med 323:1500–1504, 1990.
138. Wachter RM, Luce JM, Turner J, et al: Intensive care of patients with the acquired immunodeficiency syndrome: Outcome and changing patterns of utilization. Am Rev Respir Dis 134:891–896, 1986.
139. Morris A, Wachter RM, Luce J, et al: Improved survival with highly active antiretroviral therapy in HIV-infected patients with severe *Pneumocystis carinii* pneumonia. AIDS 17:73–80, 2003.
140. Miller RF, Allen E, Copas A, et al: Improved survival for HIV infected patients with severe *Pneumocystis jirovecii* pneumonia is independent of highly active antiretroviral therapy. Thorax 61:716–721, 2006.
141. Crothers K, Huang L: Recurrence of *Pneumocystis carinii* pneumonia in an HIV-infected patient: Apparent selective immune reconstitution after initiation of antiretroviral therapy. HIV Med 4:346–349, 2003.
142. Stansell JD: Pulmonary fungal infections in HIV-infected persons. Semin Respir Infect 8:116–123, 1993.
143. Mirza SA, Phelan M, Rimland D, et al: The changing epidemiology of cryptococcosis: An update from population-based active surveillance in 2 large metropolitan areas, 1992–2000. Clin Infect Dis 36:789–794, 2003.
144. Dromer F, Mathoulin-Pelissier S, Fontanet A, et al: Epidemiology of HIV-associated cryptococcosis in France (1985–2001): Comparison of the pre- and post-HAART eras. AIDS 18:555–562, 2004.
145. Chuck SL, Sande MA: Infections with *Cryptococcus neoformans* in the acquired immunodeficiency syndrome. N Engl J Med 321:794–799, 1989.
146. Zuger A, Louie E, Holzman RS, et al: Cryptococcal disease in patients with the acquired immunodeficiency syndrome: Diagnostic features and outcome of treatment. Ann Intern Med 104:234–240, 1986.
147. Jarvis JN, Harrison TS: Pulmonary cryptococcosis. Semin Respir Crit Care Med 29:141–150, 2008.
148. French N, Gray K, Watera C, et al: Cryptococcal infection in a cohort of HIV-1-infected Ugandan adults. AIDS 16:1031–1038, 2002.
149. Batungwanayo J, Taelman H, Bogaerts J, et al: Pulmonary cryptococcosis associated with HIV-1 infection in Rwanda: A retrospective study of 37 cases. AIDS 8:1271–1276, 1994.
150. Stansell JD: Fungal disease in HIV-infected persons: Cryptococcosis, histoplasmosis, and coccidioidomycosis. J Thorac Imaging 6:28–35, 1991.
151. Meyohas MC, Roux P, Bollens D, et al: Pulmonary cryptococcosis: Localized and disseminated infections in 27 patients with AIDS. Clin Infect Dis 21:628–633, 1995.
152. Douketis JD, Kesten S: Miliary pulmonary cryptococcosis in a patient with the acquired immunodeficiency syndrome. Thorax 48:402–403, 1993.
153. Miller KD, Mican JA, Davey RT: Asymptomatic solitary pulmonary nodules due to *Cryptococcus neoformans* in patients infected with human immunodeficiency virus. Clin Infect Dis 23:810–812, 1996.
154. Lacomis JM, Costello P, Vilchez R, Kusne S: The radiology of pulmonary cryptococcosis in a tertiary medical center. J Thorac Imaging 16:139–148, 2001.
155. Newman TG, Soni A, Acaron S, Huang CT: Pleural cryptococcosis in the acquired immune deficiency syndrome. Chest 91:459–461, 1987.
156. Torre D, Martegani R, Speranza F, et al: Pulmonary cryptococcosis presenting as pneumothorax in a patient with AIDS. Clin Infect Dis 21:1524–1525, 1995.
157. Baughman RP, Rhodes JC, Dohn MN, et al: Detection of cryptococcal antigen in bronchoalveolar lavage fluid: A prospective study of diagnostic utility. Am Rev Respir Dis 145:1226–1229, 1992.
158. Saag MS, Graybill RJ, Larsen RA, et al: Practice guidelines for the management of cryptococcal disease. Infectious Diseases Society of America. Clin Infect Dis 30:710–718, 2000.
159. Jenny-Avital ER, Abadi M: Immune reconstitution cryptococcosis after initiation of successful highly active antiretroviral therapy. Clin Infect Dis 35:e128–e133, 2002.
160. Wheat LJ, Kauffman CA: Histoplasmosis. Infect Dis Clinics North Am 17:1–19, vii, 2003.
161. Huang CT, McGarry T, Cooper S, et al: Disseminated histoplasmosis in the acquired immunodeficiency syndrome: Report of five cases from a nonendemic area. Arch Intern Med 147:1181–1184, 1987.
162. Wheat LJ, Connolly-Stringfield PA, Baker RL, et al: Disseminated histoplasmosis in the acquired immune deficiency syndrome: Clinical findings, diagnosis and treatment, and review of the literature. Medicine 69:361–374, 1990.
163. Sarosi GA, Johnson PC: Disseminated histoplasmosis in patients infected with human immunodeficiency virus. Clin Infect Dis 14(Suppl 1):S60–S67, 1992.
164. Conces DJ Jr, Stockberger SM, Tarver RD, Wheat LJ: Disseminated histoplasmosis in AIDS: Findings on chest radiographs. AJR Am J Roentgenol 160:15–19, 1993.
165. Wheat LJ, Connolly-Stringfield P, Kohler RB, et al: *Histoplasma capsulatum* polysaccharide antigen detection in diagnosis and management of disseminated histoplasmosis in patients with acquired immunodeficiency syndrome. Am J Med 87:396–400, 1989.
166. Wheat J, Sarosi G, McKinsey D, et al: Practice guidelines for the management of patients with histoplasmosis. Infectious Diseases Society of America. Clin Infect Dis 30:688–695, 2000.
167. Chiller TM, Galgiani JN, Stevens DA: Coccidioidomycosis. Infect Dis Clin North Am 17:41–57, 2003.
168. Singh VR, Smith DK, Lawerence J, et al: Coccidioidomycosis in patients infected with human immunodeficiency virus: Review of 91 cases at a single institution. Clin Infect Dis 23:563–568, 1996.
169. Woods CW, McRill C, Plikaytis BD, et al: Coccidioidomycosis in human immunodeficiency virus-infected persons in Arizona, 1994–1997: Incidence, risk factors, and prevention. J Infect Dis 181:1428–1434, 2000.
170. Fish DG, Ampel NM, Galgiani JN, et al: Coccidioidomycosis during human immunodeficiency virus infection: A review of 77 patients. Medicine 69:384–391, 1990.
171. Galgiani JN, Ampel NM: Coccidioidomycosis in human immunodeficiency virus-infected patients. J Infect Dis 162:1165–1169, 1990.
172. Marr KA, Patterson T, Denning D: Aspergillosis: Pathogenesis, clinical manifestations, and therapy. Infect Dis Clin North Am 16:875–894, vi, 2002.
173. Denning DW, Follansbee SE, Scolaro M, et al: Pulmonary aspergillosis in the acquired immunodeficiency syndrome. N Engl J Med 324:654–662, 1991.
174. Holding KJ, Dworkin MS, Wan PC, et al: Aspergillosis among people infected with human immunodeficiency virus: Incidence and survival. Adult and Adolescent Spectrum of HIV Disease Project. Clin Infect Dis 31:1253–1257, 2000.
175. Pursell KJ, Telzak EE, Armstrong D: *Aspergillus* species colonization and invasive disease in patients with AIDS. Clin Infect Dis 14:141–148, 1992.
176. Klapholz A, Salomon N, Perlman DC, Talavera W: Aspergillosis in the acquired immunodeficiency syndrome. Chest 100:1614–1618, 1991.
177. Mylonakis E, Barlam TF, Flanigan T, Rich JD: Pulmonary aspergillosis and invasive disease in AIDS: Review of 342 cases. Chest 114:251–262, 1998.

178. Staples CA, Kang EY, Wright JL, et al: Invasive pulmonary aspergillosis in AIDS: Radiographic, CT, and pathologic findings. Radiology 196:409–414, 1995.
179. Thompson GR 3rd, Patterson TF: Pulmonary aspergillosis. Semin Respir Crit Care Med 29:103–110, 2008.
180. Pappas PG, Pottage JC, Powderly WG, et al: Blastomycosis in patients with the acquired immunodeficiency syndrome. Ann Intern Med 116:847–853, 1992.
181. Bradsher RW, Chapman SW, Pappas PG: Blastomycosis. Infect Dis Clin North Am 17:21–40, vii, 2003.
182. Supparatpinyo K, Chiewchanvit S, Hirunsri P, et al: *Penicillium marneffei* infection in patients infected with human immunodeficiency virus. Clin Infect Dis 14:871–874, 1992.
183. Hung CC, Hsueh PR, Chen MY, et al: Invasive infection caused by *Penicillium marneffei:* An emerging pathogen in Taiwan. Clin Infect Dis 26:202–203, 1998.
184. Supparatpinyo K, Khamwan C, Baosoung V, et al: Disseminated *Penicillium marneffei* infection in southeast Asia. Lancet 344:110–113, 1994.
185. Sirisanthana T, Supparatpinyo K, Perriens J, Nelson KE: Amphotericin B and itraconazole for treatment of disseminated *Penicillium marneffei* infection in human immunodeficiency virus-infected patients. Clin Infect Dis 26:1107–1110, 1998.
186. Chariyalertsak S, Supparatpinyo K, Sirisanthana T, Nelson KE: A controlled trial of itraconazole as primary prophylaxis for systemic fungal infections in patients with advanced human immunodeficiency virus infection in Thailand. Clin Infect Dis 34:277–284, 2002.
187. Welch K, Finkbeiner W, Alpers CE, et al: Autopsy findings in the acquired immune deficiency syndrome. JAMA 252:1152–1159, 1984.
188. Jacobson MA, Mills J, Rush J, et al: Morbidity and mortality of patients with AIDS and first-episode *Pneumocystis carinii* pneumonia unaffected by concomitant pulmonary cytomegalovirus infection. Am Rev Respir Dis 144:6–9, 1991.
189. Rodriguez-Barradas MC, Stool E, Musher DM, et al: Diagnosing and treating cytomegalovirus pneumonia in patients with AIDS. Clin Infect Dis 23:76–81, 1996.
190. Salomon N, Gomez T, Perlman DC, et al: Clinical features and outcomes of HIV-related cytomegalovirus pneumonia. AIDS 11:319–324, 1997.
191. Mann M, Shelhamer JH, Masur H, et al: Lack of clinical utility of bronchoalveolar lavage cultures for cytomegalovirus in HIV infection. Am J Respir Crit Care Med 155:1723–1728, 1997.
192. Ramsey PG, Fife KH, Hackman RC, et al: Herpes simplex virus pneumonia: Clinical, virologic, and pathologic features in 20 patients. Ann Intern Med 97:813–820, 1982.
193. Gnann JW Jr: Varicella-zoster virus: Atypical presentations and unusual complications. J Infect Dis 186(Suppl 1):S91–S98, 2002.
194. Andiman WA, Eastman R, Martin K, et al: Opportunistic lymphoproliferations associated with Epstein-Barr viral DNA in infants and children with AIDS. Lancet 2:1390–1393, 1985.
195. Safrin S, Rush JD, Mills J: Influenza in patients with human immunodeficiency virus infection. Chest 98:33–37, 1990.
196. Oksenhendler E, Cadranel J, Sarfati C, et al: *Toxoplasma gondii* pneumonia in patients with the acquired immunodeficiency syndrome. Am J Med 88:18N–21N, 1990.
197. Rabaud C, May T, Lucet JC, et al: Pulmonary toxoplasmosis in patients infected with human immunodeficiency virus: A French National Survey. Clin Infect Dis 23:1249–1254, 1996.
198. Goodman PC, Schnapp LM: Pulmonary toxoplasmosis in AIDS. Radiology 184:791–793, 1992.
199. Pomeroy C, Filice GA: Pulmonary toxoplasmosis: A review. Clin Infect Dis 14:863–870, 1992.
200. Karp CL, Neva FA: Tropical infectious diseases in human immunodeficiency virus-infected patients. Clin Infect Dis 28:947–963, 1999.
201. McCombs SB, Dworkin MS, Wan PC: Helminth infections in HIV-infected persons in the United States, 1990–1999. Clin Infect Dis 30:241–242, 2000.
202. Clavel A, Arnal AC, Sanchez EC, et al: Respiratory cryptosporidiosis: Case series and review of the literature. Infection 24:341–346, 1996.
203. Schainberg L, Scheinberg MA: Recovery of *Strongyloides stercoralis* by bronchoalveolar lavage in a patient with acquired immunodeficiency syndrome. Am J Med 87:486, 1989.
204. Makris AN, Sher S, Bertoli C, Latour MG: Pulmonary strongyloidiasis: An unusual opportunistic pneumonia in a patient with AIDS. AJR Am J Roentgenol 161:545–547, 1993.
205. Ferreira MS, Nishioka Sde A, Borges AS, et al: Strongyloidiasis and infection due to human immunodeficiency virus: 25 cases at a Brazilian teaching hospital, including seven cases of hyperinfection syndrome. Clin Infect Dis 28:154–155, 1999.
206. Viney ME, Brown M, Omoding NE, et al: Why does HIV infection not lead to disseminated strongyloidiasis? J Infect Dis 190:2175–2180, 2004.
207. Crum NF, Riffenburgh RH, Wegner S, et al: Comparisons of causes of death and mortality rates among HIV-infected persons: Analysis of the pre-, early, and late HAART (highly active antiretroviral therapy) eras. J Acquir Immune Defic Syndr 41:194–200, 2006.
208. Mocroft A, Kirk O, Clumeck N, et al: The changing pattern of Kaposi sarcoma in patients with HIV, 1994–2003: the EuroSIDA Study. Cancer 100:2644–2654, 2004.
209. Franceschi S, Maso LD, Rickenbach M, et al: Kaposi sarcoma incidence in the Swiss HIV Cohort Study before and after highly active antiretroviral therapy. Br J Cancer 99:800–804, 2008.
210. Dukers NH, Rezza G: Human herpesvirus 8 epidemiology: What we do and do not know. AIDS 17:1717–1730, 2003.
211. Biggar RJ, Burnett W, Mikl J, Nasca P: Cancer among New York men at risk of acquired immunodeficiency syndrome. Int J Cancer 43:979–985, 1989.
212. Chang Y, Cesarman E, Pessin MS, et al: Identification of herpesvirus-like DNA sequences in AIDS-associated Kaposi's sarcoma. Science 266:1865–1869, 1994.
213. Moore PS, Chang Y: Detection of herpesvirus-like DNA sequences in Kaposi's sarcoma in patients with and without HIV infection. N Engl J Med 332:1181–1185, 1995.
214. Huang L, Schnapp LM, Gruden JF, et al: Presentation of AIDS-related pulmonary Kaposi's sarcoma diagnosed by bronchoscopy. Am J Respir Crit Care Med 153:1385–1390, 1996.
215. Gruden JF, Huang L, Webb WR, et al: AIDS-related Kaposi sarcoma of the lung: Radiographic findings and staging system with bronchoscopic correlation. Radiology 195:545–552, 1995.
216. Sullivan RJ, Pantanowitz L, Casper C, et al: HIV/AIDS: Epidemiology, pathophysiology, and treatment of Kaposi sarcoma-associated herpesvirus disease: Kaposi sarcoma, primary effusion lymphoma, and multicentric Castleman disease. Clin Infect Dis 47:1209–1215, 2008.
217. Martin-Carbonero L, Palacios R, Valencia E, et al: Long-term prognosis of HIV-infected patients with Kaposi sarcoma treated with pegylated liposomal doxorubicin. Clin Infect Dis 47:410–417, 2008.
218. Palmieri C, Dhillon T, Thirlwell C, et al: Pulmonary Kaposi sarcoma in the era of highly active antiretroviral therapy. HIV Med 7:291–293, 2006.
219. Carbone A, Gloghini A: AIDS-related lymphomas: From pathogenesis to pathology. Br J Haematol 130:662–670, 2005.
220. Polesel J, Clifford GM, Rickenbach M, et al: Non-Hodgkin lymphoma incidence in the Swiss HIV Cohort Study before and after highly active antiretroviral therapy. AIDS 22:301–306, 2008.
221. Tirelli U, Spina M, Gaidano G, et al: Epidemiological, biological and clinical features of HIV-related lymphomas in the era of highly active antiretroviral therapy. AIDS 14:1675–1688, 2000.
222. Eisner MD, Kaplan LD, Herndier B, Stulbarg MS: The pulmonary manifestations of AIDS-related non-Hodgkin's lymphoma. Chest 110:729–736, 1996.
223. Keys TC, Judson MA, Reed CE, Sahn SA: Endobronchial HIV associated lymphoma. Thorax 49:525–526, 1994.
224. Soubani AO, Michelson MK, Karnik A: Pleural fluid findings in patients with the acquired immunodeficiency syndrome: Correlation with concomitant pulmonary disease. South Med J 92:400–403, 1999.
225. Lim ST, Karim R, Tulpule A, et al: Prognostic factors in HIV-related diffuse large-cell lymphoma: Before versus after highly active antiretroviral therapy. J Clin Oncol 23:8477–8482, 2005.

226. Mbulaiteye SM, Biggar RJ, Goedert JJ, Engels EA: Pleural and peritoneal lymphoma among people with AIDS in the United States. J Acquir Immune Defic Syndr 29:418–421, 2002.
227. Chen YB, Rahemtullah A, Hochberg E: Primary effusion lymphoma. Oncologist 12:569–576, 2007.
228. Hengge UR, Ruzicka T, Tyring SK, et al: Update on Kaposi's sarcoma and other HHV8 associated diseases. Part 2: Pathogenesis, Castleman's disease, and pleural effusion lymphoma. Lancet Infect Dis 2:344–352, 2002.
229. Guihot A, Couderc LJ, Agbalika F, et al: Pulmonary manifestations of multicentric Castleman's disease in HIV infection: A clinical, biological and radiological study. Eur Respir J 26:118–125, 2005.
230. Hillier JC, Shaw P, Miller RF, et al: Imaging features of multicentric Castleman's disease in HIV infection. Clin Radiol 59:596–601, 2004.
231. Kirk GD, Merlo C, O'Driscoll P, et al: HIV infection is associated with an increased risk for lung cancer, independent of smoking. Clin Infect Dis 45:103–110, 2007.
232. Engels EA, Brock MV, Chen J, et al: Elevated incidence of lung cancer among HIV-infected individuals. J Clin Oncol 24:1383–1388, 2006.
233. Bower M, Powles T, Nelson M, et al: HIV-related lung cancer in the era of highly active antiretroviral therapy. AIDS 17:371–375, 2003.
234. Powles T, Thirwell C, Newsom-Davis T, et al: Does HIV adversely influence the outcome in advanced non-small-cell lung cancer in the era of HAART? Br J Cancer 89:457–459, 2003.
235. Johnson CC, Wilcosky T, Kvale P, et al: Cancer incidence among an HIV-infected cohort. Pulmonary Complications of HIV Infection Study Group. Am J Epidemiol 146:470–475, 1997.
236. Opravil M, Pechere M, Speich R, et al: HIV-associated primary pulmonary hypertension: A case control study. Swiss HIV Cohort Study. Am J Respir Crit Care Med 155:990–995, 1997.
237. Sitbon O, Lascoux-Combe C, Delfraissy JF, et al: Prevalence of HIV-related pulmonary arterial hypertension in the current antiretroviral therapy era. Am J Respir Crit Care Med 177:108–113, 2008.
238. Hsue PY, Deeks SG, Farah HH, et al: Role of HIV and human herpesvirus-8 infection in pulmonary arterial hypertension. AIDS 22:825–833, 2008.
239. Petitpretz P, Brenot F, Azarian R, et al: Pulmonary hypertension in patients with human immunodeficiency virus infection: Comparison with primary pulmonary hypertension. Circulation 89:2722–2727, 1994.
240. Mehta NJ, Khan IA, Mehta RN, Sepkowitz DA: HIV-Related pulmonary hypertension: Analytic review of 131 cases. Chest 118:1133–1141, 2000.
241. Aguilar RV, Farber HW: Epoprostenol (prostacyclin) therapy in HIV-associated pulmonary hypertension. Am J Respir Crit Care Med 162:1846–1850, 2000.
242. Ghofrani HA, Friese G, Discher T, et al: Inhaled iloprost is a potent acute pulmonary vasodilator in HIV-related severe pulmonary hypertension. Eur Respir J 23:321–326, 2004.
243. Wong AR, Rasool AH, Abidin NZ, et al: Sildenafil as treatment for human immunodeficiency virus-related pulmonary hypertension in a child. J Paediatr Child Health 42:147–148, 2006.
244. Barbaro G, Lucchini A, Pellicelli AM, et al: Highly active antiretroviral therapy compared with HAART and bosentan in combination in patients with HIV-associated pulmonary hypertension. Heart 92:1164–1166, 2006.
245. Rosen MJ, Lou Y, Kvale PA, et al: Pulmonary function tests in HIV-infected patients without AIDS. Pulmonary Complications of HIV Infection Study Group. Am J Respir Crit Care Med 152:738–745, 1995.
246. Morris AM, Luang L, Bacchetti P, et al: Permanent declines in pulmonary function following pneumonia in human immunodeficiency virus-infected persons. The Pulmonary Complications of HIV Infection Study Group. Am J Respir Crit Care Med 162:612–616, 2000.
247. Poirier CD, Inhaber N, Lalonde RG, Ernst P: Prevalence of bronchial hyperresponsiveness among HIV-infected men. Am J Respir Crit Care Med 164:542–545, 2001.
247a. George MP, Kannass M, Hung L, et al: Respiratory symptoms and airway obstruction in HIV-infected subjects in the HAART era. PLoS One 4:e6328, 2009.
248. O'Donnell CR, Bader MB, Zibrak JD, et al: Abnormal airway function in individuals with the acquired immunodeficiency syndrome. Chest 94:945–948, 1988.
249. Lin RY, Lazarus TS: Asthma and related atopic disorders in outpatients attending an urban HIV clinic. Ann Allergy Asthma Immunol 74:510–515, 1995.
250. Foster SB, McIntosh K, Thompson B, et al: Increased incidence of asthma in HIV-infected children treated with highly active antiretroviral therapy in the National Institutes of Health Women and Infants Transmission Study. J Allergy Clin Immunol 122:159–165, 2008.
251. Verghese A, al-Samman M, Nabhan D, et al: Bacterial bronchitis and bronchiectasis in human immunodeficiency virus infection. Arch Intern Med 154:2086–2091, 1994.
252. Bard M, Couderc LJ, Saimot AG, et al: Accelerated obstructive pulmonary disease in HIV infected patients with bronchiectasis. Eur Respir J 11:771–775, 1998.
253. Diaz PT, King MA, Pacht ER, et al: Increased susceptibility to pulmonary emphysema among HIV-seropositive smokers. Ann Intern Med 132:369–372, 2000.
254. Crothers K, Butt AA, Gibert CL, et al: Increased COPD among HIV-positive compared to HIV-negative veterans. Chest 130:1326–1333, 2006.
255. St Germain RM, Yigit S, Wells L, et al: Cushing syndrome and severe adrenal suppression caused by fluticasone and protease inhibitor combination in an HIV-infected adolescent. AIDS Patient Care STDS 21:373–377, 2007.
256. Calverley PM, Anderson JA, Celli B, et al: Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. N Engl J Med 356:775–789, 2007.
257. Innes AL, Huang L, Nishimura SL: Resolution of lymphocytic interstitial pneumonitis in an HIV infected adult after treatment with HAART. Sex Transm Infect 80:417–418, 2004.
258. Oldham SA, Castillo M, Jacobson FL, et al: HIV-associated lymphocytic interstitial pneumonia: Radiologic manifestations and pathologic correlation. Radiology 170:83–87, 1989.
259. Carignan S, Staples CA, Muller NL: Intrathoracic lymphoproliferative disorders in the immunocompromised patient: CT findings. Radiology 197:53–58, 1995.
260. Dufour V, Wislez M, Bergot E, et al: Improvement of symptomatic human immunodeficiency virus-related lymphoid interstitial pneumonia in patients receiving highly active antiretroviral therapy. Clin Infect Dis 36:e127–e130, 2003.
261. Sattler F, Nichols L, Hirano L, et al: Nonspecific interstitial pneumonitis mimicking *Pneumocystis carinii* pneumonia. Am J Respir Crit Care Med 156:912–917, 1997.
262. Simmons JT, Suffredini AF, Lack EE, et al: Nonspecific interstitial pneumonitis in patients with AIDS: Radiologic features. AJR Am J Roentgenol 149:265–268, 1987.
263. Morris DG, Jasmer RM, Huang L, et al: Sarcoidosis following HIV infection: Evidence for $CD4^+$ lymphocyte dependence. Chest 124:929–935, 2003.
264. Foulon G, Wislez M, Naccache JM, et al: Sarcoidosis in HIV-infected patients in the era of highly active antiretroviral therapy. Clin Infect Dis 38:418–425, 2004.
265. Naccache JM, Antoine M, Wislez M, et al: Sarcoid-like pulmonary disorder in human immunodeficiency virus-infected patients receiving antiretroviral therapy. Am J Respir Crit Care Med 159:2009–2013, 1999.
266. DeSimone JA, Pomerantz RJ, Babinchak TJ: Inflammatory reactions in HIV-1-infected persons after initiation of highly active antiretroviral therapy. Ann Intern Med 133:447–454, 2000.
267. French MA, Price P, Stone SF: Immune restoration disease after antiretroviral therapy. AIDS 18:1615–1627, 2004.
268. Lortholary O, Fontanet A, Memain N, et al: Incidence and risk factors of immune reconstitution inflammatory syndrome complicating HIV-associated cryptococcosis in France. AIDS 19:1043–1049, 2005.
269. Lawn SD, Myer L, Bekker LG, Wood R: Tuberculosis-associated immune reconstitution disease: Incidence, risk factors and impact in an antiretroviral treatment service in South Africa. AIDS 21:335–341, 2007.

CHAPTER 81

PULMONARY COMPLICATIONS OF STEM CELL AND SOLID ORGAN TRANSPLANTATION

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INTRODUCTION

INFECTIOUS COMPLICATIONS
Bacterial Infections
Viral Infections
Fungal Infections

NONINFECTIOUS COMPLICATIONS

EARLY COMPLICATIONS
Pulmonary Edema and Respiratory Failure
Venous Thromboembolic Disease
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LATE COMPLICATIONS
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INTRODUCTION

Transplantation of human organs and tissues is an accepted option for otherwise untreatable end-stage diseases of renal, thoracic, gastrointestinal, and hematologic origin. With the development of advanced transplantation techniques and increased organ donation awareness, the number of solid organ transplants has increased dramatically. According to 2009 data from the Organ Procurement and Transplantation Network, over 486,000 solid organ transplants have been performed since 1988 in the United States. Pharmacologic advances for prophylaxis and prevention of rejection have also helped increase patient survival. Because of chronic immunosuppression, these patients are at increased risk of infection and drug toxicity, as well as pulmonary complications from their underlying disease or the transplant itself. For example, the incidence of pulmonary toxicities following hematopoietic stem cell transplantation has been estimated to be anywhere from 2% to 70%, varying with the specific patient population being analyzed, details of the individual therapeutic regimens, and the criteria used to define lung toxicity.[1,1a]

The aim of this chapter is to review the infectious and noninfectious complications of solid and hematologic transplantation as well as the diagnostic and therapeutic options available for this group of patients.

INFECTIOUS COMPLICATIONS

Despite the practice of prophylaxis against opportunistic pathogens in the posttransplantation period and better antibiotics available for resistant organisms, infection after transplantation remains a major concern. Infections in the posttransplantation patient range from common pathogens found in the community (although the severity of disease may be greater), to health care–associated pathogens and opportunistic infections. Signs and symptoms of infection in immunosuppressed individuals may complicate the clinical picture, since fundamental immunologic processes have been altered by these drugs and symptoms of rejection or reactions to medications can mimic an infectious process. For example, fever is a common sign in posttransplantation patients, but its correlation with infection is not as well defined. Chang and colleagues reported that, in liver transplant patients, fever was due to infection in 78% of cases. Of infectious causes for fever, 80% were due to bacterial infections and 20% due to viruses. None of these febrile illnesses were shown to be due to fungi.[2]

Due to direct exposure to the environment, the lung is particularly susceptible to infections. For instance, infection remain the major cause of death in patients with kidney and kidney-pancreas transplants. In a recent study from a single institution following kidney-pancreas transplantation, bacterial pulmonary infection occurred

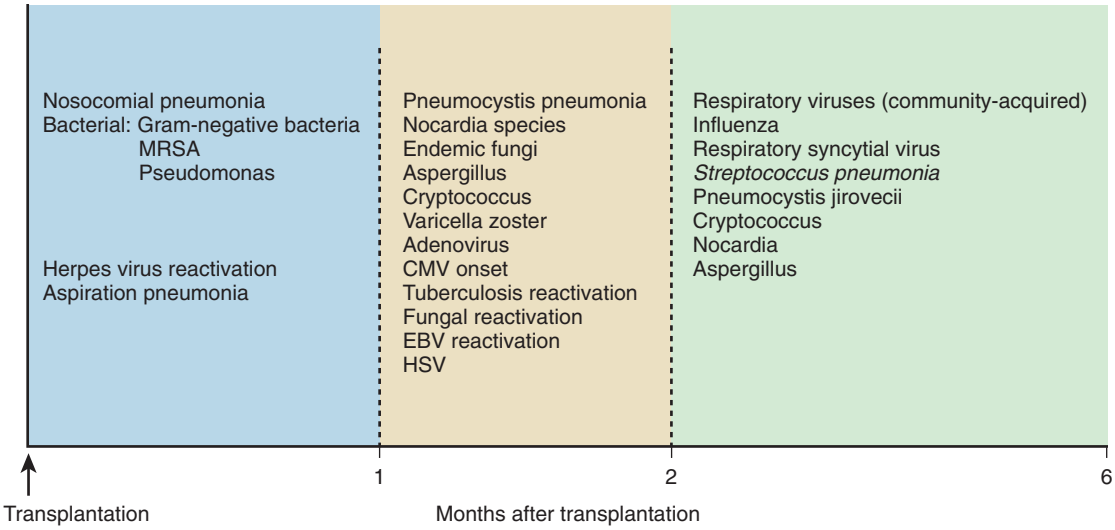

FIGURE 81-1 ■ Timing of infections in the posttransplantation period. CMV, cytomegalovirus; EBV, Epstein-Barr virus; HSV, herpes simplex virus; MRSA, methicillin-resistant *Staphylococcus aureus*.

in 25% of patients. The pathogens identified were *Pseudomonas aeruginosa, Klebsiella* species, *Staphylococcus warneri,* and *Aerococcus viridans.*[3] Additionally, a recent study from Stanford University evaluated 620 consecutive heart transplant patients with 1073 infectious episodes. Lung infections in this cohort accounted for 28% of all infections. Pulmonary infection was the cause of death for 18% of patients in the early (<30 days) posttransplantation period and 33% of those in the late (>30 days) posttransplantation period.[4]

Infection in posttransplantation patients depends on the degree of immunosuppression as well as individual exposure to the pathogen. In addition, the risk of infection differs in individual patients. There is a higher risk of infection in patients who are taking pulsed-dose corticosteroids as well as with prolonged intubation, wound dehiscence, high risk of rejection, early graft-versus-host disease, latent infection in the recipient or donor, use of plasmapheresis, history of bleeding, or prolonged use of surgical, vascular, or urinary catheters. Numerous risk factors have been identified that may predispose to the development of pulmonary complications following stem cell transplantation (SCT). Many of these risk factors are interrelated. For example, the development of chronic graft-versus-host disease increases the risk for the subsequent development of bronchiolitis obliterans.[5] Additionally, multivariable analysis showed that age greater than 60, pretransplantation FEV_1/FVC less than 80%, respiratory virus infection, and quiescent or progressive-onset chronic graft-versus-host disease were all associated with the development of airflow obstruction.[6] Furthermore, the presence of airflow obstruction significantly and independently demonstrated a 2.3-fold increased risk for mortality following SCT.[6]

The lungs are the most common organs affected by infections in lung and heart transplant patients, the most common cause of infectious death after hematopoietic SCT, and the second most common site of infectious complication in liver transplant patients. Renal transplant patients have the lowest incidence of infections, probably because of the low level of immunosuppression needed. The risk and type of infection depends on the time it is acquired relative to the date of transplantation. In the immediate postoperative period (<30 days), the most common organisms are gram-positive and gram-negative bacteria such as *Staphylococcus aureus* and *P. aeruginosa.* The second time line is from 1 to 6 months after transplantation—a time when intense immunosuppression is given to avoid acute rejection and the patient is once again exposed to the community environment. Opportunistic organisms such as *Aspergillus, Pneumocystis jirovecii,* and cytomegalovirus (CMV) are particularly important. The third stage of the time line is after 6 months of immunosuppression, when the immunosuppressive drug levels are decreased. At this time, opportunistic organisms become less prominent and community-acquired organisms once again become the major cause of pulmonary infection. Figure 81-1 lists the major pathogens for pulmonary infection in the posttransplantation period.

Bacterial Infections

The incidence of bacterial pneumonia is dependent on different factors. Infection following a previous insult or secondary to a latent infection in the donor organ is a particular problem in lung transplantation. For example, infection may occur in patients with a history of latent tuberculosis or fungal disease or recipients with infections from other sites, such as patients with cystic fibrosis colonized with chronic sinus pathogens. Also, insults to the lung during the operative procedure itself may occur, such as superinfection following manipulation of the upper abdomen in liver transplantation.

Bacterial pneumonias are of particular importance in the immediate postoperative phase. Nosocomial organisms are the most common pathogens identified in this period. The incidence of pneumonia depends on the

surgical technique used, site of transplantation (upper abdominal manipulation leads to highest risk of infection),[7] increased transfusion of blood products, increasing age,[8] choice of immunosuppressive therapy,[9] and prolonged intubation.[7]

In general, the most commonly reported organisms are gram-negative organisms, such as *Pseudomonas, Klebsiella, Escherichia, Legionella, Acinetobacter,* and *Stenotrophomonas.* Important nosocomial gram-positive bacteria include *Staphylococcus, Corynebacterium,* and *Enterococcus.* Anaerobic infection appears rare.[7] In a cohort of orthotopic liver transplant recipients, the incidence of bacterial pneumonia was 45%, with gram-negative organisms accounting for 93% of all cases. In this group of patients, *P. aeruginosa* was the most common gram-negative organism.[10] Lung transplant patients who develop bronchiolitis obliterans with bronchiectasis have a higher risk of *P. aeruginosa* infection.[7] In renal transplantation, which is the most common type of solid organ transplantation performed, bacterial infection has been reported to be most commonly associated with *S. aureus, Streptococcus pneumoniae, P. aeruginosa, Acinetobacter* species, *Haemophilus influenzae,* and *Klebsiella pneumoniae.* Lenner and coworkers reported that the most common pulmonary complication following cardiac transplantation was pneumonia (17.0%), followed by bronchitis (9.4%).[9] Of the patients with post–cardiac transplantation pneumonias, the causative pathogens were bacteria in half of the patients. Community pathogens can emerge after the immediate posttransplantation period as well. *Haemophilus influenzae* is the most common isolate, followed by *S. pneumoniae* and *Legionella* species.[7]

The extent to which bacterial bronchopneumonia is present in SCT patients is not known but has been estimated to be 2% by open lung biopsy or greater than 25% when documented at autopsy.[11] Bacterial pathogens can account for over 50% of pulmonary infections and include *P. aeruginosa, S. aureus, Mycobacterium tuberculosis,* atypical mycobacterial infection, *Escherichia coli, Xanthomonas maltophilia, K. pneumoniae, Serratia* species, *Legionella* species, *Enterococcus faecium,* and *Mycoplasma* species.[12,13] In one series, staphylococcal species accounted for 24% and streptococcal species accounted for 13% of all pulmonary organisms isolated.[14] Althought the prevalence of *M. tuberculosis* infection following SCT has been estimated to be about 0.6%, delayed diagnoses due to slow growth of the bacterium can lead to delays in initiating therapy.[15] Particularly in endemic areas, a high index of suspicion should be maintained.

Viral Infections

In a recent study of 152 heart, kidney, and liver transplant recipients, 81 episodes of infection due to respiratory viruses were isolated in 67 patients.[16] Most cases of viral infection were present after 1 year (87%). Only 3% were complicated by pneumonia. No specific risk factors, including gender, age, type of immunosuppression, number of cohabitants, or contact with children, were identified. Heart recipients had more episodes and more complications due to respiratory viral infections compared with liver and kidney recipients.

Cytomegalovirus infection remains the most common etiology for viral illness in solid organ transplant recipients. Most people are infected with CMV early in life. In industrialized countries, the prevalence of CMV seropositivity is approximately 50%. Up to two thirds of transplant recipients have latent CMV infection. Primary infection occurs due to transmission in seronegative recipients, sometimes from the donor, although this is much less common in recent years due to preoperative screening. This form of primary infection is associated with a higher degree of recurrence, higher risk of dissemination, and higher mortality.[17] CMV can also be reactivated from a preoperative seropositive recipient with immunosuppression or by superinfection with a new strain of CMV in a previously seropositive patient in the posttransplantation period.[18] Cytomegalovirus infection causes immediate and delayed complications in this group of patients. Direct effects include a viral syndrome with symptoms such as generalized malaise, fever, and myalgias or a more specific tissue-invading picture with pneumonitis, gastritis, colitis, or hepatitis. These effects are often associated with high viral loads. Indirect effects are caused by a release of cytokines that may lead to allograft injury and rejection. Since a substantial number of CMV infections are asymptomatic, CMV disease can become chronic with low levels of viremia existing for prolonged periods of time that are related to the indirect effects of infection. Antilymphocyte preparations (e.g., OKT3) are clearly associated with an increased risk of CMV disease, as is the use of methylprednisolone.[18a] Cytomegalovirus infection is also associated with an increase in the risk of further complications, including Epstein-Barr virus–associated posttransplantation lymphoproliferative disorder, vasculopathy in heart allograft recipients, and bronchiolitis obliterans syndrome in lung allograft recipients.

Symptoms of CMV pneumonitis range from mild dyspnea to respiratory failure. Signs and symptoms are very similar to rejection. The diagnosis of CMV pneumonitis is usually based on symptoms, diffuse infiltrates on radiologic imaging, and a positive viral culture in bronchoalveolar lavage (BAL) fluid, or cytologic CMV-positive immunostaining. Newer methods for the detection of CMV pneumonitis after lung transplantation makes use of polymerase chain reaction (PCR) analysis of DNA obtained from BAL cells.[19] Most transplantation centers recommend CMV prophylaxis for the first 3 to 6 months after transplantation, using valcyclovir, acyclovir, gancyclovir, or valgancyclovir.

Herpes simplex virus can cause pneumonia in heart-lung transplant and bone marrow transplant recipients. Diagnosis is made by the presence of intracellular inclusion bodies in biopsy or BAL cytology specimens. The clinical picture ranges from normal radiologic findings and dyspnea to failure to wean and acute respiratory distress syndrome (ARDS). Acyclovir is an effective treatment that results in prompt improvement.[20] Varicella-zoster virus has also been reported as a rare cause of pneumonia in transplant recipients. Usually patients will present with the vesicular rash, followed by respiratory

symptoms. Acyclovir is still the treatment of choice. However, the role of human herpesvirus (HHV)6 and HHV7 in transplant patients is not well understood.

Solid organ transplant patients are exposed to the same community-acquired viruses as the rest of the population. Respiratory syncytial virus (RSV) pneumonia can be frequently seen in SCT recipients.[21] McCarthy and associates showed over a 5-year period that 26 (6.3%) of 336 allo-SCT recipients developed RSV pneumonia (19.2% mortality), and this correlated with lower respiratory tract infection and a poor overall outcome.[22]

RSV and adenovirus, among others, can cause significant complications. Lung and heart-lung recipients are most vulnerable to pneumonia. The incidence of respiratory viral infection in immunosuppressed patients has been well described: influenza, parainfluenza 1 and 2, and RSV infections have their peak mostly in the winter months, whereas infections with parainfluenza 3 and adenovirus occur year-round. Viral infections tend to have lower mortality rates, but they may have more long-term consequences. Viral infection predisposes transplant patients to secondary bacterial pneumonias. Superinfection with *S. aureus, Pseudomonas,* and *Acinetobacter* as well as other gram-negative organisms is well documented. Recently influenza and parainfluenza viruses have been reported as an important etiology of respiratory illness in solid organ transplant recipients. In lung transplant patients, the majority of patients with influenza and parainfluenza respiratory viral infection who had transbronchial biopsies had evidence of acute lung allograft rejection.[23] Herpes viruses, influenza A and B, and adenoviruses have also been associated with allograft rejection. RSV has been associated with obliterative bronchiolitis in children and in animal models. Decreases in FEV_1, on the order of 10% to 58%, have also been reported with parainfluenza infections.[24] Respiratory viral infection is usually present after 1 year posttransplantation.[25] In reported cases of parainfluenza infection, serotype 3 is the most common.[24,25]

Prophylaxis for viral infections has greatly improved morbidity and mortality in transplant recipients. Zanamivir and oseltamivir are approved for prophylaxis and treatment of influenza A and B. The Cochrane review has published a meta-analysis of 34 studies (3850 participants) that shows that the antiviral medications gancyclovir, valacyclovir, and acyclovir reduced the risk of CMV disease, all-cause mortality, and bacterial superinfection in heart, kidney, and liver transplant recipients.[26] Maribavir is a new drug that inhibits the *UL97* viral protein kinase of human CMV, causing inhibition of viral encapsidation and nuclear egress of viral particles from cells infected with CMV. This drug is in clinical trials in both SCT and solid organ transplant recipients. Herpes prophylaxis is given in the form of acyclovir once CMV prophylaxis is stopped for latent infection. Currently there are no studies on RSV or adenovirus prophylaxis for adult transplant patients.

Fungal Infections

Fungal infections in the solid organ transplant recipient depend on a number of factors: type of transplant, endemic mycoses in the community, previous colonization, degree of immunosupression, and metabolic abnormalities influencing the immune state (e.g., diabetes, malnutrition). Up to 8% of patients with solid organ transplants will have a pulmonary infection with *Aspergillus* species. Disease of the lung includes invasive pulmonary aspergillosis, tracheobronchitis, sinusitis, and disseminated disease. Lung transplant patients are at particular risk, especially in the anastomosis site. Patients with liver and heart transplants are also commonly at risk, with a lower incidence in pancreas, small bowel, and kidney recipients. Early infection (<6 months posttransplantation) is most common, and there is a high risk of dissemination, particularly to the central nervous system. Cytomegalovirus disease has also been associated with increased risk of invasive aspergillosis. Mortality for *Aspergillus* invasion has been reported to be 50% to 75%, with the higher rates corresponding to invasive disease.

Definitive diagnosis involves histologic evidence of septated hyphae with acute angle branching. Unfortunately, open lung biopsy is not always possible in this group of patients due to poor functional status, thrombocytopenia, and other comorbidities. Recovery of *Aspergillus* from respiratory secretions is not diagnostic, since it is a common colonizer of the respiratory tract, but could suggest the diagnosis along with other clinical criteria. *Aspergillus* can also be identified using PCR with enzyme-linked immuosorbent assay in BAL fluid or tissue samples. In recent years, the determination of galactomannan levels has proven useful in the diagnosis of *Aspergillus*-related disease. Galactomannan is a polysaccharide component of the cell wall of *Aspergillus* and is released during its growth. Serum levels greater than 0.5 ng/dL are suggestive of active aspergillosis. Galactomannan has also been detected in BAL and cerebrospinal fluid. In fact, the diagnostic yield of galactomannan in BAL fluid is higher than that from serum in lung transplant patients. Nevertheless, false positives can occur in patients receiving piperacillin-tazobactam, in the presence of autoreactive antibodies in autoimmune diseases or graft-versus-host disease, in the presence of other fungi, and with translocation of galactomannan antigen present in milk and some cereals across the gut wall. False negatives may occur if antifungal medication is given prior to sample acquisition since it lowers fungal titers.

Pneumocystis jirovecii (previously *Pneumocystis carinii*) is still an important cause of morbidity in immunocompromised patients, though its prominence has decreased due to effective prophylaxis. *Pneumocystis* pneumonitis (PCP) appears to be the result of the surfacing of latent infection during immunosuppression, since there is serologic evidence that many individuals are exposed by age 4.[27–29] Clinical presentation is variable depending on the degree of immunosuppression and neutropenia. Radiologic findings range from normal chest radiographs to bilateral interstitial infiltrates, but other findings may include pulmonary nodules, cystic lesions, and pneumothorax. Diagnosis requires morphologic identification of the *Pneumocystis* organisms in sputum, BAL fluid, or tissue since the organism cannot

be cultured. Sputum samples induced with hypertonic saline or BAL both have a 90% diagnostic yield, and the yield approaches 100% when transbronchial biopsies are added to the BAL samples.

The incidence of infection in recipients of solid organ transplants has been reported to be 2% to 12% in different cohorts. Torres and coworkers reported an incidence of 12% of microbiologically proven PCP in a cohort of patients with orthotopic liver transplantation.[10] In a study in a kidney transplant population, the incidence of PCP was 7% despite 70% of patients receiving prophylaxis with trimethoprim-sulfamethoxazole.[30] Median time between transplantation and PCP diagnosis was approximately 5 months, and the mortality was 35%. The presence of PCP diagnosis has been associated with an increased risk of rejection in both kidney and heart transplant recipients. Invasive infection with CMV seems to augment the virulence of *Pneumocystis*.[30–32]

Most transplantation centers use trimethoprim-sulfamethoxazole prophylaxis to prevent PCP. Low-dose trimethoprim-sulfamethoxazole is usually well tolerated for prophylaxis, although higher levels used for treatment may lead to toxicity, including bone marrow suppression, renal disease, and liver toxicity. Also, cases of Steven-Johnson syndrome have been reported. Alternative agents for prophylaxis against *P. jirovecii* are pentamidine, dapsone, and atovaquone, but they are less effective than trimethoprim-sulfamethoxazole.

Other fungal infections depend on the geographical location of the patient. Endemic mycoses account for approximately 3% of fungal pneumonias in the transplant population in endemic areas. *Histoplasma capsulatum* is prevalent in the Ohio River valley, along the Mississippi River, the St. Lawrence River valley, the eastern half of the United States, and most of Latin America. In immunocompromised patients it may lead to disease ranging from primary infection to disseminated disease. *Blastomyces dermatitidis* is found in the south central and southeastern states, areas along the Mississippi and Ohio River basins, the Great Lakes, and areas of Canada and New York. *Coccidioides immitis* is prevalent in the southwestern part of the United States as well as in Mexico and Central America. The mean time for infection in solid organ transplant patients is within 6 months after transplantation.

NONINFECTIOUS COMPLICATIONS

Due to the degree of immunosuppression, solid organ transplant patients have a higher risk for posttransplantation infection. Nevertheless, there are several factors that can lead to noninfectious complications in this group of patients: toxicity from medications, postsurgical complications, comorbidities, immunologic processes induced by the transplant itself or by previous infections (e.g., CMV), and rejection. Liver transplant patients have a particular predisposition for respiratory complications due to operative manipulation in the upper abdomen and involvement of the diaphragm. Table 81-1 describes the most common complications in the immediate postoperative period. Also, many of these patients have been critically ill prior to the transplantation and have a higher risk of pneumonia.

TABLE 81-1. The Most Common Noninfectious Complications in the Immediate Postoperative Period

Transplantation	Noninfectious Postoperative Complications
Liver	Pulmonary edema/ARDS
	Diaphragmatic dysfunction
	Pleural effusions
Heart	Diaphragmatic dysfunction
	Mediastinitis
	Pleural effusions
	Pulmonary edema
Lung/heart-lung	Reperfusion pulmonary edema
	Primary graft failure
	Bronchial anastomosis dehiscence
	Acute hyperinflation of native lung
	Diaphragmatic dysfunction
Kidney	Pulmonary edema
	Venous thromboembolic disease

ARDS, acute respiratory distress syndrome.

In SCT, the individual components of the conditioning regimen likely play a key role in the development of pulmonary toxicity. In the case of autologous SCT, for example, carmustine (or bischloroethylnitrosourea [BCNU]), one of the chemotherapeutic agents used with autologous bone marrow transplantation, has been shown to cause pulmonary toxicity when used as a single agent or in combination with other agents.[33–38] In fact, a National Heart, Lung, and Blood Institute workshop has suggested that more than 50% of breast cancer patients receiving regimens containing carmustine may develop clinically apparent lung injury.[39] By inhibiting antioxidant enzymes,[40,41] BCNU may deplete epithelial lining fluid glutathione levels,[42–44] resulting in increased oxidative stress. Cyclophosphamide (also used with both autologous and allogeneic SCT regimens) has also been shown to cause lung injury, deplete glutathione stores,[45–47] increase the generation of reactive oxygen species by alveolar macrophages,[48] inhibit prostaglandin E_2 production by macrophages[45] and modulate BAL cell populations.[48] Acrolein, a cyclophosphamide metabolite, can also react directly with glutathione, forming irreversible conjugates.[49] Additionally, cisplatin has been shown to increase the production of superoxide anions[50] and to decrease the activity of lipid peroxide-protecting enzymes, such as catalase, Cu,Zn-superoxide dismutase, glutathione peroxidase, and glutathione-*S*-transferase, in the liver and kidneys of rats.[51] Animal models of lung toxicity following allogeneic SCT generally require the following three components: (1) infusion of alloreactive T cells, (2) total body irradiation, and (3) cyclophosphamide.[52–57] The effects of other chemotherapeutic agents

and radiation on lung pathophysiology are discussed in more depth elsewhere in this text. The following sections review the noninfectious complications in the solid organ transplant population.

EARLY COMPLICATIONS

Pulmonary Edema and Respiratory Failure

Postoperative respiratory failure and ARDS have been well described in the transplantation literature as an early cause of morbidity. Liver transplant patients are at particularly high risk. The incidence of post–liver transplantation pulmonary edema has been reported to be anywhere from 5% to 52%.[8,58] Overall, pulmonary edema in the postoperative period is associated with intraoperative fluid overload, large intravascular fluid shifts, and the use of blood products. Underlying cardiac or renal dysfunction in combination with medications such as antibiotics and immunosupressants are also related to its development. In liver transplant recipients, the most common risk factors for posttransplantation noncardiogenic pulmonary edema include sepsis, pneumonia, gastric aspiration, acute allograft rejection, and multiple transfusions. In an observational study, Yost and colleagues described that transfusion-related acute lung injury was the most likely cause of pulmonary edema in a small group of patients, since there were no other risk factors present and all patients had received blood products immediately prior to its development.[58] In a study of 34 patients, 16 developed pulmonary edema in the postoperative period.[59] There were no differences in the characteristics and hepatic disease severity between the patients who never developed pulmonary edema and the patients who did. However, a greater proportion of Child's class C recipients developed pulmonary edema. Figure 81-2 depicts an orthotopic liver transplant recipient with acute respiratory failure immediately posttransplantation.

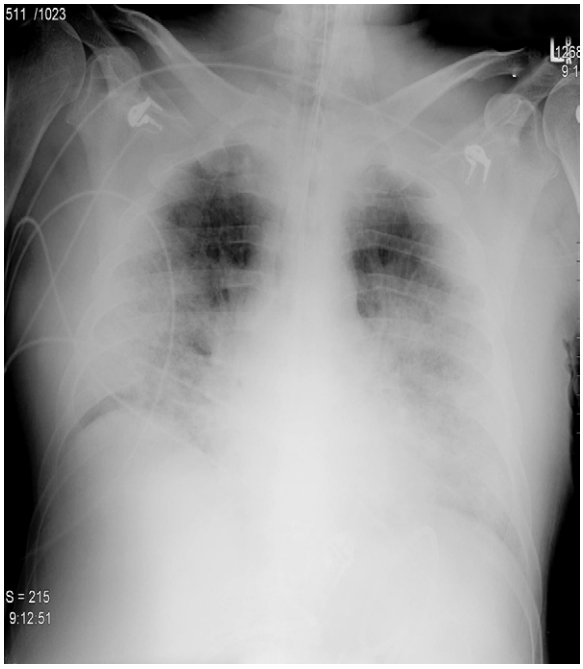

FIGURE 81-2 ■ Pulmonary edema in a 58-year-old man after liver transplantation. The patient developed acute respiratory failure in the postoperative period. Low central venous pressure, hypotension, and a history of multiple transfusions in the absence of other etiologies are suggestive of transfusion-related acute lung injury. An elevated right hemidiaphragm is noted.

Reperfusion syndrome after orthotopic liver transplantation is also associated with an increased risk of pulmonary edema and respiratory failure. It is characterized by hypotension with a decrease in mean arterial pressure of approximately 30%, vasodilation, and pulmonary hypertension. It occurs immediately after restoration of blood flow through the graft. Its pathophysiology is poorly understood but has been attributed to vasoconstriction and intracellular edema resulting in failure of the microcirculation. Alteration of nitric oxide, oxygen-derived free radicals, and endothelin results in prolonging ischemia in certain areas of the liver, resulting in worsening hepatic injury.

Perioperative respiratory failure is less common in the kidney and cardiac transplant population.[60] Orthotopic heart transplantation has a low risk of respiratory failure. Most cases of respiratory failure and ARDS are associated with sepsis. In a recent study, Lenner and associates reported a 4% incidence of respiratory failure in a cohort of 157 cardiac transplant recipients.[9] Allograft rejection, impaired renal function, comorbid cardiac conditions, and uremic cardiomyopathy have been identified as causes for pulmonary edema and respiratory failure in renal transplant patients.[61] Cardiac disease is of particular interest since renal failure patients have an increased risk of cardiac disease, including ischemic cardiomyopathy. In some cases, recipients will have low ejection fractions prior to transplantation. During the postoperative period, fluid overload is fairly common to maintain graft integrity and adequate blood flow. Carlier and coworkers showed that high central venous pressures (up to17 mm Hg) and diastolic pulmonary pressures above 20 mm Hg were associated with improved early graft function.[62] However, this increases the risk of cardiogenic pulmonary edema in kidney recipients.

Respiratory failure immediately after lung transplantation is associated with an increased risk of early mortality and poor 1-year survival. The most common causes for respiratory failure in this population are infections and ischemic reperfusion injury. Ischemic reperfusion syndrome is characterized by alveolar damage, pulmonary infiltrates, noncardiogenic pulmonary edema, and hypoxemia occurring within 72 hours after lung transplantation in the absence of infection or acute rejection. Respiratory failure was documented in 55% of patients undergoing lung transplantation at Temple University.[63] The main etiology for respiratory failure was ischemic reperfusion syndrome, and half of those patients died. Khan and associates reported

their experience at the Cleveland Clinic Foundation, where 57% of patients had reperfusion syndrome after transplantation.[64] Ischemic reperfusion injury appears in a biphasic fashion: initially the ischemic insult results in increases in xanthine oxidase and hypoxanthine; then restoration of blood flow results in increase in oxygen free radicals that appears to worsen cellular damage. Ischemia triggers the activation of macrophages, releasing interleukin (IL)-8, IL-12, and IL-18, tumor necrosis factor-α (TNF-α), and interferon-γ, which in turn activates recipient neutrophils and T lymphocytes, resulting in severe early graft dysfunction and further lung injury.[65–67] Methods for ischemic preconditioning of the harvested organ, such as ischemic hypothermia, the use of preconditioning solutions containing different electrolyte concentrations, attenuating the donor's inflammatory response, and experimental treatments in various animal models, are currently under investigation.

A similar spectrum of noninfectious pulmonary complications affect SCT patients, mainly the idiopathic pneumonia syndrome (IPS). The National Heart, Lung, and Blood Institute convened a workshop in 1991 to review clinical and pathologic features of lung toxicity following hematopoietic SCT, focusing primarily on IPS. IPS is the most severe form of SCT-related lung toxicity and is associated with widespread alveolar injury, respiratory failure, and death.[39,68] Early estimates reported a 35% incidence of IPS in SCT recipients,[69] but in more recent studies, the overall incidence of IPS appears about 10%.[69–73] Mortality can reach 65%.[74–76] While steroids are often used to treat IPS,[77] the efficacy of such treatment has not been proven.[72] The precise pathogenesis of IPS is not yet understood but remains under active investigation. Clark and colleagues showed that proinflammatory cytokine activation may play an important role in the development of lung injury.[78] Analysis of BAL fluid in patient with IPS showed elevated levels of IL-1, IL-2, IL-6, and TNF-α, whereas SCT patients without IPS showed levels of these inflammatory cytokines comparable to those obtained from normal volunteers. The appearance of IPS is delayed by several weeks to months following SCT.[39]

Diffuse alveolar hemorrhage (DAH) has been described in patients receiving autologous and allogeneic stem cells and has been termed *diffuse alveolar hemorrhage* to reflect the finding that sequential BAL aliquots become progressively bloodier and that these later aliquots predominantly sample alveoli.[79–81] DAH is considered to be a syndrome with nonspecific radiologic and clinical presentations. Even though certain infections (bacteria, *Aspergillus,* etc.) can lead to pulmonary hemorrhage,[80] the diagnosis of DAH is reserved for hemorrhage due to noninfectious etiologies.[82]

An increasingly more common, noninfectious, posttransplantation pulmonary complication primarily affecting the airways is best characterized by chronic progressive airflow obstruction otherwise known as bronchiolitis obliterans (BO). BO occurring in SCT patients was originally described in the mid-1980s and was seen exclusively in allo-SCT patients and believed to be a manifestation of graft-versus-host disease of the small airways.[83]

The term *delayed pulmonary toxicity syndrome* (DPTS) is used to describe lung injury following autologous bone marrow transplantation.[84,85] Clinically, DPTS manifests as an acute to subacute onset of progressive exertional dyspnea, shortness of breath, and dry cough, with or without fever and/or hypoxemia. Radiographic changes may or may not be present.[85] Closely following the D_{LCO} is the best way to monitor for its development.[85] The D_{LCO} reaches a nadir level in 15 to 18 weeks following high-dose chemotherapy and SCT.[85] When compared with IPS, DPTS has an overall higher incidence (72%) but lower mortality.[85]

Venous Thromboembolic Disease

Venous thromboembolism (VTE) may be underdiagnosed in the posttransplant population. In a recent report, pulmonary embolism (PE) was identified at autopsy in 34 (27%) of 126 lung- and heart-lung transplant recipients.[86] The prevalence of PE was highest, at 36.4%, in the early group (who died <1 month posttransplantation) compared with 20.0% who died between 1 month and 364 days, versus 23% in the group with greater than 365 days' survival. Kahan and coworkers identified the following risk factors for VTE in lung transplant recipients: gender (women have a higher incidence), longer hospitalization times, and longer ischemic period at the time of transplantation. These all had a higher probability for VTE.[87] In a cohort of 121 lung recipients at New York Presbyterian Hospital, 22% developed VTE despite prophylaxis with subcutaneous heparin.[88] In this group of patients with VTE, 89% presented within their first year posttransplantation.

Renal transplant recipients also have a particularly higher risk for VTE, especially those treated with cyclosporine. It is postulated that this group of patients has impaired fibrinolysis and a hypercoagulable state. The incidence of VTE in renal transplant patients ranges from 0.6% to 25% in some cohorts. Previous studies have linked higher rates of VTE in kidney recipients in association with increased homocysteine levels, CMV infection, D-dimer and prothrombin fragment 1+2 levels, and renal dysfunction.[89–91]

VTE is uncommon after cardiac and hepatic transplantation. In a cohort of 159 heart recipients from Mount Sinai Medical Center, only 2 patients developed VTE: 1 within 6 months posttransplantation and 1 after 6 months.[9] After heart transplantation, VTE may occur in the presence of heparin-induced thrombocytopenia or other hypercoagulable states.

Diaphragmatic Dysfunction

Data on heart and lung transplantation and the incidence of diaphragmatic paralysis are limited. Diaphragmatic dysfunction was present in 12.1% of heart transplant recipients and 7.4% of lung transplant recipients in a study by Dorffner and colleagues.[92] Phrenic nerve injury is in part due to hypothermia and mechanical damage

during surgery. In addition to the transplant procedure, left ventricular assist devices provide cardiovascular support in the pretransplantation period, which allows for 70% survival in patients awaiting an orthotopic heart transplant.[93] Nevertheless, there is up to a 15% incidence of diaphragmatic hernia during explantation depending on the timing for the closure of cannula defects. Persistence of the paralysis may lead to higher risk for pneumonia, respiratory failure, and mortality. Incidence of diaphragmatic paralysis has been reported from 1% to 34%. The difference between the reported incidences may be due to methods used for identification of phrenic nerve damage. In a group of lung transplant patients in Toronto, a retrospective study found 6 patients with documented diaphragmatic paralysis confirmed by imaging in a group of 185 single or sequential single lung transplantations.[94] In a lung recipient cohort, Sheridan and associates reported a 29% incidence of phrenic nerve injury as assessed by phrenic nerve conduction studies and fluoroscopy.[95] Complete diaphragmatic paralysis was present in 89% of those cases, and the highest incidence was after bilateral lung transplantation. The right phrenic nerve was most commonly affected.

The incidence of diaphragmatic paralysis is higher among liver recipients. Injury to the right phrenic nerve is possible because of the close proximity to the diaphragm and inferior vena cava. In a comparison with liver resection, in which the suprahepatic vena cava is not clamped, patients with liver transplantation, in which clamping is performed, have a higher incidence of phrenic nerve crush injury. Gurakar and coworkers found that 44% of patients have diaphragmatic dysfunction after orthotopic liver transplantation.[96] In a prospective study of 48 liver recipients, 38% had diaphragmatic paralysis.[97] Nevertheless, the clinical symptoms range in severity from no symptoms to failure to wean from mechanical ventilation.

LATE COMPLICATIONS

Drug Toxicity and Interstitial Lung Disease

Noncardiogenic pulmonary edema, the pulmonary capillary leak syndrome, and ARDS have been reported in the literature in association with intravenous cyclosporine after liver, kidney, and bone marrow transplantations. Pulmonary capillary leak syndrome is characterized by normal left atrial pressures, low central venous pressures, and pulmonary edema due to extravasation of plasma. These disorders have been reported in both the adult and pediatric transplantation populations.[98,99] There is resolution of the pulmonary symptoms and radiologic findings when the medication is discontinued. This reaction does not commonly occur with oral cyclosporine.

Sirolimus inhibits T-lymphocyte activation and binds to FK binding protein 12, suppressing cytokine-mediated T-cell proliferation. This immunosuppressant, used both for induction and for long-term maintenance, has been recently reported as the etiology for pulmonary toxicity in renal, hepatic, heart, and heart-lung recipients. Exertional dyspnea and dry cough appear to be the most common symptoms, but cases of hemoptysis and biopsy-proven interstitial pneumonitis and cryptogenic organizing pneumonia that resolve after discontinuation or decrease in sirolimus dose have also been described. Radiologic findings include bilateral alveolar patchy infiltrates, ground-glass opacities, and consolidation. In cases of pulmonary toxicity, sirolimus had been started within 6 months after transplantation in 50% of the patients.[100] Sirolimus has also been recently associated with a high rate of bronchial anastomosis dehiscence after lung transplantation, which has prompted a black box warning in the prescribing insert.[101,102] Other immunosuppressive therapies have also been reported to cause long-term pulmonary toxicity. Some relevant interactions are listed in Table 81-2.

TABLE 81-2. Immunosuppressant Therapy and Pulmonary Toxicity

Mycophenolate mofetil (MMF) and mycophenolic acid (MPA)	Pulmonary fibrosis, pulmonary edema, ARDS
Tacrolimus	Cryptogenic organizing pneumonia
OKT3 (muromonab-CD3)	Capillary leakage (pulmonary permeability edema), ARDS
Antithymocyte globulin	Pulmonary edema, pulmonary fibrosis
Azathioprine	Cryptogenic organizing pneumonia, interstitial pneumonitis, alveolar hemorrhage, laryngeal edema, vasculitis
Basiliximab and daclizumab	Capillary leakage (pulmonary permeability edema)
Rituximab	Hypersensitivity pneumonitis, interstitial pneumonitis, pulmonary fibrosis, alveolar hemorrhage

ARDS, acute respiratory distress syndrome.

Obliterative Bronchiolitis

Late allograft dysfunction continues to be an obstacle in solid organ transplantation despite advances in immunosuppressive therapy. Obliterative bronchiolitis appears to be a distinctive pulmonary manifestation of organ rejection. In lung and heart-lung recipients, the transplanted lung contains a large population of macrophages, lymphocytes, and bronchus-associated lymphoid tissue. In allogeneic stem cell transplant the incidence of late onset noninfectious pulmonary complications can be as high as 10–26%.[102a] It is postulated that allorecognition of human leukocyte antigen (HLA) class I peptides will incite sensitization of T cells, leading to the production of anti–HLA class I antibodies. Data suggest that the degree of allorecognition of HLA class I peptides corre-

lates with the development of obliterative bronchiolitis syndrome.[103,104] Proliferation of epithelial cells may also up-regulate growth factors such as transforming growth factor-β.[104] Recruitment of recipient bone marrow–derived circulating fibroblasts has been described after transplantation, as well as increases in fibroblast proliferation factors and platelet-derived growth factor (PDGF). Inhibition of PDGF receptor protein-tyrosine kinase activation prevents these obliterative changes.[105,106] Pathologic findings in BO vary considerably. There are several degrees of luminal obliteration, adventitial and submucosal scarring, bronchiolar inflammation, collagen deposition, and mucoid impaction with or without organizing pneumonia. Fibroblastic proliferation may occur along the airway epithelium and smooth muscle.

Transbronchial lung biopsies are not useful for the diagnosis of obliterative bronchiolitis, due to the small size of the biopsy samples and the patchy distribution of the pathologic changes. Thoracoscopic or open lung biopsies are needed for a definitive diagnosis. Nevertheless, due to the clinical status of these patients, which includes deterioration of pulmonary function and symptoms, patients are not always good surgical candidates to tolerate this procedure. Surveillance bronchoscopy for evaluation of early signs of rejection and to exclude infectious etiologies is valuable in this setting. A recent study from Washington University found a diagnostic yield of 31% for acute rejection during surveillance bronchoscopy in a cohort of 257 lung transplant recipients.[107] An Australian study found an overall 20% yield of acute rejection in 1235 transbronchial biopsies.[108] The differences between diagnostic yields in different centers may be due to immunosuppressive regimens, bronchoscopic surveillance protocols, or clinical bronchoscopy criteria. A detailed discussion on obliterative bronchiolitis syndrome is available in the chapter on lung transplantation (see Chapter 95).

Pulmonary Metastatic Calcifications

Pulmonary calcifications can occur in renal patients due to uremia and parathyroid hormone and calcium imbalance. Rarely, calcifications can progress despite renal transplantation. These calcifications may be diffuse or localized and can lead to restrictive lung disease on rare occasions. There is a predilection for upper lobes and apices. In renal transplant recipients, there may not be a correlation with hypercalcemia.

Malignancy

Malignancy is a well-known complication of prolonged immunosuppression. Transplant-related malignancy affecting the lung includes bronchogenic carcinoma, lymphoma, metastatic calcifications, Kaposi's sarcoma (KS), and posttransplantation lymphoproliferative disorder (PTLD). The risk of malignancy increases with the length of immunosuppression, and the progression of disease is accelerated compared with the general population. The association between lymphocyte-depleting immunosuppressants such as OKT3 and daclizumab and malignancy has been well established. Hibberd and colleagues described the use of polyclonal (antithymocyte globulin) and monoclonal (OKT3) anti–T cell immunosuppressive agents, which increased the risk for non-Hodgkin's lymphoma by 60% in a population of renal transplant patients over a 30-year period.[109] The incidences of vaginal, cervical, and vulvar cancer were also increased; no increased risk was associated with administration of azathioprine, prednisolone, or cyclosporin A. However, other immunosuppressive agents have also been linked to an increased risk of cancer.

The Cincinnati Transplant Tumor Registry has reported a 5% incidence of carcinomas of the lung occurring in transplant recipients.[110] The incidence of bronchogenic carcinoma after solid organ transplantation varies in different studies, mostly because of differences in sample size and because most reports do not take into account age, smoking history, occupational exposure, or other risk factors. Lung cancer developed in 0.28% of a solid organ transplant recipient population of 5400 over a 25-year period at the University of Pennsylvania.[111] The incidence of bronchogenic carcinoma after heart transplantation has been reported to be as high as 4%,[112] with an incidence of 2% in liver recipients[113] and up to 4% in the lung recipient population.[114-116] In solid organ transplantation, KS has been reported in recipients of renal allografts. The Cincinnati Transplant Tumor Registry reported an incidence of 6% at an average of 22 months posttransplantation in this group of patients.[117] An association with herpes simplex infection, and specifically HHV8, has been suggested to play a possible role.[118]

PTLD encompasses a diverse group of altered B-cell monoclonal and polyclonal proliferation disorders associated with immunosuppressed states. Virtually all are associated with Epstein-Barr virus (EBV) infection, although there have been case reports of EBV-seronegative PTLD and T-cell lymphoproliferative disorders. EBV infects B cells, binding to the CD21 receptor, which results in B-cell proliferation. Despite a primary EBV-specific cytotoxic T-lymphocyte response, not all infected B cells are eliminated. Immunosuppressive therapy, which depletes T cells, disrupts the balance of B to T cells, resulting in PTLD. Risk factors for PTLD include seronegativity to EBV prior to transplantation (especially with an EBV-seropositive donor), CMV and hepatitis C infection, high intensity of immunosuppression, and use of T-cell–depleting drugs (such as OKT3), and there is higher risk during the first year after transplantation when the levels of immunosuppressants are higher.[119] The risk of PTLD after solid organ transplantation is approximately 2%, but the organ site also affects the incidence. Patients receiving lung and liver transplants have a risk of PTLD of approximately 3%, and heart recipients 6%, and the risk in renal transplant recipients have been reported as 1%.[120,121] The lower incidence of PTLD for renal transplant recipients may be due to a lower degree of immunosuppression. PTLD responds to decreased immunosuppression and rituximab therapy. Figure 81-3 presents a patient with pulmonary nodules in whom pathology showed PTLD.

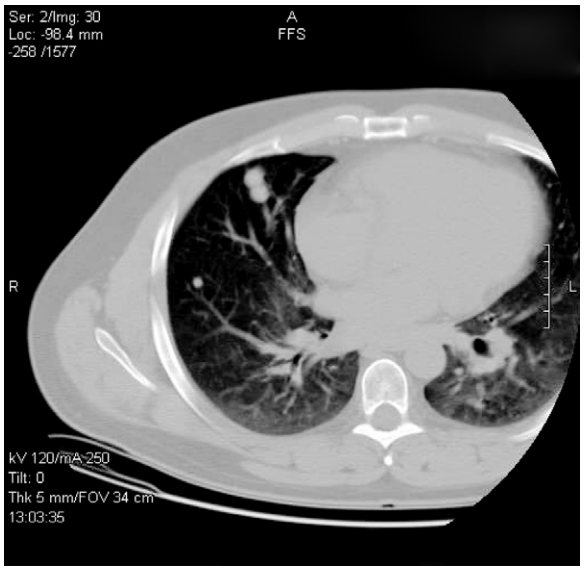

FIGURE 81-3 ■ Posttransplantation lymphoproliferative disorder (PTLD) presenting as pulmonary nodules in a 36-year-old man on chronic immunosuppression. Most pulmonary nodules in a transplant recipient are due to PTLD or invasive aspergillosis.

Conclusion

Pulmonary complications of solid organ transplantation are varied, depending on degree and type of immunosuppression, method of surgery, time from transplantation, previous exposure to CMV or EBV, and early rejection or acute infection in the postoperative period. Few of these complications are unique to one type of transplant. The clinician must have a high level of suspicion since signs and symptoms in the transplant recipient may be attenuated or absent when compared to an immunocompetent patient. Regional exposures must also be considered when infection is suspected.

KEY POINTS

- Pulmonary complications are common following solid organ and hematopoietic stem cell transplant.
- The types of pulmonary complications are related to the time course following transplant.
- Risk factors for the development of pulmonary complications are varied and include degree and duration of immunosuppression, pre-existing lung disease, concomitant medication administration, radiation exposure, perioperative insults and surrounding environmental variables.
- Infectious etiologies must be aggressively assessed and promptly treated.
- Invasive lung sampling is often needed for accurate diagnosis and treatment.
- In some cases, closely following pulmonary function tests can identify and classify early pulmonary disease.
- The use of prophylaxis agents for commonly encountered pathogens is a successful method to reduce the incidence of pulmonary complications in transplant recipients.

References

1. Folz RJ: Mechanisms of lung injury after bone marrow transplantation. Am J Respir Cell Mol Biol 20:1097–1099, 1999.
1a. Kaya Z, Weiner DJ, Yilmaz D, et al: Lung function, pulmonary complications, and mortality after allogeneic blood and marrow transplantation in children. Biol Blood Marrow Transplant 15:817–826, 2009.
2. Chang FY, Singh N, Gayowski T, et al: Fever in liver transplant recipients: Changing spectrum of etiologic agents. Clin Infect Dis 26:59–65, 1998.
3. Michalak G, Kwiatkowski A, Bieniasz M, et al: Infectious complications after simultaneous pancreas-kidney transplantation. Transplant Proc 37:3560–3563, 2005.
4. Montoya JG, Giraldo LF, Efron B, et al: Infectious complications among 620 consecutive heart transplant patients at Stanford University Medical Center. Clin Infect Dis 33:629–640, 2001.
5. Socie G, Clift RA, Blaise D, et al: Busulfan plus cyclophosphamide compared with total-body irradiation plus cyclophosphamide before marrow transplantation for myeloid leukemia: Long-term follow-up of 4 randomized studies. Blood 98:3569–3574, 2001.

6. Chien JW, Martin PJ, Gooley TA, et al: Airflow obstruction after myeloablative allogeneic hematopoietic stem cell transplantation. Am J Respir Crit Care Med 168:208–214, 2003.
7. Kotloff RM, Ahya VN, Crawford SW: Pulmonary complications of solid organ and hematopoietic stem cell transplantation. Am J Respir Crit Care Med 170:22–48, 2004.
8. Pirat A, Ozgur S, Torgay A, et al: Risk factors for postoperative respiratory complications in adult liver transplant recipients. Transplant Proc 36:218–220, 2004.
9. Lenner R, Padilla ML, Teirstein AS, et al: Pulmonary complications in cardiac transplant recipients. Chest 120:508–513, 2001.
10. Torres A, Ewig S, Insausti J, et al: Etiology and microbial patterns of pulmonary infiltrates in patients with orthotopic liver transplantation. Chest 117:494–502, 2000.
11. Hackman RC, Madtes DK, Petersen FB, Clark JG: Pulmonary venoocclusive disease following bone marrow transplantation. Transplantation 47:989–992, 1989.
12. Jain P, Sandur S, Meli Y, et al: Role of flexible bronchoscopy in immunocompromised patients with lung infiltrates. Chest 125:712–722, 2004.
13. Feinstein MB, Mokhtari M, Ferreiro R, et al: Fiberoptic bronchoscopy in allogeneic bone marrow transplantation: Findings in the era of serum cytomegalovirus antigen surveillance. Chest 120:1094–1100, 2001.
14. Dunagan DP, Baker AM, Hurd DD, Haponik EF: Bronchoscopic evaluation of pulmonary infiltrates following bone marrow transplantation. Chest 111:135–141, 1997.
15. Aljurf M, Gyger M, Alrajhi A, et al: *Mycobacterium tuberculosis* infection in allogeneic bone marrow transplantation patients. Bone Marrow Transplant 24:551–554, 1999.
16. Lopez-Medrano F, Aguado JM, Lizasoain M, et al: Clinical implications of respiratory virus infections in solid organ transplant recipients: A prospective study. Transplantation 84:851–856, 2007.
17. Singh N: Infections in solid-organ transplant recipients. Am J Infect Control 25:409–417, 1997.
18. Fishman JA, Rubin RH: Infection in organ-transplant recipients. N Engl J Med 338:1741–1751, 1998.

18a. Lee JW, Kang HJ, Park JD, et al: Early pulmonary complications after hematopoietic stem cell transplantation in pediatric patients: association with cytomegalovirus infection. J Pediatr Hematol Oncol 31:545–551, 2009.

19. Bewig B, Haacke TC, Tiroke A, et al: Detection of CMV pneumonitis after lung transplantation using PCR of DNA from bronchoalveolar lavage cells. Respiration 67:166–172, 2000.
20. Cunha BA, Eisenstein LE, Dillard T, Krol V: Herpes simplex virus (HSV) pneumonia in a heart transplant: Diagnosis and therapy. Heart Lung 36:72–78, 2007.
21. Ghosh S, Champlin RE, Ueno NT, et al: Respiratory syncytial virus infections in autologous blood and marrow transplant recipients with breast cancer: Combination therapy with aerosolized ribavirin and parenteral immunoglobulins. Bone Marrow Transplant 28:271–275, 2001.
22. McCarthy AJ, Kingman HM, Kelly C, et al: The outcome of 26 patients with respiratory syncytial virus infection following allogeneic stem cell transplantation. Bone Marrow Transplant 24:1315–1322, 1999.
23. Vilchez RA, McCurry K, Dauber J, et al: The epidemiology of parainfluenza virus infection in lung transplant recipients. Clin Infect Dis 33:2004–2008, 2001.
24. Wendt CH, Fox JM, Hertz MI: Paramyxovirus infection in lung transplant recipients. J Heart Lung Transplant 14:479–485, 1995.
25. Vilchez R, McCurry K, Dauber J, et al: Influenza and parainfluenza respiratory viral infection requiring admission in adult lung transplant recipients. Transplantation 73:1075–1078, 2002.
26. Hodson EM, Craig JC, Strippoli GF, Webster AC: Antiviral medications for preventing cytomegalovirus disease in solid organ transplant recipients. Cochrane Database Syst Rev (2):CD003774, 2008.
27. Frenkel JK: *Pneumocystis jiroveci* n. sp. from man: Morphology, physiology, and immunology in relation to pathology. Natl Cancer Inst Monogr 43:13–30, 1976.
28. Meuwissen JH, Tauber I, Leeuwenberg AD, et al: Parasitologic and serologic observations of infection with pneumocystis in humans. J Infect Dis 136:43–49, 1977.
29. Peglow SL, Smulian AG, Linke MJ, et al: Serologic responses to *Pneumocystis carinii* antigens in health and disease. J Infect Dis 161:296–306, 1990.
30. Radisic M, Lattes R, Chapman JF, et al: Risk factors for *Pneumocystis carinii* pneumonia in kidney transplant recipients: A case-control study. Transpl Infect Dis 5:84–93, 2003.
31. Arend SM, Westendorp RG, Kroon FP, et al: Rejection treatment and cytomegalovirus infection as risk factors for *Pneumocystis carinii* pneumonia in renal transplant recipients. Clin Infect Dis 22:920–925, 1996.
32. Cardenal R, Medrano FJ, Varela JM, et al: *Pneumocystis carinii* pneumonia in heart transplant recipients. Eur J Cardiothorac Surg 20:799–802, 2001.
33. Durant JR, Norgard MJ, Murad TM, et al: Pulmonary toxicity associated with bischloroethylnitrosourea (BCNU). Ann Intern Med 90:191–194, 1979.
34. Seiden MV, Elias A, Ayash L, et al: Pulmonary toxicity associated with high dose chemotherapy in the treatment of solid tumors with autologous marrow transplant: An analysis of four chemotherapy regimens. Bone Marrow Transplant 10:57–63, 1992.
35. Lieberman A, Ruoff M, Estey E, et al: Irreversible pulmonary toxicity after single course of BCNU. Am J Med Sci 279:53–56, 1980.
36. Ryan BR, Walters TR: Pulmonary fibrosis: A complication of 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) therapy. Cancer 48: 909–911, 1981.
37. Litam JP, Dail DH, Spitzer G, et al: Early pulmonary toxicity after administration of high-dose BCNU. Cancer Treat Rep 65:39–44, 1981.
38. Weinstein AS, Diener-West M, Nelson DF, Pakuris E: Pulmonary toxicity of carmustine in patients treated for malignant glioma. Cancer Treatment Reports 1986;70:943–946.
39. Cherniack RM, Abrams J, Kalica AR: Pulmonary disease associated with breast cancer therapy. Am J Respir Crit Care Med 150:1169–1173, 1994.
40. Kehrer JP: The effect of BCNU (carmustine) on tissue glutathione reductase activity. Toxicol Lett 17:63–68, 1983.
41. Smith AC, Boyd MR: Preferential effects of 1,3-bis(2-chloroethyl)-1-nitrosurea (BCNU) on pulmonary glutathione reductase and glutathione/glutathione disulfide ratios: Possible implications for lung toxicity. J Pharmacol Exp Ther 229:658–663, 1984.
42. Baz MA, Tapson VF, Trigt PV, Piantadosi CA: Glutathione depletion in epithelial lining fluid of lung allografts. Am J Respir Crit Care Med 149:A744, 1994.
43. Cantin AM, Hubbard RC, Crystal RG: Glutathione deficiency in the epithelial lining fluid of the lower respiratory tract in idiopathic pulmonary fibrosis. Am Rev Respir Dis 139:370–372, 1989.
44. Pacht E, Timerman A, Lykens M, Merola A: Deficiency of alveolar fluid glutathione in patients with sepsis and adult respiratory distress syndrome. Chest 100:1397–1403, 1991.
45. Cooper JA Jr, Merrill WW: Modulation of endoperoxide product levels and cyclophosphamide-induced injury by glutathione repletion. J Appl Physiol 67:2316–2322, 1989.
46. Patel JM, Block ER: Cyclophosphamide-induced depression of the antioxidant defense mechanisms of the lung. Exp Lung Res 8:153–165, 1985.
47. Venkatesan N, Chandrakasan G: Cyclophosphamide induced early biochemical changes in lung lavage fluid and alterations in lavage cell function. Lung 172:147–158, 1994.
48. Cooper JA Jr, Merrill WW, Reynolds HY: Cyclophosphamide modulation of bronchoalveolar cellular populations and macrophage oxidative metabolism: Possible mechanisms of pulmonary pharmacotoxicity. Am Rev Respir Dis 134:108–114, 1986.
49. Grafstrom RC, Dypbukt JM, Willey JC, et al: Pathobiological effects of acrolein in cultured human bronchial epithelial cells. Cancer Res 48:1717–1721, 1988.
50. Masuda H, Tanaka T, Takahama U: Cisplatin generates superoxide anion by interaction with DNA in a cell-free system. Biochem Biophys Res Commun 203:1175–1180, 1994.
51. Sadzuka Y, Shoji T, Takino Y: Effect of cisplatin on the activities of enzymes which protect against lipid peroxidation. Biochem Pharmacol 43:1872–1875, 1992.
52. Cooke KR, Kobzik L, Martin TR, et al: An experimental model of idiopathic pneumonia syndrome after bone marrow transplanta-

tion: I. The roles of minor H antigens and endotoxin. Blood 88:3230–3239, 1996.
53. Cooke KR, Krenger W, Hill G, et al: Host reactive donor T cells are associated with lung injury after experimental allogeneic bone marrow transplantation. Blood 92:2571–2580, 1998.
54. Shankar G, Bryson JS, Jennings CD, et al: Idiopathic pneumonia syndrome after allogeneic bone marrow transplantation in mice: Role of pretransplant radiation conditioning. Am J Respir Cell Mol Biol 20:1116–1124, 1999.
55. Shankar G, Bryson JS, Jennings CD, et al: Idiopathic pneumonia syndrome in mice after allogeneic bone marrow transplantation. Am J Respir Cell Mol Biol 18:235–242, 1998.
56. Panoskaltsis-Mortari A, Strieter RM, Hermanson JR, et al: Induction of monocyte- and T-cell-attracting chemokines in the lung during the generation of idiopathic pneumonia syndrome following allogeneic murine bone marrow transplantation. Blood 96:834–839, 2000.
57. Panoskaltsis-Mortari A, Taylor PA, Yaeger TM, et al: The critical early proinflammatory events associated with idiopathic pneumonia syndrome in irradiated murine allogeneic recipients are due to donor T cell infusion and potentiated by cyclophosphamide. J Clin Invest 100:1015–1027, 1997.
58. Yost CS, Matthay MA, Gropper MA: Etiology of acute pulmonary edema during liver transplantation: A series of cases with analysis of the edema fluid. Chest 119:219–223, 2001.
59. Snowden CP, Hughes T, Rose J, Roberts DR: Pulmonary edema in patients after liver transplantation. Liver Transpl 6:466–470, 2000.
60. Sadaghdar H, Chelluri L, Bowles SA, Shapiro R: Outcome of renal transplant recipients in the ICU. Chest 107:1402–1405, 1995.
61. Alam S, Chan KM: Noninfectious pulmonary complications after organ transplantation. Curr Opin Pulm Med 2:412–418, 1996.
62. Carlier M, Squifflet JP, Pirson Y, et al: Maximal hydration during anesthesia increases pulmonary arterial pressures and improves early function of human renal transplants. Transplantation 34: 201–204, 1982.
63. Chatila WM, Furukawa S, Gaughan JP, Criner GJ: Respiratory failure after lung transplantation. Chest 123:165–173, 2003.
64. Khan SU, Salloum J, O'Donovan PB, et al: Acute pulmonary edema after lung transplantation: The pulmonary reimplantation response. Chest 116:187–194, 1999.
65. Kusaka M, Pratschke J, Wilhelm MJ, et al: Activation of inflammatory mediators in rat renal isografts by donor brain death. Transplantation 69:405–410, 2000.
66. Fisher AJ, Donnelly SC, Hirani N, et al: Elevated levels of interleukin-8 in donor lungs is associated with early graft failure after lung transplantation. Am J Respir Crit Care Med 163:259–265, 2001.
67. McCord JM: Oxygen-derived free radicals in postischemic tissue injury. N Engl J Med 312:159–163, 1985.
68. Clark JG, Hansen JA, Hertz MI, et al: NHLBI workshop summary: Idiopathic pneumonia syndrome after bone marrow transplantation. Am Rev Respir Dis 147:1601–1606, 1993.
69. Krowka MJ, Rosenow EC 3rd, Hoagland HC: Pulmonary complications of bone marrow transplantation. Chest 87:237–246, 1985.
70. Wingard JR, Chen DY, Burns WH, et al: Cytomegalovirus infection after autologous bone marrow transplantation with comparison to infection after allogeneic bone marrow transplantation. Blood 71:1432–1437, 1988.
71. Crawford SW, Longton G, Storb R: Acute graft-versus-host disease and the risks for idiopathic pneumonia after marrow transplantation for severe aplastic anemia. Bone Marrow Transplant 12:225–231, 1993.
72. Kantrow SP, Hackman RC, Boeckh M, et al: Idiopathic pneumonia syndrome: Changing spectrum of lung injury after marrow transplantation. Transplantation 63:1079–1086, 1997.
73. Wingard JR, Mellits ED, Sostrin MB, et al: Interstitial pneumonitis after allogeneic bone marrow transplantation: Nine-year experience at a single institution. Medicine 67:175–186, 1988.
74. Demirer T, Weaver CH, Buckner CD, et al: High-dose cyclophosphamide, carmustine and etoposide followed by allogeneic bone marrow transplantation in patients with lymphoid malignancies who had received prior dose-limiting radiation therapy. J Clin Oncol 13:596–602, 1995.
75. Weaver CH, Appelbaum FR, Peterson FB, et al: High-dose cyclophosphamide, carmustine, and etoposide followed by autologous bone marrow transplantation in patients with lymphoid malignancies who have received dose-limiting radiation therapy. J Clin Oncol 11:1329–1335, 1993.
76. Reece D, Barnett M, Shepherd J, et al: High-dose cyclophosphamide, carmustine (BCNU), and etoposide (VP16-213) with or without cisplatin (CBV +/− P) and autologous transplantation for patients with Hodgkin's disease who fail to enter a complete remission after combination chemotherapy. Blood 86:451–456, 1995.
77. Griese M, Rampf U, Hofmann D, et al: Pulmonary complications after bone marrow transplantation in children: Twenty-four years of experience in a single pediatric center. Pediatr Pulmonol 30:393–401, 2000.
78. Clark JG, Madtes DK, Martin TR, et al: Idiopathic pneumonia after bone marrow transplantation: Cytokine activation and lipopolysaccharide amplification in the bronchoalveolar compartment. Crit Care Med 27:1800–1806, 1999.
79. Robbins RA, Linder J, Stahl MG, et al: Diffuse alveolar hemorrhage in autologous bone marrow transplant recipients. Am J Med 87:511–518, 1989.
80. Agusti C, Ramirez J, Picado C, et al: Diffuse alveolar hemorrhage in allogeneic bone marrow transplantation: A postmortem study. Am J Respir Crit Care Med 151:1006–1010, 1995.
81. Srivastava A, Gottlieb D, Bradstock KF: Diffuse alveolar haemorrhage associated with microangiopathy after allogeneic bone marrow transplantation. Bone Marrow Transplant 15:863–867, 1995.
82. Afessa B, Tefferi A, Litzow MR, et al: Diffuse alveolar hemorrhage in hematopoietic stem cell transplant recipients. Am J Respir Crit Care Med 166:641–645, 2002.
83. Epler GR: Bronchiolitis obliterans and airways obstruction associated with graft-versus-host disease. Clin Chest Med 9:551–556, 1988.
84. Wilczynski SW, Petros WP, Hussein AM, et al: Increased incidence of pulmonary toxicity in breast cancer patients undergoing high dose chemotherapy. Am J Respir Crit Care Med 153:A273, 1996.
85. Wilczynski SW, Erasmus JJ, Petros WP, et al: Delayed pulmonary toxicity syndrome following high-dose chemotherapy and bone marrow transplantation for breast cancer. Am J Respir Crit Care Med 157:565–573, 1998.
86. Burns KE, Iacono AT: Pulmonary embolism on postmortem examination: An under-recognized complication in lung-transplant recipients? Transplantation 77:692–698, 2004.
87. Kahan ES, Petersen G, Gaughan JP, Criner GJ: High incidence of venous thromboembolic events in lung transplant recipients. J Heart Lung Transplant 26:339–344, 2007.
88. Yegen HA, Lederer DJ, Barr RG, et al: Risk factors for venous thromboembolism after lung transplantation. Chest 132:547–553, 2007.
89. Poli D, Zanazzi M, Antonucci E, et al: High rate of recurrence in renal transplant recipients after a first episode of venous thromboembolism. Transplantation 80:789–793, 2005.
90. Malyszko J, Malyszko JS, Pawlak K, Mysliwiec M: The coagulolytic system and endothelial function in cyclosporine-treated kidney allograft recipients. Transplantation 62:828–830, 1996.
91. Hryszko T, Malyszko J, Malyszko JS, et al: A possible role of thrombin-activatable fibrinolysis inhibitor in disturbances of fibrinolytic system in renal transplant recipients. Nephrol Dial Transplant 16:1692–1696, 2001.
92. Dorffner R, Eibenberger K, Youssefzadeh S, et al: Diaphragmatic dysfunction after heart or lung transplantation. J Heart Lung Transplant 16:566–569, 1997.
93. Mancini D, Burkhoff D: Mechanical device-based methods of managing and treating heart failure. Circulation 112:438–448, 2005.
94. Maziak DE, Maurer JR, Kesten S: Diaphragmatic paralysis: A complication of lung transplantation. Ann Thorac Surg 61:170–173, 1996.
95. Sheridan PH Jr, Cheriyan A, Doud J, et al: Incidence of phrenic neuropathy after isolated lung transplantation. The Loyola University Lung Transplant Group. J Heart Lung Transplant 14:684–691, 1995.

96. Gurakar A, Hassanein T, Van Thiel DH: Right diaphragmatic paralysis following orthotopic liver transplantation. J Okla State Med Assoc 88:149–153, 1995.
97. McAlister VC, Grant DR, Roy A, et al: Right phrenic nerve injury in orthotopic liver transplantation. Transplantation 55:826–830, 1993.
98. Mackie FE, Umetsu D, Salvatierra O, Sarwal MM: Pulmonary capillary leak syndrome with intravenous cyclosporin A in pediatric renal transplantation. Pediatr Transplant 4:35–38, 2000.
99. Powell-Jackson PR, Carmichael FJ, Calne RY, Williams R: Adult respiratory distress syndrome and convulsions associated with administration of cyclosporine in liver transplant recipients. Transplantation 38:341–343, 1984.
100. Pham PT, Pham PC, Danovitch GM, et al: Sirolimus-associated pulmonary toxicity. Transplantation 77:1215–1220, 2004.
101. Groetzner J, Kur F, Spelsberg F, et al: Airway anastomosis complications in de novo lung transplantation with sirolimus-based immunosuppression. J Heart Lung Transplant 23:632–638, 2004.
102. King-Biggs MB, Dunitz JM, Park SJ, et al: Airway anastomotic dehiscence associated with use of sirolimus immediately after lung transplantation. Transplantation 75:1437–1443, 2003.
102a. Patriarca F, Poletti V, Costabel U, et al: Clinical presentation, outcome and risk factors of late-onset non-infectious pulmonary complications after allogeneic stem cell transplantation. Curr Stem Cell Res Ther 4:161–167, 2009.
103. SivaSai KS, Smith MA, Poindexter NJ, et al: Indirect recognition of donor HLA class I peptides in lung transplant recipients with bronchiolitis obliterans syndrome. Transplantation 67:1094–1098, 1999.
104. Jaramillo A, Smith MA, Phelan D, et al: Development of ELISA-detected anti-HLA antibodies precedes the development of bronchiolitis obliterans syndrome and correlates with progressive decline in pulmonary function after lung transplantation. Transplantation 67:1155–1161, 1999.
105. Kallio E, Koskinen P, Buchdunger E, Lemstrom K: Inhibition of obliterative bronchiolitis by platelet-derived growth factor receptor protein-tyrosine kinase inhibitor. Transplant Proc 31:187, 1999.
106. Aubert JD, Pare PD, Hogg JC, Hayashi S: Platelet-derived growth factor in bronchiolitis obliterans-organizing pneumonia. Am J Respir Crit Care Med 155:676–681, 1997.
107. Chakinala MM, Ritter J, Gage BF, et al: Yield of surveillance bronchoscopy for acute rejection and lymphocytic bronchitis/bronchiolitis after lung transplantation. J Heart Lung Transplant 23:1396–1404, 2004.
108. Hopkins PM, Aboyoun CL, Chhajed PN, et al: Prospective analysis of 1,235 transbronchial lung biopsies in lung transplant recipients. J Heart Lung Transplant 21:1062–1067, 2002.
109. Hibberd AD, Trevillian PR, Wlodarzcyk JH, et al: Cancer risk associated with ATG/OKT3 in renal transplantation. Transplant Proc 31:1271–1272, 1999.
110. Penn I: Incidence and treatment of neoplasia after transplantation. J Heart Lung Transplant 12:S328–S336, 1993.
111. Ahmed Z, Marshall MB, Kucharczuk JC, et al: Lung cancer in transplant recipients: A single-institution experience. Arch Surg 139:902–906, 2004.
112. Dorent R, Mohammadi S, Tezenas S, et al: Lung cancer in heart transplant patients: A 16-year survey. Transplant Proc 32:2752–2754, 2000.
113. Jimenez C, Manrique A, Marques E, et al: Incidence and risk factors for the development of lung tumors after liver transplantation. Transpl Int 20:57–63, 2007.
114. Roithmaier S, Haydon AM, Loi S, et al: Incidence of malignancies in heart and/or lung transplant recipients: A single-institution experience. J Heart Lung Transplant 26:845–849, 2007.
115. Collins J, Kazerooni EA, Lacomis J, et al: Bronchogenic carcinoma after lung transplantation: Frequency, clinical characteristics, and imaging findings. Radiology 224:131–138, 2002.
116. Arcasoy SM, Hersh C, Christie JD, et al: Bronchogenic carcinoma complicating lung transplantation. J Heart Lung Transplant 20:1044–1053, 2001.
117. Penn I: Sarcomas in organ allograft recipients. Transplantation 60:1485–1491, 1995.
118. Sleiman C, Mal H, Roue C, et al: Bronchial Kaposi's sarcoma after single lung transplantation. Eur Respir J 10:1181–1183, 1997.
119. Lim WH, Russ GR, Coates PT: Review of Epstein-Barr virus and post-transplant lymphoproliferative disorder post-solid organ transplantation. Nephrology (Carlton) 11:355–366, 2006.
120. Kremers WK, Devarbhavi HC, Wiesner RH, et al: Post-transplant lymphoproliferative disorders following liver transplantation: Incidence, risk factors and survival. Am J Transplant 6:1017–1024, 2006.
121. Gao SZ, Chaparro SV, Perlroth M, et al: Post-transplantation lymphoproliferative disease in heart and heart-lung transplant recipients: 30-year experience at Stanford University. J Heart Lung Transplant 22:505–514, 2003.

CHAPTER 82

PULMONARY COMPLICATIONS OF PRIMARY IMMUNODEFICIENCIES

John M. Routes, MD

INTRODUCTION

DIAGNOSTIC WORKUP
Antibody Deficiencies
Cellular Immunodeficiency
Complement Deficiencies
Phagocyte Deficiencies

DEFICIENCY IN BOTH CELLULAR IMMUNITY AND ANTIBODY PRODUCTION
Severe Combined Immunodeficiencies

ANTIBODY DEFICIENCIES
Immunoglobulin A Deficiency
X-Linked Agammaglobulinemia
Common Variable Immunodeficiency
Specific Antibody Deficiency
Immunoglobulin G Subclass Deficiency
X-Linked Lymphoproliferative Syndrome
Hyper–Immunoglobulin M Syndrome

DEFICIENCIES IN CELLULAR IMMUNITY/COMPLEX IMMUNODEFICIENCIES
DiGeorge Syndrome
Wiskott-Aldrich Syndrome
Ataxia-Telangiectasia
Hyper–Immunoglobulin E Syndrome

PHAGOCYTIC CELL DISORDERS
Phagocytic Defects: Increased Apoptosis of Neutrophils
Decreased Adherence/Chemotaxis
Defects in Oxidative Killing
Disorders of Leukocyte Signaling

DISORDERS IN INNATE IMMMUNITY
IRAK-4 and MyD88 Deficiencies
Complement Deficiencies

INTRODUCTION

Primary immune deficiency disorders (PIDDs) are disorders of the immune system that predispose individuals to infection and frequently malignancy and autoimmunity as well.[1] Most PIDDs are inherited disorders; however, in some PIDDs, such as common variable immunodeficiency (CVID), a family history is often lacking and a genetic cause has yet to be found. Furthermore, in some individuals, somatic mutations, not germline mutations, cause autoimmune lymphoproliferative disease, a disease of immune dysregulation.[2] Thus, we should not limit the diagnosis of PIDD to disorders that are inherited.

Many incorrectly believe that PIDDs are rare and are diagnosed almost exclusively in children. The incidence of immunoglobulin A (IgA) deficiency is approximately 1 in 400 live births, and more serious PIDDs occur in approximately 1 in 2000 individuals.[3] The majority of people affected with PIDD are now adults, not children.[4] Among the patients in the United States receiving intravenous immune globulin (IVIG), 23% are ages 30 to 44 years and 34% are in the 45- to 65-year age group. There are several factors that contribute to the increasing age of patients with PIDD, such as improvements in the treatment with a concomitant increase in survival rates, and the predominance of antibody deficiencies in patients with PIDD.

A diagnostic evaluation for PIDD is a fundamental, but often overlooked issue in the evaluation of patients with pulmonary infections. This oversight may have significant, detrimental consequences for the long-term survival and quality of life of the patient. Numerous studies indicate the importance of the early diagnosis of PIDD in reducing the morbidity and mortality associated with

recurrent infections. For example, early hematopoietic stem cell tranplantation (HSCT) (<3 months of age) results in dramatically improved outcome in infants with severe combined immunodeficiency (SCID).[5] Treatment with high-dose IVIG can prevent many of the infectious sequelae in patients with primary antibody deficiency states.[6] Many routine childhood vaccines use attenuated, live organisms, and the use of such vaccines may lead to disseminated infections in patients with antibody or cellular immunodeficiencies and are contraindicated. Thus, the early diagnosis of PIDD can prevent these life-threatening infections, further supporting the fact that early detection leads to improved outcomes.

The decision to evaluate patients with pulmonary infection for primary immunodeficiencies cannot be made in the context of the pulmonary infection alone; several factors need to be considered (Table 82-1). In general, an evaluation of the immune system is warranted in patients with two or more radiographically documented pneumonias. However, a single infection of the lung with an opportunistic pathogen warrants an evaluation to exclude both primary and secondary immunodeficiencies. A patient with first pneumonia, but with a history of intractable sinus disease or recurrent gastrointestinal infection or with other disorders found more frequently in patients with primary PIDD (e.g., autoimmunity, intractable eczema, unusual facies) should also be evaluated for a PIDD. Approximately 20% of patients with CVID are diagnosed at 50 years of age or later. Therefore, advanced age should not be used to exclude the diagnosis of a PIDD.

There are several clues in the history and clinical presentation of patients with primary immunodeficiencies that suggest the type of immunologic defect present (Table 82-2). The onset of diseases associated with cellular immunodeficiencies usually begins in early infancy. Infections with opportunistic or unusual pathogens, mycobacteria, disseminated viral infections, and severe oral candidiasis may occur. Diarrhea and malabsorption are common and growth is delayed. In contrast, the onset of infections in patients with antibody deficiencies, such as X-linked agammaglobulinemia (XLA), is usually delayed until after 6 months when maternal antibodies are not longer present. Recurrent and severe upper and lower respiratory tract infections are the usual mode of presentation. Complement deficiencies may present in a manner similar to antibody deficiencies or with recurrent *Neisseria* spp. infections. In contrast to patients with cellular immunodeficiencies, growth is usually not delayed in patients with complement or antibody deficiencies.

One common misconception is that opportunistic pathogens are overwhelmingly the cause of most infections in patients with primary immunodeficiencies. In fact, many infections in immunodeficient patients occur with pathogens that are common in the community; however, these infections may be of unusual severity and respond poorly to therapy. For example, recurrent infections with *Streptococcus pneumoniae* occur frequently in patients with several types of PIDD, such as antibody deficiencies, complement deficiencies, Toll-like receptor signaling deficiencies (MyD88, IRAK-4), and mutations in nuclear factor-κB essential modulator.[7] Finally, although this section deals exclusively with primary immunodeficiency disorders, it is essential to exclude secondary immunodeficiencies or other medical conditions (e.g., lymphoproliferative disorders and malignancy, malnutrition, immunosuppressive drugs, protein-losing states, kidney failure, liver failure, heart failure, sickle cell anemia) that predispose patients to recurrent infection.

TABLE 82-1. General Criteria for Immunologic Evaluation

Chronic infections
Recurrent infections
Opportunistic or unusual pathogens
Unusual sites of infections
Incomplete clearing of infection
Poor response to antimicrobial therapy
Associated conditions (unusual facies, tetany, failure to thrive, intractable diarrhea, thrush, intractable eczema, autoimmunity)

TABLE 82-2. Examples of Primary Immunodeficiencies

Type of Immunodeficiency	Example	Mode of Presentation
Antibody	XLA, CVID	Upper and lower respiratory tract infections (encapsulated and atypical bacteria), giardiasis
T cell	DiGeorge syndrome	Abnormal facies, lymphopenia, thrush, recurrent sinopulmonary infections
Combined B cell and T cell	SCID (multiple causes)	Opportunistic infections, thrush, intractable diarrhea, failure to thrive
Cellular/complex	IFN-γ/IL-12/IL-23 axis	Atypical mycobacterial and *Salmonella* infections
Phagocyte	CGD	Recurrent abscesses (*Staphylococcus aureus, Burkholderia cepacia, Aspergillus* spp.)
Complement	C5–C9	Recurrent *Neisseria meningitidis* infections

CGD, chronic granulomatous disease; CVID, common variable immunodeficiency; IFN, interferon; IL, interleukin; SCID, severe combined immunodeficiency; XLA, X-linked agammaglobulinemia.

DIAGNOSTIC WORKUP

There are a number of readily available and inexpensive screening tests that should be used in the evaluation of a patient with a possible immunodeficiency (Table 82-3).[8] Abnormalities found in these screening tests indicate the need for more sophisticated studies in collaboration with a clinical immunologist. The goal in the evaluation of immunodeficient patients should be to define the specific genetic abnormality whenever possible.

Antibody Deficiencies

The quantitative measurement of immunoglobulin G (IgG), IgA, and immunoglobulin M (IgM) is the single best test to screen for primary antibody deficiencies.[9] An abnormality in the level of one or more of these classes of immunoglobulins is present in the majority of patients with primary antibody deficiencies. The pattern of the levels of IgG, IgA, and IgM gives important insight into the likely etiology of the antibody deficiency. For example, frequently clinical immunologists are consulted about the issue of whether a patient on corticosteroids has a primary antibody deficiency. In steroid-induced hypogammaglobulinemia, IgG levels are usually only moderately depressed (usually >400 mg/dL) and the magnitude of reduction reflects the dosage and duration of corticosteroid usage.[10] IgA and IgM levels tend to be preserved. In CVID, IgG levels are usually more profoundly depressed (<400 mg/dL); IgA levels are reduced (<10 mg/dL) in 70% of patients and IgM levels are reduced (<25 mg/dL) in over 80% of patients.[9] Finally, patients with CVID are unable to make antigen-specific antibodies following immunization. In contrast, patients with steroid-induced hypogammaglobulinemia make specific antibodies, although the response may be blunted.[11]

The enumeration of B cells, typically measured by flow cytometry using monoclonal antibodies directed against the CD19 or CD20 surface antigens, may also provide clues to the type of B-cell immunodeficiency present. XLA and autosomal recessive (AR) forms of aggammaglobulinemia usually have severely reduced numbers of B cells. In contrast, the number of B cells in CVID is frequently, but not always, normal. It is important to obtain a careful medication treatment history as novel agents such as rituximab, a chimeric monoclonal antibody directed against CD20, can lead to profound decreases in B-cell numbers for months after treatment.

In assessing response to immunization, it is important to immunize with both a protein and polysaccharide (PS) antigen and to assess the response 4 to 6 weeks postimmunization. The immunologic requirements to make antibodies (e.g., T-cell help, cytokine requirements) in response to immunization with a protein or PS antigen differ. Some patients with normal quantitative immunoglobulins or selective IgA deficiency exhibit a selective inability to make antibody to PS, but not to protein antigens. This immunologic defect results in recurrent sinopulmonary infections and in selected instances may require replacement immunoglobulin therapy.

Protein antigens commonly used to assess specific antibody responses include tetanus and diphtheria toxoids. The *Haemophilus influenzae* type B (Hib) vaccine in present use conjugates the capsular PS (polyribose phosphate) to a protein carrier, thereby making the antibody response thymus-dependent and allowing children under 2 years of age to make specific antibodies to a PS antigen. Therefore, quantitation of antibodies to *H. influenzae* following immunization with the Hib vaccine measures competence of the immune system to make specific antibodies to a protein, not PS antigens. Many adults have not been immunized to Hib, making the Hib vaccine particularly useful in the evaluation of this group of patients.

There are two readily available unconjugated vaccines that can be used to assess antibody responses to PS antigens: the pneumococcal PS and *Neisseria meningitidis* vaccines. Some pneumococcal vaccines are conjugated to a protein carrier and cannot be used to measure a response to the PS antigen (e.g., Prevnar). When using the pneumococcal vaccine, the measurement of antibody responses to several (12 or more)

TABLE 82-3. Screening Tests for Immune Function

Immune Function	Quantitative Assays	Functional Assays
Cellular immunity	CBC with differential*	Cutaneous delayed hypersensitivity
	Flow cytometry	Enzyme assays (ADA, PNP)
	$CD3^+CD4^+$	NK cell cytolysis assay
	$CD3^+CD8^+$	
	$CD16^+CD56^+$	
	FISH for 22q11 and 10p11 deletion	
B cells	Flow cytometry	IgG, IgA, IgM levels
	$CD19^+$ or $CD20^+$	Specific antibody response to immunization
PMN	CBC with differential	Oxidase function (NBT, DHR, chemiluminescence)
	Flow cytometry	Enzyme assays (MPO, G6PD)
	LFA-1 (CD18/CD11a)	Phagocyte function
	CD15	Chemotaxis
Complement	C3, C4	AH_{50} (alternative pathway)
	Specific complement components	CH_{50} (classical pathway)
	Complement split products	

*Preferred initial screening tests are underlined.

ADA, adenosine deaminase; CBC, complete blood count; DHR, dihydrorhodamine; FISH, fluorescence in situ hybridization; G6PD, glucose-6-phosphate dehydrogenase; Ig, immunoglobulin; LFA-1, lymphocyte function antigen 1; MPO, myeloperoxidase; NBT, nitroblue tetrazolium; NK, natural killer; PMN, polymorphonuclear leukocytes; PNP, purine nucleoside phosphorylase.

capsular antigens is indicated. There is considerable controversy about what constitutes a normal response to the pneumococcal vaccine. In the absence of more definitive studies, the only clearly abnormal response to a pneumococcal vaccine in adults is an absent response to all or nearly all capsular antigens measured 3 to 6 weeks after vaccination. Finally, children less than 2 years of age frequently do not make antibody responses to PS antigens. Thus, the use of PS vaccines to diagnose antibody-deficient states in this age group is not indicated.

Cellular Immunodeficiency

Many patients with impaired cellular immunity will have either reduced T-cell numbers or abnormal T-cell function or both (see Table 82-3). Quantitation of T-cell numbers is easily screened by enumeration using flow cytometry. The CD3 antigen measures the total numbers of T cells, whereas CD4 and CD8 antigens are present on the T-helper and T-cytotoxic subsets, respectively. Cutaneous delayed-type hypersensitivity (DTH) is an easily performed test for T-cell function. In the DTH test, a small amount of an antigen is injected into the dermis and a positive reaction is indicated by induration (>2 mm) 48 to 72 hours later at the site of the injection. Antigens such as tetanus toxoid, *Candida,* and *Trichophyton* are frequently used because most individuals will have had a prior immune response to these antigens. However, DTH responses are frequently absent in normal infants, and in vitro assays of T-cell function are indicated in this group of patients.[12] The measurement of natural killer (NK) cell numbers ($CD16^+/CD56^+$) and function is indicated in the evaluation of infants for possible SCID or patients with recurrent, severe herpesvirus infection. The pattern of abnormalities in the numbers of specific lymphocyte subpopulations (T cells, NK cells, B cells) is helpful in identifying the molecular abnormality in infants with SCID (Table 82-4).

Complement Deficiencies

The screening tests for complement deficiency states associated with increased infections are the CH_{50} and AH_{50}, which measure the integrity of the classical and alternative pathways of complement activation, respectively[13] (see Table 82-3). Abnormalities in CH_{50} or AH_{50} could be due to deficiencies in individual components of complement or inappropriate activation and consumption of the complement pathway. Many times these possibilities can be distinguished by the measurement of two or more individual components of the classical or alternative complement pathway and the measurement of complement split products. Complement consumption is indicated by low levels of more than one component of complement and the elevation of complement split products. In contrast, complement deficiency states show depressed levels of individual members of the complement pathway with normal levels of complement split products.

Phagocyte Deficiencies

The initial screening test for phagocytic defect includes a complete blood count, with quantitation of leukocyte number and morphology (see Table 82-3). The dihydrorhodamine (DHR) test has replaced the nitroblue tetrazolium (NBT) test in many centers to diagnose defects in the generation of oxidase activation, such as seen in chronic granulomatous disease (CGD).[14] Advantages to the DHR test include the ease, rapidity, and reproducibility of the test, along with the capacity to readily detect CGD carrier states. Both the NBT and DHR tests measure the ability of phagocytes to generate superoxide free radicals. In the DHR test, phagocytes are loaded with a fluorescent dye (DHR) and activated with phorbol myristate acetate. Activated phagocytes then produce superoxide free radicals that reduce DHR, leading to a change in fluorescence that is quantitated by flow cytometry. Other functional assays for phagocytes include enzyme assays for myeloperoxidase and glucose 6-phosphate dehydrogenase, chemotaxis assays, phagocytic tests, and bactericidal assays. Abnormalities in the adhesion molecules CD18 and CD15 that result in leukocyte adhesion deficiency 1 and leukocyte adhesion deficiency 2, respectively, are detected by flow cytometry.

TABLE 82-4. Common Etiologies of Severe Combined Immunodeficiencies

Form of SCID	Prevalence	T/B/NK*	Inheritance
Common γ chain IL-2 receptor deficiency	45–50%	−/+/−	X-linked
ADA deficiency	15–20%	−/−/−	AR
RAG1/RAG2	10%†	−/−/+	AR
JAK3	5–10%	−/+/−	AR

*Presence (+) or absence (−) of the indicated cell type.
†Total prevalence of patients with mutations in either RAG1 or RAG2 gene.
AR, autosomal recessive.

DEFICIENCY IN BOTH CELLULAR AND ANTIBODY PRODUCTION

Severe Combined Immunodeficiency

SCID is a syndrome that encompasses a variety of molecular defects that result in absent or severely impaired T-cell and B-cell function.[15,16] One commonly used method to classify SCID is based on whether the molecular defects decrease the numbers of T cells only, T cells and B cells, or T cells, B cells, and NK cells (see Table 82-4).

The molecular defects that lead to SCID include mutations that lead to abnormalities in cytokine signaling (e.g., the common γ chain [γc] of the interleukin [IL]-2 receptor; Janus activating kinase 3 [JAK3], IL-7 receptor)

and T-cell receptor signaling (CD45, ZAP-70, CD3γ, CD3ε, CD3ζ); defective T-cell and B-cell receptor gene recombination (*RAG1, RAG2*); defective nucleotide salvage pathway (adenosine deaminase [ADA] deficiency); and defects in the expression of major histocompatibility complex class I or class II molecules. X-linked SCID (γc mutation) is the most common form of SCID, accounting for approximately 50% of all cases. The γc of the IL-2 receptor is utilized by several other cytokine receptors, including the receptors for IL-4, IL-7, IL-11, IL-15, and IL-21. Consequently, the immunodeficiency due to mutation of the γc is due to the combined effects of loss of function in all of these cytokine receptors. Milder or atypical forms of SCID due to gene defects usually associated with classical SCID may also occur. Additionally, there are other gene defects that can lead to diseases of similar severity to SCID such as Wiskott-Aldrich syndrome, DiGeorge syndrome, Ataxia-telangiectasia, X-linked lymphoproliferative disorder, and some forms of hyper-IgM syndrome. For purposes of this chapter, these latter diseases are discussed separately from SCID.

The clinical presentation of SCID is characterized by severe infections most commonly of the respiratory and gastrointestinal tract in early infancy. Infections are caused by common and opportunistic pathogens, and disseminated infections are frequent. Other common manifestations of the syndrome include oral thrush, persistent diarrhea, interstitial pneumonitis, impaired growth, and the absence of lymph nodes. Engraftment of maternal T cells in an infant with SCID can lead to graft-versus-host disease. The prompt treatment of infection, administration of IVIG, and prophylaxis against *Pneumocystis jirovecii* are indicated until HSCT can take place. In the event blood transfusions are needed, only irradiated, cytomegalovirus (CMV)-negative blood should be used. No live virus vaccinations should be given to infants with known or suspected SCID.

Early mortality due to disseminated infections is extremely common in SCID. Therefore, it is incumbent on the physician to make a prompt diagnosis of SCID. The absence of a thymic shadow on chest radiograph in an infant with recurrent infections should prompt further studies to exclude the diagnosis of SCID. In the vast majority of infants with SCID, severe lymphopenia is present (<1500/μl). This important clue to the diagnosis of SCID is frequently overlooked. Lymphocyte enumeration studies quantifying the numbers and subsets of T cells, B cells, and NK cells by flow cytometry and a deficiency in the capacity of T cells to proliferate to mitogens confirms the diagnosis of SCID. Population-based newborn screening of SCID is a promising approach to reduce the mortality in these infants, and the state of Wisconsin began screening all newborns for SCID in 2008.[15,15a,15b]

With the exception of ADA deficiency, HSCT is the preferred treatment for SCID. Early HSCT (<3 months of age) and the use of human leukocyte antigen–identical donors have markedly improved the prognosis of infants with SCID, with long-term survival rates as high as 95%.[16] The administration of polyethylene glycol–ADA is an alternative treatment for SCID due to ADA deficiency. Ten patients with X-linked SCID were immunologically reconstituted by gene therapy.[17] Replication-incompetent retroviruses encoding the γc of the IL-2 receptor were used to transduce autologous $CD34^+$ stem cells, which were then infused into the infants. Retroviral insertion leading to activation of the proto-oncogene LMO-2 resulted in γδ T-cell leukemia in two patients, with an additional leukemia in another patient unrelated to activation of LMO-2.[17,18] More recently, gene therapy used to treat SCID due to ADA deficiency was shown to be safe and efficient.[18a]

ANTIBODY DEFICIENCIES

Immunoglobulin A Deficiency

The prevalence of IgA deficiency varies among different ethnic groups, but the overall prevalence is approximately 1 in 400 live births.[19] The etiology of IgA deficiency remains obscure. Rarely, IgA deficiency may evolve into CVID, and familial occurrences of both IgA deficiency and CVID arise, suggesting a common genetic basis.[20] Medications, in particular anticonvulsants, infrequently cause IgA deficiency or panhypogammaglobulinemia, and immunoglobulins may normalize with elimination of the drug.

There is considerable controversy as to whether IgA deficiency alone predisposes people to infection.[19,21] Most patients with IgA deficiency do not have increased numbers of infection and are often discovered during an evaluation for problems unrelated to infection. However, some patients with IgA deficiency have recurrent infections, predominantly respiratory tract infections.[22] Whether IgG subclass deficiency and/or deficiencies in mannose-binding lectin identify a subgroup of patients with IgA deficiency who are more prone to infection is not clear.[23] Unlike patients with more severe forms of antibody deficiency such as CVID or XLA, replacement therapy with IVIG is not warranted with isolated IgA deficiency. In patients with IgA deficiency and concomitant IgG subclass deficiency who have recurrent and persistent respiratory tract infections, determination of the antibody response following vaccination should be used to ascertain if IVIG therapy is warranted.[24]

Clinical manifestations of IgA deficiency are highly variable. Infectious complications of IgA deficiency include recurrent upper (otitis media, sinusitis) and lower respiratory tract infections.[22] Gastrointestinal tract infections, in particular recurrent giardiasis, may be present. The prevalence of atopic diseases (asthma, allergic rhinitis, eczema) and autoimmune diseases (systemic lupus erythematosus, celiac disease, rheumatoid arthritis) is increased in patients with IgA deficiency.[24] Patients with IgA deficiency may develop IgG anti-IgA antibodies and are at risk to develop anaphylactic reactions following administration of blood or blood products.[25] Although these anaphylactic reactions are rare, blood transfusions using IgA-deficient donors

should be used whenever possible. Extensively washed, packed red blood cells may be used for transfusion in an emergency situation or when an IgA-deficient donor cannot be found.

Serologic studies in IgA deficiency may be subject to false-positive and false-negative results. Due to the presence of heterophile antibodies, which are human antibodies cross reactive to animal proteins, positive serum β-human chorionic gonadotropin pregnancy tests were found in as many as 30% of patients with IgA deficiency.[26] The diagnosis of celiac disease in patients with IgA deficiency is problematic as the most specific serologic assay for celiac disease, IgA anti–tissue transglutaminase, is absent in IgA-deficient patients. Therefore, other assays should be performed in the laboratory assessment of celiac disease in IgA-deficient patients.

X-Linked Agammaglobulinemia

XLA (Bruton's agammaglobulinemia) is a primary antibody deficiency with an estimated prevalence of 1 in 190,000 male live births.[27] Mutations in various locations of the cytoplasmic tyrosine kinase gene Bruton's tyrosine kinase (*Btk*) are responsible for this immunodeficiency.[28] Btk is required for B-cell receptor signaling, playing a key role in the phosphorylation of phospholipase Cγ2, which is necessary for the generation of inositol triphosphate leading to release of calcium from the endoplasmic reticulum. Btk function is essential for the survival and differentiation of immature B cells. Consequently, nearly all patients with XLA have a marked deficiency in B cells (<2% of lymphocytes) and profound panhypogammaglobulinemia. XLA accounts for approximately 85% of inherited forms of agammaglobulinemia due to defects in early B-cell development, with autosomal recessive (AR) forms of antibody deficiency accounting for the remainder.[28] The clinical manifestations of the AR forms of agammaglobulinemia are similar to XLA.

In addition to B cells, Btk is expressed on myeloid cells and platelets but not NK cells or T cells. Consequently, T-cell function is normal in XLA, which contrasts with some other antibody deficiency disorders such as CVID or some forms of the hyper-IgM syndrome in which abnormalities in cellular immunity are frequently present. As many as 25% of patients with XLA present with neutropenia, which may contribute to the severity of infection.[29]

Small or absent tonsils and lymph nodes are the only characteristic physical findings in XLA. The vast majority of patients with XLA have recurrent upper (otitis media; sinusitis) and lower respiratory tract infections, with over 50% of patients having recurrent infections by 1 year of age and nearly all patients symptomatic by age 5. The most common pathogens causing pneumonia are encapsulated bacteria (*S. pneumoniae, H. influenzae, Haemophilus parainfluenzae, Staphylcoccus* spp. and *Pseudomonas* spp.).[27] Respiratory tract infections due to atypical bacteria such as *Mycoplasma pneumoniae* or *Ureaplasma urealyticum* are also frequently encountered. Gastrointestinal tract infections occur in nearly one quarter of patients and are most commonly due to *Giardia lamblia,* although bacteria (*Salmonella* spp., *Shigella* spp., *Campylobacter fetus, Helicobacter pylori*) and viruses (*Rotavirus,* enteroviruses) are also frequently isolated. Disseminated infections that include encephalitis due to infection with enteroviruses, in particular echovirus, were a major cause of mortality in patients with XLA. However, these infections appear to be declining with use of high-dose immunoglobulin replacement therapy.[27]

The pulmonary complications of XLA continue to be a major cause of morbidity and mortality and include bronchiectasis, hypoxemia, and cor pulmonale.[27] Complete pulmonary function tests (if possible) and a high-resolution computed tomography (HRCT) scan of the chest are indicated in the initial evaluation of these patients. High-dose IVIG has been shown to decrease pulmonary infections in these patients, but may not prevent the progression of bronchiectasis. Bronchiectasis, if detected, should be treated with daily pulmonary hygiene (e.g., inhaled β-agonists, chest physiotherapy) and aggressive antimicrobial therapy for intercurrent pulmonary infections. The efficacy of rotating antibiotics or chronic antimicrobial therapy in patients with bronchiectasis is unknown.

IVIG is the most commonly used form of antibody replacement for the treatment of profound antibody deficiencies such as XLA and CVID. Subcutaneous infusion of gamma globulin administered at home is an increasingly used alternative form of therapy and has far fewer infustion-related adverse reactions.[30] Higher doses of IVIG (500 to 600 mg/kg) are superior in preventing infections compared to "conventional" doses of IVIG (100 to 150 mg/kg).[31] Intercurrent sinopulmonary infections should be aggressively treated with appropriate antimicrobial therapy to include coverage of common encapsulated bacteria as well as atypical bacterial pathogens (*Mycoplasma* spp., *Ureaplasma*).[32]

A common mistake in managing patients with profound antibody deficiencies (e.g., XLA, CVID) is the inappropriate use of serologic assays in the diagnosis of infectious disorders. With the exception of IgA and IgG subclass deficiency, patients with antibody deficiency do not make specific antibodies in response to exogenous antigens. Therefore, the use of diagnostic studies to detect specific antibodies against pathogens is unreliable and, if positive, usually reflects antibodies present in the IVIG used to treat such patients. Diagnostic studies that detect microbial antigens or nucleic acids (polymerase chain reaction assays) from the pathogen must be used in place of serologic assays.

Common Variable Immunodeficiency

CVID, also known as acquired hypogammaglobulinemia, is a primary immunodeficiency affecting approximately 1:20,000 to 1:50,000 live births.[33] CVID is a clinical syndrome and represents a family of disorders that exhibit a common phenotype. Although highly variable, the mean onset of symptoms in patients with CVID is in the third decade of life. There remains a considerable

delay between the onset of symptoms and the diagnosis of CVID (>7 to 10 years).[9,34,35] Unlike in XLA, T-cell abnormalities are common in patients with CVID and contribute to the more protean clinical manifestations of this disease.[9] The diagnosis of CVID should be considered in any person with recurrent respiratory tract infections (i.e., two or more confirmed pneumonias) and greater than 2 years of age.

The etiology in the vast majority of cases of CVID is unknown. Recent studies show that mutations in inducible T-cell costimulator (*ICOS*) or CD19 as well as polymorphisms of *TACI* or *Msh5* cause CVID in a small percentage of patients.[36–42] Collectively, mutations or polymorphisms of these genes account for less than 10% to 15% of all cases of CVID. Patients with CVID due to polymorphisms in *TACI,* the most common of the genetic abnormalities occurring in approximately 7% of patients with CVID, are more likely to have autoimmune disease and splenomegaly.[43]

The laboratory evaluation of patients with CVID demonstrates the complex nature of the disease.[9] The definitive diagnosis of CVID requires the demonstration of a low serum level of IgG, low serum level of IgA or IgM, and impaired capacity to make specific antibodies in response to immunization or infection, and the exclusion of other primary or secondary antibody deficiencies. IgG levels are reduced by greater than 2 standard deviations from the mean in all patients. IgA levels are low in nearly all patients and IgM levels are reduced in the majority of patients. B-cell numbers are variable in CVID, and if reduced may indicate a poorer prognosis.[9] B-cell subset analysis by flow cytometry is valuable in predicting risk to develop certain complications of CVID. Low numbers of switched memory B cells ($CD27^+$, IgM^-, IgD^-) in the peripheral blood are frequently found in patients with multisystemic granulomatous disease, which is a risk factor for early mortality. Patients with autoimmune complications frequently have increased numbers of CD21 (lo) B cells in the peripheral blood.[44] T-cell abnormalities occur in approximately 40% of patients and include anergy, T-cell lymphopenia, and poor in vitro proliferative responses to mitogens and antigens.

Nearly all patients present with recurrent upper or lower respiratory tract infections, including bronchitis, sinusitis, otitis media, and pneumonia. Common pathogens include encapsulated (*H. influenzae, S. pneumoniae*) or atypical (*Mycoplasma* spp.) bacteria.[9,32,45] Pulmonary infections with gram-negative rods should also be considered, in particular in patients with longstanding CVID or impaired cellular immunity. Opportunistic infections occur in less than 10% of patients. Patients with CVID appear to be particularly susceptible to infections with atypical bacteria such as *Mycoplasma* spp. and *Ureaplasma* spp., and antimicrobial therapy of respiratory tract infections should be used that is effective against these organisms.[32] Apart from respiratory tract infections, joint and bone infections due to these organisms have also been reported. Gastrointestinal tract infections with pathogens similar to those found in XLA (*Campylobacter jejuni, Salmonella* spp., *G. lamblia*) are also common.[9] The prevalence of hepatitis is increased in CVID, occurring in approximately 12% of patients. The prognosis from hepatitis secondary to infection with hepatitis C is poor and may be rapidly progressive in patients with CVID.

The mortality of CVID due to common infectious pathogens has declined with the increased use of high-dose immunoglobulin replacement.[6] Complications such chronic lung disease, malignancy, and autoimmune disease are now the most common cause of morbidity and mortality. Although patients with CVID are unable to make antibodies to foreign antigens, they exhibit increased propensity to make autoantibodies. Consequently, the prevalence of autoimmune disorders, in particular idiopathic thrombocytopenic purpura (ITP) and autoimmune hemolytic anemia (AHA) is increased.[9,46] Oral corticosteroids, the use of immunomodulatory dosages of IVIG (2 g/kg per month), and rituximab have been used to treat AHA or ITP in patients with CVID.[46]

Patients with CVID are at high risk to develop malignancy. In particular, the prevalence of non-Hodgkin's lymphomas and gastric carcinoma are increased in CVID and are a major cause of morbidity and mortality in this disorder.[47] Careful periodic examination of the lymph nodes and spleen is important, as patients with CVID also frequently have adenopathy and splenomegaly that is nonmalignant in nature. The use of periodic abdominal computed tomography (CT) scans to assess spleen size, and/or the presence of intra-abdominal and retroperitoneal adenopathy, along with upper and lower endoscopic evaluation for gastrointestinal symptoms, may also be useful.

The pulmonary disorders associated with CVID are complex and a major cause of mortality.[44,48–51] Bronchiectasis is the most common pulmonary disorder, occurring in over 20% of patients. Although not consistently found, some investigators report that patients with low serum levels of mannose-binding lectin or low numbers of IgM^+ switched memory B cells with low serum levels of antipneumococcal IgM antibodies may be at risk for increased pulmonary infections and bronchiectasis.[52,53] It is not clear that high-dose gamma globulin replacement therapy can prevent the development of bronchiectasis in patients with CVID.[35] Treatment of bronchiectasis in patients with CVID is similar to the therapy of idiopathic bronchiectasis. Mobilization of pulmonary secretions through the use of medications such as β_2-agonists along with chest physiotherapy is frequently used, although there are few trials that demonstrate the effectiveness of pulmonary hygiene.[54] The early, aggressive treatment of pulmonary infection is indicated in these patients. The efficacy of rotating antimicrobial therapy or thrice-weekly, low-dose azithromycin is also unproven, but individual patients may benefit from such therapy. Diffuse interstitial lung disease (granulomatous lung disease, lymphocytic interstitial pneumonia [LIP], follicular bronchiolitis, bronchiolitis obliterans with organizing pneumonia) occurs in approximately 10% to 25% of patients with CVID and is refractory to IVIG therapy.[44,48–51,55]

There has been considerable controversy regarding the nature and clinical course of granulomatous lung disease in CVID. Some believe that the granulomatous disease in CVID represents a form of sarcoidosis.[56] Common features shared with sarcoidosis include the systemic nature of the disease, frequent presence of mediastinal and hilar adenopathy, and noncaseating granulomas in the lungs and other organs. It now appears likely that this disorder represents a distinct disease entity.[44,51] Unlike sarcoidosis, granulomatous and lymphoproliferative histopathologic patterns (LIP, follicular bronchiolitis, and lymphoid hyperplasia) often appear together, and the term *granulomatous-lymphocytic interstitial lung disease* (GLILD) has been used to characterize this disorder.[51] Other distinguishing features of GLILD in comparison to sarcoidosis include the lack of spontaneous remission of lung disease, poor response to corticosteroid therapy, panhypogammaglobulinemia with low numbers of switched memory B cells, and high prevalence of autoimmune disease, in particular ITP. Patients with granulomatous lung disease and CVID frequently have diffuse adenopathy with splenomegaly and T-cell lymphopenia and are at increased risk to develop non-Hodgkin's lymphoma and of early mortality.[44,51] HRCT of the chest is indicated in the evaluation of patients with GLILD and demonstrates numerous abnormalities, including mediastinal adenopathy and diffuse ground-glass and nodular opacities.[57]

The etiology of GLILD is unknown. In a study of a small cohort of patients, human herpesvirus 8 (HHV8) infection was found in the lung in the majority of patients with GLILD, suggesting that HHV8 infection may underlie the lung and lymphoproliferative disease in a subgroup of patients with GLILD.[58] The overproduction of tumor necrosis factor-α (TNF-α) may also contribute to propagation of granulomatous disease in these patients.[59] Case reports have demonstrated that the use of TNF-α antagonists may lead to regression of granulomatous disease in patients with CVID, lending further support to this hypothesis.[60] Limited anecdotal experience suggests that the GLILD may also respond to low-dose cyclosporine therapy.[61]

The combination of CVID in conjunction with thymoma is known as Good's syndrome.[62] Whether this disorder is unique from CVID or represents another manifestation of the disease is unclear. The thymoma is often not apparent on routine chest radiograph. Autoimmune disorders and opportunistic infections appear to be more common in this group of patients. Resection of the thymoma is recommended, although this will not result in resolution of the immunodeficiency or autoimmunity.[62]

Due to the complexity of the pulmonary disease, periodic chest radiographs, full pulmonary function tests, and HRCT scans of the chest in patients with CVID are indicated. In the diagnostic evaluation of patients with GLILD or other forms of interstitial lung disease, it is essential to obtain sufficient tissue to exclude the diagnosis of lymphoma. Therefore, such patients frequently require an open lung biopsy or mediastinoscopy with lymph node biopsy.

Specific Antibody Deficiency

Specific antibody deficiency (SAD) is a primary antibody deficiency disorder that is characterized by normal levels of IgG, IgA, and IgM but an inability to make specific antibodies, most commonly in response to PS antigens such as Pneumovax.[63,64] Patients with specific antibody deficiency present with recurrent sinopulmonary infections, similar to other forms of hypogammaglobulinemia. The diagnosis of SAD is made by measuring an absence of specific antibody responses following immunization with PS vaccines, most commonly the unconjugated pneumococcal vaccine. Cellular immunity is normal in this disorder. As pointed out earlier in this chapter, considerable controversy exists in regard to what constitutes an "abnormal" response to the pneumococcal vaccine sufficient to make the diagnosis of SAD. Therefore, the prevalence of this disorder is unknown. The initial treatment of SAD is similar to IgA deficiency. However, IVIG is indicated in patients with SAD who fail more conservative treatment.

Immunoglobulin G Subclass Deficiency

IgG subclass deficiency is defined by normal total serum IgG levels with a low level of one or more IgG subclasses. There are four isotypes of IgG in humans, IgG1, IgG2, IgG3, and IgG4. The predominant subclass is IgG1, accounting for over 60% of the total IgG. In some patients evaluated for recurrent sinopulmonary infections, low levels of one of the IgG subclasses are found. However, the significance of IgG subclass abnormality is unclear.[65,66] Some believe that isolated IgG subclass deficiencies predispose patients to recurrent sinopulmonary infections. In contrast, IgG subclass deficiencies, including genetic deletions of IgG subclass loci, are well documented in healthy individuals.[67] Because the clinical significance of isolated IgG subclass deficiencies is unclear, the measurement of IgG subclasses is not warranted in the intial evaluation of patients with recurrent sinopulmonary infections. In patients with an isolated IgG subclass deficiency and recurrent infections, the decision to use IVIG should be based on antibody responses following vaccination.

X-linked Lymphoproliferative Syndrome

X-linked lymphoproliferative syndrome (XLP), or Duncan's disease, is a rare primary immunodeficiency characterized by an extreme sensitivity to infection with Epstein-Barr virus (EBV). Aproximately 80% of XLP (XLP-1) is caused by mutations in the adaptor protein gene *SH2D1A* (also known as *SAP,* the gene for slam-associated protein).[68,69] The SH2D1A adaptor protein affects multiple intracellular signaling pathways in several different lymphocyte subpopulations, including T cells, B cells, and NK cells, a property that leads to the complex immunologic abnormalities seen in these patients. Mutations in the X-linked inhibitor of apoptosis gene (*XIAP*) account for the remainder of patients with XLP (XLP-2), which results in premature apoptosis of

lymphocytes in response to a variety of stimuli.[69] The clinical phenotypes of XLP-1 and XLP-2 are similar with the exception that splenomegaly is frequently the first clinical manifestation of the disease in patients with XLP-2. Patients with XLP have a unique predisposition to infection with EBV, an infection that triggers the immunodeficiency in the vast majority of cases. Approximately 60% of patients with XLP present with overwhelming EBV infection leading to hemophagocytic lymphohistiocytosis. Lymphomas or hypogammaglobulinemia develops following EBV infection in approximately 30% of patients with XLP. Patients may have one or all of the manifestations of the syndrome at the same time. The onset of disease is variable, occurring as early as infancy or well into adulthood. Immunologic abnormalities apart from hypogammaglobulinemia also include markedly reduced NK-cell function and impaired T-cell responses. A deficiency in the numbers of natural killer T cells has been reported to be present in all patients with XLP-1 and XLP-2. The only definitive therapy for XLP is HSCT,[70,71] although IVIG is commonly used in an effort to prevent infections.

Hyper–Immunoglobulin M Syndrome

Hyper-IgM syndrome (HIGM) is a descriptive term that reflects a common laboratory abnormality (high serum IgM level with low serum IgA and IgG levels) that occurs in several otherwise dissimilar types of immunodeficiencies (Table 82-5). Despite the name, high levels of IgM are inconsistently found in all forms of hyper-IgM syndrome.[72,73] Furthermore, many believe that grouping together these distinct immunodeficiencies, some of which are intrinsic B-cell abnormalities, whereas others are complex cellular and humoral immunodeficiencies, leads to diagnostic confusion and is fundamentally flawed. Nevertheless, the classification remains widely used despite the obvious drawbacks. Although we group HIGM under "predominantly antibody deficiencies," only mutations in activation-induced cytodine deaminase (AICD)[74] or uracil nucleotide glycosylase (UNG)[75] result in primary immunodeficiencies that are largely due to antibody deficiency. The other forms of HIGM are complex cellular and humoral immunodeficiencies.

X-Linked Hyper-IgM Syndrome

The classic, X-linked form of HIGM (XHIGM), which accounts for approximately two thirds of cases, is due to a mutation in the CD40 ligand (CD40-L) gene.[72,76] CD40-L is inducibly expressed on activated, CD4 T cells and interacts with CD40, which is expressed on the surface of B cells. The interaction of CD40 on B cells with CD40-L on activated T cells in conjunction with specific cytokines (IL-4) is required for immunoglobulin class switching. Consequently, mutations in CD40-L (or CD40) results in a failure to class switch, leading to defective production of the later immunoglobulin isotypes (IgG, IgA, immunoglobulin E [IgE]). CD40 is also expressed on monocytes and dendritic cells. The lack of CD40-L T-cell interaction with CD40 on monocytes and dendritic cells also contributes to defective cellular immunity.[77] Mutations within the CD40 gene are a rare cause of HIGM with a clinical phenotype similar to that of XHIGM. Low serum levels of IgG are consistently found, and serum levels of IgA are reduced in the majority of patients. However, high serum levels of IgM are an inconsistent finding, occurring in approximately 50% of patients.[72] Antibody responses to immunization show a weak IgM response, without development of IgG- or IgA-specific responses and the absence of immunologic memory. The numbers of switched memory B cells ($CD27^+$, IgD^-, IgM^-) are extremely low. Neutropenia is found in approximately 50% of patients and may respond to treatment with granulocyte colony-stimulating factor (G-CSF).

Patients with XHIGM have recurrent infections beginning early in life. Over half of patients with XHIGM are diagnosed by age 1 and nearly all by age 4. Pneumonia, frequently caused by infection with *P. jirovecii,* is common, occurring in as many as 80% of patients. Sinusitis, otitis media, and other respiratory tract infections occur frequently. Intractable diarrhea, sometimes due to infection with *Cryptosporidium* or more frequently idiopathic, occurs in nearly one third of patients. *Cryptosporidium* infection is also a major cause of sclerosing cholangitis in these patients. Infection of the central nervous system (encephalitis, meningitis), frequently due to infection with echovirus,

TABLE 82-5. Etiologies of Hyper-IgM Syndrome

Mutation	Inheritance	Clinical Phenotype
CD40-L	X-linked	Abnormal cellular immunity, neutropenia in 50%, early onset, recurrent sinopulmonary infections, *Pneumocystis jirovecii* (*carinii*) pneumonia, chronic diarrhea due to *Cryptosporidium* infection, diarrhea, inflammatory bowel disease, autoimmunity
CD40	Autosomal recessive	Similar to CD40-L mutation
NEMO (IKK-γ)	X-linked	Impaired cellular immunity, variable serum levels of IgM or IgA, ectodermal dysplasia (most), recurrent pyogenic infections, viral infections, mycobacterial infections
AICD or UNG	Autosomal recessive	Impaired humoral immunity, normal cellular immunity, later age of onset than other types of hyper-IgM syndrome, increased autoimmunity and lymphadenopathy
Unknown	Variable	Similar to AICD/UNG mutations

AICD, activation-induced cytodine deaminase; AR, autosomal recessive; Ig, immunoglobulin; UNG, uracyl nucleotide glycosylase; see text for other abbreviations.

is a major cause of morbidity and mortality. Treatment of XHIGM includes IVIG, prophylaxis against *P. jirovecii,* G-CSF for neutropenia, and consideration for HSCT.[78]

Mutations of NF-κB Essential Modifier

Hypomorphic mutations within the NF-κB essential modifier (NEMO) gene, an X-linked gene, cause an immunodeficiency characterized by recurrent pyogenic infections, increased susceptibility to mycobacterial infections, and variable B-cell and T-cell abnormalities.[79,80] NEMO, also known as IKK-γ, is part of the IκB kinase (IKK) complex. IKK is responsible for phosphorylating the inhibitor of NF-κB (IκB), thereby releasing NFκB and allowing for its nuclear translocation. The protean immunologic and clinical manifestations due to mutations in NEMO reflect the importance of NF-κB in multiple biologic processes. Approximately 80% of patients with mutations in NEMO have ectodermal dysplasia (abnormal teeth, decreased numbers of sweat glands, fine hair, frontal bossing). The ectodermal dysplasia in these patients is due to the inability of the ectodysplasin A receptor to induce the activation of NF-κB. The susceptibility to mycobacterial infection is likely due to an inability of CD40 ligation to activate the NF-κB pathway, leading to deficient IL-12 production by monocytes and dendritic cells and deficient interferon (IFN)-γ production by T cells and NK cells.[81]

Common immunologic screening tests of immune function may be normal in patients with NEMO deficiency. For example, hypogammaglobulinemia or decreased specific responses to vaccination occur in approximately 60% of patients and high serum level of IgM in only 15% of patients. NK cell function has been reported to be abnormal in all patients with mutations in NEMO and may be a reasonable adjunctive screening test for this disorder.[80,82]

Patients with NEMO mutations have severe infections usually beginning early in life. Common sites of infection include the lung, sinuses, middle ear, skin, and deep tissues (abscesses), blood (septicemia), gastrointestinal tract, and central nervous system. Pyogenic infections are frequently due to *Staphylococcus aureus, S. pneumoniae,* and *H. influenzae* and occur in nearly 90% of patients. Mycobacterial infections (pneumonia, cellulitis, lymphadenitis, osteomylelitis) occur in over 40% of patients and are usually caused by *Mycobacterium avium-intracellulare.* Severe viral infections (encephalitis, gastroenteritis, viremia) occur in approximately 20% of patients. Herpesviruses (herpes simplex virus, CMV) and adenoviruses are the most frequent viral pathogens. Opportunistic infections due to *P. jirovecii* or fungi occur in 10% of patients. Autoimmune disease—in particular, inflammatory colitis—occurs in approximately 20% of patients and can lead to intractable diarrhea. Treatment of patients with NEMO mutation frequently includes replacement gamma globulin and antimicrobial prophylaxis (*Pneumocystis,* mycobacteria). HSCT has had variable success in treating this disorder.[83]

Mutations in AICD or UNG

Mutations in AICD[74] or UNG[75] are causes of AR forms of HIGM. AICD and UNG are essential for class switch recombination.[84] Hence, mutations in AICD or UNG result in high serum levels of IgM, with low serum levels of IgG and IgA. Patients with mutations in either AICD or UNG have a similar clinical phenotype with impaired humoral immunity and intact cellular immunity.[85] Recurrent upper and lower respiratory tract infections and gastrointestinal tract infections frequently occur. Lymphadenapathy is frequent and autoimmunity (AHA and ITP) occurs in approximately 20% of patients.

DEFICIENCIES IN CELLULAR IMMUNITY/ COMPLEX IMMUNODEFICIENCIES

DiGeorge Syndrome

DiGeorge syndrome (DGS), also known as 22q11.2 deletion syndrome or velocardiofacial syndrome, is one of the most common primary immunodeficiencies, occurring in approximately 1 in 3000 live births. The vast majority of patients with DGS have hemizygous deletion of varying degrees in chromosome 22q11.2, with rare cases due to deletion of 10p13. The molecular basis for many of the clinical manifestations of DGS appears to be deletions or mutations in TBX1, a T-box transcription factor important in embryonic development.[86] Background genes also contribute to the phenotype in DGS as patients with identical deletions of 22q11.2 may have a markedly different clinical phenotypes. Patients with DGS exhibit a characteristic facies that includes hypertelorism, saddle nose, shortened philtrum, and low-set ears.[87] Other common features of DGS include hypoplasia of the thymus and parathyroid glands, immunodeficiency, autoimmunity, cardiac abnormalities, velopharyngeal insufficiency, speech delay, developmental delay, and behavioral and psychiatric problems. Nearly 90% of infants diagnosed with DGS in infancy have cardiac abnormalities, and screening for DGS should be considered in any infant with an interrupted aortic arch, truncus arteriosus, tetralogy of Fallot, and anomalous aortic arch (with or without a ventral septal defect).[33,87]

In patients who are not diagnosed in infancy, recurrent infections are common and frequently lead to the diagnosis of DGS.[33] The immunodeficiency associated with DGS is highly variable and correlates with the degree of thymic hypoplasia.[87–89] Patients with "complete DGS," comprising less than 0.5% of the overall numbers of DGS patients, have a profound deficiency of T cells and T-cell function that requires thymic transplantation.[90] In contrast, the majority of patients with DGS are referred to as "partial DGS." Patients with partial DGS generally have a variable, usually non–life-threatening immunodeficiency. Patients with partial DGS may have moderately diminished numbers of T cells, and T-cell defects in these patients are usually mild with relatively normal in vitro and in vivo (delayed-type hypersensitivity

skin tests) assessment of T-cell function. Intact thymic function is essential for deletion of autoreactive T cells. Consequently, patients with DGS have an increased prevalence of autoimmune disorders. Approximately 10% of patients with DGS have autoimmune disease. Juvenile arthritis, AHA, and IPT are the most common autoimmune diseases in DGS. Studies of humoral function have yielded conflicting results. An abnormality in humoral immunity (IgA deficiency, decreased specific antibody production) in one cohort of patients was reported to be as high as 40%.[91] However, most studies show that the need for immunoglobulin therapy is low (<15%) in patients with DGS.

Most patients with DGS tolerate live virus vaccines without complications, but an assessment of humoral and cellular immune function should be performed prior to their administration. Infectious complications of partial DGS usually include recurrent sinopulmonary infections and otitis media. Structural abnormalities of the palate may contribute to recurrent sinus disease in these patients. Opportunistic infections are infrequent in partial DGS, although oral and esophageal thrush is seen. Patients with complete DGS are highly susceptible to infection with opportunistic pathogens, reflecting the much more severe cellular immunodeficiency. Attenuated live virus vaccines should be avoided and irradiated blood and blood products used to avoid graft-versus-host disease.

Wiskott-Aldrich Syndrome

Wiskott-Aldrich syndrome (WAS) is an X-linked disorder characterized by recurrent infections, eczematous skin disease, and thrombocytopenia due to a mutation in the WAS protein (WASp) gene.[92] The function of WASp is complex, but through its interaction with a variety of adaptor molecules and kinases, WASp is involved in the integration of cytoplasmic signaling with the reorganization of the actin cytoskeleton. Consequently, WASp function is critical in the formation of the immunologic synapse, cellular motility, cellular trafficking, and protection against autoimmunity.[93] Mutations in the WASp gene cause four distinct diseases: (1) classic WAS; (2) X-linked thrombocytopenia; (3) intermittent thrombocytopenia; and (4) congenital X-linked neutropenia without other features of WAS.[94] We limit this section to classic WAS.

The laboratory evaluation of patients with WAS usually demonstrates increased levels of serum IgE and IgA with low a level of IgM and normal level of IgG. Despite normal serum IgG levels, impaired antibody responses following immunization to PS antigens is consistently present.[95] Abnormalities in T-cell and NK-cell function occur frequently, resulting in a partial combined immunodeficiency.[96] Decreased platelet counts, platelet function, and platelet size are hallmarks of the disorder and lead to the marked bleeding diathesis.

The clinical expression of WAS includes prolonged bleeding episodes beginning in infancy, recurrent pygogenic infections, autoimmunity, eczematous dermatitis, and an increased prevalence of EBV-related lymphomas. Upper and lower respiratory infections due to encapsulated organisms (*S. pneumoniae* and *H. influenzae*) are common and reflect the inability of patients with WAS to make specific antibody to PS antigens.[95] Pulmonary infections with opportunistic pathogens (*P. jirovecii,* herpesviruses) are also common. Infection and hemorrhage are common causes of death. The treatment of WAS includes aggressive treatment of intercurrent infections and administration of IVIG.[95] The thrombocytopenia usually responds to splenectomy. HSCT is the treatment of choice for WAS, with long-term survival rates over 70%.[93]

Ataxia-Telangiectasia

Ataxia-telangiectasia (AT) is an AR disorder due to a mutation in the AT gene, which is involved in the repair of DNA breaks.[97,98] The clinical manifestations of AT include neurologic dysfunction (cerebellar ataxia, oculomotor apraxia, delayed motor development), telangiectasias, and immunodeficiency. The mutation in the AT gene with an attendant increased radiosensitivity leads to the increased prevalence of malignancies (lymphomas, epithelial tumors) in this disorder.[97,98] The manifestations of immunodeficiency typically begin in infancy or early childhood and resemble antibody deficiencies. Serum immunoglobulins are usually normal in AT, but hypogammaglobulinemia and defective responses to immunization with pneumococcus vaccine are not infrequent. Elevated levels of carcinoembryonic antigen and alpha-fetoprotein are present in nearly all patients with AT. There is no definitive treatment of AT. Patients with AT should be sent to tertiary referral centers with experience in these disorders to assist in their management.

Hyper–Immunoglobulin E Syndrome

Hyper-IgE syndrome (HIES), also known as Job's syndrome, is a syndrome characterized by recurrent skin and lung infections, severe eczema, and elevated levels of serum IgE. There are two forms of HIES. The more common autosomal dominant (AD) form of HIES is caused by mutations in the transcription factor signal transducer and activator of transcription-3 (STAT-3) and has extra-immunologic features (connective tissue disorders, skeletal abnormalities) not present in the AR form.[99] In addition, the AR form is complicated by a much higher incidence of cutaneous viral infections and neurologic complications and lacks the characteristic facies present in the AD form of HIES.[99,100] Mutations in the kinase Tyk2 may cause the AR form of HIES in a small minority of patients.[101] The remainder of this discussion will focus on the AD form of HIES.

The clinical features of HIES include the onset of moderate to severe eczema and eosinophilic pustular folliculitis in early infancy, skin infections (abscesses), mucocutaneous candidiasis, and recurrrent pneumonias with pneumatoceles. Pneumatoceles are thought to develop as a consequence of disordered healing following primary infection of the lung. Common primary pathogens in HIES syndrome include *S. aureus, S. pneumoniae, H. influenzae,* and *Candida albicans.*

Secondary infection of the pneumatocoeles with *Aspergillus* spp. or *Pseudomonas aeruginosa* often results in invasion of the pulmonary vasculature leading to pulmonary hemorrhage or central nervous system infection, which are major causes of death.[102] The signs and symptoms of serious infection are frequently absent in patients with HIES. Abscesses may develop without signs of external inflammation (cold abscess) or pneumonia may be present with limited clinical symptoms. Therefore, increased vigilance for infection is necessary in the management of patients with HIES.

There are several nonimmunologic features of HIES that aid in the early diagnosis of this disease. Patients with HIES have a characteristic facies (coarse facial features with a protuberant mandible and forehead, hypertelorism, and a broad, fleshy nasal tip), retained primary teeth, severe osteopenia with fractures following minimal trauma, scoliosis, and hyperextendible joints. A recently discovered abnormality in patients with HIES is the proclivity to develop aneurysms, in particular aneurysms of the coronary arteries.[103] The clinical significance of the aneurysms and proper management are unknown at this time.

The diagnosis of HIES cannot be made by routine assays of immunologic function. Typical abnormalities in the laboratory evaluation of patients with HIES include an elevated IgE (>2000 IU/mL) and eosinophilia. These laboratory abnormalities are not pathognomic of HIES and may be present in patients with severe atopic dermatitis. Elevated levels of serum IgE may wane with age, and a normal IgE level does not exclude the diagnosis of HIES.

An understanding of the molecular pathogenesis of HIES was significantly advanced with the discovery that mutations in the STAT-3 gene are the cause of this disorder. The STAT-3 gene codes for a transcription factor that is essential for the biologic activities of numerous cytokines, including IL-6 and IL-10.[104] The absence of the anti-inflammtory effects of IL-10 likely contributes to the dysregulated inflammatory response seen in HIES patients.[105] Interleukin-6 is required for the genesis of $CD4^+$ Th17 cells in humans and, therefore, there is a deficiency of Th17 cells in HIES.[106] Th17 cells are important in the defense against extracellular bacteria and fungi.[107]

The treatment of HIES focuses on the prevention and prompt treatment of infection. Antimicrobial prophylaxis to prevent infection with *S. aureus* is often given. The role of antifungal prophylaxis is unknown. Optimal skin care, including the use of bleach baths, topical corticosteroids, and hydrating measures for eczema, is essential. IVIG or IFN-γ may benefit some patients.[108] As the treatment of HIES is not optimal, other therapies, including HSCT, may be considered in the future.

PHAGOCYTIC CELL DISORDERS

Phagocytic defects can initially be separated by abnormalities intrinsic or extrinsic to the phagocyte. Examples of intrinsic phagocyte defects include defects in adhesion, chemotaxis, signaling, or killing. Alternatively, there are examples of primary immunodeficiencies in which phagocytic cell function is normal, but auxiliary components necessary to optimal phagocytic function are absent. For example, immunoglobulins and complement are necessary for optimal phagocytic function.

There are several indications for evaluation of patients for phagocytic abnormalities, including neutropenia or the lack of neutrophilia with significant infection, infections with unusual or opportunistic pathogens (e.g., fungi such as *Aspergillus or Nocardia;* bacteria such as *Serratia marcescens or Burkholderia cepacia*), unusual sites of infection (e.g., recurrent osteomyelitis, abscesses in the brain, lung, or liver), systemic bacterial infections, recurrent skin or upper or lower respiratory tract infections, and cold abscesses. Apart from infection, patients with phagocytic defects may have ongoing chronic inflammatory responses in the skin (e.g., eczematoid dermatitis) or mucous membranes (e.g., periodontitis, aphthous stomatitis) and disordered inflammatory responses leading to delayed or abnormal wound healing.

Phagocytic Defects: Increased Apoptosis of Neutrophils

Cyclic Neutropenia and Congenital Agranulocytosis (Kostmann's Syndrome)

Cyclic neutropenia is an AD disorder due to a mutation in the gene for neutrophil elastase-2 (ELA2). It is thought that mutations of ELA2 induce premature apoptosis of neutrophil precursors by the induction of the unfolded protein response.[109] In cyclic neutropenia there is a regular, 21-day fluctuation of neutrophils and other blood components (platelets, monocytes, reticulocytes).[109,110] During the periods of neutropenia, patients are predisposed to bacterial infection with pyogenic bacteria and opportunistic pathogens. The diagnosis of cyclic neutropenia should be suspected in the context of cyclic hematopoiesis and neutropenia that coincide with recurrent infections. To document concurrent infection with neutropenia, serial complete blood counts (two to three times/week) for at least 6 weeks should be performed. Most cases of AR congenital agranulocytosis (Kostmann's syndrome) are due to mutations in the gene for HAX1, a mitochondrial protein that is thought to protect myeloid cells against apoptosis.[111]

The clinical manifestations of congenital agranulocytosis typically begin in early infancy with life-threatening infections (cellulitis, meningitis, perirectal abscesses, sepsis).[112] Patients with congenital agranulocytosis have severe neutropenia with an absolute neutrophil count of less than 200/μL. The clinical manifestations of congenital agranulocytosis are more severe than those of cyclic neutropenia. The use of G-CSF is indicated in cyclic neutropenia and congenital agranulocytosis; it will increase neutrophil counts and reduce infection in the vast majority of patients with either disorder.[112] In patients with severe neutropenia unresponsive to G-CSF, HSCT should be performed.[113]

Decreased Adherence/Chemotaxis

Leukocyte Adhesion Deficiency Types I–III

The influx of leukocytes in general and neutrophils in particular to sites of infection is a complex process involving the production and release of neutrophils from the bone marrow, and the activation of neutrophils by chemotactic factors with subsequent adhesion of neutrophils to the endothelium, followed by transmigration of neutrophils through the endothelium of postcapillary venules. The first step in the egress of neutrophils from the circulation to sites of infection is mediated by the rolling (loose) adhesion of neutrophils to endothelium, mediated predominantly by CD15s (sialyl $Lewis_x$) on the neutrophil and its counter-ligands (E-selectin, P-selectin) on the endothelium. The following step in adhesion, which is of higher affinity, is mediated predominantly by the interaction of the integrin leukocyte function–associated antigen (LFA-1; CD11a/CD18) on the leukocyte with its counter-ligand intracellular adhesion molecule-1 on the endothelium. Integrins are composed of two subunits, (α,β), which are non-covalently associated. The common β chain of CD18 associates with CD11a (LFA-1), CD11b (Mac-1 or CR3), CD11c (gp150. 95) and CD11d, which are expressed on a variety of leukocytes. Therefore, mutations in CD18 reduce the expression of CD11a, CD11b, and CD11c, resulting in defects in the endothelial adhesion of all leukocytes. Mutations in CD18 and CD15s lead to the primary immunodeficiencies leukocyte adhesion deficiency type I (LAD-I) and LAD type II (LAD-II), respectively.[114,115] LAD type III (LAD-III) is a neutrophil defect characterized by a failure to activate integrins in response to cytokines and chemokines. A minority of cases of LAD-III are due to mutations in the calcium- and diacylglycerol-regulated guanine nucleotide exchange factor 1 (CalDAG-GEFI), a Rap-1/2 guanine exchange factor.[116]

LAD-I is divided into two broad categories based on whether the deficiency of LFA-1 is severe (<0.5% of normal levels) or moderate (5% to 10% of normal levels).[117] Patients with a complete deficiency in LFA-1 expression often present in the neonatal period with delayed separation of the umbilical cord, omphalitis, and severe infections of the skin, gingiva, gastrointestinal and upper and lower respiratory tracts. Moderate deficiencies of LFA-1 result in a milder phenotype that may contribute to a delay in the diagnosis. Patients with LAD-I exhibit neutrophilia, even in the absence of systemic infection, due to the inability of leukocytes to adhere to the endothelium. The definitive diagnosis of LAD-I deficiency is made by the demonstration of extremely low levels of LFA-1 on neutrophils by flow cytometry. The treatment of LAD-I deficiency includes the aggressive use of antimicrobials in the treatment of infection. HSCT is the only definitive treatment for patients with severe deficiencies of LFA-1.[114,118] Moderate deficiencies of LFA-1 may improve with recombinant IFN-γ therapy and chronic antimicrobial prophylaxis.

LAD-II is an extremely rare disorder characterized by developmental delay, mental retardation, and recurrent infection similar to LAD-I. A mutation in the GDP-fucosyl transporter leads to the absence of CD15s on leukocytes and expression of the Bombay blood phenotype (hh).[119] Oral fucose administration can induce the expression of CD15s, leading to improvement of the central nervous system abnormalities and decreased infection.[120] LAD-III is also a rare disorder characterized by recurrent infections, bleeding tendency, and leukocytosis. Patients with LAD-III and mutations in CalDAG-GEFI also have neurologic abnormalities (developmental delay or mental retardation, seizure disorders). CalDAG-GEFI is expressed in hematopoietic cells and neurons and serves as a Rap-1/2 guanine exchange factor, and is necessary for activation of β_1-, β_2-, and β_3-integrins. The leukocytosis, bleeding tendency, and neurologic manifestations reflect the importance of β-integrins in diverse biologic processes.

Defects in Oxidative Killing

Chronic Granulomatous Disease

CGD is a rare (1 in 1 million live births) immunodeficiency due to mutation in one of the four subunits of the phagocyte NADPH oxidase (PHOX) system. The function of NADPH oxidase is to transfer an electron to molecular oxygen (O_2), leading to the formation of superoxide.[121–123] Approximately two thirds of cases of CGD are X-linked due to a mutation in the g91phox subunit of NADPH oxidase. Mutations of the other subunits of NADPH oxidase (p22, p47, p67) are inherited in an AR pattern and account for the remainder of cases.

The clinical manifestations of CGD usually begin early in life (mean age of onset, 4.4 years) but may not manifest until adulthood. CGD is characterized by recurrent infections with catalase-positive organisms (*Aspergillus* spp., *S. aureus, B. cepacia,* and others). The lungs (pneumonia) and skin are the most common sites of infection, but osteomyelitis, liver abscesses, lymphadenitis, and anorectal infections occur frequently as well.[124] The most common chest CT abnormalities include areas of consolidation and nodular opacities, both associated with either infection or granulomatous inflammation.[125] Invasive aspergillosis is the most common primary cause of death. Autoimmune diseases appear to be increased in CGD, and carriers of X-linked CGD are at increased risk for discoid lupus and photosensitivity.[126] As previously discussed, the diagnosis of CGD is readily made by the use of either the NBT or the DHR test.

Apart from infectious complications, disordered inflammation and wound healing are hallmark manifestations of the disease.[127] Inflammatory granuloma formation may lead to urinary or gastrointestinal tract obstruction. Exuberant granulation tissue leads to disordered wound healing, including wound dehiscence following surgical procedures. The molecular basis for the disordered inflammatory response that is characteristic of CGD is complex. Gene array experiments comparing global gene expression of normal and X-linked CGD neutrophils indicate that CGD neutrophils constitutively

overproduce proinflammatory mediators and exhibit defective neutrophil apoptosis due to the overproduction of the antiapoptotic protein Bcl-xl.[128] Additionally, upon apoptosis, CGD neutrophils do not properly externalize phosphatidylserine. Phosphatidylserine is the ligand for the phosphatidylserine receptor, which is present on macrophages and mediates the efficient clearance of apoptotic cells.[129] Consequently, there is a delay in the removal of apoptotic CGD neutrophils by macrophages.[130] The deficiency in uptake of apoptotic cells may lead to decreased production of anti-inflammatory mediators such as transforming growth factor-β, thereby contributing to the overproduction of inflammatory cytokines.[127] Thus, the increased production of proinflammatory mediators, reduced apoptosis, and delayed clearance of apoptotic neutrophils all likely lead to the disordered inflammatory response in CGD.

The therapy of CGD includes aggressive treatment of infection, including surgical incision and drainage when indicated.[131] The prophylactic administration of trimethoprim-sulfamethoxazole markedly reduces infection, in particular infections caused by *S. aureus.*[132] Prophylactic itraconazole reduces serious fungal infections.[133] Interferon-γ reduces infections and decreases mortality in both X-linked and AR CGD, although the benefits of interferon therapy have been challenged recently.[124,134] Gastrointestinal and urinary tract obstruction due to granuloma formation is treated with systemic corticosteroids.

Disorders of Leukocyte Signaling

Defects in the IFN-γ/IL-12/IL-23 Axis

Th1 type T cells are defined by their capacity to produce high levels of cytokines (IL-2, IFN-γ, TNF-α) that are essential in the generation of a robust cellular immune response. Interferon-γ, which is also produced by NK cells, interacts with a heterodimeric receptor, IFN-γ receptor 1 (IFN-γR1), the ligand binding receptor, and IFN-γ receptor 2 (IFN-γR2), which is required for downstream signaling. Upon ligand binding by IFN-γR1/R2, the Janus activating kinases 1 and 2 (JAK1 and JAK2) are activated, which subsequently phosphorylate the STAT-1 protein in the cytoplasm, leading to homodimerization of STAT-1, translocation to the nucleus, and transcriptional activation of STAT-1–dependent genes. One important biologic function of IFN-γ is to induce the production of IL-12 p70 by dendritic cells and macrophages, which then feeds back in a positive loop to further induce the production of IFN-γ by NK cells and T cells. Interleukin-12 p70 is composed of two disulfide-linked subunits, p35 and p40, the latter of which also associates with the p19 subunit to form IL-23. The IL-12 receptor (IL-12R) is composed of two subunits, IL-12Rβ1 and IL-12Rβ2. Interleukin-12Rβ1 also serves as part of the heterodimeric IL-23 receptor (IL-12Rβ1 and IL-23R). Thus, the IFN-γ/IL-12/IL-23 axis is intrinsically linked due to the biologic functions of IFN-γ and IL-12, the shared cytokine subunit of IL-12 and IL-23 (p40), and the common cytokine receptor subunit of IL-12R and IL-23R (IL-12Rβ1).

Mutations of the genes for IFN-γR1 or IFN-γR2, STAT-1, IL-12 p40, IL-12Rβ1, and NEMO (see earlier discussion) define a group of primary immunodeficiencies known as mendelian susceptibility to mycobacterial disease (MSMD) (Table 82-6).[135,136] Due to the marked hetereogeneity in inheritance, the functional consequences of mutations in these six genes (complete or partial) leads to 13 distinct genetic disorders associated with MSMD. Patients with mutations in one of these six genes are susceptible to infection with *Mycobacteria* and/or *Salmonella,* but are usually resistant to infections with most other pathogens.[135,136] This narrow susceptibility to infection is somewhat surprising based on the importance of Th1 responses in combating infection with a wide variety of pathogens in studies using mice.

AR complete IFN-γR1 deficiency is characterized by the onset of infection with environmental mycobacteria, frequently rapid growers such as *Mycobacterium fortuitum* and *Salmonella,* at an early age (<3 years). The disorder is fatal without HSCT. However, HSCT is frequently not successful in patients with IFN-γR1 deficiency due to preexisting high IFN-γ levels that prevent engraftment. AD partial IFN-γR1 deficiency has a much less severe phenotype, with a mean age of onset at 13 years of age. These patients are susceptibile to infection with environmental mycobacteria and may develop disseminated disease following vaccination with bacille

TABLE 82-6. Etiologies of Mendelian Susceptibility to Mycobacterial Disease (MSMD)

Gene	Inheritance	Defect	Percentage of Patients with MSMD	Treatment
IL12RB1	AR	C	40%	IFN-γ
IFNGR1	AR/AD	C/P	39%	AR-C: HSCT AD-P: IFN-γ
IL12B	AR	C	9%	IFN-γ
STAT1	AD	P	5%	Varies depending on location of mutation
IFNGR2	AR	C/P	4%	AR-C: HSCT AR-P: IFN-γ
NEMO (*IKBKG*)	X-linked	P	3%	HSCT

AD, autosomal dominant; AR, autosomal recessive; C, complete deficiency; HSCT, hematopoietic stem cell transplantation; IFN, interferon; P, partial deficiency.

Calmette-Guérin. Additionally, patients with partial IFN-γR1 deficiency are uniquely predisposed to mycobacterial osteomyelitis, which should trigger an evaluation for this disorder. AR complete IFN-γR2 deficiency and AR partial IFN-γR2 deficiency are rare, and the described phenotype to date is similar to AR complete IFN-γR1 deficiency and AD partial IFN-γR1 deficiency, respectively. The phenotype of patients with a STAT-1 mutation varies depending on the site of the mutation. As previously discussed, STAT-1 homodimers mediate the transcriptional effects of IFN-γ. STAT-1 also forms a heterodimer with STAT-2, which is the transcription factor formed following binding of IFN-α/β with its receptor. Consequently, some patients with mutations in STAT-2 are susceptible to viral infections and mycobacterial disease. AR complete mutations of IL-12 p40, which is the only described immunodeficiency of a cytokine gene to date, result in a markedly increased susceptibility to infection with *Salmonella* in addition to mycobacterial disease. Similarly, AR complete IL-12Rβ1 deficiency, which is the most common cause of MSMD, also results in an increased susceptibility to infection with mycobacteria and *Salmonella.* The clinical phenotype of AR complete IL-12Rβ1 deficiency is milder than complete defects in IFN-γR1 or IFN-γR2 and only a few patients (17%) succumb to disease. Interferon-γ is useful in the treatment of patients with either IL-12Rβ1 deficiency or IL-12 p40 deficiency.

DISORDERS IN INNATE IMMUNITY

IRAK-4 and MyD88 Deficiencies

Toll-like receptors (TLRs) are a family of pattern recognition receptors that are activated following microbial infection, resulting in the activation of innate immune responses. TLRs recognize conserved motifs derived from a variety of pathogenic microorganisms, including bacteria, fungi, and viruses. Upon ligand binding, all members of the TLR family, with the exception of TLR3, use MyD88 as a key adaptor molecule to recruit IL-1 receptor–associated kinases (IRAKs) leading to downstream signaling events resulting in the activation of the transcription factors NF-κB and AP-1. Mutations in either MyD88 or IRAK-4 result in phenotypically similar primary immunodeficiencies. The primary immunodeficiencies caused by mutations in either MyD88 or IRAK-4 are characterized by invasive infections (meningitis, septicemia, liver abscess) predominantly with *S. pneumoniae* (79% of patients) or *S. aureus* (50% of patients).[137,138] Infections with gram-negative rods occur in approximately 25% of patients. No severe infections with viruses, fungi, or parasites were observed, which is surprising based on the broad immunodeficiency found in mice with targeted deletion of MyD88. The onset of invasive infection is early in life (vast majority before age 2) and improves with age. All deaths in patients with IRAK-4 deficiency occurred by age 8. Standard screening tests of immune function are normal. Peripheral blood mononuclear cells exhibited decreased inflammatory cytokine production in response to IL-1 and all TLR agonists except agonists of TLR3. The proper management of patients with MyD88 or IRAK-4 mutations remains to be determined, but prophylactic antibiotics and IVIG may be useful.

Complement Deficiencies

Complement has many important functions that include the modulation of inflammatory responses (e.g., vasodilation, leukocytosis, and chemotaxis), clearance of immune complexes, modulation of the immune response (e.g., enhanced production of antibodies), and microbial elimination (opsonization, neutralization, and microbicidal activity). Complement may also be important in the efficient removal of apoptotic cells, resulting in the presentation of self antigens and the induction of autoimmunity. Deficiencies in components of the complement system are usually manifest by an increased propensity to infection or autoimmunity.[1,139] There are several indications for the evaluation of the complement system, such as a strong family history of autoimmune diseases, recurrent infections caused by encapsulated bacteria, a family history of meningococcal disease, infection caused by unusual types of meningococcus (Y, W-135), age greater than 9 years at the time of meningococcal disease, and recurrent angioedema.

Defects in the early components of complement (C1q, C1s, C2, C4), which are inherited in an autosomal codominant manner, typically lead to an increased prevalence of autoimmune disease (primarily systemic lupus erythematosus). Redundancies in the complement pathway, including the alternative and mannose-binding lectin pathways, may explain why only a minority of patients with early complement deficiencies develops serious bacterial infections. Encapsulated bacteria (*S. pneumoniae, H. influenzae*) are the most common pathogens in people with recurrent infection due to deficiency in early complement components.[13] C2 deficiency is the most common early component deficiency, occurring in 1:10,000 to 1:28,000 live births.

The classical, alternative, and mannose-binding lectin pathways all converge at C3. For this reason, deficiencies in C3 result in more severe infections than deficiencies in other components of complement. Patients with C3 deficiency have an increased prevalence of autoimmune disease and present in a manner similar to those with antibody deficiency.

Deficiencies in the terminal components of the complement pathway (C5 to C9) are inherited in an autosomal codominant manner. Patients with late-component deficiencies are highly predisposed to infection with *N. meningitidis and Neisseria gonorrhoeae.* For reasons that are not clear, meningococcus serogroups W-135 and Y account for the vast majority of meningococcal meningitis infections in patients with late-component complement deficiencies. The prevalence of autoimmune disease is also increased in these patients, but to a much lesser extent than deficiencies in the early components of the complement cascade. Patients with late-component deficiencies usually have the onset of

infection at an older age, and many are asymptomatic well into adolescence.[13]

Deficiencies in components of the alternative pathway (factor D, properdin) are extremely rare and present with increased bacterial infections, including infections with *Neisseria* spp. Properdin deficiency is an X-linked inherited disorder in contrast to the other complement deficiencies (with the exception of hereditary angioneurotic edema), which are inherited in an autosomal codominant manner.

Therapy for complement deficiencies is primarily supportive. Individuals should be vaccinated against common bacterial pathogens associated with complement deficiency (e.g., *S. pneumoniae, H. influenzae, N. meningitidis*). Prophylactic antibiotics may be used in selected situations.

KEY POINTS

- PIDD frequently are not diagnosed in a timely manner, leading to increased morbidity and mortality.
- Patients recurrent upper infections, intractable sinusitis or more than one radiographically documented pneumonia should be evaluated for PIDD.
- Although infection with opportunistic pathogens should always lead to a search for primary or secondary immunodeficienies, common pathogens frequently cause infections in patients with PIDD.
- Advanced age does not exclude the diagnosis of PIDD as there are more adults than children with PIDD.
- Screening tests for most PIDD will frequently be abnormal and should lead to referral to a clinical immunologist for a specific diagnosis.
- The pulmonary complications of PIDD are varied and depend on the nature and severity of the specific disorder.

References

1. Coutinho A, Carneiro-Sampaio M: Primary immunodeficiencies unravel critical aspects of the pathophysiology of autoimmunity and of the genetics of autoimmune disease. J Clin Immunol 28(Suppl 1):S4–S10, 2008.
2. Holzelova E, Vonarbourg C, Stolzenberg MC, et al: Autoimmune lymphoproliferative syndrome with somatic Fas mutations. N Engl J Med 351:1409–1418, 2004.
3. Bonilla FA, Bernstein IL, Khan DA, et al: Practice parameter for the diagnosis and management of primary immunodeficiency. Ann Allergy Asthma Immunol 94(5 Suppl 1):S1–S63, 2005.
4. Immune Deficiency Foundation: Primary Immune Deficiency Diseases in America: 2002. Towson, MD: Immune Deficiency Foundation, 2002.
5. Puck JM: Population-based newborn screening for severe combined immunodeficiency: Steps toward implementation. J Allergy Clin Immunol 120:760–768, 2007.
6. Busse PJ, Razvi S, Cunningham-Rundles C: Efficacy of intravenous immunoglobulin in the prevention of pneumonia in patients with common variable immunodeficiency. J Allergy Clin Immunol 109:1001–1004, 2002.
7. Bustamante J, Zhang SY, von Bernuth H, et al: From infectious diseases to primary immunodeficiencies. Immunol Allergy Clin North Am 28:235–258, vii, 2008.
8. Folds JD, Schmitz JL: Clinical and laboratory assessment of immunity. J Allergy Clin Immunol 111(2 Suppl):S702–S711, 2003.
9. Cunningham-Rundles C, Bodian C: Common variable immunodeficiency: Clinical and immunological features of 248 patients. Clin Immunol 92:34–48, 1999.
10. Nelson HS, Hamilos DL, Corsello PR, et al: A double-blind study of troleandomycin and methylprednisolone in asthmatic subjects who require daily corticosteroids. Am Rev Respir Dis 147:398–404, 1993.
11. Hamilos DL, Young RM, Peter JB, et al: Hypogammaglobulinemia in asthmatic patients. Ann Allergy 68:472–481, 1992.
12. Buckley RH: Primary cellular immunodeficiencies. J Allergy Clin Immunol 109:747–757, 2002.
13. Frank MM: Complement deficiencies. Pediatr Clin North Am 47:1339–1354, 2000.
14. Elloumi HZ, Holland SM: Diagnostic assays for chronic granulomatous disease and other neutrophil disorders. Methods Mol Biol 412:505–523, 2007.
15. Puck JM: Severe combined immunodeficiency: New advances in diagnosis and treatment. Immunol Res 38:64–67, 2007.

15a. Routes JM, Grossman WJ, Verbsky J, et al: Statewide newborn screening for severe T-cell lymphopenia. JAMA 302:2465–2470, 2009.

15b. Baker MW, Grossman WJ, Laessig RH, et al: Development of a routine newborn screening protocol for severe combined immunodeficiency. J Allergy Clin Immunol 124:522–527, 2009.

16. Buckley RH: Molecular defects in human severe combined immunodeficiency and approaches to immune reconstitution. Annu Rev Immunol 22:625–655, 2004.
17. Hacein-Bey-Abina S, Le Deist F, Carlier F, et al: Sustained correction of X-linked severe combined immunodeficiency by ex vivo gene therapy. N Engl J Med 346:1185–1193, 2002.
18. Chinen J, Davis J, De Ravin SS, et al: Gene therapy improves immune function in preadolescents with X-linked severe combined immunodeficiency. Blood 110:67–73, 2007.

18a. Aiuti A, Cattaneo F, Galimberti S, et al: Gene therapy for immunodeficiency due to adenosine deaminase deficiency. N Engl J Med 360:447–458, 2009.

19. Ballow M: Primary immunodeficiency disorders: Antibody deficiency. J Allergy Clin Immunol 109:581–591, 2002.
20. Aghamohammadi A, Mohammadi J, Parvaneh N, et al: Progression of selective IgA deficiency to common variable immunodeficiency. Int Arch Allergy Immunol 147:87–92, 2008.
21. Cunningham-Rundles C: Common variable immunodeficiency. Curr Allergy Asthma Rep 1:421–429, 2001.
22. Cunningham-Rundles C: Physiology of IgA and IgA deficiency. J Clin Immunol 21:303–309, 2001.

23. Santaella ML, Peredo R, Disdier OM: IgA deficiency: Clinical correlates with IgG subclass and mannan-binding lectin deficiencies. P R Health Sci J 24:107–110, 2005.
24. Latiff AH, Kerr MA: The clinical significance of immunoglobulin A deficiency. Ann Clin Biochem 44(Pt 2):131–139, 2007.
25. Vassallo RR: Review: IgA anaphylactic transfusion reactions. Part I. Laboratory diagnosis, incidence, and supply of IgA-deficient products. Immunohematology 20:226–233, 2004.
26. Knight AK, Bingemann T, Cole L, Cunningham-Rundles C: Frequent false positive beta human chorionic gonadotropin tests in immunoglobulin A deficiency. Clin Exp Immunol 141:333–337, 2005.
27. Winkelstein JA, Marino MC, Lederman HM, et al: X-linked agammaglobulinemia: Report on a United States registry of 201 patients. Medicine (Baltimore) 85:193–202, 2006.
28. Conley ME, Broides A, Hernandez-Trujillo V, et al: Genetic analysis of patients with defects in early B-cell development. Immunol Rev 203:216–234, 2005.
29. Jacobs ZD, Guajardo JR, Anderson KM: XLA-associated neutropenia treatment: A case report and review of the literature. J Pediatr Hematol Oncol 30:631–634, 2008.
30. Moore ML, Quinn JM: Subcutaneous immunoglobulin replacement therapy for primary antibody deficiency: Advancements into the 21st century. Ann Allergy Asthma Immunol 101:114–121, 2008.
31. Eijkhout HW, van Der Meer JW, Kallenberg CG, et al: The effect of two different dosages of intravenous immunoglobulin on the incidence of recurrent infections in patients with primary hypogammaglobulinemia: A randomized, double-blind, multicenter crossover trial. Ann Intern Med 135:165–174, 2001.
32. Gelfand EW: Unique susceptibility of patients with antibody deficiency to mycoplasma infection. Clin Infect Dis 17(Suppl 1):S250–S253, 1993.
33. Fasth A: Primary immunodeficiency disorders in Sweden: Cases among children, 1974–1979. J Clin Immunol 2:86–92, 1982.
34. Chapel H, Lucas M, Lee M, et al: Common variable immunodeficiency disorders: Division into distinct clinical phenotypes. Blood 112:277–286, 2008.
35. Quinti I, Soresina A, Spadaro G, et al: Long-term follow-up and outcome of a large cohort of patients with common variable immunodeficiency. J Clin Immunol 27:308–316, 2007.
36. Grimbacher B, Hutloff A, Schlesier M, et al: Homozygous loss of ICOS is associated with adult-onset common variable immunodeficiency. Nat Immunol 4:261–268, 2003.
37. Salzer U, Maul-Pavicic A, Cunningham-Rundles C, et al: ICOS deficiency in patients with common variable immunodeficiency. Clin Immunol 113:234–240, 2004.
38. Sekine H, Ferreira RC, Pan-Hammarstrom Q, et al: Role for Msh5 in the regulation of Ig class switch recombination. Proc Natl Acad Sci U S A 104:7193–7198, 2007.
39. Zhang L, Radigan L, Salzer U, et al: Transmembrane activator and calcium-modulating cyclophilin ligand interactor mutations in common variable immunodeficiency: Clinical and immunologic outcomes in heterozygotes. J Allergy Clin Immunol 120:1178–1185, 2007.
40. Pan-Hammarstrom Q, Salzer U, Du L, et al: Reexamining the role of TACI coding variants in common variable immunodeficiency and selective IgA deficiency. Nat Genet 39:429–430, 2007.
41. Salzer U, Chapel HM, Webster AD, et al: Mutations in *TNFRSF13B* encoding TACI are associated with common variable immunodeficiency in humans. Nat Genet 37:820–828, 2005.
42. Castigli E, Wilson SA, Garibyan L, et al: TACI is mutant in common variable immunodeficiency and IgA deficiency. Nat Genet 37: 829–834, 2005.
43. Cunningham-Rundles C: Autoimmune manifestations in common variable immunodeficiency. J Clin Immunol 28(Suppl 1):S42–S45, 2008.
44. Wehr C, Kivioja T, Schmitt C, et al: The EUROclass trial: Defining subgroups in common variable immunodeficiency. Blood 111: 77–85, 2008.
45. Oksenhendler E, Gerard L, Fieschi C, et al: Infections in 252 patients with common variable immunodeficiency. Clin Infect Dis 46:1547–1554, 2008.
46. Lopes-da-Silva S, Rizzo LV: Autoimmunity in common variable immunodeficiency. J Clin Immunol 28(Suppl 1):S46–S55, 2008.
47. Salavoura K, Kolialexi A, Tsangaris G, Mavrou A: Development of cancer in patients with primary immunodeficiencies. Anticancer Res 28(2B):1263–1269, 2008.
48. Arnold DF, Wiggins J, Cunningham-Rundles C, et al: Granulomatous disease: Distinguishing primary antibody disease from sarcoidosis. Clin Immunol 128:18–22, 2008.
49. Busse PJ, Farzan S, Cunningham-Rundles C: Pulmonary complications of common variable immunodeficiency. Ann Allergy Asthma Immunol 98:1–8, 2007.
50. Buckley RH: Pulmonary complications of primary immunodeficiencies. Paediatr Respir Rev 5(Suppl A):S225–S233, 2004.
51. Bates CA, Ellison MC, Lynch DA, et al: Granulomatous-lymphocytic lung disease shortens survival in common variable immunodeficiency. J Allergy Clin Immunol 114:415–421, 2004.
52. Carsetti R, Rosado MM, Donnanno S, et al: The loss of IgM memory B cells correlates with clinical disease in common variable immunodeficiency. J Allergy Clin Immunol 115:412–417, 2005.
53. Fevang B, Mollnes TE, Holm AM, et al: Common variable immunodeficiency and the complement system; low mannose-binding lectin levels are associated with bronchiectasis. Clin Exp Immunol 142:576–584, 2005.
54. Indinnimeo L, Tancredi G, Barreto M, et al: Effects of a program of hospital-supervised chest physical therapy on lung function tests in children with chronic respiratory disease: 1-year follow-up. Int J Immunopathol Pharmacol 20:841–845, 2007.
55. Mechanic LJ, Dikman S, Cunningham-Rundles C: Granulomatous disease in common variable immunodeficiency. Ann Intern Med 127(8 Pt 1):613–617, 1997.
56. Fasano MB, Sullivan KE, Sarpong SB, et al: Sarcoidosis and common variable immunodeficiency: Report of 8 cases and review of the literature. Medicine (Baltimore) 75:251–261, 1996.
57. Torigian DA, LaRosa DF, Levinson AI, et al: Granulomatous-lymphocytic interstitial lung disease associated with common variable immunodeficiency: CT findings. J Thorac Imaging 23:162–169, 2008.
58. Wheat WH, Cool CD, Morimoto Y, et al: Possible role of human herpesvirus 8 in the lymphoproliferative disorders in common variable immunodeficiency. J Exp Med 202:479–484, 2005.
59. Mullighan CG, Marshall SE, Bunce M, Welsh KI: Variation in immunoregulatory genes determines the clinical phenotype of common variable immunodeficiency. Genes Immun 1:137–148, 1999.
60. Lin JH, Liebhaber M, Roberts RL, et al: Etanercept treatment of cutaneous granulomas in common variable immunodeficiency. J Allergy Clin Immunol 117:878–882, 2006.
61. Davies CW, Juniper MC, Gray W, et al: Lymphoid interstitial pneumonitis associated with common variable hypogammaglobulinaemia treated with cyclosporin A. Thorax 55:88–90, 2000.
62. Agarwal S, Cunningham-Rundles C: Thymoma and immunodeficiency (Good syndrome): A report of 2 unusual cases and review of the literature. Ann Allergy Asthma Immunol 98:185–190, 2007.
63. Ambrosino DM, Siber GR, Chilmonczyk BA, et al: An immunodeficiency characterized by impaired antibody responses to polysaccharides. N Engl J Med 316:790–793, 1987.
64. Tuerlinckx D, Vermeulen F, Pekus V, et al: Optimal assessment of the ability of children with recurrent respiratory tract infections to produce anti-polysaccharide antibodies. Clin Exp Immunol 149:295–302, 2007.
65. Maguire GA, Kumararatne DS, Joyce HJ: Are there any clinical indications for measuring IgG subclasses? Ann Clin Biochem 39(Pt 4):374–377, 2002.
66. Stiehm RE: The four most common pediatric immunodeficiencies. Adv Exp Med Biol 601:15–26, 2007.
67. Shackelford PG, Granoff DM, Madassery JV, et al: Clinical and immunologic characteristics of healthy children with subnormal serum concentrations of IgG2. Pediatr Res 27:16–21, 1990.
68. Latour S: Natural killer T cells and X-linked lymphoproliferative syndrome. Curr Opin Allergy Clin Immunol 7:510–514, 2007.
69. Rigaud S, Fondaneche MC, Lambert N, et al: XIAP deficiency in humans causes an X-linked lymphoproliferative syndrome. Nature 444:110–114, 2006.

70. Gross TG, Filipovich AH, Conley ME, et al: Cure of X-linked lymphoproliferative disease (XLP) with allogeneic hematopoietic stem cell transplantation (HSCT): Report from the XLP registry. Bone Marrow Transplant 17:741–744, 1996.
71. Hoffmann T, Heilmann C, Madsen HO, et al: Matched unrelated allogeneic bone marrow transplantation for recurrent malignant lymphoma in a patient with X-linked lymphoproliferative disease (XLP). Bone Marrow Transplant 22:603–604, 1998.
72. Winkelstein JA, Marino MC, Ochs H, et al: The X-linked hyper-IgM syndrome: Clinical and immunologic features of 79 patients. Medicine (Baltimore) 82:373–384, 2003.
73. Bonilla FA, Geha RS: CD154 deficiency and related syndromes. Immunol Allergy Clin North Am 21:61–89, 2001.
74. Revy P, Muto T, Levy Y, et al: Activation-induced cytidine deaminase (AID) deficiency causes the autosomal recessive form of the Hyper-IgM syndrome (HIGM2) [see comments]. Cell 102:565–575, 2000.
75. Imai K, Slupphaug G, Lee WI, et al: Human uracil-DNA glycosylase deficiency associated with profoundly impaired immunoglobulin class-switch recombination. Nat Immunol 4:1023–1028, 2003.
76. Notarangelo LD, Lanzi G, Toniati P, Giliani S: Immunodeficiencies due to defects of class-switch recombination. Immunol Res 38:68–77, 2007.
77. Lougaris V, Badolato R, Ferrari S, Plebani A: Hyper immunoglobulin M syndrome due to CD40 deficiency: Clinical, molecular, and immunological features. Immunol Rev 203:48–66, 2005.
78. Filipovich A: Hematopoietic cell transplantation for correction of primary immunodeficiencies. Bone Marrow Transplant 42(Suppl 1):S49–S52, 2008.
79. Aradhya S, Courtois G, Rajkovic A, et al: Atypical forms of incontinentia pigmenti in male individuals result from mutations of a cytosine tract in exon 10 of NEMO (IKK-gamma). Am J Hum Genet 68:765–771, 2001.
80. Hanson EP, Monaco-Shawver L, Solt LA, et al: Hypomorphic nuclear factor-kappaB essential modulator mutation database and reconstitution system identifies phenotypic and immunologic diversity. J Allergy Clin Immunol 122:1169–1177, 2008.
81. Filipe-Santos O, Bustamante J, Haverkamp MH, et al: X-linked susceptibility to mycobacteria is caused by mutations in NEMO impairing CD40-dependent IL-12 production. J Exp Med 203: 1745–1759, 2006.
82. Orange JS, Brodeur SR, Jain A, et al: Deficient natural killer cell cytotoxicity in patients with IKK-gamma/NEMO mutations. J Clin Invest 109:1501–1509, 2002.
83. Fish JD, Duerst RE, Gelfand EW, et al: Challenges in the use of allogeneic hematopoietic SCT for ectodermal dysplasia with immune deficiency. Bone Marrow Transplant 43:217–221, 2009.
84. Stavnezer J, Guikema JE, Schrader CE: Mechanism and regulation of class switch recombination. Annu Rev Immunol 26:261–292, 2008.
85. Notarangelo LD, Lanzi G, Peron S, Durandy A: Defects of class-switch recombination. J Allergy Clin Immunol 117:855–864, 2006.
86. Yagi H, Furutani Y, Hamada H, et al: Role of TBX1 in human del22q11.2 syndrome. Lancet 362:1366–1373, 2003.
87. Sullivan KE: Chromosome 22q11.2 deletion syndrome: DiGeorge syndrome/velocardiofacial syndrome. Immunol Allergy Clin North Am 28:353–366, 2008.
88. McLean-Tooke A, Spickett GP, Gennery AR: Immunodeficiency and autoimmunity in 22q11.2 deletion syndrome. Scand J Immunol 66:1–7, 2007.
89. Bonilla FA, Geha RS: 2. Update on primary immunodeficiency diseases. J Allergy Clin Immunol 117(2 Suppl Mini-Primer):S435–S441, 2006.
90. Markert ML: Treatment of infants with complete DiGeorge anomaly. J Allergy Clin Immunol 121:1063, 2008.
91. Finocchi A, Di Cesare S, Romiti ML, et al: Humoral immune responses and CD27+ B cells in children with DiGeorge syndrome (22q11.2 deletion syndrome). Pediatr Allergy Immunol 17:382–388, 2006.
92. Ochs HD: The Wiskott-Aldrich syndrome. Isr Med Assoc J 4:379–384, 2002.
93. Notarangelo LD, Miao CH, Ochs HD: Wiskott-Aldrich syndrome. Curr Opin Hematol 15:30–36, 2008.
94. Ochs HD, Thrasher AJ: The Wiskott-Aldrich syndrome. J Allergy Clin Immunol 117:725–738, 2006.
95. Ochs HD: The Wiskott-Aldrich syndrome. Clin Rev Allergy Immunol 20:61–86, 2001.
96. Orange JS, Ramesh N, Remold-O'Donnell E, et al: Wiskott-Aldrich syndrome protein is required for NK cell cytotoxicity and colocalizes with actin to NK cell-activating immunologic synapses. Proc Natl Acad Sci U S A 99:11351–11356, 2002.
97. Mavrou A, Tsangaris GT, Roma E, Kolialexi A: The ATM gene and ataxia telangiectasia. Anticancer Res 28(1B):401–405, 2008.
98. Lavin MF: Ataxia-telangiectasia: From a rare disorder to a paradigm for cell signalling and cancer. Nat Rev Mol Cell Biol 9:759–769, 2008.
99. Holland SM, DeLeo FR, Elloumi HZ, et al: STAT3 mutations in the hyper-IgE syndrome. N Engl J Med 357:1608–1619, 2007.
100. Freeman AF, Holland SM: The hyper-IgE syndromes. Immunol Allergy Clin North Am 28:277–291, viii, 2008.
101. Minegishi Y, Saito M, Morio T, et al: Human tyrosine kinase 2 deficiency reveals its requisite roles in multiple cytokine signals involved in innate and acquired immunity. Immunity 25:745–755, 2006.
102. Freeman AF, Kleiner DE, Nadiminti H, et al: Causes of death in hyper-IgE syndrome. J Allergy Clin Immunol 119:1234–1240, 2007.
103. Paulson ML, Freeman AF, Holland SM: Hyper IgE syndrome: An update on clinical aspects and the role of signal transducer and activator of transcription 3. Curr Opin Allergy Clin Immunol 8:527–533, 2008.
104. Stepkowski SM, Chen W, Ross JA, et al: STAT3: An important regulator of multiple cytokine functions. Transplantation 85: 1372–1377, 2008.
105. Li MO, Flavell RA: Contextual regulation of inflammation: A duet by transforming growth factor-beta and interleukin-10. Immunity 28:468–476, 2008.
106. Milner JD, Brenchley JM, Laurence A, et al: Impaired T_H17 cell differentiation in subjects with autosomal dominant hyper-IgE syndrome. Nature 452:773–776, 2008.
107. Ouyang W, Kolls JK, Zheng Y: The biological functions of T helper 17 cell effector cytokines in inflammation. Immunity 28:454–467, 2008.
108. Wakim M, Alazard M, Yajima A, et al: High dose intravenous immunoglobulin in atopic dermatitis and hyper-IgE syndrome. Ann Allergy Asthma Immunol 81:153–158, 1998.
109. Xia J, Link DC: Severe congenital neutropenia and the unfolded protein response. Curr Opin Hematol 15:1–7, 2008.
110. Palmblad J, Papadaki HA: Chronic idiopathic neutropenias and severe congenital neutropenia. Curr Opin Hematol 15:8–14, 2008.
111. Germeshausen M, Grudzien M, Zeidler C, et al: Novel HAX1 mutations in patients with severe congenital neutropenia reveal isoform-dependent genotype-phenotype associations. Blood 111: 4954–4957, 2008.
112. Zeidler C, Welte K: Kostmann syndrome and severe congenital neutropenia. Semin Hematol 39:82–88, 2002.
113. Toyoda H, Azuma E, Hori H, et al: Successful unrelated BMT in a patient with Kostmann syndrome complicated by pre-transplant pulmonary "bacterial" abscesses. Bone Marrow Transplant 28: 413–415, 2001.
114. Malech HL, Hickstein DD: Genetics, biology and clinical management of myeloid cell primary immune deficiencies: Chronic granulomatous disease and leukocyte adhesion deficiency. Curr Opin Hematol 14:29–36, 2007.
115. Rosenzweig SD, Holland SM: Phagocyte immunodeficiencies and their infections. J Allergy Clin Immunol 113:620–626, 2004.
116. Kilic SS, Etzioni A: The clinical spectrum of leukocyte adhesion deficiency (LAD) III due to defective CalDAG-GEF1. J Clin Immunol 29:117–128, 2009.
117. Etzioni A: Leukocyte adhesion deficiencies: Molecular basis, clinical findings, and therapeutic options. Adv Exp Med Biol 601:51–60, 2007.

118. Farinha NJ, Duval M, Wagner E, et al: Unrelated bone marrow transplantation for leukocyte adhesion deficiency. Bone Marrow Transplant 30:979–981, 2002.
119. Lubke T, Marquardt T, Etzioni A, et al: Complementation cloning identifies CDG-IIc, a new type of congenital disorders of glycosylation, as a GDP-fucose transporter deficiency. Nat Genet 28:73–76, 2001.
120. Etzioni A, Tonetti M: Fucose supplementation in leukocyte adhesion deficiency type II. Blood 95:3641–3643, 2000.
121. Reeves EP, Lu H, Jacobs HL, et al: Killing activity of neutrophils is mediated through activation of proteases by K^+ flux. Nature 416:291–297, 2002.
122. Holland SM: Update on phagocytic defects. Pediatr Infect Dis J 22:87–88, 2003.
123. Messina CG, Reeves EP, Roes J, Segal AW: Catalase negative *Staphylococcus aureus* retain virulence in mouse model of chronic granulomatous disease. FEBS Lett 518:107–110, 2002.
124. Martire B, Rondelli R, Soresina A, et al: Clinical features, long-term follow-up and outcome of a large cohort of patients with chronic granulomatous disease: an Italian multicenter study. Clin Immunol 126:155–164, 2008.
125. Godoy MC, Vos PM, Cooperberg PL, et al: Chest radiographic and CT manifestations of chronic granulomatous disease in adults. AJR Am J Roentgenol 191:1570–1575, 2008.
126. De Ravin SS, Naumann N, Cowen EW, et al: Chronic granulomatous disease as a risk factor for autoimmune disease. J Allergy Clin Immunol 122:1097–1103, 2008.
127. Rosenzweig SD: Inflammatory manifestations in chronic granulomatous disease (CGD). J Clin Immunol 28(Suppl 1):S67–S72, 2008.
128. Kobayashi SD, Voyich JM, Braughton KR, et al: Gene expression profiling provides insight into the pathophysiology of chronic granulomatous disease. J Immunol 172:636–643, 2004.
129. Fadok VA, Bratton DL, Rose DM, et al: A receptor for phosphatidylserine-specific clearance of apoptotic cells. Nature 405:85–90, 2000.
130. Hampton MB, Vissers MC, Keenan JI, Winterbourn CC: Oxidant-mediated phosphatidylserine exposure and macrophage uptake of activated neutrophils: Possible impairment in chronic granulomatous disease. J Leukoc Biol 71:775–781, 2002.
131. Kang EM, Malech HL: Advances in treatment for chronic granulomatous disease. Immunol Res 43:77–84, 2009.
132. Mouy R, Fischer A, Vilmer E, et al: Incidence, severity, and prevention of infections in chronic granulomatous disease. J Pediatr 114(4 Pt 1):555–560, 1989.
133. Gallin JI, Alling DW, Malech HL, et al: Itraconazole to prevent fungal infections in chronic granulomatous disease. N Engl J Med 348:2416–2422, 2003.
134. Bemiller LS, Roberts DH, Starko KM, Curnutte JT: Safety and effectiveness of long-term interferon gamma therapy in patients with chronic granulomatous disease. Blood Cells Mol Dis 21:239–247, 1995.
135. Holland SM: Interferon gamma, IL-12, IL-12R and STAT-1 immunodeficiency diseases: Disorders of the interface of innate and adaptive immunity. Immunol Res 38:342–346, 2007.
136. Filipe-Santos O, Bustamante J, Chapgier A, et al: Inborn errors of IL-12/23- and IFN-gamma-mediated immunity: Molecular, cellular, and clinical features. Semin Immunol 18:347–361, 2006.
137. Ku CL, von Bernuth H, Picard C, et al: Selective predisposition to bacterial infections in IRAK-4-deficient children: IRAK-4-dependent TLRs are otherwise redundant in protective immunity. J Exp Med 204:2407–2422, 2007.
138. von Bernuth H, Picard C, Jin Z, et al: Pyogenic bacterial infections in humans with MyD88 deficiency. Science 321:691–696, 2008.
139. Sjoholm AG, Jonsson G, Braconier JH, et al: Complement deficiency and disease: An update. Mol Immunol 43:78–85, 2006.

CHAPTER 83

PULMONARY COMPLICATIONS OF ABDOMINAL DISEASE

Roberto Rodriguez-Roisin, MD • Joan Albert Barberà, MD

INTRODUCTION

GASTROESOPHAGEAL AND GASTROINTESTINAL DISORDERS
Gastroesophageal Reflux
Inflammatory Bowel Disease

HEPATIC DISEASES
Pleural Effusion
Pulmonary Functional Disturbances
Hepatopulmonary Syndrome
Portopulmonary Hypertension
Primary Biliary Cirrhosis
Chronic Active Hepatitis
Sclerosing Cholangitis
Alpha$_1$-Antitrypsin Deficiency

PANCREATITIS
Respiratory Failure
Pleural Effusion

KIDNEY DISEASES
Pulmonary Edema
Pleural Disease
Pulmonary Calcification
Sleep Apnea
Hemodialysis-Induced Hypoxemia

INTRODUCTION

This chapter is devoted to the pulmonary complications of abdominal disease and begins with a discussion of the most relevant esophageal and bowel disorders. Then the lung-liver syndromes and the specific liver disorders associated with particular pulmonary complications are reviewed. Finally, the respiratory consequences of diseases of the pancreas and kidney are described. The objective in each section is the same: to update the most relevant clinical, pathophysiologic, pathogenetic, and therapeutic aspects of the principal abdominal disease states and thereby assist the clinician in diagnosing and managing their sometimes complex and challenging pulmonary complications.

GASTROESOPHAGEAL AND GASTROINTESTINAL DISORDERS

Gastroesophageal Reflux

An international consensus group recently defined gastroesophageal reflux disease—or GERD as it is more commonly known—as follows: "a condition that develops when the reflux of stomach contents causes troublesome symptoms and/or complications."[1] The same group subclassified GERD into "esophageal and extraesophageal syndromes." Among the esophageal syndromes of interest to family physicians and pulmonologists are episodes of chest pain, which may vary from recurrent mild retrosternal "heartburn" to acute crushing substernal distress that is indistinguishable from the pain of angina or even myocardial infarction (see also Chapter 30). Among the extraesophageal syndromes, chronic cough, chronic laryngitis, and refractory asthma have attracted the most attention, but other associations have been made, including bronchitis, bronchiectasis, pulmonary fibrosis, and, most recently, chronic obstructive pulmonary disease (COPD).[2]

GERD is a common condition with a prevalence that varies from 10% to 20% in North America and Western Europe, but that is lower in Asia.[1] A higher prevalence of gastroesophageal reflux than in the general population has been observed in patients with chronic cough and asthma, but the exact contribution of reflux to the patient's symptoms is often difficult to define. For example, Irwin and associates[3] reported that gastroesophageal reflux was clinically silent in 24% of patients with difficult-to-control asthma; by contrast, symptoms

of gastroesophageal reflux were significantly associated with the occurrence of COPD exacerbations.[4]

Pathogenesis

The pathogenesis of respiratory abnormalities associated with gastroesophageal reflux can be divided into three basic mechanisms. First, gross aspiration-linked pulmonary syndromes are usually the result of free esophageal reflux with large-volume retrograde flow. Frequently, there is reduced basal lower esophageal tone and impaired esophageal motility and clearance.[5] These patients may have recurrent aspiration pneumonia, bronchiectasis, or pulmonary infiltrates. Endoscopic examination usually reveals severe anatomic changes, such as visible breaks of the distal esophageal mucosa or Barrett's epithelialization of the mucosa.

A second pathogenic mechanism is related to the microaspiration of gastric contents from the proximal (upper) esophagus. This results from small-volume aspirates that produce an exudative mucosal reaction in the larynx and in the tracheobronchial tree. Respiratory symptoms are less apparent and range from hoarseness or chronic cough to difficult-to-control asthma. Jack and coworkers,[6] using simultaneous tracheal and esophageal pH measurements in asthmatics with gastroesophageal reflux, showed that episodes of reflux that were followed by a fall in intratracheal pH resulted in a marked fall in peak expiratory flow rate, which was several times greater than that observed when reflux was not followed by tracheal aspiration (Fig. 83-1). Accordingly, microaspiration into the bronchial tree not only occurs but also may induce an important increase in airway resistance. Nevertheless, reflux episodes that do not reach the upper sphincter, and hence are without aspiration, may also increase airway resistance.

The third pathogenic mechanism is produced by gastroesophageal reflux activation of a vagal reflex between the distal (lower) esophagus and the tracheobronchial tree. This reflex mechanism can be reproduced by the

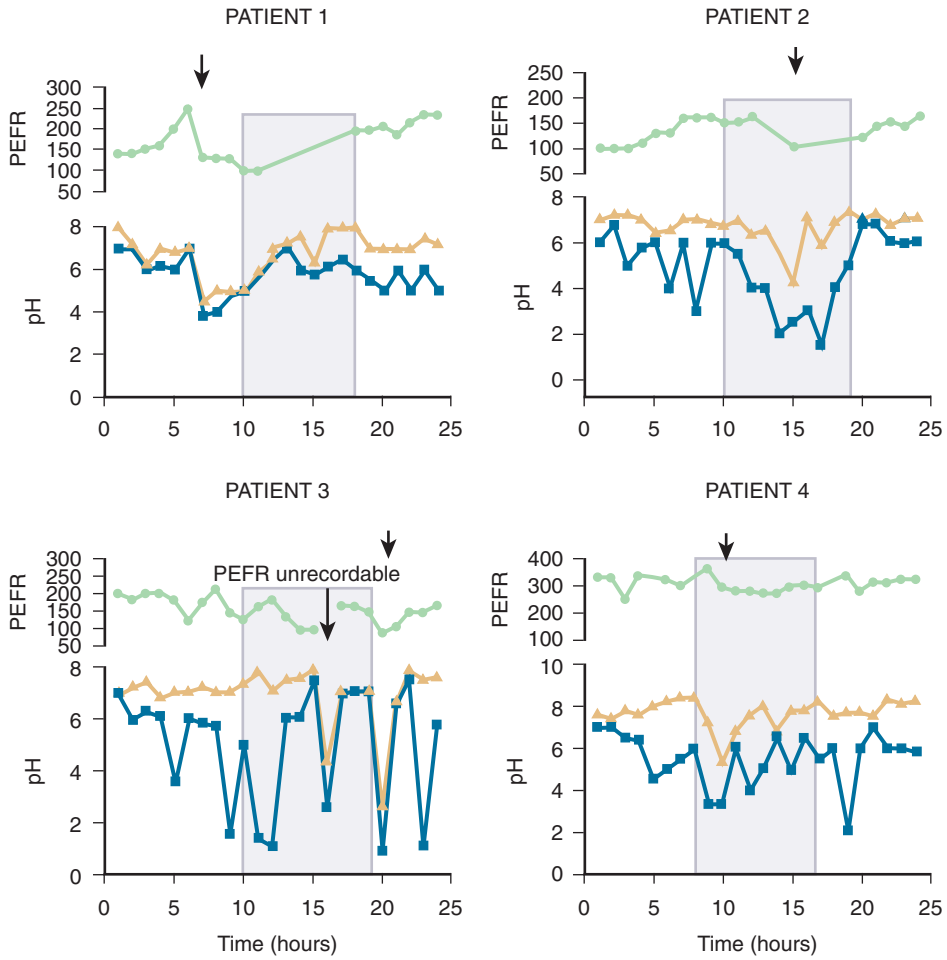

FIGURE 83-1 ■ Graphs showing simultaneous esophageal (*solid blue squares*) and tracheal (*solid beige triangles*) pH measurements in four patients with both gastroesophageal reflux and asthma, along with recordings of peak expiratory flow rate (PEFR, *solid pale-green circles*), over a 24-hour period. There were 37 significant falls in esophageal pH suggestive of gastroesophageal reflux. Five of these episodes were followed by a fall in tracheal pH and were associated with a significant decrease in PEFR (mean change –84 ± 16 L/min), whereas during the remaining 32 episodes of gastroesophageal reflux without tracheal aspiration, the mean change in PEFR was minimal (–8 ± 4 L/min). *Arrows* show representative episodes. (From Jack CI, Calverley PMA, Donnelly RJ, et al: Simultaneous tracheal and oesophageal pH measurements in asthmatic patients with gastro-oesophageal reflux. Thorax 50:201–204, 1995.)

infusion of hydrochloric acid into the esophagus of some,[7] but not all,[8] patients with asthma. Earlier work on the role of gastroesophageal reflux–induced vagally mediated reflexes in expiratory flow rates in experimental models and inpatients with asthma is summarized in the previous edition of this textbook.[9]

The relationship between gastroesophageal reflux and respiratory disorders is further complicated by the fact that physiologic alterations associated with asthma or cough, or with bronchodilator therapy, may themselves promote gastroesophageal reflux. Episodes of bronchospasm and cough are accompanied by an increase in the negative pressure within the thorax, and hence in the esophagus, that may promote reflux. In addition, hyperinflation and "air trapping" may lead to flattening of the diaphragm, allowing the lower esophageal sphincter to be drawn up into the thorax, impairing the antireflux barrier. Bronchodilator therapy may also promote gastroesophageal reflux. Theophylline increases gastric acid secretion and decreases lower esophageal sphincter tone. Indeed, asthmatics with gastroesophageal reflux who receive theophylline show an increase in esophageal acid exposure and reflux symptoms.[10] Specific β-adrenergic agents relax smooth muscle tone throughout the body and thereby may promote gastroesophageal reflux. A decrease in lower esophageal sphincter pressure has been shown with β-adrenergic drugs administered orally or intravenously,[11] but not when these agents were given by inhalation.[12]

Diagnosis

The possibility of associated gastroesophageal reflux should be suspected in patients with refractory chronic cough or difficult-to-treat asthma. Patients should be questioned about symptoms of gastroesophageal reflux, which include heartburn, regurgitation, or dysphagia. However, some patients may complain of atypical symptoms, including substernal chest pain, hoarseness, sore throat, otalgia, hiccups, or even teeth erosion. It is also important to record whether asthma or cough worsens with recumbency, after meals, or during alcohol ingestion. If the clinical history is typical of gastroesophageal reflux, no further diagnostic workup may be necessary and a trial of antacid therapy will confirm that the symptoms are due to acid reflux.

However, gastroesophageal reflux may be clinically silent in a number of patients. If dysphagia is present, a barium radiographic study should be performed in order to rule out esophageal obstruction or obvious motility abnormalities. Until recently, the "gold standard" for diagnosing gastroesophageal reflux was ambulatory esophageal pH monitoring owing to its high sensitivity and specificity. However, demonstration of reflux by pH monitoring shows an association but not always a cause-and-effect relationship.[13] A new method of reflux testing, using a Multichannel Intraluminal Impedance–pH (MII-pH) catheter, adds impedance measurements to those of pH and provides additional informational about the role of nonacid or weakly acid reflux as a cause of atypical symptoms, and is helpful in detecting the importance of ongoing reflux in patients receiving acid suppression therapy.[14]

Treatment

Therapy for gastrointestinal reflux should begin with several changes in lifestyle, such as raising the head of the bed, avoiding meals before bedtime, eating low-fat foods, reducing body weight, and eliminating caffeine and alcohol. Pharmacologic strategies for treating gastroesophageal reflux are now mainly focused on proton pump inhibitors (omeprazole, lansoprazole), which directly inhibit gastric acid secretion.[14a] Treatment with proton pump inhibitors is often started empirically, but they have to be given in sufficient doses to ensure round-the-clock acid suppression and for long periods of time (at least 3 months) to reliably determine effectiveness.[15] If cough or bronchospasm has not improved, testing with the MII-pH catheter should be considered to check the level of acid suppression and to determine if ongoing reflux of non- or weakly acid secretions are related to the patient's symptoms.

Other treatment strategies include prokinetic agents (cisapride, domperidone), which improve esophageal contractility, increase lower esophageal sphincter pressure, and increase gastric emptying, as well as surgical interventions, such as the Nissen/Toupet/Belsey fundoplication and the Hill gastropexy. Total remission of symptoms is unusual no matter what the therapy, which strengthens the conclusion that gastroesophageal reflux plays an aggravating rather than causative role in most patients' extraesophageal symptoms.

Inflammatory Bowel Disease

Extraintestinal complications of inflammatory bowel disease have been described in virtually all organ systems, but—surprisingly—pulmonary disease appears "much less frequently" than manifestations in other organs[16]: "surprisingly" because the gut and lungs share a common embryologic origin, and thus might possess similar vulnerability to immunologically mediated comorbidities. Pulmonary complications occur more commonly with ulcerative colitis than with Crohn's disease; respiratory involvement may occur at any age, and some conditions (e.g., airway disease) appear more often in women than in men.[16] In most cases, respiratory symptoms develop after the diagnosis of inflammatory bowel disease has been made, frequently several years afterward. Nonetheless, in some reports respiratory symptoms antedated or were concomitant with those of the bowel disease.[17]

A recent review of over 400 published cases has confirmed and extended earlier observations.[16] Based on these and newly reported studies, the pulmonary complications of inflammatory bowel disease can be classified as shown in Table 83-1. Most intrinsic (non–drug-related) pulmonary complications involve airways—anywhere from the larynx to the bronchioles—and may take the form of epiglottitis, tracheal stenosis, bronchiectasis, chronic bronchitis, or bronchiolitis. Endoscopic examination shows marked erythema, swelling of

TABLE 83-1. Patterns of Respiratory Involvement in Inflammatory Bowel Disease

AIRWAY DISEASE
Pleural effusion
Pleuropericarditis
Epiglottic-subglottic stenosis
Tracheobonchitis
Chronic bronchitis
Chronic bronchial suppuration
Bronchiectasis
Chronic bronchiolitis
Bronchiolitis
PARENCHYMAL LUNG DISEASE
Drug-induced
BOOP
Sarcoidosis
Eosinophilic pneumonia
Interstitial fibrosis
Necrotic nodules
PLEURAL DISEASE
Pleural effusion
Pleuropericarditis
OTHER DISEASES
Fistulas
Pulmonary vasculitis
Pulmonary embolism
PULMONARY FUNCTION ABNORMALITIES
Obstructive impairment
Restrictive impairment
Bronchial hyperresponsiveness
Decreased diffusion

BOOP, bronchiolitis obliterans with organizing pneumonia.

the mucosa, and deformation of the airway lumen. Biopsy specimens have revealed mucosal ulceration, thickening of the basement membrane, and marked infiltration by neutrophils and plasma cells.[16,17] In some cases, the inflammatory process in the subglottic area can take the form of pseudotumoral lesions, with the potential of producing life-threatening acute upper airway obstruction requiring aggressive airway management.[17,18] This panoply of discrete airway pathology has been enriched by the addition of asthma, which proved to be the most common pulmonary comorbidity of both ulcerative colitis and Crohn's disease identified in a large cohort surveyed in Manitoba, Canada.[19] The association between inflammatory bowel disease and asthma supports the belief that patients suffering from one autoimmune condition are more likely than the general population to have a second immune-mediated disorder, which may result from shared susceptibility genes.[20]

Another, major category of pulmonary complications of inflammatory bowel disease is parenchymal (including interstitial) lung diseases, such as bronchiolitis obliterans with organizing pneumonia, sarcoidosis, interstitial fibrosis, and pulmonary infiltrations with eosinophilia. According to Storch and coauthors,[16] drugs, particularly mesalamine, sulfasalazine, and methotrexate, are "the most frequent cause of the pulmonary manifestations of [inflammatory bowel disease]." Although not all reports agree with that assessment, commonly used medications must always be considered in the differential diagnosis of new-onset interstitial lung disease, because the offending drug(s) must be recognized and discontinued to prevent a potentially fatal outcome.

Pulmonary function testing in patients with inflammatory bowel disease, even when asymptomatic and with normal chest radiographs, may reveal a variety of abnormalities. Probably the most common is an obstructive ventilatory defect, but pulmonary restriction is also well described. A reduction in carbon monoxide diffusing capacity (D_{LCO}) during the active phases of inflammatory bowel disease has been reported,[21] which also suggests that subclinical pulmonary parenchymal involvement may be more prevalent than previously suspected. Furthermore, bronchoalveolar lavage examination in patients with Crohn's disease who did not have clinical evidence of pulmonary involvement revealed the presence of a lymphocytic alveolitis, chiefly owing to an increase of CD4-positive T lymphocytes.[21]

Other pulmonary lesions include necrobiotic nodules, corresponding histologically to aggregates of neutrophils with areas of necrosis, which have been reported in a few patients.[17] Serositis affecting the pleura or the pericardium, or both, has been reported in a small number of cases, especially during the periods of increased disease activity. Finally, colobronchial fistulas have been reported in some cases of Crohn's disease, the majority of them presenting with left lower pneumonia.[16] Involvement of the esophagus is rare in Crohn's disease, but four cases of bronchoesophageal fistula associated with esophageal Crohn's disease have been reported.[16] Although conservative management can be attempted, most patients with fistulas will require surgical treatment.

In the majority of patients with pulmonary disorders associated with inflammatory bowel disease, glucocorticosteroids given by inhalation or by mouth usually result in a rapid control of symptoms,[17,22] especially in those patients who do not have severe structural impairment (e.g., bronchiectasis). Lung transplantation has been performed in some cases of severe respiratory compromise.[17]

HEPATIC DISEASES

Pleural Effusion

Between 5% and 10% of patients with cirrhosis of the liver develop pleural effusion, traditionally referred to as *hepatic hydrothorax,* in the absence of a coexisting cardiopulmonary disease. (For further discussion of hepatic hydrothorax, see Chapter 73). Unless the pleural fluid is complicated by infection, hepatic hydrothoraces

are transudates, and are most commonly located in the right hemithorax. Effusions may also be left-sided or bilateral, and are strongly associated with pronounced ascites; rare patients have been reported in whom ascites is almost undetectable. The effusion is usually mild to moderate in size and asymptomatic, but in some cases it can be massive and provoke shortness of breath. The mechanism is related to the presence of anatomic communications (usually small diaphragmatic defects) and to the pressure gradient between the abdominal and pleural cavities that facilitates movement of ascitic fluid into the chest. The presence of pleural fluid disturbs lung mechanics, resulting in decreased lung volumes and pulmonary compliance. Accordingly, pulmonary gas exchange becomes abnormal and leads to moderate hypoxemia and an increased alveolar-arterial P_{O_2} difference ([A − a] P_{O_2}), caused both by a slight right-to-left intrapulmonary shunt through the nonventilated, fluid-compressed lung parenchyma, and by a mild ventilation-perfusion imbalance. Either because of lasting effects of the effusion or because of coexistent hepatopulmonary syndrome (see later), these abnormalities do not easily reverse after thoracentesis.[23]

The clinical management of pleural effusion in the context of liver disease is often difficult. Repeated thoracenteses will have transitory effects only, and thoracostomy tube drainage may result in substantial protein loss. The use of transjugular intrahepatic portosystemic shunting (TIPS) to decrease portal hypertension and, in turn, to reduce the size of both the ascites and hydrothorax, is often beneficial, at least in the short term, but long-term outcome depends on the severity of the underlying liver dysfunction.[24] If the patient is not a candidate for TIPS, other approaches, including video-assisted thoracoscopic surgery to repair diaphragmatic defects and induce a pleurodesis, should also be considered.[25]

Pulmonary Function Disturbances

The most common lung function abnormality in patients with end-stage hepatic disease is a decreased $D_{L_{CO}}$; likewise, both obstructive and restrictive ventilatory defects have been observed.[26] The coexistence of massive ascites can decrease lung compliance, increase pleural pressure, and reduce diaphragmatic motility. Together, these pathophysiologic alterations restrict ventilatory capacity and reduce the efficiency of gas exchange, causing increased (A − a)P_{O_2} values with or without associated hypoxemia.[27]

Hepatopulmonary Syndrome

Severe hypoxemia (arterial P_{O_2} < 60 mm Hg) is uncommon in patients with chronic hepatic disease, and when present in patients without coexisting cardiopulmonary disease, should strongly suggest hepatopulmonary syndrome (HPS). Because patients with advanced liver disorders characteristically hyperventilate and are hypocapnic, measurement of the (A − a)P_{O_2} becomes more sensitive than P_{O_2} alone to detect gas-exchange disturbances in HPS.

TABLE 83-2. Grading of Severity of Hepatopulmonary Syndrome*

Stage	Alveolar-Arterial Oxygen Difference	Partial Pressure of Oxygen
Mild	≥15 mm Hg	≥80 mm Hg
Moderate	≥15 mm Hg	<80 to ≥60 mm Hg
Severe	≥15 mm Hg	<60 to ≥50 mm Hg
Very severe	≥15 mm Hg	<50 (<300 mm Hg [40.0 kPa] on 100% oxygen breathing)

*All with positive contrast-enhanced echocardiography, breathing room air at rest and at sea level; for patients greater than 64 years of age, cut-off values ≥20 mm Hg and <70 mm Hg, respectively, can be recommended.
From Rodriguez-Roisin R, Krowka MJ, Hervé P, et al, for the ERS Task Force Pulmonary-Hepatic Vascular Disorders (PHD) Scientific Committee: Pulmonary-hepatic vascular disorders (PHD). Eur Respir J 24:861–880, 2004.

HPS is rigorously defined as a syndrome characterized by a clinical triad: advanced chronic liver disease; arterial oxygenation defect, which ultimately leads to severe arterial hypoxemia; and widespread pulmonary vascular dilations.[28] The pulmonary gas-exchange disturbance is characterized by arterial oxygen desaturation that may be mild, moderate, severe, or very severe (Table 83-2). There is an increased (A − a)P_{O_2}, commonly associated with hypocapnia and respiratory alkalosis. At sea level, while breathing room air, resting (A − a)P_{O_2} values equal to or above 15 mm Hg can be considered abnormal for most adults; for those older than 64 years, an (A − a)P_{O_2} equal to or above 20 mm Hg can be considered abnormal. HPS is prevalent in most kinds of common chronic liver diseases, such as chronic active hepatitis; it may also occur in other unusual liver disorders (noncirrhotic portal hypertension, alpha$_1$-antitrypsin deficiency, and Budd-Chiari syndrome).[29] At present, there is a special clinical interest in HPS because of its high prevalence (an estimated 20% in some series) among patients with end-stage hepatic disease,[30] its life-threatening nature, the lack of beneficial medical therapy, and its unique improvement or full resolution after liver transplantation in more than 80% of the reported cases.[28]

The most conspicuous pathologic finding is a pronounced vascular dilation of all peripheral branches of the pulmonary vasculature, at both the precapillary and capillary levels of the lung (15 to 150 μm in diameter), near the gas-exchange area in an otherwise intact pulmonary parenchyma.

Pathogenesis

The precise pathogenetic mechanism underlying HPS remains uncertain despite numerous investigations. Whether the mechanism of hemodynamic disturbances is related to failure of metabolism, to insufficient production of one or more circulating vasoactive substances by the injured liver, or to altered clearance of putative vasodilator molecules produced by endothelial cells[31] remains unknown. Circulating humoral vasodilating

substances, such as glucagon and prostacyclin, which may contribute to the development of vascular abnormalities in patients with chronic hepatitis, including a blunted hypoxic pulmonary vasoconstrictor response, have been investigated. However, clear evidence of their involvement in HPS is lacking.

Nitric oxide (NO), a ubiquitous biologic agent considered to be a "fine-tuner" of vascular tone, has been presumed to be a pivotal signaling molecule of potential importance in the pathobiology of HPS.[28,32] Persistent induction of NO synthase (NOS) could account for the hyperkinetic circulatory hallmarks of HPS.[32] Both a constitutive isoform of NOS, expressed in endothelial cells (eNOS, or type III NOS),[33] and the inducible NOS (iNOS, or type II NOS), expressed in target tissues such as human bronchial epithelial cells after exposure to proinflammatory cytokines,[34] have been implicated in experimental models in the pathogenesis of HPS. In keeping with this contention, increased levels of exhaled NO have been observed in patients with advanced hepatic cirrhosis and in those with HPS.[35] However, the results of measurements of exhaled NO after several interventions have been discrepant. For example, administration of methylene blue, which blocks the guanylate cyclase by which NO may mediate vasodilation,[36] or performance of liver transplantation[37] produces significant decrements in exhaled NO. By contrast, N^G-nitro-L-arginine methyl ester (L-NAME) had no effect on gas-exchange abnormalities.[38] In patients with liver cirrhosis, the close correlations between exhaled NO concentration and Child-Pugh score, alkaline phosphatase, bilirubin, aspartate and alanine aminotransferases, and albumin suggest that NO formation in the lung may be triggered by stimulating factors normally inactivated by the liver.[36] Recent work suggests that endothelin-1 and tumor necrosis factor-α can both interact in the development of experimental HPS.[28,39,40] The association between arterial P_{O_2} and carboxyhemoglobin in patients with HPS supports the contention of increased carbon monoxide production in abnormal gas exchange.[41]

Clinically, most patients with HPS are cyanotic, show conspicuous finger clubbing, may complain of shortness of breath and platypnea (increased dyspnea in the upright position relieved by recumbency), and have a hyperkinetic circulation. The majority of patients exhibit the typical clinical and functional stigmata of advanced liver failure, including those of portal hypertension; in a few cases, severe pulmonary abnormalities may antedate those of hepatic dysfunction. The presence of abundant cutaneous spider angiomata has been postulated as a clinical marker of the severity of the systemic and pulmonary circulatory and gas-exchange abnormalities observed in HPS.[42] The more severe the hepatic failure, the greater the severity of HPS, as suggested by the findings of a prospective study in cirrhotic patients: the hypoxemic subpopulation exhibited more severe liver failure and higher Child-Pugh scores and hepatic venous pressure gradients,[43] as well as scores from the Model for End-Stage Liver Disease (MELD).[44] Unlike the situation in hereditary hemorrhagic telangiectasia and other pulmonary arteriovenous malformations (see Chapter 54), hemoptysis and paradoxical emboli are extremely uncommon clinical manifestations of HPS. A single case of brain abscess has been reported.[45] In approximately one third of HPS patients, the syndrome can coexist with other chronic respiratory comorbidities such as COPD or pulmonary fibrosis. Nevertheless, the prevailing clinical and functional pulmonary features in patients with such comorbidities are generally those of HPS.[46]

Diagnosis

The diagnostic criteria for HPS are as follows[28]: presence of liver disease; gas-exchange abnormalities, more specifically an increased $(A - a)P_{O_2}$ (≥15 mm Hg), with or without concomitant arterial hypoxemia (arterial P_{O_2} < 80 mm Hg); and a positive contrast-enhanced echocardiogram or an abnormal intravenous radiolabeled perfusion lung scan, or both. Other additional features that can be useful for further establishing the diagnosis of HPS include decreased $D_{L_{CO}}$, dyspnea with or without platypnea and orthodeoxia (i.e., arterial hypoxemia that worsens by 5% or more or by 4 mm Hg or more when the patient is upright compared to recumbent), and a hyperkinetic circulatory state (high cardiac output and low systemic arterial pressures) with normal or low pulmonary artery pressure (P_{PA}). Although thoracic computed tomography scanning appears to be nonspecific, it may be useful to exclude coexistent respiratory comorbidities.[28]

Two-dimensional contrast-enhanced echocardiography appears to be the most sensitive and accurate noninvasive diagnostic procedure to identify right-to-left shunts of blood by finding microbubbles of air in the left heart cavities within 3 to 6 beats of their visualization in the right-sided chambers[28] (Fig. 83-2). Normally, echogenicity in the left chambers is not detected because the intravenously injected microbubbles (60 to 90 μm in diameter) are trapped in the pulmonary capillaries (<8 to 15 μm in diameter). Contrast-enhanced echocardiography cannot distinguish among the different forms of pulmonary vascular deformities (i.e., precapillary, capillary, and pleural dilations versus direct arteriovenous communications), but it can clearly differentiate them from intracardiac malformations, such as a patent foramen ovale, in which the microbubbles would appear in the left heart almost simultaneously with their appearance in the right. Alternatively, the demonstration of technetium-99m–macroaggregated albumin activity over extrapulmonary organs (e.g., liver, spleen, kidneys, and brain) strongly suggests the presence of right-to-left intrapulmonary shunting, because under normal conditions the albumin macroaggregates (20 to 60 μm in diameter) are trapped in the pulmonary capillary bed.[28]

To date, the exact prevalence of HPS remains unknown, and has ranged between 5% and 32%.[28] Using contrast-enhanced echocardiography as the gold standard tool to identify intrapulmonary vascular dilations, the prevalence of a positive echocardiography test in patients with chronic liver disease is approximately 20%.[30,47] However, the relevance of a positive contrast-enhanced echocardiography result in patients without coexisting

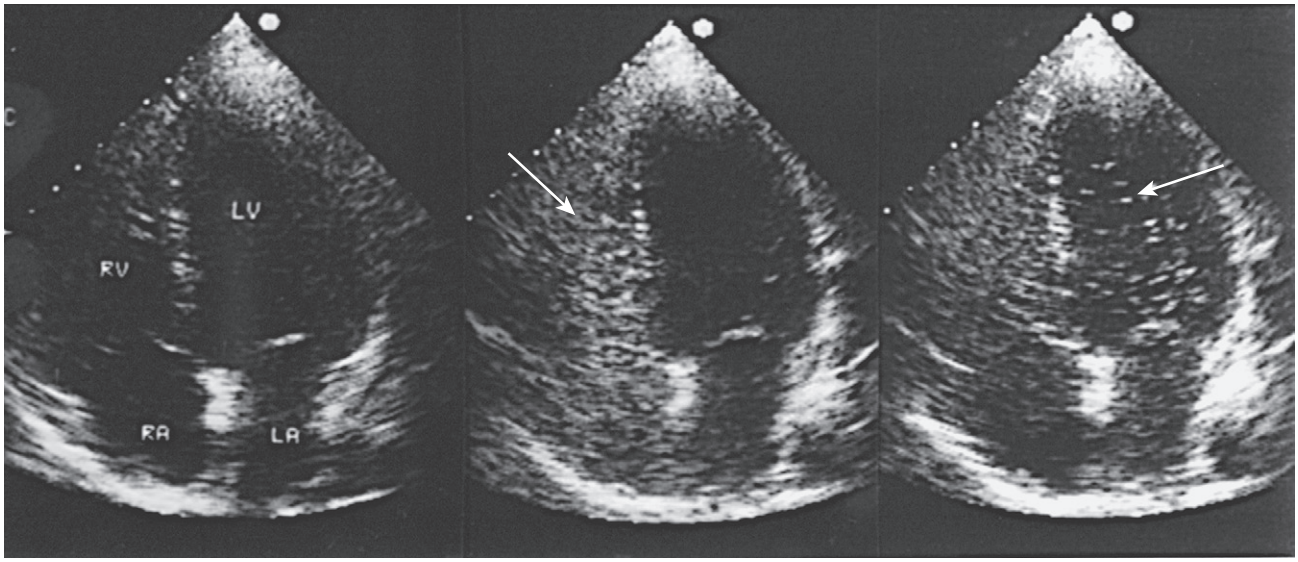

FIGURE 83-2 ■ Contrast-enhanced echocardiograms in a patient with hepatopulmonary syndrome. *Left,* Normal four-chamber view (LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle). *Center,* Injected microbubbles appear in the RV (*arrow*). *Right,* Within 5 beats, microbubbles appear in the LV (*arrow*). The demonstration of microbubbles in the left cardiac chambers is highly suggestive of the presence of intrapulmonary vascular dilations, or, alternatively, of anatomic arteriovenous malformations. (Courtesy of Dr. C. Paré, Hospital Clínic, Universitat de Barcelona, Barcelona.)

gas-exchange disturbances, some of whom may have a normal $(A - a)P_{O_2}$, remains unsettled. These patients are considered to have a *forme fruste* of HPS whose natural history is unknown as yet.[47,48]

Systemic hypotension, a normal or low P_{PA} with normal or low pulmonary vascular resistance (PVR) (<1.5 mm Hg/L per minute), an inordinately high cardiac output, and a reduced pulmonary vascular reactivity are the hemodynamic hallmarks of HPS. When the constellation of hypoxemia, normal or low P_{PA}, and finger clubbing is observed in a patient with advanced liver disease, the diagnosis of HPS is likely. Although data describing the natural history of HPS are scant, it appears that HPS patients not undergoing liver transplantation worsen progressively and have an adverse outcome, with median survival of 41 months following diagnosis of HPS.[28] In a recent prospective study, HPS was an independent risk factor for poor prognosis in patients with cirrhosis; those with HPS had a significantly shorter median survival (approximately 11 months) than those without HPS (41 months) even after adjusting for differences in liver disease.[49]

Gas-Exchange Abnormalities

The mechanisms of the gas-exchange abnormalities in patients with HPS have recently been reviewed.[28] When HPS is mild to moderate, the predominant mechanism of hypoxemia is ventilation-perfusion inequality, essentially due to the presence of areas in which ventilation is preserved but perfusion is profoundly increased. In contrast, when HPS is severe, increased intrapulmonary shunt coexists and, along with ventilation-perfusion imbalance, constitutes the primary abnormalities. Collectively, as the severity of the liver dysfunction advances, the greater the systemic and pulmonary dilation, the lower the hypoxic pulmonary vascular response, and the greater the degree of ventilation-perfusion inequalities, including increased intrapulmonary shunt.[28,50] A "diffusion-perfusion defect" has also been postulated to explain an increased diffusion gradient for oxygen in dilated pulmonary capillaries (Fig. 83-3). The contention is that pulmonary vascular dilation causes inadequate diffusion of oxygen to the center of the enlarged capillary. Moreover, the coexistence of a hyperkinetic state and the resulting shorter transit time of red blood cells would exaggerate further this diffusion-induced gas-exchange disturbance.[50a]

Treatment

Many therapeutic agents have been tried in HPS, including bismesylate almitrine, cyclophosphamide, garlic preparation, indomethacin, long-term oxygen therapy, methylene blue, propranolol, prostaglandin, and somatostatin, with disappointing results.[50a] The only successful treatment thus far is liver transplantation. In theory, replacement of the damaged organ should prevent all HPS-induced abnormalities, except for persistent low $D_{L_{CO}}$, whose mechanism remains unclear.[28] As might be expected, the worse the hypoxemia before transplantation, the longer it takes to resolve after surgery.[51] In the largest reported single-institution study thus far, 5-year survival after liver transplantation for HPS was 76%, and did not differ from the rate in patients without HPS who received transplants.[52]

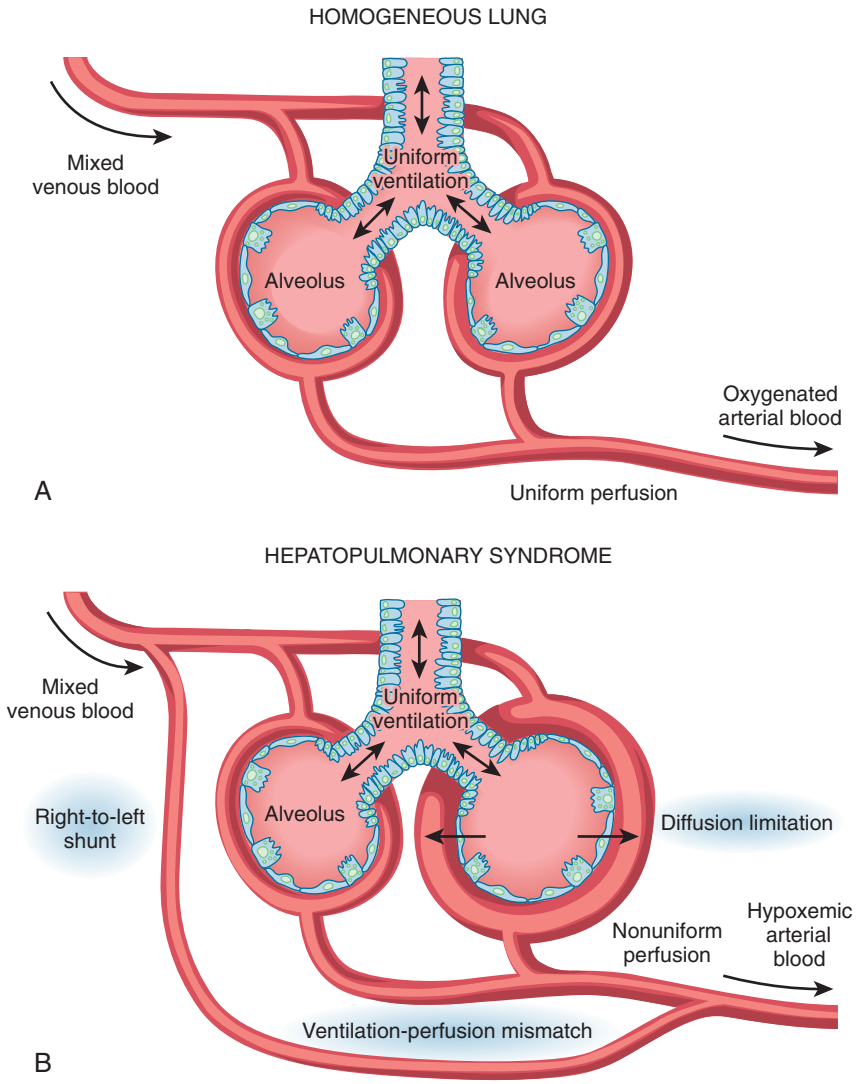

FIGURE 83-3 ■ Mechanisms of arterial hypoxemia in hepatopulmonary syndrome in a two-compartment gas exchange model. **A,** In the homogeneous lung of a healthy individual, with uniform alveolar ventilation and pulmonary blood flow, the capillary ranges between 8 and 15 μm in diameter and oxygen diffuses properly into the capillary while ventilation-perfusion is well balanced. **B,** In hepatopulmonary syndrome, where many capillaries are dilated and blood flow is nonuniform, alveolar ventilation–to–pulmonary perfusion mismatch emerges as the predominant mechanism at any clinical stage, either with or without the presence of intrapulmonary shunt and coexistent with oxygen diffusion limitation into the center of the dilated capillaries (*large arrow*) in the most advanced stages. (From Rodriguez-Roisin R, Krowka MJ. Hepatopulmonary syndrome—a liver-induced lung vascular disorder. N Engl J Med 358:2378–2387, 2008.)

Youth, a good arterial P_{O_2} response to 100% oxygen breathing, and lower presurgical hypoxemia are all factors that seem to predict a favorable response to liver transplantation.[53] Collectively, these elements may indicate a more reactive pulmonary vasculature and less profound intrapulmonary shunt. Recent work indicates that mortality may be higher after liver transplantation in patients with advanced HPS with preoperative arterial P_{O_2} values below 50 mm Hg alone or together with an abnormal (>20%) radionuclide extrapulmonary uptake.[52]

Portopulmonary Hypertension

Pulmonary hypertension (PH) associated with portal hypertension, or portopulmonary hypertension (POPH), is another mysterious pulmonary vascular disorder that appears to be associated with chronic hepatic disease.[53,54] Because both the diagnosis and the outcome of POPH, particularly in relation to the therapeutic benefits of liver transplantation, appear to be substantially different from those of HPS, it is important to highlight the distinctions between the two disorders. According to the European Respiratory Society–European Association for the Study of the Liver, POPH is defined by the following triad of hemodynamic abnormalities in a patient with portal hypertension: (1) a mean P_{PA} exceeding 25 mm Hg at rest; (2) a mean pulmonary artery wedge pressure below 15 mm Hg; and (3) a pulmonary vascular resistance of greater than 240 dynes • sec^{-1} • cm^{-5}.[54]

The results of a recent prospective study of a cohort of 536 patients evaluated for liver transplantation or pulmonary hypertension at seven centers in the United States between 2003 and 2006 documented the presence of POPH in 34 patients: a prevalence of 6%. Furthermore, findings from the cooperative trial established that female gender and associated autoimmune hepatitis conferred increased risk of developing POPH, whereas hepatitis C was associated with decreased risk. There were no major differences between cases and controls in the severity of the underlying liver disease as assessed by various means.[55]

In the classic retrospective postmortem studies, the prevalence of histopathologic evidence of PH in patients

with liver cirrhosis or POPH (or both) ranged between 0.25% and 0.73%[56]; by contrast, PH was detected on histologic examination in only 0.13% of a noncirrhotic population. In a case-control study conducted by the International Primary Hypertension Study Group to investigate the incidence of primary PH, the condition was found in 7.3% of patients with cirrhosis, 3.1% of those with human immunodeficiency virus infection, 2.1% of those with a family history of primary PH, and none of the controls.[57] These and many subsequent observations have documented a causal association between the two conditions, such that POPH has been classified as a category of secondary PH with hemodynamic criteria consistent with the definitions and classification proposed by the Third World Symposium on Pulmonary Artery Hypertension.[58,58a]

From a histopathologic viewpoint, the vascular lesions in POPH are indistinguishable from those identified in primary (idiopathic) PH (see Chapter 52), namely intimal thickening, smooth muscle proliferation, plexogenic pulmonary arteriopathy, and in situ thrombosis,[59] all of which—plus vasoconstriction—contribute to the greatly increased pulmonary vascular resistance.[60] (Of interest, primary PH is also a disease with a female predominance, but generally about a decade younger than in women with POPH.) Chemla and colleagues[61] postulated that the portosystemic shunting of vasoactive agents such as thromboxanes, serotonin, bradykinin, and neuropeptide Y, which are normally metabolized by the healthy liver, may result in pulmonary arterial vasoconstriction; in addition, in primary PH, an attractive alternative pathogenic hypothesis that cannot be ruled out is pulmonary endothelial dysfunction, with decreased production of the endogenous vasodilator NO.

The most common symptom is shortness of breath on exertion; chest pain, syncope, and hemoptysis can also occur.[62] Radiographically, both an enlarged cardiac silhouette and pulmonary artery prominence are noted in from approximately one half to two thirds of patients with hemodynamic confirmation of POPH.[55,62] Overall, maximal airflow rates and lung volumes are within or near normal limits, whereas D_{LCO}, arterial P_{O_2}, and (A – a) P_{O_2} are reduced,[55] although not to the strikingly low levels observed in HPS. Compared with patients with primary PH, the mean P_{PA} is lower in patients with POPH, and cardiac index and mixed venous oxygen saturation are higher.[60]

Transthoracic echocardiography is now routine in patients being considered for liver transplantation because the presence of POPH affects the outcome of surgery; echocardiography should also be performed in other patients with hepatic disease suspected of having PH. Findings such as increased tricuspid peak regurgitant jet velocity, pulmonary valve insufficiency, paradoxical septal motion, right ventricular hypertrophy-dilation, and an increased right ventricular systolic pressure estimate in the setting of portal hypertension suggest, but do not prove, POPH. Right heart catheterization is needed to confirm the diagnosis. A retrospective analysis showed that a screening Doppler echocardiogram with a right ventricular systolic pressure greater than 50 mm Hg identifies essentially all patients who should proceed to right heart catheterization.[54] Until recently, it was believed that median survival in POPH was extremely poor; new information, however, indicates overall survival rates at 1 and 3 years of 88% and 75%, similar to that in patients with idiopathic PH.[58a,59]

Patients with a clinical suspicion of POPH, like all patients with primary PH, should have a pharmacologic vasodilator test to assess the degree of reversibility of the pulmonary vasculature in response to common drugs such as nifedipine, NO, and prostacyclin.[52] A 20% reduction in both P_{PA} and PVR is considered to be a criterion of vascular responsiveness. Although none of the patients with POPH in the series reported by Hervé and colleagues[60] showed a positive vasodilator response, a recent report of 19 patients with POPH revealed that one third were able to reach more favorable hemodynamic status, with better responsiveness to intravenous epoprostenol than to inhaled NO.[63] Vasodilator responsiveness open the possibility of treatment of patients with POPH, with a goal of either preparing patients for liver transplantation by lowering mean P_{PA} below 35 mm Hg, the cutoff for surgery, or improving long-term survival.

Treatment for POPH, however, remains problematic because there are no randomized controlled studies for guidance: available agents include epoprostenol, iloprost, sildenafil, and bosentan.[64] In a recent retrospective study, the safety and efficacy of inhaled iloprost and bosentan were assessed in 31 patients with POPH for up to 3 years; although both agents were safe with regard to liver function, bosentan exhibited significantly superior effects on exercise capacity and hemodynamics, and—of note—had higher survival rates.[65] Prospective trials are clearly needed to provide further guidance.

Primary Biliary Cirrhosis

Primary biliary cirrhosis (PBC), an autoimmune disease, is characterized by a chronic, cholestatic, granulomatous, and destructive process that involves the intrahepatic bile ducts.[66] When severe, these processes result in cholestasis, cirrhosis, and liver failure. The autoimmunologic basis is reflected in the presence of several immunologic alterations, such as depressed T-suppressor cell function, hypergammaglobulinemia, and the presence of antimitochondrial antibodies. Connective tissue diseases such as the sicca complex, Sjögren's syndrome, and scleroderma are frequently associated with PBC,[67,68] which also has a near association ($P = 0.07$) with POPH.[55] Several respiratory abnormalities have been associated with PBC: interstitial lung disorders, such as lymphocytic interstitial pneumonitis and fibrosing alveolitis; subclinical intrapulmonary granulomas that mimic sarcoidosis[69]; increased numbers of $CD4^+$ lymphocytes in the bronchoalveolar lavage fluid; and obstructive airway disease, such as bronchiectasis.[70] Occasionally, the pulmonary manifestations precede the liver involvement.[71] In addition, thoracic wall deformities secondary to osteopenic vertebral complications induced by abnormal vitamin D metabolism related to poor absorption of fat-soluble vitamins can be also observed.[70] A reduced D_{LCO}, with or

without ventilatory defects, is one of the functional hallmarks of the disease, particularly when a connective tissue disorder coexists.[71-73] Furthermore, the clinical, radiographic, and functional respiratory abnormalities in patients with PBC are more likely to be associated with underlying connective tissue disorders than with PBC itself.[73] As with many chronic liver diseases, PBC can be complicated by HPS (discussed previously).

Chronic Active Hepatitis

Chronic active hepatitis, an increasingly frequent liver disease that is characterized by diffuse parenchymal inflammation and hepatic cell necrosis, may be caused by viral hepatitis (most commonly hepatitis C virus), autoimmune disorders, and drug-related liver injury. Pulmonary fibrosis and lymphoid interstitial pneumonitis have been reported but are rare.[72,74] After years of smoldering inflammation, which is often asymptomatic, chronic active hepatitis can lead to cirrhosis and liver failure, which has been associated with HPS.[70] Patients with chronic hepatitis C virus infection and coexistent COPD may demonstrate an accelerated annual decline in FEV_1.[75]

Sclerosing Cholangitis

Sclerosing cholangitis is an unusual disease that results from chronic inflammation affecting both intrahepatic and extrahepatic bile ducts. It has been linked with inflammatory obstructive airway diseases such as bronchiectasis; however, the relationship remains unproven because ulcerative colitis, a frequent clinical accompaniment, has also been associated with the same respiratory complications.[76]

Alpha$_1$-Antitrypsin Deficiency

The discovery that certain patients with COPD had low levels of circulating alpha$_1$-antitrypsin led to the current protease-antiprotease theory of the pathogenesis of pulmonary emphysema (see Chapter 39 for complete discussion). This hereditary disorder is nearly always associated with the homozygous PiZZ phenotype. Genetically predisposed infants often present with hepatomegaly or hepatosplenomegaly and evidence of cholestasis. Most children with alpha$_1$-antitrypsin–induced liver disease recover, but about 15% go on to develop cirrhosis, presumably from toxic effects of the mutant antitrypsin protein retained in the endoplasmic reticulum of hepatocytes[77]; HPS has been reported as a complication of this form of cirrhosis.[78] By far the more common pulmonary complication, COPD is unrelated to the presence of liver disease, occurs in adults, and is characterized by panacinar emphysema and bronchial abnormalities, including bronchiectasis.[70]

PANCREATITIS

Most episodes of acute pancreatitis are mild, but severe injury occurs in about 20% of patients, of whom 15% to 25% will die.[79] Pulmonary complications are frequent and, when present, account for significant mortality. Intrathoracic complications have been implicated as important contributing factors to death from pancreatitis in 22% to 29% of fatal cases.[80] Furthermore, respiratory failure, as defined by an arterial P_{O_2} value lower than 60 mm Hg, is considered one of the major factors adversely affecting survival in acute pancreatitis.[81] Several intrathoracic complications have been linked to acute pancreatitis, including hypoxemia with and without pulmonary infiltrates—basilar atelectasis, pleural effusion, and the pattern of acute respiratory distress syndrome (ARDS)—each of which affects the incidence and outcome of respiratory failure.[82]

Respiratory Failure

Gas-exchange disturbances, ranging from mild hypoxemia to ARDS, may occur during episodes of acute pancreatitis. Arterial hypoxemia (arterial $P_{O_2} < 80$ mm Hg) with a normal chest radiograph is a frequent finding in the early stages of acute pancreatitis.[83] In one study of 116 patients, 69% showed an arterial P_{O_2} lower than 76 mm Hg during the first 48 hours of the episode.[84] Although arterial hypoxemia may be asymptomatic and mild during the initial hours of acute pancreatitis, it should not be dismissed, because these patients are at increased risk for respiratory failure.[82] Ranson and associates[84] reported that 67% of the patients who had an initial arterial P_{O_2} lower than 66 mm Hg developed clinical respiratory symptoms afterward, and 39% of them died. Accordingly, patients who present with hypoxemia during an episode of acute pancreatitis should be closely monitored for worsening respiratory failure.[82]

The mechanisms of arterial hypoxemia with a normal chest radiograph during acute pancreatitis remain poorly understood. Murphy and associates[85] showed that hypoxemia in these patients was caused by an increase in the right-to-left shunt fraction, which improved after recovery in most cases. No changes in expiratory flow rates, lung volumes, or closing capacity were shown, compared with measurements performed after recovery. These authors suggested that hypoxemia in the absence of radiologic abnormalities may be related to changes in pulmonary vascular permeability, similar but milder than that described in ARDS.[85] In a similar group of patients, De Troyer and colleagues[86] measured a transient reduction of $D_{L_{CO}}$ during the episodes of pancreatitis; they suggested that factors released from the injured organ could have increased capillary permeability and impaired $D_{L_{CO}}$. In addition, Greenberg and coworkers[87] demonstrated a reduction in the oxygen affinity of hemoglobin in patients with acute pancreatitis, which was related to the increase in circulating fatty acids.

Because of the normal chest radiograph, arterial hypoxemia may be clinically undetected but profound; therefore, a high index of suspicion should be present for respiratory impairment in patients with acute pancreatitis, and arterial blood gases should be measured

periodically during the initial 48 to 72 hours of hospitalization.[80] When hypoxemia occurs, the patient should receive supplemental oxygen to raise the arterial P_{O_2} to more than 70 mm Hg.[88]

Approximately 15% to 20% of patients with severe acute pancreatitis develop ARDS, the most dangerous of all pulmonary complications, which is associated with a mortality rate of 56%.[89] The incidence of ARDS is higher in patients with hemorrhagic compared with nonhemorrhagic pancreatitis.[90,91] Respiratory symptoms appear 2 to 7 days after the onset of the acute episode. The chest radiograph usually shows signs of pulmonary vascular congestion that progress to bilateral, diffuse infiltrates. Studies of arterial blood gases confirm severe hypoxemia, usually associated with marked hypocapnia. Pathologic findings in these patients reveal evidence of acute lung injury that is indistinguishable from that observed in ARDS attributable to other causes.[90]

The mechanisms of lung injury associated with acute pancreatitis are not completely understood. It is not clear whether the injury results from a direct toxic effect of pancreatic products or is secondary to the release of inflammatory mediators, or both. Several pancreatic products, production of which is markedly increased during acute pancreatitis, have the potential to induce lung injury. Phospholipase A_2 has been extensively studied as a putative mediator, because it binds to pulmonary capillaries and has the ability to induce the enzymatic degradation of the phospholipid components of surfactant, thereby promoting alveolar collapse and increased vascular permeability.[79,82] Free fatty acids, produced from triglyceride degradation by circulating lipase, may induce alveolar edema and hemorrhage.[82] Pancreatic enzymes also have the capability to induce lung injury and cause increased vascular permeability, which has been demonstrated by the radioactive transferring method.[92] In addition to the direct effect of pancreatic products, sequestration of polymorphonuclear neutrophilic leukocytes within the alveolar and interstitial spaces is postulated to play an important role.[79] Moreover, various inflammatory mediators that may be released during pancreatic injury, such as reactive oxygen species,[93] adhesion molecules, platelet-activating factor,[82,94] and many cytokines, possess the potential to produce diffuse lung injury and increase pulmonary vascular permeability.[79,82]

Treatment of pancreatitis-associated lung injury is essentially supportive and does not differ from that for other forms of ARDS (see Chapter 55). Key measures include cardiovascular support and lung protective ventilation.[79] Additional treatment includes suppression of the secretory function of the pancreas by elimination of oral intake, use of nasogastric suction, and inhibition of gastric acid secretion with $histamine_2$ blockers. Studies suggest that octreotide, a potent inhibitor of exocrine pancreatic secretion, may decrease both mortality rates and the incidence of ARDS among patients with severe acute pancreatitis.[95,96] Nevertheless, controlled, randomized trials of the effectiveness of octreotide in the prevention and treatment of pancreatitis-associated ARDS are needed.

Pleural Effusion

Pleural effusions may be associated with both acute and chronic pancreatitis (see also Chapter 73). In acute pancreatitis, pleural effusion is a relatively frequent finding, being present in about 20% of reported patients,[97] but in as high as 50% in one series.[98] In most cases these effusions are of small size; the majority (68%) are left sided, 22% are bilateral, and only 10% are right sided.[82]

Various pathogenic mechanisms have been proposed to explain the development of pleural effusions associated with acute pancreatitis[97]: (1) increased permeability of lymphatics and fluid leak caused by pancreatic enzymes that may diffuse from the peritoneal side to the thoracic side of the diaphragm, (2) impaired lymphatic drainage of pleural exudate caused by obstruction of lymphatic vessels by the high enzymatic content of the pleural fluid, and (3) increased permeability of diaphragmatic capillaries caused by the inflammatory process in the adjacent pancreas.

In patients with pleural effusion associated with acute pancreatitis, symptoms are primarily abdominal (pain, nausea and vomiting); occasionally, respiratory symptoms (pleuritic pain and dyspnea) may also be present. The diagnosis is established by demonstrating an elevated amylase concentration in the pleural fluid, which may be 30 times higher than the concentration in plasma.[79] The pleural fluid usually is an exudate, which is sometimes bloody, and has a high concentration of both protein and lactic acid dehydrogenase; the differential white blood cell count reveals a predominance of polymorphonuclear cells.

Pleural effusions associated with acute pancreatitis usually are self-limited and resolve when the pancreatic inflammation decreases without requiring therapeutic drainage. Therefore, if the pleural effusion does not resolve within 2 weeks after treatment for the pancreatic disease, the possibility of a pancreatic abscess or a pseudocyst should be considered.

Chronic pleural effusions are usually associated with chronic relapsing pancreatitis and pancreatic pseudocyst. In most cases a history of alcohol abuse is present.[99] Chronic effusions are large, may occupy the entire hemithorax, and reaccumulate rapidly after thoracentesis.

The typical mechanism of chronic effusion is a pancreaticopleural fistula, a direct communication between the pancreas and the pleural space. In chronic pancreatitis, the pancreatic duct may rupture because of high internal pressure. Once it is disrupted, pancreatic secretions are able to flow into the retroperitoneum, from which they can enter the mediastinum through the esophageal or aortic hiatuses and then penetrate into the pleural space (Fig. 83-4). Occasionally, a direct communication exists between a pancreatic pseudocyst and the pleural cavity, through the diaphragmatic dome.[99]

Patients with chronic pancreatic effusions usually complain of respiratory symptoms such as chest pain and shortness of breath. Abdominal symptoms may be absent, probably because the pancreaticopleural communication decompresses the pseudocyst.[97] Therefore, the diagnosis of a chronic pancreatic pleural effusion

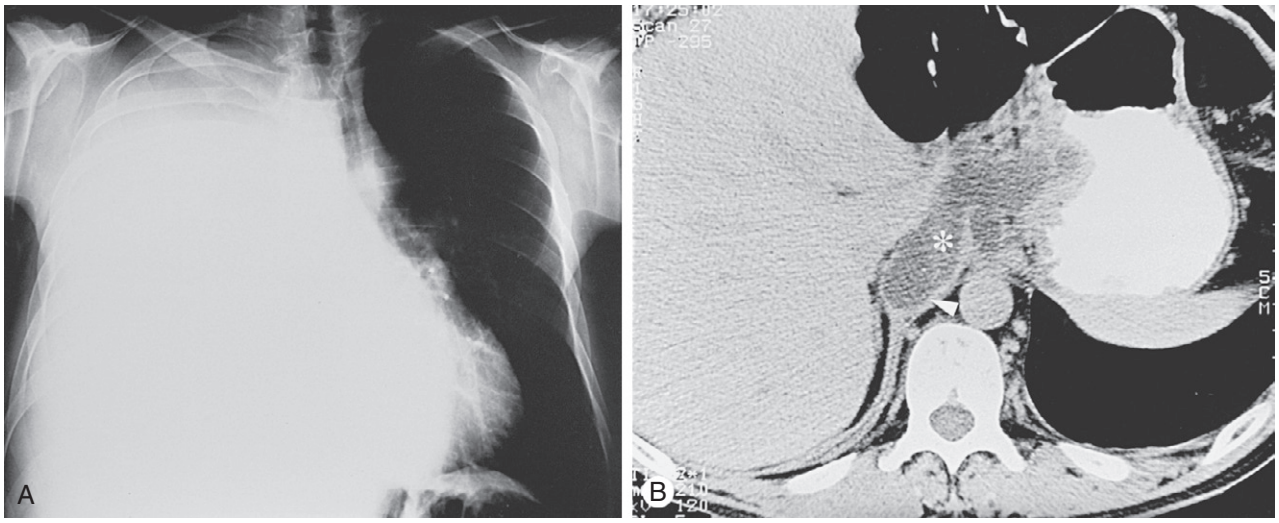

FIGURE 83-4 ■ This massive pleural effusion is associated with a pancreatic pseudocyst. **A,** Chest radiograph demonstrates a massive pleural effusion in the right hemithorax. **B,** Computed tomography scan of the upper abdomen, performed after pleural drainage, shows the cephalad extension of the pseudocyst (*asterisk*) through the right crural insertion (*arrowhead*) and the esophageal hiatus. (Courtesy of Dr. S. Navarro, Hospital Clínic, Universitat de Barcelona, Barcelona.)

should be suspected in any patient with a large pleural effusion who appears to be chronically ill or has a history of pancreatic disease or alcohol abuse.[100] The diagnosis is established by the demonstration of a high concentration of amylase in the pleural fluid. Ultrasonography and computed tomographic scanning of the chest and abdomen usually reveal the presence of a pseudocyst and occasionally may even show the pancreaticopleural fistula[100] (see Fig. 83-4). Endoscopic retrograde cholangiopancreatography provides additional information on ductal structures and may demonstrate passage of contrast material from the pancreatic duct or a pseudocyst into the peritoneal cavity, although visualization of the fistula may be difficult.[99,101] Endoscopic retrograde cholangiopancreatography and computed tomographic scanning together provide complementary information, which is useful especially if the patient has to undergo surgical intervention.

Patients with chronic pancreatic pleural effusions should be treated initially with nasogastric tube placement, no oral intake, parenteral nutrition, and repeated therapeutic thoracenteses. Inhibition of pancreatic secretion with octreotide has been shown to be useful in promoting the closure of pancreaticopleural fistulas in some cases.[102] Nonetheless, if, after 2 to 3 weeks of medical therapy, the pleural fluid continues to accumulate and the patient remains symptomatic, surgery to close the fistula should be considered.

KIDNEY DISEASES

Acute and chronic renal diseases are associated with a variety of respiratory manifestations. Pulmonary edema occurs in both conditions, and pleural disease, pulmonary calcification, and sleep apnea syndrome are fairly common in patients with chronic renal failure. Historically, treatment with hemodialysis caused transient changes in pulmonary gas exchange. These disorders are discussed in this section. Systemic necrotizing vasculitis and diseases associated with autoantibodies, which usually affect both the lung and the kidney, are considered in Chapters 58 and 60.

Pulmonary Edema

Pulmonary edema is common in patients with acute or chronic renal failure. A variety of conditions may favor edema formation: fluid overload, left ventricular failure, hypoalbuminemia, and increased pulmonary microvascular permeability. The relative importance of increased microvascular permeability versus left ventricular failure in the pathogenesis of pulmonary edema in renal failure has been largely a subject of controversy. Autopsy findings showing the presence of protein-rich edema fluid, hyaline membranes, and alveolar hemorrhage[103,104] all pointed to an increased vascular permeability to proteins as the likely mechanism of pulmonary edema formation. The demonstration of an increased protein content in edema fluid sampled directly by endotracheal aspiration reinforced this hypothesis.[105] Furthermore, pulmonary edema has been reported in the absence of volume overload and in the presence of normal intracardiac and pulmonary wedge pressures. However, studies using a double-isotope technique failed to show a significant accumulation of radiolabeled transferrin in patients with renal failure and pulmonary edema.[106] The rate of protein accumulation in patients with renal failure was similar to that in patients with cardiogenic pulmonary edema and in normal volunteers, and significantly lower than in patients with ARDS; these observations suggest that pulmonary edema in most patients with renal failure is probably not related to increased pulmonary vascular permeability to proteins.[106]

Heart failure is believed to play an important role in the development of pulmonary edema associated with chronic renal failure. Cardiac disorders are common in end-stage renal disease, and a variety of factors, including hypertension, diabetes mellitus, anemia, surgical arteriovenous fistulas, and ischemic heart disease, may adversely affect cardiac function.[107,108] Left ventricular dysfunction may be reversible after dialysis or renal transplantation, which suggests that patients with chronic renal failure may have a specific "uremic cardiomyopathy."[107,109,110]

Subclinical lung congestion in patients with chronic renal failure may reduce lung volumes and maximal expiratory flow rates, which usually reverse after hemodialysis.[111–113] In contrast to the findings in patients with left ventricular dysfunction,[114] subclinical pulmonary edema in renal failure is not associated with bronchial hyperresponsiveness, either before or after hemodialysis.[115]

From a clinical standpoint, most instances of pulmonary edema associated with renal failure, both acute and chronic, involve increased intravascular volume from abnormal left ventricular function and fluid overload. Accordingly, its treatment should essentially consist of removal of excess body fluid with dialysis.

Pleural Disease

Approximately 20% to 40% of patients who die from chronic renal failure have fibrinous pleuritis detected at autopsy.[103,116] This fibrinous pleuritis can be manifested as pleuritic chest pain with pleural friction rubs,[117] pleural effusion,[118] or fibrothorax.[119,120]

Pleural effusions were detected in 20% of 257 hospitalized patients receiving long-term hemodialysis; their most common symptom was dyspnea.[121] Other patients may be asymptomatic or they may present with fever, chest pain, or cough. The effusions usually are unilateral and in some cases may be large, occupying more than 50% of the hemithorax. In one study the pleural fluid was transudative in about two thirds of the patients and exudative in the remainder.[121] In patients with exudates, the leukocyte count reveals a predominance of lymphocytes, and the biopsy specimens usually demonstrate chronic fibrinous pleuritis.[122] The pathogenesis of "chronic uremic pleuritis" associated with renal failure is not known, but it is probably related to the effect of retained metabolic toxins.

The effusion usually disappears gradually after several weeks of dialysis. In about 25% of patients, it may persist, progress, or recur. If fibrothorax develops and produces a symptomatic restrictive ventilatory impairment, surgical decortication should be considered.[119,120]

Pulmonary Calcification

Metastatic calcification is a common complication of chronic renal failure that may affect many visceral organs, and is found in 60% to 80% of dialysis patients at autopsy or by bone scintigraphy.[123] Similar diffuse calcifications may occur in other systemic or pulmonary conditions.[124] Pulmonary involvement is common, but it is generally undetectable by ordinary chest films and most patients are asymptomatic.[125] At times, the chest radiograph or computed tomogram may show infiltrates composed of nodular opacities less than 2 mm in diameter that can be diffuse or localized or computed tomogram (see Fig. 85-2). The infiltrates are relatively stable, in contrast to infectious processes. Pulmonary function tests may reveal a restrictive ventilatory defect and/or a reduction in D_{LCO}.

The pathogenesis of pulmonary calcification in patients with chronic renal failure is complex; several factors—in concert—may play a role: (1) the effect of chronic acidosis, which leaches calcium from bones; (2) the effect of intermittent alkalosis, which favors the deposition of calcium salts; (3) the effect of hyperparathyroidism, which causes bone reabsorption and intracellular hypercalcemia; and (4) the effect of low glomerular filtration rate, which causes hyperphosphatemia and a greatly elevated calcium-phosphorus product.[123]

The diagnosis of pulmonary calcification can be confirmed by pulmonary uptake during technetium-99m–diphosphonate scanning (see Fig. 85-3).[126] Treatment is generally unsatisfactory and consists of maintaining adequate dialysis, lowering the calcium-phosphorus product, and treating hyperparathyroidism, when present; renal transplantation may improve or worsen the condition.[123]

Sleep Apnea

Disturbed sleep, including sleep apnea, has long been recognized in patients with end-stage renal disease. (Other causes of sleep apnea, as well as its pathophysiology and treatment, are described in Chapter 79.) The mounting evidence in favor of a high prevalence of sleep apnea in dialysis patients—greater than 50%[127]—has been reinforced by the results of comparisons between patients on standard thrice-weekly hemodialysis and closely matched control subjects from the community-based Sleep Heart Health Study: dialysis patients had a fourfold increase in sleep apnea and episodes of severe nocturnal hypoxemia, after adjusting for comorbid conditions that might have affected outcome.[128]

Various mechanisms have been proposed to explain the high prevalence of sleep apnea in patients with end-stage renal disease undergoing hemodialysis. Perhaps the most persuasive of the pathogenetic speculations involves the importance of fluid overload and its corollary that intermittent hemodialysis fails to reduce "upper airway edema (especially during sleep while supine)," thereby facilitating the presence of airway obstruction.[129] Support for this postulate comes from the increased pharyngeal resistance that accompanies rostral shifts of fluid produced by lower body positive pressure in healthy subjects.[130] Follow-up studies using the same methodology documented an increase in upper airway collapsibility.[131]

Accumulation of uremic toxins might also play a role, independently or in conjunction with fluid overload, in the pathogenesis of sleep disorders. Increasing the frequency and length of nocturnal hemodialysis, which

does not distinguish between the presence of toxins and fluid overload as possible mechanisms, caused a significant decrease in the severity of sleep apnea in all 14 patients in whom it was tried,[132] thus offering a potential, but logistically complicated, solution to an otherwise difficult-to-treat and serious clinical problem.

Standard treatment of obstructive sleep apnea might be beneficial, but experience in patients with end-stage kidney disease is limited.[133] There are anecdotal reports of improvement after renal transplantation,[134] but according to a recent report, only 3 of 18 patients had significant improvement after the procedure.[135]

Hemodialysis-Induced Hypoxemia

Another clinical problem associated with end-stage renal disease and hemodialysis—now largely of historic interest—was the prompt reduction in arterial P_{O_2} of 10 to 15 mm Hg after initiation of dialysis, which reached a nadir after 30 to 60 minutes and persisted for the duration of the procedure.[136–138] The severity of hypoxemia varied according to the type of dialysis membrane and the chemical nature of the dialysate buffer.[139,140] Once-popular explanations for the phenomenon, pulmonary vascular leukostasis and activation of complement, have been excluded. Exposure of blood to certain dialysis membranes activates the alternative complement pathway, and within minutes C3a and C5a are generated, which may induce intrapulmonary sequestration of leukocytes and a fall in circulating leukocytes. Based on the temporal association between the onset of hypoxemia and the transient leukopenia, it was postulated that the decrease in arterial P_{O_2} resulted from ventilation-perfusion mismatching due to leukostasis in small pulmonary vessels.[141] However, studies using the multiple inert gas elimination technique ruled out ventilation-perfusion mismatching as the principal mechanism of hypoxemia,[142–144] even though Romaldini and colleagues[143] showed a tendency for ventilation-perfusion matching to improve during the dialysis procedure, which was most likely explained by a dialysis-induced decrease in extravascular lung water. Furthermore, hypoxemia was observed during dialysis with membranes that do not cause leukopenia.[145]

Currently, the most accepted explanation for the decrease in arterial P_{O_2} during hemodialysis is the hypoventilation associated with the removal of carbon dioxide by the dialysate, which is substantial with acetate buffer but minimal with bicarbonate buffer[146]; in addition, acetate buffer may further reduce respiratory carbon dioxide elimination due to carbon dioxide consumption during acetate metabolism.[147] In one study of patients being hemodialyzed with acetate buffer, minute ventilation dropped from an average of 7.2 L/min to 5.7 L/min within 15 minutes of the start of hemodialysis.[148] The $(A - a)P_{O_2}$ value during hemodialysis actually remains stable despite a significant fall in arterial P_{O_2}.[138,143] An additional consequence of the nonrespiratory carbon dioxide "unloading" was to destabilize resting ventilation, which was manifested by an irregular breathing pattern, with the development of periodicity and sometimes apneas.[148,149]

Currently, the former complications of hypoxia and leukopenia during hemodialysis have been largely eliminated by the use of both synthetic (inert) membranes, which do not activate complement, and dialysates such as bicarbonate, which do not remove carbon dioxide. Supplemental oxygen should still be given during the procedure to patients with coexisting cardiopulmonary diseases.

KEY POINTS

- Gastroesophageal reflux, a common disorder, may cause chest pain, varying from heartburn to myocardial ischemia–like distress, may provoke or exacerbate chronic cough, and may trigger asthma attacks or worsen the underlying condition.
- Inflammatory bowel diseases, ulcerative colitis more so than Crohn's disease, have been associated with a variety of chronic pulmonary diseases, particularly of the airways (asthma, chronic bronchitis, and bronchiectasis), and, less commonly, of the lung parenchyma (interstitial fibrosis and bronchiolitis obliterans with organizing pneumonia) and other sites.
- Between 5% and 10% of patients with cirrhosis of the liver develop pleural effusion(s) (hepatic hydrothorax); as many as 20% of patients with end-stage liver disease develop the hepatopulmonary syndrome, characterized by hypoxemia from marked dilation of pulmonary capillaries; and another 6% of patients develop portopulmonary hypertension (mean Ppa > 25 mm Hg).
- Episodes of severe acute pancreatitis are associated with a high frequency of pulmonary complications, especially hypoxemia, pleural effusions, and acute respiratory distress syndrome, which are major causes of excess morbidity and mortality.
- Diseases of the kidney also are important causes of pulmonary edema, pleural disease, pulmonary calcification, and sleep apnea, some of which may be alleviated by dialysis and/or renal transplantation.

References

1. Vakil N, van Zanten SV, Kahrilas P, et al: The Montreal definition and classification of gastroesophageal reflux disease: A global evidence-based consensus. Am J Gastroenterol 101:1900–1920, 2008.
2. Garcia Rodriguez LA, Martin-Merino E, Johansson S, Wallander MA: Relationship between gastroesophageal reflux disease and COPD in UK primary care. Chest 134:1223–1230, 2008.
3. Irwin RS, Curley FJ, French CL: Difficult-to-control asthma: Contributing factors and outcome of a systematic management protocol. Chest 103:1662–1669, 1993.
4. Terada K, Muro S, Sato S, et al: Impact of gastro-oesophageal reflux disease symptoms on chronic obstructive pulmonary disease exacerbation. Thorax 63:951–955, 2008.
5. DeMeester TR, Bonavina L, Iascone C, et al: Chronic respiratory symptoms and occult gastroesophageal reflux: A prospective clinical study and results of surgical therapy. Ann Surg 211:337–345, 1990.
6. Jack CI, Calverley PMA, Donnelly RJ, et al: Simultaneous tracheal and oesophageal pH measurements in asthmatic patients with gastro-oesophageal reflux. Thorax 50:201–204, 1995.
7. Mansfield LE, Stein MR: Gastroesophageal reflux and asthma: A possible reflex mechanism. Ann Allergy 41:224–226, 1978.
8. Tan WC, Martin RJ, Pandey R, et al: Effects of spontaneous and simulated gastroesophageal reflux on sleeping asthmatics. Am Rev Respir Dis 141:1394–1399, 1990.
9. Rodrigues-Roisin R, Barberà JA: Pulmonary complications of abdominal disease. *In* Mason RJ, Broaddus VC, Murray JF, Nadel JA (eds): Murray and Nadel's Textbook of Respiratory Medicine (4th ed). Philadelphia: Elsevier Saunders, 2005, pp 2223–2241.
10. Ekstrom T, Tibbling L: Influence of theophylline on gastro-oesophageal reflux and asthma. Eur J Clin Pharmacol 35:353–356, 1988.
11. DiMarino AJ, Cohen S: Effect of an oral beta-2 adrenergic agonist on lower esophageal sphincter pressure in normals and in patients with achalasia. Dig Dis Sci 27:1063–1066, 1982.
12. Schindlbeck NE, Heinrich C, Huber RM, et al: Effects of albuterol (salbutamol) on esophageal motility and gastroesophageal reflux in healthy volunteers. JAMA 260:3156–3158, 1988.
13. Cappell MS: Cliinical presentation, diagnosis, and management of gastroesophageal reflux disease. Med Clin North Am 89:243–291, 2005.
14. Malhotra A, Frestonn JW, Aziz K: Use of pH-impedance testing to evaluate patients with suspected gastroesophageal manifestations of gastroesophageal reflux disease. J Clin Gastroenterol 42:271–278, 2008.

14a. American Lung Association Asthma Clinical Research Centers, Mastronarde JG, Anthonisen NR, et al: Efficacy of esomeprazole for treatment of poorly controlled asthma. N Engl J Med 360:1487–1499, 2009.

15. Tokayer AZ: Gastroesophageal reflux disease and chronic cough. Lung 186(Suppl 1):S29–S34, 2008.
16. Storch I, Sachar D, Katz S: Pulmonary manifestations of inflammatory bowel disease. Inflamm Bowel Dis 9:104–115, 2003.
17. Camus P, Piard F, Ashcroft T, et al: The lung in inflammatory bowel disease. Medicine (Baltimore) 72:151–183, 1993.
18. Rickli H, Fretz M, Hoffman A, et al: Severe inflammatory upper airway stenosis in ulcerative colitis. Eur Respir J 7:1899–1902, 1994.
19. Bernstein CN, Wajda A, Blanchard JF: The clustering of other chronic inflammatory diseases in inflammatory bowel disease: A population-based study. Gastroenterology 129:827–836, 2005.
20. Loftus EV Jr: Inflammatory bowel disease: Extending its reach. Gastroenterology 129:1117–1120, 2005.
21. Kuzela L, Vavrecka A, Prikazska M, et al: Pulmonary complications in patients with inflammatory bowel disorders. Hepatogastroenterology 46:1714–1719, 1999.
22. Higenbottam T, Cochrane GM, Clark TJH, et al: Bronchial disease in ulcerative colitis. Thorax 35:581–585, 1980.
23. Agusti AG, Cardus J, Roca J, et al: Ventilation-perfusion mismatch in patients with pleural effusion: Effects of thoracentesis. Am J Respir Crit Care Med 156:1205–1209, 1997.
24. Wilputte JY, Goffette P, Zech F, et al: The outcome after transjugular intrahepatic portosystemic shunt (TIPS) for hepatic hydrothorax is closely related to liver dysfunction: A long-term study in 28 patients. Acta Gastroenterol Belg 70:6–10, 2007.
25. Cerfolio RJ, Bryant AS: Efficacy of video-assisted thoracoscopic surgery with talc pleurodesis for porous diaphragm syndrome in patients with refrectory hepatic hydrothorax. Ann Thorac Surg 82:457–459, 2006.
26. Hourani M, Bellamy PE, Tashkin DP, et al: Pulmonary dysfunction in advanced liver disease: Frequent occurrence of an abnormal diffusing capacity. Am J Med 90:693–700, 1991.
27. Agusti AG, Roca J, Bosch J, et al: The lung in patients with cirrhosis. J Hepatol 10:251–257, 1990.
28. Rodriguez-Roisin R, Krowka MJ: Hepatopulmonary syndrome—a liver-induced lung vascular disorder. N Engl J Med 358:2378–2387, 2008.
29. De BK, Sen S, Biswas PK, et al: Occurrence of hepatopulmonary syndrome in Budd-Chiari syndrome and the role of venous decompression. Gastroenterology 122:897–903, 2002.
30. Martinez-Palli G, Barbera JA, Visa J, et al: Hepatopulmonary syndrome in candidates for liver transplantation. J Hepatol 34:651–657, 2001.
31. Vanhoutte PM: The endothelium-moderator of vascular smooth muscle tone. N Engl J Med 319:512–513, 1998.
32. Vallance P, Moncada S: Hyperdynamic circulation in cirrhosis: A role for nitric oxide? Lancet 337:776–778, 1991.
33. Sogni P, Moreau R, Gadano A, et al: The role of nitric oxide in the hyperdynamic circulatory syndrome associated with portal hypertension. J Hepatol 23:218–224, 1995.
34. Fallon MB, Abrams GA, Ifou Z, et al: The role of endothelial nitric oxide synthase in the pathogenesis of a rat model of hepatopulmonary syndrome. Gastroenterology 113:606–614, 1997.
35. Matsumoto A, Ogura K, Hirata Y, et al: Increased nitric oxide in the exhaled air of patients with decompensated liver cirrhosis. Ann Intern Med 123:110–113, 1995.
36. Schenk P, Madl C, Rezale-Majd S, et al: Methylene blue improves the hepatopulmonary syndrome. Ann Intern Med 133:701–708, 2000.
37. Rolla G, Brussino L, Colagrande P, et al: Exhaled nitric oxide and impaired oxygenation in cirrhotic patients before and after liver transplantation. Ann Intern Med 129:375–378, 2001.
38. Gomez FP, Barbera JA, Roca J, et al: Effects of nebulized N^G-nitro-L-arginine methyl ester in patients with hepatopulmonary syndrome. Hepatology 43:1084–1091, 2006.
39. Luo B, Liu L, Tang L, et al: ET-1 and TNF-α in HPS: Analysis in prehepatic portal hypertension and biliary and nonbiliary cirrhosis in rats. Am J Physiol Gastrointest Liver Physiol 286:G294–G303, 2004.
40. Dinh-Xuan AT, Naeije R: The hepatopulmonary syndrome: NO way out? Eur Respir J 23:661–662, 2004.
41. Arguedas MR, Drake BB, Kapoor A, Fallon MB: Carboxyhemoglobin levels in cirrhotic patients with and without hepatopulmonary syndrome. Gastroenterology 128:328–333, 2005.
42. Rodriguez-Roisin R, Roca J, Agustí AGN, et al: Gas exchange and pulmonary vascular reactivity in patients with liver cirrhosis. Am Rev Respir Dis 135:1085–1092, 1987.
43. Vachiery F, Moreau R, Hadengue A, et al: Hypoxemia in patients with cirrhosis: Relationship with liver failure and hemodynamic alterations. J Hepatol 27:492–495, 1997.
44. Swanson KL, Wiesner RH, Krowka MJ: Natural history of hepatopulmonary syndrome: Impact of liver transplantation. Hepatology 41:1122–1129, 2005.
45. Molleston JP, Kaufman BA, Cohen A, et al: Brain abscess in hepatopulmonary syndrome. J Pediatr Gastroenterol Nutr 29:225–226, 1999.
46. Martinez G, Barbera JA, Navasa M, et al: Hepatopulmonary syndrome associated with cardiorespiratory disease. J Hepatol 30:882–889, 1999.
47. Castro M, Krowka MJ: Hepatopulmonary syndrome: A pulmonary vascular complication of liver disease. Clin Chest Med 17:35–48, 1996.
48. Hopkins WE, Waggoner AD, Barzilai B: Frequency and significance of intrapulmonary right-to-left shunting in end-stage hepatic disease. Am J Cardiol 70:516–519, 1992.

49. Schenk P, Schöniger-Hekele M, Fuhrmann V, et al: Prognostic significance of the hepatopulmonary syndrome in patients with cirrhosis. Gastroenterology 125:1042–1052, 2003.
50. Gómez FP, Martínez-Pallí G, Barberà JA, et al: Gas exchange mechanism of orthodeoxia in hepatopulmonary syndrome. Hepatology 40:660–666, 2004.
50a. Degano B, Mittaine M, Guénard H, et al: Nitric oxide and carbon monoxide lung transfer in patients with advanced liver cirrhosis. J Appl Physiol 107:139–143, 2009.
51. Taillé C, Cadrenael J, Belocq A, et al: Liver transplantation for hepatopulmonary syndrome: A ten-year experience in Paris, France. Transplantation 75:1482–1489, 2003.
52. Arguedas MR, Abrams GA, Krowka MJ, et al: Prospective evaluation of outcomes and predictors of mortality in patients with hepatopulmonary syndrome. Hepatology 37:192–197, 2003.
53. Hoeper M, Krowka MJ, Strassbourg CP: Portopulmonary hypertension and hepatopulmonary syndrome. Lancet 363:1461–1468, 2004.
54. Rodriguez-Roisin R, Krowka MJ, Herve P, Fallon MB: Pulmonary hepatic vascular disorders (PHD). Eur Respir J 24:861–880, 2004.
55. Kawut SM, Krowka MJ, Trotter JF, et al: Clinical risk factors for portopulmonary hypertension. Hepatology 48:196–203, 2008.
56. McDonnell PJ, Toye PA, Hutchins GM: Primary pulmonary hypertension and cirrhosis: Are they related? Am Rev Respir Dis 127:437–441, 1983.
57. Abenhaim L, Moride Y, Brenot F, et al: Appetite-suppressant drugs and the risk of primary pulmonary hypertension. N Engl J Med 335:609–616, 1996.
58. Proceedings of the 3rd World Symposium on Pulmonary Artery Hypertension, Venice, Italy, June 23–25, 2003. J Am Coll Cardiol 42(12 Suppl S):1S–90S, 2004.
58a. Simonneau G, Robbins IM, Beghetti M, et al: Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol 54(Suppl 1):S43–S54, 2009.
59. Le Pavic J, Souza R, Herve P, et al: Portopulmonary hypertension: Survival and prognostic factors. Am J Respir Crit Care Med 178:637–641, 2008.
60. Hervé P, Lebrec D, Brenot F, et al: Pulmonary vascular disorders in portal hypertension. Eur Respir J 11:1153–1166, 1998.
61. Chemla D, Castelain V, Hervé P, et al: Haemodynamic evaluation of pulmonary hypertension. Eur Respir J 20:1314–1331, 2002.
62. Robalino BD, Moodie DS: Association between primary pulmonary hypertension and portal hypertension: Analysis of its pathophysiology and clinical, laboratory and hemodynamic manifestations. J Am Coll Cardiol 17:492–498, 1991.
63. Ricci GL, Melgosa MT, Burgos F, et al: Assessment of acute pulmonary vascular reactivity in portopulmonary hypertension. Liver Transpl 13:1506–1514, 2007.
64. Wells JT, Runo JR, Lucey MR: Portopulmonary hypertension. Hepatology 48:13–15, 2008.
65. Hoeper MM, Seyfarth HJ, Hoeffken G, et al: Experience with inhaled iloprost and bosentan in portopulmonary hypertension. Eur Respir J 30:1096–1102, 2007.
66. Leuschner U: Primary biliary cirrhosis—presentation and diagnosis. Clin Liver Dis 7:741–758, 2003.
67. Sherlock S, Scheuer PJ: The presentation of and diagnosis of 100 patients with primary biliary cirrhosis. N Engl J Med 289:674–678, 1973.
68. Wallaert B, Bonniere P, Prin L, et al: Primary biliary cirrhosis: Subclinical inflammatory alveolitis in patients with normal chest roentgenograms. Chest 90:842–848, 1986.
69. Maddrey WC: Sarcoidosis and primary biliary cirrhosis: Associated disorders? N Engl J Med 308:472–475, 1983.
70. Krowka MJ: Recent pulmonary observations in alpha$_1$-antitrypsin deficiency, primary biliary cirrhosis, chronic hepatitis C, an other hepatic problems. Clin Chest Med 17:67–82, 1996.
71. Izsdebka-Makosa Z, Zielinski U: Primary biliary cirrhosis in a patient with interstitial lung fibrosis. Chest 92:766–767, 1987.
72. Turner-Warwick M: Fibrosing alveolitis and chronic liver disease. Q J Med 37:133–149, 1968.
73. Rodriguez-Roisin R, Parés A, Bruguera M, et al: Pulmonary involvement in primary biliary cirrhosis. Thorax 36:208–212, 1981.
74. Helman CA, Keeton GR, Benatat SR: Lymphoid interstitial pneumonia with associated chronic active hepatitis and renal tubular acidosis. Am Rev Respir Dis 115:161–164, 1977.
75. Kanazawa H, Hirata K, Yoshikawa J: Accelerated decline of lung function in COPD patients with chronic hepatitis C virus infection: A preliminary study based on small number of patients. Chest 123:596–599, 2003.
76. Wiesner RH, LaRusso NF: Clinicopathologic features of the syndrome of primary sclerosing cholangitis. Gastroenterology 79:200–206, 1980.
77. Sveger T: Liver disease in alpha-1 antitrypsin deficiency detected by screening 200,000 infants. N Engl J Med 294:1316–1321, 1976.
78. Eriksson S: Alpha$_1$-antitrypsin deficiency and liver cirrhosis in adults. Acta Med Scand 221:461–467, 1987.
79. Pastor C, Maatthay MA, Frossard J-L: Pancreatitis-associated acute lung injury. New insights. Chest 124:2341–2351, 2003.
80. Shapiro MS, Dobbins JW, Matthay RA: Pulmonary manifestations of gastrointestinal disease. Clin Chest Med 10:617–643, 1989.
81. Agarwal N, Pitchumoni CS: Assessment of severity in acute pancreatitis. Am J Gastroenterol 86:1385–1391, 1991.
82. Browne GGW, Pitchumoni CS: Pathophysiology of pulmonary complications of acute pancreatitis. World J Gastroenterol 12: 7087–7096, 2006.
83. Basran GS, Ramasubramanian R, Verma R: Intrathoracic complications of acute pancreatitis. Br J Dis Chest 81:326–331, 1987.
84. Ranson JHC, Turner JW, Roses DF, et al: Respiratory complications in acute pancreatitis. Ann Surg 179:557–566, 1974.
85. Murphy D, Pack AI, Imrie CW: The mechanism of arterial hypoxia occurring in acute pancreatitis. Q J Med 194:151–163, 1980.
86. De Troyer A, Naeije R, Yernault JC, et al: Impairment of pulmonary function in acute pancreatitis. Chest 73:360–363, 1978.
87. Greenberg AG, Terlizzi L, Peskin G: Oxyhemoglobin affinity in acute pancreatitis. J Surg Res 22:561–565, 1977.
88. Imrie CW, Blumgart LH: Acute pancreatitis: A prospective study on some factors in mortality. Bull Int Soc Surg 6:601–605, 1975.
89. McFadden DW: Organ failure and multiple organ system failure in parcreatitis. Pancreas 6(Suppl 1):S37–S43, 1991.
90. Lankisch PG, Rahlf G, Koop H: Pulmonary complications in fatal acute hemorrhagic pancreatitis. Dig Dis Sci 28:110–116, 1983.
91. Renner IG, Savage WT, Pantoja JL, et al: Death due to acute pancreatitis: A retrospective analysis of 405 autopsy cases. Dig Dis Sci 30:1005–1018, 1985.
92. Robertson C, Basran G, Hardy J: Lung vascular permeability in patients with acute pancreatitis. Pancreas 3:162–165, 1988.
93. Guice KS, Oldham KT, Caty MG, et al: Neutrophil-dependent, oxygen-radical mediated lung injury associated with acute pancreatitis. Ann Surg 210:740–747, 1989.
94. Steer ML: Relationship between pancreatitis and lung diseases. Respir Physiol 128:13–16, 2001.
95. Fiedler F, Jauernig G, Keim V, et al: Octreotide treatment in patients with necrotizing pancreatitis and pulmonary failure. Intensive Care Med 22:909–915, 1996.
96. Paran H, Neufeld D, Mayo A, et al: Preliminary report of a prospective randomized study of octreotide in the treatment of severe acute pancreatitis. J Am Coll Surg 181:121–124, 1995.
97. Light RW: Pleural Diseases (5th ed). Philadelphia: Lippincott Williams & Wilkins, 2007, pp 250–253.
98. Raghu MG, Wig JD, Kochhar R, et al: Lung complications in acute pancreatitis. J Pancreas (Online) 8:177–185, 2007.
99. Uchiyama T, Suzuki T, Adachi A, et al: Pancreatic pleural effusion: Case report and review of 113 cases in Japan. Am J Gastroenterol 87:387–391, 1992.
100. Pottmeyer EW, Frey CF, Matsuno S: Pancreaticopleural fistulas. Arch Surg 122:648–654, 1987.
101. McCarthy S, Pellegrini CA, Moss AA, et al: Pleuropancreatic fistula: Endoscopic retrograde cholangiopancreatography and computed tomography. AJR Am J Roentgenol 142:1151–1154, 1984.
102. Chan KL, Lau WY, Sung JY: Octreotide therapy for pancreaticopleural fistula. J Gastroenterol Hepatol 9:530–532, 1994.
103. Hopps HC, Wissler RW: Uremic pneumonitis. Am J Pathol 31:261–273, 1953.
104. Henkin RI, Maxwell MH, Murray JF: Uremic pneumonitis: A clinical, physiological study. Ann Intern Med 57:1001–1008, 1962.

105. Rackow EC, Fein IA, Sprung C, et al: Uremic pulmonary edema. Am J Med 64:1084–1088, 1978.
106. Rocker GM, Morgan AG, Pearson D, et al: Pulmonary vascular permeability to transferrin in the pulmonary oedema of renal failure. Thorax 42:620–623, 1987.
107. Hung J, Harris PJ, Uren RF, et al: Uremic cardiomyopathy: Effect of hemodialysis on left ventricular function in end-stage renal failure. N Engl J Med 302:547–551, 1980.
108. Scharf S, Wexler J, Longnecker RE, et al: Cardiovascular disease in patients on chronic hemodialytic therapy. Prog Cardiovasc Dis 22:343–356, 1980.
109. Burt RK, Gupta-Burk S, Suki WN, et al: Reversal of left ventricular dysfunction after renal transplantation. Ann Intern Med 111:635–640, 1989.
110. Lai KN, Barneden L, Mathew TH: Effect of renal transplantation on left ventricular function in hemodialysis patients. Clin Nephrol 16:74–78, 1982.
111. Zidulka A, Despas PJ, Milic-Emili J, et al: Pulmonary function with acute loss of excess lung water by hemodialysis in patients with chronic uremia. Am J Med 55:134–141, 1973.
112. Zarday Z, Benjamin JJ, Koerner SK, et al: Effects of hemodialysis and renal transplantation on pulmonary function. Chest 63:532–535, 1973.
113. Stanescu DC, Veriter C, de Plaen JF, et al: Lung function in chronic uraemia before and after removal of excess fluid by hemodialysis. Clin Sci Mol Med 47:143–151, 1974.
114. Cabanes LR, Weber SN, Matran R, et al: Bronchial hyperresponsiveness to methacholine in patients with impaired left-ventricular function. N Engl J Med 320:1317–1322, 1989.
115. Ferrer A, Roca J, Rodriguez-Roisin R, et al: Bronchial reactivity in patients with chronic renal failure undergoing haemodialysis. Eur Respir J 3:387–390, 1990.
116. Fairshter RD, Vaziri ND, Mirahmadi MK: Lung pathology in chronic hemodialysis patients. Int J Artif Organs 5:97–100, 1982.
117. Nidus BD, Matalon R, Cantacuzino D, et al: Uremic pleuritis: A clinopathological entity. N Engl J Med 281:255–256, 1969.
118. Berger HW, Rammohan G, Neff MS, et al: Uremic pleural effusion: A study in 14 patients on chronic dialysis. Ann Intern Med 82:362–364, 1975.
119. Gilbert L, Ribot S, Frankel H, et al: Fibrinous uremic pleuritis: A surgical entity. Chest 67:53–56, 1975.
120. Rodelas R, Rakowski TA, Argy WP, et al: Fibrosing uremic pleuritis during hemodialysis. JAMA 243:2424–2425, 1980.
121. Bakirci T, Sasak G, Ozturk S, et al: Pleural effusion in long-term hemodialysis patients. Transplant Proc 39:889–891, 2007.
122. Light RW: Pleural Diseases (5th ed). Philadelphia: Lippincott Williams & Wilkins, 2007, pp 296–297.
123. Eggert CH, Albright RC: Metastatic pulmonary calcification in a dialysis patient: Case report and a review. Hemodial Int 10(Suppl 2):S51–S55, 2006.
124. Chan ED, Morales DV, Welsh CH, et al: Calcium deposition with or without bone formation in the lung. Am J Respir Crit Care Med 165:1654–1669, 2002.
125. Conger JD, Hammond WS, Alfrey AC, et al: Pulmonary calcification in chronic dialysis patients. Ann Intern Med 83:330–336, 1975.
126. Faubert PF, Shapiro WB, Porush JG, et al: Pulmonary calcification in hemodialyzed patients detected by technetium-99m diphosphonate scanning. Kidney Int 18:95–102, 1980.
127. Kimmel PL, Miller G, Mendelson WB: Sleep apnea syndrome in chronic renal disease. Am J Med 86:308–314, 1989.
128. Unruh ML, Sanders MH, Redline S, et al: Subjective and objective sleep quality in patients on conventional thrice-weekly hemodialysis: Comparison with matched controls from the Sleep Heart Health Study. Am J Kidney Dis 52:305–313, 2008.
129. Chen CT: Sleep apnea with intermittent hemodialysis: Time for a wake-up call! Am Soc Nephrol 17:3279–3280, 2006.
130. Chiu KL, Ryan CH, Shiota S, et al: Fluid shift by lower body positive pressure increases pharyngeal resistance in healthy subjects. Am J Respir Crit Care Med 174:1378–1383, 2006.
131. Su MC, Chiu KL, Ruttanaumpawan P, et al: Lower body positive pressure increases upper airway collapsibility in healthy subjects. Respir Physiol Neurobiol 161:306–312, 2008.
132. Hanly PJ, Pierratos A: Improvement of sleep apnea in patients with chronic renal failure who undergo nocturnal hemodialysis. N Engl J Med 344:102–107, 2001.
133. Pressman MR, Benz RL, Schleifer CR, Peterson DD: Sleep disordered breathing in ESRD: Acute beneficial effects of treatment with nasal continuous positive pressure. Kidney Int 43:1134–1139, 1993.
134. Auckley DH, Schmidt-Nowara W, Brown LK: Reversal of sleep apnea hypopnea syndrome in end-stage renal disease after kidney transplantation. Am J Kidney Dis 34:739–744, 1999.
135. Beecroft JM, Zaltzman J, Prasad R, et al: Impact of kidney transplantation on sleep apnoea in patients with end-stage renal disease. Nephrol Dial Transplant 22:3028–3033, 2007.
136. Aurigemma NM, Feldman NT, Gottlieb M, et al: Arterial oxygenation during hemodialysis. N Engl J Med 297:871–873, 1977.
137. Sherlock JE, Ledwith J, Letteri J: Hypoventilation and hypoxemia during hemodialysis: Reflex response to removal of CO_2 across the dialyzer. Trans Am Soc Artif Intern Organs 23:406–410, 1977.
138. Patterson RW, Nissenson AR, Miller J, et al: Hypoxemia and pulmonary gas exchange during hemodialysis. J Appl Physiol 50:259–264, 1981.
139. De Backer WA, Verpooten GA, Borgongjon DJ, et al: Hypoxemia during hemodialysis: Effects of different membranes and dialysate compositions. Kidney Int 23:738–743, 1983.
140. Munger MA, Ateshkadi A, Cheung AK, et al: Cardiopulmonary events during hemodialysis: Effects of dialysis membranes and dialysate buffers. Am J Kidney Dis 36:130–139, 2000.
141. Craddock PR, Fehr J, Brigham KL, et al: Complement and leukocyte-mediated pulmonary dysfunction in hemodialysis. N Engl J Med 296:769–774, 1977.
142. Ralph DD, Ott SM, Sherrard DJ, et al: Inert gas analysis of ventilation-perfusion matching during hemodialysis. J Clin Invest 73:1385–1391, 1984.
143. Romaldini H, Rodriguez-Roisin R, Lopez FA, et al: The mechanisms of arterial hypoxemia during hemodialysis. Am Rev Respir Dis 129:780–784, 1984.
144. Rodriguez-Roisin R, Wagner PD: Clinical relevance of ventilation-perfusion inequality determined by inert gas elimination. Eur Respir J 3:469–482, 1990.
145. Dumler F, Levin NW: Leukopenia and hypoxemia: Unrelated effects of hemodialysis. Arch Intern Med 139:1103–1106, 1979.
146. Cardoso M, Vinay P, Vinet B, et al: Hypoxemia during hemodialysis: A critical review of the facts. Am J Kidney Dis 11:281–297, 1988.
147. Oh MS, Uribarri J, Del Monte ML, et al: A mechanism of hypoxemia during hemodialysis: Consumption of CO_2 in metabolism of acetate. Am J Nephrol 5:366–371, 1985.
148. Dolan MJ, Whipp BJ, Davidson WD, et al: Hypopnea associated with acetate hemodialysis: Carbon dioxide flow-dependent ventilation. N Engl J Med 305:72–75, 1981.
149. De Backer WA, Heyrman RM, Wittesaele WM, et al: Ventilation and breathing patterns during hemodialysis-induced carbon dioxide unloading. Am Rev Respir Dis 136:406–410, 1987.

CHAPTER 84

PULMONARY COMPLICATIONS OF HEMATOLOGIC DISEASE

Roberto F. Machado, MD • Mark T. Gladwin, MD

INTRODUCTION

RED BLOOD CELL DISORDERS
Anemia
Polycythemia

HEMOGLOBINOPATHIES
Sickle Cell Disease
Thalassemia
Other Hemoglobin Disorders

WHITE BLOOD CELL DISORDERS
Leukemias
Plasma Cell Disorders

THROMBOSIS AND DISORDERS OF COAGULATION
Inherited Thrombophilia
Coagulopathies and Platelet Disorders

COMPLICATIONS OF TRANSFUSION
Transfusion Associated Acute Lung Injury

INTRODUCTION

Hematologic diseases and their specific therapies can adversely affect several aspects of cardiopulmonary function, by reducing the oxygen-carrying capacity of the blood, by impairing pulmonary vascular function and pulmonary immune defense, and by direct pulmonary parenchymal damage. This chapter reviews the clinical manifestations, epidemiology, pathophysiology, and treatment of pulmonary complications of disorders of the hematologic system.

RED BLOOD CELL DISORDERS

Anemia

Anemia is defined as a reduction in the number of circulating red blood cells. By decreasing oxygen-carrying capacity of the blood, the presence of anemia can impair cardiopulmonary function. However, since multiple compensatory mechanisms exist to adjust to a reduced oxygen-carrying capacity of blood, the signs and symptoms induced by anemia depend on the degree of anemia, the rate at which it evolves, the oxygen demands of the patient, and the presence of chronic cardiopulmonary disease. For instance, in resting adults subjected to acute isovolemic anemia, oxygen delivery can be maintained at hemoglobin concentrations as low as 5 g/dL,[1] a finding that also occurs in individuals with chronic severe anemia.[2,3] As such, anemia, even when severe, rarely causes heart failure or pulmonary edema, and, when it does, it is likely that the high-output failure is superimposed upon some cardiac abnormality. From the hemodynamic standpoint, as hemoglobin level decreases (particularly with hemoglobin values lower than 7 g/dL), cardiac output increases, filling pressures tend to decrease, and systemic and pulmonary vascular resistances decrease. Further, these abnormalities are readily reversible after red blood cell transfusions.[2–4] Finally, in severe cases and especially in patients with cardiopulmonary disease, anemic hypoxia can also occur as a consequence of reduced ability of blood to participate in gas exchange and carry oxygen.

Pulmonary hypertension is an increasingly recognized complication of chronic hereditary and acquired hemolytic anemias. Remarkably, virtually every cause of hemolytic anemia has been associated with pulmonary hypertension (Table 84-1). In contrast, there have been no reports of pulmonary hypertension associated with anemia of chronic disease or iron-deficiency anemia. This suggests that the hemolytic component of anemia is necessary for the development of pulmonary hypertension, which is discussed in detail in the section on hemoglobinopathies.

TABLE 84-1. Hemolytic Disorders Associated with Pulmonary Hypertension

Hemoglobinopathies
Sickle cell disease
Thalassemia intermedia and major
Hb Mainz unstable hemoglobin hemolytic anemia
Red cell membranopathies
Hereditary spherocytosis
Hereditary stomatocytosis
Paroxysmal nocturnal hemoglobinuria
Alloimmune hemolytic anemia
Red cell enzymopathies
Pyruvate kinase deficiency
Glucose-6-phosphate dehydrogenase deficiency
Microangiopathic hemolytic anemia
Thrombotic thrombocytopenic purpura
Hemolytic uremic syndrome
Hemolysis from mechanical heart valves
Left ventricular assist devices and cardiopulmonary bypass procedures
Malaria

Polycythemia

Polycythemia is characterized by an abnormally high hematocrit (>48% and >52% in women and men, respectively), hemoglobin concentration (>16.5 or >18.5 g/dL in women and men, respectively), or red blood cell count. These measurements are dependent upon the plasma volume as well as the red blood cell mass, and, before classifying a patient as having true polycythemia, a decrease in plasma volume as the etiology for these abnormalities must be ruled out. This state of chronically reduced plasma volume with elevated hemoglobin or hematocrit has been called Gaisböck's disease,[5] spurious polycythemia, stress erythrocytosis, apparent polycythemia, and pseudopolycythemia, and has been associated with use of diuretics, alcohol, obesity, hypertension, and renal disease. Patients with elevations in red blood cell mass have absolute polycythemia and are categorized in primary and secondary forms. Primary polycythemia is caused by an acquired or inherited mutation such as in the JAK2 gene,[5a] leading to an abnormality within red blood cell progenitor cells; it includes polycythemia vera and rare familial variants (e.g., activating mutations of the erythropoietin receptor or Chuvash polycythemia). Secondary polycythemia is caused by a circulating factor stimulating erythropoiesis, usually related to the production of erythropoietin as a physiologic response to chronic hypoxia (e.g., chronic hypoxic lung disorders and disorders affecting hemoglobin oxygen affinity), but can also result from erythropoietin-secreting tumors.

Most of the symptoms of polycythemia are related to an increase in blood viscosity, which leads to impairment in systemic and pulmonary blood flow. Thromboembolic events occur in approximately 30% of patients with polycythemia vera and account for 31% of their deaths.[6] Pulmonary nodular lesions secondary to thrombosis, stasis, or infarction have been described in these patients.[7] Late-stage polycythemia vera, which is characterized by myelofibrosis, may cause pulmonary and pleural masses that are related to extramedullary hematopoiesis.[8]

Pulmonary hypertension has been reported in patients with polycythemia and other myeloproliferative disorders.[7,9-12] In a retrospective review, 26 patients (12 with myeloid metaplasia, 5 with essential thrombocythemia, 6 with polycythemia vera, 2 with myelodysplastic syndrome, and 1 with chronic myeloid leukemia) had echocardiographic or hemodynamic evidence of pulmonary hypertension. Interestingly, the median survival after diagnosis of pulmonary hypertension was 18 months and the majority of deaths were related to cardiopulmonary causes, suggesting that the presence of pulmonary hypertension was a direct cause of death.[10] In a cohort of 14 patients with Chuvash polycythemia, the prevalence of pulmonary hypertension (defined as an estimated pulmonary artery systolic pressure ≥ 35 mm Hg) was 36%.[12] The pathogenesis of pulmonary hypertension in these disorders is not well established but can involve hypercoagulability and hyperviscosity leading to in situ thrombosis or chonic thromboembolic disease, as well as hemoglobin-dependent scavenging of endothelium-derived nitric oxide (NO)[13-17] and up-regulation of HIF-1α–mediated pathways, such as endothelin-1.[12]

In patients with polycythemia vera, the mainstay of therapy is phlebotomy and myelosuppression with hydroxyurea, to keep the hematocrit below 45% in men and 42% in women, and antithrombotic therapy with aspirin or anagrelide.[18,19] Treatment of the myeloproliferative disorder has been shown in case series to improve pulmonary hypertension.[9,10] In patients with chronic hypoxic disorders such as chronic obstructive pulmonary disease (COPD) and interstitial lung disease, long-term oxygen therapy should reduce the number of patients who become severely polycythemic. In patients with COPD and severe polycythemia, phlebotomy (to achieve a hematocrit of about 50%) is associated with a decrease in mean pulmonary artery pressure and pulmonary vascular resistance, as well as an improvement in exercise performance.[20] However, the use of phlebotomy should be reserved as adjunctive therapy in the management of the markedly polycythemic and symptomatic patient who remains significantly polycythemic despite appropriate long-term oxygen therapy.

HEMOGLOBINOPATHIES

Sickle Cell Disease

Sickle cell anemia, the most common and most severe form of sickle cell disease, occurs in individuals who are homozygous for a single nucleotide substitution in the β globin gene. This results in the synthesis of hemoglobin S (Hb S), a structural variant that is much less soluble than normal hemoglobin (Hb A) when deoxygenated.[21,22] Deoxygenated Hb S polymerizes and aggregates inside

sickled erythrocytes as they traverse the microcirculation. Rigid, dense, and sickled cells can become entrapped in the microcirculation, a process that is enhanced by their increased propensity to adhere to endothelium. Mechanistic studies in transgenic mice expressing exclusively human Hb S suggest that microvascular occlusion results in ischemia and reperfusion injury, which promotes inflammatory, thrombotic, and oxidant stress.[23–30] In patients with sickle cell disease, vaso-occlusion leads to the frequent episodes of bone pain and acute chest syndrome that complicate sickle cell disease. Furthermore, the membrane of erythrocytes containing intracellular Hb S polymer is constantly exposed to mechanical and oxidant injury as the erythrocytes traverse the microcirculation. Ultimately cumulative membrane damage shortens red cell life span so that sickle cell disease is characterized by a chronic hemolytic anemia. Intravascular hemolysis releases cell-free hemoglobin into the plasma, which scavenges NO and releases red blood cell arginase into the plasma, which catabolizes arginine, the substrate for NO synthesis.[14,31,32] Intravascular hemolysis thus produces a state of endothelial dysfunction, vascular proliferation, and pro-oxidant and proinflammatory stress.[33–35]

It is estimated that around 250,000 children worldwide are born with homozygous sickle cell anemia every year.[36] Approximately 0.15% of African Americans are homozygous for sickle cell disease, and 8% have sickle cell trait. Despite significant improvements in the life expectancy of patients with sickle cell disease, estimates of the median age at death range from 42 to 53 years for men and 48 to 58.5 years for women.[37,38]

Acute and chronic pulmonary complications of sickle cell disease are common but often underappreciated by health care providers. Acute complications include asthma and the acute chest syndrome (ACS), while chronic complications include pulmonary fibrosis, pulmonary hypertension, and cor pulmonale. Pulmonary complications account for a large proportion of deaths among adults with sickle cell disease.[37,39–41] According to the Cooperative Study of Sickle Cell Disease (CSSCD), a prospective multicenter study of 3764 patients, over 20% of adults likely had fatal pulmonary complications of sickle cell disease.[37] Among the 299 patients enrolled in the long-term follow-up study of patients who participated in the Multicenter Study of Hydroxyurea in Sickle Cell Anemia (MSH), pulmonary disease was the most common cause of mortality, accounting for 28% of all deaths.[42]

Acute Chest Syndrome

ACS represents a lung injury syndrome occurring in patients with sickle cell disease and should be considered analogous to the acute respiratory distress syndrome (ARDS). It is clinically defined by the development of a new pulmonary infiltrate in a patient with sickle cell disease, consistent with alveolar consolidation and not atelectasis, involving at least one complete lung segment, that is accompanied by chest pain, fever, tachypnea, wheezing, or cough.[43]

Epidemiology. ACS is the second most common cause of hospitalization in patients with sickle cell disease and the leading cause of admission to an intensive care unit and premature death.[37,40]

ACS can occur in any of the sickle hemoglobinopathies but is more common in individuals with homozygous sickle cell disease (Hb SS). In the CSSCD, there was a 29% incidence of the ACS in 3751 subjects over a 2-year period, representing an attack rate of 12.8 episodes per 100 patient-years for Hb SS disease.[37] The incidence is higher in children than in adults (24.5 events vs. 8.8 events per 100 patient-years). As many as half of ACS episodes occur in association with vaso-occlusive pain crisis, and a sizable proportion of patients will have a painful event within 2 weeks of the diagnosis.[44,45] Since up to 20% of patients admitted with acute vaso-occlusive pain crisis will develop ACS in the first 3 days of hospitalization, physicians must be vigilant for this common and potentially lethal complication.

Laboratory parameters in steady state associated with an increased risk for the development of ACS include an elevated white blood cell count, a higher steady-state hemoglobin level, and a lower steady-state fetal hemoglobin level.[44,45] In children, a number of studies now suggest that asthma is a risk factor for the development of ACS.[46–48] Other clinical events that appear to increase the risk of (or are associated with) the development of ACS include major surgical procedures, acute rib infarcts, avascular necrosis of the hips, pregnancy, use of narcotics, acute anemic events, and previous pulmonary events.[44,45]

During acute hospitalization for vaso-occlusive crisis, the development of ACS is often preceded by an abrupt drop in hemoglobin levels (mean decrease of 0.78 g/dL from steady-state levels) and increases in markers of hemolysis, such as lactate dehydrogenase (LDH). The platelet count also drops preceding ACS, and levels less than 200,000 cells/μL constitute an independent risk factor for ACS severity, associated with increased risk of neurologic complications and mechanical ventilation. In our units, we monitor trends in hemoglobin and platelet counts and pay careful attention to patients with drops in steady-state values.

Pathophysiology. Three major mechanisms appear to be involved in the pathogenesis of ACS: infection, bone marrow fat embolization, and direct red cell intravascular sequestration causing lung injury and infarction (Table 84-2, Fig. 84-1).

The most common etiology of ACS in both children and adults is infection by a community-acquired pathogen, with an excessive inflammatory lung injury response. More than 80% of adults with sickle cell disease report a history having been admitted to the hospital for "pneumonia."[33] The National Acute Chest Syndrome Study Group analyzed 671 episodes of ACS in 538 patients with sickle cell disease to determine the cause, outcome, and response to therapy, and respiratory samples obtained from sputum and bronchoalveolar lavage were analyzed for viral and bacterial infections.[43] Among the infectious agents identified most were atypical bacteria and viruses (see Table 84-2), including *Chlamydia pneumoniae*

TABLE 84-2. Causes of the Acute Chest Syndrome*

Cause	All Episodes (*N* = 670) and No. of Episodes (%)	AGE AT EPISODE OF ACUTE CHEST SYNDROME		
		0–9 yr (*n* = 329)	10–19 yr (*n* = 188)	≥20 yr (*n* = 153)
Fat embolism, with or without infection†	59 (8.8)	24	16	19
Chlamydia‡	48 (7.2)	19	15	14
Mycoplasma§	44 (6.6)	29	7	8
Virus	43 (6.4)	36	5	2
Bacteria	30 (4.5)	13	15	12
Mixed infections	25 (3.7)	16	6	3
Legionella	4 (0.6)	3	0	1
Miscellaneous infections¶	3 (0.4)	0	3	0
Infarction¶	108 (16.1)	50	43	15
Unknown**	306 (45.7)	139	88	79

*Data on one episode were excluded because the patient's birth date was not known.
†Nineteen of the episodes of pulmonary fat embolism were associated with infectious pathogens.
‡This category included episodes in which *Chlamydia* alone was identified but not episodes involving mixed infections or pulmonary fat embolism.
§This category included only episodes in which *Mycoplasma pneumoniae* or *Mycoplasma hominis* was identified, but not episodes involving mixed infections, *Mycobacterium tuberculosis*, or pulmonary fat embolism.
¶This category included two cases of tuberculosis and one case of *Mycobacterium avium* complex infection.
¶A pulmonary infarction was presumed to have occurred when the results of the analysis for pulmonary fat embolism, bacterial studies, viral isolation studies, and serologic tests were complete and were all negative.
**The cause of episodes for which some or all of the diagnostic data were incomplete and no etiologic agent was identified was considered to be unknown.
Reproduced with permission from Vichinsky EP, Neumayr LD, Earles AN, et al: Causes and outcomes of the acute chest syndrome in sickle cell disease. National Acute Chest Syndrome Study Group. N Engl J Med 342:1855–1865, 2000.

(29%), *Mycoplasma pneumoniae* (20%), *Legionella pneumophila* (2%), respiratory syncytial virus (10%), parvovirus (4%), rhinovirus (3%), parainfluenza virus (2%), influenza A virus (2%), cytomegalovirus (2%), Epstein-Barr virus (1%), and herpes simplex virus (1%). Community-acquired encapsulated bacteria were rarely isolated, despite the fact that patients with Hb SS disease rarely have normal splenic function. *Staphylococcus aureus* was isolated in 5% of cases and *Streptococcus pneumonia* in only 4% of cases.

Fat embolization syndrome is the second most common cause of the ACS. It occurs as a complication of vaso-occlusive pain crisis involving multiple bones, which results in bone marrow edema, infarction, and necrosis. As a consequence, bone marrow contents are released into the systemic circulation and are trapped in the pulmonary circulation, producing acute pulmonary hypertension, severe lung inflammation, and hypoxemia (Fig. 84-2).[49-51] Bone marrow fat released into the bloodstream is also converted to free fatty acids by secretory phospholipase A_2, which can also produce direct inflammatory lung injury.[52] Finally, in approximately 20% of patients, direct lung infarction or lung vaso-occlusion is associated with the development of the ACS, with a small percentage of patients actually developing wedge-shaped infarction, sometimes followed by central cavitation.[53]

Clinical Features and Evaluation. The clinical features at presentation are age dependent, which likely reflects the different etiologies of ACS in different age groups, with children having a higher proportion of infectious etiologies in comparison to adults, who tend to have fat embolization as a major etiology. Overall, 80% of patients present with fever, 62% with cough, and approximately 40% have chest pain, tachypnea, dyspnea, and abdominal, arm, leg, rib, or sternal pain.[43] Most adult patients present with severe extremity or chest pain and 24 to 72 hours later develop ACS. Reactive airways disease is observed in 13% of cases of ACS, and is much more common in children.[43]

ACS is associated with signs of systemic inflammation, with mean peak temperatures of 38.9° C and mean white blood cell counts of 23,000 cells/μL^3.[43] As mentioned earlier, while a high steady-state hemoglobin level is a major risk factor for developing ACS, the acute presentation is often associated with a drop in hemoglobin levels (mean decrease of 0.78 g/dL from steady-state levels) and increases in markers of hemolysis. Thrombocytopenia can also occur, and a platelet count less than 200,000 cells/μL appears to be a marker of ACS severity, associated with increased risk of neurologic complications and mechanical ventilation.[43] Secretory phospholipase A_2 levels are elevated early in the course of ACS, even before the development of radiographic changes, and have been used to predict the onset of the syndrome.[54]

The diagnosis of pulmonary fat embolization syndrome relies on the identification of oil-red O–positive lipid accumulations within alveolar macrophages since the clinical manifestations can be indistinguishable from the other causes of ACS (see Fig. 84-1). In a 30-center clinical trial, the National Acute Chest Syndrome Study Group identified fat embolization syndrome in 16% of ACS cases in adults and children based on positive lipid accumulations in alveolar macrophages.[43] Traditionally bronchoscopy has been used as the diagnostic modality of choice for the diagnosis of pulmonary fat embolization syndrome. However, a recent study compared induced

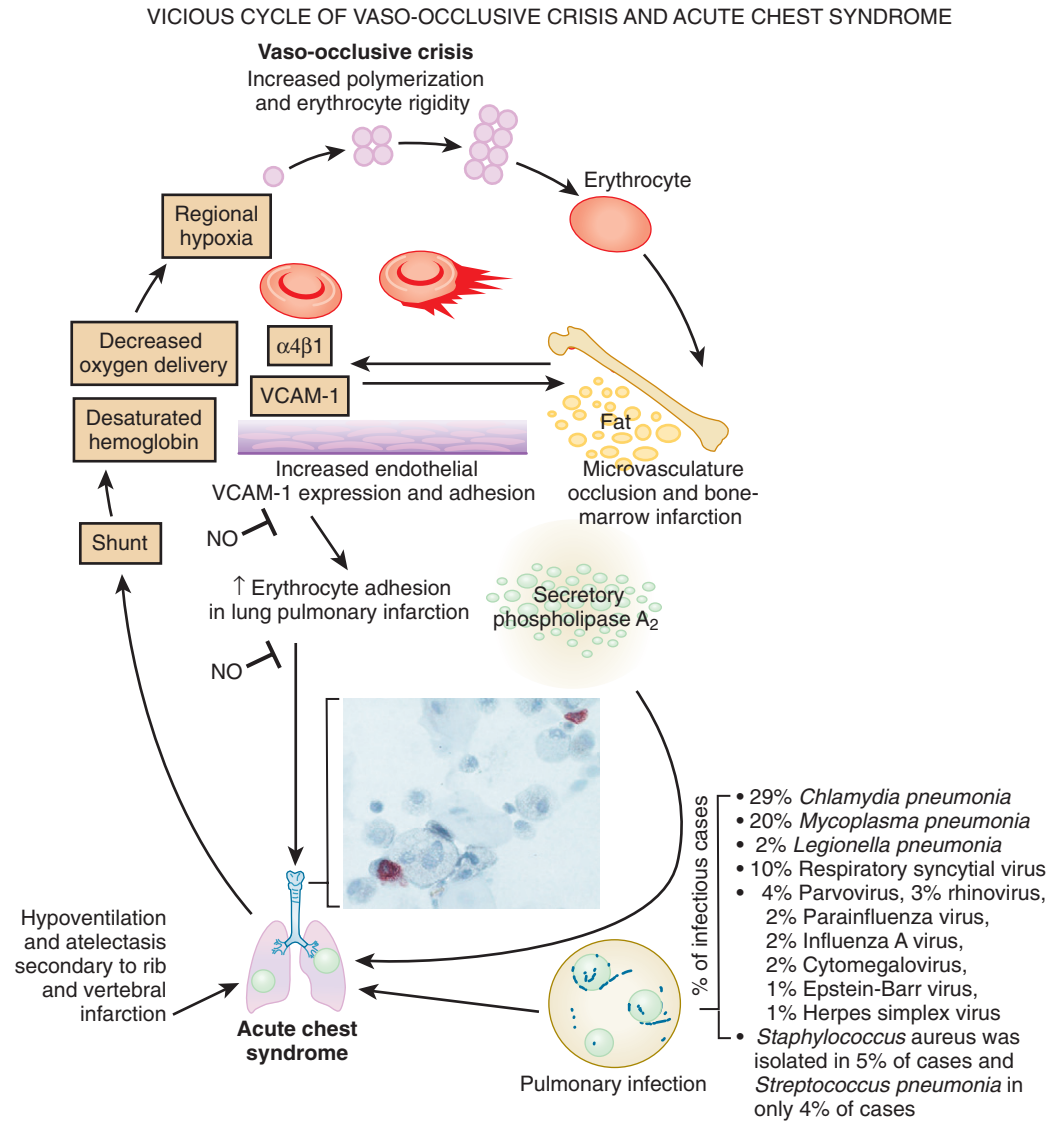

FIGURE 84-1 ■ Pathogenesis of the acute chest syndrome (ACS). Three major triggers are associated with the development of ACS: infection, bone marrow fat embolization, and direct red cell intravascular sequestration causing lung injury and infarction. Lung injury results in ventilation-perfusion mismatch and hypoxemia, which leads to increased hemoglobin S polymerization, and erythrocyte vaso-occlusion. This worsens bone marrow infarction and pulmonary vaso-occlusion to promote a vicious cycle. Fat embolization can be diagnosed by oil-red O staining of pulmonary alveolar macrophages, revealing the characteristic red lipid inclusions, as shown in panel. Common infectious organisms identified in cases of ACS are listed.

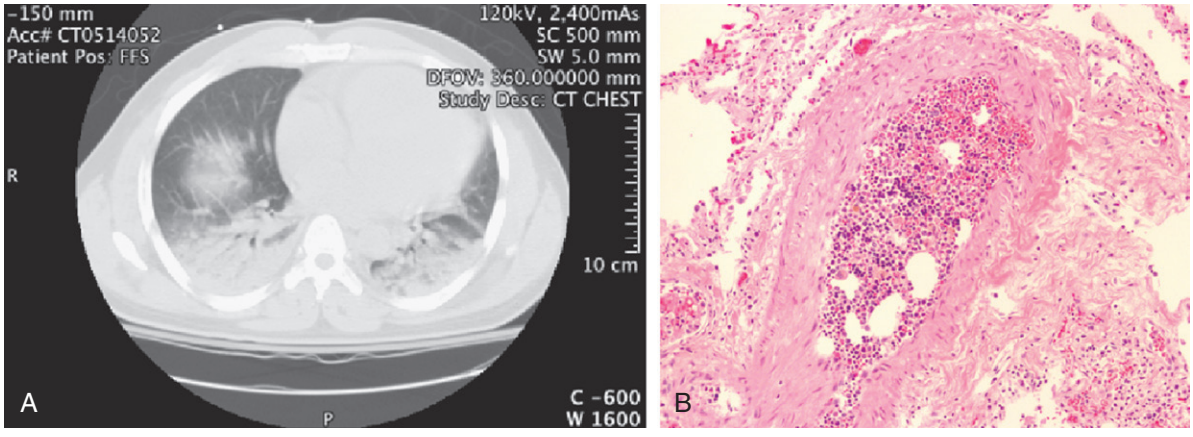

FIGURE 84-2 ■ Fat emoblization in acute chest syndrome. **A,** Chest computed tomography scan of a patient with acute chest syndrome and fat embolization syndrome. **B,** Postmortem examination specimen of a patient who died suddenly during an episode of vaso-occlusive crisis and acute chest syndrome demonstrating bone marrow elements lodged in the small pulmonary artery.

sputum sampling of alveolar macrophages with samples obtained from bronchoalveolar lavage and found a modest but significant correlation between the two measurements ($r = 0.65$).[55]

Some patients manifest evidence of systemic fat embolization, and in this case ACS is part of the spectrum of the systemic fat embolization syndrome, also called the acute multiorgan failure syndrome. This should be suspected in patients presenting with acute multiorgan failure characterized by the development of acute hypoxic respiratory failure, right heart failure, renal and hepatic dysfunction, alterations in mental status, seizures, thrombocytopenia, and coagulopathy.[56,57] In this context, patients with ACS who have lipid-laden macrophages detected in the induced sputum have significantly more extrathoracic pain than those without evidence of fat emboli, more neurologic symptoms, a lower platelet count, and higher transaminase levels.[55] This suggests that the fat embolization syndrome is a major cause of ACS and has a more severe course with systemic complications.

The mean length of hospitalization for ACS is 10.5 days, compared with 3 to 4 days for uncomplicated vaso-occlusive pain crisis. Thirteen percent of all patients with ACS require mechanical ventilation, and the overall mortality is 3% for all patients and 9% for adults. Risk factors for mechanical ventilation and poor outcome include platelet count less than 200,000/μL (likely indicative of the fat embolization syndrome), the number of lobes involved on radiograph, and a self-reported or medical record history of cardiac disease. The latter complication is now thought to represent occult pulmonary hypertension and cor pulmonale. In fact, in a recent study of 84 consecutive hospitalized patients with ACS, 13% of patients manifested right heart failure, and this subgroup had the highest risk for mechanical ventilation and death.[58] These data suggest that pulmonary hypertension and right heart dysfunction represents a major comorbidity during ACS, and that right heart failure should be considered in patients presenting with shock or severe hypoxia. The outcome of patients with severe ACS on mechanical ventilation is better that that of patients with ARDS, with a mortality rate of 19% in contrast to the approximate 30% mortality rate reported in modern ARDS studies.[43]

Treatment. A summary of treatment strategies is outlined in Table 84-3. Since the triggers and risk factors for ACS are well known, clinical surveillance plus aggressive and early therapy of this patient population are likely to improve prognosis. This could be accomplished by close monitoring of patients with vaso-occlusive crisis, a febrile illness, and in the postoperative state. In acutely ill patients, strategies such as aggressive pain management and incentive spirometry can minimize chest wall splinting, with consequent atelectasis and alveolar hypoxia. In fact, the use of incentive spirometry has been shown to decrease the incidence of new pulmonary infiltrates in patients admitted with vaso-occlusive pain affecting the chest wall.[53] Patients with a history of ACS should be treated with hydroxyurea in the outpatient setting as its use has been shown to reduce the risk of developing ACS by approximately 50%.[59,60] A chronic transfusion regimen is also effective in reducing the incidence of ACS.[61]

TABLE 84-3. Treatment of the Acute Chest Syndrome (ACS)

Oxygen therapy to maintain arterial hemoglobin oxygen saturation above 92%
Pain control and incentive spirometry to reduce chest wall splinting and pulmonary atelectasis
Close clinical observation, particularly Po_2/Fio_2 ratio: early diagnosis of worsening respiratory function
Asthma therapy if indicated
Empirical antibiotics
Cover typical and atypical respiratory pathogens.
Consider the regional and seasonal risk of methicillin-resistant *Staphylococcus aureus* and influenza A or B and tailor therapy accordingly.
Transfusion therapy
The main indication for transfusion therapy in ACS is worsening respiratory function.
Simple transfusion is as effective as erythrocytopheresis.
Patients with high initial hemoglobin concentrations (≥9 g/dL), or patients with more severe disease should receive erythrocytopheresis.
Transfused blood should be matched to Rh, C, E, and Kell antigens and obtain transfusion records documenting history of prior alloantibodies.

Given the high prevalence of infectious etiologies for ACS, we recommend the use of empirical antimicrobial therapy in all patients. Considering the high prevalence of atypical bacteria and encapsulated organisms, empirical coverage should include agents effective against these organisms, such as the macrolides or fluoroquinolones. It is also important to consider alternative organisms such as methicillin-resistant *S. aureus* or influenza viruses, especially in patients not responding to therapy or during influenza season.

Although not demonstrated in randomized trials, blood transfusion remains the mainstay of ACS therapy. Acute red cell transfusion increases arterial Po_2 and hemoglobin oxygen saturation and may rapidly resolve the pulmonary event.[43,62] In order to avoid the effects of increasing viscosity and the consequent risk of vaso-occlusion, it is not recommended to increase the hemoglobin level higher than 11 g/dL after simple transfusion. The National Acute Chest Syndrome Study Group found no significant differences in outcomes between patients treated with simple transfusion or a red cell exchange (erythrocytopheresis), suggesting that the former approach is preferred as initial therapy.[43] Patients with high initial hemoglobin concentrations (≥9 g/dL), or patients with more severe disease should receive erythrocytopheresis. However, most patients have a significant decrease in hemoglobin at presentation, allowing for the transfusion of 2 to 4 units of packed red cells over 24 to 48 hours without complication. In order to decrease the risk of delayed hemolytic transfusion reactions related to alloimmunization against minor red

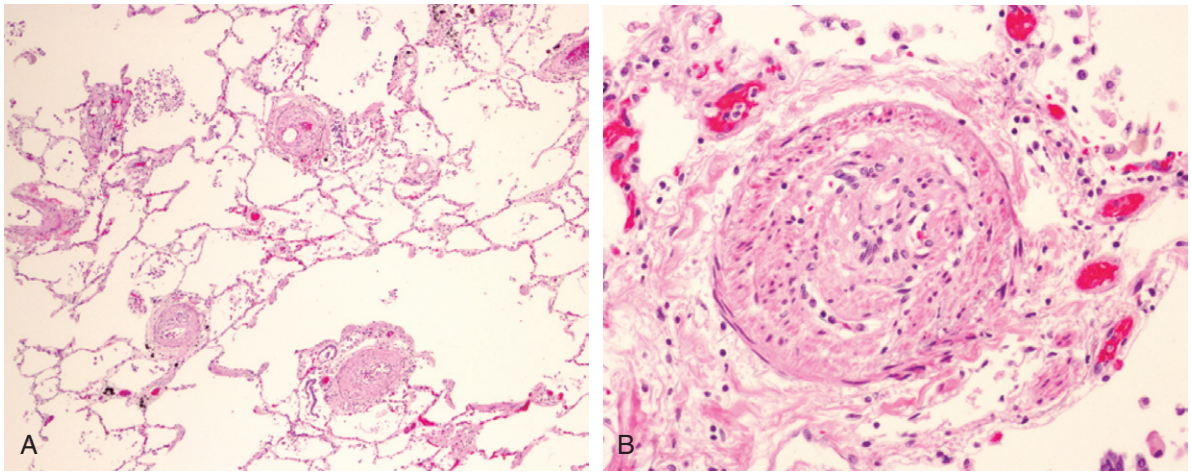

FIGURE 84-3 ■ Pulmonary arteriopathy in sickle cell–related pulmonary hypertension. **A,** Low-power photomicrograph demonstrating pulmonary arterial smooth muscle hypertrophy. (Hematoxylin and eosin stain). **B,** Plexogenic lesion. (Hematoxylin and eosin stain).

blood cell antigens, all transfused blood should be matched to Rh, C, E, and Kell antigens.

Treatment with corticosteroids has been shown to reduce the severity of pain and length of hospitalization, but this therapy is complicated by a high rate of rebound pain and hospitalization.[63,64] Ongoing studies are evaluating strategies to maintain the beneficial effects of corticosteroids while limiting rebound pain and readmission using slow tapering protocols. Inhaled NO has been shown in case studies to improve oxygenation and reduce pulmonary hypertension in mechanically ventilated patients with severe lung injury, and active clinical trials for vaso-occlusive crisis are ongoing.[65-67]

Pulmonary Hypertension

Among the chronic cardiopulmonary complications of sickle cell disease, pulmonary hypertension has emerged as the major threat to the well-being and longevity of patients with sickle cell disease. Sickle cell disease could represent one of the most common causes of pulmonary hypertension. There are 30 million individuals worldwide with sickle cell disease.[68] Given that pulmonary hypertension occurs in 10% to 30% of these patients, there may be as many as 3 to 9 million patients with the disease worldwide.

Epidemiology. Retrospective studies have reported that 20% to 30% of patients with sickle cell disease have pulmonary hypertension.[57,69] In these studies, patients with pulmonary hypertension had a significantly increased mortality rate compared with patients without pulmonary hypertension. Sutton and colleagues reported a 40% mortality rate at 22 months with an odds ratio for death of 7.86 (range, 2.63 to 23.4).[69] Powars and colleagues reported a mean 2.5-year survival in sickle cell patients with chronic lung disease with pulmonary hypertension.[40] Castro and colleagues[70] similarly reported a 50% 2-year mortality rate in patients with sickle cell disease with pulmonary hypertension confirmed by right heart catheterization. In addition, autopsy studies suggest that up to 75% of sickle cell patients have histologic evidence of pulmonary arterial hypertension at the time of death (Fig. 84-3).[71]

These data are now corroborated by three prospective studies.[33,72,73] In the National Institutes of Health pulmonary hypertension echocardiographic screening study, 23% of patients with sickle cell disease had borderline to mild elevations in pulmonary artery systolic pressures (defined by a tricuspid regurgitant jet velocity [TRV] of ≥ 2.5 to 2.9 m/sec, which corresponds to a pulmonary artery systolic pressure of approximately 30 to 39 mm Hg) and 9% had moderately to severely elevated pressures (defined by a TRV ≥ 3.0 m/sec, which corresponds to a pulmonary artery systolic pressure of approximately 40 to 45 mm Hg).[33] Similar rates were found in echocardiographic screening studies performed at two other centers.[72,73] Measurement of N-terminal pro–brain natriuretic peptide (NT-proBNP), a prohormone released by the right and left ventricular myocardium under pressure stress, in stored plasma samples showed that 30% of individuals enrolled in the MSH in 1996 had elevated levels, suggesting the possible presence of pulmonary hypertension.[74] Two centers independently reported the follow-up of adult sickle patients who on initial echocardiographic screening had normal TRVs. After 2 to 3 years of follow-up, 13% to 15% of these patients developed high TRVs, suggesting a pulmonary hypertension incidence of about 4% to 7% per year.[72,75]

Increasing age is associated with an increased risk of pulmonary hypertension. For example, in the National Institutes of Health pulmonary hypertension echocardiographic screening study, patients with pulmonary hypertension were significantly older than patients without pulmonary hypertension (38 ± 19 years for patients with TRV ≥ 3.0 m/sec, 39 ± 12 years for patients with TRV 2.5 to 2.9 m/sec, and 34 ± 10 years for patients with TRV < 2.5 m/sec; $P = 0.02$).[33] An increasing number of studies suggest that pulmonary hypertension is developing in children with sickle cell disease; however, few children have TRV values greater than 3.0 m/sec, and the implications in terms of functional capacity and associated mortality have not been determined.[76-79]

Epidemiologic risk factors associated with pulmonary hypertension include a history of renal or cardiovascular complications, increased systemic systolic blood pressure, elevations in the marker of hemolysis (LDH), elevated alkaline phosphatase, and low transferrin levels.[33,74] In men, a history of priapism was also an independent factor associated with pulmonary hypertension.[33] These data suggest that pulmonary hypertension represents a component of the systemic vasculopathy of sickle cell disease (characterized by systemic hypertension, renal failure, and priapism), and that it is linked to hemolytic rate, iron overload, and cholestatic hepatic dysfunction. Interestingly, the development of pulmonary hypertension was not associated with the number of vaso-occlusive episodes, markers of inflammation, fetal hemoglobin levels, or platelet counts.[33,74] Finally, a high pulmonary artery pressure could also result from the high cardiac output state associated with chronic anemia. However, this hyperdynamic state does not seem to be a major contributor to significant elevations in pulmonary artery pressures as there has been no report of pulmonary hypertension associated with non-hemolytic anemia.

Pulmonary hypertension increases the risk of death for patients with sickle cell disease. In the National Institutes of Health study, compared to patients with TRV less than 2.5 m/sec, the rate ratios for death for TRVs of 2.5 to 2.9 m/sec and greater than 3.0 m/sec were 4.4 (95% confidence interval [CI], 1.6 to 12.2; $P < 0.001$) and 10.6 (95% CI, 3.3 to 33.6; $P < 0.001$), respectively.[33] In support of these findings, De Castro and colleagues found that 6 of 42 patients (14%) with pulmonary hypertension and 2 of 83 patients (2%) without pulmonary hypertension died during a 2-year follow-up period.[73] Similarly, in the study by Ataga and colleagues, 9 of 36 patients with pulmonary hypertension and 1 of 57 patients without pulmonary hypertension died during the 2.5-year follow-up period (relative risk, 9.24 [95% CI, 1.2 to 73.3]).[72]

Pathogenesis. Epidemiologic studies suggest that the central risk factor for the development of pulmonary hypertension in patients with sickle cell disease is the severity of hemolytic anemia (Fig. 84-4).[33,72,73,80] The association between the development of pulmonary hypertension and the intensity of hemolytic anemia has been observed in three prospective screening studies of adult patients with sickle cell disease,[33,72,73] and in an expanding number of pediatric studies.[76–78,81,82] This suggests that hemolysis is related mechanistically to pulmonary hypertension. That relationship is plausible and biologically significant since free hemoglobin inactivates the intrinsic vasodilator NO.[14,32] Hemolysis also releases arginase, which depletes L-arginine, the substrate for NO synthesis.[31] These combined mechanisms result in a state of decreased NO bioavailability and "resistance" to NO-dependent vasodilation.[14]

Hemolysis and decreased NO bioavailability also induce platelet activation,[83] thrombin generation, and tissue factor activation.[84] There is also a correlation between the rate of hemolysis and the levels of procoagulant factors in blood in patients with sickle cell disease.[85–87] Hemolysis is also associated with the formation of red blood cell microvesicles expressing phosphatidylserine, which activates tissue factor.[87,88] These factors all contribute to an increased risk of thrombosis. In addition, sickle cell patients with functional asplenia and thalassemia patients with surgical splenectomy have increased levels of cell-free hemoglobin and red cell microvesicles, providing a potential mechanism for the hypercoagulability associated with both diseases, with possible exacerbation by asplenia.[87] Finally, the accumulation of redox-active heme and iron from lysed red blood cells further contributes to the generation of reactive oxygen species that can exacerbate ischemia-reperfusion injury, thrombosis, and vascular proliferative responses.[89]

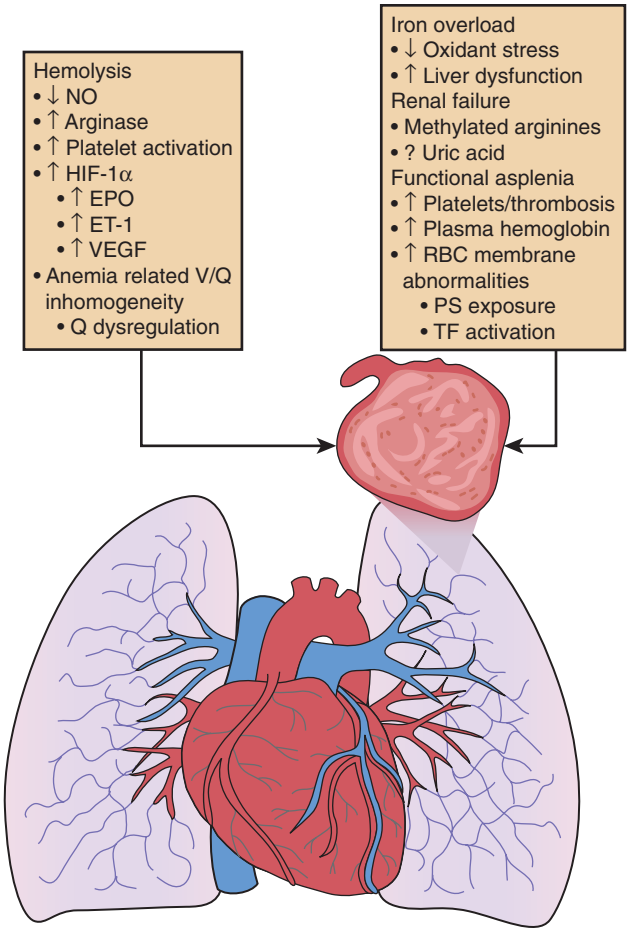

FIGURE 84-4 ■ Multifactorial pathogenesis of pulmonary hypertension in sickle cell disease. EPO, erythropoietin; ET-1, endothelin-1; HIF, hypoxia inducible factor; NO, nitric oxide; PS, phosphatidylserine; Q, cardiac output; TF, tissue factor; VEGF, vascular endothelial growth factor.

Another downstream effect of hemolytic anemia includes increased endothelin-1–mediated vasoconstrictive and proliferative responses. In patients with sickle cell disease, both at steady state and during vaso-occlusive pain crises, plasma endothelin-1 levels are increased.[90] In vitro, sickled erythrocytes increase endothelin-1 production by cultured human endothelial cells. In addition, endothelin receptor A antagonism abolishes the vasoconstrictive effects of media from pulmonary endothelial cells exposed to sickled erythrocytes on aortic rings.[90]

Functional or surgical asplenia could also contribute to the development of pulmonary hypertension in patients with sickle cell disease. Splenectomy has been reported to be a risk factor for the development of pulmonary hypertension,[91] particularly in patients with hemolytic disorders.[92–94] Loss of splenic function may trigger platelet activation, promoting pulmonary microthrombosis and red cell adhesion to the endothelium.[95] The spleen also plays a critical function in the removal of senescent and damaged erythrocytes.[96,97] Following splenectomy, moreover, the rate of intravascular hemolysis increases.[87]

Historically, pulmonary hypertension in patients with sickle cell disease was thought to derive from the repetitive episodes of pulmonary vaso-occlusive crisis and ACS leading to pulmonary fibrosis, vascular obstruction, and chronic hypoxia. However, this association has not been supported by epidemiologic studies, since the number of episodes of vaso-occlusive crisis and ACS is not associated with pulmonary hypertension.[33,74]

Clinical Manifestations and Evaluation. The diagnostic evaluation of patients with sickle cell disease suspected of having pulmonary hypertension should follow the same guidelines established for other causes of pulmonary hypertension.[98,99] Given the high prevalence of pulmonary hypertension in this population and the associated high mortality, we recommend universal noninvasive screening of all adults with Doppler echocardiography or by assessment of steady-state plasma NT-proBNP levels. In patients with sickle cell disease, the echocardiographic estimation of pulmonary artery systolic pressures (where pulmonary artery systolic pressure = $4^{*}TRV^{2}$ + estimate of the right atrial pressure) correlates well with measured pulmonary systolic pressures by right heart catheterization.[33] A TRV greater than or equal to 2.5 m/sec (which corresponds to an estimated pulmonary artery systolic pressure of 35 mm Hg), is approximately 2 standard deviations above normal for individuals less than 40 years of age (normal reference mean is 27.5 ± 4.2 with a 95% CI of 19.3 to 35.5 mm Hg).[100] In addition, even considering that a more traditional echocardiographic definition of pulmonary hypertension would be a TRV greater than or equal to 3.0 m/sec, in patients with sickle cell disease values between 2.5 and 2.9 m/sec are associated with high a risk of death.[33,72,73]

While no prospective data on prevalence and risk of pulmonary hypertension are available for children, we currently recommend that children with hypoxemia, high hemolytic rates (hemoglobin values < 7 g/dL with high LDH values), and/or recurrent ACS be screened. It is important that such screening be performed in the steady state, as pulmonary pressures rise during vaso-occlusive painful crisis.[101]

The diagnosis of pulmonary hypertension in patients with sickle cell disease can be challenging (Fig. 84-5). Exertional dyspnea, the most typical presentation of pulmonary hypertension, is also a cardinal symptom of chronic anemia, and therefore a high index of suspicion for the disease is necessary. Other conditions commonly present in patients with sickle cell disease, such as left ventricular dysfunction, pulmonary fibrosis, and liver cirrhosis, could also present in a similar fashion and could also result in pulmonary hypertension. Patients with pulmonary hypertension tend to be older and have higher systolic arterial blood pressure, lower hemoglobin levels, higher indices of hemolysis (such as high bilirubin or LDH values), lower hemoglobin oxygen saturation, greater degree of renal and liver dysfunction, and a higher number of lifetime red blood cell transfusions.[33] As such, the diagnostic evaluation of these patients should include an aggressive search for other conditions that might contribute to pulmonary hypertension, such as iron overload, chronic liver disease, human immunodeficiency virus (HIV), nocturnal hypoxemia, and thromboembolism. A diagnostic right heart catheterization is essential to confirm the diagnosis and exclude diastolic dysfunction.[98] The 6-minute walk test is a useful surrogate for functional capacity in this patient population even considering the high prevalence of confounding factors such as the presence of avascular necrosis of the hip. Specifically, the 6-minute walk test inversely correlates with the severity of pulmonary hypertension,[102] and pulmonary hypertension–specific therapy improves walk distance.[103]

Most adult patients with sickle cell disease develop abnormal pulmonary function characterized by mild restrictive lung disease (mean total lung capacity values of approximately 79% of predicted), abnormal diffusing capacity, and radiographic signs of mild pulmonary fibrosis,[40,104–108] and the severity of these defects seems to be slightly greater in those patients with pulmonary hypertension.[102] However, in these patients the degree of pulmonary function abnormalities is rarely severe enough to be a major contributor to the etiology of pulmonary hypertension.

A ventilation-perfusion scan is an indispensable component of the evaluation because chronic thromboembolic pulmonary hypertension if amenable to pulmonary endarterectomy is a potential curable cause of pulmonary hypertension that has been reported in patients with chronic hemolytic disorders. In the majority of cases, observed scintigraphic evidence of thromboembolic disease is uncommon, and the most commonly seen abnormality is patchy areas of abnormal perfusion, similar to findings described in other forms of pulmonary hypertension.[102,109] However, chronic thromboembolic pulmonary hypertension occurs in approximately 5% of sickle cell patients with severe pulmonary hypertension,[102] and the disease has been treated surgically with success in two patients with sickle cell disease (Fig. 84-6).[110] As such, patients should undergo imaging studies and, if suggestive of chronic thromboembolic pulmonary hypertension, should undergo more invasive studies (i.e., angiography) to exclude this potentially surgically treatable condition.

Measurement of NT-proBNP levels can be used as a pulmonary hypertension biomarker for diagnosis and risk stratification in patients with sickle cell disease.[74] In a contemporaneous cohort, NT-proBNP levels were higher in patients with sickle cell pulmonary hypertension and correlated directly with the severity of pulmonary arterial hypertension and the degree of functional impairment. An NT-proBNP level of 160 pg/mL or greater

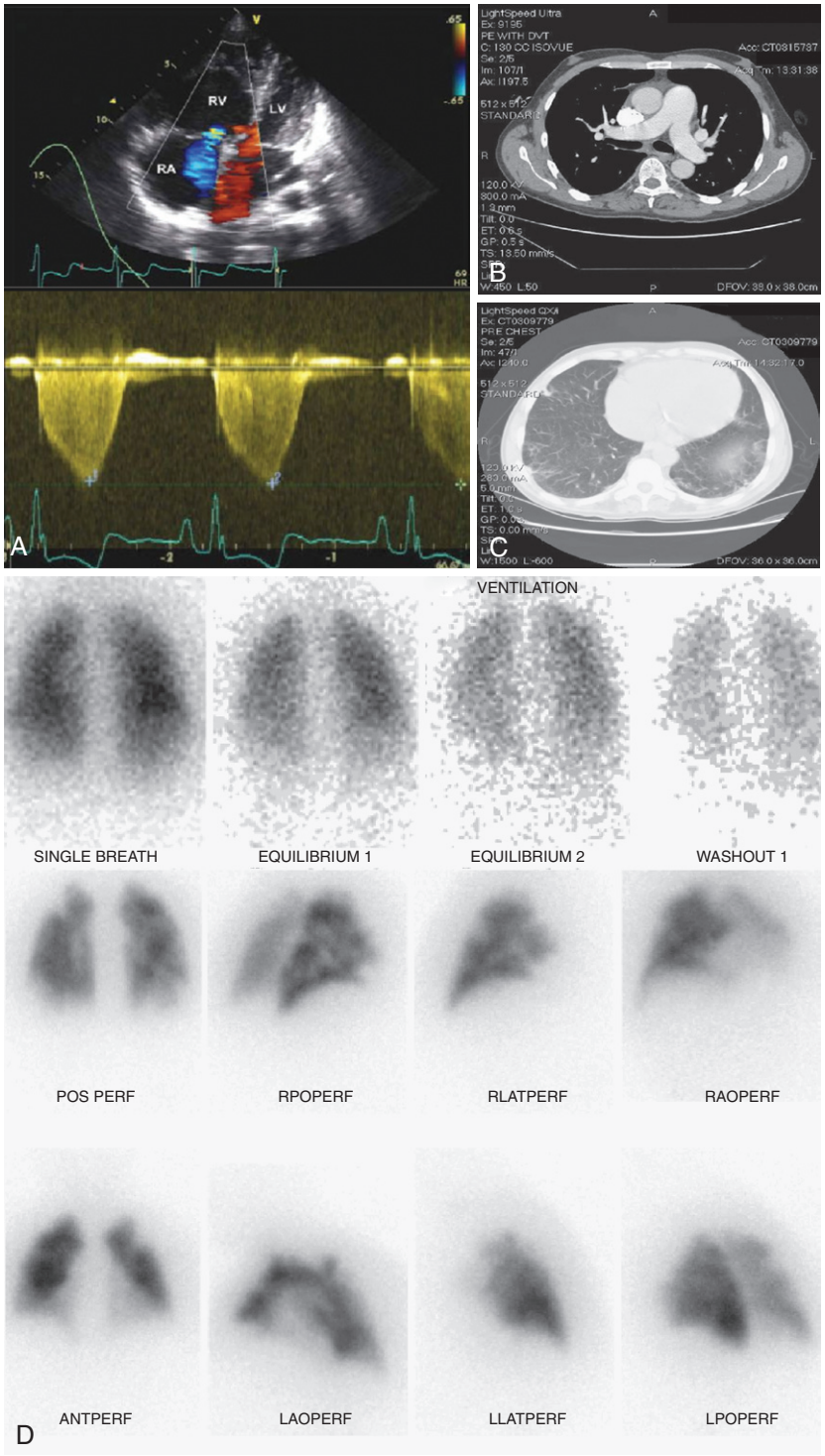

FIGURE 84-5 ■ Imaging features of sickle cell disease and pulmonary hypertension. **A,** Echocardiographic four-chamber view of the heart, illustrating severe right ventricular (RV) and right atrial (RA) dilation and moderate tricuspid regurgitation (blue color Doppler). Doppler tracing from a patient with severe pulmonary hypertension reveals a jet velocity of more than 4 m/sec. **B,** Enlargement of pulmonary arteries in severe pulmonary hypertension. **C,** Mild pulmonary fibrosis typical of patients with sickle cell disease and pulmonary hypertension. **D,** Ventilation-perfusion scan demonstrating patchy areas of abnormal perfusion.

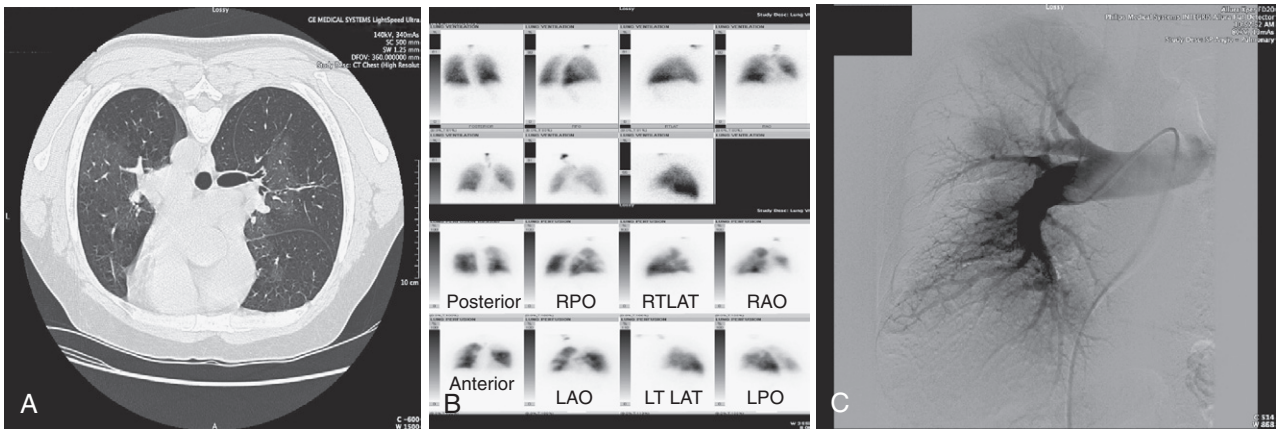

FIGURE 84-6 ■ Chronic thromboembolic pulmonary hypertension in a patient with sickle cell disease. **A,** High-resolution computed tomography scan demonstrating mosaic pattern of attenuation. **B,** Ventilation-perfusion scan demonstrating multiple unmatched perfusion defects. **C,** Digital subtraction pulmonary angiogram demonstrating peripheral filling defects in the pulmonary arteries.

TABLE 84-4. Hemodynamic Profiles in Patients with Sickle Cell Disease

	Without PH	With PH
PAP mean (mm Hg)	19 ± 0.7	36 ± 1
RAP (mm Hg)*	6 ± 0.4	10 ± 1
PCWP (mm Hg)	11 ± 0.5	17 ± 1
CO (L/min)	10 ± 0.5	9 ± 0.3
PVR (dyn/sec · cm^{-5})*	59 ± 6	197 ± 14

*Not reported by Castro et al.[70]
CO, cardiac output; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure.
Data from references 3, 70, 102.

had a 78% positive predictive value for the diagnosis of pulmonary hypertension and was an independent predictor of mortality (risk ratio, 5.1; 95% CI, 2.1 to 12.5; $P < 0.001$). In a subset of individuals participating in the MSH patient follow-up study in 1996, 30% of patients had an NT-proBNP level of 160 pg/mL or greater. An NT-proBNP level of 160 pg/mL or greater in the MSH cohort was independently associated with mortality by Cox proportional hazards regression analysis (2.87; 95% CI, 1.2 to 6.6; $P = 0.02$).

In contrast to patients with traditional forms of pulmonary arterial hypertension (e.g., idiopathic, scleroderma associated), who are symptomatic with mean pulmonary artery pressures (mPAPs) in the range of 50 to 60 mm Hg, in patients with sickle cell disease the degree of elevation in mPAPs is mild to moderate, in the range of 30 to 40 mm Hg, with mild elevations in pulmonary vascular resistance. These patients also have coexistent mild elevation in pulmonary capillary wedge pressure, suggesting left heart failure (Table 84-4). Right heart catheterization data show that the hemodynamic etiology of the pulmonary hypertension in these patients is multifactorial: pulmonary arterial hypertension (defined by an mPAP ≥ 25 mm Hg and a wedge pressure ≤ 15 mm Hg) was present in 54% of catheterized patients at the National Institutes of Health, while pulmonary venous hypertension secondary to left heart disease (defined by an mPAP ≥ 25 mm Hg and a wedge pressure > 15 mm Hg) was present in 46%.[102] Further, using echocardiography in a cohort of 141 patients with sickle cell disease, Sachdev and associates[111] found that 47% of patients had pulmonary hypertension, diastolic dysfunction, or both (29% had pulmonary hypertension alone, 11% had diastolic dysfunction and pulmonary hypertension, and 7% had diastolic dysfunction alone). Pulmonary hypertension and diastolic dysfunction were associated with a relative risk of death of 5.1 (95% CI, 2.0 to 13.3) and 4.8 (95% CI, 1.9 to 12.1), respectively, while the relative risk of death when both were present was 12.0 (95% CI, 3.8 to 38.1).[111] These data suggest that both pulmonary hypertension and diastolic dysfunction independently carry additive mortality risk.

Regardless of the hemodynamic etiology, sickle cell disease patients with chronic anemia, who maintain a high compensatory resting cardiac output in order to ensure adequate oxygen delivery, appear to be poorly tolerant of even small additional increases in pulmonary vascular resistance. When compared to age-, gender-, and hemoglobin-matched patients with sickle cell disease without pulmonary hypertension, individuals with pulmonary hypertension and mPAP of 36 mm Hg exhibit lower 6-minute walk distance (435 ± 31 vs. 320 ± 20 meters; $p = 0.002$) and peak oxygen consumption on cardiopulmonary exercise testing (50 ± 3% vs. 41 ± 2% of predicted; $P = 0.02$).[102] Patients with pulmonary arterial hypertension from other etiologies with a higher mPAP (54 mm Hg) also perform better on 6-minute walk testing (398 m) and exercise testing (46% of predicted).[112] In addition, in patients with sickle cell disease, pulmonary artery vascular resistance sharply rises with exercise suggesting that pulmonary vascular disease contributes to functional limitation in these patients.[101] Taken together, these data suggest that, in patients with chronic anemia, mild to moderate pulmonary hypertension has

a severe adverse impact on functional and aerobic exercise capacity.

Treatment. There are limited data on the specific management of patients with sickle cell disease and pulmonary hypertension. Most of the recommendations are based on expert opinion or extrapolated from data derived from other forms of pulmonary hypertension. The general approach should include maximization of sickle cell disease–specific therapy (i.e., treatment of primary hemoglobinopathy), treatment of hypoxia with chronic oxygen therapy, treatment of associated cardiopulmonary conditions (such as iron overload, chronic liver disease, HIV infection, nocturnal hypoxemia, and thromboembolic disorders), and targeted therapy with pulmonary vasodilator/anti-remodeling agents (Fig. 84-7).

Because chronic intravascular hemolysis is a central mechanism in the development of pulmonary hypertension, it is likely that optimizing sickle cell disease therapy would be beneficial through amelioration of the principal mechanism involved in the pathogenesis of pulmonary hypertension. Hydroxyurea has been shown to decrease the incidence of pain episodes and ACS, to reduce the need for transfusions, and to lower overall mortality.[42,59] It is possible that some of the decreases in pulmonary and cardiovascular deaths seen in hydroxyurea-treated patients could be related to an improvement in pulmonary hypertension. However, these considerations have to be balanced with the lack of association between fetal hemoglobin levels and the use of hydroxyurea, and protection against the development of pulmonary hypertension.[33] For patients with creatinine levels less than 1 mg/dL, hydroxyurea is started at a dose of 15 mg/kg/day and titrated up to a maximum of 35 mg/kg/day. Recent detailed treatment guidelines have been published.[60,113] Patients with renal dysfunction tend not to tolerate the myelosuppressant effects of hydroxyurea, and in those cases, we recommend the addition of erythropoietin to the regimen. Long-term transfusion therapy lowers the risk of most complications of the disease, including the risks of pulmonary events and central nervous system vasculopathy,[114-116] and might improve cardiopulmonary function and prevent the progression of pulmonary hypertension.

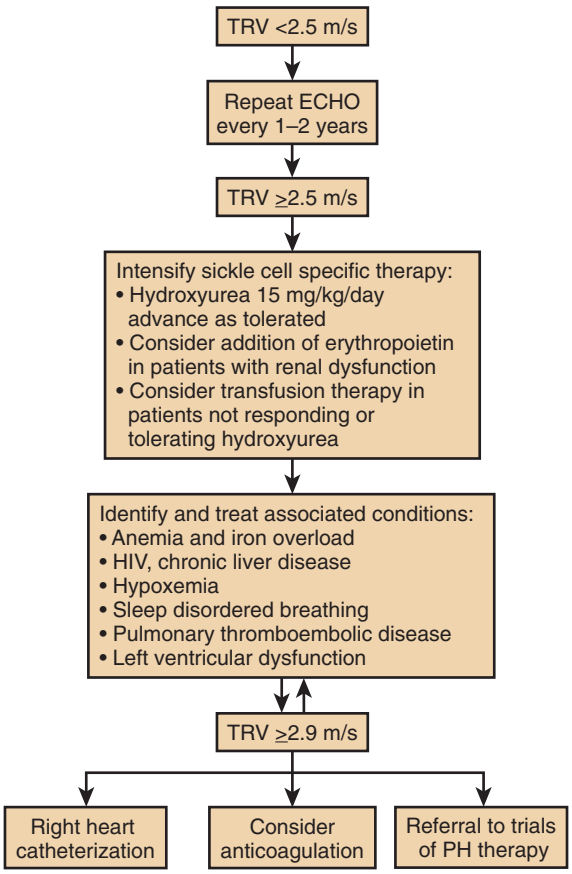

FIGURE 84-7 ■ Treatment algorithm in patients with sickle cell disease and pulmonary hypertension. TRV, tricuspid regurgitation velocity.

The potential benefits of warfarin therapy observed in patients with idiopathic pulmonary arterial hypertension[117] have to be weighed against the risk of hemorrhagic stroke in adults with sickle cell disease or hemorrhage in chronically anemic individuals. We believe that the relatively low risk of hemorrhagic stroke (0.21 events per 100 patient-years[118]) compared with the high risk of death in patients with severe pulmonary hypertension supports anticoagulation in patients with hemodynamic evidence of pulmonary arterial hypertension or chronic thromboembolic pulmonary hypertension and without a specific contraindication.

There are no long-term data on the specific treatment of pulmonary hypertension in sickle cell disease, and the choice of agents is largely empirical and based on the safety profile of the drugs and physician preference. However, there are specific treatment concerns regarding the use of these drugs in patients with hemolytic diseases. The use of prostanoids can produce systemic vasodilation and increases in cardiac output, raising the concern for the potential development of high-output heart failure in anemic patients. In addition, the risk of chronic intravenous-line–related complications such as thrombosis and sepsis is likely higher in patients with sickle cell disease. The main toxicity of endothelin-1 receptor antagonists is hepatocellular injury, which could limit their applicability in patients with sickle cell disease at risk for liver dysfunction (e.g., iron overload, hepatitis C). Another class effect of these agents is a dose-related decrease in hemoglobin levels, usually in the range of 1 g/dL.[112] The main concern related to the use of sildenafil is the potential for the development of priapism in men with sickle cell disease.

Therapeutic interventions that enhance NO effects may be of potential benefit since alterations in NO bioavailability are involved in the pathogenesis of the pulmonary hypertension associated with sickle cell disease. Chronic inhaled NO selectively dilates the pulmonary vasculature, but its use is investigational and expensive and requires a complicated delivery system.[119] L-Arginine (0.1 g/kg three times daily) has been shown to decrease pulmonary artery systolic pressure by 15% in a small study of sickle cell patients[120] and seems promising as

another approach to improving NO bioavailability. Sildenafil functions by inhibiting the metabolism of cyclic guanosine monophosphate, the second messenger that mediates the effects of NO. In a series of seven patients with either thalassemia or sickle thalassemia and severe pulmonary hypertension, treatment with sildenafil from 4 weeks to 48 months resulted in an improvement in TRV, New York Heart Association functional class, and 6-minute walk distance.[121] In another case series, 12 patients with sickle cell disease were treated with sildenafil for a mean of 6 months. Mean pulmonary artery systolic pressure decreased by 9 mm Hg (95% CI, 0.3 to 17; p = 0.047), 6-minute walk distance improved by 78 m (95% CI, 40 to 117; p = 0.003), and mean brain natriuretic peptide decreased by 448 pg/ml (p = 0.002).[103]

The published experience with endothelin antagonists in the treatment of pulmonary hypertension is also very limited. Minniti et al[121a] reported on the use of bosentan and ambrisentan in a cohort of 14 patients with sickle cell disease and pulmonary hypertension documented by heart catheterization. Endothelin antagonist therapy either as monotherapy or in combination with sildenafil was well tolerated and resulted in a modest improvement in six-minute walk distance (baseline 357 ± 22 vs. 398 ± 18 m 6 months post-therapy, $P < 0.05$). There are no published case series of prostanoid therapy in this population.

Two randomized multicenter placebo controlled studies evaluating the role of pulmonary hypertension therapy in patients with sickle cell disease have been conducted. The ASSET-1 and ASSET-2 studies enrolled patients with pulmonary arterial hypertension and pulmonary venous hypertension, respectively who were randomized to bosentan or placebo. After enrollment of 26 subjects the studies were terminated due to slow site activation and patient recruitment. In that limited sample of patients bosentan was well tolerated with no significant differences in serious averse events or laboratory tests between patients receiving study drug or placebo but efficacy endpoints could not be formally analyzed.[121b] Walk-PHaSST (Pulmonary Hypertension and Sickle Cell Disease with Sildenafil Therapy) was a trial evaluating the safety and efficacy of oral sildenafil for the treatment of Doppler defined pulmonary hypertension (tricuspid regurgitant jet velocity ≥2.7 m/s) in adults and children (aged >12 years) with sickle cell disease. After 74 (out of a planned 132) subjects were enrolled the study was discontinued due to a significant increase in hospitalizations due to vaso-occlusive pain crisis in the sildenafil arm. In that study, patients were not required to be on hydroxyurea and/or chronic transfusion therapy for sickle cell disease. Thus, it is uncertain whether these adverse effects could be mitigated by intensification of sickle cell disease specific therapy prior to the initiation of sildenafil treatment.

Chronic Lung Disease

"Sickle cell chronic lung disease" has been used as a wastebasket term to encompass pulmonary fibrosis from recurrent ACS and pulmonary hypertension.[40] Our current understanding of sickle cell chronic lung disease suggests that pulmonary fibrosis is quite mild, and that pulmonary hypertension is a more important cause of chronic pulmonary disease. For this reason, we feel that this older terminology should be replaced with a more specific diagnostic classification.

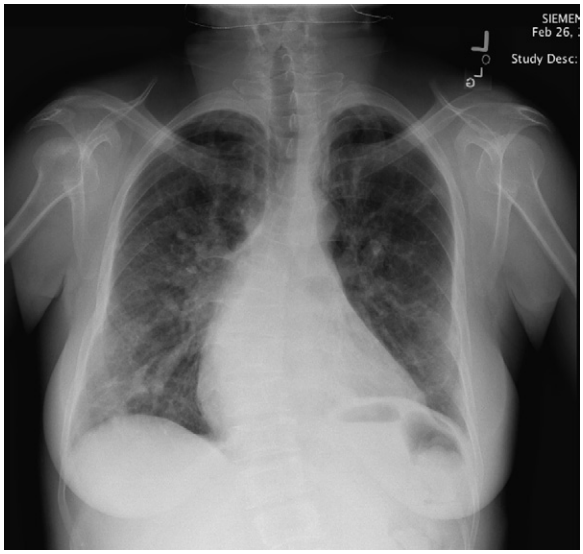

FIGURE 84-8 ■ Pulmonary fibrosis complicating multiple episodes of acute chest syndrome.

In patients with sickle cell disease, repetitive episodes of acute lung injury (ALI) related to ACS can result in parenchymal damage and typically mild restrictive lung disease (Fig. 84-8). In a study of 310 patients with homozygous sickle cell disease, pulmonary function was abnormal in 90% of adult patients; the most common abnormalities included mild restrictive physiology and decreased D_{LCO}.[122] These abnormalities worsen with age and are associated with increases in pulmonary artery pressures.[102,122] In contrast, airway hyperactivity is much more common in children.[123] Data are conflicting on whether children with sickle cell disease have a much higher prevalence of asthma and airway hyperactivity, when compared to ethnically and aged-matched controls.[47,124] It is increasingly apparent that children with a history of asthma appear to have a higher incidence of ACS, cerebral vascular accidents, and need for blood transfusions, arguing for aggressive diagnosis and treatment of asthma in this population.[47,48,125]

Sleep-disordered breathing has been reported in both children and adults with sickle cell disease. In children, sleep-related upper airway obstruction and hypoxemia are the most common disturbances. In an uncontrolled study, adenotonsillectomy led to symptomatic improvement and amelioration of oxygen desaturation.[126,127] Several lines of evidence suggest that nocturnal hypoxemia contributes to the development of neurologic events and vaso-occlusive crisis via mechanisms that could involve up-regulation of several inflammatory endothelial cell adhesion molecules.[128–130]

Thalassemia

Thalassemia refers to a spectrum of diseases characterized by reduced or absent production of one or more α or β globin chains. β-Thalassemia is due to impaired production of β globin chains, which leads to a relative excess of α globin chains.[131] These excess α globin chains are unstable, incapable of forming soluble tetramers on their own, and precipitate within the cell, leading to ineffective erythropoiesis and hemolytic anemia.[131] Thalassemia major, or homozygous β-thalassemia, is a severe disorder due to the inheritance of two β-thalassemia alleles. Starting during the first year of life, patients develop severe and lifelong transfusion-dependent anemia, hepatosplenomegaly, and skeletal deformities due to bone marrow expansion; they are prone to infection and skeletal fractures. β-Thalassemia minor, also called β-thalassemia trait, occurs in heterozygotes who have inherited a single gene leading to reduced β globin chain production. Such patients are asymptomatic, may be only mildly anemic, and are usually discovered when a blood count has been obtained for other reasons. β-Thalassemia intermedia occurs in patients with disease of intermediate severity, such as those who are compound heterozygotes of two thalassemic variants. Such patients may have the skeletal abnormalities and hepatosplenomegaly seen in thalassemia major. However, their hemoglobin concentrations usually range from 5 to 10 g/dL and they usually require transfusions only when they have an intercurrent event, such as an infection, that impairs erythropoiesis. Their clinical symptoms may not be apparent until well after the first year of life. Hemoglobin E, which is the most common hemoglobin variant in the world, is mostly asymptomatic or associated with a mild microcytic anemia in its heterozygous or homozygous states. Because hemoglobin E is synthesized at a reduced rate, it can interact with β-thalassemia to produce a condition called hemoglobin E–thalassemia. About half of these patients are phenotypically similar to patients with thalassemia major and require regular transfusion therapy, with the other half having courses similar to patients with thalassemia intermedia.

Several physiologic abnormalities arise in patients with β-thalassemia, including restrictive and obstructive defects, hyperinflation, abnormal diffusion, and decreases in aerobic exercise capacity.[132–134] However, in the majority of cases, these pulmonary function abnormalities are not associated with clinical symptoms. Several of the clinical complications related to thalassemia are related to complications of therapy such as transfusion-related iron overload, infection, thrombosis, possibly acute deterioration in pulmonary function associated with the use of the iron chelator deferoxamine, and pulmonary hypertension related to splenectomy. In patients who are poorly transfused, extramedullary erythropoiesis can rarely cause pulmonary parenchymal masses and pleural effusions.

Similar to sickle cell disease, pulmonary hypertension is a common complication of thalassemia. Echocardiographic screening studies of patients with thalassemia intermedia suggest that approximately 40% to 50% of patients with thalassemia intermedia[135] and 10% to 75% of patients with thalassemia major have echocardiographic evidence of pulmonary hypertension.[136–138] In spite of its potential complications, chronic transfusion therapy in severe thalassemia has changed the clinical course of the disease and is likely to have a favorable impact in individuals with pulmonary hypertension. This idea is supported by a report that, in well-transfused, iron-chelated patients with thalassaemia major, pulmonary hypertension was completely prevented.[139] A favorable response to sildenafil has been reported in patients with thalassemia major and intermedia.[121,140] To date, however, there are no studies evaluating the specific hemodynamic derangements associated with pulmonary hypertension nor the impact of pulmonary hypertension on survival in this patient population.

Other Hemoglobin Disorders

Hemoglobin gene mutations can result in functional abnormalities in the globin chains that alter gas ligand affinity and alter oxygen uptake and delivery. Remarkably, there are more than 120 human hemoglobin gene mutations that have been associated with abnormal hemoglobin oxygen affinity.[141] Patients with high-affinity hemoglobins usually present with erythrocytosis and are usually asymptomatic, but patients with variants associated with very high oxygen affinity can present with cyanosis or symptoms related to increased red blood cell mass (polycythemia). While patients with low-oxygen-affinity hemoglobin variants are usually asymptomatic, some can present with cyanosis. The initial step in the workup of patients suspected of having a hemoglobinopathy affecting oxygen affinity is to evaluate the red cell oxygen equilibrium curve, where both the oxygen saturation of hemoglobin and partial pressure of oxygen are directly measured to obtain a p50, the partial pressure of oxygen at which hemoglobin is 50% saturated. This approach should obviate the need for unnecessary and potentially invasive diagnostic procedures.

Methemoglobin is a nonfunctional state of hemoglobin in which the irons of heme are oxidized to the ferric (Fe^{3+}) state and are unable to bind oxygen. In addition, the oxygen affinity of any accompanying ferrous hemes in the hemoglobin tetramer are increased such that the oxygen dissociation curve is "left-shifted" and oxygen delivery to the tissues is impaired.[142] Three mechanisms are associated with the development of methemoglobinemia: genetic mutation resulting in abnormal hemoglobin (hemoglobin M), congenital deficiency of methemoglobin reductase enzyme (cytochrome b_5 or cytochrome-b_5 reductase deficiency), and drug/toxin-induced oxidation of hemoglobin. Most individuals with congenital methemoglobinemia are asymptomatic, and their primary complaint is "cyanosis" presenting as a slate-blue color of the skin and mucous membranes.

Cyanosis is clinically detected when the absolute concentration of methemoglobin exceeds 1.5 g/dL, equivalent to approximately 10% methemoglobin.[143] In cases associated with drugs and toxins, the severity of the

methemoglobinemia depends on the dose of the agent and the individual's susceptibility. Methemoglobin levels greater than 35% cause headaches, weakness, and dyspnea; levels greater than 80% are typically incompatible with life.[141] Symptomatic patients should be treated with methylene blue given intravenously at a dose of 1 to 2 mg/kg, which acts as a cofactor for the enzyme NADPH methemoglobin reductase. Electrons are transferred from NADPH to methylene blue, which leads to a reduction of the heme iron, in the form of deoxyhemoglobin.[144] Methylene blue should not be administered to individuals with glucose 6-phosphate dehydrogenase deficiency as it may precipitate hemolysis.[145]

Carbon monoxide (CO) binds to hemoglobin with much greater affinity than oxygen, forming carboxyhemoglobin (COHb). Once CO binds to heme, an allosteric change occurs that diminishes the ability of hemoglobin oxygen binding sites to off-load oxygen to peripheral tissues, resulting in impaired oxygen transport and utilization. As such, CO poisoning is a major cause of morbidity and mortality. The clinical effects of CO poisoning are non-specific and easily confused with other illnesses, such as viral illness, benign headache, and various cardiovascular and neurologic syndromes.[145a] As the severity of exposure increases, patients develop more pronounced symptoms, with oxygen-dependent organs (the brain and the heart) showing the earliest signs of injury. Oxygen therapy improves tissue hypoxia and accelerates elimination of CO. Hyperbaric oxygen therapy should be considered in patients with severe CO poisoning (such as COHb > 25%, evidence of tissue ischemia and loss of consciousness) and may reduce the incidence of the late neurocognitive deficits associated with severe CO intoxication.[145b,145c]

Cyanide binds the ferric ion (Fe3+) of cytochrome oxidase a3, inhibiting this final enzyme in the mitochondrial cytochrome complex preventing oxygen utilization by tissues. A small amount of cyanide can bind to the ferrous (Fe2+) iron of hemoglobin, forming cyanohemoglobin, which is unable to transport oxygen, and further exacerbates tissue hypoxia in patients exposed to cyanide.[145d]

WHITE BLOOD CELL DISORDERS

Leukemias

Although the majority of clinical pulmonary manifestations in patients with leukemia are not related to the disease itself, autopsy studies show that thoracic involvement is common in all leukemia types. Overall, the most common finding is mediastinal and lymph node involvement, but pleural and pulmonary infiltration is found in 20% to 65% of autopsy series.[146-148]

The mediastinum is the most commonly affected intrathoracic site. This is often manifest as a focal mass or generalized mediastinal involvement. Hilar adenopathy occurs in 15% to 25% of patients.[149,150] Pleural effusion, usually unilateral, can occur in up to 25% of cases and presents more frequently in myeloid leukemias.[151] In the majority of cases, the effusion is related to lymphatic obstruction, congestive heart failure, or infections, with only approximately 5% of cases caused by leukemic infiltration.[151]

Clinically significant leukemic pulmonary infiltrates occur in approximately 10% of patients (Fig. 84-9).[146] The usual radiographic pattern of involvement is a bilateral reticular pattern with septal lines resembling interstitial edema or lymphangitic carcinomatosis. Interlobular smooth or nodular septal thickening is the most common high-resolution computed tomography finding, followed by thickening of bronchovascular bundles. Other manifestations include peribronchovascular or random nodules, which can coalesce into masslike consolidation, focal areas of air space disease, and ground-glass opacities.[151-154] The diagnosis of leukemic infiltrates is one of exclusion as most of the pulmonary parenchymal abnormalities in these patients are associated with processes other than the hematologic disease, such as infections, hemorrhage, or pulmonary edema.

Pulmonary leukostasis or hyperleukocytosis is characterized by the distention of small pulmonary vessels by leukemic blast cells. It is most commonly seen in patients with acute leukemias and white blood cell counts greater than 100,000/mm^3 with a predominance of blast cells.[155]

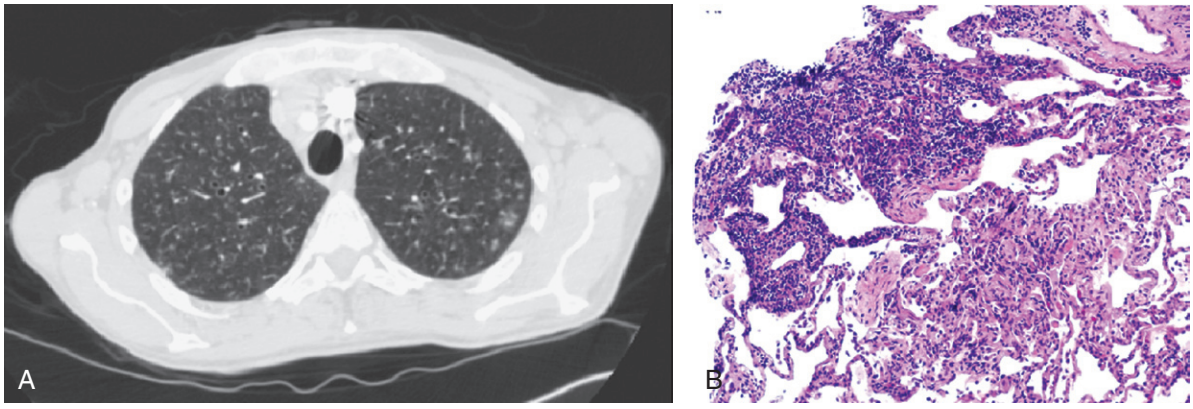

FIGURE 84-9 ■ Leukemic infiltrates in a patient with chronic lymphocytic leukemia. **A,** Diffuse nodular infiltrates. **B,** Transbronchial biopsy specimen demonstrating diffuse infiltration of lung interstitium by leukemic cells. (Hematoxylin and eosin stain).

Clinical and radiographic findings include dyspnea and hypoxia that are associated with a bilateral reticular pattern with septal lines or air space consolidation.[155,156] Symptomatic leukostasis is a medical emergency, and efforts should be made to lower the white blood cell count rapidly. In most patients, rapid cytoreduction can be achieved by chemotherapy, but leukapheresis should be considered in severe cases or in patients who cannot receive chemotherapy immediately. Finally, patients can present with acute spurious hypoxemia caused by an ex vivo decrease in arterial P_{O_2} mediated by the enhanced metabolism of the malignant cells; this process has been referred to as "leukocyte larceny." Pulse oximetry provides an accurate assessment of O_2 saturation in such circumstances.

Leukemic cell lysis pneumopathy occurs in patients with high leukocyte counts undergoing chemotherapy and is part of the spectrum of tumor lysis syndrome. Severe hypoxia and diffuse bilateral infiltrates develop within 48 hours after the initiation of chemotherapy, resembling the clinical and pathologic presentation of ARDS.[157] In patients at intermediate or high risk for the development of tumor lysis syndrome preventive measures such as aggressive intravenous hydration, urine alkalinization in selected patients and the use of agents to decrease uric acid levels such as allopurinol and rasburicase is recommended.[157a] These therapeutic strategies also apply to patients with established tumor lysis syndrome.

Plasma Cell Disorders

Thoracic involvement in multiple myeloma is common, occurring in 46% of patients, with the majority of cases related to neoplastic infiltration of the skeleton.[158] Pleural effusion caused by malignant infiltration has been reported, and for unclear reasons the effusion appears to more frequently involve the left lung.[159] Pulmonary parenchymal or airway involvement is also rare, taking the form of single or multiple masses, diffuse parenchymal infiltrates, or endobronchial lesions.[158] Pulmonary amyloidosis can also occur secondary to systemic amyloid deposition.[160]

Plasmacytoma is a circumscribed proliferation of plasma cells that are not associated with a plasma cell disorder. The vast majority of plasmocytomas involving the respiratory tract occur in the pharynx, followed by the trachea and, much less commonly, the lower airways and the pulmonary parenchyma.[161,162] Pulmonary parenchymal plasmocytomas present as a nodule or mass that is indistinguishable from bronchogenic carcinoma.

THROMBOSIS AND DISORDERS OF COAGULATION

Inherited Thrombophilia

Inherited thrombophilia encompasses the various mutations associated with venous thromboembolism. The most frequent causes of an inherited thombophilia are the factor V Leiden mutation and a prothrombin gene (G20210A) mutation, which together account for 50% to 60% of cases. Mutations in the genes coding for protein S, protein C, and antithrombin account for most of the remaining cases, while dysfibrinogenemias are rare causes of hypercoagulability (Table 84-5). [163,164] Patients with these disorders usually present with recurrent thromboembolism at a young age, typically less than 50 years of age.

It seems evident that several of these disorders are associated with an increased risk of initial and recurrent thromboembolism (see Table 84-5). There is, however, controversy about whether screening of individuals with venous thromboembolism for the presence of these inherited defects is warranted. Expert opinion suggests that evaluation for inherited thrombophilic disorders should be pursued in individuals presenting with idiopathic thrombosis at a young age (≤50 years), a history of recurrent thrombosis, or an unusual site of thrombosis; in those with a first-degree relative with thrombosis at a young age; or in women with thrombotic events during pregnancy or while taking oral contraceptives.[165-167] These recommendations have to be contrasted with the results of epidemiologic studies suggesting that a thrombophilic workup after a

TABLE 84-5. Inherited Thrombophilic Disorders

Disorder	Prevalence in Healthy Individuals (%)	Frequency in Patients with VTE (%)	Relative Risk of First Episode of DVT	Relative Risk of Recurrence
Factor V Leiden (heterozygous)	0.05–4.8	18.8	7	1.4
Factor V Leiden (homozygous)	0.02	1.5	80	n/a
Prothrombin G20210A allele	0.06–2.7	7.1	2.8	1.7
Protein C deficiency	0.2–0.4	3.7	6.5	1.8
Protein S deficiency	0.16–0.21	2.3	5.0	1.0
Antithrombin III deficiency	0.02	1.9	20	2.6
Hyperhomocysteinemia	5–7	10	2.95	0.9

DVT, deep venous thrombosis; VTE, venous thromboembolism.
Adapted from Whitlatch NL, Ortel TL: Thrombophilias: When should we test and how does it help? Semin Respir Crit Care Med 29:25–39, 2008; and Dalen JE: Should patients with venous thromboembolism be screened for thrombophilia? Am J Med 121:458–463, 2008.

first thrombotic event is unlikely to confer clinical benefit.[168–170] The presence of a thrombophilic disorder does not impact the acute management of a thromboembolic event but could have an impact on the duration of chronic anticoagulant therapy.[171] Patients with antithrombin, protein C, or protein S deficiency should be considered for indefinite anticoagulation. Patients with heterozygous factor V Leiden or prothrombin gene mutations generally do not need indefinite anticoagulation but will likely benefit from extended anticoagulant therapy to reduce the risk of recurrence, as shown in other patients with idiopathic thromboembolism.[172,173] Patients with more that one allelic abnormality should be considered for indefinite anticoagulation.

Coagulopathies and Platelet Disorders

Spontaneous pulmonary hemorrhage does not appear to be a common complication of disorders of coagulation such as the hemophilias, von Willebrand's disease, or thrombocytopenia. The risk of bleeding appears to increase in individuals with preexisting pulmonary lesions or in situations in which physical or procedural trauma to the respiratory system occurs. However, episodes of pulmonary hemorrhage, hemomediastinum, and tracheal and pleural hematomas have been described in patients with hemophilias.[174] Radiographic abnormalities such as scarring, fibrosis, pleural thickening, abnormalities in pulmonary vessels, and hyperinflation and cases of pulmonary hypertension have also been described in patients with hemophilia.[141]

COMPLICATIONS OF TRANSFUSION

Transfusion-Associated Acute Lung Injury

Transfusion-related acute lung injury (TRALI) is an ALI syndrome occurring after the transfusion of blood products containing plasma, most commonly whole blood, fresh frozen plasma, platelets, and packed red blood cells. TRALI is currently the leading cause of transfusion-related morbidity and mortality.[175] TRALI is defined as an acute onset hypoxemia (the ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen ≤ 300 mmHg), new chest radiographic opacities, without evidence of elevated left atrial pressure within 6 hours of infusion of a blood product.[176]

Epidemiology

The incidence of TRALI is not well established but appears to be one episode for every 5000 blood component transfusions.[177] This likely underestimates the true incidence of the disease. Recent studies using systematic methods to identify TRALI cases suggest that the incidence can be 5 to 50 times higher than previously thought.[178–181]

TRALI has been reported in all age groups and occurs equally in men and women. A single-center study suggested that patients with hematologic malignancies or cardiovascular disease requiring cardiopulmonary bypass operations are at a higher risk of developing this complication.[178] Administration of fresh frozen plasma, prolonged storage of blood products, and acute underlying conditions such as recent surgery, massive transfusion, cytokine therapy, sepsis, and thrombocytopenia have also been implicated as risk factors for TRALI.[178,180,182–186] Multiparous women are the donors most commonly associated with cases of TRALI, which reflects formation of antibodies related to exposure to paternal leukocyte antigens during pregnancy (see next section on pathogenesis).[177,187,188]

Pathogenesis

Two leading hypotheses have been put forth to explain the mechanisms underlying the pathogenesis of TRALI. One theory involves the transfusion-associated interaction between leukocyte antigens and antibodies causing granulocyte activation and lung injury. An alternative "two hit" hypothesis proposes that active substances accumulate as the blood product is stored and are transferred to a susceptible host, causing granulocyte priming that then secondarily produces lung injury in the setting of systemic inflammation from another insult such as sepsis.

Several lines of evidence support the notion that antileukocyte antibodies are a common cause of TRALI. Antigranulocyte antibodies are found in samples of donors or recipients after clinical episodes of TRALI, and infusion of antigranulocyte antibodies in animals causes a similar form of lung injury.[189,190] There have been three case reports of TRALI occurring in medical studies in which plasma containing strong leukocyte antibodies was infused in healthy volunteers.[191] Antibodies against human leukocyte antigen class I and II antigens and HNA-3a antigens are found in patients with TRALI.[192]

The "two hit" hypothesis is also supported by several studies. The age of transfused blood has been reported as a risk factor for multiorgan failure in trauma patients.[193] The presence of bioactive lipids implicated in the pathogenesis of lung injury, such as lysophosphatidyl choline, is higher in blood products given to patients who develop TRALI.[180,185] CD40 ligand, which induces injury to activated microvascular endothelial cells, accumulates in stored blood products, and significantly higher levels are found in blood products given to patients who develop TRALI.[194]

Clinical Features and Evaluation

Patients typically present with the sudden onset of respiratory distress 1 to 2 hours after the transfusion of blood products. Clinical signs include fever, tachypnea, tachycardia, and occasionally hypotension.[183] Pink frothy secretions with a high albumin content indicative of noncardiogenic pulmonary edema may be observed. Chest radiography classically reveals bilateral alveolar

infiltrates with a normal cardiac silhouette and without pleural effusion. The finding of granulocyte, leukoagglutinating, or lymphotoxic antibodies in the serum from either the donor or recepient supports the diagnosis of TRALI, but these abnormalities do not occur in all patients. The main differential diagnosis in these patients is transfusion-associated circulatory overload, and the differentiation of these two conditions can de difficult. The measurement of brain natriuretic peptide levels has been described as a helpful tool to discriminate these two entities.[195]

Approximately 70% of patients require mechanical ventilation at the time of presentation.[192] Resolution occurs rapidly, within the first 48 hours, and with few exceptions chest radiographs return to normal typically in 4 days. The estimated mortality associated with TRALI is 5%.[192]

Treatment

The management of TRALI is supportive as patients usually improve spontaneously. In patients requiring mechanical ventilation, the management should follow the same approach recommended for patients with ARDS. There is no convincing evidence to support the use of corticosteroids in patients with TRALI. Individuals developing TRALI should not receive further blood products from the implicated donor but do not appear to be at increased risk for recurrent episodes with products from other donors.[196]

KEY POINTS

Hemoglobin Disorders

- Pulmonary hypertension is a common complication of hemolytic disorders.
- Pulmonary complications are a major cause of morbidity and mortality in patients with sickle cell disease.
- Acute chest syndrome (ACS) is the second most common cause of hospitalization in patients with sickle cell disease and the leading cause of admission to an intensive care unit and premature death.
- Patients with ACS frequently develop acute right heart failure (13%).
- Pulmonary hypertension occurs in up to 30% of patients with sickle cell disease and is a major cause of morbidity and mortality in these patients.
- Echocardiography with assessment of TRV and measurements of NT-proBNP levels can be used to identify patients with sickle cell disease at a high risk of death.
- There is emerging evidence that pulmonary hypertension–specific therapy could improve outcomes in patients with sickle cell disease and thalassemia.

White Blood Cell Disorders

- Direct parenchymal involvement by leukemias and plasma cell disorders is uncommon.

Thrombosis and Coagulation Disorders

- There is controversy about whether screening of individuals with venous thromboembolism for the presence of inherited thrombophilic defects is warranted.
- The optimal chronic management of patients with inherited thrombophilia is not well established.
- Spontaneous pulmonary hemorrhage does not appear to be a common complication of disorders of coagulation.

Complications of Transfusion

- Transfusion-related acute lung injury (TRALI) is a leading cause of transfusion-related morbidity and mortality.

References

1. Weiskopf RB, Viele MK, Feiner J, et al: Human cardiovascular and metabolic response to acute, severe isovolemic anemia. JAMA 279:217–221, 1998.
2. Brannon ES, Merrill AJ, Warren JV, et al: The cardiac output in patients with chronic anemia as measured by the technique of right atrial catheterization. J Clin Invest 24:332–336, 1945.
3. Leight L, Snider TH, Clifford GO, et al: Hemodynamic studies in sickle cell anemia. Circulation 10:653–662, 1954.
4. Roy SB, Bhatia ML, Mathur VS, et al: Hemodynamic effects of chronic severe anemia. Circulation 28:346–356, 1963.

5. el-Yousef MK, Bakewell WE Jr: The Gaisbock syndrome. JAMA 220:864, 1972.

5a. James C, Ugo V, Le Couédie JP, et al: A unique clonal JAK2 mutation leading to constitutive signaling causes polycythaemia vera. Nature 434:1144-1148, 2005.

6. Nand S, Orfei E: Pulmonary hypertension in polycythemia vera. Am J Hematol 47:242–244, 1994.
7. Scharenberg C, Riera R, Gorg C, et al: Thrombotic pulmonary arteriopathy in polycythemia vera. Pathol Res Pract 195:653–656, 1999.
8. Hocking WG, Golde DW: Polycythemia: Evaluation and management. Blood Rev 3:59–65, 1989.
9. Marvin KS, Spellberg RD: Pulmonary hypertension secondary to thrombocytosis in a patient with myeloid metaplasia. Chest 103:642–644, 1993.
10. Dingli D, Utz JP, Krowka MJ, et al: Unexplained pulmonary hypertension in chronic myeloproliferative disorders. Chest 120:801–808, 2001.
11. Murata M, Kuroda T, Nakajima K, et al: Primary pulmonary hypertension with severe systemic hypertension, Raynaud's phenomenon and relative polycythemia. Intern Med 40:905–910, 2001.
12. Bushuev VI, Miasnikova GY, Sergueeva AI, et al: Endothelin-1, vascular endothelial growth factor and systolic pulmonary artery pressure in patients with Chuvash polycythemia. Haematologica 91:744–749, 2006.
13. Defouilloy C, Teiger E, Sediame S, et al: Polycythemia impairs vasodilator response to acetylcholine in patients with chronic hypoxemic lung disease. Am J Respir Crit Care Med 157(5 Pt 1):1452–1460, 1998.
14. Rother RP, Bell L, Hillmen P, et al: The clinical sequelae of intravascular hemolysis and extracellular plasma hemoglobin: A novel mechanism of human disease. JAMA 293:1653–1662, 2005.
15. Azarov I, Huang KT, Basu S, et al: Nitric oxide scavenging by red blood cells as a function of hematocrit and oxygenation. J Biol Chem 280:39024–39032, 2005.
16. Jeffers A, Gladwin MT, Kim-Shapiro DB: Computation of plasma hemoglobin nitric oxide scavenging in hemolytic anemias. Free Radic Biol Med 41:1557–1565, 2006.
17. Ruschitzka FT, Wenger RH, Stallmach T, et al: Nitric oxide prevents cardiovascular disease and determines survival in polyglobulic mice overexpressing erythropoietin. Proc Natl Acad Sci U S A 97:11609–11613, 2000.
18. Spivak JL: Polycythemia vera: Myths, mechanisms, and management. Blood 100:4272–4290, 2002.
19. Streiff MB, Smith B, Spivak JL: The diagnosis and management of polycythemia vera in the era since the Polycythemia Vera Study Group: A survey of American Society of Hematology members' practice patterns. Blood 99:1144–1149, 2002.
20. Wiedemann HP, Matthay RA: Cor pulmonale in chronic obstructive pulmonary disease: Circulatory pathophysiology and management. Clin Chest Med 11:523–545,1990.
21. Bunn HF: Pathogenesis and treatment of sickle cell disease. N Engl J Med 337:762–769, 1997.
22. Noguchi CT, Schechter AN, Rodgers GP: Sickle cell disease pathophysiology. Baillieres Clin Haematol 6:57–91, 1993.
23. Aslan M, Ryan TM, Adler B, et al: Oxygen radical inhibition of nitric oxide-dependent vascular function in sickle cell disease. Proc Natl Acad Sci U S A 98:15215–15220, 2001.
24. Belcher JD, Mahaseth H, Welch TE, et al: Critical role of endothelial cell activation in hypoxia-induced vasoocclusion in transgenic sickle mice. Am J Physiol Heart Circ Physiol 288:H2715–H2725, 2005.
25. Belcher JD, Marker PH, Weber JP, et al: Activated monocytes in sickle cell disease: Potential role in the activation of vascular endothelium and vaso-occlusion. Blood 96:2451–2459, 2000.
26. Frenette PS: Sickle cell vaso-occlusion: Multistep and multicellular paradigm. Curr Opin Hematol 9:101–106, 2002.
27. Kaul DK, Hebbel RP: Hypoxia/reoxygenation causes inflammatory response in transgenic sickle mice but not in normal mice. J Clin Invest 106:411–420, 2000.
28. Platt OS: Sickle cell anemia as an inflammatory disease. J Clin Invest 106:337–338, 2000.
29. Wood KC, Hebbel RP, Granger DN: Endothelial cell NADPH oxidase mediates the cerebral microvascular dysfunction in sickle cell transgenic mice. FASEB J 19:989–991, 2005.
30. Wood KC, Hebbel RP, Lefer DJ, et al: Critical role of endothelial cell-derived nitric oxide synthase in sickle cell disease-induced microvascular dysfunction. Free Radic Biol Med 40:1443–1453, 2006.
31. Morris CR, Kato GJ, Poljakovic M, et al: Dysregulated arginine metabolism, hemolysis-associated pulmonary hypertension, and mortality in sickle cell disease. JAMA 294:81–90, 2005.
32. Reiter CD, Wang X, Tanus-Santos JE, et al: Cell-free hemoglobin limits nitric oxide bioavailability in sickle-cell disease. Nat Med 8:1383–1389, 2002.
33. Gladwin MT, Sachdev V, Jison ML, et al: Pulmonary hypertension as a risk factor for death in patients with sickle cell disease. N Engl J Med 350:886–895, 2004.
34. Frei AC, Guo Y, Jones DW, et al: Vascular dysfunction in a murine model of severe hemolysis. Blood 112:398–405, 2008.
35. Hsu L, McDermott T, Brown L, et al: Transgenic HbS mouse neutrophils in increased susceptibility to acute lung injury: Implications for sickle acute chest syndrome. Chest 116(1 Suppl):92S, 1999.
36. Serjeant GR: Sickle-cell disease. Lancet 350:725–730, 1997.
37. Platt OS, Brambilla DJ, Rosse WF, et al: Mortality in sickle cell disease: Life expectancy and risk factors for early death. N Engl J Med 330:1639–1644, 1994.
38. Wierenga KJ, Hambleton IR, Lewis NA: Survival estimates for patients with homozygous sickle-cell disease in Jamaica: A clinic-based population study. Lancet 357:680–683, 2001.
39. Gray A, Anionwu EN, Davies SC, et al: Patterns of mortality in sickle cell disease in the United Kingdom. J Clin Pathol 44:459–463, 1991.
40. Powars D, Weidman JA, Odom-Maryon T, et al: Sickle cell chronic lung disease: Prior morbidity and the risk of pulmonary failure. Medicine (Baltimore) 67:66–76, 1988.
41. Thomas AN, Pattison C, Serjeant GR: Causes of death in sickle-cell disease in Jamaica. Br Med J Clin Res Ed 285:633–635, 1982.
42. Steinberg MH, Barton F, Castro O, et al: Effect of hydroxyurea on mortality and morbidity in adult sickle cell anemia: Risks and benefits up to 9 years of treatment. JAMA 289:1645–1651, 2003.
43. Vichinsky EP, Neumayr LD, Earles AN, et al: Causes and outcomes of the acute chest syndrome in sickle cell disease. National Acute Chest Syndrome Study Group. N Engl J Med 342:1855–1865, 2000.
44. Vichinsky EP, Styles LA, Colangelo LH, et al: Acute chest syndrome in sickle cell disease: Clinical presentation and course. Cooperative Study of Sickle Cell Disease. Blood 89:1787–1792, 1997.
45. Castro O, Brambilla DJ, Thorington B, et al: The acute chest syndrome in sickle cell disease: Incidence and risk factors. The Cooperative Study of Sickle Cell Disease. Blood 84:643–649, 1994.
46. Boyd JH, Macklin EA, Strunk RC, et al: Asthma is associated with acute chest syndrome and pain in children with sickle cell anemia. Blood 108:2923–2927, 2006.
47. Knight-Madden JM, Forrester TS, Lewis NA, et al: Asthma in children with sickle cell disease and its association with acute chest syndrome. Thorax 60:206–210, 2005.
48. Nordness ME, Lynn J, Zacharisen MC, et al: Asthma is a risk factor for acute chest syndrome and cerebral vascular accidents in children with sickle cell disease. Clin Mol Allergy 3:2, 2005.
49. Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 34-1997. A 22-year-old man with a sickle cell crisis and sudden death. N Engl J Med 337:1293–1301, 1997.
50. Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 52-1983. Pulmonary hypertension associated with abnormal hemoglobin. N Engl J Med 309:1627–1636, 1983.
51. Gladwin MT, Rodgers GP: Pathogenesis and treatment of acute chest syndrome of sickle-cell anaemia. Lancet 355:1476–1478, 2000.
52. Styles LA, Schalkwijk CG, Aarsman AJ, et al: Phospholipase A2 levels in acute chest syndrome of sickle cell disease. Blood 87:2573–2578, 1996.

53. Bellet PS, Kalinyak KA, Shukla R, et al: Incentive spirometry to prevent acute pulmonary complications in sickle cell diseases. N Engl J Med 333:699–703, 1995.
54. Styles LA, Aarsman AJ, Vichinsky EP, et al: Secretory phospholipase A_2 predicts impending acute chest syndrome in sickle cell disease. Blood 96:3276–3278, 2000.
55. Lechapt E, Habibi A, Bachir D, et al: Induced sputum versus bronchoalveolar lavage during acute chest syndrome in sickle cell disease. Am J Respir Crit Care Med 168:1373–1377, 2003.
56. Vichinsky E, Williams R, Das M, et al: Pulmonary fat embolism: A distinct cause of severe acute chest syndrome in sickle cell anemia. Blood 83:3107–3112, 1994.
57. Castro O: Systemic fat embolism and pulmonary hypertension in sickle cell disease. Hematol Oncol Clin North Am 10:1289–1303, 1996.
58. Mekontso Dessap A, Leon R, Habibi A, et al: Pulmonary hypertension and cor pulmonale during severe acute chest syndrome in sickle cell disease. Am J Respir Crit Care Med 177:646–653, 2008.
59. Charache S, Terrin ML, Moore RD, et al: Effect of hydroxyurea on the frequency of painful crises in sickle cell anemia. Investigators of the Multicenter Study of Hydroxyurea in Sickle Cell Anemia. N Engl J Med 332:1317–1322, 1995.
60. Platt OS: Hydroxyurea for the treatment of sickle cell anemia. N Engl J Med 358:1362–1369, 2008.
61. Miller ST, Wright E, Abboud M, et al: Impact of chronic transfusion on incidence of pain and acute chest syndrome during the Stroke Prevention Trial (STOP) in sickle-cell anemia. J Pediatr 139:785–789, 2001.
62. Styles LA, Vichinsky E: Effects of a long-term transfusion regimen on sickle cell-related illnesses. J Pediatr 125(6 Pt 1):909–911, 1994.
63. Bernini JC, Rogers ZR, Sandler ES, et al: Beneficial effect of intravenous dexamethasone in children with mild to moderately severe acute chest syndrome complicating sickle cell disease. Blood 92:3082–3089, 1998.
64. Strouse JJ, Takemoto CM, Keefer JR, et al: Corticosteroids and increased risk of readmission after acute chest syndrome in children with sickle cell disease. Pediatr Blood Cancer 50:1006–1012, 2007.
65. Oppert M, Jorres A, Barckow D, et al: Inhaled nitric oxide for ARDS due to sickle cell disease. Swiss Med Wkly 134(11–12):165–167, 2004.
66. Gladwin MT, Schechter AN, Shelhamer JH, et al: The acute chest syndrome in sickle cell disease: Possible role of nitric oxide in its pathophysiology and treatment. Am J Respir Crit Care Med 159(5 Pt 1):1368–1376, 1999.
67. Atz AM, Wessel DL: Inhaled nitric oxide in sickle cell disease with acute chest syndrome. Anesthesiology 87:988–990, 1997.
68. Cavalli-Sforza LL, Menozzi P, Piazza A: The History and Geography of Human Genes. Princeton, NJ: Princeton University Press, 1994.
69. Sutton LL, Castro O, Cross DJ, et al: Pulmonary hypertension in sickle cell disease. Am J Cardiol 74:626–628, 1994.
70. Castro O, Hoque M, Brown BD: Pulmonary hypertension in sickle cell disease: Cardiac catheterization results and survival. Blood 101:1257–1261, 2003.
71. Haque AK, Gokhale S, Rampy BA, et al: Pulmonary hypertension in sickle cell hemoglobinopathy: A clinicopathologic study of 20 cases. Hum Pathol 33:1037–1043, 2002.
72. Ataga KI, Moore CG, Jones S, et al: Pulmonary hypertension in patients with sickle cell disease: A longitudinal study. Br J Haematol 134:109–115, 2006.
73. De Castro LM, Jonassaint JC, Graham FL, et al: Pulmonary hypertension associated with sickle cell disease: Clinical and laboratory endpoints and disease outcomes. Am J Hematol 83:19–25, 2008.
74. Machado RF, Anthi A, Steinberg MH, et al: N-terminal pro-brain natriuretic peptide levels and risk of death in sickle cell disease. JAMA 296:310–318, 2006.
75. Castro O, Gladwin MT: Pulmonary hypertension in sickle cell disease: Mechanisms, diagnosis, and management. Hematol Oncol Clin North Am 19:881–896, vii, 2005.
76. Ambrusko SJ, Gunawardena S, Sakara A, et al: Elevation of tricuspid regurgitant jet velocity, a marker for pulmonary hypertension in children with sickle cell disease. Pediatr Blood Cancer 47:907–913, 2006.
77. Liem RI, Young LT, Thompson AA: Tricuspid regurgitant jet velocity is associated with hemolysis in children and young adults with sickle cell disease evaluated for pulmonary hypertension. Haematologica 92:1549–1552, 2007.
78. Onyekwere OC, Campbell A, Teshome M, et al: Pulmonary hypertension in children and adolescents with sickle cell disease. Pediatr Cardiol 29:309–312, 2008.
79. Pashankar FD, Ment LR, Pearson HA: Sickle cell disease complicated by post-streptococcal glomerulonephritis, cerebral hemorrhage and reversible posterior leucoencephalopathy syndrome. Pediatr Blood Cancer 50:864–866, 2008.
80. Kato GJ, Gladwin MT, Steinberg MH: Deconstructing sickle cell disease: Reappraisal of the role of hemolysis in the development of clinical subphenotypes. Blood Rev 21:37–47, 2007.
81. Kato GJ, Onyekwere OC, Gladwin MT: Pulmonary hypertension in sickle cell disease: Relevance to children. Pediatr Hematol Oncol 24:159–170, 2007.
82. Pashankar FD, Carbonella J, Bazzy-Asaad A, et al: Prevalence and risk factors of elevated pulmonary artery pressures in children with sickle cell disease. Pediatrics 121:777–782, 2008.
83. Villagra J, Shiva S, Hunter LA, et al: Platelet activation in patients with sickle disease, hemolysis-associated pulmonary hypertension, and nitric oxide scavenging by cell-free hemoglobin. Blood 110:2166–2172, 2007.
84. Hagger D, Wolff S, Owen J, et al: Changes in coagulation and fibrinolysis in patients with sickle cell disease compared with healthy black controls. Blood Coagul Fibrinolysis 6:93–99, 1995.
85. Ataga KI, Moore CG, Hillery CA, et al: Coagulation activation and inflammation in sickle cell disease-associated pulmonary hypertension. Haematologica 93:20–26, 2008.
86. van Beers EJ, Spronk HM, Ten Cate H, et al: No association of the hypercoagulable state with sickle cell disease related pulmonary hypertension. Haematologica 93:e42–e44, 2008.
87. Westerman M, Pizzey A, Hirschman J, et al: Microvesicles in haemoglobinopathies offer insights into mechanisms of hypercoagulability, haemolysis and the effects of therapy. Br J Haematol 142:126–135, 2008.
88. Setty BN, Rao AK, Stuart MJ: Thrombophilia in sickle cell disease: The red cell connection. Blood 98:3228–3233, 2001.
89. Nath KA, Katusic ZS, Gladwin MT: The perfusion paradox and vascular instability in sickle cell disease. Microcirculation 11:179–193, 2004.
90. Ergul S, Brunson CY, Hutchinson J, et al: Vasoactive factors in sickle cell disease: In vitro evidence for endothelin-1-mediated vasoconstriction. Am J Hematol 76:245–251, 2004.
91. Hoeper MM, Niedermeyer J, Hoffmeyer F, et al: Pulmonary hypertension after splenectomy? Ann Intern Med 130:506–509, 1999.
92. Atichartakarn V, Likittanasombat K, Chuncharunee S, et al: Pulmonary arterial hypertension in previously splenectomized patients with beta-thalassemic disorders. Int J Hematol 78:139–145, 2003.
93. Chou R, DeLoughery TG: Recurrent thromboembolic disease following splenectomy for pyruvate kinase deficiency. Am J Hematol 67:197–199, 2001.
94. Hayag-Barin JE, Smith RE, Tucker FC Jr: Hereditary spherocytosis, thrombocytosis, and chronic pulmonary emboli: A case report and review of the literature. Am J Hematol 57:82–84, 1998.
95. Atichartakarn V, Angchaisuksiri P, Aryurachai K, et al: In vivo platelet activation and hyperaggregation in hemoglobin E/beta-thalassemia: A consequence of splenectomy. Int J Hematol 77:299–303, 2003.
96. Atichartakarn V, Angchaisuksiri P, Aryurachai K, et al: Relationship between hypercoagulable state and erythrocyte phosphatidylserine exposure in splenectomized haemoglobin E/beta-thalassaemic patients. Br J Haematol 118:893–898, 2002.
97. Kisanuki A, Kietthubthew S, Asada Y, et al: Intravenous injection of sonicated blood induces pulmonary microthromboembolism in rabbits with ligation of the splenic artery. Thromb Res 85:95–103, 1997.
98. Barst RJ, McGoon M, Torbicki A, et al: Diagnosis and differential assessment of pulmonary arterial hypertension. J Am Coll Cardiol 43(12 Suppl S):40S–47S, 2004.

99. McGoon M, Gutterman D, Steen V, et al: Screening, early detection, and diagnosis of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. Chest 126(1 Suppl): 14S–34S, 2004.
100. McQuillan BM, Picard MH, Leavitt M, et al: Clinical correlates and reference intervals for pulmonary artery systolic pressure among echocardiographically normal subjects. Circulation 104:2797–2802, 2001.
101. Machado RF, Kyle Mack A, Martyr S, et al: Severity of pulmonary hypertension during vaso-occlusive pain crisis and exercise in patients with sickle cell disease. Br J Haematol 136:319–325, 2007.
102. Anthi A, Machado RF, Jison ML, et al: Hemodynamic and functional assessment of patients with sickle cell disease and pulmonary hypertension. Am J Respir Crit Care Med 175:1272–1279, 2007.
103. Machado RF, Martyr S, Kato GJ, et al: Sildenafil therapy in patients with sickle disease and pulmonary hypertension. Br J Haematol 130:445–453, 2005.
104. Koumbourlis AC, Hurlet-Jensen A, Bye MR: Lung function in infants with sickle cell disease. Pediatr Pulmonol 24:277–281, 1997.
105. Koumbourlis AC, Zar HJ, Hurlet-Jensen A, et al: Prevalence and reversibility of lower airway obstruction in children with sickle cell disease. J Pediatr 138:188–192, 2001.
106. Lonsdorfer J, Bogui P, Otayeck A, et al: Cardiorespiratory adjustments in chronic sickle cell anemia. Bull Eur Physiopathol Respir 19:339–344, 1983.
107. Santoli F, Zerah F, Vasile N, et al: Pulmonary function in sickle cell disease with or without acute chest syndrome. Eur Respir J 12:1124–1129, 1998.
108. Young RC Jr, Rachal RE, Reindorf CA, et al: Lung function in sickle cell hemoglobinopathy patients compared with healthy subjects. J Natl Med Assoc 80:509–514, 1988.
109. van Beers EJ, van Eck-Smit BL, Mac Gillavry MR, et al: Large and medium-sized pulmonary artery obstruction does not play a role of primary importance in the etiology of sickle-cell disease-associated pulmonary hypertension. Chest 133:646–652, 2008.
110. Yung GL, Channick RN, Fedullo PF, et al: Successful pulmonary thromboendarterectomy in two patients with sickle cell disease. Am J Respir Crit Care Med 157(5 Pt 1):1690–1693, 1998.
111. Sachdev V, Machado RF, Shizukuda Y, et al: Diastolic dysfunction is an independent risk factor for death in patients with sickle cell disease. J Am Coll Cardiol 49:472–479, 2007.
112. Barst RJ, Langleben D, Frost A, et al: Sitaxsentan therapy for pulmonary arterial hypertension. Am J Respir Crit Care Med 169:441–447, 2004.
113. Lanzkron S, Strouse JJ, Wilson R, et al: Systematic review: Hydroxyurea for the treatment of adults with sickle cell disease. Ann Intern Med 148:939–955, 2008.
114. Adams RJ, McKie VC, Hsu L, et al: Prevention of a first stroke by transfusions in children with sickle cell anemia and abnormal results on transcranial Doppler ultrasonography. N Engl J Med 339:5–11, 1998.
115. Koshy M, Burd L, Wallace D, et al: Prophylactic red-cell transfusions in pregnant patients with sickle cell disease: A randomized cooperative study. N Engl J Med 319:1447–1452, 1988.
116. Pegelow CH, Adams RJ, McKie V, et al: Risk of recurrent stroke in patients with sickle cell disease treated with erythrocyte transfusions. J Pediatr 126:896–899, 1995.
117. Fuster V, Steele PM, Edwards WD, et al: Primary pulmonary hypertension: Natural history and the importance of thrombosis. Circulation 70:580–587, 1984.
118. Ohene-Frempong K, Weiner SJ, Sleeper LA, et al: Cerebrovascular accidents in sickle cell disease: Rates and risk factors. Blood 91:288–294, 1998.
119. Channick RN, Newhart JW, Johnson FW, et al: Pulsed delivery of inhaled nitric oxide to patients with primary pulmonary hypertension: An ambulatory delivery system and initial clinical tests. Chest 109:1545–1549, 1996.
120. Morris CR, Morris SM Jr, Hagar W, et al: Arginine therapy: A new treatment for pulmonary hypertension in sickle cell disease? Am J Respir Crit Care Med 168:63–69, 2003.
121. Derchi G, Forni GL, Formisano F, et al: Efficacy and safety of sildenafil in the treatment of severe pulmonary hypertension in patients with hemoglobinopathies. Haematologica 90:452–458, 2005.
121a. Minniti CP, Machado RF, Coles W, et al: Endothelin receptor antagonists for pulmonary hypertension in adult patients with sickle cell disease. Br J Haematol 147:737–743, 2009.
121b. Barst RJ, Mubarak K, Machado R, et al: Exercise capacity and hemodynamics in patients with sickle cell disease with pulmonary hypertension treated with bosentan: results of the ASSET studies. Br J Haematol 2010, Epub ahead of print.
122. Klings ES, Wyszynski DF, Nolan VG, et al: Abnormal pulmonary function in adults with sickle cell anemia. Am J Respir Crit Care Med 173:1264–1269, 2006.
123. Leong MA, Dampier C, Varlotta L, et al: Airway hyperreactivity in children with sickle cell disease. J Pediatr 131:278–283, 1997.
124. Sylvester KP, Patey RA, Rafferty GF, et al: Airway hyperresponsiveness and acute chest syndrome in children with sickle cell anemia. Pediatr Pulmonol 42:272–276, 2007.
125. Bryant R: Asthma in the pediatric sickle cell patient with acute chest syndrome. J Pediatr Health Care 19:157–162, 2005.
126. Samuels MP, Stebbens VA, Davies SC, et al: Sleep related upper airway obstruction and hypoxaemia in sickle cell disease. Arch Dis Child 67:925–929, 1992.
127. Sidman JD, Fry TL: Exacerbation of sickle cell disease by obstructive sleep apnea. Arch Otolaryngol Head Neck Surg 114:916–917, 1988.
128. Hargrave DR, Wade A, Evans JP, et al: Nocturnal oxygen saturation and painful sickle cell crises in children. Blood 101:846–848, 2003.
129. Kirkham FJ, Hewes DK, Prengler M, et al: Nocturnal hypoxaemia and central-nervous-system events in sickle-cell disease. Lancet 357:1656–1659, 2001.
130. Setty BN, Stuart MJ, Dampier C, et al: Hypoxaemia in sickle cell disease: Biomarker modulation and relevance to pathophysiology. Lancet 362:1450–1455, 2003.
131. Weatherall DJ: The thalassaemias. BMJ 314:1675–1678, 1997.
132. Piatti G, Allegra L, Ambrosetti U, et al: Beta-thalassemia and pulmonary function. Haematologica 84:804–808, 1999.
133. Santamaria F, Villa MP, Ronchetti R: Pulmonary function abnormalities in thalassemia major. Am J Respir Crit Care Med 151(3 Pt 1):919, 1995.
134. Youngchaiyud P, Suthamsmai T, Fucharoen S, et al: Lung function tests in splenectomized beta-thalassemia/Hb E patients. Birth Defects Orig Artic Ser 23(5A):361–370, 1987.
135. Aessopos A, Farmakis D, Karagiorga M, et al: Cardiac involvement in thalassemia intermedia: A multicenter study. Blood 97:3411–3416, 2001.
136. Derchi G, Fonti A, Forni GL, et al: Pulmonary hypertension in patients with thalassemia major. Am Heart J 138(2 Pt 1):384, 1999.
137. Du ZD, Roguin N, Milgram E, et al: Pulmonary hypertension in patients with thalassemia major. Am Heart J 134:532–537, 1997.
138. Grisaru D, Rachmilewitz EA, Mosseri M, et al: Cardiopulmonary assessment in beta-thalassemia major. Chest 98:1138–1142, 1990.
139. Aessopos A, Farmakis D, Hatziliami A, et al: Cardiac status in well-treated patients with thalassemia major. Eur J Haematol 73:359–366, 2004.
140. Littera R, La Nasa G, Derchi G, et al: Long-term treatment with sildenafil in a thalassemic patient with pulmonary hypertension. Blood 100:1516–1517, 2002.
141. Prakash UB: Lungs in hemoglobinopathies, erythrocyte disorders, and hemorrhagic diatheses. Semin Respir Crit Care Med 26:527–540, 2005.
142. Darling R, Roughton F: The effect of methemoglobin on the equilibrium between oxygen and hemoglobin. Am J Physiol 137:56–68, 1942.
143. Jaffe ER, Neumann G: Hereditary methemoglobinemia, toxic methemoglobinemia and the reduction of methemoglobin. Ann N Y Acad Sci 151:795–806, 1968.
144. Abu-Laban RB, Zed PJ, Purssell RA, et al: Severe methemoglobinemia from topical anesthetic spray: Case report, discussion and qualitative systematic review. CJEM 3:51–56, 2001.

145. Rosen PJ, Johnson C, McGehee WG, et al: Failure of methylene blue treatment in toxic methemoglobinemia: Association with glucose-6-phosphate dehydrogenase deficiency. Ann Intern Med 75:83–86, 1971.
145a. Kao LW, Nanagas KA: Carbon monoxide poisoning. Med Clin North Am 89:1161–1194, 2005.
145b. Juurlink DN, Buckley NA, Stanbrook MB, et al: Hyperbaric oxygen for carbon monoxide poisoning. Cochrane Database Syst Rev 2005:CD002041.
145c. Weaver LK, Hopkins RO, Chan KJ, et al: Hyperbaric oxygen for acute carbon monoxide poisoning. N Engl J Med 347:1057–1067, 2002.
145d. Morocco AP: Cyanides. Crit Care Clin 21:691–705, vi, 2005.
146. Hildebrand FL Jr, Rosenow EC 3rd, Habermann TM, et al: Pulmonary complications of leukemia. Chest 98:1233–1239, 1990.
147. Marsh WL Jr, Bylund DJ, Heath VC, et al: Osteoarticular and pulmonary manifestations of acute leukemia: Case report and review of the literature. Cancer 57:385–390, 1986.
148. Rossi GA, Balbi B, Risso M, et al: Acute myelomonocytic leukemia: Demonstration of pulmonary involvement by bronchoalveolar lavage. Chest 87:259–260, 1985.
149. Klatte EC, Yardley J, Smith EB, et al: The pulmonary manifestations and complications of leukemia. Am J Roentgenol Radium Ther Nucl Med 89:598–609, 1963.
150. Takasugi JE, Godwin JD, Marglin SI, et al: Intrathoracic granulocytic sarcomas. J Thorac Imaging 11:223–230, 1996.
151. Hartweg H: [The roentgenogram of the thorax in chronic leukoses.] Fortschr Geb Rontgenstr Nuklearmed 92:477–490, 1960.
152. Potenza L, Luppi M, Morselli M, et al: Leukaemic pulmonary infiltrates in adult acute myeloid leukaemia: A high-resolution computerized tomography study. Br J Haematol 120:1058–1061, 2003.
153. Tanaka N, Matsumoto T, Miura G, et al: HRCT findings of chest complications in patients with leukemia. Eur Radiol 12:1512–1522, 2002.
154. Tanaka N, Matsumoto T, Miura G, et al: CT findings of leukemic pulmonary infiltration with pathologic correlation. Eur Radiol 12:166–174, 2002.
155. Vernant JP, Brun B, Mannoni P, et al: Respiratory distress of hyperleukocytic granulocytic leukemias. Cancer 44:264–268, 1979.
156. van Buchem MA, Wondergem JH, Kool LJ, et al: Pulmonary leukostasis: Radiologic-pathologic study. Radiology 165:739–741, 1987.
157. Tryka AF, Godleski JJ, Fanta CH: Leukemic cell lysis pneumonopathy: A complication of treated myeloblastic leukemia. Cancer 50:2763–2770, 1982.
157a. Coiffier B, Altman A, Pui CH, et al: Guidelines for the management of pediatric and adult tumor lysis syndrome: an evidence-based review. J Clin Oncol 26:2767–2778, 2008.
158. Kintzer JS Jr, Rosenow EC 3rd, Kyle RA: Thoracic and pulmonary abnormalities in multiple myeloma: A review of 958 cases. Arch Intern Med 138:727–730, 1978.
159. Badrinas F, Rodriguez-Roisin R, Rives A, et al: Multiple myeloma with pleural involvement. Am Rev Respir Dis 110:82–87, 1974.
160. Iwasaki T, Hamano T, Aizawa K, et al: A case of pulmonary amyloidosis associated with multiple myeloma successfully treated with dimethyl sulfoxide. Acta Haematol 91:91–94, 1994.
161. Joseph G, Pandit M, Korfhage L: Primary pulmonary plasmacytoma. Cancer 71:721–724, 1993.
162. Wiltshaw E: The natural history of extramedullary plasmacytoma and its relation to solitary myeloma of bone and myelomatosis. Medicine (Baltimore) 55:217–238, 1976.
163. Grandone E, Margaglione M, Colaizzo D, et al: Genetic susceptibility to pregnancy-related venous thromboembolism: Roles of factor V Leiden, prothrombin G20210A, and methylenetetrahydrofolate reductase C677T mutations. Am J Obstet Gynecol 179:1324–1328, 1998.
164. Mateo J, Oliver A, Borrell M, et al: Laboratory evaluation and clinical characteristics of 2,132 consecutive unselected patients with venous thromboembolism—results of the Spanish Multicentric Study on Thrombophilia (EMET-Study). Thromb Haemost 77:444–451, 1997.
165. Bauer KA: The thrombophilias: Well-defined risk factors with uncertain therapeutic implications. Ann Intern Med 135:367–373, 2001.
166. Moll S: Thrombophilias—practical implications and testing caveats. J Thromb Thrombolysis 21:7–15, 2006.
167. Perry SL, Ortel TL: Clinical and laboratory evaluation of thrombophilia. Clin Chest Med 24:153–170, 2003.
168. Baglin T, Luddington R, Brown K, et al: Incidence of recurrent venous thromboembolism in relation to clinical and thrombophilic risk factors: Prospective cohort study. Lancet 362:523–526, 2003.
169. Christiansen SC, Cannegieter SC, Koster T, et al: Thrombophilia, clinical factors, and recurrent venous thrombotic events. JAMA 293:2352–2361, 2005.
170. Ho WK, Hankey GJ, Quinlan DJ, et al: Risk of recurrent venous thromboembolism in patients with common thrombophilia: A systematic review. Arch Intern Med 166:729–736, 2006.
171. Whitlatch NL, Ortel TL: Thrombophilias: When should we test and how does it help? Semin Respir Crit Care Med 29:25–39, 2008.
172. Kearon C, Ginsberg JS, Kovacs MJ, et al: Comparison of low-intensity warfarin therapy with conventional-intensity warfarin therapy for long-term prevention of recurrent venous thromboembolism. N Engl J Med 349:631–639, 2003.
173. Ridker PM, Goldhaber SZ, Danielson E, et al: Long-term, low-intensity warfarin therapy for the prevention of recurrent venous thromboembolism. N Engl J Med 348:1425–1434, 2003.
174. Bogdan CJ, Strauss M, Ratnoff OD: Airway obstruction in hemophilia (factor VIII deficiency): A 28-year institutional review. Laryngoscope 104:789–794, 1994.
175. Goldman M, Webert KE, Arnold DM, et al: Proceedings of a consensus conference: Towards an understanding of TRALI. Transfus Med Rev 19:2–31, 2005.
176. Toy P, Popovsky MA, Abraham E, et al: Transfusion-related acute lung injury: Definition and review. Crit Care Med 33:721–726, 2005.
177. Popovsky MA, Moore SB: Diagnostic and pathogenetic considerations in transfusion-related acute lung injury. Transfusion 25: 573–577, 1985.
178. Silliman CC, Boshkov LK, Mehdizadehkashi Z, et al: Transfusion-related acute lung injury: Epidemiology and a prospective analysis of etiologic factors. Blood 101:454–462, 2003.
179. Finlay HE, Cassorla L, Feiner J, et al: Designing and testing a computer-based screening system for transfusion-related acute lung injury. Am J Clin Pathol 124:601–609, 2005.
180. Gajic O, Rana R, Winters JL, et al: Transfusion-related acute lung injury in the critically ill: Prospective nested case-control study. Am J Respir Crit Care Med 176:886–891, 2007.
181. Rana R, Fernandez-Perez ER, Khan SA, et al: Transfusion-related acute lung injury and pulmonary edema in critically ill patients: A retrospective study. Transfusion 46:1478–1483, 2006.
182. Popovsky MA, Haley NR: Further characterization of transfusion-related acute lung injury: Demographics, clinical and laboratory features, and morbidity. Immunohematology 16:157–159, 2000.
183. Silliman CC, Ambruso DR, Boshkov LK: Transfusion-related acute lung injury. Blood 105:2266–2273, 2005.
184. Silliman CC, McLaughlin NJ: Transfusion-related acute lung injury. Blood Rev 20:139–159, 2006.
185. Silliman CC, Paterson AJ, Dickey WO, et al: The association of biologically active lipids with the development of transfusion-related acute lung injury: A retrospective study. Transfusion 37:719–726, 1997.
186. Toy P, Gajic O: Transfusion-related acute lung injury. Anesth Analg 99:1623–1624, 2004.
187. Densmore TL, Goodnough LT, Ali S, et al: Prevalence of HLA sensitization in female apheresis donors. Transfusion 39:103–106, 1999.
188. Kopko PM, Popovsky MA, MacKenzie MR, et al: HLA class II antibodies in transfusion-related acute lung injury. Transfusion 41:1244–1248, 2001.
189. Kopko PM, Paglieroni TG, Popovsky MA, et al: TRALI: Correlation of antigen-antibody and monocyte activation in donor-recipient pairs. Transfusion 43:177–184, 2003.

190. Seeger W, Schneider U, Kreusler B, et al: Reproduction of transfusion-related acute lung injury in an ex vivo lung model. Blood 76:1438–1444, 1990.
191. Wallis JP: Transfusion-related acute lung injury (TRALI): Presentation, epidemiology and treatment. Intensive Care Med 33(Suppl 1):S12–S16, 2007.
192. Sachs UJ: Pathophysiology of TRALI: Current concepts. Intensive Care Med 33(Suppl 1):S3–S11, 2007.
193. Zallen G, Offner PJ, Moore EE, et al: Age of transfused blood is an independent risk factor for postinjury multiple organ failure. Am J Surg 178:570–572, 1999.
194. Khan SY, Kelher MR, Heal JM, et al: Soluble CD40 ligand accumulates in stored blood components, primes neutrophils through CD40, and is a potential cofactor in the development of transfusion-related acute lung injury. Blood 108:2455–2462, 2006.
195. Zhou L, Giacherio D, Cooling L, et al: Use of B-natriuretic peptide as a diagnostic marker in the differential diagnosis of transfusion-associated circulatory overload. Transfusion 45:1056–1063, 2005.
196. Win N, Montgomery J, Sage D, et al: Recurrent transfusion-related acute lung injury. Transfusion 41:1421–1425, 2001.

CHAPTER 85

Pulmonary Complications of Endocrine Diseases

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INTRODUCTION
DIABETES MELLITUS
THYROID DISORDERS
Hyperthyroidism
Hypothyroidism
PARATHYROID DISEASES
ADRENAL DISEASES
ACROMEGALY

INTRODUCTION

Common endocrine disorders may affect the respiratory system in a variety of ways, from an increased risk of specific infections in patients with diabetes to upper airway compression in patients with goiter. Many studies of pulmonary physiology have been done on patients with endocrine disorders, some of which have revealed clinically significant abnormalities. In other studies, however, physiologic abnormalities do not translate into clinical dysfunction, but they help add to our understanding of lung parenchymal growth and development, response to extrathoracic influences, and perhaps even aging. This chapter reviews the effects of various endocrine abnormalities on the pulmonary system.

DIABETES MELLITUS

Diabetes mellitus is the most common of all endocrine disorders, affecting 180 million people worldwide, and the prevalence is expected to rise to 366 million by 2030.[1] Because of the chronic metabolic derangements, many patients with diabetes develop cardiovascular and end-organ dysfunction. The effects of diabetes on the respiratory system are numerous (Table 85-1), but data are mixed with regard to the effect of diabetes on pulmonary function. Some studies have revealed lower than predicted vital capacity,[2,3] total lung capacity,[2] diffusion capacity for carbon monoxide,[2] maximal oxygen uptake,[2] and inspiratory muscle strength.[4] These mild functional abnormalities have been ascribed to premature aging of the lungs in a fashion similar to nonenzymatic protein glycosylation and microangiopathic changes that occur in many affected organs in patients with diabetes.[5] However, other studies showed no significant impairment in total lung capacity,[6-8] and none to only minor decreases in diffusion capacity for carbon monoxide,[6-8] vital capacity,[6,7] pulmonary distensibility,[6] or maximal inspiratory pressure.[9] Results of the Offspring Cohort of the Framington Heart Study[10] found that patients with diabetes had a lower forced vital capacity, with the greatest effect seen in current smokers. There did not seem to be an association between the diagnosis of diabetes and chronic obstructive pulmonary disease, nor did diabetes seem to accelerate chronic obstructive pulmonary disease in smokers. In summary, diabetes mellitus (in the absence of cystic fibrosis) may cause a mild decline in pulmonary function measurements, generally well within 80% of the reference value,[11] but does not appear to cause clinically significant pulmonary impairment, and routine pulmonary function testing in patients with diabetes is not warranted.

The presence of cystic fibrosis–related diabetes has been associated with a higher rate of decline of FEV_1 and forced vital capacity than in cystic fibrosis patients without diabetes.[12] Compared to patients with cystic fibrosis alone, patients with cystic fibrosis–related diabetes had a higher rate of airway colonization with *Pseudomonas,* which might contribute to the accelerated decline in lung function. However, a decline in lung function has been found even in the absence of airway colonization with *Pseudomonas* in females with cystic fibrosis–related diabetes.[13]

From 2006 to 2007, dry powder inhaled insulin was approved in the United States for nonsmoking adults

TABLE 85-1. Pulmonary Complications of Diabetes Mellitus

Pulmonary function abnormalities (typically minor decreases)
↓ Vital capacity
↓ Total lung capacity
↓ Diffusion capacity for carbon monoxide
↓ Carbon monoxide transfer factor
↓ Maximal oxygen uptake
↓ Inspiratory muscle strength
Left ventricular dysfunction
Pleural effusions
Obstructive sleep apnea
Infections
Poorer outcome with:
Community-acquired pneumonia
Legionella pneumonia
Increased risk of:
Aspiration pneumonia
Zygomycetes (mucormycosis) infection
Tuberculosis

with type 1 or type 2 diabetes and without pulmonary disease. Additional inhaled formulations are being developed and will likely be available in the near future. Inhaled insulin improves glycemic control when added to oral agents[14] (though it is not as efficacious as subcutaneous insulin), and has good patient acceptability.[15] The most common pulmonary side effect associated with inhaled insulin is a mild nonproductive cough occuring in 12% to 31%.[14,15] Patients who received inhaled insulin had no change in pulmonary function[14] or a very small decline in FEV_1 over the first weeks to months of therapy.[15,16] Active smoking increases the rate and extent of insulin absorption[17,18]; asthma and chronic obstructive pulmonary disease are associated with unpredictable delivery of the drug. Longer term data on pulmonary function are not yet available.

Cardiovascular factors appear to contribute more than pulmonary factors to impaired physical performance in patients with diabetes. In addition to the increased risk of cardiovascular events in patients with diabetes, there is an increased frequency of heart failure not explained by hypertension or coronary artery disease.[19] Left ventricular systolic and diastolic dysfunction with exercise appears to be more common in patients with insulin-dependent diabetes than in those without diabetes.[20] In addition, when compared with patients with similar degrees of left ventricular dysfunction, exercise limitation and pleural effusions are more common in patients with diabetes.[21] There have been reports of peripheral and pulmonary edema in heart failure patients with diabetes treated with the class of oral hypoglycemic drugs known as the thiazolidinediones[22,23]; the mechanism is likely multifactorial and appears to reverse upon withdrawal of the drug.

Acute respiratory distress syndrome (ARDS) has been reported as a complication of diabetic ketoacidosis.[24] Interestingly, in patients with septic shock, the presence of diabetes has been associated with a lower risk of developing ARDS compared to patients without diabetes, although without a difference in mortality.[25] Diabetes has also been associated with a higher risk of developing idiopathic pulmonary fibrosis.[26]

Newborn babies of diabetic mothers are at increased risk for macrosomia, preterm delivery, and neonatal respiratory distress syndrome[27,28]; infants born to mothers with poor self-care are at the greatest risk.[28] However, with good maternal metabolic control and accurate estimations of gestational age, most pregnant women with diabetes can deliver at or near term with a low rate of respiratory distress syndrome.[29]

Obesity is a risk factor both for type 2 diabetes mellitus and for obstructive sleep apnea. (See Chapter 79 for a full discussion of sleep apnea.) The prevalence of obstructive sleep apnea in patients with type 2 diabetes has been reported to be from 23% to 36%, ranging as high as 70% in patients with type 2 diabetes with a body mass index greater than 35 kg/m^2.[30,31] In addition, obstructive sleep apnea may impose a stress that increases sympathetic output during sleep, which in turn contributes to insulin resistance.[32] Animal models suggest that intermittent hypoxia increases insulin resistance.[33]

Patients with diabetes are at greater risk for some upper and lower airway infections. Patients with diabetes are particularly predisposed to infection with zygomycetes (mucormycosis), a group of infections caused by fungi in the *Mucor, Rhizopus,* and *Cunninghamella* genera. These ubiquitous, saprophytic fungi are found in soil and decaying vegetation. Infection typically occurs during or after an episode of diabetic ketoacidosis, perhaps because the fungi have an enzyme, ketone reductase, that allows them to grow best in an acidic, hyperglycemic environment. Most patients have some underlying predisposition, of which diabetes mellitus is the most important.[33] Five infectious manifestations have been described: rhinocerebral, pulmonary, disseminated, cutaneous, and gastrointestinal. Rhinocerebral infection is the most common form, especially in patients with diabetes. Presentation includes sudden periorbital or paranasal swelling and pain, bloody nasal discharge, and black necrotic nasal mucosa. Characteristic findings on computed tomography (CT) are helpful in suggesting the diagnosis.[34] Treatment requires control of the diabetes, antifungal therapy, and often aggressive surgical debridement. Mortality remains high, especially in patients with intracranial involvement. Pulmonary mucormycosis mimics invasive aspergillosis and occurs mostly in patients with hematologic malignancy, glucocorticoid or deferoxamine therapy, organ transplantation, and diabetes. Inhaled mold spores penetrate bronchiole walls, invade arterioles, and cause thrombosis and ischemia. Patients develop nonspecific cough, fever, and pleuritic chest pain. Hemoptysis occurs in one fourth of cases and can be massive.[35] The most common chest radiographic pattern is consolidation; cavitation occurs in about one third of patients,[36] and adenopathy and pleural effusions may also be present, but are less common. Patients with diabetes appear to have a predilection for endobronchial

disease; however, sputum culture appears to have a very low yield for diagnosis. For specimens obtained at bronchoscopy, histopathologic examination appears to be more sensitive than fungal cultures. Treatment requires antifungal therapy (see Chapter 36) and, if localized, surgical resection. Bronchial stenosis is a potential sequela.

Diabetes mellitus is an independent risk factor for tuberculosis,[37,38] both drug sensitive and multidrug resistant.[38] A recent review of 13 observational studies revealed that diabetes mellitus was associated with an increased risk of tuberculosis (relative risk = 3.11, 95% CI 2.27–4.26)[38a]; an association that was validated in a study of diabetic children in South Africa.[38b] Treatment of latent tuberculosis in patients with diabetes with a positive purified protein derivative test of greater than 10 mm of induration is currently recommended.[39] The radiographic location of tuberculosis in diabetes (i.e., upper or lower lobe predilection) depends on the case series; patients with diabetes and tuberculosis appear to have a higher rate of cavitation.[38,40]

Bacterial pneumonia may or may not be more frequent in patients with diabetes. In a study of over 4000 elderly inhabitants in one township, diabetes mellitus was not an independent risk factor for community-acquired pneumonia.[41] Moreover, diabetes does not appear to be an independent risk factor for either nosocomial pneumonia or ventilator-associated pneumonia.[42] Nonetheless, diabetes may be a risk factor for poorer outcome in those persons who develop pneumonia. In a meta-analysis, diabetes was found to be a risk factor for higher mortality in community-acquired pneumonia.[43] Diabetes also appears to be a risk for higher mortality and bacteremia in patients with pneumococcal pneumonia.[44] Given the high prevalence of and mortality from pneumococcal pneumonia, the demonstrated efficacy of pneumococcal vaccine, and the increasing prevalence of penicillin resistance in pneumococcal strains, pneumococcal vaccination is recommended for virtually all people with diabetes. Diabetes appears to be a risk factor for mortality for critically ill patients with *Legionella* pneumonia.[45] Diabetes may also predispose patients to aspiration pneumonia because of pharyngeal dysfunction and diabetic gastroparesis.[46] Diabetes is a risk factor for chronic oral infections of caries and periodontitis, which may contribute to the increased risk of aspiration pneumonia.[47] There is an increased incidence and mortality of bacterial pneumonia in patients with diabetes during seasonal influenza outbreaks.[48] Consistent with the recommendations of the Advisory Committee on Immunization Practices, influenza vaccination is recommended for patients with diabetes over the age of 6 months.[49] In terms of other viruses, mortality from severe acute respiratory syndrome may be higher in patients with preexisting diabetes.[50]

THYROID DISORDERS

The incidence of multinodular goiter is declining in the United States due the routine use of iodized salt; however, neglected goiters still occur. Because of the thyroid's ability to easily expand anteriorly, bound only by skin, thin muscle, and connective tissue, even large goiters may not cause tracheal impingement. However, some goiters can cause dyspnea, stridor, wheezing, hoarseness, and cough via tracheal deviation (typically if there is unilateral or unequal lobe enlargement) and airway compression.[51–53] Compression or concentric narrowing of the trachea is more common if the goiter extends posteriorly to the trachea (Fig. 85-1). Although goiters typically grow slowly, occasionally patients present with acute respiratory distress requiring urgent intubation or semi-urgent surgery. Some goiters are substernal or intrathoracic, defined as more than 50% of the thyroid below the thoracic inlet. Substernal goiters may cause orthopnea because of increased airflow limitation in the supine position. In these patients, flow-volume loops in

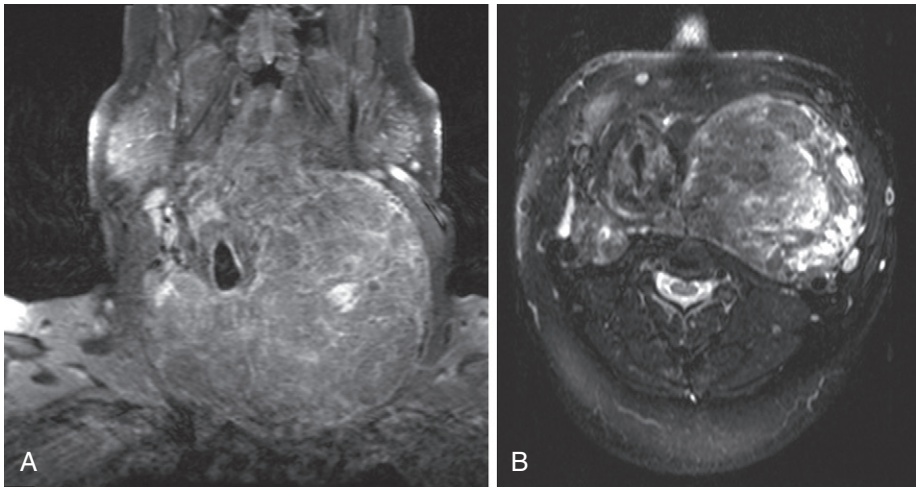

FIGURE 85-1 ■ A massive goiter was found in a 55-year-old man who presented with a change in his voice and increased shortness of breath. Endotracheal intubation required flexible bronchoscopy, followed by uneventful resection of a 900-g multinodular goiter. On coronal **(A)** and axial **(B)** gadolinium-enhanced magnetic resonance images of the neck, tracheal deviation and compression are apparent.

the recumbent position may illustrate upper airway obstruction not demonstrated in upright testing.[53] CT scanning and magnetic resonance imaging generally are the most useful diagnostic imaging studies. CT scanning with iodinated contrast media should generally be avoided because it precludes thyroid nuclear imaging for several weeks and can trigger hyperthyroidism. Surgical resection of substernal goiters is recommended and usually relieves compressive symptoms.[51,54] Postoperative tracheomalacia appears to be rare.[51] Iodine-131 is an alternative therapy for some patients with large goiters who are not surgical candidates because of comorbid illnesses.[55] For patients with baseline tracheal compression, there is often some temporary goiter enlargement from edema and additional airway compromise in the week following ^{131}I treatment. Despite this, with glucocorticoid prophylaxis, most patients do well, and have subsequent goiter shrinkage.[56] Alternatively, bronchoscopic insertion of tracheal stents can relieve large airway obstruction from compressive benign or malignant nonoperable thyroid disease.[57]

Hyperthyroidism

Many patients with hyperthyroidism complain of both resting and exertional dyspnea. Congestive heart failure likely explains some of these complaints,[58] and is the presenting feature in 6% of patients with newly diagnosed hyperthyroidism.[59] Some hyperthyroid patients have decreased vital capacity,[60] decreased respiratory muscle strength,[59–63] and an elevated resting minute ventilation (perhaps due to increased central ventilatory drive) that becomes excessive with exercise.[62] Anaerobic thresholds are typically lower than those of age-matched controls.[62] With treatment, vital capacity and respiratory muscle strength improve,[60,62] although some patients have persistent dyspnea.[61,62]

Patients with coincident asthma and thyrotoxicosis may have worsening of asthma control if β-blocker agents are used to control hyperthyroid manifestations. There may be an association between atopic disease, asthma, and Graves' disease.[64] Approximately 30% of patients with hyperthyroid Graves' disease have an elevation in serum immunoglobin E (IgE) levels, and those with elevated serum IgE are more likely to have a personal or family history of atopy.[65]

Several reports have suggested a link between hyperthyroidism, especially Graves' disease, and pulmonary hypertension in which the pulmonary artery pressures can improve and even normalize with treatment of the hyperthyroidism.[66–68] The explanation for this association is not clear, but may be due to a generalized autoimmune state, a direct influence of thyroid hormone on pulmonary vasculature, changes in metabolism of pulmonary vasculature vasodilators/vasoconstrictors, decreased surfactant production and function, or excess cardiovascular stimulation by the sympathoadrenal system. Interestingly, there may also be an increased prevalence of hypothyroidism in patients with primary pulmonary hypertension.[69] Rarely, mothers with hyperthyroidism from Graves' disease deliver infants with hyperthyroidism via placental passage of maternal thyrotropin receptor-stimulating antibodies. In addition to a variety of infant metabolic and developmental problems, neonatal Graves' disease has been associated with persistent pulmonary hypertension in newborns.[70]

There have been several reports of an increased presence of antinuclear cytoplasmic antibodies and even Wegener's granulomatosis in patients with Graves' disease treated with propylthiouracil.[71,72]

Hypothyroidism

Hypothyroidism has been associated with dyspnea on exertion, alveolar hypoventilation, respiratory failure, obstructive and central sleep apnea, and pleural effusions. Lung volumes are generally normal or mildly decreased in mixed populations of obese and nonobese hypothyroid patients.[73,74] Lung volumes typically, though not uniformly, improve with thyroid replacement and/or weight loss. A reduced diffusion capacity for carbon monoxide can be seen in some hypothyroid, nonobese patients with normal lung volumes and arterial blood gases that improves to near-normal after replacement therapy.[74] Hypothyroidism is associated with overall respiratory muscle weakness as measured by maximal inspiratory and expiratory pressures, and the degree of impairment is linearly related to the degree of pretreatment hypothyroidism.[75] Both obese and nonobese hypothyroid patients may develop diaphragmatic muscle weakness that can range from mild impairment, which limits exercise tolerance, to severe dysfunction, with marked resting dyspnea and chronic hypercarbia.[73] Thyroid replacement therapy can improve respiratory muscle strength. Some nonobese and obese hypothyroid patients have a markedly blunted ventilatory response to hypoxia and hypercapnia,[74,76] which improves often within weeks of initiation of thyroid hormone replacement. This improvement is not associated with changes in spirometric function or maximal voluntary ventilation, thus suggesting a central cause for the abnormal ventilatory response. Respiratory failure from hypothyroidism can occur and may require prolonged mechanical ventilation.[76]

Although up to 25% of patients with hypothyroidism have radiographic evidence of a pleural effusion, most patients also have underlying congestive heart failure (Table 85-2).[77] A small percentage of hypothyroid patients do not have another disease process that would explain the effusion. In these patients, the hypothyroid-related effusions tend to be small, less than one third of the chest cavity; unilateral or bilateral; serous or serosanguineous; and transudates or exudates, although generally noninflammatory.[77] Hypothyroid-related effusions typically resolve with treatment of the hypothyroidism.[77]

Hypothyroidism can predispose patients to sleep apnea,[78–80] possibly from narrowing of the upper airway from mucopolysaccharide and protein deposition in the tongue and oropharynx,[81] from abnormalities in ventilatory control, or from weight gain. In a case series, only 3.1% of patients with obstructive sleep apnea were found to have hypothyroidism[80]; however, 25% of newly diagnosed hypothyroid patients were found to have obstructive sleep apnea. Hypothyroid patients with

TABLE 85-2. Etiologies of Pleural Effusions in Hypothyroid Patients (n = 28)

Etiology	No.
Non–hypothyroid-associated pleural effusions	22
Pneumonia	7
Congestive heart failure	7
Malignancy	4
Atelectasis	2
Pancreatitis	1
Cirrhosis with ascites	1
Hypothyroid pleural effusion	5
Hypothyroid-associated effusion due to pericardial involvement	1

Modified from Gottehrer A, Roa J, Stanford GG, et al: Hypothyroidism and pleural effusions. Chest 98:1130–1132, 1990.

FIGURE 85-2 ■ Metastatic calcification occurring in the lungs because of chronic renal failure. A 59-year-old man with end-stage renal disease for 5 years complained of chronic progressive shortness of breath. The serum calcium level was 9.9 mg/dL (normal range, 8.5 to 10.5 mg/dL) and the parathyroid hormone level was 271 pg/mL (normal for the laboratory, 11 to 54 pg/mL). High-resolution computed tomography revealed numerous nodular ground-glass densities in a peribronchial pattern, most prominently in the upper lobes. (Courtesy of Marcia McCowin, MD.)

obstructive sleep apnea have blunted ventilatory responses to hypoxia and hypercapnia; age and body weight were the best predictors of associated obstructive sleep apnea.[80] Some studies have shown improvement in sleep respiratory disturbance index and awake ventilatory response to hypoxia and hypercapnia with thyroid replacement[80,82]; in other studies, however, investigators found less than full improvement or no improvement in sleep apnea with thyroid replacement.[78,83] Central sleep apnea can also occur in hypothyroid patients, and the blunted ventilatory response to hypoxia may improve with thyroid replacement.[78]

Thyroid hormones play an important role in the growth and development of the lung and in the maturation of the lung's surfactant system.[84,85] Transient hypothyroxinemia is common in premature infants, as is respiratory distress syndrome. However, the administration of maternal antenatal thyrotropin-releasing hormone, which increases fetal thyroid hormone levels, did not decrease the frequency or severity of respiratory distress syndrome in premature babies in a large multicenter trial.[86] Treatment of premature infants with thyroxine also did not decrease the incidence of respiratory distress syndrome, the use of surfactant therapy, or the overall developmental outcome at 24 months.[87]

PARATHYROID DISEASES

Hyperparathyroidism, typically secondary hyperparathyroidism in patients with end-stage renal disease, can cause diffuse metastatic calcification in the lungs. Metastatic calcification is the deposition of calcium salts in previously normal tissue; in contrast, dystrophic calcification is the calcification of diseased or abnormal tissue, as in granulomatous processes. Despite dietary phosphate restriction, administration of phosphate binders, and hemodialysis, renal failure patients are at risk for metastatic calcification, especially if the calcium-phosphorus product increases above 70 mg^2/dL^2. Pulmonary metastatic calcific nodules occur predominantly in the alveolar septa and are associated with varying degrees of fibrosis and septal thickening. This phenomenon appears to be quite common; from 60% to 80% of chronic dialysis patients have autopsy or scintigraphic evidence of pulmonary metastatic calcification.[88] Metastatic calcification can also rarely occur in primary hyperparathyroidism.[89] Most patients with end-stage renal disease and metastatic pulmonary calcification are asymptomatic and have normal chest radiographs and pulmonary function; patients with heavy deposition of calcific nodules, however, may complain of dyspnea and nonproductive cough. Pulmonary function tests in patients with extensive metastatic calcification may show ventilatory restriction with hypoxemia and low diffusion capacity for carbon monoxide.[90]

Calcium salts tend to precipitate in alkaline conditions. Indeed, metastatic calcification has a predilection for the apical portions of the lungs, the stomach, and the kidneys—all tissues with a relative alkalinity, because of either carbon dioxide removal or hydrogen ion excretion. Due to the higher ventilation-perfusion ratio and lower carbon dioxide concentration at the lung apex, it is estimated that the pH at the apex is 7.5 compared to a pH of 7.3 at the base.[90,91] Other common sites of deposition include soft tissues and the skin. Radiographically, patients with more extensive calcification typically have numerous nodules about 3 to 10 mm in size, better visualized on CT scans than on plain chest radiographs (Fig. 85-2).[92] In addition to the nodular densities, patchy consolidation and ground-glass attenuation may be seen. The calcific nature of the nodules may not be apparent on plain radiographic or even CT images, perhaps due to the small size of the calcium deposits. However, radionuclide bone scans usually reveal intense uptake in the lungs and other affected organs (Fig. 85-3).[88] Parathyroid-

FIGURE 85-3 ■ Metastatic calcification in the lungs caused by chronic renal failure. This is the same patient as in Figure 85-2. Whole-body bone imaging with technetium-99m-diphosphonate revealed diffuse soft-tissue avidity in both lungs.

ectomy or treatment with vitamin D analogues can decrease the calcium-phosphorus double product, reverse bone scan abnormalities and organ deposition, and presumably improve pulmonary function. Hyperparathyroidism is also associated with calcification in pulmonary arterial and bronchial walls. Of note, about one third of patients with end-stage renal disease on long-term hemodialysis via arteriovenous access have pulmonary hypertension,[93,94] but pulmonary hypertension does not seem to correlate with the presence or severity of pulmonary artery calcification[93,95] or parathyroid hormone levels.[96]

Rarely, enlarged mediastinal parathyroid cysts can cause tracheal compression with stridor or vocal cord impingement and hoarseness, or both. Surgical excision is the treatment of choice.[96]

Hyperparathyroidism is frequently associated with muscle weakness and fatigue. Respiratory muscle function can be affected as well, and postparathyroidectomy improvement in forced vital capacity and FEV_1 values correlates with preoperative serum calcium and preoperative parathyroid hormone values.[97]

ADRENAL DISEASES

Endogenous Cushing's syndrome (i.e., not from glucocorticoid administration) may be caused by pituitary Cushing's disease, by adrenal neoplasia, or by ectopic adrenocorticotropic hormone production from small cell lung cancer or from carcinoids arising from a variety of organs, especially the lung, including the variation of pulmonary carcinoid tumorlets, gastrinoma, pheochromocytoma, or islet cell carcinoma of the pancreas.[98,99,99a] Cortisol levels tend to be much higher with ectopic adrenocorticotropic hormone production and adrenal neoplasia than with pituitary Cushing's disease, and pose a greater risk for infection. Hypercortisolism particularly predisposes patients to mucocutaneous fungal infections and opportunistic pulmonary infections. The most common pulmonary infections are caused by *Cryptococcus, Aspergillus, Nocardia, Pneumocystis,* and *Mycobacterium tuberculosis.*[100-103] *Pneumocystis jirovecii* pneumonia tends to occur in patients with the highest morning cortisol levels.[103] Correction of hypercortisolism is an important adjunct to antimicrobial therapy. Cushing's syndrome is also associated with a hypercoagulable state and fourfold increase in thromboembolic disease.[104,105] The risk may be due to an increase in various coagulation factors.[104] Even in patients without baseline hypercortisolism, cortisol levels increase in stress and extremely elevated cortisol levels at presentation appear to be independent predictors of worse outcome in community-acquired pneumonia.[106,107]

Adrenal insufficiency may be due to either primary adrenal failure (Addison's disease) or secondary adrenal insufficiency. Secondary adrenal insufficiency is most commonly iatrogenic as a result of the withdrawal of exogenous glucocorticoid therapy, or results directly from disease of the hypothalamic-pituitary axis. In industrialized countries, 70% to 80% of cases of Addison's disease are autoimmune in origin; in contrast, in resource-poor countries, tuberculosis remains the most common cause.[108,109] CT scanning can be somewhat helpful in determining the cause of Addison's disease, because tuberculosis and histoplasmosis may cause adrenal calcification.[110] Adrenal insufficiency via the hypothalamic-pituitary axis may be seen in stressed, very-low-birth-weight infants and may render them more susceptible to bronchopulmonary dysplasia.[111]

ACROMEGALY

Acromegaly is a disorder of excess growth hormone secretion in adults, most commonly from a benign pituitary adenoma. Rarely, bronchial carcinoid or small cell lung cancer can produce excess growth hormone–releasing factor, which stimulates excess growth hormone secretion. Clinically, acromegaly is characterized by excessive bone growth, soft-tissue hypertrophy, and coarsening of facial features. These changes appear to be due to high levels of growth hormone and insulin-like growth factor-1, which is secreted in response to growth hormone; the net effect is an increase in somatic growth and metabolic disturbances. Mortality in acromegaly is increased primarily from cardiovascular disease.[112,113]

Patients with acromegaly can develop macroglossia, nasal polyps, oropharyngeal airway narrowing, and vocal cord restriction and edema. In addition, coincidental goiter is not uncommon and can contribute to upper airway narrowing.[112,114] Respiratory manifestations of

acromegaly include sleep apnea, extrathoracic airway obstruction, vocal cord dysfunction, and difficult intubation.[112,114] The prevalence of sleep apnea has been reported as between 20% and 60%.[115,116] Increased rates of obstructive sleep apnea may be due to a narrowed upper airway from osseous enlargement, hypertrophy of tissues in the oropharynx, inspiratory collapse of the hypopharynx, and macroglossia. The circumference of the neck and fingers, but not body mass index, are predictive of the development of sleep apnea in acromegaly.[116] Obstructive sleep apnea may improve with treatment of acromegaly with pituitary ablation[117] or with octreotide, a somatostatin analogue.[115,118] Persistence of obstructive sleep apnea after treatment may be due to irreversible upper airway remodeling. Central sleep apnea is also common. Patients with central sleep apneas and acromegaly have higher growth hormone and insulin-like growth factor-1 levels and higher ventilatory responses to carbon dioxide than acromegalic patients with obstructive sleep apnea.[119] Central sleep apnea in these patients may therefore be due to altered ventilatory control.

Total lung capacity and vital capacity are typically increased in patients with acromegaly compared with controls,[120–125] and appear to correlate with the duration of acromegaly.[122] Possible causes for the increased lung volumes in these patients include hypertrophy or enlargement of individual alveoli, or an increase in the number of alveoli.[120,123,124] Diffusion capacity for carbon monoxide may be within normal limits[120,123] or elevated.[121] Changes in vertebrae and rib morphology contribute to the barrel chest of patients with acromegaly. In addition, with acromegaly, there is a decrease in respiratory muscle force that may contribute to increased dyspnea and fatigue with exercise.[125]

Evidence of a variable extrathoracic airway obstruction on flow-volume loops in seen in 30% to 50% of patients with acromegaly.[122] As noted, intubation may be more difficult in patients with acromegaly because of vocal cord fixation, vocal cord edema, prolapse of an enlarged tongue, and soft-tissue thickening of the oropharynx.[126] Preoperative treatment of patients with somatostatin analogues may decrease soft-tissue swelling and enable easier intubation.[118]

KEY POINTS

- Diabetes mellitus, by far the most common endocrine disorder, is associated with sleep apnea and predisposes to certain fungal and mycobacterial respiratory infections; although the incidence of other bacterial and viral infection is not increased, when they occur in diabetics, mortality is elevated.
- Patients with diabetes should receive pneumococcal and influenza vaccinations.
- Thyroid enlargement may cause upper airway compression; in addition, partly reversible decreases in vital capacity and respiratory muscle strength worsen dyspnea in patients with hyperthyroidism; more commonly, patients with hypothyroidism suffer from dyspnea, alveolar hypoventilation, pleural effusion(s), and, sometimes, respiratory failure.
- Secondary hyperparathyroidism from end-stage renal disease often causes diffuse metastatic pulmonary calcification.
- Endogenous Cushing's syndrome predisposes to a variety of opportunistic infections, whereas acromegaly from excess growth hormone is associated with a high prevalence of sleep apnea, and may lead to upper airway structural disorders.

References

1. World Health Organization: Diabetes Fact Sheet No. 312, 2006. Available at http://www.who.int/mediacntre/fact sheets/fs312/en/index.html.
2. Niranjan V, McBrayer DG, Ramirez LC, et al: Glycemic control and cardiopulmonary function in patients with insulin-dependent diabetes mellitus. Am J Med 103:504–513, 1997.
3. Yeh HC, Duncan BB, Punjabi NM, et al: Cross-sectional and prospective study of lung function in adults with type 2 diabetes. Diabetes Care 31:741–746, 2008.
4. Wanke T, Formanek D, Auinger M, et al: Inspiratory muscle performance and pulmonary function changes in insulin-dependent diabetes mellitus. Am Rev Respir Dis 143:97–100, 1991.
5. Sandler M: Is the lung a "target organ" in diabetes mellitus? Arch Intern Med 150:1385–1388, 1990.
6. Maccioni FJ, Colebatch HJH: Lung volume and distensibility in insulin-dependent diabetes mellitus. Am Rev Respir Dis 143:1253–1256, 1991.
7. Fuso L, Cotroneo P, Basso S, et al: Postural variations of pulmonary diffusing capacity in insulin-dependent diabetes mellitus. Chest 110:1009–1013, 1996.
8. Benbasssat CA, Stern E, Kramer M, et al: Pulmonary function in patients with diabetes mellitus. Am J Med Sci 322:127–132, 2001.
9. Enright PL, Kronmal RA, Manolio TA, et al: Respiratory muscle strength in the elderly. Am J Respir Crit Care Med 149:430–438, 1994.
10. Walter RE, Beiser A, Givelber RJ, et al: Association between glycemic state and lung function: The Framingham Heart Study. Am J Respir Crit Care Med 167:911–916, 2003.
11. Hsia CCW, Raskin P: Lung involvement in diabetes: Does it matter? Diabetes Care 31:828–829, 2008.

12. Milla CE, Warwick WJ, Moran A: Trends in pulmonary function in patients with cystic fibrosis correlate with the degree of glucose intolerance at baseline. Am J Respir Crit Care Med 162:891–895, 2000.
13. Sims EJ, Green MW, Mehta A: Decreased lung function in female but not male subjects with established cystic fibrosis-related diabetes. Diabetes Care 28:1581–1587, 2005.
14. Rosenstock J, Zinman B, Murphy LJ, et al: Inhaled insulin improves glycemic control when substituted for or added to oral combination therapy in type 2 diabetes. Ann Intern Med 143:549–558, 2005.
15. Ceglia L, Lau J, Pittas AG: Meta-analysis: Efficacy and safety of inhaled insulin therapy in adults with diabetes mellitus. Ann Intern Med 145:665–675, 2006.
16. Teeter JG, Riese RJ: Dissociation of lung function changes with humoral immunity during inhaled insulin therapy. Am J Respir Crit Care Med 173:1194–1200, 2006.
17. Becker RH, Sha S, Frick AD, Fountaine RJ: The effect of smoking cessation and subsequent resumption on absorption of inhaled insulin. Diabetes Care 29:277–282, 2006.
18. Himmelmann A, Jendle J, Mellen A, et al: The impact of smoking on inhaled insulin. Diabetes Care 26:677–682, 2003.
19. MacDonald MR, Petrie MC, Hawkins NM, et al: Diabetes, left ventricular systolic dysfunction, and chronic heart failure. Eur Heart J 29:1224–1240, 2008.
20. Jermendy G, Khoor S, Koltai MZ, et al: Left ventricular diastolic dysfunction in type 1 (insulin dependent) diabetic patients during exercise. Cardiology 77:9–16, 1990.
21. Guazzi M, Brambilla R, Pontone G, et al: Effect of non-insulin-dependent diabetes mellitus on pulmonary function and exercise tolerance in chronic congestive heart failure. Am J Cardiol 89:191–197, 2002.
22. Tang WHW, Francis GS, Hoogwerf BJ, Young JB: Fluid retention after initiation of thiazolidinedione therapy in diabetic patients with established chronic heart failure. J Am Coll Cardiol 41:1394–1398, 2003.
23. Nesto RW, Bell D, Bonow RO, et al: Thiazolidinedione use, fluid retention, and congestive heart failure: A consensus statement from the American Heart Association and American Diabetes Association. Circulation 108:2941–2948, 2003.
24. Russel J, Follansbee S, Matthay MA: Adult respiratory distress syndrome complicating diabetic ketoacidosis. West J Med 135: 148–150, 1981.
25. Moss M, Guidot DM, Steinberg KP, et al: Diabetic patients have a decreased incidence of acute respiratory distress syndrome. Crit Care Med 28:2187–2192, 2000.
26. Enomoto T, Usuki J, Azuma A, et al: Diabetes mellitus may increase risk for idiopathic pulmonary fibrosis. Chest 123:2007–2011, 2003.
27. HAPO Study Cooperative Research Group: Hyperglycemia and adverse pregnancy outcomes. N Engl J Med 358:1991–2002, 2008.
28. Jensen DM, Damm P, Moelsted-Pedersen L, et al: Outcomes in type 1 diabetic pregnancies. Diabetes Care 27:2819–2823, 2004.
29. Tanasijevic MJ, Winkelman JW, Wybenga DR, et al: Prediction of fetal lung maturity in infants of diabetic mothers using the FLM S/A and desaturated phosphatidylcholine tests. Am J Clin Pathol 105:17–22, 1996.
30. West SD, Nicoll DJ, Stradling JR: Prevalence of obstructive sleep apnoea in men with type 2 diabetes. Thorax 61:945–950, 2006.
31. Einhorn D, Stewart DA, Erman MK et al: Prevalence of sleep apnea in a population of adults with type 2 diabetes mellitus. Endocr Pract 13:355–362, 2007.
32. Ip MSM, Ng MMT, Lam WK, et al: Obstructive sleep apnea is independently associated with insulin resistance. Am J Respir Crit Care Med 165:670–676, 2002.
33. Iiyori N, Alonso LC, Li J, et al: Intermittent hypoxia causes insulin resistance in lean mice independent of autonomic activity. Am J Respir Crit Care Med 175:851–857, 2007.
34. Roden MM, Zaoutis TE, Buchanan WL, et al: Epidemiology and outcome of zygomycosis: A review of 929 reported cases. Clin Infect Dis 41:634, 2005.
35. Kim KH, Choi YW, Jeon SC, et al: Mucormycosis of the central airway: CT findings in three patients. J Thorac Imaging 14:210–214, 1999.
36. McAdams HP, Rosado de Christenson M, Strollo DC, Patz EF Jr: Pulmonary mucormycosis: Radiographic findings in 32 cases. AJR Am J Roentgenol 186:1541–1548, 1997.
37. Pablos-Mendez A, Blustein J, Knirsch CA: The role of diabetes mellitus in the higher prevalence of tuberculosis among Hispanics. Am J Public Health 87:574–579, 1997.
38. Bashar M, Alcabes P, Rom WN, Condos R: Increased incidence of multidrug-resistant tuberculosis in diabetic patients on the Bellevue Chest Service, 1987–1997. Chest 129:1514–1519, 2001.
38a. Jeon CY, Murray MB: Diabetes mellitus increases the risk of active tuberculosis: a systematic review of 13 observational studies. PloS Med 5:1091–1101, 2008.
38b. Webb EA, Hesseling AC, Schaaf HS, et al: High prevalence of *Mycobacterium tuberculosis* infection and disease in children and adolescents with type 1 diabetes mellitus. Int J Tuberc Lung Dis 13:868–874, 2009.
39. Jasmer RM, Nahid P, Hopewell PC: Clinical practice: Latent tuberculosis infection. N Engl J Med 347:1860–1866, 2002.
40. Perez-Guzman C, Torres-Cruz A, Villareal-Velarde H, Vargas MH: Progressive age-related changes in pulmonary tuberculosis images and the effect of diabetes. Am J Respir Crit Care Med 162:1738–1740, 2000.
41. Koivula I, Sten M, Makela PH: Risk factors for pneumonia in the elderly. Am J Med 96:313–320, 1994.
42. Vardakas KZ, Siempos II, Falagas ME: Diabetes mellitus as a risk factor for nosocomial pneumonia and associated mortality. Diabet Med 24:1168–1171, 2007.
43. Fine MJ, Smith MA, Carson CA, et al: Prognosis and outcomes of patients with community-acquired pneumonia: A meta-analysis. JAMA 274:134–141, 1995.
44. Marrie TJ: Bacteraemic pneumococcal pneumonia: A continuously evolving disease. J Infect 24:247–255, 1992.
45. El-Ebiary M, Sarmiento X, Torres A, et al: Prognostic factors of severe *Legionella* pneumonia requiring admission to ICU. Am J Respir Crit Care Med 156:1467–1472, 1997.
46. Harrington OB, Duckworth JK, Starnes CL, et al: Silent aspiration after coronary artery bypass grafting. Ann Thorac Surg 65:1599–1603, 1998.
47. Taylor GW, Loesche WJ, Terpenning MS: Impact of oral diseases on systemic health in the elderly: Diabetes mellitus and aspiration pneumonia. J Public Health Dent 60:313–320, 2000.
48. Koziel H, Koziel MJ: Pulmonary complications of diabetes mellitus: Pneumonia. Infect Dis Clin North Am 9:65–96, 1995.
49. American Diabetes Association: Immunization and the prevention of influenza and pneumococcal disease in patients with diabetes. Diabetes Care 26:S126–S128, 2003.
50. Booth CM, Matukas LM, Tomlinson GA, et al: Clinical features and short-term outcomes of 144 patients with SARS in the greater Toronto area. JAMA 289:2801–2809, 2003.
51. McHenry CR, Piorowski JJ: Thyroidectomy in patients with marked thyroid enlargement: Airway management, morbidity, and outcome. Am Surg 60:586–591, 1994.
52. Torchio R, Gulotta C, Perboni A, et al: Orthopnea and tidal expiratory flow limitation in patients with euthyroid goiter. Chest 124:133–140, 2003.
53. Meysman M, Noppen M, Vincken W: Effect of posture on the flow-volume loop in two patients with euthyroid goiter. Chest 110:1615–1618, 1996.
54. Shen WT, Kebebew E, Duh QY, Clark OH: Predictors of airway complications after thyroidectomy for substernal goiter. Arch Surg 139:656–659, 2004.
55. Huysmans D, Hermus A, Corstens F, et al: Large, compressive goiters treated with radioiodine. Ann Intern Med 121:757–762, 1994.
56. Bonnema SJ, Bertelsen H, Mortensen J, et al: The feasibility of high dose iodine 131 treatment as an alternative to surgery in patients with a very large goiter: Effect on thyroid function and size and pulmonary function. J Clin Endocrinol Metab 84:3636–3641, 1999.
57. Noppen M, Poppe K, D'Haese J, et al: Interventional bronchoscopy for treatment of tracheal obstruction secondary to benign or malignant thyroid disease. Chest 125;723–730, 2004.

58. Forfar JC, Muir AL, Sawers SA, et al: Abnormal left ventricular function in hyperthyroidism: Evidence for a possible reversible cardiomyopathy. N Engl J Med 307:1165–1170, 1982.
59. Siu CW, Yeung CY, Lau CP, et al: Incidence, clinical characteristics and outcome of congestive heart failure as the initial presentation in patients with primary hyperthyroidism. Heart 93: 483–487, 2007.
60. Mier A, Brophy C, Wass JAH, et al: Reversible respiratory muscle weakness in hyperthyroidism. Am Rev Respir Dis 139:529–533, 1989.
61. McElvaney GN, Wilcox PG, Fairbarn MS, et al: Respiratory muscle weakness and dyspnea in thyrotoxic patients. Am Rev Respir Dis 141:1221–1227, 1990.
62. Kendrick AH, O'Reilly JF, Laszlo G: Lung function and exercise performance in hyperthyroidism before and after treatment. Q J Med 68:615–627, 1988.
63. Goswami R, Guleria R, Gupta AK, et al: Prevalence of diaphragmatic muscle weakness and dyspnoea in Graves' disease and their reversibility with carbimazole therapy. Eur J Endocrinol 147:299–303, 2002.
64. Sato A, Takemura Y, Yamada T, et al: A possible role of immunoglobulin E in patients with hyperthyroid Graves' disease. J Clin Endocrinol Metab 84:3602–3605, 1999.
65. Yamada T, Sato A, Komiya I, et al: An elevation of serum immunoglobulin E provides a new aspect of hyperthyroid Graves' disease. J Clin Endocrinol Metab 85:2775–2778, 2000.
66. Chu JW, Kao PN, Faul JL, Doyle RL: High prevalence of autoimmune thyroid disease in pulmonary arterial hypertension. Chest 122:1668–1673, 2002.
67. Marvsis M, Brianti M, Marani G, et al: Hyperthyroidism and pulmonary hypertension. Respir Med 96:215–220, 2002.
68. Ismail HM: Reversible pulmonary hypertension and isolated right-sided heart failure associated with hyperthyroidism. J Gen Intern Med 22:148–150, 2007.
69. Curnock AL, Dweik RA, Higgins BH, et al: High prevalence of hypothyroidism in patients with primary pulmonary hypertension. Am J Med Sci 318:289–292, 1999.
70. Oden J, Cheifetz IM: Neonatal thyrotoxicosis and persistent pulmonary hypertension necessitating extracorpeal life support. Pediatrics 115:e105–e108, 2005.
71. Pillinger M, Staud R: Wegener's granulomatosis in a patient receiving propylthiouracil for Graves' disease. Semin Arthritis Rheum 28:124–129, 1998.
72. Wada N, Mukai M, Kohno M, et al: Prevalence of serum anti-myeloperoxidase antineutrophil cytoplasmic antibodies (MPO-ANCA) in patients with Graves' disease treated with propylthiouracil and thiamazole. Endocr J 49:329–334, 2002.
73. Martinez FJ, Bermudez-Gomez M, Celli BR: Hypothyroidism: A reversible cause of diaphragmatic dysfunction. Chest 96:1059–1063, 1989.
74. Wilson WR, Bedell GN: The pulmonary abnormalities in myxedema. J Clin Invest 39:42–55, 1960.
75. Siafakas NM, Salesiotou V, Filaditaki V, et al: Respiratory muscle strength in hypothyroidism. Chest 102;189–194, 1992.
76. Behnia M, Clay AS, Farber MO: Management of myxedematous respiratory failure: Review of ventilation and weaning principles. Am J Med Sci 320:368–373, 2000.
77. Gottehrer A, Roa J, Stanford GG, et al: Hypothyroidism and pleural effusions. Chest 98:1130–1132, 1990.
78. Millman RP, Bevilacqua J, Peterson DD, Pack AI: Central sleep apnea in hypothyroidism. Am Rev Respir Dis 127:504–507, 1983.
79. Grunstein RR, Sullivan CE: Sleep apnea and hypothyroidism: Mechanisms and management. Am J Med 85:775–779, 1988.
80. Lin CC, Tsan KW, Chen PJ: The relationship between sleep apnea syndrome and hypothyroidism. Chest 102:1663–1667, 1992.
81. Orr WC, Males JL, Imes NK: Myxedema and obstructive sleep apnea. Am J Med 70:1061–1066, 1981.
82. Jha A, Sharma SK, Tandon N, et al: Thyroxine replacement therapy reverses sleep-disordered breathing in patients with primary hypothyroidism. Sleep Med 7:55–61, 2006.
83. Misiolek M, Marek B, Namyslowski G, et al: Sleep apnea syndrome and snoring in patients with hypothyroidism with relation to overweight. J Physiol Pharmacol 58:77–85, 2007.
84. Ballard PL, Hovey ML, Gonzales LK: Thyroid hormone stimulation of phosphatidylcholine synthesis in cultured fetal rabbit lung. J Clin Invest 74:898–905, 1984.
85. Gonzales LW, Ballard PL, Ertsey R, et al: Glucocorticoids and thyroid hormones stimulate biochemical and morphological differentiation of human fetal lung in organ culture. J Clin Endocrinol Metab 62:678–691, 1986.
86. Collaborative Santiago Surfactant Group: Collaborative trial of prenatal thyrotropin-releasing hormone and corticosteroids for prevention of respiratory distress syndrome. Am J Obstet Gynecol 178:33–39, 1998.
87. Van Wassenaer AG, Kok JH, de Vijlder JJM, et al: Effects of thyroxine supplementation on neurological development in infants born at less than 30 weeks' gestation. N Engl J Med 336:21–26, 1997.
88. Eggert CH, Albright RC: Metastatic pulmonary calcification in a dialysis patient: Case report and a review. Hemodial Int 10(Suppl 2):S51–S55, 2006.
89. Poddar B, Bharti S, Parmar VR, et al: Respiratory failure due to pulmonary calcification in primary hyperparathyroidism. Arch Dis Child 87:257, 2002.
90. Murris-Espin M, Lacassagne L, Didier A, et al: Metastatic pulmonary calcification after renal transplantation. Eur Respir J 10:1925–1927, 1997.
91. Chan ED, Morales DV, Welsh CH, et al: Calcium deposition with or without bone formation in the lung. Am J Respir Crit Care Med 1165:1654–1669, 2002.
92. Hartman TE, Muller NL, Primack SL, et al: Metastatic pulmonary calcification in patients with hypercalcemia: Findings on chest radiographs and CT scans. AJR Am J Roentgenol 162:799–802, 1994.
93. Amin M, Fawzy A, Hamid MA, Elhendy A: Pulmonary hypertension in patients with chronic renal failure. Chest 124:2093–2097, 2003.
94. Yigla M, Nakhoul F, Sabag A, et al: Pulmonary hypertension in patients with end-stage renal disease. Chest 123:1577–1582, 2003.
95. Yigla M, Keidar Z, Safadi I, et al: Pulmonary calcification in hemodialysis patients: Correlation with pulmonary artery pressure values. Kidney Int 66:806–810, 2004.
96. Landau O, Chamberlain DW, Kennedy RS, et al: Mediastinal parathyroid cysts. Ann Thorac Surg 63:951–953, 1997.
97. Giles Y, Baspinar I, Tunca F, et al: Impact of surgical treatment on respiratory muscle dysfunction on symptomatic hyperparathyroidism. Arch Surg 140:1167–1171, 2005.
98. Ilias I, Torpy DJ, Pacak K, et al: Cushing's syndrome due to ectopic corticotropin secretion: Twenty years' experience at the National Institutes of Health. J Clin Endocrinol Metab 90:4955–4962, 2005.
99. Povedano ST, Pastor CV, Seoane CP, et al: Ectopic ACTH syndrome caused by pulmonary carcinoid tumourlets. Clin Endocrinol (Oxf) 54:839–842, 2001.
99a. Falhammar H: Cyclic ectopic Cushing's syndrome and somatostatin analogue treatment. N Z Med J 122:92–95, 2009.
100. Drew PA, Takezawa K: Pulmonary cryptococcosis and pituitary Cushing's disease. Diagn Cytopathol 18:365–367, 1998.
101. Anthony LB, Greco FA: *Pneumocystis carinii* pneumonia: A complication of Cushing's syndrome. Ann Intern Med 94:488–489, 1981.
102. Hill AT, Stewart PM, Hughes EA, et al: Cushing's disease and tuberculosis. Respir Med 92:604–606, 1998.
103. Graham BS, Tucker WS: Opportunistic infections in endogenous Cushing's syndrome. Ann Intern Med 101:334–338, 1984.
104. Jacoby RC, Owings JT, Ortega T, et al: Biochemical basis for the hypercoagulable state seen in Cushing syndrome. Arch Surg 136:1003–1007, 2001.
105 Small M, Lowe GD, Forbes CD, Thomson JA: Thromboembolic complications in Cushing's syndrome. Clin Endocrinol (Oxf) 19:503–511, 1983.
106. Christ-Crain M, Stolz D, Jutia S, et al: Free and total cortisol levels as predictors of severity and outcome in community-acquired pneumonia. Am J Respir Crit Care Med 176:913–920, 2007.

107. Salluh JIF, Bozza FA, Soares M, et al: Adrenal response in severe community-acquired pneumonia: Impact on outcomes and disease severity. Chest 134:947–954, 2008.
108. Bhatia E, Jain SK, Gupta RK, et al: Tuberculous Addison's disease: Lack of normalization of adrenocortical function after anti-tuberculous chemotherapy. Clin Endocrinol (Oxf) 48:355–359, 1998.
109. Kelestimur F: The endocrinology of adrenal tuberculosis: The effects of tuberculosis on the hypothalamo-pituitary-adrenal axis and adrenocortical function. J Endocrinol Invest 27:380–386, 2004.
110. Vita JA, Silverberg SJ, Goland RS, et al: Clinical clues to the cause of Addison's disease. Am J Med 78:461–466, 1985.
111. Watterberg KL, Gerdes JS, Cole CH, et al: Prophylaxis of early adrenal insufficiency to prevent bronchopulmonary dysplasia: A multicenter trial. Pediatrics 114:1649–1657, 2004.
112. Melmed S: Acromegaly. N Engl J Med 355:2558–2573, 2006.
113. Kauppinen-Makelin R, Sane T, Reunanen A, et al: A nationwide survey of mortality in acromegaly. J Clin Endocrinol Metab 90:4081–4086, 2005.
114. Colao A, Ferone D, Marzullo P, Lombardi G: Systemic complications of acromegaly: Epidemiology, pathogenesis, and management. Endocr Rev 25:102–153, 2004.
115. Herrmann BL, Wessendorf TE, Ajaj A, et al: Effects of octreotide on sleep apnoea and tongue volume (magnetic resonance imaging) in patients with acromegaly. Eur J Endocrinol 151:309–315, 2004.
116. Rosenow F, Reuter S, Deuss U, et al: Sleep apnoea in treated acromegaly: Relative frequency and predisposing factors. Clin Endocrinol 45:563–569, 1996.
117. Sze L, Schmid C, Bloch KE, et al: Effect of transsphenoidal surgery on sleep apnoea in acromegaly. Eur J Endocrin 156:321–329, 2007.
118. Ben-Shlomo A, Melmed S: The role of pharmacotherapy in perioperative management of patients with acromegaly. J Clin Endocrinol Metab 83:2730–2734, 2003.
119. Grunstein RR, Ho KY, Berthon-Jones M, et al: Central sleep apnea is associated with increased ventilatory response to carbon dioxide and hypersecretion of growth hormone in patients with acromegaly. Am J Respir Crit Care Med 150:496–502, 1994.
120. Donnelly PM, Grunstein RR, Peat JK, et al: Large lungs and growth hormone: An increased alveolar number? Eur Respir J 8:938–947, 1995.
121. Trotman-Dickenson B, Weetman AP, Hughes JMB: Upper airflow obstruction and pulmonary function in acromegaly: Relationship to disease activity. Q J Med 79:527–538, 1991.
122. Harrison BDW, Millhouse KA, Harrington M, et al: Lung function in acromegaly. Q J Med 47:517–532, 1978.
123. Brody JS, Fisher AB, Gocmen A, et al: Acromegalic pneumonomegaly: Lung growth in the adult. J Clin Invest 49:1051–1060, 1970.
124. Garcia-Rio F, Pino JM, Diez JJ, et al: Reduction of lung distensibility in acromegaly after suppression of growth hormone hypersecretion. Am J Respir Crit Care Med 164:852–857, 2001.
125. Iandelli I, Gorini M, Duranti R, et al: Respiratory muscle function and control of breathing in patients with acromegaly. Eur Respir J 10:977–982, 1997.
126. Kitahata LM: Airway difficulties associated with anaesthesia in acromegaly. Br J Anaesth 43:1187–1190, 1971.

CHAPTER 86

THE LUNGS IN OBSTETRIC AND GYNECOLOGIC DISEASE

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INTRODUCTION

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INTRODUCTION

Both respiratory physiology and the respiratory tract's susceptibility to disease are uniquely altered in gynecologic and obstetric conditions, including normal pregnancy. This chapter summarizes normal physiologic alterations during pregnancy and then considers pathologic diseases and disorders that arise during pregnancy. Airway disorders, infectious diseases, pulmonary vascular and embolic disorders, and acute lung injury are considered in turn. Finally, pleural and parenchymal diseases that arise as a consequence of gynecologic conditions are addressed.

PHYSIOLOGIC ALTERATIONS DURING NORMAL PREGNANCY

Profound alterations of respiratory function and cardiovascular physiology accompany normal pregnancy in healthy women; these conditions contribute to many of the disorders of the lungs that may occur during pregnancy. The adaptive changes during the gravid period are designed to support maternal and fetal well-being during the special stresses of fetal growth and parturition, but they may exacerbate some underlying disorders and confuse interpretation of laboratory and imaging studies used to assess many other common conditions.

Alterations in Respiratory Physiology

Upper airway, particularly nasal, mucosal edema is a common finding in normal pregnancy. About 20% of gravid women complain of rhinitis symptoms, now attributed at least partially to placental growth hormone's effects on mucosal congestion.[1] Animal studies appear to support this attribution. The symptoms begin in the first trimester and persist throughout gestation. Many patients thought to have rhinitis of pregnancy may actually have other or coincident causes of rhinitis.[2] An important implication of nasal mucosal edema in pregnancy is that it predisposes to nosebleeds from nasal intubations, so an oral approach is favored if intubation is required at the time of delivery.

Chest wall configuration is also altered, partially due to a 50% increase in the average costal angle[3] and partially due to an increase in the circumference of the lower chest wall. Diaphragmatic position is elevated 4 to 5 cm, but excursion does not diminish.[3] Muscle strength, as measured by maximum transdiaphragmatic pressure, does not appear to be diminished from its usual mean value of about 95 cm H_2O,[4] allowing reserve for

both the augmented minute ventilation of pregnancy and the stresses of delivery.

Important changes occur in lung function and lung volumes. Because the loss of lung volume resulting from elevation of the diaphragm is only partially offset by the smaller increase in chest wall diameter, functional residual capacity (FRC) is usually diminished by about 18%, or 300 to 500 mL.[5] The FRC diminution is partitioned almost equally between the expiratory reserve volume and the residual volume.[3,5] The loss of FRC at term is made worse by recumbency, when diaphragm elevation is greatest because of the higher intra-abdominal pressure. Increased pulmonary blood volume in pregnancy may also serve to lower the FRC.[6] This reduction in FRC is associated clinically with increased uptake and elimination of inhalational anesthetics and with rapid desaturation during hypopnea, as a result of the loss of the oxygen reservoir function of end-expiratory lung volume. Endotracheal intubation at term is thus substantially more hazardous than in nongravid patients.

Although the FRC is lower, total lung capacity decreases only marginally, and vital capacity does not change.[5] Inspiratory capacity actually increases slightly due to the decrease in FRC, so incentive spirometry is effective in preventing postpartum atelectasis.

Airway function is also largely unchanged during pregnancy.[3] Airway resistance may actually slightly decrease. Routine measurements of air flow, such as the FEV_1 and flow rates at mid-expiratory lung volume (forced expiratory flow between 25% and 75% of FVC, or $FEF_{25-75\%}$) are thus valuable in assessing dyspnea during pregnancy.

The most striking changes are in respiratory drive and minute ventilation. Central drive, as assessed by the inspiratory pressure measured 100 msec after airway occlusion at the onset of inspiration ($P_{0.1}$), has been measured during pregnancy.[4] $P_{0.1}$ is increased by 13 weeks and continues to increase to week 37 of gestation, returning to normal by 24 weeks after delivery. These serial changes in respiratory drive appear to correlate with changes in serum progesterone levels,[4,7] which either stimulate respiration directly or increase the sensitivity of the respiratory center to P_{CO_2}.[4,7] Carbon dioxide production itself increases one third to one half by the last trimester, but this is more than made up for by the greatly augmented minute and alveolar ventilation, so primary respiratory alkalosis with renal bicarbonate wasting as compensation is a normal finding.[8] Arterial blood gas measurements typically show the pH ranging from 7.40 to 7.47, with P_{CO_2} reaching as low as 28 to 32 mm Hg. P_{O_2} rises slightly as a result of the increase in alveolar ventilation.

Most of the increase in minute ventilation is due to a 30% to 35% increase in tidal volume. Respiratory rate is unchanged early and rises only about 10% later in pregnancy. Oxygen consumption increases 20% to 33% in pregnancy, owing to both maternal and fetal metabolic demands. Changes in some of these parameters are shown in Figure 86-1.

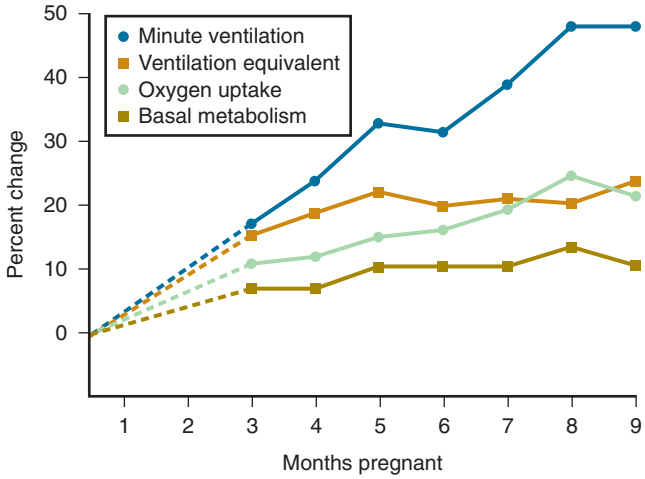

FIGURE 86-1 Changes in minute ventilation, oxygen uptake, basal metabolism, and the ventilatory equivalent for oxygen at monthly intervals throughout pregnancy. (From Prowse CM, Gaensler EA: Respiratory and acid-base changes during pregnancy. Anesthesiology 26:381, 1965.)

Alterations in Cardiovascular Physiology

Adaptive cardiovascular changes are designed to support both maternal and fetal circulations, but contribute to the risk for hydrostatic pulmonary edema, so cardiac disorders during pregnancy often present as respiratory failure. During normal pregnancy, maternal blood volume increases by about 2 L, or 40%.[9,10] Red blood cell mass increases as well, but only by 20% to 30%, accounting for the normal 10% to 12% decrease in hematocrit.[10,11] Plasma oncotic pressure also drops as intravascular volume expands, increasing the risk for pulmonary edema at lower intravascular hydrostatic pressures. During the 24 hours after parturition, oncotic pressure falls further because of blood loss and mobilization of extravascular fluid.

The enlarged intravascular volume of pregnancy is accommodated chiefly by venous capacitance vessels. Central venous pressure and pulmonary capillary occlusion ("wedge") pressure are unchanged, reflecting an increase in left ventricular compliance, as evidenced by the enlarged cardiac silhouette seen on chest radiograph. The increased left ventricular end-diastolic volume results in an augmented stroke volume (ejection fraction is little changed), but systemic vascular resistance (SVR) diminishes.[11,12] These changes account for the 30% to 45% increase in cardiac output reached by 25 to 32 weeks of gestation. After 5 weeks, heart rate increases as well,[13] but less so than stroke volume. The time frame of these changes is depicted in Figure 86-2, which also illustrates the profound effect of vena caval and aortic compression by the gravid uterus when the supine position is assumed.

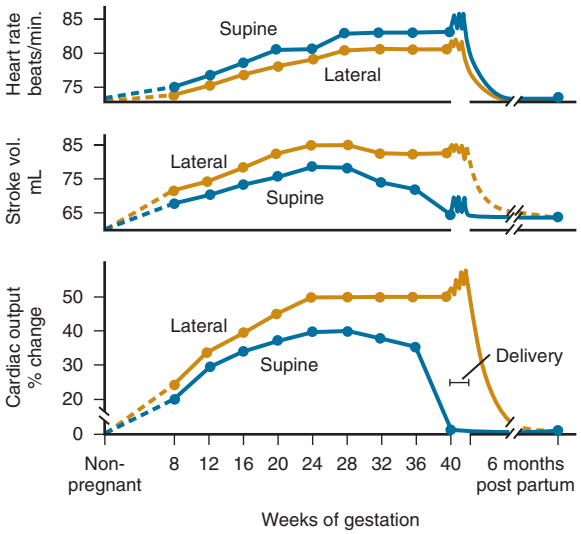

FIGURE 86-2 ■ Changes in maternal heart rate, stroke volume, and output during pregnancy with the gravida in the supine and lateral positions. (From Cheek TG, Gutsche BB: Maternal physiologic alterations during pregnancy. *In* Shnider SM, Levinson G [eds]: Anesthesia for Obstetrics. Baltimore: Williams & Wilkins, 1993, p 8.)

OBSTETRIC DISORDERS AND THE LUNGS

Gravid and newly postpartum patients may acquire disorders and diseases unique to pregnancy but also continue to experience common disorders that occur outside of pregnancy; the natural history or frequency of coexisting disorders is sometimes altered by the gravid state. Even for diseases not altered by pregnancy, management requires special knowledge of the safety of therapies.[14] Specific diseases are considered here with these principles in mind.

Obstructive Airway Disease

Asthma

Asthma affects 4% to 8% of the general population and is the most common pulmonary disorder in pregnancy. The Working Group on Asthma and Pregnancy of the National Asthma Education and Prevention Program (NAEPP) estimated that an almost identical 3.7% to 8.4% of pregnancies are complicated by asthma.[15] Maternal asthma increases the risk of preeclampsia, preterm birth, infants with low birth weight, intrauterine growth restriction or congenital malformations, and perinatal death.[16] The effects of pregnancy on asthma vary with severity, with exacerbations occurring in only an eighth of mild asthmatics, but in over half of those with severe asthma.

Investigations of the interaction of asthma and pregnancy have been of two types: natural history and outcome studies. Studies examining the hormonal milieu have suggested that progesterone might diminish smooth muscle contractility in the lung, as it does in the uterus and the gut. Juniper and colleagues[17] performed serial measurements of bronchial reactivity to methacholine challenge in 16 women before and during pregnancy and found that airway responsiveness improved. Clinical and epidemiologic studies, however, have failed to provide convincing evidence of any consistent change in the natural history of asthma during pregnancy. Turner and coworkers,[18] for example, compiled the results of nine studies of asthma symptoms reported by pregnant women. Among them, 22% reported worsening, 29% reported improvement, and 22% reported no change. Other studies have reported similar figures, with about 23% to 42% worsening, 18% to 36% improving, and 40% to 41% exhibiting no change.[19,20] The differences reported in the natural history probably reflect differences in study populations, smoking history, ethnicity, or other variables.[21]

Fetal and maternal outcome for asthma and pregnancy have also been examined in a variety of studies since 1980. Adverse outcomes, including an increased incidence of preterm labor, low neonatal birth weight, increased perinatal mortality, preeclampsia, vaginal hemorrhage, chronic hypertension, and complicated labor, have been reported.[15,21] A large epidemiologic study from Sweden did confirm an association with perinatal mortality and low birth weight.[22] Nonetheless, adequate therapy tailored to disease severity is associated with good outcomes.[23] Therapy of asthma in pregnancy should be individualized according to severity of disease and frequency of symptoms, as outlined by the NAEPP.[15] Objective measurement of lung volumes and flow should be part of the regimen. Initial office spirometry is recommended, and home peak flow monitoring should be considered for patients taking medication daily. Serial ultrasonography, starting at 32 weeks, and fetal heart rate monitoring may be needed in the third trimester. Patients can supplement this with recordings of fetal activity using "kick counts." For women who have asthma attacks during labor, fetal monitoring is considered essential by the NAEPP.

Environmental control measures are also important to reduce exposure to stimuli that exacerbate the disease.[15,21] Avoidance of cigarette smoke is particularly important. Other specific triggers in individual patients should be identified and controlled, but because of the small risk for anaphylaxis, immunotherapy should be deferred until after delivery.

Therapy should be based on a step approach.[15] Mild intermittent asthma is best managed with albuteral alone, based on safety studies. Asthma that causes more than occasional symptoms should be treated daily with anti-inflammatory therapy, with the preferred choice being inhaled corticosteroids. Budesonide is the best studied and hence preferred. Alternative therapies include cromolyn, sustained-release theophylline, or a leukotriene antagonist.[15] Inhaled short-acting β_2-agonists should be prescribed for symptomatic relief in mild episodic asthma. Although still controversial, long-acting β-agonists should only be used concurrently with long-acting inhaled corticosteroids.[16a] Frequent need for β_2-agonists should prompt institution of, or an increase in, the use of anti-inflammatory agents to treat, rather than to mask,

a deteriorating clinical course. Finally, the addition of rapidly tapered courses of oral corticosteroids should be considered for active symptoms occurring in patients already using inhaled steroids and β-agonists but failing therapy. Daily or alternate-day oral steroid administration at doses up to 2 mg/kg is sometimes required.[15] Extensive practice algorithms have been made available by the NAEPP Working Group on Asthma and Pregnancy.[15]

A large body of literature has examined the topic of possible teratogenicity of agents used in the pharmacotherapy of asthma in pregnancy. In general, the risks of poorly controlled asthma far outweigh the possible hazards of drug therapy. Both animal and human studies of β_2-agonists, administered either by inhalation or systemically, have indicated an acceptable safety profile for the fetus. They are also safe for use during lactation. Nonselective β-agonists, such as epinephrine, carry a risk of uterine vasoconstriction in animal models[24] and are probably best avoided. Acceptable β_2-agonists in pregnancy include metaproterenol, albuterol, pirbuterol, bitolterol, and terbutaline. Because the toxicology and pharmacology of the long-acting β-agonists salmeterol and formoterol are expected to be similar to shorter acting β_2-agonists, these drugs have been recommended in patients with poor control on a combination of inhaled long-acting corticosteroids and short-acting β-agonists.[16a,23] Among long-acting β_2-agonists, there is longer experience with salmeterol in the United States.

Theophylline also has a long history of use during pregnancy and is considered safe, but the therapeutic range in plasma should be lowered to 5 to 12 μg/mL because of diminished protein binding during pregnancy. Theophylline passes freely to the fetus, and newborns occasionally show signs of theophylline toxicity, particularly when maternal blood levels are high. Theophylline is also transmitted to breast milk, with a milk-to-serum ratio of about 0.70; but, in general, less than 1% of the maternal dose is transferred to the infant. Animal studies suggest that the leukotriene inhibitors montelukast and zafirlukast are safe in pregnancy, and they can be continued in patients who have previously responded.[24,25] Zileuton should be avoided, as animal studies have raised questions about its safety in pregnancy.

Animal studies have shown an increased incidence of cleft palate with use of corticosteroids, and limited human data support this association, with an estimated excess risk of 0.2% to 0.3% when used in the first trimester.[15] Systemic corticosteroids have also been reported to cause intrauterine growth retardation, but of a relatively modest degree. Halogenated corticosteroids do not cross the placenta easily, and so fetal and neonatal adrenal suppression is not a major concern with these compounds.[15] Overall, risk-benefit considerations nonetheless favor their use in persistent severe asthma with exacerbations unresponsive to other measures. Among the inhaled steroids, beclomethasone and budesonide are preferred because of their long history of use in pregnancy and the absence of any demonstrated toxicity to the fetus.[24] Table 86-1 summarizes the U.S. Food and Drug Administration (FDA) safety classification for agents useful for the treatment of asthma in pregnancy.

TABLE 86-1. Potential Fetal Risk of Drug Therapy in Pregnancy According to the FDA Classification for Safety in Pregnancy*

Drug	FDA Classification†
ASTHMA THERAPY	
Inhaled Bronchodilators	
Albuterol (salbutamol)	C
Terbutaline	B
Ipratropium	B
Salmeterol	C
Formoterol	B
Inhaled Corticosteroids	
Beclomethasone	C
Budesonide	B
Fluticasone	C
Leukotriene Antagonists	
Zafirlukast	B
Montelukast	B
Zileuton	C
Other Agents for Asthma	
Theophylline	C
Cromolyn	B
Systemic corticosteroids	B
Anticoagulants	
Heparin	C
Low-molecular-weight heparin	B
Warfarin	X
ANTIBIOTICS	
Penicillins	B
Cephalosporins	B
Macrolides	B/C
Quinolones	C
Clindamycin	B
Tetracyclines	D

*Although the Food and Drug Administration (FDA) classification provides an overview of fetal risk, detailed information should be consulted for individual drugs. Classification of individual drugs may change as the literature evolves.

†Class A: Controlled studies in women fail to demonstrate a risk to the fetus in the first trimester, and the possibility of fetal harm seems remote. Class B: Animal studies do not indicate a risk to the fetus, and there are no controlled human studies; *or* animal studies do show an adverse effect on the fetus, but well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus. Class C: Studies in animals have shown the drug to have teratogenic or embryocidal effects, but there are no controlled studies in women; *or* no studies are available in either animals or women. Class D: Positive evidence of human fetal risk exists, but benefits in certain situations (e.g., life-threatening situations or diseases for which safer drugs cannot be used or are ineffective) may make use of the drug acceptable despite its risks. Class X: Studies in animals or humans have demonstrated fetal abnormalities, *or* there is evidence of fetal risk based on human experience, and the risk of the drug clearly outweighs any possible benefit. These drugs are contraindicated in pregnancy.

Labor and delivery can be especially hazardous for asthmatic patients, partly because of the drugs commonly administered. Narcotics other than fentanyl release histamine, which may worsen bronchospasm. Lumbar epidural analgesia is generally preferred, but if general anesthesia is to be used, pretreatment with atropine or glycopyrrolate assists bronchodilation. Ketamine

is the preferred anesthetic, although halogenated anesthetics at low concentrations may provide bronchodilation as well.[15] Preterm labor may be safely treated with nifedipine or magnesium sulfate. Oxytocin is the optimal labor induction agent and is useful for postpartum hemorrhage, but 15-methyl prostaglandin $F_{2\alpha}$, methylergonovine, and ergonovine may cause bronchospasm and should be avoided if possible.

Cystic Fibrosis

Cystic fibrosis (CF), occurring in about 1 in 1500 whites and 1 in 17,000 blacks, is a common genetic disease. With improved therapy, median survival has now increased to 37 years,[26] and as many as 4% of female CF patients between the ages of 17 and 37 may be pregnant at any time.[27] This occurs despite the frequent infertility of women due to delayed sexual development. Pregnancy in CF patients, as might be anticipated, has been associated with adverse fetal and maternal outcomes.[28,29] In a retrospective French study including data from 75 pregnancies between 1980 and 1999, there were 10 premature deliveries, 10 abortions, and 1 maternal death.[30] However, in a large U.S. review of 680 gravid women with CF enrolled in the U.S. Cystic Fibrosis Foundation National Patient Registry, from 1985 to 1997, survival was actually better in the gravid group than in the matched 3327 control patients with CF.[31] Women with CF who became pregnant had higher predicted percentages of FEV_1 and higher weights. Pregnancy was not clearly harmful in any subgroup, after severity adjustment for age, *Pseudomonas aeruginosa* colonization, pancreatic function, and FEV_1. In another case-control study, pregnancy had little effect on patients with stable CF, although poor outcomes were seen in those with severe disease.[32] As might be anticipated, most studies suggest that risk stratifies according to severity of illness.[29,32] Declines in pulmonary function tend to mirror severity-adjusted control subjects, and clearly CF patients require substantially more care and have more visits to physicians when pregnant than when not.[33] Prepregnancy counseling, particularly for women with more severe disease, is essential in limiting excessive maternal and fetal risk.

Infectious Diseases

Bacterial Pneumonia

Pneumonia is a leading cause of maternal and fetal morbidity and mortality.[34-38] Maternal mortality from pneumonia in nonimmunocompromised hosts ranged from 0 to 4% in series published since 1980.[33-35] The reported incidence varies widely, from 1 per 367 to 1 per 2388 deliveries,[34-35] but may not be higher than that in the general population. One report, however, indicated that pneumonia may be increasing in incidence, with human immunodeficiency virus (HIV) infection and chronic disease the major risk factors.[34]

Pregnancy increases the risk for major complications of pneumonia. In the series by Madinger and colleagues,[36] of 25 patients culled from 25,000 deliveries, 40% suffered major complications, including five intubations, two empyemas, one pneumothorax, and one pericardial tamponade. Similarly, in the series by Briggs and associates,[39] 7 of 34 patients required mechanical ventilation, and 2 died. Gestation is also threatened; preterm labor occurs in 4% to 44%.[34-37] The small-for-gestational-age rate is as high as 12%,[34] and intrauterine and neonatal death rates have ranged from 1.9% to 12.0%.[35,36] In all series, underlying chronic illness in the mother has been a powerful predictor of adverse outcome in both fetus and mother.

Pneumonia in pregnancy is most commonly bacterial in origin; the microbiologic spectrum mirrors community-acquired pneumonia, with *Streptococcus pneumoniae* and *Haemophilus influenzae* the most common organisms.[34-36] Other common organisms include *Mycoplasma pneumoniae* and *Chlamydia pneumoniae.* As in other community-acquired pneumonias, the causative agent is identified in only about half the cases. Unfortunately, the diagnosis of pneumonia is frequently delayed because of reluctance to obtain a chest radiograph; a posteroanterior radiograph performed with a grid and a peak voltage of 90 to 120 kV exposes the mother to 5 to 30 mrad but the fetus to 100 times less, or about 300 μrad.[40] A lateral chest radiograph produces greater maternal exposure (150 to 250 mrad) but is usually not required.[40] The hazard to both fetus and mother of delaying the diagnosis greatly exceeds the risk of this very small radiation dose. Antibacterial therapy is similar to treatment in the nonpregnant patient, although tetracyclines, quinolones, clarithromycin, and metronidazole should be avoided if possible.[40] Erythromycin, azithromycin, and β-lactam antibiotics are preferred because of their favorable safety profile (see Table 86-1).

Viral Pneumonia

Viral pneumonia remains a serious concern in pregnancy. In the influenza pandemic of 1918 to 1919, the maternal rate of mortality from pneumonia was as high as 50%. In the more recent epidemic of 1957 to 1958, pregnant women accounted for 10% of fatalities, and about half of the women of childbearing age who died were pregnant.[41] Since the epidemic of 1957 to 1958, the maternal mortality rate from influenza A and B pneumonia has been relatively low but still very much higher than that in the general population. Because of this, the Centers for Disease Control and Prevention (CDC) recommends inactivated influenza vaccine in otherwise healthy women during the second and third trimesters of pregnancy.[42] Although influenza virus does cross the placenta, current opinion holds that it is not likely to be teratogenic to the fetus, despite isolated reports that link influenza with neural tube and other malformations. Amantadine has been used in pregnancy successfully, both as treatment and as prophylaxis, although there have been case reports of cardiovascular defects occurring after first-trimester use; and there is considerable influenza resistance to the drug. The newer neuraminidase inhibitors zanamivir and oseltamivir, given by

inhalation, have an insufficient safety profile for routine use in pregnancy (FDA category C). The chief risk of seasonal influenza in the modern era probably resides in its dreaded complication of superimposed staphylococcal or gram-negative bacillary pneumonia.

In the spring of 2009, a previously unrecognized strain of influenza A (H1N1) virus emerged and quickly spread around the world. Recent reports of clinical experiences with large numbers of hospitalized patients with H1N1 influenza in Australia-New Zealand and throughout the U.S. confirm that pregnancy confers a high risk of serious disease and appreciable mortality.[42a,42b] Early treatment of pregnant women and women up to two weeks postpartum with oseltamivir or zanamavir appears to be beneficial. Pregnant women are also strongly urged to be vaccinated with the monovalent inactivated injectable H1N1 vaccine—not with the live attenuated vaccine.[42c]

Varicella pneumonia, caused by a virus of the DNA herpesvirus group, has also been linked to particularly adverse outcomes during pregnancy. In one review, Haake and coworkers[43] reported a 35% mortality rate in pregnant subjects, compared with 10% in other adults. Data are conflicting, and not all prospective studies have confirmed an increased incidence or mortality in pregnancy.[40] Treatment with acyclovir does appear to reduce mortality in gravid patients and probably should be used as therapy for active disease.[44] Use of varicella-zoster immune globulin (VariZIG) should be considered for susceptible pregnant women who have been exposed to varicella within 96 hours of the exposure. Administration of VariZIG reduces but does not abolish risk for fetal infection or congenital varicella syndrome, and it is effective in preventing complications of varicella in the mother. Patients should be evaluated similarly to other adults and a decision made to administer the immune globulin based on immune status, type of exposure, and health status. The currently licensed attenuated live virus against varicella is contraindicated in pregnancy.

Rubeola viral infection, often complicated by viral and then superimposed bacterial pneumonia, has also been associated with adverse outcomes, including preterm labor, spontaneous abortion, and perinatal mortality.[45] In contrast to rubella (German measles), fetal malformation, however, does not appear to be a consequence of rubeola disease. Nonimmune, exposed pregnant patients can receive passive immunoprophylaxis with immune globulin within 6 days of exposure; the live virus vaccine is contraindicated during pregnancy.

Hantavirus, which usually presents as a hemorrhagic fever and renal syndrome, can be accompanied by pneumonitis and acute respiratory distress syndrome (ARDS). It has been reported to have a similar presentation and course in pregnancy; outcomes of pregnant patients with hantavirus appear similar to those for nonpregnant patients with hantavirus and to those of pregnant patients with other causes of ARDS.[46]

Severe acute respiratory syndrome (SARS), due to a novel coronavirus (HuCoV-SARS), causes pneumonia and ARDS, with respiratory failure occurring in 15% of patients and a mortality rate of 8% to 30%.[47,48] Although data are limited, pregnant women appear to do worse than nonpregnant patients, with four of seven patients requiring ventilatory support in one series.[49] SARS adversely affects pregnancy, with miscarriage, fetal distress, and intrauterine death reported, presumably related to hypoxemia.

Fungal Pneumonias

Fungal pneumonias are uncommon in pregnancy. Although there is no evidence that blastomycosis and histoplasmosis are more severe during pregnancy, it does appear that coccidioidomycosis is more likely to disseminate in pregnancy.[50] In the southwestern United States, about 1 in 5000 pregnancies is complicated by *Coccidioides immitis.*[51] Dissemination is highly probable during the third trimester and has been related both to subtle impairment of cell-mediated immunity and to a stimulatory effect of progesterone and 17-β-estradiols on fungal proliferation. Amphotericin is the accepted therapy for disseminated coccidioidomycosis; azoles administered in the first trimester have been associated with brachial cleft abnormalities and should be only used after delivery.

Tuberculosis

Tuberculosis does not appear to be more common or severe in pregnancy. Classically, it has been said that tuberculosis improves during the latter stages of pregnancy, but then worsens after delivery. Pregnancy does not alter reactivity to tuberculin skin testing and hence the test should be performed in the recommended groups during pregnancy. Interferon-γ-release assays are also an acceptable means of testing for tuberculous infection (see Chapter 34). Asymptomatic patients with positive skin tests should have their chest radiograph deferred until after 16 weeks of gestation. Symptomatic patients with positive skin tests merit chest radiographs regardless of gestational stage. Isoniazid, rifampin, and ethambutol have acceptable safety profiles in pregnancy and are part of the standard treatment regimens advised by the CDC and the American Thoracic Society for pregnant women.[52] There is less collective experience with pyrazinamide, but this drug is recommended for use in pregnancy by the World Health Organization.[52] Worldwide data are accumulating, and pyrazinamide appears to be emerging as a drug that can be considered for treating multidrug-resistant tuberculosis and for HIV-infected women. Streptomycin, by contrast, is clearly associated with congenital deafness and is contraindicated during pregnancy.

Pulmonary Edema and Pulmonary Vascular Disease

Gravid women are at special risk for pulmonary edema for a variety of reasons, including the hypervolemia and high cardiac output of pregnancy, the occasional need for tocolytic drugs that affect the vascular bed, and the unique vascular and endothelial disorders of pregnancy.

Among these effects, it is noteworthy that colloid osmotic pressure diminishes during pregnancy, although the effect on transcapillary pressure gradients is partially offset by a decrease in interstitial fluid colloid osmotic pressure (as explained in Chapter 6).[53] Etiologically, underlying cardiac disease, use of tocolytic drugs, fluid overload, and preeclampsia are the most common causes for acute pulmonary edema in pregnancy.[53]

Hydrostatic (Cardiogenic) Pulmonary Edema

The cardiovascular adaptations to pregnancy have already been summarized. Their effects on underlying cardiac disorders are predictable. Stenotic valvular lesions are particularly poorly tolerated.[54] Of these, mitral stenosis is the most common symptomatic valvular disease in pregnancy and frequently presents with pulmonary edema, not only during gestation but also immediately postpartum, because of the large shifts in intravascular volume associated with delivery. The gradient across a stenotic mitral valve is augmented by the increases in blood volume, cardiac output, and heart rate that occur during gestation and the puerperium. In aortic stenosis, the increase in cardiac output required for pregnancy worsens the gradient across the valve. As a compensatory mechanism, the end-diastolic volume increases, but the low SVR in aortic stenosis impairs diastolic coronary artery filling and can precipitate ischemic syndromes. The reduction in SVR of pregnancy mitigates the consequences of mitral and aortic regurgitation and of the left-to-right intracardiac shunts of endocardial cushion defects, but worsens the consequences of Eisenmenger's syndrome and uncorrected tetralogy of Fallot. Depending on the cardiac disorder, perturbations induced by pregnancy can alter fractional shunts, induce hypoxemia, and precipitate pulmonary edema.

A special problem of pregnancy is peripartum cardiomyopathy, a disorder that occurs in 1 of 1300 to 15,000 deliveries, may present with congestive heart failure, and is associated with a special propensity for pulmonary and systemic embolization during the last month of pregnancy and for up to 5 months thereafter.[55] Standard therapy for heart failure, including β-blockers, diuretics, angiotensin-converting enzyme inhibitors, and blockaders are usually effective, but sometimes implantable defibrillators and even heart transplantation are required.[56]

Tocolysis-Associated Pulmonary Edema

The systemic administration of β_2-sympathomimetic agents to retard premature labor has been associated with a 0 to 4.4% incidence of pulmonary edema.[57] The etiology of this disorder is controversial.[58] One speculation is that it is due to myocardial dysfunction from prolonged sympathetic stimulation, but descriptions of cases in which hemodynamic parameters were measured reported normal pulmonary capillary wedge pressures. The idea that increased vascular permeability may contribute to the syndrome is given weight by its association with maternal infection.[59] Some authors have speculated that the development of the disorder requires a coexisting condition, such as volume overload, sepsis, or preeclampsia.[60] It usually presents after at least 24 hours of β-adrenergic therapy, with relatively acute onset of dyspnea and pulmonary edema seen on chest radiographs (Fig. 86-3). Simple discontinuation of β-adrenergic therapy often results in rapid improvement; whether diuretics need to be given is unresolved, but furosemide is usually administered. Pulmonary edema has complicated tocolysis performed with calcium channel blockers.[61]

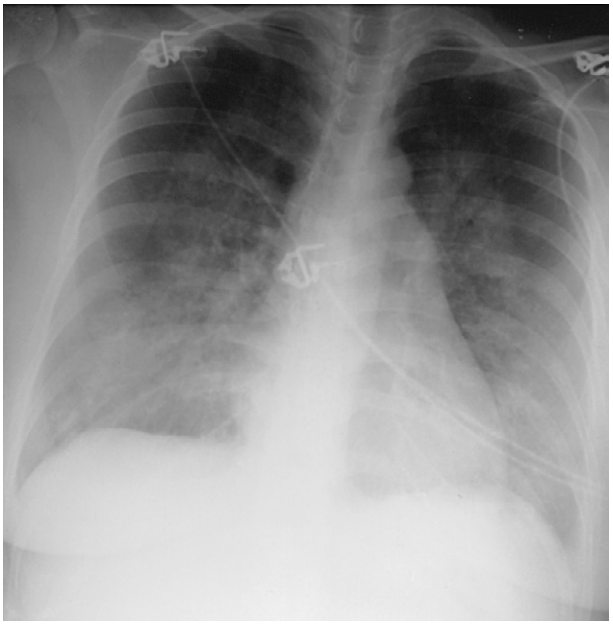

FIGURE 86-3 ■ Tocolysis-associated pulmonary edema in a 38-year-old woman in premature labor.

Pulmonary Edema Associated with Preeclampsia

About 2.9% of patients with preeclampsia or eclampsia develop pulmonary edema.[62] The spectrum of hemodynamic findings associated with pregnancy-induced hypertension and preeclampsia is wide, but, in general, left ventricular preload is normal or low, afterload is high, and cardiac output is normal or low (Fig. 86-4). Systolic and diastolic function may also be impaired.[63] The pulmonary edema commonly first presents in the postpartum period,[62,63] reflecting fluid administration at delivery. Low colloid oncotic pressure and abnormal vascular permeability likely contribute as well. Hemodynamic monitoring of these patients is probably warranted if oliguria complicates the picture.

Pulmonary Embolism

Pulmonary embolism is a leading cause of maternal mortality,[64] accounting for 9% of 95 pregnancy-related deaths in a large health care delivery system in the United States between 2000 and 2006.[64] Even though the risk for venous thromboembolism in pregnant women is about five times as great as in age-matched and sex-matched

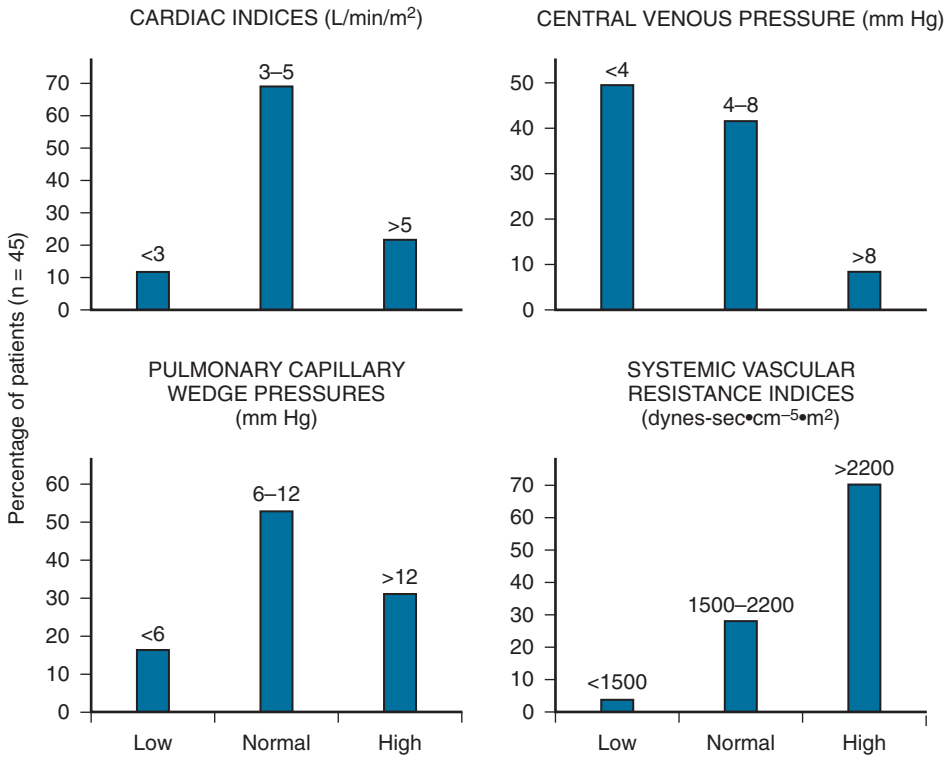

FIGURE 86-4 ■ Spectrum of hemodynamic profiles seen in 45 women with severe pregnancy-induced hypertension, one of the disorders sometimes complicated by pulmonary edema. Pulmonary edema in pregnancy-induced hypertension usually does not reflect simple volume overload. (From Cotton DB, Lee W, Huhta JC, et al: Hemodynamic profile of severe pregnancy-induced hypertension. Am J Obstet Gynecol 158:523–529, 1988.)

nongravid controls, it is still relatively infrequent. A Danish population-based study of 63,000 deliveries found a cumulative incidence of 0.85 in 1000 deliveries from 1984 to 1994.[65] In this study, the incidence of detected venous thromboembolism increased to 1.23 in 1000 deliveries after the introduction of ultrasonography, demonstrating that its reported incidence may depend on the adequacy of diagnostic procedures employed. Other studies have reported rates of 0.5 to 1.3 per 1000, with a lower incidence in younger patients and higher incidence in those over 35 years of age.[66,67]

The risk for thrombosis is increased in pregnancy, partly because of the increase in the coagulation factors, particularly V, VIII, X, and von Willebrand factor antigen, and partly because of a marked fall in protein S.[68] Venous stasis, an important contributor to thrombosis, is caused by uterine compression of the inferior vena cava and the left iliac vein. Local trauma to pelvic veins at the time of delivery probably accounts for the peak incidence of thromboembolism in the postpartum period, especially after cesarean section. Specific risk factors for thromboembolism include previous thromboembolism during pregnancy or while taking oral contraceptives, prolonged bed rest, a complicated or cesarean delivery, age, and inherited coagulation defects. The latter include deficiencies of protein S, protein C, and antithrombin III or the presence of antiphospholipid antibodies, factor V Leiden, and prothrombin G20210A.[66,68] The first two risk factors probably warrant prophylactic subcutaneous heparin administration throughout pregnancy, now more commonly accomplished with low-molecular-weight heparins (LMWHs) due to their safety and decreased risk of heparin-induced osteopenia and thrombocytopenia.

Clinical diagnosis of deep venous thrombosis during pregnancy and the puerperium is exceptionally difficult because of the peripheral edema associated with pregnancy and the asymmetrical compression of the left-sided common iliac vein by the gravid uterus. The initial diagnostic test should be duplex ultrasonography (combined real-time B-mode compression ultrasonography plus Doppler venous ultrasonography). In the patient with high clinical suspicion but a negative test, a repeat examination at 5 to 7 days may be valuable. The "gold standard" for detecting lower extremity thrombosis remains venography, but in pregnancy thrombosis is typically confined to the iliac veins and may be difficult to visualize, even by this technique. When venous thrombosis of the lower extremity is documented, it is usually left-sided, as it was in 58 of 60 cases reported by Ginsberg and colleagues.[69]

The diagnosis of pulmonary embolism in pregnant women is relatively straightforward. Both ventilation-perfusion scanning and pulmonary angiography can be performed during pregnancy in a modified fashion. Estimated fetal radiation exposure for a standard technetium-labeled macroaggregated albumin perfusion scan is about 0.018 cGy (18 mrad),[70] which can be

reduced further by simply halving the dose without greatly impairing resolution. There is no need for the ventilation portion of the study if perfusion is normal. Computed tomographic (CT) angiography is an acceptable imaging modality and is associated with similarly low radiation doses to the fetus.[71] Pulmonary angiography, when performed by the brachial route, exposes the fetus to only about 0.050 cGy (50 mrad).[72] Such levels of exposure are not believed to cause teratogenicity, which is associated with exposure of greater than 5 to 10 cGy (5 to 10 rad). However, an increased incidence of childhood leukemia has been documented with lower fetal radiation exposure, in the range of 1 to 5 cGy (1 to 5 rad). A recent comparison of lung scintigraphy and pulmonary CT-angiography concluded that the former method was more accurate than the latter for diagnosing pulmonary embolism during pregnancy.[72a] Magnetic resonance imaging with gadolinium contrast also has promise because it can image pelvic and lower extremity veins as well as the pulmonary arteries, and it has little contrast-associated toxicity. Its widespread use requires availability of ultrafast scanners and more evaluation of its accuracy.

Embolism in pregnancy is treated with heparin because warfarin crosses the placenta and causes nasal, ophthalmologic, and central nervous system abnormalities. LMWH appears to be safe in pregnancy and, compared to unfractionated heparin, is associated with fewer adverse effects such as thrombocytopenia and osteoporosis.[73,74] A consensus is emerging that LMWH is preferable in pregnancy, but some authors also advocate titrating the dose to achieve anti–factor X levels of 0.5 to 1.24 units/mL 4 hours after injection.[73,74] Weight gain in pregnancy makes formulaic dosing less reliable. Thrombolytic therapy has been used successfully in life-threatening thromboembolism during pregnancy, with a complication rate similar to that in nonpregnant women.[75]

Standard therapy of thromboembolism antepartum encompasses either continuous intravenous unfractionated heparin or LMWH until 24 hours before elective induced or planned surgical delivery. For spontaneous deliveries, because of the risk of epidural hematoma formation with regional anesthesia, LMWH should be switched to unfractionated heparin about 2 weeks prior to the anticipated delivery. If labor begins unexpectedly, reversal of the heparin effect with protamine is advisable. Postpartum, warfarin can be given safely during lactation.

Amniotic Fluid Embolism

Small amounts of amniotic fluid may enter the circulation during uncomplicated pregnancy, but in 7.7 per 100,000 deliveries there is a catastrophic syndrome of amniotic fluid embolism.[76] The onset is usually during labor and delivery or immediately after uterine manipulation, when severe dyspnea, hypoxemia, and then seizures and cardiovascular collapse or arrest occur. If the patient survives the initial insult, disseminated intravascular coagulation and ARDS usually supervene.[77] Risk factors include older maternal age, high parity, cesarean section, low uterine segment laceration, and meconium staining of amniotic fluid.[60] Abruptio placentae is present in 50% of cases, and fetal demise occurs in 40%.[77] The maternal mortality rate has been as high as 86%[78] but has appeared more recently to be as low as 22%[76]; overall, amniotic fluid embolism may account for 14% of all maternal deaths.[64]

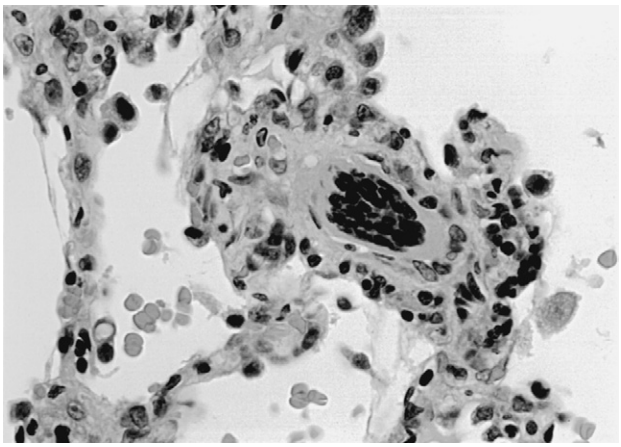

FIGURE 86-5 ■ Small pulmonary vessel filled and distended by fetal squamous cells from a fatal case of amniotic fluid embolism in a 39-year-old woman who succumbed within 4 hours of delivery. (Keratin stain; original magnification ×400.) (Courtesy of Dr. Gerald Berry.)

In a U.S. registry of cases, 78% of the patients with amniotic fluid embolism had ruptured membranes, and several had just undergone intrauterine procedures,[79] clearly implicating traumatic opening of uterine vessels in the pathogenesis. The exact quantity or constituent of the amniotic fluid required to initiate the syndrome is unknown. Pathologically, fetal squamous cells are found in the maternal pulmonary circulation at autopsy (Fig. 86-5), but even in symptom-free patients fetal cells may be recovered from pulmonary artery catheters placed for other reasons.[80] Hemodynamically, the process is often biphasic, with pulmonary hypertension initially followed by left ventricular failure.[81,82] These changes may be caused by leukotrienes and arachidonic acid metabolites, particularly prostaglandin $F_{2\alpha}$, which appear in amniotic fluid during labor. An immunologic basis for some of the changes seems likely because women with male fetuses are more likely to acquire the disorder.[82] Clark and associates[79] seized on the similarities to anaphylaxis and suggested that the disorder be renamed *anaphylactoid syndrome of pregnancy.* A small study did not demonstrate evidence of mast cell degranulation but suggests a role for complement activation.[83]

Radiographically, the patients usually develop bilateral parenchymal infiltrates consistent with pulmonary edema and then acute lung injury. Treatment consists of supportive care for the associated disseminated intravascular coagulation and left ventricular and respiratory failure. If the fetus survives the initial insult and is intrauterine, it should be promptly delivered. In cases of

maternal demise, emergency postmortem or periresuscitative cesarean section is warranted, as in other instances of cardiopulmonary resuscitation in pregnancy.[84]

Arteriovenous Malformations

Pulmonary arteriovenous malformations may expand during pregnancy because of the increase in blood volume and venous distensibility.[85] This increases the likelihood of bleeding, with life-threatening complications occurring in about 1% of pregnant women with hereditary hemorrhagic telangiectasia.[86] Embolization and surgical management have been utilized successfully during pregnancy.

Air Embolism

Occasionally, venous air embolism occurs during pregnancy, presumably through the subplacental venous sinuses.[87] This disorder has been clearly documented during labor and delivery, during cesarean sections and abortions, in patients with placenta previa, and in those engaging in orogenital sex during pregnancy.

Acute Lung Injury in Pregnancy

Aspiration Pneumonitis

Since Mendelson's[88] original report of 66 cases of gastric aspiration in 44,016 deliveries between 1932 and 1945 (an incidence of 0.15%), aspiration has continued to be a major cause of maternal morbidity and mortality. Increased intra-abdominal pressure due to the gravid uterus, the inhibitory effect of progesterone on the tone of the esophageal sphincter, and the assumption of the supine position for delivery all contribute. Eating during or just before labor increases the volume of emesis.[89] Aspiration of gastric contents with pH 2.5 or lower is known to cause chemical pneumonitis and increased permeability edema. Both in Mendelson's original report and today, about two thirds of cases of aspiration occur in the delivery suite. Emergency intubation of the obstetric airway is particularly difficult,[90] and failed intubation in the delivery suite occurs at a rate eight times that in the general surgical population.[91] To reduce the risk for aspiration and to minimize the chance of acid aspiration at intubation, oral administration of histamine$_2$ blockers or sodium citrate before intubation, in conjunction with a formal airway assessment, is desirable. Identified risk factors in intubation include a high Mallampati class, indicating poor visibility of the posterior pharynx, a short neck, protruding maxillary incisors, and a receding mandible.[92]

Acute Respiratory Distress Syndrome

Acute respiratory distress syndrome occurs relatively frequently in pregnancy; in one obstetric intensive care unit, it was the leading cause of maternal death during a 6-year period.[93] The three most common nonobstetric causes are pneumonia, sepsis, and aspiration. Common obstetric causes include chorioamnionitis, amniotic fluid embolism, and trophoblastic embolism.[94] Ventilator management is unaltered in pregnancy; the prognosis also appears to be the same, with an anticipated 40% to 75% survival rate.[94,95]

Other Respiratory Diseases in Pregnancy

Obstructive Sleep Apnea

Pregnancy may be complicated by obstructive sleep apnea (OSA), potentially adversely affecting both mother and fetus.[96] In general, apnea and hypopnea are uncommon in pregnancy because of the respiratory stimulatory effect of progesterone. OSA usually occurs in obese patients, precipitated by the airway mucosal edema and vascular congestion that accompany pregnancy. Snoring and OSA are more common in women with preeclampsia.[97] Nocturnal hypoxemia may produce poor fetal growth, although snoring alone is not associated with fetal risk.[98] Treatment with nasal continuous positive airway pressure is safe and effective.

Interstitial Lung Disease

Most cases of interstitial lung disease occur in patients older than those in their childbearing years. When interstitial disease exists in pregnant women, the reduced diffusing capacity may cause difficulty in meeting the increased oxygen consumption requirements of pregnancy. Associated pulmonary hypertension carries significant risks, because cardiac output increases during pregnancy. Few data exist on the management and outcome in these patients, but restrictive lung disease appears reasonably well tolerated in pregnancy.[99] Patients who have a vital capacity of less than 1 L and those who have pulmonary hypertension should consider avoiding pregnancy.[100] Lymphangioleiomyomatosis and systemic lupus erythematosus may worsen as a result of pregnancy.

Pleural Disease

Pleural effusions may accompany obstetric complications such as preeclampsia and choriocarcinoma, but many women with normal pregnancies develop small, asymptomatic pleural effusions in the postpartum period.[101] They occur as a result of the increased blood volume and reduced colloid osmotic pressure that occur in pregnancy, as well as from impaired lymphatic drainage due to the Valsalva maneuver during labor. Moderate-size effusions or the presence of symptoms should prompt a full clinical evaluation. The Valsalva maneuver of labor may also produce spontaneous pneumothorax and pneumomediastinum, particularly in patients with predisposing conditions such as asthma. This diagnosis should be considered in the woman who develops chest discomfort and dyspnea during, or immediately following, delivery.

GYNECOLOGIC DISORDERS AND THE LUNGS

Catamenial Pneumothorax

Lillington and colleagues[102] introduced in 1972 the term *catamenial pneumothorax* to describe the already reported phenomenon of spontaneous pneumothorax occurring within 24 to 72 hours after onset of menses. More than 200 cases have been reported. It appears to account for about 2.8% to 5.6% of spontaneous pneumothoraces in women,[103,104] most often affecting women in the third or fourth decade of life. About 30% to 60% of cases are attributable to thoracic endometriosis, as judged by inspection at thoracotomy[105]; other cases have a more obscure etiology, however, so a number of theories have been advanced. First, during menstruation, the absence of the normal cervical mucus plug permits an open connection between ambient air and the abdominal cavity through the uterus and fallopian tubes. Air can move transdiaphragmatically through right-sided diaphragmatic fenestrations into the pleural space, as it sometimes does during abdominal laparoscopy.[106] This may account for the condition's 90% to 95% right-sided predominance.[107] A second theory is that high levels of prostaglandin $F_{2\alpha}$ during menstruation cause bronchospasm with attendant air trapping and pneumothorax, but wheezing is not a common symptom of this disorder. A third theory is that pleural blebs or bullae are more susceptible to rupture during menstruation because of hormonal changes,[105,107] but visceral pleural leaks are rarely found at surgery (see also Chapter 74 for a full discussion).

For cases of endometriosis-associated pneumothorax, a trial of gonadotropin-releasing hormones is warranted if the phenomenon is repetitive but not life-threatening. Oral contraceptives, other progestational agents, and tubal ligation have also been used with some success. For cases not clearly associated with systemic endometriosis, thoracoscopy during menstruation serves to define the etiology and can be used to achieve pleurodesis.[106]

Endometriosis

Endometriosis probably affects about 10% of women, shows no clear ethnic differences in prevalence, and is most commonly diagnosed at 30 to 34 years of age.[108] Although pelvic pain, dysmenorrhea, and infertility are its predominant manifestations, atypical locations, including diaphragmatic, pleural, and endobronchial sites, have been documented. As described previously, endometriosis can result in recurrent catamenial pneumothorax, which is its most common thoracic presentation. In one review of 110 cases with thoracic endometriosis, catamenial pneumothorax was the presenting symptom in 73% of cases, followed by hemothorax in 14% and hemoptysis in 7%.[108] It also has been associated with right-sided pleural pain, pleuritic effusions, and hemothorax. Inspection at thoracotomy or thoracoscopy typically reveals blue-brown nodules on the pleural surface, sometimes in a "gunshot" distribution.[109] The absence of known pelvic endometriosis is not helpful in making the diagnosis because only 20% to 70% of patients have associated pelvic disease. The diagnosis is suspected on clinical grounds, since neither CT nor endoscopy is specific.[110] Rarely, the implants are found in lung parenchyma, accounting for the catamenial hemoptysis. Most pleural and diaphragmatic disease is thought to arise from transdiaphragmatic spread from retrograde menses, even when abdominal disease is not evident. Massive ascites is sometimes related, although only 27 cases have been reported.[111] Pneumothoraces may be attributed to cyclical sloughing of implants on key surfaces, such as the visceral pleura,[112] or to air trapping from airway involvement or compression.[102] Pulmonary parenchymal disease may be embolic in origin, as it is presumed to be in the central nervous system. The diagnosis can be established only by biopsy showing the characteristic ectopic endometrial glands in involved sites. Medical therapy consists of progestational agents or gonadotropin-releasing hormones; surgical approaches include excision, local laser ablation, or pleurodesis.

Lymphangioleiomyomatosis

Lymphangioleiomyomatosis (LAM) is a rare disorder, with only about 300 reported cases, which afflicts premenopausal women predominantly.[113,114] The most common presenting event is a pneumothorax, occurring in 86.5% of patients in the National Heart, Lung, and Blood Institute registry.[113] It is fundamentally a disorder of smooth muscle proliferation that results in functional obstruction of vessels, lymphatics, and airways. (See Chapter 62 for a complete discussion of LAM.) Involvement of pulmonary vascular structures is responsible for the hemoptysis, whereas lymphatic obstruction accounts for the chylous effusions. Mediastinal and retroperitoneal lymphatic proliferation may be a feature of the disease as well. LAM is also associated with renal angiomyolipomas, another hamartomatous disorder, and with tuberous sclerosis. Conventional therapy has included oophorectomy or progestational agents, mainly medroxyprogesterone acetate. Lung transplantation has been performed in more than 60 patients with this disorder, but it has clearly recurred in some of them. Current research focuses on growth factors and genetic factors that have been implicated in the disease's causation.[115] Particularly intriguing is the identification of lesions on chromosome 16p13 in patients with tuberous sclerosis and LAM or renal angiomyolipomas. Most recently sirolimus, in a trial in patients with angiomyolipomas and tuberous sclerosis complex or LAM, showed ameliorative effects on lung function and volume of angiomyolipomas, presumably by suppressing signaling pathways involved in products of the defective genes.[116]

Trophoblastic Embolization

Trophoblastic embolism is a rare complication of hydatidiform mole. In one series, only 2.6% of 189 patients

with hydatidiform mole had an embolic event, so most episodes of respiratory distress in patients with molar gestations are not caused by embolic events but, rather, by pulmonary edema, anemia, or another complicating event.[117] Embolization, when it does occur, is most common at the time of evacuation of the mole. Chorionic neoplasms that arise during gestation are suggested by a large discrepancy between gestational date and uterine size and should be evaluated by transvaginal ultrasonography.[118] Moles can also arise outside of gestation from the gonads of either sex.

Ovarian Hyperstimulation Syndrome

The use of exogenous gonadotrophins to stimulate ovulation for in vitro fertilization has been associated with pulmonary complications.[119] This ovarian hyperstimulation syndrome usually manifests with ovarian cysts, bilateral pleural effusions, ascites, and intravascular volume depletion. Hypovolemic shock, renal failure, and ARDS may result. Pulmonary embolism may occur due to the hypercoagulable state induced by estrogens associated with intravascular volume depletion. The mechanism of the effusions is unclear but is related to increased permeability due to release of vasoactive mediators, of which vascular endothelial growth factor appears to be the most important.[120] Recent evidence points to mutations in the follicle-stimulating hormone receptor as etiologic in at least some cases.[121] Treatment is supportive and involves maintaining intravascular volume and thoracentesis if required for respiratory distress.

KEY POINTS

- Normal pregnancy is associated with profound alterations in respiratory and cardiovascular physiology, which—although designed for maternal and fetal well-being—may exacerbate underlying cardiopulmonary conditions or cause new ones.
- Major physiologic perturbations found in normal pregnancies include (1) an increase in central drive to breathe, with resulting changes in P_{CO_2} (28 to 32 mm Hg) and pH (7.40 to 7.47); and (2) an increase in both maternal blood volume, of about 2 L (40%), and cardiac output, after 25 to 32 weeks of gestation, of 30% to 45%.
- The most common pulmonary disease to impair outcome in pregnancy is asthma, but the effects of pregnancy on asthma are variable: it worsens, improves, or remains unchanged in roughly one third of afflicted women.
- The risks of poorly controlled asthma for both mother and fetus during pregnancy far outweigh the risks of drug therapy. Some standard drugs are safer than others (see Table 86-1) and should be used whenever possible.
- Cystic fibrosis and infectious pneumonias have all been linked with adverse fetal and maternal outcomes, the risk of which depends largely on the severity of the complicating disorder. Prepregnancy counseling and avoidance of certain antimicrobial drugs (as noted in Table 86-1) are strongly recommended.
- Pulmonary edema may occur during pregnancy in women with underlying heart disease, especially valvular stenosis, or in association with either tocolytic therapy to retard premature labor or preeclampsia. Because the causative mechanisms differ, so does specific therapy.
- Pulmonary embolism is a leading cause of maternal mortality while gravid and immediately afterward. During pregnancy, low-molecular-weight heparins are indicated for both treatment and prevention; warfarin is contraindicated. Ventilation-perfusion imaging and computed tomographic angiography can be used when needed. Magnetic resonance imaging is useful when available.

References

1. Ellegard EK: Clinical and pathologic characteristics of pregnancy rhinitis. Clin Rev Allergy Immunol 26(3):149–159, 2004.
2. Blaiss MS, for the Food and Drug Administration (US), ACAAI-ACOG (American College of Asthma and Immunology and American College of Obstetricians and Gynecologists): Management of rhinitis and asthma in pregnancy. Ann Allergy Asthma Immunol 90(Suppl 3):16–22, 2003.
3. Weinberger SE, Weiss ST, Cohen WR, et al: Pregnancy and the lung: State of the art. Am Rev Respir Dis 121:559–581, 1980.
4. Contreras G, Gutierrez M, Berioza T, et al: Ventilatory drive and respiratory function in pregnancy. Am Rev Respir Dis 144:837–841, 1991.
5. Cugell DW, Frank NR, Gaensler EA: Pulmonary function in pregnancy. I. Serial observations in normal women. Am Rev Tuberc 67:568–597, 1953.

6. Gilroy RJ, Mangura BT, Layietes MH: Ribcage and abdominal volume displacements during breathing in pregnancy. Am Rev Respir Dis 137:668–672, 1988.
7. Skatrud JB, Bempsey JA, Kaiser DG: Ventilatory response to medroxyprogesterone acetate in normal subjects: Time course and mechanism. J Appl Physiol 44:939, 1978.
8. Lucius H, Gahlenbeck HO, Kleine O, et al: Respiratory functions, buffer system, and electrolyte concentrations of blood during human pregnancy. Respir Physiol 9:311–317, 1970.
9. Pritchard JA, Baldwin RM, Dickey JC, et al: Blood volume changes in pregnancy and the puerperium. Am J Obstet Gynecol 84:1271–1281, 1962.
10. Silver HM, Seebeck M, Carlson R: Comparison of total blood volume in normal, preeclamptic and nonproteinuric gestational hypertensive pregnancy by simultaneous measurement of red blood cell and plasma volumes. Am J Obstet Gynecol 179:87–93, 1998.
11. Crapo RO: Normal cardiopulmonary physiology during pregnancy. Clin Obstet Gynecol 39:3–16, 1996.
12. Clark SL, Cotton DB, Lee W, et al: Central hemodynamic assessment of normal near term pregnancy. Am J Obstet Gynecol 161:1439–1442, 1989.
13. Hunter S, Robson SC: Adaptation of the maternal heart in pregnancy. Br Heart J 68:540–543, 1992.
14. Rizk N, Kalassian K, Gilligan T, et al: Obstetric complications in pulmonary and critical care medicine. Chest 110:791–809, 1996.
15. NAEPP Working Group Report on Managing Asthma during Pregnancy: Recommendations for Pharmacologic Treatment—Update 2004 (NIH Publication No. 05-3279). Bethesda, MD: National Heart, Lung, and Blood Institute, 2004.
16. Schata M, Dombrowski MP: Asthma in pregnancy. N Engl J Med 360:1862–1869, 2009.

16a. Kramer JM: Balancing the benefits and risks of inhaled long-acting beta-agonists—the influence of values. N Engl J Med 360:1592–1595, 2009.

17. Juniper EF, Daniel EE, Roberts RS, et al: Improvement in airway responsiveness and asthma severity during pregnancy. Am Rev Respir Dis 140:924–931, 1989.
18. Turner ES, Greenberger PA, Patterson R: Management of the pregnant asthmatic patient. Ann Intern Med 93:905–918, 1980.
19. Gluck JC, Gluck PA: The effects of pregnancy on asthma: A prospective study. Ann Allergy 37:164–168, 1976.
20. Stenius-Aarniala B, Piirila P, Terampo K: Asthma and pregnancy: A prospective study of 198 pregnancies. Thorax 43:12–18, 1988.
21. Nelson-Piercy C: Asthma in pregnancy. Thorax 56:325–328, 2001.
22. Kallen B, Rydhstroem H, Averg A: Asthma during pregnancy—a population based study. Eur J Epidemiol 16:167–171, 2000.
23. Dombrowski MP, Schatz M, Wise R, et al: Asthma during pregnancy. National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network aned the National Heart, Lung, and Blood Institute. Obstet Gynecol 103:5–12, 2004.
24. Briggs GE, Freeman RK, Yaffe SJ: Drugs in Pregnancy and Lactation (6th ed). Philadelphia: Lippincott Williams & Wilkins, 2002, pp 483–484.
25. Spector SL, for the Antileukotriene Working Group: Safety of antileukotriene agents in asthma management. Ann Allergy Asthma Immunol 86(Suppl 1):18–23, 2001.
26. Cystic Fibrosis Foundation: Cystic Fibrosis Foundation Annual Report 2007. Bethesda, MD: Cystic Fibrosis Foundation, 2007.
27. Kotloff RM, FitzSimmons SC, Fiel SB: Fertility and pregnancy in patients with cystic fibrosis. Clin Chest Med 13:623–635, 1992.
28. Edenborough FP, Stableforth DE, Webb AK, et al: The outcome of pregnancy in cystic fibrosis. Thorax 50:170, 1995.
29. Boyd JM, Metha A, Murphy DJ: Fertility and pregnancy outcomes in men and women with cystic fibrosis in the United Kingdom. Hum Reprod 19:2238–2243, 2004.
30. Gillet D, de Braekeleer M, Bellis G, et al: Cystic fibrosis and pregnancy: Report from the French data (1980–1999). BJOG 109:912–918, 2002.
31. Goss CH, Rubenfeld GD, Ottok X, Aitken ML: The effect of pregnancy on survival in women with cystic fibrosis. Chest 124:1460–1468, 2003.
32. Frangolias DD, Nakielna EM, Wilcox PG: Pregnancy and cystic fibrosis: A case-controlled study. Chest 111:963–969, 1997.
33. McMullen AH, Pasta DJ, Frederick PD, et al: Impact of pregnancy on women with cystic fibrosis. Chest 129:706–711, 2006.
34. Berkowitz K, LaSala A: Risk factors associated with the increasing prevalence of pneumonia during pregnancy. Am J Obstet Gynecol 163:981–985, 1990.
35. Goodnight WH, Soper DE: Pneumonia in pregnancy. Crit Care Med 33:S390–S397, 2005.
36. Madinger NE, Greenspoon JS, Ellrodt AG: Pneumonia during pregnancy: Has modern technology improved maternal and fetal outcome? Am J Obstet Gynecol 161:657–662, 1989.
37. Richey SD, Roberts SW, Ramin KD, et al: Pneumonia complicating pregnancy. Obstet Gynecol 84:525–528, 1994.
38. Jin Y, Carriere KIC, Marrie TJ, et al: The effects of community-acquired pneumonia during pregnancy ending in a live birth. Am J Obstet Gynecol 18:800–806, 2003.
39. Briggs RG, Mabie WC, Sibai BM: Community acquired pneumonia in pregnancy. Am J Obstet Gynecol 174:389, 1996.
40. Lim WS, Macfarlane JT, Colthorpe CL: Pneumonia and pregnancy. Thorax 56:398–405, 2001.
41. McKinney P, Volkert P, Kaufman J: Fatal swine influenza pneumonia occurring during late pregnancy. Arch Intern Med 150:213–215, 1990.
42. Centers for Disease Control and Prevention: Prevention and control of influenza: Recommendations of the Advisory Committee on Immunization Practices. MMWR Recomm Rep 55(RR-10):11–12, 2006.

42a. ANZIC influenza investigators: Critical care services and 2009 influenza in Australia and New Zealand. N Engl J Med 361:1925–1934, 2009.

42b. Jain S, Kamimoto LM, Bramley AM, et al: Hospitalized patients with 2009 H1N1 influenza in the United States, April-June 2009. N Engl J Med 361:1935–1944, 2009.

42c. CDC: Update on influenza A (H1N1) 2009 monovalent vaccines. MMWR 58:1100–1101, 2009.

43. Haake DA, Zakokwski PC, Haake DL, et al: Early treatment with acyclovir for varicella pneumonia in otherwise healthy adults: Retrospective controlled study and review. Rev Infect Dis 12:788, 1990.
44. Broussard RC, Payne K, George RB: Treatment with acyclovir of varicella pneumonia in pregnancy. Chest 99:1045, 1991.
45. Rosa C: Rubella and rubeola. Semin Perinatol 22:318–322, 1998.
46. Howard MJ, Doyle TJ, Koster FT, et al: Hantavirus pulmonary syndrome in pregnancy. Clin Infect Dis 29:1538–1544, 1999.
47. Fowler R, Lapinsky SE, Hallett D, et al: Critically ill patients with severe acute respiratory syndrome (SARS). JAMA 290:367–373, 2003.
48. Lam CM, Wong SF, Leung TN, et al: A case-controlled study comparing clinical course and outcomes of pregnant and non-pregnant women with severe acute respiratory syndrome. BJOG 111:771–774, 2004.
49. Wong SF, Chow KM, de Swiet M: Severe acute respiratory syndrome and pregnancy. BJOG 110:641–642, 2003.
50. Wack EE, Ampel NM, Galgiani JN, et al: Coccidioidomycosis during pregnancy: An analysis of ten cases among 47,120 pregnancies. Chest 94:376–379, 1988.
51. Crum NF, Ballon-Landa G: Coccidioidomycosis in pregnancy: Case report and review of the literature. Am J Med 119:993.e11–993.e17, 2006.
52. Blumberg HM, Burman WJ, Chaisson RE, et al, for the American Thoracic Society/Centers for Disease Control and Prevention/Infection Diseases Society of America: Treatment of tuberculosis. Am J Respir Crit Care Med 167:603–662, 2003.
53. Oian P, Maltari JM, Noddeland H, et al: Oedema preventing mechanisms in subcutaneous tissue of normal pregnant women. Br J Obstet Gynaecol 92:113–119, 1985.
54. Scisciore AC, Ivester T, Largoza M, et al: Acute pulmonary edema in pregnancy. Obstet Gynecol 101:511–515, 2003.

55. Siu SC, Sermer M, Colman JM: Prospective multicenter study of pregnancy outcomes in women with heart disease. Circulation 104:515–521, 2001.
56. Murali S, Baldisseri MR: Peripartum cardiomyopathy. Crit Care Med 33(10 Suppl):S3406, 2005.
57. Pisani RJ, Rosenow EC: Pulmonary edema associated with tocolytic therapy. Ann Intern Med 110:714–718, 1992.
58. Lapinsky SE, Kruczynski K, Slutsky A: Critical care in the pregnant patient. Am J Respir Crit Care Med 152:427–455, 1995.
59. Hatjos CG, Swain M: Systemic tocolysis for premature labor is associated with an increased incidence of pulmonary edema in the presence of maternal infection. Am J Obstet Gynecol 159:723–728, 1988.
60. Karetzky M, Ramirez M: Acute respiratory failure in pregnancy: An analysis of 19 cases. Medicine (Baltimore) 77:41–49, 1998.
61. van Geijn HP, Lenglet JE, Bolte AC: Nifedipine trials: Effectiveness and safety aspects. BJOG 112(Suppl 1):79–83, 2005.
62. Sibai BM, Mabie BC, Harvey CJ, et al: Pulmonary edema in severe preeclampsia-eclampsia: Analysis of thirty-seven consecutive cases. Am J Obstet Gynecol 156:1174–1179, 1987.
63. Benedetti TJ, Kates R, Williams V: Hemodynamic observation of severe preeclampsia complicated by pulmonary edema. Am J Obstet Gynecol 152:33–34, 1985.
64. Clark SL, Belfort MA, Dildy GA, et al: Maternal death in the 21st century: Causes, prevention, and relationship to cesarean delivery. Am J Obstet Gynecol 199:36e1–36e5, 2008.
65. Andersen BS, Steffensen FH, Sorensen HT, et al: The cumulative incidence of venous thromboembolism during pregnancy and puerperium: An 11 year Danish study population-based study of 63,000 pregnancies. Acta Obstet Gynecol Scand 77:170–173, 1998.
66. Brown HL, Hiett AK: Deep venous thrombosis and pulmonary embolism. Clin Obstet Gynecol 39:87–100, 1996.
67. Greer IA: Prevention and management of venous thromboembolism in pregnancy. Clin Chest Med 24:123–137, 2003.
68. McColl MD, Walker ID, Greer IA: Risk factors for venous thromboembolism in pregnancy. Curr Opin Pulm Med 5:227–232, 1999.
69. Ginsberg JS, Brill-Edwards P, Burrows RF, et al: Venous thrombosis during pregnancy: Leg and trimester of presentation. Thromb Haemost 67:519, 1992.
70. Ginsberg JS, Hirsh J, Rainbow AJ, et al: Risks to the fetus of radiologic procedures used in the diagnosis of maternal venous thromboembolic disease. Thromb Haemost 61:189–196, 1989.
71. Parry RA, Glaze SA, Archer BR: The AAPM/RSNA physics tutorial for residents: Typical patient radiation doses in diagnostic radiology. Radiographics 19:1289–1302, 1999.
72. Howie PW: Thromboembolism. Clin Obstet Gynecol 4:397–417, 1977.
72a. Ridge CA, McDermott S, Freyne BJ, et al: Pulmonary embolism in pregnancy: comparison of pulmonary CT angiography and lung scintigraphy. AJR 193:1223–1227, 2009.
73. Ginsberg JS, Greer I, Hirsh J: Use of antithrombotic agents during pregnancy. Chest 119(Suppl 1):122S–131S, 2001.
74. Kher A, Bauersachs R, Nielsen JD: The management of thrombosis in pregnancy: role of low-molecular-weight heparin. Thromb Haemost 97:505–513, 2007.
75. Leonhardt G, Gaul C, Nietsch HH, et al: Thrombolytic therapy in pregnancy. J Thromb Thrombolysis 21:271–276, 2006.
76. Abenhaim HA, Azoulay L, Kramer MS, Leduc L: Incidence and risk factors of amniotic fluid embolisms: a population-based study on 3 million births in the United States. Am J Obstet Gynecol 199:49.e1–49.e8, 2008.
77. Clark SL: Amniotic fluid embolism. Crit Care Clin 7:877–882, 1991.
78. Morgan M: Amniotic fluid embolism. Anesthesia 34:20–32, 1979.
79. Clark SL, Hankins GD, Dudley DA, et al: Amniotic fluid embolism: Analysis of the national registry. Am J Obstet Gynecol 172:1158–1169, 1995.
80. Clark SL, Pavlova Z, Greenspoon J, et al: Squamous cells in the maternal pulmonary circulation. Am J Obstet Gynecol 154:104–106, 1986.
81. Clark SL: New concepts of amniotic fluid embolism: A review. Obstet Gynecol Surv 45:360–368, 1990.
82. Martin RW: Amniotic fluid embolism. Clin Obstet Gynecol 39:101–106, 1996.
83. Benson MD, Kobayashi H, Silver RK, et al: Immunologic studies in presumed amniotic fluid embolism. Obstet Gynecol 97:510–514, 2001.
84. American Heart Association: Guidelines 2000 for cardiopulmonary resuscitation and emergency cardiovascular care. Part 8: Advanced challenges in resuscitation. Section 3: Special challenges in ECC. Circulation 102(Suppl I):I229–I252, 2001.
85. Esplin MS, Varner MW: Progression of pulmonary arteriovenous malformation during pregnancy: Case report and review of the literature. Obstet Gynecol Surv 52:248–253, 1997.
86. Shovlin C, Sodhi V, McCarthy A, et al: Estimates of maternal risks of pregnancy for women with hereditary haemorrhagic telangiectasia (Osler-Weber-Rendu syndrome): Suggested approach for obstetric services. BJOG 115:1108–1115, 2008.
87. Gottlieb JD, Ericcson JA, Sweet RB: Venous air embolism. Anesth Analg 44:773, 1965.
88. Mendelson CJ: The aspiration of stomach contents into the lungs during obstetric anesthesia. Am J Obstet Gynecol 52:191–204, 1946.
89. Scrutton MJ, Metcalfe GA, Lowry C, et al: Eating in labor: A randomised controlled trial assessing the risks and benefits. Anesthesia 54:529–534, 1999.
90. Rasmussen GE, Malinow AM: Toward reducing maternal mortality: The problem airway in obstetrics. Int Anesthesiol Clin 32:83–101, 1994.
91. King TA, Adams AP: Failed tracheal intubation. Br J Anaesth 65:400–414, 1990.
92. Rocke DA, Murray WB, Rout CC, et al: Relative risk analysis of factors associated with difficult intubation in obstetric anesthesia. Anesthesiology 77:67–73, 1992.
93. Kirshon BG, Hinkley CM, Cotton DB, et al: Maternal mortality in a maternal-fetal medicine intensive care unit. J Reprod Med 35:25–28, 1990.
94. Cole DE, Taylor TL, McCullough DM, et al: Acute respiratory distress syndrome in pregnancy. Crit Care Med 33(10 Suppl):S269–S278, 2005.
95. Perry KG, Martin RW, Blake PG, et al: Maternal mortality associated with the adult respiratory distress syndrome. South Med J 91:441–444, 1998.
96. Edwards N, Middleton PG, Blyton DM, Sullivan CE: Sleep disordered breathing and pregnancy. Thorax 57:555–558, 2002.
97. Pérez-Chada D, Videla AJ, O'Flaherty ME, et al: Snoring, witnessed sleep apnoeas and pregnancy-induced hypertension. Acta Obstet Gynecol Scand 86:788–792, 2007.
98. Littner MR, Brock BJ: Snoring in pregnancy: Disease or not? Chest 109:859–860, 1996.
99. Boggess KA, Easterling TR, Raghu G: Management and outcome of pregnant women with interstitial and restrictive lung disease. Am J Obstet Gynecol 173:1007–1014, 1995.
100. King TE: Restrictive lung disease in pregnancy. Clin Chest Med 13:607–622, 1992.
101. Heffner JE, Sahn SA: Pleural disease in pregnancy. Clin Chest Med 13:667–668, 1992.
102. Lillington GA, Mitchell SP, Wood GA: Catamenial pneumothorax. JAMA 219:1328–1332, 1972.
103. Nakamura H, Konishiike K, Sugamura A, et al: Epidemiology of spontaneous pneumothorax in women. Chest 89:378–382, 1986.
104. Shearin RPN, Hepper NPG, Payne WS: Recurrent spontaneous pneumothorax concurrent with menses. Mayo Clin Proc 49:98–101, 1974.
105. Korom S, Canyurt H, Missbach A, et al: Catamenial pneumothorax revisited: Clinical approach and systematic review of the literature. J Thorac Cardiovasc Surg 128:502–508, 2004.
106. Bagan P, Le Pimpec Barthes F, Assouad J, et al: Catamenial pneumothorax: retrospective study of surgical treatment. Ann Thorac Surg 75:378–381, 2003.
107. Carter EJ, Ettensohn DB: Catamenial pneumothorax. Chest 98:713–716, 1990.
108. Joseph J, Sahn SA: Thoracic endometriosis syndrome: New observations from an analysis of 110 cases. Am J Med 100:164–170, 1996.

109. Van Schil PE, Vercauteren SR, Vermeire PA, et al: Catamenial pneumothorax caused by thoracic endometriosis. Ann Thorac Surg 62:585–586, 1996.
110. Augoulea A, Lambrinoudaki I, Christodoulakos G: Thoracic endometriosis syndrome. Respiration 75:113–119, 2008.
111. Muneyyirci-Delale O, Neil G, Serur E, et al: Endometriosis with massive ascites. Gynecol Oncol 69:42–46, 1998.
112. Blanco S, Hernando F, Gomez A, et al: Catamenial pneumothorax caused by diaphragmatic endometriosis. J Thorac Cardiovasc Surg 116:179–180, 1998.
113. Ryu JH, Moss J, Beck GK, et al: The NHLBI lymphangioleiomyomatosis registry: Characteristics of 230 patients at enrollment. Am J Respir Crit Care Med 173:105–111, 2006.
114. Kalassian K, Doyle R, Kao P, et al: Lymphangioleiomyomatosis: New insights. Am J Respir Crit Care Med 155:1183–1186, 1997.
115. NHLBI Workshop Summary: Report of workshop on lymphangioleiomyomatosis: NHLBI. Am J Respir Crit Care Med 159:679, 1999.
116. Bissler JJ, McCormack FX, Young LR, et al: Sirolimus for angiomyolipomas in tuberous sclerosis complex or lymphangioleiomyomatosis. N Engl J Med 358:140–151, 2008.
117. Kohorn EI: Clinical management and the neoplastic sequelae of trophoblastic embolization associated with hydatidiform mole. Obstet Gynecol Surv 42:484–488, 1987.
118. Coukos G, Makrigiannakis A, Chung J, et al: Complete hydatidiform mole: A disease with a changing profile. J Reprod Med 44:698–704, 1999.
119. Abramov Y, Elchalal U, Schenker JG: Obstetric outcome of in vitro fertilized pregnancies complicated by severe ovarian hyperstimulation syndrome: A multicenter study. Fertil Steril 70:1070, 1998.
120. Elchalal U, Schenker JG: The pathophysiology of ovarian hyperstimulation syndrome: Views and ideas. Hum Reprod 12:1129, 1997.
121. Kaiser UB: The pathogenesis of the ovarian hyperstimulation syndrome. N Engl J Med 349:729–732, 2003.

CHAPTER 87

THE RESPIRATORY SYSTEM AND NEUROMUSCULAR DISEASES

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INTRODUCTION

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INTRODUCTION

Gas exchange between the atmosphere and the human body depends not only on the lungs but also in large part on the function of the "ventilatory pump," which consists of the respiratory control centers located in the brain, the bony rib cage, diaphragm, and intercostal, accessory, and abdominal muscles. A wide variety of neuromuscular disorders can result in dysfunction of the ventilatory pump that in turn can lead to respiratory failure, pneumonia, and even death. Breathing disorders are recognized as the leading cause of mortality in neuromuscular disease,[1] and appropriate interventions can prevent complications and prolong life in individuals with neuromuscular disease affecting the respiratory system.

FUNCTIONAL ANATOMY OF THE RESPIRATORY SYSTEM

The ventilatory pump is designed to bring oxygen into the body to fuel energy generation and remove carbon dioxide as a waste product of cellular metabolism. The system is made up of the cortex of the brain that controls voluntary breathing; the brain stem, which is involved with automatic breathing; the spinal cord and motor neurons that transmit nerve impulses; the respiratory muscles that are the effectors of the system; and a complex system of feedback receptors and nerves that regulate ventilation (Fig. 87-1). The system is remarkably flexible and can precisely maintain CO_2 and acid-base balance despite encountering large variations in metabolic demands that result from the activities of daily living. The following is a discussion of each of the components of this complex network.

Central Nervous System

Voluntary Breathing Controllers

Voluntary breathing is controlled by signals from the cerebral cortex. Centers located within the parietal cortex send volitional signals that initiate inspiration and expiration.[2] These cortical areas project to the motor neurons in the spinal cord via the corticospinal tracts. These tracts are separate pathways from the reticulospinal pathways that connect the central automatic breathing centers to the motor neurons.

Automatic Breathing Controllers

Automatic breathing is controlled by a complex system that includes respiratory centers in the pons and medulla,

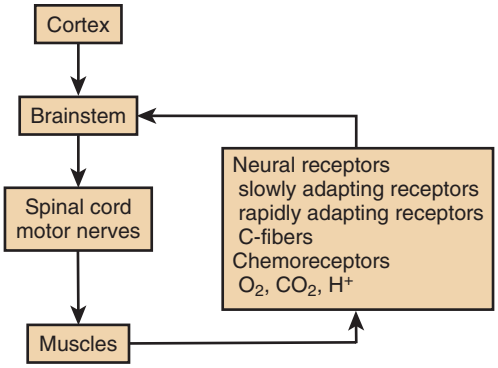

FIGURE 87-1 ■ Neuromechanical respiratory system shows the neuromuscular pathways and feedback control.

nerve tracts in the lower brain stem, the reticulospinal pathways in the spinal cord, and the feedback mechanisms that are both chemical and mechanical in nature. There are thought to be three centers that generate the rhythm and drive to breathe, one located in the pons and two in the medulla. More detailed reviews of this topic are available.[3,4]

Spinal Cord

The spinal cord and motor nerves conduct nerve impulses from the cortex and brain stem to the anterior horn cells of the motor neurons supplying the respiratory muscles. As noted previously, the nerve fiber tracts in the spinal cord responsible for voluntary (corticospinal tract) and automatic (reticulospinal tract) breathing are separate within the spinal cord.[5] The fibers in both of these tracts travel through the spinal cord to synapse with the lower motor neurons.

Peripheral Nervous System

Lower Motor Neurons

The lower motor neuron has its cell body in the spinal cord (anterior horn cell) but exits the spinal cord to become the spinal nerve roots and the nerves that supply the respiratory muscles. When the nerves arrive at the muscle, they divide into branches known as *twigs* that, upon reaching the muscle fiber, further divide into bulbous projections called *boutons* that apply themselves to the muscle membrane at a specialized anatomic junction called the *motor end plate*. These boutons contain acetylcholine, which is the chemical transmitter that serves to excite the muscle to contract. With nerve firing, there is release of acetylcholine at the motor end plate into the cleft between the nerve and the muscle. The acetylcholine binds to receptors on the muscle side of the motor end plate, which results in a *suprathreshold excitatory end plate potential* and depolarization of the muscle membrane.[6] A muscle action potential then results in contraction of the muscle fiber.

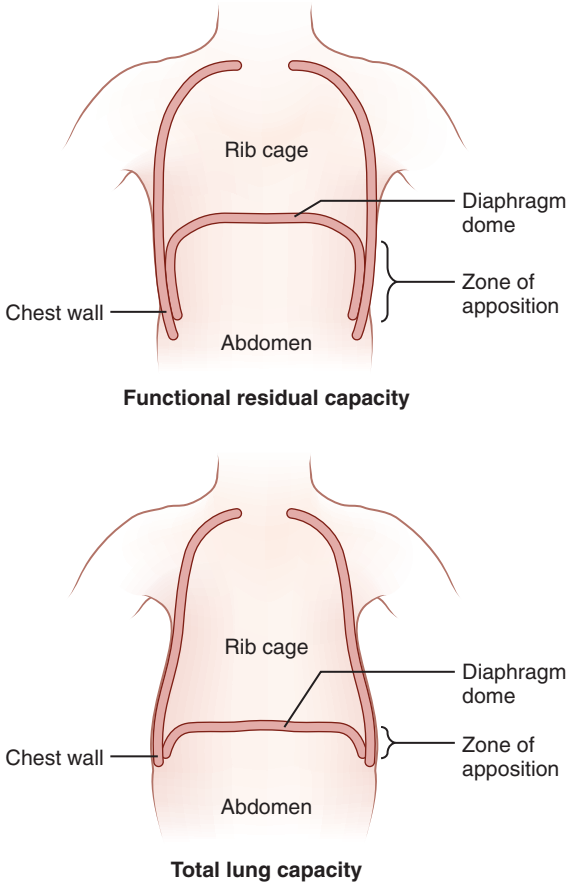

FIGURE 87-2 ■ Diaphragmatic positions at rest (*top*) and at full contraction (*bottom*). At functional residual capacity (FRC; *top*), the diaphragm lies within the chest with a zone of apposition along the chest wall. At total lung capacity (TLC), the contracted diaphragm has displaced abdominal contents and, via the increase in abdominal pressure, has expanded the chest wall outward.

Respiratory Muscles

The respiratory muscles are the mechanical effectors of the breathing system. They are often divided into three major groups: (1) the inspiratory muscles, (2) the expiratory muscles, and (3) the accessory muscles of respiration. The muscles that maintain patency of the upper airway during the respiratory cycle are sometimes also considered muscles of respiration because of their close interaction with the other respiratory muscles.

The diaphragm is the major muscle of inspiration and accounts for approximately 70% of the inhaled tidal volume in the normal individual[7] (Fig. 87-2). Contraction of the diaphragm results in a downward piston motion of the muscle as well as outward and upward movement of the ribs through the *zone of apposition*. The innervation of the diaphragm is via the phrenic nerve that originates from cervical nerve roots three through five. The intercostal muscles are thin sheets of muscular fibers that run between the ribs in the costal spaces.[8] There are two sheets of muscle fibers, the external and internal intercostals. The external intercostals function to expand the

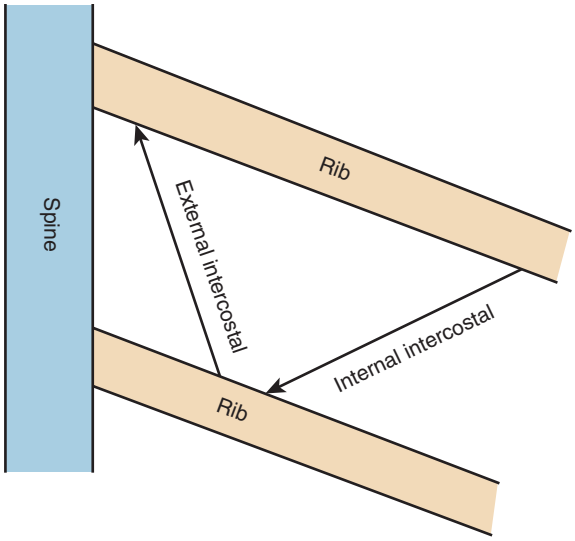

FIGURE 87-3 ■ Actions of the intercostal muscles on the ribs. Contraction of the external intercostals results in an upward and outward movement of the ribs during inhalation. Contraction of the internal intercostals results in a downward and inward movement of the ribs during exhalation.

rib cage during inspiration. The internal intercostals are deeper and function to decrease rib cage size during expiration. The mechanism of action of the intercostal muscles on the ribs is shown in Figure 87-3. The orientation of the muscle fibers with respect to the ribs results in the increase or decrease in the size of the rib cage. Innervation of the intercostals is via the intercostal nerves originating from the thoracic spinal nerve roots.

The abdominal muscles (rectus abdominis, internal oblique, external oblique, and tranversus abdominis) serve a number of functions in respiration that mainly assist expiration but can also function in inspiration. The internal and external obliques and the transversus abdominis result in an inward movement of the abdominal wall that displaces the diaphragm upward into the thoracic cavity and assists exhalation. The rectus abdominis as well as the internal and external obliques pull the lower rib cage caudally and thereby increase pleural pressure and exhalation. The abdominal muscles also may play a minor role in inspiration[9]; if their contraction reduces lung volume below function residual capacity (FRC), abdominal muscles can store elastic recoil energy in the chest wall that then assists expansion of the chest wall during the next inspiration.

The accessory muscles of respiration (sternocleidomastoid, scalenes, trapezii, latissimus dorsi, platysma, and pectoralis major and minor muscles) can expand the rib cage and assist inspiration during situations of increased ventilatory demand such as during exercise or during circumstances in which other inspiratory muscles are impaired as in tetraplegia or chronic obstructive pulmonary disease (COPD). It is now clear that some of them function during minimal exertion and even during quiet tidal breathing.[10]

The muscles of the upper airway are also considered to be muscles of respiration because they maintain patency of the upper airway and allow air to flow into and out of the lungs without interruption.[11] Some of these also participate in protection of the lower airway during swallowing, a key function in the defense of the respiratory system. The upper airway muscles include the abductors of the vocal cords, the palatal elevators, retractors of the tongue, and dilators of the nares. These muscles are innervated by cranial nerves V, VII, and IX-XII. The central control centers for these muscles are the same as those described previously for the more commonly considered ventilatory muscles.

Controller Feedback

The respiratory control mechanisms depend on both neural and chemical receptors found in peripheral and central sites. An excellent discussion of this topic is available.[12] The automatic respiratory centers in the brain stem respond to feedback from these receptors and adjust neural output to the ventilatory and upper airway muscles that expand the chest wall and maintain upper airway patency (see Fig. 87-1).

Neural receptors are present in the upper airway, respiratory muscles, lungs, and pulmonary vessels.[12] Once stimulated, these receptors project signals to the central respiratory controller via the vagus nerve. The respiratory centers then adjust their output to the respiratory muscles to alter ventilation and modulate reflexes such as cough and sneeze. There are several different types of neural receptors. *Muscle spindles* and *slowly adapting pulmonary stretch receptors (SARS)* predominantly respond to changes in lung and thoracic cage volume. As the lung and chest wall inflate, these receptors are stretched and dampen the output from the inspiratory centers in the medulla. These receptors are involved in the "Hering-Breuer" reflex in which inspiration is halted as lung volume increases.[13] *Rapidly acting irritant receptors (RARS)* respond to changes in lung volume, to chemical stimuli such as histamines and prostaglandins, and to noxious stimuli. *C fibers* in the airways and lung are stimulated by chemical stimuli in the local environment. The C fibers likely mediate the hyperventilation that is seen in normoxic circumstances in a number of pulmonary disorders such as asthma, pulmonary embolism, pneumonia, and pulmonary edema.

Chemical receptors or *chemoreceptors* are located both peripherally as well as in the central nervous system.[12] The *peripheral chemoreceptors*, which include the carotid and aortic bodies, are the primary site for sensing low levels of arterial oxygen pressure (Pa_{O_2}) but also respond to a lesser extent to changes in arterial carbon dioxide pressure (Pa_{CO_2}) and pH. They are stimulated when the Pa_{O_2} falls below 75 mm Hg as well as when the Pa_{CO_2} increases and pH decreases. Whereas both receptors stimulate ventilation in hypoxia, the aortic chemoreceptors are more important in infants and the carotid receptors are more important in adults.[14] Once stimulated, the carotid bodies send impulses via cranial nerve IX to the nucleus tractus solitarius (NTS) where neurotransmitters are released that increase

ventilation.[15] Although the control of ventilation during exercise is not completely understood, the predominant stimulus for increased ventilation is thought to arise from the peripheral receptors. It is postulated that additional peripheral receptors exist that are yet to be identified because the hyperventilatory response of exercise cannot be fully accounted for by the carotid bodies.[16] The *central chemoreceptors* are crucial in the adjustments of ventilation to acid-base disturbances and $PaCO_2$. There are four groups of chemosensitive neurons in the brain stem: the locus ceruleus, the NTS, the midline raphe, and the ventrolateral quadrant of the medulla. The central chemoreceptors are responsible for most of the response to carbon dioxide. They respond to increases in $PaCO_2$ by their detection of the fall in pH of the cerebrospinal fluid associated with an increase in cerebrospinal fluid (CSF) $PaCO_2$,[3] which closely follows an increase in serum $PaCO_2$. Of note, it appears that the parasympathetic nervous system is important in the response to CSF pH changes because inhibition of acetylcholine transmission can abolish the central pH response in animals.[15]

DISEASES AFFECTING THE RESPIRATORY SYSTEM

The diseases of the neurorespiratory system can be organized most logically in the framework of functional anatomy. Diseases of the central nervous system known to affect the respiratory system are listed in Table 87-1, and those affecting the peripheral nervous system are shown in Table 87-2.

TABLE 87-1. Diseases of the Central Nervous System Associated with Respiratory Dysfunction

Cerebral Cortex	Brain Stem/Basal Ganglia	Spinal Cord
Stroke	Stroke	Trauma
Neoplasm	Neoplasm	Infarction or hemorrhage
Cerebral degeneration	Poliomyelitis	Demyelinating disease
Seizures	Central alveolar hypoventilation	Disc compression
	Progressive bulbar palsy	Syringomyelia
	Multiple system atrophy	Tumor
	Anoxic encephalopathy	Epidural abscess
	Encephalitis	
	Multiple sclerosis	
	Parkinson's disease	
	Chorea	
	Dyskinesias	

TABLE 87-2. Diseases of the Peripheral Nervous System Associated with Respiratory Dysfunction

Motor Nerves/Anterior Horn Cell	Neuromuscular Junction	Myopathies
Acute idiopathic polyneuropathy (Guillain-Barré syndrome)	Myasthenia gravis	Muscular dystrophies
Motor neuron disease	Lambert-Eaton myasthenic syndrome	Myotonic dystrophy
Amyotrophic lateral sclerosis	Toxins	Poly- and dermatomyositis
Spinal muscular atrophy	Botulism	Glycogen storage diseases
Primary lateral sclerosis	Snake venoms	Pompe disease
Critical illness neuropathy	Scorpion bites	Forbes-Cori disease
Vasculitides	Shellfish	Thick filament myopathy
Toxins (e.g., lithium, arsenic, gold)	Crab poisoning	Mitochondrial myopathy
Metabolic	Drugs	Nemaline body myopathy
Diabetes	Antibiotics	Severe hypokalemia
Porphyria	Neuromuscular junction blockers	Hypophosphatemia
Uremia	Anticholinesterase inhibitors	
Diphtheria	Corticosteroids	
	Lidocaine	
	Quinidine	
	Lithium	
	Antirheumatics	

Central Nervous System Diseases

Cortical and Brain Stem Disorders

Diseases of Voluntary Breathing. The pathways that connect the voluntary respiratory centers of the cortex with spinal motor neurons (corticospinal tracts) can be affected in a number of disorders. Midpontine strokes can damage the corticospinal tracts and cause what is known as the "locked-in syndrome,"[17] a syndrome with total paralysis with the exception of eye movement. Because injury to the reticulospinal tracts causes loss of volitional but not automatic breathing, the response to automatic breathing is preserved.[18] This syndrome is most commonly due to ischemic stroke but can be due to pontine tumor, central pontine myelinolysis, high cervical demyelination, syphilitic arteritis, and head injury. Extrapyramidal disorders such as parkinsonism can also affect voluntary breathing.[19] In these disorders, patients have less ability to alter their breathing pattern voluntarily. They also may demonstrate periodic breathing or a Cheyne-Stokes respiratory pattern.

Diseases of Automatic Breathing. Automatic breathing but not voluntary breathing is classically disrupted in central alveolar hypoventilation, otherwise known as "Ondine's curse,"[20] caused by injury to the automatic respiratory centers in the brain stem. Because automatic triggering controls breathing during sleep, individuals with central hypoventilation develop central sleep apnea. Congenital central alveolar hypoventilation is a rare genetic disorder affecting infants and children, although it has now been described in adults as well.[21] Acquired central alveolar hypoventilation can result from uni- or bilateral medullary infarction, from bulbar poliomyelitis, or from bilateral cervical tractotomy performed to control chronic pain. Although disorders of the neurorespiratory system generally lead to hypoventilation and the need for ventilatory support, diseases of the automatic respiratory centers in the brain stem can also lead to hyperventilation. Hyperventilation may be caused by diseases such as central nervous system infection or tumor[22] or by stimulation of an otherwise normal autonomic respiratory center by fever, sepsis, pain, pregnancy, medications such as progesterone or salicylates, and high altitude. A variety of irregular breathing patterns have also been associated with central nervous system disease including Cheyne-Stokes respiration and ataxic breathing.[23]

Diseases of the Spinal Cord

Spinal Cord Injury. Spinal cord injury (SCI) is most commonly due to traumatic injury caused by motor vehicle accidents, falls, sports accidents, and gunshot wounds. In the United States, there are an estimated 250,000 individuals who have suffered significant SCI; the incidence is approximately 12,000 incident cases per year with 78% of the injuries occurring in males (National Spinal Cord Injury Statistical Center http://www.spinalcord.uab.edu). Respiratory complications including atelectasis, pneumonia, and respiratory failure are the leading cause of morbidity and mortality for individuals with SCI.[24,25] After acute SCI, a number of physiologic changes can affect the respiratory system and predispose to respiratory complications. These aberrations include (1) cough inefficiency due to expiratory muscle weakness, (2) ciliary dysfunction, (3) mucous hypersecretion possibly due to impairment of the peripheral autonomic nervous system, (4) glottic dysfunction or gastric hypomotility increasing the risk of aspiration, and (5) loss of consciousness at the time of the injury increasing the risk of aspiration.[26,27]

Acute respiratory failure immediately after the injury may be due to direct disruption of respiratory muscle innervation (cervical cord injury), aspiration at the scene due to loss of consciousness, pulmonary edema, or other traumatic injuries to the chest or head. Many individuals with SCI are intubated at the scene of the accident or shortly thereafter. Prevention of further respiratory complications is important. Preventive measures include encouragement of deep breathing and cough, frequent changes of position, postural drainage, assisted cough (manual or mechanical), and bronchoscopy when other measures fail. Patients with SCI are at high risk of venous thromboembolism with the greatest risk 3 days to 2 weeks post injury. Prophylaxis for deep venous thrombosis is highly recommended during the initial hospitalization.

The extent of respiratory muscle impairment following SCI will depend mainly on the level and severity of the spinal injury because the function of respiratory muscles innervated below the site of the cord injury is lost. The innervation of the respiratory muscles is shown

TABLE 87-3. Respiratory Muscles and Their Innervation

Muscle Group	Spinal Cord Level	Nerve (s)
INSPIRATORY MUSCLES		
Diaphragm	C3-5	Phrenic
Parasternal intercostals	T1-7	Intercostal
Lateral external intercostals	T1-12	Intercostal
Scalenes	C4-8	Cervical (deep branches)
Sternocleidomastoids	Above spinal cord	Spinal accessory
EXPIRATORY MUSCLES		
Lateral internal intercostals	T1-12	Intercostal
Rectus abdominis	T7-L1	Lumbar
External and internal obliques	T7-L1	Lumbar
Transversus abdominis	T7-L1	Lumbar
UPPER AIRWAY MUSCLES		
Muscles of mastication	—	CN V, VII
Laryngeal and pharyngeal	—	—
Abductors	—	CN IX-XII
Adductors	—	CN IX-XII

CN, cranial nerve.

in Table 87-3. The overall pattern of pulmonary function abnormality is one of restriction. In the first few months to a year following the initial SCI, there is a significant improvement in lung volumes and maximal inspiratory and expiratory pressures,[28,29] possibly due to resolution of spinal cord edema and/or strengthening of the diaphragm and accessory muscles of inspiration.

In general, the higher the SCI, the more likely that ventilatory assistance will be needed. Treatment of ventilatory failure following SCI can be accomplished by invasive (tracheostomy) or noninvasive (mask or mouthpiece) methods.[30] Many individuals will be ventilated through a tracheostomy tube for some time after their injury; however, transfer to noninvasive means can often be achieved even for those requiring full-time ventilatory support. The choice of invasive versus noninvasive ventilation will be determined by the degree of local expertise with these forms of ventilation as well as by patient preference. For those with high cervical SCI (C1-2) and intact phrenic nerve function, diaphragm pacing is also a possibility. It should be noted that those with diaphragm pacemakers implanted will still need a tracheostomy in place to avoid airway obstruction during sleep owing to the absence of the normal neurologic coordination of diaphragm contraction and upper airway dilation during inspiration. Although traumatic SCI is the major cause of spinal cord pathology, other causes include vascular accidents, demyelinating diseases (multiple sclerosis, transverse myelitis), syringomyelia, tumors, and epidural abscess (see Table 87-1).

Ventilator dependence in patients with SCI is more common with high (cervical) SCI. Because the diaphragm is the major muscle of inspiration (C3-5 spinal nerve roots), those with lesions at C3 and above invariably require ventilatory support and are at the highest risk of respiratory complications.[25,31] Those with injuries between C3 and C5 will vary in their requirements for ventilatory support. Even if they require ventilation initially, these individuals may become independent of ventilatory support eventually.[29,32] The risk of ventilator dependence in this group of patients is greatest for those with injury close to C3 or age older than 50 years.[29] Individuals with lesions below C5 almost always become independent of continuous ventilator support.[27] In contrast to inspiratory muscle function, expiratory muscle function is impaired at all levels of cervical cord injury resulting in expiratory muscle weakness and ineffective cough. Because an effective cough depends in large part on abdominal and intercostal muscle function (spinal nerve roots T1-L1), cervical, thoracic, and even some high lumbar SCI can impair the ability to cough and clear secretions. Therefore, measurement of cough function in these patients is very important.

Other Respiratory Effects of Spinal Cord Injury. For unknown reasons, the frequency of sleep apnea appears to be increased by as much as fourfold in patients with SCI over similar aged normal populations.[33,34] A sleep study should be considered when symptoms of nocturnal hypoventilation such as morning headache, daytime hypersomnolence, or unexplained nocturnal awakenings are present or when daytime hypercarbia ($PaCO_2$ > 45 mm Hg), unexplained cor pulmonale, or forced vital capacity (FVC) less than 50% predicted are present.[35] Bronchial hyperreactivity and bronchial hypersecretion are also present in some individuals following SCI likely due to interference with normal autonomic control of the airways after injury.[36]

Peripheral Nervous System Diseases

Diseases of Motor Nerves or Anterior Horn Cells

Disorders of the motor nerves and the neuromuscular junction (NMJ) can arise acutely as in acute inflammatory polyneuropathy (Guillain-Barré syndrome) or botulinum toxicity or can arise more chronically as in motor neuron disease (e.g., amyotrophic lateral sclerosis [ALS]) or myasthenia gravis (see Table 87-2). The level of motor nerve root involvement will dictate the effects of the disorder on the respiratory system.

Acute Diseases Affecting Motor Nerves

Acute Inflammatory Polyneuropathy. Acute inflammatory polyneuropathy, also referred to as Guillain-Barré syndrome, is a heterogeneous group of diseases that are now thought to be caused by antiglycolipid antibodies.[37] Acute idiopathic demyelinating polyneuropathy (AIDP) is the most common form, making up about 85% to 90% of cases. It is an acute progressive process characterized by symmetrical, ascending muscle weakness progressing over a 2-week period and associated with loss of deep tendon reflexes. It is thought that an antecedent viral infection induces an immune response to viral epitopes that then cross-react with lipid components of the peripheral nerve.[38] The process usually starts in the lower extremities but may start in the arms or the face, head, and neck primarily (Miller-Fisher variant).[39]

AIDP affects the respiratory system by causing (1) weakness of the upper airway muscles, (2) weakness of the inspiratory and expiratory muscles, and (3) secondary complications such as pneumonia or pulmonary embolism.[40] Approximately 25% to 50% of patients develop respiratory insufficiency severe enough to necessitate intubation and mechanical ventilation.[41,42] A number of variables used to predict impending respiratory failure and the need for mechanical ventilatory support have been utilized including FVC, maximal inspiratory pressure (MIP), maximal expiratory pressure (MEP), and nocturnal desaturation. Generally accepted guidelines for intubation and mechanical ventilation include an FVC less than 15 ml/kg, an FVC less than 1 L, a decline in FVC to 50% or less of the normal predicted value for that individual or an MIP of 30 cm H_2O or less.[40] FVC and MIP should be monitored frequently (multiple times per day depending on rapidity of progression). With rapidly progressive disease, the intensive care unit (ICU) is considered the best location for monitoring. Absolute indications for intubation include impaired consciousness, respiratory or cardiac arrest, shock, arrhythmias, blood-gas alterations, or bulbar dysfunction with confirmed aspiration.[40] Noninvasive ventilation is generally not an option for these individuals because

they are at a high risk for aspiration because of bulbar muscle involvement. Successful extubation may be achieved once treatment such as steroids, immune globulin, and plasmapheresis is begun and respiratory muscle strength returns.[43] Until respiratory muscle strength returns, scrupulous supportive ICU care including tracheostomy for prolonged mechanical ventilation is required to prevent complications such as ventilator-associated pneumonia and sepsis.

Poliomyelitis. Poliomyelitis is a viral disease caused by a human enterovirus that caused significant epidemics with frequent respiratory complications in the United States and Western Europe during the 20th century. Owing to improved sanitation and vaccine development, polio is no longer a major public health issue in the developed world. However, in the developing world, acute infections still occur.[44]

In the developed world, the major health issue arising from polio currently is the postpolio syndrome, in which new weakness develops in survivors of the polio epidemics of the mid-20th century.[45,46] The cause of progressive neurologic deterioration in postpolio syndrome is unknown. Theories of pathogenesis suggested include (1) progressive degeneration of reinnervated motor units, (2) persistence of poliovirus in neural tissue, or (3) induction of autoimmunity with subsequent destruction of neural structures.[47,48] The average time to onset from the time of the initial infection is 35 years but ranges from 8 to 71 years. A high percentage of polio survivors, between 20 and 60% of individuals, complain of new muscle weakness.[48] Although the exact incidence of respiratory system involvement in postpolio syndrome is not known, sleep-disordered breathing is common and noninvasive nocturnal ventilation can be highly effective.[49] Fortunately, it appears that frank hypoventilation associated with the postpolio syndrome is unusual.[50]

Chronic Diseases Affecting Motor Nerves. ALS is a progressive neurodegenerative disease with no known cure. The usual clinical presentation is that of an individual with gradually progressive asymmetrical weakness associated with hyperreflexia due to upper motor nerve involvement and muscle fasciculations due to lower motor nerve involvement. Like most neurologic diseases, ALS has no direct effect on the lung; however, it significantly affects the upper airway, chest wall, and diaphragm impairing respiratory muscle function. Indeed, ALS affects all of the major muscle groups of the respiratory system including (1) upper airway muscles leading to abnormal swallowing and inadequate cough, (2) expiratory muscles leading to inadequate cough, and (3) inspiratory muscles leading to inadequate ventilation. Therefore, all patients with ALS are at significant risk of respiratory complications. Respiratory failure, the leading cause of death in this population, has been reported as the initial clinical presentation of ALS.[51] Patients may complain of dyspnea, difficulty managing secretions, or inability to cough effectively. Monitoring pulmonary function in the outpatient setting is crucial. The FVC is the most commonly used measurement and has prognostic significance.[52,53] Attention must be given to glottic and cough function as well.[54] Sleep-disordered breathing is very common in ALS and noninvasive positive-pressure ventilation (NPPV) has been used both at night and, as the disease progresses, during the day to improve quality and duration of life.[55–57] Patients often have difficulty managing secretions owing to swallowing dysfunction. Secretions can be reduced by utilizing anticholinergic agents,[58] by low-dose irradiation of salivary glands,[59] or by injecting the glands with botulinum toxin.[58,60] As ALS progresses, NPPV will cease to be effective and a decision will need to be made concerning the appropriateness of tracheostomy and long-term invasive ventilation. Although tracheostomy can prolong survival substantially,[61] it does not alter the progression of the disease and patients will ultimately become completely paretic. Due to different cultural approaches, rates of invasive ventilation vary substantially among countries.[62]

Spinal muscular atrophy (SMA 1, 2, or 3) is a group of autosomal recessive genetic motor neuron diseases that affect infants and children and is associated with respiratory muscle weakness and breathing failure.[63] Noninvasive ventilation and tracheostomy with mechanical ventilation have both been applied in this disorder.

Neuromuscular Junction Diseases

Myasthenia Gravis. Myasthenia gravis is the most common disease affecting neuromuscular transmission. It is an autoimmune disease characterized by an antibody-mediated immune attack directed at acetylcholine receptors and/or receptor-associated proteins in the postsynaptic membrane of the NMJ. It causes weakness of several muscle groups including the respiratory muscles. The respiratory muscles are particularly susceptible to fatigue during the severe, potentially life-threatening, exacerbations known as *myasthenic crisis*. The clinical considerations during myasthenic crisis are very similar to those for AIDP noted earlier and the indications for intubation are the same.[40] Acute treatment of myasthenic crisis focuses on rapid therapies including intravenous immunoglobulin (IVIG) as well as plasmapheresis and corticosteroid therapy.[64,65] Assiduous attention to respiratory care provides support of the patient, allowing time for therapy of the underlying myasthenia to be effective.

Myasthenia gravis can also occur as a paraneoplastic syndrome in association with thymoma. It has been estimated that approximately 15% of all patients with thymoma will exhibit myasthenia gravis. Removal of the thymoma may result in amelioration of the myasthenia symptoms.

The Lambert-Eaton myasthenic syndrome (LEMS) is a myasthenic syndrome associated with small cell lung cancer that can affect the respiratory muscles in a fashion similar to that of myasthenia gravis. In patients with small cell lung cancer, LEMS may be present in approximately 3% of cases.[66] In patients with LEMS, the small cell lung cancer may also be occult and should be sought for up to 5 years after the diagnosis of LEMS. LEMS is thought to be due to autoantibodies directed against presynaptic voltage-gated calcium channels (VGCCs),[67] thereby interfering with synaptic function. Although

respiratory involvement is often a late finding, frank respiratory failure can be a manifestation of LEMS,[68] and this disorder should be considered in individuals with unexplained neuromuscular weakness. Although LEMS shares a similar pathophysiologic mechanism with myasthenia gravis, the clinical presentation is different and is characterized by (1) an increase in the compound muscle action potential with repetitive nerve stimulation, a feature not seen in myasthenia, (2) more frequent presence of proximal leg weakness, which is worse in the morning, (3) greater autonomic dysfunction, and (4) frequent association with malignancy.[69]

Botulism. Botulism is a neuroparalytic syndrome that is caused by a toxin produced by the gram-positive bacterium *Clostridium botulinum*. It can be acquired by humans in one of five different ways: (1) food-borne botulism, in which there is ingestion of food contaminated with preformed toxin, (2) wound botulism, in which the bacteria growing in the wound produce toxin in vivo, (3) infant botulism, in which there is ingestion of clostridial spores allowing colonization of the host's gastrointestinal tract by the bacteria and production of the toxin in vivo, (4) adult enteric infectious botulism, which is similar to infant botulism, and (5) inhalational botulism, which follows inhalation of aerosolized toxin released in an act a bioterrorism.[70]

C. botulinum produces a number of toxins that can produce paralysis by binding to synaptotagmin I and II receptors that mediate their entry into the nerve cell cytoplasm.[71] Once intracellular, the toxin produces irreversible disruption in stimulation-induced acetylcholine release. The botulinum toxin is one of the most potent toxins known. Recovery from the injury requires regrowth of new synapses, a process than can take 6 months. The clinical syndrome is one of progressive paralysis with early cranial nerve involvement causing blurred vision, dysphagia, dysarthria, and facial weakness. Descending muscle weakness is the usual course and involvement of the upper airway, diaphragm, and intercostal muscles often leads to the requirement for intubation and mechanical ventilation.[72] All patients should be monitored in the ICU and intubation should be undertaken for those who cannot protect their airway or who have a vital capacity of less than 30 % predicted. Botulism antitoxin (IV botulinum immune globulin) is available for use in the United States and is given to infants younger than 1 year of age.[73] For adults, supportive care is the mainstay of therapy. Prolonged hospitalization is common.

Other Neuromuscular Junction Toxins. A number of other toxins can affect the NMJ. The insecticides, organophosphates and carbamates, are potent inhibitors of acetylcholinesterase, leading to high levels of acetylcholine in the NMJ, resulting in parasympathetic and sympathetic overstimulation, skeletal muscle paralysis, and, sometimes, respiratory failure.[74] Several species of tick produce toxins that can inhibit NMJ neurotransmission (tick paralysis) by inhibiting influx of sodium ions and preventing presynaptic terminal axon depolarization and the release of acetylcholine at the nerve terminal.[75] Snake venom from a number of families of snakes produces neurotoxins that can cause paralysis, respiratory failure, and death owing to inhibition of neurotransmission.[76] Finally, a wide range of medications can cause NMJ blockade including D-penicillamine, aminoglycoside antibiotics, fluoroquinolone antibiotics, phenytoin and other anticonvulsants, lithium, β-blockers, glucocorticoids, and magnesium sulfate.[77]

Diseases of the Respiratory Muscles

A large number of disorders both acute and chronic can directly affect the respiratory muscles (see Table 87-2). There are many causes of chronic muscle disease resulting in respiratory muscle dysfunction including genetic muscular dystrophies, myopathies, and myotonias as well as inflammatory myopathies and those associated with systemic diseases.

Duchenne and Becker Muscular Dystrophies. Duchenne and Becker muscular dystrophies are both progressive myopathic disorders caused by mutations of the dystrophin gene on chromosome Xp21.[78] Dystrophins are glycoproteins that coat sarcolemmal, sarcomeric, and cytosolic muscle proteins. In Duchenne dystrophy, dystrophin is absent, whereas, in Becker dystrophy, a milder variant, dystrophin is reduced in quantity or quality. Both disorders are inherited as X-linked recessive traits and are characterized by progressive muscle wasting and weakness,[79] typically of limbs. However, both can involve the respiratory muscles leading to major morbidity and mortality. The diaphragm, however, may be less susceptible than limb muscle because of different gene transcription patterns.[80]

In Duchenne muscular dystrophy, weakness of proximal muscle groups usually manifests itself by age 2 to 3 with respiratory muscle weakness becoming evident later in childhood.[81] In Becker muscular dystrophy, weakness manifests later in childhood and individuals can remain ambulatory often into adult life. Because exercise is limited by limb muscle weakness, affected individuals may not complain of dyspnea on exertion despite involvement of the respiratory muscles. However, severe inspiratory muscle weakness (maximum inspiratory pressure [P_{Imax}] < 50% predicted) will lead to a reduction in lung volumes. This restrictive process can be worsened by other consequences of muscular dystrophy such as scoliosis, kyphosis, or muscle contractures.

The diagnosis is often suspected by noting an elevated serum creatine kinase. However, this finding is not specific for these disorders. Often, a muscle biopsy is obtained to distinguish muscular dystrophies from inflammatory skeletal muscle disorders and other forms of dystrophy. With muscular dystrophy, there is degeneration and regeneration of muscle fibers as well as replacement of muscle by fat and connective tissue. Immunoblots for dystrophin can aid in distinguishing Duchenne from Becker muscular dystrophy. Finally, analysis for deletions in the dystrophin gene may be useful but detection of point mutations of this gene may be difficult.[82] Sisters of individuals with Duchenne or Becker muscular dystrophy should be tested to determine if they are carriers of the disease. Carriers will often

have elevated creatine kinase levels.[83] It is important to identify carriers not only for genetic counseling but also because they may be at higher than average risk of developing cardiomyopathy.

The combination of a restrictive pulmonary deficit and expiratory muscle weakness predisposes these individuals to developing respiratory complications such as atelectasis and pneumonia. Therefore, it is important that these individuals get prompt treatment for bronchitis and pneumonia. In addition, cough-assist devices or assisted cough can be helpful in aiding removal of airway secretions. As the respiratory muscles further weaken and the restriction becomes severe, patients often need nocturnal ventilatory assistance. Nocturnal ventilation is usually initiated if there are symptoms related to nocturnal hypoventilation, right heart failure, or the presence of an elevated $Paco_2$ either at night or during the day. Noninvasive ventilation is a therapeutic intervention that typically can be delivered with a positive-pressure device using an interface such as a nasal mask, nasal-oral mask, or mouthpiece (discussed further later). Although there are no randomized, controlled trials in patients with muscular dystrophy, noninvasive ventilation is likely to improve quality of life, physical activity, and hemodynamics and normalize arterial blood gases.[84,85] Endurance and strength training targeting the inspiratory muscles may slow the progression of the disease in individuals with mild to moderate weakness.[86] If individuals with Duchenne or Becker muscular dystrophy require surgery, they may be at higher risk of respiratory complications.[87] A consensus statement has been published addressing the respiratory and other risks of anesthesia and suggesting methods for avoiding excessive morbidity and mortality.[88]

Other muscular dystrophies such as limb girdle muscular dystrophy (LGMD), fascioscapulohumeral dystrophy (FSHD), and myotonic dystrophy can affect the respiratory muscles but do not generally cause respiratory impairment until later in the course of the disease.

Chronic Inflammatory Myopathies. Dermatomyositis, polymyositis and inclusion body myositis (IBM) are systemic inflammatory diseases of unknown etiology that cause profound skeletal muscle weakness.[89] Dermatomyositis and polymyositis involve proximal muscle groups, whereas IBM may involve both proximal and distal muscle groups. Dermatomyositis can be seen in children and adults, whereas polymyositis and IBM are generally seen only in adults. Inflammatory myopathies can involve the diaphragm, intercostal muscles, and accessory muscles but other peripheral muscle groups are usually more severely affected than the respiratory muscles.[90] Symptoms are due to slowly progressive muscle weakness. IBM is similar to polymyositis except that the onset of symptoms is usually after age 50, it is more commonly seen in men than in women, and characteristic vacuoles are seen in affected muscle. Symptoms related to respiratory muscle weakness usually are not the presenting complaints. However, respiratory muscle weakness can occur in 5% to 10% of the patients with dermatomyositis and polymyositis[90] and may be found in as many as 75% of individuals if respiratory muscle function is carefully evaluated.[91] Interstitial lung disease may occur in up to 70% of patients with dermatomyositis or polymyositis.[92] Individuals diagnosed with dermatomyositis or polymyositis should be evaluated for the presence of restrictive pulmonary disease, which may be due to respiratory muscle weakness as well as to underlying interstitial lung disease. If respiratory muscle weakness is pronounced (P_{Imax} < 30% of predicted), ventilatory failure may ensue.[90] Respiratory muscle weakness can also impair cough, which, in concert with esophageal dysfunction and lymphopenia, can predispose these patients to pneumonia. Occasionally, patients with severe and progressive muscle weakness can develop respiratory failure. However, most cases of dermatomyositis and polymyositis respond to treatment with cortcosteroids whereas IBM is generally resistant to all therapies. As with other diseases, treatment with glucocorticoids and cytotoxic agents increases the risk of opportunistic pulmonary infection with fungi, nocardia, or *Pneumocystis jirovecii*.[93]

Metabolic Myopathies

Glycogen Storage Disease. A number of enzyme deficiencies can lead to disordered glycogen metabolism, resulting in accumulation of glycogen in tissue including skeletal and cardiac muscle. The glycogen storage diseases that are most likely to affect the respiratory system are acid maltase deficiency (type II—Pompe disease) and debranching enzyme deficiency (type III—Forbes-Cori disease). These disorders usually present in childhood, but some, such as Pompe disease, have separate adult-onset forms. In general, glycogen storage disorders are inherited as autosomal recessive conditions.

Acid Maltase Deficiency. Acid maltase deficiency, also known as glycogen storage disease type II or Pompe disease, is due to the deficiency of acid α-glucosidase, an enzyme responsible for the degradation of glycogen polymers to glucose. Deficiency of this enzyme allows accumulation of glycogen within cardiac and skeletal muscle lysosomes, resulting in myopathy. Although typically involving infants, this disease can manifest in adulthood.[94] Complete enzyme deficiency results in cardiorespiratory failure and death, usually in the first year of life.[95] When the onset of weakness occurs after age 1, the disease is less severe and does not involve the heart. Initially, subjects develop symptoms related to muscle weakness; those with a later onset of symptoms have a better prognosis. With respiratory muscle involvement, there may be restrictive ventilatory limitation and, in most severe cases, respiratory failure. Results from trials of enzyme replacement therapy with recombinant acid α-glucosidase are promising, showing potential improvements in motor status, function, and survival.[96]

Other Metabolic Myopathies. Myopathies can be caused by defects of lipid metabolism (carnitine, palmitoyl transferase deficiency) or disorders involving the mitochondria directly.

Disorders of lipid metabolism may be caused by an abnormal carnitine transporter protein ("primary" carnitine deficiency) or a deficiency of carnitine secondary to other metabolic diseases.[97] These disorders usually do not cause respiratory disability but involve other skeletal

muscle groups (arms and legs) and may involve cardiac muscle.

Mitochondrial disorders include those due to deficiencies of enzymes in the mitochondrial respiratory chain complexes and to defects of phosphorylation-respiration coupling. Disorders of mitochondrial metabolism involving complex I, II, III, IV, and V cause multiple respiratory chain defects.[98] The main symptoms of mitochondrial myopathy are muscle weakness and wasting and exercise intolerance. Individuals may exhibit external ophthalmoplegia, ptosis, and hypertrophic or dilated cardiomyopathy. Occasionally, mitochondrial myopathies cause significant respiratory muscle weakness resulting in nocturnal hypoventilation and the need for assisted ventilation. Treatments that focus on bypassing the defective mitochondria include dietary supplements based on dietary substances involved in adenosine triphosphate production such as creatine.[99]

SPECIAL TOPICS

Neuromuscular Disease Related to Critical Illness

Neuromuscular weakness is a very common finding in patients who are in the ICU. More than 25% of patients who are ventilated in the ICU for more than 7 days develop neuromuscular weakness.[100] The possible causes of weakness in the ICU include Guillain-Barré syndrome, rhabdomyolysis, cachectic myopathy, and critical illness neuropathy and myopathy. Weakness in the ICU is most commonly due to the combination of critical illness neuropathy and myopathy now often referred to as "ICU-related weakness" or critical illness polyneuromyopathy. It is now recognized that most individuals will suffer from both neuropathy and myopathy and that the precise cause of the disease process is unknown.

The incidence of critical illness polyneuromyopathy is quite high, with risk estimated in prospective studies at between 33% and 82%.[101–103] The major risk factors for critical illness polyneuromyopathy include sepsis and systemic inflammatory response syndrome (SIRS),[104] treatment with steroids[100] or neuromuscular blocking agents,[105] and hyperglycemia.[102] Other factors that are thought to contribute to this disorder include total parenteral nutrition, aminoglycoside use, catecholamines, hyperosmolality, female gender, longer duration of multiorgan failure, greater illness severity, and renal failure.[106]

The pathophysiologic mechanisms leading to critical illness polyneuromyopathy are not well understood. However, the pathology of the myopathy has been well described and includes two major patterns of disease: (1) type II myocyte atrophy with thick filament (myosin) destruction[107] and (2) widespread myocyte necrosis with intracellular vacuolization and phagocytosis of muscle fibers.[108] The neuropathic changes described by electrophysiologic testing with nerve conduction studies reveal reduced motor and often sensory nerve action potentials and muscle fibrillation suggestive of denervation.[109]

Critical illness polyneuropathy should be distinguished from other neuromuscular diseases. Compared with demyelinating diseases such as Guillain-Barré syndrome, critical illness polyneuromyopathy has normal nerve conduction velocity; compared with rhabdomyolysis, critical illness polyneuromyopathy will have a normal creatine phosphokinase, lack of muscle tenderness, and minimal electromyographic changes; and compared with cachectic myopathy, critical illness polyneuromyopathy is not usually associated with severe malnutrition.[110]

The only intervention thus far shown to reduce the incidence of ICU-acquired neuromuscular disorders is intensive insulin therapy. In one randomized, controlled study, the use of insulin to maintain serum glucose at 80 to 110 mg/dL, compared with a conventional range of 180 to 200 mg/dL, reduced critical illness polyneuropathy in patients in the ICU for at least 1 week by 44%.[111]

Diseases Affecting Diaphragm Function

The diaphragm is the major muscle of inspiration. It is a dome-shaped structure composed of two muscular leaflets attached to a central tendinous dome (see Fig. 87-2). The diaphragm inserts into the bony rib cage along the inner surface of the lower six ribs and costal cartilages anterolaterally and the upper three lumbar vertebral bodies posteriorly. It separates the thorax from the abdomen and, when it contracts, serves to increase the volume of the thorax and inflate the lung by decreasing intrapleural pressure. The diaphragm increases thoracic size in two main ways: by the descent of the diaphragm in a piston-like fashion and by the expansion of the rib cage via an increase in abdominal pressure. Diaphragm weakness or paralysis can involve either one of the diaphragm leaflets (unilateral) or both (bilateral).

Unilateral Diaphragm Paralysis

Unilateral diaphragm paralysis is more common than bilateral diaphragm paralysis. The list of potential causes is similar (Table 87-4). The most frequent causes of unilateral paralysis include phrenic nerve injury related to cardiac or thoracic surgery, herpes zoster, cervical spinal disease, or invasive or compressive tumors.[112] In unilateral diaphragm paralysis, patients may be asymptomatic at rest but have dyspnea with exertion.[113] Orthopnea may be present but is not as common or severe as in bilateral paralysis.

The diagnosis is often suggested by an elevated hemidiaphragm on chest x-ray and confirmed with a fluoroscopic sniff test.[114] In this test, an upward or "paradoxical" movement of the paralyzed hemidiaphragm is seen during a vigorous sniff maneuver performed by the patient. The paradoxical motion is the passive movement of a paralyzed hemidiaphragm in response to the increase in abdominal pressure (and decrease in pleural pressure) created by the contraction of the normal hemidiaphragm. Thus, the unilateral hemidiaphragmatic paralysis can be recognized readily by the different func-

TABLE 87-4. Causes of Diaphragm Weakness and Paralysis

Neuropathic Causes	Myopathic Causes
TRAUMA	**MUSCULAR DYSTROPHIES**
Cardiac surgery with cold cardioplegia	Limb girdle
Blunt trauma	Duchenne and Becker
Spinal cord injury	**METABOLIC MYOPATHIES**
Radiation injury	Hyper- or hypothyroidism
Cervical manipulation	Acid maltase deficiency
Scalene and brachial nerve block	**RHEUMATOLOGIC**
Tumor compression	Systemic lupus erythematosus
Lung cancer	Dermatomyositis
Metastatic mediastinal tumor	Mixed connective disease
METABOLIC	**MISCELLANEOUS**
Diabetes	Amyloidosis
Vitamin deficiency (B_6,B_{12}, folate)	Malnutrition
Hypothyroidism	Idiopathic
INFLAMMATORY NEURITIS	
Idiopathic (neuralgic amyotrophy, Parsonage-Turner)	
Mononeuritis multiplex	
Vasculitis	
Paraneoplastic	
MISCELLANEOUS	
Cervical spondylosis	
Poliomyelitis	
Amyotrophic lateral sclerosis	

tion of the two hemidiaphragms. Ultrasonographic imaging of the diaphragm in the zone of apposition provides an alternate means of diagnosing chronic unilateral diaphragm paralysis by showing a thin diaphragm that fails to thicken with inspiration.[115] There is no specific treatment for this disorder, but recovery following the initial injury is occasionally seen. When disabling symptoms are present and there is significant elevation of the hemidiaphragm on chest radiography, surgical plication of the paralyzed hemidiaphragm to minimize its paradoxical motion has had some success in improving vital capacity and FEV_1, especially in the supine position, and in reducing dyspnea.[116]

Bilateral Diaphragm Paralysis

Bilateral diaphragm paralysis is most often seen in the setting of a disease producing severe generalized muscle weakness. The most common causes are diffuse muscle diseases or motor neuron disease such as ALS.

The symptoms of bilateral paralysis include significant dyspnea with exertion and even at rest, especially when supine. Orthopnea is very common,[117] and dyspnea on immersion in water has been described,[118] probably due to the increases in abdominal pressure and elevation of the diaphragm in either the supine position or after submersion in water. Sleep-disordered breathing with hypoventilation and hypoxemia is common.[119] Pulmonary function is impaired when the vital capacity is reduced and when there are significant drops of vital capacity in the supine position of up to 50%.[120] The P_{Imax} is reduced in most cases. Disability can be quite pronounced. The astute clinician may initially suspect the condition by observing paradoxical breathing in a resting or sleeping supine patient; instead of rising normally due to diaphragmatic contraction, the abdomen may actually fall on inspiration as the negative pleural pressure "sucks" the abdominal contents into the chest.

Interestingly, bilateral diaphragmatic paralysis can be difficult to diagnose. For one thing, there is no normal hemidiaphragm to use for comparison with an abnormal one. Therefore, chest radiography and fluoroscopic sniff testing can yield false negative results. Two-dimensional echocardiography of the movement of the diaphragm dome shares the same limitations as fluoroscopy.[121] Phrenic nerve conduction studies can be useful in diagnosing a neuropathic cause of diaphragmatic paralysis but can have technical limitations.[122] Diaphragm electromyographic measurements may be useful, but technical issues such as "cross-talk" from adjacent muscles, electrode placement, or variable muscle-to-electrode distances due to subcutaneous fat limit its utility. The "gold standard" diagnostic test is measuring transdiaphragmatic pressure using thin balloon-tipped polyethylene catheters placed in the esophagus and stomach (Fig. 87-4A) and showing a lack of ability to generate a transdiaphragmatic pressure[123] (see Fig. 87-4B). B-mode ultrasound of the diaphragm muscle in the zone of apposition showing a lack of thickening on inspiration is a less invasive means of diagnosing bilateral diaphragm paralysis.[124] Bilateral diaphragm paralysis is rarely reversible unless the underlying disease is treatable. However, recovery has been noted in more than 50% of individuals with idiopathic diaphragmatic paralysis or paralysis due to neuralgic amyotrophy (brachial plexus neuritis) with the recovery taking an average of 15 months from the onset of symptoms.[122] The sleep-disordered breathing and orthopnea commonly seen in individuals with diaphragmatic paralysis can be treated with NPPV.[125]

Phrenic nerve pacing is not applicable in most cases of diaphragm paralysis because it requires intact phrenic nerves and normal diaphragmatic motor function. As mentioned previously, in unilateral diaphragm paralysis, hemidiaphragm plication has been used to shorten the paralyzed hemidiaphragm and allow the unaffected hemidiaphragm to contract more effectively.[126]

APPROACH TO RESPIRATORY EVALUATION AND MANAGEMENT OF THE INDIVIDUAL WITH NEUROMUSCULAR DISEASE

Although each neuromuscular disease has a different etiology and natural history as well as potential

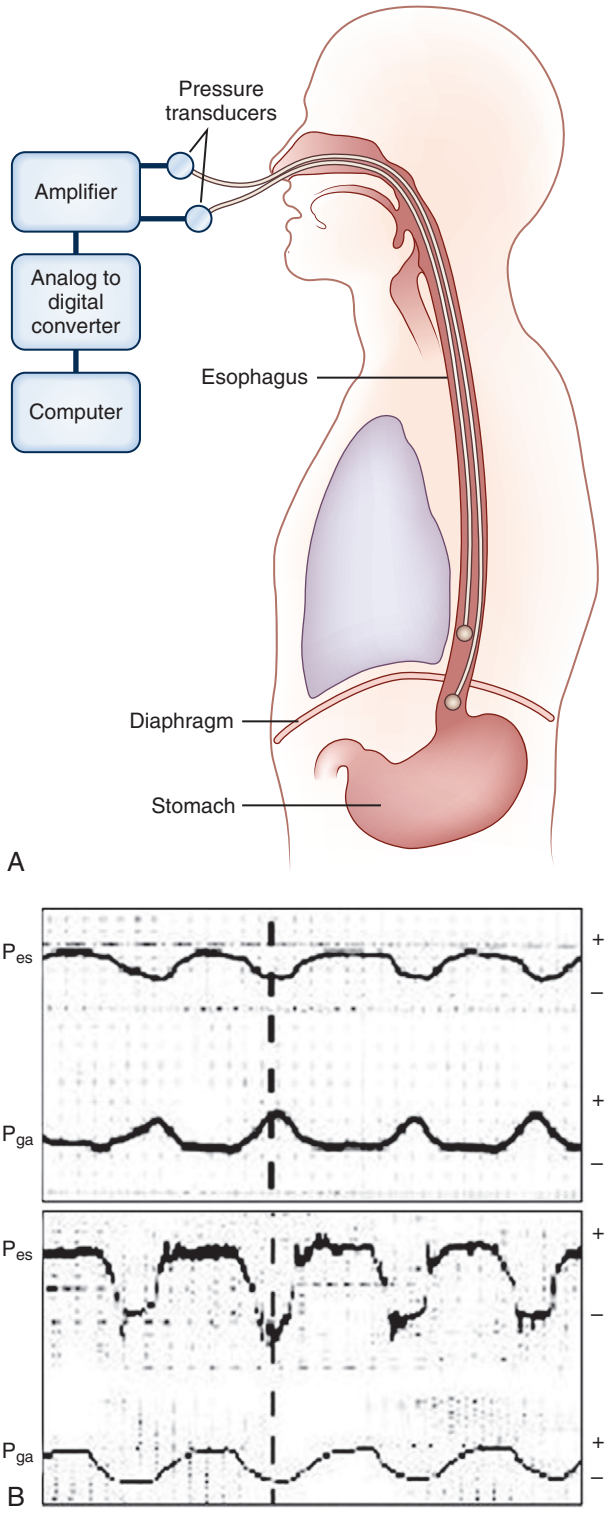

FIGURE 87-4 ■ **A,** Apparatus used to measure transdiaphragmatic pressure. Esophageal and gastric balloons placed through the nose into the esophagus and stomach, respectively, allow measurement of the pressures above and below the diaphragm simultaneously. **B,** *Top,* Normal esophageal (Pes) and gastric (Pga) pressure tracings. Note Pes becomes more negative and Pga more positive during normal inspiration owing to the action of the diaphragm. *Bottom,* Diaphragmatic paralysis where Pes and Pga deflect in the same direction showing no muscular activity of the diaphragm.

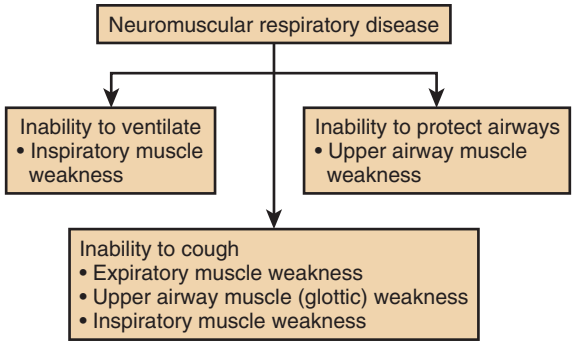

FIGURE 87-5 ■ Clinical effects of weakness or dysfunction of inspiratory, expiratory and upper airway muscles. Neuromuscular conditions lead to respiratory disease mainly via inability to ventilate, to cough, or to protect the upper airway from aspiration.

treatment, the respiratory effects of neuromuscular diseases can be approached in a systematic way that can be applied to any neuromuscular diagnosis. This approach utilizes the fact that the three major muscle groups involved in maintaining ventilation and protecting the airway and lungs are (1) the inspiratory muscles responsible predominantly for ventilation, (2) the expiratory muscles responsible predominantly for cough, and (3) the upper airway muscles responsible for cough, swallowing, and airway protection (Fig. 87-5). For the patient with neuromuscular disease, cough function and airway protection from an intact swallowing mechanism are as important as maintenance of ventilation.[127,128] For patients with Duchenne muscular dystrophy, a consensus committee of the American Thoracic Society[128] has recommended that clinic visits should include evaluation of each of the three areas by eliciting appropriate history, physical examination, and laboratory testing.

Inspiratory function can be tested by measurement of FVC, MIP, and carbon dioxide levels. Carbon dioxide can be measured as Pa_{CO_2}, the traditional measure of adequate ventilation, or as exhaled or end-tidal CO_2 (E_TCO_2), transcutaneous or capillary P_{CO_2}. Arterial blood gas sampling is the most accurate means of assessing alveolar ventilation but can be uncomfortable for the patient. E_TCO_2 measurement in patients without intrinsic lung disease is an easy and accurate method of estimating Pa_{CO_2}.[129] Transcutaneous P_{CO_2} has been successfully measured in children and improving technology may allow more widespread use.[130]

Hypoventilation usually manifests itself by symptoms during sleep. Symptoms consistent with sleep-disordered breathing include more frequent nocturnal awakenings, nocturia, vivid nightmares, night sweats, daytime hypersomnolence, morning headaches, nausea, depression, decreased concentration, and diminished daytime performance. Polysomnography can be used to evaluate sleep in patients with neuromuscular disease, but an overnight stay in a sleep laboratory may be especially difficult for such individuals if they require a personal care attendant, position changes, or help with toileting. Thus, ensuring a high pretest probability prior to order-

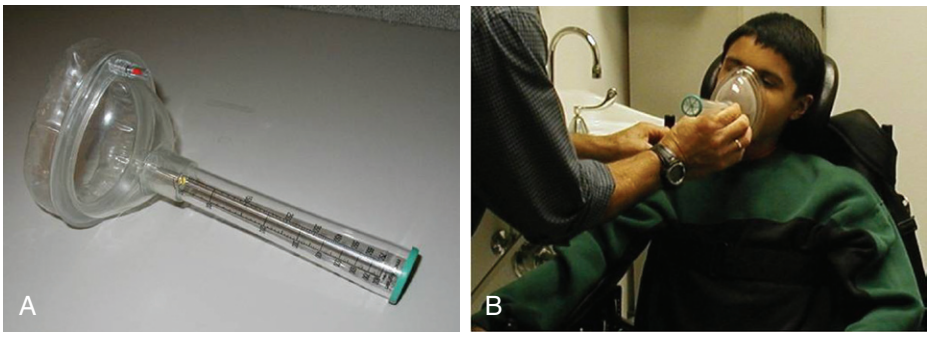

FIGURE 87-6 ■ **A,** Device to measure peak cough flow consists of an asthma peak flowmeter connected to a face mask. **B,** Peak cough flow device being used for measurement in a patient with muscular dystrophy.

ing a sleep study is important. Baseline values of awake $PaCO_2$ 45 or greater or base excess of 4 mEq or greater may correlate with sleep hypoventilation.[131] An unattended sleep study in the home[132] or overnight oximetry and E_TCO_2 monitoring[128] may substitute for a full laboratory polysomnogram; however, the sensitivity and specificity of these portable tests remains to be determined in this population.[132] These studies may serve to screen for those who will benefit from a full polysomnographic study in a sleep laboratory.

Cough insufficiency may be suspected if the patient describes an inability to bring secretions to the mouth for expectoration or if there is a history of frequent respiratory tract infections. Cough function is best assessed by measuring peak cough flow (PCF) rate. This can be easily measured with an asthma peak flowmeter connected to a face mask or mouthpiece (Fig. 87-6). Normal values range from 360 to 960 L/min[133]; a value below 160 L/min may place individuals at high risk for cough insufficiency and ventilator dependence.[127] During a respiratory tract infection, PCF may drop substantially and a PCF below 270 L/min during a healthy period can drop below 160 L/min during infection. Cough assistance is suggested for those with a PCF below 160 L/min.

Patients with neuromuscular diseases such as ALS frequently develop bulbar muscle dysfunction due to motor neuron involvement in the brain stem. Dysfunction of the lips, tongue, and pharyngeal and laryngeal muscles can result in an increased risk of aspiration as well as difficulty with generating adequate glottic closure for effective cough function. Swallowing may be impaired and ingesting adequate nutrition can be challenging for the patient. Choking is common and may even be triggered by aspiration of saliva. Malnutrition or rapid weight loss should signal the clinician to assess the swallowing mechanism.[134] Swallowing may be tested by barium swallow or direct visualization of swallowing endoscopically.[135–137] Referral to a speech and swallowing clinic can be very helpful in diagnosing swallowing and airway protection problems as well as instructing patients and their families in ways to reduce the risk of aspiration.

Ventilatory Support

Ventilatory support for patients with neuromuscular disease has been available for over 60 years[138] (Table 87-5). Some of the first ventilators were known as body ventilators and included devices such as the iron lung, rocking bed, and pneumobelt.[139] With the advent of positive pressure via either invasive (tracheostomy) or noninvasive (face mask) ventilation, these body ventilators are used only very rarely, as in the case of patients who have already been using them for years.

Invasive positive-pressure ventilation utilizing an indwelling tracheostomy has been successfully employed in neuromuscular disease. Benefits of this type of ventilator support include complete control of machine-delivered tidal volume and ease of access to the central airways for suctioning of secretions. In addition, if there is an acute decline in respiratory function, the same method of ventilation can be used for ventilatory support. The development of convenient, portable, positive-pressure generators has made this form of ventilation practical even in the home environment.[140] Invasive positive pressure should be considered in those with (1) coexisting lung disease, (2) copious secretions, (3) poor oropharyngeal muscle strength associated with

TABLE 87-5. Methods of Ventilation Used in Treatment of Neuromuscular Disease

NEGATIVE-PRESSURE VENTILATORS[138]
Tank ventilator (iron lung)
Raincoat ventilator (poncho or pneumowrap)
Cuirass ventilator (chest shell)
Pneumosuit ventilator with leggings
POSITIVE-PRESSURE VENTILATORS
Invasive (tracheostomy)
Noninvasive
Via full face mask
Via nasal mask
Via mouthpiece
VENTILATORS RESULTING IN PASSIVE MOVEMENT OF THE DIAPHRAGM
Pneumobelt
Rocking bed
PHRENIC NERVE PACING
DIAPHRAGM PACING

ineffective clearing of secretions, (4) uncontrolled seizure disorders that can cause upper airway obstruction, (5) a preference for invasive rather than noninvasive methods, (6) orthopedic or other conditions that interfere with placement of noninvasive devices, and (7) limited access to individuals with expertise in noninvasive techniques.

Unfortunately, invasive long-term positive-pressure ventilation via a tracheostomy has been associated with several complications such as damage to the trachea from the indwelling tracheostomy tube leading to tracheal necrosis, stenosis, hemorrhage, or tracheoesophageal fistulas.[141] However, the development of low-pressure, high-volume cuffed plastic tracheostomy tubes has lowered the incidence of these complications. Tracheostomy tubes can interfere with the normal swallowing mechanism and predispose patients to swallowing problems and food aspiration; they can also increase the risk of airway colonization with bacteria and lower respiratory tract infection. The use of a tracheostomy tube requires supplemental humidification, an additional daily respiratory care task. Finally, social interactions and psychological well-being may be impaired by the inability to speak. However, a number of devices and techniques have been designed to allow speech and communication while a patient has a tracheostomy and is mechanically ventilated. These include one-way valves that allow gas to pass through the vocal cords during exhalation (Passy-Muir valve, Irvine, CA) or channels to direct compressed air through the vocal cords ("Trach Talk" tracheostomy tube, Portex, Keene, NH). Unfortunately, not all individuals can utilize these devices.

NPPV is becoming the preferred method for treatment of patients with neuromuscular respiratory disease. The noninvasive delivery of positive-pressure ventilation was first used during the polio epidemics of the 1950s to allow patients time outside the iron lung. Since the 1980s, there have been considerable refinements in the application of this technique. There are currently three ways in which NPPV may be delivered: (1) via mouthpiece with or without a lipseal, (2) via nasal mask, or (3) via full face mask (Fig. 87-7). Occasionally, more than one method may be used in the same patient, for instance, a mouthpiece may be used during the day and a nasal mask used at night.

The mouthpiece was the first interface to be used with a positive-pressure ventilator. Patients hold the mouthpiece devices between their teeth and often are able to use them while sleeping, especially when lipseal devices are added.[142] Since the late 1990s, nasal interfaces have been developed and used successfully. Initially, nasal masks were designed to deliver continuous positive airway pressure (CPAP) for the treatment of patients with sleep apnea.[143] Currently, they are also used to deliver intermittent positive pressure to patients with neuromuscular disease. Tidal volume is most effectively delivered when there are no leaks around the nasal mask or through the mouth. Patients who experience air leaks may develop oxyhemoglobin desaturation, elevation of $PaCO_2$, and associated symptoms. In this situation, the use of a full oral-facial mask interface may be more appropriate. Utilizing custom-designed appliances also can eliminate leaks via the mouth and may be more comfortable for some patients. Pressure-cycled rather than volume-cycled devices are generally utilized for mask ventilation. With these machines, positive pressure can be delivered at two levels, a higher level during inspiration and a lower level during expiration (bilevel support, BiPAP). The positive-pressure gradient during inspiration results in delivery of a tidal volume to the patient. Exhalation occurs passively and is terminated when the airway pressure returns to the lower expiratory level. Maintenance of a positive expiratory pressure is important for two reasons. First,

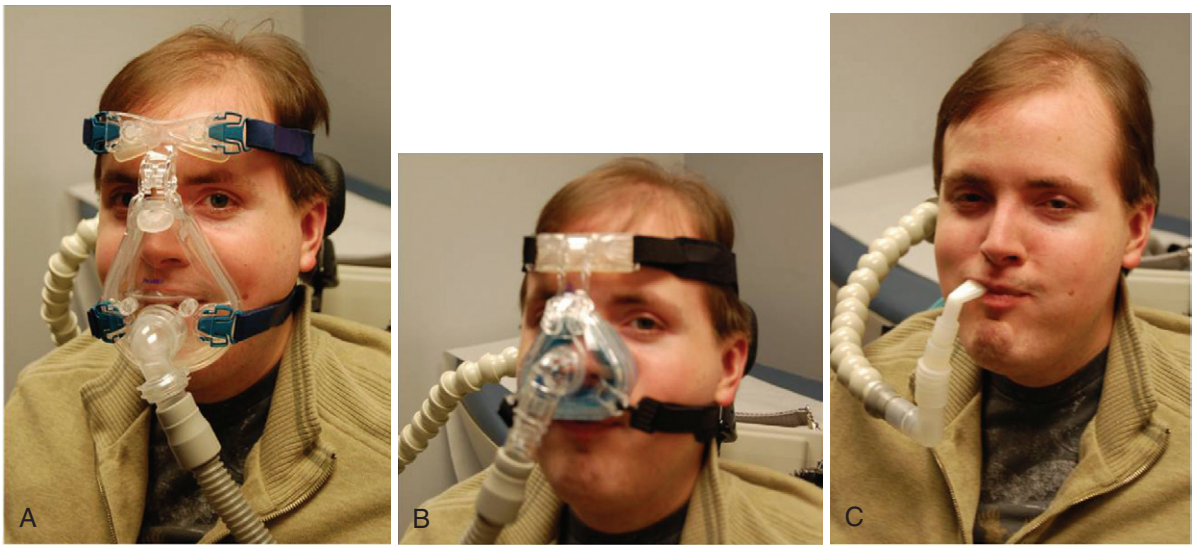

FIGURE 87-7 ■ Different means of delivering noninvasive positive-pressure ventilation. **A,** Full mask. **B,** Nasal mask. **C,** Mouthpiece.

because exhalation valves are not used with bilevel devices, end-expiratory positive airway pressure flushes the ventilator tubing of exhaled CO_2 and prevents rebreathing.[144] Second, because the expiratory pressure is positive and greater than atmospheric, the end-expiratory lung volume is increased, which may be associated with less atelectasis and fewer areas of low ventilation-perfusion or shunt than seen with low end-expiratory lung volumes.

Data Supporting Noninvasive Positive-Pressure Ventilation in Neuromuscular Disease

Nocturnal Ventilatory Support

The use of nocturnal ventilation in patients with neuromuscular disease with sleep disordered breathing has been shown to have a number of benefits, which include (1) reduced $Paco_2$ and increased Pao_2 on and off ventilator, (2) decreased symptoms of sleep-disordered breathing such as morning headache, nocturnal awakenings, vivid nightmares, and night sweats, (3) improved quality of life, and (4) reduced morbidity and most likely reduced mortality. Nocturnal ventilation has become widely accepted, providing ventilatory assistance for patients while sleeping and allowing them to breathe on their own during the day. In one study of patients with late-stage Duchenne muscular dystrophy who had symptoms of ventilatory failure and $Paco_2$ of 60 mm Hg or greater, nocturnal negative-pressure ventilation utilizing cuirass or tank ventilators significantly improved arterial $Paco_2$ values (60.8 mm Hg pretreatment to 45.5 mHg posttreatment) and Pao_2 values (59.3 mm Hg pretreatment and 74.6 mm Hg posttreatment).[145] Since that study, a number of studies have been published using nocturnal ventilation that have supported these findings and an excellent review of these data is available.[146]

The mechanism by which nocturnal ventilation ameliorates daytime symptoms and arterial blood gases in patients with neuromuscular disease is not entirely clear. A number of explanations have been suggested including (1) resting of chronically fatigued respiratory muscles, (2) reversal of mechanical problems associated with neuromuscular disease such as reduced chest wall and lung compliance, and (3) a resetting of the central respiratory control centers with an increase in chemosensitivity to $Paco_2$ during the daytime, thus maintaining blood gas homeostasis.[147–149] In addition to improvement in arterial blood gases, other measures of physiologic function have been shown to improve with intermittent ventilation. Vital capacity increases, right-sided heart failure improves, and there is a reduction in erythrocytosis following nighttime ventilation.[150]

For ethical reasons, the effects of mechanical ventilation on survival have not been studied in a randomized, controlled fashion in patients with neuromuscular disease. In most progressive neuromuscular diseases, once an elevation in $Paco_2$ and a decrease in Pao_2 are noted, cor pulmonale and death are inevitable within a short period of time. It is therefore generally accepted that mechanical ventilation in the home leads to improved survival in most patients.

Full-time Ventilatory Support

For those who require full-time ventilatory support, it is possible to provide NPPV for 24 hours per day.[151–153] As with nocturnal NPPV for neuromuscular disease, there have been no randomized, controlled trials of continuous ventilation. In one cohort study, 24 patients with Duchenne muscular dystrophy using NPPV were compared with 22 patients who received positive-pressure ventilation by tracheostomy.[154] The individuals who used NPPV had significantly fewer hospitalizations and hospital days per year. In another retrospective study by the same group, Duchenne muscular dystrophy patients using a protocol consisting of mouthpiece positive-pressure ventilation and breath stacking plus mechanical insufflation-exsufflation to assist cough (see discussion of "Cough Support," later) had significantly less mortality (3 of 34 patients) than a group that did not have access to the protocol and either received tracheostomy or used NPPV on a near-continuous basis (27 of 31 patients).[155] Further studies of continuous NPPV are needed to assess whether this treatment is truly better than tracheostomy ventilation in a community setting. A consensus statement of the ATS on the respiratory care of patients with Duchenne muscular dystrophy has suggested that NPPV be considered when expertise is available for initiation of appropriate protocols.[156]

Cough Support

Therapeutic interventions aimed at improving cough and airway clearance are equally if not more important than ventilatory support because pneumonia is one of the leading causes of morbidity and mortality in patients with neuromuscular respiratory disease. Normally, the cough reflex is initiated by stimulation of cough receptors in the airways that activate brain stem centers that initiate inhalation, glottic closure, and forceful contraction of expiratory muscles during which intrathoracic gas is compressed under high pressures.[133] The glottis then rapidly opens and an explosive release of gas occurs from the airways through the vocal cords. The high-velocity gas flow causes shearing of secretions away from the airway walls and propels them out of the lung. Adequate cough is essential for airway hygiene. Fortunately, there are a number of ways that an impaired cough can be augmented to maintain pulmonary hygiene without the use of a tracheostomy.

Manually-assisted cough is a method of applying a rapid positive pressure to the abdomen. The increase in abdominal pressure is transmitted to the thorax and expiratory flow ensues, leading to airway clearance and enhanced cough expiratory flow rates. A number of

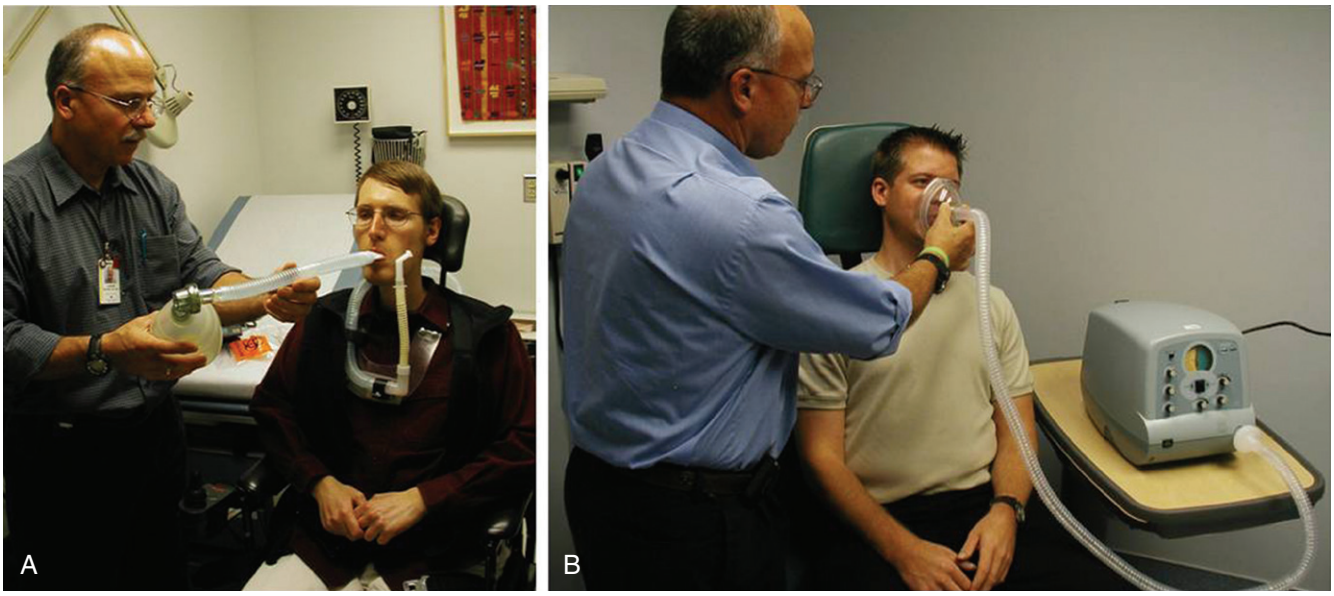

FIGURE 87-8 ■ **A,** Resuscitator bag used to "stack breaths" to increase lung volume and thereby increase cough flow. **B,** Mechanical insufflator-exsufflator being used to assist in secretion removal.

techniques are available for an attendant to apply rapid abdominal thrusts, resulting in effective clearance of secretions.[157] Increasing the volume of air in the respiratory system prior to the assisted cough increases the volume of gas in the lungs for exhalation, optimizes the length-tension relationship of the expiratory muscles so greater intrathoracic pressures can be achieved, and also increases the inward elastic recoil pressure of the respiratory system, which can further increase the expiratory pressures. This maximal achievable inspired volume has been labeled the maximal insufflation capacity or MIC.[158] Inspired lung volume can be increased by patients using breath stacking or glossopharyngeal ("frog breathing") techniques[159] or by use of a resuscitator bag and mouthpiece (Fig. 87-8A). Breath stacking involves taking multiple breaths to increase lung volumes above the single breath volume, holding each successive breath in the lungs using the glottis. Glossopharyngeal breathing is a form of respiration that involves forcing air into the trachea using the tongue and pharyngeal muscles.[159]

A very effective secretion management device, available for over 50 years but only recently used to any great extent, is the mechanical insufflator-exsufflator MI-E or CoughAssist (In-exsufflator, JH Emerson Co., Cambridge, MA) (see Fig. 87-8B). This device consists of an electric motor that can generate positive and negative pressures of up to 50 cm H_2O to insufflate and then rapidly exsufflate the lung. The pressure is applied to the patient's airway via a face mask or mouthpiece; first, a positive pressure of 30 to 50 cm H_2O is applied over a 1- to 3-second period followed immediately by a negative pressure of between 30 and 50 cm H_2O for a short duration. By simulating a cough, this technique moves secretions out of the airway noninvasively without violating airway integrity.[160] Other noninvasive mechanical aids include devices that oscillate the chest wall or airway directly.[161] These have not been well studied in neuromuscular disease patients without tracheostomy and their role in support of secretion management of these disorders is unclear.

The decision to initiate cough assistance is determined by measurement of cough function in the form of PCF. It is recommended that one or more of the previously discussed techniques should be made available to the patient when values of PCF fall below 270 L/min while the patient is well, because this correlates with a value of less than 160 L/min when the patient develops a respiratory tract infection.[127] This drop in cough function with respiratory illness may be due to increased muscle weakness or to the effects of the secretions themselves in reducing expiratory flow.

Treatments for swallowing muscle dysfunction are limited. The risk of aspiration and development of pneumonia in patients with ALS is due primarily to problems with upper airway function and cough. Pharyngeal and laryngeal muscle dysfunction can lead directly to aspiration of oral contents into the lungs. Other than surgical diversion of the airway,[162] no treatment directly aimed at laryngeal and glottic function is available. When patients develop significant dysphagia and aspiration of solids or liquids, many experts recommend placement of a percutaneous endoscopic gastrostomy tube.[163,164]

KEY POINTS

- Respiratory failure is a leading cause of morbidity and mortality in individuals with neuromuscular disease.
- Spinal cord injury is a common traumatic injury worldwide. The degree of respiratory impairment depends on the level of injury in the spinal cord.
- AIDP (Guillain-Barré syndrome) is an ascending paralytic disease thought to be due to antiglycolipid antibodies. Intubation can be life-saving and should be considered when the FVC is 15 mL/kg or less, the FVC is 1 L or less, or the MIP is 30 cm H_2O or less, or there is a lack of upper airway protection.
- Diaphragm paralysis can be unilateral or bilateral. Unilateral disease is most commonly due to injury to the phrenic nerve. Bilateral disease is most commonly due to diffuse muscle or motor neuron disease.
- Respiratory assessment of the individual with neuromuscular respiratory impairment should include evaluation of muscle groups responsible for inspiration, expiration and cough, and airway protection.
- Either noctural or full-time noninvasive ventilation is now commonly used in chronic neuromuscular respiratory disease and likely prolongs survival.
- Neuromuscular weakness is a common occurrence in the ICU and results in increased mortality and hospital length of stay.
- Cough can be aided noninvasively by manual or motorized means and should be considered when the peak cough flow (PCF) rate is less than 270 L/min in a patient without respiratory tract infection and definitely when the PCF rate is less than 160 L/min.

References

1. Bergofsky EH: Respiratory failure in disorders of the thoracic cage. Am Rev Respir Dis 119:643–669, 1979.
2. Evans KC, Shea SA, Saykin AJ: Functional MRI localisation of central nervous system regions associated with volitional inspiration in humans. J Physiol 520(Pt 2):383–392, 1999.
3. Nattie E: CO_2, brainstem chemoreceptors and breathing. Prog Neurobiol 59:299–331, 1999.
4. St.-John WM: Neurogenesis of patterns of automatic ventilatory activity. Prog Neurobiol 56:97–117, 1998.
5. Howard RS, Thorpe J, Barker R, et al: Respiratory insufficiency due to high anterior cervical cord infarction. J Neurol Neurosurg Psychiatry 64:358–361, 1998.
6. Caputo C, Bezanilla F, Horowicz P: Depolarization-contraction coupling in short frog muscle fibers. A voltage clamp study. J Gen Physiol 84:133–154, 1984.
7. Mead J: Functional significance of the area of apposition of diaphragm to rib cage [proceedings]. Am Rev Respir Dis 119:31–32, 1979.
8. De Troyer A, Kelly S, Zin WA: Mechanical action of the intercostal muscles on the ribs. Science 220:87–88, 1983.
9. De Troyer A, Sampson M, Sigrist S, et al: How the abdominal muscles act on the rib cage. J Appl Physiol 54:465–469, 1983.
10. Legrand A, Schneider E, Gevenois PA, et al: Respiratory effects of the scalene and sternomastoid muscles in humans. J Appl Physiol 94:1467–1472, 2003.
11. Chia LG: Locked-in syndrome with bilateral ventral midbrain infarcts. Neurology 41:445–446, 1991.
12. Hlastala MP, Berger AJ (eds): Central mechanisms of respiratory control. *In* Physiology of Respiration. New York: Oxford University Press, 1996, pp 162–208.
13. Wang H, Zhang H, Song G, et al: Modulation of Hering-Breuer reflex by ventrolateral pons. Adv Exp Med Biol 605:387–392, 2008.
14. Daly M, Ungar A: Comparison of the reflex responses elicited by stimulation of the separately perfused carotid and aortic body chemoreceptors in the dog. J Physiol 182:379–403, 1966.
15. Burton MD, Kazemi H: Neurotransmitters in central respiratory control. Respir Physiol 122:111–121, 2000.
16. Evans AB, Tsai LW, Oelberg DA, et al: Skeletal muscle ECF pH error signal for exercise ventilatory control. J Appl Physiol 84:90–96, 1998.
17. Patterson JR, Grabois M: Locked-in syndrome: A review of 139 cases. Stroke 17:758, 1986.
18. Bolton CF, Chen R, Wijdics EFM, et al (eds): Anatomy and physiology of the nervous system control of respiration. *In* Neurology of Breathing. Philadelphia: Butterworth-Heinemann, 2004, pp 19–35.
19. Vincken WG, Gauthier SG, Dollfuss RE, et al: Involvement of upper-airway muscles in extrapyramidal disorders. A cause of airflow limitation. N Engl J Med 311:438–442, 1984.
20. Munschauer FE, Loh L, Bannister R, et al: Abnormal respiration and sudden death during sleep in multiple system atrophy with autonomic failure. Neurology 40:677–679, 1990.
21. Liess BD, Dost JS, Templer JW, et al: Congenital central alveolar hypoventilation syndrome (Ondine's curse) with survival into adulthood. Clin Pediatr (Phila) 47:941–946, 2008.
22. Plum F, Swanson G: Central neurogenic hyperventilation in man. Arch Neurol Psychiatry 81:535–549, 1959.
23. Plum F, Posner JB (eds): The pathologic physiology of signs and symptoms of coma. *In* The Diagnosis of Stupor and Coma. Philadelphia: FA Davis, 1966, pp 1–86.
24. Fishburn MJ, Marino RJ, Ditunno JF Jr: Atelectasis and pneumonia in acute spinal cord injury. Arch Phys Med Rehabil 71:197–200, 1990.
25. Jackson AB, Groomes TE: Incidence of respiratory complications following spinal cord injury. Arch Phys Med Rehabil 75:270–275, 1994.
26. Bhaskar KR, Brown R, O'Sullivan DD, et al: Bronchial mucus hypersecretion in acute quadriplegia. Macromolecular yields and glycoconjugate composition. Am Rev Respir Dis 143:640–648, 1991.
27. Reines HD, Harris RC: Pulmonary complications of acute spinal cord injuries. Neurosurgery 21:193–196, 1987.
28. Oo T, Watt JW, Soni BM, et al: Delayed diaphragm recovery in 12 patients after high cervical spinal cord injury. A retrospective

review of the diaphragm status of 107 patients ventilated after acute spinal cord injury. Spinal Cord 37:117–122, 1999.
29. Wicks AB, Menter RR: Long-term outlook in quadriplegic patients with initial ventilator dependency. Chest 90:406–410, 1986.
30. Bach JR, Alba AS: Noninvasive options for ventilatory support of the traumatic high level quadriplegic patient. Chest 98:613–619, 1990.
31. DeVivo MJ, Black KJ, Stover SL: Causes of death during the first 12 years after spinal cord injury. Arch Phys Med Rehabil 74:248–254, 1993.
32. Ledsome JR, Sharp JM: Pulmonary function in acute cervical cord injury. Am Rev Respir Dis 124:41–44, 1981.
33. Berlowitz DJ, Brown DJ, Campbell DA, et al: A longitudinal evaluation of sleep and breathing in the first year after cervical spinal cord injury. Arch Phys Med Rehabil 86:1193–1199, 2005.
34. McEvoy RD, Mykytyn I, Sajkov D, et al: Sleep apnoea in patients with quadriplegia. Thorax 50:613–619, 1995.
35. Brown R, DiMarco AF, Hoit JD, et al: Respiratory dysfunction and management in spinal cord injury. Respir Care 51:853–868, 2006 [discussion appears 869–870].
36. Singas E, Lesser M, Spungen AM, et al: Airway hyperresponsiveness to methacholine in subjects with spinal cord injury. Chest 110:911–915, 1996.
37. Chitnis T, Khoury SJ: 20. Immunologic neuromuscular disorders. J Allergy Clin Immunol 111(2 Suppl):S659–S668, 2003.
38. Vucic S, Kiernan MC, Cornblath DR: Guillain-Barre syndrome. J Clin Neurosci 16:733–741, 2009.
39. Lo YL: Clinical and immunological spectrum of the Miller Fisher syndrome. Muscle Nerve 36:615–627, 2007.
40. Mehta S: Neuromuscular disease causing acute respiratory failure. Respir Care 51:1016–1021, 2006 [discussion appears 1021–1023].
41. Orlikowski D, Prigent H, Sharshar T, et al: Respiratory dysfunction in Guillain-Barré syndrome. Neurocrit Care 1:415–422, 2004.
42. Ropper AH: The Guillain-Barré syndrome. N Engl J Med 326:1130–1136, 1992.
43. Cheng BC, Chang WN, Chang CS, et al: Predictive factors and long-term outcome of respiratory failure after Guillain-Barré syndrome. Am J Med Sci 327:336–340, 2004.
44. Bartels MN, Omura A: Aging in polio. Phys Med Rehabil Clin N Am 16:197–218, 2005.
45. Willen C, Thoren-Jonsson AL, Grimby G, et al: Disability in a 4-year follow-up study of people with post-polio syndrome. J Rehabil Med 39:175–480, 2007.
46. Gooding L: Polio's painful legacy. Nurs Stand 21:20, 2007.
47. Emeryk B, Rowinska-Marcinska K, Ryniewicz B, et al: Disintegration of the motor unit in post-polio syndrome. Part II. Electrophysiological findings in patients with post-polio syndrome. Electromyogr Clin Neurophysiol 30:451–458, 1990.
48. Trojan DA, Cashman TR: Post-poliomyelitis syndrome. Muscle Nerve 31:6–19, 2005.
49. Steljes DG, Kryger MH, Kirk BW, Millar TW: Sleep in post-polio syndrome. Chest 98:133–140, 1990.
50. Blomstrand A, Bake B: Post-polio lung function. Scand J Rehabil Med 24:43–49, 1992.
51. de Carvalho M, Matias T, Coelho F, et al: Motor neuron disease presenting with respiratory failure. J Neurol Sci 139:117–122, 1996.
52. Haverkamp LJ, Appel V, Appel SH: Natural history of amyotrophic lateral sclerosis in a database population. Validation of a scoring system and a model for survival prediction. Brain 118:707–719, 1995.
53. Stambler N, Charatan M, Cedarbaum JM: Prognostic indicators of survival in ALS. ALS CNTF Treatment Study Group. Neurology 50:66–72, 1998.
54. Miller RG, Jackson CE, Kasarskis EJ, et al: Practice parameter update: the care of the patient with amyotrophic lateral sclerosis: drug, nutritional, and respiratory therapies (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 73:1218–1226, 2009.
55. Aboussouan LS, Khan SU, Meeker DP, et al: Effect of noninvasive positive-pressure ventilation on survival in amyotrophic lateral sclerosis [see comments]. Ann Intern Med 127:450–453, 1997.
56. Bourke SC, Tomlinson M, Williams TL, et al: Effects of non-invasive ventilation on survival and quality of life in patients with amyotrophic lateral sclerosis: A randomised controlled trial. Lancet Neurol 5:140–147, 2006.
57. Lyall RA, Donaldson N, Fleming T, et al: A prospective study of quality of life in ALS patients treated with noninvasive ventilation. Neurology 57:153–156, 2001.
58. Newall AR, Orser R, Hunt M: The control of oral secretions in bulbar ALS/MND. J Neurol Sci 139(Suppl):43–44, 1996.
59. Neppelberg E, Haugen DF, Thorsen L, et al: Radiotherapy reduces sialorrhea in amyotrophic lateral sclerosis. Eur J Neurol 14:1373–1377, 2007.
60. Verma A, Steele J: Botulinum toxin improves sialorrhea and quality of living in bulbar amyotrophic lateral sclerosis. Muscle Nerve 34:235–237, 2006.
61. Moss AH, Oppenheimer EA, Casey P, et al: Patients with amyotrophic lateral sclerosis receiving long-term mechanical ventilation. Advance care planning and outcomes. Chest 110:249–255, 1996.
62. Borasio GD, Gelinas DF, Yanagisawa N: Mechanical ventilation in amyotrophic lateral sclerosis: A cross-cultural perspective. J Neurol 245(Suppl 2):S7–S12, 1998 [discussion appears S29].
63. Mellies U, Dohna-Schwake C, Stehling F, et al: Sleep disordered breathing in spinal muscular atrophy. Neuromuscul Disord 14:797–803, 2004.
64. Gajdos P, Chevret S, Toyka K: Intravenous immunoglobulin for myasthenia gravis. Cochrane Database Syst Rev 1:CD002277, 2008.
65. Qureshi AI, Choudhry MA, Akbar MS, et al: Plasma exchange versus intravenous immunoglobulin treatment in myasthenic crisis. Neurology 52:629–632, 1999.
66. Elrington GM, Murray NM, Spiro SG, et al: Neurological paraneoplastic syndromes in patients with small cell lung cancer. A prospective survey of 150 patients. J Neurol Neurosurg Psychiatry 54:764–767, 1991.
67. Motomura M, Johnston I, Lang B, et al: An improved diagnostic assay for Lambert-Eaton myasthenic syndrome. J Neurol Neurosurg Psychiatry 58:85–87, 1995.
68. Laroche CM, Mier AK, Spiro SG, et al: Respiratory muscle weakness in the Lambert-Eaton myasthenic syndrome. Thorax 44:913–918, 1989.
69. Lang B, Vincent A: Autoimmune disorders of the neuromuscular junction. Curr Opin Pharmacol 9:336–340, 2009.
70. Dowell VR Jr: Botulism and tetanus: Selected epidemiologic and microbiologic aspects. Rev Infect Dis 6(Suppl 1):S202–S207, 1984.
71. Rummel A, Karnath T, Hinke T, et al: Synaptotagmins I and II act as nerve cell receptors for botulinum neurotoxin G. J Biol Chem 279:30865–30870, 2004.
72. Sobel J: Botulism. Clin Infect Dis 41:1167–1173, 2005.
73. Dembek ZF, Smith LA, Rusnak JM: Botulism: Cause, effects, diagnosis, clinical and laboratory identification, and treatment modalities. Disaster Med Public Health Prep 1:122–134, 2007.
74. Leikin JB, Thomas RG, Walter FG, et al: A review of nerve agent exposure for the critical care physician. Crit Care Med 30:2346–2354, 2002.
75. Edlow JA, McGillicuddy DC: Tick paralysis. Infect Dis Clin North Am 22:397–413, vii, 2008.
76. Lewis RL, Gutmann L: Snake venoms and the neuromuscular junction. Semin Neurol 24:175–179, 2004.
77. Howard JF Jr: Adverse drug effects on neuromuscular transmission. Semin Neurol 10:89–102, 1990.
78. Muntoni F, Torelli S, Ferlini A. Dystrophin and mutations: One gene, several proteins, multiple phenotypes. Lancet Neurol 2:731–740, 2003.
79. Manzur AY, Muntoni F. Diagnosis and new treatments in muscular dystrophies. J Neurol Neurosurg Psychiatry 80:706–714, 2009.
80. van Lunteren E, Leahy P: Gene expression microarrays and respiratory muscles. Respir Physiol Neurobiol 156:103–115, 2007.
81. Cardamone M, Darras BT, Ryan MM: Inherited myopathies and muscular dystrophies. Semin Neurol 28:250–259, 2008.
82. Griggs RC, Bushby K: Continued need for caution in the diagnosis of Duchenne muscular dystrophy. Neurology 64:1498–1499, 2005.

83. Rosalki SB: Serum enzymes in disease of skeletal muscle. Clin Lab Med 9:767–781, 1989.
84. Shneerson JM, Simonds AK: Noninvasive ventilation for chest wall and neuromuscular disorders. Eur Respir J 20:480–487, 2002.
85. Simonds AK, Muntoni F, Heather S, et al: Impact of nasal ventilation on survival in hypercapnic Duchenne muscular dystrophy. Thorax 53:949–952, 1998.
86. Topin N, Matecki S, Le Bris S, et al: Dose-dependent effect of individualized respiratory muscle training in children with Duchenne muscular dystrophy. Neuromuscul Disord 12:576–583, 2002.
87. Driessen JJ: Neuromuscular and mitochondrial disorders: What is relevant to the anaesthesiologist? Curr Opin Anaesthesiol 21:350–355, 2008.
88. Birnkrant DJ, Panitch HB, Benditt JO, et al: American College of Chest Physicians consensus statement on the respiratory and related management of patients with Duchenne muscular dystrophy undergoing anesthesia or sedation. Chest 132:1977–1986, 2007.
89. Crestani B: The respiratory system in connective tissue disorders. Allergy 60:715–734, 2005.
90. Braun NMT, Aurora NS, Rochester DF: Respiratory muscle and pulmonary function in poliomyositis and other proximal myopathies. Thorax 38:316–323, 1983.
91. Teixeira A, Cherin P, Demoule A, et al: Diaphragmatic dysfunction in patients with idiopathic inflammatory myopathies. Neuromuscul Disord 15:32–39, 2005.
92. Fathi M, Lundberg IE, Tornling G: Pulmonary complications of polymyositis and dermatomyositis. Semin Respir Crit Care Med 28:451–458, 2007.
93. Lakhanpal S, Lie JT, Conn DL, et al: Pulmonary disease in polymyositis/dermatomyositis: A clinicopathological analysis of 65 autopsy cases. Ann Rheum Dis 46:23–29, 1987.
94. Winkel LP, Hagemans ML, van Doorn PA, et al: The natural course of non-classic Pompe's disease: A review of 225 published cases. J Neurol 252:875–884, 2005.
95. Fukuda T, Roberts A, Plotz PH, et al: Acid alpha-glucosidase deficiency (Pompe disease). Curr Neurol Neurosci Rep 7:71–77, 2007.
96. Koeberl DD, Kishnani PS, Chen YT: Glycogen storage disease types I and II: Treatment updates. J Inherit Metab Dis 30:159–164, 2007.
97. Kumar M, Kabra NS, Paes B: Carnitine supplementation for preterm infants with recurrent apnea. Cochrane Database Syst Rev 4:CD004497, 2004.
98. Taylor RW, Schaefer AM, Barron MJ, et al: The diagnosis of mitochondrial muscle disease. Neuromuscul Disord 14:237–245, 2004.
99. van Adel BA, Tarnopolsky MA: Metabolic myopathies: Update 2009. J Clin Neuromusc Dis 10:97–121, 2009.
100. De Jonghe B, Lacherade JC, Durand MC, et al: Critical illness neuromuscular syndromes. Neurol Clin 26:507–520, ix, 2008.
101. Coakley JH, Nagendran K, Ormerod IE, et al: Prolonged neurogenic weakness in patients requiring mechanical ventilation for acute airflow limitation. Chest 101:1413–1416, 1992.
102. de Letter MA, Schmitz PI, Visser LH, et al: Risk factors for the development of polyneuropathy and myopathy in critically ill patients. Crit Care Med 29:2281–2286, 2001.
103. Witt NJ, Zochodne DW, Bolton CF, et al: Peripheral nerve function in sepsis and multiple organ failure. Chest 99:176–184, 1991.
104. Thiele RI, Jakob H, Hund E, et al: Sepsis and catecholamine support are the major risk factors for critical illness polyneuropathy after open heart surgery. Thorac Cardiovasc Surg 48:145–150, 2000.
105. Griffin D, Fairman N, Coursin D, et al: Acute myopathy during treatment of status asthmaticus with corticosteroids and steroidal muscle relaxants. Chest 102:510–514, 1992.
106. Deem S: Intensive-care-unit-acquired muscle weakness. Respir Care 51:1042–1052, 2006 [discussion appears 1052–1053].
107. Amaya-Villar R, Garnacho-Montero J, Garcia-Garmendia JL, et al: Steroid-induced myopathy in patients intubated due to exacerbation of chronic obstructive pulmonary disease. Intensive Care Med 31:157–161, 2005.
108. Helliwell TR, Coakley JH, Wagenmakers AJ, et al: Necrotizing myopathy in critically-ill patients. J Pathol 164:307–314, 1991.
109. Bolton CF, Gilbert JJ, Hahn AF, et al: Polyneuropathy in critically ill patients. J Neurol Neurosurg Psychiatry 47:1223–1231, 1984.
110. Bolton CF: Neuromuscular manifestations of critical illness. Muscle Nerve 32:140, 2005.
111. van den Berghe G, Wouters P, Weekers F, et al: Intensive insulin therapy in the critically ill patients. N Engl J Med 345:1359–1367, 2001.
112. Gibson G: Diaphragmatic paresis: Pathophysiology, clinical features, and investigation. Thorax 44:960–970, 1989.
113. Hart N, Nickol AH, Cramer D, et al: Effect of severe isolated unilateral and bilateral diaphragm weakness on exercise performance. Am J Respir Crit Care Med 165:1265–1270, 2002.
114. Gierada DS, Slone RM, Fleishman MJ: Imaging evaluation of the diaphragm. Chest Surg Clin N Am 8:237–280, 1998.
115. Gottesman E, McCool FD: Ultrasound evaluation of the paralyzed diaphragm. Am J Respir Crit Care Med 155:1570–1574, 1997.
116. Versteegh MI, Braun J, Voigt PG, et al: Diaphragm plication in adult patients with diaphragm paralysis leads to long-term improvement of pulmonary function and level of dyspnea. Eur J Cardiothorac Surg 32:449–456, 2007.
117. Sandham JD, Shaw DT, Guenter CA: Acute supine respiratory failure due to bilateral diaphragmatic paralysis. Chest 72:96–98, 1977.
118. McCool F, Mead J: Dyspnea on immersion: Mechanisms in patients with bilateral diaphragm paralysis. Am Rev Respir Dis 139:275–276, 1989.
119. Stradling JR, Warley AR: Bilateral diaphragm paralysis and sleep apnoea without diurnal respiratory failure. Thorax 43:75–77, 1988.
120. Mier-Jedrzelowicz A, Brophy C, Moxham J, et al: Assessment of diaphragm weakness. Am Rev Respir Dis 137:877–883, 1988.
121. Miller SG, Brook MM, Tacy TA: Reliability of two-dimensional echocardiography in the assessment of clinically significant abnormal hemidiaphragm motion in pediatric cardiothoracic patients: Comparison with fluoroscopy. Pediatr Crit Care Med 7:441–444, 2006.
122. Kumar N, Folger WN, Bolton CF: Dyspnea as the predominant manifestation of bilateral phrenic neuropathy. Mayo Clin Proc 79:1563–1565, 2004.
123. Laporta D, Grassino A: Assessment of transdiaphragmatic pressure in humans. J Appl Physiol 58:1469–1476, 1985.
124. Summerhill EM, El-Sameed YA, Glidden TJ, et al: Monitoring recovery from diaphragm paralysis with ultrasound. Chest 133:737–743, 2008.
125. Qureshi A: Diaphragm paralysis. Semin Respir Crit Care Med 30:315–320, 2009.
126. Versteegh MI, Braun J, Voigt PG, et al: Diaphragm plication in adult patients with diaphragm paralysis leads to long-term improvement of pulmonary function and level of dyspnea. Eur J Cardiothorac Surg 32:449–456, 2007.
127. Bach JR, Saporito LR: Criteria for extubation and tracheostomy tube removal for patients with ventilatory failure. A different approach to weaning. Chest 110:1566–1571, 1996.
128. Finder JD, Birnkrant D, Carl J, et al: Respiratory care of the patient with Duchenne muscular dystrophy: ATS consensus statement. Am J Respir Crit Care Med 170:456–465, 2004.
129. Lindahl SG, Yates AP, Hatch DJ: Relationship between invasive and noninvasive measurements of gas exchange in anesthetized infants and children. Anesthesiology 66:168–175, 1987.
130. Janssens JP, Laszlo A, Uldry C, et al: Non-invasive (transcutaneous) monitoring of P_{CO_2} (TcP_{CO_2}) in older adults. Gerontology 51:174–178, 2005.
131. Hukins CA, Hillman DR: Daytime predictors of sleep hypoventilation in Duchenne muscular dystrophy. Am J Respir Crit Care Med 161:166–170, 2000.
132. Kirk VG, Flemons WW, Adams C, et al: Sleep-disordered breathing in Duchenne muscular dystrophy: A preliminary study of the role of portable monitoring. Pediatr Pulmonol 29:135–140, 2000.

133. Leith DE, Butler JP, Sneddon SL, et al: Cough. *In* Macklem PT, Mead J (eds): Handbook of Physiology, Section 3: The Respiratory System, Vol 3, Part 2. Bethesda, MD: American Physiologic Society, 1990, pp 315–336.
134. Kasarskis EJ, Neville HE: Management of ALS: Nnutritional care. Neurology 47:S118–S120, 1996.
135. Mujica VR, Conklin J: When it's hard to swallow. What to look for in patients with dysphagia. Postgrad Med 105:131–134, 141–2, 145, 1999.
136. Tilton AH, Miller MD, Khoshoo V: Nutrition and swallowing in pediatric neuromuscular patients. Semin Pediatr Neurol 5:106–115, 1998.
137. Briani C, Marcon M, Ermani M, et al: Radiological evidence of subclinical dysphagia in motor neuron disease. J Neurol 245:211–216, 1998.
138. Plum F, Whedon DA: The rapid-rocking bed: It's effect on the ventilation of poliomyelitis patients with respiratory paralysis. N Engl J Med 245:235–241, 1956.
139. Hill NS: Clinical applications of body ventilators. Chest 90:897–905, 1986.
140. Simonds AK: Home ventilation. Eur Respir J Suppl 47:38s–46s, 2003.
141. Epstein SK: Late complications of tracheostomy. Respir Care 50:542–549, 2005.
142. Bach JR, Alba AS: Sleep and nocturnal mouthpiece IPPV efficiency in postpoliomyelitis ventilator users. Chest 106:1705–1710, 1994.
143. Sullivan CE, Ellis ER: Nocturnal positive pressure ventilation via a nasal mask (letter). Am Rev Respir Dis 136:791–792, 1987
144. Ferguson GT, Gilmartin M. CO_2 rebreathing during BiPAP ventilatory assitance. Am J Respir Crit Care Med 151:1126–1135, 1995.
145. Curran FJ: Night ventilation by body respirators for patients in chronic respiratory failure due to late stage Duchenne muscular dystrophy. Arch Phys Med Rehabil 62:270–274, 1981.
146. Mehta S, Hill NS: Noninvasive ventilation. Am J Respir Crit Care Med 163:540–577, 2001.
147. Marino W, Braun NMT: Reversal of the clinical sequelae of respiratory failure with nasal positive pressure ventilation. Am Rev Resp Dis 125:85, 1982.
148. Sinha R, Bergofsky EH: Prolonged alteration of lung mechanics in kyphoscoliosis by positive pressure hyperinflation. Am Rev Respir Dis 106:47–57, 1972.
149. Rochester DF, Braun NT, Lane S: Diaphragmatic energy expenditure in chronic respiratory failure. Am J Med 63:223–232, 1977.
150. Ozsancak A, D'Abrosio C, Hill NS: Nocturnal noninvasive ventilation. Chest 133:1275–1286, 2008.
151. Bach JR, Wang TG: Noninvasive long-term ventilatory support for individuals with spinal muscular atrophy and functional bulbar musculature. Arch Phys Med Rehabil 76:213–217, 1995.
152. Benditt JO: Full-time noninvasive ventilation: Possible and desirable. Respir Care 51:1005–1012, 2006 [discussion appears 1012–1015].
153. Toussaint M, Soudon P, Kinnear W: Effect of noninvasive ventilation on respiratory muscle loading and endurance in patients with Duchenne muscular dystrophy. Thorax 63:430–434, 2008.
154. Bach JR, Ishikawa Y, Kim H: Prevention of pulmonary morbidity for patients with Duchenne muscular dystrophy. Chest 112:1024–1028, 1997.
155. Gomez-Merino E, Bach JR: Duchenne muscular dystrophy: Prolongation of life by noninvasive ventilation and mechanically assisted coughing. Am J Phys Med Rehabil 81:411–415, 2002.
156. ACCP Consensus Conference: Clinical indications for noninvasive positive pressure ventilation in chronic respiratory failure due to restrictive lung disease, COPD, and nocturnal hypoventilation—A consensus conference report. Chest 116:521–534, 1999.
157. Hardy KA, Anderson BD: Noninvasive clearance of airway secretions. Respir Care Clin N Am 2:323-345, 1996.
158. Kang SW, Bach JR: Maximum insufflation capacity: Vital capacity and cough flows in neuromuscular disease. Am J Phys Med Rehabil 79:222–227, 2000.
159. Nygren-Bonnier M, Wahman K, Lindholm P, et al: Glossopharyngeal pistoning for lung insufflation in patients with cervical spinal cord injury. Spinal Cord 47:418–422, 2009. Epub 2008; November 11.
160. Homnick DN: Mechanical insufflation-exsufflation for airway mucus clearance. Respir Care 52:1296–1305, 2007.
161. Lange DJ, Lechtzin N, Davey C, et al: High-frequency chest wall oscillation in ALS: An exploratory randomized, controlled trial. Neurology 67:991–997, 2006.
162. Carter GT, Johnson ER, Bonekat HW, et al: Laryngeal diversion in the treatment of intractable aspiration in motor neuron disease. Arch Phys Med Rehabil 73:680–682, 1992.
163. Birnkrant DJ, Ferguson RD, Martin JE, et al: Noninvasive ventilation during gastrostomy tube placement in patients with severe Duchenne muscular dystrophy: Case reports and review of the literature. Pediatr Pulmonol 41:188–193, 2006.
164. Park JH, Kang SW: Percutaneous radiologic gastrostomy in patients with amyotrophic lateral sclerosis on noninvasive ventilation. Arch Phys Med Rehabil 90:1026–1029, 2009.

CHAPTER 88

THE LUNGS AND CHEST WALL DISEASES

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INTRODUCTION

This chapter focuses on diseases of the soft tissue and bony structures of the chest wall. Kyphoscoliosis and ankylosing spondylitis are disorders that involve the spine and its articulations, pectus excavatum involves the sternum, flail chest affects the ribs, and obesity adds to the soft tissues of the rib cage and abdomen. These disorders primarily affect the respiratory system by altering the elasticity of the chest wall, from kyphoscoliosis with the most severe impact on respiratory function to pectus excavatum with the least impact. Pathophysiology of these disorders is discussed in the framework of respiratory mechanics. The most recent developments in treatment are reviewed. Neuromuscular diseases that affect the chest wall are reviewed in Chapter 87.

KYPHOSCOLIOSIS

Diagnosis and Etiology

The term *kyphoscoliosis* is derived from the Greek words *kuphos* and *scolios* ("humpback" and "crooked") and refers to a group of disorders characterized by excessive spinal curvature in the lateral plane (scoliosis) and sagittal plane (kyphosis) as well as rotation of the spinal axis (Fig. 88-1). Scoliosis, which is defined as a lateral curvature greater than 10 degrees,[1] is generally associated with kyphosis and rotation of the spine around its long axis. First described in detail by Hippocrates, kyphoscoliosis is one of the most common abnormalities of the spine, with an estimated prevalence for mild deformity of 1 in 1000 people and that for severe deformity of 1 in 10,000 people in the United States.[1]

Kyphoscoliosis is classified as idiopathic (no known cause), secondary or paralytic (associated with neuromuscular disease), and congenital (associated with vertebral malformation present at birth) (Table 88-1). Idiopathic kyphoscoliosis, the most common form, usually manifests in late childhood or early adolescence and involves females more often than males with a ratio of 4:1. Idiopathic kyphoscoliosis is often seen in multiple members of one family. It is believed to be a multigene condition, with autosomal or sex-linked inheritance with variable phenotypic expression.[2] Recently, a defect in the chromatin-remodeling gene family, CHD7, has been

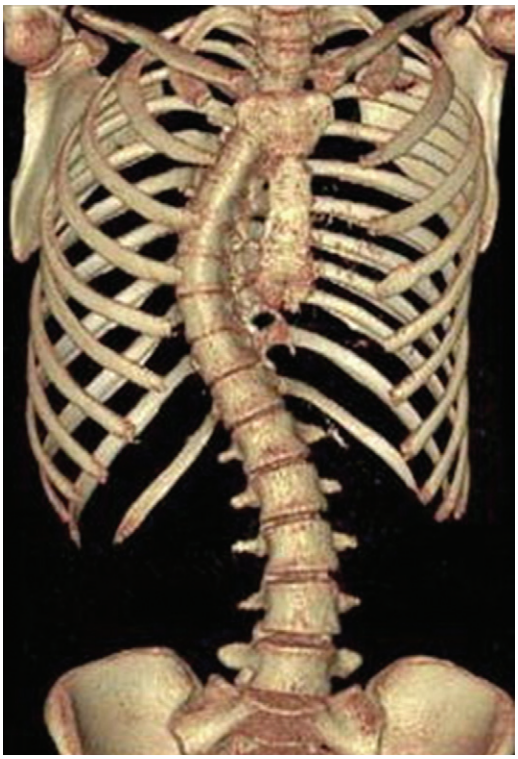

FIGURE 88-1 ■ Spiral computed tomography reconstruction showing the rotation of the spine and rib cage in kyphoscoliosis. (Adapted from Chun EM, Suh SW, Modi HN, et al: The change in ratio of convex and concave lung volume in adolescent idiopathic scoliosis. Eur Spine J 17:224–229, 2008.)

TABLE 88-1. Causes of Kyphoscoliosis

Idiopathic
Multigene disorder, developing by childhood/adolescence
Paralytic or Secondary
Neuromuscular (poliomyelitis, muscular dystrophy, cerebral palsy, Friedreich's ataxia, Charcot-Marie-Tooth disease)
Disorders of Connective Tissue (Marfan's syndrome, Ehlers-Danlos syndrome, Morquio's syndrome)
Vertebral Disease (osteoporosis, osteomalacia, vitamin D–resistant rickets, tuberculous spondylitis, spina bifida)
Post-thoracoplasty
Congenital
Due to spinal/vertebral malformations at birth

associated with idiopathic kyphoscoliosis.[3] The most important sequelae of progressive kyphoscoliosis are back pain, psychosocial problems, and development of respiratory failure.

Severe kyphoscoliosis can be readily diagnosed on physical examination. Typical findings are the dorsal hump, which is due to the angulated ribs and shoulder asymmetry, and hip tilt, which is related to spinal rotation. In children and adolescents with idiopathic kyphoscoliosis, the initial changes may be subtle and require careful inspection such as by Adam's forward bend test. With this test, the examiner observes for thoracic or lumbar region asymmetry while the patient bends forward at the waist until the spine becomes parallel to the floor. In severe kyphoscoliosis complicated by right heart failure, clinical examination may reveal cyanosis, distended neck veins, peripheral edema, and hepatomegaly.

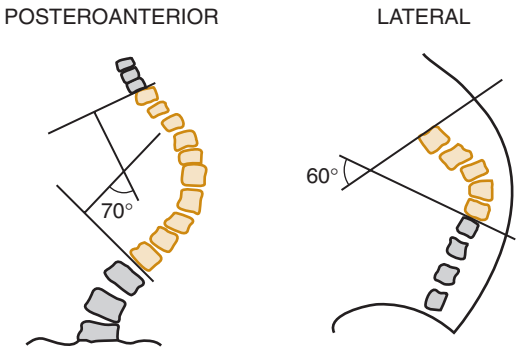

FIGURE 88-2 ■ Drawings of the spine illustrating the lines constructed to measure the Cobb angle of scoliosis and kyphosis. The degree of scoliosis can be assessed on the posteroanterior radiograph (*left*) and the degree of kyphosis on the lateral radiograph (*right*). The angle can be calculated in two ways: either from the intersection of the lines parallel to the vertebra (as shown for kyphosis, on the *right*) or from the intersection of lines perpendicular to these lines (as shown for scoliosis, on the *left*).

The severity of the spinal deformity is assessed by measuring the Cobb angle on a radiograph of the spine.[4] This is the angle formed by the intersection of two lines, one parallel to the top and the other parallel to the bottom vertebrae of the scoliotic or kyphotic curves (Fig. 88-2). The greater the Cobb angle the more severe is the deformity. Angles greater than 100 degrees are usually associated with respiratory symptoms (i.e., dyspnea on exertion) and angles greater than 120 degrees with respiratory failure.[5]

Pathophysiology

Pulmonary Function and Respiratory Mechanics

Kyphoscoliosis can produce the most severe restrictive impairment of all chest wall diseases[6,7] (Table 88-2). Total lung capacity (TLC) and vital capacity (VC) may be reduced to as low as 30% of predicted values; residual volume (RV) may be normal or slightly increased, thus resulting in an elevated RV/TLC.[8] In children with severe deformity, hypoplastic lung may contribute to reduced lung volumes.[9] Restrictive pathophysiology is invariably present when the Cobb angle is greater than 90 degrees. Other factors contributing to the restrictive process include the number of vertebrae involved, curve location, patient's age, presence of kyphosis, degree of spinal rotation, and respiratory muscle strength.[10–12]

Respiratory muscle strength may be normal or reduced in patients with kyphoscoliosis. Individuals with idiopathic kyphoscoliosis and Cobb angles of less than 50 degrees usually have normal respiratory muscle strength,

whereas those with angles greater than 50 degrees may have mild to moderate reductions in maximal inspiratory pressure (PI_{max}) and maximal expiratory pressure (PE_{max})[13] due either to respiratory muscle weakness or to altered chest wall mechanics. In patients with paralytic kyphoscoliosis, profound respiratory muscle weakness may be present and contribute to respiratory failure. Perhaps because of this primary involvement of the respiratory muscles, these patients have a relatively greater restrictive defect for a given degree of spinal deformity than those with idiopathic kyphoscoliosis.[14] Likewise, in congenital kyphoscoliosis, the loss in VC is 15% greater than in patients with idiopathic kyphoscoliosis and a similar Cobb angle, most likely due to associated rib deformities or underlying lung abnormalities.[14]

TABLE 88-2. Representative Values for Pulmonary Function and Respiratory Mechanics in Chest Wall Diseases

	CHEST WALL DISEASE*			
Parameter†	**KS**	**Post-Thor**	**PE**	**AS**
TLC (% predicted)	45	65	90	85
VC (% predicted)	30	50	90	80
RV (% predicted)	95	90	100	100
FEV_1 (% predicted)	40	40	95	80
FEV_1/FVC	80	60	80	75
C_{RS} (% predicted)	50	50	—	70
C_W (% predicted)	30	40	—	60
C_L (% predicted)	60	50	80	80
PI_{max} (cm H_2O)	40	50	90	80
MVV (L/min)	37	37	107	80

*KS, kyphoscoliosis; Post-Thor, post-thoracoplasty; PE, pectus excavatum; AS, ankylosing spondylitis.
†TLC, total lung capacity; VC, vital capacity; RV, residual volume; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; C_{RS}, compliance of respiratory system; C_W, compliance of chest wall; C_L, compliance of lungs; PI_{max}, maximum inspiratory pressure; MVV, maximum voluntary ventilation.
Representative values are from Bergofsky EH: Thoracic deformities. *In* Roussos C (ed): The Thorax. New York: Marcel Dekker, 1995, pp 1915–1949.

Respiratory system compliance is reduced in kyphoscoliosis, primarily due to reduction in chest wall compliance and, to a lesser degree, reduction in lung compliance due to microatelectasis. Cobb angles up to 50 degrees have minimal effect in decreasing respiratory compliance, whereas angles greater than 100 degrees may reduce compliance to levels seen in acute respiratory distress syndrome.[15] The stiff chest wall reduces the resting position of the respiratory system (functional residual capacity [FRC]). These factors result in tidal breathing moving to a flatter, stiffer portion of the respiratory volume-pressure curve. This requires greater inspiratory effort for relatively small tidal breaths, which increases the work and oxygen cost of breathing (Fig. 88-3). The increase in the oxygen cost of breathing may reach values three to five times those measured in healthy individuals and thus place patients at risk for respiratory muscle fatigue.[16]

Exercise Capacity

Adolescents with mild idiopathic kyphoscoliosis usually have normal exercise capacity,[17] whereas those with moderate idiopathic kyphoscoliosis (Cobb angles 25 to 70 degrees) have reduced exercise capacity. In these individuals, exercise limitation may be due to deconditioning rather than ventilatory constraints.[18–20] With severe deformities, ventilatory and cardiovascular factors may each contribute to exercise limitation.[18,19] Supplemental O_2 may improve oxygenation during exercise but usually does not affect walk distance.

Control of Breathing and Sleep-Disordered Breathing

Patients with kyphoscoliosis compensate for the increased elastic loads on the inspiratory muscles by adopting a rapid shallow breathing pattern consisting of low tidal volumes and shortened inspiratory time. Both of these factors correlate with the angle of scoliosis.[21] In the setting of a stiff chest wall, this breathing pattern minimizes the work per breath and the pressure needed to inhale, thereby lowering the risk for respiratory

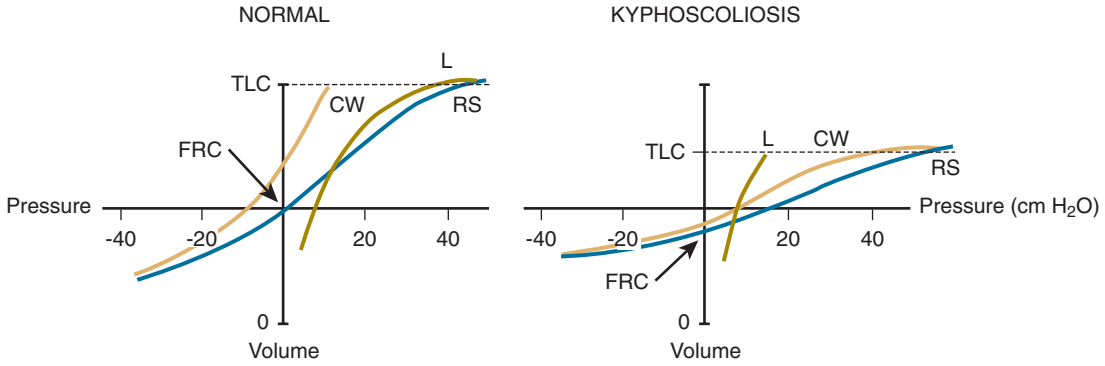

FIGURE 88-3 ■ Schematic illustration of alterations in volume-pressure relationship of the lung (L), chest wall (CW), and respiratory system (RS) in kyphoscoliosis. The chest wall is less compliant, leading to a reduction in functional residual capacity (FRC), and tidal breathing takes place on a flatter portion of the respiratory system volume-pressure curve. TLC, total lung capacity.

muscle fatigue. However, this breathing pattern promotes dead space ventilation and microatelectasis, thus further decreasing lung compliance. Patients also may compensate for the increased elastic load by increasing neural drive to the respiratory muscles. Indirect evidence for this compensatory strategy is the elevated mouth occlusion pressure at 100 msec ($P_{0.1}$) seen during quiet breathing, exercise, or breathing stimulated by hypercapnia. In addition, $P_{0.1}$ correlates positively with the angle of deformity in these patients.[21] This increased neural drive may not be accompanied by increased ventilation as the mechanical limitations imposed by the stiffened chest wall and weak inspiratory muscles limit the augmentation of ventilation when neural drive is increased.

Sleep-related breathing disorders may significantly impact the clinical course and quality of life of patients with kyphoscoliosis.[5] Nocturnal hypoxemia typically predates onset of respiratory failure in these patients.[5,22] Hypoventilation is the most common abnormality during sleep and is related to a reduction in inspiratory muscle activity during rapid-eye-movement sleep. Decreased neural drive to the diaphragm combined with a reduction in chest wall compliance may also contribute to hypoventilation during sleep.[22] However, the magnitude of nocturnal oxyhemoglobin desaturation may not correlate with the angle of deformity, highlighting the importance of overnight oximetry as a screening tool even in patients with moderate spinal deformity.[23] Obstructive sleep apnea may occur with a frequency similar to that seen in the general population and can further aggravate nocturnal hypoventilation.[24] Adverse sequelae of nocturnal hypoxemia and hypercapnia include respiratory muscle dysfunction, persistent hypercapnia and hypoxemia, pulmonary vascular remodeling, pulmonary hypertension, and ultimately cardiorespiratory failure and death.[22] Because sleep-related abnormalities and their effects on cardiorespiratory function are potentially treatable, they should always be evaluated in kyphoscoliosis patients well in advance of development of daytime hypercapnia so that noninvasive ventilation can be instituted early.[5,25]

Clinical Course

Etiology and spinal deformity importantly influence the natural history of kyphoscoliosis.[2] In secondary kyphoscoliosis, progression is largely dependent on underlying disease and age of onset. For example, onset at an early age, rapid curve progression during growth, and progression after skeletal maturity are risk factors for respiratory complications.[26] Congenital kyphoscoliosis may also progress rapidly and compromise respiratory function. In contrast, idiopathic kyphoscoliosis generally has a overall more benign course, with curve progression, cardiopulmonary problems, and psychosocial concerns developing at a variable rate in most untreated patients.[2] Large curves at presentation, skeletal immaturity, and a thoracic, as opposed to a thoracolumbar or lumbar, location of the curve apex are generally considered risk factors for curve progression.[2] In general, the spinal deformity worsens at a rate of about 1 degree per year in individuals with thoracic deformities greater than 50 degrees at skeletal maturity.

In mild idiopathic kyphoscoliosis, the probability of developing respiratory failure with aging is similar to that in a healthy population. However, the risk is higher for patients with moderate or severe deformities. Middle-aged or older patients with severe deformities (i.e., angles around 100 degrees) need to be monitored closely for respiratory complications. The initial symptom is usually dyspnea on exertion, which may then progress to dyspnea at rest. As deformity progresses with aging, respiratory failure may ensue. When cor pulmonary develops, the prognosis is poor and, without therapy, death may occur within 1 year. In addition to chest wall deformity, other factors that contribute to ventilatory failure in these patients are inspiratory muscle weakness, underlying neuromuscular disease, sleep-disordered breathing, and airway compression due to distortion of the lung parenchyma and twisting of airways. These factors should be investigated in individuals with respiratory failure and Cobb angles smaller than 100 degrees.

Treatment

Medical Treatment

General supportive measures include immunizations against influenza and pneumococci, smoking cessation, maintenance of a normal body weight, supplemental oxygen, and treatment of respiratory infections in a timely fashion (instructing patients to call when they first notice a change in sputum characteristics). Physical activity should be encouraged to minimize deconditioning. For chronic respiratory failure, chest physiotherapy, bronchodilators, and diuretics may be needed.

Nocturnal hypoventilation should be treated with noninvasive positive-pressure ventilation, which is typically delivered via a nasal or full-face mask. Pressure or volume preset ventilators can be used with similar efficacy.[5] Indications for instituting noninvasive ventilation include symptoms suggestive of nocturnal hypoventilation or signs of cor pulmonale with either an elevated daytime arterial P_{CO_2} or nocturnal oxygen saturation less than 88% for 5 consecutive minutes[27] (Table 88-3). Supplemental oxygen will be needed if hypoxemia persists despite correction of hypoventilation. Tracheostomy is considered for patients with inability to manage excessive bronchial secretions and for those not responding to or not tolerating noninvasive ventilation.

The benefits of noninvasive ventilation are well documented and include improvements in gas exchange, hemodynamic parameters, sleep architecture, and quality of life[5,25] (Table 88-4). The likely mechanism of improvement in respiratory failure is by increasing ventilatory response to carbon dioxide rather than improving respiratory muscle contractility.[28] Additional benefits of long-term noninvasive ventilation are a reduction in the number and duration of hospitalizations.[5] An increase in survival is also likely, although this evidence is not supported by randomized controlled studies.[29–31] Lung

TABLE 88-3. Indications for Instituting Long-Term Noninvasive Ventilation for Kyphoscoliosis (and Other Chest Wall Diseases)

Symptoms (e.g., fatigue, morning headaches, dyspnea) or *signs* of cor pulmonale and one of the following:
- Daytime arterial $P_{CO_2} \geq 45$ mm Hg
- Nocturnal oxygen saturation < 88% for >5 consecutive minutes
- Progressive neuromuscular disease with $P_{I_{max}} < 60$ cm H_2O or FVC < 50% of predicted

FVC, forced vital capacity; $P_{I_{max}}$, maximal static inspiratory pressure.
Adapted from Consensus Conference: Clinical indications for noninvasive positive pressure ventilation in chronic respiratory failure due to restrictive lung disease, COPD, and nocturnal hypoventilation—a consensus conference report. Chest 116:521–534, 1999.

TABLE 88-4. Benefits of Noninvasive Nocturnal Ventilation in Chest Wall Diseases

- Gas exchange
  - Increased arterial P_{O_2}
  - Decreased arterial P_{CO_2}
- Hemodynamics
  - Decreased pulmonary arterial pressure
  - Improved right ventricular function
- Mechanics
  - Reduced work of breathing
  - Increased maximal static inspiratory pressure ($P_{I_{max}}$)
- Sleep hygiene
  - Normalized sleep patterns
  - Fewer apneic episodes
- Outcome
  - Fewer hospitalizations
  - Improved quality of life
  - Relief of dyspnea
  - Possible increased survival

volumes, respiratory muscle strength, and respiratory endurance are not consistently improved with noninvasive ventilation.

Surgical Treatment

Surgical and nonsurgical (brace) orthopedic treatments have been used in skeletally immature patients with idiopathic kyphoscoliosis in an effort to prevent or correct the spinal deformity. A brace is generally recommended for growing children with angles between 25 and 40 degrees, whereas surgery is indicated for adolescents with an angle greater than 45 degrees.[2] In general, surgery involves fusion of the affected vertebral bodies via the posterior approach and use of modern instrumentation such as rods, wires, hooks, and pedicle screws to support the spine. This technique, which has significantly improved since the initial introduction of Harrington rods, allows for multiplanar correction, stable fixation with less spinal fusion, and no need to use postoperative immobilization with a cast or brace.[2] Immediately following surgery, chest wall and respiratory system compliance may decrease due to rib cage trauma and changes in the chest wall caliber.[32] The long-term benefits of spinal surgery on pulmonary function remain unclear.[33–35] Pulmonary function is more likely to improve in young children and adolescents than in adults. In the absence of randomized controlled studies assessing the efficacy of bracing or surgery, the overall role of surgical management in restoring function to that of nonscoliotic individuals and minimizing the possibility of respiratory failure is not clear.[2]

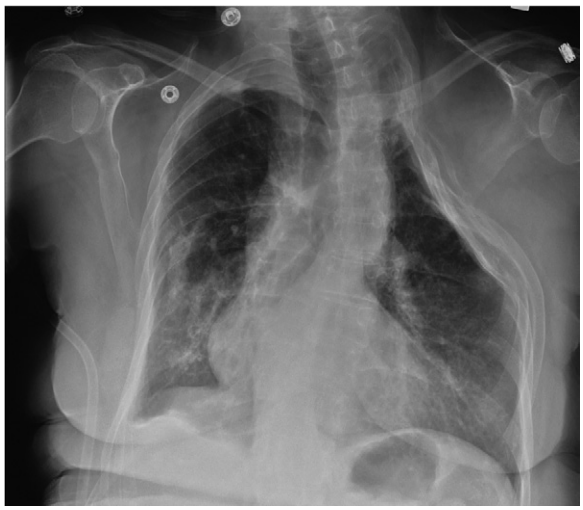

FIGURE 88-4 ■ Frontal chest radiograph in a patient with history of prior *Mycobacterium tuberculosis* infection shows extensive deformity of the left hemithorax consistent with prior thoracoplasty. Scoliosis of the thoracic spine is probably related to the chest wall deformity.

THORACOPLASTY

Thoracoplasty was used frequently in the pre-antibiotic era to treat tuberculosis. The goal of thoracoplasty (Fig. 88-4) was to reduce lung volume by removing ribs, producing rib fractures, resecting the phrenic nerve, or filling the pleural space with foreign material (i.e., ping-pong balls). Severe restrictive impairment usually manifests itself decades following the procedure. Since this procedure was performed in the 1940s and 1950s, very few people are alive today who underwent thoracoplasty,[36,37] but the natural history of this condition is instructive. Symptoms of dyspnea on exertion followed by acute or chronic respiratory failure typically develop after a long asymptomatic phase. Factors such as slowly progressive kyphoscoliosis account, in part, for the delay in the onset of symptoms. The severity of the restrictive defect can be similar to that seen in kyphoscoliosis (see Table 88-2), and is due to reduction in respiratory system compliance, fibrothorax, lung fibrosis related to underlying granulomatous disease, lung resection, phrenic nerve

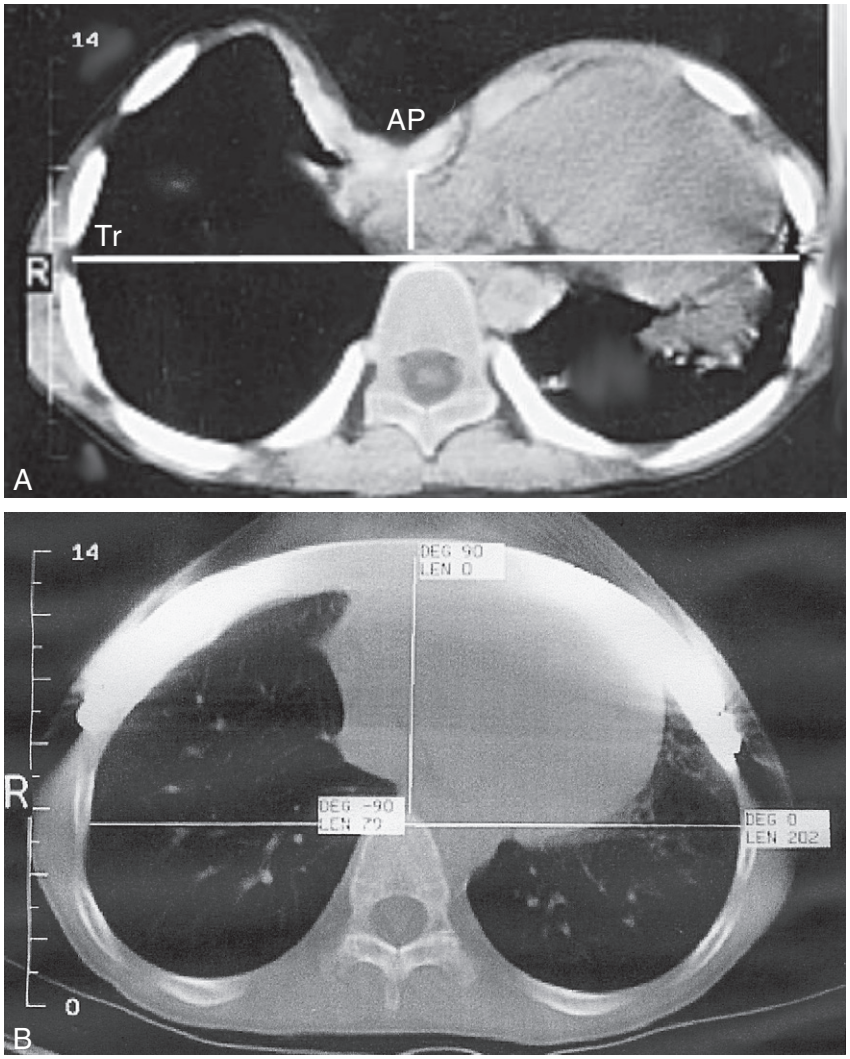

FIGURE 88-5 ■ **A,** Preoperative chest CT scan of a patient with pectus excavatum, demonstrating a severely reduced anteroposterior (AP) diameter relative to the transverse rib cage diameter (Tr) (transverse/AP ratio = 8.6). **B,** Following the minimally invasive Nuss procedure, the AP distance increases and the ratio becomes more normal (transverse/AP ratio = 2.7) (Normal = 2.5).

damage, and scoliosis.[36,37] The substantial elastic loads imposed by the stiff respiratory system lead to an increase in the work of breathing, impaired gas exchange, and ultimately cor pulmonale. As with severe kyphoscoliosis, the treatment consists of oxygen, antibiotics when appropriate, and noninvasive mechanical ventilation. It is important for the clinician to be aware of the natural history of post-thoracoplasty individuals because one may encounter patients with a similar progressive impairment of respiratory function following aggressive surgery on the rib cage to resect tumors or for other reasons such as treatment of unrelenting empyema. Patients undergoing extensive chest wall surgery of any type should have their pulmonary function monitored periodically.

PECTUS EXCAVATUM

Diagnosis and Etiology

Pectus excavatum is a congenital chest wall deformity characterized by excessive depression of the sternum and its adjacent costal cartilages (Fig. 88-5). It is the most common chest wall deformity, occurring in approximately 0.5% to 2% of the population, more frequently in males than in females (ratio of 4:1).[38] Although pectus excavatum may be apparent in infancy, the majority of cases become noticeable at puberty.

Pectus excavatum may result from abnormal cartilage growth that displaces the sternum inward.[38] A genetic predisposition is supported by a large study in which 43% of patients gave a family history of pectus excavatum.[39] Approximately 6% of patients have a connective tissue disorder such as Marfan or Ehlers-Danlos syndrome, and 40% to 60% have scoliosis.[40] Congenital heart disease may coexist in about 2% of cases.[38]

Individuals with pectus excavatum, especially teenagers, often seek medical advice for cosmetic concerns. Dyspnea with activity or exercise intolerance, often out of proportion to any abnormality in cardiopulmonary function, is present in 30% to 70% of patients. There is a considerable range of sternal deformity that is best assessed by computed tomography (CT) measurements

of the ratio of the transverse to anterior-posterior diameter of the rib cage at the level of the deepest sternal depression. A ratio greater than 3.25 (normal 2.5) signifies a pectus deformity that may need correction.

Pathophysiology

Respiratory Mechanics and Exercise Capacity

Most patients with pectus excavatum have normal pulmonary function, although a small percentage of individuals have a mild restrictive deficit.[38,40] Unlike ankylosing spondylitis, the mobility of the rib cage in those with pectus during quiet breathing or mild exercise is not limited.[41] Despite a perception of exercise limitation, cardiopulmonary exercise testing is usually normal. Those with the most severe deformities may exhibit a mild reduction in the maximal work rate and oxygen consumption.[42,43] Although the concept is not widely accepted, right ventricular compression by the depressed sternum may be a mechanism underlying exercise limitation in some individuals.

Treatment

Surgical correction of pectus excavatum is usually considered for patients with a CT index greater than 3.5 in conjunction with symptoms or laboratory evidence of cardiac or pulmonary impairment.[38] Initially, surgical approaches involved resection of costal cartilage combined with sternal osteotomy (Ravitch procedure). Less invasive approaches now entail the substernal placement of a curved metal rod through small incisions on each side of the rib cage; after insertion, the rod is rotated, forcing the sternum outward (Nuss procedure). The bar is removed after 2 years once the sternum is stabilized in its original position.[39] Currently, gradual correction procedures using magnets to pull out the sternum are being tested, and such remodeling approaches may be available in the future.[44] Compared with more invasive procedures, the less invasive Nuss procedure has a lower incidence of complications such as sternal necrosis and infection. With either corrective procedure, improvement of symptoms and function is difficult to predict. In fact, to date, there is no convincing evidence that correction of the deformity improves either cardiopulmonary function or exercise capacity.[45–48]

FLAIL CHEST

Diagnosis and Etiology

Flail chest arises when fractures of adjacent ribs produce a segment of the rib cage that deforms with normal breathing.[49,50] To produce flail chest, double fractures of three or more contiguous ribs or combined sternal and rib fractures are required. This results in an unstable segment of the chest wall that moves paradoxically, inward with inspiration and outward with expiration.

Blunt chest trauma is the most common cause of flail chest in adults. In children, flail chest is infrequent because the chest wall is more compliant; thus, when it does occur, flail chest signifies a much greater degree of trauma.[51] Automobile accidents and falls account for most cases of flail chest, whereas aggressive cardiopulmonary resuscitation and pathologic rib fractures in patients with multiple myeloma or other metastatic rib lesions are less frequent causes. Rarely, flail chest may complicate corrective rib resection or appear in neonatal life due to congenital rib abnormalities.[49,52–55]

The diagnosis of flail chest can be made at the bedside by observing the characteristic paradoxical movement of a segment of the chest wall during spontaneous ventilation. In subtle cases, palpation of the chest wall may aid in appreciating chest wall paradox. Although not highly sensitive, chest radiographs may confirm the presence of multiple rib fractures. A three-dimensional reconstruction of thoracic helical CT or multidetector CT scans,[56] which are often performed to assess the extent of thoracic injuries after blunt chest wall trauma, provides a more sensitive means of identifying rib fractures. However, these more sophisticated techniques are not necessary to confirm the diagnosis of flail chest, which can be made at the bedside by inspecting or palpating the chest wall. In the fully sedated, mechanically ventilated trauma patient, the diagnosis of flail chest may be delayed for days or even weeks and become apparent only after withdrawal of sedation and resumption of spontaneous breathing.[57]

Trauma and Flail Chest

The presence of flail chest following trauma signifies severe thoracic injury and is an independent risk factor for respiratory complications, respiratory failure, and death. Pulmonary complications such as lung contusion, pneumothorax, or hemothorax can occur in up to 60% of patients with flail chest.[51] Flail chest and its associated pain promote atelectasis, impair cough effectiveness, and may lead to respiratory failure. Patients with flail chest are twice as likely to develop respiratory failure and require mechanical ventilation as patients with isolated lung contusion.[51] Overall, mortality from chest wall trauma is high, ranging from 7% to 14%; with concomitant flail chest, the mortality rate increases even further.[51] In a series of over 1000 multiple-trauma patients, overall mortality was 27% while mortality for those with flail chest was 68%.[58] The associated high mortality is in part due to coexistence of other injuries such as fractures of long bones or vertebrae, head trauma, rupture of major vascular structures, or laceration of abdominal organs. Concomitant head injury is a particularly poor prognostic factor in patients with traumatic flail chest.[51] Older age is another poor prognostic factor; in fact, mortality increases by 132% in patients with flail chest for every decade of increase in age above the age of 10 years starting at the second decade and continuing to the eighth decade of life.[59] Of special note, flail chest in a cardiac arrest victim may render manual compressions ineffective by blunting the increase in intrathoracic pressures with compression and thus necessitate internal cardiac massage. Chronic disability related to flail chest may occur in patients who survive the acute injury. Chest tightness, chest pain, or dyspnea on exertion has

been described in as many as half of such patients. However, with operative fixation of the flail segment, these symptoms can improve dramatically.[60,61]

Pathophysiology

Respiratory Mechanics

Flail chest disrupts the anatomic integrity of the chest wall and seriously alters its function. With flail chest, a segment of the chest wall is uncoupled from the forces that promote rib cage expansion, thereby making the flail segment responsive to intrapleural pressure changes. Thus, with inspiration and the decrease in intrapleural pressure, the flail segment moves inward and, during expiration with positive intrapleural pressure, it moves outward. When the normal swings in pleural pressure are amplified by a decrease in lung compliance due to concomitant pulmonary contusion and/or atelectasis, there is greater paradoxical motion of the flail segment. The location of the flail segment may impact the magnitude of disordered chest wall motion. Lateral flail, which is the most common, is generally associated with greater clinical derangement; in contrast, posterior flail has less impact due to splinting provided by the back muscles. However, the patterns of chest wall distortion are not specific to a given location of the flail segment, and the same anatomic location may be associated with different patterns of distortion. For example, paradoxical motion may occur within the rib cage itself or between the rib cage and the abdomen.[62] These disparate patterns include (1) inward displacement of the lateral rib cage as the lower anterior rib cage and abdomen are expanding, (2) inward displacement of the anterior lower rib cage and abdomen as the lateral rib cage is expanding, and (3) inward displacement of the anterior lower rib cage as the lateral rib cage and abdomen are expanding.[62]

Disordered patterns of respiratory muscle recruitment are another factor contributing to motion of the flail segment.[63,64] Normal recruitment patterns may be altered because of severe chest wall pain associated with flail chest. Thus, activation of different respiratory muscles may increase or decrease the degree of rib cage paradox.[65] Clinical observations suggest that the change in the recruitment pattern of the respiratory muscles that follows traumatic flail chest may explain why some cases of flail chest remain unstable following prolonged mechanical ventilation,[66,67] and why lateral flail segments have a higher propensity for dislocation following surgical fixation.[66,67]

Respiratory Failure

Understanding the pathogenesis of respiratory failure in flail chest has markedly evolved over the last 4 decades. The simplistic theory of *pendelluft* (movement of air back and forth between the injured and the uninjured side) has long been abandoned, and recent clinical observations and experimental data suggest that a combination of events, including hypoventilation and flail-induced changes in lung and respiratory muscle function, are key factors. In addition, it has become clear that the effects of the flail segment on respiratory function are complex and that the presence of flail chest alone, without associated pulmonary contusion, has important physiologic sequelae. When present, lung contusion undoubtedly contributes further to the pathogenesis of respiratory failure.

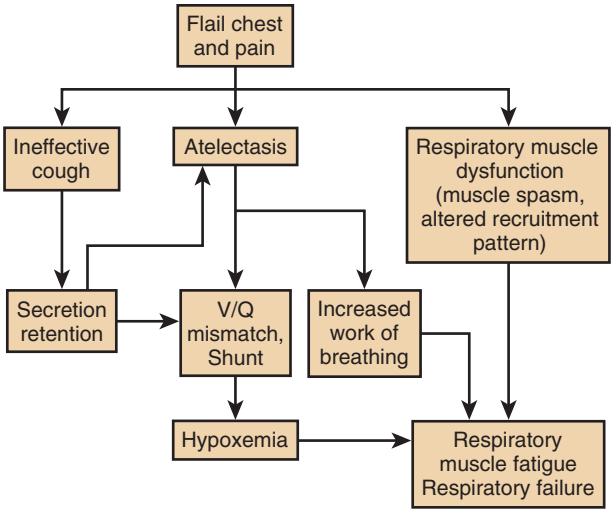

FIGURE 88-6 ■ Factors involved in the pathophysiology of respiratory failure in flail chest.

Both the flail segment and its associated pain contribute to cough impairment, regional atelectasis, intercostal muscle spasm, and alterations in the patterns of respiratory muscle recruitment (Fig. 88-6). In addition to the previously mentioned adverse effects on the lung, the flail segment can impair respiratory muscle performance.[62-65] First, the paradox increases the degree of muscle shortening for a given tidal volume so that, during inspiration, the inspiratory muscles contract at shorter lengths.[62] These effects, combined with the increase in elastic load related to lung contusion and/or atelectasis, reduce respiratory muscle efficiency and increase the work of breathing.[62,68] With the additional effects of hypoxemia, the respiratory muscles are weakened and predisposed to fatigue (see Fig. 88-6).

Pulmonary Function Tests

Reductions in forced vital capacity (FVC) and FRC to as low as 50% of predicted may occur in patients with flail chest. These reductions are related to disordered chest wall motion and, in some patients, to underlying lung contusion. In patients with flail chest without lung contusion treated conservatively, FVC and FRC return to baseline values within 6 months from the acute injury, although mild reductions in pulmonary function may occasionally persist. In contrast, in patients with concomitant lung contusion treated conservatively, reductions in pulmonary function are recorded up to 4 years postinjury, most likely due to fibrosis of the contused area. After operative fixation of flail chest, evidence from controlled[69] and uncontrolled[67] studies showed that the

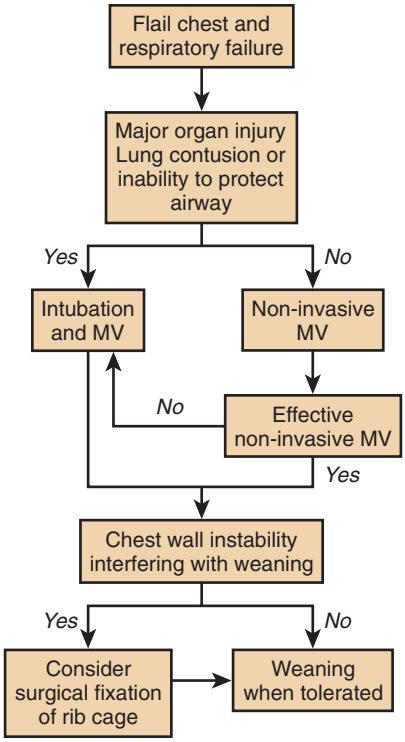

FIGURE 88-7 ■ Algorithm for the management of acute respiratory failure due to flail chest.

impairment in pulmonary function is significantly less than after conservative treatment.

Treatment

General Aspects

The management of flail chest has evolved significantly over the last 2 decades as our understanding of the contribution of the flail segment to respiratory failure continues to be refined. The restoration of anatomic and functional integrity of the chest wall can be achieved with conservative management (with or without mechanical ventilation) or with surgical intervention (Fig. 88-7). However, which modality is best suited for a given patient remains a difficult question to answer.

Nonsurgical Management

Conservative management is based on administration of adequate analgesia, clearing of bronchial secretions, and mechanical ventilatory assistance if needed. Adequate pain relief can be accomplished by oral medications, patient-controlled analgesia pumps, intermittent intercostal nerve blocks, or epidural anesthesia. Control of pain is crucial in averting further atelectasis, arteriovenous shunting, and hypoxemia. Adequate analgesia in combination with supplemental oxygen, effective tracheobronchial toilet, and cautious fluid replacement, often results in successful treatment of flail chest with avoidance of respiratory failure. If respiratory failure ensues, mechanical ventilation is standard treatment. In addition to enhancing gas exchange, positive-pressure ventilation will provide internal pneumatic stabilization of the flail segment. However, mechanical ventilation solely for the purpose of providing stability to the chest wall, as was formerly recommended in the 1960s and 1970s, is no longer recommended due to the increased morbidity and mortality associated with mechanical ventilation. By contrast, noninvasive positive-pressure ventilation may be beneficial to patients with flail chest with less morbidity. When delivered via a nasal or face mask to patients who are spontaneously breathing and able to protect their upper airway, this ventilatory mode in conjunction with patient-controlled analgesia improves gas exchange, allows for early patient mobilization and access for physiotherapy, and significantly reduces morbidity and mortality when compared to mechanically ventilated, intubated patients.[70,71]

If intubation and mechanical ventilation are needed, the choice of ventilator mode may affect the stability of the flail segment. The magnitude of paradoxical motion of the flail segment is related to changes in pleural pressure and is therefore quite sensitive to changes in resistive and elastic loads imposed by the ventilator and its circuit.[62] For example, with the intermittent mandatory ventilation mode, the spontaneous breaths through the added resistance of the circuit may aggravate chest wall distortion. In contrast, high-flow continuous positive airway pressure may reduce chest distortion during inspiration. As a general rule, low-impedance ventilator modes are optimal choices for stabilizing the flail segment and for weaning.[62]

Surgical Management

Surgical fixation of the unstable flail segment has been employed over the last 6 decades to reduce patient ventilator time and the associated ventilator-associated morbidity and mortality. Surgical techniques include mobilization of large chest wall flaps or open thoracotomy and stabilizing the fractured ribs with devices such as medullary wires or nails, Judet struts, or titanium plates. A few controlled studies involving small numbers of patients[69,72] suggested that surgical fixation to restore pulmonary function and chest wall integrity may be superior to conservative management by reducing the length of ventilatory support, duration of intensive care unit stay, infection rate, and incidence of chest wall deformities.

The indications for operative fixation are not fully defined; candidates may be patients with flail chest who are unable to be weaned from mechanical ventilation due to chest wall instability, or those undergoing thoracotomy for concomitant injuries. In addition, patients with persistent pain, with severe chest wall instability, or with progressive decline in pulmonary function could be considered for surgical stabilization.[49,73] Although surgical fixation appears to be a promising therapeutic modality, its benefits and indications need to be clarified by large randomized, well-controlled studies comparing the surgical approach with modern conservative treatment.[73a,73b]

ANKYLOSING SPONDYLITIS

Diagnosis and Etiology

Ankylosing spondylitis (AS) is a chronic progressive inflammatory disease involving primarily the ligamentous structures of the spine and the sacroiliac and large peripheral joints.[74] It usually affects men, with the most common age of onset between 15 and 25 years. The annual incidence is 6.6 per 100,000 white Americans and 3 to 4 times less frequent in black Americans. There is a genetic predisposition for the disease, with nearly 95% of white patients positive for the HLA-B27 antigen.[74]

Compared to other spondyloarthritides, AS exhibits more severe spinal involvement and respiratory complications. The chronic inflammation of the spinal joints and adjacent structures causes fibrosis and ossification of these structures and bony ankylosis of the costovertebral and sternoclavicular joints.[74,75]

Pathophysiology

Respiratory Mechanics

Although the direction of rib cage motion is similar to that in healthy individuals, the magnitude of motion is severely restricted[76] (Fig. 88-8). This limited motion is the hallmark of respiratory dysfunction in AS and is due to stiffening and fusion of the costovertebral and sternoclavicular articulations, to rigidity of the spine, and possibly to intercostal muscle atrophy with advanced disease.[75] Despite a pronounced reduction in rib cage elasticity, lung compliance remains normal except in cases with fibrobullous or interstitial lung disease.[75,77,78] Since the abdomen is compliant and the rib cage is stiff, there is preferential caudal descent of the diaphragm and more expansion of the abdomen than of the rib cage (i.e., the lung expands along the "path of least resistance"). This strategy may minimize the work and energy needed to inflate the lung.[79] Thus, during quiet breathing, exercise, or speech, most of the lung volume change is accomplished by caudal displacement of the diaphragm and expansion of the abdominal wall.[75,79,80] Consequently, transdiaphragmatic pressure increases by 2.4-fold in AS patients at levels of ventilation where healthy individuals increase transdiaphragmatic pressure by 1.4-fold.[75] Greater recruitment of the diaphragm in AS may potentially provide a strength-training stimulus to the diaphragm.

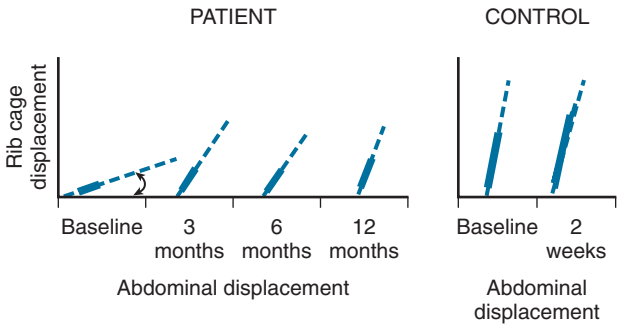

FIGURE 88-8 ■ Representative plots of the rib cage and abdominal displacements during quiet breathing in a seated patient with ankylosing spondylitis, before and at various time points during therapy with anti–TNF-α. Note the diminished contribution of the rib cage to tidal volume at baseline and the progressive increase in the rib cage contribution to breathing with treatment, becoming closer to the normal patterns obtained about 2 weeks apart in a healthy individual (control). (Adapted from Tzelepis GE, Kalliakosta G, Tzioufas AG, et al: Thoracoabdominal motion in ankylosing spondylitis: Association with standardised clinical measures and response to therapy. Ann Rheum Dis 66:966–971, 2009.)

Pulmonary and Respiratory Muscle Function

Despite limited rib cage mobility, there may be only mild decrements in FVC and TLC. The mild restrictive impairment appears to be proportional to disease activity and duration, as well as to the degree of spinal and rib cage immobility.[81,82] The restrictive defect is worsened by concomitant kyphosis, which may occur in advanced disease or be secondary to osteoporosis. Up to 50% of patients with long-standing AS may have some degree of kyphosis.[83] The rigid spine is also susceptible to fracture with minimal trauma. Spinal fractures worsen kyphosis and further impair respiratory function.[84] Cervical spine fractures (typically C6 or C7) can cause tetraplegia and respiratory failure.

The effects of AS on the respiratory muscles are not fully defined. Some, but not all, studies have found that patients with AS have mild reductions in $P_{I_{max}}$ and $P_{E_{max}}$.[82,85,86] Individuals with normal respiratory muscle strength may have impaired respiratory muscle endurance.[86] The mild reductions in strength and endurance may be related to intercostal muscle atrophy secondary to decreased rib cage mobility[75] or to poor coordination of the respiratory muscles during the testing maneuvers.[87]

Gas Exchange and Exercise Capacity

In the majority of patients, arterial P_{O_2} and diffusion capacity are either normal or slightly decreased. The mild impairment in gas exchange is most likely related to the mild reduction in lung volumes.[82] In patients with concomitant fibrobullous disease, gas exchange may be severely compromised. Regional ventilation is usually normal despite the limited expansion of the rib cage.[88]

Exercise capacity may be reduced in patients with AS.[86] The mechanisms underlying this limitation are poorly understood. However, the lack of correlation between the degree of rib cage expansion and maximal oxygen consumption or work rate suggests that exercise is limited by deconditioning rather than ventilation.[86] Others postulate that a decrease in cardiac output related to rib cage stiffness, possibly due to reduced preload from reduced negative swings in intrathoracic pressure, may contribute to exercise limitation.[89,90]

Interstitial Lung Disease

About 1% to 4% of patients with AS, especially men with chronic disease, develop fibrobullous upper lobe

disease.[91–93] The cause of apical fibrobullous disease is unknown. Possible causes include diminished upper lobe ventilation and apical mechanical stress due to thoracic rigidity, as well as recurrent pulmonary infections due to impaired cough. The spectrum of fibrobullous disease ranges from unilateral or bilateral minimal upper lobe interstitial infiltrates to marked fibrosis, honeycombing, and cavitary lesions that may be mistaken for tuberculosis. In a limited number of cases, histologic examination has revealed prominent interstitial fibrosis with hyaline and elastic degeneration of collagen, and absence of granulomas.[92] These patients usually do not have symptoms but are at risk for spontaneous pneumothorax, aspergillosis, or mycobacterial infection. Corticosteroids do not prevent progression of the disease.[93] Because thoracic surgery for fibrobullous disease is complicated by bronchopleural fistula in 50% to 60% of patients, it is recommended only for treatment of major hemoptysis.[93] Another 10% to 20% of patients with AS develop nonapical interstitial lung disease, which can be detected by high-resolution CT scans of the chest.[92]

Treatment

The use of biologic agents has constituted a significant adjunct to standard medical therapy of AS. The tumor necrosis factor-α (TNF-α) antagonists (infliximab, etanercept, and adalimumab) provide significant symptom relief, reduce spinal inflammation, and dramatically improve the quality of life in these patients.[74,94,95] Anti–TNF-α therapy is associated with improvement in respiratory parameters (see Fig. 88-8). Rib cage expansion increases with anti–TNF-α therapy as documented by measurements of maximal rib cage expansion with a tape measure or by measurements of the partitioning of rib cage displacement relative to tidal volume during quiet breathing[79] (see Fig. 88-8). For the standard approach to therapy, exercise continues to be a mainstay.[96] Cardiorespiratory fitness and spinal mobility may be enhanced by instituting exercise and physiotherapy programs.[74,96] Tobacco use should be avoided. Patients should be monitored with baseline chest radiography and spirometry and followed up with repeat studies should respiratory symptoms develop. For patients treated with anti–TNF-α agents, a high index of suspicion for possible reactivation of latent tuberculosis is required. Similarly, specific pulmonary rehabilitation has been tried with varied success. If intubation is required, it should be performed with caution because these patients are at increased risk for spinal cord injury because of involvement of the cricoarytenoid joint.

OBESITY

Diagnosis and Etiology

Obesity has become a major health problem throughout the world, affecting not only adults but also children.[97] In the United States, recent estimates indicate that over half of the population is either overweight or obese.[98] In the year 2000, obesity was responsible for approximately 400,000 deaths, and accounted for about 7% of total health care costs.[99] Body fat usually constitutes 15% to 20% of body mass in healthy men and 25% to 30% in healthy women. In obesity, the body fat content may increase by as much as 500% in women and 800% in men.[100] Along with the fat, fat-free mass also increases in obese individuals, accounting for 15% to 30% of the total weight gain.[101,102] The degree of obesity can be assessed by the body mass index (BMI), which is the ratio of body weight (BW) in kilograms to the square of the height (Ht) in meters (BW/Ht^2). (The BMI can also be calculated as the weight in pounds multiplied by 703 and divided by the square of the height in inches.) Individuals with a BMI between 18.5 and 24.9 kg/m^2 are normal, with a BMI between 25 and 29.9 kg/m^2 are overweight, and those with a BMI greater than 30 kg/m^2 are considered obese. Obesity is severe (morbid) when the BMI is greater than 40 kg/m^2.[97]

The risk of death and likelihood of morbidity becomes greater as BMI increases.[103] In nonsmokers, compared to those with a normal BMI, the overweight have a 20% to 40% higher risk of death and those with a BMI greater than 30 kg/m^2 have a 300% to 400% higher risk of death.[103] Intra-abdominal fat is also an independent risk for cardiovascular disease and mortality.[104] Morbidity is primarily due to cardiovascular and respiratory factors.[105,106]

Dyspnea and exercise intolerance are the most frequent complaints of obese individuals[106]; however, the severity of the respiratory impairment may not correlate with the degree of obesity. For example, even in those with the same BMI, arterial P_{CO_2} may be elevated in some individuals but not in others. The level of arterial P_{CO_2} is used to classify obese individuals as either having simple obesity (SO; individuals who are eucapnic) or obesity hypoventilation syndrome (OHS; individuals who are hypercapnic). In obesity, respiratory symptoms and signs may be due to (1) disordered chest wall mechanics and pulmonary function, (2) alterations in the control of breathing, and/or (3) the presence of inflammatory-mediated effects such as those linking obesity to airway hyper-responsiveness.

Pathophysiology

Pulmonary Function

The most common abnormalities of pulmonary function seen in obesity are reductions in expiratory reserve volume (ERV) and FRC.[107,108] For each unit increase in BMI from 20 to 30 kg/m^2, FRC and ERV decrease approximately 3% and 5%, respectively; thereafter, both FRC and ERV decrease approximately 1%.[107] Consequently, an individual with a BMI of 30 kg/m^2 will have an FRC of approximately 75% of predicted and an ERV of only 47% of predicted.[107] The mechanism underlying the reduction in FRC is the decrease in chest wall compliance related to adipose tissue compressing the rib cage and abdomen, thereby reducing the elastic recoil of the chest wall. Accordingly, the balance between the inward recoil of the lung and the outward recoil of the chest wall resets at a lower lung volume (i.e., a lower FRC). FRC and ERV may be reduced further in patients with OHS.[109]

TABLE 88-5. Representative Values of Respiratory Pathophysiology of Simple Obesity and Obesity Hypoventilation Syndrome

Parameter*	Normal	Simple Obesity	Obesity Hypoventilation
BW (% ideal)	100	200	200
BMI (kg/m^2)	24	45	45
TLC (% predicted)	100	95	80
CRS (L/cm H_2O)	0.10	0.05	0.06
RRS (cm H_2O L^{-1} s^{-1})	1.2	4.0	7.8
Work of ventilation (J/L)	0.43	0.74	1.64
MVV (L/min)	160	130	90
PI_{max} (cm H_2O)	100	95	60

*BW, body weight; BMI, body mass index; TLC, total lung capacity; CRS, compliance of the respiratory system; RRS, respiratory system resistance; J, joule; MVV, maximum ventilatory volume; PI_{max}, maximal static inspiratory pressure.

Adapted from Rochester DF: Obesity and abdominal distention. *In* Roussos C (ed): The Thorax. New York: Marcel Dekker, 1995, pp 1950–1973.

TLC, VC, and RV may be normal or only mildly reduced in those with SO and be significantly reduced (TLC and VC < 80% of predicted) in those with morbid obesity or OHS.[108,110] The more substantial reductions in TLC and VC in these individuals are probably related to weakness of the respiratory muscles.[109] In addition, since pulmonary function is more severely affected in OHS than in SO, factors other than the BMI must be involved (Table 88-5). For example, the distribution of body fat in the upper body (central fat distribution from waist to hips) impairs pulmonary function more than lower body fat distribution (below hips). A waist circumference of 35 inches or more for women and 40 inches or more for men indicates upper body fat distribution.[111]The correlation of respiratory impairment with upper body fat appears to be more apparent in men than in women.[112]

Other tests of pulmonary function such as the FEV_1/FVC ratio, maximal voluntary ventilation, peak inspiratory flow rate, and the ratio of dead space to tidal volume are normal.[109] The single-breath diffusion capacity is usually normal or increased in SO and slightly reduced in OHS.[109]

Respiratory Mechanics

Obesity reduces respiratory system compliance (CRS), primarily by lowering chest wall compliance (CW). In SO, values for CRS and CW are approximately 80% to 90% of normal[109,113] but are further reduced as BMI increases or when changing from the upright to supine position.[114–116] In OHS, CW and CRS are generally less than 45% of normal.[109] The reduced CW is thought to be due to the mass of adipose tissue compressing the rib cage and abdomen. Consequently, breathing occurs at lower lung volumes where the slope of the volume-pressure curve is flatter and a greater pressure is needed for a given volume. In addition, the excess weight on the chest wall imposes a threshold load, that is, a load the inspiratory muscles must overcome before inspiratory flow ensues. This threshold load may account for much of the disordered chest wall mechanics.[113]

Airway and total respiratory system resistance increase as BMI increases.[117] The values for airway and respiratory system resistance are usually double those seen in nonobese individuals.[117–119] Chest wall and total respiratory system resistances are increased more in OHS than in SO.[109] Since airway resistance remains elevated even after normalizing for lung volume (i.e., specific airway conductance is reduced to 50% to 70% of normal), breathing at low lung volumes accounts for part but not all of the change in airway resistance.[109] The normal FEV_1/FVC ratio suggests that the greatest resistance to airflow may be at the level of the small airways and lung tissue itself rather than the large airways. The transition from the upright to supine position may further increase respiratory resistance in severe obesity.[119] The increase in the intra-abdominal pressure when supine also may limit expiratory flow during tidal breathing, resulting in orthopnea in severe obesity.[120] The negative impact of the supine position on respiratory mechanics must be considered when evaluating patients for sleep-related disorders or for general anesthesia.[114]

The work of breathing is increased in both SO and OHS because of the increased forces needed to inflate the lung. Three factors that contribute to the increase in work include increased elastic loads (reductions in CRS and CW), resistive loads (higher airways resistance), and threshold loads (greater force needed to lower alveolar pressure and initiate inspiration). The work of breathing can be up to 60% greater in SO and as much as 250% higher in OHS; the oxygen cost of breathing can be 5-fold greater in SO and 10-fold greater in OHS.[109] The combination of increased work and oxygen costs of breathing may place obese patients at risk for respiratory failure during states of increased ventilatory demands such as an intercurrent illness.[121] To minimize the elastic load during inspiration and optimize the O_2 cost of breathing, obese patients adapt a rapid, shallow breathing pattern. This strategy is more pronounced in OHS than in SO. In subjects with SO, the respiratory rate during quiet breathing is about 40% higher than in normal-weight subjects, with most of the lung volume change during tidal breathing accomplished by rib cage rather than by abdominal displacement.[122] In OHS, however, breathing frequency is 25% higher and tidal volume 25% lower than in SO. The adverse effect of adopting a rapid shallow breathing pattern is increased dead space ventilation, which may contribute to carbon dioxide retention.[121]

Gas Exchange

In individuals with SO, the arterial P_{O_2} is usually normal or slightly reduced.[123,124] However, severely obese patients and those with OHS have hypoxemia and a widened alveolar-arterial oxygen tension gradient.[123,124]

Gas exchange is comparatively worse in obese men than in obese women[124] and more pronounced when assuming the supine position.[119,123–125] The mechanism responsible for hypoxemia is premature airway closure, which promotes ventilation-perfusion mismatch.[124] In OHS, hypoventilation may further contribute to hypoxemia. During exercise, oxygenation may improve due to enhanced ventilation of the lung bases.[125,126] Weight loss, via the resultant increase in FRC and prevention of airway closure during tidal breathing, improves arterial P_{O_2} roughly by 1 mm Hg for every 5 kg reduction in weight.[124] A practical corollary of hypoxemia and the increased metabolic rate in obesity is that, during apnea, the arterial oxygen saturation may fall three times faster in obese individuals than in normal-weight subjects.[127]

Control and Pattern of Breathing

In eucapnic obese individuals, central ventilatory drive is intact. Respiratory drive, as measured by the $P_{0.1}$, ventilatory, and electromyographic (EMG) responses to hypoxia and hypercapnia, is either normal or increased when compared with nonobese subjects.[109,127a] If ventilatory drive is increased, it is considered an appropriate compensatory response to increased elastic and resistive loads placed on the inspiratory muscles. This compensatory increase in ventilatory drive decreases following weight loss.[128,129] In patients with OHS, central ventilatory drive is reduced and the $P_{0.1}$, ventilatory, and EMG responses to hypoxia and hypercapnia are blunted when compared with nonobese subjects.[130,131] In patients with OHS, the ventilatory response to carbon dioxide is reduced by about 65%, but arterial P_{CO_2} can be lowered to a normal level by voluntary hyperventilation.[132] The attenuated ventilatory drive in patients with OHS may be related to a genetic predisposition or to other factors such as chronic hypoxemia, hypercapnia, or sleep apnea. However, the finding that ventilatory drive is intact in first-degree relatives of patients with OHS argues against a genetic abnormality.[133] Alternatively, leptin, a protein produced by adipose tissue that acts in the hypothalamus to decrease appetite and increase metabolic rate, has recently emerged as a possible mediator of the ventilatory response. Serum leptin levels are generally increased in obesity, more so in OHS than in SO,[134] suggesting a central resistance to leptin. Although the precise role of leptin in the pathogenesis of OHS is still evolving, it is believed that development of leptin resistance or relative leptin deficiency may contribute to diminished ventilatory responsiveness and hypercapnia in OHS.[135]

Respiratory Muscle Function and Dyspnea

Obesity may be associated with normal or weakened respiratory muscles. Chronically elevated elastic and resistive loads imposed on the respiratory muscles may help maintain strength in SO,[136,137] whereas deconditioning or other factors related to chronic disease may reduce inspiratory muscle endurance and weaken the inspiratory muscles in OHS.[109,138] In severely obese subjects, especially those with dyspnea or OHS, reductions of diaphragmatic function are often found, especially in the supine position.[137,139] Impaired diaphragmatic function may also be a result of increased intra-abdominal pressure and cephalad displacement of the diaphragm.[140]

Dyspnea, especially with exertion, is a very frequent and disabling symptom in obese individuals. Dyspnea is associated with a greater BMI, airways disease,[136–138] and, in SO, increased ventilatory drive.[129,141] However, other causes such as disordered respiratory mechanics (decreased C_{RS}, increased airway resistance, expiratory flow limitation) or an enhanced perception of dyspnea should be considered.[142,143] Finally, dyspnea may be due to cardiac disease, a frequent comorbid condition.

Exercise Capacity

Individuals with SO generally have near-normal exercise capacity.[126,144,145] Symptom-limited peak oxygen consumption ($\dot{V}_{O_2}$) and ventilatory rate are similar in absolute terms to those of lean individuals.[126] When normalized to fat-free mass, however, the peak $\dot{V}_{O_2}$ is lower in obese than in nonobese individuals.[126,144] For a given rate of external work, obese individuals require a greater $\dot{V}_{O_2}$ and ventilatory rate.[126,145] Likewise, dyspnea ratings at any submaximal work rate appear to be higher in obese individuals, reflecting the relatively higher ventilation and metabolic cost.[126] However, dyspnea scores at any given ventilatory rate or $\dot{V}_{O_2}$ are not higher in obesity, suggesting that respiratory mechanical factors do not significantly contribute to respiratory discomfort.[126] Indeed, during exercise, obese individuals rectify respiratory mechanics with an increase in end-expiratory volume, which serves to optimize operating lung volumes and attenuate expiratory flow limitation.[126]

Treatment

A detailed summary of treatment of obesity is beyond the scope of this chapter. However, to summarize briefly, weight loss is the optimal therapy but is not always attainable, and long-term weight loss maintenance is even more difficult.[146] Guidelines for weight loss treatment emphasize diet, enhanced physical activity, and behavioral therapy as initial treatments in all obese individuals regardless of the severity of obesity. Pharmacotherapy or bariatric surgery should be considered in obese individuals who do not achieve weight control with conventional therapy.[146] Weight loss in obese individuals is associated with improved ERV and FRC; however, there is no strict correlation between the magnitude of weight loss and the degree of improvement of lung volumes. Weight loss also may improve respiratory muscle performance,[147] resting gas exchange,[148] diffusion capacity,[124] dyspnea scores,[129,149,150] sleep apnea,[149] 6-minute walk test,[150] and respiratory drive.[129] Overall, weight reduction appears to be the most effective solution to OHS, with bariatric surgery providing the best option for the various comorbid conditions related to extreme obesity, such as hypertension, hyperlipidemia, and type 2 diabetes.[151,152]

KEY POINTS

Pathophysiology

- Diseases that affect the chest wall, including obesity, primarily affect the respiratory system by reducing chest wall compliance. The degree to which the chest wall stiffens varies with the disease process. Kyphoscoliosis (and individuals with OHS) have the greatest degree of chest wall stiffness, whereas individuals with pectus excavatum or ankylosing spondylitis may have normal chest wall compliance.
- The lung is usually an "innocent bystander" in the sense that it is usually not primarily affected by a pathologic process. As the lung cannot be fully inflated in restrictive chest wall disorders, microatelectesis ensues. Eventually this leads to a reduction in lung compliance and impaired gas exchange.
- Flail chest is the most likely to precipitate acute respiratory failure, whereas kyphoscoliosis and severe obesity are the diseases most likely to lead to chronic ventilatory failure, pulmonary hypertension, and cor pulmonale. Coincident inspiratory muscle weakness in any of these disorders will further worsen restrictive pathophysiology and predispose these individuals to respiratory failure.

Treatment

- Acute respiratory failure may complicate flail chest and can be treated with positive-pressure ventilation. In some patients with flail chest, surgical fixation of the flail segment may reduce the duration of mechanical ventilation.
- Chronic respiratory failure, which can be seen in kyphoscoliosis or with severe obesity, can be successfully managed with nocturnal positive-pressure ventilation. This latter intervention has markedly improved morbidity and mortality in this group of individuals.

References

1. Kane WJ: Scoliosis prevalence: a call for a statement of terms. Clin Orthop Relat Res (126):43–46, 1977.
2. Weinstein SL, Dolan LA, Cheng JC, et al: Adolescent idiopathic scoliosis. Lancet 371:1527–1537, 2008.
3. Gao X, Gordon D, Zhang D, et al: CHD7 gene polymorphisms are associated with susceptibility to idiopathic scoliosis. Am J Hum Genet 80:957–965, 2007.
4. Cobb JR: Outline for the study of scoliosis. AAOS Instruct Course Lect 5:261–275, 1948.
5. Shneerson JM, Simonds AK: Noninvasive ventilation for chest wall and neuromuscular disorders. Eur Respir J 20:480–487, 2002.
6. Bergofsky EH, Turino GM, Fishman AP: Cardiorespiratory failure in kyphoscoliosis. Medicine (Baltimore) 38:263–317, 1959.
7. Lisboa C, Moreno R, Fava M, et al: Inspiratory muscle function in patients with severe kyphoscoliosis. Am Rev Respir Dis 132:48–52, 1985.
8. Kafer ER: Respiratory function in paralytic scoliosis. Am Rev Respir Dis 110:450–457, 1974.
9. Day GA, Upadhyay SS, Ho EK, et al: Pulmonary functions in congenital scoliosis. Spine 19:1027–1031, 1994.
10. Kearon C, Viviani GR, Kirkley A, et al: Factors determining pulmonary function in adolescent idiopathic thoracic scoliosis. Am Rev Respir Dis 148:288–294, 1993.
11. Lin MC, Liaw MY, Chen WJ, et al: Pulmonary function and spinal characteristics: Their relationships in persons with idiopathic and postpoliomyelitic scoliosis. Arch Phys Med Rehabil 82:335–341, 2001.
12. Newton PO, Faro FD, Gollogly S, et al: Results of preoperative pulmonary function testing of adolescents with idiopathic scoliosis: A study of six hundred and thirty-one patients. J Bone Joint Surg (Am) 87:1937–1946, 2005.
13. Leech JA, Ernst P, Rogala EJ, et al: Cardiorespiratory status in relation to mild deformity in adolescent idiopathic scoliosis. J Pediatr 106:143–149, 1985.
14. Owange-Iraka JW, Harrison A, Warner JO: Lung function in congenital and idiopathic scoliosis. Eur J Pediatr 142:198–200, 1984.
15. Kafer ER: Respiratory and cardiovascular functions in scoliosis. Bull Eur Physiopathol Respir 13:299–321, 1977.
16. McCool FD, Tzelepis GE, Leith DE, et al: Oxygen cost of breathing during fatiguing inspiratory resistive loads. J Appl Physiol 66:2045–2055, 1989.
17. Smyth RJ, Chapman KR, Wright TA, et al: Ventilatory patterns during hypoxia, hypercapnia, and exercise in adolescents with mild scoliosis. Pediatrics 77:692–697, 1986.
18. Barrios C, Perez-Encinas C, Maruenda JI, et al: Significant ventilatory functional restriction in adolescents with mild or moderate scoliosis during maximal exercise tolerance test. Spine 30:1610–1615, 2005.
19. Kearon C, Viviani GR, Killian KJ: Factors influencing work capacity in adolescent idiopathic thoracic scoliosis. Am Rev Respir Dis 148:295–303, 1993.
20. Kesten S, Garfinkel SK, Wright T, et al: Impaired exercise capacity in adults with moderate scoliosis. Chest 99:663–666, 1991.
21. Ramonatxo M, Milic-Emili J, Prefaut C: Breathing pattern and load compensatory responses in young scoliotic patients. Eur Respir J 1:421–427, 1988.
22. Sawicka EH, Branthwaite MA: Respiration during sleep in kyphoscoliosis. Thorax 42:801–808, 1987.
23. Mezon BL, West P, Israels J, et al: Sleep breathing abnormalities in kyphoscoliosis. Am Rev Respir Dis 122:617–621, 1980.
24. Guilleminault C, Kurland G, Winkle R, et al: Severe kyphoscoliosis, breathing, and sleep: The "Quasimodo" syndrome during sleep. Chest 79:626–630, 1981.
25. Perrin C, D'Ambrosio C, White A, et al: Sleep in restrictive and neuromuscular respiratory disorders. Semin Respir Crit Care Med 26:117–130, 2005.
26. McCarthy RE: Management of neuromuscular scoliosis. Orthop Clin North Am 30:435–449, viii, 1999.
27. Consensus Conference: Clinical indications for noninvasive positive pressure ventilation in chronic respiratory failure due to

restrictive lung disease, COPD, and nocturnal hypoventilation—a consensus conference report. Chest 116:521–534, 1999.
28. Nickol AH, Hart N, Hopkinson NS, et al: Mechanisms of improvement of respiratory failure in patients with restrictive thoracic disease treated with non-invasive ventilation. Thorax 60:754–760, 2005.
29. Buyse B, Meersseman W, Demedts M: Treatment of chronic respiratory failure in kyphoscoliosis: Oxygen or ventilation? Eur Respir J 22:525–528, 2003.
30. Gustafson T, Franklin KA, Midgren B, et al: Survival of patients with kyphoscoliosis receiving mechanical ventilation or oxygen at home. Chest 130:1828–1833, 2006.
31. Mehta S, Hill NS: Noninvasive ventilation. Am J Respir Crit Care Med 163:540–577, 2001.
32. Baydur A, Swank SM, Stiles CM, et al: Respiratory mechanics in anesthetized young patients with kyphoscoliosis: Immediate and delayed effects of corrective spinal surgery. Chest 97:1157–1164, 1990.
33. Kim YJ, Lenke LG, Bridwell KH, et al: Prospective pulmonary function comparison of anterior spinal fusion in adolescent idiopathic scoliosis: Thoracotomy versus thoracoabdominal approach. Spine 33:1055–1060, 2008.
34. Newton PO, Perry A, Bastrom TP, et al: Predictors of change in postoperative pulmonary function in adolescent idiopathic scoliosis: A prospective study of 254 patients. Spine 32:1875–1882, 2007.
35. Pehrsson K, Danielsson A, Nachemson A: Pulmonary function in adolescent idiopathic scoliosis: A 25 year follow up after surgery or start of brace treatment. Thorax 56:388–393, 2001.
36. Bredin CP: Pulmonary function in long-term survivors of thoracoplasty. Chest 95:18–20, 1989.
37. Phillips MS, Kinnear WJ, Shneerson JM: Late sequelae of pulmonary tuberculosis treated by thoracoplasty. Thorax 42:445–451, 1987.
38. Kelly RE Jr: Pectus excavatum: Historical background, clinical picture, preoperative evaluation and criteria for operation. Semin Pediatr Surg 17:181–193, 2008.
39. Nuss D, Kelly RE Jr, Croitoru DP, et al: A 10-year review of a minimally invasive technique for the correction of pectus excavatum. J Pediatr Surg 33:545–552, 1998.
40. Kelly RE Jr, Shamberger RC, Mellins RB, et al: Prospective multicenter study of surgical correction of pectus excavatum: Design, perioperative complications, pain, and baseline pulmonary function facilitated by Internet-based data collection. J Am Coll Surg 205:205–216, 2007.
41. Mead J, Sly P, Le SP, et al: Rib cage mobility in pectus excavatum. Am Rev Respir Dis 132:1223–1228, 1985.
42. Castile RG, Staats BA, Westbrook PR: Symptomatic pectus deformities of the chest. Am Rev Respir Dis 126:564–568, 1982.
43. Wynn SR, Driscoll DJ, Ostrom NK, et al: Exercise cardiorespiratory function in adolescents with pectus excavatum: Observations before and after operation. J Thorac Cardiovasc Surg 99:41–47, 1990.
44. Harrison MR, Estefan-Ventura D, Fechter R, et al: Magnetic Mini-Mover Procedure for pectus excavatum: I. Development, design, and simulations for feasibility and safety. J Pediatr Surg 42:81–85, 2007.
45. Guntheroth WG, Spiers PS: Cardiac function before and after surgery for pectus excavatum. Am J Cardiol 99:1762–1764, 2007.
46. Johnson JN, Hartman TK, Pianosi PT, et al: Cardiorespiratory function after operation for pectus excavatum. J Pediatr 153:359–364, 2008.
47. Malek MH, Berger DE, Marelich WD, et al: Pulmonary function following surgical repair of pectus excavatum: A meta-analysis. Eur J Cardiothorac Surg 30:637–643, 2006.
48. Malek MH, Berger DE, Housh TJ, et al: Cardiovascular function following surgical repair of pectus excavatum: A metaanalysis. Chest 130:506–516, 2006.
49. Bastos R, Calhoon JH, Baisden CE: Flail chest and pulmonary contusion. Semin Thorac Cardiovasc Surg 20:39–45, 2008.
50. Todd TRJ, Shamji F: Pathophysiology of chest wall trauma. *In* Roussos C, Macklem P (eds): The Thorax, Part B. New York: Marcel Dekker, 1985, pp 979–997.
51. Wanek S, Mayberry JC: Blunt thoracic trauma: Flail chest, pulmonary contusion, and blast injury. Crit Care Clin 20:71–81, 2004.
52. Abisheganaden J, Chee CB, Wang YT: Use of bilevel positive airway pressure ventilatory support for pathological flail chest complicating multiple myeloma. Eur Respir J 12:238–239, 1998.
53. Adams JW, Hazard PB, Gooch JB: Flail chest injury in a patient with surgical absence of the sternum. Chest 92:185–186, 1987.
54. Enarson DA, Didier EP, Gracey DR: Flail chest as a complication of cardiopulmonary resuscitation. Heart Lung 6:1020–1022, 1977.
55. Winter RB: Flail chest secondary to excessive rib resection in idiopathic scoliosis: Case report. Spine 27:668–670, 2002.
56. Miller LA: Chest wall, lung, and pleural space trauma. Radiol Clin North Am 44:213–224, viii, 2006.
57. Landercasper J, Cogbill TH, Strutt PJ: Delayed diagnosis of flail chest. Crit Care Med 18:611–613, 1990.
58. Gaillard M, Herve C, Mandin L, et al: Mortality prognostic factors in chest injury. J Trauma 30:93–96, 1990.
59. Albaugh G, Kann B, Puc MM, et al: Age-adjusted outcomes in traumatic flail chest injuries in the elderly. Am Surg 66:978–981, 2000.
60. Landercasper J, Cogbill TH, Lindesmith LA: Long-term disability after flail chest injury. J Trauma 24:410–414, 1984.
61. Slater MS, Mayberry JC, Trunkey DD: Operative stabilization of a flail chest six years after injury. Ann Thorac Surg 72:600–601, 2001.
62. Tzelepis GE, McCool FD, Hoppin FG Jr: Chest wall distortion in patients with flail chest. Am Rev Respir Dis 140:31–37, 1989.
63. Cappello M, Yuehua C, De TA: Respiratory muscle response to flail chest. Am J Respir Crit Care Med 153:1897–1901, 1996.
64. Cappello M, De TA: Actions of the inspiratory intercostal muscles in flail chest. Am J Respir Crit Care Med 155:1085–1089, 1997.
65. Cappello M, Legrand A, De TA: Determinants of rib motion in flail chest. Am J Respir Crit Care Med 159:886–891, 1999.
66. Borrelly J, Aazami MH: New insights into the pathophysiology of flail segment: The implications of anterior serratus muscle in parietal failure. Eur J Cardiothorac Surg 28:742–749, 2005.
67. Lardinois D, Krueger T, Dusmet M, et al: Pulmonary function testing after operative stabilisation of the chest wall for flail chest. Eur J Cardiothorac Surg 20:496–501, 2001.
68. Tzelepis G, McCool FD, Leith DE, et al: Increased lung volume limits endurance of inspiratory muscles. J Appl Physiol 64:1796–1802, 1988.
69. Granetzny A, El-Aal M, Emam E, et al: Surgical versus conservative treatment of flail chest: Evaluation of the pulmonary status. Interact Cardiovasc Thorac Surg 4:583–587, 2005.
70. Gunduz M, Unlugenc H, Ozalevli M, et al: A comparative study of continuous positive airway pressure (CPAP) and intermittent positive pressure ventilation (IPPV) in patients with flail chest. Emerg Med J 22:325–329, 2005.
71. Tanaka H, Tajimi K, Endoh Y, et al: Pneumatic stabilization for flail chest injury: An 11-year study. Surg Today 31:12–17, 2001.
72. Tanaka H, Yukioka T, Yamaguti Y, et al: Surgical stabilization or internal pneumatic stabilization? A prospective randomized study of management of severe flail chest patients. J Trauma 52:727–732, 2002.
73. Pettiford BL, Luketich JD, Landreneau RJ: The management of flail chest. Thorac Surg Clin 17:25–33, 2007.
73a. Nirula R, Diaz JJ, Trunkey DD, Mayberry JC: Rib fracture repair: indications, technical issues, and future directions. World J Surg 33:14–22, 2009.
73b. Mayberry JC, Ham LB, Schipper PH, et al: Surveyed opinion of American trauma, orthopedic, and thoracic surgeons on rib and sternal fracture repair. J Trauma 66:875–879, 2009.
74. Braun J, Sieper J: Ankylosing spondylitis. Lancet 369:1379–1390, 2007.
75. Romagnoli I, Gigliotti F, Galarducci A, et al: Chest wall kinematics and respiratory muscle action in ankylosing spondylitis patients. Eur Respir J 24:453–460, 2004.
76. Jordanoglou J: Rib movement in health, kyphoscoliosis, and ankylosing spondylitis. Thorax 24:407–414, 1969.

77. Aggarwal AN, Gupta D, Wanchu A, et al: Use of static lung mechanics to identify early pulmonary involvement in patients with ankylosing spondylitis. J Postgrad Med 47:89–94, 2001.
78. van Noord JA, Cauberghs M, Van de Woestijne KP, et al: Total respiratory resistance and reactance in ankylosing spondylitis and kyphoscoliosis. Eur Respir J 4:945–951, 1991.
79. Tzelepis GE, Kalliakosta G, Tzioufas AG, et al: Thoracoabdominal motion in ankylosing spondylitis: Association with standardised clinical measures and response to therapy. Ann Rheum Dis 68:966–971, 2009.
80. Kalliakosta G, Mandros C, Tzelepis GE: Chest wall motion during speech production in patients with advanced ankylosing spondylitis. J Speech Lang Hear Res 50:109–118, 2007.
81. Fisher LR, Cawley MI, Holgate ST: Relation between chest expansion, pulmonary function, and exercise tolerance in patients with ankylosing spondylitis. Ann Rheum Dis 49:921–925, 1990.
82. Vanderschueren D, Decramer M, Van den Daele P, et al: Pulmonary function and maximal transrespiratory pressures in ankylosing spondylitis. Ann Rheum Dis 48:632–635, 1989.
83. Vosse D, van der HD, Landewe R, et al: Determinants of hyperkyphosis in patients with ankylosing spondylitis. Ann Rheum Dis 65:770–774, 2006.
84. Thumbikat P, Hariharan RP, Ravichandran G, et al: Spinal cord injury in patients with ankylosing spondylitis: A 10-year review. Spine 32:2989–2995, 2007.
85. Sahin G, Calikoglu M, Ozge C, et al: Respiratory muscle strength but not BASFI score relates to diminished chest expansion in ankylosing spondylitis. Clin Rheumatol 23:199–202, 2004.
86. Carter R, Riantawan P, Banham SW, et al: An investigation of factors limiting aerobic capacity in patients with ankylosing spondylitis. Respir Med 93:700–708, 1999.
87. Steier J, Kaul S, Seymour J, et al: The value of multiple tests of respiratory muscle strength. Thorax 62:975–980, 2007.
88. Parkin A, Robinson PJ, Hickling P: Regional lung ventilation in ankylosing spondylitis. Br J Radiol 55:833–836, 1982.
89. Coast JR, Cline CC: The effect of chest wall restriction on exercise capacity. Respirology 9:197–203, 2004.
90. Miller JD, Beck KC, Joyner MJ, et al: Cardiorespiratory effects of inelastic chest wall restriction. J Appl Physiol 92:2419–2428, 2002.
91. Fenlon HM, Casserly I, Sant SM, et al: Plain radiographs and thoracic high-resolution CT in patients with ankylosing spondylitis. AJR Am J Roentgenol 168:1067–1072, 1997.
92. Quismorio FP Jr: Pulmonary involvement in ankylosing spondylitis. Curr Opin Pulm Med 12:342–345, 2006.
93. Rosenow E, Strimlan CV, Muhm JR, et al: Pleuropulmonary manifestations of ankylosing spondylitis. Mayo Clin Proc 52:641–649, 1977.
94. Gorman JD, Sack KE, Davis JC Jr: Treatment of ankylosing spondylitis by inhibition of tumor necrosis factor alpha. N Engl J Med 346:1349–1356, 2002.
95. Rudwaleit M, Claudepierre P, Wordsworth P, et al: Effectiveness, safety, and predictors of good clinical response in 1250 patients treated with adalimumab for active ankylosing spondylitis. J Rheumatol 36:801–808, 2009.
96. Nghiem FT, Donohue JP: Rehabilitation in ankylosing spondylitis. Curr Opin Rheumatol 20:203–207, 2008.
97. James WP: The epidemiology of obesity: The size of the problem. J Intern Med 263:336–352, 2008.
98. Hedley AA, Ogden CL, Johnson CL, et al: Prevalence of overweight and obesity among US children, adolescents, and adults, 1999–2002. JAMA 291:2847–2850, 2004.
99. Mokdad AH, Marks JS, Stroup DF, et al: Actual causes of death in the United States, 2000. JAMA 291:1238–1245, 2004.
100. Strain GW, Zumoff B: The relationship of weight-height indices of obesity to body fat content. J Am Coll Nutr 11:715–718, 1992.
101. Leibel RL, Rosenbaum M, Hirsch J: Changes in energy expenditure resulting from altered body weight. N Engl J Med 332:621–628, 1995.
102. Verga S, Buscemi S, Caimi G: Resting energy expenditure and body composition in morbidly obese, obese and control subjects. Acta Diabetol 31:47–51, 1994.
103. Adams KF, Schatzkin A, Harris TB, et al: Overweight, obesity, and mortality in a large prospective cohort of persons 50 to 71 years old. N Engl J Med 355:763–778, 2006.
104. Gasteyger C, Tremblay A: Metabolic impact of body fat distribution. J Endocrinol Invest 25:876–883, 2002.
105. Bjorge T, Engeland A, Tverdal A, et al: Body mass index in adolescence in relation to cause-specific mortality: A follow-up of 230,000 Norwegian adolescents. Am J Epidemiol 168:30–37, 2008.
106. Gibson GJ: Obesity, respiratory function and breathlessness. Thorax 55(Suppl 1):S41–S44, 2000.
107. Jones RL, Nzekwu MM: The effects of body mass index on lung volumes. Chest 130:827–833, 2006.
108. Sood A: Altered resting and exercise respiratory physiology in obesity. Clin Chest Med 30:445–454, 2009.
109. Rochester DF: Obesity and pulmonary function. *In* Alpert M, Alexander J (eds): The Heart and Lung in Obesity. Armonk, NY: Futura, 1998, pp 109–131.
110. Biring MS, Lewis MI, Liu JT, et al: Pulmonary physiologic changes of morbid obesity. Am J Med Sci 318:293–297, 1999.
111. Foster GD: Principles and practices in the management of obesity. Am J Respir Crit Care Med 168:274–280, 2003.
112. Busetto L, Sergi G: Visceral fat and respiratory complications. Diabetes Obes Metab 7:301–306, 2005.
113. Suratt PM, Wilhoit SC, Hsiao HS, et al: Compliance of chest wall in obese subjects. J Appl Physiol 57:403–407, 1984.
114. Pelosi P, Croci M, Ravagnan I, et al: Total respiratory system, lung, and chest wall mechanics in sedated-paralyzed postoperative morbidly obese patients. Chest 109:144–151, 1996.
115. Pelosi P, Croci M, Ravagnan I, et al: The effects of body mass on lung volumes, respiratory mechanics, and gas exchange during general anesthesia. Anesth Analg 87:654–660, 1998.
116. Morgan EJ, Zwillich CW: The obesity-hypoventilation syndrome. West J Med 129:387–393, 1978.
117. Zerah F, Harf A, Perlemuter L, et al: Effects of obesity on respiratory resistance. Chest 103:1470–1476, 1993.
118. Watson RA, Pride NB: Postural changes in lung volumes and respiratory resistance in subjects with obesity. J Appl Physiol 98:512–517, 2005.
119. Yap JC, Watson RA, Gilbey S, et al: Effects of posture on respiratory mechanics in obesity. J Appl Physiol 79:1199–1205, 1995.
120. Ferretti A, Giampiccolo P, Cavalli A, et al: Expiratory flow limitation and orthopnea in massively obese subjects. Chest 119:1401–1408, 2001.
121. Kress JP, Pohlman AS, Alverdy J, et al: The impact of morbid obesity on oxygen cost of breathing (VO_{2RESP}) at rest. Am J Respir Crit Care Med 160:883–886, 1999.
122. Sampson MG, Grassino AE: Load compensation in obese patients during quiet tidal breathing. J Appl Physiol 55:1269–1276, 1983.
123. Thomas PS, Cowen ER, Hulands G, et al: Respiratory function in the morbidly obese before and after weight loss. Thorax 44:382–386, 1989.
124. Zavorsky GS, Hoffman SL: Pulmonary gas exchange in the morbidly obese. Obes Rev 9:326–339, 2008.
125. Tucker DH, Sieker HO: The effect of change in body position on lung volumes and intrapulmonary gas mixing in patients with obesity, heart failure, and emphysema. Am Rev Respir Dis 82:787–791, 1960.
126. Ofir D, Laveneziana P, Webb KA, et al: Ventilatory and perceptual responses to cycle exercise in obese women. J Appl Physiol 102:2217–2226, 2007.
127. Jense HG, Dubin SA, Silverstein PI, et al: Effect of obesity on safe duration of apnea in anesthetized humans. Anesth Analg 72:89–93, 1991.
127a. Steier J, Jolley CJ, Seymour J, et al: Neural respiratory drive in obesity. Thorax 64:719–725, 2009.
128. Chapman KR, Himal HS, Rebuck AS: Ventilatory responses to hypercapnia and hypoxia in patients with eucapnic morbid obesity before and after weight loss. Clin Sci (Lond) 78:541–545, 1990.
129. El-Gamal H, Khayat A, Shikora S, et al: Relationship of dyspnea to respiratory drive and pulmonary function tests in obese patients before and after weight loss. Chest 128:3870–3874, 2005.

130. Piper AJ, Grunstein RR: Current perspectives on the obesity hypoventilation syndrome. Curr Opin Pulm Med 13:490–496, 2007.
131. Sampson MG, Grassino K: Neuromechanical properties in obese patients during carbon dioxide rebreathing. Am J Med 75:81–90, 1983.
132. Leech J, Onal E, Aronson R, et al: Voluntary hyperventilation in obesity hypoventilation. Chest 100:1334–1338, 1991.
133. Jokic R, Zintel T, Sridhar G, et al: Ventilatory responses to hypercapnia and hypoxia in relatives of patients with the obesity hypoventilation syndrome. Thorax 55:940–945, 2000.
134. Phipps PR, Starritt E, Caterson I, et al: Association of serum leptin with hypoventilation in human obesity. Thorax 57:75–76, 2002.
135. Campo A, Fruhbeck G, Zulueta JJ, et al: Hyperleptinaemia, respiratory drive and hypercapnic response in obese patients. Eur Respir J 30:223–231, 2007.
136. Kelly TM, Jensen RL, Elliott CG, et al: Maximum respiratory pressures in morbidly obese subjects. Respiration 54:73–77, 1988.
137. Sahebjami H: Dyspnea in obese healthy men. Chest 114:1373–1377, 1998.
138. Collet F, Mallart A, Bervar JF, et al: Physiologic correlates of dyspnea in patients with morbid obesity. Int J Obes (Lond) 31:700–706, 2007.
139. Sharp JT, Druz WS, Kondragunta VR: Diaphragmatic responses to body position changes in obese patients with obstructive sleep apnea. Am Rev Respir Dis 133:32–37, 1986.
140. Chlif M, Keochkerian D, Mourlhon C, et al: Noninvasive assessment of the tension-time index of inspiratory muscles at rest in obese male subjects. Int J Obes (Lond) 29:1478–1483, 2005.
141. Unterborn J: Pulmonary function testing in obesity, pregnancy, and extremes of body habitus. Clin Chest Med 22:759–767, 2001.
142. Banzett RB, Loring SH: Heavy breathing. J Appl Physiol 102:2090–2091, 2007.
143. Salome CM, Munoz PA, Berend N, et al: Effect of obesity on breathlessness and airway responsiveness to methacholine in non-asthmatic subjects. Int J Obes (Lond) 32:502–509, 2008.
144. Babb TG, Korzick D, Meador M, et al: Ventilatory response of moderately obese women to submaximal exercise. Int J Obes 15:59–65, 1991.
145. Salvadori A, Fanari P, Mazza P, et al: Work capacity and cardiopulmonary adaptation of the obese subject during exercise testing. Chest 101:674–679, 1992.
146. Eckel RH: Clinical practice: Nonsurgical management of obesity in adults. N Engl J Med 358:1941–1950, 2008.
147. Weiner P, Waizman J, Weiner M, et al: Influence of excessive weight loss after gastroplasty for morbid obesity on respiratory muscle performance. Thorax 53:39–42, 1998.
148. Carey IM, Cook DG, Strachan DP: The effects of adiposity and weight change on forced expiratory volume decline in a longitudinal study of adults. Int J Obes Relat Metab Disord 23:979–985, 1999.
149. Karason K, Lindroos AK, Stenlof K, et al: Relief of cardiorespiratory symptoms and increased physical activity after surgically induced weight loss: Results from the Swedish Obese Subjects study. Arch Intern Med 160:1797–1802, 2000.
150. Maniscalco M, Zedda A, Giardiello C, et al: Effect of bariatric surgery on the six-minute walk test in severe uncomplicated obesity. Obes Surg 16:836–841, 2006.
151. Mokhlesi B, Kryger MH, Grunstein RR: Assessment and management of patients with obesity hypoventilation syndrome. Proc Am Thorac Soc 5:218–225, 2008.
152. Picot J, Jones J, Colquitt JL, et al: The clinical effectiveness and cost-effectiveness of bariatric surgery for obesity: a systematic review and economic evaluation. Health Technol Assess 13:1–190, 215–357, 2009.

CHAPTER 89

PRINCIPLES OF MECHANICAL VENTILATION

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INTRODUCTION

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INTRODUCTION

Mechanical ventilation is the process of using devices to support the total or partial transport of O_2 and CO_2 between the environment and the pulmonary capillary bed. The desired effect of mechanical ventilation is to maintain adequate levels of P_{O_2} and P_{CO_2} in arterial blood while also unloading the inspiratory muscles. Although negative-pressure chambers or wraps and extracorporeal circuits might fulfill this definition, this discussion focuses on the use of positive airway pressure for respiratory life support.

The use of positive-pressure mechanical ventilation is widespread. In the United States, estimates range from 1 to 3 million patients annually requiring mechanical ventilatory support outside the operating room.[1] Traditionally, this support has been provided in intensive care unit (ICU) settings, but there are clear trends toward expanding the venues to subacute facilities, long-term care facilities, and the home. As the aged population expands and as more aggressive surgical and immunosuppressive therapies are developed, the need for mechanical ventilation in all of these venues is likely to increase.[1] In addition, increasing concerns about widespread outbreaks of respiratory pandemics has led many government agencies to stockpile large numbers of mechanical ventilators that can be quickly mobilized.[1a]

POSITIVE-PRESSURE MECHANICAL VENTILATOR DESIGN FEAURES

Gas Delivery Systems

Positive-Pressure Breath Controller

Most modern ventilators utilize piston/bellows systems or controllers of high-pressure sources to drive gas flow.[2,3] Tidal breaths are generated by this gas flow and can either be controlled entirely by the ventilator or be

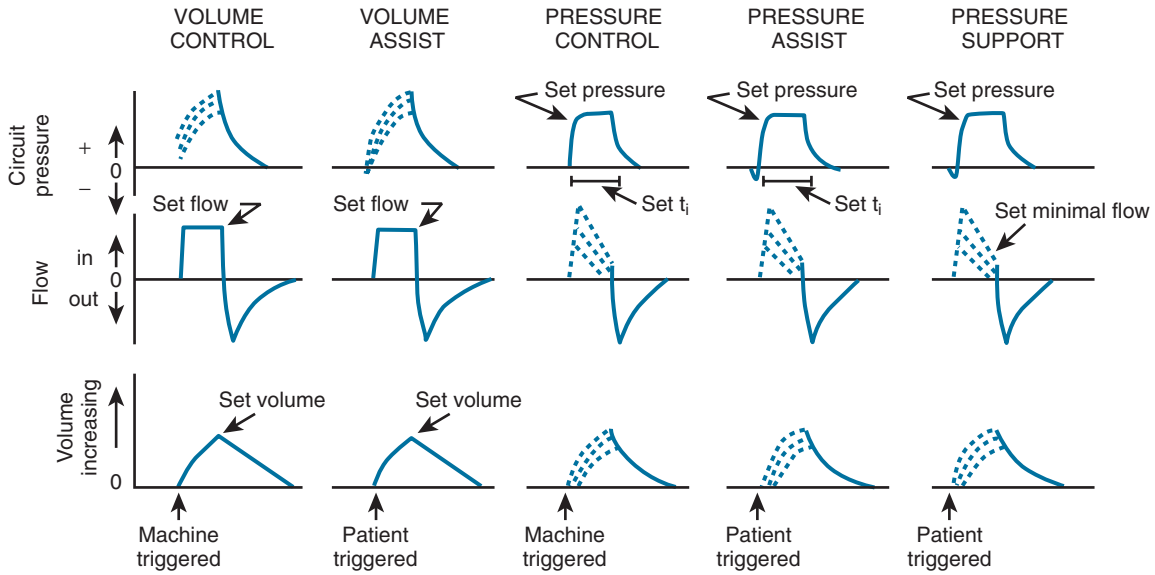

FIGURE 89-1 ■ Circuit pressure, flow, and volume tracings over time depicting the five basic breaths available on most modern mechanical ventilators. Breaths are classified by the variables that determine the trigger (machine time or patient effort), target/limit (set flow or set pressure), and cycle (set volume, set time, or set flow). The *solid lines* represent set or independent responses, and the *dashed lines* represent dependent responses. In all of these breaths, pressure is usually a "backup" cycle variable designed to terminate gas delivery if circuit pressure rises above an alarm limit.

interactive with patient efforts. Pneumatic, electronic, or microprocessor systems provide for various breath types. In general, these can be classified by what initiates the breath (trigger variable), what controls gas delivery during the breath (target or limit variable), and what terminates the breath (cycle variable).[4,5]

These three variables control the delivery of breaths to the patient. Breaths are initiated by a trigger variable, either a change in pressure or flow due to patient effort or a set time. During the breath, gas delivery is controlled to meet a target or limit variable, which is generally either a set flow or a set inspiratory pressure. The breath is then terminated by a cycle variable, which can either be a set volume, a set inspiratory time, or a set flow. A safety high-pressure cycle variable is usually also present as a backup. Figure 89-1 uses this classification scheme to describe the five most common breath types available on the current generation of mechanical ventilators: volume assist (VA), volume control (VC), pressure assist (PA), pressure control (PC), and pressure support (PS).

Mode Controller/Feedback Systems

The availability and delivery logic of different breath types define the "mode" of mechanical ventilatory support.[2,4,5] The mode controller is an electronic, pneumatic, or microprocessor-based system that is designed to provide the proper combination of breaths according to set algorithms and feedback data (conditional variables) (Table 89-1).

The simplest mode is assist-control ventilation (ACV), which can provide either flow-targeted volume-cycled breaths (volume assist-control ventilation [VACV]) or pressure-targeted time-cycled breaths (pressure assist-control ventilation [PACV]). A simple feedback system is employed with ACV that guarantees a set number of positive-pressure breaths. If the patient's underlying respiratory rate exceeds this guarantee, all breaths are patient-triggered breaths (VA or PA breaths). If the patient's respiratory rate is below this guarantee, the ventilator will "make up the difference" with mandatory breaths (VC or PC breaths).

Another relatively simple mode is synchronized intermittent mandatory ventilation (SIMV), which can provide either flow-targeted volume-cycled breaths (volume SIMV) or pressure-targeted time-cycled breaths (pressure SIMV). Like ACV, SIMV guarantees a set minimal number

TABLE 89-1. Breath Types Available on Common Modes of Mechanical Ventilation*

Mode	BREATH TYPES AVAILABLE†					
	VC	VA	PC	PA	PS	Sp
Volume assist-control	X	X				
Pressure assist-control			X	X		
Volume SIMV	X	X			X	X
Pressure SIMV			X	X	X	X
Pressure support					X	

*In addition to the five "basic" breaths depicted in Figure 89-1, this table also includes spontaneous unassisted/unsupported breaths.
†VC, volume control; VA, volume assist; PC, pressure control; PA, pressure assist; PS, pressure support; Sp, spontaneous unassisted.
SIMV, synchronized intermittent mandatory ventilation.

of positive-pressure breaths. Unlike ACV, however, if the patient's respiratory rate exceeds this guarantee, the ventilator will provide assisted breaths up to the set rate and then allow unassisted (SIMV alone) or flow-cycled pressure support breaths (SIMV + PS) thereafter. If the patient's respiratory rate is below the set guarantee, the ventilator will again "make up the difference" with mandatory (controlled) breaths. Note that, although PS breaths are often provided during SIMV, PS breaths can also be provided as a stand-alone mode without any guaranteed breaths (pressure support ventilation). Importantly, many modern systems also have so-called apnea ventilation, which is a backup algorithm (usually a simple volume control mode setting) for safety when modes with either low or no set guaranteed rates are provided and patient respiratory efforts are suddenly reduced or absent.

In recent years, more sophisticated feedback systems have been developed for these basic modes and are now available on many modern devices. These include pressure-regulated volume control (PRVC), volume support (VS), and adaptive support ventilation (ASV).

PRVC is an assist-control, pressure-targeted, time-cycled mode (PACV) that uses tidal volume as a feedback control for continuously adjusting the pressure target.[6] The clinician sets a tidal volume target and the ventilator then automatically sets the inspiratory pressure within a clinician-set range to achieve this goal. VS is a similar feedback design using patient-triggered, pressure-targeted, flow-cycled (PS) breaths. As a patient's respiratory drive exceeds the clinician-set guaranteed rate, some PRVC systems will provide additional patient-triggered time-cycled PRVC breaths while others will provide patient-triggered flow-cycled VS breaths. It is important to note that, with both PRVC and VS breaths, an improvement in respiratory mechanics will result in a lower applied inspiratory pressure while a worsening in respiratory mechanics will result in a higher applied inspiratory pressure. Similarly, increasing respiratory effort by the patient will result in a lower applied inspiratory pressure while decreasing respiratory effort by the patient will result in a higher applied inspiratory pressure.

ASV is also an assist-control, pressure-targeted, time-cycled mode of ventilation (PACV) that utilizes respiratory system mechanics to set the tidal volume-frequency pattern.[7] Using controlled breaths, ASV initially calculates resistance and compliance as well as the expiratory time constant (resistance × compliance). The clinician sets only a desired minute ventilation and a patient weight (for estimating anatomic dead space). ASV then partitions the frequency–tidal volume pattern in such a way as to minimize ventilator work (pressure × volume) and thus conceptually minimizes applied forces to the lung. As respiratory mechanics change, the frequency–tidal volume pattern is automatically adjusted to maintain this "optimal" pattern. ASV behavior when a patient's respiratory drive increases beyond the minute ventilation set by the clinician is complex and involves continually attempting to minimize ventilator work for the higher minute ventilation (see "Patient-Ventilator Interactions" section later).

Subsystems of Mechanical Ventilators

Effort (Demand) Sensors

Current ventilators allow for a number of patient-ventilator interactions.[8,9] Examples include patient-triggered breaths in which the ventilator initiates flow in response to patient demand and pressure-targeted/limited breaths in which the ventilator adjusts flow in response to patient demand (see "Patient-Ventilator Interactions" section later). Patient effort sensors are needed to allow the ventilator to deliver these interactive breaths properly. These sensors are usually either pressure or flow transducers in the ventilatory circuitry and are characterized by their sensitivity (the circuit pressure or flow change necessary to initiate a ventilator response) and their responsiveness (the delay in providing this response).[10]

Gas Blenders

Blenders mix air and O_2 to produce a delivered fractional concentration of O_2 in inspired gas (F_{IO_2}) ranging from 0.21 to 1.0. On newer systems, blenders are also available for other gases such as heliox, nitric oxide (NO), and anesthetic agents.

Humidifiers

With the upper airway bypassed by tracheal intubation, sufficient heat and moisture must be added to the inspired gas mixtures to avert mucosal desiccation. "Active" humidifiers utilize external water sources and electrical power to adjust blended gas mixtures to near body conditions (tracheal temperature of > 35° C, water content of > 40 mg/L).[11] Heated wire circuits help facilitate this by preventing condensation and "rainout" in ventilator tubing. "Passive" humidifiers use simple heat/moisture exchange devices in the ventilator circuit that reutilize heat and moisture trapped from expired gas. These disposable units can usually supply adequate heat and moisture (i.e., greater than 30° to 33° C and greater than 28 to 32 mg/L H_2O) for many patients, particularly those receiving mechanical ventilation for only short periods of time.[11]

Expiratory Pressure Generator

Positive airway pressure can be sustained throughout expiration (positive end-expiratory pressure [PEEP]) to help maintain alveolar patency and improve ventilation-perfusion ($\dot{V}/\dot{Q}$) matching (see "Physiologic Effects of Positive-Pressure Mechanical Ventilation" section later). PEEP is usually applied by regulating pressure in the expiratory valve of the ventilator system but can also be applied by providing a continuous flow of source gas during the expiratory phase. Note that some expiratory valves, even when fully open, have measurable resistance, which may result in inadvertent PEEP.[12] As discussed in more detail below, PEEP can also be generated in alveoli if the expiratory time is inadequate for the lung

to return to its "rest volume" or if significant flow limitation exists. Such inadvertent PEEP is referred to as intrinsic PEEP, or as "auto-PEEP," "occult PEEP," or "air trapping."[13]

Gas Delivery Circuit

The circuit usually consists of flexible tubing that often contains pressure or flow sensors and an exhalation valve. It is important to remember that, because this tubing has measurable compliance (2 to 4 mL/cm H_2O are representative values), high circuit pressures may induce significant amounts of delivered gas to distend the circuitry rather than to enter the patient's lungs.

The Patient–Ventilator Circuit Interface

Positive-pressure ventilation is generally supplied through a tube inserted into the patient's airway (oro- or nasotracheal tube or tracheostomy). These tubes generally have air-filled balloons to provide a proper seal in the airway. An alternative to the tracheal tube is a mask system. Both full-face and nasal masks have been utilized with a variety of ventilatory support systems and modes.[14] Leak around masks, however, can be significant and thus ventilatory support modes using masks must be able to provide adequate volumes and proper inspiratory timing. To this end, special mask ventilators with pressure-targeted and either time-cycled or leak-compensated, flow-cycled capabilities have been developed.[14]

Aerosol Generators

Therapeutic aerosols (e.g., bronchodilators, steroids, vasodilators, antibiotics) can be delivered through the ventilator circuitry.[15] This can be accomplished either by in-line nebulizers or by special adapters designed for metered-dose inhalers. Lung deposition is generally less in an intubated than in a nonintubated patient because the endotracheal tube serves as a significant barrier to aerosol delivery. Higher dosing is thus advisable.

The location of the aerosol generator in the ventilator circuit can affect deposition. The optimal site appears to be in the inspiratory limb several centimeters proximal to the patient "wye" connector.[15] This location allows either nebulized medications or a metered-dose actuation to "charge" the inspiratory limb of the circuit during exhalation. Aerosol particle velocity is slowed and becomes the leading portion of the next inspiration.

Monitors and Graphic Displays

Although electronic and microprocessor-based systems have considerable internal monitoring of electronic and pneumatic function, the three variables generally displayed for clinical use are circuit pressures, flows, and volumes.[16] Alarms can be utilized on all of these monitors.[5,17] Importantly, trending capabilities for up to 72 hours or more are now available on many modern systems. Most modern positive-pressure ventilators also have oxygen sensors in the circuitry to assure that the desired F_{IO_2} is being delivered. In addition, some ventilators may also have analyzers for exhaled CO_2 and inhaled therapeutic gases such as NO or heliox.

PHYSIOLOGIC EFFECTS OF POSITIVE-PRESSURE MECHANICAL VENTILATION

Ventilation and Respiratory System Mechanics

Equation of Motion

The lungs are inflated by mechanical ventilation when pressure and flow are applied at the airway opening. These applied forces interact with respiratory system compliance (both lung and chest wall components), airway resistance, and, to a lesser extent, respiratory system inertance and lung tissue resistance to effect gas flow.[18,19] For simplicity, since inertance and tissue resistance are relatively small, they can be ignored so that the interactions of pressure, flow, and volume with respiratory system mechanics can be expressed by the simplified equation of motion:

$$\text{Driving pressure} = (\text{flow} \times \text{resistance}) + (\text{volume}/\text{system compliance})$$

In the mechanically ventilated patient, this relationship is expressed as:

$$\Delta Pcir = (\dot{V} \times R) + (V_T/C_{RS})$$

where $\Delta Pcir$ is the change in ventilator circuit pressure above baseline (peak pressure minus end-expiratory pressure: Ppeak − PEEP), $\dot{V}$ is the flow into the patient's lungs, R is the resistance of the circuit, artificial airway, and natural airways combined, V_T is the tidal volume, and C_{RS} is the respiratory system compliance.

During an inspiratory hold at end-inspiration (i.e., no-flow conditions: $\dot{V} = 0$), the ventilator circuit pressure "plateaus" at a pressure commonly referred to as the plateau pressure (Pplat). By use of this inspiratory hold, the components of Pcir required for flow and for respiratory system distention can be separated. Specifically, the difference in Pcir during flow and during no-flow (the "peak to plateau difference") allows for a calculation of total inspiratory resistance:

$$R = (Ppeak - Pplat)/\dot{V}$$

Also, when $\dot{V} = 0$ at end-inspiration, Pplat − PEEP allows calculation of the static respiratory system compliance:

$$C_{RS} = V_T/(Pplat - PEEP)$$

Separating chest wall and lung compliance (C_{CW} and C_L, respectively) during a machine-controlled positive-pressure breath requires a measurement of esophageal pressure (Pes) to estimate pleural pressure. With this

measurement, the inspiratory change in Pes (ΔPes) can be used in the following calculations:

$$C_{CW} = V_T/\Delta Pes$$
$$C_L = V_T/(Pplat - PEEP - \Delta Pes)$$

In clinical practice, because C_{CW} is usually quite high and ΔPes is thus quite low, Pplat − PEEP alone is often taken as an approximation of lung-distending pressure. However, in situations in which C_{CW} is reduced (e.g., obesity, anasarca, ascites, or surgical dressings), the stiff chest wall can have significant effect on Pplat and must therefore be considered when using these measurements to assess lung stretch.[20,21]

Flow-Targeted vs Pressure-Targeted Breaths

In considering Figure 89-1, it can be seen that there are two basic approaches to delivering positive-pressure breaths: flow targeting and pressure targeting.[2,4] With flow targeting (breaths 1 and 2 in Fig. 89-1), the clinician sets an inspiratory flow so that circuit pressure is the dependent variable. With pressure targeting (breaths 3 through 5 in Fig. 89-1), the clinician sets an inspiratory pressure target (with either time or flow as the cycling criterion) so that flow and volume are dependent variables (i.e., varying with the lung mechanics and patient effort). With a flow-targeted breath, changes in compliance, resistance, or patient effort will change Pcir (but not flow); in contrast, with a pressure-targeted breath, similar changes in compliance, resistance, or effort will cause a change of tidal volume (but not Pcir) (see dashed lines in Fig. 89-1).

Each strategy has advantages. For flow-targeted breaths, a minimal tidal volume is guaranteed. For pressure-targeted breaths, the rapid initial flow and subsequent adjustable flow of pressure targeting may enhance gas mixing and patient synchrony (see discussions in later "Distribution of Ventilation" and "Patient-Ventilator Interactions" sections).

Pressure-targeted breaths can also be modified with a volume feedback feature described earlier for PRVC and VS breaths to combine the enhanced gas mixing and patient-ventilator synchrony effects of a pressure-targeted breath with a certain volume guarantee. However, it is important to realize that providing a volume guarantee negates the absolute pressure-limiting feature of a clinician-set pressure control level because, with PRVC/VS, worsening respiratory system mechanics will drive applied pressures up. Alternatively, another potential problem with PRVC/VS is that an increase in the patient's demand and tidal volume will drive the pressure level down, a change that may not be appropriate for a patient in respiratory failure.[22]

Intrinsic PEEP and the Ventilatory Pattern

Intrinsic PEEP is the positive end-expiratory pressure that develops within alveoli because of inadequate expiration, either because of inadequate time for expiration or increased airway resistance during expiration (or both). Intrinsic PEEP depends upon three factors: minute ventilation, the expiratory time fraction, and the respiratory system's expiratory time constant (the product of resistance and compliance).[23] With increases in minute ventilation, decreases in the expiratory time fraction, or increases in the expiratory time constant (i.e., with higher R or C_{RS} values), the potential for developing intrinsic PEEP increases.[23]

The development of intrinsic PEEP will have different effects on pressure-targeted compared to flow-targeted ventilation. In flow-targeted ventilation, the constant delivered flow and volume (and thus ΔPcir) in the setting of a rising intrinsic PEEP will increase both the Ppeak and the Pplat. In contrast, in pressure-targeted ventilation, the set Pcir limit coupled with a rising intrinsic PEEP level will decrease ΔPcir and thus the delivered tidal volume (and minute ventilation). Importantly, this may help limit the build-up of intrinsic PEEP.

In the patient without respiratory effort, intrinsic PEEP can be recognized in two ways. First, when an inadequate expiratory time produces intrinsic PEEP, analysis of the flow graphic will show that expiratory flow has not returned to zero before the next breath is given. Second, intrinsic PEEP in alveoli with patent airways can be quantified during an expiratory hold maneuver that permits equilibration of the intrinsic PEEP with Pcir.[11]

In the patient with active respiratory effort, intrinsic PEEP can be assumed to be present if the expiratory flow has not reached zero before the next breath begins. However, the expiratory hold maneuver is impossible to do in an actively breathing patient. As noted in more detail later, in an actively breathing patient, intrinsic PEEP can function as an inspiratory threshold load. This is best quantified by using an esophageal balloon to estimate pleural pressures. With this technique, the change in Pes before a change in Pcir is a reflection of the threshold load imposed by intrinsic PEEP (see "Patient-Ventilator Interactions" section later).

Distribution of Ventilation

A positive-pressure tidal breath must be distributed among the millions of alveolar units in the lung.[24,25] Factors affecting this distribution include regional resistances, compliances, functional residual capacities, and the delivered flow pattern (including inspiratory pause). In general, positive-pressure breaths will tend to distribute more to units with high compliance and low resistance and away from obstructed or stiff units (Fig. 89-2). This creates the potential for regional overdistention of healthier lung units, even in the face of "normal"-sized tidal volumes (see "Ventilator-Induced Lung Injury" below).

The flow pattern may also affect ventilation distribution. For example, when there are obstructive inhomogeneities, slow and constant flows will tend to distribute gas more evenly (although consequent shorter expiratory times may worsen air trapping).[24] In addition, inspiratory pauses can also allow *pendelluft* action to fill slowly filling alveoli (see Fig. 89-2B, High Regional R_{AW}). In contrast, when there is parenchymal lung injury

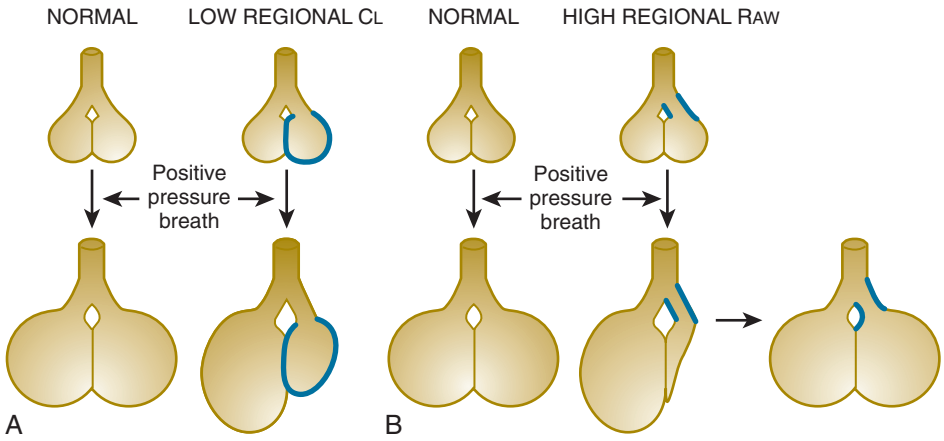

FIGURE 89-2 ■ The distribution of ventilation in lung models with heterogeneous mechanical properties. Models of the lung are shown as two units with homogeneous mechanical properties (normal): (**A**) with abnormal compliance distribution (low regional lung compliance [CL]), and (**B**) abnormal resistance distribution (high regional airway resistance [RAW]). Note that in situations with heterogeneous lung mechanics, positive-pressure breaths are preferentially distributed to "healthier" regions of the lung and can produce regional overdistention—even when a normal-sized tidal volume is delivered. Note that in the obstructed example (high regional RAW), the overdistention may be transitory as gas moves from the low-resistance to the high-resistance unit over time (*pendelluft*). (Redrawn from MacIntyre NR: Mechanical ventilatory support. *In* Dantzker D, MacIntyre NR, Bakow E [eds]: Comprehensive Respiratory Care. Philadelphia: WB Saunders, 1995, p 453.)

without obstructive airway inhomogeneity, initially rapid flows with subsequent deceleration (typically seen in pressure-targeted breaths) may distribute gas more evenly and will pressurize lung units rapidly, producing a higher mean inspiratory alveolar pressure for a given breath volume.[26]

It should be noted that more uniform ventilation distribution does not necessarily mean better $\dot{V}/\dot{Q}$ matching (i.e., more homogeneous ventilation distribution may actually worsen $\dot{V}/\dot{Q}$ matching in a lung with inhomogeneous perfusion). Because of all these considerations, predicting which flow pattern will optimize ventilation-perfusion matching is difficult and often an exercise of empirical trial and error.

Alveolar Recruitment and Gas Exchange

Because of alveolar flooding and collapse, parenchymal lung injury leads to $\dot{V}/\dot{Q}$ mismatching and shunts.[27] In many (but not all) of these disease processes, substantial numbers of collapsed alveoli can be recruited during a positive-pressure ventilatory cycle.[28-31] Additional recruitment can sometimes be provided with the use of formal recruitment maneuvers or prolongation of inspiratory time.[32,33] The application of PEEP is designed to prevent derecruitment during exhalation.

Recruitment Maneuvers

Recruitment maneuvers (RMs) are performed using sustained inflations (e.g., 30 to 40 cm H_2O) for up to 2 minutes.[32] Alternative approaches use transient elevations of the PEEP–tidal volume setting, and single or multiple "sigh breaths" that take the lung briefly to near total lung capacity.[32] Importantly, these transient pressure elevations can sometimes have adverse hemodynamic consequences and, to avoid patient inspiratory or expiratory efforts, the patient may require additional sedation (or even neuromuscular blockade). It also must be pointed out that RMs provide initial alveolar recruitment only—the duration of recruitment depends on an appropriate setting of PEEP to prevent subsequent derecruitment.[32]

Inspiratory Time Prolongations

A positive-pressure breath produces a flow magnitude and a flow profile that, as noted previously, can affect ventilation distribution (and thus $\dot{V}/\dot{Q}$). Prolonging inspiratory time, generally by adding a pause often in conjunction with a rapid decelerating flow (i.e., pressure-targeted breath), has several physiologic effects. First, the longer inflation period may recruit more alveoli.[34,35] Second, increased gas mixing time may improve $\dot{V}/\dot{Q}$ matching in parenchymal lung injury (*pendelufft*).[34,35] Third, the development of intrinsic PEEP from consequently shorter expiratory times can have effects similar to those of applied PEEP (see earlier).[35] It should be noted, however, that the distribution of intrinsic PEEP (most pronounced in lung units with long time constants) may be different from that of applied PEEP and thus, the effects on $\dot{V}/\dot{Q}$ may also be different. Fourth, since these long inspiratory times significantly increase total intrathoracic pressures, cardiac output may be reduced (see "Positive-Pressure Ventilation and Cardiac Function" section later). And finally, inspiratory-to-expiratory ratios that exceed 1:1 (so called inverse-ratio ventilation) are uncomfortable, and patient sedation/paralysis is often required unless a relief mechanism allows spontaneous breathing during the inflation period (see "Airway Pressure Release Ventilation" section later).

Positive End-Expiratory Pressure

PEEP is defined as an elevated transpulmonary pressure at the end of expiration.[28] As noted earlier, PEEP can be produced either by expiratory circuit valves (applied PEEP) or by inadequate expiratory times in lung units with long expiratory time constants (intrinsic PEEP).[18,19,34] Note that expiratory muscle contraction can also raise intrathoracic pressures at end-expiration, but this should not be considered PEEP since it is not a transpulmonary pressure (i.e., alveolar-pleural pressure).

Alveoli prevented from collapsing or "derecruiting" by PEEP provide several potential benefits. First, recruited alveoli improve $\dot{V}/\dot{Q}$ matching and gas exchange throughout the ventilatory cycle.[28] Second, as discussed in more detail later, patent alveoli throughout the ventilatory cycle are not exposed to the risk of injury from the shear stress of repeated opening and closing.[36,37] Third, open alveoli with intact surfactant monolayers improve lung compliance.[38] This is the rationale behind applying PEEP after an RM: recruited alveoli are on the deflation limb of the pressure-volume relationship and thus the pressure required to maintain recruitment is lower than that required for initial recruitment.

PEEP, however, can also be detrimental. Because the tidal breath is delivered on top of the baseline PEEP, end-inspiratory pressures are usually raised by the application of PEEP (although this increase may be less than the actual added PEEP because of improved compliance). This increase must be considered if the lung is at risk for regional overdistention (see "Ventilator-Induced Lung Injury" section later). Moreover, since parenchymal lung injury is often quite heterogeneous, appropriate PEEP in one region may be suboptimal in another and excessive in yet another.[31,39,40] Optimizing PEEP is thus a balance between recruiting the recruitable alveoli in diseased regions without overdistending already recruited alveoli in healthier regions. Another potential detrimental effect of PEEP is that it raises mean intrathoracic pressure, thereby compromising cardiac filling in susceptible patients (see "Positive-Pressure Ventilation and Cardiac Function" section later).

Mechanical Loads

Mechanical loads describe the physical requirements of ventilation with a single value, either the pressure-time product (PTP) or work (W).[18,19] Because mechanical loads correlate with inspiratory muscle oxygen demands,[41–43] the concept of load is useful in considering inspiratory muscle energy requirements during spontaneous or interactive partial ventilatory support (see "Patient-Ventilator Interactions" section later). Moreover, as described in more detail later, load referenced to muscle strength and/or endurance properties (e.g., PTP or W divided by muscle pressure-generating capability) can be used to set levels of partial ventilatory support or predict spontaneous breathing capabilities.[43]

The PTP expresses load as the integral of pressure over time ($PTP = \int P dt$). Work expresses load as the integral of pressure over volume ($W = \int P dV$). Compliance, resistance, and the flow and volume all contribute to the magnitude of the load per breath. During spontaneous breaths, Pcir is zero and integrating Pes over time or volume (referenced to the passive inflation pressure) describes the load borne by the inspiratory muscles to inflate the lungs. During a controlled breath, integrating Pcir over time or volume describes the load borne by the ventilator to inflate the entire respiratory system (lungs and chest wall), whereas integrating Pes over time or volume describes the loads imposed by the chest wall only. During partially supported breaths in which the load is shared between patient and ventilator, the sum of the contributions of patient and ventilator PTP or work should be the same as during a controlled or spontaneous breath of the same volume and flow profile.[44]

Under heavy loading conditions (e.g., the patient with abnormal respiratory system mechanics and thus high pressure requirements), the duration of pressure (i.e., the PTP) correlates better with muscle energetics and fatigue potential than does the volume moved with pressure (i.e., work).[41,42] Indeed, during ventilation requiring high pressures, multiplying PTP by the inspiratory time fraction and referencing this to the maximal pressure that the inspiratory muscles can generate results in the pressure-time index (PTI). Muscle fatigue can be expected if the PTI value exceeds 0.15.[44,45] The concern with high pressure loads in patients receiving partial ventilatory support is one of the rationales for providing ventilator pressure assistance with every spontaneous effort (i.e., pressure-assisted or supported breaths), as opposed to supporting breaths intermittently as in intermittent mandatory ventilation without pressure support (see "Patient-Ventilator Interactions" section later).[46]

Inspiratory muscle overload is one of the major determinants of continuing ventilator dependency and can result either from excessive mechanical loads or from inspiratory muscle dysfunction. Loads can be increased either by disease or by inappropriate ventilatory assistance (see "Patient-Ventilator Interactions" section later). Inspiratory muscle dysfunction can be a result of the systemic inflammatory response syndrome, metabolic disturbances, drugs (e.g., steroids, previous use of neuromuscular blockers), malnutrition, or malpositioning (i.e., diaphragm flattening from lung overinflation).[47] Clinically, inspiratory muscle overload is manifested by rapid, shallow breathing patterns and patient distress. Overt inspiratory muscle fatigue is probably a rare occurrence because clinicians usually intervene under these circumstances to provide ventilatory assistance.

Finally, insufficient loading may also affect inspiratory muscles. Specifically, controlled mechanical ventilation without any patient effort, perhaps for as little as 24 hours, may produce muscle changes similar to disuse atrophy—a condition described as "ventilator-induced diaphragmatic dysfunction" (VIDD).[48–50]

Patient-Ventilator Interactions

Mechanical ventilation modes that permit spontaneous ventilatory activity are termed "interactive" modes

because patients can affect various aspects of the mechanical ventilator's functions. These interactions can range from simple triggering of mechanical breaths to more complex processes affecting delivered flow patterns and breath timing. Interactive modes allow for muscle "exercise," which, when performed at nonfatiguing or physiologic levels, may prevent VIDD and facilitate fatigue recovery.[48-50] In addition, permitting spontaneous patient ventilatory activity and using comfortable interactive modes may reduce the need for the sedation and/or neuromuscular blockers that may otherwise be required to prevent patients from "fighting" positive-pressure ventilation.[51]

Interactive modes can be either synchronous or dyssynchronous with patient efforts. Synchronous interactions mean that the ventilator is sensitive to the initiation, modulation, and termination of a patient's ventilatory effort.[8,9] In the following discussion, synchrony is considered during the three phases of interactive breath delivery: breath triggering, ventilator flow delivery, and breath cycling.

Ventilator Breath Triggering

Interactive mechanical ventilators must sense a spontaneous effort by either an airway pressure drop or airway flow change in order to trigger a mechanical response.[8,9,51a] Even with modern sensors, however, there is unavoidable dyssynchrony in the triggering process. First, a certain level of insensitivity must be incorporated in the sensor to avoid artifacts triggering the ventilator (i.e., "autocycling"). Second, even when the patient effort has been sensed, demand valve systems have a certain inherent delay (up to 100 msec or more) before they physically open and achieve target flow into the airway (system responsiveness). Both of these factors can result in significant "isometric-like" pressure loads on the inspiratory muscles during the triggering process. In addition, in the setting of air trapping and positive end-expiratory pressure (intrinsic PEEP), the elevated alveolar pressure at end-expiration can serve as a significant triggering threshold load on the inspiratory muscles. Under these conditions, judicious use of applied PEEP can equilibrate expiratory pressure throughout the lungs and ventilator circuit to reduce this triggering load.[52,53]

Ventilator-Delivered Flow Pattern

During an interactive breath, inspiratory muscles are contracting[54,55] and the ventilator flow delivery should be adequate to meet one of two goals: (1) reduce the load on the contracting inspiratory muscles to comfortable levels or (2) avoid increasing the loads on contracting inspiratory muscles. Synchronous flow interactions can be defined accordingly.

In general, flow synchrony is best assessed by clinical assessment and by analyzing the graphic representation of circuit pressure over time. Clinical signs of flow dyssynchrony are tachypnea and dyspnea. Synchronous circuit pressure graphic patterns depend upon the clinical goal. With assisted/supported breaths designed to reduce loads, the circuit pressure graph should maintain a convex upward shape indicating that flow is proportional to demand. In contrast, in the setting of providing CPAP only, the circuit pressure graph should be flat. Dyssynchrony (and imposed loading) is said to exist when the circuit pressure graph is literally "sucked downward" below these target patterns (Fig. 89-3).

Breath Cycling

Cycling dyssynchrony can occur in one of two ways. First, if the breath lasts beyond the duration of patient effort, an inadequate expiratory time may develop (along with air trapping) and/or patient expiratory efforts may be required to terminate the breath. This can be a particular concern when using PS breaths in obstructive airway disease—the relatively steady inspiratory flow coupled with the PS flow-cycling algorithm may significantly delay breath termination in patients with severe airway obstruction.[56] Second, if the breath terminates before the patient effort is finished, the patient may be left demanding additional flow without any being delivered. Significant imposed loading and/or double breath triggering may result.

Positive-Pressure Ventilation and Cardiac Function

In addition to affecting ventilation and ventilation distribution, intrathoracic pressure applications from positive-pressure ventilation can also affect cardiovascular function.[57-59] In general, as mean intrathoracic pressure increases, right ventricular filling decreases and cardiac output/pulmonary perfusion consequently decreases. This is the rationale for using volume repletion to maintain cardiac output in the setting of high intrathoracic pressure. Of note is that the effect of reduced cardiac filling on cardiac output may be partially counteracted by the improvement in left ventricular function due to elevated intrathoracic pressures functioning to reduce left ventricular afterload.[60] Importantly, in patients with left heart failure, the reduced cardiac filling and reduced left ventricular afterload effects of elevated intrathoracic pressure may actually improve cardiac function to the point that the removal of intrathoracic pressure may produce weaning failure.[61] An interesting corollary to these concepts is the notion of using high-frequency ventilation timed to ventricular systole to augment cardiac output in patients with severe heart failure.[62]

Intrathoracic pressures can also influence distribution of perfusion. The relationship of alveolar pressures to perfusion pressures in the West model of the three-zone lung helps explain this.[63] Specifically, the supine human lung is generally in a zone 3 (capillary distention) state. As intra-alveolar pressures rise, however, zone 2 and zone 1 (capillary collapse/dead space) regions can appear, creating high $\dot{V}/\dot{Q}$ units. Indeed, increases in dead space can be a consequence of ventilatory strate-

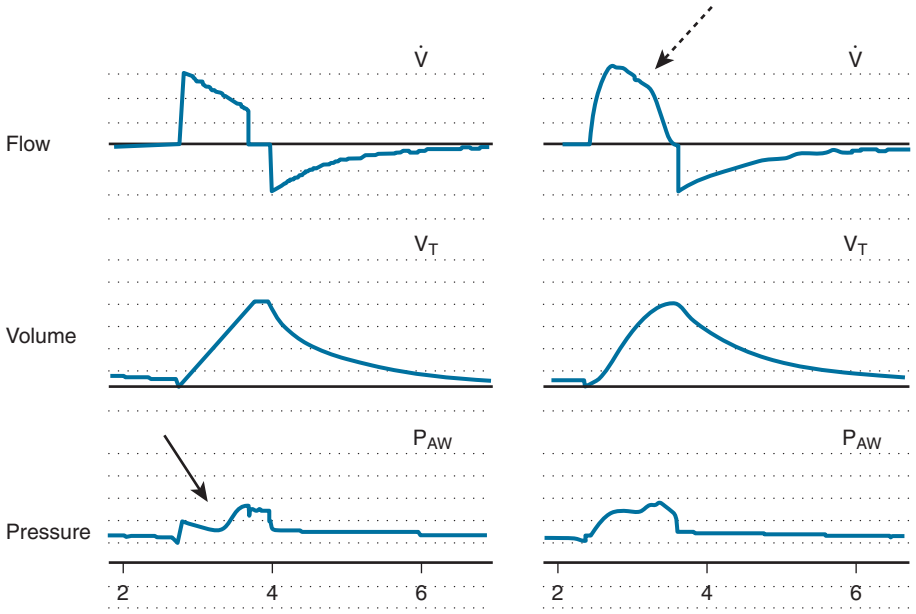

FIGURE 89-3 ■ Flow and pressure pattern differences during dyssynchronous and synchronous breaths in a patient with a vigorous inspiratory effort. Depicted are flow (*upper panel*), volume (*middle panel*), and pressure (*lower panel*) for a dyssynchronous flow-targeted breath (*left*) and a more synchronous pressure-targeted breath (*right*) with matched mean flow, inspiratory time, and tidal volume. Note that, during the flow-targeted breaths (*left*), the fixed flow does not respond to the vigorous inspiratory effort, resulting in the circuit pressure being "sucked" downward (*solid arrow*). In contrast, with the pressure-targeted breath, flow adjusts and increases to meet the inspiratory effort better (*dashed arrow*). (Redrawn from Yang LY, Huang YC, MacIntyre NR: Patient-ventilator synchrony during pressure-targeted versus flow-targeted small tidal volume assisted ventilation. J Crit Care 22:252–257, 2007.)

gies employing high ventilatory pressures as well as with those producing intrinsic PEEP.

Positive-pressure mechanical ventilation can affect other aspects of cardiovascular function. Specifically, dyspnea, anxiety, and discomfort from inadequate ventilatory support can lead to stress-related catechol release with subsequent increases in myocardial oxygen demands and risk of dysrhythmias.[61] In addition, coronary blood vessel oxygen delivery can be compromised by inadequate gas exchange from the lung injury coupled with low mixed venous P_{O_2} due to high oxygen consumption demands by the inspiratory muscles.

COMPLICATIONS OF POSITIVE-PRESSURE MECHANICAL VENTILATION

Ventilator-Induced Lung Injury

The lung can be injured when it is stretched excessively by positive-pressure ventilation. The most well-recognized injury is that of alveolar rupture presenting as extra-alveolar air in the mediastinum (pneumomediastinum), pericardium (pneumopericardium), subcutaneous tissue (subcutaneous emphysema), pleural space (pneumothorax), and vasculature (air emboli).[64] The risk for extra-alveolar air increases as a function of the magnitude and duration of alveolar overdistention. Thus, interactions of respiratory system mechanics and mechanical ventilation strategies (high regional V_T and PEEP—both applied and intrinsic) that produce regions of excessive alveolar stretch for prolonged periods create alveolar units at risk for rupture.

Even without producing extra-alveolar air and rupture, mechanical ventilation can induce a lung injury called ventilator-induced lung injury (VILI). In experimental animals, acute lung injury can be produced by mechanical ventilation strategies that stretch the lungs beyond the normal maximum (transpulmonary distending pressures of 30 to 35 cm H_2O).[65,66] A number of recent clinical trials clearly indicate that ventilator strategies exposing the injured human lung to transpulmonary pressures in excess of 30 to 35 cm H_2O are associated with lung injury.[67–70] Importantly, this injury may be more than simply a consequence of excessive end-inspiratory stretch. Even in the setting of transpulmonary pressures less than 30 cm H_2O, excessive tidal stretch from repetitive cycling of the lung with tidal volumes in excess of 9 mL/kg may contribute to VILI.[67,68] Other ventilatory pattern factors, such as the frequency of stretch[71] or the acceleration/velocity of stretch,[72] may also be involved in the development of VILI. VILI appears to be potentiated by a shear stress phenomenon that occurs when injured alveoli repetitively open and collapse during the ventilatory cycle (i.e., cyclical atelectasis).[36,73,74] Vascular pressure elevations may also contribute to VILI.[75]

VILI likely develops regionally when low-resistance/high-compliance units receive a disproportionately high

regional tidal volume in the setting of high alveolar distending pressures (see Fig. 89-2). This can be appreciated using computed tomography under circumstances when pressures required for recruitment of diseased atelectatic regions simultaneously produce overdistention in already open, less-diseased regions (Fig. 89-4). Regional protection of these healthier lung units is the rationale for using "lung-protective" ventilator strategies that accept less than normal values for pH and P_{O_2} in exchange for lower (and safer) distending pressures (see "Applying Mechanical Ventilatory Support" section later).

VILI is manifest pathologically as diffuse alveolar damage.[36,65,66,76] Moreover, VILI is associated with cytokine release[76,77] and bacterial translocation[78] that are implicated in the systemic inflammatory response with multiorgan dysfunction that results in VILI-associated mortality.

Oxygen Toxicity

Oxygen concentrations approaching 100% are known to cause oxidant injuries in airways and lung parenchyma.[79] Much of the data supporting this concept, however, has come from animals that often have quite different tolerances to oxygen than humans. It is thus not clear what the "safe" oxygen concentration or duration of exposure is in sick humans. Most consensus groups have argued that F_{IO_2} values less than 0.4 are safe for prolonged periods of time and that F_{IO_2} values of greater than 0.80 should be avoided if at all possible.

Patient-Ventilator Interface Complications

The patient-ventilator interface links the patient to the ventilator and includes the ventilator circuitry and the

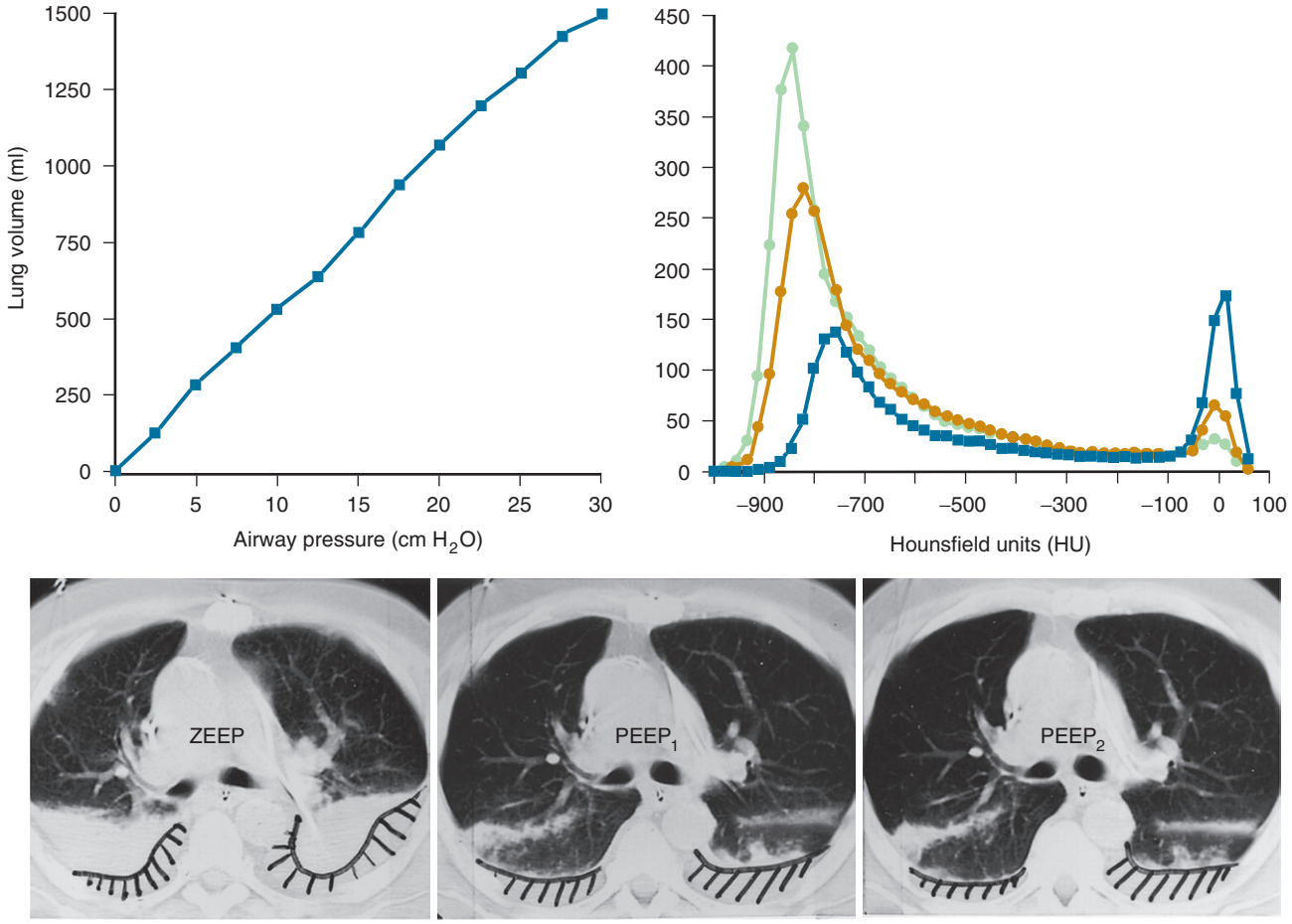

FIGURE 89-4 ■ Effects of positive airway pressure in a lung with heterogeneous injury. The *upper left panel* shows the almost linear pressure-volume relationships as positive airway pressure is applied to the lungs. At the bottom are three representative computed tomographic (CT) lung slices at low, midrange, and maximal airway pressure. In the lung at low airway pressure (ZEEP, *lower left*), note the substantial atelectasis in the dependent lung regions, which is progressively reduced as airway pressure is increased ($PEEP_1$ and $PEEP_2$, in the right two images). The *upper right panel* depicts the distribution of Hounsfield units (HU) in each of these three CT slices, at low pressure (*dark blue squares*), at midrange airway pressure (*brown circles*), and at the highest airway pressure (*light green circles*). Note that, although increasing pressure progressively reduces the number of atelectatic units (those with CT numbers near zero), these same pressures simultaneously increase the number of overdistended lung units elsewhere in the lungs (those with CT numbers less than –900 HU). (From Vieira SR, Puybasset L, Lu Q, et al: A scanographic assessment of pulmonary morphology in acute lung injury. Am J Resp Crit Care Med 159:1612–1623, 1999.)

artificial airway. The most important complications associated with this apparatus are ventilator disconnections (including artificial airway dislodgment). Disconnections have been reported in up to 8% to 13% of ventilated patients[80] and, if left uncorrected, can be fatal. Because circuit pressure and flow can be maintained despite the disconnection of the ventilator from the patient (e.g., if the airway is in the esophagus or if the disconnected circuit remains partially occluded), it is critical that carefully set, redundant (i.e., pressure *and* flow) alarms are present.[5] Other complications of the patient-ventilator interface include obstructions from secretions, circuit leaks, airway injury from inadequate heat/humidity, tracheal injury from the artificial airway, and loss of delivered tidal volume in a compliant circuit.

Pulmonary Infectious Complications

Mechanically ventilated patients are at risk for pulmonary infections for several reasons.[81] First, the natural glottic closure protective mechanism is compromised by an endotracheal tube. This permits continuous seepage of oropharyngeal material into the airways. Second, the endotracheal tube itself impairs the cough reflex and serves as an additional potential portal for pathogens to enter the lungs. This is particularly important if the circuit is contaminated. Third, airway and parenchymal injury from both the underlying disease and management complications make the lung prone to infections. Fourth, the ICU environment with its heavy antibiotic use and presence of very sick patients in close proximity is itself a risk for a variety of infections.

Preventing ventilator-associated pneumonias (VAP) is critical because the development of VAP heavily influences both length of stay and mortality.[81–83a] Handwashing, elevating the head of the bed, and carefully chosen antibiotic regimens for other infections can have important beneficial effects. Management strategies that avoid breaking the integrity of the circuit (i.e., changing the circuit only when visibly contaminated) also appear to be helpful.[82,83] Continuous drainage of subglottic secretions may be another simple way of reducing lung contamination by oropharyngeal material.[82,83] Another concept explored in small trials is the use of aerosolized antibiotics in patients with purulent secretions to reduce the progression of tracheobronchitis to ventilator-associated pneumonia.[84] Finally, it must always be remembered that prompt discontinuation of ventilatory support when clinically appropriate will help minimize the time patients are exposed to infection risks.

APPLYING MECHANICAL VENTILATORY SUPPORT

Mechanical Ventilatory Support Involves Tradeoffs

To provide adequate support while minimizing the risk of VILI, mechanical ventilation goals must involve tradeoffs. Specifically, the need for potentially injurious pressures, volumes, and supplemental O_2 must be weighed against the benefits of supporting gas exchange. To this end, a "re-thinking" of gas exchange goals has taken place over the last decade so that now, pH goals as low as 7.15 to 7.20 and P_{O_2} goals as low as 55 mm Hg are often considered acceptable in order to protect the lung from VILI.[85] Ventilator settings are thus selected to provide at least this level of gas-exchange support while meeting two mechanical goals: (1) provision of enough PEEP to recruit the "recruitable" alveoli and (2) avoidance of a PEEP–tidal volume combination that unnecessarily overdistends lung regions at end-inspiration. These goals embody the concept of a lung-protective mechanical ventilatory strategy. Currently, these principles guide recommendations for the specific management of parenchymal and obstructive lung disease.[86–89]

Considerations in Choosing Ventilator Settings for Different Forms of Respiratory Failure

Parenchymal Lung Injury

Parenchymal lung injury describes disease processes that involve the air spaces and the interstitium of the lung. In general, parenchymal injury stiffens lungs and decreases lung volumes. It is important to realize, however, that, in all but the most diffuse diseases (e.g., diffuse cardiogenic edema), there are often marked regional differences in the degree of inflammation present and thus the degree of mechanical abnormalities that exist. This heterogeneity can have significant impact on the effects of a particular mechanical ventilation strategy. This is because delivered gas will preferentially go to the more normal regions, those with higher compliance and lower resistance, rather than to sicker regions (see Fig. 89-2). A "normal-sized" tidal volume may thus be distributed preferentially to the healthier regions, resulting in a regional overdistention injury.

Parenchymal injury can also affect the airways, especially the bronchioles and alveolar ducts. These narrowed and collapsible small airways can also reduce regional ventilation to injured lung units, leading to regions of air trapping and possibly cyst formation during the healing phase.

Gas-exchange abnormalities in parenchymal lung injury are a consequence of alveolar consolidation, flooding, and/or collapse producing a maldistribution of ventilation and resulting in $\dot{V}/\dot{Q}$ mismatching and shunts. Because $\dot{V}/\dot{Q}$ mismatch and shunt are more of an issue than dead space ($\dot{V}/\dot{Q} = \infty$) in parenchymal lung disease, hypoxemia tends to be more of a clinical problem than CO_2 elevation.

Frequency–tidal volume settings for patients with parenchymal lung injury must focus on limiting end-inspiratory stretch. The benefit of reducing stretch in improving outcome has been suggested by several recent clinical trials[67–70,90] but has been most convincingly demonstrated by the National Institutes of Health (NIH)–sponsored ARDS Network Trial in which a ventilator

TABLE 89-2. The PEEP/F_{IO_2} Combinations Used during the NIH ARDS Network Study*

F_{IO_2}	.30	.40	.40	.50	.50	.60	.70	.70	.70	.80	.90	.90	.90	1.0	1.0	1.0	1.0
PEEP	5	5	8	8	10	10	10	12	14	14	14	16	18	18	20	22	24

*The clinical target is an arterial P_{O_2} of 55 to 80 mm Hg or pulse oximeter oxygen saturation (S_{pO_2}) of 88% to 95%. If the patient is below these target values, move along the table to the right. If the patient is above these targets, move to the left.
Data from NIH ARDS Network: Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 342:1301–1308, 2000.

strategy using a VT of 6 mL/kg ideal body weight (IBW) as compared to 12 mL/kg led to a 10% absolute reduction in mortality.[70] Because of this, initial VT settings should start at 6 mL/kg IBW.[90a] Moreover, strong consideration should be given to reducing this setting further if end-inspiratory Pplat, adjusted for any effects of excessive chest wall stiffness, exceeds 30 cm H_2O.[67–70] Increases in VT settings might be considered if there is marked patient discomfort or suboptimal gas exchange *provided that* the subsequent Pplat values do not exceed 30 cm H_2O.[67–70] Respiratory rate settings are then adjusted to control pH. Unlike the case in obstructive diseases, the potential for air trapping in parenchymal lung injury is low if the breathing frequency is less than 35 breaths/min; air trapping may not develop even at frequencies exceeding 50 breaths/min.

The inspiratory time and the I:E ratio in parenchymal injury is set with consideration of several issues. The usual initial I:E ratio setting is 1:2 to 1:4, the normal and the most comfortable setting. The flow graphic should also be assessed to ensure that the expiratory time is adequate to avoid air trapping. An I:E ratio higher than the physiologic range of 1:1 is referred to as inverse-ratio ventilation (IRV). In severe respiratory failure, IRV can be employed as an alternative to increasing PEEP to improve $\dot{V}/\dot{Q}$ matching.[34,35] The beneficial mechanisms involved include longer mixing times, recruitment of slowly filling alveoli, and development of intrinsic PEEP. A variation on IRV is airway pressure release ventilation (APRV).[91–93] APRV incorporates the ability to breathe spontaneously during the long inflation period of a pressure-controlled breath—a feature that may enhance recruitment and gas mixing. APRV is discussed in more detail later.

The PEEP/F_{IO_2} settings are optimized using both mechanical and gas-exchange approaches. Conceptually, in setting the PEEP level in parenchymal lung injury, the mechanical goal is to provide ventilator settings between the upper and lower inflection points on the pressure-volume curve.[94] The most direct mechanical approaches use the static pressure-volume plot to set the PEEP and VT. This traditionally involves multiple VT/Pplat measurements and requires considerable clinician time along with patient sedation or even neuromuscular blockade. A simpler approach is to use a "slow-flow" maneuver, so called because only a single inspiration is required using very small inspiratory flows (e.g., <10 L/min) so that flow-related pressures are minimal. Under these conditions, the single dynamic loop approximates the true static pressure-volume relationship.[95] Another mechanical approach uses step changes in PEEP to determine the PEEP level that gives the best compliance.[96] A simpler mechanical approach analyzes the Pcir profile during a constant-flow breath (stress index) to detect overdistention (late rising profile) or collapse/reopening injury (early rising profile).[97] With all of these approaches, a recruitment maneuver is often used to recruit the maximal number of recruitable alveoli prior to setting the PEEP. F_{IO_2} adjustments are then set as low as clinically acceptable.

PEEP can also be guided by gas-exchange criteria usually involving algorithms designed to provide adequate values for arterial P_{O_2} (e.g., 55 to 80 mm Hg) while minimizing F_{IO_2}. An example would be the NIH ARDS Network PEEP/F_{IO_2} algorithm in Table 89-2.[70] Note that constructing a PEEP/F_{IO_2} algorithm is usually an empirical exercise in balancing pressure, arterial S_{O_2}, and F_{IO_2} and depends upon the clinician's perception of the relative "toxicities" of high thoracic pressures, high F_{IO_2}, and low arterial S_{O_2}. Several recent trials have compared a number of PEEP/F_{IO_2} algorithms in conjunction with low tidal volume/limited Pplat strategies. These studies find that PEEP settings, whether aggressive (i.e., average 13 to 15 cm H_2O) or conservative (i.e., average 7 to 9 cm H_2O), that target adequate, not maximal, arterial P_{O_2} targets have comparable outcomes (see Chapters 90 and 91).[98–100a]

Obstructive Airway Disease

Respiratory failure from airflow obstruction is a direct consequence of increases in airway resistance. This leads to two important pathophysiologic changes. First, the increased pressures required for airflow may overload inspiratory muscles, producing a "ventilatory pump failure" in which spontaneous minute ventilation becomes inadequate for gas exchange. Second, the narrowed airways create regions of lung that cannot properly empty and return to their normal "resting volume," thereby producing intrinsic PEEP. These regions of overinflation create dead space and put inspiratory muscles at a substantial mechanical disadvantage that further worsens muscle function. Overinflated regions may also compress more healthy regions of the lung, impairing $\dot{V}/\dot{Q}$ matching. Regions of air trapping and intrinsic PEEP also function to increase the threshold load the patient must overcome to trigger mechanical breaths, as noted earlier.

The gas-exchange abnormalities in the setting of worsening airflow obstruction are several. First, although

there may be a transient hyperventilation due to dyspnea in the asthmatic patient, the worsening respiratory failure in obstructive lung disease is generally characterized by a falling minute ventilation as inspiratory muscles fatigue in the face of airflow obstruction. The result is termed *hypercapnic respiratory failure.* Second, as noted earlier, regional lung compression and regional hypoventilation produces $\dot{V}/\dot{Q}$ mismatch that results in progressive hypoxemia. Alveolar inflammation and flooding, however, are not characteristic features of respiratory failure due to pure airflow obstruction, and thus shunts are less of an issue than in parenchymal lung injury. Third, overdistended regions of the lung coupled with underlying emphysematous changes in some patients result in capillary loss and increasing dead space. This wasted ventilation further compromises the ability of the inspiratory muscles to supply an adequate ventilation for alveolar gas exchange. These emphysematous regions also have low recoil properties, which can worsen air trapping. Fourth, hypoxemic pulmonary vasoconstriction coupled with chronic pulmonary vascular changes in some airway diseases overload the right ventricle, further decreasing blood flow to the lung and making the dead space worse.

Frequency–tidal volume settings in obstructive diseases are chosen based on many considerations similar to those in parenchymal lung injury. Specifically, tidal volumes should be sufficiently low (e.g, 6 mL/kg IBW) to assure that Pplat values are less than 30 cm H_2O.[67–70] In obstructive diseases, however, clinicians should also be aware that high *peak* airway pressures, even in the presence of acceptable values for Pplat, may transiently subject regions of the lung to periods of overdistention injury (see Fig. 89-2). As with parenchymal lung injury, VT reductions should be considered to meet Pplat goals. VT increases can be considered for comfort or gas exchange *provided that* Pplat values do not exceed 30 cm H_2O.[67–70] The ventilatory rate is used to control pH. Unlike parenchymal disease, however, the elevated airway resistance (and often the low recoil pressures of emphysema) greatly increase the potential for air trapping, a complication that limits the range of breath rates available. Hypoventilation and "permissive hypercapnia" may be an appropriate tradeoff to limit intrinsic PEEP development and overdistention.

The I:E ratio in obstructive lung disease is generally set as low as possible to minimize the development of air trapping. For the same reason, approaches using IRV strategies are almost always contraindicated.

The PEEP/FIO_2 settings assume a different role in obstructive lung disease than in parenchymal lung disease. Because alveolar recruitment is less of an issue and overdistention is more of an issue in obstructive lung injury than in parenchymal lung injury, the strategy in using the PEEP/FIO_2 steps in Table 89-2 should probably be shifted more toward the use of FIO_2 for oxygenation support instead of PEEP. A specific role for PEEP in the obstructed patient arises when intrinsic PEEP serves as an added inspiratory threshold load on the patient attempting to trigger a breath, as described earlier. Under these conditions, judicious application of circuit PEEP (at levels up to 75% to 85% of intrinsic PEEP) can "balance" intrinsic PEEP throughout the ventilator circuitry to reduce this triggering load and facilitate the triggering process.[52,53]

In severe airflow obstruction, the use of the low-density gas helium can help facilitate ventilator settings. Helium is available as 80:20, 70:30, or 60:40 helium : oxygen breathing gas mixtures (heliox) and can both reduce patient inspiratory work and facilitate lung emptying (recall that driving pressure decreases and/or flow increases as gas density decreases).[101] With a helium : oxygen gas mixture, it must be remembered that many flow sensors must be recalibrated to account for the change in gas density.

Finally, it is important to note that it is in the obstructed diseases that noninvasive ventilation has been demonstrated most convincingly to improve outcomes.[102] In setting up noninvasive ventilation, the same principles described previously for invasive mechanical ventilation also apply (see Chapter 92).

Neuromuscular Respiratory Failure

The risk of VILI is generally less in a patient with neuromuscular failure since lung mechanics are often near normal and regional overdistention less likely. More "generous" tidal volumes may thus be used to improve comfort, maintain recruitment, prevent atelectasis, and avoid hypercarbia that may adversely affect central nervous system function. At the same time, however, maximal distending pressures should be kept as low as possible while still being compatible with the other goals noted previously. Certainly Pplat should always be kept well below 30 cm H_2O.[67–70]

Mode selection in neuromuscular disease patients is often determined by patient comfort. As in other patients, the rapid initial flow and the subsequent variable flow provided by pressure-targeted modes is often more synchronous with patient efforts than those provided by volume-targeting modes. Comfort must be weighed against the "reliability" of the patient effort to maintain consistent minute ventilation in the setting of pressure-targeted breaths. Thus, in patients with fluctuating ventilatory drives who may be prone to periods of hypoventilation or atelectasis, volume-targeting offers an advantage. PEEP, even at low levels, is often beneficial at preventing derecruitment (atelectasis) in these patients who are often supine and unable to clear secretions or sigh. Noninvasive ventilation plays an increasingly important role in patients with neuromuscular disease (see Chapter 87).

Recovering Respiratory Failure—The "Weaning" and Discontinuation Process

As respiratory failure stabilizes and begins to reverse, clinical attention shifts to the process of ventilator withdrawal. Unfortunately, a number of large clinical trials have clearly demonstrated that current assessment/management strategies are not optimal, resulting in considerable delay in ventilator withdrawal.[103] Such delay leads to increased length of ICU stay, increased costs, prolonged exposure to circuit pressure, and increased risk

of infection. Attempts to increase withdrawal aggressiveness, however, must be balanced against the risk of premature withdrawal with consequent loss of airway patency, aspiration, and inspiratory muscle fatigue. An evidence-based task force[103] has recommended a two-step process:

1. Consider a patient a candidate for withdrawal *if* (a) the lung injury is stable/resolving, (b) the gas exchange is adequate with low PEEP/F_{IO_2} requirements, (c) hemodynamics are stable without pressors, and (d) the patient has the capability to initiate spontaneous breaths.
2. In these patients, perform a spontaneous breathing trial (using T-piece, CPAP, or pressure support at 5 cm H_2O) for 30 to 120 minutes. Assessments should include the ventilatory pattern, gas exchange, hemodynamics, and comfort. Patients "passing" this trial should be considered for ventilator withdrawal.

In patients passing the spontaneous breathing trial (SBT), separate assessments are required to determine if the artificial airway can be removed. These involve cough strength, suctioning frequency, and, to a certain extent, the ability to follow commands.[103] Cuff leak, however, does not appear to be an important predictor of success except perhaps in the setting of prior upper airway injury. Extubation failures can be expected in 10% to 20% of all extubations. Many of these involve airway protection issues and thus prompt reintubation is indicated. However, in some patients, especially those with chronic obstructive pulmonary disease, an extubation failure caused by increasing inspiratory muscle overload might be managed by noninvasive ventilation.[102]

In patients failing the SBT, a stable and comfortable level of support should be provided until the next SBT.[103] Frequent (e.g., every 2 to 12 hours) support reductions are usually not necessary as they have not been shown to speed up the withdrawal process and only serve to consume resources and expose the patients to muscle overload risks. Repeating assessments for SBTs, however, should be done daily.[103] Importantly, aggressive strategies to reduce sedation can accelerate this process.[104]

To provide comfortable support, modes of partial support are used. By definition, these modes provide some, but not all, of the work of breathing. Ideally, these modes should provide adequate muscle unloading by providing breaths that are initiated promptly in accordance with patient demand. Accordingly, sensitive and responsive triggering systems should be used. Once the breath is initiated, a flow pattern that is synchronous with the patient's ventilatory demands should be provided.

RECENT INNOVATIONS IN MECHANICAL VENTILATORY SUPPORT

Innovative Strategies for "Lung Protection"

There have been several innovations recently introduced that may assist clinicians in reducing ventilator-induced lung injury. Among the more promising are airway pressure release ventilation (APRV), tracheal gas insufflation (TGI), adaptive support ventilation (ASV), and high-frequency ventilation (HFV).

Airway Pressure Release Ventilation

APRV (also known as biphasic ventilation, bilevel ventilation, and bilevel positive airway pressure) is a time-cycled, pressure-targeted form of ventilatory support.[91–93] It is actually a modification of pressure-targeted SIMV that allows spontaneous breathing (with or without PS) during both the inflation and deflation phases. Its differences from pressure-targeted SIMV thus only become evident when the inflation phase is prolonged (producing IRV) and patients breathe during this phase.

The putative advantages of this approach are similar to others with long inspiratory times. Specifically, the long inflation phase recruits more slowly filling alveoli and raises mean airway pressure without increasing applied PEEP (although intrinsic PEEP can develop with short deflation periods). Unlike older IRV strategies that required paralysis, however, the additional spontaneous efforts during inflation may enhance both recruitment and cardiac filling when compared to other controlled forms of support. Although IRV strategies are usually reserved for very severe forms of respiratory failure in which airway pressures and F_{IO_2} levels are approaching potentially injurious levels, the comfort and recruitment potential associated with APRV may prompt consideration of its use in less severe forms of lung injury.

Good gas exchange has been demonstrated with APRV in several small observational clinical trials, often with lower maximal airway pressures than used with control ventilation.[91–93] However, the end-inspiratory lung distention in APRV may not be less than that provided during other forms of support (and, indeed, it could be substantially higher) since spontaneous tidal volumes can occur even while the lung is inflated with the APRV set pressure. In the only randomized study that exists comparing APRV to a true lung-protective strategy, no difference in outcome was found.[93]

Adaptive Support Ventilation

As noted earlier, ASV is an assist-control, pressure-targeted, time-cycled mode of ventilation that automatically sets the frequency–tidal volume pattern according to respiratory system mechanics in order to minimize ventilator work.[7] Conceptually, this minimal ventilator work may translate into minimal stretching forces on the lungs, which may, in turn, reduce VILI. Importantly, the delivered "minimal work" tidal volume with ASV may sometimes be higher than the 6 mL/kg recommended by the ARDS Network trial. In addition, the PEEP settings are not part of the ASV algorithm and must therefore be set by the clinician. ASV has been shown to supply reasonable ventilatory support in a variety of patients with respiratory failure.[105,106] However, outcome studies comparing ASV to conventional lung-protective strategies have not been done.

Tracheal Gas Insufflation

In TGI, fresh gas is insufflated by a catheter placed at the distal end of the endotracheal tube to flush the endotracheal tube free of CO_2 during exhalation.[107] The concept is that the next delivered breath will effectively be free of endotracheal tube CO_2, thereby reducing dead space. This approach has particular appeal when the P_{CO_2} is rising during lung-protective ventilatory strategies. A number of studies have shown that TGI does reduce dead space but also has the potential to increase PEEP.

TGI catheters can deliver fresh gas either continuously or just during exhalation. Continuous delivery is easier to implement, but the exhalation-only approach reduces the potential for excessive end-inspiratory overinflation. TGI catheters can also be designed to deliver gas directly into the lung or in a retrograde fashion back up the endotracheal tube. Direct delivery enhances gas mixing, but retrograde delivery reduces the likelihood of increasing PEEP. At the present time, it is unclear whether TGI can significantly affect outcome and, if so, how best to deliver it. Clearly, however, TGI systems need to have safeguards to protect the lung from inadvertent overdistention.[107]

High-Frequency Ventilation

HFV uses very high breathing frequencies (120 to 900 breaths/min in the adult) coupled with very small tidal volumes (usually less than anatomic dead space and often <1 mL/kg at the alveolar level) to provide gas exchange in the lungs.[108] Gas transport under these seemingly unphysiologic conditions may involve such mechanisms as Taylor dispersion, coaxial flows, and augmented diffusion.[109]

HFV can be supplied by either jets or oscillators. Jets inject high-frequency pulses of gas into the airways. Oscillators literally vibrate a fresh bias flow of gas delivered at the tip of the endotracheal tube. Because of this, oscillatory HFV has sometimes been referred to as "CPAP with a wiggle."

The putative advantages of HFV are twofold. First, the very small alveolar tidal pressure swings minimize cyclical overdistention and derecruitment. Second, a high mean airway pressure can also prevent derecruitment. Interestingly, mean pressures used during HFV are often reported to exceed the 30 to 35 cm H_2O threshold employed during conventional ventilation. This tolerance of a higher mean pressure with HFV may be explained by a better maintained alveolar structure with a slowly applied (albeit vibrating) constant pressure as opposed to cyclical brief tidal pressures.

Clinical experience with HFV has been most extensive in the neonatal and pediatric age groups.[110–112] Experience in the adult population is less because HFV devices have only recently become available to support adequate gas exchange in this setting. Nevertheless, the one randomized trial to date evaluating HFV in severe acute respiratory distress syndrome suggested a trend toward improved survival with HFV.[112]

Automated Weaning Strategies

Over the years, a number of attempts have been made to "automate" the weaning process.[6] An early example is minimum minute ventilation, which adjusted the intermittent mandatory breath rate according to the level of spontaneous ventilation. The concept behind automated weaning was that significant clinician time could be saved and ventilatory support could be reduced in a timely fashion based on simple ventilator measurements.

Volume support (VS, also known by trade names such as "Automatic Pressure Ventilation") is the latest of these strategies with the potential for automatic support reduction.[6] VS is a dual-control breath-to-breath pressure support mode that uses tidal volume as a feedback control for continuously adjusting the pressure support level. All breaths are patient-triggered, pressure-limited, and flow-cycled, but clinicians select a target tidal volume. Depending upon the specific algorithm employed, automatic adjustments in inspiratory pressure are made by the ventilator within a clinician-prescribed range.

Proponents claim that this approach could "automatically" wean a patient by reducing pressure support as patient effort increases and respiratory system mechanics improve. Conversely, pressure support would increase if patient effort diminished or respiratory system mechanics worsened. Similarly, it has also been suggested that VS may be a useful way to maintain a more constant level of partial support in patients with fluctuating levels of effort related to drugs or neurologic conditions. All of these effects have been demonstrated in small studies focused on patients with rapidly recovering respiratory failure.[6]

Unfortunately, the simplicity of VS may introduce problems.[22] For instance, if the volume set by the clinician is excessive for patient demand, a recovering patient may not attempt to take over the work of breathing for that volume and thus weaning may not progress. In addition, if the pressure level increases in an attempt to maintain an inappropriately high set tidal volume in the patient with airflow obstruction, intrinsic PEEP may result. Conversely, if the volume set by the clinician is not adequate for patient demand, a patient may not receive adequate support. Under these conditions, a patient will perform excessive work to maintain a certain tidal volume even as the inspiratory pressure is being reduced.

Although no outcome studies have been performed using VS, there are specific clinical situations in which VS may be useful, as in a patient with fluctuating demand or in the rapidly recovering patient. However, clinicians need to be aware of the behavior of VS under a variety of circumstances to use this mode properly.

ASV, like VS, also has a volume feedback capability on delivered pressure during patient-triggered breaths. However, the ASV feedback control is more complex than VS and incorporates, as noted earlier, a "minimal work" setting for the desired minute ventilation based on respiratory system mechanics. Small clinical studies have demonstrated that ASV can automatically wean ven-

tilatory support safely.[106,113] However, large trials comparing ASV weaning to aggressive daily SBT strategies have not been done.

Other feedback systems controlling pressure support breaths have been touted as being capable of automatic weaning. These feedback systems use end points such as respiratory rate, patient respiratory drive (assessed by measuring inspiratory pressure against a closed circuit 100 msec after effort initiation), and end-tidal CO_2 to adjust ventilator settings.[114] As with other strategies described earlier, these approaches have been demonstrated to reduce pressure support safely in patients during weaning. Again, however, none of these strategies has been compared to aggressive daily SBT strategies in a large trial.

Optimizing Synchrony during Interactive Breaths

Interactive breaths are commonly used during mechanical ventilatory support to improve comfort (and reduce sedation), especially during the recovery phase of respiratory failure. As noted previously, interactive breaths need to be synchronous with patient efforts during all three phases of breath delivery: trigger, flow delivery, and cycle. To this end, a number of recent innovations have been introduced and are reviewed here.[114a]

It must be realized that, while all of these innovations have conceptual appeal and have been shown to perform as designed in both bench testing and small clinical observational trials, patient outcomes, including sedation needs, ventilator days, or patient comfort assessments, often have not been studied. Nevertheless, their straightforward designs, ease of operation, and safety make these innovations appropriate to consider in patients receiving interactive breaths.

Endotracheal Tube Resistance Compensation

The endotracheal tube provides a significant resistance to flow during both inspiration and expiration. During the inspiratory phase, this means that pressure build-up in the airways "lags" behind the pressure build-up in the ventilator circuity. Thus, the "square" wave of pressure in the circuitry provided by a pressure-targeted breath is distorted in the airways to a slower rise of pressure. This may create significant initial flow dyssynchrony in patients with vigorous inspiratory efforts. During expiration, a similar gradient between airway pressures and set circuit PEEP can develop.

One way to address this is to target ventilator pressures to a measured tracheal pressure distal to the endotracheal tube. Unfortunately, readings from intra-airway pressure sensors over prolonged periods are not reliable. Another approach is to account for endotracheal tube resistance mathematically in the ventilator flow delivery pattern.[115] Known by various trade names (e.g., "Automatic Airway Compensation," "Automatic Tube Compensation"), this approach initially provides an inspiratory pressure higher than the set pressure target. As inspiration proceeds, this delivered pressure then tapers to the set inspiratory pressure target. This compensation mechanism also can operate in expiration with an initial expiratory airway pressure below the set PEEP that then rises to the set PEEP. A more square wave pattern of inspiratory and expiratory tracheal pressures is the result.

Applying endotracheal tube resistance compensation is relatively straightforward. Clinicians must input the characteristics of the endotracheal tube. Thereafter, the ventilator provides the appropriate circuit pressure profile during both inspiration and expiration to create the desired square wave pattern in the trachea. Although outcome studies using this compensation approach have not been done, the conceptual appeal should make it a consideration in virtually all patients receiving assisted/supported pressure-targeted breaths—especially those with vigorous inspiratory efforts.

Pressure-Targeted Inspiratory Pressure Slope Adjusters

The original design for pressure-targeted breaths (pressure support and pressure assist-control) had a programmed flow delivery algorithm that attempted to reach the target inspiratory pressure quickly, without causing an uncomfortable overshoot. Newer ventilators, however, allow the clinicians to adjust this pressure rate of rise (slope adjusters), and clinical studies have suggested that slope adjustment could significantly enhance flow synchrony in many patients.[116] Specifically, these studies found that a rapid rate of rise was often desired in a patient with vigorous flow demands, while a much slower rate of rise was often preferable in patients with less vigorous demands.

There are several approaches to setting the slope adjuster. The most direct way is to use the circuit pressure graph and adjust the slope to create a "smooth square wave" appearance to the circuit pressure profile. Studies have also shown that an optimal slope setting correlates with the greatest V_T for a given pressure setting.[116] Patient comfort should always be considered in determining optimal slope settings.

Pressure Support Cycle Adjusters

Cycle dyssynchrony has recently been recognized as a potential problem due to the flow cycling mechanism of pressure support. On earlier machines, a set flow criterion was usually determined by the manufacturer (e.g., 25% to 35% of peak flow). While this set flow was often effective, it could sometimes terminate breaths too early in patients with long inspiratory demands and it could sometimes terminate too late, typically in patients with obstructive airway disease. In this latter situation, air trapping could also be made worse because of the resulting shorter expiratory time.

There are several approaches to improving cycle synchrony with pressure support. One is to switch from pressure support to a pressure assist breath (patient-

triggered, pressure-targeted, time-cycled breath as is usually available on most machines providing pressure ACV if the set rate is turned low or off). This breath provides direct clinician control of inspiratory time and thus of cycling. Another strategy is to adjust the pressure slope setting described previously on pressure support breaths. A very rapid peak initial flow will have a correspondingly high flow cycle variable (and thus short inspiratory time); a very slow peak initial flow will have a correspondingly low flow cycle variable (and thus long inspiratory time).

A newer, more direct approach, however, is to allow adjustments of the flow criteria of the pressure support cycle to assure appropriate synchrony of the cycle with the end of patient effort. As with other adjustments of interactive breaths, airway pressure graphics and assessments of patient comfort should guide adjustments. Proper breath synchrony is characterized by a comfortable patient and no evidence on the circuit pressure graph of continued inspiratory effort after cycling (premature cycling) or of expiratory efforts beginning during the inspiratory phase (delayed cycling). Although no outcome studies have been performed using these cycle adjusters, their physiologic appeal, ease of use, and apparent safety should make them a consideration in virtually every patient receiving pressure support.

Proportional Assist Ventilation

Proportional assist ventilation (PAV) is a novel approach to assisted ventilation in which the clinician sets the "gain" on patient-generated flow and volume.[117,118] In PAV, there is thus no set pressure, flow, or volume. Instead, the sensed patient effort is boosted according to a proportion of the measured work of breathing set by the clinician. The greater the patient effort, the greater the delivered pressure, flow, and volume. This contrasts with volume assist ventilation, where flow and volume are not affected by effort and where, in fact, applied pressure may be "pulled down" by effort. PAV also contrasts with pressure assist/support ventilation, where flow and volume are affected by effort but presure is not.

PAV has been compared to other forms of assisted ventilation and has been found to be comparable in terms of muscle unloading and patient comfort over a range of clinically meaningful settings.[118] Whether PAV improves clinical outcomes remains to be determined.

Neurally Adjusted Ventilatory Assistance

Neurally adjusted ventilatory assistance (NAVA) utilizes a diaphragmatic electromyographic (EMG) signal to trigger and cycle ventilatory assistance. The EMG sensor is positioned in the esophagus at the level of the diaphragm. Triggering of the ventilator breath is thus virtually simultaneous with the onset of phrenic nerve excitation of the inspiratory muscles. Moreover, breath cycling becomes tightly linked to the cessation of inspiratory muscle contraction. Small clinical studies have demonstrated improved trigger and cycle synchrony with NAVA,[119] but data demonstrating improved outcomes (e.g., duration of mechanical ventilation, sedation needs) are lacking. Another concern with NAVA is the expense associated with the EMG sensor.

KEY POINTS

- Positive-pressure breaths are characterized by three variables: the breath trigger, the flow delivery target (pressure or flow), and the cycle criteria.
- The interactions of positive-pressure breaths and respiratory system mechanics are described by the equation of motion: Pressure = (flow × resistance) + (volume/system compliance).
- In lungs with collapsed alveoli, alveolar recruitment is accomplished by a positive-pressure inflation and is maintained by positive end-expiratory pressure.
- Ventilator-induced lung injury can be caused by several mechanisms, including alveolar overdistention and repetitive alveolar collapse/reopening.
- Removing mechanical ventilatory support expeditiously requires regular sedation adjustments and assessments of spontaneous breathing capabilities.

References

1. MacIntyre NR: Mechanical ventilation: The next 50 years. Respir Care 43:490–493, 1998.

1a. ANZIC Influenza Investigators: Critical care services and 2009 H1N1 influenza in Australia and New Zealand. N Engl J Med 361:1925–1934, 2009.

2. Mushin M, Rendell-Baker W, Thompson PW, Mapleson WW: Automatic Ventilation of the Lungs. Oxford, UK: Blackwell, 1980, pp 62–160.

3. American Society for Testing and Materials: Standards Specifications for Ventilators Intended for Use in Critical Care (ASTM Standards No. 36). Philadelphia: American Society for Testing and Materials, 1991, pp 1123–1155.

4. Chatburn RL, Branson RD: Classification of mechanical ventilators. *In* MacIntyre NR, Branson RD (eds): Mechanical Ventilation (2nd ed). St. Louis: Saunders Elsevier, 2009, pp 1–49.

5. American Association for Respiratory Care Consensus Group: Essentials of mechanical ventilators. Respir Care 37:1000–1008, 1992.

6. Branson RD, MacIntyre NR: Dual control modes of mechanical ventilation. Respir Care 41:294–305, 1996.
7. Campbell RS, Branson RD, Johannigman JA: Adaptive support ventilation. Respir Care Clin N Am 7:425–440, 2001.
8. Kondili E, Xirouchaki N, Georgopoulos D: Modulation and treatment of patient-ventilator dyssynchrony. Curr Opin Crit Care 13:84–89, 2007.
9. Tom LR, Sasoon CSH: Patient ventilator interactions. *In* MacIntyre NR, Branson RD (eds): Mechanical Ventilation (2nd ed). St. Louis: Saunders Elsevier, 2009, pp 182–197.
10. Sassoon CSH: Mechanical ventilator design and function: The trigger variable. Respir Care 37:1056–1069, 1992.
11. Branson RD: Humidification and aerosol therapy. *In* MacIntyre NR, Branson RD (eds): Mechanical Ventilation (2nd ed). St. Louis: Saunders Elsevier, 2009, pp 111–124.
12. Pinsky MR, Hrehocik D, Culpepper JA, Snyder JV: Flow resistance of expiratory positive pressure systems. Chest 94:788–791, 1988.
13. Pepe PE, Marini JJ: Occult positive end-expiratory pressure in mechanically ventilated patients with airflow obstruction. Am Rev Respir Dis 126:166–170, 1982.
14. Hill NS, Brennan J, Garpestad E, Nava S: Noninvasive ventilation in acute respiratory failure. Crit Care Med 35:2402–2407, 2007.
15. Dhand R, Guntur VP: How best to deliver aerosol medications to mechanically ventilated patients. Clin Chest Med 29:277–296, 2008.
16. Marini JJ: What derived variables should be monitored during mechanical ventilation? Respir Care 37:1097–1107, 1992.
17. MacIntyre NR: Ventilator monitors and displays. *In* MacIntyre NR, Branson RD (eds): Mechanical Ventilation (2nd ed). St. Louis: Saunders Elsevier, 2009, pp 146–158.
18. Truwit JD, Marini JJ: Evaluation of thoracic mechanics in the ventilated patient. Part I: Primary measurements. J Crit Care 3:133–150, 1988.
19. Truwit JD, Marini JJ: Evaluation of thoracic mechanics in the ventilated patient. Part II: Applied mechanics. J Crit Care 3:192–213, 1988.
20. Ranieri VM, Brienza N, Santostasi S, et al: Impairment of lung and chest wall mechanics in patients with acute respiratory distress syndrome: Role of abdominal distension. Am J Respir Crit Care Med 156:1082–1091, 1997.
21. Chiumello D, Carlesso E, Cadringher P, et al: Lung stress and strain during mechanical ventilation for acute respiratory distress syndrome. Am J Respir Crit Care Med 178:346–355, 2008.
22. Jaber S, Delay JM, Matecki S, et al: Volume-guaranteed pressure-support ventilation facing acute changes in ventilatory demand. Intensive Care Med 31:1181–1188, 2005.
23. Marini JJ, Crooke PS: A general mathematical model for respiratory dynamics relevant to the clinical setting. Am Rev Respir Dis 147:14–24, 1993.
24. Macklen PT: Relationship between lung mechanics and ventilation distribution. Physiology 16:580–588, 1973.
25. Mili-Emili J, Henderson JAN, Dolovich MB, et al: Regional distribution of inhaled gas in the lung. J Appl Physiol 21:749–759, 1966.
26. Abraham E, Yoshihara G: Cardiorespiratory effects of pressure controlled ventilation in severe respiratory failure. Chest 98:1445–1449, 1990.
27. Pratt PC: Pathology of the adult respiratory distress syndrome. *In* Thurlbeck WM, Ael MR (eds): The Lung: Structure, Function and Disease. Baltimore: Williams & Wilkins, 1978, pp 43–57.
28. Kacmarek RM, Pierson DJ (eds): AARC Conference on Positive End Expiratory Pressure. Respir Care 33:419–527, 1988.
29. Gattinoni L, Pesenti A, Baglioni S, et al: Inflammatory pulmonary edema and PEEP: Correlation between imaging and physiologic studies. J Thorac Imaging 3:59–64, 1988.
30. Gattinoni L, Pelosi P, Crotti S, et al: Effects of positive end expiratory pressure on regional distribution of tidal volume and recruitment in adult respiratory distress syndrome. Am J Respir Crit Care Med 151:1807–1814, 1995.
31. Gattinoni L, Caironi P, Cressoni M, et al: Lung recruitment in patients with the acute respiratory distress syndrome. N Engl J Med 354:1775–1786, 2006.
32. Lim SC, Adams AB, Simonson DA, et al: Intercomparison of recruitment maneuver efficacy in three models of acute lung injury. Crit Care Med 32:2371–2377, 2004.
33. Armstrong BW, MacIntyre NR: Pressure controlled inverse ratio ventilation that avoids air trapping in ARDS. Crit Care Med 23:279–285, 1995.
34. Cole AGH, Weller SF, Sykes MD: Inverse ratio ventilation compared with PEEP in adult respiratory failure. Intensive Care Med 10:227–232, 1984.
35. Tharratt RS, Allen RP, Albertson TE: Pressure controlled inverse ratio ventilation in severe adult respiratory failure. Chest 94:755–762, 1988.
36. Webb HJH, Tierney DF: Experimental pulmonary edema due to intermittent positive pressure ventilation with high inflation pressures: Protection by positive end-expiratory pressure. Am Rev Respir Dis 110:556–565, 1974.
37. Manzano F, Fernandez-Mondejar E, Colmenero M, et al: Positive-end expiratory pressure reduces incidence of ventilator-associated pneumonia in nonhypoxemic patients. Crit Care Med 36:2225–2231, 2008.
38. Wyszogrodski I, Kyei-Aboagye K, Taaeusch HW Jr, Avery ME: Surfactant inactivation by hyperventilation: Conservation by end-expiratory pressure. J Appl Physiol 38:461–466, 1975.
39. Grasso S, Stripoli T, De Michele M, et al: ARDSnet ventilatory protocol and alveolar hyperinflation: Role of positive end-expiratory pressure. Am J Respir Crit Care Med 176:761–767, 2007.
40. Ferragni PP, Rosbosh G, Tealdi A, et al: Tidal hyperinflation during low tidal volume ventilation in acute respiratory distress syndrome. Am J Respir Crit Care Med 175:160–166, 2007.
41. MacIntyre NR, Leatherman NE: Mechanical loads on the ventilatory muscles. Am Rev Respir Dis 144:968–973, 1989.
42. McGregor M, Bechlake MR: The relationship of oxygen cost of breathing to mechanical work and and respiratory force. J Clin Invest 40:971–980, 1961.
43. Bellemare F, Grassino A: Effect of pressure and timing of contraction on human diaphragm fatigue. J Appl Physiol 53:1190–1195, 1982.
44. Banner MJ, Kirby RR, MacIntyre NR: Patient and ventilator work of breathing and ventilatory muscle loads at different levels of pressure support ventilation. Chest 100:531–533, 1991.
45. Marini JJ: Exertion during ventilator support: How much and how important? Respir Care 31:385–387, 1986.
46. MacIntyre NR: Weaning from mechanical ventilatory support: Volume-assisting intermittent breaths versus pressure-assisting ever breath. Respir Care 33:121–125, 1988.
47. American Thoracic Society and European Respiratory Society: Skeletal muscle dysfunction in chronic obstructive pulmonary disease: A statement of the American Thoracic Society and European Respiratory Society. Am J Respir Crit Care Med 159:S1–S40, 1999.
48. Vassilakopoulos D, Petrof B: Ventilator induced diaphragmatic dysfunction. Am J Respir Crit Care Med 169:336, 2004.
49. Levine S, Nguyen T, Taylor N, et al: Rapid disuse atrophy of diaphragm fibers in mechanically ventilated humans. N Engl J Med 358:1327–1335, 2008.
50. Anzueto A, Peters JI, Tobin MJ, et al: Effects of prolonged controlled mechanical ventilation on diaphragmatic function in healthy adult baboons. Crit Care Med 25:1187–1190, 1997.
51. Hansen-Flaschen J, Brazinsky S, Bassles C, Lanken PV: Use of sedating drugs and neuromuscular blockade in patients requiring mechanical ventilation for respiratory failure. JAMA 266:2870–2875, 1991.

51a. de Wit M, Miller KB, Green DA, Ostman HE: Ineffective triggering predicts increased duration of mechanical ventilation. Crit Care Med 37:2740–2745, 2009.

52. Petrof BJ, Legare M, Goldberg P, et al: Continous positive airway pressure reduces work of breathing and dyspnea during weaning from mechanical ventilation in severe chronic obstructive pulmonary disease. Am Rev Respir Dis 141:281–289, 1990.
53. MacIntyre NR, McConnell R, Cheng KC: Applied PEEP reduces the inspiratory load of intrinsic PEEP during pressure support. Chest 1111:188–193, 1997.
54. Flick GR, Belamy PE, Simmons DH: Diaphragmatic contraction during assisted mechanical ventilation. Chest 96;130–135, 1989.
55. Marini JJ, Smith TC, Lamb VJ: External work output and force generation during synchronized intermittent mechanical ventilation. Am Rev Respir Dis 138:1169–1179, 1988.

56. Jubran A, Van de Graaf WB, Tobin MJ: Variability of patient ventilator interactions with pressure support ventilation in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 152:129–136, 1995.
57. Marini JJ, Culver BH, Butler J: Mechanical effect of lung inflation with positive pressure on cardiac function. Am Rev Respir Dis 124:382–386, 1979.
58. Scharf SM, Caldini P, Ingram RH Jr: Cardiovascular effects of increasing airway pressure in dogs. Am J Physiol 232:1135–1143, 1977.
59. Pinsky MR, Guimond JG: The effects of positive end-expiratory pressure on heart-lung interactions. J Crit Care 6:1–15, 1991.
60. Pinsky MR, Summer WR, Wise RA, et al: Augmentation of cardiac function by elevation of intrathoracic pressure. J Appl Physiol 54:450–455, 1983.
61. Lemaire F, Teboul JL, Cinotti L, et al: Acute left ventricular dysfunction during unsuccessful weaning from mechanical ventilation. Anesthesiology 69:171–179, 1988.
62. Pinsky MR, Marquez J, Martin D, Klain M: Ventricular assist by cardiac cycle-specific increases in intrathoracic pressure. Chest 91:709–715, 1987.
63. Hughes JM, Glazier JB, Maloney JE, West JB: Effect of lung volume on the distribution of pulmonary blood flow in man. Respir Physiol 4:58–72, 1968.
64. Anzueto A, Frutos-Vivar F, Esteban A, et al: Incidence, risk factors and outcome of barotrauma in mechanically ventilated patients. Intensive Care Med 30:612–619, 2004.
65. Kolobow T, Morentti MP, Fumagalli R, et al: Severe impairment in lung function induced by high peak airway pressure during mechanical ventilation. Am Rev Respir Dis 135:312–315, 1987.
66. Dreyfuss D, Savmon G: Ventilator induced lung injury: Lessons from experimental studies. Am J Respir Crit Care Med 157:294–323, 1998.
67. Jia X, Malhotra A, Saeed M, et al: Risk factors for ARDS in patients receiving mechanical ventilation for > 48 h. Chest 133:853–861, 2008.
68. Yilmaz M, Keegan MT, Iscimen R, et al: Toward the prevention of acute lung injury: Protocol-guided limitation of large tidal volume ventilation and inappropriate transfusion. Crit Care Med 35:1660–1666, 2007.
69. Villar J, Kacmarek RM, Perez-Mendez L, Aguirre-Jaime A: A high positive end-expiratory pressure, low tidal volume ventilatory strategy improves outcome in persistent acute respiratory distress syndrome: A randomized, controlled trial. Crit Care Med 34:1311–1318, 2006.
70. NIH ARDS Network: Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 342:1301–1308, 2000.
71. Vaporidi K, Voloudakis G, Priniannakis G, et al: Effects of respiratory rate on ventilator-induced lung injury at a constant $PaCO_2$ in a mouse model of normal lung. Crit Care Med 36:1277–1283, 2008.
72. Rich BR, Reickert CA, Sawada S, et al: Effect of rate and inspiratory flow on ventilator induced lung injury. J Trauma 49:903–911, 2000.
73. Crotti S, Mascheroni D, Caironi P, et al: Recruitment and derecruitment during acute respiratory failure. Am J Respir Crit Care Med 164:131–140, 2001.
74. Rimensberger PC, Prisine G, Mullen BM, et al: Lung recruitment during small tidal volume ventilation allows minimal positive end expiratory pressure without augmenting lung injury. Crit Care Med 27:1940–1945, 1999.
75. Marini JJ, Hotchkiss JR, Broccard AF: Bench-to-bedside review: Microvascular and airspace linkage in ventilator-induced lung injury. Crit Care (Lond) 7:435–444, 2003.
76. Trembly L, Valenza F, Ribiero SP, et al: Injurious ventilatory strategies increase cytokines and C-fos mRNA expression in an isolated rat lung model. J Clin Invest 99:944–952, 1997.
77. Ranieri VM, Suter PM, Totorella C, et al: Effect of mechanical ventilation on inflammatory mediators in patients with acute respiratory distress syndrome. JAMA 282:54–61, 1999.
78. Nahum A, Hoyt J, Schmitz L, et al: Effect of mechanical ventilation strategy on dissemination of interacheally instilled *E. coli* in dogs. Crit Care Med 25:1733–1743, 1997.
79. Jenkinson SG: Oxygen toxicity. New Horizons 1:504–511, 1993.
80. Betbese AJ, Perez M, Bak E, et al: A prospective study of unplanned endotracheal extubation in ICU patients. Crit Care Med 26:1180–1186, 1998.
81. Tejerina E, Frutos-Vivar F, Restrepo MI, et al: Incidence, risk factors, and outcome of ventilator-associated pneumonia. J Crit Care 21:56–65, 2006.
82. Collard HR, Saint S, Matthay M, et al: Prevention of ventilator-associated pneumonia: An evidence-based systematic review. Ann Intern Med 138:494–501, 2003.
83. Dodek P, Keenan S, Cook D, et al: Evidence-based clinical practice guideline for the prevention of ventilator-associated pneumonia. Ann Intern Med 141:305–313, 2004.
83a. Nachtigall I, Tamarkin A, Tafelski S, et al: Impact of adherence to standard operating procedures for pneumonia on outcome of intensive care unit patients. Crit Care Med 37:159–166, 2009.
84. Palmer LB, Smaldone GC, Chen JJ, et al: Aerosolized antibiotics and ventilator-associated tracheobronchitis in the intensive care unit. Crit Care Med 36:2008–2013, 2008.
85. Hickling KG, Walsh J, Henderson S, Jackson R: Low mortality rate in adult respiratory distress syndrome using low-volume, pressure-limited ventilation with permissive hypercapnia: A prospective study. Crit Care Med 22:1568–1578, 1994.
86. MacIntyre NR: Is there a best way to set the tidal volume for mechanical ventilatory support? Clin Chest Med 29:225–232, 2008.
87. MacIntyre NR: Is there a best way to set positive end expiratory pressure for mechanical ventilatory support in acute lung injury? Clin Chest Med 29:233–240, 2008.
88. Checkley W, Brower R, Korpak A, et al: Effects of a clinical trial on mechanical ventilation practices in patients with acute lung injury. Am J Respir Crit Care Med 177:1215–1222, 2008.
89. Esteban A, Ferguson ND, Meade MO, et al: Evolution of mechanical ventilation in response to clinical research. Am J Respir Crit Care Med 177:170–177, 2008.
90. Amato MB, Barbas CSV, Medievos DM, et al: Effect of a protective ventilation strategy on mortality in ARDS. N Engl J Med 338:347–354, 1998.
90a. Cooke CR, Kahn JM, Watkins TR, et al: Cost effectiveness of implementing low tidal volume ventilation in patients with acute lung injury. Chest 136:79–88, 2009.
91. Habashi NM: Other approaches to open-lung ventilation: Airway pressure release ventilation. Crit Care Med 33(3 Suppl):S228–S240, 2005.
92. Putensen C, Zech S, Wrigge H, et al: Long term effects of spontaneous breathing during ventilatory support in patients with ALI. Am J Respir Crit Care Med 164:43–49, 2001.
93. Varpula T, Valta P, Niemi R, et al: Airway pressure release ventilation as a primary ventilatory mode in acute respiratory distress syndrome. Acta Anaesth Scand 48:722–731, 2004.
94. Ranieri VM, Giuliani R, Fiore T, et al: Volume-pressure curve of the respiratory system predicts effects of PEEP in ARDS: "Occlusion" versus "constant flow" technique. Am J Respir Crit Care Med 149:19–27, 1994.
95. Putensen C, Bain M, Hormann C: Selecting ventilator settings according to the variables derived from the quasi static pressure volume relationship in patients with acute lung injury. Anesth Analg 77:436–447, 1993.
96. Suter PM, Fairley HB, Isenberg MD: Optimal end expiratory pressure in patients with acute pulmonary failure. N Engl J Med 292: 284–289, 1975.
97. Grasso S, Terragni P, Mascia L, et al: Airway pressure-time curve profile (stress index) detects tidal recruitment/hyperinflation in experimental acute lung injury. Crit Care Med 32:1018–1027, 2004.
98. Meade MO, Cook DJ, Guyatt GH, et al: Ventilation strategy using low tidal volumes, recruitment maneuvers, and high positive end-expiratory pressure for acute lung injury and acute respiratory distress syndrome: A randomized controlled trial. JAMA 299:637–645, 2008.

99. Mercat A, Richard JC, Vielle B, et al: Positive end-expiratory pressure setting in adults with acute lung injury and acute respiratory distress syndrome: A randomized controlled trial. JAMA 299:646–655, 2008.
100. Brower RG, Lanken PN, MacIntyre N, et al: Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. N Engl J Med 351:327–336, 2004.
100a. Phoenix SI, Paravastu S, Columb M, et al: Does a higher positive end expiratory pressure decrease mortality in acute respiratory distress syndrome? A systematic review and meta-analysis. Anesthesiology 110:1098–1105, 2009.
101. Hurford WE, Cheifetz IM: Respiratory controversies in the critical care setting: Should heliox be used for mechanically ventilated patients? Respir Care 52:582–594, 2007.
102. Ferrer M: Non-invasive ventilation in the weaning process. Minerva Anestesiol 74:311–314, 2008.
103. ACCP/AARC/SCCM Task Force: Evidence based guidelines for weaning and discontinuing mechanical ventilatory support. Chest 120(Suppl 6), 2001. [Also in Respir Care 47:20–35, 2002.]
104. Girard TD, Kress JP, Fuchs BD, et al: Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): A randomized controlled trial. Lancet 371:126–134, 2008.
105. Gruber PC, Gomersall CD, Leung P, et al: Randomized controlled trial comparing adaptive-support ventilation with pressure-regulated volume-controlled ventilation with automode in weaning patients after cardiac surgery. Anesthesiology 109:81–87, 2008.
106. Tassaux D, Dalmas E, Gratadour P, Jolliet P: Patient-ventilator interactions during partial ventilatory support: A preliminary study comparing the effects of adaptive support ventilation with synchronized intermittent mandatory ventilation plus inspiratory pressure support. Crit Care Med 30:801–807, 2002.
107. Hess DR, MacIntyre NR: Tracheal gas insufflation: Overcoming obstacles to clinical implementation. Respir Care 46:198–199, 2001.
108. Froese AB: High frenquency oscillatory ventilation for ARDS: Let's get it right this time. Crit Care Med 25:906–908, 1998.
109. Chang HK: Mechanisms of gas transport during high frequency ventilation. J Appl Physiol 56:553–563, 1984.
110. Bollen CW, Uiterwal SPM, vanVught AJ: Cumulative meta analysis of high frequency vs conventional ventilation in premature neonates. Am J Respir Crit Care Med 168:1150–1155, 2003.
111. Courtney SE, Durand DJ, Asselin JM, et al: High frequency oscillatory ventilation vs conventional mechanical ventilation for very low birth weight infants. N Engl J Med 347:643–652, 2002.
112. Derdak S: High frequency oscillatory ventilation for acute respiratory distress syndrome in adult patients. Crit Care Med 31(4 Suppl):S317–S323, 2003.
113. Petter AH, Chiolero RL, Cassina T, et al: Automatic "respirator/weaning" with adaptive support ventilation: The effect on duration of endotracheal intubation and patient management. Anesth Analg 97:1743–1750, 2003.
114. Lellouche F, Mancebo J, Jolliet P, et al: A multicenter randomized trial of computer-driven protocolized weaning from mechanical ventilation. Am J Respir Crit Care Med 174:894–900, 2006.
114a. Lellouche F, Brochard L: Advanced closed loops during mechanical ventilation (PAV, NAVA, ASV, SmartCare). Clin Anaesthesiol 23:81–93, 2009.
115. Fabry B, Zappe D, Guttman J: Breathing pattern and additional work of breathing in spontaneously breathing patients with different ventilatory demand during inspiratory pressure support and automatic tube compensation. Intensive Care Med 23:545–552, 1997.
116. Ho L, MacIntyre NR: Effects of initial flow rate and breath termination criteria on pressure support ventilation. Chest 99:134–138, 1991.
117. Younes M: Proportional assist ventilation, a new approach to ventilatory support. Am Rev Respir Dis 145:114–120, 1992.
118. Grasso S, Ranieri VM: Proportional assist ventilation. Respir Care Clin N Am 7:465–473, 2001.
119. Sinderby C: Neurally adjusted ventilatory assist (NAVA). Minerva Anestesiol 68:378–380, 2002.

CHAPTER 90

ACUTE RESPIRATORY DISTRESS SYNDROME

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Diagnosis

The acute respiratory distress syndrome (ARDS) is characterized by noncardiogenic pulmonary edema, lung inflammation, hypoxemia, and decreased lung compliance. Unlike some disorders (e.g., coronary artery disease), ARDS is a syndrome reflecting a constellation of clinical and physiologic observations thought to represent a common pathology. In coronary artery disease, narrowing of the coronary vasculature and disruption of an unstable atherosclerotic plaque are known to underpin the symptoms of angina and unstable angina respectively. A diagnostic "gold standard," namely coronary angiography, exists. In contrast, the pathogenesis of ARDS remains elusive and there is no gold standard diagnostic test. The heterogeneity of the clinical conditions associated with ARDS (discussed later) suggests that ARDS is a collection of different diseases that have not yet been separately identified.

The first description of ARDS appeared in a remarkable case series reported in 1967.[1] Ashbaugh and colleagues[1] described 12 patients ranging in age from 11 to 48 years, who presented with respiratory distress, hypoxemic respiratory failure, and patchy bilateral infiltrates on chest radiographs (Fig. 90-1). Most of the cases were preceded by severe trauma or viral infection and the onset of symptoms was relatively rapid, with most patients developing respiratory distress within 48 to 72 hours of the beginning of their illness. Most of the patients required positive-pressure ventilation and had low respiratory system compliance, and some experienced improvement in oxygenation with the application of positive end-expiratory pressure (PEEP). This syndrome was initially termed the *adult* respiratory distress syndrome to distinguish it from the respiratory distress syndrome seen in infants. When it was recognized that it also occurs in children, it was renamed the *acute* respiratory distress syndrome.

The cases described by Ashbaugh and colleagues[1] generated interest and research about ARDS. Unfortunately, the lack of either specific diagnostic criteria or an understanding of the pathogenesis of the disorder made it difficult to identify consistent patient populations in order to compare studies. In 1988, a formalized

and expanded definition of ARDS was proposed that consisted of three parts: (1) the first part described whether the illness was acute or chronic; (2) the second part identified associated risk factors or medical conditions (e.g., sepsis)[2]; (3) in the third part, points were assigned based on the severity of pulmonary dysfunction (the Lung Injury Score [LIS]), as measured by the degree of hypoxemia, the level of PEEP required, the respiratory system compliance, and the degree of radiographic abnormality. An average score was calculated and a final value greater than 2.5 was used to make a diagnosis of ARDS. One advantage of this system was its description of associated medical conditions, which might be pertinent to the etiology of ARDS. Because different etiologies of ARDS might reflect different pathogenetic pathways and perhaps confer different responses to therapy, knowing the cause of ARDS could be important in designing and comparing studies. The 1988 definition, however, made no attempt to exclude cardiogenic pulmonary edema because it was assumed that clinicians would do so automatically.

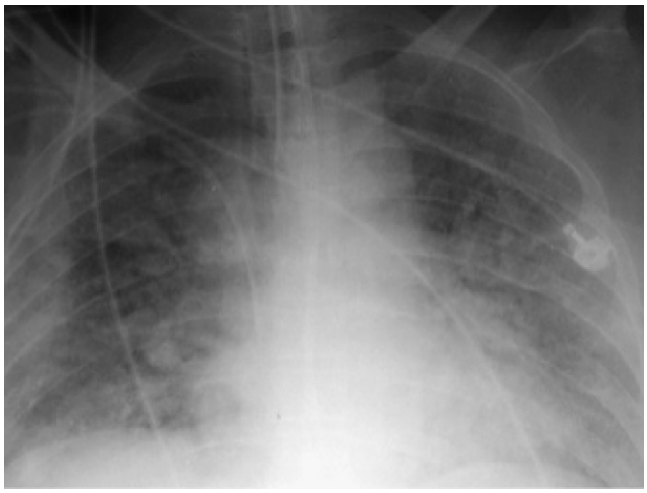

FIGURE 90-1 ■ Frontal radiograph of the chest in a patient with acute respiratory distress syndrome. Note the presence of bilateral infiltrates. (Courtesy of Michael B. Gotway, MD, Department of Radiology, University of California, San Francisco.)

Subsequently, a consensus conference of American and European investigators published their definition of ARDS, which has since been widely adopted[3] (Table 90-1). Aiming for simplicity, ARDS was defined as a syndrome of acute onset, with bilateral infiltrates on chest radiography consistent with pulmonary edema, pulmonary artery (PA) occlusion pressure of 18 mm Hg or less (or absence of clinical evidence of increased left atrial pressure), and hypoxemia as measured by the ratio of the arterial partial pressure of oxygen (Pa_{O_2}) to the fraction of oxygen inspired (F_{IO_2}). Recognizing the spectrum of severity of the disease, the consensus panel recommended that a Pa_{O_2}/F_{IO_2} ratio of 300 or less would define an entity termed *acute lung injury (ALI)*. ARDS was the most severe form of ALI and was diagnosed with Pa_{O_2}/F_{IO_2} of 200 or less.

The simplicity of the definition led to its general acceptance by clinicians and its incorporation into clinical research. However, such a straightforward definition could not take into account the heterogeneity of the disease or the ambiguity of clinical practice. For example, the requirement for bilateral infiltrates on chest radiograph is open to interpretation. One study presented a random series of chest radiographs from intubated hypoxemic patients ($Pa_{O_2}/F_{IO_2} < 300$) to an international group of expert clinicians, the majority of whom had conducted clinical research on ARDS. The clinicians were asked to examine each radiograph and to decide whether it fulfilled the American-European consensus conference (AECC) definition of ARDS (bilateral infiltrates consistent with pulmonary edema). This select group of physicians demonstrated only moderate agreement (κ statistic 0.55) in their classification of the radiographs. When the percentage of radiographs deemed by each physician to be consistent with ARDS was examined, the percentages ranged from a low of 36% to a high of 71%.[4] Another larger study on this issue also found only moderate agreement when two physicians were asked to rate radiographs on the presence or absence of diffuse bilateral infiltrates consistent with ARDS. However, with prior training and discussion, the agreement between an intensivist and a radiologist in the rating of the films was excellent.[5]

The AECC definition has also been criticized for not taking the level of PEEP into consideration. Clinicians

TABLE 90-1. American-European Consensus Conference Criteria for Acute Respiratory Distress Syndrome

	Timing	Oxygenation	Frontal Chest Radiograph	Pulmonary Artery Wedge Pressure
Acute lung injury	Acute	$Pa_{O_2}/F_{IO_2} \leq 300$ mm Hg*	Bilateral infiltrates	≤18 mm Hg if measured, or no clinical evidence of left atrial hypertension
ARDS	Acute	$Pa_{O_2}/F_{IO_2} \leq 200$ mm Hg*	Bilateral infiltrates	≤18 mm Hg if measured, or no clinical evidence of left atrial hypertension

*Regardless of PEEP.

ARDS, acute respiratory distress syndrome; F_{IO_2}, fractional concentration of oxygen in inspired gas; Pa_{O_2}, arterial pressure of oxygen; PEEP, positive end-expiratory pressure.

Adapted from Bernard GR, Artigas A, Brigham KL, et al: The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Resp Crit Care Med 149:818–824, 1994.

have long appreciated that applying PEEP can improve oxygenation, an observation that was noted in the first description of ARDS. This implies that the Pa_{O_2}/F_{IO_2} will change as the level of applied PEEP changes; indeed, a patient who initially meets the AECC criteria for ARDS may no longer meet them once PEEP has been increased.[6] It also has been shown that patients who meet the AECC definition for ARDS can be stratified based on their response to standard ventilator settings 24 hours later; many of the patients at that point have a lesser degree of hypoxemia and a significantly lower mortality rate.[7] Thus, the AECC definition, although simple to use, encompasses a very heterogeneous group of patients.

When the LIS and the AECC definitions have been compared, they have been found to identify similar patients with a similar mortality rate.[8,9] In other words, the differences in the definitions of ARDS do not seem to have prognostic importance. This finding is reassuring to clinicians because it suggests that results from studies that used one or the other definition can still be meaningfully compared. Nonetheless, the difficulties with the definition may partly explain some of the negative therapeutic clinical trials in ARDS (see later).

Two additional points should be made about the diagnosis of ARDS. First, physicians have become less likely to insert PA catheters into patients, because of data suggesting that their use does not change outcome.[10,11] Thus, in practice, left atrial hypertension is usually excluded on clinical grounds (i.e., lack of history of heart failure and normal echocardiogram). It is important to note that many patients with ALI/ARDS will have left atrial hypertension during the course of their illness.[12] Second, despite the increasing use of B-type natriuretic peptides as diagnostic tools for acute congestive heart failure, their use in critically ill patients is controversial because of a lack of specificity.[13] The utility of measuring B-type natriuretic peptide as a means of distinguishing ARDS from cardiogenic pulmonary edema remains unclear.[14,15]

Incidence

Because of the multitude of definitions, and the difficulty in making a diagnosis of ARDS or ALI, it is not surprising that determining the incidence of the disease has been challenging. The reported incidence of ARDS has ranged from 75/100,000 population[16] to as low as 1.5/100,000.[17] Many studies did not use the AECC definition and did not include ALI. The incidence of ALI has been estimated to be 78.9 cases/100,000 person-years.[18] One study calculated an incidence of ARDS and ALI of 22 cases/100,000 using data from a large prospective trial of ARDS and the American Hospital Association.[19] One of the methodologic strengths of the study was its inclusion of cases of both ALI and ARDS over a 3-year period, thereby decreasing the effect of seasonal variability. The heterogeneity of the published estimates of incidence probably reflects differences in the methodology of the various studies but may also reflect true variation in different populations. Regional differences in genetic or environmental factors and specific disease associations such as cardiopulmonary bypass or lung transplant may account for some of the regional variability in the incidence of ARDS and ALI.[20]

Risk Factors

Data from a number of studies have shown that sepsis, aspiration of gastric contents, and multiple blood transfusions (>15 units/24 hr in one study) were associated with the highest risk of developing ARDS.[21,22] In particular, almost 40% of patients with sepsis developed ARDS. The presence of more than one presumed risk factor for ARDS increased the incidence of ARDS, although the sample sizes of these subsets were small.[21] In these studies, over a third of patients receiving massive blood transfusion and a quarter of patients with multiple trauma (one or more of pulmonary contusion, multiple fractures, multiple transfusions) developed ARDS.[22]

One of the predisposing factors for ARDS is a history of chronic alcoholism (relative risk [RR] 1.98; 95% confidence interval [CI], 1.32–2.85). This relationship remained significant after adjustment for gender, at-risk diagnosis, and severity of illness. Among those who developed ARDS, patients with a history of alcoholism had a higher mortality rate than those without this history (odds ratio 6.26; 95% CI 2.22–20.38).[23] The mechanisms responsible for this association are not clear, but abnormal concentrations of glutathione in the lung parenchyma, with a shift in antioxidant balance, might be involved.

The same investigators examined whether patients with diabetes might be protected against the development of ARDS, reasoning that hyperglycemia is known to impair neutrophil function, and neutrophils are thought to be central to the pathogenesis of ARDS (see "Etiology and Pathogenesis" section). More than 100 patients admitted to the intensive care unit with septic shock were followed prospectively for the onset of ARDS. Over a 2-year period, diabetes was associated with a significantly decreased risk of ARDS (RR 0.53; 95% CI 0.28–0.98), which persisted after adjustment for the source of sepsis and other potential confounders. Interestingly, there was no difference in mortality between patients with or without diabetes who developed ARDS.[24]

A systematic overview of studies examining potential risk factors for ARDS concluded that the strongest evidence of a causal relationship was for sepsis, trauma, multiple transfusions, aspiration of gastric contents, pulmonary contusion, pneumonia, and smoke inhalation.[25]

The heterogeneity of risk factors for ARDS is remarkable. At the AECC, investigators divided the known risk factors into those thought to cause *direct* lung injury (e.g., pneumonia) and those in which the mechanism of lung injury was thought to be *indirect* (e.g., pancreatitis) (Table 90-2). Whether this conceptually attractive classification scheme (also known as the *pulmonary* vs. *nonpulmonary* risk factor classification) reflects underlying differences in the mechanisms, severity, or outcome of lung injury is still uncertain. For example, one group of investigators has shown that patients with direct pulmonary causes of ARDS had significantly higher lung

TABLE 90-2. Conditions Associated with Acute Respiratory Distress Syndrome, by Possible Mechanisms of Injury

Indirect Injury	Direct Injury
Sepsis	Pneumonia
Major trauma	Aspiration
Multiple blood transfusions	Pulmonary contusion
Pancreatitis	Toxic inhalation
Cardiopulmonary bypass	Near-drowning
Drug overdose	Reperfusion injury (e.g., post lung transplant)
Adverse effect of medication	

elastance than patients with indirect or nonpulmonary causes of ARDS.[26] In addition, increasing PEEP led to improved recruitment of the lung in the nonpulmonary group but to decreased recruitment in patients with ARDS from a pulmonary source. Despite these interesting observations, whether these two groups of patients have different prognoses or different responses to therapy is unclear.[27] This issue is discussed in more detail in the "Long-term Outcomes" section.

ETIOLOGY AND PATHOGENESIS

Overview of Pathophysiology

In the past, ARDS has also been called "noncardiogenic pulmonary edema," a descriptive term that nonetheless reflected what was known about the pathogenesis of the disorder. Unlike congestive heart failure, in which elevated left-sided cardiac pressures cause hydrostatic pulmonary edema, in ARDS, the edema fluid that fills the alveoli is exudative in origin due to increased permeability of the alveolar-capillary barrier, which allows leakage of protein-rich fluid into the airspaces. Alveolar filling leads to decreased respiratory system compliance as well as functional right-to-left shunting and profound hypoxemia. Although arterial carbon dioxide pressure (P_{CO_2}) is generally within the normal range, dead-space ventilation is significantly increased, as demonstrated by elevated minute ventilation. Pulmonary hypertension is also commonly observed in ARDS, and a number of mechanisms have been proposed, including hypoxic vasoconstriction, intravascular fibrin deposition in the pulmonary capillaries, and compression of blood vessels by the positive-pressure ventilation used to treat the disorder. Much of the research about ARDS has focused on determining the basis for the increase in alveolar-capillary permeability.

Pathology

The pathologic features of ARDS have classically been described using three overlapping and sequential stages.[28] In the first or exudative phase of lung injury, the pathologic findings have been termed "diffuse alveolar damage." There are hyaline membranes and protein-rich edema fluid in the alveolar spaces, as well as epithelial disruption and infiltration of the interstitium and air spaces with neutrophils and macrophages. Areas of alveolar hemorrhage also are present. This phase, which is thought to last for 5 to 7 days, is followed in some patients by a proliferative phase. At this point, hyaline membranes are reorganized and areas of fibrosis are visible. Obliteration of pulmonary capillaries and deposition of interstitial and alveolar collagen may be observed, along with a decrease in the number of neutrophils and the extent of pulmonary edema. The initial proliferative phase is followed by a fibrotic phase, emphasizing the appearance of pulmonary fibrosis in the subset of patients with persistent (i.e., >2 wk) ARDS.

More recent evidence suggests that the development of areas of fibrosis probably occurs sooner than previously appreciated. Elevated levels of N-terminal procollagen peptide III, thought to represent collagen synthesis, can be detected in bronchoalveolar lavage fluid of patients with ARDS as early as 24 hours into the course of the illness. In addition, the bronchoalveolar lavage fluid from these patients has been shown to stimulate cultured fibroblasts to proliferate.[29] These and other observations suggest that fibroproliferation begins simultaneously with (rather than after) inflammatory lung injury.[30]

The Alveolar-Capillary Membrane

Because ARDS is a disorder of increased alveolar-capillary permeability, it stands to reason that the pulmonary microvascular endothelium or the alveolar epithelium (or both) must be involved in its pathophysiology. Damage to the alveolar epithelium is thought to be a key event in the increased permeability of the alveolar-capillary membrane in ARDS.[31] In the lung, epithelial cells are normally more resistant than endothelial cells to the injurious effects of circulating endotoxin,[32] and epithelial disruption may, therefore, be conceptualized as an important event in the development of alveolar flooding. The importance of the alveolar epithelium once ARDS has occurred is also clear: type II pneumocytes must differentiate into type I cells to help cover the denuded epithelial surface, whereas both type I and II cells express the Na^+,K^+-ATPase, which is thought to be important in clearance of edema fluid (discussed in some detail later). In addition, injury to type II pneumocytes affects the production and metabolism of surfactant. How the damage to the alveolar-capillary membrane occurs is not known for certain, although neutrophils are suspected to play a role (see later).

Surfactant

Surfactant is a complex mixture of phospholipids and surfactant proteins that reduces alveolar surface tension. Many researchers have described alterations to surfactant lipids and proteins in patients with ARDS. The surfactant of patients with ARDS contains decreased amounts of surfactant-related proteins and decreased dipalmitoyl-

phosphatidylcholine and phosphatidylglyercol. The proportion of large (active) to small (inactive) aggregates of surfactant is diminished due to both decreased production of surfactant and increased conversion of the large to small forms. In addition, plasma proteins that have leaked through the alveolar-capillary barrier may interfere with surfactant function.[33] For example, reduced concentrations of surfactant protein A have been found in patients with ARDS.[34] The impairment in surfactant function observed in ARDS would predispose alveolar units to collapse. In addition, surfactant proteins have been found to have antimicrobial properties,[35,36] but whether the loss of these properties is relevant to the pathogenesis of ARDS is not known. Indeed, despite the abnormalities in surfactant that have been described,[37] the extent to which these alterations contribute to the pathogenesis of ARDS remains controversial. Unlike the *neonatal* respiratory distress syndrome, in which a deficiency of surfactant underlies the pathophysiology of the disease, it is possible that the abnormalities of surfactant in ARDS are the result rather than the cause of altered physiology. Indeed, five large randomized, controlled trials of exogenous surfactant supplementation in ARDS failed to show any improvement in mortality or requirement for mechanical ventilation[33,37a] (see "Therapy" section). Only one trial, using calfactant (a natural surfactant, distinct from previous trials) in pediatric patients with ARDS, has shown any benefit.[38] Whether this is due to the unique surfactant used in this study or to differences between the patients enrolled in this trial and those in the negative trials is not clear.

Neutrophils and Other Inflammatory Mediators

Histologically, one of the hallmarks of ALI/ARDS is the accumulation of neutrophils in the microvasculature of the lung.[39] As key cells in innate immunity, neutrophils generate an array of cytotoxic compounds. These include reactive oxygen species, cationic peptides, eicosanoids, and proteolytic enzymes such as leukocyte elastase. In addition, once activated, neutrophils release growth factors and cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β) that enhance inflammatory responses. Given this destructive potential, it has long been theorized that neutrophils may be central to the pathogenesis of ALI[40] (Fig. 90-2), and an abundance of clinical and preclinical data supports this hypothesis. For example, in humans with ARDS following sepsis, bronchoalveolar lavage neutrophilia is associated with a poor prognosis.[41] Neutrophil-depleted mice exposed to hyperoxia develop less lung injury than normal mice.[42] Similarly, in a hamster model of ALI induced by endotoxin inhalation, the administration of a specific inhibitor of neutrophil elastase (NE; even hours after administration of endotoxin) prevented the development of lung injury.[43]

If neutrophils are involved in the pathogenesis of ARDS, some defect in their regulation also might be involved. For example, in an uncomplicated bacterial pneumonia, the pulmonary inflammatory response is limited by counter-regulatory processes that prevent tissue damage. Why this regulation is ineffective or insufficient in ARDS is an unanswered question.[44]

One of the earliest manifestations of ARDS, even before hypoxemia, is a transient leukopenia due to sequestration of neutrophils in the lung microvasculature.[45] On average, the pulmonary capillaries are smaller than neutrophils, so that neutrophils must deform in order to pass through the microvasculature. Activated neutrophils "stiffen" and cannot negotiate narrow capillary segments.[46] Inhibitors of actin polymerization can abrogate this stiffening, implicating a change in the actin cytoskeleton in neutrophil sequestration in the lung.[47] Durable neutrophil sequestration is thought to involve interactions between molecules on the surface of the neutrophil and the lung capillary endothelium. For example, in rabbits, blocking the adhesion molecule L-selectin on the surface of the neutrophil prevented neutrophil sequestration in alveolar capillaries induced by exposure to endotoxin.[48]

After the initial sequestration, neutrophils must translocate (diapedesis) across the alveolar-capillary barrier to enter the alveolar space. The determinants of this seemingly simple movement remain incompletely understood. Integrins on the surface of the neutrophil are thought to mediate emigration of neutrophils from the pulmonary circulation in response to some, but not all, inflammatory stimuli.[49] Proteases secreted by the alveolar epithelium, in concert with regional cytokine production and glycosaminoglycans on the epithelial surface, may act together to form chemotactic gradients that neutrophils follow.[50]

Many studies have focused on the mechanisms of neutrophil activation. Recent work has investigated the interaction between platelets and neutrophils and how mutual activation may contribute to ALI or sepsis.[51] Others have investigated various components of intracellular signal transduction pathways, such as kinases (enzymes that phosphorylate substrates) and transcription factors. For example, one such kinase is the p38 mitogen-activated protein (MAP) kinase, which is activated when cells are stimulated with lipopolysaccharide (LPS).[52] Activation of this kinase stimulates TNF-α production and the release of macrophage inflammatory protein-2 (MIP-2, a CXC chemokine that is a chemotactic factor for neutrophils).[53] Interestingly, inhibition of p38 MAP kinase in mice, even hours after the mice are exposed to aerosolized LPS, attenuates neutrophil chemotaxis and migration from the lung microvasculature into alveoli.[54] Another kinase often discussed in the context of inflammation is phosphatidylinositol 3-kinase (PI3K). This enzyme phosphorylates phosphatidylinositol, a lipid-derived second messenger whose phosphorylated forms have been implicated in many intracellular signaling events. PI3K-γ is preferentially activated in neutrophils exposed to IL-8 or fMLP (a homologue of bacterial-derived chemotactic peptides).[55] Despite exposure to intraperitoneal endotoxin, PI3K-γ knockout mice displayed decreased neutrophil accumulation, cytokine production, and lung injury as compared with control

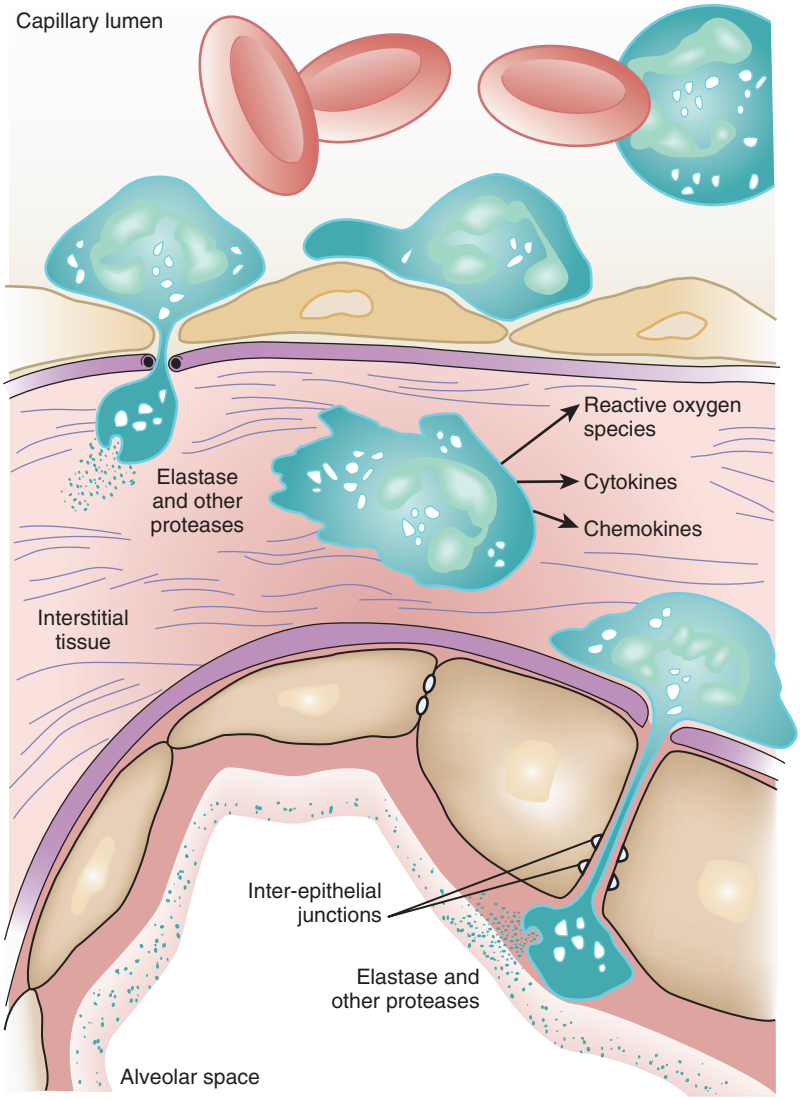

FIGURE 90-2 ■ Role of neutrophils in the pathogenesis of acute lung injury. Activated neutrophils exit the bloodstream and transmigrate across the alveolar-capillary membrane, releasing cytokines, proteases, reactive oxygen species, and other compounds. Although crucial to host defense against pathogens, the compounds secreted or released by the neutrophil have the capacity to damage the tissue of the host. (Adapted from Lee WL, Downey GP: Leukocyte elastase: Physiological functions and role in acute lung injury. A state of the art review. Am J Respir Crit Care Med 164:896–904, 2001.)

mice. The neutrophils in the lungs of the knockout mice also had diminished activation of nuclear factor-κB (NF-κB), an important transcription factor known to mediate the up-regulation of many cytokines and proinflammatory mediators.[56]

Many potential mechanisms might explain how activated neutrophils mediate ALI. In addition to secreting cytokines and growth factors that stimulate local and systemic inflammatory responses, neutrophils generate reactive oxygen species that mediate tissue damage.[57] In animal studies, inhibition of the assembly of nicotinamide adenine dinucleotide phosphate, reduced form (NADPH) oxidase (the major source of reactive oxygen species) by apocynin attenuates sepsis-induced lung injury.[58] The nitric oxide synthase (NOS) pathway has also been implicated in lung injury because knockout mice lacking the gene for inducible NOS developed less severe lung injury than wild-type animals when treated with LPS.[59]

Neutrophils contain proteolytic enzymes that can contribute to ALI. In particular, both NE and metalloproteinases have been extensively studied.[60] Because of its ability to degrade diverse substrates, including growth factors and cytokines, NE may be involved in regulation of inflammatory responses. NE also has been shown to degrade epithelial and endothelial cadherins, proteins that are major components of the adherens junctions that hold cells together. It is possible that elastase-mediated destruction of cadherin junctions between endothelial and/or epithelial cells could promote alveolar flooding.

Although NE might cause tissue damage, it is also important for effective antimicrobial defenses in the lungs. In NE-deficient mice, the administration of intraperitoneal *Klebsiella pneumoniae* caused 100% mortality within 48 hours, as compared with only 50% mortality in normal mice.[61] Interestingly, NE-deficient mice are paradoxically resistant to doses of LPS that are usually lethal. Furthermore, mice that lack both NE and another neutrophil protease (cathepsin G) are protected against alveolar damage induced by endotoxic shock.[62] These apparently contradictory results suggest that NE, although important in a regulated inflammatory response, may nonetheless participate in inflammatory injury in

some situations. Many studies in different species of animals using different experimental models suggest that NE has an important role in the pathogenesis of ALI in animals. Whether it is also important in the development of ALI or ARDS in humans remains unanswered. A clinical trial of a leukocyte elastase inhibitor in ARDS was halted when preliminary analysis suggested lack of efficacy.[63]

Other studies have indicated the importance of metalloproteinases in leukocyte-mediated lung injury. Elevated concentrations of the matrix metalloproteinases gelatinase A and B have been found in the epithelial lining fluid of patients with ARDS.[64] Mice lacking the genes for gelatinase B or stromelysin 1 had less severe injury in an animal model of ALI.[65] Matrilysin (matrix metalloproteinase-7) has been shown to regulate the formation of chemotactic gradients and the transmigration of neutrophils across the alveolar epithelium in a mouse model of ALI.[50] The administration of an inhibitor of elastase and metalloproteinases (chemically modified tetracycline-3) attenuated ALI after cardiopulmonary bypass in pigs.[66]

Despite the emphasis on neutrophils in the causal pathway for ALI, it is important to note that ARDS has been described in patients with profound neutropenia.[67,68] Indeed, it is possible that the neutrophil infiltration observed in some cases of ALI/ARDS is adaptive (i.e., a physiologic response to a primary injury) rather than destructive. At present, however, we believe that the balance of the evidence implicates neutrophils as causative in the development of most cases of ALI. Comparatively little is known about the mechanisms of neutrophil-independent ALI, which should be a major goal of future investigations.

Inflammation and Coagulation

One of the most common precipitants for ARDS is sepsis, and effective therapies for sepsis have the potential to either prevent the onset or improve the outcome of ALI. The current concept of sepsis is of an initial inflammatory state, with up-regulation of inflammatory cytokines such as TNF-α and IL-1β and recruitment and activation of inflammatory cells such as neutrophils, monocyte/macrophages, and lymphocytes. This early stage of inflammation is followed by relatively depressed innate immunity, in which the patient is vulnerable to nosocomial infections.[69] The theory that dysregulation of the inflammatory response is responsible for sepsis has led to a search for agents that would selectively block components of inflammatory pathways. More recent evidence has identified important connections between the molecular cascades that regulate both inflammation and coagulation. For example, TNF-α causes an increase in thrombin and fibrin formation, whereas fibrin fragments themselves are known to attract neutrophils.[70] TNF-α increases tissue factor expression on endothelial cells and inhibits fibrinolysis, both of which favor fibrin formation. Activated protein C (APC), an endogenous anticoagulant, has direct and indirect anti-inflammatory effects, which include decreasing circulating concentrations of IL-6 and attenuating neutrophil activation in sepsis.[71,72] Because sepsis is the most common cause of ARDS and because abnormalities of coagulation are very common in sepsis, investigators have wondered whether altered coagulation is involved in the pathogenesis of ARDS. How this might occur is largely speculative, but intra-alveolar, interstitial, and intravascular fibrin deposition have all been observed in patients with ARDS. Indeed, fibrin is a major component of hyaline membranes. Intra-alveolar fibrin has been postulated to serve as a nidus for fibroblast proliferation and potentially, as ALI resolves, as a stimulus for pulmonary fibrosis. Fibrin might also contribute to ongoing lung injury through its chemotactic properties, and intravascular fibrin deposition, causing intravascular microthrombi, might contribute to the elevated pulmonary vascular pressures observed in ARDS.

Interest in the role of coagulation in the pathogenesis of ARDS has been buttressed in part by observations in animal studies that anticoagulation can attenuate the severity of sepsis-induced lung injury.[73] In addition, a randomized, controlled trial of APC in humans with sepsis showed a significant reduction in mortality.[74] However, a small randomized, controlled trial of APC in patients at risk for ALI was stopped prematurely owing to lack of efficacy.[75]

Other molecular determinants of inflammation continue to be identified. Recent data have implicated transforming growth factor-β (TGF-β) in an animal model of ALI.[76] In one study, TGF-β was postulated to cause increased alveolar epithelial cell permeability by depleting intracellular glutathione levels.[77] Other investigators have attempted to improve the endogenous counterinflammatory response. In one study, the gene for heat shock protein 70 (HSP70) was attached to an adenoviral promoter, and the resultant recombinant construct was instilled into the lungs of rats in which lung injury had been induced by cecal ligation and perforation. Administration of the HSP70 construct increased HSP70 expression specifically in the lungs, and remarkably, this increased expression was associated with a significant reduction in pulmonary edema and inflammation and mortality.[78] Indeed, mice deficient in HSP70 showed increased mortality and lung injury after cecal ligation and perforation.[79] The mechanisms underlying this protective effect of HSP70 are not clear, but may involve suppression of the activity of the proinflammatory transcription factor NF-κB.

Na^+ and Water

Na^+ channels at the apical surface of alveolar epithelial cells mediate intracellular Na^+ uptake from the alveoli. This creates an osmotic gradient, which causes alveolar fluid to follow, thereby allowing for the clearance of pulmonary edema. The Na^+,K^+-ATPases in the basolateral membrane of the epithelial cell exchange intracellular Na^+ for extracellular K^+, maintaining the intracellular sodium concentration low enough for the apical Na^+ reabsorption to continue. This process allows for the net removal of Na^+ and water from the alveolar space and

can be accelerated by catecholamines in experimental preparations.

Dysfunction of either the apical Na^+ channels or the basolateral Na^+,K^+-ATPases (or both) have been postulated to be involved in the pathogenesis of ARDS. For example, it is known that hypoxia decreases epithelial Na^+ reabsorption by impairing the expression of subunits of the epithelial Na^+ channel.[80] Hypoxia also decreases the activity of both the apical Na^+ channel[81] and the Na^+,K^+-ATPase.[82] In an animal model of ALI induced by hemorrhagic shock, the normal upregulation of alveolar fluid reabsorption in response to catecholamines was absent. This defect was attributed to an increase in nitric oxide (NO) in the lung, with a possible effect on β-adrenergic receptor signaling.[83] In a retrospective study of patients with ALI, alveolar fluid clearance was measured. When patients were stratified by their rate of fluid clearance, those with the highest rates had the lowest mortality and the shortest duration of mechanical ventilation.[84] In a model of ventilator-induced lung injury (VILI) in rats, overexpression of the Na^+,K^+-ATPase improved the clearance of lung liquid.[85] Whether alveolar fluid clearance can be manipulated in a clinical setting (e.g., by β-adrenergic agonists) to improve prognosis is the subject of ongoing clinical trials.[86]

Angiopoietins

Angiopoietins are peptides involved in embryonic vascular development. Of the four angiopoietins which have been identified, angiopoietin 1 and angiopoietin 2 (Ang-1 and Ang-2, respectively) are the best studied. Ang-1 is expressed by many cell types whereas Ang-2 is expressed primarily by endothelial cells. Both act on the Tie-2 receptor tyrosine kinase, which is found predominantly on endothelial cells and hematopoietic stem cells.[87] A number of observations have generated interest in the potential role of these proteins in the pathophysiology of ARDS. First, elevated levels of Ang-2 have been found in patients with sepsis and ARDS, and treatment of mice with Ang-2 causes pulmonary vascular leak.[88,89] The effect of Ang-2 in disrupting endothelial cell integrity could be reversed in vitro by Ang-1. Second, overexpression of Ang-1 was protective against both endotoxin-induced shock and ALI in mice.[90] Although the cellular mechanism of these effects is the subject of intense investigation,[91,92] the data to date emphasize the important role for endothelial cells in the development of and recovery from ARDS.

Ventilator-Induced Lung Injury

Although mechanical ventilation for ARDS is often lifesaving, there is abundant preclinical and clinical evidence that it can also be harmful.[93] Whereas it was quickly recognized that excessive airway pressure could lead to *barotrauma* (Fig. 90-3), including pneumothorax, pneumomediastinum, and subcutaneous emphysema, attention has since turned to subtler but more common manifestations of lung injury related to mechanical ventilation. Mechanical ventilation can induce pulmonary edema by causing increases in both epithelial and endothelial permeability.[93] Indeed, investigators noted in 1991 that mechanical ventilation could produce a form of increased-permeability pulmonary edema remarkably similar to ARDS.[94] Now, the accumulated evidence suggests that inappropriate mechanical ventilation strategies may aggravate if not induce ARDS in some patients.[95]

FIGURE 90-3 ■ Barotrauma as a consequence of acute respiratory distress syndrome. Note the presence of a pneumothorax, pneumomediastinum, pneumoperitoneum, and subcutaneous air in this patient receiving positive-pressure ventilation. (Courtesy of Dr. Thomas E. Stewart.)

A major mechanism causing VILI is overdistention of lung units, whereas the absolute airway pressure appears to be less important. Normal rats ventilated with high airway pressure due to a high tidal volume (VT) developed increased permeability, whereas rats ventilated with smaller VTs, but with the same end-inspiratory pressure (obtained by strapping the chest walls of the rats) did not develop increased permeability.[96] Rats were also ventilated with low airway pressure using negative inspiratory pressure (applied at the chest wall) and high VTs. The rats ventilated with high VTs had significantly more edema. In particular, the negative (low)-pressure and high-VT group had the worst edema. These important observations, confirmed in other species,[97] led to the appreciation that a large VT, rather than high airway pressure per se, is an important determinant of ventilator-induced pulmonary edema. The term *volutrauma* was created to recognize this fact.

The repetitive opening and closing of terminal lung units during mechanical ventilation is also detrimental. This injury has been called *atelectrauma*,[98] and the

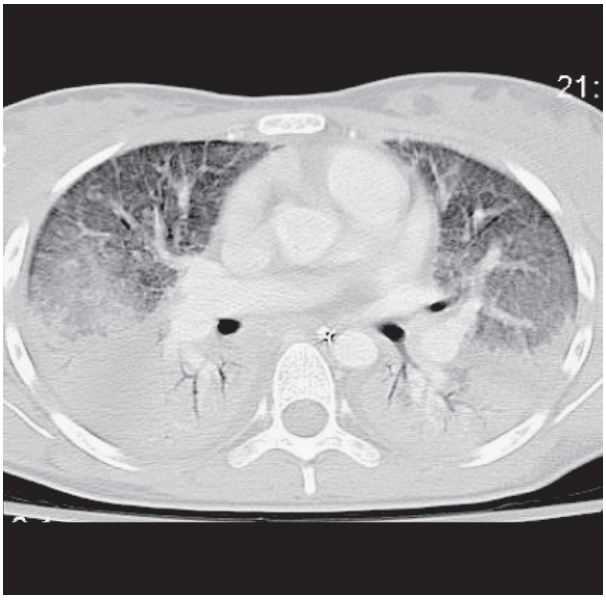

FIGURE 90-4 ■ Section from a computed tomography scan of the chest in a patient with acute respiratory distress syndrome. Note the presence of dense consolidation with air bronchograms in the dependent dorsal lung, with relative sparing of the ventral lung. (Courtesy of Dr. Thomas E. Stewart.)

mechanism is thought to be the high shear stresses generated at the interface of collapsed and aerated tissue when a collapsed airway is reopened.[99] Theoretically, PEEP would be helpful in minimizing this injury by keeping the lung recruited and promoting greater lung homogeneity by maintaining open distal airway and alveolar units.

Patients with ARDS may be especially vulnerable to VILI because of the heterogeneous nature of the pulmonary parenchymal injury. On computed tomography (CT) scans of the lungs, normal-appearing lung and densely consolidated injured lung are both present; consequently, there are marked regional differences in lung compliance[100] (Fig. 90-4). A VT designed to inflate an entire lung would preferentially inflate the normal-appearing areas, leading to overdistention and volutrauma. Similarly, patients with ARDS may be more vulnerable to atelectrauma. Although some evidence suggests that normal lungs can tolerate short periods of cyclic opening and closing of airways during mechanical ventilation,[101] injured lungs would be exposed to much higher shear stresses, which would be expected to be very injurious.[102]

Since the late 1990s, there has been a growing appreciation that VILI not only is a mechanical injury but also reflects an underlying complex cellular and molecular response. The term *biotrauma* has been coined to emphasize this change in thinking.[103] One of the most significant advances made in our understanding of VILI is that mechanical ventilation per se can induce both local and systemic inflammatory responses. In animal studies, it has been shown that ventilation with either zero PEEP or high VTs increases the concentration of inflammatory cytokines in lung lavage fluid. Lungs ventilated with *both* high VTs and zero PEEP had a synergistic elevation in cytokine levels.[104] This inflammatory response to an injurious ventilation strategy also has been shown to extend beyond the lung. In an acid aspiration rat model of lung injury, a ventilatory strategy using high VTs and zero PEEP was associated with an increase in blood levels of various cytokines. This was not observed either in groups ventilated with a small VT or in a group ventilated with the large VT but higher PEEP levels.[105]

Similar observations have been made in patients with ARDS. In one study, patients were randomized to "lung-protective" ventilation, in which the VT was set to avoid overdistention and PEEP was set above the lower inflection point of the pressure-volume curve.[106] Patients in the control group were treated with a strategy that would have been considered conventional ventilation at the time. Whereas bronchoalveolar lavage and plasma cytokine concentrations declined in the lung-protective group, they rose significantly in the control group. Post hoc analyses revealed significantly more ventilator-free days in the lung-protective group than did controls and significant correlations between the development of multisystem organ failure and plasma cytokines. The effect of the ventilator strategy on the development of biotrauma can be remarkably rapid. Stuber and coworkers[107] found an increase in a number of proinflammatory cytokines in the lungs and plasma of patients with ARDS within 1 hour after switching the patients from a protective to a nonprotective ventilatory strategy.

Patients with ARDS often die of the systemic inflammatory response syndrome (SIRS) and multiorgan dysfunction, rather than respiratory failure. Hence, the observation that mechanical ventilation can influence pulmonary and systemic cytokine concentrations is intriguing. Taken together, these findings suggest that mechanical ventilation has the potential not only to injure the lungs but also to cause loss of compartmentalization of the pulmonary inflammatory response. Systemic dissemination of the lung inflammatory response could be associated with the development of SIRS and multisystem organ failure (Fig. 90-5).[108] One study has shown that injurious mechanical ventilation in rabbits causes not only elevated plasma and lung cytokine concentrations but also increased renal epithelial cell apoptosis and renal dysfunction.[109]

Finally, patients with ARDS often require very high F_{IO_2}. The toxic effects of hyperoxia on the lung have been well described,[110] and the histologic appearance mirrors that of human ARDS. Oxygen toxicity is thought to be mediated by the formation of both reactive oxygen and nitrogen species, which damage tissues by a number of different mechanisms,[57] and hyperoxia appears to worsen VILI.[111] Antioxidants have been considered as a potential therapeutic strategy for preventing and treating ARDS, although clinical trials have so far been disappointing (see the section on "Therapy").

Genetic Determinants

To date, little is known about which genes might affect the development or prognosis of ARDS. A small

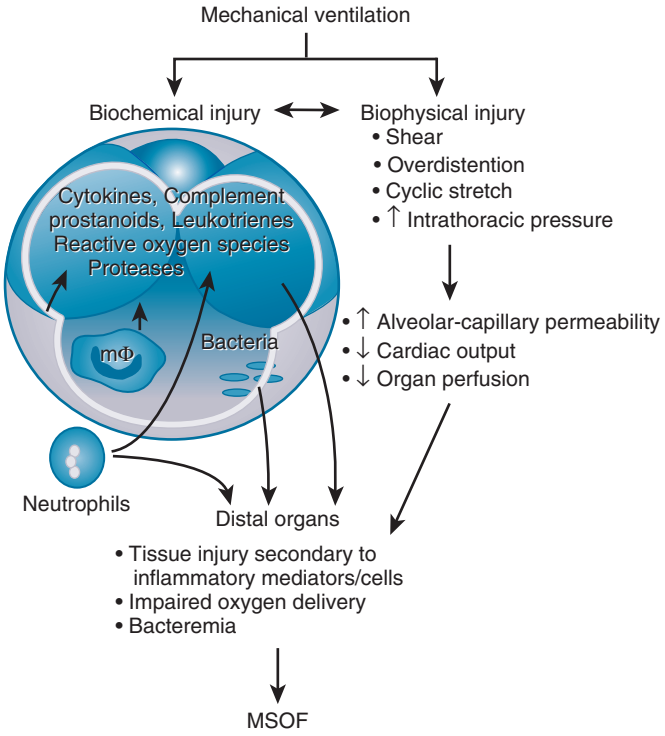

FIGURE 90-5 ■ Potential mechanisms by which mechanical ventilation might cause or contribute to multisystem organ failure (MSOF). mΦ, macrophage. (Redrawn from Slutsky AS, Tremblay LN: Multiple system organ failure: Is mechanical ventilation a contributing factor? Am J Respir Crit Care Med 157:1721–1725, 1998.)

pilot study has reported an association between a polymorphism in the gene for surfactant protein B[112] and ARDS, whereas a larger study described an association between a polymorphism in the angiotensin-converting enzyme[113] and both the incidence and the outcome of ARDS. Subsequent studies have reported conflicting results.[114,115] The heterogeneity of patients with ARDS makes it difficult to identify clinically important genetic associations, except in clearly defined subsets of patients.

MORTALITY AND COMPLICATIONS

Mortality

The mortality rate for ARDS has fallen since the syndrome was first described, with a number of studies describing a decline in the rate from over 60% to about 40% since 1993.[116–118] The reasons for this improvement in survival are not known, although some have attributed it to better supportive care in the intensive care unit and the use of smaller VTs.

Predictors of Poor Prognosis

Despite the prominence of hypoxemia among the clinical manifestations of ARDS, early trials did not find that the severity of hypoxemia early in the course of the illness was a good predictor of subsequent mortality.[119] Pulmonary injury scoring systems like the LIS and the ARDS score have been shown to predict a prolonged (>2 wk) requirement for intubation and ventilation,[120] whereas scoring systems that measure the overall severity of illness, such as the Simplified Acute Physiology Score (SAPS), correlate better with survival.[121] The classic finding is that patients with ARDS do not usually die of refractory hypoxemia, which is paradoxical because hypoxemia is frequently the focus of initial resuscitative efforts. In fact, most patients with fatal ARDS die of sepsis and multiorgan failure.[122,123] The explanation for this apparent paradox is unknown, although it has been hypothesized that injurious mechanical ventilation during the course of ARDS might be involved.[108] As discussed earlier, ventilation using excessive VTs has been shown to cause elevations in pulmonary and systemic cytokine levels and has more recently been linked in an animal model to apoptosis of renal cells and renal dysfunction.[109]

Data from several studies have suggested that the mortality rate from ARDS varies depending on the precipitating factor. The highest risk of death has consistently been reported to occur in sepsis, whereas ARDS following major trauma has a much better prognosis.[124] In addition, it is known that chronic liver disease,[119] older age,[125] chronic alcoholism,[23] and nonpulmonary organ dysfunction[119] are associated with higher mortality from ARDS. Other predictors of death from ARDS have included a history of organ transplantation and human immunodeficiency virus (HIV) infection,[126] whereas another study found higher mortality in men and African Americans than in non–African Americans.[127]

As mentioned earlier, risk factors for ARDS have been classified as being pulmonary or nonpulmonary in origin. Whether this distinction has prognostic importance is still unclear. In one prospective cohort study of patients with ARDS, investigators found a trend toward higher mortality in patients with a pulmonary cause, although the difference was not statistically significant.[128] In contrast, the ARDS Network investigators retrospectively analyzed the data from their large randomized study of low-VT ventilation versus traditional VT ventilation. Although confirming that the mortality rate for ARDS was highest in patients with sepsis and lowest in patients with trauma, there was no difference in mortality, days off the mechanical ventilator, or the development of organ failure between patients with pulmonary and those with nonpulmonary risk factors. In addition, there was no statistically significant evidence that the low-VT strategy was less efficacious in any subgroup.[124] A meta-analysis came to a similar conclusion.[27]

Because hypoxemia is not a reliable predictor of mortality from ARDS, investigators have searched for other lung-specific markers of prognosis. In one prospective study of 179 patients with ARDS, a multiple logistic regression was performed to identify which clinical and physiologic variables predicted mortality.[129] The analysis found that the dead-space fraction (as calculated by the Bohr equation) was elevated in ARDS and was an inde-

pendent predictor of mortality. For every increase of 0.05 in the dead-space fraction, the odds of death from ARDS increased by 45%. The mechanism responsible for this association is not known: it is possible that the extent of pulmonary vascular injury in ARDS may be greater than previously suspected and may account for the increase in dead space.

The development of pulmonary fibrosis is also thought to carry a worse prognosis. Elevated procollagen III levels, which is a marker of collagen synthesis, have been found in the pulmonary edema fluid of patients with ARDS and have been shown to correlate with increased mortality.[130,131] In another study, 22 of 25 consecutive patients with ARDS underwent transbronchial biopsies of the most abnormally appearing areas on the chest radiographs. The mortality rate of patients whose biopsies showed fibrosis, regardless of severity, was significantly higher than the mortality rate of patients whose biopsies showed no fibrosis.[132]

Complications

ARDS is complicated by ventilator-associated pneumonia (VAP) in about 30% to 65% of cases. In this setting, VAP usually occurs more than 5 to 7 days after the onset of mechanical ventilation and is often preceded by colonization of the lower respiratory tract by potential pathogens.[133] The likely organisms include nonfermenting gram-negative rods, methicillin-resistant *Staphylococcus aureus*, and *Enterobacteriaceae*.[134] Although the development of VAP prolongs the duration of mechanical ventilation in ARDS, it does not appear to result in increased mortality.[133,135,136] Making a definitive diagnosis of VAP in patients with ARDS can be challenging because patients with ARDS have bilateral radiographic infiltrates and typically have leukocytosis and fever. If diagnostic techniques such as bronchoalveolar lavage or protected specimen brushes are used, the yield is higher when the lung is sampled bilaterally and when the patient is not receiving antibiotics.[136,137]

Barotrauma is another major complication of ARDS (pneumothorax, pneumomediastinum, subcutaneous emphysema), which occurs because of the effect of positive-pressure ventilation in heterogeneous lung regions with reduced compliance. Because most patients with ARDS are treated in the supine position (rather than erect), diagnosing a pneumothorax requires vigilance. The radiographic appearance of a pneumothorax is different and can be more subtle in the supine patient (e.g., air in the costophrenic angle, the "deep sulcus" sign). Data from a number of prospective studies suggest that the incidence of barotrauma in ARDS is 10% or less.[95,138,139]

THERAPY

Supportive Care

One of the first goals of therapy in ARDS is to treat the underlying cause. In particular, patients with sepsis may respond to aggressive source control, including antibiotics and, when possible, surgical débridement and drainage. In patients with ARDS and sepsis of unknown origin, both the lung and the abdomen should be considered and excluded as foci of infection.[122,123] Additional goals are the prevention of complications and the provision of supportive care (e.g., nutrition, ventilation) to allow the body time to heal. Typically, such treatment should include prophylaxis against gastrointestinal stress ulceration and deep venous thrombosis.

Hemodynamic Management

The optimal approach to hemodynamic management in ARDS has become less controversial. Until recently, it was not clear whether clinicians should try to treat pulmonary edema using diuresis at the risk of causing hypovolemia and renal dysfunction and inducing or aggravating shock.

This issue has been addressed by a large multicenter randomized, controlled trial from the ARDS Network, which consists of investigators at a number of different hospitals in the United States. The investigators randomized 1000 patients with ARDS to one of two strictly protocolized fluid strategies: using the administration of fluids, diuretics, or vasoactive agents, the two protocols targeted either a higher or a lower intravascular pressure for 7 days, as measured by a PA or central venous catheter. Patients randomized to the conservative fluid strategy (targeting a lower intravascular pressure) had significant improvements in oxygenation and more ventilator-free and intensive care unit–free days than the patients in the liberal strategy. Importantly, patients in the conservative arm did not have a higher incidence of dialysis or shock than those in the liberal arm. In addition, the mortality rates in the two arms were similar. Thus, the results of this study suggest that conservative administration of fluids after the initial 24 hours of resuscitation is safe and beneficial for patients with ARDS.

Superficially, this recommendation may seem at odds with the principle of early goal-directed therapy, whereby patients with sepsis are aggressively resuscitated with fluid in accordance with the randomized, controlled trial reported by Rivers and associates.[140] In that study, which did not specifically enroll patients with ARDS or consider ARDS as an outcome, patients with severe sepsis or septic shock who arrived in the emergency department were randomized to 6 to 8 hours of goal-directed therapy versus standard therapy before admission to the intensive care unit. Goal-directed therapy involved protocolized administration of crystalloid, red blood cells, and vasoactive and inotropic agents to achieve a central venous pressure of 8 to 12 mm Hg, a mean arterial pressure of 65 to 90 mm Hg, a central venous oxygen saturation of 70% or higher, and a hematocrit of 30% or higher. In the first 6 hours of the study (but not subsequently), patients in the goal-directed group received significantly more blood and crystalloid than patients in the control group. In addition, more patients in the goal-directed

group received dobutamine. The study found that patients randomized to the goal-directed group had a significantly lower in-hospital mortality rate than those in the control arm. In addition, patients in the goal-directed group were significantly less likely to require mechanical ventilation than patients receiving standard therapy, although the incidence of ARDS was not reported.

The apparently disparate results of these clinical trials are not difficult to reconcile. First, it is important to note that patients in the ARDS Network study were enrolled an average of 24 hours after meeting the criteria for ALI, much later than the 6-hour window in the study by Rivers and associates. In addition, the study protocol of the ARDS Network trial was strictly designed to avoid aggravating or inciting shock or pulmonary edema. An additional caveat is that the ARDS Network study used a very complex algorithm for fluid administration that may not be widely adopted. A simplified protocol has recently been proposed but has not been validated.[141] At present, the best clinical trial evidence suggests that clinicians should manage fluids conservatively, taking care to avoid overdiuresis and hypovolemia.

PA catheters have been used widely in patients with pulmonary edema in order to help establish the diagnosis and guide therapy. However, numerous clinical trials have shown that for most patients, the information from a PA catheter does not improve outcome.[10] PA catheters are no longer recommended for routine monitoring in patients with ARDS.

Which fluid to use in patients with ARDS remains an open question. Starch-based colloids are no longer used in patients with severe sepsis because of evidence from a randomized clinical trial showing a higher incidence of renal failure in patients with severe sepsis who received 10% pentastarch as compared with patients randomized to receive Ringer's lactate.[142] Whether pentastarch has the same detrimental effect in patients with ARDS without severe sepsis is unknown. On a theoretical basis, the use of albumin is appealing because it could increase intravascular oncotic pressure and favor less pulmonary edema formation. A small placebo-controlled study in ARDS demonstrated that a regimen of albumin and furosemide infusions over 5 days caused a substantial and statistically significant improvement in oxygenation accompanied by a decrease in heart rate. However, most of the patients had ARDS following trauma, with fewer than 5% having sepsis. There were no differences in important clinical outcomes (e.g., mortality), although the study was not designed to address these issues.[143] A follow-up study established that the beneficial effect on oxygenation was due to the albumin, not the furosemide.[144] Although a large clinical trial of patients admitted to the intensive care unit has concluded that albumin was as safe as crystalloid,[145] the study did not specifically enroll patients with ARDS and evaluated only short-term outcomes. It is important to remember that as a blood product, the administration of albumin is associated with a small but measurable risk of transmissible diseases. Thus, the role of albumin in the management of patients with ARDS is unclear and the routine use of albumin is not recommended.

Nutrition

Manipulations in diet have been hypothesized to favorably affect the immune system and improve the outcome of inflammatory diseases such as sepsis and ARDS. Dietary strategies have included supplementing enteral feedings with one or more of arginine, glutamine, omega-3 fatty acids, and antioxidants.

One small randomized study examined the effect of a modified enteral feed containing eicosapentaenoic acid, gamma-linolenic acid, and various antioxidants compared with a control enteral feed in patients with ARDS.[146] The authors found that the modified feed improved oxygenation, reduced the number of neutrophils in alveolar lavage fluid, decreased length of stay, and decreased the requirement for mechanical ventilation. A more recent study also found improved oxygenation from modified enteral feeds (containing eicosapentaenoic acid, gamma-linolenic acid, and various antioxidants), although clinically important outcomes were unchanged.[147] Other studies of modified enteral feeds (often called "immunonutrition") have been conducted in less well defined populations of critically ill patients, with conflicting results. A meta-analysis on the topic highlighted the heterogeneity of the studies and suggested that the effect of immunonutrition varied depending on the group of patients being studied.[148] At this point, the role of immunonutrition in the management of ARDS remains unclear.

Pharmacotherapy

Attempts to develop pharmacologic therapies for ARDS have been unsuccessful, with no pharmacotherapies that unequivocally reduce mortality from ARDS, despite randomized, controlled trials of many different therapeutic agents.[149] Despite the heterogeneity of the agents that have been evaluated, three generalizations can be observed:

1. Despite showing effectiveness in in vitro or in animal studies, most potential therapies have failed to reduce mortality or other important clinical outcomes in human clinical trials.
2. A number of agents improve oxygenation but do not affect mortality from ARDS.
3. Post hoc analyses of subsets of patients from a number of studies of various agents suggest benefit, but prospective data are lacking

Corticosteroids

Because of the presumed inflammatory pathophysiology underlying ARDS, a number of trials of high-dose corticosteroids have been performed. In some, the goal was the prevention of ARDS in patients at risk (e.g., with septic shock), whereas in others, steroids were given to patients with established ARDS. The initial regimens included methylprednisolone 30 mg/kg in divided doses

every 6 hours for 1 to 2 days. None of the trials using this treatment regimen showed any benefit from the use of steroids,[150,151] and one showed a higher incidence of infection in patients who were treated with corticosteroids.[152] More recently, the use of steroids has been evaluated later in the course of ARDS, during the fibroproliferative phase. Persistently elevated plasma cytokine concentrations have been shown to correlate with worsened survival from ARDS, prompting some to theorize that late ARDS (>7 days after onset) is characterized by persistent inflammation that might be responsive to treatment with steroids. A small study randomized 24 patients with late ARDS to 2 mg/kg of methylprednisolone (followed by a 32-day taper) or placebo. Patients in the steroid group had lower mortality, improved oxygenation, decreased organ dysfunction, and earlier extubation but also had a higher (but not statistically significant) rate of infection.[153] However, these data have been controversial because of the small sample size and the number of patients who crossed over to the alternate therapy.

A randomized, placebo-controlled trial of 180 patients with ARDS of at least 7 days' duration was subsequently performed by the ARDS Network.[154] Patients were randomized to either placebo or a single dose of 2 mg/kg of methylprednisolone followed by 0.5 mg/kg every 6 hours for 14 days, then every 12 hours for 7 days, then tapering. Although the patients randomized to methylprednisolone had improvements in ventilator-free and shock-free days (during the first 28 days) as well as in oxygenation, there was no difference in the overall 60-day mortality. A subgroup analysis revealed that patients who were treated with steroids beginning more than 14 days after the onset of ARDS had a significantly increased 60- and 180-day mortality rate. The issue of whether to use steroids in late ARDS remains controversial.[155]

Vasodilators

Prostaglandin E_1 (PGE_1) is a vasodilator that has been studied as a potential therapy for ARDS, based largely on its anti-inflammatory properties. In vitro and preclinical studies in animals suggested that PGE_1 given parenterally, especially when administered in a liposome, had the potential to decrease neutrophil activation. Despite promising early data,[156] a large randomized, double-blind, multicenter trial of liposomal PGE_1 found that there was no improvement in survival or in ventilator dependence, even though the drug improved oxygenation.[157]

Prostacyclin (prostaglandin I_2 [PGI_2]) is another vasodilator that when administered by nebulizer, acts on the pulmonary vasculature. Because the aerosolized solution will distribute in the better-ventilated areas of the lung, vasodilation of the branches of the PA that supply these areas will lead to improved ventilation-perfusion matching and improved oxygenation. Although PGI_2 has been used as rescue therapy for refractory hypoxemia and is well tolerated,[158] there are no large randomized studies and no placebo-controlled studies of its use in ARDS.[159,160]

NO is a highly reactive gas formed endogenously by NOS from the amino acid arginine. It stimulates cellular guanylate cyclase, leading to increased cyclic guanosine monophosphate levels. NO acts as a potent vasodilator, and when administered by inhalation, NO causes vasodilation of the pulmonary circulation. NO is rapidly inactivated in the bloodstream by combining with hemoglobin to form methemoglobin, which is usually rapidly metabolized and does not accumulate to levels that are thought to be toxic (i.e., methemoglobin < 5%). Because of this rapid inactivation, inhaled NO is a selective vasodilator in the pulmonary circulation that does not affect the systemic circulation. Like aerosolized PGI_2, NO causes the most vasodilation in the areas of lung that are best ventilated, thereby improving ventilation-perfusion matching.[161] In addition, NO has both anti- and pro-inflammatory properties, although the contributions of these properties to its effects in a clinical setting are unclear.[162] NO also reacts with oxygen and water to form toxic metabolites, such as NO_2 and nitrous and nitric acid, although at concentrations of NO of less than 40 parts per million (ppm), this problem is not usually clinically significant. A soda lime absorber can be placed in the inspiratory limb of the NO circuit in order to remove any NO_2 before the inspired gas reaches the patient.

In a large randomized, double-blind, placebo-controlled study of NO in ARDS, over 170 patients were randomized to different doses of NO (ranging from 1.25 to 80 ppm) or placebo. Although approximately 60% of the patients had a significant improvement in oxygenation within 4 hours of NO administration, there were no differences between the groups in survival or in weaning from mechanical ventilation.[163] In addition, the initial improvement in oxygenation from NO was not sustained over the course of study. There were few adverse effects of NO, and for patients who were treated with less than 40 ppm inhaled NO, the methemoglobin and NO_2 levels were the same as in the placebo group. The results of this study confirmed the findings of other smaller unblinded trials of NO in ARDS,[164,165] and were repeated in a more recent systematic review.[166] In another large randomized but unblinded study of NO in ARDS, a higher proportion of patients in the NO group required renal replacement therapy than in the control group.[167] A recent meta-analysis of trials using NO for ARDS concluded that although NO caused initial improvement in oxygenation, it had no effect on survival and was associated with an increased risk of renal dysfunction.[168] Therefore, NO should not be used routinely in the treatment of patients with ARDS, other than as a "rescue" therapy for life-threatening hypoxemia, despite the lack of evidence for an improvement in survival.

Surfactant

A number of surfactant abnormalities have been described in ARDS (see section on "Etiology and Pathogenesis"). These include an increase in relatively inactive forms, inactivation of surfactant by plasma proteins that

have leaked into the alveolar space, damage to type II epithelial cells (which produce surfactant lipids and proteins), and destruction of surfactant constituents by the inflammatory process.[37] These changes, along with the efficacy of surfactant supplementation in the neonatal respiratory distress syndrome, led to clinical trials of surfactant supplementation in patients with ARDS. Data from animal studies and small case series were promising.[169] In a small randomized trial, patients with ARDS were treated with bovine surfactant administered through an endotracheal catheter. One subgroup of patients showed an improvement in oxygenation and a trend to decreased mortality.[170]

Enthusiasm for surfactant was dampened by the results of a large multicenter randomized, blinded, placebo-controlled trial. In this study, investigators administered an aerosolized synthetic (protein-free) surfactant or saline placebo continuously for up to 5 days to patients with new-onset (<48 hr) ARDS associated with sepsis. There was no physiologic or clinical benefit from the surfactant. Despite its methodologic rigor, the study has been criticized because less than 5% of the administered dose of surfactant was thought to have reached the distal lung. In addition, the lack of surfactant proteins in the synthetic surfactant may have diminished its ability to reduce surface tension.[171] Because of these issues, the role of surfactant supplementation continues to be studied.

In a phase I-II trial, 40 patients with new-onset ARDS were randomized to a surfactant protein C preparation (given up to four times over 24 hr) or to no drug. The surfactant was administered through a catheter placed in the endotracheal tube. The drug had no effect on oxygenation or on ventilator-free days, which were the primary outcomes of the study. The authors reported a significant decrease in IL-6 levels in bronchoalveolar lavage fluid from patients who received the surfactant preparation, although it is unclear whether this was a prespecified end point.[172]

Two phase III trials of the recombinant surfactant protein C–based preparation have been completed. The studies demonstrated that the surfactant improved oxygenation but had no effect on mortality or ventilator-free days. Only one trial, using calfactant (a natural surfactant, distinct from previous trials) in pediatric patients with ARDS, has shown any mortality benefit.[38] Whether this was due to the unique surfactant used in this study or to differences between the patients enrolled in this trial and the negative trials (e.g., adult vs. pediatric) is unknown. Whether surfactant will prove to be useful in well-defined subgroups of patients with ARDS remains an open question.[33,37a]

Antioxidants and Anti-inflammatory Agents Other than Steroids

Oxidative stress is thought to be involved in the pathogenesis of ARDS.[57] In fact, lung injury due to hyperoxia is a commonly used model to study ARDS in animals. Reactive oxygen species form as a by-product of the activation of neutrophils and macrophages; in addition, the requirement for a high F_{IO_2} in many patients with ARDS is likely to predispose to oxidative stress in the lungs. Decreased levels of glutathione, a major endogenous scavenger of reactive oxygen species, have been found in the alveolar fluid of patients with ARDS, including those who have a history of excessive alcohol use. Small clinical trials with *N*-acetylcysteine and procysteine were promising.[173] However, larger clinical trials of antioxidants in ARDS have been disappointing. A multicenter trial of the antioxidant procysteine in ARDS showed no beneficial effect of the drug.[39]

Various agents with potential anti-inflammatory effects have been tested in ARDS. These include ketoconazole, lisofylline, and (in patients with sepsis at risk for ARDS) the nonsteroidal anti-inflammatory drug ibuprofen. In separate, well-conducted, randomized, blinded, controlled trials, none of these agents showed a benefit in patients with ARDS.[174–176] A prospective randomized, controlled trial tested the effect of recombinant platelet-activating factor acetylhydrolase on preventing ARDS in patients with severe sepsis. This trial of over 100 patients showed no reduction in the development of ARDS in patients who received the drug; however, the mortality rate was lower in patients treated with an intermediate dose of the study drug.[177] Other trials of potential anti-inflammatory therapies in sepsis have been disappointing.[69]

Novel Therapies

As discussed earlier in the section on "Etiology and Pathogenesis," alveolar fluid clearance can be augmented by catecholamines. A small trial randomized 40 patients with ALI/ARDS to intravenous salbutamol or placebo for 7 days.[86] Patients receiving salbutamol had a decrease in extravascular lung water but a higher incidence of arrhythmias. A new clinical trial of aerosolized albuterol for ALI/ARDS is being performed by the ARDS Network.[141]

Stem cell therapy for ARDS is being actively explored. Experimental studies have shown beneficial effects in animals treated with endotracheal or intravenous hematopoietic stem cells[178] as well as hematopoietic stem cells transfected with Ang-1.[179]

Discrepancies between Studies in Animals and Humans

Virtually all large-scale clinical trials of pharmacotherapy in patients with ARDS have been negative, despite often promising preclinical studies in animal models of lung injury. There are a number of reasons why positive results in animal studies have not been replicated in human clinical trials. First, in animal studies, the agent being investigated is often administered at the same time or shortly after the lungs are injured (e.g., cecal ligation and perforation followed by administration of the drug within a few hours). In contrast, the onset of lung injury in humans is often much more difficult to define, and experimental therapies are often given hours or days after the diagnosis is made. Thus, agents that might have been effective at preventing or attenuating ARDS may

have be given too late. Second, most "proof of principle" animal studies are of relatively short duration and do not mimic the complicated clinical course of human ARDS. Third, animals in most studies represent a homogeneous group; in contrast, human patients have multiple comorbidities and often have multiple cointerventions. Fourth, the underlying precipitating factor for ARDS, even in carefully selected subgroups of patients, often differs in severity and duration among the study patients, unlike the situation in animals, in which a uniform injury is applied. This heterogeneity makes it challenging to identify agents that may be of only modest clinical benefit. Finally, the current definition of ARDS is imprecise, and as a result, clinical studies might include many patients with different pathophysiology or biology.

Mechanical Ventilation

Introduction

Mechanical ventilation is lifesaving and is the standard therapy for ARDS. Ventilatory management of ARDS has undergone a dramatic change since the early 1990s, in large part due to increased usage of computed tomography (CT) to image the lungs and to advances in our understanding of VILI.

Pressure and Volume Limitation

Mechanical ventilation of patients under anesthesia for surgery traditionally involves large VTs of 10 to 15 mL/kg, with the dual goals of achieving normal arterial oxygenation and arterial pH. A similar approach to ventilating patients with ARDS was followed in the past. This emphasis on achieving normal physiologic parameters in patients with ARDS was understandable at the time: in addition to being characterized by profound hypoxemia and diminished pulmonary compliance, ARDS was thought to involve the lungs diffusely and homogeneously based on chest radiography.[1] A large VT, therefore, appeared to be the best approach to ventilate patients and maintain oxygenation. Subsequently, studies using CT[180] demonstrated that the lungs of many patients with ARDS appear heterogeneous: instead of the diffuse involvement suggested by plain chest radiographs, CT scans often show patchy infiltrates, interspersed with more normal-appearing areas of lung (see Fig. 90-4). The heterogeneous distribution of the injury in ARDS implies that the VT administered to a patient will preferentially inflate the more compliant (or normal) areas of lung. These regions of the lung, exposed to VTs meant for an entire lung, are therefore at risk for overdistention and VILI. As discussed earlier, mechanical ventilation with excessive VTs can cause pulmonary edema due to increased alveolar-capillary permeability, remarkably similar histologically to ARDS.

Despite the clear physiologic rationale and abundant experimental data to support pressure and volume limitation when ventilating patients with ARDS, it was not until the late 1990s that data from randomized clinical trials in humans began to accrue. Between 1998 and 2000, five randomized controlled trials of ventilation strategies in ARDS were published.[95,139,181–183] In all of the trials, patients were randomized either to a strategy involving some degree of VT and pressure limitation or to a "conventional" ventilation strategy with higher VT and pressure limits. Of the five studies, the largest was conducted by the ARDS Network, composed of investigators from hospitals in the United States and supported by the U.S. National Institutes of Health NIH National Heart, Lung, and Blood Institute.[95] This study, which was more than seven times larger than any of the other four studies, randomized 861 patients to lower VTs or traditional VTs. In the traditional group, plateau pressure was also kept below 50 cm H_2O. In the small-volume group, VT was set at 6 mL/kg of predicted body weight and reduced if necessary to maintain plateau pressure between 25 and 30 cm H_2O. Respiratory acidosis was treated aggressively, with the ventilator rate being set at 6 to 35 breaths/min to achieve a pH of 7.3 to 7.45. Bicarbonate infusions were allowed for acidosis that persisted despite a ventilator rate of 35/min. VT was increased for refractory acidemia, until pH was higher than 7.15. Only preset combinations of PEEP and F_{IO_2} were allowed in the two groups, for a target oxygen saturation of 88% to 95%. Patient-ventilator dyssynchrony was reduced by sedating patients when necessary (Table 90-3).

The trial, which originally set out to enroll 1000 patients, was stopped early because an interim analysis showed benefit in the small-VT group. The mortality rate was 39.8% in the traditional group compared with 31.0% in the small-VT group (P = .007). Breathing without assistance at day 28 was also significantly more frequent

TABLE 90-3. Ventilation Protocol Used in the Acute Respiratory Distress Syndrome Network Study

Parameter	Protocol
Mode of ventilation	Volume assist-control
Tidal volume	≤6 mL/kg predicted body weight*
Plateau pressure	≤30 cm H_2O
Frequency	6–35 breaths/min, titrated for pH 7.30–7.45
I:E ratio	1:1 to 1:3
Oxygenation goal	Pa_{O_2} 55–80 mm Hg, or Sp_{O_2} 88%–95%
F_{IO_2}/PEEP (cm H_2O) combinations allowed	0.3/5, 0.4/5, 0.4/8, 0.5/8, 0.5/10, 0.6/10, 0.7/10, 0.7/12, 0.7/14, 0.8/14, 0.9/14, 0.9/16, 0.9/18, 1.0/18, 1.0/20, 1.0/22, 1.0/2
Weaning	By pressure support, required when F_{IO_2}/PEEP ≤ 0.4/8

*See text for formula to calculate predicted body weight.
F_{IO_2}, fractional concentration of oxygen in inspired gas; I:E ratio, ratio of inspired to expired gas; Pa_{O_2}, arterial oxygen pressure; PEEP, positive end-expiratory pressure; Sp_{O_2}, pulse oximetry.
Data from Anonymous: Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network (comment). N Engl J Med 342:1301–1308, 2000.

in the small-volume group, and the number of ventilator-free days was higher. The number of days without organ failure was also higher in the small-volume arm.

The other study to show a survival benefit was much smaller, involving just over 50 patients.[183] In this study, unlike the ARDS Network study, static inspiratory pressure-volume curves of the total respiratory system were determined in all patients after their condition was stabilized, but before randomization. Patients were randomized to either conventional ventilation or a "protective" ventilation strategy. Conventional ventilation consisted of VTs of 12 mL/kg and PEEP was set according to an algorithm to optimize oxygenation with a F_{IO_2} of 0.6 or lower. There was no stated limit to airway pressures in the control group. Protective ventilation included a VT of 6 mL/kg or lower and peak pressures of less than 40 cm H_2O. Driving pressures (plateau pressure, PEEP) were kept at less than 20 cm H_2O. PEEP was set at 2 cm H_2O above the lower inflection point of the pressure-volume curve (as measured prior to randomization), and the protective ventilation group also underwent "frequent" recruitment maneuvers, in which continuous positive airway pressure of 35 to 40 cm H_2O was applied for 40 seconds. In the protective group, pressure-controlled inverse-ratio ventilation was used if the F_{IO_2} exceeded 0.5.

The study was stopped early because a significant survival difference was detected: 38 % of the protective-ventilation group had died at 28 days compared with 71% in the conventional group ($P < .001$). There was no significant difference in survival to hospital discharge between the two arms, although there was a very strong trend in favor of the protective group. The rate of barotrauma was also significantly different: 7% in the protective ventilation arm versus 42% in the conventional ventilation group.

Unfortunately, multiple confounding factors affect the interpretation of this small trial. Airway pressure was not limited in the control arm, and mean plateau pressure exceeded 35 cm H_2O in those patients. Although the study showed an impressive 33% absolute reduction in 28-day mortality, the mortality rate in the traditional ventilation group was 71%, much higher than in all of the other trials. In addition, the population studied was substantially younger than patients in other trials, with a mean age of about 35 (compared with 50–60 years in the other studies). Finally, the rate of barotrauma in the traditional group, 42%, was approximately four times higher than in other trials.

A key factor in comparing trials is to appreciate that the ARDS Network study used predicted body weight, whereas other studies used ideal body weight or measured body weight. The distinction is worth emphasizing because data from the ARDS Network study showed that measured body weight was approximately 20% higher than predicted body weight. In other words, the VT used in other studies may have been higher than appreciated based on predicted body weight. Predicted body weight in kilograms can be calculated for male patients as 50 + 0.91(height [in cm] − 152.4), and for female patients as 45.5 + 0.91(height [in cm] − 152.4).[95]

The ARDS Network study adopted an aggressive approach to hypercarbia and acidemia, including tachypnea, bicarbonate infusions, and loosening of ventilatory restrictions. As a result, hypercarbia and subsequent low pH in the treatment arm was less marked than in other studies. This too may have contributed to the lower mortality in the lower-VT arm.

Some investigators have proposed that mechanical ventilation in a particular patient should be based on the static inspiratory pressure-volume curve of the patient's respiratory system.[183] In ARDS, such curves often have a sigmoidal shape, with a lower inflection point at low lung volumes and an upper inflection point at high volumes. Initially, it was thought that the lower inflection point represented the pressure at which collapsed lung units reexpand, explaining the abrupt change in compliance. The upper inflection point was felt to represent the pressure at which alveolar overdistention occurs. On this basis, it was proposed that PEEP should be set higher than the pressure of the lower inflection point, and plateau pressure should be kept lower than the upper inflection point. Although conceptually appealing, this interpretation of the static inspiratory pressure-volume curve is likely to be erroneous. Recruitment of the lung is known to continue even above the lower inflection point,[184] and tidal ventilation in patients with ARDS may take place on the expiratory (rather than the inspiratory) limb of the pressure-volume curve.[185] Because of this, setting ventilatory parameters based on the static inspiratory pressure-volume curve remains controversial.[186]

The Role of Positive End-Expiratory Pressure and Recruitment Maneuvers

The first description of ARDS commented on the utility of PEEP in improving oxygenation. From a theoretical standpoint, PEEP may be beneficial in avoiding damage from cyclic opening and closing of terminal lung units (atelectrauma, see "Etiology and Pathogenesis" section) and in allowing for a reduction in VT (and hence volutrauma). In addition, the improvement in oxygenation that often occurs with PEEP may allow for lowering of the F_{IO_2}, decreasing the risk of oxygen toxicity. Conversely, PEEP that is too high can cause excessive end-inspiratory lung volume and volutrauma. PEEP also has the potential to depress cardiac output and blood pressure by raising mean intrathoracic pressures. The optimal level of PEEP to use in patients with ARDS has, therefore, been a source of controversy.[187–189]

Along the same lines, the low VTs and pressures advocated for lung-protective ventilation can lead to progressive derecruitment of the lungs, which can worsen hypoxemia and aggravate atelectrauma. To counteract derecruitment, the use of recruitment maneuvers has been proposed. These maneuvers involve increasing the airway pressure for a defined period of time, although the pressure to be applied and the duration of its application have not been standardized. An example of a recruitment maneuver would be to apply 40 cm of H_2O of continuous positive airway pressure for 40 seconds.

Similar to the problems with setting the level of PEEP, however, it is difficult to predict which patients might benefit from recruitment maneuvers and which might be harmed by overdistension of the lungs. Overdistention of well-perfused lung units could result in diversion of blood to poorly perfused alveoli, with consequent worsening of right-to-left shunt and hypoxemia.[190]

Several randomized, controlled trials have addressed the issue of PEEP and recruitment maneuvers in the management of ARDS. The ARDS Network investigators randomized 549 patients with ALI/ARDS to lower or higher PEEP levels, according to preset combinations of PEEP and F_{IO_2}. The patients in the lower PEEP arm received the PEEP/F_{IO_2} levels used in the original ARDS Network trial of lung-protective ventilation (see earlier). The precise level of PEEP used in the higher arm varied with the F_{IO_2}, but was on average 5 cm of H_2O higher than the control arm (mean of 13–15 over the first 7 days). Recruitment maneuvers were initially used in the higher PEEP group but were discontinued after the first 80 patients because they were not very effective.[191] The study was stopped early due to perceived futility and the mortality rate in both arms was about 25%, significantly lower than had been reported in other trials of ARDS.[192]

A second large trial randomized almost 1000 patients with ALI/ARDS to what was described as an "open-lung" strategy versus the ventilation protocol used in the original ARDS Network trial.[193] The "open-lung" strategy consisted of pressure-control ventilation, recruitment maneuvers, and high PEEP (Pplat < 40) in addition to the low V_Ts used in the control group. On average, on day 1 of the study, PEEP in the open-lung arm was 16 cm H_2O, compared with 10 cm H_2O in the control group. This trial also found no difference in the mortality rates between the two groups (~40%), although the open-lung group had improvements in secondary end points related to hypoxemia.

Finally, a large French trial randomized 767 patients with ALI to PEEP of 5 to 9 cm H_2O or PEEP maximized as long as Pplat was less than 28 to 30.[194] On day 1 of the study, the mean applied PEEP level in the control arm was about 7 cm H_2O, or marginally lower than that of patients in the original ARDS Network trial of lung-protective ventilation, whereas the higher PEEP arm had an average applied PEEP of 15 cm H_2O. The study demonstrated no difference in mortality, but the higher PEEP arm had improved compliance, oxygenation, and a decreased duration of mechanical ventilation and organ failure.[194]

Taken together, the data from these trials suggest that higher levels of PEEP than used in the original ARDS Network trial are safe and improve oxygenation but they do not appear to change mortality. Why these clinical studies are generally negative despite very strong animal data showing the benefits of higher levels of PEEP is puzzling. One possibility is the yin-yang of PEEP. When PEEP recruits lung units, it may be beneficial; but when PEEP leads to greater overdistention of lung units, it may be harmful. In all studies to date, PEEP has been applied to all patients whether or not their lungs are recruitable. As such, one reasonable approach to be tested in future studies of PEEP is to randomize only patients to a high/low PEEP strategy if they have lung regions that are potentially recruitable.[189,195]

The data also suggest that the role of recruitment maneuvers in the management of ARDS is primarily supportive, in that they are unlikely to improve clinically important outcomes. Many studies report a variable and transient improvement in oxygenation after some form of recruitment maneuver,[191] although it is possible that the same degree of recruitment could be achieved by simply raising the level of PEEP.[196,197] Although recruitment maneuvers are generally safe, the patient must be closely monitored for any adverse effects on hemodynamics or oxygenation.

Permissive Hypercapnia and Tracheal Gas Insufflation

The use of lower V_Ts (to avoid VILI) often results in respiratory acidemia, an effect that has been termed "permissive hypercapnia." The theoretical detrimental effects of hypercapnia include myocardial depression, increased pulmonary vascular resistance, and decreased renal blood flow. Perhaps the most clinically important adverse effect of hypercapnia is elevated intracranial pressure from increased cerebral blood flow. However, there are data suggesting that hypercapnia has protective effects, including attenuation of free radical–mediated lung injury and pulmonary inflammation[198,199]; other studies have reported an injurious effect on alveolar epithelial cells.[200] Given the uncertainty about permissive hypercapnia, it is worth remembering that the only large randomized, controlled trial to show a reduction in mortality in ARDS treated respiratory acidosis aggressively. In the absence of other data, following the protocol used in that study seems prudent.

One approach that has been used to decrease high levels of arterial carbon dioxide pressure (P_{aCO_2}) is tracheal gas insufflation (TGI). TGI is a technique whereby a gas flow is introduced via a small catheter placed in the endotracheal tube, with its tip near the carina. TGI has been proposed as an adjunct to permissive hypercapnia, as the insufflated gas improves CO_2 clearance from the anatomic dead space and ventilator tubing. However, the gas flow has the potential to increase alveolar volume and pressure and may increase PEEP.[201] Although many case reports describe the use of TGI,[202] there have been no randomized studies of TGI in patients with ARDS. Because of technical and monitoring issues related to TGI, routine use of TGI in ARDS is not recommended.

Mechanical Ventilation of Patients in the Prone Position (Proning)

Placing patients with ARDS in the prone position was described almost 30 years ago as a means of improving oxygenation. The mechanisms by which this improvement occurs are multiple, but the most important factor is probably the effect that the prone position has on chest wall and lung compliance.[203] In the supine posi-

tion, the most dorsal and caudal regions of lung (along the spine and diaphragm) are the worst affected in many patients with ARDS. Some of this is due to gravity, but the weight of the heart and of the abdominal organs on the lungs also contributes. When a patient is placed in the prone position, the anterior chest wall is fixed (by the bed) and becomes less compliant, thus increasing the proportion of ventilation directed to the dorsal lung. In addition, the volume of lung that is being compressed by the heart due to gravity is substantially decreased. The net result is more homogenous ventilation of the lungs and improved ventilation-perfusion matching. Data from a study in dogs suggest that ventilation in the prone position can attenuate the severity of VILI.[204]

A number of multicenter randomized, controlled trials have now examined the efficacy of ventilating patients with ARDS in the prone position. One study enrolled over 300 patients with ALI or ARDS and randomized them to conventional treatment (supine) or treatment in the prone position for 6 or more hours for 10 days. The study found that oxygenation improved in approximately 70% of prone treatment procedures and that most of the improvement was evident within 1 hour of placing patients in the prone position. However, although oxygenation improved significantly each time the patients were placed in the prone position, there was no difference in mortality between the groups. Retrospective analyses of the quartile of patients with the poorest oxygenation or the highest acuity of illness (or the highest VT) showed a lower mortality rate at 10 days in the patients who had been treated in the prone position, but this difference did not persist beyond discharge from the intensive care unit.[205] The study has been criticized for the relative short duration of the intervention and the fact that most patients spent the majority of the day supine.[206]

A subsequent study randomized over 700 patients with acute hypoxemic respiratory failure to ventilation in the prone or supine position; patients were placed in the prone position an average of 50 hours after intubation for a median of 8 hr/day for a median of 4 days.[207] Patients who were treated in the prone position had improved oxygenation but no improvement in mortality or the duration of mechanical ventilation. These patients also suffered from a higher incidence of complications, including pressure sores, selective intubation, and obstruction of the endotracheal tube. A study of prone positioning in pediatric patients with lung injury (median age 2 yr) was similarly negative,[208] and two recent Spanish trials of prone treatment for adults with ARDS were inconclusive, but suggestive of benefit.[209,210]

Prone ventilation should not be used routinely in all patients with ARDS. It is a reasonable salvage maneuver for a patient at imminent risk of death from hypoxemia, because multiple studies have demonstrated that it can increase oxygenation. A more difficult question is how to manage patients who have severe ($PaO_2/FiO_2 < 100$), but not life-threatening, hypoxemia. Evidence from 4 trials[205,207,209,210a] (admittedly post hoc and each statistically insignificant) suggests a reduction in mortality in such patients.[210b] This, along with a biologically plausible mechanism-less oxygen toxicity attributable to lower FiO_2 during prone positioning, which is likely to be more important at higher FiO_2 levels (i.e., in patients with severe hypoxemia), suggests that prone ventilation is a reasonable treatment option for these patients. However, given the potential complications of proning, it should ideally be performed only in centers that have expertise with this modality.

Volume-Control versus Pressure-Control Ventilation

The volume- and pressure-limited protocol in the ARDS Network study used volume-assist control as the mode of ventilation. The Lung Open Ventilation study showed that pressure-control ventilation could be used with equivalent outcomes.[193] Other studies that have examined this issue have also found little difference in physiologic parameters or outcome between the two modes of ventilation.[211,212]

High-Frequency Jet Ventilation and High-Frequency Oscillation

In high-frequency jet ventilation (HFJV), a small-gauge catheter is used to introduce gas under high pressure into the endotracheal tube. The high velocity of the gas entrains additional oxygen and humidified air from side ports in the system. This form of mechanical ventilation achieves a VT of 2 to 5 mL/kg and involves frequencies of 100 to 200 breaths/min.[213] Exhalation is passive, requiring recoil of the lungs and chest wall. There is little evidence that HFJV is superior to conventional mechanical ventilation for ARDS. A randomized trial of over 300 oncology patients compared conventional ventilation (using volume-cycled ventilation) to HFJV. The end points of the study were physiologic and differed between the two groups of patients, making it difficult to interpret the data. Nonetheless, the authors found no significant difference in any clinically important outcome.[214]

In high-frequency oscillation (HFO), lung recruitment is maintained using a constant mean airway pressure, generated by an inspiratory bias flow and limitation of gas outflow from the circuit. Ventilation is achieved through rapid (e.g., 5 Hz) regular oscillations of a piston or diaphragm. The push-and-pull action of the piston causes oscillations in pressure in the endotracheal tube and proximal airways, creating peak and trough pressures around the set mean airway pressure. The VTs achieved through HFO are small, on the order of 1 to 5 mL/kg. In theory, HFO seems ideally suited for avoiding VILI; atelectrauma is minimized because of the relatively high mean airway pressure, which along with small VTs, limits derecruitment of the lung, and volutrauma is minimized because the small VTs limit end-inspiratory stretch.[215] Recruitment maneuvers (e.g., application of continuous positive airway pressure for ~30–40 sec) should be applied after each time the patient is disconnected from the ventilator (e.g., open suctioning), because loss of pressure from the circuit during

disconnection will lead to portions of the lung becoming atelectatic (derecruited).

In the first of two randomized trials of HFO in adults, 148 patients with ARDS were randomized to conventional ventilation using the pressure-control mode or to HFO.[216] The specific ventilatory parameters for both the conventional group and the HFO group were adjusted to achieve adequate oxygenation at a minimum F_{IO_2} (i.e., 88% at $F_{IO_2} \leq 0.60$) as well as an arterial pH > 7.15. As the study was begun before the publication of the ARDS Network trial on V_T limitation, the conventional ventilation arm of this study targeted V_Ts of 6 to 10 mL/kg. The trial was not powered to detect a mortality difference, and there was no significant difference in 30- or 90-day mortality or in any other outcome. The authors performed a retrospective analysis of predictors of mortality and discovered that being on conventional ventilation for more than 5 days correlated with a poor outcome.

A smaller study enrolled patients with ARDS an average of 2 days after intubation and randomized them to HFO versus ventilation using a conventional ventilator (V_T 8–9 mL/kg predicted body weight, peak inspiratory pressure < 40 cm H_2O). The study was stopped prematurely after enrolling only 37 patients and there was no difference in outcome between the two groups.[217]

In summary, although the physiologic rationale for using HFO in ARDS seems sound, the lack of data showing any clinically important advantage has limited its general acceptance.

Inverse-Ratio Ventilation

The normal ratio of inspiration to expiration (I:E) ranges from 1:2 to 1:4, varying with the respiratory rate. Inverse-ratio ventilation (IRV) refers to a mode of ventilation in which the duration of inspiration is extended to yield an I:E ratio greater than 1. Clinicians found that IRV could improve oxygenation (by decreasing right-to-left shunt) in ARDS while allowing lower peak inspiratory and end-expiratory airway pressures. However, the mechanism of the improvement in oxygenation is likely due to the increase in mean airway pressure due to the longer inspiratory time or as I:E is increased due to the generation of auto-PEEP because of the shortened time available for expiration. This latter mechanism would lead to an increase in end-expiratory alveolar volume. IRV causes an increase in mean airway pressure relative to conventional ventilation, even though peak airway pressure is lower. The same reduction in right-to-left shunt can be achieved using a normal I:E ratio by increasing the applied (extrinsic) PEEP alone. For the same reduction in shunt, the mean airway pressure is elevated more by IRV than by simply raising the PEEP. Because of concerns about volutrauma, the fact that IRV increases mean airway pressure (and hence mean alveolar volume) relative to extrinsic PEEP makes it less attractive. In addition, IRV is uncomfortable for patients and often requires the administration of sedatives and neuromuscular blocking agents. For these reasons, IRV is not usually used in the management of ARDS.[218]

Liquid Ventilation

Liquid ventilation relies on the oxygen- and carbon dioxide–carrying capacity of organic liquids such as perfluorocarbons. Perfluorocarbons are modified hydrocarbons in which hydrogen atoms are replaced with fluorine, generating inert liquids that are nontoxic and minimally absorbed through the respiratory epithelium. The most widely studied perfluorocarbon, perflubron (perfluorooctylbromide), can dissolve about 17 times more O_2 than saline solution and almost four times more CO_2.[219] Total liquid ventilation is a technique in which the lungs are completely filled with liquid and an extracorporeal exchanger is used to add O_2 and remove CO_2 from the liquid. Partial liquid ventilation, which is much easier to use clinically, involves partially filling the lungs with liquid and then using a traditional ventilator to deliver gas V_Ts.[220]

The theoretical benefits of liquid ventilation stem largely from improved lung recruitment, due to the lower surface tension of the perfluorocarbons and because the liquid tends to distribute to the dependent regions of the lung. Deposition of liquid with low surface tension in these areas may enhance alveolar recruitment. In addition, the weight of the liquid is thought to cause diversion of pulmonary blood flow to the nondependent (better-ventilated) areas, improving ventilation-perfusion matching. Clearance of secretions (due to their displacement by the liquid) is also improved. Anti-inflammatory effects of perflubron have been described, although the clinical relevance of these effects is not well understood.

Two randomized, controlled trials of partial liquid ventilation in adults with ARDS have been published.[221] The first randomized 90 patients with ARDS to partial liquid ventilation with perflubron or to conventional mechanical ventilation. Other than very general guidelines (such as target arterial oxygen saturation [Sa_{O_2}] > 90%), neither of the two ventilation strategies was protocolized. In addition, the inclusion and exclusion criteria were modified slightly during the course of the study. There was no significant difference in the number of ventilator-free days (the primary outcome measure) or in any other predefined outcome. More patients in the liquid ventilation arm experienced hypoxia, bradycardia, and respiratory acidosis, although the increase in the incidence of these adverse events was not statistically significant.

More recently, a multicenter randomized trial of partial liquid ventilation with perfluorocarbon compared with conventional mechanical ventilation (V_T 10 mL/kg) enrolled over 300 patients with ARDS.[222] The study found a trend toward higher mortality in the groups receiving perfluorocarbon, in addition to a higher incidence of barotrauma, hypoxia, and hypotension.[222] Based on these data, partial liquid ventilation cannot be recommended for patients with ARDS.

Extracorporeal Membrane Oxygenation

Extracorporeal membrane oxygenation (ECMO), also referred to as extracorporeal life support (ECLS) or

extracorporeal lung assist (ELA), refers to the process by which the patient's blood is circulated to an external machine that provides oxygenation and/or carbon dioxide removal.[223] In theory, ECMO could be used to oxygenate patients with ARDS while minimizing VILI and oxygen toxicity and allowing the lungs time to heal. There are many case reports of ECMO being used in ARDS,[223a] and it is used routinely in neonates with severe respiratory failure. A randomized, controlled trial of ECMO in ARDS was published in 1979 and did not show any benefit.[224] However, the mortality rate in that study was approximately 90% in both the ECMO and the control arms. Subsequently, a variant of ECMO dedicated to carbon dioxide removal (extracorporeal carbon dioxide removal, or $ECCO_2R$) was developed and showed promise in a case series when compared with a historical control group.[225] This was followed by a randomized, controlled trial using pressure-controlled IRV and $ECCO_2R$ in ARDS, but this trial failed to find any improvement in survival.[226] This study illustrates the importance of using concurrent controls when assessing a novel therapy.

Patients on ECMO have a high rate of bleeding; in the most recent randomized trial, patients randomized to the device were transfused an average of 1.7 L of blood/day. Because of its cost and the lack of evidence to support its use, ECMO is not recommended in the management of most patients with ARDS.

Summary

The modern approach to mechanical ventilation of patients with ARDS is based on two facts: first, the pathogenetic injury in ARDS affects the lungs heterogeneously; and second, that mechanical ventilation itself can cause ALI. Thus, until new data emerge, the lung-protective ventilatory strategy adopted by the ARDS Network[95] is the standard of care for patients with ARDS. Plateau pressure should be maintained lower than 30 cm H_2O, and V_T should be limited to 6 mL/kg predicted body weight as much as possible. Further study will be required to determine whether intermediate V_Ts (6 mL/kg < V_T < 10 mL/kg), which might be easier to implement, are as safe in ARDS.

The optimal level of PEEP in ARDS remains unclear, although randomized trials indicate that using higher PEEP levels than the original ARDS Network study is safe and may improve oxygenation. Higher levels of PEEP are useful in order to prevent atelectrauma, reduce F_{IO_2}, and prevent hyperoxic lung injury, as long as the patient's hemodynamic status is stable. The lowest possible F_{IO_2} should be used that maintains Sa_{O_2} above 90%, with an empirical target F_{IO_2} of less than 0.6. Although prone positioning of patients with ARDS may transiently improve oxygenation, it does not improve survival. Finally, despite the theoretical appeal of HFO, no survival benefit has yet been demonstrated.

LONG-TERM OUTCOMES

Despite the profound derangement in oxygenation and respiratory system compliance that is characteristic of ARDS, it is remarkable that patients who survive often have near-normal pulmonary function tests 6 to 12 months later. Lung volumes and flows are generally slightly reduced or normal at 6 to 12 months, whereas the diffusion capacity sometimes remains slightly reduced.[227,228] Follow-up chest radiographs are usually normal, with a minority showing subtle abnormalities including pleural thickening or small cysts.[228]

Despite this impressive physiologic and radiologic recovery, patients who survive ARDS continue to have important functional limitations and a decreased health-related quality of life for at least 2 years after their illness.[229] This reduction in quality of life seems attributable to ARDS or to its management or complications, because in one parallel cohort study, patients with ARDS were matched to patients with sepsis or trauma with an equivalent severity of illness. The ARDS survivors continued to report significant decrements in health-related quality of life, particularly as related to physical function and pulmonary symptoms.[230] This reduced quality of life (in areas reflecting physical function) has been correlated with the presence of persistent abnormalities in pulmonary function tests.[227] In other patients, a persistent reduction in functional capacity (as measured by a 6-minute walk test) has been ascribed to persistent muscle weakness and wasting.[228] A multivariate analysis in that study found that lack of systemic corticosteroid administration, absence of illness acquired in the intensive care unit, and rapid resolution of lung injury and multiorgan dysfunction were associated with better functional status after hospital discharge. Patients who ultimately survive an episode of ARDS do not appear to have an increased mortality compared with other intensive care unit survivors who were similarly ill.[231]

Psychological problems have been described in survivors of ARDS. In a retrospective case-control study, survivors of ARDS were found to have significantly more signs and symptoms of posttraumatic stress disorder (PTSD) than patients who had undergone maxillofacial (and presumably elective) surgery; they also had more signs and symptoms of PTSD than soldiers who had served for prolonged periods of time in Bosnia.[232] Persistent cognitive impairment has also been observed in survivors of ARDS for as long as 1 year after hospital discharge.[233] Most patients in that study had impairments in one or more parameters, including memory, concentration, attention, or mental processing speed. Interestingly, these abnormalities were correlated with the degree and duration of hypoxemia that the patients experienced.

KEY POINTS

- ARDS is a syndrome defined by acute hypoxemia, bilateral infiltrates on chest radiograph, and the absence of left atrial hypertension.
- ARDS has been associated with diseases that directly involve the lungs (e.g., pneumonia) and also with diseases that do not obviously involve the lungs (e.g., pancreatitis).
- The pathogenesis of ARDS is not clear, but increased permeability of the alveolar-capillary membrane due to neutrophilic infiltration of the lungs is thought to be an important factor.
- ARDS is a syndrome, not a specific diagnosis; clinicians must, therefore, look for the cause in order to institute specific therapy.
- The mortality rate for ARDS has fallen since the 1980s and is now about 40%.
- Mechanical ventilation is lifesaving but, when inappropriately applied, can induce or aggravate lung injury.
- Most deaths in patients with ARDS are from multiorgan failure rather than hypoxia per se.
- No pharmacologic therapies have been shown to improve survival in ARDS; thus, management consists of treating the underlying cause, lung-protective ventilation, conservative management of fluids, and excellent supportive care.
- Many survivors of ARDS suffer from a reduced quality of life and cognitive impairment.

References

1. Ashbaugh DG, Bigelow DB, Petty TL, Levine BE: Acute respiratory distress in adults. Lancet 2:319–323, 1967.
2. Murray JF, Matthay MA, Luce JM, Flick MR: An expanded definition of the adult respiratory distress syndrome. Am Rev Respir Dis 138:720–723, 1988 [published erratum appears in Am Rev Respir Dis 139:1065, 1989].
3. Bernard GR, Artigas A, Brigham KL, et al: The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med 149:818–824, 1994.
4. Rubenfeld GD, Caldwell E, Granton J, et al: Interobserver variability in applying a radiographic definition for ARDS (comment). Chest 116:1347–1353, 1999.
5. Meade MO, Cook RJ, Guyatt GH, et al: Interobserver variation in interpreting chest radiographs for the diagnosis of acute respiratory distress syndrome. Am J Respir Crit Care Med 161:85–90, 2000.
6. Villar J, Perez-Mendez L, Kacmarek RM: Current definitions of acute lung injury and the acute respiratory distress syndrome do not reflect their true severity and outcome (comment). Intensive Care Med 25:930–935, 1999.
7. Villar J, Perez-Mendez L, Lopez J, et al: An early PEEP/FIO_2 trial identifies different degrees of lung injury in patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 176:795–804, 2007.
8. Moss M, Goodman PL, Heinig M, et al: Establishing the relative accuracy of three new definitions of the adult respiratory distress syndrome (comment). Crit Care Med 23:1629–1637, 1995.
9. Meade MO, Guyatt GH, Cook RJ, et al: Agreement between alternative classifications of acute respiratory distress syndrome. Am J Respir Crit Care Med 163:490–493, 2001.
10. The National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network: Pulmonary-artery versus central venous catheter to guide treatment of acute lung injury. N Engl J Med 354:2213–2224, 2006.
11. Richard C, Warszawski J, Anguel N, et al: Early use of the pulmonary artery catheter and outcomes in patients with shock and acute respiratory distress syndrome: A randomized controlled trial. JAMA 290:2713–2720, 2003.
12. Ferguson ND, Meade MO, Hallett DC, Stewart TE: High values of the pulmonary artery wedge pressure in patients with acute lung injury and acute respiratory distress syndrome. Intensive Care Med 28:1073–1077, 2002.
13. Omland T: Advances in congestive heart failure management in the intensive care unit: B-type natriuretic peptides in evaluation of acute heart failure. Crit Care Med 36:S17–S27, 2008.
14. Karmpaliotis D, Kirtane AJ, Ruisi CP, et al: Diagnostic and prognostic utility of brain natriuretic peptide in subjects admitted to the ICU with hypoxic rspiratory failure due to noncardiogenic and cardiogenic pulmonary edema. Chest 131:964–971, 2007.
15. Levitt JE, Vinayak AG, Gehlbach BK, et al: Diagnostic utility of B-type natriuretic peptide in critically ill patients with pulmonary edema: A prospective cohort study. Crit Care 12:R3, 2008.
16. Anonymous: Conference report: Mechanisms of acute respiratory failure. Am Rev Respir Dis 115:1071–1078, 1977.
17. Villar J, Slutsky AS: The incidence of the adult respiratory distress syndrome. Am Rev Respir Dis 140:814–816, 1989.
18. Rubenfeld GD, Caldwell E, Peabody E, et al: Incidence and outcomes of acute lung injury. N Engl J Med 353:1685–1693, 2005.
19. Goss CH, Brower RG, Hudson LD, Rubenfeld GD, ARDS Network: Incidence of acute lung injury in the United States (comment). Crit Care Med 31:1607–1611, 2003.
20. Rubenfeld GD: Epidemiology of acute lung injury. Crit Care Med 31:S276–S284, 2003.
21. Pepe PE, Potkin RT, Reus DH, et al: Clinical predictors of the adult respiratory distress syndrome. Am J Surg 144:124–130, 1982.
22. Hudson LD, Milberg JA, Anardi D, Maunder RJ: Clinical risks for development of the acute respiratory distress syndrome. Am J Respir Crit Care Med 151:293–301, 1995.
23. Moss M, Bucher B, Moore FA, et al: The role of chronic alcohol abuse in the development of acute respiratory distress syndrome in adults. JAMA 275:50–54, 1996.
24. Moss M, Guidot DM, Steinberg KP, et al: Diabetic patients have a decreased incidence of acute respiratory distress syndrome (comment). Crit Care Med 28:2187–2192, 2000.
25. Garber BG, Hebert PC, Yelle JD, et al: Adult respiratory distress syndrome: A systemic overview of incidence and risk factors (comment). Crit Care Med 24:687–695, 1996.
26. Gattinoni L, Pelosi P, Suter PM, et al: Acute respiratory distress syndrome caused by pulmonary and extrapulmonary disease. Different syndromes? (comment). Am J Respir Crit Care Med 158:3–11, 1998.
27. Agarwal R, Srinivas R, Nath A, Jindal SK: Is the mortality higher in the pulmonary vs the extrapulmonary ARDS? A Meta-analysis. Chest 133:1463–1473, 2008.
28. Tomashefski JF Jr: Pulmonary pathology of the adult respiratory distress syndrome. Clin Chest Med 11:593–619, 1990.

29. Marshall RP, Bellingan G, Webb S, et al: Fibroproliferation occurs early in the acute respiratory distress syndrome and impacts on outcome. Am J Respir Crit Care Med 162:1783–1788, 2000.
30. Marshall R, Bellingan G, Laurent: The acute respiratory distress syndrome: Fibrosis in the fast lane. Thorax 53:815–817, 1998.
31. Matthay MA, Wiener-Kronish JP: Intact epithelial barrier function is critical for the resoluation of alveolar edema in humans. Am Rev Respir Dis 142:1250–1257, 1990.
32. Wiener-Kronish JP, Albertine KH, Matthay MA: Differential responses of the endothelial and epithelial barriers of the lung in sheep to *Escherichia coli* endotoxin. J Clin Invest 88:864–875, 1991.
33. Lewis JF, Brackenbury A: Role of exogenous surfactant in acute lung injury. Crit Care Med 31:S324–S328, 2003.
34. Baker CS, Evans TW, Randle BJ, Haslam PL: Damage to surfactant-specific protein in acute respiratory distress syndrome. Lancet 353:1232–1237, 1999.
35. Tino MJ, Wright JR: Surfactant protein A stimulates phagocytosis of specific pulmonary pathogens by alveolar macrophages. Am J Physiol 270:L677–L688, 1996.
36. Kuan SF, Rust K, Crouch E: Interactions of surfactant protein D with bacterial lipopolysaccharides. Surfactant protein D is an *Escherichia coli*–binding protein in bronchoalveolar lavage. J Clin Invest 90:97–106, 1992.
37. Lewis JF, Jobe AH: Surfactant and the adult respiratory distress syndrome. Am Rev Respir Dis 147:218–233, 1993 [published erratum appears in Am Rev Respir Dis 147:following 1068, 1993].

37a. Kesecioglu J, Beale R, Stewart TE, et al: Exogenous natural surfactant for treatment of acute lung injury and the acute respiratory distress syndrome. Am J Respir Crit Care Med 180:989–994, 2009.

38. Willson DF, Thomas NJ, Markovitz BP, et al: Effect of exogenous surfactant (calfactant) in pediatric acute lung injury: A randomized controlled trial. JAMA 293:470–476, 2005.
39. Ware LB, Matthay MA: The acute respiratory distress syndrome (comment). N Engl J Med 342:1334–1349, 2000.
40. Rinaldo JE: Mediation of ARDS by leukocytes. Clinical evidence and implications for therapy. Chest 89:590–593, 1986.
41. Steinberg KP, Milberg JA, Martin TR, et al: Evolution of bronchoalveolar cell populations in the adult respiratory distress syndrome. Am J Respir Crit Care Med 150:113–122, 1994.
42. Folz RJ, Abushamaa AM, Suliman HB: Extracellular superoxide dismutase in the airways of transgenic mice reduces inflammation and attenuates lung toxicity following hyperoxia. J Clin Invest 103:1055–1066, 1999.
43. Kawabata K, Hagio T, Matsumoto S, et al: Delayed neutrophil elastase inhibition prevents subsequent progression of acute lung injury induced by endotoxin inhalation in hamsters. Am J Respir Crit Care Med 161:2013–2018, 2000.
44. Lee WL, Downey GP: Neutrophil activation and acute lung injury. Curr Opin Crit Care 7:1–7, 2001.
45. Thommasen HV, Russell JA, Boyko WJ, Hogg JC: Transient leucopenia associated with adult respiratory distress syndrome. Lancet 1:809–812, 1984.
46. Worthen GS, Schwab B 3rd, Elson EL, Downey GP: Mechanics of stimulated neutrophils: cell stiffening induces retention in capillaries. Science 245:183–186, 1989.
47. Skoutelis AT, Kaleridis V, Athanassiou GM, et al: Neutrophil deformability in patients with sepsis, septic shock, and adult respiratory distress syndrome (comment). Crit Care Med 28:2355–2359, 2000.
48. Kuebler WM, Borges J, Sckell A, et al: Role of L-selectin in leukocyte sequestration in lung capillaries in a rabbit model of endotoxemia. Am J Respir Crit Care Med 161:36–43, 2000.
49. Doerschuk CM, Tasaka S, Wang Q: CD11/CD18-dependent and -independent neutrophil emigration in the lungs: How do neutrophils know which route to take? Am J Respir Cell Mol Biol 23:133–136, 2000.
50. Li Q, Park PW, Wilson CL, Parks WC: Matrilysin shedding of syndecan-1 regulates chemokine mobilization and transepithelial efflux of neutrophils in acute lung injury. Cell 111:635–646, 2002.
51. Zarbock A, Singbartl K, Ley K: Complete reversal of acid-induced acute lung injury by blocking of platelet-neutrophil aggregation. J Clin Invest 116:3211–3219, 2006.
52. Nick JA, Avdi NJ, Young SK, et al: Selective activation and functional significance of p38alpha mitogen-activated protein kinase in lipopolysaccharide-stimulated neutrophils. J Clin Invest 103:851–858, 1999.
53. Nick JA, Young SK, Brown KK, et al: Role of p38 mitogen-activated protein kinase in a murine model of pulmonary inflammation. J Immunol 164:2151–2159, 2000.
54. Nick JA, Young SK, Arndt PG, et al: Selective suppression of neutrophil accumulation in ongoing pulmonary inflammation by systemic inhibition of p38 mitogen-activated protein kinase. J Immunol 169:5260–5269, 2002.
55. Naccache PH, Levasseur S, Lachance G, et al: Stimulation of human neutrophils by chemotactic factors is associated with the activation of phosphatidylinositol 3-kinase gamma. J Biol Chem 275:23636–236341, 2000.
56. Yum HK, Arcaroli J, Kupfner J, et al: Involvement of phosphoinositide 3-kinases in neutrophil activation and the development of acute lung injury. J Immunol 167:6601–6608, 2001.
57. Fink MP: Role of reactive oxygen and nitrogen species in acute respiratory distress syndrome. Curr Opin Crit Care 8:6–11, 2002.
58. Wang W, Suzuki Y, Tanigaki T, et al: Effect of the NADPH oxidase inhibitor apocynin on septic lung injury in guinea pigs. Am J Respir Crit Care Med 150:1449–1452, 1994.
59. Kristof AS, Goldberg P, Laubach V, Hussain SN: Role of inducible nitric oxide synthase in endotoxin-induced acute lung injury. Am J Respir Crit Care Med 158:1883–1889, 1998.
60. Lee WL, Downey GP: Leukocyte elastase: Physiological functions and role in acute lung injury. Am J Respir Crit Care Med 164:896–904, 2001.
61. Belaaouaj A, McCarthy R, Baumann M, et al: Mice lacking neutrophil elastase reveal impaired host defense against gram negative bacterial sepsis. Nat Med 4:615–618, 1998.
62. Tkalcevic J, Novelli M, Phylactides M, et al: Impaired immunity and enhanced resistance to endotoxin in the absence of neutrophil elastase and cathepsin G. Immunity 12:201–210, 2000.
63. Zeiher BG, Artigas A, Vincent JL, et al: Neutrophil elastase inhibition in acute lung injury: Results of the STRIVE study. Crit Care Med 32:1695–1702, 2004.
64. Delclaux C, d'Ortho MP, Delacourt C, et al: Gelatinases in epithelial lining fluid of patients with adult respiratory distress syndrome. Am J Physiol 272:L442–L451, 1997.
65. Warner RL, Beltran L, Younkin EM, et al: Role of stromelysin 1 and gelatinase B in experimental acute lung injury. Am J Respir Cell Mol Biol 24:537–544, 2001.
66. Carney DE, Lutz CJ, Picone AL, et al: Matrix metalloproteinase inhibitor prevents acute lung injury after cardiopulmonary bypass (comment). Circulation 100:400–406, 1999.
67. Ognibene FP, Martin SE, Parker MM, et al: Adult respiratory distress syndrome in patients with severe neutropenia. N Engl J Med 315:547–551, 1986.
68. Vansteenkiste JF, Boogaerts MA: Adult respiratory distress syndrome in neutropenic leukemia patients. Blut 58:287–290, 1989.
69. Hotchkiss RS, Karl IE: The pathophysiology and treatment of sepsis (comment). N Engl J Med 348:138–150, 2003.
70. Laterre PF, Wittebole X, Dhainaut JF: Anticoagulant therapy in acute lung injury. Crit Care Med 31:S329–S336, 2003.
71. Marshall JC: Inflammation, coagulopathy, and the pathogenesis of multiple organ dysfunction syndrome. Crit Care Med 29:S99–S106, 2001.
72. Esmon CT: Protein C anticoagulant pathway and its role in controlling microvascular thrombosis and inflammation. Crit Care Med 29:S48–S51 2001 [discussion appears 51–52].
73. Welty-Wolf KE, Carraway MS, Miller DL, et al: Coagulation blockade prevents sepsis-induced respiratory and renal failure in baboons. Am J Respir Crit Care Med 164:1988–1996, 2001.
74. Bernard GR, Vincent JL, Laterre PF, et al: Efficacy and safety of recombinant human activated protein C for severe sepsis (comment). N Engl J Med 344:699–709, 2001.
75. Liu KD, Levitt J, Zhuo H, et al: Randomized clinical trial of activated protein C for the treatment of acute lung injury. Am J Respir Crit Care Med 178:618–623, 2008.

76. Wesselkamper SC, Case LM, Henning LN, et al: Gene expression changes during the development of acute lung injury: Role of transforming growth factor beta. Am J Respir Crit Care Med 172:1399–1411, 2005.
77. Pittet JF, Griffiths MJ, Geiser T, et al: TGF-beta is a critical mediator of acute lung injury. J Clin Invest 107:1537–1544, 2001.
78. Weiss YG, Maloyan A, Tazelaar J, et al: Adenoviral transfer of HSP-70 into pulmonary epithelium ameliorates experimental acute respiratory distress syndrome (comment). J Clin Invest 110:801–806, 2002.
79. Singleton KD, Wischmeyer PE: Effects of HSP70.1/3 gene knockout on acute respiratory distress syndrome and the inflammatory response following sepsis. Am J Physiol Lung Cell Mol Physiol 290:L956–L961, 2006.
80. Planes C, Blot-Chabaud M, Matthay MA, et al: Hypoxia and beta 2-agonists regulate cell surface expression of the epithelial sodium channel in native alveolar epithelial cells. J Biol Chem 277:47318–47324, 2002.
81. Mairbaurl H, Mayer K, Kim KJ, et al: Hypoxia decreases active Na transport across primary rat alveolar epithelial cell monolayers. Am J Physiol Lung Cell Mol Physiol 282:L659–L665, 2002.
82. Dada LA, Chandel NS, Ridge KM, et al: Hypoxia-induced endocytosis of Na,K-ATPase in alveolar epithelial cells is mediated by mitochondrial reactive oxygen species and PKC-zeta. J Clin Invest 111:1057–1064, 2003.
83. Pittet JF, Lu LN, Morris DG, et al: Reactive nitrogen species inhibit alveolar epithelial fluid transport after hemorrhagic shock in rats. J Immunol 166:6301–6310, 2001.
84. Ware LB, Matthay MA: Alveolar fluid clearance is impaired in the majority of patients with acute lung injury and the acute respiratory distress syndrome (comment). Am J Respir Crit Care Med 163:1376–1383, 2001.
85. Adir Y, Welch LC, Dumasius V, et al: Overexpression of the Na-K-ATPase alpha2-subunit improves lung liquid clearance during ventilation-induced lung injury. Am J Physiol Lung Cell Mol Physiol 294:L1233–L1237, 2008.
86. Perkins GD, McAuley DF, Thickett DR, Gao F: The beta-agonist lung injury trial (BALTI): A randomized placebo-controlled clinical trial. Am J Respir Crit Care Med 173:281–287, 2006.
87. Fiedler U, Augustin HG: Angiopoietins: a link between angiogenesis and inflammation. Trends Immunol 27:552–558, 2006.
88. Parikh SM, Mammoto T, Schultz A, et al: Excess circulating angiopoietin-2 may contribute to pulmonary vascular leak in sepsis in humans. PLoS Med 3:e46, 2006.
89. van der Heijden M, van Nieuw Amerongen GP, Koolwijk P, et al: Angiopoietin-2, permeability oedema, occurrence and severity of ALI/ARDS in septic and non-septic critically ill patients. Thorax 63:903–909, 2008.
90. Witzenbichler B, Westermann D, Knueppel S, et al: Protective role of angiopoietin-1 in endotoxic shock. Circulation 111:97–105, 2005.
91. Gavard J, Patel V, Gutkind JS: Angiopoietin-1 prevents VEGF-induced endothelial permeability by sequestering Src through mDia. Dev Cell 14:25–36, 2008.
92. Fiedler U, Reiss Y, Scharpfenecker M, et al: Angiopoietin-2 sensitizes endothelial cells to TNF-alpha and has a crucial role in the induction of inflammation. Nat Med 12:235–239, 2006.
93. Dreyfuss D, Saumon G: Ventilator-induced lung injury: Lessons from experimental studies. Am J Respir Crit Care Med 157:294–323, 1998.
94. Tsuno K, Miura K, Takeya M, et al: Histopathologic pulmonary changes from mechanical ventilation at high peak airway pressures. Am Rev Respir Dis 143:1115–1120, 1991.
95. Anonymous: Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network ([comment). N Engl J Med 342:1301–1308, 2000.
96. Dreyfuss D, Soler P, Basset G, Saumon G: High inflation pressure pulmonary edema. Respective effects of high airway pressure, high tidal volume, and positive end-expiratory pressure. Am Rev Respir Dis 137:1159–1164, 1988.
97. Hernandez LA, Peevy KJ, Moise AA, Parker JC: Chest wall restriction limits high airway pressure-induced lung injury in young rabbits. J Appl Physiol 66:2364–2368 1989.
98. Slutsky AS: Lung injury caused by mechanical ventilation. Chest 116:9S–15S, 1999.
99. Mead J, Takishima T, Leith D: Stress distribution in lungs: A model of pulmonary elasticity. J Appl Physiol 28:596–608, 1970.
100. Gattinoni L, D'Andrea L, Pelosi P, et al: Regional effects and mechanism of positive end-expiratory pressure in early adult respiratory distress syndrome (comment). JAMA 269:2122–2127, 1993 [published erratum appears in JAMA 270:1814, 1993].
101. Taskar V, John J, Evander E, et al: Healthy lungs tolerate repetitive collapse and reopening during short periods of mechanical ventilation. Acta Anaesthesiol Scand 39:370–376, 1995.
102. Taskar V, John J, Evander E, et al: Surfactant dysfunction makes lungs vulnerable to repetitive collapse and reexpansion. Am J Respir Crit Care Med 155:313–320, 1997.
103. Tremblay LN, Slutsky AS: Ventilator-induced injury: from barotrauma to biotrauma. Proc Assoc Am Physicians 110:482–488, 1998.
104. Tremblay L, Valenza F, Ribeiro SP, et al: Injurious ventilatory strategies increase cytokines and c-fos m-RNA expression in an isolated rat lung model. J Clin Invest 99:944–952, 1997.
105. Chiumello D, Pristine G, Slutsky AS: Mechanical ventilation affects local and systemic cytokines in an animal model of acute respiratory distress syndrome. Am J Respir Crit Care Med 160:109–116, 1999.
106. Ranieri VM, Suter PM, Tortorella C, et al: Effect of mechanical ventilation on inflammatory mediators in patients with acute respiratory distress syndrome: A randomized controlled trial (comment). JAMA 282:54–61, 1999.
107. Stuber F, Wrigge H, Schroeder S, et al: Kinetic and reversibility of mechanical ventilation-associated pulmonary and systemic inflammatory response in patients with acute lung injury. Intensive Care Med 28:834–841, 2002.
108. Slutsky AS, Tremblay LN: Multiple system organ failure. Is mechanical ventilation a contributing factor? Am J Respir Crit Care Med 157:1721–1725, 1998.
109. Imai Y, Parodo J, Kajikawa O, et al: Injurious mechanical ventilation and end-organ epithelial cell apoptosis and organ dysfunction in an experimental model of acute respiratory distress syndrome. JAMA 289:2104–2112, 2003.
110. de los Santos R, Seidenfeld JJ, Anzueto A, et al: One hundred percent oxygen lung injury in adult baboons. Am Rev Respir Dis 136:657–661, 1987.
111. Quinn DA, Moufarrej RK, Volokhov A, Hales CA: Interactions of lung stretch, hyperoxia, and MIP-2 production in ventilator-induced lung injury. J Appl Physiol 93:517–525, 2002.
112. Lin Z, Pearson C, Chinchilli V, et al: Polymorphisms of human SP-A, SP-B, and SP-D genes: Association of SP-B Thr131Ile with ARDS. Clin Genet 58:181–191, 2000.
113. Marshall RP, Webb S, Bellingan GJ, et al: Angiotensin converting enzyme insertion/deletion polymorphism is associated with susceptibility and outcome in acute respiratory distress syndrome (comment). Am J Respir Crit Care Med 166:646–650, 2002.
114. Villar J, Flores C, Perez-Mendez L, et al: Angiotensin-converting enzyme insertion/deletion polymorphism is not associated with susceptibility and outcome in sepsis and acute respiratory distress syndrome. Intensive Care Med 34:488–495, 2008.
115. Jerng JS, Yu CJ, Wang HC, et al: Polymorphism of the angiotensin-converting enzyme gene affects the outcome of acute respiratory distress syndrome. Crit Care Med 34:1001–1006, 2006.
116. Milberg JA, Davis DR, Steinberg KP, Hudson LD: Improved survival of patients with acute respiratory distress syndrome (ARDS): 1983–1993. JAMA 273:306–309, 1995.
117. Abel SJ, Finney SJ, Brett SJ, et al: Reduced mortality in association with the acute respiratory distress syndrome (ARDS). Thorax 53:292–294, 1998.
118. Zambon M, Vincent JL: Mortality rates for patients with acute lung injury/ARDS have decreased over time. Chest 133:1120–1127, 2008.
119. Doyle RL, Szaflarski N, Modin GW, et al: Identification of patients with acute lung injury. Predictors of mortality. Am J Respir Crit Care Med 152:1818–1824, 1995.

120. Heffner JE, Brown LK, Barbieri CA, et al: Prospective validation of an acute respiratory distress syndrome predictive score. Am J Respir Crit Care Med 152:1518–1526, 1995.
121. Roupie E, Lepage E, Wysocki M, et al: Prevalence, etiologies and outcome of the acute respiratory distress syndrome among hypoxemic ventilated patients. Intensive Care Med 25:920–929, 1999.
122. Montgomery AB, Stager MA, Carrico CJ, Hudson LD: Causes of mortality in patients with the adult respiratory distress syndrome. Am Rev Respir Dis 132:485–489, 1985.
123. Bell RC, Coalson JJ, Smith JD, Johanson WG Jr: Multiple organ system failure and infection in adult respiratory distress syndrome. Ann Intern Med 99:293–298, 1983.
124. Eisner MD, Thompson T, Hudson LD, et al: Efficacy of low tidal volume ventilation in patients with different clinical risk factors for acute lung injury and the acute respiratory distress syndrome. Am J Respir Crit Care Med 164:231–236, 2001.
125. Sloane PJ, Gee MH, Gottlieb JE, et al: A multicenter registry of patients with acute respiratory distress syndrome—Physiology and outcome. Am Rev Respir Dis 146:419–425, 1992.
126. Zilberberg MD, Epstein SK: Acute lung injury in the medical ICU: Comorbid conditions, age, etiology, and hospital outcome. Am J Respir Crit Care Med 157:1159–1164, 1998.
127. Moss M, Mannino DM: Race and gender differences in acute respiratory distress syndrome deaths in the United States: An analysis of multiple-cause mortality data (1979– 1996) (comment). Crit Care Med 30:1679–1685, 2002.
128. Suntharalingam G, Regan K, Keogh BF, et al: Influence of direct and indirect etiology on acute outcome and 6-month functional recovery in acute respiratory distress syndrome. Crit Care Med 29:562–566, 2001.
129. Nuckton TJ, Alonso JA, Kallet RH, et al: Pulmonary dead-space fraction as a risk factor for death in the acute respiratory distress syndrome (comment). N Engl J Med 346:1281–1286, 2002.
130. Clark JG, Milberg JA, Steinberg KP, Hudson LD: Type III procollagen peptide in the adult respiratory distress syndrome. Association of increased peptide levels in bronchoalveolar lavage fluid with increased risk for death (comment). Ann Intern Med 122:17–23, 1995.
131. Chesnutt AN, Matthay MA, Tibayan FA, Clark JG: Early detection of type III procollagen peptide in acute lung injury. Pathogenetic and prognostic significance. Am J Respir Crit Care Med 156:840–845, 1997.
132. Martin C, Papazian L, Payan MJ, et al: Pulmonary fibrosis correlates with outcome in adult respiratory distress syndrome. A study in mechanically ventilated patients (comment). Chest 107:196–200, 1995.
133. Delclaux C, Roupie E, Blot F, et al: Lower respiratory tract colonization and infection during severe acute respiratory distress syndrome: Incidence and diagnosis. Am J Respir Crit Care Med 156:1092–1098, 1997.
134. Chastre J, Trouillet JL, Vuagnat A, et al: Nosocomial pneumonia in patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 157:1165–1172, 1998.
135. Markowicz P, Wolff M, Djedaini K, et al: Multicenter prospective study of ventilator-associated pneumonia during acute respiratory distress syndrome. Incidence, prognosis, and risk factors. ARDS Study Group. Am J Respir Crit Care Med 161:1942–1948, 2000.
136. Sutherland KR, Steinberg KP, Maunder RJ, et al: Pulmonary infection during the acute respiratory distress syndrome. Am J Respir Crit Care Med 152:550–556, 1995.
137. Meduri GU, Reddy RC, Stanley T, El-Zeky F: Pneumonia in acute respiratory distress syndrome. A prospective evaluation of bilateral bronchoscopic sampling. Am J Respir Crit Care Med 158:870–875, 1998.
138. Weg JG, Anzueto A, Balk RA, et al: The relation of pneumothorax and other air leaks to mortality in the acute respiratory distress syndrome (comment). N Engl J Med 338:341–346, 1998.
139. Stewart TE, Meade MO, Cook DJ, et al: Evaluation of a ventilation strategy to prevent barotrauma in patients at high risk for acute respiratory distress syndrome. Pressure- and Volume-Limited Ventilation Strategy Group (comment). N Engl J Med 338:355–361, 1998.
140. Rivers E, Nguyen B, Havstad S, et al: Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 345:1368–1377, 2001.
141. Calfee CS, Matthay MA: Nonventilatory treatments for acute lung injury and ARDS. Chest 131:913–920, 2007.
142. Brunkhorst FM, Engel C, Bloos F, et al: Intensive insulin therapy and pentastarch resuscitation in severe sepsis. N Engl J Med 358:125–139, 2008.
143. Martin GS, Mangialardi RJ, Wheeler AP, et al: Albumin and furosemide therapy in hypoproteinemic patients with acute lung injury (comment). Crit Care Med 30:2175–2182, 2002.
144. Martin GS, Moss M, Wheeler AP, et al: A randomized, controlled trial of furosemide with or without albumin in hypoproteinemic patients with acute lung injury. Crit Care Med 33:1681–1687, 2005.
145. The SAFE Study Investigators: A comparison of albumin and saline for fluid resuscitation in the intensive care unit. N Engl J Med 350:2247–2256, 2004.
146. Gadek JE, DeMichele SJ, Karlstad MD, et al: Effect of enteral feeding with eicosapentaenoic acid, gamma-linolenic acid, and antioxidants in patients with acute respiratory distress syndrome. Enteral Nutrition in ARDS Study Group (comment). Crit Care Med 27:1409–1420, 1999.
147. Singer P, Theilla M, Fisher H, et al: Benefit of an enteral diet enriched with eicosapentaenoic acid and gamma-linolenic acid in ventilated patients with acute lung injury. Crit Care Med 34:1033–1038, 2006.
148. Heyland DK, Novak F, Drover JW, et al: Should immunonutrition become routine in critically ill patients? A systematic review of the evidence. JAMA 286:944–953, 2001.
149. dos Santos C CG, Slutsky AS: Pharmacotherapy of acute respiratory distress syndrome (a review). Expert Opin Pharmacother 3:875–888, 2002.
150. Lucas CE, Ledgerwood AM: Pulmonary response of massive steroids in seriously injured patients. Ann Surg 194:256–261, 1981.
151. Bernard GR, Luce JM, Sprung CL, et al: High-dose corticosteroids in patients with the adult respiratory distress syndrome. N Engl J Med 317:1565–1570, 1987.
152. Weigelt JA, Norcross JF, Borman KR, Snyder WH 3rd: Early steroid therapy for respiratory failure. Arch Surg 120:536–540, 1985.
153. Meduri GU, Headley AS, Golden E, et al: Effect of prolonged methylprednisolone therapy in unresolving acute respiratory distress syndrome: A randomized controlled trial (comment). JAMA 280:159–165, 1998.
154. The National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network: Efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome. N Engl J Med 354:1671–1684, 2006.
155. Meduri GU, Marik PE, Chrousos GP, et al: Steroid treatment in ARDS: A critical appraisal of the ARDS Network trial and the recent literature. Intensive Care Med 34:61–69, 2008.
156. Abraham E, Park YC, Covington P, et al: Liposomal prostaglandin E1 in acute respiratory distress syndrome: A placebo-controlled, randomized, double-blind, multicenter clinical trial (comment). Crit Care Med 24:10–15, 1996.
157. Abraham E, Baughman R, Fletcher E, et al: Liposomal prostaglandin E1 (TLC C-53) in acute respiratory distress syndrome: A controlled, randomized, double-blind, multicenter clinical trial. Crit Care Med 27:1478–1485, 1999.
158. Walmrath D, Schneider T, Pilch J, et al: Aerosolised prostacyclin in adult respiratory distress syndrome (comment). Lancet 342:961–962, 1993.
159. Walmrath D, Schneider T, Schermuly R, et al: Direct comparison of inhaled nitric oxide and aerosolized prostacyclin in acute respiratory distress syndrome. Am J Respir Crit Care Med 153:991–996, 1996.
160. Zwissler B, Kemming G, Habler O, et al: Inhaled prostacyclin (PGI_2) versus inhaled nitric oxide in adult respiratory distress syndrome. Am J Respir Crit Care Med 154:1671–1677, 1996.
161. Rossaint R, Falke KJ, Lopez F, et al: Inhaled nitric oxide for the adult respiratory distress syndrome (comment). N Engl J Med 328:399–405, 1993.

162. van der Vliet A, Eiserich JP, Cross CE: Nitric oxide: A pro-inflammatory mediator in lung disease? Respir Res 1:67–72, 2000.
163. Dellinger RP, Zimmerman JL, Taylor RW, et al: Effects of inhaled nitric oxide in patients with acute respiratory distress syndrome: Results of a randomized phase II trial. Inhaled Nitric Oxide in ARDS Study Group (comment). Crit Care Med 26:15–23, 1998.
164. Troncy E, Collet JP, Shapiro S, et al: Inhaled nitric oxide in acute respiratory distress syndrome: A pilot randomized controlled study. Am J Respir Crit Care Med 157:1483–1488, 1998.
165. Michael JR, Barton RG, Saffle JR, et al: Inhaled nitric oxide versus conventional therapy: effect on oxygenation in ARDS (comment). Am J Respir Crit Care Med 157:1372–1380, 1998.
166. Sokol J, Jacobs SE, Bohn D: Inhaled nitric oxide for acute hypoxemic respiratory failure in children and adults. Cochrane Database Syst Rev 1:CD002787, 2003.
167. Lundin S, Mang H, Smithies M, et al: Inhalation of nitric oxide in acute lung injury: results of a European multicentre study. The European Study Group of Inhaled Nitric Oxide. Intensive Care Med 25:911–919, 1999.
168. Adhikari NK, Burns KE, Friedrich JO, et al: Effect of nitric oxide on oxygenation and mortality in acute lung injury: Systematic review and meta-analysis. BMJ 334:779, 2007.
169. Spragg RG, Gilliard N, Richman P, et al: Acute effects of a single dose of porcine surfactant on patients with the adult respiratory distress syndrome (comment). Chest 105:195–202, 1994.
170. Gregory TJ, Steinberg KP, Spragg R, et al: Bovine surfactant therapy for patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 155:1309–1315, 1997.
171. Anzueto A, Baughman RP, Guntupalli KK, et al: Aerosolized surfactant in adults with sepsis-induced acute respiratory distress syndrome. Exosurf Acute Respiratory Distress Syndrome Sepsis Study Group (comment). N Engl J Med 334:1417–1421, 1996.
172. Spragg RG, Lewis JF, Wurst W, et al: Treatment of acute respiratory distress syndrome with recombinant surfactant protein C surfactant. Am J Respir Crit Care Med 167:1562–1566, 2003.
173. Bernard GR, Wheeler AP, Arons MM, et al: A trial of antioxidants N-acetylcysteine and procysteine in ARDS. The Antioxidant in ARDS Study Group. Chest 112:164–172, 1997.
174. Anonymous: Randomized, placebo-controlled trial of lisofylline for early treatment of acute lung injury and acute respiratory distress syndrome (comment). Crit Care Med 30:1–6, 2002.
175. Anonymous: Ketoconazole for early treatment of acute lung injury and acute respiratory distress syndrome: A randomized controlled trial. The ARDS Network. JAMA 283:1995–2002, 2000 [published erratum appears in JAMA 284:2450, 2000].
176. Bernard GR, Wheeler AP, Russell JA, et al: The effects of ibuprofen on the physiology and survival of patients with sepsis. The Ibuprofen in Sepsis Study Group (comment). N Engl J Med 336:912–918, 1997.
177. Schuster DP, Metzler M, Opal S, et al: Recombinant platelet-activating factor acetylhydrolase to prevent acute respiratory distress syndrome and mortality in severe sepsis: Phase IIb, multicenter, randomized, placebo-controlled, clinical trial (comment). Crit Care Med 31:1612–1619, 2003.
178. Gupta N, Su X, Popov B, et al: Intrapulmonary delivery of bone marrow–derived mesenchymal stem cells improves survival and attenuates endotoxin-induced acute lung injury in mice. J Immunol 179:1855–1863, 2007.
179. Mei SH, McCarter SD, Deng Y, et al: Prevention of LPS-induced acute lung injury in mice by mesenchymal stem cells overexpressing angiopoietin 1. PLoS Med 4:e269, 2007.
180. Maunder RJ, Shuman WP, McHugh JW, et al: Preservation of normal lung regions in the adult respiratory distress syndrome—Analysis by computer tomography. J AMA 255:2463–2465, 1986.
181. Brower RG, Shanholtz CB, Fessler HE, et al: Prospective, randomized, controlled clinical trial comparing traditional versus reduced tidal volume ventilation in acute respiratory distress syndrome patients (comment). Crit Care Med 27:1492–1498, 1999.
182. Brochard L, Roudot-Thoraval F, Roupie E, et al: Tidal volume reduction for prevention of ventilator-induced lung injury in acute respiratory distress syndrome. The Multicenter Trial Group on Tidal Volume reduction in ARDS. Am J Respir Crit Care Med 158:1831–1838, 1998.
183. Amato MB, Barbas CS, Medeiros DM, et al: Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome (comment). N Engl J Med 338:347–354, 1998.
184. Jonson B, Richard JC, Straus C, et al: Pressure-volume curves and compliance in acute lung injury: Evidence of recruitment above the lower inflection point. Am J Respir Crit Care Med 159:1172–1178, 1999.
185. Rimensberger PC, Cox PN, Frndova H, Bryan AC: The open lung during small tidal volume ventilation: Concepts of recruitment and "optimal" positive end-expiratory pressure (comment). Crit Care Med 27:1946–1952, 1999.
186. Pelosi P, Gattinoni L: Respiratory mechanics in ARDS: Asiren for physicians? (comment). Intensive Care Med 26:653–656, 2000.
187. Rouby JJ, Lu Q, Goldstein I: Selecting the right level of positive end-expiratory pressure in patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 165:1182–1186, 2002.
188. Grasso S, Stripoli T, De Michele M, et al: ARDSnet ventilatory protocol and alveolar hyperinflation: Role of positive end-expiratory pressure. Am J Respir Crit Care Med 176:761–767, 2007.
189. Gattinoni L, Caironi P, Cressoni M, et al: Lung recruitment in patients with the acute respiratory distress syndrome. N Engl J Med 354:1775–1786, 2006.
190. Villagra A, Ochagavia A, Vatua S, et al: Recruitment maneuvers during lung protective ventilation in acute respiratory distress syndrome. Am J Respir Crit Care Med 165:165–170, 2002.
191. Brower RG, Morris A, MacIntyre N, et al: Effects of recruitment maneuvers in patients with acute lung injury and acute respiratory distress syndrome ventilated with high positive end-expiratory pressure. Crit Care Med 31:2592–2597, 2003.
192. The National Heart, Lung, and Blood Institute ARDS Clinical Trials Network: Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. N Engl J Med 351:327–336, 2004.
193. Meade MO, Cook DJ, Guyatt GH, et al: Ventilation strategy using low tidal volumes, recruitment maneuvers, and high positive end-expiratory pressure for acute lung injury and acute respiratory distress syndrome: A randomized controlled trial. JAMA 299:637–645, 2008.
194. Mercat A, Richard JC, Vielle B, et al: Positive end-expiratory pressure setting in adults with acute lung injury and acute respiratory distress syndrome: A randomized controlled trial. JAMA 299:646–655, 2008.
195. Slutsky AS, Hudson LD: PEEP or no PEEP—Lung recruitment may be the solution. N Engl J Med 354:1839–1841, 2006.
196. Richard JC, Maggiore SM, Jonson B, et al: Influence of tidal volume on alveolar recruitment. Respective role of PEEP and a recruitment maneuver. Am J Respir Crit Care Med 163:1609–1613, 2001.
197. Foti G, Cereda M, Sparacino ME, et al: Effects of periodic lung recruitment maneuvers on gas exchange and respiratory mechanics in mechanically ventilated acute respiratory distress syndrome (ARDS) patients (comment). Intensive Care Med 26:501–507, 2000.
198. Laffey JG, Tanaka M, Engelberts D, et al: Therapeutic hypercapnia reduces pulmonary and systemic injury following in vivo lung reperfusion (comment). Am J Respir Crit Care Med 162:2287–2294, 2000.
199. Takeshita K, Suzuki Y, Nishio K, et al: Hypercapnic acidosis attenuates endotoxin-induced nuclear factor-[kappa]B activation. Am J Respir Cell Mol Biol 29:124–132, 2003.
200. Lang JD Jr, Chumley P, Eiserich JP, et al: Hypercapnia induces injury to alveolar epithelial cells via a nitric oxide-dependent pathway. Am J Physiol Lung Cell Mol Physiol 279:L994–L1002, 2000.
201. Kacmarek RM: A workable alternative to the problems with tracheal gas insufflation? (comment). Intensive Care Med 28:1009–1011, 2002.
202. Kalfon P, Rao GS, Gallart L, et al: Permissive hypercapnia with and without expiratory washout in patients with severe acute respiratory distress syndrome. Anesthesiology 87:6–17, 1997 [discussion appears 25A–26A].

203. Pelosi P, Tubiolo D, Mascheroni D, et al: Effects of the prone position on respiratory mechanics and gas exchange during acute lung injury. Am J Respir Crit Care Med 157:387–393, 1998.
204. Broccard AF, Shapiro RS, Schmitz LL, et al: Influence of prone position on the extent and distribution of lung injury in a high tidal volume oleic acid model of acute respiratory distress syndrome (comment). Crit Care Med 25:16–27, 1997.
205. Gattinoni L, Tognoni G, Pesenti A, et al: Effect of prone positioning on the survival of patients with acute respiratory failure (comment). N Engl J Med 345:568–573, 2001 [summary for patients in Aust J Physiother 48:237, 2002].
206. Slutsky AS: The acute respiratory distress syndrome, mechanical ventilation, and the prone position (comment). N Engl J Med 345:610–662, 2001.
207. Guerin C, Gaillard S, Lemasson S, et al: Effects of systematic prone positioning in hypoxemic acute respiratory failure: A randomized controlled trial. JAMA 292:2379–2387, 2004.
208. Curley MA, Hibberd PL, Fineman LD, et al: Effect of prone positioning on clinical outcomes in children with acute lung injury: A randomized controlled trial. JAMA 294:229–237, 2005.
209. Mancebo J, Fernandez R, Blanch L, et al: A multicenter trial of prolonged prone ventilation in severe acute respiratory distress syndrome. Am J Respir Crit Care Med 173:1233–1239, 2006.
210. Fernandez R, Trenchs X, Klamburg J, et al: Prone positioning in acute respiratory distress syndrome: A multicenter randomized clinical trial. Intensive Care Med 34:1487–1491, 2008.
210a. Taccone P, Pesenti A, Latini R; for the Prone-Supine II Study Group: Prone positioning in patients with moderate and severe acute respiratory distress syndrome: A randomized controlled trial. JAMA 302:1977–1984, 2009.
210b. Slutsky AS: Improving outcomes in critically ill patients: The seduction of physiology. JAMA 302:2030–2032, 2009.
211. Prella M, Feihl F, Domenighetti G: Effects of short-term pressure-controlled ventilation on gas exchange, airway pressures, and gas distribution in patients with acute lung injury/ARDS: Comparison with volume-controlled ventilation. Chest 122:1382–1388, 2002 [published erratum appears in Chest 123:315, 2003].
212. Esteban A, Alia I, Gordo F, et al: Prospective randomized trial comparing pressure-controlled ventilation and volume-controlled ventilation in ARDS. For the Spanish Lung Failure Collaborative Group. Chest 117:1690–1696, 2000.
213. Krishnan JA, Brower RG: High-frequency ventilation for acute lung injury and ARDS (comment). Chest 118:795–807, 2000.
214. Carlon GC, Howland WS, Ray C, et al: High-frequency jet ventilation. A prospective randomized evaluation. Chest 84:551–559, 1983.
215. Ferguson ND, Slutsky AS: Point: High-frequency ventilation is the optimal physiological approach to ventilate ARDS patients. J Appl Physiol 104:1230–1231, 2008.
216. Derdak S, Mehta S, Stewart TE, et al: High-frequency oscillatory ventilation for acute respiratory distress syndrome in adults: A randomized, controlled trial (comment). Am J Respir Crit Care Med 166:801–808, 2002.
217. Bollen CW, van Well GT, Sherry T, et al: High frequency oscillatory ventilation compared with conventional mechanical ventilation in adult respiratory distress syndrome: A randomized controlled trial. Crit Care 9:R430–R439, 2005.
218. Shanholtz C, Brower R: Should inverse ratio ventilation be used in adult respiratory distress syndrome? Am J Respir Crit Care Med 149:1354–1358, 1994.
219. Hirschl RB, Conrad S, Kaiser R, et al: Partial liquid ventilation in adult patients with ARDS: A multicenter phase I-II trial. Adult PLV Study Group. Ann Surg 228:692–700, 1998.
220. Fuhrman BP, Hernan LJ, Holm BA, et al: Perfluorocarbon associated gas exchange (PAGE): Gas ventilation of the perfluorocarbon filled lung. Artif Cells Blood Substit Immobil Biotechnol 22:1133–1139, 1994.
221. Hirschl RB, Croce M, Gore D, et al: Prospective, randomized, controlled pilot study of partial liquid ventilation in adult acute respiratory distress syndrome. Am J Respir Crit Care Med 165:781–787, 2002.
222. Kacmarek RM, Wiedemann HP, Lavin PT, et al: Partial liquid ventilation in adult patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 173:882–889, 2006.
223. Wassermann J, Mazer CD: ECMO in adults: What is its role? (comment). Can J Anaesth 45:1044–1048, 1998.
223a. Australia and New Zealand Extracorporeal Membrane Oxygenation (ANZ ECMO) Influenza Investigators, Davies A, Jones D, et al: Extracorporeal membrane oxygenation for 2009 influenza A (H1N1) acute respiratory distress syndrome. JAMA 302: 1888–1895, 2009.
224. Zapol WM, Snider MT, Hill JD, et al: Extracorporeal membrane oxygenation in severe acute respiratory failure. A randomized prospective study. JAMA 242:2193–2196, 1979.
225. Gattinoni L, Pesenti A, Mascheroni D, et al: Low-frequency positive-pressure ventilation with extracorporeal CO_2 removal in severe acute respiratory failure. JAMA 256:881–886, 1986.
226. Morris AH, Wallace CJ, Menlove RL, et al: Randomized clinical trial of pressure-controlled inverse ratio ventilation and extracorporeal CO_2 removal for adult respiratory distress syndrome (comment). Am J Respir Crit Care Med 149:295–305, 1994 [published erratum appears in Am J Respir Crit Care Med 149:838, 1994].
227. Orme J Jr, Romney JS, Hopkins RO, et al: Pulmonary function and health-related quality of life in survivors of acute respiratory distress syndrome. Am J Respir Crit Care Med 167:690–694, 2003.
228. Herridge MS, Cheung AM, Tansey CM, et al: One-year outcomes in survivors of the acute respiratory distress syndrome (comment). N Engl J Med 348:683–693, 2003.
229. Cheung AM, Tansey CM, Tomlinson G, et al: Two-year outcomes, health care use, and costs of survivors of acute respiratory distress syndrome. Am J Respir Crit Care Med 174:538–544, 2006.
230. Davidson TA, Caldwell ES, Curtis JR, et al: Reduced quality of life in survivors of acute respiratory distress syndrome compared with critically ill control patients. JAMA 281:354–360, 1999.
231. Davidson TA, Rubenfeld GD, Caldwell ES, et al: The effect of acute respiratory distress syndrome on long-term survival. Am J Respir Crit Care Med 160:1838–1842, 1999.
232. Schelling G, Stoll C, Haller M, et al: Health-related quality of life and posttraumatic stress disorder in survivors of the acute respiratory distress syndrome (comment). Crit Care Med 26:651–659, 1998.
233. Hopkins RO, Weaver LK, Pope D, et al: Neuropsychological sequelae and impaired health status in survivors of severe acute respiratory distress syndrome. Am J Respir Crit Care Med 160:50–56, 1999.

CHAPTER 91

HYPOXEMIC RESPIRATORY FAILURE

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INTRODUCTION

DIAGNOSIS

CLASSIFICATION

Time of Onset

Underlying Etiology

Anatomic Dysfunction

Pathophysiologic Mechanisms

MECHANISMS OF HYPOXEMIC RESPIRATORY FAILURE

Decreased Inspired Oxygen Pressure

Hypoventilation

Impaired diffusion

Shunt

Ventilation-Perfusion Mismatch

CLINICAL APPROACH

INTRODUCTION

The main goal of cardiopulmonary function is to deliver an adequate amount of oxygen (O_2) to meet the metabolic requirements of the peripheral tissues. Proper oxygenation of tissues depends on two factors: (1) the amount of O_2 delivery (Do_2), and (2) the rate of O_2 consumption ($\dot{V}o_2$) in the tissues. Do_2 is proportional to the arterial content of O_2 and the cardiac output (Do_2 = arterial O_2 content × cardiac output). $\dot{V}o_2$ is expressed by the following equation:

$$\dot{V}o_2 = 1.34 \times [Hb] \times (\text{arterial } O_2 \text{ saturation} - \text{venous } O_2 \text{ saturation}) \times \text{cardiac output}$$

This equation highlights the importance of mixed or central venous blood O_2 saturation as a parameter to monitor cardiopulmonary function. An impairment in any of these factors will result in a lack of tissue oxygenation or hypoxia, which when severe is life-threatening.

Among all the potential pathophysiologic alterations causing hypoxia, this chapter focuses on *hypoxemic respiratory failure*, defined as the impairment of respiratory function characterized by the presence of hypoxemia, diagnosed by reduced partial pressure of oxygen in arterial blood (Pao_2). Normally, Pao_2 ranges between 85 and 100 mm Hg, but the Pao_2 declines progressively during life, reaching values of 85 mm Hg at sea level by the age of 60. It is important to note that Pao_2 does not measure the entire content of oxygen in the arterial blood, but rather the partial pressure of the dissolved fraction of O_2, which drives its binding to proteins in blood, particularly hemoglobin (Hb), which has the highest ability to bind O_2 (1.34 mL O_2/1 g Hb). The Pao_2 determines the percentage of Hb saturated with O_2, according to the oxyhemoglobin dissociation curve (Fig. 91-1). Therefore, the actual oxygen content in the blood depends on the solubility of oxygen gas in the plasma and on the Hb concentration, according to the following equation:

$$O_2 \text{ content} = 1.34 \times [Hb] \times O_2 \text{ saturation} + 0.0031 \times Pao_2$$

DIAGNOSIS

Hypoxemic respiratory failure is diagnosed when there is a clinically significant decrease in Pao_2. Most commonly, the critical threshold of Pao_2 is considered to be 60 mm Hg, which is an anchor point in the oxyhemoglobin dissociation curve. This means that when the Pao_2 is less than 60 mm Hg, the saturation of hemoglobin with oxygen begins to fall rapidly with further decreases in Pao_2. Conversely, when the Pao_2 is above 60 mm Hg, the slope of the saturation curve is almost flat, implying that further increases in Pao_2 will result in small gains in oxygen saturation (see Fig. 91-1). It is important to recall that the oxyhemoglobin dissociation curve can be shifted horizontally by changes in temperature, partial pressure of carbon dioxide ($Paco_2$), concentration of H^+ ion, and red blood cell 2,3-diphosphoglycerate (DPG). In particular, the curve is shifted to the right when there is an increase in temperature, $Paco_2$, H^+ concentration, or DPG concentration, favoring the unloading of oxygen to the peripheral tissues, which is advantageous during muscle exercise, respiratory distress, or prolonged hypoxia.

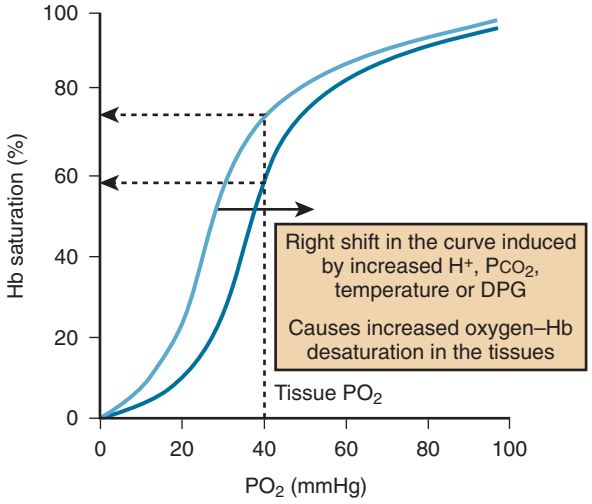

FIGURE 91-1 ■ Oxygen-hemoglobin dissociation curve shows the affinity-binding of oxygen to hemoglobin based on the partial pressure of oxygen (P_{O_2}) under normal conditions (*light blue line*) and during conditions of increased H^+ concentration, carbon dioxide pressure (P_{CO_2}), temperature, and/or DPG (2,3-diphosphoglycerate) (*dark blue line*). Note that at a P_{O_2} of less than 60 mm Hg, the oxygen saturation of hemoglobin begins to fall with increasing rapidity.

The measurement of P_{aO_2} is performed by arterial blood gas analysis (ABG), which also yields direct measurement of O_2 saturation of Hb, P_{aCO_2}, and pH and requires the puncture of an artery or the insertion of an indwelling arterial catheter to allow periodic sampling of arterial blood. Although crucial for the diagnosis and management of hypoxemic diseases, continuous monitoring of P_{aO_2} is not currently feasible, as would be ideal for the management of critically ill patients. The degree of hypoxemia is not specific for disease states because similar values of P_{aO_2} characterize patients with a broad spectrum of severity of illness, revealing that the definition of hypoxemia using arterial blood measurements is simplistic and suggesting that a more detailed pathophysiologic classification of hypoxemia would be useful.

Although measurement of P_{aO_2} remains the most commonly used technique to identify hypoxemia, other modes of monitoring oxygenation are also used to assist in the management and diagnosis of hypoxemic respiratory failure.

Pulse oximetry allows the continuous pulsatile monitoring of Hb O_2 saturation as the percentage of oxyhemoglobin, which is calculated based on the absorption of two wavelengths of light by Hb using a noninvasive probe applied to a perfused cutaneous area (usually a finger). One wavelength reflects oxyhemoglobin, and the other reflects deoxyhemoglobin, Arterial O_2 saturation is a very useful parameter, and values of 92% or greater represent adequate oxygenation; however, a specifically defined threshold to diagnose tissue hypoxia has not been identified.[1]

Another useful parameter to monitor oxygenation is the *alveolar-arterial P_{O_2} difference (A – a)P_{O_2}*, which is defined as the difference between the partial pressure of O_2 in the alveoli (P_{AO_2}) and the partial pressure of O_2 dissolved in the plasma of arterial blood ($P_{AO_2} - P_{aO_2}$). The (A – a)P_{O_2} gradient is normally less than 10 mm Hg; however, the range of normality changes with age and can be estimated as follows:

$$(A - a)\ \text{gradient} = 2.5 + 0.21 \times \text{age (in yr)}$$

The P_{AO_2} is calculated using the alveolar gas equation:

$$P_{AO_2} = F_{IO_2} \times [\text{Patm} - P_{H_2O}] - [P_{ACO_2} \div R] + F$$

where F_{IO_2} is the fraction of inspired O_2 (21% at room air), Patm is the atmospheric pressure (760 mm Hg at sea level, decreasing progressively with increasing altitude), P_{H_2O} is the partial pressure of saturated vapor (47 mm Hg at 37°C), P_{ACO_2} is the partial pressure of carbon dioxide in the alveoli (assumed to be equal to the partial pressure of CO_2 in the arterial blood [P_{aCO_2}] given the high diffusion coefficient of CO_2), R is the respiratory quotient (~0.8), and finally, F is a correction factor that is usually ignored. Clinically, it is worth noting that the (A – a)P_{O_2} difference increases with increasing F_{IO_2}, because oxygen support is often administered to patients suffering from hypoxemic respiratory failure.

Another parameter using similar information to that of the (A – a)P_{O_2} difference, is the A – a oxygen ratio, which is calculated by dividing the P_{aO_2} by the P_{AO_2} and normally exceeds a value of 0.77. However, this analysis of oxygenation is rarely used compared with the (A – a)P_{O_2} difference, which is in wide clinical use.

An additionally important measure of oxygenation is the P_{aO_2}/F_{IO_2} ratio, normally ranging between 300 and 500. In clinical practice, this index is routinely used to monitor the severity of noncardiogenic hypoxemic respiratory failure. Following the guidelines of the American European Consensus Conference, in the presence of bilateral lung infiltrates and hypoxemia from noncardiogenic origin, a P_{aO_2}/F_{IO_2} ratio less than 300 mm Hg indicates acute lung injury (ALI) and below 200 mm Hg indicates acute respiratory distress syndrome (ARDS). Like the (A – a)P_{O_2} difference, the P_{aO_2}/F_{IO_2} ratio is affected by alterations in the F_{IO_2}.

In particular clinical settings, such as pediatric departments, oxygenation is commonly monitored using the oxygenation index (OI), which is calculated using the following equation:

$$\text{OI} = \frac{\text{Mean airway pressure} \times F_{IO_2} \times 100}{P_{aO_2}}$$

where increasing values of OI indicated a worsening of oxygenation. The OI could be considered a more robust index than the P_{aO_2}/F_{IO_2} ratio, because it takes into consideration the mean airway pressure, thus providing a better pathophysiologic assessment of impaired lung function.

CLASSIFICATION

A classification of hypoxemia is helpful in order to allow a systematic approach to managing patients with hypoxemia. Various classifications of hypoxemic respiratory

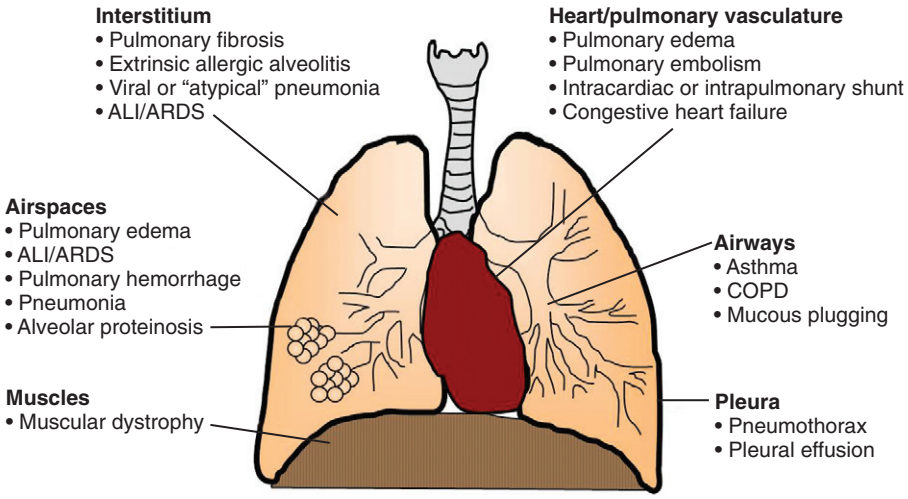

FIGURE 91-2 ■ Anatomic classification of hypoxemic respiratory failure displays examples of possible diagnoses based on structural dysfunction. This is not an exhaustive list and is meant for illustrative purposes only.

failure have been used that highlight important clinical aspects of the hypoxemia.

Time of Onset

The first classification uses time as the main parameter to define hypoxemic respiratory failure as acute or chronic. *Acute hypoxemia* occurs over a period of hours to days, and *chronic hypoxemia* occurs over a period of weeks to months. These two categories of hypoxemia, acute and chronic, are also characterized by differences in diagnostic approach, therapeutic strategy, and pathophysiologic mechanisms (considering the physiologic adaptations to hypoxemia that develop over time). Thus, acute and chronic hypoxemia reflect two different disease processes.

Underlying Etiology

Hypoxemic respiratory failure can also be classified based on its underlying cause; however, there is such a large number of possible diseases inducing hypoxemia that it is difficult to list them in a comprehensive classification. Several multicentered international studies have reported the most frequent causes of acute hypoxemic respiratory failure. In particular, in two large prospective studies of patients with acute hypoxemic respiratory failure requiring mechanical ventilation, the most common cause of hypoxemia aside from cardiogenic pulmonary edema was pneumonia, followed by sepsis, aspiration, trauma, and multiple transfusions.[2,3] Furthermore, in a randomized clinical trial investigating the use of noninvasive mechanical ventilation during severe hypoxemic respiratory failure, the leading underlying etiologies in order of frequency, were pneumonia, cardiogenic pulmonary edema, thoracic trauma, ARDS, acute severe asthma, postoperative respiratory failure, and interstitial pneumonitis.[4] For a further detailed discussion of many of the specific causes of hypoxemic respiratory failure (e.g., pneumonia), the reader is referred to Chapters 55, 57, and 92.

Anatomic Dysfunction

A third method used to classify hypoxemic respiratory failure is the identification of the anatomic structure primarily affected by the disease causing the drop in Pa_{O_2}. Dysfunction in many different areas of the chest—including diseases of the alveoli, interstitium, bronchi, airways, pleura, pulmonary vasculature, heart, and muscles—can induce hypoxia (Fig. 91-2). Furthermore, damage to the respiratory muscles and to specific areas of the central nervous system can also induce hypoxemia; however, these anatomic dysfunctions are usually characterized by an elevation in Pa_{CO_2}. Each of these anatomic areas can be targeted by different diseases. For example, alveoli can be filled with exudates, transudates, blood, inflammatory cells and proteins, hyaline membranes, fibrin, fibroblasts, and tumor cells, each one corresponding to different acute or chronic diseases, such as pneumonia, cardiogenic pulmonary edema, ALI, alveolar hemorrhage, cancer, idiopathic pulmonary fibrosis, cryptogenic organizing pneumonia, and pulmonary alveolar proteinosis.

Pathophysiologic Mechanisms

Finally, hypoxemic respiratory failure can be classified according to the pathophysiologic mechanisms leading to hypoxemia. This classification is particularly important because the identification of the pathophysiologic cause often allows the physician to administer a more appropriate treatment. However, understanding the pathophysiologic mechanism is not always helpful in making a specific diagnosis, which is crucial for determining prognosis, so this information must be used in combination with the parameters discussed previously.

MECHANISMS OF HYPOXEMIC RESPIRATORY FAILURE

There are five pathophysiologic mechanisms of hypoxemia: (1) decreased inspired oxygen pressure (P_{IO_2}) or fraction, (2) hypoventilation, (3) impaired diffusion, (4) shunt, and (5) ventilation-perfusion (V/Q) mismatch.[5]

Decreased Inspired Oxygen Pressure

The P_{IO_2} depends on the F_{IO_2} multiplied by the difference between the Patm and the pressure of saturated vapor (P_{H_2O}):

$$P_{IO_2} = F_{IO_2} \times (Patm - P_{H_2O})$$

As mentioned previously, the F_{IO_2} at room air is 0.21 and can decrease only in rare circumstances, such as the saturation of a closed environment with toxic fumes, where the inspired gas mixture contains a lower oxygen fraction.

Therefore, according to the equation, a naturally occurring lower P_{IO_2} can be observed only in conditions of low Patm. Patm progressively declines as altitude increases, going from 760 mm Hg at sea level to 253 mm Hg at the summit of Mount Everest (8848 m [29,029 ft]). Hence, P_{IO_2} ranges from 150 mm Hg at sea level ((0.21 × (760 mm Hg − 47 mm Hg)) to 43 mm Hg on top of Mount Everest (0.21 × (253 mm Hg − 47 mm Hg)) (Fig. 91-3).[5a]

According to the alveolar gas equation (see earlier), a reduction in P_{IO_2} results in a decrease in P_{AO_2}, which consequently reduces the driving pressure for oxygen through the alveolar-capillary membrane, inducing respiratory hypoxemia.

Hypoventilation

Hypoventilation is the condition defined by the reduction of alveolar ventilation ($\dot{V}_A$), which is a determinant of P_{ACO_2} ($PACO_2 = K \times \dot{V}CO_2/\dot{V}A$, where K is a constant and $\dot{V}CO_2$ is the rate of production of CO_2, and depends on the metabolic rate). According to the alveolar gas equation:

$$P_{AO_2} = F_{IO_2} \times [Patm - P_{H_2O}] - [P_{ACO_2} \div R] + F$$

if the respiratory exchange ratio (R, normally = 0.8) remains constant, any increase in P_{ACO_2} results in a reduction of P_{AO_2}, which can lead, in severe cases of hypercapnia, to hypoxemia. For example, if the $PaCO_2$ is increased to 80 mm Hg, the resulting P_{AO_2} on room air (at sea level) would be decreased to 50 mm Hg. This form of hypoxemia, exclusively due to hypoventilation, is readily recognizable because it is characterized by a normal (A − a)P_{O_2} difference, and a high $PaCO_2$, and is easily corrected by increasing the F_{IO_2} or reducing the P_{ACO_2} by increasing alveolar ventilation (e.g., with mechanical ventilation).

The reduction of alveolar ventilation leading to an increase in $PaCO_2$ is the result of an imbalance between the function of the respiratory pump and the load applied to the respiratory system. The respiratory pump encompasses all of the neuromuscular structures from the central nervous system to the respiratory muscles, including the motor-neuron and the neuromuscular junction, responsible for the expansion of the chest during inspiration. The respiratory load can be subclassified as the resistive load (due to the resistance of the airways), elastic load (due to the compliance of the lungs and chest wall), and the CO_2 production load, determined by the metabolic demands of peripheral tissue, which

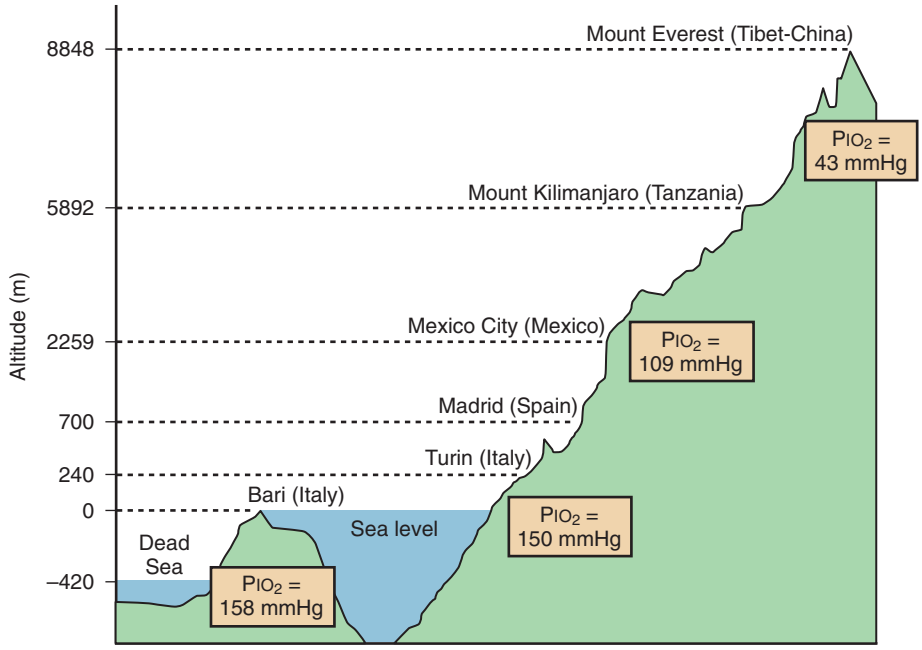

FIGURE 91-3 ■ Altitude effects on the pressure of inspired oxygen (P_{IO_2}), which geographically can range from 43 mm Hg at the summit of Mount Everest to 158 mm Hg at the Dead Sea. Most major world cities are located near sea level, where the P_{IO_2} is 150 mm Hg.

can increase dramatically during exercise, sepsis, trauma, and other factors.

Impaired Diffusion

Alveolar oxygen must diffuse through the alveolar-endothelial membranes in order to dissolve in the bloodstream and bind to Hb in red blood cells. Under normal conditions, complete oxygenation of blood in the pulmonary capillaries requires only 0.25 second, which is only a third of the total time in which the blood remains in contact with the alveolar-endothelial membrane (Fig. 91-4). Consequently, the relatively long alveolar capillary transit time can compensate for any impairment in oxygen diffusion. Thickening of the blood-gas barrier occurs in several diseases such as diffuse interstitial fibrosis, idiopathic pulmonary fibrosis, cryptogenic organizing pneumonia, asbestosis exposure, ARDS. Nevertheless, owing to this reserve of diffusion time, hypoxemia due solely to impaired diffusion is rarely observed in resting conditions, even during disease states. Impairment in oxygen diffusion through the blood-gas barrier can become clinically significant during exercise or other circumstances causing increased cardiac output, which induces a faster transition of the red cells through the alveolar capillaries. Therefore, rises in cardiac output will increase the flow through the pulmonary capillaries, thereby significantly reducing the time available for oxygen diffusion, which, if combined with an impaired diffusion rate, can lead to the development of hypoxemic respiratory failure because of a diffusion limitation (see Fig. 91-4).

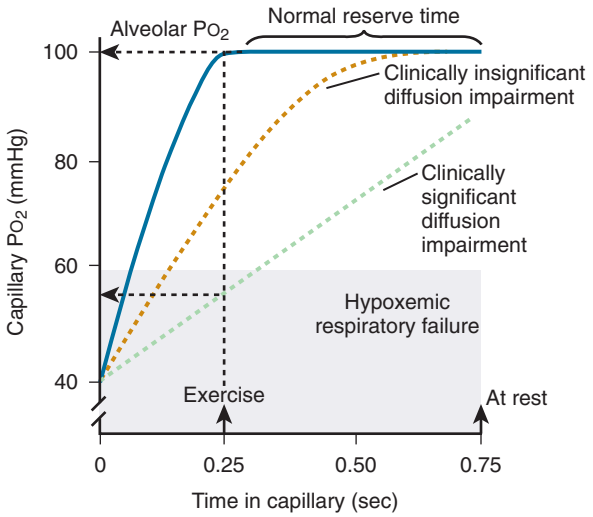

FIGURE 91-4 ■ Oxygen diffusion at the alveolar-capillary barrier requires only a third of the available time to obtain complete equilibration under normal resting conditions (*blue line*). Small impairments in diffusion (*dashed brown line*) use the available "reserve time," maintaining capillary oxygenation of greater than 60 mm Hg, so this impairment will be clinically insignificant. Larger diffusion impairments (*dashed pale line*) may prevent complete oxygenation, which during exercise when blood flow is increased may become clinically significant, leading to hypoxemic respiratory failure.

Shunt

Shunt is defined as the passage of venous blood into the arterial circulation without passing ventilated alveoli and, consequently, not becoming oxygenated. It is more accurate to define this mechanism as "right-to-left shunt," because the communication between the venous and the arterial circulation can cause hypoxemia only if the direction of the shunted blood flow is right to left.

Hypoxemic respiratory failure can be caused by intrapulmonary or extrapulmonary shunts. Examples of diseases with intrapulmonary shunts are pulmonary arteriovenous malformations, hepatopulmonary syndrome, and diseases characterized by alveolar consolidation or collapse (e.g., pneumonia, atelectasis). This latter condition of alveolar consolidation or collapse can also be viewed as an extreme *V/Q mismatch*, defined by areas of the lung that are unventilated but still perfused (discussed later). An interesting clinical example of intrapulmonary shunt is hepatopulmonary syndrome, which is cause by a regional dilation of pulmonary capillaries at the bases of the lungs. In this condition, the shunt increases when the patient is in the upright position, leading to hypoxemia. Because perfusion is redistributed toward the apex of the lung when the patient is placed in the supine position, this positioning will allow progressive reduction of shunt, thereby lessening the hypoxemia.

Extrapulmonary shunts are caused by the presence of intracardiac communication between the ventricles or the atria, due to atrial or ventricular septal defects, or by patency of the ductus arteriosus.

The presence of hypoxemia caused by shunt is characterized by the failure of Pa_{O_2} to rise despite inhalation of pure oxygen (100%).

The shunt fraction can be estimated by the following equation:

$$\dot{Q}s/\dot{Q}T = (Cc'_{O_2} - Ca_{O_2}) \div (Cc'_{O_2} - C\bar{v}_{O_2})$$

where, $\dot{Q}s$ is the shunt flow, $\dot{Q}T$ is the total blood flow, Cc'_{O_2} is the end-capillary O_2 content, calculated from the P_{AO_2}, Ca_{O_2} is the arterial O_2 content and $C\bar{v}_{O_2}$ is the mixed venous O_2 content, measured from the venous blood sampled through the pulmonary artery catheter.

Ventilation-Perfusion Mismatch

To become fully oxygenated and allow the total removal of CO_2, all the blood perfusing the lungs needs to be in contact with ventilated alveolar units. Ideally, the V/Q ratio should be equal to 1. Physiologically, in the upright position, the perfusion of the lungs changes anatomically, increasing from the apex to the base, due to either gravitational or anatomic considerations. Likewise, the ventilation is greater at the base of the lung, as opposed to the apical regions. However, from apex to base, the perfusion increases more rapidly than that of ventilation, resulting in a progressive decrease of V/Q ratio. The overall V/Q ratio of the lungs is normally around 0.8. This mild difference of the real V/Q from the ideal value of 1 is responsible for a physiologically appreciable $(A-a)P_{O_2}$ difference.

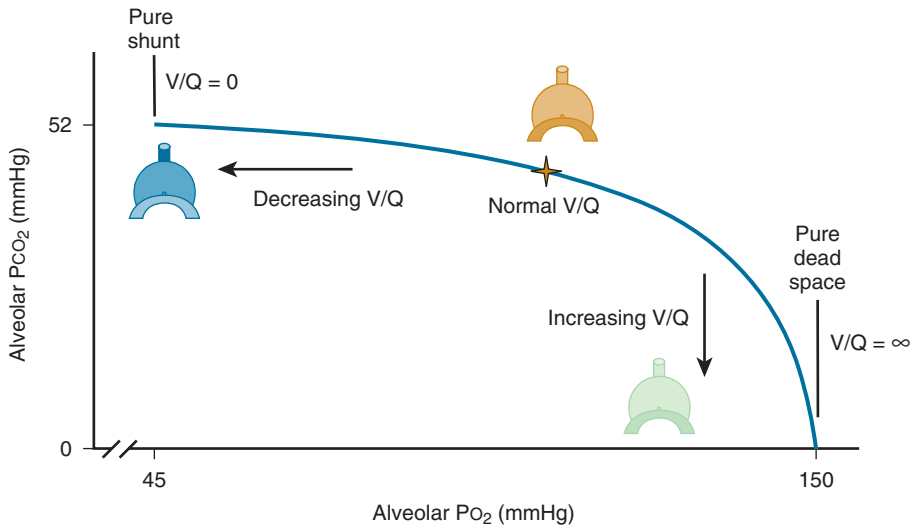

FIGURE 91-5 ■ Ventilation-perfusion (V/Q) ratio displays the normal balance (*star*) between alveolar ventilation and vascular perfusion allowing for proper oxygenation. When ventilation is reduced, the V/Q ratio decreases, in the most extreme case resulting in pure shunt, where V/Q = 0. When perfusion is reduced, the V/Q ratio increases, in the most extreme case resulting in pure dead space, where V/Q = infinite (∞).

V/Q varies broadly between pathophysiologic extremes. On one side, there are alveolar units with no ventilation but normal perfusion, resulting in a V/Q ratio of 0. This phenomenon is referred to as right-to-left shunt, as discussed previously. In these alveolar units, the oxygen content is similar to that of the mixed venous blood and the CO_2 is elevated. At the other extreme, some alveolar units are fully ventilated but not perfused, resulting in an infinite V/Q ratio. This area of ventilation is called "dead space," in which the alveolar oxygen content is similar to that of the inspired gas mixture and the CO_2 is almost absent (Fig. 91-5).

Between these two extremes, any alteration of V/Q matching can lead to severe impairments in gas exchange with clinically significant hypoxemia, hypercapnia, or a combination of both. In the majority of respiratory failure cases, V/Q mismatch is the cause of hypoxemia and can be identified by an increased $(A - a)P_{O_2}$ difference and exclusion of the other four mechanisms of hypoxemia. Moreover, arterial oxygenation can normally be improved by adding supplemental O_2 to the mixture of inspired gas, which increases P_{AO_2} in poorly ventilated alveolar units.

Overall, among all five pathophysiologic mechanisms causing hypoxemia, shunt and V/Q mismatch are the most relevant from a clinical perspective. In fact, reduction of P_{IO_2} and impaired diffusion are rarely significant, and hypoventilation-induced hypoxemia can be easily corrected with minimal increments of F_{IO_2}. However, in clinical practice, more than one mechanism often contributes at the same time to the development of hypoxemia. It is important to stress that adequate cardiac output is necessary to avoid hypoxemia, because a reduced cardiac output is associated with lung perfusion impairment and consequent inequality of the V/Q ratio. Moreover, a low cardiac output is associated with a significant reduction in mixed venous oxygen saturation, which can thereby cause other mechanisms of hypoxemia (i.e., impaired diffusion), which under normal conditions are clinically insignificant, to contribute to the development of hypoxemia.

CLINICAL APPROACH

Hypoxemic respiratory failure can present with diverse signs and symptoms, depending on the time of occurrence (acute or chronic), the responsible pathophysiologic mechanism, the underlying etiology, and confounding comorbidities. For example, patients with hypoxemia can be tachypneic and tachycardiac or have a very low respiratory rate, as is seen in severe hypercapnia caused by hypoventilation. Hypoxic patients can have signs of severe respiratory distress, in cases of acute causes of hypoxemia, or appear completely comfortable, as is sometimes seen in patients with chronic obstructive pulmonary disease. Therefore, a systematic, clinical approach is very useful to identify a specific diagnosis from a large number of possible alternatives and to accelerate the initiation of proper treatment, which is urgently needed in cases of acute hypoxemic respiratory failure (Fig. 91-6).

The ABC evaluation (airway, breathing, and circulation) should be performed in every case. Supplemental oxygen should be given and intravenous access should be obtained. Patients with severe hypoxemic respiratory failure should be referred immediately to facilities that have the ability to continuously monitor vital signs, arterial oxygen saturation, blood pressure, and the electrocardiogram. Details of the presenting illness and the past medical history should be obtained rapidly in order to differentiate acute and chronic forms of hypoxemia and to identify the possible cause of hypoxemia and the important comorbidities that the patient might have. In

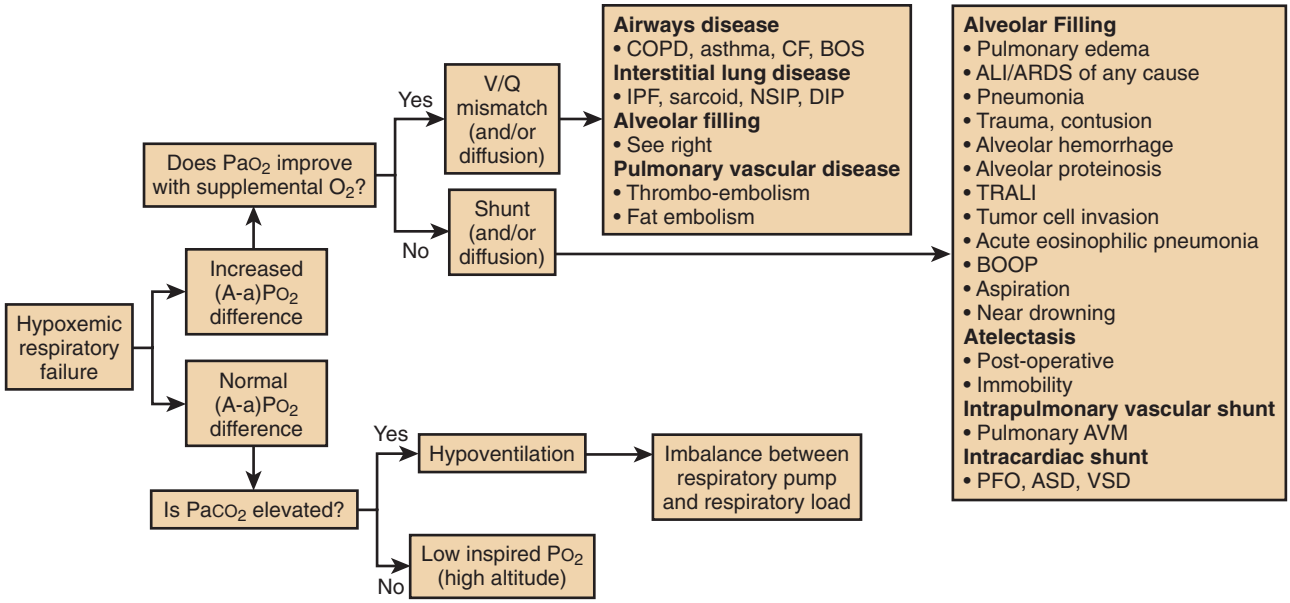

FIGURE 91-6 ■ Patient diagnostic algorithm shows a general approach to treating patients with hypoxemic respiratory failure based on the (A – a)P_{O_2} difference, Pa_{CO_2}, and/or response to supplemental oxygen. This is by no means an exhaustive list. In addition, it should be noted that multiple mechanisms can contribute simultaneously, thereby complicating the diagnostic process.

cases of acute hypoxemic respiratory failure, cardiac dysfunction, pulmonary infection or aspiration, venous thromboembolism, obstructive lung diseases, pneumothorax, hemothorax, and pulmonary contusion must be considered and excluded as the most frequent causes. An accurate physical examination of the respiratory and cardiac system is still necessary and sometimes sufficient to distinguish the different etiologic possibilities. In particular, the recognition on physical examination of congestive heart failure, a focal area of pulmonary consolidation, or a possible pneumothorax can expedite the diagnostic approach by excluding a large number of diseases and hasten the appropriate therapy. Therapy of patients with acute or severe hypoxemic respiratory failure must be initiated at the same time the diagnostic evaluation is under way in order to prevent delays in treatment.

Every patient with hypoxemic respiratory failure should be investigated with a chest radiograph, an electrocardiogram, routine blood work, and ABG. Other useful diagnostic tools include echocardiography, computed tomography angiography of the chest, ultrasound of the chest, bronchoscopy, and scintigraphy.

In particular, the values of arterial Pa_{O_2} and Pa_{CO_2} are essential to discriminate among the five mechanisms leading to hypoxemia. In fact, excluding a reduction in P_{IO_2} usually related to a stay at altitude, the measurement of Pa_{O_2} and Pa_{CO_2} allows calculation of the (A – a)P_{O_2} difference, which is normal (<10 mm Hg) in cases of hypoventilation as an isolated cause of hypoxemia and increased in cases of impaired diffusion, shunt, and V/Q mismatch. However, impaired diffusion is rarely a cause of clinically significant hypoxemia. Therefore, the differential diagnosis usually involves distinguishing V/Q mismatch and shunt, which can be identified by the response to 100% oxygen, because treatment with 100% supplemental O_2 does not improve the Pa_{O_2} when shunt is the primary cause of hypoxemia, but causes a significant increase in Pa_{O_2} when V/Q mismatch is present.

The treatment of hypoxemia has the immediate goal of increasing the Pa_{O_2}, in order to provide adequate oxygen delivery to the cells throughout the body. Therefore, in the management of patients with hypoxemic respiratory failure, it is also important to optimize the Hb concentration and cardiac output because each contributes significantly to the delivery of oxygen to peripheral tissues.

The most common strategies used to improve a patient's Pa_{O_2} rely on the administration of oxygen with positive pressure by means of either noninvasive or invasive mechanical ventilation. The historic "gold standard" for the treatment of hypoxemic respiratory failure is invasive mechanical ventilation, using various modalities of mechanical ventilation to provide adequate respiratory support to hypoxemic patients.[6] In particular, there is a large body of literature focused on improving mechanical ventilation in patients with the most severe forms of hypoxemia, including ARDS and its milder form, ALI[7] (see Chapter 90).

Another way to deliver supplemental oxygen with positive pressure is through the use of noninvasive ventilation, which can be dispensed through different types of interfaces, such as the helmet, nasal mask, and facial masks with different shapes to accommodate different facial features. Noninvasive ventilation is currently recommended by international guidelines as the first choice for the treatment of hypoxemic respiratory failure due to cardiogenic pulmonary edema or exacerbation of chronic obstructive pulmonary disease.[8] Moreover, there is evidence showing that noninvasive ventilation is also

effective in the treatment of postoperative hypoxemic respiratory failure in patients who have undergone abdominal surgery.[9] Furthermore, there are several studies of the administration of noninvasive ventilation to patients with hypoxemic respiratory failure of noncardiac origin, but these are not conclusive.[4,10,11]

In cases of severe hypoxemic respiratory failure that are refractory to all conventional treatments, there remain additional therapeutic options, such as prone positioning of the patient, administration of inhaled nitric oxide, use of high-frequency oscillatory ventilation, and extracorporeal membrane oxygenation.[12-14] However, these are still considered as rescue therapies because these therapies have not been shown to improve overall outcome, even though they often improve oxygenation.

ACKNOWLEDGMENTS

We acknowledge the contribution of Dr. Warren L. Lee and Dr. Arthur S. Slutsky to this chapter in previous editions.

KEY POINTS

- Hypoxemic respiratory failure is diagnosed when Pa_{O_2} is less than 60 mm Hg.
- There are several methods of measuring oxygenation that can be used when evaluating hypoxemia.
- Classification of hypoxemic respiratory failure, based on time of onset, underlying etiology, anatomic dysfunction, and/or pathophysiologic mechanism, can assist in diagnosis and management of hypoxemia.
- There are five pathophysiologic mechanisms leading to hypoxemia: decreased P_{IO_2}, hypoventilation, impaired diffusion, right-to-left shunt, and V/Q mismatch.
- The measurement of Pa_{O_2}, Pa_{CO_2}, $(A - a)P_{O_2}$ difference, and the response to supplemental oxygen are crucial steps in the diagnostic approach to hypoxemic respiratory failure.
- Low cardiac output associated with reduced mixed venous oxygen saturation can contribute to the development of hypoxemia,
- Owing to the large number of diseases that can induce hypoxemic respiratory failure, a systematic clinical approach is needed when evaluating and treating patients.

References

1. American Thoracic Society, American College of Chest Physicians: ATS/ACCP Statement on cardiopulmonary exercise testing. Am J Respir Crit Care Med 167:211–277, 2003.
2. National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network, Wiedemann HP, Wheeler AP, Bernard GR, et al: Comparison of two fluid-management strategies in acute lung injury. N Engl J Med 354:2564–2575, 2006.
3. Steinberg KP, Hudson LD, Goodman RB, et al: Efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome. N Engl J Med 354:1671–1684, 2006.
4. Ferrer M, Esquinas A, Leon M, et al: Noninvasive ventilation in severe hypoxemic respiratory failure: A randomized clinical trial. Am J Respir Crit Care Med 168:1438–1444, 2003.
5. West JB: *In* Sun B, Taylor C (eds): Pulmonary Pathophysiology: The Essentials (6th ed). Philadelphia: Lippincott Williams & Wilkins, 2003, pp 17–36.
5a. Grocott MPW, Martin DS, Levett DZH, et al: Arterial blood gases and oxygen content in climbers on Mount Everest. N Engl J Med 360:140–149, 2009.
6. Tobin MJ: Advances in mechanical ventilation. N Engl J Med 344:1986–1996, 2001.
7. Tremblay LN, Slutsky AS: Ventilator-induced lung injury: From the bench to the bedside. Intensive Care Med 32:24–33, 2006.
8. International Consensus Conferences in Intensive Care Medicine approved by ATS Board of Directors: Noninvasive positive pressure ventilation in acute respiratory failure. Am J Respir Crit Care Med 163:283–291, 2001.
9. Squadrone V, Coha M, Cerutti E, et al: Continuous positive airway pressure for treatment of postoperative hypoxemia: A randomized controlled trial. JAMA 293:589–595, 2005.
10. Antonelli M, Conti G, Esquinas A, et al: A multiple-center survey on the use in clinical practice of noninvasive ventilation as a first-line intervention for acute respiratory distress syndrome. Crit Care Med 35:18–25, 2007.
11. Randolph AG: Management of acute lung injury and acute respiratory distress syndrome in children. Crit Care Med 37:2448–2454, 2009.
12. Fan E, Mehta S: High-frequency oscillatory ventilation and adjunctive therapies: Inhaled nitric oxide and prone positioning. Crit Care Med 33:S182–S187, 2005.
13. Taccone P, Pesenti A, Latini R, et al: Prone positioning in patients with moderate and severe acute respiratory distress syndrome: a randomized controlled trial. JAMA 302:1977–1984, 2009.
14. Brown JK, Haft JW, Bartlett RH, Hirschl RB: Acute lung injury and acute respiratory distress syndrome: Extracorporeal life support and liquid ventilation for severe acute respiratory distress syndrome in adults. Semin Respir Crit Care Med 27:416–425, 2006.

CHAPTER 92

ACUTE VENTILATORY FAILURE

Nicholas S. Hill, MD • Gregory A. Schmidt, MD

INTRODUCTION

PATHOPHYSIOLOGY OF ACUTE VENTILATORY FAILURE

ACUTE VENTILATORY FAILURE DUE TO INSUFFICIENT VENTILATORY DRIVE

Pharmacologic Causes

Congenital or Acquired Central Hypoventilation

Principles of Management

ACUTE VENTILATORY FAILURE DUE TO NEUROMUSCULAR IMPAIRMENT

Cervical Spinal Cord Injury

Injury or Disease Affecting the Phrenic Nerve

Neuromuscular Disease

Neuromuscular Weakness Associated with Critical Illness

Assessment for Need for Mechanical Ventilation in Neuromuscular Weakness

Principles of Ventilator Management

ACUTE VENTILATORY FAILURE DUE TO THORACIC OR LUNG RESTRICTIVE MECHANISMS

Chest Wall and Pleural Disease

Parenchymal Lung Disease

Principles of Ventilator Management

ACUTE VENTILATORY FAILURE DUE TO AIRWAY OBSTRUCTION

Upper Airway Obstruction

Chronic Obstructive Pulmonary Disease

Asthma

ACUTE VENTILATORY FAILURE DUE TO VASCULAR IMPAIRMENT

INTRODUCTION

Respiratory failure exists when the respiratory system cannot maintain gas exchange, causing dysfunction in other organs or threatening life. Such impairment can affect primarily oxygenation, manifested by hypoxemia, or ventilation, manifested by hypercapnia and respiratory acidosis. This chapter deals with this latter circumstance, commonly called *ventilatory failure*.

Carbon dioxide (CO_2) tension in the arterial blood (Pa_{CO_2}) is a function of alveolar ventilation ($\dot{V}_A$) and CO_2 production ($\dot{V}_{CO_2}$), according to the following relationship.

$$Pa_{CO_2} = \left(\dot{V}_{CO_2} \times k\right) / \dot{V}_A \quad (1)$$

Total minute ventilation is the sum of both $\dot{V}_A$ and dead space ventilation. Either a decrease in total minute ventilation or an increase in dead-space ventilation can thus decrease $\dot{V}_A$. Any decrease in $\dot{V}_A$, or increase in $\dot{V}_{CO_2}$ relative to $\dot{V}_A$, results in an increase in Pa_{CO_2}. Because bicarbonate retention by the kidney in response to hypercapnia occurs slowly, a sudden increase in Pa_{CO_2} will not be buffered readily by bicarbonate and thus will abruptly lower arterial pH. Ventilatory failure exists whenever Pa_{CO_2} is substantially elevated, and acute ventilatory failure is present when the change from the patient's baseline state develops rapidly enough to produce a clinically important drop in arterial pH. Because patients with severe chronic obstructive pulmonary disease (COPD), chronic neuromuscular disease, and other disorders may already have hypercapnia at baseline, the presence of acute ventilatory failure is determined not so much by the Pa_{CO_2} value as by the presence of acidemia, typically to an arterial pH of less than 7.30. The presence of acute ventilatory failure cannot be determined accurately by physical examination, pulse oximetry, exhaled CO_2, or other noninvasive tests. Thus, making the diagnosis requires arterial blood gas analysis.[1]

PATHOPHYSIOLOGY OF ACUTE VENTILATORY FAILURE

Alveolar ventilation becomes inadequate in relation to CO_2 production either because of a failure of the patient's

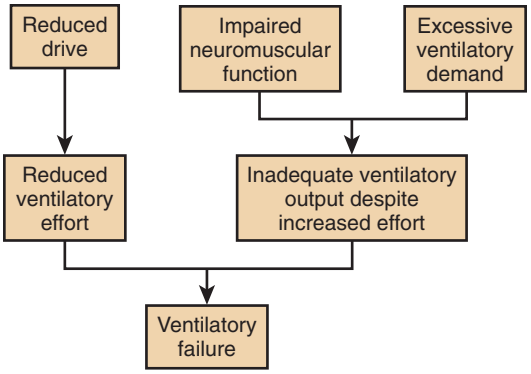

FIGURE 92-1 ■ The physiologic mechanisms of acute ventilatory failure.

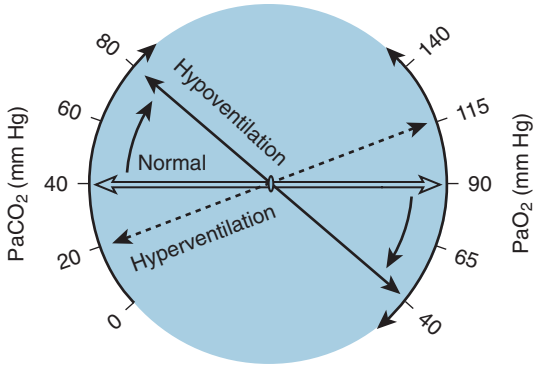

FIGURE 92-2 ■ The relationship between arterial oxygen pressure (Pa_{O_2}) and arterial carbon dioxide pressure (Pa_{CO_2}) as ventilation increases or decreases, assuming that the alveolar-arterial oxygen pressure (A – a)P_{O_2} difference does not change and the respiratory exchange ratio is 0.8. (Redrawn from Pierson DJ, Kacmarek RM [eds]: Foundations of Respiratory Care. New York: Churchill Livingstone, 1992, p 298.)

ventilatory capability (pump failure) or because of a failure of the ventilatory effort (drive failure)[2,3] (Fig. 92-1). These two mechanisms are distinct in their clinical presentations. Patients with acute failure of the ventilatory pump are dyspneic and tachypneic with other signs of distress and sympathetic nervous system activation, whereas patients with failure of ventilatory drive are not short of breath and typically demonstrate bradypnea or apnea.

Although acute ventilatory failure is primarily a disorder of alveolar ventilation, hypoxemia is also usually present. Alveolar hypoventilation causes a proportional fall in alveolar oxygen pressure ($P_{A_{O_2}}$), according to the alveolar gas equation.

$$P_{A_{O_2}} = P_{I_{O_2}} - (Pa_{CO_2}/R) \quad (2)$$

where Pa_{CO_2} can be assumed to be nearly the same as alveolar carbon dioxide pressure ($P_{A_{CO_2}}$), $P_{I_{O_2}}$ is the inspired P_{O_2} (i.e., the inspired oxygen fraction multiplied by the difference of barometric pressure and 47 [water vapor pressure at body temperature]), and R is the respiratory exchange ratio. This relationship explains the fall in Pa_{O_2} that accompanies alveolar hypoventilation, as shown in Figure 92-2.[2] Calculating Pa_{O_2} using Equation 2 permits determination of the alveolar-arterial oxygen pressure difference [(A – a)P_{O_2}] (commonly but imprecisely called the "A – a gradient" and more precisely called the "A – a oxygen tension difference"). This calculation distinguishes between pure hypoventilation as an explanation for hypoxemia (in which case [(A – a)P_{O_2}] is normal) and the presence of other mechanisms such as low ventilation-perfusion (V/Q) ratios and right-to-left shunt (in which case (A – a)P_{O_2} is increased).

Finally, hypercapnia can be a feature of hypoxemic respiratory failure if the derangement in gas exchange is sufficiently severe. Both right-to-left shunt and low V/Q ratios are present in the acute respiratory distress syndrome (ARDS) and can increase dead space–to–tidal volume ratios (V_D/V_T) as determined by the Bohr equation,[4] thus impairing CO_2 elimination and contributing to hypercapnia.

Table 92-1 classifies the typical clinical presentations of acute ventilatory failure according to the site or type of defect and the physiologic mechanism or category of disorder responsible. Not every listed example is discussed in this chapter.

More than one mechanism may coexist in a given patient, producing a life-threatening condition even when the individual processes are only moderate in severity. For example, in decompensated obesity-hypoventilation syndrome, a patient whose underlying respiratory drive is reduced and whose obesity poses an increased elastic load on the ventilatory pump may develop acute-on-chronic ventilatory failure in the presence of a relatively modest increase in the work of breathing from the additional restrictive effects of cardiomegaly and pleural effusions.

ACUTE VENTILATORY FAILURE DUE TO INSUFFICIENT VENTILATORY DRIVE

Pharmacologic Causes

Depression of the drive to breathe by drugs is by far the most common circumstance of this form of acute ventilatory failure and, it may be argued, the only one in which it is the primary mechanism. In the conditions discussed later, and even in acute drug overdose, an inability to protect the airway and the increased work of breathing usually play a major role in the genesis of acute respiratory acidosis. The opioids are the most potent depressors of both hypoxic and hypercapnic ventilatory drive, but any sedative, hypnotic, or anxiolytic agent causes respiratory depression if administered in sufficient quantity.[5]

Respiratory depression resolves as the drug is cleared from the body or is pharmacologically antagonized, as signaled by the return of spontaneous breathing efforts. Because the central nervous system effects of some agents may wax and wane due to the enterohepatic circulation, lipid storage, or other mechanisms, patients should be observed until it is clear that the ventilatory drive has been reestablished before they are weaned

TABLE 92-1. Clinical Classification of Ventilatory Failure

Site or Type of Defect	Mechanism or Category	Clinical Examples
Ventilatory drive	Pharmacologic	Drug overdose (opioids, sedatives, alcohol); general anesthesia
	Congenital	Primary alveolar ventilation (Ondine's curse)
	Acquired	Cerebrovascular accident; neoplasm; carotid body resection
	Combination	Obesity-hypoventilation syndrome; myxedema
Neural transmission to ventilatory muscles	Cervical spinal cord injury	Trauma; tumor; vascular accident
	Demyelinating peripheral neuropathy	Guillain-Barré syndrome
	Anterior horn cell disease	Poliomyelitis; amyotrophic lateral sclerosis
	Phrenic nerve lesion	Trauma; cardiac surgery; neoplasm; idiopathic
Ventilatory muscles	Pharmacologic	Neuromuscular blocking agents
	Primary muscle disorder	Muscular dystrophy; polymyositis; dermatomyositis
	Disorders of the neuromuscular junction	Myasthenia gravis; botulism; tetanus; tick paralysis
	Electrolyte and metabolic disturbances	Hypophosphatemia; hypokalemia; hypomagnesemia; myxedema
Chest wall	Decreased mobility	Kyphoscoliosis; traumatic asphyxia; tight casts or bandages; severe obesity; ankylosing spondylitis; flail chest
Pleural disorders	Extrapulmonary restriction	Pneumothorax; pleural effusion; pleural thickening or malignancy
Airway obstruction	Upper airway obstruction	Epiglottitis; foreign body; tumor; vocal cord paralysis; tracheomalacia
	Lower airway obstruction	COPD; acute severe asthma
Increased dead-space ventilation	Very high V/Q	COPD
	Very low V/Q; right-to-left shunt	Severe ARDS
	Generalized pulmonary hypoperfusion	Hypovolemic or cardiogenic shock; during CPR; pulmonary hyperinflation (excessive applied PEEP; intrinsic PEEP)
	Localized pulmonary hypoperfusion	Pulmonary thromboembolism*; venous air embolism
Increased CO_2 production*	Inflammation; hypermetabolism	Fever; sepsis; burns; severe trauma
	Muscle activity	Shivering; tetany; seizures; malignant hyperthermia
	Excessive caloric intake	Increased overall caloric intake (especially carbohydrate calories)
Exogenous CO_2 inhalation	Increased inspired P_{CO_2}	Laboratory or industrial accident; therapeutic use; rebreathing

*In the absence of ability to compensate with increased overall ventilation.
ARDS, acute respiratory distress syndrome; COPD, chronic obstructive pulmonary disease; CPR, cardiopulmonary resuscitation; PEEP, positive end-expiratory pressure; P_{CO_2}, carbon dioxide pressure; V/Q, ventilation-perfusion ratio.

from ventilatory support. In the case of drug overdoses and other poisoning, identifying the specific agent or agents involved and the use of any specific therapies available, such as antidotes or dialysis, is important to expedite the weaning process from ventilatory support.[5]

Patients who fail to wean from mechanical ventilation because of inadequate drive from depressant drugs breathe slowly or not at all when ventilatory support is briefly discontinued. The much more common reason for difficulty weaning after drug overdose is that other mechanisms (e.g., aspiration pneumonia or sepsis) intervene. In these circumstances, with a return of respiratory drive, patients become tachypneic and manifest signs of respiratory distress when ventilatory support is discontinued.[6]

Congenital or Acquired Central Hypoventilation

Decreased ventilatory drive is a frequent contributor to the development of chronic ventilatory insufficiency, but it is typically not the sole mechanism for acute ventilatory failure, except for those patients presenting with drug-induced suppression. When patients with underlying abnormalities of ventilatory drive develop respiratory infections, congestive heart failure, or other acute illness, they are more likely than individuals without such defects to develop acute ventilatory failure.

The obesity-hypoventilation syndrome, discussed in Chapter 88, is characterized by blunted responses to hypoxia and hypercapnia[7] and is one disorder in which patients may first present in acute ventilatory failure. Typically, such patients have a history of recent weight gain and are found to be markedly fluid-overloaded, with features of cor pulmonale. The increased work of breathing from decreased chest wall compliance, cardiomegaly, and often large pleural effusions, as well as worsening hypoxemia, all contribute to respiratory muscle fatigue and the development of severe hypercapnia and respiratory acidosis. Hypoventilation is more common among hospitalized patients with severe obesity than has previously been appreciated.[8] As the

prevalence of obesity increases, ventilatory failure from decompensation of the obesity-hypoventilation syndrome is likely to be encountered more frequently.

Disorders in addition to the obesity-hypoventilation syndrome that may be associated with diminished hypoxic or hypercapnic ventilatory drive include myxedema,[9] the Prader-Willi syndrome,[10] and hypogonadism treated with exogenous testosterone.[11] These disorders may contribute to the development of acute ventilatory failure in susceptible individuals.

Acute stroke is another setting in which disordered ventilatory drive may contribute to acute ventilatory failure. The prognosis of patients with strokes who require intubation and mechanical ventilation is poor.[12] Outcomes in patients with ischemic and hemorrhagic strokes were equally poor in one study.[12] Other reports have found an especially unfavorable prognosis after basilar artery occlusion.[13] However, acute ventilatory failure in the setting of acute stroke does not preclude survival; in one series of 124 patients with hemispheric stroke requiring mechanical ventilation, one third of the patients were alive after 1 year.[14] Although impaired ventilatory drive may contribute to acute ventilatory failure following acute stroke, other processes, especially the inability to protect the lower airway and adequately clear respiratory tract secretions, are usually present.[12,15]

Principles of Management

Because the underlying physiologic defect is inadequate drive for ventilation with a presumably normal ventilatory pump, management focuses on restoring normal alveolar ventilation. Although noninvasive positive-pressure ventilation (NPPV) is being applied in an increasing number of clinical settings to augment alveolar ventilation, its utility lies mainly in maintaining respiration in patients with failure of the ventilatory pump, whereas endotracheal intubation is generally necessary following acute failure of respiratory drive. This is not only because restoration of alveolar ventilation can be attained more rapidly and reliably with invasive mechanical ventilation but also because the concomitant problems with airway protection and secretion clearance in most patients with acute depression of ventilatory drive are relative contraindications to NPPV.

Because of the patient's impaired ventilatory drive, a ventilator mode should initially be chosen that provides full support, such as volume-targeted assist-control ventilation. In the absence of acute lung injury or severe airflow obstruction, ventilator settings should be chosen to aim for values for arterial pH and P_{ACO_2} in the normal range, and supplemental oxygen should be supplied (with positive end-expiratory pressure [PEEP] if necessary) to maintain normal arterial P_{AO_2}. Unless there are serious coexisting pulmonary conditions, weaning should be carried out as soon as there is evidence that ventilatory drive is restored (see Chapter 89). Extubation is probably safe if the patient has a spontaneous cough, does not require frequent suctioning, and is judged able to protect the airway, even if alertness remains impaired.[16]

ACUTE VENTILATORY FAILURE DUE TO NEUROMUSCULAR IMPAIRMENT

Cervical Spinal Cord Injury

Injury to the upper cervical spinal cord may interrupt transmission of the stimulus to breathe from the respiratory centers in the brain stem to the diaphragm and other ventilatory muscles. Because the phrenic nerve roots that supply the diaphragm arise from spinal segments C3 to C5, patients with acute injury at this level or above usually require mechanical ventilation. Patients with C1–2 spinal injury levels are permanently ventilator-dependent, whereas those with C3–4 injuries may eventually achieve at least partial ventilator-independence. Lesions below C4 are usually compatible with unassisted ventilation unless there are complicating processes such as intrinsic lung disease or impaired mental status (see also Chapter 87).

Adverse physiologic effects of cervical spinal cord injury in the initial days or weeks include loss of lung volumes and inability to take deep breaths (which predispose to atelectasis), inability to cough normally (which predisposes to the development of pneumonia and complicates its management), and impaired hypoxic pulmonary vasoconstriction (which predisposes to severe and often refractory hypoxemia when atelectasis or pneumonia occurs). Although it is accurate to say that the short-term prognosis is generally related to the level of the injury,[16a] retrospective studies have shown that both mortality[17] and intensive care unit (ICU) length of stay[16a] for patients with cervical spinal cord injury are more strongly influenced by the development of pneumonia and other respiratory complications than by the specific cord injury level.

Although there are reports of initial management of patients with high cervical spinal cord injury with NPPV,[18] great expertise is required to avoid aspiration and other complications; in most centers, invasive ventilatory support is preferable, at least initially. Phrenic nerve pacing,[19,20] thereby permitting extubation or decannulation from tracheostomy, has also been reported in the later period following injury. The eventual ability to wean from ventilatory support and undergo decannulation from tracheostomy are major determinants not only of survival but also of quality of life for patients with cervical spinal cord injury.[16a,17]

Injury or Disease Affecting the Phrenic Nerve

Although loss of diaphragm function as a cause for ventilatory failure is often due to spinal cord injury, paralysis of the diaphragm leading to ventilatory failure may also result from phrenic nerve injury or disease. The most common setting is phrenic nerve injury following cardiac surgery, which is almost always unilateral and likely due to either cold cardioplegia or physical injury during internal mammary artery harvesting. The presentation ranges

from an incidentally discovered radiographic abnormality without clinical impact (most common) to ventilatory failure requiring long-term mechanical ventilation.[20,21]

As first outlined by Diehl and associates,[22] post–cardiac surgery phrenic nerve injury can be a severe problem. They retrospectively evaluated 13 patients encountered during a 2-year period who could not be weaned from ventilatory support for several weeks after cardiac surgery and were found to have severely impaired respiratory muscle function. Clinically relevant diaphragmatic dysfunction was estimated to be 0.5% when no topical cooling was used and 2.1% when iced slush with no insulation pad was added for myocardial protection.[22]

Bilateral diaphragmatic paralysis can present unassociated with trauma or surgical manipulation. In some patients, no systemic disease or specific cause could be found.[23] One case of bilateral diaphragm paralysis complicating von Recklinghausen's neurofibromatosis has been reported.[24] Isolated ventilatory muscle weakness can also be the initial manifestation of generalized neuromuscular disorders such as myasthenia gravis[25] and amyotrophic lateral sclerosis (ALS).[26]

Neuromuscular Disease

The most common cause of acute paralysis and neuromuscular ventilatory failure presenting to acute care hospitals is Guillain-Barré syndrome,[27] in which one third of patients may develop acute ventilatory failure.[28–30] Therapy with plasma exchange and immune globulins has improved the outlook for patients who develop Guillain-Barré syndrome, although 3% to 8% die, and 5% to 10% of individuals who survive remain seriously disabled.[27,31] Theoretically, death should be preventable in most if not all patients with this disease, because mortality is primarily from potentially avoidable respiratory complications (see also the discussion in Chapter 87). It remains unclear whether the need for mechanical ventilation can be predicted prior to the onset of frank ventilatory failure in this condition.[32]

Myasthenia gravis is a relatively infrequent cause of acute ventilatory failure. Investigators at one large regional neuromuscular disease center reported 18 patients with 24 episodes of ventilatory failure requiring mechanical ventilation during a 9-year period.[33] Acute ventilatory failure usually occurs in patients with an established diagnosis of myasthenia gravis, although isolated ventilatory muscle weakness requiring mechanical ventilation has been reported as the initial manifestation of the disorder.[25]

ALS and other motor neuron diseases may demonstrate progressive weakness of the bulbar and ventilatory muscles that is variable both in presentation and in the rate of progression.[34,35] Typically, ventilatory muscle weakness develops in patients in whom the diagnosis of ALS is already well established.[34–38] Repeated assessment can usually detect the onset of ventilatory muscle dysfunction during outpatient management.[37,38] However, dyspnea or even acute ventilatory failure can be the initial clinical manifestation of motor neuron disease.[39,40] Elective initiation of noninvasive ventilation is becoming more common in patients with gradually progressive ventilatory insufficiency.[37,38] Its successful use has also been reported in acute ventilatory failure complicating ALS,[41] although bulbar weakness and a high risk of aspiration make invasive mechanical ventilation a safer choice for such patients, at least initially. With appropriate counseling and management, only a small proportion of patients with ALS receive invasive mechanical ventilation, and presentation with acute ventilatory failure should be an unusual occurrence.[42]

Botulism remains an important cause of acute ventilatory failure worldwide, although only about 25 cases of food-borne illness and 3 cases of wound botulism have been reported annually in the United States since the 1970s.[43] A high proportion of patients with both forms of botulism develop clinically important respiratory muscle weakness. In one food-borne outbreak, 81% of patients developed pulmonary involvement, and 11 of 34 patients required mechanical ventilation for acute ventilatory failure.[44]

Because it is infrequent and does not occur in outbreaks, wound botulism poses a challenge in both diagnosis and appropriate early management. Historically associated with dirty traumatic wounds, especially those sustained in rural areas, wound botulism has also been encountered in recent years as a complication of injecting "black tar" heroin.[45,46] In a series of 20 consecutive patients with black tar heroin–associated wound botulism,[45] acute ventilatory failure developed in 15 (75%) and was more frequent in those patients in whom the administration of antitoxin or antibiotics was delayed beyond 12 hours of initial presentation. Ventilatory failure in wound botulism may be prolonged. Twelve of 15 patients with black tar heroin–associated botulism needed ventilatory support for more than 30 days.[45] Recovery may likewise be prolonged, with residual ventilatory muscle weakness detectable as long as 2 years after presentation.[47]

Dermatomyositis may also cause respiratory muscle weakness severe enough to cause acute ventilatory failure,[48,49] although not as an initial manifestation in the absence of other typical symptoms and signs of this condition. In these reported cases, ventilatory function recovered as the disease was brought under control with immunosuppressive therapy.

Neuromuscular Weakness Associated with Critical Illness

Neuromuscular dysfunction associated with critical illness commonly contributes to the subsequent inability to wean such patients from mechanical ventilation.[50] Several forms of critical illness–associated neuromuscular dysfunction are recognized.

Prolonged Neuromuscular Blockade

Neuromuscular blocking drugs are sometimes administered to ventilated patients, in conjunction with

sedation, to facilitate mechanical ventilation, to reduce oxygen consumption, or to control intracranial pressure. The clinical kinetics of these agents have been determined mainly in the context of short-term general anesthesia, and their effects on ventilatory muscle function in critically ill patients are much more variable. Most neuromuscular blocking drugs are cleared more slowly in the presence of hepatic—and especially renal—insufficiency. This is particularly true for pancuronium and vecuronium, and the effects of these drugs can last days or even weeks in the presence of renal failure.[51] Because they are metabolized in plasma and thus do not depend on renal or hepatic function for clearance, atracurium and cisatracurium are not associated with prolonged muscle weakness as a result of delayed clearance.[50]

Train-of-four stimulation can be used to monitor the depth of neuromuscular blockade, avoiding excessive paralysis and reducing the quantity of drug used as well as the recovery time of neuromuscular function in critically ill patients.[52] Although these benefits may not be seen when atracurium and cisatracurium are used,[53] train-of-four testing is sufficiently simple and inexpensive to perform that many experts believe it should be employed routinely.[54] Minimizing the use of neuromuscular blocking drugs in ventilator management and using train-of-four stimulation to monitor the degree of muscle relaxation as well as daily interruptions of paralysis can prevent unsuspected prolonged paralysis.[55]

Intensive Care Unit–Acquired Weakness

Unexpected, acute weakness and prolonged ventilatory failure was first reported in patients with status asthmaticus treated with corticosteroids and neuromuscular blocking drugs.[56,57] Subsequently, a similar syndrome has been recognized in other groups of ICU patients, especially those with sepsis and systemic inflammation, even without corticosteroid administration or therapeutic paralysis.[50] Both muscle and nerve abnormalities can predominate, leading to a confusing array of diagnostic terms, such as "critical illness myopathy," "critical illness polyneuropathy," "postparalytic myopathy," "ICU-acquired paresis," "acute quadriplegic myopathy," and the preferred term, "ICU-acquired weakness." The pathophysiology of ICU-acquired neuromuscular dysfunction is poorly understood, but may involve elements of disuse and active muscle catabolism sparked by systemic inflammation. Electromyography reveals reduced compound muscle action potential upon motor nerve stimulation (with normal conduction velocity); increased action potential duration; and spontaneous electrical activity on muscle needle recording (e.g., fibrillation potentials; positive sharp waves).[58] Biopsy findings may include primary axonal degeneration, type II muscle fiber atrophy, thick filament (myosin) loss, and (occasionally) necrotizing myopathy.

One quarter to one half of all patients who require more than 7 days of ICU care and the majority of patients who develop the systemic inflammatory response syndrome can be shown by neurophysiologic testing to have ICU-acquired weakness.[50] These neurophysiologic abnormalities arise early, accumulate during the course of illness, and usually affect both nerves and muscles.[59] Prospective studies have shown that about one third of critically ill patients exhibit weakness on clinical evaluation.[50,60] The typical patient exhibits symmetrical extremity weakness in which proximal function is more impaired than distal and the facial muscles are spared. Clinically, this disorder can produce severe neuromuscular weakness, often affects the respiratory muscles, and may prolong the need for ventilatory support.[60,61] This syndrome should be suspected in patients who are weak (Medical Research Council [MRC] score < 48[60]) in the context of critical illness, have the typical clinical examination, and in whom no better alternative cause for weakness can be identified. Handgrip strength may serve as a simple test to identify ICU-acquired weakness.[62] Nerve conduction studies, electromyography, and muscle biopsy generally are not necessary, but their role in diagnosis remains an area of active investigation. The prognosis for recovery of strength is variable, with many patients improving rapidly over days to weeks while others remain weak for many months or longer. The incidence of ICU-acquired weakness can be reduced by intensive insulin therapy,[61,63,64] avoiding neuromuscular blocking drugs and corticosteroids where possible, and possibly by physical therapy.[64a] Because ICU-acquired weakness is so strongly associated with severity of illness, length of ICU stay, and the presence of multiple organ system dysfunction, prevention focuses on scrupulous attention to good general ICU care and avoidance of sepsis.[50]

Ventilator-Induced Diaphragmatic Dysfunction

Many critically ill patients develop muscle weakness that impedes functional recovery and is associated with prolonged mechanical ventilation. Some component of this represents ICU-acquired weakness,[65] but mechanical ventilation itself (without systemic inflammation) is sufficient to weaken respiratory muscles.[66-68] The lack of neural stimulation or associated contraction plays a role in the evolution of weakness because measures to keep muscles contracting can ameliorate weakness. The diaphragm, the muscle most responsible for sustaining the work of breathing, may be even more sensitive than other skeletal muscles to the effects of critical illness. In animal models, the diaphragm weakens during the first 1 to 3 days of mechanical ventilation. Using phrenic nerve stimulation, one study demonstrated a reduction in maximal transdiaphragmatic pressure in a group of ventilated patients in comparison to findings in normal volunteers.[69] As in studies of peripheral skeletal muscle, stimulating the diaphragm to contract serves to attenuate greatly the loss of strength.[70] This raises the possibility that partial rather than full ventilatory support may serve to maintain diaphragmatic strength, potentially reducing time on the ventilator.[70]

Assessment of Need for Mechanical Ventilation in Neuromuscular Weakness

Respiratory muscle weakness should be considered when there is obvious peripheral muscle weakness, but neuromuscular abnormalities may not always be evident. Respiratory muscle weakness may also be suspected when dyspnea is out of proportion to radiographic and respiratory mechanical abnormalities seen during mechanical ventilation. Further confirmation can be gained by measuring the maximal inspiratory pressure or, in some instances, by performing ultrasound examination of the diaphragms.

Early clinical indicators of the need for mechanical ventilation in patients with neuromuscular weakness remain controversial. In addition to subjective assessments of symptoms of dyspnea and of respiratory distress, objective assessments of vital capacity and maximum inspiratory pressure have generally been used to evaluate ventilatory muscle capability. In one retrospective study, 60 patients with Guillain-Barré syndrome who required intubation and ventilation were compared with 54 similar patients who did not. Clinical evidence of rapid disease progression, development of bulbar weakness, bilateral facial weakness, and dysautonomia were highly correlated with the need for intubation and mechanical ventilation.[29] Other findings associated with intubation were a vital capacity of less than 20 mL/kg, a maximum inspiratory pressure that failed to reach −30 cm H_2O, a maximum expiratory pressure of less than 40 cm H_2O, or a decrease in one or more of these functions by at least 30% of the initial value.[29] However, without prospective randomized studies, the predictive value of these thresholds cannot be confirmed.

A prospective study of electromyography in 60 patients with Guillain-Barré syndrome, in which the managing clinicians were unaware of the test results, showed that electrophysiologic evidence of demyelination was highly correlated with the need for intubation and mechanical ventilation.[71] In another study of patients with Guillain-Barré syndrome, 44 patients who required mechanical ventilation were more likely to have cranial nerve involvement and immunoglobulin G (IgG) anti-GQ1b antibodies than were 87 patients who did not require ventilation.[72]

For patients with myasthenia gravis, not all studies have found bedside tests of pulmonary function to be predictive of the need for intubation and mechanical ventilation.[73] Nonetheless, most authors recommend serial assessments such as vital capacity in patients hospitalized with acute neuromuscular disease in order to detect as early as possible the need for ventilatory assistance.[74] Although the optimal means for monitoring respiratory muscle function remain uncertain, it is clear that intubation and mechanical ventilation should be undertaken prior to the development of severe respiratory acidosis or respiratory arrest. For this reason, patients with acute neuromuscular disease who show signs of pulmonary compromise should be monitored in an ICU. Although the rate of progression may fluctuate, serial measurements of vital capacity and maximal inspiratory pressure along with repeated physical examinations focusing on bulbar function and ability to cough are advisable to avoid emergent intubations (Fig. 92-3).[75]

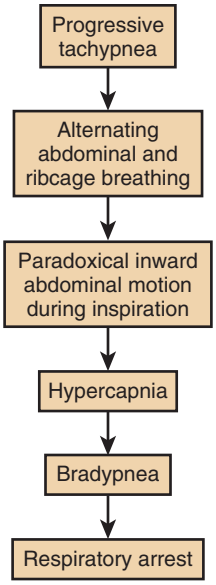

FIGURE 92-3 ■ The sequence leading to respiratory arrest with failure of the ventilatory pump. Individual patients proceed through the steps shown at variable rates and may skip one or more stages. However, except for sudden events affecting the central nervous system or the administration of paralyzing drugs, respiratory arrest does not occur abruptly without preceding physical manifestations. (Adapted in part from Cohen CA, Zagelbaum G, Gross D, et al: Clinical manifestations of inspiratory muscle fatigue. Am J Med 73:308–316, 1982.)

Principles of Ventilator Management

Patients with acute ventilatory failure due to neuromuscular disease usually have normal underlying lung function. Because atelectasis is especially common for these patients,[76,77] it has been common practice in the past to use larger than usual tidal volumes, typically 12 to 15 mL/kg or more. Anecdotally, many patients with neuromuscular disease seem less dyspneic with large tidal volumes, although this has not been subjected to prospective evaluation. As a result of the use of large tidal volumes, such patients commonly manifest respiratory alkalosis. A reasonable alternative is to use more typical tidal volumes (~6 mL/kg), faster rates, and 5 to 10 cm H_2O PEEP to prevent atelectasis while avoiding respiratory alkalosis. Patients incapable of breathing unassisted should be ventilated in a manner that makes them comfortable; there is no convincing evidence that "exercising" their respiratory muscles speeds recovery. Also, no evidence supports the use of weaning approaches other than those currently recommended for other patients with acute ventilatory failure,[78] although, prior to extubation,

special attention should be paid to the patient's ability to protect the airway and clear secretions once the patient can breathe unassisted.

ACUTE VENTILATORY FAILURE DUE TO THORACIC OR LUNG RESTRICTIVE MECHANISMS

Many restrictive diseases of the lungs or chest wall progress insidiously over months or years. Critical illness may represent the natural history of the underlying condition but may also signal an acutely superimposed, potentially reversible crisis such as infection, pneumothorax, or thromboembolism.

Chest Wall and Pleural Disease

Thoracic restriction and ventilatory muscle dysfunction due to severe kyphoscoliosis typically leads to gradually progressive ventilatory insufficiency, and patients can present with acute or acute-on-chronic ventilatory failure and require intensive care. Physiologic studies have shown that both lung and chest wall mechanics are impaired during acute respiratory failure in patients with kyphoscoliosis.[79] Primary disease of the pleura, such as asbestos-related diffuse pleural thickening or postinflammatory fibrothorax, could potentially present in similar fashion; but dyspnea and hyperventilation are more common with these diseases, and respiratory acidosis develops late in the course of the disorder unless ventilatory drive is depressed or there is concomitant lung involvement. Pleural effusion or pneumothorax can likewise precipitate acute ventilatory failure but usually in the presence of underlying obstructive or restrictive pulmonary disease. Obesity-hypoventilation syndrome with decompensated cor pulmonale, discussed earlier, is another example of acute-on-chronic ventilatory failure involving pulmonary restriction. The fact that most severely obese individuals do not have hypercapnia or develop acute ventilatory failure emphasizes the fact that this phenomenon is multifactorial.

Long-term noninvasive ventilation appears to be beneficial in selected patients with kyphoscoliosis and other chest wall diseases,[80] and has been reported to be successful in acute-on-chronic ventilatory failure[81,82] as well as in obesity-hypoventilation.[83] However, patients with acute ventilatory failure due to restrictive mechanisms may require intubation during the acute phase of their illness because noninvasive ventilation may be a less effective option in restrictive than in obstructive lung disease. For example, patients with restrictive disease may need higher inflation pressures due to increased chest wall elasticity; the lower volumes and superimposed neuromuscular weakness in restrictive disease may limit expiratory flow and cough efficiency leading to retained secretions. In a recent study of patients with chest trauma complicated by persistent hypoxemia, NPPV reduced the need for intubation and shortened the hospital stay.[84]

Parenchymal Lung Disease

Idiopathic pulmonary fibrosis and other pulmonary parenchymal restrictive diseases are usually associated with hyperventilation rather than hypoventilation. However, acute ventilatory failure can occur in the late stages of these conditions, either as a manifestation of the primary disease process[85,86] or, more often, in conjunction with pneumonia, surgery, or other intercurrent illness.[87-89] Physiologic assessment has demonstrated markedly increased lung stiffness and resistance in patients with end-stage idiopathic pulmonary fibrosis requiring mechanical ventilation,[89] explaining the development of hypercapnia and acute ventilatory failure in such individuals.

Several series have documented the poor prognosis of patients who present with acute respiratory failure in the setting of advanced interstitial fibrosis.[86,88,89] In one retrospective report of 14 consecutive patients with idiopathic pulmonary fibrosis admitted to the ICU with acute respiratory failure, all 14 died despite aggressive ventilatory support.[87] In a second report, of 23 similar patients, 22 patients died, the single survivor received a lung transplant shortly after admission.[88] In a third series of 19 patients with pulmonary fibrosis who received mechanical ventilation mostly for acute respiratory failure complicating the underlying disease, 13 died.[89] Outcomes appear equally poor regardless of whether ventilation is invasive or noninvasive.[90]

Principles of Ventilator Management

During NPPV of patients with restrictive disease, the need for higher airway pressures than are used for COPD, and thus the difficulty in achieving a seal at the interface and in avoiding gastric insufflation, lowers the likelihood of success. Furthermore, considering that a superimposed confounder such as a respiratory infection often precipitates the acute bout of respiratory failure, accompanied by increased work of breathing and secretion retention, invasive ventilatory support (as with volume-targeted assist-control ventilation) is usually required. The best way to ventilate patients with acute respiratory failure in the setting of underlying restrictive thoracic or lung disease has not been determined by clinical trials. The potential for hemodynamic compromise, barotrauma, and ventilator-induced lung injury with the use of high pressures and the physiologic similarity to ARDS in patients with deteriorating pulmonary fibrosis make it reasonable to apply similar lung-protective ventilator strategies and management targets (see Chapter 89). Low tidal volumes (e.g., 6 mL/kg predicted body weight) should be applied, attempting to keep the end-inspiratory plateau pressure at less than 30 cm H_2O if possible. Patients with restrictive lung disease typically breathe rapidly and shallowly, so tachypnea may not be avoidable during the weaning process and should not be used

as the sole reason for delaying extubation if gas exchange and other assessments are acceptable.

ACUTE VENTILATORY FAILURE DUE TO AIRWAY OBSTRUCTION

Upper Airway Obstruction

Upper airway obstruction is an occasional cause of acute ventilatory failure. The onset can be precipitous, as with occlusion of the glottis by an aspirated foreign body (i.e., "café coronary") or a swollen and edematous epiglottis due to acute epiglottitis.[91] The onset can also be insidious, occurring over months, as with a tracheal tumor. The severity and length of narrowing and air flow determine the resistance and thereby the additional work of breathing imposed by the obstruction. Gradually progressive upper airway narrowing may be well tolerated, at least during breathing at rest, until a critical limit is reached, often when the airway diameter drops to the range of 5 to 6 mm.

The location and variability of the narrowing are also important in determining the clinical manifestations. Extrathoracic variable upper airway narrowing affects mainly inspiratory flow because the negative intraluminal pressure exacerbates the narrowing during inspiration. During expiration, the positive intraluminal pressure tends to push variable extrathoracic obstructions open. Vocal cord paralysis is an excellent example of a variable extrathoracic upper airway obstruction, producing stridor and severe airway obstruction during inspiration but no significant obstruction during expiration. The opposite pertains to variable intrathoracic obstructions, with narrowing becoming less severe during inspiration as pressure gradients favor airway widening. During expiration, the airways narrow and the severity of the obstruction worsens. Tracheomalacia can cause variable intrathoracic airway obstruction. Fixed obstructions affect both inspiration and expiration regardless of their location.

Pathophysiologically, upper airway obstruction causes ventilatory failure by increasing airway resistance to the point at which respiratory muscles can no longer maintain minute volume at a level adequate to maintain CO_2 homeostasis. Negative-pressure pulmonary edema can contribute to the gas-exchange impairment.[92] Conceptually, the therapeutic aim is to relieve the obstruction. This may be achieved by removal of a foreign body, laser therapy of an endotracheal tumor, placement of a stent in an area of tracheomalacia or stenosis, or tracheostomy to bypass an area of obstruction. Inhalation of heliox, continuous positive airway pressure (CPAP), or noninvasive ventilation can be useful to reduce the work of breathing and avoid intubation in patients who have reversible causes of their upper airway obstruction, such as postextubation stridor, or who are awaiting tracheostomy or surgical repair of an obstruction. However, these temporizing measures require close monitoring with the recognition that the patient can deteriorate abruptly.

Chronic Obstructive Pulmonary Disease

COPD is the fourth leading cause of death among adults aged 65 to 84 in the United States and poses enormous costs to the U.S. health care system. Exacerbation of COPD is the most common cause of acute ventilatory failure in the U.S. adult population. Although COPD exacerbations are most commonly infectious in etiology, either viral or bacterial, a number of other etiologies should be considered when patients with COPD have respiratory deterioration, including acute pneumonia, congestive heart failure, pulmonary embolism, pneumothorax, or environmental exposure.

Pathophysiology

Exacerbations of COPD lead to acute ventilatory failure in perhaps one third of patients admitted to an acute care hospital for exacerbation. Those with severe COPD (stage 2 or 3, forced expiratory volume in 1 second [FEV_1] < 50%) are at the highest risk. Severe COPD places the respiratory muscles at a mechanical disadvantage.[93] As depicted in Figure 92-4 for a patient with emphysema, hyperinflation flattens the diaphragm, increasing its radius of curvature. According to Laplace's law, this increases muscle tension and the impedance to blood flow. Even at residual volume, the diaphragm remains flat with a relatively short sarcomere length, and inspiratory-force generation is compromised by the diaphragm's inability to reach a sufficient length on its length-tension curve. Also, because of the horizontal orientation of the diaphragm and the loss of the zone of apposition between the diaphragm and the chest wall, the force vector on the lower rib cage becomes inward rather than cephalad, so lower rib cage motion during inspiration becomes paradoxical, moving inward on inspiration instead of outward, a movement referred to as the "Hoover sign." Accessory muscles are recruited to maintain ventilation at the hyperinflated lung volumes, contributing to the already increased oxygen cost of breathing. Finally, incomplete emptying leading to positive pressure in alveoli at end-expiration (intrinsic or auto-PEEP) poses an inspiratory threshold load requiring that the inspiratory muscles work to reduce this pressure to subatmospheric levels in order to initiate airflow for the next inspiration.

During an exacerbation of COPD, this precarious situation becomes potentially catastrophic. Usually related to a combination of swelling, secretions, and bronchospasm caused by acute inflammation, the airway resistance increases adding to the work of breathing. As depicted in Figure 92-5, patients with severe COPD often reach a limitation to expiratory flow, even during resting breathing, and a small increase in airway resistance lowers airflow further at any given lung volume. The patient's only workable strategy, if airflow is to be maintained, is to breathe at even higher lung volumes, a futile compensatory response that adds further to the work of breathing. Patients adopt a rapid, shallow breathing pattern, thus shortening the time for expiration and aggravating intrinsic PEEP. The diaphragm flattens more and

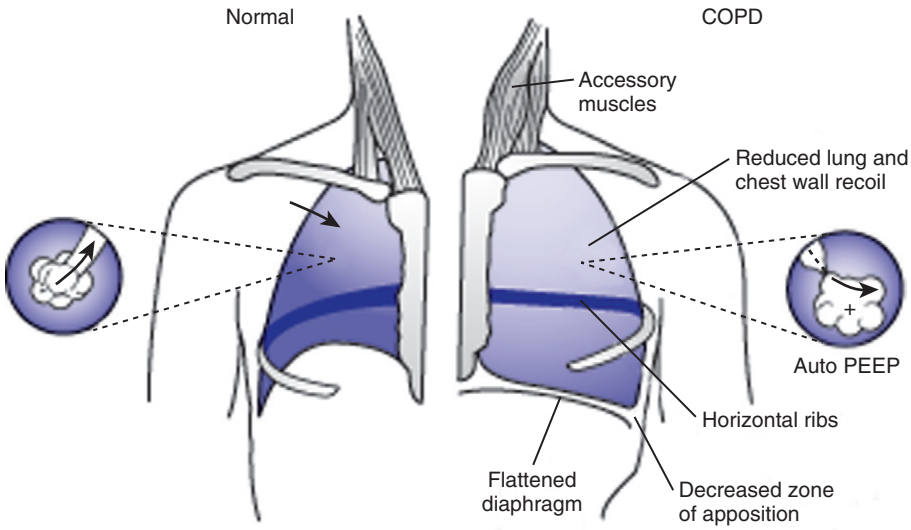

FIGURE 92-4 ■ Schema depicting the chest wall configuration at functional residual capacity of a normal individual (left hemithorax) and a patient with severe chronic obstructive pulmonary disease (COPD; right hemithorax). The COPD patient has a flattened diaphragm, which increases its radius of curvature and increases the tension for a given pressure. The COPD patient's ribs are horizontal, and the zone of apposition between the diaphragm and chest wall is reduced, greatly reducing the diaphragm's efficiency in expanding the chest wall. Also, intrinsic positive end-expiratory pressure (Auto PEEP) poses an inspiratory load, adding further to the inspiratory work. Exhalation is slowed by airway collapse and the loss of elastic recoil. (Redrawn from Hill NS: Current concepts in mechanical ventilation for chronic obstructive pulmonary disease. Semin Respir Crit Care Med 20:375–395, 1999.)

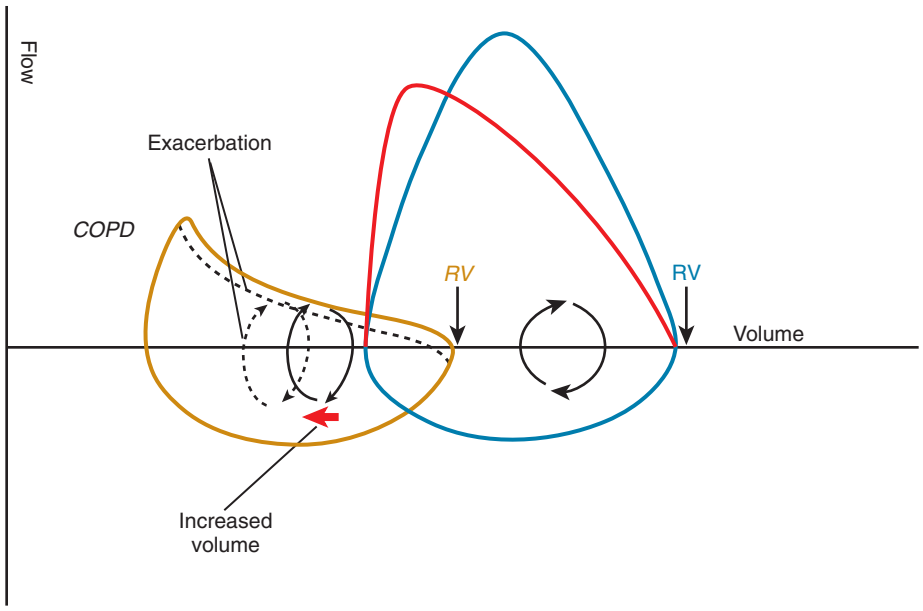

FIGURE 92-5 ■ The flow-volume loops are shown for a patient with a normal lung (*blue line on right*) and one with COPD (*brown line on left*) along with their respective tidal volume loops (*inner black loops with arrows*). Note that the expiratory flow during tidal breathing in the COPD patient reaches maximal expiratory flow. During an exacerbation (*interrupted lines*), expiratory flow drops; because the flow during tidal breathing is already maximal, the only mechanism available for maintaining flow is to increase lung volume during tidal breathing (leftward shift of tidal breathing loop, shown by *thick red arrow*). Although this strategy maintains expiratory flow, it increases the work of breathing and oxygen consumption, predisposing to inspiratory muscle fatigue and eventual respiratory failure. (Redrawn from Hill NS: Current concepts in mechanical ventilation for chronic obstructive pulmonary disease. Semin Respir Crit Care Med 20:375–393, 1999.)

develops increased tension, augmenting impedance to blood flow. The resulting limitation in the supply of substrate to the muscle is aggravated by progressive hypoxemia, caused by worsening hypoventilation and V/Q imbalance related to secretion retention. Thus, as the demand for breathing increases, the capacity to supply the increased work of breathing becomes further compromised. Despite the worsening alveolar hypoventilation, the drive to breathe is increased and the diaphragm becomes fatigued, characterized by reduced muscular performance despite a steady or increased neural drive. A vicious circle ensues, leading inexorably to worsening respiratory muscle fatigue, ventilatory failure, and death unless therapeutic interventions interrupt the cycle.

Clinical Assessment

Patients with exacerbations of COPD must be carefully evaluated to identify those at risk of developing respiratory failure and to exclude other causes of respiratory failure. Historical and physical features are very useful. Although Borg's or visual analogue scales help gauge the level of dyspnea in clinical studies, a subjective assessment that dyspnea is worse than baseline and of at least moderate severity places the patient at risk for respiratory failure. Physical findings seen with severe exacerbations include tachypnea, accessory muscle use, abdominal paradox, Hoover's sign (inspiratory inward motion of the lower, lateral rib cage), cyanosis, and mental status alterations.

In addition to a sputum examination for purulence, a white blood cell count, an electrocardiogram, a chest radiograph, and arterial blood gases should be obtained to assess the severity of an exacerbation. The widespread use of continuous pulse oximetry has decreased, but not eliminated, the need for arterial blood gases. Arterial blood gases provide a rapid assessment of arterial P_{CO_2} and pH, information that is critical when deciding to place patients in critical care units or to initiate mechanical ventilation and in assessing response to therapy. During severe exacerbations, chronic CO_2 retainers develop acute-on-chronic hypercapnia, manifested by a drop in pH indicative of retained CO_2 uncompensated by bicarbonate, an important indicator requiring measurement of arterial blood gases.

Medical Therapy

When patients with severe exacerbations come to medical attention, they are promptly begun on medical therapy, such as bronchodilators, corticosteroids, and antibiotics. Additional therapies include diuretics and nitrates if congestive heart failure is thought to be contributing and anticoagulation if pulmonary embolism is considered a risk. Oxygen supplementation is routine but must be administered with caution in patients with CO_2 retention. Overzealous oxygen supplementation in such patients has long been known to aggravate CO_2 retention, by either blunting the hypoxic ventilatory drive, increasing physiologic dead space (perhaps due to oxygen-induced bronchodilation in poorly perfused lung regions), or both. Because hypoxemia in COPD patients is usually due mainly to the hypoventilation and is easily reversed, initial supplementation with nasal oxygen at 2 L/min is often adequate. In patients with severe exacerbations, arterial blood gases should be repeated periodically to assess the effect of oxygen supplementation on arterial P_{CO_2}.

Noninvasive Mechanical Ventilation

Medical therapy alone is often effective and is the therapy of choice for mild COPD exacerbations. However, when exacerbations are more severe or medical therapy fails, manifested by persisting or worsening tachypnea and dyspnea as well as CO_2 retention, respiratory muscles may begin to fatigue, requiring ventilatory assistance. In the past, patients who failed medical therapy were endotracheally intubated and mechanically ventilated; if they declined intubation, they were kept comfortable and usually died. Invasive mechanical ventilation was successful in the majority of cases, but hospital mortality rates were substantial, averaging 30% in several studies.[94] Complications of invasive mechanical ventilation were common, including upper airway trauma, pneumothorax, and nosocomial infection, contributing to patient mortality.[95]

In the early 1990s, noninvasive positive-pressure ventilation (NPPV) began to be used increasingly to treat COPD exacerbations. Consisting of a mask (or interface) that conducts pressurized air into the lungs from a positive-pressure ventilator, NPPV has appeal for the therapy of COPD exacerbations because it is an effective way of providing partial ventilatory assistance.[96] It also avoids airway invasion and many of the complications of invasive mechanical ventilation, such as upper airway trauma, nosocomial infection, and prolonged intubation.[95]

NPPV has the potential to reverse the vicious circle leading to respiratory failure in patients with severe exacerbations of COPD. CPAP reduces the work of breathing during COPD exacerbations by counterbalancing the effects of intrinsic PEEP, effectively reducing or even eliminating the inspiratory threshold load.[97] Pressure support also reduces the work of breathing in COPD patients, assisting each breath by increasing airway pressure during inspiration.[97] However, when CPAP and pressure support are combined, NPPV reduces the transdiaphragmatic pressure more than either CPAP or pressure support alone.[97] Thereby, NPPV has the potential to serve as a "crutch," reducing the work of breathing and halting the progression of respiratory muscle fatigue while medical therapies are given time to work.

Acute Exacerbations. NPPV is effective in treating acute respiratory failure due to COPD exacerbations. Starting with Brochard and coworkers[96] using historically matched controls and subsequent randomized, controlled trials,[98–100] a number of benefits have been attributed to NPPV in these patients. These include more rapid improvements in arterial P_{CO_2},[98] heart and respiratory rates, and dyspnea scores[98–100] within the first hour in noninvasively-treated patients compared with rand-

omized conventionally-treated controls. Encephalopathy scores also improve more rapidly,[100] intubation rates drop precipitously (from roughly 75% in controls to 25% in NPPV-treated patients),[98,99] and the mortality rate is lowered (from 30% in controls to ~10% with NPPV).[99] In addition, complication rates and hospital lengths of stay fall significantly compared with those of controls.[98–100]

In the largest study thus far reported,[100] 236 patients with exacerbations of COPD were randomized to receive NPPV or standard therapy administered by nurses in general medical respiratory wards at 14 medical centers in England. Intubation and mortality rates were significantly lower in the NPPV group than in controls (15% vs. 27%, $P = .02$, and 10% vs. 20%, $P = .05$, respectively), and the study confirmed the earlier findings of more rapid improvements in arterial pH, respiratory rate, and breathlessness in the NPPV group compared with the control group. Notably, the mortality benefit was not apparent in patients with pH less than 7.30. The authors speculated that these sicker patients might have fared better had they been monitored in an ICU. In the only study with negative findings,[101] NPPV failed to lower intubation or mortality rates or hospital lengths of stay in patients admitted consecutively to the hospital with COPD exacerbations, but it is notable that no intubations or mortality occurred in the control group. This suggests that patients with relatively mild COPD exacerbations are not likely to benefit from NPPV, implying that NPPV should be applied to selected patients who have a demonstrable need for ventilatory assistance.

Several meta-analyses have combined the results of the previous studies.[102,103] These concluded that NPPV is effective in avoiding intubation (relative risk 0.42 and absolute risk reduction 28%, respectively), reducing mortality (relative risk 0.41 and absolute risk reduction 10%, respectively), and shortening hospital length of stay (by ~4 days). Based on this evidence, the authors of these meta-analyses, reviews, and consensus groups[102–106] have advised that NPPV should be used early in the course of COPD exacerbations.

Chronic Obstructive Pulmonary Disease Complicated by Pneumonia. Pneumonia has been associated with a poor outcome in patients treated with NPPV.[107] However, in one trial of patients with "severe community-acquired pneumonia," defined as patients with severe hypoxemia ($PaO_2/FIO_2 < 200$) and respiratory distress (respiratory rate > 35/min), randomized to NPPV or to standard oxygen therapy, NPPV reduced the need for intubation (21% vs. 50%, $P = .03$), shortened the ICU length of stay (1.8 vs. 6.0 days, $P = .04$), and lowered the mortality rate among the COPD subgroup of patients determined 2 months after hospital discharge (11% vs. 63%).[108] Thus, although the presence of pneumonia is a risk factor for poorer outcome with NPPV, these patients can still benefit from NPPV. Moreover, a COPD exacerbation complicated by pneumonia is an appropriate indication for NPPV.

Postoperative Patients. A randomized trial of NPPV in post–lung resection patients with acute respiratory insufficiency showed significant reductions in the need for intubation, ICU length of stay, and mortality rate compared with conventionally-treated controls.[109] Although only a portion of these patients had COPD, accumulating evidence now supports the use of NPPV in selected postoperative (including COPD) patients to maintain improved gas exchange and avoid reintubation and its attendant complications. Noninvasive positive-pressure techniques (CPAP or NPPV) are also being used prophylactically to reduce secretion problems, atelectasis, and hypoxemia after some high-risk operations such as thoracoabdominal[110] and major abdominal[111] surgery.

To Facilitate Extubation. NPPV has been used to facilitate early extubation after bouts of acute respiratory failure in patients who fail to meet standard extubation criteria, with the aim of shortening the duration and thereby avoiding the complications of invasive mechanical ventilation. One randomized controlled trial of 56 COPD patients who had been intubated for 48 hours and failed a T-piece trial[112] found that, compared with controls left intubated, the early extubation/NPPV group had a higher overall weaning rate after 60 days (88% vs. 68%), a shorter duration of mechanical ventilation (10.2 vs. 16.6 days), a briefer stay in the ICU (15 vs. 24 days), and an improved 60-day survival (92% vs. 72%) (all $P < .05$). A more recent randomized, controlled trial in patients with "persistent weaning failure" (failure of spontaneous weaning trials on 3 consecutive days) showed that the early extubation/NPPV group had significant reductions in ICU and hospital days, a lower incidence of nosocomial pneumonia (from 59% to 24%, $P < .05$), diminished hospital and 90-day mortality (odds ratio 3.5), and fewer complications.[113] Thus, these randomized, controlled studies have yielded results supporting early extubation to NPPV. However, if early extubation is contemplated, it should be reserved for carefully selected intubated COPD patients. Patients should be on 15 cm H_2O or less of pressure support, able to sustain 5 to 10 minutes of unassisted breathing, have an adequate cough without excessive secretions, be easy to intubate, and have few if any comorbidities.

Extubation Failure. NPPV can be used in an attempt to avoid reintubation in patients who fail extubation. Extubation fails after 5% to 20% of planned[114] and 40% to 50% of unplanned[115] extubations and extubation failure has been associated with a mortality of 43% compared with only 12% in those who succeed after extubation.[114] In a historically controlled study of 30 COPD patients with extubation failure,[116] NPPV lowered the reintubation rate (20% vs. 67%, $P < .05$) and ICU length of stay. In a subsequent randomized trial of patients at high risk for extubation failure and who developed respiratory distress within 48 hours of extubation, however, NPPV did not reduce the need for intubation, duration of mechanical ventilation, length of hospital stay, or mortality.[117] However, COPD patients were excluded from this study after the first year because of ethical concerns. In an international randomized trial of 221 patients with risk factors for extubation failure, those randomized to NPPV showed an unexpected increase in mortality rate compared with the standard treatment group, most likely related to a longer delay before proceeding with reintubation.[118] Notably, only 10% of patients in this

study had COPD and 25% of controls were crossed over to NPPV when they further deteriorated and met criteria for reintubation. These crossover patients had reintubation rates of only 25%, half that of the intention-to-treat NPPV group. This led to the speculation that results would have been favorable if more patients with COPD had been enrolled and NPPV had been reserved for patients with frank extubation failure but good candidates for NPPV, similar to the crossover group. This speculation has been borne out by two subsequent randomized, controlled trials, one showing drastic reductions in respiratory failure, need for reintubation, and mortality in a subgroup of hypercapnic patients[119] and the other demonstrating that patients at "high risk" for postextubation failure had better outcomes when treated with NPPV.[120,120a] Thus, the best current recommendation is to use NPPV selectively in patients with extubation failure, mainly for COPD or other hypercapnic patients, but to avoid delays in needed intubation should NPPV fail.

Do-Not-Intubate Patients. The use of NPPV to treat respiratory failure in patients who have declined intubation accounted for 10% of acute applications in one survey.[121] This application has been controversial, with some arguing that there is little to lose because it may reverse the acute deterioration or, at least, provide relief of dyspnea and a few extra hours to finalize affairs.[122] Others have argued that this merely prolongs the dying process, consumes resources inappropriately, and may add to discomfort or counter patients' wishes about avoiding life-prolonging measures.[123] In prospective observational studies of 113[121]and 131[124] "do-not-intubate" (DNI) patients treated with NPPV, survival to hospital discharge was greater than 50% for COPD and congestive heart failure patients, whereas it was lower (14%–25%) for those with a diagnosis of hypoxemic respiratory failure (pneumonia) or advanced cancer. Thus, NPPV can be used to treat respiratory failure for DNI patients with acutely reversible processes such as COPD exacerbations or acute cardiogenic pulmonary edema. Alternatively, it can be used to palliate DNI patients, by alleviating dyspnea or providing temporary support. The patient or the family should be informed that NPPV is being used as a form of life support that may be uncomfortable and can be removed at any time.

Heliox Combined with Noninvasive Ventilation. By virtue of its lower density compared with nitrogen, helium can be combined with oxygen to lower the airway resistance attributable to turbulent flow. The oxygen concentration can be increased to 40% in the helium-oxygen mixture but not higher without losing the density advantage of the added helium. Heliox has been combined with NPPV to treat patients with COPD exacerbations, with beneficial physiologic responses including reduced airway resistance and more rapid improvements in gas exchange.[125] However, a randomized, prospective trial on patients with COPD in respiratory failure found that the addition of heliox to NPPV offered no significant advantages over NPPV alone in terms of intubation or mortality rates or hospital lengths of stay.[126]

TABLE 92-2. Predictors of Success for Noninvasive Positive-Pressure Ventilation in the Acute Setting

ABLE TO COOPERATIVE
Synchronous breathing with NPPV
Good neurologic status
Better "compliance"*
ABLE TO PROTECT AIRWAY
Low volume of secretions
Minimal air leaking
Dentate (dentition corresponds with minimal air leak)
NOT TOO ACUTELY ILL
No pneumonia
Low APACHE score
Initial arterial P_{CO_2} < 92 mm Hg
Initial pH > 7.10
GOOD INITIAL RESPONSE TO NPPV (WITHIN FIRST HR OR TWO)
Improvement in pH
Reduction in respiratory rate
Reduction in arterial P_{CO_2}
Improved level of consciousness

*"Compliance" refers to the clinician's assessment of the patient's acceptance of the technique.
APACHE, Acute Physiology, Age, and Chronic Health Evaluation; NPPV, noninvasive positive-pressure ventilation; P_{CO_2}, carbon dioxide pressure.
Adapted from Ambrosino N, Foglio K, Rubini F, et al: Non-invasive mechanical ventilation in acute respiratory failure due to chronic obstructive pulmonary disease: Correlates for success. Thorax 50:755–757, 1995; and Soo Hoo GW, Santiago S, Williams AJ: Nasal mechanical ventilation for hypercapnic respiratory failure in chronic obstructive pulmonary disease: Determinants of success and failure. Crit Care Med 22:1253–1261, 1994.

Patient Selection. Selection of appropriate patients is key to the successful application of NPPV. The selection process takes into account a number of factors, including the patient's clinical characteristics and risk of failure on NPPV. Ultimately, it becomes a clinical judgment depending largely on physician experience. Predictors of success of NPPV have been identified[107,127] (Table 92-2) and include a better neurologic status (and hence more cooperativeness), ability to protect the airway, and no more than moderate acid-base or gas-exchange derangement. Several studies have also found that improvements in pH, Pa_{CO_2}, and level of consciousness within the first hour or two of NPPV initiation are strong predictors of success.[107,127] These studies indicate that there is a "window of opportunity" when initiating NPPV that opens when patients need ventilatory assistance but closes if they progress too far and become severely acidemic. Thus, early initiation of NPPV is recommended so patients have time to adapt and respiratory crises can be averted. Conversely, NPPV begun too early might be unhelpful and wasteful of resources if treated patients would have done well without any ventilatory assistance. For this reason, selection guidelines suggest first establishing the need for ventilatory assistance according to clinical and blood gas criteria (indicating that the

TABLE 92-3. Selection Criteria for Noninvasive Positive-Pressure Ventilation in Acute Exacerbations of Chronic Obstructive Pulmonary Disease

ESTABLISH NEED FOR VENTILATORY ASSISTANCE
Moderate to severe respiratory distress
Tachypnea (RR > 24 breaths/min)
Accessory muscle use or abdominal paradox
Blood gas derangement
pH < 7.35, arterial P_{CO_2} > 45 mm Hg *or*
Arterial P_{O_2}/F_{IO_2} > 200
EXCLUDE PATIENTS WITH CONTRAINDICATIONS TO NPPV
Respiratory arrest
Medically unstable (septic or cardiogenic shock, uncontrolled upper gastrointestinal bleeding, acute myocardial infarction with planned intervention, uncontrolled arrhythmias)
Unable to protect airway
Excessive secretions
Uncooperative or agitated
Unable to fit mask
Recent upper airway or upper gastrointestinal surgery

F_{IO_2}, fractional concentration of oxygen in inspired gas; NPPV, noninvasive positive-pressure ventilation; P_{CO_2}; carbon dioxide pressure; P_{O_2}, oxygen pressure; RR, respiratory rate.
Adapted from Liesching T, Kwok H, Hill NS: Acute applications of noninvasive positive pressure ventilation. Chest 124:699–713, 2003.

window of opportunity has opened) and excluding patients in whom NPPV is contraindicated or likely to fail (indicating that the window of opportunity has closed) (Table 92-3).[128]

Practical Application of NPPV. A thorough discussion of the application of NPPV is beyond the scope of this chapter, and the reader is referred elsewhere for a more complete description.[105,129] The following sections focus on aspects relevant to applications in COPD patients with acute respiratory failure.

Mask Selection. The full face (oronasal) mask is usually the preferred initial mask choice for the acute setting because it avoids the leaking of air through the mouth that can be significant with nose masks.[130] Nasal masks, however, may be more comfortable for long-term applications,[131] so transitioning from a full face mask to a nasal mask should be contemplated after the first few days if NPPV is to be continued. Masks should fit optimally; a mask that is too small is uncomfortable, and one that is too large may require excessive tightening of the straps to minimize air leakage, predisposing to ulceration over the nose. Within each mask category (nasal and oronasal), many types of masks are now available. Practitioners should have a current knowledge of available masks in order to maximize the likelihood of success.

Ventilator Selection. In the acute setting, both "critical care" and "bilevel" ventilators (portable pressure-limited devices designed especially for the administration of NPPV) have been used with similar success rates. A bilevel device designed for use in the acute care setting that includes an oxygen blender and displays waveforms has gained popularity. In addition, many ventilators designed primarily for invasive mechanical ventilation now offer noninvasive modes that are programmed to improve leak compensation, silence "nuisance" alarms that are triggered by air leaks, and permit limitation of inspiratory time to enhance patient-ventilator synchrony.[132] The capabilities of these modes differ considerably between one another, however, and may require additional adjustment in the face of mask leaks.[133]

Ventilator Initiation. To begin NPPV, the properly sized mask is placed on the patient's face and attached to the ventilator. Patients often feel more comfortable if they can hold the mask themselves. Pressure-limited modes may be better tolerated than volume-limited.[134] Initial ventilator pressures are usually low, to enhance patient comfort and acceptance, but adjusted upward as tolerated to provide adequate ventilatory assistance. Typical initial settings on pressure-limited ventilators are 8 to 12 cm H_2O for inspiratory pressures (IPAP) and 4 to 5 cm H_2O for expiratory pressures (EPAP or PEEP), with subsequent adjustments as needed to alleviate respiratory distress (inspiratory pressure ≤ 20 cm H_2O) or to counterbalance intrinsic PEEP or treat hypoxemia (expiratory pressure ≤ 8 cm H_2O). The difference between IPAP and EPAP is the level of pressure support and should be adequate to alleviate inspiratory effort while avoiding excessive discomfort.

Coaching is usually necessary to enhance synchrony between the patient and the ventilator. Some ventilators permit adjustments in airflow to enhance synchrony, such as the "rise time," which determines the time to reach the target IPAP, and the adjustable inspiratory time. These may be helpful in optimizing comfort in COPD patients who tend to prefer relatively high inspiratory flows[135] (and hence short rise times, often 0.1 sec) and short inspiratory times (often < 1 sec) to avoid prolongation of delivered IPAP during expiration.

Oxygenation and Humidification. Most patients with COPD exacerbations do not have severe oxygenation defects and can be managed successfully with bilevel ventilators lacking oxygen blenders. With these ventilators, oxygen is administered at rates up to 15 L/min into ports in the mask or via a T-connector at the proximal end of the ventilator tubing, adjusted to maintain the desired level of oxygenation (usually to an arterial oxygen saturation [Sa_{O_2}] > 90%–92%). Because F_{IO_2} using this arrangement cannot exceed 45% to 50%, ventilators with oxygen blenders are necessary when the oxygen defect is more severe, such as may occur when COPD is complicated by pneumonia. Humidification should be used routinely because it may reduce the work of breathing and enhance comfort and tolerance during NPPV.[136,137]

Adaptation and Monitoring. The first few hours are critical in achieving successful adaptation. Coaching and encouragement are usually required to assist patients in synchronizing with the ventilator and reducing their breathing effort. Instructions such as "try to take slow deep breaths" and "let the machine breathe for you" may be helpful. Also, judicious administration of low doses of sedatives may enhance patient acceptance.

TABLE 92-4. Monitoring Noninvasive Positive-Pressure Ventilation in Chronic Obstructive Pulmonary Disease

ACUTE SETTING
Patient comfort
Mask fit and leak
Patient-ventilator synchrony
Sternocleidomastoid muscle activity
Vital signs (heart and respiratory rate; systemic blood pressure)
Continuous oximetry (until stabilized)
Occasional blood gases (initial and after 30–120 min, then as clinically indicated)
CHRONIC SETTING
Patient comfort
Mask fit and leak
Hours of use
Problems with adaptation (e.g., nasal congestion, dryness, gastric insufflation, conjunctival irritation, inability to sleep)
Symptoms (e.g., dyspnea, fatigue, morning headache, hypersomnolence)
Gas exchange (daytime, nocturnal oximetry, blood gases periodically to assess arterial P_{CO_2})
Polysomnography (if symptoms of sleep disturbance persist or nocturnal desaturation persists without clear explanation)

P_{CO_2}, partial pressure of carbon dioxide.

TABLE 92-5. Indications for Invasive Mechanical Ventilation in Chronic Obstructive Pulmonary Disease

Severe dyspnea with the use of accessory muscles and paradoxical abdominal motion
Respiratory frequency > 35 breaths/min
Life-threatening hypoxemia (arterial P_{O_2} < 40 mm Hg or arterial P_{O_2}/F_{IO_2} < 200)
Severe acidosis (pH < 7.25) and hypercapnia (arterial P_{CO_2} > 60 mm Hg)
Respiratory arrest
Somnolence; impaired mental status
Cardiovascular complications (hypotension; shock; heart failure)
Other complications (metabolic abnormalities; sepsis; pneumonia; pulmonary embolism; barotrauma; massive pleural effusion)
Failure of noninvasive positive-pressure ventilation

F_{IO_2}, fractional concentration of oxygen in inspired gas; NPPV, noninvasive positive-pressure ventilation; P_{CO_2}, partial pressure of carbon dioxide; P_{O_2}, partial pressure of oxygen.

From Pauwels RA, Buist AS, Calverley PM, et al: Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) workshop summary. Am J Respir Crit Care Med 163:1256–1276, 2001.

Close bedside monitoring is essential until the patient's respiratory status stabilizes. Although NPPV can easily be administered on general medical wards, the acuteness of the patient's illness and need for close monitoring should dictate the site of administration. Acutely ill patients should be treated in an ICU or step-down unit until their condition stabilizes, regardless of whether they are treated with invasive ventilation or noninvasive ventilation. As shown in Table 92-4, patient comfort and tolerance are key initial goals. In COPD patients, a drop in respiratory rate and reduction in sternocleidomastoid muscle activity are important salutary signs that should be apparent early. They are usually accompanied by good patient-ventilator synchrony, and upward adjustments in IPAP may enhance these effects. Sa_{O_2} is monitored continuously, and blood gases are obtained as is clinically indicated, usually at least once during the first hour or two.

Commonly Encountered Problems and Possible Remedies. Noninvasive ventilation is safe and well-tolerated in most properly selected patients. The most commonly encountered problems in COPD patients are similar to those in other patients and are related to the mask, air pressure, or airflow (see Table 92-4). Patients often complain of mask discomfort, which can be alleviated by minimizing strap tension or by trying different mask sizes or types. Patients may be anxious and experience difficulty synchronizing their breathing efforts with the ventilator. Adjustments in ventilator settings (increasing or lowering IPAP or titrating EPAP to counterbalance intrinsic PEEP) and judicious use of sedation often improve synchrony.

Excessive air pressure leading to sinus or ear pain is another common complaint, alleviated by lowering the pressure temporarily and then gradually raising it again as tolerance improves. Other commonly encountered problems include erythema, pain, or ulceration on the bridge of the nose related to pressure from the mask seal. Minimizing strap tension, using artificial skin, or switching to alternative masks such as nasal "pillows" can alleviate this problem. Gastric insufflation occurs frequently but is usually not severe, probably because inflation pressures are low.

Air leaking through the mouth (with nasal masks) or around the mask (with all interfaces) is inevitable during NPPV. Nasal and oronasal masks, particularly if too large, may leak air onto the eyes causing conjunctival irritation. Refitting or reseating the mask usually addresses this problem. Pressure-limited devices compensate for air leaks by maintaining inspiratory airflow during leaking but, during nasal ventilation, patients should keep their mouths shut, try chin straps to assist in mouth closure or, failing these measures, try an oronasal mask.

Invasive Mechanical Ventilation

Indications and Patient Selection. The increasing use of NPPV has reduced the need for invasive mechanical ventilation. However, there remain patients who are too ill and are not candidates for NPPV upon arrival to the hospital or who fail a trial of NPPV. Indications for the use of invasive mechanical ventilation for COPD are listed in Table 92-5.

Invasive mechanical ventilation in COPD must be administered with caution to minimize the risk of complications. Excessive tidal volumes and rates must be

avoided, and the urge to normalize $PaCO_2$ must be repressed in an effort to minimize intrinsic PEEP and excessive hyperinflation. Excessive respiratory rates reduce the respiratory cycle, shorten expiratory time, and prevent complete exhalation. This problem is aggravated by large tidal volumes. The consequence is air trapping and the potential for the adverse consequences of intrinsic PEEP. With intrinsic PEEP, increased intrathoracic pressure reduces venous return and lowers cardiac output. Patients with severe intrinsic PEEP may be hypotensive with low cardiac output and elevated pulmonary artery wedge pressure due to transmission of the intrathoracic pressure. In their clinical presentation, they may therefore mimic those with cardiac shock. Temporary disconnection from the ventilator can differentiate hemodynamic compromise due to intrinsic PEEP from true cardiogenic shock because the release of intrathoracic pressure permits rapid resolution of the former but not the latter. Intrinsic PEEP may also cause patient-ventilator asynchrony related to missed triggering due to the delay before the patient can lower the inspiratory threshold load.

Recommended Ventilator Settings. Volume-limited or pressure-limited modes can be used, but volume-limited assist-control is the most frequent choice initially and provides control over the tidal volume, which is important in avoiding dynamic hyperinflation. A small tidal volume (e.g., 5–7 mL/kg predicted body weight) should be used. Care should be taken to avoid overventilation and alkalemia. The need for sedation varies among patients, although muscle relaxants are seldom necessary. The backup respiratory rate for COPD patients receiving invasive mechanical ventilation should be set between 10 and 14/min. Given an inspiratory time of 1 second, if the respiratory rate is 20/min, the expiratory time is only 2 seconds; at a respiratory rate of 15/min, expiratory time increases to 3 seconds. Thus, relatively small changes in rate can effect large changes in expiratory time. Another way to increase expiratory time is to shorten the inspiratory time by increasing the inspiratory flow rate. However, this strategy is not as fruitful because substantial increases in flow rate result in only minor decreases in inspiratory time. For example, if the inspiratory time is 1 second and inspiratory flow is 60 L/min, an increase in the inspiratory flow rate to 100 L/min decreases the inspiratory time to 0.6 second (if tidal volume is held constant); thus, expiratory time increases only from 2.0 to 2.4 seconds. Furthermore, rapid flow rates may increase the spontaneous respiratory rate[138] as well as respiratory distress. COPD patients prefer flow rates in the 60 L/min range and tend to sense faster or slower rates as less comfortable.[135]

Weaning Chronic Obstructive Pulmonary Disease Patients from Invasive Mechanical Ventilation. Minimizing the duration of mechanical ventilation is desirable to minimize potential complications such as ventilator-associated pneumonia. When patients no longer require high levels of oxygen ($SaO_2 > 89\%$ on $FIO_2 \leq 40\%$), are hemodynamically stable and not excessively sedated, spontaneous breathing trials should be initiated. Pairing the spontaneous breathing trial with a daily interruption of sedation speeds liberation from the ventilator, reduces hospital and ICU length of stay, and lowers mortality.[139] If the patient can comfortably tolerate a trial of 30 to 120 minutes without excessive tachypnea, hemodynamic instability, or oxygen desaturation, extubation should be undertaken so long as the patient has an adequate cough without excessive airway secretions. If the patient fails to meet extubation criteria but is otherwise a good candidate for noninvasive ventilation, extubation to NPPV should be considered with the caveats discussed earlier.

Asthma

Acute ventilatory failure due to acute asthma should be unusual if patients adhere to a medical regimen including corticosteroid inhalers, monitor their peak flows, and alter their medical regimen (with the addition of enteral steroids) when peak flows begin to drop. Unfortunately, some patients are not treated with optimal regimens, some do not adhere to the regimen, and some have severe exacerbations even with optimal regimens, so acute ventilatory failure in asthmatics remains a problem. Studies on near-fatal asthma have identified several risk factors for exacerbation including poor access to health care, substance abuse, nonadherence with therapy, underuse of corticosteroids, and underestimation of the severity of attacks.[140]

Medical Management of Acute Asthma

Patients presenting with severe asthma should be promptly treated with systemic as well as inhaled corticosteroids and bronchodilators. Rapidly acting β_2-agonists are administered by inhalation, although no optimal route of administration or dose has been established. Metered-dose inhalers with spacers or nebulizers may be used, usually every 20 minutes for the first hour. Some centers use continuous nebulization for severe acute asthma. Magnesium, either intravenous or inhaled, has been administered, with some evidence to suggest that it aids aggressive β_2-agonist therapy, especially in the most severely ill asthmatics.[141]

Mixtures of helium and oxygen have been used since the 1930s to lower resistance to flow related to turbulence in the airways of asthma patients, just as in COPD patients. Several randomized, controlled trials of heliox have been performed with patients with acute asthma, but the results are inconclusive. Two demonstrated more rapid improvements in dyspnea and airflow with heliox than with oxygen alone,[142,143] but another showed no improvement in airflow rates (although dyspnea was reduced more by heliox).[144] The study showing little or no improvement with heliox enrolled less severely obstructed patients than the favorable studies, but a subgroup analysis of sicker patients in the negative study showed no benefit in that subgroup either. A Cochrane analysis concluded that there is no defined role for heliox in treating severe acute asthma,[145] but many centers use it when patients are not responding promptly to standard therapy.

Ventilatory Management

Assessment of Ventilatory Status. In patients with acute asthma exacerbations, frank ventilatory failure is unusual. Signs of severe respiratory distress, such as excessive use of accessory muscles, extreme tachypnea, or abdominal paradox, warrant the initiation of ventilatory assistance. Arterial blood gases showing normocapnia in a patient with severe respiratory distress should also cause alarm because patients reach a "crossover" point as they fail, when they can no longer sustain hyperventilation but have not become sufficiently fatigued to retain CO_2. These patients should be monitored closely so that noninvasive ventilatory aids can be initiated promptly in order to avert the need for invasive ventilation with its attendant potential complications.

Continuous Positive Airway Pressure. CPAP alone may ameliorate respiratory distress in asthmatics by stenting airways open, reducing atelectasis, and offsetting intrinsic PEEP. However, the unequal distribution of airways resistance in asthma, in contrast to the more simultaneous closure of airways in COPD, creates areas with very different expiratory time constants. In this setting, CPAP can promote overdistention of some lung regions. Thus, caution should be exercised when applying CPAP to these patients, at least at levels exceeding 5 cm H_2O and CPAP should be reduced to 5 cm H_2O or less if there is no further amelioration of respiratory distress at higher levels.

Noninvasive Ventilation. Despite the success of noninvasive ventilation in COPD exacerbations, its role in treating asthma exacerbations has not been clearly defined. An early cohort study observed substantial improvements in blood gases ($PaCO_2$ dropping from 65 to 52 mm Hg in the first 2 hours) among 17 patients treated with NPPV, only 2 of whom required intubation.[146]

In the one randomized trial on acute asthma that yielded favorable results,[147] patients treated with NPPV had significantly greater improvements in FEV_1 in the first hour compared with sham-treated patients (53.5% vs. 28.5%), and the need for hospitalization was significantly reduced. These results are encouraging, suggesting that the positive pressure might exert a bronchodilator effect; however, the results are not conclusive, because there was no evidence for reduced need for intubation or mortality. Nonetheless, a trial of noninvasive ventilation seems reasonable when patients fail to respond promptly to initial bronchodilator therapy, particularly if they manifest signs of respiratory muscle fatigue including a respiratory rate of more than 30 breaths/min, accessory muscle use, abdominal paradox, normocapnia in patients with respiratory distress, hypercapnia, or hypoxemia.

Invasive Mechanical Ventilation. Invasive mechanical ventilation in patients with acute ventilatory failure due to asthma should be used as a last resort but is necessary when patents present with coma or delirium or with hemodynamic instability. Another clear indication is failure of medical therapy that may include NPPV. Of patients admitted to the ICU with acute severe asthma, about one third have been reported to require invasive mechanical ventilation,[140,148] however, the proportion of patients who require intubation when its avoidance is a specific goal of therapy has not been determined. Invasive mechanical ventilation is best avoided because of the frequency and severity of the potential complications, but, if needed, intubation and ventilation should be initiated before a respiratory arrest, an emergent situation that heightens the risk of complications. Complications of mechanical ventilation in asthmatics include barotrauma such as pneumothorax and pneumomediastinum, reported in 6.5% of patients in one series,[149] the need for sedation and paralysis, which should be avoided because of the risk of postparalysis myopathy, ventilator-associated pneumonia, and mortality rates in the 5% to 10% range.[150]

If invasive mechanical ventilation is necessary, great care must be exercised to minimize the risk of complications, using an approach similar to that used for COPD patients. Excessive respiratory rates and tidal volumes should be avoided, with the ultimate goal of keeping plateau pressures under 30 to 35 cm H_2O. "Permissive hypercapnia,"[151] first described in invasively ventilated asthma patients,[152] remains a sensible approach in severely obstructed patients. In permissive hypercapnia, plateau pressures are maintained in the safe range as the first priority while allowing the CO_2 to rise, in some reports up to 70 to 100 mm Hg. Using this strategy, the major risks of positive-pressure ventilation can be minimized while providing time for the medical therapy to take effect. Bicarbonate or other buffers such as trishydroxymethyl aminomethane (THAM) can be administered if the pH drops too low but this is probably not necessary and may not even be effective in raising the pH, a situation also described in patients with acute lung injury.[153] Because of the variability of resistance between airways, some of which may be entirely obstructed, measurement of intrinsic PEEP using the expiratory hold technique may underestimate the severity of regional hyperinflation.[154] When ventilation remains difficult, even with use of lung-protective ventilation and permissive hypercapnia, the addition of heliox to the ventilator circuit may help (although heliox may alter ventilator performance and not all ventilators can accommodate heliox). As a last resort, extreme measures such as general anesthesia with bronchodilator anesthetics (e.g., halothane)[155] or induced hypothermia may be helpful. Anecdotally, *N*-acetylcysteine may be helpful in treating severe acute asthma with excessive mucus plugging, although no properly designed trials have tested efficacy, and worsening of bronchospasm is a potential side effect.

ACUTE VENTILATORY FAILURE DUE TO VASCULAR IMPAIRMENT

An increase in physiologic dead space by disorders affecting the pulmonary vasculature reduces alveolar ventilation in relation to overall minute ventilation. Although hypercapnia might be expected in such a cir-

cumstance, it is typically prevented by a modest increase in overall ventilation. Thus, acute ventilatory failure is seldom seen in primary pulmonary vascular disease. In pulmonary thromboembolism, for example, hypercapnia is unusual. Hypercapnia following pulmonary embolism can be seen, however, in patients with a comorbid condition such as severe COPD or a depression of the ventilatory drive by drugs that impair the function of the ventilatory pump. Indeed, acute respiratory acidosis, with or without concomitant worsening in oxygenation, may be the initial manifestation of pulmonary thromboembolism in a patient on controlled mechanical ventilation or with a high cervical spinal cord injury or pharmacologic paralysis who cannot increase minute ventilation.

Another rare circumstance in which acute ventilatory failure may develop as a result of a disorder of the pulmonary circulation is venous air embolism, in which hypercapnia and a marked discrepancy between arterial and end-tidal exhaled CO_2 levels may be observed.[156] Hypercapnia may also complicate the acute chest syndrome in patients with sickle cell disease; one series documented respiratory acidosis in 42% of patients who developed this syndrome.[157]

KEY POINTS

- Respiratory failure is the consequence of inadequate alveolar ventilation, generally due to poor central drive, neuromuscular disease, or profound mechanical derangement of lungs or chest wall.
- Respiratory muscle weakness may either precipitate ICU admission, as in Guillain-Barré syndrome, or result from other critical illness, as in ICU-acquired weakness; measuring the maximal inspiratory pressure or visualizing the diaphragm with a bedside ultrasound can be used to identify weakness.
- Noninvasive positive-pressure ventilation (NPPV) is especially useful in exacerbations of COPD, but may also play a role in other forms of acute respiratory failure, such as in facilitating extubation of those who fail a trial of spontaneous breathing or in avoiding reintubation in those who fail extubation.
- Invasive mechanical ventilation can generally be accomplished using tidal volumes of roughly 6 mL/kg, which limits the risk of ventilator-induced lung injury in those with parenchymal lung disease and minimizes the circulatory compromise that can complicate restrictive chest wall conditions.
- When initiating NPPV, there is a "window of opportunity" that opens when patients need ventilatory assistance but closes if they progress too far and become severely acidemic. Improvements in pH, arterial P_{CO_2}, and level of consciousness within the first hour or two of NPPV initiation are strong predictors of success.
- In patients with respiratory failure due to asthma or COPD, attempts to normalize arterial P_{CO_2} generally lead to dynamic hyperinflation, thereby risking hypotension and pneumothorax; instead, to minimize the risk of barotrauma, "permissive hypercapnia" is used to limit minute ventilation and maintain airway pressures in a safe range while allowing the arterial P_{CO_2} to rise.

References

1. Epstein SK, Singh N: Respiratory acidosis. Respir Care 46:366–383, 2001.
2. Roussos C, Macklem PT: The respiratory muscles. N Engl J Med 307:786–797, 1982.
3. Roussos C, Koutsoukou A: Respiratory failure. Eur Respir J Suppl 47:3s–14s, 2003.
4. Swenson E, Robertson HT: What do dead-space measurements tell us about the lung with acute respiratory distress syndrome? Respir Care 49:1006–1007, 2004.
5. Zimmerman JL: Poisonings and overdoses in the intensive care unit: General and specific management issues. Crit Care Med 31:2794–2801, 2003.
6. Aubier M, Murciano D, Fournier M, et al: Central respiratory drive in acute respiratory failure of patients with chronic obstructive pulmonary disease. Am Rev Respir Dis 122:191–199, 1980.
7. Piper AJ, Grunstein RR: Big breathing—the complex interaction of obesity, hypoventilation, weight loss and respiratory function. J Appl Physiol 2009 (Epub ahead of print).
8. Nowbar S, Burkart KM, Gonzales R, et al: Obesity-associated hypoventilation in hospitalized patients: Prevalence, effects, and outcome. Am J Med 116:1–7, 2004.
9. Zwillich CW, Pierson DJ, Hofeldt FD, et al: Ventilatory control in myxedema and hypothyroidism. N Engl J Med 292:662–665, 1975.
10. Orenstein DM, Boat TF, Owens RP, et al: The obesity hypoventilation syndrome in children with the Prader-Willi syndrome: A possible role for familial decreased response to carbon dioxide. J Pediatr 97:765–767, 1980.
11. Sandblom RE, Matsumoto AM, Schoene RB, et al: Obstructive sleep apnea syndrome induced by testosterone administration. N Engl J Med 308:508–510, 1983.
12. Gujjar AR, Deibert E, Manno EM, et al: Mechanical ventilation for ischemic stroke and intracerebral hemorrhage: Indications, timing, and outcome. Neurology 51:447–451, 1998.

13. Wijdicks EF, Scott JP: Outcome in patients with acute basilar artery occlusion requiring mechanical ventilation. Stroke 27:1301–1303, 1996.
14. Steiner T, Mendoza G, De Georgia M, et al: Prognosis of stroke patients requiring mechanical ventilation in a neurological critical care unit. Stroke 28:711–715, 1997.
15. Berrouschot J, Rossler A, Koster J, et al: Mechanical ventilation in patients with hemispheric ischemic stroke. Crit Care Med 28:2956–2961, 2000.
16. Coplin WM, Pierson DJ, Cooley KD, et al: Implications of extubation delay in brain-injured patients meeting standard weaning criteria. Am J Respir Crit Care Med 161:1530–1536, 2000.
16a. Winslow C, Bode RK, Felton D, et al: Impact of respiratory complications on length of stay and hospital costs in acute cervical spine injury. Chest 121:1548–1554, 2002.
17. Claxton AR, Wong DT, Chung F, et al: Predictors of hospital mortality and mechanical ventilation in patients with cervical spinal cord injury. Can J Anaesth 45:144–149, 1998.
18. Bach JR, Hunt D, Horton JA III: Traumatic tetraplegia: Noninvasive respiratory management in the acute setting. Am J Phys Med Rehabil 81:792–797, 2002.
19. Chervin RD, Guilleminault C: Diaphragm pacing for respiratory insufficiency. J Clin Neurophysiol 14:369–377, 1997
20. DiMarco AF, Onders RP, Ignagni A, et al: Phrenic nerve pacing via intramuscular diaphragm electrodes in tetraplegic subjects. Chest 127:671–678, 2005.
21. Tripp HF, Bolton JW: Phrenic nerve injury following cardiac surgery: A review. J Card Surg 13:218–223, 1998.
22. Diehl JL, Lofaso F, Deleuze P, et al: Clinically relevant diaphragmatic dysfunction after cardiac operations. J Thorac Cardiovasc Surg 107:487–498, 1994.
23. Valls-Sole J, Solans M: Idiopathic bilateral diaphragmatic paralysis. Muscle Nerve 25:619–623, 2002.
24. Hassoun PM, Celli BR: Bilateral diaphragm paralysis secondary to central von Recklinghausen's disease. Chest 117:1196–1200, 2000.
25. Dushay KM, Zibrak JD, Jensen WA: Myasthenia gravis presenting as isolated respiratory failure. Chest 97:232–234, 1990.
26. Czaplinski A, Strobel W, Gobbi C, et al: Respiratory failure due to bilateral diaphragm palsy as an early manifestation of ALS. Med Sci Monit 9:CS34–CS36, 2003.
27. Teitelbaum JS, Borel CO: Respiratory dysfunction in Guillain-Barré syndrome. Clin Chest Med 15:705–714, 1994.
28. Chalela JA: Pearls and pitfalls in the intensive care management of Guillain-Barré syndrome. Semin Neurol 21:399–405, 2001.
29. Lawn ND, Fletcher DD, Henderson RD, et al: Anticipating mechanical ventilation in Guillain-Barré syndrome. Arch Neurol 58:893–898, 2001.
30. Sharshar T, Chevret S, Bourdain F, et al: French Cooperative Group on Plasma Exchange in Guillain-Barré syndrome: Early predictors of mechanical ventilation in Guillain-Barré syndrome. Crit Care Med 31:278–283, 2003.
31. Hund EF, Borel CO, Cornblath DR, et al: Intensive management and treatment of severe Guillain-Barré syndrome. Crit Care Med 21:433–446, 1993.
32. Orlikowski D, Terzi N, Blumen M, et al: Tongue weakness is associated with respiratory failure in patients with severe Guillain-Barré syndrome. Acta Neurol Scand 119:364–370, 2009.
33. Varelas PN, Chua HC, Natterman J, et al: Ventilatory care in myasthenia gravis crisis: Assessing the baseline adverse event rate. Crit Care Med 30:2663–2668, 2002.
34. Lechtzin N, Rothstein J, Clawson L, et al: Amyotrophic lateral sclerosis: Evaluation and treatment of respiratory impairment. Amyotroph Lateral Scler Other Motor Neuron Disord 3:5–13, 2002.
35. Kaplan LM, Hollander D: Respiratory dysfunction in amyotrophic lateral sclerosis. Clin Chest Med 15:675–681, 1994.
36. Bonekat HW: Noninvasive ventilation in neuromuscular disease. Crit Care Clin 14:775–797, 1998.
37. Benditt JO: Management of pulmonary complications in neuromuscular disease. Phys Med Rehabil Clin N Am 9:167–185, 1998.
38. Perrin C, Unterborn JN, Ambrosio CD, et al: Pulmonary complications of chronic neuromuscular diseases and their management. Muscle Nerve 29:5–27, 2004.
39. De Carvalho M, Matias T, Coelho F, et al: Motor neuron disease presenting with respiratory failure. J Neurol Sci 139(Suppl):117–122, 1996.
40. Meyrignac C, Poirier J, Degos JD: Amyotrophic lateral sclerosis presenting with respiratory insufficiency as the primary complaint: Clinicopathological study of a case. Eur Neurol 24:115–120, 1985.
41. Vianello A, Bevilacqua M, Arcaro G, et al: Non-invasive ventilatory approach to treatment of acute respiratory failure in neuromuscular disorders: A comparison with endotracheal intubation. Intensive Care Med 26:384–390, 2000.
42. Lechtzin N, Wiener CM, Clawson L, et al. Use of noninvasive ventilation in patients with amyotrophic lateral sclerosis. Amyotroph Lateral Scler Other Motor Neuron Disord 5:9–15, 2004.
43. Shapiro RL, Hatheway C, Swerdlow DL: Botulism in the United States: A clinical and epidemiologic review. Ann Intern Med 129:221–228, 1998.
44. Schmidt-Nowara WW, Samet JM, Rosario PA: Early and late pulmonary complications of botulism. Arch Intern Med 143:451–456, 1983.
45. Sandrock CE, Murin S: Clinical predictors of respiratory failure and long-term outcome in black tar heroin–associated wound botulism. Chest 120:562–566, 2001.
46. Mitchell PA, Pons PT: Wound botulism associated with black tar heroin and lower extremity cellulitis. J Emerg Med 20:371–375, 2001.
47. Wilcox P, Andolfatto G, Fairbarn MS, Pardy RL: Long-term follow-up of symptoms, pulmonary function, respiratory muscle strength, and exercise performance after botulism. Am Rev Respir Dis 139:157–163, 1989.
48. Astudillo LM, Carreiro M, Sailler L, et al: Hypercapnic coma due to diaphragmatic involvement in a patient with dermatomyositis. Clin Exp Rheumatol 19:456–458, 2001.
49. Haskard DO: Successful treatment of dermatomyositis complicated by ventilatory failure. Ann Rheum Dis 42:460–461, 1983.
50. Deem S, Lee CM, Curtis JR: Acquired neuromuscular disorders in the intensive care unit. Am J Respir Crit Care Med 168:735–739, 2003.
51. Segredo V, Caldwell JE, Matthay MA, et al: Persistent paralysis in critically ill patients after long-term administration of vecuronium. N Engl J Med 327:524–528, 1992.
52. Rudis MI, Sikora CA, Angus E: A prospective, randomized, controlled evaluation of peripheral nerve stimulation versus standard clinical dosing of neuromuscular blocking agents in critically ill patients. Crit Care Med 25:575–583, 1997.
53. Baumann MH, McAlpin BW, Brown K, et al: A prospective randomized comparison of train-of-four monitoring and clinical assessment during continuous ICU cisatracurium paralysis. Chest 126:1267–1273, 2004.
54. Sessler CN: Train-of-four to monitor neuromuscular Bblockade? Chest 126:1018–1022, 2004.
55. Murray MJ, Cowen J, DeBlock H, et al: Clinical practice guidelines for sustained neuromuscular blockade in the adult critically ill patient. Crit Care Med 30:142–156, 2002.
56. Hansen-Flaschen J, Cowen J, Raps EC: Neuromuscular blockade in the intensive care unit: More than we bargained for. Am Rev Respir Dis 147:234–236, 1993.
57. Leatherman JW, Fluegel WL, David WS, et al: Muscle weakness in mechanically ventilated patients with severe asthma. Am J Respir Crit Care Med 153:1686–1690, 1996.
58. Bolton CF: Neuromuscular manifestations of critical illness. Muscle Nerve 32:140–163, 2005.
59. Kahn J, Harrison TB, Rich MM, Moss M: Early development of critical illness myopathy and neuropathy in patients with severe sepsis. Neurology 67:1421–1425, 2006.
60. De Jonghe B, Sharshar T, Lefaucheur JP, et al: Paresis acquired in the intensive care unit: A prospective multicenter study. JAMA 288:2859–2867, 2002.
61. Hermans G, Wilmer A, Meersseman W, et al: Impact of intensive insulin therapy on neuromuscular complications and ventilator

dependency in the medical intensive care unit. Am J Respir Crit Care Med 175:480–489, 2007.
62. Ali NA, O'Brien JM, Hoffmann SP, et al: Acquired weakness, handgrip strength, and mortality in critically ill patients. Am J Respir Crit Care Med 178:261–268, 2008.
63. Van den Berghe G, Wouters PJ, Bouillon R, et al: Outcome benefit of intensive insulin therapy in the critically ill: Insulin dose versus glycemic control. Crit Care Med 31:359–366, 2003.
64. Van den Berghe G, Wouters PJ, Weekers F, et al: Intensive insulin therapy in the critically ill patient. N Engl J Med 345:1359–1367, 2001.
64a. Schweickert WD, Pohlman MC, Pohlman AS, et al: Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. Lancet 373:1874–1882, 2009.
65. De Jonghe B, Bastuji-Garin S, Durand M-C, et al: Respiratory weakness is associated with limb weakness and delayed weaning in critical illness. Crit Care Med 35:2007–2015, 2007.
66. Sassoon CS, Zhu E, Caiozzo VJ: Assist-control mechanical ventilation attenuates ventilator-induced diaphragmatic dysfunction. Am J Respir Crit Care Med 170:626–632, 2004.
67. Powers SK, Shanely RA, Coombes JS, et al: Mechanical ventilation results in progressive contractile dysfunction in the diaphragm. J Appl Physiol 92:1851–1858, 2002.
68. Levine S, Nguyen T, Taylor N, et al: Rapid disuse atrophy of diaphragm fibers in mechanically ventilated humans. N Engl J Med 358:1327–1335, 2008.
69. Vassilakopoulos T, Petrof BJ: Ventilator-induced diaphragmatic dysfunction. Am J Respir Crit Care Med 169:336–341, 2004.
70. Watson AC, Hughes PD, Louise Harris M, et al: Measurement of twitch transdiaphragmatic, esophageal, and endotracheal tube pressure with bilateral anterolateral magnetic phrenic nerve stimulation in patients in the intensive care unit. Crit Care Med 29:1325–1331, 2001.
71. Durand MC, Lofaso F, Lefaucheur JP, et al: Electrophysiology to predict mechanical ventilation in Guillain-Barré syndrome. Eur J Neurol 10:39–44, 2003.
72. Kaida K, Kusunoki S, Kanzaki M, et al: Anti-GQ1b antibody as a factor predictive of mechanical ventilation in Guillain-Barré syndrome. Neurology 62:821–824, 2004.
73. Rieder P, Louis M, Jolliet P, Chevrolet JC: The repeated measurement of vital capacity is a poor predictor of the need for mechanical ventilation in myasthenia gravis. Intensive Care Med 21:663–668, 1995.
74. Rabinstein AA, Wijdicks EF: Warning signs of imminent respiratory failure in neurological patients. Semin Neurol 23:97–104, 2003.
75. Cohen CA, Zagelbaum G, Gross D, et al: Clinical manifestations of inspiratory muscle fatigue. Am J Med 73:308–316, 1982.
76. Schmidt-Nowara WW, Altman AR: Atelectasis and neuromuscular respiratory failure. Chest 85:792–795, 1984.
77. Henderson RD, Lawn ND, Fletcher DD, et al: The morbidity of Guillain-Barré syndrome admitted to the intensive care unit. Neurology 60:17–21, 2003.
78. ACCP-AARC-SCCM Collective Weaning Task Force: Evidence-based guidelines for weaning and discontinuing ventilatory support. I. Guidelines. Chest 120(Suppl):375s–395s, 2001.
79. Conti G, Rocco M, Antonelli M, et al: Respiratory system mechanics in the early phase of acute respiratory failure due to severe kyphoscoliosis. Intensive Care Med 23:539–544, 1997.
80. Annane D, Chevrolet JC, Chevret S, et al: Nocturnal mechanical ventilation for chronic hypoventilation in patients with neuromuscular and chest wall disorders. Cochrane Database Syst Rev 2:CD001941, 2000.
81. Finlay G, Concannon D, McDonnell TJ: Treatment of respiratory failure due to kyphoscoliosis with nasal intermittent positive pressure ventilation (NIPPV). Ir J Med Sci 164:28–30, 1995.
82. Masa JF, Celli BR, Riesco JA, et al: The obesity hypoventilation syndrome can be treated with noninvasive mechanical ventilation. Chest 119:1102–1107, 2001.
83. Perez De Llano LA, Golpe R, Piquer MO, et al: Short-term and long term effects of nasal intermittent positive pressure ventilation in patients with obesity-hypoventilation syndrome. Chest 128:587–594, 2005.
84. Hernandez G, Fernandez R, Lopez-Reina P, et al: Noninvasive ventilation reduces intubation in chest trauma-related hypoxemia: a randomized clinical trial. Chest 137:74–80, 2010.
85. Ambrosini V, Cancellieri A, Chilosi M, et al: Acute exacerbation of idiopathic pulmonary fibrosis: Report of a series. Eur Respir J 22:821–826, 2003.
86. Al-Hameed FM, Sharma S: Outcome of patients admitted to the intensive care unit for acute exacerbation of idiopathic pulmonary fibrosis. Can Respir J 11:117–122, 2004.
87. Fumeaux T, Rothmeier C, Jolliet P: Outcome of mechanical ventilation for acute respiratory failure in patients with pulmonary fibrosis. Intensive Care Med 27:1868–1874, 2001.
88. Stern JB, Mal H, Groussard O, et al: Prognosis of patients with advanced idiopathic pulmonary fibrosis requiring mechanical ventilation for acute respiratory failure. Chest 120:213–219, 2001.
89. Nava S, Rubini F: Lung and chest wall mechanics in ventilated patients with end stage idiopathic pulmonary fibrosis. Thorax 54:390–395, 1999.
90. Al-Hameed FM, Sharma S: Outcome of patients admitted to the intensive care unit for acute exacerbation of idiopathic pulmonary fibrosis. Can Respir J 11:117–122, 2004.
91. Ames WA, Ward VM, Trantor RM, Street M: Acute epiglottitis: An under-recognized life-threatening condition. Br J Anaesth 85:795–797, 2000.
92. Chuang YC, Wang CH, Lin YS: Negative pressure pulmonary edema: Report of three cases and review of the literature. Eur Arch Otorhinolaryngol 261:1113–1116, 2007.
93. Rochester DF, Braun NMT, Arora NS: Respiratory muscle strength in chronic obstructive pulmonary disease. Am Rev Respir Dis 119:151–154, 1979.
94. Groenewegen KH, Schols AM, Wouters EF: Mortality and mortality-related factors after hospitalization for acute exacerbation of COPD. Chest 124:459–467, 2003.
95. Pingleton SK: Complications of acute respiratory failure. Am Rev Respir Dis 137:1463–1493, 1988.
96. Brochard L, Isabey D, Piquet J, et al: Reversal of acute exacerbations of chronic obstructive lung disease by inspiratory assistance with a face mask. N Engl J Med 323:1523–1530, 1990.
97. Appendini L, Palessio A, Zanaboni S, et al: Physiologic effects of positive end-expiratory pressure and mask pressure support during exacerbations of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 149:1069–1076, 1994.
98. Kramer N, Meyer TJ, Meharg J, et al: Randomized, prospective trial of noninvasive positive pressure ventilation in acute respiratory failure. Am J Respir Crit Care Med 151:1799–1806, 1995.
99. Brochard L, Mancebo J, Wysocki M, et al: Noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease. N Engl J Med 333:817–822, 1995.
100. Plant PK, Owen JL, Elliott MW: Early use of non-invasive ventilation for acute exacerbations of chronic obstructive pulmonary disease on general respiratory wards: A multicenter randomized controlled trial. Lancet 355:1931–1935, 2000.
101. Barbe F, Togores B, Rubi M, et al: Noninvasive ventilatory support does not facilitate recovery from acute respiratory failure in chronic obstructive pulmonary disease. Eur Respir J 9:1240–1245, 1996.
102. Lightowler JV, Wedjicha JA, Elliot MW, et al: Non-invasive positive pressure ventilation to treat respiratory failure resulting from exacerbations of chronic obstructive pulmonary disease: Cochrane systematic review and meta-analysis. BMJ 326:185–189, 2003.
103. Keenan SP, Sinuff T, Cook DJ, et al: Which patients with exacerbation of chronic obstructive pulmonary disease benefit from noninvasive positive pressure ventilation? A systematic review of the literature. Ann Intern Med 138:861–870, 2003.
104. International Consensus Conferences in Intensive Care Medicine: Noninvasive positive pressure ventilation in acute respiratory failure. Am J Respir Crit Care Med 163:283–291, 2001.
105. Mehta S, Hill NS: Noninvasive ventilation: State of the art. Am J Respir Crit Care Med 163:540–577, 2001.
106. Hill NS: Noninvasive positive pressure ventilation for respiratory failure caused by exacerbations of chronic obstructive pulmonary disease: A standard of care? Crit Care 7:400–401, 2003.

107. Ambrosino N, Foglio K, Rubini F, et al: Non-invasive mechanical ventilation in acute respiratory failure due to chronic obstructive pulmonary disease: Correlates for success. Thorax 50:755–757, 1995.
108. Confalonieri M, Potena A, Carbone G, et al: Acute respiratory failure in patients with severe community-acquired pneumonia: A prospective randomized evaluation of noninvasive ventilation. Am J Respir Crit Care Med 160:1585–1591, 1999.
109. Auriant I, Jallot A, Herve P, et al: Noninvasive ventilation reduces mortality in acute respiratory failure following lung resection. Am J Respir Crit Care Med 164:1231–1235, 2001.
110. Kindgen-Milles D, Müller E, Buhl R, et al: Nasal-continuous positive airway pressure reduces pulmonary morbidity and length of hospital stay following thoracoabdominal aortic surgery. Chest 128:821–828, 2005.
111. Ferreyra GP, Baussano I, Squadrone V, et al: Continuous positive airway pressure for treatment of respiratory complications after abdominal surgery: A systematic review and meta-analysis. Ann Surg 247:617–626, 2008.
112. Nava S, Ambrosino N, Clini E, et al: Noninvasive mechanical ventilation in the weaning of patients with respiratory failure due to chronic obstructive pulmonary disease: A randomized, controlled trial. Ann Intern Med 128:721–728, 1998.
113. Ferrer M, Esquinas A, Arancibia F, et al: Noninvasive ventilation during persistent weaning failure. Am J Respir Crit Care Med 168:70–76, 2003.
114. Epstein SK, Ciubotaru RL, Wong JB: Effect of failed extubation on the outcome of mechanical ventilation. Chest 112:186–192, 1997.
115. Chevron V, Menard JF, Richard JC, et al: Unplanned extubation: Risk factors of development and predictive criteria for reintubation. Crit Care Med 26:1049–1053, 1998.
116. Hilbert G, Gruson D, Portel L, et al: Noninvasive pressure support ventilation in COPD patients with post-extubation hypercapnic respiratory insufficiency. Eur Respir J 11:1349–1353, 1998.
117. Keenan SP, Powers C, McCormack DG, et al: Noninvasive positive pressure ventilation for postextubation respiratory distress: A randomized controlled trial. JAMA 287:3238–3244, 2002.
118. Esteban A, Frutos-Vivar F, Ferguson ND, et al: Noninvasive positive-pressure ventilation for respiratory failure after extubation. N Engl J Med 350:2452–2460, 2004.
119. Ferrer M, Valencia M, Nicolas JM, et al: Early noninvasive ventilation averts extubation failure in patients at high risk: A randomized trial. Am J Respir Crit Care Med 173:164–170, 2006.
120. Nava S, Gregoretti C, Fanfulla F, et al: Noninvasive ventilation to prevent respiratory failure after extubation in high-risk patients. Crit Care Med 33:2465–2470, 2005.
120a. Ferrer M, Sellarés J, Valencia M, et al: Non-invasive ventilation after extubation in hypercapnic patients with chronic respiratory disorders: randomized controlled trial. Lancet 374:1082–1088, 2009.
121. Levy M, Tanios MA, Nelson D, et al: Outcomes of patients with do-not-intubate orders treated with noninvasive ventilation. Crit Care Med 32:2002–2007, 2004.
122. Freichels TA: Palliative ventilatory support: Use of noninvasive positive pressure ventilation in terminal respiratory insufficiency. Am J Crit Care 3:6–10, 1994.
123. Clarke DE, Vaughan L, Raffin TA: Noninvasive positive pressure ventilation for patients with terminal respiratory failure: The ethical and economic costs of delaying the inevitable are too great. Am J Crit Care 3:4–5, 1994.
124. Schettino G, Altobelli N, Kacmarek RM: Noninvasive positive pressure ventilation reverses acute respiratory failure in select "do-not-intubate" patients. Crit Care Med 33:1976–1982, 2005.
125. Jaber S, Fodil R, Carlucci A, et al: Noninvasive ventilation with helium-oxygen in acute exacerbations of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 161:1191–1200, 2000.
126. Jolliet P, Tassaux D, Roeseler J, et al: Helium-oxygen versus air-oxygen noninvasive pressure support in decompensated chronic obstructive disease: A prospective, multicenter study. Crit Care Med 31:878–884, 2003.
127. Soo Hoo GW, Santiago S, Williams AJ: Nasal mechanical ventilation for hypercapnic respiratory failure in chronic obstructive pulmonary disease: Determinants of success and failure. Crit Care Med 22:1253–1261, 1994.
128. Ambrosino N, Vagheggini G: Noninvasive positive pressure ventilation in the acute care setting: where are we? Eur Respir J 31:874–886, 2008.
129. Garpestad E, Brennan J, Hill NS: Noninvasive ventilation for critical care. Chest 132:711–720, 2007.
130. Kwok H, McCormack J, Cece R, et al: Controlled trial of nasal versus oronasal masks in patients with acute respiratory failure. Crit Care Med 127:699–713, 2003.
131. Navalesi P, Fanfulla F, Frigerio P, et al: Physiologic evaluation of noninvasive mechanical ventilation delivered with three types of masks in patients with chronic hypercapnic respiratory failure. Crit Care Med 28:1785–1790, 2000.
132. Vignaux L, Tassaux D, Jolliet P: Performance of noninvasive ventilation modes on ICU ventilators during pressure support: A bench model study. Intensive Care Med 33:1444–1451, 2007.
133. Ferreira JC, Chipman DW, Hill NS, Kacmarek RM: Bilevel vs ICU ventilators providing noninvasive ventilation. Effect of system leaks: A COPD lung model comparison. Chest 136:448–456, 2009. Epub 2009;May 8.
134. Vitacca M, Rubini F, Foglio K, et al: Noninvasive modalities of positive pressure ventilation improve the outcome of acute exacerbations in COLD patients. Intensive Care Med 19:450–455, 1993.
135. Bonmarchand G, Chevron V, Chopin C, et al: Increased initial flow rate reduces inspiratory work of breathing during pressure support ventilation in patients with exacerbation of chronic obstructive pulmonary disease. Intensive Care Med 22:1147–1154, 1996.
136. Lellouche F, Maggiore SM, Deye N, et al: Effect of the humidification device on the work of breathing during noninvasive ventilation. Intensive Care Med 28:1582–1589, 2002.
137. Nava S, Cirio S, Fanfulla F, et al: Comparison of two humidification systems for long-term noninvasive mechanical ventilation. Eur Respir J 32:460–464, 2008.
138. Laghi F: Effect of inspiratory time and flow settings during assist-control ventilation. Curr Opin Crit Care 9:39–44, 2003.
139. Girard TD, Kress JP, Fuchs BD, et al: Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): A randomised controlled trial. Lancet 371:126–134, 2008.
140. McFadden ER Jr: Acute severe asthma. Am J Respir Crit Care Med 168:740–759, 2003.
141. Rowe BH, Bretzlaff JA, Bourdon C, et al: Intravenous magnesium sulfate treatment for acute asthma in the emergency department: A systematic review of the literature. Ann Emerg Med 36:181–190, 2000.
142. Kass JE, Terregino CA: The effect of heliox in acute severe asthma: A randomized controlled trial. Chest 116:296–300, 1999.
143. Kress JP, Noth I, Gehlbach BK, et al: The utility of albuterol nebulized with heliox during acute asthma exacerbations. Am J Respir Crit Care Med 165:1317–1321, 2002.
144. Rose JS, Panacek EA, Miller P: Prospective randomized trial of heliox-driven continuous nebulizers in the treatment of asthma in the emergency department. J Emerg Med 22:133–137, 2002.
145. Rodrigo G, Pollack C, Rodrigo C, et al: Heliox for nonintubated acute asthma patients. Cochrane Database Syst Rev 4:CD002884, 2003.
146. Meduri GU, Cook TR, Turner RE, et al: Noninvasive positive pressure ventilation in status asthmaticus. Chest 110:767–774, 1996.
147. Soroksky A, Stav D, Shpirer I: A pilot prospective, randomized, placebo-controlled trial of bilevel positive airway pressure in acute asthmatic attack. Chest 123:1018–1025, 2003.
148. Afessa B, Morales I, Cury JD: Clinical course and outcome of patients admitted to an ICU for status asthmaticus. Chest 120:1616–1621, 2001.
149. Anzueto A, Frutos-Vivar F, Esteban A, et al: Incidence, risk factors and outcome of barotrauma in mechanically ventilated patients. Intensive Care Med 30:612–619, 2004.
150. Zimmerman JL, Dellinger RP, Shah AN, et al: Endotracheal intubation and mechanical ventilation in severe asthma. Crit Care Med 21:1727–1730, 1993.

151. Bigatello LM, Patroniti N, Sangalli F: Permissive hypercapnia. Curr Opin Crit Care 7:34–40, 2001.
152. Darioli R, Perret C: Mechanical controlled hypoventilation in status asthmaticus. Am Rev Respir Dis 129:385–387, 1984.
153. Kallet RH, Jasmer RM, Luce JM, et al: The treatment of acidosis in acute lung injury with tris-hydroxymethyl aminomethane (THAM). Am J Respir Crit Care Med 161:1149–1153, 2000.
154. Leatherman JW, Ravenscraft SA: Low measured auto-positive end-expiratory pressure during mechanical ventilation of patients with severe asthma: Hidden auto-positive end-expiratory pressure. Crit Care Med 24:541–546, 1996.
155. Mutlu GM, Factor P, Schwartz DE, et al: Severe status asthmaticus: Management with permissive hypercapnia and inhalation anesthesia. Crit Care Med 30:477–480, 2002.
156. Souders JE: Pulmonary air embolism. J Clin Monit Comput 16:375–383, 2000.
157. Maitre B, Habibi A, Roudot-Thoraval F, et al: Acute chest syndrome in adults with sickle cell disease. Chest 117:1386–1392, 2000.

CHAPTER 93

CARE AT THE END OF LIFE FOR PATIENTS WITH RESPIRATORY FAILURE

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INTRODUCTION

Patients with acute, chronic, and acute-on-chronic respiratory failure often suffer from symptoms such as pain and dyspnea, and they manifest a high mortality. These patients may be aggressively treated when they, their families, and their physicians believe that the patients' health and quality of life can be restored. Nevertheless, treatment goals at the end of life generally should be more palliative than restorative. In keeping with this approach, therapies such as mechanical ventilation, which can reverse respiratory failure in patients with acute decompensation, may be forgone for the terminally ill. When clinically appropriate, the withholding and withdrawal of life-sustaining therapy is supported by ethical and legal principles. These principles, along with the process of medical decision making and the desirable components of end-of-life care, are discussed in detail in this chapter.

THE BURDEN OF RESPIRATORY FAILURE

Respiratory failure is characterized by inadequate ventilation, inadequate oxygenation, or both (see Chapter 89). These inadequacies are reflected in increased systemic

arterial P_{CO_2}, decreased systemic arterial P_{O_2}, or a combination of the two. Acute respiratory failure may be caused by conditions such as pneumonia and the acute respiratory distress syndrome (ARDS). Chronic respiratory failure may be due to chronic obstructive pulmonary disease (COPD), lung cancer, and other disorders. Many patients are healthy and feel well before they develop acute respiratory failure. In contrast, most patients with chronic respiratory failure experience progressively more severe symptoms as their pulmonary function declines.[1,2] Their downhill course often is punctuated by acute exacerbations (acute-on-chronic respiratory failure) caused either by worsening of their primary disorder or by superimposed secondary illnesses such as pneumonia.[3]

Respiratory failure and the diseases responsible for it are a major cause of death throughout the world. For example, of the 2,337,256 people who were known to have died during 1998 in the United States, 154,972 (6.6%) did so because of malignant neoplasms of the lungs, trachea, bronchi, or pleura. Another 117,966 people (5.1%) died because of COPD and related conditions, and 64,144 (2.7%) died because of pneumonia or influenza. These data from the Division of Vital Statistics of the Department of Health and Human Services were derived from death certificates containing *International Classification of Diseases*, 9th Revision (ICD-9) codes for the underlying cause of death.[4] Deaths attributable to ARDS are more difficult to identify because a specific ICD-9 code is lacking for this condition, and death due to ARDS may be attributed to pneumonia or other disorders. Nevertheless, ARDS probably accounts for approximately 75,000 deaths in the United States each year.[5]

Respiratory failure and the diseases that cause it are associated with considerable morbidity as well as mortality. This association was demonstrated by the Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments (SUPPORT).[6] The SUPPORT study was based on a large cohort of hospitalized adult patients with at least one of nine conditions, including pneumonia, ARDS, COPD, and stage III or stage IV non–small cell lung cancer. Many SUPPORT patients with acute respiratory failure due to pneumonia or ARDS had normal physiologic function and enjoyed a good quality of life before hospitalization. Yet they had an in-hospital death rate of 26% and a 6-month mortality rate of 47%. Dying patients who were in an intensive care unit (ICU) spent an average of 9 days on a mechanical ventilator, most with severe pain and confusion, according to their families.[7] Of the ventilated patients who survived hospitalization and lived to 6 months, 29% rated their quality of life as only fair or poor.[8]

Regarding the impact of chronic respiratory failure on morbidity and mortality, SUPPORT demonstrated that an exacerbation of COPD among patients with an arterial P_{CO_2} of 50 mm Hg or more on hospital admission was associated with an in-hospital death rate of 11% and a 6-month mortality rate of 33%.[9] The families of patients who died in the hospital reported that their relatives generally experienced intense pain and dyspnea. Most of the patients who survived hospitalization were dyspneic for the rest of their lives, and their quality of life generally was poor. Of SUPPORT patients with advanced non–small cell lung cancer, 16% died during hospitalization, and an additional 42% did so in the following year. Suffering was commonplace among lung cancer patients during death in the hospital; those patients who were discharged demonstrated a progressive loss of function and an increase in symptoms as death approached.[10]

PREDICTING THE OUTCOME OF RESPIRATORY FAILURE

The prevalence of diseases that cause respiratory failure, coupled with the morbidity and mortality they cause, has prompted clinicians and investigators alike to seek prognostic information about patients with these disorders. Some of this prognostic information has been derived from single- or multi-institutional studies of specific conditions such as COPD,[11] *Pneumocystis jirovecii* pneumonia in patients with the acquired immunodeficiency syndrome (AIDS),[12] and ARDS.[13] Other information has come from studies of certain age groups, such as the elderly,[14] or from studies of interventions, such as mechanical ventilation.[15] These studies in turn have been used to develop tools to predict not only patient outcome but also the need for admission to the ICU for diseases such as pneumonia.[16]

Additional information has been obtained from the use of prognostic scoring systems based largely on physiologic variables such as arterial P_{CO_2} and P_{O_2} recorded on hospital admission or on other occasions. Although many of these systems were developed specifically for patients in ICUs, where physiologic variables are routinely measured, they also have been applied to patients elsewhere. Perhaps the best known prognostic scoring system is the Acute Physiology and Chronic Health Evaluation (APACHE), which has gone through four iterations.[17–20] The prognostic system developed for SUPPORT is similar to APACHE. It was based on patient diagnosis, age, number of days in the hospital before study entry, presence of cancer, neurologic function, and 11 physiologic variables recorded on day 3 of study entry.[21]

Prognosis based on the experience of individual clinicians or institutions is necessarily limited; despite wide use, such prognostication has never been subjected to rigorous evaluation. Although prognostication based on broader investigations of specific diseases should be more accurate, the changing outcome from *P. jirovecii* pneumonia,[22] ARDS,[23] and other conditions over time limits the use of these investigations in predicting outcome unless they are frequently updated. Furthermore, the tools based on these studies that may be used to determine the need for intensive care for pneumonia and other diseases have limited predictive value, presumably in part because the outcome from these conditions has changed over time.

Physiologically-based prognostic scoring systems have been shown to be as accurate—or inaccurate—as clinical assessment by physicians and nurses.[24] They have

demonstrated good calibration in that the overall hospital mortality predicted by the systems is comparable with that actually observed in research studies. Nevertheless, the systems have not discriminated well between individual survivors and nonsurvivors. For example, recommended prediction criteria were not effective in identifying a SUPPORT population with a survival prognosis of 6 months or less, limiting their use in determining which patients might generally meet hospice eligibility requirements.[25] Furthermore, when derived on the day before actual death, the median predicted likelihood of survival for 2 months among patients using the SUPPORT prognostic system was 17%, and when derived 1 week before actual death, the predicted likelihood was 51%, indicating how poorly the system could predict death shortly before it occurred.[26]

Prognostic scoring systems have contributed greatly to our understanding of the general outcomes of patients with respiratory failure and other conditions. Furthermore, the calibration and discriminatory power of the systems may improve as more studies of the systems are performed and more patients are entered into their databases. Yet, at present, the systems are imperfect in predicting outcome in individual patients. For the foreseeable future, therefore, the use of prognostic scoring systems should continue to be adjunctive in that they provide information to help in medical decision making but cannot be used by themselves to decide who is destined to die despite intensive care.

TREATMENT GOALS AT THE END OF LIFE

The limitations of prognostication are unfortunate because patients' and their families' predictions of prognosis largely determine their treatment preferences, just as physicians often base their recommendations to patients and families on their own prognostic estimates. Presumably because their quality of life was good and their deaths were not anticipated prior to becoming ill, SUPPORT patients with acute respiratory failure due to pneumonia and ARDS and their families and physicians generally preferred life-sustaining therapies until death appeared imminent.[7] In contrast, hospitalized SUPPORT patients with advanced COPD and lung cancer usually preferred care that was focused on their comfort rather than on extending their lives.[27] These preferences were related primarily to the patients' perceptions of how far advanced their underlying conditions were. For example, hospitalized patients with lung cancer who thought they were going to live at least 6 months were more likely to favor life-sustaining treatment over comfort care than patients who thought they had at least a 10% chance of dying within the next 6 months.[28]

The SUPPORT data suggest that as patients with respiratory failure become more symptomatic and perceive that death is near, they, their families, and their physicians become interested less in therapies that improve physiologic function and prolong life than in those that ease suffering and provide a peaceful and dignified death. Of course, these treatment goals are neither distinctly different nor mutually exclusive: life support and symptom relief often are sought simultaneously. Nevertheless, inside and outside the ICU, the emphasis often changes from restorative to palliative care among patients at the end of life. This change was described as "the transition from cure to comfort" in the title of the first published textbook on end-of-life care in the ICU.[29]

The term *end-of-life care* is meant to encompass two processes. One, the withholding and withdrawal of life support, represents the tapering of life-sustaining interventions such as pulmonary rehabilitation in the outpatient setting and mechanical ventilation in the ICU.[30–33] The other, the administration of palliative treatment, applies, among other things, to improving patient comfort through the giving of sedatives and analgesics. Combining these two processes signifies that end-of-life care involves more than removing something—in this case, life-saving treatments—from patients. It also means giving something to them: proper medical decision making; thoughtful communication; an appreciation of their needs and those of their families, physicians, and other caregivers; the use of an appropriate setting for death; and the management of pain, dyspnea, and other symptoms. This comprehensive and compassionate approach is what is meant by the expression "intensive caring at the end of life."[34]

WHERE AND HOW DEATH OCCURS

In less developed countries, most patients with respiratory failure who die do so at home largely because they have limited access to hospitals and other institutional settings. In the United States and other developed nations, however, death increasingly occurs outside the home. For example, of the large cohort of hospitalized patients in SUPPORT, 47% died within 6 months of study enrollment, and 55% of these deaths occurred during the enrollment hospitalization. Of the patients who survived the enrollment hospitalization, 46% died during hospitalization later that year, and only a minority died in a nursing home or hospice, let alone at home.[35] Similarly, in one investigation of all the deaths recorded in six states during 1999, 38% occurred in hospitals and 22% occurred following ICU admission.[36] Using these data to project national estimates, the investigators concluded that 540,000—fully one fifth—of all patients who die in the United States do so in ICUs each year.

Many factors account for the high prevalence of in-hospital and in-ICU deaths in the United States and, presumably, other developed countries. Among them are the availability of these facilities and of the physicians who admit patients to them and the fact that fewer elderly persons still reside with their families. In the United States, patients must be determined to have fewer than 6 months to live to qualify for hospice placement, but it is difficult to predict with accuracy which patients have such a limited life expectancy. Most patients want to live as long as possible unless life is a burden to them

and their families, and most physicians want to use all the means at their disposal to prolong life. Given these factors and the limits of prognostication, it is understandable that many patients with respiratory failure die in hospitals and ICUs, not in hospices or at home.

When ICUs were first developed during the 1950s and 1960s in the United States and Europe, patients who died in them did so despite full support, including attempted cardiopulmonary resuscitation (CPR). The wishes of patients and their surrogates regarding such support rarely were solicited, and do-not-attempt-resuscitation (DNAR) orders were rarely written for the patients because most hospitals felt obligated to perform CPR on everyone. Indeed, a host of potentially restorative treatments were automatically provided with little concern about their effectiveness or desirability. This approach was based on the belief, held by both health professionals and the public, that technologies should be used to preserve life whenever possible regardless of the human and economic costs.[37]

In recent years, however, the "technologic imperative" has been challenged, just as the expenses of the ICU have been scrutinized.[38] CPR has been shown to be ineffective in hospitalized patients.[39] Similarly, SUPPORT[6] has demonstrated that many seriously ill patients never leave the hospital alive or do so only after prolonged pain and suffering. Patients have been found not to prefer attempted restorative therapy in all instances, and courts in the United States have declared that these patients have a "right to die."[40] The ethical, legal, and economic consensus that has resulted from these developments has been reflected in a series of statements from professional societies[41,42] on the appropriateness of forgoing life-sustaining therapies at the end of life. As a result, although hospitalized patients once died despite attempted restorative treatment, they are more likely to die today during the withholding and withdrawal of life support and the administration of palliative care, especially in the ICU.[32,33]

TABLE 93-1. Ethical (Worldwide) and Legal (United States) Principles for Withholding and Withdrawing Life-Sustaining Therapy

ETHICAL PRINCIPLES
Beneficence
Nonmaleficence
Autonomy
Justice
LEGAL PRINCIPLES: RIGHT OF INFORMED CONSENT AND REFUSAL
Exercised by Patients with Decision-Making Capacity
Exercised by Family Members for Incapacitated Patients
As authorized under proxy directives
Using a substituted-judgment standard (facilitated by instructional directives)
Using a best-interests standard
Exercised by a Court-Appointed Conservator
Using a substituted-judgment standard (facilitated by instructional directives)
Using a best-interests standard
Exercised by Physicians, Often after Ethics Committee Review
Using a substituted-judgment standard (facilitated by instructional directives) (legal justification in a few states)
Using a best-interests standard (no legal justification)

From Beauchamp TL, Childress JF (eds): Principles of Biomedical Ethics (4th ed). Oxford: Oxford University Press, 1994; and Luce JM, Alpers A: End-of-life care: What do the American courts say? Crit Care Med 29:N40–N45, 2001.

ETHICAL AND LEGAL JUSTIFICATION FOR END-OF-LIFE CARE

Justification for Withholding and Withdrawing Life-Sustaining Therapy

The withholding and withdrawal of life support is justified by four ethical principles[43] (Table 93-1). The first principle is *beneficence*: the physicians' obligation to do good for patients. Relieving pain and suffering, rather than sustaining life at all costs, may be beneficent in certain situations. The second principle is *nonmaleficence*: the physicians' obligation to avoid harm. Life-sustaining interventions may be painful and incapable of sustaining life, and limiting such interventions may reduce harm in some patients. The third principle is *autonomy*: respect for the patients' right of self-determination. Patient autonomy is reinforced when patients are allowed to refuse unwanted life-sustaining therapies. The fourth principle is *justice*: the fair allocation of medical resources. Justice may be served if life support is withdrawn from one patient with a poor prognosis to help another patient with a better prognosis during a mass casualty occurrence or in an influenza pandemic.[44]

In the United States, the withholding and withdrawal of life-sustaining therapies is justified legally by the principles of informed consent and refusal, which have strong roots in common law.[45] The right of adults who are capable of making medical decisions either to consent to or to refuse treatment was first established in *Schloendorff v. Society of New York Hospitals* in 1914.[46] In this case, the Court of Appeal of New York declared that "Every being of adult years and sound mind has the right to determine what should be done with his own body; and a surgeon who performs an operation without his patient's consent commits an assault, for which he is liable in damages, except in cases of emergency when the patient is unconscious or when it is necessary to operate before consent can be obtained."

The right of adults with decision-making capacity to refuse treatment was furthered in cases such *as Bartling v. Superior Court*[47] and *Bouvia v. Superior Court*[48] in California. In the first of these cases, the Court of Appeals allowed a man with advanced COPD to have a mechanical ventilator removed against the wishes of his physicians and of the hospital. In the second, the appeals court ordered a hospital to stop force-feeding a quadriplegic woman against her will even though she might

die in the process. Most states have dealt with similar cases, and the principle that adults with capacity can refuse unwanted therapies is now widely accepted.

As SUPPORT[6] and other studies have shown, because of their illness and sedation, many critically ill patients cannot make medical decisions. In this circumstance, family members and other surrogates, if available, may consent to or refuse treatment for them. Parents have a long-standing right, indeed an obligation, to speak for their dependent children. The legal right of surrogates to act for incapacitated adult patients was established in *In re Quinlan*[49] in which the Supreme Court of New Jersey allowed the parents of a vegetative patient to refuse mechanical ventilation for their daughter through the mechanism of surrogate decision making. Through this mechanism, family members also were allowed to make life-determining decisions for their adult relative in *Barber v. Superior Court*[50] in California. In this case, the court determined that not only mechanical ventilation but also nutrition and hydration—indeed, any therapy that was not clearly benefiting the patient—could be forgone.

The U.S. Supreme Court dealt with the issue of surrogate decision making in the case of *Cruzan v. Director, Missouri Department of Health*.[51] In this case, a family argued that it was unconstitutional for a chronic care facility in Missouri to deny their request to remove a feeding tube from their vegetative adult daughter. The facility argued that the daughter had not specified her wishes not to be fed artificially in advance of incapacity. In its *Cruzan* decision, the Supreme Court allowed Missouri and other states to require "clear and convincing evidence" of patients' prior wishes before care was forgone for them. Nevertheless, it did not demand this requirement of other states, and it accepted the argument that the right of adult patients with decision-making capacity to refuse any and all therapies was protected under the Constitution.

Substituted judgment, through which surrogates know patients' wishes and can articulate them, is the highest standard under which surrogates may make medical decisions for incapacitated patients. Nevertheless, surrogates also may consider the patients' best interests. One delineation of a best-interests standard is that of the New Jersey Supreme Court relative to *In re Conroy*.[52] In this case, a nephew asked that a feeding tube be withdrawn from his elderly aunt, who had not declared her wishes before becoming demented, on the grounds that forgoing nutrition and hydration was in her best interest. The court would allow the best-interests standard in this case only because the burdens of the patient's life with treatment outweighed the benefits of continuing life, and because the recurring, unavoidable pain of life with treatment was such that administering therapies such as nutrition and hydration was inhumane. These requirements were imposed because the court considered the best-interest standard less compelling than the substituted-judgment standard.

Another legal perspective on the standards of substituted judgment and best interests came in the case of *Wendland v. Wendland*.[53] This case involved a middle-aged man who was conscious but hemiplegic, uncommunicative, and unable to feed himself after a motor vehicle accident. After his feeding tube repeatedly became dislodged, his wife, who was his conservator, refused to authorize its reinsertion. In support of her decision, she cited her husband's statements prior to his accident that he would not want to live in a severely debilitated condition. At this point, his mother went to court to block the plan not to reinsert the feeding tube, and it was reinserted. Mr. Wendland subsequently died, but the California Supreme Court deliberated on the issue of whether a conservator could withhold or withdraw life support from a patient who was conscious but incapable of articulating his current wishes. The Court ultimately ruled that feedings could be discontinued only if there was clear and convincing evidence that "the patient wished to refuse life-sustaining treatment or that to withhold such treatment would have been in his best interest," which was not thought to be true of Mr. Wendland. The decision in his case suggests that the courts are unlikely to allow surrogates to limit treatment in patients who are neither terminally ill nor severely neurologically impaired on the basis of a best-interests standard unless the patients have specified what they would want done in such a situation or unless their best interests can be objectively defined.[54]

Legal guidelines are less clear when incapacitated patients lack family members or other surrogates. Some states (e.g., Hawaii, Connecticut) allow physicians to make decisions for such patients based on wishes expressed to the physicians when the patients had decision-making capacity. However, no state explicitly allows physicians to make decisions based on a best-interests standard. Be that as it may, some physicians do make decisions to withhold or withdraw life-sustaining therapy from incapacitated patients, usually after consultation with their colleagues or with a hospital ethics committee, on the basis of best interests, as documented in a study from seven U.S. medical centers.[55] Other physicians ask the probate court to appoint conservators or other advocates for the patients, presumably under the unproven assumption that such advocates can determine what is in the patients' interests better than physicians can.

The U.S. Congress supported patient autonomy and the substituted-judgment standard by passing the Patient Self-Determination Act. This statute mandates that patients admitted to medical facilities be asked whether they have advance directives and that they be assisted in drawing up directives if they do not already have them.[56] Advance directives are of two types: instructional directives that state what patients want done in a given situation (e.g., living wills) and proxy directives that appoint surrogates to make decisions for them in these situations (e.g., the durable power of attorney for health care). SUPPORT has shown that most hospitalized patients have not filled out advance directives, that physicians are often unaware of the directives when they have been filled out, and that the directives have little impact on decision making or the use of hospital resources.[57] Nevertheless, advance directives have the potential for

reinforcing patient autonomy, even though this potential has not been realized.[58]

Before leaving the subject of justification for withholding and withdrawing life support, it is important to mention that decisions regarding this process are different for brain-dead patients than they are in patients who have lesser degrees of neurologic impairment. In the United States, death is defined as the total and irreversible loss either of cardiopulmonary function or of the function of the entire brain.[59] The determination of death by whole-brain criteria requires the demonstration of coma, indicating the loss of cerebral hemispheric function, and the documentation of absent corneal, oculovestibular, and ventilatory reflexes, indicating loss of function of the brain stem. Absence of ventilatory reflexes is demonstrated by an abnormal apnea test in which intubated, nonparalyzed patients removed from mechanical ventilation and given oxygen fail to initiate respiratory muscle efforts despite an increase of their arterial P_{CO_2} to at least 60 mm Hg.

Life-sustaining therapy usually can be forgone without a formal declaration of brain death. Conversely, some surrogates may insist that therapy be continued until patients die, in which case determining death by whole-brain criteria may be desirable. That said, the only patients in whom brain death must be determined are those who seem to be dead and whose organs will be transplanted after life support is withheld or withdrawn. Regarding the latter patients, one might argue that withdrawing life support from someone who is dead is an oxymoron. Because of this argument, and because brain-dead patients usually receive mechanical ventilation and other interventions only until their organs can be harvested, "life support" for them can be likened to "organ support."

The ethical and legal justification for removing therapies from brain-dead patients is not just that the therapies generally are unwanted by patients and surrogates in this situation but also that the patients are dead and cannot benefit from them. Inasmuch as the patients are dead, physicians have no obligation to treat them, and they do not need to obtain consent from surrogates before withholding or withdrawing treatment. Nevertheless, consent is required for organ retrieval and transplantation. Furthermore, the families of brain-dead patients frequently do not understand the concept of brain death and consider the patients to be alive because their chests rise and fall as the ventilator cycles and a tracing of their cardiac rhythms is displayed on the bedside monitor. Families also may reject the concept of brain death for religious reasons.

Motivated by consideration for such families and by a desire to gain their consent for organ donation, many physicians are appropriately nonconfrontational in addressing the issue of brain death. They take time to explain what death means in a biologic and legal sense, how brain death is determined, and how valuable transplantation can be for organ recipients as well as for the families of patients who serve as organ donors and even for the patients themselves. This approach generally is helpful to families, regardless of whether they ultimately approve transplantation. It also is useful in maintaining emotional equilibrium during a difficult time for all parties in the ICU.[60]

Medical Futility

Although the ethical principle of autonomy and the legal principles of informed consent and refusal are the most compelling justifications for withholding and withdrawing life support, the concept of futility also has been used as a justification. This concept is invoked on the relatively rare occasions when patients or their surrogates request interventions (particularly those that are costly, scarce, or both) that physicians object to because they believe the patients cannot benefit from them. Some treatments, such as brain transplantation for patients who are brain-dead, are physiologically futile in that they cannot be accomplished. Other treatments, such as the administration of vasopressors to raise blood pressure, can succeed physiologically, but some physicians may consider them medically futile because they cannot prolong life indefinitely or improve its quality in patients whose life expectancy is short and whose quality of life is poor.

One group of investigators[61] sought to define medical futility as an intervention that has been useless in the last 100 cases or that "merely preserves unconsciousness and cannot end dependence on intensive medical care." In a similar vein, the American Thoracic Society[42] argued that "a life-sustaining intervention may be withheld or withdrawn from a patient without the consent of the patient or surrogate if the intervention is judged to be futile. A life-sustaining intervention is futile if reasoning and experience indicate that the intervention would be highly unlikely to result in a meaningful survival for that patient. Here, meaningful survival specifically refers to a quality or duration of survival that would have value to that patient as an individual. Survival in a state with permanent lack of consciousness (i.e., completely lacking cognitive and sentient capacity) may be generally regarded as having no value for such a patient."

Despite what has been called the "futility movement," a broad concept of futility has never achieved consensus within the medical community in the United States or elsewhere, and the American Thoracic Society position has not gained broad support.[62] A contrary position has been advanced by the Society of Critical Care Medicine,[63] which holds that "Treatments should be defined as futile only when they will not accomplish their intended goal. Treatments that are extremely unlikely to be beneficial, are extremely costly, or are of uncertain benefit may be considered inappropriate and hence inadvisable, but should not be labeled futile. Futile treatments constitute a small fraction of medical care. Thus, employing the concept of futile care in medical decision-making will not primarily contribute to a reduction in resource use."

In some ways, the development of prognostic scoring systems can be seen as an attempt to predict which patients cannot benefit from therapies with very low efficacy, especially those that are expensive, and thereby provide a rationale for denying such therapies to them.[64] Yet most patients and families are quite willing to forgo

such therapies even when physicians are not, as indicated by SUPPORT.[8] Furthermore, a study of the theoretical implementation of a strict futility guideline for over 4000 SUPPORT patients demonstrated that only minimal cost savings could be realized by not treating patients who were predicted to have a 1% or less 2-month survival.[65] Nearly 75% of the savings in hospital days would have resulted from stopping treatment for 12 patients, one half of whom were under 51 years of age and 1 of whom lived 10 months when treatment was continued.

The emphasis on cost savings in the aforementioned study speaks to the fact that arguments about futility often have economic overtones. At one time, it appeared that American society could transition from a "rule of rescue," in which large sums of money were spent on therapies providing only marginal benefit, to a "rule of reason," in which this money could be used for primary and preventive care.[66] Yet health care reform failed in the United States, and managed care became identified as a tool for increasing corporate profits by denying medical services.[67] Arguments based on futility seem to provide a rationale for forgoing treatment on the grounds that it is not worthwhile, apart from the matter of cost. Yet these arguments conceal value-laden assumptions, and they obscure the underlying issue of rationing.[68] American physicians lack a social mandate to perform such rationing, a fact that is overlooked when they invoke futility.

Thus, the greatest problem with medical futility is not how it is defined but who defines it.[69] In this regard, the debate over futility pits physicians, who believe that their training and experience enables them to know what therapies are truly useful and cost-effective, against patients and families, who feel entitled to such therapies regardless of whether they pay for them directly. Physicians certainly are able to identify physiologic futility, and they are not legally or ethically required to perform procedures they consider nonbeneficial and below professional standards. Benefit, however, seems often to be in the eyes of the beholder: although physicians may regard mere prolongation of life as undesirable in certain circumstances, patients and families may consider it valuable. When these persons want treatments that physicians consider futile in more than a physiologic sense, which party should decide?

The American Medical Association Council on Ethical and Judicial Affairs has stated that, "Since definitions of futile care are value laden, universal consensus on futile care is unlikely to be achieved."[70] At the same time, the Council has recommended a process-based approach to futility determinations whereby patients or families who insisted on therapies that physicians considered futile would be required to undergo a dispute resolution process. Central to this process would be mediation by a hospital ethics committee. If resolution was not reached through mediation, the patients would be transferred to another institution or care would be terminated if transfer were impossible. So-called futility policies based on this model have been developed in Houston, Texas, and other cities.[71]

Based on the Houston experience, the State of Texas adopted a law providing an extrajudicial due process mechanism for resolving medical futility disputes. A survey[72] of Texas hospitals' experience with this law indicates that a minority of the hospitals had used the due process mechanism and that life-sustaining treatment was discontinued against patients' or surrogates' wishes in only a small number of cases. Furthermore, the constitutionality of the Texas statute has not been determined at the appellate or U.S. Supreme Court level. As a result, the implications of the Texas statute for that state and for the rest of the United States are unclear.

To date, legal cases such as *In re Helen Wanglie*[73] and *In the Matter of Baby K*[74] suggest that judges are unwilling to allow physicians to withhold or withdraw support from patients when the physicians ask to do so and the patients or families object. In the first of these cases, a court in Minneapolis refused to replace a husband who was seeking continued life support for his wife, life support which her physicians considered nonbeneficial, with another conservator who might allow support to be forgone. In the second, a Virginia court required that physicians repeatedly resuscitate an anencephalic infant at the request of its mother but against their own wishes, reasoning that to do otherwise would violate the Emergency Medical Treatment and Active Labor Act.

In contrast, the case of *Gilgunn v. Massachusetts General Hospital*[75] indicates that physicians are likely to obtain legal results more to their liking when they refuse to provide care they consider futile and defend their decisions in court as consistent with professional standards. In this case, a jury in Boston exonerated physicians at Massachusetts General Hospital for removing a patient from life support and writing a DNAR order for her over the objections of her daughter. The patient's husband and other children did not protest the physicians' actions, and the jury apparently believed that the physicians acted within the standard of care. This case does not set legal precedent because a written judgment was not rendered. Nevertheless, the jury decision in *Gilgunn* suggests some public support for the concept of futility.

How the debate over futility will be resolved is uncertain. Because patient autonomy is so widely accepted in the United States, because national health insurance does not exist there, and because patients and families are suspicious of managed care organizations, it seems unlikely that American physicians will soon be granted a mandate to restrict services on the basis of futility. This is not the case in other countries, however, where resources are limited, national health insurance exists, and physicians implicitly and explicitly are allowed to ration care.[76] Whether physicians will continue to exercise this and other prerogatives if American-style patient autonomy becomes more prevalent in their countries remains to be seen.

Justification for Administering Palliative Care

One reason that the concept of futility remains unresolved in the United States is that the Supreme Court has

not dealt with this issue. Nevertheless, the Court has provided ethical and legal justification for the administration of palliative care at the end of life, as in the cases of *Washington v. Glucksberg*[77] and *Vacco v. Quill*.[78] These cases dealt with the constitutionality of laws prohibiting physician-assisted suicide in the states of Washington and New York. In *Glucksberg*, the Court decided that terminally ill patients do not have a liberty interest in committing suicide or in receiving a physician's assistance in committing suicide because of both the long tradition of prohibiting suicide in the United States and the states' legitimate interest in continuing to make suicide illegal. In *Vacco*, it distinguished between assisted suicide and withholding and withdrawal of life support. "Everyone, regardless of physical condition, is entitled, if competent, to refuse lifesaving medical treatment; no one is permitted to assist a suicide," the Court wrote. "When a patient refuses life-sustaining medical treatment, he dies from an underlying fatal disease or pathology; but if a patient ingests lethal medicine prescribed by a physician, he is killed by that medication."

In *Glucksberg* and *Vacco*, five justices reasoned that Washington and New York could prohibit assisted suicide because these states had no barriers that prevented patients from receiving medications to relieve pain and suffering. However, as Justice Breyer wrote, "Were state laws to prevent the provision of palliative care, including the administration of drugs as needed to avoid pain at the end of life, an action against such law might be called for by the Supreme Court." Through this and other statements, a majority of the justices suggested that being free of pain while dying was a liberty interest protected under the Constitution.[79]

The Supreme Court distinguished assisted suicide from palliative care in *Glucksberg* and *Vacco* by accepting the ethical principle of double effect. Under this rule, acts such as giving sedatives and analgesics that lead to morally good effects, such as the relief of suffering, are permissible even if they produce morally bad effects, such as the hastening of death, provided that only the good effect is intended. The morally bad effect may be foreseen in that physicians are aware of its possibility and even its likelihood, but they may not wish that it occur. The bad effect also may not be a means to the good effect, and the good effect must outweigh the bad one; that is, risking death is reasonable in palliating a terminally ill patient only if there are no less risky ways of relieving suffering.[80]

The Supreme Court's approval of palliative care included sanctioning the practice of *terminal sedation*, in which patients are rendered unconscious while life-sustaining therapies, including nutrition and hydration, are withdrawn. Under *Vacco*, a state may allow terminal sedation if it is "based on informed consent and the double effect. Just as a state may prohibit assisted suicide while permitting patients to refuse unwanted lifesaving treatment, it may permit palliative care related to that refusal, which may have the foreseen but unintended 'double effect' of hastening the patient's death."

Some have argued that the rule of double effect has many shortcomings as an ethical guideline, in particular because it overlooks the complexity of human intention.[81] Such complexity was demonstrated in a study of the administration of sedatives and analgesics during the withholding and withdrawal of life support in two ICUs.[82] In this study, physicians indicated that they ordered these agents primarily to decrease pain, anxiety, and dyspnea—but also to hasten death—in 39% of critically ill patients. In another investigation, 16% of a sample of ICU nurses reported that they had engaged in assisted suicide or euthanasia while trying to relieve patient suffering, often without physicians' knowledge.[83]

Just as some physicians and nurses have mixed motives in caring for dying patients, so do some family members want to ease suffering and hasten death simultaneously in their relatives. That such motivation is widespread presumably accounts for the fact that few physicians who are suspected of participating in assisted suicide or euthanasia have been punished through the criminal justice system in the United States.[84] In general, physicians and other caregivers are unlikely to be prosecuted or even criticized if they act compassionately in administering sedatives and analgesics to dying patients and do so with informed consent.

The Supreme Court did not judge the laws prohibiting physician-assisted suicide in Washington and New York to be unconstitutional in *Glucksberg* and *Vacco*. Nevertheless, it also did not prevent other states from permitting physician-assisted suicide if they chose to do so. Physician-assisted suicide was legalized in Oregon in 1997 under that state's Death with Dignity Act. Experience over the subsequent 2 years indicated that few patients requested lethal medications, that physicians granted few requests, and that palliative interventions led some, but not all, patients to change their minds about assisted suicide.[85] By and large, the decision to request and use a prescription for lethal medication stemmed from patients' concern about loss of autonomy or control of bodily functions, not from fear of intractable pain or financial loss.[86]

Although the Death with Dignity Act has not been abused, the U.S. Congress and the Bush administration have tried to overturn it. In 1999, Congress considered a so-called Pain Relief Promotion Act, which would have amended the federal Controlled Substance Act, a law designed to prevent drug abuse and drug trafficking within the United States. This amendment "to promote pain relief and palliative care without permitting assisted suicide and euthanasia" would have interfered with Oregon's law had it not died in Congress. In 2001, Attorney General John Ashcroft ruled that the Death with Dignity Act violated the Controlled Substance Act and authorized the Drug Enforcement Administration to take action against Oregon physicians who prescribe lethal medications. This directive was blocked, however, by a U.S. District Court judge. As a result, physician-assisted suicide remains legal in Oregon. The U.S. Supreme Court may ultimately decide the fate of that state's Death with Dignity Act.[87]

Physician-assisted suicide (in which physicians prescribe potentially lethal medications that patients themselves can take) and euthanasia (in which physicians

actually administer the medications) are practiced in several European countries.[88] Although none of these countries has legalized the practices, physicians in the Netherlands have not been punished for performing them since 1991, when a national study revealed that assisted suicide and euthanasia were being performed.[89] Instead, Dutch physicians are required to report all cases in which they administered or supplied drugs with the explicit intent of hastening death. Patient requests for assisted suicide or euthanasia rose from 8900 in 1990 to 9700 in 1995 and remained stable at 9700 in 2001, according to one study.[90] Assisted suicide was listed as the cause of death on only 0.2% of all death certificates in the Netherlands during the same years. In 1990, 64% of Dutch physicians thought that patients have a right to decide about their own life or death; the percentage of physicians was the same in 1995 but fell to 56% in 2001. These data suggest that, in the Netherlands as in Oregon, the demand for assisted suicide has not increased; in fact, over time, Dutch physicians appear to have grown more reluctant in their attitude toward this practice. How common assisted suicide will become in other European countries and how their laws will deal with these practices are unclear.

MEDICAL DECISION MAKING AT THE END OF LIFE

Two Models of the Physician-Patient Relationship

Medical decisions may be made by physicians, patients, their families, or other surrogates alone or in combination. How decisions are actually made depends in large part on the model of the physician-patient relationship that is used. Perhaps the oldest model is *paternalistic*; this model also has been called *parental* or *priestly*. According to it, physicians using superior knowledge and experience act as guardians in defining what their patients' interests are and then serving these interests as they see fit, with little or no input from the patients themselves.[91] With pediatric patients, the families' input similarly might not be sought or might be disregarded. The paternalistic model overlooks patient autonomy and is supported primarily by the ethical principles of beneficence and nonmaleficence: acting to benefit patients and to avoid harm.

Another model of the physician-patient relationship is the *deliberative* one. Under this model, physicians help patients define their best interests, provide treatment alternatives through which the interests can be served, and assist the patients in deciding which alternative is best. With pediatric patients, families decide what the patients' interests are and how best to serve them with the physicians' assistance. This process is more than the mere passing of information: a moral deliberation, based on a mutual understanding of patients' wishes and values, is pursued. Physicians functioning under the deliberative model serve as teachers, not guardians as they do under the paternalistic model.[91] The deliberative model is a model of shared decision making. It is supported primarily by the ethical principle of autonomy: respect for the patients' right of self-determination.

The paternalistic model is particularly well suited to decision making in emergency situations wherein time is of the essence, patients may be unable to communicate, and their consent for treatment is considered to be implied because most of them presumably would want to be treated in emergencies. The deliberative model is best suited for situations in which physicians, patients, and families have ample time to discuss alternatives, extensive communication is possible, and consent can be informed. Consent can be informed only if patients or their surrogates are competent to make decisions, are provided with information relevant to their situation, can ask questions, and can act voluntarily.[92]

The paternalistic model once dominated medical decision making at the end of life in the United States. In fact, the early cases such as *Bartling*, *Bouvia*, and *Quinlan* were brought because physicians and hospitals were unwilling to let patients or surrogates refuse therapy. The deliberative model is more widely used today because the ethical principle of autonomy and the legal principles of informed consent and refusal are more widely accepted. Nevertheless, paternalism is implicit when physicians argue that therapies they consider futile should be withheld or withdrawn. It is ironic that some physicians today demand that patients and families forgo treatment that other physicians once insisted they accept.

Medical decision making and the attitudes that underlie it vary from country to country. Although the deliberative model is gaining popularity in France, the paternalistic model still is employed at the end of life in ICUs there. Physicians are granted decision-making prerogatives in these ICUs that are not permitted for their American counterparts. Furthermore, French families have no legal right to make decisions for patients who cannot make decisions for themselves.[93] In response to a questionnaire distributed to members of the European Society of Intensive Care Medicine, only 49% of physician respondents included patients and families in end-of-life decisions, and physicians differed in implementing the decisions.[94] The paternalistic model also is prevalent in Hong Kong, where people fear that acknowledging impending death is like casting a curse, physicians and families commonly make decisions for patients, and there is no legislation regarding patient autonomy or the status of advanced directives.[95]

Variations in attitudes also exist within a given country depending on its ethnic and cultural composition. For example, in one study in the United States, Korean Americans and Mexican Americans were significantly less likely than European Americans and African Americans to believe that a patient should be told the diagnosis of metastatic cancer or that the patient should make the decision about the use of life-sustaining therapy.[96] In another study, African Americans were more likely than European Americans to want to be kept alive on life support.[97] Interviews of these African Americans subjects documented a deep distrust of the health care

system and a fear that access to health care was based on one's ability to pay.

Importance of Physician, Patient, and Family Communication

Of course, American families would not need to be so involved in medical decision making in the ICU setting if physicians facilitated such decision making when the patients' diseases were not far advanced and they could speak for themselves.[98] Yet SUPPORT[6] and other studies have shown that physicians and patients rarely discuss end-of-life issues in advance of the patients' deterioration, even when patients reside in nursing homes. A study of patients with severe COPD enrolled in pulmonary rehabilitation revealed that almost all had health concerns, the most common of which was fear of increasing dyspnea.[99] Although many of the patients had concerns about being intubated, a minority had completed an advance directive describing their choices in regard to that intervention. Furthermore, although the patients generally wanted discussions with their physicians, only 19% had such discussions, only 15% had discussed life support, and only 14% thought that their physicians understood their end-of-life wishes.

Why patients with chronic and terminal diseases do not discuss end-of-life care with their physicians has been the subject of several investigations. In the study of patients with COPD enrolled in pulmonary rehabilitation, those patients who had not had discussions identified their own procrastination and the fact that their physicians had not brought up the topic as the most important reasons.[99] When these patients participated in an end-of-life educational intervention as part of their rehabilitation, they were more likely to have such discussions subsequently with their physicians and to complete durable powers of attorney for health care.

In another study of patients with advanced AIDS, structured interviews of the patients and their physicians were used to identify barriers to communication.[100] Patients who had not had discussions with their physicians about end-of-life care most frequently agreed that, "I don't like talking about getting very sick" and "I would rather concentrate on staying alive than talking about death." Physicians who did not initiate discussions most often agreed that, "There is too little time during our appointments to discuss everything we should" and "I worry that discussing end-of-life with [patient name] will take away his or her hope." Many physicians in this study acknowledged that they felt uncomfortable discussing end-of-life issues, suggesting that their own discomfort was as important as the lack of time for discussions in inhibiting communication.

Limited communication between physicians and patients was also reported in SUPPORT.[6] Furthermore, SUPPORT disclosed that communication was frequently inadequate between physicians and the families of critically ill patients. This finding was corroborated by a study from an ICU in France in which half the families of critically ill patients reported the same inadequacy.[101] A follow-up investigation from that and other ICUs in France indicated that family satisfaction with their relatives' care was due in part to their being of French descent and having a language and cultural values similar to those of the ICU caregivers.[102] Family satisfaction also related to information provided by hospital physicians, a patient-to-nurse ratio of 3:1 or less, knowledge of the specific role of each caregiver, help from the family's own physician, sufficient time spent giving information, and an absence of perceived contradictions in information provided by caregivers. Distribution of a family information leaflet in the ICUs improved family understanding of how the units functioned and increased their satisfaction with the care given therein.[103]

The importance of good communication also has been highlighted in a study of the quality of end-of-life care assessed through the responses of family members to a quality of death and dying (QODD) questionnaire after their relatives had died in and outside of hospitals.[104] In this study, higher QODD scores, which reflected a better quality of care at the end of life, were associated with death at home, death in the location the patient wanted, lower symptom burden, and better ratings of symptom treatment. Although the presence of an advance directive was not associated with a higher QODD score, higher scores were associated with communication about treatment preferences, compliance with treatment preferences, and family satisfaction regarding communication with the health care team.

In a study from one U.S. hospital, families were interviewed about their experiences in the ICU and the decision-making process for withholding or withdrawing life support.[105] They reported a high incidence of conflicts, the vast majority of which were between themselves and physicians. The conflicts most often involved problems in communication or perceived unprofessional behavior, such as disregarding the primary caregiver in treatment decisions. These families identified pastoral care and prior discussion of treatment preferences as sources of psychological support. They appreciated lenient visiting hours and the availability of family conference rooms. Most of the families singled out attending physicians as the preferred source of information and reassurance. In this regard, a study from another institution demonstrated that intensive communication achieved through regular family meetings led by attending physicians increased family satisfaction and also decreased ICU length of stay among patients who died.[106] Still another study indicated that allowing family members more opportunity to speak during conferences may increase their satisfaction.[107]

Another investigation looked at priorities and problems in end-of-life care identified by parents of children who had died after withdrawal of life support in three pediatric ICUs.[108] In response to a parental perspectives questionnaire, these parents placed highest priorities on their children's quality of life, likelihood of improvement, and their perceptions of their children's pain when considering withdrawal of support. Twenty percent of parents disagreed that their children were comfortable in their final days, a finding that echoed the SUPPORT study involving adult patients.[6] Fifty-five

percent of parents felt that they had little to no control during their children's final days, and nearly one fourth reported that, if able to do so, they would have made decisions differently. At the same time, the parents generally reported that ICU nurses and physicians were available and helpful to them, and many also had access to their community pediatricians.

Successful conflict resolution at the end of life is a process of negotiation between physicians and patients and families.[109] This process varies depending on whether the paternalistic or deliberative model of decision making is used, which in turn depends on the cultural context. In the United States, the process involves educating patients and families about likely prognoses, deferring to requests for seemingly benign treatments, convincing patients or families to forgo potentially harmful interventions, and occasionally refusing requests for therapy that physicians consider nonbeneficial.[110] Proper negotiation requires cross-cultural understanding and the use of communication skills, particularly that of listening to patients and families.[111,111a] Ethics committee consultations appear to be useful in resolving conflicts about treatments said to be futile and also are associated with reductions in ICU hospital days and life-sustaining therapy among patients who ultimately fail to survive until discharge from the hospital.[112] Whether such consultations also increase family satisfaction with the dying process of their loved ones is unclear.

UNDERSTANDING WHAT PHYSICIANS, PATIENTS, AND FAMILIES NEED AT THE END OF LIFE

End-of-life care could be optimized if the needs of the parties involved in the dying process were better understood. In this regard, a survey of seriously ill patients, recently bereaved families, physicians, and other caregivers revealed that decisions about treatment preferences, knowing what to expect about one's physical condition, and preparation for death were important to all four groups at the end of life.[113] Other important needs were sharing time with family and friends; being kept clean; being free of pain, anxiety, and dyspnea; and being treated as a "whole person." Patients, but not physicians, also rated as important being mentally aware, coming to peace with God, not being a burden to their families, being able to help others, praying, having funeral arrangements planned, and gaining a sense of completion in life (Table 93-2).

The needs of families have also been assessed in several studies using a survey tool called the Critical Care Family Needs Inventory. In an overview of recommendations for end-of-life care in the ICU, the Ethics Committee of the Society of Critical Care Medicine[114] combined these studies to determine what these needs are. Overall, family needs include being with the dying patient, being helpful to that patient, being informed of the dying patient's changing condition, understanding what is being done to the patient and why, being assured of the patient's comfort, being comforted, having an opportunity to express emotions, being assured that the family's decisions were right, finding meaning in the patient's death, and having personal needs attended to during the dying process.

TABLE 93-2. Factors Considered Important by Patients at the End of Life

Being kept clean
Naming a decision-maker
Having a nurse with whom one feels comfortable
Knowing what to expect about one's physical condition
Having someone who will listen
Maintaining one's dignity
Trusting one's physician
Having financial affairs in order
Being free of pain
Maintaining a sense of humor
Saying goodbye to important people
Being free of shortness of breath
Being free of anxiety
Having a physician with whom one can discuss fears

From Steinhauser KE, Christakis NA, Clipp EC, et al: Factors considered important at the end of life by patients, family, physicians, and other care providers. JAMA 284:2476–2482, 2000.

Unfortunately, the needs of physicians and others who care for dying patients have not been well addressed. Nevertheless, at a minimum, all caregivers probably need to feel comfortable during the dying process, to gain experience from it, to feel supported by their colleagues and by their institutions, and to have opportunities for bereavement themselves. Nurses, respiratory therapists, social workers, and clergy who work alongside physicians want to know that the physicians respect them, provide them with adequate information, take their opinions into account, and engage in proper decision-making practices at the end of life.[115]

PROVIDING APPROPRIATE SETTINGS FOR DYING PATIENTS

Under the deliberative model of the physician-patient relationship, physicians are obligated to help patients understand their conditions, explore their therapeutic options, and decide what is best for them. Essential to this relationship is preparing patients for death when appropriate. Such preparation should include consideration of whether the patients' interests are best served by hospital and ICU admission when death is imminent, assuming that the imminence of death can be identified. Many patients, especially those with COPD and other chronic diseases that allow time for advance planning as death approaches, decide to die in a hospice or at home if given the opportunity.

Terminal patients who prefer a trial of attempted restorative treatment in the hospital or undergo it

because their wishes are not known should at least die in an environment that is comfortable for them and their families when the trial fails. A private room with enough space to accommodate visitors might be such an environment. Visiting hours should be relaxed, if necessary, to allow families and friends to spend as much time as they wish with dying patients. Some hospitals have separate palliative care units for this purpose. Others offer palliative care teams or services that consult throughout the hospital.[116,117]

EMOTIONAL AND SPIRITUAL SUPPORT

Reviews of end-of-life care in and outside the ICU have emphasized the importance of providing emotional and spiritual support to dying patients and their families.[118] Physicians contribute to this support, of course, and their regular communications and presence at the bedside are greatly appreciated. Nurses, social workers, clergy, and other members of the health care team deliver most of the support, however. Occasionally, patients or their families request that friends, caregivers, and religious persons from outside a particular institution provide consultations or participate in bedside rituals or observances. These should be allowed, if not encouraged, unless they interfere with patient care.

End-of-life care may extend after death in that physicians, nurses, and others who have helped the patients' families when the patients were alive have much to offer them thereafter. Advising on the disposition of bodies, reporting the results of autopsy studies, coordinating burials and funeral services, and attending funerals are among the professional responsibilities of caregivers that are greatly appreciated by families. These responsibilities can be assumed by independent bereavement follow-up services, which have been described at one hospital.[119] Alternatively, caregivers who have established personal relationships with families in the ICU and other settings may maintain them after the patients' death.

Physicians, nurses, and other caregivers have their own emotional and spiritual needs, of course, and caring for dying patients and their families exacts an appreciable toll on them. Because of this, caregivers themselves should have opportunities to grieve. Conferences scheduled after patients die provide both an opportunity for bereavement and a mechanism for evaluating the processes of withholding and withdrawal of life support and of administering palliative care to them. Such evaluation may lead to improvements in these processes for future patients.

SYMPTOM MANAGEMENT

Why Symptoms May Be Poorly Managed

Management of pain and other symptoms is a traditional role and responsibility of the medical profession. Nevertheless, patients too frequently die with pain and other symptoms. Nearly 50% of SUPPORT patients or their surrogates interviewed after study enrollment reported that the patients experienced pain during hospitalization.[120] Nearly 15% reported extremely or moderately severe pain occurring at least half the time, and many of those patients with pain were dissatisfied with its control. Uncontrolled pain was most common among patients with more dependence on others in activities of daily living and who had more comorbid conditions, more anxiety, more depression, and a poor quality of life.[120]

That pain and other symptoms are poorly managed in some patients probably is due in large part to the strong emphasis restorative care places on the diagnosis and treatment of diseases rather than on the relief of symptoms. Palliative care reverses this emphasis and, when properly applied, should help increase patient comfort at the end of life. Nevertheless, the transition from restorative to palliative care is far from seamless for many patients. In this regard, it is difficult for patients and their families to know when to stop requesting treatment, just as it is for physicians and other caregivers to stop recommending life-sustaining therapies.

Pain and other symptoms may also be poorly managed because they are subjective experiences that are not easily assessed by objective methods. Pain and sedation scales have been developed to quantify the levels of pain and anxiety among patients who can self-report. Nevertheless, some patients cannot adequately communicate these sensations, either because they cannot find the words or because they are intubated and sedated. To detect pain in these patients, physicians and other caregivers must attend to patient grimacing and other admittedly nonspecific manifestations of pain, including tachycardia and hypertension. Although bispectral analysis of the electroencephalogram has been used to assess the level of sedation in ICU patients, the correlation of this technique with sedation scales and, most important, the subjective experiences of patients is unclear.[121]

Another reason that symptoms are poorly managed at the end of life is that patients differ in their desire to have symptoms relieved. Some patients value symptom relief highly and would prefer to be rendered unconscious rather than to experience pain, anxiety, or dyspnea, especially at the end of life. Others, however, would be willing to tolerate these symptoms or have them mitigated only slightly in order to stay awake. Dying patients may find it difficult to titrate sedatives and analgesics to their desired level of consciousness, although they should be encouraged to do so. Physicians and caregivers may find it even more difficult to achieve the ideal level of sedation and analgesia for patients who cannot communicate or administer drugs to themselves.

Finally, symptoms may be inadequately managed because physicians and other caregivers feel uncomfortable about giving high doses of sedatives, analgesics, and other mood-altering agents. In some instances, this discomfort stems from a reluctance to cause drug addiction in dying patients, a concern irrelevant to the patients' condition. Other discomfort results from awareness that the agents may hasten death by depressing not only consciousness but also respiratory and cardiovascular

function. That the U.S. Supreme Court has justified the administration of sedatives and analgesics under the principle of the double effect should help put caregivers at ease. Although one third of physicians in one study who ordered these agents to dying adult patients did so in part to hasten death,[82] virtually all the physicians in a comparable study[122] conducted in a pediatric ICU viewed hastening death only as an "acceptable, unintended side effect."

Management of Pain

Pain can be managed indirectly by nonpharmacologic means. For example, placing patients in a quiet environment where friends and family can visit may diminish the sense of pain, as may the proper treatment of anxiety and depression. Although respiratory depression due to drugs or underlying disease usually is undesirable in patients with COPD, the encephalopathy that results from the hypercapnia and hypoxia may be tolerated, if not favored, in terminal patients because it attenuates pain. Similarly, patients who forgo nutrition and hydration at the end of life may develop a euphoria that has been attributed to the release of endogenous opioids or the analgesic effects of ketosis.

A direct approach to pain control generally centers on the use of opioids, and morphine is the opioid most commonly used. In addition to causing analgesia, morphine induces some degree of sedation, respiratory depression, constipation, urinary retention, nausea, and euphoria. It also produces vasodilation, which may cause hypotension, in part through the release of histamine. Fentanyl, a synthetic opioid that is approximately 100 times more potent than morphine, does not release histamine and, therefore, causes less hypotension. Hydromorphone, a semisynthetic morphine derivative, is more sedating than morphine and produces little euphoria.[123]

Morphine, fentanyl, and hydromorphone can be administered orally, subcutaneously, rectally, or intravenously. Opioids usually are given by the intravenous route to ICU patients, including those who are dying. These agents may be administered to inpatients and outpatients alike through the technique of patient-controlled analgesia. Long-acting oral preparations of morphine and hydromorphone are available for outpatients. Fentanyl can be administered orally in the form of a lollipop. It can also be given by the transcutaneous route, which makes this agent particularly suitable for patients who have difficulty with oral medications.

Opioids ideally should be administered in anticipation of pain and not after its occurrence. The optimal doses of these drugs given for pain relief are unknown and certainly vary among patients. Nevertheless, opioids generally should be started in relatively low doses if respiratory depression and other side effects are to be avoided and titrated upward until their analgesic effect is realized. In reports of critically ill patients undergoing the withholding and withdrawal of life support in both adult and pediatric ICUs, opioids were used in doses sufficient to achieve pain relief that caregivers considered adequate.[82] In dying patients, the use of opioids should not be limited by some arbitrary amount but by the balance between analgesia and any undesirable side effects.

Management of Anxiety

As in the case of pain, anxiety and its physical manifestation agitation can be managed nonpharmacologically. If drugs are required, benzodiazepines and propofol are preferred. Benzodiazepines cause anterograde amnesia in addition to anxiolysis, and they exert a synergistic sedating effect with opioids. Benzodiazepines also cause hypotension and cardiac depression, especially when administered quickly and in high doses. Lorazepam, an intermediate-acting agent, can be given by the oral, intramuscular, or intravenous route; when given intravenously, it can be done so by bolus or by constant infusion. Midazolam, which is short-acting, usually is administered intravenously by constant infusion, although boluses may be required when therapy is initiated.[124]

Propofol is an intravenous general anesthetic agent with sedating, amnestic, and anxiolytic properties when administered in subanesthetic doses. In such doses, propofol is similar to midazolam in that it usually is given by constant infusion after bolus injection. The drugs also are comparable in the sedation they produce, although propofol has a greater propensity to cause hypotension.[124] Neither propofol nor midazolam is appropriate for the management of anxiety in outpatients and, in hospitals, their continuous use may be restricted to the ICU.

Management of Delirium

Delirium may be confused with anxiety because it too can cause agitation. The confusion is clinically important both because the conditions are treated pharmacologically with different drugs and because the drugs used to treat anxiety can exacerbate delirium.[117] Delirious patients should be helped to obtain regular sleep, should be oriented regularly to their environment, and should avoid benzodiazepines, which cloud consciousness. Haloperidol, a butyrophenone neuroleptic agent, is widely used to treat delirium in critically ill patients. It may be given orally, rectally, intramuscularly, or intravenously. Haloperidol may cause QT prolongation on the electrocardiogram and should be used cautiously with other agents that have a similar effect. Haloperidol also can cause rigidity, restlessness, and other dyskinesias.

Management of Dyspnea

Dyspnea should be understood and managed according to its underlying pathophysiology, especially in its earlier stages[3,125] (see Chapter 28). For example, patients with moderate to severe COPD may benefit from oral bronchodilators that decrease airflow resistance, inhaled corticosteroids that decrease airway inflammation, and lung volume reduction surgery that decreases hyperinflation. These patients also may become less dyspneic through exercise training and the emotional support available through pulmonary rehabilitation programs.[126] At the same time, patients with lung cancer may feel less breath-

less after drainage of malignant pleural effusions or placement of stents to overcome airway obstruction.

In patients with far advanced lung disease, attention to pathophysiologic mechanisms is less important, and treatment is more palliative than restorative. Bronchodilators may not reduce breathlessness in such patients; corticosteroids may cause more unwanted side effects than symptom relief; lung reduction surgery may prove fatal. Patients with COPD who are dying, at home or in hospice, do not benefit from exercise training and may be too breathless to attend pulmonary rehabilitation programs; these patients should be encouraged to use wheelchairs and to rest. In most terminal cancer patients, malignant effusions and airway obstruction should not be diagnosed or treated.[3]

Patients with chronic respiratory failure of whatever cause should receive supplemental oxygen, which has been shown to both increase survival and decrease breathlessness.[127] In the United States, Medicare reimbursement for long-term oxygen therapy is based on physiologic criteria (e.g., $Pa_{O_2} \leq 55$ mm Hg while breathing room air), not symptomatology. Despite this fact, many patients use oxygen primarily to relieve dyspnea, and hospice patients do not have to meet physiologic criteria to receive reimbursement. Supplemental oxygen usually is started in low doses (e.g., 1–3 L/min) and titrated to effect. The results of titration are difficult to predict inasmuch as neither the flow rate nor the route of administration of oxygen determines its impact on breathlessness.[3] Furthermore, air may relieve dyspnea as well as oxygen does in patients with advanced malignancy.[128] In addition, breathless patients frequently are relieved by exposure to fresh air in the outdoors or during automobile rides with the windows down. Those who are bedridden may benefit from using fans to blow air over their faces.[3]

Opioids such as oral morphine have been demonstrated to increase exercise tolerance acutely and to alleviate dyspnea in occasional patients with COPD.[129] Nevertheless, the long-term administration of sustained-release morphine has not been shown to be superior to placebo in reducing breathlessness in such patients, most of whom reported nausea, constipation, and other adverse effects.[130] Although many patients become tolerant to these adverse effects over time, opioids probably should be used only on a trial or as-needed basis for patients with recalcitrant dyspnea who do not respond to oxygen or air. However, because their analgesic properties are undisputed, these agents may be particularly useful in patients who have pain in addition to breathlessness, such as those with lung cancer.[3] Although the use of morphine and other opioids to relieve dyspnea in patients with ARDS and other causes of acute respiratory failure is widespread and seems reasonable, this practice is not supported by research studies.

Benzodiazepines such as alprazolam have been shown to reduce dyspnea in some patients with COPD.[131] Yet these agents also may cause drowsiness, uncoordination, and dysphoria; and they probably should be used only in outpatients whose dyspnea is not relieved by oxygen and opioids.[3] As is true of opioids, benzodiazepines and propofol are commonly used to reduce dyspnea, in addition to anxiety, among patients with acute respiratory failure, particularly those receiving mechanical ventilation. Again, this practice appears reasonable, especially if the patients are not experiencing unwanted side effects. Nevertheless, benefits of treating dyspnea with sedatives in ICU patients have not been demonstrated scientifically.

Management of Nausea and Vomiting

Nausea and vomiting may result from systemic illnesses such as diabetes, renal failure, hypercalcemia, adrenal insufficiency, and viral infections. These symptoms also may be caused by central nervous system disorders, including cerebral metastases and other conditions that increase intracranial pressure; primary gastrointestinal diseases such as gastric outlet obstruction; and a variety of drugs, including theophylline, phenytoin, opioids, antibiotics, and chemotherapeutic agents. Nausea and vomiting may remit with treatment of the disorder or discontinuing use of the drugs that cause them. Because eating can increase nausea, patients may benefit by being placed on a nothing-by-mouth status or undergoing gastric decompression. Clear liquid diets may be administered to patients as tolerated. Supplemental oxygen has been shown to reduce the incidence of postoperative nausea and vomiting.[132]

Patients with nausea and vomiting who do not respond to more conservative measures may be candidates for prophylactic or therapeutic antiemetic therapy, which can be given orally, intramuscularly, intravenously, or in suppository form. Among the older antiemetics are dexamethasone and other corticosteroids; butyrophenones such as haloperidol and droperidol; chlorpromazine, promethazine, prochlorperazine, and other phenothiazines; and muscarinic receptor antagonists such as scopolamine, which is particularly helpful in patients with vestibular symptoms. Of these agents, dexamethasone, droperidol, and promethazine are the most widely used.

Newer antiemetics include the serotonin receptor antagonists ondansetron, dolastron, granisetron, and tropisetron. These drugs have been tested primarily in the postoperative period and among patients who have received chemotherapy or radiation therapy. Because of their expense, they probably should be used only after other agents are found to be unsuccessful in preventing or relieving symptoms.[133] Cannabinoids, administered either orally or through smoking the *Cannabis sativa* (marijuana) plant, are as effective as older antiemetic agents such as chlorpromazine, prochlorperazine, and metaclopramide in reducing nausea and vomiting caused by chemotherapy. Nevertheless, although some patients welcome the sedation and euphoria they experience with cannabinoids, others complain of dizziness and dysphoria.[134]

Management of Hunger and Thirst

People eat food and drink fluids to relieve hunger and thirst and to sustain metabolic processes. Food and fluids

are administered to hospitalized patients under the assumption that they are staples of life and components of routine medical and nursing care. Under this assumption, some have argued that refusal of nutrition and hydration is tantamount to suicide and that food and fluids should be administered to all patients other than those who reject them because of intolerable pain and suffering in the last moments of life.[135] Others have noted that voluntary forgoing of nutrition and hydration by terminal patients represents only a refusal of unwanted treatment that is ethically and legally justified.[136] Still others have argued that force-feeding violates patient autonomy and that voluntary "terminal dehydration" on the part of patients offers substantial advantages over physician-assisted suicide with respect to self-determination, access, and professional integrity.[137]

Of course, patients may desire food and fluids until they die; alternatively, they may choose not to eat or drink. In fact, one study has documented that in Oregon, where physician-assisted suicide is allowed, many hospice patients forgo eating and drinking, perhaps as an alternative to assisted suicide.[138] As was the case in this study, another investigation conducted in a comfort care unit demonstrated that most cancer patients either never experienced hunger and thirst or did so only initially during their terminal illnesses.[139] In the few patients who were symptomatic, hunger, thirst, and dry mouth usually could be alleviated with small amounts of food and fluids or by the application of ice chips or lubrication to the lips. Similar measures can be used in other settings, including the ICU.

WITHHOLDING AND WITHDRAWAL OF LIFE-SUSTAINING THERAPY

What Therapies Are Withheld and Withdrawn

Life-sustaining therapies are withheld and withdrawn in many settings. Nevertheless, most of the studies of this process have been conducted in ICUs. These studies, from pediatric and adult ICUs around the world, reveal that, although any and all interventions may be withheld or withdrawn, variation exists in the type, number, and sequence of interventions forgone.[31,32,140] In one investigation in an adult ICU in the United States, an average of five separate interventions were forgone per patient.[141] CPR, intubation and mechanical ventilation, and dialysis generally were the first interventions withheld; thereafter, vasopressors, transfusions, intravenous fluids, parenteral nutrition, antibiotics, and tube feedings were either withheld or withdrawn. Decisions regarding withdrawing therapy occurred later than decisions regarding withholding it. Whereas a decision not to intubate a patient was made early for patients not already on ventilators, once patients were on ventilators, decisions to withdraw ventilatory support were generally made late, after several other interventions were first forgone.

Another study in which physicians were surveyed about the withdrawal process indicated distinct preferences about the form of support withdrawn.[142] From most likely to least likely, the order was blood products, dialysis, vasopressors, parenteral nutrition, antibiotics, mechanical ventilation, tube feedings, and intravenous fluids. Four biases in decision making also were identified. Physicians preferred to withdraw therapies supporting organs that failed for natural, rather than iatrogenic, reasons and therapies that were instituted only recently. They also preferred to withdraw therapies resulting in an immediate, rather than a delayed, death and to withdraw therapies resulting in a delayed death only when faced with diagnostic uncertainty.

Withholding and Withdrawal of Intubation and Mechanical Ventilation

Intubation and mechanical ventilation are often used in patients with acute, chronic, or acute-on-chronic respiratory failure and are among the therapies most commonly withheld or withdrawn. As noted earlier, some patients with advanced COPD and other causes of chronic respiratory failure have concerns about intubation and mechanical ventilation and decide against these therapies in advance of decompensation. Nevertheless, other patients with chronic respiratory failure request intubation and mechanical ventilation or are intubated and ventilated—either in the field, in the emergency department, or in the ICU—without having decided on their wishes or having communicated them. Similarly, patients with acute respiratory failure often end up on ventilators because their conditions are assumed to be reversible. When they and their counterparts with chronic respiratory failure do not improve, intubation and mechanical ventilation may be withdrawn. One study revealed that the strongest determinants of withdrawal of mechanical ventilation in critically ill patients were the physicians' perception that the patients preferred not to use life support, the physicians' prediction of a low likelihood of survival in the ICU and a high likelihood of poor cognitive function, and the use of inotropes or vasopressors.[143]

How intubation and mechanical ventilation are withdrawn varies among institutions. One approach is rapid extubation: the patient is given analgesics and sedatives, and both the endotracheal (or tracheotomy) tube and the ventilator are removed. Patients then are given either supplemental oxygen or, more commonly, room air to breathe. Rapid extubation is direct and, in the pediatric setting, it offers the potential advantage of allowing parents to hold their infants without being encumbered by the ventilator or its tubing. A potential disadvantage is that patients may appear distressed due to upper airway obstruction after the tube is removed.

A second process, called *terminal weaning*, involves decreasing the inspired oxygen fraction, the ventilator rate, the level of positive end-expiratory pressure, or some combination of these variables before the ventilator

is removed. Patients are given drugs during this process, and they most often die before extubation. First described in 1983, this technique was developed in order to avoid abruptly discontinuing treatment in such a way that "might be interpreted with intent to kill" and might make patients and their families uncomfortable.[144] The first part of this rationale is not relevant today because the differences between terminal weaning and euthanasia have been delineated by the U.S. Supreme Court. Nevertheless, terminal weaning still may cause less discomfort than rapid extubation by preventing upper airway obstruction.

The relative advantages and disadvantages of rapid extubation and terminal weaning have been debated. They have not been compared scientifically, although one study of what was called "rapid terminal weaning" demonstrated that patients could be kept comfortable during the procedure with relatively low doses of opioids and benzodiazepines.[145] A survey of critical care physicians indicated that 15% of respondents almost never withdrew intubation and mechanical ventilation from dying patients.[146] Of physicians who did, 13% preferred rapid extubation, 33% preferred terminal weaning, and the remainder used both methods. Reasons for preferring rapid extubation included the directness of the action, family perceptions, and patient comfort. Reasons for preferring terminal weaning included patient comfort, family perceptions, and the belief that terminal weaning was less abrupt.

When intubation and mechanical ventilation are withdrawn, most patients with respiratory failure die from their underlying diseases. Nevertheless, some survive, and their survival should not be prevented by drugs that hasten death. At the same time, even patients who are too sick to survive should not receive drugs that interfere with observing tachypnea and other signs that may signal the need for symptom relief. For these reasons, although sedatives and analgesics may be given to relieve suffering, neuromuscular blocking agents should not be introduced to patients while intubation and mechanical ventilation are withdrawn. Furthermore, if the patients are already receiving them, a common situation with infants, these agents should be continued only if two requirements are met. First, death is expected to be both rapid and certain after removal of the endotracheal tube, the ventilator, or both. Second, the burdens to patients and families of waiting for neuromuscular blockade to diminish to a reversible level exceed the benefits of allowing better assessment of the patients' comfort and possible interaction with their families.

IMPROVING THE QUALITY OF CARE AT THE END OF LIFE

Palliative care is a robust, well-recognized discipline, and it is extensively practiced in the outpatient setting. Yet end-of-life care has been incorporated into inpatient practice only recently, as patients in developed countries increasingly die in hospitals and in ICUs. Despite its fledgling status, however, inpatient end-of-life care is rapidly being improved upon as more physicians and other caregivers participate in it. Such improvement and participation were stimulated in large part by publication of the SUPPORT study[6] and the articles drawn from the SUPPORT database, many of which are cited in this chapter. For the most part, these publications documented the deficiencies of care at the end of life for hospitalized patients with respiratory failure and other critical illnesses.

In response to SUPPORT and its spin-offs have come a number of articles recommending possible improvements in end-of-life care; again, many of these articles are referred to in this chapter. Also referenced are an international consensus conference on challenges in end-of-life care in the ICU[147] and the first textbook on end-of-life care in the ICU.[29] Publication of this textbook was accompanied by release of a research agenda that outlines some of the questions about end-of-life care that must be answered before such care can be improved.[148] One strategy noted in the agenda is the need for structural changes, such as the expansion of family waiting areas, and for procedural changes, such as the development of clinical guidelines for palliative care. Pursuing this strategy has led to the articulation of end-of-life care domains and quality indicators[149] (Table 93-3), a content analysis of forms and other materials documenting end-of-life care in ICUs, and the creation of standardized comfort care orders for the withdrawal of life-sustaining therapies.[150,151] In the future, tools such as these will be used to assess and improve the quality of care at the end of life in ICUs.

TABLE 93-3. Seven Domains of End-of-Life Care

Patient- and family-centered decision-making
Communication
Continuity of care
Emotional and practical support
Symptom management and comfort care
Spiritual support
Emotional and organizational support for staff

From Clark EB, Curtis JR, Luce JM, et al: Quality indicators for end-of-life care in the intensive care unit. Crit Care Med 31:2255–2262, 2003.

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KEY POINTS

- End-of-life care is a combination of palliative treatment and withholding and withdrawal of life-sustaining therapy provided to patients who are terminally ill, including those with acute, chronic, and acute-on-chronic respiratory failure.
- End-of-life care is justified by the ethical principles of beneficence, nonmaleficence, autonomy, and justice and by the legal right of informed patients to consent to or refuse any or all therapy, including that which sustains life.
- The legal right of consent or refusal may be exercised by patients themselves or by their family members and legally appointed surrogates through substituted-judgment and best-interests standards. It also may be exercised by the patients' physicians using the same standards, although little legal support exists for this practice.
- End-of-life care is enhanced by a shared model of medical decision making and by intensive communication among patients, family members, and caregivers. Such care should attend to the needs of patients, families, and caregivers alike.
- The components of end-of-life care include providing appropriate settings for dying patients; supplying emotional and spiritual support; managing such symptoms as pain, anxiety, delirium, dyspnea, nausea and vomiting, and hunger and thirst; and removing unwanted therapies.

References

1. Ferrer M, Alonso J, Morera J, et al: Chronic obstructive pulmonary disease stage and health-related quality of life. Ann Intern Med 127:1072–1079, 1997.
2. Mercadante S, Casuccio A, Fulfaro F: The course and symptom frequency and intensity in advanced cancer patients followed at home. J Pain Symptom Manage 20:104–112, 2000.
3. Luce JM, Luce JA: Management of dyspnea in patients with far-advanced lung disease: "Once I lose it, it's kinda hard to catch it. …" JAMA 285:1331–1337, 2001.
4. Arias E, Smith BL: Deaths: Preliminary data for 2001. Natl Vital Stat Rep 51:1–44, 2003.
5. Ruberfeld GD, Caldwell E, Peabody E, et al: Incidence and outcome of acute lung injury. N Engl J Med 353:1685–1693, 2005.
6. The SUPPORT Principal Investigators: A controlled trial to improve care for seriously ill hospitalized patients: The Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments (SUPPORT). JAMA 274:1591–1598, 1995.
7. Somogyi-Zalud E, Zhong Z, Lynn J, et al: Dying with acute respiratory failure or multiple organ system failure with sepsis. J Am Geriatr Soc 48:S140–S145, 2000.
8. Hamel MB, Phillips RS, Davis RB, et al: Outcomes and cost-effectiveness of ventilator support and aggressive care for patients with acute respiratory failure due to pneumonia or acute respiratory distress syndrome. Am J Med 109:614–620, 2000.
9. Conners AF Jr, Dawson NV, Thomas C, et al: Outcomes following acute exacerbations of chronic obstructive lung disease. Am J Respir Crit Care Med 154:959–967, 1996.
10. McCarthy EP, Phillips RS, Zhong Z, et al: Dying with cancer: Patients' function, symptoms, and care preferences as death approaches. J Am Geriatr Soc 48:S110–S121, 2000.
11. Seneff MG, Wagner DP, Wagner RP, et al: Hospital and 1-year survival of patients admitted to intensive care units with acute exacerbations of chronic obstructive pulmonary disease. JAMA 274:1852–1857, 1995.
12. Wachter RM, Luce JM, Safrin S, et al: Cost and outcome of intensive care for patients with AIDS, *Pneumocystis carinii* pneumonia, and severe respiratory failure. JAMA 273:230–235, 1995.
13. Ely EW, Wheeler AP, Thompson BT, et al: Recovery rate and prognosis in older persons who develop acute lung injury and the acute respiratory distress syndrome. Ann Intern Med 136:25–36, 2002.
14. Chelluri L, Pinsky MR, Donahoe MP, et al: Long-term outcome of critically ill elderly patients requiring intensive care. JAMA 269:3119–3123, 1993.
15. Ely EW, Evans GW, Haponik EF: Mechanical ventilation in a cohort of elderly patients admitted to an intensive care unit. Ann Intern Med 131:96–104, 1999.
16. Fine MJ, Auble E, Yealy DM, et al: A prediction rule to identify low-risk patients with community-acquired pneumonia. N Engl J Med 336:243–250, 1997.
17. Knaus WA, Zimmerman JE, Wagner DP, et al: APACHE—Acute Physiology and Chronic Health Evaluation: A physiologically based classification system. Crit Care Med 9:591–597, 1981.
18. Knaus WA, Draper EA, Wagner DP, et al: APACHE II—A severity of disease classification system. Crit Care Med 13:818–829, 1985.
19. Knaus WA, Wagner DP, Draper EA, et al: The APACHE III prognostic system: Risk prediction of hospital mortality for critically ill hospitalized adults. Chest 100:1619–1636, 1991.
20. Zimmerman JE, Kramer A, McNair DS, et al: Acute Physiology and Chronic Health Evaluation (APACHE) IV: Hospital mortality assessment for today's critically ill patients. Crit Care Med 34:1297–1301, 2006.
21. Knaus WA, Harrell FE, Lynn J, et al: The SUPPORT prognostic model: Objective estimates of survival for seriously ill hospitalized adults. Ann Intern Med 122:191–203, 1995.
22. Morris A, Creasman J, Turner J, et al: Intensive care of human immunodeficiency virus–infected patients during the era of highly active antiretroviral therapy. Am J Respir Crit Care Med 166:262–267, 2002.
23. Milberg JA, Davis DR, Steinberg KP, et al: Improved survival of patients with acute respiratory distress syndrome (ARDS): 1983–1993. JAMA 273:306–309, 1995.
24. Kruse JA, Thill-Baharozian MC, Carlson RW: Comparison of clinical assessment with APACHE II for predicting mortality risk in patients admitted to a medical intensive care unit. JAMA 260:1739–1742, 1988.
25. Fox E, Landrum-McNiff K, Zhong Z, et al: Evaluation of prognostic criteria for determining hospice eligibility in patients with advanced lung, heart, or liver disease. JAMA 282:1638–1645, 1999.
26. Lynn J, Harrell F, Cohn F, et al: Prognoses of seriously ill hospitalized patients on the days before death: Implications for patient care and public policy. New Horiz 5:56–61, 1997.
27. Claessens MT, Lynn J, Zhong Z, et al: Dying with lung cancer or chronic obstructive pulmonary disease: Insights from SUPPORT. J Am Geriatr Soc 48:S146–S153, 2000.

28. Weeks JC, Cook EF, O'Day SJ, et al: Relationship between cancer patients' predictions of prognosis and their treatment preferences. JAMA 279:1709–1714, 1998.
29. Curtis JR, Rubenfeld GD (eds): Managing Death in the Intensive Care Unit: The Transition from Cure to Comfort. Oxford: Oxford University Press, 2001.
30. Luce JM: Withholding and withdrawal of life support from critically ill patients. West J Med 167:411–416, 1997.
31. Smedira NG, Evans BH, Grais LS, et al: Withholding and withdrawal of life support from the critically ill. N Engl J Med 322:309–315, 1990.
32. Prendergast TJ, Luce JM: Increasing incidence of withholding and withdrawal of life support from the critically ill. Am J Respir Crit Care Med 155:15–20, 1997.
33. Prendergast TJ, Claessens MT, Luce JM: A national survey of end-of-life care for critically ill patients. Am J Respir Crit Care Med 158:1163–1167, 1998.
34. Prendergast TJ, Puntillo KA: Withdrawal of life support: Intensive caring at the end of life. JAMA 288:2732–2740, 2002.
35. Lynn J, Teno JM, Phillips RS, et al: Perceptions by family members of the dying experience of older and seriously ill patients. Ann Intern Med 126:97–106, 1997.
36. Angus DC, Barnato AE, Linde-Zwirble WT, et al: The use of intensive care at the end of life in the United States: An epidemiologic study. Crit Care Med 32:638–643, 2004.
37. Luce JM, Prendergast TJ: The changing nature of death in the ICU. *In* Curtis JR, Rubenfeld GD (eds): Managing Death in the Intensive Care Unit: The Transition from Cure to Comfort. Oxford: Oxford University Press, 2001, pp 19–29.
38. Fuchs VR (ed): Who Shall Choose? Health, Economics, and Social Choice. New York: Basic Books, 1974.
39. Bedell SE, Delblarco TL, Cook F, et al: Survival after cardiopulmonary resuscitation in the hospital. N Engl J Med 309:569–576, 1983.
40. Gostin LO: Deciding life and death in the courtroom: From Quinlan to Cruzan, Glucksberg, and Vacco—A brief history and analysis of constitutional protection of the "right to die." JAMA 278:1523–1528, 1997.
41. Task Force on Ethics of the Society of Critical Care Medicine: Consensus report on the ethics of foregoing life-sustaining treatments in the critically ill. Crit Care Med 18:1435–1439, 1990.
42. American Thoracic Society: Withholding and withdrawing life-sustaining therapy. Am Rev Respir Dis 144:726–731, 1991.
43. Beauchamp TL, Childress JF (eds): Principles of Biomedical Ethics (4th ed). Oxford: Oxford University Press, 1994.
44. White DB, Katz MH, Luce JM, Lo B: Who should receive life support during an influenza pandemic? Using ethical principles to improve allocation decisions. Ann Intern Med 150:132–138, 2009.
45. Luce JM, Alpers A: Legal aspects of withholding and withdrawing life support from critically ill patients in the United States and providing palliative care to them. Am J Respir Crit Care Med 162:2029–2032, 2000.
46. Schloendorff v. Society of New York Hospitals, 211 NY 125, 105 NE 92 (1914).
47. Bartling v. Superior Court, 163 Cal. App. ed 190, 209 Cal. Rptr. 220 (1984).
48. Bouvia v. Superior Court, 179 Cal. App. ed 190, 225 Cal. Rptr. 297 (1986).
49. In re Quinlan, 755 A2A 647 (NJ), cert. Denied, 429 US 922 (1976).
50. Barber v. Superior Court, 147 Cal. App. 3d 1006 (Cal. App. 1983).
51. Cruzan v. Director, Missouri Department of Health, 497 US 261 (1990).
52. In re Conroy, 486A: 2d 1209 (N.J. 1985).
53. Wendland v. Wendland, 26 Cal. 4th 519, 28 P.3d 151 (2001).
54. Lo B, Dornbrand L, Wolf LE, et al: The Wendland case—Withdrawing life support from incompetent patients who are not terminally ill. N Engl J Med 346:1489–1494, 2002.
55. White DB, Curtis JR, Wolf LE, et al: Life support for patients without a surrogate decision maker. Who decides? Ann Intern Med 147:34–40, 2007.
56. Grew PJ, Schulman KA, Lavison MR, et al: The Patient Self-Determination Act and the future of advance directives. Ann Intern Med 115:639–643, 1991.
57. Covinsky KE, Fuller JD, Yaffe K, et al: Communication and decision-making in seriously ill patients: Findings of the SUPPORT project. J Am Geriatr Soc 48:S187–S193, 2000.
58. Quill TE, Brody H: Physician recommendations and patient autonomy: Finding a balance between physician power and patient choice. Ann Intern Med 125:763–769, 1996.
59. President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research: Guidelines for the determination of brain death. JAMA 246:2184–2186, 1981.
60. Luce JM: Ethical principles in critical care. JAMA 263:696–700, 1990.
61. Schneiderman LJ, Jecker NS, Jonsen AR: Medical futility: Its meaning and ethical implications. Ann Intern Med 112:949–954, 1990.
62. Helft PR, Siegler M, Lantos J: The rise and fall of the futility movement. N Engl J Med 343:293–296, 2000.
63. The Ethics Committee of the Society of Critical Care Medicine: Consensus statement of the Society of Critical Care Medicine's Ethics Committee regarding futile and other possibly inadvisable treatments. Crit Care Med 25:887–891, 1997.
64. Knaus WA, Wagner DP, Lynn J: Short-term mortality predictions for critically ill hospitalized adults: Science and ethics. Science 254:389–394, 1991.
65. Teno JM, Murphy D, Lynn J, et al: Prognosis-based futility guidelines: Does anyone win? J Am Geriatr Soc 42:1202–1207, 1994.
66. Luce JM: The changing physician-patient relationship in critical care medicine under health care reform. Am J Respir Crit Care Med 150:266–270, 1994.
67. Luce JM: Making decisions about the forgoing of life-sustaining therapy. Am J Respir Crit Care Med 156:1715–1718, 1997.
68. Truog RD, Brett AS, Frader J: The problem with futility. N Engl J Med 326:1560–1564, 1992.
69. Younger SJ: Who defines futility? JAMA 260:2094–2095, 1988.
70. Council on Ethical and Judicial Affairs, American Medical Association: Medical futility in end-of-life care. JAMA 281:937–941, 1999.
71. Halevy A, Brody BA: A multi-institutional collaborative policy on medical futility. JAMA 276:571–574, 1996.
72. Smith ML, Gremillion G, Slomka J, et al: Texas hospitals' experience with the Texas Advance Directives Act. Crit Care Med 35:1271–1276, 2007.
73. In re Helen Wanglie, Fourth Judicial District (Dist. Ct., Probate Ct. Div.). PX-91-283. Minnesota. Hennipin County.
74. In the Matter of Baby K, 832 F. Supp. 1022 (E.D. Va. 1993).
75. Gilgunn v. Massachusetts General Hospital, Na: 92-4820 (Mass. Super. Ct. Civ. Action Suffolk S. April 22, 1995).
76. Aaron HJ, Schwartz WB (eds): The Painful Prescription: Rationing Hospital Care. Washington, DC: Brookings Institution, 1984.
77. Washington v. Glucksberg, 521 US 702 (1997).
78. Vacco v. Quill, 521 US 797 (1997).
79. Burt RA: The Supreme Court speaks: Not assisted suicide but a constitutional right to palliative care. N Engl J Med 337:1234–1236, 1997.
80. Sulmasy DP: The rule of double effect: Clearing up the double talk. Arch Intern Med 159:545–550, 1999.
81. Quill TE, Dressner R, Brock DW: The rule of double effect: A critique of its role in end-of-life decision making. N Engl J Med 337:1768–1772, 1997.
82. Wilson WC, Smedira NG, Fink C, et al: Ordering and administration of sedatives and analgesics during the withholding and withdrawal of life support from critically ill patients. JAMA 267:949–953, 1992.
83. Asch DA: The role of critical care nurses in euthanasia and assisted suicide. N Engl J Med 334:1374–1379, 1996.
84. Alpers A: Criminal act or palliative care? Prosecutions involving the care of the dying. J Law Med Ethics 26:308–331, 1998.
85. Ganzini L, Nelson HD, Schmidt TA, et al: Physicians' experiences with the Oregon Death With Dignity Act. N Engl J Med 342:557–563, 2000.
86. Chin AE, Hedberg K, Higginson GK, et al: Legalized physician-assisted suicide in Oregon: The first year's experience. N Engl J Med 340:577–583, 1999.
87. Steinbrook R: Physician-assisted suicide in Oregon—An uncertain future. N Engl J Med 346:460–464, 2002.

88. Van der Heide A, Dekliens L, Faisst K, et al: End-of-life decision-making in six European countries: Descriptive study. Lancet 361:345–350, 2003.
89. Van der Maas PJ, van der wal G, Haverkate I, et al: Euthanasia, physician assisted suicide, and other medical practices involving the end of life in The Netherlands, 1990–1995. N Engl J Med 335:1699–1705, 1996.
90. Onwuteaka-Phillipsen BD, van der Heide A, Keij-Deerenberg I, et al: Euthanasia and other end-of-life decisions in The Netherlands in 1990, 1995, and 2003. Lancet 362:395–399, 2003.
91. Emanuel EJ, Emanuel LL: Four models of the physician-patient relationship. JAMA 267:2221–2226, 1992.
92. Faden RR, Beauchamp TL (eds): A History and Theory of Informed Consent. Oxford: Oxford University Press, 1986.
93. Luce JM, Lemaire F: Two trans-Atlantic viewpoints on an ethical quandary. Am J Respir Crit Care Med 163:818–821, 2001.
94. Vincent J-L: Forgoing life support in western European intensive care units: The results of an ethical questionnaire. Crit Care Med 27:1626–1633, 1999.
95. Ip M, Gilligan T, Koenig B, et al: Ethical decision-making in critical care in Hong Kong. Crit Care Med 26:447–451, 1998.
96. Blackhall LJ, Murphy ST, Frank G, et al: Ethnicity and attitudes toward patient autonomy. JAMA 274:820–825, 1995.
97. Blackhall LJ, Frank G, Murphy ST, et al: Ethnicity and attitudes towards life sustaining technology. Soc Sci Med 48:1779–1789, 1999.
98. Quill TE: Initiating end-of-life discussions with seriously ill patients: Addressing the "elephant in the room." JAMA 284:2502–2507, 2000.
99. Heffner JE, Fahy B, Hilling L, et al: Attitudes regarding advance directives among patients in pulmonary rehabilitation. Am J Respir Crit Care Med 154:1735–1740, 1996.
100. Curtis JR, Patrick DL, Caldwell ES, et al: Why don't patients and physicians talk about end-of-life care? Barriers to communication for patients with acquired immunodeficiency syndrome and their primary care clinicians. Arch Intern Med 160:1690–1696, 2000.
101. Azoulay E, Chevret S, Leleu G, et al: Half the families of intensive care unit patients experience inadequate communication with physicians. Crit Care Med 28:3044–3049, 2000.
102. Azoulay E, Pochard F, Chevret S, et al: Meeting the needs of intensive care unit patient families: A multicenter study. Am J Respir Crit Care Med 163:135–139, 2001.
103. Azoulay E, Pochard F, Chevret S, et al: Impact of a family information leaflet on effectiveness of information provided to family members of intensive care unit patients. Am J Respir Crit Care Med 165:438–442, 2002.
104. Curtis JR, Patrick DL, Engelberg RA, et al: A measure of the quality of dying and death: Initial validation using after-death interviews with family members. J Pain Symptom Manage 24:17–31, 2002.
105. Abbott KH, Sago JG, Breen CM, et al: Families looking back: One year after discussion of withdrawal or withholding of life-sustaining support. Crit Care Med 29:197–201, 2001.
106. Lilly CM, DeMeo DL, Sonna LA, et al: An intensive communication intervention for the critically ill. Am J Med 109:469–475, 2000.
107. McDonagh JR, Elliott TB, Engelberg RA, et al: Family satisfaction with family conferences about end-of-life care in the intensive care unit: Increased proportion of family speech is associated with increased satisfaction. Crit Care Med 32:1484–1488, 2004.
108. Meyer EC, Burns JP, Griffith JL, et al: Parental perspectives on end-of-life care in the pediatric intensive care unit. Crit Care Med 30:226–231, 2002.
109. White DB, Luce JM: Palliative care in the intensive care unit: Barriers, advances, and unmet needs. Crit Care Clin 20:329–343, 2004.
110. Fetters MD, Churchill L, Danis M: Conflict resolution at the end of life. Crit Care Med 29:921–925, 2001.
111. Kagawa-Singer M, Blackhall LJ: Negotiating cross-cultural issues at the end of life: "You got to go where he lives." JAMA 286:2993–3001, 2001.
111a. Curtis JR, White DB: Practical guidance for evidence-based ICU family conferences. Chest 134:835–843, 2008.
112. Schneiderman LJ, Gilmer T, Teetzel HD, et al: Effects of ethics consultations on nonbeneficial life-sustaining treatments in the intensive care setting: A randomized controlled trial. JAMA 290:1166–1172, 2003.
113. Steinhauser KE, Christakis NA, Clipp EC, et al: Factors considered important at the end of life by patients, family, physicians, and other care providers. JAMA 284:2476–2482, 2000.
114. Truog RD, Cist EFM, Brackett SE, et al: Recommendations for end-of-life care in the intensive care unit: The Ethics Committee of the Society of Critical Care Medicine. Crit Care Med 29:2332–2348, 2001.
115. Ferrand E, Lemaire F, Regnier B, et al: Discrepancies between perceptions by physicians and nursing staff of intensive care unit end-of-life decisions. Am J Respir Crit Care Med 167:1310–1315, 2003.
116. Campbell ML, Frank RR: Experience with an end-of-life practice at a university hospital. Crit Care Med 25:197–202, 1997.
117. Brock H, Campbell ML, Faber-Langendoen K, et al: Withdrawing intensive life-sustaining treatment: Recommendations for compassionate clinical management. N Engl J Med 336:652–657, 1997.
118. Faber-Langendoen K, Lanken PN: Dying patients in the intensive care unit: Forgoing treatment, maintaining care. Ann Intern Med 133:886–893, 2000.
119. Cuthbertson SJ, Margetts MA, Streat SJ: Bereavement follow-up after critical illness. Crit Care Med 28:1196–1201, 2000.
120. Desbiens NA, Wu AW, Broste SK, et al: Pain and satisfaction with pain control in seriously ill hospitalized adults: Findings from the SUPPORT research investigations. Crit Care Med 24:1953–1961, 1996.
121. Simmons LE, Riker RR, Prato BS, et al: Assessing sedation during intensive care unit mechanical ventilation with the bispectral index and the sedation-agitation scale. Crit Care Med 27:1499–1504, 1999.
122. Burns JP, Mitchell C, Outwater KM, et al: End-of-life care in the pediatric intensive care unit after the forgoing of life-sustaining treatment. Crit Care Med 28:654–661, 2000.
123. Shapiro BA, Warren J, Egol AB, et al: Practice parameters for intravenous analgesia and sedation in adult patients in the intensive care unit: An executive summary. Crit Care Med 23:1596–1600, 1995.
124. Kress JP, Pohlman AS, Hall JB: Sedation and analgesia in the intensive care unit. Am J Respir Crit Care Med 166:1024–1028, 2002.
125. American Thoracic Society: Dyspnea: Mechanisms, assessment, and management; a consensus statement. Am J Respir Crit Care Med 159:321–340, 1999.
126. American Thoracic Society: Pulmonary rehabilitation—1999. Am J Respir Crit Care Med 159:1666–1682, 1999.
127. Nocturnal Oxygen Therapy Trials Group: Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease. Ann Intern Med 93:391–398, 1980.
128. Booth S, Kelly MJ, Cox NP, et al: Does oxygen help dyspnea in patients with cancer? Am J Respir Crit Care Med 153:1515–1518, 1996.
129. Light RW, Muro JR, Sato RI, et al: Effects of oral morphine on breathlessness and exercise tolerance in patients with chronic obstructive pulmonary disease. Am Rev Respir Dis 139:126–133, 1989.
130. Poole PJ, Veale AG, Black PN: The effect of sustained-release morphine on breathlessness and quality of life in severe chronic obstructive pulmonary disease. Am J Respir Crit Care 157:1877–1880, 1998.
131. Man GCW, Hsu K, Sproule BJ: Effect of alprazolam on exercise and dyspnea in patients with chronic obstructive pulmonary disease. Chest 90:832–836, 1986.
132. Greif R, Laciny S, Rapf B, et al: Supplemental oxygen reduces the incidence of postoperative nausea and vomiting. Anesthesiology 91:1246–1252, 1999.
133. Roscoe JA, Morrow GR, Hickok JT, et al: Nausea and vomiting remain a significant clinical problem: Trends over time in controlling chemotherapy-induced nausea and vomiting in 1413 patients treated in community clinical practices. J Pain Symptom Manage 20:113–121, 2000.
134. Tramer MR, Carroll D, Campbell FA, et al: Cannabinoids for control of chemotherapy induced nausea and vomiting: Quantitative systematic review. BMJ 323:16–21, 2001.

135. Rosner F: Why nutrition and hydration should not be withheld from patients. Chest 104:1892–1896, 1993.
136. Jansen LA, Sulmasy DP: Sedation, alimentation, hydration, and equivocation: Careful conversation about care at the end of life. Ann Intern Med 136:845–849, 2002.
137. McCann RM, Hall WJ, Groth-Juncker A: Comfort care for terminally ill patients: The appropriate use of nutrition and hydration. JAMA 272:1263–1266, 1994.
138. Miller FG, Meier DE: Voluntary death: A comparison of terminal hydration and physician-assisted suicide. Ann Intern Med 128:559–562, 1998.
139. Ganzini L, Goy ER, Miller LL, et al: Nurses' experience with hospice patients who refuse food and fluids to hasten death. N Engl J Med 349:359–365, 2003.
140. McLean RF, Tarshis J, Mazer CD, et al: Death in two Canadian intensive care units: Institutional differences and changes over time. Crit Care Med 28:100–103, 2000.
141. Faber-Langendoen K, Bartels DM: Process of forgoing life-sustaining treatment in a university hospital: An empiric study. Crit Care Med 20:570–577, 1992.
142. Christakis NA, Asch DA: Biases in how physicians choose to withdraw life support. Lancet 342:642–646, 1993.
143. Cook D, Rocker G, Marshall J, et al: Withdrawal of mechanical ventilation in anticipation of death in the intensive care unit. N Engl J Med 349:1123–1132, 2003.
144. Grenvik A: "Terminal weaning": Discontinuance of life-support therapy in the terminally ill patient. Crit Care Med 11:394–395, 1983.
145. Campbell ML, Bizek KS, Thill M: Patient responses during rapid terminal weaning from mechanical ventilation: A prospective study. Crit Care Med 27:73–77, 1999.
146. Faber-Langendoen K: The clinical management of dying patients receiving mechanical ventilation. Chest 106:880–888, 1994.
147. Thompson BT, Cox PN, Antonelli M, et al: Challenges in end-of-life care in the ICU: Statement of the 5th International Consensus Conference in Critical Care. Brussels, Belgium, April 2003: Executive summary. Crit Care Med 32:1781–1784, 2004.
148. Rubenfeld GD, Curtis JR: End-of-life care in the intensive care unit: A research agenda. Crit Care Med 29:2001–2006, 2001.
149. Clark EB, Curtis JR, Luce JM, et al: Quality indicators for end-of-life care in the intensive care unit. Crit Care Med 31:2255–2262, 2003.
150. Treece PD, Engelberg RA, Crowley L, et al: Evaluation of a standardized order form for the withdrawal of life support in the intensive care unit. Crit Care Med 32:1141–1148, 2004.
151. Luce JM, White DB: A history of ethics and law in the intensive care unit. Crit Care Clin 25:221–237, 2009.

CHAPTER 94

PULMONARY REHABILITATION

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INTRODUCTION

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SMOKING CESSATION

COMPONENTS OF A COMPREHENSIVE PULMONARY REHABILITATION PROGRAM

Exercise Training

Education

Psychosocial Training and Support

Nutritional Support

Breathing Training, Inspiratory Muscle Training, and Chest Physical Therapy

Vaccination

Oxygen Assessment and Therapy

Long-term Adherence

Pulmonary Rehabilitation and the Integrated Care of the Respiratory Patient

Promoting Physical Activity in the Patient with Respiratory Disease

PROGRAM ORGANIZATION

OUTCOME ASSESSMENT

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INTRODUCTION

Patients with advanced chronic respiratory disease frequently have distressing symptoms, limitations in exercise ability, and reductions in health and functional status that persist despite optimal pharmacologic management. Pulmonary rehabilitation complements standard medical therapy and can provide additional, clinically meaningful benefit in these areas. Indeed, pulmonary rehabilitation has become the standard of care for patients who are motivated to participate in such programs. As is described in this chapter, patients can improve their exercise and functional capacity, decrease their dyspnea, improve their health status, and (perhaps) reduce their risk of premature morbidity and mortality. Pulmonary rehabilitation is now accepted as a standard of care for patients with chronic obstructive pulmonary disease (COPD), and it has been incorporated into international guidelines for this disease.[1,2] Although pulmonary rehabilitation was designed and is applied primarily to symptomatic patients who are limited due to the burden of COPD, the same fundamental principles appear applicable to other chronic respiratory disease states leading to disability.

DEFINITION AND GOALS

The American Thoracic Society and European Respiratory Society define pulmonary rehabilitation as "an evidence-based, multidisciplinary, and comprehensive intervention for patients with chronic respiratory diseases who are symptomatic and often have decreased daily life activities. Integrated into the individualized treatment of the patient, pulmonary rehabilitation is designed to reduce symptoms, optimize functional status, increase participation, and reduce health care costs through stabilizing or reversing systemic manifestations of the disease."[1] As this definition indicates, there is now a strong evidence base demonstrating the effectiveness of pulmonary rehabilitation, and it should be considered in the general care of the individual with chronic respiratory disease.

Pulmonary rehabilitation and exercise training have been erroneously considered to be equivalent. Although exercise training is a necessary component of pulmonary rehabilitation, other interventions are also necessarily provided in this comprehensive management. Pulmonary rehabilitation programs generally include patient assessment, exercise training, education (especially

involving collaborative self-management strategies), nutritional intervention, psychosocial support, as well as discussion of advance directives. Activity promotion in the home and community settings is becoming recognized as an essential component in pulmonary rehabilitation. Smoking cessation, breathing retraining, chest physical therapy, oxygen therapy, and adjunctive therapies are also given to selected individuals.

It may appear paradoxical that pulmonary rehabilitation does not have a significant, direct effect on pulmonary function, yet it provides the greatest improvements in dyspnea, exercise tolerance, and health status of any therapy for COPD. Emerging data suggest that it may also be beneficial for other chronic respiratory diseases. This apparent paradox is explained by that fact that COPD can be considered as a systemic disease,[3] and comorbidity (such as decreased oxidative capacity of the muscles of ambulation, physical deconditioning, fear of dyspnea-producing activities, improper pacing) contributes to the symptoms and disability of patients. Patients with other chronic respiratory diseases also frequently have this comorbidity. The 6-minute walk distance, which reflects the systemic nature of the disease, is therefore a stronger predictor of survival in COPD patients than measurements of airflow limitation such as the forced expiratory volume in 1 second (FEV_1).[4] Similarly, mid-thigh cross-sectional area[5] and mid-arm cross-sectional area,[6] measures of muscle mass depletion, are better predictors of survival than lung function.

Pulmonary rehabilitation is effective in reducing the negative impact of some of this comorbidity. For example, exercise tolerance in COPD is limited by multiple factors, including increased resistive work of breathing (due to breathing through narrowed airways), increased elastic work of breathing (due to static and dynamic hyperinflation), and abnormalities in the muscles of ambulation (leading to lactate production and fatigue at low exercise intensities). Pulmonary rehabilitation exercise training leads to a decreased ventilatory requirement at a given level of exercise due in part to physiologic changes in the leg muscles. This decrease in ventilatory requirement allows the patient to breathe at a lower respiratory rate during exercise, thereby reducing the effects of dynamic hyperinflation. In addition, recent evidence suggests that dynamic hyperinflation decreases cardiac function and may also decrease exercise tolerance by this mechanism.[7] Thus, pulmonary rehabilitation exercise training leads to increased exercise capacity by its direct effects on the leg muscles that reduce the ventilatory requirement and its direct effects on dynamic hyperinflation[8] and cardiac output[7]—despite the fact there is no measurable change in FEV_1.

Comprehensive pulmonary rehabilitation requires contributions from different health care professionals. Physicians, nurses, nurse practitioners, physical therapists, respiratory therapists, nutritionists, or occupational therapists may be involved in a particular program, depending on availability and resources. A physician medical director and a professional pulmonary rehabilitation coordinator are necessary for program certification in the United States. The goals of pulmonary rehabilitation are to reduce symptoms, improve functional status, and reduce health care costs.[1]

HISTORY

Pulmonary rehabilitation and its components have been recognized by clinicians as an effective intervention since at least the middle of the 20th century.[9,10] However, since the mid 1990s, it has risen to prominence as a state-of-the-art, scientifically proven intervention for individuals with chronic lung disease. Its current importance as a therapeutic option is underscored by four events.

- Its incorporation as the "best therapy" to which lung volume reduction surgery was compared in the National Emphysema Treatment Trial (NETT).[11]
- A Cochrane report demonstrating the effectiveness of pulmonary rehabilitation in their meta-analyses.[12]
- Its endorsement by the Global Initiative for Obstructive Lung disease (GOLD), and its prominent position in their current treatment algorithm for COPD.[13]
- Its acceptance as an approved medical benefit in the United States under the Centers for Medicare and Medicaid Services (CMS) beginning in January 2010.[14]

Over time, what was considered a form of therapy reserved only for patients with the most severe impairment is now recommended for all patients with symptoms that limit their performance and a moderate severity of disease. Prior to 1991, much of the literature supporting pulmonary rehabilitation consisted of descriptions of comprehensive pulmonary rehabilitation and presentations of uncontrolled, preintervention-postintervention studies showing its effectiveness primarily in reducing hospital utilization.[15,16] However, in 1991 Casaburi and colleagues[17] reported on a study of 19 COPD patients who were randomized to either higher or lower levels of exercise training on a cycle ergometer. Training was 5 days per week for a total of 8 weeks. The patients who trained at lower levels exercised longer, so the total amount of work was roughly equivalent in the two groups. Both levels of training led to significant physiologic benefits manifested by reduced lactic acidosis and ventilatory requirement at the same work rate. However, those who trained at higher intensity had more physiologic benefit than those who trained at lower intensity. Prior to this study, many believed that patients with advanced COPD, often being ventilatory-limited during exercise, could not derive true physiologic benefit from this type of intervention. This was the first randomized, controlled trial to demonstrate that a training effect could result from exercise training, the cornerstone of pulmonary rehabilitation.

In 1994, Goldstein and associates[18] reported a prospective, randomized, controlled trial of pulmonary rehabilitation. Eighty-nine patients with COPD were ran-

domized to either pulmonary rehabilitation, initially given in an inpatient setting, or conventional medical care. The group that participated in pulmonary rehabilitation had significantly greater increases in the 6-minute walk distance, submaximal cycle endurance time, and health status compared with the group given standard medical care. This was the first of several randomized, controlled trials of pulmonary rehabilitation that established the effectiveness of pulmonary rehabilitation as a treatment option for chronic lung disease.

That same year, Reardon and coworkers[19] reported on 20 COPD patients who were randomized either to comprehensive outpatient pulmonary rehabilitation or to a waiting period during which they were given conventional medical care. Rehabilitation led to significant improvements in exertional dyspnea, measured by incremental treadmill exercise testing and by questionnaire-rated dyspnea with daily activities. Exertional dyspnea was probably reduced at levels of exercise common to activities of daily living, underscoring its clinical meaningfulness. This was the first study to demonstrate the effectiveness of pulmonary rehabilitation on dyspnea, the most important symptom in advanced lung disease. Subsequent studies by O'Donnell and colleagues[20,21] showed that the reduction in postexercise training dyspnea was associated with decreased ventilatory demand, probably due to physiologic changes in the leg muscles.

In 1996, Ries and associates[22] reported on 119 patients with COPD who were randomized either to comprehensive outpatient pulmonary rehabilitation with exercise training or to education alone. Compared with education alone, rehabilitation led to significant relief of dyspnea, maximal exercise capacity, exercise endurance, and self-efficacy for walking. "Self-efficacy" refers to the patient's confidence in successfully managing respiratory symptoms associated with an activity. Positive results declined over time, approaching those of the control group by 18 to 24 months. This was the first large randomized, controlled study showing the effectiveness of outpatient pulmonary rehabilitation on multiple outcomes. The decline in gains made over time underscored the importance of strategies to improve long-term adherence with rehabilitation.

In 1996, Maltais and coworkers[23] reported on 11 patients with COPD who were evaluated before and after 36 sessions of high-intensity endurance training. In addition to the expected physiologic training effect including reduced exercise-induced lactic acidosis, exercise training led to increased levels of oxidative enzymes in muscle biopsy specimens. Of additional importance, the improvement in biochemical markers correlated with reduced lactic acid production during exercise. Along with other work, this study shows that exercise training improves skeletal muscle oxidative capacity in COPD patients and that this improvement has clinical value.

In 2000, Griffiths and colleagues[24] presented data on 200 patients with chronic lung disease who were randomized to either 6 weeks of multidisciplinary pulmonary rehabilitation or standard medical management. In addition to showing substantial improvements in exercise performance and health-related quality of life, the pulmonary rehabilitation intervention led to fewer days in the hospital and fewer primary care home visits in the 1-year follow-up period. Thus, this large randomized trial demonstrated a substantial reduction in health care utilization following pulmonary rehabilitation, confirming conclusions from earlier noncontrolled studies. A subsequent study from this group[25] provided evidence supporting the cost-effectiveness of pulmonary rehabilitation.

Bourbeau and associates[26] demonstrated in 2003 that a self-management program in the home led to fewer hospital admissions and other health utilization variables and improvement in health status. Self-management skills are prominent components of comprehensive pulmonary rehabilitation. This study provides scientific evidence supporting this educational component of comprehensive pulmonary rehabilitation.

In 2005, Casaburi and coworkers[27] showed that increasing bronchodilation in patients with COPD led to enhanced outcomes when they participated in pulmonary rehabilitation. Patients with optimized lung function could exercise at higher intensities and achieve greater increases in exercise capacity. Thus, not only does pulmonary rehabilitation add to the positive outcomes from pharmacologic therapy, pharmacologic therapy also adds to the benefits from pulmonary rehabilitation.

In 2007, joint guidelines from the American College of Chest Physicians (ACCP) and the American Association of Cardiovascular and Pulmonary Rehabilitation (AACVPR)[28] summarized the current evidence base underlying pulmonary rehabilitation. The document cited very strong evidence supporting the effectiveness of pulmonary rehabilitation on improvements in dyspnea and quality of life. There was also substantial evidence supporting its effectiveness in health care utilization and psychological outcomes. Longer-term pulmonary rehabilitation, maintenance strategies following pulmonary rehabilitation, and the incorporation of education and strength training were also supported by new evidence.

Pulmonary rehabilitation is the most effective therapy available for increasing the exercise capacity of patients with chronic respiratory disease. However, its effectiveness in promoting increased activity in the home and community setting was not proved until fairly recently. Increased physical activity is an important outcome because patients with COPD are often very sedentary,[29] and lower levels of physical activity are associated with poorer long-term outcomes.[30] In 2008, Walker and colleagues[31] demonstrated that directly measured activity (from activity monitors) was indeed increased following 8 weeks of pulmonary rehabilitation. This study corroborates results from two other studies that also demonstrated this positive effect.[32,33] These studies, therefore, provide strong support for the idea that the increased exercise capacity attained in the pulmonary rehabilitation center is translated into increased activity in other settings.

RATIONALE

Pulmonary rehabilitation has a minimal, if any, effect on the abnormal lung function or respiratory physiology of individuals with chronic lung disease. Despite this, it usually results in clinically meaningful improvement in multiple outcome areas of considerable importance to the patient, including a reduction in exertional dyspnea and dyspnea associated with daily activities, improvement in exercise performance and in health status, and reduction in health care utilization. The apparent paradox is explained by the fact that a considerable portion of the dyspnea and the health status limitations from chronic lung disease results from extrapulmonary effects of the disease, which do respond to treatment. Some of the associated systemic manifestations of chronic lung disease include nutritional depletion,[34,35] a decrease in lower extremity muscle mass and peripheral muscle weakness and fatigability,[36,37] alterations in peripheral muscle fiber type,[38] and a reduction in peripheral muscle oxidative enzymes.[39] In addition, poor pacing techniques, maladaptive coping skills, and fear of dyspnea-producing activities result in a vicious circle of further deconditioning and debilitation. Pulmonary rehabilitation is effective in interrupting this cycle.

INDICATIONS

Pulmonary rehabilitation is indicated for individuals with chronic respiratory disease who have persistent symptoms or disability despite standard medical therapy. Figure 94-1 represents the course of patients with lung function limitation over time and the role of pulmonary rehabilitation. Figure 94-2 represents the relative roles of medical therapy and pulmonary rehabilitation during disease progression. Although all individuals with chronic respiratory disease are eligible for consideration for pulmonary rehabilitation, to date COPD is the most common disease for which patients are referred, often for one or more of the following symptoms or conditions[40]:

1. Severe dyspnea and/or fatigue.
2. Decreased exercise ability.
3. Interference with performing activities of daily living.
4. Impaired health status.
5. Decreased occupational performance.
6. Nutritional depletion.
7. Increased medical resource utilization.

It should be noted that persistent symptoms and/or limitation in these clinical areas—not just the specific physiologic impairment of the lungs (such as a low FEV_1 or hypoxemia)—dictate the need for this intervention. Furthermore, symptoms, exercise performance, functional status, and health status correlate relatively poorly with pulmonary function abnormalities. Because of this, there are no specific threshold pulmonary function inclusion criteria for pulmonary rehabilitation.

Often the referral to pulmonary rehabilitation has been reserved for advanced lung disease. Although patients in this category can still benefit from the intervention,[41] referral at an earlier stage would allow more emphasis on preventive strategies such as smoking cessation and would permit exercise training at higher levels of intensity.

Traditionally, pulmonary rehabilitation has dealt primarily with COPD, whereas its effectiveness for other pulmonary conditions has received less attention.[42] Nonetheless, patients with chronic asthma and airways remodeling, bronchiectasis, cystic fibrosis, chest wall disease, or interstitial lung disease may be appropriate candidates.[42a] Pulmonary rehabilitation is the standard of care before and after lung transplantation and lung volume reduction surgery. Based on these accepted indications, pulmonary rehabilitation should also be useful to recondition patients for other major surgical procedures.

There are two primary exclusion criteria for pulmonary rehabilitation:

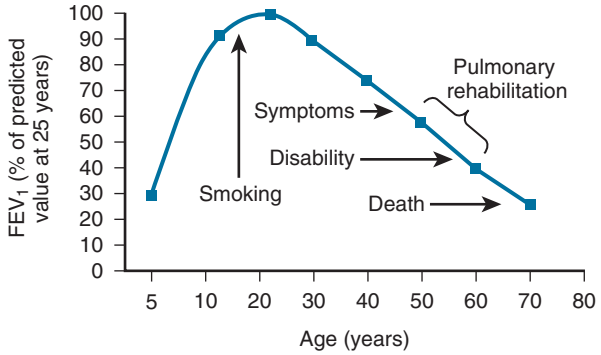

FIGURE 94-1 ■ Change in forced expiratory volume in 1 second (FEV_1) over time in persons susceptible to the effect of cigarette smoking and who develop chronic obstructive pulmonary disease (COPD). The progressive decline results in functional limitation, poor health status, and eventual death. Pulmonary rehabilitation has a role once persistent symptoms or disabilities develop and for as long as patients benefit.

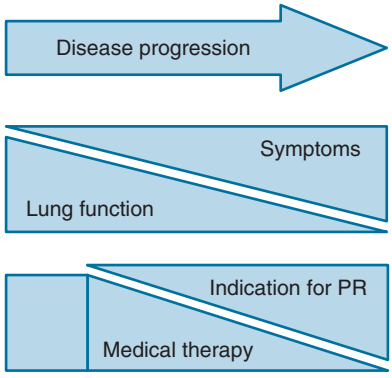

FIGURE 94-2 ■ Indication for pulmonary rehabilitation in disease progression. Pulmonary rehabilitation is an appropriate therapy in the course of respiratory disease when, after usual medical therapy, physiologic impairment is associated with significant symptoms and functional status limitation.

1. An associated condition that might interfere with the rehabilitative process. Examples include disabling arthritis and severe neurologic, cognitive, or psychiatric disease.
2. A comorbid condition that might place the patient at undue risk during exercise training. Examples include severe pulmonary hypertension or unstable cardiovascular disease.

It should be noted that many patients with pulmonary hypertension have safely (and successfully) participated in pulmonary rehabilitation programs, often while awaiting lung transplantation. The exercise training component has to be modified in this situation and patients require close monitoring. In addition, poor motivation is a relative contraindication to pulmonary rehabilitation. However, the level of motivation might change during therapy, especially if patients perceive demonstrable benefit from the sessions.

SMOKING CESSATION

Cigarette smoking is the cause of COPD in over 90% of affected patients. Furthermore, there is no doubt that smoking cessation is the single most important therapy that can retard the progression of airflow limitation and positively influence survival. The various pharmacologic and behavior modification techniques that are available to assist persons to stop smoking are reviewed in Chapter 40. Although controversy still exists, active cigarette smokers are reasonable candidates for pulmonary rehabilitation provided smoking cessation interventions become an important component of the process. Indeed, frequent contact and reinforcement during the rehabilitation program can influence a patient to adopt a proactive role in cessation.

COMPONENTS OF A COMPREHENSIVE PULMONARY REHABILITATION PROGRAM

Exercise Training

Exercise training, including upper and lower extremity endurance training and strength training, is an essential component of comprehensive pulmonary rehabilitation. This follows the current knowledge that the peripheral muscles in patients with chronic lung disease not only are wasted but also appear to have alterations in fiber-type distribution and decreased metabolic capacity. Exercise training improves endurance, increases the level of functioning, aids in performance of activities of daily living, helps reduce systemic blood pressure, improves lipid profiles, tends to counteract depression, reduces anxiety associated with dyspnea-producing activities, and facilitates sleep.

Exercise training for individuals with chronic lung disease, similar to that in healthy individuals, is based on general principles of intensity (higher levels of training produce more results), specificity (only those muscles trained show an effect), and reversibility (cessation of regular exercise training leads to loss of training effect).[43]

Ventilatory or gas-exchange limitations are common in advanced chronic lung disease and limit the intensity of exercise training. However, exercise capacity in many patients is also limited by peripheral muscle and cardiovascular deconditioning, with an early onset of anaerobic metabolism and the production of lactic acidosis during exercise. Peripheral muscle dysfunction is responsive to the exercise training intervention. Many respiratory patients are capable of exercising for prolonged periods of time at levels close to capacity,[44] and the higher level of exercise training results in greater improvement in exercise performance.[34] The demonstrated reduction in ventilation and lactate levels at identical submaximal work rates[17] following high-intensity exercise training strongly suggests that a training effect is attainable in many patients with advanced lung disease. A dose-related increase in oxidative enzymes in the peripheral muscles accompanies these physiologic adaptations to training.[39] A reduction in lactic acid production has been demonstrated to be associated with improvement in oxidative capacity of the peripheral muscles.[45]

Most pulmonary rehabilitation programs emphasize endurance training of the lower extremities, often advocating sustained exercise for about 20 to 30 minutes two to five times a week. This may include exercise on a stationary cycle ergometer or motorized treadmill, climbing stairs, or walking on a flat surface such as a corridor or auditorium. Training is usually performed at levels at or greater than 50% or 60% of the maximal work rate. For those unable to maintain this intensity for the recommended duration, interval training, consisting of 2 to 3 minutes of high-intensity training (60%-80% maximal exercise capacity) alternating with equal periods of rest, has similar results with less dyspnea.[46,47] Optimization of bronchodilator therapy is desirable because it will allow patients to exercise at higher intensities. Similarly, supplemental oxygen therapy for hypoxemic patients, in addition to increasing safety, will allow patients to train at higher work rates. Oxygen supplementation may even promote exercise training at higher intensities in nonhypoxemic COPD patients,[48] but further studies will be needed before this can be endorsed. If patients cannot achieve high work rates during exercise training, lower work rates have also been demonstrated to produce positive outcomes.[49]

Although the strength of the upper extremity muscles is relatively preserved compared with that of the lower extremities in COPD,[50] the former are very important to many activities of daily living. The use of upper extremity muscles is often associated with considerable dyspnea, probably because the arm muscles are also accessory muscles of respiration. Endurance training of the upper extremities is thus an important component of pulmonary rehabilitation. Its effectiveness has recently been demonstrated in a randomized clinical trial.[50a] Training can be accomplished using supported arm exercises, such as with arm ergometry, or unsupported arm exercises, such as by lifting free weights or dowels or by stretching elastic bands.[51]

Because peripheral muscle weakness and/or atrophy contributes to exercise limitation in patients with lung disease,[52] strength training is a rational component of exercise training during pulmonary rehabilitation.[53] Training in weight-lifting exercises alone, involving the upper and lower extremities, increases muscle strength and endurance performance on a cycle ergometer.[54] In the current practice of pulmonary rehabilitation, strength training is usually added to standard aerobic training. This combination increases muscle strength and mass, but its additive effect on health status has not been proved.[55]

The total duration of exercise training in pulmonary rehabilitation should reflect the patient's underlying respiratory disease, his or her level of physical and cardiovascular conditioning, and the progress made during the exercise training sessions. The Global Initiative for Obstructive Lung Disease (GOLD) guidelines[13] report that the optimum length of exercise training has not been determined in randomized, controlled trials, but suggests there is evidence that programs of longer duration provide greater benefit. Ideally, the optimal length of an exercise training program should depend on whether the patient continues to progress toward goals. However, in reality, the program length is generally set by resources, reimbursement, and continued patient motivation. Longer programs may provide more sustained benefits in outcomes.[56]

Exercise training is typically given in the pulmonary rehabilitation facility under supervision. Generally, this is supplemented with patient-specific instructions for additional exercise training at home or in the community. Early incorporation of home exercise into the routine of daily life may promote long-term adherence with the exercise prescription. Carrying this concept one step further, a recent randomized trial has demonstrated that after 4 weeks of standardized education, 8-weeks of exercise training *in the home* was as effective in its primary outcome as 8 weeks of supervised training in the pulmonary rehabilitation center.[57] The primary outcome in this study was questionnaire-rated dyspnea at 1 year following rehabilitation. Similar improvements were noted in exercise capacity, although the mean changes in the 6-minute walk distance were well below the established minimum clinically important difference of 54 m. Of importance, there were no significant differences in adverse events in the two groups, and the treating physicians and the study steering committee did not identify any serious adverse events attributable to the exercise training. It remains to be determined whether this home exercise approach to pulmonary rehabilitation will become a practical alternative to the traditional approach.

Education

Education is an important component of pulmonary rehabilitation programs, and its incorporation alongside exercise training provides a good setting to promote the health behavior change necessary to optimize disease control. Educational needs are determined as part of the initial patient assessment and then are reassessed over the course of the program. Education provides the patient and family important information on the disease process, its comorbidity, and its treatment. This information encourages active participation in health care, thereby promoting adherence to therapy and important self-management skills.[58,59] Education also helps the patient and family find ways to cope with chronic illness and its comorbidities.[60] Some standard educational topics are listed in Table 94-1. In pulmonary rehabilitation, education is usually provided both in small-group settings and in a one-to-one format.

The educational process includes the promotion of a healthy lifestyle, the incorporation of adaptive techniques (such as self-pacing) into the home setting, and the promotion of long-term adherence with the postrehabilitative instructions. Self-management education is an essential component of pulmonary rehabilitation. It emphasizes "learning through doing," enhances patient self-confidence, and encourages a "take charge" attitude (in collaboration with the health care providers) toward managing the disease.[14] Some strategies in collaborative self-management include interventions for smoking cessation, encouragement of regular exercise at home, incorporation of increased levels of physical activity into the home setting, and early recognition and treatment of respiratory exacerbations. The development of a patient-specific, collaborative self-management plan for COPD exacerbations is an important goal of pulmonary rehabilitation; this includes education about the symptoms and signs associated with exacerbations to foster early recognition followed by the implementation of an action plan, which often includes using filled prescriptions for a short course of systemic steroids and an antibiotic. Ongoing collaboration among

TABLE 94-1. Educational Elements of a Comprehensive Pulmonary Rehabilitation Program

Normal pulmonary anatomy and physiology
Pathophysiology of lung disease
Description and interpretation of medical tests
Collaborative self-management strategies
Breathing retraining
Bronchial hygiene
Medications
Exercise principles
Activities of daily living and energy conservation
Respiratory modalities
Self-assessment and symptom management
Nutrition
Psychosocial issues
Ethical issues
Advance directives

Adapted from Casaburi R, ZuWallack R: Pulmonary rehabilitation for management of chronic obstructive pulmonary disease. N Engl J Med 360:1329–1335, 2009.

the patient and the medical team members is the key to effective self-management. Advance directive discussions are also an important component of pulmonary rehabilitation.[61]

Because education is a component of virtually all pulmonary rehabilitation programs, there are few studies evaluating its individual contribution to the overall effectiveness of the comprehensive program. However, self-management strategies applied to the home setting have been shown to be effective in improving health status and reducing utilization of medical resources.[26]

Psychosocial Training and Support

Psychosocial problems, such as anxiety, depression, deficiencies with coping, and decreased self-efficacy, contribute to the burden of advanced respiratory disease.[62] Psychosocial and behavioral interventions vary widely among comprehensive pulmonary rehabilitation programs but often involve educational sessions or support groups, focusing on areas such as coping strategies or stress management techniques. Techniques of progressive muscle relaxation, stress reduction, and panic control may reduce not only anxiety but dyspnea as well.[63] Educational efforts may also improve coping skills. Participation by family members or friends in pulmonary rehabilitation support groups is encouraged. Informal discussions of the common symptoms and concerns of patients with chronic lung disease may provide emotional support to patients and their families. Because of these interventions, it should come as no surprise that a randomized clinical trial has demonstrated that comprehensive pulmonary rehabilitation can decrease psychosocial morbidity in patients with severe COPD even when no specific psychological intervention is provided.[64] Individuals with substantial psychiatric disease should, of course, be referred for appropriate professional care outside the program.

Nutritional Support

Nutritional depletion, including decreased weight and abnormalities in body composition such as decreased lean body mass, is present in 20% to 35% of patients with stable COPD.[65,66] Depletions in lean body mass undoubtedly contribute to the morbidity of patients with chronic respiratory disease by leading to decreased respiratory muscle strength,[67] handgrip strength,[68] exercise tolerance,[69,70] and health status.[71] Nutritional depletion and alteration in body composition are also significant predictors of the mortality of COPD, independent of FEV_1.[5,6,72] Because of this, nutritional intervention is a recommended component of comprehensive pulmonary rehabilitation.

However, the benefit from simple nutritional supplementation to underweight patients with chronic lung disease has not been substantial, with one meta-analysis of nutritional intervention for COPD reporting only a 1.65-kg increase in weight following intervention.[73] In view of these disappointing results with calorie supplementation alone, consideration is being given to hormonal supplementation with anabolic steroids.[74] This has led to increases in weight, lean body mass, respiratory muscle strength, and arm and thigh muscle circumference.[75] In addition, one study has demonstrated that the combination of testosterone and weight training in men with COPD and low testosterone levels leads to greater increases in muscle mass and strength than either alone.[76] Whether these preliminary findings in this select group can be applied with safety and efficacy to a more generalized population remains unknown. The Joint ACCP/AACVPR Guidelines on Pulmonary Rehabilitation[2] do not recommend routine use of anabolic steroids for COPD patients.

Breathing Training, Inspiratory Muscle Training, and Chest Physical Therapy

These modalities have been part of pulmonary rehabilitation over the years, but conclusive evidence supporting their effectiveness in pulmonary rehabilitation is for the most part lacking. Breathing training is aimed at controlling the respiratory rate and breathing pattern, with a goal of decreasing air trapping. *Pursed-lip breathing* takes place when the patient inhales through the nose and exhales over 4 and 6 seconds through lips pursed in a whistling/kissing position. This technique facilitates the recruitment of abdominal muscles during exhalation and has a favorable effect on the breathing pattern, thereby increasing tidal volume and reducing end-expiratory lung volumes. The result is less hypoxemia, decreased oxygen cost of breathing, and decreased dyspnea. In selected patients, pursed-lip breathing has also been shown to reduce the oxygen cost of breathing.[77] Patients with COPD can usually be readily trained in pursed-lip breathing; in fact, they often spontaneously adopt this breathing pattern when dyspneic. *Breathing while bending forward* has been shown to decrease dyspnea in some patients with severe COPD, both at rest and during exercise. Similar improvements can be achieved by breathing in the supine and Trendelenberg positions. The best explanation for the reduction in dyspnea is that the increased abdominal pressure caused by bending over stretches the diaphragm, moving it into a better contracting position and leading to improved diaphragmatic function. *Diaphragmatic breathing* has not been shown to be beneficial; in fact, this technique may actually *decrease* breathing efficiency.[77]

The rationale behind inspiratory muscle training (IMT) is that COPD patients have weak inspiratory muscles and that training them may improve outcomes. The Joint ACCP/AACVPR Evidence-Based Clinical Practice Guidelines reviewed the relatively numerous studies on IMT and concluded that this treatment does increase inspiratory muscle strength, increases exercise performance, and decreases dyspnea. Their recommendation is to consider IMT in selected COPD patients with decreased inspiratory muscle strength and breathlessness despite optimal medical therapy.[2]

Chest physical therapy is used in an attempt to remove airway secretions. The techniques include postural drainage, chest percussion and vibration, and directed cough. Postural drainage uses gravity to help drain the individual lung segments. Chest percussion should be performed with care in patients with osteoporosis or bone problems. Cough would be an effective technique for removing excess mucus from the larger airways; unfortunately, patients with COPD have impaired cough mechanisms (maximum expiratory flow is reduced, ciliary beat is impaired), and the mucus itself has altered viscoelastic properties. Because spasms of coughing may lead to dyspnea, fatigue, and worsened obstruction, directed cough might be helpful by enhancing the beneficial effect and preventing the untoward ones. With directed coughs, patients are instructed to inhale deeply, hold their breath for a few seconds and then cough two or three times with the mouth open. They are also instructed to compress the upper abdomen to assist in the cough. These techniques are probably useful in selected patients with difficulty mobilizing secretions.

Vaccination

The causes of exacerbations of COPD are poorly understood and are probably multifactorial; both influenza virus and *Streptococcus pneumoniae* may play a role; and there is no doubt that when either of these infections occurs, patients with chronic lung disease are at increased risk for serious complications, including death.[78] One of the national health objectives in the United States for the year 2000 was to increase influenza and pneumococcal vaccination levels to higher than 60% among persons at high risk for complications and for everyone 65 years of age or older.[79] As stated, this includes all patients with COPD and other forms of chronic lung disease, regardless of age. Because the influenza vaccine is type-specific and serotypes are constantly changing, vaccination must be repeated every year, preferably at the beginning of the season in the fall. In contrast, the pneumococcal vaccine is polyvalent and its benefits should last a lifetime.[80] One of the responsibilities of a rehabilitation program is to educate enrollees about the importance of vaccination against influenza and pneumococcal infections and to ensure that it is carried out and (for influenza) repeated annually.

Oxygen Assessment and Therapy

Background

Although not in itself a unique component of pulmonary rehabilitation, testing for oxygen needs and/or adjusting the oxygen to achieve its full benefits is part of all rehabilitation programs. Two landmark studies clearly showed improved survival in patients with COPD and hypoxemia (arterial oxygen pressure Pa_{O_2} < 55 mm Hg) who breathed supplementary oxygen at night compared with those who received no oxygen; there was even better survival in those who breathed oxygen for longer periods through the aid of an ambulatory delivery system.[81,82] Contemporary guidelines for prescribing home oxygen for patients with COPD, based in part on these trials, are shown in Table 94-2. The chief criterion is a significant level of hypoxemia, defined as a Pa_{O_2} of 55 mm Hg or less for 3 weeks or more when the patient is in a clinically stable state (i.e., has been free from exacerbation of bronchitis, heart failure, or other intercurrent complications). Additional criteria were also used in the North American multicenter trial to enroll stable patients with COPD whose Pa_{O_2} values were between 55 and 59 mm Hg.[81] They included evidence of pulmonary hypertension as judged by radiographic abnormalities (an enlarged pulmonary outflow tract); electrocardiographic findings of elevated right-sided intracardiac pressures (*P* waves in standard leads II, III, and aVF > 2-mm amplitude); clinical evidence of cor pulmonale with heart failure; or secondary polycythemia from chronic hypoxemia. Patients with COPD who have echocardiographic evidence of right ventricular hypertrophy and/or pulmonary hypertension also qualify.

TABLE 94-2. Guidelines for Prescribing Home Oxygen for Advanced Chronic Obstructive Pulmonary Disease

PATIENT SELECTION CRITERIA
Accepted Indications
Resting Pa_{O_2} consistently 55 mm Hg or less, *or* consistently 55–59 mm Hg plus cor pulmonale clinically diagnosed and/or hematocrit > 55%
Stable course of disease on optimum medical therapy
Arterial blood gas determinations while breathing room air at rest for a minimum of 20 min
Patients with substantial nocturnal hypoxemia (i.e., Pa_{O_2} < 55 mm Hg on multiple occasions, *or* patients with hematocrit > 55%, *or* clinical evidence of pulmonary hypertension)
Possible Indications
Normoxic patients in whom less dyspnea and substantially increased exercise capability is demonstrated with oxygen
Supplementation during exercise training
OXYGEN DOSE
Continuous flow by double or single nasal cannulas (see text) or by demand system with demonstration of adequate oxygen saturation
Lowest liter flow to raise Pa_{O_2} to 60–65 mm Hg or oxygen saturation to 90%–94%
Increase baseline liter flow by 1 L/min during exercise and sleep. Consider higher flows if patient traveling by air

Pa_{O_2}, arterial oxygen pressure.

Dosage

The therapeutic goal of administering supplementary oxygen is to raise Pa_{O_2} to the range of 60 to 65 mm Hg or, alternatively, to reach an oxygen saturation of 90% to 94%. The results of the Nocturnal Oxygen Therapy Trial

(NOTT)[81] established the fact that the great majority of patients with advanced COPD and hypoxemia achieve this goal with oxygen delivered by nasal cannula at 1 to 2 L/min. Less than 10% of the patients require 3 L/min or more while at rest. Additional results obtained during the conduct of the trial indicate that additional oxygen of 1 L/min was required during the stress of exercise and while sleeping; those extra needs are undoubtedly caused by the increased metabolic demands of exercise and the modest degree of hypoventilation and/or worsening of gas exchange that occurs during sleep.

Thus, if the baseline flow of oxygen is 2 L/min with patients at rest, the flow rate should be turned up to 3 L/min when they are exercising or sleeping. Periodic monitoring of oxygenation is essential to determine who should receive supplementary oxygen in the first place; moreover, in those who are being treated, monitoring is used to evaluate whether therapeutic goals are being met or exceeded. Two techniques are available: arterial puncture with direct measurement of Pa_{O_2} and pulse oximetry to quantify oxygen saturation. The latter is being increasingly used given the convenience and improved accuracy of the newer oximeters.

Delivery Systems

The oxygen delivery systems available for home use are as follows: compressed gas in high-pressure cylinders; liquid gas in lightweight canisters; and stationary oxygen concentrators. Large compressed gas cylinders are fixed in place, but patients can move short distances while using long (50-ft) tubing; smaller cylinders can be attached to wheelchairs or installed in automobiles to allow journeys out of the home. Ambulatory patients are best served with a small portable, liquid system, which is the only practicable way to deliver oxygen to someone who is working or active. Liquid gas–containing canisters are constantly being improved to reduce weight and to increase duration of use. Because the goal of pulmonary rehabilitation is to restore the patients' functional capacity to its optimal level and exercise is a fundamental part of pulmonary rehabilitation, every effort must be made to provide hypoxemic patients with portable devices that help achieve these goals.

Oxygen as an Adjunct to Pulmonary Rehabilitation Exercise Training

In addition to life-prolonging effects, supplemental oxygen therapy increases exercise capacity in hypoxemic[83] and even nonhypoxemic[84] COPD patients. Part of this beneficial effect is probably mediated through a reduction in carotid body respiratory drive, resulting in a lower respiratory rate and, consequently, less dynamic hyperinflation. Because supplemental oxygen increases exercise capacity in COPD patients, it may enhance outcomes in pulmonary rehabilitation by allowing patients to exercise and train at higher intensities. Oxygen therapy for individuals with exercise-induced hypoxemia is a standard of care in the United States, but the role of oxygen therapy for nonhypoxemic patients as a potential exercise-enhancer is not well-established. To date, a few clinical trials have demonstrated that supplemental oxygen (or oxygen plus helium) during pulmonary rehabilitation exercise training in nonhypoxemic patients with COPD may allow for exercise training at higher intensities and greater short-term improvement from the intervention.[85,85a] Further research is needed in this area.

Long-term Adherence

Although the short-term effects of pulmonary rehabilitation in multiple outcome areas are firmly established, the long-term effectiveness of this therapy is often disappointing. In controlled trials of pulmonary rehabilitation, gains in exercise performance and health status obtained after 6 to 8 weeks of therapy essentially disappear by 18 to 24 months.[22] However, it seems illogical to expect that a therapy that is only applied for 6 to 8 weeks could substantially modify the natural course of the disease. In all likelihood, two factors are mainly responsible for this drop-off in effectiveness: (1) exacerbations of underlying lung disease, leading to prolonged symptoms and reassuming a more sedentary lifestyle and (2) a gradual decline in adherence with the postrehabilitation exercise prescription. With these factors in mind, the pulmonary rehabilitation program must include strategies to promote long-term adherence. One approach is to incorporate the principles of pulmonary rehabilitation, including exercise training, more actively into the home setting. This is supported by studies of home-based programs, which suggest that gains made in this setting may be longer lasting[86] than those of hospital-based programs. Promoting regular walking seems to help prolong effectiveness in some outcome areas.[87] Although regularly scheduled repeated pulmonary rehabilitation sessions do not give additional prolonged benefit,[88] giving a "booster shot" of pulmonary rehabilitation following an exacerbation, by emphasizing short periods of supervised exercise training to return the patient to baseline performance, appears to be a reasonable intervention in selected cases. Longer-duration pulmonary rehabilitation seems to confer longer-lasting effectiveness.[56]

Pulmonary Rehabilitation and the Integrated Care of the Respiratory Patient

The American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines define pulmonary rehabilitation as "a spectrum of intervention strategies integrated into the lifelong management of patients with chronic respiratory disease and involves a dynamic, active collaboration among the patient, family and healthcare providers."[1] Depending on the specific needs of the individual patient, this care might include smoking-cessation counseling and therapy, activity promotion, education on a healthy lifestyle, vaccinations, the incorporation of regular exercise training into the individual's lifestyle, optimization of pharmacology, an exacerbation

prevention strategy, a collaborative management plan for the early recognition and treatment of exacerbations, and discussion of advance directives. These interventions can be conveniently bundled into a comprehensive outpatient or inpatient pulmonary rehabilitation program administered by a multidisciplinary staff. However, if pulmonary rehabilitation is not available or feasible for a particular patient, the onus of this patient-centered comprehensive management rests on the health care provider. Unfortunately, our current acute care health model is poorly suited for this type of management. Another approach—which has not yet been implemented to any significant degree—is the concept of *integrated care*.[14] Integrated care, as it applies to individuals with respiratory disease, has been described as "a system-wide, multidisciplinary, collaborative approach that is individualized to the specific needs of the patient. This approach stresses comprehensive assessment, self-management education, agreement on an individually-tailored care plan, and communication among health care professionals, patients, and families/caregivers."[14] An integrated care approach would be particularly useful during COPD exacerbations, when there is an abrupt deterioration in the patient's condition and a far greater likelihood of increased health care utilization. Some data suggest that an integrated care approach in this setting reduces health care costs.[89]

Promoting Physical Activity in the Patient with Chronic Respiratory Disease

Daily activity energy expenditure is an important predictor of mortality in healthy community-dwelling older adults,[90] and patients with COPD are more sedentary than age-matched healthy individuals.[91] Hypoxemic COPD patients are generally very sedentary and, disappointingly, supplemental oxygen is not particularly effective in reversing this maladaptive behavior.[91a] Because decreased physical activity in COPD patients appears to be related to increased health care utilization and mortality,[92,93] an important goal of pulmonary rehabilitation is to promote increased physical activity in the home and community settings. Although pulmonary rehabilitation unequivocally increases exercise capacity, it is less clear whether the increase in exercise capacity is translated into increased physical activity outside the pulmonary rehabilitation environment: "*can do*" versus "*do do*" (R.Casaburi, personal communication). Clinical trials incorporating direct measurements of physical activity using motion detectors (accelerometers worn at the waist or on the leg) have demonstrated that pulmonary rehabilitation does indeed increase physical activity.[31–33]

PROGRAM ORGANIZATION

The pulmonary rehabilitation program needs a coordinator to organize the various components into a functioning unit. The coordinator develops the integrated program and monitors its progress and function. The program should have resources available to teach and supervise respiratory therapy (oxygen, use of inhalers, nebulizers), physical therapy (breathing techniques, chest physical therapy, postural drainage), exercise conditioning (upper and lower extremities), and activities of daily living (work simplification, energy conservation). Also desirable are services to evaluate and advise on nutritional, psychological, and vocational needs.

Whether to have an inpatient or an outpatient program depends on the methods of reimbursement, patient population, available personnel, and institutional policy. The ideal system is one that provides an in-hospital component for patients who may benefit from the program while recovering from acute exacerbations and an outpatient component (including home therapy) that could complete the program started in the hospital. This program ensures good continuity of care.

OUTCOME ASSESSMENT

Outcome assessment can be defined as the assessment of the "consequences" of an intervention. As stated earlier, pulmonary rehabilitation does not affect the degree of respiratory impairment as measured by tests of physiologic pulmonary function. However, exercise training in rehabilitation increases the content of oxidative enzymes in the trained muscles, accompanied by a beneficial delay in the generation of lactate (a marker of muscle performance). This results in improved exercise performance and reduced dyspnea, and it may be responsible, at least in part, for improved functional capacity. Therefore, even though pulmonary rehabilitation does not change the impairment of lung function, it ameliorates the disability and handicap of the patient.

Outcome assessment for pulmonary rehabilitation encompasses three areas: (1) a generalized audit of the effectiveness of the global pulmonary rehabilitation program and its components; (2) evaluation of individual patient response to the intervention; and (3) assessment of the effect of pulmonary rehabilitation on society, especially with respect to its effect on health care utilization and its cost-effectiveness. Some commonly used outcome measures are listed in Table 94-3.

Evaluating the effectiveness of the pulmonary rehabilitation program is important in continuous quality assessment. Testing can be made in several areas, especially in the measurements of dyspnea, exercise performance, and health status. Dyspnea evaluation falls into two categories: measurement of exertional dyspnea during standardized exercise testing and measurement of breathlessness by questionnaire. Exertional dyspnea is usually rated using a Borg scale[94] or a visual analogue scale. Measurement of dyspnea by questionnaire usually assesses the dyspnea associated with daily activities or the way in which exertional dyspnea limits activities.[95]

Exercise performance can be measured in the laboratory using protocols involving incremental treadmill or stationary bicycle exercise. However, field tests of exercise performance, such as the 6-minute walk test

TABLE 94-3. Examples of Outcome Assessment for Pulmonary Rehabilitation

Measurement	Scales/Tests
Exertional dyspnea	Borg scale or visual analogue scale during exercise testing
Dyspnea with daily activities	Modified Medical Research Council (MRC) questionnaire Baseline and Transitional Dyspnea Indexes (BDI/TDI) San Diego Shortness of Breath Questionnaire
Functional exercise capacity	Six-minute walk test Incremental and endurance shuttle walk tests
Laboratory measures of exercise performance	Incremental cardiopulmonary exercise testing Endurance testing at constant work rate
Health status	Chronic Respiratory Disease Questionnaire (CRQ) St. George's Respiratory Questionnaire (SGRQ) Medical Outcomes Study Short Form-36 (SF-36)
Functional performance	Pulmonary Functional Status Scale (PFSS) Pulmonary Function Status and Dyspnea Questionnaire (PFSDQ)
Nutritional status/body composition	Body mass index (BMI) Body composition using bioelectrical impedance or dual-energy x-ray absorption (DEXA)
Psychological variables	Measurement of anxiety and depression using the Hospital Anxiety and Depression (HAD) questionnaire

or the shuttle walk test, are more commonly performed. The 6-minute test is easy to perform, relates well to functional status, and is responsive to the pulmonary rehabilitation intervention. As stated earlier, the 6-minute walk test is a better predictor of mortality in patients with COPD than is lung function. For the shuttle walk test,[96] the patient is instructed to walk around a 10-m course at gradually increasing speeds. Speed is determined by an auditory beeping signal that sets the pace. The test is terminated when the patient cannot complete the course in time, usually because of breathlessness. Total distance traveled is the variable assessed.

Health status is often assessed using respiratory-specific questionnaires, such as the Chronic Respiratory Disease Questionnaire (CRQ)[97] or the St. George's Respiratory Questionnaire (SGRQ).[98] Some pulmonary rehabilitation programs may also use a generic instrument, such as the Medical Outcomes Study Short Form-36 (SF-36),[99] to complement information from the respiratory-specific questionnaires. Assessment in the areas of nutrition/body composition, educational goal achievement, and psychosocial variables (e.g., anxiety, depression, coping skills) is also possible.

In the evaluation of the response to therapy of an individual patient, exercise tests such as the timed walk, a questionnaire assessment of dyspnea, or measurements of functional status or health status may provide some useful information. However, to date, these outcome measures, which have become routine for program assessment, have not been extensively validated for *individual* patient assessment. Traditional one-on-one clinical assessment remains necessary for the individual patient. Outcome assessment in health care utilization or cost-effectiveness generally requires participation of several centers in a multicenter study to accrue the necessary number of subjects for this type of analysis.

RECENT ADJUNCTS

Several adjuncts may prove to be beneficial in patients with severe disability from chronic respiratory disease. Noninvasive positive-pressure ventilation (NPPV), through its effect in helping unload the respiratory muscles, may improve breathlessness in COPD.[100,101] The use of proportional assist ventilation in pulmonary rehabilitation in patients without hypercapnia had no appreciable added benefits in mild COPD.[102] However, in patients with more severe lung disease, this form of therapy allowed the patient to exercise at a higher intensity, resulting in the achievement of a greater maximum exercise capacity.[103] The Joint ACCP/AACVPR Evidence-Based Clinical Practice Guidelines stated that NPPV does confer a postrehabilitation benefit in *selected* patients.[2] Similarly, the application of electrical stimulation combined with active limb mobilization in COPD patients on mechanical ventilation or with severe disability improves muscle strength and provides other benefits.[104–106] Finally, the inhalation of less-dense, oxygen-enhanced gas mixtures, such as 72% helium–28% oxygen, can improve exercise performance in patients with severe COPD.[107] These techniques remain experimental and therefore appropriate topics for research.

KEY POINTS

- Pulmonary rehabilitation is a multidisciplinary, patient-centered approach to the treatment of patients with chronic respiratory disease.
- Although pulmonary rehabilitation has no direct effect on lung function, it nonetheless produces substantial improvements in dyspnea, exercise performance, and quality of life. It also reduces health care utilization.
- Pulmonary rehabilitation works through decreasing the effect of comorbidity that is frequently present in patients with chronic respiratory disease.
- Whereas most patients referred for pulmonary rehabilitation have COPD, this therapy should be beneficial for patients with other respiratory diseases.
- Important components of pulmonary rehabilitation include education, exercise training, nutritional therapy, and psychosocial support.
- Exercise training is the cornerstone of pulmonary rehabilitation; high-intensity, low-intensity, and strength training are all utilized.
- Developing collaborative self-management strategies, especially involving the early detection and treatment of COPD exacerbations, is an important educational component of pulmonary rehabilitation.
- Pulmonary rehabilitation should be considered part of the integrated care of the patient with COPD and other chronic respiratory diseases.
- Physical activity promotion in the home and community setting is an important goal of pulmonary rehabilitation.
- Optimization of pharmacologic therapy and supplemental oxygen (when indicated) may allow the patient to exercise at higher intensity and thereby achieve greater increases in exercise performance.

References

1. Nici L, Donner C, Wouters E, et al: American Thoracic Society/European Respiratory Society statement on pulmonary rehabilitation. Am J Respir Crit Care Med 173:1390–1413, 2006.
2. Ries AL, Bauldoff GS, Carlin BW, et al: Pulmonary rehabilitation: Joint ACCP/AACVPR evidence-based clinical practice guidelines. Chest 131:4–42, 2007.
3. Fabbri LM, Luppi F, Beghe B, Rabe KF: Complex chronic comorbidities of COPD. Eur Respir J 31:204–212, 2008.
4. Pinto-Plata VM, Cote C, Cabral H, et al: The 6-min walk distance: Change over time and value as a predictor of survival in COPD. Eur Respir J 23:28–33, 2004.
5. Marquis K, Debigaré R, Lacasse Y, et al: Midthigh muscle cross-sectional area is a better predictor of mortality than body mass index in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 166:809–813, 2002.
6. Soler-Cataluna JJ, Sanchez-Sanchez L, Martinez-Garcia MA, et al: Mid-arm muscle area is a better predictor of mortality than body mass index in COPD. Chest 128:2108–2115, 2005.
7. Vassaux C, Torre-Bouscoulet L, Zeineldine S, et al: Effects of hyperinflation on the oxygen pulse as a marker of cardiac performance in COPD. Eur Respir J 32:1275–1282, 2008.
8. Porszasz J, Emtner M, Goto S, et al: Exercise training decreases ventilatory requirements and exercise-induced hyperinflation at submaximal intensities in patients with COPD. Chest 128:2025–2034, 2005.
9. Barach AL: Breathing exercises in pulmonary emphysema and allied chronic respiratory disease. Arch Phys Med Rehabil 36:379–390, 1955.
10. Petty TL, Nett L, Finigan NM, et al: A comprehensive care program for chronic airway obstruction: Methods and preliminary evaluations of symptomatic and functional improvement. Ann Intern Med 70:1109–1120, 1969.
11. National Emphysema Treatment Trial Research Group: A randomized trial comparing lung-volume–reduction surgery with medical therapy for severe emphysema. N Engl J Med 348:2059–2073, 2003.
12. Lacasse Y, Brosseau L, Milne S, et al: Pulmonary rehabilitation for chronic obstructive pulmonary disease (Cochrane Review). *In* The Cochrane Library. Chichester, UK: John Wiley, Issue 4, 2003.
13. Global Initiative for Obstructive Lung Disease: Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (updated 2008). Available at www.GOLD-COPD.com (accessed January 4, 2009).
14. Nici L, Raskin J, Rochester C, et al : Pulmonary rehabilitation: What we know and what we need to know. J Cardiopulm Rehabil Prev 29:141–151, 2009.
15. Petty TL: Ambulatory care for emphysema and chronic bronchitis. Chest 58:441, 1970.
16. Hodgkin JE, Balchum OJ, Kass I, et al: Chronic obstructive airway disease: Current concepts in diagnosis and comprehensive care. JAMA 232:1243, 1975.
17. Casaburi R, Patessio A, Ioli F, et al: Reductions in exercise lactic acidosis and ventilation as a result of exercise training in patients with obstructive lung disease. Am Rev Respir Dis 143:9–18, 1991.
18. Goldstein RS, Gort EH, Stubbing D, et al: Randomized controlled trial of respiratory rehabilitation. Lancet 344:1394–1397, 1994.
19. Reardon J, Awad E, Normandin E, et al: The effect of comprehensive outpatient pulmonary rehabilitation on dyspnea. Chest 105:1046–1052, 1994.
20. O'Donnell DE, McGuire M, Samis L, Webb KA: The impact of exercise reconditioning on breathlessness in severe airflow limitation. Am J Respir Crit Care Med 152:2005–2013, 1995.
21. O'Donnell DE, McGuire M, Samis L, Webb KA: General exercise training improves ventilatory and peripheral muscle strength and endurance in chronic airflow limitation. Am J Respir Crit Care Med 157:1489–1497, 1998.

22. Ries AL, Kaplan RM, Limberg TM, et al: Effects of pulmonary rehabilitation on physiologic and psychosocial outcomes in patients with chronic obstructive pulmonary disease. Ann Intern Med 122:823–832, 1995.
23. Maltais F, LeBlanc P, Simard C, et al: Skeletal muscle adaptation to endurance training in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 154:442–447, 1996.
24. Griffiths TL, Burr ML, Campbell IA, et al: Results at 1 year of outpatient multidisciplinary pulmonary rehabilitation: A randomised controlled trial. Lancet 355:362–368, 2000.
25. Griffiths TL, Phillips CJ, Davies S, et al: Cost effectiveness of an outpatient multidisciplinary pulmonary rehabilitation programme. Thorax 56:779–784, 2001.
26. Bourbeau J, Julien M, Maltais F, et al: Reduction in hospital utilization in patients with chronic obstructive pulmonary disease. Arch Intern Med 163:585–591, 2003.
27. Casaburi R, Kukafka D, Cooper CB, et al: Improvement in exercise tolerance with the combination of tiotropium and pulmonary rehabilitation in patients with COPD. Chest 127:809–817, 2005.
28. Ries AL, Bauldoff GS, Carlin BW, et al: Pulmonary rehabilitation: Joint ACCP/AACVPR evidence-based clinical practice guidelines. Chest 131:4–42, 2007.
29. Pitta F, Troosters T, Probst VS, et al: Characteristics of physical activities in daily life in COPD. Am J Respir Crit Care Med 171:972–977, 2005.
30. Garcia-Aymerich J, Lange P, Benet M, et al: Regular physical activity reduces hospital admission and mortality in chronic obstructive pulmonary disease: A population based cohort study. Thorax 61:772–778, 2006.
31. Walker PP, Burnett A, Flavahan PW, Calverely PMA: Lower limb activity and its determinants in COPD. Thorax 63:68, 2008.
32. Sewell L, Singh SJ, Williams JEA, et al: Can individualized rehabilitation improve functional independence in elderly patients with COPD? Chest 128:1194–1200, 2005.
33. Pitta F, Troosters T, Probst VS, et al: Are patients with COPD more active after pulmonary rehabilitation? Chest 134:273–280, 2008.
34. Wouters EFM, Schols AMWJ: Prevalence and pathophysiology of nutritional depletion in chronic obstructive pulmonary disease. Respir Med 87(Suppl B):45–47, 1993.
35. Schols AMWJ, Soeters PB, Dingemans MC, et al: Prevalence and characteristics of nutritional depletion in patients with stable COPD eligible for pulmonary rehabilitation. Am Rev Respir Dis 147:1151–1156, 1993.
36. Bernard S, LeBlanc P, Whittom F, et al: Peripheral muscle weakness in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 158:629–634, 1998.
37. Mador MJ, Deniz O, Aggarwal A, Kufel TJ: Quadriceps fatigability after single muscle exercise in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 168:102–108, 2003.
38. Whittom F, Jobin J, Simard PM, et al: Histochemical and morphological characteristics of the vastus lateralis muscle in COPD patients: Comparison with normal subjects and effects of exercise training. Med Sci Sports Exerc 30:1467–1474, 1998.
39. Maltais F, Simard AA, Simard C, et al: Oxidative capacity of the skeletal muscle and lactic acid kinetics during exercise in normal subjects and in patients with COPD. Am J Respir Crit Care Med 153:288–293, 1996.
40. Available at www.brit-thoracic.org.uk
41. ZuWallack RL, Patel K, Reardon JZ, et al: Predictors of improvement in the 12-minute walking distance following a six-week outpatient pulmonary rehabilitation program. Chest 99:805–808, 1991.
42. Novitch RS, Thomas HM: Rehabilitation of patients with chronic ventilatory limitation from nonobstructive lung diseases. *In* Casaburi R, Petty T (eds): Principles and Practice of Pulmonary Rehabilitation. Philadelphia: WB Saunders, 1993, pp 416–423.
42a. Salhi B, Troosters T, Behaegel M, et al: Effects of pulmonary rehabilitation in patients with restrictive lung disease. Chest 137:273–279, 2010.
43. American College of Sports Medicine position stand: The recommended quantity and quality of exercise for developing and maintaining cardiorespiratory and muscular fitness in healthy adults. Med Sci Sports Exerc 22:265–274, 1990.
44. Maltais F, LeBlanc P, Jobin J, et al: Intensity of training and physiologic adaptation in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 155:555–561, 1997.
45. Sala E, Roca J, Marrades RM, et al: Effects of endurance training on skeletal muscle bioenergetics in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 159:1726–1734, 1999.
46. Coppoolse R, Schols AMWJ, Baarends EM, et al: Interval versus continuous training in patients with severe COPD: A randomized clinical trial. Eur Respir J 14:258–263, 1999.
47. Vogiatzis I, Nanas S, Roussos C: Interval training as an alternative modality to continuous exercise in patients with COPD. Eur Respir J 20:12–19, 2002.
48. Emtner M, Porszasz J, Burns M, et al: Benefits of supplemental oxygen in exercise training in non-hypoxemic COPD patients. Am J Respir Crit Care Med 168:1034–1042, 2003.
49. Normandin EA, McCusker C, Connors ML, et al: An evaluation of two approaches to exercise conditioning in pulmonary rehabilitation. Chest 121:1085–1091, 2002.
50. Bernard S, Leblanc P, Whittom F, et al: Peripheral muscle weakness in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 158:629–634, 1998.
50a. Costi S, Crisafulli E, Antoni FD, et al: Effects of unsupported upper extremity exercise training in patients with COPD. A randomized clinical trial. Chest 136:387–395, 2009.
51. Celli BR: Physical reconditioning of patients with respiratory disease: Legs, arms, and breathing retraining. Respir Care 39:482–501, 1994.
52. Hamilton N, Killian KJ, Summers E, Jones NL: Muscle strength, symptom intensity, and exercise capacity in patients with cardiorespiratory disorders. Am J Respir Crit Care Med 152:2021–2031, 1995
53. Mador MJ, Bozkanat E, Aggarwal A, et al: Endurance and strength training in patients with COPD. Chest 125:2036–2045, 2004.
54. Simpson K, Killian K, McCartney N, et al: Randomised controlled trial of weightlifting exercise inpatients with chronic airflow limitation. Thorax 47:70–75, 1992.
55. Bernard S, Whittom F, LeBlanc P, et al: Aerobic and strength training in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 159:896–901, 1999.
56. Troosters T, Gosselink R, Decramer M: Short- and long-term effects of outpatient rehabilitation in patients with chronic obstructive pulmonary disease: A randomized trial. Am J Med 109:207–212, 2000.
57. Maltais F, Bourbeau J, Shapiro S, et al: Effects of home-based pulmonary rehabilitation in patients with chronic obstructive pulmonary disease: A randomized trial. Ann Intern Med 149:869–878, 2008.
58. Von Korff M, Gruman J, Schaefer SJ, et al: Collaborative management of chronic illness. Ann Intern Med 127:1097–1102, 1997.
59. Casaburi R, ZuWallack R: Pulmonary rehabilitation for management of chronic obstructive pulmonary disease. N Engl J Med 360:1329–1335, 2009.
60. Neish CM, Hopp JW: The role of education in pulmonary rehabilitation. J Cardiopulm Rehabil 11:439–441, 1988.
61. Heffner JE, Fahy B, Hilling L, Barbieri C: Outcomes of advance directive education of pulmonary rehabilitation patients. Am J Respir Crit Care Med 155:1055–1059, 1997.
62. Norwood R: Prevalence and impact of depression in COPD patients. Curr Opin Pulm Med 12:113–117, 2006.
63. Renfroe KL: Effect of progressive relaxation on dyspnea and state anxiety in patients with chronic obstructive pulmonary disease. Heart Lung 17:408–413, 1988.
64. Guell R, Resqeti V, Sangenis M, et al: Impact of pulmonary rehabilitation on psychosocial morbidity in patients with severe COPD. Chest 129:899–904, 2006.
65. Wilson DO, Rogers RM, Wright E, Anthonisen NR: Body weight in chronic obstructive pulmonary disease. Am Rev Respir Dis 139:1435–1438, 1989.
66. Wouters EFM, Schols AMWJ: Prevalence and pathophysiology of nutritional depletion in chronic obstructive pulmonary disease. Respir Med 87(Suppl B):45–47, 1993.

67. Nishimura Y, Tsutsumi M, Nakata H, et al: Relationship between respiratory muscle strength and lean body mass in men with COPD. Chest 107:1232–1236, 1995.
68. Engelen MPKJ, Schols AMWJ, Baken WC, et al: Nutritional depletion in relation to respiratory and peripheral skeletal muscle function in out-patients with COPD. Eur Respir J 7:1793–1797, 1994.
69. Schols AMWJ, Mostert R, Soeters PB, Wouters EFM: Body composition and exercise performance in patients with chronic obstructive pulmonary disease. Thorax 46:695–699, 1991.
70. Palange P, Forte S, Felli A, et al: Nutritional status and exercise tolerance in patients with COPD. Chest 107:1206–1212, 1995.
71. Shoup R, Dalsky G, Warner S, et al: Body composition and health-related quality of life in patients with obstructive airways disease. Eur Respir J 10:1576–1580, 1997.
72. Schols AMWJ, Slangen J, Volovics L, Wouters EFM: Weight loss is a reversible factor in the prognosis of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 157:1791–1797, 1998.
73. Ferreira IM, Brooks D, Lacasse Y, Goldstein RS: Nutritional intervention in COPD: A systematic overview. Chest 119:353–363, 2001.
74. Schols AMWJ, Soeters PB, Mostert R, et al: Physiological effects of nutritional support and anabolic steroids in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 152:1268–1274, 1995.
75. Ferreira IM, Verreschi IT, Nery LE, et al: The influence of 6 months of oral anabolic steroids on body mass and respiratory muscles in undernourished COPD patients. Chest 114:19–28, 1998.
76. Casaburi R, Bhasin S, Cosentino L, et al: Effects of testosterone and resistance training in men with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 170:870–878, 2004.
77. Troosters T, Casaburi R, Gosselink R, Decramer M: Pulmonary rehabilitation in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 172:19–38, 2005.
78. Gordon A: Vaccines and vaccinations. N Engl J Med 345:1042–1053, 2001.
79. Centers for Disease Control and Prevention: Influenza and pneumococcal vaccinations levels among adults aged >65 years. MMWR Morb Mortal Wkly Rep 46:797–802, 1998.
80. Nichol K, Margolis KL, Wuorenma J, Von Sternberg T: The efficacy and cost effectiveness of vaccination against influenza among elderly persons living in the community. N Engl J Med 331:778–784, 1994.
81. Nocturnal Oxygen Therapy Trial Group: Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: A clinical trial. Ann Intern Med 93:391–398, 1980.
82. Report of the Medical Research Council Working Party: Long term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. Lancet 1:681–686, 1981.
83. O'Donnell DE, D'Arisigny C, Webb KA: Effects of hyperoxia on ventilatory limitation during exercise in advanced chronic obstructive pulmonary disease. Am J Respir Crit Care Med 163:892–898, 2001.
84. Somfay A, Porszasz J, Lee SM, Casaburi R: Dose-response effect of oxygen on hyperinflation and exercise endurance in nonhypoxaemic COPD patients. Eur Respir J 18:77–84, 2001.
85. Emtner M, Porszasz J, Burns M, et al: Benefits of supplemental oxygen in exercise training in non-hypoxemic COPD patients. Am J Respir Crit Care Med 168:1034–1042, 2003.
85a. Eves ND, Sandmeyer LC, Wong EY, et al: Helium-hyperoxia: a novel intervention to improve the benefits of pulmonary rehabilitation for patients with COPD. Chest 135:609–613, 2009.
86. Wijkstra PJ, Van der Mark TW, Kraan J, et al: Long-term effects of home rehabilitation on physical performance in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 153:1234–1241, 1996.
87. Heppner PS, Morgan C, Kaplan RM, Ries AL: Regular walking and long-term maintenance of outcomes after pulmonary rehabilitation. J Cardiopulm Rehabil 26:44–53, 2006.
88. Foglio K, Bianchi L, Ambrosino N: Is it really useful to repeat outpatient pulmonary rehabilitation programs in patients with chronic airway obstruction? A 2-year controlled study. Chest 119:1696–1704, 2001.
89. Casas A, Troosters T, Garcia-Aymerich J, et al: Integrated care prevents hospitalisations for exacerbations in COPD patients. Eur Respir J 28:123–130, 2006.
90. Manini TM, Everhart JE, Patel KV, et al: Daily activity energy expenditure and mortality among older adults. JAMA 296:171–179, 2006.
91. Pitta F Troosters T, Probst VS, et al: Characteristics of physical activities in daily life in COPD. Am J Respir Crit Care Med 171:972–977, 2005.
91a. Sandland CJ, Morgan MDL, Singh SJ: Patterns of domestic activity and ambulatory oxygen usage in COPD. Chest 134:753–760, 2008.
92. Garcia-Aymerich J, Lange P, Benet M, et al: Regular physical activity reduces hospital admission and mortality in chronic obstructive pulmonary disease: A population based cohort study. Thorax 61:772–778, 2006.
93. Pitta F, Troosters T, Probst VS, et al: Physical activity and hospitalization for exacerbation of COPD. Chest 129:536–544, 2006.
94. Borg GAV: Psychophysical bases of perceived exertion. Med Sci Sports Exerc 14:377–381, 1982.
95. Mahler DA, Weinberg DH, Wells CK, et al: The measurement of dyspnea: Contents, interobserver agreement, and physiologic correlations of two new clinical indexes. Chest 85:751–758, 1984.
96. Singh SJ, Morgan MDL, Scott S, et al: Development of a shuttle walking test of disability in patients with chronic airways obstruction. Thorax 47:1019–1024, 1992.
97. Guyatt GH, Berman LB, Townsend M, et al: A measure of quality of life for clinical trials in chronic lung disease. Thorax 42:773–778, 1987.
98. Jones PW, Quirk FH, Baveystock CM, Littlejohns P: A self-complete measure of health status for chronic airflow limitation: The St. George's Respiratory Questionnaire. Am Rev Respir Dis 145:1321–1327, 1992.
99. Mahler DA, Mackowiak JI: Evaluation of the short-form 36-item questionnaire to measure health-related quality of life in patients with COPD. Chest 107:1585–1589, 1995.
100. Keilty SEJ, Ponte J, Fleming TA, Moxham J: Effect of inspiratory pressure support on exercise tolerance and breathlessness in patients with severe stable chronic obstructive pulmonary disease. Thorax 49:990–994, 1994.
101. Maltais F, Reissmann H, Gottfried SB: Pressure support reduces inspiratory effort and dyspnea during exercise in chronic airflow obstruction. Am J Respir Crit Care Med 151:1027–1033, 1995.
102. Bianchi L, Foglio K, Porta R, et al: Lack of additional effect of adjunct of assisted ventilation to pulmonary rehabilitation in mild COPD patients. Respir Med 96:359–367, 2002.
103. Hawkins P, Johnson LP, Nikoletou D, et al: Proportional assist ventilation as an aid to exercise training in severe chronic obstructive pulmonary disease. Thorax 57:853–859, 2002.
104. Zanotti E, Felicetti G, Maini M, Fracchia C: Peripheral muscle strength training in bed-bound patients with COPD receiving mechanical ventilation: Effect of electrical stimulation. Chest 124:292–296, 2003.
105. Neder JA, Sword D, Ward SA, et al: Home-based neuromuscular electrical stimulation as a new rehabilitative strategy for severely disabled patients with chronic obstructive pulmonary disease (COPD). Thorax 57:333–337, 2002.
106. Vivodtzev I, Pepin JL, Vottero G, et al: Improvement in quadriceps strength and dyspnea in daily tasks after 1 month of electrical stimulation in severely deconditioned and malnourished COPD. Chest 129:1540–1548, 2006.
107. Laude EA, Duffy NC, Baveystock C, et al: The effect of helium and oxygen on exercise performance in chronic obstructive pulmonary disease. A randomized crossover trial. Am J Respir Crit Care Med 173:865–870, 2006.

CHAPTER 95

LUNG TRANSPLANTATION

Robert M. Kotloff, MD

INTRODUCTION

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INTRODUCTION

Human lung transplantation was first attempted in 1963, but it was not until nearly 2 decades later that extended survival was achieved. Further refinements in patient selection, surgical technique, immunosuppression, and postoperative care have since facilitated the successful application of lung transplantation to a wide variety of advanced disorders of the airways, lung parenchyma, and pulmonary vasculature. The field has realized dramatic growth, with over 28,000 procedures performed worldwide to date and approximately 2500 procedures now performed annually.[1] Nonetheless, serious problems persist that limit the utility of this procedure. The donor pool remains insufficient to meet the demands of the many desperately ill patients awaiting transplantation. Immunosuppressive therapy is associated with a number of troubling side effects, most notably a significant risk of infection and malignancy. Despite the use of immunosuppressive agents, rejection occurs frequently and continually threatens organ function. Though lung transplantation offers the prospect of improved functional status and quality of life, long-term survival remains an elusive goal, with only half of recipients living beyond 5 years. In order to optimize outcomes in the face of these shortcomings, judicious selection of candidates is essential and care of recipients must be rendered in a meticulous and vigilant fashion by clinicians familiar with the hazards of posttransplant life.

INDICATIONS AND CANDIDATE SELECTION

Lung transplantation is a therapeutic option for a broad spectrum of chronic debilitating pulmonary disorders of the airways, parenchyma, and vasculature. Chronic obstructive pulmonary disease (COPD) represents the leading indication for lung transplantation and together with alpha$_1$-antitrypsin deficiency accounts for over 40% of all procedures performed worldwide.[1] Other leading indications include idiopathic pulmonary fibrosis (IPF) (21% of cases) and cystic fibrosis (CF; 16% of cases). Once a common indication for transplantation, idio-

pathic pulmonary arterial hypertension now accounts for less than 4% of procedures, reflecting major advances in the medical management of these patients. Transplantation of patients with lung involvement due to collagen vascular disease (e.g., scleroderma) remains controversial owing to concerns that extrapulmonary manifestations of the systemic disease could compromise the posttransplant course. Nonetheless, short-term functional outcomes and survival following transplantation are comparable with those of other patient populations and most centers are willing to offer transplantation to carefully selected patients without significant extrapulmonary organ dysfunction.[2] In contrast, lung transplantation for bronchioalveolar carcinoma, a subtype of lung cancer that tends to remain localized to the lung parenchyma, has largely been abandoned due to an unacceptably high rate of cancer recurrence.[3]

The scarcity of organs and the somewhat inferior outcomes achieved with recipients of advanced age have prompted many lung transplant programs to establish an upper age limit of 60 to 65 years. Notably, however, there has been a steady increase in the percentage of recipients exceeding this traditional age cutoff; in 2008, 35% of transplant recipients were 60 years or older and 9% were over the age of 65.[1] Candidates should be functionally disabled (New York Heart Association class III or IV) but, ideally, still ambulatory. Many programs screen for and exclude profoundly debilitated patients by requiring a minimum distance on a standard 6-minute walk test, commonly set at 600 ft.[4] The presence of significant renal, hepatic, or left ventricular dysfunction precludes isolated lung transplantation, but multiorgan transplantation can be considered in highly select patients. Other absolute contraindications include recent malignancy (other than nonmelanoma skin cancer); active infection with the human immunodeficiency virus, hepatitis B virus, or hepatitis C virus with histologic evidence of significant liver damage; active or recent cigarette smoking, drug abuse, or alcohol abuse; severe psychiatric illness; and extremes of weight.[5] The risk posed by other chronic medical conditions such as diabetes mellitus, osteoporosis, gastroesophageal reflux, and coronary artery disease must be assessed individually based on severity of disease, presence of end-organ damage, and ease of control with standard therapies. Among CF candidates, colonization with *Burkholderia cepacia* complex, in particular genomovar III (also known as *Burkholderia cenocepacia*), is considered a strong contraindication by the majority of centers, owing to the demonstrated propensity of this organism to cause lethal posttransplant infections.[6,7] In contrast, the presence of pan-resistant *Pseudomonas aeruginosa* in this patient population is associated with acceptable outcomes and should not be viewed as a contraindication.[8] Transplantation of patients on mechanical ventilation is associated with an increased risk of death within the first year and is generally restricted to patients early in the course of respiratory failure prior to onset of profound debility or intercurrent complications of critical illness. Prior thoracic surgery and pleurodesis render the native lung more difficult to explant and increase the risk of intraoperative bleeding, particularly when cardiopulmonary bypass is required, but do not contraindicate transplantation in most instances. Pleural thickening associated with aspergillomas similarly complicates anatomic dissection and explantation of the native lung and carries the additional risk of soiling the pleural space with fungal organisms. Defining the degree of pleural reaction that contraindicates transplantation is a judgment call influenced by the experience and aggressiveness of the transplant surgeon.

TIMING OF REFERRAL AND LISTING

Listing for transplantation is considered at a time when the lung disease limits basic activities of daily living and is deemed to pose a high risk of death in the short term. Disease-specific guidelines for timely referral and listing of patients, based on available predictive indices, have recently been updated (Table 95-1).[5] The imprecise nature of these predictive indices can make decisions about transplant listing problematic for all but the most severely ill patients. The patient's perception of an unacceptably poor quality of life is an important additional factor to consider but should not serve as the sole justification for listing of a patient whose disease is not deemed to be at an advanced and potentially life-threatening stage.

ALLOCATION SYSTEM

Methods governing allocation of organs vary between different countries but typically employ a time-based or need-based ranking of candidates on the waiting list, or some combination of the two systems. Examination of the systems that have been operative in the United States permits an appreciation of the advantages and limitations of both approaches. From 1990 to 2005, lung allocation in the United States prioritized candidates on the basis of the amount of time they had accrued on the waiting list, without regard to severity of illness. Based on a simple and objective parameter, this system was easily understood but was ultimately called into question because it failed to accommodate those patients with a more rapidly progressive course who often could not survive the prolonged waiting times.[9] In response to the perceived inequities of the time-based system, and under mandate of the federal government, a new system was implemented in May of 2005 that allocates lungs on the basis of both medical urgency (i.e., risk of death without a transplant) and "net transplant benefit" (i.e., the extent to which transplantation will extend survival). By incorporating this latter concept, the system attempts to avoid the pitfall of preferentially allocating the limited donor organ pool to critically ill patients with an unacceptably high posttransplantation mortality rate.

The new model, derived from an analysis of the comprehensive United Network of Organ Sharing (UNOS) national database, identifies 10 factors independently predictive of 1-year survival on the waiting list and 7

TABLE 95-1. Disease-Specific Guidelines for Listing for Lung Transplantation

CHRONIC OBSTRUCTIVE PULMONARY DISEASE
- BODE index of 7-10 **or** at least one of the following:
- History of hospitalization for exacerbation associated with acute hypercapnia (P_{CO_2} > 50 mm Hg)
- Pulmonary hypertension or cor pulmonale, or both, despite oxygen therapy
- FEV_1 < 20% and either DL_{CO} < 20% or homogenous distribution of emphysema

IDIOPATHIC PULMONARY FIBROSIS
- Histologic or radiographic evidence of UIP **and** any of the following:
- A DL_{CO} < 39% predicted.
- A ≥ 10% decrement in FVC during 6 months of follow-up
- A decrease in pulse oximetry < 88% during a 6MWT
- Honeycombing on HRCT (fibrosis score > 2)

CYSTIC FIBROSIS
- FEV_1 < 30%of predicted, or rapidly declining lung function if FEV_1 > 30% (females and patients < 18 yr of age have a poorer prognosis; consider earlier listing) **and/or** any of the following:
- Increasing oxygen requirements
- Hypercapnia
- Pulmonary hypertension

IDIOPATHIC PULMONARY ARTERIAL HYPERTENSION
- Persistent NYHA class III or IV on maximal medical therapy
- Low (350-m) or declining 6MWT
- Failing therapy with intravenous epoprostenol or equivalent
- Cardiac index < 2 L/min/m^2
- Right atrial pressure > 15 mm Hg

SARCOIDOSIS
- NYHA functional class III or IV **and** any of the following:
- Hypoxemia at rest
- Pulmonary hypertension
- Elevated right atrial pressure > 15 mm Hg

BODE, [b]ody mass index, airflow [o]bstruction, [d]yspnea, [e]xercise capacity; DL_{CO}, diffusing capacity for carbon dioxide; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; HRCT, high-resolution computed tomography; 6MWT, 6-minute walk test; NYHA, New York Heart Association; P_{CO_2}, pressure of carbon dioxide; UIP, usual interstitial pneumonia.

Modified from Orens JB, Estenne M, Arcasoy S, et al: International guidelines for the selection of lung transplant candidates: 2006 update. J Heart Lung Transplant 25:745–755, 2006.

TABLE 95-2. Standard Lung Donor Criteria

- Age < 55 yr
- Clear chest radiograph
- Pa_{O_2} > 300 mm Hg on F_{IO_2} 1.0, PEEP 5 cm H_2O
- Cigarette smoking history < 20 pack-years
- Absence of significant chest trauma
- No evidence of aspiration or sepsis
- No prior thoracic surgery on side of harvest
- Absence of organisms on sputum Gram stain
- Absence of purulent secretions and gastric contents at bronchoscopy
- Negative for HIV antibody, hepatitis B surface antigen, and hepatitis C antibody
- No active or recent history of malignancy (excluding localized squamous or basal cell skin cancer, localized cervical cancer, and primary brain tumors with low metastatic potential and in the absence or invasive procedures to the brain and skull)
- No history of significant chronic lung disease

F_{IO_2}, fractional concentration of oxygen in inspired gas; HIV, human immunodeficiency virus; Pa_{O_2}, arterial oxygen pressure; PEEP, positive end-expiratory pressure.

factors predictive of 1-year survival following transplantation.[10] For each patient, these factors are utilized to calculate a lung allocation score (LAS). Patients who demonstrate a large net difference in survival (predicted posttransplant—pretransplant survival) in conjunction with a high degree of medical urgency (low predicted pretransplant survival) receive the highest LAS.

An analysis of data from the 2008 Organ Procurement and Transplantation Network (OPTN)/Scientific Registry of Transplant Recipients (SRTR) Annual Report sheds light on the impact of the new LAS system in the initial 2 years since it was implemented.[11] Because there is no longer an incentive to place patients on the active waiting list simply to accrue time (many of whom were ultimately deactivated rather than transplanted), the number of actively listed patients has fallen to approximately one half of the previous level. Median waiting time, which had ranged from 2 to 3 years under the time-based allocation system, has decreased to roughly 4 months, and one quarter of patients are waiting less than 35 days. By prioritizing patients with more rapidly progressive diseases, the LAS system has led to an increase in the percentage of transplants performed for IPF and a commensurate decline in the percentage performed for COPD. Importantly, there has been a significant reduction in the annual death rate of patients on the waiting list, one of the stated objectives of the new system. Notably, preferential transplantation of sicker patients has not resulted in an increase in early mortality following transplantation. Further experience will be required to determine the impact of the new system on long-term outcomes following transplantation. Of concern is the fact that the IPF population, the group receiving the highest priority under the LAS system, has the poorest long-term outcomes, with a median survival of only 4.1 years.[1]

DONOR SELECTION AND MANAGEMENT

In addition to meeting strict criteria for declaration of brain death, cadaveric lung donors are selected on the basis of established guidelines (Table 95-2).[12] Lungs are a particularly fragile organ in the brain-dead patient and are frequently compromised by volume overload, contusion, aspiration of gastric contents, or pneumonia as well as by extensive prior smoking. As a result, the vast major-

ity of donors fail to meet standard criteria for organ donation, leading to a historical recovery rate of only 15% from cadaveric organ donors deemed able to donate other organs. There is mounting evidence that these standard criteria may in fact be too stringent, leading to unnecessary wastage of suitable lungs. In one study, 29 pairs of lungs that had been rejected for transplantation were assessed for the magnitude of extravascular water content, intactness of alveolar fluid clearance capacity, and presence of pneumonia or emphysema.[13] Twelve pairs (41%) were found to have minimal or no abnormalities and thus to be potentially suitable for use. Additional evidence comes from published reports documenting that outcomes with use of "extended criteria" donors are similar to those achieved with use of donors meeting standard criteria.[14–18] Use of modified donor management protocols to optimize lung function through judicious fluid management and lung recruitment maneuvers has also been shown to enhance lung harvest rates.[19] This has been put into practice at a national level through the Organ Donation Breakthrough Collaborative, an initiative to increase the number of organ donors through increased consent for donation and through optimization and standardization of donor management practices. As a combined result of this initiative and liberalization of lung donor selection criteria, there has been a recent 20% increase in the number of lung transplants performed annually in the United States.[11]

Despite increases in the number of organs harvested, the demand for organs continues to outstrip supply, prompting a search for alternatives to the brain-dead donor pool. One emerging source is the non–heart beating or "donation after cardiac death (DCD)" donor who has experienced either an out-of-hospital (i.e., uncontrolled) arrest or a planned withdrawal of life-support in the operating room. Approximately 40 lung transplant procedures utilizing DCD donors were performed in the United States as of 2007, and centers in Spain and Australia have reported small numbers as well.[20,21] Preliminary data suggest that short-term outcomes approximate those associated with use of traditional brain-dead donors.

Once a donor has been identified, matching with potential recipients is based on size and ABO blood group compatibility. Prospective human leukocyte antigen (HLA) matching is not performed. However, potential candidates identified through standard pretransplant screening as having preformed circulating antibodies to foreign HLA antigens require either prospective donor-recipient lymphocytotoxic cross-matching or avoidance of donors with specific incompatible antigens.[22]

AVAILABLE SURGICAL TECHNIQUES

Four surgical techniques are currently utilized to varying degrees: heart-lung, single-lung, bilateral-sequential, and living donor bilobar transplantation. The choice of procedure is dictated by such factors as the underlying disease, age of the patient, survival and functional advantages, and center-specific preferences.

Heart-Lung Transplantation

Heart-lung transplantation was the first procedure to be successfully performed, but it has largely been supplanted by techniques to replace the lungs alone. Currently, fewer than 100 procedures are performed worldwide on an annual basis. Indications are largely restricted to Eisenmenger's syndrome with surgically irreparable cardiac lesions and to advanced lung disease with concurrent severe left ventricular dysfunction or extensive coronary artery disease. In the past, the presence of profound right ventricular dysfunction in the setting of severe pulmonary hypertension was deemed to be an indication for heart-lung transplantation. However, subsequent experience with isolated lung transplantation has demonstrated the remarkable ability of the right ventricle to recover once pulmonary artery pressures have normalized. The small number of patients requiring heart-lung transplantation in the United States face potentially protracted waiting times due to the preferential allocation of hearts to status 1A cardiac transplant candidates.

Single-Lung Transplantation

Single-lung transplantation was, until recently, the most commonly performed procedure. Traditionally, a standard posterolateral thoracotomy was utilized, but some surgeons now employ a less invasive anterior axillary muscle–sparing approach in select cases. Three anastomoses are executed—main-stem bronchus, pulmonary artery, and left atrium (incorporating the two pulmonary veins). Major advantages of the procedure are its technical ease and its efficient use of the limited donor pool, permitting two recipients to benefit from a single donor. Single-lung transplantation is an acceptable procedure for patients with pulmonary fibrosis and COPD, though in the latter setting, progressive native lung hyperinflation may occasionally complicate perioperative ventilator management.[23] Single-lung transplantation also has been performed successfully in carefully selected patients with severe pulmonary hypertension. However, concerns about exaggerated reperfusion pulmonary edema in an allograft that must bear the burden of nearly the entire cardiac output have prompted the vast majority of centers to abandon this approach in favor of the bilateral procedure. Because of infectious concerns, single-lung transplantation is contraindicated in patients with suppurative lung disorders such as CF.

Bilateral-Lung Transplantation

Bilateral sequential lung transplantation involves the performance of two single-lung transplant procedures in succession during a single operative session. Surgical approaches include transverse thoracosternotomy ("clamshell") incision, bilateral anterolateral thoracotomies (sparing the sternum), and median sternotomy. In the absence of severe pulmonary hypertension, cardiopulmonary bypass can often be avoided by sustaining

the patient on the contralateral lung during implantation of each allograft. The principal indications for this procedure are CF, other forms of bronchiectasis, and severe primary and secondary forms of pulmonary hypertension. In addition, many programs now advocate its use for patients with COPD, arguing that it offers functional and survival advantages over single-lung transplantation.[24–27] Although it is also being employed with increasing frequency in treatment of fibrotic lung disorders, the justification for this is less clear.[28,29] As a result of these trends, bilateral-lung transplantation now accounts for two thirds of all procedures performed worldwide.[1]

Living Donor Bilobar Transplantation

Living donor bilateral-lobar transplantation was developed chiefly to serve the needs of candidates with far-advanced or deteriorating status that would not allow them to tolerate a protracted wait for a cadaveric donor. The procedure involves transplantation of lower lobes from each of two living, blood group–compatible donors. In order to ensure that the lobes will adequately fill the hemithoraces, it is preferable to employ donors who are taller than the recipient. Patients with CF are particularly well suited as a target population because, even as adults, they tend to be of small stature. Intermediate-term functional outcomes and survival among recipients are similar to those achieved with cadaveric transplantation.[30,31] Concerns about excessive risk to the donor have thus far proved to be unfounded. In the two largest series published to date involving a combined total of 315 donors, there were no deaths or episodes of postoperative respiratory failure, and only 9 donors (2.9%) experienced complications of sufficient magnitude to warrant surgical reexploration.[32,33] Donation of a lobe results in an average decrement in vital capacity of 17%, a degree of loss that should be of little functional significance in an otherwise normal individual.[34] Despite the apparent low risk posed to the donor, living donor transplantation has not gained widespread acceptance, accounting for only 3.5% of annual transplant volume at its peak.[35] Its use has been further undermined by the new UNOS allocation system that expedites transplantation of more severely ill candidates.

ROUTINE POSTTRANSPLANTATION MANAGEMENT

Care of the lung transplant recipient requires close surveillance to ensure that the allograft is functioning properly, that immunosuppressive medications are properly administered and tolerated, and that complications are detected early and treated expeditiously. Most centers require patients to return frequently for office visits, blood tests, and chest radiographs during the initial 2 to 3 months following transplantation and to participate in an intensive pulmonary rehabilitation program during this time. Analogous to home glucose monitoring of the diabetic patient, lung transplant recipients chart their pulmonary function on a daily basis with a handheld microspirometer and are instructed to contact the transplant center if a sustained fall of greater than 10% in the forced expiratory volume in 1 second (FEV_1) or forced vital capacity is documented.

Many transplant programs employ frequent surveillance bronchoscopies and transbronchial lung biopsies within the first posttransplant year as a means of monitoring the allograft. Such an approach has been demonstrated to detect low-grade rejection or subclinical cytomegalovirus (CMV) pneumonitis in up to 30% of asymptomatic, clinically stable patients.[36] However, it has yet to be determined whether treatment of clinically silent disease has a beneficial impact on long-term graft function.

Immunosuppressive therapy is initiated immediately at the time of transplantation and is maintained lifelong. No consensus currently exists on the role of induction therapy with lymphocyte/thymocyte-depleting globulin preparations or interleukin-2 (IL-2) receptor antagonists (basiliximab and daclizumab), and only half of all centers currently employ this strategy. The lack of consensus reflects insufficient and conflicting data on the ability of these agents to reduce the incidence of acute and chronic rejection specifically in the lung transplant population.[37] Maintenance therapy consists of a calcineurin-inhibitor (cyclosporine or tacrolimus), purine synthesis inhibitor (azathioprine or mycophenolate), and prednisone. Sirolimus (also known as rapamycin), an inhibitor of IL-2–stimulated T-cell proliferation, is the newest immunosuppressive agent to be introduced into clinical practice. Its role in maintenance immunosuppression has yet to be established. Lacking inherent nephrotoxicity, sirolimus has been successfully substituted for calcineurin-inhibitors in patients with renal insufficiency, leading to recovery of renal function without undue risk of rejection.[38,39] Sirolimus impairs wound healing and has been associated with life-threatening bronchial anastomotic dehiscence when used immediately following transplantation.[40] As a result, the drug should never be initiated until complete healing of the bronchial anastomosis has been documented.

Individuals providing care to transplant recipients must be familiar with the administration, side effects, and drug interactions of these immunosuppressive agents (Table 95-3). Although serving as the cornerstone of therapy, the use of calcineurin inhibitors is particularly problematic. When administered orally, the bioavailability of these agents is poor and unpredictable, necessitating frequent monitoring of blood levels to ensure appropriate dosing. These drugs are metabolized via the hepatic cytochrome P-450 system and blood levels are influenced by the concurrent administration of other drugs that affect this enzymatic pathway. Adverse effects of these agents, as well as of the other drugs commonly utilized, are legion and contribute significantly to the morbidity associated with transplantation.

Management of medical comorbidities is an essential component of the care of the lung transplant recipient. Common medical issues that emerge in this population include osteoporosis, hypertension, renal insufficiency, coronary artery disease, diabetes mellitus, and hyperlipidemia.[41] Treatment of these conditions is similar to that of the general population.

TABLE 95-3. Commonly Used Immunosuppressive Medications

Medication (Class)	Dosing*	Adverse Effects	Drug Interactions
Cyclosporine and tacrolimus (calcineurin inhibitors)	Cyclosporine: dosed to achieve a whole blood trough level of 250–350 ng/ml (first year), then 200–300 ng/mL† Tacrolimus: dosed to achieve a whole blood trough level of 10–12 ng/mL (first year), then 6–8 ng/ml)	Nephrotoxicity Hypertension Neurotoxicity (tremor, seizures, white matter disease, headache) Hyperkalemia, hypomagnesemia Hyperuricemia/gout Hemolytic-uremic syndrome Gastroparesis Hyperglycemia Hirsutism, gingival hyperplasia (cyclosporine)	**INCREASED BLOOD LEVELS** Macrolide antibiotics (except azithromycin) Azole antifungals Diltiazem, verapamil Grapefruit juice **DECREASED BLOOD LEVELS** Phenobarbitol Phenytoin Rifampin
Sirolimus (mTOR inhibitor)	Dosed to achieve a whole blood trough level of 6–12 ng/mL	Thrombocytopenia Anemia Hyperlipidemia Peripheral edema Rash Impaired wound healing Interstitial pneumonitis	Same as calcineurin inhibitors
Azathioprine (purine synthesis inhibitor)	2 mg/kg/d	Leukopenia Macrocytic anemia Thrombocytopenia Hepatotoxicity Pancreatitis Hypersensitivity reaction (fever, hypotension, rash)	Synergistic bone marrow suppression when administered with allopurinol
Mycophenolate mofetil (purine synthesis inhibitor)	1000–1500 mg bid	Diarrhea Leukopenia Anemia	Concurrent use of cyclosporine may decrease serum concentrations of mycophenolate by limiting biliary secretion/enterohepatic recycling
Prednisone (corticosteroid)	0.5 mg/kg/d for 6–12 wk, then tapered to 0.15 mg/kg/d	Hyperglycemia Hypertension Hyperlipidemia Weight gain Osteoporosis Avascular necrosis Myopathy Mood changes, insomnia Cataracts	No significant interactions
Polyclonal antilymphocyte or antithymocyte globulin	Dose depends on specific preparation used	Leukopenia Thrombocytopenia Anaphylaxis Serum sickness "Cytokine release syndrome"—fever, hypotension	No significant interactions
Basiliximab and daclizumab (monoclonal IL-2 receptor antagonists)	Basiliximab: 20 mg IV on dayS 1 and 4 Daclizumab: 1 mg/kg every 2 wk for 5 doses	Hypersensitivity reactions (rare)	No significant interactions

*Dosing is based on the protocol used at the University of Pennsylvania Medical Center; dosing may vary between transplant centers.
†Measured by high-performance liquid chromatography assay.
IL-2, interleukin-2.

OUTCOMES

Survival

Current 1-, 5- and 10-year survival rates documented in the Registry of the International Society for Heart and Lung Transplantation (ISHLT) are 79%, 52%, and 29%, respectively.[1] Although 1-year survival approximates that achieved following heart and liver transplantation, 5-year survival remains considerably below the 75% rate associated with these other procedures. Modest gains have been made in survival rates associated with lung trans-

plantation since the early 1990s, principally due to improvements in perioperative outcomes. There are disease-specific differences in survival that likely reflect the degree of technical difficulty in performing the transplant, the average age of the particular patient population, and the extent of accompanying comorbidities. In descending order, median survival is 7 years for CF, 6.1 years for alpha$_1$-antitrypsin deficiency, 5.6 years for idiopathic pulmonary arterial hypertension, 5.1 years for COPD, and 4.3 years for IPF.[1] The preferential use of bilateral- over single-lung transplantation favorably affects long-term survival in patients with COPD, but data are conflicting on whether this holds true for recipients with IPF.[1,24,27–29]

Mortality is highest during the first year, with primary graft dysfunction and infection representing the most common causes of death. Factors portending an increased risk of early death include ventilator-dependence or inotropic support of the recipient prior to transplantation, an underlying diagnosis of pulmonary fibrosis or idiopathic pulmonary arterial hypertension, elevated bilirubin, and advanced recipient or donor age.[1] Beyond the first year, attrition slows to an annual rate of approximately 5% to 10%. Most late deaths are attributable to the development of bronchiolitis obliterans, the lethal effects of which are due to both progressive respiratory failure and to an increased susceptibility to infection.

Whether lung transplantation truly extends survival compared with the natural history of the underlying disease remains a matter of some debate. In the absence of randomized trials, this question has been approached by comparing observed posttransplant survival to survival of wait-list patients or by simulating survival with and without transplantation by statistical modeling; both of these approaches suffer from significant methodologic shortcomings. In the case of IPF, a disease with an extremely poor short-term prognosis, studies have suggested that lung transplantation does confer a survival advantage.[9,42] This has been more difficult to demonstrate for COPD, which typically follows a protracted course even in the advanced stages, and available studies have yielded conflicting results.[9,43,44]

A complex statistical model analyzing survival benefit for the COPD population has recently been published.[27] Although it employs many of the same variables as the UNOS LAS system, this model differs in two important ways—it takes into account the type of transplant performed and it carries the predicted survival curves with and without transplantation well beyond the first year. The model suggests that approximately 50% of COPD patients undergoing single-lung transplantation and two thirds of those undergoing bilateral transplantation would derive benefit. Survival benefit is heavily influenced by FEV_1 as well as a number of other functional and physiologic parameters. As an example, nearly 80% of patients with an FEV_1 less than 16% but only 11% of those with an FEV_1 greater than 25% are predicted to gain at least a year of life with bilateral transplantation. Notably, survival benefit is often not apparent until several years after transplantation and would, therefore, not be detected by the LAS model. A calculator that generates an estimate of survival benefit for an individual patient with a particular set of parameters is available at the following web site—http://www.copdtransplant.fr/

Using similar statistical modeling in the CF population, it has been suggested that only those patients with a predicted 5-year survival without transplantation of less than 50% and without *B. cepacia* and CF-arthropathy are likely to demonstrate enhanced survival with transplantation.[45] An extremely controversial and unsettling prediction of this model is that lung transplantation rarely improves survival in CF patients younger than 18 years old.[45,46]

Pulmonary Function

The peak effect of lung transplantation on pulmonary function parameters is usually not realized until 3 to 6 months following the procedure, at which time the adverse impact of such factors as postoperative pain, weakness, altered chest wall mechanics, and ischemia-reperfusion lung injury has dissipated. Complete normalization of pulmonary function is the anticipated result of bilateral-lung transplantation. Following single-lung transplantation for COPD, the FEV_1 increases severalfold to a level of approximately 50% to 60% of the predicted normal value. Similarly, single-lung transplantation for pulmonary fibrosis results in marked but incomplete improvement in lung volumes, with persistence of a restrictive pattern.

Transplantation also leads to correction of gas-exchange abnormalities. Oxygenation improves rapidly, permitting the majority of patients to be weaned off of supplemental oxygen within the first week. Hypercapnia may take longer to resolve, due to lingering abnormalities in the ventilatory response to CO_2.[47]

Exercise Capacity

Exercise tolerance improves sufficiently to permit the majority of transplant recipients to achieve functional independence and resume an active lifestyle. Although free of limitations with usual activity, transplant recipients with normal allograft function demonstrate a characteristic reduction in peak exercise performance as assessed by cardiopulmonary exercise testing. Specifically, patients typically achieve a maximum oxygen consumption at peak exercise of only 40% to 60% of predicted.[48] Suboptimal exercise performance persists in subjects tested as late as 1 to 2 years following transplantation. Despite the greater magnitude of improvement in pulmonary function experienced by bilateral transplant recipients, there is no significant difference in peak exercise performance between this group and those who receive only one lung.[49]

Characteristically, breathing reserve, oxygen saturation, and heart rate reserve remain normal during exercise while anaerobic threshold is reduced, a pattern most consistent with skeletal muscle dysfunction. Factors possibly contributing to this include chronic deconditioning, steroid myopathy, and calcineurin

inhibitor–induced impairment in muscle mitochondrial respiration.[48,50]

Hemodynamics

When performed in patients with pulmonary hypertension, both single- and bilateral-lung transplantation lead to immediate and sustained normalization of pulmonary arterial pressure and enhanced cardiac output.[51] In response to a decrease in afterload, right ventricular geometry and performance gradually normalize in the majority of patients.[52,53] A threshold of right ventricular dysfunction, below which recovery will not occur, has yet to be defined.

Quality of Life

After successful lung transplantation, quality of life measures improve markedly across most domains, achieving levels approximating that of the general population.[54–58] Nonetheless, several important limitations have been observed. Although improved from pretransplant status, impairments in psychological functioning—including increased levels of depression and anxiety, and poor perception of body image—persist.[54,55] In addition, troubling side effects from immunosuppressive medications adversely affect quality of life.[55,58] Finally, the development of bronchiolitis obliterans syndrome (BOS) is associated with a significant deterioration in quality of life measures.[57]

Despite improvements in performance status and quality of life, fewer than half of lung transplant recipients return to the workforce.[59,60] Factors cited by recipients as barriers to employment include employer bias against hiring an individual with a chronic medical condition, the potential loss of disability income or medical benefits, side effects of medications, concerns about risk of infection in the workplace, and prioritization of recreational activities over work as a posttransplantation goal.

COMPLICATIONS

Primary Graft Dysfunction

Primary graft dysfunction (PGD) is a term applied to the development within 72 hours of transplantation of radiographic opacities in the allograft(s) associated with impaired oxygenation, in the absence of identifiable insults such as volume overload, pneumonia, rejection, atelectasis, or pulmonary venous outflow obstruction.[61] PGD is presumed to be a consequence of ischemia-reperfusion injury, but inflammatory events associated with donor brain death, surgical trauma, and lymphatic disruption may be contributing factors. Supporting the concept of PGD as a form of acute, nonimmunologic lung injury, histologic examination of lung tissue from affected patients reveals a prevailing pattern of diffuse alveolar damage.[61] A grading system proposed by a working group of the ISHLT classifies the severity of PGD based on the arterial oxygen pressure–to–fractional concentration of oxygen in inspired gas (Pao_2/Fio_2) ratio (Table 95-4).[62] In most cases, the process is mild and transient, but in approximately 10% to 20% of cases, injury is sufficiently severe to cause life-threatening hypoxemia (PGD grade 3) and a clinical course analogous to the acute respiratory distress syndrome.

TABLE 95-4. Grading System for Primary Graft Dysfunction

Grade	Pao_2/Fio_2	Radiographic Evidence of Pulmonary Edema
0	>300	Absent
1	>300	Present
2	200–300	Present
3	<200	Present

Pao_2/Fio_2, ratio of arterial oxygen pressure to fractional concentration of oxygen in inspired gas.
From Christie JD, Carby M, Bag R, et al: Report of the ISHLT Working Group on Primary Lung Graft Dysfunction Part II: Definition. A consensus statement of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant 24:1454–1459, 2005.

A number of risk factors for development of PGD have been identified, but their applicability in clinical practice is limited by the absence of corroborative studies in some cases and by frankly conflicting studies in others. Identified donor-related risk factors include female gender, African American race, older age, and low donor Pao_2/Fio_2 ratio.[63–65] An elevated level of IL-8 in bronchoalveolar lavage (BAL) fluid recovered from the donor has been associated with the development of severe PGD, supporting the notion that inflammatory events preceding organ harvest may play a role.[66] Recipient risk factors include an underlying diagnosis of idiopathic pulmonary arterial hypertension[63] as well as the more generic presence of elevated pulmonary artery pressures.[63] Intuitively, one would anticipate an association between graft ischemic time and PGD, but this has not been consistently demonstrated.[63,67,68] Rather than a linear relationship, ischemic time may become a factor only when it exceeds a certain threshold, suggested by one study as occurring beyond 6 hours.[68]

Treatment of severe PGD is supportive, relying on conventional mechanical ventilation utilizing low tidal volume strategies, as well as on such adjunct measures as independent lung ventilation and extracorporeal life support for select patients who otherwise cannot be stabilized.[69,70] The use of nitric oxide in patients with established graft injury has been associated with sustained reduction in pulmonary artery pressures and improvement in oxygenation.[71] However, the prophylactic administration of nitric oxide to all recipients at the time of reperfusion does not reduce the incidence of severe PGD.[72] Results of emergent retransplantation in this setting have been poor.[73,74]

With an associated perioperative mortality rate of 30% to 40%, severe PGD is a leading cause of early deaths among transplant recipients.[75,76] The risk of death remains

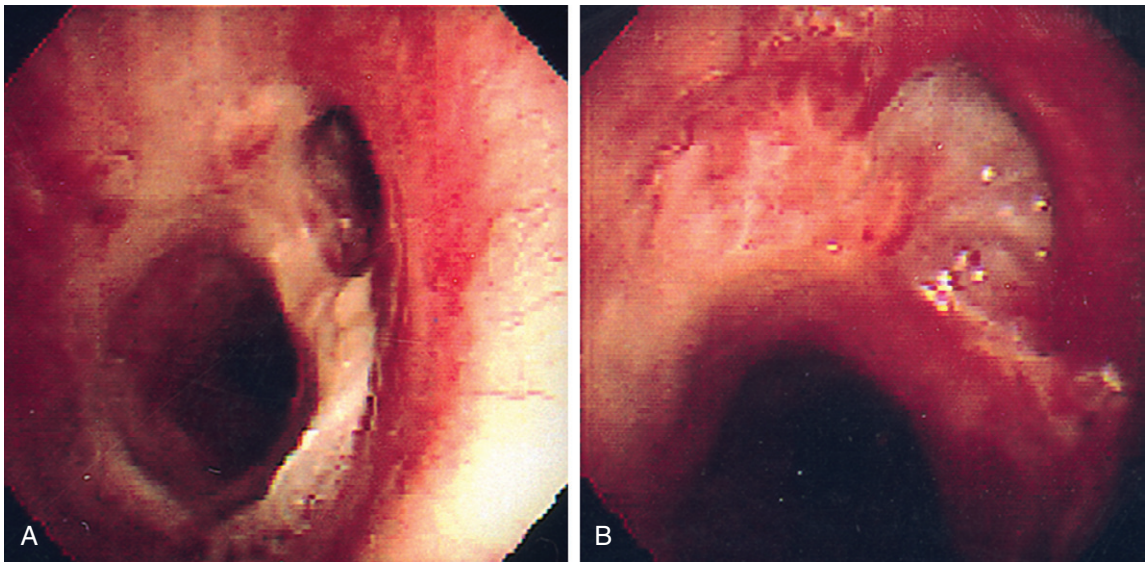

FIGURE 95-1 ■ Bronchial anastomotic dehiscence. **A,** Bronchoscopic view immediately distal to the main carina demonstrates partial dehiscence of the right bronchial anastomosis at the 1 o'clock position. **B,** Repeat view several weeks later demonstrates near-complete healing of the dehiscence with expectant management only.

excessive even beyond the first year, suggesting that PGD has lingering adverse consequences well after resolution of the acute event. Recovery among survivors is often protracted and incomplete, though attainment of normal lung function and exercise tolerance is possible.[77] There appears to be an increased risk of BOS following development of PGD, but data are conflicting on whether the increased risk spans all grades of PGD or is seen exclusively following the most severe grade.[78,79]

Airway Complications

During implantation of the allograft, no attempt is routinely made to reestablish the bronchial arterial circulation. As a consequence, the donor bronchus is precariously dependent upon retrograde blood flow through low-pressure pulmonary venous to bronchial vascular collaterals, placing the airway at risk for ischemic injury. Rarely, this may result in bronchial anastomotic dehiscence, which, when extensive, can lead to mediastinitis, pneumothorax, hemorrhage, and death. Treatment of this life-threatening complication previously required risky and often unsuccessful surgical intervention to buttress the anastomosis. More recently, success has been reported with temporary placement of a bare metal airway stent across the dehiscence in order to provide a scaffolding upon which granulation tissue can form.[80] For lesser degrees of dehiscence, conservative management with reduction in corticosteroid dosing and chest tube evacuation of associated pneumothorax will often lead to successful healing (Fig. 95-1).

Ischemic injury to the airway more commonly manifests as necrosis of the anastomotic cartilage and as patchy areas of bronchial mucosal ulceration and pseudomembranes. These devitalized areas in turn place the patient at increased risk for fungal superinfection of the airway (see later).

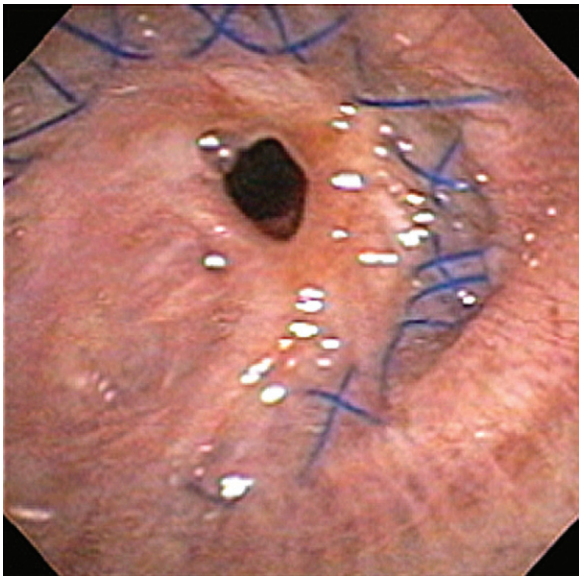

FIGURE 95-2 ■ Bronchial anastomotic stricture. Bronchoscopic view of a left main-stem bronchial anastomosis demonstrates marked narrowing of the lumen due to formation of a fibrous web. The true outer margin of the bronchus is outlined by the suture material.

The most common airway complication currently encountered is bronchial anastomotic stenosis, with a reported frequency of 12% to 24% in contemporary series.[81,82] Narrowing can be due to excessive granulation tissue, fibrotic stricture (Fig. 95-2), or bronchomalacia (the latter two mechanisms likely a sequela of prior ischemic injury). Occasionally, fibrotic strictures can extend beyond the anastomosis, leading to narrowing of the bronchus intermedius or lobar bronchi. Anastomotic narrowing typically develops within several weeks to

months following transplantation. Clues to its presence include focal wheezing on the involved side, recurrent bouts of pneumonia or purulent bronchitis, and suboptimal pulmonary function studies demonstrating airflow obstruction and truncation of the flow-volume loop. Bronchoscopy both confirms the diagnosis and permits therapeutic interventions including balloon dilation, laser débridement, endobronchial brachytherapy, and stent placement.[81,83] Although these measures are often successful in the short term, recurrent stenosis is common, necessitating repeated interventions and leading to compromised functional outcomes and excess mortality.[84]

Phrenic Nerve Injury

Phrenic nerve injury following lung transplantation can result from intraoperative traction, use of an iced slurry to cool the allograft in the chest cavity prior to reperfusion, or transection of the nerve in the setting of extensive fibrous adhesions and difficult hilar dissection. Depending in part on whether screening is restricted to clinically suspected cases or more broadly to all recipients, the reported incidence of phrenic nerve injury ranges from 3% to 30%.[85–88] Important albeit nonspecific clues to the presence of phrenic nerve injury include difficulty in weaning from mechanical ventilation, persistent hypercapnia, orthopnea, and radiographic evidence of persistent elevation of the diaphragm and associated basilar atelectasis. Phrenic nerve injury has been associated with increases in ventilator days, tracheostomy rates, and intensive care unit length of stay.[86] Achievement of a normal functional outcome is ultimately possible for those with reversible injury, but recovery in some cases may be protracted or incomplete. For severely impaired patients, nocturnal noninvasive ventilatory support and diaphragmatic plication have been successfully employed.[89,90]

Native Lung Hyperinflation

Acute hyperinflation of the native lung leading to respiratory and hemodynamic compromise in the immediate postoperative period has been reported in 15% to 30% of emphysema patients undergoing single-lung transplantation.[23,91] Although risk factors remain poorly defined, the combination of positive-pressure ventilation and significant allograft edema serves to magnify the compliance differential between the two lungs and may predispose to this complication. Acute hyperinflation can be rapidly addressed by initiation of independent lung ventilation, ventilating the native lung with a low respiratory rate and prolonged expiratory time to facilitate complete emptying. Beyond the perioperative period, some single-lung transplant recipients with underlying emphysema demonstrate exaggerated or progressive native lung hyperinflation that more insidiously compromises the function of the allograft. In this setting, surgical volume reduction of the native lung can result in significant functional improvement.[92]

Infection

Infection rates among lung transplant recipients are severalfold higher than among recipients of other solid organs. The greater risk is likely related to the unique exposure of the lung allograft to microorganisms via inhalation and aspiration and to the higher level of immunosuppression maintained in these patients. A comprehensive discussion of infectious complications is beyond the scope of this chapter; only the most common pathogens are discussed.

Bacteria

Bacterial infections of the lower respiratory tract account for the majority of infectious complications and have a bimodal temporal distribution.[93,94] Bacterial pneumonia is most frequently encountered within the first month posttransplantation. In addition to the immunosuppressed status of the recipient, factors that predispose to early bacterial pneumonia include the need for prolonged mechanical ventilatory support, blunted cough due to postoperative pain and weakness, disruption of lymphatics, and ischemic injury to the bronchial mucosa with resultant impairment in mucociliary clearance. Although passive transfer of occult infection with the transplanted organ is an additional concern, the presence of organisms on Gram stain of donor bronchial washings is not predictive of subsequent pneumonia in the recipient.[95] Bacterial infections, in the form of purulent bronchitis, bronchiectasis, and pneumonia, reemerge as a late complication among patients who develop BOS. Gram-negative pathogens, in particular *P. aeruginosa*, are most frequently isolated in association with both early and late infectious events.[93,94]

Cytomegalovirus

CMV is the most common viral pathogen encountered following lung transplantation, though in the era of effective prophylaxis, its incidence and impact have diminished considerably.[94] Infection can occur by transfer of virus with the allograft or transfused blood products or by reactivation of latent virus remotely acquired by the recipient. Seronegative recipients who acquire organs from seropositive donors are at greatest risk for developing infection, and these primary infections tend to be the most severe.

CMV infection typically emerges 1 to 3 months following transplantation, though onset is commonly delayed in patients receiving antiviral prophylaxis. Infection is often subclinical, evidenced only by silent viremia or shedding of virus in the respiratory tract. Clinical disease may present as a mononucleosis-like syndrome of fever, malaise, and leukopenia ("CMV syndrome") or as organ-specific invasion of the lung, gastrointestinal tract, central nervous system, or retina. Detection of virus in peripheral blood by either the pp65 antigenemia assay or polymerase chain reaction techniques establishes a diagnosis of CMV infection but does not necessarily reflect events at the tissue level. A diagnosis of

CMV pneumonia, the most common manifestation of invasive disease in the lung transplant recipient, is unequivocally established only by demonstration of characteristic viral cytopathic changes on lung biopsy or on cytologic specimens obtained by BAL, but the sensitivity of these findings is relatively low. Caution must be exercised in interpretation of a positive rapid shell viral culture of BAL specimens, because shedding of virus into the respiratory tract can occur in the absence of tissue invasion.

Standard treatment of CMV syndrome and tissue-invasive disease consists of a 2- to 3-week course of intravenous ganciclovir at a dose of 5 mg/kg twice daily, adjusted for renal insufficiency. Monitoring of peripheral blood viral load should be performed weekly to confirm response to therapy. Treatment should be continued until at least 1 week after an undetectable viral load is documented.[96] Some experts advocate the addition of CMV hyperimmune globulin in treatment of severe disease, but evidence supporting this practice is scant. Although treatment is effective, relapse rates of up to 60% in primary infection and 20% in seropositive recipients have been reported.[97] Initiation of oral valganciclovir as secondary prophylaxis after completion of definitive treatment is a common practice, but its impact on relapse rates is uncertain.

In an attempt to minimize the adverse impact of CMV infection on the posttransplantation course, emphasis has shifted to preventive strategies. Numerous prospective, randomized trials have documented the efficacy of antiviral prophylaxis in delaying the onset and reducing the incidence and severity of CMV infection.[98] Ganciclovir, administered orally or intravenously, has historically been the drug most commonly employed for this purpose. In current practice, oral valganciclovir has emerged as an attractive alternative, owing to its excellent bioavailability after oral administration, once-daily prophylactic dosing requirement, and demonstrated efficacy.[99] Universal prophylaxis of all donor-seropositive/recipient-seronegative patients is recommended because the risk of CMV disease is high.[96] Because the risk of disease is significantly lower in seropositive recipients (independent of donor status), it has been argued that universal prophylaxis of this group leads to overtreatment, increasing costs and unduly exposing patients to the risk of drug toxicity. In this population, preemptive strategies targeting antiviral therapy exclusively to patients demonstrating a rising viral load in peripheral blood have been advocated, but many programs still adhere to a universal prophylaxis strategy.[100]

Emergence of ganciclovir-resistant strains of CMV has been reported in 5% to 15% of lung transplant recipients with CMV infection.[101,102] Risk factors that have been identified include donor-positive/recipient-negative CMV status, use of potent immunosuppressive agents such as antilymphocyte antibodies and daclizumab, increased number of CMV episodes, and prolonged exposure to ganciclovir.[103,104] Foscarnet, administered alone or in combination with ganciclovir, is the agent of choice for treatment of ganciclovir-resistant disease.[102] The drug is potentially nephrotoxic, and careful monitoring of renal function is essential. Although treatment is often successful, the presence of ganciclovir-resistant disease is associated with decreased survival in lung transplant recipients.[104,105]

Aspergillus

Aspergillus species are by far the most frequently encountered fungal organisms in the lung transplant population. As a ubiquitous organism acquired by inhalation, *Aspergillus* colonizes the airways of approximately one quarter of transplant recipients.[106] Airway colonization itself does not appear to pose a major risk of subsequent progression to invasive disease.[106] Whether this is due to the inherently benign nature of colonization or to the common practice of initiating fungal prophylaxis when colonization is detected is unclear.

Aspergillus infection of the bronchial tree occurs in approximately 5% of lung transplant recipients.[106] In most cases, infection is localized to the bronchial anastomosis, where devitalized cartilage and foreign suture material create a nurturing environment. Less commonly, infection may present as a more diffuse ulcerative bronchitis with formation of pseudomembranes, typically following in the wake of a severe ischemic injury to the bronchial mucosa. Clustered within the first 6 months posttransplantation, these airway infections are usually asymptomatic and detected only by surveillance bronchoscopy. Although usually responsive to oral azoles or to inhaled or intravenous amphotericin, airway infections have rarely progressed to invasive pneumonia or have resulted in fatal erosion into the adjacent pulmonary artery.[106,107] An increased risk of subsequent bronchial stenosis or bronchomalacia has also been reported, but it is unclear whether this is a consequence of the infection or of an underlying ischemic injury to the bronchus that predisposed to infection.[108,109]

Invasive aspergillosis, a highly lethal form of infection, occurs in 5% of lung transplant recipients, most commonly within the first year.[106] It nearly always involves the lung but dissemination to distant sites, particularly the brain, occurs in a minority of patients. Symptoms are nonspecific and include fever, cough, pleuritic chest pain, and hemoptysis. Radiographically, pulmonary aspergillosis may appear as single or multiple nodular or cavitary opacities or as alveolar consolidation (Fig. 95-3). The "halo sign"—a rim of ground-glass attenuation surrounding a central nodular opacity—is a suggestive but uncommon finding on chest computed tomography (CT) scans.

Diagnosis of invasive pulmonary aspergillosis can be problematic. As discussed previously, many lung transplant recipients are colonized with *Aspergillus*, making it difficult to interpret the significance of positive fungal stains and cultures derived from BAL specimens. Conversely, the sensitivity of bronchoscopic studies has been reported in the range of only 45% to 62% in solid organ transplant recipients with invasive disease.[110] Measurement of galactomannon levels in serum or BAL fluid has been touted as a useful test for establishing a diagnosis of invasive disease in certain patient

populations, but performance characteristics in the lung transplant population are not sufficiently robust to endorse its use at the present time.[111,112] In the context of compatible clinical and radiographic features and/or demonstration of *Aspergillus* in respiratory secretions by culture or cytology, the clinician must exercise judgment in deciding whether to initiate an empirical trial of antifungal therapy or pursue more definitive proof by means of transthoracic needle biopsy or surgical lung biopsy.

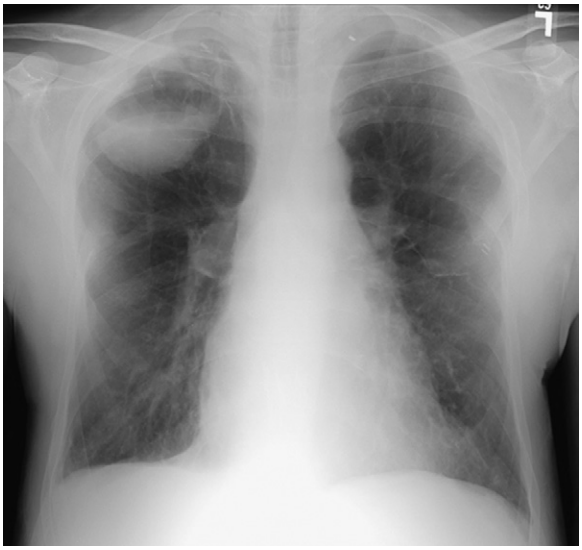

FIGURE 95-3 ■ Invasive aspergillosis. Bilateral lung transplant recipient with a large right upper lobe cavity containing an air-fluid level. Transthoracic needle biopsy demonstrated fungal elements morphologically consistent with *Aspergillus* species. The patient failed to respond to antifungal therapy and surgical resection was required for definitive cure.

Amphotericin B was traditionally the mainstay of therapy for invasive aspergillosis. More recently, however, the triazole voriconazole has been shown to have superior efficacy and less toxicity than amphotericin B and has emerged as the treatment of choice.[113] Voriconazole is a potent inhibitor of the cytochrome P-450 hepatic enzyme system and can lead to dangerously high blood levels of concurrently administered calcineurin inhibitors and sirolimus if appropriate adjustments in the dosing of these agents are not made. The echinocandins (e.g., caspofungin) represent a third class of agents that have been successfully employed in the treatment of invasive aspergillosis.[114] Despite the availability of antifungal therapy, mortality rates in the range of 60% to 80% have been reported.[106,115] The therapeutic role of surgical resection remains uncertain, but surgery has been advocated in cases of localized infection refractory to medical therapy.[116,117]

Rejection

Despite the use of potent immunosuppressive agents, allograft rejection remains a pervasive problem. Features of the various forms of rejection are summarized in Table 95-5 and elaborated upon later.

TABLE 95-5. Features of Allograft Rejection

Feature	Hyperacute Rejection	Acute Rejection	Chronic Rejection
Onset after transplant	Minutes to hours	Days to months	Beyond first year
Risk Factors	Recipient preformed antibodies to donor HLA antigens	Uncertain	Acute rejection, lymphocytic bronchiolitis, community respiratory viruses, primary graft dysfunction, silent aspiration
Histology	Marked interstitial neutrophilic infiltrate, alveolar edema, and platelet and fibrin thrombi in small arterioles	Perivascular lymphocytic infiltrates	Bronchiolar submucosal inflammation and fibrosis; luminal obliteration
Signs and symptoms	Copious production of pink, frothy edema fluid; severe hypoxemia; hypotension	Low-grade fever, dyspnea, cough, impaired oxygenation, leukocytosis	Dyspnea, chronic cough, recurrent bouts of purulent bronchitis
Chest radiograph	Dense consolidation of allograft	Alveolar or interstitial opacities, pleural effusions	Clear lung fields (may show hyperinflation)
High-resolution CT	Not applicable	Ground-glass or alveolar opacities, interlobular septal thickening	Tree-in-bud opacities, bronchiectasis, air trapping
Pulmonary function testing	Not applicable	Proportional decline in FEV_1 and FVC	Disproportionate decline in FEV_1 with worsening obstructive pattern
Yield of transbronchial biopsy	Not applicable	High	Low
Treatment	Plasmapheresis, cyclophosphamide, mechanical ventilation	High-dose corticosteroids	Uncertain: azithromycin is a popular but unproven option
Outcome	High mortality rate	Favorable response to treatment	Poor response to treatment; progressive allograft dysfunction

CT, computed tomography; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; HLA, human leukocyte antigen.

Hyperacute Rejection

Hyperacute rejection is a rare but highly lethal complication mediated by preformed antibodies of recipient origin directed against HLA antigens contained on donor tissue. The pulmonary microvascular endothelium is the principal target, leading to complement- and neutrophil-mediated damage and widespread deposition of platelet/fibrin thrombi.[118] Hyperacute rejection becomes clinically manifest within minutes to hours of establishing perfusion to the freshly implanted lung. The allograft appears dusky, mottled, and grossly edematous on direct inspection and densely opacified on chest x-ray. Reflecting the severity of pulmonary edema, copious amounts of pink, frothy edema fluid often are produced by the allograft and must be frequently suctioned from the endotracheal tube. Profound graft dysfunction and hemodyamic instability ensue. Four of the five cases reported in the literature resulted in death.[119] The one surviving patient was successfully managed with a combination of plasmapheresis, antithymocyte globulin, and cyclophosphamide.[120] Routine screening of all lung transplant candidates for preformed anti-HLA antibodies and either avoidance of donors with the targeted antigens or prospective cross-matching prior to transplantation have proved to be highly effective in minimizing the risk of hyperacute rejection.

Acute Rejection

Frequent surveillance of the allograft by transbronchial biopsy has demonstrated that most transplant recipients experience at least one episode of acute cellular rejection in the first year.[36] Beyond this initial period, the incidence of acute rejection declines considerably. Risk factors for development of acute rejection remain poorly defined. Data are conflicting on whether the degree of HLA discordance between donor and recipient represents a risk factor.[36,121,122] Polymorphisms in Toll-like receptor 4 that down-regulate recipient innate immune responsiveness are associated with a lower incidence of acute rejection.[121]

Episodes of acute rejection may be clinically silent in up to 40% of cases.[36] When present, clinical manifestations are nonspecific and include malaise, low-grade fever, dyspnea, cough, and leukocytosis. Radiographic opacities, a decline in arterial oxygenation at rest or with exercise, and an abrupt fall of greater than 10% in spirometric values are important clues to the possible presence of rejection, but similar findings accompany bouts of infection.

Reliance on clinical and radiographic criteria alone runs the risk of misdiagnosis and needless augmentation of immunosuppression. Transbronchial lung biopsy has emerged as the "gold standard" for diagnosis of acute rejection. The procedure is safe, can be performed in serial fashion over time, and has a high sensitivity and specificity. The histologic hallmark of acute rejection is the presence of perivascular lymphocytic infiltrates that in more severe cases, spill over into the adjacent interstitium and alveolar airspaces. Lymphocytic bronchiolitis may accompany the parenchymal involvement or may be an independent feature. A histologic classification system has been universally adopted to grade the severity of acute cellular rejection (Table 95-6).[123]

TABLE 95-6. Histologic Grading System for Acute Cellular Rejection

Grade	Description
0 (none)	Normal pulmonary parenchyma
1 (minimal)	Scattered, infrequent perivascular mononuclear infiltrates
2 (mild)	Frequent perivascular mononuclear infiltrates surrounding venules and arterioles; readily recognizable at low magnification
3 (moderate)	Easily recognizable cuffing of venules and arterioles by dense perivascular mononuclear cell infiltrates, with extension of the inflammatory cell infiltrate into perivascular and peribronchiolar alveolar septa and air spaces
4 (severe)	Diffuse perivascular, interstitial, and air space infiltrates of mononuclear cells with prominent alveolar pneumocyte damage and endothelialitis

From Stewart S, Fishbein MC, Snell GI, et al: Revision of the 1996 working formulation for the standardization of nomenclature in the diagnosis of lung rejection. J Heart Lung Transplant 26:1229–1242, 2007.

Conventional treatment of acute rejection consists of a 3-day pulse of intravenous solumedrol at a daily dose of 15 mg/kg. In most cases, this results in rapid improvement in symptoms, pulmonary function, and radiographic abnormalities, but follow-up biopsies show histologic evidence of persistent rejection in 30% of patients with prior mild (A2) acute rejection and 44% of patients with prior moderate (A3) acute rejection.[124] Asymptomatic and functionally stable patients with minimal (A1) rejection have typically been observed without treatment, but data demonstrating progression to a higher grade of acute rejection in one quarter of cases and an increased risk of developing BOS have challenged this approach.[125] A variety of modalities have been employed for refractory or recurrent acute rejection including antilymphocyte antibody preparations and photopheresis.

Chronic Rejection (Bronchiolitis Obliterans Syndrome)

Chronic rejection, in the form of bronchiolitis obliterans, develops in approximately half of recipients by 5 years and represents the major impediment to long-term graft and patient survival. Bronchiolitis obliterans is a fibroproliferative process characterized by submucosal inflammation and fibrosis of the bronchiolar walls, ultimately leading to complete obliteration of the airway lumen. The functional consequence of this process is progressive and largely irreversible airflow obstruction. Because the characteristic histology is difficult to demonstrate by transbronchial lung biopsy, the clinical

schema of "bronchiolitis obliterans syndrome" (BOS) was developed, employing the FEV_1 as an easily obtained diagnostic surrogate for histology (Table 95-7).[126] As originally conceived, BOS was defined as an otherwise unexplained and sustained fall in FEV_1 by at least 20% from posttransplant baseline. Concern that this definition might delay diagnosis beyond a stage amenable to treatment prompted the more recent introduction of a BOS 0-potential (BOS 0-p) stage, defined as a decline in FEV_1 by 10% to 19% or in mean forced expiratory flow between 25% and 75% of the forced vital capacity ($FEF_{25\%-75\%}$) by at least 25%. The FEV_1 criterion for BOS 0-p has proved to be a reasonable predictor of patients at risk for progression to more advanced BOS, with a positive predictive value of 60% for progression within 1 year and 80% for progression within 4 years.[127,128] The positive predictive value of the FEV_1 criterion is lower in single-lung transplant recipients with native lung emphysema, likely because of the confounding impact of native lung hyperinflation on lung function.[128] Notably, the $FEF_{25\%-75\%}$ criterion suffers from a low positive predictive value in all recipient populations and is of questionable clinical utility.[127,128]

TABLE 95-7. Grading System for Bronchiolitis Obliterans Syndrome

Stage	Spirometric Criteria
0	FEV_1 > 90% of baseline and $FEF_{25\%-75\%}$ > 75% of baseline
0-potential	FEV_1 81%–90% of baseline and/or $FEF_{25\%-75\%}$ ≤ 75% of baseline
1	FEV_1 66%–80% of baseline
2	FEV_1 51%–65% of baseline
3	FEV_1 ≤ 50% of baseline

$FEF_{25\%-75\%}$, mean forced expiratory flow between 25% and 75% of forced vital capacity; FEV_1, forced expiratory volume in 1 second.
From Estenne M, Maurer JR, Boehler A, et al: Bronchiolitis obliterans syndrome 2001: An update of the diagnostic criteria. J Heart Lung Transplant 21:297–310, 2002.

Acute rejection and lymphocytic bronchiolitis have been consistently identified as major risk factors for development of BOS, supporting the view that BOS is a consequence of alloimmune injury.[129,130] Whereas the risk of BOS appears to correlate with the severity and frequency of these immunologic insults, even minimal (A1) acute rejection is associated with an increased risk.[125,131] Nonimmune factors may also be important in initiating or perpetuating injury but have been more variably substantiated. These factors include CMV infection, community respiratory viral infections, a synergistic interaction between older donor age and prolonged ischemic times, primary graft dysfunction, and gastroesophageal reflux with occult aspiration.[78,130,132,133]

The decline in FEV_1 that heralds the onset of BOS may be either insidious or abrupt, the latter more commonly seen in patients who develop this complication within the first 3 years.[134] Dyspnea, weight loss, cough, and recurrent bouts of purulent tracheobronchitis, with recovery of *P. aeruginosa* from sputum cultures, are characteristic clinical features. Although chest radiographs are usually unremarkable, high-resolution CT commonly reveals air trapping, tree-in-bud opacities, and/or bronchiectasis (Fig. 95-4). Progressive airflow obstruction is the rule, though the pace of decline is highly variable and the course may be interrupted by periods of functional stability. The prognosis is generally poor, with a 40% mortality rate within 2 years of onset.[135] Recipients who develop BOS early after transplantation and those with abrupt onset generally experience more rapid decline in lung function and higher mortality.[134,136,137]

A myriad of immunosuppressive strategies have been employed in the treatment of BOS, including use of conventional agents (e.g., pulse corticosteroids), inhaled cyclosporine, antilymphocyte antibodies, photopheresis, and total lymphoid irradiation, but consensus is lacking on the optimal approach.[135,138,139] At best, immunosuppressive measures appear to slow the rate of decline rather than to fully arrest or reverse the process. A potential role for macrolide therapy is suggested by several retrospective studies documenting short-term

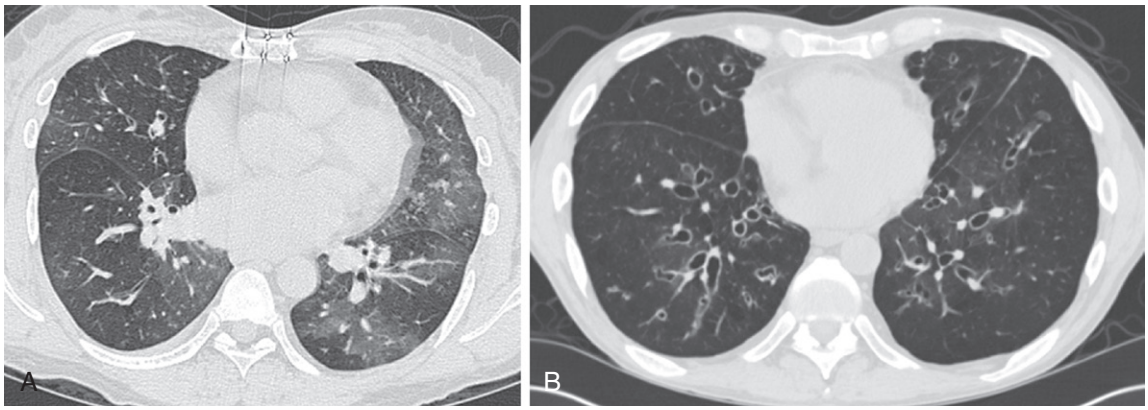

FIGURE 95-4 ■ Radiographic features of bronchiolitis obliterans syndrome (BOS). **A,** High-resolution computed tomography (CT) image obtained during expiration demonstrates a mosaic attenuation pattern consistent with air trapping. **B,** Image obtained from another patient with BOS demonstrates extensive bronchiectasis.

improvement in the FEV_1 in approximately 30% to 45% of patients with BOS treated with azithromycin.[140-143] In contrast to nonresponders, responders demonstrate higher pretreatment levels of BAL neutrophilia and a marked reduction in neutrophilia following initiation of therapy. This lends credence to the notion that the beneficial effects of macrolides relate in large part to their ability to suppress airway IL-8 production and neutrophil recruitment.[141,142] Although still controversial, performance of surgical fundoplication to control gastroesophageal reflux has been associated with improvement in lung function in some patients with BOS.[144] Adjuvant measures to mobilize respiratory secretions and control bacterial infection of the airways—including chest percussion, flutter or acapella valve, and inhaled and systemic antibiotics—may be of benefit in patients with accompanying bronchiectasis. The only definitive treatment for advanced BOS is retransplantation, but this strategy remains problematic in the context of a scarce donor organ pool.

The development of strategies to prevent BOS is an area of intense interest but, to date, little substantive progress. In recognition of the established link between acute rejection and BOS, most transplant centers routinely perform surveillance lung biopsies to detect and treat clinically silent acute rejection, but the impact of this strategy on risk of BOS remains uncertain.[145,146] Preliminary observations from the Duke transplant group suggest that early identification of recipients with gastroesophageal reflux and aggressive correction with fundoplication may delay or prevent onset of BOS.[147] Perhaps most promising is the demonstration in a recent randomized, placebo-controlled trial that the addition of inhaled cyclosporine to a conventional immunosuppressive regimen was associated with a dramatic reduction in the incidence of BOS.[148]

Posttransplantation Lymphoproliferative Disorder

Posttransplant lymphoproliferative disorder (PTLD) describes a spectrum of abnormal proliferative responses involving B cells in the majority of cases and ranging from benign polyclonal hyperplasia to malignant lymphomas. In approximately 90% of cases, Epstein-Barr virus (EBV) can be identified as the stimulus for B-cell proliferation, which proceeds in an unchecked fashion due to the muted cytotoxic T-cell response in the immunosuppressed host. EBV-naive recipients who acquire primary infection at the time of organ transplantation are at greatest risk of developing PTLD.[149] A higher intensity of immunosuppression and, in particular, the use of antilymphocyte antibody preparations have also been implicated as risk factors.

Among the myriad neoplasms that arise following lung transplantation, PTLD is second in frequency only to nonmelanoma skin cancers, with an incidence of approximately 5%.[150] The risk of developing PTLD is greatest within the first posttransplantation year, though up to half of all cases occur beyond this point. The majority of early-onset cases involve the allograft, typically presenting as one or more pulmonary nodules that may be accompanied by mediastinal adenopathy (Fig. 95-5). In contrast, intra-abdominal and disseminated forms of disease predominate in cases presenting beyond the first year.[150]

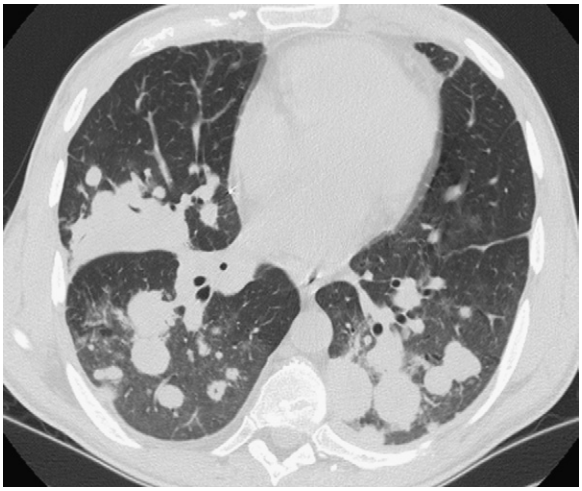

FIGURE 95-5 ■ Posttransplantation lymphoproliferative disorder. CT image demonstrates multiple nodules and masses, proven on biopsy to represent a high-grade B-cell lymphoma. In situ hybridization studies revealed the presence of Epstein-Barr virus RNA.

The diagnosis of PTLD is most firmly established by tissue biopsy, though fine-needle aspiration may occasionally yield sufficient material to make a cytologic diagnosis. Care must be exercised in interpreting transbronchial lung biopsies, because the aggregates of lymphocytes associated with acute cellular rejection can appear similar to foci of PTLD on these small tissue specimens. Demonstration of the presence of EBV-infected cells by in situ hybridization or immunohistochemical staining can help to confirm a diagnosis in difficult cases. Determination of EBV viral load in the peripheral blood using DNA amplification techniques has been touted as an ancillary diagnostic tool. Preliminary studies involving adult lung transplant recipients suggest that an elevated viral load correlates with the presence of PTLD with a high degree of specificity (i.e., low false-positive rate), but the sensitivity is as low as 39%.[151,152] Additional studies employing uniform assay techniques and threshold values for positive results are required before conclusions can be drawn about the clinical utility of this test.

Initial treatment of PTLD involves reduction in the magnitude of immunosuppression to permit partial restoration of host cellular immunity against EBV. Regression of tumor is seen in up to two thirds of cases, but there is an attendant risk of precipitating acute or chronic rejection and patients must be monitored closely.[153] For patients who fail to achieve a complete remission, cannot tolerate reduced immunosuppression, or have rapidly progressive disease, immunotherapy with anti-CD20 monoclonal antibodies (rituximab) has emerged as the preferred option. Use of this agent in the solid organ

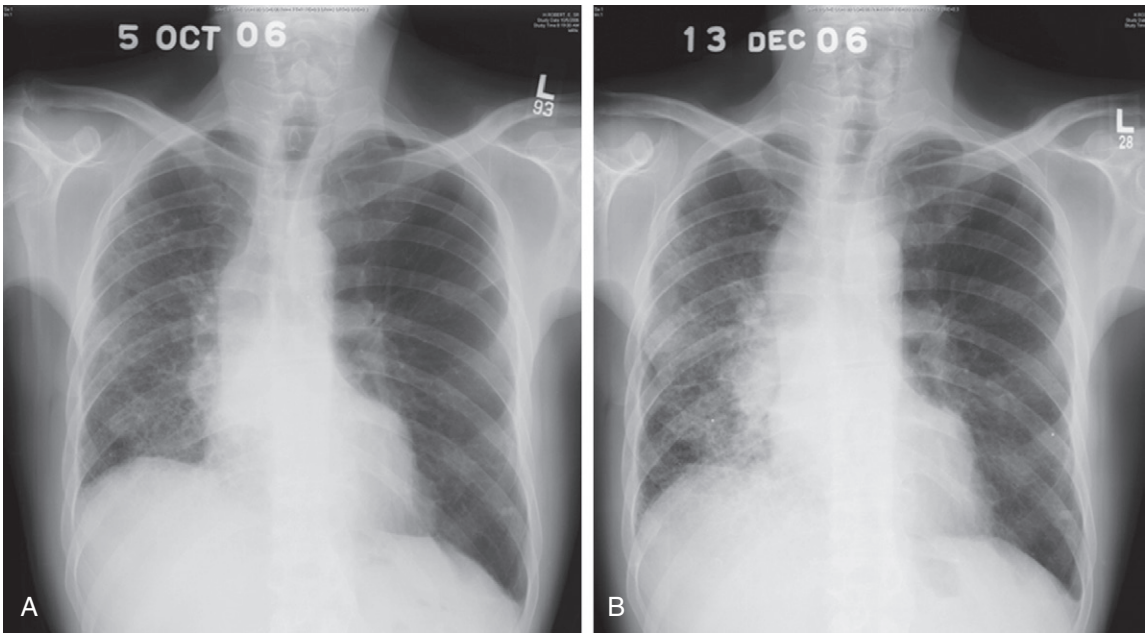

FIGURE 95-6 ■ Bronchogenic carcinoma arising in the native lung. The patient had undergone a left single lung transplant for idiopathic pulmonary fibrosis (IPF). **A,** Chest radiograph demonstrates slight fullness in the infrahilar region of the native right lung. **B,** Repeat chest radiograph only 2 months later demonstrates marked enlargement of the right infrahilar mass as well as an increase in adjacent interstitial opacities. This proved to be a right lower lobe squamous cell lung cancer with associated lymphangitic spread.

transplant population is generally well tolerated and associated with a complete response rate of 60%.[154] In contrast, experience with standard chemotherapy has been poor, with up to one quarter of patients succumbing to treatment-related complications.[154] There is no proven role for antiviral therapy in the setting of established PTLD, though there is suggestive evidence that the prophylactic use of antiviral agents may reduce the subsequent risk of developing PTLD.[155]

Lung Cancer

The development of lung cancer following lung transplantation has been reported almost exclusively in patients with underlying COPD or pulmonary fibrosis, the majority of whom have had significant prior smoking histories. The reported incidence of lung cancer following transplantation is 2% to 6% in patients with COPD and 3% to 4% for the pulmonary fibrosis population.[156,157,157a,157b] Data are conflicting on whether transplantation confers an increased likelihood of developing this form of cancer or whether the incidence is comparable with that of the general population with similar risk factors. Lung cancer most commonly arises in the native lung of single-lung transplant recipients. Less commonly, a previously unsuspected cancer may be incidentally detected in the explanted lung at the time of transplantation and may then recur in the allograft or distant sites. A high rate of recurrence has also been documented in instances when lung transplantation has been performed as definitive treatment for underlying bronchioalveolar carcinoma.[3] Finally, there are rare reports of lung cancer of donor origin transmitted to the recipient.[158]

Lung cancer in the transplant recipient often progresses at a rapid pace, potentially leading to initial confusion with an infectious process (Fig. 95-6).[156] This aggressive behavior may reflect loss of antitumor immune surveillance in the immunosuppressed host or may be due to a more specific effect of cyclosporine in promoting tumor growth.[159] Overall prognosis is poor but should not preclude attempts at curative resection in the rare instances in which early-stage disease is encountered.

Recurrence of Primary Disease

A number of primary disorders have now been documented to recur in the allograft following transplantation.[160] Although accurate figures are not available, sarcoidosis appears to have the greatest propensity to do so. Recurrence of sarcoidosis is typically asymptomatic and marked by incidental recovery of noncaseating granulomas on bronchoscopy and occasionally by the presence of micronodular opacities in the upper lobes on CT scan. Cases of recurrent lymphangioleiomyomatosis have also been reported. The abnormal smooth muscle cells found in the allograft are of recipient origin, suggesting that the mechanism of recurrence involves migration or metastasis from an extrapulmonary site.[161] Other diseases for which recurrence has been reported include Langerhans cell histiocytosis, desquamative interstitial pneumonia, and diffuse panbronchiolitis.

Recurrence of emphysema in the allograft was documented in a recipient 11 years after transplantation for alpha$_1$-antitrypsin deficiency.[162] The patient had resumed smoking and this was presumed to play a central role in accelerating the recurrence of disease. BAL fluid obtained after disease recurrence demonstrated free elastase activ-

ity, suggesting that the endogenous antiprotease defenses had been overwhelmed. These observations highlight the need for alpha$_1$-antitrypsin–deficient transplant recipients to abstain from smoking but do not provide justification for the routine use of enzyme replacement therapy following transplantation.

As previously mentioned, attempts to utilize lung transplantation as a definitive treatment for bronchioalveolar carcinoma resulted in recurrence rates of approximately 50%, leading the vast majority of centers to abandon this approach.[3]

RETRANSPLANTATION

Retransplantation has been utilized as a salvage technique for refractory graft failure. Outcomes following early, emergent retransplantation for primary graft dysfunction are poor, and consequently, use of this intervention in this setting is discouraged.[74,163] In contrast, retransplantation of carefully selected patients with chronic graft failure due to BOS results in survival rates that approach that of initial transplantation. The new allocation system introduced in the United States assigns a high priority to candidates with BOS, on par with that afforded to patients with IPF. This has led to shortened waiting times and to a doubling in number of retransplant procedures performed annually.[74] Although the feasibility and reasonable success of retransplantation for BOS have been established, the issue of its appropriateness in the setting of severe organ shortages remains a vexing ethical dilemma.

FUTURE DIRECTIONS

Since its introduction in 1963, lung transplantation has evolved from a medical curiosity to a standard option for select patients with advanced lung disease. Two major hurdles must yet be overcome in order to facilitate wider applicability of lung transplantation and more enduring results: the donor organ supply must be expanded to meet demand, and more effective and less toxic immunosuppressive strategies must be developed to prevent graft loss from chronic rejection. Increased utilization of "donation after cardiac death" donors may offer a partial solution to the former problem but the ultimate solution will likely come with advances in stem cell, tissue engineering, and xenotransplantation research. Similarly, a definitive solution to the issue of chronic rejection resides in research efforts to promote immune tolerance, a state of permanent graft acceptance in the absence of chronically administered immunosuppressive agents. It is only through these basic research initiatives that lung transplantation will truly fulfill its potential as a safe, effective, and durable treatment option.

KEY POINTS

- Lung transplantation is a therapeutic option for a broad spectrum of advanced nonmalignant disorders of the airways, lung parenchyma, and pulmonary vasculature. The most common indications are COPD, IPF, and CF.
- The lung allocation system now utilized in the United States grants priority to patients with the greatest predicted "net transplant benefit"—the difference between predicted 1-year survival with versus without transplantation.
- One-, 5-, and 10-year survival rates following transplantation are 79%, 52%, and 29%, respectively.
- Common early complications include primary graft dysfunction due to ischemia-reperfusion injury, bronchial anastomotic stenosis, and bacterial pneumonias.
- Acute cellular rejection, characterized by perivascular lymphocytic infiltration, occurs in the majority of recipients in the first year. It usually responds to high-dose corticosteroid therapy but is a major risk factor for subsequent development of chronic rejection (bronchiolitis obliterans).
- The major limitation to long-term allograft function and patient survival is bronchiolitis obliterans, characterized histologically by fibroproliferative obliteration of the small airways and physiologically by progressive airflow obstruction.

References

1. Christie JD, Edwards LB, Aurora P, et al: Registry of the International Society for Heart and Lung Transplantation: Twenty-sixth official adult lung and heart-lung transplantation report—2009. J Heart Lung Transplant 28:1031–1049, 2009.
2. Schachna L, Medsger TA Jr, Dauber JH, et al: Lung transplantation in scleroderma compared with idiopathic pulmonary fibrosis and idiopathic pulmonary arterial hypertension. Arthritis Rheum 54:3954–3961, 2006.
3. de Perrot M, Chernenko S, Waddell TK, et al: Role of lung transplantation in the treatment of bronchogenic carcinomas for patients with end-stage pulmonary disease. J Clin Oncol 22:4351–4356, 2004.
4. Levine SM: A survey of clinical practice of lung transplantation in North America. Chest 125:1224–1238, 2004.

5. Orens JB, Estenne M, Arcasoy S, et al: International guidelines for the selection of lung transplant candidates: 2006 update—A consensus report from the Pulmonary Scientific Council of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant 25:745–755, 2006.
6. Aris RM, Routh JC, LiPuma JJ, et al: Lung transplantation for cystic fibrosis patients with *Burkholderia cepacia* complex. Survival linked to genomovar type. Am J Respir Crit Care Med 164:2102–2106, 2001.
7. Chaparro C, Maurer J, Gutierrez C, et al: Infection with *Burkholderia cepacia* in cystic fibrosis: Outcome following lung transplantation. Am J Respir Crit Care Med 163:43–48, 2001.
8. Hadjiliadis D, Steele MP, Chaparro C, et al: Survival of lung transplant patients with cystic fibrosis harboring panresistant bacteria other than *Burkholderia cepacia*, compared with patients harboring sensitive bacteria. J Heart Lung Transplant 26:834–838, 2007.
9. Hosenpud JD, Bennett LE, Keck BM, et al: Effect of diagnosis on survival benefit of lung transplantation for end-stage lung disease. Lancet 351:24–27, 1998.
10. Egan TM, Murray S, Bustami RT, et al: Development of the new lung allocation system in the United States. Am J Transplant 6:1212–1227, 2006.
11. McCurry KR, Shearon TH, Edwards LB, et al: Heart and lung transplantation in the United States, 1998–2007. Am J Transplant 9:942–958, 2009.
12. Orens JB, Boehler A, de Perrot M, et al: A review of lung transplant donor acceptability criteria. J Heart Lung Transplant 22:1183–1200, 2003.
13. Ware LB, Wang Y, Fang X, et al: Assessment of lungs rejected for transplantation and implications for donor selection. Lancet 360:619–620, 2002.
14. Fischer S, Gohrbandt B, Struckmeier P, et al: Lung transplantation with lungs from donors fifty years of age and older. J Thorac Cardiovasc Surg 129:919–925, 2005.
15. Kawut SM, Reyentovich A, Wilt JS, et al: Outcomes of extended donor lung recipients after lung transplantation. Transplantation 79:310–316, 2005.
16. Luckraz H, White P, Sharples LD, et al: Short- and long-term outcomes of using pulmonary allograft donors with low Po_2. J Heart Lung Transplant 24:470–473, 2005.
17. Sundaresan S, Semenkovich J, Ochoa L, et al: Successful outcome of lung transplantation is not compromised by the use of marginal donor lungs. J Thorac Cardiovasc Surg 109:1075–1079, 1995.
18. De Perrot M, Waddell TK, Shargall Y, et al: Impact of donors aged 60 years or more on outcome after lung transplantation: Results of an 11-year single-center experience. J Thorac Cardiovasc Surg 133:525–531, 2007.
19. Angel LF, Levine DJ, Restrepo MI, et al: Impact of a lung transplantation donor-management protocol on lung donation and recipient outcomes. Am J Respir Crit Care Med 174:710–716, 2006.
20. de Antonio DG, Marcos R, Laporta R, et al: Results of clinical lung transplant from uncontrolled non–heart-beating donors. J Heart Lung Transplant 26:529–534, 2007.
21. Snell GI, Levvey BJ, Oto T, et al: Early lung transplantation success utilizing controlled donation after cardiac death donors. Am J Transplant 8:1282–1289, 2008.
22. Appel JZ 3rd, Hartwig MG, Cantu E, et al: Role of flow cytometry to define unacceptable HLA antigens in lung transplant recipients with HLA-specific antibodies. Transplantation 81:1049–1057, 2006.
23. Weill D, Torres F, Hodges TN, et al: Acute native lung hyperinflation is not associated with poor outcomes after single lung transplant for emphysema. J Heart Lung Transplant 18:1080–1087, 1999.
24. Meyer DM, Bennett LE, Novick RJ, Hosenpud JD: Single vs bilateral, sequential lung transplantation for end-stage emphysema: Influence of recipient age on survival and secondary end-points. J Heart Lung Transplant 20:935–941, 2001.
25. Pochettino A, Kotloff RM, Rosengard BR, et al: Bilateral versus single lung transplantation for chronic obstructive pulmonary disease: Intermediate-term results. Ann Thorac Surg 70:1813–1818, 2000.
26. Sundaresan SR, Shiraishi Y, Trulock EP, et al: Single or bilateral lung transplantation for emphysema? J Thorac Cardiovasc Surg 112:1485–1495, 1996.
27. Thabut G, Christie JD, Ravaud P, et al: Survival after bilateral versus single lung transplantation for patients with chronic obstructive pulmonary disease: A retrospective analysis of registry data. Lancet 371:744–751, 2008.
28. Meyer DM, Edwards LB, Torres F, et al: Impact of recipient age and procedure type on survival after lung transplantation for pulmonary fibrosis. Ann Thorac Surg 79:950–957, 2005.
29. Meyers BF, Lynch JP, Trulock EP, et al: Single versus bilateral lung transplantation for idiopathic pulmonary fibrosis: A ten-year institutional experience. J Thorac Cardiovasc Surg 120:99–107, 2000.
30. Bowdish ME, Pessotto R, Barbers RG, et al: Long-term pulmonary function after living-donor lobar lung transplantation in adults. Ann Thorac Surg 79:418–425, 2005.
31. Starnes VA, Bowdish ME, Woo MS, et al: A decade of living lobar lung transplantation: Recipient outcomes. J Thorac Cardiovasc Surg 127:114–122, 2004.
32. Battafarano RJ, Anderson RC, Meyers BF, et al: Perioperative complications after living donor lobectomy. J Thorac Cardiovasc Surg 120:909–915, 2000.
33. Bowdish ME, Barr ML, Schenkel FA, et al: A decade of living lobar lung transplantation: Perioperative complications after 253 donor lobectomies. Am J Transplant 4:1283–1288, 2004.
34. Starnes VA, Barr ML, Cohen RG, et al: Living donor lobar lung transplantation experience: Intermediate results. J Thorac Cardiovasc Surg 112:1284–1291, 1996.
35. 2008 Annual Report of the U.S. Organ Procurement and Transplantation Network and the Scientific Registry of Transplant Recipients: Transplant Data 1998–2007. Rockville, MD: Department of Health and Human Services, Health Resources and Services Administration, Healthcare Systems Bureau, Division of Transplantation, 2008.
36. Hopkins PM, Aboyoun CL, Chhajed PN, et al: Prospective analysis of 1,235 transbronchial lung biopsies in lung transplant recipients. J Heart Lung Transplant 21:1062–1067, 2002.
37. Snell GI, Westall GP: Immunosuppression for lung transplantation: Evidence to date. Drugs 67:1531–1539, 2007.
38. Snell GI, Levvey BJ, Chin W, et al: Sirolimus allows renal recovery in lung and heart transplant recipients with chronic renal impairment. J Heart Lung Transplant 21:540–546, 2002.
39. Venuta F, De Giacomo T, Rendina EA, et al: Recovery of chronic renal impairment with sirolimus after lung transplantation. Ann Thorac Surg 78:1940–1943, 2004.
40. King-Biggs MB, Dunitz JM, Park SJ, et al: Airway anastomotic dehiscence associated with use of sirolimus immediately after lung transplantation. Transplantation 75:1437–1443, 2003.
41. Kotloff RM, Ahya VN: Medical complications of lung transplantation. Eur Respir J 23:334–342, 2004.
42. Thabut G, Mal H, Castier Y, et al: Survival benefit of lung transplantation for patients with idiopathic pulmonary fibrosis. J Thorac Cardiovasc Surg 126:469–475, 2003.
43. Charman SC, Sharples LD, McNeil KD, Wallwork J: Assessment of survival benefit after lung transplantation by patient diagnosis. J Heart Lung Transplant 21:226–232, 2002.
44. Geertsma A, Ten Vergert EM, Bonsel GJ, et al: Does lung transplantation prolong life? A comparison of survival with and without transplantation. J Heart Lung Transplant 17:511–516, 1998.
45. Liou TG, Adler FR, Huang D: Use of lung transplantation survival models to refine patient selection in cystic fibrosis. Am J Respir Crit Care Med 171:1053–1059, 2005.
46. Liou TG, Adler FR, Cox DR, Cahill BC: Lung transplantation and survival in children with cystic fibrosis. N Engl J Med 357:2143–2152, 2007.
47. Trachiotis GD, Knight SR, Hann M, et al: Respiratory responses to CO_2 rebreathing in lung transplant recipients. Ann Thorac Surg 58:1709–1717, 1994.
48. Reinsma GD, ten Hacken NH, Grevink RG, et al: Limiting factors of exercise performance 1 year after lung transplantation. J Heart Lung Transplant 25:1310–1316, 2006.

49. Lands LC, Smountas AA, Mesiano G, et al: Maximal exercise capacity and peripheral skeletal muscle function following lung transplantation. J Heart Lung Transplant 18:113–120, 1999.
50. Hokanson JF, Mercier JG, Brooks GA: Cyclosporine A decreases rat skeletal muscle mitochondrial respiration in vitro. Am J Respir Crit Care Med 151:1848–1851, 1995.
51. Gammie JS, Keenan RJ, Pham SM, et al: Single- versus double-lung transplantation for pulmonary hypertension. J Thorac Cardiovasc Surg 115:397–402, 1998.
52. Kramer MR, Valantine HA, Marshall SE, et al: Recovery of the right ventricle after single-lung transplantation in pulmonary hypertension. Am J Cardiol 73:494–500, 1994.
53. Moulton MJ, Creswell LL, Ungacta FF, et al: Magnetic resonance imaging provides evidence for remodeling of the right ventricle after single-lung transplantation for pulmonary hypertension. Circulation 94:II312–II319, 1996.
54. Limbos MM, Joyce DP, Chan CK, Kesten S: Psychological functioning and quality of life in lung transplant candidates and recipients. Chest 118:408–416, 2000.
55. Rodrigue JR, Baz MA, Kanasky WF Jr, MacNaughton KL: Does lung transplantation improve health-related quality of life? The University of Florida experience. J Heart Lung Transplant 24:755–763, 2005.
56. Kugler C, Fischer S, Gottlieb J, et al: Health-related quality of life in two hundred-eighty lung transplant recipients. J Heart Lung Transplant 24:2262–2268, 2005.
57. van Den BJ, Geertsma A, van Der BW, et al: Bronchiolitis obliterans syndrome after lung transplantation and health-related quality of life. Am J Respir Crit Care Med 161:1937–1941, 2000.
58. Smeritschnig B, Jaksch P, Kocher A, et al: Quality of life after lung transplantation: A cross-sectional study. J Heart Lung Transplant 24:474–480, 2005.
59. Cicutto L, Braidy C, Moloney S, et al: Factors affecting attainment of paid employment after lung transplantation. J Heart Lung Transplant 23:481–486, 2004.
60. Paris W, Diercks M, Bright J, et al: Return to work after lung transplantation. J Heart Lung Transplant 17:430–436, 1998.
61. Christie JD, Bavaria JE, Palevsky HI, et al: Primary graft failure following lung transplantation. Chest 114:51-60, 1998.
62. Christie JD, Carby M, Bag R, et al: Report of the ISHLT Working Group on Primary Lung Graft Dysfunction part II: Definition. A consensus statement of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant 24:1454–1459, 2005.
63. Christie JD, Kotloff RM, Pochettino A, et al: Clinical risk factors for primary graft failure following lung transplantation. Chest 124:1232–1241, 2003.
64. Pilcher DV, Snell GI, Scheinkestel CD, et al: High donor age, low donor oxygenation, and high recipient inotrope requirements predict early graft dysfunction in lung transplant recipients. J Heart Lung Transplant 24:1814–1820, 2005.
65. Whitson BA, Nath DS, Johnson AC, et al: Risk factors for primary graft dysfunction after lung transplantation. J Thorac Cardiovasc Surg 131:73–80, 2006.
66. Fisher AJ, Donnelly SC, Hirani N, et al: Elevated levels of interleukin-8 in donor lungs is associated with early graft failure after lung transplantation. Am J Respir Crit Care Med 163:259–265, 2001.
67. Fiser SM, Kron IL, Long SM, et al: Influence of graft ischemic time on outcomes following lung transplantation. J Heart Lung Transplant 20:1291–1296, 2001.
68. Thabut G, Mal H, Cerrina J, et al: Graft ischemic time and outcome of lung transplantation: A multicenter analysis. Am J Respir Crit Care Med 171:786–791, 2005.
69. Fischer S, Bohn D, Rycus P, et al: Extracorporeal membrane oxygenation for primary graft dysfunction after lung transplantation: Analysis of the Extracorporeal Life Support Organization (ELSO) registry. J Heart Lung Transplant 26:472–477, 2007.
70. Gavazzeni V, Iapichino G, Mascheroni D, et al: Prolonged independent lung respiratory treatment after single lung transplantation in pulmonary emphysema. Chest 103:96–100, 1993.
71. Ardehali A, Laks H, Levine M, et al: A prospective trial of inhaled nitric oxide in clinical lung transplantation. Transplantation 72:112–115, 2001.
72. Meade MO, Granton JT, Matte-Martyn A, et al: A randomized trial of inhaled nitric oxide to prevent ischemia-reperfusion injury after lung transplantation. Am J Respir Crit Care Med 167:1483–1489, 2003.
73. Aigner C, Jaksch P, Taghavi S, et al: Pulmonary retransplantation: Is it worth the effort? A long-term analysis of 46 cases. J Heart Lung Transplant 27:60–65, 2008.
74. Kawut SM, Lederer DJ, Keshavjee S, et al: Outcomes after lung retransplantation in the modern era. Am J Respir Crit Care Med 177:114–120, 2008.
75. Christie JD, Kotloff RM, Ahya VN, et al: The effect of primary graft dysfunction on survival after lung transplantation. Am J Respir Crit Care Med 171:1312–1316, 2005.
76. Prekker ME, Nath DS, Walker AR, et al: Validation of the proposed International Society for Heart and Lung Transplantation grading system for primary graft dysfunction after lung transplantation. J Heart Lung Transplant 25:371–378, 2006.
77. Christie JD, Sager JS, Kimmel SE, et al: Impact of primary graft failure on outcomes following lung transplantation. Chest 127:161–165, 2005.
78. Daud SA, Yusen RD, Meyers BF, et al: Impact of immediate primary lung allograft dysfunction on bronchiolitis obliterans syndrome. Am J Respir Crit Care Med 175:507–513, 2007.
79. Whitson BA, Prekker ME, Herrington CS, et al: Primary graft dysfunction and long-term pulmonary function after lung transplantation. J Heart Lung Transplant 26:1004–1011, 2007.
80. Mughal MM, Gildea TR, Murthy S, et al: Short-term deployment of self-expanding metallic stents facilitates healing of bronchial dehiscence. Am J Respir Crit Care Med 172:768–771, 2005.
81. Chhajed PN, Malouf MA, Tamm M, et al: Interventional bronchoscopy for the management of airway complications following lung transplantation. Chest 120:1894–1899, 2001.
82. Herrera JM, McNeil KD, Higgins RS, et al: Airway complications after lung transplantation: Treatment and long-term outcome. Ann Thorac Surg 71:989–993, 2001 [discussion appears 993–984].
83. Halkos ME, Godette KD, Lawrence EC, Miller JI Jr: High dose rate brachytherapy in the management of lung transplant airway stenosis. Ann Thorac Surg 76:381–384, 2003.
84. Murthy SC, Blackstone EH, Gildea TR, et al: Impact of anastomotic airway complications after lung transplantation. Ann Thorac Surg 84:401–409, 409.e1–4, 2007.
85. Dorffner R, Eibenberger K, Youssefzadeh S, et al: Diaphragmatic dysfunction after heart or lung transplantation. J Heart Lung Transplant 16:566–569, 1997.
86. Ferdinande P, Bruyninckx F, Van Raemdonck D, et al: Phrenic nerve dysfunction after heart-lung and lung transplantation. J Heart Lung Transplant 23:105–109, 2004.
87. Maziak DE, Maurer JR, Kesten S: Diaphragmatic paralysis: A complication of lung transplantation. Ann Thorac Surg 61:170–173, 1996.
88. Sheridan PH Jr, Cheriyan A, Doud J, et al: Incidence of phrenic neuropathy after isolated lung transplantation. The Loyola University Lung Transplant Group. J Heart Lung Transplant 14:684–691, 1995.
89. Shihata M, Mullen JC: Bilateral diaphragmatic plication in the setting of bilateral sequential lung transplantation. Ann Thorac Surg 83:1201–1203, 2007.
90. Berk Y, van der Bij W, Erasmus ME, Wijkstra PJ: Non-invasive ventilation in phrenic nerve dysfunction after lung transplantation: An attractive option. J Heart Lung Transplant 25:1483–1485, 2006.
91. Yonan NA, el-Gamel A, Egan J, et al: Single lung transplantation for emphysema: Predictors for native lung hyperinflation. J Heart Lung Transplant 17:192–201, 1998.
92. Reece TB, Mitchell JD, Zamora MR, et al: Native lung volume reduction surgery relieves functional graft compression after single-lung transplantation for chronic obstructive pulmonary disease. J Thorac Cardiovasc Surg 135:931–937, 2008.
93. Valentine VG, Bonvillain RW, Gupta MR, et al: Infections in lung allograft recipients: Ganciclovir era. J Heart Lung Transplant 27:528–535, 2008.
94. Aguilar-Guisado M, Givalda J, Ussetti P, et al: Pneumonia after lung transplantation in the RESITRA Cohort: A multicenter prospective study. Am J Transplant 7:1989–1996, 2007.

95. Weill D, Dey GC, Hicks RA, et al: A positive donor gram stain does not predict outcome following lung transplantation. J Heart Lung Transplant 21:555–558, 2002.
96. Preiksaitis JK, Brennan DC, Fishman J, Allen U: Canadian Society of Transplantation consensus workshop on cytomegalovirus management in solid organ transplantation final report. Am J Transplant 5:218–227, 2005.
97. Rubin RH: Prevention and treatment of cytomegalovirus disease in heart transplant patients. J Heart Lung Transplant 19:731–735, 2000.
98. Hodson EM, Craig JC, Strippoli GF, Webster AC: Antiviral medications for preventing cytomegalovirus disease in solid organ transplant recipients. Cochrane Database Syst Rev 2:CD003774, 2008.
99. Paya C, Humar A, Dominguez E, et al: Efficacy and safety of valganciclovir vs. oral ganciclovir for prevention of cytomegalovirus disease in solid organ transplant recipients. Am J Transplant 4:611–620, 2004.
100. Strippoli GF, Hodson EM, Jones CJ, Craig JC: Pre-emptive treatment for cytomegalovirus viraemia to prevent cytomegalovirus disease in solid organ transplant recipients. Cochrane Database Syst Rev 1:CD005133, 2006.
101. Lurain NS, Bhorade SM, Pursell KJ, et al: Analysis and characterization of antiviral drug-resistant cytomegalovirus isolates from solid organ transplant recipients. J Infect Dis 186:760–768, 2002.
102. Reddy AJ, Zaas AK, Hanson KE, Palmer SM: A single-center experience with ganciclovir-resistant cytomegalovirus in lung transplant recipients: Treatment and outcome. J Heart Lung Transplant 26:1286–1292, 2007.
103. Limaye AP, Corey L, Koelle DM, et al: Emergence of ganciclovir-resistant cytomegalovirus disease among recipients of solid-organ transplants. Lancet 356:645–649, 2000.
104. Bhorade SM, Lurain NS, Jordan A, et al: Emergence of ganciclovir-resistant cytomegalovirus in lung transplant recipients. J Heart Lung Transplant 21:1274–1282, 2002.
105. Kruger RM, Shannon WD, Arens MQ, et al: The impact of ganciclovir-resistant cytomegalovirus infection after lung transplantation. Transplantation 68:1272–1279, 1999.
106. Mehrad B, Paciocco G, Martinez FJ, et al: Spectrum of *Aspergillus* infection in lung transplant recipients: Case series and review of the literature. Chest 119:169–175, 2001.
107. Kessler R, Massard G, Warter A, et al: Bronchial-pulmonary artery fistula after unilateral lung transplantation: A case report. J Heart Lung Transplant 16:674–677, 1997.
108. Nathan SD, Shorr AF, Schmidt ME, Burton NA: *Aspergillus* and endobronchial abnormalities in lung transplant recipients. Chest 118:403–407, 2000.
109. Nunley DR, Gal AA, Vega JD, et al: Saprophytic fungal infections and complications involving the bronchial anastomosis following human lung transplantation. Chest 122:1185–1191, 2002.
110. Paterson DL, Singh N: Invasive aspergillosis in transplant recipients. Medicine (Baltimore) 78:123–138, 1999.
111. Husain S, Kwak EJ, Obman A, et al: Prospective assessment of *Platelia Aspergillus galactomannan* antigen for the diagnosis of invasive aspergillosis in lung transplant recipients. Am J Transplant 4:796–802, 2004.
112. Husain S, Paterson DL, Studer SM, et al: *Aspergillus galactomannan* antigen in the bronchoalveolar lavage fluid for the diagnosis of invasive aspergillosis in lung transplant recipients. Transplantation 83:1330–1336, 2007.
113. Herbrecht R, Denning DW, Patterson TF, et al: Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. N Engl J Med 347:408–415, 2002.
114. Groetzner J, Kaczmarek I, Wittwer T, et al: Caspofungin as first-line therapy for the treatment of invasive aspergillosis after thoracic organ transplantation. J Heart Lung Transplant 27:1–6, 2008.
115. Singh N, Husain S: *Aspergillus* infections after lung transplantation: Clinical differences in type of transplant and implications for management. J Heart Lung Transplant 22:258–266, 2003.
116. Salerno CT, Ouyang DW, Pederson TS, et al: Surgical therapy for pulmonary aspergillosis in immunocompromised patients. Ann Thorac Surg 65:1415–1419, 1998.
117. Sandur S, Gordon SM, Mehta AC, Maurer JR: Native lung pneumonectomy for invasive pulmonary aspergillosis following lung transplantation: A case report. J Heart Lung Transplant 18:810–813, 1999.
118. Choi JK, Kearns J, Palevsky HI, et al: Hyperacute rejection of a pulmonary allograft. Immediate clinical and pathologic findings. Am J Respir Crit Care Med 160:1015–1018, 1999.
119. Camargo J, Camargo S, Schio SM, et al: Hyperacute rejection after single lung transplantation: A case report. Transplant Proc 40:867–869, 2008.
120. Bittner HB, Dunitz J, Hertz M, et al: Hyperacute rejection in single lung transplantation—Case report of successful management by means of plasmapheresis and antithymocyte globulin treatment. Transplantation 71:649–651, 2001.
121. Palmer SM, Burch LH, Davis RD, et al: The role of innate immunity in acute allograft rejection after lung transplantation. Am J Respir Crit Care Med 168:628–632, 2003.
122. Schulman LL, Weinberg AD, McGregor C, et al: Mismatches at the HLA-DR and HLA-B loci are risk factors for acute rejection after lung transplantation. Am J Respir Crit Care Med 157:1833–1837, 1998.
123. Stewart S, Fishbein MC, Snell GI, et al: Revision of the 1996 working formulation for the standardization of nomenclature in the diagnosis of lung rejection. J Heart Lung Transplant 26:1229–1242, 2007.
124. Guilinger RA, Paradis IL, Dauber JH, et al: The importance of bronchoscopy with transbronchial biopsy and bronchoalveolar lavage in the management of lung transplant recipients. Am J Respir Crit Care Med 152:2037–2043, 1995.
125. Hopkins PM, Aboyoun CL, Chhajed PN, et al: Association of minimal rejection in lung transplant recipients with obliterative bronchiolitis. Am J Respir Crit Care Med 170:1022–1026, 2004.
126. Estenne M, Maurer JR, Boehler A, et al: Bronchiolitis obliterans syndrome 2001: An update of the diagnostic criteria. J Heart Lung Transplant 21:297–310, 2002.
127. Hachem RR, Chakinala MM, Yusen RD, et al: The predictive value of bronchiolitis obliterans syndrome stage 0-p. Am J Respir Crit Care Med 169:468–472, 2004.
128. Lama VN, Murray S, Mumford JA, et al: Prognostic value of bronchiolitis obliterans syndrome stage 0-p in single-lung transplant recipients. Am J Respir Crit Care Med 172:379–383, 2005.
129. Glanville AR, Aboyoun CL, Havryk A, et al: Severity of lymphocytic bronchiolitis predicts long-term outcome after lung transplantation. Am J Respir Crit Care Med 177:1033–1040, 2008.
130. Sharples LD, McNeil K, Stewart S, Wallwork J: Risk factors for bronchiolitis obliterans: A systematic review of recent publications. J Heart Lung Transplant 21:271–281, 2002.
131. Khalifah AP, Hachem RR, Chakinala MM, et al: Minimal acute rejection after lung transplantation: A risk for bronchiolitis obliterans syndrome. Am J Transplant 5:2022–2030, 2005.
132. Khalifah AP, Hachem RR, Chakinala MM, et al: Respiratory viral infections are a distinct risk for bronchiolitis obliterans syndrome and death. Am J Respir Crit Care Med 170:181–187, 2004.
133. D'Ovidio F, Mura M, Tsang M, et al: Bile acid aspiration and the development of bronchiolitis obliterans after lung transplantation. J Thorac Cardiovasc Surg 129:1144–1152, 2005.
134. Brugiere O, Pessione F, Thabut G, et al: Bronchiolitis obliterans syndrome after single-lung transplantation: Impact of time to onset on functional pattern and survival. Chest 121:1883–1889, 2002.
135. Date H, Lynch JP, Sundaresan S, et al: The impact of cytolytic therapy on bronchiolitis obliterans syndrome. J Heart Lung Transplant 17:869–875, 1998.
136. Jackson CH, Sharples LD, McNeil K, et al: Acute and chronic onset of bronchiolitis obliterans syndrome (BOS): Are they different entities? J Heart Lung Transplant 21:658–666, 2002.
137. Lama VN, Murray S, Lonigro RJ, et al: Course of FEV(1) after onset of bronchiolitis obliterans syndrome in lung transplant recipients. Am J Respir Crit Care Med 175:1192–1198, 2007.
138. Iacono AT, Keenan RJ, Duncan SR, et al: Aerosolized cyclosporine in lung transplant recipients with refractory chronic rejection. Am J Respir Crit Care Med 153:1451–1455, 1996.
139. Fisher AJ, Rutherford RM, Bozzino J, et al: The safety and efficacy of total lymphoid irradiation in progressive bronchiolitis obliterans syndrome after lung transplantation. Am J Transplant 5:537–543, 2005.

140. Gerhardt SG, McDyer JF, Girgis RE, et al: Maintenance azithromycin therapy for bronchiolitis obliterans syndrome: Results of a pilot study. Am J Respir Crit Care Med 168:121–125, 2003.
141. Gottlieb J, Szangolies J, Koehnlein T, et al: Long-term azithromycin for bronchiolitis obliterans syndrome after lung transplantation. Transplantation 85:36–41, 2008.
142. Verleden GM, Vanaudenaerde BM, Dupont LJ, Van Raemdonck DE: Azithromycin reduces airway neutrophilia and interleukin-8 in patients with bronchiolitis obliterans syndrome. Am J Respir Crit Care Med 174:566–570, 2006.
143. Yates B, Murphy DM, Forrest IA, et al: Azithromycin reverses airflow obstruction in established bronchiolitis obliterans syndrome. Am J Respir Crit Care Med 172:772–775, 2005.
144. Davis RD Jr, Lau CL, Eubanks S, et al: Improved lung allograft function after fundoplication in patients with gastroesophageal reflux disease undergoing lung transplantation. J Thorac Cardiovasc Surg 125:533–542, 2003.
145. Valentine VG, Taylor DE, Dhillon GS, et al: Success of lung transplantation without surveillance bronchoscopy. J Heart Lung Transplant 21:319–326, 2002.
146. Tamm M, Sharples LD, Higenbottam TW, et al: Bronchiolitis obliterans syndrome in heart-lung transplantation: Surveillance biopsies. Am J Respir Crit Care Med 155:1705–1710, 1997.
147. Cantu E, 3rd, Appel JZ 3rd, Hartwig MG, et al: J. Maxwell Chamberlain Memorial Paper. Early fundoplication prevents chronic allograft dysfunction in patients with gastroesophageal reflux disease. Ann Thorac Surg 78:1142–1151, 2004 [discussion appears 1142–1151].
148. Iacono AT, Johnson BA, Grgurich WF, et al: A randomized trial of inhaled cyclosporine in lung-transplant recipients. N Engl J Med 354:141–150, 2006.
149. Aris RM, Maia DM, Neuringer IP, et al: Post-transplantation lymphoproliferative disorder in the Epstein-Barr virus–naive lung transplant recipient. Am J Respir Crit Care Med 154:1712–1717, 1996.
150. Paranjothi S, Yusen RD, Kraus MD, et al: Lymphoproliferative disease after lung transplantation: Comparison of presentation and outcome of early and late cases. J Heart Lung Transplant 20:1054–1063, 2001.
151. Stevens SJ, Verschuuren EA, Pronk I, et al: Frequent monitoring of Epstein-Barr virus DNA load in unfractionated whole blood is essential for early detection of posttransplant lymphoproliferative disease in high-risk patients. Blood 97:1165–1171, 2001.
152. Tsai DE, Nearey M, Hardy CL, et al: Use of EBV PCR for the diagnosis and monitoring of post-transplant lymphoproliferative disorder in adult solid organ transplant patients. Am J Transplant 2:946–954, 2002.
153. Tsai DE, Hardy CL, Tomaszewski JE, et al: Reduction in immunosuppression as initial therapy for posttransplant lymphoproliferative disorder: Analysis of prognostic variables and long-term follow-up of 42 adult patients. Transplantation 71:1076–1088, 2001.
154. Elstrom RL, Andreadis C, Aqui NA, et al: Treatment of PTLD with rituximab or chemotherapy. Am J Transplant 6:569–576, 2006.
155. Levine SM, Angel L, Anzueto A, et al: A low incidence of posttransplant lymphoproliferative disorder in 109 lung transplant recipients. Chest 116:1273–1277, 1999.
156. Arcasoy SM, Hersh C, Christie JD, et al: Bronchogenic carcinoma complicating lung transplantation. J Heart Lung Transplant 20:1044–1053, 2001.
157. Collins J, Kazerooni EA, Lacomis J, et al: Bronchogenic carcinoma after lung transplantation: Frequency, clinical characteristics, and imaging findings. Radiology 224:131–138, 2002.
157a. Dickson RP, Davis RD, Rea JB, Palmer SM: High frequency of bronchogenic carcinoma after single-lung transplantation. J Heart Lung Transplant 25:1297–1301, 2006.
157b. Minai OA, Shah S, Mazzone P, et al: Bronchogenic carcinoma after lung transplantation: characteristics and outcomes. J Thorac Oncol 3:1404–1409, 2008.
158. de Perrot M, Wigle DA, Pierre AF, et al: Bronchogenic carcinoma after solid organ transplantation. Ann Thorac Surg 75:367–371, 2003.
159. Hojo M, Morimoto T, Maluccio M, et al: Cyclosporine induces cancer progression by a cell-autonomous mechanism. Nature 397:530–534, 1999.
160. Collins J, Hartman MJ, Warner TF, et al: Frequency and CT findings of recurrent disease after lung transplantation. Radiology 219:503–509, 2001.
161. Karbowniczek M, Astrinidis A, Balsara BR, et al: Recurrent lymphangiomyomatosis after transplantation: Genetic analyses reveal a metastatic mechanism. Am J Respir Crit Care Med 167:976–982, 2003.
162. Mal H, Guignabert C, Thabut G, et al: Recurrence of pulmonary emphysema in an alpha-1 proteinase inhibitor–deficient lung transplant recipient. Am J Respir Crit Care Med 170:811–814, 2004.
163. Strueber M, Fischer S, Gottlieb J, et al: Long-term outcome after pulmonary retransplantation. J Thorac Cardiovasc Surg 132:407–412, 2006.

APPENDIX

GLOSSARY OF TERMS AND STANDARD SYMBOLS

I. PRIMARY AND QUALIFYING SYMBOLS

General

P	Pressure (Includes also *partial* pressure of a gas in a mixture of gases or in blood.)
L	Lung
W	Chest wall
RS	Respiratory system
Pl	Pleura

Ventilation

V	Volume of gas
$\dot{V}$	Flow of gas
I	Inspired
E	Expired
A	Alveolar
T	Tidal
ET	End-tidal
D	Dead space
STPD	*Standard Conditions: s*tandard *t*emperature (0° C), barometric *p*ressure (760 mm Hg), and *d*ry.
BTPS	*Body Conditions: b*ody *t*emperature and ambient *p*ressure, *s*aturated with water vapor at these conditions.
ATPS	*Ambient Conditions: a*mbient *t*emperature and *p*ressure, *s*aturated with water vapor at these conditions.

Gas Exchange–Blood Flow

Q	Volume of blood
$\dot{Q}$	Flow of blood
F	Fractional concentration of gas
C	Concentration in blood
S	Saturation in blood
b	Blood, in general
a	Arterial blood
v	Venous blood
$\bar{v}$	Mixed venous blood
c	Capillary blood
c′	Pulmonary end-capillary blood

II. VENTILATION AND LUNG MECHANICS

Static Lung Volumes

VC	*Vital Capacity:* The maximum volume of gas that can be exhaled after fully inflating the lungs.
FRC	*Functional Residual Capacity:* The volume of gas remaining in the lungs at the end of quiet expiration.
TLC	*Total Lung Capacity:* The volume of gas in the lungs after a maximum inspiration.
RV	*Residual Volume:* The volume of gas remaining in the lungs after a maximum exhalation.
IC	*Inspiratory Capacity:* The volume of gas that can be inhaled from resting end-expiration (FRC) to full inflation (TLC).
ERV	*Expiratory Reserve Volume:* The volume of gas that can be exhaled from resting end-expiration (FRC) to full exhalation (RV).
IRV	*Inspiratory Reserve Volume:* The volume of gas that can be inhaled from resting end-inspiration to full inflation (TLC).

Descriptors of Forced Breathing Maneuvers

FVC	*Forced Vital Capacity:* The volume of gas that can be forcibly exhaled after fully inflating the lungs.
FEV_t	*Timed Forced Expiratory Volume:* The volume of gas exhaled at a specified time after beginning the forced vital capacity maneuver. For example, FEV_1 = forced expiratory volume in 1 second.

FEV_t/FVC *Ratio of Timed Expiratory Volume to Forced Vital Capacity:* For example, FEV_1/FVC, usually expressed as a percentage.

FEF_x *Specified Forced Expiratory Flow:* The forced expiratory flow rate during a specified portion of the forced vital capacity. For example, $FEF_{200-1200\,mL}$ = forced expiratory flow rate between 200 and 1200 mL of the forced vital capacity; $FEF_{25-75\%}$ = forced expiratory flow rate between 25% and 75% of the forced vital capacity.

$\dot{V}max_{x\%}$ *Specified Maximum Expiratory Flow:* The instantaneous expiratory flow rate when *x* percent of the forced vital capacity has been exhaled. For example, $\dot{V}max_{50\%}$ = maximum expiratory flow rate at 50% of the forced vital capacity.

MVV *Maximum Voluntary Ventilation:* Volume of gas exhaled while making maximum breathing efforts during a certain time interval (often 12 seconds).

VR *Ventilatory Reserve:* The difference between ventilatory capacity during maximum exercise (estimated as MVV or calculated from FEV_1) and minute ventilation at peak exercise; VR, which is also known as *breathing reserve,* represents the potential for further increase in ventilation during maximum (or peak) exercise.

PImax *Maximum Inspiratory Pressure:* The maximum pressure generated by the respiratory muscles during an attempted inspiration.

PEmax *Maximum Expiratory Pressure:* The maximum pressure generated by the respiratory muscles during an attempted exhalation.

Descriptors of Ventilation

f *Respiratory Frequency:* The number of breaths during 1 minute.

VT *Tidal Volume:* The volume of gas inspired or expired during each breath.

$\dot{V}_E$ *Expired Ventilation:* The volume of gas (BTPS), usually measured at the mouth, exhaled during 1 minute.

$\dot{V}_I$ *Inspired Ventilation:* The volume of gas (BTPS), measured or calculated, inhaled during 1 minute.

$\dot{V}_A$ *Alveolar Ventilation:* The volume of gas (BTPS), exhaled from the lungs during 1 minute, that contributed to gas exchange; calculated as expired volume minus dead space ventilation.

$\dot{V}_D$ *Dead Space Ventilation:* The volume of gas (BTPS), exhaled from the lungs during 1 minute, that did not contribute to gas exchange; also known as *wasted ventilation.* Calculated from the equation

$$\dot{V}_D = \dot{V}_E \frac{Pa_{CO_2} - PE_{CO_2}}{Pa_{CO_2} - PI_{CO_2}}$$

where Pa_{CO2}, PE_{CO2}, and PI_{CO2} are the partial pressures of CO_2 in arterial blood, mixed expired gas, and inspired gas, respectively.

VD *Dead Space Volume:* The volume of the physiologic dead space; calculated as $\dot{V}_D/f$.

VD/VT *Ratio of Dead Space to Tidal Volume:* The proportion, usually expressed as a percentage, of each breath that does not contribute to CO_2 removal (i.e., the proportion of each breath that is wasted).

VE *Ventilatory Equivalent:* The minute ventilation required for each liter of gas exchanged, either O_2 or CO_2; used as a measure of the efficiency of the lungs as a gas exchanger. For O_2:

$$VE_{O_2} = \frac{\dot{V}_E(BTPS)}{\dot{V}_{O_2}(STPD)}$$

Volume-Pressure Relationships

C *Compliance:* General symbol for compliance, or the ratio of volume change of the structure per unit change in applied pressure across the structure.

CL *Lung Compliance:* The volume change divided by the difference between alveolar pressure (Palv) and pleural pressure (Ppl), which is also known as the transpulmonary pressure (PL).

CW *Chest Wall Compliance:* The volume change divided by the difference between pleural pressure (Ppl) and body surface pressure (Pbs), which is also known as the transthoracic pressure (PW).

CRS *Respiratory System Compliance:* The volume change divided by the difference between alveolar pressure (Palv) and body surface pressure (Pbs), or transpulmonary pressure (PL) plus transthoracic pressure (PW).

Cdyn *Dynamic Compliance:* Value for compliance based on measurements made during uninterrupted breathing.

Cst *Static Compliance:* Value for compliance based on measurements made during periods of no airflow.

C/V_L *Specific Compliance:* Value for compliance divided by the lung volume at which it was measured, usually functional residual capacity.

Flow-Pressure Relationships

R *Resistance:* General symbol for frictional resistance, or the pressure difference divided by flow.

R_{AW} *Airway Resistance:* Resistance calculated from pressure difference between airway opening (Pao) and alveoli (Palv) divided by the airflow.

RL *Total Pulmonary Resistance:* Resistance calculated by dividing flow-dependent transpulmonary pressure by airflow at the mouth.

G_{AW} *Airway Conductance:* The reciprocal of R_{AW}.

G_{AW}/V_L *Specific Conductance:* Value for airway conductance divided by the lung volume at which it was measured.

III. GAS EXCHANGE

Blood

Examples shown are for O_2; other gases (e.g., CO_2, N_2, CO) or other sites (e.g., $\bar{v}$, c') can be substituted when appropriate.

P_{O_2} *Partial Pressure of O_2:* General designation (expressed in mm Hg); source usually specified (e.g., arterial P_{O_2} or Pa_{O2}).

S_{O_2} *Blood Saturation:* General designation (expressed as a percentage); source usually specified (e.g., arterial S_{O_2} or Sa_{O2}).

C_{O_2} *Oxygen Content:* General designation (expressed in mL/dL); source usually specified (e.g., arterial C_{O_2}).

$\dot{V}_{O_2}$ *Oxygen Consumption:* The volume of O_2 (STPD) utilized by the body during 1 minute; usually calculated as the amount of O_2 extracted from inspired gas.

$\dot{V}_{O_2}$ max *Maximum Oxygen Consumption:* The maximal volume of O_2 (STPD) that can be utilized by the body during 1 minute of maximally attainable exercise.

$\dot{V}_{CO_2}$ *Carbon Dioxide Output:* The volume of CO_2 (STPD) produced by the body during 1 minute; usually calculated as the amount of CO_2 added to exhaled gas.

RQ *Respiratory Quotient:* The ratio of $\dot{V}_{CO_2}$ to $\dot{V}_{O_2}$ during steady-state metabolic activity.

RER *Respiratory Exchange Ratio:* The ratio of $\dot{V}_{CO_2}$ to $\dot{V}_{O_2}$, as in RQ, but also including the influence of transient changes in body stores of respiratory gases.

Gas to Blood

$(A–a)P_{O_2}$ *Alveolar-Arterial PO_2 Difference:* The difference in PO_2 between mean alveolar gas and arterial blood (expressed in mm Hg).

Alveolar Gas Equation: Often used to calculate mean alveolar P_{O_2} (P_{AO_2}):

$$P_{A_{O_2}} = P_{I_{O_2}} - P_{A_{CO_2}}\left[F_{I_{O_2}} + \frac{1 - F_{I_{O_2}}}{R}\right]$$

where $P_{I_{O2}}$ is the P_{O_2} of inspired gas; $P_{A_{CO2}}$ is the alveolar P_{CO_2} (usually assumed to equal arterial P_{CO_2}); $F_{I_{O_2}}$ is the fractional concentration of O_2 in inspired gas; and R is the respiratory exchange ratio.

DL *Diffusing Capacity of the Lung:* Expressed as the volume of gas transferred per minute per unit of alveolar-capillary pressure difference for the gas used, which is usually specified (e.g., $D_{L_{CO}}$ or $D_{L_{O_2}}$).

DM *Diffusing Capacity of the Alveolocapillary Membrane*.

$1/D_L$ *Total Resistance to Diffusion:* The sum of the resistance to diffusion of the test gas across the alveolocapillary membrane ($1/D_M$) and the resistance to diffusion within the red blood cells attributable to the chemical reaction between the test gas and hemoglobin ($1/\theta V_C$). These relationships are expressed by the Roughton-Forster equation:

$$\frac{1}{D_L} = \frac{1}{D_M} + \frac{1}{\theta V_C}$$

D_L/V_A *Diffusion per Unit of Alveolar Volume:* The value of D_L (STPD) divided by V_A (BTPS), both measured in the same breathing maneuver.

IV. HEMODYNAMIC DESCRIPTORS

$\dot{Q}_T$ *Cardiac Output:* The total output of the left ventricle during one minute.

$\dot{Q}_S$ *Pulmonary Shunt Flow:* The total amount of blood per minute perfusing completely nonventilated gas-exchange units; hence, blood that does not come in contact with inspired gas and contribute to oxygen uptake. Often called the *right-to-left shunt,* but this term also includes intracardiac shunts.

$\dot{Q}S/\dot{Q}T$ *Pulmonary Shunt Fraction:* The total pulmonary shunt ($\dot{Q}S$), or venous admixture, expressed as a percentage of total cardiac output ($\dot{Q}T$) according to the equation:

$$\frac{\dot{Q}S}{\dot{Q}T} = \frac{Cc'_{O_2} - Ca_{O_2}}{Cc'_{O_2} - C\bar{v}_{O_2}} \times 100$$

where Cc'_{O_2} is the O_2 content of end-capillary blood; Ca_{O_2} is the O_2 content of arterial blood; and $C\bar{v}_{O_2}$ is the O_2 content of mixed venous blood. When determined from specimens obtained while breathing 100% O_2, $\dot{Q}S/\dot{Q}T$ is a measure of right-to-left shunting of blood.

PPA *Pulmonary Artery Pressure:* The pressure—systolic, diastolic, or mean—measured in the pulmonary artery.

PLA *Left Atrial Pressure:* The pressure, usually mean, measured in the left atrium.

Pcap *Pulmonary Capillary Pressure:* The mean pressure in the pulmonary capillaries, sometimes abbreviated Pc, which cannot be measured directly in humans but is frequently estimated by the equation:

$$Pcap = PLA + 0.4(PPA - PLA)$$

PPW *Pulmonary Wedge Pressure:* The mean pressure measured by the pulmonary artery occlusion technique, which provides an estimate of the postcapillary, or pulmonary venous, pressure.

PVR *Pulmonary Vascular Resistance:* The resistance to blood flow through the lungs; a calculated value from the equation:

$$PVR = \frac{PPA - PLA}{\dot{Q}T}$$

in which PPW is often used to approximate PLA.

V. OTHER USEFUL TERMS AND EQUATIONS

PEEP *Positive End-Expiratory Pressure:* The condition in which the pressure in the lungs at the end of expiration is positive (i.e., higher than atmospheric). Usually applied externally by ventilator adjustments; when PEEP results from failure to exhale fully at the end of expiration, it is called *intrinsic* in origin (PEEPi).

$P_{0.1}$ *Mouth Occlusion Pressure:* The pressure measured in the mouth during the first 0.1 second of attempted inspiration after the airway is temporarily occluded while the subject is breathing. An estimate of the central drive to breathe.

TI/TTOT *Duty Cycle:* The ratio of the duration of inspiration (TI) to the duration of inspiration and expiration (TTOT), a reflection of respiratory timing.

Henderson-Hasselbalch Equation: Useful for calculating any one of three variables, pH, HCO_3^-, or H_2CO_3, when two of them are known:

$$pH = pK + \log\frac{[HCO_3^-]}{[H_2CO_3]}$$

where pK, the dissociation constant, is 6.10 for plasma at 37° C; $[HCO_3^-]$ is the concentration of bicarbonate in plasma; and $[H_2CO_3]$ is the concentration of carbonic acid in plasma (both in mol/L). The equation can be rearranged by using P_{CO_2} (in mm Hg) and its solubility in plasma so that

$$pH = pK + \log\frac{[HCO_3^-]}{[P_{CO_2} \times 0.0301]}$$

Starling Equation: Net fluid exchange (Jv) across the microvascular barrier in the lungs:

$$Jv = LpS[(Pc - Pi) - \sigma d(\pi c - \pi i)]$$

where Lp is the hydraulic conductivity ("permeability"); S is the surface area; Pc is the microvascular hydrostatic pressure; Pi is the perimicrovascular hydrostatic pressure; σd is the osmotic reflection coefficient; πc is the microvascular colloid osmotic pressure; and πi is the perimicrovascular colloid osmotic pressure.

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